

Murray & Nadel's
Textbook of Respiratory
Medicine

Murray & Nadel's Textbook of Respiratory Medicine

SIXTH EDITION

Volume 1

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We dedicate this textbook to Dr. Julius H. Comroe, Jr., who was our mentor during the formative years of our professional development. Dr. Comroe was one of the truly great academicians of his generation. He was an investigator of exceptional merit, an educator whose influence was worldwide, and a medical statesman of exemplary integrity and vision. In dedicating this book, we acknowledge especially Dr. Comroe's scholarly contributions and his commitment to the importance of basic science in the solution of clinical problems.

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Ch. 25 Pulmonary Function Testing

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Ch. 22 Diagnostic Bronchoscopy

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Ch. 32 Viral Infections

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Ch. 37 Endemic Mycoses

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Ch. 103 Extracorporeal Support of Gas Exchange

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Ch. 64 Hypersensitivity Pneumonitis

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Ch. 103 Extracorporeal Support of Gas Exchange

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Ch. 55 Metastatic Malignant Tumors

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Ch. 89 Central Sleep Apnea

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Ch. 29 Dyspnea

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Ch. 63 Idiopathic Interstitial Pneumonias

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Ch. 98 The Respiratory System and Chest Wall Diseases

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Ch. 21 Positron Emission Tomography

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Ch. 83 Mediastinal Tumors and Cysts

Ch. 84 Pneumomediastinum and Mediastinitis

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Ch. 43 COPD: Pathogenesis and Natural History

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Ch. 23 Therapeutic Bronchoscopy

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Ch. 104 End-of-Life Care in Respiratory Failure

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Diseases*

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Ch. 105 Pulmonary Rehabilitation

Preface to the Sixth Edition

In this *Preface to the Sixth Edition of Murray & Nadel's Textbook of Respiratory Medicine*, the Editors are pleased to highlight the new features that enhance the readability and educational value of the book. Whereas advances in both the Fourth and Fifth Editions increasingly incorporated online resources, with the Sixth Edition, the textbook has become truly digital.

The Expert Consult eBook version of the Sixth Edition now provides easier navigation, more thorough and precise searching and retrieval capabilities, and extensive resource material. Via the eBook, readers will have access to nearly 200 videos and audio files and more than 600 new eFigures; there are also extensive cross references to other figures and videos throughout the book. Whereas Key Readings are listed for each chapter in both hardcover and electronic versions, the eBook contains the entire, extensive bibliography where the reader can access each reference by clicking the in-text citation, thereby opening the abstract and accessing direct links to PubMed. The eBook contains new and revised multiple choice questions from each chapter as rich sources of educational challenge and, using the eBook, readers will be able to take notes and highlight important content for later reference. Importantly, the Expert Consult eBook will feature updates, making it a living textbook.

New chapters have been created, former chapters divided, and still others consolidated; in all, the number of chapters has increased from 95 in the Fifth Edition to 106 in the Sixth, as a reflection of the growth in knowledge of scientific and clinical aspects of respiratory health and disease. For example, the chapters on asthma and COPD have both been split: each of these major pulmonary diseases now has one chapter encompassing its molecular phenotypes and pathogenesis and another chapter outlining diagnosis and management. In addition, a chapter on the genetics of asthma and COPD has been added. The section on sleep has been expanded from one to four chapters and sections on pleural disease and fungal disease have also been expanded. New chapters have been added on positron emission tomography, therapeutic bronchoscopy, interventional radiology, bronchiolitis, pulmonary hypertension due to lung disease, non-invasive ventilation, and extra-corporeal membrane oxygenation.

Two new positions have been created: an Editor-in-Chief, who has orchestrated this complex project, and an Editor of Thoracic Imaging, who has edited all clinical images and added hundreds more to the publication. Of the total of 227 authors, 44% are first-time authors to Murray & Nadel and more than 25% hold academic positions outside the United States.

As the partnership between the scientific and clinical applications of respiration has grown and evolved since 1988—when the *Textbook of Respiratory Medicine* was initially published—two guiding axioms have reinforced every edition: first, our staunch belief in the benefit of integrating basic science with the practice of respiratory medicine and, second, the value of having an extensive and inclusive bibliography of classic works and current relevant articles.

Technical advances in publishing have led to extraordinary improvements in how information is gathered, packaged, and displayed for optimum educational benefit. We want to congratulate our publisher, Elsevier, for ensuring that these opportunities were fully realized; moreover, we wish to compliment the entire, talented publishing staff that contributed to this Sixth Edition. Particular thanks go to Jennifer Shreiner, Senior Content Development Editor, who shepherded the project from beginning to end; to Helene Caprari, Content Strategist, for guiding the book through its various stages of production; and to Mary Pohlman, Senior Project Manager, for her proofing and copyediting prowess. Finally, we acclaim the superb work of all the authors and various contributors for bringing this textbook to life, in both hard copy and in its newest digital form.

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Preface to the First Edition

The rapid growth of knowledge of basic scientific principles and their application to respiratory medicine has resulted in a proliferation of monographs and texts dealing with selected aspects of pulmonary science and clinical medicine, but no single work has provided a comprehensive description of all that is currently known. The *Textbook of Respiratory Medicine* is an attempt to provide a well-balanced, authoritative, and fully documented book that integrates scientific principles with the practice of respiratory medicine. The text is sufficiently detailed and referenced to serve as the definitive source for interested students, house officers, and practitioners, both pulmonary specialists and generalists. It is written by leading experts, to guarantee that the material is authoritative and contemporary.

To deal with such an enormous amount of material, we have divided the book into three major sections. This organization should help guide interested readers from the intricacies of basic science to their application at the bedside. We begin in Part I with Scientific Principles of Respiratory Medicine. As implied, this is where the reader will find detailed information about the anatomy and development of the respiratory tract, respiratory physiology, pharmacology and pathology, and defense mechanisms and immunology. A strong foundation in these basic sciences will make possible a rational and scientific approach to the more specialized clinical material included in the subsequent sections. Part II, Manifestations and Diagnosis of Respiratory Disease, contains four chapters on the cardinal signs and symptoms of respiratory disorders and ten chapters on diagnostic evaluation, ranging from the history and physical examination to the newest and most sophisticated imaging, applied physiologic, and invasive techniques. Discrete clinical disorders are included in Part III, Clinical Respiratory Medicine. There are sections on Infectious Diseases, Obstructive Diseases, Neoplasms, Disorders of the Pulmonary Circulation, Infiltrative and Interstitial Diseases, Environmental and Occupational Disorders, Disorders of the Pleura, Disorders of the Mediastinum, Disorders in the Control of Breathing, Respiratory Manifestations of Extrapulmonary Disorders, and Respiratory Failure. All but one of the sections dealing with a generic clinical problem begin with a chapter entitled "General Principles and Diag-

nostic Approach." New challenges to adult respiratory medicine have sprung up, and these are reflected in chapters on subjects such as cystic fibrosis (previously a disease only of childhood!), environmental and occupational diseases, disorders of breathing, and respiratory problems associated with unusual atmospheres (high altitude, diving). The book ends with a novel and important section on Prevention and Control.

Putting together a *Textbook* of this scope and magnitude is no easy task and involves making certain decisions that all readers may not agree with. For example, while trying to keep the length of the book as manageable as possible, we decided to permit some overlap of content. Thus readers will find bronchodilators discussed in the chapter on airway pharmacology and again in the pertinent chapters on obstructive airway diseases. We have also welcomed differences of opinion among authors, provided the issues were clearly stated and the reasons for the author's position documented.

Our struggles were not as arduous as they might have been because we have had considerable help from many sources. First of all was the help from the 95 authors, who worked long and hard on their various contributions. The two editors worked in San Francisco, where they had the benefit of expert secretarial support from Ms. Dorothy Ladd and Mrs. Beth Cost. Special acknowledgment goes to Ms. Aja Lipavsky who, as editorial assistant, handled correspondence, proofing, permissions, and innumerable other details, and prepared the index. At W.B. Saunders in Philadelphia, the book was the brainchild of then-president John Hanley and was published with the guidance of J. Dereck Jeffers, William Lamsback, and the new president Lewis Reines. Production was supervised by Evelyn Weiman.

The long gestation of this book is over, parturition is near, and it will soon begin a life of its own. Like all expectant parents, we are concerned about how our offspring will make its way in the real world. We hope people will like it and find it useful.

John F. Murray, MD

Jay A. Nadel, MD

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Murray & Nadel's
Textbook of Respiratory
Medicine

ANATOMY AND DEVELOPMENT OF THE RESPIRATORY TRACT

1

ANATOMY OF THE LUNGS

KURT H. ALBERTINE, PhD

INTRODUCTION
GROSS AND SUBGROSS
ORGANIZATION
AIRWAYS
BRONCHIAL CIRCULATION

PULMONARY CIRCULATION
TERMINAL RESPIRATORY UNITS
LYMPHATICS
INNERVATION

THE PLEURAL SPACE AND PLEURAS
COMPARISON OF THE LUNG OF MICE
AND HUMANS

INTRODUCTION

The lung has two essential, interdependent functions. One function is ventilation-perfusion matching to deliver oxygen to the body and to remove carbon dioxide that is produced by the body (Fig. 1-1). The second function is host defense against the onslaught of airborne pathogens, chemicals, and particulates. These essential functions are emphasized through the gross, subgross, histologic, and ultrastructural determinants of respiratory gas exchange in the normal human lung. Secondary functions of the lung also are important, such as surfactant synthesis, secretion, and recycling; mucociliary clearance; neuroendocrine signaling; and synthesis and secretion of a myriad of molecules by its epithelial and endothelial cells. The diversity of secondary functions emphasizes the importance of the lung in homeostasis. The chapter finishes with comparison of the lung of mice and humans, an important subject given the widespread use of murine models in lung research. Videos 1-1 to 1-5 provide views of lung movements related to changes in tidal volume, airway pressures, and respiratory rate.

GROSS AND SUBGROSS ORGANIZATION

The position of the lungs in the chest and in relationship to the heart is shown in Fig. 1-2. Figure 1-2A shows a

midfrontal section through the thorax of a frozen human cadaver. Figure 1-2B shows a posterior-anterior chest radiograph of a normal human at *functional residual capacity* (FRC). The two illustrations represent the extremes of the approaches to lung anatomy. The cadaver lung (see Fig. 1-2A) shows the gross anatomic arrangements and relationships. The main distortion is that the lungs are at low volume. The vertical height of the lungs is only approximately 18 cm, which is well below that at FRC (see Fig. 1-2B). The diaphragm is quite elevated in Figure 1-2A, and is approximately 5 cm higher than its end-expiratory position in life. Another distortion is the abnormally wide pleural space; however, this fixation shrinkage artifact serves as a useful reminder that the lung is not normally attached to the chest wall. In life the separation between the parietal and visceral pleuras is only several micrometers.^{1,2} The chest radiograph (see Fig. 1-2B) shows that the vertical height of the lung at FRC is approximately 24 cm, with the level of the bifurcation of the pulmonary artery approximately halfway up the lungs. The diaphragm is lower and flatter than in the cadaver.

In life the human lungs weigh 900 to 1000 g, of which nearly 40% to 50% is blood.^{3,4} At end-expiration, the gas volume is approximately 2.5 L whereas, at maximal inspiration, it may be 6 L. Thus overall lung density varies from 0.30 g/mL at FRC to 0.14 g/mL at total lung capacity. But the density of the lung is not distributed uniformly, being approximately 1 g/mL near the hilum and 0.1 g/mL peripherally. If one likens each lung to a half cylinder, more than

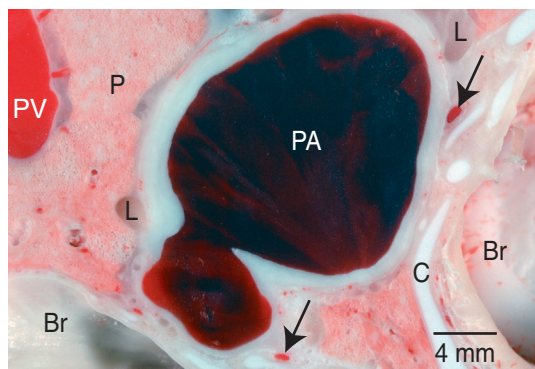


Figure 1-1 Frozen block of lung tissue. Air is brought into the lung via the bronchus (Br) outside of which is a plate of cartilage (C). Pulmonary arterial (PA) blood is dark purple because it is poorly oxygenated. Gas exchange across the lung's parenchyma (P) results in oxygenated pulmonary venous (PV) blood, which is crimson. Also present in the peribronchovascular connective tissue are bronchial arteries (arrows) and lymphatics (L). (Frozen sheep lung, unstained.)

50% of all the lung's alveoli are located in the outer 30% of the lung radius (hilum to chest wall). This is why the peripheral portion of the lung appears relatively empty in the chest radiograph (see Fig. 1-2). Variability in density also exists from top to bottom. In Figure 1-2 the blood vessels are more distended in the lower lung fields. The increasing distention of vessels from apex to base also illustrates the increase in vascular distending pressures at the rate of 1 cm H₂O/cm height down the lung.

The disposition of the various tissues that constitute the lung is summarized in Table 1-1. An amazing point is how little tissue is involved in the architecture of the alveolar walls.^{5,6} But this is as it should be because the major physical problem of gas exchange is the slowness of oxygen diffusion through water.^{7,8} Thus the alveolar walls must be extremely thin. In fact, the thickness of the red blood cell forms a substantial portion of the air-blood diffusion pathway. Advantage was taken of this fact to separate the carbon monoxide diffusing capacity measurement into two components: the capillary blood volume and the membrane diffusing capacity.⁹ (For a discussion of diffusing capacity, see Chapters 4 and 25.)

The lung has two well-defined interstitial connective tissue compartments arranged in series, as described by Hayek¹⁰ (Fig. 1-3). These are the parenchymal (alveolar wall) interstitium and the loose-binding (extra-alveolar) connective tissue (peribronchovascular sheaths, interlobular septa, and visceral pleura). The connective tissue fibrils (collagen, elastin, and reticulin) form a three-dimensional basket-like structure around the alveoli and airways (Fig. 1-4).¹¹ This basket-like arrangement allows the lung to expand in all directions without developing excessive tissue recoil. Because the connective tissue fibrils in the parenchymal interstitium are extensions of the coarser fibers in the loose-binding connective tissue, stresses imposed at the alveolar wall level during lung inflation are transmitted not only to adjacent alveoli, which abut each other, but also to surrounding alveolar ducts and bronchioles, and then to the loose-binding connective tissue supporting the whole lobule, and ultimately to the visceral pleural surface (see Fig. 1-3). These relations become more apparent in certain pathologic conditions. For example, in interstitial emphy-

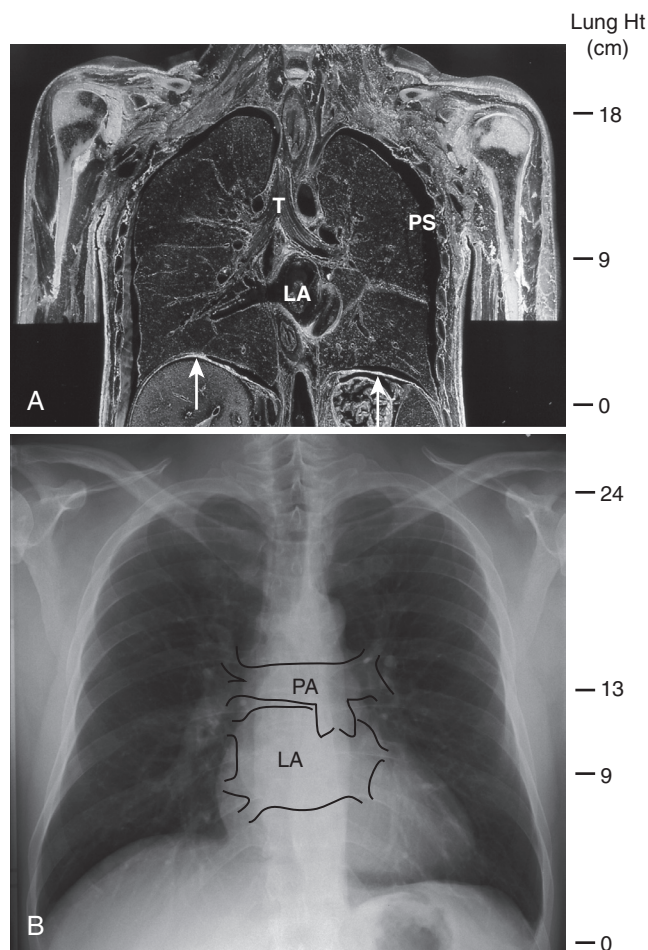


Figure 1-2 Comparison views of lung position in the chest and relationship to the heart. **A**, Midfrontal section through the thorax of a frozen cadaver of a 35-year-old human. The cadaver was prepared by routine embalming procedures, stored horizontally for 3 months in 30% alcohol, and frozen in the horizontal position for 1 week at -20°C . Frontal sections were cut with a band saw. Because the cadaver was preserved in the horizontal position, the weight of the abdominal organs compressed the contents of the thoracic cavity. The domes of the diaphragm (arrows) are elevated approximately 5 cm relative to their end-expiratory position in life. Pleural space (PS) width is artifactually enlarged; normally, in life, it is several micrometers in width. The trachea (T) is flanked on its left by the aortic arch and on its right by the azygos vein. The left pulmonary artery lies on the superior aspect of the left main-stem bronchus. Pulmonary veins from the right lung enter the left atrium (LA), which is located approximately 7 cm above the lung's base. These structures at the root of the lungs caused the esophagus to be cut twice as it follows a curved path behind them to reach the stomach. **B**, Chest radiograph of a normal human adult taken in the upright position at functional residual capacity. The lung height (cm) was measured from the costodiaphragmatic angle to the tubercle of the first rib. The main pulmonary artery (PA) and left atrium (LA) are outlined. The vascular structures, especially the pulmonary veins, are more easily seen near the bottom of the lung. This is partly because vascular distending pressures are greater near the bottom. The density of the lung is also graded, being higher at the bottom than the top and higher near the hilum than peripherally. (**A**, Reprinted with permission from Koritké JG, Sick H: *Atlas of sectional human anatomy*. Vol 1: Head, neck, thorax. Baltimore, 1988, Urban and Schwarzenberg, FT3a, p 83.)

sema,¹² air enters the loose-binding connective tissue and dissects along the peribronchovascular sheaths to the hilum and along the lobular septa to the visceral pleura. Interstitial pulmonary edema liquid enters and moves along the same interstitial pathways (Fig. 1-5).¹³

Table 1-1 Components of Normal Human Lung

Component	Volume or Mass (mL)	Thickness (μm)	Reference No.
Gas	2400		8
Tissue	900		3, 4
Blood	400		4
Lung	500		8
Support structures	225		5
Alveolar walls	275		5, 6
Epithelium	60	0.18	5, 6
Endothelium	50	0.10	5, 6
Interstitial	110	0.22	5, 6
Alveolar macrophages	55		6

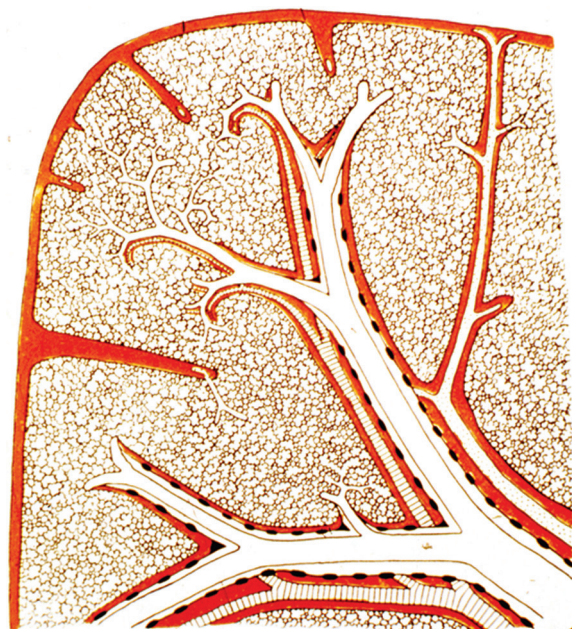


Figure 1-3 General plan depicting the interstitial connective tissue compartments of the lung. All of the support structures (airways, blood vessels, interlobular septa, visceral pleura) are subsumed under the loose-binding connective tissue. The alveolar walls' interstitium comprises the parenchymal interstitium. This organizational plan of the lung follows the general organization of all organs. (Reproduced with permission from Hayek H: *The human lung*, New York, Hafner, 1960, pp 298–314.)

The bulk of the interstitium is occupied by a matrix of proteoglycans (Fig. 1-6).^{14,15} Proteoglycans constitute a complex group of gigantic polysaccharide molecules (≈ 30 different core proteins, with great diversity of glycosaminoglycan side chains) whose entanglements impart a gel-like structure to the interstitium. That structural role, although essential, is not the sole role of these important molecules. A growing view is emerging of the lung's extracellular matrix components as regulators of lung physiology, helping in determining epithelial cell phenotype; binding of and subsequent signaling by cytokines, chemokines, and growth factors; and mediating cell proliferation, migration, differentiation, and apoptosis.^{16–23} In disease states, degradation products of extracellular matrix components may activate the Toll-like receptor pathways (see later discussion); thus the degradation products may serve as endogenous

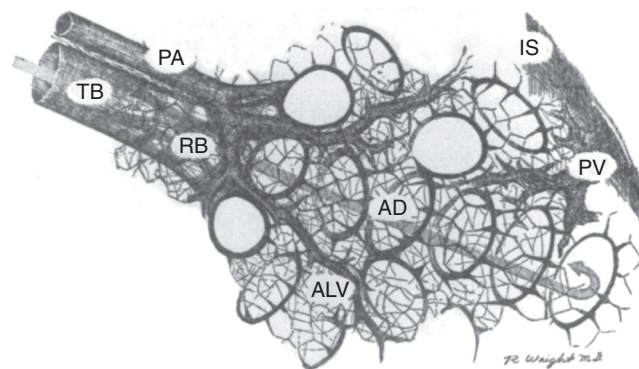


Figure 1-4 A drawing of the connective tissue support of the normal human adult lung lobule demonstrates the weave of fibers composing the “elastic continuum.” AD, alveolar duct; ALV, alveolus; IS, interstitial space; PA, pulmonary artery; PV, pulmonary vein; RB, respiratory bronchiole; TB, terminal bronchiole. (Reprinted with permission from Wright RR: Elastic tissue of normal and emphysematous lungs. *Am J Pathol* 39:355–367, 1961.)

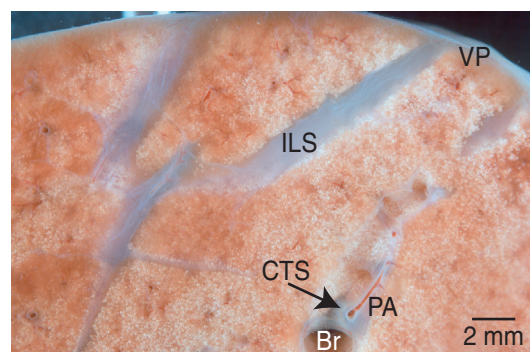


Figure 1-5 Interstitial pulmonary edema demonstrating the loose-binding (peribronchovascular) connective tissue spaces (CTS) that surround the bronchi (Br) and pulmonary arteries (PA). Interstitial edema also expanded the interlobular septa (ILS) that are contiguous with the connective tissue of the visceral pleura (VP). (Frozen sheep lung, unstained.)

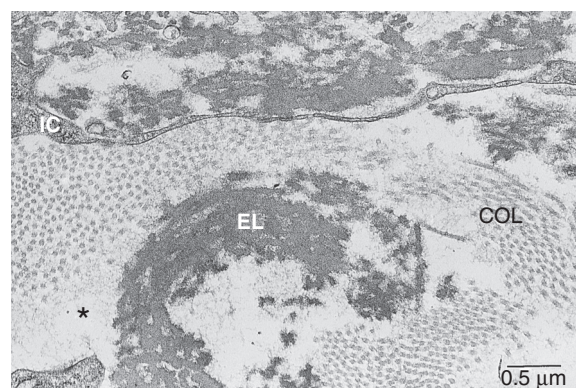


Figure 1-6 The interstitium. The connective tissue compartment of the lung contains interstitial cells (IC), fibrils of collagen (COL), and bundles of elastin (EL). The bulk of the interstitium, however, is occupied by matrix constituents (*) such as glycosaminoglycans. (Human lung surgical specimen, transmission electron microscopy.)

sentinels of tissue damage and initiators of innate immune responses.^{18,22–24} Within this gel-like interstitium reside several varieties of interstitial cells (contractile and noncontractile interstitial cells,^{25,26} mast cells, plasma cells, and occasional leukocytes). The remainder of the interstitium is

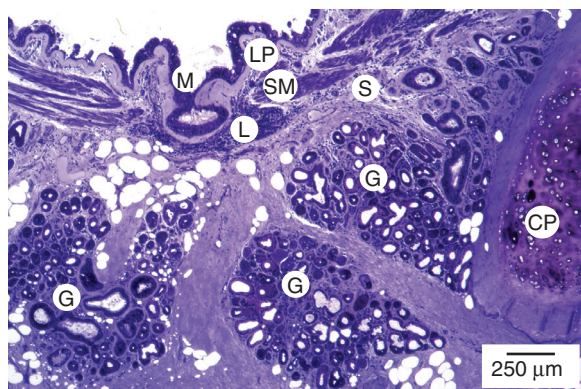


Figure 1-7 A bronchus. The bronchial wall is composed of mucosa (M), lamina propria (LP), smooth muscle (SM), and submucosa (S). Seromucous glands (G) are located between the spiral bands of smooth muscle and cartilaginous plates (CP). Diffuse lymphoid tissue (L) has infiltrated the lamina propria and submucosa. (Human lung surgical specimen, right middle lobar bronchus, 2-μm-thick glycol methacrylate section, light microscopy.)

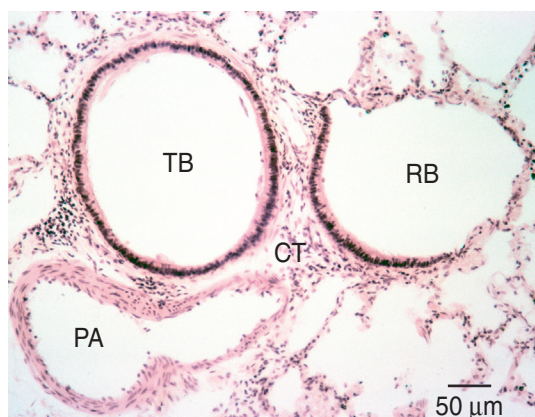


Figure 1-8 A terminal bronchiole and respiratory bronchiole. The wall of the terminal bronchiole (TB) is constructed of a single layer of ciliated cuboidal epithelium that rests over thin, discontinuous bands of smooth muscle and loose areolar connective tissue (CT). In contrast, the wall of the respiratory bronchiole (RB) is only partially lined by ciliated cuboidal epithelium (lower left side). The remainder of its wall is lined by squamous epithelium (upper right side). The connective tissue also surrounds the adjacent pulmonary arteriole (PA). (Human lung surgical specimen, 10-μm-thick paraffin section, light microscopy.)

composed of laminin, collagens, elastin and reticulin fibrils, fibronectin, and tenascin (see Fig. 1-6).

AIRWAYS

The airways, forming the connection between the outside world and the terminal respiratory units, are of central importance to our understanding of lung function in health and disease. Intrapulmonary airways are divided into three major groups: *bronchi* (Fig. 1-7), *bronchioles* (including the terminal bronchioles) (Fig. 1-8), and *respiratory bronchioles* (Fig. 1-9; see Fig. 1-8). By definition, bronchi have cartilage in their wall, whereas bronchioles do not. Respiratory bronchioles serve a dual function as airways and as part of the alveolar volume (gas exchange).

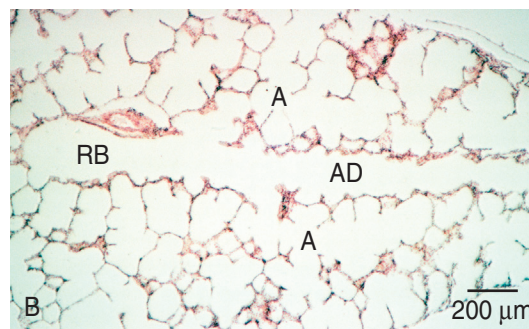
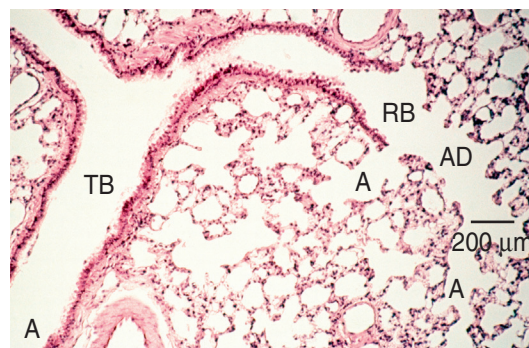


Figure 1-9 Longitudinal sections along bronchioles. **A**, Diameter remains relatively constant along the terminal bronchiole (TB), respiratory bronchiole (RB), and alveolar duct (AD). Alveoli (A) communicate with the gas-exchange ducts (RB and AD). **B**, This longitudinal section along a respiratory bronchiole (RB) and alveolar duct (AD) also shows that their diameter is relatively constant and that both gas-exchange ducts communicate with clusters of alveoli (A). (Human lung surgical specimens, 10-μm-thick paraffin section, light microscopy.)

The anatomic dead space, as measured by the single-breath nitrogen dilution technique, is approximately 30% of each tidal volume. Anatomically this dead space is accounted for principally by the volume of the extrapulmonary (upper) airway, including the nasopharynx and trachea, and the intrapulmonary bronchi.²⁷ The trachea and bronchi are cartilaginous, do not change shape significantly with ventilation, and do not participate in gas exchange. Bronchioles, approximately 1 mm in diameter or less, have no cartilage and are exceedingly numerous and short. They consist of approximately five branching generations and end at the terminal bronchioles. In contrast to the bronchi, the bronchioles are tightly embedded in the connective tissue framework of the lung and therefore enlarge passively as lung volume increases.²⁸ Histologically the bronchioles down to and including the terminal bronchioles ought to contribute approximately 25% to the anatomic dead space. In life, however, they contribute little because of gas-phase diffusion and mechanical mixing in the distal airways resulting from the cardiac impulse. By definition, the respiratory bronchioles and alveolar ducts participate in gas exchange and thus do not contribute to the anatomic dead space. The volume of the respiratory bronchiole-alveolar duct system is approximately one third of the total alveolar volume, and it is into this space that the fresh-air ventilation enters during inspiration.

Most airway resistance resides in the upper airway and bronchi. Normally the large airways maintain partial constriction. The minimal airway diameter in the human lung,

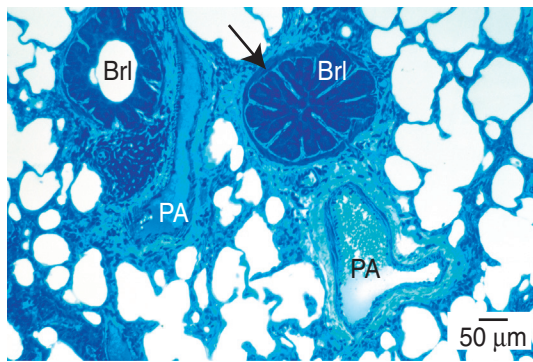


Figure 1-10 Cross sections of two bronchioles (Brl) that would contribute to increased airway resistance. On the left is a bronchiole that is partially narrowed, evident by the folded and thick epithelium. The bronchiole to the right is completely narrowed. Its lumen is obliterated by the infolded epithelium. This bronchiole's smooth muscle is thick (arrow), suggesting that the narrowing is related to constriction of the smooth muscle. Each bronchiole is flanked by a pulmonary arteriole (PA). (Sheep lung, 5-μm-thick paraffin section, light microscopy.)

approximately 0.5 mm, is reached at the level of the terminal bronchioles; succeeding generations of exchange ducts (respiratory bronchioles and alveolar ducts) are of constant diameter (see Fig. 1-9).^{29,30} The functional significance of centralized resistance is that the terminal respiratory units (the physiologic alveoli) are regionally ventilated chiefly in proportion to their individual distensibilities (compliances) because most of their airway resistance is common. This is demonstrated normally by the finding that regional lung ventilation is dependent upon the initial volumes of the alveoli. Terminal respiratory units toward the top of the lung, which are more expanded at FRC, do not receive as great a share of the inspiratory volume as do the terminal respiratory units near the bottom of the lung.

The balance between anatomic dead space volume, for which the airway diameter ought to be as small as possible to maximize efficient alveolar ventilation (dead space-to-tidal volume ratio), and airflow resistance, for which the airway diameter ought to be as large as possible to minimize the work of breathing, requires a compromise. Normally, anatomic dead space is not maximal, nor is resistance minimal. In disease, by contrast, airways may narrow (Fig. 1-10), which increases resistance.

The cellular complexity of the airways is indicated by the nearly 50 distinct cell types found there, at least 12 of which are epithelial cells on the airway surface.³¹ Nearly half of the epithelial cells in the normal human airway are ciliated at all airway generations (Fig. 1-11) down to bronchioles (Fig. 1-12).³² Cilia move the superficial liquid lining layer (Fig. 1-13; see Fig. 1-11) continually toward the pharynx from deep within the lung. As the superficial lining liquid moves centripetally, the total perimeter of the airways decreases markedly.⁵ If the lining liquid volume remained constant, the liquid layer ought to thicken but this does not happen, suggesting that much of the liquid is reabsorbed during its ascent along the airways.

The presence of apical junctional complexes between airway epithelial cells (see Fig. 1-13) has important functional implications for metabolically-regulated secretion into and absorption of electrolytes and water from the lining liquid. Apical junctional complexes consist of three

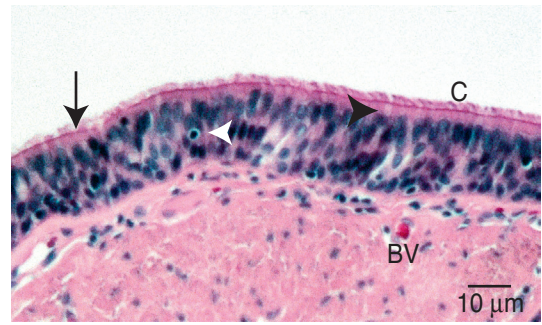


Figure 1-11 The bronchial mucosa consists of pseudostratified, columnar epithelium with cilia (C) and goblet cells (black arrowhead). The cilia, which form a thick carpet, move rhythmically and thereby propel liquid, mucus, cells, and debris centrally toward the pharynx. The dark band immediately beneath the cilia (black arrow) is produced by the basal bodies. By transmission electron microscopy, basal bodies are recognized as modified centrioles. A lymphocyte (white arrowhead) is intercalated among the epithelial cells. A bronchial blood vessel (BV) is located beneath the mucosal layer. (Human lung surgical specimen, 10-μm-thick paraffin section, light microscopy.)

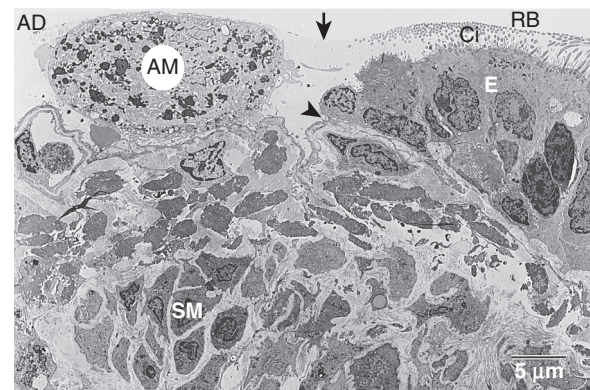


Figure 1-12 The respiratory bronchiole (RB)-alveolar duct (AD) junction is demarcated by an abrupt transition (arrowhead) from low cuboidal epithelial cells (E) with cilia to squamous epithelial cells. Submerged in the lining liquid (arrow) are an alveolar macrophage (AM) and cilia (Ci). Airway smooth muscle cells (SM) extend to this level of the airway tree. (Human lung surgical specimen, transmission electron microscopy.)

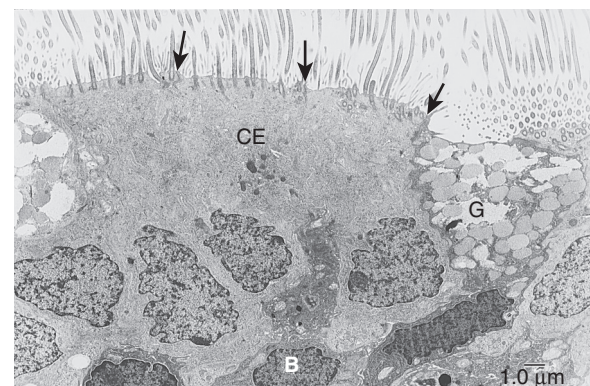


Figure 1-13 Cells constituting the bronchial epithelium are ciliated epithelial cells (CE), goblet cells (G), and basal cells (B). Goblet cells have abundant mucous granules in the cytoplasm, and their apical surface is devoid of cilia. Basal cells, as their name indicates, are located along the abluminal portion of the lining epithelium, adjacent to the basal lamina. The arrows at the apical surface of the airway cells indicate the location of junctional complexes between contiguous epithelial cells. (Human lung surgical specimen, transmission electron microscopy.)

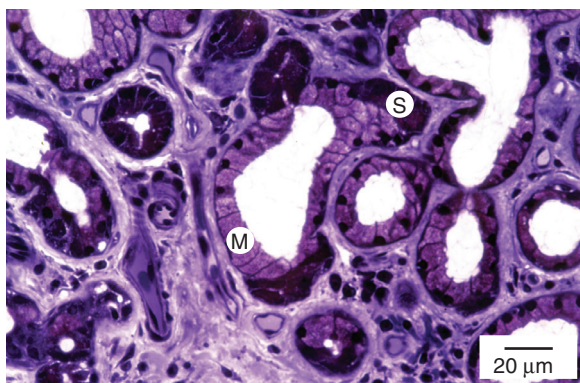


Figure 1-14 Submucosal glands shown at a higher magnification view than in [Figure 1-7](#). These mixed, compound tubuloacinar glands contain mucus-secreting cells (M) and serous-secreting cells (S). The latter type form crescentic caps, or demilunes, over the ends of the acini. Mucus-secreting cells are the predominant glandular cell type.

elements: *zonula occludens* (tight junction), *zonula adherens*, and *macula adherens* (desmosome).³³ Tight junctions subserve two important functions: (1) restriction of passive diffusion by blocking the lateral intercellular space and (2) polarization of cellular functions (ion and water transport) between the apical and basolateral membranes.³⁴ Polarization of chloride and sodium transport allows the airway epithelium either to secrete or to absorb ions, with associated water movement.

Trapping of foreign material, such as particulates or bacteria, is accomplished by mucins. Mucins are complex glycoproteins that form gels, exemplified by MUC5A. MUC5A is present in the lung of humans.^{35,36} Other mucins (e.g., MUC5B, MUC7)^{37,38} become expressed by airway epithelial cells in diseases, such as cystic fibrosis. In that disease, MUC5B is produced by airway epithelial cells.³⁹ Normally MUC5B is produced by airway glandular cells,³⁷ but, in a variety of pulmonary diseases, its cell source is expanded.

Glands are limited to the submucosa of the bronchi. Airway glands secrete water, electrolytes, and mucins into the lumen ([Fig. 1-14](#); see [Fig. 1-7](#)). Studies of the regulation of secretion in vivo and in vitro have shown that release can be modulated by neurotransmitters, including cholinergic, adrenergic, and peptidergic transmitters,^{40,41} and by inflammatory mediators such as histamine,⁴² platelet-activating factor,⁴³ and eicosanoids.⁴⁴ Goblet cells, which are mucin-secreting epithelial cells, also are present at most airway levels (see [Fig. 1-13](#)). Goblet cells decrease in number peripherally, normally disappearing at terminal bronchioles.^{10,45} The absence of airway glands and goblet cells distal to ciliated epithelial cells makes sense because that arrangement should minimize the flow of mucus backward into alveolar ducts and alveoli.

Lymphocytes are frequently seen intercalated between airway epithelial cells ([Fig. 1-15](#); see [Fig. 1-11](#)). These cytotoxic T lymphocytes undergo IgA class antibody responses.⁴⁶ T and B lymphocytes also accumulate in the lamina propria beneath the airway epithelium.⁴⁷

Although most foreign material and immunologic stimuli are carried up the airways by mucociliary action, some are cleared by the lymphatics (discussed at the end of this chapter). In addition, lymphoid tissue is located in the lungs. Patches are distributed along the tracheobronchial

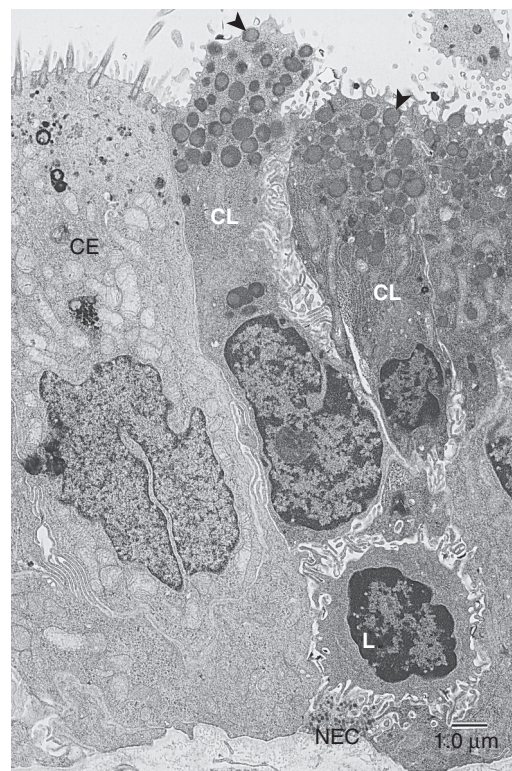


Figure 1-15 The terminal airway epithelium consists mainly of ciliated epithelium (CE) and nonciliated club cells (Clara) (CL). Club cells have the ultrastructural features of secretory cells; namely, they possess basally located rough endoplasmic reticulum, perinuclear Golgi apparatus, apically located smooth endoplasmic reticulum, and prominent membrane-bound granules (arrowheads). A lymphocyte (L) is intercalated among the epithelial cells. A small portion of a neuroendocrine cell (NEC) containing characteristic dense-cored vesicles is also visible at the base of the epithelial cells. (Human lung surgical specimen, transmission electron microscopy.)

tree (see [Fig. 1-7](#)) and, to a lesser extent, along the blood vessels.^{48,49} These patches apparently develop in response to antigenic stimulation because they are not present at birth in humans or in germ-free animals.^{48,49} Lymphocytes in these aggregates are principally B cells that express mainly IgA immunoglobulins.⁴⁷ The presence of lymphocytes along the airways provides a reminder that the respiratory system is constantly challenged by airborne immunologic stimuli. The tracheobronchial lymphoid tissue, including bronchus-associated lymphoid tissue, appears to provide an important locus for both antibody-mediated and cell-mediated immune responses. Another important locus of immune response is provided by the epithelial cells that line the airways and constitute the airway glands. Their importance stems from production of Toll-like receptors, whose role is identification of pathogen-associated molecular patterns.⁵⁰ Activation of Toll-like receptors leads to downstream signaling cascades that are involved in mucin production, leukocyte recruitment, antimicrobial peptide production, wound repair, and vascular formation.⁵¹⁻⁵⁵

Some of the other cells associated with the airways are smooth muscle cells, mast cells, basal cells, and club cells (Clara). Smooth muscle cells form circular bands around the airway epithelium as far peripherally as the respiratory bronchioles (see [Figs. 1-7](#) and [1-8](#)). Smooth muscle tone is

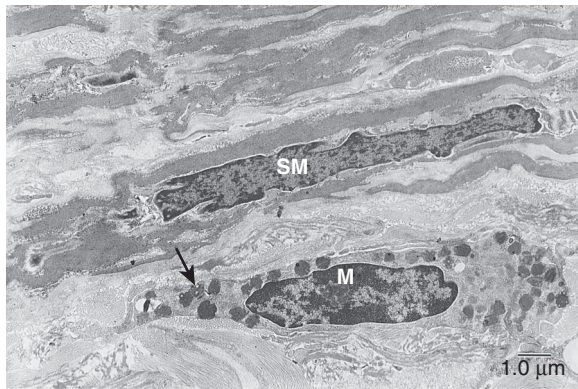


Figure 1-16 Mast cell (M) located adjacent to an airway. The mast cell flanks airway smooth muscle cells (SM). Granules in mast cells have heterogeneous morphologic characteristics, including whorled and scrolled contents (arrow). (Human lung surgical specimen, transmission electron microscopy.)

altered by the autonomic nervous system and by mediators released from mast cells, inflammatory cells, and neuroendocrine cells. During normal breathing, slight tonic contraction of small airway smooth muscle cells and reflex contraction of the larger airways stiffens them against external compression, as may result from forced expiration or coughing. The effector of these responses is the parasympathetic limb of the autonomic nervous system (vagus nerves). Therefore excessive vagal input causes severe contraction of airway smooth muscle and increases mucus secretion by submucosal glands, both of which limit airflow through conducting airways by decreasing airway lumen diameter and increasing airway resistance.

Mast cells in the human lung contain membrane-bound secretory granules that are characteristically filled by scrolled, crystalline, or particulate inclusions (Fig. 1-16). These granules contain a host of inflammatory mediators, including histamine, proteoglycans, lysosomal enzymes, and metabolites of arachidonic acid.⁵⁶ Not only can these mediators induce bronchoconstriction, they can also stimulate mucus production and induce mucosal edema by increasing permeability of bronchial vessels.

Basal cells are located along the basal lamina of airways (see Fig. 1-13). These small epithelial cells have been classically thought to be precursor cells for other airway epithelial cells, including ciliated cells.^{31,57} However, more recent experiments suggest that columnar secretory cells or club cells may also differentiate into ciliated epithelial cells following tissue injury.^{58,59}

Club cells (Clara), prominent in the terminal airways, are interspersed among the ciliated epithelial cells, are nonciliated, and have large apical granules (see Fig. 1-15).^{60,61} Club cells have at least four functions in the lung. One function is serving as progenitor cells for themselves and for ciliated epithelial cells.^{62,63} A second function is xenobiotic metabolism via the cytochrome P-450 monooxygenase system.⁶⁴⁻⁶⁷ A third function is secretion: club cells are a source of surfactant proteins (SPs; SP-A, -B, and -D)⁶⁸⁻⁷⁰ and also of lipids, proteins (club cell 10-kDa protein), glycoproteins, and modulators of inflammation (leukocyte protease inhibitor and trypsin-like protease).⁷¹⁻⁷³ A fourth function is liquid balance by influencing ion channels.^{74,75}

BRONCHIAL CIRCULATION

The trachea (and esophagus), main-stem bronchi, and pulmonary vessels into the lung (see Fig. 1-1), as well as the visceral pleura in humans (see “The Pleural Space and Pleuras” toward the end of this chapter), are supplied by the bronchial (systemic) circulation.^{45,76,77} Measurements of bronchial circulation, by microsphere studies in animals, indicate that flow is 0.5% to 1.5% of cardiac output and is predominantly to the large airways.^{45,76,78-81} The bronchial arteries arborize into bronchial capillaries that form a network in the lamina propria, in the submucosa, and in the region external to the cartilage of bronchi, as well as in the lamina propria of neighboring pulmonary arteries.⁸² Venous blood from the trachea and large airways enters bronchial venules, which converge to form bronchial veins that drain into the azygos or hemiazygos veins. Thus a substantial part of bronchial blood flow returns to the right side of the heart. Deeper in the lung, however, bronchial blood passes via short anastomotic vessels into the pulmonary venules, thus reaching the left side of the heart to contribute to the venous admixture.

The bronchial circulation has enormous growth potential, which is in contrast to the pulmonary circulation, which after childhood is unresponsive. In long-standing inflammatory and proliferative diseases, such as bronchiectasis or carcinoma, bronchial blood flow may be greatly increased.^{76,83} Scar tissue and tumors larger than 1 mm in diameter receive their blood supply via the bronchial circulation.^{84,85} The bronchial circulation is also the primary source of new vessels for repair of tissue after lung injury. As will be discussed near the end of this chapter, the bronchial circulation also supplies the visceral pleura of species that have thick visceral pleura, including humans.

PULMONARY CIRCULATION

In humans the pulmonary artery enters each lung at the hilum in a loose connective tissue sheath adjacent to the main bronchus (see Fig. 1-1). The pulmonary artery travels adjacent to and branches with each airway generation down to the level of the respiratory bronchiole (Fig. 1-17). The anatomic arrangements of the pulmonary arteries and the airways are a continual reminder of the relationship between perfusion and ventilation that determines the efficiency of normal lung function. Although the pulmonary veins also lie in loose connective tissue sheaths adjacent to the pulmonary artery and main-stem bronchus at the hilum, once inside the lung they follow Miller’s dictum⁴⁵ that the veins will generally be found as far away from the arteries and airways as possible. Peripherally, in the respiratory tissue the pulmonary arteries branch out from the core of the terminal respiratory unit, whereas the veins occupy the surrounding connective tissue envelope (Fig. 1-18). Each small muscular pulmonary artery supplies a specific volume of respiratory tissue, whereas the veins drain portions of several such zones.

Considerable quantitative data about the pulmonary circulation are available for the human lung (Table 1-2).⁸⁶⁻⁸⁸ Although most of the intrapulmonary blood volume is in

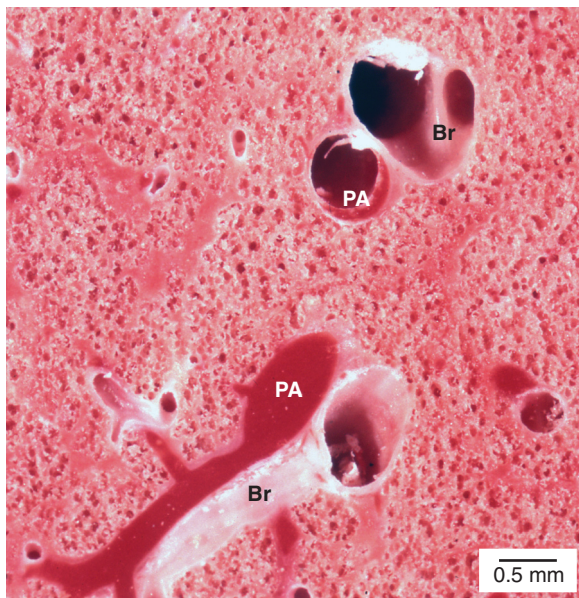


Figure 1-17 Divisions of the pulmonary artery (PA) travel beside the bronchi and bronchioles (Br) out to the respiratory bronchioles. Thus at all airway generations an intimate relationship exists with pulmonary arterial generations. Note that the loose-binding (peribronchovascular) connective tissue sheaths are not distended, compared to the interstitial edema cuffs in [Figure 1-5](#). (Frozen normal sheep lung, unstained.)

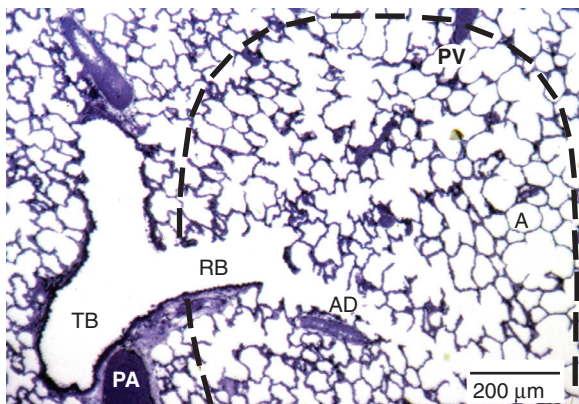


Figure 1-18 The terminal respiratory unit (the physiologist's alveolus) consists of the alveoli (A) and alveolar ducts (AD) arising from a respiratory bronchiole (RB). Each unit is roughly spherical, as suggested by the *dashed outline*. Pulmonary venules (PV) are peripherally located. PA, pulmonary artery; TB, terminal bronchiole. (Normal sheep lung, somewhat underinflated, 2-μm-thick glycol methacrylate section, light microscopy.)

Table 1-2 Quantitative Data on Intrapulmonary Blood Vessels in Humans

Vessel Class (with Diameter)	Volume (mL)	Surface Area (m ²)	Reference No.
Arteries (>500 μm)	68	0.4	86
Arterioles (13–500 μm)	18	1.0	86
Capillaries (10 μm)	60–200	50–70	87
Venules (13–500 μm)	13	1.2	88
Veins (>500 μm)	58	0.1	88

the larger vessels down to approximately 500 μm in diameter, nearly all of the surface area is in the smaller vessels. For example, the surface area of arterioles 13 to 500 μm in diameter exceeds that of the larger vessels by a factor of two, and the maximal capillary surface area is 20 times that of all other vessels.

Because the vertical height of the lung at FRC is 24 cm (see [Fig. 1-2](#)), the pressure within the pulmonary blood vessels varies by 24 cm H₂O over the full height of the lung. Thus, if pulmonary arterial pressure is taken as 20 cm H₂O (15 mm Hg, 1.9 kPa) at the level of the main pulmonary artery, which is halfway up the height of the lung, pressure in the pulmonary arteries near the top of the lung will be 12 cm H₂O, whereas pressure in pulmonary arteries near the bottom will be 36 cm H₂O. Pulmonary venous pressure, which is 8 cm H₂O at the level of the pulmonary artery in midchest (left atrial pressure), would be −4 cm H₂O near the top of the lung and +20 cm H₂O at the bottom. In the normal lung the blood volume is greater at the bottom because of increased luminal pressure, which expands those vessels and increases their volume. This effect of distention also decreases the contribution of the blood vessels at the bottom of the lung to total pulmonary vascular resistance.

From the time after birth through adulthood, the normal pulmonary circulation is a low-resistance circuit. The resistance is distributed somewhat differently, however, than in the systemic circulation, where the major drop in resistance is across the arterioles. Although the pressure drop along the pulmonary capillaries is only a few centimeters of water (similar to the pressure drop in systemic capillaries), the pulmonary arterial and venous resistances are low, so a relatively larger fraction of the total pulmonary vascular resistance (35% to 45%) resides in the alveolar capillaries at FRC.^{89,90} (For further information about pulmonary circulation in health and disease see Chapters 6 and 58.)

Vasoactivity plays an important part in the local regulation of blood flow in relation to ventilation.^{91,92} Because smooth muscle can be found in the pulmonary vessels on both the arterial and the venous side down to precapillary and postcapillary vessels,^{93,94} any segment can contribute to active vasomotion.⁹⁵ In pathologic conditions, vascular smooth muscle may extend down to the capillary level.^{96,97}

Theoretically, gas exchange may take place through the thin wall of almost any pulmonary vessel. At normal alveolar oxygen tensions, however, little oxygen and carbon dioxide is exchanged before the blood reaches the true capillaries.⁹⁸ In the pulmonary arterioles, because of their small volume (see [Table 1-2](#)), blood flow is rapid. As blood enters the vast alveolar wall capillary network, its velocity slows, averaging approximately 1000 μm/sec (or 1 mm/sec). Flow in the microcirculation is pulsatile because of the low arterial resistance.⁹⁹ Pulsations reach the microvascular bed from both the arterial and the venous sides. In fact, one sign of severe pulmonary hypertension is the disappearance of capillary pulsations.¹⁰⁰

The capillary network is long and crosses several alveoli ([Fig. 1-19](#)) of the terminal respiratory unit before coalescing into venules. The vast extent of the capillary bed together with the length of the individual paths means a reasonable transit time for red blood cells, during which gas exchange can take place. The anatomic estimate of

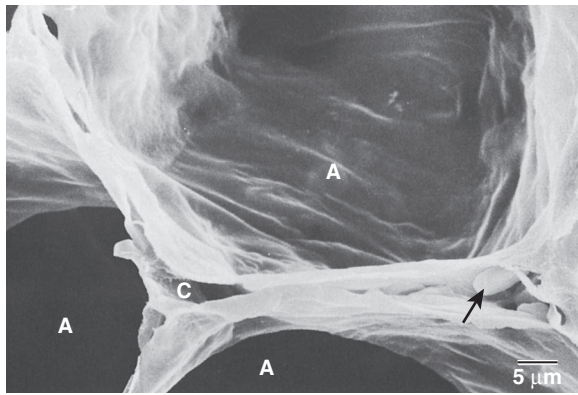


Figure 1-19 An alveolar capillary (C) is shared longitudinally along its path across three alveoli (A). The alveolar walls are flattened, and the wall junctions are sharply curved because the lung is fixed in zone 1 conditions. Some red blood cells remain in the capillary at an alveolar corner (arrow). (Perfusion-fixed normal rat lung, PAW = 30 cm H₂O, PPA = 25 cm H₂O, PLA = 6 cm H₂O, scanning electron microscopy. PAW, airway pressure; PLA, left atrial pressure; PPA, pulmonary artery pressure.)

approximately 0.5 to 1 second average transit time is essentially the same as that found using the carbon monoxide diffusing capacity method, in which one divides capillary blood volume by cardiac output to obtain mean capillary transit time.¹⁰¹ In the normal lung sufficient time is available for equilibrium between the oxygen and carbon dioxide tensions in the alveoli and the erythrocytes in the pulmonary capillaries. Only under extreme stress (heavy exercise at low inspired oxygen tensions) or in severe restrictive lung disease would the red blood cells be predicted to pass through the microcirculation without enough time to reach diffusion equilibrium.¹⁰²

Normally, capillary blood volume is equal to or greater than stroke volume. Under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity, however. Recruitment can increase this volume by a factor of about three. Thus the normal capillary blood volume of 60 to 75 mL is one third of the capacity (200 mL) measured by quantitative histologic analysis.⁵

Anatomically, the pulmonary blood vessels can be divided into two groups in a manner similar to the connective tissue compartments: extra-alveolar and alveolar. *Extra-alveolar vessels* lie in the loose-binding connective tissue (peribronchovascular sheaths, interlobular septa). Extra-alveolar vessels extend into the terminal respiratory units. Arteries as small as 100 µm in diameter have loose connective tissue sheaths. This is in contrast to the bronchioles, which are tightly embedded in the lung framework from the bronchioles (1 mm in diameter) onward. *Alveolar vessels* lie within the alveolar walls and are embedded in the parenchymal connective tissue. They are subject to whatever forces operate at the alveolar level. They are referred to as alveolar vessels in the sense that the effective hydrostatic pressure external to them is alveolar pressure. Not all of the alveolar vessels are capillaries, however. Small arterioles and venules, which bulge into the air spaces, may be affected by changes in alveolar pressure. Likewise, not all of the capillary bed is alveolar under all conditions.¹⁰³ The corner capillaries in the alveolar wall junctions are protected from the full effects of alveolar pressure by the curvature and alveolar air-liquid

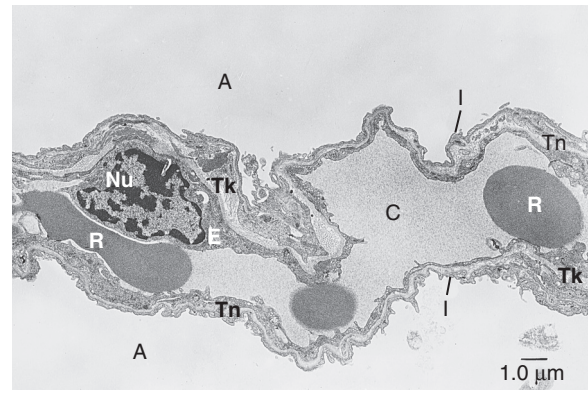


Figure 1-20 The thick (Tk) and thin (Tn) sides of an alveolar capillary (C) change as the capillary crosses between alveoli (A). The basal laminae of the capillary endothelium and alveolar epithelium fuse in the thin regions. The nucleus (Nu) of an endothelial cell (E) is visible above a red blood cell (R). I, alveolar type I cell. (Human lung surgical specimen, transmission electron microscopy).

surface tension.¹⁰⁴ This may account for the fact that, even under zone 1 conditions in which alveolar pressure exceeds both arterial and venous pressure, some blood continues to flow through the lung.¹⁰⁵ One has to go several centimeters up into zone 1 before blood flow stops completely. (For a discussion of distribution of pulmonary blood flow and lung zones, see Chapter 4.)

An important question is whether the normal human lung contains connections between the pulmonary arteries and veins that permit some portion of pulmonary blood flow to bypass the capillary network. Such vessels may develop congenitally or pathologically.¹⁰⁶ In the normal lung, however, functioning short circuits probably do not exist. (Pathologic arteriovenous communications are discussed in Chapter 61.)

Pulmonary capillaries are lined by continuous (non-fenestrated) endothelial cells (Fig. 1-20). These attenuated cells have an individual area of 1000 to 3000 µm² and an average volume of 600 µm³.¹⁰⁷ These large, flat cells cover a total surface area of approximately 130 m².¹⁰⁷ Other structural features of pulmonary capillary endothelial cells are the large number of plasmalemmal vesicles and small number of organelles (see Fig. 1-20). Despite having relatively few organelles, pulmonary capillary endothelial cells do have organelles involved in protein synthesis, such as endoplasmic reticulum, ribosomes and Golgi apparatus, and endocytosis (caveolae, multivesicular bodies, and lysosomes).¹⁰⁸ The endocytic apparatus appears to participate in receptor-mediated uptake and transport (transcytosis) of albumin, low-density lipoproteins, and thyroxine.¹⁰⁹⁻¹¹³ Another route for passage of solutes and water is between adjacent endothelial cells (transcellular transport). However, that passage route is restricted by specialized junctional complexes called “tight junctions.”^{114,115}

In addition to its function in gas exchange, the pulmonary circulation is involved in a number of other functions important to homeostasis. The pulmonary vascular bed serves as a capacitance reservoir between the right and left sides of the heart. Consequently, the reservoir of blood in the pulmonary circulation is sufficient to buffer changes in right ventricular output for two to three heartbeats. The

pulmonary vascular bed also serves as a filter, trapping any embolic material from systemic vascular beds. For example, during intravascular coagulation or in processes involving platelet or neutrophil aggregation, the predominant site of sequestration is the lung. The main anatomic reason for this is that 75% of the total circulating blood volume is in the venous circuit, and the lung's microvascular bed is the first set of small vessels through which the blood flows. Moderate numbers of microemboli generally produce no detectable dysfunction because of the huge array of parallel pathways in the microcirculation. At most, microemboli temporarily block flow to a portion of or to an entire terminal respiratory unit. The fate of such emboli is not clear. Some are phagocytosed and removed into the lung tissue.¹¹⁶ Some emboli can be degraded to a small size, pass through into the systemic circulation, and be removed by the reticuloendothelial system. One example of particulate matter that filters in the lung is the macroaggregated serum albumin used in lung-scanning procedures. (Further information about the pathophysiology of thromboembolic disorders is presented in Chapter 57.)

The endothelial cells of the pulmonary circulation are capable of a remarkable number of metabolic activities. This is not to say that endothelial cells in other organs do not have similar activities. But the central position of the lung, through which the entire cardiac output passes, places extra responsibility and extra importance upon its endothelial cells.¹¹⁷⁻¹¹⁹ For example, angiotensin I, bradykinin, and prostaglandin E₁ are nearly completely inactivated during a single pass through the lungs. Pulmonary endothelial cells also express at least two subtypes of endothelin receptors (A and C).¹²⁰⁻¹²² Their expression coincides with rapid removal of endothelin, suggesting that the lung microcirculation participates in clearance of this potent vasoconstrictor peptide from the blood. Conversely, a potent vasodilator, nitric oxide, is generated locally in the lung, through expression of endothelial nitric oxide synthase.¹²³⁻¹²⁹

Endothelial cells may have a role in regulating vascular tone and reactivity. An indication of this regulatory role can be seen in the direct contacts between pulmonary endothelial cells in small arteries and veins and the surrounding smooth muscle cells. Such myoendothelial contacts have been described in the lungs of a number of small animals,¹³⁰⁻¹³³ and we have seen them in the human lung (Fig. 1-21). Although their functional importance is unknown, they may have some bearing on endothelial-dependent vasoactivity.¹³⁴

Regulation of vasoactivity by endothelial cells may be facilitated by site-specific phenotypes of endothelial cells (reviewed by Garland and Dejana¹³⁵ and Gebb and Stevens¹³⁶). For example, endothelial nitric oxide protein is more evident in small pulmonary arterial vessels than in capillaries.¹²³⁻¹²⁸ Presumably the more evident localization reflects the functional role of nitric oxide in regulating pulmonary artery smooth muscle tone. On the other hand, capillary endothelial cells appear to have more expression-activated message for leukocyte adhesion molecules than arterial endothelial cells.^{135,136} Greater expression by capillary endothelial cells may contribute to sequestration of leukocytes in the capillary bed during acute inflammatory reactions. Another endothelial cell function that is site specific in the lung is Ca²⁺ transients that are induced by pres-

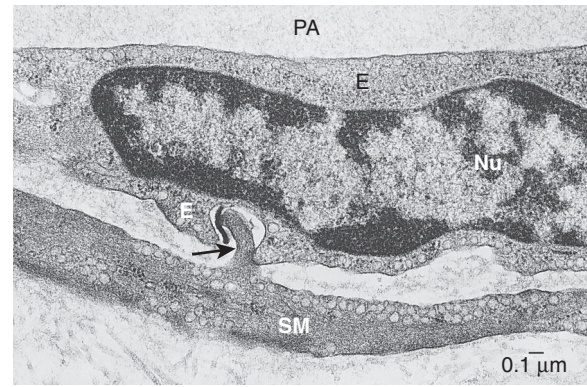


Figure 1-21 A myoendothelial cell contact (arrow) is made between a pulmonary arteriolar (PA) endothelial cell (E) and a subjacent vascular smooth muscle cell (SM). The distribution and functional significance of such contacts is unknown. One potential role may be to facilitate delivery of endothelium-derived relaxing factor to smooth muscle cells. Nu, nucleus of the endothelial cell. (Human lung surgical specimen, transmission electron microscopy).

sure elevations as small as 5 cm H₂O. The calcium transients seen in a subset of Ca²⁺ oscillating cells are referred to as “pacemakers” and are located in pulmonary venular capillaries.¹³⁷ The oscillations are propagated to adjacent endothelial cells. This endothelial response may be relevant in the pathogenesis of pressure-induced lung microvascular injury.

TERMINAL RESPIRATORY UNITS

The “alveolus” of which the physician or pulmonary physiologist speaks is referred to as the “terminal respiratory unit” by the anatomist. The terminal respiratory unit consists of all the alveolar ducts, together with their accompanying alveoli, that stem from the most proximal (first) respiratory bronchiole (see Fig. 1-18). The terminal respiratory unit has both a structural and a functional existence and was first described by Hayek.¹⁰ In the human lung this unit contains approximately 100 alveolar ducts and 2000 alveoli. At FRC the unit is approximately 5 mm in diameter, with a volume of 0.02 mL. In normal adult humans, there are approximately 150,000 such units in both lungs combined.⁵ The acinus, an anatomic unit popular among pathologists, contains 10 to 12 terminal respiratory units.¹³⁸⁻¹⁴⁰

The functional definition of the terminal respiratory unit is that, because gas phase diffusion is so rapid, the partial pressures of oxygen and carbon dioxide are uniform throughout the unit.¹⁴¹ Diffusion is the name for a thermodynamic process by which molecules express their kinetic energy. Net diffusion takes place when a concentration difference of a substance exists between two volumes. Thus oxygen in the alveolar duct gas will diffuse into the alveoli, because the incoming air has a higher oxygen concentration than the alveolar gas. Oxygen will also diffuse from the gas adjacent to the alveolar wall through the air-blood barrier into the red blood cells flowing in the capillaries (Fig. 1-22), where oxygen combines with hemoglobin. Carbon dioxide diffuses in the opposite direction. A key point about

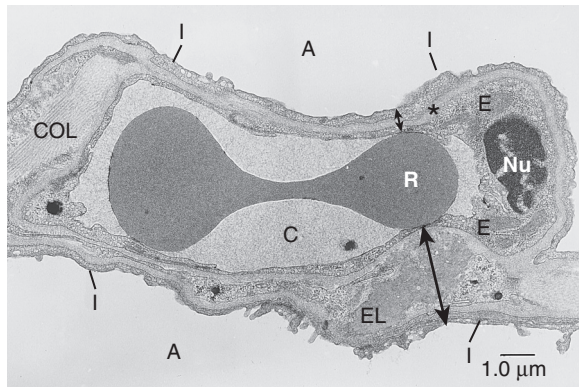


Figure 1-22 Cross section of an alveolar wall showing the path for oxygen and carbon dioxide diffusion. The thin side of the alveolar wall barrier (short double-headed arrow) consists of type I epithelium (I), interstitium (*) formed by the fused basal laminae of the epithelial and endothelial cells, capillary endothelium (E), plasma in the alveolar capillary (C), and finally the cytoplasm of the red blood cell (R). The thick side of the gas-exchange barrier (long double-headed arrow) has an accumulation of elastin (EL), collagen (COL), and matrix that jointly separate the alveolar epithelium from the alveolar capillary endothelium. As long as the red blood cells are flowing, oxygen and carbon dioxide probably diffuse across both sides of the air-blood barrier. A, alveolus; Nu, nucleus of the capillary endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

diffusion is that the process is much faster in the gas phase than in water. Thus the terminal respiratory unit size is defined in part by the fact that gas molecules can diffuse and equilibrate anywhere within the unit more rapidly than they can diffuse through the membrane into the blood. The main problem is that the solubility of oxygen in water is low relative to its concentration in gas. Water becomes a problem when edema liquid accumulates in alveoli and/or interstitium in the alveolar walls. Carbon dioxide is much more soluble in water (20 times the solubility of oxygen in water), and therefore carbon dioxide diffuses rapidly into the gas phase, even though the driving pressure for carbon dioxide diffusion is only one tenth that for oxygen entering the blood.

It is almost impossible to demonstrate that diffusion is limiting in the normal lung, except during heavy exercise while breathing gas containing very low oxygen concentrations.¹⁰² Even then, diffusion limitation may not be as important as the reduced transit time of the red blood cells. However, apart from these observations during heavy exercise, most disorders of oxygenation are due to ventilation-perfusion inequalities.¹⁴²

All portions of the terminal respiratory unit participate in volume changes with breathing.^{143,144} Thus, if a unit were to increase its volume from FRC, the alveolar gas that had been in the alveolar duct system would enter the expanding alveoli, together with a small portion of the fresh air. Most of the fresh air would remain in the alveolar duct system. This does not lead to any significant gradient of alveolar oxygen and carbon dioxide partial pressures because diffusion in the gas phase is so rapid that equilibrium is established within a few milliseconds. But nondiffusible (suspended or particulate) matter would remain away from the alveolar walls and be expelled in the

subsequent expiration.¹⁴⁵ This explains why it is difficult to deposit aerosols on the alveolar walls and why large inspired volumes and breath-holding are important for obtaining efficient alveolar deposition.

The anatomic alveolus is not spherical (Fig. 1-23; see Fig. 1-19). It is a complex geometric structure with flat walls and sharp curvature at the junctions between adjacent walls. The most stable configuration is for three alveolar walls to join together, as in foams.⁵ The resting volume of an alveolus is reached at minimal volume, which is 10% to 14% of total lung capacity. When alveoli go below their resting volume, they must fold up because their walls have a finite mass. Most of the work required to inflate the normal lung is expended across the air-liquid interface to overcome surface tension; the importance of the air-liquid interface is demonstrated by the low pressure required to “inflate” a liquid-filled lung with more liquid.¹⁴⁶

The phenomenon of terminal respiratory unit, or alveolar, stability is confused because not only is air-liquid interfacial tension involved, but each flat alveolar wall is part of two alveoli and both must participate in any change. Therefore atelectasis does not usually involve individual alveoli but rather relatively large units (Fig. 1-24).¹⁴⁷

The alveolar walls are composed predominantly of pulmonary capillaries. In the congested alveolar wall, the blood volume may be more than 75% of the total wall volume. Alveoli near the top of the lung show less filling of the capillaries than those at the bottom.^{148,149} This affects regional diffusing capacity, which is dependent on the volume of red cells in the capillaries (see also eFig. 25-10).

The transition from the cuboidal epithelium of the respiratory bronchiole to alveolar squamous epithelium is abrupt (see Fig. 1-12). Although Macklin¹⁵⁰ speculated that the permeability of the bronchiole-alveolar epithelial junctions may be special, no definitive difference has been demonstrated.¹⁵¹ The controversy continues as to whether this region shows unique permeability features that might participate in clearance of particles or leakage of edema.¹⁵²⁻¹⁵⁴

The pleomorphic nature of the alveolar epithelium and the light and electron microscopic structure of its constituent cells have been described many times and will be only briefly summarized here. In normal mammals and other air-breathing species, including reptiles and amphibians, the alveolar epithelium is composed of cuboidal alveolar type II cells and flattened type I cells (Fig. 1-25). Alveolar type II cells outnumber type I cells ($\approx 15\%$ versus 8% to 10% of total peripheral lung cells, respectively), but type I cells account for approximately 90% to 95% of the alveolar surface area of the peripheral lung.¹⁵⁵ The two cell types have different functions and structure.

The alveolar type II cell is the major synthesizing and secreting factory of surfactant-associated proteins that affect adsorption of surfactant lipids to an air-liquid interface, surfactant recycling, and immunomodulatory functions. Alveolar type II cells also express receptors for several growth factors and secretagogues, enzymes, matrix proteins, and epithelial mucins.¹⁵⁶⁻¹⁶¹ The presence of various ion channels and transporters supports earlier evidence that alveolar type II cells are actively involved in liquid resorption and transepithelial water fluxes.¹⁶² Alveolar type II cells are reported to express some species of aquaporin

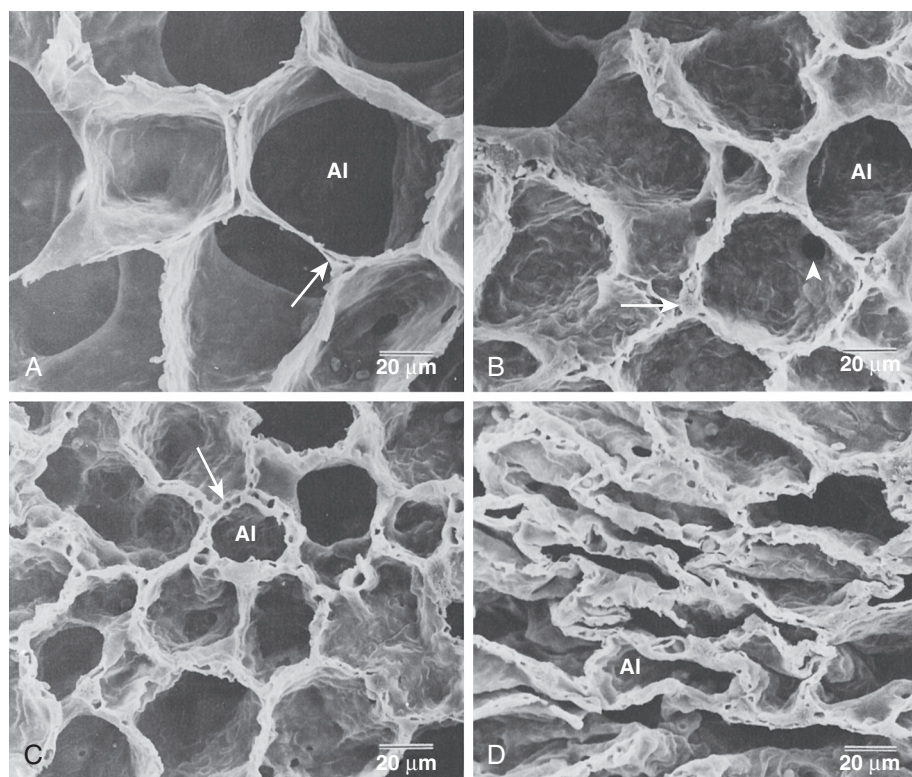


Figure 1-23 Alveolar shape changes at representative points along the air deflation pressure-volume curve of the lung. The four micrographs are at the same magnification. The air deflation pressures are as follows: **A**, 30 cm H₂O (total lung capacity; TLC); **B**, 8 cm H₂O (approximately 50% TLC); **C**, 4 cm H₂O (near functional residual capacity; FRC); and **D**, 0 cm H₂O (minimal volume). Vascular pressures are constant (PPA = 25 cm H₂O and PLA = 6 cm H₂O). Intrinsic alveolar shape (AI) is maintained from TLC to FRC (**A–C**). The alveolar walls are flat, and there is sharp curvature at the junctions between adjacent walls. Note the flat shape of the alveolar capillaries (*arrow*) at TLC (**A**, lung zone 1 conditions) compared to their round shape (*arrow*) at FRC (**C**, lung zone 3 conditions). The alveolar walls are folded, and alveolar shape is distorted at minimal lung volume (**D**). The *arrow* in **B** identifies an alveolar type II cell at an alveolar corner. The *arrowhead* in **B** identifies a pore of Kohn. PAW, airway pressure; PLA, left atrial pressure; PPA, pulmonary artery pressure. (Perfusion-fixed normal rat lungs, scanning electron microscopy.)

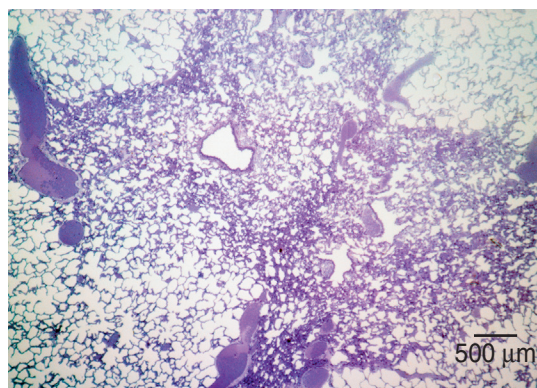


Figure 1-24 Histologic appearance of atelectasis. Atelectasis usually involves relatively large units of lung parenchyma, rather than individual alveoli. Alveolar walls in the atelectatic units are folded, distorting the shape of alveoli and capillaries, as shown in [Fig. 1-23D](#). (Sheep lung injured by air emboli, 2-µm-thick glycol methacrylate section, light microscopy.)

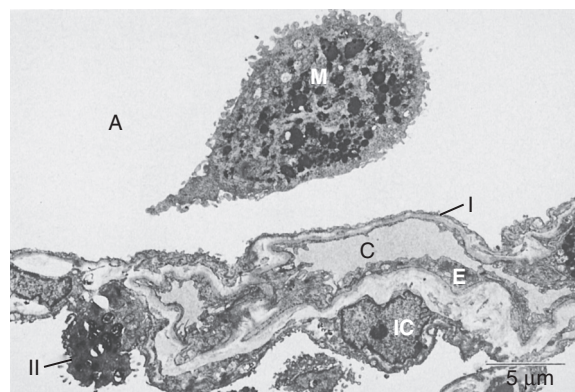


Figure 1-25 Cells of the terminal respiratory unit. An alveolar macrophage (M) is located in an alveolus (A). Alveolar macrophages are the air space scavengers that are cleared either up the mucociliary escalator or into the interstitium. These cells can be activated to express and secrete cytokines, which may interact with other cells. Cells of the alveolar wall are the lining alveolar type I and II cells (I and II, respectively) and the enclosed capillary (C), endothelial cells (E), and interstitial cells (IC). (Human lung surgical specimen, transmission electron microscopy.)

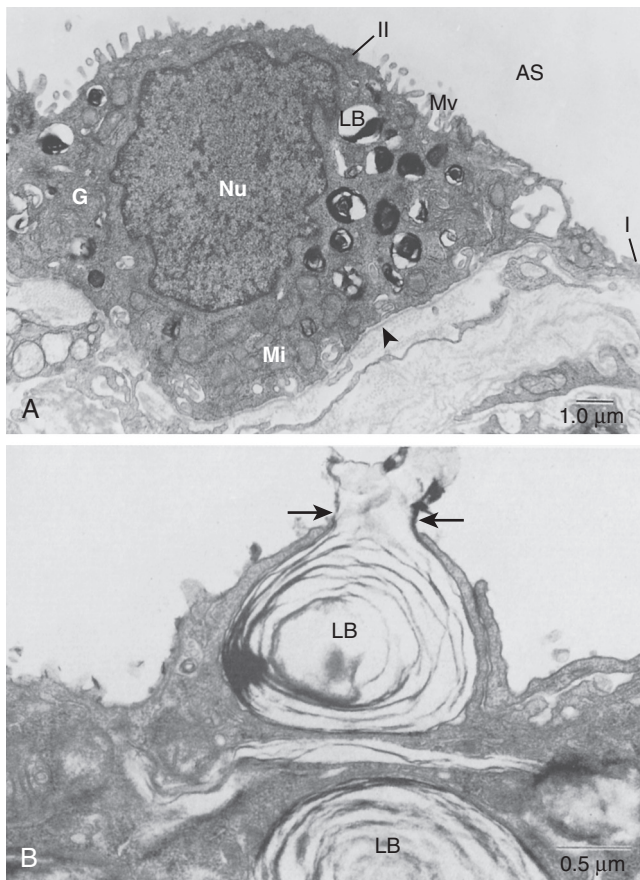


Figure 1-26 **A**, Alveolar type II (or granular) cells (II) are cuboidal epithelial cells that contain characteristic lamellar bodies (LB) in their cytoplasm and have stubby microvilli (Mv) that extend from the apical surface into the alveolar air space (AS). Other prominent cytoplasmic organelles in alveolar type II cells are mitochondria (Mi) and Golgi apparatus (G). Adjacent to the type II cell is a process of a type I cell (I). The abluminal surface of the epithelial cells rests on a continuous basal lamina (arrowhead). Nu, nucleus of an alveolar type II cell. **B**, The apical region of an alveolar type II cell has two lamellar bodies (LB), one of which has been fixed in the process of secretion by exocytosis (arrows). The lamellar osmophilic bodies are believed to be the source of surface-active material (surfactant). Alveolar type II cells are usually located in the alveolar corners (see Fig. 1-23B). (Human lung surgical specimen, transmission electron microscopy.)

(AQP3, AQP1),^{163,164} water channels that may facilitate transepithelial liquid fluxes.

The typical alveolar type II cell (e.g., human, rodent) is a small (300 μm^3), cuboidal cell with short stubby apical microvilli (Fig. 1-26). The distinguishing structural feature of an alveolar type II cell is its content of intracellular lamellar bodies, which are membrane-bound inclusions (diameter from <0.1 to 2.5 μm ; mean, $\approx 1 \mu\text{m}$) composed of stacked layers of cell membrane-like material (see Fig. 1-26). These bodies contain pulmonary surfactant and are composed of phospholipid species similar to those of lavaged surfactant.¹⁶⁵ Lamellar bodies also contain various proteins, including SP-A, SP-B, and SP-C but probably not SP-D, typical lysosomal enzymes, an H^+ transporter, a unique α -glucosidase, and other molecules.¹⁶⁶⁻¹⁶⁸ Alveolar type II cells also internalize and recycle surfactant lipids and proteins, but the cellular pathways are not well characterized in terms of participating organelles, signaling mecha-

nisms, and general molecular regulation. Multivesicular bodies, organelles generally involved in endocytosis, are unusually abundant in alveolar type II cells and also express the ABC-type transporter membrane protein.¹⁶⁹

Alveolar type I cells have extensive, attenuated cytoplasmic processes that form a large, thin surface area for gas exchange (see Fig. 1-25). The enormous surface area of these cells presents a logistical problem for transport of new proteins and other substances within the cell over long distances and most likely contributes to the vulnerability of the type I cell to injury. Under normal conditions, alveolar type I cells attach via tight junctions to neighboring alveolar type II cells to form a relatively impermeable seal between alveolar air and alveolar wall interstitial spaces. Although the cells express connexin proteins used to form gap junctions,¹⁷⁰ such junctions have not been consistently observed by electron microscopy. Lectin-binding and histochemical studies show that the chemical nature of the alveolar type I cell apical membrane differs markedly from that of type II cells, and this concept is confirmed by the identification of novel type I cell proteins. The alveolar type I cell protein aquaporin-5 is of particular interest because this water channel has the highest water permeability known, at least in vitro.¹⁷¹ Type I cells also express epithelial Na^+ channels and membrane Na^+, K^+ -ATPase.^{172,173} These observations collectively imply that type I cells may play a role in pulmonary water flux, although this is not yet proven.^{174,175}

Alveolar type I cells contain many small, non-clathrin-coated vesicles, or caveolae, that are open either to the alveolar lumen or interstitium or are detached from the surface as free vesicles in the cytoplasm.¹⁷⁶ Immunohistochemistry shows that the vesicles contain caveolin-1 protein.¹⁷⁷ Likewise, biochemical analyses¹⁷⁸ show high concentrations of caveolin protein and messenger RNA in lung where it is expressed mainly by type I and vascular endothelial cells. Caveolin-1 is a scaffolding protein that organizes specialized membrane phospholipids and proteins into vesicles. Caveolin-1 can bind free cholesterol and modulate the efflux of cholesterol from the cell when intracellular concentrations rise,¹⁷⁹ and, in other cell systems, its expression is tightly linked to the availability of free cholesterol. Caveolae appear to sequester various proteins into the vesicles; such proteins include growth factor receptors, signaling molecules such as G proteins, Ca^{2+} receptors and pumps, and, in endothelial cells, endothelial nitric oxide synthase. The general effect of sequestration of receptors and signaling molecules into caveolae is to maintain them in a functionally quiescent state.

Trapping and clearance of particulate matter impinging on the alveolar surfaces is vital and takes place in the alveolar surface liquid. Within this liquid are suspended alveolar macrophages (see Fig. 1-12). The cytoplasm of alveolar macrophages contains numerous storage granules that are blackened by ingested particulate matter that reach the alveoli (see Fig. 1-25). Alveolar macrophages actively express and secrete cytokines, such as tumor necrosis factor- α and transforming growth factor- α , that are important for innate immunity. Some of these alveolar macrophages penetrate into the lung interstitium and can be seen as deposits of black pigment within interstitial foci. The majority of alveolar macrophages that reach the terminal airways via the slow, upward flow of alveolar lining liquid

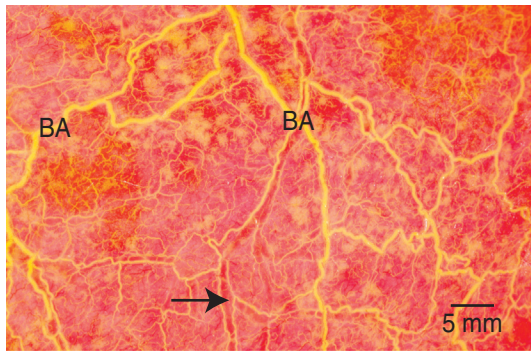


Figure 1-27 Surface view of the visceral pleura. Yellow latex polymer (Microfil) was perfused through the bronchial artery trunk to fill the bronchial arteries (BA) that supply the visceral pleura. Bronchial arterioles flank lymphatics (arrow) that constitute the superficial lymphatic plexus of the lung. (Sheep whole lung, macroscopic view).

are expelled with the surface film as it is pulled up onto the mucociliary escalator.¹⁸⁰⁻¹⁸²

LYMPHATICS

Another route for clearance of particulate matter and liquid from the lung is the pulmonary lymphatic system. Lymphatics of the lung are subdivided into two principal groups based on their location: a deep plexus and a superficial plexus.^{10,45,183,184} Both plexuses are made up of initial and collecting lymphatics, with communications between the two.^{10,45,153,183} The *deep plexus* is situated in the peribronchovascular connective tissue sheaths of the lung (see Fig. 1-1).^{10,45,153,183} Lymphatics in the deep plexus are distributed around the airways, extending peripherally to the respiratory bronchioles and next to branches of the pulmonary arteries and veins.^{10,45,153,183} The *superficial plexus* is located in the connective tissue of the visceral pleura (Fig. 1-27). This plexus is prominent in the lung of species with thick visceral pleura, including humans (see “*The Pleural Space and Pleuras*”).^{10,45,183} Lymphatics are not found in the alveolar walls.

Lymph is propelled centripetally toward the lung's hilum or pulmonary ligament to reach regional lymph nodes. In the human, pulmonary lymph flows to extrapulmonary lymph nodes located around the primary bronchi and trachea.^{10,45,183}

INNERVATION

Innervation of the human lung consists of sensory (afferent) and motor (efferent) pathways.^{183,185-187} The sensory pathways originate in relation to the airway epithelium, submucosa, interalveolar septa, and smooth muscle. Mapping the complete distribution of the mucosal sensory nerve endings has been hampered by the lack of dependable morphologic methods that identify intraepithelial sensory axons. Ultrastructural techniques have shown that axons, when found, resemble known sensory endings in other organs (<1 μm in diameter, electron lucent, and containing microtubules and smooth endoplasmic reticulum).¹⁸⁸ Fibers of this pathway include myelinated, slowly adapting stretch

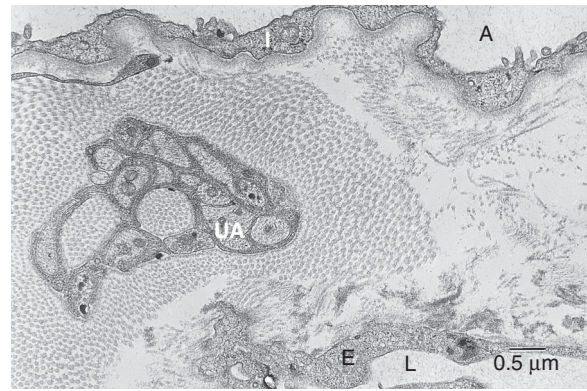


Figure 1-28 Unmyelinated axons (UA) known as C fibers are shown situated in the interstitium of a respiratory bronchiole, between an alveolar type I cell (I) lining an alveolus (A) and an initial lymphatic (L). Although the presence of small clear vesicles is suggestive of cholinergic (autonomic) axons, unequivocal identification as either motor or sensory fibers is not possible in random thin sections. E, lymphatic endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

receptors (Hering-Breuer reflex) and irritant receptors, but most are unmyelinated, slow-conducting C fibers located in the terminal respiratory units, either along the bronchioles or within the alveolar walls (Fig. 1-28). There has been speculation about the function of C fibers since Paintal first suggested that they played a role in sensing parenchymal connective tissue distortion, as during pulmonary vascular congestion and interstitial edema.¹⁸⁹⁻¹⁹² The speculation has been neither proven nor disproven.

Chemosensory cells are also present in the upper and lower airways.^{193,194} This sensory role is subserved in the human lung by ciliated airway epithelium of the upper and lower airways, which have functional components for bitter taste receptors.¹⁹⁵ In addition, solitary epithelial brush cells with a chemosensory function are present in upper and lower airways.¹⁹⁶ The afferent fibers travel in the vagus nerves and terminate in the vagal nuclei in the medulla oblongata.¹⁹⁷

Submucosal sensory nerve endings, in contrast, are more reliably identifiable because the axon can be stained with methylene blue or silver nitrate. Furthermore, studies of axonal transport indicate that the peripheral processes of sensory ganglia project to the submucosa.¹⁹⁸ Ultrastructural observations of these fibers reveal axonal terminals containing numerous membranous inclusions and mitochondria, which are characteristic of mechanoreceptors.

The motor pathways reach the lung through the sympathetic and parasympathetic nervous systems. Preganglionic contributions to the sympathetic nerves arise from the upper four or five thoracic paravertebral ganglia, whereas the preganglionic parasympathetic nerves originate in the brain stem motor nuclei associated with the vagus nerves. Postganglionic sympathetic nerve fibers terminate near an airway, innervating vascular smooth muscle cells and submucosal glands. Postganglionic parasympathetic fibers extend from ganglia mainly located external to the smooth muscle and cartilage. Some submucosal ganglia exist, but they are generally smaller and have fewer neurons.

Mucosal motor nerve endings also exist.¹⁹⁹ Characteristic ultrastructural features are axonal profiles containing many small, agranular vesicles and few mitochondria.

Unfortunately, the source and function of these axons is unknown. A goblet cell secretomotor role is doubtful because goblet cells in isolated epithelial strips do not secrete glycoproteins when bathed in drugs that mimic neurotransmitters.²⁰⁰ Alternatively, a role may be the release of mucus by direct response to mechanical and chemical signals. Another effector role of nerves in the lung is epithelial ion transport, a process that is stimulated by catecholamines,²⁰¹ acetylcholine,²⁰² and neuropeptides.²⁰³ This role is further supported by the presence of α -adrenergic, β -adrenergic, and muscarinic receptors throughout the airway epithelium.²⁰⁴

Submucosal tracheal gland efferent nerve endings consist of cholinergic, adrenergic, and peptidergic axonal profiles.^{205,206} Discrimination among these axonal types is partially aided by their ultrastructural appearance: cholinergic axons have small, agranular vesicles; adrenergic axons have small, dense-cored vesicles; peptidergic axons have many large, dense-cored vesicles. One must realize, however, that these descriptive definitions are not absolutely reliable.

The lung also contains a component of the diffuse neuroendocrine system called the amine uptake and decarboxylation system.^{207,208} Despite the growing recognition that a diffuse neuroendocrine system is located in the lung, we do not understand its normal functional role, although one can postulate that these cells release hormones that affect smooth muscle.^{209,210} This system is composed of single neuroendocrine cells and clusters of such cells, known as neuroepithelial bodies, distributed along the airway epithelium to the region of alveolar ducts.²¹¹⁻²¹⁴ The neuroepithelial bodies are preferentially located at airway bifurcations. Pulmonary neuroendocrine cells are ultrastructurally characterized by dense-cored vesicles in their cytoplasm (Fig. 1-29). The dense-cored vesicles are considered to be the storage sites of amine hormones (serotonin, dopamine, norepinephrine) and peptide hormones (bombesin, calcitonin, leu-enkephalin).²¹⁵ Neurons are also associated with the airway epithelial and neuroendocrine cells; they appear to be the storage sites for vasoactive intestinal peptide^{215,216} and substance P.^{217,218}

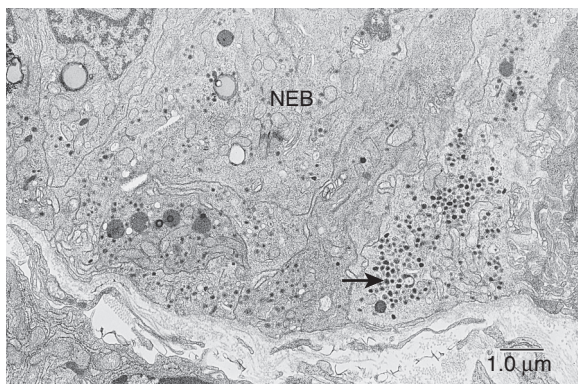


Figure 1-29 Neuroepithelial body (NEB) located in a peripheral airway. Neuroepithelial bodies contain aggregates of neuroendocrine cells. A characteristic ultrastructural feature of neuroendocrine cells is the presence of small (0.1 to 0.3 μm in diameter) dense-cored vesicles in their cytoplasm (arrow). Each dense-cored vesicle is bounded by a unit membrane. (Human lung surgical specimen, transmission electron microscopy.)

THE PLEURAL SPACE AND PLEURAS

As stated at the outset of this chapter, the primary function of the lung is ventilation-perfusion matching, ensuring efficient gas exchange between alveolar air and alveolar capillary blood. This vital function is met, in part, by extensive and rapid movement of the lung within the pleural space and its pleural liquid.^{219,220} Online supplemental digital videos linked to this chapter provide a glimpse of the view that surgeons have during dissection through the intercostal muscles: the lungs glide along the deep surface of the translucent endothoracic fascia and parietal pleura (see Videos 1-1 to 1-5). The pleural space also serves as an outlet into which pulmonary edema liquid can escape.^{221,222} The pleural liquid also serves to couple the lung to the chest wall.²²³ What are the anatomic features of the pleural space and pleuras that contribute to these functions?

An important anatomic fact is that the pleural space is a real space (Fig. 1-30); it is not a potential space.^{2,223} The pleural space surrounds the lung, except at its hilum, where the parietal pleura and visceral pleura are contiguous.^{10,116} Separations are present between the parietal and visceral pleuras along the interlobar fissures and costodiaphragmatic recesses. The normal volume of pleural liquid is 0.1 to 0.2 mL/kg body weight in most mammals.^{223,224} This specific volume is distributed across a pleural surface area of approximately 1000 cm^2 per lung and pleural space width of 10 to 20 μm (see Fig. 1-30).^{2,223} Normally there is little or no contact across the pleural space because the microvilli that extend from the parietal and visceral mesothelial cells are only 3 to 5 μm long.^{1,2,225,226}

Visceral pleural anatomy is characterized by a single layer of mesothelial cells that have microvilli extending from their surface into the pleural space.²²⁵ However, the thickness of the visceral pleura is not uniform across species (Fig. 1-31). Visceral pleural anatomy is characterized as

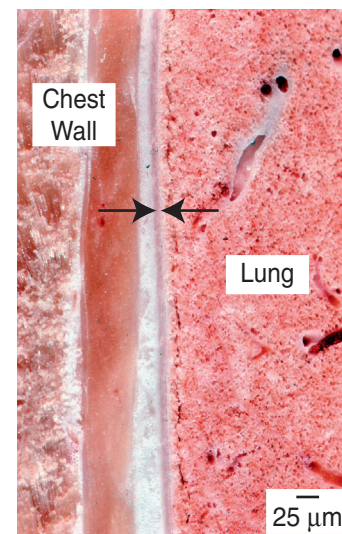


Figure 1-30 The pleural space is a real space. The dark band delimited by the opposed arrows is the pleural space, which is located between the chest wall and lung. (Frozen sheep chest wall and lung, unstained.)

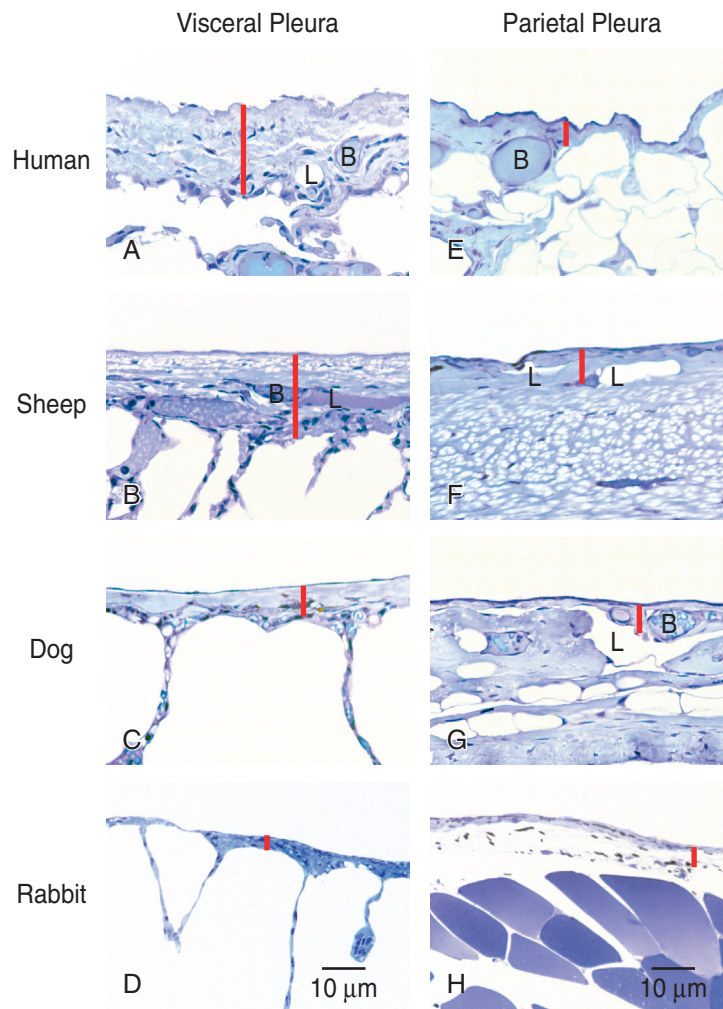


Figure 1-31 Comparative histologic features of the visceral and parietal pleuras among humans, sheep, dogs, and rabbits. The eight panels are shown at the same magnifications. **A–D**, Visceral pleura. **E–H**, Parietal pleura. The most obvious feature of the visceral pleura is its greater thickness (*longer red vertical bars*) in humans and sheep compared to the thinner visceral pleura of dogs and rabbits (*shorter red vertical bars*). The parietal pleura is thinner and consistently so among all the same species. Both the visceral and parietal pleuras are lined by a single layer of mesothelial cells that have microvilli extending from their surface into the pleural space. Subjacent to the mesothelial cell lining layer is loose areolar connective tissue. Among species with “thick” visceral pleura, the loose areolar connective tissue is traversed by bronchial microvessels (B), lymphatics (L), and nerves. By comparison, among species with “thin” visceral pleura, the loose areolar connective tissue is devoid of microvessels, other than the subjacent pulmonary microvessels at the perimeter of the most superficial alveoli. Lymphatics and nerves are infrequent. In the parietal pleura’s loose areolar connective tissue are systemic blood microvessels (B), lymphatics (L), and nerves. This histologic organization is consistent among species. (Human, sheep, dog, and rabbit lung, 2- μ m-thick glycol methacrylate sections, light microscopy.)

“thick” or “thin.”²²⁷ Species with a thick visceral pleura (range is 25 to 100 μ m) are humans, sheep, cows, pigs, and horses.²²⁵ Species with a thin visceral pleura (range 5 to 20 μ m) are dogs, rabbits, rats, and mice.²²⁸ The variability in thickness is related to the connective tissue layer beneath the visceral pleural mesothelial cells. The other anatomic difference among species with thick or thin visceral pleura is their arterial blood supply. Species with a thick visceral pleura has an arterial blood supply from the systemic circulation, via bronchial arteries (see Fig. 1-27).^{45,183,225,227} By comparison, species with a thin visceral pleura has an arterial blood supply from the pulmonary circulation. The reason for this striking difference in visceral pleural anatomy among mammals is not known.

Parietal pleural anatomy is also characterized by a single lining layer of mesothelial cells with microvilli extending

from their surface.²²⁶ The thin subjacent loose areolar connective tissue layer contains systemic blood vessels, lymphatics, and nerves. Unlike the situation with the visceral pleura, this thin histologic organization of the parietal pleura is consistent among species, including humans (see Fig. 1-31).^{10,116,226,229,230}

The unique anatomic features of the parietal pleura are the lymphatic stomata.^{226,230-233} They are openings (\approx 1 to 3 μ m in diameter) between parietal mesothelial cells (Fig. 1-32). Tracer studies revealed that India ink and chicken red blood cells (which are nucleated and therefore easily identifiable) are cleared almost exclusively from the pleural space by the stomata, which are located over the intercostal spaces in the distal half of the thorax, and along the sternum and pericardium of experimental animals that have been studied.^{226,229} The openings are continuous with

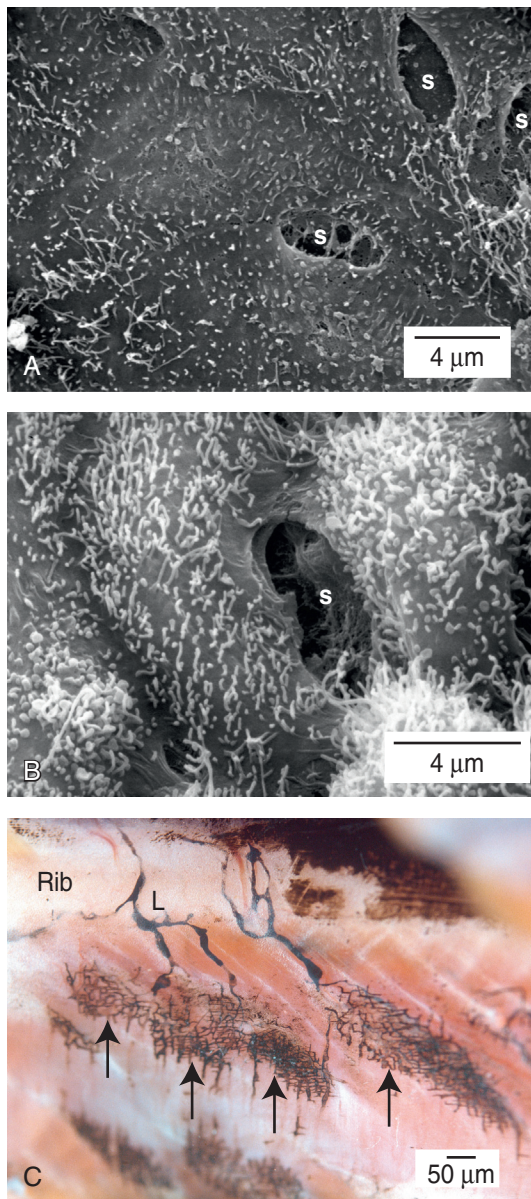


Figure 1-32 Surface view of lymphatic stomata, initial lymphatics, and collecting lymphatics of the parietal pleura. **A** and **B** are scanning electron micrographs that show the unique structure of lymphatic stomata (S). Stomata are apertures between the pleural space and the initial lymphatics in the parietal pleura. Three stomata are visible in a low-magnification field of view in **A**. Stomata are located over intercostal muscles. **B** shows a different stoma at a higher magnification. Microvilli are not present at the aperture of stomata, which are lined by mesothelial cells. **C** shows a portion of the parietal pleura where colloidal carbon is seen in four beds of initial lymphatics (arrows) that are located over an intercostal space. Colloidal carbon is also in collecting lymphatics (L) that cross a rib, where the collecting lymphatics drain into lymphatic vessels that accompany the intercostal vessels. (Rabbit, macroscopic view of the parietal pleura after colloidal carbon was placed in the pleural space in situ.)

the lumen of lymphatic capillaries. Physiologic studies showed that protein and particulate matter in the pleural space are cleared almost exclusively by the parietal pleural system of stomata and lymphatics.^{231,234} The lymphatics convey the pleural liquid to regional lymph nodes along the sternum and vertebral column; from there, lymph is carried

to the thoracic duct and right lymphatic duct. In this regard, normal pleural liquid is cleared by mechanisms that are consistent with normal interstitial liquid turnover in tissues throughout the body.

COMPARISON OF THE LUNG OF MICE AND HUMANS

A point made in the previous section is that species variations are significant in visceral pleural structure and blood supply. This point raises a question of what other species variations are found in the lung. For the purpose of this chapter, comparison is made between mouse and human, owing to the fantastic discoveries about genetic and molecular regulation of lung biology by making mouse constructs to identify normal lung structure and function, as well as to study the impact of disease on lung structure and function. Key structural features of mouse and human pulmonary morphology are summarized in [Table 1-3](#).²³⁵⁻²³⁷ This table reveals that many anatomic and developmental differences are present that may be helpful to keep in mind.

In the mouse lung, in contrast to the human, the walls of intrapulmonary conducting airways do not have cartilage, which may affect the distribution of airway resistance compared to the human lung ([Fig. 1-33](#)). In addition, in the mouse lung, respiratory bronchioles are essentially absent, whereas the human lung has approximately 150,000 respiratory bronchioles (see [Fig. 1-33](#)). Thus the mouse lung has fewer airway generations and a significantly smaller total surface area for gas exchange than the human lung. Another potential impact of the fewer airway generations, as well as narrower conducting airways, is that the deposition of inhaled particulates may have a different distribution in the lungs of mice compared to those of humans. Also, because the mouse lung has fewer airway generations, the parenchyma makes up a larger proportion of total lung volume in mice ($\approx 18\%$) compared to humans ($\approx 12\%$).

Another notable species difference is the distribution of various cell types. In the upper airway of the human lung, the principal secretory cells are goblet cells (see [Fig. 1-13](#)), whereas in the upper airway of the mouse lung, the principal secretory epithelial cells are the club cells (Clara). Club cells in the human lung are found in the terminal airways (see [Fig. 1-15](#)). In addition, in the upper airway of the human lung, additional secretory cells are mucous and serous epithelial cells in submucosal glands (see [Figs. 1-14 and 1-33](#)), which are not found in the upper airway of the mouse lung (see [Fig. 1-33](#)). Thus different cell types contribute to airway secretions in the two species.

Lastly, the lung's developmental stage at full term is different between mice and humans. In mice, lung development at full term is at the saccular stage. In humans, lung development at full term is at the beginning of the alveolar stage. This timing difference is helpful to keep in mind when developmental comparisons are made (see also Chapter 2).

In general, those who use animal models should recognize that, even in the normal setting, important differences in the structure, cellular composition, and development may affect the applicability of findings to the human lung.

Table 1-3 Comparative Anatomy of Mouse and Human Lungs

Anatomic Feature of the Lung	Mouse	Human
Visceral pleura thickness	5-20 μm	25-100 μm
Visceral pleura arterial supply	Pulmonary	Systemic (bronchial)
Lobes	4 right; 1 left	3 right; 2 left
Airway generations	13-17	17-21
Airway branching pattern	Single	Dichotomous
Main bronchus diameter	$\approx 1\text{ mm}$	$\approx 10\text{-}15\text{ mm}$
Intrapulmonary airway cartilage	No	Yes
Tracheal epithelium thickness	11-14 μm	50-100 μm
Tracheal club cells (Clara)	$\approx 50\%$	None
Tracheal goblet cells	Absent	Present
Tracheal submucosal glands	Absent	Present
Proximal intrapulmonary airway thickness	8-17 μm	40-50 μm
Proximal intrapulmonary airway club cells	$\approx 60\%$	None
Proximal intrapulmonary airway goblet cells	Absent	Present
Proximal intrapulmonary airway submucosal glands	Absent	Present
Terminal bronchiole diameter	$\approx 10\text{ }\mu\text{m}$	$\approx 600\text{ }\mu\text{m}$
Terminal bronchiole thickness	$\approx 8\text{ }\mu\text{m}$	Not determined
Terminal bronchiole club cells	$\approx 70\%$	None
Respiratory bronchioles	Absent (or one)	Present ($\approx 150,000$)
Lung parenchyma-total lung volume ratio	$\approx 18\%$	$\approx 12\%$
Alveolar diameter	30-80 μm	100-200 μm
Air-blood barrier thickness	$\approx 0.32\text{ }\mu\text{m}$	$\approx 0.68\text{ }\mu\text{m}$
Pulmonary venule location	Next to bronchioles	Along interlobular septa
Developmental stage at full term	Saccular	Alveolar

Adapted from [references 235–237](#).

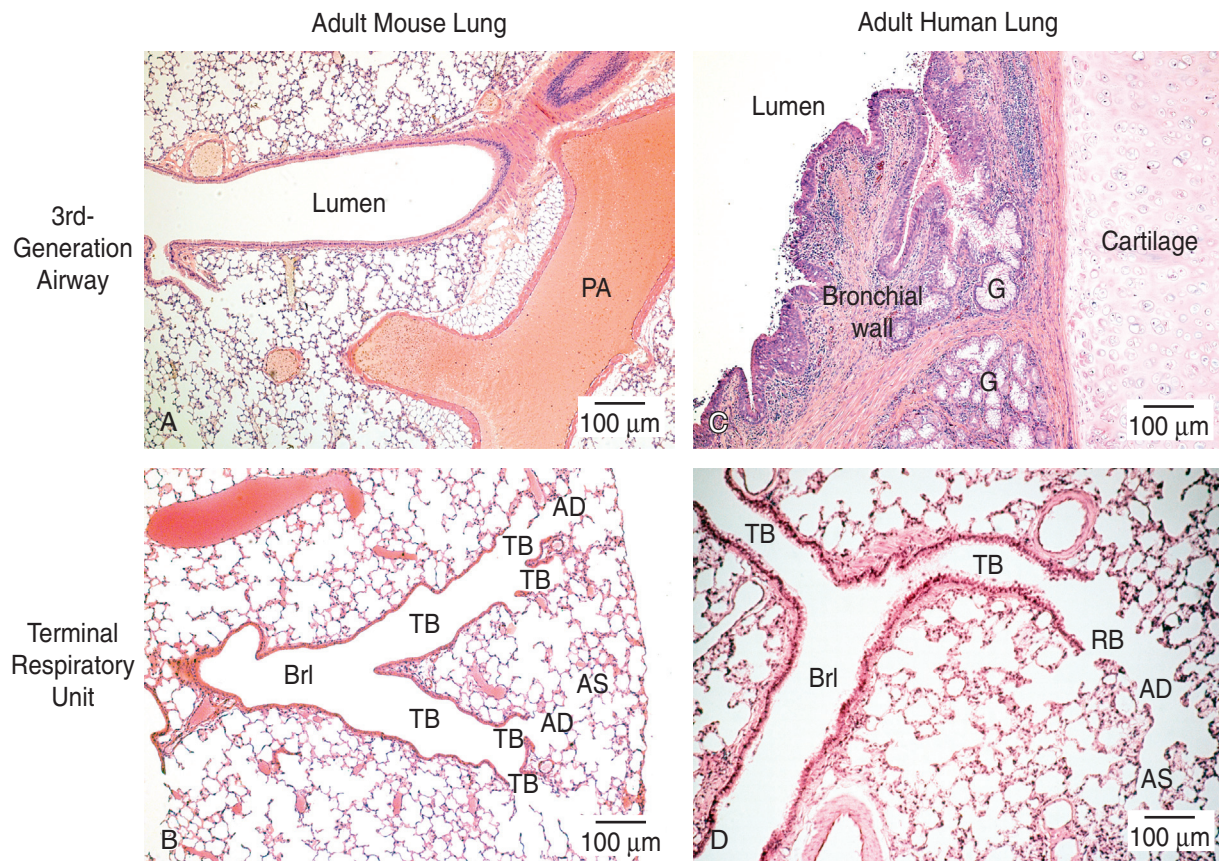


Figure 1-33 Comparison of lung morphologic features between adult mice (left column) and humans (right column). The four panels are the same magnification, as shown by the scale bar in each panel. The upper row compares 3rd-generation, intrapulmonary airways between mouse (A) and human (C). The mouse's airway lumen is narrower than the same-generation airway (bronchus) in the human. Absent from the wall of the mouse's airway wall are cartilage and submucosal glands (G), both of which are obvious in the wall of the bronchus of the human airway. The lower row compares terminal respiratory units between mouse (B) and human (D). The mouse's terminal respiratory units do not have respiratory bronchioles; therefore terminal bronchioles (TB) open directly into alveolar ducts (AD). By comparison, the human's terminal respiratory units have respiratory bronchioles (RB), which open into alveolar ducts (AD) and air space (AS). Brl, bronchiole; PA, pulmonary artery. (Mouse and human lung tissue, 5- μm -thick paraffin-embedded sections, light microscopy.)

Key Points

- The primary function of the lung is ventilation-perfusion matching for efficient gas exchange between alveolar air and alveolar capillary blood.
- The anatomic arrangements of the pulmonary arteries beside the airways are a reminder of the relationship between perfusion and ventilation that determines the efficiency of normal lung function.
- The major physical problem of gas exchange is the slowness of oxygen diffusion through water. Thus the alveolar walls must be extremely thin. Because of that thinness, the thickness of the red blood cell forms a substantial portion of the air-blood diffusion pathway.
- The airways form the connection between the outside world and the terminal respiratory units; therefore the airways are of central importance to our understanding of lung function in health and disease.
- The terminal respiratory unit consists of all the alveolar ducts, together with their accompanying alveoli, that stem from the most proximal (first) respiratory bronchiole, and contains approximately 100 alveolar ducts and 2000 alveoli. The functional definition of the terminal respiratory unit is that, because gas-phase diffusion is so rapid, the partial pressures of oxygen and carbon dioxide are uniform throughout the unit.
- Smooth muscle cells form circular bands around the airway epithelium as far peripherally as the respiratory bronchioles. Tone in the smooth muscle is altered by the autonomic nervous system and by mediators released from mast cells, inflammatory cells, and neuroendocrine cells.
- Because smooth muscle is in the pulmonary vessels on both the arterial and the venous side down to precapillary and postcapillary vessels, any segment can contribute to active vasomotion and therefore pulmonary vascular resistance.
- Normally, capillary blood volume is equal to or greater than stroke volume. Thus, under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity. Recruitment can increase capillary blood volume threefold.
- The endothelial cells of the pulmonary circulation manifest a remarkable number of metabolic activities.
- The type II cell is the major synthesizing and secreting factory of the alveolar epithelium and implements epithelial repair via its ability to proliferate.
- The clearance of particulate matter impinging on the alveolar surfaces is dependent on the slow turnover and movement of the alveolar surface liquid, as well as on the phagocytic function of the macrophages and the clearance function of the pulmonary lymphatics.

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Complete reference list available at *ExpertConsult*.

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LUNG GROWTH AND DEVELOPMENT

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INTRODUCTION

Multicellular life requires the use of oxygen for the generation of high-energy compounds (e.g., adenosine triphosphate) to sustain the metabolic activities of complex organisms. Because multicellular organisms depend on oxygen, they have evolved systems for its efficient acquisition and distribution. A benchmark in the adaptation of vertebrates living on land was the development of a gas exchange system that provided a sufficient amount of oxygen to meet the metabolic requirements of cellular respiration. As organisms increased in size, the surface area required for adequate gas exchange became significantly larger; for example, the surface area of the adult human lung epithelium has been estimated to be 70 m².¹ The problem of generating such a large surface area in a confined space has been solved in the basic structure of the lung, where branched epithelial tubules conduct air to millions of alveoli that lie closely apposed to the lung microvasculature. The epithelium lining the surface of the lung is continuously exposed to biologic and chemical hazards from the environment, which has also necessitated the development of an innate defense system in the lung. Early embryologic experiments established that lung morphogenesis is critically dependent on reciprocal interactions between the lung endoderm and its surrounding splanchnic mesoderm, which supplies progenitors of endothelial cells, smooth muscle cells, mesothelial cells, and fibroblasts. As we will discuss, these interactions are complex and highly regulated in time and space. Disruptions in the lung developmental program, be it for genetic or epigenetic reasons, can lead to compromised structure and function. A better understanding of the molecular mechanisms controlling lung development will optimize therapeutic strategies to treat the diseased or malformed lung. Several additional recent reviews are also available.²⁻⁶

STAGES OF LUNG DEVELOPMENT

Lung development has traditionally been divided into five stages that are primarily based on histologic appearance (Fig. 2-1). After lung bud formation the basic branching pattern of the pulmonary tree and an associated vascular plexus is established during the **embryonic** and **pseudo-**

glandular stages. The epithelial branching program, which is under genetic control, is stereotyped and uses three geometrically distinct local modes of branching that proceed in three different sequences.⁷ Human lung development begins with the emergence of the laryngotracheal groove from the floor of the foregut endoderm during the fourth week of gestation. A few days later the caudal end of the primordium enlarges and bifurcates, giving rise to the left and right bronchial buds (see Fig. 2-1A). These buds elongate caudally during the fifth week of gestation, when a second round of branching takes place, resulting in three secondary buds in the right lung and two in the left. These buds will become the primary lobes of the left and right lung. A third round of branching gives rise to bronchial tubules that will become the bronchopulmonary segments in the mature lung. Concurrent with these events in the distal region, the cranial portion of the primordium gives rise to the trachea and larynx, which separate from the esophagus by the end of this stage. The lung epithelium at this stage is tall columnar and shows no morphologic evidence of differentiation. At the molecular level, however, some aspects of epithelial differentiation have already begun; for example, the most distal epithelial cells express messenger RNA for the lung-specific marker *surfactant protein (SP) C*.⁸ The lung mesenchyme, which is derived from splanchnic mesoderm, is loosely organized at the beginning of this stage and appears to lack vascular structures. In situ hybridization studies probing for the *vascular endothelial growth factor (VEGF)* receptor FLK1 have demonstrated, however, that vascular precursors are closely apposed to the distal epithelium at the time of bud induction.⁹ These cells form a vascular plexus (see Fig. 2-1B) by a process termed “vasculogenesis,” wherein vessels are formed de novo by the organization of vascular precursors. By the end of the embryonic stage, pulmonary arteries and veins connect this plexus to the atria; the pulmonary arteries and veins grow into the lung by angiogenesis, with new branches arising from preexisting vessels.

Dichotomous and lateral branching of the lung epithelium continues during the **pseudoglandular** stage, which lasts from week 5 to week 17 of gestation. This results in the final pattern of the pulmonary tree, which comprises 22 to 23 generations of bronchial tubules. Terminal bronchioles branch distally to give rise to the acinar tubules and buds that will eventually form pulmonary acini in the adult

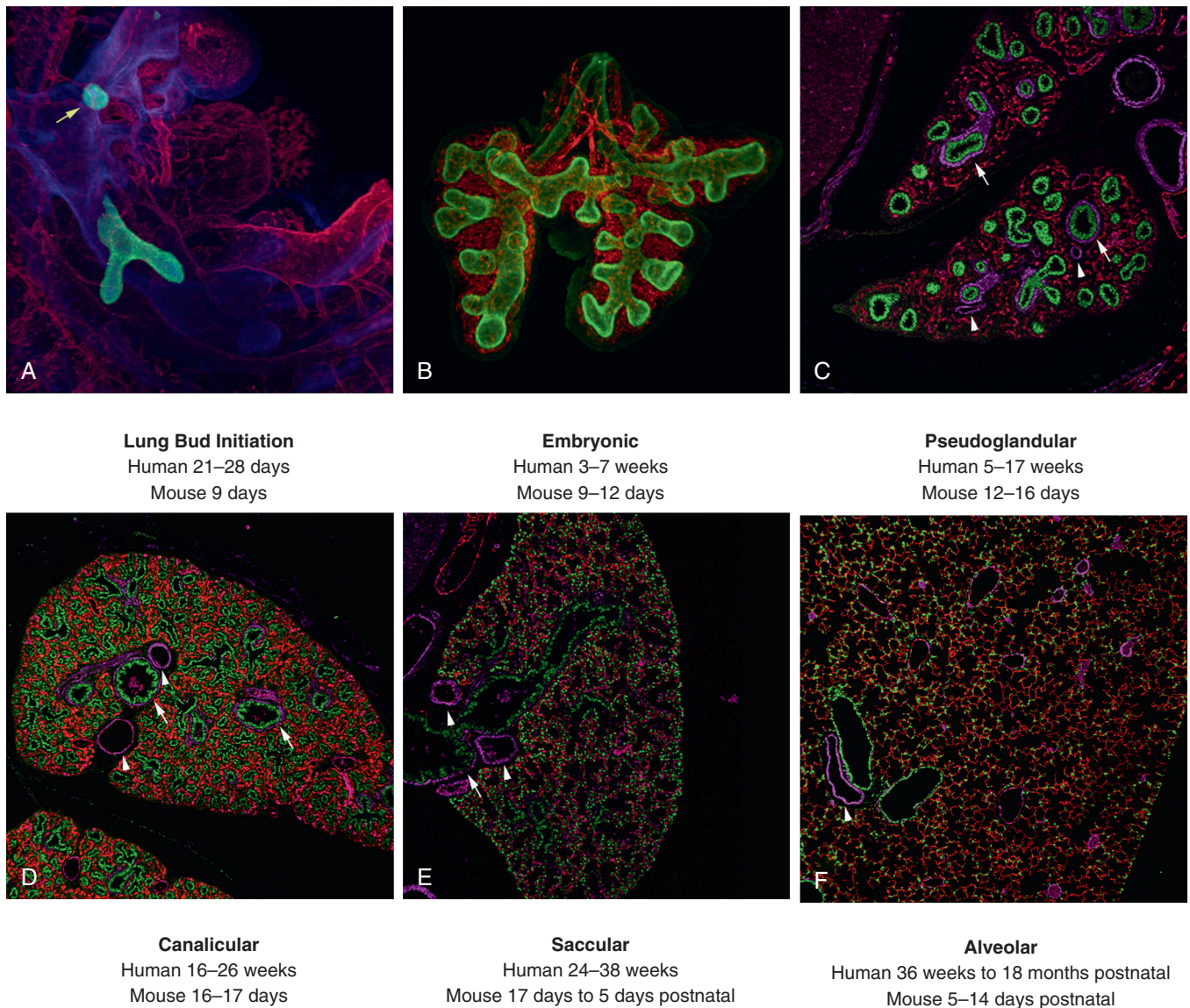


Figure 2-1 Morphology of the stages of lung development. Mouse lungs from the indicated developmental stages were stained with an antibody against Nkx2-1 to identify epithelial cells in the respiratory lineage (*green*), an antibody against endomucin to identify vascular cells (*red*), and an antibody against α -smooth muscle actin to identify smooth muscle cells (*magenta*). An antibody against E-cadherin identifies the foregut endodermal epithelium (*blue*) (**A**). All images of sectioned lungs (**C–F**) are at the same magnification. **A**, Lung buds originate as a pair of outpocketings from the ventral foregut endoderm on day E9.5 in the mouse; the lung endoderm stains positive for Nkx2-1, as does the primitive thyroid rudiment (*yellow arrow*). **B**, During the embryonic stage, dichotomous and lateral branching of the lung epithelium continues. Vascular precursors are already present and form a plexus surrounding the epithelium. **C**, During the pseudoglandular stage, the lung primarily consists of epithelial tubules surrounded by a relatively thick mesenchyme. Proximal epithelial cells show tall columnar morphologic characteristics, whereas more distal epithelial cells are cuboidal. The vasculature branches in parallel with the epithelium, and smooth muscle cells surrounding airways (*white arrows in all panels*) and vessels (*white arrowheads in all panels*) are evident. **D**, During the canicular stage, epithelial acini appear, and the vasculature becomes more abundant and closely apposed to the epithelium. **E**, During the saccular stage, type I cell differentiation increases air space size. The vasculature has continued to expand, fully investing the lung parenchyma. Fusion of the epithelial and endothelial basal laminae brings capillaries and type I epithelial cells into close association. **F**, During the alveolar stage, the formation, lengthening, and thinning of secondary septa markedly increase the epithelial surface area. The capillaries, which until now have existed as a double septal network, have fused into one. (Confocal images generated by Jamie Havrilak, Graduate Program in Molecular and Developmental Biology, Cincinnati Children's Hospital Medical Center.)

(see Fig. 2-1C). Morphologic differences in the epithelium are apparent. The proximal epithelium is initially populated by relatively undifferentiated columnar, glycogen-rich cells, but ciliated, nonciliated, goblet, mucous, basal, and neuroendocrine cells are identifiable by the end of this stage. The distal epithelium is populated by distal epithelial

cells, the precursors of alveolar type II cells, which are cuboidal columnar and contain copious amounts of glycogen. Smooth muscle cells differentiate in the mesenchyme and surround the epithelium perpendicular to the long axis of the tubules; this proceeds in a proximal-to-distal manner. The pulmonary vasculature branches in parallel with the

airway epithelium (see Fig. 2-1C), and pulmonary lymphatics initiate as buds from the veins.¹⁰

Patterning of the pulmonary tree is completed at the beginning of the **canalicular** stage (16 weeks to 26 weeks; see Fig. 2-1D), and the cells constituting the proximal epithelium continue to differentiate as ciliated, nonciliated, and secretory cells. Among the latter are club cells (Clara), identifiable by the presence of the cell-specific *club cell secretory protein* (Clara) (CCSP). Acinar tubules and buds, which are lined by cuboidal epithelial cells, expand and differentiate to form pulmonary acini consisting of respiratory bronchioles, alveolar ducts, and alveoli. Nascent type II cells containing increasing amounts of surfactant-associated proteins and phospholipids become prominent in the distal epithelium. Differentiation of squamous type I cells from type II cells begins. A dramatic expansion of the pulmonary capillary bed (vascular canals) in the lung parenchyma gives this stage its name (see Fig. 2-1D). These vessels surround the developing acini and come in direct contact with the epithelium, giving rise to the primordial air-blood barrier.

During the **saccular** stage, which persists from week 24 until term, the terminal acinar tubules in the lung periphery continue to branch and air space size increases. Alveolar type II cells undergo significant maturation, as evidenced by increased synthesis of SP-A, SP-B, SP-C,¹¹ and SP-D¹² and of surfactant phospholipids.¹³ Glycogen stores, which serve as a substrate for phospholipid synthesis,¹⁴ decrease, while the number of lamellar bodies increases. Squamous type I cells continue to differentiate and constitute an increased proportion of the distal lung surface, thereby increasing the effective area for gas exchange (see Fig. 2-1E). Septal walls consist of a central connective tissue core with a capillary network on each side. Subsequent fusion of the basal laminae of the distal epithelium and endothelium brings capillaries into close association with type I cells, which decreases the diffusion distance between air spaces and capillaries to allow more efficient gas exchange (see Fig. 2-1E).

The transition from the canalicular to saccular stage of lung development marks the threshold of viability for preterm infants who have access to neonatal intensive care support.^{15,16} Before 22 weeks' gestation there is insufficient surface area in the distal pulmonary tree to support safe, reliable oxygenation and ventilation, even when surfactant replacement therapy and sophisticated mechanical ventilation techniques are available. Survival at 23 weeks' gestation ranges from 15% to 30%. Mortality decreases with each additional week of gestation; by 25 weeks, survival exceeds 60%, although significant morbidity in the form of *bronchopulmonary dysplasia* (BPD) and neurodevelopmental compromise persists.¹⁷

As the threshold of viability is crossed, *respiratory distress syndrome* (RDS) becomes the primary source of morbidity and mortality for the preterm infant. RDS is a consequence of deficient surfactant production, leading to terminal airway atelectasis and epithelial injury. The subsequent capillary leak produces the hyaline membranes that are classically associated with this disease. Surfactant replacement therapy has dramatically improved RDS survival rates and reduced morbidity. Term infants affected by RDS

often have comorbid conditions such as maternal diabetes, which delay maturation of the surfactant production system.

Genetic mutations leading to SP-B deficiency result in a clinical presentation indistinguishable from the early stages of RDS. Affected infants, however, are typically full term and have only a transient response to surfactant replacement therapy, which leads to early neonatal death or the development of severe neonatal chronic lung disease. The only definitive treatment is lung transplantation. Lethal respiratory failure in a mouse model of SP-B deficiency can be reversed with targeted expression of an SP-B transgene, demonstrating the potential for gene therapy.¹⁸ Mutations of SPC produce a spectrum of pulmonary disorders during infancy, including interstitial pulmonary fibrosis.¹⁹ As with SP-B deficiency, surfactant replacement therapy has little or no benefit, with lung transplantation as the only documented potential cure. Other genetic defects of the surfactant production system also lead to fatal surfactant deficiency in the neonate. Infants deficient in ABCA3, which transports surfactant phospholipids to lamellar bodies, have normal SP-B expression but develop unexplained lethal respiratory failure and death within 1 month of birth.²⁰

The final stage of lung development is the **alveolar** stage, which lasts from week 36 of gestation through the first 18 months of postnatal life. As the name implies, true alveoli are generated from terminal saccules during this stage. Interstitial tissue in primary septa is reduced, while secondary septa markedly lengthen and thin (see Fig. 2-1F). Concomitant with these changes is the fusion of the double septal capillary network into one (see Fig. 2-1F). This remodeling requires an initial burst of interstitial fibroblast proliferation, which subsequently slows down, and the cells synthesize increased amounts of collagen and elastin. Septation results in a marked increase in the number of alveoli from approximately 30 million at term to 300 million in the adult. Increased numbers of type II and type I cells accompany alveolar expansion, with type I cells now covering 95% of the alveolar surface area.²¹

BPD, which is typically restricted to infants born before 32 weeks' gestation, represents a particularly challenging complication.^{21a} The condition is only associated with preterm birth and is defined by a characteristic appearance on chest radiograph and persistent requirement for supplemental oxygen beyond 36 weeks after conception.²² In the era of surfactant replacement therapy, BPD is distinguished by alveolar simplification due to the apparent arrest of the alveolarization during the third trimester.²³ Compromised oxygenation and ventilation may worsen as infant somatic growth progresses and attendant metabolic demands outstrip pulmonary function. Respiratory morbidity is not restricted to infants born before 32 weeks' gestation. Late-preterm infants born between 32 and 37 weeks' gestation are more likely than term infants to require respiratory support, including positive-pressure ventilation, after birth.²⁴ Given the dramatic increase in alveolar number during the late third trimester, it follows that late-preterm infants may have a smaller margin of safety when making the transition to extrauterine life.

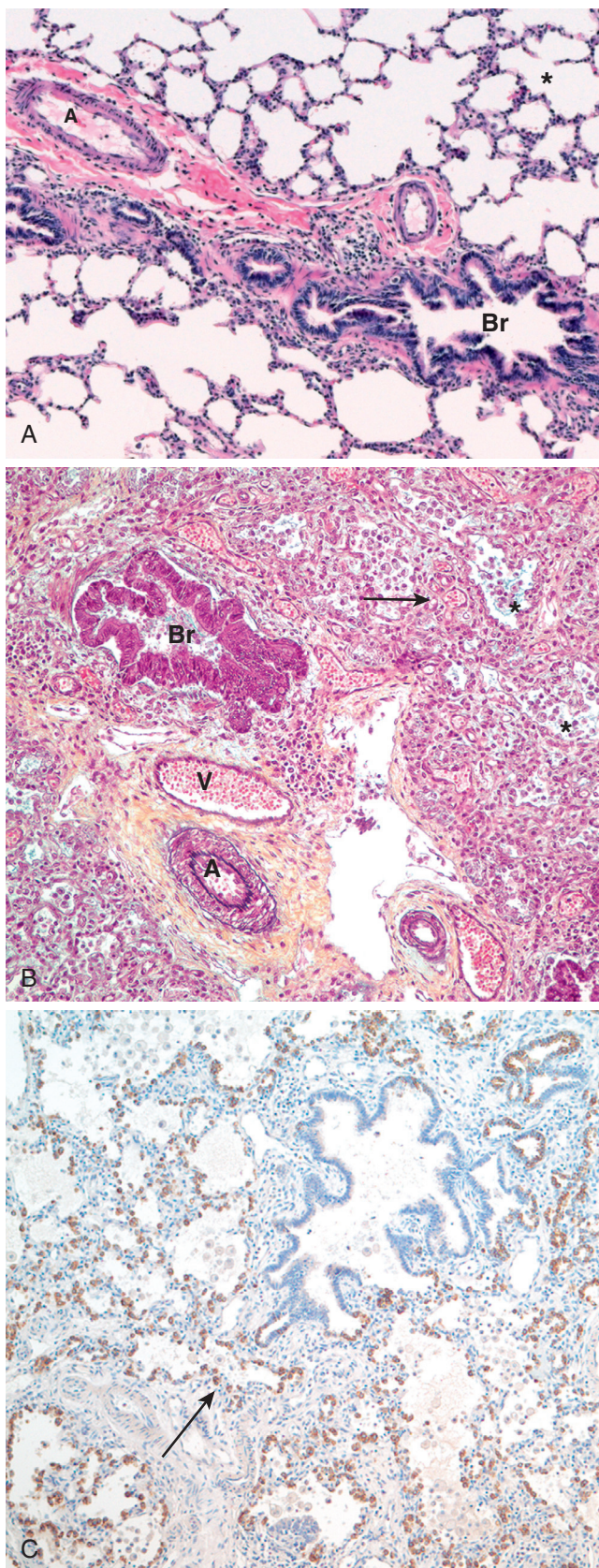


Figure 2-2 Histopathologic features of human alveolar capillary dysplasia and extralobar pulmonary sequestration. **A**, Section of normal infant lung stained with hematoxylin and eosin demonstrates a typical bronchovascular bundle incorporating a small bronchus (Br) and artery (A), without an accompanying vein. A typical alveolar network with abundant air spaces (asterisk) is present. **B**, Pentachrome-stained section from a full-term newborn with alveolar capillary dysplasia. There is abundant mesenchyme separating rudimentary, dysplastic terminal air spaces (asterisk). Alveolar capillaries (arrow) are sparse in number and distended. There is misalignment of the pulmonary vasculature. A pulmonary artery (A) and prominent muscularis and bronchus (Br) are accompanied by an anomalous pulmonary vein (V). The paucity of alveolar capillary structures accounts for the profound pulmonary hypertension in these patients. (x10 original magnification.) **C**, Immunohistochemistry of extralobar pulmonary sequestration from a full-term neonate demonstrates expression of pro-surfactant protein C in the epithelium (brown-staining cells). The sequestration has the histologic appearance of primitive lung at the canalicular stage of development with an abundance of mesenchyme separating nascent air space structures (arrow). (Micrographs courtesy of Dr. Susan Wert, Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, and Dr. Gail Deutsch, Division of Pathology, Seattle Children's Hospital.)

TISSUE INTERACTIONS AND LUNG DEVELOPMENT

A basic tenet of lung development is that it requires inductive interactions between the endodermal epithelium and the mesodermal mesenchyme. Reciprocal inductive interactions involve one cell type signaling to another cell type and then responding to signals sent back; both cell types are thus signaling and responding to each other. This is particularly evident in the embryonic and pseudoglandular stages, where it has been shown conclusively that lung epithelium must be associated with lung mesenchyme in order to survive²⁵ and branch.²⁶ The factors that drive branching morphogenesis are diffusible, because embryonic lung epithelium branches when separated from lung mesenchyme by a filter that prevents direct cell-cell contact but allows diffusion of soluble factors.²⁷ Importantly, these experiments also showed that survival of lung mesenchyme is dependent on the presence of lung epithelium, underscoring that induction is reciprocal. The fate of the entire respiratory endoderm, from the trachea to the bud tips, however, is not fully committed during the embryonic stage. Reciprocal recombination experiments have shown that distal lung mesoderm can reprogram tracheal endoderm to branch and differentiate like lung,^{28,29} and that tracheal mesoderm can reprogram lung endoderm to differentiate like trachea.^{30,31}

Bronchopulmonary sequestration may represent an intriguing manifestation of aberrant pulmonary endoderm-mesoderm interaction. These masses of abnormal lung tissue, which may be contained within the lung or in an extrapulmonary location within the abdomen, may be in direct communication with gastrointestinal tract structures, suggesting ectopic induction of embryonic foregut. The histopathologic appearance of these lesions includes typical cellular components of pulmonary parenchyma along with inflammatory and fibrotic components (Fig. 2-2C).³²

Normal lung function requires the precise alignment of the distal epithelium and the vasculature to meet the

respiratory requirements of the developing organism. Certain lethal congenital malformations of the lung, such as *alveolar capillary dysplasia with misalignment of pulmonary veins* (ACD/MPV), are due to a perturbation in the relationship between vascular and airway development. ACD/MPV is characterized by a paucity of alveolar capillaries, thickened pulmonary mesenchyme, and misalignment of the pulmonary veins, which reflect the reciprocal relationship required for airway and vascular development (see Fig. 2-2B). ACD/MPV is associated with mutations in the transcription factor *FOXF1*, which is expressed in the lung mesenchyme.³³ The alveolar simplification of BPD is also accompanied by a relative paucity of alveolar capillaries that is reminiscent of ACD/MPV. Evidence that *vascular endothelial growth factor A* (VEGF-A), which is produced by lung epithelial cells, can reverse the alveolar defect further reinforces the concept of interdependent development of vascular and airway structures.³⁴

MOLECULAR REGULATION OF LUNG DEVELOPMENT

Elucidation of the factors that regulate lung growth and development has been the focus of an intense research effort.^{34a} This stems not only from a desire to understand the basis of pulmonary pathologic conditions present at birth, but also from the possibility that understanding how the lung develops will provide insight into how the lung repairs itself following injury or disease. Given the morphogenetic precision required to generate a lung that can function effectively in gas exchange, coupled with the fact that the lung contains over 40 differentiated cell types,¹ it is not surprising that the molecular regulation of lung development is proving to be very complex. Identifying the factors involved provides only part of the story. When, where, how much of, and for how long these factors are expressed must also be considered. The fact that there is crosstalk between some of the identified pathways significantly increases the level of complexity.

DIFFUSIBLE MEDIATORS OF LUNG DEVELOPMENT

Fibroblast Growth Factors and Fibroblast Growth Factor Receptors

In both humans and mice, the *fibroblast growth factor* (FGF) family comprises 22 structurally related molecules³⁵; among these, FGF1, 2, 7, 9, 10, and 18 have been localized to the developing lung. FGFs bind and signal through high-affinity, ligand-dependent transmembrane receptors (*fibroblast growth factor receptors* [FGFRs]) that contain an intracellular tyrosine kinase domain. There are four FGFRs, all of which are expressed in the lung. Alternative messenger RNA splicing results in two isoforms each for FGFR1, FGFR2, and FGFR3 that have distinct ligand specificities.³⁶ FGFR activation is modulated by heparin or heparan sulfate.³⁷

FGF1 and *FGF2* are not critical for lung development, because the single deletion of either gene or the double

ablation of both has no effect on lung development. FGF10 is an ideal candidate for mediating tissue interactions in the lung, because it is expressed in the mesenchyme, whereas its primary receptor, FGFR2b, is expressed by epithelial cells. Ablation of either *FGF10*³⁸ or *FGFR2b*³⁹ results in complete pulmonary agenesis caudal to the trachea. The basis for this phenotype comes from the ability of FGF10 to induce lung epithelial budding by chemoattraction^{40,41}; in the absence of FGF10, primary buds cannot form. FGF10 affects the expression of many target genes in early lung epithelium,⁴² including other important signaling molecules such as *bone morphogenetic protein 4* (BMP4)⁴⁰ and Notch family members.⁴³

Like FGF10, FGF9 acts as a mediator of reciprocal tissue interactions, because it is expressed in the epithelium and mesothelium, whereas its receptor (FGFR2c) is found in the mesenchyme. FGF9 controls lung mesenchyme size by regulating cell proliferation.⁴⁴ The observation that the amount of available mesenchyme appears to control lung branching²⁵ is consistent with the finding that the lungs of *Fgf9*-null mice are severely hypoplastic, with decreased amounts of mesenchyme and reduced *Fgf10* expression.⁴⁵ The observation that *Fgf18*-null mice exhibit reduced alveolar size resulting from reduced cell proliferation during the saccular stage⁴⁶ suggests a role for FGF18 in late lung development. FGF7 has been shown to stimulate lung epithelial cell proliferation,⁴⁷ as well as surfactant protein gene expression and surfactant phospholipid synthesis in type II cells.^{48,49} Transgenic overexpression of *Fgf7* in the developing mouse lung epithelium results in lesions resembling congenital cystic adenomatoid malformations⁵⁰; examination of human congenital cystic adenomatoid malformations, however, shows that FGF7 expression is actually decreased and FGF10 expression is unchanged.⁵¹ Although intraperitoneal injection of neutralizing antibodies against *Fgf7* inhibits postnatal lung growth and alveolus formation,⁵² mice with a targeted deletion of *Fgf7* have no apparent lung phenotype.⁵³ Other FGFs are also required during alveologenesis, because mice with deletions of both *Fgfr3* and *Fgfr4* fail to form normal alveoli.⁵⁴

The Sprouty (SPRY) proteins, which antagonize FGFR signaling, modulate the effects of FGFs in the developing lung. Although single deletion of either *Spry2* or *Spry4* has no effect on lung development, mice null for both genes have defects in multiple organs, including the lung.⁵⁵

Retinoic Acid

Retinoic acid (RA), the active derivative of vitamin A, is essential for the normal development of many tissues, including the lung. Maternal vitamin A deficiency results in severe respiratory phenotypes in offspring, including tracheoesophageal fistula, lung hypoplasia, and lung agenesis.⁵⁶ RA signals through RAR and RXR nuclear receptors, both of which have α , β , and γ isoforms, and these are expressed in the lung from the outset of development. Mice with double deletions of *Rara/Rarb* or *Rara/Rarb* show the same lung abnormalities as those seen in vitamin A-deficient embryos.⁵⁷ The mechanism by which RA controls lung morphogenesis is not fully resolved. Data from cultured early embryonic foreguts suggest that RA allows activation of *Wingless* (Wnt) signaling by inhibiting *Dickkopf1* (DKK1); this affects FGF10 expression in the mesoderm, as

well as maintenance of lung progenitor cell fate.⁵⁸ RA further affects lung bud induction by inhibiting *transforming growth factor-β* (TGF-β) activity in the prospective lung field, which in turn allows expression of FGF10.⁵⁹

RA also enhances perinatal alveolus formation in rodents,⁶⁰ which has led to its clinical use for the prevention of BPD.⁶¹ The effect is modest but significant; about 15 infants must be treated to prevent one case of BPD.⁶² The mechanism is not understood in detail but is likely related to maintenance of alveolarization after preterm delivery, reducing the potential for alveolar simplification.

Sonic Hedgehog

The hedgehog signaling pathway plays an important role in the development of multiple organs.⁶³ *Sonic hedgehog* (SHH) is highly expressed in the developing lung epithelium,⁶⁴ and its primary receptor, *patched 1* (PTCH1), is found in mesenchymal cells,⁶⁵ suggesting that SHH is part of an epithelial-mesenchymal inductive loop. Shh is initially expressed throughout the epithelium but becomes restricted to subsets of cells from day E16.5 onward.⁶⁶ *Shh*-null mice form lungs, indicating that Shh is not required for lung specification and bud induction; however, these lungs are severely hypoplastic,⁶⁷ suggesting that Shh is involved in regulating branching morphogenesis. *Shh* deletion profoundly affects lung growth and patterning, but the specification of epithelial cell types appears to be unaffected.⁶⁸ Because Shh serves as a survival factor for lung mesenchymal cells,⁶⁹ the lung hypoplasia seen in *Shh*-null embryos may be due to a decrease in mesenchymal mass. Shh is also a negative regulator of Fgf10, and *Shh*-null embryos exhibit expanded Fgf10 expression.⁶⁸ A clinical syndrome with a respiratory phenotype that is consistent with disruption of SHH signaling is Smith-Lemli-Opitz.⁷⁰ Smith-Lemli-Opitz syndrome is phenocopied by mutations in Δ -7-dehydrocholesterol reductase (*DHCR7*), which is involved in cholesterol synthesis⁷¹; cholesterol modification of SHH is required for effective signaling.^{72,73}

SHH levels are modulated by its binding to PTCH1.⁷³ In the absence of ligand, PTCH1 represses *Smoothed* (SMO) and prevents activation of the hedgehog signaling pathway. SHH also up-regulates PTCH1 expression, and any PTCH1 in excess of that involved in controlling signaling binds SHH and sequesters it, creating a negative feedback loop that restricts its spread. Another molecule regulating SHH levels is *hedgehog interacting protein* (HHIP), a membrane-bound protein that binds all mammalian hedgehog proteins and, like PTCH1, is up-regulated in response to SHH.⁷⁴ Targeted deletion of *HHIP* results in lung hypoplasia⁷⁵ that may be due to a loss of FGF10 expression at the prospective sites of bud formation as a result of increased SHH signaling.

Transforming Growth Factor-β Superfamily

The TGF-β superfamily comprises activins, inhibins, the BMPs, müllerian inhibiting substance, and TGF-β1, 2, and 3. TGF-β1 treatment of cultured embryonic lung explants⁷⁶ or misexpression of TGF-β1 targeted to the lung *in vivo*⁷⁷ severely inhibits branching morphogenesis. This is likely due to the ability of TGF-β1 to inhibit FGF10 expression.⁵⁹ TGF-β1 signals through a heteromeric complex of type I (TGF-βRI) and type II (TGF-βRII) receptors and exerts its effects on downstream target genes via the Smad family of

proteins.⁷⁸ Inhibition of TGF-βRII in cultured embryonic lungs increases lung branching,⁷⁹ as does attenuation of SMAD2/3,⁸⁰ underscoring the inhibitory nature of TGF-β1 on lung morphogenesis. *Tgfb1*-null mice show no apparent lung phenotype, although it should be noted that 50% of these mice die on E10.5, just after the onset of lung development.⁸¹ Most *Tgfb2*-null mice die shortly before or during birth with a wide range of developmental defects. The lungs of neonates have dilated conducting airways and collapsed terminal and respiratory bronchioles.⁸² Deletion of *Tgfb3* results in retarded development and differentiation of the lung epithelium, mesenchyme, and vasculature.⁸³ The fact that TGF-β3 appears to promote morphogenesis contrasts with the inhibitory function of TGF-β1, suggesting that these ligands affect distinct aspects of lung development.

Of the four BMPs expressed in the developing lung (BMP3, 4, 5, and 7), BMP4 has been the focus of the most studies. *Bmp4* is expressed in the ventral foregut mesenchyme before lung bud induction and then is expressed in the distal epithelium and proximal mesenchyme after the lung has formed. In the mouse, epithelial expression declines in the distal epithelium before birth but begins in the capillary endothelium. *Bmp4* expression is up-regulated by Fgfs in the epithelium and by Shh in the mesenchyme. Specific deletion of *Bmp4* or *BMP receptor 1a* (*Bmpr1a*) from the distal lung epithelium results in reduced proliferation, increased apoptosis, and cystic morphogenesis.⁸⁴ Early endodermal deletion of both *Bmpr1a* and *Bmpr1b* results in reduced ventral *Nkx2.1* expression, which is replaced by expanded expression of dorsal *Sox2*.⁸⁵ These data support a model in which BMP4 promotes the proliferation and survival of undifferentiated lung progenitor cells.

Wnts and β-Catenin

Members of the Wnt family of secreted glycoproteins are critically involved in cell fate determination, proliferation, survival, and motility in organogenesis.⁸⁶ Wnt ligands bind their receptors to activate a pathway that ultimately stabilizes β-catenin, which then interacts with nuclear *T-cell factor/lymphoid enhancer factor* (TCF-LEF) transcription factors to modulate transcription of downstream target genes.⁸⁷ Wnts1, 2, 2b, 5a, 7b, and 11 are expressed in the lung. Their secretion is mediated by the transmembrane protein *Wntless* (WLS); deletion of WLS from the lung endoderm disrupts branching morphogenesis and pulmonary endothelial differentiation.⁸⁸ Canonical Wnt signaling plays a critical role in lung development, because endodermal deletion of β-catenin abrogates specification of lung progenitors and leads to complete lung agenesis.⁸⁹ The ligands responsible for lung progenitor specification are likely Wnt2/2b, because their dual deletion phenocopies exactly the endodermal loss of β-catenin.⁹⁰ Proximal-distal airway patterning and epithelial cell differentiation are disrupted when Wnt signaling is inhibited after specification of lung progenitors, either by targeted epithelial deletion of β-catenin⁹¹ or by misexpression of the Wnt antagonist *Dkk1*.⁹² In addition to its role in specifying lung endoderm, Wnt2 also activates a signaling network necessary for smooth muscle differentiation.⁹³ Inactivation of Wnt5a results in a foreshortened trachea, distended distal airways, and retarded lung maturation.⁹⁴ Mice null for *Wnt7b* die at birth from respiratory failure. Early proliferation is reduced

in both epithelial and mesenchymal tissue compartments, leading to lung hypoplasia, although cell fate specification and overall tissue architecture are unchanged.⁹⁵ Constitutive activation of Wnt signaling in the developing lung epithelium with hyperactive β -catenin results in lungs that lack fully differentiated cell types and instead contain multiple intestinal and nonlung secretory cell types.⁹⁶ Taken together, these observations indicate that the temporospatial regulation of Wnt signaling must be tightly regulated to ensure normal lung morphogenesis and differentiation.

Platelet-Derived Growth Factor

The *platelet-derived growth factor* (PDGF) family consists of five different disulphide-linked dimers built up of four different polypeptide chains encoded by four different genes. PDGF-A, which homodimerizes with itself or heterodimerizes with PDGF-B, plays an important role in lung development. PDGF-A is expressed in distal lung epithelium, whereas its receptor, PDGFRA, is expressed in nearby mesenchymal cells, indicative of a paracrine signaling loop between the epithelium and mesenchyme. Deletion of *PDGF-A* results in arrested alveolus formation and postnatal death.⁹⁷ The lungs lack the differentiated alveolar myofibroblasts that produce elastin, which is critical for alveolus formation.

Vascular Endothelial Growth Factor

VEGF-A, C, and D are all found in the lung. The temporal and spatial expression of VEGF-A during lung development implies a central role in the maturation and organization of the pulmonary vascular network. VEGF-A is expressed in epithelial and mesenchymal compartments during the embryonic and pseudoglandular stages, becoming more restricted to the epithelium as development progresses into the canalicular stage.^{9,98} VEGF-A exists as three isoforms (120, 164, and 188) that have distinct functions in vascular development.⁹⁹ Genetic studies in mice demonstrate the importance of local tissue concentrations of Vegf-a to effect appropriate vascular development and distal airway structures. Increased expression of Vegf164 in distal epithelium disrupts assembly of the vascular plexus and arrests airway branching without affecting endothelial cell proliferation or survival, indicating that crosstalk between the developing epithelium and vasculature is required for normal morphogenesis.¹⁰⁰ Vascular ablation in the early lung causes significant alterations in stereotypic branching of the epithelium.¹⁰¹ VEGF-A expression is controlled by multiple mediators, such as FGFs and SHH.¹⁰²

Glucocorticoids

Glucocorticoids exert potent effects on a variety of different tissues, with a common theme that they induce the precocious appearance of normal developmental events. The effects of glucocorticoids on lung function have been a topic of intense interest since the observation that dexamethasone accelerates lung maturation in premature lambs.¹⁰³ Glucocorticoid receptors are present on the developing pulmonary epithelium as airway branching progresses during the pseudoglandular stage of lung development. Epithelial expression persists through the saccular and alveolar stages, accompanied by the onset of expression within the mesenchymal compartment.¹⁰⁴ Exogenous glucocorticoids stimulate morphologic maturation and many aspects of

surfactant phospholipid biosynthesis.¹⁰⁵ Targeted disruption of the glucocorticoid receptor in mice leads to respiratory distress and early neonatal death¹⁰⁶; the lungs of these animals are atelectatic with blunted alveolarization. Although the number of type II cells is increased by 30%, the relative expression of Sp-a and Sp-c is decreased by 50%. The number of type I cells is decreased by 50%, as are the type I cell markers T1 α and aquaporin-5, suggesting that glucocorticoids facilitate the differentiation of type II cells into type I cells.¹⁰⁷ Somewhat paradoxically, however, mice null for corticotropin-releasing hormone show deficits in septal thinning, air space formation, and content of Sp-a and Sp-b but have no deficit in surfactant phospholipid biosynthesis.¹⁰⁸

Given the broad distribution of pulmonary glucocorticoid receptors in the developing lung, it is not surprising that the therapeutic effects of glucocorticoid treatment are complex. Clinical experience suggests that glucocorticoids have contrasting biologic effects depending upon whether treatment is directed toward the fetal lung or the preterm neonatal lung. Women in preterm labor are routinely treated with glucocorticoids to reduce the incidence and severity of neonatal RDS.¹⁰⁹ Antenatal steroid treatment accelerates fetal lung maturation by inducing mesenchymal thinning and enhancing pulmonary function, presumably through stimulation of surfactant production. Morphometric studies in sheep suggest that antenatal steroid treatment may also induce some blunting of alveolarization.¹¹⁰ Glucocorticoid treatment has also been employed to treat preterm infants experiencing severe BPD. Although early studies and anecdotal reports suggested that steroid treatment could reverse the fibrosis and scarring associated with BPD and significantly improve pulmonary mechanics,¹¹¹ subsequent studies demonstrated no clear improvement in long-term pulmonary outcome and increased risk for neurodevelopmental impairment.¹¹²

TRANSCRIPTIONAL REGULATION OF LUNG DEVELOPMENT

The diffusible molecules mediating tissue interactions in the developing lung initiate signaling cascades that lead to changes in gene expression. The diversity of cell types found in the lung, which all differentiate under tight spatial and temporal control, makes regulation of gene expression by transcription factors in the developing lung highly complex. Although no lung-specific transcription factors have yet been found, research over the last decade has identified several transcription factors in addition to those described earlier that are crucial to normal lung development.

NKX2-1

NKX2-1 (also known as “*thyroid transcription factor 1*” [TTF1]) is found in the presumptive respiratory region of the foregut endodermal epithelium before lung bud induction. NKX2-1 is expressed in the forebrain, thyroid, and lung, where it interacts with multiple partners to influence several key aspects of development.¹¹³ Mice null for *Nkx2-1* develop tracheoesophageal fistulas, with main-stem bronchi connecting to hypoplastic, cystic lungs.¹¹⁴ Whereas differentiation of the most proximal epithelium is somewhat preserved in *Nkx2-1*-null lungs, markers of distal epithelial

differentiation, including the surfactant proteins, are completely lacking. Haploinsufficiency for the *NKX2-1* gene in humans leads to brain-lung-thyroid syndrome, which is characterized by benign hereditary chorea, respiratory disease, and congenital hypothyroidism.¹¹⁵⁻¹¹⁸ The respiratory phenotypes include RDS at birth, as well as recurrent pulmonary infections and interstitial lung disease later in childhood. The control of *NKX2-1* expression in lung development is not fully understood.

GLI Genes

Three *GLI* genes (1, 2, and 3) code for zinc finger transcription factors that are the principal effectors of hedgehog signaling. All three *Gli* genes are expressed in distinct but overlapping domains in lung mesenchyme, with expression being highest in the distal tips.^{119,120} The analysis of compound mutant mice has demonstrated the complexity of how *Gli* genes affect lung development. Embryos expressing different combinations of *Gli* genes show a range of lung defects, the most striking of which is the absence of lungs, trachea, and esophagus in *Gli2*^{-/-}, *Gli3*^{-/-} compound mutants.¹²¹ The presence of a single *Gli3* allele (*Gli2*^{-/-}, *Gli3*^{+/-}) is sufficient to allow formation of hypoplastic lungs in which the left and right lungs do not separate, and the embryos have tracheoesophageal fistulas. The phenotype seen in *Gli2/Gli3* double-null embryos is more severe than that seen in *Shh*-null animals; this suggests that the *GLI* genes may lie downstream in signaling pathways other than SHH, or that the other hedgehog proteins (Indian and desert) may be active in the lung. Mutations in the human *GLI3* gene cause Pallister-Hall and Greig syndromes, which affect development of several organ systems, including the lung.¹²²

FOX Family

The FOX family of transcription factors contains more than 50 members, all of which share a winged-helix DNA binding domain. FOXA1 and FOXA2 are closely related proteins found in the foregut endoderm and its derivatives. Their spatial and temporal expression patterns are similar in the lung. Mice lacking *Foxa2* do not form endoderm and hence cannot form lungs¹²³; targeted deletion of *Foxa2* in lung epithelial cells, however, demonstrates that it is required for alveolarization and epithelial cell differentiation.¹²⁴ Deletion of *Foxa1* in mice delays some aspects of sacculization and alveolarization prenatally and perinatally, but these differences normalize by 2 weeks of age,¹²⁵ suggesting compensation by *Foxa2*. Deletion of both genes inhibits cell proliferation, branching morphogenesis, and epithelial cell differentiation,¹²⁶ indicating that FOXA1/2 play a central role in lung development.

Foxa1 is expressed in lung mesenchyme and controls genes involved in epithelial-mesenchymal interactions, because a haploinsufficiency results in defective branching, lobation, and epithelial differentiation in the mouse lung.¹²⁷ In humans, FOXF1 mutations are associated with ACD/MPV.³³ Foxj1 controls expression of left-right dynein, which is required for correct anchoring of basal bodies; deletion of *Foxj1* causes situs inversus, the loss of motile cilia in airway epithelial cells, sinusitis, and bronchiectasis.¹²⁸ Although these features are associated with Kartagener syndrome in humans, no mutations in the FOXJ1

gene have been directly linked to this disorder. FOXP1 and FOXP2, which are known transcriptional repressors, are expressed in the lung epithelium; both genes are expressed distally, but only FOXP1 is expressed proximally. *Foxp2*^{-/-} mice show impaired alveolarization, an effect exacerbated in compound mutant *Foxp2*^{-/-}, *Foxp1*^{+/-} mice, which have hypoplastic lungs and die at birth. Foxp1 acts cooperatively with Foxp4 to restrict goblet cell specification, thereby regulating the balance of cell types in the airway epithelium.¹²⁹

GATA6

GATA6, a zinc finger transcription factor that is required for visceral endoderm differentiation,¹³⁰ is the only GATA family member expressed in the distal epithelium of the developing lung. Mice bearing a dominant-negative Gata6/engrailed fusion protein under control of the *Sftpc* promoter show reduced numbers of proximal airway tubules. Lung epithelial cell differentiation is also affected, with these mice completely lacking detectable alveolar type I cells.¹³¹ Loss of Gata6 in the lung epithelium causes a loss of differentiation and the precocious appearance of bronchioalveolar stem cells that is the result of increased Wnt signaling.¹³² GATA6 regulates expression of WNT7B and also interacts with NKX2-1 to control expression of SP-A, B, and C.¹¹³

SOX Family

Members of the SOX family of transcription factors function as key regulators of cell fate and differentiation. Of the 20 known SOX proteins, SOX2, 4, 9, 11, and 17 are found in the developing lung. Sox2 is highly expressed in non-branching epithelium but repressed by Fgf10 in epithelial cells that are actively invading the surrounding mesenchyme,¹³³ suggesting that silencing of Sox2 is required for the epithelium to branch. The repression of Sox2 by Fgf10 may be mediated by BMP signaling.⁸⁵ Overexpression of Sox2 in lung epithelial cells inhibits lung branching by forcing the cells to commit prematurely to a differentiation program, thereby rendering the cells incompetent to respond to branching signals.¹³⁴ Sox11 is also expressed throughout the developing lung epithelium, and mice null for *Sox11* have significant lung hypoplasia.¹³⁵ Sox17 expression in the lung is dynamic, being first detected in the mesenchyme during the embryonic stage, then in the conducting airway epithelium during the canalicular stage. Because its misexpression in the distal epithelium disrupts branching and causes the ectopic expression of proximal airway markers, Sox17 is thought to play a key role in specifying differentiation of airway epithelial cells.¹³⁶

POSTTRANSCRIPTIONAL GENE REGULATION IN LUNG DEVELOPMENT

Micro-RNAs (miRNAs) are small noncoding RNA molecules that modulate physiologic and pathologic processes by inhibiting gene expression through RNA translation repression or messenger RNA degradation. Functionally mature miRNAs are generated by a series of ribonuclease III cleavage steps. Key enzymes in miRNA biogenesis include DROSHA, which cleaves primary miRNAs into precursor miRNAs in the nucleus, and DICER1, which cleaves precursor

sor miRNAs to the mature form in the cytoplasm. Mature miRNAs are incorporated into the large multiprotein RNA-induced silencing complex, which represses RNA translation or induces messenger RNA degradation. miRNAs regulate key biologic processes important in lung development, including cellular proliferation, apoptosis, and differentiation. miRNA profiling reveals that the lung has a specific miRNA expression profile that is conserved across species (including mouse and human) and regulated specific to developmental stage, sex, and cell type.¹³⁷⁻¹⁴⁰ miRNAs have a critical role in controlling organogenesis. Loss- and gain-of-function studies, as well as differing expression profiles between patients or animal models with lung disease and normal controls, implicate miRNAs in the pathogenesis of many lung diseases, including chronic obstructive pulmonary disease, lung cancer, pulmonary inflammatory disease, idiopathic pulmonary fibrosis, asthma, and cystic fibrosis (for reviews see references 141 to 144). Additionally, studies in model systems have identified a critical role for miRNA-mediated regulation in lung development. Inactivation of *Dicer1*, a key enzyme in miRNA biogenesis, targeted to the developing lung epithelium results in neonatal death because of arrested airway-branching morphogenesis, increased cell death, and altered expression of critical epithelial-mesenchymal signaling molecules.¹⁴⁵ Specific miRNAs that have been identified to influence lung development include the miR302/367 cluster that directs lung endoderm development by coordinating proliferation, differentiation, and apical-basal polarity of lung progenitor cells,¹⁴⁶ the miR17-92 cluster that is required for lung growth as well as for promoting proliferation and inhibiting differentiation of lung epithelial progenitor cells,^{147,148} miR127, which regulates terminal bud size and number,¹⁴⁹ and miR221 and miR130a, which have opposing effects on airway and vascular morphogenesis.¹³⁷ The recent discovery of heterozygous germline loss-of-function *DICER1* mutations in familial *pleuropulmonary blastoma* (PPB), a rare pediatric lung tumor that often arises during lung development, provides evidence that the *DICER1*/miRNA pathway controls human lung development and suppresses tumorigenesis.¹⁵⁰ The majority of car-

riers with *DICER1* mutations are phenotypically normal, suggesting that loss of one *DICER1* allele is compatible with normal development and insufficient for tumor formation. PPB is composed of both epithelial and mesenchymal cells.^{151,152} In a subset of patients, overgrowth of the mesenchymal cells results in a sarcoma that is associated with a poorer prognosis. Interestingly, the protein DICER1 was found to be lost in the epithelial tumor component but retained in the mesenchymal cells by immunohistochemistry, suggesting that loss of DICER1 specifically in the lung epithelium promotes PPB formation.¹⁵⁰ Consistent with this notion, *Dicer1* gene ablation targeted to the developing murine pulmonary epithelium results in a PPB-like phenotype (Fig. 2-3). Because PPB often arises in the setting of an inherited tumor predisposition syndrome characterized by increased incidence of other neoplasms, including cystic nephroma, ovarian sex cord-stromal tumor, embryonal rhabdomyosarcoma, and multinodular goiter, the *DICER1*/miRNA pathway functions that control lung development are probably also operative in other organs.¹⁵³⁻¹⁵⁵

Key Points

- The lung epithelium begins as two buds from foregut endoderm. Subsequent branching morphogenesis and alveolarization leads to a mature organ containing over 300 million alveoli.
- The pulmonary vasculature develops in parallel with the branching epithelium.
- Lung development requires reciprocal interactions between the epithelium and mesenchyme derived from splanchnic mesoderm.
- Tissue interactions are mediated by an array of diffusible signaling molecules. Variations in the temporal and spatial expression of these mediators add complexity to these interactions.
- Diverse classes of transcription factors that lie downstream of diffusible mediators further regulate morphogenesis and effect the differentiation of individual cell types.

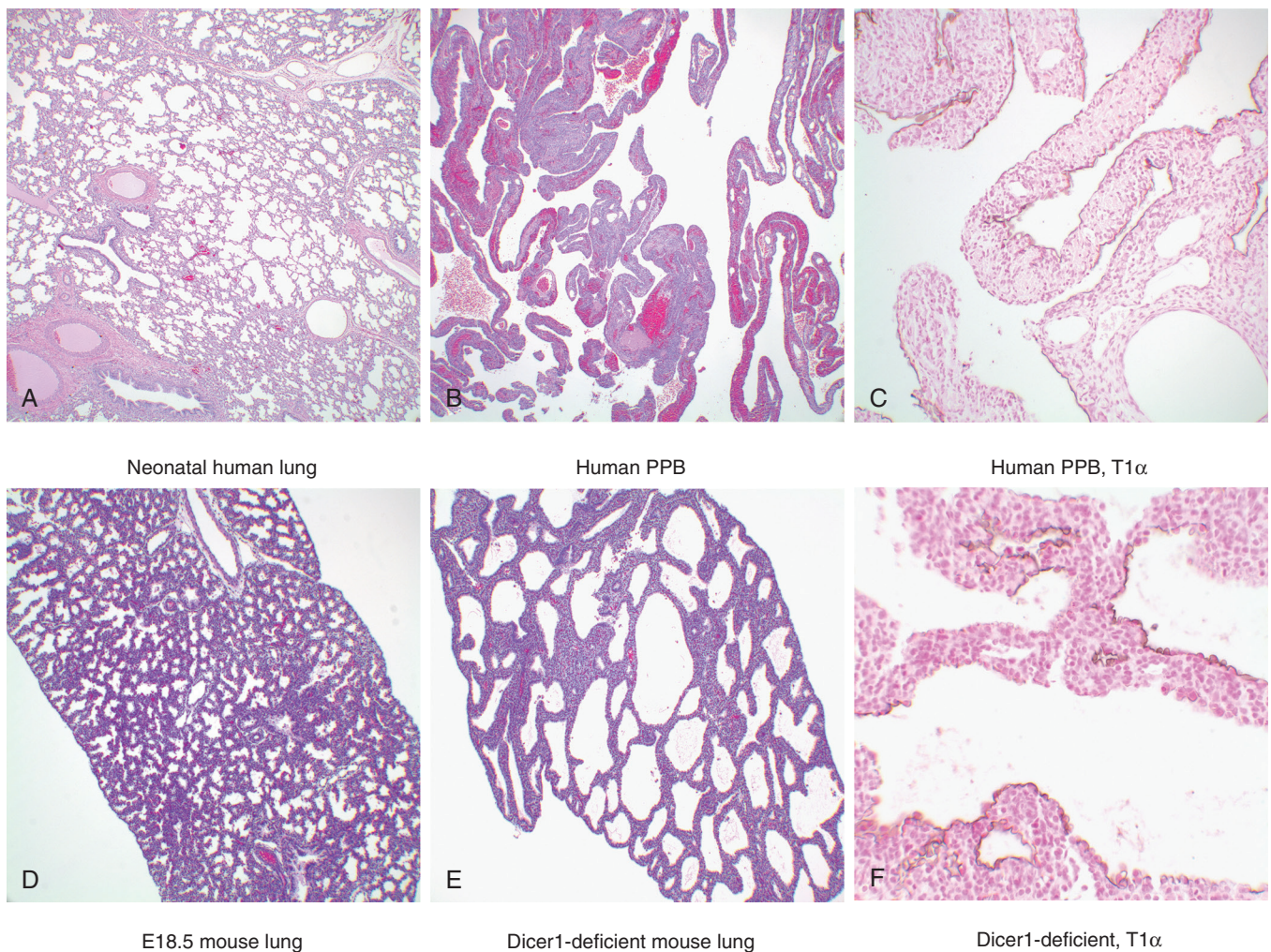


Figure 2-3 Mouse lungs with *Dicer1* loss mimic pleuropulmonary blastoma (PPB) in neonates. Human PPB (**B** and **C**), adjacent normal neonatal lung (**A**), *Dicer1*-deficient mouse embryonic day 18.5 lungs (**E** and **F**), and normal lungs from *Dicer1*-proficient littermates (**D**) were compared by hematoxylin and eosin staining. PPB and *Dicer1*-deficient murine lung sections were also immunostained for the type I cell marker, T1α (**C** and **F**), to determine the phenotype of the epithelial cells lining the cysts. **A** and **D**, The neonatal human lung adjacent to the tumor shows normal morphologic characteristics for the alveolar stage of lung development, and the mouse lung shows morphologic characteristics typical of the saccular stage of development. **B**, Early-stage type I PPB is characterized by epithelium-lined cysts with intervening septa containing mesenchymal cells. **E**, The *Dicer1*-deficient mouse lungs have morphologic characteristics similar to those of human PPB, including epithelium-lined cysts separated by septa containing mesenchymal cells. Many of the epithelial cells lining the PPB cysts have a type I cell phenotype as determined by expression of T1α (**C**). Similarly, the *Dicer1*-deficient epithelial cells lining the cysts in the murine model also express T1α (**F**). (**A** and **B**, $\times 4$ original magnification; **C**, $\times 20$ original magnification; **D** and **E**, $\times 10$ original magnification; **F**, $\times 40$ original magnification.)

Complete reference list available at ExpertConsult.

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3

GENETICS OF LUNG DISEASE

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INTRODUCTION

The human genome comprises approximately 3.2 billion base pairs. With the exception of identical twins, each human being has a unique DNA sequence. There are at least 10 million locations in the genome where DNA sequence varies between individuals. These locations are referred to as “polymorphic” when at least two variants (also known as “alleles”) are present at a frequency greater than 1%. Most human diseases are the result of the interplay between these genetic polymorphisms and environmental exposures. The first step in any investigation of the genetic causes of a disease or phenotype is to determine the relative importance of these two causes of the disorder among the population of interest. To begin this process, one must determine the heritability of the disease of interest. Heritability is defined as the percentage of phenotypic variation that is due to variation in genetic factors. Often the first step is to determine if the trait, disease, or phenotype aggregates in families, but this will not prove that the trait of interest is genetic because traits can aggregate in families for purely environmental reasons, such as cigarette smoking, or because the prevalence of the trait is high, such as obesity. The most direct way to estimate the contribution of genetic variation to a disease is to measure heritability. Heritability can be estimated using families. For example, in twin studies a greater concordance of the phenotype between identical (monozygotic) twins than fraternal (dizygotic) twins can provide evidence of heritability of that phenotype. For lung disorders, heritabilities range from 20% to 90% depending on the type of lung disease, the mode of inheritance, and the degree of environmental influence.

There are two primary types of genetic disorders, monogenic (due to variation in a single gene) or complex (due to variation in multiple genes). Monogenic disorders demonstrate high heritability, segregate in families in a predictable way, and are caused by variation in a single major gene with less obvious environmental influence. The single gene usually has specific variation in the coding region of the gene that leads to an abnormal protein that causes an obvious clinical phenotype. Often the phenotype has multiple components, suggesting multiple effects of the gene

variant(s). This is called “pleiotropy,” in which one variant has many effects. There are currently over 10,000 monogenic disorders that have been identified and are characterized in the Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>). Positional cloning (linkage mapping followed by association mapping; described later) has been the primary means of the identification of these genetic variants until recently. With the completion of the Human Genome Project and the rapid advancement of genotyping technologies, attention has turned to identification of genetic variation associated with complex genetic disorders. Those efforts initially used positional cloning but now primarily rely on genetic association studies.

In contrast to monogenic disorders, complex genetic disorders are caused by variation in multiple genes and multiple environmental exposures, with each genetic variant having a much smaller effect than those seen in monogenic disorders. Because of the multiple gene-gene and gene-environment interactions, there is no obvious mendelian mode of inheritance in families for complex traits. One of the most prominent hypotheses for the genetic basis of common disease is the common disease/common variant hypothesis. This hypothesis suggests that key genetic determinants of common diseases have a relatively high allele frequency (i.e., 5% to 40%) and modest effect sizes. Given the modest effect sizes (odds ratios on the order of 1.1 to 1.4), large sample sizes are necessary to identify the genetic variants associated with complex traits despite the high allele frequency expected in these disorders. It is likely that there is a range of allele frequencies that predispose to complex diseases, with a corresponding range of effect sizes, but large-scale studies to evaluate the evidence for rare variation as a contributor to complex disease are only beginning to emerge.

The dichotomy described earlier between monogenic and complex disease is somewhat artificial because the clinical phenotype of many monogenic disorders varies as a result of the specific mutation present, other modifier genes, and environmental exposures. As genes for complex traits begin to be identified, their role in monogenic disorders is also being elucidated.

SCOPE OF THE PROBLEM

Some complex genetic disorders, such as age-related macular degeneration, are oligogenic, in which a small number of genes, three to five, explain the bulk of the clinical phenotype. However, for most complex traits, literally hundreds of genes with small effects are likely involved in disease causation. Thus a series of challenges have faced complex trait geneticists in the genome era of medicine.

The field of human genetics has continued to expand as the type of genomic variation that can be measured expands. Parallel advances in data analysis strategies are necessary to ensure efficient and valid inferences based on the ever-increasing volume of data that can be collected on large numbers of individuals. This cyclical pattern of advancement has been typical of the last several decades and is likely to be typical going forward. For example, initial problems relating to genotyping reliability and completeness for common variants (those with frequency > 5% in a given population) that were present at the time of release of the initial sequence of the genome have been largely resolved, as have the methods necessary to detect and control for population stratification (confounding by allele frequency differences in cases and controls, discussed later) and to account appropriately for the hundreds of thousands or millions of tests conducted in a genome-wide association study. Since 2010, large efforts have been focused on resequencing technologies, which sequence the same site in multiple individuals to capture sequence variation and thus capture uncommon and rare variation (frequency ≤ 5%). As we are able to measure a larger variety of genomic data (e.g., transcriptomic and epigenetic data) on ever-increasing numbers of individuals, the major analytic challenges will be in developing methods for integration of the different types of data. For all types of genetic variation, the ability to determine if genetic effects are real or not requires replication of results in independent populations, a process that can be difficult with the presence of phenotypic heterogeneity across populations. In particular, varying genetic backgrounds and environmental influences can result in variability in the effects of genetic variants across populations. Finally, the ultimate challenge of finding and verifying the functional variants in putative disease genes is still a laborious process without a clear-cut methodology for success.

POTENTIAL IMPACT OF HUMAN GENETICS

Genetics has the potential, because of its hypothesis-free nature, to identify novel mechanisms of disease pathobiology and hence to identify novel targets for a therapeutic intervention or disease prevention. In addition, genetics has the potential to predict specific subgroups of patients with a different clinical course or response of their disease, or differences in treatment. Finally, genetics has the potential to allow for early detection of susceptible individuals at risk for a specific disease phenotype or to allow avoidance of environmental factors that are known to cause the disease or to institute preventive therapy before disease develops. These genetic insights are still just beginning to be applied, and it will take time for genetics to become routinely used at the bedside.

MOLECULAR CHARACTERIZATION OF GENETIC VARIATION

Molecular genetics is elegant in its simplicity. Just four base pairs (two purines [adenine and guanine] bind to two pyrimidines [thymine and cytosine]) code for 20 amino acids that form the molecular building blocks of complex proteins. However, the assemblage of inherited genes (genotypes), control mechanisms, resultant proteins, and post-translational modifications have the capacity to create a complex panoply of unique biologic, physiologic, or visible traits of an organism (phenotypes). The relationship between these rather simple molecular characteristics and the vast array of complex phenotypes is, in part, explained by a number of seminal discoveries that were made more than 50 years ago.

Gregor Mendel¹ was the first to demonstrate that discrete traits could be inherited as separable factors (genes) in a mathematically predictable manner. Mendel's laws describe the relationship between genotype and phenotype and established the concept that each gene has alternative forms (alleles). Charles Darwin² made the observation that evolution represents a series of environmentally responsive "genomic" upgrades. Thomas Morgan³ established the concept of linkage by using *Drosophila* to discover that genes were organized (and inherited) on individual chromosomes, and that genetic material was recombined or exchanged between maternal and paternal chromosomes during meiosis and that the frequency of recombination could be used to establish the relative genomic distance between genes. However, it was not until 1944 that Avery, MacLeod, and McCarty while working with *Pneumococcus* discovered that DNA was identified as the essential molecule that transmitted the genetic code.⁴ The double-helix structure of DNA was discovered by Watson, Crick, Chargaff, Franklin, and Wilkins in 1953,⁵ and over the next 50 years genetics assumed a central role in understanding the biologic and physiologic differences between and among species and between states of health and states of disease. In aggregate, these seminal discoveries led to a number of fundamental principles in molecular genetics that provide the basic mechanisms that link the four base pairs (adenine [A] binding to thymine [T] and guanine [G] binding to cytosine [C]) to health and disease.

GENOMIC MAPS

Over the past several decades genomic maps have evolved from karyotypes (microscopic visualization of chromosomes during metaphase) to restriction enzyme sites to genetic maps to maps with specific base pair sequence. In fact, to date there are hundreds of vertebrate, invertebrate, protozoan, plant, fungal, bacterial, and viral genomes that have been sequenced and are available on the National Center for Biotechnology Information (NCBI) Web site (www.ncbi.nlm.nih.gov). These genomic maps have not only been essential for identifying which genes and sequence changes cause disease or enhance the risk for adverse outcomes, these species-specific maps have also led to a very clear understanding of molecular evolution and have provided essential tools for understanding aspects of molecular

Table 3-1 Commonly Used DNA Markers

Restriction fragment length polymorphisms—Presence or absence of a specific nucleotide sequence that can be cleaved by a restriction enzyme. These bacterial restriction enzymes fragment DNA only at sites that contain very specific base pair sequences.

Variable number of tandem repeat polymorphisms—Noncoding polymorphic base pair repeats in DNA (dinucleotide, trinucleotide, and tetranucleotide repeats of CA or GT) that are present throughout the genome. At each site the number of times a sequence is repeated may vary from one individual to the next.

Microsatellite polymorphism—Variable number of repetitions of a small number of base pairs within a sequence.

Single nucleotide polymorphisms—Individual point substitutions of a single nucleotide that do not change the length of the DNA sequence and are present throughout the genome (every several hundred base pairs).

A, adenine; C, cytosine; G, guanine; T, thymine.

biology. The construction of these genomic maps is based on the observation that the sequence of DNA is different from one organism to the next within the same species, and these allelic/sequence differences have been exploited to develop a number of commonly used DNA markers to create genomic maps (Table 3-1).

Genetic maps are based on the frequency of recombination events, defined as a specific form of exchange of genetic material between the maternal and paternal chromosomes during meiosis. Although Mendel's second law states that traits (or genes) are inherited independently, we now know that some genes do not segregate independently because they are on the same chromosome. Humans have 24 linkage groups, corresponding to the 22 autosomes, plus X and Y chromosomes. Genes on the same chromosome that are closer together are more likely to be inherited together (linked) than genes that are farther apart, which may demonstrate independent assortment. In general, the greater the distance between genes on the same chromosome, the higher the recombination frequency (Fig. 3-1). Thus the recombination frequency represents a measure of genetic linkage and is the fundamental event used to create a genetic linkage map. The unit of measurement for genetic linkage maps is the *centimorgan* (cM), with 1 cM equivalent to a recombination frequency of 1% (one recombinant event per 100 meioses). Although recombination frequencies vary across the chromosome, in general, at least for the human genome, a recombination frequency of 1% is equivalent to approximately 1 million base pairs. Genetic maps are constructed by identifying the number of recombinant events observed in parental meioses and are dependent on several factors: (1) the meioses observed, (2) the heterozygosity of the marker, (3) the physical distance between markers, and (4) the likelihood of recombination at that site. Genetic maps use a rather indirect method to estimate the order of genes and the relative distance between genes.

Genetic maps are routinely used in family-based linkage studies to identify the general location of genes that influence human traits and conditions. Highly polymorphic markers can be used as tags to identify regions of DNA that are linked with a disease locus in families. These regions (often 20 to 40 cM in length) of DNA then serve as the targets to interrogate via association studies. However, a

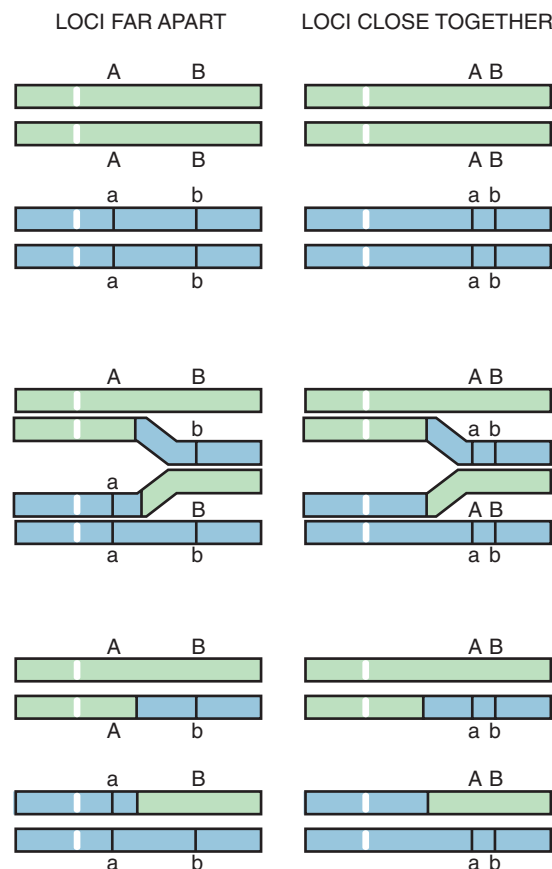


Figure 3-1 Crossover between homologous chromosomes in meiosis. On the left is an example in which two loci are far apart on the chromosomes and so remain unlinked. On the right the loci are relatively close to one another and so, after recombination, are more likely to remain together.

genetic linkage map should not be confused with a physical map of the genome because genetic maps are based on the rate of recombination, not the physical distance, between markers, although these two features are related.

In contrast to a genetic map, a physical map describes the physical location of genes and the physical relationship between genes on each chromosome. Although the gene order from a genetic map and a physical map should theoretically be the same, the relative distance between genes may be quite different when comparing a genetic map (based on recombination frequency) to a physical map (based on genetic distance along the chromosome). The reason for this discrepancy is that the recombination rate across chromosomes is not constant. However, genetic maps provided the first framework for the construction of physical maps.

Although we typically think of physical maps as sequence based, many years before sequence-based maps became available, investigators relied on lower-resolution cytogenetic (chromosomal) and radiation hybrid maps. Cytogenetic maps are based on chromosomal banding patterns and have been used to locate genes in patients with chronic granulomatous disease, Duchenne muscular dystrophy, and fragile X syndrome.

Two major breakthroughs at the end of the 20th and beginning of the 21st centuries changed human genetics

forever—the sequencing of the human genome^{6,7} and the creation of the International HapMap Project to identify the common sequence differences and similarities between individuals.⁸ With the sequencing of the human genome, investigators for the first time had a detailed road map of the human genome that identified the genes, regulatory units, and noncoding sequence with a very high degree of resolution. Of the 3.2 billion base pairs in the human genome, less than 1% uniquely identify each human being.⁹ There are approximately 12 million *single nucleotide polymorphisms* (SNPs) in the human genome. These are single base pair changes that result in allelic variation at a locus. Although only a small proportion of these SNPs will result in amino acid changes, these SNPs provide some of the genetic diversity that underlies the variable susceptibility to environmental stimuli and the variable risk for disease development and progression.⁹ Although the initial HapMap project focused on populations from African, Asian, and European ancestry, more recent work expanded the collection to include a wide variety of ancestry groups. Because the HapMap project was focused on common variation, the 1000 Genomes Project¹⁰ was developed to catalog uncommon and rare variation among human populations using resequencing. Like the HapMap project, this publically available resource provides the empirical data necessary for scientists to design disease-specific studies aimed at understanding the role of uncommon and rare variation.

In aggregate, the human DNA sequence and the shared genetic patterns between individuals have enabled geneticists to define the organization of genetic variants on chromosomes and the common inheritance of genetic variants. These developments have provided the polymorphic markers and the regions that are tagged to these markers to facilitate the identification of regions and genes that contribute to risk for disease. Consequently, real progress is now being made in identifying common and rare genetic variations that contribute to complex diseases such as asthma,¹¹ age-related macular degeneration,¹² type 2 diabetes,¹³ and prostate cancer.¹⁴

COMPARATIVE GENOMICS

Because DNA structure and protein functions are often conserved through evolution, the use of model organisms can enhance the efficiency of gene discovery and can provide insights into biologic responses to endogenous and exogenous forms of stress. Although genes present in humans often have counterparts in other species, the homology between gene and chromosomal structure across species does not necessarily lead to conserved protein function. However, the conservation of gene sequence and chromosomal structure in different organisms has resulted in accelerated gene discovery, insights into human biology, and a data-driven understanding of evolution. Despite this excitement, the field of comparative genomics is at a very early stage of development¹⁵ and is dependent on evolving databases, like Gene Ontology functional classifications,¹⁶ to facilitate these cross-species comparisons.

Comparative genomics is a powerful approach to searching for disease-causing genes. Identifying similar regions of DNA associated with concordant phenotypes in multiple species enhances the confidence that a gene causing that

disease resides in that locus. The overlapping DNA for concordant phenotypes between species can be used to narrow the region of interest substantially. Because there are approximately 340 known conserved segments between mice and humans,¹⁷ a mouse region of interest associated with a trait can be used to narrow the human region of interest associated with a disease. Additionally, the genomes of model organisms, such as mice, flies, worms, or yeast, can be manipulated through genetic engineering (resulting in deficiency or overexpression of a gene, or controlled expression of a human allele) to understand the function of a specific gene. For example, the importance of the Toll-like receptors in innate immunity in mammals was discovered as a direct result of the observation that a defective receptor in flies caused them to be much more susceptible to *Aspergillus fumigatus*.^{18,19} The importance of this finding is clearly illustrated in the variations in the Toll-like receptors that alter the response to microbial pathogens²⁰ and modify the risk for developing a variety of diseases that are associated with innate immunity.²¹ The ease with which we can observe and apply knowledge across model systems should be exploited so that we can efficiently understand the biologic and clinical importance of key regulatory genes.

PUBLIC DATABASES

If compiled in books, the data produced in defining the human genome would fill 200 volumes, each the size of a 1000-page phone book. Reading it would require 26 years working around-the-clock. Although new tools are being developed to analyze, store, and present the data from genome maps and sequences, several databases presently exist that can be accessed through the Internet.

Important lessons can be learned from a detailed consideration of the characteristics of identified mutations in mendelian diseases using online resources such as the Online Mendelian Inheritance in Man, the Human Gene Mutation Database, and LocusLink.²² For example, the data on the relative frequency of types of mutations underlying disease phenotypes indicate that mendelian disease genes most often have alterations in the normal protein-coding sequence. For general information on accessing sequence information, several available reviews provide details on available databases and searching strategies.²³ The NCBI is responsible for the final and reference assembly of the human genome. Each DNA sequence is annotated with sequence features and other experimental data, including location of SNPs, expressed sequence tags, and clones. Up-to-date genetic sequence information can be obtained from Ensembl (<http://www.ensembl.org>), the University of California at Santa Cruz Genome Browser, and the NCBI's GenBank. The NCBI's Map Viewer provides a tool through which genetic maps and sequence data can be visualized and is linked to other tools such as Entrez, the integrated retrieval system providing access to numerous component databases. The database of Single Nucleotide Polymorphisms at the NCBI allows the user to search for SNPs within a region of interest (<http://www.ncbi.nlm.nih.gov/SNP>). The HapMap (<http://hapmap.ncbi.nlm.nih.gov/>) and 1000 Genomes (<http://www.1000genomes.org/>) databases provide raw and summary genotype and linkage

disequilibrium data about common and rare genetic variation across several racial and ethnic groups.

GENETIC EPIDEMIOLOGY

POSITIONAL CLONING

Advances in our understanding of the variation across the human genome have allowed wide application of the positional-cloning approach to identification of genetic variants that contribute to phenotypes of interest. Positional cloning refers to identification of a chromosomal position that is related to the phenotype based on scanning the genome for a relationship between each locus and the phenotype, rather than relying on the known biochemical properties of a gene to identify it as a candidate for being related to the phenotype. The first approach to positional cloning relied on linkage analysis, most often followed by association analysis; since 2007, genome-wide association analyses have been the standard positional-cloning approach. Whole-exome resequencing studies are now feasible for sample sizes in the hundreds, and whole-genome resequencing studies are rapidly decreasing in cost.

LINKAGE STUDIES

Linkage analysis encompasses a group of statistical methods to examine the inheritance pattern of DNA markers within families to determine if there is a relationship between a particular region of the genome and a phenotype of interest. Most linkage studies have been based on short tandem repeat (repeats of a short sequence of nucleotides) or SNP markers distributed through the genome.

Linkage analyses use family data, which can be made up by a wide range of pedigree structures from extended pedigrees to affected sibling pairs. There are two broad types of linkage analysis, parametric and nonparametric; both rely on the coinheritance of disease alleles with genetic markers used in the analysis. When a mutation arises on a particular chromosome, initially there is a large shared segment of DNA and hence linkage disequilibrium around it. With each subsequent generation, this region of linkage disequilibrium becomes smaller as a result of meiotic recombination. The basic approach in parametric linkage analysis is to determine if alleles at a genotyped marker segregate with the alleles at a putative disease locus together more often than one would expect by random assortment, or chance. This can be assessed by comparing the frequency of recombinant chromosomes in which a crossing over event has rearranged the parental chromosomes to the frequency of nonrecombinant chromosomes. When two loci are linked, parental chromosomes are more common than recombinant chromosomes. The strength of the linkage between a marker and a putative disease locus is expressed as the recombination fraction. Parametric linkage analyses require that a particular genetic model be specified. Thus the approach is ideal for classic mendelian, monogenic disorders but is less well adapted for complex traits, where these parameters are often not known. Nonparametric linkage analysis refers to a group of analysis methods that, in contrast to parametric linkage analysis, do not require assump-

tions about a particular form of inheritance. The general approach for nonparametric linkage analysis is to contrast observed allele sharing between affected relatives to that expected given their relationship (e.g., siblings) at a given locus. Regions that show statistically significant excess sharing among affected relatives are regions that may harbor loci important for the phenotype of interest. This nonparametric approach has been combined with genetic association within the linked region to identify disease susceptibility genes for asthma, Crohn disease, and pulmonary fibrosis.²⁴⁻²⁹

Linkage results are usually expressed as an LOD score, which is a function of a statistical test for linkage. LOD scores are log of base 10 of the odds that the loci are linked, and their distribution depends on the study design.

ASSOCIATION STUDIES

Genetic association studies are the most commonly used study designs to find disease genes in complex traits. Association studies can be used in conjunction with linkage studies, *de novo* with candidate genes or *genome wide association studies* (GWAS). There are two basic types of study designs used for genetic association studies, the case-control study and the family-based study; both types rely on the concept of linkage disequilibrium between the alleles at a genotyped marker(s) and the disease allele(s).

When two SNPs are on separate chromosomes, they will segregate randomly (i.e., carrying the minor allele at SNP A does not affect your chances of carrying the minor allele at SNP B). If, on the other hand, the alleles at the SNPs are in linkage disequilibrium, with little or no recombination between them, the genotype at SNP B can serve as a surrogate for the genotype at SNP A. Thus testing of all SNPs in a gene or a region of the genome is unnecessary. One need only genotype a subset of SNPs to capture the linkage disequilibrium pattern among common variants (>5%) of the region of interest to be comprehensive. Importantly, detecting phenotype association with a genetic marker does not indicate that the genetic marker is causally related to the phenotype, but may only reflect linkage disequilibrium with the causal variant.

Case-control studies are the most frequently performed type of genetic association studies because they are simpler to implement than family-based designs. In their simplest form, population-based genetic association studies are similar to epidemiologic case-control studies and involve identifying genetic markers with significant allele, genotype, or haplotype frequency differences between individuals with the phenotype of interest (cases) and a set of unrelated control individuals.³⁰ A statistical association between genotypes at a marker locus and the phenotype can arise for three reasons: (1) the allele is the actual disease allele, (2) the allele being studied is in linkage disequilibrium with the true disease allele, and (3) there is a spurious association due to population stratification. Indeed, case-control genetic association studies have already contributed to identifying genes associated with complex disorders, as in the cases of apolipoprotein E-4 with late-onset Alzheimer disease³¹ and factor V gene with venous thrombosis.³² Thus, performing valid case-control studies remains important in elucidating genetic risk factors for complex

traits. Silverman and Palmer³³ have reviewed these factors that may adversely affect the results of any association study in complex diseases. They have recommended five key elements in the performance of valid case-control genetic association studies for complex diseases: (1) proper selection of gene polymorphisms, (2) accounting for population stratification, (3) assessment of Hardy-Weinberg equilibrium, (4) replication, and (5) adjustment for multiple comparisons.

Ideally, cases and control study subjects should be drawn from the same base population. Failure to do so will often result in biased selection that can adversely influence the results, often resulting in a spurious association. When subjects with different evolutionary histories and hence different genetic backgrounds are differentially selected to be cases and controls, this can cause spurious results, termed “population stratification.” An approach useful in case-control studies to control this problem is to detect and control for population stratification in case and control groups by genotyping randomly distributed polymorphic markers.^{34,35} If population stratification is demonstrated between the case and control populations, methods to detect significant disease gene associations have been developed based on correction for the degree of stratification.³⁵⁻³⁸ A second major problem with early case-control studies has been that often too-small sample size is used to allow for robust evaluation of the evidence for association. Because of the small genetic effect sizes seen and expected for complex traits, sample sizes in the thousands are generally required in addition to replication to generate rigorously validated association results.

Family-based genetic association tests are based on the transmission disequilibrium test, which provides a test of linkage and association without bias from population stratification or admixture.^{39,40} For the transmission disequilibrium test, parents and an individual offspring (child or proband) with the disease phenotype are recruited. Only trios with at least one heterozygous parent at the genetic marker of interest are used for testing. The test is predicated on the assumption that if a genetic locus is uninvolved (neither linked nor associated) in the phenotype of interest, one would expect the two parental alleles at that locus to be transmitted equally to an affected child (i.e., mendelian, transmitted 50% of the time). However, if the locus is actually linked and associated with disease, there will be overtransmission (or undertransmission) of one allele at that locus—and its transmission will differ significantly from the expected 50%.

Family-based association studies cost more than case-control studies because one has to recruit and genotype three people instead of two. In addition, not all diseases can use the family-based design because often parents have died and hence are not available for study. Despite these disadvantages, there are also powerful reasons to use trios if possible. First, unlike the case-control study, the family-based association study is immune to population stratification because the parental genotype is used as the control. Second, within each trio, only one person (the subject) must be phenotyped. This is particularly useful when phenotyping is very expensive or invasive. Family-based testing also offers an important method of assessing genotyping quality, because data can be analyzed for mendelian errors. The

transmission disequilibrium test has been extended in many ways, for instance, to allow family-based tests of association for extended pedigrees.⁴¹⁻⁴⁶

GENOME-WIDE ASSOCIATION STUDIES

In GWAS, SNPs are selected to cover as much of the genome as possible. SNPs across all chromosomes and most genes are selected to assess association with a phenotype of interest. There are two currently two companies, Affymetrix and Illumina, which have different SNP selection strategies and different chip chemistry for performing GWAS. Both platforms provide excellent coverage of common variants across the genome for most racial/ethnic groups based on millions of markers.

GWAS are the standard approach to identification of phenotype-associated common genetic variations, and there are well-accepted approaches to the design, data collection, data cleaning, and data analysis required for these large, complex studies. The approximate cost for the most recent genotyping platforms is about \$250 per subject with a per-SNP cost of less than 1 cent. Although this genotyping cost is reasonable, the large sample size required for these studies results in millions of dollars for a single case-control study. In addition, the computational speed and electronic storage capacity required for the data analyses increase the cost of the studies. The investment in these studies has yielded great insight into complex disease genetics, because the number of robustly associated genetic loci for complex diseases has increased dramatically between 2000 and 2013.

GENE BY ENVIRONMENT INTERACTION

Since both genes and environmental exposures are known to be related to complex traits, performing studies to test both factors in one study design is of great value. Both family-based and case-control designs allow for testing for association while considering both the genetic and environmental exposures and perhaps their interaction. The two major challenges for these studies are statistical power and accurate measurement of exposure. Tests for gene-environment interaction require larger sample sizes than tests for the genetic effect alone.

Much has been made of the difficulties of accurately measuring the environment as an exposure for genetic association studies. Although some environmental factors such as diet are hard to measure accurately and require complex techniques, other exposures such as lifetime cigarette smoking can be measured with relatively high precision. Accurate measures of exposure will greatly enhance the ability of these studies to provide new insights into disease pathogenesis. It will likely be challenging to replicate these types of studies because finding several studies with similar exposures measured in similar ways is often impossible.

EPIGENETICS

Epigenetics is the study of changes in gene transcription that are dependent on the molecules that bind to DNA,

rather than the base-pair sequence of DNA.^{47,48} This includes both heritable changes in gene expression in the progeny of cells or of individuals and stable, long-term alterations in the transcriptional potential of a cell or tissue that are not necessarily heritable. Because epigenetic processes are highly interdependent and regulate gene expression in an age-, state-, cell-, and tissue-dependent manner, collectively these mechanisms constitute a complex system of molecular controls that affects biologic processes and human diseases.

Although the fundamental mechanisms of epigenetics continue to evolve, it is recognized that epigenetic regulation of the genome results in a hierarchy of transcriptional switches that facilitate development and differentiation, normal tissue function, and the ability of the host to respond to stress.^{47,48} There are three primary mechanisms that are known to govern gene expression (DNA methylation, histone modifications, and noncoding RNAs) and may be inherited, independent of the sequence of DNA (Table 3-2 and Fig. 3-2). DNA methylation is controlled by cytosine-methyltransferase, which transfers the methyl group from *S*-adenosylmethionine to the C-5 position of cytosine. Hypermethylation of cytosine-guanosine motifs, particularly at promoter and enhancer sites, silences gene transcription. Alternatively, hypomethylation of these motifs enhances gene transcription. Histones, the building blocks of nucleosomes, undergo numerous posttranslational mod-

ifications (methylation, acetylation, or phosphorylation with > 100 conserved, covalent modifications) that affect chromatin structure and alter gene expression. Noncoding RNAs bind to DNA and interfere with transcription and posttranscriptional regulation of gene expression. In aggregate these mechanisms serve to regulate the transcriptional activity of specific genes, at specific stages of development, and in response to specific forms of endogenous and exogenous stress. Importantly, these mechanisms are conserved in eukaryotic organisms, from yeast to humans.

Table 3-2 Known Epigenetic Mechanisms

DNA methylation—The methyl group is transferred from *S*-adenosylmethionine to the C-5 position of cytosine by a cytosine-methyltransferase. Hypermethylation of CpG motifs, particularly at promoter and enhancer sites, silences gene transcription. Alternatively, hypomethylation of these motifs enhances gene transcription.

Histone modification—Histones, the building blocks of nucleosomes, undergo numerous posttranslational modifications (methylation, acetylation, or phosphorylation with > 100 conserved, covalent modifications) that regulate chromatin structure and gene expression.

Noncoding RNAs—Bind to DNA and interfere with transcription and posttranscriptional regulation of gene expression (e.g., miRNA).

CpG, cytosine-guanosine; miRNA, micro-RNA.

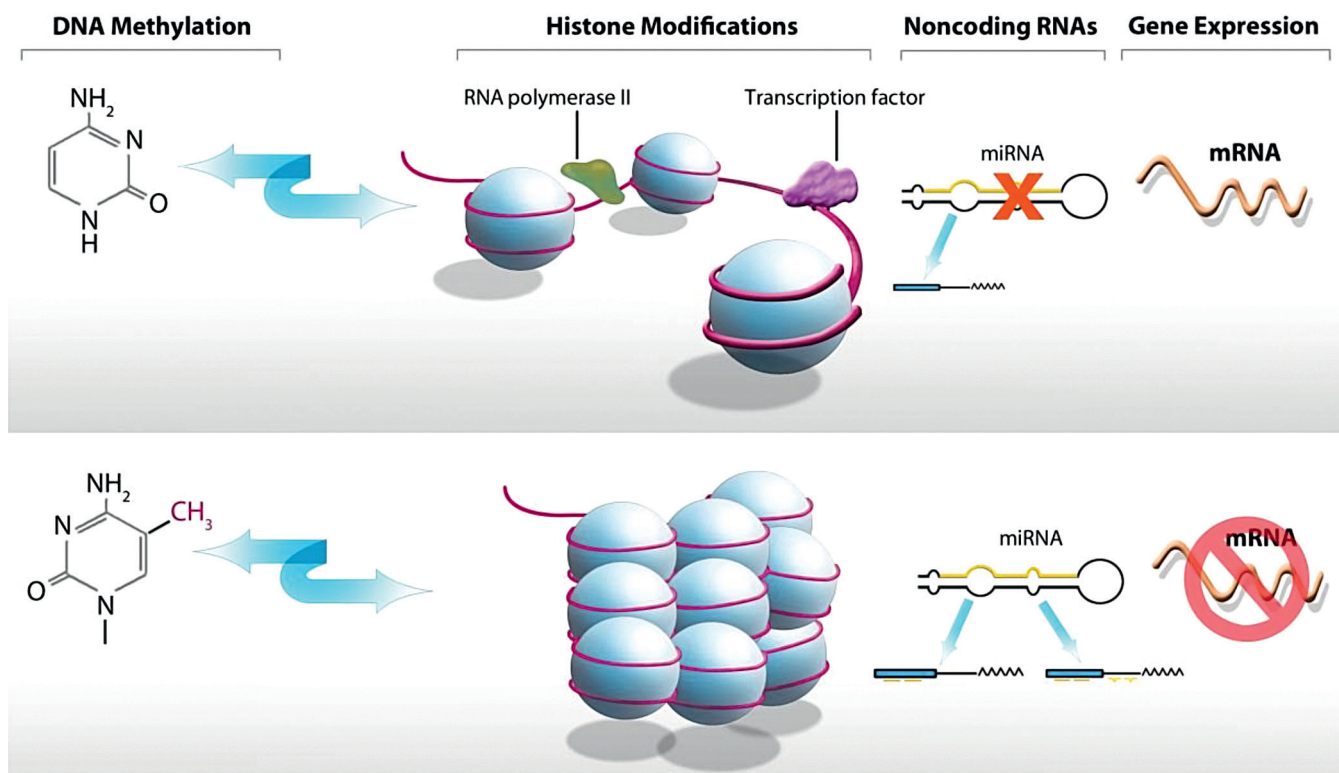


Figure 3-2 Effect of epigenetic marks on gene expression. Epigenetic mechanisms include DNA methylation, modification of histone tails, and generation of non-coding RNAs. Each of these can affect gene expression. The top panel shows how these three epigenetic mechanisms can increase gene expression; the bottom panel shows how these three epigenetic mechanisms can decrease gene expression. Blue arrows indicate crosstalk between DNA methylation and histone modifications. The relationship between histones and DNA methylation is bidirectional; in addition to histones playing a role in the establishment of DNA methylation patterns, DNA methylation is important for maintaining patterns of histone modification through cell division. mRNA, messenger RNA. (From Yang IV, Schwartz DA: Epigenetic control of gene expression in the lung. *Am J Respir Crit Care Med* 183:1295–1301, 2011. Epub 2011;May 21. Reprinted with permission of the American Thoracic Society.)

Epigenetic mechanisms can have profound effects on cellular, tissue, and whole-organism phenotype. Phenotypes that are known to be affected by epigenetic regulation include fundamental mechanisms such as stem cell differentiation⁴⁹ and inactivation of the X chromosome,⁵⁰ carcinogenesis⁵¹ and cancer prognosis,⁵² and even basic aspects of learning and memory.^{53,54} Moreover, genomic imprinting (epigenetic mechanisms that lead to preferential expression of either the maternal or paternal allele) has been shown to be the cause of rare genetic anomalies such as the Prader-Willi, Angelman, Beckwith-Wiedemann, and Silver-Russell syndromes.

Although epigenetic marks (i.e., methylation changes and histone modifications) can be inherited, these potent regulators of transcription can also be modified throughout development⁵¹ and by the environment.⁵⁵ For instance, although monozygotic twins are genetically identical, twin pairs often differ in phenotype (anthropomorphic features as well as disease outcomes). Global and locus-specific differences in DNA methylation and histone acetylation patterns indicate that early in life, monozygotic twins are epigenetically identical, whereas older twin pairs have divergent epigenetic marks that are associated with differences in gene expression.⁵¹ These findings suggest that various life events can alter epigenetic marks that may account, in part, for these phenotypic differences in twin pairs. Moreover, environmental endocrine disruptors (methoxychlor and vinclozolin) have been shown to induce transgenerational effects on male fertility as a result of DNA methylation.⁵⁵ In aggregate, these findings suggest that the epigenome can be reprogrammed, potentially affecting the risk, cause, and treatment of various disease states.

The technology to measure epigenetic changes is continuing to evolve, and, with the advent of methylation sequencing, it will soon be feasible to detect the epigenetic modifications of the entire genome during states of stress and disease. DNA methylation has been traditionally evaluated using methylation-sensitive restriction enzymes in conjunction with Southern blot analysis. However, this labor-intensive approach has been largely replaced by bisulfite modification of DNA that deaminates unmethylated cytosines to uracils without affecting methylated cytosines. The cloned region of DNA is then amplified by polymerase chain reaction and sequenced, with the unmethylated cytosine (which was converted to a uracil) being replaced by a thymine and the methylated cytosine amplifying as a cytosine. Methylation-specific PCR, a method that uses primers specific for methylated or unmethylated genomic DNA, has higher throughput but is unable to detect the exact pattern of DNA methylation. Thus more global approaches, such as methylation-specific digital karyotyping,⁵⁶ array-based methylation hybridization, or methylated DNA immunoprecipitation coupled with either tiling arrays that include most of the human promoters or pyrosequencing are now being used. Functionally relevant methylation changes can be investigated using demethylating agents followed by expression microarrays. However, the expression changes induced by demethylating agents could also be caused by indirect effects of the drug.

High-quality antibodies have been used to detect known modifications in the amino acid residues of histones. Although these antibodies can be used for Western blot

analysis, they are more commonly used in a chromatin immunoprecipitation assay to measure the concentration of specific histone modifications at specific loci. Chromatin immunoprecipitation can be used in conjunction with either microarrays (chromatin immunoprecipitation–chip) or pyrosequencing (chromatin immunoprecipitation–sequencing) to evaluate global changes in histone modifications. As the cost of sequencing decreases, these assays will become increasingly accessible.

Considering the importance of the environment in the development of lung disease, it is somewhat surprising that more attention has not been devoted to epigenetic mechanisms that lead to acute and chronic forms of lung disease. Epigenetic mechanisms (silencing of tumor suppressor genes) and patterns (hypomethylated DNA) have been associated with a number of tumors. In fact, it has been reported that the methylation pattern of six genes is associated with the development of lung cancer.⁵⁷ However, research is just beginning to emerge demonstrating the relevance of epigenetic changes to nonmalignant forms of lung disease. Emerging findings in pulmonary fibrosis suggest that DNA methylation is markedly altered in lung tissue from patients with *idiopathic pulmonary fibrosis* (IPF).⁵⁸ In humans, bronchial biopsy specimens and alveolar macrophages have increased histone acetyltransferase activity and reduced histone deacetylase activity.^{59–61} These consequent increases in histone acetylation enhance gene transcription and are thought to be important in the transcriptional regulation of inflammatory mediators in airway diseases. In fact, steroid-treated asthmatic patients have reduced histone acetyltransferase and increased histone deacetylase activity, presumably resulting in less airway inflammation.⁶¹ In murine studies, methylation has been shown to alter the expression and activity of lineage-specific transcription factors that affect the maturation of naive T cells.^{62–64} These results suggest that a hypomethylated state results in a type 1 T helper phenotype, whereas a hypermethylated state results in a type 2 T helper phenotype. Because cigarette smoke, vitamin supplementation, and other environmental exposures can alter the epigenetic marks along the human genome, studying the importance of changes in DNA methylation, expression of noncoding RNAs, and structural changes in amino acid residues of histones should help us to understand the fundamental mechanisms associated with the etiology and progression of several types of lung disease.

Moreover, the epigenome can be modified by a variety of drugs. Compounds that alter DNA methylation and the amino acid residues on histones are most actively being investigated among patients with cancer. Two DNA methylation inhibitors, 5-aza-deoxycytidine and 5-azacytidine, have recently been approved by the U.S. Food and Drug Administration for the treatment of myelodysplastic syndrome, a preleukemic disease. Compounds that inhibit histone deacetylase have proapoptotic and antitumor properties and are undergoing Phase I trials. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, has been approved for the treatment of T-cell cutaneous lymphoma. Interestingly, trichostatin A, another histone deacetylase inhibitor, has been shown to decrease ovalbumin-induced allergic airway disease in a murine model of asthma.⁶⁵ As we begin to understand the role of epigenetic mechanisms

in the development of lung disease, it will become much more obvious how we can modify these mechanisms therapeutically to reduce the burden of lung disease among our patients.

APPLICATION TO PULMONARY DISEASES

ASTHMA

To date there have been reports of positive associations between variants in over 100 genes and asthma phenotypes (e.g., serum immunoglobulin E levels) based on candidate gene, linkage region, and GWAS.⁶⁶ Although there are hundreds of genetic association studies for asthma, many studies suffer from the methodologic problems discussed earlier, and most of the findings have not been adequately replicated. With regard to many genes “replicated” in additional association studies, careful review finds a substantial number of negative studies for all of them, which is likely due to several factors, including population differences, false-positive initial reports, and inadequately powered replication studies. Space constraints do not allow us to cover all of the potential asthma susceptibility genetic variants identified to date, but we review some genes of particular interest with an emphasis on the methodology used to identify the genetic variants and the biologic pathways implicated.

Several potential asthma susceptibility genes have been identified using a positional-cloning approach.^{25-28,67-71} An example of one gene with substantial additional evidence for relevance to asthma susceptibility is G protein–coupled receptor (*GPR154*, also known as *NPSR1*) on chromosome 7p.²⁸ The investigators provided adequate functional data on *GPR154* by showing not only that the mouse orthologue of *GPR154* (*Grpa*) is up-regulated in murine lung after ovalbumin challenge in sensitized mice, but also that in humans *GPR154* encodes protein isoforms that are produced in distinct patterns by bronchial epithelial cells and smooth muscle cells in asthmatic and healthy individuals.

Since the first bronchial asthma GWAS was published in 2007,¹¹ over 30 GWAS have been published for asthma or asthma-related phenotypes. In that first study, *ORMDL3* (a gene involved in the endoplasmic reticulum found to regulate sphingolipid synthesis) on chromosome 17q21 was identified, and the association finding at 17q21 has been confirmed by others.⁷²⁻⁷⁵ However, many of the subsequent GWAS were underpowered for modest effects and failed to find significant associations that could be replicated. However, a few large GWAS studies^{74,75} have provided strong evidence, via meta-analysis and replication, for variants in a number of genes being associated with asthma. Importantly, four of these loci show evidence for association across European American, African American or African Caribbean, and Latino ancestries: chromosome 17q21, *interleukin-1* (IL-1) receptor-like 1 (*IL1RL1*), thymic stromal lymphopoietin (*TSLP*), and IL-33 (*IL33*). *IL1RL1*, *TSLP*, and *IL33* are all implicated in type 2 T helper cell–mediated immune responses, making them strong biologic candidates for asthma susceptibility.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is characterized by incompletely reversible airflow obstruction and excess mucus production in the airways. In the United States, COPD affects 16 million individuals, is the fourth leading cause of death, and is the only one among the leading causes of death to be increasing in prevalence.⁷⁶ The role of genetic predisposition in the pathogenesis of COPD had been overlooked until recently, and yet there are intriguing features in this disease to suggest gene–environment interactions. First, the Framingham study demonstrated that longitudinal decline in lung function is inherited with a heritability of approximately 20%, which increases substantially when the subjects were stratified according to smoking status.⁷⁷ Environmental exposures such as smoking and pollution have been implicated in the pathogenesis of COPD since the 1960s, yet “only” 10% to 20% of smokers develop COPD symptoms, further indicating that a susceptibility factor may exist in some individuals. Alpha₁-antitrypsin is a prototypical susceptibility gene that is associated with increased rates of COPD development in active smokers. Recent studies have also implicated alpha₁-antitrypsin in the decline in pulmonary function observed in passive smoke exposure and occupational exposures in susceptible individuals with severely or moderately decreased levels. Furthermore, although traditionally emphysema and chronic bronchitis are considered to be clinically distinct chronic obstructive diseases, in practice there is a substantial gray zone between “pure” irreversible airway obstruction (i.e., COPD) and “pure” reversible obstruction (i.e., asthma). Many physicians are therefore now suspecting that asthma and COPD may be sharing common characteristics and genetic background (the so-called Dutch hypothesis). However, the GWAS to date have not supported that hypothesis. GWAS have identified variants in several genes associated with COPD, but the genes do not overlap with the replicated signals found to date for asthma. There may instead be distinct genetic risk factors for COPD–asthma overlap.^{77a} The first GWAS for COPD⁷⁸ identified a region on chromosome 15q25 containing genes in the aminoglycoside phosphotransferase domain containing 1 (*AGPHD1*) and the nicotinic acetylcholine receptors (*CHRNA3/5*), which are also associated with smoking intensity. That study also identified hedgehog-interacting protein gene (*HHIP*), which has been replicated in other studies of COPD^{79,80} and is associated with pulmonary function.⁸¹ Other GWAS have identified family with sequence similarity 13, member A (*FAM13A*)⁷⁹ and a locus on chromosome 19q13⁸²; the functional relevance of these genes in relationship to COPD is not yet understood. Additional insight into the genetics of COPD might come from the genetics of primary ciliary dyskinesia.^{82a}

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute lung injury (ALI) leading to *acute respiratory distress syndrome* (ARDS) is a common complication of systemic inflammation and sepsis, seen in approximately 50% of such patients. The mortality of ARDS remains high at about 30% to 40%, despite recent advances in mechanical ventilation and patient management. The pathogenesis

of ALI/ARDS is thought to derive from the effects of systemic inflammation, cytokine production, and oxidative damage. However, the sporadic (nonfamilial) nature of ARDS hampers genetic analysis of human subjects. Genetic analysis of inbred mouse strains first revealed that ALI susceptibility was strain dependent and therefore may, in part, be genetically determined.⁸³ Human studies identified *angiotensin-converting enzyme (ACE)* as a candidate gene for ARDS susceptibility.⁸⁴ Subsequent animal studies verified the role of ACE in ARDS susceptibility and further showed that ACE2, an ACE isoform that metabolizes the ACE product angiotensin II, is protective against ARDS.⁸⁵ This was the first set of studies to show a link and a mechanism for genetic susceptibility and ARDS pathogenesis. Subsequently, variants in over 25 genes have been found to be associated with either the development or outcome of ALI/ARDS,⁸⁶ and, not surprisingly, these candidate genes are involved in inflammation, innate immunity, oxidative stress, apoptosis, and coagulation. A number of candidate genes, mostly from the inflammation and coagulation pathways, were identified: IL-1 β , IL-6, tissue factor, plasminogen activator inhibitor 1, and chemokine receptors were the most abundantly up-regulated proteins.⁸⁷ Surfactant protein B polymorphisms have also been associated with increased susceptibility to ARDS.⁸⁸ Surfactant protein B has not been used therapeutically in adults with ARDS; however, a recent study in infants and children with ARDS showed significant improvement in survival with a surfactant that contained surfactant protein B.⁸⁹ The only genome-wide association study in ALI that has been published identified a region on chromosome 11 (11q13.3) that contained a cell adhesion gene, *PPFIA1*.⁹⁰ Although the genetic risks for ALI/ARDS are continuing to emerge, attention is beginning to focus on disease prevention by identifying those at risk and using the genetic findings to direct therapy in this severe form of ALI.⁹¹ However, results remain preliminary, and susceptibility testing for ALI/ARDS will require more definitive research findings.

LUNG CANCER

Lung cancer is now the most common cause of cancer-related deaths in the United States, and yet no more than 100 years ago lung cancer was quite rare. The rise in lung cancer incidence demonstrates the effects of changing environmental exposures on human disease. Inhalation of environmental carcinogens causes the vast majority of lung cancer cases. Cigarette smoke dominates this list. Since at least the 1950s, it has been recognized that cigarette smoking causes most lung cancer cases. However, only a minority of smokers develop lung cancer, again suggesting the role of susceptibility in lung cancer pathogenesis. Unfortunately, cigarette smoke contains more than 4000 chemicals, a fact that makes the search for a single susceptibility factor much more difficult. Investigators have focused on specific classes of tobacco compounds that are known carcinogens, such as the polycyclic aromatic hydrocarbons. These are nontoxic in themselves but are metabolized in the body by enzymes such as CYP1A1 into DNA-binding diol-epoxides. Several studies from Japan have shown a significant association of high-activity CYP1A1 variants with the development of lung cancer.⁹² On the other hand, the main

polycyclic aromatic hydrocarbon–detoxifying enzymes are the glutathione S-transferases GSTM1 and GSTP1. Polymorphisms in these enzymes that lead to reduced activity have also been linked to lung cancer susceptibility.⁹³ Variants in other genes known to metabolize inhaled carcinogens (*NAT1*, *NAT2*, *MEH*, *NQO1*, and *MPO*) are reported to be associated with lung cancer.⁹⁴ The carcinogenic effect of cigarette smoke is thought to rely upon DNA binding and mutations of tumor suppressor genes, such as P53. Polycyclic aromatic hydrocarbon and other smoke constituents like acrolein can bind to so-called mutational hotspots of the P53 gene and induce DNA damage.⁹⁵ Accordingly, the ability of the organism to correct and repair DNA damage is closely linked to cancer susceptibility.^{96,97} For example, a recent analysis of a European cohort of 116 patients with lung cancer showed a significant association between SNPs in the DNA repair enzymes XRCCI and BRCA2 and exposure to urban pollution in the susceptibility to cancer.⁹⁸ Other DNA repair genes associated with the development of lung cancer include *ERCC2/XPD*, *ERCC1/XPF*, *XPA*, *XPC*, *ERCC5/XPG*, *OGG1*, *APE*, and *XRCC3*.⁹⁴

Genomic medicine not only is helpful in detecting genes associated with the development of lung cancer, but can also be used to guide therapy⁹⁹ and to determine the prognosis of the patient^{100,101} (Fig. 3-3). Indeed, lung cancers can now be categorized based on their gene expression profile.^{100,102,103} Furthermore, somatic mutations in proto-oncogenes such as *KRAS*, *BRAF*, and *EGFR* have been

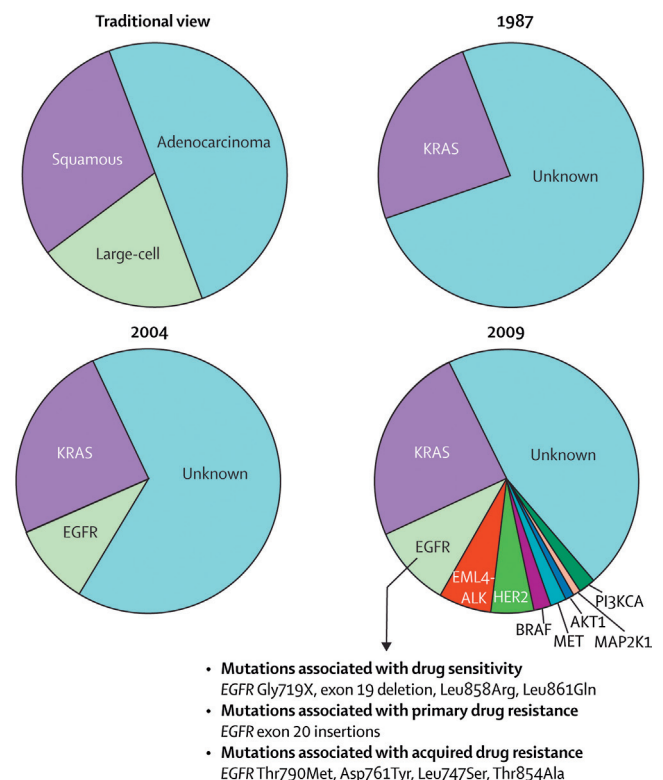


Figure 3-3 Evolution of knowledge in non-small-cell lung cancer. Traditionally, non-small-cell lung cancers have been classified according to histological features. More recently, various driver mutations have been associated with these cancers. The mutations are mutually exclusive, except for those in PIK3CA. (From Pao W, Girard N: New driver mutations in non-small-cell lung cancer. *Lancet Oncol* 12:175-180, 2011.)

identified that have become targets of cancer drugs.^{104,104a,104b} Indeed, the most encouraging reports in lung cancer research were the recent findings that certain non-small cell lung cancers harbor mutations in the *epidermal growth factor receptor* (*EGFR*) gene and gain-of-function tyrosine kinase-activating *ALK* gene rearrangements that predict prognosis and response to therapy.¹⁰⁴ These cell lines become malignant through *EGFR*-induced inhibition of apoptosis but simultaneously become extremely sensitive to *EGFR* tyrosine kinase inhibitors like gefitinib or erlotinib. Similarly, the lung cancers with *ALK* gene rearrangements show improved progression-free survival with the first-in-class *ALK* tyrosine kinase inhibitor, crizotinib.¹⁰⁵ These are impressive accomplishments of genomic medicine that provided a seamless link between the pathogenesis of lung cancer, the prediction of treatment effect based on genetic cancer characteristics, and the successful application of treatment to patients with lung cancer.

FIBROSING IDIOPATHIC INTERSTITIAL PNEUMONIA

Fibrosing *idiopathic interstitial pneumonia* (IIP) refers to a group of lung diseases that are characterized by progressive scarring of the alveolar interstitium that leads to significant morbidity and mortality. IPF is the most common and severe form of fibrosing IIP; 50,000 individuals are newly diagnosed each year in the United States,¹⁰⁶ and patients with IPF have a median survival of 3 years. There is substantial

evidence for a genetic basis for IPF, including familial aggregation confirmed through studies in twins, siblings raised apart, and multigenerational families.^{107,108,108a} Fibrosing IIP has been associated with several pleiotropic genetic disorders.¹⁰⁸ Rare mutations in the *TERT*, *TERC*, *SFTPC*, and *SFTPA2* genes have been associated with familial interstitial pneumonia (defined as two or more family members with IIP) and IPF,¹⁰⁹⁻¹¹⁴ and a common polymorphism in *TERT* has been associated with IPF.¹¹⁵ However, in aggregate, these mutations account for a small proportion of the population attributable risk for development of IPF. Recently a promoter variant in the *MUC5B* gene (rs35705950) has been found to be present in approximately 50% to 60% of individuals with familial or sporadic forms of IPF and is estimated to increase the risk 6-fold for heterozygotes and 20-fold for homozygotes²⁹ (Fig. 3-4). Independent investigators have verified a similar relationship between the *MUC5B* promoter variant (rs35705950) and IPF,¹¹⁶⁻¹¹⁹ and this effect appears to be present, though less pronounced, among patients with idiopathic nonspecific interstitial pneumonia.¹²⁰ Importantly, the *MUC5B* promoter SNP also appears to be both predictive and prognostic in IPF. In the Framingham population (N = 2639), the *MUC5B* promoter SNP is associated with a threefold to sixfold excess risk per allele for radiographic evidence of interstitial lung disease,¹²¹ suggesting that the *MUC5B* promoter SNP could be used to identify individuals with preclinical forms of IPF. Moreover, in two independent cohorts of patients with IPF, the *MUC5B* promoter polymorphism (rs35705950) is associated with a

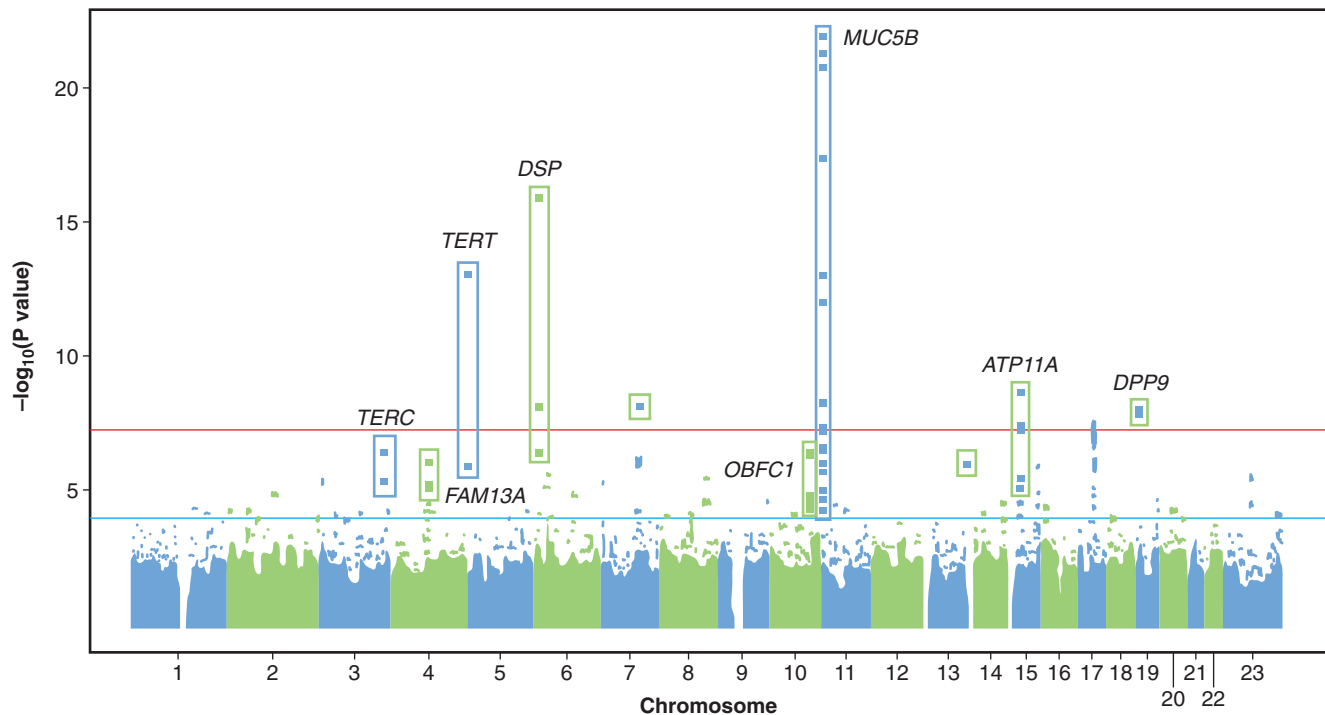


Figure 3-4 Genome-wide association (GWA) studies results for pulmonary fibrosis across 439,828 single nucleotide polymorphisms (SNPs) with 1616 cases and 4683 controls under an additive model. GWA studies have become the standard approach for identification of common sequence alleles associated with complex diseases and are typically conducted in two phases: discovery across the genome and replication of a smaller set of SNPs in independent samples. For the pulmonary fibrosis example, the results of the first discovery phase are shown in this “Manhattan plot.” In the second phase, SNPs above the red line that were genome-wide significant at $P < 5 \times 10^{-8}$ and the SNPs between the red and blue lines (corresponding to $5 \times 10^{-8} < P < 0.0001$) were selected for follow-up in 876 cases and 1890 controls. After considering both phases of the study, seven novel loci for pulmonary fibrosis were identified. (From Fingerlin TE, Murphy E, Zhang W, et al: Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet* 45:613–620, 2013. Epub 2013;April 16. Reprinted with permission from Nature Genetics).

twofold improved survival per allele.¹²² However, the *MUC5B* variant is observed in approximately 19% of unaffected individuals, and approximately one third of individuals with IPF do not have any identifiable genetic risk factors for disease, suggesting that other genetic variants and/or environmental exposures contribute to disease risk alone or in combination with the *MUC5B* variant. A recent genome-wide association study has provided additional understanding of the genetic features of IPF by confirming *TERT* (5p15), *MUC5B* (11p15), and the chromosome 3q26 region near *TERC* and identifying seven novel risk loci.¹¹⁹ The novel loci include *FAM13A* (4q22), *DSP* (6p24), *OBFC1* (10q24), *ATP11A* (13q34), *DPP9* (19p13), and chromosomal regions 7q22 and 15q14-15. Further characterizing these IPF-associated loci will provide important targets for functional studies that will ultimately allow for the development of new prevention and treatment strategies.¹²³

THE PATH FORWARD

Although the Human Genome Project has successfully mapped the human genome and has developed innovative technology for genomic studies, we remain limited in how this information can be used to improve clinical medicine and public health. This limitation arises from the simple fact that genetics is not the sole determinant of health or disease. In fact, although an emerging consensus suggests that many of the complex and prevalent diseases that humans develop as a result of multiple biologically unique gene-gene and gene-environment interactions, even this conceptual framework is limited. The development of disease in humans, environmental and otherwise, is simply far more complex. Environmental exposures affect those that are vulnerable temporally (age), spatially (geographically), and by unique circumstance (comorbid disease, nutritional status, economic status, race, and genetics). Even this paradigm fails to address the complex interaction of endogenous and exogenous risks that ultimately interact to cause disease. Moreover, diseases are not usually single entities; rather, most diseases represent several or many specific pathophysiologic processes that can be fully understood only by focusing on the genetic and environmental contributions to etiology and pathogenesis. Environmental health research and genomic research are logical, even necessary, partners. Ultimately, the discoveries that are made in environmental genomics will lead to better diagnosis, treatment, and prevention of these common, complex human diseases.

Key Points

- Heritability is a measure of the contribution of genetic variation to variation in a phenotype.
- Complex genetic disorders account for the majority of lung diseases and are caused by multiple genetic variations and multiple environmental factors.
- The human genome comprises approximately 3 billion base pairs. There are approximately 12 million single nucleotide polymorphisms in the human genome.
- Linkage analysis is a group of analysis methods to analyze the distribution of DNA markers within

families to determine if there is a relationship between a particular region of the genome and a phenotype of interest.

- Genome-wide association studies have emerged as the most commonly used study design to find disease genes in complex disorders.
- Epigenetics is the study of changes in gene transcription that are dependent on the molecules that bind to DNA rather than on the base pair sequence of DNA. This includes both heritable changes in gene expression and stable, long-term alterations in the transcriptional potential of a cell or tissue that are not necessarily heritable.
- Asthma is a heritable disorder, but the genetics are very complex, with almost every chromosome demonstrating linkage and over 100 genes found to be associated with the development of asthma, which explain less than 10% of the inheritance of this disease.
- COPD has many intriguing features to suggest gene-environment interactions.
- Lung cancer develops in only a minority of smokers, and thus genetic and epigenetic mechanisms need to be considered. Non-small cell lung cancers harbor mutations in the epidermal growth factor receptor and gain-of-function tyrosine kinase-activating *ALK* gene rearrangements that predict prognosis and response to therapy.
- Interstitial lung disease is caused by environmental and genetic factors. Mutations in surfactant protein C and the telomerase genes have been shown to enhance the risk for developing this disorder. A common polymorphism in the promoter of the *MUC5B* gene is strongly associated with the development of familial and sporadic forms of idiopathic pulmonary fibrosis. Recently seven novel loci have been found to be associated with the development of pulmonary fibrosis.

Complete reference list available at *ExpertConsult*.

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RESPIRATORY PHYSIOLOGY

4

VENTILATION, BLOOD FLOW, AND GAS EXCHANGE

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INTRODUCTION

VENTILATION

Lung Volumes
Total and Alveolar Ventilation
Anatomic Dead Space
Physiologic Dead Space
Inequality of Ventilation

BLOOD FLOW

Pressures of the Pulmonary Circulation

Pulmonary Vascular Resistance

Distribution of Pulmonary Blood Flow

Active Control of the Pulmonary Circulation

Damage to Pulmonary Capillaries by High Wall Stresses

Nonrespiratory Functions of the Pulmonary Circulation

BLOOD-GAS TRANSPORT

Oxygen

Carbon Dioxide

GAS EXCHANGE

Causes of Hypoxemia

Oxygen Sensing

INTRODUCTION

This first chapter in the section on respiratory physiology is devoted to the primary function of the lung: gas exchange. In addition, the principles of ventilation and blood flow that underlie gas exchange are reviewed. Although the lung has other functions, such as metabolizing some compounds, filtering unwanted materials from the circulation, and acting as a reservoir for blood, gas exchange is its chief function. Respiratory diseases frequently interfere with ventilation, blood flow, and gas exchange and may ultimately lead to respiratory failure and death.

VENTILATION

The anatomy of the airways and the alveolar region of the lung is discussed in Chapter 1. There we saw that the airways consist of a series of branching tubes that become narrower, shorter, and more numerous as they penetrate deeper into the lung. This process continues down to the terminal bronchioles, which are the smallest airways without alveoli. All these bronchi make up the *conducting airways*. Their function is to channel inspired gas to the gas-exchanging regions of the lung. Because the conducting

airways contain no alveoli and therefore take no part in gas exchange, they constitute the *anatomic dead space*.

Each terminal bronchiole subtends a respiratory unit, or *acinus*. The terminal bronchioles divide into respiratory bronchioles that have occasional alveoli budding from their wall, and these then transition to the alveolar ducts, structures that are completely lined with alveoli. This alveolated region of the lung where gas exchange takes place is known as the *respiratory zone*. The distance from the terminal bronchiole to the most distal alveolus is only approximately 5 mm, but the respiratory zone makes up most of the lung in terms of gas volume (some 2 to 3 L).

The morphologic characteristics of the human airways were greatly clarified by Weibel.¹ He measured the number, length, width, and branching angles of the airways, and he proposed models that, although they are idealized, make pressure-flow and other analyses much more tractable.

The most commonly used Weibel model is the so-called model A, shown in [Figure 4-1](#). Note that the first 16 generations (Z) make up the conducting airways ending in the terminal bronchioles. The next three generations constitute the respiratory bronchioles, in which the degree of alveolation steadily increases. This is called the *transitional zone* because the nonalveolated regions of the respiratory bronchioles do not have a respiratory function. Finally, there are

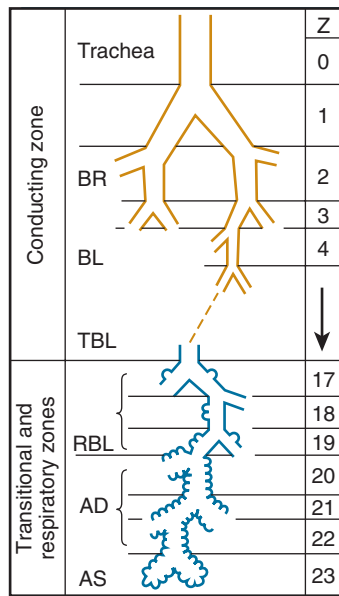


Figure 4-1 Idealization of the human airways according to Weibel's model A. AD, alveolar duct; AS, alveolar sac; BL, bronchiole; BR, bronchus; RBL, respiratory bronchiole; TBL, terminal bronchiole; Z, airway generation. Note that the RBL, AD, and AS make up the transitional and respiratory zones. (Redrawn from Weibel ER: *Morphometry of the human lung*, Berlin, 1963, Springer-Verlag.)

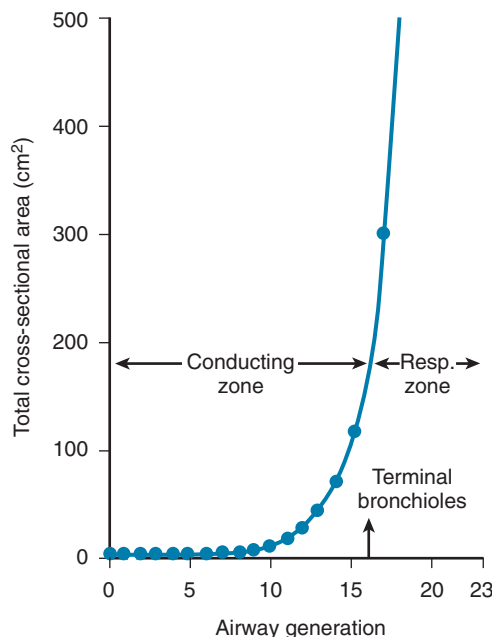


Figure 4-2 Diagram showing the extremely rapid increase in total cross-sectional area of the airways in the respiratory (Resp.) zone as predicted from the Weibel model in Figure 4-1. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

three generations of alveolar ducts and one generation of alveolar sacs. These last four generations constitute the true *respiratory zone*.

Other models of the airways have been proposed.² However, the Weibel model has been of great value to respiratory physiology, and an example of its use is shown in Figure 4-2. Here the model clarifies the nature of gas flow

in all generations of the airways in the lung. Figure 4-2 shows that, if the total cross-sectional area of the airways of each generation is calculated, there is relatively little change in area until we approach generation 16, that is, the terminal bronchioles. However, near this level, the cross-sectional area increases very rapidly. This has led some physiologists to suggest that the shape of the combined airways is similar to a trumpet or even a thumbtack!

The result of this rapid change in area is that the mode of gas flow changes in the region of the terminal bronchioles. Proximal to this point, flow is convective, or “bulk,” that is, similar to the sort of flow that results when beer is poured out of a pitcher. However, when the gas reaches the region approximating the level of the terminal bronchioles, its forward velocity decreases dramatically because of the very sudden increase in cross-sectional area. As a consequence, diffusion begins to take over as the dominant mode of gas transport. Naturally, there is no sharp transition; flow changes gradually from primarily convective to primarily diffusive in the general vicinity of generation 16.

One implication of this change in mode of flow is that many aerosol particles penetrate to the region of the terminal bronchioles by convective flow, but they do not penetrate further because of their large mass and resulting low diffusion rate. Thus sedimentation of these particles is heavy in the region of the terminal respiratory bronchioles. This is one reason why this region of the lung is particularly vulnerable to the effects of particulate air pollutants.

Another implication of this dichotomously branching airway tree is that the greater the number of branch points, the greater the potential for nonuniform distribution of airflow among the distal airways and alveoli. In addition, repeated, possibly minor, differences in flow distribution at each branch point will give rise to spatial correlation of flow; in other words, neighboring regions will tend to have more similar flows than regions located far apart, other factors being equal.

LUNG VOLUMES

Figure 4-3 shows the major divisions of lung volume. *Total lung capacity* is the volume of gas contained in the lungs at maximal inspiration. The *vital capacity* is the volume of gas that can be exhaled by a maximal expiration from total lung capacity. The volume remaining in the lung after maximal expiration is the *residual volume* (RV). *Tidal volume* refers to the normal respiratory volume excursion. The lung volume at the end of a normal expiration is the *functional residual capacity* (FRC). The diagram also indicates the *inspiratory reserve volume* and the *expiratory reserve volume*. These volumes change in characteristic directions with different respiratory diseases, and so their measurement becomes important. Indeed, they have for years formed the basis for diagnosis and monitoring of chronic diseases such as *chronic obstructive pulmonary disease* (COPD) and lung fibrosis (see Chapter 25).

Functional Residual Capacity, Residual Volume, and Total Lung Capacity

These three volumes cannot be measured with a spirometer (a device that measures the volume of air being exhaled or

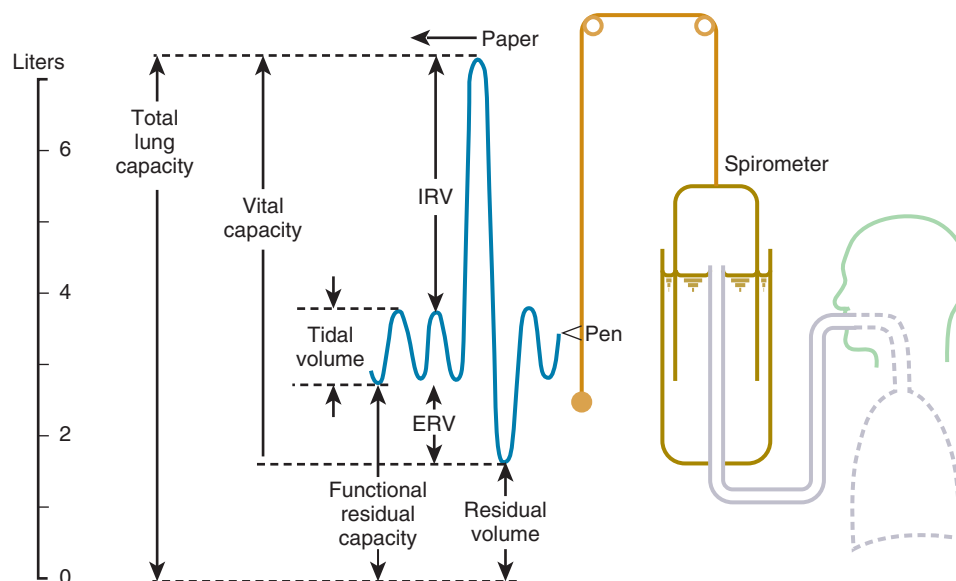


Figure 4-3 Major divisions of lung volumes. Values are illustrative only; there is considerable normal variation. ERV, expiratory reserve volume; IRV, inspiratory reserve volume. (Modified from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

inhaled) because there is no way of knowing the volume remaining in the lung after a maximal expiration (i.e., the RV). However, if any one of these three volumes is measured by an independent method, the other two can be derived by spirometry.

The FRC can be measured conveniently by helium dilution in a closed circuit. The subject is connected to a spirometer of known volume that contains a known concentration of helium (a very insoluble gas) and then rebreathes until the helium concentration in the spirometer and in the lungs is the same. The exhaled carbon dioxide is absorbed with soda lime, and oxygen is added to maintain a constant total volume. After equilibration, the total amount of helium is assumed to be unchanged because so little of it is removed by the blood because of its very low solubility. The FRC can then be derived from the following equation that expresses this conservation of mass principle:

$$C_1 \times V_1 = C_2 \times (V_1 + V_2) \quad [1]$$

where C_1 and C_2 are the helium concentrations before and after equilibration, V_1 is the volume of the spirometer, and V_2 is the volume of the lung. If the subject is switched into the equipment when at FRC, V_2 gives that volume.

Another common way of measuring the FRC is with a body plethysmograph. This is a large airtight box in which the subject sits. At the end of a normal expiration, a shutter closes the mouthpiece, and the subject is asked to make respiratory efforts. As the subject tries to inhale, the gas in the lungs expands, lung volume increases slightly, and the pressure in the box rises slightly because its gas volume decreases. Boyle's law (pressure times volume is constant at constant temperature) can then be used to calculate the change of volume of the plethysmograph. The equation is $P_1V_1 = P_2(V_1 - \Delta V)$, where P_1 and P_2 are the box pressures before and after the inspiratory effort, V_1 is the preinspiratory box volume, and ΔV is the change in the volume of the box (or lung). If mouth pressure is also measured during the respiratory efforts, Boyle's law can also be applied to the

lung and FRC can be derived. The equation here is $P_3V_2 = P_4(V_2 + \Delta V)$, where P_3 and P_4 are the mouth pressures before and after the inspiratory effort, and V_2 is the FRC. Because this is the only unknown (ΔV was measured previously), V_2 can be calculated.

In patients with lung disease the FRC measured by helium dilution may be substantially less than that measured by body plethysmography. The reason is that the body plethysmograph measures the total volume of gas in the lung, including any that is trapped behind closed airways (i.e., unventilated regions that contain gas). By contrast, the helium dilution method measures only ventilated lung regions. In young normal subjects, these volumes are virtually identical, but they may be considerably different in patients with severe lung disease. Also in these patients, regions that are poorly ventilated reduce the overall speed of equilibration of helium, which will lead to volume underestimation if rebreathing is stopped too soon.

TOTAL AND ALVEOLAR VENTILATION

Total Ventilation

Total ventilation, also called minute ventilation, is the total volume of gas exhaled per minute. It is equal to the tidal volume times the respiratory frequency. The volume of inhaled air is slightly greater than the exhaled volume because more oxygen is inhaled than carbon dioxide is exhaled, but the difference is usually less than 1%.

Alveolar ventilation is the amount of fresh inspired air (non-dead space gas) that enters the alveoli per minute and is therefore available for gas exchange. Strictly, the alveolar ventilation is also measured during expiration, but the inhaled and exhaled volumes are almost the same.

Alveolar Ventilation

Because the tidal volume (V_T) is made up of the dead space volume (V_D) and the volume of gas entering (or coming

from) the alveoli (VA), the alveolar ventilation can be measured from the following equations:

$$V_T = V_D + V_A \quad [2]$$

Multiplying by respiratory frequency gives

$$\dot{V}_E = \dot{V}_D + \dot{V}_A \quad [3]$$

where \dot{V}_A is the alveolar ventilation, and \dot{V}_E and \dot{V}_D are the expired total ventilation and dead space ventilation, respectively.

Therefore,

$$\dot{V}_A = \dot{V}_E - \dot{V}_D \quad [4]$$

A difficulty with this method is that the anatomic dead space is not easy to measure, although a value for it can be assumed with little error. One milliliter per pound of body weight is a common assumption. This approximation will overestimate dead space in obese subjects and so should be applied using ideal body weight for height.

Another way of measuring alveolar ventilation in normal subjects is to use the *alveolar ventilation equation*, which expresses mass conservation of carbon dioxide by defining *carbon dioxide production* (\dot{V}_{CO_2}) as the product of *alveolar ventilation* (\dot{V}_A) and *fractional alveolar concentration of carbon dioxide* (F_{ACO_2}). Because concentration is proportional to partial pressure, the relationship can be written as:

$$\dot{V}_{CO_2} = \dot{V}_A \times F_{ACO_2} = \dot{V}_A \times P_{ACO_2} / K \quad [5]$$

This can then be rearranged as follows:

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{ACO_2}} \times K \quad [6]$$

where \dot{V}_{CO_2} is the volume of carbon dioxide exhaled per unit time, P_{ACO_2} is the alveolar PCO_2 , and K is a constant (0.863 when \dot{V}_A is expressed in LBTSP/min, \dot{V}_{CO_2} in mlSTPD/min, and P_{ACO_2} in mm Hg). In patients with normal lungs, the PCO_2 of alveolar gas and that of arterial blood are virtually identical. Therefore the arterial PCO_2 can be used to determine alveolar ventilation from Equation 6. The equation then becomes

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{ACO_2}} \times K \quad [7]$$

This equation is often used in patients with lung disease, but the value then obtained is the “effective” alveolar ventilation. This is not the same as the alveolar ventilation as defined in Equation 4. Because patients with lung disease must increase their total ventilation to overcome the inefficiency of gas exchange caused by ventilation-perfusion inequality just to keep arterial PCO_2 normal, \dot{V}_A from Equation 7 will be less than that from Equation 4.

ANATOMIC DEAD SPACE

The anatomic dead space is the gas volume contained within the conducting airways. The normal value is in the range of 130 to 180 mL and depends on the size and posture of the subject. The value increases slightly with large inspirations because the radial traction exerted on the bronchi by the surrounding lung parenchyma increases their size. Anatomic dead space can be measured by Fowler’s method,³ in which a single breath of oxygen is inhaled

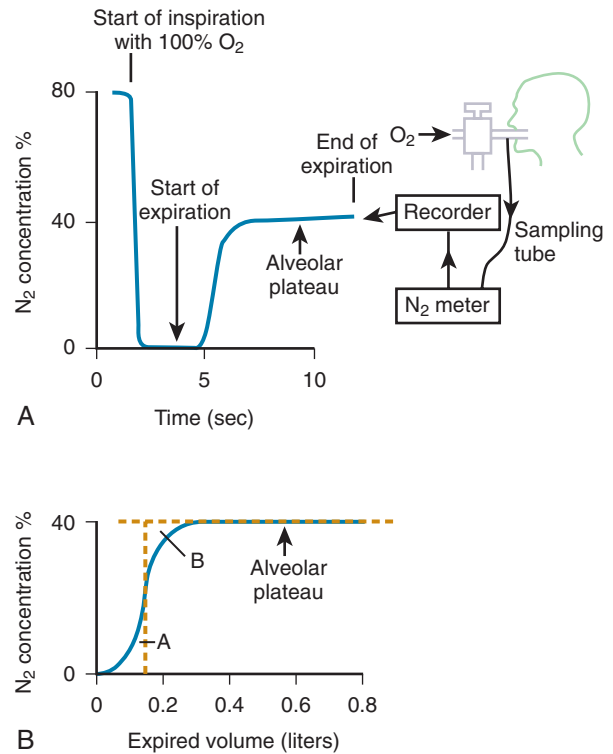


Figure 4-4 Fowler’s method of measuring the anatomic dead space with a rapid N_2 analyzer. A shows that, following a test inspiration of 100% O_2 , the N_2 concentration rises during expiration to an almost level “plateau” representing pure alveolar gas. B, N_2 concentration is plotted against expired volume, and the dead space is the volume up to the vertical dashed line, which makes the areas A and B equal. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

and the concentration of nitrogen in the subsequent expiration is analyzed, as shown in Figure 4-4.

PHYSIOLOGIC DEAD SPACE

Unlike anatomic dead space, which is determined by the anatomy of the airways, physiologic dead space is a functional measurement based on the ability of the lungs to eliminate carbon dioxide. It is defined by the Bohr equation:

$$\frac{V_D}{V_T} = \frac{P_{ACO_2} - P_{ECO_2}}{P_{ACO_2}} \quad [8]$$

where A and E refer to alveolar and mixed expired gas, respectively. In subjects with normal lungs, the PCO_2 of alveolar gas and that of arterial blood are virtually the same, so that the equation is often written

$$\frac{V_D}{V_T} = \frac{P_{ACO_2} - P_{ECO_2}}{P_{aCO_2}} \quad [9]$$

Physiologic dead space includes and is very nearly the same as anatomic dead space when the lung is normal. However, in the presence of ventilation-perfusion inequality (i.e., when the ratio of local ventilation to local blood flow is not everywhere the same), physiologic dead space is increased, chiefly because of the ventilation going to lung units with abnormally high ventilation-perfusion ratios. Indeed, the physiologic dead space is often reported as one of the indices

of the degree of mismatching of ventilation and blood flow within the lung. It is important to understand that, when dead space is expressed as a fraction of tidal volume as in Equation 9, the result is sensitive to tidal volume; for example, a dead space of 150 mL is 30% of a 500-mL tidal volume but only 15% of a 1000-mL tidal volume.

INEQUALITY OF VENTILATION

Not all the alveoli are equally ventilated, even in the normal lung. There are several reasons for this, related both to gravitational (topographic) and to nongravitational influences on gas distribution.

Topographic Inequality

Regional differences in ventilation can be measured by having the patient inspire a radioactive gas such as xenon (^{133}mXe). In one technique the patient inhales a single breath of gas, and its concentration is detected by a radiation camera placed behind the chest. An additional measurement is made after the patient has rebreathed long enough to allow the xenon to equilibrate throughout the different regions of the lungs, thus reflecting regional lung volumes. By comparing the first and the second measurements, the ventilation per unit alveolar volume can be obtained.

Measurements in upright normal subjects show that the ventilation per unit volume of the lung is greatest near the base of the lung and becomes progressively smaller toward the apex. When the subject lies supine, this difference becomes much less, but the ventilation of the lowermost (posterior) lung exceeds that of the uppermost (anterior). In the lateral decubitus position, again, the dependent lung is better ventilated. (These results refer to an inspiration from FRC.)

An explanation of this topographic inequality of ventilation is shown in Figure 4-5A, which depicts conditions at FRC.⁴ The intrapleural pressure is less negative at the bottom than at the top of the lung. This pattern can be attributed to the weight of the lung, which requires a larger pressure below the lung than above it to balance the downward-acting weight forces.⁵ There are two consequences of this lower expanding pressure on the base of the lung. First, the resting volume of the basal alveoli is smaller, as shown by the pressure-volume curve. Second, the change in volume

for a given change in intrapleural pressure is greater because the alveoli are operating on a steeper part of the pressure-volume curve. Thus the ventilation (change in volume per unit resting volume) is greater at the base than the apex. However, if a normal subject makes a small inspiration from RV (rather than from FRC), an interesting change in the distribution of ventilation is seen. The major share of the ventilation goes to the apex of the upright lung, whereas the base is very poorly ventilated. Figure 4-5B shows why a different pattern is seen in this case. Now the intrapleural pressures are less negative, and the pressure at the base of the lung actually exceeds atmospheric pressure. For a small fall in intrapleural pressure, no gas will enter the extreme base of the lung, and only the apex will be ventilated. Thus the normal pattern of uneven ventilation is reversed in this early phase of inhalation.

Hyperpolarized helium and xenon magnetic resonance imaging have been used to measure regional ventilation and give similar results, although there are small differences in results obtained with the two gases for reasons that remain to be determined.^{6,7}

Airway Closure

At RV the compressed region of the lung at the base in Figure 4-5B does not have all its gas squeezed out because small airways, probably in the region of the respiratory bronchioles, close first and trap gas in the distal alveoli. This is known as *airway closure*. In young normal subjects, airways close only at lung volumes below FRC. However, in older normal subjects, the volume at which the basal airways close (*closing volume*) increases with age and may encroach on the FRC. The reason for this increase is that the aging lung loses some of its elastic recoil and the intrapleural pressures therefore become less negative, thus approaching the situation shown in Figure 4-5B. Under these conditions, basal regions of the lung may be ventilated only intermittently, with resulting defective gas exchange. A similar situation frequently develops in patients with COPD in whom lung elastic recoil may be reduced.

Nontopographic Inequality

In addition to the topographic inequality of ventilation caused by gravitational factors (see Fig. 4-5), nongravitational mechanisms also exist. This is proved by the fact that

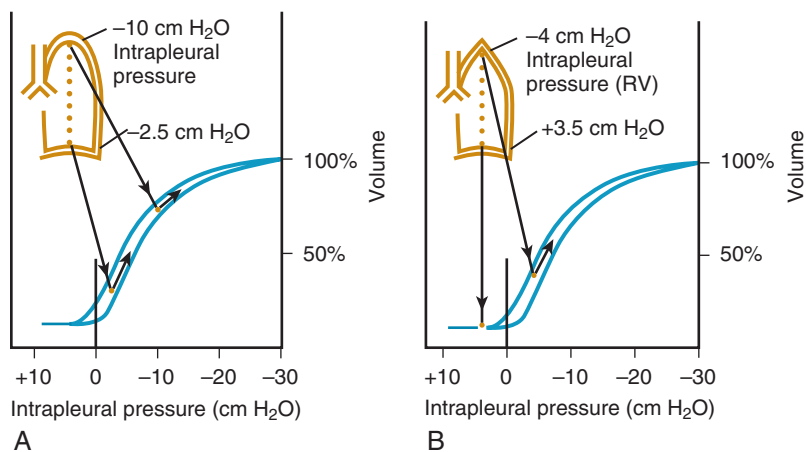


Figure 4-5 The topographic inequality of ventilation down the lung. A, An inspiration from functional residual capacity. B, The situation at very low lung volumes (see text for details). (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

even astronauts in space beyond the reach of gravity show uneven ventilation by both the single-breath and the multi-breath nitrogen washout methods.^{8,9} These methods are described in Chapter 25. Such findings have been confirmed by studies in which inspired gas is labeled by small particles. Such studies show considerable variability in ventilation at a given horizontal level.⁶

Several factors are responsible for uneven ventilation in the distal, smaller regions of the lung. One of these is the existence of uneven time constants.¹⁰ The *time constant* of a region of lung is given by the product of its resistance and compliance (analogous to the time constant in electrical circuits, which is the product of electrical resistance and capacitance). Lung units with different time constants inflate and deflate at different flow rates. Depending on the breathing frequency, a unit with a large time constant does not complete its filling before expiration begins and therefore is poorly ventilated; the faster the frequency, the less time for ventilation. In contrast, a unit with a small time constant, which fills rapidly, may receive a higher proportion of gas from the anatomic dead space, which also reduces its effective alveolar ventilation.

Another cause of uneven ventilation in small lung units is the asymmetry of their structure, which can result in a greater penetration of gas by diffusion into the smaller units than into the larger.¹¹ The resulting somewhat complex behavior is known as diffusion- and convection-dependent inhomogeneity and may play an important role in lung disease.

A further possible reason for uneven ventilation at the level of small lung units is the presence of concentration gradients along the small airways. This is known as *series inequality*. Recall that inspired gas reaches approximately the region of the terminal or respiratory bronchioles by convective flow, but gas flow over the rest of the distance to the alveoli is accomplished principally by diffusion within the airways. If there is abnormal dilatation of an airway, the diffusion process may not be complete within the breathing cycle, and the distal alveoli will be less well ventilated than the proximal alveoli.

BLOOD FLOW

Blood flow is as important for gas exchange as is ventilation. This has not always been appreciated, partly because the process of ventilation is more obvious, especially in the dyspneic patient, and is more accessible to measurement. Much has been learned about the pulmonary circulation in the past few years, especially its metabolic functions. The anatomy and function of the pulmonary circulation is also described in Chapters 1 and 6.

PRESSURES OF THE PULMONARY CIRCULATION

The pressures in the pulmonary circulation are very low compared with those in the systemic circulation, and this feature is responsible for much of its special behavior. The normal pressures in the human pulmonary artery are typically approximately 25 mm Hg systolic, 8 mm Hg diastolic, and 15 mm Hg mean. Normal mean systemic arterial pressure is approximately 100 mm Hg, which is six times higher

than that in the pulmonary circulation. The evolutionary force to keep the pressures in the pulmonary circulation so low is the mechanical vulnerability of the extremely thin blood-gas barrier. Higher pressures in the pulmonary capillaries would cause stress failure of the capillary wall.¹²

Pressure Inside Blood Vessels

Because the pulmonary arterial pressure is so low, hydrostatic effects within the pulmonary circulation are very important. The adult upright human lung is some 30 cm high, giving a hydrostatic difference in pressure of 30 cm blood between the extreme apex and the base, which is equivalent to approximately 23 mm Hg. As a result, there are very substantial differences in flow within the small pulmonary arteries and the capillaries between the top and bottom of the upright lung. This topic is discussed further in the section on the distribution of pulmonary blood flow.

Various techniques have been used to determine the pattern of pressure drop along the pulmonary blood vessels. These include measurement of the transudation pressure on the pleural surface of isolated lung, measurement of the pressure transient resulting from the injection of a slug of low- or high-viscosity blood into the pulmonary artery,¹³ and direct puncture of different-sized vessels along with direct measurement of hydrostatic pressure.¹⁴ The direct puncture measurements indicate that much of the normal pressure drop in the pulmonary circulation probably takes place in the pulmonary capillaries, and that the mean capillary pressure is approximately halfway between that in the pulmonary artery and that in the pulmonary vein (Fig. 4-6). This distribution of the pressure drop is consistent with the main function of the pulmonary circulation, which is to expose as large an area of blood as possible to the alveolar gas.

The distribution of pressure along the pulmonary blood vessels depends on lung volume. At low states of lung inflation, the resistance of the extra-alveolar vessels (see next section) increases, and more pressure drop then takes place across the pulmonary arteries and veins. By contrast, there is evidence that, at very high states of lung inflation, the

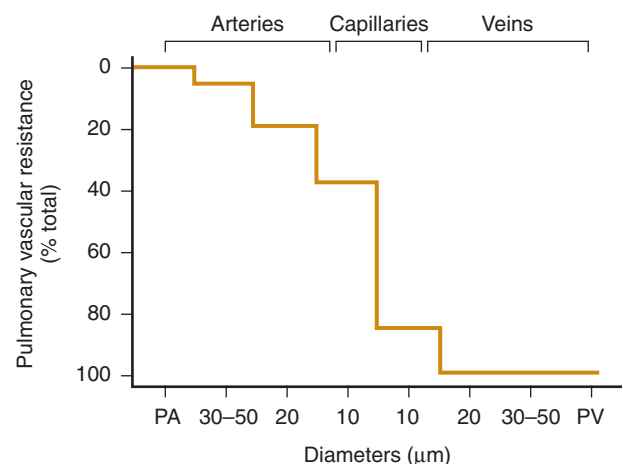


Figure 4-6 Pressure drop along the pulmonary circulation as determined by direct puncture of vessels. PA, pulmonary artery; PV, pulmonary vein. (Redrawn from Bhattacharya J, Nanjo S, Staub NC: Factors affecting lung microvascular pressure. *Ann N Y Acad Sci* 384:107–114, 1982.)

resistance of the capillary bed is increased, and therefore there will be an additional pressure drop in the capillaries.

The pressures in the pulmonary circulation are highly pulsatile; indeed, if we take the normal systolic and diastolic pressures in the main pulmonary artery as 25 and 8 mm Hg, respectively, this represents a much greater proportional change than the systolic-diastolic difference in systemic arteries (120 and 80 mm Hg, respectively). There is good evidence that the pulsatility of pressure, and therefore flow, extends to the pulmonary capillaries.¹⁵

Pressures Outside Blood Vessels

Some pulmonary blood vessels are exposed to alveolar pressure (or very nearly), whereas others are outside the influence of alveolar pressure but are very sensitive to the state of lung inflation. These two types of vessels are known as alveolar and extra-alveolar, respectively (Fig. 4-7).

The alveolar vessels are largely capillaries that course through the alveolar walls. The pressure to which they are exposed is very nearly alveolar pressure. However, it can be shown that, when the lung is expanded from a very low lung volume, this pericapillary pressure falls below alveolar pressure because of surface tension effects in the alveolar lining layer.¹⁶ By contrast, during deflation from high lung volumes, the pericapillary pressure is very close to alveolar pressure.

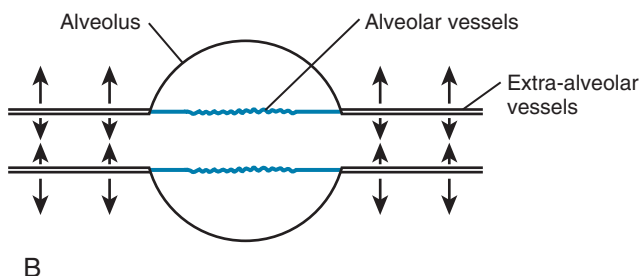
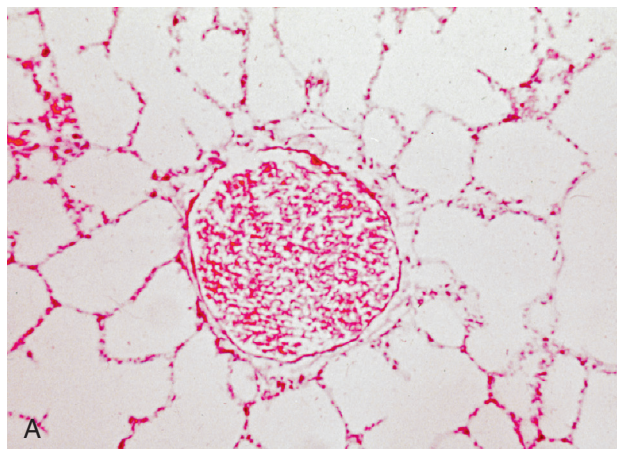


Figure 4-7 **A**, Section of lung showing an extra-alveolar vessel (in this case, a small vein) surrounded by alveoli. Note the potential perivascular space. **B**, Diagram of alveolar and extra-alveolar vessels. The alveolar vessels are mainly the capillaries and are exposed to alveolar pressure. The extra-alveolar vessels have their lumina enlarged by the pull of radial traction (outward-oriented arrows) of the surrounding parenchyma. (Modified from *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

The extra-alveolar vessels are not exposed to alveolar pressure. The caliber of these vessels is determined by the radial traction of the surrounding alveolar walls and therefore depends on lung volume. When the lung inflates, the caliber of these vessels increases; when the lung deflates, their caliber decreases because of the elastic tissue in their walls and also because of a small amount of smooth muscle tone. The important point is that extra-alveolar vessel resistance falls with lung inflation, whereas alveolar vessel (capillary) resistance rises with lung inflation.

The small vessels (of approximately 30 μm diameter) in the corners of the alveolar walls behave in a manner that is intermediate between that of the capillaries and the extra-alveolar vessels. These corner vessels can remain open when the capillaries are closed. Indeed, this is the normal appearance in zone 1 lung¹⁷ (see later section on the distribution of blood flow). However, the shape and attachments of the corner vessels are very different from those of the larger extra-alveolar vessels, and it is unlikely that the pressure outside them varies in the same way when the lung expands.

The extra-alveolar vessels are surrounded by a potential perivascular space, which has an important role in the transport of extravascular fluid in the lung. The lymph vessels run in this space, although lymph can also traverse the space outside lymph vessels. One of the earliest histologic signs of interstitial pulmonary edema is “cuffing” of the perivascular space around the extra-alveolar vessels.^{18,19} A distinction should be drawn between the net pressure (sum of forces per unit area) pulling on the wall of an extra-alveolar vessel on the one hand, and the fluid hydrostatic pressure in the perivascular space on the other. The fluid hydrostatic pressure determines the movement of fluid into this region, and there is evidence that this pressure is very low compared with the hydrostatic pressure in the interstitium of the alveolar wall. As a consequence, fluid that passes from the capillaries into the interstitial space of the alveolar wall eventually finds its way to the perivascular low-pressure region by virtue of the hydrostatic pressure gradient.²⁰

PULMONARY VASCULAR RESISTANCE

Pulmonary vascular resistance is given by the following relationship:

$$\text{Pulmonary vascular resistance} = \frac{\text{Pulmonary arterial pressure} - \text{pulmonary venous pressure}}{\text{Pulmonary blood flow}} \quad [10]$$

Because all three variables vary between systole and diastole, mean values are generally used. This definition is similar to that used for electrical resistance, which is the difference of voltage across a resistor divided by the current. However, whereas the resistance of an electrical resistor is independent of the voltage at both ends and the current, this is not the case for pulmonary vascular resistance. For example, an increase in either pulmonary arterial pressure or pulmonary venous pressure generally results in a decrease in pulmonary vascular resistance because as capillary pressure rises, there is both capillary recruitment and distention (see later). Similarly, if pulmonary blood flow is

increased (e.g., by raising pulmonary arterial pressure), pulmonary vascular resistance usually decreases.

It is important to appreciate that a single number for pulmonary vascular resistance is a very incomplete description of the pressure-flow properties of the pulmonary circulation. However, in practice, pulmonary vascular resistance is often a useful measurement because, although the normal value varies considerably, we often wish to compare the normal lung with a markedly abnormal one in which the vascular resistance is greatly increased.

In practice, pulmonary venous pressure is difficult to measure. Therefore the ratio of pulmonary artery pressure to blood flow is sometimes reported and is termed *total pulmonary vascular resistance*. An estimate of pulmonary venous pressure can be obtained by wedging a catheter in a small pulmonary artery (the so-called pulmonary wedge pressure).

Pressure-Flow Relations

If pulmonary blood flow is measured in an isolated, perfused lung, when pulmonary arterial pressure is raised (while pulmonary venous pressure, alveolar pressure, and lung volume are held constant), then flow increases relatively more than pressure (Fig. 4-8). This figure shows that pulmonary vascular resistance decreases both when pulmonary arterial pressure is raised and when pulmonary venous pressure is raised (other pressures held constant) even as flow now falls. The unifying explanation for reduced resistance in both cases is vascular distention and recruitment due to raised intravascular pressure.

The decreases in pulmonary vascular resistance shown in Figure 4-8 help to limit the work of the right heart under conditions of high pulmonary blood flow. For example, during exercise, both pulmonary arterial and venous pressures rise. Although the normal pulmonary vascular resistance is remarkably small (the normal 5 L/min pulmonary blood flow is associated with an arterial-venous pressure difference of only approximately 10 mm Hg), the resistance falls to even lower values when the pulmonary arterial and venous pressures rise, as during exercise.

Two mechanisms responsible for the fall in pulmonary vascular resistance are *recruitment*, that is, opening up of previously closed blood vessels, and *distention*, that is, increase in caliber of vessels. Figure 4-9A shows experimental data from rapidly frozen dog lung preparations, indicating the importance of recruitment as the pulmonary arterial pressure is raised from low values.²¹ Note that the number of open capillaries per millimeter of length of alveolar wall increased from approximately 25 to over 50 as pulmonary arterial pressure was raised from zero to almost 15 cm H₂O. Figure 4-9B shows data on the importance of distention of pulmonary capillaries.¹⁷ Note that the mean width of the capillaries increased from approximately 3.5 to nearly 7 μ m as the capillary pressure was increased to approximately 50 cm H₂O. Beyond that, there was very little change.

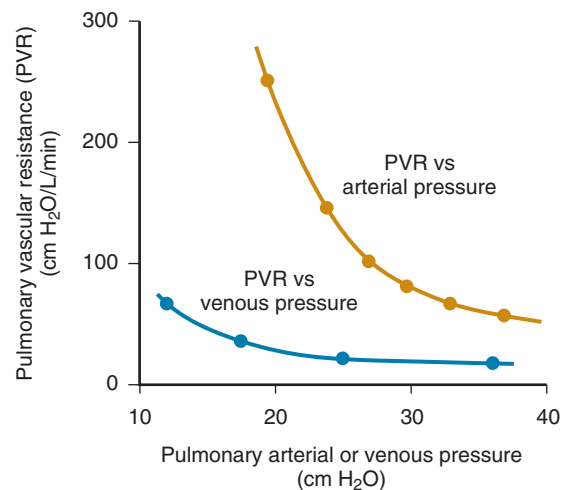


Figure 4-8 The drop in pulmonary vascular resistance (PVR) seen as the pulmonary arterial or venous pressure is raised in a canine lung preparation. When one pressure was changed, the other was held constant. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

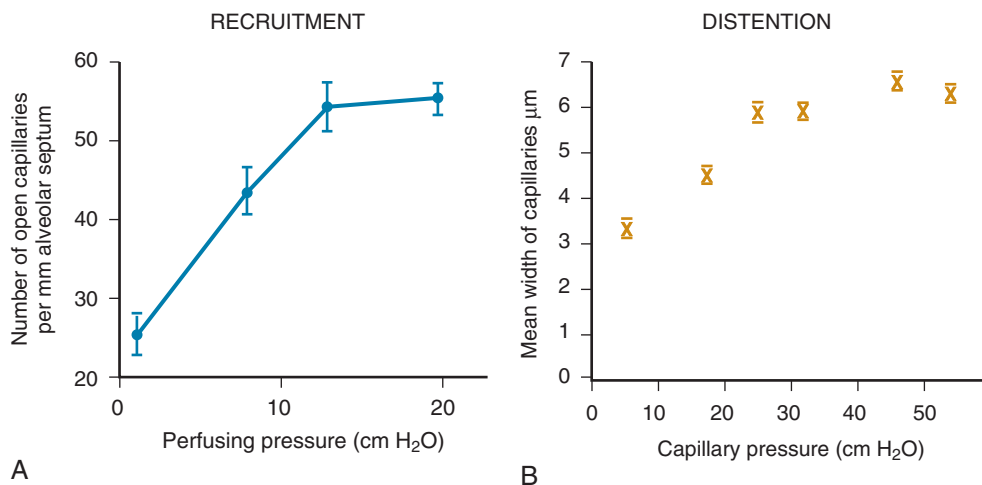


Figure 4-9 **A**, Recruitment of pulmonary capillaries as the pulmonary arterial pressure, the perfusing pressure, is raised. **B**, Distention of pulmonary capillaries as their pressure is increased. (**A**, Redrawn from Warrell DA, Evans JW, Clarke RO, et al: Pattern of filling in the pulmonary capillary bed. *J Appl Physiol* 32:346–356, 1972. **B**, Redrawn from Glazier JB, Hughes JMB, Maloney JE, West JB: Measurements of capillary dimensions and blood volume in rapidly frozen lungs. *J Appl Physiol* 26:65–76, 1969.)

The mechanism of recruitment of pulmonary capillaries is not fully understood. It has been suggested that, as the pulmonary arterial pressure is increased, the critical opening pressures of various arterioles are successively overcome. However, it has been shown that the red blood cell concentration, used as a measure of perfusion, varied within areas supplied by single arterioles indicating that capillaries, not arterioles, probably accounted for the heterogeneous perfusion.²¹ This suggests that vessels are recruited at the capillary rather than the arterial level.

A possible mechanism of recruitment of pulmonary capillaries is based on the stochastic properties of a dense network of numerous interconnected capillary segments.²² It can be shown in such a model that, if each capillary segment requires a very small critical pressure before flow begins and the network contains a distribution of these critical pressures, capillaries can be recruited over a large range of arterial pressures. For example, in a network with as many elements as in the human pulmonary capillary bed,¹ a critical pressure of the order of only 0.02 cm H₂O for the individual segments could result in recruitment over a range of arterial pressures from 0 to 30 cm H₂O. Such a very small critical pressure could result from the intrinsic flow properties of blood, especially when the diameter of the red cells equals that of the capillary lumen.

The mechanism of distention of pulmonary capillaries is apparently simply the bulging of the capillary wall as the transmural pressure of the capillaries is raised. As [Figure 4-9B](#) shows, the mean capillary diameter increases as capillary transmural pressure rises. Probably this behavior is caused by a change in shape of the capillaries rather than actual stretching of the capillary wall. There is evidence that the strength of the wall (at least on the thin side) comes from the type IV collagen in the basement membranes (see later), which has a high tensile strength and Young's modulus (i.e., it is very stiff). It is unlikely that it stretches appreciably when the capillary transmural pressure rises to 30 cm H₂O. However, surface tension forces and also longitudinal tension in the alveolar wall associated with lung inflation tend to flatten the capillaries at low capillary transmural pressures, and this means that their diameter can increase when capillary pressure rises. In photomicrographs of rapidly frozen lung preparations, pulmonary capillaries with very high intracapillary pressures show remarkable bulging.¹⁷

Recruitment and distention also provide mechanisms for increasing both the surface area of the lung microvasculature in contact with alveolar gas and the red cell transit time through the microvasculature, which may facilitate gas exchange.

Effect of Lung Volume

Lung volume has an important influence on pulmonary vascular resistance. [Figure 4-10](#) shows that, as lung volume is increased from very low values, vascular resistance first decreases and then increases. The lung normally operates near the minimal value of vascular resistance, that is, FRC coincides with a low vascular resistance.

The increase in pulmonary vascular resistance at very low lung volume is caused by the decrease in caliber of the extra-alveolar vessels. Because these vessels are normally held open by the radial traction of the surrounding paren-

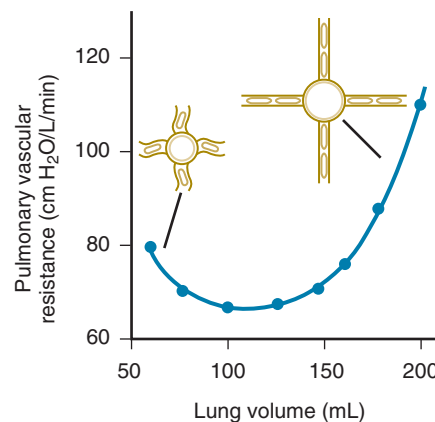


Figure 4-10 Effect of changing lung volume on pulmonary vascular resistance. Data were taken from a canine lung preparation. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

chyma, their caliber is least in the collapsed lung. Under these conditions the presence of elastic tissue and smooth muscle with tone in the wall of these vessels may result in a critical opening pressure of approximately 7 cm H₂O.²³ Also, at low lung volumes, vascular resistance is extremely sensitive to vasoconstrictor drugs, such as serotonin, which cause contraction of vascular smooth muscle.²⁴

Another factor that may contribute to the high pulmonary vascular resistance at low states of lung inflation is folding and distortion of pulmonary capillaries.^{25,26} However, the possible importance of distortion of the pulmonary capillaries as a cause of the increase of vascular resistance at low lung volumes is still uncertain.

At high states of lung inflation, the increase in pulmonary vascular resistance is probably caused by narrowing of the pulmonary capillaries. An analogy is a piece of thin rubber tubing that narrows considerably when it is stretched across its diameter. This distortion increases the resistance to fluid moving through it. Direct measurements on rapidly frozen dog lungs show that the mean width of the capillaries is greatly decreased at high states of lung inflation.¹⁷

In considering the effects of lung inflation, a distinction should be made between “positive” and “negative” pressure inflation. The results shown in [Figure 4-10](#) were found with negative-pressure inflation, that is, when the lung was expanded by reducing pleural pressure and the relationship between pulmonary arterial and alveolar pressures was held constant. If positive-pressure inflation is used (i.e., alveolar pressure is increased with respect to pulmonary arterial pressure), pulmonary vascular resistance increases even more at high states of lung inflation. The reason is that lung inflation is then associated with a decrease in the transmural pressure of the capillaries and they are, in effect, squashed by the increased alveolar pressure. This is actually the case in normal subjects, for example, during inhalation to total lung capacity. Although alveolar pressure remains at atmospheric pressure at the end of inspiration (glottis open), pulmonary arterial and venous pressures fall along with intrapleural pressure. Thus the net result is to decrease the transmural pressure across the pulmonary capillaries, and this is an additional contributing factor in the increase of pulmonary vascular resistance.

Other Factors Affecting Pulmonary Vascular Resistance

Various drugs affect pulmonary vascular resistance. In some instances, the effects depend on the species of animal. However, in general, serotonin, histamine, and norepinephrine cause contraction of pulmonary vascular smooth muscle and increase vascular resistance. These drugs are particularly effective as vasoconstrictors when the lung volume is small and the radial traction of surrounding parenchyma on the extra-alveolar vessels is weak. Drugs that often relax smooth muscle in the pulmonary circulation include acetylcholine and isoproterenol. However, normal pulmonary blood vessels have little resting tone, so the degree of potential relaxation is small.

The autonomic nervous system exercises a weak control on the pulmonary circulation. There is evidence that increased sympathetic tone can cause vasoconstriction and stiffening of the walls of the larger pulmonary arteries. Both α - and β -adrenergic receptors are present.²⁷ Increased parasympathetic activity has a weak vasodilator action. As already indicated, any changes of vascular smooth muscle tone are much more effective at low states of lung inflation (when the extra-alveolar vessels are narrowed) or in the fetal state (when the amount of smooth muscle present is much greater than in the adult).

Pulmonary edema increases vascular resistance by a mechanism that is poorly understood. It may be that there are different mechanisms, depending on the type and stage of edema. Interstitial pulmonary edema causes marked cuffing of the perivascular spaces of the extra-alveolar vessels. Presumably this increases their vascular resistance,²⁸ because, as already indicated, these vessels rely on the radial traction of the surrounding parenchyma to hold them expanded. In addition, however, it may be that edema in the interstitium of the alveolar wall encroaches on the pulmonary capillaries to some extent, thus increasing their vascular resistance.²⁹ Pulmonary edema results in reduced ventilation of the most affected regions. This (see [gas exchange](#) section) reduces their local alveolar P_{O_2} , and this in turn may stimulate what is known as hypoxic pulmonary vasoconstriction. This is discussed in a later section and in Chapter 6.

DISTRIBUTION OF PULMONARY BLOOD FLOW

Just as for ventilation, blood flow is not partitioned equally to all alveoli, even in the normal lung. Both gravitational (topographic) and nongravitational factors affect the distribution of blood flow.

Normal Distribution

The topographic distribution of pulmonary blood flow can conveniently be measured using radioactive materials. In one technique, ^{133}mXe is dissolved in saline and injected into a peripheral vein. When the xenon reaches the pulmonary capillaries, it evolves into the alveolar gas because of its low blood solubility. The resulting distribution of radioactivity within the lung can be measured using a gamma camera or similar device and reflects the regional distribution of blood flow. Subsequently the distribution of alveolar volume is obtained by having the subject rebreathe radioactive

xenon to equilibrium. By combining the two measurements, the blood flow per unit alveolar volume of the lung can be obtained. The distribution of blood flow can also be measured with radioactive albumin macroaggregates and with a variety of other radioactive gases, including ^{15}O -labeled carbon dioxide and ^{13}N . Functional magnetic resonance imaging of the lung has been used to assess distribution of pulmonary blood flow.³⁰ This noninvasive technique does not expose subjects to radioactivity; therefore it can be used repetitively and shows great promise for the future.

In the normal upright human lung, pulmonary blood flow decreases approximately linearly with distance up the lung, reaching very low values at the apex.³¹ However, if the subject lies supine, apical and basal blood flow become the same, and now blood flow is less in the anterior (uppermost) than posterior (lowermost) regions of the lung. Thus blood flow distribution is highly dependent on gravitational effects. During exercise in the upright position, both apical and basal blood flow rates increase and the relative differences are reduced.

The factors responsible for the uneven topographic distribution of blood flow can be studied conveniently in isolated lung preparations. These studies show that, in the presence of normal vascular pressures, blood flow decreases approximately linearly up the lung³² as it does in intact humans. However, if the pulmonary arterial pressure is reduced, blood flows only up to the level at which pulmonary arterial equals alveolar pressures; above this point, no flow can be detected. If venous pressure is raised, the distribution of blood flow may become more uniform in the region of the lung below the point at which pulmonary venous equals alveolar pressure.

Three-Zone Model for the Distribution of Blood Flow

Figure 4-11 shows a simple model for understanding the factors responsible for the topographic inequality of blood

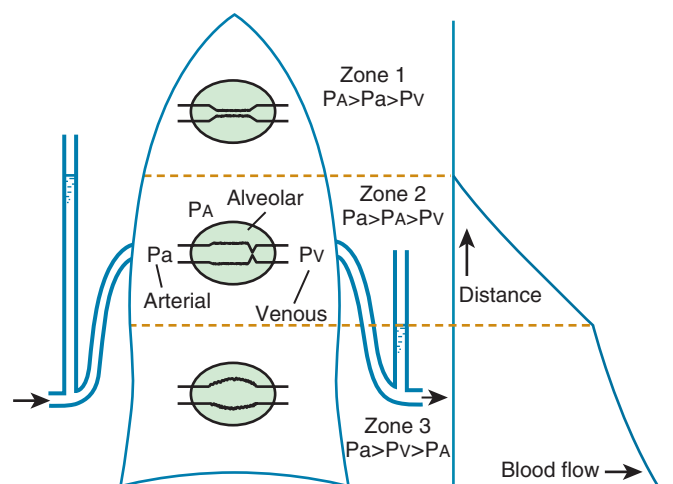


Figure 4-11 Three-zone model designed to account for the uneven topographic distribution of blood flow in the lung. Pa, pulmonary arterial pressure; PA, pulmonary alveolar pressure; PV, pulmonary venous pressure. (Redrawn from West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung: relation to vascular and alveolar pressures. *J Appl Physiol* 19:713–724, 1964.)

flow in the lung.³² The lung is divided into three zones according to the relative magnitudes of the pulmonary arterial, alveolar, and venous pressures.

Zone 1 is that region of the lung above the level at which pulmonary arterial equals alveolar pressures; in other words, in this region, alveolar pressure exceeds arterial pressure. Measurements in isolated lungs show that there is no blood flow in zone 1, the explanation being that the collapsible capillaries close because the pressure outside exceeds the pressure inside. Micrographs of rapidly frozen lung from zone 1 show that the capillaries have collapsed, although occasionally trapped red blood cells can be seen within them.¹⁷

The vertical level of blood flow can be influenced by the surface tension of the alveolar lining layer, as discussed earlier. If measurements are made on a lung immediately after it is inflated from a near-collapsed state, blood flow reaches 3 or 4 cm above the level at which pulmonary arterial and alveolar pressures are equal.¹⁶ This can be explained by the reduced surface tension, which lowers the pericapillary hydrostatic pressure.

Zone 2 is that part of the lung in which pulmonary arterial pressure exceeds alveolar pressure, but alveolar pressure exceeds venous pressure. Here the vessels behave like Starling resistors,³³ that is, as collapsible tubes surrounded by a pressure chamber. Under these conditions, flow is determined by the difference between arterial and alveolar pressures, rather than by the expected arterial-venous pressure difference. One way of looking at this is that the thin wall of the vessel offers no resistance to the collapsing pressure, so the pressure inside the tube at the downstream end is equal to chamber pressure. Thus the pressure difference responsible for flow is perfusion minus chamber pressure. This behavior has been variously referred to as the water-fall³³ or sluice³⁴ effect and can be demonstrated in rubber-tube models on the laboratory bench. The increase in blood flow down zone 2 can be explained by the hydrostatic increase in pulmonary arterial pressure down the zone, whereas the alveolar pressure remains constant. Thus the pressure difference determining flow increases linearly with distance.

Zone 3 is that part of the lung in which venous pressure exceeds alveolar pressure. Radioactive gas measurements show that blood flow increases as one measures vertically down this zone, although, in some preparations at least, the rate of increase is apparently less than found in zone 2. Because the pressure difference responsible for flow is arterial minus venous pressure and because these two pressures increase similarly with distance down the zone, the increase in blood flow is not explained by changes in perfusing pressure. Instead, blood flow increases down this zone because vascular resistance falls with distance down the zone, likely because of progressive distention (confirmed histologically¹⁷) from the increasing transmural pressure (intravascular pressure increasing down the zone while alveolar pressure is constant). However, resistance may also be reduced by recruitment of capillaries.

The Effect of Lung Volume on the Distribution of Blood Flow—Zone 4

In spite of its simplicity, the three-zone model of [Figure 4-11](#), based on the effects of pulmonary arterial, alveolar,

and venous pressures, accounts for many of the distributions seen in the normal lung. However, other factors play a role; one of these is lung volume. For example, under most circumstances, a zone of reduced blood flow, known as zone 4, is seen in the lowermost region of the upright human lung.³⁵ This zone becomes smaller as lung volume is increased, but careful measurements indicate that a small area of reduced blood flow is present at total lung capacity at the lung base. As lung volume is reduced, this region of reduced blood flow extends further and further up the lung, so that at FRC, blood flow decreases in the bottom half of the lung. At RV the zone of reduced blood flow extends all the way up the lung, so that blood flow at the apex exceeds that at the base.³⁵

These patterns cannot be explained by the interactions of the pulmonary arterial, venous, and alveolar pressures as in [Figure 4-11](#). Instead, we have to take into account the contribution of the extra-alveolar vessels. As pointed out previously (see [Fig. 4-10](#)), the caliber of these vessels is determined by the degree of lung inflation; as lung volume is reduced, the vessels narrow. In the upright human lung, the alveoli are less well expanded at the base than at the apex because of distortion of the elastic lung caused by its weight (see [Fig. 4-5](#)). As a result the extra-alveolar vessels are relatively narrow at the base, and their increased contribution to pulmonary vascular resistance results in the presence of a zone of reduced blood flow in that region. As overall lung volume is reduced, the contribution of the extra-alveolar vessels to the distribution of blood flow increases, and zone 4 extends further up the lung. At residual volume the caliber of the extra-alveolar vessels is so small that they completely dominate the picture and determine the distribution of blood flow.

Vasoactive drugs and interstitial edema can modify the contribution of extra-alveolar vessels to pulmonary vascular resistance. For example, the role of the extra-alveolar vessels can be exaggerated by injecting vasoconstrictor drugs such as serotonin.³⁶ Under these conditions, zone 4 extends even further up the lung. The opposite effect is seen if a vasodilator drug such as isoproterenol is infused into the pulmonary circulation. With interstitial edema, the contribution of the extra-alveolar vessels increases, because the edema creates a cuff of fluid around the vessels and thereby narrows them. This is thought to be the cause of the increased pulmonary vascular resistance seen at the base of the human lung in conditions of interstitial pulmonary edema,²⁸ in which the distribution of blood flow often becomes inverted (e.g., in chronic mitral stenosis).³⁷ Under these conditions the blood flow to the apex of the upright lung consistently exceeds the flow to the basal regions. However, the effects of interstitial edema on blood flow distribution are still not fully understood.

Other Factors Affecting the Distribution of Blood Flow

Because the topographic distribution of blood flow in the normal lung can be attributed to gravity, it is not surprising that, during increased acceleration, the distribution of blood flow becomes more uneven.³⁸ For example, during exposure to +3g acceleration, that is, three times the normal acceleration experienced by someone in the upright posture,

the upper half of the lung is completely unperfused. The amount of unperfused lung is approximately proportional to the g level.

By contrast, in astronauts during sustained microgravity in space, the distribution of blood flow becomes more uniform.³⁹ Because it is not possible to use radioactive gases in this environment, the inequality of blood flow has been determined indirectly from the size of the cardiogenic oscillations for PCO_2 . Cardiogenic oscillations are fluctuations in the concentrations of gases such as oxygen, carbon dioxide, and nitrogen during a single expiration. They have the same frequency as heart rate and are considered to be caused by differential rates of emptying of different parts of the lung due to contraction and dilatation of the heart exerting direct pressure on nearby but not distant lung parenchyma. For oscillations to be detected, these differentially emptying regions must also have different alveolar PO_2 and PCO_2 values, and this happens when blood flow and ventilation are not uniformly distributed throughout the lung. Microgravity almost abolishes cardiogenic oscillations, implying greater uniformity in the distribution of blood flow and/or ventilation in the absence of gravity. Interestingly, because these oscillations can still be seen, albeit to a much smaller extent than on earth, some inequality remains, indicating that gravity-independent mechanisms are also present.

Although gravity is a major factor determining the uneven distribution of blood flow in the upright human lung, it is now clear that nongravitational factors also play an important role. There are several possible mechanisms. One is that there may be regional differences of vascular conductance, with some regions of the pulmonary vasculature having an intrinsically higher vascular resistance than others. This has been shown to be the case in isolated dog lungs,⁴⁰ and there is some evidence for higher blood flows in the dorsal-caudal than the ventral regions of the lung in both intact dogs and horses. Another possible factor is a difference in blood flow between the central and peripheral regions of the lung,⁴¹ although this finding is controversial. Some measurements show differences in blood flow along the acinus, with the more distal regions of the acinus being less well perfused than the proximal regions.^{42,43} Finally, as pointed out earlier, because of the complexity of the pulmonary circulation at the alveolar level, including the very large number of capillary segments, it is likely that there is inequality of blood flow at this level. Reference has already been made to the possibility of recruitment of pulmonary capillaries based on the stochastic properties of a dense network of numerous interconnected capillary segments.²² There is also work suggesting that the distribution of pulmonary blood flow in small vessels may follow a fractal pattern.⁴⁴ The term *fractal* describes a branching pattern of both structure (blood vessels) and function (blood flow) that repeats itself with each generation. This means that any subsection of the vascular tree exhibits the same branching pattern as the entire tree. Were a picture of such a subsection to be enlarged, it would overlap and match the pattern of the whole tree. Just as mentioned for ventilation earlier, repeated branching of blood vessels has implications for how blood flow is distributed independently of gravitational influences. The greater the number of branch points, the greater the likely inequality of perfusion among alveoli. This implies that the finer the spatial resolution of the

method used to assess flow distribution, the greater the amount of inequality likely to be detected.

Abnormal Patterns of Blood Flow

The normal distribution of pulmonary blood flow is frequently altered by lung and heart disease. Localized lung disease, such as fibrosis and cyst formation, usually causes a local reduction of flow. The same is true of pulmonary embolism, in which the local reduction in blood flow, as determined from a perfusion scan, is usually coupled with normal ventilation, and this pattern provides important diagnostic information. Bronchial carcinoma may reduce regional blood flow, and occasionally a small hilar lesion can cause a marked reduction of blood flow to one lung, presumably through compression of the main pulmonary artery. Generalized lung diseases, such as COPD and bronchial asthma, also frequently cause patchy inequality of blood flow. Sometimes, asthmatic patients whose disease is thought to be fairly well controlled show marked impairment of blood flow in some lung regions.

Heart disease frequently alters the distribution of blood flow, as might be expected from the factors responsible for the normal distribution (see Fig. 4-11). For example, patients with pulmonary hypertension or increased blood flow through left-to-right shunts usually show a more uniform distribution of blood flow.⁴⁵ Diseases in which pulmonary arterial pressure is reduced, such as tetralogy of Fallot with oligemic lungs, are associated with reduced perfusion of the lung apices. Increased pulmonary venous pressure, as in mitral stenosis, initially causes a more uniform distribution than normal. However, in advanced disease, an inversion of the normal distribution of blood flow is frequently seen, with more perfusion to the upper than to the lower zones. The mechanism for this shift is not fully understood, but, as indicated earlier, perivascular edema causing an increased vascular resistance of the extra-alveolar vessels is thought to be a factor.

ACTIVE CONTROL OF THE PULMONARY CIRCULATION

The distribution of pulmonary blood flow and the pressure-flow relations of the pulmonary circulation are normally dominated by the passive effects of the hydrostatic pressure gradient described earlier. Thus the roles of gravity, of variation in vascular lengths and diameters, and of recruitment and distention can account for much of the behavior of the normal circulation. The normal adult pulmonary circulation has a limited amount of smooth muscle in the walls of the vessels, and active control of vascular tone is weak. However, in some conditions, there is an increase in the amount of smooth muscle. This is the case in the fetal lung, in long-term residence at high altitude, and in prolonged pulmonary hypertension. In these situations the tone of the vascular smooth muscle plays a more significant role. However, some active control of the circulation is seen in the normal lung.

Hypoxic Pulmonary Vasoconstriction

In a region of a lung with alveolar hypoxia, vascular smooth muscle contracts and raises local vascular resistance, which may reduce blood flow. The precise mechanism of such

hypoxic pulmonary vasoconstriction is still not known, but, because it can be observed in excised isolated lungs, it clearly does not depend on central nervous system connections. Furthermore, excised segments of pulmonary artery can be shown to constrict if their environment is made hypoxic, so it appears to be a local action of the hypoxia on the artery itself. It is also known that it is the PO_2 of the alveolar gas, not of the pulmonary arterial blood, that chiefly determines the response.⁴⁶ This can be proved by perfusing a lung with blood with a high PO_2 while keeping the alveolar PO_2 low; under these conditions the vasoconstrictive response is still seen.

The mechanisms of hypoxic pulmonary vasoconstriction are still not fully understood. Studies indicate that voltage-gated potassium channels in the smooth muscle cells are involved, leading to increased intracellular calcium ion concentrations.⁴⁷⁻⁵⁰ There may be roles for vasoactive substances generated by the endothelial cell. More details are covered in Chapter 6.

Endothelium-derived vasoactive substances play a role. Nitric oxide (NO) is an endothelium-derived relaxing factor for blood vessels. It is formed from L-arginine and is a final common pathway for a variety of biologic processes. NO activates soluble guanylate cyclase, which leads to smooth muscle relaxation by the synthesis of cyclic guanosine monophosphate. Inhibitors of NO synthesis augment hypoxic pulmonary vasoconstriction in animal preparations, and inhaled NO reduces hypoxic pulmonary vasoconstriction in humans.⁵¹ The required inhaled concentration of NO is extremely low (approximately 20 parts per million), and the gas is very toxic at high concentrations. The effects of NO on ventilation-perfusion matching (see later) and arterial PO_2 in patients with lung disease depends on whether vasodilatation increases perfusion of well-ventilated regions of the lung or not.⁵²

Vasoconstrictor peptides, known as endothelins and released by pulmonary vascular endothelial cells, may participate as well.⁵³ Their role in normal physiologic processes and disease is still being evaluated, but endothelin antagonists have become important therapeutic agents in pulmonary arterial hypertension.

The stimulus-response curve of hypoxic pulmonary vasoconstriction is very nonlinear (Fig. 4-12). When the alveolar PO_2 is altered in the region above 100 mm Hg, little change in vascular resistance is seen. However, when the alveolar PO_2 is reduced to approximately 70 mm Hg, vasoconstriction begins, and, at a very low PO_2 approaching that of mixed venous blood, the local blood flow may be almost abolished. The data shown in Figure 4-12 are from anesthetized cats.⁵⁴ However, there are species differences in the stimulus-response curves. For example, in the coatimundi (a small South American mammal), there is an almost linear reduction of blood flow between alveolar PO_2 values of 150 and 40 mm Hg.⁵⁵ The preparation in which these measurements were made had the additional advantages that the chest was closed and the measurements were made in a very small region of lung. These conditions probably give the best information on the role of the phenomenon in the local regulation of blood flow.

The major site of the vasoconstriction is in the small pulmonary arteries.⁵⁶ In the normal human lung the small arteries have a meager amount of smooth muscle, which

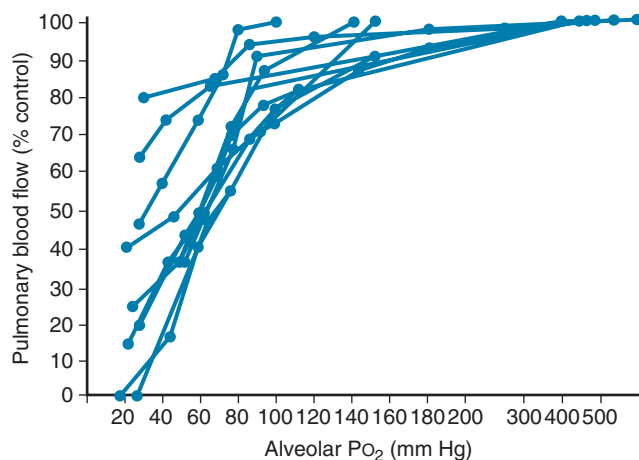


Figure 4-12 Stimulus-response curves of hypoxic pulmonary vasoconstriction. Pulmonary blood flow is shown in relation to alveolar PO_2 in feline lung preparations. (Redrawn from Barer GR, Howard P, Shaw JW: Stimulus-response curves for the pulmonary vascular bed to hypoxia and hypercapnia. *J Physiol [Lond]* 211:139-155, 1970.)

may be uneven in its distribution. This may explain why, even in global alveolar hypoxia (e.g., at high altitude), vasoconstriction is nonetheless uneven. For example, alveolar hypoxia nearly doubles the dispersion of transit times through the pulmonary circulation of a lobe of dog lung,⁵⁷ and the distribution of India ink particles injected into the pulmonary circulation during alveolar hypoxia is more uneven than during normoxia.⁵⁸ This uneven vasoconstriction probably plays a role in the mechanism of high-altitude pulmonary edema⁵⁹ (see later).

Hypoxic pulmonary vasoconstriction has the effect of directing blood flow away from hypoxic regions of lung, which is beneficial to gas exchange. Other things being equal, this reduces the amount of ventilation-perfusion inequality in a diseased lung and limits the depression of the arterial PO_2 . An example of this is seen in patients with asthma when they are treated with certain bronchodilators. These sometimes reduce arterial PO_2 as a result of an increase in blood flow to poorly ventilated areas.^{60,61} In patients with severe COPD with elevated pulmonary arterial pressure, prolonged nocturnal treatment with oxygen has been shown to reduce the degree of pulmonary hypertension and to improve the prognosis in these patients. The mechanism is presumably gradual inhibition by hyperoxia of increased smooth muscle tone originally caused by the hypoxia. The reduction in pulmonary hypertension in turn reduces afterload on the right ventricle.

Residence at high altitude results in hypoxic pulmonary vasoconstriction, both in newcomers and in permanent residents. The increase in pulmonary arterial pressure is especially marked during exercise. If 100% oxygen is given to normal subjects after they have been exposed to hypoxia for as little as 2 weeks, the pulmonary arterial pressure does not immediately return to the normal level.⁶² This suggests that hypoxia has already induced some structural change in the pulmonary vessels and new experiments show changes in ion channels controlling smooth muscle contraction in pulmonary vessels that depend on HIF-1 α .^{62a} There is considerable variation in the response of pulmonary arterial pressure to alveolar hypoxia, leading some investigators to divide people into “responders” and “nonresponders.”

Probably the most important role for hypoxic pulmonary vasoconstriction is in the perinatal period. During fetal life, when the lungs do not undertake gas exchange, pulmonary vascular resistance is very high, partly because of hypoxic vasoconstriction, and only some 15% of the cardiac output flows through the lungs. The rest bypasses the lungs via the ductus arteriosus. The vasoconstriction is particularly effective because of the abundance of smooth muscle in the pulmonary arteries. At birth, when the first few breaths oxygenate the alveoli, the vascular resistance falls dramatically because of relaxation of vascular smooth muscle, and pulmonary blood flow increases enormously. In this situation the release of hypoxic vasoconstriction is critical in the transition from placental to air breathing, and it is this situation that is presumably responsible for the evolutionary pressure to maintain the phenomenon.

Other Physiologic Substances Affecting the Pulmonary Circulation

Many peptides and other substances can potentially alter the tone of muscular pulmonary blood vessels, although the roles of these substances under physiologic conditions are still being clarified.⁶³ They include angiotensin II, bradykinin, vasopressin, atrial natriuretic peptide, endothelin, somatostatin, products of both the cyclooxygenase and lipoxygenase arms of the arachidonic acid cascade, and calcitonin gene-related peptide. Some substances show species differences, and some evoke either vasoconstriction or vasodilation, depending on their concentration. Biogenic amines such as acetylcholine, histamine, serotonin, and norepinephrine also affect pulmonary vascular smooth muscle.

DAMAGE TO PULMONARY CAPILLARIES BY HIGH WALL STRESSES

The blood-gas barrier has a basic dilemma. On the one hand, the barrier has to be extremely thin to allow efficient gas exchange by passive diffusion. On the other hand, the blood-gas barrier must be immensely strong because of the large mechanical stresses that develop in the capillary wall when the pressure in the capillaries rises or when the wall is stretched by inflating the lung to high volumes. There is evidence that the blood-gas barrier is just strong enough to withstand the highest stresses to which it is normally subjected. Unusually high capillary pressures or lung volumes result in ultrastructural damage or "stress failure" of the capillary wall, leading to a high-permeability type of pulmonary edema, or even pulmonary hemorrhage.

When the capillary transmural pressure is raised in animal preparations, disruption of the capillary endothelium, alveolar epithelium, or sometimes all layers of the capillary wall is seen. In the rabbit lung the first changes are seen at a transmural pressure of approximately 24 mm Hg, and the frequency of breaks increases as the pressure is raised.⁶⁴ Although at first sight these capillary pressures seem to be very high, there is now good evidence that the capillary pressure rises to the mid-30s (mm Hg) in the normal lung during heavy exercise.⁶⁵ This is largely secondary to the increase in left ventricular filling pressure.⁶⁶

It can be shown that, at these increased capillary transmural pressures, the "hoop" or circumferential stresses in

the capillary wall become extremely high. Indeed, they approach the breaking stress of collagen. The main reason for the very high stresses is the extreme thinness of the wall, which, in the human lung, is less than 0.3 μm in some places. It is now believed that the strength of the blood-gas barrier on the thin side comes from type IV collagen in the basement membranes. The thickness of the type IV collagen layer is only approximately 50 nm.

Stress failure is the mechanism of several clinical conditions characterized by high-permeability pulmonary edema or hemorrhage.⁶⁷ Neurogenic pulmonary edema has been shown to be associated with very high capillary pressures, the edema is of the high-permeability type, and ultrastructural damage to the capillaries has been demonstrated, consistent with stress failure. High-altitude pulmonary edema is apparently caused by uneven hypoxic pulmonary vasoconstriction (referred to earlier), which allows some of the capillaries to be exposed to high pressure.⁶⁸ Again, the edema is of the high-permeability type, and typical ultrastructural changes in the capillaries have been demonstrated in animal preparations.⁶⁹

A particularly interesting condition is seen in racehorses, which can suffer bleeding into the lungs while galloping. This is very common and is caused by the extremely high pulmonary capillary pressures, which approach 100 mm Hg. Direct evidence of stress failure of pulmonary capillaries has been shown in these animals.⁷⁰ In fact, there is evidence that elite human athletes develop some ultrastructural changes in their blood-gas barrier during extreme exercise because significantly higher concentrations of red blood cells, total protein, and leukotriene B₄ are seen in their bronchoalveolar lavage fluid than in sedentary controls.⁷¹ This only happens at extremely high levels of exercise.⁷² A similar group of athletes who exercised at submaximal levels for 1 hour showed no changes in the bronchoalveolar lavage fluid.⁷³

Overinflation of the lung is known to increase the permeability of pulmonary capillaries. Stress failure is apparently the mechanism because it has been shown that, for the same capillary transmural pressure, the frequency of capillary wall damage is greatly increased at high lung volumes.⁷⁴ This is because some of the increased tension in the alveolar wall associated with lung inflation is transmitted to the capillary wall. This may be important in ventilator-induced lung injury. Finally, conditions in which the basement membrane of the capillary wall is damaged are associated with alveolar bleeding.

NONRESPIRATORY FUNCTIONS OF THE PULMONARY CIRCULATION

Although the primary purpose of the pulmonary circulation is to provide the lung with mixed venous blood so that oxygen can be added and carbon dioxide removed, the pulmonary circulation has other functions, particularly those of metabolism.

A number of vasoactive substances are metabolized by the lung.⁷⁵ Because it is the only organ whose microcirculation receives the whole cardiac output, the lung is uniquely situated to modify blood-borne substances. Indeed, a substantial fraction of all the vascular endothelial cells in the body is located in the lung.

The only known example of biologic activation by passage through the pulmonary circulation is the conversion of the relatively inactive polypeptide angiotensin I to the potent vasoconstrictor angiotensin II.⁷⁶ The latter is up to 50 times more active than its precursor but is unaffected by passage through the lung. The conversion of angiotensin I is catalyzed by an enzyme, angiotensin I-converting enzyme, which is located in small pits (caveolae intracellulares) in the surface of the capillary endothelial cells.

A number of vasoactive substances are completely or partially inactivated during passage through the lung. Bradykinin is largely inactivated (up to 80%), and the enzyme responsible is angiotensin I-converting enzyme. The lung is the major site of inactivation of serotonin (5-hydroxytryptamine), not by enzymatic degradation, but by an uptake and storage process. Some of the serotonin may be transferred to platelets in the lung or stored in some other way and released during anaphylaxis. The prostaglandins E_1 , E_2 , and $F_{2\alpha}$ are also inactivated in the lung. Norepinephrine is also taken up by the lung to some extent (up to 30%). Histamine appears not to be affected by the intact lung.⁷⁵

Some vasoactive materials pass through the lung without significant gain or loss of activity. These include epinephrine, prostaglandins A_1 and A_2 , angiotensin II, and vasopressin (also called antidiuretic hormone).

Several vasoactive substances are normally synthesized or stored within the lung but may be released into the circulation in pathologic conditions. For example, in anaphylaxis, or during an asthma attack, histamine, bradykinin, prostaglandins, and “slow-reacting substance” are discharged into the circulation. Other conditions in which the lung may release potent chemicals include pulmonary embolism (see Chapter 57) and alveolar hypoxia.

There is also evidence that the lung plays a role in the clotting mechanism of blood under normal and abnormal conditions. For example, in the interstitium, there are large numbers of mast cells containing heparin. In addition, the lung is able to secrete special immunoglobulins, particularly immunoglobulin A, in bronchial mucus, which contribute to its defenses against infection. The synthesis of phospholipids such as dipalmitoylphosphatidylcholine, a component of pulmonary surfactant (see Chapter 8), is an important function of alveolar type II cells that prevents lung collapse. Surfactant turnover is rapid, and, if the blood flow to a region of lung is obstructed (e.g., by an embolus), surfactant may become locally depleted with consequent atelectasis. Protein synthesis is also significant because collagen and elastin form the structural framework of the lung. Under abnormal conditions, proteases are apparently liberated from leukocytes or macrophages in the lung, causing breakdown of proteins and possibly emphysema (see Chapter 43). Another important activity is carbohydrate metabolism, especially the elaboration of the mucins and proteoglycans of bronchial mucus (see Chapter 10).

In addition to its metabolic functions, the lung has other functions apart from its primary gas-exchanging role. One is to act as a reservoir for blood. As stated previously, the lung has a remarkable ability to reduce its pulmonary vascular resistance through the mechanisms of recruitment and distention as vascular pressures are raised. The same mechanisms allow the lung to increase its blood volume

with relatively small rises in pulmonary arterial or venous pressures. Such changes can be seen, for example, when a subject lies down after standing and blood drains from the legs into the lung.

Another function of the lung is to filter blood. Small intravascular thrombi are removed from the circulation before they can reach the brain or other vital organs. There is also evidence that many white blood cells are sequestered by the lung, although the significance of this is not clear.

BLOOD-GAS TRANSPORT

The partial pressure of a gas is an important concept in any discussion of gas exchange, as described later the section on gas exchange. The partial pressure of a gas (P) is found by multiplying its concentration by the total pressure. For example, the PO_2 in dry room air at sea level is 159 mm Hg (0.209×760 mm Hg), where oxygen is 20.9% of room air and barometric pressure is 760 mm Hg. However, the relationship between oxygen concentration and PO_2 in blood is not linear and is commonly described by a oxygen dissociation curve. Similar considerations apply to carbon dioxide in blood. The physiologic factors that determine the oxygen and carbon dioxide dissociation curves are considered later.

OXYGEN

Oxygen is carried in the blood in two forms. A small amount is dissolved, but by far the most important component is in combination with hemoglobin.

Dissolved oxygen plays a small role in oxygen transport because the solubility of oxygen is so low (0.003 mL O_2 /100 mL blood/mm Hg). Thus normal arterial blood with a PO_2 of approximately 100 mm Hg contains only 0.3 mL of dissolved oxygen per 100 mL, whereas approximately 20 mL is combined with hemoglobin.

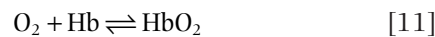
Dissolved oxygen can become important under some conditions. The most common is when a patient is given 100% oxygen to breathe. This typically raises the alveolar PO_2 to over 600 mm Hg, with the result that, if the lungs are normal, the dissolved oxygen may increase from 0.3 to approximately 2 mL/100 mL blood. This dissolved oxygen then becomes a significant proportion of the normal arterial-venous oxygen concentration difference of approximately 5 mL O_2 /100 mL blood.

Hemoglobin consists of heme, an iron-porphyrin compound, and a protein (globin) that has four polypeptide chains. There are two types of chains, α and β , and differences in their amino acid sequences give rise to different types of human hemoglobin. The newborn infant has predominantly hemoglobin F (fetal), which is gradually replaced over the first year or so of postnatal life. The abnormal hemoglobin, hemoglobin S (sickle), has a reduced affinity for oxygen, and, in addition, the deoxygenated form tends to crystallize within the red cell. This causes the cell shape to change from biconcave to sickle, and the result is an increased fragility and likelihood of thrombus formation. Many abnormal hemoglobins with altered oxygen affinities have been described.

Methemoglobin is formed when the ferrous ion of normal hemoglobin A is oxidized to the ferric form, often as a result of exposure to various drugs and chemicals, including nitrites, sulfonamides, and acetanilide. In one form of hereditary methemoglobinemia, there is a deficiency of the enzyme cytochrome *b5* reductase within the red cell. Methemoglobin is not useful for carrying oxygen; in addition, it increases the oxygen affinity of the remaining hemoglobin, thus impairing the unloading of oxygen to the tissues.

Cyanosis refers to the blue color of skin and mucous membranes when the hemoglobin is desaturated. It is not a reliable sign of hypoxemia; if hypoxemia is suspected, the arterial PO_2 should be measured. Cyanosis depends on the amount of reduced hemoglobin present and therefore is often marked in patients with polycythemia but is difficult to detect in the presence of anemia.

Blood is able to transport large amounts of oxygen because that molecule forms an easily reversible combination with hemoglobin (Hb) to give oxyhemoglobin (HbO_2):



The relationship between the partial pressure of oxygen and the number of binding sites of the hemoglobin that have oxygen attached is known as the *oxygen dissociation curve* (Fig. 4-13). Each gram of pure hemoglobin can combine with 1.39 mL of oxygen and, in normal blood with 15 g Hb/100 mL, the *oxygen capacity* (reached when all the binding sites are full) is 1.39×15 , or approximately 20.8 mL O_2 /100 mL of blood. The total *oxygen concentration* of a sample of blood (expressed as mL O_2 /100 mL of blood), which includes the oxygen combined with hemoglobin and the dissolved oxygen, is given by

$$\text{O}_2 \text{ concentration} = (1.39 \times \text{Hb}) \times \frac{\% \text{ saturation}}{100} + (0.003 \times \text{PO}_2) \quad [12]$$

where Hb is the hemoglobin concentration.

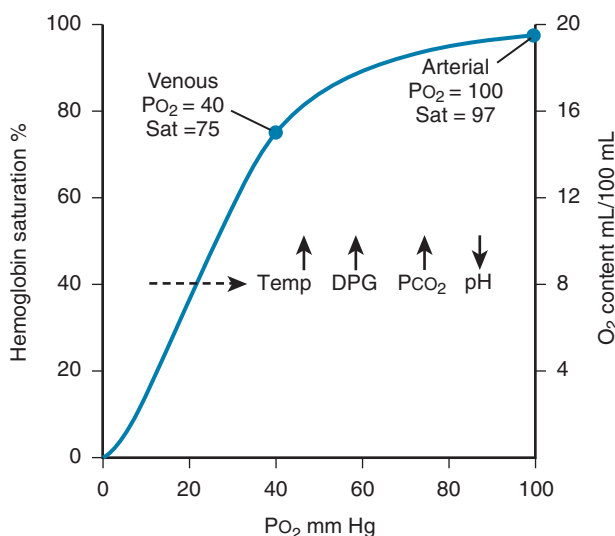


Figure 4-13 Oxygen dissociation curve showing typical values for arterial and mixed venous blood. The curve is shifted to the right by increases of temperature, PCO_2 , 2,3-diphosphoglycerate (DPG), and H^+ concentration. Sat, saturation. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

The characteristic shape of the oxygen dissociation curve has several advantages. The fact that the upper portion is almost flat means that a fall of 20 to 30 mm Hg in arterial PO_2 in a healthy subject with an initially normal value (e.g., approximately 100 mm Hg) causes only a minor reduction in arterial oxygen concentration. However, this also means that noninvasive monitoring of oxygen saturation by pulse oximetry will often fail to indicate substantial falls in arterial PO_2 . Another consequence of the flat upper part of the curve is that the diffusive loading of oxygen in the pulmonary capillary is hastened. This results from the large partial pressure difference between alveolar gas and capillary blood that continues to exist even when most of the oxygen has been loaded. The steep lower part of the oxygen dissociation curve means that considerable amounts of oxygen can be unloaded to the peripheral tissues with only a relatively small drop in capillary PO_2 . This maintains a large partial pressure difference between the blood and the tissues, which assists in the diffusion process. A useful measure of the position of the dissociation curve is the PO_2 for 50% oxygen saturation; this is known as the P_{50} . The normal value for human blood is approximately 27 mm Hg.

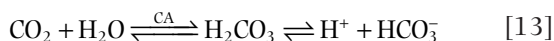
Various factors affect the position of the oxygen dissociation curve (see Fig. 4-13). It is shifted to the right by an increase of temperature, hydrogen ion concentration, PCO_2 , and concentration of 2,3-diphosphoglycerate (2,3-DPG) in the red cell. A rightward shift indicates that the affinity of oxygen for hemoglobin is reduced. Most of the effect of the increased PCO_2 in reducing the oxygen affinity is due to the increased H^+ concentration. This is called the *Bohr effect*, and one consequence is that, as peripheral blood loads carbon dioxide, the unloading of oxygen is assisted. A rightward shift is also caused by 2,3-DPG, an end product of red cell metabolism.^{77,78} The concentration of 2,3-DPG can be increased in the setting of chronic hypoxia. The concentration of 2,3-DPG falls in stored blood, which can lead to blood with a high affinity for oxygen but with difficulty releasing oxygen to the tissues.

Small amounts of carbon monoxide in the blood increase the affinity of the remaining oxygen for hemoglobin and therefore cause a leftward shift of the dissociation curve. As a result, the unloading of oxygen in the peripheral tissue is hampered. In addition, of course, the oxygen concentration of the blood is reduced because some of the hemoglobin is bound to carbon monoxide. This is particularly dangerous because arterial chemoreceptors respond to decreases in PO_2 and not content, so the usual physiologic responses to hypoxemia may be absent.

CARBON DIOXIDE

Carbon dioxide is transported in the blood in three forms: dissolved (approximately 5% of the total), as bicarbonate (approximately 90%), and in combination with proteins as carbamino compounds (approximately 5%). Because carbon dioxide is some 24 times more soluble than oxygen in blood, dissolved carbon dioxide plays a much more significant role in its carriage compared to oxygen. For example, approximately 10% of the carbon dioxide that evolves into the alveolar gas from the mixed venous blood comes from the dissolved form.

Bicarbonate is formed in blood by the following hydration reaction:



The hydration of carbon dioxide to carbonic acid (and vice versa) is catalyzed by the enzyme carbonic anhydrase (CA), which is present in high concentrations in the red cells but is absent from the plasma (some carbonic anhydrase is apparently located on the surface of the endothelial cells of the pulmonary capillaries). Because the majority of the carbonic anhydrase is in the red cell, carbon dioxide is mostly hydrated there, and bicarbonate ion moves out of the red cell to be replaced by chloride ions to maintain electrical neutrality (chloride shift). Some of the hydrogen ions formed in the red cell are bound to hemoglobin, and, because reduced hemoglobin is a better proton acceptor than the oxygenated form, deoxygenated blood can carry more carbon dioxide for a given PCO_2 than oxygenated blood can (Fig. 4-14). This is known as the *Haldane effect*.

Carbamino compounds are formed when carbon dioxide combines with the terminal amine groups of blood proteins. The most important protein is the globin of hemoglobin. Reduced hemoglobin can bind more carbon dioxide than oxygenated hemoglobin, so the unloading of oxygen in peripheral capillaries facilitates the loading of carbon dioxide, whereas oxygenation has the opposite effect.

The carbon dioxide dissociation curve describing the relationship between PCO_2 and total carbon dioxide concentration is shown in Figure 4-14. Note that the curve is much more linear in its working range than the oxygen dissociation curve (see Fig. 4-13) and also that, as we have seen, the lower the saturation of hemoglobin with oxygen, the larger the carbon dioxide concentration for a given PCO_2 .

The transport of carbon dioxide by the blood plays an important role in the acid-base status of the body. This topic is discussed at length in Chapter 7.

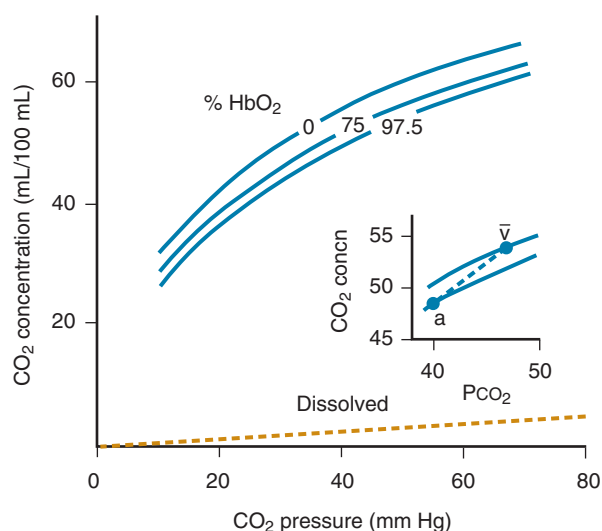


Figure 4-14 Carbon dioxide dissociation curves for blood of different oxygen saturations (HbO_2). Inset, The “physiologic curve” between arterial (a) and mixed venous (\bar{v}) blood. concn, concentration. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

GAS EXCHANGE

The primary function of the lungs is gas exchange, that is, to allow oxygen to move from the air into the blood and to allow carbon dioxide to move out. It is now established that movement of gas across the blood-gas interface is by simple passive diffusion—that is, by random (brownian) motion at a rate determined by temperature. Diffusion results in net transfer of molecules from an area of high to an area of low partial pressure, and active transport is not required. The structure of the lung is well suited to this mechanism of gas exchange. The blood-gas barrier is extremely thin (only $0.3 \mu\text{m}$ over much of its extent), and its area is between 50 and 100 m^2 . Because Fick’s law of diffusion states that the amount of gas that moves across a tissue sheet is proportional to its area and inversely proportional to its thickness, the blood-gas barrier is ideal for its gas-exchanging function.

An important concept in any discussion of gas exchange is partial pressure. As described earlier in “Blood-Gas Transport,” the partial pressure of a gas is the product of its concentration and the total pressure. For example, $\text{PO}_2 = 0.209 \times 760 \text{ mm Hg} = 159 \text{ mm Hg}$ in dry air with 20.9% oxygen at sea level, where the barometric pressure is 760 mm Hg. When air is inhaled into the upper airway, it is warmed and saturated with water vapor. The water vapor pressure at 37°C is 47 mm Hg. Under these conditions the total dry gas pressure is only $760 - 47 = 713 \text{ mm Hg}$. The PO_2 of moist inspired air is therefore $(20.9/100) \times 713 = 149 \text{ mm Hg}$. In general, the relationship between the partial pressure (P) and fractional concentration (F) of a gas when water vapor is present is given by $P_x = F_x (P_b - P_{\text{H}_2\text{O}})$, where P_b stands for barometric pressure and x refers to the species of gas.

Figure 4-15 shows an overview of the oxygen cascade from the air that we breathe to the tissues where it is utilized. The solid line marked “perfect” represents an ideal situation that does not actually exist but does make a useful backdrop for purposes of discussion. One of the first surprises is that, by the time the oxygen has reached the alveoli, its partial pressure has fallen from approximately 150 mm Hg to 100 mm Hg. The reason for this decline is

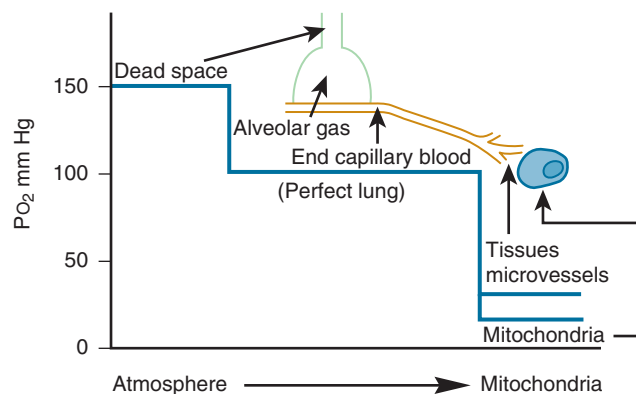


Figure 4-15 Scheme of the oxygen partial pressures from air to tissues. This shows a hypothetically perfect situation. (Redrawn from West JB: *Ventilation/blood flow and gas exchange*, ed 5, Oxford, 1990, Blackwell Scientific.)

that the PO_2 in the alveolar gas is determined by a balance between two factors. On the one hand, we have the essentially continuous addition of oxygen by the process of alveolar ventilation, and on the other, the continuous removal of oxygen by the pulmonary blood flow. The net result is that the alveolar PO_2 settles out at approximately 100 mm Hg.

It is true that the process of ventilation is intermittent with each breath and not continuous. By the same token, pulmonary capillary blood flow is known to be pulsatile. However, the volume of gas in the lung at FRC is sufficient to dampen these oscillations, with the result that the alveolar PO_2 varies by only 3 or 4 mm Hg with each breath, and less with each heartbeat. Thus alveolar ventilation and capillary blood flow can be regarded as continuous processes from the point of view of gas exchange. This greatly simplifies consideration of gas exchange.

In an ideal lung (see Fig. 4-15), the effluent pulmonary venous blood (which becomes the systemic arterial blood) would have the same PO_2 as that of the alveolar gas, namely, approximately 100 mm Hg. This is very nearly the case in the normal lung. However, when the arterial blood reaches the peripheral tissues, PO_2 falls substantially en route to the mitochondria. The movement of oxygen in the peripheral tissues is also essentially by passive diffusion, and the mitochondrial PO_2 is certainly considerably lower than that in arterial or mixed venous blood. Indeed, the PO_2 in the mitochondria may vary considerably throughout the body, depending on the type of tissue and its oxygen uptake. Nevertheless, it is useful to bear in mind that the mitochondria are the targets for the oxygen transport system and that any fall in the arterial PO_2 caused, for example, by inefficient pulmonary gas exchange must be reflected in a reduced tissue PO_2 , other factors being equal.

For carbon dioxide, the process is reversed. There is essentially no carbon dioxide in the inspired air, and the alveolar PCO_2 is approximately 40 mm Hg. Under normal conditions, arterial and alveolar PCO_2 values are the same, whereas the PCO_2 of mixed venous blood is in the range of 45 to 47 mm Hg. The PCO_2 of the tissues is probably quite variable, depending, for example, on the state of metabolism. Nevertheless, any inefficiency of the lung for carbon dioxide removal tends to raise the PCO_2 of the tissues, other factors being equal.

CAUSES OF HYPOXEMIA

Hypoxemia refers to a reduction in arterial PO_2 to below normal values. There are four major processes that can impair pulmonary gas exchange and cause hypoxemia when breathing room air at sea level: hypoventilation, diffusion limitation, shunt, and ventilation-perfusion inequality. These are now discussed in turn.

Hypoventilation

Hypoventilation is used here to refer to conditions in which alveolar ventilation is abnormally low in relation to oxygen uptake or carbon dioxide output. Alveolar ventilation is the volume of fresh inspired gas going to the alveoli (i.e., non-dead space ventilation), as mentioned earlier. As we shall see, hypoventilation always causes a raised arterial PCO_2 and also arterial hypoxemia (unless the patient is breathing an enriched oxygen mixture). It should be noted that other

conditions (e.g., ventilation-perfusion inequality) can also result in carbon dioxide retention, and some use the terms *hypoventilation* and *carbon dioxide retention* interchangeably. However, this can be confusing because carbon dioxide can be retained even when a patient is breathing more than normal, so we do not use the terms interchangeably.

We saw in the last section that the PO_2 of alveolar gas is determined by a balance between the rate of addition of oxygen by alveolar ventilation and the rate of removal by the pulmonary blood flow to satisfy the oxygen demands of the tissues. Hypoventilation results when the alveolar ventilation is reduced and the alveolar PO_2 therefore settles out at a lower level than normal. For the same reason the alveolar PCO_2 , and therefore arterial PCO_2 , are also raised.

Causes of hypoventilation include depression of the respiratory center by drugs, such as morphine derivatives and barbiturates; diseases of the brain stem, such as encephalitis; abnormalities of the spinal cord conducting pathways, such as high cervical dislocation; anterior horn cell diseases, including poliomyelitis, affecting the phrenic nerves or supplying the intercostal muscles; diseases of nerves to respiratory muscles (e.g., Guillain-Barré syndrome); diseases of the myoneural junction, such as myasthenia gravis; diseases of the respiratory muscles themselves, such as progressive muscular dystrophy; thoracic cage abnormalities (e.g., crushed chest); upper airway obstruction (e.g., thymoma); hypoventilation associated with extreme obesity (pickwickian syndrome); and other miscellaneous causes, such as metabolic alkalosis and idiopathic states. For discussion of hypoventilation, see Chapters 86 and 99.

Note that, in all these conditions, the lungs are normal. Thus this group can be clearly distinguished from those diseases in which the carbon dioxide retention is associated with chronic lung disease. In the latter conditions the lungs are abnormal, and a major factor in the raised PCO_2 is the ventilation-perfusion inequality that causes gross inefficiency of pulmonary gas exchange (see later).

The rise in alveolar PCO_2 as a result of hypoventilation can be calculated using the *alveolar ventilation equation* (see earlier section “[Total and Alveolar Ventilation](#)” for derivation):

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{PACO_2} \times K \quad [6]$$

where K is a constant. This can be rearranged as follows:

$$PACO_2 = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K \quad [14]$$

Because in normal lungs the alveolar ($PACO_2$) and arterial ($PaCO_2$) PCO_2 are almost identical, we can write:

$$PaCO_2 = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K \quad [15]$$

This very important equation indicates that the level of PCO_2 in alveolar gas or arterial blood is inversely related to the alveolar ventilation. For example, if the alveolar ventilation is halved, the PCO_2 doubles. Note, however, that this is true only after a steady state has been reestablished and the carbon dioxide production rate is the same as before. In practice, if the alveolar ventilation of a patient is suddenly decreased (e.g., by changing the setting on a ventilator), the

PCO₂ rises over a period of 10 to 20 minutes. The rise is rapid at first and then is more gradual as the body stores of carbon dioxide are gradually filled.⁷⁹

The same principles used for carbon dioxide can be applied to oxygen to understand the effect of hypoventilation on alveolar (and thus arterial) PO₂. The corresponding mass conservation equation for oxygen is as follows:

$$\dot{V}O_2 = \dot{V}I \times F_{IO_2} - \dot{V}A \times F_{AO_2} \quad [16]$$

Here, $\dot{V}I$ is inspired alveolar ventilation (sometimes written as $\dot{V}IA$), whereas $\dot{V}A$ is expired alveolar ventilation. Equation 16 expresses oxygen uptake as the difference between the amount of oxygen inhaled per minute (volume of inspired gas [$\dot{V}I$] \times fractional concentration of oxygen [F_{IO_2}]) and that exhaled per minute (volume of alveolar ventilation [$\dot{V}A$] \times fractional concentration of oxygen in alveolar gas [F_{AO_2}]). Normally, because a little more oxygen is taken up per minute than carbon dioxide exhaled, $\dot{V}I$ exceeds $\dot{V}A$. However, this difference is usually no more than 1% of the ventilation, and clinically it can most often be ignored. If this is done, $\dot{V}I$ may then be replaced by $\dot{V}A$, and Equation 16 simplifies to

$$\begin{aligned} \dot{V}O_2 &= \dot{V}A \times (F_{IO_2} - F_{AO_2}) \text{ or} \\ \dot{V}O_2 &= \dot{V}A \times \frac{(P_{IO_2} - P_{AO_2})}{K} \end{aligned} \quad [17]$$

where P_{IO_2} is the partial pressure of oxygen in the inspired gas. Thus, as ventilation falls, P_{AO_2} must fall as well to maintain the rate of oxygen uptake necessary for metabolic function. Equations 14 (reexpressed as $\dot{V}CO_2 = \dot{V}A \times P_{ACO_2}/K$) and 17 can be usefully combined. If Equation 14 is divided by Equation 17, we get

$$\frac{\dot{V}CO_2}{\dot{V}O_2} = R = \frac{P_{ACO_2}}{(P_{IO_2} - P_{AO_2})} \quad [18]$$

Here, R is the respiratory exchange ratio (volume of carbon dioxide exhaled/oxygen taken up in the same time). Both K and $\dot{V}A$ cancel out when the division is performed. Rearranging this equation yields

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} \quad [19]$$

This is called the *alveolar gas equation*, and it uniquely relates alveolar PO₂ to PCO₂ for given values of inspired PO₂ and R . It is the basis of calculations of the alveolar-to-arterial PO₂ difference, a commonly used index of inefficiency of pulmonary gas exchange. Because we assumed that $\dot{V}I = \dot{V}A$ in deriving this equation, it is an approximation. It is possible to account for the difference between $\dot{V}I$ and $\dot{V}A$, and, when this is done, the alveolar gas equation contains an additional term:

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} + \left[P_{ACO_2} \times F_{IO_2} \times \frac{(1-R)}{R} \right] \quad [20]$$

The term in brackets is the correction factor for the difference between inspired and expired volumes. It is generally small during air breathing (1 to 3 mm Hg) and can be ignored in most clinical settings if the patient is breathing air. However, if the patient is being given an enriched oxygen mixture, the correction factor increases; for example to 10 mm Hg in someone with normal arterial blood gas levels breathing pure oxygen.

As an example of the use of this equation, suppose that a patient with normal lungs takes an overdose of a barbiturate drug that depresses alveolar ventilation. The patient's alveolar PCO₂ might rise from 40 to 60 mm Hg (the actual value is determined by the alveolar ventilation equation). Before the drug, the patient's alveolar PO₂ can be calculated assuming $R = 1.0$, and the small correction factor is neglected:

$$\begin{aligned} P_{AO_2} &= P_{IO_2} - (P_{ACO_2}/R) \\ &= 149 - (40/1) \\ &= 109 \text{ mm Hg} \end{aligned}$$

After the drug and making the same assumptions, alveolar PO₂ falls by 20 mm Hg:

$$\begin{aligned} P_{AO_2} &= P_{IO_2} - (P_{ACO_2}/R) \\ &= 149 - (60/1) \\ &= 89 \text{ mm Hg} \end{aligned}$$

Hence, when $R = 1.0$, alveolar PO₂ falls by 20 mm Hg, which is the same amount by which the PCO₂ rises. If $R = 0.8$, which is a more typical resting value, and we ignore the small correction factor in Equation 20, then, when alveolar PCO₂ increases by 20 mm Hg, alveolar PO₂ decreases by 25 mm Hg, from 99 to 74 mm Hg.

Both examples emphasize that, in practical terms, the hypoxemia is generally of minor importance compared with the carbon dioxide retention and consequent respiratory acidosis. This is further illustrated in Figure 4-16, which shows calculated changes in gas exchange as a result of hypoventilation. Note that severe hypoventilation sufficient to double the PCO₂ from 40 to 80 mm Hg decreases the alveolar PO₂ from only, say, 100 to 50 or 60 mm Hg. Although the arterial PO₂ is likely to be a few millimeters of mercury lower than the alveolar value, the arterial oxygen saturation is approximately 80%. However, there is substantial respiratory acidosis with an arterial pH of

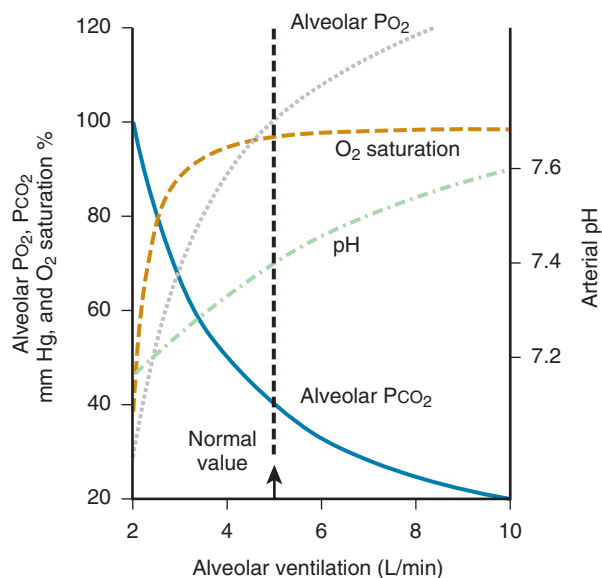


Figure 4-16 Gas exchange during changes in ventilation. With hypoventilation, note the relatively large rise in PCO₂ and consequent fall in pH compared with the modest fall in arterial oxygen saturation. (Redrawn from West JB: *Pulmonary physiology—the essentials*, ed 8, Baltimore, 2013, Lippincott Williams & Wilkins.)

approximately 7.2. This fact emphasizes again that the hypoxemia is usually not as important as the carbon dioxide retention and respiratory acidosis in pure hypoventilation.

A feature of alveolar hypoventilation is that, although the arterial PCO_2 is always raised, the arterial PO_2 may be returned to normal very easily by giving supplementary oxygen. Suppose that the patient with barbiturate intoxication just discussed is given 30% oxygen to breathe. If we assume that the ventilation remains unchanged, it can be shown (from Equation 20) that the alveolar PO_2 rises from 74 to approximately 140 mm Hg. Thus a relatively small increase in inspired PO_2 is very effective in eliminating the arterial hypoxemia of hypoventilation.

Diffusion Limitation

It is now generally believed that oxygen, carbon dioxide, and indeed all gases cross the blood-gas barrier by simple passive diffusion. Fick's law of diffusion states that the rate of transfer of a gas through a sheet of tissue is proportional to the tissue area (A) and the difference in partial pressure ($P_1 - P_2$) between the two sides, and is inversely proportional to the thickness (T):

$$\dot{V}_{\text{gas}} = \frac{A}{T} \times D \times (P_1 - P_2) \quad [21]$$

As we have seen already, the area of the blood-gas barrier in the lung is enormous (50 to 100 m^2), and the thickness is less than 0.3 μm in some places, so the dimensions of the barrier are ideal for diffusion.

The rate of diffusion is also proportional to a constant (D), which depends on the properties of the tissue and the particular gas. The constant is proportional to the solubility (Sol) of the gas, and inversely proportional to the square root of the molecular weight (MW):

$$D \propto \frac{\text{Sol}}{\sqrt{\text{MW}}} \quad [22]$$

This means that, per the millimeters of mercury difference between capillary and alveolar partial pressures, carbon dioxide diffuses approximately 20 times more rapidly than oxygen through tissue sheets, because carbon dioxide has a much higher solubility (24:1 at 37° C), but the square roots of the molecular weights are not very different (1.17:1). Note that this calculation applies only to tissue sheets and does not fully account for the uptake of oxygen or output of carbon dioxide by the lung, because the chemical reactions between these gases and components of blood also play a role (see later discussion).

Oxygen Uptake along the Pulmonary Capillary

Figure 4-17 shows calculated changes in the PO_2 of the blood along the pulmonary capillary as oxygen is taken up under normal conditions. The calculation is based on Fick's law of diffusion (see Equation 21). One of the several assumptions is that the diffusion characteristics of the blood-gas barrier are uniform along the length of the capillary. The calculation is complicated by the fact that the change in the PO_2 of the capillary blood depends on the oxygen dissociation curve. This is not only nonlinear but is also influenced by the simultaneous elimination of carbon dioxide. The calculation is often known as the Bohr integration because it was first carried out in a simplified form by

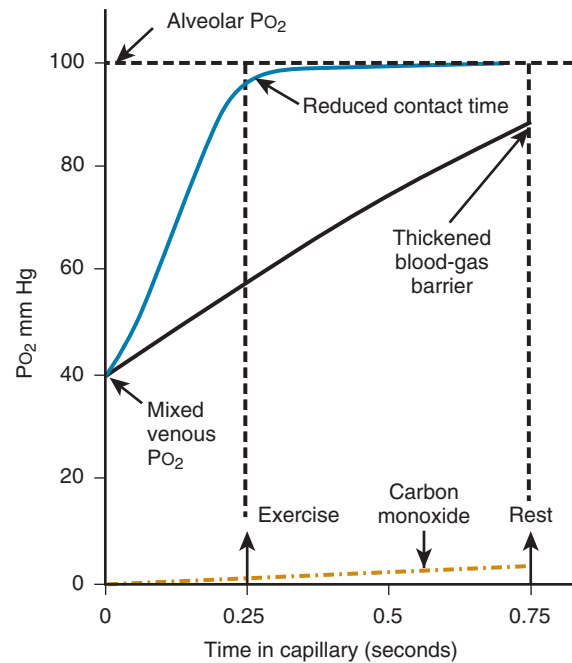


Figure 4-17 Typical time courses for the change in PO_2 in the pulmonary capillary when diffusion is normal, when the contact time is reduced, and when the blood-gas barrier is abnormally thick. The time course for carbon monoxide uptake is also shown. (Redrawn from West JB: *Pulmonary physiology—the essentials*, ed 8, Baltimore, 2013, Lippincott Williams & Wilkins.)

Christian Bohr.⁸⁰ Modern computations take into account reaction times of oxygen with hemoglobin and also reaction rates associated with carbon dioxide elimination (see later discussion).⁸¹

Figure 4-17 shows that the time spent by the blood in the pulmonary capillary under normal resting conditions is approximately 0.75 second. This number is obtained by dividing the volume of blood calculated to be in the pulmonary capillaries (75 mL) by the cardiac output (6 L/min).⁸² The figure shows that the PO_2 of pulmonary capillary blood very nearly reaches that of alveolar gas after approximately a third of the available time in the capillary. This means that there is normally ample time for essentially complete oxygenation of the blood or, as it is sometimes said, the normal lung has substantial diffusion “reserves.”

If the blood-gas barrier is thickened, the rate of transfer of oxygen across the barrier is reduced in accordance with Fick's law, and the rate of rise of PO_2 is slower, as shown in Figure 4-17. Under these circumstances a PO_2 difference between alveolar gas and end-capillary blood may develop. This means that there is some diffusion limitation of oxygen transfer. It is important to appreciate that under most conditions at sea level oxygen transfer is perfusion limited and only under unusual conditions such as severe interstitial lung disease is there some diffusion limitation. However, at high altitude, diffusion limitation during exercise is universal, even in health. In well-trained athletes, diffusion may be limiting even at sea level.

It can be shown⁸³ that whether diffusive transfer of any gas is perfusion or diffusion limited depends on the ratio of D , the diffusive conductance of the blood-gas barrier, to the product of the solubility of the gas in blood (commonly referred to as β) and the total pulmonary blood flow

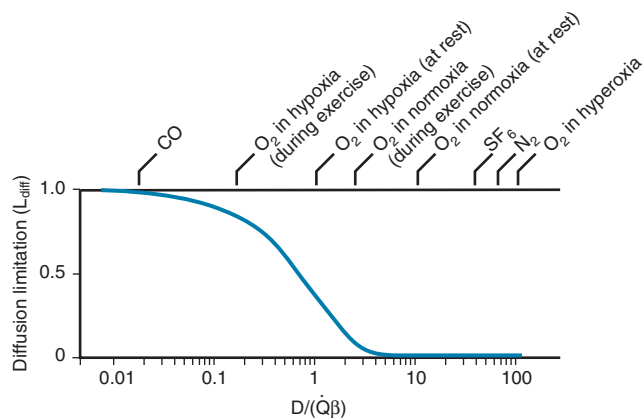


Figure 4-18 Diffusion-limited transfer of various gases in the lung. Diffusion limitation (L_{diff}) is on a scale of 0 (no limitation) to 1 (complete limitation) (see text for details). (From Scheid P, Piiper J: Blood gas equilibration in lungs and pulmonary diffusing capacity. In Chang HK, Paiva M, editors: *Respiratory physiology: An analytical approach*, New York, 1989, Marcel Dekker, pp 453–497.)

rate (\dot{Q}): $D/(\dot{Q}\beta)$. For oxygen, β refers to the slope of the oxygen-hemoglobin dissociation curve. Diffusive equilibration is more likely the higher the $D/(\dot{Q}\beta)$ ratio.

It is clear that for oxygen the slope of the blood dissociation curve is not a constant, which makes this ratio difficult to apply. It depends on the P_{O_2} and also to a lesser extent on factors that shift the dissociation curve, such as pH, PCO_2 , temperature, and red cell 2,3-DPG concentration. Under hypoxic conditions, when the lung is operating on the lower, steeper part of the oxygen dissociation curve, β is much greater than in normoxia when arterial P_{O_2} is on the flat portion of the curve, and the ratio is thus lower. This explains why diffusion limitation for oxygen, unusual at sea level, is common at high altitude. Figure 4-18 shows the extent to which perfusion and diffusion limit the transfer of gas under various conditions.⁸³ Although the figure is based on a number of simplifying assumptions, it is conceptually valuable.

Note that physiologically inert gases such as nitrogen and sulfur hexafluoride (right-hand end of Fig. 4-18) are completely perfusion limited in their transfer. (*Physiologically inert* means that, being carried in blood only in physical solution, their blood concentration is directly proportional to partial pressure; that is, they obey Henry's law of solubility.) The same perfusion limitation applies to oxygen in hyperoxia because, high on the dissociation curve, the value of β is very low so that $(D/\dot{Q}\beta)$ is very high and diffusion limitation is not seen. However, oxygen transfer under conditions of hypoxia can be partly diffusion limited because the lung is working low on the dissociation curve, where the slope (β) is much higher than normal. This is particularly the case for oxygen transfer during hypoxic exercise and explains why diffusion is limiting in the normal lung during maximal exercise at extreme high altitude, even in well-acclimatized subjects.^{84,85} On the summit of Mount Everest, there is apparently diffusion limitation even at rest.

Figure 4-18 also shows that the transfer of carbon monoxide by the lung is markedly diffusion limited. This follows from the very steep slope of the dissociation curve of carbon monoxide with blood (that is, β is very large). Another way

of looking at this is to say that the avidity of hemoglobin for carbon monoxide is so high that the partial pressure in the blood hardly rises along the pulmonary capillary (see Fig. 4-17). Under these conditions it is intuitively clear that the amount of carbon monoxide that is taken up depends almost entirely on the diffusion properties of the blood-gas barrier, explaining why this gas is so well suited to measuring the lung's diffusing capacity.

Reaction Rates with Hemoglobin

When oxygen (or carbon monoxide) is added to blood, its combination with hemoglobin is quite fast, being close to completion in 0.2 second. Such reaction rates can be measured using special equipment in which reduced hemoglobin and dissolved oxygen are rapidly mixed and the rate of formation of oxyhemoglobin is measured photometrically. Although hemoglobin is oxygenated rapidly within the pulmonary capillary, even this rapid reaction significantly delays the loading of oxygen by the red cell.

The transfer of oxygen from the alveolar gas to its combination with hemoglobin in the red cell can therefore be regarded in two stages: (1) diffusion of oxygen through the blood-gas barrier, including the plasma and red cell interior; and (2) reaction of the oxygen with hemoglobin (Fig. 4-19A). Although at first sight these two processes are very different, it is possible to treat them mathematically in a similar way and to regard each as contributing its own "resistance" to the transfer of oxygen. Such an analysis was carried out by Roughton and Forster,⁸⁶ who showed that the following relationship exists:

$$\frac{1}{DL} = \frac{1}{DM} + \frac{1}{(\theta \times Vc)} \quad [23]$$

where DL refers to the diffusing capacity of the lung, DM is the diffusing capacity of the membrane (which includes the plasma and red cell interior), θ is the rate of reaction of oxygen (or carbon monoxide) with hemoglobin (expressed per milliliter of blood), and Vc is the volume of blood in the pulmonary capillaries.

In the normal lung the resistances offered by the membrane and blood reaction components are approximately equal. This means that, if the capillary blood volume is reduced by disease, the measured diffusing capacity of the lung is lowered. In fact, the equation can be used to separate the two components. To do this, the diffusing capacity is measured at both high and normal alveolar P_{O_2} values. Increasing the alveolar P_{O_2} reduces the value of θ for carbon monoxide because the carbon monoxide has to compete with a high pressure of oxygen for the hemoglobin. If the resulting measurements of $1/DL$ are plotted against $1/\theta$, as shown in Figure 4-19B, the slope of the line is $1/Vc$, whereas the intercept on the vertical axis is $1/DM$.

Diffusing Capacity

Carbon monoxide is usually the gas of choice for measuring the diffusion properties of the lung because, as Figure 4-18 shows, its transfer is almost entirely diffusion limited. It is true that part of the limitation has to do with the rate of reaction of carbon monoxide with hemoglobin (see Fig. 4-19A), but this is conveniently included in the measurement of diffusion properties. Although it could be argued that we are really more interested in oxygen and the effects

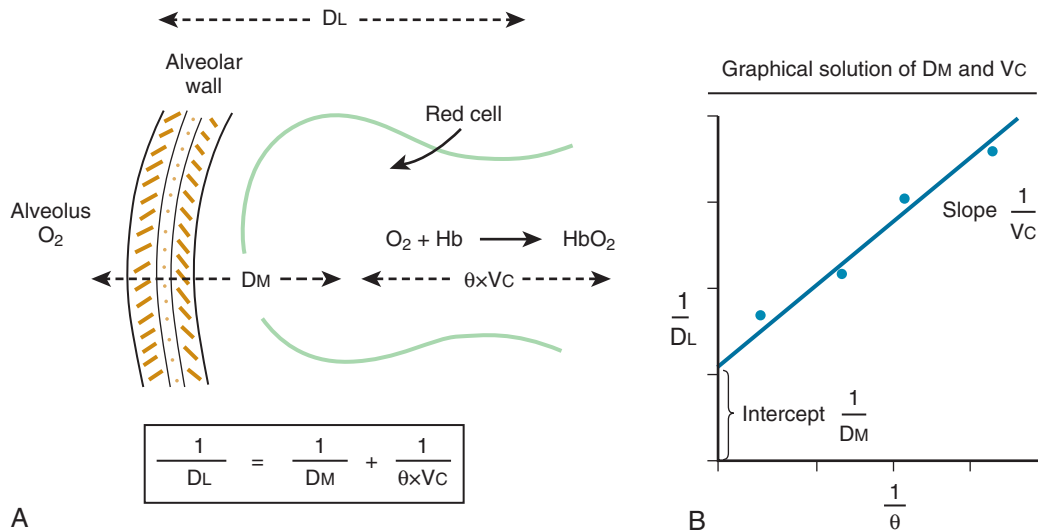


Figure 4-19 **A**, The two components of the measured diffusing capacity (DL) of the lung: that due to the diffusion process itself (DM) and that attributable to the time taken for oxygen (or carbon monoxide) to react with hemoglobin (Hb) ($\theta \times VC$). **B**, $1/DL$ plotted against $1/\theta$ can be used to derive DM and VC, vital capacity.

of any diffusion limitation on this gas, oxygen uptake is typically perfusion limited under normoxic conditions (see Fig. 4-18) and partly perfusion and diffusion limited under hypoxic conditions. For this reason, measurements using oxygen are often difficult to interpret, although techniques using isotopes of oxygen have been proposed.⁸³ However, for the measurement of diffusion properties in the pulmonary function laboratory, carbon monoxide is the best gas.

As indicated earlier, Fick's law states that the amount of gas transferred across a tissue sheet is proportional to the area, a diffusion constant, and the difference in partial pressure, and is inversely proportional to the thickness:

$$\dot{V}_{\text{gas}} = \frac{A}{T} \times D \times (P_1 - P_2) \quad [21]$$

The actual lung is so complex that it is not possible to determine the area and the thickness of the blood-gas barrier during life. Instead, the equation is written to combine the factors A, T, and D into one constant, DL, as follows:

$$\dot{V}_{\text{gas}} = DL \times (P_1 - P_2) \quad [24]$$

where DL is called the diffusing capacity of the lung and consequently includes the area, thickness, and diffusion properties of the tissue sheet, as well as the properties of the diffusing gas. Thus the diffusing capacity for carbon monoxide is given by:

$$DL = \frac{\dot{V}_{\text{CO}}}{(P_1 - P_2)} \quad [25]$$

where P_1 and P_2 are the partial pressures of carbon monoxide in alveolar gas and capillary blood, respectively. Because the partial pressure of carbon monoxide in capillary blood is so small (see Fig. 4-17), it can generally be neglected. In this case, the equation becomes:

$$DL = \frac{\dot{V}_{\text{CO}}}{P_{\text{ACO}}} \quad [26]$$

or, in words, the diffusing capacity of the lung for carbon monoxide is the volume of carbon monoxide transferred in

milliliters per minute per millimeters of mercury of alveolar partial pressure of carbon monoxide.

Some people, for example, cigarette smokers, have sufficient carboxyhemoglobin in their blood that the partial pressure of carbon monoxide in the pulmonary capillaries cannot be neglected. In this case, an estimate of the partial pressure of carbon monoxide in pulmonary capillary blood can be made using a rebreathing technique, and Equation 25 is then used to determine diffusing capacity.

Several techniques are available for measuring the diffusing capacity of the lung for carbon monoxide. In the *single-breath method*, a single inspiration of a dilute mixture (approximately 0.3%) of carbon monoxide is made, and the rate of disappearance of carbon monoxide from the alveolar gas during a 10-second breath-hold is calculated. This is usually done by measuring the inspired and expired concentrations of carbon monoxide with an infrared analyzer. Alternatively, a respiratory mass spectrometer can be used if ¹⁸O-labeled carbon monoxide is employed. At the end of the breath-holding period, a post-dead space sample of alveolar gas is obtained by discarding the first 750 mL of the expiration. The alveolar concentration of carbon monoxide is not constant during the breath-holding period, but allowance can be made, assuming that the disappearance of carbon monoxide follows an exponential law. Helium (or methane) is also added to the inspired gas to give a measurement of lung volume by dilution. The appropriate equation is:

$$DL = \frac{\dot{V}_A \times K}{t} \log_e \left[\frac{F_{\text{ICO}} \times F_{\text{AHe}}}{F_{\text{IHe}} \times F_{\text{ACO}_2}} \right] \quad [27]$$

where \dot{V}_A is the alveolar volume in liters, t is breath-holding time in seconds, K is a constant, and the fractional concentrations of carbon monoxide and helium in inspired and expired gas are as indicated. Further details of this method, which requires considerable care for accurate results, can be found in more specialized texts.⁸⁷

The diffusing capacity can also be measured using the steady-state method. The subject breathes a low

concentration of carbon monoxide (approximately 0.1%) for 0.5 minute or so, until a steady state of gas exchange has been reached. The constant rate of disappearance of carbon monoxide from alveolar gas is then measured for a further short period, along with the alveolar concentration. This technique is better suited to measurements during exercise in which breath-holding becomes a problem. The normal value of the diffusing capacity for carbon monoxide depends on age, sex, and height (as is the case for most pulmonary function tests), and appropriate regression equations are available.⁸⁷ Experiments comparing measured arterial PO_2 with that predicted for a given degree of ventilation-perfusion mismatching (see later) without any diffusion limitation agree until the actual diffusing capacity decreases by 50%.⁸⁸ This emphasizes the large safety factor in the normal lung before hypoxemia results from a diffusion limitation.

As Figure 4-19A indicates, the uptake of carbon monoxide is determined by the diffusion properties of the blood-gas barrier (including plasma and red cell interior) and the rate of combination of carbon monoxide with blood. The *diffusion properties* of the alveolar membrane depend on its thickness and area. Thus the diffusing capacity is reduced by diseases in which the thickness is increased, including diffuse interstitial pulmonary fibrosis, asbestosis, and sarcoidosis. It is also reduced when the area is decreased, for example, by pneumonectomy. The diffusing capacity in emphysema may fall because of the loss of alveolar walls and capillaries, but also perhaps because of the unevenness of ventilation and diffusion (see later discussion).

The *rate of combination* of carbon monoxide with blood is reduced whenever the number of red cells in the capillaries is reduced. This happens in anemia and also in diseases that may reduce the capillary blood volume in certain regions of the lung, such as pulmonary embolism.

Figure 4-19B shows how it is possible to separate the membrane and blood components of the diffusing capacity by making measurements at high and normal values of alveolar PO_2 . However, this is only possible in subjects with nearly normal lungs. In many patients in whom the measured diffusing capacity is low, the interpretation is uncertain. The reason for this is the unevenness of ventilation and diffusion properties throughout the diseased lung. Such lungs tend to empty unevenly, with the result that the post-dead space sample of expired gas that is analyzed for carbon monoxide is not representative of the whole lung. Partly as a consequence of this, different methods of measuring diffusing capacity in patients with diseased lungs frequently give very different results. For this reason the diffusing capacity is sometimes referred to as the *transfer factor* (especially in Europe) to emphasize that it is more a measure of the lung's overall ability to transfer carbon monoxide into the blood than a specific test of diffusion characteristics. Nevertheless, the test gives considerable information in the nearly normal lung, and, even in patients with severe disease, the results are empirically useful for assessing the severity and type of lung disease in the pulmonary function laboratory. (For a discussion of clinical tests, see Chapter 25).

Shunt

Shunt refers to the entry of blood into the systemic arterial system without going through ventilated areas of lung.

Even the normal cardiopulmonary system shows some depression of the arterial PO_2 as a result of this factor. For example, in the normal lung some of the bronchial artery blood is collected by the pulmonary veins after it has perfused the bronchi. Because the oxygen concentration of this blood has been reduced, its addition to the normal end-capillary blood results in a reduction of arterial PO_2 . Another source is a small amount of coronary venous blood that drains directly into the cavity of the left ventricle through the thebesian veins. Of course, most of the coronary venous blood ends up in the coronary sinus, and only a minute fraction reaches the left ventricle directly. Such shunts depress arterial PO_2 only by approximately 1 to 2 mm Hg.

In patients with congenital heart disease, there may be a direct addition of venous blood to arterial blood across a defect between the right and left sides of the heart. Generally this is associated with some increase in pressure on the right side; otherwise, the shunt is only from left to right. In lung disease there may be gas-exchanging units that are completely unventilated because of airway obstruction, atelectasis, or alveolar filling with fluid or cells. The blood draining from these constitutes a shunt. It could be argued that such units are simply at the extreme end of the spectrum of ventilation-perfusion inequality (see next section), but the gas-exchange properties of unventilated units are so different (e.g., during oxygen breathing) that it is convenient to separate them.

When the shunt is caused by the addition of mixed venous blood (pulmonary arterial) to blood draining from the capillaries (pulmonary venous), it is possible to calculate the amount of shunt flow. This is done using a mixing equation. The total amount of oxygen delivered into the systemic circulation per minute is the total blood flow (\dot{Q}_T) multiplied by the oxygen concentration in the systemic arterial blood (Ca_{O_2}), or $\dot{Q}_T \times Ca_{O_2}$. This must equal the sum of the amounts of oxygen in the shunted blood ($\dot{Q}_s \times C\bar{v}O_2$) and the nonshunted or end-capillary blood [$(\dot{Q}_T - \dot{Q}_s) \times Cc'O_2$]. Also, it is assumed that all regions of lung not subject to shunt are normal. Thus

$$\dot{Q}_T \times Ca_{O_2} = (\dot{Q}_s \times C\bar{v}O_2) + (\dot{Q}_T - \dot{Q}_s) \times Cc'O_2 \quad [28]$$

Rearranging, this gives

$$\frac{\dot{Q}_s}{\dot{Q}_T} = \frac{(Cc'O_2 - Ca_{O_2})}{(Cc'O_2 - C\bar{v}O_2)} \quad [29]$$

The oxygen concentration of end-capillary blood is usually calculated from the alveolar PO_2 and the hemoglobin concentration, assuming 100% oxyhemoglobin saturation (hence the assumption of normalcy of all regions not subject to shunt).

When the shunt is caused by blood that does not have the same oxygen concentration as mixed venous blood (e.g., bronchial venous blood), it is generally not possible to calculate its true magnitude. However, it is often useful to calculate an "as if" shunt, that is, what the shunt *would* be if the observed depression of arterial oxygen concentration were caused by the addition of mixed venous blood. An analogous procedure is frequently used to quantitate the degree of hypoxemia caused by ventilation-perfusion inequality, although it is clearly recognized in this case that there may be relatively little or even no blood flow to completely unventilated lung units.

An important diagnostic feature of a shunt is that the arterial PO_2 does not rise to the normal level (which in theory should be 670 mm Hg) when the patient is given 100% oxygen to breathe. The reason for this is that the shunted blood that bypasses ventilated alveoli is never exposed to the higher alveolar PO_2 . Its addition to end-capillary blood therefore continues to depress the arterial PO_2 . Nevertheless, the arterial PO_2 is elevated somewhat because of the oxygen added to the capillary blood of the ventilated lung. Most of this added oxygen is in the dissolved form rather than attached to hemoglobin because the blood that is perfusing lung regions with normal ventilation-perfusion ratios (see later) is normally nearly fully saturated.

The administration of 100% oxygen to a patient with a shunt is a very sensitive method of detecting small amounts of shunting. This is because when the arterial PO_2 is very high, a very small reduction of arterial oxygen concentration caused by the addition of the shunted blood causes a relatively large fall in PO_2 . This is directly attributable to the almost flat slope of the oxygen dissociation curve in this region.

A patient with a shunt usually does not have an increased PCO_2 in the arterial blood in spite of the fact that the shunted blood is rich in carbon dioxide. The reason is that the chemoreceptors sense any elevation of arterial PCO_2 and respond by increasing the ventilation. As a consequence, the PCO_2 of the unshunted blood is reduced by the hyperventilation until the arterial PCO_2 is back to normal. Indeed, in some patients with large shunts caused, for example, by cyanotic congenital heart disease, the arterial PCO_2 is low because the arterial hypoxemia increases the respiratory drive.

Ventilation-Perfusion Relationships

It has been known for many years that mismatching of ventilation and blood flow is the most common cause of hypoxemia in lung disease. Uneven ventilation and blood flow are also a cause of carbon dioxide retention. Early intimations of the importance of the subject go back to Krogh and Lindhard⁸⁹ and Haldane.⁹⁰ However, our understanding advanced in the late 1940s when Fenn and colleagues⁹¹ and Riley and Courmand⁹² introduced graphic analysis of gas exchange. This was an important advance because the interrelationships of ventilation, blood flow, and gas exchange depend on the oxygen and carbon dioxide dissociation curves, which are not only nonlinear but interdependent, and direct solutions to the gas exchange equations that relate the ventilation-perfusion ratio to gas exchange (see later, Equations 31 and 32) are not possible.

A more recent phase began with the use of computers to describe the oxygen and carbon dioxide dissociation curves.^{93,94} These procedures enabled investigators to answer questions about gas exchange that had been impossibly difficult before that time. The behavior of distributions of ventilation-perfusion ratios was analyzed,⁹⁵ and Wagner and colleagues⁹⁶ introduced the multiple inert gas elimination technique, which allowed, for the first time, information about the dispersion, number of modes, and shape of the distributions of ventilation, of perfusion, and of their ratio to be obtained.

Gas Exchange in a Single Lung Unit

The PO_2 , PCO_2 , and PN_2 in any gas-exchanging unit of the lung are uniquely determined by three major factors: (1) the ventilation-perfusion ratio, (2) the composition of the inspired gas and the composition of the mixed venous blood, and (3) the slopes and positions of the relevant blood-gas dissociation curves.

Formally, the key role of the ventilation-perfusion ratio can be derived as follows. The amount of carbon dioxide exhaled into the air from alveolar gas per minute is given by Equation 5:

$$\dot{V}CO_2 = \dot{V}_A \times PACO_2 / K \quad [5]$$

where $\dot{V}CO_2$ is the carbon dioxide output, \dot{V}_A is the alveolar ventilation, K is a constant, and there is no carbon dioxide in the inspired gas.

The amount of carbon dioxide lost into alveolar gas from capillary blood per minute is given by:

$$\dot{V}CO_2 = \dot{Q}(C\bar{V}CO_2 - Cc'CO_2) \quad [30]$$

where \dot{Q} is blood flow, and $C\bar{V}CO_2$ and $Cc'CO_2$ are the concentrations of carbon dioxide in mixed venous and end-capillary blood, respectively. Now, in a steady state, the amount of carbon dioxide lost from the alveoli and from the capillary blood must be the same. Therefore:

$$\begin{aligned} \dot{V}_A \times PACO_2 \times K &= \dot{Q}(C\bar{V}CO_2 - Cc'CO_2) \text{ or} \\ \frac{\dot{V}_A}{\dot{Q}} &= \frac{(C\bar{V}CO_2 - Cc'CO_2)}{PACO_2} \times K \end{aligned} \quad [31]$$

Thus the alveolar PCO_2 and the corresponding end-capillary carbon dioxide concentration (assuming end-capillary and alveolar PCO_2 are identical) are determined by (1) the ventilation-perfusion ratio, (2) the mixed venous carbon dioxide concentration, and (3) the carbon dioxide dissociation curve relating PCO_2 to carbon dioxide concentration.

Although this equation looks simple, its appearance is deceptive because, when the ventilation-perfusion ratio increases (for example), the alveolar PO_2 rises. This means that the oxygen saturation of the blood increases and therefore that the relationship between PCO_2 and carbon dioxide concentration is altered. Thus the alveolar PO_2 is an implicit variable in the equation. In addition, the relationship between PCO_2 and carbon dioxide concentration is nonlinear. This is the reason that it was possible to solve the equation only graphically until the introduction of computers.

Just as, in the context of the alveolar ventilation equation (see “Hypoventilation” earlier), both oxygen and carbon dioxide exchange were able to be expressed in equations of similar form, it is possible to write an equation similar to Equation 31 for oxygen exchange based on the same principles as applied for carbon dioxide. Again, the approximation is made that inspired alveolar ventilation (\dot{V}_I) equals expired alveolar ventilation (\dot{V}_A) to keep the equation simple, but, as for the alveolar gas equation, the fact that \dot{V}_I and \dot{V}_A are generally not quite the same can formally be taken into account. Using this approximation, the equation for oxygen is

$$\frac{\dot{V}_A}{\dot{Q}} = K \times \frac{(Cc'O_2 - C\bar{V}O_2)}{(PIO_2 - PAO_2)} \quad [32]$$

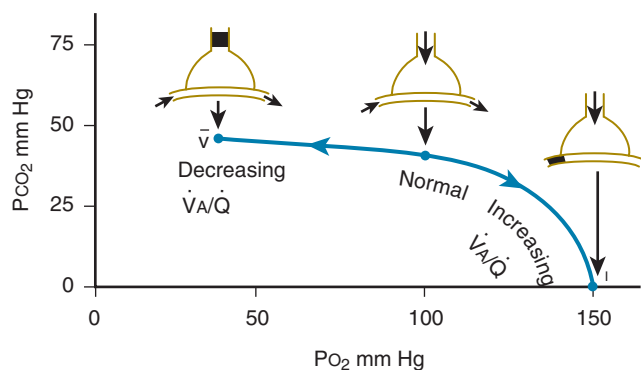


Figure 4-20 Oxygen-carbon dioxide diagram shows how the PO_2 and PCO_2 of a lung unit alter as the ventilation-perfusion ratio (\dot{V}_A/\dot{Q}) is changed. I, inspired gas; \bar{v} , mixed venous blood. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

Just as for carbon dioxide, the alveolar and end-capillary PO_2 values are taken to be identical, implying diffusion equilibrium across the blood-gas barrier. It is seen that the determinants of alveolar PO_2 , as for carbon dioxide, are threefold: (1) the ventilation-perfusion ratio, (2) inspired and mixed venous oxygen levels, and (3) the relationship between PO_2 and oxygen concentration (i.e., the oxygen dissociation curve).

Graphic analysis of these relationships is assisted by the use of the oxygen-carbon dioxide diagram, in which PO_2 is on the horizontal axis and PCO_2 is on the vertical axis. This diagram has been used to solve many problems related to ventilation-perfusion relationships.⁹⁷ A simple introduction to the diagram is given elsewhere.⁹⁸ It shows the solutions to Equations 31 and 32 for each value of the ventilation-perfusion ratio from zero (unventilated lung) to infinity (unperfused lung).

Figure 4-20 is an example of the use of the oxygen-carbon dioxide diagram to show how the PO_2 and PCO_2 of a lung unit change as the ventilation-perfusion ratio is either decreased below or increased above the normal value. Note that for a given composition of inspired gas (I) and mixed venous blood (\bar{v}), the possible combinations of PO_2 and PCO_2 are constrained to a single line known as the ventilation-perfusion ratio line. Each point on that line uniquely corresponds to a value of the ventilation-perfusion ratio. Note also that, at the extremes of the spectrum of ventilation-perfusion ratios, the PO_2 and PCO_2 of end-capillary blood are those of mixed venous blood when the ventilation-perfusion ratio is zero, and the PO_2 and PCO_2 of alveolar gas are the same as those of inspired gas for a ventilation-perfusion ratio of infinity. In this diagram and in the rest of this section, we assume that there is complete diffusion equilibration between the PO_2 and PCO_2 of alveolar gas and end-capillary blood. This is a reasonable assumption unless there is marked thickening of the blood-gas barrier or one is considering a subject exercising in hypoxia.

Figure 4-21 shows the PO_2 , PCO_2 , and oxygen concentration of end-capillary blood of a lung unit as its ventilation-perfusion ratio is increased from extremely low to extremely high values. The lung is assumed to be breathing air, the PO_2 and PCO_2 of mixed venous blood are normal (40 and 45 mm Hg, respectively), and the hemoglobin concentration is 14.8 g/100 mL. The normal value of the ventilation-

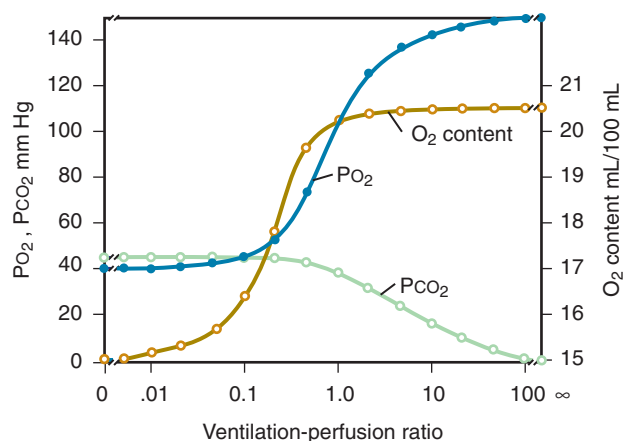


Figure 4-21 Changes in PO_2 , PCO_2 , and end-capillary oxygen content in a lung unit are shown as its ventilation-perfusion ratio is altered. See text for assumptions. (Redrawn from West JB: *State of the art: ventilation-perfusion relationships*. *Am Rev Respir Dis* 116:919–943, 1977.)

perfusion ratio is in the range of 0.8 to 1. Note that as the ratio is altered either above or below that value, the PO_2 changes considerably. By contrast, the oxygen concentration increases little as the ventilation-perfusion ratio is raised above the normal value because the hemoglobin is normally almost fully saturated. The PCO_2 falls considerably as the ventilation-perfusion ratio is raised, but rises relatively little at lower ventilation-perfusion ratio values. The quantitative information in this figure is consistent with the graphic analysis of Figure 4-20.

Pattern in the Normal Lung

Both ventilation and perfusion vary throughout the lung. It is thus instructive to look at the topographic inequality of gas exchange in the normal upright lung as a result of ventilation-perfusion inequality. We saw previously that both ventilation and blood flow per unit volume decrease from the bottom to the top of the upright lung. However, the changes for blood flow are more marked than those for ventilation. As a consequence, the ventilation-perfusion ratio increases from low values at the base to high values at the apex of the normal upright lung (Fig. 4-22).

Because the ventilation-perfusion ratio determines the gas exchange in any region (Equations 31 and 32), the corresponding pattern of variation in PO_2 and PCO_2 in the lung can be calculated. Normal composition of mixed venous blood is here assumed. Note that the PO_2 increases by some 40 mm Hg from base to apex, whereas the PCO_2 falls by 14 mm Hg. The pH is high at the apex because the PCO_2 there is low (the base excess is the same throughout the lung). Very little of the total oxygen uptake occurs at the apex, principally because the blood flow there is very low.

Figure 4-22 also helps to explain why ventilation-perfusion inequality interferes with overall gas exchange. Note that the base of the lung has most of the blood flow, but the PO_2 and oxygen concentration of the end-capillary blood are lowest there. As a result, the effluent pulmonary venous blood (which becomes the systemic arterial blood) is loaded with moderately oxygenated blood from the base. The net result is a depression of the arterial PO_2 below that which would be seen if ventilation and blood flow were uniformly distributed.

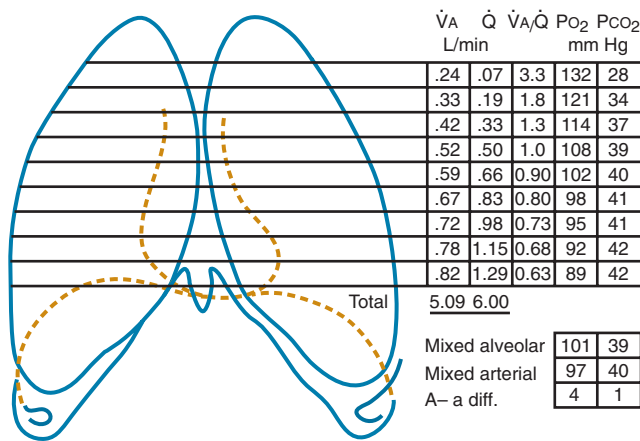


Figure 4-22 Regional differences of gas exchange down the upright normal lung. The lung is divided into nine imaginary slices. \dot{Q} , blood flow; \dot{V}_A , alveolar ventilation. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

The same argument applies to carbon dioxide. In this case the PCO_2 and carbon dioxide concentrations of the end-capillary blood are highest at the base, where the blood flow is greatest. As a result, the PCO_2 of arterial blood is elevated above that which would be seen if there were no ventilation-perfusion inequality. In other words, a lung with mismatched ventilation and blood flow is inefficient at exchanging gas, be this oxygen or carbon dioxide. In fact, the inefficiency applies to any gas that is being transferred by the lung. The extent of the impairment of gas exchange caused by any given amount of ventilation-perfusion inequality depends mostly on the solubility, or slope of the blood dissociation curve, of the gas. For example, in a log-normal distribution of ventilation-perfusion ratios, gases with medium solubility experience the greatest interference with pulmonary transfer.⁹⁹ In the normal lung the effect of inequality due to gravity on arterial PO_2 can be modeled, as shown in Figure 4-22. The overall effect of such ventilation-perfusion inequality on gas exchange is very small, reducing arterial PO_2 by only approximately 4 mm Hg from that in a homogeneous lung.

Traditional Assessment of Ventilation-Perfusion Inequality

A central question that has engaged the attention of physiologists and physicians for many years has been how best to assess the amount of ventilation-perfusion inequality. Ideally, we would like to know the actual distribution of ventilation-perfusion ratios (see next section), but the procedure required for this is too complicated for many clinical situations. Traditionally we rely on measurements of PO_2 and PCO_2 in arterial blood and expired gas.

The arterial PO_2 certainly gives some information about the degree of ventilation-perfusion inequality. In general, the lower the PO_2 , the more marked is the mismatching of ventilation and blood flow. The chief merit of this measurement is its simplicity, but a disadvantage is that its value is sensitive to the overall ventilation and pulmonary blood flow, to inspired PO_2 , and to other potential causes of hypoxemia already discussed.

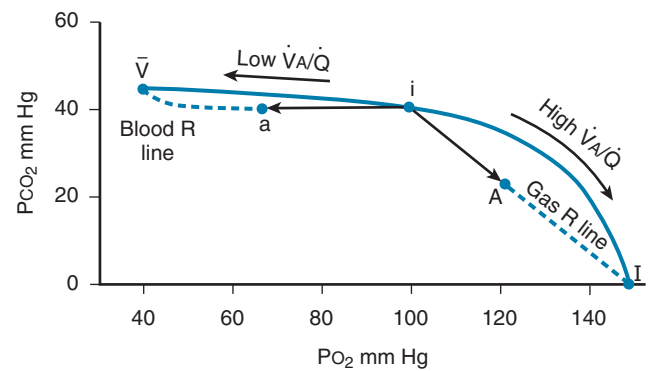


Figure 4-23 Oxygen-carbon dioxide diagram showing the ideal point (i) and the points for arterial blood (a) and alveolar gas (A) (see text for details). I, inspired gas; \dot{Q} , blood flow; R, respiratory exchange ratio; \bar{V} , mixed venous blood; \dot{V}_A , ventilation. (Redrawn from West JB: *Respiratory physiology—the essentials*, ed 9, Baltimore, 2012, Lippincott Williams & Wilkins.)

Arterial PCO_2 is so sensitive to the level of ventilation that it gives little information about the extent of the ventilation-perfusion inequality. However, the most common cause of an increased PCO_2 in chronic lung disease is mismatching of ventilation and blood flow as explained later in the section on ventilation-perfusion inequality and carbon dioxide retention.

Because of these limitations, the alveolar-arterial PO_2 difference is frequently measured and is more informative than the arterial PO_2 alone because it is less sensitive to the level of overall ventilation. To understand the significance of this measurement, we need to look in more detail at how gas exchange is altered by the imposition of ventilation-perfusion inequality.

Figure 4-23 shows an oxygen-carbon dioxide diagram with the same ventilation-perfusion line as that in Figure 4-20. Suppose initially that this lung has no ventilation-perfusion inequality. The PO_2 and PCO_2 of the alveolar gas and arterial blood would then be represented by point i, known as the ideal point. This is at the intersection of the gas and blood respiratory exchange ratio (R) lines; these are the lines that indicate the possible compositions of alveolar gas and arterial blood that are consistent with the overall respiratory exchange ratio (carbon dioxide output/oxygen uptake) of the whole lung. In other words, a lung in which $R = 0.8$ would have to have its mixed alveolar gas point (A) located somewhere on the line joining points i and I. A similar statement can be made for the arterial gas point (a).

What happens to the composition of mixed alveolar gas and arterial blood as ventilation-perfusion inequality is imposed on the lung? The answer is that both points diverge away from the ideal point (i), along the gas and blood R lines. The more extreme the degree of ventilation-perfusion inequality, the further the divergence. Moreover, the type of ventilation-perfusion inequality determines how much each point will move. For example, a distribution containing a large amount of ventilation to units with high ventilation-perfusion ratio especially moves point A down and to the right away from point i. By the same token, a distribution containing large amounts of blood flow to units with low ventilation-perfusion ratios predominantly moves point a leftward along the blood R line.

It is clear that the horizontal distance between points A and a (i.e., the mixed alveolar-arterial PO_2 difference) would be a useful measure of the degree of ventilation-perfusion inequality. Unfortunately, this index is impossible to obtain in most patients because A denotes the composition of *mixed* expired gas, excluding the anatomic dead space gas. In most diseased lungs, the alveoli empty sequentially, with poorly ventilated alveoli emptying last, so that a post-dead space sample is not representative of all mixed expired alveolar gas. In a few patients who have essentially uniform ventilation but uneven blood flow, this index can be used, and it is occasionally reported in patients with pulmonary embolism. In this instance, the PO_2 of end-tidal gas is taken to represent mixed expired alveolar gas.

Because the mixed expired alveolar PO_2 is usually impossible to obtain, a more useful index is the PO_2 difference between ideal alveolar gas and arterial blood, that is, the horizontal distance between points i and a. The ideal alveolar PO_2 is calculated from the alveolar gas equation:

$$PAO_2 = PIO_2 - \frac{PACO_2}{R} + \left[PACO_2 \times FIO_2 \times \frac{(1-R)}{R} \right] \quad [20]$$

To use this equation, we assume that the PCO_2 of ideal alveolar gas is the same as the PCO_2 of arterial blood. The rationale for this is that the line along which point a moves (in Fig. 4-23) is so nearly horizontal that the value is close enough for clinical purposes. It is important to note that this ideal alveolar-arterial PO_2 difference is caused by units situated on the ventilation-perfusion ratio line between points i and \bar{v} , that is, units with abnormally low ventilation-perfusion ratios. This means that a diseased lung may have substantial ventilation-perfusion inequality but a nearly normal ideal alveolar-arterial PO_2 difference if most of the inequality is caused by units with abnormally high ventilation-perfusion ratios.

Physiologic shunt is another useful index of ventilation-perfusion inequality. It measures that movement of the arterial point away from the ideal point along the blood R line (see Fig. 4-23). It is therefore caused by blood flow to lung units with abnormally low ventilation-perfusion ratios. To calculate physiologic shunt, we pretend that all of the leftward movement of the arterial point a is caused by the addition of mixed venous blood \bar{v} to ideal blood i. This is not so unreasonable as it might at first seem because units with very low ventilation-perfusion ratios put out blood that has essentially the same composition as that of mixed venous blood (see Figs. 4-20 and 4-21). The shunt equation is used in the following form:

$$\frac{\dot{Q}_{PS}}{\dot{Q}_T} = \frac{(CiO_2 - CaO_2)}{(CiO_2 - C\bar{v}O_2)} \quad [33]$$

where \dot{Q}_{PS} refers to physiologic shunt, \dot{Q}_T refers to total blood flow through the lung, and CiO_2 , CaO_2 , and $C\bar{v}O_2$, refer to the oxygen concentrations of ideal, arterial, and mixed venous blood, respectively. The oxygen concentration of ideal blood is calculated from the ideal PO_2 and the oxygen dissociation curve. The normal value for *physiologic shunt* is less than 0.05.

The last traditional index to be discussed is *physiologic dead space* (also known as wasted ventilation). Whereas physiologic shunt reflects the amount of blood flow going to lung units with abnormally low ventilation-perfusion

ratios, physiologic dead space is a measure of the amount of ventilation going to units with abnormally high ventilation-perfusion ratios. Thus the two indices provide measurements of both ends of the spectrum of ventilation-perfusion ratios.

To calculate physiologic dead space, we pretend that all the movement of the alveolar point A away from the ideal point i (see Fig. 4-23) is caused by the addition of inspired gas I to ideal gas. Again, this is not so unreasonable as it may first appear, because units with very high ventilation-perfusion ratios behave very much like point I (see Fig. 4-23). Because, as indicated earlier, it is usually impossible to obtain a pure sample of mixed expired gas, we generally collect mixed expired gas and measure its composition, E. The mixed expired gas contains a component from anatomic dead space, which therefore moves its composition further toward point I. The Bohr equation (Equation 9) is then used in the form

$$\frac{VD_{phys}}{VT} = \frac{(PACO_2 - PECO_2)}{PACO_2} \quad [34]$$

where VD_{phys} is physiologic dead space, VT is tidal volume, and $PECO_2$ is mixed expired PCO_2 , and again we exploit the fact that the PCO_2 of ideal gas and that of arterial blood are virtually the same. The physiologic dead space-to-tidal volume ratio is sensitive to tidal volume because of the large contribution of anatomic dead space. The normal value for physiologic dead space is less than 0.3. (For applications of these principles in pulmonary function testing, see Chapter 25.)

Distributions of Ventilation-Perfusion Ratios

The analysis of ventilation-perfusion inequality briefly described in the last section is sometimes known as the *three-compartment model* because the lung is conceptually divided into an unventilated compartment (shunt), an unperfused compartment (dead space), and a compartment that is normally ventilated and perfused (ideal). This way of looking at the diseased lung, which was introduced by Riley and Cournand,⁹² has proved to be of great clinical usefulness in assessing the effects of mismatching of ventilation and blood flow.

However, it was recognized many years ago that real lungs must contain some sort of distribution of ventilation-perfusion ratios and that a three-compartment model is therefore very remote from reality. The great difficulty of dealing with distributions of ventilation-perfusion ratios made progress very slow, although many clinical physiologists saw the measurement of distributions as an important goal.

The breakthrough came with the application of computer analysis of the behavior of distributions, a very complex area because of the nonlinear and interdependent oxygen and carbon dioxide dissociation curves. With computer analysis, it was possible to make considerable advances in the understanding of the behavior of distributions of ventilation-perfusion ratios.⁹⁵ This allowed the multiple inert gas elimination technique to become the standard research technique for measuring patterns of ventilation-perfusion distributions in normal subjects and patients with lung disease.⁹⁶

Multiple Inert Gas Elimination Technique. The principles governing inert gas elimination by the lung are identical to those of oxygen and carbon dioxide, and are dictated by equations corresponding to Equations 31 and 32. When an inert gas dissolved in saline is steadily infused into the peripheral venous circulation, it arrives at the lungs, and some of the gas will be exhaled. The proportion of gas that is eliminated by ventilation from the blood of a given lung unit depends only on the blood-gas partition coefficient of the gas (λ) and the ventilation-perfusion ratio (\dot{V}_A/\dot{Q}).^{100,101} The relationship is given by the following equation:

$$\frac{Pc'}{P\bar{v}} = \frac{\lambda}{(\lambda + \dot{V}_A/\dot{Q})} \quad [35]$$

where Pc' and $P\bar{v}$ are the partial pressures of the gas in end-capillary blood and mixed venous blood, respectively. Equation 35 looks different from Equations 31 and 32 only because inert gases obey Henry's law, allowing concentration to be replaced by the product of solubility and partial pressure. This in turn permits the rearrangement of terms ending up with Equation 35. The ratio of end-capillary to mixed venous partial pressure is known as the *retention*. This equation is derived from exactly the same considerations of mass balance as applied to carbon dioxide in Equation 5.

In practice, a mixture of six gases (typically, sulfur hexafluoride, ethane, cyclopropane, isoflurane, ether, and acetone) is dissolved in saline and infused into a peripheral arm vein at the rate of 3 mL/min until a steady state of gas exchange is achieved (10 to 20 minutes). Samples of mixed expired gas and arterial blood are then taken, and the gas concentrations in each are determined by gas chromatography. At the same time, cardiac output is obtained (e.g., by indicator dilution, echocardiography, or other method), and total ventilation is also measured. From these data, mixed venous concentrations of each inert gas can be calculated and retention determined. In patients who already have an indwelling pulmonary arterial catheter, a sample of mixed venous blood could be taken instead to measure mixed venous inert gas levels directly.

A graph is then constructed, as shown in Figure 4-24. The upper panel shows the data points of inert gas retention (arterial partial pressure divided by mixed venous partial pressure), which are joined for clarity by the broken line. Below this are the data points for excretion (mixed expired partial pressure divided by mixed venous partial pressure). Both are plotted against the partition coefficient. Again, the points are joined by a broken line. For comparison, the two solid lines show the values of retention and excretion for a lung with no ventilation-perfusion inequality but with the same overall ventilation and blood flow. The broken and solid lines are very close together in Figure 4-24, and the differences are more easily seen in Figure 4-25, where the lung is diseased.

These plots, called the retention-solubility and excretion-solubility curves, contain information about the distribution of ventilation-perfusion ratios in the lung. For example, if a lung contains units that are perfused but not ventilated (shunt), these particularly increase the retention of the least soluble gas, sulfur hexafluoride. Conversely, if the distribution contains large amounts of ventilation to lung units with very high ventilation-perfusion ratios, the excre-

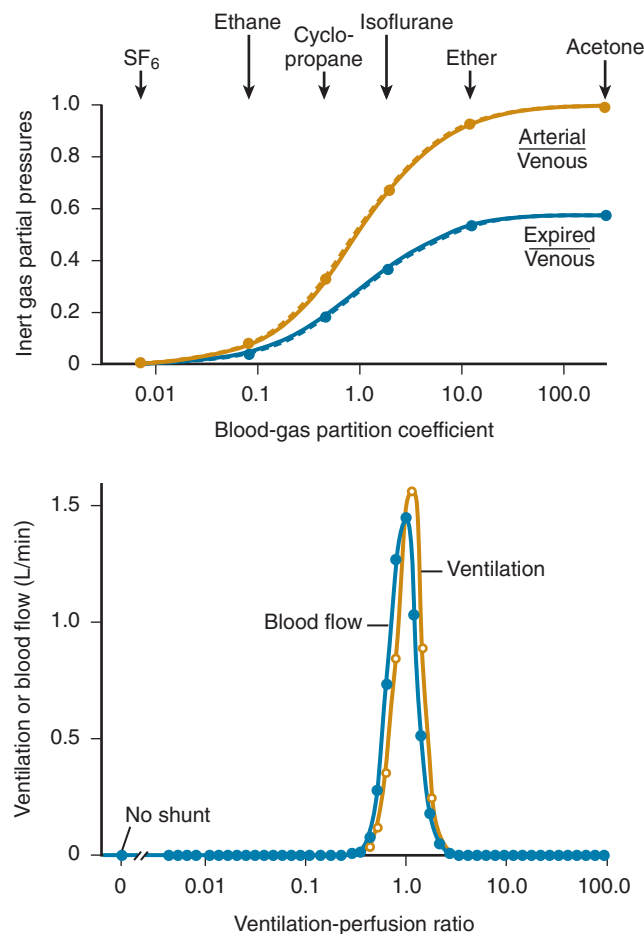


Figure 4-24 Use of the multiple inert gas elimination technique to determine the distribution of ventilation-perfusion ratios in a 22-year-old normal subject. Upper panel, Data points for inert gas retention (upper curve) and excretion (lower curve). Broken lines join the points. The two solid lines show the values of retention and excretion for a lung with no ventilation-perfusion inequality. Lower panel, The recovered distribution of ventilation-perfusion ratios. SF_6 , sulfur hexafluoride. (Redrawn from Wagner PD, Laravuso RB, Uhl RR, West JB: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2 . *J Clin Invest* 54:53–68, 1974.)

tion of the high-solubility gases is chiefly affected. The relationship between the distribution of ventilation-perfusion ratios and the retention-solubility and excretion-solubility curves can be expressed formally by a set of simultaneous linear equations.¹⁰² These equations, one for each inert gas, simply reflect the principles of mass conservation and relate the ventilation-perfusion distribution (i.e., the paired set of gas-exchange unit blood flows and ventilations) to a measured set of inert gas retention and excretion values. The distribution of ventilation-perfusion ratios that is consistent with the pattern of inert gas retention and excretion is then determined using computer programs that solve these simultaneous equations.

The potential and limitations of this transformation have been explored in great detail.¹⁰² The recovered distribution is not unique, but, in most cases, the range of possible distributions compatible with the data is small. No more than three modes of a distribution can be recovered, and only smooth distributions can be obtained. In spite of these limitations, however, the technique gives much more

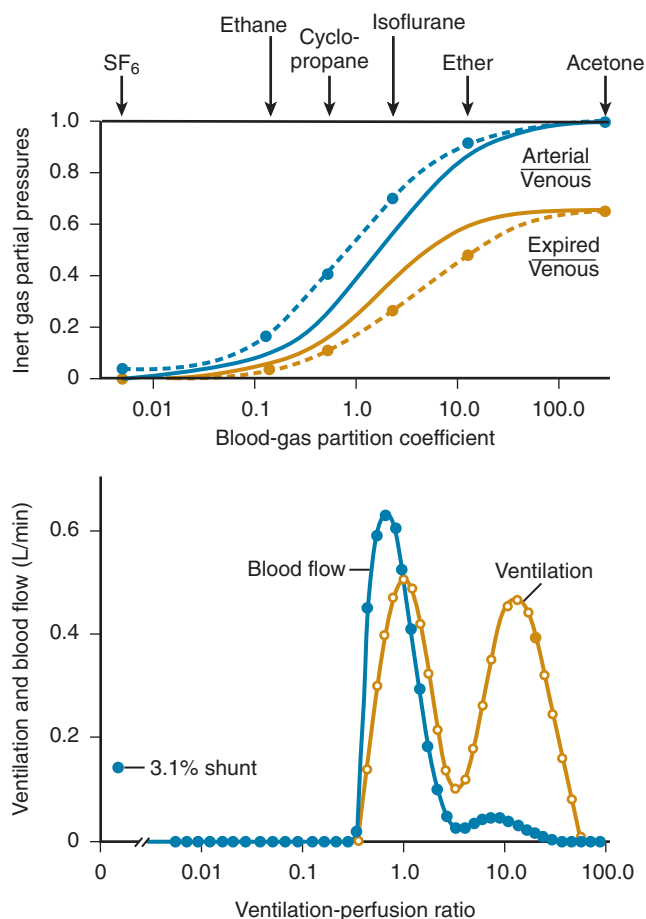


Figure 4-25 Distribution of ventilation-perfusion ratios in a 60-year-old patient with COPD, predominantly emphysema. Upper panel, The retention and excretion solubility curves. Lower panel, The recovered distribution of ventilation-perfusion ratios. SF_6 , sulfur hexafluoride. (Redrawn from Wagner PD, Dantzker DR, Dueck R, et al: Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest* 59:203–216, 1977.)

information about patterns of distribution of ventilation-perfusion ratios in patients with lung disease than has previously been available.

Distribution in Normal Subjects. Figure 4-24 shows retention- and excretion-solubility curves and the derived distribution of ventilation-perfusion ratios from a 22-year-old normal volunteer.¹⁰³ First, note that the retentions and excretions as indicated by the data points and broken lines in the upper panel are almost superimposed on the solid lines for a homogeneous lung. The recovered distribution (lower panel) is consistent with these data and shows that the plots of both ventilation and blood flow are narrow, spanning only one decade of ventilation-perfusion ratios (i.e., from a ventilation-perfusion ratio of 0.3 to one 10 times higher, of 3). As expected, this range of ventilation-perfusion ratios is slightly greater than the regional differences, which mainly depend on gravity alone (see Fig. 4-22). However, there was essentially no ventilation or blood flow outside this range on the ventilation-perfusion ratio scale. Note also that there was no shunt, that is, blood flow to unventilated alveoli. The absence of shunt was a consistent finding in all the normal subjects studied and was initially surprising. It should be pointed out that, first,

this technique is very sensitive, in that a shunt of only 0.5% of the cardiac output approximately doubles the arterial concentration of sulfur hexafluoride. Apparently, young normal subjects are able to ventilate essentially all of their alveoli. Second, bronchial and thebesian shunts are not detected by the method.

In normal subjects the measured arterial PO_2 value is consistent with that modeled for a given ventilation-perfusion distribution and assuming diffusion equilibrium for oxygen. This means that ventilation-perfusion heterogeneity explains all of the difference between ideal alveolar PO_2 and arterial PO_2 in normal lungs. For example, in older normal subjects the dispersion of the ventilation-perfusion distribution increases, and this explains the gradual fall in arterial PO_2 observed with aging. Ventilation-perfusion mismatching must take place between lung units perfused by vessels 150 μm in diameter or larger to have a significant effect on arterial PO_2 .¹⁰⁴ This means the functional unit of oxygen exchange in terms of ventilation-perfusion matching is the acinus, or lung units distal to a terminal bronchiole.

Distributions in Lung Disease. Figure 4-25 shows a typical distribution of ventilation-perfusion ratios from a patient with COPD. The distribution is typical of the pattern seen in patients believed to have, predominantly, emphysema.¹⁰⁵ The upper panel shows that the measured retentions and excretions (dots, dashed lines) deviated greatly from those expected in a homogeneous lung with the same total ventilation and blood flow (solid lines). Consistent with this, the lower panel shows a broad bimodal distribution, with large amounts of ventilation to lung units with extremely high ventilation-perfusion ratios (alveolar dead space). Note the small shunt of 3.1%. The mild hypoxemia in this patient (arterial PO_2 of 63 mm Hg) is explained mostly by the slight displacement of the main mode of blood flow to the left of normal. Presumably the high ventilation-perfusion ratio mode reflects ventilation to lung units in which many capillaries have been destroyed by the emphysematous process, reducing their perfusion. Patients with acute pulmonary embolism often show a ventilation-perfusion ratio pattern similar to that in Figure 4-25. This is well explained by continuing ventilation in poorly perfused embolized regions. Sometimes shunts are seen as well, possibly from scattered atelectasis, possibly from edema, and possibly from right-to-left shunting through a patent foramen ovale when right atrial pressure is elevated.

Patients with COPD whose predominant lesion is severe bronchitis generally show a different pattern. The main abnormality in the distribution is a large amount of blood flow going to lung units with very low ventilation-perfusion ratios, between 0.005 and 0.1. This explains the more severe hypoxemia in this type of patient and is consistent with a large physiologic shunt. Presumably, the low ventilation-perfusion ratios in some lung units are the result of partially blocked airways due to retained secretions and airway disease that reduces airway diameter. However, it is interesting that these patients generally do not show much shunting (blood flow to unventilated alveoli), and a possible explanation is collateral ventilation. It should be emphasized that the distributions found in severe chronic bronchitis show considerable variability.

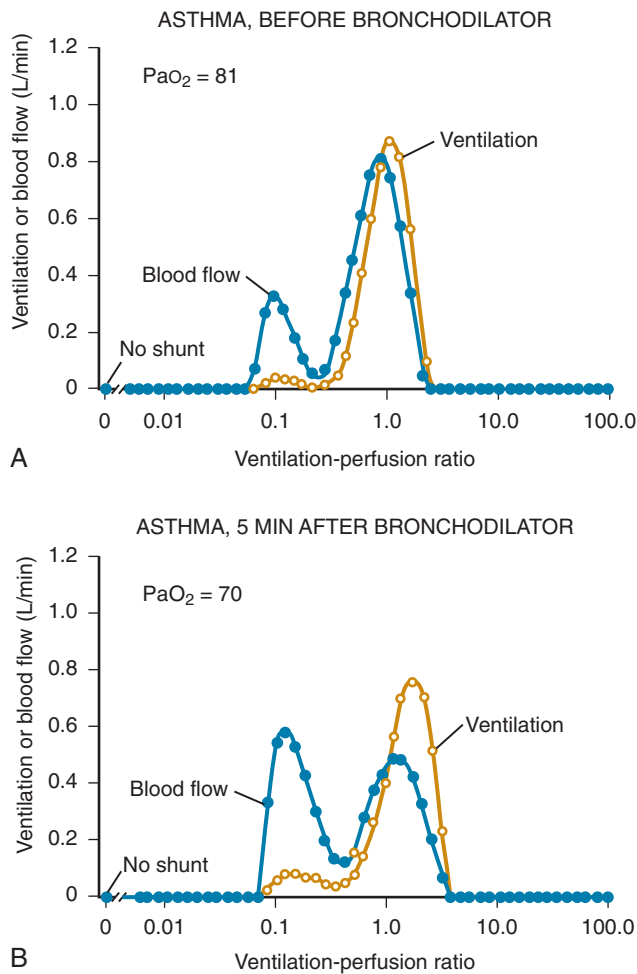


Figure 4-26 Distribution of ventilation-perfusion ratios in a patient with asthma before (A) and after (B) the administration of isoproterenol by aerosol. (Redrawn from Wagner PD, Dantzker D, Lacovoni VE, et al: Ventilation-perfusion inequality in asymptomatic asthma. *Am Rev Respir Dis* 118:511–524, 1978.)

A particularly interesting pattern of ventilation-perfusion ratios has been seen in some patients with asthma, even in remission.¹⁰⁶ Figure 4-26A shows an obvious bimodal appearance, with some 25% of the total blood flow going to lung units with ventilation-perfusion ratios in the region of 0.1. However, there was no blood flow to unventilated units. When this patient was given a β -adrenergic bronchodilator by aerosol, the distribution changed, as shown in Figure 4-26B. There was a marked increase in the amount of blood flow to low ventilation-perfusion ratio units, and this was associated with a corresponding decrease in arterial PO_2 from 81 to 70 mm Hg. However, the pattern was short lived; 5 minutes later, the distribution had returned to the pattern shown in Figure 4-26A, and the PO_2 was back to the prebronchodilator level. The bronchodilator effects of the drug on the airflow had a much longer duration.

Such a fall in arterial PO_2 is often seen in asthmatics after bronchodilator therapy even with improved airflow.^{60,61} The reason for the redistribution of blood flow is probably that the blood vessels supplying the hypoxic low ventilation-perfusion ratio units dilate preferentially in response to the β -adrenergic agonists. Modern bronchodilators cause less

hypoxemia than shown in Figure 4-26 and also less deterioration in the ventilation-perfusion ratio distribution.

It was surprising that this almost asymptomatic patient had as much ventilation-perfusion ratio inequality as shown in Figure 4-26. The extent of the abnormality of the distribution suggests that there were many more abnormalities in the lung, including obstruction of small airways, than were indicated by the patient's symptoms. One lung model consistent with the observed data is that half of the small airways may have been totally occluded by mucous plugs and/or airway wall edema, and that the lung subtended by them was ventilated through collateral channels. However, it should be emphasized that not all well-managed asthmatics show such abnormal distributions of ventilation-perfusion ratios. In some, the distribution is unimodal with little or no increase in dispersion. Importantly, the extent of ventilation-perfusion ratio inequality cannot be predicted from the impairment in spirometry.

Patients with acute respiratory distress syndrome commonly show a full spectrum of ventilation-perfusion ratio abnormalities, especially shunt, but also low ventilation-perfusion ratio regions, areas of normal ventilation-perfusion ratio, high ventilation-perfusion ratio regions, and increased ventilation of unperfused lung.

Newer techniques are being developed to image and quantify ventilation-perfusion matching, and even alveolar PO_2 , but they do not yet have the resolution of the multiple inert gas elimination technique.^{6,107} However, with sufficient spatial and temporal resolution, such methods could be useful for determining whether high ventilation-perfusion regions in patients with COPD (see Fig. 4-25) are indeed explained by the emphysematous bullae or whether the bimodal ventilation-perfusion distribution found in asthma (see Fig. 4-26) is regionally fixed or moves around.

Ventilation-Perfusion Inequality and Carbon Dioxide Retention

It is important to remember that ventilation-perfusion inequality interferes with the uptake and elimination of all gases by the lung (oxygen, carbon dioxide, carbon monoxide, and anesthetic gases). In other words, mismatching of ventilation and blood flow reduces the overall gas-exchange efficiency of the lung. There has been considerable confusion in this area, particularly about the role of ventilation-perfusion inequality in carbon dioxide retention.

Imagine a lung that is uniformly ventilated and perfused and that is transferring normal amounts of oxygen and carbon dioxide. Suppose that the matching of ventilation and blood flow is suddenly disturbed while everything else remains unchanged. What happens to gas exchange? It can be shown that the effect of this "pure" ventilation-perfusion inequality (i.e., with all other factors held constant) is to reduce both the oxygen uptake and carbon dioxide output of the lung.⁹⁵ The lung becomes less efficient as a gas exchanger for both gases, and therefore mismatching of ventilation and blood flow must cause hypoxemia and hypercapnia (carbon dioxide retention), other things being equal.

In practice, however, patients with ventilation-perfusion inequality often have a normal arterial PCO_2 . The reason for this is that, whenever the chemoreceptors sense a rising PCO_2 , there is an increase in ventilatory drive. The

consequent increase in ventilation to the alveoli usually returns the arterial PCO_2 to normal. However, such patients can only maintain a normal PCO_2 at the expense of this increased ventilation to their alveoli. The ventilation in excess of what they would normally require is sometimes referred to as *wasted ventilation* and is necessary because the lung units with abnormally high ventilation-perfusion ratios contribute little to eliminating carbon dioxide. Such units are part of the alveolar (physiologic) dead space.

Patients with ventilation-perfusion ratio inequality that causes carbon dioxide retention are sometimes said to be “hypoventilating,” but in fact they may actually be breathing more than normal. “Hypoventilation” as a synonym for hypercapnia is used by people who define the adequacy or inadequacy of alveolar ventilation by whether it maintains a normal arterial PCO_2 . “Alveolar ventilation” in this context does not refer to all the gas entering the lung alveoli but is related to “ideal alveolar” gas and excludes alveolar dead space gas. In this chapter the term *alveolar* has been used to refer to all the gas in the lung, excluding the conducting airways that contain anatomic dead space. True hypoventilation was discussed in an earlier section when the relationship between alveolar ventilation and PCO_2 was examined.

Historically it is easy to see how the term *hypoventilation* came to be applied so indiscriminately. When in the late 1950s it became possible to measure the PCO_2 of the arterial blood in the clinical setting, carbon dioxide retention was found to be a common and serious complication of chronic lung disease that could always be abolished by artificially increasing the ventilation. Thus it was natural to say that these patients had an abnormally low ventilation, and the term *hypoventilation* had the advantage of keeping an important therapeutic option in the forefront.

However, far from having a reduced ventilation, most of these patients are moving far more air into their alveoli than normal subjects. Indeed, all patients with chronic lung disease and ventilation-perfusion inequality who have a *normal* arterial PCO_2 must have *increased* the ventilation to their alveoli, and this applies to most patients with carbon dioxide retention as well.

Although patients with mismatched ventilation and blood flow can usually maintain a normal arterial PCO_2 by increasing the ventilation to the alveoli, this strategy is much less effective at increasing the arterial PO_2 . The reason for the different behavior of the two gases lies in the different shapes of the carbon dioxide and oxygen dissociation curves. The carbon dioxide dissociation curve is almost straight in the physiologic range, with the result that an increase in ventilation raises the carbon dioxide output of lung units with both high and low ventilation-perfusion ratios. By contrast, the nonlinearity of the oxygen dissociation curve means that not all lung units benefit from increased ventilation in terms of increasing oxygen concentration in their effluent blood. Those units with high ventilation-perfusion ratio, which operate high on the flat portion of the dissociation curve, increase the oxygen concentration in blood very little despite large increases in PO_2 . In units with a low ventilation-perfusion ratio, PO_2 in blood will increase more but, because such units operate on the steep portion of the dissociation curve, oxygen concentration remains close to that of mixed venous blood. The net

result is that the mixed arterial PO_2 rises only modestly, and some hypoxemia always remains.

In summary, carbon dioxide retention can result from two clearly distinct mechanisms: pure hypoventilation and ventilation-perfusion inequality. The latter is a common cause in clinical practice.

Effect of Changes in Cardiac Output on Gas Exchange in the Presence of Ventilation-Perfusion Inequality

In a lung with no ventilation-perfusion inequality, the cardiac output has no effect on arterial PO_2 or PCO_2 . This follows from Equations 5 and 17, which do not contain cardiac output. By contrast, these equations show that the level of total ventilation is very important.

However, in a lung with ventilation-perfusion inequality, cardiac output can have a major effect on arterial PO_2 , and this is important in some clinical settings. A reduction in cardiac output reduces the PO_2 of mixed venous blood, which in turn exaggerates the hypoxemia. This is sometimes seen in patients with myocardial infarction, in whom the reduction in arterial PO_2 seems to be out of proportion to the degree of ventilation-perfusion inequality. The opposite is sometimes seen in patients with bronchial asthma, who may have unusually high cardiac outputs, especially when treated with some β -agonist drugs. The result is that the arterial PO_2 is higher than would be expected from the degree of ventilation-perfusion inequality. This important modulating effect of cardiac output on gas exchange is often overlooked in the clinical setting.

OXYGEN SENSING

The responses of the body to hypoxia have been greatly clarified by the discovery of *hypoxia inducible factors* (HIFs). The initial finding was of a protein that bound to the hypoxia response element of the erythropoietin gene under hypoxic conditions.¹⁰⁸ Later it became clear that HIFs are critically important in a large number of responses of cells to hypoxia. In fact, it is now known that in cellular hypoxia the transcription of over a hundred messenger RNAs is increased and the expression of an equal number of messenger RNAs is decreased.¹⁰⁹

HIFs are transcription factors that are influenced by the amount of oxygen in the cell. A transcription factor is a protein that binds to specific DNA sequences in a gene and thus controls the flow of genetic information from DNA to messenger RNA. Cellular hypoxia causes an increased concentration of HIF-1 α which then binds to HIF-1 β and consequently influences the hypoxia response element. It is now known that most oxygen-breathing species express these transcriptional factors, indicating that HIFs have been highly conserved. For example HIF-1 is expressed in very primitive animals such as the worm *Caenorhabditis elegans* that do not have specialized respiratory or circulatory systems. This implies that HIF was initially developed to enhance the survival of individual cells in low-oxygen environments.

HIFs control genes that have many functions throughout the physiologic spectrum. These include mitochondrial genes involved with energy utilization, glycolytic enzyme genes influencing anaerobic metabolism, genes associated

with vascular endothelial growth factor controlling angiogenesis, genes of nitric oxide metabolism and ion channels on smooth muscle cells involved with the control of pulmonary blood flow, erythropoietin genes affecting red cell production, and genes controlling the induction of tyrosine hydroxylase, which plays a role in the function of the carotid body chemoreceptor.^{62a} Of particular interest is cancer, a condition that requires more energy¹¹⁰ that can be supplied by a HIF pathway. Furthermore, tumor-associated inflammation causes the induction of glycolytic pathways¹¹¹ that utilize HIF signaling. Thus HIFs constitute a master switch in the general response of the body to hypoxia.

Key Points

- The magnitudes of ventilation and perfusion, as well as their distribution, are key factors determining pulmonary gas exchange.
- Distribution of ventilation and perfusion is predominantly affected by gravity in the normal lung, but intrinsic lung structure also plays a role.
- Distribution of ventilation-perfusion (\dot{V}_A/\dot{Q}) ratios is nonuniform, the \dot{V}_A/\dot{Q} ratio being generally higher in nondependent lung regions and lower in dependent lung regions.
- Regional alveolar P_{O_2} and P_{CO_2} are determined principally by the \dot{V}_A/\dot{Q} ratio of each region. Secondary factors are the P_{O_2} and P_{CO_2} of inspired gas and mixed venous blood and also the shape of the oxygen and carbon dioxide dissociation curves.
- There are four causes of hypoxemia: hypoventilation, alveolar-capillary diffusion limitation, shunt, and \dot{V}_A/\dot{Q} inequality.
- There are two principal causes of hypercapnia: hypoventilation and \dot{V}_A/\dot{Q} inequality.
- \dot{V}_A/\dot{Q} inequality is the most important cause of gas-exchange abnormalities in most lung diseases.

Complete reference list available at *ExpertConsult*.

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RESPIRATORY SYSTEM MECHANICS AND ENERGETICS

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INTRODUCTION

The movement of gases in and out of the respiratory system may be described by the physical laws that govern pressure, volume, and flow of gas. The study of these relationships is called “respiratory mechanics,” and the study of the energy cost of gas movement is called “energetics.”

This chapter reviews basic terminology, respiratory mechanics under static and dynamic conditions, and energetics, including measurements of the work of breathing. The chapter also highlights how physiologic principles can be applied to specific clinical problems.

TERMINOLOGY

FLOW

Flow is defined as the volume of gas passing a fixed point per unit of time. Flow is usually measured with a pneumotachygraph (flowmeter), which consists of a tube with a known fixed resistance. Flow can be calculated by measuring the pressure drop across the resistor.

Gas velocity is the distance moved by a gas molecule per unit of time and should not be confused with flow. At a constant flow, gas velocity will be greater in narrower tubes (Fig. 5-1).

VOLUME

Volume is defined by the space occupied by a gas. The volume occupied by a fixed number of gas molecules is determined by temperature and pressure.

The volume of gas entering and leaving the lung can be determined by a spirometer that measures volume displacement or by integrating the flow signal measured by a pneumotachygraph. The subdivisions of lung volumes are shown in Figure 5-2. Some of these subdivisions can be measured

by spirometry alone (vital capacity, tidal volume), whereas others require use of plethysmography or helium dilution. *Total lung capacity* (TLC) is the lung volume at the end of a maximal inspiration. Residual volume is the volume at the end of a maximal expiratory effort. *Functional residual capacity* (FRC) refers to the volume in the lung at the end of a normal tidal exhalation, when there is normally relaxation of both inspiratory and expiratory muscles.

Total gas volume in the lung is usually measured at FRC using plethysmographic methods or by inert gas dilution methods, and each of these techniques has advantages and disadvantages.¹ Traditional body plethysmography is widely available and accurate. For the body plethysmography technique, subjects are completely enclosed in a gas-tight container. Lung volume can be calculated by comparing changes in alveolar pressure (measured at the mouth while the patient pants against an occluded mouthpiece) with changes in pressure in the container.² Body plethysmography may overestimate lung volumes because it will include measurement of abdominal gas if that gas is compressed and decompressed during the panting maneuver. Plethysmographs that use electrical inductance^{3,4} or optical data⁵ have been advanced as noninvasive methods for the measurement of lung volumes in those not able to tolerate traditional plethysmography. However, given the limited experience with these modalities in clinical settings, they are best considered experimental advances at this time.^{6,7}

Because spirometry cannot estimate FRC, one of several inert gas dilution techniques (usually with helium or nitrogen) or radiologic assessments is used. Historically, inert gas methods have usually used helium. For this method, subjects at FRC inhale a known concentration and volume of helium. The helium mixes with and is diluted by the gas already in the lung. A sample of exhaled gas is analyzed for helium concentration, allowing calculation of the FRC thus:

$$C_1 \times V_1 = C_2 \times (V_1 + \text{FRC})$$

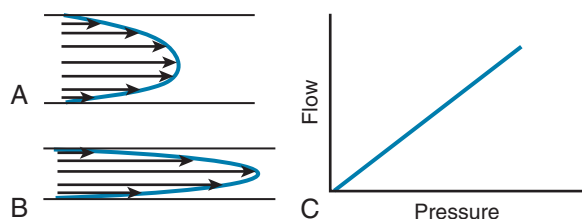


Figure 5-1 Laminar flow through a tube. A, Schematic depiction of the spatial and velocity profiles of gas molecules within a laminar flow system. The velocity of the gas molecules is proportional to the length of the arrows. For laminar flow, velocity is greatest in the center of the tube and least close to the edge. B, When tube diameter is reduced, the same gas flow rate will result in increased velocity of the individual gas molecules. C, During laminar flow, there is a linear relationship between pressure and flow.

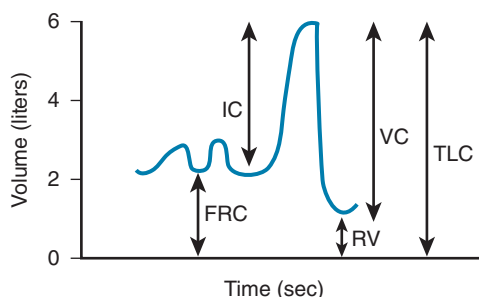


Figure 5-2 Subdivisions of lung volume. Volume-time tracing of a subject taking two normal tidal breaths, inhaling to total lung capacity (TLC), and exhaling to residual volume (RV). Vital capacity (VC) and inspiratory capacity (IC) may be measured with a spirometer. The measurement of functional residual capacity (FRC), RV, and TLC requires a determination of intrathoracic gas volume by plethysmography, helium dilution, or nitrogen washout.

where C_1 is the initial (known) helium concentration in the bag, C_2 is the final (measured) helium concentration, and V_1 is the initial volume of gas in the bag. Therefore

$$FRC = V_1 \times (C_1 - C_2) / C_2$$

By the same principle other nonrespiratory gases, such as sulfur hexafluoride (SF_6), may be used to calculate FRC. In general, inert gas dilution measurements tend to underestimate total lung volume, especially in patients with substantial airway obstruction who may have gas trapped in lung units that does not mix with inspired gas.

Another method uses the respiratory gases naturally present in a subject's lungs (such as nitrogen) to be used for FRC determination. In the simplest form, measurement of FRC using the nitrogen dilution method requires the subject to be ventilated with a 100% oxygen gas mixture to allow the washout of nitrogen from the respiratory system. Once all the nitrogen has been washed out, the initial gas mixture (oxygen/air) is reinstituted, and the concentration of nitrogen is repeatedly sampled until it returns to the baseline level. The trajectory of nitrogen concentration in the exhaled gas allows the estimation of FRC. Unfortunately, the basic technique is complicated by time delays from gas analyzers. Adjustment for these delays is possible but is complex because the delay depends on gas viscosity, which changes as the nitrogen and oxygen concentrations change.⁸

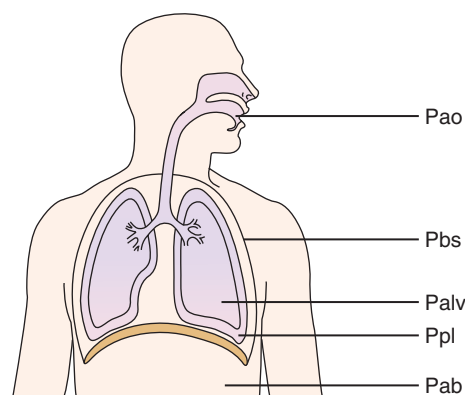


Figure 5-3 Respiratory system pressures. Pao, pressure at airway opening; Pbs, pressure at body surface; Palv, pressure in alveolus; Ppl, pressure in pleural space; Pab, pressure in abdomen. Transpulmonary pressure: $P_{ao} - P_{pl}$; translung pressure: $P_{alv} - P_{pl}$; transchest wall pressure: $P_{pl} - P_{bs}$; transrespiratory system pressure: $P_{ao} - P_{bs}$; transdiaphragmatic pressure: $P_{pl} - P_{ab}$. Under static conditions, when the subject is not on assisted ventilation, Pao is equal to 0 (atmospheric pressure). However, Pao may be positive when the patient is receiving positive-pressure mechanical ventilation. Pbs is equivalent to atmospheric pressure unless the subject is in a negative pressure device such as an iron lung.

Imaging modalities such as computed tomography (CT) and magnetic resonance imaging can provide accurate assessment of FRC.^{6,9-12} CT may overestimate the volume of alveolar gas available for gas exchange because it measures the entire volume of gas in the lung irrespective of whether that gas is trapped and is not partaking in gas exchange.⁸

PRESSURE

The pressure of a gas is generated from the momentum of molecules colliding against a surface and is expressed as the force per unit area. Pressure, as opposed to force, is the same in all directions. Respiratory system pressures are usually reported relative to atmospheric pressure.

The pressures relevant to the respiratory system are shown in Figure 5-3. Although it is possible to measure pleural pressure directly, it is usual to use esophageal pressure as a less invasive surrogate. Esophageal pressure may be measured using an air-filled balloon inserted into the middle third of the esophagus, approximately 35 to 45 cm from the nares.¹³⁻¹⁵ Balloons placed in the proximal third can be affected by movement of the neck, and balloons placed in the distal third can record falsely high readings owing to compression by the heart. Absolute values of pressure may be difficult to interpret in the supine position owing to the weight of the mediastinum.

THE COMBINED GAS LAW

For an ideal gas the relationship between volume, pressure, temperature, and the number of molecules of gas is described by the combined gas law:

$$PV = nRT$$

where P is the absolute pressure of the gas, V is the volume, n is the number of moles of gas, R is the universal gas

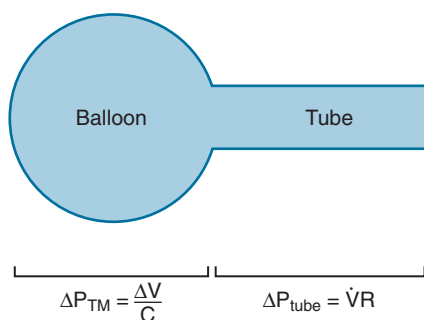


Figure 5-4 Balloon-and-tube analogy of the respiratory system, where ΔP_{TM} = change in transmural pressure (inside – outside) of the balloon; ΔV = change in volume; C = compliance; \dot{V} = flow; R = resistance; and ΔP_{tube} = pressure difference from one end of the tube to the other.

constant (8.3145 J/[mol K]), and T is the temperature in degrees Kelvin.

This equation summarizes earlier gas laws, including Boyle's law ($PV = \text{constant}$), Charles' law ($V/T = \text{constant}$), Gay-Lussac's law ($P/T = \text{constant}$), and Avogadro's law ($n/V = \text{constant}$). The volume of a gas should thus increase as the number of molecules of gas increases, the temperature increases, or the applied pressure decreases. Although this equation theoretically applies only to an ideal or perfect gas, it is an adequate approximation for clinical purposes.

COMPLIANCE, RESISTANCE, AND TIME CONSTANTS

The respiratory system can be thought of as a combination of balloons and tubes (Fig. 5-4). As the pressure across the wall of a balloon increases (called “transmural pressure,” or “pressure inside minus pressure outside”), the volume inside the balloon increases (see Fig. 5-4). The ratio between the change in volume and the change in transmural pressure is the compliance of the balloon. The units of compliance are volume/pressure. A large compliance indicates that volume changes markedly for every change in pressure. The inverse of compliance is elastance, with a greater value indicating a stiffer system.

Resistance is a measure of the pressure required to generate flow through a tube. The narrower the tube, the greater the pressure needed and the higher the resistance. The units of resistance are pressure/flow. The inverse of resistance is conductance, with a greater value indicating a more dilated airway. Flow in a tube may be laminar or turbulent, with significant implications for the amount of pressure drop or energy required to drive gas movement.

When a pressure is applied to a lung unit (Fig. 5-5), the time required to fill the unit is dependent on its compliance and resistance. That is, it will take longer to fill if resistance is high because the flow will be reduced. Similarly, it will take longer to fill the unit if compliance is high because it will require more volume. The product of the *resistance and compliance* (RC) of a lung unit is the time constant and represents the time required for the lung unit to fill to 63% of the final volume if a constant pressure is applied. Areas of the lung with small time constants (i.e., low resistance and/or low compliance) will fill more rapidly than areas with larger time constants.

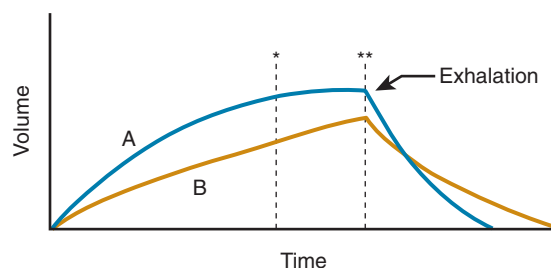


Figure 5-5 Time constants. Shown are two units of equal volume, one with a very short time constant, A, and one with a long time constant, B. Each is inflated under a constant pressure until point **, and then exhalation is passive. At point **, unit A is completely filled, but unit B is not. Of note, when time constants are uneven as shown here, decreasing inspiration time to point * will worsen heterogeneity in ventilation.

The effect of variations in time constants of lung units is shown in Figure 5-5. This concept has clinical implications when there are heterogeneous time constants between parallel lung units, as in patients with chronic airflow obstruction or with patchy alveolar edema/atelectasis as is found in *acute respiratory distress syndrome* (ARDS). As long as respiratory frequency is slow, all units will fill to their static equilibrium. However, if respiratory rate increases so that the inspiratory time becomes less than the time constant of some units, these units will receive less ventilation and contribute to ventilation-perfusion mismatch.

RESPIRATORY MECHANICS IN STATIC CONDITIONS

We first consider the lung during static conditions, during which measurements are made while the respiratory system is maintained at a fixed volume with no gas flow. Even under static or no-flow conditions, pressure gradients are still required to distend the respiratory system (analogous to the balloon described previously). The energy used to distend the respiratory system during inhalation (elastic work) is stored as potential energy. Because of this stored energy, normal exhalation does not require work and is a passive process. This contrasts with resistive work (discussed later in this chapter), which cannot be stored as potential energy and is dissipated as heat. The elastic work performed to inflate the respiratory system has both lung and chest wall components.

ELASTIC RECOIL OF THE LUNGS

If removed from the body, an isolated lung will deflate because of its elastic recoil to a minimal volume containing only trapped gas. Because airways close before complete alveolar emptying, application of a negative pressure to the airway opening will not remove the trapped gas. The relationship between lung volume and transpulmonary pressure during inflation is shown in Figure 5-6. Lung compliance is fairly high at the lung volumes associated with normal breathing but then decreases markedly near TLC. At TLC, very large increases in transmural pressure result in small changes in volume.

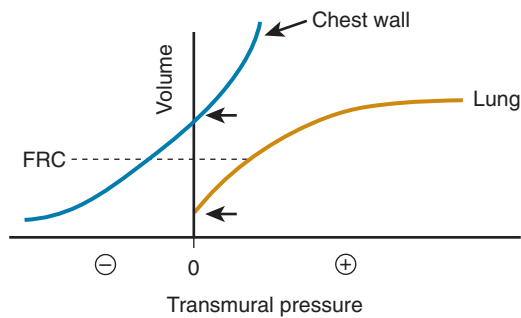


Figure 5-6 Volume-pressure curves of lung and chest wall. The relationship between transmural (inside – outside) pressure of lung and relaxed chest wall volume are shown. The static equilibrium of the chest wall is above FRC, whereas that for the lung is below FRC (arrows).

Two major factors are responsible for the elastic recoil of the lung: (1) lung connective tissue and (2) surface tension related to the air-liquid interface of the alveolar surface.

Lung Connective Tissue

A network of connective tissue fibers provides the framework for the alveoli and structural integrity for the lung. The fibers are composed mostly of collagen and elastin. Collagen fibers exhibit high tensile strength but are relatively noncompliant. They can be extended by only 2% of their length.¹⁶ This contrasts with elastin, which has a lower tensile strength and is more compliant; elastin fibers can be stretched by as much as 130% of their length. Experiments using selective destruction of fibers by collagenase or elastase show that elastin fibers are the major contributors to the volume-pressure relationships at low lung volumes, whereas collagen is more important at higher volumes approaching TLC.^{17,18} At low lung volumes, elastin fibers bear much of the stress, and collagen fibers are curled and unstressed. As lung volume increases, collagen fibers uncurl and straighten and have a major stiffening effect on the lung. In other words, the major role of collagen is to limit overdistention of the lung, and the major role of elastin is to facilitate inflation while providing lung stability to maintain the configuration of internal structures.

Destruction of lung connective tissue, from smoking-induced emphysema for instance, can substantially increase lung compliance.¹⁹ Contraction of smooth muscle in the airways and alveolar ducts may also affect elastic recoil because contraction of smooth muscle reduces volume by exerting traction on the lung (similar to a drawstring).²⁰ Although contraction of airway smooth muscle in the peripheral lung units (small airways and alveolar ducts) changes lung compliance in several different animal species, there is little effect of contraction of lung smooth muscle on the shape of the volume-pressure curve in humans.²¹⁻²³

Alveolar Surface Forces and Surfactant

When a lung is completely filled with water, compliance is much greater than when it is filled with air.²⁴ This suggests that the majority of lung elastic recoil is due to surface tension at the air-liquid interface lining the alveoli, rather than the recoil from elastin and collagen connective tissue fibers (see Chapter 8 for more details).

Because there are intermolecular forces of attraction between molecules of liquids, the surface of an air-liquid

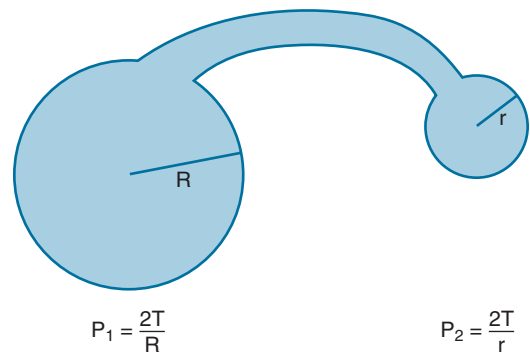


Figure 5-7 Laplace's law. Consider two gas-filled fluid bubbles with equal surface tension (T) but differing radii (R and r), connected by a tube. Because of the smaller radius of curvature, the pressure in the smaller bubble will exceed that of the larger ($P_2 > P_1$), leading to gas flow from the smaller to the larger bubble.

interface is under tension. That is, a molecule in the interior of a liquid is subjected to an equal force in all directions by other liquid molecules. However, the molecules at the surface are pulled toward each other and by molecules below the surface, and these forces (surface tension) cause a tendency for the surface to collapse.

Because of surface tension, a positive pressure must be present to prevent the collapse of a gas-filled bubble in a liquid. The pressure of gas (P) within a bubble is related to the surface tension (T) and the radius of curvature of the bubble (r) by Laplace's law ($P = 2T/r$) (Fig. 5-7). The surface of the alveolus with an air-liquid interface can be likened to a bubble with a radius of approximately 0.1 mm at FRC. If the surface tension were similar to that of water (72 mN/m), the lungs would be very noncompliant and ventilation with transpulmonary pressures in the physiologic range (3 to 5 cm H₂O) would be impossible. Furthermore, the high surface tension would lead to alveolar instability and cause alveolar collapse. That is, smaller alveoli with smaller radii of curvature, by the nature of Laplace's law, would have higher alveolar pressures than larger alveoli with greater radii of curvature. Because gas travels from an area of higher pressure to one of lower pressure, smaller alveoli would tend to empty into larger alveoli, eventually resulting in one large air-filled alveolus with all other alveolar units collapsed.

A number of factors contribute to alveolar stability in normal lungs. First, the connective tissue scaffolding limits overdistention of alveoli. Second, alveoli are interconnected (alveolar interdependence) by common walls and structures. Therefore, if one alveolus began to collapse, it would stretch adjacent alveolar walls, creating a tethering effect on the collapsing unit. Third, surfactant has an important stabilizing effect.

Hysteresis and Stress Adaptation

When normal lungs are inflated and deflated slowly, the volume-pressure curves are not identical. During inflation of the lung, the pressure required at any given lung volume is greater than that during deflation (Fig. 5-8). The difference between the inflation and the deflation curves is due to hysteresis and stress adaptation.

Hysteresis refers to changes in mechanical properties due to the volume history of the lung and is caused by several

factors. First, the effect of surfactant on surface tension is dependent on volume history, with surfactant less effective at reducing surface tension during inspiration than during expiration. During inspiration the phospholipids of surfactant move to the surface of the liquid layer, and during exhalation the surface film is compressed, the phospholipids are concentrated, and surface tension falls. Second, much higher pressures are required to open collapsed airways or alveoli than are required to keep them open. In disease states characterized by collapse of alveoli (e.g., ARDS), significant hysteresis of the pressure volume curve can be seen²⁵ (see Fig. 5-8). This has clinical significance in patients with ARDS because higher inflation pressures are required to ventilate the lungs.

In contrast, stress adaptation refers to the time dependence of mechanics measurements. When lung tissue is stretched to a particular length, the tension required to maintain the length gradually diminishes due to time-dependent properties of surfactant and deformation of viscoelastic tissues of the lung. Therefore, after a sustained lung inflation, the pressure required to keep the lung at that volume will decrease.

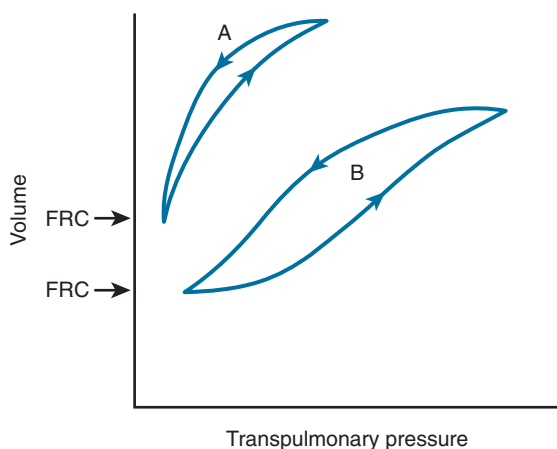


Figure 5-8 Hysteresis in a normal lung (A) and in an acutely injured lung (B). In acute respiratory distress syndrome (ARDS), the lung is stiffer than the normal lung, and greater inflation pressure is required at any given lung volume. Furthermore, the degree of hysteresis is much greater in ARDS lungs, with a greater separation of the volume-pressure curves on inspiration (upward arrow) and exhalation (downward arrow). FRC, functional residual capacity.

Recruitment Maneuvers in Acute Respiratory Distress Syndrome

ARDS is a disease known to have surfactant dysfunction. The dysfunction of surfactant increases surface tension at the air-liquid interface of the alveoli, leading to collapse, intrapulmonary shunting, and hypoxemia.²⁶ Because of alveolar collapse, hysteresis may be especially apparent in patients with ARDS (see Fig. 5-8). The lung collapse necessitates high inflation pressures to ventilate the lungs, thereby increasing the work of breathing and potentially leading to barotrauma; low tidal volumes are used in ARDS to mitigate further lung injury.²⁷

Due to hysteresis the pressure required to open an alveolus (“opening pressure”) is significantly greater than the pressure at which an already open alveolus will collapse (“closing pressure”). Because of this, “recruitment maneuvers” have been used in ventilated patients with ARDS who remain hypoxemic despite moderate levels of externally applied *positive end-expiratory pressure* (PEEP).²⁸⁻³² A recruitment maneuver consists of a sustained inflation at a constant high pressure, which opens collapsed alveoli. Because closing pressures are much less than opening pressures, the alveoli stay open (at least temporarily) after the sustained inflation is ended, as long as the lung is not allowed to return to a very low volume (Fig. 5-9).

ELASTIC RECOIL OF THE CHEST WALL

The chest wall is made up of the rib cage laterally, the sternum anteriorly, the vertebral column posteriorly, and the diaphragm caudally. Movement of the chest wall by the muscles of ventilation generates pressure gradients between the alveoli and the surrounding air, enabling gas to be moved in and out of the lungs.

Respiratory Muscles (see Chapter 97)

The diaphragm consists of two separate muscles joined by a central tendon. The crural diaphragm arises from the first three lumbar vertebrae and the medial and lateral arcuate ligaments. The costal diaphragm arises from the inner surfaces and upper margins of the lower six ribs and sternum. Both costal and crural fibers insert onto the central tendon. The phrenic nerve innervates the diaphragm, with costal fibers innervated from the 3rd and 4th cervical spinal segments, and crural fibers from the 4th and 5th segments. In

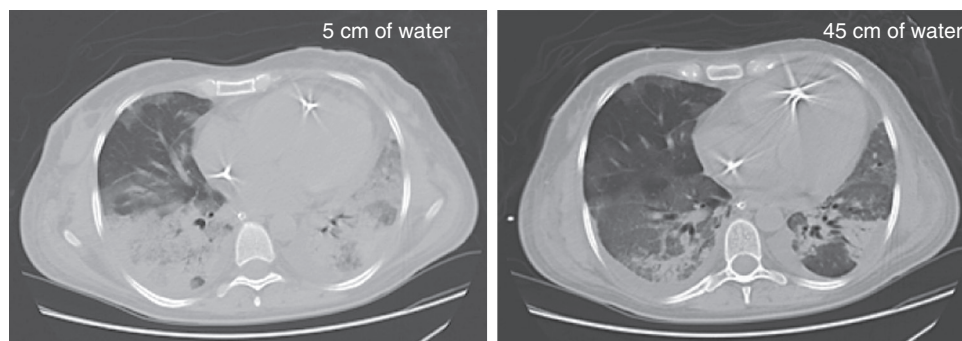


Figure 5-9 Recruitment in acute respiratory distress syndrome (ARDS). CT scan of the lung in a patient with ARDS at 5 cm H₂O airway pressure (left) and at 45 cm H₂O pressure (right), demonstrating lung recruitment with higher airway pressures. (From Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 354:1775–1786, 2006, with permission.)

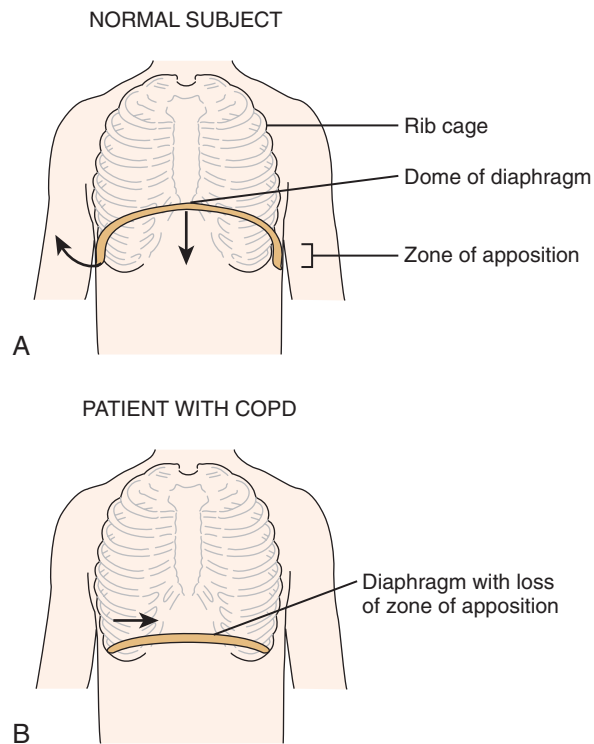


Figure 5-10 Normal subject and patient with chronic obstructive pulmonary disease (COPD). A, In a normal subject the lower part of the diaphragm lies next to the lower rib cage (zone of apposition). As indicated by the arrows, contraction of the diaphragm will pull the dome downward and push the lower rib cage upward and outward (due to increased abdominal pressure). B, In a patient with COPD and hyperinflation, there is loss of the zone of apposition. As indicated by the arrow, contraction of the diaphragm may lead to inward movement of the lower rib cage.

normal subjects the lower part of the rib cage encloses the upper part of the abdomen at FRC. In this area the diaphragm is pushed against the lower rib cage (zone of apposition) with fibers arranged in a cranial-caudal direction (Fig. 5-10). Contraction of the diaphragm leads to a piston-like up-and-down motion of the diaphragm. Furthermore, diaphragm contraction leads to an increase in abdominal pressure, which pushes the rib cage upward and outward.^{33,34}

In patients with substantial hyperinflation (e.g., emphysema), the position of the diaphragm is lower, with loss of the zone of apposition.³⁵ When the zone of apposition is lost, contraction of the diaphragm is less mechanically advantageous and can result in paradoxical inward movement of the lower rib cage during inhalation (the Hoover sign) and less piston-like motion of the diaphragm dome.³⁶ Furthermore, the length of the diaphragm is shortened, which creates a further mechanical disadvantage because the ability of the muscle to generate force is attenuated at shorter lengths (Fig. 5-11). However, in animals and humans, compensatory shortening of the diaphragm through loss of sarcomeres has been shown to mitigate these effects and help to improve the length-tension characteristics of the diaphragm.^{37,38} The improved symptoms experienced by patients with *chronic obstructive pulmonary disease* (COPD) following lung volume reduction surgery or after removal of pleural effusions may be related to increased length of the zone of apposition and improved mechanical function of the diaphragm.³⁹

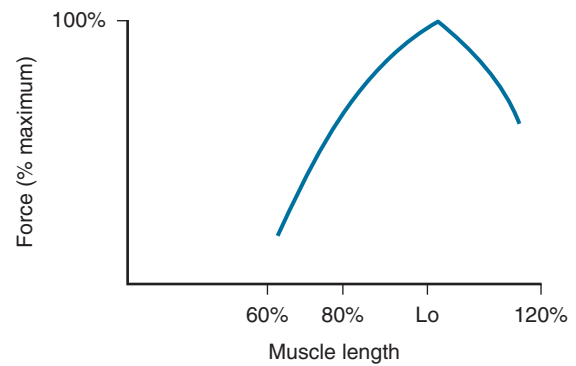


Figure 5-11 Force-length characteristics of skeletal muscle. Skeletal muscle displays a characteristic force-length curve with a reduction in force-generating capacity at lengths below or above optimal length (Lo).

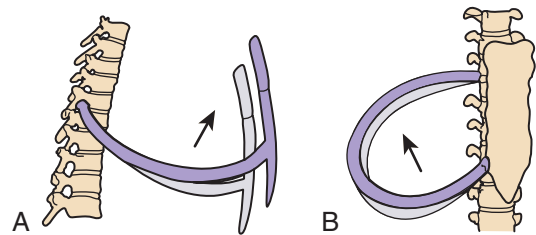


Figure 5-12 Movement of rib cage during inspiration. Diagram indicating pump-handle (A) and bucket-handle (B) rotations of the ribs. In both panels the sternum and rib are shown before (gray) and after (purple) rib cage expansion. (From De Troyer A, Loring SH: Actions of the respiratory muscles. In Roussos C, editor: *The thorax*, part A. New York, 1995, Marcel Dekker, pp 535–563.)

During inhalation the rib cage moves laterally and anteriorly. The anterior motion of the sternum is akin to a “pump-handle,” motion, and the lateral movement and elevation of the ribs is akin to a “bucket-handle” motion (Fig. 5-12). The muscles of the rib cage include the internal intercostal muscles, the external intercostal muscles, and the parasternal muscles. Internal intercostal muscles are used mainly for exhalation, whereas external muscles are used for inhalation.⁴⁰ The parasternal muscles are located next to the sternum; although they are part of the internal intercostal muscle layer, their major function is to raise the sternum during inhalation.⁴¹

Other muscles used in inhalation include the scalene muscles, which help to elevate the rib cage and prevent paradoxical inward movement of the upper rib cage with diaphragm displacement.⁴² Under conditions of ventilatory stress, other muscles not normally used for respiration can be recruited. These include the sternocleidomastoid, pectoralis, trapezius, and muscles of the vertebral column. Contraction of the muscles in the abdominal wall can be used to aid exhalation.

Fatigue of Respiratory Muscles

Fatigue develops when the rate of work required by the muscles exceeds the rate of energy supply. Usually there is substantial reserve of the respiratory muscles that prevents fatigue. However, under conditions of excessive elastic or resistive load (either experimentally induced or due to disease states) and/or inadequate energy supply (e.g., during hypoxemia or cardiogenic shock), fatigue develops

and impairs respiratory muscle performance.⁴³⁻⁴⁵ Recovery from fatigue usually requires more than 24 hours of rest.⁴⁶

One measure of workload of the diaphragm is the pressure-time index. This is the product of the percentage of maximal pressure (i.e., transdiaphragmatic pressure/maximal transdiaphragmatic pressure) exerted by the muscle multiplied by the percentage of time spent during inspiration (inspiratory time/total time). In normal subjects a value greater than 15% to 18%, if sustained, will lead to fatigue and loss of force-generating capacity of the diaphragm.⁴⁷

Central respiratory fatigue arises when there is a reduction in central motor output to the muscles. Central fatigue can be identified when direct electrical stimulation of respiratory muscles produces more muscle force generation than the patient generates with a maximal voluntary effort.⁴⁸ This decrease in central motor output may represent an attempt to prevent damage to the muscles under conditions of inadequate energy supply. Peripheral fatigue represents failure at or past the level of the neuromuscular junction. With peripheral fatigue, force generation is reduced despite a constant electrical stimulation. Peripheral fatigue may arise because of failure of transmission at the neuromuscular junction, reduced adenosine triphosphate level, reduced calcium availability from the sarcoplasmic reticulum, or reduced calcium sensitivity of the myofilaments (caused by acidosis or increased inorganic phosphate).⁴⁹

Respiratory Muscle Atrophy during Positive-Pressure Mechanical Ventilation

Although excessive loading of the respiratory muscles can lead to fatigue and a reduction in force generation, excessive unloading of the muscle may lead to muscle atrophy. Mechanical ventilation in paralyzed rats and baboons leads to diaphragmatic atrophy.^{50,51} Furthermore, human studies in organ donors have shown significant diaphragmatic atrophy after 18 to 69 hours of diaphragmatic inactivity.⁵² However, the clinical significance of disuse atrophy in ventilated patients is still unclear. Patients who are not paralyzed may still have substantial activation of respiratory muscles while receiving mechanical ventilation,^{53,54} and this degree of stimulation may be adequate to prevent atrophy.⁵⁵⁻⁵⁷ Furthermore, there are other potential causes of muscle weakness or injury in the intensive care unit, including electrolyte disturbances, malnutrition, medications and toxins (e.g., alcohol, corticosteroids, aminoglycosides), sepsis-related cytokines, and inflammatory disorders (e.g., polymyositis), so that attributing muscle weakness to disuse atrophy of muscle fibers in the clinical setting is difficult.

Chest Wall Compliance (see Chapter 98)

The compliance of the chest wall can be determined by measuring changes in the transmural pressure across the thorax (pleural pressure minus body surface pressure) relative to change in volume. The volume-pressure curve of the relaxed chest wall is shown in Figure 5-6. In contrast to the lung, the resting volume of the relaxed chest wall is approximately 1 L above FRC. The difference between the resting volume of the lung and chest wall can be appreciated in patients with a pneumothorax, in which the chest wall recoils outward and the lung recoils inward. When the

chest wall is distended above this resting volume, the relaxed chest wall recoils inward, and when the chest wall is moved below this resting volume, it recoils outward. The compliance of the normal chest wall is approximately 200 mL/cm H₂O, but it becomes progressively stiffer at lower lung volumes, and it is this stiffness that predominantly determines residual volume in normal young subjects.⁵⁸

Factors such as ossification of costal cartilage, arthritis of costovertebral joints, skin eschars from burns, obesity, and abdominal distention may reduce chest wall compliance. Chest wall compliance increases in the sitting position compared with the supine position, but the overall effect is usually modest.⁵⁹

INTEGRATION OF LUNG AND CHEST WALL MECHANICS

The chest wall and lung are juxtaposed and, in the absence of pleural disease (such as pneumothorax or pleural fibrosis), changes in chest wall volume are essentially identical to changes in lung volume (Fig. 5-13). An integration of lung and chest wall mechanics can be graphically represented by plotting the pleural pressure against the relaxed volumes of the lung and chest wall (Campbell diagram) (Fig. 5-14). These plots help to explain the determinants of the commonly measured static lung volumes. At FRC (relaxation volume), the outward recoil pressure of the chest wall is balanced by the inward recoil of the lung. The pleural pressure at FRC is negative (approximately -3 to -4 cm H₂O) in normal subjects. Changes in the compliance of the lung or chest wall may change the relaxation volume (see Fig. 5-14).

Increases in lung compliance (e.g., due to emphysema) will tend to shift the volume-pressure curve of the lung upward and to the left. If chest wall compliance remains constant, FRC will increase. In contrast, if lung compliance is reduced (e.g., due to pulmonary fibrosis or ARDS), the

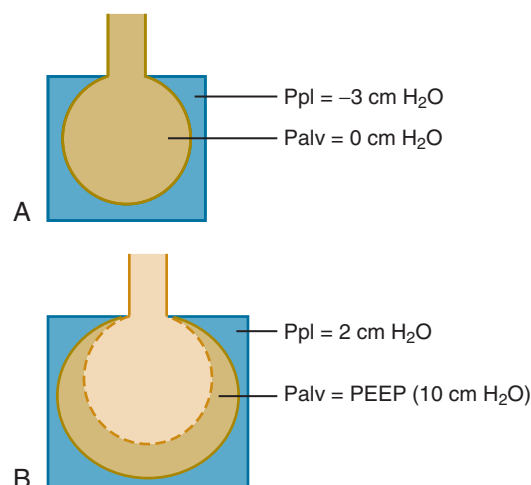


Figure 5-13 Changes in pleural pressure with applied positive end-expiratory pressure (PEEP). A, A lung is shown at end-expiration with no PEEP. B, With the application of PEEP, there is an increase in the volume of the respiratory system (lung and chest wall) and an increase in pleural pressure (Ppl). The magnitude of the increase in Ppl is dependent on the relative compliances of the lung and chest wall. Palv, pressure in alveolus.

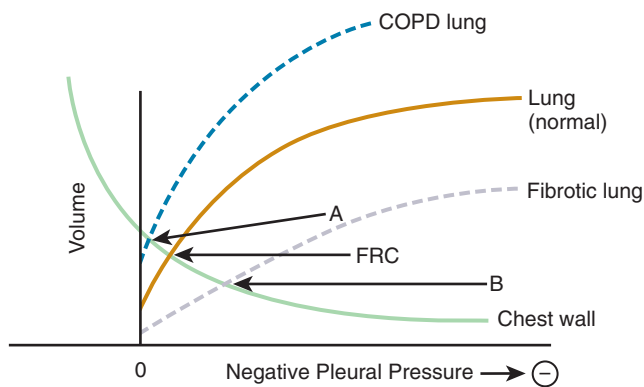


Figure 5-14 Integration of lung and chest wall mechanics. Changes in lung and relaxed chest wall volumes as a function of pleural pressure (Campbell diagram). This is basically the same plot as in Fig. 5-6 except that the x-axis is simply pleural pressure rather than transmural pressure for the lung and chest wall. The point at which the two curves meet is the functional residual capacity (FRC) (lung recoil balanced by chest wall recoil). If lung compliance is increased (e.g., in chronic obstructive pulmonary disease [COPD]), the point at which the two curves meet (FRC) is greater (point A). In contrast, if lung compliance is reduced (e.g., in pulmonary fibrosis), the point at which the two curves meet is less (point B).

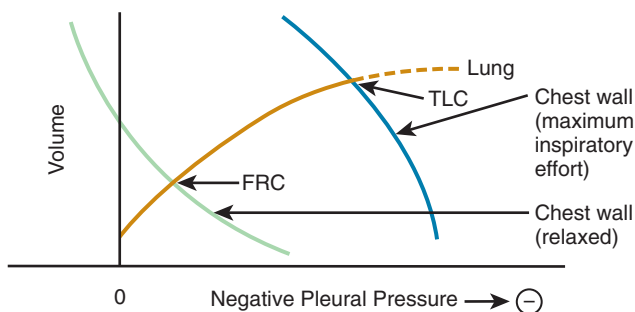


Figure 5-15 Maximal inspiratory effort (Campbell diagram). With maximal inspiratory effort the volume-pressure curve of the chest wall moves to the right. The point at which there is intersection of this curve and the lung volume-pressure curve is the total lung capacity (TLC). FRC, functional residual capacity.

volume-pressure curve of the lung will shift downward and to the right, leading to a reduction in FRC. Similarly, changes in chest wall compliance can lead to increases or decreases in FRC.

FRC is believed to represent the balance of forces in a relaxed state at which there is no muscle activation. However, FRC may not be completely passively determined. There is a reduction in FRC with paralysis compared with the relaxed state, suggesting that inspiratory muscle tone of the rib cage muscles and diaphragm may contribute to “passive” chest wall compliance and thus to FRC.⁶⁰

With activation of inspiratory and expiratory muscles, the configuration of the chest wall changes. This is demonstrated in Figure 5-15. Activation of inspiratory muscles effectively shifts the pressure-volume curve of the chest wall, so that at any given pleural pressure, the chest wall volume is increased relative to the relaxed state. The horizontal difference between the relaxed curve and the curve with inspiratory muscle activation represents the net pressure generated by the inspiratory muscles.

TLC is determined by the balance between the strength of the inspiratory muscles counterbalanced by the inward lung recoil plus the inward chest wall recoil. However, in normal subjects, TLC is predominantly determined by the markedly increased stiffness of the lung at high lung volume, rather than the recoil of the chest wall or respiratory muscle strength.⁶¹ In support of this concept, inspiratory muscle training in normal subjects increases strength substantially (55% increase in maximal inspiratory pressure) but results in a very modest change in TLC and VC (about 4%).⁶² The situation in patients with neuromuscular disease is very different; in such individuals, reduced TLC is largely due to respiratory muscle weakness and can be improved to some extent by inspiratory muscle training.⁶³

Activation of expiratory muscles shifts the pressure-volume curve of the chest wall in the other direction, and the degree of shift is a measure of the net pressure exerted by the expiratory muscles. In young subjects, residual volume is determined by the balance of the strength of the expiratory muscles counterbalanced by the outward recoil of the chest wall and inward lung recoil (small component).⁶¹

In older subjects or patients with obstructive lung disease, residual volume is not determined by this balance of forces but is rather determined by airway closure. In such individuals, airways close and gas is trapped during exhalation before a static balance is achieved.⁶¹

Calculation of Total Respiratory System Compliance from Lung and Chest Wall Compliance

The chest wall and lung act as capacitors in series, analogous to electrical capacitors. The relationship between total respiratory system compliance and lung and chest wall compliance is indicated by the following formula:

$$1/\text{Total compliance} = 1/\text{Lung compliance} + 1/\text{Chest wall compliance}$$

Alternatively, since elastance = 1/compliance,

$$\text{Total elastance} = \text{Elastance of lung} + \text{Elastance of chest wall}$$

As an example, in a supine paralyzed subject, lung compliance is approximately 150 mL/cm H₂O pressure, and chest wall compliance is approximately 200 mL/cm H₂O pressure⁶⁴; the calculated compliance of the respiratory system would thus be approximately:

$$1/(1/200 + 1/150) = 85.7 \text{ mL/cm H}_2\text{O}$$

CLINICAL APPLICATIONS

The Impact of Positive End-Expiratory Pressure on Pleural Pressure

In patients receiving positive-pressure mechanical ventilation for diseases that decrease lung compliance, pressure is usually applied at the end of exhalation to prevent alveolar collapse.⁶⁵ Some—but not all—of this PEEP is transmitted from the alveolar space to the pleural space (see Fig. 5-13). This is important because pericardial pressure will increase

to a similar extent as pleural pressure. An increase in pericardial pressure reduces venous return and can lead to reduced cardiac output and hypotension.⁶⁶ Furthermore, PEEP will increase central venous pressure and pulmonary artery occlusion pressure to a magnitude similar to the increase in pleural pressure. If this is not taken into account, errors may be made when using these pressures to assess patients' intravascular volume status.

During mechanical ventilation, changes in both pleural pressure and transpulmonary pressure depend on the relationships between the elastance of the chest wall (E_w), the lung (E_L), and the total respiratory system (E_{rs} , which is the sum of E_w and E_L), a relationship (see Fig. 5-13) that may be described by the equation:

$$P_{pl} = PAW \times E_w / E_{rs}$$

where P_{pl} is the pleural pressure and PAW is the flow-resistive pressure in the airway.

In healthy individuals, E_w and E_L are approximately equal, and E_w/E_{rs} has a value of approximately 0.5⁶⁷ and remains constant within the range of normal ventilation. In this situation it is reasonable to infer the value of P_{pl} from PAW . However, in disease, both E_w and E_L demonstrate great variability, such that the ratio of E_w to E_{rs} is unpredictable.⁶⁸ In this situation, P_{pl} cannot be assumed to be directly related to PAW .⁶⁹ If lung compliance is low and chest wall compliance is high, very little of the alveolar pressure will be transmitted to the pleural space and vice versa. In healthy individuals the chest wall and lung compliances are equal, and thus the increase in pleural pressure is roughly equal to half of the applied PEEP (e.g., 5 cm H₂O pressure if the PEEP is 10 cm H₂O pressure).

However, if lung compliance is much less than chest wall compliance (e.g., in a thin patient with severe ARDS), the pleural pressure will change minimally with PEEP. In contrast, if lung compliance is much greater than chest wall compliance (e.g., in a patient with emphysema and kyphoscoliosis), a much greater proportion of PEEP will be transmitted to the pleural space.

Plateau Pressures in Patients Receiving Positive-Pressure Mechanical Ventilation

In patients receiving positive-pressure mechanical ventilation, the plateau pressure is the distending pressure of the respiratory system at end inspiration, when there is no flow. When possible, plateau pressures should be limited to a maximum of 30 to 35 cm H₂O because higher pressures can damage the lung through overdistention. This recommendation is based in part on animal studies that show that pressures below this range seem to protect the lungs from injury.⁷⁰ There is also a physiologic basis for this practice because at TLC in a normal subject, the distending pressure across the lung (alveolar pressure minus pleural pressure) is approximately 35 cm H₂O.⁷¹ Therefore limiting the plateau pressure to less than 35 cm H₂O should limit lung expansion to below TLC and not overdistend the lung. The use of low tidal volumes during mechanical ventilation for lung injury has led to improved clinical outcomes, presumably because of decreased alveolar distention and volutrauma.⁷² In a landmark study, tidal volumes were limited to 4 to 6 mL/kg of ideal body weight in an attempt to limit

lung overdistention.⁶⁵ However, others have argued that alveoli may become overdistended and undergo cyclic recruitment-derecruitment even with low tidal volumes in some patients,⁷³⁻⁷⁵ whereas ultralow tidal volumes (4 mL/kg of ideal body weight or less) may decrease this phenomenon further.⁷⁶

Although limiting plateau pressures and tidal volumes during mechanical ventilation has demonstrated some benefit in decreasing ventilator-associated lung injury, there is no clear limit below which further decreases will not improve outcomes.⁷⁷ This may be because neither plateau pressure nor tidal volume measurements account for the effect of pleural pressure on lung mechanics. During mechanical ventilation, plateau pressure is often used as a surrogate for transpulmonary pressure (pressure used to distend the lung), when it is actually a measure of transrespiratory system pressure. When lung compliance is much less than chest wall compliance, this is a reasonable assumption, because during mechanical ventilation, pleural pressure will not be substantially greater than body surface pressure. However, in conditions in which the chest wall is stiff (e.g., obesity, after abdominal surgery), the plateau pressure may substantially overestimate the distending pressure of the lung, because pleural pressure may be much greater than body surface pressure.⁷⁸ Indeed, some investigators have suggested that measurement of pleural pressure (with an esophageal balloon) could be useful in titrating mechanical ventilation in ARDS.⁷⁹

Stress and Strain

A discussion of the mechanics of stress and strain is available online.



THE RESPIRATORY SYSTEM IN DYNAMIC CONDITIONS

The work to distend the chest wall and lung during inhalation is stored as potential energy (elastic work). Work also must be done to overcome the inertia of the gas (which is negligible when breathing air at normal breathing frequency and atmospheric pressures) and nonelastic resistance (resistive work), which cannot be stored, but is dissipated as heat. Resistive work has two components that must be considered.

RESISTIVE WORK DUE TO GAS FLOW THROUGH AIRWAYS

When gas flows through an airway, frictional and viscous forces cause energy loss and a pressure drop along the airway. The extent of this pressure drop is dependent on the resistance to gas flow, physical properties of the gas (e.g., density and viscosity), and the nature of flow (laminar versus turbulent).

Laminar versus Turbulent Flow

The frictional drop is least with pure laminar flow, in which gas molecules travel in a straight line. The velocity profile of the gas is parabolic, with the molecules closer to the wall

To an engineer, stress is the net difference between forces acting on a body (in this case, the lung parenchyma). From the point of view of lung mechanics, stress reflects the difference between distending forces (for example, alveolar pressure) and collapsing forces (the pleural pressure in this case), and stress is therefore represented by the transpulmonary pressure.⁸⁰

The deformation of a structure by stress is called “strain,” which is defined as the change in size or shape compared to the structure’s initial shape or volume. That is:

$$\text{Strain} = \Delta V / \text{FRC}$$

For example, if a lung is inflated with a 500-mL tidal volume from an initial FRC of 1500 mL, the strain associated with this is 0.33 (500 mL/1500 mL). The recommendation of a specific tidal volume for lung-protective ventilation is predicated on the assumption that there is a uniform amount of lung able to receive the inspired volume. This volume is the amount of aerated lung at end expiration—the FRC. Underlying this is the assumption that the FRC can be predicted by ideal body weight—an assumption that is not correct in injured lungs.⁸¹ It is therefore understandable that, given the same ideal body weights and tidal volume prescriptions, two patients with ARDS might have significantly different lung strain if they have different

FRCs. It therefore may be prudent to attempt to minimize strain during mechanical ventilation by measuring FRC and titrating tidal volume to this assessment rather than ideal body weight. Indeed, there is some evidence that maintaining strain less than 1.5 to 2 reduces markers of lung parenchymal injury.⁸² From a practical point of view, however, it is time consuming and laborious to measure FRC in a serial fashion. Although there are commercially available FRC measurement systems, either as stand-alone systems or integrated into mechanical ventilators, the cost of these systems is not insignificant. Fortunately, it is possible to estimate strain from measurements of stress because the two values are linked by a constant (the specific elastance of lung [EL_{spec}]) such that:

$$\text{Strain} = \text{Stress} / EL_{\text{spec}}$$

Fortunately, the value of EL_{spec} is fairly constant throughout health and disease, with a value of approximately 13 cm H₂O.^{83,84} Thus by measuring stress, strain may be inferred (i.e., approximately one thirteenth of stress). Unfortunately, neither of these measures accounts for the local heterogeneity of mechanical characteristics found in injured lung. It is therefore possible that susceptible lung units are subject to critically injurious forces even when global measures of stress and strain appear acceptable.⁸⁵

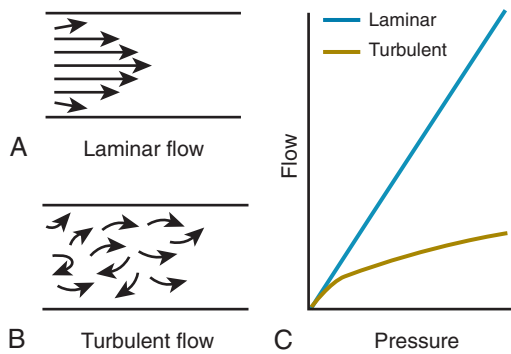


Figure 5-16 Laminar versus turbulent flow. Schematic depiction of the spatial and velocity profiles of gas molecules with laminar (A) and turbulent (B) flow. The velocity of the gas molecules is proportional to the length of the arrows. During turbulent flow there is chaotic molecular movement between lamina that results in ever-greater pressure being required to achieve incremental flow. C, Note the nonlinear pressure-flow relationship with turbulent flow and the lower flows in the setting of turbulent than laminar flow at the same pressure.

traveling slower than molecules in the center of the airway (Fig. 5-16). When gas flow is laminar, the flow is proportional to the pressure gradient (ΔP) along the airway and inversely proportional to resistance (R).

$$\text{Flow} = \Delta P / R$$

For a straight airway under conditions of laminar flow, resistance of a tube is related to viscosity, length, and radius of the tube by the Poiseuille equation:

$$\text{Resistance} = 8 \times \text{length} \times \text{viscosity} / (\pi \times \text{radius}^4)$$

Because of this relationship, flow through a tube is dramatically affected by even small changes in tube diameter because resistance increases as the fourth power of the radius (i.e., reducing the radius by half causes a 16-fold increase in resistance).

In turbulent flow the orderly pattern of gas molecule movement is replaced with a haphazard pattern (see Fig. 5-16). When gas flow is turbulent, the flow is proportional to the square root of the pressure gradient (as opposed to a linear relationship to the pressure gradient itself in the case of laminar flow).⁶⁶

$$\text{Flow} = \text{constant} \times (\Delta P)^{1/2}$$

Stated another way, the pressure drop for turbulent flow is much greater than for laminar flow, with the drop along the airway proportional to the square of flow as follows:

$$\Delta P = \text{constant} \times \text{flow}^2$$

Because resistance is defined as the pressure gradient divided by the flow rate, the “resistance” for turbulent flow is not constant but increases in proportion to flow.

In contrast to laminar flow, turbulent flow is inversely proportional to gas density but is not affected by viscosity. The driving pressure required is proportional to the fifth power of the radius of the airway.

The Reynolds Number

The *Reynolds number* (Re) is a dimensionless coefficient that predicts whether flow through an unbranched airway will

be predominantly laminar, turbulent, or mixed. The equation is as follows:

$$\text{Re} = \rho dV / \mu$$

where ρ is the gas density, d is the diameter of the airway, V is the mean gas velocity, and μ is the viscosity. In general, a value of Re of less than 2000 is associated with laminar flow, whereas a value greater than 4000 is associated with predominantly turbulent flow.⁶⁴ Intermediate values are associated with mixed flow patterns.

The cross-sectional diameter of the central airways (e.g., trachea) is much greater than the smaller peripheral airways (e.g., bronchioles). However, the entire cross-sectional area of the peripheral airways is much greater than that of the central airways. Therefore, as gas moves from the peripheral to the central airways during exhalation, the gas velocity increases as the airway diameter increases. This results in predominantly turbulent flow in the larger central airways (except at very low flow rates) and predominantly laminar flow in the periphery.

Clinical Effects of Heliox

Heliox is a mixture of oxygen and helium. Heliox has a density less than air and a viscosity greater than air. For instance, a mixture of 20% oxygen and 80% helium has a density of 0.33 relative to air and a viscosity of 1.08 relative to air.⁶⁴ Because gas density influences the resistance during turbulent flow, this gas mixture can be especially beneficial in patients who have upper airway narrowing (e.g., partial tracheal obstruction).⁸⁶ Substituting heliox for air or oxygen reduces gas density, lowering the Reynolds number, and helps to convert turbulent to laminar flow. This reduces the pressure required to move gas through the airways and diminishes the work of breathing, unloading the respiratory muscles.

Heliox may be useful in patients with asthma or COPD, although this is controversial.⁸⁷⁻⁸⁹ The reason for a beneficial effect is unclear, because flow in the smaller bronchioles, which contribute most of the increased airways resistance in asthma and COPD, should be laminar rather than turbulent. The effectiveness of heliox in asthma might be related to narrowing of large central airways from secretions and conversion of flow from turbulent to laminar in larger airways. Heliox might also be beneficial in vocal cord dysfunction for a similar reason.

Flow Limitation

In a normal subject, increasing expiratory effort will increase air flow until a threshold is reached. Once this effort threshold is exceeded, expiratory flow will not increase despite a further increase in effort, resulting in flow limitation as opposed to pressure limitation⁹⁰ (Fig. 5-17). In contrast, patients with very poor effort or marked expiratory muscle weakness may be unable to generate high expiratory pressures, resulting in pressure limitation before flow limitation is reached. Flow limitation is an important concept; if flow were not relatively effort independent, measures such as forced expiratory volume in 1 second would have little utility in monitoring patients because variable effort would result in poorly reproducible results.

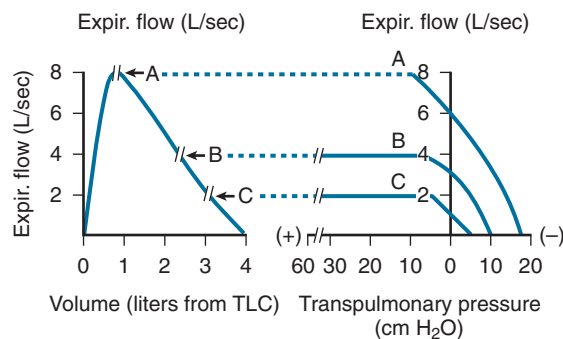


Figure 5-17 Expiratory flow limitation. Left, The expiratory flow-volume curve for a normal subject. Maximal flow rates are plotted against their corresponding volumes at A, B, and C and define the maximal expiratory flow-volume curve. Right, Three isovolume pressure-flow curves for the same subject. Once a threshold transpulmonary pressure is achieved, no increase in flow is seen. TLC, total lung capacity. (From Hyatt RE: Forced expiration. In Macklem PT, Mead J, editors: *Handbook of physiology*. Section III. The respiratory system. Vol 3: Mechanics of breathing, part 1. Bethesda, MD, 1986, American Physiological Society, pp 295–314.)

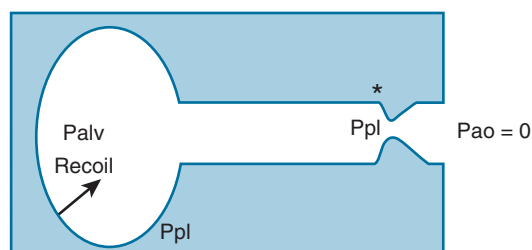


Figure 5-18 Equal pressure point theory. At the equal pressure point (*), pressure inside the tube is equal to the pressure outside the tube (pleural pressure [Ppl]) due to pressure drop related to flow-resistive losses from alveolus to *. Downstream (mouthward) from the equal pressure point, the airway is compressed. Once an equal pressure point develops, increasing expiratory effort, although increasing the alveolar pressure (Palv), simply increases the downstream compression and causes no increase in flow. Pao, airway opening pressure.

Flow is limited because of the properties of the airways. For simplicity, the airways are often likened to a rigid tube, but, in reality, the airways are partially collapsible. During inhalation, pleural pressure is negative, and the intrathoracic airways tend to be pulled open. During forced exhalation, pleural pressure becomes positive, increasing pressure around the intrathoracic airways and predisposing to their collapse.

Several theories have been developed to explain the limitation of flow at below maximal effort.

Equal Pressure Point Theory (Fig. 5-18). Consider the respiratory system depicted as a balloon (lung) inside a box (chest wall) connected by a tube that extends through the box (intrathoracic airway). The pressure inside of the lung is equal to the pleural pressure (created by expiratory muscle activation) plus the recoil pressure of the lung. As air travels down the airway, pressure in the airway will decrease, predominantly because of frictional losses. A point is eventually reached where the pressure inside the airway equals the pleural pressure outside the airway, termed the *equal pressure point* (EPP).^{91,92} Downstream (mouthward) of this EPP, the pressure inside the airway

drops below the pressure outside the airway, and the airway tends to collapse. Further increases in effort will increase pleural pressure, but this simply causes greater narrowing of the airway downstream of the EPP, so that flow remains constant. Under these conditions, the airway acts as a Starling resistor; flow is now not proportional to the difference between alveolar and mouth pressure but rather is proportional to the difference between alveolar pressure and pressure at the EPP. In this case, the pressures downstream from the EPP have no effect on expiratory flow.

This concept can be mathematically expressed as follows: Because

$$\text{Alveolar pressure} = \text{Pleural pressure} + \text{Elastic recoil pressure of the lung}$$

and

$$\text{Pressure at EPP} = \text{Pleural pressure}$$

and

$$\text{Driving pressure for flow} = \text{Alveolar pressure} - \text{Pressure at EPP}$$

therefore

$$\begin{aligned} \text{Driving pressure} &= (\text{Pleural pressure} \\ &\quad + \text{Lung recoil pressure}) \\ &\quad - \text{Pleural pressure} \\ &= \text{Lung recoil pressure} \end{aligned}$$

Therefore further increases in effort will increase alveolar and EPP pressure equally, resulting in no difference in driving pressure and airflow.

The Bernoulli Effect and Wave Speed Theory. The Bernoulli effect provides an alternative explanation for flow limitation.⁹³ As gas flows through a tube, the lateral pressure exerted by the gas is less than the pressure driving flow by an amount proportional to the velocity of the gas. If the tube is collapsible, as gas velocity increases, there is a tendency for the tube to collapse, leading to a reduction in airflow.

The wave speed theory is yet another explanation for expiratory flow limitation.⁹⁴ When fluid is pushed through a collapsible tube, a pressure wave is propagated along the wall of the tube. The speed of this pressure wave is dependent on the characteristics of the tube and the density of the gas rather than the driving pressure. The velocity of the gas in the tube cannot exceed the velocity of the pressure wave, and thus the velocity of this wave represents a “speed limit” for the gas in the tube.

Interestingly, the maximal flow of gas derived using the Bernoulli effect and wave speed theory are identical, as shown by the following formula:

$$\text{Maximal flow} = A\sqrt{(A/\text{gas density})(dP/dA)}$$

where A represents the cross-sectional area of the airway wall and dP/dA represents the slope of the relationship between changes in transmural pressure of the tube and changes in tube area. Therefore maximal flow should increase if the tube area increases, gas density decreases, or tube stiffness increases.

The EPP mechanism might be more important at lower lung volumes and flows, whereas the Bernoulli and wave

Table 5-1 Components of Respiratory System Resistance

	Mouth/ Pharynx	Large Airways	Small Airways	Lung Tissue	Chest Wall	Total
Resistance (cm H ₂ O/ L/sec)	0.5	0.5	0.2	0.2	1.2	2.6
% of resistance	19	19	8	8	46	100

Modified from O'Donnell DE, Laveneziana P: Dyspnea and activity limitation in COPD: mechanical factors. *COPD* 4:225–236, 2007.

speed effects might predominate at higher volumes and flows.⁹⁵

OTHER RESISTIVE WORK

Besides the elastic work done by the respiratory muscles on the lung and chest wall, an additional component of work is expended to overcome what is sometimes called “tissue resistance.” This is energy required to distort the lung and chest wall during inhalation and is dissipated as heat.

The breakdown of the various components of the total resistive work is shown in [Table 5-1](#).

Equation of Motion

During ventilation, gas moves along a pressure gradient (ΔP). This pressure difference must be created by either the patient's own muscular efforts (P_{mus}) or a mechanical ventilator (P_{AW}). The energy loss represented by this pressure drop is used to overcome resistance to airflow and tissue deformation, to expand the lungs and chest wall, and to overcome gas inertance (resistance to changes in velocity or direction of gas flow). The first-order linear equation of motion describes the relationship between these variables as:

$$\begin{aligned}\Delta P &= P_{\text{AW}} + P_{\text{mus}} \\ &= \dot{V}R + V_T/C + I \ddot{V} + P_{\text{EEPi}} + P_{\text{EEPset}}\end{aligned}$$

Where \dot{V} is gas flow, R is resistance, $\dot{V}R$ is the work done by pressure to overcome airflow and tissue resistance, V_T is tidal volume, C is compliance, V_T/C is the work done by pressure to expand the respiratory system, and $I \ddot{V}$ (I represents inertance, and \ddot{V} represents acceleration) is the pressure needed to overcome gas inertance. P_{EEPi} represents intrinsic positive end-expiratory pressure, and P_{EEPset} represents the positive end-expiratory pressure created by the ventilator. In most practical situations involving adults, inertance is ignored because it makes such a small contribution to work. In patients with either trapped gas due to P_{EEPi} or clinician-instigated PEEP (P_{EEPset}), the PEEP should be accounted for in this equation.

INTRINSIC PEEP DURING POSITIVE-PRESSURE VENTILATION OF COPD

An appreciation of the dynamics of the respiratory system aids in understanding clinical scenarios, such as patients with COPD who are treated with positive-pressure ventilation for respiratory failure.⁷⁷ Because lung resistance and

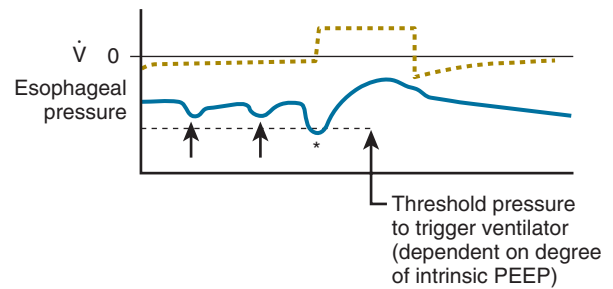


Figure 5-19 Failure to trigger the ventilator in a patient with COPD. Graph of flow (\dot{V}) and esophageal pressure over time in a patient with COPD and intrinsic positive end-expiratory pressure (PEEP) receiving positive-pressure mechanical ventilation. The patient has made two attempts (\dagger) at triggering inspiration but could not, because of the intrinsic PEEP. When pleural pressure is sufficiently negative to exceed the ventilator's threshold (dotted line), this triggers the ventilator (*) and a breath is provided. Note the failure of expiratory flow to reach 0 before a triggered breath.

compliance are variable in these patients, their lungs contain individual lung units with long time constants, and there may be insufficient time for the lungs to empty completely at the end of exhalation. Heterogeneity of time constants will result in heterogeneity of emptying times. If insufficient time is allowed for complete emptying of lung units, the result will be a positive mean alveolar pressure in the alveolus at the end of exhalation. This has been termed “intrinsic PEEP.”

PEEP has a number of adverse consequences. First, the positive pressure at end-expiration increases intrathoracic pressure and can reduce venous return, causing hypotension.⁶⁶ Second, the high end-expiratory alveolar pressure acts as an inspiratory threshold load. That is, in order to generate a negative pressure that is great enough to trigger the ventilator and initiate inspiratory flow, the inspiratory respiratory muscles must exert adequate pressure to counteract the intrinsic PEEP pressure and reduce alveolar pressure to a subatmospheric value before inspiratory flow can be initiated.⁹⁶ Third, high intrinsic PEEP may lead to inspiratory efforts that are ineffective in triggering the ventilator if the respiratory muscles cannot reduce alveolar pressure to less than the applied PEEP⁹⁷ ([Fig. 5-19](#)). This may lead to patient-ventilator dyssynchrony and discomfort. Fourth, intrinsic PEEP and the consequent hyperinflation of the lung at end-expiration place the inspiratory muscles at a mechanical disadvantage,³⁶ which can lead to failure of weaning from mechanical ventilation.

Intrinsic PEEP can be treated by increasing the applied PEEP from the ventilator, which may improve patient-ventilator synchrony.⁹⁸ Increasing applied PEEP will not reduce expiratory flow if the applied PEEP is less than the level of intrinsic PEEP because these patients are usually flow rather than pressure limited. However, increasing the applied PEEP will decrease inspiratory muscle work and facilitate ventilator triggering.

The end-expiratory occlusion method is commonly used to measure intrinsic PEEP ([Fig. 5-20](#)) (static intrinsic PEEP). The expiratory line in the ventilator is occluded at the end of an exhalation.⁹⁹ If intrinsic PEEP is present, airway pressure will increase until a plateau is reached (usually 4 to 5 seconds). This value represents an “average” measure of

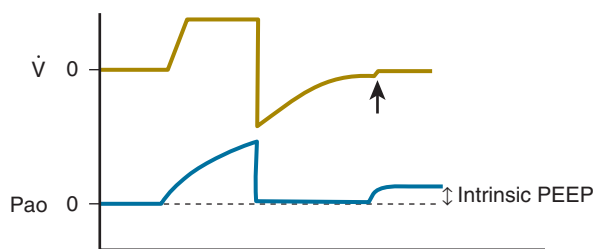


Figure 5-20 Measurement of intrinsic positive end-expiratory pressure (PEEP) while on a ventilator. Flow (\dot{V}) and airway pressure (P_{ao}) over time. The arrow represents the point at which the expiratory line is occluded, leading to an increase in measured pressure that represents the degree of intrinsic PEEP.

intrinsic PEEP after redistribution of volume from some alveoli to others depending on regional compliance (pendelluft). Pendelluft is the transient movement of gas from one lung unit to another.

Alternatively, intrinsic PEEP may be measured under dynamic conditions (dynamic intrinsic PEEP) when the patient is spontaneously breathing.⁹⁹ This can be done by inserting an esophageal balloon to measure pleural pressure and measuring the reduction in pleural pressure necessary to initiate inspiratory flow. Dynamic intrinsic PEEP is usually less than that measured under static conditions because it reflects the region of the lung with the least amount of intrinsic PEEP, as opposed to the average amount of intrinsic PEEP.

Intrinsic PEEP is not limited to patients on mechanical ventilation. Spontaneously breathing patients who have COPD can develop positive end-expiratory alveolar pressure, especially when they increase their inspiratory rate during exertion, a phenomenon that has been termed “dynamic hyperinflation.” This increases work of breathing (see later discussion) and contributes to exercise limitation in these patients.

Measurement of Static Compliance and Resistance during Mechanical Ventilation

In the intensive care unit, measurement of respiratory system compliance and resistance can be helpful in assessing the timing for weaning from mechanical ventilation or determining the reasons for failure of a spontaneous breathing trial. Normal respiratory system compliance in a supine subject is approximately 100 mL/cm H₂O. A markedly decreased compliance should prompt a search for causes of reduced lung (e.g., edema) and/or chest wall compliance (abdominal distention) that might be potentially reversible. Similarly, a markedly increased resistance should prompt a search for reversible causes, including bronchospasm, or partial obstruction of the endotracheal tube from kinking or secretions.

Calculation of compliance and resistance should be performed with a square wave flow pattern after an inspiratory pause. Patients need to be relaxed or paralyzed to obtain accurate measurements. If respiratory efforts are present, airway pressures may not reflect transmural pressures across the respiratory system but rather may reflect pleural pressures.

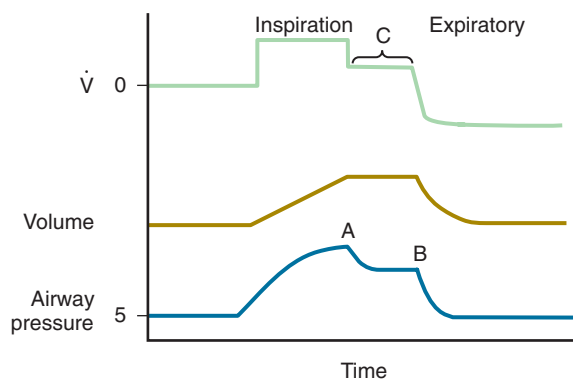


Figure 5-21 Ventilator mechanics. Point A is the peak pressure (40 cm H₂O). Point B is the plateau pressure (35 cm H₂O). Point C is the inspiratory pause.

Consider a paralyzed sedated patient treated with positive-pressure mechanical ventilation in the assist-control mode. The changes in flow, volume, and pressure over time are shown in Figure 5-21. Assume a constant inspiratory flow rate (1 L/sec) and a tidal volume of 500 mL (0.5 second inspiratory time). Because flow is constant, volume increases linearly over time. Peak pressure is 40 cm H₂O, plateau pressure is 35 cm H₂O, and PEEP is set at 5 cm H₂O.

Using the balloon-and-tube analogy of the respiratory system (see Fig. 5-4), the components of pressure required are as follows:

$$\begin{aligned} \text{Total pressure} = & \text{Pressure to distend respiratory system} \\ & + \text{Pressure to maintain gas flow} \\ & + \text{Inertial pressure losses} \end{aligned}$$

Because the inertial component can be ignored at the respiratory rates commonly used:

$$\begin{aligned} \text{Total pressure} = & \text{Pressure to distend respiratory system} \\ & + \text{Pressure to maintain gas flow} \\ = & \Delta \text{Volume}/\text{compliance} + \text{Flow} \times \text{resistance} \end{aligned}$$

The difference between plateau pressure (measured during an inspiratory hold) and PEEP represents the pressure required to distend the respiratory system at 0 flow.

Therefore,

$$\text{Plateau pressure} - \text{PEEP} = \Delta \text{Volume}/\text{compliance}$$

Rearranging the equation yields:

$$\text{Compliance} = \Delta \text{Volume}/(\text{Plateau pressure} - \text{PEEP}) \quad [1]$$

The difference between peak pressure (point A in Fig. 5-21) and plateau pressure (point B in Fig. 5-21) represents the pressure required to overcome resistance of the respiratory system (this predominantly represents flow resistance, but also includes contributions from tissue resistance, stress relaxation, and pendelluft).

Therefore,

$$\begin{aligned} \text{Peak pressure} - \text{PEEP} = & \Delta \text{Volume}/\text{compliance} \\ & + \text{Flow} \times \text{resistance} \end{aligned} \quad [2]$$

Rearranging Equations 1 and 2:

$$\text{Peak pressure} - \text{Plateau pressure} = \text{Flow} \times \text{resistance}$$

Because flow is known:

$$\text{Resistance} = (\text{Peak pressure} - \text{Plateau pressure}) / \text{Flow}$$

Going back to our patient:

$$\text{Compliance} = 500 \text{ mL} / (30 \text{ cm H}_2\text{O}) = 16.7 \text{ mL/cm H}_2\text{O}$$

$$\text{Resistance} = 40 - 35 \text{ cm H}_2\text{O} / \text{L/sec} = 5 \text{ cm H}_2\text{O/L/sec}$$

In other words, the patient's compliance is severely reduced, suggesting an extremely stiff respiratory system. However, the resistance is relatively low. By placing an esophageal catheter to estimate pleural pressure, one could ascertain the separate contributions of the lung and the chest wall to the reduced respiratory system compliance, further clarifying the source of the impediment to weaning.

ENERGETICS AND WORK OF BREATHING

When a force is applied to an object over a distance, energy is required; the work done is equal to:

$$\text{Work} = \text{force} \times \text{distance}$$

Similarly, because pressure is force over an area and volume is an area multiplied by a distance, work in a fluid system may be defined as the integral of applied pressure over a change in volume:

$$\text{Work} = \int P dV$$

During inspiration, work must be performed to distend the respiratory system (elastic work), which is stored as potential energy. Also, nonelastic work must be done to generate flow through the airways (to overcome resistance to gas flow), to overcome lung and chest wall tissue resistance, and to accelerate gas (to generate the inertial component). This work cannot be stored as potential energy and is dissipated as heat. The inertial component is minimal and is usually ignored in measuring total work.

MEASURING WORK OF BREATHING DONE BY A POSITIVE-PRESSURE VENTILATOR IN A PARALYZED PATIENT

Consider a paralyzed patient receiving positive-pressure mechanical ventilation, such that the entire work of breathing is performed by the ventilator (Fig. 5-22). On a volume-pressure plot, pressure applied to the airway will track to the right of the static volume-pressure curve of the respiratory system because additional pressure is required to overcome resistive forces. The blue shaded area represents the elastic work done by the ventilator during one inhalation, and the gray shaded area represents the resistive work that was expended to generate flow and overcome tissue resistance. With exhalation, the stored elastic energy can be used to deflate the lungs, so that exhalation is normally a passive process. Increases in resistance or decreases in compliance can markedly increase the work of breathing.

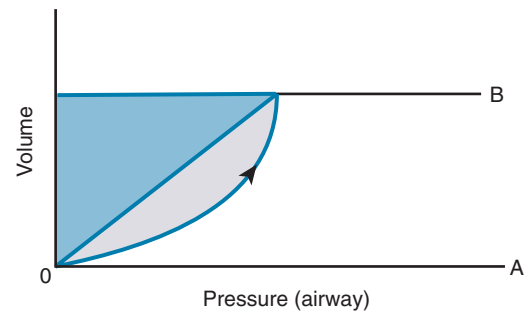


Figure 5-22 Work of breathing during mechanical ventilation. Consider a paralyzed patient receiving one tidal breath while on positive-pressure mechanical ventilation (point A to point B). The *diagonal blue line* represents the volume-pressure curve of the static respiratory system; the *shaded blue area* to the left of this line thus represents the elastic work done during the inflation. This work can be stored as potential energy and can be used during exhalation. The *gray shaded area* to the right of the line represents the resistive work done.

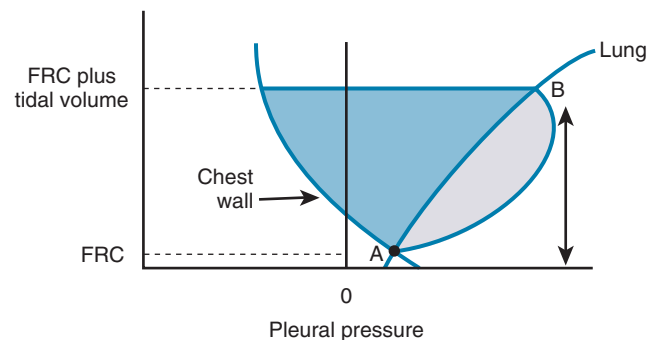


Figure 5-23 Work of breathing during spontaneous breathing (Campbell diagram). A portion (from functional residual capacity [FRC] to FRC plus tidal volume) of the volume-pleural pressure curves of the lung and relaxed chest wall are shown. Consider a patient taking a spontaneous breath from FRC (point A) with a volume equal to the height of the *double-headed arrow* (point B). In order to overcome elastic forces of the lung and chest wall, the inspiratory muscles must exert a force equal to the horizontal distance between the chest wall and lung volume-pleural pressure curves. Thus the entire elastic work done will be equal to the *blue shaded area*. Furthermore, resistive work must also be done, requiring the inspiratory muscles to generate an even greater negative pleural pressure. This is indicated by the *gray shaded area*. The total work done will be the sum of both areas.

MEASURING WORK OF BREATHING IN A SPONTANEOUSLY BREATHING PATIENT

In a spontaneously breathing patient, work is performed by the inspiratory muscles rather than a ventilator. Graphing the pressure-volume characteristics of the lung and chest wall against pleural pressure is useful in illustrating the work performed by the inspiratory muscles (Fig. 5-23). During inspiration, pleural pressure decreases to expand the lungs (see Fig. 5-23). The distance between the two curves at any given lung volume represents the pressure the inspiratory muscles must exert to overcome elastic forces of the lung and chest wall. The blue shaded area thus represents the elastic work of breathing against the lung and chest wall. To overcome the resistive forces, additional pressure and work are required, as indicated by the gray shaded area.

Under normal conditions, exhalation is passive because the stored potential energy from elastic work is more than sufficient to overcome resistive work. However, in the presence of severe airflow obstruction (e.g., an asthma attack), the necessary resistive work may exceed this stored energy, requiring active generation of force by expiratory muscles and additional work for exhalation.

OXYGEN COST OF BREATHING

The oxygen cost of breathing is an indicator of the total amount of energy required by the respiratory muscles for ventilation. At rest, the oxygen cost of breathing is low, 0.25 to 0.5 mL/L of ventilation, or 1% to 2% of total body oxygen consumption. However, at maximal exercise in normal subjects, the oxygen cost of breathing represents approximately 10% to 15% of total oxygen consumption.¹⁰⁰ The oxygen cost of breathing can increase markedly as minute ventilation increases (eFig. 5-1).

Patients with COPD have an increased oxygen cost of breathing as a function of ventilation (see eFig. 5-1). This may be related to a combination of increased work of breathing and decreased efficiency due to dynamic hyperinflation. Dynamic hyperinflation is an increase in end-expiratory lung volume that results when patients with airflow obstruction develop intrinsic PEEP due to long time constants for gas distribution in the lungs and the increased respiratory rate they often exhibit.¹⁰¹

In addition, tonic inspiratory muscle activity at end-expiration contributes to dynamic hyperinflation. Although this dynamic increase in lung volume can have a beneficial effect by dilating intraparenchymal airways to decrease the resistive work, the end-expiratory alveolar pressure acts as an inspiratory threshold load, which increases the work of breathing. Furthermore, the mechanical efficiency of the inspiratory muscles is compromised by hyperinflation because the zone of diaphragmatic apposition is reduced and the inspiratory muscles are shorter than the optimal length for force generation. The efficiency of breathing (defined as the ratio between the rate of mechanical work accomplished and the rate of energy consumed) may be further diminished if postural or other stabilizing muscles (trunk, neck, shoulder) need to be recruited.

Key Points

- An understanding of the mechanical properties of the lung and chest wall under static and dynamic conditions is important for appreciating the determinants of lung volumes and expiratory flows under normal and pathologic conditions.
- Under conditions of laminar flow, flow is directly proportional to the pressure difference along the path of flow. Under conditions of turbulent flow, flow is directly proportional to the square root of the pressure difference. For turbulent flow the pressure drop is greater for any given flow than for laminar flow.
- In turbulent flow the substitution of a mixture of helium and oxygen can lower airway resistance because its gas density is less than air or oxygen. Turbulent flow can be present in upper airway obstruction

and perhaps in asthma if there is large-airway narrowing.

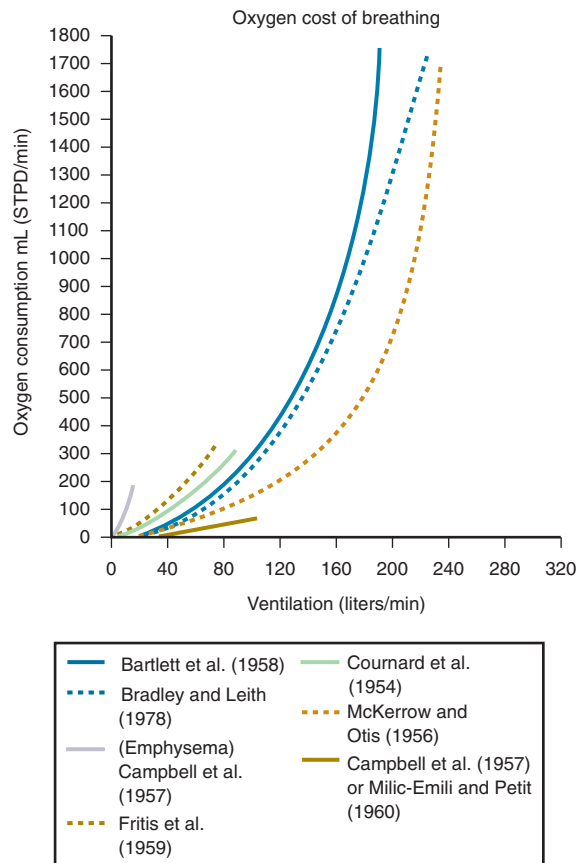
- The majority of the elastic recoil of the lung is due to surface forces generated by fluid lining the alveoli.
- The unique properties of surfactant help to reduce surface tension and stabilize alveoli at low lung volumes, thereby preventing their collapse.
- At functional residual capacity (relaxation volume), the outward recoil pressure of the chest wall is balanced by the inward recoil of the lung. Total lung capacity is determined by the balance between the maximal inspiratory pressure generated by the respiratory muscles and the opposing pressure generated by the inward recoil of the lungs and chest wall. In young subjects, residual volume is determined by the balance of pressure generated by the expiratory muscles, the minimal inward recoil of the lung, and the opposing pressures generated by the outward recoil of the chest wall. In older subjects or patients with obstructive lung disease, residual volume is not determined by this balance of forces but is rather determined by airway closure.
- Measuring respiratory system resistance and compliance can be easily accomplished in ventilated patients and is useful for assessing reasons for difficulty in weaning from the ventilator.
- In ventilated patients the proportion of the applied airway pressure that is transmitted to the pleural space is dependent on the ratio of lung and chest wall compliance. Knowing the change in pleural pressure is important because it influences venous return. Insertion of an esophageal balloon may be needed to measure the actual change in pleural pressure produced by applied airway pressure.
- In patients with airflow obstruction who are treated with positive-pressure ventilation, dynamic hyperinflation (intrinsic positive end-expiratory pressure) can lead to hemodynamic compromise, increased work of breathing, an inspiratory threshold load, mechanical inefficiency of the diaphragm, and patient-ventilator asynchrony.

Complete reference list available at **ExpertConsult**.

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eFIGURE IMAGE GALLERY



eFigure 5-1 Oxygen cost of breathing. Oxygen cost of breathing at varying levels of ventilation. Note the variability among studies and the steeper slope in patients with emphysema. STPD, standard temperature, pressure, and dry conditions. (From Roussos C, Zakynthinos S: Respiratory muscle energetics. In Roussos C, editor: *The thorax*, part A. New York, 1995, Marcel Dekker, pp 681–749.)

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PULMONARY CIRCULATION AND REGULATION OF FLUID BALANCE

JOE G. N. GARCIA, MD

INTRODUCTION

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An expanded version of this chapter is available online at ExpertConsult.

functions include direct lung vascular barrier regulation, participation in the initiation and resolution of inflammatory responses and the processing of mediators before delivery to the systemic circulation.

INTRODUCTION

The pulmonary circulation is interposed between the right and left ventricles with the following primary functions: (1) to deliver the entire cardiac output under low pressure from the right ventricle to the pulmonary microvessels and, in the process, to exchange carbon dioxide for oxygen across the alveolar-capillary membrane; (2) to act as a source of production, release, and processing of humoral mediators; and (3) to serve as a barrier to the exchange of fluid and solutes and thus maintain lung fluid balance. The morphologic characteristics of the pulmonary circulation are ideally adapted for these functions. Nearly the entire cardiac output is brought into contact with alveolar gas at the 1- to 2- μ m-thick alveolar-capillary membrane for approximately 0.75 to 1 second. This juxtaposition of capillaries with alveoli provides the vast surface area needed for effective gas exchange: approximately 70 m² (two thirds the area of a tennis court). The structural arrangement is such that the distance through which oxygen and carbon dioxide must diffuse between gas and blood is approximately one tenth the distance of diffusion in peripheral tissues. (Additional information about the anatomy of the pulmonary circulation is found in Chapter 1, and about the physiologic factors that govern the distribution of blood flow in Chapter 4.)

The pulmonary circulation has important additional functions beyond its role in gas exchange. The microvessels exchange solutes and water, and the mechanisms regulating the balance of fluid and solutes in extravascular spaces of the lung are critical to the understanding of the pathophysiology of pulmonary edema (see section “Pathogenesis of Pulmonary Edema” and Chapter 62). The pulmonary vascular endothelium, the monolayer of cells that lines all vessels, is a multidimensional tissue whose specialized

ANATOMY

The pulmonary circulation begins at the pulmonary valve, marking the vascular exit from the right side of the heart, and extends to the orifices of the pulmonary veins in the wall of the left atrium, which marks the entrance into the left side of the heart. The pulmonary circulation includes the pulmonary trunk (also called the “right ventricular outflow tract”), the right and left main pulmonary arteries and their lobar branches, intrapulmonary arteries, large elastic arteries, small muscular arteries, arterioles, capillaries, venules, and large pulmonary veins. Because of this heterogeneity and differences in physiologic behavior, the vessels of the pulmonary circulation are subdivided on a functional basis into *extra-alveolar vessels* and *alveolar vessels*. In addition, the small vessels that participate in liquid and solute exchange are often collectively termed the “pulmonary microcirculation.” The anatomic boundaries of the extra-alveolar and alveolar vessels and the microcirculation are undefined and likely depend on conditions such as lung volume and levels of intrapleural and interstitial pressures.

Additional information on the anatomy of the pulmonary circulation as well as the bronchial circulation can be found in the online version of the text (eFig. 6-1) and in Chapter 1.

PULMONARY HEMODYNAMICS

PULMONARY VASCULAR PRESSURES

Pressure and flow are highly pulsatile throughout the pulmonary circulation. Although the pressure pulsatility

Additional information on the anatomy of the pulmonary circulation as well as the bronchial circulation can be found in Chapter 1.

GENERAL DESIGN

The *pulmonary trunk* arises from the infundibulum of the right ventricle through the orifice of the pulmonary valve. The trunk, which is approximately 3 cm in diameter and 5 cm in length, lies entirely within the pericardium, as does the adjacent ascending aorta. The pulmonary trunk passes upward and backward into the concavity of the aortic arch, where it divides into the two main pulmonary arteries.

The *right main pulmonary artery* is slightly larger and longer than the *left main pulmonary artery*, and both vessels show little variation in either position or mode of branching. The right main artery divides into two branches: a larger lower branch that supplies the right middle and lower lobes, and a smaller upper branch that supplies the upper lobe. On the left the main artery lies above the main bronchus until the first branch arises and subsequently traverses in a downward direction behind the bronchus. The arterial branches supplying the lobes of both the right and left lungs, in contrast, show considerable variation. The pulmonary arteries and bronchi are enclosed in the same connective tissue sheath and generally branch together until reaching the smallest units: the alveoli and capillaries.¹ The pulmonary veins are also enveloped in connective tissue sheaths that are distinct from those enclosing the arteries and bronchi.²

The pulmonary arterial circulation has two sets of branches: the conventional arteries that accompany airways, and supernumerary arteries that travel alone and are commonly of smaller dimensions. The supernumerary arteries are entirely intrapulmonary, emerging from the main arterial channels at approximately right angles as far in the periphery as the end of respiratory bronchioles. These branches provide approximately 25% of the total cross-sectional area of the pulmonary arterial bed near the hilum and approximately 40% of the total cross-sectional area of the peripheral pulmonary arterial bed. The supernumerary arteries that are present at birth are mainly those that lead to terminal respiratory units, the structures distal to terminal bronchioles that participate in gas exchange (respiratory bronchioles, alveolar ducts, and alveoli).³ Extensive growth of conventional and supernumerary branches accompanies the development of alveolar ducts and alveoli during the first 18 months of life.^{4,5} Whereas the appearance of conventional arteries virtually ceases at 18 months, supernumerary arteries continue to increase in number up to approximately age 8 years as new alveoli are formed. Supernumerary vessels undoubtedly serve as an auxiliary arterial supply to the capillary beds of the terminal respiratory units and thus constitute a critical source of collateral blood flow to sites of gas exchange.

The *pulmonary vascular resistance* is approximately one tenth the systemic peripheral vascular resistance. This unique low-resistance characteristic of the pulmonary circulation is the result of specialized morphologic features of pulmonary arteries and veins combined with a normally low vascular tone. Both pulmonary arteries and veins have

significantly less smooth muscle content than do vessels of the same diameter in other organs, and the smooth muscle is distributed less evenly than in systemic microvessels.⁶ Pulmonary arteries exhibit more smooth muscle than pulmonary veins and represent the main sites of constriction in response to vasoactive mediators.⁷

In humans the larger pulmonary arteries (>1 to 2 mm in diameter) are largely elastic. The *elastic pulmonary arteries* contain distinctive layers of elastic fibers embedded in a coat of smooth muscle cells. In fact, the pulmonary artery trunk, its main branches, and all extra-alveolar pulmonary arteries are of the elastic type. Arteries gradually become more muscular at diameters of greater than 2 mm followed by progressively less muscularization as diameter decreases to below 100 μm .^{8,9} The smooth muscle is unevenly distributed in the medial layer of the vessel wall in a way that is distinct from the thick circumferential distribution of smooth muscle in systemic arterioles. The *muscular pulmonary arteries* exhibit a thin medial layer of muscle embedded between well-delimited internal and external elastic laminae. Muscular pulmonary arteries lie within lung lobules and hence accompany the bronchioles. Although these vessels are designated by their muscular elements, the thickness of the muscle layer does not exceed approximately 5% of the external diameter of the vessel; any increase above this value connotes a pathologic state, as is clinically associated with conditions characterized by the presence of pulmonary arterial hypertension. As the smooth muscle content decreases in these vessels, the smooth muscle assumes a spiral orientation so that in a cross section of the vessel, the smooth muscle content is observed in only a portion of the vessel wall. These *pulmonary arterioles* are the terminal branches of the pulmonary arterial system. At their origin from muscular arteries, pulmonary arterioles contain a partial layer of muscle that gradually disappears until the vessel wall consists of only the endothelial monolayer and an elastic lamina. Pulmonary arterioles supply alveolar ducts and alveoli. In vessels smaller than 30 μm in diameter, smooth muscle is virtually absent. Chronic exposure to hypoxia causes extensive vascular remodeling, especially with significant increase in smooth muscle in small arteries.¹⁰ There is considerable species variability in pulmonary artery smooth muscle content and in the pulmonary hypertensive response to hypoxia.^{11,12}

Pulmonary veins have thinner walls than arteries because the muscular layer is not as well developed. Like the arterial system, the venous system is composed of both conventional and supernumerary veins. Small intrapulmonary venules successively unite to form increasingly larger veins, and finally a single *lobar vein* emerges from each lobe. Because the right upper and right middle lobar veins generally join together, the venous drainage from each lung terminates in a *superior pulmonary vein* and an *inferior pulmonary vein*. These four pulmonary veins then enter the left atrium through orifices in the upper posterior part of the chamber wall, although occasionally the two left veins join and enter through a common opening. The pulmonary vascular bed consists of a set of highly distensible vessels, a unique feature of this circulation in that pulmonary vessels are approximately seven times more compliant than peripheral systemic arteries¹³ due to the reduced smooth muscle content, fewer elastin and collagen fibers, and the lack of

tissue surrounding the small vessels. The resistance and distensibility functions of a pulmonary vessel overlap in the same vessel. Thus pulmonary vessels are able to accommodate relatively large increases in blood volume (as in exercise) in relation to same-sized systemic arteries and serve as an important blood volume reservoir. Smooth muscle cells are intercalated with the elastin and collagen fibers, thereby enabling reflex contraction of smooth muscle cells to vary the distensibility of the pulmonary vessels.¹⁴ In the microvasculature, pericytes, polymorphic and multifunctional cells that line the basal surface of endothelial cells, are involved in the production of the microvessel basal lamina¹⁵ and contribute to the contractile regulation of lung capillary permeability.¹⁶

Pulmonary vessels are innervated by cholinergic and sympathetic fibers, although the extent of the innervation is species specific and may vary from animal to animal.¹⁷⁻¹⁹ In comparison with peripheral vessels, the innervation pattern is sparse, with innervation most evident in the branching-off point of pulmonary arteries. Sympathetic and parasympathetic efferents are most prominent in small bronchioles and arterioles of the bronchial circulation, in contrast to pulmonary vessels,¹⁹ although the exact function remains incompletely defined. Recent studies have shown the densest innervation in the vessels in the bronchial walls, and that synaptophysin-immunoreactive terminals are formed by efferent axons of neurons arising from the intrapulmonary parasympathetic ganglia.²⁰ Furthermore, sympathetic pulmonary vascular neurons appear to be activated via arterial chemoreceptors in response to low PO_2 .²¹

BRONCHIAL CIRCULATION

A separate systemic circulation supplies blood flow to the airways from the carina to the terminal bronchioles. In addition, bronchial arteries provide nutritive flow to the lower trachea, airway nerves, and lymph nodes.^{22,23} The drainage of bronchial vessels into the pulmonary circulation and the large veins has a complex arrangement (eFig. 6-1). Interconnections have been demonstrated between bronchial vessels and precapillary, capillary, and postcapillary vessels of the pulmonary circulation.²⁴ Despite the fact that the normal adult lung remains viable without the bronchial circulation (as well as in the absence of innervation), as is the case in the transplanted lung, bronchial blood flow is critical in the lung development in the fetus and contributes to gas exchange in the presence of congenital cardiac anomalies. There is a striking increase in the size and number of bronchial arteries (due to angiogenesis) in lung disorders such as pulmonary fibrosis, lung carcinoma, and disorders characterized by pulmonary vascular occlusion.²⁵⁻²⁷ Neovascularization of the systemic circulation into the lung after pulmonary artery obstruction is now well recognized in multiple species.^{22,26}

There is considerable variation in the number and origin of the bronchial arteries in the human adult. One large cadaveric study found the majority of bronchial arteries arising directly from the aorta.²⁸ Over 40% of cadavers had two arteries branching to the left lung and one artery to the right lung. Occasionally the right bronchial artery originates from the first right intercostal artery. Variable numbers of smaller minor branches emerged from vessels in and

near the mediastinum and crossed into each lung. Upon entering the lung, bronchial arteries invest in connective tissue surrounding the bronchi and begin branching with two or three branches anastomosing to form a peribronchial plexus with an elongated and irregular mesh and accompany each subdivision of the conducting airways.

Blood flow to the lung via the bronchial circulation is low, presumed to be less than 3% of the cardiac output, but has never been measured accurately in humans. Canine studies indicate that bronchial blood flow to the left lung is approximately 1% of the cardiac output, with approximately 50% of this flow directed to the lung parenchyma and the remainder to the trachea and bronchi.²⁷ If bronchial blood flow in humans is similar to canine findings, total bronchial blood flow estimates to both lungs would be approximate 1% to 2% of the cardiac output.

Venous blood from capillaries supplied by bronchial arteries returns to the heart by two different pathways (see eFig. 6-1). True *bronchial veins* are found only at the hilum; formed from tributaries that originate around the lobar and segmental bronchi and from branches from the pleura in the neighborhood of the hilum. Bronchial venous blood empties into the azygos, hemiazygos, or intercostal veins and flows into the right atrium. Veins that originate from bronchial capillaries within the lungs unite to form venous tributaries that join the pulmonary veins with these communicating vessels termed the “bronchopulmonary veins.” Blood leaving the capillary bed around terminal bronchioles flows through anastomoses with alveolar capillaries, and the mixture returns to the left atrium via pulmonary veins.

The distribution of bronchial arterial inflow between the two available venous outflow pathways is unknown in humans, with tentative conclusions drawn from the technically demanding studies in experimental animals. These indicate that approximately 25% to 33% of the bronchial arterial supply returns ultimately to the right atrium via bronchial veins, and 67% to 75% flows into the left atrium via pulmonary veins.²⁷

Controversy still exists concerning the presence and significance of *bronchopulmonary arterial anastomoses* (i.e., direct vascular connections between pulmonary arteries and bronchial arteries). Available evidence suggests that bronchopulmonary arterial anastomoses exist,²⁷ are readily identifiable in neonatal lungs but are infrequent in normal lungs, and increase considerably in certain lung pathologic conditions.^{29,30}

BLOOD-GAS INTERFACE

The pulmonary capillaries form an extensive network interwoven with a meshwork of parenchymatous connective tissue (fine collagen and elastin fibers)³¹ in the interalveolar *septa*, the walls that separate adjacent alveoli. The capillary bed has been described either as a hexagonal meshwork of cylinders only minimally longer than its diameter, or as a sheet with the two sides periodically connected by septal tissue posts.³² These two models are useful for theoretical analysis of flow in pulmonary capillaries, but each represents simplification of a complex capillary network. Capillary perfusion begins when intracapillary pressure begins to exceed alveolar pressure and additional capillaries are

recruited, with further increases in capillary pressure depending on the tension in the alveolar wall, whether imposed by positive airway pressure or by gravity when the lung is suspended in an intact thorax.³³

Pulmonary capillaries, composed of capillary endothelium contiguously arranged to form a thin vascular tube, weave through the interstitial space of the interalveolar septum, facing first one alveolus and then another, thereby crossing several alveoli. Both the endothelium and the neighboring type I and type II alveolar epithelium rest on individual basement membranes, which appear to be fused over more than 50% of the capillary perimeter, thereby forming the *thin portion* of the alveolar-capillary septum. This is an ideal site for gas exchange because of the maximum surface area available for gas exchange combined with an extremely short diffusion distance. The thin septum consists of connective tissue elements (primarily collagens I and IV) that provide structural support.³⁴ In the remaining half of the capillary perimeter, the endothelial and epithelial basement membranes are separated to form an interstitial space (i.e., the *thick portion* of the alveolar septum, which represents the primary site of transcapillary fluid and solute exchange and consists of a variety of collagen fibers, elastin, and proteoglycans).³⁴ The existing barriers from the air space to the vessel lumen are the *alveolar epithelium*, *basement membranes* of the epithelium and endothelium, the *interstitial space* that exists within the thick septum but not the thin septum, and the *endothelium*.

IMAGING THE PULMONARY CIRCULATION

Advances in techniques to image the pulmonary circulation in recent years serve as invaluable tools to evaluate patients with potential pulmonary vascular abnormalities or diseases. Although *computed tomography* is one useful modality for these purposes, *magnetic resonance imaging* (MRI) is recognized as the most effective approach currently in use by virtue of its ability to visualize vessels regardless of orientation and to provide functional in addition to anatomic information.^{35,36} In addition, MRI, unlike computed tomography, does not require administration of potentially toxic radiation or contrast agents.

Two MRI techniques of high utility are contrast-enhanced *magnetic resonance angiography* and *phase-contrast magnetic resonance velocity mapping*. Magnetic resonance angiography relies on the intravenous administration of gadolinium to obtain rapid and detailed imaging of lung vascular anatomy with a total imaging time of less than 20 seconds,³⁷ often acquiring relatively high resolution three-dimensional images within 3 to 4 seconds. This allows for pulmonary vasculature visualization even in significantly dyspneic patients unable to hold their breath for a prolonged period of time.^{38,39} Relying on a pixel-by-pixel analysis of signal intensity-time course curves, magnetic resonance angiography is also capable of providing functional data, including quantitation of regional perfusion in terms of flow, mean transit time, and volume throughout the lungs.³⁹ Alternatively, phase-contrast MRI provides similar functional assessments derived from measurements of phase shifts of moving nuclei relative to stationary nuclei.⁴⁰ Although precise measurements can most reliably be obtained from the central vessels using this technique, flow patterns can be accurately determined throughout the lung vasculature, including the peripheral veins, and, in general, phase-contrast MRI flow measurements provide greater than 95% accuracy.^{41,42}

MRI of the pulmonary circulation offers significant clinical applications. For example, MRI provides full visualization of anomalous pulmonary venous connections (representing approximately 2% of congenital heart diseases)⁴³ and assessment of hemodynamic parameters. Thoracic MRI has improved its potential in pulmonary thromboembolism,⁴⁴ whereas use of multidetector-row CT has been used in quantifying bilateral bronchial narrowing.⁴⁵ Separately, magnetic resonance angiography is now the optimal modality to evaluate pulmonary vein stenosis, surpassing the sensitivity of echocardiography³⁷ and allowing assessment of stenotic lesions in addition to the collateral circulation. A number of other potential clinical applications with respect to the pulmonary vasculature have shown high promise and continue to be the focus of investigation, including the evaluation of patients with chronic thromboembolic disease,⁴⁶ arteriovenous malformations,^{47,48} and pulmonary vasculitis.⁴⁹

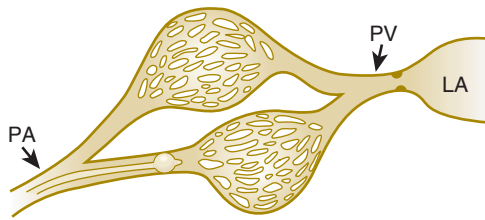


Figure 6-1 Method of determining pulmonary wedge pressure. By placing a catheter through the right heart and pulmonary artery (PA) and occluding a small PA with a balloon, the static fluid column within the catheter is functionally extended from the catheter tip through the capillaries and into pulmonary veins (PVs). The pressure measured is at the confluence of veins, where flow is again present. Because the pressure drop from a large vein to the left atrium (LA) is small, wedge pressure is a reflection of left atrial pressure except when (1) there is a change in downstream resistance, indicated by constriction (solid semicircles) proximal to the LA or (2) the catheter is in an artery perfusing a capillary bed where alveolar pressure exceeds PV pressure (i.e., zone 1 or 2). In the latter case, when the balloon is inflated, pressure within the capillary bed falls toward PV pressure, capillaries are compressed, the fluid column is interrupted, and wedge pressure will no longer reflect left atrial pressure (see Fig. 6-2).

decreases across the pulmonary circuit, the pulsatile nature of the flow persists on the venous side.⁵⁰ *Pulmonary artery pressure* (PPA) is normally approximately 25 mm Hg during systole and 9 mm Hg during diastole. Relative to systemic arterial pressure, PPA is low, and hydrostatic pressure differences due to gravity result in a substantial difference in vascular pressure from the top to the bottom of the lung. If the pulmonary artery is considered to be a column of blood approximately 25 cm high, there will be a 25 cm H₂O (or 18 mm Hg) PPA increase from the bottom to the top of the lung (1 mm Hg pressure = 1.36 cm H₂O pressure). This pressure difference results in a nonuniform distribution of blood flow, as discussed subsequently in the “Regional Distribution of Pulmonary Perfusion” section.

PPA is measured by inserting a cardiac catheter or a balloon-tipped flotation catheter into the pulmonary artery.⁵¹ Inflating the balloon leads to advancement (“floating”) of the catheter (Fig. 6-1) until it “wedges” and occludes a peripheral pulmonary artery. With the balloon inflated the pressure measured in the tip of the catheter is called the *pulmonary wedge pressure* (PPW).^{52,53} This procedure effectively extends the static fluid within the catheter lumen into the vascular bed, and the measured pressure is thus at the site where this extended column next joins a vessel in which blood is flowing. The wedge pressure (normally 5 to 10 mm Hg) is an estimate of the vascular pressure at the point of confluence of pulmonary veins and hence reflects *left atrial pressure* (PLA).

Changes in pressure distal to the confluence of the pulmonary veins, such as that induced by constriction of the pulmonary venules, can alter the relationship between PLA and PPW. Also, the precise location of the catheter tip in the lung influences the measurement of PPW (Fig. 6-2). Zone 1 is the region of the lung in which the *alveolar pressure* (Palv) is greater than PPA, which is greater than the *pulmonary venous pressure* (PPV), and therefore there is minimal blood flow through the alveolar vessels. Zone 2 is where PPA is greater than Palv, which is greater than PPV, and therefore flow increases linearly as one moves down the lung. Positioning the catheter in the upper lung (in zone 1 or 2)

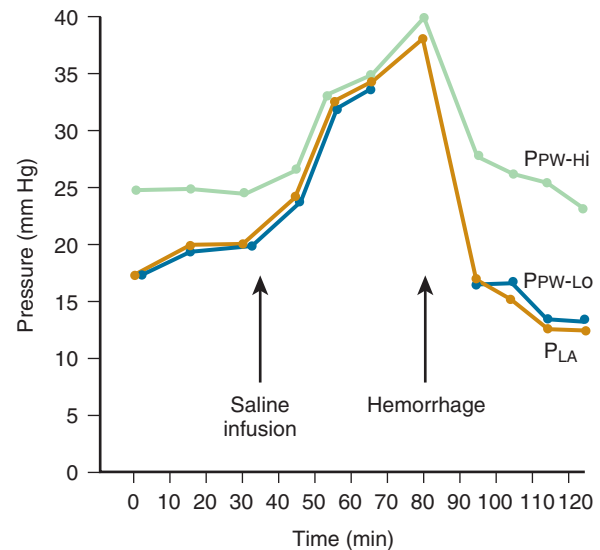


Figure 6-2 Illustration of the influence of catheter position on wedge pressure measurement over time. When the catheter is wedged in a *low* position (i.e., zone 3), wedge pressure (PPW-Lo) reflects left atrial pressure (PLA) (see at 10 minutes). When the catheter is wedged in a *high* position (PPW-Hi), however, the pressure does not reflect PLA because, when the catheter is wedged, pulmonary venous pressure is less than alveolar pressure (i.e., zone 2), the capillary bed is compressed, and the catheter measures alveolar pressure. With a saline infusion, pulmonary venous pressure rises, capillaries open (i.e., zone 3), and PPW-Hi now measures pulmonary venous pressure, becoming equal to PLA. With hemorrhage, pulmonary venous pressure falls again, and PPW-Hi again becomes greater than PLA. (From Todd TR, Baile EM, Hogg JC: Pulmonary arterial wedge pressure in hemorrhagic shock. *Am Rev Respir Dis* 118:613–616, 1978.)

results in a PPW different from PLA because higher alveolar pressures occlude the fluid column. Under these conditions, PPW provides an incorrect measurement of pulmonary vascular outflow pressure. A catheter wedged in zone 3, where PPA is greater than PPV, which is greater than Palv, more accurately reflects the PLA.^{54,55} Various algorithms have been proposed to validate measurements of PPW.⁵⁵

PULMONARY VASCULAR RESISTANCE

Pulmonary vascular resistance (PVR) is calculated by the following equation:

$$PVR = \frac{PPA - PLA}{\dot{Q}_T} \quad (1)$$

where \dot{Q}_T is cardiac output, PPA is mean pulmonary artery (inflow) pressure, and PLA is mean left atrial (outflow) pressure, which is often estimated by PPW. PVR is expressed in units of mm Hg/L/min or in dyne·sec·cm⁻⁵ (to convert units to dyne·sec·cm⁻⁵, PVR in mm Hg/L/min is multiplied by 1332). The normal PVR value is approximately 0.1 mm Hg/L/min, or 100 dyne·sec·cm⁻⁵. This value is approximately one tenth the value of systemic vascular resistance.

The use of Equation 1 (from Ohm's law) is complicated by the fact that resistance is not independent of PPA or PLA. As an example, if both PPA and PLA were elevated to such a degree that the pressure difference remained unchanged, PVR would nevertheless decrease because of distention of vessels by higher intravascular pressures. Thus inferences regarding resistance changes in the vasculature require

consideration of multiple mechanical factors that affect vascular resistance, including not only vascular pressures but also lung volume and inflation pressure. PVR is a function of lung volume because inflation distends some vessels and compresses others, as described later in the discussion of alveolar and extra-alveolar vessels.

PVR can also be potentially modeled by Poiseuille's law, which, for laminar flow, describes the relationship of resistance (R) of a tube to the tube's physical characteristics and viscosity of perfusing fluid:

$$R = \frac{8}{\pi} \cdot \frac{l}{r^4} \cdot \eta \quad (2)$$

where l is the length of the tube, r is the radius of the tube, and η is the viscosity of the perfusion fluid. It is evident from this equation that the critical factor determining PVR is the change in the tube's radius because resistance is proportional to $1/r^4$. Although this suggests that a 50% decrease in the tube radius, potentially encountered with vessel constriction, increases resistance 16-fold, this derived relationship may be excessively robust. Ohm's law and Poiseuille's law, although useful in describing the resistance properties of pulmonary vessels, have limitations that must be considered when changes in the calculated PVR value are interpreted. Characteristics unaccounted for in either equation include the following: blood flow is pulsatile, blood vessels are complex distensible branching tubes (not rigid cylinders), and blood-formed elements in the plasma constitute a nonhomogeneous fluid. Nevertheless, the ratio of pulmonary perfusion pressure to blood flow under strictly controlled conditions is a useful measure of pulmonary vasomotor tone with the caveat that its usefulness depends on knowledge of levels of intravascular pressure, pulmonary blood volume, and lung volume. Recent estimations of PVR using the ratio of pulmonary artery systolic pressure to the right ventricular outflow tract velocity time integral may provide a superior assessment of PVR.⁵⁶

Vascular Resistance Profile

The vascular resistance profile in the pulmonary circuit has been estimated by micropuncture studies.^{57,58} In zone 3 conditions, where vascular resistance is not influenced by alveolar pressure, the majority of the resistance lies in pulmonary microvessels with nearly 50% of total resistance residing in alveolar capillaries (Fig. 6-3). These results indicate that the small pulmonary arteries and capillaries account for most of the pressure drop across the pulmonary vascular bed, a finding in striking contrast to the systemic circulation, where the arterioles account for the greatest pressure drop.

Mechanical Effects on Pulmonary Vascular Resistance

Transmural Pressure. The importance of transmural pressure is highlighted by the experiments described in Figure 6-4 where, at a constant PLA, increases in PPA caused a decrease in PVR; however, as PLA was raised, increases in PPA had progressively less effect.^{59,60} This indicates that the vessels are nearly maximally dilated at high levels of PLA and that, after a certain PLA is reached, additional increases in transmural pressure (produced by elevating PPA) do not produce further decreases in PVR.

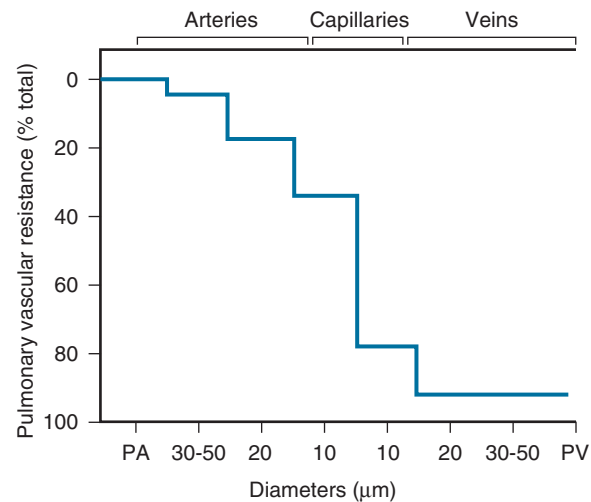


Figure 6-3 Distribution of vascular resistance as determined by micropuncture measurement of pressures. Unlike the situation in the systemic circulation, the majority of the vascular resistance in the pulmonary circuit resides in the capillaries. Measurements were made in subpleural vessels of isolated dog lungs under zone 3 conditions. PA, pulmonary artery; PV, pulmonary vein. (From Bhattacharya J, Staub NC: Direct measurement of microvascular pressures in isolated perfused dog lung. *Science* 210:327–328, 1980.)

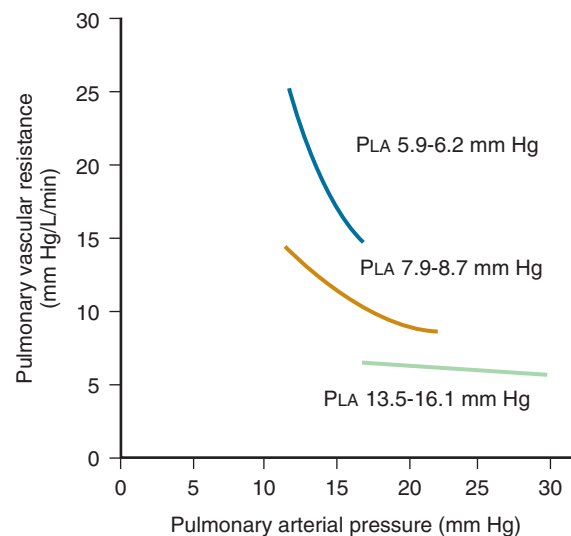


Figure 6-4 Pulmonary vascular resistance is dependent upon the pulmonary arterial pressure. As pulmonary arterial pressure increases, vessels are distended and resistance falls. This effect is diminished at higher left atrial pressures (PLA) because the vascular bed is already near maximal distention. (Data from Borst HG, McGregor M, Whittenberger JL, Berglund E: Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance. *Circ Res* 4:393–399, 1956.)

Lung Volume. Changes in lung volume produce opposite effects on the caliber and the resistance of alveolar and extra-alveolar vessels (Fig. 6-5). For alveolar vessels, the perivascular pressure is generally slightly lower than alveolar pressure as a result of the elastic recoil of alveolar walls, reflecting both surface tension created by the layer of liquid at the air-liquid interface⁶¹ and traction on membranes surrounding the interstitial space produced by alveolar wall attachments.⁶² In effect, surface tension forces tend to collapse alveoli, thereby decreasing perivascular

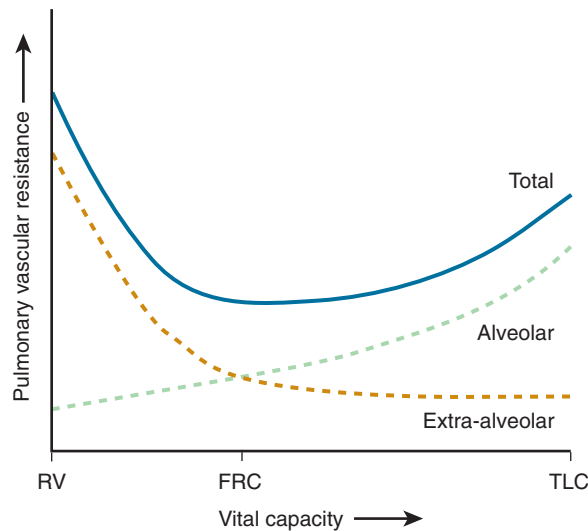


Figure 6-5 Pulmonary vascular resistance increases as lung volume is decreased from functional residual capacity (FRC) to residual volume (RV) because of the influence of rising interstitial pressure on extra-alveolar vessels. Resistance also increases with lung inflation from FRC to total lung capacity (TLC) because of stretched and flattened alveolar vessels. (From Murray JF: *The normal lung*, ed 2, Philadelphia, 1986, WB Saunders.)

pressure relative to alveolar pressure. However, during lung inflation, alveolar vessels are compressed and elongated.⁶³ Therefore, as the lung increases from residual volume to total lung capacity, resistance of alveolar vessels progressively increases.

In contrast, extra-alveolar vessels are subjected to different stresses. When interstitial pressure surrounding extra-alveolar vessels decreases with lung inflation, the resulting increased transmural pressure causes a decrease in resistance of these vessels. Corner vessels are also subjected to this same decreasing interstitial pressure and also show a decreased resistance with lung inflation. Thus, with lung inflation, the resistance of extra-alveolar vessels progressively decreases (see Fig. 6-5).

Because the resistances of alveolar and extra-alveolar vessels are in series, the resistances are additive and the change in PVR forms a “U”-shaped curve, with the nadir of the curve operating at approximately functional residual capacity, the usual end-expiratory lung volume. Any increase in the perivascular pressure of alveolar vessels or extra-alveolar vessels increases the resistance of these vessels. For example, tissue edema is associated with an increase in the interstitial fluid pressure,⁶⁴ which decreases the transmural pressure and thereby leads to the increase in PVR associated with pulmonary edema. Severe alveolar edema serves to compress alveolar vessels and can contribute to the increased PVR associated with alveolar flooding.

Viscosity. The viscosity term (η) of Poiseuille’s law (Equation 2) predicts that an increase in blood viscosity produces a proportional increase in the PVR. Viscosity is a function of the deformability of red blood cells in pulmonary microvessels, the viscosity of plasma⁶⁵ with the hematocrit being the primary factor determining viscosity of the blood.⁶⁶ Figure 6-6 shows the effects of changes in the hematocrit on pulmonary arterial pressure at three levels

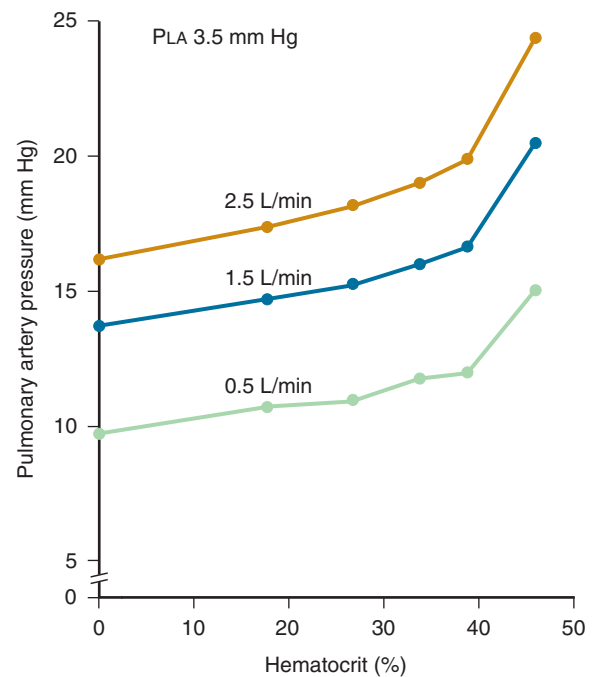


Figure 6-6 Effect of hematocrit on pulmonary artery pressure at three levels of blood flow (0.5, 1.5, and 2.5 L/min are depicted). Left atrial pressure (PLA) was held constant at 3.5 mm Hg. As the hematocrit (Hct) is increased at constant levels of pulmonary flow, pulmonary artery pressure increases, reflecting the higher vascular resistance caused by increased blood viscosity. With an increase in Hct above 40%, the pressure and resistance rise rapidly. (From Murray JF, Karp RB, Nadel JA: Viscosity effects on pressure-flow relations and vascular resistance in dogs’ lungs. *J Appl Physiol* 27:336–341, 1969.)

of blood flow. At each level of blood flow, it is evident that blood hematocrit values greater than 40% produce rapid increases in PPA and PVR. Although controversial, hypoxia-induced polycythemia and the resulting increased viscosity appear to be major factors contributing to the increased PVR at high altitude.⁶⁷

PULMONARY VASCULAR COMPLIANCE

Pulmonary Vascular Pressure-Volume Curve

The pulmonary vasculature is a highly compliant circuit¹³ with the pulmonary blood volume normally constituting approximately 10% of total blood volume. The distribution of blood volume among the arterial, capillary, and venous volumes is, however, highly dependent on the technique of measurement and on whether arteries, capillaries, and veins are defined functionally or anatomically. Human capillary blood volume has been functionally estimated⁶⁸ to be approximately 75 mL or approximately 10% to 20% of total pulmonary blood volume. However, estimates in animals have generally shown a higher proportion of pulmonary blood volume within the capillaries.^{34,51}

The pressure-volume curve of the pulmonary vasculature is linear at low levels of pulmonary perfusion pressure, where small changes in volume result in small changes in pressure, and becomes nonlinear at higher pressures, where small changes in volume cause large changes in pressure. Pulmonary vascular compliance is defined as $\Delta V / \Delta P$, where ΔV is the change in pulmonary vascular volume and ΔP is

the change in transmural pressure. Microvessels^{69,70} are usually the primary site of vascular compliance, although others have postulated that larger pulmonary vessels may also contribute to vascular compliance.⁷¹

Changes in Vascular Compliance

Pulmonary vascular compliance decreases with increases in sympathetic nerve activity.⁷² The pulmonary circulation thus serves as a vascular reservoir that responds to sympathetic stimulation by increasing left atrial filling pressure and increasing cardiac output. Pulmonary vascular compliance is also influenced by changes in lung volume secondary to alterations in intrapleural pressure. Because a substantial fraction of blood volume is localized in large pulmonary arteries and veins (largely extra-alveolar vessels), lung inflation increases transmural pressure, passively enlarges these vessels, and thereby increases blood volume within the pulmonary circuit. In contrast, reductions in lung volume reduce pulmonary blood volume within the pulmonary circuit.⁷³

PULMONARY PERFUSION

Distention and Recruitment

Pulmonary microvessels can either be recruited (i.e., new vessels “brought into play” in the microcirculation) or be distended (i.e., already perfused vessels dilating as a result of increased transmural pressure). It is not always clear which process predominates in response to increasing pulmonary capillary pressures.⁵⁰ It is likely that there are regional differences in the relative importance of recruitment and distention of pulmonary vessels. In zone 1, alveolar vessels are more likely to be recruited when transmural pressure rises, because vessels are normally collapsed in this region.⁷⁴ In zone 2, both recruitment and distention are likely, due to the uneven perfusion in this region.^{74,75} In zone 3, distention is likely to predominate, because this lung region is more consistently perfused than other regions.⁷⁴

Regional Distribution of Pulmonary Perfusion

Because of gravity, mean intravascular pressures are lowest at the apex of the lung and highest at the base. Therefore, because alveolar pressure is constant throughout the lung, pulmonary blood flow is a function of its vertical height; blood flow is dependent upon the interactions among mean PPA, mean PPV, and Palv.

In zone 1, the uppermost region, blood flow is limited and alveolar vessels are collapsed because Palv is greater than PPA and PPV.^{74,76-78} Flow in zone 1 persists to a limited degree because pericapillary pressures in zone 1 are slightly lower than Palv because of the surface tension of the alveolar lining layer⁷⁹ and because corner vessels are not subject to changes in Palv.⁵⁹ A final factor contributing to continuing zone 1 perfusion is the pulsatile nature of pulmonary capillary pressure, which recruits capillaries with intermittent bursts of flow during systole.⁸⁰

In zone 2, where PPA is greater than Palv, which is greater than PPV, blood flow begins just below the level of lung where PPA equals Palv; moving linearly downward, PPA progressively increases in relation to Palv, and blood flow steadily increases. Pulmonary perfusion in zone 2 is deter-

mined by the pulmonary arterial minus *alveolar* pressure difference, or $PPA - Palv$, rather than the arterial minus *venous* pressure difference, the gradient that normally governs blood flow in most vascular beds. Zone 2 conditions have been compared to a “vascular waterfall” or “sluice,” because perfusion is independent of PPV, the downstream pressure.

In Zone 3, a more dependent region of the lung, PPA is greater than PPV, which is greater than Palv and results in a more gradual increase in flow because the increasing intravascular pressures progressively dilate the vessels, thereby lowering regional vascular resistance and causing blood flow to increase steadily. This region is the major site of gas exchange because it receives the preponderance of blood flow and of ventilation.⁷⁶⁻⁷⁸

Zone 4 is the region in the most dependent portion of the lung in which blood flow decreases from the peak observed in zone 3. This zone is a reflection of conditions at the base of the lung, where alveoli may be poorly ventilated or even nonventilated because airways leading to the region are narrowed or closed, producing local alveolar hypoxia, arterial vasoconstriction, and an increase in PVR. In addition, at low lung volumes, extra-alveolar vessels become compressed because interstitial pressure increases, causing PVR to rise.⁷⁸ Moreover, pathologic conditions that lead to perivascular edema may be associated with the development or enlargement of zone 4.⁸¹

Because of the prevailing intravascular pressures, zone 1 does not exist in the lungs of healthy humans under ordinary conditions, even when upright. The majority of the normal lung functions in zone 3 and only the uppermost region in zone 2. Decreases in intravascular pressures (hemorrhagic shock or positive end-expiratory pressure-induced increase in intra-alveolar pressure) expands zone 2 and possibly creates zone 1 conditions. Increased resolution in blood flow measurements has resulted in proposed modifications of the zone gravity model⁸² with incorporation of newer concepts of fractal vascular trees and perfusion heterogeneity, together suggesting that the pulmonary vascular structure is an additional critical factor in determining regional blood flow.^{82,83}

Additional in-depth reviews of hemodynamic aspects of the pulmonary circulation should be consulted for supplementary material and perspectives.^{50,51,84,85} The effect of gravity on blood flow and the implications of this effect in terms of gas exchange are also discussed in Chapter 4.

MECHANICAL STRESS AND THE LUNG CIRCULATION

Lung inflation and the pulsatile nature of blood pressure and flow exposes blood vessels to hemodynamic forces in the form of shear stress and cyclic stretch. The endothelium converts these mechanical stimuli to intracellular signals that affect cellular functions, including proliferation, migration, remodeling, permeability, and apoptosis. The cytoskeleton is the key structural framework for endothelial cells to transmit mechanical forces from its luminal, abluminal, and junctional surfaces to its interior. Changes in vascular mechanical stress activate multiple sensing mechanisms and signaling networks resulting in physiologic and pathologic functional responses.

Shear Stress

The flow of blood parallel to the vessel surface produces fluid shear stress from the friction of blood against the vessel wall. Endothelial cells are the primary vascular cells exposed to shear stress from laminar blood flow. The response of endothelial cells to physiologic levels of shear stress serves a number of regulatory functions including (1) vascular remodeling, (2) modulation of hemostasis and thrombosis, (3) modulation of inflammation through the expression of chemotactic and adhesion molecules on membrane surfaces, and (4) vascular smooth muscle cell contraction through the release of vasodilators and vasoconstrictors.⁸⁶ Endothelial cell perfusion at the physiologic shear stress of 10 dynes/cm² has been associated with vascular barrier enhancement (Fig. 6-7), suggesting that shear stress is important in normal vascular barrier maintenance.⁸⁷ In the systemic circulation, disruption or unsteady blood flow at atherosclerosis-prone regions of blood vessels can impair these functions, leading to proatherogenic and/or prothrombotic states. Endothelial cells use multiple sensors for shear stress, including membrane receptors such as integrins,^{88,89} vascular endothelial growth factor receptor-2,⁸⁹ ion channels,⁹⁰ platelet endothelial cell adhesion molecule-1, and components of the endothelial glycocalyx.^{91,92} These sensors can interact with each other and transactivate multiple signaling pathways,^{93,94} including p38 and p42/44 mitogen-activated protein kinase,^{95,96} and tyrosine kinases

such as c-Abl⁹⁷ and focal adhesion kinase.⁹⁸ These signals lead to altered gene expression^{86,99} and rapid cytoskeletal rearrangement evidenced by flow-directed reorientation of the endothelium.^{100,101} Shear stress-mediated production of *reactive oxygen species* (ROS) via nicotinamide adenine dinucleotide phosphate, reduced form activation regulates normal cell growth, proliferation, and differentiation.^{102,103} ROS signaling in settings of chronic inflammation, however, exacerbates smooth muscle contractility and vascular remodeling associated with pulmonary hypertension, acute lung injury, or pulmonary edema.¹⁰⁴ Shear stress also serves a protective role by reducing endothelial cell turnover through inhibition of cell proliferation and suppression of apoptosis via activation of the PI3K-AKT survival pathway and nitric oxide production.¹⁰⁵⁻¹⁰⁷ The variability of vessel properties along with the pulsatile nature of blood flow results in temporal and spatial variations of shear stress on the vessel wall. In the straight part of the vessel, blood flow is undisturbed with a mean shear stress of 10 to 70 dynes/cm².¹⁰⁸ However, blood flow patterns in the bends and bifurcations are disturbed, leading to eddies in which peak shear stresses can exceed 100 dynes/cm².^{109,110}

Cyclic Stretch

Cyclic stretch is also an important mechanical force generated in the lung circulation by either circulating blood (which produces pulsatile distention of the arterial wall) or by tidal breathing. Blood pressure represents the major

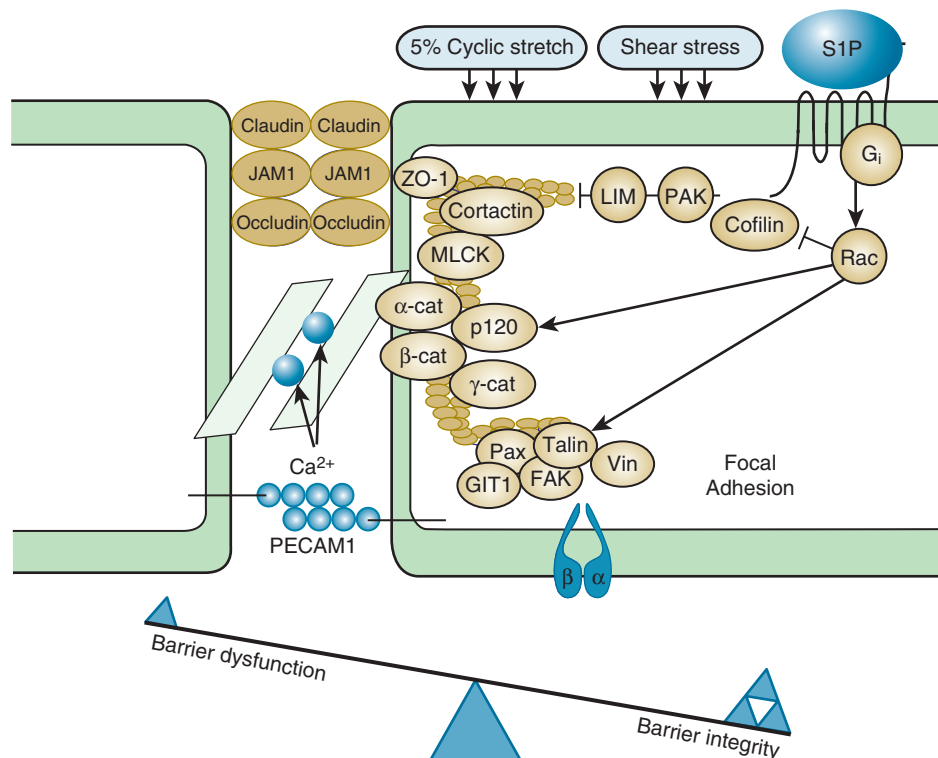


Figure 6-7 Schematic depicting enhanced endothelial cell barrier function by sphingosine-1-phosphate. Sphingosine-1-phosphate (S1P), an angiogenic growth factor, activates specific G protein-coupled S1P receptors, leading to profound cytoskeletal rearrangement and increased barrier function in vitro and in vivo.^{261,331,336,337} Ligand of S1PR1 results in activation of Rac GTPase, a signaling cascade that results in cytoskeletal rearrangement and increased cortical actin with increased linkage to the adherens junction and focal adhesions. Rac activation initiates intracellular events dependent on specific protein kinase C isotypes, p21-associated kinase (PAK), LIM-kinase, the actin-severing protein cofilin, and myosin light chain kinase (MLCK), which all contribute to increased cell-cell and cell-matrix tethering. cat, catenin; Gi, inhibitory G protein; FAK, focal adhesion kinase; GIT1, G protein-coupled receptor kinase interacting protein 1; Pax, paxillin; PECAM1, platelet-endothelial cell adhesion molecule-1; Vin, vinculin.

determinant of vessel stretch.^{111,112} Similar to shear stress, cyclic stretch induces reorientation of the endothelium in a transverse direction.^{111,113,114} In vitro endothelial cell exposure to 5% cyclic stretch (a physiologic level of mechanical stress) results in rapid Rac GTPase-mediated signaling¹¹⁵ and redistribution of actin¹¹¹ and cortactin,^{87,115} an actin-binding protein, toward the cell periphery (see Fig. 6-7). Furthermore, in comparison to static conditions, physiologic stretch induces desensitization to edemagenic agents, as evidenced by the reduction of thrombin-induced paracellular gap formation.^{111,115} In contrast, endothelial exposure to 18% cyclic stretch, a pathologic level of excessive distention mimicking high tidal volume mechanical ventilation, induces Rho GTPase activation¹¹⁴ and increased sensitivity to edemagenic agonists (Fig. 6-8). This is reflected by increased vascular leak^{111,114} via increased signaling and expression of contractile proteins including Rho GTPase, myosin light chains, myosin light chain kinase, PAR1, caldesmon, and HSP27, suggesting regulation at both the translational and posttranslational level.^{111,116} Sustained in vitro or in vivo exposure to excessive cyclic stretch also increases microparticle shedding from the endothelial surface and provides yet another pathway of sustained

inflammation. Clinically, lung overdistention caused by mechanical ventilation at high tidal volumes induces remodeling of the extracellular matrix.¹¹⁷ Cellular responses to mechanical stress include increased inflammatory cytokine production, macrophage activation, acute inflammation, and barrier dysfunction resulting in pulmonary edema. Reductions in tidal volume serve to decrease mechanical stress and extracellular matrix disorganization,¹¹⁷ resulting in improved patient mortality from ventilator-induced lung injury.^{118,119} Chronic exposure of the pulmonary circulation to increased cyclic stretch induces vascular cell proliferation, collagen and fibronectin synthesis, and alveolar and vascular remodeling.^{120,121}

PULMONARY VASCULAR RESPONSES TO HYPOXIA

Response Elements

Alveolar hypoxia, defined as an alveolar PO_2 of less than 70 mm Hg, typically elicits pulmonary vasoconstriction.¹²² Isolated lung experiments have shown that the most important stimulus for vasoconstriction is hypoxia at the alveolus,

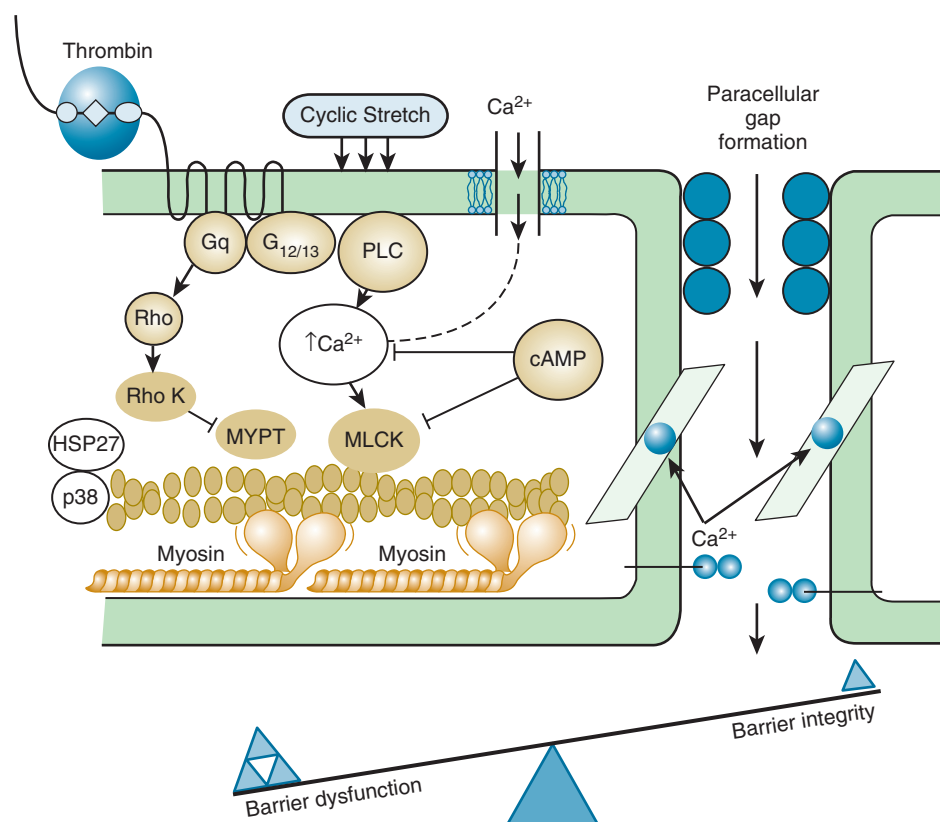


Figure 6-8 Schematic depicting the disruption of endothelial cell barrier homeostasis by thrombin. In this working model of lung vascular barrier regulation, a balance exists under basal conditions between actomyosin contractile and cellular adhesive forces. Thrombin cleavage of the PAR1 receptor on the surface of the endothelial cell results in activation of contractile forces via both heterotrimeric G proteins (G_q , $G_{12/13}$) and small GTPases such as Rho. Activated Rho (Rho-GTP) induces increased Rho kinase (Rho K) activity and phosphorylation of the phosphatase regulatory subunit thereby inhibiting the myosin phosphatase (MYPT). Rho K and myosin light chain kinase (MLCK) are activated via independent pathways. Increased cytosolic calcium (via inositol triphosphate production) activates the calcium/calmodulin-dependent MLCK, with conformational changes allowing the enzyme to access the preferred substrate, myosin light chain (MLC). Rho K and MLCK activation both culminate in increased MLC phosphorylation, which in turn enables actomyosin contraction resulting in increased stress fiber formation, cellular contraction, paracellular gap formation, and ultimately barrier dysfunction. Increases in cyclic adenosine monophosphate (cAMP) influence both calcium mobilization and MLCK activity. Additional regulatory proteins, such as heat shock protein (HSP27) and the actin capping/severing proteins, cofilin and gelsolin, are also involved in stress fiber rearrangement. PLC, phospholipase C.

as opposed to hypoxemia of pulmonary arterial blood.⁵¹ Vasoconstriction mainly involves the small precapillary vessels.¹²³⁻¹²⁵ The vasoconstrictor response to hypoxia is unique to pulmonary vessels; exposure of systemic vessels to hypoxia results in vasodilation. The hypoxic pulmonary vasoconstrictor response serves a regulatory function in matching perfusion to ventilation by shunting perfusion away from poorly oxygenated regions of the lung. Alveolar hypoxia in a lung segment causes significant diversion of blood flow to the more normoxic regions of the lung.¹²⁶

Neurohumoral signals generated during hypoxia have been invoked to explain the response, but the basis of the constriction still remains unknown.¹²⁷ Because the hypoxic pulmonary vasoconstrictor response is retained in isolated-perfused lungs and in isolated small (<300 μ m) pulmonary arteries,¹²⁸ it is unlikely that it is the result of nerve stimulation. However, local activation of peptidergic nerves and axon reflexes cannot be discounted. No study to date has identified a blood-borne or released mediator that accounts for the hypoxic vasoconstriction response, although several candidates identified by genomic strategies have been suggested.¹²⁹ Several bioactive mediators potentially modulate the magnitude of the hypoxic response by influencing the basal pulmonary vasomotor tone. The extent of the response to hypoxia is species dependent and correlates with the amount of smooth muscle present in pulmonary arteries.¹³⁰ Calves with an abundant amount of pulmonary vascular smooth muscle, such as those born at high altitude, have a pulmonary vascular bed that is highly reactive to hypoxia.¹³¹ In humans, nitroglycerin or *nitric oxide* (NO) attenuate hypoxic pulmonary vasoconstriction and, by disrupting the matching of ventilation to perfusion, can produce hypoxemia.¹³²

Chronic exposure to hypoxia increases the muscular content of small arteries that are normally devoid of smooth muscle.¹⁰ People native to high altitude in the Andes have an increased muscularization of arteries as small as 20 μ m.¹³³ However, not all high-altitude natives¹³⁴ nor all animals living at high altitudes exhibit this response.¹¹ This suggests that genetic factors exist that regulate the pulmonary vascular remodeling seen during hypoxia.^{135,136}

The hypoxic pulmonary vasoconstrictor response is augmented by increases in plasma hydrogen ion concentration.¹³⁷ The partial pressure of carbon dioxide acts only via its effect on pH.^{138,139} The increased hydrogen ion concentration in pulmonary vascular smooth muscle cells resulting from hypoxia or carbon dioxide is an important intracellular signal mediating the interaction between actin and myosin filaments and thus vascular tone.

The hypoxic pulmonary vasoconstrictor response is also affected indirectly by a variety of mediators. The vasoconstrictor response is augmented by cyclooxygenase inhibitors¹⁴⁰ via prevention of prostacyclin generation. An increase in left atrial pressure and in blood volume can prevent the hypoxia-induced pulmonary vasoconstriction, which indicates that transmural pressure changes influence the response.¹⁴¹ Another significant factor potentially influencing the hypoxic pulmonary vasoconstrictor response is NO. As shown in pulmonary artery ring studies, acetylcholine-mediated vasodilation depends upon an intact endothelium that releases NO.^{142,143} Antagonists of

endothelium-dependent relaxation potentiate hypoxic pulmonary vasoconstriction.¹⁴⁴ Pulmonary vascular endothelial cells activated by hypoxia may not release NO to the same extent as systemic vessels. In addition to NO, there are other endothelium-derived relaxing factors. For example, endothelium-derived hyperpolarizing factor is the likely mediator of endothelium-derived relaxation that cannot be attributed to NO.¹⁴⁵ Endothelium-derived hyperpolarizing factor mediates its vasodilator effect by causing the calcium-dependent potassium channels to open, leading to hyperpolarization.¹⁴⁶ However, the role of endothelium-derived hyperpolarizing factor in the control of basal and hypoxic pulmonary vasoconstriction is not known. The bioactive peptide, endothelin, is a constricting factor released by systemic and pulmonary endothelial cells by hypoxia. However, these experiments were made with arteries larger than those generally considered to be responsible for hypoxic pulmonary vasoconstriction.

In addition to these indirect effects on vasoconstriction, there may be direct effects of hypoxia on the vascular smooth muscle cells. Hypoxia may be sensed via the proximal mitochondria electron transport chain, which decreases ROS production in response to hypoxia. This event results in a decrease in superoxide or hydrogen peroxide and inhibition of the potassium channel that elicits membrane depolarization.¹⁴⁷⁻¹⁴⁹ This results in the opening of a calcium channel and an influx of calcium that mediates pulmonary arterial smooth muscle contraction.¹⁴⁷⁻¹⁴⁹ Because metabolic inhibitors enhance hypoxic vasoconstriction, a hypoxia-induced decrease in oxidative phosphorylation has also been suggested as a possible mechanism.¹⁵⁰ Evidence of energy failure has not been found except at such low oxygen levels that vessels actually dilate rather than constrict.¹⁵¹ However, it is likely that changes in oxidative phosphorylation may be a sensing and signal transduction mechanism that activates the inhibition of potassium channels.¹⁵⁰

Once stimulated, vasoconstriction is mediated by an increase in intracellular calcium ion concentration in smooth muscle cells, the "Ca²⁺ hypothesis."¹⁵² The increased intracellular calcium ion combines with the calcium-binding protein calmodulin to activate the enzyme *myosin light chain kinase* (MLCK), resulting in contraction. Calcium channel blockers inhibit and calcium channel agonists enhance^{153,154} the hypoxia-induced constriction of pulmonary vessels. At the same time, hypoxia augments RhoA and Rho kinase-mediated calcium ion sensitization. The increased RhoA and Rho kinase activity leads to dephosphorylation of myosin light chain phosphatase and increased myosin light chain phosphorylation leading to contraction.¹⁵⁵ The importance of Rho kinase signaling in this context is suggested by the attenuation of hypoxia-induced pulmonary vasoconstriction in mice treated with a Rho kinase inhibitor.¹⁵⁶ Calcium influx may result from membrane depolarization induced by hypoxia,¹²⁸ with resulting increased calcium permeability, release of intracellular stores of calcium, or both. However, it is not clear how hypoxia causes depolarization of the pulmonary vascular smooth muscle membrane or whether this leads to the influx of calcium via voltage-gated channels responsible for activating pulmonary vascular smooth muscle contractility.¹⁵⁷

Intermittent hypoxia is a clinically relevant problem in many patients, including those with obstructive sleep apnea or with chronic obstructive pulmonary disease. Animal models confirm that the physiologic consequences of intermittent hypoxia may be evident even after exceedingly brief but repeated exposures to low oxygen levels. For example, mice and rats subjected to intermittent 6% to 10% oxygen (30-second to 2-minute duration) for 8 hr/day over 4 to 5 weeks demonstrate significant increases in both right ventricular systolic pressure and right ventricular mass index,^{158,159} a significant increase in the number of muscular arterioles,¹⁵⁶ and significantly increased pulmonary artery pressures.¹⁵⁹ Although humans subjected to intermittent hypoxia may not manifest pulmonary hemodynamic changes to the same degree as observed in animal models,¹⁶⁰ efforts are ongoing to characterize pulmonary vascular responses to intermittent hypoxia.

NEURAL CONTROL OF PULMONARY VASCULAR RESISTANCE

Adrenergic and cholinergic efferent nerves are present in pulmonary arteries and veins in all mammals examined,¹⁹ although with considerable variation in both distribution and degree of innervation. Innervation of the pulmonary vasculature is typically less than that of the systemic arterial vessels. The concentration of fibers is greatest in large vessels and at branch points.¹⁶¹ α -Adrenergic receptors predominate in the pulmonary vascular bed,¹⁹ particularly in the fetal circulation, where there is high basal vasomotor tone and greater reactivity to α -adrenergic stimulation.¹⁶² Stimulation of α -adrenergic receptors mediates the constriction of pulmonary vessels, whereas β -adrenergic receptors mediate dilation.^{162,163} α -Adrenergic mechanisms contribute minimally to normal adult pulmonary vasomotor tone because antagonism of α -adrenergic receptors modifies neither baseline pulmonary vasomotor tone nor the response to hypoxia.¹⁶⁴ Because pulmonary vessels are normally in a dilated state, β -adrenergic responses are not evident. However, β -adrenergic blockade enhances the vasoconstrictor response to catecholamines, which stimulate both α - and β -receptors, and increases in tone augment responses to β -adrenergic agents.¹⁶⁵

There is limited understanding of the functional significance of sympathetic and parasympathetic innervation of pulmonary vessels. It is unclear why stimulation of these nerves produces relatively small changes in vasomotor tone in the adult lung. One possibility is that neural mechanisms balance the distribution of vascular resistance and compliance in the pulmonary vascular bed and thereby finely regulate regional and total pulmonary perfusion.⁵⁰ It is also possible that vasodilator influences (i.e., NO, endothelium-derived hyperpolarizing factor, and prostacyclin) normally predominate and thus mask the effect of nerve stimulation.

HUMORAL REGULATION OF PULMONARY VASCULAR RESISTANCE

Numerous pulmonary vasoconstrictor mediators (norepinephrine, angiotensin II, histamine, endothelin, serotonin, thromboxane, leukotrienes C₄ and D₄, platelet-activating

factor)^{50,84,166} bind to receptors on pulmonary vascular smooth muscle cells and induce pulmonary vascular smooth muscle contraction via second messenger pathways. Similar to the peripheral circulation, changes in pulmonary vasomotor tone induced by these constrictors are regulated by NO.¹⁶⁷

Various pulmonary vasodilator substances identified include acetylcholine (which mediates its effects in part by NO release) and bradykinin (which has heterogeneous responses with direct as well as NO-dependent actions), prostacyclin, and prostaglandin E₁.¹⁶⁷ It is important to note that the magnitude of the effects of both pulmonary vasoconstrictors and vasodilators is species dependent and influenced by baseline pulmonary vasomotor tone. The latter is particularly important because, depending on vasomotor tone, pulmonary vasoconstrictors such as platelet-activating factor can have dual effects: inducing constriction in the pulmonary vascular bed when it has low basal tone, but inducing dilation in the pulmonary vascular bed when it has increased tone. The basis for these divergent effects is unclear but may reflect differential activation of second messenger pathways in pulmonary vascular smooth muscle cells in the basal state compared to a state of increased tone.

The role of the renin-angiotensin system in pulmonary vascular regulation is now well recognized. Angiotensin II, a key component of the renin-angiotensin system, is generated primarily by *angiotensin converting enzyme* (ACE) from angiotensin I, and its effects are mediated through angiotensin I and angiotensin II receptors, both of which are expressed in the normal lung.¹⁶⁸ The pulmonary endothelium represents a major site of ACE expression and angiotensin II production. Notably, ACE2 is a homologue of ACE expressed in the lung that inactivates angiotensin II, leading to the downstream generation of angiotensin I to VII, which acts through angiotensin II receptors to induce vasodilation, serving as a counterbalance to the vasoconstrictive effects of angiotensin II via angiotensin I receptors. Although components of the renin-angiotensin system have been implicated in a variety of lung diseases, including pulmonary hypertension¹⁶⁹ and fibrotic lung diseases, the system has also been strongly linked to the pathophysiologic processes of pulmonary vascular leak syndromes. For example, ACE and angiotensin II have been found to serve a protective role in *acute respiratory distress syndrome* (ARDS), whereas ACE2, angiotensin II, and angiotensin I appear to mediate lung edema and injury associated with ARDS.^{170,171}

LUNG FLUID AND SOLUTE EXCHANGE

TRANSCAPILLARY EXCHANGE AND THE FLUID FLUX EQUATION

The Starling equation describes filtration of fluid across the capillary wall. The equation states:

$$J_v = L_p S [(P_c - P_i) - \sigma d(\pi_c - \pi_i)] \quad (3)$$

where J_v is the net fluid exchange (in cm³/sec), L_p is the hydraulic conductivity of the membrane, S is the surface

area, P_c is the microvascular hydrostatic pressure, P_i is the perimicrovascular hydrostatic pressure, π_c is the microvascular colloid osmotic pressure, and π_i is the perimicrovascular colloid osmotic pressure. The term σ_d is the osmotic reflection coefficient; $\sigma_d = 0$ means that the membrane was freely permeable to the molecules crossing the membrane; $\sigma_d = 1$ means that the membrane “rejected” the molecule, thus being impermeable. Because albumin is the plasma protein with the highest concentration, we consider here primarily the σ_d of albumin. L_pS has been defined as the capillary filtration coefficient.^{172,173}

According to convention, P_c acts outward (i.e., from the vessel to the extravascular space) and P_i acts inward (i.e., from the extravascular space to the vessel), whereas π_c acts inward and π_i acts outward (Fig. 6-9). The direction and magnitude of movement of water across the vessel wall are determined by the sum of hydrostatic and colloid osmotic pressure differences across the wall. $P_c + \pi_i$ constitutes the driving force for filtration, and $\pi_c + P_i$ is the driving force for absorption. The ability of these pressures, called the “Starling forces,” to determine filtration and absorption is dependent on the semipermeable nature of the endothelial barrier—that is, the ability of the endothelial barrier to restrict the free flux of plasma proteins, a characteristic involving the endothelial glycocalyx layer, endothelial basement membrane, and extracellular matrix.^{174,175}

Because P_c decreases along the alveolar capillary, filtration is more likely to take place at the arterial end of the pulmonary capillary, and absorption at the venous end.

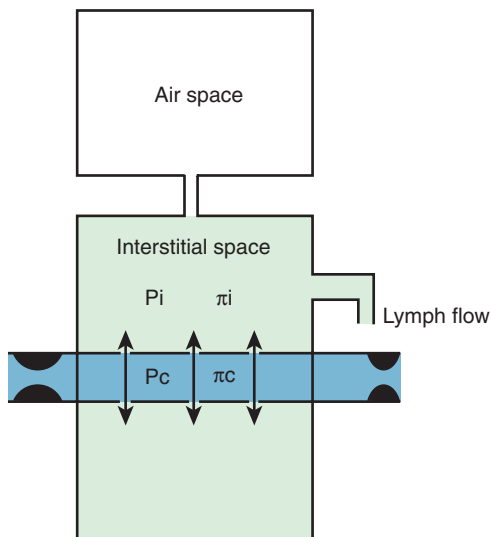


Figure 6-9 Schematic representation of the pulmonary capillary tissue-lymphatic system. The Starling forces are microvascular hydrostatic pressure (P_c), microvascular colloid osmotic pressure (π_c), perimicrovascular hydrostatic pressure (P_i), and perimicrovascular colloid osmotic pressure of interstitial fluid (π_i). The alveolar epithelial junctions are tight compared with the interendothelial junctions in the lung and thereby restrict solute transport into the air spaces. The background shading represents plasma proteins in plasma, tissue fluid, and lymph. The lymph flow represents the overflow in the system, that is, the difference between the amount of fluid filtered and the amount reabsorbed. A major determinant of P_c is the precapillary-to-postcapillary resistance ratio as regulated by the smooth muscle tone of the arteries and veins, represented by the narrowings in the precapillary and postcapillary vessels. (From Malik AB: Mechanisms of neurogenic pulmonary edema. *Circ Res* 57:1–20, 1985.)

However, this is an idealized situation, because some vessels only filter fluid and other vessels only absorb fluid. Regional pulmonary capillary pressures can also determine whether vessels filter or absorb fluid. Dilation of a small pulmonary artery increases P_c , and this increases the net transcapillary filtration rate, whereas constriction of a pulmonary artery reduces P_c and increases the net absorption rate. Approximately 2% to 5% of the plasma perfusing the pulmonary circulation is filtered and, of this, 80% to 90% is absorbed back into capillaries and venules. The residual fluid in the extravascular space ultimately enters the lymphatic circulation and thus returns to the circulation.^{62,176}

In the normal lung the Starling forces have the following average values: P_c at midlung level is 10 mm Hg, P_i is –3 mm Hg, π_c is 25 mm Hg, and π_i is 19 mm Hg.⁶² The most accurately known of these pressures is π_c , which is a direct function of plasma protein concentration and thus can be easily determined by an osmometer. The other values are determined indirectly and hence represent best estimates. The summation of the Starling forces in the lung indicates that there is a net outward filtration pressure with filtration across pulmonary vessels exceeding absorption. As noted earlier, P_c and P_i vary according to the height in the lung. In an upright person, both pressures are greater in the dependent regions of the lung than in the lung apex. The forces tending to produce the negative P_i value are the elastic wall tension of vessels and radial traction exerted by the alveolar attachment sites during lung inflation.⁶² Increasing lung volume decreases P_i , whereas reducing lung volume increases P_i because of the reduction of radial traction exerted by alveolar attachment sites.¹⁷⁷

Critical to the Starling model is the transcapillary osmotic pressure gradient ($\Delta\pi = \pi_c - \pi_i$) that is determined by the albumin concentration gradient:

$$\Delta\pi = \sigma_d RT(C_{iv} - C_i) \quad (4)$$

where R is the gas constant, T is the absolute temperature, σ_d is the albumin osmotic reflection coefficient, and C_{iv} and C_i are the intravascular and interstitial albumin concentrations, respectively. The equation indicates that $\Delta\pi$ varies in proportion to the transcapillary albumin concentration difference ($C_{iv} - C_i$). The equation also indicates that the effective $\Delta\pi$ is determined by σ_d , which is dependent on the permeability characteristic of the vessel (see subsequent explanation).

The reflection coefficient (σ_d) defines the permeability of the capillary to the specific molecule. The reflection coefficient is a critical constant in determining the effective $\Delta\pi$ value. The reflection coefficient for albumin, which does not pass freely across the pulmonary endothelial barrier, is 0.8.⁶² Albumin σ_d decreases when endothelial albumin permeability is increased. A decrease in σ_d results in a decrease in $\Delta\pi$, which then becomes less of an absorptive force.

SITES OF FLUID AND SOLUTE EXCHANGE

Capillary Endothelium

The pulmonary microvessel endothelium is continuous and nonfenestrated (eFig. 6-2). The majority of fluid and solute exchanges at the level of the pulmonary microvascular

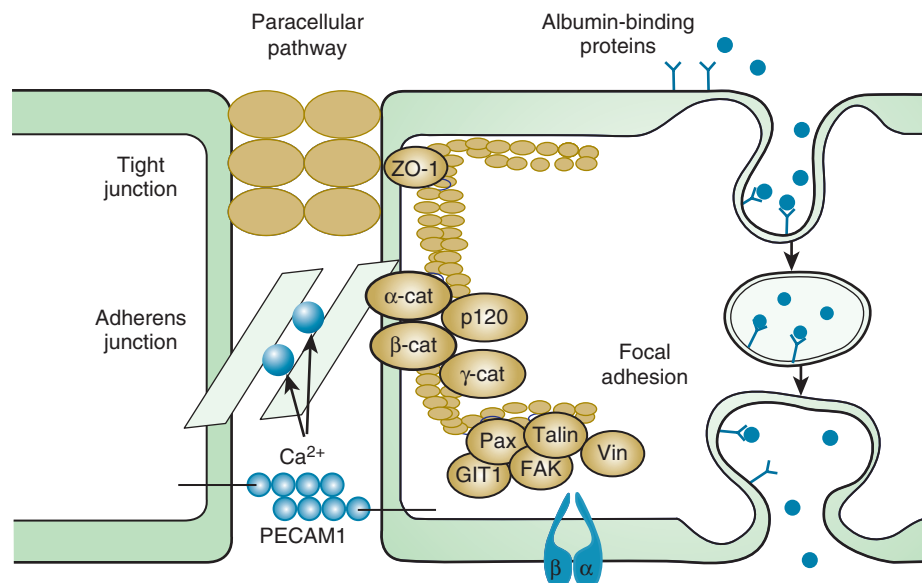


Figure 6-10 Schematic representation of molecular pathways of transendothelial transport. Shown is the *paracellular pathway* of diffuse transport at intercellular junctions with polar organization of tight and adherens junctions of endothelial cells and interactions of linking proteins that form junctions. Solutes of less than 7.5 nm radius (e.g., albumin is 3.6 nm) can diffuse through junctions.^{180,181} Cell-cell connections include tight junctions composed of transmembrane occluding proteins linked to the actin cytoskeleton by the zona occludens family (ZO-1); adherens junctions mediated by calcium-dependent association of cadherin proteins in turned linked to the α -, β -, and γ -catenin (cat) complex; and platelet-endothelial cell adhesion molecule-1 (PECAM1)-associated junctions. Cell-matrix tethering is maintained by focal adhesion plaques composed of α - and β -integrin transmembrane proteins linked to the actin cytoskeleton by a complex of proteins, including talin, paxillin (Pax), vinculin (Vin), and focal adhesion kinase (FAK).³⁷⁸ The *transcellular pathway* of vesicular (nondiffusive) transport of albumin is shown by either solid- or fluid-phase pathways. The endothelial cell surface expresses albumin-binding proteins (Y) that bind albumin (solid circles).¹⁸⁶⁻¹⁸⁸ Vesicles contain albumin bound to albumin-binding proteins and albumin free in the cytosol. The vesicle membrane fuses with the abluminal cell membrane, and albumin bound to binding protein and free albumin are extruded to the abluminal side (at bottom). GIT1, G protein-coupled receptor kinase interacting protein 1.

endothelium, the layer with the largest surface area available for both diffusion and filtration. Several pathways are available for transport of solutes and water: (1) transcellular pathways (directly across the cell, pathway 1 in eFig. 6-2), (2) vesicular pathways, (3) paracellular pathways (between cells via small or large pores, and (4) plasmalemmal channel pathways (pathways across the cell created by fused vesicles). In addition, soluble molecules such as carbon dioxide and oxygen diffuse rapidly across the entire capillary endothelial surface area. Water also freely crosses the entire surface area of the membrane by means of aquaporin water channels.^{178,179} The molecular basis of the endothelial transport pathways is summarized in Figure 6-10, demonstrating interactions of the paracellular junctions and a specific vesicular pathway.¹⁸⁰⁻¹⁸⁹ In addition, the pulmonary endothelial glycocalyx, significantly thicker than the systemic glycocalyx, forms a substantial *in vivo* endothelial surface layer and structural barrier to solute transport that is critical to inflammation, barrier regulation, and mechanotransduction.^{174,175,190} Prominent components of the endothelial glycocalyx include the proteoglycans heparan sulfate and chondroitin sulfate,¹⁹¹ highly anionic molecules composed of 20% protein and 80% glycosaminoglycans with a molecular weight ranging from 1000 to 4000 kD. Thus the endothelial surface layer serves additional functions in vascular physiology. Factors governing plasma protein transport across the vascular endothelial monolayer are presented in Table 6-1 and subdivided into plasma and hemodynamic forces, properties of

Table 6-1 Factors Governing the Transport of Plasma Molecules across Vascular Endothelium

PLASMA, HEMODYNAMIC, AND MECHANICAL FORCES

Hydrostatic pressure gradient
Osmotic pressure gradient
Shear stress
Cyclic stretch

PROPERTIES OF THE PERMEANT MOLECULES

Molecular size
Molecular shape
Molecular charge
Molecular chemistry (binding of molecules to cell surface receptors)
Generation of transendothelial gradients by the concentration of the permeating molecule

PROPERTIES OF ENDOTHELIAL CELLS AND MATRIX

Endothelial surface charge
Structure of the endothelial cell surface
Location in vasculature (site specificity)
Composition, charge, and density of the extracellular matrix

the permeant molecules, and properties of the lung endothelium and the underlying extracellular matrix.

Alveolar Epithelium

Alveolar epithelial type I and type II cells lining the terminal alveoli also serve as a barrier to movement of water and solutes into the alveolar space. The calculated intraepithelial junctional radius of alveolar epithelium is only

approximately 2Å , much smaller than the junctional radius of the pulmonary endothelium,¹ and differs considerably from that in the pulmonary artery.¹⁹² Most lipid-insoluble molecules do not cross the epithelial barrier. Water and ions can penetrate this barrier only to a limited degree, whereas low-molecular-weight lipid-soluble substances such as oxygen and carbon dioxide are freely permeable. The alveolar epithelial barrier is much tighter than the endothelial barrier in terms of fluid flux and has, in addition, an active ion transport function that can actively pump fluid from the alveolar space into the interstitium (see Chapter 9 for more details).

Alveolar-Capillary Septum

The alveolar-capillary barriers have both thin and thick portions (described previously) with the thick septum defined by its larger interstitial space. Fluid and solute exchange takes place primarily in the thick septum because it is the more compliant portion of the barrier. The thin septum is a relatively noncompliant space where endothelial and epithelial cells are virtually fused to each other.⁶²

PULMONARY LYMPHATIC VESSELS

The lung has an extensive network of lymphatic channels involved in fluid and solute drainage and trafficking of lymphocytes and other blood-formed elements. The terminal lymphatics are found in loose areolar tissue surrounding pulmonary vessels and, to some extent, in the thick interstitial septum and are largely confined to the extra-alveolar interstitium.¹⁹³ Fluid that leaks from capillaries in the alveolar walls moves toward the spaces surrounding airways, entering the distal ends of lymphatics.¹⁷⁶ Alveolar wall fluid is propelled by the prevailing pressure gradient away from the alveolus and toward the extra-alveolar space.¹⁹⁴⁻¹⁹⁶ Increases in interstitial fluid volume are handled by increases in pulmonary lymph flow.^{197,198} However, the relationship between interstitial fluid volume and lymph flow is not linear because, beyond a critical fluid volume, pulmonary lymph flow no longer increases in proportion to the increase in fluid volume. This “lymphatic failure” may be related to impairment of the pumping force of lymphatics, constriction of terminal lymphatics by extravascular fluid compression, or compartmentalization of alveolar fluid in areas inaccessible to the lymphatic system. The relative inability to drain the interstitium beyond a certain point is a primary cause of edema formation.^{176,199,200}

LUNG INTERSTITIUM

Interstitial Pressures

Interstitial liquid pressure gradients have been measured from the alveolar wall to the lung hilum¹⁹⁴⁻¹⁹⁶ (Fig. 6-11), and these pressure gradients from the alveoli to hilar interstitial space form the basis for interstitial drainage of the liquid filtered across the microvessels. The filtered fluid moves along the interstitial fluid pressure gradient into the connective tissue surrounding the pulmonary artery, airways, and veins.¹⁷⁶ When fluid filtration exceeds the

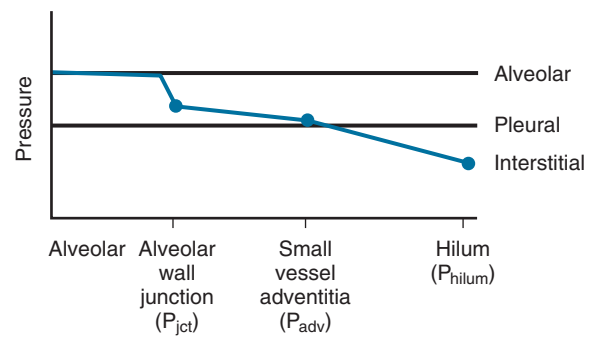


Figure 6-11 Pressure gradient in the interstitium of the lung. Fluid from alveolar vessels in the thick septa moves down the pressure gradient to alveolar wall junctions (P_{jct}), to the adventitia surrounding small vessels (P_{adv}), and to the hilum (P_{hilum}). Experiments were done in isolated dog lung with an alveolar pressure of $5\text{ cm H}_2\text{O}$ and a pleural pressure of $0\text{ cm H}_2\text{O}$, and pressures were measured at the hilum, in small vessel adventitia, and at the alveolar wall junction. (Created with data from Staub NC: Pathophysiology of pulmonary edema. In Staub NC, Taylor AE, editors: *Edema*. New York, 1984, Raven, pp 719–746.)

pumping capacity of the lymphatic system, fluid first accumulates in the hilar regions and in sheaths around the large pulmonary vessels,²⁰¹ where pressure is lowest and interstitial compliance is highest. This accounts for the “cuffs” of fluid typically observed around vessels in edematous lungs and that are often visible near the hila in chest radiographs.

Composition of Pulmonary Interstitium

An important component of the pulmonary capillary wall barrier is the endothelial extracellular matrix consisting of a complex array of molecules: laminin, type I and type IV collagen, proteoglycans, fibronectin, and vitronectin.⁶² The three-dimensional arrangement of matrix proteins provides a restrictive barrier to the transport of molecules, and the matrix can sieve molecules of different molecular weights²⁰² and form a dense connective sheath surrounding bronchi and blood vessels, the alveolar septum, and terminal alveoli. The ability of the interstitial matrix to retain water is similar to a sponge where water is incorporated in the dense matrix network of proteoglycans.²⁰³ Albumin is distributed in 60% of the fluid volume as a result of steric and electrostatic exclusion,²⁰⁴ an exclusion that decreases protein diffusion rates through the matrix, in comparison with its diffusion rate in water. Water movement through the interstitial matrix proteins increases as the matrix is hydrated,²⁰⁵ suggesting that increased hydraulic conductivity of lung interstitium during edema may assist in the drainage of water from the interstitial space and thence to the lymphatic vessels (eFig. 6-3).

Interstitial Compliance

The compliance of the lung interstitial tissue is a nonlinear function¹⁹⁵ and has two phases: a low compliance at low interstitial fluid volumes and high compliance during the interstitial edema or alveolar flooding phase. At low levels of tissue hydration, tissue pressure changes markedly in response to a small change in tissue volume, indicative of low tissue compliance. Tissue expands with increased levels

of hydration, and compliance increases dramatically. Compliance increases as the tissue fluid pressure approaches the alveolar pressure. At an interstitial fluid pressure of greater than zero (i.e., values greater than the alveolar pressure), the tissue fluid accumulates with only a small change in the interstitial pressure. The high-compliance portion of the curve may represent the transition from interstitial edema to alveolar edema⁶²; that is, the pressure inflection point may be the maximum interstitial volume before alveolar flooding. This inflection point is seen at a lung weight gain of 35% to 50% and an interstitial pressure of 2 to 3 cm H₂O.⁵⁰ The abrupt increase in compliance attenuates further increases in interstitial hydrostatic pressure. The lung also exhibits regional differences in compliance of the lung interstitium. The interstitial spaces surrounding large vessels or bronchi have higher compliance than the interstitium in the septal region.^{195,206} When the perivascular spaces surrounding extra-alveolar vessels and bronchi are filled with fluid, the interstitial pressures equilibrate throughout the interstitial space. The continuing high level of fluid filtration then increases interstitial pressure to a critical level, and the epithelial barrier is breached (potentially facilitated by injury to the alveolar epithelium), resulting in rapid alveolar flooding.⁶²

PATHOGENESIS OF PULMONARY EDEMA

PHASES AND SITES OF EDEMA ACCUMULATION

Pulmonary edema is defined as the accumulation of water in the lung extravascular spaces and is a sequential process initially developing in the hilar region of the lungs followed by fluid filling of the interstitial compartment and finally resulting in fluid entering alveoli in an all-or-nothing manner.^{201,207} Vertical pressure gradients within the pulmonary circulation, the result of differences in hydrostatic pressure in pulmonary microvessels at different lung heights, vertical pleural fluid pressure, and regional lung volume, produce a greater capillary hydrostatic pressure in the dependent lung regions that favors edema formation in these regions. Although greater lung water content is predicted in the dependent lungs, no such vertical gradient has been found by either measurement of extravascular lung water content or morphometric determinations of the interstitial space.^{62,208-210} Fluid that cannot be cleared by the lymphatic channels accumulates in the connective tissue surrounding smaller vessels and bronchioles²⁰⁷ and migrates down the interstitial fluid pressure gradient to interstitial spaces around larger vessels and airways and becomes compartmentalized, forming perivascular cuffs.²¹¹ After an increase in the interstitial fluid volume from 35% to 50%, individual alveoli begin to flood in an all-or-nothing manner¹⁹⁵ with the distribution of alveolar flooding patchy but followed by rapid flooding. These abnormalities explain the characteristic sequential impairments of gas exchange in pulmonary edema (see Chapter 62), with alveolar flooding a cataclysmic event that results in impaired gas exchange, arterial hypoxemia, and respiratory failure. The sequence of pulmonary edema formation¹⁷⁶ reflects a

breakdown of the normal homeostatic mechanisms that maintain lung fluid balance.¹⁷⁶ The characteristics of fluid exchange between the vascular space and interstitium of lungs have been reviewed,^{62,176} as have the factors regulating pulmonary vascular endothelial permeability,²¹² and are detailed below.

Starling Forces in Pulmonary Edema Formation

Increases in lung vascular permeability are operationally defined in the Starling equation by an increased capillary filtration coefficient (LpS), which indicates decreased resistance to water flow across the capillary wall barrier, and a decreased albumin reflection coefficient (σ_{alb}), which describes the albumin permeability of the vascular endothelial barrier. The critical functional definition of increased lung vascular permeability is the extravasation of protein-rich fluid into the interstitial space²⁰⁷ and ultimately into the alveolar space, resulting in fulminant pulmonary edema. In high-permeability pulmonary edema, the alveolar fluid protein concentration approximates the plasma protein concentration, whereas in hydrostatic edema (i.e., edema resulting from increase in the pulmonary capillary hydrostatic pressure), the ratio of plasma to alveolar fluid protein concentration is usually less than 0.6.⁶²

Pulmonary Capillary Pressure and Plasma Osmotic Pressure in Edema Formation

The relationship between left atrial pressure and the rate of formation of pulmonary edema is shown in Figure 6-12. For left atrial pressures up to 20 to 25 mm Hg, water content does not increase in the normal lung²¹³ because fluid accumulation is minimized by “safety factors.”⁶² When capillary hydrostatic pressure increases above a critical value, the pulmonary extravascular water content increases progressively as a result of the inability of these safety factors to

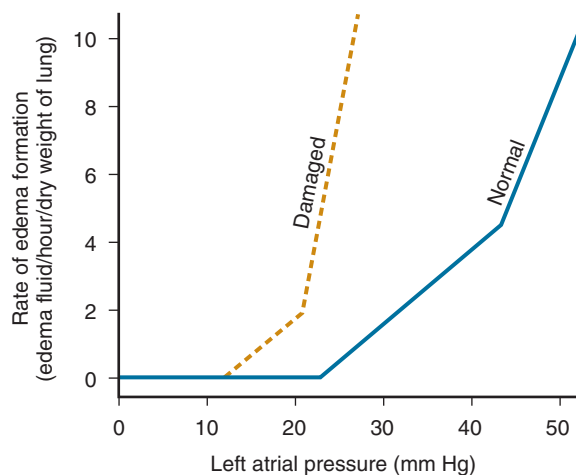


Figure 6-12 Graph showing the rate of edema formation as a function of left atrial pressure. In the normal lung (solid line), edema does not form until left atrial pressure exceeds 20 to 25 mm Hg. Above this pressure, edema forms slowly at first, and then more rapidly at higher pressures. If the endothelium is damaged (dashed line) or if plasma colloid osmotic pressure is reduced, edema begins to form at lower left atrial pressures and at a more rapid rate. (From Guyton AC, Lindsay AW: Effect of elevated left atrial pressure and decreased plasma protein concentration in the development of pulmonary edema. *Circ Res* 7:649–653, 1959.)

reduce fluid filtration rate. The primary safety factors acting at the capillaries are the increase in lymph flow; decrease in π_i , which results from greater transcapillary flux of water than protein; increase in P_i ; and decrease in the albumin exclusion volume (see later). These changes serve to minimize the increase in the extravascular lung water content when left atrial pressure is increased.

In contrast, decreases in the plasma protein concentration can contribute to edema formation. These events reduce the absorptive pressure (π_c) and thus increase the net transcapillary filtration pressure. Importantly, the critical capillary pressure at which lungs begin to gain water decreases in direct proportion to the reduction in plasma osmotic pressure.⁶²

Lymphatic Insufficiency and Edema Formation

The lymphatic vessels are capable of removing excess extravascular fluid because of their effectiveness as pumps. Lymphatic propulsion is determined by the intrinsic contractility of lymphatic vessels, by the pumping action of inspiration and expiration, and by lymphatic valves, which account for the unidirectional lymph flow.²⁰⁷ Lymphatics, however, have a limited capacity to increase lymph flow. Beyond their critical capacity, lymph flow does not increase in direct proportion to the increase in interstitial fluid volume and may actually decrease because of compression of the lymphatic channels.²¹⁴ The extent to which lymphatic insufficiency serves as an important mechanism of fluid accumulation in the lung is not clear. Some studies have indicated that surgical removal of the lymphatics predisposes the lung to edema, although the increase in water content is usually transient.²¹⁵

Safety Factors in Lung Fluid Homeostasis

The safety factors cited in the discussion of increased pulmonary capillary pressure become operative when fluid begins to accumulate in the interstitial space. When fluid accumulates in the interstitial space, there are two consequences that serve to decrease π_i : one consequence is that the excess fluid decreases the albumin concentration directly and thus decreases π_i ; the other consequence is that the excess fluid alters the interstitial matrix proteins and decreases the albumin exclusion volume, further decreasing π_i .⁶² The *exclusion volume of albumin* is the volume of the interstitium from which albumin is excluded by matrix proteins. If the exclusion volume increases, albumin is concentrated in the remaining interstitial fluid, thereby raising π_i ; if the exclusion volume decreases, albumin is distributed in a larger interstitial volume, thereby lowering π_i . Albumin is normally excluded from approximately 40% of the pulmonary interstitial space by the matrix proteins collagen, hyaluronic acid, and laminin.⁶² An increase in the interstitial fluid volume disrupts the structure of interstitial matrix proteins (see eFig. 6-3); thus the volume available for albumin distribution increases. The albumin protein concentration decreases to a greater extent because of this decrease in albumin exclusion volume. Therefore the increase in the albumin distribution volume amplifies the decrease in π_i , which would not drop to the same extent without this concomitant decrease in the exclusion volume. Examination of the effect of albumin exclusion on the colloid osmotic pressure when

the interstitial fluid volume is increased (see eFig. 6-3) reveals that for the same increase in the interstitial fluid volume, the interstitial osmotic pressure is lower when albumin exclusion is decreased.⁶²

In addition, the role of the bronchial circulation may modulate lymph clearance under basal conditions and after lung injury.^{125,216,217} Movement of interstitial fluid across the visceral pleura into the pleural space is a further means of clearance of edema fluid from the lung and can be considered another safety factor.²¹⁸

Effects of Cellular and Molecular Charge

The intact endothelial cell membrane is nonthrombogenic due to release of prostacyclin and the meshwork of glycoproteins (glycosaminoglycans²¹⁹⁻²²²) forming the endothelial glycocalyx,^{223,224} which accounts for the negatively charged anionic endothelial cell surface layer. The selective permeability of the endothelial barrier to plasma proteins such as albumin is related in part to the anionic charge of the albumin molecule as well as to the surface charge on the endothelial cell. Surface negative charge disruption results in albumin “leakage” across the capillary-matrix complex.²²⁵ Endothelial cell membrane surface charges influence albumin transport with an isoelectric point of 4.1.²²⁰ The distribution of charge sites provides a means of preferentially gating albumin across the endothelial monolayer. Another charge-related effect is the negative charge distribution of interstitial macromolecules (heparan sulfate, chondroitin sulfate, and other complex proteoglycans) leading to albumin repulsion and increased transport through specific matrix domains.²²⁶⁻²²⁸

Because of the negative albumin charge, albumin permeability is greater than predicted from its molecular size. For example, dextran sulfate (negatively charged dextran, molecular weight 500 kd) is threefold more permeable than neutral dextran of the same molecular weight. Sheep lung lymph studies also indicate plasma-to-lymph transport of negative dextrans across the pulmonary endothelial barrier is greater than neutral dextran transport.²²⁸ Thus the negatively charged molecules are preferentially transported across the endothelial barrier because of charge-related gating phenomena, despite the net negative charge of endothelial cell membranes.²²⁸

Regional Differences in Endothelial Permeability

Endothelial cell heterogeneity confers specific properties that distinguish endothelium from large vessels and from small vessels within an organ and among those from different organs (e.g., between the blood-brain barrier and pulmonary endothelium).^{219,229} The albumin permeability in pulmonary microvascular endothelium is one half to one fifth the values of similar endothelium from the main-stem pulmonary artery, a feature noted in vivo.²³⁰ Microvascular endothelium is significantly more restrictive to sucrose and inulin than large-vessel endothelium, indicating that transport via paracellular pathways is reduced to a greater degree. Microvascular endothelium also proliferates at a higher level than large-vessel endothelium and retains phenotypically distinct calcium and cyclic nucleotide signaling responses.²²⁹ Endothelial studies from different vascular sites have identified organ-specific antigens on microvascular endothelium that may be responsible for differential

degrees of permeability in regional vascular beds.²²⁹⁻²³¹ Phenotypic differences in lectin-binding domains of pulmonary endothelium from different vascular beds (*Ricinus communis* agglutinin and peanut agglutinin) are related to permeability characteristics.^{232,233}

MECHANISMS OF INCREASED ENDOTHELIAL PERMEABILITY

As depicted in [Figure 6-10](#), two general pathways describe the movement and flow of fluid, macromolecules, and leukocytes into the interstitium and subsequently into the alveolar air spaces, to produce clinically significant pulmonary edema during lung inflammation (see [eFig. 6-2](#)). The *transcellular pathway* uses a tyrosine kinase-dependent, glycoprotein 60-mediated transcytotic albumin route whose regulation and function may serve to uncouple protein and fluid permeability.^{234,235} However, there is general consensus that in the context of inflammatory lung injury, the primary mode of fluid and transendothelial leukocyte trafficking is by the *paracellular pathway*,²¹² as shown by electron microscopy studies that demonstrate the formation of paracellular gaps at sites of active inflammation within the vasculature.^{236,237} The mechanisms that mediate alterations in pulmonary vascular endothelial permeability as a result of a variety of mechanical stress factors, inflammatory mediators, and activated neutrophil products (such as reactive oxygen species, proteases, and cationic peptides) have been discussed earlier. Fortunately, there has been progress in identifying agents capable of reversing or restoring vascular integrity with therapeutic potential in acute and chronic inflammatory lung diseases.²³⁸ In the following sections, important mechanisms contributing to the increase in pulmonary vascular permeability are discussed and covered in greater detail in the cited reviews.^{212,239}

Characteristics of Increased Vascular Endothelial Permeability

A variety of bioactive agonists, cytokines, growth factors, and mechanical forces alter pulmonary vascular barrier properties and increase vascular permeability.^{111,212,240-246} The serine protease thrombin represents an ideal model for the examination of agonist-mediated lung endothelial activation and barrier dysfunction (see [Fig. 6-8](#)) because it evokes numerous responses that regulate hemostasis, thrombosis, and vessel wall pathophysiologic characteristics and is recognized as an important mediator in the pathogenesis of ARDS.²¹² Thrombin increases vascular leakiness to macromolecules by ligation and proteolytic cleavage of the extracellular domain of PAR1, a member of the proteinase-activated receptors.²⁴⁷ The cleaved receptor, acting as a tethered ligand, activates and initiates a number of downstream effects²⁴⁷⁻²⁵¹ (see [Fig. 6-8](#)). Thrombin binding without receptor cleavage fails to elicit the complex signaling cascade that increases endothelial permeability.²⁴⁹ The effect of thrombin on endothelial permeability is rapid (within 2 minutes) and reversible²⁴⁵ and critically dependent on G protein-transduced signals^{115,212} that increase cytosolic calcium and activate the contractile apparatus, a common feature of other inflammatory mediators as well.^{111,212,240-244}

Cytoskeletal Alterations

Majno and Palade²³⁷ first observed that lung endothelial cells exhibit a rounded form, producing paracellular gaps during inflammatory edema. This profound conformational change and subsequent disruption in the integrity of the endothelial cell monolayer is now recognized as a cardinal feature of inflammation.^{245,246,252-255} The formation of paracellular gaps implicates the direct involvement of endothelial structural components composed of cytoskeletal proteins (microfilaments, microtubules, intermediate filaments).²¹² A useful paradigm to understand cytoskeletal influences on vascular barrier regulation involves a balance of competing forces: adhesive cell-cell and cell-matrix tethering forces (promoting monolayer integrity) and contractile forces (generating centripetal tension).²¹² This equilibrium is intimately influenced by the dynamic actin-based endothelial cytoskeleton via actin-binding proteins (capping, nucleating, and severing proteins), which are critical participants in cytoskeletal rearrangement, tensile force generation, and regulation of endothelial junctional stability.²¹² Polymerized actin fibers (or F-actin) confer strength to structural elements regulating cell shape, particularly when accompanied by phosphorylated myosin within peripherally distributed cortical bands.²¹² These elements are essential for maintenance of endothelial integrity and basal barrier function. Edemagenic agents, such as thrombin, initiate cytoskeletal rearrangement characterized by the loss of peripheral actin filaments with a concomitant increase in organized F-actin cables that span the cell as “stress fibers” to increase intracellular tension.²⁴⁵ Cytoplasmic stress fibers form via the coordinate activation of the small GTPase Rho and calcium/calmodulin-dependent MLCK, which together increase the level of phosphorylated *myosin light chains* (MLCs) in a spatially distinct manner (see [Fig. 6-8](#)).^{115,241,256-258} The resultant increases in stress fiber formation and actomyosin cellular contraction disrupt the barrier-regulatory balance and destabilize cytoskeletal-junctional linkages, culminating in increased vascular permeability (see [Fig. 6-8](#)). Consistent with this model, thrombin-induced permeability and intercellular gap formation disrupt the integrity of paracellular adherens junctions and reorganization of focal adhesion plaques.^{241,259-262} Inhibition of MLCK or Rho kinase or calcium antagonism attenuates agonist-induced MLC phosphorylation, gap formation, and barrier dysfunction²⁵⁶⁻²⁵⁸ in many models of lung edema.^{241,242,255,263-269}

Microtubules are polymers of α - and β -tubulin that also contribute to barrier regulation.²⁷⁰⁻²⁷⁵ They form a lattice network of rigid hollow rods spanning the cell, undergoing frequent assembly and disassembly,^{276,277} and exhibit complex but intimate functional interactions with actin filaments during dynamic cellular processes.²⁷²⁻²⁷⁸ Microtubule disruption with agents such as nocodazole or vinblastine induces rapid assembly of actin filaments and focal adhesions,^{272,273,278} isometric cellular contraction²⁷² that correlates with the level of MLC phosphorylation, increased permeability across endothelial cell monolayers,^{272,273,278} and increased transendothelial leukocyte migration,²⁷⁸ events that can be reversed or attenuated by microtubule stabilization with paclitaxel. Microfilament-microtubule crosstalk represents an intriguing area of endothelial cell

barrier regulation.²⁷⁹ The function of intermediate filaments in endothelial cell barrier regulation is much less defined,²¹² although recent studies have highlighted the consequence of redistribution of vimentin, an intermediate filament protein, in barrier stabilization in hypoxic endothelium.²⁸⁰

Besides receptor-mediated pathways, mechanical signals are also transduced to the endothelial cytoskeleton^{87,111} via, in part, the complex array of proteins of the lung endothelial glycocalyx. Nuclear magnetic resonance techniques have demonstrated that cell surface proteoglycans behave as viscoelastic anionic polymers, undergoing shear-dependent conformational changes that may function as blood flow sensors to transduce signals into endothelial cells.²⁸¹ Components of the glycocalyx, such as heparan sulfate proteoglycans and sialoproteins, modulate cell-cell and cell-matrix adhesions via effects on the cytoskeleton and represent endothelial surface-binding domains for inflammatory cationic peptides.^{282,283} Syndecan is a heparan sulfate proteoglycan that has been shown to influence cytoskeletal organization, cell-cell adhesion, and motility;²⁸³ syndecan mediates cationic peptide-induced signaling that, via syndecan-1 and syndecan-4 clustering and actin stress fiber formation, leads to cytoskeletal rearrangement and barrier dysfunction.²⁸² This provides a mechanistic basis for activated neutrophil-derived cationic peptide-induced increases in vascular permeability.^{244,284}

Intracellular Calcium Shifts and Other Barrier-Regulatory Signals

Increases in vascular permeability are signaled in many edemagenic models by a rapid initial rise in intracellular calcium^{240,255,285} followed by a second phase of slow decay.^{246,248,286,287} The initial calcium rise in endothelial cells is caused by mobilization from intracellular stores in response to increased inositol 1,4,5-triphosphate generation (derived from phospholipase C-activated hydrolysis of phosphoinositides).^{286,288} The second phase is caused by calcium influx through store-operated channels²⁸⁷ and is critical to increases in permeability.^{285,289} Direct increases in intracellular calcium (by calcium ionophore) increase endothelial albumin permeability,²⁶⁷ decrease transendothelial electrical resistances,²⁶⁵ and increase hydraulic conductivity of intact microvessels.^{248,257,267,288} Increased intracellular calcium signals cytoskeletal rearrangement via actin polymerization/depolymerization that requires activation of calcium-dependent kinase systems (e.g., MLCK, calcium/calmodulin-dependent kinase II, protein kinase C)²⁹⁰⁻²⁹³ and subsequent phosphorylation of key cytoskeletal proteins involved in endothelial barrier regulation (vimentin,^{290,294} caldesmon,²⁹⁴ β -catenin,²⁶¹ vinculin,²⁶² α -actinin,²⁹⁵ MLC,²⁵⁷ filamin,²⁹¹ cortactin,²⁹⁶ vasodilator-stimulated phosphoprotein,²⁹⁷ microtubule-associated proteins).²⁷⁸

Alternate pathways exist that do not require increased MLC phosphorylation and are involved in barrier regulation. For example, protein kinase C, a family of serine/threonine kinases comprising at least 12 isotypes,^{294,298} is causally linked to phosphorylation of cytoskeletal proteins such as caldesmon, an actin-, myosin-, and calmodulin-binding protein present in actomyosin cross-bridges and stress fibers.²⁹⁴ Finally, p60src kinase and p38 mitogen-

activated protein kinase activation regulate endothelial stress fiber formation and contractile regulation, endothelial cell migration, and both vascular endothelial growth factor- and cytokine-induced permeability.^{241-243,296,299-301}

Focal Adhesions and Extracellular Matrix Components

Cell-matrix adhesions are essential for barrier maintenance and restoration and exist in dynamic equilibrium with endothelial contractile forces. An organized basement membrane and extracellular matrix surrounding the endothelium³⁰² may control transendothelial solute flux, and this may be dependent on particular extracellular matrix constituents (e.g., certain matrix proteins are known to restrict albumin transport because of the negative charge of their glycosaminoglycan constituents).³⁰³ In vivo studies indicate that the interstitial matrix is capable of a 14-fold reduction in diffusive transport of albumin.

Endothelial focal adhesions are composed of extracellular matrix proteins (collagen, fibronectin, laminin, vitronectin, proteoglycans), transmembrane integrin receptors, and cytoplasmic focal adhesion plaques (containing α -actinin, vinculin, paxillin, and talin), which combine to provide additional adhesive forces in barrier regulation and form a critical bridge for bidirectional signal transduction between the actin cytoskeleton and the cell-matrix interface^{302,304} (see Fig. 6-7). The core matrix proteins, because of position and points of contact with endothelium, may determine cell-substratum adhesion²²⁵ and vascular permeability in normal conditions and in response to inflammatory mediators.³⁰⁵ Extracellular stimuli can be transmitted to the cytoskeleton through focal adhesion rearrangement linked to integrin ligation, which directly influences endothelial attachment, cell spreading, and permeability.³⁰⁶ Integrin binding to the extracellular matrix induces the attachment of integrins to intracellular actin fibers, a process that stimulates tyrosine phosphorylation of multiple focal adhesion proteins as well as tyrosine phosphorylation-dependent calcium influx.^{307,308} The extracellular matrix can also be remodeled by endothelial cell-released proteases, causing endothelial cells layered on this matrix to become more permeable.³⁰⁵ Integrin β_4 is a key mediator of the attenuation of lung inflammatory responses by statins and is linked to activation of Rac1 GTPase. Additional β integrins are increasingly recognized as important regulators of endothelial cell barrier function and include β_3 and β_5 .^{309,310}

Endothelial Water Permeability and Albumin Transcytosis

The pulmonary vascular endothelium provides the primary resistance to the transvascular flow of water,³⁰³ although the relative distribution of transcapillary water flow through the paracellular and transcellular pathways remains controversial.^{236,225,311} Albumin is a major determinant of endothelial water permeability because the interaction of albumin with the vessel wall regulates vessel wall hydraulic conductivity.^{311,312}

Receptor-mediated transcytosis of solutes is an important mechanism of transport across the pulmonary microvascular endothelial barrier. The transendothelial flux of proteins such as albumin, insulin, and transferrin involves

recognition by receptors located on the luminal side of the endothelial cell^{187,313-317} (see Fig. 6-10). Albumin binds to the endothelial cell surface protein glycoprotein 60 on the luminal side of the endothelium^{187,313,314,315-318} signaling (via tyrosine kinase activities) the formation of vesicles²³⁴ with albumin shuttling from the luminal to abluminal cellular sites.^{187,313,315,319} In addition, there may be transport of albumin from the abluminal to the luminal side of the endothelial monolayer,^{233,319} presenting an intriguing potential for an active mechanism of albumin transport. Albumin binding to endothelial cells is reversible.^{186,320,321} Albumin binds with a higher affinity in pulmonary microvessel endothelial cells,³¹⁴ consistent with the greater number of vesicles present in these cells.

Apoptosis and Endothelial Cell Dysfunction

Pulmonary endothelial cells have relatively low turnover rates due in part to protective effects of physiologic mechanical forces, including shear stress and cyclic stretch. However, because of the positioning of the endothelium at the surface of blood and tissue, endothelial cells are constantly exposed to multiple biochemical and biophysical stresses, such as endotoxins, tumor necrosis factor- α , oxidative stress, and excessive mechanical stress that potentially initiate apoptosis, or programmed cell death. Apoptotic cells undergo a well-ordered morphologic and molecular pattern of death, including cytoskeletal rearrangement, membrane blebbing, nuclear condensation, DNA fragmentation, and cell shrinkage (see cited review).³²² Usually, apoptotic cells do not elicit an inflammatory response and are phagocytosed by neighboring cells. In contrast, cells undergoing necrosis demonstrate cellular and nuclear swelling, often accompanied by inflammation in damaged tissues.

If damage is limited to a small fraction of the endothelial cell lining, viable neighboring cells can spread to cover the damaged space and thereby attenuate procoagulant effects. Extensive damage, however, results in extensive endothelial loss, exposing the damaged basement membrane to platelets and subsequent thrombosis. Extrinsic and intrinsic pathways share mechanisms using the aspartate-specific cysteinyl proteases (caspase) cascades. The best characterized extrinsic pathways are the binding of FAS ligand to FAS receptors³²³ and tumor necrosis factor- α to tumor necrosis factor receptor 1,³²⁴ which trigger the caspase cascade. FAS/FAS ligand-mediated lung apoptosis has been implicated in acute lung injury and ARDS.^{325,326} In contrast, the intrinsic pathway may be initiated upon exposure to stresses, such as cytotoxic drugs, oxidants, radiation, and growth factor deprivation, which result in mitochondria release of several apoptogenic proteins into the cytosol such as cytochrome *c*, which serves to activate caspase-9. A common mediator of endothelial cell injury is neutrophil-generated ROS, either alone or combined with nitric oxide to form peroxynitrite. ROS is catalyzed by the enzyme phagocyte oxidase, expressed by neutrophils and macrophages, whereas vascular cells express the homologous nonphagocyte oxidase. These oxidative stresses can cause barrier dysfunction and may antagonize tumor necrosis factor responses.³²⁷ Several preclinical studies have targeted apoptosis in novel therapeutic strategies for preserving the pulmonary vasculature.³²⁸

STRATEGIES TO REVERSE PERMEABILITY AND RESTORE BARRIER INTEGRITY

Significant progress in understanding the molecular and cellular events regulating lung vascular permeability has led to the development of novel therapeutic agents for modulating barrier function in a clinically advantageous way.

The endothelial barrier can be enhanced and protected by angiogenic growth factors (hepatocyte growth factor,³²⁹ angiopoietin,³³⁰ sphingosine-1-phosphate [S1P]).^{271,329-332} For example, S1P, a sphingolipid metabolite generated by numerous cell types, including endothelium and platelets, is a potent endothelial cell chemotactic and angiogenic factor producing robust and sustained enhancement of the endothelial barrier.^{300,331,333,334} Ligand of the S1PR1 receptor by S1P strongly enhances lung vascular barrier function in vitro^{331,335} and in vivo^{336,337} and produces highly significant reductions in multiple indices of endotoxin- and radiation-induced inflammatory lung injury, including vascular leak, demonstrated in both murine^{336,337} and canine³³⁶ ARDS models. This profound barrier enhancement is mediated by G protein-dependent signaling cascades, which lead to cytoskeletal rearrangement and increased endothelial junctional integrity (see Fig. 6-7).^{331,338,339} The S1PR3 receptor, in contrast, activates Rho GTPase, produces barrier disruption, and is released in lung endothelial exosomes by inflammatory processes; it may serve as a novel biomarker and predictor of survival in ARDS.³⁴⁰

Other barrier-promoting agonists include the S1P analogue, FTY720, statins, activated protein C, adenosine triphosphate, high-molecular-weight hyaluronan, methyl-naltrexone, and oxidized phospholipids (for review, see Chiang and Garcia³⁴¹). FTY720, an unphosphorylated S1P analogue, is a Food and Drug Administration-approved immunosuppressant for multiple sclerosis and produces lymphopenia via inhibition of cellular egress from lymphoid tissues.³⁴² However, intraperitoneal FTY720 protects against lipopolysaccharide-mediated murine acute lung injury.³³⁷ As noted above, simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, improves lung endothelial barrier function in lipopolysaccharide and ventilator-induced lung injury models of lung injury, as well as in radiation-induced lung permeability,³⁴³ through activation of an Rac1-dependent cytoskeleton mechanism that is independent of cholesterol-lowering effects.³⁴⁴ Activated protein C, a previously Food and Drug Administration-approved anticoagulant for severe sepsis, also enhances vascular barrier function in vitro and in vivo^{345,346} but was withdrawn for lack of efficacy.³⁴⁷ Adenosine triphosphate induces barrier enhancement via phospholipase C- and Rac1-dependent cytoskeleton reorganization,^{348,349} conferring protection from endotoxin-induced lung injury.³⁵⁰ Both activated protein C, via the endothelial protein C receptor, and high-molecular-weight hyaluronan, via the CD44 receptor, transactivate S1PR1 to induce AKT1- and Rac1-dependent barrier enhancement.³⁵¹ Oxidized phospholipids also confer barrier enhancement through activation of Rac1- and CDC42-dependent pathways³⁵² and are protective in murine models of ventilator-induced lung injury.³⁵³ These novel agents that preserve or restore vascular integrity offer promise for the future management of

increased vascular leak in the critically ill and await translation to clinical practice.

PULMONARY VASCULAR GENOMICS AND GENETICS

Understanding the genetic and epigenetic basis of pulmonary vascular disease offers the potential for valuable insights into the functional significance of individual genes in normal lung physiology and in complex lung diseases characterized by vascular dysfunction. For example, expression profiling of tumor-associated murine lung endothelial cells produced a six-gene inflammatory gene signature that significantly predicted reduced survival in humans with breast cancer, colon cancer, and lung cancer, indicating the potential role for lung vascular endothelial gene expression and variation in the prognosis of human cancers.³⁵⁴ Pulmonary hypertension genomics and genetics are discussed in Chapter 58.

ARDS represents the ultimate in genetic stress and an unparalleled derangement in lung vascular function. Early genetic studies identified mutations in the gene encoding ACE, an enzyme extensively expressed in pulmonary endothelium to regulate angiotensin II production. These ACE mutations, which correspond with variance in plasma ACE activity,³⁵⁵ increased risk and poor prognosis in ARDS in European-descent populations.³⁵⁶ Genomic-intensive approaches with expression profiling of lung tissues from preclinical models of ARDS and ventilator-induced lung injury have successfully identified novel ARDS candidate genes. For example, these studies identified an obscure cytokine, pre-B-cell colony-enhancing factor, encoded by *NAMPT* and also known as NAMPT and visfatin,^{357,358} as a novel biomarker in preclinical and human studies of ARDS.³⁵⁹ *NAMPT*/pre-B-cell colony-enhancing factor induces increased lung endothelial permeability,³⁶⁰ and gene sequencing identified a single nucleotide polymorphism haplotype that altered a transcription factor-binding site for signal transducer and activator of transcription 5, conferring increased susceptibility to excessive mechanical stress and ARDS mortality.³⁵⁹ Subsequent studies focusing on genes highly relevant to regulation of vascular barrier function³⁶¹ have validated single nucleotide polymorphisms that confer risk for developing ARDS and that influence ARDS mortality³⁶²⁻³⁶⁶ and have highlighted important racial differences in minor allelic frequencies, a finding relevant to the disproportionate morbidity and mortality rates observed in Hispanic and African Americans.³⁶⁷ This health disparity, although reflecting differences in socioeconomic status and access to care, also implicates epigenetic/genetic variation as a risk factor.³⁶⁸ For example, a trio of coding single nucleotide polymorphisms in *MYLK*, the barrier-regulatory gene encoding MLCK (discussed earlier), are rare in European descendants but frequent in those of African descent, and confer susceptibility to ARDS³⁶⁹ and risk for severe asthma in African Americans.^{370,371} Similarly, the functional rs2814778 polymorphism in the gene encoding the Duffy antigen/chemokine receptor is associated with worse clinical outcomes among African Americans with

ARDS,³⁶⁸ and single nucleotide polymorphisms in *ANGPT2*, encoding angiotensin-2, the natural antagonist for angiotensin-1, are implicated in pulmonary vascular leak syndromes and confer increased risk for trauma-associated ARDS in an African descent cohort. Additional ARDS-associated genes plausibly related to vascular pathobiologic changes include *S1PR1*, *S1PR3*,³⁷² *IL6*,³⁷³ *IL10*,³⁷⁴ *DIO2* (encoding an iodothyronine deiodinase), macrophage migration inhibitory factor or *MIF*,^{375,376} and vascular endothelial growth factor (*VEGF*).^{361,377} The study of the genetic contribution to ARDS pathogenesis, severity, and response to therapy remains a nascent, albeit exciting, field that may define novel biomarkers and therapeutic targets in disorders of the pulmonary circulation.

ACKNOWLEDGMENTS

The author is grateful to Alexander N. Garcia, who did an enormous amount of work preparing the background for this chapter.

Key Points

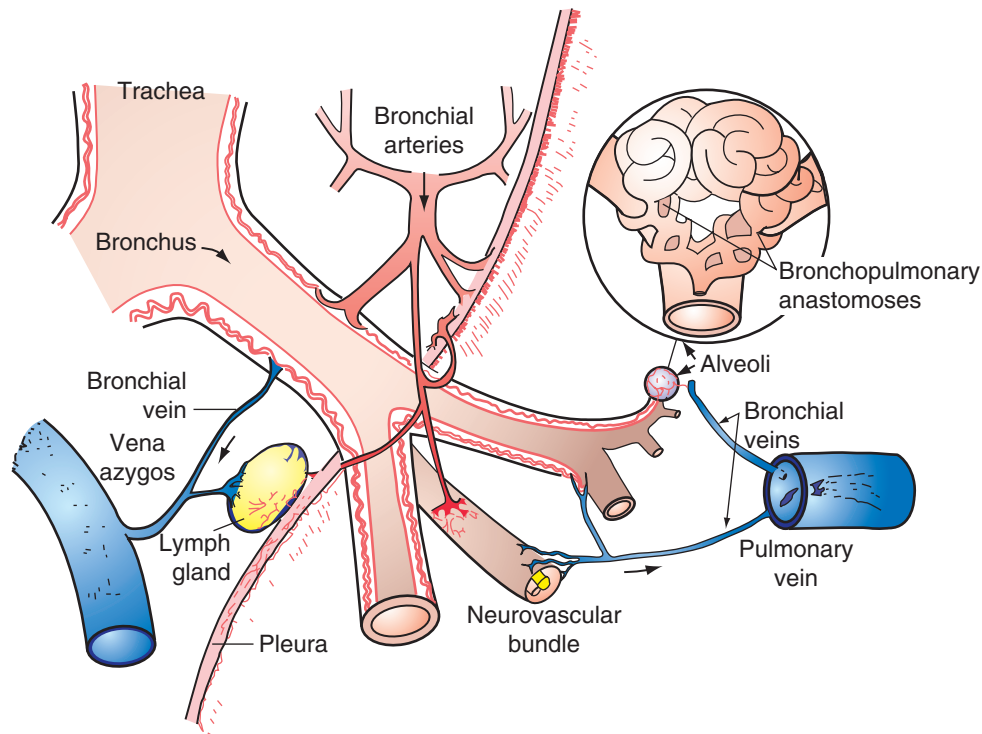
- The pulmonary circulation serves both respiratory and hemodynamic functions contributing to gas exchange in the terminal respiratory units.
- Gravity profoundly affects the distribution of blood flow within the lung.
- The juxtaposition of capillaries with alveoli provides the vast surface area needed for effective gas exchange; this arrangement is a unique feature of the lung microcirculation.
- The pulmonary circulation is a low-pressure, low-vascular-resistance circulation functionally different from the systemic circulation.
- Pulmonary vessels vasoconstrict in response to hypoxia, whereas systemic vessels vasodilate.
- Pressure and flow are highly pulsatile throughout the pulmonary circulation.
- A variety of pathophysiologic events and mediators produce either hydrostatic or high-permeability pulmonary edema.
- Vascular integrity is dependent upon the endothelial cell monolayer and is influenced by the negatively charged glycocalyx, by cell-cell apposition, and by the cell-cell matrix interactions.
- A leaky pulmonary microvasculature is intimately linked to the endothelial cytoskeleton.
- Genomic and genetic factors influence pulmonary circulation responses such as the development of vascular permeability in a racial- and ethnic-specific fashion.

Complete reference list available at *ExpertConsult*.

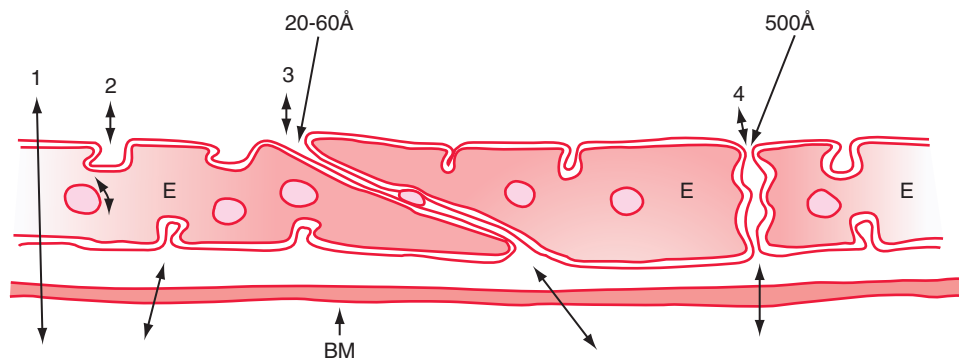
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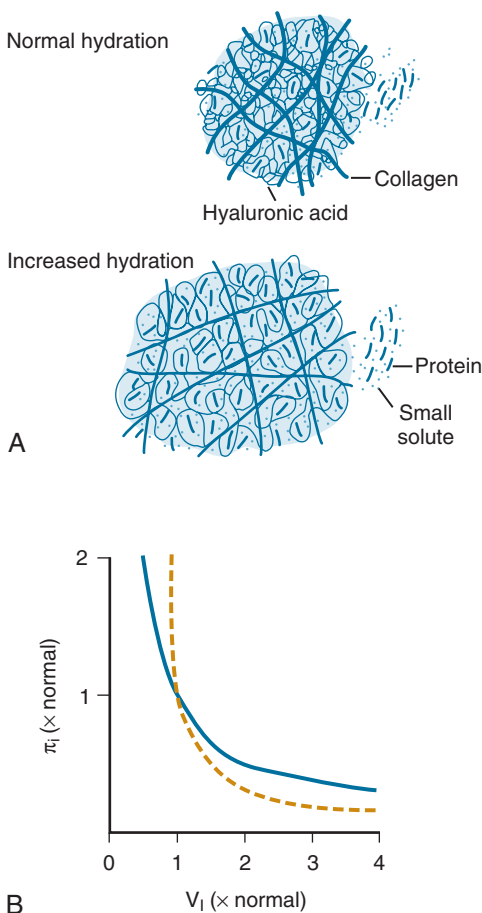
eFIGURE IMAGE GALLERY



eFigure 6-1 Schematic illustration of the components of the bronchial circulation. Flow from capillary beds supplying large airways and lymph glands drains to bronchial veins and into the azygos vein and superior vena cava. Intrapulmonary flow drains into the pulmonary circulation at the level of the alveoli (bronchopulmonary anastomoses) or pulmonary veins (bronchopulmonary veins). (From Deffebach ME, Charan NB, Lakshminarayan S, Butler J: The bronchial circulation. *Am Rev Respir Dis* 135:463–481, 1987.)



eFigure 6-2 Schematic representation of hypothetical pathways of transport in continuous endothelium: 1, transcellular pathway; 2, vesicular pathway; 3, small- and large-pore pathway; and 4, fused plasmalemmal channel pathway. BM, basement membrane; E, endothelial cell. See eTables 6-1 and 6-2 for detailed explanation.



eFigure 6-3 A, Schematic diagram showing the pulmonary interstitial matrix. Normally protein is excluded from 40% of the interstitial space. When interstitial water content increases, the matrix is disrupted and the exclusion volume decreases, making more of the matrix accessible to proteins. The increased distribution volume helps to maintain a lower concentration of protein and decreased colloid osmotic pressure than otherwise and constitutes an important edema safety factor opposing filtration. **B**, With an increase in interstitial volume (V_i), the colloid osmotic pressure (π_i) of extravascular proteins decreases. The *solid line* represents the decrease in π_i by dilution of a fixed interstitial space. The *dashed line* represents the decrease in π_i when the exclusion volume decreases with increasing V_i . (A, Reproduced with permission from Parker JC, Falgout HJ, Parker RE, et al: The effect of fluid volume loading on exclusion of interstitial albumin and lymph flow in the dog lung. *Circ Res* 45:440–450, 1979; B, reproduced with permission from Taylor AE, Parker JC, Kvietys PR, Perry M: Pulmonary interstitium in capillary exchange. *Ann NY Acad Sci* 384:148–168, 1982.)

eTable 6-1 Routes of Endothelial Transport of Lipid-Insoluble Molecules

TRANSCELLULAR (CELL MEMBRANE)

Consists of three barriers in series (plasma membrane, cytoplasm, plasma membrane).

VESICLES

Involves equilibration of luminal and abluminal fluids. Transport may be dependent on concentration gradient and rate of vesicular turnover.

SMALL AND LARGE "PORES"

Continuous route exists from the luminal to the abluminal sides. Flux of water and solutes across these pathways can be diffusive and convective.

Diffusive and convective transport may be coupled. Molecular sieving (i.e., restriction of solute permeation as molecular size approaches the pore dimension) is a characteristic of pore pathways.

FUSED PLASMALEMMAL CHANNELS

Created by transient fusion of two or more vesicles. Exhibit the same characteristics as junctional large pores.

eTable 6-2 Physical Characteristics of Tracer Molecules Used to Determine Selectivity of the Pulmonary Vascular Endothelial Barrier

Molecule	Molecule Weight (kd)	Stokes-Einstein Radius (Å)	D_{37}^*
Mannitol	0.182	4.4	0.9
Sucrose	0.342	5.2	0.721
Inulin	5.5	11–15	0.296
Cytochrome c	12	16.5	0.13 [†]
α -Thrombin	36.6	28	0.08 [‡]
Ovalbumin	43	27.6	0.11
Albumin (BSA)	69	36.1	0.093
Plasminogen	82	45.1	0.043
Fibrinogen	340	106	0.033

*Diffusion coefficient in water at 37° C = $D_{37} \times 10^{-5}$.

[†]Free diffusion coefficient in water at 20° C.

[‡]Free diffusion coefficient in water at 27° C.

BSA, bovine serum albumin.

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7

ACID-BASE BALANCE

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FUNDAMENTAL CONCEPTS

As pulmonary physicians have become increasingly involved in the care of critically ill patients, a thorough understanding of acid-base metabolism has become indispensable. Regulation of arterial pH is a critical factor in maintaining stable extracellular fluid and intracellular acid-base homeostasis. Arterial pH is kept under tight control by both pulmonary and renal mechanisms, each of which must also regulate other processes such as gas exchange in the lungs and fluid and electrolyte balance by the kidneys. Although arterial pH is usually well guarded, it can be preempted by other priorities. For example, hypoxia stimulates the carotid bodies, resulting in hyperventilation and respiratory alkalosis. Furthermore, metabolic alkalosis is often perpetuated by the renal response to contraction of the extracellular volume in patients who have had severe vomiting.

Understanding how respiratory and metabolic mechanisms interact to govern pH has been complicated by the introduction of a bewildering assortment of conflicting acid-base approaches. The relative merits of each must be judged in terms of carefully selected chemical definitions and concepts, which are briefly considered in this chapter. This is followed by a review of some of the more important disorders of acid-base balance.

ACID-BASE CHEMISTRY

pH Versus H^+

In aqueous solutions, “free” hydrogen ions (protons) are associated with clusters of water molecules, but for convenience these are designated as H^+ or H_3O^+ . Rather than expressing acidity in terms of H^+ concentration ($[\text{H}^+]$, normally 35 to 45 nanomoles/L in plasma), the logarithmic function (“pH,” normally 7.35 to 7.45 in plasma) is gener-

ally preferred both for convenience of representing a broad range of concentrations and because the free energy associated with changes in hydrogen concentration is related to the ratio rather than the difference between these concentrations:

$$\text{pH} = -\log_{10}[\text{H}^+] \quad [1]$$

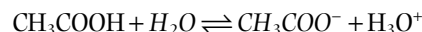
or more precisely,

$$\text{pH} = -\log_{10}(a_{\text{H}^+}) \quad [2]$$

where (a_{H^+}) designates the “activity,” of H^+ . (a_{H^+}) is determined with a hydrogen ion electrode and numerically approaches the concentration of H^+ in dilute solutions. Although the concentrations of H^+ in tissue fluids are typically very low compared to those of electrolytes, they can be responsible for important free energy differences across cellular membranes if the ratio between compartmental concentrations is large. For example, much of the energy stored in mitochondria is attributable to the ratio of H^+ ion concentrations which is maintained across the inner membrane of the mitochondria (see later). Because the concentration of H^+ is routinely divided by the thermodynamic standard state activity of a solution containing 1 mole/L of H^+ ions, no units are used for a_{H^+} or pH.

Conjugate Acids and Bases

The *Brønsted-Lowry* (BL) concept has largely supplanted the Arrhenius and earlier approaches for describing acid-base reactions in chemical, physiologic, and clinical studies. By the BL criteria, an acid is a proton (H^+) donor, whereas a base is an H^+ acceptor. For example, BL acids are designated in roman font and BL bases in italics in the following reaction:



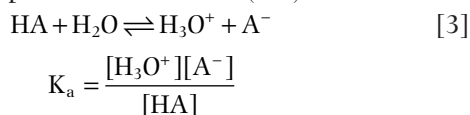
where CH_3COOH and CH_3COO^- represent the “conjugate acid-base pair” for acetic acid. CH_3COOH loses one H^+ when

the reaction proceeds to the right. H_3O^+ and H_2O represent the conjugate acid-base pair of water. H_2O accepts one H^+ as the reaction proceeds to the right.

Strong Versus Weak Ions

Ions that are completely ionized in water (e.g., Na^+ , K^+ , and Cl^-) are not considered as BL bases or acids because they neither accept nor donate H^+ ions, and they are sometimes referred to as “spectator ions.” Because the pH of the extracellular fluid is normally approximately 7.4, some interpretations of acid-base chemistry categorize many organic acids (with dissociation constants below ≈ 4.0 , see later) as “strong” acids because less than 0.1% of these acids remains undissociated in the extracellular milieu. Detection of excess concentrations of relatively strong anions such as lactate may indicate excessive intake, production, or retention of lactic acid. However, from the BL perspective, the corresponding lactate anion behaves as a weak base rather than an acid because lactate anions can accept H^+ ions. Furthermore, the presence of lactate anions may actually reflect infusions of solutions that promote alkalosis rather than acidosis. For example, an infusion of Ringer lactate initially dilutes the plasma, which tends to cause a dilutional acidosis (see later). However, subsequent metabolism of lactate to HCO_3^- results in alkalization.

Buffer Systems. Conjugate acid-base pairs can be used to minimize changes in pH when strong acids or bases (e.g., HCl and NaOH) are added to aqueous solutions. If the constituents of a solution are neither created nor destroyed and do not exchange with the environment, the system is referred to as “closed.” The effectiveness of a closed buffer system is maximal when the concentrations of the conjugate acids and bases are similar and exceed those of the strong acids or bases that are added, in other words, when the H_3O^+ of the solution is close to the dissociation constant (K_a) of the buffer pair. For a weak acid (HA):



where K_a is the acid-dissociation constant. Rearranging this equation and taking the logarithms of both sides yields the *generalized* Henderson-Hasselbalch equation:

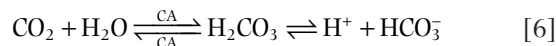
$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]} = \text{p}K_a + \log \frac{[\text{base}]}{[\text{acid}]} \quad [4]$$

Buffering is maximal when $\text{pH} = \text{p}K_a$. It is usually assumed that concentrations of H^+ released from water are negligible compared to those derived from the acid.

Arterial pH is maintained at approximately 7.4, well above the $\text{p}K_a$ of $\text{HCO}_3^-/\text{PCO}_2$ buffer pair (6.1). This reflects the fact that this buffer pair is volatile and bicarbonate concentrations are kept at concentrations 20 times greater than those of dissolved carbon dioxide. Relatively high concentrations of HCO_3^- relative to those of carbon dioxide reflect in part a *steady state* relationship between the lungs and kidney that presumably consumes more energy than buffers maintained at *equilibrium*, but that allows this acid-base pair to efficiently neutralize nonvolatile acids produced in the body.

CARBON DIOXIDE AND BICARBONATE

By the early 20th century the importance of reactions of carbon dioxide and bicarbonate ion (HCO_3^-) with H^+ and OH^- in acid-base balance was well established¹:



reaction 6 provides the dominant pathway to HCO_3^- from carbon dioxide, but rates of formation of either H_2CO_3 (carbonic acid) in reaction 6 or HCO_3^- directly in reaction 5 are relatively slow in the absence of a catalyst. These rates are normally accelerated by *carbonic anhydrase* (CA) present in erythrocytes, vascular endothelium, alveolar epithelium, and in most other organs, including the kidney.²⁻⁴ Under physiologic conditions, $[\text{H}_2\text{CO}_3]$ is much less concentrated than $[\text{carbon dioxide}]$, and the relative amounts of HCO_3^- and carbon dioxide can be calculated from the *conventional* Henderson-Hasselbalch equation:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{HCO}_3^-]}{\alpha \text{PCO}_2} \quad [7]$$

where the constant $\text{p}K_a$ ($= 6.1$ at 37°C) designates the negative logarithm of the apparent dissociation constant of carbon dioxide, which characterizes its equilibria with carbonic acid and the dissociation products in reaction 5 and 6. As noted earlier, $\text{p}K_a$ equals the pH when concentrations of HCO_3^- and dissolved carbon dioxide are equal. In [Equation 7](#), solute concentrations rather than activities are usually shown, and the dissolved carbon dioxide has been replaced by αPCO_2 , where α is the solubility coefficient, which is equal to 0.03 (mmol/L)/mm Hg at 37°C . The $\text{p}K_a$ and α remain relatively constant with clinical changes in pH and ionic strength⁵; however, they are significantly influenced by temperature. Fortunately, it is seldom necessary to correct pH for alterations in body temperature because of the manner in which the dissociation of constants of blood buffers (primarily imidazole groups in proteins) are affected by temperature.⁶ Some clinicians prefer to use the equation

$$\text{H}^+ = 24 \text{ PCO}_2 / [\text{HCO}_3^-] \quad [8]$$

where the units of H^+ , PCO_2 , and HCO_3^- are nanomoles/L, mm Hg, and mEq/L, and then convert calculated $[\text{H}^+]$ to pH.

MEASUREMENTS

PCO_2 and pH are readily measured with electrodes in arterial blood, but the pH detected is that in the plasma rather than in the red blood cells. Plasma pH is approximately 0.2 units greater than in red cells or in most other cells. The intracellular acid-base status of the body compartments is seldom measured; the plasma pH is often assumed to be representative of the body as a whole, and changes in plasma pH are assumed to reflect comparable changes within cells. This simplification is frequently inappropriate. For example, intracellular pH may be acidotic in patients with hypokalemia but who have an alkaline plasma. It is therefore more exact to refer to deviations from normal of plasma pH as *acidemia* and *alkalemia* rather than as acidosis and alkalosis. The latter terms refer to processes and do

not designate the actual pH or compartments. Intracellular pH is regulated by a complex array of transporters, and the pH of intracellular organelles can be extremely heterogeneous (as low as 4 to 5 in phagosomes and as high as 8 in nearby compartments of the mitochondria) (see Casey and associates⁷).

Plasma HCO_3^- is routinely calculated in the blood gas laboratory from measurements of arterial PCO_2 and pH using Equation 7. Alternatively, $[\text{HCO}_3^-]$ can be estimated from the total carbon dioxide that can be released from plasma with a strong acid (the *carbon dioxide content*). Carbon dioxide content is usually measured with electrolyte concentrations in venous blood and is usually approximately 5% higher than arterial HCO_3^- because it also includes H_2CO_3 , dissolved carbon dioxide, carbonate, and carbon dioxide bound to amino acids (carbamates) and because PCO_2 is higher in venous blood. If estimates of $[\text{HCO}_3^-]$ made from arterial and venous samples differ by more than 4 mEq/L, a variety of problems should be suspected, including very low cardiac output, clerical or technical errors, and collection at different times.

The pH and PCO_2 of blood are particularly likely to change if blood samples are exposed to air, if they are not kept cool, or if analysis is delayed. Exposure to air decreases PCO_2 , raises pH, and more gradually decreases carbon dioxide content. Fortunately, differences in carbon dioxide content of arterial and venous plasma are usually quite small, and venous samples can be used to provide reasonable estimates of the arterial HCO_3^- and directional changes in this parameter unless cardiac output is very low.

VENTILATORY PARAMETER: ARTERIAL PCO_2

The Henderson-Hasselbalch equation (Equation 7) indicates that pH can be calculated from two variables, PCO_2 and HCO_3^- , without consideration of other acid-base pairs in the plasma (isohydric principle). Arterial PCO_2 can be interpreted as a “ventilatory” parameter that reflects the adequacy of ventilation relative to the rate of carbon dioxide production. If arterial PCO_2 exceeds the normal range (35 to 45 mm Hg), then the patient is hypoventilating, and, conversely, if the arterial PCO_2 is lower, the patient is hyperventilating. These terms should be distinguished from hyperpnea and hypopnea, which refer to the increases or decreases of ventilation to meet respiratory requirements, as, for example, the hyperpnea during exercise, and from tachypnea and bradypnea, which indicate rapid and slow respiratory rates. Furthermore, the key parameter that determines arterial PCO_2 at any rate of carbon dioxide production is *alveolar* ventilation, because ventilation of dead space does not lead to the loss of carbon dioxide. Arterial PCO_2 is determined by the rate of carbon dioxide production, the ratio of the dead space to tidal volume, and minute ventilation.

The utility of arterial PCO_2 as a ventilatory parameter is readily illustrated by a few brief examples. Arterial PCO_2 is usually normal during moderate exercise, and the subject is neither hyperventilating nor hypoventilating, despite obvious hyperpnea and tachypnea. Patients with severe lung disease frequently hypoventilate despite both hyperpnea and tachypnea at rest, because much of the inhaled air is delivered to an enlarged physiologic dead space as a result of both shunting and regions of low \dot{V}_A/\dot{Q} ratio. An

increase in carbon dioxide production may be caused by an increased metabolic rate (e.g., exercise or fever) or occasionally by an acute release of carbon dioxide from HCO_3^- stores due to a severe, acute metabolic acidosis (e.g., during and after cardiopulmonary arrest or a grand mal seizure, when large amounts of lactic acid are produced and HCO_3^- is converted to carbon dioxide). Regardless of the reason that ventilation fails to keep pace with carbon dioxide production, the concomitant increase in arterial PCO_2 is classified as hypoventilation. Conversely, hyperventilation is frequently seen as a respiratory compensation for metabolic acidosis, or in response to hypoxia, anxiety, or other conditions that stimulate the carotid bodies and respiratory centers.

METABOLIC PARAMETERS

Titrimetry

Conceptually, the quantity of excess nonvolatile base or acid in samples of plasma or blood should be determined by titrating them to pH 7.4 with small volumes of a strong acid (HCl) or base (NaOH) in fully oxygenated samples kept at PCO_2 of 40 mm Hg and 37°C . It should be noted that when the PCO_2 is kept constant in the normal range, solutions of NaOH absorb carbon dioxide and are converted to solutions of NaHCO_3 , which can also be used to titrate acidic samples of plasma to pH 7.4. Titrimetry should in principal be used as the standard reference for all other methods of evaluating metabolic acidosis and metabolic alkalosis. It provides information regarding the concentration of acid or base in the plasma and the amount of HCl or NaOH that must be added to return the pH to 7.4. Unfortunately, titrimetry is difficult to perform, especially in blood, and it does not indicate which metabolic acids and bases are present. Three alternative metabolic parameters are currently in use: bicarbonate, base excess, and the strong ion difference.

Bicarbonate

Rather than laboriously titrating blood or plasma with strong acids and bases, measurements are usually made of plasma HCO_3^- to estimate the amount of nonvolatile acid or base that would be needed to restore pH_a to normal. Although it represents the oldest and most popular metabolic parameter, changes in plasma HCO_3^- underestimate the amount of acid (or base) that must actually be used to titrate samples of blood, plasma, or the body as a whole to a pH of 7.4. This reflects the presence of other buffer pairs that are also titrated by the strong acids and bases, which are generally nonvolatile and conserved (e.g., proteins and phosphates).

There is a second problem with using bicarbonate as a metabolic parameter: an ideal metabolic parameter should not be influenced by changes in arterial PCO_2 . As shown in Figure 7-1, in well-buffered solutions, HCO_3^- may increase significantly when arterial PCO_2 increases. If carbon dioxide is bubbled through a saline solution containing HCO_3^- without other buffers, the bicarbonate remains relatively constant over a broad range of PCO_2 . In contrast, when carbon dioxide is bubbled through samples of plasma or blood, HCO_3^- concentrations rise significantly, an effect due to the nonvolatile buffers available in plasma and blood (see Fig. 7-1, *in vitro* blood plot). As indicated in the reaction in

this figure, buffering by R^- can decrease concentrations of H^+ and promote formation of HCO_3^- (in accordance with the Le Chatelier principle.) The production of HCO_3^- from carbon dioxide in blood is increased when H^+ becomes associated with nonvolatile buffer anions (R^-) in the blood, which include hemoglobin, proteins, and inorganic phosphates. Red cell hemoglobin is particularly effective in buffering H^+ , for three reasons. First, the hemoglobin concentration is extremely high within red blood cells. Second, there is an abundance of titratable imidazole groups on the hemoglobin molecule, whose pK_a is very close to the pH within the cells and thus able to titrate large amounts of H^+ . Third, the buffering capacity of hemoglobin is nearly doubled by its oxylatable character (the Haldane effect) so that, at low PO_2 values, such as those encountered in systemic capillaries and venous blood, its affinity for H^+ is increased, allowing

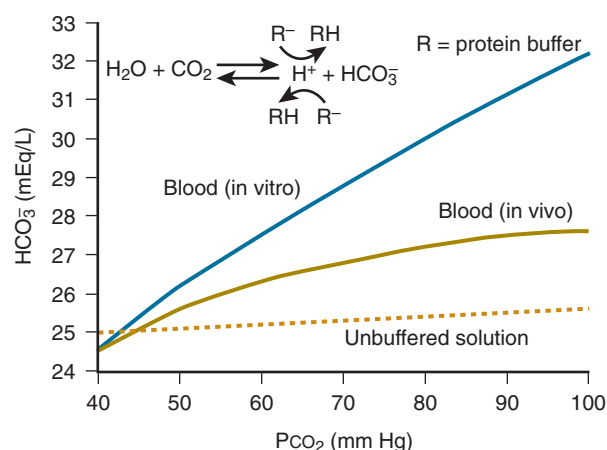


Figure 7-1 The relation between PCO_2 and HCO_3^- in samples of isotonic saline with 25 mEq/L $NaHCO_3$ (unbuffered solution), in samples of whole blood (in vitro), and in samples of arterial blood drawn from patients 20 minutes after exposure to elevations of PCO_2 (in vivo).

more carbon dioxide conversion to HCO_3^- . At high PO_2 values, such as those encountered in the pulmonary capillaries, the affinity for H^+ is reduced, HCO_3^- is converted to carbon dioxide, and the carbon dioxide is removed from the lungs by ventilation.

Base Excess

The reliability of plasma HCO_3^- as a metabolic parameter has been challenged because the proteins and phosphate buffers in plasma and blood promote increases in $[HCO_3^-]$ when samples of plasma or blood are exposed to high carbon dioxide tensions. This led to the development of alternative approaches that use other parameters that are relatively independent of PCO_2 . Among many schemes devised for this purpose, mention should be made of the HCO_3^- -pH graphs of Davenport⁸ and the concepts of buffer base and base excess of Astrup and Sigaard-Anderson.⁹ The base excess estimates how much strong acid or alkali must be added to titrate fully oxygenated blood to a pH of 7.4 at 37°C and at the hemoglobin concentration in that sample.

Although the base excess can accurately predict the in vitro changes in the pH of samples of blood after addition of acid or base or exposure to high or low PCO_2 , it is less reliable in predicting the in vivo changes of pH when blood samples are collected from patients who are exposed to metabolic and respiratory challenges. When the in vivo response of HCO_3^- to an acute change in arterial carbon dioxide tensions (arterial PCO_2) was determined empirically in normal subjects, it was found that increases in arterial PCO_2 from 40 to 78 mm Hg resulted in arterial plasma HCO_3^- increases of only 3 mEq/L.¹⁰ The range of HCO_3^- that would be expected in 95% of samples obtained in a normal population after acute increases in arterial PCO_2 is indicated in the acute respiratory acidosis band in Figure 7-2A. This graph also indicates (in the acute respiratory alkalosis band) that there is a tendency for HCO_3^- to fall somewhat

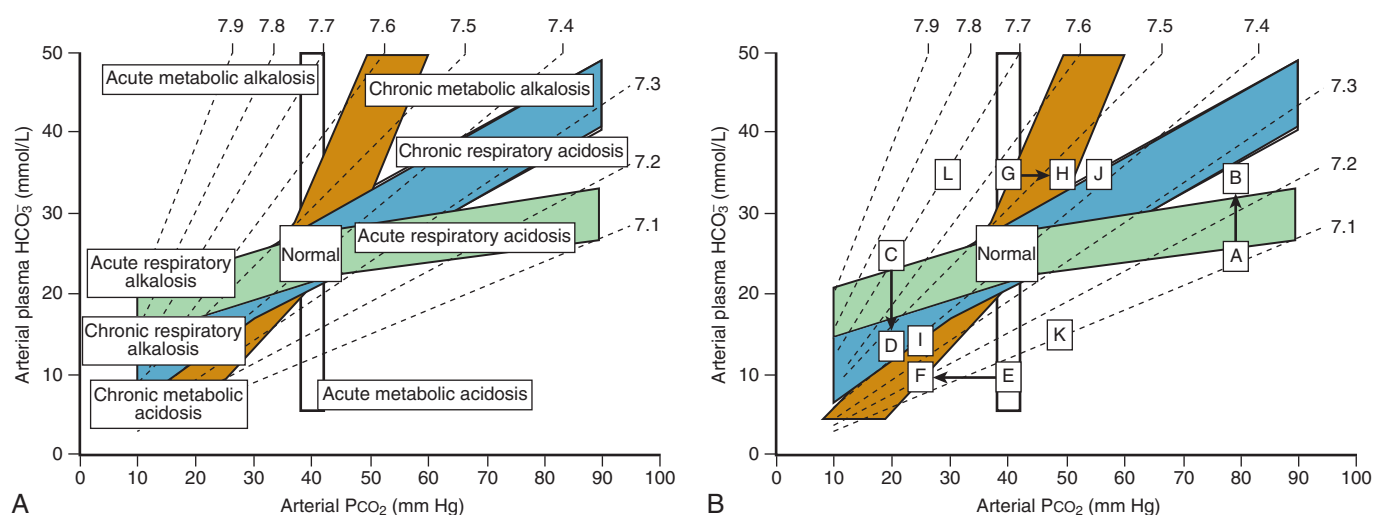


Figure 7-2 The relation between HCO_3^- and PCO_2 in a variety of clinical disorders. For discussion, see text. **A**, The 95% confidence levels for acute and chronic respiratory and metabolic abnormalities. **B**, The interpretation of examples in Table 7-1 is based on the assumption that PCO_2 is a purely respiratory parameter and HCO_3^- is a purely metabolic parameter. The vertical, colorless bar indicates the absence of any change in arterial PCO_2 with acute changes in bicarbonate. However, the respiratory response to the onset of metabolic acidosis and alkalosis is rapid, and the metabolic band rotates clockwise toward the chronic metabolic position within a matter of minutes to hours. Compensatory metabolic responses to respiratory changes in arterial PCO_2 are much slower, making it easier to observe the acute respiratory bands before metabolic compensation.

more with decreases in arterial PCO_2 than to rise with increases in arterial PCO_2 .^{11,12} This is due in part to a slight increase in lactate in patients who are hyperventilating, which in turn may be due to an alkalosis-mediated increase in the activity of the enzyme phosphofructokinase (see later discussion). Recognition that increases in arterial PCO_2 in vivo result in smaller increases in base excess in patients than those observed in vitro led to the somewhat arbitrary practice of assuming that the nonbicarbonate buffering of the extracellular fluid is equivalent to an “anemic” sample of blood that has been diluted threefold or contains only 50 g/L hemoglobin. (These assumptions could obviously be misleading if the patient is very edematous or anemic.) This revised metabolic parameter is usually referred to as the “standard base excess” and normally varies between -2 and $+2$ mEq/L. A further corrected form of the standard base excess incorporates plasma concentrations of both albumin and phosphate (SBEc).¹³

The relative stability of HCO_3^- in the face of acute changes in arterial PCO_2 is responsible for much of the popularity of HCO_3^- as a useful, though approximate, metabolic parameter and for the gradual decline in the use of the buffer base and base excess systems for diagnostic purposes. Regardless of which metabolic parameter is used, it must ultimately be validated with empirical observations made in subjects who are intentionally hyperventilated or hypoventilated (see Fig. 7-2). Of course, the assumption that the same criteria and normograms should apply to all patients, regardless of age, gender, or other characteristics, is unrealistic. It should also be emphasized that immediately after exposure to elevated alveolar carbon dioxide tensions in the alveoli, the HCO_3^- concentrations in the plasma within pulmonary capillaries and veins and then within the systemic arteries should increase in a manner similar to that observed in vitro. However, arterial HCO_3^- concentrations rapidly fall from peak values as carbon dioxide and HCO_3^- diffuse into the tissues and as the buffering capacity of conserved buffers (primarily proteins) in the blood is exhausted. Both the bicarbonate and standard base excess measurements are conveniently made in samples of whole blood at the same time that pH, PCO_2 , and PO_2 and hemoglobin concentration and saturation as well as carboxyhemoglobin and methemoglobin concentrations can be evaluated in the arterial blood gas laboratory.

Strong Ion Difference

Stewart¹⁴ and subsequently Constable^{15,16} endeavored to analyze acid-base disorders on the basis of the concentrations and dissociation constants of each of the strong and weak acids and bases present in the plasma, thereby avoiding either titration or the use of some of the approximations associated with earlier approaches. They modified a method that has long been used by chemists to estimate the effect of multiple acids and bases on arterial pH. Stewart¹⁴ and Constable^{15,16} calculated the arterial plasma pH and HCO_3^- from (1) the difference between total concentrations of strong cations and strong anions in the plasma (*strong ion difference* [SID], which is normally 40 to 42 mEq/L), (2) the total concentration and dissociation constants of all nonvolatile weak acids and bases (primarily albumin and phosphates), and (3) the PCO_2 . The SID is normally close to the difference between Na^+ and Cl^- concentrations, and albumin

usually accounts for much of the weak nonbicarbonate anions in the SID. Stewart assumed that all of the constituents in the plasma other than H^+ , carbon dioxide, HCO_3^- , and CO_3^{2-} were conserved and that the solution remained electroneutral. Furthermore, he included organic anions such as lactic acid with pK_a below 4 among the “strong” ions because these molecules are largely ionized at physiologic pH. The simultaneous equations for pH and HCO_3^- were then solved iteratively as a fourth-order polynomial using a computer program. Stewart concluded that “metabolic” changes in acid-base balance are due to alterations in either SID or the total concentration. If serum albumin concentrations are normal, then an increase in SID indicates a metabolic alkalosis and a decrease in SID indicates a metabolic acidosis.

In principle there is merit in defining the effects of each of the acid-base pairs upon the plasma pH. However, it is difficult to make sufficiently precise measurements of the constituents of the SID and the concentrations of weak acids and bases in the plasma, many of which have not been identified or properly quantified, especially in patients with liver or kidney disease.^{17,18} Furthermore, the assumption that a single dissociation constant can be assumed for all of the weak acids is questionable. Stewart’s distinctions between “independent” and “dependent” variables as well as his assumption that H^+ and HCO_3^- transport do not alter compartmental pH have also been challenged.¹⁹⁻²¹ Nor does the SID approach distinguish between acute and chronic disorders. The original suggestion that pH and HCO_3^- can be calculated rather than measured is particularly unfortunate because these two variables can be much more easily and reliably measured than indirectly estimated from concentrations of all of the nonvolatile acids and bases in the blood.

It can be concluded that none of the three most popular metabolic parameters (bicarbonate, base excess, and strong ion difference) provides a completely reliable estimate of the quantity of nonvolatile H^+ or OH^- that has been added to the blood or plasma samples, as judged by actually titrating the samples. Nor is it clear that either in vitro titration or SID calculations would provide a reliable guide to the in vivo acid-base status of patients. Consequently, frequent monitoring of arterial blood is essential in patients with metabolic acid-base disorders who are receiving infusions of acidic or alkaline fluids.

In conclusion, it remains unproven that any of the alternative approaches yields more reliable information than the conventional practice of using PCO_2 as a respiratory parameter, bicarbonate as a metabolic parameter, and the “anion gap” to interpret the effects of changes in concentrations of nonvolatile constituents in the blood (see later). The conventional approach will therefore be retained in the remainder of this chapter.

ROLE OF THE KIDNEYS

Approximately 1 mEq/kg of “fixed” acids (i.e., acids other than H_2CO_3) are produced daily in the metabolism of a typical protein diet.^{22,23} These nonvolatile acids cannot be excreted by the lungs and must be removed from the body by other routes, or buffered, to avoid progressive acidosis. Both sulfate and phosphate are produced, and these may be

accompanied by a variety of organic acids, some of which escape metabolism and contribute to the daily acid load. Successful excretion of these ions by the kidneys depends on both tubular H^+ transport and the presence of urinary buffers. In the absence of buffers, less than 0.1 mEq of acid per liter would be excreted even at the lowest urinary pH (4.5) generated by the kidneys.

The three most important buffers found in urine are bicarbonate/carbon dioxide, ammonium/ammonia, and titratable acids. Approximately 3600 mEq of HCO_3^- are filtered through the glomeruli daily, but losses in the urine are trivial. Most of the filtered HCO_3^- is reclaimed by an exchange of intracellular H^+ for Na^+ (through a Na^+-H^+ antiporter, NHE3) rather than by direct HCO_3^- reabsorption, although the latter process may be stimulated in acidotic states. Intracellular H^+ generation is mediated by hydration of carbon dioxide to H_2CO_3 , which is enhanced by carbonic anhydrase and is followed by the dissociation of H_2CO_3 to H^+ and HCO_3^- . H^+ entering the proximal tubule combines with HCO_3^- and rapidly regenerates carbon dioxide and H_2O , accelerated by the presence of carbonic anhydrase (types IV and XIV) on the luminal surface of the proximal tubule cells. The HCO_3^- formed within proximal tubule cells moves across the basolateral membranes in exchange for chloride through channels facilitated by basolateral membrane carbonic anhydrase (type XII).

Removal of HCO_3^- from proximal tubular fluid is essential, and failure to do so inevitably leads to hyperchloremic acidosis. However, HCO_3^- reabsorption does not result in acid excretion in the urine and therefore cannot contribute to fixed acid excretion. Unlike HCO_3^- , which is usually reabsorbed by the nephrons, titratable acids and ammonium reach the urine, and most H^+ is carried into the urine by these buffers. The principal titratable anion is $H_2PO_4^-$, most of which is secreted into the proximal tubule. During ketoacidosis, β -hydroxybutyric acid also can act as an effective buffer.

NH_4^+ is produced from glutamine by the proximal tubular cells, and this process can be stimulated by chronic acidosis, which increases glutamine uptake through H^+ -dependent glutamine transporters on the proximal tubular cells. NH_4^+ is secreted into the proximal tubule through a *sodium-hydrogen exchanger* (NHE3). Some of this ion is reabsorbed in the thick ascending limb of the tubule, and a fraction is converted into NH_3 . This increases medullary concentration of NH_3 , which diffuses into the collecting ducts. Because the collecting duct fluid tends to be very acidic, NH_3 becomes “trapped” as NH_4^+ . Details regarding renal metabolism and excretion of NH_3 and NH_4^+ can be found elsewhere.^{22,23}

Movement of H^+ into the proximal nephron differs in a number of important respects from transport in the distal nephron. Because the proximal tubule is responsible for absorbing most of the filtered HCO_3^- , considerably more H^+ is transported at this location than distally (≈ 3600 mEq, as described earlier, versus 50 to 100 mEq of fixed acids). However, the ability of the proximal tubule to concentrate H^+ is limited, and the fluid leaving the proximal tubule has a pH of approximately 6.8. Although the more distal portions of the tubule secrete less total H^+ than the proximal tubules, they increase H^+ concentration by almost 1000-fold compared with plasma, producing a urinary pH as low as 4.5. This permits net renal excretion of the acids

normally generated by metabolism. Distal tubular acid secretion is mediated by a vacuolar H^+ -ATPase and K^+/H^+ -ATPase on the luminal surface of the alpha intercalated cells of the collecting tubules and by transporters on inner medullary cells. This process is accelerated by electrogenic Na^+ reabsorption by adjacent principal cells, a process that makes the electrical potential of the tubular lumen more negative and thereby enhances secretion of H^+ . When alkalosis is present, a second population of intercalated cells designated as beta cells secretes HCO_3^- into the distal tubules.

Because carbon dioxide readily diffuses across cell membranes, the PCO_2 and pH of the renal tubular cells are affected promptly by changes in arterial PCO_2 . These changes initiate changes in renal H^+ excretion, with an increase during hypercapnia and decrease during hypocapnia.

NOMENCLATURE OF ACID-BASE DISORDERS

Procedures for naming acid-base disorders become quite simple if carbon dioxide and HCO_3^- are used as the respiratory and metabolic parameters. An additional assumption is made that compensation is incomplete. If arterial pH is low, the primary disorder must be an acidosis, and, if high, the primary disorder is an alkalosis. A secondary or compensatory change in either the respiratory or the metabolic parameter restores pH toward normal, but this effect should remain incomplete. On the basis of this approach, abnormal combinations of pH, PCO_2 , and HCO_3^- can be designated in terms of a primary disorder and any compensation that might be present.

Examples of virtually every combination of primary and secondary changes are provided in Table 7-1 and illustrated in Figure 7-2. Figure 7-2A indicates the ranges in which HCO_3^- and PCO_2 changes have been observed in normal persons subjected to acute or chronic respiratory or metabolic changes. Figures 7-2A and B are based on the simple assumption that HCO_3^- changes reflect metabolic events, whereas changes in PCO_2 reflect respiratory events (as indicated in Table 7-1). Some comments concerning the reliability of this preliminary analysis are provided in Table 7-1 and are discussed later in the chapter. Horizontal deviations on these coordinates indicate respiratory changes, whereas vertical deviations designate metabolic changes. Four primary disorders (A, C, E, and G) and four compensatory responses (B, D, F, and H) are shown in Figure 7-2. Each of the latter responses returns the pH toward 7.4. However, the pH remains abnormal in the same direction as the primary change. Note that if respiratory and metabolic parameters change proportionately, pH does not change and, in this case, remains normal (I and J). In this circumstance the disorder is considered a “mixed” combination of primary disorders. Another mixed disorder arises when both parameters are altered in a fashion that changes the pH in the same direction (K and L) and neither change can be considered as compensatory. A third type of mixed disorder must be entertained if a patient simply fails to “compensate” in the expected manner for a primary disorder after sufficient time has elapsed, perhaps indicating a failure of renal or pulmonary function.

Because the three variables must be related by Equation 3, not all combinations of pH, PCO_2 , and HCO_3^- are possible. One combination (M), which is chemically impossible and

Table 7-1 Laboratory Classification of Acid-Base Disorders

Location in Figure 7-2	Metabolic Parameter HCO_3^- (mEq/L)	pH	Respiratory Parameter PCO_2 (mm Hg)	Preliminary Interpretation	Comments Based on Bands (Fig. 7-2)
Normal range	23-27	7.35-7.45	38-42		
A	25	7.12	80	Respiratory acidosis	A small increase in (uncompensated) HCO_3^- is usually seen with acute respiratory acidosis
B	35	7.25	80	Respiratory acidosis (compensated)	Compensation has not reached expected confidence levels
C	25	7.71	20	Respiratory alkalosis (uncompensated)	A decrease in HCO_3^- would be expected; acute respiratory alkalosis
D	15	7.50	20	Respiratory alkalosis (compensated)	Compensation exceeded expected range
E	10	7.03	40	Metabolic acidosis (uncompensated)	A completely uncompensated metabolic acidosis should be very transient if the ventilatory response is normal
F	10	7.23	25	Metabolic acidosis (compensated)	Compensation is nearly maximal
G	35	7.56	40	Metabolic alkalosis (uncompensated)	
H	35	7.46	50	Metabolic alkalosis (compensated)	Compensation is in expected range
I	16	7.40	25	Metabolic acidosis and respiratory alkalosis	Mixed disorder
J	35	7.40	56	Metabolic alkalosis and respiratory acidosis	Mixed disorder
K	15	7.10	50	Metabolic acidosis and respiratory acidosis	Mixed disorder
L	35	7.67	30	Metabolic alkalosis and respiratory alkalosis	Mixed disorder
M	15	7.30	60	Laboratory error	

Interpretation based on assumption that PCO_2 is a respiratory parameter and HCO_3^- is a metabolic parameter.

cannot be plotted, must represent a laboratory error or timing differences at which various parameters were obtained, is indicated in Table 7-1. “Triple disorders” may also be encountered, involving a mixture of two or more independent processes that induce metabolic acidosis (detected by abnormal anions) in the presence of a respiratory disorder. Measurement of additional anions in plasma may permit identification of even more complex disorders. However, it is obviously not possible to have both hyperventilation and hypoventilation at the same time.

Several caveats should be heeded regarding both this and other systems that classify acid-base disorders strictly on the basis of pH, PCO_2 , and a metabolic parameter. Distinction between primary and compensatory disorders in the laboratory is based simply on which alteration is proportionately greater at the time the blood was drawn rather than on the sequence of events involved. For example, it is common for patients with *chronic obstructive pulmonary disease* (COPD) to be admitted to the hospital with compensated respiratory acidosis. With therapy the PCO_2 may decrease, leaving what might otherwise in the absence of the clinical history be taken as “a primary metabolic alkalosis with secondary respiratory compensation.” Winters²⁴ suggested that a distinction be made between the “physiologic” language commonly used by the physician and the “laboratory” terminology that is strictly based on blood parameters.

Laboratory definitions of primary and secondary or compensatory alterations of acid-base disorders assume that one is greater than the other and that there has been sufficient time for compensatory processes to reach their full quantitative expression. As discussed later, complete respiratory compensation takes hours, but full renal compensation takes several days. Thus, in any rapidly evolving and changing disease scenarios, clinicians should not always assume that lack of an expected compensation mandates consideration of a second or third primary disorder. Under some circumstances, however, compensation (correction to normal pH) may be complete in the apparent absence of what could be identified as a second primary disorder. For example, full compensation is observed among COPD patients who are chronically hypercapnic, whose lung function can improve over the course of the day with clearance of secretions. With better ventilation and \dot{V}_A/\dot{Q} matching, arterial PCO_2 falls and pH increases to normal or even higher than normal levels before the kidneys can quantitatively respond (see later discussion on [compensations](#)). Full compensation is also characteristic of the chronic hyperventilation observed at high altitude.

If HCO_3^- were a strictly metabolic (“nonrespiratory”) variable, then changes in PCO_2 would result in movement along a line perpendicular to the HCO_3^- axis (e.g., A and C in Fig. 7-2B). The actual response of HCO_3^- to acute and chronic changes can be indicated by the 95% confidence bands

Table 7-2 Rules of Chronic Compensation

Primary Disorder	Secondary Compensation	EXAMPLES	
		Primary Change	Compensation
↑ PCO ₂	↑ HCO ₃ ⁻ : 4 mEq/L for each 10-mm Hg increase in PCO ₂ (±3 mEq/L)	PCO ₂ : 40 → 80	HCO ₃ ⁻ : 24 → 40 pH: 7.1 → 7.32
↓ PCO ₂	↓ HCO ₃ ⁻ : 2.5 mEq/L for each 10-mm Hg decrease in PCO ₂ (±3 mEq/L)*	PCO ₂ : 40 → 20	HCO ₃ ⁻ : 24 → 19 pH: 7.70 → 7.60
↓ HCO ₃ ⁻	↓ PCO ₂ : 1–1.5 mm Hg for each mEq/L decrease in HCO ₃ ⁻	HCO ₃ ⁻ : 24 → 9	PCO ₂ : 40 → 25 pH: 7.00 → 7.20
↑ HCO ₃ ⁻	↑ PCO ₂ : 0.5–1.0 mm Hg for each mEq/L increase in HCO ₃ ⁻	HCO ₃ ⁻ : 24 → 34	PCO ₂ : 40 → 50 pH: 7.56 → 7.46

*HCO₃⁻ seldom falls below 18 mEq/L in acute and 16 mEq/L in chronic respiratory alkalosis.

shown in Figure 7-2. Note that both A and C deviate from the expected responses to acute changes in PCO₂ (see comments in Table 7-1). Because PCO₂ is assumed to be a reliable index variable of ventilation, E and G represent metabolic changes without respiratory compensation.

COMPENSATIONS

Respiratory Acidosis

Although the acute increase in HCO₃⁻ is relatively modest after onset of hypercapnia, HCO₃⁻ continues to rise if hypercapnia persists and reaches a peak value after approximately 5 days (Table 7-2). This is related primarily to an increase in the exchange of H⁺ for Na⁺ in the proximal tubule and increased HCO₃⁻ reabsorption (see later discussion). Increases in plasma HCO₃⁻ require an initial net loss of H⁺, which is made possible by the loss of increased quantities of NH₄⁺ in the urine. Once plasma HCO₃⁻ has reached a new steady state, H⁺ secretion need only be sufficient to reabsorb HCO₃⁻ from the tubular fluid, and NH₄⁺ and H⁺ excretion usually return to normal. In contrast, excretion of both net NH₄⁺ and net H⁺ remains elevated in chronic metabolic acidosis, because the daily load of nonvolatile acids must be excreted, over and above the acid excretion needed for reabsorption of HCO₃⁻. Differences in NH₄⁺ and net H⁺ excretion in chronic respiratory and metabolic acidosis may be related to the fact that proximal tubular fluid contains high concentrations of HCO₃⁻ in chronic respiratory acidosis but low concentrations are present in chronic metabolic acidosis. Increased HCO₃⁻ flux into the proximal tubular cells in chronic respiratory acidosis keeps intracellular pH relatively alkaline compared with the situation observed in chronic metabolic acidosis. Intracellular acidosis stimulates secretion of NH₄⁺ in chronic metabolic acidosis.²⁵

Respiratory Alkalosis

Hypocapnia results in a decrease in renal acid excretion and a fall in HCO₃⁻ that becomes fully evident within 2 to 3 days. As indicated in Table 7-2, HCO₃⁻ decreases by 2.5 mEq/L for each decrease of 10 mm Hg in PCO₂²⁶ and does not generally fall much below 16 mEq/L in respiratory alkalosis unless there is an independent metabolic acidosis present. In contrast, an increase of approximately 4 mEq/L of HCO₃⁻ may be expected when PCO₂ is increased in steps of

10 mm Hg. Confidence bands for chronic compensation are indicated in Figure 7-2A.

Metabolic Acidosis

Respiratory compensation for metabolic disorders is quite fast (within minutes) and reaches maximal values within 24 hours. A decrease in PCO₂ of 1 to 1.5 mm Hg should be observed for each mEq/L decrease of HCO₃⁻ in metabolic acidosis.²⁷ A simple rule for deciding whether the fall in PCO₂ is appropriate for the degree of metabolic acidosis is that the PCO₂ should be equal to the last two digits of the pH. For example, compensation is adequate if the PCO₂ decreases to 28 when the pH is 7.28. Alternatively, the PCO₂ can be predicted by adding 15 to the observed HCO₃⁻ (down to a value of 12). Although reduction in PCO₂ plays an important role in correcting any metabolic acidosis, evidence suggests that it may in some respects be counterproductive because it inhibits renal acid excretion.

Metabolic Alkalosis

Compensation for metabolic alkalosis results in a decrease of ventilation and a rise of PCO₂ by approximately 0.6 to 0.7 mm Hg for each mEq/L increase in HCO₃⁻, but it seldom results in a PCO₂ much greater than 55 mm Hg²⁸ because the accompanying hypoxemia from hypoventilation generates an opposing ventilatory stimulus. Furthermore, compensatory increases in PCO₂ may be more pronounced in patients with metabolic alkalosis who have not lost K⁺. Losses of K⁺ are associated with an intracellular rise in H⁺, including the neurons of the respiratory center.²⁸ A variety of other factors have been reported that can increase PCO₂ values in patients with metabolic alkalosis.²⁹ Respiratory compensation for metabolic alkalosis, like that for metabolic acidosis, can have a counterproductive effect on renal H⁺ transport: increases in PCO₂ associated with metabolic alkalosis decrease intracellular pH in the kidney, thereby promoting acid secretion and further increasing serum HCO₃⁻ levels.³⁰

METABOLIC ACIDOSIS

ANION GAP CONCEPT

The most useful classification of metabolic acidosis is based on the concept of the anion gap, which is calculated by

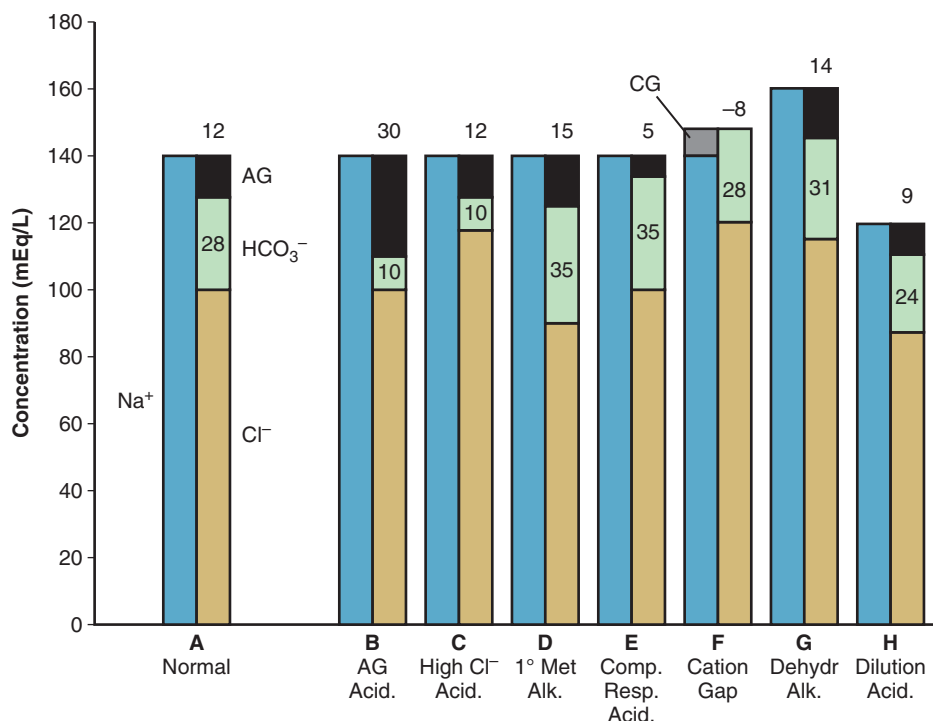


Figure 7-3 Typical anion gap (AG) profiles are shown for eight different acid-base conditions (see text). Because these histograms do not show pH, $[H^+]$, or PCO_2 , they do not indicate whether acidemia or alkalemia are present, but they do provide useful information about the nature of these disorders. The value of the AG is shown above each bar, and the bicarbonate concentrations are indicated (mEq/L). **A**, Normal. **B**, Anion gap acidosis. **C**, Hyperchloremic acidosis. **D**, Primary metabolic alkalosis. **E**, Compensated respiratory acidosis. **F**, Excess cations other than Na^+ creating a cation gap (CG). **G**, Contraction alkalosis. **H**, Dilutional acidosis.

subtracting the sum of plasma concentrations of Cl^- and HCO_3^- from that of Na^+ (Fig. 7-3). This difference, which uses fewer ion concentrations than the strong ion difference, provides a convenient index of the relative concentrations of plasma anions other than Cl^- and HCO_3^- . Normally the anion gap is between 8 and 16 mEq/L, although somewhat lower values (5 to 11 mEq/L) have been observed when newer techniques for measuring ion activities rather than total concentrations are used.³¹⁻³³ Among other anions present in plasma are albumin (with multiple anionic groups at physiologic pH that normally constitute approximately half of the gap), lactate, pyruvate, sulfate, and phosphate. Elevations of the anion gap usually indicate accumulation of some acid other than HCl in the plasma and are generally accompanied by a similar decrease in HCO_3^- ("anion gap acidosis") (see B in Fig. 7-3). Alternatively, reduction in $[HCO_3^-]$ may be caused by an increase in $[Cl^-]$ without an increase in the anion gap (hyperchloremic acidosis) (see C in Fig. 7-3).

Appropriate application of the anion gap approach requires appreciation of a number of factors:

1. Although addition of acids other than H_2CO_3 and HCl to plasma tends to increase the anion gap, this effect is somewhat less than might be expected, because H^+ tends to combine with negative groups on the albumin molecules, thereby reducing the contribution of this protein to the anion gap. In contrast, alkalemia tends to increase the number of anionic groups on albumin, thereby increasing the anion gap. Recognition of this phenomenon may be helpful when high HCO_3^- concentrations

are reported with electrolytes in the venous blood but arterial pH and PCO_2 are unavailable. For example, if an elevated HCO_3^- is related to a primary metabolic alkalosis (see Fig. 7-3D), the blood is alkaline and hydrogen ions are removed from albumin and other buffers. The anion gap will consequently be increased (e.g., 15 mEq/L). On the other hand, if the elevation in HCO_3^- is due to respiratory acidosis with a secondary increase in reabsorption of HCO_3^- from the renal tubules, the primary acidemia will tend to reduce the anion gap (e.g., 5 mEq/L) (see Fig. 7-3E).

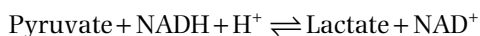
2. Because approximately half of the anion gap is normally related to negative charges on albumin, hypoalbuminemia decreases the anion gap by approximately 2.5 mEq/L for each decrease in albumin concentration of 1 g/dL.³²
3. A low anion gap, which may be less than zero, may reflect an increase in cations other than Na^+ (e.g., calcium $[Ca^{2+}]$, magnesium $[Mg^{2+}]$, lithium $[Li^+]$, and abnormal cationic proteins in multiple myeloma). As illustrated in Figure 7-3F, the anion gap may be low or even negative, because of an increase in the concentration of unknown cations. This can be considered as a negative anion gap or a positive cation gap.
4. Losses of water during dehydration increase the levels of all solute concentrations, including bicarbonate and the anion gap (see Fig. 7-3G). Because the respiratory center keeps PCO_2 relatively constant compared to HCO_3^- , metabolic alkalosis may ensue. Retention of water (or saline), has the opposite effect, reducing HCO_3^- relative to PCO_2 , thereby promoting a "dilutional acidosis" (see Fig. 7-3H).

5. Administration of large quantities of sodium salts of anionic antibiotics (e.g., penicillin and related drugs) or other anions (e.g., lactate, citrate, acetate) can also increase the anionic gap without acidosis. If anions of this type have not been administered and the patient is not dehydrated, then an increased anion gap suggests an underlying metabolic acidosis, even if the pH is normal or high.
6. Because much of the H^+ produced in the body is buffered by non- HCO_3^- buffers within cells, the decrease in HCO_3^- tends to be less than the increase in the anion gap when metabolic acidosis is present. For example, the increase in the anion gap averages approximately 60% more than the decrease of HCO_3^- in lactic acidosis. Because ketones are more readily lost in the urine than lactate, the increase in the anion gap is generally similar to the decrease in HCO_3^- in conditions that result in ketoacidosis³³ (see later discussion). Conversely, if the decrease in HCO_3^- exceeds the increase in the anion gap, it is likely that at least part of the acidosis is caused by a non-anion gap hyperchloremic acidosis.

ANION GAP ACIDOSIS^{33a}

Lactic Acidosis

Approximately 1400 mEq of lactate are normally produced each day,³⁴ but production can increase by an order of magnitude in heavy exercise. At rest, production is balanced by consumption and precisely regulated so that serum levels are kept at approximately 1 mEq/L. Most lactate is produced by the skeletal muscles, but with various stresses such as ischemia, profound hypoxemia, sepsis, and high sympathetic tone, other tissues may also generate lactate. In resting healthy individuals, the liver and, to a lesser extent, the kidneys are responsible for most of its consumption,³⁴ with oxidation in red skeletal muscle accounting for the remainder. Although lactate is the main gluconeogenic precursor in liver and kidneys during physical exertion, oxidation in working muscle accounts for 70% to 80% of lactate disposal. Newer work and analysis of glycolytic intermediary metabolism suggest that we may have to reconsider our classic thinking about what we have long termed “lactic acidosis.” From a strict biochemical standpoint, it is lactate and not lactic acid that is generated at the terminal point in glycolysis when pyruvate is reduced to lactate by lactate dehydrogenase, a step that consumes rather than produces a proton (Fig. 7-4).



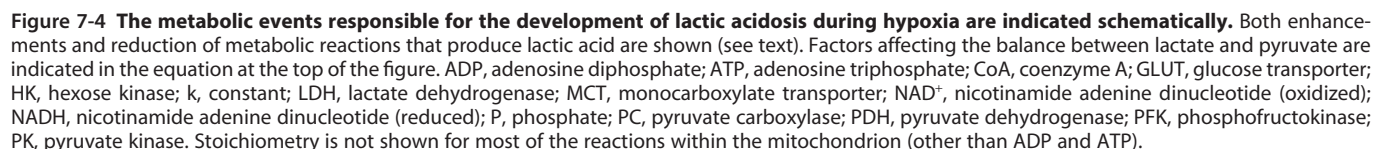
In terms of proton production, analysis of the glycolytic pathway shows the pathway to be proton neutral. Thus the acidosis that develops when lactate rises with exercise and possibly with other conditions associated with lactate accumulation and acidosis may be misleading.³⁵ It has been suggested, in fact, that if there were no lactate formation, the degree of acidosis arising in these circumstances would even be greater. The hydrogen ion that is formed in states of “lactic acidosis” arises from *adenosine triphosphate* (ATP), whose hydrolysis generates a hydrogen ion.



Under conditions where *adenosine diphosphate* (ADP) is not rephosphorylated, H^+ will accumulate. This occurs with true oxygen deficiency in ischemic (severe hypoperfusion) or very hypoxemic states when oxygen delivery cannot be maintained to support aerobic metabolism. Although the production of excessive quantities of lactate is thought to be linked in some way to tissue hypoxia in many clinical conditions associated with lactic acidosis, there has been little evidence of tissue hypoxia in maximally exercising muscle³⁶ or in sepsis,³⁷ though it would be difficult to detect small local regions of tissue hypoxia. The benign, or rather efficacious, nature of lactate has been demonstrated in “lactate clamp” studies,³⁸ in which lactate concentration is raised to 4 mM by infusion of a sodium lactate–lactic acid mixture along with glucose and lactate tracers. Under these conditions, lactate is the preferred fuel, and, because its disposal via gluconeogenesis or oxidation involves proton removal, lactate infusions have a mild alkalinizing effect. Nevertheless, the increase in lactate and production of acid during heavy exercise is presumably attributable to an increase in the fraction of glucose diverted to glycolytic rather than mitochondrial metabolism.

As indicated in Figure 7-4, glucose is normally metabolized to pyruvate, which is in equilibrium with lactate, at a ratio of 1:10 at rest and rising to 1:100 with exercise. Lactate can be metabolized only if it is converted back to pyruvate either in the cytosol or in the mitochondria (see later discussion). Pyruvate can be transported into the mitochondria in either of two ways. In gluconeogenic organs, carbon dioxide can be added to pyruvate by the enzyme pyruvate carboxylase to form oxaloacetate, which can then be converted to phosphoenolpyruvate and converted to glucose-6-phosphate and glucose. Alternatively, pyruvate can be oxidized to acetyl coenzyme A (CoA) by pyruvate dehydrogenase. Acetyl CoA then combines with oxaloacetate and is metabolized to form both ATP and *nicotinamide adenine dinucleotide* (NAD^+). In the absence of sufficient oxygen, *nicotinamide adenine dinucleotide*, reduced ($NADH$) cannot be oxidized to NAD^+ , and ATP production by the cytochrome system is blocked. Because the carboxylase reaction requires ATP and the dehydrogenase reaction requires NAD^+ , pyruvate can no longer enter the mitochondria, and concentrations of both cytosolic pyruvate and lactate increase. Increased cytosolic $NADH$ results in a disproportionate lactate increase. In addition, accumulation of cytosolic ADP, adenosine monophosphate, and phosphates activates phosphofructokinase and pyruvate kinase. This in turn increases metabolism of glycogen and glucose, which are effectively converted to lactate, a sequence of events referred to as the “Pasteur effect.” In effect, hypoxia promotes lactic acidosis both by increasing lactate production and by reducing its metabolism (see Fig. 7-4).

Lactate concentrations over 4 mM are associated with high mortality in most disease states. Increased lactate:pyruvate ratios may indicate the presence of tissue hypoxia, but it is difficult to measure pyruvate concentrations, especially when lactate levels are elevated. Venous concentrations are close to arterial, but it may be preferable to collect blood from the pulmonary artery or systemic arteries to be sure that the values represent an average of the body as a whole rather than from one extremity.



As mentioned previously, in many supposedly hypoxic tissue states, such as heavy exercise, seizures, and sepsis, oxygen delivery is not necessarily insufficient, and other causes for increased lactate formation and acidosis must be considered. One important cause is heightened sympathetic activation and catecholamine stimulation of glycolysis in excess of mitochondrial capacity for pyruvate uptake and metabolism arising from stimulated membrane ATP utilization by Na^+/K^+ -ATPase and accumulation of ADP, H^+ , and phosphate.³⁷ It has been suggested that lactate itself can enter the mitochondria in what has been termed the “intracellular lactate shuttle” under conditions in which pyruvate entry for reasons not entirely known may be insufficient by the classic entry pathways.^{38,39} Mitochondrial lactate entry is facilitated by a monocarboxylic transporter–lactate dehy-

Considering the marked arterial hypoxemia in some patients with severe respiratory insufficiency or cyanotic

heart diseases, it may seem paradoxical that lactic acidemia is not observed more frequently. Lactic acidosis is much more likely to appear when tissue perfusion is impaired than when arterial P_{O_2} is moderately reduced. Several compensations for chronic arterial hypoxemia help minimize tissue hypoxia: cardiac output rises, the hematocrit rises, and, if pH declines in those with carbon dioxide retention, hemoglobin oxygen affinity falls because of increased 2,3-diphosphoglycerate concentrations.

Skeletal muscle represents the principal site of lactate turnover. During moderate exercise, blood lactate levels normally remain unchanged despite elevated production. In a progressive (ramp) test, when work rates increase above what is referred to as the “anaerobic threshold,” lactate concentrations increase because the rate of rise in lactate production exceeds its rate of disposal. Although it was formerly thought at this level of exercise that oxygen consumption exceeds oxygen delivery to the muscle cell mitochondria, this now seems somewhat less likely, and increasing lactate concentrations may be linked to rising catecholamine-stimulated nonhypoxic glycolysis.⁴⁰ During vigorous exercise, lactate levels may transiently increase to 20 mEq/L or greater. Excessive production of lactate by skeletal muscles can also be observed during grand mal seizures and may accompany severe shivering in the hypothermic patient (Table 7-3).

Cohen and Woods⁴² divided the causes of lactic acidosis into two types: type A, in which tissue hypoxia is evident, and type B, in which the tissue P_{O_2} appears to be normal. Type A disorders include all forms of shock, acute respiratory distress syndrome, acute hypoxemia, and a variety of conditions that impair oxygen delivery, such as carbon monoxide poisoning and severe anemia. As explained earlier, the actual role of tissue hypoxia in type A disorders remains somewhat controversial. Type B disorders, which are not usually associated with tissue hypoxia, include common illnesses that may be associated with lactic acid accumulation, a variety of drugs and poisons that can induce lactic acidosis (associated with myoglobinemia following propofol administration⁴³), and congenital metabolic enzyme deficiencies. In diabetic patients, low insulin levels reduce the metabolism of pyruvate by pyruvate dehydrogenase, resulting in an increased lactate concentration. Evidence has also been reported that accumulation of ketones in the plasma may inhibit the monocarboxylic acid pump that is responsible for hepatic uptake of lactate.⁴⁴ In some patients with *diabetic ketoacidosis* (DKA), elevated lactate may be caused by extracellular fluid volume depletion due to osmotic diuresis induced by hyperglycemia. Malignancies, particularly lymphoproliferative and myeloproliferative disorders, may result in overproduction of lactic acid. This phenomenon recognized by Otto Warburg and so named appears to represent the need of rapidly growing cells for large amounts of two to three carbon intermediates (such as lactate) necessary to sustain the anabolic requirements of nucleic acid, lipid, and protein metabolism.

Renal or hepatic failure may also lead to lactic acidosis. As noted in Table 7-3, many drugs have been implicated in lactic acidosis, and the presence of polyethylene glycol as an excipient in a wide variety of drug preparations may also be associated with lactic acidosis.

Table 7-3 Causes of Anion Gap Acidosis

LACTIC ACIDOSIS

Type A: Tissue Hypoxia

Poor tissue perfusion: shock due to hypovolemia, sepsis, cardiogenic, idiopathic
Severe hypoxemia: pulmonary disorders (e.g., asthma, excessive inhaled β_2 -adrenergic agents), acute respiratory distress syndrome, carbon monoxide poisoning
Exercise above anaerobic threshold, seizures, shivering
Rhabdomyolysis
Severe anemia, carbon monoxide

Type B: Altered Lactate Metabolism without Hypoxia

Liver disease, renal failure, diabetes mellitus, malignancies (especially hematopoietic), SIRS, HIV
Drugs: acetaminophen, β -agonists, biguanides, cocaine, cyanide, ethanol, diethyl ether, fluorouracil, halothane, iron, methanol, salicylates, ethylene and propylene glycol, isoniazid toxicity, linezolid, nalidixic acid, niacin, zidovudine (AZT), metformin, chemotherapy, nitroprusside and cyanide, propofol, total parenteral nutrition, valproic acid
Rhabdomyolysis
Hereditary: glucose-6-phosphatase deficiency, fructose-1,6-phosphatase deficiency
D-Lactic acidosis

KETOACIDOSIS

Diabetes mellitus
Starvation
Ethanol
Inheritable errors of metabolism

UREMIA

TOXIC ANIONS

Ethylene glycol (glyceraldehyde, oxalate, hippurate)
Methanol (formaldehyde, formate)
Paraldehyde (acetoacetate)
Salicylates
Aminocaproic acid

HIV, human immunodeficiency virus; SIRS, systemic inflammatory response syndrome.

Although L-lactate is usually the cause of lactic acidosis, D-lactate accumulation due to intestinal bacterial metabolism has been documented in patients with short bowel syndrome, bowel ischemia, or obstruction; it can be detected only if an appropriate bacterial enzyme is used in the lactic acid assay.⁴⁴ D-Lactic acidosis can also be expected with use of those Ringer lactate solutions that contain a racemic mixture of lactic acid stereoisomers. However, much of the D-lactate is lost in the urine because, unlike L-lactate, it is not reabsorbed by the renal tubules, and some of the D-lactate is metabolized in mammals.⁴⁵ The anion gap therefore may be relatively normal. D-Lactic acidosis can be associated with neurologic and psychiatric symptoms. It may be treated by avoiding foods that contain lactobacillus (e.g., yogurt and sauerkraut), by decreasing dietary carbohydrates, and by administration of oral antibiotics.

Diabetic Ketoacidosis

Accumulation of acetoacetate, β -hydroxybutyrate, and acetone (“ketone bodies”) in the body is referred to as “ketoacidosis.” This disorder appears to require both

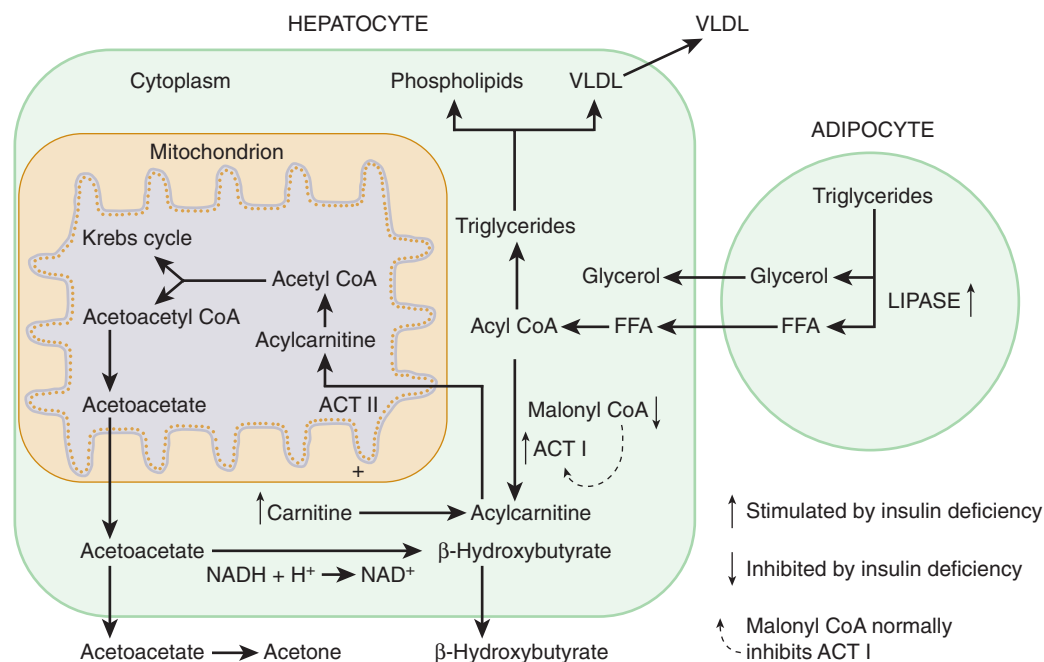


Figure 7-5 Factors encouraging ketoacidosis. Some reactions are stimulated by insulin deficiency (arrow up), whereas others (arrow down) are inhibited by insulin deficiency and increased glucagon. The open curved arrow indicates that acylcarnitine transferase (ACT) I is normally inhibited by malonyl coenzyme A (CoA). FFA, free fatty acid; NAD⁺, nicotinamide adenine dinucleotide (oxidized); NADH, nicotinamide adenine dinucleotide (reduced); VLDL, very-low-density lipoprotein.

increased mobilization of free fatty acids from lipid stores and their excessive conversion within hepatocytes to ketone bodies (Fig. 7-5). Triglycerides within fat are normally broken down by lipase into free fatty acids and glycerol. The activity of lipase is enhanced by low concentrations of insulin and increased concentrations of glucagon, catecholamines, and growth hormone. Free fatty acids released from adipocytes are taken up by the liver and linked to CoA to form acyl CoA. Acyl CoA is either transformed by esterification to triglycerides and lipoproteins or transferred into the mitochondria as a complex with carnitine and then metabolized to carbon dioxide and water in the Krebs cycle or converted to ketone bodies. The fraction of acyl CoA that is transferred into the mitochondrial matrix is increased by raised glucagon concentrations. This transport is mediated by the enzyme acylcarnitine transferase I, which in turn is inhibited by the amount of malonyl CoA present. Normal inhibition of acylcarnitine transferase I by malonyl CoA is indicated by the curved arrow in Figure 7-5. The concentration of malonyl CoA falls when glucagon is increased or insulin deficiency is present, and transport of the acyl fragment into the mitochondrial matrix is consequently increased. Increased glucagon also increases the amount of carnitine present, further accelerating movement of acyl CoA into the mitochondria. The acyl CoA complex entering the mitochondria is degraded successively to form acetyl CoA, which under normal circumstances is incorporated into the Krebs cycle and oxidatively metabolized to carbon dioxide. In DKA the quantities of acetyl CoA produced exceed the capacity of handling by the Krebs cycle and are converted to ketone bodies. Ketoacids are normally taken up and metabolized to carbon dioxide and water by muscle and kidney rather than by the liver, but this process may be reduced in DKA.⁴⁵

An equilibrium normally exists between β-hydroxybutyrate, acetoacetate, and acetone. There is usually two to three times as much β-hydroxybutyrate as acetoacetate, but this ratio may be significantly increased if tissue Po₂ is reduced. Because standard tests for ketones measure acetone (which is not an acid) and acetoacetate but do not detect β-hydroxybutyrate (which is not a ketone), hypoxia may lead to an underestimate of the severity of “ketoacidosis.” In normal subjects the ratio of β-hydroxybutyrate to acetoacetate is 2:1. With DKA this ratio increases to 2.5:1 to 3:1, and with poor tissue perfusion and associated lactic acidosis, it can exceed 8:1.⁴⁶ As insulin sensitivity and volume status improve with therapy, conversion of β-hydroxybutyrate to acetoacetate may increase the amount of ketone bodies detected, which may be misinterpreted as worsening of the ketoacidosis.⁴⁶ Treatment of diabetic ketoacidosis is discussed in detail elsewhere.⁴⁷

Starvation often leads to ketoacidosis within 1 or 2 days, particularly after exercise,⁴⁸ but HCO₃⁻ levels seldom decline below 18 mEq/L. Starvation ketoacidosis is also attributed to decreased insulin concentrations, but these do not fall to levels as low as those encountered in DKA, and there is evidence that ketosis stimulates insulin secretion in those with normal pancreatic function. Alcoholics who binge and then abruptly stop drinking and eating may develop severe ketoacidosis,^{49,50} which may be underestimated because of a disproportionate rise in β-hydroxybutyrate. They usually become dehydrated from vomiting before hospital admission, and they may develop severe acidosis, frequently with concomitant lactic acidosis. Glucose concentrations are frequently low, and glucose (given with thiamine to avoid the Wernicke-Korsakoff syndrome of cerebral beriberi) stimulates insulin secretion and corrects the ketoacidosis. Insulin

must generally be avoided in these patients. Supplementation with K^+ , phosphate, and Mg^{2+} is frequently required. Several congenital errors of metabolism that result in ketoacidosis have also been described. Ingestion of a high-fat diet, paraldehyde, or isopropyl alcohol may also result in a positive test for ketones.

Uremic Acidosis

Renal insufficiency does not usually produce an anion gap acidosis until the glomerular filtration rate falls below 20 mL/min and blood urea nitrogen and creatinine levels increase to more than 40 mg/dL (14.3 mmol/L) and 4 mg/dL (354 μ mol/L), respectively. However, there is some variation in the filtration threshold at which anion gap acidosis develops because of differences in diet and sites of renal damage.⁴⁶ The loss of nephrons is accompanied by a decrease in the ability to excrete both NH_4^+ and anions. Numerous anions normally kept low by normal renal clearance contribute to the anion gap, including sulfate, phosphate, and lactate. With acute renal failure, HCO_3^- concentrations characteristically decline by 1 to 2 mEq/day but decline more rapidly in the presence of hypercatabolism. Hemodialysis becomes necessary when HCO_3^- level falls to less than 10 mEq/L. Milder forms of renal insufficiency may be accompanied by hyperchloremic acidosis (see later discussion).

Toxic Forms of Anion Gap Acidosis

As noted in Table 7-3, numerous substances can be converted to hydrogen ions and anions by metabolism, resulting in an anion gap acidosis. *Central nervous system* (CNS) stimulation by large ingestions of aspirin initially can cause hyperventilation in adults, but this is soon followed by an anion gap metabolic acidosis. Salicylates are themselves anions, but most of the acidosis observed after an overdose is related to formation of organic acids, particularly lactic acid and ketones.⁵¹ With very high aspirin concentrations, red cell HCO_3^-/Cl^- exchange is impaired, and this may lead to tissue carbon dioxide retention, which may not be apparent in arterial blood owing to the previously mentioned ventilatory stimulation. The initial respiratory alkalosis contributes to lactate production. $NaHCO_3$ administration promotes both redistribution of salicylates from tissues to blood and urinary excretion by ionic trapping, but severe alkalosis and K^+ losses must be avoided; hemodialysis may be helpful. Glucose infusions are used to increase the cerebrospinal fluid concentration of glucose, which is frequently decreased.⁵²

Volatile alcohol ingestions are frequent causes of metabolic acidosis, most commonly methanol, isopropanol, or ethylene glycol. Methanol (rubbing alcohol) is converted to formic acid, and ethylene glycol (radiator fluid) is converted to oxalic acid and other toxic anions. Both of these alcohols are metabolized by alcohol dehydrogenase and cause acidosis directly through their metabolites. Although isopropyl alcohol ingestion leads to CNS depression and the presence of urinary ketones (acetone), it is not metabolized to an organic acid, and acidosis is seen only with vascular collapse and lactic acidemia. Ethanol (to a serum concentration of 100 to 150 mg/L), or preferably fomepizole,⁵³ should be used to inhibit the formation of toxic metabolites from

methanol and ethylene glycol, and hemodialysis may be used to clear these metabolites. Toluene, which induces euphoria when inhaled, is converted to benzoic hippuric acids and may cause severe hypokalemia.

Alcohols and ethylene glycol should be suspected if the serum osmolality by freezing point depression exceeds by more than 20 mmol/L the osmolality calculated from laboratory values of Na^+ , glucose, and urea by the following equation:

$$\text{Serum osmolality} = 2 \times [Na^+] + BUN/2.8 + \text{glucose}/18 \quad [9]$$

where sodium is in milliequivalents per liter and *blood urea nitrogen* (BUN) and glucose are in milligrams per deciliter. (Vapor pressure measurements of osmolality should not be used because they do not detect the presence of volatile alcohols.) The “osmolar gap” may also be increased in “pseudohyponatremia” (due to the presence of excess lipid or protein in the plasma) and after administration of mannitol or radiopaque dyes, and these factors also need to be assessed. The mnemonic “mudpiles” is frequently used by clinicians to remember many of the causes for anion gap acidosis (methanol, uremia, diabetic ketoacidosis, propylene glycol, infection, lactic acidosis, ethylene glycol, salicylates).

HYPERCHLOREMIC ACIDOSIS

Metabolic acidosis in the absence of an elevated anion gap is usually associated with hyperchloremia. Hyperchloremic acidosis may be observed in a variety of renal and gastrointestinal disorders, the latter being more common.

Renal Tubular Acidosis

Metabolic acidosis arises from a variety of renal tubular disorders. Disorders of renal tubular function that result in hyperchloremic acidosis can be divided into four categories that can be differentiated by their clinical and laboratory characteristics.⁵⁴⁻⁵⁶ Particular defects in various membrane transport proteins that account precisely for certain inherited forms of *renal tubular acidosis* (RTA) have been identified, but the classic definitions still remain the most useful clinically, and these are outlined here.

Type 1 Renal Tubular Acidosis. Type 1, or “classic,” RTA involves defects in distal tubular acid secretion. Only distal nephrons can produce an acidic urine, so that with injury or dysfunction it is impossible for urine pH to be lowered below 5.3, regardless of how acidotic the patient is. Serum HCO_3^- can be below 10 mEq/L. Urinary HCO_3^- excretion is usually low, because most HCO_3^- is reabsorbed proximally. HCO_3^- infusion therefore can be used to prove that the defect is distal (type 1 RTA) rather than proximal (type 2 RTA): the fraction of filtered HCO_3^- lost in urine remains low in type 1 but is high in type 2 RTA. Another defect observed with type 1 RTA is an inability to generate high PCO_2 in the urine after infusion of HCO_3^- . Normal subjects produce urine with PCO_2 values that exceed those in the plasma by more than 30 to 100 mm Hg. This phenomenon is related to distal tubular H^+ transport to form H_2CO_3 . The subsequent generation of carbon dioxide from HCO_3^- in the distal nephron is relatively slow because there is little carbonic

anhydrase on the luminal surface. Dissipation of the carbon dioxide from urine beyond the collecting ducts is inefficient because of the small surface-to-volume ratio of the lower urinary tract. Because patients are unable to secrete H^+ ions in the distal tubules, their urinary PCO_2 remains less than 40 mm Hg.

As indicated in Table 7-4, many disorders are associated with distal RTA. It can be caused by a wide variety of mutations, most of which affect carbonic anhydrase II, anion exchanger, or the proton pump (H^+ -ATPase) in intercalated cells of the renal cortical collecting duct. Chronic acidosis

leads to osteopenia with Ca^{2+} , Mg^{2+} , and PO_4^{2-} loss in the urine. Precipitation of Ca^{2+} and PO_4^{2-} is normally inhibited by tubular secretion of citrate. As citrate secretion tends to be reduced, this and an alkaline urine with calciuria and hypocitraturia appears to be responsible for nephrolithiasis and nephrocalcinosis that characterize distal but not proximal RTA. K^+ losses tend to be increased because of increased exchange of K^+ for Na^+ in the distal tubule. Concentration defects are common.

In the absence of therapy, acidosis progresses relentlessly in distal RTA because fixed acids cannot be excreted at their rate of production. Hypokalemia may be particularly severe with consequent muscle weakness or even paralysis. Treatment with 1 mEq/kg $NaHCO_3$ daily (roughly the rate of bodily fixed acid generation) is usually sufficient in adults; more is required in children. Bone demineralization is reduced by this therapy, and K^+ losses are minimized.

Type 2 Renal Tubular Acidosis. In type 2 or proximal RTA, HCO_3^- reabsorption is impaired because of a defect in the proximal ion exchange of H^+ for Na^+ , which is mediated by an apical membrane Na^+-H^+ antiporter. Normally, HCO_3^- is completely removed from glomerular filtrate until serum HCO_3^- concentrations exceed 22 to 24 mEq/L, and maximal reabsorption rates are not observed until concentrations are approximately 28 mEq/L. In proximal RTA, maximal reabsorption values may top out at a serum concentration of approximately 18 mEq/L. The distal tubules cannot absorb more than 15% to 20% of the filtered load of HCO_3^- , so HCO_3^- is lost in the urine, causing the urine pH to rise even when the patient is acidotic. When serum HCO_3^- is normalized to 25 mmol/L by HCO_3^- infusion, more than 10% of the filtered HCO_3^- is lost in the urine in type 2 RTA, compared with less than 5% in normal subjects and those with type 1 RTA. If the serum HCO_3^- level falls below the HCO_3^- recovery threshold, then urinary HCO_3^- loss ceases, urine pH falls, and the acidosis does not progress. A typical patient will have a stable serum HCO_3^- value in the range of 12 to 20 mEq/L. It is common to find that patients with proximal RTA do maximally acidify their urine, but only in the presence of a significant metabolic acidosis. In some patients it may be necessary to decrease serum HCO_3^- to less than their usual level with NH_4Cl administration before maximal urine acidification is observed.

Proximal RTA may be an isolated tubular lesion, but it is more frequently associated with other proximal tubular defects that lead to loss of glucose, phosphate, amino acids, and low-molecular-weight proteins (Fanconi syndrome). Nephrolithiasis and nephrocalcinosis are not characteristic, but patients are susceptible to osteomalacia and rickets, if the acidification defect is associated with calcium and phosphate loss. They require much more $NaHCO_3$ (10 to 15 mEq/kg/day) to correct their acidosis than do patients with distal RTA. Sodium citrate is better tolerated than $NaHCO_3$, and thiazides can decrease administered alkali needs. Large amounts of $NaHCO_3$ exacerbate losses of K^+ , and supplements and/or potassium-sparing diuretics are commonly required. Serum phosphate level may be reduced if there is a defect in reabsorption, and alkaline phosphatase level may be increased. Some illnesses associated with proximal RTA are indicated in Table 7-4.

Table 7-4 Causes of Hyperchloremic Acidosis

RENAL TUBULAR ACIDOSIS

Type 1 (Distal, Classic), Hypokalemic

Congenital defects without systemic disease (anion exchanger, AE1 deficient) or with systemic disease (e.g., Ehlers-Danlos syndrome, sickle cell anemia)
 Hyperglobulinemia (e.g., systemic lupus erythematosus, idiopathic pulmonary fibrosis, Sjögren syndrome, thyroiditis, chronic active hepatitis, biliary cirrhosis, vasculitis)
 Drug toxicity (e.g., amphotericin B, toluene, analgesics, lithium)
 Nephrocalcinosis (e.g., primary hyperparathyroidism, vitamin D intoxication, hyperoxaluria, Fabry disease, Wilson disease)
 Tubular and interstitial renal disease (e.g., pyelonephritis and obstructive renal disease, renal transplant rejection)

Type 2 (Proximal), Hypokalemic

Congenital disorders: isolated or associated with mental retardation, ocular abnormalities
 Selective (acetazolamide, sulfonamides) or associated with loss of glucose, phosphate, amino acids, low-molecular-weight proteins, lysozyme, light chains, uric acid
 Genetic (e.g., cystinosis, Wilson disease)
 Dysproteinemias (e.g., multiple myeloma, monoclonal gammopathy)
 Drug or chemical toxicity (e.g., outdated tetracycline, heavy metals, ifosfamide)
 Secondary hyperparathyroidism with hypocalcemia (e.g., vitamin D deficiency or resistance)
 Renal interstitial disease (e.g., medullary cystic disease, Sjögren syndrome, renal transplant)

Type 3

Type 1 and 2 RTA, carbonic anhydrase II deficiency

Type 4, Hyperkalemic

Mineralocorticoid deficiency: Addison disease, tuberculosis, metastatic carcinoma, autoimmune, adrenal hemorrhage, acquired immunodeficiency syndrome (AIDS), critically ill patients, drugs (ketoconazole, phenytoin, rifampin)
 Hyporeninemic states: diabetes mellitus, nephritis, lupus, AIDS
 Mineralocorticoid resistance: pseudohypoaldosteronism (congenital, spironolactone)
 Medications: potassium-sparing diuretics (amiloride, triamterene), angiotensin-converting enzyme inhibitors, trimethoprim, pentamidine, nonsteroidal anti-inflammatory drugs, cyclosporine A, β -adrenergic inhibitors, α -adrenergic agonists, heparin, digitalis overdose, lithium, insulin antagonists (diazoxide, somatostatin), succinylcholine

NONRENAL HYPERCHLOREMIC ACIDOSIS

Diarrhea
 Pancreatic drainage
 Ureterosigmoidostomy
 Cholestyramine (diarrhea), NH_4Cl and hyperalimentation with amino acid infusions, $CaCl_2$
 Toluene exposure (hippurate production)
 Loss of ketones that could have been converted to bicarbonate

Type 3 Renal Tubular Acidosis. A true type 3 RTA includes features of both proximal and distal forms, but it does not have great clinical significance. The largest patient group in this category, rarely seen nowadays, was infants or young children with hereditary distal RTA that manifested some proximal bicarbonate loss transiently. A similar combination of defects is also observed in a small number of patients with an inherited form of carbonic anhydrase II deficiency.

Type 4 Renal Tubular Acidosis. Type 4 RTA is caused by either decreased aldosterone production or tubular hyporesponsiveness to the hormone. Because aldosterone stimulates distal secretion of H^+ and K^+ , deficiency results in hyperchloremic hyperkalemic acidosis, whereas other forms of RTA are usually associated with hypokalemia. Hyperkalemia suppresses proximal NH_3 production. Consequently, even though urine pH may be low, the amount of acid lost may be insufficient to avoid acidosis. A wide variety of disorders lead to low aldosterone production (see Table 7-4), but decreased renin secretion in older patients with diabetic renal disease is common. Aldosterone production decreases in critically ill patients with sepsis and cardiogenic shock. Potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, intravenous solutions, and heparin (which can inhibit aldosterone secretion) may also cause hyperkalemia and type 4 RTA. Hyperkalemia is associated with a high incidence of arrhythmias (25%), hypertension, and weakness.

Most K^+ found in the urine is secreted into the cortical collecting duct, and detection of decreased secretion is facilitated by calculating the *transtubular potassium gradient* (TTKG):

$$TTKG = \{[K^+]_{urine} / [K^+]_{plasma}\} / \{[Osm]_{urine} / [Osm]_{plasma}\} \quad [10]$$

where $[Osm]$ designates osmolality. This ratio corrects the urine-to-plasma potassium ratio for urine concentration, which occurs more distally in the nephron. The TTKG should be greater than 8 in patients with hyperkalemia and should increase after administration of mineralocorticoids in patients with aldosterone deficiency. Failure of TTKG to increase after mineralocorticoids suggests loss of tubular sensitivity.

Acidosis of Progressive Renal Failure. Hyperchloremic RTA without hyperkalemia is characteristic of many renal diseases associated with loss of renal tissue and a decrease in the glomerular filtration rate. Retention of acid in these patients is attributable to a decrease in the ability of the kidneys to excrete NH_4^+ . Although the decline in serum bicarbonate is relatively modest, it is generally recommended that serum HCO_3^- concentrations should be maintained above 22 mEq/L with modest $NaHCO_3$ supplementation to minimize bone reabsorption, insulin resistance, and protein catabolism.⁵⁷

Gastrointestinal Causes of Hyperchloremic Acidosis

Diarrhea is a more common cause of hyperchloremic acidosis than are renal tubular disorders. In the normal bowel, Cl^- is selectively absorbed in exchange for HCO_3^- , more so in the colon than proximally. Normally, stool fluid volume and

Cl^- losses are modest, but, when there is diarrhea, significant amounts of HCO_3^- can be lost. Lactic acid and other organic acids are also produced by bowel microorganisms, and these reduce the actual HCO_3^- stool concentrations.⁵⁸ However, these organic anions are not readily absorbed from the colon with fast transit, and the net result is that HCO_3^- is lost from the body, whereas serum Cl^- is increased without a rise in the anion gap. Absorption of NH_4^+ generated by gut bacteria contributes to the acidosis. Passage of urine into the bowel after ureterosigmoidostomy or ureteroileostomy can also produce hyperchloremic acidosis, because the Cl^- tends to be absorbed instead of the HCO_3^- .

Each liter of diarrheal fluid can result in the loss of 200 mEq of HCO_3^- . Pancreatic and biliary fluids contain 50 to 100 mEq of HCO_3^- per liter, and severe hyperchloremic acidosis can arise after losses of these fluids. Cholestyramine contains an anion-exchange resin that can generate hyperchloremic acidosis by releasing Cl^- in exchange for HCO_3^- . K^+ losses in diarrheal stool (30 to 60 mEq K^+ per liter) in exchange for Na^+ can be severe. Furthermore, extracellular volume depletion promotes aldosterone secretion, which in turn enhances urinary K^+ loss. Chronic acidosis increases renal NH_4^+ secretion, distinguishing it from RTA, which can be detected by measuring the urine net charge (see later).

Miscellaneous Causes of Hyperchloremic Acidosis

Respiratory alkalosis is normally compensated by a decrease in proximal HCO_3^- reabsorption. Correction of respiratory alkalosis may transiently produce a hyperchloremic acidosis, as can some hyperalimentation fluids, NH_4Cl , or $CaCl_2$. Toluene, inhaled by glue sniffers, is converted to benzoic acid and hippurate, which are rapidly renally excreted with cations, resulting in hyperchloremic acidosis. Some intravenous solutions of synthetic amino acids that may be titrated with excess HCl (hydrochloric acid) and saline infusions lower HCO_3^- and increase Cl^- concentrations (see later discussion).

Urine Net Charge and Osmolar Gap

Measurement of the *urine net charge* (UNC), or urine anion gap, can be used to help distinguish between hyperchloremic acidosis due to diarrhea or to RTA. Unlike serum, the urine seldom contains significant HCO_3^- in acidotic patients, but K^+ and NH_4^+ concentrations can be considerable. The UNC is calculated from the following equation:

$$UNC = Na^+ + K^+ - Cl^- \quad [11]$$

If urinary NH_4^+ is high, then urinary Cl^- concentration will exceed that of Na^+ plus K^+ , and the UNC will be negative by 20 to 50 mEq/L. UNC provides an estimate of urine NH_4^+ and is negative with hyperchloremic acidosis caused by diarrhea because renal NH_4^+ production is increased in response to the metabolic acidosis. In contrast, UNC is more positive in patients with RTA, with impaired production and/or excretion of NH_4^+ . The presence of ketones and other anions can also cause UNC to be negative, and direct NH_4^+ measurements provide a more reliable index of renal tubular acid metabolism. NH_4^+ concentrations have also been estimated by calculating the urine osmolar gap, which represents the difference between observed and calculated urine osmolality.

DILUTIONAL ACIDOSIS

A modest acidemia is observed when water dilutes blood after being pulled from cells by increased extracellular solute concentrations such as glucose.⁵⁹ It is generally attributed to the fact that plasma HCO_3^- falls to a greater degree than does PCO_2 , which is regulated by the brain.⁶⁰ Saline infusions may have a similar effect; however, the dilution associated with inappropriate antidiuretic hormone secretion is not usually accompanied by acidosis.⁵⁷

CLINICAL MANIFESTATIONS

Perhaps the most obvious sign of metabolic acidosis is the respiratory response, which consists of slow but deep breathing known as Kussmaul respiration. It is particularly effective because the dead-space contribution to ventilation is minimized. Patients with metabolic acidosis are often asymptomatic, and their hyperventilation may not be clinically obvious. With more severe acidosis, dyspnea may be troubling, and patients complain of headache, nausea, and vomiting. This may be followed by confusion, stupor, and even coma, which are particularly likely to be present in respiratory acidosis. Acidosis may reduce the myocardial catecholamine responsiveness and induce arteriolar vasodilation, but these effects are largely blunted by increased catecholamine and cortisol secretion.⁶¹ Venoconstriction is characteristic of acidosis⁶² and may shift blood into the central volume and trigger pulmonary edema.⁶³ Arrhythmias, including ventricular fibrillation, can be fatal.

Hyperkalemia (despite total body K^+ depletion) is sometimes observed with metabolic acidosis. It is often associated with DKA, but this is related in large part to the plasma hyperosmolality that causes water and K^+ , the main intracellular cation, to exit cells. Infusions of organic acids are much less likely to cause hyperkalemia than are infusions of inorganic acids,⁶⁴ and the conventional wisdom that serum K^+ increases in a predictable fashion with metabolic acidosis⁶⁵ has not proved to be very useful. Nor is hyperkalemia found in most patients with types 1, 2, or 3 RTA or with diarrhea because of the simultaneous losses of both HCO_3^- and K^+ with these disorders.

Chronic retention of more than 10 mEq H^+ per day may be tolerated over a period of years in patients with chronic renal disease because of buffering by bone alkaline constituents (calcium, phosphate, and carbonate).^{66,67} When acid production exceeds the release of bone buffers, a fall in HCO_3^- is inevitable. Recent evidence suggests that the acid load of the typical protein-rich Western diet may not be fully excreted by the kidneys and the very slight failure to eliminate the entirety must be handled by bone buffering. Over many decades of life, this cumulative bone buffering may help to explain the high incidence of osteopenia and osteoporosis in older adults.

THERAPY

Treatment of metabolic acidosis should focus primarily on correcting the metabolic disorder responsible for its emergence and the hemodynamic, oxygenation, and electrolyte derangements that ensue, rather than the acidemia itself. For example, insulin and volume replacement are the

mainstays of diabetic therapy, dialysis for uremic acidosis, and reversal of shock, local ischemia, and hypoxemia for lactic acidosis. If another illness is responsible for lactic acidosis (see Table 7-3), then appropriate therapy must be selected.²

NaHCO_3 administration or other alkaline agents for metabolic acidosis is clearly indicated in patients with chronic metabolic acidosis, such as those with significant hyperchloremic acidosis (e.g., RTA) to prevent bone and muscle catabolism, relieve exertional dyspnea, and promote growth in children. In acute severe metabolic acidosis (especially the endogenous anion gap acidoses), it is becoming clear that HCO_3^- administration is not always helpful or effective. However, alkalinizing agents are still indicated to counter the associated severe hyperkalemia or to enhance excretion of acid metabolites of certain toxins.⁶⁸ In severe DKA despite arterial pH as low as 6.8, bicarbonate administration does not alter rates of glucose correction or ketoacid clearance when compared with equivalent sodium administration given as NaCl. Equivalent evidence in sepsis, severe hypoxemia, and cardiogenic shock (again in randomized saline-controlled studies described previously for DKA) found no obvious benefits and often slightly worse parameters in the bicarbonate-treated patients (for review of these studies, see Swenson⁶⁹). A number of possible negative consequences of attempted alkalization in these conditions have been recognized.^{68,70-73} These include a shift of the oxygen-hemoglobin dissociation curve to the left that may impair oxygen delivery in already hypoxic tissues, greater lactic acid production or suppression of hepatic lactate clearance with an increase in pH, and nonmetabolic generation of carbon dioxide from HCO_3^- with paradoxical intracellular acidosis. Increases in PCO_2 associated with NaHCO_3 may not be observed in the arterial blood even though mixed venous PCO_2 is significantly increased. Excessively rapid infusions of NaHCO_3 may result in a paradoxical diminution of cerebrospinal fluid and brain interstitial pH if they reduce the drive to breathe. Equilibration of HCO_3^- with the cerebrospinal fluid is much slower than the corresponding equilibration of carbon dioxide, and the rise in PCO_2 caused by hypoventilation tends to make the cerebrospinal fluid more acid before the HCO_3^- can diffuse into this compartment. Because the usual alkaline solutions administered are extremely hypertonic, there may be an abrupt fall in serum K^+ as potassium is returned to the cellular compartment. NaHCO_3 infusions should be kept as low as possible (usually <200 mmol) to avoid volume overload, which may alternatively be minimized by hemodialysis against a NaHCO_3 solution. As the underlying disorders improve, both ketone bodies and lactate may be metabolized to HCO_3^- , resulting in the development of posttherapeutic alkalosis. Although it is often claimed that when the pH is much lower than 7.2, NaHCO_3 infusions may prove to be lifesaving by enhancing cardiac contractility and response to pressors, the supporting data are rather unconvincing. As mentioned previously in studies comparing equivalent NaCl and NaHCO_3 , any brief benefits noted with bicarbonate in blood pressure may simply be the result of volume expansion by any sodium-containing fluid. Regardless of the cause of acidemia, if base administration is considered necessary, NaHCO_3 is preferable to lactate solutions, because lactate is completely ionized at any pH still compatible with life and it does not

provide buffering until it is converted to HCO_3^- by normal hepatic function.

As a first estimate of the amount required to raise serum HCO_3^- by a given number of milliequivalents per liter, it is common practice to assume that HCO_3^- enters a space 40% or 50% of the total body weight. Not infrequently, much more is required to repair the deficit. However, no attempt should be made to increase the pH to more than 7.2 with such infusions, and it is prudent to raise the HCO_3^- concentration no more than halfway toward normal during the first day. Determinations of arterial blood PO_2 , PCO_2 , HCO_3^- , pH, glucose, and electrolytes must be repeated at frequent intervals to monitor the response to therapy.

However, given the failure of controlled trials to show any benefit with bicarbonate administration in the most severe endogenous anion gap metabolic acidoses and the negative observations alluded to earlier, it may be better, although difficult, to refrain from using alkalinizing fluids at all in these circumstances. In fact, animal organ and cellular studies reveal the surprising and counterintuitive findings that recovery from ischemia or oxygen deprivation is clearly enhanced when the perfusing media is acidic and recovery is worse under alkalotic conditions, a phenomenon termed “the pH paradox.”⁶⁸ Many explanations have been offered, the most intriguing being that acidosis may blunt the activity of many enzymes and proteins responsible for much of the associated excessively activated oxidative and proinflammatory pathways in hypoxic and septic injuries that may perpetuate ongoing injury. Another potential argument against aggressive attempts to reduce lactic acidosis, independent of treating the initial cause(s), is the failure of dichloroacetate, a compound that stimulates pyruvate dehydrogenase activity and pyruvate entry into the mitochondria, to alter outcomes in patients with severe lactic acidosis.⁷⁴ By limiting lactate formation, the drug may deny cells a preferred fuel under stress.⁴⁰

METABOLIC ALKALOSIS

GENERAL CONSIDERATIONS

For both diagnostic and therapeutic reasons, it is helpful to divide the causes of metabolic alkalosis into those associated with a decrease in the extracellular volume (chloride-sensitive) and those associated with a normal or increased extracellular volume (chloride-resistant)^{74a} (Table 7-5).

CHLORIDE-RESPONSIVE ALKALOSIS

Gastrointestinal Losses

As indicated previously, upper gastrointestinal tract acid losses generate an alkalosis that is initially associated with increased renal Na^+ excretion. *Extracellular fluid* (ECF) volume depletion causes the glomerular filtration rate to fall and is associated with increased aldosterone secretion. This enhances HCO_3^- reabsorption, and alkalosis persists even after all initiating factors (e.g., protracted vomiting and continuous nasogastric suction) have abated. In these patients, Cl^- is avidly reabsorbed from the tubules, and urine concentrations remain lower than 10 mEq/L. Correction of

Table 7-5 Causes of Metabolic Alkalosis

LOSS OF H^+ FROM THE BODY

Chloride-Responsive with Urine $\text{Cl}^- < 20$ mEq/L and Normotension

Gastrointestinal losses of chloride: stomach (vomiting, aspiration, some villous adenomas, congenital chloride-wasting diarrhea, high-volume ileostomy drainage)
Renal losses of chloride: loop and thiazide diuretics, posthypercapnic
Sweat losses of chloride: cystic fibrosis
Posthypercapnia: elevated HCO_3^- after resolution of chronic respiratory acidosis

Chloride-Resistant with Urine $\text{Cl}^- > 20$ mEq/L and Hypertension

Hyperaldosteronism (primary or secondary), Cushing syndrome, cortisol 11- β -ketoreductase deficiency, licorice, etc.
Liddle syndrome: increased epithelial sodium channel (ENaC) in collecting duct

Chloride-Resistant with Urine $\text{Cl}^- > 20$ mEq/L, Hypotension or Normotension

Bartter syndrome: impaired reabsorption of sodium ions and chloride ions in the thick ascending loop of Henle (variants)
Gitelman syndrome: impaired thiazide-sensitive sodium/chloride transporter (NCCT) in the distal convoluted tubule

EXCESSIVE INTAKE OF HCO_3^-

Milk-alkali syndrome
Administration of poorly absorbed anions (e.g., penicillin)
Bicarbonate dialysis in end-stage renal disease
Recovery from ketoacidosis or lactic acidosis after bicarbonate administration
Massive blood transfusions (citrate)

EXTRACELLULAR FLUID VOLUME REDUCTION

the metabolic alkalosis depends on replacement of Cl^- losses, principally given as saline. Although diarrhea usually generates a hyperchloremic acidosis (see earlier discussion), alkalosis may rarely be seen with Cl^- - HCO_3^- exchange across the ileal mucosa⁷⁵ and in a minority of villous adenomas of the colon.

Diuretics

These agents are the most common cause of excessive renal fluid losses. When Na^+ delivery to the distal nephron persists despite extracellular volume depletion (e.g., after diuretic therapy), H^+ secretion by this segment is enhanced. In these conditions, Cl^- concentrations in the urine may be appreciable. Both loop diuretics (furosemide, bumetanide, ethacrynic acid) and thiazides can promote H^+ and K^+ secretion from the more distal segments of the nephron. This frequently results in severe hypokalemic alkalosis.

Sweat

Metabolic alkalosis has also been reported in patients with cystic fibrosis, who tend to lose proportionately more Cl^- than HCO_3^- in their sweat.

Mechanical Ventilation

Alkalosis is not infrequently observed in mechanically ventilated patients treated for chronic hypercapnia. Care must be taken to avoid abrupt increases in ventilation, which may result in life-threatening metabolic alkalosis. The arterial

pH and plasma levels of HCO_3^- of these persons may remain high and inhibit spontaneous ventilation unless Cl^- losses are restored, generally in the form of KCl. Acetazolamide may also be helpful because it inhibits renal tubular HCO_3^- reabsorption, but its use requires careful monitoring in those not mechanically ventilated with limited lung function (forced expiratory volume in 1 second < 1 L) and avoided in those with renal or hepatic insufficiency.

Nonreabsorbable Anions

Sodium salts of penicillin or other anions that cannot be reabsorbed by the renal tubules may stimulate acid and K^+ losses in patients who are volume depleted.

CHLORIDE-RESISTANT ALKALOSIS

Metabolic alkalosis may also be associated with either normal or increased ECF volume, particularly in the presence of excessive aldosterone secretion. Mineralocorticoids act to increase both H^+ and K^+ secretion and Na^+ retention by the distal nephron. This results in a hypokalemic alkalosis that is associated with a modest ECF volume expansion. Na^+ and Cl^- retention appears to be limited by ECF expansion, and output and intake of Na^+ become equal. Unlike situations in which the ECF is decreased, Cl^- is lost in the urine with metabolic alkalosis that is caused by excessive mineralocorticoid secretion (urine $\text{Cl}^- > 20$ mEq/L). Maintenance of the metabolic alkalosis is a result of persistent excess mineralocorticoid secretion as well as hypokalemia.

Any alteration in the renin-angiotensin-aldosterone axis that promotes aldosterone secretion also causes this form of metabolic alkalosis (see Table 7-5) by its stimulatory effects on two different populations of cells in the distal nephron.⁷⁶ Distal tubular exchange of K^+ for Na^+ appears to be confined to principal cells, located in the cortical collecting duct. Because more Cl^- ions than cations are left behind, a negative lumen potential is established that facilitates H^+ secretion by the more distally positioned alpha intercalated cells. Patients with edema due to liver disease, nephrotic syndrome, or congestive heart failure may secrete excessive aldosterone because their effective arterial blood volume is reduced, even though their total ECF volume is increased. The development of hypokalemic alkalosis is particularly likely when they receive diuretics.

The pathogenesis of several forms of congenital hypokalemic, hypochloremic metabolic alkalosis not associated with hyperaldosteronism (Bartter syndrome and Gitelman syndrome) has been traced to abnormalities in renal tubular transporters.⁷⁷

EXCESSIVE INTAKE OF ALKALI

Although the kidneys normally can excrete large quantities of HCO_3^- , metabolic alkalosis may occasionally be generated by excessive intake of HCO_3^- or other anions that are metabolized to HCO_3^- , especially in patients with renal insufficiency. For example, metabolic alkalosis may be observed in patients who ingest extremely large amounts of HCO_3^- and milk (milk-alkali syndrome, which is associated with renal calcification), after fasting (due to conversion of ketones to HCO_3^-),⁷⁴ and after transfusions of large amounts of blood (conversion of citrate to HCO_3^-).⁷⁸ In the absence of volume

depletion or renal disease, alkalosis due to increased HCO_3^- intake rapidly resolves once intake is restricted.

EXTRACELLULAR FLUID CONTRACTION

Water loss from plasma may induce a modest alkalemia that is sometimes referred to as a “contraction” alkalosis and is related to the relatively greater increase of HCO_3^- , compared with PCO_2 . It would probably be more appropriate to designate this as a *concentration alkalosis* to distinguish it from the alkalosis of contraction that is caused by ECF fluid depletion, which promotes renal acid excretion and alkalemia (see earlier discussion).

CLINICAL MANIFESTATIONS

Metabolic alkalosis frequently remains asymptomatic and is often untreated even after discovery. Nevertheless, it may be associated with significant mortality, particularly when $\text{pH} > 7.5$ and $[\text{HCO}_3^-] > 45$ mM.⁷⁹⁻⁸¹ Alkalosis tends to increase the affinity of hemoglobin for oxygen, thereby reducing oxygen delivery to the tissues. It also decreases ventilation by suppressing the carotid body and may constrict the peripheral vasculature, further limiting oxygen supply to tissues.

Neuromuscular hyperirritability may be observed in alkalosis and has been attributed in part to increased calcium binding to albumin. Twitching and tetany may be preceded by the Chvostek and Trousseau signs, and seizures can ensue. Metabolic alkalosis is usually associated with hypokalemia, which may be responsible for both supraventricular and ventricular arrhythmias.⁸⁰ Alkalosis promotes intracellular movement of K^+ and may also cause an increase in the anion gap because of removal of H^+ from albumin and increased generation of lactate.

THERAPY

Treatment of metabolic alkalosis depends on the status of the ECF volume. Patients with ECF volume loss can be distinguished from those with excess volume on the basis of urine Cl^- , which is usually less than 10 mEq/L in the former and greater than 20 mEq/L in the latter setting. For patients who have sustained severe volume losses, fluids that contain Na^+ , Cl^- , K^+ , and Mg^{2+} are frequently indicated.

Fluid administration to edematous patients with alkalosis is usually inappropriate. Spironolactone is useful in the presence of excessive mineralocorticoid secretion. The carbonic anhydrase inhibitor acetazolamide may be helpful in patients with posthypercapnic alkalosis, although it may increase loss of K^+ and occasionally cause liver damage and hepatic encephalopathy. Although NH_4Cl and arginine hydrochloride may be used to treat alkalosis, their use must be avoided in patients with severe liver disease because these agents may precipitate hepatic coma by decreasing urea synthesis and/or elevating NH_3 concentrations. They may also induce hyperkalemia and increase urea levels in patients with azotemia.

Infusions of HCl (at a concentration of 100 to 200 mEq/L) may be safer than NH_4Cl in patients with liver and kidney disease, but these infusions require central access confirmed

radiologically by location of the catheter tip in the superior vena cava to minimize the likelihood of tissue necrosis and hemolysis caused by the acid infusion. Alternatively, intubation and intentional hypoventilation to increase the PCO_2 , thereby reducing arterial pH, may be employed. Severe metabolic alkalosis can also be treated by hemodialysis. Histamine H_2 receptor antagonists or gastric proton pump ($\text{H}^+/\text{K}^+\text{-ATPase}$) inhibitors are useful in patients receiving nasogastric suction.

RESPIRATORY ACIDOSIS

GENERAL CONSIDERATIONS

Respiratory acidosis is a frequently frustrating problem for patients with respiratory insufficiency. PCO_2 is normally kept within narrow limits by the respiratory center within the CNS. Chemoreceptors that respond to changes in PCO_2 are present in the medulla, close to the floor of the fourth ventricle, and in the carotid bodies. Both sites are stimulated by pH changes associated with alterations in PCO_2 . Normally, arterial PCO_2 is controlled primarily by the central chemoreceptors, which may have increased sensitivity because of concomitant hypercapnic peripheral chemoreceptor input. However, they may be suppressed by chronic hypoxia and hypercapnia, mostly in patients with severe COPD. When this happens, ventilation is maintained by the carotid bodies responding to alterations in PO_2 and pH. If PO_2 is raised excessively, carotid body output may be suppressed, leading to progressive hypercapnia and narcosis. Acute increases in PCO_2 are buffered by non- HCO_3^- buffers to form HCO_3^- , but HCO_3^- concentrations seldom exceed 30 mEq/L during the first 24 hours of hypercapnia. Increases in PCO_2 result in an intracellular acidosis within the renal tubular cells that favors acid excretion, and over the next few days, acid excretion is accelerated by a rise in NH_4^+ formation.

CAUSES

Any process interfering with ventilation can lead to respiratory acidosis (Table 7-6; see also Chapter 99). COPD is the most frequent cause of this problem, related primarily to mechanical conditions that decrease alveolar ventilation. Interstitial lung disease is less likely to increase PCO_2 values unless it becomes severe. Extensive infiltrative processes (including pneumonias and all forms of pulmonary edema) and large pleural effusions can decrease alveolar ventilation. With significant acute pulmonary artery embolic obstruction, wasted ventilation due to increased alveolar dead space can explain sudden increases in ventilation, or hypercapnia may ensue if ventilation cannot be increased. In such situations, dead-space ventilation may be measured directly by sampling both arterial blood and mixed expired gases. A paralyzed diaphragm or extensive rib fractures that lead to a unilateral flail chest can produce an inefficient mode of ventilation.

Hypoventilation is the most serious complication of a wide variety of neuromuscular disorders (see Table 7-6). The central respiratory centers may be depressed acutely or chronically by narcotics or by any process that injures the

Table 7-6 Causes of Respiratory Acidosis

CENTRAL NERVOUS SYSTEM DEPRESSION

Drugs: opiates, sedatives, anesthetics
Oxygen therapy in COPD
Obesity-hypoventilation syndrome
Central nervous system disorders

NEUROMUSCULAR DISORDERS

Neurologic: multiple sclerosis, poliomyelitis, phrenic nerve injuries, high cord lesions, Guillain-Barré syndrome, botulism, tetanus, amyotrophic lateral sclerosis
End plate: myasthenia gravis, succinylcholine chloride, curare, aminoglycosides, organophosphorus
Muscle: hypokalemia, hypophosphatemia, muscular dystrophy, polio

AIRWAY OBSTRUCTION

COPD
Acute aspiration, laryngospasm

CHEST WALL RESTRICTION

Pleural: effusions, empyema, pneumothorax, fibrothorax
Chest wall: kyphoscoliosis, scleroderma, ankylosing spondylitis, extreme obesity

SEVERE PULMONARY RESTRICTIVE DISORDERS

Pulmonary fibrosis
Parenchymal infiltration: pneumonia, edema

ABNORMALITIES IN BLOOD CO_2 TRANSPORT

Decreased perfusion: heart failure, cardiac arrest with cardiopulmonary resuscitation, extensive pulmonary embolism, severe anemia
Carbonic anhydrase inhibition—high-dose acetazolamide

brain stem, including chronic hypoxemia and hypercapnia. A complex disturbance of the respiratory center may be encountered in patients with the obesity-hypoventilation syndrome. Apneic episodes during sleep are common in these persons and are related to airway obstruction or to a central failure to initiate ventilation, or both.

Rarely, if cardiac output is low, if anemia is severe, and/or if certain drugs are used that interfere with the normal high efficiency of red cell carbon dioxide transport and exchange (see Table 7-6), carbon dioxide retention in the tissues may develop and yet not be reflected in the arterial PCO_2 .^{82,83} In fact, as carbon dioxide rises in the vicinity of the central chemoreceptors, ventilation may be stimulated sufficiently to cause a paradoxical arterial hypocapnia that can be mistaken as evidence of a primary respiratory alkalosis. If PCO_2 is measured in the venous circulation (mixed venous PCO_2), one will find an elevated PCO_2 and lower pH, revealing the true state of carbon dioxide homeostasis.

CLINICAL MANIFESTATIONS

If hypoventilation is caused by neuromuscular or mechanical problems, the patient will be dyspneic and tachypneic. In contrast, if the respiratory center is impaired, ventilation may be reduced without any sensation of dyspnea.

The physiologic and clinical consequences of respiratory acidosis tend to be more serious in acute than in chronic states. Elevations in PCO_2 cause systemic vasodilation that is particularly evident in the cerebral circulation. Cerebral blood flow and intracerebral pressures increase and may lead to a picture of pseudotumor cerebri with papilledema, retinal venous distention, and retinal hemorrhages. The

patient may complain of dyspnea and manifest myoclonic jerks, asterixis, tremor, restlessness, and confusion. Coma may be observed at PCO_2 values of 70 to 100 mm Hg when the onset of hypercapnia is abrupt. Significantly higher levels may be well tolerated in patients with chronic respiratory acidosis, who have much higher HCO_3^- concentrations from renal compensation. Peripheral vasodilation and increased cardiac output promote warm, flushed skin and a bounding pulse. Arrhythmias are observed occasionally. Mild increases in serum phosphate and K^+ and decreases in lactate and pyruvate have been described in acute respiratory acidosis, and serum Na^+ may increase modestly in both acute and chronic hypercapnia.

THERAPY

Treatment of respiratory acidosis depends on the restoration of adequate ventilation. In COPD, attention must be focused on bronchodilation, adequate oxygen supplementation, and relief of anxiety or other causes of an increased metabolic rate. Indiscriminate and uncontrolled administration of high concentrations of oxygen should be avoided. The phenomenon of oxygen-induced hypercapnia in these patients is usually observed in the emergency department and intensive care unit when patients present severely hypoxemic, already hypercapnic, and fatigued. Sudden correction of arterial hypoxemia causes further hypercapnia by a combination of three mechanisms: (1) by depression of a high hypoxia-driven peripheral chemoreceptor drive that causes more hypoventilation, (2) by relief of hypoxic pulmonary vasoconstriction in poorly ventilated lung regions that further reduces the ability of the lung to eliminate carbon dioxide as local perfusion to poorly ventilated regions increases, and (3) by saturation of hemoglobin with oxygen that causes previously buffered protons on deoxyhemoglobin to be released with subsequent generation of new carbon dioxide from HCO_3^- stores (Haldane effect). Low-flow oxygen generally suffices to increase PO_2 to satisfactory levels (60 mm Hg and arterial oxygen saturation [arterial SO_2] $\approx 90\%$); greater elevations are neither needed nor advisable. If the use of a ventilator becomes necessary, care must be taken that PCO_2 is not decreased by more than 10 mm Hg each hour to avoid life-threatening metabolic alkalosis. If opiates are responsible for central respiratory depression, the respiratory acidosis may be relieved by naloxone. Aminophylline acts as a respiratory center stimulant, but blood levels must be monitored carefully. Bicarbonate is generally contraindicated because it tends to decrease respiratory drive and increases carbon dioxide levels in the tissues.

“Permissive hypercapnia” with gradual increases in PCO_2 of 10%/hr to levels as high as 100 mm Hg may help mitigate lung damage by barotrauma associated with mechanical ventilation. This approach is frequently used in patients with acute lung injury, acute respiratory distress syndrome, neonatal respiratory failure, or asthma by hypoventilation with tidal volumes less than 7 mL/kg and plateau pressures less than 30 to 35 cm H_2O . The value of bicarbonate infusions to reverse acidosis in these patients remains uncertain. Permissive hypercapnia should be avoided in those with head trauma, increased intracerebral pressure, or cardiac dysfunction.

RESPIRATORY ALKALOSIS

GENERAL CONSIDERATIONS

Although respiratory alkalosis is a common disorder and at times is a serious prognostic sign, it seldom has a significant impact on the clinical status of patients and generally requires little in the way of specific therapy to reverse the hyperventilation directly. Changes in pH related to hyperventilation are quickly moderated by tissue buffering and, to a lesser extent, by release of lactic acid, as described earlier. However, HCO_3^- concentrations do not usually fall below 18 mEq/L acutely, and even with renal compensation, a HCO_3^- concentration below 16 mEq/L should raise the possibility of an independent metabolic acidosis.

CAUSES

It is convenient to divide the causes of respiratory alkalosis into three major categories: hypoxia, pulmonary diseases, and CNS disorders (Table 7-7). Both central (arterial) and peripheral (capillary) hypoxia are causes of hyperventilation. Decreases in arterial PO_2 stimulate the carotid bodies directly. In contrast, tissue hypoxia caused by decreased cardiac output, shock, severe anemia, or excessive hemoglobin oxygen affinity results in the production of lactic acid and other stimuli, which are sensed in blood by the carotid chemoreceptors and by other less well defined chemoreception in the affected tissues themselves. Acute ascent to altitudes greater than 8000 feet may lead to acute mountain sickness. Symptoms generally include dyspnea, malaise, headache, insomnia, anorexia, nausea, vomiting, periodic respiration, and tachycardia. These hypoxic manifestations diminish gradually over a few days with acclimatization.

Many pulmonary disorders are associated with hyperventilation. Hypoxia certainly plays a role but, in addition, receptors have been described in lung tissue that are

Table 7-7 Causes of Respiratory Alkalosis

CENTRAL NERVOUS SYSTEM STIMULATION

Hyperventilation syndrome, anxiety, pregnancy
Cerebrovascular disease, subarachnoid hemorrhage
Meningitis, encephalitis
Septicemia, hypotension
Hepatic failure
Drugs: salicylates, nicotine, xanthines, quetiapine, progestational hormones (and pregnancy)

EXCESS CO_2 REMOVAL

Mechanical ventilators
Acetate hemodialysis, heart-lung machine, extracorporeal membrane oxygenation

HYPOXIA

High altitude
Severe anemia, hemoglobinopathy
Decreased cardiac output

PULMONARY DISEASE

Pneumonia, interstitial fibrosis, pulmonary fibrosis, embolism, edema
Right-to-left shunt

DECREASED CO_2 PRODUCTION

Myxedema, hypothermia

activated by local irritant stimuli and fluid accumulation and remain activated even after hypoxemia has been corrected.

CNS disorders are among the most common causes of respiratory alkalosis. Anxiety can provoke hyperventilation (hyperventilation syndrome). Central stimulation of respiration is also common in a wide variety of intracerebral injuries. Many drugs and hormones (notably salicylates, theophylline, and progesterone) stimulate ventilation (see Table 7-7), and hyperventilation may be an early sign of both sepsis due to gram-negative bacteria and hepatic insufficiency due to the accumulation of ammonia and amines that are known to be responsible for respiratory center stimulation.

CLINICAL MANIFESTATIONS

Many manifestations of respiratory alkalosis may be related in part to a fall in free serum Ca^{2+} due to increased binding to serum proteins. Phosphate may also decline slightly and sometimes fall to rather low concentrations in patients who have prolonged severe respiratory alkalosis. It has been suggested that this decline in phosphate is related to activation of glycolysis and phosphorylation of the glucose metabolites thereby produced. Mild hyponatremia and hyperchloremia, as well as hypokalemia,⁷⁰ have also been reported in patients with acute respiratory alkalosis. Some of the CNS changes of acute respiratory alkalosis may be caused by hypocapnic cerebral vasoconstriction leading to reduced blood flow and tissue hypoxia. Often, deliberate hyperventilation is used to reduce cerebral blood flow in states of impending brain herniation from high intracranial pressure, but evidence is mounting that it is useful only for a few hours as a temporizing measure to allow more definitive pressure relief by other means.

Panic, weakness, and a sense of impending doom are common, as are paresthesias and muscle weakness or cramping. As in metabolic alkalosis, Trousseau and Chvostek signs can often be elicited, and overt tetany or seizures may follow, particularly in patients with previous seizure diatheses. Vision and speech may become impaired, and syncope can follow. Transient electrocardiographic changes can resemble those of myocardial ischemia; this finding can be particularly misleading because it is not uncommon for hyperventilating patients to complain of chest discomfort. Indeed, acute hypocapnia, for example with mechanical ventilation, can induce coronary artery spasm, angina, ominous cardiac arrhythmias, and ST elevations in patients with coronary artery disease. Acute respiratory alkalosis can increase serum chloride level and lactate and anion gap concentrations and reduce serum K^+ concentrations.

THERAPY

Reassurance and rebreathing in a small paper bag are frequently all that is needed to control hyperventilation associated with anxiety attacks. In more severe cases, β -adrenergic inhibitors have proved useful, and specific therapy for anxiety may be indicated. Administration of acetazolamide or corticosteroids before ascent to high altitudes may prevent acute mountain sickness in susceptible persons. Ventilation is stimulated by acetazolamide, but the mechanism by which corticosteroids work remains unknown.

Correction of respiratory alkalosis in other conditions, such as hepatic coma and pulmonary disorders, depends on treatment of the primary disorder. Carbon dioxide inhalation by patients with hepatic coma has not been helpful.

Key Points

- Clinical acid-base analyses should be consistent with the Brønsted-Lowry terminology, which has supplanted older definitions that are not sufficiently comprehensive or precise. The use of pH is preferable to hydrogen ion concentration for quantifying acidity.
- Arterial PCO_2 provides a suitable “respiratory” criterion for determining whether alveolar ventilation is appropriate for the rate at which carbon dioxide is produced in the body. Abnormalities in arterial PCO_2 may be “primary” causes of abnormal pH or “secondary” responses, which minimize pH disturbances.
- A “metabolic” disorder refers to a net accumulation or loss of nonvolatile acids and bases from the body and can be primary or secondary. Both the kidneys and other organs, including the gastrointestinal tract and skin, may be involved. No single parameter represents an ideal index of in vivo metabolic acid-base disorders, but the traditional use of HCO_3^- is probably the easiest to use for distinguishing among primary, compensatory, and mixed disorders.
- Incorporation of electrolyte concentrations into the analysis permits calculation of the anion “gap” and strong ion differences and identification of various processes involved in both metabolic acidosis and alkalosis. However, these measurements must always be accompanied by measurement of conventional acid-base parameters (pH_a , arterial PCO_2 , and HCO_3^-).
- Correction of the underlying metabolic or respiratory disorder represents the most effective way to treat the acid-base disorder.

Complete reference list available at [ExpertConsult](#).

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DEFENSE MECHANISMS AND IMMUNOLOGY

8

ALVEOLAR EPITHELIUM AND PULMONARY SURFACTANT

ROBERT J. MASON, MD • LELAND G. DOBBS, MD

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INTRODUCTION

The major function of the lung is to facilitate gas exchange between the air and blood compartments, which takes place in the alveolar region of the lung. In the adult lung, the alveolar-capillary barrier that permits efficient gas exchange is formed by thin cytoplasmic extensions of *alveolar type I* (TI) cells and capillary endothelial cells, separated by a common fused basement membrane.¹

The alveolar surface area comprises more than 99.5% of the large internal surface area of the lung,² estimated in the adult human to be approximately 100 to 150 m². Efficient diffusion of gases between the air and blood is dependent on the thin aqueous/lipid lining layer and the cellular compartments (epithelial, interstitial, and endothelial). Capillaries are located in the interalveolar septum that bridges different alveolar surfaces.³ On the air side, the alveolus is lined by two morphologically distinct epithelial cells, TI and *alveolar type II* (TII) cells. The morphologic and morphometric characteristics of both TI and TII cells are remarkably constant over an approximately 10,000-fold range in mam-

malian lung size,⁴ from which one may infer that there is a conservation of functions of both cell types. Although the distinctive anatomic features of alveolar cells permit the efficient diffusion of gases by forming a thin cellular barrier, alveolar epithelial cells have also evolved to perform other necessary functions, including producing pulmonary surfactant, maintaining an optimal alveolar liquid layer by regulating ion and water transport, protecting against inhaled toxins and infecting agents, and repairing the alveolar epithelium following lung injury or inflammation.^{4,5}

Pulmonary surface-active material (surfactant) is critical for normal lung function. Without surfactant, the work of breathing increases markedly and respiratory distress develops rapidly. In the absence of surfactant the work of breathing may increase from less than 2% to more than 10% of total oxygen consumption. Surfactant provides the low surface tension at the air-liquid interface that is necessary to prevent atelectasis, alveolar flooding, and severe hypoxia. A complex but highly regulated process has evolved for the synthesis, secretion, and reutilization of surface-active material. In addition to its well-recognized

property of providing alveolar stability, surfactant is also important for maintaining the patency of small airways and preventing alveolar flooding.

This chapter reviews the functions of TI cells and TII cells, the physiologic properties of pulmonary surfactant, the use of surfactant replacement therapy in the treatment of hypoxic respiratory failure (*newborn respiratory distress syndrome* [NRDS]), and the role of the alveolar epithelium and surfactant in selected lung diseases. Additional discussion of the alveolar epithelium can be found in Chapter 1, and comprehensive reviews of *acute respiratory distress syndrome* (ARDS) can be found in Chapter 100.

ALVEOLI

The number of alveoli in a lung is largely dependent on the size of the lungs, with larger lungs containing more alveoli. On average, Ochs and colleagues⁶ have estimated that the adult human lung contains approximately 480 million alveoli, each approximately 4.2×10^6 cu μ in size. Recently, the number of the alveoli in the mouse lung has been estimated to be 560 in young mice (12 weeks) and 880 in old mice (91 weeks); these estimates were derived by use of computed tomography imaging, a technique that is quite different from traditional stereology, and may allow quantitative measurements in disease and lung injury models.⁷ In the adult lung, the average alveolar fluid depth is estimated to be 0.14 to 0.20 μ m.⁸

ALVEOLAR EPITHELIAL INTERCELLULAR JUNCTIONS

Early physiologic studies⁹ demonstrated that transport of water and low-molecular-weight solutes out of the pulmonary capillaries is rapid, whereas transport of solutes out of the alveoli is extremely slow. The anatomic basis for the barrier function of the alveolar epithelium became clear from freeze-fracture studies of the lung^{10,11} that demonstrated that epithelial intercellular junctions had morphologic characteristics of “tight junctions,” in contrast to endothelial intercellular junctions that had morphologic characteristics of gap or “leaky” junctions.

Epithelial cells are attached to one another at their lateral membranes by a series of different junctional complexes, including tight junctions, adherens junctions, and gap junctions. These junctional complexes are each composed of different proteins that convey specific functions. Although both tight junctions and adherens junctions associate with the actin cytoskeleton, they have somewhat different functions; tight junctions regulate paracellular movement of ions and solutes, whereas adherens junctions mediate cell-cell adhesion and participate in cell signaling.

The most apical of the intercellular junctions is the tight junction or *zona occludens* (e.g., “closing belt”). By ultrastructural analyses, tight junctions appear as a series of anatomic appositions between the lateral membranes of adjacent cells that extend in a beltlike network surrounding cells, attaching them to adjacent cells and forming a continuous seal. The tight junction is the major factor in

determining paracellular permeability. In addition to the “barrier” functions that regulate the passage of water, ion, and various molecules through paracellular spaces, tight junctions also have a “fence” function, which prevents intermixing of proteins and lipids in the apical and lateral membranes, establishing cell polarity. The tight junction is composed of a dynamic complex of proteins that include transmembrane proteins, cytoplasmic scaffolding proteins, signaling proteins, and adaptors that link to the cytoskeleton. Claudins play key roles in forming tight junction strands and determining paracellular permeability.¹² Permeability can be further modulated by various other factors, including Rho-associated protein kinase, protein kinase C, and other kinases, as well as various cytokines, growth factors, and hormones.¹³

A second type of intercellular junction, the adherens junction, is located more basally. Adherens junctions are composed of clusters of adherens molecules, such as vascular endothelial-cadherin, β -catenin, and plakoglobin, linked to the actin cytoskeleton. There are also associations with kinases, phosphatases, and growth factor receptors. Complex intermolecular interactions mediate cell-cell adhesion and modulate cell signaling from growth factors and from mechanical forces such as sheer stress. Adherens junctions play important roles in both development and wound healing. The complex field of adherences junctions has been well reviewed.¹⁴⁻¹⁶

A third type of junction, the gap junction, is ubiquitous in most mammalian tissues. Gap junctions are composed of connexins, proteins that form intercellular channels, enabling the diffusion of molecules throughout interconnected cells, enabling cells to function in a coordinated measure. In the alveolar epithelium, gap junctions mediate intercellular calcium fluxes, which play a role in surfactant secretion.¹⁷

ALVEOLAR TYPE I CELLS

In the mammalian lung, TI cells comprise only approximately 10% of the cells in the alveolar region but cover more than 95% of the internal alveolar surface area; TII cells (\approx 18% of alveolar cells) cover the remaining less than 5% of the surface area.⁴ TI cells are large (surface area $\approx 7 \times 10^3$ sq μ m) squamous cells with thin cytoplasmic extensions that form the epithelial component of the air-blood barrier. The cytoplasmic extensions of TI cells are only 50 to 100 nm thick, below the resolution of conventional light microscopy. Prior to the development of the electron microscope, there was intense debate about whether the lining of the lung was cellular or acellular. Electron microscopic studies definitively demonstrated that the alveolar surface was lined by a continuous epithelium.^{18,19} TII cells are much smaller cells (\approx 30% of the volume and 3% of the surface area of TI cells) that are often, but not always, cuboidal in shape (Fig. 8-1).⁴ Both TI cells and TII cells are not necessarily confined to one side of the alveolar septum but can bridge two or three different alveoli¹⁹ (see Fig. 8-3B). These complex three-dimensional morphologic relationships may complicate simple interpretations of cellular function that assume distinct apical, basal, and lateral membrane domains.³

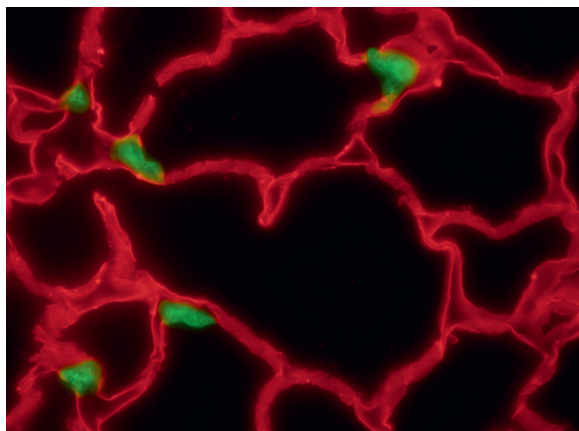


Figure 8-1 Immunofluorescent TI and TII cells in the mouse lung. The majority of the alveolar epithelial surface area is composed of TI cells. Transgenic mouse with TII cells expressing enhanced green fluorescent protein (green) and TI cells expressing rat podoplanin (secondary immunofluorescence, red). (J. Vanderbilt, L. Allen, and L. Dobbs, unpublished micrograph.)

We have learned a considerable amount about the biology of TII cells from the study of isolated and cultured TII cells and the development of transgenic mouse models. In contrast, techniques to isolate and study TI cells took many years to develop because of the lack of biochemical or molecular reagents to isolate and evaluate the cells and the fragility of isolated TI cells. Until fairly recently, the accepted concept was that the TI cell was a biologically inactive, terminally differentiated cell. However, recent evidence based on studies of isolated TI cells and gene expression profiling suggests that TI cells play important roles in numerous alveolar functions.

Many published images show only small portions of TI cells because of the large surface area of the cell and limited sampling area of electron microscopy. These images have given rise to an incorrect impression that TI cells do not contain either microvilli or subcellular organelles necessary for biosynthetic and other pathways. In fact, TI cells contain microvilli, abundant mitochondria, Golgi, rough and smooth endoplasmic reticulum, small intracellular vesicles, and caveolae, subcellular domains consistent with both metabolic and endocytic functions (Fig. 8-2).

More detailed analyses of the differences in TI cells and TII cells from both specific studies and gene expression profiling have provided some insight into the functional differences between the two cell types.^{20,21} For example, there are differences in the expression of intercellular junctional proteins. Both TI and TII cells express primarily three claudins (claudin-3, claudin-4, and claudin-18.1).^{22,23} Claudin-3 is associated with decreased barrier function, whereas claudins 4 and 18 are associated with increased barrier function. The proportion of each claudin is different between the two cell types.¹² In TI cells, the lung-specific claudin-18.1 constitutes more than 50% of claudin mRNA, whereas in TII cells, claudin-3 is the dominant claudin. Because TII cells contain approximately 20-fold more claudin-3 protein than do TI cells, it has been suggested that claudin-3 is localized mainly to TI-TII cell junctions and that TI-TII and TI-TI cell junctions may have different paracellular permeability characteristics; for example, it has been proposed

that TI-TII cell junctions are more permeable than the TI-TI cell junctions that constitute the majority of the alveolar epithelial surface.^{12,22} There may be other differences between TI-TI and TI-TII junctions. For example, in models of lung injury, neutrophils appear to migrate across the epithelial barrier selectively between TI and TII cells, although the molecular mechanisms responsible for this apparent selectivity are unknown.^{24,25}

Our concepts about alveolar fluid homeostasis have evolved over the past 10 years. Studies of clearance of exogenously added lung liquid demonstrate rapid clearance of liquid from the alveolar space, suggesting that clearance is mediated by Na^+ channels with a high conductance and/or large numbers of channels with a lower conductance. Ions are transported actively, with water following passively. The osmotic water permeability of TI cells is one of the highest found in mammalian cell membranes, suggesting that TI cells play a major role in passive water transport.²⁶ Presumably aquaporin 5, which is localized in the apical plasma membrane of TI cells,²⁷ is responsible for the high osmotic water permeability; the molecular basis for water transport across the basal surface remains unknown.¹⁴ TI and TII cells also differ in the content of certain ion channels. Studies with either freshly isolated TI and TII cells²⁸ or TII cells cultured under special conditions²⁹ demonstrated that both cell types contain high-conductance sodium channels. TI cells, unlike TII cells, contain *cyclic nucleotide gated* (CNG) channels and K^+ channels, and TII cells contain more *cystic fibrosis transmembrane conductance regulator* (CFTR) than do TI cells per unit area.²⁸ By immunohistochemical methods and Western blotting, TI cells contain the *epithelial sodium channel* (ENaC) and various subunits of the Na^+ , K^+ -ATPase.³⁰ In addition to high-conductance sodium channels, both cell types contain less selective Na^+ channels, although these are far less abundant.²⁸ In most species, less than half of fluid transport in the lung is inhibitable by amiloride^{31,32}; thus, it has been postulated that the amiloride-insensitive CNG channels are responsible for the bulk of transport. The importance of amiloride-insensitive sodium transport was recently reviewed by O'Brodovich and associates.³³ Although patch clamping data are consistent with the presence of CNG channels in TI cells but not TII cells, the presence of CNG channels in TII cells cannot be definitively excluded.

Whereas, in the adult, the epithelium from the alveolus to the nose is, in general, a sodium absorbing epithelium, in utero the alveolar epithelium actively secretes chloride into the developing airspace.^{8,34} Chloride secretion in the adult alveolar epithelium has not been clearly established and probably varies depending on microenvironmental conditions. However, human alveolar epithelial cells in vitro can be stimulated to secrete chloride.³⁵ Both TI cells (CFTR, $\text{Cl}^-/\text{HCO}_3^-$ anion exchanger, and voltage-gated Cl^- channels) and TII cells (CFTR) contain Cl^- channels, and TI cells have been shown to transport Cl^- .³⁶ In addition, the TII cell has a proton sodium exchanger that is likely important in acidifying alveolar fluid.^{8,37}

The pump linked to active sodium resorption is the Na^+ , K^+ -ATPase. It has been estimated that approximately 60% of unstimulated fluid transport in the lung is mediated through the $\alpha 2$ subunit of Na^+ , K^+ -ATPase, which is expressed in TI cells but not in TII cells.³⁸ Data at present

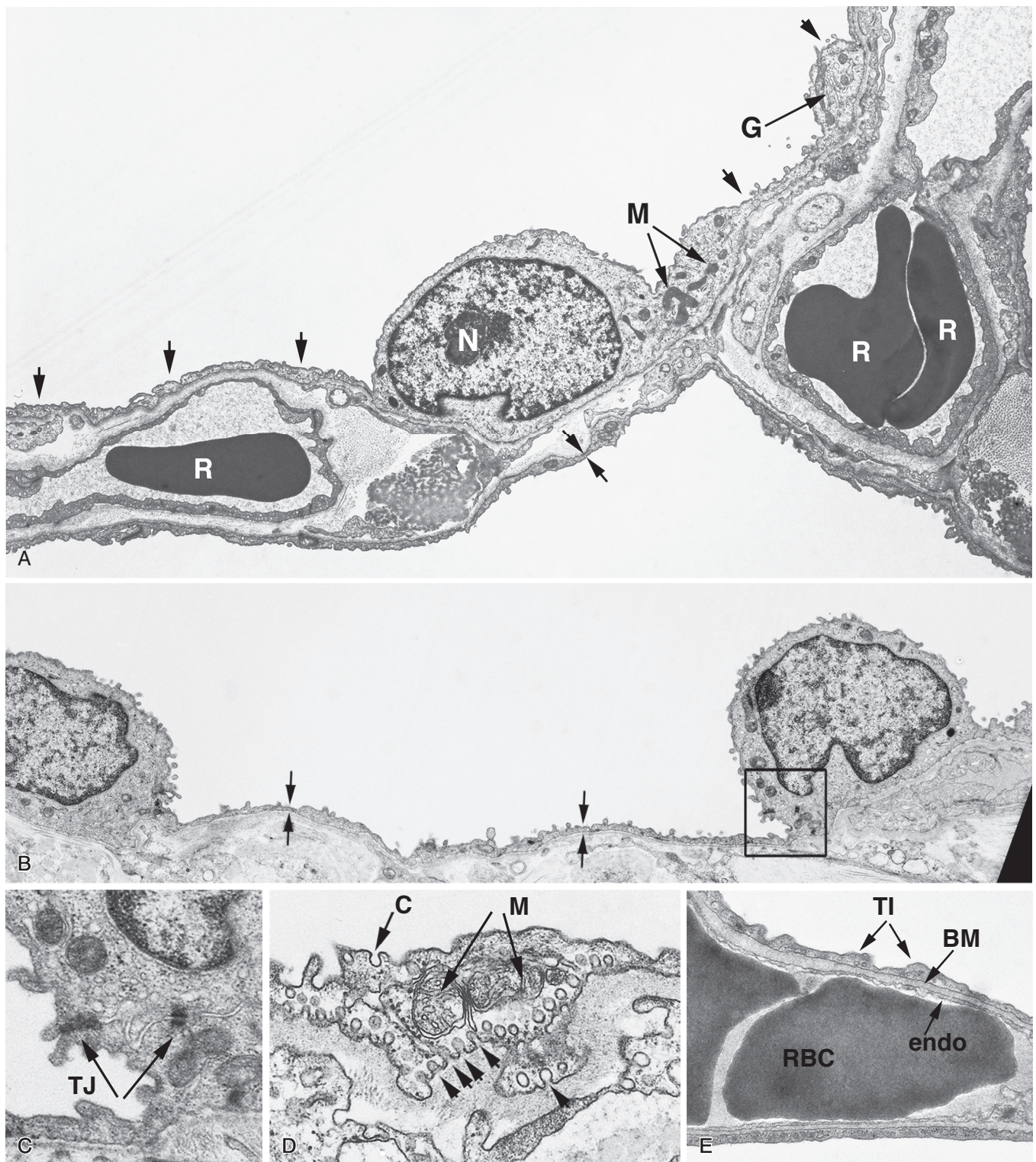


Figure 8-2 Alveolar septum and TI cells. **A**, Low magnification electron micrograph showing the alveolar area of the lung. A TI cell is in the center of the image; from the perinuclear area (N), thin cytoplasmic extensions (arrows) cover the alveolar surface. TI cells contain mitochondria (M) and abundant Golgi apparatus (G). Erythrocytes (R) can be seen in capillaries. Opposing arrowheads delineate the width of an extension of a different TI cell. **B**, The cytoplasmic extensions (arrows) of two different TI cells form a tight junction (boxed area). **C**, Higher magnification of the boxed area in panel B showing more detailed ultrastructure of the tight junction (TJ). **D**, Higher magnification view of a different TI cell showing mitochondria (M), flasklike membrane invaginations typical of caveolae (arrow, C) and other endocytic structures (arrowheads). **E**, Anatomic detail of the air-blood barrier, with thin extensions of a TI cell (TI, arrows) and an endothelial cell (endo, arrow) and the common basement membrane (BM) between the endothelial and epithelial compartments. The capillary contains erythrocytes (RBC). (Lennell Allen and L. Dobbs, unpublished micrographs.)

Table 8-1 Ratios of Various Transport Parameters in TI and TII Cells

	TI:TII Cell Ratio	References
Cell surface area	43	4
Osmotic water permeability	7	26
Na ⁺ and K ⁺ uptake/μg protein	≈3	30
Apical Na ⁺ channels/cell	≈40	28
CNG and K ⁺ channels	*	28
CFTR	6	28

*Present in TI cells, not TII cells.
CFTR, cystic fibrosis transmembrane conductance regulator; CNG, cyclic nucleotide gated.

support the hypothesis that ions and water are transported across the entire alveolar epithelium. Taken together, the large discrepancy in surface area between the cell types, the channel density per unit area (Table 8-1), the likely central role for CNG channels, and the relative importance of the $\alpha 2$ subunit of Na⁺-, K⁺-ATPase all suggest that the TI cell, rather than the TII cell, plays the major role in bulk fluid transport in the alveolar region.

The innate immune functions of TII cells have been well documented, but it is only recently that TI cells have also been shown to have potential immunomodulatory functions.³⁹ TI cells produce proinflammatory cytokines such as TNF- α , IL-6, and IL-1 β after treatment with *lipopolysaccharide* (LPS).⁴⁰ The production of cytokines in TI cells appears to be modulated by the renin-angiotensin system.⁴⁰

TI cells appear to be more susceptible to acute lung injury than are TII cells,⁴¹ and their cellular repair processes are relevant to restoring lung function after injury. TI cells contain abundant caveolae (see Fig. 8-2D) and express caveolin-1.⁴² Caveolae have diverse functions including endocytosis and membrane trafficking,⁴³ and, in addition, they are believed to play an important protective role by providing a source of membrane to protect against cellular lysis. Recent studies of TI cells injured *in vitro* have confirmed that membrane repair by lipid recruitment is facilitated by the caveolar endocytic pathway and by the remodeling of the actin cytoskeleton close to the site of wounding.^{44,45}

On the basis of studies in animal models of lung injury, it has been believed that the injured alveolar epithelium is repaired by proliferation and transdifferentiation of TII cells to TI cells, with TI cells regarded as terminally differentiated cells without proliferative potential.^{46,47} However, on the basis of recent *in vitro* studies, cultured TI cells have been shown to have a high proliferative potential.^{48,49} Both the potential proliferative capacity and phenotypic plasticity of the TI cell *in vitro* raise the possibility that TI cells *in vivo* may participate in lung repair after injury.

Some researchers have stressed the concept that pulmonary epithelium in the conducting airways can sense the environment (e.g., oxidant gases, cigarette smoke, nanoparticles) (see Chapter 10). If this is also true in the alveolus, then it likely that the TI cells, which cover nearly all the alveolar surface, will be shown to be important sensors of the environment.

ALVEOLAR TYPE II CELLS

TII cells were first comprehensively described by C. C. Macklin before the advent of electron microscopy.⁵⁰ Many of his initial predictions about the function of these cells have been verified over the past 60 years. In electron micrographs, TII cells are readily identified by the presence of lamellar bodies, the intracellular storage form of pulmonary surfactant (Fig. 8-3). The major functions of TII cells include: producing pulmonary surfactant, serving as the progenitor cells for maintaining the alveolar epithelium under normal circumstances and after mild injury, transporting fluid to keep the alveoli from flooding, and playing an important role in innate immunity. The high density of mitochondria and high glucose and oxygen consumption indicate that TII cells are highly metabolic. Because TII cells are the only source of surfactant, which is rich in phospholipids, lipid metabolism of the TII cells has been studied extensively.⁵¹ TII cells are highly enriched in genes involved in lipid synthesis.^{52,53} For example, TII cells can be identified in the lung by expression of two enzymes of lipid metabolism, fatty acid synthase and stearoyl CoA desaturase-1, as well as by expression of the traditional markers such as *surfactant protein* (SP) C.⁵² Lipogenesis is upregulated at the end of gestation and is regulated by the transcription factors sterol regulatory element binding protein-1c and CCAAT/enhancer binding protein (C/EBP) alpha, similar to other lipogenic cells.^{52,54} TII cells also are unique in expression of one of the surfactant proteins, SP-C, and the promoter for SP-C has been extremely useful for expressing or deleting genes in murine TII cells. However, while the TII cells express other surfactant proteins, SP-A, SP-B, and SP-D, these proteins are also expressed in nonciliated bronchiolar cells (club cells [Clara]) and at low levels in some extrapulmonary issues.^{55,56}

The turnover of TII cells in the normal, uninfamed lung is relatively slow. However, in response to injury to TI cells, TII cells proliferate rapidly to restore the epithelium. These TII cells become a transit-amplifying population.⁵⁷ The initial studies to demonstrate this relationship used oxidant injuries in rodents to identify the proliferating cells with titrated thymidine.⁵⁸⁻⁶² In these studies, there was an initial labeling of TII cells and, with time, the labeled cells differentiated into TI cells. More recently, the ability of TII cells to proliferate and transdifferentiate into TI cells was documented by lineage tracing techniques in mouse lung.⁴⁶ This recent report demonstrated that TII cells are the source of new TI cells and TII cells under normal conditions and under conditions of mild injury. Hence, TII cells can serve as a transient proliferating cell population to maintain the alveolar epithelium under normal circumstances. However, in response to severe injury such as after influenza or toxins specific to TII cells, other epithelial cells from the bronchioalveolar junction or terminal airways that express keratin V, α_6/β_4 integrin, or club cell secretory protein (Clara), can proliferate, migrate, and, in some circumstances, express SP-C.⁶³ These additional pathways have been reported in mice and, although they are not fully defined, may be important in ARDS. Although the precise regulation of the transition of the TII cell to TI cell phenotype is not known, bone morphogenic protein 2 and *transforming growth factor- β 1* (TGF- β 1) have been suggested as regulators of the TII cell

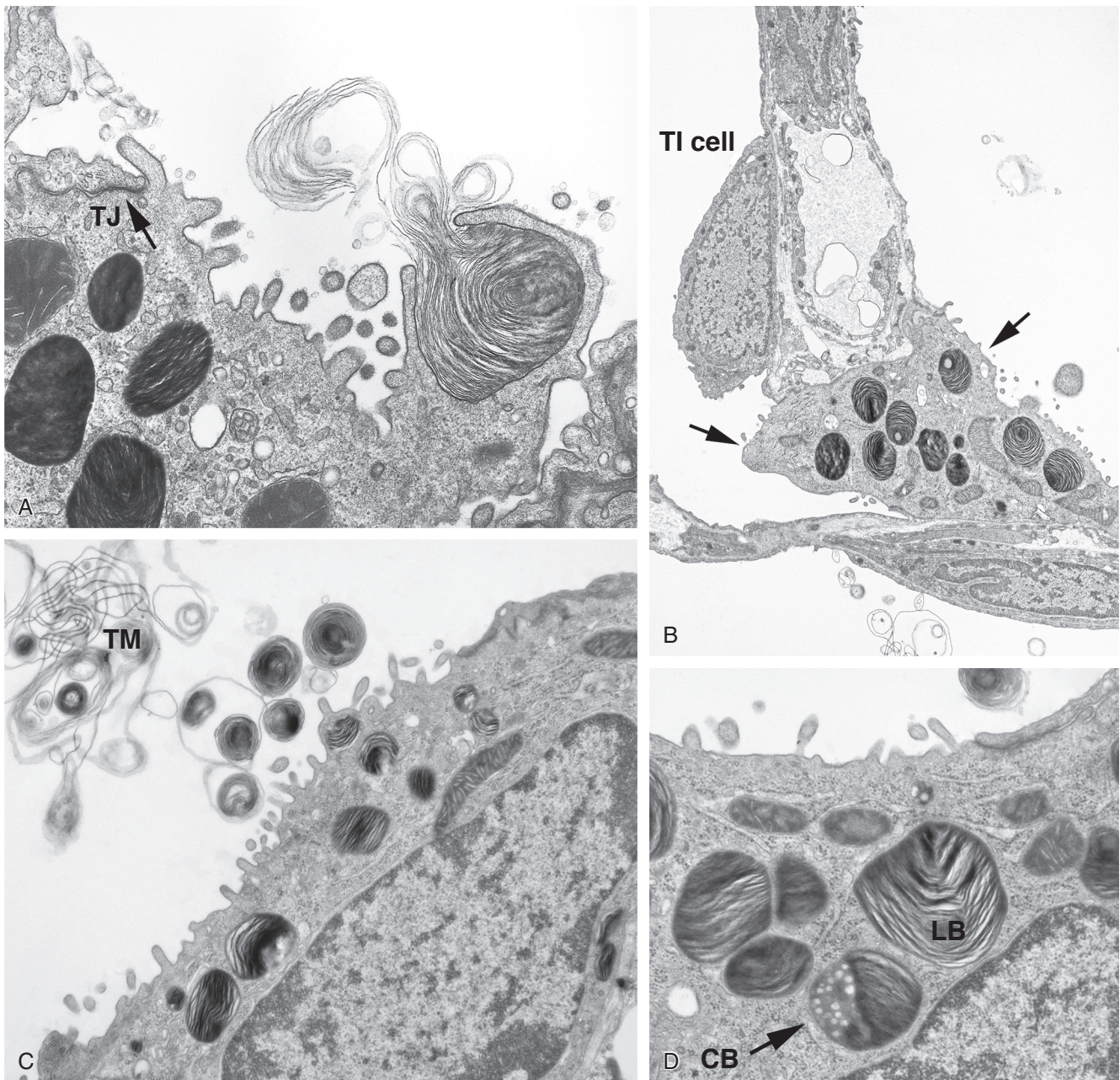


Figure 8-3 Alveolar epithelial TII cells. **A**, A portion of a TII cell, showing lamellar bodies, a portion of a tight junction (TJ, arrow) between TI and TII cells, and a lamellar body undergoing exocytosis. **B**, Alveolar epithelium showing a TII cell bridging two different alveolar surfaces (arrows) and the perinuclear region of a TI cell. **C**, A portion of a TII cell and secreted lamellar bodies and tubular myelin (TM) in the alveolar space. **D**, A portion of a TII cell with lamellar body (LB) and a composite body (CB). (Lennell Allen and L. Dobbs, unpublished micrographs.)

to TI cell transdifferentiation in vitro.⁶⁴ Keratinocyte growth factor and hepatocyte growth factor are also important mitogens for TII cells in vivo and in vitro.^{65-71,71a}

As stated earlier, alveolar TII cells can also transport sodium and chloride to help maintain alveolar fluid volume.^{72,73} This apical to basal surface fluid transport was first shown in vitro by the formation of *domes*, collections of fluid under the cells that lifted them up into a domelike structure.^{72,73} Under normal circumstances, TII cells resorb fluid by transporting sodium through amiloride-sensitive and amiloride-insensitive sodium channels, thereby keeping the alveolus relatively free of fluid.³³ However, under certain in vitro conditions, TII cells can also *secrete* chloride.³⁵ Unfortunately, defining the precise transport functions of

alveolar TII cells in vitro is compromised by the fact that the culture conditions employed to study transport do not maintain the TII cell phenotype, as determined by the loss of expression of cell differentiation-specific markers, such as the surfactant proteins.

Alveolar TII cells are also important in the initial innate immune response to environmental insults, such as air pollutants, toxins, bacteria, and viruses. Alveolar TII cells are part of the first responders when microbes and other toxic agents enter the alveolus. *Surfactant proteins A* and *D* (SP-A and SP-D) are important components of the innate immune system and are discussed in detail later in this chapter. SP-A and SP-D are multivalent *lectins* (i.e., proteins that bind to carbohydrates and can play numerous roles in biologic

recognition). Indeed, SP-A and SP-D can bind to a variety of viruses, bacteria, and fungi. However, TII cells can also be the target of specific respiratory viruses such as SARS-CoV and influenza.^{74,75} For example, if influenza is instilled into excised human lung, it mainly infects TII cells and does not infect TI cells.⁷⁶ In response to viral infection, TII cells secrete a variety of cytokines to activate macrophages, recruit monocytes, and trigger the adaptive immune system.⁷⁵ The dominant interferon produced by TII cells is interferon- λ (IL29), a type III interferon. The overall magnitude of the cytokine response is robust and similar to the response in alveolar macrophages. The major cytokines produced in response to influenza include CXCL10, IL6, RANTES, and IL29.⁷⁵ Microbes can be recognized by *pathogen recognition receptors* (PRRs), such as *Toll-like receptors* (TLRs). At the mRNA level, human TII cells have significant expression of TLR2, TLR3, and TLR5 but low expression of TLR4 and TLR7, similar to that in bronchial epithelial cells.⁷⁵ TII cells can also respond to *danger-associated molecular patterns* (DAMPs).⁷⁷

TII cells are thought to be important in various lung diseases.⁷⁸ In ARDS and models of acute lung injury, TII cells can repair the alveolar epithelium, although it is possible that other cell populations also participate in this process during severe injury.⁷⁹ TII cells are necessary for restoring the surfactant system, which is critical for gas exchange and for minimizing transudation of fluid into the alveolar space. In interstitial lung disease, TII cell hyperplasia is a common pathologic feature. One of the current hypotheses on the pathogenesis of *idiopathic pulmonary fibrosis* (IPF) is that the fibrotic response is caused by TII cell dysfunction due to protein misfolding and *endoplasmic reticulum* (ER) stress, which ultimately leads to secretion of TGF- β and other profibrogenic factors.^{80,81} Although some have considered an *epithelial mesenchymal transition* (EMT) to be an important part of the fibrotic response, this is unlikely to be important on the basis of recent lineage tracing studies.⁴⁷ Mutations of SP-A and SP-C are thought to cause some types of familial pulmonary fibrosis, and this is thought to be due to protein misfolding and endoplasmic reticular stress.⁸²⁻⁸⁶ Potentially more will be learned about the role of TII cells in interstitial lung disease when these cells are isolated from diseased lung. Finally, TII cells can be a source of adenocarcinomas.⁸⁷ Bronchioalveolar carcinomas and some adenocarcinomas likely arise in TII cells. Surfactant proteins and the transcription factor TTF1 have been used to differentiate lung adenocarcinomas from extrapulmonary sources and the presence of micrometastases in regional lung nodes in staging adenocarcinomas. In the mouse, urethane adenomas all express SP-C, which indicates that they are of TII cell origin⁸⁸ and adenocarcinomas induced by KRAS mutations are also of TII cell origin.⁸⁹

PHYSIOLOGIC FUNCTIONS OF PULMONARY SURFACTANT

The discovery of pulmonary surfactant came from direct physiologic observation and an understanding of the Laplace relationship for calculating surface tension. In 1929, von Neergaard⁹⁰ discovered that there was a differ-

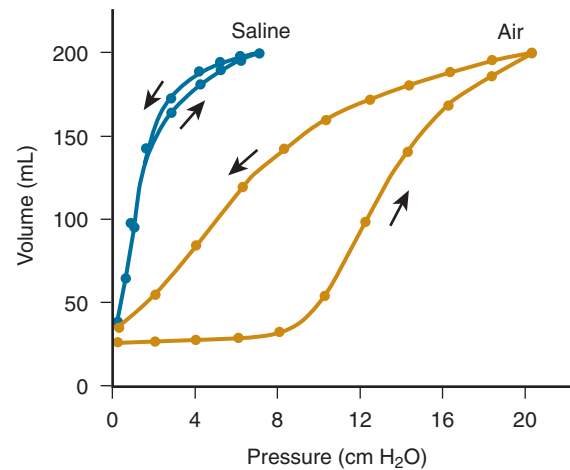


Figure 8-4 Air and saline volume-pressure curves. This figure depicts the classic physiologic observation that led to the discovery of surfactant. It takes more pressure to inflate the lung with air than with saline. However, the pressure difference is much less than would be expected if the alveolar lining had the same surface tension as other biologic fluids, which indicates the presence of a surface active material. The descending limb of the air volume-pressure curve is very reproducible and is used to estimate the surface tension of the lung and static compliance. (Adapted from Radford EP Jr: Recent studies of mechanical properties of mammalian lungs. In Remington JW, editor: *Tissue elasticity*. Washington, DC, 1957, American Physiological Society, pp 177–190.)

ence in the elastic recoil properties of the lung depending on whether the lung was inflated with air or saline so that it took more pressure to inflate a lung with air than with saline (Fig. 8-4). Even though it takes more pressure to inflate the lungs with air than with saline, von Neergaard⁹⁰ calculated that the pressure needed to inflate the lungs with air was much less than expected at low lung volumes. From these observations, von Neergaard deduced that the surface tension in the lung was low.⁹⁰ By studying extracts of lung, Clements and Pattle^{91,92} independently demonstrated that surfactant, specifically the phospholipids of surfactant, was responsible for lowering the surface tension. The low surface tension, produced by pulmonary surfactant, markedly decreases the work of breathing, prevents alveolar collapse and atelectasis, allows for alveoli of different size (radius of curvature) to be stable, and prevents alveolar flooding. Soon after these discoveries, Avery and Mead demonstrated that a deficiency in surface-active material caused NRDS.⁹³ The critical component of surfactant that provides the low surface tension is *dipalmitoylphosphatidylcholine* (DPPC). This is an unusual species of phosphatidylcholine in that both fatty acids are saturated. DPPC molecules can pack closely together and allow the surface monolayer to withstand the high film pressures required to produce a low surface tension at low lung volumes.^{93a}

Film pressure is the pressure required to maintain a surface film and is easiest measured and conceptualized in a Langmuir-Whilhem balance in which a moveable barrier is used to compress a surface monolayer. Compression of the surface balance reduces the area of the surface film similar to exhalation. Surfactant produces a stable film and is able to withstand high film pressures without collapsing. During inflation, surfactant must be absorbed into the surface. During deflation, as the surface area decreases, the film pressure rises and the surface tension falls.

Phospholipid molecules already present in the air-liquid interface get packed closely together. High film pressures squeeze some components of the film, such as unsaturated phospholipids and the surfactant proteins, out of the monolayer. The surface film generated at low lung volumes is thought to be composed of nearly pure (95%) DPPC.⁹⁴ Epi-fluorescence studies with hydrophilic markers have shown that, as the film is compressed, there are areas from which aqueous markers are excluded. Fixation of the lung with osmium vapors has shown that some of the alveolar surface is covered with multilayers of phospholipids, which serve as a reservoir of surfactant to enter the film at high lung volumes. The surfactant system provides a low surface tension in the alveoli and small airways but not in the large airways or trachea.^{95,96}

There are four surfactant-associated proteins, each of which has different functions. From *in vitro* studies on film formation, it is clear that SP-A, SP-B, and SP-C can increase the rate of delivery of phospholipids to the air-liquid interface; by itself, DPPC has an extremely low rate of adsorption to the surface. In addition, SP-A and SP-B were found to be necessary for the formation of tubular myelin (Fig. 8-5).⁹⁷ Tubular myelin is a unique extracellular form of surfactant, in which an organized lattice of surfactant bilayers is formed. These bilayers appear to form at right angles in both transmission electron micrographs and freeze fracture images.¹¹ Tubular myelin is the form of surfactant intermediate between the lamellar body, which is secreted, and the surface monolayer. Tubular myelin is a major component of large-aggregate surfactant, the form that sediments rapidly on centrifugation and is surface active. However, because SP-A-deficient mice lack tubular myelin and have normal respiratory mechanics, the formation of tubular myelin is not absolutely necessary for surfactant function.⁹⁸

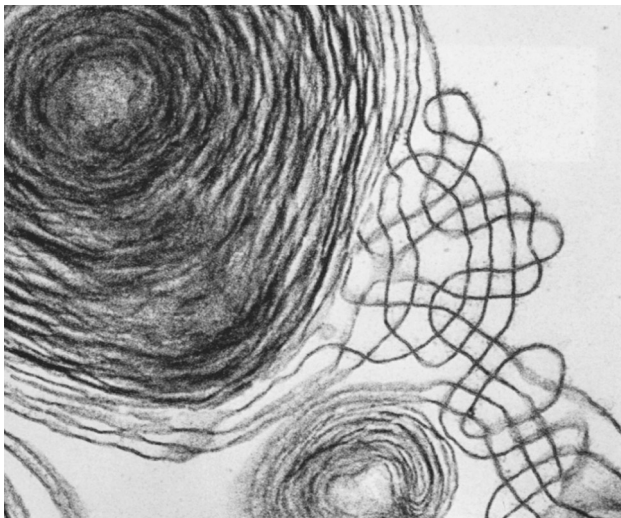


Figure 8-5 Tubular myelin. Pulmonary surfactant forms a unique three-dimensional structure composed of phospholipids and the surfactant proteins SP-A, SP-B, and presumably SP-C. Tubular myelin is found only extracellularly and is thought to represent a reservoir of surfactant that can rapidly adsorb into the air-liquid interface. Tubular myelin is isolated as a component of large aggregate surfactant, which is the fraction that sediments readily and is most surface active. (Electron micrograph courtesy Mary Williams, Boston University.)

The major physiologic function of surfactant is to lower surface tension and thereby provide alveolar stability, but surfactant has other functions as well.⁹⁹ Surfactant is important for maintaining the patency and stabilization of small airways.^{100,101} Studies in narrow fluid-filled tubes have demonstrated the critical importance of low surface tension and the need for added surfactant to reduce opening pressures. For this reason, surfactant is important in asthma, constrictive bronchiolitis, and other diseases of small airways. Finally, there is compelling evidence that SP-A and SP-D play important roles in host defense (see later).^{102,103}

COMPOSITION AND POOL SIZES

The critical components of purified surfactant are DPPC, unsaturated phosphatidylcholine, phosphatidylglycerol, and the surfactant proteins (Table 8-2).¹⁰⁴ In a variety of species, the quantity of saturated phosphatidylcholine is related to the alveolar surface area.¹⁰⁵ Phosphatidylglycerol is an anionic phospholipid that is thought to be important in the electrostatic and calcium-dependent interactions with the surfactant proteins. In lung injury, a reduction in the percentage of phosphatidylglycerol is the earliest and most sensitive alteration in the composition of surfactant. Recently, pure phosphatidylglycerol liposomes have been reported to have antiviral properties.¹⁰⁶ However, the phosphatidylglycerol found in mixed micelles with other phospholipids in natural surfactant likely does not have significant antiviral properties. The mechanism by which pool sizes of surfactant are regulated is not understood. However,

Table 8-2 Composition of Pulmonary Surfactant

PHOSPHOLIPIDS: 85%*	% OF PHOSPHOLIPIDS
Phosphatidylcholine	76.3
Dipalmitoylphosphatidylcholine	47.0
Unsaturated phosphatidylcholine	29.3
Phosphatidylglycerol	11.6
Phosphatidylinositol	3.9
Phosphatidylethanolamine	3.3
Sphingomyelin	1.5
Other	3.4
NEUTRAL LIPIDS: 5%†	
Cholesterol, free fatty acids	
PROTEINS: 10%‡	
SP-A	++++
SP-B	+
SP-C	+
SP-D	++
Other	

*The phospholipid composition is constant in most mammalian species.

Unsaturated phosphatidylcholine represents about two thirds of the total phosphatidylcholine. Dipalmitoylphosphatidylcholine makes up the majority species of the disaturated phosphatidylcholine fraction and is the critical molecule for providing the low surface tension.

†There is about 5% neutral lipid, most of which is cholesterol and free fatty acids. There is relatively little triglyceride and cholesterol ester.

‡The composition of the surfactant proteins is not known precisely, but on a mass basis there appears to be more SP-A than SP-D and more SP-A than SP-B and SP-C. However, there is significant uncertainty about the exact values for SP-B and SP-C.

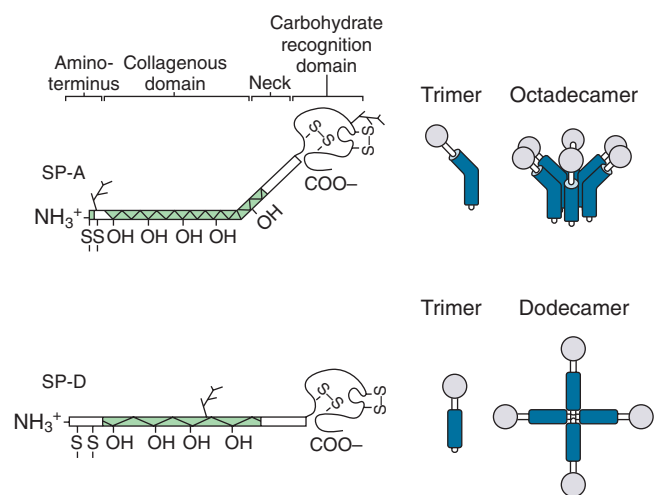


Figure 8-6 Structural organization of surfactant proteins A and D (SP-A and SP-D). SP-A (top) and SP-D (bottom) are collagenous glycoproteins with four important domains. The amino-terminal region contains cysteines for intermolecular disulfide bonding to form covalent oligomeric units. The collagen-like domain imparts structural rigidity and elongated molecular structure to both proteins. In SP-A, the collagen region has a kink, which accounts for the bend in the collagen region and the bouquet-like structure of the octadecamer. In SP-D, the collagen domain is straight and allows formation of a cross-shaped dodecamer. The neck contributes to the trimeric assembly of polypeptide subunits and spacing for the terminal carbohydrate recognition domain (CRD). The CRD is a globular region of the molecule that plays a major role in the recognition of multiple ligands. In SP-A, the CRD accounts for most of the binding to dipalmitoylphosphatidylcholine vesicles, TII cells, macrophages, and inhaled organisms. In SP-D, the CRD unit is responsible for all the reported interactions with viruses and bacteria. (Adapted from Kuroki Y, Voelker DR: Pulmonary surfactant proteins. *J Biol Chem* 269:25943–25946, 1994.)

recently it has been suggested that the TII cell senses the pool of surfactant via SP-D and the orphan receptor Hepta/GPR116.¹⁰⁷⁻¹⁰⁹ A major physiologic regulator of surfactant pool size is clearance by alveolar macrophages as discussed later in this chapter and in Chapter 70.

SURFACTANT PROTEIN A

SP-A was the first surfactant protein identified by its association with surfactant phospholipids (Fig. 8-6). SP-A is a large octadecameric protein with a molecular mass of about 650 kDa.^{110,111} SP-A is a collagenous glycoprotein with a complex, highly ordered tertiary structure. The overall organizational structure of SP-A is similar to serum mannose-binding lectin and the complement component C1q. These molecules form a polarized bouquet-like structure composed of 18 monomers that are organized as six trimeric units. The C-terminal *carbohydrate recognition domain* (CRD) is critical for most SP-A functions and consists of a globular domain that binds carbohydrate and other ligands recognized by SP-A. The structure of the CRD is highly conserved in this class of calcium-dependent lectins. The macromolecular structure of SP-A is 20 nm from the N-terminal to the C-terminal CRD unit and across the array of CRD units. The crystal structure has revealed a hydrophobic binding pocket in the CRD that likely accounts for the lipid binding properties of SP-A.¹¹²

SP-A is localized primarily in the gas-exchange units of the lung and small airways. In rodents, SP-A is found in

alveolar TII cells and also in nonciliated bronchiolar cells (club cells) that line the conducting airways. In humans almost all the SP-A is found in the alveoli, and little is found in the respiratory pseudostratified epithelium that lines the conducting airways. However, there is SP-A in human tracheal submucosal glands.¹¹³

The gene for SP-A is located on chromosome 10 near the closely related proteins, SP-D and mannose-binding lectin. Humans have two genes for SP-A, which code for proteins with minor amino acid alterations in the collagen domain.¹¹⁴ Newly synthesized SP-A undergoes a variety of posttranslational modifications that include proteolytic removal of the signal peptide, addition of N-linked carbohydrates, sialylation, acetylation, and sulfation. Secreted SP-A is highly glycosylated, whereas most of the intracellular form of SP-A is not. A number of factors have been reported to increase the synthesis of SP-A, including cyclic adenosine monophosphate (AMP), keratinocyte growth factor, and interleukin (IL)-1. Corticosteroids produce a biphasic dose response with stimulation at low concentrations and inhibition at high concentrations.

SP-A is secreted from TII cells by two different routes. The dominant route is by direct constitutive secretion independent of exocytosis of the lamellar bodies.^{115,116} In addition, there is secretion of SP-A contained within lamellar bodies. Directly secreted SP-A is newly synthesized, whereas the SP-A found in lamellar bodies is likely derived from recycled SP-A.

In vitro the functions of SP-A include lipid binding and formation of tubular myelin, acceleration of the adsorption of surfactant to the air-liquid interface, and inhibition of surfactant secretion. However, the physiologic importance of these in vitro observations on surfactant regulation has been seriously questioned because the SP-A-deficient mouse has normal surfactant function.^{98,117} More than 99% of SP-A in lavage fluid is bound to phospholipid.^{118,119} SP-A may also be important for maintaining the function of surfactant during acute lung injury, when a variety of serum factors can inhibit surfactant function; SP-A partially inhibits these effects.

However, the major function of SP-A appears to be in innate immunity; SP-A binds to a variety of microorganisms, promotes their clearance by phagocytic cells, and directly alters the function of immune effector cells.^{102,120,121} SP-A, like SP-D, is a multivalent pattern recognition molecule and binds to a wide variety of glycoproteins and other ligands. Because the binding is somewhat promiscuous with a low affinity, the physiologic effects of SP-A are likely due to its polyvalent structure and multiple binding sites on cells and organisms. It has been proposed that SP-A associated with tubular myelin might be one of the first barriers for host protection; multivalent SP-A could bind both surfactant lipid in alveolar fluid and inhaled organisms or particles.¹²²

SP-A binds to both gram-positive and gram-negative bacteria and is thought to be an important component of host defense. SP-A binds gram-negative bacteria with the rough form of LPS, aggregates these bacteria, and increases phagocytosis and killing.^{123,124} SP-A binds poorly to the smooth variants of *Escherichia coli*. Gram-negative bacteria that colonize the respiratory tract usually display the smooth form of LPS, whereas those that colonize the

gastrointestinal tract display rough forms of LPS. SP-A also enhances the adherence and subsequent phagocytosis of mycobacteria by macrophages. Lipoglycans, especially mannosylated lipoarabinomannan, are important ligands for SP-A on mycobacteria. SP-A also binds to a variety of viruses including influenza and respiratory syncytial virus and likely aggregates extracellular virus, which may inhibit infection.

SP-A has been reported to bind to several receptors on macrophages and to modulate the expression of microbicidal factors, TLR2 and 4, and the clearance of apoptotic cells.^{102,125,126} The binding of SP-A to alveolar macrophages appears to be specific and not seen to other mononuclear phagocytes as Kupffer cells, resident peritoneal macrophages, or peritoneal macrophages.¹²⁷ The studies on direct activation of inflammatory cells are complex and depend on the method of SP-A isolation and the state of the inflammatory cells, especially if they have been primed by a cytokine such as interferon- γ . In addition, for in vitro studies to simulate the in vivo situation, it is important that the effect of SP-A is assessed in the presence of surfactant phospholipids because SP-A may bind surfactant phospholipids with a higher affinity than microbes or inflammatory cells. Finally, some preparations of SP-A may have contained TGF- β , which could account for some anti-inflammatory properties.¹²⁸

SP-A appears to suppress the secretion of inflammatory cytokines by macrophages in the normal lung but enhances cytokine production during infection or lung injury. This is sometimes referred to as the *inflammatory paradox* of SP-A. Gardai and colleagues¹²⁹ formulated an interesting mechanism for these observations. In the normal setting, SP-A interacts with macrophages via its CRD domain and binds to signal-inhibitory regulatory protein α , which suppresses cytokine production. However, during infection, SP-A binds the invading organism with its CRD domain and instead interacts with macrophages via its N-terminal domain and binds to the calreticulin/CD91 complex to stimulate the production of inflammatory cytokines. Hence, SP-A can both stimulate and inhibit inflammatory cytokine production in vitro. It is important to recall that in vivo there is a complex interaction among SP-A, the phospholipids of surfactant, inhaled microbes, and receptors on inflammatory cells. Each has a different binding affinity for SP-A and independent regulation. Finally, SP-A has also been shown to bind to apoptotic cells and increase their uptake and removal by macrophages,¹²⁵ although SP-A appears to be less important than SP-D in the clearance of apoptotic cells in vivo (see Chapter 12).

Identifying functional cell receptors for SP-A and SP-D has been challenging because both are polyvalent lectins and can bind to a variety of glycoproteins and glycolipids.^{111,130} Receptors for SP-A are presumably on TII cells for surfactant recycling and on macrophages for surfactant clearance and modulation of the innate immune response. There have been several putative receptors on macrophages, including the calreticulin/CD91 complex, signal-inhibitory regulatory protein α , and SP-R210.^{131,132} The major functional receptor for SP-A on TII cells is P63 (CKAP4).^{130,133} Currently, we do not know the precise role of these receptors in normal surfactant metabolism or in disease.

SP-A also serves as a fetal hormone of parturition. Mendelson and colleagues¹³⁴ have suggested that the fetal lung secretes SP-A, which activates fetal macrophages that migrate to the uterine wall, where they produce IL-1 β and initiate labor.

SP-A-deficient mice have demonstrated the importance of SP-A in host defense for viral and bacterial pathogens.¹³⁵⁻¹³⁷ SP-A-deficient mice are more susceptible to infection by a variety of organisms. There are no reported genetic diseases due to the deficiency of SP-A in humans. However, there is a suggestion that mutation in SP-A may contribute to a familial form of pulmonary fibrosis.⁸⁵

In summary, SP-A is bound to pulmonary surfactant phospholipids in vivo and functions primarily in innate immunity and host defense.

SURFACTANT PROTEIN B

SP-B is the only surfactant protein that has been demonstrated to be crucial for surfactant function and is thought to be critical for the adsorption and surface spreading of phospholipids.¹³⁸⁻¹⁴⁰ Mature SP-B is a homodimer composed of two 79 amino acid polypeptide chains linked by disulfide bonds. The monomer has an expected mass of 8.7 kDa and the homodimer 17.4 kDa. Each monomer has five amphipathic helices that interact with the surface of the monolayer but do not span the monolayer. There are three internal disulfide bridges within the monomer (C8–C17, C11–C71, and C35–C46) and an interchain disulfide at C48.

There is one gene for SP-B that is located on human chromosome 2. The synthesis of SP-B is markedly stimulated by corticosteroids in vitro. This protein undergoes extensive intracellular processing before the mature homodimer is formed. Within the ER, the signal peptide is cleaved and a precursor 42-kD species of SP-B is formed. In multivesicular bodies, additional proteolysis removes a 16-kD amino terminal peptide and a 30-kD carboxy terminal peptide. The final processing of SP-B probably takes place within the multivesicular bodies, and the mature SP-B homodimer is formed by the time it arrives in the lamellar body.

SP-B is required for organizing phospholipids in lamellar bodies, for the formation of tubular myelin, and for delivering phospholipids to the alveolar air-liquid interface. SP-B is thought to be important in film formation and in the entry of phospholipids into the surface monolayer when the film is expanded during inspiration. The five amphipathic helices of SP-B are envisioned to lie along the lipid bilayer or surface monolayer.¹³⁸ SP-B interacts with phospholipid bilayers by electrostatic interactions between the polar head groups of the phospholipids and its positively charged amino acids and through the nonpolar faces of the amphipathic helices that interact with the phospholipid acyl chains. SP-B is positively charged and has a preference for interacting with negatively charged phospholipids, such as phosphatidylglycerol. This surfactant protein is squeezed out of the monolayer at moderate film pressures (40 to 45 mN/m) and does not insert directly into the monolayer or lipid bilayers. SP-B can convert lipid vesicles into phospholipid sheets and is likely to be important in moving lipid into the monolayer with each respiratory cycle.

Mice with homozygous null alleles for SP-B die of respiratory insufficiency shortly after birth, and heterozygotes have impaired surfactant function.^{139,141-143} In genetically targeted mice with conditional expression of SP-B, reduction of SP-B below 25% of the wild-type level results in respiratory failure.¹³⁹ As demonstrated in congenital SP-B deficiency in infants and in genetically altered mice, SP-B is absolutely required for the formation of highly structured lamellar bodies.¹⁴²⁻¹⁴⁵ SP-B is secreted exclusively as a component of lamellar bodies, and lamellar body formation may depend on the ability of SP-B to organize and bind two adjacent lipid bilayers. SP-B is found in natural surfactant preparations, although the content may vary from batch to batch and may differ from that found in surfactant isolated from normal animals. SP-B is also found in club cells (Clara), but the function of SP-B associated with club cells is not known. In SP-B deficiency, there is also aberrant processing of SP-C, which results in the secretion of a partially processed 12 kDa form of SP-C.

In summary, SP-B is a hydrophobic protein critical for the function of surfactant, and a total deficiency in SP-B is a cause of respiratory distress in the newborn. This form of respiratory distress is not responsive to surfactant replacement therapy and requires lung transplantation.

SURFACTANT PROTEIN C

SP-C is an extremely hydrophobic protein that is unique to surfactant and alveolar TII cells.¹⁴⁶⁻¹⁴⁸ SP-C is expressed only in the lung and is a highly specific marker for identifying TII cells. However, the precise physiologic function of this protein is not completely understood. The fully processed form of SP-C is a 35–amino acid lipopeptide that has two palmitates attached as thioesters at amino acids C5 and C6. The segment between residues 13 and 28 forms a hydrophobic α -helix containing aliphatic amino acids, mainly valine. This α -helix is the membrane-spanning portion of SP-C and is extremely stable. In most species, there are two positively charged amino acids, lysine at position 11 and arginine at position 12, which appear to be necessary to move the protein from the ER into the Golgi network, where it is palmitoylated. The precise orientation of the palmitates relative to the valine-rich α -helix is not fully resolved, but both regions are probably important for interactions with phospholipid bilayers or monolayers. SP-C can mix with phospholipids and promote spreading and fusion of phospholipids. SP-C inserts into the monolayer and is squeezed out of the surface monolayer only at relatively high film pressures (>55 mN/m). Presumably, SP-C is important in organizing the phospholipids during the respiratory cycle. SP-C is thought to stabilize the surface film and minimize film collapse. Unlike SP-B, SP-C does not appear to interact with SP-A and is not critical for the formation of tubular myelin. SP-C is found in all preparations of natural surfactant, and a recombinant form of SP-C is used in one type of surfactant replacement therapy.

In humans, there is one gene for SP-C that is located on human chromosome 8. Like SP-B, SP-C is synthesized as a larger precursor form of 21 kDa and processed by proteolytic cleavage of both N-terminal and C-terminal fragments. Most of the posttranslational processing has been com-

pleted before SP-C arrives at the lamellar body. There is apparently some interaction between the processing of SP-B and SP-C because, in hereditary deficiency of SP-B, an aberrantly processed 12 kDa form of a precursor SP-C accumulates in TII cells and in alveolar fluid. The SP-C promoter has been an important tool for overexpressing a variety of transgenes in TII cells in mice.

The physiologic role of SP-C is still not completely known. In one strain, SP-C null mice appear normal until about 6 months of age, at which time they develop chronic pneumonitis and air space enlargement.¹⁴⁹ This demonstrates that SP-C is not absolutely necessary for surfactant function. However, in another strain, mice develop chronic pneumonitis sooner, within 3 months.¹⁵⁰ The genetic background and disease-modifying genes are, therefore, likely involved in clinical manifestations of SP-C deficiency and mutations. Some SP-C mutations in humans also produce a misfolded protein that accumulates and causes ER stress in TII cells and a chronic interstitial lung disease.^{151,152} These observations provide the background for investigating genetic variants in SP-C as a cause of idiopathic interstitial lung diseases, which is discussed later.

In summary, SP-C is a hydrophobic protein that inserts into the surfactant monolayer but does not appear to be critical for surfactant function. However, mutations in this protein and total absence can result in interstitial lung disease. This is the one surfactant protein that is restricted to TII cells.

SURFACTANT PROTEIN D

SP-D is a calcium-dependent lectin and an important component of innate immunity.^{102,153-155} Recombinant SP-D has even been proposed as a therapeutic agent in the treatment of pulmonary infections. Serum SP-D is increased in interstitial lung diseases and may predict outcome in lung transplant recipients.¹⁵⁶ In humans, the gene for SP-D is located near the locus of SP-A on chromosome 10. SP-D is a collagenous glycoprotein with a complex but highly ordered tertiary structure (see Fig. 8-6). The primary structure consists of four domains. The N-terminal segment contains cysteines that form interchain disulfide bonds that cross-link subunits to form covalent oligomeric structures. The adjacent collagen-like region promotes the formation of noncovalent trimers, imparts a rigid longitudinal structure to the molecules, and organizes the spatial distribution of the C-terminal CRDs. The coiled-coil motif of the neck contributes to the spatial organization of the CRD domains. The C-terminal CRD domain contains the calcium and carbohydrate binding sites. The crystal structure of the CRD and neck region of SP-D has shown a distinct spatial distribution of the three CRDs, has defined the carbohydrate binding pocket, and has allowed for computer docking studies to demonstrate the importance of specific vinyl hydroxyl groups in sugars for binding.^{157,158} Identical monomers of SP-D assemble as trimers and then combine to form the final dodecamer, a large symmetric cruciform-shaped molecule with a distance of about 100 nm between the terminal CRDs, about five times larger than SP-A. The CRD unit is primarily responsible for the multivalent binding to surface ligands on microorganisms. As in the case of SP-A, the full oligomerization of SP-D appears to play an

important role in maintaining biologic potency that may result from specific spatial cross-linking of ligands, as well as amplification of relatively weak interactions through multiple binding sites.

Conceptually, SP-D should be thought of as a protein distinct from the surfactant system. SP-D binds the phospholipids of surface-active material weakly and is mostly soluble in alveolar fluid. However, SP-D does bind two lipids with carbohydrate motifs, phosphatidylinositol and glucosylceramide, but not phosphatidylcholine. The location of SP-D in the lung also suggests that it is not directly involved with the surfactant system. SP-D is found in ER of TII cells and in the secretory granules of club cells or nonciliated bronchiolar cells but not in lamellar bodies of TII cells or in tubular myelin. SP-D is highly expressed in the hyperplastic TII cells present in interstitial lung diseases. Like SP-A, SP-D is highly expressed in conducting airways of rodents but sparsely in the major conducting airways in humans. SP-D is also present on many other mucosal surfaces.^{56,159}

SP-D is an important host defense molecule and binds a variety of organisms, usually through its CRD domain.¹⁶⁰ In terms of monosaccharide binding, SP-D has a preference for maltose, glucose, and mannose. The binding of SP-D to organisms can be altered by physiologic glucose concentrations, and impaired binding in the presence of glucose may be important in diabetics.¹⁶¹ SP-D binds influenza A, inhibits hemagglutination, and inhibits infection.^{162,163,163a,163b} It is interesting to note that the annual severity of influenza infections is related to the ability of SP-D to bind to the circulating strains of influenza.^{163,164} Strains with less SP-D binding such as the 1918 H1N1 strain and the pandemic 2009 strain are clinically more virulent. Although studies on the interaction of SP-D with viruses have been reported for only a few viruses, it is likely that SP-D binds to many respiratory viruses. SP-D also binds to bacteria and should be considered an important molecule in host defense. SP-D binds both major components of gram-positive cell walls, peptidoglycan, and lipoteichoic acid.^{154,165} SP-D also binds to LPS and gram-negative bacteria with the rough form of LPS and aggregates these bacteria. SP-D also is likely important in defense against fungal infections. SP-D binds to *Aspergillus fumigatus* conidia and histoplasma and enhances their phagocytosis and killing. SP-D also binds to and agglutinates *Saccharomyces cerevisiae*, and the cell wall ligand for binding is β (1 \rightarrow 6) glucan.¹⁶⁶ This binding is inhibited by pustulan, an extremely effective competitive inhibitor of SP-D. SP-D also binds *Alternaria*, a common mold and aeroallergen, and SP-D may be important in clearing a variety of inhaled fungal spores. Finally, SP-D agglutinates *Mycobacterium tuberculosis* but inhibits its phagocytosis by human macrophages. Once in macrophages, SP-D promotes phagosome-lysosome fusion and thereby intracellular killing of mycobacteria.¹⁶⁷

SP-D has been reported to bind to several different receptors on macrophages and to stimulate microbicidal metabolism, as indicated by the production of reactive oxygen species.¹⁰² Rat SP-D enhances oxygen radical production by alveolar macrophages but not peritoneal macrophages.¹⁶⁸ However, there remain concerns that, in the early studies, the stimulation of macrophages by SP-D could be due to endotoxin contamination.¹⁶⁹ SP-D is also involved in the

clearance of apoptotic cells. SP-D binds to apoptotic cells and facilitates their ingestion by macrophages through the calreticulin and CD91 complex.^{125,170}

The phenotype of the SP-D knockout mouse was unexpected from prior in vitro studies. The knockout mouse shows an increase in the extracellular pools of surfactant and an accumulation of large foamy macrophages with excess metalloprotease activity, which results in alveolar wall destruction and subsequent air space enlargement.¹⁷¹ The implications are that SP-D assists in clearance of surfactant and regulates macrophage function. In addition, a large number of apoptotic cells are found in the air spaces and lavage fluid of SP-D null mice, indicating that SP-D has an important role in the clearance of apoptotic cells. SP-D-deficient mice are also susceptible to infection with various microbes, including influenza A virus and *Aspergillus*.^{136,172}

The interactions of SP-D and SP-A with organisms and phagocytic cells are complex, and the clear identification of the receptors for these proteins is awaited in order to sort out apparently conflicting observations. The interaction will be affected by the organism, growth cycle of the organism, phagocytic cell, and state of activation of the phagocytic cell, as well as the source of SP-A or SP-D and the presence or absence of contaminating endotoxin or TGF- β in the surfactant protein preparation.

In summary, SP-D is a host defense protein like mannose binding lectin and should not be considered as part of the surfactant system. The major functions of SP-D are the clearance of heavily glycosylated viruses such as influenza and the removal of apoptotic cells.

SECRETION AND EXTRACELLULAR PROCESSING OF SURFACTANT

Secretion of the phospholipid components of surfactant has been studied extensively (Fig. 8-7).¹⁷³ Turnover studies have demonstrated that the surfactant system is dynamic; 10% to 20% of the surfactant pool is secreted each hour.^{174,175} Secretion requires active extrusion of the lamellar body contents,¹⁷⁶ which involves fusion of the lamellar body limiting membrane with the plasma membrane.⁹⁷ Several different independent pathways for stimulating secretion work through different receptors and signaling mechanisms. In vivo secretion is stimulated by hyperventilation or even a single deep breath or sigh. Stretch is an important physiologic stimulation, which signals exocytosis through an elevation of intracellular calcium that may in part be stimulated by waves of calcium increases in neighboring cells transmitted through gap junctions.^{12,177} In vitro, tetradecanoyl acetate and adenosine triphosphate (ATP) greatly stimulate basal secretion. Agents that stimulate secretion via cyclic AMP-dependent pathways such as β -agonists and cholera toxin stimulate secretion more modestly. In vivo secretion is likely to be highly regulated, and multiple checks and balances may be present so that alteration in one pathway does not alter turnover.

After exocytosis by alveolar TII cells, the secreted lamellar bodies undergo physical rearrangements extracellularly (see Fig. 8-5). The initial change is the conversion from the

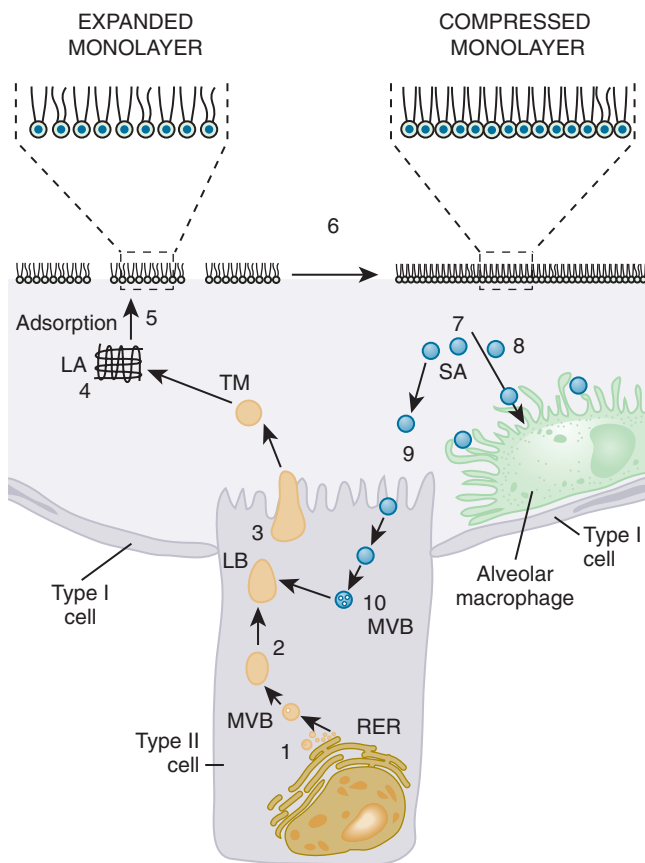


Figure 8-7 Metabolic trafficking of surfactant phospholipids. The phospholipids are synthesized in the rough endoplasmic reticulum (RER) of the alveolar TII cell (1). They are transported to the multivesicular bodies (MVB) (2), where the first lamellae are formed. These lamellae increase to form lamellar bodies (LB), which are subsequently secreted by exocytosis (3). The secreted lamellar body unfolds to form tubular myelin (TM) (4) and other large aggregates (LA). These forms adsorb into the expanded surface monolayer (5). This is a critical step for producing a low surface tension in the alveolus. During the respiratory cycle, as the film is compressed during exhalation, the film pressure rises, and a compressed, closely packed monolayer of nearly pure dipalmitoylphosphatidylcholine is formed (6). Material is excluded from the monolayer (7) and forms small aggregates (SA). Some of these aggregates are ingested by macrophages (8), but most are endocytosed for reprocessing by alveolar type II cells (9 and 10).

multilamellar state to tubular myelin (see Fig. 8-7). This requires SP-A, SP-B, and calcium and can be reproduced *in vitro*.⁹⁷ In lavage samples, *large aggregate* (LA) surfactant can be isolated by differential centrifugation. These aggregates contain SP-A and SP-B and are composed of tubular myelin, multilamellar structures, and other loose lipid arrays, which are the expected forms of secreted and unraveling lamellar bodies. LA adsorbs rapidly to the air-liquid interface and can be considered an extracellular reservoir of surfactant. LA can be converted into *smaller aggregates* (SAs), which are much less surface active. These SAs are thought to represent surfactant that has left the air-liquid interface and are available to be taken up by TII cells and reprocessed. The two dominant routes for the catabolism of surface-active material are uptake by TII cells and catabolism by alveolar macrophages.¹⁷⁴ The current estimates are that about 85% of secreted surfactant is recycled by adult TII cells and about 15% is catabolized by macrophages.^{178,179}

Relatively little pulmonary surfactant goes up the mucociliary escalator, and very little enters the bloodstream or lymphatics. Catabolism of extracellular surface-active material is regulated by *granulocyte-macrophage colony-stimulating factor* (GM-CSF) and its ability to activate macrophages.¹⁸⁰ The autoimmune alveolar proteinosis syndrome is caused by an autoantibody to GM-CSF^{181,182}; some pediatric forms of alveolar proteinosis are due to mutations in the receptor for GM-CSF.^{183,184} The extracellular pool of surfactant appears to be regulated predominately by alveolar macrophages. Deficiency in macrophages or inhibition of their state of activation impairs surfactant clearance and leads to the accumulation of surfactant in the alveolar spaces (see Chapter 70 for additional details).

SURFACTANT ABNORMALITIES IN LUNG DISEASE

PRIMARY SURFACTANT DEFICIENCY OF THE NEWBORN

The importance of the pulmonary surfactant system in the pathophysiology of the NRDS was first reported by Avery and Mead in the late 1950s.⁹³ The observation that NRDS was due to a primary surfactant deficiency has been confirmed by the tremendous impact that exogenous surfactant administration has had on infant mortality.^{185,186} The incidence of NRDS varies with gestational age and birth weight. Approximately 15% of infants born between 34 and 37 weeks (<1700 g) develop NRDS, whereas 50% of infants between 30 and 34 weeks (<1500 g) and 70% of those born at less than 30 weeks (<1250 g) develop this disease. These rates may also be influenced by other factors, including race, gender, socioeconomic status, and maternal health.

Even though artificial ventilation and exogenous surfactant have decreased infant mortality, there still exists a major disability rate among the survivors, particularly in the infants of very low birth weight. Amniotic fluid surfactant analysis reliably predicts the risk of NRDS. Pathologic changes typical of NRDS include widespread atelectasis, capillary congestion, micro-hemorrhage, edema, and the presence of hyaline membranes.⁹³

Fujiwara and colleagues¹⁸⁷ reported the first successful use of exogenous surfactant in neonates with NRDS in 1980. Several large clinical trials demonstrated significant improvement in gas exchange, decreased barotrauma, and decreased infant mortality in response to this therapy. Results of these trials have also shown that surfactant administered prophylactically (i.e., before the first breath) is superior to surfactant given after a period of ventilation. These differences were particularly notable in the infants of very low birth weight (<28 weeks of gestational age) and thus, prophylactic treatment is reserved for infants in this group. Otherwise, surfactant should be administered once the diagnosis of NRDS is established, usually within 30 minutes after birth. The usual dose of surfactant administered to these infants is approximately 100 mg phospholipid/kg body weight. Although surfactant therapy is effective for NRDS, approximately 30% of affected infants do not respond to this therapy.

HEREDITARY SURFACTANT PROTEIN B DEFICIENCY

Although most cases of NRDS result from immaturity, there are inherited forms specifically due to SP-B deficiency.¹⁸⁸⁻¹⁹² Associated abnormalities include aberrantly structured tubular myelin, a decreased number of lamellar bodies, and an abnormal processing of the SP-C protein. Regardless of gestational age, affected patients develop respiratory distress in the first few days of life that is refractory to all therapy, including surfactant supplementation. These infants usually die in the first few months of life, unless they receive a lung transplant. Although the most common abnormality involves a 1-bp deletion and 3-bp insertion in codon 121 in exon 4, which results in a premature stop codon, other mutations can also lead to respiratory failure. The heterozygotes, representing about 1 in 3000 individuals in the general population, would be predicted to have about half the SP-B level and might be more susceptible to ARDS. In mice about 20% of wild-type SP-B is required for normal ventilatory function, but more than 50% of SP-B may be necessary to protect against susceptibility to acute lung injury. NRDS also results from other deficiencies in surfactant synthesis and assembly. The most common deficiency is of the *ATP-binding cassette family member A3* (ABCA3), a lamellar body phospholipid transport protein.^{190,191,193-195} *Thyroid transcription factor 1* (TTF-1) deficiency also produces respiratory failure in infancy accompanied by thyroid and neurologic abnormalities.^{196,197}

HEREDITARY SP-C DEFICIENCY AND MUTATIONS

Deficiency of SP-C would not be expected to produce acute respiratory failure. In mice SP-C deficiency causes diffuse nonspecific chronic interstitial pneumonitis over months to years and depends on the genetic strain. A splice site mutation in intron 4 of the SP-C gene produces chronic interstitial lung disease with an autosomal dominant inheritance pattern.^{189,198,199} Recently additional cases of nonspecific interstitial pneumonitis and usual interstitial pneumonitis have been reported with a single gene mutation.²⁰⁰ This kindred also showed an autosomal dominant inheritance pattern. The hypothesis is that the mutations cause a misfolded SP-C protein, which accumulates and produces ER stress and chronic lung disease. The same genetic abnormality may have a variable phenotype, which indicates the importance of other disease-modifying genes.

ACUTE RESPIRATORY DISTRESS SYNDROME

Early descriptions of ARDS suggested that surfactant abnormalities play an important role in the lung dysfunction. Petty and Ashbaugh²⁰¹ recorded abnormal pressure-volume curves in lungs isolated from patients dying of ARDS. Morphologic changes noted in the lung tissue of these patients at autopsy were similar to those of preterm infants suffering from NRDS. The clinical criteria used to diagnose ARDS, including severe hypoxemia, decreased lung compliance, and bilateral infiltrates on chest radiograph, are also similar to those used to diagnose NRDS. As opposed to a primary

deficiency of surfactant, however, ARDS is much more complex, with many different etiologies and an inflammatory cascade resulting in lung injury and alveolar edema. The alveolar epithelium is severely damaged in ARDS, whereas the alveolar epithelium is relatively intact at the onset of NRDS.

Extensive animal studies and several human reports characterizing surfactant alterations in ARDS and acute lung injury have shown a decrease in the percentage of phosphatidylcholine, phosphatidylglycerol, and DPPC and a corresponding increase in phosphatidylinositol, sphingomyelin and, in some cases, lysophosphatidylcholine.²⁰²⁻²⁰⁴ Decreased levels of SP-A and SP-B have also been demonstrated in *bronchoalveolar lavage* (BAL) samples from patients with ARDS, and the surface tension-lowering properties of the isolated surfactant are abnormal.²⁰³ These abnormalities correlated with the severity of ARDS. BAL samples isolated from patients with severe ARDS also show a decrease in LA surfactant and an increase in poorly surface-active SA. In animal models of acute lung injury, there is a severe reduction of surfactant protein gene expression at the onset of respiratory insufficiency.²⁰⁵ With increased alveolar permeability in patients with ARDS, a number of proteins enter the air space and bind surfactant phospholipids and proteins or directly compete with surfactant molecules for space at the air-liquid interface. Interestingly, this nonstoichiometric inhibition of surfactant by plasma proteins can be overcome *in vitro* by increasing the concentration of surfactant. This observation provides rationale for administering large doses of exogenous surfactant to patients with ARDS. Thrombogenic components leaking into the airspace can also coagulate and incorporate surfactant phospholipids into fibrin clots, thereby rendering the surfactant inaccessible to the air-liquid interface. Surfactant inactivation has also been described due to an increase in the neutral lipids, primarily cholesterol. Another mechanism contributing to surfactant dysfunction in ARDS involves the increased conversion of LA into SA. *In vivo* studies have shown that increased tidal volumes, but not respiratory rates or *positive end-expiratory pressure* (PEEP) levels, correlated with an increased conversion of LA into SA²⁰⁶ and with physiologic deterioration. Minimizing these phasic changes in surface area by means of smaller tidal volumes allows surfactant to be maintained in LA forms and results in improved physiologic outcomes.²⁰⁶ These findings are supported by clinical trials demonstrating improved patient outcomes when lower tidal volumes are used in treating patients with ARDS.^{207,208}

Exogenous surfactant administration has been shown to improve oxygenation but not mortality in patients with ARDS.^{209,209a} A few large multicenter clinical trials have evaluated this therapy and have shown disappointing results.²¹⁰⁻²¹² Presumably, the complexity of ARDS is not addressed by administering exogenous surfactant alone.

INTERSTITIAL LUNG DISEASES

In addition to diseases involving acute alveolar inflammation, alterations in surfactant have also been characterized in various interstitial lung diseases. Decreased levels of DPPC and phosphatidylglycerol, increased levels of phosphatidylinositol, and reduced levels of SP-A have been

observed in BAL fluid from patients with IPF.²¹³⁻²¹⁵ The reduction in SP-A in BAL fluid is found in a variety of diffuse interstitial lung diseases. The ratio of SP-A to phospholipid, used to correct for recovery of total surfactant, is reduced in patients with IPF. In addition, Günther and colleagues²¹⁶ demonstrated that biophysical properties of surfactant are impaired in IPF.

SP-A and SP-D have also been measured in serum and may serve as biomarkers of lung disease, especially when alveolar epithelial integrity is compromised. Serum concentrations of SP-A and SP-D are increased in patients with alveolar proteinosis, ARDS, and IPF.^{214,217,218} Measuring SP-A and SP-D in serum might be useful in the diagnosis of alveolar proteinosis because, together with a highly specific image on high-resolution computed tomographic scanning, high levels of SP-A and D might obviate the need for a biopsy. A small subset of patients with familial pulmonary fibrosis has been attributed to SP-C mutations. Most of the cases have a histopathologic diagnosis of nonspecific interstitial pneumonia, but a few have the morphologic features of usual interstitial pneumonia.²⁰⁰ Mutations in the gene coding for SP-A2 have been also reported to be associated with interstitial lung disease and lung cancer.²¹⁹

OBSTRUCTIVE LUNG DISEASES

The role of surfactant as a down-regulator of inflammation and the importance of surfactant in maintaining the openness of conducting airways suggest that surfactant alterations may be important in obstructive lung diseases.^{101,220} BAL samples from patients with asthma showed decreased SP-A levels and a normal phospholipid composition.¹¹⁹ No surfactant alterations have been demonstrated in patients with chronic bronchitis or emphysema.

Cystic fibrosis is characterized by colonization of both gram-negative and gram-positive bacteria and early airway inflammation. Both SP-A and SP-D are reduced in BAL from patients with cystic fibrosis, and the relative deficiency could contribute to bacteria colonization.²²¹

OTHER LUNG DISEASES

Autoimmune alveolar proteinosis has been shown to be a disease produced by an antibody to GM-CSF, which results in decreased macrophage clearance of surfactant (see Chapter 70 for more information).^{181,182} Alveolar phospholipids and surfactant proteins SP-A, SP-B, and SP-D are markedly increased in the BAL from affected patients. Serum SP-A and SP-D are also increased in these patients.^{214,218} Decreased catabolism of surfactant results in an excess accumulation of multilamellated structures within the alveoli. Effective treatment involves removing this material through whole lung lavage and/or treatment with exogenous GM-CSF. Pediatric forms of alveolar proteinosis can be due to alterations in GM-CSF signaling, usually due to alterations in the GM-CSF receptor.^{183,184} Other forms of genetic impairment of macrophage function in mice lead to an alveolar proteinosis syndrome.²²²

The ischemia-reperfusion injury associated with lung transplantation results in alterations in pulmonary surfactant similar to those observed in patients with severe ARDS. Surfactant administered shortly after transplantation and

reperfusion results in improved gas exchange in comparison with non-surfactant-treated lungs. Moreover, when surfactant is administered to donor lungs before storage, longer storage times are tolerated (up to 38 hours) with relatively better physiologic function after reperfusion.

Measurement of SP-A and SP-D in pleural fluid might also be useful to distinguish metastatic adenocarcinoma of the lung from other adenocarcinomas or mesothelioma.²²³ In addition, surfactant protein gene expression can be used to screen for micrometastases in lymph nodes.²²⁴ In mice with pulmonary adenomas, serum SP-D correlates extremely well with tumor size.²²⁵

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Key Points

- Alveolar type I epithelial cells cover about 95% of the alveolar surface of the normal lung, are critical for effective gas exchange, participate in transepithelial fluid movement, and play a role in innate immunity.
- Alveolar type II epithelial cells cover about 5% of the alveolar surface in the normal lung, produce pulmonary surfactant, participate in transepithelial fluid movement, are the precursors of type I cells in normal injury and repair, and play a role in innate immunity.
- Pulmonary surfactant allows for the low surface tension in the gas-exchange portions of the lung and prevents atelectasis, decreases the work of breathing, improves oxygenation, and helps maintain patency of small airways.
- Surfactant protein B is the only surfactant protein critical to surfactant formation in vivo.
- Mutations in the genes encoding SP-A, SP-B, and SP-C can lead to parenchymal lung disease.
- SP-A and SP-D are polyvalent lectins (i.e., proteins that bind to carbohydrates) and are thought to be important components of innate immunity. They bind to both microorganisms and inflammatory cells.
- Surfactant replacement therapy in neonatal respiratory distress syndrome improves survival, whereas replacement therapy in acute respiratory distress syndrome improves oxygenation but not survival.

Complete reference list available at *ExpertConsult*.

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ALVEOLAR EPITHELIUM AND FLUID TRANSPORT

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INTRODUCTION

This chapter discusses how the distal lung epithelium regulates lung fluid balance by active ion transport mechanisms across both the alveolar and the distal airway epithelium. Both experimental models of pulmonary edema and clinical studies are considered to illustrate how active sodium and chloride ion transport regulate the resolution of alveolar edema. Some of the material in this chapter has been included in recent reviews.¹⁻³

For many years it was generally believed that differences in hydrostatic and protein osmotic pressures (Starling forces) accounted for the removal of excess fluid from the air spaces of the lung. This misconception persisted in part because some experiments that measured solute flux across the epithelial and endothelial barriers of the lung were done at room temperature⁴ and the studies were done in dogs, a species that turned out to have a very low rate of active sodium and fluid transport.⁵ Although the removal of interstitial pulmonary edema by lung lymphatics and the lung microcirculation was known for a long time,⁶ there was no information on how pulmonary edema was removed from the distal air spaces of the mature lung. Insights into the contribution of active ion transport came from experimental studies of the clearance of alveolar fluid in the mature lung and at the time of birth as well as the development of culture systems to study pulmonary epithelial cells.

LUNG EPITHELIAL FLUID ABSORPTION

With few exceptions, the general model for transepithelial fluid movement is that active salt transport drives osmotic water transport. This paradigm is also correct for fluid clearance from the distal air spaces of the lung.^{7,8} The results of several in vivo studies demonstrated that changes in hydrostatic or protein osmotic pressures cannot account for the removal of excess fluid from the distal air spaces. Furthermore, pharmacologic inhibitors of sodium transport can reduce the rate of fluid clearance in the lungs of several different species, including the human lung.⁹ In addition,

there is good evidence that isolated epithelial cells from the distal air spaces of the lung actively transport sodium and other ions, resulting in osmotic water absorption of fluid from the distal air spaces of the lung.

The large surface area of the alveoli favors the hypothesis that most fluid is reabsorbed at the alveolar level, although fluid may be actively reabsorbed across all of the different segments of the pulmonary epithelium of the distal lung. The precise contribution of each anatomic segment in the distal air spaces to fluid reabsorption is not firmly established. The distal airway epithelium is composed of terminal respiratory and bronchiolar units containing polarized epithelial cells that have the capacity to transport sodium and chloride, including ciliated cells and nonciliated cuboidal club cells (Clara). The alveoli themselves are composed of a thin alveolar epithelium (0.1 to 0.2 μm) that covers 99% of the air space surface area in the lung and contains thin, squamous type I cells and cuboidal type II cells.¹⁰ The alveolar type I cell covers 95% of the alveolar surface. The close apposition between the alveolar epithelium and the vascular endothelium facilitates efficient exchange of gases but also forms a tight barrier to movement of liquid and proteins from the interstitial and vascular spaces, thus assisting in maintaining relatively dry alveoli.

Ion transporters and other membrane proteins are asymmetrically distributed on opposing cell surfaces, conferring vectorial transport properties to the epithelium. Physiologic studies of the barrier properties of tight junctions in the alveolar epithelium indicate that diffusion of water-soluble solutes between alveolar epithelial cells is much slower than through the intercellular junctions of the adjacent lung capillaries.¹¹ Large quantities of soluble protein are removed from the air spaces primarily by restricted diffusion, although there is evidence for some endocytosis and transcytosis of albumin across the alveolar epithelium.¹²

EVIDENCE FOR ACTIVE FLUID TRANSPORT IN THE INTACT LUNG

A substantial number of innovative experimental methods have been used to study fluid and protein transport from the distal air spaces of the intact lung, including isolated

perfused lung preparations, in situ lung preparations, surface fluorescence methods, and intact lung preparations in living animals for short time periods (30 to 240 minutes) or for extended time periods (24 to 144 hours). The advantages and disadvantages of these preparations have been reviewed in some detail.⁸

The first in vivo evidence that active ion transport could account for the removal of alveolar edema fluid across the distal pulmonary epithelium of the mature lung was obtained in studies of anesthetized, ventilated sheep.¹³ In those studies the critical discovery was that isosmolar fluid clearance of salt and water occurred in the face of a rising concentration of protein in the air spaces of the lung, whether the instilled solution was autologous serum or an isosmolar protein solution. The initial protein concentration of the instilled protein solution was the same as that of the circulating plasma. After 4 hours the concentration of the protein had risen from approximately 6.5 g/100 mL to 8.4 g/100 mL, whereas the plasma protein concentration was unchanged. In longer-term studies in unanesthetized, spontaneously breathing sheep, alveolar protein concentrations increased to very high levels. After 12 and 24 hours, the alveolar protein concentrations increased to 10.2 and 12.9 g/100 mL, respectively.¹⁴ The overall rise in protein concentration was equivalent to an increase in distal air space protein osmotic pressure from 25 to 65 cm H₂O. Because the epithelial barrier was intact and thus prevented protein leak into the lung, the only way that the protein concentration could have risen was if water had been removed (i.e., absorbed).

Other studies in the intact lung have supported the hypothesis that removal of alveolar fluid requires active transport.¹⁵ For example, elimination of ventilation to one lung did not change the rate of fluid clearance in sheep, thus ruling out changes in transpulmonary airway pressure as a major determinant of fluid clearance, at least in the uninjured lung.¹⁶ Furthermore, if active ion transport were responsible for alveolar fluid removal, then fluid clearance should be temperature dependent. In an in situ rat lung preparation, fluid clearance was inhibited by low temperature.¹⁷ Similar results were obtained in ex vivo human lung studies,⁹ in which hypothermia inhibited sodium and fluid transport.

Additional evidence for active ion transport was obtained in intact animals with the use of amiloride, an inhibitor of sodium uptake by the apical membrane of alveolar epithelium and distal airway epithelium. Amiloride inhibited 40% to 70% of basal fluid clearance in sheep, rabbits, rats, guinea pigs, and mice and in the human lung.¹ Amiloride also inhibited sodium uptake in distal airway epithelium from sheep and pigs.¹⁸ To explore further the role of active sodium transport, experiments were designed to inhibit Na⁺,K⁺-ATPase. It has been difficult to study the effect of ouabain in intact animals because of cardiac toxicity. However, in the isolated rat lung, ouabain inhibited greater than 90% of fluid clearance.¹⁹ Following the development of an in situ sheep preparation for measuring fluid clearance in the absence of blood flow, it was reported that ouabain inhibited 90% of fluid clearance over a 4-hour period.¹⁶ Other investigators also established the likely role of active fluid transport for removal of fluid from the fetal lung.¹⁵

ION TRANSPORT IN ALVEOLAR AND DISTAL AIRWAY EPITHELIAL CELLS

The success in obtaining nearly pure cultures of alveolar epithelial type II cells from rats made it possible to study the transport properties of these cells and relate the results to the findings in the intact lung studies. When alveolar epithelial type II cells were cultured on a nonporous surface such as plastic, they formed a continuous confluent layer of polarized cells after 2 to 3 days.^{20,21} Interestingly, after 3 to 5 days, small domes of fluid could be appreciated below which the substratum was detached by the formation of the domes. The domes were thought to result from active ion transport from the apical to the basal surface, with water following passively, because they were inhibited by the replacement of sodium by another anion or by pharmacologic inhibitors of sodium transport, such as amiloride and ouabain. More detailed information on the nature of ion transport across alveolar type II cells was obtained by culturing these cells on porous supports and mounting them in Ussing chambers and measuring short-circuit current and ion flux under voltage clamp conditions.^{1,20,22,23}

The coordinated role of apical and basolateral sodium transport has been studied in several in vitro studies. Sodium ions that enter the epithelial cells at the apical membrane are pumped out of the cells at the basolateral membrane by the Na⁺,K⁺-ATPase enzyme. Because of the continuous pumping, sodium chemical potential is lower inside the cell. The entry step is passive, and sodium flows down a chemical potential gradient through specialized pathways, where basolateral transport requires energy to move ions against the gradient. Because of the pump activity, potassium electrochemical potential is larger inside the cell, and potassium leaks through the basolateral membrane and is then recycled by the Na⁺,K⁺-ATPase. The pathways for sodium entry into alveolar type II cells are numerous. Amiloride blocked dome formation^{20,21} and decreased short-circuit current in the in vitro studies,²² a finding that supported the critical importance of sodium uptake through an amiloride-sensitive pathway in the apical membrane of alveolar epithelial cells. As already discussed, the efficacy of amiloride as an inhibitor of fluid clearance in the intact lung was demonstrated in several in vivo studies, although the fraction of amiloride-sensitive transport was as low as 40% to 50% in some lung preparations, particularly in the rat and the human lung. The amiloride-insensitive sodium influx may be represented in vivo in part by the Na⁺-glucose cotransport. A detailed discussion of the pharmacologic, biophysical, and molecular bases for fluid clearance across the alveolar and distal airway epithelium is available in other references.^{1,3,24,25}

The role of the alveolar type I cell in vectorial fluid transport in the lung was unknown until recently; investigators have now assessed the potential contribution of the alveolar type I cell to vectorial fluid transport. On the basis of studies in freshly isolated type I cells, it is known that these cells have a high osmotic permeability to water with expression of aquaporin-5 on the apical surface.²⁶ Recent studies of freshly isolated alveolar type I cells from rats demonstrated

that these cells express the Na^+, K^+ -ATPase α_1 - and α_2 -subunit isoforms.^{27,28} In the same study there was evidence for Na^+, K^+ -ATPase α_1 -subunit expression on the basolateral surface of the alveolar epithelial type I cells in situ in the rat lung. In addition, there is evidence for expression of all the subunits of the *epithelial Na^+ channel* (ENaC) in freshly isolated alveolar type I cells, as well as in situ in the rat lung.²⁹ Finally, there is some evidence that Na uptake can be partially inhibited by amiloride in freshly isolated rat alveolar type I cells,²⁴ although definitive studies of cultured, polarized type I cells have not yet been achieved. Recent data demonstrate that the alveolar epithelial type I cells express a multitude of sodium transporting proteins, ENaC, cyclic nucleotide-gated sodium channels, and the Na^+, K^+ -ATPase.³⁰ In addition, the cells express chloride transporters, that is, the *cystic fibrosis transmembrane regulator* (CFTR), and thus have the ion transporters necessary to participate in vectorial ion transport and clearance of alveolar fluid.³¹ The relative contribution of the type I and type II cells to alveolar edema fluid clearance is still unresolved.

The alveolar epithelium constitutes 99% of the surface area of the lung, a finding that suggests that edema fluid from the lung might be removed primarily across the alveolar epithelium. However, it has been demonstrated that the distal airway epithelium also actively transports sodium, a

process that depends on amiloride-inhibitable uptake of sodium on the apical surface and extrusion of sodium through a basolateral Na^+, K^+ -ATPase.^{1,18} Club cells actively absorb and transport sodium from the apical to the basal surface.²⁸ In addition, there are new data on the possible role of CFTR in up-regulating *cyclic 3',5'-adenosine monophosphate* (cAMP) fluid clearance (see “[Regulation of Lung Epithelial Fluid Transport](#)” section). This information provides support for a possible role of distal airway epithelia in fluid clearance, because CFTR is expressed abundantly in distal airway epithelial cells, as well as in alveolar epithelial cells. Thus, even though their surface area is limited, a contribution from distal airway epithelia to the overall fluid transport is probable, especially because cells from the distal airway epithelium primarily transport salt from the apical to the basolateral surface. [Figure 9-1](#) provides a schematic diagram of our current understanding of the location of ion transporters in the distal airway and alveolar epithelium that are responsible for vectorial fluid transport or net distal air space fluid clearance.

There are also new data confirming the importance of ENaC for alveolar fluid clearance using RNA interference against the αENaC subunit.³² In those studies, inhibition of αENaC expression by specific small interfering RNA against αENaC attenuated the amiloride sensitivity of both normal

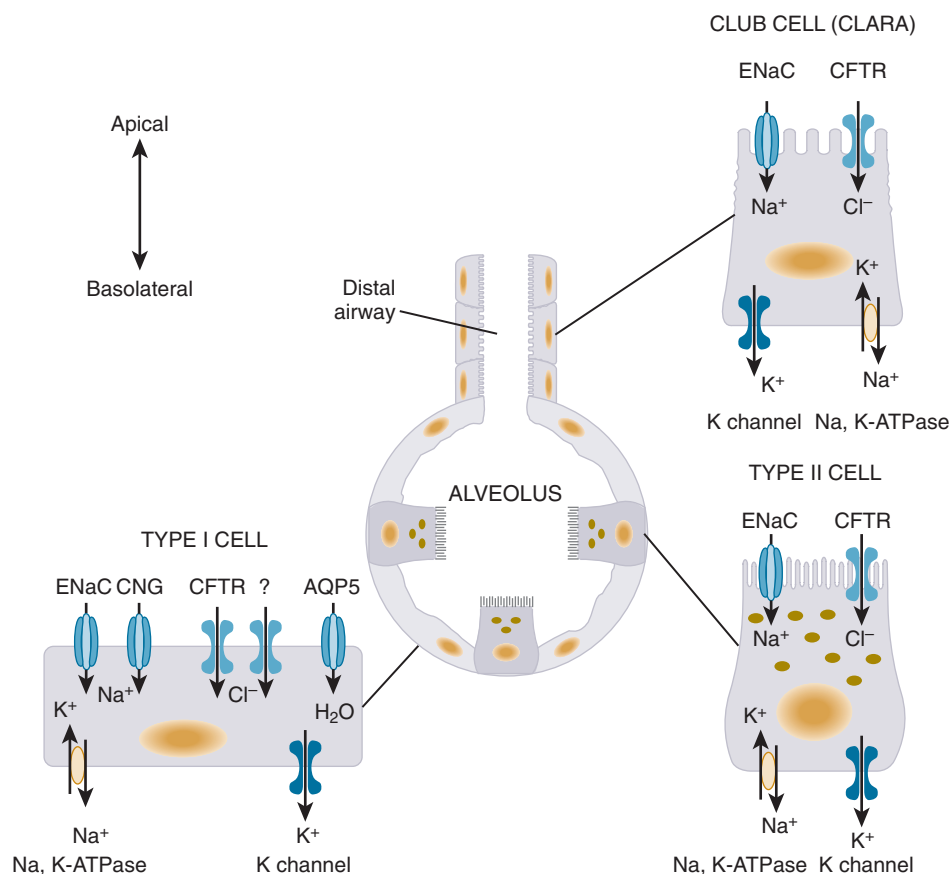


Figure 9-1 A schematic diagram of the distal pulmonary epithelium that is relevant for salt and water transport. AQP5, aquaporin-5; CFTR, cystic fibrosis transmembrane regulator; CNG, cyclic nucleotide-gated sodium channel; ENaC, epithelial Na^+ channel. (Modified from Matthay MA, Folkesson HG, Clerici C: Lung epithelial fluid transport and the resolution of pulmonary edema. *Physiol Rev* 82:569–600, 2002.)

and stimulated alveolar fluid clearance, thus demonstrating the importance of ENaC. Finally, there is a newly cloned δ subunit of ENaC that has been identified in human lungs and may play a role in fluid balance in the lung.³³

REGULATION OF LUNG EPITHELIAL FLUID TRANSPORT

This section considers how the rate of vectorial fluid transport across the distal pulmonary epithelium can be increased by catecholamine or cAMP-dependent mechanisms. The potential relevance of these mechanisms under pathologic conditions is evaluated in the section “Alveolar Fluid Transport under Pathologic Conditions,” later in this chapter.

Studies in newborn animals indicated that endogenous release of catecholamines, particularly epinephrine, may stimulate reabsorption of fetal lung fluid from the air spaces of the lung.^{15,34,35} In most adult mammalian species, stimulation of β_2 -adrenergic receptors by either salmeterol, terbutaline, or epinephrine increases fluid clearance.^{5,36–38} This stimulatory effect rapidly follows intravenous administration of epinephrine or instillation of terbutaline into the alveolar space and is prevented by either a nonspecific β_2 -receptor antagonist (propranolol) or, in rats, by a specific β_2 -antagonist.

The increased fluid clearance by β_2 -agonists can be prevented by amiloride or RNA interference against α ENaC, indicating that the stimulation is related to an increased transepithelial sodium transport.^{32,38} In anesthetized ventilated sheep, terbutaline-induced stimulation of fluid clearance was also associated with an increase in lung lymph flow, a finding that reflected increased removal of some of the alveolar fluid volume to the interstitium of the lung.⁵ Although terbutaline increased pulmonary blood flow, this effect was not important because control studies with nitroprusside, an agent that increased pulmonary blood flow, did not increase fluid clearance. Other studies have demonstrated that β -adrenergic agonists increased fluid clearance in rat, dog, guinea pig, and mouse, as well as human lung.¹ The presence of β_1 - and β_2 -receptors on alveolar type II cells has been demonstrated in vivo by autoradiographic and immunochemistry techniques.¹

It has been difficult to quantify the effect of catecholamines on the rate of alveolar fluid clearance and edema resolution in humans.³⁹ However, studies of fluid clearance in the isolated human lung have demonstrated that β -adrenergic agonist therapy increases fluid clearance, and the increased fluid clearance can be inhibited with propranolol or amiloride.⁹ Subsequent studies suggested that long-acting lipid-soluble β -agonists may be more potent than hydrophilic β -agonists in the ex vivo human lung.³⁸ The magnitude of the stimulatory effect is similar to that observed in other species, with a β -agonist-dependent doubling of fluid clearance over baseline levels.⁴⁰ These data are particularly important because aerosolized β -agonist treatment in some patients with pulmonary edema might accelerate the resolution of alveolar edema (see “Alveolar Fluid Transport under Pathologic Conditions” section).

What has been learned about the basic mechanisms that mediate the catecholamine-dependent up-regulation of sodium transport in the lung? Based on in vitro studies, it was proposed that an increase in intracellular cAMP resulted in increased sodium transport across alveolar type II cells by an independent up-regulation of the apical sodium conductive pathways and the basolateral Na^+, K^+ -ATPase. Proposed mechanisms for up-regulation of sodium transport proteins by cAMP include augmented sodium channel open probability,^{1,41} increases in Na^+, K^+ -ATPase α -subunit phosphorylation, and delivery of more ENaC channels to the apical membrane and more Na^+, K^+ -ATPases to the basolateral cell membrane.¹

Although most experimental studies have attributed a primary role for active sodium transport in the vectorial transport of salt and water from the apical to the basal surface of the alveolar epithelium of the lung, the potential role of chloride, especially in mediating the cAMP-mediated up-regulation of fluid clearance across distal lung epithelium, has been the subject of several studies. A study of cultured alveolar epithelial type II cells suggested that cAMP-mediated apical uptake of sodium might depend on an initial uptake of chloride.⁴² A more recent study of cultured alveolar type II cells under apical surface–air interface conditions reported that β -adrenergic agonists produced acute activation of apical chloride channels with enhanced sodium absorption.⁴³ However, the results of these studies were considered to be inconclusive by some investigators,⁴⁴ partly because the data depend on cultured cells of an uncertain phenotype. Type II cells cultured under conditions for studying transepithelial transport are usually studied under conditions that no longer maintain their phenotype as defined by surfactant protein expression. Furthermore, studies of isolated alveolar epithelial type II cells do not address the possibility that vectorial fluid transport may be mediated by several different epithelial cells, including alveolar epithelial type I cells as well as distal airway epithelial cells. The relative contribution of alveolar type I cells and alveolar type II cells to transepithelial transport remains unresolved.³

In order to define the role of chloride transport in the active transport of salt and water across the distal pulmonary epithelium of the lung, one group has used in vivo lung studies to define the mechanisms and pathways that regulate chloride transport during the absorption of fluid from the distal air spaces of the lung.⁴⁵ This approach may be important because studies in several species, as already discussed, have indicated that distal airway epithelia are capable of ion transport and that both ENaC and CFTR are expressed in alveolar and distal airway epithelia.

Both inhibition and ion substitution studies demonstrated that chloride transport was necessary for basal fluid clearance. The potential role of CFTR under basal and cAMP-stimulated conditions was tested using intact lung studies in which CFTR was not functional because of failure in trafficking of CFTR to the cell membrane, the most common human mutation in cystic fibrosis ($\Delta F508$ mice). The results supported the hypothesis that CFTR was essential for cAMP-mediated up-regulation of isosmolar fluid clearance from the distal air spaces of the lung because fluid clearance could not be increased in the $\Delta F508$ mice either

with β -agonists or with forskolin, unlike in the wild-type control mice.⁴⁵ Additional studies using pharmacologic inhibition of CFTR in both mouse and human lungs with glibenclamide supported the same conclusion, namely that chloride uptake and CFTR-like transport seemed to be required for cAMP-stimulated fluid clearance from the distal air spaces of the lung.⁴⁶ Glibenclamide can also inhibit potassium channels, so the inhibitory effects may not be specific for CFTR, but the $\Delta F508$ mouse studies have provided more direct evidence. Although the absence of CFTR in the upper airways results in enhanced sodium absorption, the data in these studies provide evidence that the absence of CFTR prevents cAMP-up-regulated fluid clearance from the distal air spaces of the lung, a finding that is similar to the results from studies on the importance of CFTR in mediating cAMP-stimulated sodium absorption in human sweat ducts.⁴⁷ Because CFTR is distributed throughout the distal airway epithelium, as well as at the alveolar level in the human lung,⁴⁸ the data also suggest that the cAMP-mediated up-regulated reabsorption of pulmonary edema fluid may take place across distal airway epithelium as well as at the level of the alveolar epithelium. Finally, additional studies indicated that the lack of CFTR results in a greater accumulation of pulmonary edema in the presence of a hydrostatic stress, thus demonstrating the potential physiologic importance of CFTR in up-regulating fluid transport from the distal air spaces of the lung.⁴⁵ There is evidence that functional CFTR chloride channels are present in adult rat alveolar epithelial type II cells based on whole cell patch-clamp experiments.⁴⁹ In addition, there is expression of CFTR in both alveolar type I and II cells.^{30,31} A study using a novel CFTR-specific inhibitor, CFTR_{inh-172}, in human lungs again demonstrated the importance of CFTR and chloride transport for cAMP-driven fluid absorption.⁵⁰

In the last few years, several interesting catecholamine-independent mechanisms have been identified that can up-regulate fluid transport across the distal air spaces of the lung as well as in cultured alveolar type II cells. Hormonal factors such as glucocorticoids can up-regulate transport by transcriptional mechanisms, whereas thyroid hormone may work by a posttranslational mechanism. Some growth factors can work by either transcriptional or direct membrane effects or by enhancing the number of alveolar type II cells. For example, keratinocyte growth factor is a potent mitogen for alveolar type II cells. Administration of keratinocyte growth factor (5 mg/kg) into the distal air spaces of the rat lung increases fluid clearance by 66% over baseline levels.⁵¹ Other investigators have shown that keratinocyte growth factor can enhance sodium and fluid transport in normal and injured rat lungs.^{52,53} Keratinocyte growth factor may also work by enhancing the expression of sodium transport proteins.⁵⁴ There is also evidence that a proinflammatory cytokine, tumor necrosis factor- α , can rapidly up-regulate sodium uptake and fluid transport. The effect of tumor necrosis factor- α is amiloride-inhibitable in both rats and isolated A549 human cells.^{55,56} Finally, serine proteases can regulate the activity of ENaC and potentially increase fluid clearance across the distal airway epithelium.⁵⁷ These catecholamine-independent mechanisms are explored in more detail in one review.¹ Recent work has demonstrated that isolated human alveolar epithelial type

II cells have the capacity to absorb sodium by ENaC-dependent mechanisms and secrete chloride by CFTR-dependent pathways. Based on these *in vitro* studies, alveolar epithelial type II cells (1) achieved an extracellular nucleotide concentration-dependent steady state alveolar surface liquid height of approximately 4 μ m *in vitro*, (2) absorbed liquid when the lumen was flooded, and (3) secreted liquid when treated with uridine triphosphate or forskolin or subjected to cyclic compressive stresses mimicking tidal breathing. Collectively these studies suggest that human alveolar epithelial type II cells *in vitro* have the capacity to absorb or secrete liquid in response to local alveolar conditions.⁵⁸

MECHANISMS THAT CAN IMPAIR THE RESOLUTION OF ALVEOLAR EDEMA

Several mechanisms have been identified that can impair fluid transport from the distal air spaces of the lung. This section considers three conditions that have relevance to human disease: hypoxia, the use of anesthetics, and the presence of reactive oxygen and nitrogen species. The next section reviews mechanisms that impair fluid transport under specific pathologic conditions.

Hypoxia may arise during residence or recreation at high altitudes and under a variety of pathologic conditions associated with acute and chronic respiratory disease. Therefore it is important to understand the effect of hypoxia on the ion and fluid transport capacity of the lung epithelium. The effect of hypoxia under *in vivo* conditions has been studied primarily in rats. In anesthetized rats, as well as in isolated perfused lungs, hypoxia decreased alveolar liquid clearance by inhibition of the amiloride-sensitive component.^{59,60} The effect of hypoxia could not be explained by transcriptional effects on ENaC or Na⁺,K⁺-ATPase. The results suggested a posttranslational mechanism such as a direct change of sodium transporter protein activity or transport to the plasma membrane. This latter hypothesis was supported by the normalization of fluid clearance by a cAMP agonist (terbutaline), which appears to increase the trafficking of sodium transporter proteins from the cytoplasm to the membrane.^{61,62} Direct evidence for this mechanism in hypoxic alveolar epithelial type II cells was demonstrated for ENaC²³ as well as for an inhibitory effect of hypoxia on Na⁺,K⁺-ATPase activity in isolated A549 cells.⁶³

In alveolar epithelial cells the halogenated anesthetics affect sodium and fluid transport at the physiologic level as well as on a cellular level. In the rat, halothane and isoflurane decrease fluid clearance by inhibition of the amiloride-sensitive component. This effect was rapidly reversible after cessation of halothane exposure.⁶⁴ *In vitro*, exposure to a low concentration of halothane (1%) for a short time (30 minutes) induced a reversible decrease in Na⁺,K⁺-ATPase activity and amiloride-sensitive ²²Na influx in rat alveolar type II cells.⁶⁵ The mechanisms whereby halothane induced a decrease in sodium transport protein activity have not been yet elucidated, but they are not related *in vitro* to a decrease in intracellular adenosine triphosphate content or

to a change in cytosolic free calcium. Taken together, these observations suggest that halogenated anesthetics may interfere with the clearance of alveolar edema.

Lidocaine is widely used in patients with acute cardiac disorders and has also been recently implicated as a possible cause of pulmonary edema following liposuction. In experimental studies in rats, either intravenous or intra-alveolar lidocaine reduced fluid clearance in rats by 50%.⁶⁶ Because lidocaine did not inhibit ENaC when expressed in oocytes, it seems that the inhibitory effect on vectorial fluid transport was primarily on the basal surface of alveolar epithelial cells, either through an effect on the activity of $\text{Na}^+\text{K}^+\text{ATPase}$ or through an indirect effect via blockade of potassium channels, a well-known property of lidocaine. The effect of lidocaine was also completely reversible with β_2 -agonist therapy.⁶⁶

Under several pathologic conditions, in response to pro-inflammatory cytokines, activated neutrophils and macrophages can localize in the lung and migrate into the air spaces of the lung, and release reactive oxygen species by the membrane-bound enzyme complex nicotinamide adenine dinucleotide phosphate oxidase and *nitric oxide* (NO) via the calcium-insensitive inducible form of NO synthase. NO decreased short-circuit current across cultured rat type II cells without affecting transepithelial resistance. NO also inhibited 60% of amiloride-sensitive short-circuit current across type II cell monolayers following permeabilization of the basolateral membrane with amphotericin B.⁶⁷ NO reacted with superoxide (O_2^-) to form peroxynitrite (ONOO^-), a potent oxidant and nitrating species that directly oxidizes a wide spectrum of biologic molecules, such as DNA constituents, lipids, and proteins.²⁴ Boluses of peroxynitrite (0.5 to 1 mM) delivered into suspensions of freshly isolated type II cells from rabbits decreased amiloride-inhibitable sodium uptake to 68% and 56% of control values, respectively, without affecting cell viability. Some investigators reported that products of macrophages, including NO, can down-regulate sodium transport in fetal distal lung epithelium stimulated with endotoxin.⁶⁸ The data indicate that oxidation of critical amino acids residues in ENaC protein is probably responsible for this effect. This evidence matches well with other studies that have shown that protein nitration and oxidation by reactive oxygen and nitrogen species have been associated with diminished function of a variety of important proteins present in the alveolar space, including surfactant protein A.⁶⁹

There is also evidence that transforming growth factor- β 1 decreases expression of ENaC and alveolar epithelial sodium and fluid transport by an ERK 1/2-dependent mechanism in both primary rat and human alveolar type II cells.⁷⁰

ALVEOLAR FLUID TRANSPORT UNDER PATHOLOGIC CONDITIONS

Fluid clearance from the distal air spaces of the lung has been measured in mechanically ventilated patients with acute respiratory failure from pulmonary edema as well as

in several animal models designed to simulate clinically relevant pathologic conditions.

Studies of fluid clearance have been done in intubated, ventilated patients by measuring the concentration of total protein in sequential samples of undiluted pulmonary edema fluid aspirated from the distal air spaces of the lung with a standard suction catheter passed through the endotracheal tube into a wedged position in the distal airways of the lung.^{39,71,72} This method for measuring fluid clearance in patients was adapted from the method for aspirating fluid from the distal air spaces of the lung in experimental studies in small and large animals.^{5,8} The clinical procedure has been validated in patients by demonstrating that there is a relationship between fluid clearance and the improvement in oxygenation and the chest radiograph.^{39,72}

In patients with severe hydrostatic pulmonary edema, there was net fluid clearance in the majority during the first 4 hours after endotracheal intubation and the onset of positive-pressure ventilation.⁷³ The rate of fluid clearance was 14%/hr in 38% of the patients. Overall, 75% of the patients had intact fluid clearance. There was no significant correlation between the levels of fluid clearance and endogenous plasma levels of epinephrine, although twice as many of the patients with intact fluid clearance received aerosolized β -adrenergic therapy as did those with impaired fluid clearance; this difference did not reach statistical significance, perhaps because the total number of studied patients was modest. In a recent study of congestive heart failure in rats, it was demonstrated that β -adrenergic stimulation increased alveolar fluid clearance and that type II cell hyperplasia might be responsible for the stimulation.⁷¹

The majority of patients with increased permeability edema and *acute lung injury* (ALI) have impaired alveolar epithelial fluid transport, a finding that is associated with more prolonged respiratory failure and a higher mortality (Fig. 9-2). In contrast, a minority of patients can remove alveolar edema fluid rapidly, and these patients have a higher survival rate.^{39,72} These results indicate that a functional, intact distal lung epithelium is associated with a

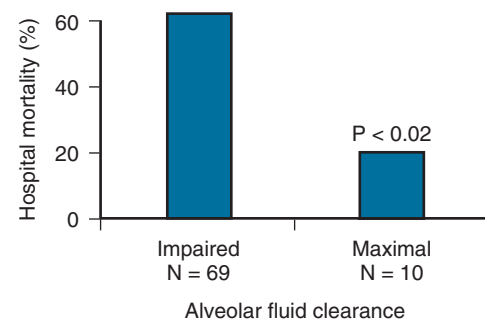


Figure 9-2 Hospital mortality is increased in patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) with impaired fluid clearance. Impaired fluid clearance ($<14\%/hr$) was compared with those with maximal fluid clearance ($>14\%/hr$). The columns represent percent hospital mortality in each group. Hospital mortality of patients with maximal fluid clearance was significantly less ($P < 0.02$). N, number of patients. (Data from Ware LB, Matthay MA: Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 163:1376–1383, 2001.)

better prognosis in patients with ALI, thus supporting the hypothesis that the degree of injury to the distal lung epithelium is an important determinant of the outcome in patients with increased permeability pulmonary edema from ALI. There is also new evidence that alveolar fluid clearance in patients with sepsis is inversely related to the severity of shock (number of vasopressors) in patients with ALI.⁷⁴

What are the mechanisms that may impair fluid clearance from the air spaces of the lung in patients with ALI? As already explained, alveolar hypoxia can depress alveolar epithelial fluid transport. Also, viral or bacterial lung infection can depress alveolar fluid transport, either by interfering with normal ion transport or by inducing apoptosis or necrosis of the distal lung epithelium. In addition, a decrease in fluid clearance may be associated with higher levels of nitrate and nitrite in pulmonary edema fluid, a finding that supports the hypothesis that proteins essential to epithelial fluid transport may undergo nitration and oxidation in some patients with lung injury, further depressing their ability to remove alveolar edema fluid.⁶⁹ Further, the receptor for advanced glycation end products may be a marker for alveolar type I cell injury and predict a reduced rate of clearing pulmonary edema fluid.⁷⁵

FUTURE DIRECTIONS

It is possible to quantify the rate of edema reabsorption from the distal air spaces of the lung in ventilated, critically ill patients with acute pulmonary edema. In conjunction with progress in experimental studies of lung fluid balance under clinically relevant pathologic conditions, further studies should be done to test the potential role of catecholamine-dependent and catecholamine-independent therapies that might enhance the resolution of clinical pulmonary edema. Experimental data in a rat model of ALI indicated that β_2 -adrenergic agonist therapy can decrease lung endothelial permeability, increase alveolar fluid clearance, and decrease pulmonary edema when given after lung injury had developed.⁷⁶ The feasibility of delivering therapeutic concentrations of aerosolized β_2 -adrenergic agonist therapy to the distal air spaces of ventilated patients was demonstrated.⁷⁷ However, clinical trials with aerosolized or intravenous β_2 -agonists did not improve clinical outcomes in patients with ALI, perhaps because the injury to the alveolar epithelium was too severe.^{78,79} β_2 -adrenergic agonists may still have a therapeutic role in increasing the rate of alveolar fluid clearance in patients with hydrostatic or cardiogenic pulmonary edema.

Key Points

- The distal conducting airways and alveolar surface are lined with epithelial cells that provide a tight barrier to protect the distal air spaces for gas exchange.
- The primary mechanism for reabsorption of excess alveolar fluid is active vectorial sodium and chloride transport.
- The best-understood transporters are the epithelial Na^+ channel and cystic fibrosis transmembrane regulator.
- The resolution of alveolar edema is driven by active ion transport and can be up-regulated by cyclic 3',5'-adenosine monophosphate stimulation.
- Alveolar fluid transport is impaired in patients with acute lung injury.

Complete reference list available at [ExpertConsult](#).

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AIRWAY EPITHELIUM AND MUCOUS SECRETION

JAY A. NADEL, MD, DSc (Hon), DLaw (Hon)

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INTRODUCTION

When animals migrated from sea to land, gills were exchanged for lungs, thus increasing the surface area for gas exchange, and the respiratory organ (lungs) was relocated deep within the thorax. This new apparatus required a connection from the areas of gas exchange in the alveoli to the external environment, which was provided by the airways. The airway epithelium is exposed to a wide array of environmental “invaders,” such as bacteria, viruses, allergens, and environmental toxins such as cigarette smoke and air pollutants. Particulate invaders first deposit on the luminal airway epithelial surface and move across the surface to enter the body of the host. In healthy individuals the scarcity of secretions, the effectiveness of clearance of invaders from the epithelial surface, and the efficiency of the host systems for defensive cellular responses to invaders allows protection of the host without symptoms or significant pathologic changes. However, in chronic inflammatory airway diseases, pathologic responses are overexuberant, impairing rather than protecting the host. This chapter focuses on mucus and its major constituent, mucins, and the effects of their hypersecretion.

COMPONENTS OF MUCUS

Mucous secretion normally plays a protective role in the epithelium. Airway mucus is a complex mixture of proteins and liquids and includes a sol phase composed of water and electrolytes.^{1,2} Mucus consists of water (95%), most of which is bound in a viscoelastic gel containing mucins.^{3,4} The gel-forming mucins in mucus are high-molecular-weight glycoproteins that are key components of mucous cells and are rich in carbohydrates.⁵ Mucin oligosaccharides

are joined by an initial α_0 -glycoside linkage of N-acetylgalactosamine to the hydroxyl moieties of serine or threonine of the mucin protein backbone.⁶ Mucins produced intracellularly are packed tightly within granules. During exocytosis the cells secrete their granule contents in a condensed form, and the secreted mucins undergo rapid hydration to form a gel with unusual viscoelastic properties that allow the mucins to interact with cilia to effect mucociliary clearance. Various mucins may have very different biophysical properties, and future studies are needed to characterize these properties and their potential pathophysiologic implications. Currently approximately 19 *mucin* (MUC) genes have been cloned. They are divided into two groups: membrane-associated and gel-forming secreted mucins.^{7,8} Of the secreted mucins, two are especially prominent in inflammatory airway diseases: MUC5AC in airway goblet cells⁹⁻¹² and MUC5B in submucosal gland mucous cells.^{9,10,13,14}

NORMAL AIRWAY MUCINS

Gel-forming mucins are produced by mucous tubules in submucosal glands in the large conducting airways and by goblet cells located in the surface epithelium in both large and small airways. MUC5AC is the predominant mucin produced by the surface epithelium¹⁵ and by airway epithelial cells in culture.^{11,16} MUC5B is the predominant mucin in the submucosal glands.¹⁷ MUC5AC is more susceptible to proteolytic degradation than is MUC5B.¹⁸ Thus mucins have a complicated structure, which is likely to contribute to their functions. In the normal surface epithelium, goblet cells are sparse^{11,19,20} but present at all levels, decreasing in number peripherally, presumably reflecting less contact of peripheral airways with invading environmental particulates. Pathogen-free animals have few goblet cells in the airway

epithelium. In healthy airways, multiple stimuli induce mucin production, but the amount of mucin production is small.

On the surface of the airways is a periciliary sol phase, above which the mucous gel floats. The contracting cilia propel the mucous blanket mouthward, along with trapped environmental particles that have deposited on the epithelial surface.

MUCOUS HYPERSECRETORY DISEASES AND THEIR CLINICAL CONSEQUENCES

DIFFERENCES IN CLINICAL PRESENTATION AMONG VARIOUS HYPERSECRETORY DISEASES

Chronic inflammatory airway diseases are associated with mucous hypersecretion, and the stimuli involved may vary. For example, allergic factors are involved in asthma (see Chapter 41), genetic abnormalities underlie *cystic fibrosis* (CF) (see Chapter 47), and the inhalation of toxic components of cigarette smoke is the main cause of *chronic obstructive pulmonary disease* (COPD) (see Chapter 43). Regardless of the variety of causes, the similarities that exist in cellular responses among these various disease states (including mucous hypersecretion) suggest that some common mechanisms are likely to exist that could be useful in therapy.

In patients with severe asthma,²¹ CF,¹⁹ and COPD,²² exaggerated airway epithelial mucin production can lead to mucous plugging and sometimes to death. MUC5AC contributes importantly to mucous plugging in these diseases.^{9-12,19} In patients with hypersecretory diseases, multiple stimuli can exaggerate mucus production and cause clinical exacerbations. Examples of these stimuli are listed in Table 10-1.

Table 10-1 Examples of Stimuli That Induce Mucin Synthesis In Vitro or In Vivo by EGFR Activation In Airways

IN VITRO EXPERIMENTS

- Bacterial products
 - Pseudomonas aeruginosa supernatant⁷³
 - Lipopolysaccharide (LPS)^{73,76}
 - Lipoteichoic acid (LTA)⁹²
- Phorbol 12-myristate 13-acetate (PMA)⁷⁶
- Cigarette smoke¹¹¹
- Inflammatory cells
 - Neutrophils¹⁶
 - Eosinophils¹²
- Serine proteases
 - Human neutrophil elastase⁸³
 - Human airway trypsin-like protease¹¹³

IN VIVO EXPERIMENTS

- Th2 cells
 - Antigen (ovalbumin)⁵⁴
 - IL-13¹¹⁴
- Mechanical damage of epithelium⁸⁸
- Cigarette smoke¹¹¹
- Leukotrienes¹¹⁵
- Cathelicidin¹¹⁶

EGFR, epidermal growth factor receptor; IL, interleukin; Th2, type 2 T helper. From Burgel PR, Nadel JA: Roles of epidermal growth factor receptor activation in epithelial cell repair and mucin production in airway epithelium. *Thorax* 59:992, 2004.

MANIFESTATIONS OF MUCOUS HYPERSECRETION DEPEND ON AIRWAY LOCATION

Intrathoracic airways branch continuously from the trachea to small airways (terminal bronchioles) before they finally arrive in the alveolar zone. Because of their peripheral location, the small airways remain relatively “silent.”

In the 1950s, clinicians recognized a clinical condition consisting of cough and sputum production (which they called “chronic bronchitis” or “simple bronchitis”).²³ They recognized the symptoms as part of a disease of the conducting airways that was disturbing to patients but did not cause serious clinical deterioration or death. One logical explanation for this clinical condition was as follows: in disease of the conducting airways, overproduction of mucins in the submucosal glands travels to the airway lumen via ducts localized to airway bifurcations.²⁴ The cough receptors are colocalized at airway bifurcations. Stimulation of these receptors (e.g., by chronic smoking) causes cough and activates mucous secretion (Fig. 10-1).

Together, anatomists and physiologists advanced the structural analysis of mucin production in submucosal glands and in epithelial goblet cells. These innovators paid little attention to the importance of the peripheral airways. However, it was pathologists who became intrigued by bronchiolar mucous plugging and suggested that plugging was an early event in the development of emphysema.²⁵ In the study of mucins, this seminal observation lost out to the interest in mucin studies in the large airways,²⁶ which led to the discoveries of the mucin genes and the signaling pathways involved in mucin production. However, the importance of the small airways soon resurfaced: in 1963 the anatomist Ewald Weibel analyzed the total airway cross

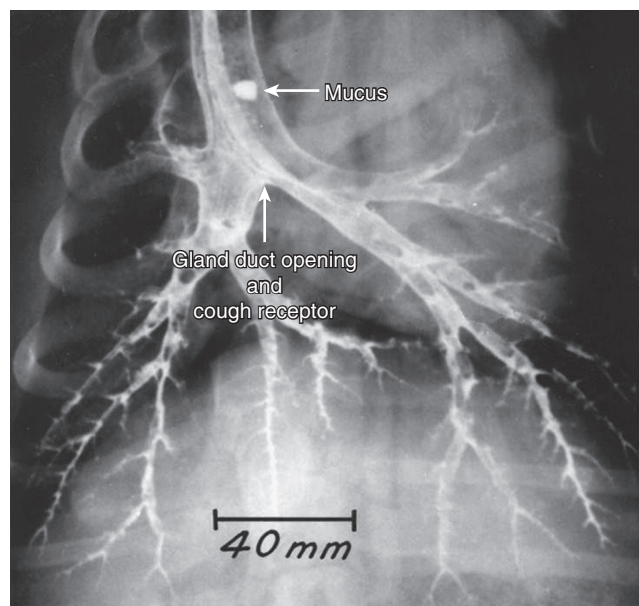


Figure 10-1 Colocalization of gland duct opening and cough receptors at airway bifurcations. Tantalum bronchogram outlines airways. Arrow indicates site of submucosal gland duct opening and site of cough receptor concentration at large airway bifurcation. (From Nadel JA: Mucous hypersecretion and relationship to cough. *Pulm Pharmacol Ther* 26[5]:510–513, 2013.)

section as a function of generation number.²⁷ He showed that the first five generations occupy a small cross-sectional area and that the bronchioles occupy an exponentially increased cross-sectional area (see Fig. 4-2). Using Weibel's data, it was predicted that normally most of the airflow resistance resides in the large airways and that the airflow resistance contributed by the bronchioles is normally very small.

Early studies implicated bronchioles in lung disease, but their study has been impeded because (1) bronchoscopy, which is very useful for examination and biopsy of large airways, is unable to visualize bronchioles; (2) clinical radiologic techniques still cannot resolve bronchioles; and (3) for structural reasons, biopsies are not usually useful in bronchiolar pathologic conditions. For these reasons, bronchioles still remain a relatively “silent zone” of the lungs!

In bronchioles, because of striking differences in structure from the large airways, the effects of mucous hypersecretion have different manifestations. Bronchiolar hypersecretion is not associated with cough because bronchioles do not possess cough receptors. Furthermore, the number of bronchioles and therefore the total cross-sectional area is very large,²⁸ so obstruction of bronchioles will not have a measurable effect on airflow resistance until most of the bronchioles are occluded.²⁹ In acute asthma the importance of bronchiolar obstruction has often only been discovered postmortem, when microscopic examination of bronchioles has shown extensive bronchiolar plugging.²¹ Diffuse bronchiolar plugging is also found in advanced CF at the time of lung transplantation.¹⁹ Remarkably, the potential importance of bronchiolar obstruction was reported as long ago as 1956 by pathologists as an early manifestation of emphysema, but the role of plugging in lung tissue breakdown was not explored.²⁵

Because of the small diameters, bronchioles are more likely to become obstructed (“plugged”) than airways with larger diameters. Therapy for airway obstruction usually focuses on smooth muscle contraction (“bronchospasm”). However, in chronic obstructive airway diseases, thickening of the airway wall and mucous hypersecretion are predicted to contribute significantly to the airflow limitation that is present (shown schematically in Fig. 10-2). In spite of the fact that chronic progressive mucous plugging is common in chronic inflammatory airway diseases such as COPD,²² CF,¹⁹ and acute fatal asthma,^{21,30-33} the clinical detection of peripheral mucous plugging is very difficult. This is due to the fact that these small structures are not visualized radiologically or visually during bronchoscopy and are difficult to sample in biopsies. Novel methods for further examination of bronchiolar structure and function are sorely needed.

IMPORTANCE OF MUCOUS HYPERSECRETION IN CHRONIC INFLAMMATORY AIRWAY DISEASES

In healthy subjects, mucous secretion is involved in innate immune defense of the host (see Chapter 12). These host responses normally defend efficiently against inhaled

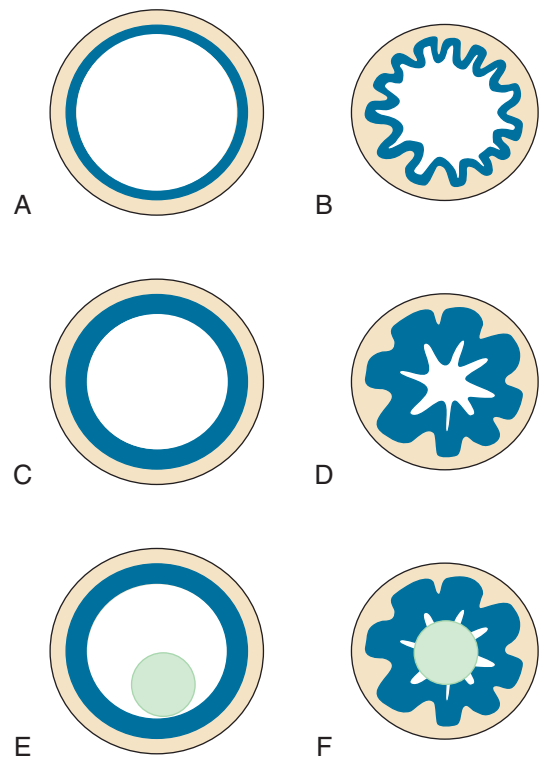


Figure 10-2 Schematic representation of the potential impact of goblet cell hyperplasia and mucous plugging on small airway obstruction. In normal individuals the surface epithelium covering small airways (blue) contains few goblet cells and is composed of a thin layer of epithelial cells. **A** and **B**, Normal, thin epithelium contributes little to luminal narrowing both when airway smooth muscles are relaxed (**A**) and when smooth muscles shorten (**B**). **C** and **D**, In various airway inflammatory diseases (e.g., acute asthma, COPD, cystic fibrosis), epithelial cell hyperplasia is present in small airway epithelium, resulting in epithelial thickening. **C**, When airway smooth muscles are relaxed, thickened epithelium may contribute little to airflow limitation. **D**, However, when smooth muscles shorten, the hyperplastic epithelium (composed of epithelium, lamina propria, muscle, and adventitial compartments) becomes an important determinant of airflow limitation. **E** and **F**, When hyperplastic goblet cells release mucins in the airway lumen (pale green circle), swelling of secreted mucins during hydration may result in mucous obstruction. **F**, The contribution of mucous secretions to airflow limitation is increased when smooth muscles shorten. Thus both goblet cell hyperplasia and mucous obstruction in small airways are predicted to contribute significantly to the airflow limitation in chronic inflammatory airway diseases. (Redrawn from Burgel PR, Montani D, Danel C, et al: A morphometric study of mucins and small airway plugging in cystic fibrosis. *Thorax* 62:153, 2007.)

“invaders” (e.g., microbes, inhaled irritants), usually without obvious interference with function. However, in various chronic inflammatory airway diseases, there is evidence of abnormal inflammatory responses, which are involved in the pathophysiologic changes of the diseases. Thus, although secretion of mucus normally plays a protective role in host defense, hypersecretion plays important roles in the pathophysiologic characteristics of various chronic airway diseases. The following section is a brief discussion of some current issues related to mucous hypersecretion in selected obstructive airway diseases. Detailed reviews are provided in the chapters on chronic bronchitis and COPD (see Chapters 43 and 44), asthma (see Chapters 41 and 42), and cystic fibrosis (see Chapter 47).

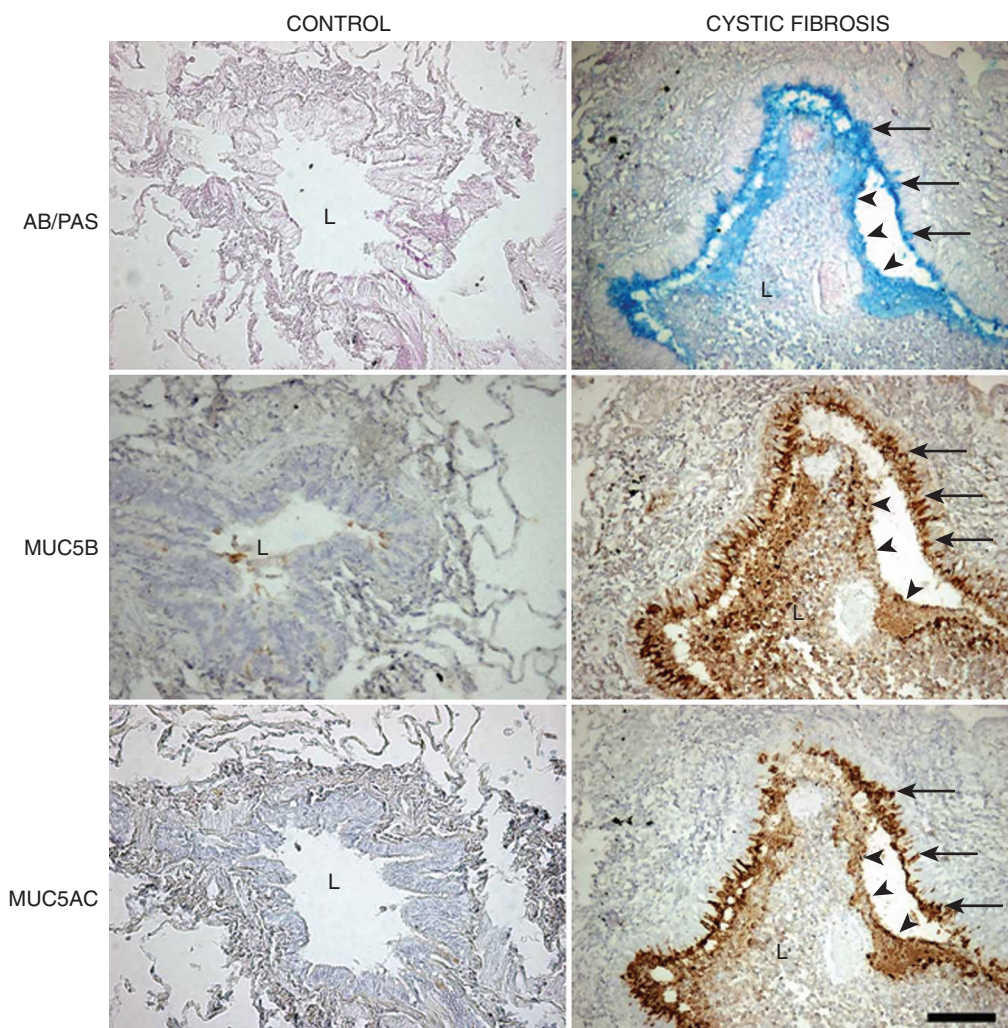


Figure 10-3 Mucous glycoconjugates and mucins in airway lumens of controls and patients with cystic fibrosis (CF). Representative photomicrographs. Sections containing small airways in a typical control subject (*left panels*) and in a patient with CF (*right panels*) were stained with Alcian blue/periodic acid-Schiff (AB/PAS) for mucous glycoconjugates, blue staining (*upper panels*) or with antibodies to mucin MUC5B (brown staining; *middle panels*) and MUC5AC (brown staining, *lower panels*). In the control subject the airway lumen (L) is empty; no staining for AB/PAS, MUC5B, or MUC5AC is observed in the lumen or in the epithelium. In the patient with CF, the airway lumen is obstructed by a plug containing mucous glycoconjugates (AB/PAS), MUC5B, and MUC5AC only at the periphery of the plug (*arrowheads*), adjacent to the epithelium. Staining for mucins is absent in the center of the plug. Goblet cells in the epithelium are stained positively with AB/PAS and with MUC5AC and MUC5B antibodies (*arrows*). (Original magnification $\times 100$; bar = 100 μm .) (From Burgel PR, Montani D, Danel C, et al: A morphometric study of mucins and small airway plugging in cystic fibrosis. *Thorax* 62:153, 2007.)

BRIEF REVIEW OF CYSTIC FIBROSIS, ASTHMA, AND CHRONIC BRONCHITIS/COPD

Cystic Fibrosis (see Chapter 47)

In CF, mucous plugging has long been known to play a major role in the pathophysiologic changes of the disease, but the extent and characteristics of plugging have previously escaped analysis. Various investigators have reported that mucins contribute to the pathophysiologic changes in CF.^{10,34,35} A biopsy study of conducting airways in CF showed an increase in goblet cell size and an enlarged submucosal gland volume.¹⁷ Kreda and colleagues³⁶ described the relationship between the *cystic fibrosis transmembrane conductance regulator* (CFTR), mucins, and mucous obstruction. In a quantitative analysis of lungs removed at the time of lung transplantation, Burgel and associates¹⁹ reported that in CF most small airways contained extensive plugging,

whereas control lungs contained only rare plugs (*Fig. 10-3*). Another example of plugging in small noncartilaginous airways is shown in *Figure 10-4*. Pulmonary function studies in these CF patients before transplantation were indicative of severe airway obstruction, and the authors suggested that the extensive peripheral airway plugging contributed to the loss of lung function. In the airways with plugs, there was extensive goblet cell hyperplasia, with mucins streaming into the luminal plugs. These studies indicate that CF patients with late-stage disease and severe airway obstruction have extensive peripheral airway plugging, which contributes to the advanced obstruction present and the need for transplantation.

Although mucins play a role in the production of mucous plugs, other components (e.g., neutrophil products), including DNA and extravasated blood products (such as albumin), also contribute. It should be noted that the observation that

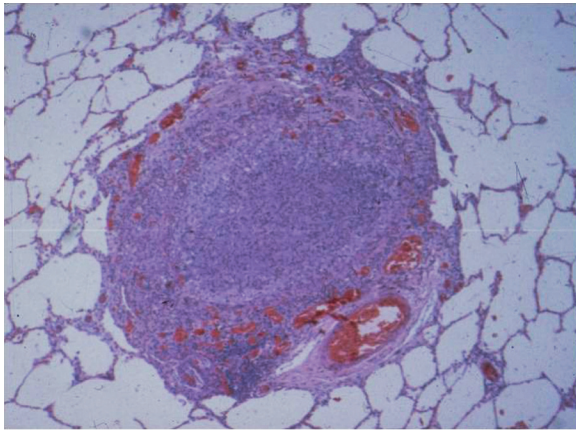


Figure 10-4 Mucin plug in terminal bronchiole in a patient with cystic fibrosis (CF). This section was stained with Alcian blue/periodic acid-Schiff (AB/PAS). The plugged bronchiole is surrounded by alveoli.

mucin production is increased in CF does not necessarily imply that CF epithelial cells have increased responsiveness to mucin production, but only that, in the area of plugs, there are stimuli (e.g., *Pseudomonas* bacteria) that effectively stimulate production and secretion of mucins.

In CF, Burgel and associates¹⁹ noted that the staining for mucins occupied approximately 20% of the plugged lumen volume, indicating that mucins contributed to the plugs but that other molecules were also present. Neutrophils were also conspicuous in the plugs. Voynow and coworkers³⁷ reported that elastase, a product secreted by neutrophils, causes the degradation of MUC5AC. Davies and colleagues¹⁸ reported findings that suggested that one airway mucin (MUC5AC) is more vulnerable to proteolytic degradation than the other (MUC5B). The findings reported by Burgel and associates¹⁹ confirmed this observation. The prominent presence of neutrophils in plugged airways suggests the possibility that neutrophil-mediated effects could be involved in proteolytic inactivation of secreted mucins. Many other molecules may also be components of mucous plugs. For example, albumin is a normal component of blood, but, in states of inflammation with increased vascular permeability, albumin is reported to move from the vascular lumen to the airway lumen. Albumin is a plasma protein that can move across the endothelial surface via multiple mechanisms.³⁸ When albumin is present in renal tubular epithelial cells, it activates *epidermal growth factor receptors* (EGFRs) and causes the production of inflammatory mediators.³⁹ If albumin has similar actions in airways, perhaps in diseases with increased vascular permeability, albumin might play a role in activating the EGFR and leading to mucous hypersecretion.

In CF, a disease caused by mutations in the CFTR,^{40,41} exaggerated airway epithelial cell *interleukin-8* (IL-8) production^{42,43} leads to persistent neutrophilic inflammation, a severe and untreated feature of CF airway disease.⁴⁴ Some investigators suggest that inflammatory changes in CF result from infection, and others suggest that the exaggerated effects are intrinsic elements of CF disease. It is known that activation of the EGFR is responsible for the production of IL-8, which is a potent neutrophil chemokine.⁴⁵ Kim and associates⁴⁶ recently hypothesized that normal CFTR sup-

presses EGFR-dependent IL-8 production and that loss of CFTR at the epithelial surface exaggerates IL-8 production via activation of a proinflammatory EGFR cascade. Airway epithelial cells known to contain normal CFTR were treated with a *CFTR-selective inhibitor*, CFTR(inh)-172. The authors found that CFTR(inh)-172 increased IL-8 production via an epithelial surface signaling cascade via the production and release of *interleukin-1- α* (IL-1 α), and binding of IL-1 α to its receptor, leading to EGFR activation and hence exaggerated IL-8 production. (For a description of the cascade leading to exaggerated IL-8 production see Kim.⁴⁶) Similar exaggerated effects were seen in CF epithelial cells. If this cascade is also activated in CF patients in vivo, one would predict that the increased responsiveness of the airway epithelium accounts for the marked increase in the patient's responses. In CF this could explain the effects of *Pseudomonas* infections on the patients' symptoms and their responses to bacterial therapy. These studies are of interest because they suggest that inflammatory responses such as mucous hypersecretion in CF may be due to exaggeration of EGFR proinflammatory responses when CFTR is absent from the epithelial surface. In addition, in other airway diseases, down-regulation of CFTR may also increase EGFR-mediated proinflammatory responses. A limitation of the study is the fact that it was performed in isolated airway epithelial cells. In addition, CFTR(inh)-172 could conceivably have other side effects. Further studies are indicated to determine the validity of the antagonism of CFTR and EGFR and to further investigate the implications. It is possible that understanding the interactions of the CFTR and the EGFR signaling cascades could provide novel therapies.

Asthma (see Chapters 41 and 42)

In contrast to normal individuals, for patients with asthma, sputum secretion and cough, symptoms of hypersecretion in large airways, are common. Thus Turner-Warwick and Openshaw⁴⁷ reported that 77% of asthma patients had a history of sputum production, and 56% reported maximum sputum production at the peak of asthma attacks. Goblet cell numbers in the conducting airways⁴⁸ are increased even in mild asthma.^{11,49}

Chronic asthma has increased as a public health burden over the past 20 years, and acute exacerbations of asthma play important roles in morbidity and cost. Respiratory viruses, mainly rhinoviruses, cause the majority of exacerbations.⁵⁰ Asthma attacks cause the acute onset of symptoms and acute deterioration of lung function. Chronic mucus hypersecretion is a common symptom in adults with stable asthma, particularly in smokers and in patients with severe disease.^{50a} A history of asthma with chronic sputum overproduction is associated with an accelerated decline in maximal expiratory airflow (indicative of airway obstruction).⁵¹ Morgan and colleagues⁵² reported that asthmatic subjects show a greater decline in lung function over time than normal subjects.

Mucous hypersecretion in the large conducting airways causes significant symptoms (cough and mucous hypersecretion).²⁴ Hypersecretion in small airways generally is asymptomatic early but is often ultimately associated with marked airway narrowing (mucous plugging). Further evidence for the involvement of peripheral airways in asthma was provided by Yanai and coworkers,⁵³ who reported that

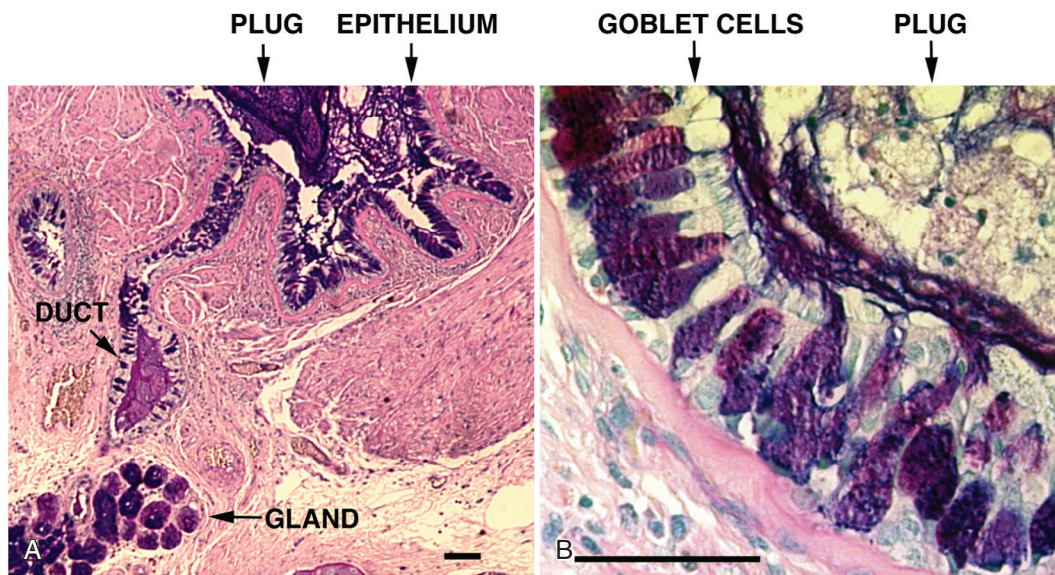


Figure 10-5 Mucous hypersecretion in fatal asthma. **A**, Alcian blue/periodic acid-Schiff (AB/PAS) staining for mucous glycoconjugates in a proximal airway section in a patient with fatal asthma. The airway lumen is plugged (PLUG) with mucus. The epithelium shows marked goblet cell metaplasia. The submucosal gland (GLAND) has intense staining for mucous glycoconjugates and has released its contents into a gland duct (DUCT) that is filled with AB/PAS-stained material. **B**, Another AB/PAS-stained section of airway epithelium in the same patient at higher magnification. Although goblet cells here remain intact, mucus can be seen streaming from the luminal tips of the goblet cells into the lumen. The lumen is filled with mucus. Both scale bars = 50 μ m.

the majority of the increased airflow resistance in asthmatics resides in small airways.

Widespread mucous hypersecretion was reported in fatal asthma by Cardell and Pearson²¹ in 1959 and was confirmed by other studies.³⁰⁻³³ Mortality in acute asthma is associated with mucous plugging, which is considered to be a major cause of death in asthma. An example of mucous plugging in fatal asthma is shown in Figure 10-5.

In experimental models of allergic airway disease, mucous hypersecretion has also been reported. For example, allergic sensitization by ovalbumin in rats increased mucin production in the airway epithelium,⁵⁴ an effect that was prevented by a selective inhibition of EGFR activation. For details of signaling involved in mucin production, see “[Epithelial Signaling Pathways for Mucin Production](#)” section.

Chronic Bronchitis and COPD (see Chapters 43 and 44)

In the past, mucous hypersecretion was often considered to be an annoying but otherwise benign aspect of airway diseases associated with smoking. Gradually researchers have realized that the clinical implications of the effects of cigarette smoke and other chronic irritants depend on the location and composition of the inhaled irritant. Originally, clinical researchers described a group of patients with symptoms of cough and sputum that were only weakly associated with decline in lung function. The disease was called “chronic bronchitis.” Unlike those in normal healthy persons, submucosal glands located in the large conducting airways of these individuals became enlarged and produced copious secretions, which were cleared in the sputum, assisted by cough.^{55,56} It was reasoned that, if disease in smokers is limited to the large airways and airway obstruction is not prominent, mucous hypersecretion may be disturbing but deterioration of lung function may not become

conspicuous. A correlation was found between the presence of bronchitis and the presence of submucosal gland hypertrophy in the central airways of smokers.⁵⁷ However, it was subsequently shown that chronic mucous hypersecretion is often associated with excessive decline in pulmonary function and increased risk for hospitalization. Mucin production is increased, especially with disease exacerbation and is associated with a decline in forced expiratory volume in 1 second.⁵⁸

Chronic smoking can also lead to progressive obstruction in the small airways, but the changes have been difficult to visualize because of their peripheral location. In addition, the airways are large in number,²⁷ so the majority of small airways must be obstructed before the airflow resistance is increased and causes symptoms. For these reasons, these peripheral airways remain a relatively silent zone until late in the disease. However, morphologic specimens of small airways in COPD, such as in the study of surgical specimens,⁵⁹ showed increased expression of mucins in bronchioles in COPD and an increased number of goblet cells in peripheral airways.⁶⁰ From these results it was concluded that exaggerated mucin production takes place in the bronchioles in COPD.

To examine the role of peripheral airway narrowing, in 1968 Hogg and colleagues⁶¹ showed that the major sites of airway obstruction in COPD are the smaller bronchi and bronchioles less than 2 mm in diameter. In 2004 Hogg and associates²² performed a quantitative assessment of small airways in surgically resected lung tissue in patients with COPD with different degrees of airway obstruction. The progression of COPD was strongly associated with an increase in inflammatory mucous exudates in the lumens of small airways. In addition, they reported an increase in the volume of tissue in the airway wall, which potentiates the

effects of luminal plugging (see Fig. 10-2). These results emphasize the roles of repair processes in the airway wall that decrease the luminal area and thus play important roles in airway obstruction in COPD.⁶²

In a review in 2010 it was concluded that mucus accumulation in conducting airways accounts for the symptoms of patients with COPD.^{63,64} Thus COPD affects central and peripheral airways; effects of the large airways leads to the majority of symptoms, but the peripheral airways appear to be the major sites of airway obstruction. The nature of small airway obstruction in COPD is reviewed by Hogg and colleagues.²² For a more recent review of the roles of small airways in COPD, see Burgel and associates.⁶⁵

EPITHELIAL SIGNALING PATHWAYS FOR MUCIN PRODUCTION

EARLY STUDIES OF MUCINS

Chronic airway diseases have long been associated with mucous hypersecretion. The gel-forming mucins, which are large glycoproteins, became recognized as being responsible for the major characteristics of mucus. Cloning of mucin genes (reviewed by Rose and coworkers⁶⁶) provided tools for studying mucin regulation. In the 1990s, intense research on mucins began, and many stimuli were shown to produce mucins in airway epithelial cells. Based on the newly available cell and molecular tools, rapid advances began to clarify the pathways involved in mucin production. In 1997 Li and associates³⁵ reported that *Pseudomonas* bacteria stimulate epithelial mucin production via a Src-dependent Ras/Raf/MAPK pathway.

EPIDERMAL GROWTH FACTOR RECEPTOR ACTIVATION

Many of the stimuli, such as microbes and cigarette smoke, that induce mucin production in airways are derived from the environment and are inhaled, depositing on the airway epithelial surface. Takeyama and colleagues⁵⁴ hypothesized that receptors on the surface of the airway epithelium could be candidates for epithelial signaling, resulting in mucin production in response to the deposition of the inhaled foreign particulates. EGF, an EGFR ligand, was discovered by Cohen,⁶⁷ and subsequently his group expanded the understanding of EGF and its receptor EGFR, focusing on epithelial cell proliferation and cancer. EGFR is a 170-kd membrane glycoprotein that is activated by multiple ligands.

Takeyama and coworkers hypothesized that epithelial responses to inhaled microbes such as *Pseudomonas* are initiated on the epithelial luminal surface, where the microbes are deposited, by activation of EGFR.⁵⁴ The authors discovered that activation of EGFR by its ligands (such as EGF, transforming growth factor [TGF]- α) cause mucin production in cultured human airway epithelial cells, an effect that is prevented by EGFR inhibition. They confirmed these results in rats in vivo and also found that ovalbumin sensitization increases MUC5AC mucin.

Perrais and associates confirmed that EGFR ligands activate EGFR to produce mucins and reported that downstream pathways include a Ras/Raf/MAPK cascade.⁶⁸ Subsequent reports identified EGFR as a key player in mucin synthesis/goblet cell metaplasia in response to multiple stimuli in vitro and in vivo (see Table 10-1).

METALLOPROTEASES CLEAVE MEMBRANE-BOUND EGFR LIGANDS TO PRODUCE MUCINS

Airway epithelial cells themselves synthesize EGFR ligands in the airway epithelium⁶⁹ as transmembrane precursors that can be cleaved by metalloproteases, releasing soluble active growth factors.⁷⁰ In 1999 Dong and colleagues⁷¹ reported that general metalloprotease inhibitors prevent the effects of EGFR proliferation in proportion to the release of the membrane-bound EGFR ligand TGF- α , and they concluded that the soluble ligand was responsible for the effects of EGFR activation. Prenzel and coworkers⁷² similarly reported that a general metalloprotease inhibitor prevented EGFR ligand release and subsequent EGFR activation. These papers were the first to implicate cleavage of EGFR ligands by metalloprotease(s) in EGFR surface signaling. Subsequently Kohri and colleagues⁷³ linked *Pseudomonas* bacterial supernatant to mucin production. EGFR activation was required, but the mode of EGFR signaling in the airway epithelium was unclear. One clue came from the study of tumor necrosis factor- α -converting enzyme (TACE), a member of the ADAM family of proteases, which is bound to the luminal surface of the airway epithelium. Shao and Nadel⁷⁴ recognized that TACE was capable of cleaving membrane-bound EGFR proligands (e.g., tumor necrosis factor alpha).⁷⁵ Shao and associates⁷⁶ showed that *Pseudomonas* and their product lipopolysaccharide increase mucin production in human airway epithelial cells, an effect that was reported to be EGFR dependent and associated with the cleavage and release of the membrane-bound EGFR ligand, TGF- α . Selective knockdown of TACE prevented the sequence leading to mucin production, establishing TACE as important in autocrine signaling involved in mucin production. These results established the role of TACE in the autocrine activation of EGFR and in mucin production in airways. Subsequently a variety of stimuli have been shown to stimulate mucin production via autocrine EGFR signaling in the airway epithelium.

ROLES OF REACTIVE OXYGEN SPECIES IN AIRWAY EPITHELIAL MUCIN PRODUCTION

Excess production of reactive oxygen species (ROS) is known to cause cell damage in chronic inflammatory diseases.⁷⁷ For example, ROS scavengers inhibit IL-8 production.⁷⁸ Recent studies have contributed to the understanding of the role of ROS in epithelial signaling and mucin production. Thus ROS stimulation (e.g., with H₂O₂) activates EGFR^{79,80} and results in mucin production.¹⁶

Dual oxidase-1 (DUOX1) was found in human airway epithelial cells and was reported to generate ROS.^{81,82} Shao and associates⁷⁴ suggested that DUOX1 could release ROS and thereby activate TACE. They used human neutrophil elastase as the stimulus, because human neutrophil elastase had been previously reported to produce mucin via

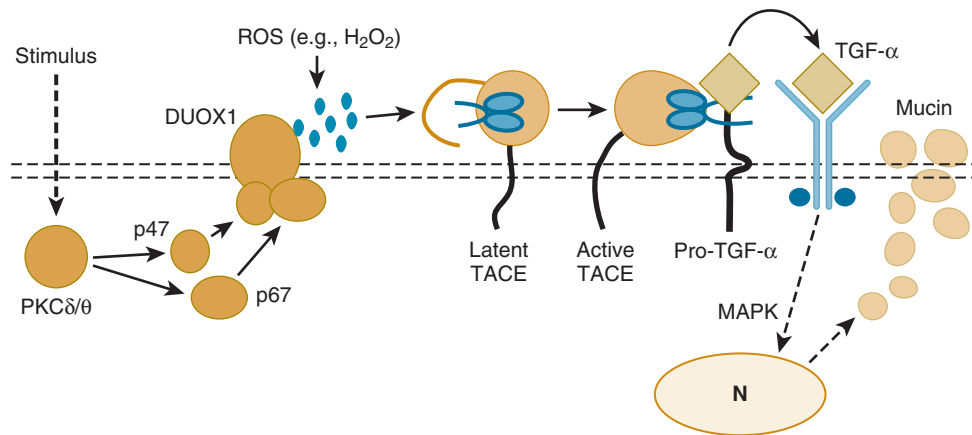


Figure 10-6 Diagrammatic scheme of epidermal growth factor-dependent cascade that causes mucin production. Deposition of a stimulus on the airway epithelium activates an epithelial receptor (not shown), stimulating protein kinase C (PKC) isoforms PKC δ/θ , which recruit cytosolic components (e.g., p47phox) to plasma membrane (double-dotted lines) to join dual oxidase-1 (DUOX1) to form an active enzyme system for generating reactive oxygen species (ROS; e.g., H₂O₂; represented by blue dots). ROS activate the latent form of tumor necrosis factor- α -converting enzyme (TACE), which has an inhibitory prodomain (represented by a curved line) covering its catalytic domain (represented by scissors), removing the prodomain and exposing the catalytic domain to cleave pro-transforming growth factor- α (TGF- α ; yellow diamond with a dark tail) into soluble TGF- α (yellow diamond without a tail), which binds to and activates epidermal growth factor receptor, initiating mitogen-activated protein kinase (MAPK) signaling to the nucleus ([N]), leading to mucin gene expression and mucin protein production. (Redrawn from Shao MX, Nadel JA: Dual oxidase 1-dependent MUC5AC mucin expression in cultured human airway epithelial cells. *Proc Natl Acad Sci U S A* 102:767, 2005.)

EGFR ligand-dependent activation.⁸³ Shao and associates⁷⁴ reported that human neutrophil elastase induced TACE activation, TGF- α release, and mucin expression, effects that were inhibited by ROS scavengers, implicating ROS in the response. Knockdown of DUOX1 expression with small interfering RNA prevented the responses. Furthermore, the protein kinase C (PKC)- δ /PKC- θ inhibitor rottlerin prevented the effects of human neutrophil elastase, suggesting that DUOX1 plays a critical role in mucin production via a PKC- δ /PKC- θ -DUOX1-ROS-TACE-proligand-EGFR cascade. The scheme is shown diagrammatically in Figure 10-6. It is of interest that DUOX1 may release ROS in a limited cell compartment adjacent to TACE, thus producing a signal in defense of the host without harmful effects on epithelial cell viability. In fact, DUOX1 is now recognized as playing a role in multiple epithelial defensive responses such as wound healing.⁸⁴ Activation of DUOX1 stimulates the production of the chemokine IL-8.⁸⁵ It is hoped that future studies in various epithelia will evaluate the importance of the proinflammatory cascade in a variety of epithelial-based diseases.

ROS liberated by inflammatory cells recruited to the epithelium may also play roles in mucin production. Neutrophils recruited to the airways and activated are known to produce ROS.^{86,87} When neutrophil supernatant from activated neutrophils was added to human airway epithelial cells, the cells became EGFR phosphorylated and increased mucin synthesis, effects that were shown to be due to EGFR phosphorylation.⁸⁸ However, neutrophils can also produce large amounts of ROS that may cause DNA damage and death of epithelial cells.⁸⁹ Thus, at low concentrations, molecules such as ROS can induce defensive responses such as mucin production, whereas, at higher concentrations, ROS can be destructive. Because ROS appears to play important roles in mucin production, and because studies of ROS-induced modulation are limited, further examination of ROS effects on epithelial cell signaling are in order.

MECHANISMS FOR HYPERSECRETION AND OTHER EXAGGERATED RESPONSES IN OBSTRUCTIVE AIRWAY DISEASES

A major characteristic of chronic obstructive airway diseases is the presence of excess mucous secretion and an increased responsiveness of airway mucous cells to a variety of stimuli. Because these abnormal responses are believed to play major roles in the deterioration and death of these patients, understanding the underlying mechanisms could result in effective therapies. Here we will provide an example of signaling pathways that could produce the exaggerated mucin production in airway diseases. Because exaggerated responses other than mucins also use proinflammatory EGFR cascades, an example involving neutrophil chemokine (IL-8) is included.

On the surface of the airway epithelium, there are two families of receptors of interest: (1) *Toll-like receptors* (TLRs) and (2) *G protein-coupled receptors* (GPCRs) (Fig. 10-7).

TOLL-LIKE RECEPTORS

Multiple stimuli activate airway epithelial cells and produce defensive responses. (For a discussion on innate immune responses see Chapter 12). Because of their importance in studies performed on mucin production, TLRs are included here. Recognition of inhaled stimuli was initiated with studies of inhaled microorganisms. Recognition of pathogens is mediated by a set of germline-encoded receptors called “pattern recognition receptors,” which recognize conserved molecular patterns shared by large groups of microorganisms. An important group of these receptors was discovered in fruit flies (so-called Toll receptors). When

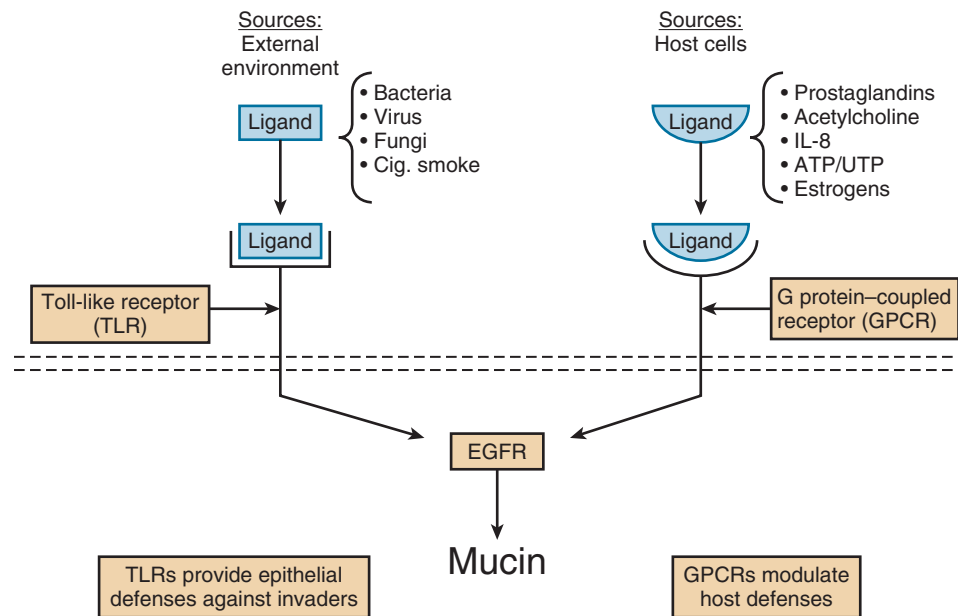


Figure 10-7 Airway epithelial surface signaling cascades activating the epidermal growth factor receptor (EGFR) belong to two major receptor families. (1) Toll-like receptors (TLRs). Inhaled microbes, allergens, and environmental contaminants depositing in the airways signal receptors called TLRs that transmit signals in a cascade to activate EGFRs; this activation, in turn, stimulates downstream pathways that result in defensive responses, including mucin production, interleukin-8 (IL-8) production that causes neutrophilic inflammation, angiogenesis, and production of antibacterial peptides. These receptors relate environmental stimuli to host defensive responses. The signaling may vary over time, and it is likely that the signaling is modified in different disease states. (2) G protein-coupled receptors (GPCRs). This large family of receptors generally modulates epithelial responses from signals generated within the host in the vicinity of the airway epithelium. Stimulation of GPCRs may result in a variety of different cellular responses. ATP, adenosine triphosphate; UTP, uridine triphosphate. (From Nadel JA: Twenty-five years of airway research: personal thoughts. *Proc Am Thor Soc* 7:338–342, 2010.)

they were found in mammals, they were called “Toll-like receptors.”⁹⁰

Early studies of TLRs showed that these receptors are responsible for many of the pathophysiologic effects of microbes. For example, the outer membranes of gram-negative bacteria contain the glycolipid lipopolysaccharide, which is responsible for many of the pathophysiologic features of these bacteria and is due to stimulation of TLR4. Subsequently, many TLRs have been described in mammalian cells, including the airway epithelium. The discovery of TLRs provides a mechanism for microbes to bind to the host epithelium and thus invade. Viral binding to these receptors is important for entry of many viruses into the cell, with consequent viral multiplication. This binding is also an important sensing device, allowing the epithelium to detect the presence of the microbe and then to initiate signaling that provides defensive responses. For example, multiple TLRs are involved in signaling responses to various viruses by IL-8 and by vascular endothelial growth factor production.⁹¹ These results show that multiple TLRs play roles in airway epithelial cell responses by activating EGFR via a complex epithelial cell cascade. Multiple stimuli such as bacterial products,^{76,92} respiratory viruses,¹⁰ and cigarette smoke¹¹ induce mucin production. TLRs receive messages from environmental stimuli (e.g., viruses, bacteria, cigarette smoke) and activate pathways downstream, resulting in EGFR activation and subsequent production of cell products including mucins, and the neutrophil chemoattractant IL-8. Interestingly, the antibacterial peptide cathelicidin LL-37 is also produced by EGFR activation.^{92a} LL-37 also causes activation of EGFR.^{92b} It is likely that selective pathways are produced to modulate these various activities.

G PROTEIN-COUPLED RECEPTORS AND THEIR ROLES IN MODULATING AIRWAY EPITHELIAL MUCINS AND OTHER EPITHELIAL RESPONSES

This family of receptors is very large, constituting almost 1% of the human genome.⁹³ These receptors play a role in regulating cell responses such as in allergic inflammation.⁹³ (For review of G proteins and their receptors see Barnard and colleagues,⁹⁴ Gilman,⁹⁵ and Pierce and associates⁹⁶.) Here we focus on the effects of GPCRs on the exaggeration of airway epithelial mucin responses.

GPCR Can Exaggerate EGFR-Dependent Mucin Production

As described earlier in the chapter, mucins are produced and recruited in the airways as an innate immune response to inhaled “irritants.” In obstructive airway diseases such as COPD,²² fatal asthma,⁹⁷ and CF,¹⁹ exaggerated mucin production leads to mucous plugging.^{9-12,19} Because multiple stimuli cause mucin production in human airway epithelial cells via an EGFR cascade, and because many GPCR ligands induce EGFR activation, Kim and coworkers⁹⁸ hypothesized that EGFR activation could lead to the production of a GPCR ligand, which could induce rephosphorylation of EGFR, leading to exaggerated mucin production in patients with chronic obstructive airway diseases. They used an available, widely used NCI-H292 cancer cell model system for mucin production.⁹⁹ In these cells, but not in the normal epithelial cells, EGFR activation resulted in stimulation of endogenous production and secretion of CCL20 (a GPCR ligand). This resulted in reactivation of EGFR, which led to further mucin production downstream of the second phase

of the EGFR activation. This second phase of EGFR activation was absent in the normal cells. The authors concluded that exaggerated mucin production in the abnormal cells took place via a positive feedback pathway where activation of EGFR leads to the production of CCL20, a GPCR ligand, resulting in EGFR reactivation and exaggerated mucin production. These findings may have potentially important therapeutic implications. Future studies should focus on chronic obstructive lung diseases using epithelial cells from subjects with asthma, COPD, and CF. In vivo studies could help to determine their utility in therapy.

GPCR Can Exaggerate EGFR-Dependent Interleukin-8 Production

In addition to mucins, EGFR activation results in the production of the chemokine IL-8, a potent neutrophil chemoattractant in airway epithelial cells.⁴⁵ In some lung cancers and in chronic obstructive airway diseases, epithelial EGFR activation results in exaggerated production of the neutrophil-recruiting chemokine IL-8.^{100,101} Because both mucin and IL-8 production are exaggerated in some chronic lung diseases and in lung cancer, Kim and associates¹⁰² suggested that GPCRs are involved in the exaggerated IL-8 “proinflammatory” responses. The authors stimulated epithelial (NHBE and NCI-H292) cells directly with an EGFR ligand (TGF- α). In the NCI-H292 cancer cells, EGFR activation led early IL-8 production, followed by the *cyclooxygenase-2* (COX2) dependent *prostaglandin* (PG) E2 production and release. PGE2 stimulated a rephosphorylation of EGFR and resulted in exaggerated IL-8 production by binding to its Gi protein-coupled *E prostanoïd* (EP) 3 receptor. In the normal human epithelial cells, TGF- α -induced EGFR activation did not reactivate EGFR, and less total IL-8 was produced. From these studies we conclude that in hyperresponsive airway epithelial cells, EGFR activation causes a feedback exaggeration of neutrophilic chemoattractant activity via a positive feedback pathway involving COX2/PGE2/EP3 receptor-dependent EGFR phosphorylation.

CFTR MODULATES EGFR-DEPENDENT PROINFLAMMATORY CHEMOKINE PRODUCTION

Mutations in the CFTR protein causes CF, a disease characterized by exaggerated airway epithelial IL-8 production of the neutrophil chemokine IL-8 production, which results in severe neutrophilic inflammation.^{42-44,103} There is growing evidence that the exaggerated IL-8 production is an intrinsic property of airway epithelial cells lacking normal CFTR. Because IL-8 production in airway epithelial cells depends on activation of EGFR,⁴⁵ Kim and coworkers hypothesized that CFTR normally suppresses EGFR-dependent IL-8 production and that the loss of CFTR exaggerates EGFR-dependent IL-8 production via an exaggerated EGFR cascade.⁴⁶ In cultured airway epithelial cells containing CFTR, treatment with the CFTR(inh)-172 induced increased IL-8 production dependent on EGFR, which led to the production and release of IL-1 α . The secreted IL-1 α , bound to its receptor (IL-1R), caused EGFR activation and downstream exaggerated IL-8 production (in excess of constitutive IL-8 production). This study suggests that up-and-

down regulation of CFTR on the epithelial surface may play roles in modulating epithelial inflammatory responses in health and may play important roles in disease. Components of this signaling cascade such as IL-1 α , EGFR, and CFTR may be therapeutic targets for exuberant neutrophilic inflammation in CF and in other inflammatory diseases.

EGFR ACTIVATION DECREASES EPITHELIAL ANTIVIRAL DEFENSES

Because the airway epithelial luminal surface is the first locus of contact of the host and environmental invaders such as respiratory viruses, it is not surprising that the epithelial surface contains an innate antiviral signaling pathway. (For full discussion of innate immunity, see Chapter 12.) *Interferon* (IFN)- λ , a recently discovered type III IFN,^{104,105} has been reported to provide antiviral protection against viral infection.^{105,106} Viruses also stimulate EGFR on the airway epithelial surface, inducing inflammatory responses.^{107,108} Because both of these signaling pathways are initiated at the epithelial luminal surface, it was suggested that this IFN antiviral pathway can be suppressed by viral activation of an EGFR response.¹⁰⁹ The authors report that virus-induced EGFR activation suppresses endogenous airway epithelial antiviral signaling. Influenza virus and *Rhinovirus*-induced EGFR activation suppressed IFN regulatory factor 1-induced IFN- λ production and increased viral infection. Conversely, inhibition of EGFR during viral infection increased IFN regulatory factor 1 and IFN- λ , which resulted in decreased viral titers. Future studies can investigate the EGFR downstream signaling involved. Interestingly, Wark and colleagues¹¹⁰ reported that asthmatic bronchial epithelial cells have a deficient innate immune response, suggesting that there is a link between deficient IFN- β and increased virus replication. These results suggest that epithelial interferons might be therapeutic targets for antiviral therapy.

Future studies are recommended to examine such exaggerated pathways in specific diseases such as asthma, COPD, CF, and cancer.

MUCUS BIOLOGY: PRESENT STATUS AND FUTURE OPPORTUNITIES

The studies of mucus/mucins has resulted in exciting advances, including the importance of the following: (1) the role of airways in the defense against inhaled particulate invaders; (2) epithelial mucins in the clearance of foreign particulates via mucociliary clearance and cough; (3) the physicochemical properties of mucus that lead to effective clearance of invaders; (4) the signaling pathways responsible for efficient clearance of invaders and the abnormal signaling that results in symptoms, deterioration of lung function, and death; and (5) the special and relatively neglected role of mucous obstruction (plugging) of peripheral airways, presently a silent zone in the lungs. We must also encourage further research on the interactions of cells and molecules that lead to disease and the discovery of therapeutics that can alleviate or prevent disease.

Key Points

- Because of their location at the luminal airway surface, the epithelial cells are key components of the host's defensive system.
- Epithelial mucin production and secretion play major roles in clearance of inhaled "invaders" by cough and by mucociliary clearance. Normally mucin production is modest, and inhaled foreign substances are cleared asymptotically and without obvious pathologic changes.
- Multiple stimuli (e.g., viruses, bacteria, cigarette smoke, allergens) induce mucin production by stimulating Toll-like receptors, which recognize the presence of a foreign molecule (e.g., a virus) and respond by activating a signaling pathway that results in mucin production via an *epidermal growth factor receptor* (EGFR) cascade.
- In chronic obstructive airway diseases (e.g., COPD, cystic fibrosis, acute asthma), mucous hypersecretion develops via EGFR-dependent signaling, which causes exaggerated mucin production.
- Mucous hypersecretion in the large conducting airways is manifested in symptoms, predominantly cough and sputum production. Unlike the effects in the large airways, bronchiolar hypersecretion is generally asymptomatic early and consists of luminal mucous plugging, which can ultimately lead to incapacitation and death.
- There is evidence that mucous secretion is EGFR dependent. Recent studies suggest that a special family of receptors, G protein-coupled receptors, could be involved in the exaggerated mucin responses in chronic airway diseases via EGFR positive feedback pathways.
- Recent studies suggest that the proinflammatory effects of EGFR activation are normally antagonized by the presence of the *cystic fibrosis transmembrane conductance regulator* (CFTR) on the epithelial luminal surface. Thus modulation of CFTR could affect EGFR-mediated responses.
- In addition to mucous hypersecretion, chronic airway obstructive diseases also often show other exaggerated inflammatory responses, such as neutrophilic inflammation, which are also EGFR dependent. Analysis of the pathways responsible for the abnormal airway epithelial responses suggests important strategies for therapy of the hypersecretory and proinflammatory effects that are recognized as important in chronic airway diseases.

Complete reference list available at *ExpertConsult*.

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AEROSOL DEPOSITION AND CLEARANCE

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INTRODUCTION

The human lung has a large surface area, which for an average-size person approximates half a doubles tennis court, thus maximizing the approximation and apposition of capillaries to the epithelial surface. Whereas this design optimizes gas exchange, it also has the intrinsic risk of exposing the delicate alveolar tissues to potentially noxious particles that may be present in the ambient air. There are various safeguards against the danger posed by inhaled particles. The first line of defense is that the configuration of the nasopharynx and serial branching of the airways causes particles to deposit proximal to the more vulnerable alveolar structures.^{1,2} Second, if an insoluble particle deposits in the lung, there are processes by which it can be cleared from the airways or alveoli. Clearance of insoluble particles that deposit in the ciliated airways is achieved by mucociliary clearance.³ The particles are trapped in a mucous blanket, which is then transported proximally by beating cilia. If the cilia are not functioning optimally or if the quantity/quality of the airway mucus is abnormal, the mucus and its entrapped particulates can be cleared by cough. Particles that deposit distal to the ciliated airways are removed by alveolar clearance, mainly by macrophages ingesting the particles and transporting them to regional lymph nodes.

The branching structure of the airways is a barrier not only to noxious environmental aerosols but also to therapeutic aerosols. However, the application of the principles of deposition facilitates the design of therapeutic aerosol development.⁴ For the most part therapeutic aerosols are "targeted" to the lungs, that is, they are designed to treat lung diseases directly and avoid systemic toxicity. Theoretically, the lungs' large surface area can facilitate the sys-

temic delivery of nonrespiratory drugs via the lung as aerosols, usually proteins such as insulin that cannot be given by the oral route. However, to date, the use of this pathway has not had a major impact on clinically successful systemic therapeutic drugs.

DEFINITION AND DESCRIPTION OF AN AEROSOL

An *aerosol* can be defined as a system of solid particles or liquid droplets that can remain dispersed in a gas, usually air. Naturally occurring aerosols, as well as those emitted by clinical aerosol generators, almost always contain a wide range of particle sizes. Because the aerodynamic behavior of an aerosolized particle is critically influenced by its mass, it is important to be able to describe precisely the size distribution of aerosolized particles. In clinical studies the *mass median aerodynamic diameter* (MMAD) and the *geometric standard deviation* (σ_g) are often used to characterize the dimensions of an aerosol. When the mass distribution of particles in an aerosol is fractionated and the cumulative particle distribution plotted as a lognormal distribution on probability paper, it often approximates a straight line. However, recent studies of clinical aerosols have indicated that nebulized particles are often not lognormal in distribution.⁵ The MMAD represents the point in the distribution above which 50% of the mass resides, expressed as the diameter of a unit density (1 g/mL) sphere having the same terminal settling velocity as the aerosol particle in question, regardless of its shape and density.

The lognormal plot is convenient because, if linear, it defines a statistically "normal" distribution and the data

can be described accurately by the MMAD and the standard deviation alone. For a lognormal distribution, one standard deviation is called the “geometric standard deviation,” or σ_g . The σ_g is the ratio of the size at 84% (or 16%) to the MMAD and is an indicator of the variability in particle diameters. If the particle size varies over a wide range ($\sigma_g > 1.2$), it is described as having a *polydisperse* particle distribution; if the particles are of similar size ($\sigma_g < 1.2$), the particle distribution is described as *monodisperse*. Monodisperse aerosols are usually encountered only in research studies where specialized generators are used to create such an aerosol.⁶ For clinical aerosols that are not lognormal and are widely polydisperse, it is best to relate deposition studies to the entire distribution of particles and avoid focusing on simple descriptive terms like the MMAD and σ_g .^{5,7}

The definition of the *mass median diameter* is the same as that of the MMAD except that the data are not normalized to unit density.

PRINCIPLES OF DEPOSITION

The fraction of inhaled particles that deposit (as opposed to being exhaled) is called the “deposition fraction.”^{1,2} The likelihood that a particle will deposit in a particular airway depends on the interaction of three factors: the physical characteristics of the particle (e.g., mass, shape), the gas flow in which the particle is transported (the patient’s breathing pattern⁸ and any velocity provided to the particle by a propellant), and the airway anatomy (especially the presence of airway obstruction⁹). In general, the greater the mass, the faster the velocity, and the narrower the airway, the greater the predisposition of the particle to deposit by a process called “inertial impaction.” Inertial impaction is the dominant mechanism by which particles deposit in the nasopharynx and more proximal airways and describes the process by which a particle fails to follow the air stream in which it is suspended, thereby impacting on an obstacle instead of circumventing it. The probability of a particle undergoing inertial impaction (I) can be estimated using the following equation:

$$I = \alpha(V_t V_a \sin \theta / gR) \quad [1]^1$$

where V_t is the settling velocity of the entrained particle, V_a is the air stream velocity, θ is the angle required to circumvent the obstacle, g is the acceleration due to gravity, and R is the airway radius. The settling velocity (defined in Equation 2) increases as particle size increases. This equation applies to situations in which laminar flow predominates. The presence of turbulent nonlaminar flow will tend to increase impaction further. Particles that fail to deposit in proximal airways by inertial impaction can deposit in peripheral airways and alveoli by a process called “gravitational sedimentation.”

Gravitational sedimentation is the process by which a particle accelerates under gravity until it reaches a terminal settling velocity (V_t), which is determined by the equation¹

$$V_t = (\rho - \sigma)gd^2 / 18\gamma \quad [2]$$

where ρ is the density of the particle, σ is the density of air, g is the acceleration due to gravity, d is the diameter of the

particle, and γ is the viscosity of air. Therefore, for a given velocity, the greater the aerodynamic mass of an aerosol, the shorter the time it will remain suspended in the air stream. Gravitational sedimentation is the main mechanism by which particles (0.5 to 5.0 μm in diameter) deposit in the peripheral regions of the lung.

Sedimentation is critically dependent on the patient’s breathing pattern.⁸ If there is a breath-hold before exhalation, particles are more likely to sediment; without a breath-hold, particles are more likely to be exhaled rather than deposited. It has also been suggested that alveolar volume may affect deposition fraction (larger air spaces require more time for sedimentation).

Very small particles ($<0.2 \mu\text{m}$) can deposit by diffusion. The diffusion coefficient of a particle (D) can be expressed² as

$$D = kT / 3\pi\eta d \quad [3]$$

where k is the Boltzmann constant, T is the temperature in Kelvin, η is the gas viscosity, and d is particle diameter.

These tiny particles are rarely important in therapeutic aerosols, but in inhalation toxicology studies these particles can be produced by combustion and may be clinically relevant, even though they tend to be transient because of the tendency to agglomeration. In addition, man-made nanoparticles, which are of increasing interest in electronics and biomedical research, would, if inadvertently inhaled, be likely to deposit by diffusion (discussed later under “Environmental Aerosols”).

Particles between 0.2 and 0.5 μm in diameter tend to be too small to deposit efficiently by sedimentation and yet too large to deposit efficiently by Brownian diffusion and tend to be exhaled rather than deposited in the lung.^{1,2}

MEASUREMENTS OF PARTICLE SIZE

EVALUATION OF AEROSOL PARTICLE SIZE

Particle size is an important factor in determining whether a particle will undergo nasopharyngeal deposition, airway deposition, or alveolar deposition.¹⁰ Particle size is usually measured by light scattering or cascade impaction: light scattering is based on the principle that there is differential scattering of polarized light by particles of different sizes; cascade impaction is based on a different trajectory of particles of different mass. In cascade impaction, particles at a set flow rate go through a series of apertures of decreasing diameter and impact on a series of plates if they fail to follow the air stream.

Cascade impactors with high flow rates (e.g., 28 L/min) were originally designed for environmental sampling of ambient air to collect 100% of the emitted dose. They have been adopted as the method of choice for monitoring quality control in a manufacturing plant for aerosol delivery. Cascade impaction has an advantage over light scattering in that it facilitates the correlation of different methods of quantifying the distribution of the active drug (e.g., chemical analysis of drug on each plate compared with radioactive label or weight). However, measuring the emitted dose of aerosol using a high-flow cascade impactor is not ideal

for predicting how an aerosol will perform in clinical practice. Although low-flow cascade impactors sample only some of the output, they more closely duplicate *in vivo* conditions.^{5,11,12}

APPLICATION OF IN VITRO MEASUREMENTS OF PARTICLE SIZE TO CLINICAL STUDIES

Particle size measurements using different techniques are not necessarily interchangeable. Meaningful comparisons of the sizes of clinical aerosols, especially those produced by a pressurized *metered-dose inhaler* (MDI; which emits high-velocity particles), can be made only if obtained with identical techniques. Nevertheless, despite the technical difficulties encountered in measuring the size of polydisperse clinical aerosols, some investigators have established that, when used with appropriate caution, data obtained by *in vitro* measurement of particle size do provide useful predictive data for subsequent clinical studies.^{5,7,11}

The classic studies of the influence of particle size on lung deposition were performed with monodisperse aerosols consisting of particles that would not absorb moisture from the air (*nonhygroscopic*).⁶ In contrast, pharmaceutical aerosols tend to be polydisperse liquid droplets, with the active pharmaceutical ingredient (as well as in some cases pharmaceutically inactive excipients such as preservatives and freon) being either in solution or suspended as micronized particles. Droplets can change size by exchanging water with either the dry carrier gas or the humid environment of the upper airway.^{2,13} In addition, some drug ingredients are hygroscopic, and some diluent solutions are hypertonic, both of which could lead to an increase in particle size; the clinical significance of such changes is not known with certainty. It has been reported that hypotonic saline aerosols were associated with a slightly more peripheral deposition pattern on gamma scintigraphy compared with hypertonic saline aerosols.¹⁴ Measuring the particle distribution of droplet aerosols is difficult because the particles can be affected by ambient humidity. Therefore the predictive value of cascade impaction data from droplet aerosols for *in vivo* deposition (e.g., for upper airway deposition as measured by gamma scintigraphy) is strongly dependent on the specific technique used for cascade impaction.¹²

GENERATION OF THERAPEUTIC AEROSOLS

There are three common ways in which therapeutic aerosols can be generated. First, the patient's inspiratory airflow can aerosolize a micronized dry powder (dry powder inhalers). Second, micronized particles can be suspended in a volatile pressurized liquid that vaporizes when at atmospheric pressure, thus imparting velocity to the emitted particles (MDIs). Third, a dispersal force can be applied to a liquid to generate droplets, which are then inhaled by tidal breathing. The generation of the dispersal force can be as simple as using a compressed air source attached to a narrow orifice to generate a Venturi effect (i.e., jet nebulizer) or by more complex vibrating membranes and meshes.

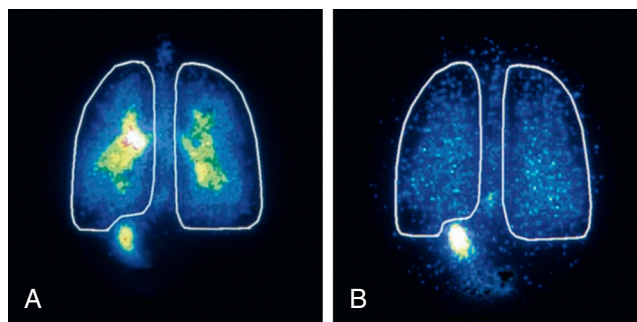


Figure 11-1 Importance of inspiratory impaction using common aerosol delivery systems. Deposition images following inhalation of radio-labeled aerosols: Turbuhaler, a dry powder inhaler (A), and a metered-dose inhaler (MDI), a pressurized chlorofluorocarbon propellant (B). Turbuhaler provided more lung deposition than the MDI. With the MDI, most of the inhaled dose was deposited in the oropharynx and detected in the stomach, after being swallowed (Turbuhaler, 57%; metered-dose inhaler, 81%).

DRY POWDER DEVICES^{4,15,16}

Because dry powder inhaler aerosols are generated by the patient's inspiration, they are by definition coordinated with inspiration (Fig. 11-1A). In optimizing the design of new devices, there is a need to minimize resistance to flow so that weak and tachypneic patients will be able to generate a threshold flow rate. Furthermore, it is desirable that the emitted dose should not vary significantly with changes in inspiratory flow so that intersubject dosing remains consistent. For high-potency drugs, lactose is often used as an inert, bulking agent. Devices can be single-dose devices in which a capsule of powder is perforated in the device (Spiriva HandiHaler, Boehringer Ingelheim, Ridgefield, CT), multidisk with individual doses wrapped in foil blisters¹⁶ (Advair/Seretide Diskus, GlaxoSmithKline, Research Triangle Park, NC), or multidose metered reservoir (Pulmicort Flexhaler, AstraZeneca, Wilmington, DE.). For dry powder devices to maintain reproducible dosing over time, it is critical that the powder be protected from moisture. Despite these technical challenges, the design of dry powder inhalers has greatly improved, and the devices described previously perform at high levels of efficiency and reproducibility.¹⁷

PRESSURIZED METERED-DOSE INHALERS

Pressurized MDIs using chlorofluorocarbon propellants have been used in clinical practice for 50 years and remain the most popular method of administering short-acting rescue inhalers and inhaled corticosteroids. They are portable and discreet. The velocity of the emitted particles, however, requires that for adequate lung deposition, there must be precise coordination with a patient's respiration. Studies have shown that actuation technique is suboptimal in most patients. Even with optimal technique, 80% of the emitted dose may deposit on the pharynx and can cause local irritation (see Fig. 11-1B). In addition, some orally bioavailable medications cause significant systemic exposure from swallowed medication. Valved holding chambers reduce pharyngeal deposition because high-velocity

particles impact on the inside of the chamber and, if the chamber has valves, the need for precise coordination with respiration is obviated.¹⁸ For young children, a face mask can be used in conjunction with a valved holding chamber. Unfortunately, registration studies for MDI medications are almost always performed without a holding chamber because manufacturers do not want their product's prescription tied to a specific holding chamber. To make the chambers more acceptable to patients, effective small-volume chambers (140 mL) and collapsible chambers have been developed.

For the past decade there has been a phase-out program for chlorofluorocarbon-containing pressurized MDIs because of concerns about the impact of chlorofluorocarbons on the environment. Short-acting β -agonists and corticosteroid pressurized MDIs have been reformulated using hydrofluoroalkane as a propellant. The U.S. Food and Drug Administration mandated that these new hydrofluoroalkane-containing pressurized MDIs have performance standards at least equal to existing chlorofluorocarbon-containing pressurized MDIs. Although this task has been far more difficult and expensive than anticipated, the last remaining chlorofluorocarbon-containing pressurized MDIs were removed from the U.S. market in early 2009.¹⁹⁻²¹

JET NEBULIZERS

The ubiquitous small-volume jet nebulizer is the mainstay of bronchodilator delivery in hospitalized patients and patients at the extremes of age. These devices are cheap and require little patient cooperation. In addition, they are useful for delivering medications that have a relatively large mass such as antibiotics. Generation of the driving pressure requires either a tank of pressurized gas or an electric compressor. Although the manufacturers of compressors have made these devices more portable, they are far from convenient for ambulatory patients. In addition, conventional nebulizers tend to take 10 to 20 minutes to deliver a single treatment, which interferes with adherence. Most generic nebulizers are inefficient and deliver less than 10% of the nebulizer charge to the lung. The remainder is left in the nebulizer chamber as so-called dead volume (droplets and dried particles left on the nebulizer walls), lost through the expiratory port because the device generates aerosol throughout the respiratory cycle, or deposited in the extrapulmonary upper airway because most of the emitted dose is contained in large, poorly respirable particles.

NEW DEVELOPMENTS IN AEROSOL DELIVERY SYSTEMS

Manufacturers have made enhancements in nebulizers.²² Internal recycling baffles reduce emitted particle size. Expiratory filters have been added for potentially hazardous aerosols to reduce collateral exposure. Significant enhancements in drug delivery by nebulizers are possible by coordinating nebulization with inspiration (e.g., "breath actuation") that essentially turns the nebulizer off during expiration. Another improvement in efficiency is called "breath enhancement," which uses the patient's inspiratory flow through the nebulizer to increase drug delivery

(e.g., LC Star, Pari, Germany; Ventstream, Medicaid, Bognor Regis, UK).²³

The newer devices include the AKITA (Activaero GmbH, Gemünden, Germany), AER_x (Aradigm, Hayward, CA), eFlow (Pari, Midlothian, VA), and I-neb (Philips/Respironics, Pittsburgh, PA). Each device employs unique proprietary technologies that distinguishes it from the traditional devices. Some tend to be more precise in their coordination with breathing patterns of individual patients (AKITA, I-neb, AER_x); they usually have a lower dead volume in the nebulizer chamber, a greater fraction of particles in the respirable range (i.e., $<5\ \mu\text{m}$), and shorter treatment times.²⁴ They eschew bulky compressors, use either vibrating mesh or crystal, or extrude the liquid through tiny holes or a combination of both vibration and microextrusion.²⁵ They vary in their durability and the relative ease with which they can be cleaned between treatments.

Recently the design of aerosol delivery systems has combined slow and deep inspiration with direct mechanical feedback to the patient for particles of relatively large MMAD. As discussed earlier, a "slow" inspiration reduces particle inertia and allows inhalation of particles that would otherwise deposit in the oropharynx during tidal breathing and will thus minimize oropharyngeal deposition.²⁴

PRINCIPLES OF ASSESSMENT OF DELIVERY SYSTEMS

Assessing effects of an aerosolized drug requires the understanding of three major factors: the characteristics of the aerosol delivery system, the quality of the aerosol produced, and the quantification of deposition within the lungs.^{25a} Quantification of deposition is performed *in vivo* and is time consuming and costly and involves some degree of risk and uncertainty to the patient. The other two components of the aerosol delivery process can be well characterized and studied *in vitro*. The field of aerosol delivery has advanced significantly in the last 10 years so that aerosol delivery characteristics and the quality of the aerosol can be significantly optimized on the bench before exposure to patients.

THE INHALED MASS

Figure 11-2 depicts a simple *in vitro* setup for measuring the quantity of aerosol produced by a nebulizer. A filter that captures the aerosolized particles has replaced the mouthpiece. This system does not require an understanding of nebulizer function from first principles. Because the nebulizer is attached to a breathing device (Harvard pump, Harvard Apparatus, South Natick, MA), the conditions of delivery such as routine tidal breathing can be duplicated. The quantity of drug captured on the inspiratory filter represents the amount that passes the lips of the patient. To distinguish this quantity from a "dose" or deposited drug, the term *inhaled mass* has been coined. The inhaled mass represents "delivery" of drug to the patient constrained by conditions that should mimic actual clinical delivery.

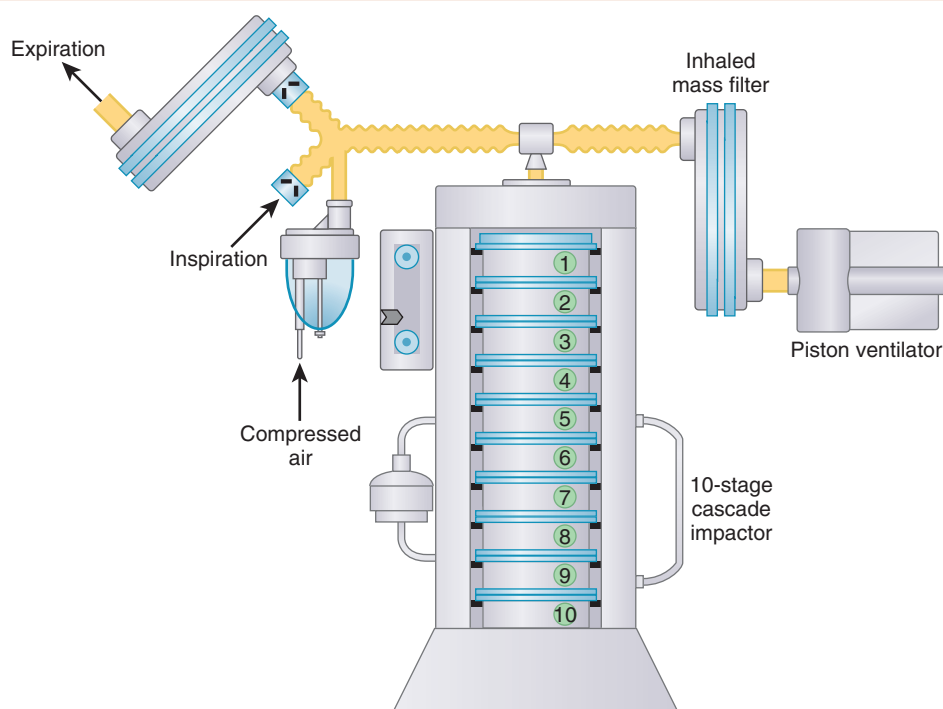


Figure 11-2 Modern testing of aerosol delivery systems can measure inhaled mass and particle distribution for a nebulizer. Breathing patterns are defined by settings on the piston ventilator. Particles presented to the “patient” (the ventilator) are captured on the inhaled mass filter. In separate experiments the cascade impactor measures inspired aerosol. These methods have been useful in simulating patient exposures. (Redrawn from Smaldone GC: Drug delivery via aerosol systems: concept of “aerosol inhaled.” *J Aerosol Med* 4:229–235, 1991, with permission.)

DEPOSITION

The term *deposition* begins to imply a “dose” to the patient. The term *deposition* needs to be further refined in a given situation (e.g., oropharyngeal versus parenchymal deposition, or central versus peripheral deposition within the lung). Each of these terms may be important depending upon the disease entity to be treated. Obviously, the measurement of the actual deposition requires an *in vivo* experiment. However, deposition can be estimated based on parameters that are measured *in vitro* as shown in [Equation 4](#):

$$\text{Deposition} = \text{inhaled aerosol} - \text{exhaled aerosol} \quad [4]$$

Because the term *aerosol* is a little vague with respect to drug activity, [Equation 4](#) can be rewritten as

$$\text{Deposition} = \text{inhaled mass} - \text{exhaled mass} \quad [5]$$

Bench models are useful in identifying the parameters that define the *inhaled mass* for different devices and experimental conditions ([Equation 5](#)).¹¹ Investigators have developed protocols to test the output *in vitro* in ways that more closely replicate clinical practice. For example, bench testing of jet nebulizers can incorporate a piston ventilator to duplicate breathing patterns of spontaneously breathing patients or a ventilator circuit and endotracheal tube to duplicate aerosol delivery in the setting of mechanical ventilation. These *in vitro* protocols can be used to evaluate aerosolization protocols in ways that can optimize pulmonary drug deposition in subsequent clinical studies. For example, in patients undergoing mechanical ventilation, the brand of nebulizer, humidification, ventilator settings, and nebulizer

fill volume are factors that can be optimized *in vitro* before proceeding to clinical studies.^{26,27}

Because pulmonary anatomy is an important determinant of drug deposition, *in vitro* studies are a useful adjunct but not a substitute for clinical deposition studies. Clinical deposition studies are used both to quantify the mass of an inhaled drug deposited in the patient and to determine the regional distribution of drug deposited in the patient.²⁸ Deposition can be divided into extrapulmonary deposition versus pulmonary deposition, whereas pulmonary deposition can be further subdivided into deposition in central airways versus peripheral air spaces. Gamma scintigraphy can be used to acquire both types of data. A radiotracer (usually technetium) is mixed with the study drug and aerosolized and inhaled. The drug deposition images on the gamma camera are superimposed on an outline of the patient’s lung (obtained by a separate radioactive gas study^{29,30} or a transmission image from an external standardized radioactive source³¹). Quantification of lung deposition can be obtained by expressing the radioactivity detected in the lungs as a percentage of the radioactivity initially placed in the nebulizer. One must correct for the attenuation of radioactivity by the patient’s body habitus using the transmission image. It is also necessary to confirm with a cascade impactor that the distribution of radiotracer and drug is identical throughout the range of particle sizes.²⁶ For example, analyzing and correlating both the chemical composition and radioactivity of therapeutic aerosols captured on the stages of a cascade impactor verifies that the distribution radiotracer measured by gamma scintigraphy is a reflection of the distribution of an inhaled gene therapy vector.³²

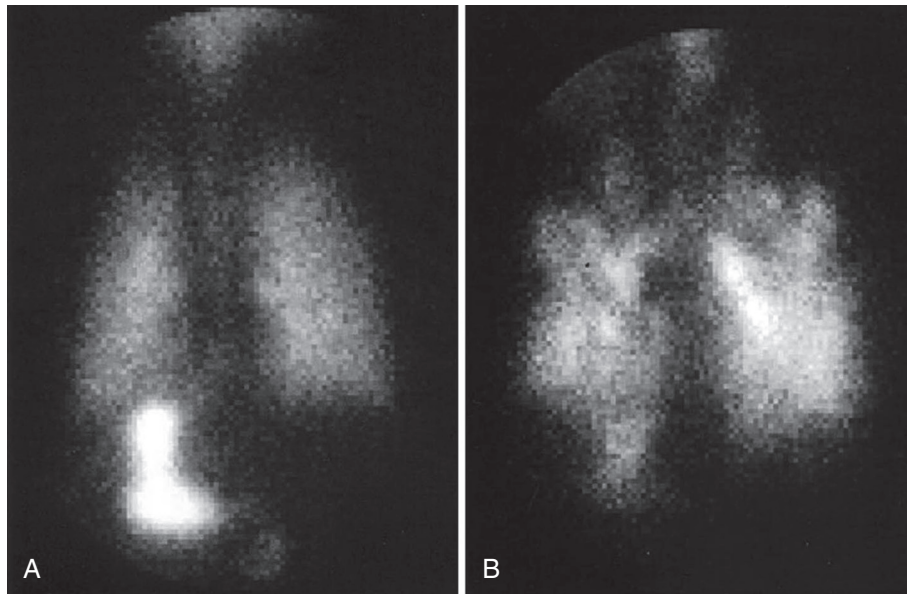


Figure 11-3 Differences in aerosol deposition between adults and children illustrated by deposition scans from patients with cystic fibrosis breathing the same aerosol. A, A 9-year-old boy with 48% upper airway (stomach) deposition. **B,** A 31-year-old woman demonstrating a more peripheral but patchy distribution but minimal activity in stomach. Aerosols that can readily bypass the upper airways of an adult frequently deposit in the oropharynx of a child. (From Diot P, Palmer LB, Smaldone A, et al: RhDNase I aerosol deposition and related factors in cystic fibrosis. *Am J Respir Crit Care Med* 156:1662–1668, 1997, with permission.)

There are other methods of measuring drug deposition that do not require gamma scintigraphy. A mass balance technique uses filters placed near a patient's mouth to measure the first amount inhaled and the amount exhaled, with the difference being what was deposited in the patient.^{29,30} Pharmacokinetic approaches include comparison of blood levels of aminoglycosides obtained after an intravenous calibration standard to blood levels obtained after inhalation³³ or the urinary concentrations of pentamidine after inhalation.^{34,35} Oral charcoal can be used to block the absorption of swallowed pharyngeal deposited drug so that blood levels will be due entirely to drug absorbed through lung deposition and absorption.¹⁵

STRATEGIES TO OPTIMIZE DEPOSITION OF THERAPEUTIC AEROSOLS

The determinants of aerosol deposition apply to both therapeutic and environmental inhaled particles. To optimize deposition of therapeutic aerosols, a number of strategies have been developed.

GETTING PARTICLES PAST THE OROPHARYNX

In clinical studies, predicting penetration of aerosol beyond the oropharynx and subsequent lung deposition is a major criterion for device selection. Deposition estimations are often based on particle size measurements defined by in vitro characterization of the aerosol produced by a given device. During tidal breathing, most investigators would expect aerosols with particles below 5 μm to be deposited primarily in the lungs (the "fine particle fraction"). Con-

ventional aerosol delivery devices (jet nebulizer, pressurized MDI, and dry powder inhaler) emit particles with a wide range of sizes and velocities. It is estimated that the combined effect of particle size, particle inertia, and the geometry of the oropharynx result in upper airway deposition ranging from 30% to 90% of the total deposition in the patient. Only nebulizers producing particles with particularly small MMAD (e.g., AeroTech II, Biodex, Shirley, NY; MMAD, 1.0 μm) bypass the upper airways (5% oropharyngeal deposition in adults).³⁶ In children the smaller oropharyngeal airways make the task more difficult.³⁷ In children, compared to adults, significantly more drug may be deposited in the oropharynx and less in the lung (Fig. 11-3).

CONTROL OF BREATHING PATTERN AND AEROSOL DEPOSITION

In normal subjects the pattern of breathing is the most important factor affecting aerosol delivery and deposition. How the patient breathes can affect the performance of the device, the particle distribution, the penetration of particles past the oropharynx, and the deposition within the parenchyma. Earlier studies suggested that much of the variation in parenchymal deposition was related to differences in airway geometry between subjects. However, variability in deposition between subjects appears well controlled if the pattern of breathing is controlled. Figure 11-4 depicts data from 11 subjects inhaling 2.6- μm monodisperse particles. The fraction of particles depositing in the lung can be closely related to the period of breathing. In simplified form, points near the origin of the horizontal axis represent normal tidal volumes and frequencies. As tidal volume increases and breathing frequency decreases, the time of inspiration is prolonged (e.g., "slow and deep inspiration"). The curve depicted in Figure 11-4 represents maximum

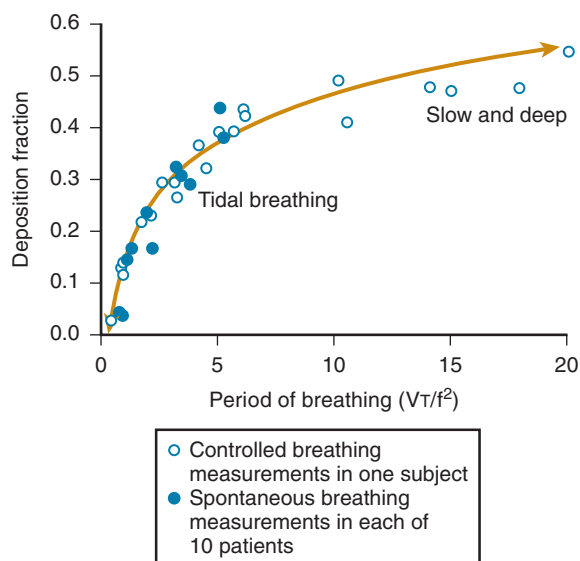


Figure 11-4 Deposition in the lungs is primarily determined by the pattern of breathing. The data are from 1 subject during controlled breathing (open circles) and from 10 patients during spontaneous breathing (filled circles; data for 2.6- μ m monodisperse particles). The deposition fraction is the fraction of inhaled particles that deposited in the subject. Breathing pattern is defined by a relationship that represents a measure of the period of breathing (tidal volume divided by breathing frequency squared, or V_T/f^2). Typical tidal breathing is found near the origin, slow and deep inspirations appear away from the origin. The deposition fraction varied over a wide range, but changes in the deposition fraction were accounted for by changes in the breathing parameter. (Modified from Bennet WD, Smaldone GC: Human variation in the peripheral airspace deposition of inhaled particles. *J Appl Physiol* 62:1603–1610, 1987, with permission.)

deposition with a slow and deep inspiration for particles of 2.6 μ m. For larger particles the curve would be shifted upward, with deposition approaching 100%.

EXPIRATION AND PROBLEMS WITH AEROSOL DEPOSITION

In normal subjects, those particles that do not deposit during inspiration are largely exhaled completely. Particles that pass through the oropharynx during inspiration enter the central airways and traverse them without difficulty because lobar and segmental bronchi are generally widely patent during inspiration. Then the particles enter alveoli with a few depositing by sedimentation, and, like cigarette smoke, the bulk of the aerosol is exhaled. Deposition is controlled by sedimentation in small airways and is influenced by local geometry and, to a strong degree, by the residence time (period of breathing).

In obstructive lung disease, maximal expiratory flows are diminished. With moderate disease, maximal flows can be superimposed on tidal breathing; as the disease progresses, maximal flows can be reduced even further. Therefore it is common to observe that patients are often breathing on their maximal expiratory flow volume curves even during quiet tidal breathing³⁸ (Fig. 11-5). In these patients, flow-limiting segments exist in the same airways found in normal subjects during forced expiration, but in these patients they form during every tidal breath. Therefore, in patients with obstructive lung disease, deposition in the peripheral lung

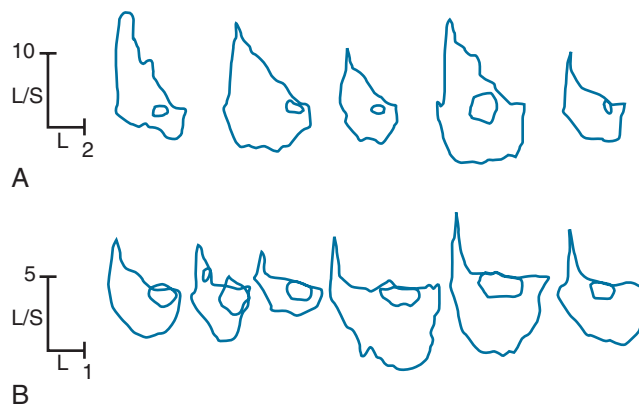


Figure 11-5 Tracings of maximal flow and tidal flow versus volume for normal subjects (A) and patients with severe obstructive lung disease (B). Note the difference in size of the axes for the two panels (ordinate: flow range from 0 to 10 or 0 to 5 L/sec; abscissa: volume range from 0 to 2 or 0 to 1 L, respectively). B, For the patients, tidal loops are superimposed on maximal flow volume curves. (Modified from Smaldone GC, Messina M: Flow-limitation, cough and patterns of aerosol deposition in humans. *J Appl Physiol* 59:515–520, 1985, with permission.)

poses a significant challenge because deposition of aerosol is enhanced during expiration at sites of flow limitation (Fig. 11-6). Based on these physiologic considerations, peripheral deposition of aerosol in these subjects would be favored by using a system that combines a slow prolonged inspiration with a breath of sufficiently long duration to promote deposition by settling and to minimize the particles available to the airways during expiration.

For many aerosol applications, inhaling particles “slowly and deeply” solves the problems outlined previously. A slow inhalation will minimize oropharyngeal deposition. “Slow” inspiration reduces particle inertia and allows inhalation of larger particles that would have deposited in the oropharynx during tidal breathing. This concept has been exploited in physiologic studies of mucociliary clearance in the distal airways using particles as large as 6 μ m.³⁹ More recently, commercial applications of these principles have combined slow and deep inspiration with direct mechanical feedback to the patient for particles of relatively large MMAD, resulting in more efficient delivery to the more distal airways (Fig. 11-7).⁴⁰

ADDITIONAL FACTORS INFLUENCING DEVELOPMENT OF THERAPEUTIC AEROSOLS

In addition to efforts to bypass the oropharynx and optimize lung deposition, other factors influence the design of therapeutic aerosols. Some of these factors are disease related and others relate to specific populations.

ASTHMA

One of the most important features of the commercial formulations of inhaled corticosteroids, the mainstay of maintenance therapy for asthma, is reduced oral bioavailability.^{41–43} Many delivery systems for inhaled

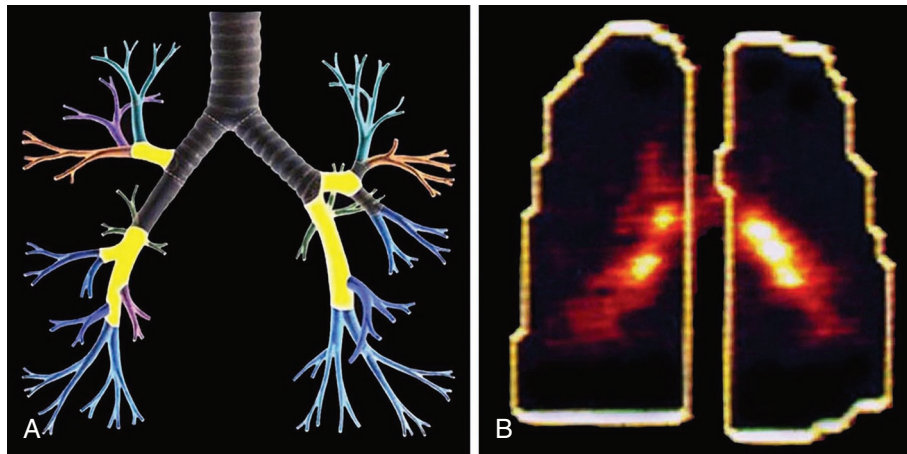


Figure 11-6 Particles are deposited preferentially at sites of flow-limiting segments in patients with COPD. Sites of flow-limiting segments (A) and the corresponding deposition image (B) in a patient with severe COPD (posterior view) with a maximal expiratory flow volume curve superimposed on tidal loop (as shown for patients in Figure 11-5B). (Redrawn from Smaldone GC: Advances in aerosols: adult respiratory disease. *J Aerosol Med* 19:36–46, 2006, with permission.)

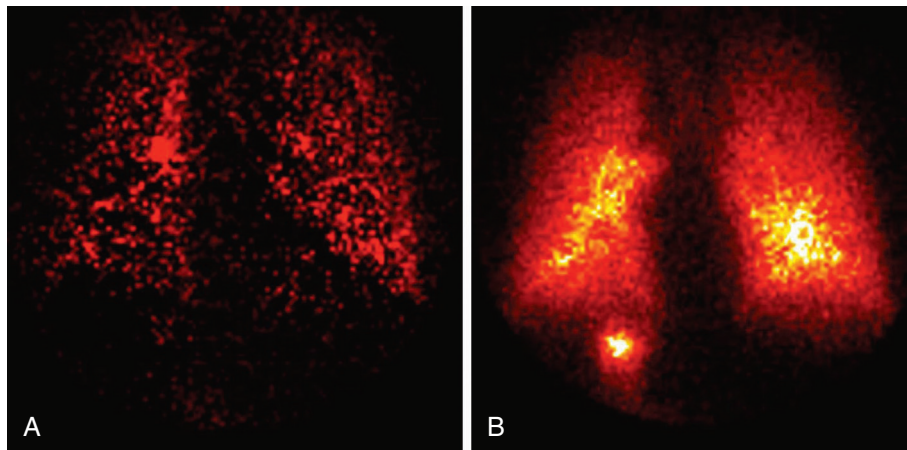


Figure 11-7 Slow and deep breathing improves aerosol delivery and deposition. Deposition scans from a normal subject after breathing from I-neb, a breath-actuated vibrating nebulizer in which particles are generated only during inspiration: **A**, Following 20 breaths of normal tidal breathing. **B**, Scan repeated after 3 breaths of very slow and deep inspiration (~7 seconds per breath). For slow and deep breathing, deposition was 50 times more efficient per breath, a combination of enhanced delivery and more efficient deposition (unpublished data).

corticosteroids have high levels of oropharyngeal deposition (up to 80% with pressurized MDIs and dry powder inhalers), and it is crucial that, when this oropharyngeal-deposited drug is subsequently swallowed, its systemic exposure be kept as low as possible. The oral bioavailability of beclomethasone as one of the oldest of the inhaled corticosteroids is approximately 20%, fluticasone is approximately 1%, and mometasone less than 1%. A newer drug, ciclesonide, does not become activated until it deposits in lung tissue.⁴³ However, even if there is no oral bioavailability, systemic exposure can still occur when inhaled corticosteroids are absorbed directly into the lung after deposition. It appears that alveolar deposition may give rise to more systemic exposure than airway deposition because particles depositing in the alveoli are not removed by mucociliary clearance and because the alveoli may be more permeable to diffusion than the airway. There are some pharmacodynamic data that suggest that when fluticasone is administered to both normal subjects and asthmatics, the asthmatic subjects are less susceptible to hypothalamic-pituitary-

adrenal axis suppression. This finding is most likely due to the more proximal deposition in the asthmatic subjects because of reduced airway caliber.⁴⁴ Most pharmaceutical manufacturers have therefore tried to target airway deposition while avoiding alveolar deposition. This appears reasonable because asthma is thought to be an airways disease. Some investigators, however, have suggested that there may be an alveolar inflammatory component in asthma, thus suggesting that alveolar deposition may be beneficial.⁴⁵ Nonetheless, this remains a minority viewpoint.

Targeting the airways in asthma is complicated by the polydisperse nature of therapeutic aerosols. Making average aerosol diameter smaller reduces oropharyngeal deposition but increases the amount of alveolar deposition. A low oral bioavailability is more important for polydisperse aerosols with larger MMADs in order to minimize systemic exposure from swallowed drug. Systemic exposure to inhaled corticosteroids can lead to short-term growth suppression in children, decreases in bone mineral density, and possibly an increase in cataracts.^{41–43} Whereas the potential role of

inhaled corticosteroids in prevalence of cataracts is confounded by concomitant use of intermittent systemic corticosteroids, smoking, and ultraviolet light exposure,⁴⁶ an epidemiologic study from Australia that controlled for use of systemic and ocular steroid use found an association between inhaled steroids and the prevalence of cataracts.⁴⁷ Cataracts could be theoretically due to inadvertent spraying of aerosol into the eyes in addition to systemic exposure.

While the search continues for the ideal method of delivery for inhaled steroids to patients with asthma, advances in drug design, formulation, and delivery now provide a wider array of options to the clinician. However, no delivery system can be considered to be intrinsically superior to all others. The delivery system should be judged instead by its ability to optimize the pharmacokinetic properties of the drug, most notably oral bioavailability, and by its suitability for the target subpopulation of asthmatics.⁴

CYSTIC FIBROSIS

Antimicrobials are inhaled for the treatment of cystic fibrosis, for example, tobramycin, aztreonam, and polymyxin. Antibiotics usually require the aerosolization of several hundred milligrams of medication. Jet nebulizers or vibrating mesh devices are usually required to deliver such a large mass of drug. However, only approximately 10% of the dose is deposited in the lungs because of inefficiencies of the delivery systems. Nevertheless, inhalation can be effective at targeting the drug to the lung and avoiding systemic side effects and toxicity. For example, aminoglycosides, when given systemically, have poor airway penetration and are limited by renal and ototoxicity. Inhalation of tobramycin, on the other hand, can result in sputum levels two orders of magnitude higher than those associated with systemic delivery. For the purposes of inhalation, tobramycin was reformulated without the preservative present in the intravenous preparation.⁴⁸ Aztreonam was reformulated with a lysine side chain for inhalation instead of the methionine side chain found in the intravenous formulation, in order to reduce the risk for airway irritation.⁴⁹

For patients with cystic fibrosis, antimicrobials and mucolytics (recombinant DNase) and osmotic hydrating agents (hypertonic saline and mannitol) have been shown to be of benefit.⁵⁰ The multiplicity of inhaled treatments, however, is likely to have a negative impact on patient adherence and therefore creates the need to explore the use of devices with shorter treatment duration in order to improve adherence.

DELIVERY OF INHALED MEDICATIONS TO YOUNG CHILDREN

Asthma is common in children, and delivery of aerosols poses special challenges. There is a need for cooperation and coordination with breathing pattern and a need to generate a threshold inspiratory flow. Thus those younger than 4 years old cannot use a dry powder inhaler. At this age, children may benefit from face masks incorporated with either holding chambers or jet nebulizers. Children between 4 and 6 years of age can use a pressurized MDI, but it should be used with a valved holding chamber because they will have difficulty coordinating actuation with the respiratory

cycle.⁵¹ After age 6 children can be taught how to use a pressurized MDI without a spacer, although the use of spacers should continue to be encouraged.

For young children with asthma, nebulized treatment with a suspension of budesonide is an effective and well-tolerated alternative.⁵² It should be noted that nebulizers tend to be less effective at aerosolizing suspensions than solutions, and clinicians are advised to prescribe budesonide only with the brand of nebulizers used in the clinical trials of this product.

Physicians should be aware that face masks affect MDI-valved holding chambers differently than nebulizers. For masks used with MDI-valved holding chambers, there should be a “tight seal” between the face mask and the face. The lack of a seal will result in marked decreases in effective aerosol delivery, and aerosol experts and package inserts for aerosolized drugs have recommended that aerosol masks should be “sealed tightly to the face.” Recent studies suggest that clinically relevant *in vitro* modeling should include mimicking a child’s breathing pattern and placing the face mask on a model of a child’s face.⁵¹ For a pressurized MDI used with a valved holding chamber, leaks around the face mask have been shown to limit the exchange of tidal air with air in the chamber, thereby reducing the inhalation of aerosol by the patient. For nebulizers, this is not the case. For nebulizers operated with compressors, the face mask can be kept filled with particles in spite of leaks because the compressor flow can exceed the minute ventilation of the child.⁵³ When used with a mask, nebulizers appear to result in less variability in inhaled mass than results with the valved holding chambers.⁵³

It is impossible to seal a mask perfectly to the face. Small leaks, particularly along the nasal-labial fold, create high-velocity jets of aerosol directed to the eyes. Deposition of drugs in the eye may be clinically relevant as shown in Figure 11-8.⁵⁴ Using breathing manikin models and radioactive aerosols, recent experiments have defined the

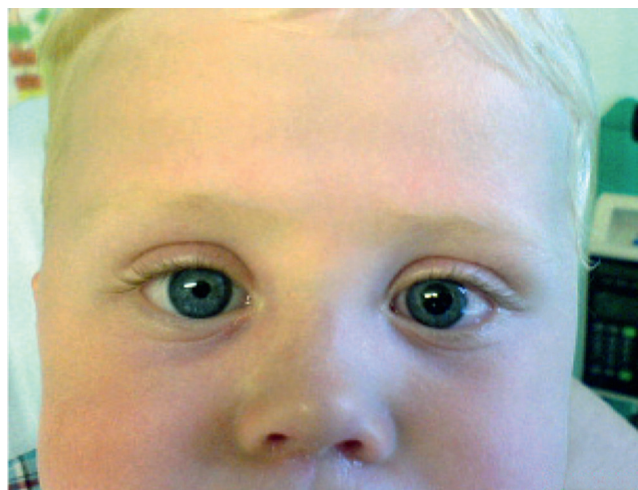


Figure 11-8 Dilated left pupil in a child following aerosol treatment for asthma. The boy was prescribed both salbutamol and ipratropium bromide inhalers, which were given via a spacer and face mask. This picture demonstrates that aerosolized particles can directly deposit in the eye (see Fig. 11-10). Similar findings have been reported in adults following nebulizer therapy.⁵⁵ (From Brodie T, Adalat S: Unilateral fixed dilated pupil in a well child. *Arch Dis Child* 91:961, 2006, with permission.)

mechanism of this deposition. As shown in [Figure 11-9A](#), nebulized drug can be directed into the eyes using tight-fitting face masks. This effect can be reversed if masks are designed such that linear velocity in the region of the leaks near the bridge of the nose is reduced (see [Figure 11-9B](#)).⁵¹ Although we commonly think that the face mask is a simple

conduit for aerosol particles, human deposition studies in young children have confirmed that face masks commonly cause facial deposition, consistent with the findings outlined earlier using the pediatric manikin. In [Figure 11-10](#), all the commercial face masks were associated with facial deposition.⁵⁶ Even though the incidence of cataract in

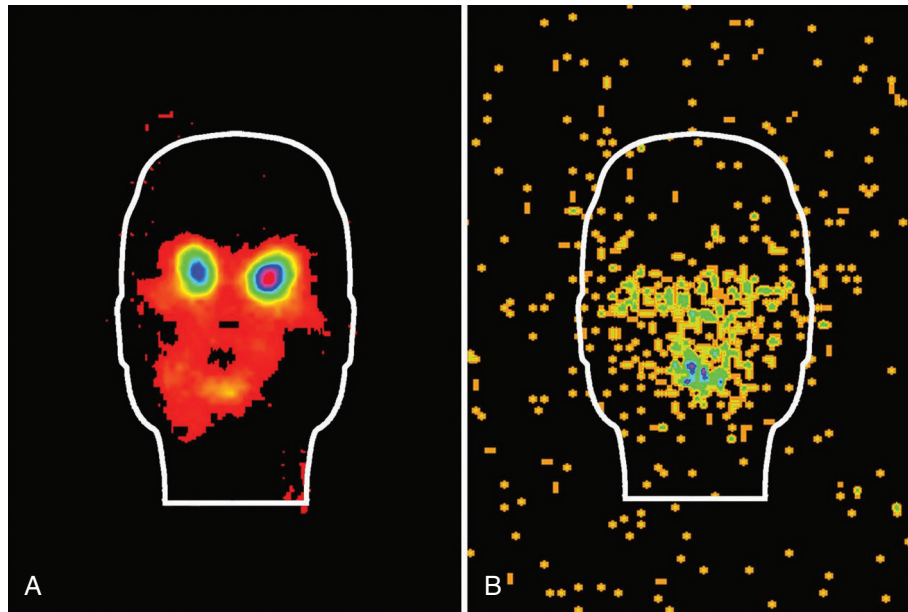


Figure 11-9 Serial gamma camera images of a breathing pediatric manikin face following a nebulizer treatment with a face mask. **A**, Facial and eye deposition following nebulizer treatment with a Pari nebulizer and tight-fitting face mask. In this study, more drug deposited on the face than was delivered to the lungs. **B**, Reduced deposition with the same nebulizer and prototype face mask designed to reduce particle acceleration in the region of the eyes. The face mask was modified by opening the area near the nasolabial fold preventing a tight seal and reducing the jet of aerosol directly into the eyes. (Modified from Smaldone GC: Assessing new technologies: patient-device interactions and deposition. *Respir Care* 50:1151–1160, 2005, with permission.)

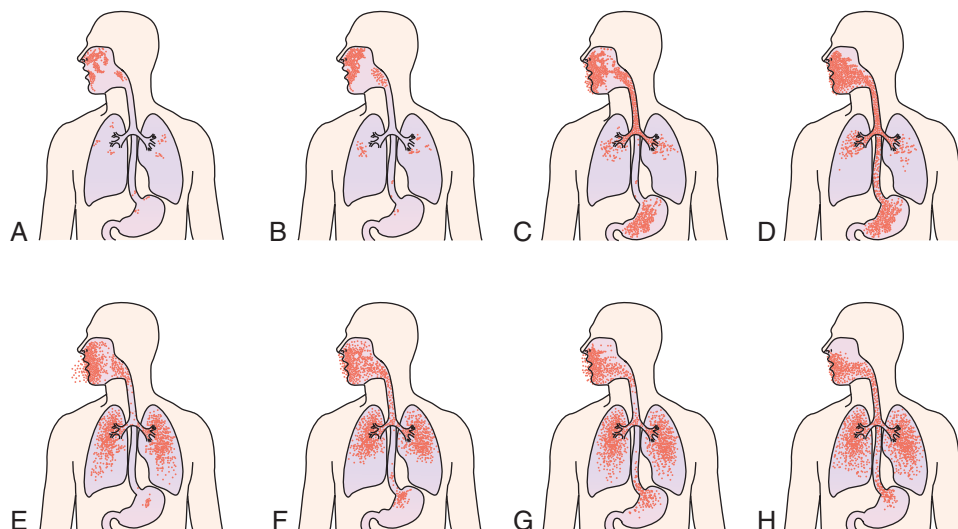


Figure 11-10 Drug deposition of radiolabeled salbutamol in young children. For all combinations of devices and face masks, the images clearly show facial deposition. This figure illustrates in vivo the important principles demonstrated in the manikin study described in [Figure 11-9](#). Efficient lung delivery requires quiet breathing. Coaching is an important part of nebulized therapy. **A**, Inhaling from a pressurized metered-dose inhaler (MDI)/spacer through a non-tightly fitted face mask. **B**, Inhaling from a nebulizer through a non-tightly fitted face mask. **C**, Inhaling from a pressurized MDI/spacer through a tightly fitted face mask, screaming during inhalation. **D**, Inhaling from a nebulizer through a tightly fitted face mask, screaming during inhalation. **E** and **F**, Inhaling from a pressurized MDI/spacer through a tightly fitted face mask, quietly inhaling. **G** and **H**, Inhaling from a nebulizer through a tightly fitted face mask, quietly inhaling. Deposition on the face is apparent especially for the tight-fitting masks (**C-H**). These principles apply to all patients treated with face masks.⁵⁵ (A-H, Redrawn from Erzinger S, Schuepp KG, Brooks-Wildhaber J, et al: Face masks and aerosol delivery in vivo. *J Aerosol Med* 20[Suppl]:S78–S84, 2007, with permission.)

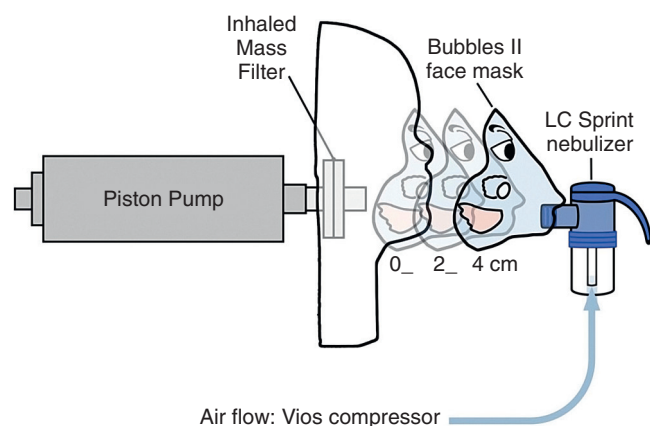


Figure 11-11 A “blow-by” system can be used for drug delivery with uncooperative children. A ventilated pediatric manikin face is shown during a nebulizer treatment using a face mask. The mask is held away from the face in an attempt to prevent patient withdrawal seen in Video 11-1. Although blow-by is controversial, recent studies have shown that reasonable quantities of aerosol can be delivered (e.g., to the inhaled mass filter) using this technique, provided the proper device-mask combination is used. (From Mansour MM, Smaldone GC: Blow-by as potential therapy for uncooperative children: an in-vitro study. *Respir Care* 57:2004–2011, 2012, with permission).

children receiving inhaled corticosteroids is very low, there is epidemiologic evidence linking inhaled steroid use in adults to an increased risk for cataract.⁴⁷

Finally, children often will not cooperate with face mask therapy. An MDI-valved holding chamber combination will fail to deliver aerosol unless the mask is pressed and sealed to the face. A nebulizer combined with a mask may not be tolerated (Video 11-1). Jet nebulization affords the possibility of “blow-by” therapy, in which the mask is held away from the face and the aerosol directed toward the patient, often in an attempt to minimize patient irritation. Blow-by has been criticized as ineffective,⁵⁷ but recent studies have demonstrated that drug delivery can be maintained using properly tested combinations of nebulizer and face mask⁵⁸ (Fig. 11-11). A newer mask called the “soother mask” incorporates a pacifier in the mask (Video 11-2) that can relax some children.⁵⁹ The points made earlier again reinforce the principle that the physician must work with the patient to decide on the proper device-drug combination when prescribing aerosolized drugs.

DELIVERY OF THERAPEUTIC AEROSOLS TO THE NASAL MUCOSA

Corticosteroids, antihistamines, cromoglycate, and decongestants are inhaled nasally to treat rhinitis. These formulations use large particle sizes to maximize nasal deposition. For children who use inhaled corticosteroids for perennial rhinitis, formulations with low oral bioavailability such as fluticasone, mometasone, and ciclesonide are preferable and reduce the risk for growth suppression.^{60,61}

Among an increasing list of aerosolized medications that are being used to treat diseases of the nasal mucosa are corticosteroids, anticholinergics (ipratropium bromide), saline, and decongestants. Manual pumps that produce large, relatively low velocity particles are being used as an

alternative to high-velocity, freon-based pressurized MDIs. There are isolated reports of nasal perforation with high-velocity inhalers,⁶² and patients should be advised to direct the spray in the direction of the ipsilateral ear and away from the nasal septum. In addition, actuating the inhaler against the lateral wall of the nares reduces the risk for epistaxis (caused by irritating the septum by medial orientation) or headache (caused by stimulating the olfactory nerve by a vertical delivery). In severe allergic sinusitis, the mucosa may be so congested that a short course of systemic corticosteroids may be needed to allow penetration of aerosolized therapy. Prolonged use of topical decongestant sprays may lead to rebound hyperemia and intractable nasal congestion. In certain cases, systemic administration of decongestants may be preferable.

AEROSOL DELIVERY DURING MECHANICAL VENTILATION

Bronchodilators are used to treat patients with airway obstruction while they undergo mechanical ventilation. There is also interest in delivering topical antimicrobial therapy in patients with purulent tracheobronchitis. The dose delivered in this setting can be highly variable, and delivery can be subtherapeutic if certain factors are not optimized. Delivery can be improved by reduced humidification (temporary discontinuation of humidification doubles the delivered dose by reduced rainout of medication), coordination with the respiratory cycle, and the appropriate selection of delivery system. If these factors are considered, delivery can be consistently achieved at doses that approximate those delivered in spontaneously breathing subjects.^{26,27} Using such optimized delivery techniques in critically ill patients with ventilator-associated tracheobronchitis, aerosolized antibiotics decrease ventilator-associated pneumonia and other signs and symptoms of respiratory infection, facilitate weaning, and reduce bacterial resistance and use of systemic antibiotics.⁶³

Delivery of aerosolized β -sympathomimetic agents can also be optimized to a patient undergoing mechanical ventilation. The use of pressurized MDI is feasible provided certain conditions are met.⁶⁴ For example, it is necessary to use a spacer/holding chamber when using a pressurized MDI in this setting. Not all holding chambers are equivalent in efficiency, and different brands are not necessarily interchangeable. In contrast to the treatment of spontaneously breathing patients, delivery during mechanical ventilation must be synchronized with respiration. It is essential that a dose-escalation protocol be employed because doses far in excess of those used for maintenance therapy may be needed. Hence efforts to obtain objective evidence on response to treatment (e.g., peak airway pressure, dynamic compliance) and toxicity (tachycardia, arrhythmias) should be sought. In endeavoring to maximize delivered doses, however, it must be remembered that the efficiency of pressurized MDI delivery decreases significantly if the interval between serial actuations is less than 1 minute and if the synchronization with the respiratory cycle is suboptimal.⁶⁵

In conclusion, once technical factors have been identified and optimized, efficient delivery of aerosolized medications

to patients undergoing mechanical ventilation is readily attainable.²⁷

DIAGNOSTIC RADIOAEROSOLS

In this chapter we primarily discuss the use of radioaerosols as research tools to measure lung deposition and mucociliary clearance. However, radioaerosols are also used in clinical practice.

The radiolabeled ventilation-perfusion scan is an important clinical tool for detection of pulmonary emboli. Perfusion is measured by injecting radiolabeled macroaggregates of protein that impact in capillaries while ventilation is evaluated by a radioactive gas or aerosol. Discrepancies between perfusion abnormalities and ventilation abnormalities are used to assess the probability of pulmonary emboli. The measurement of ventilation should ideally be performed by the use of a radioactive gas (e.g., xenon-133). However, xenon has a relatively long half-life and needs to be trapped after exhalation. In response to these concerns, aerosols labeled with technetium were developed on the assumption that, if ventilation were absent from a lung region, then the aerosol would not deposit in that region. In general, that assumption is true if submicron aerosols are inhaled, but it must be remembered that aerosol behavior is not identical to that of a gas.⁶⁶ For example, patients who are tachypneic with high inspiratory flows and who have airway obstruction will have central “hot spots” (see Fig. 11-6).³⁸ This limits the use of the aerosol techniques in certain patient groups.

MUCOCILIARY CLEARANCE AND DISEASE

Inhaled particles that deposit in the ciliated airways are trapped in a blanket of mucus. This free-floating mucous gel overlies the respiratory epithelium. The equilibrium between the osmotic modulus of the gel and brush layers maintains an adequate periciliary depth to facilitate optimal movement of cilia.⁶⁷ Mucus is transported proximally by the rhythmic beating of these cilia (a fast, forward-power stroke and slower, backward-recovery stroke) to the pharynx, where it is swallowed, a process called “mucociliary clearance.”³

Ciliated respiratory epithelial cells are most numerous in the tracheal and lobar bronchi and decrease progressively in more distal airways. Secretory cells are also more numerous in proximal airways: goblet cells produce thick carbohydrate-rich secretions, whereas other cells produce more serous secretions. In diseases such as chronic bronchitis and bronchiectasis, the number of goblet cells increases in more distal airways. Airway secretions are also produced by submucosal glands. The latter are lined by mucinous and serous epithelial cells and become hypertrophic and hyperplastic in chronic bronchitis and other types of chronic airway inflammation.

Mucociliary clearance can be impaired by intrinsic defects in ciliary function, which can be congenital (primary ciliary

dyskinesias) or acquired (tobacco smoking, influenza). Mucociliary clearance impairment can also be due to changes in the quantity and composition of airway secretions (chronic bronchitis, cystic fibrosis). Adequate hydration of airway secretions is essential for optimal mucociliary clearance.⁶⁷ Chloride and sodium channels in the airway epithelium have key roles in regulating the water content of airway secretions.^{68,69}

If the mucociliary apparatus is significantly impaired, secretions are cleared predominantly by coughing. If both mucociliary clearance and cough clearance become ineffective, retained secretions produce both physical obstruction of the airway lumen and amplification of the underlying inflammatory processes.

Mucociliary clearance in healthy subjects is usually completed within 24 hours of deposition.³ The mucous path can be followed using radiolabeled aerosols (Video 11-3). Particles containing technetium-99m and bound to a molecule that prevents absorption into the circulation can deposit on ciliated airways and follow the clearing mucus. Particles deposit in proximal airways by inspiratory impaction (larynx, mainstem, lobar, and segmental bronchi). Extrapulmonary deposited particles will be swallowed and appear in the gamma scintigraphy as stomach “hot spots” overlying the left lower lung field.

Primary ciliary dyskinesia is a congenital disorder of the dynein arms of the cilia.^{3,69a} The normal cilium has nine pairs of dynein peripheral arms and two central pairs. Each pair consists of an inner and outer dynein arm. A variety of genetic abnormalities can result in loss of the ciliary movement. In the absence of the ciliary movement, these patients will have mucous stasis and develop bronchiectasis and sinusitis. In males, ciliary dyskinesia is also associated with infertility due to immotile spermatozoa. There are associated abnormalities of visceral organs, such as situs inversus and dextrocardia.⁶⁷

Cystic fibrosis, the most common fatal single-gene genetic disease in Europe and North America, is associated with severe bronchiectasis.^{3,69b} The mucus becomes dehydrated and less easy to clear because of an impaired chloride channel (*cystic fibrosis transmembrane conductance regulator* [CFTR]) which leads to reduced secretion of chloride into the airway lumen.⁶⁸ In addition, an increase in epithelial sodium channel activation due to inflammatory proteases promotes absorption of sodium from the lumen, further exacerbating the dehydration of mucus. Hypertonic saline, when administered to the airways of patients with cystic fibrosis, creates an osmotic gradient that draws water into the airway lumen, and this treatment is associated with decreased rates of acute exacerbation.⁷⁰ Inhaled mannitol is an alternative inhaled osmolyte for patients with cystic fibrosis that has been approved by some regulatory authorities.⁷¹ In patients with a rare mutation of the CFTR gene (G551D), ivacaftor, a novel agent administered orally, can potentiate the opening of the CFTR channel.⁶⁹ The clinical benefits associated with ivacaftor therapy, including improving lung function and decreasing rates of acute exacerbation, would appear to validate the concept of the need to optimize airway hydration. Trials are underway to determine if the more common genotypes of cystic fibrosis would benefit from potentiator therapy. In addition, there is

interest in studying if blocking epithelial sodium channels in the presence of hypertonic saline could also increase the water content of mucus. Inhaled amiloride can block epithelial sodium channels, but its brief half-life at the airway epithelium limits its clinical effectiveness.^{69,72} The airway secretions in cystic fibrosis not only contain mucus secreted by the airway but also consist of DNA and actin from dead neutrophils. Recombinant DNase, administered by inhalation, can facilitate clearance of secretions and destroy neutrophil extracellular traps, the extracellular DNA released by neutrophils at sites of infection.

In chronic bronchitis there is hypertrophy and hyperplasia of the submucosal glands, as well as an increase in the number of goblet cells and the presence of goblet cells in more distal airways compared to normal. The resultant mucus has an increase in the mucous component relative to the serous component, which means that the mucous layer is relatively dehydrated.^{68,73}

In patients who die of status asthmaticus, the airways at autopsy are filled with inspissated mucus. The mucus in patients with status asthmaticus has abnormal viscoelastic static properties that may be due in part to excessive cross-linking of mucous glycoproteins.⁷⁴ Clearance of radiolabeled mucus is severely impaired in patients with status asthmaticus, but mucociliary clearance can recover within weeks.⁷⁵

Impairment of radiolabeled mucociliary clearance may be an index of disease severity in asthma,^{75,76} COPD,⁷⁷ and cystic fibrosis.⁷⁸ Serial measurements of mucociliary clearance can be useful in measuring pharmaceutical enhancement of mucociliary clearance, as for example, in the sustained effects of hypertonic saline in cystic fibrosis.

In conclusion, mucociliary clearance is impaired in asthma, chronic bronchitis/COPD, cystic fibrosis, bronchiectasis, and primary ciliary dyskinesia. Cough clearance augmented by physical therapy and other mechanical interventions (flutter valves, vibration vests) provides some treatment, but pharmaceutical interventions are limited.

ALVEOLAR CLEARANCE

Particle solubility affects clearance in alveoli. Soluble particulates may be absorbed through the thin membrane of the peripheral air spaces.^{3,79,80} Insoluble particulates, however, tend to be phagocytosed by alveolar macrophages. Their metal content influences the free radical generating properties of the particle and can promote inflammation, especially when the particle is delivered to the lysosomes. Lysosomes have a very low pH designed to kill microorganisms, but the low pH may promote solubility of transition metals such as ferrous iron and therefore be proinflammatory.

Responses to preexisting inflammation may be important because cells that are primed by one type of inflammation (e.g., by tobacco smoke or endotoxin) may be more reactive to a second stimulus from an inhaled particulate. Inhaled dose is important, and excessive exposure can lead to overloading of alveolar macrophages, which can be proinflammatory even with relatively nonreactive particulates.⁸⁰

Macrophages migrate to regional lymph nodes, and some particles are characterized by a distinctive adenopathy (e.g., silicosis and its eggshell calcifications).

ENVIRONMENTAL AEROSOLS

TOXINS

An appreciation of the principles of aerosol deposition and clearance is essential both in understanding the epidemiology of illness from exposure to environmental aerosols and in developing rational strategies to reduce the impact of those exposures. The impact of exposure to an aerosol depends on a number of factors, some of which are self-evident and others that are less apparent. These factors include the total mass of particulates in the air, the size distribution, the shape and surface area of particles, the chemical composition of the particles, the level of ambient turbulence, the airway anatomy and breathing patterns of exposed individuals, and the immune response to inflammatory or infectious agents.^{80,81} Exposure of rodents to high doses of low-toxicity, poorly soluble particulates results in pulmonary inflammation,⁸¹ impairment of alveolar clearance,⁸² and an increased tendency to develop tumors.⁸¹ It is, however, not yet clear if it is appropriate to extrapolate from studies using high-dose exposures in rodents to determine rational exposure thresholds for humans.⁸¹ Unfortunately, it appears that in vitro exposure of cell cultures to environmental particulates correlates poorly with in vivo animal exposures.^{83,84}

In December of 1952 in London, England, 4000 excess deaths were attributed to smog. This disaster had a huge impact on public health policy and led to efforts to reduce the impact of air pollution. At the time, it was assumed that it was the total concentration of particulates that was the most important determinant of mortality. However, retrospective analysis of stored autopsy specimens suggested that exposure to fine particulates and metals may have been more important than the total mass of exposure.⁸⁵ The increased emphasis on particle size was supported by a series of urban epidemiologic studies that found correlations between daily concentrations of particulates and mortality. Using data from urban sampling devices that can measure the amount of particles less than 10 μm in diameter, it was demonstrated that even small increases in particles less than 10 μm in diameter produced an increase in acute death rates.⁸⁶ Interestingly, it was cardiovascular deaths that seemed to dominate over respiratory deaths, leading to speculation that the deposition of particles in the lung could activate proinflammatory cascades. Later studies, using even more sophisticated samplers, found a correlation between mortality and fluctuations in the fine particles less than 2.5 μm in diameter.⁸⁷ More recent research has focused on even smaller particles between 1 and 100 nm.⁸⁸ When these are found in the atmosphere, usually as result of combustion, they are referred to as “ultrafine” particles; when they are manufactured in the semiconductor, pharmaceutical, or chemical industries, even though their dimensions are also 1 to 100 nm, they are referred to as “nanoparticles.” In contrast to ambient ultrafine particles, which tend to be polydisperse,

nanoparticles are more monodisperse. Measuring particle size distributions in the nano spectrum requires more sophisticated techniques than for conventional particles. Spectrophotometry, atomic force microscopy, and complex light scattering techniques have been developed to make these measurements. As particles approach the nano range, their behavior can change. Both ultrafine and nanoparticles can deposit by diffusion, have a very high deposition fraction, and are small enough to pass between epithelial cells in the lung and cause systemic toxicity. Surface area of the inhaled particles may become more important than total inhaled mass in understanding their toxicity. For example, titanium is a relatively inert and nontoxic substance when inhaled as a typical respirable aerosol (0.5 to 5 μm particle size), but exposure to titanium particles within the nano range results in marked cytotoxicity and proinflammatory effects in the lungs of rats. These effects have led to calls for tighter regulation of nanoparticle manufacture and distribution of nanomaterials.

Application of the principles of aerosol deposition can reduce exposure to toxic environmental aerosols. For example, dust mite fecal aerosols tend to be large and have a relatively rapid settling velocity.⁸⁹ However, the energy imparted by a ceiling fan can prolong their residence time and facilitate their inhalation; hence asthmatic patients are advised to eschew the use of ceiling fans in their bedrooms. Most naturally occurring aerosols have sufficiently large particles to be filtered by the nose and the branching structure of the large central airways. Some aerosols, however, pose particular dangers. Asbestos fibers, despite being relatively large, can deposit in small peripheral air spaces because their cylindrical structure allows them to follow the air stream to the lung periphery.⁹⁰ As discussed previously, ultrafine aerosols pose an additional danger if inhaled. They can pass between the protective epithelial cells of the lung and cause systemic toxicity. Deposition of environmental aerosols is affected by particle size and shape and also by breathing pattern. Generation of aerosols by workers who are performing manual labor and have increased inspiratory flow rates and minute ventilation can result in an increased dose deposited in the lung. Although larger particles have low peripheral deposition, these particles can nevertheless be hazardous because of their mass. For example, after the attack on the World Trade Center, particles greater than 50 μm were deposited in peripheral air spaces because they were present in very high concentrations in the air for hours after the collapse of the towers. Consequently, New York City firefighters who responded to the disaster site on the day the towers collapsed had significantly higher rates of lung injury than those who reported on day 2.⁹¹ The toxicity of inhaled inorganic particles is complex and beyond the scope of this text. Factors influencing toxicity include the metal content of particles, especially transitional metals such as iron, which may influence free radical generation.⁹²

Tobacco smoke remains one of the most important indoor exposures to toxic aerosols. Some of the principles of aerosol delivery and deposition are useful in explaining some of the epidemiologic associations with different types of cigarettes.^{89,93} Despite marked differences in “smoking-machine”-generated concentrations of tar, cigarettes marked as medium tar, low tar (“lite”), and ultralow tar

(“ultralite”) are associated with similar incidences of lung cancer. (High-tar unfiltered cigarettes are associated with an even higher incidence of lung cancer.) The explanation for this paradox appears to lie in part with the fact that a standardized smoke generator does not reproduce the actual smoker’s exposure. For one thing, ventilation holes in the “lite” cigarettes that dilute the machine-generated smoke can be occluded by human lips, thereby increasing the exposure to smoke from the “lite” cigarettes. However, a more important factor may be that people tend to inhale the smoke of the “lite” cigarettes more deeply and deposit carcinogenic particulates in the more distal air spaces. This latter theory is supported by the observation of a relative increase in the incidence of more peripheral adenocarcinomas relative to more central squamous carcinomas following the introduction of “lite/ultralite” cigarettes to the U.S. market, where they now hold an 80% market share.⁹³

INFECTIOUS AEROSOLS

Toxic aerosol exposures, although complex and multifactorial, can usually be reduced by avoidance. Infectious aerosols raise additional problems because simple avoidance is not always possible. For example, the health care worker must provide care, and it is often not possible to define minimal safe exposures.

Pulmonary tuberculosis is an infection spread exclusively through the inhalation of infected droplet nuclei (1 to 5 μm), nuclei that form after the evaporation of expectorated droplets and that can remain airborne for hours in ambient air.⁹⁴ Influenza can be spread by direct contact and by large (>10 μm) and small (<5 μm) droplets. Prevention of spread of airborne infections is a growing health care problem in hospitals and in the community. Current practice includes placement of a face mask on patients with suspected tuberculosis or communicable respiratory viral infections to intercept cough-generated aerosols before they have the opportunity to dry and become airborne, where they can float for many hours. In hospitals, current practice also includes use of tight-fitting masks on the health care worker so that all their inspired air is filtered by the mask with the thought that the aerosols are small enough to follow the air stream and pass around loosely fitting masks. However, the efficacy of this technique is unknown. The Centers for Disease Control and Prevention recommends surgical masks for seasonal influenza but recommended N95 respirators for the 2009 pandemic H1N1 virus.⁹⁵⁻⁹⁸ The former recommendation is based on the assumption that transmission of seasonal influenza is via direct contact or by inhalation of large, airborne droplets⁹⁹ (>5 μm); the latter recommendation for the more dangerous H1N1 virus is based on the assumption that all particles, including aerosolized particles (<5 μm), would be better intercepted by the greater filtration capability of N95 respirators.¹⁰⁰ However, there is no firm understanding of the various potential transmission mechanisms for influenza.^{96,97}

In vitro studies designed to assess mask efficacy have focused on filtration masks as the only mechanism of protection.¹⁰¹ More recently, interactive models of aerosol exchange in defined environments have suggested that simple filtration of particles is often not the primary mechanism of protection (Fig. 11-12). Transmission of infectious

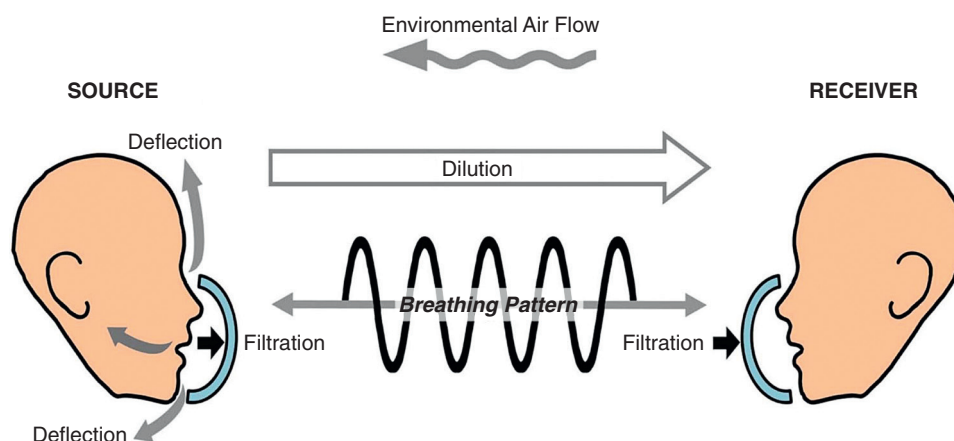


Figure 11-12 Transfer of infectious aerosols from an infected individual (Source) to an uninfected health care worker (Receiver). Infectious particles may be affected by the breathing pattern, dilution by ambient air, extraction via air flow (e.g., a negative-pressure room in a hospital), filtration by either mask, or deflection by mask. Most studies defining hospital policy and health care worker protection have focused on filtration only. (Redrawn from Diaz KT, Smaldone GC: Quantifying exposure risk: surgical masks and respirators. *Am J Infect Control* 38[7]:501–508, 2010, with permission.)

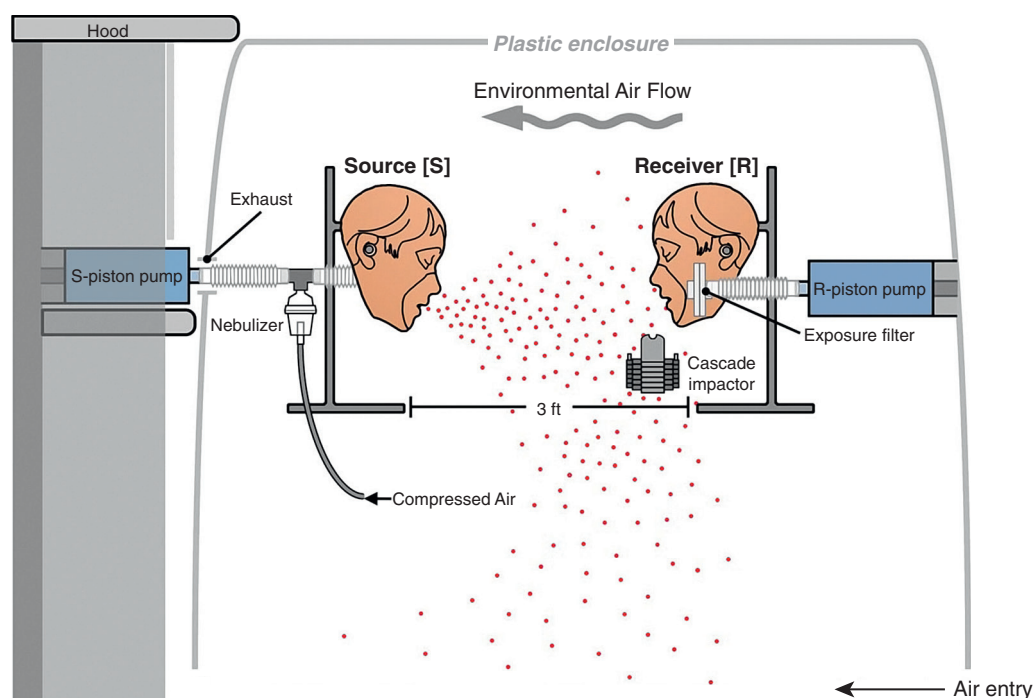


Figure 11-13 Testing chamber to evaluate the transfer of infectious aerosols depicted in Figure 11-12. The Source and Receiver are represented by ventilated manikin heads, air flow in the room mimicked a hospital negative-pressure room (e.g., air flowing in under the door and out a vent behind the patient), and radiolabeled test aerosols were generated via a nebulizer, exhaled by the Source, and inhaled by the Receiver. Receiver exposure was quantified by a filter in the Receiver, and aerosol distributions were measured by cascade impactors placed in different locations in the chamber. (Redrawn from Diaz KT, Smaldone GC: Quantifying exposure risk: surgical masks and respirators. *Am J Infect Control* 38[7]:501–508, 2010, with permission.)

aerosols between human subjects is more complex, involving multiple mechanisms of aerosol transport, and thus suggests potentially unexpected solutions. For example, which is better, putting the protective mask on the infected individual or on the uninfected health care worker? These questions are very difficult to answer in clinical situations. Recent *in vitro* studies based on the concepts illustrated in Figure 11-12 have suggested that putting a simple surgical mask on the infected source (respiratory source control) is far more effective than trying to filter out all the particles inhaled by an uninfected health care worker.¹⁰² For example,

when the behavior of exhaled and subsequently inhaled aerosols between individuals was tested in a controlled chamber designed to mimic a negative-pressure room in a hospital (Fig. 11-13), far better protection of the health care worker was achieved when an inexpensive surgical mask was placed on the source compared to all forms of masks placed on the health care worker, including one sealed directly to the face with petroleum jelly (Fig. 11-14).¹⁰² Additional epidemiologic studies are needed to design the best protection from ambient infections in the community and in health care facilities.











Source		Receiver		Workplace Protection Factor
—			—	1
Tight Surgical Mask			—	288
—			Tight Surgical Mask	2
—			N95	1
—			N95 + Petroleum Jelly Sealant	118

Figure 11-14 Data from test chamber described in Figure 11-13. Receiver exposure was quantified by a so-called simulated workplace protection factor, the ratio of exposure without face mask protection divided by exposure with face mask protection (higher numbers are better). Placing a mask on the source was far more effective than masks on the receiver. N95, an N95 respirator; N95 + petroleum jelly sealant, an N95 respirator sealed to the manikin by petroleum jelly to prevent any leaks; Tight Surgical Mask, a surgical mask tied tightly around the face. (Modified from Diaz KT, Smaldone GC: Quantifying exposure risk: surgical masks and respirators. *Am J Infect Control* 38(7):501–508, 2010, with permission.)

In conclusion, further progress in understanding of the role of environmental aerosols in health and disease will be dependent on the collaboration of several disciplines. An appreciation of the principles of deposition and clearance by the participating investigators should facilitate interdisciplinary communication and cooperation.

Key Points

- The likelihood that a particle will deposit in an airway depends on the physical characteristics of the particle, the gas flow transporting the particle, and the airway anatomy. The greater the mass, the faster the flow, and the more narrow the airway, the greater is the potential for inertial impaction. For the clinician, forces that define inertial impaction are most important in determining upper airway deposition and the passage of aerosol into the lungs.
- Once particles pass through the upper airways, deposition in the lungs is largely defined by sedimentation.

This process is dependent on a subject's breathing pattern, both the depth and the duration of the breath.

- Holding chambers reduce pharyngeal deposition and reduce the need for precise coordination to get the full dose.
- Face mask seal and design can be an important factors in the delivery of clinical aerosols.
- Compared to parenteral therapy, medicines can be delivered by aerosol in greater concentration to the target organ, the lung, with fewer side effects, but most traditional jet nebulizers are inefficient and deliver less than 10% of the drugs to the lung.
- Directing the jet of high-velocity nasal sprays laterally avoids the side effects of headache when directed vertically and epistaxis when directed medially.
- Mucociliary disorders, which can be inherited or acquired, can result from changes to the structure of the cilia or from changes in the composition or quantity of the mucus.
- Environmental aerosols, especially the fine particulates, result in excess acute deaths, often from cardiovascular events.
- Prevention of spread of infectious aerosols can be enhanced by placing a simple face mask on the patient, a strategy called “respiratory source control.”

Complete reference list available at [ExpertConsult](#).

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INTRODUCTION

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SYSTEM INTEGRATION

INTRODUCTION

The immune system is broadly conceptualized as having two separate but interconnected arms. In evolutionary terms the *innate immune* arm is an older and more primitive system that has developed to provide early host defense against viruses, fungi, and bacteria. The fundamental basis of innate immunity is a system for pathogen detection that relies on the recognition of a range of *pathogen-associated molecular patterns* (PAMPs), which include complex lipids, carbohydrates, unmethylated cytosine-guanosine DNA sequences, and double-stranded RNAs. PAMPs are recognized by a series of secreted, cell surface, and intracellular *pattern recognition receptors* (PRRs) that promote the recognition, phagocytosis, and killing of many microbes. In addition, recognition of PAMPs by PRRs initiates inflammation, which in turn leads to the recruitment of phagocytes that kill and degrade microbes, promote the repair of damaged tissues, and assist in the restoration of tissue function. Though some organisms, for example, sea urchins, have evolved a system of host defense based exclusively on the innate immune system,¹ mammals and higher animals have evolved an *adaptive immune system* that differs from the innate immune system in its exquisite antigenic specificity and the ability to develop immunologic memory, allowing a more rapid response to previously encountered microbes and antigens. Both the innate and adaptive immune systems operate together and exist in a classic symbiotic relationship to provide optimal defense of the lung and other organs and tissues (see Chapter 13).

The broad concepts of innate and adaptive immunity outlined previously have evolved to protect most organs and tissues from *microbes*, a term we use to include bacteria, yeasts, fungi, protozoa, multicellular parasites, and viruses. However, most organs and tissues, including the lung, have evolved additional mechanisms to tailor the immune system to their own specific needs. The lung epithelium has a surface area approximately the size of a tennis court and represents the largest epithelial surface in the body. With an average respiratory rate of 10–12 breaths/min and an average tidal volume of 600 mL, the lungs are exposed to over 10,000 L of ambient air per day. The air that we breathe is a complex mixture of gases and particulates that can contain pollutants, oxidants, inorganic and organic dusts, pollens, toxins, bacteria and their constituents (e.g., bacterial endotoxin, *lipopolysaccharides* [LPSS]), and viruses.

In addition, the airways and gas-exchange surfaces of the lung can be exposed by aspiration to acidic gastric contents as well as to infected mucus from the nasal sinuses. Thus all surfaces of the respiratory tract from the nasal passages to the alveoli are constantly exposed to a spectrum of harmless, harmful, and pathogenic agents, raising the key question of how the lung differentiates between what is harmful and what is essentially harmless.

Like the gut, the lung has evolved discriminative mechanisms both to suppress unwanted and potentially harmful responses to harmless materials and to retain the ability to activate a vigorous innate and adaptive immunity when encountering harmful microbes and stressors. The overall goal of this chapter is to review current concepts of lung innate immunity and its fundamental underlying mechanisms. Multiple cell lineages participate in innate protection of the lung, and many share similarities in the way they recognize and respond to microbes and other harmful agents. Therefore we have organized the chapter into four broad sections. First, we provide an overview of lung innate immunity and its fundamental components. Second, we discuss general mechanisms of innate immune recognition. Third, we review innate lung cells and the effector mechanisms they use. Fourth, we discuss how these systems and mechanisms are integrated. Throughout the chapter we also discuss how the innate immune system primes the adaptive immune system as a prelude to the chapter on adaptive immunity (see Chapter 13).

OVERVIEW OF THE COMPONENTS OF LUNG INNATE IMMUNITY

Microbial species can rarely be cultured from the lungs of healthy individuals, leading to the long-standing dogma that the lower airways and gas exchange surfaces of the lungs of healthy subjects are sterile. However, recent studies based on culture-independent methodologies, especially bacterial 16S ribosomal RNA sequencing, have begun to challenge this notion. Based on an earlier single-center study with a modest number of subjects,² a recent National Heart, Lung, and Blood Institute–sponsored multicenter study with 64 subjects has provided data to indicate that bacterial DNA is present in the bronchoalveolar lavage of healthy subjects and that most sequences resemble the

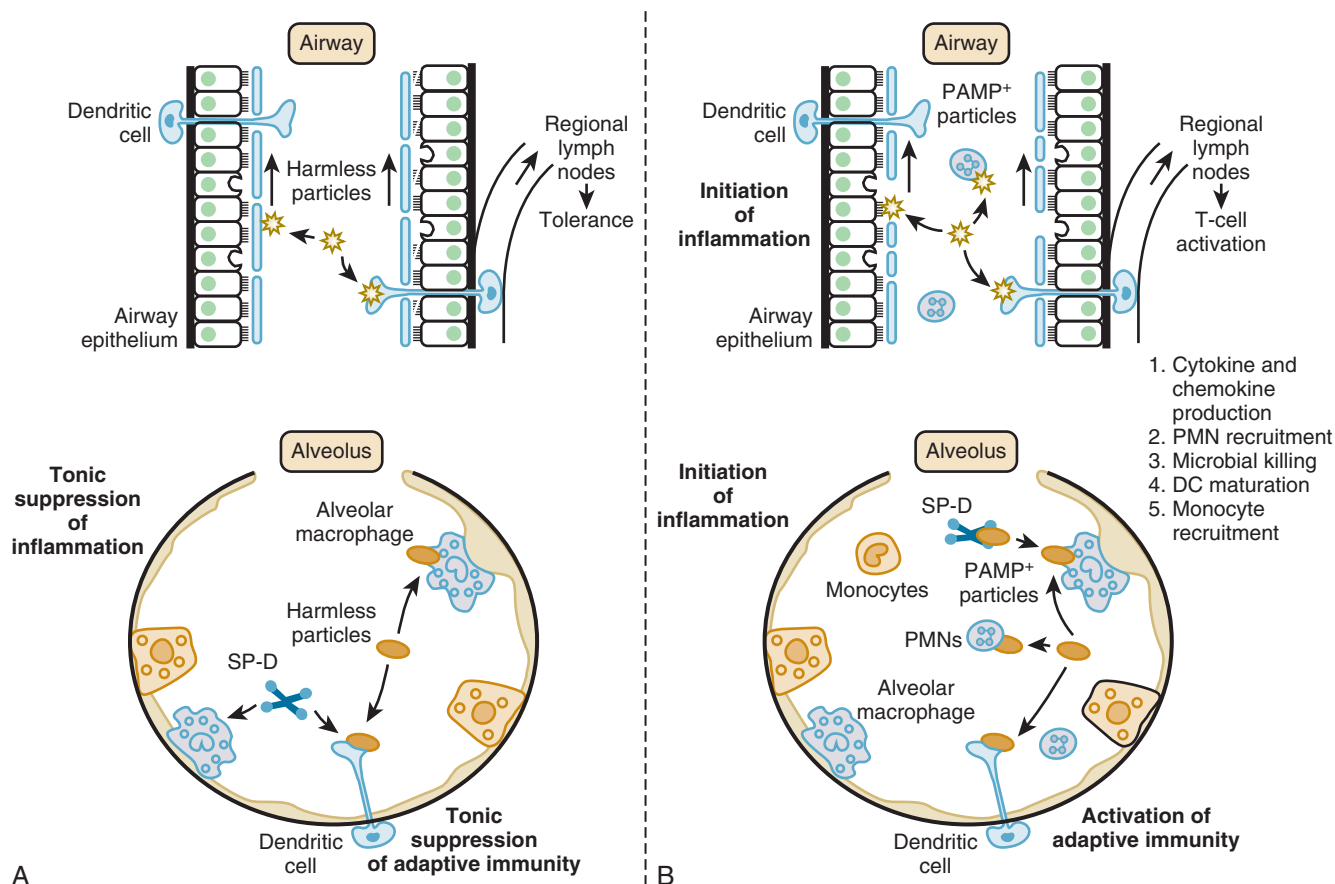


Figure 12-1 Overview of innate immune protection in the conducting airways (upper) and alveoli (lower) of the lung. **A**, In the absence of pathogen-associated molecular patterns (PAMPs), that is, in the steady state, the airways are protected by mucus that captures harmless particulates and transports them along the mucociliary escalator. Dendritic cells (DCs) also capture particles, traffic to regional lymph nodes, and promote tolerance to commonly inhaled antigens. Also in the absence of PAMPs, the alveoli are maintained in an anti-inflammatory and immunosuppressed state to prevent unwanted inflammation and immune activation toward commonly inhaled particles and antigens. **B**, In the presence of PAMPs, innate immunity is activated. PAMPs stimulate airway epithelial cells to express chemokines, cytokines, and lipid mediators that attract neutrophils (polymorphonuclear leukocytes [PMNs]), which in turn kill PAMP-expressing microbes. Airway dendritic cells respond to PAMPs by maturing, migrating to regional lymph nodes, and stimulating T-cell proliferation. A similar program is activated in the alveoli upon PAMP detection by alveolar macrophages, alveolar epithelial cells, and dendritic cells, resulting in the initiation of inflammation and activation of adaptive immunity. SP-D, surfactant protein D.

diversity seen in the mouth. However, sequences from Enterobacteriaceae, *Haemophilus*, *Methylobacterium*, and *Ralstonia* species were disproportionately represented in the lung.³ Although it is unclear if these lung enriched sequences are derived from bacterial communities colonizing the throat, nasal passages, or gastrointestinal tract (which were not sampled for comparison) or whether or not they were derived from viable bacteria, these findings provide hints that commensal bacterial communities may exist in the lungs of healthy individuals. Thus, it will become increasingly important to integrate emerging information on lung microbiota into our understanding of how the innate immune system interfaces with these potentially commensal bacteria.

Given this caveat, the innate immune system is currently conceptualized as providing protection to the lungs against a diverse spectrum of inhaled particles and antigens that range from harmless nonmicrobial particles (e.g., dusts and pollens) to harmful pathogenic microbes (e.g., *Mycobacterium tuberculosis*). To accomplish the range of protection, the lungs have evolved multiple mechanisms to survey and respond to inhaled particles based primarily on their size

and physicochemical properties, especially the presence and absence of PAMPs. As illustrated in Figure 12-1, innate immune protection in the lung can be broadly divided into considerations of the conducting airways and the gas-exchange surfaces of the alveoli. At the cellular level, innate protection is afforded by the coordinated functions of airway and alveolar epithelial cells, resident macrophages and dendritic cells (DCs), and recruited neutrophils (polymorphonuclear leukocytes [PMNs]), monocytes, and DC precursors.

Though often underestimated, an important component of airway host defense resides in the anatomic structure and epithelial cell lineages of the tracheobronchial tree. Air turbulence created by the nasal passages and the cartilaginous segmentation of the trachea and large airways ensures that particles in excess of 10 μm in diameter are deposited on the mucus-coated surfaces of the nose, pharynx, trachea, and descending airways. In turn, mucus, its ensnared particulates, and dissolved solutes are constantly wafted toward the pharynx by the coordinated beating of ciliated airway epithelial cells where their removal is aided by coughing, sneezing, and swallowing. In addition to the biophysical

Table 12-1 Some Constituents of Airway Epithelial Fluid

Lysozyme	Statherin
Lactoferrin	Secretory phospholipase A ₂
Secretory leukoprotease inhibitor	β-defensins
Uric acid	Natural IgA antibodies
Peroxidase	SP-A*
Aminopeptidases	SP-D*

*Restricted to alveoli.
IgA, immunoglobulin A; SP-A, surfactant protein A; SP-D, surfactant protein D.
Adapted from Diamond G, Legarda D, Ryan LK: The innate immune response of the respiratory epithelium. *Immunol Rev* 173:27–38, 2000.

properties of mucus in innate host defense of the airways, the gel and pericellular liquid phases also contain an array of antimicrobial peptides and proteins, antioxidants, anti-proteases, and specific *immunoglobulin A* (IgA) antibodies (Table 12-1), all of which are maintained at a modestly acidic pH (pH 6.6).⁴ Principal among airway antimicrobial peptides in humans are salt-sensitive cysteine-rich cationic β-defensins and the cathelicidin LL37/hCAP18.⁵⁻⁹ β-defensin-1 is constitutively secreted by airway epithelia and accumulates in airway surface liquid at microgram per milliliter concentrations.¹⁰ Other β-defensins and LL37/hCAP18 are inducibly expressed following exposure to LPS and other proinflammatory mediators.¹¹⁻¹³ Antimicrobial proteins, including lactoferrin and lysozyme, are also present in airway epithelial secretions and contribute to the maintenance of normal airway sterility.^{14,15}

The conducting airways are lined with ciliated and secretory epithelial cells that serve a key role in the initial evaluation of the surfaces of large particles with which they come into contact. In addition, a network of DCs resides throughout the airway epithelium and continuously samples the airway lumen (see Fig. 12-1). DCs are particularly abundant in the trachea and large conducting airways where most large particulates are deposited. In the absence of PAMPs, DCs capture airway antigens and migrate to regional lymph nodes where, for harmless antigens, they induce CD4⁺ and CD8⁺ T-cell tolerance.

In contrast to large particles, particles smaller than 5 μm in diameter are able to descend the entire tracheobronchial tree and lodge at bronchiolar-respiratory duct junctions or deposit onto the surfactant-rich surfaces of the alveoli. While sharing many similarities with innate protection of the airways—for example, the presence of antioxidants, antiproteases, and antimicrobial enzymes—additional innate protection of the alveoli is afforded by the presence of resident alveolar macrophages and the lung-specific collectins, *surfactant protein A* (SP-A) and *surfactant protein D* (SP-D) (see Fig. 12-1). In addition to expressing *Toll-like receptors* (TLRs), resident alveolar macrophages express *scavenger receptors* (SRs) that participate in the phagocytosis of microbial and nonmicrobial particles. SP-A and SP-D are secreted PRRs and are capable of binding to microbial PAMPs, leading to opsonization and phagocytosis by alveolar macrophages and intraseptal DCs, which then either crawl into the airways and move up the mucociliary escalator or migrate to regional lymph nodes, respectively. In the absence of PAMPs, resident alveolar macrophages also play

Table 12-2 Representative Genes Activated by Pattern Recognition Receptors

CXCL CHEMOKINES <i>CXCL1, CXCL2, CXCL4, CXCL9, CXCL10, CXCL11</i>
CCL CHEMOKINES <i>CCL1, CCL2, CCL7</i>
CYTOKINES <i>TNF-α, IL-1β, TGF-β, IL-10</i>
TLRS <i>TLR2, TLR4, TLR9</i>
PROSURVIVAL <i>BCL2, cIAP1, cIAP2, BCL10</i>
ANTIMICROBIAL β-defensins, cathelicidins
DC MATURATION <i>CD40, CD80, CD86, MHC Class II, Class II</i>

Transcription of most of these genes is initiated by the activation of NFκB and/or AP1. NFκB activation is initiated by most PRRs.
AP1, activator protein-1; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; DC, dendritic cell; MHC, major histocompatibility complex; NFκB, nuclear factor-κB; PRR, pattern recognition receptor; TLR, Toll-like receptor.

an important role in suppressing inflammation and adaptive immunity, thereby protecting the alveoli from unwanted responses to harmless inhaled particulates. SP-A and SP-D also play a key role in suppressing inflammation in the absence of PAMPs through tonic signaling effects on resident alveolar macrophages. Thus the innate immune system not only protects the lungs from harmful microbes, but also prevents inflammation, injury, and activation of the adaptive immune system in the steady state and in response to harmless inhaled particulates.

How then, do the airways and alveoli respond to the presence of potentially harmful microbes? As illustrated in Figure 12-1, resident airway and alveolar macrophages, DCs, and airway and alveolar epithelial cells are capable of recognizing different PAMPs through their repertoires of cell surface and intracellular PRRs, and by the interaction of PAMP-bound secreted PRRs with specific receptors on epithelial cells, macrophages, and DCs. In turn, these interactions induce signaling responses that promote the expression of an array of innate response genes (Table 12-2). These gene products collectively promote the migration of PMNs and monocytes from the pulmonary circulation into the air spaces, facilitate changes in endothelial and epithelial permeability to enhance inflammatory cell transmigration into the air spaces, and initiate the expression of specific genes involved in microbial killing. In addition, DCs phagocytose PAMP-expressing microbes, mature, and migrate to regional lymph nodes (see Fig. 12-1). During this process, ingested microbial products are digested, captured by *major histocompatibility complex* (MHC) class II molecules, and displayed on the DC plasma membrane together with co-stimulatory molecules such as CD40, CD80, and CD86 for effective presentation to naive CD4⁺ and CD8⁺ T cells. Following activation and expansion in regional lymph nodes, effector CD4⁺ and CD8⁺ T cells then migrate back to

the site of microbial infection to augment specific host defense through their ability to activate macrophages and other effector cells.

In summary, innate immune mechanisms involving the airway and alveolar epithelium, secreted antimicrobial enzymes, PRRs and peptides, mucus and mucociliary transport, and resident macrophages and DCs protect the lung against inhaled microbial and nonmicrobial particulates to maintain lung homeostasis. During steady-state conditions, the innate immune system actively suppresses inflammation and promotes tolerance to commonly inhaled harmless particulates. However, above a certain threshold and/or upon sensing the presence of PAMPs, additional mechanisms are activated to protect the lungs by promoting inflammation and adaptive immunity and by establishing communication and cooperation between these systems. Although it is convenient to think of these events separately, innate host responses to both harmless nonmicrobial particulates and harmful microbes take place simultaneously and silently to maximize lung health and protection.

INNATE RECOGNITION IN THE LUNG

With this broad overview of the key elements in innate host defense of the lung and their connections to adaptive immunity, we now consider how microbes are recognized by resident and recruited lung cells. For this purpose, we specifically focus on the mechanisms of recognition by PRRs that are expressed by epithelial cells, macrophages, and DCs or are present in airway or alveolar surface liquids.

SECRETED PATTERN RECOGNITION RECEPTORS

Secreted PRRs have evolved to serve as bridges between certain PAMPs and specific receptors for these molecules. In the lung, secreted PRRs have particularly important roles in innate protection of the alveolar surfaces.

Collectins

The collectins are a family of secreted PRRs; SP-A and SP-D are collectins that are uniquely expressed in the distal lung.¹⁶ All members of the collectin family are characterized by the presence of a cysteine-rich N-terminal noncollagenous domain, a collagen-like domain, an α -helical coiled-coil neck domain, and a globular C-type lectin domain (also called the “carbohydrate recognition domain” [CRD]) that interacts with microbial PAMPs (Fig. 12-2A). At baseline, SP-A and SP-D suppress inflammation (see later) (shown for SP-D in Fig. 12-2B); in the presence of a variety of PAMPs, SP-A and SP-D stimulate microbial phagocytosis, the production of reactive oxidant species, and the expression of proinflammatory cytokines (see Fig. 12-2C).^{17,18} A proinflammatory response is activated when PAMP-bound SP-A and SP-D interact with macrophages via their collagenous tails through CD91¹⁹⁻²¹ (see Fig. 12-2C). Consistent with these findings, SP-A-deficient and SP-D-deficient mice have increased susceptibility to pulmonary infection with *Pseudomonas aeruginosa* and *Staphylo-*

coccus aureus,^{22,23} emphasizing the important contribution of these lung-specific collectins to innate lung host defense. Additional information on SP-A and SP-D can be found in Chapter 8.

The lung is remarkable in that it is capable of eliminating harmful pathogens from the alveolar surfaces while actively suppressing unwanted and potentially harmful inflammatory responses to harmless inhaled materials. Several studies have shed new light on this dichotomy by revealing an additional role for SP-A and SP-D in the tonic suppression of lung inflammation. When initially created, SP-D-deficient mice were found to have increased numbers of foamy, activated alveolar macrophages, suggesting that SP-D may somehow tonically suppress lung macrophage activation and lung inflammation (see Fig. 12-2B).²⁴ As illustrated in Figure 12-2C, in the steady state (i.e., in the absence of PAMPs), SP-D and SP-A interact with alveolar macrophages via their globular head groups and signal via signal-inhibitory regulatory protein α to suppress proinflammatory responses.¹⁹ Thus SP-A and SP-D, through their ability to interact under different circumstances with CD91 and signal-inhibitory regulatory protein α , play a pivotal role in the maintenance of the antiinflammatory environment of the alveoli under steady-state conditions, while promoting an inflammatory and innate response when microbes are sensed. Other studies suggest that lipid and phospholipid constituents of surfactant also contribute to maintenance of the antiinflammatory environment of the alveoli.²⁵

Complement

The complement system functions as a pattern recognition system and a bridge to adaptive immunity through its ability to recognize repetitive structures on some microbes and on the Fc region of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies. Complement activation is important in lung innate immunity because it promotes the opsonization of microbes and the generation of the potent chemotactic factor C5a, which in turn assists in the recruitment of phagocytic cells. Complement components of the classical, alternative, and mannose-binding lectin activation pathways are present in lung airway and alveolar fluids²⁶⁻²⁸ and are synthesized by alveolar type II cells, macrophages, and DCs.^{15,29-31} Many microbes can directly activate the alternative complement pathway, resulting in the covalent attachment of C3b to the microbial cell wall. Microbes expressing cell wall-associated mannose-rich polysaccharides can also bind mannose-binding lectin and activate the mannose-binding lectin pathway to promote C3b attachment to the microbial cell wall. Phagocytic cells, especially macrophages, PMNs, and DCs, express various receptors for C3b and C3bi and, together with other receptors, phagocytose and kill complement-opsonized microbes.

Pentraxins and Other Secreted Pattern Recognition Receptors

The pentraxins, including C-reactive protein, serum amyloid P, and pentraxin 3, also recognize PAMPs on microbes and activate the complement system to assist in microbial removal by phagocytic cells.^{32,33} Similarly, ficolins promote phagocytosis and complement activation by

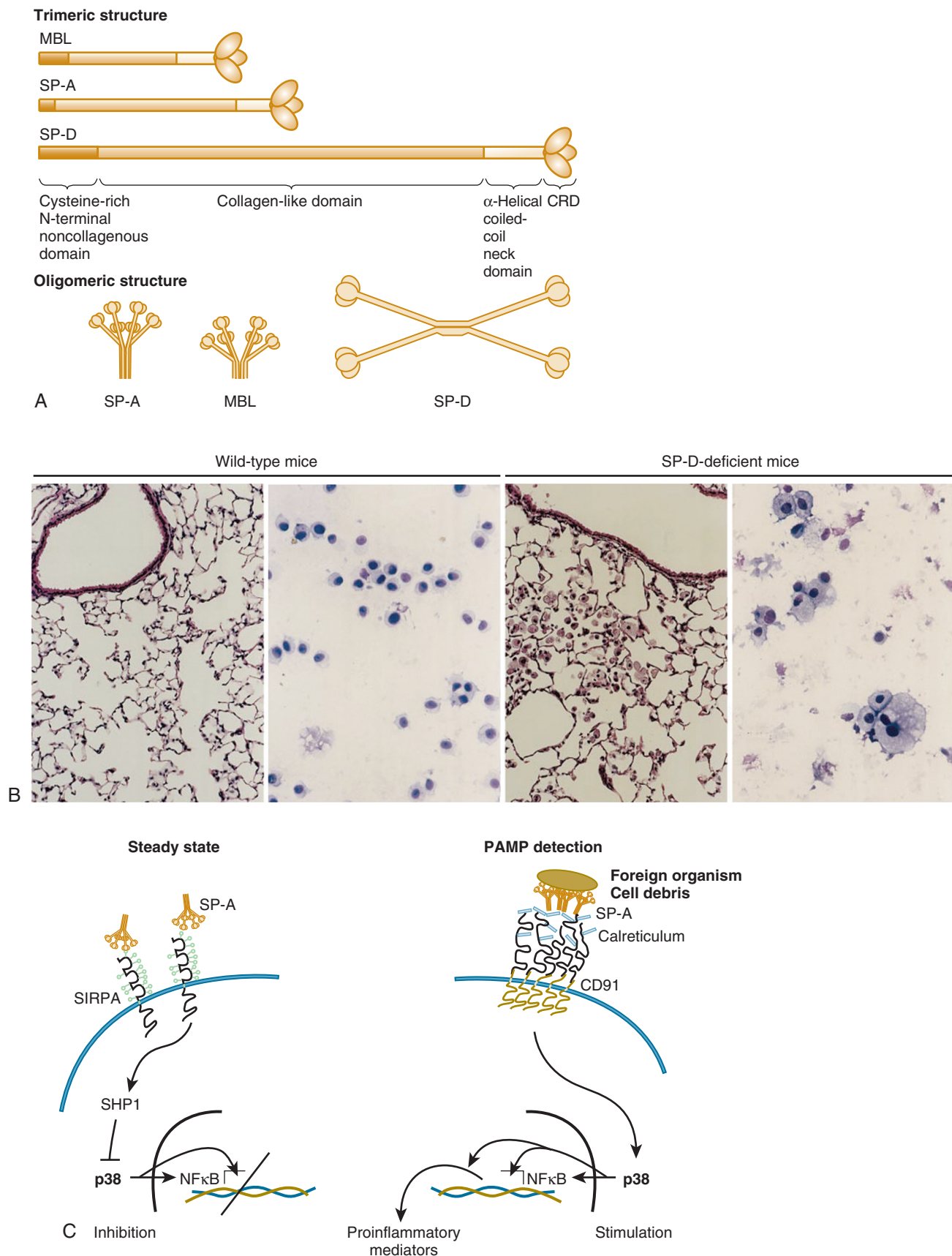


Figure 12-2 Pulmonary collectins, especially surfactant protein A (SP-A) and surfactant protein D (SP-D), play a key role in suppressing inflammation in the absence of pathogen-associated molecular patterns (PAMPs) while stimulating inflammation in the presence of PAMPs. **A**, Structure of pulmonary collectins. **B**, The importance of SP-D in tonic suppression of lung inflammation is illustrated by the spontaneous proinflammatory phenotype of SP-D-deficient mice. **C**, Tonic suppression of inflammation is mediated by the binding of collectins to signal-inhibitory regulatory protein α (SIRP α) via their head groups, whereas activation of inflammation is mediated when PAMP-bound collectins interact with CD91 via their collagenous tail regions. CRD, carbohydrate recognition domain (C-type lectin domain); MBL, mannose-binding lectin. (A, Adapted from Wright JR: Immunoregulatory functions of surfactant proteins. *Nat Rev Immunol* 5:58–8668, 2005; B, adapted from Fisher JH, Sheftelyevich V, Ho YS, et al: Pulmonary-specific expression of SP-D corrects pulmonary lipid accumulation in SP-D gene-targeted mice. *Am J Physiol Lung Cell Mol Physiol* 278:L365–L373, 2000; C, adapted from Gardai SJ, Xiao YQ, Dickinson M, et al: By binding SIRP α or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. *Cell* 115:13–23, 2003.)

binding to the gram-positive bacterial cell wall components *N*-acetylglucosamine and lipoteichoic acid.³⁴

CELLULAR PATTERN RECOGNITION RECEPTORS

Different families of PRRs have evolved to enable the host to sense the presence of PAMPs in extracellular, endosomal, and cytoplasmic compartments, in each of the lineages involved in lung innate immunity (Fig. 12-3). Transmembrane cell surface and endosome-associated PRRs include the TLRs widely expressed on epithelial cells, macrophages, PMNs, and DCs (see Fig. 12-3A), SRs primarily expressed on macrophages (see Fig. 12-3B), and C-type lectin receptors mainly expressed on DCs (see Fig. 12-3C). Cytoplasmic PRRs are composed of *nucleotide-binding and oligomerization domain* (NOD)-like receptors (NLRs) and RNA helicases of the *retinoic acid-inducible gene* (RIG) family. Each of the cytoplasmic PRRs has evolved as a strategy to alert the host to the presence of PAMPs within the cytoplasm, as often happens during the intracellular replication of facultative bacteria and viruses.

Plasma Membrane and Endosomal Pattern Recognition Receptors

Toll-like Receptors. TLRs are expressed on airway and alveolar epithelial cells, macrophages, PMNs, and DCs.³⁵⁻³⁸ Thirteen TLRs have been described in mice (Tlr1 to Tlr13) and 10 in humans. Significant progress has been made in understanding the functions and downstream signal transduction pathways of TLRs.³⁹⁻⁴² TLRs can be divided into those expressed on the cell surface (TLR1, 2, 4, 5, 6, and 11) and those expressed in intracellular compartments (TLR3, 7, 8, and 9) (see Fig. 12-3A). TLRs also recognize endogenous ligands called *danger-associated molecular patterns* (DAMPs), including heat shock proteins, low-molecular-weight hyaluronan, heparin sulfate, fibronectin, high-mobility-group box-1, protein and low-density lipoproteins. Recognition of DAMPs by TLRs and other PRRs is usually associated with the initiation of sterile inflammation. Surface TLRs recognize a wide variety of PAMPs, whereas intracellular TLRs mainly recognize nucleic acid-based PAMPs. TLRs not only recognize their individual cognate PAMPs but also combine with other TLRs to form heteromeric complexes that recognize a broader range of PAMPs.⁴²⁻⁴⁵ For example, TLR1 associates with TLR2 to recognize microbial lipopeptides,⁴⁵ TLR2 and TLR4 recognize the LPS-binding protein/myeloid differentiation protein-2 complex when presented by CD14, and TLR2 recognizes broad patterns of lipoproteins in concert with either TLR1 or TLR6.⁴⁶ TLR5 recognizes flagellin and is particularly important in the response of airway epithelial cells to *P. aeruginosa* infection. Similarly, TLR6 can functionally associate with TLR2 to recognize a variety of microbial lipopeptides and peptidoglycans from gram-positive bacterial cell walls.⁴⁷ TLR3, 7, 8, and 9 are not highly expressed at the cell surface but are expressed intracellularly in endosomal and endoplasmic reticulum membranes, where they sense nucleic acids that are released from ingested and digested microbes.³⁹⁻⁴² TLR3 recognizes viral double-stranded RNA and induces the production of type I *interferons* (IFNs) (IFN- α /IFN- β),⁴⁸ which in turn play a vital role in antiviral immunity and in DC maturation.⁴⁹ TLR7 recognizes single-

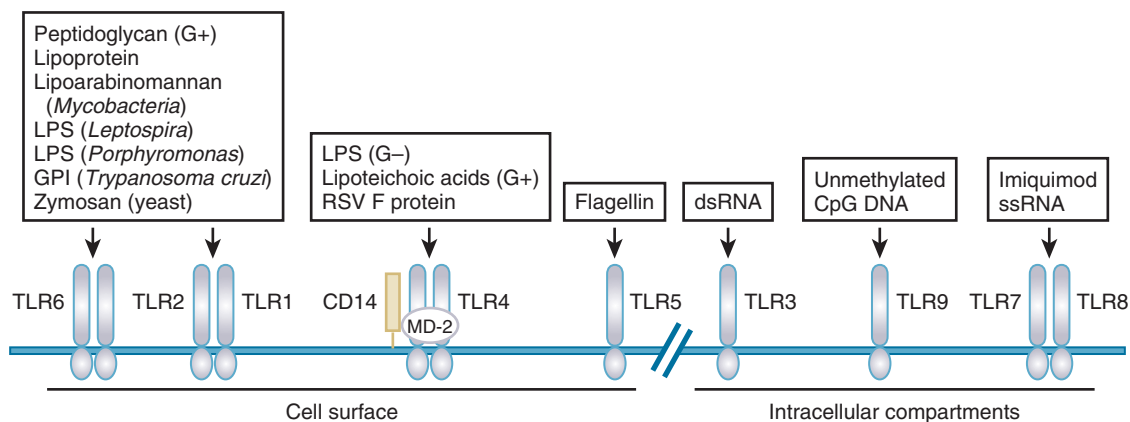
stranded RNA from viruses, whereas TLR9 recognizes unmethylated cytosine-guanosine motifs in microbial DNA.^{50,51}

Scavenger Receptors. The first macrophage SR was described by Goldstein and colleagues⁵² and Brown and associates⁵³ and was shown to bind and internalize acetylated low-density lipoprotein. Since then, multiple SRs have been identified and shown to play diverse roles in the phagocytosis of a variety of particles and molecules ranging from bacteria to lipids (see Fig. 12-3B). The SR family comprises eight classes (A to H), of which class A (SRA) and class B (SRB) are primarily involved in innate immunity through their ability to recognize and promote phagocytosis of a wide range of bacteria. Members of the SR-A and SR-B subfamilies are abundantly expressed on macrophages but do not appear to be expressed by airway or alveolar epithelial cells. The lack of expression on epithelial cells is in keeping with the notion that, during exposure to inhaled microbes and particles, the lung epithelium has evolved mechanisms to respond to PAMPs by promoting inflammation but not to engage in phagocytosis, leaving this activity to professional phagocytes.

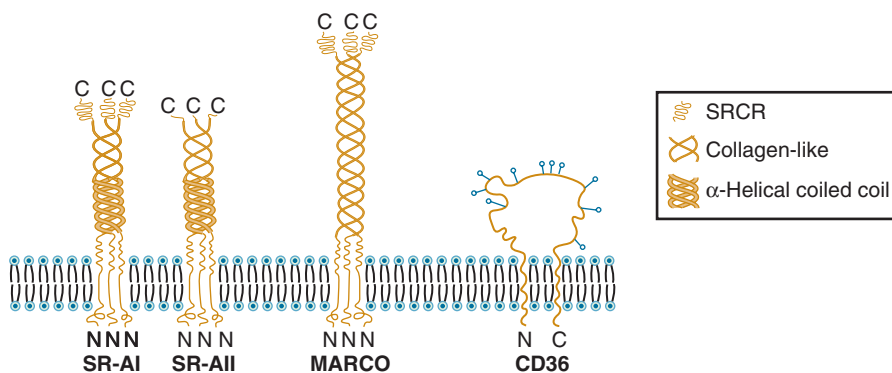
Class A SRs are homotrimeric type II transmembrane proteins (extracellular C-terminal). SRA exists as two splice variants (SRAI and SRAII) of a single gene whose primary function is to promote the phagocytosis of a range of non-opsonized bacteria, including *S. aureus*, *Streptococcus pneumoniae* and *Escherichia coli*.⁵⁴ SRA-deficient mice have increased susceptibility to systemic infections with *S. aureus* and *Listeria monocytogenes*^{55,56} and to pulmonary infections with *S. pneumoniae*.⁵⁷ *Macrophage receptor with collagenous structure* (MARCO) is an additional class A SR that is involved in innate pulmonary host defense against *S. pneumoniae*.⁵⁸ Down-regulation of MARCO by IFN- γ increases susceptibility to *S. pneumoniae* in mice and may contribute to the development of pulmonary bacterial pneumonias following influenza infections.⁵⁹ MARCO may also play a role in dampening pulmonary inflammation because MARCO-deficient mice exhibit increased lung inflammation in response to inhaled silica and oxidants.^{60,61}

Class B SRs are primarily represented in the lung by CD36. CD36 is expressed on monocytes, macrophages, DCs, and vascular endothelium.⁶²⁻⁶⁴ Like class A SRs, CD36 has been implicated in PAMP recognition⁶⁵ and in the phagocytosis of *S. aureus*.^{66,67} However, whereas CD36 deficiency in mice results in impaired host defense against *S. aureus*,⁶⁵ the absence of CD36 in humans, via a natural genetic deficiency, is not associated with a pulmonary phenotype.⁶⁸

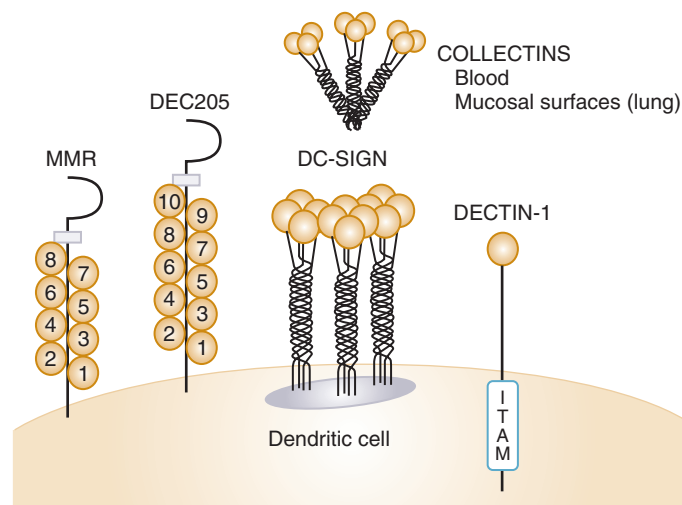
C-Type Lectin Receptors. *C-type lectin receptor* (CLR) domains are also present in a family of cell surface receptors that play an important role in the function of DCs and macrophages (see Fig. 12-3C). CLRs recognize high-density carbohydrate-based PAMPs on microbial cell walls and viral coats. Carbohydrate binding can be divided into mannose and galactose specificity.⁶⁹ Type I CLRs include *dendritic and thymic epithelial cell-205* (DEC205) and macrophage mannose receptor, and type II CLRs include dendritic cell-specific *intracellular adhesion molecule* (ICAM3), *dendritic cell-specific intercellular adhesion molecule-grabbing nonintegrin* (DC-SIGN), and *dendritic cell-specific receptor-1* (DECTIN1).



A Toll-like receptors (TLRs)



B Scavenger receptors



C C-type lectin receptors

Figure 12-3 Major classes of transmembrane cell surface pattern recognition receptors expressed by lung cells. **A**, Toll-like receptors. **B**, Scavenger receptors. **C**, C-type lectin receptors. CpG, cytosine-guanosine; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-grabbing nonintegrin; DEC205, dendritic and thymic epithelial cell-205; dsRNA, double-stranded RNA; ITAM, immunoreceptor tyrosine-based activation motif; LPS, lipopolysaccharide; MARCO, macrophage receptor with collagenous structure; MD2, myeloid differentiation protein-2; MMR, macrophage mannose receptor; RSV, respiratory syncytial virus; SRAI, scavenger receptor AI; SRAII, scavenger receptor AI; SRCR, scavenger receptor cysteine-rich domain; ssRNA, single-stranded RNA. (A, Modified from Medzhitov R: Toll-like receptors and innate immunity. *Nat Rev Immunol* 1:135–145, 2001; B, modified from Taylor PR, Martinez-Pomares L, Stacey M, et al: Macrophage receptors and immune recognition. *Annu Rev Immunol* 23:901–944, 2005; C, redrawn from Gijzen K, Cambi A, Torensma R, Figdor CG: C-type lectins on dendritic cells and their interaction with pathogen-derived and endogenous glycoconjugates. *Curr Protein Pept Sci* 7:283–294, 2006; D, redrawn from Geddes K, Magalhães JG, Girardin SE: Unleashing the therapeutic potential of NOD-like receptors. *Nat Rev Drug Discovery* 8:465–479, 2009.)

As we discuss later, studies in mice bearing targeted disruptions of CLR genes have emphasized their importance in innate host defense and particularly in DC maturation and antigen presentation.

DEC205 is a type 1 transmembrane receptor protein found on a variety of DC subsets and macrophages.⁷⁰ The natural carbohydrate ligands remain largely uncharacterized, though the receptor has been shown to induce the endocytosis of experimental antigen–anti-DEC205 receptor complexes and promote their delivery to endosomes before antigen processing and presentation. When DCs are treated with the antigen–anti-CD205 fusion protein alone, they induce tolerance to the antigen by deleting specific CD4⁺ and CD8⁺ T cells and by promoting the development of *T regulatory* (Treg) cells.⁷¹ In the presence of an inflammatory stimulus, DCs exposed to the antigen–anti-DEC205 fusion proteins promote long-lived immunity mediated by Ag-specific CD4⁺ and CD8⁺ T cells.^{72,73} Antigens delivered by targeting DEC205 may be presented in association both with MHC class II molecules and by cross-presentation with MHC class I molecules.^{74–76} Furthermore, a recent study showed that DEC205 mediates the uptake of self-antigens via the endocytosis of apoptotic cells, thereby providing a plausible mechanism for the cross-presentation of self-antigens resulting in the induction of both central and peripheral tolerance.⁷⁷

DECTIN1 was initially thought to be expressed specifically on DCs but was later shown to be expressed also on macrophages, monocytes, PMNs, and some T-cell subsets.^{78,79} DECTIN1 specifically recognizes β -(1,3)-linked glucans and β -(1,6)-linked glucans⁸⁰ and is thought to play a key role in the nonopsonic phagocytosis of a number of pathogenic yeasts, fungi, and bacteria by macrophages and DCs.⁸¹ Ligation of DECTIN1 also stimulates the production of an array of proinflammatory cytokines, oxidants, and lipid mediators.^{82–86}

DC-SIGN is also a type II CLR^{87,88} but differs from DECTIN1 by its specificity for microbial mannose-rich carbohydrates.^{87,89–91} DC-SIGN is important in DC trafficking and DC–T-cell interactions through its ability to interact with ICAM3 and ICAM2, respectively. DC-SIGN is also expressed on the surface of a subset of peripheral blood and lung BDCA-2⁺ *plasmacytoid DCs* (pDCs) and resident alveolar macrophages.⁹² Interestingly, increased expression of DC-SIGN by alveolar macrophages has been reported in response to stimulation with interleukin-13 (IL-13), suggesting a possible role for DC-SIGN⁺ cells in the pathogenesis of *type 2 T helper* (Th2)–mediated lung diseases.⁹²

Cytoplasmic Pattern Recognition Receptors

Nucleotide-Binding and Oligomerization Domain-like Receptors. In humans, NLRs are a family of 22 intracellular PRRs that have evolved to sense PAMPs in the cytoplasm of most cells. Cytoplasmic PAMPs recognized by NLRs include bacterial peptidoglycans and flagellin from gram-positive and gram-negative bacteria as well as microbial toxins such as *Bacillus anthracis* lethal factor.^{93–95} Earlier, we briefly introduced DAMPs as a collection of nuclear and cytoplasmic molecules, including high-mobility-group box-1 protein, adenosine triphosphate, *nicotinamide adenine dinucleotide* (NAD⁺), and adenosine, that are released following tissue injury.⁹⁶ Recent studies have also shown that,

though not technically DAMPs, uric acid and crystalline silica are also sensed by NLRs and, like PAMPs, initiate sterile inflammatory responses.^{97–99} In turn, the recognition of cytoplasmic PAMPs and DAMPs by NLRs activates an array of signal transduction pathways that lead to the production of proinflammatory cytokines. NLRs also induce the assembly of intracellular protein-protein complexes called “inflammasomes,”^{100–103} which stimulate IL-1 β production and initiate several different forms of programmed cell death, including apoptosis, necrosis, pyroptosis, and pyronecrosis.¹⁰⁴ NLRs may also play a role in the maturation of immature DCs after exposure to PAMPs or cytokines.¹⁰² The precise mechanisms by which NLRs signal is an area of intense investigation, but studies show that NLRs participate in the formation of three distinct inflammasomes, including the NALP1- and NALP3-containing inflammasomes and interleukin-1 β -converting enzyme protease-activating factor-containing inflammasomes.^{93,101} Although the role of NLRs in a variety of human disorders has been characterized, the complete role of these molecules in lung homeostasis and defense is not yet fully understood. More information about NLR structure and function is available in several recent reviews.^{93,95,101,104–110}

Retinoic Acid–Inducible Gene-1–like Receptors. The last group of cytoplasmic PAMP sensors is the RIG1-like receptors that have evolved to detect the presence of RNA from RNA viruses and replicating DNA viruses. Three family members, RIG1, myeloma-differentiation associated gene 5, and laboratory of genetics and physiology 2, have been identified. RIG1 has been shown to recognize viral RNA sequences from several viruses and is involved in the response of lung epithelial cells to influenza virus.^{111,112} In contrast, myeloma-differentiation associated gene 5 has been shown to respond to polyriboinosinic:polyribocytidylic acid and picornoviruses.¹¹³ Upon sensing viral RNA sequences, RIG-like family members promote the expression of type I IFNs and proinflammatory cytokines,¹¹⁴ thereby inducing and augmenting host and lung innate immunity.

SUMMARY

Secreted, plasma membrane, endosomal, and cytosolic PRRs provide remarkable flexibility in innate protection of the lung. In the descending airways, plasma membrane PRRs, especially TLRs, are poised to sense PAMPs but are generally unable to phagocytose PAMP-containing microbes. However, TLR signaling in airway epithelial cells results in the production of proinflammatory mediators, especially chemokines and cytokines, which call in PMNs and macrophages to the site of PAMP detection to enable microbial clearance. In addition, intraepithelial DCs constantly sample the airway lumen to maintain immunologic tolerance to commonly encountered antigens that do not express PAMPs, while remaining poised to activate the adaptive immune system once PAMPs are sensed. The alveoli are also protected by epithelial cells, DCs, and resident alveolar macrophages that also sense PAMPs via plasma alveolar PRRs. However, in the alveoli, two additional levels of protection exist. First, secreted PRRs, especially SP-A and SP-D, protect the alveolar surfaces by tonically suppressing unwanted

inflammation in the steady state, while remaining poised to stimulate innate responses in the presence of PAMPs. Second, resident alveolar macrophages express an additional array of PRRs, especially SRs that promote the phagocytosis of microbes and other particulates. It seems reasonable to suggest that, in the steady state, the innate immune system responds to inhaled particulates and microbes continuously, but silently. In the next section, we discuss how ligation of these various PRRs activates and regulates innate host defense responses in lung cells.

EFFECTOR MECHANISMS

The cell types that are primarily responsible for innate protection of the lung in the steady state are (1) airway and alveolar epithelial cells and (2) macrophages and DCs. Additionally, in response to the initial activation of these cells, PMNs, which though not an abundant cell type in the steady state, are rapidly recruited to augment lung phagocyte numbers once the presence of PAMPs is detected. In the following section, we review the origin and functions of these resident and recruited cells in innate protection of the lung.

EPITHELIUM

The lung epithelium has an important role in host defense against microbes that pass through the glottis and reach the conducting airways and gas-exchange parenchyma. The conducting airways of the lower respiratory tract are lined by ciliated columnar epithelial cells down to the terminal airways; these cells become nonciliated in the respiratory bronchioles. In contrast, the alveolar epithelium consists of flattened type I epithelial cells that form most of the alveolar surface and type II cuboidal epithelial cells that produce surfactant and surfactant-related proteins and project into the subepithelial structures of the lungs. The classic antimicrobial defense mechanism in the conducting airways is the mucociliary system, which moves microbes deposited on the airway epithelial surface upward and out of the lungs. In addition to this physical removal system, the airway and alveolar epithelium participate actively in the innate defense of the lungs, with the major goal of protecting the critical gas-exchange surface from microbial invasion.¹¹⁵ The mucociliary system provides for the removal of all particles that deposit on the airway epithelium, and the clearance times in the trachea and proximal airways are measured in minutes (see Video 11-3). The cilia on the epithelial surface beat in coordinated waves, directing the movement of particles upward toward the larynx. Epithelial cell activation is not required for optimal ciliary beating, although beat frequency can be speeded by β -agonists and slowed by opiates and other drugs.¹¹⁶ Additional information on mucociliary clearance can be found in Chapter 11.

The mucociliary system and antimicrobial constituents of airway epithelial fluid discussed in the “Overview of the Components of Lung Innate Immunity” section (see Table 12-1) can be thought of as constitutive host defenses, because they do not depend on specific microbial recognition mechanisms and do not need activation. However, the

airway and alveolar epithelium also participate in innate immune mechanisms in that they express bacterial recognition molecules (PRRs) common to innate immune cells and can produce an array of proinflammatory mediators that recruit leukocytes into the airways directly through the airway and alveolar epithelial walls. Bacterial products stimulate the airway epithelium to produce chemotactic signals that recruit inflammatory cells into the airways. Endogenous cytokines also stimulate airway and alveolar epithelial cells to amplify leukocyte migration. Bacterial LPS stimulates ciliated airway epithelial cells to produce CXC and CC chemokines, which recruit PMNs and monocytes, respectively, into the airway lumen.¹¹⁷ Airway epithelial cells also produce IL-1 β , IL-6, IL-8, RANTES (regulated on activation, normal T-cell expressed and secreted), *granulocyte-macrophage colony-stimulating factor* (GM-CSF), and *transforming growth factor- β* (TGF- β).¹¹⁵ As with other cells involved in innate immunity, airway epithelial cells produce cytokines via the activation of transcription factors, including *nuclear factor- κ B* (NF κ B), activator protein-1, and nuclear factor interleukin 6.¹¹⁸ Interestingly, noninfectious environmental agents like ozone,¹¹⁹ asbestos,¹²⁰ diesel exhaust particles,¹²¹ and air pollution particles¹²² all lead to NF κ B activation in airway epithelial cells under experimental conditions, which is typically followed by IL-8 production and release. Airway epithelial cells also recognize unmethylated bacterial DNA via TLR9, leading to NF κ B activation and production of IL-6, IL-8 and β_2 -defensin in the airways.¹²³ Unlike airway epithelial cells, alveolar epithelial cells do not respond directly to LPS but do produce chemokines in response to the *tumor necrosis factor- α* (TNF- α) and IL-1 β secreted by alveolar macrophages in response to bacteria or their products.

The critical role of the lung epithelium in innate immunity and microbial defense has been supported by studies using transgenic mice. When a dominant negative I κ B construct was expressed in the distal airway epithelial cells of mice, thereby preventing NF κ B activation, airway PMN recruitment in response to inhaled LPS was impaired.¹²⁴ This finding supports the importance of bacterial recognition by distal airway epithelial cells in vivo and shows that epithelium-derived cytokines produced by the NF κ B pathway probably are just as important as macrophage-derived cytokines in driving innate inflammatory responses in the airways and alveolar spaces. Hajjar and colleagues¹²⁵ created bone marrow chimeras in which either myeloid (leukocytes) or nonmyeloid (epithelial) cells lacked Myd88, a key adapter molecule required for signaling via all TLRs except TLR3. It turned out that *nonmyeloid* deficiency of Myd8 impaired bacterial clearance more than *myeloid* deficiency. Specifically, the mice lacking Myd8 (and therefore lacking TLR signaling) in nonmyeloid cells, including the airway and alveolar epithelium, had markedly impaired clearance of *P. aeruginosa*, whereas mice with or without Myd8 in myeloid cells had normal bacterial clearance. This surprising result further supports the important role of the airway and alveolar epithelium in bacterial recognition and clearance from the lungs, a role that is perhaps equivalent to that of resident and recruited leukocytes.

Innate immune responses in the airway epithelium can generate or influence adaptive responses. For example, recognition of β -(1,3)-glucan in house dust mites stimulates

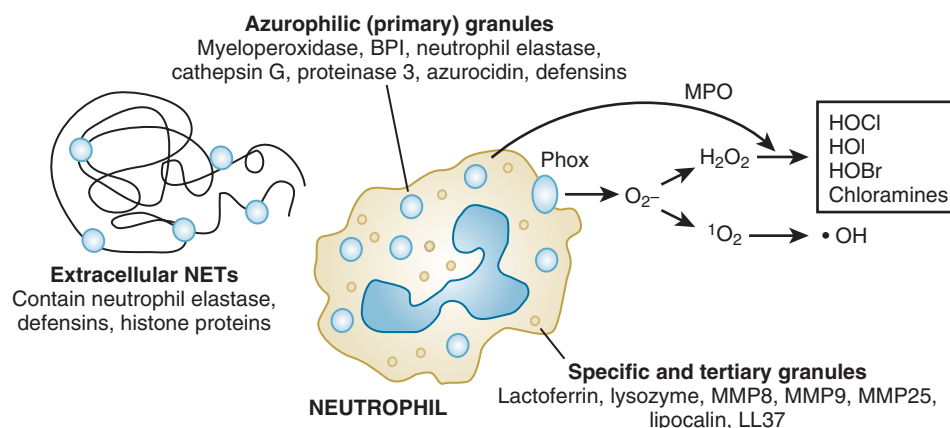


Figure 12-4 Neutrophils use several mechanisms to kill microbes. BPI, bacterial permeability-increasing protein; LL37, cathelicidin; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NET, neutrophil extracellular trap. (Modified from Nathan C: Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol* 6:173–182, 2006.)

the production of CCL20, a chemokine that recruits immature DCs into the airways.¹²⁶ The airway epithelium can directly influence the function of lung DCs, inducing adaptive Th2 responses that are thought to be important in the pathogenesis of asthma, and LPS responses in the airway epithelium are involved in some DC-driven Th2 cell responses.¹²⁷ Airway epithelial cells produce thymic stromal lymphopoietin, GM-CSF, IL-1 β , IL-25, IL-33, and osteopontin, all of which activate DCs.¹²⁸

An emerging concept is that deliberate stimulation of innate immunity in the airways and air spaces produces broad enhancement of antimicrobial defenses. Exposure of mice to a crude extract of nontypeable *Haemophilus influenzae* bacteria via aerosol initially stimulated innate immunity and then protected the mice from lethal infection with *S. pneumoniae*.¹²⁹ This was associated with enhanced production of lysozyme, lactoferrin, and defensins in the lungs. Similarly, exposure to this crude bacterial extract protected mice from *S. aureus*, *P. aeruginosa*, and the fungus *Aspergillus fumigatus*.¹³⁰ Thus prestimulation of innate immune mechanisms in the airway and perhaps alveolar epithelium enhances the antimicrobial activity and host defense of the lungs against a broad array of bacteria and fungi. The implication is that deliberate low-level stimulation of innate immunity in the lungs could be used as a protective strategy; however, the emerging recognition of the important role of lung epithelial innate immunity in stimulating and regulating adaptive immune mechanisms raises the possibility that such a strategy might have unexpected effects.

Thus innate immune mechanisms in the airways stimulate endogenous defenses by enhancing production of airway defensins and other antimicrobial products, by stimulating PMN and monocyte recruitment into the airways to augment antimicrobial defenses, and by setting the stage for DCs and Th2-mediated adaptive immune responses that could be important in the pathogenesis of allergic lung diseases.

POLYMORPHONUCLEAR LEUKOCYTES

PMNs serve as the immediate effector arm of the innate immune system.^{131,132} PMNs are produced from progenitor

cells in the bone marrow, circulate for a short time in the bloodstream, and migrate to sites of tissue inflammation in response to signals produced by local innate immune mechanisms. Mature PMNs are released from the marrow in response to granulocyte colony-stimulating factor and other stimuli and circulate for up to 6 to 8 hours. The bone marrow releases between 10^9 and 10^{10} PMNs each day, and marrow release can increase severalfold in response to acute signals from the lungs and other tissues. PMNs contain several different kinds of cytoplasmic granules, which contain an array of proteins (Fig. 12-4). Small specific granules serve as a source of new membrane and fuse with the leading edge of the cell during migration. Primary (azurophilic) granules contain myeloperoxidase, which accounts for the green color of pus, bacterial permeability-increasing protein, PMN elastase, matrix metalloproteinases, other proteinases, and defensins.

Circulating PMNs are spherical, with a diameter of approximately 8 μm and must deform to make their way through the capillary microcirculation in the lungs and other organs. PMNs bear surface adhesion molecules that recognize carbohydrate and protein moieties expressed on activated endothelial cells. In the systemic circulation, PMNs migrate into tissue through postcapillary venules in a four-step process by (1) weakly adhering to the venular endothelium, (2) rolling along the endothelial surface, (3) arresting on the endothelial surface, and (4) migrating between endothelial junctions into tissue in response to local chemotactic gradients.^{133,134} This systemic paradigm is different in the lungs, where the pulmonary capillaries slow the transit of PMNs because of the small cross-sectional capillary diameter.^{135,136} This produces a reservoir of capillary PMNs that are poised to respond directly to signals from the innate immune system in the air spaces. When bacteria or their products such as gram-negative LPS circulate in the bloodstream, PMNs undergo activation with cytoskeletal rearrangements that cause stiffening,¹³⁷ promoting increased entrapment of PMNs in the pulmonary capillaries.

When innate immunity is activated in the lungs, chemotactic factors are produced by resident alveolar macrophages and activated epithelium, which create soluble and tissue-fixed gradients that recruit PMNs into the alveolar

spaces. Leukotriene B₄ is a product of arachidonic acid metabolism in alveolar macrophages that produces an immediate and short-lived soluble gradient that recruits PMNs into the air spaces but dissipates within minutes.^{138,139} Release of leukotriene B₄ is closely followed by the release of IL-8, a chemokine that binds to heparin residues on tissue matrix, creating a tissue reservoir that promotes long-lived gradients.^{140,141} IL-8 is the dominant member of a group of CXC chemokines, which also include GRO- α , GRO- β , and GRO- γ , and ENA-78. The CXC chemokines have a C-X-C sequence at the N-terminus, which provides PMN specificity, and an N-terminal Glu-Leu-Arg peptide sequence, which is important in chemotactic receptor binding. The CXC chemokines recruit PMN to sites of inflammation, whereas chemokines with the CC N-terminal sequence recruit monocytes. IL-8 and related chemokines probably reach the endothelial luminal surface by diffusion from alveolar fluids and bind to endothelial cell surface glycosaminoglycans to create a fixed local signal that guides PMNs sequestered in pulmonary capillaries into the air spaces. Whereas PMNs bear a single receptor for leukotriene B₄, they express two different receptors with differing affinity for IL-8. The low-affinity receptor (CXCR2) is thought to recruit PMNs to sites of inflammation, whereas the high-affinity receptor (CXCR1) is thought to guide PMN migration into the tissues. The low-affinity receptor is shed from the surface of circulating PMNs in sepsis, leaving the high-affinity CXCR1 receptor as the dominant IL-8 receptor.¹⁴² This suggests that a CXCR1 receptor-targeted strategy could be effective in limiting PMN inflammation in patients with sepsis. PMNs also have receptors for the complement component C5a and for formylated peptides produced by bacteria in the air spaces, so that endogenous as well as exogenous signals attract PMNs to sites of inflammation. The diversity of chemotactic stimuli recognized by PMNs promotes the formation of combinatorial gradients that guide PMN migration toward localized sites of inflammation in the lungs and other tissues.¹⁴³

In the systemic circulation, PMN migration into tissues depends on the integrin CD11/CD18 on the PMN surface recognizing the counterligand ICAM1 on the endothelial surface. In the lungs, however, both CD18-dependent and CD18-independent mechanisms exist, and the signals that determine the dependence on CD18 are not clear.¹⁴⁴ For example, PMN migration into the lungs in response to *E. coli* and *P. aeruginosa* is CD18 dependent, whereas PMN migration in response to *S. pneumoniae* does not require CD18. TNF- α and IL-1 β appear to direct CD18-dependent migration, whereas IFN- γ is more important for CD18-independent migration.

Under normal circumstances, PMN migration from the blood into the air spaces is not associated with injury to the endothelial or epithelial barriers. At the endothelial barrier, endothelial cells undergo reversible contraction in response to thrombin and other inflammatory stimuli, thereby opening endothelial junctions and allowing the passage of leukocytes. The alveolar barrier is much tighter, and yet PMNs reach the air spaces with only minor and transient changes in epithelial permeability.^{145,146} During migration the spherical PMNs in the bloodstream change shape, and small specific granules fuse with the leading edge of the cell membrane, providing new membrane material bearing

specific adhesion molecules. PMNs in the air spaces are polarized, which is an initial sign of activation, but contain the full complement of primary azurophilic granules containing myeloperoxidase and defensins.¹⁴⁵ Metabolic studies of PMNs in rabbits with pneumococcal pneumonia and humans with bronchiectasis have shown that most PMNs become activated in the air spaces and not during migration into the lung.^{147,148} However, when endothelial activation is intense or when PMN activation signals are present within the circulation, PMNs become preactivated and migration can be associated with damage to the endothelial and epithelial barriers, with the development of increased-permeability pulmonary edema.¹⁴⁹

Once in the air spaces, PMNs ingest bacteria and fungi that have been opsonized by complement and immunoglobulins that accumulate in the air spaces at sites of inflammation. PMNs contain a series of effector mechanisms to kill bacteria and fungi, including oxidant production, microbicidal proteins in primary azurophilic granules, and extracellular traps (see Fig. 12-4). As microbes are recognized and the phagosome begins to form, the subunits of a nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) oxidase are assembled in the cell membrane, and the cell undergoes a respiratory burst, in which an electron is transferred to molecular oxygen to form superoxide anion, which is reduced again to form hydrogen peroxide. This happens on the invaginating phagosomal membrane, focusing oxidants on the contents of the developing phagosome. As the phagosome forms, the primary granules fuse with the phagosomal membrane, adding myeloperoxidase and cationic antimicrobial peptides to the phagolysosome. Myeloperoxidase catalyzes the formation of hypochlorous acid from hydrogen peroxide and a halide, typically chloride (Cl⁻) because of its high concentration in the cellular environment. Hypochlorous acid is a highly reactive oxidant that oxidizes methionines, tyrosines, and other amino acids on proteins, killing the microbe.

In addition to their presence in airway surface liquid, the primary azurophilic granules also contain high concentrations of the α -defensins, human neutrophil protein 1, 2, and 3.^{150,151} When defensins are added to the phagolysosomal space, they attach to negatively charged microbial membranes via electrostatic interactions and are thought to form lytic pores in the microbial cell wall. PMN defensins have antimicrobial activity for gram-positive and gram-negative organisms, fungi, and some viruses. Defensins are most active under conditions of low ionic strength and lose activity with increasing concentrations of salt or plasma proteins, which interfere with electrostatic interactions between the cationic defensins and the anionic microbial surface.¹⁵⁰ The loss of defensin activity in higher salt concentrations has been proposed as a contributing factor for the pathogenesis of chronic airway infection in cystic fibrosis.¹⁵² In addition to their antimicrobial activity, defensins participate directly in innate and adaptive immunity, because they stimulate IL-8 production by epithelial cells and modulate the responses of T cells and immature DCs.^{151,153}

When phagocytosis is appropriately regulated, microbes are killed within the protected environment of the PMN phagolysosome. However, at sites of intense inflammation, PMNs release superoxide anion, hydrogen peroxide, and

granular contents directly into the extracellular environment, leading to oxidant formation in the alveolar spaces with oxidation of structural proteins in the alveolar walls and intracellular proteins in leukocytes, and the accumulation of defensins and other granular contents in the alveolar spaces.¹⁵⁴ These extracellular products contribute to indirect tissue injury by PMNs.

In addition to killing intracellular microbes using oxidants, chlorination, and antimicrobial peptides, as a final act, PMNs can project uncoiled nuclear DNA into the surrounding environment to form *neutrophil extracellular traps* (NETs) that ensnare and destroy bacteria.^{155,156} NET formation depends on the initial respiratory burst of the PMN and leads to the death of the PMN in a process that is distinct from apoptosis and necrosis.¹⁵⁷ The PMNs of patients with chronic granulomatous disease, which lack a functional membrane NADPH oxidase, do not form NETs following appropriate stimulation.¹⁵⁷ A variety of proinflammatory stimuli activate NET formation, including LPS and IL-8. C5a triggers NET formation in PMNs after priming with IFNs or GM-CSF. Some microbes, including *S. aureus*, *E. coli*, *P. aeruginosa*, and *M. tuberculosis*, directly stimulate NET formation by PMNs.¹⁵⁸ The extracellular DNA mesh contains cationic proteins embedded in the negatively charged DNA net, including histones, defensins, and cathelicidin, which kill enmeshed bacteria. Similar extracellular traps are produced by eosinophils and mast cells, but unlike PMNs, eosinophils apparently survive NET formation. NET formation thickens secretions at sites of inflammation, creating a viscous pus that contains enmeshed microbes. As might be expected, some bacteria produce extracellular enzymes that degrade DNA NETs, including *Streptococcus pyogenes* (DNase Sda1/2) and *S. pneumoniae* (DNase EndA).^{159,160} The mechanisms by which NETs are cleared from the air spaces during resolution of inflammation are not clear.

PMNs have an important role in signaling the activation of adaptive immunity.¹⁶¹ In rabbits with tuberculous pleurisy, PMNs are the first cells that migrate into the infected pleural space, where they produce chemotactic factors that direct the subsequent wave of monocyte recruitment, which characterizes the full inflammatory reaction to *M. tuberculosis*.¹⁶² PMN granule proteins cathepsin G and azurocidin are chemoattractants for mononuclear cells, which mature into macrophages and DCs at sites of inflammation, and neutrophil-derived CC chemokines recruit DCs.^{163,164} PMNs release limited amounts of TNF- α and IFN- γ , which regulate macrophage, T-cell, and DC activation and maturation; however, the large numbers of PMNs at sites of inflammation can bring the concentrations of these PMN-derived cytokines into biologically relevant ranges. PMNs also produce CXC chemokine ligand 10 (IFN- γ inducible protein-10), which is a chemoattractant for natural killer cells and *type 1 T helper* (Th1) cells.¹⁶⁵

At the same time that PMNs participate in and intensify inflammation in tissue, they also produce signals that control and begin the resolution of inflammation. PMNs, like macrophages and endothelial cells, release the secretory leukocyte protease inhibitor, which inhibits PMN elastase.¹⁶⁶ After migration into tissues, PMNs produce lipoxins from membrane arachidonic acid, which inhibit PMN recruitment, superoxide anion generation, and NF κ B

activation and enhance the uptake of apoptotic PMNs by macrophages.¹⁶⁷ PMN-derived oxidants inactivate proteases and other proteins at sites of inflammation.

PMNs and their products are cleared largely by macrophages during the resolution of inflammation. PMNs die primarily by apoptosis, necrosis, or NET formation. Apoptosis is a highly regulated form of cell death and is mediated by a series of intracellular caspases.^{168,169} Apoptosis is mediated via two major pathways: ligation of membrane death receptors, principally FAS/CD95 and TNFRI (p55), and mitochondrial stress that results in the release of cytochrome *c* into the cytoplasm. PMNs undergoing apoptosis express phosphatidylserine on the outer leaflet of the cell membrane and undergo nuclear chromatin condensation and cell shrinkage. Apoptotic PMNs are recognized by macrophages via the class B SR, CD36, and are rapidly ingested, so that large numbers of apoptotic PMNs are usually not seen. Macrophages that ingest apoptotic PMNs produce TGF- β and IL-10, which have anti-inflammatory effects. This process results in the clearance of PMNs and their residual intracellular contents and dampening of inflammation. PMNs that are not ingested by macrophages undergo secondary necrosis with loss of membrane integrity, cytoplasmic swelling, and release of remaining intracellular contents into the inflammatory environment. Intracellular components are recognized as danger signals by macrophages, some of which have been included as “alarmins,” or DAMPs.¹⁷⁰ DAMPs include the nuclear protein high-mobility-group box-1, granular antimicrobial peptides, and other intracellular products. Macrophages that recognize these danger signals produce IL-1 β , TNF- α , IL-8, and other proinflammatory cytokines, initiating or perpetuating inflammatory responses. Some PMNs recovered from the lungs of patients with acute respiratory distress syndrome have features of apoptosis, with small cytoplasmic features and nuclear pyknosis, whereas many have features of necrosis, including severe degranulation, membrane blebbing, and cytoplasmic swelling. The signals that govern the balance between necrosis and apoptosis are incompletely understood.

Thus PMNs are important effector cells in innate immunity, ideally designed to circulate through the body and accumulate rapidly at tissue sites of acute inflammation. Under normal circumstances, they arrive in tissue ready to ingest and kill microbes, then quietly go away by programmed cell death. PMN-derived signals regulate local inflammation and stimulate adaptive immune responses, providing a broader role for PMNs in host defense.

MONONUCLEAR PHAGOCYTES

The concept of the mononuclear phagocyte system as a functionally and phenotypically heterogeneous system of mononuclear phagocytes distributed throughout the body was developed in the 1960s and 1970s through a series of insightful studies pioneered by van Furth and Cohn¹⁷¹ and Volkman and Gowans.¹⁷² The central concept was that the resident macrophages of all organs and tissues were derived from progenitor cells in the bone marrow. In turn, the progenitor cells gave rise to circulating blood monocytes that were recruited into organs and tissues, where they differentiated into macrophages, to maintain

macrophage homeostasis. In response to additional needs during inflammation or infection, monocyte production in the bone marrow increases, thereby enabling increased monocyte recruitment to affected tissues. Although many aspects of this conceptual framework have been confirmed, recent studies building on earlier foundational work¹⁷³⁻¹⁷⁵ have challenged the concept that resident macrophages are derived from bone marrow–derived monocytes and have provided important insights into the origins of resident tissue macrophages during early embryonic development.^{176-185,185a} Fate-mapping studies involving lineage-tagged mice and other genetic models have suggested that there is a pool of “primitive” F4/80 bright resident macrophages located within tissues that are derived from the yolk sac beginning on *embryonic day 8* (E8) (Fig. 12-5A).^{177,181,186} In addition to expressing high levels of F4/80, these yolk sac–derived macrophages express CX3CR1, *macrophage mannose receptor* (MMR), and colony-stimulating factor 1 receptor (CSF1R, *c-fms*) and are dependent upon IL-34, CSF1, and the transcription factor PU.1

for their development (see Fig. 12-5A).^{181,187-190} By E10.5, yolk sac–derived macrophages are found in most tissues, including the lung, and are able to undergo self-renewal.^{173,175,181,184,191} At E10.5 the fetal liver becomes the major site of hematopoiesis,¹⁹² and with its development, a unique “definitive” macrophage population derived from the hematopoietic stem cell can also be found.^{181,189} These cells express low levels of F4/80, high levels of CD11b, and, in contrast to the yolk sac–derived macrophages, are dependent on the transcription factor c-Myb for development.¹⁸¹ During liver hematopoiesis, macrophages constitute up to 15% of the total cells in many organs,¹⁸⁹ and their importance in embryonic development has been definitively shown in studies using *c-fms*-, colony-stimulating factor 1-, CX3CR1-, c-Myb- and PU.1-deficient mice.¹⁷⁸⁻¹⁸² These studies also showed that adult Langerhans cells, the prominent antigen-presenting cells of the skin, are produced by the fetal liver and that their development is dependent on IL-34 and CSF1R. In studies using these and other models, macrophages have been shown to play important roles in

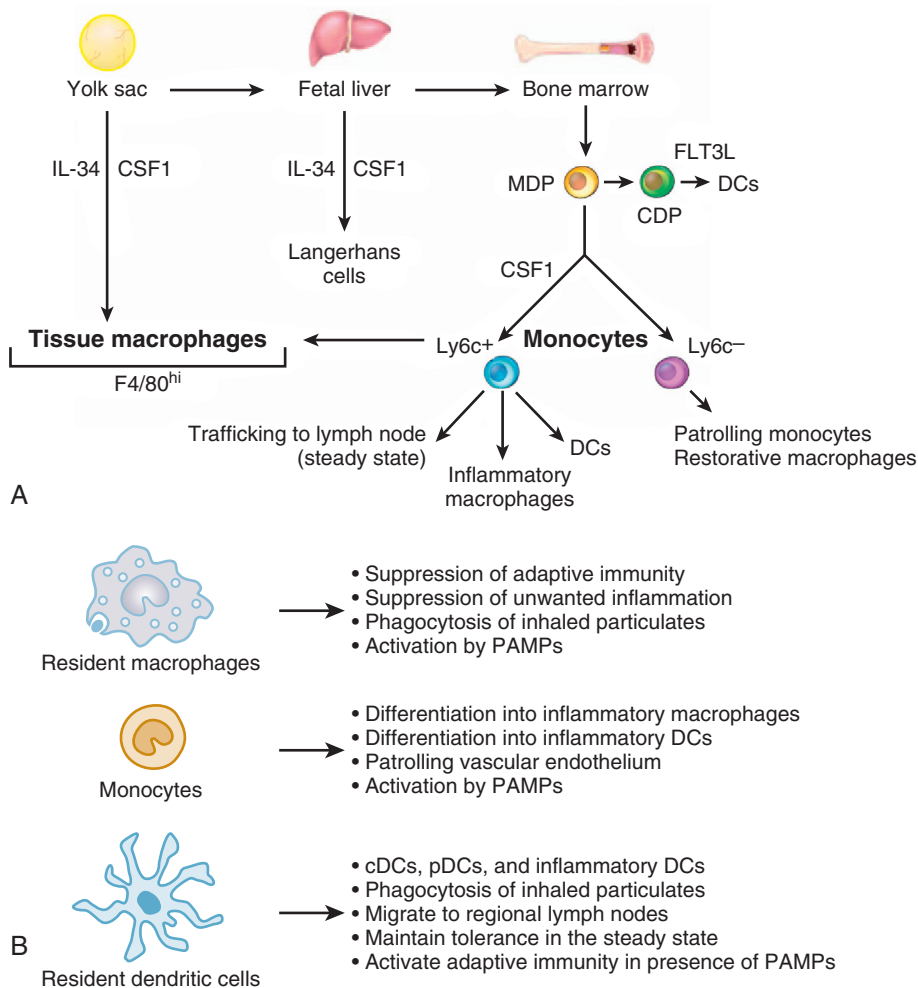


Figure 12-5 Pathways of development of resident tissue macrophages and blood monocytes. **A**, Monocytes can traffic to lymph nodes, develop into inflammatory and restorative macrophages and dendritic cells (DCs), or be maintained as patrolling cells in the circulation in mice. **B**, In the steady state, lung mononuclear phagocytes can be considered to include (1) resident macrophages of the alveoli and alveolar septae, (2) marginating monocytes of the lung microvasculature, and (3) resident dendritic cells. Each of these subsets exhibits overlapping and unique functions. cDC, conventional DC; CDP, common DC precursor cell; CSF1, colony-stimulating factor 1; FLT3L, FLT3 ligand; IL, interleukin; MDP, macrophage and DC precursor; PAMP, pathogen-associated molecular pattern; pDC, plasmacytoid DC. (A, Adapted and redrawn from Wynn TA, Chawla A, Pollard JW: Macrophage biology in development, homeostasis and disease. *Nature* 496:445–455, 2013.)

bone morphogenesis, ductal branching in the mammary gland, neuronal patterning, angiogenesis, vascular remodeling, and in kidney and endocrine development.^{180,193,194} Analysis of embryonic tissue for yolk sac–derived and hematopoietically derived macrophage populations has shown that the lungs basally contain macrophages of both yolk sac and hematopoietic stem cell origin.¹⁸¹ However, a more detailed analysis of the precise location of these subpopulations (e.g., airway or interstitium), their unique cell surface marker profiles, and how they interact with other pulmonary cells during development has yet to be conducted. Macrophages may contribute to lung development through the clearance of cellular debris associated with tissue remodeling¹⁹⁵ and through the production of growth factors that influence the airway epithelium.^{190,196} Recently, colony-stimulating factor 1 receptor–positive macrophages with a “remodeling” phenotype have been shown to be located near branch points in the lung during branching morphogenesis,¹⁹⁷ though the origin and location of these cells within the adult lung remains unknown.

In addition to macrophages, DCs play a fundamental role in lung innate immunity. Steinman¹⁹⁸ published the first report on a population of antigen-presenting cells in mouse spleen and, based on their morphologic characteristics, coined the name *dendritic cells* (DCs). This work was recognized in 2012 with the posthumous award of the Nobel Prize in Physiology or Medicine. Since the late 1980s a vast array of monoclonal antibodies against monocytes, macrophages, and DC cell surface antigens, together with lineage-tracing mice, have been developed and used to classify monocytes/macrophages and DCs.¹⁹⁹ The issue of using cell surface markers to separate macrophages and DCs is particularly relevant in the lung, where CD11c is expressed at high levels on resident alveolar macrophages, and DCs (as reviewed by Hume²⁰⁰). In addition, much of our initial understanding of the functions of resident lung mononuclear phagocytes has come from studies conducted without the use of extensive cell surface marker panels or lineage-tracing technologies. Thus, although it is clear that the cells described in many studies are mononuclear phagocytes, it is sometimes difficult to classify them further without the use of multiple antibody markers combinations.²⁰¹ As illustrated in [Figure 12-5B](#), pulmonary mononuclear phagocytes can be broadly thought of as three overlapping subpopulations: (1) resident macrophages of the alveolar surfaces and interstitium, (2) monocytes that marginate in the lung microvasculature and can be recruited into the air spaces in response to innate activation, and (3) resident and recruited DCs of the airways and lung parenchyma. In this section, we discuss the localization and innate immune functions of each group of cells.

Resident Macrophages

Resident alveolar macrophages reside in the mixed environment of epithelial lining fluid and ambient inhaled air, whereas resident interstitial macrophages are located within the interstitial tissue or alveolar septa. Morphometric analyses indicate that the number of interstitial macrophages in normal lung is between one tenth and one half of the total number of alveolar macrophages.²⁰²⁻²⁰⁴ Unlike resident alveolar macrophages that can be obtained by bronchoalveolar lavage, interstitial macrophages can be

obtained only by using tissue dispersion techniques. Consequently, considerably less is known about the biology and function of interstitial macrophages than about resident alveolar macrophages, especially in humans. In addition, interpreting current and past studies can be difficult because artifacts in cell phenotype and function can be introduced as a consequence of the tissue dispersion approach or by in vitro exposure to trace amounts of contaminating PAMPs during isolation. Despite these caveats, interstitial macrophages are thought to share many functional similarities with resident alveolar macrophages.

Functions of Resident and Interstitial Alveolar Macrophages

The primary functions of resident alveolar macrophages are (1) to dispose of inhaled microbes and particulates, (2) to clear pulmonary surfactant, and (3) to suppress the development of inappropriate inflammatory and immune responses. Resident alveolar macrophages are capable of phagocytosing a wide spectrum of harmless and harmful microbes and other particulates. Under basal conditions, most ingested phagocytosed particulates are enclosed within phagosomes, which ultimately fuse with lysosomes, leading to their degradation by an array of acid-pH optimum hydrolytic enzymes. Some inhaled microbes (e.g., *M. tuberculosis*) and some environmental particulates (e.g., crystalline silica) are resistant to this process and become sequestered in secondary lysosomes where they remain for the life span of the macrophage. Most of these latter cells probably crawl into the airways and are cleared via the mucociliary escalator.^{205,206} Some particle-laden macrophages may remain in the lung for extended periods of time before either dying and releasing their particle burden, thereby rendering it available for phagocytosis by other macrophages, or undergoing apoptosis and being cleared by other phagocytes.

Resident alveolar macrophages also actively contribute to the normal homeostasis of pulmonary surfactant. This point is most clearly emphasized in patients with pulmonary alveolar proteinosis, a disorder characterized by the accumulation of proteinaceous and lipid-rich surfactant in the alveoli, leading to impaired gas exchange. A fundamental characteristic of the disorder is the finding that alveolar macrophage numbers are reduced, and those that are present are inefficient in clearing pulmonary surfactant.^{207,208} Several studies have shown that pulmonary alveolar proteinosis is associated with the development of autoantibodies against GM-CSF,²⁰⁷⁻²⁰⁹ emphasizing the importance of GM-CSF in the activities of resident alveolar macrophages. Additional information about alveolar proteinosis can be found in Chapter 70.

Lastly, resident alveolar macrophages play a critically important role in tonic suppression of alveolar inflammation and adaptive immunity. Based in part on studies by Maclean and associates,²¹⁰ the concept has evolved that the lung can deal with inhaled microbes and particulates until a certain threshold burden is reached. The threshold is in part determined by the phagocytic capacity of alveolar macrophages. Once the threshold is exceeded, microbes and other particulates are phagocytosed by resident DCs that “snorkel” through tight junctions of the alveolar epithelium to sample the alveolar compartment. Consistent with this concept, studies have shown that depletion of alveolar

macrophages with liposome-encapsulated clodronate augments antigen presentation by pulmonary DCs, which in turn augments adaptive immune responses to intratracheal antigens.^{211,212} Other studies have shown that resident alveolar macrophages suppress the functions of natural killer cells and plasma cells.^{85,213}

The ability of resident alveolar macrophages to suppress inflammation and T-cell responses is specific to these cells and is not a characteristic of macrophages obtained from other locations or peripheral blood.^{214,215} These findings suggest that the alveolar microenvironment may play an important role in the development of suppressive activity by resident alveolar macrophages. As noted earlier, the pulmonary collectins SP-A and SP-D inhibit PAMP-dependent production of proinflammatory cytokines through their interaction with signal-inhibitory regulatory protein α .¹⁹ In addition, TGF- β , produced by alveolar macrophages and activated at the surface of alveolar epithelial cells by the integrin $\alpha\beta$ 6, has been shown to basally suppress alveolar inflammation.^{216,217} Other studies have emphasized the importance of IL-10, prostaglandin E₂, and nitric oxide in the tonic suppression of alveolar inflammation and adaptive immunity.^{218,219} Together these studies suggest that resident alveolar macrophages have several mechanisms that actively suppress alveolar inflammation and the antigen-presenting activity of interstitial DCs, while remaining poised to reverse this response upon appropriate stimulation.

The tonic suppressive activity of alveolar macrophages can be reversed in two different ways. One mechanism involves exceeding the threshold phagocytic capacity of resident alveolar macrophages, thereby allowing microbes to interact with other lung cells, for example, pulmonary DCs or epithelial cells, which respond to PAMPs and other molecules by producing proinflammatory cytokines. Indeed, GM-CSF and TNF- α have been shown to reverse tonic suppression of adaptive immunity in vivo.²²⁰ A second mechanism involves alveolar macrophages themselves. Here, PAMP recognition by the globular head groups of SP-A and SP-D enables lung collectins to interact with macrophages via calreticulin and CD91.¹⁹ In contrast to the suppressive signal initiated when SP-A and SP-D interact with macrophages via signal-inhibitory regulatory protein α in the absence of PAMPs, CD91 signaling leads to the production of proinflammatory cytokines, which then augment inflammation and the recruitment of PMNs and monocytes. Thus resident alveolar macrophages are capable of suppressing inappropriate alveolar inflammation and adaptive immune responses to commonly encountered antigens. However, mechanisms exist to overcome this suppression to allow the recruitment of inflammatory cells, especially PMNs and monocytes, and to promote adaptive immunity.

Recruitment of Mononuclear Phagocytes

After birth and postnatal bone formation, liver hematopoiesis declines and is replaced by bone marrow hematopoiesis, which then becomes the exclusive source of circulating monocytes. Circulating monocytes have the potential to differentiate into macrophages or DCs,²²¹⁻²²⁶ and until recently it was thought that circulating monocytes contribute to the replenishment of resident lung macrophages.²²⁷⁻²²⁹ However, recent incisive studies have clarified the extent

and circumstances under which monocytes replenish resident macrophage and DC populations. In 1989 Passlick and associates reported heterogeneity among human macrophages based on the differential expression of CD14 and CD16.²³⁰ “Classic” CD14^{hi}CD16⁻ monocytes make up approximately 95% of circulating monocytes in the steady state, and “nonclassic” CD14^{lo}CD16⁺ monocytes constitute the remaining 5%.^{231,232} Similar to human monocytes, mouse monocytes have also been classified into classic (Ly6C^{hi}(GR1⁺)CCR2⁺CX₃CR1^{lo}) and nonclassic (Ly6C^{lo}(GR1^{lo})CCR2^{lo}CX₃CR1^{hi}) monocyte subsets.^{185a,225,233,234} During steady-state conditions Ly6C^{lo} monocytes circulate through tissues and patrol the lung microvasculature (see Fig. 12-5A). This subset also expresses high levels of fractalkine receptor (CX₃CR1), which interacts with fractalkine (CX₃CR1L) expressed on the luminal face of vascular endothelial cells and promotes heterotypic adherence.^{233,235} The Ly6C^{hi} monocyte population transmigrates into tissue under inflammatory and injury conditions in a CCR2-CCL2 (macrophage chemotactic protein 1)-dependent manner and differentiates into inflammatory macrophages and dendritic cells (see Fig. 12-5A).^{184,226,233,236} Ly6C^{hi} monocytes have also been recognized to be a short-lived obligatory precursor intermediate for Ly6C^{lo} monocytes under steady-state conditions.¹⁸⁴ Jakubzick and colleagues²³⁷ recently provided additional insights by showing that, under steady-state conditions, circulating Ly6C^{hi} monocytes can also constitutively traffic into the lung and lymph nodes without differentiating into resident macrophages or dendritic cells. Rather, these Ly6C^{hi} monocytes acquire antigen and traffic to regional lymph nodes (see Fig. 12-5A).²³⁷ Additional information about the mechanisms of monocyte, macrophage, and dendritic cell migration can be found in Bromley and associates²³⁸ and Springer and colleagues.²³⁹

Functions of Recruited Monocytes and Macrophages.

In contrast to resident alveolar macrophages, recruited monocytes and macrophages have important proinflammatory and host-defense activities including (1) microbial killing and (2) amplification of inflammation. Monocytes and macrophages kill microbes with reactive oxygen species and reactive nitrogen species. *Superoxide anion* (O₂⁻) is mainly produced by the phagocyte NADPH oxidase.²⁴⁰ Like PMNs, monocytes subsequently convert O₂⁻ into additional reactive oxygen species in a myeloperoxidase-dependent fashion,²⁴¹ but as they differentiate into macrophages, intracellular myeloperoxidase content declines and additional reactive oxygen species (e.g., hydroxyl radical [OH⁻]) are formed by the Fenton reaction.²⁴²

The generation of reactive oxygen species is critical to host defense against commonly encountered and pathogenic bacteria. Patients with chronic granulomatous disease and mice bearing a targeted disruption of the p47^{phox} component of the NADPH oxidase^{243,244} are deficient in their ability to control pulmonary and other infections.²⁴³⁻²⁴⁶ However, inappropriate production of reactive oxygen species by macrophages (and other inflammatory cells) can result in epithelial injury that can lead to fibroproliferation, as can be seen with survivors of acute respiratory distress syndrome and patients with idiopathic pulmonary fibrosis, asbestosis, or silicosis.²⁴⁷⁻²⁵⁰ Thus, whereas reactive oxygen

species play a vital role in the protection of the lung against microbes, inappropriate production in response to nonmicrobial particulates and pollutants, including cigarette smoke,²⁵⁰ can result in a spectrum of injury to the airway and alveolar epithelium. Nitric oxide (NO) produced by inducible nitric oxide synthase (iNOS or NOS2) also contributes to macrophage-mediated microbial killing and epithelial injury following condensation with O₂[•] to form peroxynitrite.^{251,252} Whereas the importance of NO in microbial killing of *L. monocytogenes* and *M. tuberculosis* has been clearly demonstrated in mice,²⁵³ the role of NO in host defense in humans is less clear.

Recruited monocytes and macrophages also amplify inflammation through the production of cytokines, chemokines, and lipid mediators. Studies conducted in the late 1970s indicated that macrophages hydrolyze arachidonyl-containing phospholipids in response to exposure to a variety of TLR agonists through the actions of cellular and secreted phospholipase A₂ enzymes.^{254,255} The hydrolysis of arachidonyl-containing phospholipids by phospholipase A₂ enzymes results in the formation of (1) lysophosphatidylcholine, which, upon acetylation, leads to the production of platelet-activating factor²⁵⁶ and (2) arachidonic acid, which serves as a substrate for the production of all eicosanoids (as reviewed by Riches and coworkers).²⁵⁷

Platelet-activating factor is produced within minutes of exposure of macrophages to TLR agonists and has broad proinflammatory activities that promote PMN recruitment, bronchoconstriction, and vasodilation. Platelet-activating factor also primes PMNs, monocytes, and macrophages for enhanced production of proinflammatory cytokines in response to PAMPs.^{258,259} Arachidonic acid is oxidized to prostaglandin E₂, prostaglandin D₂, prostaglandin I₂, and thromboxane A₂ by cyclooxygenase-1 and cyclooxygenase-2, and these prostaglandins have important roles in the regulation of vascular tone and in the feedback inhibition of macrophage effector functions.²⁶⁰ The principal leukotriene produced by macrophages is leukotriene B₄, which is synthesized following TLR engagement and represents the major immediate PMN chemotactic factor produced in the lung before chemokine expression.^{138,261}

Whereas the production of lipid mediators contributes to aspects of early lung inflammation, the production of cytokines and chemokines by macrophages and epithelial cells is necessary for the optimal recruitment of inflammatory cells and for their activation. As discussed earlier, the human chemokine family consists of four closely related subfamilies that have been classified on the basis of the presence and pattern of conserved cysteine residues and have been designated C, CC, CXC, and CXXC families (as reviewed by Kunkel and coworkers²⁶² and Keane and Strieter²⁶³). The CXC and CC families are critical to the development of pulmonary inflammation. Members of the CXC family containing the Glu-Leu-Arg motif stimulate PMN chemotaxis, whereas family members that lack the Glu-Leu-Arg motif (e.g., CXC chemokine ligand 10) are produced in response to IFN- γ and help regulate angiogenic responses.^{264,265} In contrast, CC family members are involved primarily in the recruitment and activation of mononuclear cells. Macrophages are capable of producing CXC chemokines, especially IL-8, in the settings of acute and chronic lung inflammation in patients with bacterial

pneumonia, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, bronchiolitis obliterans with organizing pneumonia, and cystic fibrosis.²⁶⁶⁻²⁶⁹ In addition, CC chemokines, such as macrophage inflammatory protein 1 α , are produced by macrophages in interstitial lung diseases.^{270,271}

Recruited monocytes that develop into macrophages are also capable of further differentiation. Based on earlier work in which different PAMPs were found to induce distinct patterns of macrophage gene expression,^{29,272-274} the concept evolved that different patterns of gene expression could be induced in response to the conditions or stimuli that prevail at the sites to which macrophages have been recruited.²⁷⁵⁻²⁷⁷ For example, exposure of macrophages to Th1 cytokines and TLR ligands (e.g., LPS and polyribonucleic:polyribocytidylic acid) results in increased expression of nitric oxide synthase 2 (NOS2), TNF- α , IL-12, IL-23, and IL-1- β , whereas IL-10 and arginase I expression are repressed. This response generally leads to a “classically activated macrophage” (Fig. 12-6A).^{29,272-274,276,278} In contrast, exposure to Th2 cytokines, including IL-4 and IL-13, leads to a different pattern of gene expression characterized by increased expression of arginase I, FIZZ (found in inflammatory zone), and CC chemokine ligand 19 together with reduced expression of NOS2 in an overall response that leads to an “alternatively activated macrophage” (see Fig. 12-6A).²⁷⁶⁻²⁷⁹ The spectrum of cytokines identified as being capable of inducing alternative macrophage programming is growing and now includes IL-33, IL-21, IL-10, colony-stimulation factors, CXC chemokine ligand 2, CXCL4, glucocorticoids, and TGF- β .²⁸⁰ In addition, a so-called restorative macrophage programming state that is distinct from classically and alternatively programmed macrophages has recently been identified in self-resolving liver fibrosis (see Fig. 12-6A).²⁸¹

Defining these responses as distinct “phenotypes” can be useful in thinking about how macrophages participate in innate immunity and effector cells in the adaptive immune response (see Fig. 12-6A). However, macrophage programming is more complex than some of the simplistic schemes that have been proposed because there are often overlapping patterns of gene expression in response to multiple stimuli.²⁸² Thus it may be more appropriate to think about these adaptive responses as points on a continuum where the response generated is purely an adaptation to the microenvironment that macrophages encounter.^{275,277,283,284} As further evidence of the diversity of macrophage function, differences between gene-expression profiles are also dependent upon genetic background.²⁸⁵ In addition, ligation of distinct receptors and signal transduction pathways leads to differential activation of the transcriptional factors PU.1, STAT1, STAT6, interferon regulatory factors (IRF4, IRF5), PPAR- γ , cyclic 3',5'-adenosine monophosphate (cAMP) responsive element-binding proteins (CREBs), NF κ B, and activator protein-1, which in turn contribute to diversity in macrophage programming (see Fig. 12-6B).²⁸⁶ Macrophage programming is also regulated and enhanced posttranscriptionally by micro-RNAs.²⁸⁷⁻²⁸⁹ Thus diversity in PAMP and stimulus-induced patterns of gene expression by macrophages contributes greatly to their diverse roles in innate protection of the lungs, lung cancer, repair, fibrosis, and microbial elimination.²⁸⁴

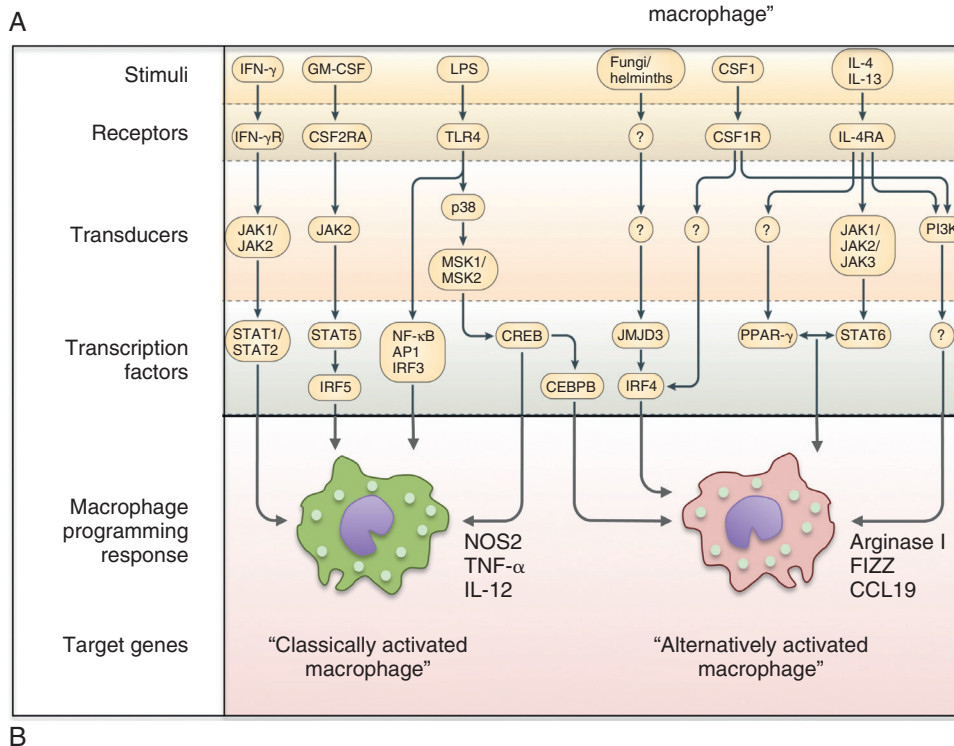
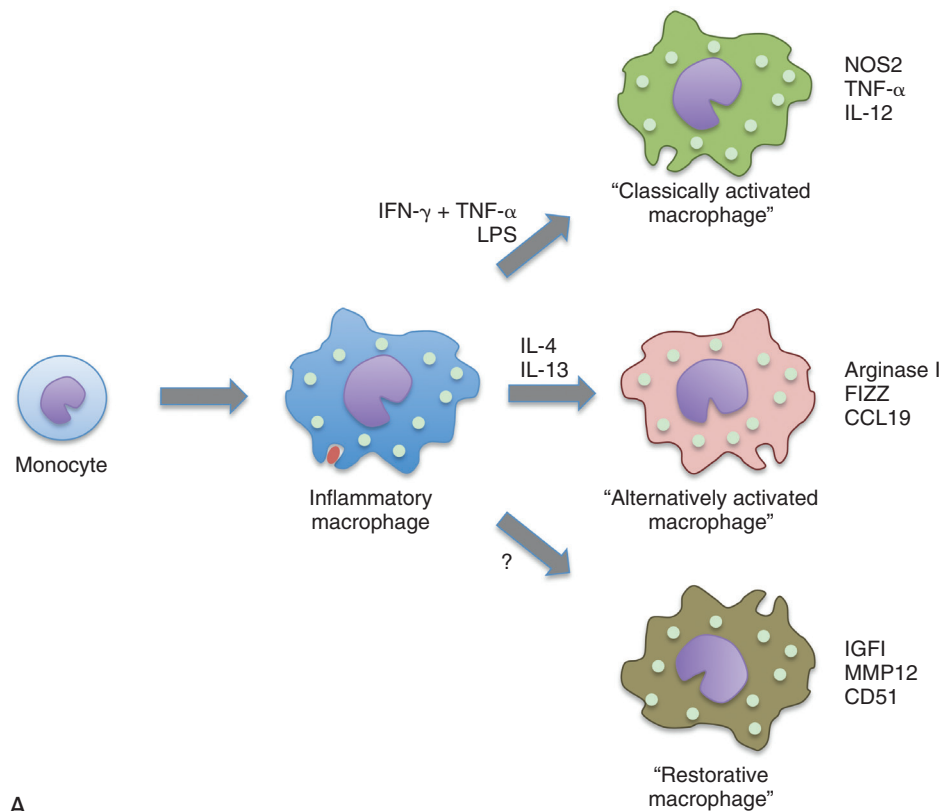


Figure 12-6 Macrophage phenotypes and gene expression. **A**, Macrophages display distinct patterns of gene expression in response to type 1 T helper (Th1) cells and Th2-type cytokines and pathogen-associated molecular patterns (PAMPs). Prototypical states are the “classically activated” and “alternatively activated” macrophages. It is likely that macrophages can exhibit a diverse repertoire of other states, including recently described “restorative” macrophages. **B**, Multiple stimuli, acting through multiple combinations of receptors, signal transduction pathways, and transcription factors, lead to complex patterns of macrophage programming-associated gene expression including the development of classically-activated macrophages and alternatively-activated macrophages. AP1, activator protein-1; CCL19, CC chemokine ligand 19; CEBPB, CCAAT/enhancer-binding protein- β ; CREB, cAMP responsive element-binding protein; CSF, colony-stimulating factor; CSF2RA, CSF 2 receptor α ; FIZZ, found in inflammatory zone protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon- γ ; IFN- γ R, interferon- γ receptor; IGF1, insulin-like growth factor-1; IL, interleukin; IL-4RA, interleukin 4 receptor- α ; IRF, interferon regulatory factor; JAK, Janus kinase; JMJD, histone H3 Lys 27 demethylase; LPS, lipopolysaccharide; MMP12, matrix metalloproteinase-12; MSK, mitogen- and stress-activated kinase; NF- κ B, nuclear factor- κ B; NOS2, nitric oxide synthase 2; PI3K, phosphatidylinositol-3-kinase; PPAR- γ , peroxisome proliferator-activated receptor- γ ; STAT, signal transducer and activator of transcription; TLR4, Toll-like receptor 4; TNF- α , tumor necrosis factor- α . (B, Adapted and redrawn from Lawrence T, Natoli G: Transcriptional regulation of macrophage polarization: enabling diversity with identity. *Nat Rev Immunol* 11:750–761, 2011.)



Figure 12-7 Airway dendritic cells exist as an interdigitating network within the epithelium and below the basement membrane. The section was stained for major histocompatibility complex class II. (From Vermaelen K, Pauwels R: Pulmonary dendritic cells. *Am J Respir Crit Care Med* 172:530–551, 2005.)

In summary, macrophages play key roles in the maintenance of lung homeostasis through their abilities to suppress unwanted inflammation and immune responses to harmless, commonly encountered inhaled materials. However, they remain constantly poised to respond to harmful inhaled microbes and other substances. Part of this response involves calling in additional support through the recruitment of circulating blood PMNs and monocytes. In turn, recruited monocytes can differentiate into macrophages, which can then express appropriate responses to microenvironmental cues that they sense at the site to which they have been attracted.

Dendritic Cells

DCs represent an important group of phagocytic and antigen-presenting cells that act as a bridge between the innate and the adaptive immune systems. In the lung, DCs have been shown to form an extensive intraepithelial and subepithelial network throughout the respiratory tract (Fig. 12-7). DCs are particularly abundant in the nose, trachea, large airways, and alveolar septae.²⁹⁰⁻²⁹⁸ These cells continuously sample the airway and alveolar lumen by extending and retracting bulbous dendritic projections through the epithelium into the airway and alveolar lumen.^{299,300} After encountering antigens and particulate matter in the airway, DCs then leave the epithelium and traffic into regional lymph nodes, where they deliver stimulatory or tolerogenic signals to naive T cells.^{301,302} DCs traffic constitutively in the steady state, and, as such, lung DCs can be considered transient residents that are continuously replenished by bone marrow–derived precursors in the blood.^{294,303,304}

Newly recruited resident DCs have an immature phenotype characterized by the expression of high levels of MHC class II and low levels of co-stimulatory molecules. These cells serve as the body's primary professional antigen-presenting cells that activate and initiate the clonal expansion of antigen-specific T cells. DCs continually endocytose soluble and particulate materials that enter the respiratory tract. If these materials contain PAMPs, DCs will undergo a maturation program associated with the up-regulation of co-stimulatory molecules (such as CD40, CD80, and CD86), activate the expression of genes for cytokines and growth

factors that promote naive T cell activation, and traffic to the regional lymph node (Fig. 12-8). In the absence of PAMPs, DCs encounter and present self-antigen through their ability to phagocytose apoptotic cells. These DCs do not fully mature but still traffic to lymph nodes, where they express tolerogenic receptors (MHC-peptide antigen complexes) and soluble mediators (IL-10, ICOSL, PDL1) to T-cell receptors on naive T cells generating Treg cells that prevent the development of an immune response against harmless antigen (see Fig. 12-8A). This is also seen following sterile injury. In contrast, when they ingest materials in the presence of PAMPs (from bacteria and viruses), DCs activate a program of maturation associated with the down-regulation of endocytic and phagocytic activities, the up-regulation of antigen-processing machinery, the up-regulation of co-stimulatory molecules, especially CD40, CD80, and CD86,^{295,302,305} and the activation of genes encoding cytokines and growth factors that promote downstream naive T-cell activation and maturation into Th1-effector cells,^{306,307} which recirculate to the original site of PAMP activation to augment the development of adaptive immunity (see Fig. 12-8B). When they encounter allergens, DCs elicit an expansion of Th2-effector cells that produces cytokines, including IL-4, IL-5, and IL-13, resulting in the production of *immunoglobulin E* (IgE) (see Fig. 12-8C). With this general overview of DC function as a background, we now discuss in more detail the function and control of the multiple DC subsets represented in the lung. We focus largely on mouse lung DC subsets, because most of the current knowledge has been developed in this species.

Mouse and Human Lung Dendritic Cell Subsets.

Studies using cell surface markers, particularly CD11c and CD8 α , initially suggested that DCs arose from both myeloid and lymphoid precursors that were thought to give rise to a bewildering array of DC subsets.³⁰⁸ Recent studies in mice, however, suggest that DCs can be grouped into three major subsets, namely *plasmacytoid* DCs (pDCs), *conventional* DCs (cDCs), and *inflammatory* DCs (iDCs) (Fig. 12-9).

pDCs are characterized by the presence of TLRs 7 and 9 and expression of the cell surface marker Siglec-H. They also secrete abundant quantities of type I IFNs in response to TLR ligation by PAMPs. Many TLR7 and TLR9 agonists are viral products, and their ability to stimulate type I IFN secretion by DCs is an important component in the early antiviral response. Typically pDCs are present in low numbers in lung tissues in the steady state but are rapidly recruited into the lung when viral PAMPs are detected. Like other DCs, pDCs can also process antigens, traffic to regional lymph nodes, and participate in antigen presentation to naive T cells. In addition, pDCs can also restrain the activity of conventional DCs, thereby controlling both inflammation and the induction of adaptive immunity.

cDCs are the archetypal antigen-presenting DC and can be subdivided into lymphoid *tissue resident* DCs and *migratory* DCs. As their name implies, lymphoid tissue resident DCs reside in spleen and lymph nodes and respond to antigens delivered by draining afferent lymphatic vessels. Migratory DCs also have classic antigen-presenting functions but transiently reside in the airway epithelium and alveolar septae before migrating to regional draining lymph nodes via afferent lymphatics. Migratory DCs extend their

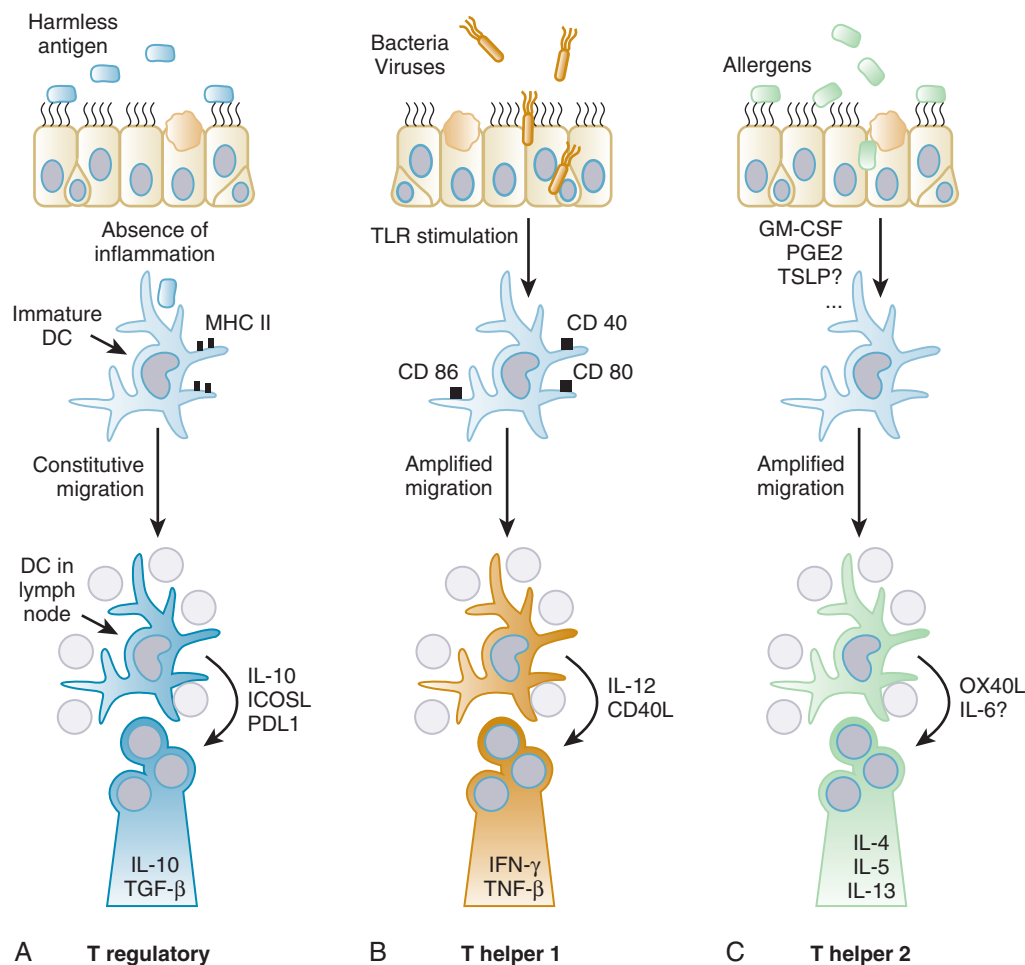


Figure 12-8 Resident lung dendritic cells are capable of inducing the activation of various CD4⁺ T cells. **A**, CD4⁺ T regulatory cells after exposure to harmless antigens. **B**, Type 1 T helper cells CD4⁺ after exposure to PAMPs from bacteria and viruses. **C**, Th2 CD4⁺ T cells after exposure to allergens. DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICOSL, inducible T-cell co-stimulator ligand; IFN- γ , interferon- γ ; IL, interleukin; MHC, major histocompatibility complex; OX40L, OX40 ligand; PDL1, programmed death-ligand 1; PGE₂, prostaglandin E₂; TGF- β , transforming growth factor- β ; TLR, Toll-like receptors; TNF- β , tumor necrosis factor- β ; TSLP, thymic stromal lymphopoietin. (Redrawn from Vermaelen K, Pauwels R: Pulmonary dendritic cells. *Am J Respir Crit Care Med* 172:530–551, 2005.)

dendritic processes through the airway and alveolar epithelial tight junctions to capture, process, and present inhaled antigens in association with MHC class II molecules. Upon migration to lymph nodes, migratory DCs present MHC-peptide antigen complexes and co-stimulatory molecules to naive T cells.

Inflammatory DCs, in contrast to migratory DCs and pDCs, are absent from lymphoid and peripheral tissues under steady-state conditions. However, in response to local activation of innate immunity, Ly6C^{hi} peripheral blood monocytes home to sites of inflammation and/or infection and differentiate into inflammatory DCs in response to specific cytokines, especially GM-CSF and Flt3 ligand.^{224,230} The functions of inflammatory DCs are similar to those of migratory DCs.

It is now recognized that all DCs and monocytes arise from a single myeloid progenitor cell called the “macrophage and DC precursor.”³⁰⁹ The macrophage and DC precursor differentiates to yield common DC precursor cells and monocytes. The common DC precursor cells can further differentiate into pre-conventional DCs and pDCs, whereas monocytes can give rise to inflammatory DCs or retain their

monocytic-like character in tissues under steady-state conditions.²³⁷ In view of these findings, it has been suggested that the earlier classification of DCs into lymphoid DCs and myeloid DCs be abandoned.³¹⁰

Based on cell surface marker expression, mouse lung contains two major subsets of conventional DCs. All mouse lung DCs express high levels of MHC class II proteins and CD11c, but the two subsets can be differentiated by the presence or absence of CD103 (see Fig. 12-9). They can be further subdivided by the presence or absence of CD11b and/or langerin (see Fig. 12-9). Langerin⁺ DCs, which resemble the langerin⁺ DC cells of the skin, exist together with langerin[−] subsets within the epithelium of the trachea and large airways.^{295,311} The langerin⁺ DC subset also expresses CD103 and low levels of CD11b, whereas the langerin[−] DC subset is CD11b^{hi}CD103[−].³⁰² Additional DC subsets are found within the submucosa of the trachea and large airways. These cells are typically CD103[−]CD11b^{hi}CD11c^{hi} and are efficient antigen-presenting cells. Though less well characterized, DCs of the murine lung parenchyma are generally characterized as being CD11c^{hi}CD11b^{lo}CD103[−]CD205⁺. In addition, information on human DC subsets

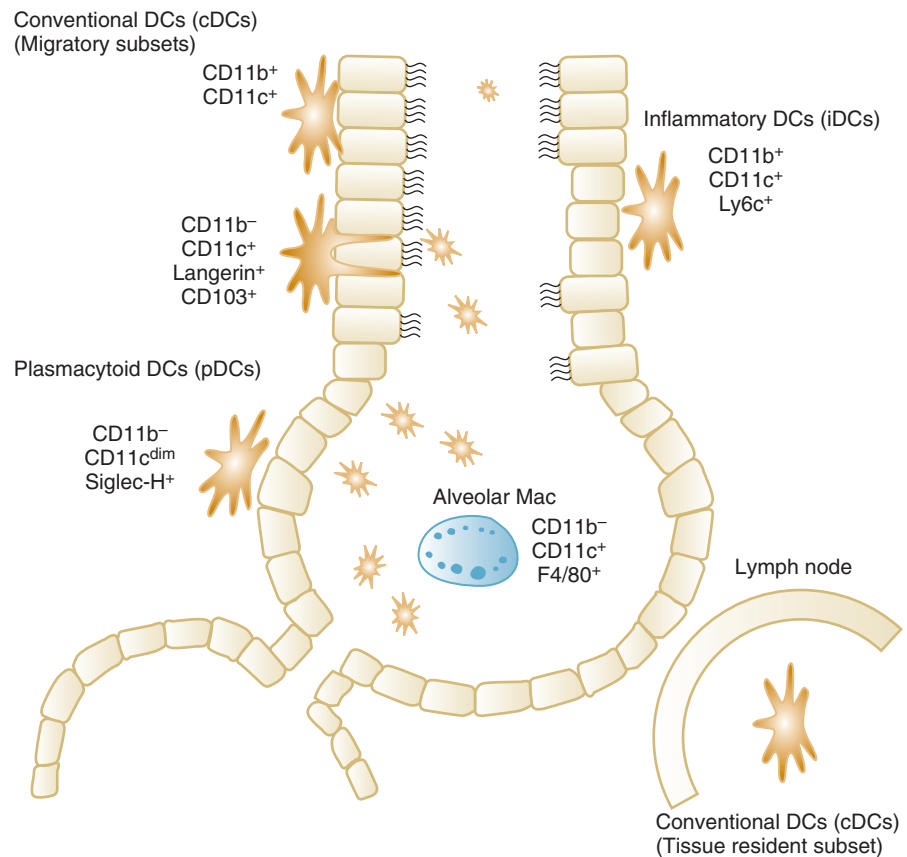


Figure 12-9 Three major subsets of dendritic cells (DCs) exist in mouse lung: conventional DCs (cDCs) (both migratory and lymphoid tissue resident), plasmacytoid DCs (pDCs), and inflammatory DCs. Each subset can be defined by the expression of distinct patterns of cell surface antigens recognized by monoclonal antibodies. Mac, macrophage. (Redrawn from Geurts-vanKessel CH, Lambrecht BN: Division of labor between dendritic cell subsets of the lung. *Mucosal Immunol* 1:442–450, 2008.)

is limited, and it is unclear to what extent the marker profiles of mouse DC subsets can be translated to humans. Several excellent reviews on mouse lung DC subsets are available.^{312,313}

Studies of human lung DC subsets are limited by difficulties in the availability of tissue samples and, as is the case for interstitial macrophages, the possibility that methods for isolating DCs from lung tissue samples may activate and/or alter DC surface marker expression, thereby introducing artifacts to the analysis. Human lung DCs are distinguished from resident alveolar macrophages by their expression of MHC class II, especially human leukocyte antigen-DR4. In addition, human resident alveolar macrophages are highly autofluorescent, whereas lung DCs exhibit low autofluorescence.³¹⁴ Human lung DCs can be distinguished from other myeloid and lymphoid cells by the absence of T-cell, B-cell, natural killer cell, monocyte, and granulocyte lineage markers. MHC class II⁺ DCs are found in normal human airway epithelium, lung parenchyma, and visceral pleura,²⁹¹ and a langerin⁺ DC subset is present in bronchioles.³¹⁵ As in the mouse, large numbers of DCs are present in alveolar septae.^{290,293} Five subsets of pulmonary cDCs have been found in human lungs. Demedts and colleagues³¹⁶ identified three DC subsets in normal human lung specimens. These include a CD1a⁺MHCII⁺BDCA-1 (blood dendritic cell antigen-1) cDC subset, another cDC subset that expresses BDCA3⁺ and CD11c⁺, and a pDC subset that expresses BDCA2⁺ and CD123⁺.³¹⁷ A fourth langerin⁺ cDC subset is associated with airway mucosal epithelium. A fifth CD103⁺Langerin⁺CD11b^{lo} subset that expresses tight junction pro-

teins, claudin 1, claudin 7, and zona occludens-2 resides beneath the basal lamina of both human and mouse mucosal epithelium.³¹⁶⁻³¹⁹

Inflammatory DCs arise by recruitment of blood monocytes and differentiation in response to activation of innate immune mechanisms. Inflammatory cDCs initially retain monocyte markers and are characterized as CD11c^{hi}CD11b^{hi}Ly6C^{hi}. Based on their ability to produce TNF- α and NOS2, these cells have also been called Tip-DCs.³²⁰

Functions of Lung Dendritic Cells. Lung DCs have the remarkable ability to change their phenotype upon exposure to PAMPs and other “danger” signals.^{321,322} The maturation of immature lung DCs results in functional changes that “polarize” the DC subset. The term *polarization* is used here to indicate that the antigen-exposed DC subset acquires the ability to skew naive T cells to become Th1 or Th2 (or possibly even Th17 or Treg cells).^{198,323-325} The ability to leave the epithelial barrier and migrate to regional lymph nodes is mediated in part by the expression of matrix metalloproteinase-9; in fact, matrix metalloproteinase-9-deficient mice fail to develop allergic airway inflammation.³²⁶ When immature DCs are activated by chemokines, they also down-regulate inflammatory chemokine pathways and traffic into draining lymph nodes by up-regulating CCR7. The CCR7 ligands, CC chemokine ligand 19 and CC chemokine ligand 21, are expressed on peripheral lymphatic endothelium and lymph node stromal cells. This mechanism serves to guide DCs from nonlymphoid into

lymphoid tissues. The use of chemokines, chemoattractant receptors, selectins, and their ligands tightly regulates the migration of pDC and cDC subsets to, from, and within lung tissue. These various interactions have been reviewed by Springer²³⁹ and Bromley and associates.²³⁸

Within draining regional lymph nodes, mature DCs that arrive from the lung are capable of delivering pathogen-specific signals to naive T cells. The further differentiation of these activated T cells into functional T-cell subsets is driven by specific patterns of DC- and T cell–derived cytokines that induce a fully mature T-cell response. These patterns of cytokines then sustain T-cell activation and downstream T-cell skewing.³²¹ For example, IL-12, IL-13, and IL-27, type I IFNs, and ICAM engagement drives the polarization of naive T cells into the Th1 phenotype. In contrast, CCL2 and OX40 ligand promote Th2 phenotype polarization, whereas IL-10, retinoic acid, and TGF- β promote Treg development. The patterns of T-cell cytokine production that develop after exposure to a pathogen are relatively specific to that pathogen and determine in large part the resultant DC subset–driven T-cell response. This mixture of signaling molecules includes proinflammatory and anti-inflammatory cytokines, reactive oxygen species, chemokines, eicosanoids, heat shock proteins, extracellular matrix proteins, and endogenous molecules such as histamine and prostaglandin E₂ that polarize the T-cell phenotype. However, T-cell polarization is not fixed and can change based on alterations in these signaling patterns, which can arise during the maturation of the host response to a pathogen. Nevertheless, in general, the concept that antigens plus PAMPs polarize lung DCs toward antigen-specific T-cell immunity, whereas antigens alone polarize lung DCs toward antigen tolerance³²⁷ appears to be correct. A major benefit of the ability of lung DCs to recognize and clear material present in inhaled air is to maintain efficient oxygen exchange in the lung.

In this way the majority of harmless antigenic materials that are encountered while breathing are eliminated and fail to trigger lung inflammation, ensuring that the lung does not mount an inflammatory or immune response that could result in lung damage.³²⁸ However, harmful PAMP-expressing materials will be recognized and promote inflammation and initiate antigen-specific adaptive immunity.

SYSTEM INTEGRATION

The innate and adaptive immune systems have evolved to protect the lungs from harm by environmentally acquired microbes and other inhaled substances, as well as from host-derived harmful stressors such as unwanted inflammation and inappropriate activation of adaptive immunity. A core concept is that innate immune protection in the lungs is not a consequence of individualized responses of individual cells but, rather, represents coordinated responses and collective cooperation between many resident and recruited lung cell types. These coordinated events result in homeostasis of the airways and gas-exchange units, tolerance to harmless inhaled substances and self-antigens, and vigilance to respond to harmful microbes and substances. In addition, innate immune mechanisms assist in the rapid resolution of injury and restoration of lung function.

From the nose to the alveolus, the respiratory epithelium, interdigitating DCs, and resident and recruited macrophages have evolved exquisite, diverse, and overlapping mechanisms to distinguish between the harmful and harmless. In its simplest form, this distinction is achieved by sensing the presence of microbial PAMPs. In the absence of PAMPs, the epithelium remains largely ignorant of inhaled particulates, whereas “snorkeling” DCs continuously sample the airways and alveoli for particles, antigens, and apoptotic cells to phagocytose and to present antigen to lymph node resident naive CD4⁺ and CD8⁺ T cells, thereby maintaining tolerance to harmless commonly encountered antigens and self-antigens. Similarly, resident macrophages phagocytose and dispose of particulates that reach the alveoli, while tonically maintaining an anti-inflammatory and immunosuppressive environment through the production of anti-inflammatory cytokines, especially TGF- β and IL-10, and eicosanoids such as prostaglandin E₂.

Integration of innate functions is dependent on cell-cell communication. In some settings, communication is fostered by proximity: DCs exist as a network within airway epithelium and contact each other through tight junctions, whereas resident alveolar macrophages use integrins to communicate with alveolar epithelial cells. In other settings, cell-cell communication is mediated through the secretion of a vast array of cytokines and lipid mediators, which can act in autocrine or paracrine fashions. Thus different cell lineages can communicate with each other and among themselves. Communication between different cell types also plays an important role in the coordination of innate immunity and in the activation of adaptive immunity. For example, depletion of resident alveolar macrophages reduces tolerance to inhaled antigens and induces alveolitis and lung injury,^{77,212} emphasizing the importance of resident alveolar macrophages for suppressing inflammation. Integration of innate immunity in the lung is also associated with “coordinated burden sharing.” For example, airway goblet cells and submucosal glands produce mucus, whereas ciliated epithelial cells propel mucus and entrapped particulates toward the pharynx. Similar coordinated burden sharing is exhibited by airway epithelial cells, which are poorly phagocytic but are highly capable of sensing PAMPs and calling in PMNs and monocytes, which in turn are highly phagocytic, microbicidal and eliminate an array of microbes. Together these integrated systems have evolved to provide the lungs with maximum protection against harmful microbes while minimizing harmful responses against harmless inhaled substances. The net result is an exquisite system for protecting the delicate and critically important gas-exchanging parenchyma of the lungs from harm.

Key Points

- A primitive host defense system is broadly based on the recognition of repetitive structures on microbes called *pathogen-associated molecular patterns* (PAMPs) by pattern recognition receptors expressed on lung cells.
- Airway epithelium of the trachea and large airways is protected by (1) airway surface liquid, which contains antibacterial proteins, (2) mucus, which traps large

inhaled particulates and transports them to the pharynx by mucociliary transport, and (3) immune cells, which produce chemokines, cytokines, and lipid mediators in response to PAMPs.

- Alveolar epithelium is protected by surfactant proteins A and D, which serve the dual purpose of (1) opsonizing microbes and (2) suppressing unwanted inflammation and adaptive immune responses to commonly encountered antigens.
- Polymorphonuclear leukocytes (i.e., neutrophils) are recruited to the airways and alveoli when airway and alveolar epithelial cells detect PAMPs. Neutrophils phagocytose and kill microbes by combined oxidative and nonoxidative mechanisms.
- Macrophages are resident phagocytic cells of the alveolar lumen that are involved in the removal of a wide range of microbial and nonmicrobial inhaled particulates. Macrophages also suppress unwanted alveolar inflammation and adaptive immunity in the steady state but can be activated by PAMPs to amplify inflammation.
- Dendritic cells are the primary antigen sensing and presenting cells of the innate immune system. In the absence of PAMPs, immature dendritic cells traffic to regional lymph nodes and promote tolerance to inhaled antigens. In the presence of PAMPs, dendritic

cells mature, express co-stimulatory molecules, and promote T-cell development into Th1, Th2, Th17, or Treg effector cells.

- The cell lineages of innate lung immunity collaborate to promote optimal responses to perceived danger signals (primarily PAMPs) while maintaining tolerance to inhaled antigens in the steady state.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION**COMPONENTS OF THE IMMUNE SYSTEM: OVERVIEW****IMMUNE RECOGNITION**

B Cells and Antibodies

T Cells and Antigen-Presenting Cells

GENERATION OF AN IMMUNE RESPONSE

T-Cell Activation and Co-Stimulation

Subsets of T Helper Cells

CD4⁺ T-Cell–B-Cell Collaboration and Regulation of Antibody Production

Generation and Regulation of Cell-Mediated Immune Responses

SPECIFIC IMMUNE RESPONSES IN THE LUNG

Lymphocyte Populations and Trafficking in the Lung

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Cell-Mediated Inflammatory Responses in the Lung

Cytotoxic T-Cell Reactions in the Lung

INTRODUCTION

The human immune system consists of many different cell types and organs that have evolved to destroy or control potentially harmful foreign substances. The immune response is essential for survival because it constitutes the principal means of defense against infection by pathogenic microorganisms, including those that enter and reside in the respiratory tract. The immune response is also critically involved in pathologic processes of the lung and upper respiratory tract. This chapter provides an understanding of the adaptive (or acquired) immune response, which depends on the specific recognition of antigens by T and B lymphocytes. Immune recognition is highly specific for a particular pathogen, and yet an individual's immune cells can collectively respond to an almost unlimited number of foreign antigens. The molecular mechanisms underlying this specificity and diversity are unique to the immune system. The adaptive immune response also changes after successive encounters with the same pathogen. For example, memory of an antigen allows the immune system to respond faster and in greater magnitude compared with the initial encounter. This chapter also describes how primary and secondary immune responses are regulated by complex cellular interactions and the release of particular types of soluble mediators. Antigen-specific immune responses are also regulated and augmented by nonspecific inflammatory cells of the immune system, such as dendritic cells, macrophages, neutrophils, eosinophils, and mast cells. Defects in the development of adaptive immunity are discussed in Chapter 92 on primary immunodeficiencies.

COMPONENTS OF THE IMMUNE SYSTEM: OVERVIEW

All of the cells of the immune system arise from pluripotent hematopoietic stem cells through two main lines of differentiation that give rise to the lymphoid lineage and the myeloid lineage.¹ Specificity within the immune system is primarily provided by lymphocytes. The two major categories of lymphocytes are T cells,² which are derived from

bone marrow stem cells and primarily develop in the thymus, and B cells, which develop in the bone marrow in adult humans. A third population of lymphocytes is *natural killer* (NK) cells.

Lymphocytes and other cells of the immune system express a large number of different molecules on their surfaces. Some of these markers can be used to separate cells with different functions or to distinguish cells at particular stages of differentiation. Monoclonal antibodies to many different cell surface markers have been produced, and a systematic nomenclature has been developed. The CD ("cluster of differentiation" or "cluster determinant") system provides a basis by which monoclonal antibodies that bind to the same surface molecule are grouped together, and the CD number is used to indicate the specific molecule recognized. Tables 13-1 to 13-3 provide a partial list of surface antigens, particularly those mentioned in this chapter. The markers are partially grouped based on the cell type expressing them. It may be necessary to refer to this list of molecules throughout this chapter.

T cells are distinguished by the presence of the *T-cell receptor* (TCR).³⁻⁵ Most T cells express a receptor composed of an α and a β chain, whereas a much smaller subset expresses a structurally similar receptor composed of a γ and a δ chain. Both receptors are associated with a complex of polypeptides, the CD3 complex, which provides a transmembrane signaling function and allows TCR engagement to be coupled to cellular activation. T cells expressing $\alpha\beta$ TCRs can be divided into CD4⁺ and CD8⁺ T-cell subsets. CD4⁺ T cells primarily recognize antigens presented by *major histocompatibility complex* (MHC) class II molecules. CD8⁺ T cells primarily recognize antigens presented by MHC class I molecules. Functionally, T cells can be divided into several major subsets. For example, T helper cells may interact with B cells and help them to survive and divide, make antibody, and become memory B cells. T helper cells also may interact with cytotoxic T cells or with phagocytic cells and help them destroy intracellular pathogens. Different subsets of T helper cells can be distinguished by the pattern of cytokines that they secrete during an immune response. T helper cells are generally encompassed within the CD4⁺ T cell subset. Another subset of T cells is responsible for destruction of cells that have become infected by virus or

Table 13-1 Selected Cell Surface Markers of Human T Cells

Cell Surface Markers	Identity/Function
TCR	Interacts with peptide/MHC complex on antigen-presenting cells
CD2	Binds to LFA3; involved in co-stimulation and adhesion
CD3	T-cell signaling complex
CD4	T-cell subset with helper function; interacts with MHC class II molecule
CD8	T-cell subset with cytotoxic function; interacts with MHC class I molecule
CD25	α chain of IL-2 receptor; expressed on activated T cells and on a subset of regulatory CD4 ⁺ T cells
CD28	Binds B7-1 (CD80) and B7-2 (CD86); co-stimulatory molecule involved in T-cell activation
CD45	Phosphatase involved in cellular activation and differentiation; different isoforms (CD45RA, CD45RO) mark naive versus previously activated T cells and stages of activation
CD62L	L-selectin; involved in lymphocyte adhesion; levels mark naive versus memory cells
CD69	Activation marker
CD95 (FAS)	FAS; receptor involved in apoptosis
CD95L (FAS ligand)	Ligand for FAS; involved in T-cell-mediated killing
CD152 (CTLA4)	Binds to B7-1 (CD80) and B7-2 (CD86); involved in down-regulation of TCR signaling
CD154 (CD40 ligand)	Ligand for CD40; important for T-cell activation and T-cell-dependent B-cell activation
CD134 (OX40), CD137 (4-1BB), ICOS, PD1	Additional co-stimulatory molecules in the TNF or CD28 family; involved in T-cell activation and regulation

CTLA4, cytotoxic T lymphocyte antigen-4; ICOS, inducible co-stimulator; IL-2, interleukin-2; LFA3, lymphocyte function-associated antigen-3; MHC, major histocompatibility complex; PD1, programmed cell death-1; TCR, T-cell receptor; TNF, tumor necrosis factor.

other intracellular pathogens. These cells are called “cytotoxic T cells” and usually express the CD8 phenotypic marker. Although not clearly distinguished by phenotypic markers, separate subsets of T cells, within both the CD4 and CD8 subsets, have been termed “T regulatory (or suppressor) cells” because they down-regulate immune responses.

B cells are identified by the expression of surface *immunoglobulin* (Ig) or antibody molecules, which represent their specific *B-cell receptor* (BCR) for antigen. Analogous to the CD3 complex on T cells, BCRs are also linked to accessory molecules, Ig- α (CD79a) and Ig- β (CD79b), which are required for cellular activation after antigen interaction.⁶ After differentiation, B cells can develop the ability to produce high levels of antibody (soluble Ig). B cells also express a large number of other surface markers that are critically involved in their function and interaction with T cells. For example, most B cells express MHC class II molecules that allow them to present antigen to T helper cells. Other B-cell surface molecules are listed in [Table 13-2](#).

Table 13-2 Cell Surface Markers of Human B Cells

Cell Surface Markers	Identity/Function
BCR	Immunoglobulin molecules; recognizes antigen
CD5	Binds to CD72; regulation of cell proliferation/activation; identifies B1a cell subset
CD19	B-cell coreceptor subunit; involved in co-stimulation
CD20	B-cell marker
CD21	Complement receptor type II; B-cell coreceptor subunit; marks certain B-cell subsets; EBV receptor
CD22	Adhesion molecule; involved in B-cell activation
CD23	Identifies B-cell subset; low-affinity receptor for IgE
CD40	Binds CD40L; involved in T-cell-dependent B-cell activation
CD79a (Ig- α)	Involved in B-cell activation; signaling through BCR
CD79b (Ig- β)	Involved in B-cell activation; signaling through BCR
CD80 (B7-1)	Binds CD28 and CD152 (CTLA4) on T cells
CD86 (B7-2)	Binds CD28 and CD152 (CTLA4) on T cells

BCR, B-cell receptor; CD40L, CD40 ligand; CTLA4, cytotoxic T lymphocyte antigen-4; EBV, Epstein-Barr virus; Ig, immunoglobulin.

A third population of lymphocytes is probably best defined as those cells that do not express either TCR or Ig and mostly includes NK cells.⁷ A large proportion of this subset contains numerous electron-dense granules and is recognized morphologically as large granular lymphocytes. Markers on these cells are frequently shared with T cells (e.g., CD2 and CD8) or cells of the myelomonocytic series, for example, the integrin molecule CD11b or the low-affinity receptor for IgG (FCGR3 or CD16). NK cells appear to play an important role in the initial (innate) host defense against infection and tumor cells. Similar to certain phagocytes, they also have the capability to destroy target cells or pathogens that have been coated with specific antibody via a process known as antibody-dependent cellular cytotoxicity.

The myeloid lineage consists primarily of monocytes (macrophages) and neutrophils, which provide nonspecific inflammatory mediators and phagocytic function. These cells are critically involved in the nonspecific component of the inflammatory response (see Chapters 12 and 15). In addition, macrophages and certain other nonlymphoid cells, such as dendritic cells, are specialized to present antigens to T cells, thus contributing to specific immune responses.

The cells involved in the immune response are organized into tissues and organs. Primary lymphoid organs are the major sites of lymphopoiesis, in which stem cells and their committed precursor cells differentiate into lymphocytes and acquire specific functions. In humans, T lymphocytes mainly develop in the thymus, and B lymphocytes develop in the fetal liver and adult bone marrow. In the thymus, T-cell differentiation also includes acquiring the ability to recognize foreign antigens in the context of self-MHC molecules and the elimination of self-reactive cells (self-tolerance). B-cell acquisition of self-tolerance during development appears to take place in the bone marrow.

Differentiated lymphocytes migrate to secondary lymphoid organs, which include lymph nodes, spleen, and

Table 13-3 Other Cell Surface Markers of General Interest

Cell Surface Markers	Distribution	Identity/Function
CD1	Thymocytes, subset of lymphocytes, antigen-presenting cells	MHC class I–like molecule; involved in presentation of nonpeptide antigens
CD11a	Leukocytes	α chain of LFA1; associates with CD18; interacts with ICAM1; involved in adhesion and migration
CD11b	NK cells, monocytes, granulocytes	α chain of CR3; adhesion molecule
CD11c	Monocytes, granulocytes	α chain of CR4; adhesion molecule; identifies dendritic cells
CD14	Granulocytes, monocytes	Receptor for LPS/LPB complex; myeloid differentiation antigen; cell activation
CD16	NK cells, monocytes	FCGR3; low-affinity receptor for IgG; involved in ADCC
CD18	Leukocytes	β chain of β_2 integrin molecules, including LFA-1, CR3, and CR4
CD29	Leukocytes	β chain of β_1 integrin molecules, including VLA1-VLA6
CD32	B cells, monocytes, granulocytes	FCGR3
CD35	B cells, subset of NK cells, monocytes, granulocytes	CR1
CD45	Leukocytes	Leukocyte common antigen; phosphatase; involved in cell signaling
CD46	Broad distribution	Membrane cofactor protein; regulates complement activation
CD54 (ICAM1)	Broad distribution	Binds LFA1; adhesion molecule
CD56	NK cells	Neural cell adhesion molecule
CD58 (LFA3)	Broad distribution	Binds CD2; adhesion molecule; involved in cell signaling

ADCC, antibody-dependent cellular cytotoxicity; CR, complement receptor; ICAM1, intercellular adhesion molecule-1; IgG, immunoglobulin G; LFA, leukocyte function–associated antigen; LPB, LPB binding protein; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NK, natural killer; VLA, vascular leukocyte adhesion molecule.

mucosa-associated lymphoid tissues, such as the tonsils, lymph nodes of the respiratory tract, and Peyer patches of the gut. These tissues provide an environment for lymphocytes to interact with each other, with antigen-presenting cells and other accessory cells, and with foreign antigens. The immune response is generated mostly within these secondary lymphoid organs, and lymphocytes migrate through the blood and lymph from one lymphoid organ to another and to nonlymphoid tissues. For example, foreign antigen exposure in the lung usually involves the movement of antigen to surrounding lymph nodes, where the specific immune response by T and B cells takes place. Generation of a cell-mediated immune response or antibody response allows antigen-specific effector T cells or specific antibodies, respectively, to travel back to lung tissue for a direct assault on foreign antigens.

Under normal conditions, there is a continuous active flow of lymphocyte traffic through the lymph nodes. About 1% to 2% of the lymphocyte pool recirculates each hour, allowing a large number of antigen-specific lymphocytes to come into contact with their appropriate antigen. Recirculating lymphocytes leave the blood and enter the lymph node through specialized postcapillary venules, known as *high endothelial venules* (HEVs). Specific interacting receptors on lymphocytes and HEV cells facilitate this homing process. Lymphocytes return to the circulation by way of afferent lymphatics that pass via the thoracic duct into the left subclavian vein. Lymphocytes also enter mucosa-associated lymphoid tissues, such as the tonsils and Peyer patches, via HEVs. The recirculation and trafficking of memory and effector T and B cells is tightly regulated, determined by unique combinations of adhesion molecules and chemokines.⁸ For example, certain lymphocytes may preferentially migrate across HEVs into intestinal lymphoid tissues (either Peyer patches or mesenteric lymph nodes) or

into respiratory tract tissues or may specifically home to the peripheral lymph nodes or the spleen.

Separate combinations of cell-surface adhesion molecules and chemokines allow activated lymphocytes and other leukocytes to migrate into nonlymphoid tissues, especially during inflammation and in response to the release of inflammatory cytokines.⁸ The difference in trafficking patterns for nonactivated (resting) versus activated lymphocytes is striking and emphasizes the importance of particular adhesion molecules in the control of lymphocyte migration.

IMMUNE RECOGNITION

B CELLS AND ANTIBODIES

Structure of Immunoglobulin and the B-Cell Receptor for Antigen

Immunoglobulin molecules, or antibodies, are glycoproteins that act as BCRs. These molecules can also be secreted in large quantities by activated B cells and plasma cells. [Figure 13-1](#) shows the basic structure of an Ig molecule. Each Ig molecule is bifunctional—one region (Fab) binds to antigen, and a different region (Fc) mediates various effector functions, such as binding to host tissues (via their cell surface Fc receptors) and binding to and activating the first component of the classic complement system.

The basic structure of all Ig molecules involves two identical light polypeptide chains and two identical heavy polypeptide chains linked together by disulfide bonds (see [Fig. 13-1A](#)). The isotype (class or subclass) of an Ig molecule is determined by its heavy chain type. There are five Ig classes—IgG, IgM, IgA, IgD, and IgE—corresponding to the

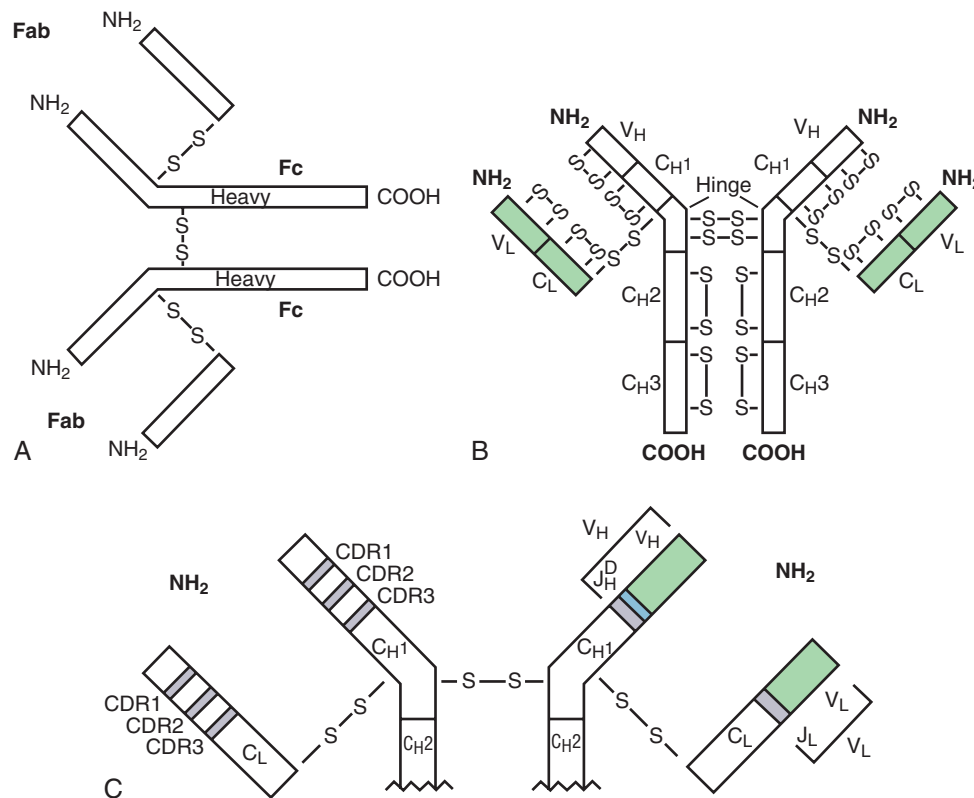


Figure 13-1 The structure of immunoglobulin molecules. **A**, Basic immunoglobulin (Ig) structure with two heavy chains and two light chains linked together by disulfide bonds. The Fab region is involved in antigen binding, whereas the Fc region mediates various effector functions. **B**, Increasing detail of IgG molecule showing domains of both heavy and light chains. Each domain has an internal disulfide bond. The sites of antigen binding involve the NH₂-terminal domains of both the heavy and the light chains and are referred to as the “variable regions” (V_H and V_L, respectively). The rest of each chain has a relatively constant structure (C_H and C_L domains). **C**, Close-up of the antigen-binding variable regions. On the left, the complementarity-determining regions (CDRs) are shaded because they are the most variable components and are most involved in actual antigen binding. The CDRs are separated by intervening segments referred to as “framework regions.” On the right, the Ig polypeptide regions are correlated with the Ig gene segment (exons) that encode the variable region. Note that CDR3 corresponds to the V_H/D_H/J_H junctional region of the rearranged heavy chain gene and the V_L/J_L junctional region of the rearranged light chain gene. (Adapted from *MKSAP in the specialty of rheumatology*, Philadelphia, 1993, American College of Physicians, p 6.)

γ , μ , α , δ , and ϵ heavy chain types. In humans, there are four IgG subclasses, IgG1 to IgG4. There are major differences in the structure and main functions of these different Ig classes and subtypes.

In [Figure 13-1B](#), the IgG molecule is shown as an example of basic antibody structure. Each chain is composed of a series of globular regions or domains. Each domain encompasses about 60 to 70 amino acids and has an internal disulfide bond. The site of antigen binding is the amino (NH₂)-terminal domain for both the *heavy* (H) and *light* (L) chains. This domain is characterized by remarkable sequence variability and is referred to as the “variable region” of the heavy and light chains (V_H and V_L region, respectively). The combination of V_H and V_L forms the antigen-binding site, and there are two such sites per IgG molecule (see [Fig. 13-1B](#)). The rest of each polypeptide has a relatively constant structure. The constant domain of the light chain is termed the “C_L region,” whereas the heavy chain has three constant domains: C_H1, C_H2, and C_H3. The hinge region, located between the C_H1 and C_H2 domains, provides flexibility and independence to the two antigen-binding sites. In both μ and ϵ heavy chains, there is an additional constant domain between C_H1 and C_H2, resulting in a total of four constant domains.

The greatest variability in antibody molecules takes place in the V_H and V_L domains, and these domains are responsible for the specificity in antigen binding.^{9,10} Within the variable domains (see [Fig. 13-1C](#)), certain short segments show exceptional variability and are called “hyper-variable regions.” These regions are also referred to as *complementarity-determining regions* (CDRs) because they are directly involved in the binding to antigen. In both the V_H and V_L regions, there are three CDRs (CDR1 to CDR3) with intervening segments referred to as “framework regions” (see [Fig. 13-1C](#)). CDR3 (a component of the polypeptide V region) is formed by parts of the V (variable), D (diversity), and J (joining) gene segments. Variation within the V_H and V_L regions distinguishes one antibody molecule from another and is referred to as “idiotypic” or “idiotypic variation.” Additional information on heavy chain rearrangement is shown in [eFig. 13-1](#).

Formation of the B-Cell Receptor Repertoire

The BCR repertoire and the Ig molecules are characterized by enormous diversity. The principal genetic mechanisms that are used to generate this diversity include (1) genetic recombination of gene segments to form a functional Ig gene, (2) combinatorial diversity of heavy and light chain

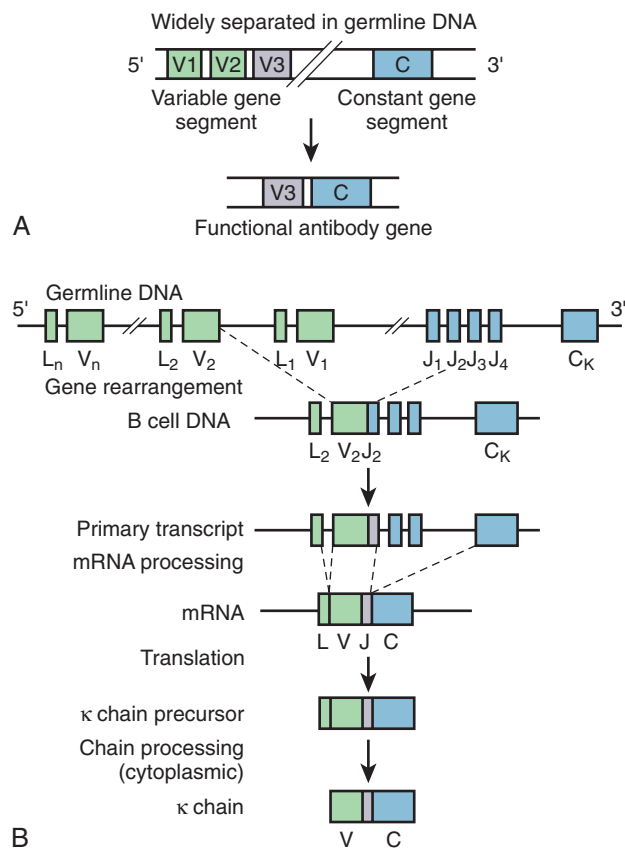


Figure 13-2 Principles of genetic recombination. **A**, In the germline DNA, the V region segments are located upstream from the D, J, and C segments on the same chromosome. Recombination, which takes place only in lymphocytes, brings the V gene segments in proximity to the downstream segments. **B**, In the B cell, rearrangement of gene segments separated in the germline DNA allows for the formation of a functional immunoglobulin light chain gene (compare with Fig. 13-1C). mRNA, messenger RNA. (Adapted from *MKSAP in the specialty of rheumatology*, Philadelphia, 1993, American College of Physicians, p 8.)

matching, and (3) somatic mutation of rearranged genes.⁹⁻¹¹ Another major force in shaping the antibody repertoire has been termed “receptor editing,” which allows receptors with self-reactive potential to be modified by additional recombination events during B-cell differentiation.^{12,13}

Figure 13-2A illustrates the principle of genetic recombination for an Ig gene.^{9,10} In this case, one of several variable (V) region gene segments (normally separated upstream from the constant [C] region gene segments on the same chromosome) can be linked to a single C region gene segment by genetic recombination. The combining of gene segments, rather than the existence of a single gene coding for every individual antibody molecule, considerably reduces the amount of genetic information required to encode many different antibody molecules. In Figure 13-2B the different gene segments that encode a κ light polypeptide chain are shown. Note that in this case, a V region rearranges proximal to a J segment, which is linked to the C region segment. Rearrangement of κ or γ light chain genes involves V, J, and C region gene segments (see Fig. 13-2A; see also Fig. 13-1C). In the formation of a functional heavy chain gene, a successful rearrangement of gene segments includes one V, one D, and one J region segment linked to a C region segment (compare Figs. 13-1C and 13-2B).

During genetic recombination, additional variability is generated by a process known as “junctional diversification.” When two gene segments are brought together during rearrangement, the linking is not precise. Instead, some nucleotides are inserted or deleted randomly at the junctional site. This introduces new codons, and therefore new amino acids, into the junctional sequence. If an incorrect number of junctional nucleotides are added or deleted, functional molecules will not be encoded, because the rest of the gene will be “out of frame” or a “stop” sequence will be introduced. Junctional diversification takes place in the hypervariable CDR3 region of the molecule (see Fig. 13-1C).

In general, a single B cell usually expresses an Ig molecule of only one antigen specificity, composed of one heavy chain molecule and one light chain molecule. Even though there are two chromosomal copies of the heavy chain genes in each cell, only one is usually functionally expressed. This phenomenon of using genes on only one parental chromosome is known as “allelic exclusion.” Once there has been a functional rearrangement of heavy chain genes on one parental chromosome, rearrangement of heavy chain genes on the other chromosome is mostly prevented. If the first rearrangement is not successful, the second one can take place. All of the genetic events described earlier happen before the B cell encounters its antigen. The B-cell (or antibody) response diversifies further after interaction with antigen by a process known as “somatic mutation,” primarily involving point mutations in the hypervariable regions of the V regions.^{10,11} Somatic mutation can be viewed as “fine tuning” of the antibody response, occurring after the primary response to a stimulus and during the development of memory B cells. It is, therefore, mostly observed during a secondary immune response. Somatic mutation allows for the production of antibodies with higher affinity for antigen, that is, the ability to bind more strongly to an antigen. Although the mutations are random, B cells with high affinity are selectively expanded (referred to as “affinity maturation”) because the stronger binding allows preferential stimulation by the target antigen. Somatic mutation is closely tied to isotype switching, and T-cell help is required. Somatic mutation usually takes place at the site of T-cell–B-cell interaction in the germinal centers of lymph node or spleen.

Isotype Switching and Function of the Different Immunoglobulin Classes

One B cell usually makes antibody of a single specificity that is fixed by the nature of V_LJ_L and $V_HD_HJ_H$ rearrangements. During the lifetime of this cell, however, it can switch from making an IgM molecule to producing a different class of antibody, such as IgG or IgA, while retaining the same antigenic specificity. This phenomenon is known as “class switching” or “isotype switching.”^{10,14}

Figure 13-3 shows the predominant mechanism by which a B cell switches from production of surface IgM to secretion of an IgG, IgA, or IgE molecule. The mechanism involves further DNA rearrangement (a process unique to Ig heavy chain genes), linking rearranged VDJ gene segments with a different heavy chain C region gene segment downstream. The switch (S) region is a stretch of repeating sequences 5' to the C region that allows a VDJ unit (previously linked to the C_μ region gene segment) to rearrange to

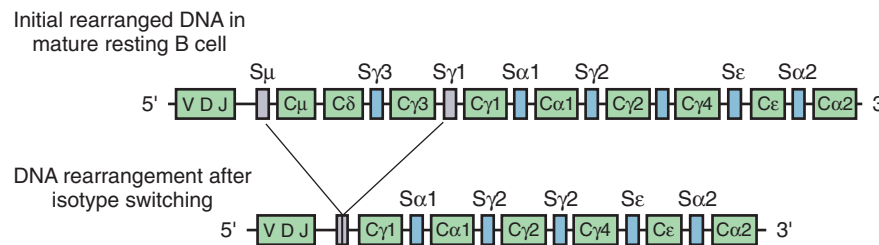


Figure 13-3 Genetic mechanisms involved in immunoglobulin (Ig) isotype switching. *Top*, The initial rearrangement of Ig heavy chain gene segments has already taken place in the B cell to put the V region proximal to the D, J, and C_μ segments. This latter genetic region contains other constant region gene segments farther downstream, including C_δ, various C_γ and C_α gene segments, and C_ε. In the process of T-cell-dependent B-cell activation in the germinal centers, the B cell is signaled to undergo isotype switching to allow high-rate secretion of an IgG1 antibody. *Bottom*, This is accomplished by additional DNA rearrangements that put the VDJ unit adjacent to the C_{γ1} segment downstream. The intervening DNA is deleted.

Table 13-4 Properties and Functional Characteristics of Immunoglobulin Classes and Subclasses*

Effector Function	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Mean serum levels (mg/mL)	1.5	0.04	9	3	1	0.5	2.1	0.00003
Opsonization	—	—	+++	—	++	+	+	—
Complement fixation	+++	—	++	+	+++	—	—	—
Binding of Fc receptor on phagocytic cells	—	—	++	—	++	+	—	—
Induction of mast cell degranulation	—	—	—	—	—	—	—	+++

*Activity levels of immunoglobulin classes and subclasses: +++ high; ++ moderate; + low; =/— minimal; — none. Ig, immunoglobulin.

another C region downstream. In the process the intervening DNA is deleted. The B cell therefore cannot return to IgM production. Class switching generally follows stimulation of the B cell by antigen and frequently is dependent on factors released by T helper cells.

Each class of secreted Ig has a different set of functions (Table 13-4).^{10,15} IgG is the major antibody of secondary immune responses and is most important for obtaining effective immunization to various toxins, toxoids, and certain extracellular pathogens. IgG accounts for 70% to 75% of the total Ig pool and is the major Ig class in normal human serum. It also crosses the placenta and confers immunity to newborns and neonates for the first few months of life. The interaction of IgG antibodies with antigen can have numerous consequences, including precipitation, agglutination, complement activation, and various cellular effector functions via IgG receptors.^{10,15-18} There are four IgG subclasses, with IgG1 and IgG3 being most effective at fixing complement and activating complement-mediated effector functions.

IgM is the predominant early-secreted antibody, frequently seen in primary immune responses. IgM is important for effective responses to antigenically complex infectious organisms, especially those with polysaccharide-containing cell walls. IgM antibodies may also be extremely effective at precipitation, agglutination, and complement activation after binding to antigen. Secreted IgM is usually found as a pentamer of the basic (four-domain) Ig unit. Polymerization is facilitated by the binding of the heavy chain tailpieces to a joining (J) peptide.

IgA plays a major role in mucosal immunity and is the predominant Ig in secretions such as saliva and tracheo-bronchial secretions. Secretory IgA exists mainly in dimeric form and contains a secretory component, which is synthe-

sized by epithelial cells and facilitates transport into secretions as well as protection from proteolysis. Secretory IgA is involved in the prevention of microbial adherence to mucosal cells and in the agglutination of microorganisms. IgA provides the first line of defense against a variety of pathogens.

IgE is scarce in the serum. Its major importance relates to its ability to bind to FcεR1 receptors on mast cells and basophils, and cross-linking of IgE bound to these cells results in cellular activation, degranulation, and release of mediators involved in allergic responses, such as histamine and various leukotrienes.¹⁹ IgE plays a role in immunity to parasites, but in developed countries, it is more commonly associated with allergic responses and allergic diseases, such as hay fever and asthma (see Chapters 41 and 42).²⁰

B-Cell Development

B cells are produced in the specialized microenvironments of the fetal liver and the adult bone marrow.²¹ After migration out of the bone marrow, the life span of mature naive B cells is limited unless there is contact with antigen. B cells interact with foreign antigen in the peripheral lymphoid tissues, particularly in the germinal centers of lymph nodes and spleen.²² The interaction with antigen, in the setting of T-cell help, results in the generation of memory B cells and cells that secrete a large amount of Ig. This frequently involves class switching and somatic mutation, which allows a secondary antibody response to generate antibodies of a different isotype with higher affinity for the stimulating antigen. An additional view of B-cell development is shown in eFig. 13-2.

The formation of the B-cell repertoire in the bone marrow is mostly random, and B cells with self-reactivity are generated. Negative selection of cells capable of strongly binding

to self-antigens is an important part of B-cell development. This process of B-cell self-tolerance involves both deletion (elimination) and functional inactivation (anergy) of self-reactive cells.²³ In addition, B cells with specificity for self-antigens can modify their receptors through a process called “receptor editing.”^{12,13} These self-reactive B cells undergo a reversible arrest of development and reinitiate light chain gene rearrangements to alter their BCR. If a B cell fails to edit its BCR, it is destined for cell death (apoptosis). Immature B cells in the bone marrow appear to be capable of receptor editing, whereas mature B cells in the peripheral lymphoid tissues normally lose this ability to initiate a new round of Ig gene rearrangements.

Immunoglobulin Interactions with Antigen

An antigen is a molecule or molecular complex recognized by B cells or T cells. The term *immunogen* usually refers to a substance capable of eliciting an immune response, and therefore it must also be capable of being recognized as an antigen. An antigen (e.g., a protein molecule) is usually much larger than the small region fitting into the binding site of an Ig molecule or the processed peptide recognized by a TCR. This smaller region is frequently referred to as an “antigenic determinant” or “epitope.” In a protein a B-cell epitope can theoretically be constructed in two ways—as a continuous or a discontinuous epitope. In a continuous epitope, the amino acid residues are part of a single uninterrupted sequence, whereas in a discontinuous epitope, residues are not contiguous in the primary structure but are brought together by the folding of the polypeptide chain. Because this kind of epitope requires a special conformation of the antigen, it is frequently referred to as a “conformational epitope.”

B cells and T cells usually recognize different parts of an antigen. B cells and their secreted Ig molecules most commonly recognize unprocessed or “native” antigens. These antigens have maintained their native configuration, and most of the epitopes are usually of the discontinuous or conformational type. In general, only a minor component of a B-cell response is directed to small linear peptide regions of the antigen. Studies indicate that epitopes recognized by B cells are not randomly distributed throughout the antigen but rather reside in regions with particular structural features. One important feature is “accessibility,” because epitopes normally must be on the outer surface of a protein and may protrude from an antigen’s globular surface to be able to interact with the BCR.

T CELLS AND ANTIGEN-PRESENTING CELLS

In contrast to B cells, T cells recognize processed pieces of a protein antigen, which are presented to the TCR by MHC molecules on the surface of antigen-presenting cells.^{4,5}

T-Cell Receptors

The TCR shows important structural similarities with Ig molecules (Fig. 13-4).³ The $\alpha\beta$ TCR is expressed by at least 90% of peripheral blood T cells. Essentially, all CD4⁺ T cells and most CD8⁺ T cells express this form of the TCR. A small percentage of $\alpha\beta$ -expressing T cells have a double-negative (CD4⁻ and CD8⁻) phenotype. As shown in Figure 13-4, each chain consists of two extracellular Ig-like domains anchored

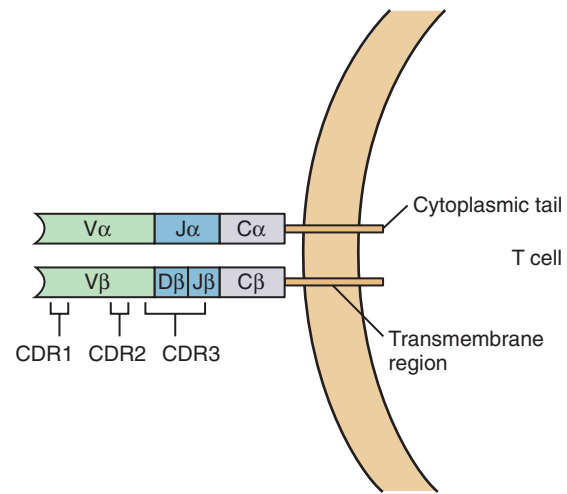


Figure 13-4 The T-cell receptor (TCR) α and β chains indicate the regions encoded by different TCR gene segments. The positions of the complementarity-determining regions (CDRs) of both the β and the α chains are also shown. These are the most variable parts of the TCR and the most important for TCR binding to the peptide/major histocompatibility complex. CDR1 and CDR2 of both the α and the β chains are encoded within the variable region genes. CDR3 is formed by the rearrangement of V, D, and J gene segments of the β chain and V and J segments of the α chain and is encoded by the distal part of the V region segment through part of the J segment. The different parts of the TCR are not drawn to scale.

into the plasma membrane by a transmembrane region and a short cytoplasmic tail. Similar to Ig molecules, the outer NH₂-terminal domain of each chain constitutes the variable region. Outside of the transmembrane region, the two chains are covalently linked together by disulfide bonds. Due to the short cytoplasmic tail, the $\alpha\beta$ heterodimer is not capable of transmitting an intracellular signal after TCR engagement. This function is accomplished by the CD3 complex of polypeptides and other signaling proteins that are associated with the TCR.

The $\gamma\delta$ TCR is an alternative form of TCR that is similar in overall structure to the $\alpha\beta$ receptor.²⁴ Although some $\gamma\delta$ cells express CD8, most are CD4⁻ and CD8⁻ (double negative). CD8 expression is largely confined to those $\gamma\delta$ cells residing in the small intestine. The $\gamma\delta$ TCR is also expressed in association with the CD3 complex. Although $\gamma\delta$ T cells form a minor proportion of the T cells in the thymus and secondary lymphoid organs, they are abundant in various intraepithelial locations, such as in the skin, intestines, and lung.^{24,25}

T-Cell Receptor Structure and T-Cell Receptor Repertoire Formation

Genes encoding the TCR are organized similarly to Ig genes^{3,26} (eFig. 13-3). In a manner similar to that described previously for B cells, rearrangement of gene segments, junctional diversity, and combinatorial joining of the two chains is responsible for the diversity of the TCR repertoire. However, in contrast to B cells, TCR genes do not undergo somatic mutation. Thus nearly the entire TCR $\alpha\beta$ repertoire is formed during T-cell development in the thymus and before any interaction with antigen. Because the T-cell repertoire is shaped to recognize self-MHC antigens, it is believed that extrathymic somatic mutation might result in the generation of deleterious self-reactive T cells.

The components of the $\alpha\beta$ TCR heterodimer are shown in Figure 13-4, and the ribbon backbone structure of the $V\alpha$ and $V\beta$ portions of a human TCR are shown in Figure 13-5.^{4,5,27,28} The upward-pointing loop structures are the CDRs. These regions are the most variable part of the TCR α and β chains and are most important for binding of the TCR to the MHC/peptide complex. The CDR1 and CDR2 regions of the α chain and β chain are encoded within the germline *TCRAV* and *TCRBV* gene segments, and variability in their sequences distinguishes the different V region subfamilies. The most diverse part of the α and β chains is the CDR3, which directly interacts with peptide in the binding groove of the MHC molecule.

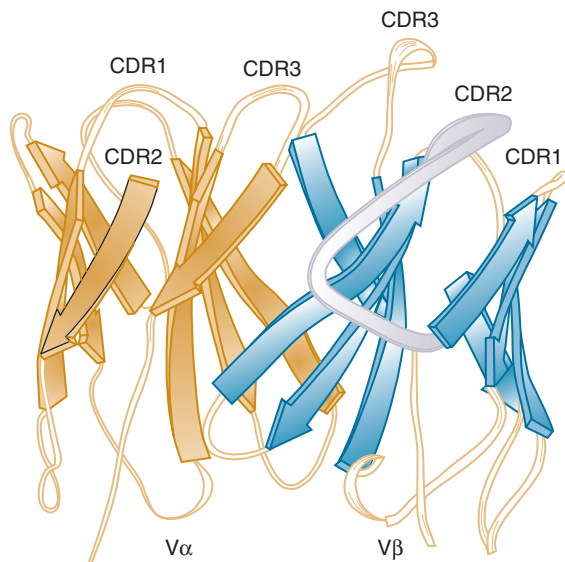


Figure 13-5 A ribbon backbone structure of the $V\alpha$ and $V\beta$ portions of a human T-cell receptor (TCR). The upward-pointing loop structures are the complementarity-determining regions (CDRs). These regions are the most variable part of the TCR α and β chains and are most important for TCR binding to peptide/major histocompatibility complex. The CDR1 and CDR2 regions of the α chain and β chain are encoded within the germline *TCRAV* and *TCRBV* gene segments, respectively. The highly variable CDR3 region is formed by the rearrangement of V, D, and J gene segments. Junctional nucleotide substitutions and deletions at the margins of rearrangement add to the potential diversity of the CDR3 region. (Adapted from Kotzin BL, Kappler J: Targeting the TCR in rheumatoid arthritis. *Arthritis Rheum* 41:1907, 1998.)

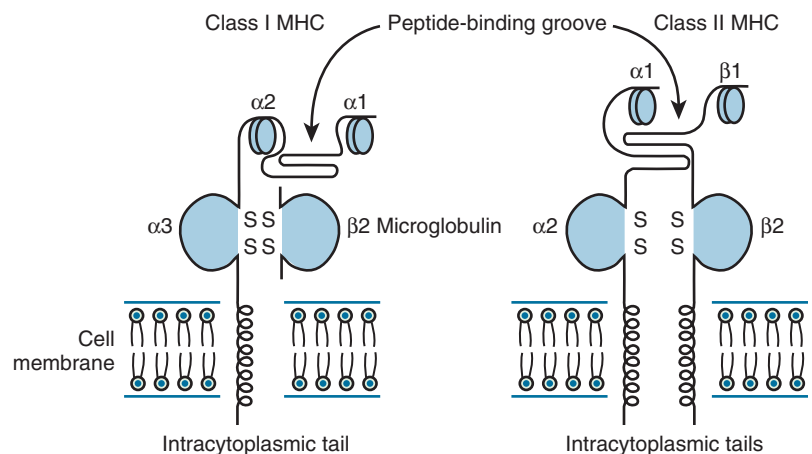
Antigen-Presenting Cells and the Major Histocompatibility Complex

There are two major varieties of MHC molecules (and genes) involved in the presentation of antigens to T cells.²⁹ MHC class I molecules include *human leukocyte antigen* (HLA)-A, HLA-B, and HLA-C molecules. MHC class II molecules include the HLA-DR, HLA-DQ, and HLA-DP molecules. Class I molecules are expressed on nearly all nucleated cells. In contrast, class II molecules have a limited distribution and are normally present only on cells involved in antigen presentation to T cells, including dendritic cells, macrophages, B cells, and thymic epithelial cells. The limited expression of class II antigens in different tissues may be extremely important in preventing various types of autoimmune reactions. After activation or exposure to certain cytokines, such as *interferon- γ* (IFN- γ), other human cell types such as activated T cells and epithelial cells can express class II molecules.

The general structures of the two classes of MHC molecules are shown in Figure 13-6. For MHC class I antigens, the α chain (encoded within the MHC) is complexed to β_2 -microglobulin (encoded outside the MHC). The α chain is highly polymorphic (variable between individuals), whereas β_2 -microglobulin is invariant. The extracellular portion of the α chain is divided into three domains: $\alpha 1$, $\alpha 2$, and $\alpha 3$. The outer $\alpha 1$ and $\alpha 2$ domains represent the polymorphic components of the molecule, and the $\alpha 3$ domain is relatively constant. MHC class II molecules are composed of an α and a β chain, both of which are encoded within the MHC. The NH_2 -terminal domains of each chain ($\alpha 1$ and $\beta 1$ domains) represent the polymorphic regions of the molecule and are important in antigen presentation, whereas the $\alpha 2$ and $\beta 2$ domains are relatively constant.

The structures of MHC class I and class II molecules have provided remarkable insight into how antigenic peptides are bound and presented to T cells.^{4,5,30-33} In Figure 13-7A, the peptide-binding groove of a class I molecule is viewed from the top, showing the surface that is contacted by a TCR. MHC class I pockets can usually only bind peptides of 8 to 10 amino acids, which are bound in a typical extended conformation with both the NH_2 terminus and the *carboxy* (COOH) terminus anchored in the peptide-binding groove. In the case of MHC class II, the peptide-binding groove is

Figure 13-6 Comparison of the composition of class I and class II major histocompatibility complex (MHC) molecules. The class I MHC α chain is variable (polymorphic) among different individuals. It is expressed with β_2 -microglobulin, which is encoded outside the MHC region and does not differ among different individuals. The class II MHC molecules are composed of α and β chains. For human leukocyte antigen (HLA)-DR molecules, only the β chain is variable, whereas for the HLA-DQ and HLA-DP molecules, both the α and the β chains are encoded by polymorphic alleles. In class I MHC molecules, the peptide-binding region is formed between the $\alpha 1$ and the $\alpha 2$ domains, which are polymorphic. The peptide-binding region of class II MHC is formed between the $\alpha 1$ and the $\beta 1$ domains of the α and β chains, respectively.



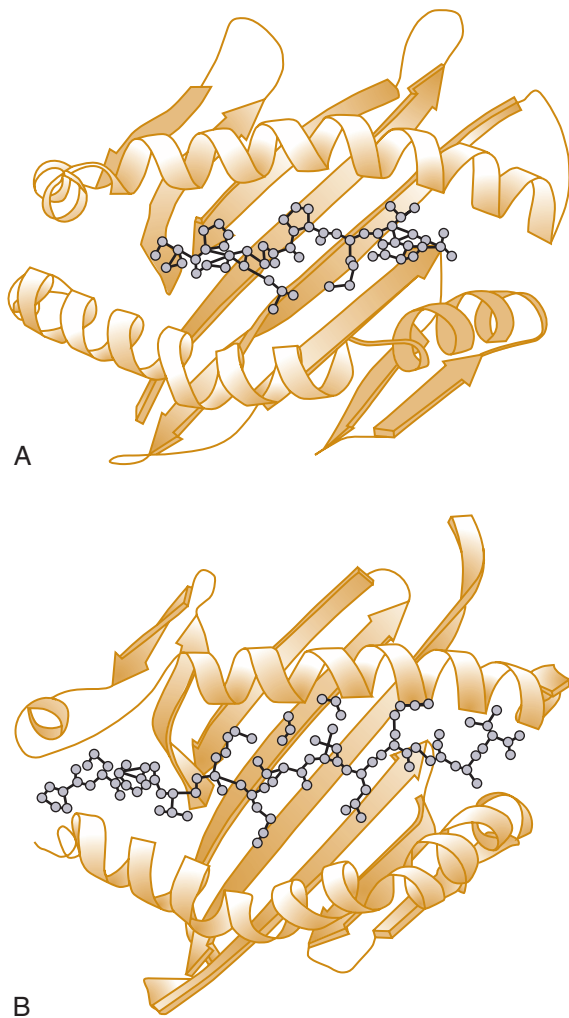


Figure 13-7 Structure of the major histocompatibility complex (MHC)/peptide complexes. **A**, A schematic view of an MHC class I binding groove with peptide. The peptide is shown in ball-and-stick representation. In class I molecules, the peptide is usually of fixed length (8–10 amino acids) and bound so that both the NH₂ and COOH termini are anchored in the peptide-binding groove. **B**, A schematic view of an MHC class II (human leukocyte antigen [HLA]-DR1) molecule with bound peptide in the groove. The peptide is shown in ball-and-stick representation. The peptide has the typical polyproline extended helical conformation seen in all class II bound peptides. The structure of class II allows peptides of varying lengths to bind because both ends of the peptide are free and can extend out of the groove on both sides. (From Jones EY: MHC class I and class II structures. *Curr Opin Immunol* 9:76–77, 1997.)

formed by the interaction of the NH₂-terminal domains of the α and β chains (see Fig. 13-7B). The structure of MHC class II allows peptides of varying lengths to bind because both ends of the peptide are free, and the peptide shown in Fig. 13-7B has the typical polyproline-like extended helical conformation seen in all class II MHC-bound peptides.

Presentation and T-Cell Recognition of Antigens

In contrast to B cells, T cells recognize processed peptides of a foreign antigen that are complexed to MHC molecules on antigen-presenting cells. Because of the process of thymic selection for self-MHC recognition, there is little capability for T cells to recognize intact or native protein antigens. CD4⁺ T cells generally recognize peptides complexed to class

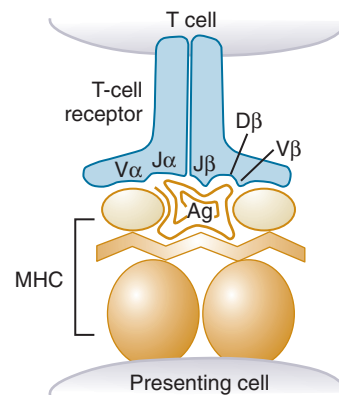


Figure 13-8 T-cell recognition of a conventional peptide antigen. The major histocompatibility complex (MHC) molecule on the antigen-presenting cell (brown) shows the peptide-binding groove with a peptide in it. The interacting TCR is shown as a blue structure. Note that the junctional regions of the TCR α chain ($V\alpha/J\alpha$) and β chain ($V\beta/D\beta/J\beta$) are depicted so that they appear to have the most important interaction with the peptide. These junctional regions form the complementarity-determining region (CDR) 3 of the α and β chains, which is the most variable component of the TCR. The CDR1 and CDR2 loops are encoded within the $V\alpha$ and $V\beta$ regions and may have more interaction with the MHC parts of the complex compared with CDR3. A ribbon diagram of the TCR CDR loops is depicted in Figure 13-5. (Adapted from Drake CG, Kotzin BL: Superantigens: biology, immunology, and potential role in disease. *J Clin Immunol* 12:140, 1992.)

II MHC molecules, whereas CD8⁺ T cells interact with peptide/class I MHC molecules.^{3–5,29} The purpose of this relatively complex antigen-presentation process may be to focus the T-cell response onto cells. For example, it is much easier for a T cell to kill a virus-infected cell before the pathogen has the opportunity to multiply than it is to kill individual virus particles. The class I MHC molecules therefore focus the cytotoxic T-cell response on cells infected with intracellular organisms, whereas free infectious particles are the targets of antibodies. Class II MHC molecules similarly focus the delivery of T-cell help on the relevant antigen-specific B lymphocytes that eventually produce antibodies. Recognition of antigen only on the surface of MHC class II-expressing cells also allows for a system by which the activation of CD4⁺ T cells can be closely regulated.

Peptide-containing MHC class I and class II molecules on the surface of antigen-presenting cells serve as ligands for TCRs of CD8⁺ and CD4⁺ T cells, respectively. To present antigenic peptides effectively, antigen-presenting cells must be capable of performing at least two functions: (1) processing and displaying parts of antigens in the peptide-binding groove of MHC molecules on their cell surface and (2) providing the other accessory signals necessary for T-cell activation. Antigen processing refers to the series of steps that generate these peptide fragments, load them onto MHC molecules, and allow expression of the peptide/MHC complex on the cell surface.³⁴ Major differences exist in the manner in which endogenous and exogenous foreign antigens are processed and presented to T cells,^{34–39} which are beyond the scope of this chapter.

Figure 13-8 shows a schematic view of antigen recognition by a CD4⁺ T cell. A foreign peptide is contained within the antigen-binding groove of a class II MHC molecule, and the TCR simultaneously recognizes the complex of peptide and class II MHC molecule. Thus residues of the variable

region of the TCR interact with the peptide and MHC residues extending out from the peptide-binding groove. The highly variable CDR3 region of the $\alpha\beta$ TCR is frequently most important in the binding of peptide, whereas other parts of the variable regions are more involved in MHC residue interactions.³⁻⁵

Development and Selection of the TCR Repertoire

Stem cells pre-committed to the T-cell lineage arise in the bone marrow and migrate to the thymus. See eFig. 13-4 for additional information on T-cell development and maturation. These cells do not express TCR molecules and do not express CD4 or CD8 molecules. These cells develop by rearranging TCR α and β chain genes and generating a functional $\alpha\beta$ TCR. In the thymus, two major processes modify this repertoire.⁴⁰⁻⁴² One process positively selects cells that have some TCR affinity for self-MHC molecules. Evidence suggests that an interaction with thymic cortical epithelial cells is involved in this positive selection step. This process allows mature cells to eventually recognize foreign antigens in the context of self-MHC antigens (a phenomenon termed “self-MHC restriction”). Cells that are not positively selected undergo programmed cell death (apoptosis) within the thymus. The other process deletes cells that have a high level of self-reactivity (termed “negative selection” or “self-tolerance”).⁴² This deletion process primarily involves an interaction with bone marrow–derived cells (macrophages, dendritic cells, B cells) that have migrated to the thymus and specialized cells within the thymic medulla (medullary epithelial cells) that express a variety of organ-specific antigens.^{43,44} The transcriptional regulator, Aire, plays an important role in T-cell tolerance induction in the thymus, mainly by promoting ectopic expression of a large repertoire of transcripts encoding proteins normally restricted to differentiated organs in the periphery.⁴⁴ Only a small percentage ($\approx 1\%$ to 3%) of thymocytes actually survive positive and negative selection and become mature thymocytes that have a relatively high level of TCR expression and express either CD4⁺ or CD8⁺ markers. In general, cells that are positively selected by an interaction with class II MHC molecules mature into the CD4 population, whereas cells that are positively selected on class I MHC molecules become the CD8 population.⁴⁵ Mature thymocytes subsequently migrate to peripheral lymphoid tissues, where they maintain these surface characteristics.

T-Cell Tolerance: Prevention of Self-Reactivity

Tolerance at the T-cell level is critical for the prevention of autoimmunity. Clonal deletion of self-reactive T cells in the thymus is a major process for eliminating T cells that are reactive to non-organ-specific cellular proteins and to circulating proteins, because these self-antigens are likely to be in the thymus during T-cell development. Some organ-sequestered antigens (e.g., certain uveal tract, brain, and endocrine organ antigens) are also expressed in the thymus.^{43,44} However, studies have clearly shown that T cells to various self-antigens, including many organ-sequestered and posttranslationally modified antigens, are not completely deleted in the thymus. Therefore self-tolerance must also involve the prevention of activation of these autoreactive T cells after they migrate from the thymus to the peripheral lymphoid tissues.^{46,47}

Studies have shown that T cells with self-reactive TCRs are present in the peripheral lymphoid organs and the circulation of healthy individuals, but they are not sufficient for the development of autoimmune disease. Different peripheral mechanisms appear to help prevent the generation of autoimmune responses. One process appears to prevent the self-antigen from being effectively presented to a self-reactive T cell, which maintains that T cell in an ignorant state. For example, resting T cells with self-reactive potential may not be able to traffic to the tissue that expresses the antigen, or the antigen may not be presented by effective antigen-presenting cells. Some studies have suggested that inappropriate expression of class II antigens in a tissue can lead to autoimmunity, perhaps by circumventing this protective mechanism. T-cell activation triggered by a separate process (e.g., an infectious agent) may also bypass this protective mechanism by allowing cells with self-reactive potential to traffic to tissues inappropriately. T cells that do recognize antigen without effective antigen-presenting cells and co-stimulation may also be functionally deactivated (or anergized)⁴⁸ and prevented from any subsequent stimulation by that self-antigen. These cells continue to be present in the peripheral T-cell repertoire, but their prior contact with self-antigen prevents any subsequent response. Current evidence indicates that anergic T cells activate some but not other signaling pathways after TCR engagement.⁴⁸ There is also evidence that the encounter of self-reactive T cells with antigen, but without effective presentation, sometimes leads to death of the autoreactive T cell rather than just anergy.

A final mechanism to prevent activation of self-reactive T cells involves regulatory (suppressor) T cells. In experimental animal models, there is evidence that CD4⁺, CD8⁺, and $\gamma\delta$ T cells may be involved in the down-regulation of certain immune responses, and their absence may be associated with pathologic autoimmune responses. At least two subsets of regulatory CD4⁺ T cells have been described that can inhibit cell-mediated immune responses and autoimmune pathologic responses: naturally occurring cells with suppressive activity and those induced by stimulation.^{49,50} The naturally occurring regulatory CD4⁺ T cells are characterized by constitutive CD25 expression and constitute 5% to 10% of the circulating CD4⁺ population.⁴⁹⁻⁵² In murine models, depletion of these CD4⁺CD25⁺ T cells results in the spontaneous onset of multiorgan autoimmunity. These cells mediate their suppressive effects in a contact-dependent, antigen-independent manner in the absence of *interleukin-10* (IL-10) or *transforming growth factor- β* (TGF- β). A novel member of the forkhead box/winged-helix family of transcription regulators, designated FOXP3, has been identified as a specific molecular marker for this type of regulatory T cell, and its expression is essential for programming both thymic development and function of these T cells.^{49,53} In sarcoidosis, FOXP3-expressing regulatory T cells accumulate at the periphery of the granuloma in subjects with active disease.⁵⁴ However, despite suppressing mitogen-induced T-cell proliferation, the regulatory T cells in lung could not completely suppress *tumor necrosis factor- α* (TNF- α) and IFN- γ secretion, suggesting that the activity of this regulatory T-cell subset was incapable of controlling granulomatous inflammation. The other type of regulatory CD4⁺ T cell is activation induced, and these cells lack CD25

and FOXP3 expression.⁴⁹ Much of the suppression from this group of regulatory cells can at least in part be attributable to cytokines such as TGF- β , because TGF- β is capable of suppressing both *type 1* (Th1) and *type 2* (Th2) *T helper* cell responses (see Th1 and Th2 responses, later). It is relevant to note that mice deficient in TGF- β show evidence of progressive inflammation and autoimmunity involving multiple organs.⁵⁵ In some cases, regulatory CD4⁺ T cells appear to release cytokines, such as IL-10 or even IL-4, that modulate the development and activation of Th1-type cells involved in a cell-mediated response.^{50,56,57}

GENERATION OF AN IMMUNE RESPONSE

T-CELL ACTIVATION AND CO-STIMULATION

Most immune responses depend on the activation of T cells, and normally, immune responses to foreign antigens are carefully orchestrated by a reciprocal communication between antigen-specific T cells and antigen-presenting cells. To be activated, naive T cells must receive several signals. One signal is antigen specific and is provided by engagement of the TCR. Additional signals are provided by co-stimulatory molecules and their interactions (Fig. 13-9). Resting antigen-presenting cells, such as resting B cells, frequently do not express significant levels of co-stimulatory molecules, and their interaction with T cells does not lead to T-cell activation. Two of the most important co-stimulatory systems involve the interaction of CD28 with B7-1 (CD80) and B7-2 (CD86) and the interaction of CD40 ligand with CD40.⁵⁸ These two systems of interacting molecules also affect each other.

CD28 is constitutively expressed on CD4⁺ T cells. Early in the immune response, B7-1 and B7-2 are up-regulated

on the antigen-presenting cells. Binding of CD28 to B7 co-stimulates T-cell activation, leading to increased T-cell production of IL-2 and other cytokines, increased cytokine receptor expression, increased cell survival, and increased T-cell proliferation.⁵⁹⁻⁶¹ Occupation of the CD28 receptor alone, without TCR engagement, has little effect on T cells; therefore signaling through CD28 is clearly a co-stimulatory event. The intracellular signaling that follows CD28 co-stimulation may overcome certain negative signals generated when the TCR is activated alone.^{58,62,63}

Presentation in an inflammatory setting also leads to up-regulation of CD40 ligand (CD154) on the CD4⁺ T cell.⁶⁴ CD40 ligand interacts with its counter-receptor, CD40, on B cells and other antigen-presenting cells, also inducing up-regulation of B7-1 and B7-2 as well as certain adhesion molecules and cytokine production by the presenting cell.⁶⁵ The interaction of CD40 ligand with CD40 is clearly bidirectional in that it provides signals important for T-cell and B-cell activation. CD40 ligand is a member of the TNF receptor family, and a variety of other TNF receptor family members, such as CD134 (OX40), CD137 (4-1BB), and CD27, have also been shown to possess co-stimulatory function following T-cell activation.^{58,66} In chronic beryllium disease, CD137 has recently been shown to be a critical co-stimulatory molecule for the induction of T-cell proliferation and prevention of activation-induced cell death in effector CD4⁺ T cells in lung.⁶⁷

Following activation, T cells express *cytotoxic T lymphocyte antigen-4* (CTLA4) on their surface, which also binds B7-1 and B7-2 on the antigen-presenting cell and with stronger affinity than CD28.⁶⁸ This interaction sends a negative signal to down-regulate the T-cell response after its initial activation. CTLA4 appears to be involved in the development of anergy and the generation of peripheral tolerance. CTLA4-deficient mice develop a lymphoproliferative disorder and die early, and alterations in the gene encoding

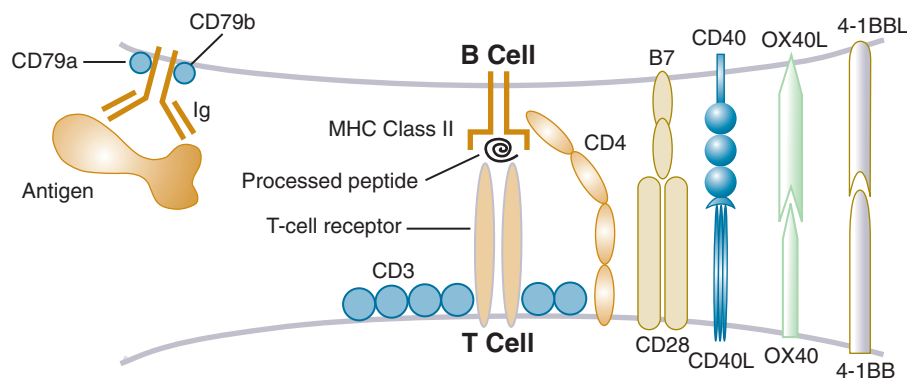


Figure 13-9 T helper cell–B-cell interactions important for T-cell–dependent antibody production. Antigen cross-links membrane immunoglobulin (Ig) on the B-cell receptor (BCR), which provides the first signal for the B cell. CD79a (Ig- α) and CD79b (Ig- β) are Ig-accessory molecules necessary for transmitting the signal intracellularly. The antigen is internalized into an intracellular compartment in the B cell, processed to peptides, and combined with major histocompatibility complex (MHC) class II molecules for expression and presentation to the T helper cell. T-cell receptor (TCR) binding to the peptide/MHC provides the first signal for the T cell. The CD3 complex and ζ chains allow for the TCR signal to be transmitted intracellularly. Activation of the T cell results in expression of CD40 ligand (CD40L), OX40, and 4-1BB. Interaction with CD40 provides the most important second signal to the B cell and is involved in T-cell activation. In addition, B7-1 (CD80) and B7-2 (CD86) are up-regulated on the B cell. Interaction with CD28 provides an important co-stimulatory signal to the T cell. This figure does not show the release of cytokines from the T helper cell that are necessary for full activation and differentiation of the B cell. In addition, this figure does not show other cellular interactions mediated by adhesion molecules. For example, the leukocyte function antigen (LFA)-1 integrin (CD11a, CD18) on the T cell interacts with intercellular adhesion molecule-1 (CD54) on the B cell. This interaction appears to be enhanced once the TCR and BCR have been engaged. CD2 on the T cell also interacts with LFA-3 on the B cell, which provides additional cell-cell adhesion.

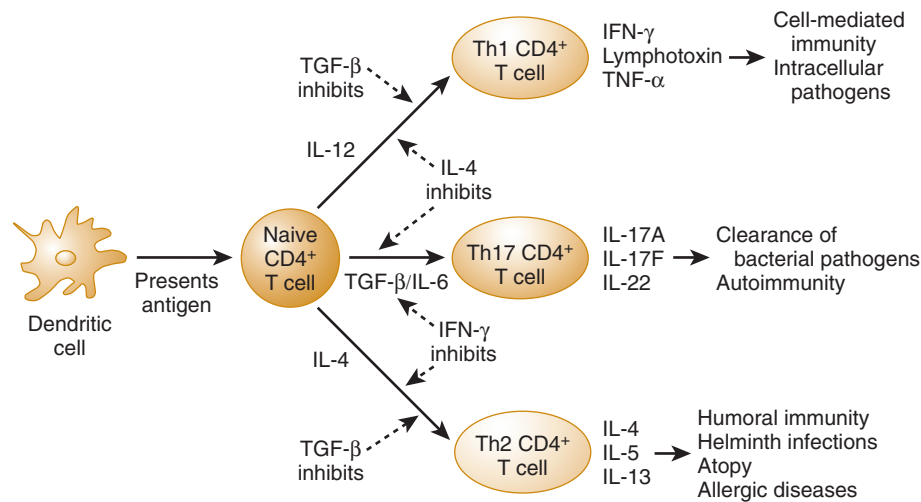


Figure 13-10 Regulation of T helper cell activation and responses. Naive CD4⁺ T cells can develop into type 1 T helper (Th1) cells if they are activated in the presence of interleukin (IL)-12, produced mostly by macrophages and other non-T cells. Interferon- γ (IFN- γ), increased by IFN- γ -inducing factor (IL-18), also enhances the development toward a Th1 response. IFN- γ appears to increase the production of IL-12 and also the expression of receptors for IL-12. The generation of a Th1 response leads to the production of IL-2, IFN- γ , lymphotoxin tumor necrosis factor- β (TNF- β), and tumor necrosis factor- α (TNF- α). These inflammatory cytokines are important for a successful immune response to intracellular pathogens. Inappropriate Th1 responses have also been implicated in organ-specific autoimmunity such as in type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. The early presence of IL-4 in the activation of a helper cell prevents Th1 responses and enhances the development of a type 2 T helper cell (Th2) response. The source of the early IL-4 is not clear, but it may come from Th2 cells already present, natural killer 1⁺ T cells, or non-T cells, such as mast cells and eosinophils. The Th2 response results in production of IL-4, IL-5, IL-10, and IL-13 and enhances humoral immunity. Although the Th2 cells are critical for the immune response to helminths, in the developed world, Th2 cells are probably most singled out for their important role in allergic disease and asthma. IL-4 and IFN- γ inhibit the development of a type 17 T helper cell (Th17) response that promotes bacterial clearance and may play a role in the development of autoimmunity. IL-6 and transforming growth factor- β (TGF- β) promote the development of Th17 cells, whereas IL-23 expressed by macrophages augments expression of Th17 cytokines by memory but not naive CD4⁺ T cells. Various regulatory CD4⁺ T cells have also been described. Regulatory CD4⁺ T cells secreting TGF- β have the capability to suppress both Th1 and Th2 responses. Evidence suggests that, in addition to the cytokines present at the time naive CD4⁺ T cells are stimulated, the type of dendritic cell may regulate the differentiation of CD4⁺ T cells into Th1, Th2, or Th17 subsets.

CTLA4 have been associated with autoimmune endocrine diseases, further emphasizing the role of CTLA4 in the control of lymphocyte homeostasis.^{69,70} Programmed cell death 1 is another activation-induced inhibitory receptor that is expressed by T cells and binds B7 family members.⁷¹ Similar to CTLA4, programmed cell death 1 receptor engagement results in down-regulation of the immune response. Deficiencies of this gene have been associated with autoimmune diseases in animals and may be a possible gene contribution to human lupus.^{72,73} In addition to these negative signals, down-regulation of the T-cell response may be further ensured by decreases in surface expression of CD40 ligand, OX40, and 4-1BB after T-cell activation.^{61,66}

As discussed earlier in the context of self-tolerance, engagement of the TCR on a naive T cell in the absence of co-stimulation can result in different outcomes.⁵⁸ In some situations the outcome is a failure to stimulate, and the T cell is oblivious to this encounter. At other times, recognition can induce death (apoptosis) of the responding T cells or anergy, in which case the T cells are unable to respond to a subsequent encounter with the same antigen (tolerance). Memory T cells appear to be less dependent on co-stimulatory molecules. However, antagonists that interrupt co-stimulatory interactions have been shown to have profound effects even later in the course of an established immune response. Blockers of the CD28-B7 interaction (with CTLA4-Ig, anti-B7, or anti-CD28 monoclonal antibodies) or of the CD40 ligand-CD40 interaction

(with anti-CD40 ligand monoclonal antibodies), separately and together, are being investigated as therapies to treat autoimmune diseases and alloreactive responses after transplantation.⁷⁴⁻⁷⁷ However, the recent development of cytokine storm in healthy volunteers receiving an anti-CD28 monoclonal antibody demonstrates the potential risk of immunotherapy.⁷⁸

SUBSETS OF T HELPER CELLS

Although more sharply defined in mice than in humans, it is clear that T cells after activation may evolve into at least three major subsets of T helper cells, distinguished by their secreted cytokines (Fig. 13-10).^{40,56,57} Th1 cells mainly synthesize IL-2, IFN- γ , and TNF- α , as well as other inflammatory cytokines, such as lymphotoxin. Th2 cells primarily are distinguished by their secretion of IL-4, IL-5, and IL-13. Th17 cells represent a distinct lineage of T cells from either Th1 or Th2 cells and express IL-17A, IL-17F, and IL-22.⁷⁹⁻⁸² These major types of T helper cells appear to serve very different functions. Th1 cells primarily enhance cell-mediated immune responses, such as delayed-type hypersensitivity reactions, which frequently involve activation of macrophages and effector T cells. Th2 cells mainly provide help for B cells by promoting class switching and enhancing the production of certain IgG isotypes and production of IgE. The ability to mediate an effective immune response against certain intracellular pathogens and the pathogenesis of certain diseases appear to be strongly influenced by the

type of T helper cells involved. For example, in leishmaniasis and leprosy the development of a response polarized toward the Th1 pathway is important for successful immune defense. The development of an early Th2 response may result in the inability to clear the offending organism. Inappropriately developed and activated Th1 cells have been implicated in the pathogenesis of certain autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. Th2 cells appear to be important for certain immune responses.²⁰ Eradication of helminths is Th2 dependent. However, Th2 cells also appear to be involved in disease by driving allergic responses, such as IgE production and eosinophil activation in asthma (see Chapter 41).²⁰ Th17 cells function at the interface between the innate and adaptive immune response, secreting cytokines that are important in bacterial clearance and in the pathogenesis of autoimmunity. Evidence suggests that in collagen-induced arthritis, T-cell-mediated colitis, and experimental autoimmune encephalitis, Th17, as opposed to Th1, cytokines are critical for the induction and maintenance of inflammation.⁸³⁻⁸⁵

Th1, Th2, and Th17 subsets develop from the same T-cell precursor, which is a naive CD4⁺ T lymphocyte producing mainly IL-2 after stimulation with antigen. Considerable evidence indicates that the cytokine microenvironment is the primary determining factor for Th1, Th2, or Th17 differentiation (see Fig. 13-10).^{40,56,57,79,80} IL-12 and IFN- γ are most important in directing the development of Th1 cells that then go on to produce IFN- γ and TNF- α . IL-12 is produced by antigen-presenting cells (e.g., macrophages and dendritic cells) in response to Toll-like receptor stimulation by pathogens. IL-12 drives Th1 differentiation through signal transducer and activator of transcription 4 and the activation of a unique Th1 transcription factor known as T-box expressed in T cells.^{86,87} Microbial products frequently induce macrophages and NK cells to release IFN- γ , which is involved in driving development of Th1 cells from their naive precursors. IFN- γ up-regulates a component of the IL-12 receptor on naive and differentiating T cells.⁸⁸ However, some organisms, such as the measles virus, have the ability to down-regulate IL-12 production by macrophages and therefore possibly evade destruction by cell-mediated immune responses. Early production of IFN- γ by Th1 cells and NK cells has been related to the production of IFN- γ -inducing factor (IL-18), and this cytokine may synergize with IL-12 for maximal early production of IFN- γ and Th1 development.

In a similar but opposite manner, the presence of IL-4 early in the immune response induces Th2 cell development from naive precursors through signal transducer and activator of transcription 6, which leads to activation of the transcription factor GATA3 and up-regulation of IL-4 and IL-5.^{87,89} The effects of IL-4 in inducing Th2 development are dominant over Th1- and Th17-polarizing cytokines.^{56,57,90} Thus, if IL-4 levels exceed a threshold, Th2 development ensues, which leads to additional IL-4 production. Th2 cells do not respond to IL-12, which may be related to the ability of IL-4 to down-regulate expression of a component of the IL-12 receptor.

TGF- β and IL-6 are necessary for the differentiation of naive CD4⁺ T cells into Th17 cells.⁹⁰⁻⁹³ The retinoic acid

orphan nuclear receptor is the master transcription factor in the differentiation of Th17 cells.⁹⁴ Expression of retinoic acid orphan nuclear receptor is TGF- β and IL-6 dependent and is both necessary and sufficient to induce Th17 development in most CD4⁺ T cells.⁷⁹ Unlike T-box expressed in T cells and GATA3, the ligand of retinoic acid orphan nuclear receptor remains unknown. Using an IL-6-independent pathway, IL-21 and TGF- β can induce Th17 cells. IL-21 is also highly expressed by Th17 cells, and IL-21 production creates a positive feedback loop to amplify Th17 responses in vivo.⁹⁰ Despite the finding that IL-23 signaling is not required for Th17 commitment and early IL-17 secretion, IL-23 is important in amplifying and/or stabilizing the Th17 phenotype.⁷⁹

The cytokines produced by Th1, Th2, and Th17 subsets cross-regulate one another's development and function. For example, IFN- γ produced by Th1 cells inhibits the development of Th2 and Th17 cells as well as certain humoral responses.^{56,57,87} In a similar manner, IL-4 produced by Th2 cells inhibits Th1 and Th17 development and activation as well as macrophage activation by Th1 cytokines. IL-4 and IL-10 inhibit IL-12 production by dendritic cells and macrophages. In addition, it is possible that the transcription factors GATA3 and T-box expressed in T cells antagonize the development of the opposite T-cell subset by directly opposing each other's expression.^{87,89} TGF- β also inhibits the development of Th1 and Th2 phenotypes.⁸⁷

Following antigen exposure, naive T cells become activated, proliferate, and migrate to sites of inflammation. Although the majority of antigen-primed cells die, a population of memory T cells develops, which allows for a more rapid and effective secondary immune response upon reexposure to antigen.^{95,96} There are at least two subsets of memory T cells, possessing different functional and migratory capabilities compared with naive lymphocytes. The effector memory T cell represents a terminally differentiated cell that immediately produces cytokine following antigen exposure and lacks the lymph node homing receptors L-selectin and CCR7. Conversely, central memory T cells express L-selectin and CCR7 and can differentiate into effector memory cells after restimulation.

CD4⁺ T-CELL-B-CELL COLLABORATION AND REGULATION OF ANTIBODY PRODUCTION

A central event in the immune response is the antigen-specific interaction between a T helper lymphocyte and a B lymphocyte, which leads to their mutual activation. Although some antigens (usually nonproteins derived from bacteria) can activate B cells in a T-cell-independent fashion, the antibody response to most protein antigens requires that the relevant B cell must recognize antigen with its surface Ig receptor and receive certain activation signals from a CD4⁺ T helper cell. These signals include both secreted T-cell-derived lymphokines and those resulting from cell-cell contact. T-cell recognition of antigenic peptides bound to class II MHC molecules on the B-cell surface and co-stimulatory signals lead to T-cell activation and secretion of T helper lymphokines. Secretion is directed toward the site of contact with the B cell. Thus far, no combination of known T-cell-derived factors can fully replace

contact with the T helper cell, indicating that the interaction of surface molecules provides additional signals to the B cell that promote its activation. Numerous interacting molecules have been identified that could transmit signals in the T-cell–B-cell interaction (see Fig. 13-9).

Similar to the process of effective T-cell stimulation, which requires interaction of TCR with MHC/peptide and co-stimulatory signals, B cells also need more than one signal for activation to take place. The first signal is provided by antigen binding to surface Ig (BCR), and cross-linking of multiple receptors is usually required. The B cell then processes and presents the antigen via its class II MHC molecule to a cognate T helper cell that is specific for that MHC/peptide complex. A major second signal to the B cells is provided via CD40 on its surface through interaction with up-regulated CD40 ligand on the T helper cell. After receiving additional co-stimulatory signals from up-regulated B7-1 and B7-2 on the B cells, the activated T helper cell delivers cytokines in a focused manner to the antigen-specific B cell it is helping. Although many reciprocal receptor-ligand pairs are expressed on T cells and B cells, the signaling between CD40 ligand and CD40 has emerged as an obligatory and nonredundant interaction for functional T-cell–dependent B-cell activation to proceed.⁷⁵ The signals transduced by CD40 are essential for the prevention of apoptosis of antigen-specific B cells in the germinal center and required for B-cell proliferation and differentiation, isotype switching, and formation of memory B cells. Mutations in the CD40 ligand gene cause X-linked hyper-IgM syndrome, characterized by absent or low levels of IgG, IgA, and IgE (Ig isotypes that require T-cell help) but normal or elevated levels of IgM. Because T-cell activation also requires co-stimulatory signals through CD40 ligand, these individuals demonstrate defects in T-cell-mediated immunity and defective T-cell activation.⁹⁷

T-cell help is required for effective antibody responses, especially those involving specific high-affinity antibodies of the IgG, IgA, and IgE isotypes. However, as emphasized earlier, T-cell–B-cell signaling is clearly bidirectional. After resting T cells are activated, which frequently requires specialized antigen-presenting cells such as dendritic cells, antigen-specific B cells may be the most efficient presenters of determinants of a specific antigen.⁹⁸ The helper CD4⁺ T cell recognizes a processed antigen presented on the B cell in the context of class II MHC antigens. The B cell focuses antigen for antigen-specific help by binding antigen through its Ig receptor, internalizing and processing the antigen, and presenting the derived peptides with class II MHC molecules (see Fig. 13-9). It is important to emphasize that the epitope on the native antigen recognized by the B cell is almost always different from the peptide epitope recognized by the helper CD4⁺ T cell.

Subsequent to T-cell recognition, the T cell is activated, and help for B-cell proliferation and differentiation can be provided. T-cell help is critically dependent on the T-cell release of various cytokines, as described earlier. These cytokines have marked effects on B-cell maturation, especially in determining which isotypes will be produced by the B cell. The reciprocal surface molecular interactions, the directed nature of T-cell cytokine release, and the controlled local action of these molecules result in “focused T-cell

help” without generalized bystander activation of surrounding B cells.

GENERATION AND REGULATION OF CELL-MEDIATED IMMUNE RESPONSES

Cell-mediated cytotoxicity is an essential defense against intracellular pathogens, including viruses and certain bacteria and parasites. Cytotoxic T cells are stimulated by presented endogenous antigens, most of them derived from intracellular pathogens and associated with class I MHC molecules. In contrast to most helper cells that express CD4, cytotoxic T cells are usually CD4[−]CD8⁺. The recognition of the antigen presented by class I MHC molecules triggers the T cell to express receptors for IL-2. Although some cytotoxic lymphocytes are able to produce their own IL-2, most depend on IL-2 produced by helper CD4⁺ T cells of the Th1 type. The binding of IL-2 and possibly other cytokines leads to some proliferation and to the development of cytotoxic function. CD4⁺ T helper cells (Th1 type) provide additional signals and cytokines for the generation of a maximal cytotoxic response.

Activated effector cells are capable of delivering a lethal message to a target cell, separating from their dying target, and moving on to strike a new target. This creates a very efficient system of killing unwanted cells. Several mechanisms are involved in the actual killing process.⁹⁹⁻¹⁰² For example, cytotoxic T cells can directly signal their targets to undergo apoptosis through the interaction of FAS ligand, expressed on the surface of activated T cells, with FAS on the target cell. The cytotoxic T cell also produces substances such as lymphotoxin (TNF-β), trimers of which bind to receptors on the cellular targets and signal for apoptosis. During binding to the target cell, the cytotoxic CD8⁺ T cells also release the contents of their granules, which include perforins and granule-associated serine esterases (granzymes), toward the adjacent membrane of the target cell. Released perforins assemble on the surface of the target cell and perforate the target cell plasma membrane, resulting in lysis and the entry of enzymes. The transmembrane channel created by the perforins resembles the membrane attack complex of the complement cascade. After entry into the target cell, activated granzymes released from the cytotoxic T cell activate proteins that mediate apoptosis and cause other types of cell damage.

SPECIFIC IMMUNE RESPONSES IN THE LUNG

LYMPHOCYTE POPULATIONS AND TRAFFICKING IN THE LUNG

The lung in healthy individuals usually harbors only a small number of lymphocytes.^{103,104} The location of CD4⁺ and CD8⁺ αβ T cells can be arbitrarily separated into four compartments: bronchoalveolar space, bronchus-associated lymphoid tissue (BALT), lung interstitial tissues, and intravascular space. Although lymphocytes from these different positions may be involved in lung immune responses, there is no clear indication that these cells represent a

resident lymphocyte population in the lung in humans. More likely, these lymphocytes belong to the recirculating lymphocyte pool. In contrast, $\gamma\delta$ T cells have been localized to intraepithelial positions in the lung, and these cells may selectively reside in the lung.²⁵

In a normal nonsmoking individual, lymphocytes account for approximately 10% to 15% of the bronchoalveolar cells obtained during bronchoalveolar lavage.¹⁰⁴ The number of bronchoalveolar lymphocytes can increase markedly in inflammatory diseases involving the alveoli and the interstitium, such as in sarcoidosis and hypersensitivity pneumonitis (see Chapters 64 and 66). Most bronchoalveolar lymphocytes are T cells, and essentially all of these cells express memory cell markers (e.g., CD45RO and low CD62L), indicating previous activation.¹⁰⁵ In disease, a significantly increased percentage of these T cells, compared with those in peripheral blood, also express markers of recent activation, such as HLA-DR, IL-2 receptor (CD25), and CD69.

BALT is a localized collection of lymphocytes in the subepithelial area of bronchi, analogous to gut-associated lymphoid tissue (e.g., Peyer patches).¹⁰⁶ These lymphoid aggregates are separated from the airway lumen by a lymphoepithelium composed of flattened epithelial cells, which lack cilia. BALT also contains HEVs facilitating the recirculation of lymphocytes between blood and lymph. However, unlike gut-associated lymphoid tissues in the form of Peyer patches, which are present in all mammals, BALT is found only in some mammalian species. Indeed, it is usually absent in humans as long as there is no respiratory tract infection. Evidence suggests that BALT may appear in patients after chronic airway inflammation and chronic obstructive pulmonary disease.^{107,108}

The interstitium of the normal lung contains few lymphoid cells, and most of these are not T cells. The majority of interstitial lymphocytes are NK cells, which constitute 10% to 15% of circulating lymphocytes. These cells do not express TCR or Ig but express markers characteristic of both T-cell and myelomonocytic lineages.⁷ NK cells recognize and kill tumor cells and virus-infected cells in a nonspecific manner.⁷ These cells also kill targets coated with antibodies via surface receptors for IgG (FCGR3 or CD16) in a process known as “antibody-dependent cellular cytotoxicity.” Furthermore, NK cells can also be an important source of cytokines (e.g., INF- γ , TNF- α , and *granulocyte-macrophage colony-stimulating factor* [GM-CSF]) early in the immune response.

$\gamma\delta$ T cells constitute only 0.5% to 10% of the peripheral blood lymphocyte population in humans.²⁵ However, they represent an enriched T-cell population in the pulmonary epithelium, intestinal epithelium, and skin. Unlike $\alpha\beta$ T cells, epithelial $\gamma\delta$ T cells do not recirculate and appear to represent resident pulmonary lymphocytes. The population of $\gamma\delta$ T cells in the lung of normal adult C57BL/6 mice is approximately 2 to 5×10^4 cells, with the majority being either V γ 4⁺ or V γ 1⁺.¹⁰⁹ Importantly, the different $\gamma\delta$ T-cell subsets are thought to have different functional capabilities. For example, in a murine model of asthma, V γ 1⁺ $\gamma\delta$ T cells enhance airway hyperresponsiveness, whereas V γ 4⁺ $\gamma\delta$ T cells suppress this response.¹¹⁰ The pulmonary $\gamma\delta$ T cells preferentially interact with F4/80⁺ macrophages and MHC class II-expressing dendritic cells, suggesting that

$\gamma\delta$ T cells represent a primitive line of defense evolved to protect epithelial integrity and provide a possible bridge between innate immunity and acquired immune responses. $\gamma\delta$ T cells have also been implicated in the regulation of various immune responses in the lung through IL-22 expression.¹¹¹

The distribution and trafficking of lymphocytes is governed by interactions between molecules on the lymphocyte surface and ligands present on vascular endothelial cells. The migration of lymphocytes from the bloodstream is not a random event, and this migration appears to be restricted to lymphoid tissue and areas of inflammation.⁸ Naive T cells lack the ability to initiate an antigenic response until they are activated within a secondary lymphoid organ. Evidence indicates that their initial interaction with an antigen entering through the lung takes place in the surrounding lymphoid tissues and not in the lung directly. Naive and resting lymphocytes represent the major population that recirculates from blood to lymph via HEVs,¹¹² with the initial attachment mediated by the homing receptor L-selectin (CD62L) to peripheral lymph node addressin and glycosylation-dependent cell adhesion molecule-1 on the surface of endothelial cells.⁸ This interaction results in lymphocyte tethering and rolling along the endothelial surface. Subsequent binding of chemokines (e.g., stromal cell-derived factor-1 α , 6-C-kine, and macrophage inflammatory protein-3b) to G protein-coupled receptors on the lymphocyte surface leads to activation of integrin molecules (lymphocyte function-associated antigen-1).⁸ After activation, lymphocyte function-associated antigen-1 binds to intercellular adhesion molecule-1 on the vascular endothelium, resulting in firm adhesion.⁸ This is followed by transendothelial migration of the lymphocyte into the lymphoid tissue. A second family of G protein-coupled receptors, known as sphingosine-1-phosphate receptor-1, is required for lymphocyte egress from the lymph node.¹¹³ As stated earlier, BALT consists of diffuse lymphoid aggregates found in the bronchial mucosa of most mammals.¹⁰⁶ In contrast to HEVs in other secondary lymphoid organs, BALT HEVs express high levels of vascular cell adhesion molecule-1, which binds $\alpha_4\beta_1$ integrin on T cells. Thus an adhesion cascade exists involving L-selectin/peripheral lymph node addressin, $\alpha_4\beta_1$ integrin/vascular cell adhesion molecule-1, and lymphocyte function-associated antigen-1/intercellular adhesion molecule-1, which targets specific lymphocyte populations to BALT and other bronchopulmonary tissues.^{8,106}

Effector and memory T lymphocytes appear to have distinct pathways of lymphocyte recirculation compared with naive lymphocytes.⁸ Effector T cells, especially after activation in the lymphoid tissues, travel to regions of inflammation where chemokines and other chemotactic molecules are generated by the underlying inflammatory process.⁸ Expression of various adhesion molecules on the lymphocyte and binding to their appropriate molecular targets expressed on inflamed vascular endothelium allow cells to enter sites of inflammation.⁸ The expression of intercellular adhesion molecule-1, P-selectin, and vascular cell adhesion molecule-1 on the surface of inflamed vascular endothelium is involved in lymphocyte entry into areas of inflammation.⁸ Tissue tropism is established by the expression of different combinations of adhesion molecules that allow a

different subset of effector cells to home to different sites. For example, circulating memory lymphocytes specific for skin-associated antigens express the cutaneous lymphocyte antigen.⁸ Conversely, memory for intestinal antigens has been localized to circulating lymphocytes expressing high levels of $\alpha_4\beta_7$ integrin.⁸ Thus memory T cells display selective homing to the tissue type where antigen was first encountered.

ANTIBODY-MEDIATED IMMUNE RESPONSES IN THE LUNG

Immune Response to Extracellular Pathogens

The humoral immune response is adapted for elimination of extracellular pathogens. An example of an antibody-mediated immune response is that which takes place after exposure to *Streptococcus pneumoniae*. This bacterium frequently colonizes the nasopharynx and is the most common cause of community-acquired pneumonia.¹¹⁴ Pneumococci gain access to the lower respiratory tract via aspiration. The upper airway is equipped with clearance mechanisms (e.g., mucociliary clearance and cough) that effectively eliminate most inhaled or aspirated bacteria from the airways (see Chapter 11). If the aspirated pneumococcus evades the upper airway defenses, the pathogen first encounters the mucosal humoral immune system. IgA provides the first line of defense against infectious agents, with IgG and IgM being less important in the bronchial secretions. The major functions of secretory IgA include the prevention of microbial adherence to the epithelial surface and the promotion of the agglutination of microorganisms. The combination of inhibition of adhesion and microbial agglutination favors the clearance of pneumococci via mechanical forces. Unlike IgG, IgA is unable to activate complement and is not an effective opsonin.

The first exposure of the host to the pneumococcus generates a primary humoral response. Bacteria in the lung are bound by antigen-presenting cells, which migrate to secondary lymphoid organs, where antigens are processed and presented with class II MHC molecules to CD4⁺ T cells (Fig. 13-11). After TCR binding and effective co-stimulation enhanced by an inflammatory environment, specific T cells are activated and multiple T helper cytokines are elaborated. During this process, naive B cells in the lymph node bind unprocessed antigen via surface IgM and present peptide fragments to specific T helper cells via class II MHC molecules. T-cell–B-cell interactions in the germinal centers lead to additional T-cell and full B-cell activation, characterized by clonal proliferation, isotype switching, and differentiation of B cells into secreting cells and memory cells. Subsequently, specific antibody, activated T cells, and perhaps some activated B cells circulate back to the lung to combat the pneumococcal infection.

In the area of infection, IgG1, IgG3, and IgM specific for intact pneumococcal antigens activate the complement system, resulting in some bacterial cell lysis. More important, antibody and complement act as opsonins, enhancing phagocytosis of encapsulated microorganisms. The release of mediators from activated T cells also enhances the antibacterial capacity of recruited nonspecific inflammatory cells in the lung. These events take place over a 4- to 7-day

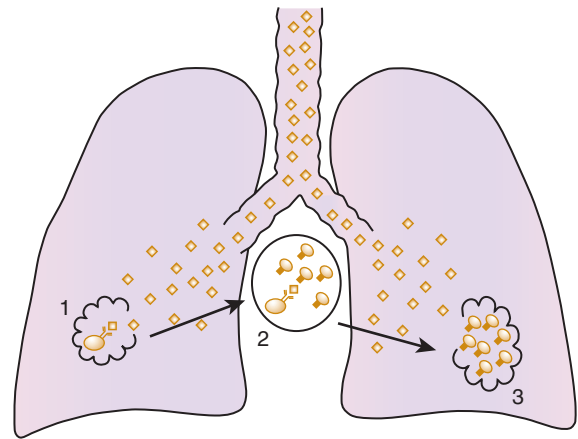


Figure 13-11 Immune responses in the lung. Antigen (e.g., bacterial pathogen) enters the lung. Microbial products create an inflammatory environment. **1**, Antigen is taken up by nonspecific phagocytic cells and transported to regional lymph nodes. **2**, In the lymph nodes a primary immune response is generated. Antigen-specific T cells are stimulated, and initial T helper cell–B-cell interactions and antibody production take place in the germinal centers. **3**, Antibodies, T helper cells, and effector cells circulate back to the lung for the immune response to target the pathogen. Trafficking of inflammatory cells is enhanced by the production of chemokines and other chemotactic factors and involves interactions of leukocytes with endothelial cells in the area of inflammation. In the process of the initial immune response, memory T cells and B cells are generated. This allows for the generation of a more effective secondary immune response if the same pathogen is encountered at a later time.

period and characterize the initial phase of a primary response. The time needed for peak response is approximately 7 to 10 days. The presence of memory B and T cells ensures that repeat exposure to *S. pneumoniae* results in a secondary immune response, which is characterized by a shorter lag phase, resulting in a more rapid response of greater magnitude and longer duration. Clinically, pneumococcal vaccination, which induces a primary humoral response, has decreased the rates of invasive pneumococcal disease in both children and adults.¹¹⁵

Immune Response to Autoantigens

Autoimmune disorders result when the normal mechanisms of immune self-tolerance fail. Essentially all autoimmune diseases, including antibody-mediated autoimmune diseases, appear to be dependent on the inappropriate activation of autoreactive CD4⁺ T cells as well as on the autoreactive B cells responsible for the pathogenic autoantibodies. One example of an autoimmune disease involving the lung is Goodpasture syndrome. This syndrome is characterized by pulmonary hemorrhage and glomerulonephritis, which are associated with elevated levels of IgG antibodies directed against basement membrane antigens. In various studies, pathologic damage has been shown to be dependent on the binding of these autoantibodies, which are primarily directed against the noncollagenous domain ($\alpha 3$ chain) of type IV collagen in basement membrane.¹¹⁶⁻¹¹⁸ Immunofluorescent staining with anti-human IgG antibodies usually reveals a linear deposition of IgG in the glomerular and alveolar basement membranes. Despite the widespread distribution of type IV collagen in the body, disease expression is mostly limited to the lungs and kidneys. This limited disease expression suggests the possibility that other factors

allow exposure of this autoantigen selectively in alveolar or glomerular basement membranes. In this regard, influenza A2 infection, hydrocarbon inhalation, and cigarette smoking have been associated with the initial episode of diffuse alveolar hemorrhage and exacerbation of disease in the setting of elevated levels of anti-basement membrane antibodies.¹¹⁹ Much is now known regarding how autoantibodies cause damage in an autoimmune disease such as Goodpasture syndrome. More recently, HLA associations and the B- and T-cell epitope have been identified.¹²⁰ *HLA-DRB1*15:01* is strongly associated with the development of Goodpasture syndrome, whereas *HLA-DRB1*07:01* and *DRB1*01:01* confer protection against development of this disease. In addition, the T-cell epitope has been mapped to the amino-terminal region of the $\alpha 3$ chain of type IV collagen.¹²¹ As noted earlier, activation of both autoreactive CD4⁺ T cells and autoreactive B cells appears to be necessary for a pathologic autoimmune response. These autoreactive CD4⁺ T cells require CD28 co-stimulation, because blockade of this co-stimulatory molecule reduces anti-basement membrane antibody production and prevents the development of experimental autoimmune glomerulonephritis.¹²²

Studies have identified an autoimmune cause underlying the development of acquired pulmonary alveolar proteinosis.¹²³ This disorder is characterized by the accumulation of a periodic acid–Schiff staining, granular, eosinophilic material within the alveolar space (see Chapter 70). Based on the development of pulmonary alveolar proteinosis in mice rendered deficient in GM-CSF, a fundamental role of this factor in surfactant homeostasis has been discovered.¹²⁴ In addition, the presence of neutralizing IgG autoantibodies directed against GM-CSF have been identified in the bronchoalveolar lavage fluid and serum of all patients with acquired pulmonary alveolar proteinosis, but not in individuals with the congenital or secondary form of the disorder or in normal control subjects.¹²⁵ The detection of this IgG autoantibody is highly sensitive and specific and thus useful in the diagnosis of the acquired form of this disease. More recently, mutations in the ligand-binding α chain of the GM-CSF receptor have been identified in pediatric patients with pulmonary alveolar proteinosis.¹²⁶

Immune Response in Allergic Disease

Atopic asthma results when an immune response and IgE antibodies are directed against normally harmless proteins present in the environment (see Chapter 41). Numerous cell types, including mast cells, eosinophils, macrophages, and CD4⁺ T lymphocytes, as well as the specific IgE-secreting B cells, are important in the development of allergy and asthma. The CD4⁺ T cells, which accumulate in the lungs of asthmatics, display a Th2 phenotype,¹²⁷ and studies using murine asthma models have shown that allergic airway inflammation is dependent on Th2-type CD4⁺ T cells. As discussed earlier, the development of a Th2 response is prompted by exposure of naive CD4⁺ T cells to IL-4 at the beginning of an immune response.^{56,57,87,89} In the presence of high expression of IL-4 and low IFN- γ , these Th2 CD4⁺ T cells induce isotype switching in antigen-specific B cells to IgE.¹²⁸ The elevated levels of IgE in the asthmatic are essential for the immediate hypersensitivity response. The presence of IL-4 and IL-5 and the production of various chemokines during T-cell activation also enhance accumu-

lation of eosinophils and basophils in the airways. Studies in murine models of allergic asthma have suggested an important role for another Th2 cytokine, IL-13, which was capable of inducing the pathologic features of asthma independent of IgE and eosinophils.¹²⁹ Related to the Th2 dependence of asthma in humans, susceptibility to disease has been linked to loci on chromosome 5q, which contains the genes for IL-4 and IL-13.¹³⁰ Studies also suggest that genetically determined abnormalities in antigen-presenting cells may also play a role in the development of allergic reactions. In atopic individuals, antigen-presenting cells were shown to underproduce IL-12 or overproduce prostaglandin E₂, which favors a Th2 response.¹³¹

CELL-MEDIATED INFLAMMATORY RESPONSES IN THE LUNG

Cell-mediated immune responses can be divided into two major categories: (1) CD4⁺ T cells that mediate delayed-type hypersensitivity reactions and (2) CD4⁺ T cells that help effector T cells with cytotoxic function.

Granulomatous Lung Disease

Granulomas are characteristic of infections that live at least partly intracellularly, such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and organisms that are large and persistent. There is considerable evidence to suggest that CD4⁺ T cells and the elaboration of Th1 cytokines are required for maximal granulomatous inflammation in the response to these infections. The triggering event in the development of noninfectious granulomatous lung disease is the deposition of antigen in the lung parenchyma. In the case of chronic beryllium disease^{67,132} and hypersensitivity pneumonitis (see Chapter 64), the antigenic stimulus is known. In sarcoidosis, the inciting agent is unknown, although the immunopathogenic events are believed to be the same (see Chapter 66).¹³³ Thus the unknown antigen is likely to be engulfed by antigen-presenting cells (i.e., dendritic cells and macrophages) in the lung parenchyma and presented to naive CD4⁺ T cells in the peripheral lymphoid organs. In the absence of IL-4, exposure of these activated naive CD4⁺ T cells to IL-12 released by macrophages directs the T cell toward a Th1 response.^{56,57,87,89} The development of a Th1 response is also influenced by early release of IFN- γ through the up-regulation of IL-12 production by macrophages and through the up-regulation of receptors for this cytokine on Th1 cells.

Production of chemokines and other chemotactic factors at the site of inflammation in the lung directs migration of activated effector CD4⁺ T cells to the lung. The Th1 cytokines and other mediators produced by these T cells are responsible for the recruitment and activation of macrophages and other nonspecific inflammatory cells. The accumulation of inflammatory cells within the alveolus (alveolitis) appears to be the initial lesion characterizing sarcoidosis and other granulomatous lung diseases. In sarcoidosis the accumulated CD4⁺ T cells (obtained at bronchoalveolar lavage) include expanded subsets, identified by expression of particular TCR V β and V α regions. Within these subsets are expansions of T-cell clones, each with a unique TCR β chain and α chain sequence. The presence of these oligoclonal expansions indicates a T-cell response to

conventional peptide antigens, and the presence of different T-cell clones with related TCRs indicates a response to the same antigen. Both the HLA haplotype (the presenting class II MHC molecule) in an individual and the stimulating antigen(s) will determine the TCRs used in these T-cell responses. In chronic beryllium disease, particular HLA-DP alleles (e.g., *HLA-DPB1* alleles expressing a glutamic acid residue at the 69th position of the β -chain) appear to be most important in the presentation of antigen to beryllium-specific T cells,¹³⁴ and this likely explains the increased disease susceptibility in individuals with the same HLA-DP alleles.¹³⁵ CD4⁺ T-cell clones expressing similar TCRs (with the same V regions and highly similar CDR3 regions) have been noted to be expanded in the lungs of different individuals with chronic beryllium disease, reflecting similarities in presenting MHC class II molecules and the same stimulating antigen (beryllium).¹³¹ In sarcoidosis an association between the TCR usage of V α 2.3 and HLA-DR17 (DR3) expression has been reported.¹³⁶ It is important to emphasize that the pathologic T-cell responses in these diseases are compartmentalized to the lung, because the same T-cell clones are either absent or rare in the peripheral blood.¹⁰⁵

The major effector cells of inflammation in chronic beryllium disease, sarcoidosis, and other granulomatous diseases appear to be macrophages primarily derived from circulating monocytes during the process of inflammation. Activated alveolar macrophages express MHC class II molecules and may contribute to antigen presentation. Noncaseating granulomas form by coalescence of activated macrophages, which can also fuse to form multinucleated giant cells. CD4⁺ T cells predominate in the center of the noncaseating granuloma, with CD8⁺ T cells located at the periphery of the granulomatous response.

CYTOTOXIC T-CELL REACTIONS IN THE LUNG

Cytotoxic T lymphocytes (CTLs) are critical in the recognition and elimination of virus-infected cells and tumor cells as well as in allograft rejection. These cells predominantly express CD8, although CD4⁺ CTLs and NK cells may also be involved in cytotoxic T-cell responses. CD4⁺ T helper cells are almost always required for full expression of a cytotoxic T-cell reaction. CTL responses have been detected in humans after infection with numerous viruses, including respiratory syncytial virus, parainfluenza, and influenza A and B. Once a CD8⁺ CTL recognizes a respiratory syncytial virus-infected cell, there are at least three distinct mechanisms by which the CTL can induce cell death.⁹⁹⁻¹⁰² As discussed earlier, CTLs can secrete cytotoxic cytokines such as TNF- α and IFN- γ in the vicinity of the target cell. In addition, CTLs can release granule enzymes, including perforins and granzymes, which cause pore formation in the membrane of the target cell and enzyme-mediated apoptosis. Finally, CTLs can induce cell death via the interaction of FAS ligand on its surface with FAS on the target cell. CD4⁺ CTLs do not have cytotoxic granules and primarily use FAS-mediated apoptosis as their mechanism of cytotoxicity.

NK cells have a role complementary to that of CTLs in combating virus-infected cells or tumor cells.⁷ NK cells appear to form the first line of defense against viral infection, providing nonspecific cytotoxic activity. These cells

differ from CTLs in their lack of TCRs, and they recognize their targets in a non-MHC-restricted fashion. However, the mechanism of NK cell killing appears to be similar to that employed by CD8⁺ CTLs. In addition, NK cells have receptors for IgG (FCGR3; CD16) and can bind to the Fc region of antibody attached to the surface of a target cell and mediate antibody-dependent cellular cytotoxicity.

Key Points

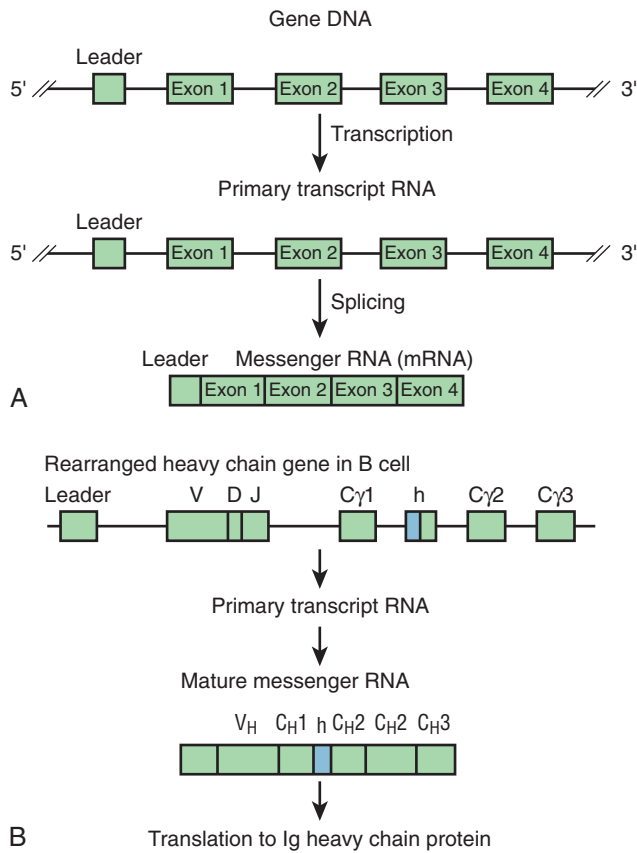
- The health of the lung and the individual depends on a functional immune system to protect against microbial invasion.
- Pathogens are targeted by both specific humoral immune responses and a variety of cell-mediated responses that result in activation and accumulation of leukocytes.
- Although effector leukocytes may be both antigen specific and antigen nonspecific, essentially all of these immune responses are dependent on specific T (helper) cells for full expression and maximal effect.
- The vast array of pathogens and their large number of strategies to subvert the immune system is combated by a system of defense with remarkable specificity and yet enormous diversity. These capabilities are achieved through unique molecular mechanisms of the B-cell receptor and the T-cell receptor repertoire formation, which are fundamental to understanding the adaptive immune response.
- The regulation of specific immune responses is dependent on cytokine expression and cellular interactions of various regulatory T cells with effector T-cell subsets.
- In occasional individuals, the defense system may break down and, in others, aberrant immune responses appear to contribute to various pathologic conditions relevant to the lung and respiratory tract.
- Granulomatous lung diseases (e.g., sarcoidosis and chronic beryllium disease) are characterized by an excessive type 1 T helper CD4⁺ T-cell response, whereas allergic diseases (e.g., asthma) are characterized by excessive type 2 T helper responses.
- Type 17 T helper polarized immune responses are typically seen in bacterial pneumonia and in subjects with severe, corticosteroid-unresponsive asthma.
- Additional knowledge of the structure and function of the immune system will likely provide new insight into lung disease development and lead to new therapeutic approaches.

Complete reference list available at *ExpertConsult*.

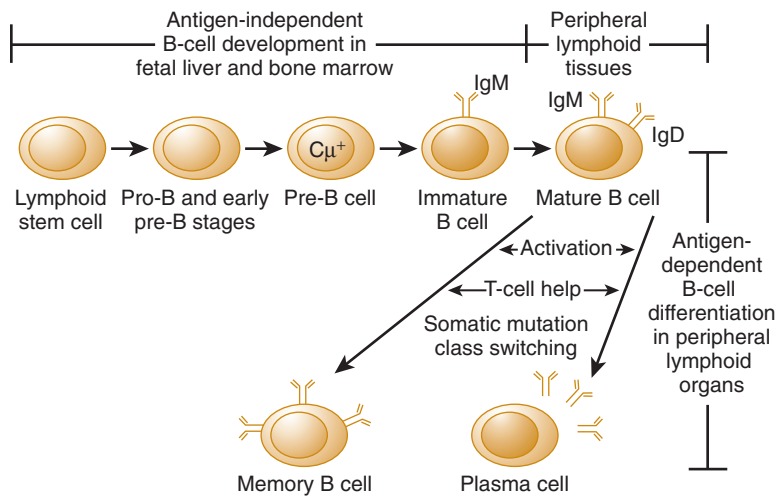
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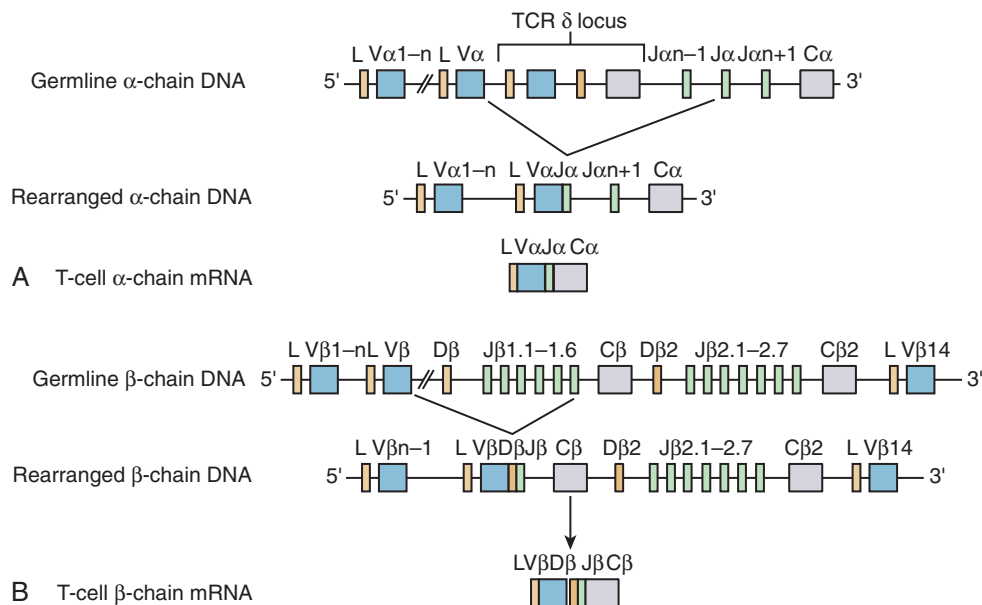
eFIGURE IMAGE GALLERY



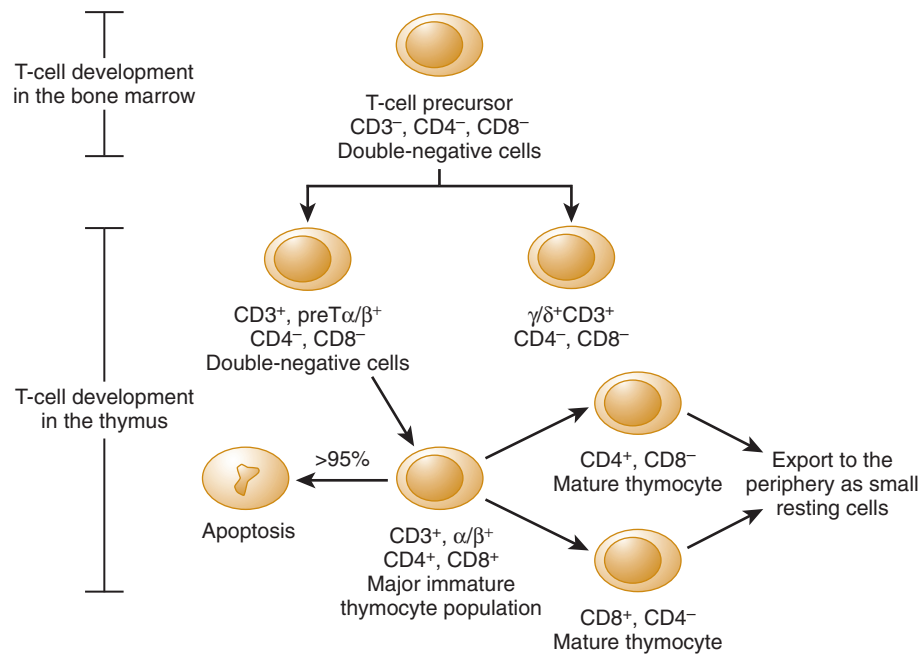
eFigure 13-1 Genes encoding immunoglobulin molecules. A, Characteristic structure of genes encoding a membrane protein. Note that the exons code for discrete structural regions of the protein, for example, an external domain, a transmembrane region, and a cytoplasmic tail. **B,** Corresponding structure of a rearranged immunoglobulin (Ig)G heavy chain gene. The leader–V region segment of DNA was initially located upstream on the same chromosome and has rearranged proximal to the DJ segment, which is proximal to the IgG C γ exons. Processing of the primary transcript brings all of the coding regions together in the messenger RNA molecule for translation of the protein. (Adapted from *MKSAP in the specialty of rheumatology*, Philadelphia, 1993, American College of Physicians, p 7.)



eFigure 13-2 B-cell development. Antigen-independent differentiation of the B cell in the adult bone marrow is shown from left to right. Pro-B and early pre-B stages involve the rearrangement of immunoglobulin (Ig) heavy chain D-J and V-DJ gene segments and transient expression of a pre-B-cell receptor (BCR). Subsequent rearrangement of immunoglobulin (Ig) light chain genes in the later pre-B cell allows for the development of a BCR-expressing immature B cell. The interaction of the mature naive B cell with antigen in the germinal centers of peripheral lymphoid organs and in the presence of T-cell help allows for somatic mutation of the Ig genes (affinity maturation), isotype switching, generation of B cells that are capable of high-rate IgG secretion, and generation of memory B cells.



eFigure 13-3 Rearrangement of genes encoding the T-cell receptor (TCR). **A,** In the germline TCR α chain gene complex, before any rearrangement in T cells, approximately 40 to 50 V α gene segments are located upstream of the multiple J α and C α gene segments. Within the TCR α chain locus is the TCR δ gene complex (expressed in $\gamma\delta$ T cells), which is deleted when V α genes are rearranged. During T-cell development, V α genes are rearranged to downstream J α gene segments to form a functional α chain gene. This process is similar to that described for immunoglobulin gene rearrangements. Expression of RNA and RNA processing allows for generation of TCR α chain messenger RNA (mRNA). **B,** A similar process allows for rearrangement of TCR β chain genes in the pre-T cell during T-cell development. In both **A** and **B**, nucleotide additions and deletions at the margins of the rearranging segments are not shown.



eFigure 13-4 T-cell development and maturation in the thymus. The rearrangement of the TCR β chain genes in the pre-T cell and then TCR α chain genes results in generation of a remarkably diverse TCR repertoire, expressed at the stage of the major immature thymocyte. These cells express TCR at relatively low density and are double positive for both CD4 and CD8. The repertoire is positively selected for (low) affinity to self-major histocompatibility complex (MHC) (self-MHC restriction). Cells with TCR that do not undergo positive selection die in the thymus by apoptosis. Immature and mature thymocytes with high affinity for self-MHC/peptide complexes are negatively selected and undergo apoptosis (deleted). Overall, greater than 95% of immature thymocytes fail to mature for export to the peripheral lymphoid organs. As immature thymocytes mature, they maintain CD4 expression and down-regulate CD8 (MHC class II restricted) or maintain CD8 expression and down-regulate CD4 (MHC class I restricted).

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RESPIRATORY PATHOLOGY AND INFLAMMATION

14

PATHOLOGY: MALIGNANT AND INTERSTITIAL LUNG DISEASES

W. DEAN WALLACE, MD • WILLIAM D. TRAVIS, MD

INTRODUCTION LUNG CANCER

Adenocarcinoma
Squamous Cell Carcinoma
Neuroendocrine Tumors
Large Cell Carcinoma

Adenosquamous Carcinoma
Carcinomas with Pleomorphic,
Sarcomatoid, or Sarcomatous Elements

PLEURAL TUMORS

Solitary Fibrous Tumor
Malignant Mesothelioma

INTERSTITIAL LUNG DISEASES

Idiopathic Interstitial Pneumonias
Other Interstitial Lung Disease

INTRODUCTION

This chapter focuses on three areas that have received considerable interest recently. The first is the use of small biopsies and cytology, which are used not only for tissue diagnosis but also for molecular studies in lung cancer. The second is the classification of lung tumors, which has changed considerably based on several consensus conferences. This includes more precise classification of lung adenocarcinomas, which frequently have a mixture of subtypes. This is important for diagnosis, predicted outcome, and therapy. The third area is the field of *interstitial lung disease* (ILD), which now has a firm foundation for clinical studies and evaluating new therapies. These are areas which have seen considerable advances in the past 5 years. Topics such as the pathology of asthma, chronic obstructive pulmonary disease, pneumonia, and infectious disease are addressed in other chapters of this book and in the key references.

LUNG CANCER

Lung cancer is the most common cause of major cancer incidence and mortality worldwide in men, while in women

it is the third most common cause of cancer incidence and the second most common cause of cancer mortality.¹ In 2013, the American Cancer Society estimated that lung cancer would account for more than 228,190 new cases in the United States and 159,480 cancer deaths.²

The pathologic diagnosis of lung cancer is established either by a histologic or cytologic approach.³⁻⁶ Major changes in the diagnosis of lung cancer were recommended by the 2011 *International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society* (IASLC/ATS/ERS) International Multidisciplinary Classification of Lung Adenocarcinoma^{5,7} (Table 14-1). Changes have been made in the diagnostic approach to small biopsies and cytologies as well as to resection specimens (eTable 14-1).^{4,5,7} This is of great importance because 70% of lung cancer patients present with advanced stage disease and the diagnosis is based on small specimens. There are four major histologic types of lung cancer including squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma.⁶ These major types can be classified into more specific subtypes such as the lepidic predominant subtype of adenocarcinoma or the basaloid variant of squamous cell carcinoma.^{4,5,7,7a}

VASCULITIS

Granulomatosis with Polyangiitis

Eosinophilic Granulomatosis with Polyangiitis

Microscopic Polyangiitis

PULMONARY HYPERTENSION**eTable 14-1** Proposed IASLC/ATS/ERS Classification for Small Biopsies/Cytology

2004 WHO Classification	Small Biopsy/Cytology: IASLC/ATS/ERS
ADENOCARCINOMA	<i>Morphologic adenocarcinoma patterns clearly present:</i> Adenocarcinoma, describe identifiable patterns present (including micropapillary pattern not included in 2004 WHO classification) <i>If pure lepidic growth—mention an invasive component cannot be excluded in this small specimen.</i> <i>Morphologic adenocarcinoma patterns not present (supported by special stains):</i> Non–small cell carcinoma, favor adenocarcinoma Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded) Mucinous adenocarcinoma (describe patterns present) Adenocarcinoma with fetal pattern Adenocarcinoma with colloid pattern Adenocarcinoma with (describe patterns present) and signet ring features Adenocarcinoma with (describe patterns present) and clear cell features
Mixed subtype Acinar Papillary Solid No 2004 WHO counterpart—most will be solid adenocarcinomas Bronchioloalveolar carcinoma (nonmucinous) Bronchioloalveolar carcinoma (mucinous) Fetal Mucinous (colloid) Signet ring Clear cell	
SQUAMOUS CELL CARCINOMA	<i>Morphologic squamous cell patterns clearly present:</i> Squamous cell carcinoma
Papillary Clear cell Small cell Basaloid No 2004 WHO counterpart	<i>Morphologic squamous cell patterns not present (supported by stains):</i> Non–small cell carcinoma, favor squamous cell carcinoma
SMALL CELL CARCINOMA	Small cell carcinoma
LARGE CELL CARCINOMA	Non–small cell carcinoma, not otherwise specified (NOS)
Large cell neuroendocrine carcinoma (LCNEC)	Non–small cell carcinoma with neuroendocrine (NE) morphology (positive NE markers), possible LCNEC
Large cell carcinoma with NE morphology (LCNEM)	Non–small cell carcinoma with NE morphology (negative NE markers)—see comment Comment: This is a non–small cell carcinoma where LCNEC is suspected, but stains failed to demonstrate NE differentiation.
ADENOSQUAMOUS CARCINOMA	<i>Morphologic squamous cell and adenocarcinoma patterns present:</i> Non–small cell carcinoma, NOS, (comment that glandular and squamous components are present) Comment: This could represent adenosquamous carcinoma.
No counterpart in 2004 WHO classification	<i>Morphologic squamous cell or adenocarcinoma patterns not present but immunostains favor separate favor glandular and adenocarcinoma component</i> Non–small cell carcinoma, NOS, (specify the results of the immunohistochemical stains and the interpretation) Comment: This could represent adenosquamous carcinoma.
SARCOMATOID CARCINOMA	Poorly differentiated NSCLC with spindle and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)

From Travis WD, Brambilla E, Noguchi M, et al: Diagnosis of lung adenocarcinoma in resected specimens: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Lung Classification. *Arch Pathol Lab Med* 137:685–705, 2013.

Table 14-1 Histologic Classification of Lung Cancer**Adenocarcinoma***Invasive Adenocarcinoma*

- Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant with mucin

Variants of Invasive Adenocarcinoma

- Invasive mucinous adenocarcinoma (formerly mucinous BAC)
- Colloid
- Fetal (low and high grade)
- Enteric

Minimally Invasive Adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)—nonmucinous, mucinous, mixed mucinous/nonmucinous

Preinvasive Lesions

- Atypical adenomatous hyperplasia
- Adenocarcinoma *in situ* (nonmucinous, mucinous, or mixed nonmucinous/mucinous)

Squamous cell carcinoma

- Keratinizing
- Nonkeratinizing
- Basaloid

Preinvasive Lesions

- Squamous dysplasia
- Carcinoma *in situ*

Neuroendocrine tumors

- Small cell carcinoma
- Combined small cell carcinoma
- Large cell neuroendocrine carcinoma
- Combined large cell neuroendocrine carcinoma
- Carcinoid tumors
- Typical carcinoid
- Atypical carcinoid
- Preinvasive lesion:*
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Large cell carcinoma**Adenosquamous carcinoma****Sarcomatoid carcinomas**

- Pleomorphic carcinoma
- Spindle cell carcinoma
- Giant cell carcinoma
- Carcinosarcoma
- Pulmonary blastoma
- Other

Other and unclassified carcinomas

- Lymphoepithelioma-like carcinoma
- NUT carcinoma
- Unclassified carcinoma

Carcinomas of Salivary Gland Type

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Epimyoeplithelial carcinoma

This classification primarily addresses histology in resected specimens. Modified from Travis WD, Brambilla E, Noguchi M, et al: Diagnosis of lung adenocarcinoma in resected specimens: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Lung Classification. *Arch Pathol Lab Med* 137:685–705, 2013; and Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC: Pathology and genetics: tumours of the lung, pleura, thymus and heart. Lyon, 2004, IARC.

BAC, bronchioloalveolar carcinoma; NUT, nuclear protein in testis.

Historically the most important distinction was between *small cell lung carcinoma* (SCLC) and *non-small cell lung carcinoma* (NSCLC)⁶ due to significant differences in clinical presentation, spread of tumor, and response to therapy. However, over the past decade, major changes in the approach to diagnosis and treatment of NSCLC have led to a greater need for more precise classification based on small biopsies and cytology.^{4,5,7} Several therapeutic advances have provided the need for pathologists to classify tumors more precisely because the choice of therapies and decision to perform molecular testing is based on histology. Molecular testing for *epidermal growth factor receptor* (EGFR) mutations and *activin receptor-like kinase* (ALK) rearrangements is recommended for patients with adenocarcinomas, “NSCLC, favor adenocarcinoma,” and *NSCLC-not otherwise specified* (NSCLC-NOS). Patients with an EGFR mutation are eligible for EGFR tyrosine kinase inhibitors and those with *echinoderm microtubule-associated protein-like 4* (EML4)-ALK rearrangements are eligible for crizotinib therapy.⁸⁻¹² If neither EGFR mutations nor ALK rearrangements are present, patients are eligible for either pemetrexed or bevacizumab-based regimens.⁸⁻¹² However, patients with squamous cell carcinoma are not eligible for these therapies. These advances have transformed the lung cancer field and resulted in multiple paradigm shifts in the clinical practice for all specialists, including pathologists. For additional information on lung cancer, see Chapters 51, 52, and 53.

ADENOCARCINOMA

Adenocarcinomas represent 36% of all lung cancers in the United States.¹³ The 2011 IASLC/ATS/ERS lung adenocarcinoma classification recommended multiple major changes (see Table 14-1).^{4,5,14} First, it is recommended to discontinue the use of the term *bronchioloalveolar carcinoma* (BAC) because the tumors formerly classified under this term are now classified as five different tumors. Second, there are new concepts of *adenocarcinoma in situ* (AIS) (see [Preinvasive Lesions](#)) and *minimally invasive adenocarcinoma* (MIA). Third, it is recommended to stop using the term “mixed subtype” and to use comprehensive histologic subtyping to estimate the percentage of histologic patterns in 5% increments within a tumor with the final classification according to the predominant subtype. Fourth, tumors with a predominant component formerly called “nonmucinous BAC” should be classified as *lepidic-predominant adenocarcinoma* (LPA). *Lepidic* refers to the noninvasive growth of tumor cells along the surface of the air spaces. Fifth, micropapillary adenocarcinoma is recognized as a new subtype with a poor prognosis. Sixth, *invasive mucinous adenocarcinoma* is the term recommended for those tumors formerly classified as mucinous BAC. Finally, specific terminology and diagnostic criteria are proposed for tumors in small biopsies and cytology specimens along with recommendations for strategic management of tissue and EGFR mutation testing in patients with advanced adenocarcinoma.^{4,5,14}

Adenocarcinoma Classification in Resected Specimens

Invasive Adenocarcinoma. Classification of overtly invasive adenocarcinomas is now made according to the predominant subtype.^{5,14} This is best determined using

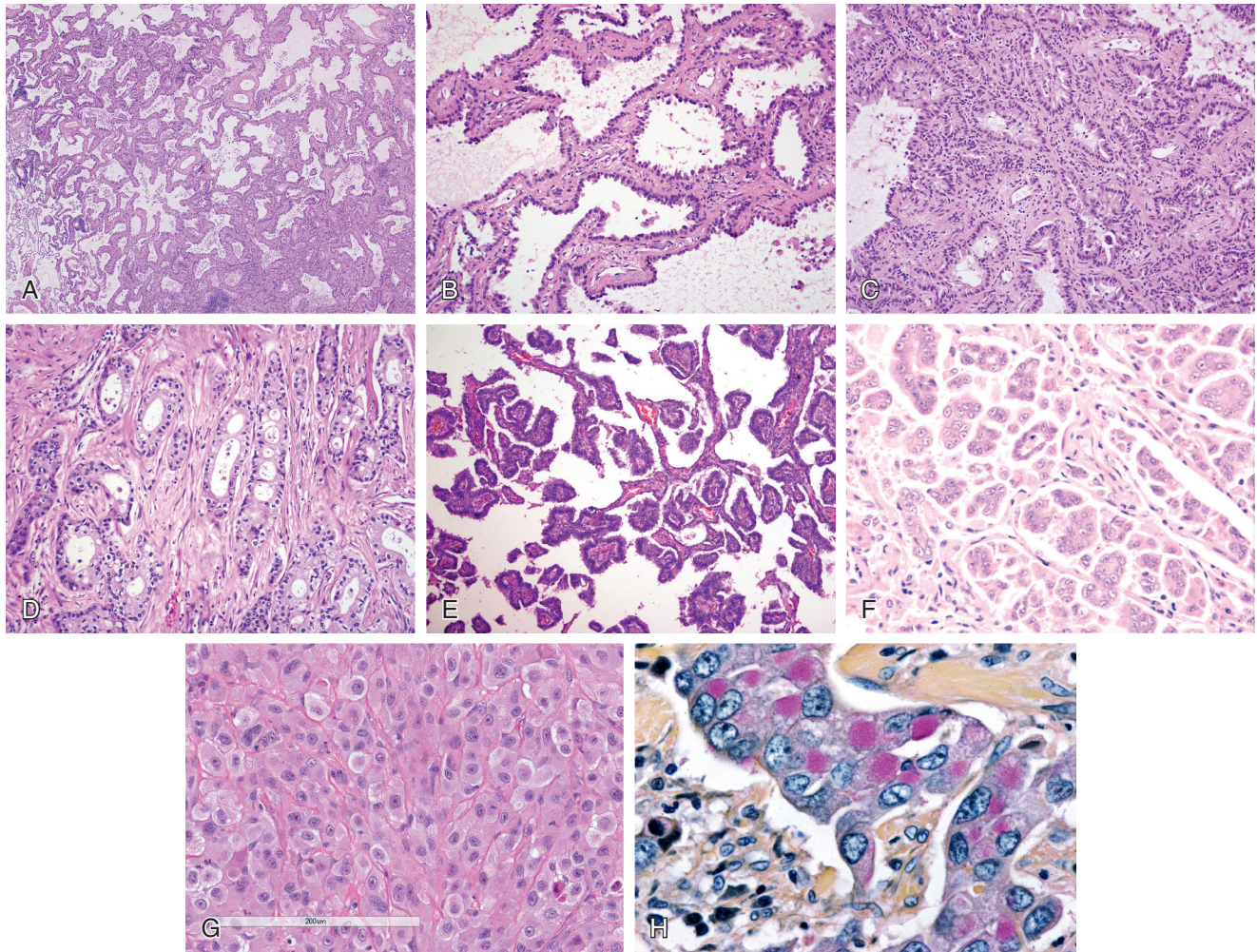


Figure 14-1 Major histologic patterns of invasive adenocarcinoma. **A**, Lepidic predominant pattern with mostly lepidic growth (left) and an area of invasive acinar adenocarcinoma (right). (H&E stain; original magnification $\times 100$.) **B**, Lepidic pattern consists of a proliferation of type II pneumocytes and club cells along the surface of the alveolar walls. (H&E stain; original magnification $\times 200$.) **C**, Area of invasive acinar adenocarcinoma (same tumor as in **A** and **B**). (H&E stain; original magnification $\times 400$.) **D**, Acinar adenocarcinoma composed of round to oval shaped malignant glands invading a fibrous stroma. (H&E stain; original magnification $\times 200$.) **E**, Papillary adenocarcinoma consists of malignant cuboidal to columnar tumor cells growing on the surface of fibrovascular cores. (H&E stain; original magnification $\times 100$.) **F**, Micropapillary adenocarcinoma consists of small papillary clusters of glandular cells growing within this airspace, most of which do not show fibrovascular cores. (H&E stain; original magnification $\times 200$.) **G**, Solid adenocarcinoma with mucin consisting of sheets of tumor cells with abundant cytoplasm and mostly vesicular nuclei with several conspicuous nucleoli. No acinar, papillary, or lepidic patterns are seen. (H&E stain; original magnification $\times 400$.) **H**, Solid adenocarcinoma with mucin. Numerous intracytoplasmic droplets of mucin (dark pink) are highlighted with this mucicarmine stain. (H&E stain; original magnification $\times 400$.)

comprehensive histologic subtyping to estimate the percentages of the various histologic subtypes within a tumor in a semiquantitative fashion in 5% to 10% increments. LPA consists of tumors formerly classified as mixed subtype tumors containing a predominant lepidic growth pattern of type II pneumocytes and/or club cells (Clara) (formerly known as nonmucinous BAC) that have an invasive component greater than 5 mm (Fig. 14-1A-C). The other major subtypes include acinar (see Fig. 14-1D), papillary (see Fig. 14-1E), micropapillary (see Fig. 14-1F), and solid with mucin-predominant adenocarcinomas (see Figs. 14-1G-H). The micropapillary-predominant subtype is a new addition due to the observation in multiple studies that it is associated with poor prognosis in early stage adenocarcinomas.^{5,14-20} It has been proposed that a cribriform pattern is associated with poor prognosis and, if this finding is validated, it may be added as a poor prognostic subtype of lung adenocarcinoma.²¹ Signet ring and clear cell carcinoma

subtypes are no longer regarded as histologic subtypes, but they are now documented as cytologic features whenever present with a comment about the percentage identified. Although clear and signet ring cell cytologic changes are seen mostly in the solid subtype, they can also be seen in acinar or papillary patterns as well.^{5,14} There is a high correlation between the appearance on *computed tomography* (CT) and the pathology features on biopsy; the ground-glass component on CT tends to correlate with lepidic growth on biopsy, whereas the solid component on CT tends to correlate with invasive components on biopsy.^{22,23}

Adenocarcinoma Variants. Lung adenocarcinoma can consist of several variants including invasive mucinous adenocarcinoma (formerly mucinous BAC), colloid adenocarcinoma, fetal adenocarcinoma, and enteric adenocarcinoma.^{5,14} Invasive mucinous adenocarcinomas (formerly mucinous BAC) differ from the nonmucinous invasive

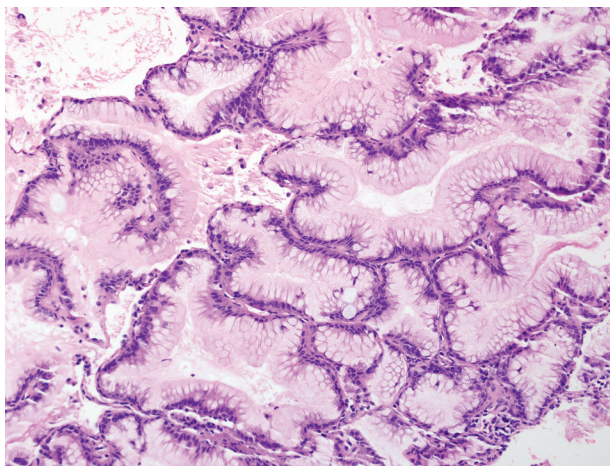


Figure 14-2 Invasive mucinous adenocarcinoma. This area of invasive mucinous adenocarcinoma demonstrates a pure lepidic growth. The tumor consists of columnar cells filled with abundant mucin in the apical cytoplasm and shows small basal oriented nuclei. (H&E stain; original magnification $\times 200$.)

adenocarcinomas due to the frequent association with *KRAS* mutations, lack of *thyroid transcription factor-1* (TTF-1), and frequent presentation with multicentric lung involvement. While historically, the lepidic pattern has been emphasized with these tumors, sometimes it is not present, and these tumors show varying amounts of other invasive patterns including acinar, papillary, or micropapillary growth. The characteristic histologic features consist of the tumor cell morphology of columnar cells with abundant apical mucin and small basally oriented nuclei (Fig. 14-2).^{5,14} By CT, these tumors typically show localized or multifocal consolidation with air bronchograms, forming nodules and/or lobar consolidation.

PROGNOSIS OF ADENOCARCINOMA SUBTYPES IN RESECTED SPECIMENS. A growing number of studies have evaluated prognosis of the adenocarcinoma subtypes according to the precise criteria and terminology of the new classification.^{15-19,24-29} Yoshizawa and colleagues¹⁶ identified three groups of tumors with different grades of clinical behavior: (1) low-grade AIS and MIA with 100% 5-year disease-free survival, (2) intermediate grade nonmucinous lepidic predominant, papillary predominant, and acinar predominant with 90%, 83%, and 84% 5-year disease-free survival, respectively, and (3) high-grade invasive mucinous adenocarcinoma, colloid predominant, solid predominant, and micropapillary predominant with 75%, 71%, 70%, and 67% 5-year disease-free survival, respectively. Generally, similar results have been demonstrated in additional independent data sets.^{15,17-19,24-29} Studies that have failed to show prognostic significance for the concepts in the new adenocarcinoma classification have either had small numbers of patients, used overall survival rather than disease-free survival, or focused on patients with advanced disease.³⁰⁻³² Because most patients with stage I lung adenocarcinomas die of causes other than lung cancer, overall survival does not reflect the true biology of the tumor, and methods such as disease-free or recurrence-free survival are more clinically relevant.

Minimally Invasive Adenocarcinoma. MIA was introduced to describe a lepidic-predominant tumor measuring 3 cm or less that has 5 mm or less of an invasive component (Fig. 14-3).^{5,14} Limited data suggest that patients with MIA will have almost a 100% 5-year disease-free survival.^{5,14-16,33,34} Most of these are nonmucinous, but rarely some of these are mucinous cases.^{5,14-16} On chest CT, nonmucinous MIA typically shows ground-glass opacity with a solid component measuring 5 mm or less, whereas mucinous MIA typically presents as a solid nodule.^{5,14}

Preinvasive Lesions. *Atypical adenomatous hyperplasia* (AAH) was previously the only preinvasive lesion for lung adenocarcinoma but now AIS has been added.

ATYPICAL ADENOMATOUS HYPERPLASIA. AAH is an atypical pneumocyte proliferation that resembles but falls short of criteria for nonmucinous AIS (see Fig. 14-1).^{6,35-38} AAH is typically found as an incidental histologic finding in a lung cancer resection specimen.

The incidence of AAH varies from 6% to 21% depending on the extent of the search and the criteria used for the diagnosis.^{39,40} Most lesions of AAH are less than 5 mm in diameter and frequently they are multiple.^{6,35-40} Histologically, AAH consists of a focal proliferation of slightly atypical cuboidal to low columnar epithelial cells along alveoli and respiratory bronchioles (Fig. 14-4). Slight thickening of alveolar septa may be present.

AAH must be distinguished from a variety of lesions; the most important of which is the nonmucinous AIS, MIA, or lepidic-predominant adenocarcinoma.⁴ This distinction can be difficult because there is considerable overlap in the morphologic features between AAH and the lepidic pattern of adenocarcinoma. Currently, there are no data to show that patients with lung cancer and AAH have any different prognosis from those without AAH.⁴¹

ADENOCARCINOMA IN SITU. In the new IASLC/ATS/ERS adenocarcinoma classification, AIS is defined as a glandular proliferation measuring 3 cm or less that has pure lepidic growth lacking invasion (Fig. 14-5).^{5,14} In most cases the tumor cells are nonmucinous, with a proliferation of type II pneumocytes or club cells, but rarely they are mucinous, consisting of tall columnar goblet cells having abundant apical mucin. If these lesions are completely resected, patients have been reported to have 100% 5-year disease-free survival.^{5,14,42-45} On chest CT, these lesions typically consist of a ground-glass opacity if nonmucinous and a solid nodule of mucinous AIS.^{5,14,46}

TNM Staging: Potential Changes According to New Classification

Several aspects of TNM (*tumor, node, metastasis*) staging may be modified based on the 2011 lung adenocarcinoma classification.^{5,14} In the setting of multiple nodules of lung adenocarcinoma, the distinction between metastases or primary cancers that are either *synchronous* (presenting within 2 months of each other) or *metachronous* (presenting more than 2 months apart) can be helped by the use of comprehensive histologic subtyping and the analysis of other morphologic features including cytologic and stromal characteristics. These morphologic features have been shown to correlate highly with molecular and clinical outcomes.⁴⁷⁻⁴⁹ The decision to classify a second tumor as an

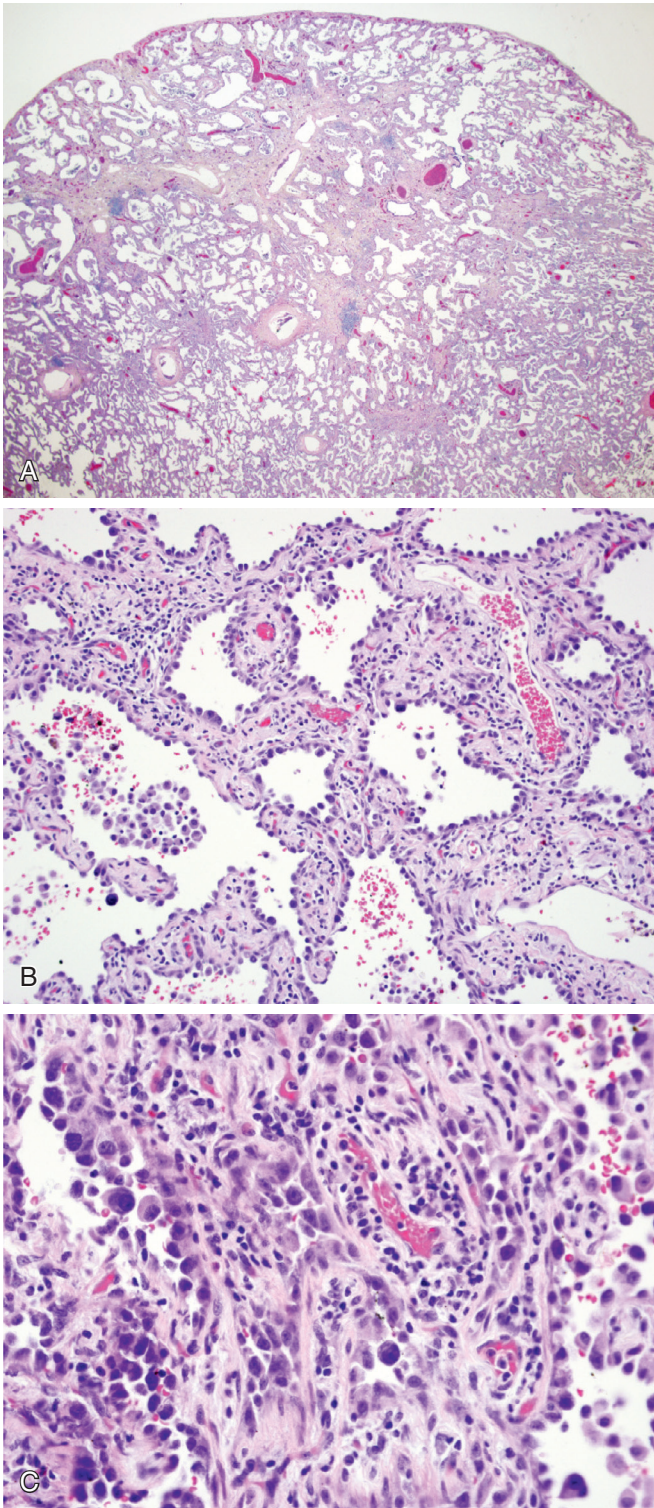


Figure 14-3 Nonmucinous minimally invasive adenocarcinoma. **A**, This adenocarcinoma tumor consists primarily of lepidic growth with a small (<0.5 cm) area of invasion (*bottom left*). (H&E stain; original magnification $\times 1$.) **B**, This area shows lepidic growth characterized by thickening of the alveolar walls which are lined by crowded atypical pneumocytes. **C**, From the area of invasion, these acinar glands are seen to be invading into the fibrous stroma. (H&E stain; original magnification $\times 200$.)

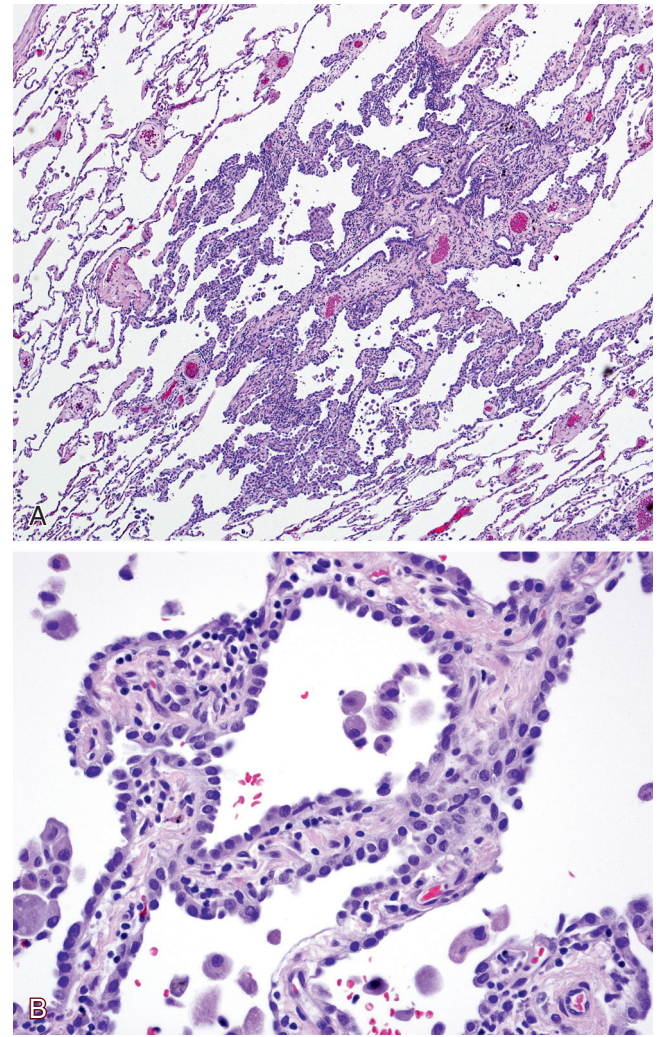


Figure 14-4 Atypical adenomatous hyperplasia (AAH). **A**, This millimeter-sized bronchioloalveolar proliferation is ill defined with mild thickening of the alveolar walls. (H&E stain; original magnification $\times 20$.) **B**, The alveolar walls show mild fibrous thickening and the hyperplastic pneumocytes show minimal atypia and gaps between the cells. (H&E stain; original magnification $\times 400$.)

intrapulmonary metastasis or a separate primary has a great impact on TNM staging and patient management (see Chapter 55).

In the future, tumor size for T-factor staging may be measured by invasive size rather than total size. Pathologically, comprehensive histologic subtyping can aid in determining the size of the invasive component by subtracting the percentage of the lepidic component. Several studies have shown that the invasive size is an independent prognostic factor.^{16,19,29,50} These data suggest that, like in breast cancer, the T factor for early lung adenocarcinomas may be best determined by the size of the invasive component rather than the total tumor size. On chest CT, the solid versus ground-glass component generally corresponds to the invasive versus lepidic pattern seen by histologic examination. Initial data also suggest that the size of the solid component rather than the total size including the ground-glass component is a better predictor of prognosis.⁵¹ Because CT

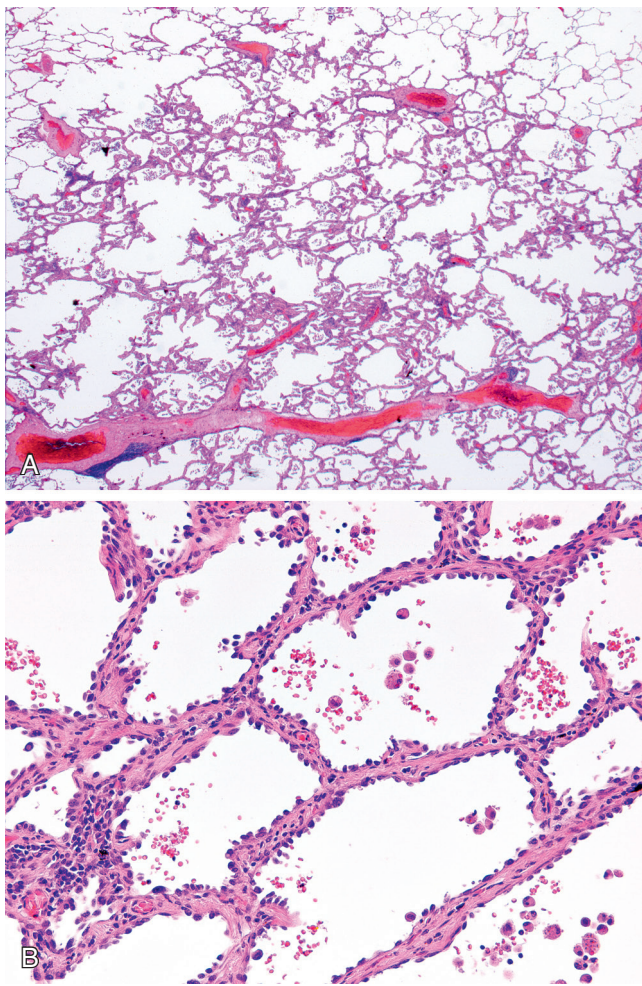


Figure 14-5 Nonmucinous adenocarcinoma in situ. **A**, This circumscribed nonmucinous tumor grows purely with a lepidic pattern. No foci of invasion or scarring is seen. (H&E stain $\times 4$). **B**, Higher magnification shows slight thickening of alveolar walls which are lined by crowded atypical pneumocytes. (H&E stain $\times 200$).

assessment is used for clinical staging, hopefully sufficient data can be accumulated before the next TNM revision to address this issue.

Adenocarcinoma Classification in Small Biopsies and Cytology

The IASLC/ATS/ERS lung adenocarcinoma classification provides criteria for diagnosis of lung cancer in small biopsies and cytology (see [eTable 14-1](#)).^{4,14} This is of great importance because 70% of lung cancer patients present with advanced stage disease and the diagnosis is based on small specimens. The new therapeutic implications based on histology provide the rationale for pathologists to distinguish adenocarcinoma from squamous cell carcinoma. Patients with advanced stage tumors who have the pathologic diagnosis of adenocarcinoma, NSCLC, favor adenocarcinoma, or NSCLC-NOS are eligible for three therapeutic options that are not available to patients with squamous cell cancer. Patients with adenocarcinoma may exhibit *EGFR* mutations and, if so, *EGFR* tyrosine kinase inhibitor therapy has benefit for response and progression-free survival.⁹⁻¹¹ In

addition, patients with adenocarcinoma are responsive to pemetrexed, whereas those with squamous cell carcinoma show little response.⁵² Finally, patients with adenocarcinoma may respond to the anti-vascular endothelial growth factor agent bevacizumab, whereas those with squamous cell carcinoma treated with bevacizumab have experienced life-threatening hemorrhage.⁵³ These clinically important differences between adenocarcinoma and squamous cell carcinoma make pathologic distinction essential.

In the 2011 lung adenocarcinoma classification, tumors that show clear morphologic features of adenocarcinoma or squamous cell carcinoma are classified with these standard terms. However, if the tumor only shows a carcinoma with no clear squamous or glandular features (NSCLC-NOS), a minimal immunohistochemical workup is recommended using a single adenocarcinoma marker and squamous marker, which should allow for classification of most tumors. At the moment, the best markers for adenocarcinoma and squamous cell carcinoma are TTF-1 and p63, respectively.^{4,14} In a tumor that shows no clear squamous or glandular morphology, but the staining results favor adenocarcinoma (i.e., TTF-1 positive, p63 negative), the tumor should be classified as NSCLC, favor adenocarcinoma ([Fig. 14-6](#)). Likewise, if the stains in such a tumor favor squamous cell carcinoma, the diagnosis would be NSCLC, favor squamous cell carcinoma ([Fig. 14-7](#)). Then, for tumors in which there is clear differentiation by light microscopy or special stains or if the results are conflicting, the diagnosis remains NSCLC-NOS. Cytology is another powerful tool in subclassifying poorly differentiated NSCLC.⁵⁴ In some cases, it may be easier to classify the tumor based on cytology than on biopsy.^{4,14} It is recommended to avoid use of the term “nonsquamous carcinoma” and state the specific diagnosis in precise terms as outlined earlier.^{4,14} Also, use of the term NSCLC should be minimized and instead the specific diagnosis (adenocarcinoma or squamous cell carcinoma) should be used when possible.^{4,14}

The approach to interpretation of small biopsies and cytology must include considerations of diagnoses other than NSCLC, such as neuroendocrine tumors (carcinoid, small cell carcinoma, or large cell neuroendocrine carcinoma) as well as metastatic tumors including metastatic malignant melanoma, breast cancer, or prostate cancer.^{4,14} Therefore, if the initial evaluation does not clearly point to adenocarcinoma or squamous cell carcinoma, some of these other diagnoses may need to be considered.

The diagnosis of NSCLC-NOS was encouraged by previous World Health Organization classifications when there was no clinical value in being more precise. In studies of advanced NSCLC, this diagnosis was made in 20% to 40% of cases and some data suggest its use has been increasing.^{52,55} However, with the new IASLC/ATS/ERS criteria and utilization of immunohistochemistry as well as cytology correlation, the percentage of NSCLC diagnosed as NSCLC-NOS, should be less than 5% of cases.^{4,14}

EGFR Mutation Testing

In the new IASLC/ATS/ERS Lung Adenocarcinoma Classification, there is a clinical recommendation that *EGFR* mutation testing should be performed in advanced lung adenocarcinomas because of the predictive benefit of

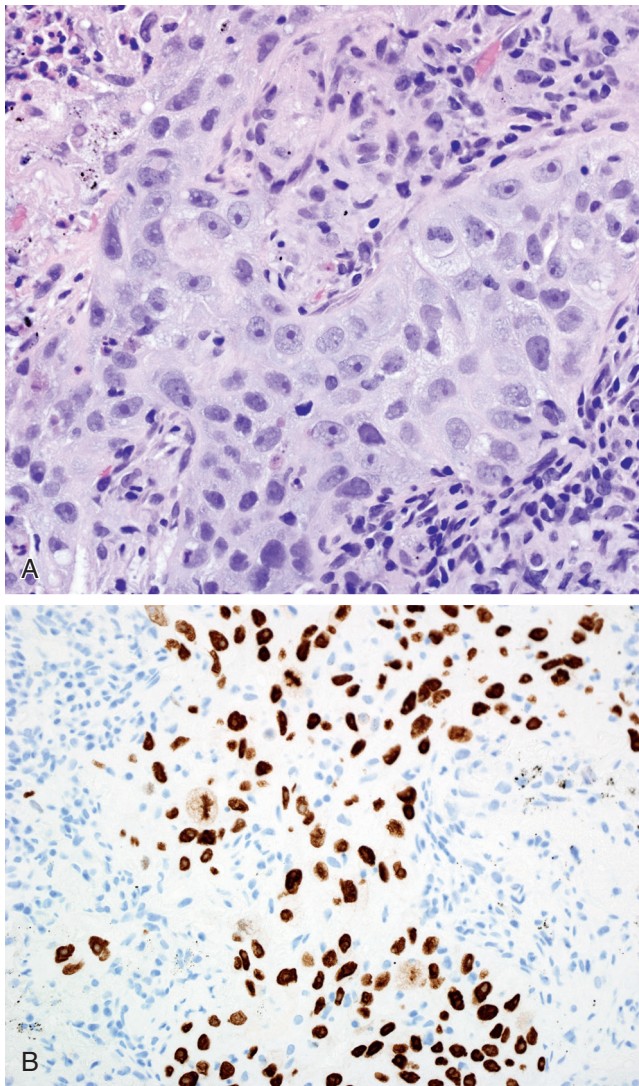


Figure 14-6 Non-small cell carcinoma, favor adenocarcinoma. **A**, This carcinoma shows no clear squamous or glandular differentiation. (H&E stain; original magnification $\times 200$.) **B**, The diffuse positive TTF-1 staining allows for the diagnosis of non-small cell carcinoma, favor adenocarcinoma. (H&E stain; original magnification $\times 200$.)

EGFR mutations with treatment by *EGFR* tyrosine kinase inhibitors as described earlier.^{4,14} *EGFR* mutation testing should be performed for all patients with a pathologic diagnosis of (1) adenocarcinoma, (2) NSCLC, favor adenocarcinoma, and (3) NSCLC-NOS. This recommendation has major implications for tissue management and pathologic diagnosis.

Multidisciplinary Strategy Needed to Obtain and Process Small Biopsies and Cytology

Each institution needs to develop a multidisciplinary strategy to manage these small pieces of tissue at each stage of handling: (1) obtaining the specimen, (2) processing it in the pathology laboratory, (3) providing material to the molecular diagnostic laboratory, and (4) documenting the results in a pathology report and the medical record.^{4,14} This process requires ongoing communication between

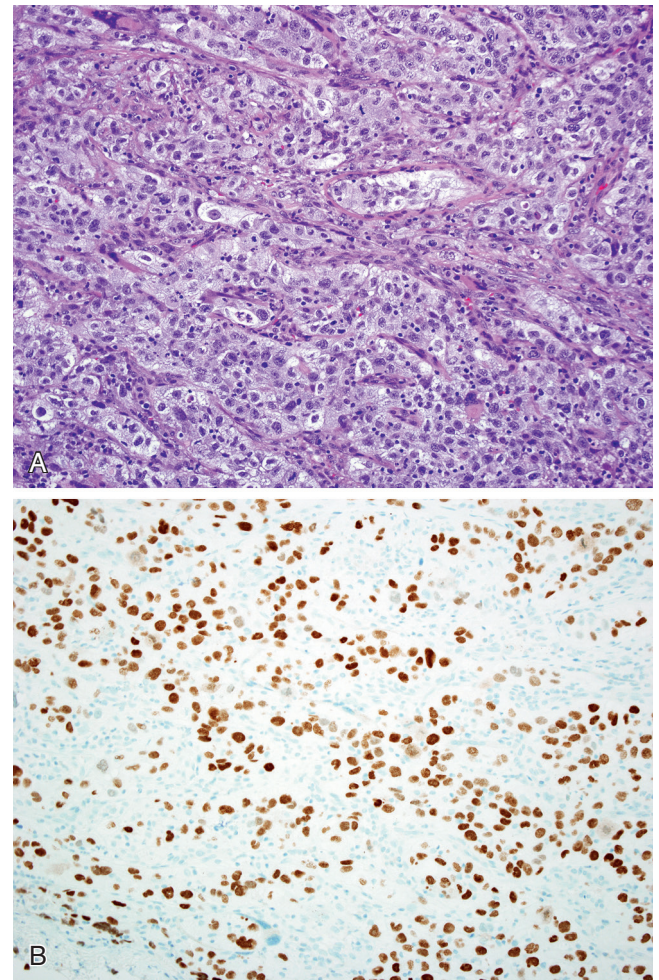


Figure 14-7 Non-small cell carcinoma, favor squamous cell carcinoma. **A**, This carcinoma shows no clear squamous or glandular differentiation. (H&E stain; original magnification $\times 200$.) **B**, The diffuse positive p63 staining and negative thyroid transcription factor 1 (TTF-1) staining (not shown) allows for the diagnosis of non-small cell carcinoma, favor squamous cell carcinoma. (Immunohistochemistry for p63; original magnification $\times 200$.)

specialists to ensure optimal management of tissues and efficient reporting of results. One of the central aspects of this process that impacts radiologists, pulmonologists, and surgeons is the need to obtain sufficient tissue not only for diagnosis, but also for molecular studies. To that end, biopsy procedures should be designed to result in either a core biopsy or a cell block from tissue samples obtained for cytology.^{4,14} Cytology specimens such as pleural fluids should also be processed to generate cell blocks such that immunostaining and molecular studies can be performed.

Use of Minimal Stains to Maximize Tissue for Molecular Testing

Pathologists should minimize the amount of tissue used for making the diagnosis, including use of as few special stains as possible.^{4,14} This is necessary to preserve as much tissue as possible for molecular testing. One helpful approach is to cut multiple unstained slides from the block after initial review in cases that are potential candidates for molecular

testing, so that the block is cut only once and valuable tissue is not lost during the process of facing the block multiple times; *facing* is the process of shaving tissue from the surface to obtain full cuts across the tissue block. This would include tumors that are either clearly adenocarcinoma or those with NSCLC-NOS patterns that will require special stains. If adenocarcinoma is suspected, a single stain for TTF-1, if positive, would confirm not only the adenocarcinoma diagnosis but also a pulmonary origin. If by morphology the tumor could be either adenocarcinoma or squamous cell carcinoma, it may be best to perform one adenocarcinoma (i.e., TTF-1) and one squamous (i.e., p63) marker as recommended in the new classification.^{4,14} Limited additional stains may be considered for the small percentage of cases that cannot be classified after this initial panel.^{4,14} Molecular testing guidelines for lung adenocarcinoma: Utility of cell blocks and concordance between fine-needle aspiration cytology and histology samples.^{55a}

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma accounts for approximately 20% of all lung cancers in the United States.¹³ Historically, two thirds of squamous cell carcinomas presented as central lung tumors, but one third were peripheral.^{56,57} However, recent reports document an increasing percentage of squamous cell carcinomas in the periphery, exceeding 50% in some studies.⁵⁸ The morphologic features that suggest squamous differentiation include intercellular bridging, squamous pearl formation, and individual cell keratinization (Fig. 14-8). In well-differentiated tumors these features are readily apparent; however, in poorly differentiated tumors, they are difficult to find.⁵⁹ Squamous cell carcinoma arises most often in segmental bronchi and involves the lobar and main-stem bronchus by extension. According to the 2004 World Health Organization classification, squamous cell carcinoma can have papillary, clear cell, small cell, and basaloid subtypes.⁶ However, this subtyping needs updating because it does not address the morphologic spectrum of appearances of lung squamous cell carcinoma, and

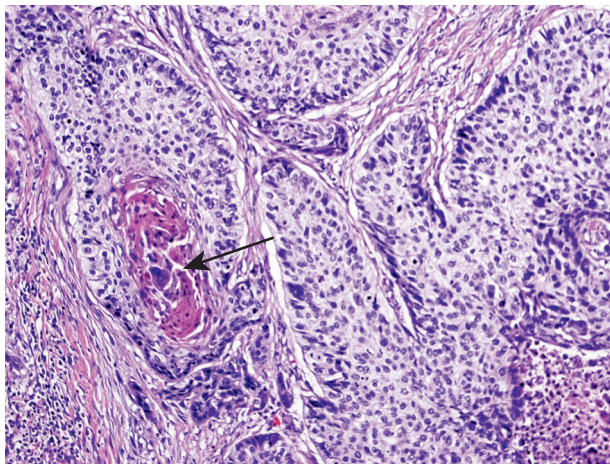


Figure 14-8 Squamous cell carcinoma. These tumor cells have abundant eosinophilic keratinized cytoplasm and form nests and keratin pearls (arrow) characteristic of squamous differentiation. (H&E stain; original magnification $\times 200$.)

it does not allow for meaningful correlations with clinical, prognostic, or molecular features. For example, the small cell variant probably should be dropped because most of these cases would be better classified as basaloid variants, and the term “small cell” creates confusion with true small cell carcinoma.

Several papers have proposed alternative approaches to subclassifying pulmonary squamous cell carcinomas.^{58,60,61} These include recognition of an alveolar space-filling variant, which corresponds to a favorable prognosis.^{58,61} However, this pattern is seen in the minority of cases, more often it is seen only focally and, in a study from North America, prognostic significance could not be demonstrated.⁶² In another study of pulmonary squamous cell cancer, minimal tumor cell nests were defined as large (more than six tumor cells), small (two to five cells), and single cell; the single cell infiltrating tumors had the worst prognosis.⁶⁰ Also, tumors associated with a background of *usual interstitial pneumonia* (UIP) and lymph node metastases had a poor prognosis.⁶⁰ Further work is needed to develop a more practical approach to subclassification of squamous cell carcinoma and to identify better histologic predictors of prognosis.

Squamous Dysplasia and Carcinoma In Situ

Squamous cell carcinoma develops through a multistep process in which the normal bronchial mucosa progresses through a series of lesions from basal cell hyperplasia to squamous metaplasia, dysplasia, and carcinoma in situ.^{6,35,36} In addition to the spectrum of histologic features, there is an accumulation of molecular events through the progression of increasing dysplasia to carcinoma in situ and invasive squamous cell carcinoma.³⁵

According to the severity of cytologic atypia and thickness of involvement of the bronchial mucosa, squamous dysplasia may be classified as mild, moderate, or severe.^{6,35,36} These changes represent a continuum of abnormalities; when there is marked cytologic atypia of the full thickness of the bronchial mucosa, the diagnosis is carcinoma in situ.⁶³ Dysplasia must be distinguished from reactive atypia associated with inflammation or granulation tissue. Microinvasive squamous cell carcinoma also needs to be distinguished from carcinoma in situ with involvement of submucosal glands.^{6,35,36}

NEUROENDOCRINE TUMORS

Small Cell Carcinoma

SCLC accounts for 14% of invasive lung cancers in the United States annually.¹³ Most cases present as a perihilar mass (see eFig. 53-21). Because most patients present in an advanced stage, the diagnosis is often made based on transbronchial biopsy and/or cytology, and these specimens are very reliable. SCLC may also present as a solitary coin lesion in up to 5% of cases,^{64,65} but the rarity of early stage tumors makes it unusual to encounter SCLC as a surgical specimen.

The morphology of SCLC characteristically shows tumor cells with small size, a round to fusiform shape, scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli (Fig. 14-9).^{6,66} Tumor cells typically

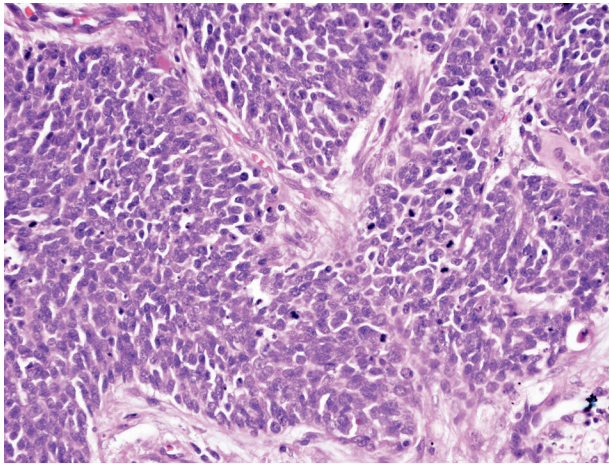


Figure 14-9 Small cell carcinoma. This tumor is composed of small cells with scant cytoplasm, finely granular chromatin, and frequent mitoses. Nucleoli are absent. (H&E stain; original magnification $\times 400$.)

grow in diffuse sheets, but may show rosettes, peripheral palisading, and organoid nesting.^{6,66,67} Mitoses are frequent, averaging 80 per 2 mm² area, and necrosis is usually extensive.^{6,66,67}

Combined SCLC. SCLC can present in combination with various types of non-small cell carcinomas in less than 10% of cases, with large cell carcinoma (Fig. 14-10) in about 4% to 6% of cases,⁶⁸ and with adenocarcinoma or squamous cell carcinoma in 1% to 3% of cases.⁶⁸⁻⁷¹ In addition, SCLC can be combined with spindle cell carcinoma,^{72,73} giant cell carcinoma,⁷³ and carcinosarcoma.⁷⁴ To date, compared with patients with pure SCLC, no significant difference has been demonstrated in clinical features, prognosis, or response to therapy.^{70,71}

A good quality hematoxylin and eosin stain is the most important stain for the diagnosis of SCLC, although immunohistochemistry is frequently used. In most tumors, a definite diagnosis can be established based on hematoxylin and eosin without immunostains. Immunohistochemistry using a pancytokeratin antibody can help confirm that the tumor is a carcinoma and make the distinction from a lymphoid lesion. A panel of neuroendocrine markers is useful, including CD56, chromogranin, and synaptophysin. TTF-1 is expressed in 70% to 80% of SCLC.⁶⁶ However, because TTF-1 can be positive in extrapulmonary small cell carcinomas, it should not be used to determine the primary site.⁷⁵ Ki-67 proliferation rate is very high, averaging 70% to 90%.⁷⁶

In up to 5% to 7% of cases, expert lung cancer pathologists disagree about the separation of SCLC and NSCLC.⁷⁷⁻⁷⁹ Agreement for the diagnosis of SCLCs for all five observers in one study was 93% and, for at least four of five observers, it was 98%.⁷⁸ When disagreements arise, it is best to use a consensus approach among other pathology colleagues. Extramural consultation may be needed if a consensus diagnosis cannot be reached locally. Comparison of problematic biopsy specimens with any available cytology specimens can be very helpful because the morphology is often easier to assess based on cytology.

One of the reasons small biopsy interpretation can be difficult is due to the frequent finding of “crush artifact,” a

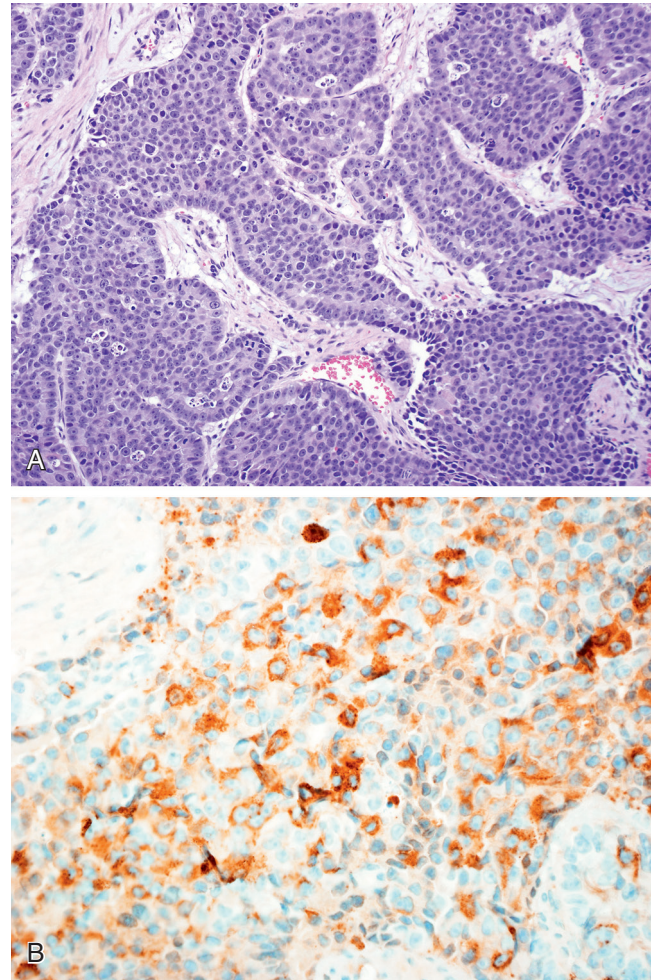


Figure 14-10 Large cell neuroendocrine carcinoma. **A**, Peripheral palisading and rosette-like structures give this tumor a neuroendocrine morphologic appearance. The tumor cells have abundant cytoplasm with large hyperchromatic nuclei. Some of the nuclei show vesicular chromatin and/or prominent nucleoli. Mitoses are frequent. (H&E stain; original magnification $\times 200$.) **B**, The tumor cells are diffusely positive for synaptophysin (Immunohistochemistry for synaptophysin; original magnification $\times 400$.)

loss of cellular detail usually seen from the crushing of tumor cells by the biopsy forceps. The vast majority of tumors with dense sheets of small blue cells showing crush artifact turn out to be SCLC, perhaps indicating fragility of the SCLC tumor cells. However, a similar crush artifact can be seen in carcinoid tumors, lymphocytic infiltrates, or poorly differentiated NSCLC. In the context of extensive artifact, the diagnosis of SCLC requires that some preserved tumor cells with diagnostic morphology compatible with SCLC should be seen to confirm the diagnosis. Even in crushed specimens, immunohistochemical markers can be useful, because SCLC may demonstrate positive staining for cytokeratin, chromogranin, CD56, synaptophysin, TTF-1, and a high proliferation index with Ki-67.⁶⁶

In the setting of keratin-negative staining in a suspected SCLC, it is important to exclude other differential diagnoses such as chronic inflammation, lymphoma, primitive neuroectodermal tumor, or small round cell sarcoma.⁶⁶ However, the distinction of SCLC from non-SCLC is primarily based on morphology rather than any immunohistochemical or molecular marker.⁶⁶

Large Cell Neuroendocrine Carcinoma

In surgical series, *large cell neuroendocrine carcinoma* (LCNEC) comprises approximately 3% of resected lung cancers.^{80,81} LCNEC differs from typical and atypical carcinoid tumors in that it is a high-grade non–small cell neuroendocrine carcinoma. It is distinction from SCLC based on morphologic characteristics (Table 14-2 and see eTable 14-1).⁶⁶ The morphologic criteria include (1) neuroendocrine morphology: organoid, palisading, trabecular, or rosette-like growth patterns (see Fig. 14-10A); (2) non–small cell cytologic features: large size, polygonal shape, low nuclear to cytoplasmic ratio, coarse or vesicular nuclear chromatin, and frequent nucleoli; (3) high mitotic rate (11 or more per 2 mm²) with a mean of 60 mitoses per 2 mm²; (4) frequent

necrosis; (5) at least one positive neuroendocrine immunohistochemical marker or neuroendocrine granules seen on electron microscopy (see Fig. 14-10B).^{6,82} The diagnosis of LCNEC based on small biopsy specimens such as needle or bronchoscopic biopsy specimens is usually very difficult because the neuroendocrine morphology is hard to appreciate without a resection specimen. *Combined LCNEC* is the term used for LCNEC that are combined with other histologic types of NSCLC such as adenocarcinoma or squamous cell carcinoma (see Table 14-1).⁶

Typical and Atypical Carcinoid

Carcinoid tumors account for 2% to 3% of all invasive lung malignancies.¹³ Patients are asymptomatic at presentation in approximately 50% of cases.^{80,83,84} The mean age of presentation for *typical carcinoid* (TC) and *atypical carcinoid* (AC) tumors is 45 to 55 years without any sex predilection (Table 14-3). Carcinoids are the most frequent tumor of the lung in children.⁸⁵ The typical presenting symptoms are hemoptysis in 18%, postobstructive pneumonitis in 17%, and dyspnea in 2% of patients. Patients may present with paraneoplastic syndromes such as the carcinoid syndrome or Cushing syndrome.^{80,83,84} Surgical resection is the primary approach to treatment.^{80,83,84} TCs have a favorable prognosis.^{80,83,84} Because 5% to 20% of TCs have regional lymph node involvement, this feature should not be used to make a distinction from AC.^{80,83,84} ACs have a larger tumor size and a higher rate of metastases than TCs, and patients have significantly worse survival; 5-year survival in AC is approximately 30%.^{80,83,84}

Carcinoid tumors may be central (see eFig. 54-7) or peripheral in location. Central tumors often have polypoid endobronchial growth, while peripheral carcinoids are usually subpleural. The classic histologic pattern consists of an organoid growth pattern and uniform cytologic features consisting of moderate eosinophilic, finely granular cytoplasm with nuclei possessing a finely granular chromatin pattern (Fig. 14-11). Both TC and AC can show a variety of histologic patterns, including spindle cell, trabecular, palisading, papillary, sclerosing papillary, rosette-like, glandular, and follicular patterns.⁸² Cytologically, the tumor cells may have acinic cell-like, signet-ring, mucin-producing, or melanocytic features.⁸²

Table 14-2 Spectrum of Neuroendocrine Lung Proliferations and Tumors	
I. Neuroendocrine cell hyperplasia and tumorlets	
A. Neuroendocrine cell hyperplasia	
1. Neuroendocrine cell hyperplasia associated with fibrosis and/or inflammation	
2. Neuroendocrine cell hyperplasia adjacent to carcinoid tumors	
3. Diffuse idiopathic NE cell hyperplasia with or without airway fibrosis/obstruction	
B. Tumorlets (<0.5 cm)	
II. Tumors with neuroendocrine morphology	
A. Typical carcinoid (≥0.5 cm)	
B. Atypical carcinoid	
C. Large cell neuroendocrine carcinoma	
1. Combined large cell neuroendocrine carcinoma*	
D. Small cell carcinoma	
1. Combined small cell carcinoma*	
III. Non–small cell carcinomas with neuroendocrine differentiation	
IV. Other tumors with neuroendocrine properties	
A. Pulmonary blastoma	
B. Primitive neuroectodermal tumor	
C. Desmoplastic round cell tumor	
D. Carcinomas with rhabdoid phenotype	
E. Paraganglioma	

*The histologic type of the other component of non-small cell carcinoma should be specified
Modified from Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC: Pathology and genetics: tumours of the lung, pleura, thymus and heart. Lyon, 2004, IARC.

Table 14-3 Typical and Atypical Carcinoid: Distinguishing Features		
Histologic or Clinical Feature	Typical Carcinoid	Atypical Carcinoid
Histologic patterns: organoid, trabecular, palisading, and spindle cell	Characteristic	Characteristic
Mitoses	Absent or < 2 per 2 mm ² in area of viable tumor	2 to 10 per 2 mm ² in area of viable tumor
Necrosis	Absent	Characteristic, usually focal or punctate
Nuclear pleomorphism, hyperchromatism	Usually absent, not sufficient by itself for diagnosis of atypical carcinoid	Often present
Regional lymph node metastases at presentation	5% to 15%	40% to 48%
Distant metastases at presentation	Rare	20%
Survival at 5 years	90% to 95%	50% to 60%
Disease-free survival at 10 years	90% to 95%	35%

Modified from Kreisman H, Wolkove N, Quoix E: Small cell lung cancer presenting as a solitary pulmonary nodule. *Chest* 101:225–231, 1992; Johkoh T, Muller NL, Pickford HA, et al: Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. *Radiology* 212:567–572, 1999.

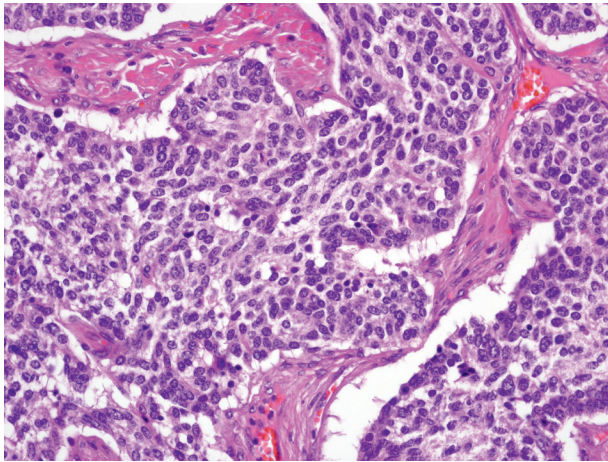


Figure 14-11 Typical carcinoid (TC). This tumor is growing in organoid nests and consists of uniform medium-sized cells with a moderate amount of eosinophilic cytoplasm. (H&E stain; original magnification $\times 200$.)

The diagnostic criteria for AC are a carcinoid tumor with mitoses between 2 and 10 per 2 mm^2 area of viable tumor or the presence of necrosis (Fig. 14-12).^{6,86} In TC, mitotic figures are rare (<2 per 2 mm^2) and necrosis is absent.^{6,86} Pleomorphism, vascular invasion, and increased cellularity are not as helpful in separating TC from AC. These tumors usually stain strongly for neuroendocrine markers such as chromogranin, synaptophysin, and CD56. The proliferation rate for TC by Ki-67 is usually low ($\leq 5\%$) compared with the rate for AC, which is usually between 5% and 20%.^{76,87} In small crushed biopsies, Ki-67 can help separate TC or AC from the high grade LCNEC or SCLC where the proliferation rates are very high.^{76,87}

Preinvasive Lesion

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is a rare condition in which the peripheral airways are diffusely involved by neuroendocrine cell hyperplasia and tumorlets (Fig. 14-13).⁸⁸⁻⁹⁰ The clinical presentation resembles ILD manifest by airway obstruction due to bronchiolar fibrosis in approximately half of patients.⁸⁸⁻⁹⁰ The remaining patients typically present with multiple incidentally discovered pulmonary nodules, often found during follow-up for an extrathoracic malignancy. Because carcinoid tumors are frequently found in patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and the tumors are often multiple, this is thought to represent a preinvasive lesion for carcinoid tumors.^{6,89} There is a distinctive CT appearance consisting of centrilobular nodules and pulmonary nodules that correspond to the tumorlets and carcinoid tumors, respectively. Furthermore, in patients who present with clinical manifestations of ILD, the chest CT can be normal or it can show mosaic perfusion from air trapping, bronchial wall thickening, and bronchiectasis.⁸⁸⁻⁹⁰

LARGE CELL CARCINOMA

According to the US NCI SEER data, large cell carcinoma comprises 3% of all lung carcinomas, which is a

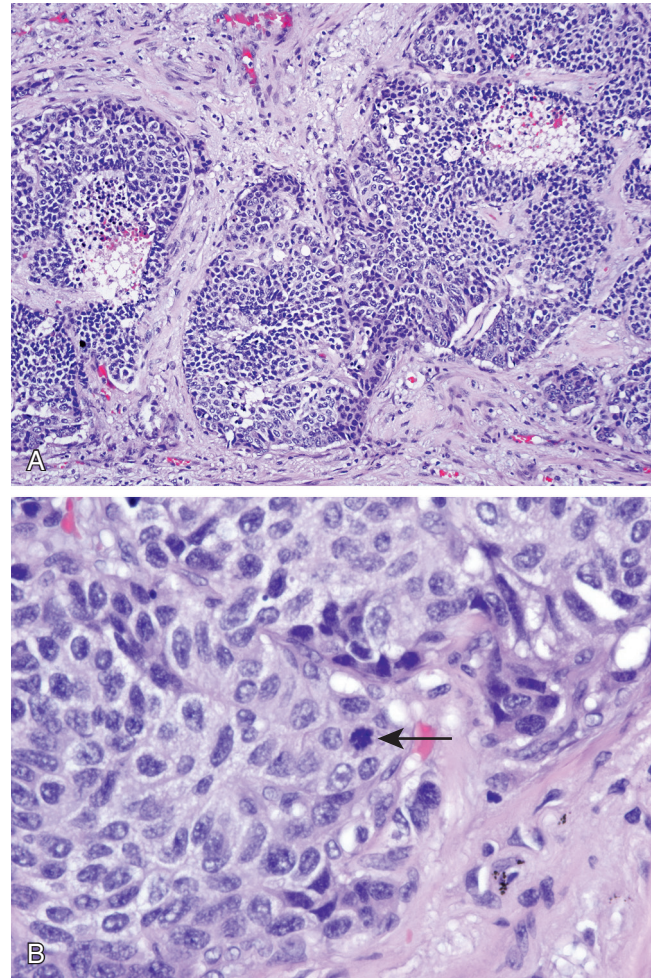


Figure 14-12 Atypical carcinoid (AC). **A**, Punctate foci of necrosis are present in the center of several organoid nests of uniform tumor cells. Necrosis is a feature characteristic of ACs. (H&E stain; original magnification $\times 200$.) **B**, The tumor cells are uniform, with moderate spindle-shaped cytoplasm, and the nuclear chromatin is finely granular. A single mitosis is present (arrow). (H&E stain; original magnification $\times 800$.)

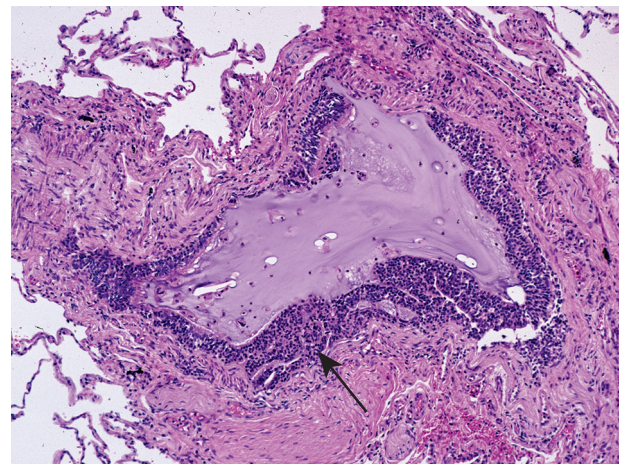


Figure 14-13 Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. This bronchiole shows mild fibrotic thickening of the wall, mucus in the lumen, and increased numbers of neuroendocrine cells in the mucosa. At the base of the mucosa are numerous neuroendocrine cells (arrow). (H&E stain; original magnification $\times 200$.)

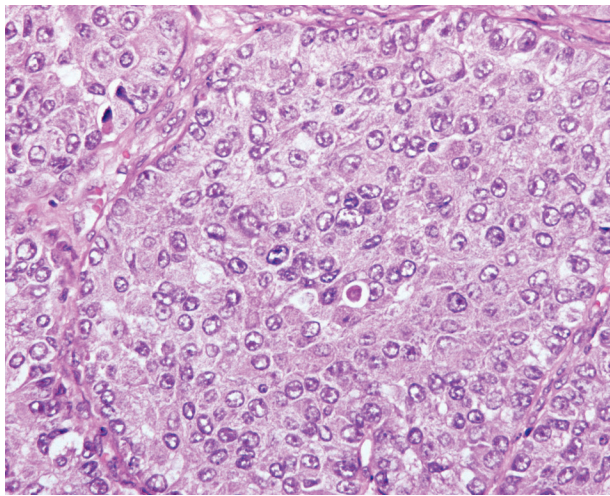


Figure 14-14 Large cell carcinoma. This tumor consists of sheets and nests of large cells with abundant cytoplasm and vesicular nuclei with prominent nucleoli. (H&E stain; original magnification $\times 400$.)

marked decrease from 9% previously reported for 1983–1987.^{6,13,90a} Large cell carcinomas present most often in the lung periphery and are usually large necrotic tumors. The diagnosis of large cell carcinoma is one of exclusion, where the presence of squamous cell or glandular differentiation could not be seen by light microscopy. The microscopic appearance consists of sheets and nests of large polygonal cells with vesicular nuclei and prominent nucleoli (Fig. 14-14).⁶ Because solid adenocarcinoma requires a minimum of five mucin-positive cells in at least two high-power fields, in large cell carcinoma, the number of mucin-positive cells should be less than this.

A surgical resection specimen with thorough histologic sampling is required for the diagnosis of large cell carcinoma, therefore the diagnosis cannot be made based on a small biopsy or cytology specimen because an adenocarcinoma or squamous cell carcinoma component cannot be excluded.⁶ Tumors that historically have been classified as large cell carcinoma in the setting of advanced lung cancer would be best classified as NSCLC-NOS according to the 2011 IASLC/ATS/ERS lung adenocarcinoma classification.^{4,14,52,91} If immunostains are performed, some of these tumors might be reclassified as NSCLC, favor adenocarcinoma, or NSCLC, favor squamous cell carcinoma, and a small percent would remain as NSCLC-NOS.^{4,14} The adenocarcinoma phenotype cases show driver mutations in 38% of cases that are typical of adenocarcinoma, including *KRAS*, *BRAF*, *ALK*, *EGFR*, *MAP2K1*, and *PIC3CA*.⁹²

ADENOSQUAMOUS CARCINOMA

Adenosquamous carcinoma accounts for 1% of all lung cancers in the United States.¹³ The diagnosis of adenosquamous carcinoma requires the presence of at least 10% squamous cell and adenocarcinoma components as seen on light microscopy.^{6,93-95} The diagnosis of adenosquamous carcinoma may be suspected but cannot be made by small biopsy or cytology because a larger resection specimen is needed.

CARCINOMAS WITH PLEOMORPHIC, SARCOMATOID, OR SARCOMATOUS ELEMENTS

The rarest histologic subgroup of major lung cancers is that of sarcomatoid carcinomas, which comprise 0.5% of all invasive lung malignancies in the United States.¹³ These poorly differentiated tumors consist of a spectrum of lung carcinomas with pleomorphic, sarcomatoid, and sarcomatous elements with poor prognosis.^{6,96} Most pleomorphic carcinomas are large peripheral tumors that frequently invade the chest wall.^{6,96} The diagnosis of pleomorphic carcinomas requires the presence of at least a 10% component of a spindle cell and/or giant cell component as well as a carcinomatous component that may consist of a single or mixture of patterns of other histologic types such as adenocarcinoma and/or squamous cell carcinoma.^{6,96}

In small biopsies or cytology specimens, one can only suggest the diagnosis of pleomorphic carcinoma because this diagnosis requires a resection specimen. Carcinomas with a pure giant cell or spindle cell pattern are classified as giant cell or spindle cell carcinoma, respectively. Giant cell carcinomas are composed of huge bizarre pleomorphic and multinucleated tumor giant cells.^{6,96} The diagnosis of pleomorphic carcinoma can be made by light microscopy but immunohistochemistry, particularly for epithelial markers such as keratin, can be helpful in confirming epithelial differentiation in poorly differentiated tumor components.^{6,96}

Carcinosarcoma and Pulmonary Blastoma

According to the 2004 World Health Organization classification, tumors composed of a mixture of carcinoma and sarcoma that show heterologous elements such as malignant cartilage, bone, or skeletal muscle are classified as carcinosarcoma.^{6,96} Pulmonary blastomas are composed of a glandular component with a fetal adenocarcinoma pattern and a primitive sarcomatous component with blastomatous stroma. These tumors are now distinguished from fetal adenocarcinoma, which are classified as a variant of adenocarcinoma.^{6,80,83,84,96}

PLEURAL TUMORS

SOLITARY FIBROUS TUMOR

Solitary fibrous tumors of the pleura are localized neoplasms arising in the pleura that are usually benign, with a small percentage that are malignant. About 80% arise on the visceral pleura, with a minority arising from the parietal pleura or rarely from the pulmonary parenchyma. These tumors are not mesothelial in origin. They are derived from submesothelial connective tissue and are not related to asbestos.

The majority of tumors are large, measuring over 10 cm in diameter, and often have a pedicle.^{6,97,98} The tumors are gray-white, with a nodular, whorled, or lobulated appearance (Fig. 14-15A; see eFig. 56-11E).

Histologically the tumors most often show a “patternless pattern” of disorderly or randomly arranged mixtures of spindle to oval shaped cells with a ropy collagenous stroma (see Fig. 14-15B). Criteria for malignancy include increased

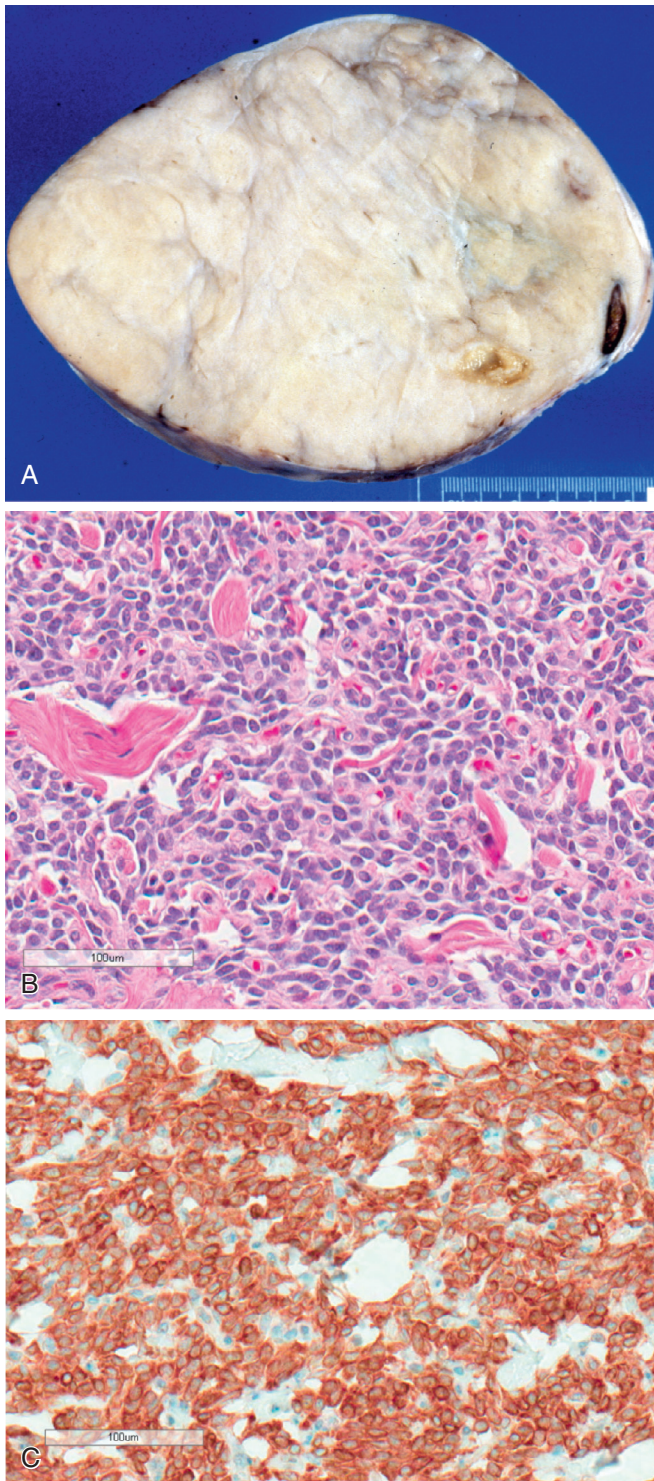


Figure 14-15 Fibrous tumor of the pleura. **A**, The tumor is circumscribed with a whorled, tan, cut surface. **B**, The tumor cells are round to oval and spindle shaped, with a dense eosinophilic or “ropy” collagen stroma. (H&E stain; original magnification $\times 200$.) **C**, The tumor cells stain strongly for CD34. (CD34 immunohistochemistry; original magnification $\times 200$.)

cellularity, pleomorphism, necrosis, and more than four mitoses per 10 high-power fields. Immunohistochemical stains for CD34 and BCL2 are positive.

MALIGNANT MESOTHELIOMA

Malignant mesothelioma is a malignant neoplasm that can have an epithelioid, sarcomatoid, or biphasic appearance.^{6,99,100} These tumors have a characteristic gross appearance with diffuse pleural thickening. The tumor typically does not invade the lung parenchyma except for spread along the interlobar fissures. Microscopically, classic mesotheliomas show both epithelial and sarcomatoid patterns (Fig. 14-16).^{6,99} The epithelioid tumors consist of glands, tubules, and solid sheets of tumor cells with abundant eosinophilic cytoplasm. The sarcomatoid tumors are composed of sheets of spindle cells that are similar to a fibrosarcoma. Biphasic mesotheliomas should have at least 10% of each component.

Immunohistochemistry plays an important role in the diagnosis of malignant mesothelioma, in particular to help make the distinction with carcinomas that metastasize to the pleura.^{100,101} Both mesotheliomas and carcinomas are positive for cytokeratins. Mesotheliomas are usually positive for calretinin, WT-1, and D2-40 (podoplanin), while adenocarcinomas are typically negative.^{6,99} Adenocarcinomas often, express carcinoembryonic antigen, Leu-M1, B72.3, and BER-EP4, while mesotheliomas are negative for these markers. Historically the absence of mucin and the presence of hyaluronic acid (positive Alcian blue staining) and long, slender microvilli seen on electron microscopy have been used to support the diagnosis of malignant mesothelioma, but immunohistochemistry has largely replaced these studies.^{6,99} See Chapter 82 for additional information on tumors of the pleura.

INTERSTITIAL LUNG DISEASES

IDIOPATHIC INTERSTITIAL PNEUMONIAS

The term *interstitial lung disease* comprises a heterogeneous group of disorders with various histopathologic features. Many different etiologies have very similar or identical pathologic ILD features and require thorough clinical and radiologic correlation to resolve. The differential diagnosis for most pathologic patterns includes collagen vascular disease, drug reaction, hypersensitivity reaction, or an idiopathic process.¹⁰²⁻¹⁰⁴ Therefore, the primary task of the pathologist is usually to recognize and categorize the pathologic pattern to expedite the correct clinical workup, inform treatment decisions, and guide prognosis. There may be histologic clues that can point toward an underlying etiologic process, as discussed in each subsequent section.

There have been various classifications of ILD, starting in 1969 by Liebow and Carrington.¹⁰⁵ In 2002, an ATS/ERS consensus classification of *idiopathic interstitial pneumonias* (IIP) was published.¹⁰⁶ Since then, there have been numerous publications and studies that have added significantly to our understanding of this category of disease with important clinical implications for management and treatment of patients with diffuse parenchymal lung disease. The ATS/ERS IIP classification was recently updated

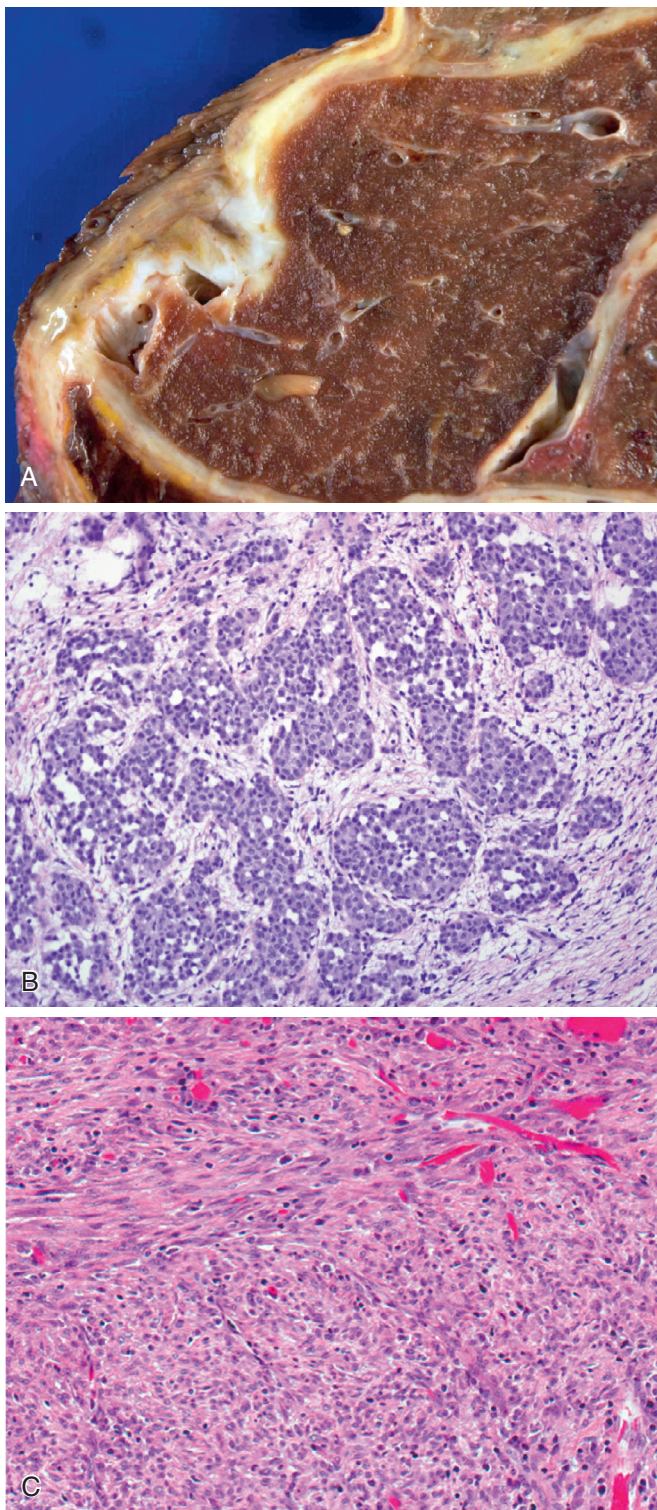


Figure 14-16 Pleural malignant mesothelioma. **A**, The lung is encased by a dense pleural tumor that extends along the interlobar fissures but does not involve the underlying lung parenchyma. **B**, This epithelioid malignant mesothelioma is composed of sheets of epithelioid malignant tumor cells. (H&E stain; original magnification $\times 200$.) **C**, This sarcomatoid malignant mesothelioma is composed of mostly spindle-shaped malignant cells (H&E stain; original magnification $\times 200$.)

by an international multidisciplinary panel comprising pulmonologists, pathologists, radiologists, and molecular biologists.¹⁰⁷ IIPs were divided into four groups: (1) fibrosing, (2) acute/subacute, (3) smoking-related, and (4) a new subcategory of “rare IIPs” was introduced and now includes *lymphocytic interstitial pneumonia* (LIP) and the newly described entity pleuropulmonary fibroelastosis.¹⁰⁷ The rare histologic patterns acute fibrinous and *organizing pneumonia* (OP) and bronchiolocentric patterns of interstitial pneumonia are recognized, but there was insufficient evidence to accept these as distinct IIPs.

In cases that prove impossible to classify, the term *unclassifiable interstitial pneumonia* has been coined. It accounts for cases with inadequate clinical or radiologic data or an inadequate or nondiagnostic biopsy. It is also the suggested diagnosis when there is a major discrepancy between clinical, radiologic, and pathologic findings, when previous therapy has resulted in alterations in the radiologic or histologic findings, or when there are discrepancies between histologic findings in different lobes not resolved after correlation with clinical and radiologic data.¹⁰⁸ Additional information on IIPs is found in Chapter 63.

Fibrosing Interstitial Lung Disease

Usual Interstitial Pneumonia/Idiopathic Pulmonary Fibrosis. UIP is the most common pattern of ILD and is the pathologic hallmark of *idiopathic pulmonary fibrosis* (IPF). The incidence of IPF, the idiopathic form of UIP, is 7 to 20 per 100,000 people and has no geographic or ethnic predilection.^{109,110} The classic clinical presentation is the gradual onset of shortness of breath with cough and clubbing in up to 50% of cases.^{104,111} Pulmonary hypertension has been reported in up to 32% of IPF patients awaiting lung transplantation and is associated with higher mortality in comparison to patients without pulmonary hypertension.¹¹² Radiographic imaging studies reveal small lung volumes with bilateral coarse reticular opacities most pronounced in the subpleural lower lobes and lower portions of the upper lobes (see Figs. 63-6 and 63-7). Honeycomb changes and traction bronchiectasis are typical features and become more pronounced as the disease progresses. When these typical features are present, the high-resolution CT appearance is 90% specific for UIP and surgical biopsy is often deferred (see Fig. 63-11 and eFigs. 63-2 through 63-5 and 63-7).^{104,106,113-115} A highly probable diagnosis of IPF can be made without lung biopsy, but definitive diagnosis of IPF requires surgical lung biopsy and exclusion of other known causes of ILD. It is important for the treating clinician to perform a thorough workup, including exposure history and serologic studies, to exclude secondary causes of pulmonary fibrosis such as chronic *hypersensitivity pneumonitis* (HP), collagen vascular disease, drug-toxicity, asbestosis, chronic aspiration, and Hermansky-Pudlak syndrome because each of these entities can cause an UIP pattern of interstitial fibrosis.^{102,103,116-118} Furthermore, after a biopsy has been performed and a pathologic diagnosis rendered, it is important to correlate the radiographic features with the pathologic findings in that cases of histologic UIP might not be associated with typical high-resolution CT findings of UIP. In this setting, multidisciplinary discussion is required for some of these patients to generate the correct diagnosis of IPF.^{104,106,107}

UIP is a diffuse fibrosing lung disease with a characteristic distribution of disease (see Fig. 63-22). The fibrosis is worse in the lower lobes and the lower portions of the upper lobe. Grossly, the pleura is firm and thickened with a cobblestone appearance. The histologic hallmark of UIP is the *heterogeneity* of the interstitial fibrosis, both in space and in time. As evidence of *spatial* heterogeneity, there should be areas of fibrosis separated by areas of more normal lung. Areas of normal lung should be present in a biopsy specimen to support the diagnosis and exclude other interstitial diseases. The fibrosis is distributed at the periphery of the lobules and is most pronounced in the subpleural regions (Fig. 14-17A). As evidence of *temporal* heterogeneity, there are areas of long-standing older interstitial fibrosis and areas of newer fibrosis characterized by *fibroblastic foci* (see Fig. 14-7B-C; see Fig. 63-24). Fibroblastic foci are composed of crescent shaped protrusions of fresh glycosaminoglycan-rich fibroblastic tissue composed of plump fibroblast and myofibroblasts. Fibroblastic foci are located in areas of ongoing or recent lung injury and are distinguished from older areas of denser fibrosis. Because the presence of numerous fibroblastic foci correlates with faster disease progression and decreased survival time, it is important to qualify the number of the fibroblastic foci in the surgical pathology report.¹¹⁹ The older areas of fibrosis are marked by architectural distortion of the underlying lung parenchyma with eventual development of honeycomb changes. There may be occasional aggregates of chronic inflammatory cells in the areas of older fibrosis but this does not tend to extend into normal-appearing lung parenchyma. Honeycomb changes are areas of abnormal dilatation of air spaces lined by bronchiolar epithelium (see Fig. 63-25). The cystic honeycomb spaces are filled with thick mucin-containing acute inflammatory cells; however, the presence of the neutrophils does not indicate an infectious process. Other characteristic features in the areas of older fibrosis and scarring include smooth muscle hyperplasia, pulmonary arterial thickening, and traction bronchiectasis. There should be no, or minimal, granulomatous inflammation, eosinophilia, acute pleuritis, or significant exogenous inorganic dust, silica, or asbestos fibers.^{102,104,106,110,111,120}

Acute exacerbation of IPF is a common but not well understood phenomenon. Acute exacerbation is the development of severe acute lung injury on a background of interstitial fibrosis and has been reported in several of the fibrosing ILDs. Five percent to 10% of patients annually develop acute respiratory worsening. Diagnostic criteria include (1) previous or concurrent diagnosis of IPF, (2) unexplained worsening or development of dyspnea within 30 days, (3) high-resolution CT demonstration of new bilateral ground-glass abnormality and/or consolidation superimposed on a background UIP pattern (see eFig. 63-11), (4) no evidence of pulmonary infection, and (5) exclusion of alternative causes, including left heart failure, pulmonary embolism, or other identifiable cause of acute lung injury. The histologic hallmark is the presence of acute lung injury with diffuse alveolar and/or OP superimposed on more established fibrosis. The histologic picture may be confusing especially when clinical or radiologic information is lacking or when acute exacerbation is the first presentation for the patient. However, the recognition of the older fibrotic injury, including honeycomb changes,

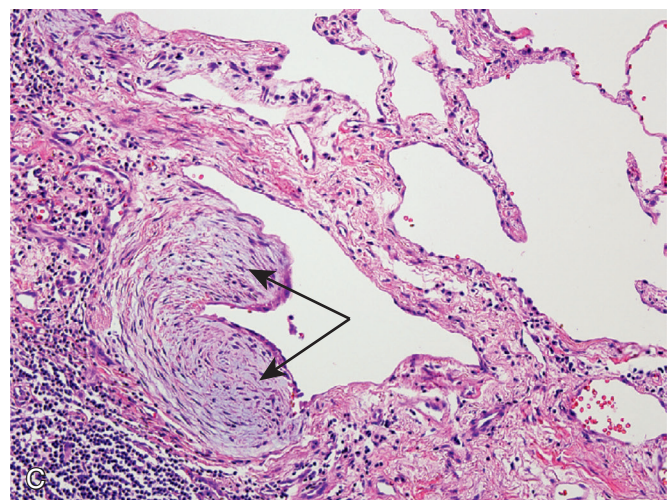
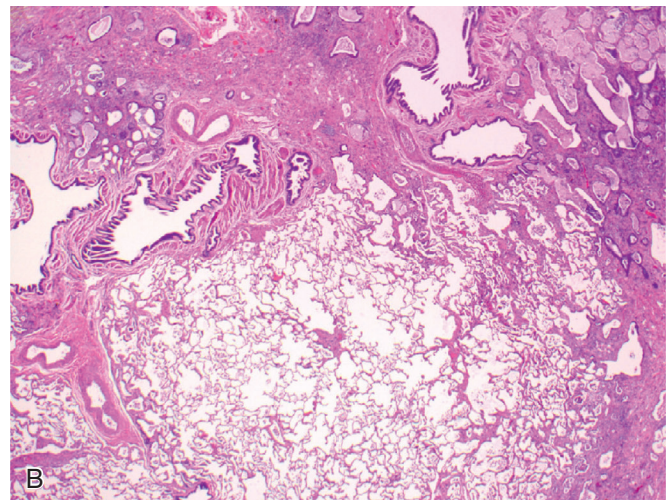
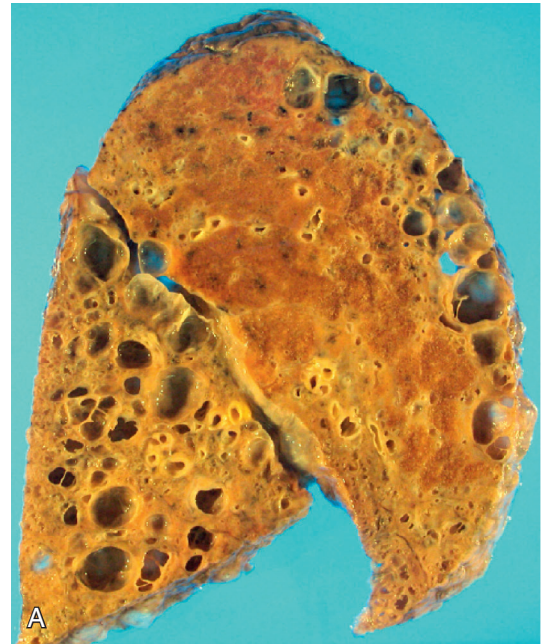


Figure 14-17 Usual interstitial pneumonia (UIP). **A**, Gross image shows lower lobe and periphery of upper lobe are replaced by pale fibrotic tissue displaying cystic honeycomb changes. The adjacent normal lung is spongy with preserved architecture. **B**, The areas of dense fibrosis contain honeycomb changes (top right) and sparse cellular inflammation. The transition with normal lung is abrupt (H&E stain; original magnification $\times 20$). **C**, The crescent-shaped fibroblastic focus is composed of loose and immature fibrous tissue (arrows). (H&E stain; original magnification $\times 200$.)

together with the acute lung injury helps establish the correct diagnosis.¹²¹⁻¹²⁵

As discussed previously, several entities can manifest a UIP pattern of fibrosis in the lungs, including chronic HP, collagen vascular disease involving the lungs, chronic aspiration, drug toxicity, asbestosis, and Hermansky-Pudlak syndrome. Clinical and radiologic evaluation often reveals the underlying etiology and distinguishes a secondary process from IPF. However, there may be some diagnostic uncertainty and pathologic evaluation may give clues as to the underlying etiology. Chronic HP is always associated with peribronchiolar metaplasia and most cases have demonstrable poorly formed granulomas. Collagen vascular disease may have pleural inflammation, prominent interstitial cellular infiltrates, and other features (Table 14-4). Chronic aspiration has sequelae of chronic airway irritation, specifically peribronchiolar metaplasia, and may have foreign material and giant cells or granulomas. Drug toxicity may have nonspecific histologic features but the accumulation of foamy macrophages could suggest amiodarone toxicity. Asbestosis is initially bronchocentric; iron stains may reveal ferruginous bodies diagnostic of asbestos. Hermansky-Pudlak syndrome is most commonly seen in albino people of Puerto Rican heritage; in this syndrome, vacuolated type II pneumocytes and alveolar macrophages are demonstrated.^{102,116,118,119,126-131} Features of usual interstitial pneumonia in patients with primary Sjögren's syndrome compared with idiopathic pulmonary fibrosis.^{131a} Drug toxicity and Hermansky-Pudlak syndrome may have similar histologic features, but clinical findings easily distinguish the two.

Nonspecific Interstitial Pneumonia. The term *nonspecific interstitial pneumonia* (NSIP) was first coined to

describe a pattern of ILD associated with HIV infection.¹³² Subsequently, Katzenstein and Fiorelli used the term to describe a *specific* pattern of ILD distinct from UIP that has since been found to have differing clinical and epidemiologic features.¹³³⁻¹³⁵ Katzenstein and Fiorelli grouped NSIP into three categories: group I, predominance of interstitial inflammation (cellular); group II, mixture of inflammation and fibrosis (mixed cellular and fibrotic); group III, primarily interstitial fibrosis (fibrotic).¹³³ When NSIP was introduced in the ATS/ERS Idiopathic Interstitial Pneumonia classification in 2002, it was given a provisional status due to uncertainties about the entity.¹⁰⁶ It has since become established as a specific pattern of ILD and found to be associated with secondary etiologies. Recent studies suggest most cases of NSIP pattern ILD are secondary to autoimmune disease, chronic HP, drug reactions, or organizing *diffuse alveolar damage* (DAD) and relatively few cases are truly idiopathic.¹³⁴⁻¹³⁷ Therefore, when the pattern of NSIP is recognized, a search for secondary causes of ILD is recommended because there may be significant differences in treatment and prognosis from idiopathic cases.

Compared to patients with UIP, patients with NSIP tend to be younger—average age 52 years—and are more likely to be female.¹³⁵ This gender difference may reflect the strong association with collagen vascular disease that tends to affect middle aged and younger women. Patients with NSIP secondary to collagen vascular disease often have serologic studies disclosing positive antinuclear antibody or rheumatoid factor.^{134,135,137} Imaging studies demonstrate bilateral reticular opacities with or without ground-glass opacifications, predominantly in the lower lobes.^{114,138,139}

In contrast to that of UIP, the pattern of interstitial disease associated with NSIP is generally uniform in space and in time. Grossly, the transition from fibrotic to normal lung is more gradual and does not display the very prominent honeycomb changes that characterize UIP (Fig. 14-18A). Histologically, the interstitial pneumonia is evenly distributed throughout the lobules without accentuation around the airways or in the subpleural regions (see Fig. 14-18B-C). The degree of cellular infiltration is variable and inversely related to fibrosis. In cellular NSIP, the interstitium is expanded by lymphocytes with scattered histiocytes and rare eosinophils and neutrophils (see Fig. 63-27). The presence of numerous eosinophils or frequent granulomas would indicate a secondary cause of NSIP. In fibrotic NSIP, the interstitium is expanded by fibrosis but the even distribution throughout the lobule is the same as in cellular NSIP (see Fig. 63-28). In mixed cellular and fibrotic NSIP, there is a gradual transition between cellular and fibrotic infiltrates. There is rarely the development of honeycomb changes and only in advanced cases of interstitial fibrosis. When honeycomb changes develop, the overall prognosis matches that of UIP.^{140,141} Similarly, fibroblastic foci are not a diagnostic feature of NSIP, but fibroblastic foci are not specific to UIP and the presence of rare fibroblastic foci does not exclude an NSIP pattern of fibrosis. Likewise, some degree of peribronchiolar metaplasia does not exclude the diagnosis of NSIP, because peribronchial metaplasia is often seen in the lungs of patients exposed to environmental irritants, especially cigarette smoke. OP is a nonspecific

Table 14-4 Histologic Features of Collagen Vascular Diseases in the Lungs	
Rheumatoid arthritis	Pleuritis, chronic interstitial pneumonia (NSIP pattern > UIP pattern), DAD, LIP, OP, necrobiotic (rheumatoid) nodule, amyloid, vasculitis, bronchiolitis, DAH
Systemic lupus erythematosus	Pleuritis, chronic interstitial pneumonia (NSIP > UIP), DAD with immune complex deposits, OP, vasculitis, bronchiolitis, DAH
Scleroderma	Pleuritis, chronic interstitial pneumonia (NSIP > UIP), DAD, OP, aspiration pneumonia, pulmonary hypertension including plexiform lesions
Polymyositis/dermatomyositis	Pleuritis, chronic interstitial pneumonia (NSIP > UIP), DAD, OP, aspiration pneumonia, vasculitis, bronchiolitis
Sjögren syndrome	Pleuritis, chronic interstitial pneumonia (NSIP pattern > UIP pattern), LIP, OP, amyloid, vasculitis, bronchiolitis
Mixed connective tissue disease	Pleuritis, chronic interstitial pneumonia (NSIP pattern > UIP pattern), DAD, LIP, OP, necrobiotic (rheumatoid) nodule, aspiration pneumonia, amyloid, vasculitis, bronchiolitis, DAH

DAD, Diffuse alveolar damage; DAH, diffuse alveolar hemorrhage; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

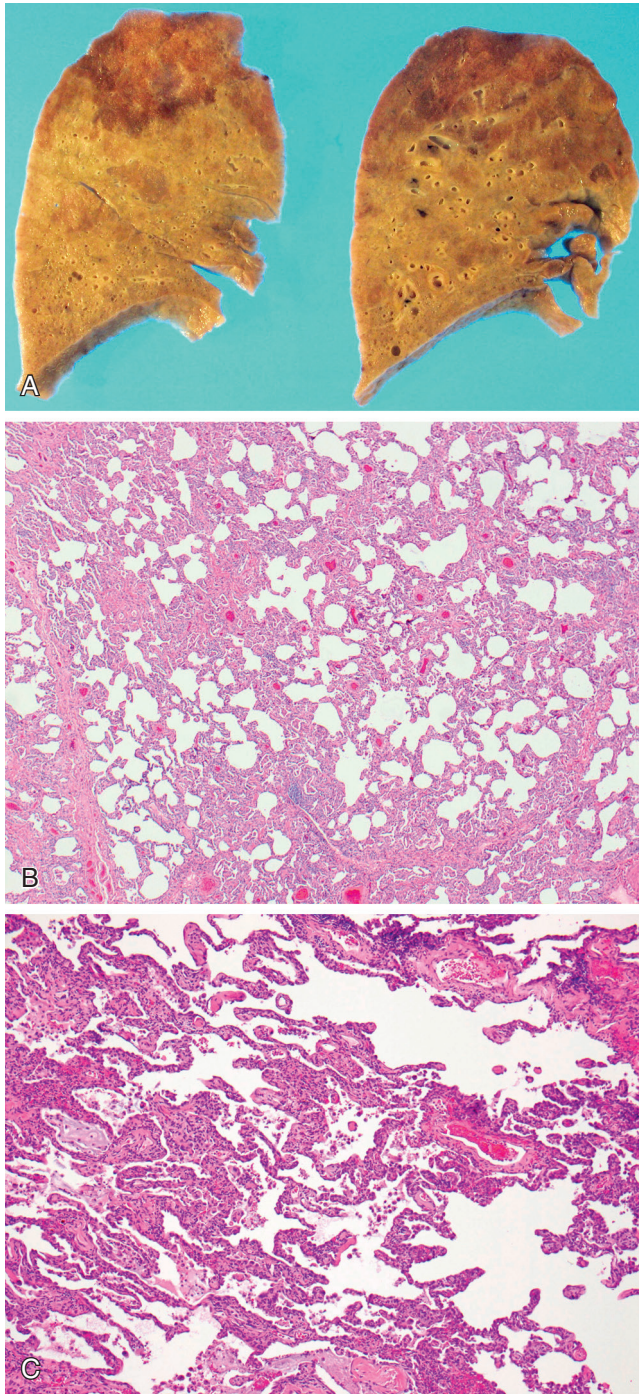


Figure 14-18 Nonspecific interstitial pneumonia. **A**, Gross image shows gradual transition of fibrosis from lower lobe to upper lobe with patchy normal lung. **B**, Low-power view of fibrotic interstitial infiltrate with preservation of alveolar architecture. (H&E stain; original magnification $\times 40$.) **C**, High-power view of mixed cellular and fibrotic infiltrate with temporal and spatial homogeneity.

reaction to lung injury and may be present in NSIP but it should not be widespread.¹⁴¹

As mentioned previously, the NSIP pattern of ILD may be seen secondary to numerous etiologies (Table 14-5). Before attempting to determine the underlying cause of the disease, it is important to distinguish NSIP from UIP. The distribu-

Table 14-5 Conditions Associated with Nonspecific Interstitial Pneumonia Pattern

Idiopathic
Hypersensitivity pneumonitis
Collagen vascular disease
HIV
Immunoglobulin deficiency
Organizing acute lung injury
Drug reaction
Viral/atypical infection

tion of the fibrosis and presence or absence of heterogeneity aids the correct diagnosis. However, if both patterns of ILD are present, the disease tends to behave as UIP, a factor that should guide management.¹²⁰ The particular pattern of NSIP also influences prognosis and treatment. Cellular NSIP has an excellent 5-year survival, with one study showing 100% survival.¹³⁴ Fibrotic NSIP has worse survival but is still much better than UIP unless honeycomb changes develop. In this setting, the survival equals that of UIP.^{114,141}

Acute/Subacute Interstitial Lung Disease

Organizing Pneumonia/Cryptogenic Organizing Pneumonia. OP is a nonspecific reparative reaction to many forms of lung injury and has been the source of some confusion over the years. OP may be encountered most commonly as a secondary reactive process, but occasionally it may be an idiopathic lesion. The clinical implications of discovering the cause of OP are very important. If the OP is associated with an autoimmune process or is idiopathic, the primary treatment will be immunosuppression; if the etiology is infectious, the treatment would be antibiotics and not immunosuppression. The confusion has been caused to some degree by the use of the name for the idiopathic disease with the histologic lesion and the similarity with an unrelated disease, *bronchiolitis obliterans*. To alleviate some of the misunderstanding, the older term for idiopathic OP, *bronchiolitis obliterans organizing pneumonia*, has been replaced with the term *cryptogenic organizing pneumonia* (COP) in the most current ATS/ERS classification.¹⁰⁶ Therefore, emphasis has been made in the latest ATS/ERS classification to use the term *organizing pneumonia* for the histologic lesion and to reserve the term COP as a clinical diagnosis of exclusion.

Patients with COP often present with fevers, chills, night sweats, and dyspnea with a dry cough. Chest imaging typically shows bilateral ground-glass opacities with air bronchograms and lower lobe predominance in most patients (see Fig. 63-33, eFigs. 63-21 and Video 63-2).¹⁴²⁻¹⁴⁴ Microscopically, OP is characterized by polypoid plugs of fresh fibrotic tissue that often develop in small airways (see Fig. 63-35) but also extend into alveolar ducts and sacs. In the idiopathic form, there is minimal cellular inflammation and no significant interstitial fibrosis^{102,145} (Fig. 14-19). If there is prominent inflammation, significant acute lung injury or interstitial fibrosis, then the OP is much more likely secondary to the disease process that is affecting the lungs. Special stains may be useful to evaluate for infections.^{145,146}

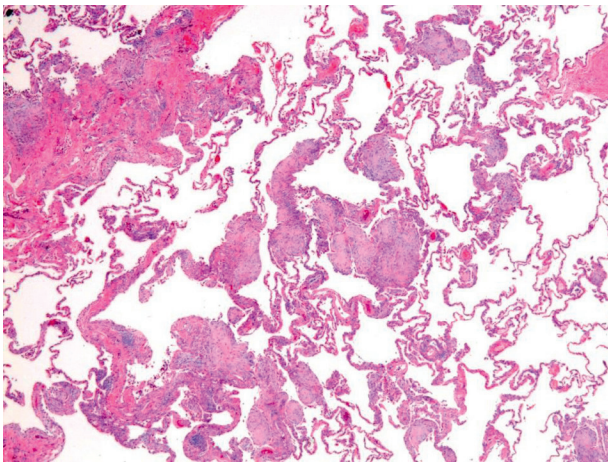


Figure 14-19 Cryptogenic organizing pneumonia (COP). Patchy foci of organizing pneumonia in absence of significant interstitial inflammation and fibrosis, characteristic of COP. (H&E stain; original magnification $\times 40$.)

Diffuse Alveolar Damage/Acute Interstitial Pneumonia. DAD is the histologic picture of severe acute lung injury and may be secondary to numerous pulmonary insults. This is the common pathologic diagnosis of patients with clinical acute respiratory distress syndrome. *Acute interstitial pneumonia* (AIP) is the idiopathic form of DAD. In this setting, there is no identifiable cause for the acute lung injury and is a diagnosis of exclusion. AIP is a rare syndrome and clinically presents as severe and sudden respiratory distress in a previously healthy individual. Mortality is greater than 50%. AIP is a diagnosis of exclusion and requires an extensive clinical workup to exclude infections or other identifiable pulmonary insults, such as drug toxicity, collagen vascular disease, radiation injury, or trauma.^{102,106,147}

The radiographic and pathologic features vary depending on the stage of the disease. Early, imaging studies reveal diffuse ground-glass opacities with increased densities in dependent parts of the lung (see [eFigs. 63-19](#) and [63-20](#)). Initially, there is no architectural remodeling or traction bronchiectasis. After 2 to 3 weeks, during the later stages, reticular opacities may become more pronounced and traction bronchiectasis and cystic changes may develop.^{148,149}

Pathologically, during the early exudative stage, the alveolar wall is thickened by interstitial edema and neutrophil margination in capillaries. Pneumocytes become hypertrophied and may undergo type II pneumocyte hyperplasia. Grossly, the lungs are heavy and boggy with a dark red cut surface. Toward the end of the first week, alveolar exudates increase and develop. The hyaline membranes are linear accumulations of dense hyaline material composed of fibrin, cellular debris, and serum proteins that line the surface of the alveolar sacs ([Fig. 14-20A](#), see [Fig. 63-32](#)). Small arteries and arterioles often contain in situ thrombi in the areas of acute lung injury. The underlying lung architecture is initially normal if the patient did not have preceding lung disease. In the later organizing stage that develops after 2 to 3 weeks, OP emerges and begins to replace the hyaline membranes (see [Fig. 14-20B](#)). Concurrently, fibrosis develops in the alveolar walls and may eventually result in an NSIP pattern of interstitial fibrosis. The

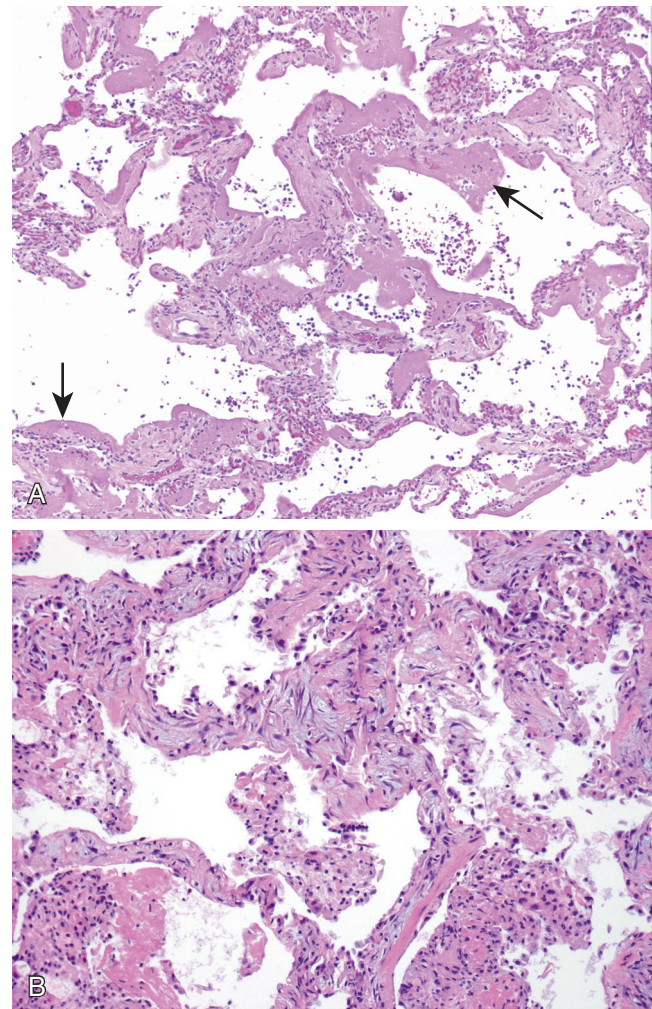


Figure 14-20 Diffuse alveolar damage (DAD). **A**, Hyaline membranes (arrows) line alveolar walls that are swollen with edema and scattered inflammatory cells. Pneumocytes are swollen and appear reactive. (H&E stain; original magnification $\times 40$.) **B**, Organizing diffuse alveolar damage shows loss of hyaline membranes with development of early fibrosis in the interstitium. There is only paucicellular inflammation. (H&E stain; original magnification $\times 400$.)

fibrosis may cause traction bronchiectasis and microcystic formation. The gross lungs in late stage DAD/AIP become firm and fibrotic with small cystic changes. In contrast to UIP/IPE, the lungs are normal in size but are heavy.^{106,147,150}

In AIP, the DAD has relatively mild cellular inflammation. The presence of certain pathologic features may suggest an etiology; clusters of neutrophils, necrotizing granulomas, or viral inclusions would indicate an infectious etiology; neutrophils, necrotizing granulomas, and tissue necrosis with or without vasculitis may also be due to vasculitis; foreign material with or without giant cells suggests aspiration pneumonia; pleural inflammation may indicate a collagen vascular disease; eosinophilia may suggest acute eosinophilic pneumonia; and accumulation of foamy histiocytes or foamy cytoplasmic changes in pneumocytes may suggest a drug toxicity. Clinical studies, including microbiologic cultures and serologic correlation for vasculitis and collagen vascular disease markers, may disclose a secondary etiology.

In some cases of diffuse fibrotic lung disease, especially UIP/IPF, acute exacerbation develops. Pathologically, this resembles organizing DAD superimposed on a background of diffuse interstitial fibrosis.^{121,122}

Smoking-Related Interstitial Lung Disease

Smoking is the primary etiology for two patterns of ILD, *respiratory bronchiolitis-ILD* (RB-ILD) and *desquamative interstitial pneumonia* (DIP), which are considered ends of a spectrum of lung disease characterized by accumulation of pigmented macrophages, mild to moderate interstitial fibrosis, and chronic airway inflammation. In RB-ILD, the macrophages are centered on and around small airways and, in DIP, the macrophages are more diffusely distributed throughout entire lobules. Between individual cases, some features may overlap; nevertheless, in general, the clinical, radiologic, pathologic, and treatment characteristics are different and the entities remain separately classified.¹⁰⁶

Respiratory Bronchiolitis-Interstitial Lung Disease.

RB-ILD is the pathologic manifestation of chronic airway inflammation, usually due to smoking, and reactive/reparative changes in and around the small airways. In clinical practice, the diagnosis is based on a history of smoking, dyspnea, ground-glass opacities with centrilobular nodules on imaging (see eFig. 63-16), and accumulation of pigmented (smokers') macrophages on *bronchoalveolar lavage* (BAL) fluid. Surgical biopsies are not performed as part of the workup unless there is concern for another process. The two histologic features of RB are peribronchiolar metaplasia of alveolar ducts surrounding terminal and respiratory bronchioles and accompanying clusters of pigmented macrophages (Fig. 14-21; see Fig. 63-30). When RB is associated with clinical features of ILD, the clinical disease is termed *respiratory bronchiolitis-interstitial lung disease*.

RB-ILD is almost always associated with smoking or another environmental irritant and is usually found in association with centrilobular emphysema. RB is a frequent incidental finding in lung excision specimens and is especially common in patients with a smoking history. Peribron-

chiolar metaplasia is a nonspecific reaction to chronic airway inflammation and is a very prominent feature of chronic HP. In contrast to chronic HP, RB usually has more conspicuous pigmented macrophages, is not associated with granulomas, and does not have lymphocytosis on BAL fluid analysis.¹⁵¹⁻¹⁵⁵

Desquamative Interstitial Pneumonia. DIP is another ILD strongly associated with smoking and is always associated with RB. DIP is an increasingly uncommon entity but has been observed in nonsmokers. It presents as dyspnea with cough and reveals bilateral ground-glass opacities with reticular markings (see eFig. 63-17) corresponding to interstitial fibrosis. Histologically, DIP is characterized by sheets of pigmented (smokers') macrophages that fill alveolar spaces and tend to clump together (see Fig. 63-31). There are usually clusters of eosinophils, but these are greatly outnumbered by the macrophages and are not sufficient to suggest eosinophilic pneumonia (Fig. 14-22). There is usually interstitial fibrosis within alveolar septa that resembles fibrotic NSIP and is more extensive than the microscopic interstitial fibrosis associated with smoking-related centrilobular emphysema.^{151,152,156-160}

The symptoms of DIP usually respond to smoking cessation and steroids when necessary, but a minority of patients fail to respond to treatment.

Rare Idiopathic Interstitial Pneumonias

To accommodate the introduction of newly described rare entities and to classify idiopathic LIP, a new subcategory of "rare IIP" was created in the latest ATS/ERS IIP classification.

Lymphocytic Interstitial Pneumonia. LIP is a rare entity most often associated with infections or underlying autoimmune or immunodeficiency diseases but can be idiopathic. Secondary causes include rheumatoid arthritis, Sjögren syndrome, lupus, Hashimoto thyroiditis, myasthenia gravis, common variable immunodeficiency, allogeneic bone marrow transplantation, and viral infections. Viruses implicated in LIP include *human immunodeficiency virus 1*

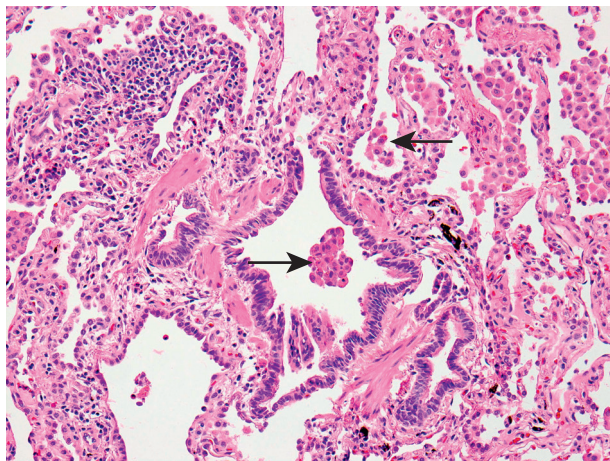


Figure 14-21 Respiratory bronchiolitis (RB). Small bronchiole with luminal pigmented macrophages (arrows) and peribronchiolar metaplasia. (H&E stain; original magnification $\times 200$.)

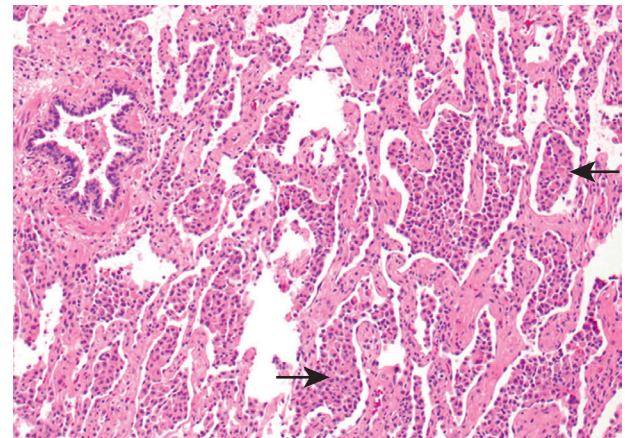


Figure 14-22 Desquamative interstitial pneumonia (DIP). Diffuse accumulation of pigmented macrophages in alveolar spaces throughout lobule (arrows). There is diffuse interstitial fibrosis in a nonspecific interstitial pneumonitis pattern (H&E stain; original magnification $\times 100$.)

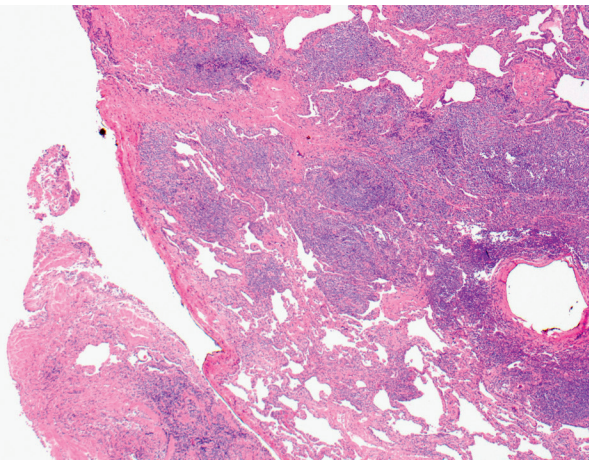


Figure 14-23 Lymphocytic interstitial pneumonia (LIP). The interstitium is greatly expanded by a dense lymphoplasmacytic infiltrate with loss of alveolar spaces. In less involved areas, the architecture is maintained. (H&E stain; original magnification $\times 40$.)

(HIV-1), *human T-cell lymphotropic virus 1* (HTLV-1), and *Epstein-Barr virus* (EBV) (especially in children). Clinically, LIP presents with cough, fever, and dyspnea; imaging studies may show various findings, including ground-glass opacity (see eFig. 63-28), nodules (see eFig. 63-29), bibasilar interstitial infiltrates, cysts (see Fig. 63-36 and eFig. 63-30), and honeycomb changes in up to one third of patients.¹⁶¹⁻¹⁶⁶

Pathologically, the interstitium is greatly expanded by a dense lymphoplasmacytic infiltrate (see Fig. 63-37) that is most pronounced in the lower lobes and is evenly distributed throughout the lobules (Fig. 14-23). The pattern resembles cellular NSIP but is distinguished by a greater degree of cellular infiltrate that disrupts the normal underlying architecture that is usually maintained in NSIP. Eventually, fibrosis with honeycomb changes may develop. The lymphoid infiltrate is nonneoplastic and consists of an organized mixture of T cells and nodular aggregates of B cells. However, secondary low grade lymphoma may develop in the setting of LIP in up to 30% of cases and is most commonly an extranodal marginal zone B cell lymphoma. LIP-associated lymphomas need to be distinguished from pseudolymphoma, another associated finding in LIP that is a localized masslike variant of LIP, which is polyclonal and shows no evidence of malignancy by immunohistochemistry or flow cytometry.^{102,167,168}

A newly described category of secondary LIP is granulomatous lymphocytic ILD that is associated with immunoglobulin deficiency, often common variable immunodeficiency. Pathologically and radiographically, it is very similar to LIP but is distinguished by the presence of numerous nonnecrotizing granulomas. The granulomas are not associated with infectious organisms but special stains should be performed to exclude an incidental infection in the setting of LIP.^{161,169}

Idiopathic Pleuroparenchymal Fibroelastosis. *Idiopathic pleuroparenchymal fibroelastosis* is a term recently coined to describe a rare entity of extensive upper lobe predominant fibroelastosis in the pleura and subpleura that is distinct from other forms of ILD. Clinically, patients are on

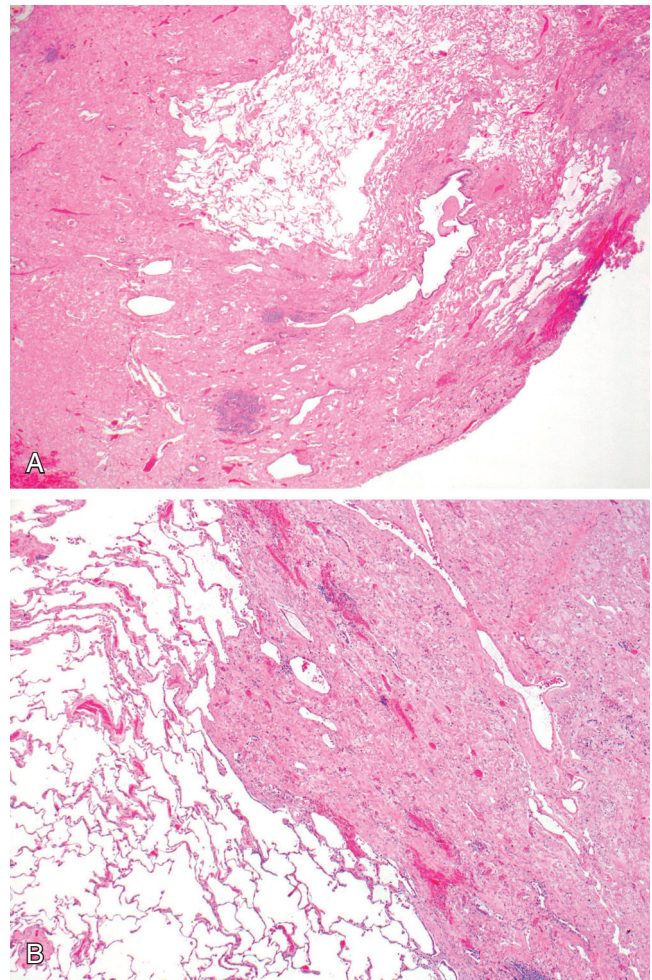


Figure 14-24 Pleuroparenchymal fibroelastosis. **A**, Low-power view showing extent of subpleural scar tissue. (H&E stain; original magnification $\times 20$.) **B**, Higher power showing sharp transition between scar and normal lung. The fibroelastic scar tissue is paucicellular and no fibroblastic foci are present. (H&E stain; original magnification $\times 40$.)

average 57 years old and have no gender predilection. Symptoms include dyspnea and cough. Imaging studies (see eFig. 63-31) show dense subpleural consolidations with upper lobe volume loss and possible architectural distortion with traction bronchiectasis in the involved lobes. The pathology is characterized by extensive fibroelastic scarring in the interstitium, entering into the alveolar space at the subpleural periphery of the lobules (Fig. 14-24). The transition between fibroelastosis and normal lung is very sharp and reminiscent of the spatial heterogeneity in UIP. However, fibroblastic foci are absent or rare in pleuropulmonary fibroelastosis, and the mild chronic inflammation present in UIP is virtually nonexistent in pleuropulmonary fibroelastosis. Despite the bland appearance of the fibrosis, the disease progresses in 60% of patients with eventual death in 40%.^{102,170-173}

Rare Histologic Patterns. The latest ATS/ERS classification includes a new category of rare histologic patterns to account for two relatively newly described entities, acute fibrinous and OP and bronchiolocentric interstitial pneumonia. Both of these entities share overlapping histologic

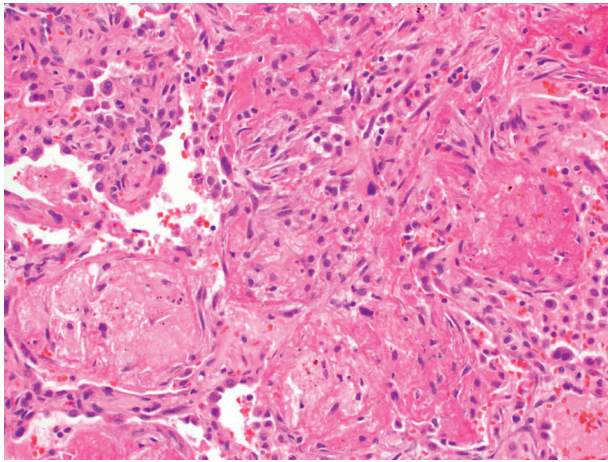


Figure 14-25 Acute fibrinous and organizing pneumonia. The alveolar spaces are occluded by rounded accumulations of fibrin and alveolar walls are edematous with reactive pneumocytes. (H&E stain; original magnification $\times 400$.)

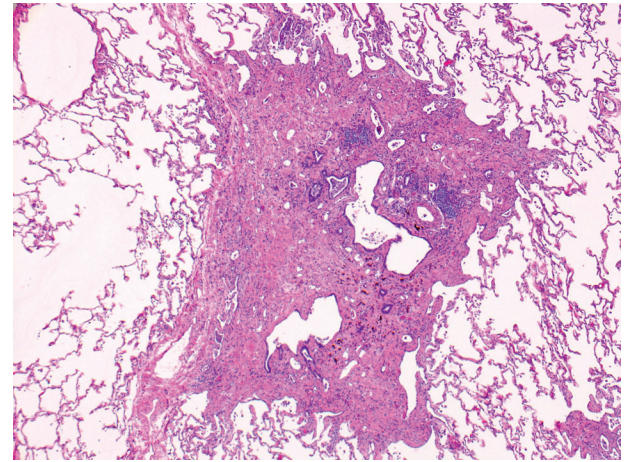


Figure 14-26 Bronchiolocentric interstitial pneumonia. There is centrilobular scar with absence of granulomas and only focal and mild chronic inflammation. (H&E stain; original magnification $\times 40$.)

features with other well-defined entities, may be seen in association with numerous secondary etiologies, and may or may not represent true and distinctive idiopathic diseases. Nevertheless, it is useful to recognize the patterns because they can guide the diagnostic workup.

ACUTE FIBRINOUS AND ORGANIZING PNEUMONIA. Acute fibrinous and OP is a histologic pattern of lung injury that is associated with acute respiratory failure with a similar mortality rate to AIP. Imaging studies reveal bilateral basal ground-glass opacities and consolidations. The diagnostic histologic feature is the accumulation of rounded intra-alveolar fibrin that may merge with OP (Fig. 14-25). Pneumocytes are reactive with type II pneumocyte hyperplasia and accompanying interstitial and intra-alveolar edema with paucicellular inflammation. There are no hyaline membranes or granulomas and eosinophils should be inconspicuous.

It is not clear whether acute fibrinous and OP is a distinctive entity, a more aggressive form of COP, or a subacute or organizing pattern of AIP. As with other forms of acute/subacute lung injury, secondary causes should be considered in the etiology, including connective tissue disease, subacute hypersensitivity pneumonitis, infection, and drug reaction. If no etiologic cause is discovered by clinical studies or special stains, it may be considered an idiopathic process.¹⁷⁴⁻¹⁷⁷

BRONCHIOLOCENTRIC INTERSTITIAL PNEUMONIA. Bronchiolocentric interstitial pneumonia is characterized by centrilobular fibrosis with peribronchiolar metaplasia (Fig. 14-26). There is variable chronic inflammation but there are no granulomas, abscesses, or eosinophils. It may be histologically indistinguishable from chronic HP without granulomas; therefore, thorough clinical evaluation to rule out HP is essential before the clinical diagnosis can be considered. Patients are middle-aged with a female predominance and demonstrate restrictive pathophysiology on pulmonary function tests. The radiographic features include reticulonodular opacities and air trapping. The secondary etiologies include all entities that may induce chronic airway inflammation, especially chronic HP, con-

nective tissue disease, and chronic aspiration/inhalational injury.^{178,179}

OTHER INTERSTITIAL LUNG DISEASES

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP), previously termed allergic extrinsic alveolitis, is an important and relatively frequently encountered cause of ILD. HP is a protean entity that has various presentations both clinically and pathologically. Other/older terms for HP include *farmer's lung*, *bird fancier's lung*, *humidifier lung*, *bat lung*, *coffee worker's lung*, and *pituitary snuff-taker's lung*, among many others. The various terms are derived from the source of the antigen that incites the autoimmune hypersensitivity reaction. More than 300 antigens have been implicated in the pathogenesis of HP. A fuller discussion of the pathogenesis of HP is found in Chapter 64.

HP may present at various stages. The traditional classification of HP separates the disease into acute, subacute, and chronic forms of HP. Acute HP is a transient process that results in chills, chest tightness, myalgia, headaches, cough, and dyspnea and lasts no more than a few days in the worst cases. Subacute and chronic cases of HP take longer to develop and are more associated with distinctive pathologic findings.¹⁸⁰

The pathology of acute HP is not well described because it is only rarely biopsied, and most case series are present in the older literature. Reports describe peribronchiolar cellular and air space edema with fibrinous exudates, consistent with organizing acute lung injury as well as neutrophilic infiltrates and capillaritis.^{176,181-183}

Subacute HP is primarily distinguished from chronic HP by the lack or paucity of well-established fibrosis. There is a dense lymphoplasmacytic interstitial infiltrate that is centered on, or accentuated around, the small airways. The bronchioles reveal cellular bronchiolitis that may include nodular lymphoid aggregates adjacent to the airways. Peribronchiolar metaplasia may not be fully developed in cases

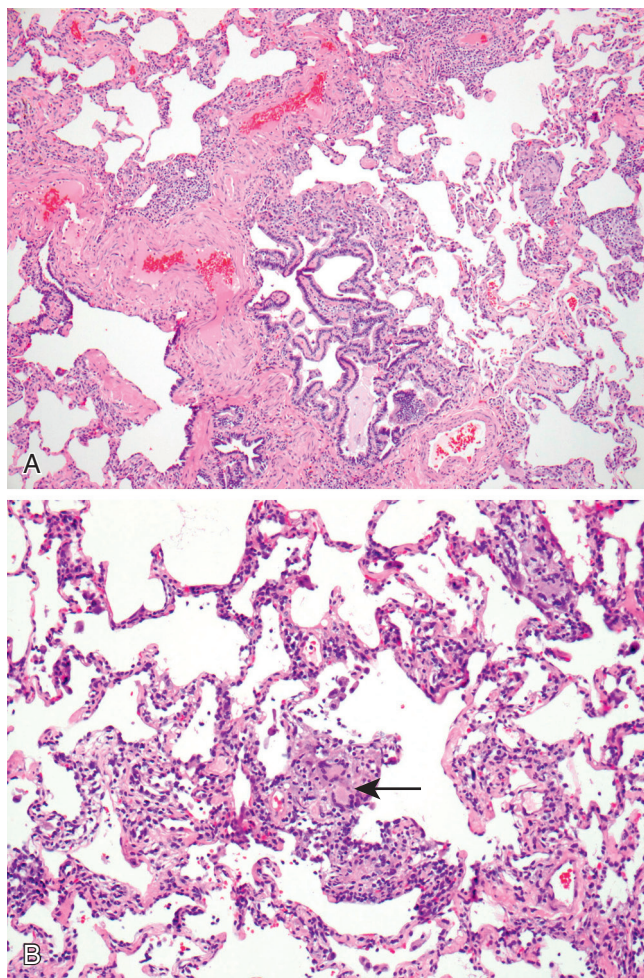


Figure 14-27 Hypersensitivity pneumonitis (HP). **A**, Bronchiole demonstrates florid peribronchiolar metaplasia. The interstitium is mildly expanded by cellular infiltrate and a poorly formed granuloma is present in the left of the field. (H&E stain; original magnification $\times 100$). **B**, Small cluster of multinucleated giant cells in center of field (arrow). (H&E stain; original magnification $\times 200$.)

of subacute HP. One of the pathologic hallmarks of HP is the presence of poorly formed nonnecrotizing granulomas in the interstitium adjacent to the airways (Fig. 14-27A). The granulomas are composed of an irregularly circumscribed collection of epithelioid histiocytes with or without multinucleated giant cells. The giant cells may contain cholesterol clefts, oxalate crystals, Schaumann bodies, or asteroid bodies (see Fig. 14-27B). The reported incidence of granulomas has been quite variable and it is recognized that as the disease progresses, the granulomas become less prevalent while fibrosis becomes more established. In cases of subacute HP, granulomas can be found in up to 70% of cases.¹⁸²

Chronic HP is distinguished from less advanced forms by the presence and distribution of well-established interstitial fibrosis.¹⁸⁴ The pattern of fibrosis is variable and may resemble UIP, fibrotic NSIP, bronchiolocentric interstitial pneumonia, or unclassifiable interstitial fibrosis. Chronic HP is invariably associated with peribronchiolar metaplasia that becomes more florid as the case becomes more advanced. The absence of peribronchiolar metaplasia should cause reconsideration of this diagnosis. As with other forms of

chronic interstitial pneumonia, pulmonary arteries become thickened with medial hypertrophy but features of idiopathic pulmonary hypertension, such as plexiform lesions, are not seen.^{126,181-183} Cigarette smokers have a lower incidence of HP than never smokers; nonetheless, smokers who do develop HP have a poorer outcome than nonsmoking counterparts.¹⁸⁵

The pathologic differential diagnosis for HP depends on the histologic features of a given case. Cases with all classic histologic and clinical features offer a straightforward diagnosis. In cases of chronic HP that lack granulomas, distinction from other patterns of ILD such as UIP, NSIP, LIP, COP, or bronchiolocentric interstitial pneumonia may be difficult. The centrilobular distribution of the fibrosis or cellular infiltrate may favor HP over UIP, NSIP, or LIP. The presence of significant fibrosis or cellular inflammation should distinguish HP from COP. In the absence of granulomas, clinical features and exposure history may be required to separate HP from bronchiolocentric interstitial pneumonia.^{102,103,155,178,181}

In cases with granulomas, the differential diagnosis includes infections, sarcoidosis, and aspiration. Infectious granulomas more frequently appear to be “floating” in air spaces and may disclose organisms with special stains; the granulomas of HP are located within the interstitium. In sarcoidosis, the granulomas are well-formed and are associated with less interstitial cellular inflammation than typically seen in HP. The discovery of foreign material, especially food or tablet fragments, may help reveal the source of a granulomatous pneumonitis to be aspiration induced. HP is bilateral and often upper lobe predominant whereas aspiration may involve the lower lobes, especially the right lower lobe. Therefore, the clinical and radiologic context may help guide the pathologic diagnosis, especially if foreign material or acute pneumonia is not seen on a small biopsy.^{116,186}

Sarcoidosis

Sarcoidosis is an idiopathic multisystem disorder that frequently affects the lungs and hilar lymph nodes; however, any organ system can be involved. Women are affected more frequently than men with the highest incidence worldwide in northern European countries. In the United States, sarcoidosis is most common in African Americans with an incidence of 35.5 per 100,000 people versus 10.9 per 100,000 Caucasians.¹⁸⁷ The peak incidence varies among different ethnicities but overall tends to affect younger patients in the third to fifth decade of life. A thorough discussion on the demographics, clinical features, and proposed etiology is found in Chapter 66.

The clinical and radiographic features of sarcoidosis are dependent upon the organ systems involved and the stage of the disease. Nonspecific symptoms include fever, weight loss, lethargy, myalgia, arthralgia, and dry eyes with blurry vision. Pulmonary symptoms include dyspnea, dry cough and, in some cases, digital clubbing. Imaging studies reveal bilateral hilar and mediastinal adenopathy (see Fig. 66-3), perilymphatic micronodules (see Figs. 18-24, 66-4, and 66-5), and upper lobe-predominant bilateral reticular opacities (see Fig. 66-6) in up to 15% of patients.¹⁸⁸⁻¹⁹¹

Grossly, lungs with sarcoidosis may reveal diffuse interstitial fibrosis with honeycomb changes in the worst affected

areas. Small pale millimeter sized nodules representing granulomas often may be seen throughout the lungs and on the pleural surfaces (Fig. 14-28A). Hilar lymph nodes may be markedly large, firm, and pale.

Histologically, the cardinal feature of sarcoidosis is the presence of numerous nonnecrotizing granulomas that are well formed and consist of clusters of multinucleated giant cells with admixed epithelioid histiocytes. Giant cells may contain asteroid bodies, Schaumann bodies, calcium oxalate, or carbonate crystals and Hamazaki-Wesenberg bodies. The granulomas may coalesce and form nodules of fibrosis, so-called nodular sarcoid. Granulomas are distributed along lymphatic channels and are frequently found in the bronchovascular bundle, on the pleural surface, and in the interlobular septa and diffusely throughout the hilar lymph nodes (see Fig. 14-28B-C). The location of granulomas in and around airways allows for high degree of diagnostic accuracy by transbronchial biopsy with up to 90% sensitivity.^{192,193} Punctate necrosis may be seen in up to one third of cases but special stains for organisms and cultures must be negative. There is relatively sparse interstitial chronic inflammation. All of these findings are nonspecific and require careful pathologic and clinical evaluation to rule out other forms of granulomatous pneumonitis.^{186,194,195} Sarcoidosis and common variable immunodeficiency: similarities and differences.^{195a}

Nonnecrotizing granulomatous vasculitis is seen in up to two thirds of open lung biopsy specimens. The involved vessel walls contain multinucleated giant cells or epithelioid granulomas. Fibrinoid necrosis of vessels and acute neutrophilic inflammation are not seen in sarcoidosis.¹⁸⁶

In up to 15% of patients, the pulmonary disease progresses and may result in extensive interstitial fibrosis with honeycombing and cystic changes. The fibrosis extends out from lymphatic areas and may resemble a UIP-pattern of fibrosis. However, the fibrosis has a temporally uniform appearance and fibroblastic foci are not conspicuous. Non-invasive aspergillomas or other fungus balls may grow in the cystic spaces with the risk of development of invasive fungal disease (see Fig. 38-3), if the patient becomes immunocompromised. As the fibrosis increases, the concentration and number of granulomas may decrease. In some cases of advanced end-stage pulmonary fibrosis, there may be no identifiable granulomas on pathologic evaluation.¹⁸⁶

The differential diagnosis encompasses many granulomatous diseases in the lungs; considerations include infection, hypersensitivity pneumonitis, drug reaction, and reaction to exogenous materials such as beryllium and talc. Clinical and microbiologic studies can exclude most entities in the differential diagnosis. In HP, granulomas are poorly formed and the process is usually associated with more prominent cellular interstitial inflammation. However, pulmonary involvement by beryllium disease may be identical to sarcoidosis, and only exposure history and/or the beryllium lymphocyte stimulation test can distinguish the two entities.¹⁹⁶

Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) describes a proliferation of Langerhans cells and has been described in multiple locations including the skin, lymph nodes, bones, and lungs. In extrapulmonary locations, the Langerhans

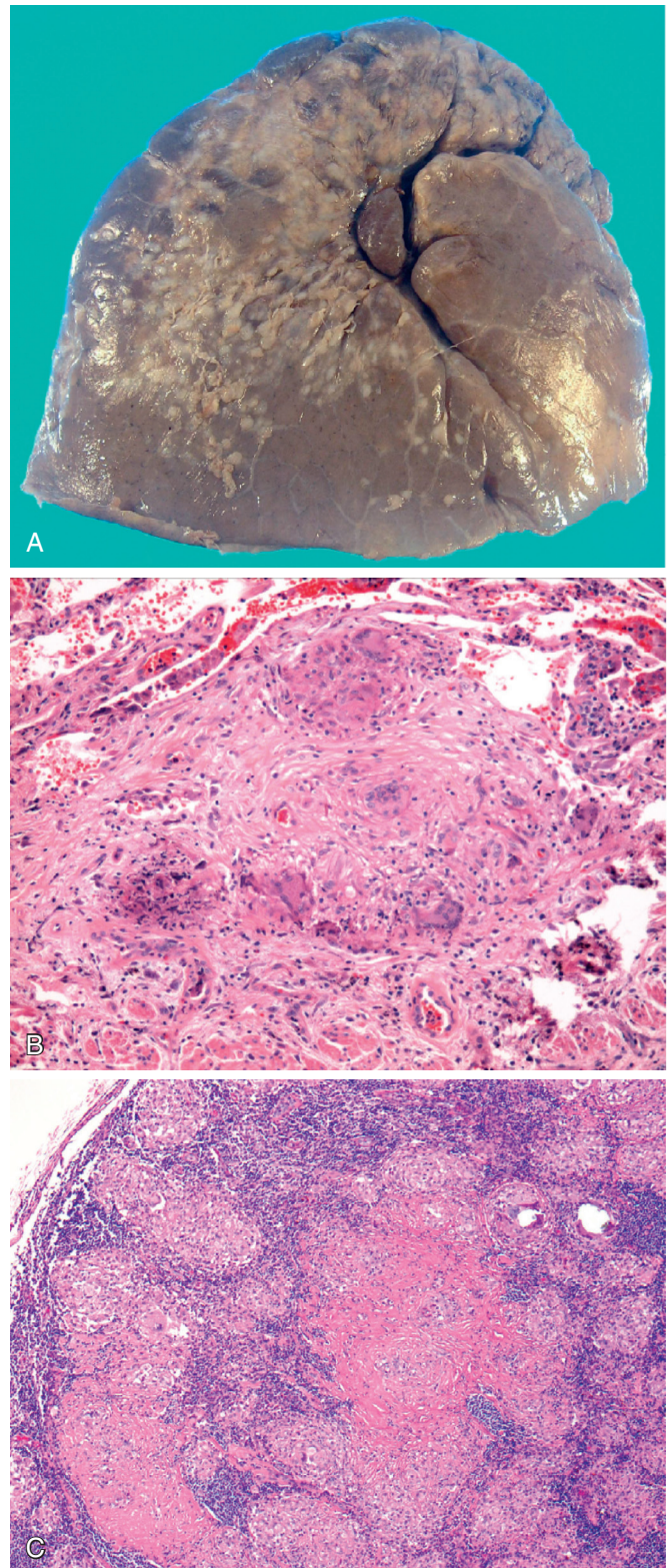


Figure 14-28 Sarcoidosis. **A**, Gross image shows numerous nodules on pleural surface corresponding to nodular sarcoid. **B**, Well-formed epithelioid granulomas in paucicellular fibrotic background. (H&E stain; original magnification $\times 200$.) **C**, Hilar lymph node with innumerable coalescing epithelioid granulomas. (H&E stain; original magnification $\times 100$.)

cell proliferation is clonal and likely a neoplastic process, usually affecting children or young adults.¹⁹⁷ In PLCH, the disease is usually associated with smoking and is most often a reactive process. The peak incidence is in young adult smokers, and the disease may remit with cessation of smoking if prominent fibrosis has not yet developed.

Clinically, patients may complain of cough, dyspnea, weight loss, and fever and are at increased risk of spontaneous pneumothorax. Radiographic studies reveal bilateral reticulonodular opacities most prominent in the midzones. As the disease progresses, the nodules become more cystic and can involve all lung zones (see eFig. 54-37).^{198,199}

Pathologically, the earliest stage of disease has multiple centrilobular stellate nodules of cellular infiltrates of Langerhans cells, eosinophils, lymphocytes, and histiocytes (Fig. 14-29A-B). The identification of clusters of Langerhans cells confirms the diagnosis. Langerhans cells have pink granular cytoplasm with vesicular, beanlike nuclei and are highlighted by CD1A (see Fig. 14-29C) and S100 immunohistochemistry staining. Initially, lesions appear rounded, but as the disease progresses, stellate-shaped fibrotic scars slowly replace the cellular infiltrates until only few inflammatory cells remain (see Fig. 14-29A). Later stage PLCH can be diagnosed by the stellate shape and centrilobular location of the scars in association with the characteristic

radiographic findings and clinical history of smoking. The infiltrate and scarring of PLCH can result in small airway obstruction and distal acinar air-trapping that may lead to the development of a pneumothorax. In severe cases of PLCH, the upper and midzone predominant pulmonary fibrosis can progress to honeycomb changes and end-stage fibrotic lung disease, resulting in a need for lung transplantation.^{159,200,201}

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disease of abnormal smooth muscle cell proliferation found almost exclusively in woman of reproductive age. LAM is seen sporadically or as a complication of tuberous sclerosis. Patients usually present with dyspnea and are prone to hemoptysis, chylous effusions, and pneumothoraces. Imaging studies show enlarged lung fields with diffuse thin-walled cystic changes throughout all lung zones and may be diagnostic if the patient has clinical features of LAM (see Fig. 18-29).

The gross appearance reveals large lungs with diffuse replacement of the parenchyma by thin-walled cysts throughout all lobes (Fig. 14-30A). Microscopically, the lung shows multiple cysts as well innumerable foci of irregular smooth muscle cell aggregates in the walls of alveoli and bronchioles in all parts of the lung and within thoracic

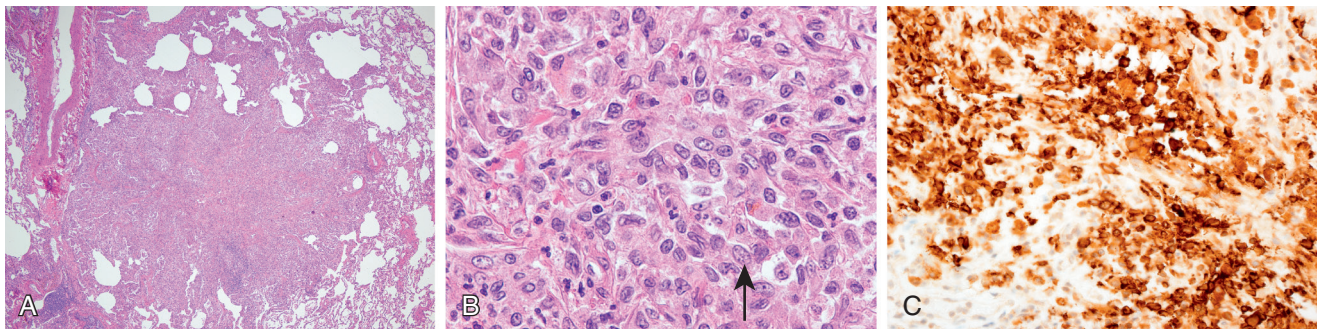


Figure 14-29 Pulmonary Langerhans cell histiocytosis (PLCH). **A**, A stellate shaped infiltrate of inflammatory and histiocytic cells expands the interstitium. (H&E stain; original magnification $\times 40$). **B**, This sheet of Langerhans cells shows a moderate amount of eosinophilic cytoplasm with nuclei showing prominent characteristic grooves (arrow). (H&E stain; original magnification $\times 800$). **C**, The Langerhans cells stain strongly with CD1a. (Immunohistochemistry for CD1a; original magnification $\times 200$.)

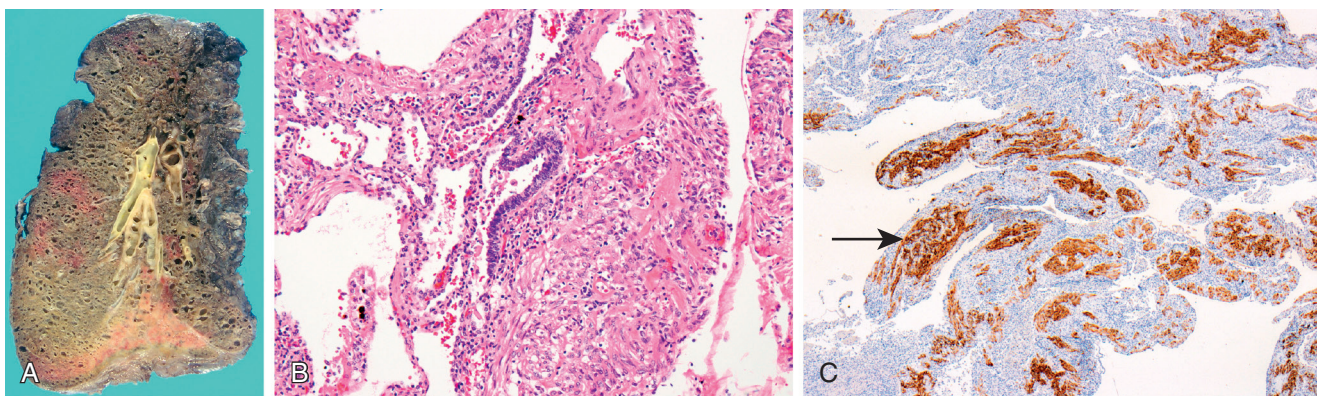


Figure 14-30 Lymphangioleiomyomatosis (LAM). **A**, Gross image shows numerous thin-walled cysts evenly distributed throughout entire lung parenchyma. **B**, Collection of abnormal cluster of smooth muscle cells in wall of respiratory bronchiole. (H&E stain; original magnification $\times 200$). **C**, Immunostain highlights diffuse infiltration of clusters of smooth muscle cells throughout parenchyma and expression of HMB-45 (arrow). (Immunohistochemistry for HMB45; original magnification $\times 200$.)

lymph nodes (see Fig. 14-30B-C). These cells arise from a somatic cell mutation and are actually a mesenchymal tumor. The smooth muscle aggregates result in obstruction of airways and lymphatic vessels that cause cystic dilatation and lymphatic obstruction distal to the lesion. The smooth muscle cells appear small with higher nuclear to cytoplasmic ratios than normal and may be spindle shaped or epithelioid with bland cigar-shaped nuclei. Along with other smooth muscle cell markers, LAM also expresses HMB-45 (see Fig. 14-30C) as well as estrogen and progesterone receptors. HMB-45 expression is a common feature of a rare category of tumors known as “perivascular epithelioid cell” class of tumors (PEComas). PEComas are mesenchymal tumors composed of clear epithelioid cells and are more commonly found in women. LAM and renal angiomyolipomas are the most common type of PEComas. LAM and other PEComas are often found in the setting of tuberous sclerosis but may also arise sporadically.^{196,202-204} Additional information on LAM can be found in Chapter 69.

Eosinophilic Pneumonia

Eosinophilic pneumonia (EP) represents a spectrum of disease from a mild transient process to severe interstitial fibrosis. In most cases, patients have peripheral eosinophilia that, when coupled with infiltrates on imaging studies, leads to the diagnosis. EP may be an idiopathic process or may be secondary to numerous other processes.

Both idiopathic and secondary forms of EP can be categorized into simple, acute, or chronic EP. Simple EP, also called Löffler syndrome, is characterized by very high but transient peripheral eosinophilia and migratory pulmonary opacities. Many patients are asymptomatic but others have dry cough and dyspnea. Many patients may ultimately demonstrate infection with *Ascaris* but idiopathic cases are seen. Due to the classic clinical and radiologic features, cases are rarely biopsied. Nevertheless, lung biopsies may show numerous eosinophils in the alveolar space and interstitium.¹⁹⁶

Acute EP is a sudden onset disease process that presents with cough, fever, dyspnea, and pleuritic chest pain and may lead to acute respiratory distress syndrome. Acute EP may be seen at any age and sexes are affected equally. Blood may have elevated or normal eosinophil levels but BAL fluid usually has more than 25% eosinophils. Imaging studies show the diffuse opacities characteristic of acute respiratory distress syndrome (see eFig. 68-4). Pathology demonstrates acute lung injury with accompanying tissue eosinophilia (Fig. 14-31). Fortunately, most cases respond quickly to corticosteroid treatment, which may eradicate the eosinophils after the first dose, making pathologic diagnosis difficult if the biopsy was performed after initiation of treatment. Nevertheless, in the appropriate clinical setting, the diagnosis of “compatible with partially treated/resolving acute eosinophilic pneumonia” may be rendered if the biopsy reveals acute lung injury/DAD only.²⁰⁵

Chronic EP is an insidious process that progresses for several months before presentation. Most patients are women with a peak incidence in the fifth decade and many have a history of asthma or other atopic illness. Symptoms include cough, dyspnea, fevers, and weight loss. Eosinophils are often very high in the blood and BAL fluid. Chest radiographs demonstrate consolidation in bilateral subpleural

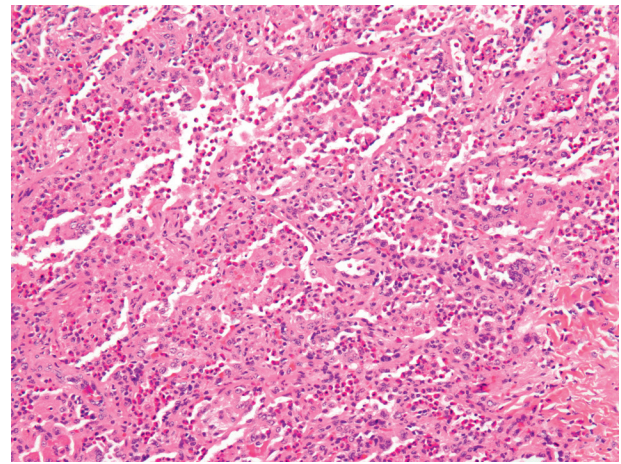


Figure 14-31 Eosinophilic pneumonia (EP). This area of acute lung injury has a florid infiltrate of eosinophils throughout the alveolar spaces and the interstitium. (H&E stain; original magnification $\times 200$.)

lung regions, a finding that has been called “reverse pulmonary edema pattern” (see eFigs. 68-1 and 68-3 and Video 68-1).²⁰⁶

Pathologically, eosinophils are clustered in alveolar spaces along with alveolar macrophages and may form small abscesses with central necrosis (see Figs. 68-1 through 68-3). In idiopathic cases, stain for organisms and culture results are negative. There may be occasional sarcoid-like granulomas and vascular inflammation but there are no lesions of necrotizing vasculitis. The pathologic hallmark of chronic EP is the presence of interstitial fibrosis, which can progress and become extensive with honeycomb changes. The fibrosis may resemble UIP or fibrotic NSIP patterns. As with acute EP, the eosinophils in chronic EP respond well to corticosteroid treatment and may become scarce after initiation of treatment. The clinical context and history of blood or BAL eosinophilia may aid in the recognition of the correct diagnosis.^{196,205-207} More information on eosinophilic lung is found in Chapter 68.

An expanded discussion of various forms of vasculitis and pulmonary hypertension is available online at *ExpertConsult*.

Key Points

- The evolution in our understanding and treatment of lung cancer now necessitates the use of specific pathologic diagnoses. The combination of morphologic features and judicious use of immunohistochemistry stains should be used to classify the type of carcinoma.
- Adenocarcinomas may have identifiable driver mutations that can represent therapeutic targets. When examining small biopsy specimens, it is important to be judicious in the use of immunohistochemistry analysis to preserve material for subsequent molecular and cytogenetic analysis. The recommended minimum molecular analysis of lung adenocarcinoma is an investigation for *EGFR* mutations and for *ALK* translocations.
- The classification of adenocarcinoma is based on the size of the pathology specimen and the predominant

VASCULITIS

Vasculitis is inflammation in a vessel wall and may be primary (idiopathic) or secondary. The idiopathic vasculitides that most commonly affect the lungs are *granulomatosis with polyangiitis* (GPA), formerly Wegener granulomatosis, *eosinophilic granulomatosis with polyangiitis* (EGPA), or Churg Strauss syndrome, and microscopic polyangiitis. The vasculitides share several clinical and radiographic features and may be distinguished by laboratory data, especially serologic studies, and pathologic findings. All three vasculitides are associated with abnormal autoimmune circulating antibodies termed ANCA (*antineutrophil cytoplasmic antibodies*) which affect small and medium-size blood vessels, often present with hemoptysis, and often have concurrent involvement of the kidneys, resulting in pulmonary renal syndrome. Other sites may also be involved, including the upper respiratory tract, skin, gastrointestinal tract, and the musculoskeletal and nervous systems.²⁰⁸⁻²¹⁰

The pathophysiology and clinical features of the various vasculitides are reviewed in more detail in Chapter 60.

GRANULOMATOSIS WITH POLYANGIITIS

GPA is a rare disease characterized by a triad of necrotizing granulomatous vasculitis in the upper respiratory tract, lower respiratory tract, and kidneys, resulting in bloody nasal discharge, hemoptysis with respiratory distress, and acute renal failure, respectively. Frequency of involvement is 90% for the upper and lower respiratory tract and 80% for the kidneys. GPA is usually associated with cytoplasmic type ANCA (c-ANCA) in contrast to the other two ANCA-associated vasculitides.²¹¹

Radiographic studies reveal multiple and bilateral lung masses that frequently cavitate and may be found in all lung zones but are most frequent in the lower lobes (see eFigs. 60-1 and 60-2). Pathologically, the lesions are composed of irregularly shaped, or “geographic,” necrosis that is usually basophilic (eFig. 14-1A; see Fig. 60-5). Small to medium sized vessel with transmural fibrinoid necrosis may be found in the lesions of geographic necrosis. There is an ill-defined granulomatous reaction of epithelioid histiocytes surrounding the inflamed vessels with scattered multinucleated giant cells with dark or basophilic cytoplasm that sometimes appear small. Alveolar capillaries may have capillaritis with engorgement of neutrophils and karyorrhectic debris (see eFig. 14-1B). Neutrophilic microabscesses rimmed by granulomatous inflammation and scattered multinucleated giant cells is a characteristic finding and does not indicate concurrent infection. Vascular injury may result in diffuse alveolar hemorrhage that can be difficult to distinguish from biopsy artifact. The presence of numerous hemosiderin-laden macrophages confirms authentic hemorrhage and discounts artifactual bleeding. Bronchioles may be involved or obliterated by the necrotizing granulomatous inflammation and, if larger airways are involved, the necrosis affects the cartilage. In older cases that have undergone repair, chronic vascular changes may be detected by identifying disruption of arterial internal elastic lamina through the aid of elastic tissue stains. The elastic layer shows abrupt disruption and fragmentation, and the

arterial intima may contain abnormal fibrosis with infiltration of mononuclear cells.²¹¹⁻²¹³

Immunofluorescence studies for evaluation of antibody deposition are very weak or negative and are only useful to rule out other entities in the differential diagnosis, such as immune complex-mediated vasculitis. Electron microscopy studies are not indicated.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

EGPA is a very rare disease defined by the presence of asthma, peripheral eosinophilia, and systemic vasculitis. The most common type of ANCA is perinuclear ANCA (p-ANCA) but c-ANCA is found in 10% of cases and 30% of cases have no identifiable ANCA. Pathologically, EGPA and GPA share many features but may be distinguished by the presence of numerous eosinophils in EGPA. As with GPA, vasculitis with palisading granulomatous inflammation, geographic necrosis, capillaritis, and diffuse alveolar hemorrhage may be seen (eFig. 14-2; see Fig. 68-6).^{205,213-215}

MICROSCOPIC POLYANGIITIS

Microscopic polyangiitis affects only small vessels and is not associated with granulomatous inflammation. It is associated with p-ANCA in 50% of cases, with c-ANCA in 40% of cases, or with no identifiable ANCA in 10% of cases. It is the most common cause of pulmonary-renal syndrome. The dominant pathologic feature is capillaritis with diffuse alveolar hemorrhage (eFig. 14-3). In this setting, immunofluorescence studies are useful to exclude other causes of diffuse alveolar hemorrhage such as Goodpasture syndrome, lupus pneumonitis, cryoglobulinemia, or other immune complex-mediated diseases.^{211-213,216,217}

PULMONARY HYPERTENSION

Pulmonary hypertension is a frequent complication of patients with underlying diffuse lung disease, left-sided heart disease, and chronic thromboembolic disease but is rare in the primary setting and usually affects young and middle-aged women. A full discussion of the clinical and pathophysiologic features of pulmonary hypertension is found in Chapter 58.

As described in Chapter 58 (see Table 58-1), pulmonary hypertension is classified into five clinical classes. Each group has subcategories and multiple etiologies.

The pathology of pulmonary arterial hypertension is graded on the severity of changes in the wall and increases as follows: pulmonary arteriopathy with isolated medial hypertrophy, pulmonary arteriopathy with medial hypertrophy and intimal thickening, pulmonary arteriopathy with plexiform and/or dilation lesions, and pulmonary arteriopathy with isolated arteritis. The plexiform lesion consists of a small focus of tightly intertwined slitlike vascular spaces lined by mildly swollen endothelial cells (eFig. 14-4). The surrounding lung may appear normal or have an increase in hemosiderin-laden macrophages. The plexiform lesions are often adjacent to dilated thin-walled vascular channels that balloon in response to the increased

pulmonary blood pressure associated with the plexiform lesion. The presence of numerous dilatation lesions indicates higher pathologic grade. In severe cases, the pulmonary hypertension can result in paucicellular necrosis of the vessel wall and necrotizing arteritis.^{196,219}

Plexiform lesions may mimic the changes associated with organizing thromboemboli but can be distinguished by several features. Plexiform lesions are found in small arteries or arterioles, whereas organizing thromboemboli often involve large or medium-sized pulmonary arteries. Plexiform lesions have slitlike channels, whereas organizing thromboemboli have larger and rounded channels. Finally, an elastin stain of plexiform lesions shows abnormal elastin, with small wisps of elastic tissue present between the slitlike spaces, whereas an elastin stain in organizing thromboemboli shows an intact internal elastic lamina.

Capillaries and pulmonary veins may also be the site of vascular obstruction. In pulmonary capillary hemangiomatosis, there is an increase in capillaries in alveolar walls, peribronchiolar tissue, pleura, and interlobular septa (eFig. 14-5A). The capillary proliferation may be demonstrated by a reticulin-collagen stain or endothelial cell marker such as CD31. In most cases, pulmonary capillary hemangiomatosis is accompanied by venous intimal thickening in interlobular septa, termed pulmonary veno-occlusive disease. The intimal thickening is due to fibrosis that is initially myxoid in character but eventually becomes denser and more collagenized (see eFig. 14-5B). There are often scattered mononuclear cells throughout the intima but no evidence of vasculitis.^{196,219,220}

subtype. Disease-free survival studies have shown the best prognosis for patients with adenocarcinoma in situ or minimally invasive adenocarcinoma.

- The diagnostic distinction between adenocarcinoma and squamous cell carcinoma is now important because of several therapeutic differences between the two pathologic types of non-small cell lung cancer.
- The most recent classification of *idiopathic interstitial pneumonias* (IIPs) divides the main diseases into four categories: *fibrosing interstitial lung disease* (ILD), acute/subacute ILD, smoking-related ILD, and rare IIPs.
- The most common pattern of fibrosing ILD is usual interstitial pneumonia, followed by nonspecific interstitial pneumonia. All patterns of ILD may be primary or secondary. Careful clinical, radiologic, and pathologic correlation is required to determine the underlying etiology.
- The differential diagnosis of *granulomatous pneumonitis* includes sarcoidosis, hypersensitivity pneumonitis, infections, drug-reaction, and chronic aspiration.

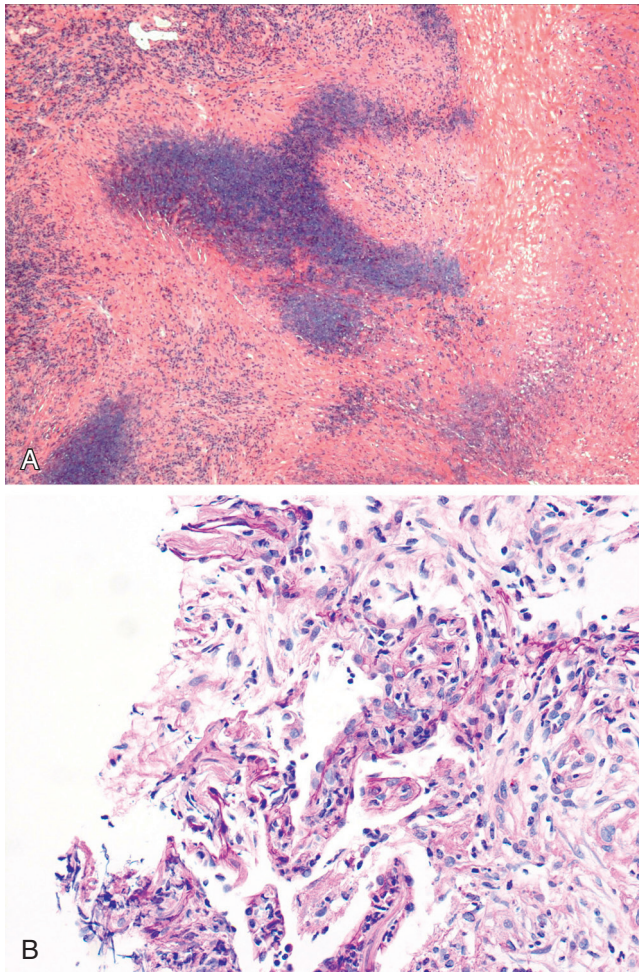
Complete reference list available at ExpertConsult.

Key Readings

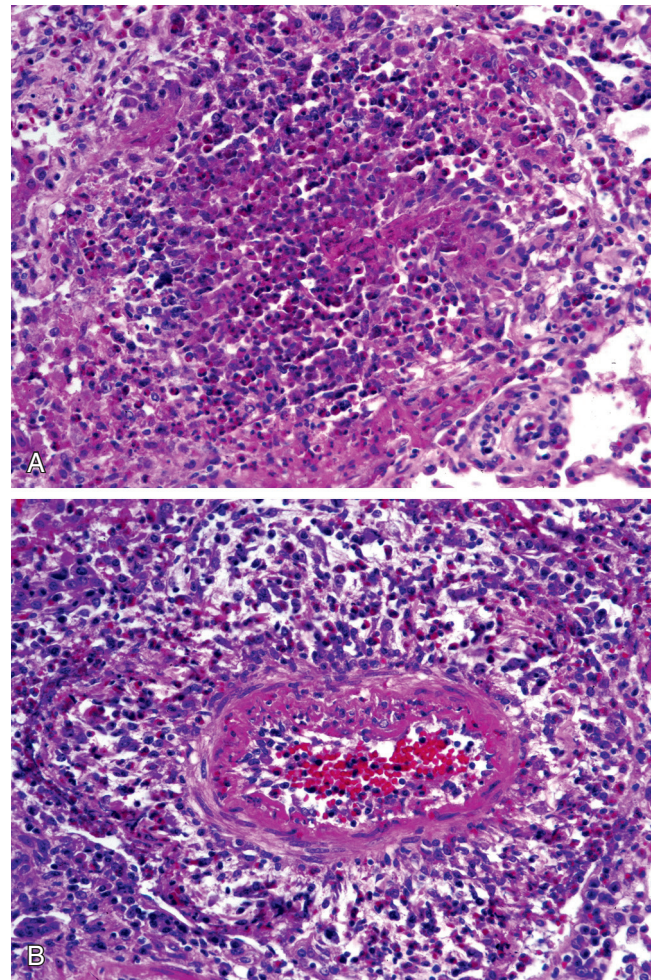
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- The three most common pulmonary vasculitides are usually associated with antineutrophil cytoplasmic antibodies and often involve other organ systems, including the kidneys and upper respiratory tract.

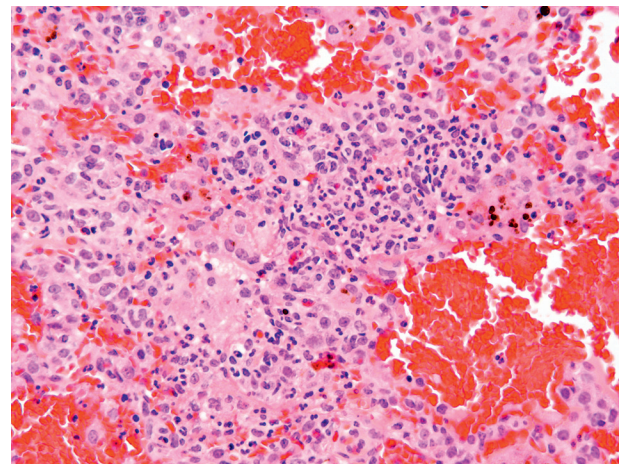
eFIGURE IMAGE GALLERY



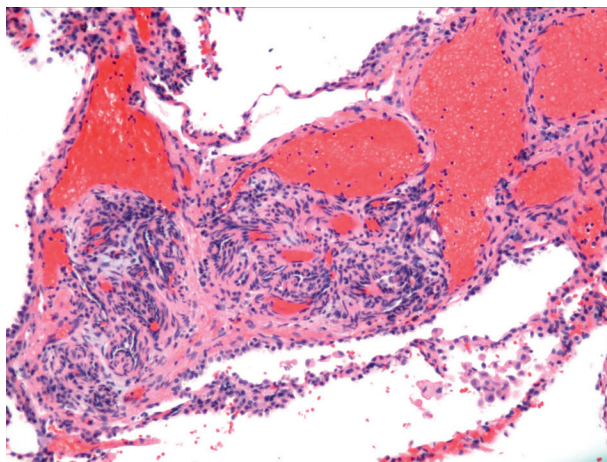
eFigure 14-1 Granulomatosis with polyangiitis (Wegener granulomatosis). **A**, At low power, this vasculitis demonstrates basophilic necrosis with irregular or "geographic" outline. (H&E stain; original magnification $\times 40$.) **B**, These alveolar capillaries have engorgement by neutrophils with the absence of significant intra-alveolar acute inflammation. (Periodic acid–Schiff stain; original magnification $\times 400$.)



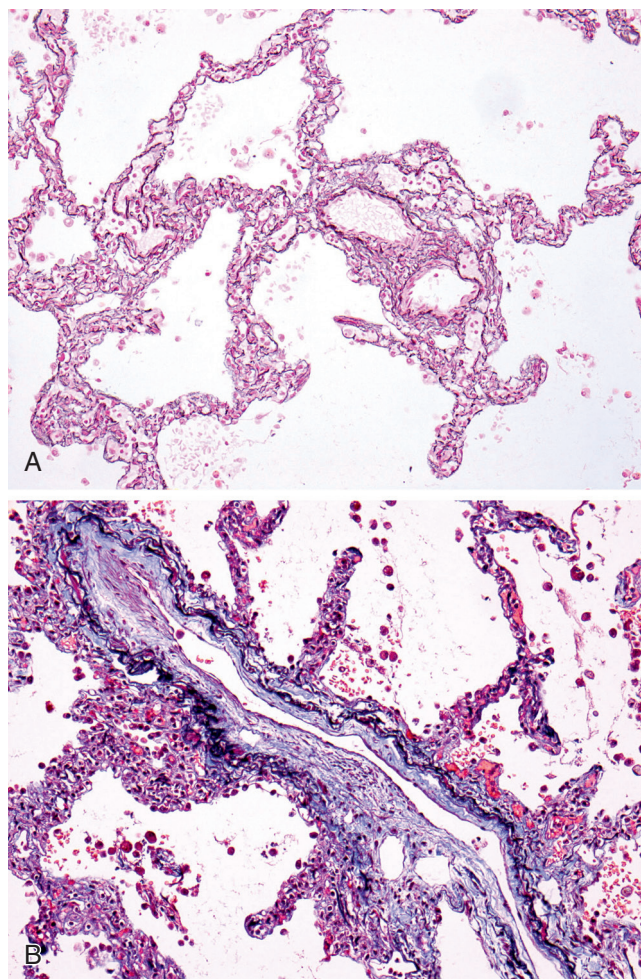
eFigure 14-2 Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). **A**, This focus of necrosis is heavily infiltrated by eosinophils and is surrounded by epithelioid histiocytes or granulomas. (H&E stain; original magnification $\times 100$.) **B**, This blood vessel shows a marked inflammatory infiltrate or vasculitis with many lymphocytes and eosinophils. (H&E stain; original magnification $\times 200$.)



eFigure 14-3 Microscopic polyangiitis. The lung shows prominent acute hemorrhage and the alveolar walls are thickened with capillaritis or neutrophilic infiltrates and prominent pneumocyte hyperplasia. (H&E stain; original magnification $\times 200$.)



eFigure 14-4 Pulmonary hypertension with plexiform and dilation lesions. The vessel is very abnormal and is composed of disorganized endothelial cells and myofibroblasts. The lumens in the plexiform lesion have slitlike openings. The vascular channels upstream from the obstructing plexiform lesion are dilated and filled with blood. (H&E stain; original magnification ×400.)



eFigure 14-5 A, Pulmonary capillary hemangiomatosis, Capillary duplication is evident in the walls of the alveoli and surrounding the venule (left center of image). (Reticulin stain; original magnification ×200.) **B,** Pulmonary veno-occlusive disease. The intima of this venule is markedly expanded by fibrosis with narrowing of the lumen. (Combined Masson trichrome/Elastic van Gieson stain; original magnification ×200.)

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INTRODUCTION**LUNG INJURY AND REPAIR DURING HOMEOSTASIS****LUNG INJURY AND REPAIR DURING DISEASE**

Lung Injury
Lung Repair

Endothelial Repair

Epithelial Repair

STEM CELLS, CONSTITUTIVE CELL TURNOVER, AND REPARATIVE CELL TYPES

Hierarchies of Reparative Cells
Classical Stem Cell Hierarchy
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GENE-ENVIRONMENT INTERACTIONS IN LUNG INJURY AND REPAIR**DOES LUNG REPAIR RECAPITULATE LUNG DEVELOPMENT?****INTRODUCTION**

The pathogenesis of many pulmonary diseases involves the processes of lung injury and repair, and indeed maintenance of normal lung homeostasis involves cycles of ongoing subclinical microinjury and repair. Injury can be viewed at different levels from the context of whole-organ function or at the level of individual cells or molecules. Similarly, repair can be considered at several levels. Repair can be considered as a sequence of pathologic processes as in repair of a skin wound, at the level of cell replacement, at the level of patching of holes in plasma membranes, or at the level of molecules broken down in the proteasome and replaced by *de novo* synthesis. Given the complexity of these processes, we provide our definition of the terms *injury* and *repair* with the aim of limiting what would otherwise be an exhaustive discussion. In this chapter we will focus on the cellular injury resulting in the dysfunction or death of cells that underlies the pathogenesis of many pulmonary diseases. Injury to any of the different cell types residing in the lung can ultimately lead to organ dysfunction (for a review of lung structure, see Chapter 1). A broad concept of lung repair includes processes by which the function of the injured lung is restored to normal. In regard to reparative processes, we will focus on the cellular aspects of repair, including replacement of destroyed cells and restoration of normal cellular function.

LUNG INJURY AND REPAIR DURING HOMEOSTASIS

As a major portal to the environment, the lung is continuously exposed to a vast array of chemical and biologic agents that can cause cellular dysfunction or even death. Acute episodes of injury to the lung, as a result of viral infection or chemical exposures, result in transient alterations in lung function. *Repair* therefore can be defined as restitution of the cells, and thus of the lung, to the preinjury level of structure and function. Normal repair returns the lung to a healthy state that is capable of responding to subsequent injuries. The response of the lung to repeated

injury and repair is shown in [Figure 15-1](#). Normal aging is manifest by steady and progressive declines in cell number and/or function and in overall lung function ([Fig. 15-1](#), straight blue line), in part due to episodes of recurrent microinjury and decreased capacity of the epithelium or endothelium to heal itself. Normal repair can return the lung function to its prior state ([Fig. 15-1](#), fluctuating blue line). Faulty repair leads to episodic loss of function that ultimately results in respiratory failure ([Fig. 15-1](#), orange line).

LUNG INJURY AND REPAIR DURING DISEASE

Many common pulmonary disorders, such as *chronic obstructive pulmonary disease* (COPD), interstitial lung disease, asthma, cystic fibrosis, and the *acute respiratory distress syndrome* (ARDS), are characterized by cellular injury and faulty repair resulting in clinically significant physiologic abnormalities. The intensity and duration of the insult contribute to the time of onset of symptoms and the chronicity of disease. In ARDS, a severe insult causes widespread lung injury and respiratory failure in hours to days. By contrast, in COPD, years of exposure to the offending agent (usually cigarette smoke in the developed world and biomass fuels in developing countries) results in slowly progressive loss of respiratory function. Patients with interstitial lung disease often have a stuttering course with periods of rapidly declining lung function interspersed with periods of relative quiescence. Importantly, in addition to injury, dysfunctional repair and “remodeling” contribute to the pathogenesis and clinical course of lung diseases, including COPD, asthma, interstitial lung disease, and fibroproliferative ARDS.

LUNG INJURY

The pathogenesis of many lung diseases involves an exogenous (e.g., inhaled toxin, allergen, infectious agent) or endogenous (inflammation or autoimmune) agent causing cellular dysfunction or death. In COPD, inhaled toxins such as those that make up cigarette smoke initiate processes

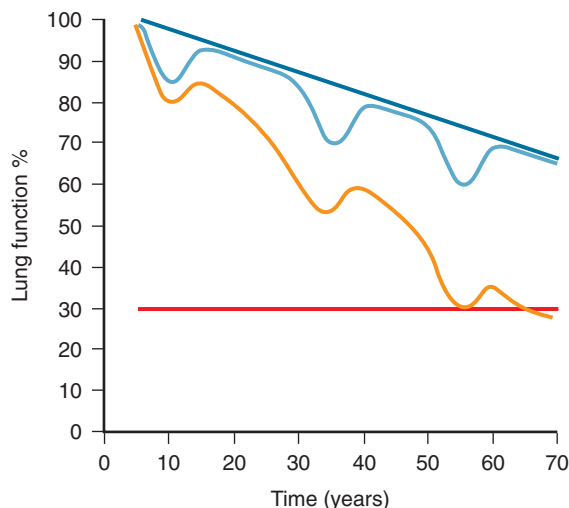


Figure 15-1 Conceptual relationship between lung function and time.

Normal aging can be viewed as a process in which steady and progressive declines in cell number and/or function reflect parallel decrements in the capacity of the epithelium or endothelium to heal itself (straight blue line). Acute episodes of injury to the lung and its cellular and structural components, such as viral infection or chemical exposures, result in temporary fluctuations in lung function (fluctuating blue line). Chronic lung disease is associated with a progressive loss of lung function that is exacerbated by environmental exposures. Individuals affected by chronic lung disease may be predisposed to repeated episodes of lung injury and may undergo cycles of injury that result in an accelerated decline in lung function (orange line). Once a hypothetical functional threshold is reached (red line), the lung may no longer have the capacity to repair itself and functionality is irreversibly lost. (Adapted from Lazaar AL, Panettieri RA Jr: Is airway remodeling clinically relevant in asthma? *Am J Med* 115:652–659, 2003.)

that culminate in epithelial and endothelial cell death,^{1–5} as well as destruction of extracellular matrix, the scaffolding of the lung.⁶ In asthma, allergens, environmental pollutants, pathogens, and the inflammatory response to these agents induce injury to the bronchial epithelium.^{7–9} Pulmonary fibrosis is thought to reflect repetitive injury to the lung epithelium interspersed with periods of relative quiescence.^{10,11}

To illustrate the processes involved in lung injury, we will focus on inflammatory lung injury in ARDS. An extensive review of the causes, pathogenesis, clinical manifestations, and treatment of ARDS is included in Chapter 100. Briefly, ARDS is defined as the acute onset (within 1 week of the inciting event) of hypoxemia and bilateral opacities on chest imaging attributable to noncardiogenic (increased permeability) pulmonary edema. The severity of ARDS is graded according to the ratio (“P/F ratio”) of the partial pressure of oxygen in the arterial blood to the fractional concentration of oxygen in the inspired air, with a P/F ratio of 200 to 300 defined as “mild,” 100 to 200 defined as “moderate,” and less than 100 defined as “severe.”¹² ARDS is a heterogeneous syndrome rather than a single disease, and predisposing causes include pneumonia, extrapulmonary sepsis, inhalational injury, aspiration, injurious (high tidal volume) mechanical ventilation, pancreatitis, trauma, and blood transfusion. In addition to the acute medical condition, risk factors for the development of ARDS include acquired disorders such as alcohol abuse¹³ or cigarette smoking¹⁴ and genetic determinants such as certain genetic polymorphisms^{15–34} (Fig. 15-2). Treatment

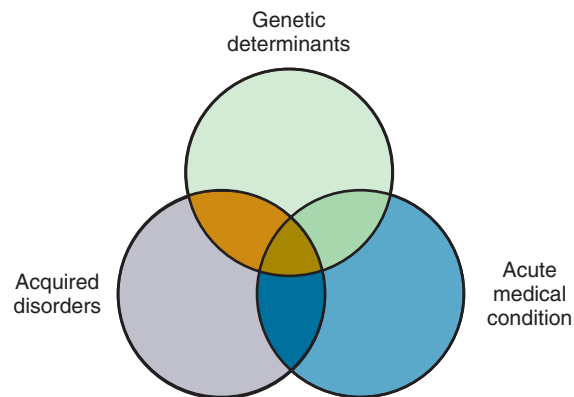


Figure 15-2 Acute lung injury (ALI): clinical risk factors. Based on the results of several epidemiologic studies published over the last 2 decades, a variety of factors have been identified that can alter the susceptibility of an individual patient to the development of ALI. These factors can be separated into three general categories: genetic determinants, preexisting acquired disorders, and the acute medical condition. The identification of such patient-specific characteristics could significantly improve both our understanding of the pathogenesis of ALI and our ability to care for these critically ill patients.

of ARDS is mainly supportive and includes lung protective (low tidal volume) mechanical ventilation³⁵ and a conservative fluid management strategy.³⁶

Epithelia and endothelia form selective barriers separating various body compartments of different composition from each other or the body from the environment. This barrier function depends on the presence of an intact layer of viable cells as well as the intercellular junctions that link adjacent cells, thus restricting the movement of fluid, ions, and macromolecules. In the healthy lung, the epithelium due to its tight intercellular junctions is the major barrier for passive fluid leak into the alveolar spaces, and, in addition, there is active fluid removal from the alveolar space via the action of specialized ion pumps and transporters in the epithelial cells. In ARDS, compromise of the selective barriers, epithelial as well as endothelial, either via disassembly of intercellular junctions or via death and sloughing of cells, results in an increase in lung permeability and the influx of protein-rich edema fluid,^{37,38} which leads to refractory hypoxemia and bilateral infiltrates on chest radiographs.^{39–42} Cellular dysfunction, such as impaired fluid transport^{43,44} and decreased surfactant production,^{45,46} further contributes to the impaired lung compliance and gas exchange abnormalities.

In ARDS, epithelial and endothelial injury is largely attributable to excessive and dysregulated inflammation^{41,47} (Fig. 15-3) (see Chapter 100). In the case of pneumonia, the most common cause of ARDS, microbial products are recognized by resident lung cells, which in turn secrete chemoattractants that recruit inflammatory cells, initially neutrophils, into the lungs.^{48–52} Chemoattractants stimulate neutrophil actin assembly, resulting in stiffening and retention of neutrophils in the pulmonary capillaries.⁵³ This is followed by intercellular adhesion molecule-mediated adhesion to the endothelium,^{54–56} a process that requires heparanase-mediated cleavage of the glycocalyx,⁵⁷ egress from the bloodstream,⁵⁸ and transmigration across the epithelium into the air spaces.⁵⁹ Neutrophils contain potent

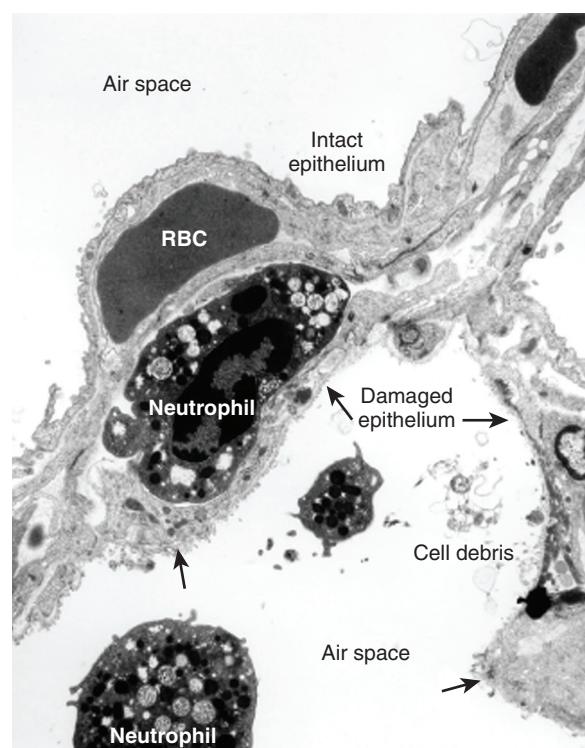


Figure 15-3 Electron micrograph of inflammatory injury in the murine lung. A key contributor to lung injury, from either the vascular or epithelial surface, is the inflammatory process, including the effects of inflammatory mediators and the accumulation and activation of inflammatory cells. This electron micrograph depicts damage to endothelial and alveolar epithelial cells accompanying sequestration and activation of neutrophils in an acute inflammatory response. The process is usually associated with increased vascular and alveolar permeability, sometimes with sufficient damage to the alveolar wall to result in coagulation (fibrin) and erythrocyte accumulation in the air spaces. RBC, red blood cell.

antimicrobial compounds, including oxidants, proteinases, and cationic peptides. During immune surveillance or a normal immune response, neutrophils ingest (phagocytose) microorganisms and release these antimicrobial compounds directly into the phagosome.⁶⁰ Neutrophil influx into the lungs under most circumstances does not result in tissue injury.^{61,62} However, during excessive and dysregulated inflammation in ARDS, large numbers of activated neutrophils release proteolytic enzymes and oxidants into the extracellular space, causing tissue injury.^{59,63,64} For example, neutrophil elastase, although inherently antimicrobial and critical for host defense,^{65,66} has been shown to cause injury not only to the extracellular matrix in COPD^{67,68} but also to the alveolar capillary membrane in ARDS.⁶⁹⁻⁷⁶ Importantly, neutrophil elastase can cause both a disruption of intercellular junctions^{77,78} and death of endothelial⁷⁹⁻⁸¹ and epithelial^{82,83} cells. ARDS patients have elevated levels of elastase in their bronchoalveolar lavage fluid and plasma, and these levels correlate with the severity of lung injury.⁸⁴⁻⁸⁷ Unfortunately, pharmacologic agents that inhibit neutrophil elastase have not proven to be effective in the treatment of ARDS.^{88,89}

In addition to neutrophil elastase, other serine proteases, *matrix metalloproteinases* (MMPs) and cysteine proteinases are released by inflammatory cells and contribute to tissue destruction during lung injury.⁶⁹ Increased levels of MMPs,

derived from both neutrophils and macrophages, are present in patients with ARDS⁹⁰⁻⁹⁴ and contribute to lung injury.⁹⁵⁻¹⁰⁰ The mechanisms by which MMPs cause lung injury have not been fully elucidated. They are known to degrade junctional proteins in both epithelial¹⁰¹⁻¹⁰³ and endothelial cells^{104,105} and induce cell death,¹⁰³ although the latter is dependent on the cell type and specific MMP. Conversely, some MMPs promote survival of the lung epithelium,¹⁰⁶ and others may attenuate injury¹⁰⁷ or even promote repair.^{108,109}

Defensins are cationic peptides released from inflammatory cells that have potent antimicrobial properties. As with other inflammatory mediators, defensins are released into the extracellular space in ARDS¹¹⁰ and can cause lung injury,^{111,112} including endothelial¹¹³ and epithelial¹¹⁴⁻¹¹⁷ cell death and noncytotoxic injury.¹¹⁸ Similar to proteinases, in certain contexts, defensins may also promote lung repair.^{119,120}

In addition to proteinases and antimicrobial peptides, oxidants, including reactive oxygen and nitrogen species, are released by inflammatory cells during ARDS¹²¹⁻¹²³ and contribute to tissue injury,¹²⁴⁻¹³² including epithelial¹³³⁻¹⁴¹ and endothelial^{142,143} cell death and disruption of tight junctions.¹⁴⁴⁻¹⁴⁶ Although the lung possesses potent endogenous antioxidant mechanisms, which serve to limit injury,¹⁴⁷⁻¹⁵⁵ in ARDS these mechanisms are overwhelmed by the large amount of reactive species generated. Additionally, oxidants can potentiate proteinase-induced lung injury, in part by inactivating antiproteinases.¹⁵⁶ Finally, lipid mediators¹³² and another recently recognized antimicrobial weapon, neutrophil extracellular traps, can cause epithelial and endothelial injury.¹⁵⁷⁻¹⁶⁰

Although much of the early injury to the alveolar capillary membrane is attributable to neutrophils (polymorphonuclear leukocytes) and their mediators,^{59,161-163} polymorphonuclear leukocytes cannot be the only perpetrators of lung injury because ARDS can develop in neutropenic patients.¹⁶⁴ Recruitment of monocytes to the lungs follows the initial neutrophilic response in ARDS.¹⁶⁵ In contrast to resident alveolar macrophages, which tend to have anti-inflammatory functions,^{165a} recruited macrophages secrete proinflammatory mediators, including cytokines, chemokines, and lipids, that propagate the inflammatory response. Recruited macrophages also release toxic mediators, including reactive oxygen and nitrogen species,^{166,167} MMPs,^{93,98,99,168} *tumor necrosis factor* (TNF)- α ,¹⁶⁹ vascular endothelial growth factor,¹⁷⁰ and interferon- β ,¹⁷¹ which may enhance host defense but also induce tissue injury.^{172,173,173a} In addition, recruited macrophages also play a critical role in both tissue repair¹⁷⁴⁻¹⁷⁶ and the resolution of inflammation^{177,178} (see later). The role of macrophages in lung inflammation, injury, and repair is further reviewed in Chapter 12. Finally, in addition to neutrophils and macrophages, platelets,¹⁷⁹ coagulation factors,^{56,180} products of infectious agents,¹⁸¹ inhaled toxins,¹⁸² oxygen,¹⁸³ and mechanical forces^{184,185} all can contribute to injury to the alveolar capillary membrane. Indeed, a diverse array of mechanisms, mediators, and signaling pathways has been implicated in lung injury.^{94,186-194} Because the spectrum of injurious agents in ARDS is so broad, it is not surprising that pharmacologic strategies to block a single pathway or class of mediators have been ineffective.

Having reviewed the pathogenic agents that induce lung injury, we will now focus on exploring what constitutes lung injury. As mentioned earlier, we define injury as cellular dysfunction or death. Although cellular dysfunction in ARDS includes impaired production of surfactant,¹⁹⁵ which is critical for lung compliance and important in host defense,¹⁹⁶ we will focus here on the cellular dysfunction and death that contribute to increased lung permeability. In inflammatory lung injury the cellular dysfunction that contributes to edema formation includes (1) disruption of intercellular junctions that are responsible for maintaining the barrier function of the endothelium and epithelium and (2) impaired active fluid transport that is responsible for fluid reabsorption and maintenance of dry air spaces. Transient opening and closing of intercellular junctions is necessary for the transmigration of immune cells during immune surveillance or during a normal immune response¹⁹⁷ and can take place without compromising barrier function.⁶² However, in ARDS, intercellular junctions of the endothelium^{144,198-201} and epithelium^{77,146} are disrupted, resulting in enhanced paracellular permeability, which contributes to the flooding of the alveolar spaces with edema fluid. This alveolar flooding is exacerbated by impaired function of the epithelial Na^+/K^+ pumps and epithelial Na^+ channels that are responsible for fluid reabsorption.²⁰²⁻²⁰⁸ Attempts at stimulating fluid clearance with β -agonists have not improved outcomes in ARDS,²⁰⁹ perhaps because the barrier must be restored before the pumps can be effective (see Chapter 9).

In addition to the disruption of intercellular junctions, severe lung injury in ARDS and other lung diseases^{5,210-212} is characterized by cell death. In ARDS, inflammatory mediators induce death of endothelial cells²¹³ as well as *alveolar epithelial type I* (ATI) cells, leaving surviving *alveolar epithelial type II* (ATII) cells, which are more resistant to injury, populating a largely denuded basement membrane.^{38,214-217} This dramatic injury to the alveolar epithelium engendered the term *diffuse alveolar damage*,²¹⁸ which describes the histologic appearance of lungs taken from patients who died of ARDS.

Endothelial and epithelial cells can be lost via necrotic cell death or via programmed cell death, the latter termed “apoptosis.” Originally a morphologic definition, apoptosis might best be defined not only on the basis of nuclear condensation and characteristic DNA fragmentation but also based biochemically on activation of intracellular proteases termed “caspases.” Many recent reviews address the various mechanisms underlying apoptosis.^{219,220} However, it is important to note that there are two major pathways leading to apoptosis: the intrinsic pathway, involving signaling from the mitochondria; and the extrinsic pathway, deriving from signals generated from external stimulation of “death” receptors. In “normal” adult humans or experimental animals, snapshot analyses of lung tissue indicate only small scattered examples of replicating cells or of cells undergoing apoptosis. Because apoptotic cells are actively extruded from epithelial surfaces and cleared rapidly, the fact that evidence of apoptosis is detectable at all may indicate a higher degree of cellular turnover than previously thought. Early reports suggested that mitochondrial regulation of alveolar epithelial apoptosis may be induced by the proapoptotic BCL2 family member BAX²²¹ and p53.²²² Additional literature suggests that death receptors of the

TNF receptor family such as FAS mediate apoptosis via the extrinsic pathway. Both FAS and FAS ligand levels are elevated in the edema fluid of ARDS patients, they induce epithelial cell apoptosis in a manner dependent on their modulation by oxidants and proteases, and elevated levels are predictive of worse clinical outcomes.²²³⁻²²⁵ In animal models of lung injury, FAS²²⁶ and TNF-related apoptosis-inducing ligand¹⁶⁹ induce epithelial cell apoptosis, and inhibition of apoptosis improves survival.²²⁷ Conversely, hyaluronan, while promoting inflammation, attenuates epithelial cell apoptosis.¹⁹¹ Apoptotic epithelial cells are engulfed by both professional phagocytes (macrophages) and other epithelial cells.^{228,229}

In ARDS, lung cells can also die by necrosis, which leads to disruption of cell membranes with subsequent release of cellular contents that may be injurious. Causes of epithelial and endothelial necrosis in ARDS include physical effects of acid from inspiration of stomach contents, inhalation of toxic materials or fumes, infection with lytic viruses or bacterial products, hyperoxia,²³⁰ and mechanical disruption of cell membranes during mechanical ventilation. In sum, cell death is a major mechanism of lung injury, resulting in denudation and contributing to lung permeability and the massive influx of edema fluid, despite the existence of endogenous protective mechanisms.

LUNG REPAIR

The ability of the lung to withstand considerable damage and repair itself enables recovery and survival from a variety of noxious stimuli.²³¹ For the purpose of this chapter, we define repair broadly as *processes by which the function of the injured lung is restored to normal*. Repair of the lung after acute injury requires restitution of the endothelial and epithelial barriers, clearance of edema fluid,²³²⁻²³⁷ and the resolution of inflammation.²³⁸ In the case of ARDS, survival depends on repair of the injured lung, although some survivors do not regain normal lung function.²³⁹

ENDOTHELIAL REPAIR

Given that lung injury involves disruption of intercellular junctions and cell death, repair requires repopulation of the denuded basement membrane and reassembly of these junctions. Elegant work has demonstrated the importance of sphingosine-1-phosphate, released from activated platelets, in stimulating reassembly of endothelial intercellular junctions via Rho- and Rac-dependent cytoskeletal rearrangement.²⁴⁰⁻²⁴² This process is dependent on $\alpha\text{v}\beta 3$ integrin.²⁴³ In addition, the SLIT/ROBO mechanism was recently identified to stabilize the endothelial adherens junctions by promoting p120-catenin/E-cadherin association.^{244,245} Stabilization of actin cytoskeleton by the Rho GTPases enhances endothelial barrier integrity.²⁴⁶ Additional information on the regulation of endothelial function is found in Chapter 6.

EPITHELIAL REPAIR

Although the alveolar epithelium is more resistant to injury than is the endothelium,²⁴⁷ increased epithelial permeability is required for the development of airspace edema.

Conversely, repair of the alveolar epithelium is critical for the resolution of edema, restoration of functions such as surfactant production and ion and fluid transport, and clinical outcome.^{202,248} In the epithelium, *keratinocyte growth factor* (KGF),¹⁴⁶ interferon- γ ,²⁴⁹ phosphatase and tensin homologue,²⁵⁰ epidermal growth factor,²³⁶ and c-Met²⁵¹ are protective of tight junctional integrity during lung injury by mechanisms that involve cytoskeletal reorganization rather than enhanced expression of junctional proteins.²⁵² Regulation of tight junctions in the alveolar epithelium after injury is an important and active area of investigation.²⁵³

If the severity of the injury is such that there has been extensive cell death, the endothelium and epithelium must be repopulated. As an illustration of the mechanisms involved, we will focus on re-epithelialization of the denuded alveolar epithelium after injury. The injured alveolar epithelium re-epithelializes in stages, many of which are orchestrated by the ATII cell, the “defender of the alveolus.”²⁵⁴ These stages include (1) ATII cell spreading and migration, (2) ATII cell proliferation, (3) differentiation of ATII cells into ATI cells to restore a normal constitution of the alveolar epithelium, and finally (4) if the injury is extensive, migration and proliferation of bronchiolar stem cells to repopulate the injured alveolus (Fig. 15-4; Video 15-1).

Recent work has identified various stem cell populations that likely contribute to this repair. Epithelial injury and repair promotes the activation of fibroblasts,^{255,256} which although important for physiologic wound repair, under certain circumstances, when dysregulated, can result in fibrotic lung disease. Each of these phenomena will be discussed in more detail in the following sections.

Cell Spreading and Migration

After death of alveolar epithelial cells, surviving ATII cells likely spread and migrate onto the denuded basement membrane. Although this has not been directly observed in the alveolar epithelium *in vivo*, cell spreading and migration is certainly the fastest mechanism for resealing the leaky epithelium²¹⁸ based on *in vitro* observations²⁵⁷⁻²⁵⁹ and on observations of the importance of these phenomena in wound repair of other organs.²⁶⁰ Cell migration depends on tightly regulated assembly of the cytoskeleton leading to protrusion of “lamellipodia” and “filopodia” from the leading edge followed by contractile forces that release the rear edge from the extracellular matrix, processes that depend on the Rho GTPases.^{261,262} In the lung epithelium, cell spreading and migration after injury are triggered by soluble factors such as KGF,²⁵⁹ transforming growth factor (TGF)- α ,²⁵⁸ TGF- β ,²⁶³ interleukin-1 β ,^{264,265} and

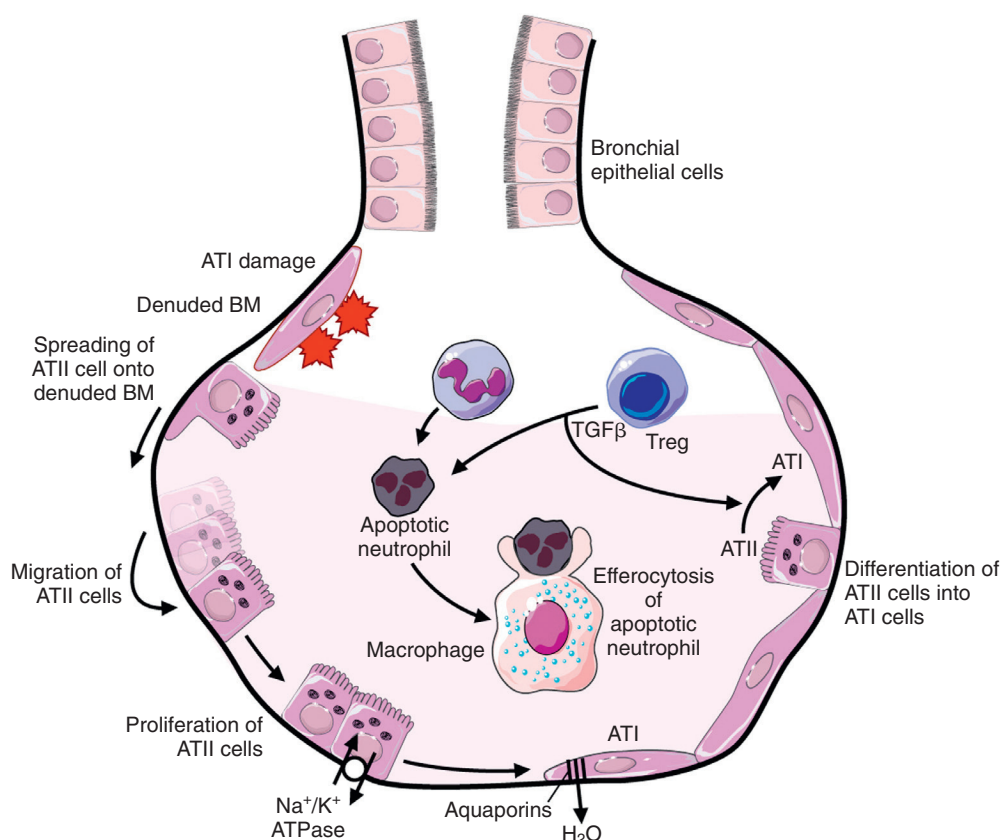


Figure 15-4 The injured alveolar epithelium re-epithelializes in stages. Alveolar epithelial type I cells (ATIs) are the most susceptible to injury. Surviving type II (ATII) cells spread and migrate onto the denuded basement membrane (BM), proliferate, and differentiate into ATI cells to restore a normal alveolar architecture. Meanwhile, active ion transport by the Na⁺/K⁺ ATPase, as well as passive ion uptake through ion channels (epithelial Na⁺ and cystic fibrosis transmembrane conductance regulator, not shown) creates an osmotic gradient. Water reabsorption follows through aquaporin channels. The resolution of inflammation depends on apoptosis of neutrophils followed by the uptake of apoptotic neutrophils by macrophages (“efferocytosis”), a process that is enhanced by transforming growth factor (TGF)- β released from T regulatory lymphocytes (Treg).

cytokine-induced neutrophil chemoattractant 2.²⁶⁶ Cell migration is further mediated by signaling pathways, including Rac1/TIAM1,²⁶⁷ phosphatase and tensin homologue,²⁶⁸ β -catenin,²⁶⁹⁻²⁷² syndecan-1,^{273,274} adenosine triphosphate and dual oxidase 1,^{275,276} and vimentin,²⁶³ as reviewed elsewhere.²⁷⁷ Integrins, which are up-regulated in the alveolar epithelium after injury,²⁷⁸ contribute to cell migration via interactions with both the actin cytoskeleton²⁷⁹ and the extracellular matrix.^{257,280-282} The production of extracellular matrix as well as MMPs are critical to cell migration.^{174,274} MMPs enhance wound healing by cleaving cell-cell and cell-extracellular matrix adhesion molecules, activating chemokines and growth factors by proteolysis, and degrading the provisional matrix.¹⁷⁵ Notably, cyclic stretch, imposed by mechanical ventilation during repair after ARDS, impedes cytoskeletal reorganization during cell spreading.²⁸³

Cell Proliferation

In addition to cell spreading and migration, the denuded epithelial basement membrane is repopulated through the proliferation of surviving ATII cells, which accounts for the epithelial cell hyperplasia observed on histologic samples.^{38,217,254,284} In animal models, significant acute lung injury resulting in cell death triggers alveolar epithelial cell proliferation.²⁸⁵ Factors that promote ATII cell proliferation after injury include the heparin-binding growth factors KGF, hepatocyte growth factor, and heparin-binding epidermal growth factor,²⁸⁶⁻²⁹² an effect that is significant enough to decrease mortality in animal models of lung injury,²⁹³ although the protective role of KGF may in part be attributable to enhanced epithelial cell survival.²⁹⁴ Other factors and pathways implicated in ATII cell proliferation after injury include granulocyte-macrophage colony-stimulating factor,^{295,296} which is also protective against injury,²⁹⁷⁻²⁹⁹ β -catenin signaling,^{300,301} macrophage migration inhibitory factor,³⁰² and FOXM1.³⁰³ Proliferating ATII cells ultimately differentiate into ATI cells^{236,285,304,305,305a} or die by apoptosis and are subsequently removed by macrophages or neighboring ATII cells.^{306,307} Mechanisms regulating differentiation of ATII cells into ATI cells are not well understood, but this process is promoted by TGF- β ³⁰⁸ and insulin-like growth factor-I.³⁰⁹ The classic concept has been that ATII cells are responsible for alveolar repair by spreading into the denuded area, proliferating, and ultimately differentiating into ATI cells. However, at least in vitro, transdifferentiation is reversible.³¹⁰ In this regard, a recent in vitro study reveals that ATI cells are also capable of cell spreading, migration, proliferation, and expression of surfactant protein-C,³¹¹ suggesting that these cells may also play a role in repair.

Role of Fibroblasts in Repair

Normal repair depends on epithelial-mesenchymal interactions, including the proliferation of subepithelial fibroblasts with deposition of granulation tissue. Mesenchymal cells provide signals and specific growth factors such as hepatocyte growth factor and KGF to epithelial cells to facilitate repair. By contrast, after repetitive and/or nonresolving injury, dysfunctional epithelial repair results in fibroblast recruitment, proliferation, and differentiation into myofibroblasts with deposition of excessive extracellular matrix

composed of collagen and fibronectin. Severe or repetitive epithelial injury with dysfunctional repair can promote fibroproliferative responses^{255,256,272,284,312-314} in ARDS^{38,40,315-317} and other lung diseases, including idiopathic pulmonary fibrosis,³¹⁸⁻³²⁰ asthma,^{7,8} and COPD,³²¹ a topic which is reviewed in detail elsewhere.^{11,322} Although cytokines and growth factors that induce physiologic repair can prevent fibrosis under certain circumstances,^{270,272,301,323,324} under other circumstances, these same factors may actually promote fibrosis,^{300,325-327} underscoring the importance of context in lung repair. Therefore caution is indicated when considering therapeutic intervention aimed at accelerating repair of the injured lung, so as not to induce fibrosis. Epithelial “regeneration,” the restoration of normal lung architecture, must be distinguished from “simple repair,” which can include repopulation by abnormal cell types and scar formation.³²⁸

Resolution of Inflammation

Ultimately, the inflammatory response must resolve in order to halt ongoing injury to the lung and allow reparative processes to proceed. An important step for resolution of inflammation is the apoptotic clearance of neutrophils. Neutrophils undergo apoptosis, a noninflammatory, non-immunogenic form of cell death during which they retain their toxic mediators within their plasma membrane. This is in contrast to a necrotic cell death, in which neutrophils disintegrate with release of their intracellular constituents, including toxic and proinflammatory mediators, resulting in prolongation of the inflammatory response. Neutrophil apoptosis can be delayed by proinflammatory mediators such as granulocyte-macrophage colony-stimulating factor and endotoxin³²⁹ and by hypoxia,^{330,331} but it is enhanced by T regulatory lymphocytes in a TGF- β -dependent manner.³³² Delayed neutrophil apoptosis is mediated by complex intracellular signaling pathways that involve hypoxia inducible factor-1³³¹ and cyclin-dependent kinases signaling through the antiapoptotic BCL2 family member MCL1.³²⁹ Apoptotic neutrophils are cleared by macrophages in a phagocytic process termed “efferocytosis” without release of toxic intracellular contents.^{177,178} Efferocytosis depends on the recognition of “eat me” signals, including phosphatidylserine³³³ and calreticulin,³³⁴ that are displayed on the apoptotic cell surface by a variety of receptors.^{335,336} This is followed by activation of Rho GTPases, leading to engulfment, which is regulated by the mitochondrial membrane protein UCP2,³³⁷ as well as HMGB1³³⁸ and urokinase-type plasminogen activator.³³⁹ Efferocytosis results in the release of anti-inflammatory mediators that further promote the resolution of inflammation³⁴⁰ rather than inducing a pro-inflammatory macrophage response. Apoptotic neutrophils can also be efferocytosed by myeloid-derived suppressor cells in an interleukin-10-dependent manner.³⁴¹ Whereas clearance of apoptotic neutrophils is usually highly efficient, yielding a low number of observable apoptotic cells at any given time,³⁴² if apoptotic clearance is defective or overloaded, apoptotic neutrophils can undergo secondary necrosis or postapoptotic cytolysis.³⁴³ Thus, impaired neutrophil apoptosis and efferocytosis would prolong the duration of the inflammatory response, likely resulting in chronic inflammatory lung disease.³⁴⁴ Lipid mediators promote the resolution of inflammation by enhancing

neutrophil apoptosis³⁴⁵ and efferocytosis,³⁴⁶⁻³⁴⁸ as well as through other mechanisms.³⁴⁹⁻³⁵² In addition to neutrophils, inflammatory macrophages must also be cleared during the resolution of lung injury.³⁵³

STEM CELLS, CONSTITUTIVE CELL TURNOVER, AND REPARATIVE CELL TYPES

HIERARCHIES OF REPARATIVE CELLS

The concept of injury and repair is fundamentally linked to the stem cell attributes of *mitotic potential* and *differentiation capacity*. Mitotic potential has two components, the number of times a cell can undergo division and the time at which these cell divisions take place. Differentiation potential is defined in terms of the variety of differentiated cell types that can be generated by an individual mitotic cell. Many of the current concepts about stem and progenitor cell function in the lung derive from studies of airway epithelial cells. Comparatively less is known regarding the identity of long-term stem cells in the alveolar region and even less is known about resident stem and progenitor cells for the diverse lung mesenchymal cell populations. The knowledge of the stem and progenitor cells' functions in the airway will be used as a foundation to illustrate the basic principles of how stem cells are involved in repair of the injured lung.

CLASSICAL STEM CELL HIERARCHY

Within a classical stem cell hierarchy (Fig. 15-5), the *stem cell* is defined as the reparative cell with the greatest mitotic and differentiation potential. A stem cell proliferates indefinitely and thus distributes its mitotic potential over the life span of the organism. These attributes of “stemness” are controlled by interaction of the stem cell with the *stem cell microenvironment or niche*. The niche serves to protect or sequester stem cells from factors that promote their differentiation. Stem cell division produces two daughter cells whose fate is determined by interactions with the stem cell niche. *Symmetrical cell division* results in both daughter cells retaining contact with the niche and maintenance of these nascent cells as stem cells. This mechanism, which results in amplification of stem cell number, has been demonstrated in tissues with rapid cell turnover, such as the bone marrow and gut. In contrast, *asymmetric cell division* results in generation of one daughter cell that maintains contact with the niche and is retained as a stem cell. The second daughter cell then loses contact with the niche and undergoes repeated cell division over a short period of time. This second daughter cell is the founding cell for the *transit-amplifying* cell population. Transit-amplifying cells are temporary constituents of the niche. They proliferate repeatedly over a short time period and then withdraw from the cell cycle as they commit to a differentiation pathway. Thus transit-amplifying cells serve to increase cell number and are destined to produce *terminally differentiated* cells. Terminally differentiated cells can have one or more phenotypes and constitute the majority of cells within a given tissue. These cells are largely responsible for conferring the

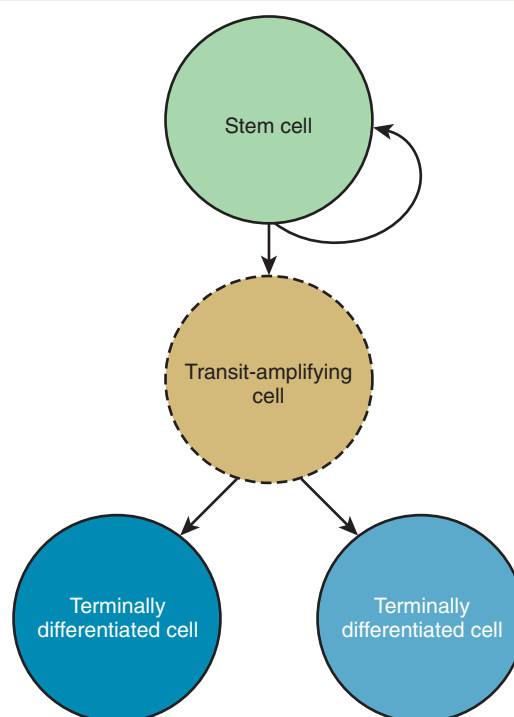


Figure 15-5 Classical stem cell hierarchy: stem cell, transit-amplifying cell, and terminally differentiated cell. Within a classical stem cell hierarchy, the *stem cell* is defined as the reparative cell with the greatest mitotic and differentiation potential. *Symmetrical cell division* results in both daughter cells retaining contact with the niche and retention of these nascent cells as stem cells. In contrast, *asymmetric cell division* (shown here) results in generation of one daughter cell that is retained as the stem cell and a second daughter cell that becomes the transit-amplifying cell. The transit-amplifying cell undergoes repeated cell division over a short period of time, ultimately producing *terminally differentiated* cells, which provide functions characteristic of a specific tissue. Terminally differentiated cells are postmitotic.

phenotypic characteristics of a specific tissue or organ. Terminally differentiated cells are postmitotic. Thus loss of the terminally differentiated cell population acts as a stimulus for the differentiation of transit-amplifying cells that resupply this population.

CELLS INVOLVED IN LUNG REPAIR

Progenitor Cell

The term *progenitor cell* is a collective term used to describe any cell that has the capacity to proliferate. It is commonly used to indicate a cell that is in the process of cell division or has the potential to enter the cell cycle. The functional distinctions among lung progenitor cells are defined in the sections that follow.

Tissue-Specific Stem Cells

A tissue-specific stem cell is a rare cell type that is undifferentiated relative to its progeny. This cell has the capacity for unlimited self-renewal as a consequence of stable interactions with a stem cell niche. In the context of a hierarchy, the stem cell is defined as the reparative cell with the greatest mitotic and differentiation potential. Adult tissue stem cells have a differentiation potential equivalent to the cellular diversity of the tissue in which they reside.³⁵⁴ Because

of the relatively quiescent state of the pulmonary epithelium, lung stem cells are identified as cells that are activated in response to severe cell depletion. As a consequence of this experimental approach, we will review the properties of lung stem cells in the context of severe injury.

Tracheobronchial tissue-specific stem cells have been evaluated in detail in mice. These cells exhibit a low cuboidal to pyramidal morphology and are termed *basal cells*. Additional studies have suggested that the tracheobronchial tissue-specific stem cell resides within specialized microenvironments located at the submucosal gland duct junction and in intercartilaginous regions of the trachea and bronchial epithelium.³⁵⁵ In murine bronchioles, tissue-specific stem cells have been identified within neuroepithelial bodies and bronchiolar duct junction microenvironments. These cells are resistant to club cell (Clara)-specific toxicants such as naphthalene and express the molecular marker *club cell secretory protein* (CCSP).³⁵⁶ The identity of alveolar stem cells remains incompletely understood. The ATII cell is generally believed to serve this function,^{305,357-360} although bronchiolar stem cell populations,^{305,358,359,361} which express $\alpha 6\beta 4$ integrin, keratin 5, or p63 but not prosurfactant C,³⁶² may function as alveolar epithelial progenitor cells after injury under certain circumstances.

Facultative Progenitor Cell Pools

A facultative progenitor cell is one that exhibits differentiated features in the quiescent state yet has the capacity to proliferate for maintenance of normal tissue and in response to injury. In contrast with the bone marrow and gut, the lung epithelium is maintained and repaired under most conditions by an abundant, broadly distributed facultative progenitor cell pool. Facultative progenitor cells exist in two states: quiescent and reparative. In the steady state, facultative progenitor cells are nonmitotic and carry out differentiated functions necessary for tissue homeostasis. In response to injury, facultative progenitor cells dedifferentiate, enter the cell cycle, self-renew, and have a context-dependent probability of differentiating into regionally specific differentiated cell types such as ciliated epithelial cells and ATII cells.³⁶³⁻³⁶⁶ Examples of facultative progenitor cells in the lung are the club cell in the airway and the ATII cell in the alveolus.³⁵⁶

Loss of Regenerative Potential: Depletion of the Facultative Progenitor Cell Pool

Multifunctional properties of pulmonary facultative progenitor cells also limit their ability to repair the injured conducting airway epithelium in the mouse lung. First, the metabolic pathways that allow the club cell to eliminate lipophilic agents also sensitize it to the toxic effects of these compounds.³⁶⁷⁻³⁶⁹ Second, the phenotypic plasticity that is essential to the club cell's ability to detect and eliminate pathogens may compromise the reparative functions of this cell type.³⁷⁰⁻³⁷² Finally, repeated participation in epithelial repair may deplete the mitotic potential of the facultative progenitor cell pool. Depletion of this cell type would leave the epithelium deficient in both regenerative and differentiated functions and could result in a cascade of changes that contribute to epithelial fragility through loss of cellular autocrine/paracrine protective

mechanisms, epithelial hypoplasia, and dysregulation of interactions between the epithelial, mesenchymal, and vascular compartments.

Histologic measures of a low abundance of club cells and CCSP support the concept that the facultative progenitor cell type(s) are depleted in acute lung injury and in chronic lung diseases. These studies suggest that four processes lead to depletion of this critical cell type. First, transition to a mucus-producing cell type may alter both progenitor function and cellular interactions. Within small airways of COPD patients and asthmatics, club cells undergo a metaplastic transition to a mucosecretory phenotype.³⁷³ In severe disease, both club cells and mucosecretory cell types are depleted, and the epithelium becomes hypoplastic.³⁷⁴⁻³⁷⁶ Analysis of colony-forming cells within the human bronchial epithelium demonstrated that human mucous cells are postmitotic cells.³⁷⁷ These observations suggest that hyperplasia of mucous cells, in the context of acute or chronic lung disease, is a consequence of a phenotypic transition by non-mucus-producing cells.

Second, transition of progenitor cells from a facultative to an obligate progenitor state may also lead to depletion of reparative cells. Increased epithelial proliferation in the lungs of smokers suggests an ongoing injury process and the potential for replicative senescence within the facultative progenitor cell pool.³⁷⁸ Senescent cells persist and consequently inhibit activation of the remaining reparative cells. Thus senescent cells could compromise differentiated functions while also blocking cell replacement mechanisms.

Third, entry of the facultative progenitor cell into the cell cycle is accompanied by loss of differentiated functions such as secretion of CCSP or production of surfactant. Extensive analysis of CCSP levels in acute and chronic lung disease, including COPD, suggests that differentiated functions of the facultative progenitor cells are compromised^{379,380} and that these cells are a direct target of toxic environmental agents. Thus injuries that activate facultative progenitor cells may adversely affect protective mechanisms and render the epithelium susceptible to further injury.

Finally, defects in cellular maturation may also contribute to a failure to establish the facultative progenitor cell pool or to deplete it after injury. The lung undergoes rapid and extensive maturation during the postnatal period. The maturation process is interrupted by preterm birth and associated oxygen treatment and is attenuated by postnatal exposure to environmental agents, including ozone and side-stream tobacco smoke in term infants.³⁸¹⁻³⁸³ These studies support the concept that failure to establish or maintain an appropriately sized pool of facultative progenitor cells fosters environmentally induced chronic injury and dysfunctional repair cycles characteristic of lung disease. Hypoplasia of bronchial club cells is associated with tissue remodeling characterized by hyperplasia of an alternative progenitor, the basal cell, and consequent squamous metaplasia.³⁸⁴⁻³⁸⁶ In contrast, club and ATII cells are progenitors of the bronchiolar and alveolar epithelium, respectively,^{285,305,364,366} although as mentioned earlier, bronchiolar stem cells may repopulate the alveolus,^{305,358,359,361} and an alveolar epithelial cell that expresses $\alpha 6\beta 4$ integrin, but not prosurfactant C, may function as an alveolar epithelial progenitor cell after injury.³⁶² Depletion of either of these cell

types leads to epithelial hypoplasia and remodeling of adjacent tissue compartments. Thus changes in function and/or abundance of the facultative progenitor may be the nexus for the complex pathophysiologic alterations in chronic lung diseases.

GENE-ENVIRONMENT INTERACTIONS IN LUNG INJURY AND REPAIR

The four Rs (regeneration, repair, remodeling, and replacement) are presented as distinct processes; however, they are actually intricately intertwined responses to acute or chronic lung injury (Fig. 15-6). These relationships are modified by gene-environment interactions, interactions based on the concept that genetic constitution determines the response to deleterious agents within the environment.

Genetic predisposition has been associated with allelic variants that modify cellular susceptibility to environmental agents, including chemical (ozone, naphthalene, cigarette smoke) and microbial (lipopolysaccharides, viral pathogens) agents. Such alleles can sensitize an individual to an initial or repeated injury but can also render him or her resistant to subsequent exposures through induction of tolerance.

Genotype can also be a determinant of the cellular response to an agent. In mice, specific genetic backgrounds are susceptible to metaplastic transitions such as conversion of airway secretory cells into a mucus-producing

goblet cell phenotype (e.g., C57BL/6 vs. Balb/c strains of mice). Such transitions are associated with protection of the epithelium from further injury. Alterations in cellular phenotype may also extend to interactions between endogenous lung elements (epithelium, mesenchyme, nerves) and itinerant (recruited) cells such as neutrophils, monocytes, and lymphocytes. Certain inbred strains of mice (e.g., C57BL/6) are more susceptible to bleomycin-induced inflammation and develop transient replacement of alveolar structures with mesenchymal cells resulting in fibrosis. Thus susceptibility to injury and the response to such an insult are determined by multiple factors, including the nature of the agent, dose and route of exposure, exposure history, the host genotype, and epigenetic factors molded by gene-environment interactions.

DOES LUNG REPAIR RECAPITULATE LUNG DEVELOPMENT?

Numerous signaling processes are known to be involved in lung development including Wnt/ β -catenin, notch-delta, sonic hedgehog-patched, fibroblast growth factor–fibroblast growth factor receptor, and bone morphogenetic protein/TGF- β .³⁸⁷ These pathways are interactive and integrate formation and appropriate differentiation of tissues (epithelium, mesenchyme, vasculature) during lung development. During lung injury and repair, reactivation of many of these pathways has been reported. It is unclear, however, whether these various signaling pathways are integrated and whether this signaling results in productive cell replacement. Indeed, analysis of damaged human lung tissue is descriptive, and thus cause and consequence usually cannot be separated. In contrast, analysis of signaling pathways in animal models relies on elimination of a specific pathway or profound misregulation of the targeted process. Consequently, feedback mechanisms are likely to be disrupted and may result in altered activation/inactivation of parallel or sequential signaling networks. Development of methods to simultaneously monitor alterations in multiple signaling cascades is needed to address this fundamental obstacle to understanding the molecular regulation of reparative processes. Hence at this time it is not known if regulatory pathways that are dominant during development also regulate repair in the adult.

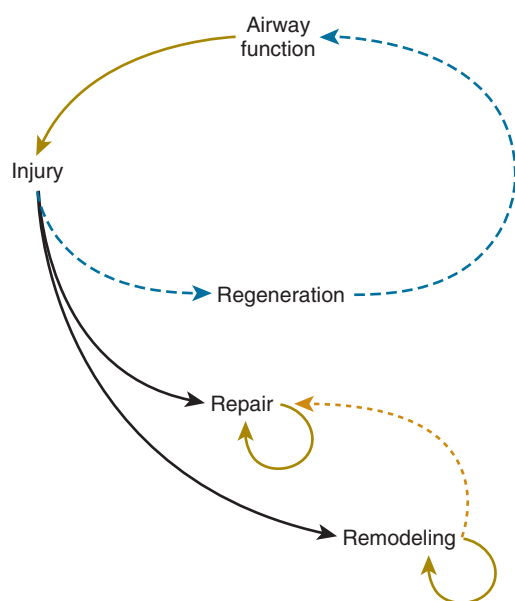


Figure 15-6 Gene-environment interactions in lung injury, regeneration, repair, and remodeling. The four Rs (regeneration, repair, remodeling, and replacement) are presented as distinct processes; however, they are actually intertwined responses to acute or chronic lung injury. These relationships are modified by gene-environment interactions, interactions based on the concept that genetic constitution determines the response to deleterious agents within the environment. (Adapted from Lazaar AL, Panettieri RA Jr: Is airway remodeling clinically relevant in asthma? *Am J Med* 115:652–659, 2003.)

Key Points

- The processes of lung injury and repair underpin the pathogenesis of myriad lung diseases, as well as the normal aging process.
- The mechanisms of injury are rooted in the cellular and molecular changes that initiate structural alterations and lead to compromised lung function. At the tissue and cellular level, exogenous insults and/or inflammatory stimuli result in increased vascular permeability and loss of alveolar epithelial barrier function due to disruption of intercellular junctions and cell death.

- Susceptibility to lung injury is determined by general health, previous exposures, and the individual's genetic constitution. This “gene-environment interaction” is the cornerstone of research initiatives directed at identification of susceptibility genes and those that modify the response to treatment.
- Lung repair involves restoration of normal cellular composition, lung architecture, barrier function, and gas exchange.
- In response to cellular injury by noxious stimuli such as microbes and toxic compounds, endogenous stem and progenitor cells undergo rapid proliferation and differentiation resulting in repair and regeneration of the injured lung. Under normal circumstances repair of the alveolar epithelium after injury depends on cell spreading, migration, and proliferation of surviving *alveolar epithelial type II* (ATII) cells, followed by differentiation of ATII cells into ATI cells. However, in severe injury, additional non-surfactant protein C-expressing cells, likely from the bronchioalveolar junction, can repopulate the alveolar epithelium.
- Repetitive epithelial injury and dysfunctional repair can lead to fibroproliferative responses in the airways and parenchyma; fibroproliferative responses are thought to be critical to the pathogenesis of some diseases, including pulmonary fibrosis, COPD, and asthma.
- Ultimately, the inflammatory response must resolve in order to halt ongoing injury to the lung and to allow repair. Inflammatory cells undergo apoptosis and are cleared by macrophages in a phagocytic process termed “efferocytosis.”

Complete reference list available at *ExpertConsult*.

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DIAGNOSIS

16

HISTORY AND PHYSICAL EXAMINATION

J. LUCIAN DAVIS, MD • JOHN F. MURRAY, MD

INTRODUCTION

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Communication Skills

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Major Pulmonary Symptoms

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INTRODUCTION

Taking a careful and complete history and performing a thorough physical examination are hallmarks of the good internist and one of the distinguishing characteristics of a master clinician. The initial visit sets the tone of the immediate and future relationship with the patient and begins the process of diagnosing and managing the illness; it is a dynamic encounter, with each of the patient's responses stimulating further probing and forming of diagnostic hypotheses. The physician must be attentive to the patient's story, piecing together each bit of evidence to form a tentative preliminary diagnosis and differential diagnoses. Nothing should escape the eyes and ears of a watchful diagnostician. History taking is more than information gathering; it affords the opportunity to decipher the patient's body language as the inquiry proceeds. At this stage, no symptom or circumstance should be disregarded. With an understanding of biology and medicine coupled with past experience, the physician tries to connect the salient parts of the patient's story to develop a plausible explanation of the physiologic or pathologic events that lead to illness.

Although striving for a single diagnosis, the physician should realize that more than one disease may be present and that rare diseases are diagnosed only by those who consider them. Nevertheless, the maxim "uncommon presentations of common diseases are more frequent than common presentations of uncommon diseases" is likely to be true. It is important to continue both to gather information and to be open to reforming the diagnostic hypothesis

as more information becomes available. Premature judgment or the failure to continue considering reasonable alternatives after an initial diagnosis is made is the single most common diagnostic error.^{1,2} In the field of decision science, these failures are postulated to arise from "cognitive dispositions to respond" and include several of the biases in judgment or reasoning defined in [Table 16-1](#).³ It is hypothesized that a greater awareness of these prejudices among clinicians may facilitate "cognitive debiasing," thereby reducing the frequency of these common errors of reasoning.⁴ An alternative or potential complementary approach is to use decision-support software to expand the differential diagnosis and avoid overlooking unusual or severe conditions.⁵

Bayes theorem implies that diagnostic tests will have a higher yield if the prior probability of the diagnosis is high (also called pretest probability). Specific details from the history raise the probability of different diagnoses and direct further tests in a productive manner. Further diagnostic investigations—imaging, blood tests, pulmonary function studies, and even parts of the physical examination—depend on the history. Historical clues raise or lower probabilities, thereby improving the value of subsequent questions and evaluations. Test results plus findings from the history and physical examination may confirm or refute the main and differential diagnoses, setting up either a management plan or the need for an alternative hypothesis.

At the end of the initial evaluation, the assessment and plan should identify problems and a course of action that

Table 16-1 Selected Biases in Judgment or Reasoning

Bias	Definition
Anchoring	Tendency to lock onto salient features in the patient's initial presentation too early in the diagnostic process, and failing to adjust this initial impression in light of later information.
Confirmation bias	Tendency to look for confirming evidence to support a diagnosis rather than to look for evidence to refute it, despite the latter often being more persuasive and definitive.
Framing effect	Tendency to be strongly influenced by how the problem is presented (e.g., perceptions of risk to the patient strongly influenced by whether the possible outcome is expressed in terms of the possibility that the patient might die or might live).
Premature closure	Tendency to accept a diagnosis before it has been fully verified. The consequences of the bias are reflected in the maxim "When the diagnosis is made, the thinking stops."
Search satisfying	Tendency to call off a search once something is found. Comorbidities, second foreign bodies, other fractures, and coingestants in poisoning may all be missed. Also, if the search yields nothing, diagnosticians should satisfy themselves that they have been looking in the right place.
Unpacking principle	Failure to elicit all relevant information (unpacking), which may result in missing significant diagnostic possibilities.

takes into account the patient's concerns and questions. The patient should feel satisfaction that the physician has done a thorough job of exploring his or her complaints, has provided a plausible explanation for them, and has planned a reasonable course of action.

ELECTRONIC DOCUMENTATION

The electronic medical record now allows documents of higher quality than written records, owing to improved organization, increased readability, use of supplementary material, and better comparisons. It eliminates poor handwriting and lost or misplaced information. Additional benefits include cost savings for storage, easy accessibility, and quick transfer to another health care provider.⁶ The electronic medical record facilitates a coordinated team approach and reduces duplication of tests. Patients with complicated illnesses often have several different physicians, and electronic records can make it easier for one team to follow what another team is doing. Easy access to a complete record is especially important in emergency situations for physicians who are unfamiliar with the presenting patient. Electronic medication lists and reminders can save time and reduce errors. Electronic prescriptions provide greater patient safety.

Writing directly into the medical record, or initially through a word processing program, makes a cogent summary and chronological story easier to produce. The ability to insert information where it belongs helps maintain a congruous timeline. Spelling and grammar checks and autocorrection of abbreviations should make the finished report an easily readable document.

The disadvantages of electronic medical records include "information overload" and potential loss of privacy. Software downtime can be crippling. Learning how to use specific applications and developing typing skills may require training. Most word processing software used in electronic medical records is less efficient than commonly used commercial word processing software.

The "cut-and-paste" technique, beginning where the last visit left off, both saves time and ensures that ongoing problems are not overlooked. The problem with the cut-and-paste approach is that too much information may get deposited and duplicated in the medical record, including information irrelevant to the purpose of the consultation. Such excess text can at times replace essential information and impair easy understanding and critical reasoning. Cutting and pasting of information from consultants and other involved persons should never substitute for one's own primary history gathering or clinical thought. Cutting and pasting information gathered by someone else implies agreement with the statements. Proofreading is essential, especially of electronic prescriptions, because of the different doses and means of delivery of certain drugs.

Transfer of electronic medical information is not foolproof. Patients and physicians find it easy and convenient to communicate and transfer information by email, but there is a risk that the record of these interchanges may fail to be placed in the patient's permanent medical record, be intentionally or unintentionally intercepted leading to loss of privacy, or otherwise cause misunderstanding. Physicians may send patients electronic copies of their record, but if these are in a word processing format, patients could alter the record for secondary gain. Many of these concerns could have medicolegal consequences.⁶

COMMUNICATION SKILLS

The ability to listen skillfully, and to communicate clearly and empathetically with the patient, is the foundation for the physician-patient relationship. Communicating effectively with patients and peers underlies the success of a physician. The physician's communication should be objective, nonjudgmental, and empathic. Physicians are often better at obtaining medical information than they are at understanding how that information affects the patients.⁷ Communication contains both verbal and nonverbal interactions.⁸ A calm atmosphere, relaxed setting, and ample time are essential, particularly when disclosing bad news,⁹ but even then, a physician with good communication skills should be able to make the patient pleased that she or he saw the physician. This can be accomplished by always stating the truth but by cushioning ominous information with hope. When realistic, the physician might say, for example, that the cancer was caught early, provide reassurance about a probable good outcome, or suggest a new and improved therapy.

The old-fashioned tutorial approach of learning how to be a good physician had many shortcomings; students, residents, and fellows learned medicine as apprentices in "a catch-as-catch-can" manner. More recently, however, scientific testing and social psychological analysis have uncovered egregious flaws in how physicians obtain, sort out, and

evaluate diagnostic information. Sir William Osler used to tell students to “listen to the patient, he (or she) will tell you the diagnosis.” Today—instead—as Dr. J. Groopman points out in his excellent book, *How Doctors Think*, physicians interrupt the patient’s initial history in just 16 seconds and frequently thereafter, make snap judgments, and fall into cognitive traps that are much more likely than factual ignorance to lead to medical errors.¹⁰ New practice guidelines from evidence-based research help steer a correct diagnostic course, but the presence of overlapping diagnoses, unusual symptoms, and uncommon diseases requires wise and discerning physicians, not inflexible algorithms.

MEDICAL INTERVIEW

There is much more to the medical history than a recitation of questions and recording of answers. Instead, the medical interview has been defined as the entire medium of patient-physician interaction.¹¹ From this interactive experience, both physicians and patients learn about each other: the knowledge shared and feelings imparted influence subsequent trust, understanding, concern, and adherence to the health plan. Experience is valuable in the acquisition of clinical pattern recognition and in accumulating clinical knowledge. Although interviewing skills can be systematically learned,¹² acquiring the art of adept history taking and physical examination is a lifelong process that is incrementally improved by careful practice.

The main purposes of the medical interview are to (1) gather useful information, (2) develop rapport, (3) respond to concerns, and (4) educate the patient. The ease with which patients can access medical information may lead to a more active role on their part; patients may be well informed or misinformed about their actual or perceived diagnoses. Whatever their knowledge, most patients want to be accurately informed about their condition and to be involved in the deliberations and decision making.¹³ At the same time they generally want their physician to direct their health care in a reasoned manner, which entails taking into account the patients’ background knowledge, prejudices, and culture in a sensitive manner. This means the physician’s plan should take into account the individuality of the patient.

Encouraging the patient to take the lead in expressing his or her symptoms and relationships to these symptoms forms the basis for the patient-centered interview¹⁴ and develops appropriate rapport. Even in this era of reliance on laboratory studies, Platt’s original claim¹⁵ that a diagnosis can be obtained by history taking alone in most patients has been reaffirmed by several subsequent investigations.¹⁶⁻¹⁸

CHIEF COMPLAINT AND PRESENT ILLNESS

The medical history has traditionally been subdivided into the chief complaint; present, past, family, and social histories; and systems review. Because of its relevance and importance in the evaluation of patients with known or suspected pulmonary diseases, the occupational history is included as a separate component of the social history. Travel history, also included in the social history, is helpful in diagnosing certain lung diseases.

Only the chief complaint stands alone as a discrete response to a single question. It is generally recommended that the chief complaint be written in the patient’s own words, lest the physician’s interpretation be substituted prematurely for the patient’s unique concern. Each chief complaint must be explored in detail, and the resulting aggregate of information constitutes the history of the present illness. The various elements of the remainder of the history are sorted into their proper categories after the interview has been completed. The resulting history of present illness is a cogent chronological story that incorporates all the facts and their relationships that support the preliminary diagnosis and differential diagnoses. Although an open-ended and free-flowing encounter, the interview still should be focused and organized. Each new question is often linked to the answer to the previous one. At the end the review of systems is a series of questions designed to cover previously unexamined territory.

Even as the clinician fulfills the roles of information gatherer and detective, a more complex process is occurring in which a patient’s verbal and nonverbal responses to symptom queries provide a personal and often explanatory narrative that may encapsulate unique and individual aspects of illness. These may include the experience of illness and its relationship to any and all aspects of the patient’s life. The emerging field of narrative medicine highlights the effects such storytelling has on patients and providers, and its ability to enrich the physician-patient relationship and the clinical experience.^{19,20}

MAJOR PULMONARY SYMPTOMS

Because dyspnea, cough, and chest pain are among the most common reasons for patients to visit physicians, and because these symptoms may result from serious underlying chest disease, careful questioning is needed to establish their etiology and significance. The anatomic and pathophysiologic basis of these cardinal symptoms is provided in Chapters 29 to 31. To aid the interviewer in obtaining a medical history, a brief overview of these three common presenting symptoms and a related one, hemoptysis, is provided in this section.

Dyspnea

When a healthy person increases his or her level of physical activity sufficiently, an awareness of breathing emerges; if the severity of activity increases even further, the sensation becomes progressively more unpleasant, until it typically compels the individual to slow down or stop.²¹ Although dyspnea, shortness of breath, and breathlessness are often used interchangeably, as in Chapter 29, some purists use the term *dyspnea* only when the symptom is abnormal, which implies that the awareness is disproportionate to the stimulus and that the sensation is pathologic. Many patients describe their breathing discomfort as “breathlessness,” but many others complain of “tightness,” “choking,” being “unable to take a deep breath,” “suffocating,” being “unable to get enough air,” or occasionally even “tiredness.”

The mechanisms that underlie the sensation of dyspnea remain poorly understood and are reviewed in Chapter 29. In contrast to pain and cough, for which specific receptors and neural pathways have been identified, similar detailed

knowledge is lacking for dyspnea, although evidence is mounting that links the symptom with pain.^{21,22} Studies of the neurophysiology of dyspnea are further complicated by the lack of objective tools to quantify a subjective sensation with interindividual variation. Rating instruments—such as the Borg scale²³ and questionnaires, such as the British Medical Research Council questionnaire²⁴ and Pulmonary Functional Status and Dyspnea Questionnaire²⁵—have been validated as useful in measuring dyspnea. Self-administered, computerized versions of the Transitional Dyspnea Index and Multidimensional Baseline Dyspnea Index appear to be at least as good as interview questioning for this assessment.²⁶ Progress, though, is being made: recent studies have clearly shown that dyspnea during exercise in patients with *chronic obstructive pulmonary disease* (COPD) is closely linked to dynamic lung hyperinflation.²⁷

Clinical Features. Patients with respiratory, cardiac, hematologic, metabolic, and neuromuscular disorders may all complain of dyspnea. A careful and detailed history is necessary to uncover the cause of the sensation. In addition, it is important to document the impact of the symptom on the patient's daily activities and to be alert to the "decreased activity phenomenon." The latter describes patients who say their dyspnea has not worsened, but only because they now walk more slowly or no longer climb stairs or engage in athletic activities. Sometimes this slowing down is so gradual, patients may be unaware or attribute it to aging. Assessing the activity required to bring about the dyspnea is important. How many stairs can be climbed before stopping? How far can someone walk on level ground at her or his own pace without stopping? Does talking on the phone, getting dressed, or eating cause dyspnea? Is the patient short of breath at rest?

The course over time should be noted. Sudden dyspnea without an obvious provocation suggests pulmonary embolism or pneumothorax, although myocardial ischemia and asthma also may have a rapid onset. Dyspnea caused by cigarette smoke, dusts, molds, perfumes, newly cut grass, cats, and strong odors is characteristic of the increased bronchial reactivity seen in asthma. Associated features, such as wheezing and the presence and type of chest tightness or pain, are important clues. Worsening dyspnea with cough producing increased quantities of purulent sputum over 1 to 3 days characterizes an exacerbation of COPD.

Special types of dyspnea are sufficiently distinctive to warrant separate designations. Episodes of breathlessness that wake persons from a sound sleep, *paroxysmal nocturnal dyspnea*, usually denote left ventricular failure but may also occur in patients with chronic pulmonary diseases because of pooling of secretions, gravity-induced decreases in lung volumes, sleep-induced increases in airflow resistance, or nocturnal aspiration. *Orthopnea*, the onset or worsening of dyspnea on assuming the supine position, like paroxysmal nocturnal dyspnea, is found in patients with heart disease and chronic lung disease. Measurement of amino-terminal pro-B-type natriuretic peptide has proved useful in differentiating between a cardiac and a respiratory origin in patients with dyspnea.²⁸

The inability to assume the supine position (*instant orthopnea*) is characteristic of paralysis of both leaves of the diaphragm. Dyspnea soon after assuming the supine

position also may be associated with other conditions, such as arteriovenous malformation, bronchiectasis, and lung abscess. *Platypnea*, which denotes dyspnea in the upright position, and *trepopnea*, an even rarer form of dyspnea that develops in either the right or the left lateral decubitus position, suggest lung vascular shunting. Both the terms *hyperpnea*, an increase in minute ventilation, and *hyperventilation*, an increase in alveolar ventilation in excess of carbon dioxide production, indicate that ventilation is abnormally increased. Neither term, however, carries any implication about the presence or absence of dyspnea.

Cough

The quantity of bronchial secretions produced each day by a nonsmoking healthy adult is not precisely known, but it is sufficiently small to be removed by mucociliary action alone: healthy persons seldom cough.²⁹ As described in Chapter 30, coughing is an essential mechanism that protects the airways from the adverse effects of inhaled noxious substances and defends the lungs by clearing excess secretions.³⁰ Coughing can be occasional, transient, and unimportant. By contrast, it may indicate the presence of severe intrathoracic disease.

Clinical Features. Most episodes of coughing are associated with short-lived upper respiratory tract infections or allergies, and patients, recognizing this, seldom visit their physicians for this type of cough. Nevertheless, cough is the most common complaint for which patients seek medical attention and the second most common reason for having a general medical examination.³¹ Physicians should realize that when patients seek their help for cough, it is often out of concern for something new, different, and alarming about the symptom. The essential first step in evaluating a patient with cough is to obtain a thorough history, paying particular attention to the following aspects: acute or chronic, productive or nonproductive, character, time relationships, type and quantity of sputum, and associated features. It is noteworthy that, of the various components of the workup used by the authors of a systematic anatomic investigation to determine the causes of chronic cough, the medical history alone led to the correct diagnosis in 70% of patients.³¹

Acute coughing is frequently associated with nasopharyngitis, laryngotracheobronchitis, or other, usually virus-induced, upper respiratory tract infections. Less commonly, it may be the chief manifestation heralding the onset of viral or bacterial bronchopulmonary infection or the inhalation of allergenic or irritating substances. The causes of cough that persisted for 3 weeks or longer in 102 patients were postnasal drip (41%), asthma (24%), gastroesophageal reflux (21%), chronic bronchitis (5%), and bronchiectasis (4%).³¹ Other important though less common conditions include eosinophilic bronchitis³² and the use of angiotensin-converting enzyme inhibitors.³³ In 1999 the importance of the "big three"—postnasal drip, asthma, and gastroesophageal reflux—was verified by the results of another survey of the causes of chronic cough.³⁴ Not everyone agrees, however, and some experts claim that emphasis on the top three conditions is unwarranted and moreover that it stifles interest and research into other important causes and mechanisms of chronic cough.³⁵

A careful history of patients with cough lasting at least 3 months revealed that nearly all the patients misdiagnosed as “psychogenic” had one of the conditions listed previously for chronic cough.³⁶ Even cough that is made worse with psychological stress is often caused by underlying lung disease. Patients with exaggerated cough responses or habitual cough may have a “psychogenic” component; therefore, even when chronic cough has a pulmonary cause, it may respond to behavioral modification.³⁷

Most physicians have heard the ancient diagnostic axiom, which is still true, that any change in the character or pattern of a chronic cough in a smoker demands a prompt chest radiographic evaluation for lung cancer. Less well known is that cough may be the sole presenting manifestation of asthma³⁸ or gastroesophageal reflux disease.³⁹

In low-income countries, where the majority of the global population lives, cough, usually productive but not always, of 3 weeks or longer has been the traditional (and reliable) clinical marker of possible pulmonary tuberculosis that should trigger examination of sputum specimens for *Mycobacterium tuberculosis*. Revised recommendations by tuberculosis experts now include cough of “2 or 3 weeks,” or longer, as an indication for sputum examination.⁴⁰

Among the many complications of persistent or recurrent cough are tussive syncope; retinal vessel rupture; persistent headache; chest wall and abdominal muscle strains, including the development of abdominal wall hernia⁴¹; and even rib fractures. Severe chronic cough may create devastating personal distress, causing patients to restrict their social and professional activities.

Hemoptysis

The expectoration of any amount of blood denotes hemoptysis. Every patient with new-onset or appreciable hemoptysis deserves a thorough diagnostic evaluation, which generally includes *computed tomography* (CT) of the thorax and bronchoscopy. For centuries, hemoptysis was considered pathognomonic of pulmonary tuberculosis, a view that is summarized in the Hippocratic aphorism “the spitting of pus follows the spitting of blood, consumption follows the spitting of this, and death follows consumption.”⁴² The frequency of the different conditions that cause hemoptysis depend to a large extent on the population studied, but bronchitis, lung cancer, tuberculosis, and bronchiectasis are usually the most common causes.⁴³⁻⁴⁵ These are also the leading causes of massive hemoptysis (defined in various series as >200 or >600 mL of blood in 24 hours). Lung cancer and bronchitis usually cause mild to moderate bleeding, whereas patients with bronchiectasis, lung abscess, fungal disease, or a bleeding diathesis are more likely to have severe bleeding.⁴³ Less common conditions associated with hemoptysis include arteriovenous malformations, broncholithiasis, foreign bodies, aspergilloma, mitral stenosis, trauma, excessive anticoagulation, pulmonary hemorrhage syndromes, heart failure, pneumonia, and granulomatosis with polyangiitis (Wegener granulomatosis).

Clinical Features. Prompt evaluation, beginning with a thorough history, is required in all patients. It is important to determine where the blood is coming from. Surprisingly, patients may not always be able to distinguish hemoptysis from hematemesis and nasopharyngeal bleeding. Vomiting

blood may follow a prolonged coughing episode. Patients may swallow or aspirate blood from the upper airway. Some patients report only that the blood “welled up” in their throats. Others will say that it is mixed with sputum. Hematemesis can usually be differentiated from hemoptysis by the presence of symptoms of gastrointestinal involvement, such as nausea and vomiting, a history of peptic ulcer disease, alcoholism, or signs of cirrhosis; when in doubt, esophagoscopy is indicated.

Following physical examination, a chest radiograph and (often) a chest CT are required. Depending on the magnitude of the blood loss and the clinical circumstances, bronchoscopy is indicated to determine the location of the bleeding. Although these studies generally reveal which region of the lungs is the source, the cause of hemoptysis cannot be determined in 20% to 30% of cases.⁴⁶ Recent radiologic advances, which enhance identification of the culprit vessel, particularly multidetector computed tomographic angiography, have greatly helped the interventionist when bronchial artery embolization is required to stop the bleeding.⁴⁷

Chest Pain

Various types of chest pain are extremely common; their mechanisms and clinical patterns are described in Chapter 31. Chest pain is one of the most common symptoms that cause the sufferer to seek medical attention. Because there is no clear relationship between the intensity of the discomfort and the importance of its underlying cause, all complaints of chest pain must be carefully considered. The recent development of dedicated chest pain centers within emergency departments has improved the accuracy and rapidity of diagnosis, the treatment, and the survival of patients with this always troublesome symptom.⁴⁸

Clinical Features. Pleurisy, or acute inflammation of the pleural surfaces, has several distinctive features. Pleuritic pain is usually localized and unilateral—and tends to be distributed along the intercostal nerve zones. Pain from diaphragmatic pleurisy is often referred to the ipsilateral shoulder and side of the neck. The most striking and defining characteristic of pleuritic pain is its clear relationship to respiratory movements. The pain may be variously described as “sharp,” “burning,” or simply “a catch,” but it is typically worsened by taking a deep breath, and coughing or sneezing causes intense distress. Patients with pleurisy frequently also experience dyspnea because the aggravation of their pain during inspiration makes them conscious of every breath.

Acute pleuritic pain is found in patients with spontaneous pneumothorax, pulmonary embolism, and pneumonia, especially pneumococcal pneumonia, whereas a gradual onset over several days is observed in patients with tuberculosis; an even slower development is characteristic of primary or secondary malignancies. Chronic pleuritic pain is characteristic of mesothelioma. It may be difficult to distinguish pleuritic pain from the pain of a rib fracture, although point localization favors the latter. Pericardial pain is typically sharp, retrosternal in location, and relieved by sitting up and leaning forward.

The distribution and the superficial, knifelike quality of the pain of intercostal neuritis or radiculitis may resemble

pleural pain because it is worsened by vigorous respiratory movements but, unlike pleurisy, not by ordinary breathing. A neuritic origin may be suggested by the presence of lancinating or electric shock–like sensations unrelated to movements, and hyperalgesia or anesthesia over the distribution of the affected intercostal nerve provides confirmatory evidence. In many instances of new-onset, neuritic chest wall pain, the diagnosis becomes clear a day or two later when the typical vesicular rash of herpes zoster appears.⁴⁹

Among the most important types of chest pain is myocardial ischemia, which is usually caused by coronary artery atherosclerosis. These attacks, which are provoked by inadequate oxygen delivery to the myocardium, span a continuum of severity from chronic stable angina to classic acute myocardial infarction. Typical anginal pain is induced by exercise, heavy meals, and emotional upsets; the pain is usually described as a substernal “pressure,” “constriction,” or “squeezing” that, when intense, may radiate to the neck or down the ulnar aspect of one or both arms.⁵⁰ Pain from variant or Prinzmetal angina is similar in location and quality to typical anginal pain but is experienced intermittently at rest rather than during exertion.⁵¹ Both typical and variant types of angina are relieved by coronary vasodilator drugs, such as nitroglycerin. Typical angina also decreases with rest or removal of the inciting stress.

By contrast, the pain of acute myocardial infarction, although similar in location and character to anginal pain, is usually of greater intensity and duration, is not alleviated by rest or by nitroglycerin, may require large doses of opiates, and is often accompanied by profuse sweating, nausea, hypotension, and arrhythmias. During attacks of myocardial ischemia and myocardial infarction, patients are often short of breath from associated pulmonary edema, which may be severe, but the pain itself is not related to breathing. Pain similar to that of myocardial ischemia also occurs in patients with aortic valve disease, especially aortic stenosis, and other noncoronary heart disease and extracardiac disorders.

Inflammation of or trauma to the joints, muscles, cartilages, bones, and fasciae of the thoracic cage is a common cause of chest pain.⁵² Redness, swelling, and soreness of the costochondral junctions is called Tietze syndrome. All of these disorders are characterized by point tenderness over the affected area.

Most pulmonary thromboemboli are not associated with chest pain; the hallmark of pulmonary infarction, however, is typical pleuritic pain. Both acute and chronic causes of pulmonary hypertension may be associated with episodes of chest pain that resemble the pain of myocardial ischemia in its substernal location and pattern of radiation and in its being described as “crushing” or “constricting.”⁵² This type of chest pain is believed to result from right ventricular ischemia owing to impaired coronary blood flow secondary to increased right ventricular mass and elevated systolic and diastolic pressures or to compression of the left main coronary artery by the dilated pulmonary artery trunk.

FAMILY HISTORY AND SOCIAL HISTORY

The family history provides important clues to the presence of heritable pulmonary diseases, such as cystic fibrosis, α_1 -antitrypsin deficiency, hereditary hemorrhagic

telangiectasia (Osler-Weber-Rendu disease), immotile cilia syndrome, and immunodeficiency syndromes, among others. Careful history taking also can uncover even more common familial disease associations, which are polygenic or in which the exact mode of genetic transmission has not yet been established. As genomic surveillance is uncovering more and more genetic linkages, the family history assumes an even more important function. The family history should encompass at least three generations to account for sex-linked traits. Family history also can identify exposures such as to tuberculosis or other contagious diseases.

Of course, no evaluation of pulmonary symptoms is complete without a detailed history of smoking habits. The physician should ask, “Have you ever smoked?” A negative answer should prompt a confirmatory response such as, “So you are a lifelong nonsmoker?” and a compliment if the second answer is yes. If the patient has smoked, the next questions should be, “When did you start?” “When did you quit?” and “How much did you smoke while you were at it?” Ask also about different forms of tobacco and exposure at home or workplace to other people’s tobacco smoke. A history of exposure to environmental smoke is also important.⁵³ In many developing countries, smoke from indoor cooking and heating fires is a major cause of lung disease, especially in women. Risk factors for *human immunodeficiency virus* (HIV) infection, such as unprotected sexual activity and injection drug abuse, should be specifically queried.

Medications and Allergies

A complete list of all medications is essential to a thorough history. Ideally, the patient should bring in all his or her medications, and the physician should carefully go through each one, checking that the prescription has been properly written and filled and that the patient understands the benefit and possible side effects of each medicine. It is vital to note whether the patient has ever had an allergic or toxic reaction and what these reactions were. A complete listing of supplements and herbal medications should also be recorded and reviewed for potential interactions with conventional medications. No drug history is complete without assessing whether the patient drinks alcoholic beverages or uses illicit drugs. The amount and frequency of their use should be recorded.

Occupational History

The occupational history, which is often included as part of the social history, is an integral part of a thorough medical interview. Identifying a relevant occupational exposure may provide the only opportunity to remove the patient from the exposure and prevent progressive and irreversible lung damage. Moreover, identifying injurious occupational exposures can facilitate justifiable compensation for the patient and removal of the hazardous materials from the workplace by the industry.

The evaluation of suspected occupational lung disease is discussed in Chapters 64, 72, 73, and 74. Although only a few questions are asked in most initial medical interviews, if occupational illness is seriously being considered, a detailed inquiry about each industry, profession, and job the patient has held needs to be performed.^{54,55} Because there are so many environmental agents and different associated

illnesses, the diagnostician should consult online resources such as the National Institute for Occupational Safety and Health, the Environmental Protection Agency, Hazardous Substances Data Bank, the Occupational Safety and Health Administration, or other online resources to learn more about the putative environmental toxin.^{56,57}

Travel History

Previous places of residence help diagnose endemic fungal diseases, especially histoplasmosis and coccidioidomycosis. A history of recent travel may help establish the possibility of exposure to infectious diseases that are restricted to specific geographic regions.⁵⁸ The physician should inquire into the duration of travel. Long trips by air or car increase the risk for deep venous thrombosis and venous thromboembolism, which are reported in up to 10% of passengers on long-haul flights.⁵⁹ It is important to consider events after travel: symptoms of pulmonary thromboembolism and infarction may arise a variable time after the inciting event. The epidemic of *severe acute respiratory syndrome* (SARS) in southeast China in 2002 and its rapid spread throughout the world by airline passengers emphasizes the importance of obtaining a careful travel history.

PAST MEDICAL HISTORY

Previous illnesses may recur (e.g., tuberculosis), and new diseases may complicate old ones (e.g., bronchiectasis as a sequela of necrotizing pneumonia). Information about previous illnesses, operations, intubations, and trauma involving the respiratory system may be essential to understanding the current problem. Although these data may be gathered as part of the past medical history, much of the pertinent information will be absorbed into the chronological sequence of the history of present illness. Prior chest radiographs are an important aid in the evaluation of any abnormal chest radiograph because of the insights they provide into the duration and trajectory of illness. Patients should be asked to bring in previous films, but if they are unavailable, physicians should make every effort to obtain them, because old radiographs may save needless, costly, and sometimes risky interventions.

INFORMATION FROM QUESTIONNAIRES AND OTHER SOURCES

Printed or computer-based questionnaires and histories taken by nurses or allied health professionals are often used to expedite history taking. They can identify problems that can be explored further in the medical interview, and they facilitate a focused yet comprehensive evaluation. Occupational questionnaires have been shown to enhance recognition of occupational illness and correlate well with the findings of an industrial hygienist.⁶⁰ Computer-based interviews can gather more information, allow more time to complete the interview, uncover sensitive information, and may be adaptable to the hearing impaired and to persons speaking a language different from that of the physician.⁶¹

These forms of information gathering should be considered adjuncts and not a substitute for the thorough history taken by the physician. The limitations of the programmed questions are that the patient may not understand or be

able to express her or his concerns when confined by a form that does not allow the free exploration of symptoms that the open interview does. Automated data collection, of course, lacks the benefits gained from the patient-physician interaction, such as the establishment of rapport and the ability to observe nonverbal behavior. The interview itself also provides both time and opportunity for the physician to fully comprehend the patient's illness and to contemplate the primary and differential diagnoses.

For monitoring the course of certain disorders such as asthma, daily recording of symptoms, such as wheezing and breathlessness, and objective assessments of severity of disease, such as peak expiratory flow, in a diary are preferable to a single questionnaire because recall of symptoms may be faulty and one measurement may not be representative. The electronic monitoring that now comes as standard equipment with most home noninvasive ventilation devices gives the date and time of the respiratory events and the use of these devices.

PHYSICAL EXAMINATION

Sadly, the declining emphasis on proficiency in physical examination during medical school and residency training and the ever-increasing reliance on technology-based diagnosis have led to a decreased interest in, some say even the "demise" of, the physical examination.⁶² However, the old observation that 88% of all diagnoses in primary care were established by taking a thorough medical history and performing a complete physical examination⁶³ probably still holds today. At the very least, a carefully executed history and physical lead to more intelligent and cost-effective use of diagnostic technology. Plus, a physical examination can be performed virtually anywhere, may provide important information, lends itself to serial observations, and increases patients' confidence in their physicians.

EXAMINATION OF THE CHEST

Physical examination of the chest employs the four classic techniques of inspection, palpation, percussion, and auscultation. Each is described subsequently, as are the constellations of abnormalities that allow the examiner to infer the presence and type of various pulmonary disorders. Apart from inspection, which is not only a visual but also sometimes an olfactory tool and is always a structured cognitive skill, the other three modalities depend on the generation and the perception of sound or tactile sensations and vibrations. As was true of the history, the environment in which the physical examination takes place must be appropriate to the needs of both the examiner and the examined. Privacy, warmth, good light, and quiet are all essential. The best light source is natural sunlight, which should be used if possible. An ill-lit, noisy, or distracting environment will likely result in a physical examination that is flawed or incomplete.

Inspection

The physical examination begins the moment the clinician first sees the patient, even before the introductions and beginning the medical interview. Keen observations, and

the ability to pursue and interpret these observations, are the keys to skilled clinical diagnosis.

Inspection of the chest is carried out after sufficient clothing has been removed and the patient has been suitably draped to permit observation of the entire thorax. Ordinarily, inspection is performed with the patient sitting, but if the patient is too weak or cannot sit unaided, he or she should be supported in this position. Observing the shape and symmetry of the chest allows such abnormalities as kyphoscoliosis, pectus excavatum, pectus carinatum, ankylosing spondylitis, osteoporosis, gynecomastia, and surgical scars or defects to become obvious.

Several classic patterns of ventilation can be readily recognized (Fig. 16-1). Examples are *tachypnea*, which is almost uniform rapid shallow breathing; *Kussmaul breathing*, which is relentless, rapid, and deep breathing (air hunger); *Cheyne-Stokes respirations*, a cyclical waxing and waning of the depth of breathing with regularly recurring periods of apnea; and *Biot breathing*, which is totally irregular breathing, both the size of breaths and the periods of apnea, which are sometimes prolonged. Impending respiratory failure from muscle fatigue can be detected by observing rapid shallow breathing, abdominal paradoxical motion, and alternation between rib cage and abdominal breathing, so-called *respiratory alternans*.⁶⁴ The Hoover sign is the paradoxical inward displacement of the costal margin at the end of inspiration or throughout inspiration. Decreased regional ventilation can be detected by seeing a lag in the motion of the affected part of the chest wall during breathing.

Palpation

Palpation of the thorax is a necessary part of the cardiac, breast, and lymph node examinations and often can detect

bony abnormalities, such as a cervical rib, and subcutaneous calcinosis seen with systemic sclerosis. It is essential in examining causes of pain to determine point tenderness and thoracic spinal tenderness. It can detect fluctuant areas associated with empyema necessitans and crepitant areas associated with subcutaneous emphysema. Location by palpation of the trachea in the suprasternal notch is a useful way to detect shifts of the mediastinum. A spastic, extrafirm-feeling back muscle recognized by palpation may identify the cause of thoracic pain. A lag in movement of the chest wall, suspected from inspection, can be confirmed by placing the two hands over opposite portions of each hemithorax and both feeling and observing whether or not the thorax moves symmetrically.⁶⁵ Symmetry is as important in palpation as it is in inspection.

A palpable vibration felt on the body, usually over the chest, is called *fremitus*. Vocal fremitus is elicited by having the patient speak “one, two, three,” while the examiner’s two palms or sides of the hands are moved horizontally from top to bottom of the two hemithoraces. Vocal fremitus is increased over regions of lungs through which there is increased transmission of sound, for example, consolidation from pneumonia. Conversely, fremitus is decreased in conditions in which sound transmission is impaired, for example, pleural effusion. Occasionally, fremitus over part of the chest wall can detect the presence of airway secretions (rhonchal fremitus) or an underlying pleural friction rub (friction fremitus).

In examining the heart the examining physician should always search for an apical impulse, heaves and lifts, thrills, and palpable valve closure. In patients with severe COPD, abnormal cardiac movements are often better felt in the subxiphoid region than over the precordium.

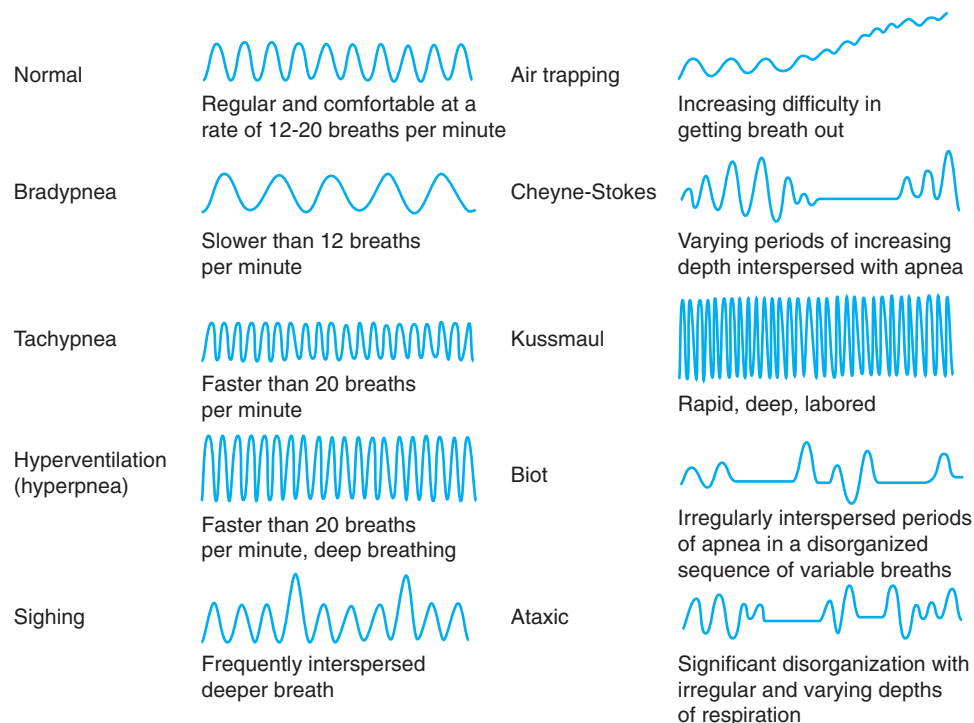


Figure 16-1 Schematic drawing of waveforms in different patterns of breathing. (Adapted from Wilkins RL, Hodgkin J, Lopez B: *Lung and heart sounds online*, St. Louis, 2011, Mosby.)

Percussion

Skillful percussion depends on a uniform free and easy stroke of the striking finger (plexor) on the finger being struck (pleximeter), the ability to sense minor changes in pitch, and a keen sense of vibration—although the percussion note is heard, it is predominantly felt. Percussion of the thorax over normal air-containing lung produces a resonant note.

Sounds and tactile perception from percussion vary depending on the thickness of the skin, subcutaneous layer, breast tissue, and chest wall, as well as on the quality, distribution, and tension of the air under the area percussed. Pathologic processes may impair or enhance the resonating quality of the thorax. For example, the percussion note over a large pneumothorax is hyperresonant and becomes tympanic when tension is present; in contrast, percussion over a pleural effusion or pneumonia produces dullness, which has been defined as a low-intensity sound of short duration, feeble carrying power, and rather high pitch.⁶⁶ Flatness is the unresonating sound obtained by percussing over the liver. Three different tonal zones can thus be detected when percussing large pleural effusions: normal resonance above the fluid, dullness in the middle, and flatness when completely below the fluid; these variations in sound may result from the presence of an internal meniscus or fluid wedge, which points upward into the lung above it. Carrying out a thoracentesis in the dull area offers the best chance of obtaining pleural fluid and avoids puncturing either an abdominal viscus or air-containing lung.

Auscultation

A stethoscope draped around the neck has long been the badge of the medical professional, and it is worn with pride by physicians, nurses, and respiratory therapists, despite predictions such as “it, too, will someday be relegated to a museum shelf.”⁶⁷ This will not happen for a long time, according to Murphy,⁶⁸ who mounts a spirited defense of stethoscopes backed up by analyses of breath sounds obtained by respiratory acoustic recording. Indeed, there is now a body of literature on computer-assisted mapping of breath sounds using both recording and imaging techniques which provides new insights into their origin and

clinical significance.⁶⁹⁻⁷¹ For example, computerized multi-sensor breath sound imaging has proved to be a sensitive and specific tool for differentiating pneumonia or pleural effusion from normal lungs.⁷² Similarly, signal analysis of heart sounds recorded by digital electronic means has promising clinical applications and is useful for teaching cardiac auscultation.⁷³ The fundamentals of lung auscultation in physical examination have been reviewed recently.⁷⁴

Stethoscopes are also helpful in picking up wheezes in asthmatics and crackles in patients with interstitial lung disease whose chest radiograph findings are normal. Moreover, patients expect their physicians to listen to their hearts and lungs if they have cardiorespiratory complaints.

Like any piece of medical equipment, there are a number of available choices, and the design and care of the stethoscope may have a substantial impact on its performance. Electronic models promise ambient noise reduction and audio amplification, features that have been shown in randomized trials to provide statistically significant improvements in acoustics, especially in noisy environments.^{75,76} However, the magnitude of improvement is small relative to the best acoustic stethoscopes, and electronic stethoscopes have not been shown to improve trainee performance.⁷⁷ Sound quality with any stethoscope can be substantially degraded by failure to maintain the integrity of the rubber fittings, and prolonged contact of the tubing with the skin when worn around the neck can lead to hardening of the tubing and decreased performance. In any case, the stethoscope must be kept clean because it is increasingly recognized as a vector of nosocomial infection.⁷⁸

The terminology of breath sounds has been standardized and simplified to enhance understanding and communication (Table 16-2). Although a standardized nomenclature has been proposed by the American Thoracic Society⁷⁹ and the Tenth International Conference on Lung Sounds,⁸⁰ communication at the bedside often strays from recommended terminology.

The basic technique of auscultation with an ordinary stethoscope is well known to most physicians: the diaphragm detects higher-pitched sounds, and the bell detects lower-pitched sounds, although if the bell is tightly pressed against the body, the taut underlying skin itself may serve

Table 16-2 Classification of Common Lung Sounds

	Acoustic Characteristics	American Thoracic Society Nomenclature	Common Synonyms
Normal	200-600 Hz Decreasing power with increasing Hz 75-1600 Hz Flat until sharp decrease in power (900 Hz)	Normal Bronchial	Vesicular Bronchial Tracheal
Adventitious	— Discontinuous, interrupted explosive sounds (loud, low in pitch), early inspiratory or expiratory Discontinuous, interrupted explosive sounds (less loud than above and of shorter duration; higher in pitch than coarse crackles or crackles), mid- to late inspiratory Continuous sounds (>250 msec, high-pitched; dominant frequency of 400 Hz or more, a hissing sound) Continuous sounds (>250 msec, low-pitched; dominant frequency < 200 Hz, a snoring sound)	Adventitious Coarse crackles Fine crackles Wheezes Rhonchi	Abnormal Coarse crackles Fine crackles, crepitation Sibilant rhonchus, high-pitched wheeze Sonorous rhonchus, low pitched wheeze

as a “diaphragm” and improve perception of higher pitches. Conversely, the bell should be applied very lightly to hear, for example, the low-pitched rumble of mitral stenosis. Full contact with the skin is necessary for best listening, which may pose a problem in a patient whose intercostal spaces are sunken from weight loss. In addition, the skin or hairs may brush against the diaphragm and produce a sound that resembles a pleural friction rub. As with examiners’ hands, a warm stethoscope head is appreciated by patients. The importance of a quiet room and of applying the stethoscope directly to the skin rather than through clothing has recently been reemphasized.⁸¹ At times, especially in the intensive care unit, it is not always possible to sit patients up to listen carefully to their backs, which compromises the completeness of auscultation.

This chapter includes links to audio recordings, some with animations. To hear the recorded lung sounds at their intended pitch and intensity, it is recommended that readers listen through a stethoscope, with the chest piece held 4–5 inches from the audio speaker.

The recommended terminology for the ordinary breathing-associated sounds heard with a stethoscope placed on the chest of a healthy person is *normal lung sounds*, but, as shown in Table 16-2, many physicians prefer the older term *vesicular breath sounds* (Audio 16-1). The usually predominating inspiratory component arises from sounds generated by turbulent airflow within the lobar and segmental bronchi, whereas the weaker expiratory component arises within the larger, more central airways.⁷⁹ Sounds are attenuated as they move peripherally along the air passages and are further damped by the large volume of the lungs’ air spaces. The intensity of normal breath sounds varies with the magnitude of regional ventilation and, like percussion notes, diminishes with increasing thickness of the tissue overlying the chest wall. There is considerable variation among persons in the quality of breath sounds, which makes it essential to compare breath sounds from one side with those heard over the same location on the opposite hemithorax.

The transmission of normal lung sounds to the chest wall in pathologic conditions may be either attenuated or exaggerated. When the lung parenchyma is consolidated and the airway leading to the involved region is patent, breath sounds are well transmitted to the chest wall and are termed *bronchial breath sounds* (Audio 16-2). Bronchial breath sounds are loud, high-pitched, tubular, or whistling sounds with expiration as loud as or louder than with inspiration. Bronchial breath sounds are similar to *tracheal breath sounds* (Audio 16-3), and their presence is the classic auscultatory sign of pneumonia with consolidation. Similar sounds are heard in patients with other types of consolidation, such as pulmonary edema and hemorrhage. The presence of this sign assumes that the sounds originate centrally and reach the chest wall.⁸²

Interposition of a sound barrier between the central airways where sounds originate and the chest wall where

they are heard also attenuates or interrupts transmission of normal lung sounds. Accordingly, normal breath sounds are diminished or absent over a pleural effusion, pneumothorax, and peripheral bullae, or distal to an obstructing mass lesion. Conversely, they may be increased if chest wall deformity or bronchial or tracheal derangement allows movement of air to be closer than usual to the stethoscope.

Adventitious Sounds

The major types of adventitious sounds are classified in Table 16-2. Two generic categories of adventitious sounds have been documented by high-speed recording techniques, and each of these has two subdivisions: discontinuous sounds, including fine crackles and coarse crackles, and continuous sounds, including wheezes and rhonchi.⁸³

Discontinuous Sounds (Crackles)

Crackles, still often referred to as “rales” in the United States and “crepitations” in Great Britain, consist of a series of short, explosive, nonmusical sounds that punctuate the underlying breath sound; fine crackles (Audio 16-4) are softer, shorter in duration, and higher in pitch than coarse crackles (Audio 16-5). There is general agreement that the brief recurrent detonations that characterize fine crackles are caused by the explosive openings of small airways that had closed owing to the surface forces within them.^{79,84} This explains why fine crackles are much more common during inspiration than during expiration and why they are best heard over dependent lung regions—where airways are more likely to close—than over uppermost regions. This is also compatible with the presence of crackles in healthy elderly persons in whom dependent airways close at resting lung volumes. Crackles therefore are best heard during the first deep breaths at the lung bases posteriorly. After several such breaths or intentional coughing, these fine crackles will disappear if the small airways remain open throughout the time the patient is being examined.⁸⁴

The timing of crackles is also important. Nath and Capel⁸⁵ have shown that late-inspiratory crackles are more often found in restrictive than obstructive lung disease. In a study by Pürilä and colleagues,⁸⁶ the crackles of pulmonary fibrosis began at 45% of inspiration, whereas those of nonfibrotic lung conditions were heard earlier: COPD at 25%, bronchiectasis at 33%, and heart failure at 37% of inspiration.⁸⁶ This suggests that more tension is required to open individual airways in fibrosis than in lungs with secretions or edema. As inspiration progresses, radial traction on airway walls increase until suddenly they pop open.⁸⁵ Thus crackles heard later in inspiratory time imply that the tension required to open individual airways is greater. Coughing or deep inspiration may change the quality of coarse crackles, such as those associated with underlying alveolar or airway disease, but the crackles rarely disappear entirely. Expiratory crackles are much less frequent than inspiratory crackles and are often seen in obstructive lung disease.⁸³

Continuous Sounds (Wheezes)

The American Thoracic Society Committee on Pulmonary Nomenclature defined wheezing as high-pitched (dominant frequency of > 400 Hz) continuous adventitious lung

sounds.⁸² Continuous sounds are longer than 250 msec in duration. Wheezes are usually louder than the underlying breath sounds and frequently noted by patients. A leading theory is that wheezes are produced by fluttering of the airway walls and fluid together induced by a critical flow velocity.⁸⁷ The pitch of the wheeze is dependent on the mass and elasticity of the airway walls and the flow velocity. The degree of bronchial obstruction is proportional to the amount of the respiratory cycle that it occupies. There is no relationship to the intensity or pitch of the wheeze and pulmonary function. Wheezes are well heard over the trachea, and listening over the trachea may be superior to listening over the lung in most asthmatic patients⁸⁷ (Audio 16-6). Wheezing with forced expiration can sometimes be provoked in healthy subjects⁷⁹ and does not establish a diagnosis of asthma. More helpful is to elicit wheezing and/or coughing at a full expiration without forced effort. Because several disease states are associated with wheezing, additional information should be obtained to make the correct diagnosis.

Rhonchi are low-pitched continuous sounds with a dominant frequency of approximately 200 Hz or less (Audio 16-7). These sounds are likely to originate from rupture of fluid films and airway wall vibrations.⁷⁹ Rhonchi may clear with cough or with suctioning in intubated patients. Some have questioned whether the term rhonchi is needed at all, finding the substitute “low-pitched wheezes” more parsimonious.⁸⁸ However, the term retains its place in classification systems and in clinical usage.^{79,80,89}

Voice-Generated Sounds

Another way of generating sounds for auscultation is to have a patient speak while the examiner listens to his or her chest. Ordinarily the patient is asked to say in a quiet voice “one, two, one, two,” “ninety-nine, ninety-nine,” or “E, E.” If enhanced responses are heard, the patient repeats the words while whispering. Because sounds of central origin are attenuated as they are transmitted peripherally through normal air-filled lung, voice-generated sounds have a muffled quality and the words are indistinct. In contrast, in the presence of consolidation, the characteristics of the sounds are remarkably different. The term *egophony* (Audio 16-8) indicates sounds that have a high-pitched, bleating quality; a change in sound-filtering properties of consolidated lungs accounts for the presence of egophony, which does not require, as often stated, the presence of an overlying pleural effusion. *Bronchophony* (Audio 16-9) and *pectoriloquy* (Audio 16-10) both mean that spoken sounds are transmitted with increased intensity and pitch; when each syllable of every word, especially when whispered, is distinct and easily recognized, pectoriloquy is the preferred description. An E-to-A sign means that the spoken letter “E” sounds like “A” while listened to over the lungs. Each of these auscultatory findings is a manifestation of the same acoustic property of consolidated lungs and thus has similar diagnostic significance.

Pleural Friction Rub

The small amount of liquid normally present in the pleural space separates the visceral and the parietal pleural layers and allows the lungs to expand and contract freely during breathing. In contrast, when the pleural surfaces are

thickened and roughened by an inflammatory or neoplastic process, easy motion is prevented and a pleural friction rub may be produced. These sounds vary in intensity but often have a leathery or creaking quality that may be exaggerated by pressure with the stethoscope (Audio 16-11). Typically rubs are heard during both inspiration and expiration, but they are evanescent and variable and may be heard in only one part of the respiratory cycle. Surprisingly, rubs may still be heard in the presence of a large pleural effusion, which prevents the coarsened pleural surfaces from actually rubbing against each other.

Extrapulmonary Sounds

The presence of air or other gas in the mediastinum may be associated with crunching, crackling sounds that are synchronous with cardiac contraction and are audible when breathing is momentarily stopped. The finding of a mediastinal crunch by auscultation usually signifies mediastinal emphysema, even when the chest radiograph shows no abnormalities. In contrast, a pleural friction rub is usually heard during both inspiration and expiration and has a higher pitch.

Stridor is a high-pitched continuous sound produced by turbulent flow in the extrathoracic airway, which—in contrast to wheezing—is louder and longer during inspiration than expiration (Audio 16-12). Stridor has many causes,⁹⁰ some of which are life-threatening and need immediate attention (see Chapter 49).

As previously mentioned, various sounds may originate from the chest wall itself. Some of these have pathologic significance; others do not. Rubbing hairs trapped between the skin and the stethoscope produce intermittent crackling sounds that may be confused with crackles (Audio 16-13). Variable crackles are also produced when the stethoscope is placed over an area of subcutaneous emphysema and is rocked back and forth (Audio 16-14). Contracting chest wall muscles may generate sounds that have a muffled, distant, low-pitched, and rumbling quality. Occasionally it is possible to hear a snapping sound during breathing from motion of a newly fractured rib (Audio 16-15).

Interpretation

When abnormalities are discovered on physical examination of the chest, it is useful to identify them by their anatomic location in the involved lung. This requires knowledge of the surface projections of the underlying bronchopulmonary lobes, which are shown in Figure 16-2. The upper and lower lobes of both lungs are separated by the two oblique fissures, which course from the spinous process of the third thoracic vertebra posteriorly to the level of the 6th rib in the midclavicular line anteriorly. On the right side anteriorly, the upper and middle lobes are separated by the horizontal fissure, which lies at about the level of the fourth costal cartilage. In the presence of either distortions of pulmonary anatomy or the shape of the rib cage, the surface projections of the underlying lung also change.

The classic findings on physical examination of the chest in some common pulmonary disorders are shown in Table 16-3. Ordinarily, consolidation must be within 1 or 2 cm of the costal surface to be reliably detected. Even then, physical examination alone cannot be relied upon to diagnose or exclude pneumonia.⁹¹ Some pneumonias,

Table 16-3 Classic Physical Findings in Some Common Pulmonary Disorders

Disorder	Inspection	Palpation	Percussion	Auscultation
Bronchial asthma (acute attack)	Hyperinflation; use of accessory muscles	Impaired expansion; decreased fremitus	Hyperresonance; low diaphragm	Prolonged expiration; inspiratory and expiratory wheezes
Pneumothorax (complete)	Lag on affected side	Absent fremitus	Hyperresonant or tympanitic	Absent breath sounds
Pleural effusion (large)	Lag on affected side	Decreased fremitus; trachea and heart shifted away from affected side	Dullness or flatness	Absent breath sounds
Atelectasis (lobar obstruction)	Lag on affected side	Decreased fremitus; trachea and heart shifted toward affected side	Dullness or flatness	Absent breath sounds
Consolidation (pneumonia)	Possible lag or splinting	Increased fremitus on affected side	Dullness	Bronchial breath sounds; bronchophony; pectoriloquy; crackles

Modified from Hinshaw HC, Murray JF, editors: *Diseases of the chest*, ed 4, Philadelphia, 1980, WB Saunders, p 23.

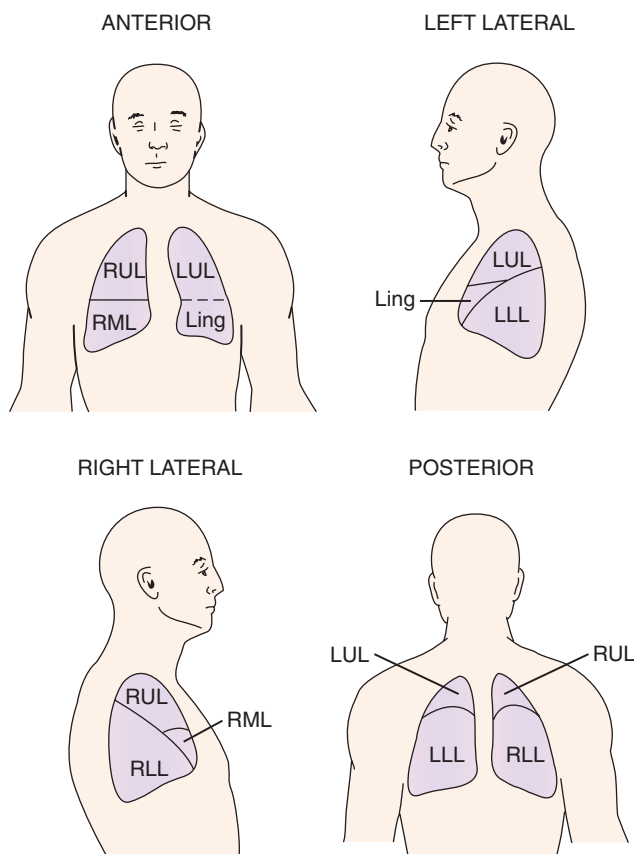


Figure 16-2 Schematic drawing shows surface projections of underlying lobar anatomy of a healthy man. Ling, lingular division of left upper lobe; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

such as *Mycoplasma pneumoniae*, typically cause surprisingly few physical abnormalities despite extensive radiographic involvement (see eFig. 33-9) but, even in patients with classic lobar pneumonia, the findings may be nonspecific. Although unable to distinguish reliably between new-onset pneumonia and other pulmonary diseases, the findings from physical examination—vital signs, mental

confusion, cyanosis, use of accessory muscles, and paradoxical breathing—are extremely important in assessing severity and in deciding whether or not to hospitalize patients with pneumonia.⁹²

The distinction between pleural effusion and atelectasis can be made on physical examination by determining whether the heart and mediastinal contents shift toward or away from the abnormal side, a finding that can usually be made only if the effusion is large or the atelectasis involves at least one lobe. When these full-blown manifestations are present, the presence of the causative disorder can be inferred with reasonable certainty. However, the absence of these findings does not exclude an abnormality, and a chest radiograph must always be taken as part of the complete pulmonary workup.

EXTRAPULMONARY MANIFESTATIONS

The examination of the lungs and pleura unlock only some of the clues to the presence of lung disease. Looking for extrapulmonary signs can often point toward a specific pulmonary disease or toward systemic diseases such as lupus erythematosus or toward diseases arising elsewhere in the body that secondarily involve the lung. Certain extrapulmonary manifestations are particularly useful.

Clubbing

The association of clubbing of the fingers or toes with disease has caught the attention of physicians since the time of Hippocrates. Clubbing is easy to recognize when it is severe (Fig. 16-3), but subtle changes are more common and less reliable. The hallmarks of clubbing are (1) a softening and periungual erythema of the nail beds, which causes the nails to seem to float rather than to be firmly attached, (2) an increase of the normal 165-degree angle that the nail makes with its cuticle, (3) an enlargement or bulging of the distal phalanx, which may be warm and erythematous, and (4) a curvature of the nails themselves. Of these features, the straightening of the nail cuticle angle appears to be the most sensitive measurement.⁹³

Patients with clubbing may also have *hypertrophic osteoarthropathy*, a condition characterized by subperiosteal formation of new cancellous bone at the distal ends of



Figure 16-3 Clubbing of the digits as seen in severe diffuse interstitial pulmonary fibrosis. (From Cashman MW, Sloan SB: Nutrition and nail disease. *Clin Dermatol* 28: 420–425, 2010, Figure 2.)



Figure 16-4 Radiographs of the leg show marked subperiosteal new bone formation (arrows) that is diagnostic of hypertrophic osteoarthropathy. A, Most of tibia and fibula. B, Detailed view near the ankle.

long bones, especially the radius and ulna and the tibia and fibula. Hypertrophic osteoarthropathy (Fig. 16-4) is almost always associated with clubbing, particularly in patients with bronchogenic carcinoma, other intrathoracic malignancies, and cystic fibrosis. It occasionally develops in patients with bronchiectasis, empyema, and lung abscess but is rare in patients with most of the other

conditions in which clubbing has been observed.⁹⁴ One of the striking features of clubbing is the speed with which it can develop, about 2 weeks in patients with new-onset empyema, and with which it can reverse, also about 2 weeks in patients after corrective cardiac surgery. The presence of clubbing, which was found in 1% of all admissions to an internal medicine department, was associated with “serious disease” in 40% of afflicted patients⁹⁵; therefore new-onset clubbing always warrants a chest radiograph, and if no abnormality is found, a CT scan to look for a pulmonary neoplasm or other lesion, which may still be localized and curable.

Clubbing has been found in many diverse conditions, such as children with HIV,⁹⁶ hepatopulmonary syndrome,⁹⁷ and benign asbestos pleural disease⁹⁸ (Table 16-4). Both clubbing and hypertrophic osteoarthropathy can be idiopathic or familial; the familial form is often transmitted as a dominant trait. The hereditary form of hypertrophic osteoarthropathy is also called *pachydermoperiostosis*, a condition in which bone and joint involvement is often mild but furrowing of the skin of the face and scalp is usually marked.

The main pathologic finding in clubbing is increased capillary density. The most potent stimulus to new capillary growth is hypoxia, which causes an intense production of vascular growth factors, such as vascular endothelial growth factor. With histochemical staining, Atkinson and Fox⁹⁹ showed increases in vascular endothelial growth factor, platelet-derived growth factor, hypoxia-inducible factor-1 α , and hypoxia-inducible factor-2 α along with increased microvessel density in the stroma of clubbed digits. The second common characteristic of patients with digital clubbing is shunting of blood past the capillary bed of either the lung or the liver, which suggests that lack of metabolism of angiogenic factors that bypass a critical organ may be involved. Several of the conditions associated with clubbing have inflammation and shunting, such as bronchiectasis and liver cirrhosis.

Other Extrapulmonary Associations

Besides clubbing, thoracic neoplasms may cause other extrathoracic abnormalities that may become evident on physical examination, including anemia, Cushing syndrome, gynecomastia, and other paraneoplastic syndromes (Table 16-5). Other common extrathoracic manifestations that provide clues to the presence or state of an underlying malignancy are wasting, hoarseness, adenopathy (especially supraclavicular), and hepatomegaly. When evaluating patients with dyspnea, a thorough examination of the neck veins for evidence of increased central venous pressure and careful cardiac auscultation for the presence of a third heart sound or distinctive murmurs should be performed to exclude heart failure.¹⁰⁰ The extremities should also be examined for evidence of peripheral edema, venous thrombosis, chronic venous stasis, and scars that suggest injection drug abuse.

The association of abnormalities in other organ systems with underlying lung disease can be very helpful in making a diagnosis.

Important lesions associated with various primary lung disorders are listed in tables available in the electronic version of the text at ExpertConsult.



A wide variety of cutaneous or subcutaneous lesions (eTable 16-1)⁹⁹ and ocular lesions (eTable 16-2)¹⁰⁰ has been associated with various primary lung disorders. Likewise, a combination of lung and kidney disease (eTable 16-3); lung

and bone, joint, muscle, or nerve lesions (eTable 16-4); and gastrointestinal and hepatic involvement (eTable 16-5) may suggest a unifying disease process that can be detected by physical examination.

Table 16-1 Skin and Subcutaneous Lesions Associated with Lung Disease**SKIN LESIONS**

Diffuse pigment change
Acanthosis nigricans—lung neoplasm
Albinism—Hermansky-Pudlak syndrome
Bronze pigmentation—hemosiderosis
Gray-brown—Whipple disease
Cutaneous draining sinus
Fungal infections (especially histoplasmosis)
Mycobacterial infections (especially tuberculosis)
Necrotizing vasculitis
Neoplasms (especially mesothelial tumors)
Other bacterial infections (especially actinomycosis)
Cutaneous ulcers
Beryllium disease
Chronic venous insufficiency
Fungal infections (especially histoplasmosis)
Mycobacterial disease
Necrotizing vasculitis
Parasitic disease
Polycythemia
Sickle cell disease
Tularemia
Cutaneous vasculitis
Behçet syndrome
Collagen vascular disease
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Granulomatosis with polyangiitis (Wegener granulomatosis)
Sarcoidosis
Erythema multiforme
Drug reactions
Fungi (especially coccidiomycosis)
Mycoplasma and other infectious agents
Neoplasms
Exfoliative dermatitis
Adverse drug reactions
Chemotherapy
Disseminated malignancy
Graft-versus-host disease
Radiation therapy
Flushing
Bronchial carcinoid, pheochromocytoma, other neoplasms
Carbon dioxide, cyanide, and other toxins
Drugs
Foods and vasodilatory substances
Hormones
Mastocytosis
Metabolic states (e.g., hyperthyroidism, fever)
Macular rash
Anti-glomerular basement membrane disease
Café-au-lait spots (neurofibromatosis)
Coal miner's scars
Collagen vascular disease
Idiopathic pulmonary fibrosis
Rose spots (psittacosis)
Sarcoidosis
Syphilis
Viral pneumonia
Maculopapular rash
Amyloidosis
Drug-induced lung disease
Collagen vascular disease
Gaucher disease
Kaposi sarcoma
Lung neoplasm
Lymphoma
Lymphomatoid granulomatosis
Parasites
Sarcoidosis
Syphilis
Vasculitis
Viral pneumonia
Sicca syndrome (dry mouth and eyes)
Gaucher disease
Lymphocytic interstitial pneumonia
Sjögren syndrome
Telangiectasia
Arteriovenous malformation
Ataxia-telangiectasia
Carcinoid syndrome
Cushing disease
Hepatopulmonary syndrome and other chronic liver diseases
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
Mastocytosis
Systemic sclerosis and other collagen vascular diseases

Urticaria
Asthma
Drug reactions
Cystic fibrosis
Exercise-induced urticaria
Food allergy
Hereditary angioneurotic edema
Infectious agents, such as *Mycoplasma* and *Helicobacter*
Inhaled antigens
Insect bites and stings
Mastocytosis
Occupational sensitization
Parasites
Vasculitis

NAIL CHANGES WITH LUNG DISEASE

Color changes
Cigarette smoking discoloration
Splinter hemorrhages
Yellow nail syndrome
Beau lines (any severe illness)
Dermatomyositis
Sarcoidosis
Seronegative arthropathies
Systemic sclerosis

LUNG DISEASE WITH SUBCUTANEOUS INVOLVEMENT

Adenopathy
Environmental mycobacteria
Fungal infections
HIV infections
Metastatic neoplasm
Leukemia
Lymphoma
Sarcoidosis
Tuberculosis
Calcinosis
Dermatomyositis
Metastatic osteosarcoma
Mixed connective tissue disease
Scleroderma
Tuberculosis
Uremic metastatic calcification
Erythema induratum (Bazin disease)
Aortic stenosis
Cryoglobulinemia
Nodular vasculitis
Panniculitis
Peripheral neuropathy
Streptococcus infection
Takayasu disease
Tuberculosis and other mycobacterial disease
Weber-Christian disease
Erythema nodosa
Neoplasm
Other infectious and inflammatory diseases
Primary coccidiomycosis, histoplasmosis
Primary tuberculosis
Psittacosis
Sarcoidosis
Subcutaneous nodules
Amyloidosis
Neoplasm
Neurofibromatosis
Rheumatoid arthritis
Tuberous sclerosis (angiofibromas)
von Recklinghausen disease
Weber-Christian disease

LUNG DISEASE WITH SALIVARY GLAND ENLARGEMENT

Bulimia and aspiration
Gaucher disease
Lymphatic carcinoma
Lymphoid interstitial pneumonitis
Lymphoma
Other causes of lymphadenopathy
Sarcoidosis
Sjögren disease

eTable 16-2 Eye Involvement in Lung Disease

BLINDNESS Amaurosis fugax Antiphospholipid syndrome Aspergillosis Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) Granulomatosis with polyangiitis (Wegener granulomatosis) Temporal arteritis Giant cell arteritis Late stage of many diseases Sarcoidosis	RETINA Antiphospholipid syndrome Behçet disease Candidiasis Cytomegalovirus, herpes, and other viruses Diabetes Disseminated intravascular coagulation Dysproteinemia Ehlers-Danlos syndrome Embolic disease Endocarditis Fat emboli Fungemia Genetic metabolic deficiencies Granulomatosis with polyangiitis HIV disease Leukemia, lymphoma Lupus erythematosus Macroglobulinemia Marfan syndrome Neoplasm (especially melanoma) Polycythemia Sarcoidosis Sickle cell disease Subacute bacterial endocarditis, sepsis (Roth spots) Syphilis Temporal arteritis Toxoplasmosis Trauma Tuberous sclerosis
CHOROID Histoplasmosis Lupus erythematosus Toxoplasmosis	
CONJUNCTIVA Allergic reaction Chlamydia Granulomatosis with polyangiitis Herpes Kaposi sarcoma Sarcoidosis	
CORNEA Chlamydia Granulomatosis with polyangiitis Herpes Syphilis	
IRIS Neoplasm Neurofibromatosis	
LENS Cataracts Steroid use Tobacco smoking Marfan syndrome (dislocated)	SCLERA AND EPISCLERA Granulomatosis with polyangiitis Inflammatory bowel disease Rheumatoid arthritis Sarcoidosis Scleroderma Systemic lupus Systemic vasculitis
LIDS Proptosis Graves disease Leukemia Neoplasm Ptosis Myasthenia gravis Muscular dystrophy	SICCA Graft-versus-host disease Rheumatoid arthritis Sjögren syndrome
OPTIC NERVE Cryptococcosis Granulomatosis with polyangiitis Graves disease Leukemia Neurofibromatosis Sarcoidosis Syphilis	UVEA Ankylosing spondylitis Behçet disease Crohn disease Granulomatosis with polyangiitis Herpes zoster Inflammatory bowel disease Reactive arthritis Rheumatoid arthritis Sarcoidosis Syphilis

eTable 16-3 Renal Involvement in Lung Disease**GLOMERULONEPHRITIS**

Anti-glomerular basement membrane disease
Sarcoidosis
Collagen vascular disease
Systemic vasculitis

NEPHROTIC SYNDROME

Amyloidosis
Disseminated Langerhans cell histiocytosis
Drug-induced lung disease
Paraneoplastic syndrome
Post transplantation
Pulmonary hydatid disease
Systemic lupus erythematosus
Vasculitis
Venous thrombosis

RENAL MASS

Granulomatosis with polyangiitis (Wegener's granulomatosis)
Lymphangioleiomyomatosis
Metastatic neoplasm
Renal carcinoid
Tuberous sclerosis

NEPHROLITHIASIS

Alveolar proteinosis
Cystic fibrosis
Hypercalcemic syndromes
Osteolysis from mycobacteria or fungi
Sarcoidosis

SYSTEMIC HYPERTENSION

Collagen vascular disease
Diffuse alveolar hemorrhage
Neurofibromatosis
Pulmonary-renal syndromes
Sleep apnea

eTable 16-4 Joint, Bone, Muscle, and Neurologic Involvement in Lung Disease**ARTHRITIS**

Ankylosing spondylitis
Collagen vascular diseases
Reactive arthritis
Sarcoidosis
Systemic vasculitis
Tuberculosis

BONE LESIONS

Ankylosing spondylitis
Blastomycosis and other fungal disease
Collagen vascular diseases
Eosinophilic granulomatosis
Fibrous histiocytoma
Gaucher disease
Neoplasm
Sarcoidosis
Tuberculosis

MUSCLE DISEASE

Collagen vascular disease
Diabetes insipidus
Eosinophilic granulomatosis
L-Tryptophan
Polymyositis
Sarcoidosis

NEUROLOGIC DISEASE

Acute inflammatory polyneuropathy
Amyotrophic lateral sclerosis
Aspiration
Botulism
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Granulomatosis with polyangiitis (Wegener granulomatosis)
Lambert-Eaton syndrome
Myasthenia gravis
Organophosphate poisoning
Polio and postpolio syndrome
Sarcoidosis

eTable 16-5 Gastrointestinal and Hepatic Involvement in Lung Disease**ESOPHAGEAL REFLUX**

Aspiration pneumonia
 Asthma
 Bronchiectasis
 Bronchitis
 Cough
 Mycobacterial disease
 Pulmonary fibrosis
 Scleroderma

INFLAMMATORY BOWEL DISEASE

Adverse reactions to drug treatments
 Bronchiectasis
 Bronchiolitis
 Bronchitis

COLOBRONCHIAL FISTULA

Desquamative interstitial lung disease
 Eosinophilic lung disease
 Interstitial lung disease
 Necrobiotic nodules
 Obstructive lung disease
 Organizing pneumonia
 Sarcoidosis
 Serositis affecting pleura or pericarditis
 Tracheal stenosis

LIVER

Alpha₁-antitrypsin deficiency
 Chronic active hepatitis
 Hepatopulmonary syndrome
 Portopulmonary hypertension
 Primary biliary cirrhosis
 Hepatosplenomegaly
 Amyloidosis
 Collagen vascular disease
 Eosinophilic granulomatosis
 Lymphatic interstitial pneumonia
 Sarcoidosis

Table 16-4 Causes of Clubbing (Partial Listing)

NOT ASSOCIATED WITH OVERT DISEASE Hereditary clubbing Sporadic clubbing Pachydermoperiostosis	GASTROINTESTINAL AND LIVER DISEASE Inflammatory bowel disease Crohn disease Ulcerative colitis Polyposis coli Amebic colitis Bacillary dysentery Liver disease Hepatoma Hepatopulmonary syndrome Biliary cirrhosis Esophageal stricture
THORACIC NEOPLASMS Lung cancer especially fibrous tumors (accounts for most clubbing) Benign and malignant pleural tumors Other thoracic neoplasms, including esophageal cancer, and lymphoma	HEMOGLOBINOPATHY Hemoglobinopathies Congenital methemoglobinemia
HEART AND VASCULAR DISEASE Cyanotic congenital heart disease Subacute bacterial endocarditis Infected aortic graft Aortic surgery Takayasu arteritis Behçet syndrome	OTHER Thyroid acropathy Secondary hyperparathyroidism HIV-related Lymphoid interstitial pneumonia Other infections Prostaglandin infusion Fabry disease Toxic exposure to arsenic, mercury, or beryllium
PULMONARY AV SHUNTING Cyanotic congenital heart disease Acquired heart disease Pulmonary AV fistula Hereditary hemorrhagic telangiectasias	UNILATERAL CLUBBING Vascular disorders Subclavian artery aneurysm Brachial AV fistula Subluxation of the shoulder Median nerve injury Local trauma Hemiplegia
INTERSTITIAL LUNG DISEASE Asbestosis Idiopathic pulmonary fibrosis Collagen vascular disease Langerhans cell histiocytosis Lipoid pneumonia	
CHRONIC INFECTIONS Bronchiectasis Bronchiectasis from sarcoidosis or tuberculosis Lung abscess Empyema Cystic fibrosis	

AV, arteriovenous.

Table 16-5 Paraneoplastic Syndromes (Partial Listing)

PARANEOPLASTIC SYNDROMES Acanthosis nigricans Clubbing Hypertrophic osteoarthropathy Intravascular thrombosis Muscle weakness	Neuropathy Pemphigoid Polymyositis-dermatomyositis Raynaud phenomenon
ENDOCRINE SYNDROMES ASSOCIATED WITH LUNG NEOPLASMS Acromegaly (growth hormone) Diarrhea (vasoactive intestinal peptide) Hypercalcemia (parathyroid-like substance) Hyponatremia (inappropriate antidiuretic hormone) Carcinoid syndrome (serotonin)	Cushing syndrome (ACTH) Gynecomastia (gonadotropins) (prolactin) Hyperglycemia and hypoglycemia (insulin) Skin pigmentation (melanocyte-stimulating hormone, ACTH)

ACTH, adrenocorticotropic hormone.

Key Points

- Taking a careful history and performing a thorough physical examination are essential first steps in formulating a preliminary differential diagnosis of a patient's complaints.
- After the clinician arrives at a tentative diagnosis, selected radiographic, laboratory, and other tests are ordered for further and confirmatory evaluation.
- The electronic medical record provides documents of higher quality than written records, owing to improved organization, increased readability, use of supplementary material, and better comparisons.
- Because dyspnea, cough with or without hemoptysis, and chest pain are among the most common reasons for patients to visit physicians and because these symptoms may result from serious underlying chest disease, careful questioning and workup is mandatory.
- Physical examination can be performed virtually anywhere, provides important information, lends itself to serial observations, and increases patients' confidence in their physicians.
- Stridor, a high-pitched continuous sound which, in contrast to wheezing, is louder and longer during inspiration than expiration, can indicate a life-threatening upper airway obstruction and requires immediate attention.
- New-onset clubbing of the digits warrants detection and investigation owing to its frequent association with serious underlying disease.

Complete reference list available at *ExpertConsult*.

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MICROBIOLOGIC DIAGNOSIS OF LUNG INFECTION

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INTRODUCTION

The clinical microbiology laboratory plays a critical role in diagnosis and management of patients with lower respiratory tract infections. By providing pathogen detection and identification and susceptibility testing the laboratory provides the basis of optimal empirical antimicrobial therapy and individually tailored regimens.¹ The microbiology laboratory also provides epidemiologic data that assist the hospital epidemiologist in the prevention, detection, investigation, and termination of nosocomial outbreaks.² When correctly and promptly used, the information provided by the clinical microbiology laboratory improves clinical outcomes, reduces unnecessary utilization of antibiotics, and prevents nosocomial transmissions.^{3,4}

The primary aim of this chapter is to assist clinicians in efficient and effective utilization of the resources of the clinical microbiology laboratory in diagnosis of the causes of infections of the lower respiratory tract. This chapter assumes that clinical laboratories are using validated methods and reporting quality-assured results and does not delve into technical or operational aspects of the clinical microbiology laboratory. For additional information on laboratory operation, the reader is referred to the latest edition of the *Manual of Clinical Microbiology* (American Society for Microbiology).⁵

PREANALYTIC PRINCIPLES

PRINCIPLES OF TESTING

The decision to order a diagnostic test should hinge on whether the result is likely to affect the clinician's treatment decisions. If the clinician is certain the patient has a disease based on clinical presentation and prevalence (high pretest probability), then the decision to treat will likely not be altered by the test result and testing should not be ordered. Similarly, testing should not be ordered if the clinician has a high degree of a priori certainty that the patient does not have a disease, because the decision not to treat will likely not be altered by the test result. Testing is most useful when the clinician is uncertain about the probability of disease and the result can sway the physician's decision about

treatment. In addition to the pretest probability, several factors affect this decision. For example, if therapy comes at a low harm (in terms of toxicity, dollar cost, and selection of resistance), then treating all patients without testing may be appropriate. If the diagnostic has a low sensitivity (i.e., the test is positive in a low percentage of patients with disease), then testing may lead to an inappropriate decision not to treat. Similarly, if a diagnostic has a low specificity (i.e., the test is positive in a high percentage of patients without disease), then testing may lead to unnecessary treatment. The determination that clinical suspicion is uncertain enough to benefit from a particular diagnostic involves the interplay of the cost and accuracy of the diagnostic test, the pretest probability of the disease, and the benefit and harm of treatment.

INFECTION PREVENTION

The clinician plays a critical role in notifying the microbiology laboratory (and the hospital infection control epidemiologist) when virulent and transmissible agents are suspected as the cause of disease. Alerting laboratory staff reduces the exposure risk of laboratory staff handling specimens and cultures harboring highly virulent pathogens. A list of such pathogens is shown [Table 17-1](#). Not all specimens from patients with infectious diseases should be handled by the on-site laboratory. According to guidelines developed by local and national public health officials, specimens potentially containing selected high-risk agents such as *Bacillus anthracis* spores, *Francisella tularensis*, *Yersinia pestis*, variola major, hemorrhagic fever viruses, or *Clostridium botulinum* toxin are directly sent to the public health laboratories, where appropriate containment facilities and diagnostic tools are applied to make a diagnosis. Other pathogens that are handled by the on-site laboratory but still require laboratory notification include *Coccidioides* and *Brucella* species, because cultures of these are associated with a high risk for laboratory-associated infection. Although the technologists are expected to handle all specimens and microbiologic cultures using universal precautions, accidental exposures can happen, especially if the findings are unexpected. Therefore laboratory notification serves to alert the staff to protect themselves from potential exposure to highly transmissible agents.

SYNDROMIC ORDER SETS

The diversity of etiologic agents of lower respiratory tract infection poses a number of diagnostic challenges to the clinician. First the provider must formulate a comprehensive yet pragmatic differential diagnosis that takes into account the clinical presentation, immune status, and the exposure history of the patient. Then the clinician must order the correct set of laboratory tests and ensure collection of the appropriate specimens and their placement in correct transport containers as well as their transport to the laboratory under permissive conditions for testing. Because improper test selection and specimen collection could reduce the analytic sensitivity and specificity of assays performed in the laboratory, syndromic order sets have been designed that consider the most common pathogens for the specific syndrome. Syndromic order sets incorporate general guidelines for the types of specimen required, collection and transport, and available assays for pathogens expected in a given clinical setting or syndrome. By prioritizing diagnostics that maximize yield and avoiding the need to repeat invasive procedures, these order sets also serve to minimize risk to the patient and to lower health care costs. However, it is the responsibility of the clinician to ensure that specimen requirements are met and the most critical tests are prioritized, especially when the amount of specimen material obtained is limited and multiple tests are ordered. [Tables 17-2, 17-3, and 17-4](#) show syndromic order sets for *community-acquired pneumonia* (CAP), *hospital-acquired and ventilator-associated pneumonia*, and *immunocompromised host pneumonia*, respectively. Order sets developed to address local epidemiologic characteristics and preanalytic practices may be tailored to serve each institution. Clinicians also should familiarize themselves with

local sample storage practices in case additional tests need to be performed.

SPECIMEN SELECTION, COLLECTION, AND TRANSPORT

In general, sterile specimens such as tissue samples and aspirates are the most valuable diagnostically because the absence of contamination with commensal organisms ensures that any organism detected likely represents a true pathogen. Histopathologic examination of tissue also provides information on the immunopathologic characteristics of the infectious process. However, a major diagnostic challenge of lower respiratory tract infection is that lower respiratory tract secretions are usually obtained through the oropharynx, which normally contains 10^{10} to 10^{12} *colony-forming units* (CFU) of aerobic and anaerobic bacteria per milliliter. Therefore lower respiratory tract secretions collected for microbiologic examination are commonly contaminated with diverse bacteria ([Table 17-5](#)),⁶ some of which, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Neisseria meningitidis*, can also be pathogens of the lower respiratory tract.⁷⁻⁹ The oropharynx can also contain *Mycoplasma pneumoniae*¹⁰ and aerobic actinomycetes including *Nocardia* and nontuberculous mycobacteria in the absence of disease.¹¹ In addition, aspiration of even minute amounts (0.1 to 1 μ L) of oropharyngeal secretions can deliver a bolus of 10^9 CFU to the tracheobronchial tree. The distinction in such cases between colonization of the upper respiratory tract and pneumonia cannot be easily made by sputum examination and culture. Another challenge is that oropharyngeal secretions, which normally contain only a few gram-negative bacilli (such as Enterobacteriaceae, *Pseudomonas*, *Acinetobacter*), often become colonized with as many as 10^7 CFU of gram-negative bacilli per milliliter in seriously ill patients requiring intensive care,¹² patients treated with antibiotics after hospitalization for acute pulmonary inflammatory disease,¹³ chronic alcoholic and diabetic patients,¹⁴ institutionalized older adults and chronically ill patients,¹⁵ and hospitalized patients with acute leukemia.¹⁶ Lastly, *Aspergillus* spores present in the environment are commonly deposited in the lower respiratory tract and may be recovered from sputum in the absence of disease, although in immunocompromised patients it is best to consider this finding seriously.¹⁷ In summary, because lower respiratory tract secretions collected through the oropharynx are nearly always contaminated with resident microflora of the oral cavity and

Table 17-1 Pathogens That Require Laboratory Notification When Clinically Suspected

ORGANISM

Bacillus anthracis
Brucella species
Clostridium botulinum
Coccidioides species
Francisella tularensis
Hemorrhagic fever viruses
Yersinia pestis
Variola major

Table 17-2 Community-Acquired Pneumonia Order Set

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
TYPICAL BACTERIA			
<i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> Aerobic gram-negative bacilli	Outpatients: microbiologic studies optional Inpatients: ■ Sputum studies for those with defined risks, complications, and/or severity ■ Blood culture for defined risk factors, including ICU admission	Sputum Bronchoscopic specimen Tissue Blood	Gram stain Aerobic culture Aerobic culture

Continued

Table 17-2 Community-Acquired Pneumonia Order Set—cont'd

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
LESS COMMON BACTERIA			
<i>Chlamydomphila pneumoniae</i> <i>Chlamydia psittaci</i> <i>Coxiella burnetii</i> <i>Legionella pneumophila</i> serogroup 1 <i>Legionella</i> spp.—other <i>Mycobacterium tuberculosis</i> <i>Mycoplasma pneumoniae</i>	<i>Mycoplasma</i> and <i>C. pneumoniae</i> : outbreaks and familial transmission <i>C. psittaci</i> : exposure to psittacines	Nasopharyngeal swab, throat swab or washings Sputum Bronchoscopic specimen Bronchoalveolar lavage Tissue (including FFPE) Serum	NAT (species specific): <i>M. pneumoniae</i> ; <i>C. pneumoniae</i> ; <i>C. psittaci</i> NAT: 16S rRNA sequencing (tissue only) DFA: <i>C. pneumoniae</i> IgM, IgG: <i>M. pneumoniae</i> ; <i>C. pneumoniae</i> ; <i>C. psittaci</i> IgM, IgA, IgG: <i>C. burnetii</i>
	<i>Legionella</i> : outbreaks, travel-associated, lack of response to cell wall-active antibiotics, severe illness	Sputum Bronchoscopic specimen Tissue (including FFPE) Urine	BCYE culture NAT: <i>Legionella</i> species NAT: 16S rRNA sequencing (tissue only) DFA: <i>L. pneumophila</i> <i>L. pneumophila</i> serogroup 1 antigen
	<i>M. tuberculosis</i> complex: appropriate epidemiology	Sputum Bronchoscopic specimen Tissue Pleural fluid	Acid-fast stain Mycobacterial culture NAT
VIRUSES			
Influenza A/B Adenovirus Parainfluenza 1/2/3 Respiratory syncytial virus Human metapneumovirus Varicella-zoster virus Hantaviruses Novel coronaviruses Novel influenza viruses	Viral testing may provide justification for discontinuing antibiotics Seasonal epidemiology	Nasopharyngeal swab Nasal aspirates or washes Bronchoscopic specimen Tissue	NAT
ASPIRATION PNEUMONIA			
Mixed anaerobic infections	Anaerobes typically already covered by broad-spectrum antibiotics; anaerobic culture rarely changes management	Pleural fluid Bronchoscopic specimen using protected specimen brush Tissue Pleural fluid Tissue	Gram stain Aerobic culture Anaerobic culture NAT
INVASIVE FUNGI			
Dimorphic mold <i>Blastomyces dermatitidis</i> <i>Coccidioides immitis</i> <i>Coccidioides posadasii</i> <i>Histoplasma capsulatum</i> <i>Paracoccidioides brasiliensis</i>	From area of high endemicity	Sputum Bronchoscopic specimen Tissue Tissue (including FFPE) Pleural fluid Serum Urine	Fungal stain Fungal culture Histology NAT: species specific NAT: rRNA locus sequencing Antigen: <i>H. capsulatum</i> ; <i>B. dermatitidis</i> IgG (complement fixation, EIA): <i>H. capsulatum</i> ; <i>C. immitis</i> ; <i>B. dermatitidis</i> IgM (immunodiffusion, latex agglutination, EIA): <i>C. immitis</i> Antigen: <i>H. capsulatum</i>
<i>Cryptococcus</i> <i>C. neoformans</i> <i>C. gattii</i>		Serum Tissue	Cryptococcal antigen test Fungal stain Culture
PARASITES			
<i>Strongyloides stercoralis</i> <i>Paragonimus</i> spp.	From area of high endemicity	Sputum Bronchoscopic specimen Tissue	Microscopic examination

BCYE, buffered charcoal yeast extract; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; FFPE, formalin-fixed paraffin-embedded; ICU, intensive care unit; Ig, immunoglobulin; NAT, nucleic acid test.

Table 17-3 Hospital-Acquired and Ventilator-Associated Pneumonia Order Set

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
TYPICAL BACTERIA			
Aerobic Gram-Positive Cocci			
<i>Staphylococcus aureus</i>	Refractoriness to antibiotics	Sputum	Gram stain
<i>Streptococcus pneumoniae</i>	Clinically ill patients with suspicious respiratory or chest radiograph findings	Endotracheal aspirate	Aerobic culture
Aerobic Gram-Negative Bacilli		Bronchoalveolar lavage	Anaerobic culture
<i>Acinetobacter</i> species	Anaerobes typically already covered by broad-spectrum antibiotics; anaerobic culture rarely changes management	Bronchoscopic specimen using protected specimen brush	
<i>Enterobacter</i> species		Tissue	
<i>Escherichia coli</i>		Tissue (including FFPE)	NAT: 16S rRNA sequencing
<i>Klebsiella pneumoniae</i>		Blood	Aerobic culture
<i>Pseudomonas aeruginosa</i>			
<i>Stenotrophomonas maltophilia</i>			
Anaerobes			
Mixed anaerobic species			
ATYPICAL BACTERIA			
<i>Legionella pneumophila</i> serogroup 1	<i>Legionella</i> outbreaks	Induced sputum	BCYE culture
<i>Legionella</i> species—other	Refractory to β -lactams or AGs	Bronchoscopic specimen	<i>Legionella</i> spp. NAT
	Immunocompromised		DFA
	Pneumonia plus GI symptoms	Urine	<i>L. pneumophila</i> serogroup 1 urine antigen
		Tissue (including FFPE)	NAT: 16S rRNA sequencing
VIRUSES			
Influenza A, B	Circulating in community/seasonality	Nasopharyngeal swab	NAT
Adenovirus	Unvaccinated host	Nasal aspirates or washes	
Parainfluenza 1, 2, 3	Outbreak/cluster	Endotracheal aspirate	
Respiratory syncytial virus	Pneumonia despite broad-spectrum antibiotics	Bronchoscopic specimen	
		Bronchoscopic specimen using protected specimen brush	
INVASIVE FUNGI			
<i>Aspergillus</i> species	Pulmonary cavity disease	Endotracheal aspirate	Fungal stain
<i>Mucorales</i>	Environmental exposure/outbreak	Bronchoalveolar lavage	Fungal culture
Mold species—other	Immunocompromised	Bronchoscopic specimen using protected specimen brush	NAT: species-specific
		Tissue	NAT: rRNA locus sequencing (tissue only)
		Tissue (including FFPE)	Histology
			NAT: 18S rRNA sequencing
		Bronchoalveolar lavage	Galactomannan
		Serum	(1 \rightarrow 3) β -D-glucan

AGs, aminoglycosides; BCYE, buffered charcoal yeast extract; DFA, direct fluorescent antibody; FFPE, formalin-fixed paraffin-embedded; GI, gastrointestinal; NAT, nucleic acid test; spp., species.

Table 17-4 Immunocompromised Host Pneumonia Order Set

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
BACTERIA			
CAP and HAP/VAP bacteria	See Tables 17-2 and 17-3	See Tables 17-2 and 17-3	See Tables 17-2 and 17-3
<i>Burkholderia cepacia</i> complex	Cystic fibrosis, CGD	Sputum Bronchoscopic specimen	Aerobic culture
Aerobic Actinomycetes <i>Nocardia</i> species <i>Rhodococcus</i> species Actinomycetes—other	Soil/environmental exposure	Sputum Bronchoscopic specimen Tissue (including FFPE)	Gram stain Modified acid-fast stain Aerobic culture including BCYE plate NAT: 16S rRNA sequencing (tissue only)
MYCOBACTERIA			
<i>M. tuberculosis</i> complex <i>M. avium-intracellulare</i> complex <i>M. kansasii</i> <i>M. xenopi</i> <i>M. haemophilum</i> <i>M. abscessus</i> <i>M. chelonae</i> —other	From area of high endemicity Known exposure/outbreak Bronchiectasis Appropriate epidemiology	Expectorated sputum Bronchoscopic specimen Tissue (including FFPE)	Cytology Acid-fast stain Mycobacterial culture NAT: <i>M. tuberculosis</i> –specific NAT: nontuberculous mycobacteria–specific NAT: 16S rRNA sequencing (tissue only)
		Tissue	Histology

Continued

Table 17-4 Immunocompromised Host Pneumonia Order Set—cont'd

Syndrome/Organisms	Testing Uses/Indications	Appropriate Specimens	Available Testing
VIRUSES			
CAP and HAP/VAP viruses	See Tables 17-2 and 17-3	See Tables 17-2 and 17-3	See Tables 17-2 and 17-3
Cytomegalovirus Herpes simplex virus Varicella-zoster virus	CMV 1-4 months after transplant Serodiscordant donor/recipient Skin lesions	Bronchoscopic specimen Tissue Tissue (fresh and FFPE) Plasma	Cytology NAT Shell vial culture: CMV; HSV Histology Immunohistochemistry: CMV; HSV NAT NAT
FUNGI			
<i>Pneumocystis jirovecii</i>		Sputum Bronchoalveolar lavage Bronchoscopic specimen	DFA Fungal stain NAT
<i>Cryptococcus neoformans</i> <i>Cryptococcus gattii</i>		Serum Tissue	Cryptococcal antigen test Fungal stain Culture
Monomorphic molds <i>Aspergillus fumigatus</i> Other <i>Aspergillus</i> species		Sputum Bronchoscopic specimen Tissue Tissue (fresh and FFPE) Pleural fluid Serum	Fungal stain Fungal culture Histology NAT: species specific NAT: rRNA locus sequencing Antigen: galactomannan Antigen: (1→3) β-D-glucan
Dimorphic molds	See Table 17-2	See Table 17-2	See Table 17-2
PARASITES			
<i>Toxoplasma gondii</i>	Cat exposure Raw meat consumption From area of high endemicity Lymphadenopathy	Induced sputum Bronchoscopic specimen Tissue Serum	Giemsa stain NAT IgM
<i>Strongyloides stercoralis</i>	From area of high endemicity	Induced sputum Bronchoscopic specimen Stool Tissue	Microscopy for larvae <i>Strongyloides</i> culture Histology

BCYE, buffered charcoal yeast extract; CAP, community-acquired pneumonia; CGD, chronic granulomatous disease; CMV, cytomegalovirus; DFA, direct fluorescent antibody; FFPE, formalin-fixed paraffin-embedded; HAP, hospital-acquired pneumonia; HSV, herpes simplex virus; IgM, immunoglobulin M; NAT, nucleic acid test; VAP, ventilator-acquired pneumonia.

Table 17-5 Oropharyngeal Bacteria That Can Be Present without Causing Disease

Commonly Present	Less Commonly Present, Transiently Present, or Present Only in Specific Contexts
<i>Actinomyces</i> , <i>Corynebacterium</i> , <i>Eikenella corrodens</i> , <i>Enterococcus</i> , <i>Haemophilus</i> , <i>Moraxella catarrhalis</i> , <i>Neisseria</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Candida</i>	Enterobacteriaceae, <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i> , nontuberculous mycobacteria

definitive diagnosis would require sterile lung tissue with demonstration of parenchymal invasion, appropriate steps must be taken to obtain specimens of highest quality for microbiologic testing.

Expectorated sputum is the specimen most frequently obtained for the laboratory diagnosis of lower respiratory tract infection.⁵ The importance of proper sputum collection was documented by Laird¹⁸ 100 years ago in studies on

the yield of *Mycobacterium tuberculosis* according to the appearance and cellular composition of the sputum examined. The first requirement for collection of a good-quality sputum specimen is an alert and cooperative patient who can be instructed to rinse out his or her mouth with water or even brush his or her teeth before producing a lower respiratory tract specimen. The patient then must be encouraged to cough deeply to expectorate a specimen of lower respiratory tract secretions. With some infections such as *tuberculosis* (TB), a larger sample volume can improve the sensitivity of culture.¹⁹ Specimens are to be collected in sterile, leakproof, screw-capped containers. Containers should be transported in a watertight plastic biohazard bag.

Although a single sputum specimen may be sufficient for establishing the diagnosis of an acute bacterial process, collection of a series of two or three sputum specimens obtained on one or two days is recommended for patients suspected of having mycobacterial infections.²⁰ In patients with non-productive cough or suspected mycobacterial, fungal, or *Pneumocystis jirovecii* infections,²¹ it may be helpful to

induce sputum production with an inhaled aerosol of hypertonic salt solution (3% to 10%).

Once collected, the specimens should be rapidly delivered to the laboratory for processing to avoid overgrowth by contaminating flora, which can compromise microscopic detection and isolation of pathogenic bacteria.^{22,23} Penn and Silberman²³ found that organisms observed microscopically on Gram-stained smears of sputum specimens and their relative numbers in cultures changed dramatically between processing within an hour of collection and processing after overnight refrigeration. Although there were no significant differences in the culture results between the immediate and delayed cultures in this study, the loss of reliable microscopic features had significant impact on the interpretation of culture results. Processing delay is particularly important for culture recovery of slow-growing mycobacteria.²⁴ Specimens that are not sent to the laboratory for processing within 2 hours should be refrigerated for no more than 5 days. If refrigeration is not possible, samples should be treated first with equal volume of 0.6% cetylpyridinium bromide or 1% cetylpyridinium chloride in 2% sodium chloride, which reduces the survival of contaminating microorganisms while preserving the viability of *M. tuberculosis* for up to 8 days.²⁴⁻²⁶ Although the recovery of fungi is optimal from cultures of fresh specimens, most clinically significant fungi appear to survive storage of 16 days or longer.²⁷ Specimens for viral cultures should be shipped refrigerated but not frozen, whereas specimens for chlamydial culture should be placed into sucrose phosphate medium and shipped frozen.

Although there is no universal agreement on the value of anaerobic culture,²⁸ protected catheter brushes may be used to obtain samples for culture and identification of organisms causing anaerobic pleuropulmonary disease.²⁹ It is essential to transport samples in an anaerobic vial to preserve the viability of anaerobic organisms.

For detection of respiratory viruses, nasopharyngeal specimens are preferred, although lower respiratory tract specimens may be necessary to detect viral infection of the lower respiratory tract.³⁰ There are a number of methods for the collection of nasopharyngeal specimens, which includes flocked and traditional swabs, as well as aspirates and washes. Flocked swabs contain perpendicular arrangements of fibers with an open structure to create a highly absorbent thin layer capable of efficient uptake of respiratory samples and elution into viral transport media. Nasopharyngeal flocked swabs have been shown to be more sensitive for the detection of respiratory viruses than traditional swabs.^{31,32} In turn, nasopharyngeal aspirates or washes have been shown to be more sensitive than nasopharyngeal flocked swabs.³³⁻³⁵ However, the modest gains in sensitivity for detection of most respiratory viruses using aspirates or washes may be offset by the ease of nasopharyngeal specimen collection using flocked swabs. Oropharyngeal specimens are less sensitive than nasopharyngeal specimens, though the combination may increase respiratory virus detection.³⁶⁻³⁹ Oropharyngeal swabs may also be used for detecting *Chlamydia pneumoniae*,⁴⁰⁻⁴³ *M. pneumoniae*,^{40,44,45} and *Legionella* species.⁴⁰

In patients who are critically ill, immunocompromised, or who cannot produce expectorate, one or more invasive approaches may be necessary to obtain diagnostic samples.

Specimens may include endotracheal aspirates, pleural fluids, bronchoalveolar lavage (BAL), percutaneous lung aspirate, or lung biopsies.^{5,46} The use of BAL has also been expanded to include diagnosis of bacterial pneumonia, especially for nosocomial cases.⁴⁷⁻⁴⁹ In patients with CAP requiring admission to the hospital, use of protected catheter brush and BAL has been shown to provide microbiologic diagnoses that are not obtainable by noninvasive means,⁵⁰ although there is little support for using these procedures to diagnose CAP.⁵¹ Although the results of cultures from protected catheter brushes and BAL specimens are quantitatively similar, Meduri and Baselski⁵⁰ concluded that BAL specimens provided a larger and more representative sample of lower respiratory tract secretions than the protected catheter brushes, allowing microscopic analysis of the cytocentrifuged BAL fluid to identify the type of bacteria present and to demonstrate the presence of neutrophils with intracellular organisms. These procedures may also yield additional pathogens not obtainable by noninvasive approaches. Much work has also been done with the use of BAL for the diagnosis of ventilator-associated pneumonia,⁴⁹⁻⁵² (see Chapter 34).

In children under 7 years of age with suspected TB, gastric aspirate is used as a surrogate for respiratory samples. Historically it has been recommended that the pH of gastric aspirate be neutralized with sodium bicarbonate before transport to the laboratory; however, a recent study suggests that neutralization of gastric aspirate may reduce the recovery of *M. tuberculosis*.⁵³ Nasopharyngeal aspirates have also been used for diagnosis of TB, although the sensitivity of culture-confirmed TB is lower compared to induced sputum.⁵⁴ Stool samples in children with pulmonary TB may become the specimen of choice if processing methods can be optimized to concentrate the tubercle bacilli.^{55,56}

Other specimen types that may aid in diagnosis of lower respiratory tract infection include whole blood for blood culture, serum for antibody and antigen testing, and urine for antigen testing. Blood culture is recommended in cases of severe pneumonia⁵⁷ but is positive only up to 37% in CAP and in less than 25% in nosocomial pneumonia.⁵⁷⁻⁶¹ It is important to note that a large blood volume (60 mL or three sets of blood culture bottles in adults) is necessary to maximize sensitivity of blood culture.^{62,63} Although routine blood culture systems have been shown to be highly sensitive for detection of candidemia and cryptococemia, automated blood culture systems are insensitive for cultivation of monomorphic and dimorphic molds. Isolation of molds (and fastidious bacteria) from blood requires the lysis-centrifugation method (Isolator)⁶⁴⁻⁶⁶ or the use of enriched fungal medium bottles.^{67,68}

S. pneumoniae can be recovered from urine cultures in as many as 38% of patients with pneumococcal pneumonia.⁶⁹ Urine may be tested for the presence of pneumococcal⁷⁰ and *Legionella pneumophila* serogroup 1⁷¹ antigens. Fungal antigen tests of urine are also available for diagnosis of histoplasmosis and blastomycosis.^{72,73} Antigen assays are discussed later in this chapter.

SPECIMEN ADEQUACY

Clinical laboratories are mandated by accrediting agencies to monitor specimen quality and quantity, and to enforce

rejection criteria when sample requirements are not met. Common causes for rejection include insufficient sample quantity, poor sample quality, and mislabeling of samples. For bacterial cultures, microscopic examination of sputum and endotracheal aspirate with Gram stain is used to screen samples for adequate quality.^{18,74} The presence of excessive squamous epithelial cells (>10 to 25 per low-power field) is indicative of oropharyngeal contamination and therefore grounds for rejection for bacterial culture (Fig. 17-1). Although earlier criteria for the adequacy of sputum specimens for bacterial cultures also required the presence of polymorphonuclear leukocytes (neutrophils), the number of neutrophils in a sample is no longer used to evaluate specimen adequacy.⁷⁵ Endotracheal aspirates are rejected if the screening Gram-stained smears show no organisms.^{74,76} For mycobacterial, fungal, and viral cultures, cytologic screening to determine specimen

acceptability is not enforced, because contamination with commensals does not interfere with interpretation of the culture results. However, the presence of respiratory columnar epithelial cells has been shown to improve respiratory virus detection by *direct fluorescent antibody* (DEA) testing.⁷⁷

MICROBIOLOGIC ASSAYS

The clinical microbiology laboratory offers a broad range of assays for diagnosis of lower respiratory tract infection. For any particular pathogen, multiple assays may be available, and therefore it is the responsibility of the clinician to choose the assay with the best performance characteristic for a particular specimen type. Table 17-6 summarizes the accuracy of assays used in the diagnosis of lower

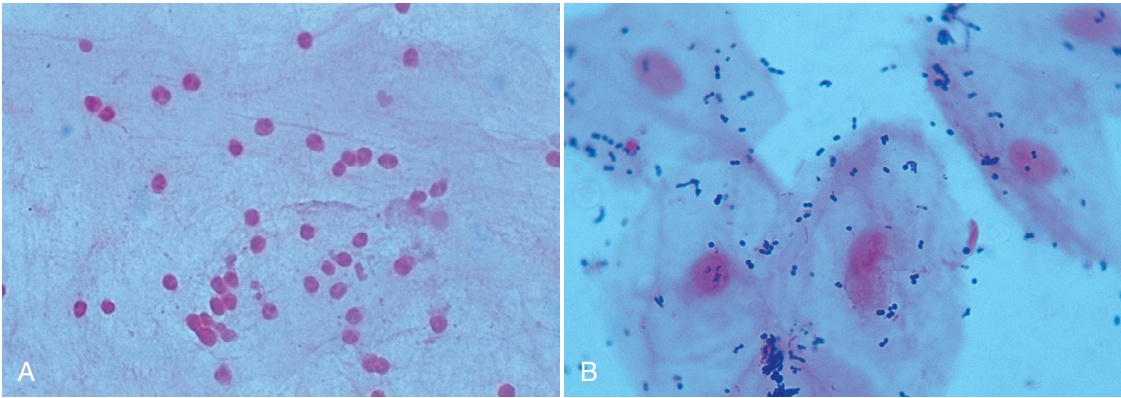


Figure 17-1 Gram stain of sputum specimens. **A**, This specimen contains numerous polymorphonuclear leukocytes and no visible squamous epithelial cells, indicating that the specimen is acceptable for routine bacteriologic culture. **B**, This specimen contains numerous squamous epithelial cells and rare polymorphonuclear leukocytes, indicating an inadequate specimen for routine sputum culture. (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 69-4.)

Table 17-6 Accuracy of Assays Used in Diagnosis of Lower Respiratory Tract Infections Caused by Bacteria, Fungi, and Parasites						
Organism	Diagnostic Target	Testing Method	Sample Type	Sensitivity (%)	Specificity (%)	References
BACTERIA						
<i>Chlamydia</i> species (excluding <i>C. trachomatis</i>)	Antibody (IgG)	Microimmunofluorescence	Serum	65–92	30–51	256
	Antibody (IgM)	Microimmunofluorescence	Serum	43–75	67–84	256
	Antibody (IgG and IgM)	Microimmunofluorescence	Serum	87–100	22–40	256
	Antibody (IgM)	Enzyme immunoassay	Serum	100	92.9	257
<i>Coxiella burnetii</i>	DNA	PCR—enzyme immunoassay	Nasopharyngeal swab	55–83	91–99	256, 258
	Antibody (IgG, IgA, and IgM)	Microimmunofluorescence	N/A	N/A	N/A	*
<i>Francisella tularensis</i>	DNA	PCR	N/A	N/A	N/A	*
	DNA	PCR	Swab/tissue	73–78	97	259
	Antibody	Enzyme immunoassay	Serum	93.9	96.1	260
<i>Legionella</i> species	Antibody	Latex microagglutination	Serum	81.8	98.0	260
	Antibody	Direct fluorescent antibody	Respiratory samples	25–66	94	95
	Antigen	Enzyme immunoassay	Urine	37.9–85.7	N/A	261
	Antigen	Lateral flow immunoassay	Urine	80	97–100	262

Table 17-6 Accuracy of Assays Used in Diagnosis of Lower Respiratory Tract Infections Caused by Bacteria, Fungi, and Parasites—cont'd

Organism	Diagnostic Target	Testing Method	Sample Type	Sensitivity (%)	Specificity (%)	References		
<i>Legionella pneumophila</i> serotype 1	Antigen	Immunoassay	Urine	74	99.1	192		
	DNA	PCR	Urine/serum	64–73	100	263		
	DNA	PCR	Throat swab	88.2	100	264		
	Antibody	Complement fixation	Serum	65	97	265		
	<i>Mycoplasma pneumoniae</i>	Antibody (IgG and IgM)	Enzyme immunoassay	Serum	35–77	49–100	265	
DNA		PCR	Throat swab	62	96	266		
<i>Nocardia asteroides</i> group	DNA	PCR	Tissue/sputum/BAL	100	100	267		
<i>Streptococcus pneumoniae</i>	Antigen	Lateral flow immunoassay	Urine	67–82	93–99.8	189		
	DNA	PCR	Plasma or sputum	26–100	58–99	268		
<i>Streptococcus pyogenes</i>	Antigen	Enzyme immunoassay	Throat swab	70–90	90–100	269		
MYCOBACTERIA								
<i>M. tuberculosis</i> complex	DNA	NAT	Smear negative	33.3–92.9	N/A	91		
	DNA	NAT	Smear positive	85.7–94.6	98	91		
	Organism	Microscopy	Carbolfuchsin	32–94	N/A	90		
	Organism	Microscopy	Fluorochrome (HIV–)	52–97	N/A	90		
	Organism	Microscopy	Fluorochrome (HIV+)	26–100	N/A	90		
INVASIVE FUNGI								
<i>Aspergillus</i> species	DNA	PCR	Serum	80	100	270		
	Antigen	Galactomannan enzyme immunoassay	Serum	71	89	203		
<i>Blastomyces dermatitidis</i>	Antigen	Enzyme immunoassay	Urine	80.7–92.9	77–79 [†]	271, 272		
	Antigen	Enzyme immunoassay	Serum	81.8	100 [†]	272		
	Antibody	Immunodiffusion	Serum	28	100	273		
	Antibody	Enzyme immunoassay	Serum	77–100	86–96	273		
	Antibody	Complement fixation	Serum	9	100	273		
	Organism	Microscopy	Body fluid/tissue	38–97	N/A	274		
<i>Coccidioides</i> species	DNA	Real-time PCR	Respiratory sample	92.9–100	98.1–98.4	275		
	Antibody (IgG)	Complement fixation	Serum	67–75	N/A	237		
			Serum (IC patients)	33–100	N/A	237		
			Serum	53–73	N/A	237		
			Serum (IC patients)	0–75	N/A	237		
<i>Cryptococcus neoformans</i> (and <i>Cryptococcus gattii</i>)	Antibody (IgG and IgM)	Enzyme immunoassay	Serum	75–92.6	84.6–98.3	276		
	Antibody (IgG and IgM)		Serum (IC patients)	25–90	N/A	237		
	Antigen	Latex agglutination	Serum	83–91.1	92.9–100	277, 278		
	Antigen	Latex agglutination	Urine	N/A	100	277		
	Antigen	Latex agglutination	CSF	93–100	93–98	278		
	Antigen	Lateral flow assay	Serum	90.1–100	92.9–100	279		
	Antigen	Lateral flow assay	Urine	70.3–94.4	100	277		
	Antigen	Enzyme immunoassay	Serum	94.1–100	93–100	278, 279		
	Antigen	Enzyme immunoassay	Urine	92%	Unknown	279		
	<i>Histoplasma capsulatum</i>	Antibody (IgG)	Complement fixation	Serum/urine	72.8–94.3	70–80	280	
Antibody (IgM)		Microimmunodiffusion	Serum	70–100	100	280, 281		
Antibody (IgG)		Enzyme immunoassay	Serum	91–100	66–97	280, 281		
			Serum (AIDS, disseminated)	69.2	N/A	199		
			Serum (other IC patients, disseminated)	84.2	N/A	199		
			Serum (non-IC patients, disseminated)	85.7	N/A	199		
			Serum (pulmonary subacute infection)	92.3	N/A	199		
			Antigen	Enzyme immunoassay	Urine	30.4–100	Variable	199
			Urine (AIDS, disseminated)	92.1	N/A	199		
			Urine (other IC patients, disseminated)	93.5	N/A	199		
Antigen		Enzyme immunoassay	Urine (non-IC patients, disseminated)	63.6	N/A	199		
			Urine (pulmonary subacute infection)	38.9	N/A	199		
			Antibody	Latex agglutination	Serum	65–97	39	280

Continued

Table 17-6 Accuracy of Assays Used in Diagnosis of Lower Respiratory Tract Infections Caused by Bacteria, Fungi, and Parasites—cont’d

Organism	Diagnostic Target	Testing Method	Sample Type	Sensitivity (%)	Specificity (%)	References
<i>Pneumocystis jirovecii</i>	DNA	PCR	Respiratory samples	93	90	158
	Organism	Microscopy with silver stain	Induced sputum/BAL	86–92	92–97	98
	Antigen	Direct fluorescent antibody	Induced sputum/BAL	90–97	85–90	98
	Antigen	Indirect fluorescent antibody	Induced sputum/BAL	86–97	100	98
	Organism	Diff-Quik stain	Induced sputum/BAL	81–92	97–100	98
Other (fungi excluding <i>P. jirovecii</i>)	Antigen	β-D-glucan assay	Serum/plasma	78–100	70–100	218
	Antigen	β-D-glucan assay	Serum/plasma	76.8	85.3	218
PROTOZOA						
<i>Toxoplasma gondii</i>	Antibody (IgG)	Sabin-Feldman dye test	Serum	N/A	N/A	*
		Enzyme immunoassay				
		Immunofluorescence antibody				
	Antibody (IgG and IgM)	IgG avidity	Serum	N/A	N/A	*
	DNA	Agglutination				
		PCR	Serum/CSF/aqueous humor/BAL	15–85	95	282

*Testing for acute Q fever and toxoplasmosis should be done using a battery of tests that must be interpreted together because sensitivity and specificity of individual tests are not available.

†Cross reaction is seen with *Histoplasma capsulatum*.

AIDS, acquired immunodeficiency syndrome; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IC, immunocompromised; Ig, immunoglobulin; N/A, not available; NAT, nucleic acid test; PCR, polymerase chain reaction.

respiratory tract infections caused by bacteria, fungi, and parasites. In addition, the clinician must be familiar with the turnaround time for each assay to optimize use of the results in managing the patient.

MICROSCOPY

Microscopic examination of lower respiratory tract specimens offers a rapid approach to detection and identification of many pathogens. However, as discussed earlier, a major limitation of microscopic examination is that it cannot distinguish between infection, colonization, and contamination when the specimen is collected through the oropharynx.⁷⁸⁻⁸⁰ In addition, microscopy lacks sensitivity in specimens with less than 10⁴ CFU per milliliter. Microscopy does routinely provide valuable information on the quality of specimen and the type of inflammatory response present. Specimens demonstrating a preponderance of polymorphonuclear leukocytes, ciliated columnar epithelial cells, or alveolar macrophages with few, if any, squamous epithelial cells (<10 per low-power field) represent lower respiratory tract secretions. The presence of alveolar macrophages is a more specific marker of lower respiratory tract secretions than neutrophils and is more likely to be associated with a significantly lower incidence of oropharyngeal contamination.⁸¹ The finding of neutrophils with intracellular organisms is considered indicative of an active infectious process.⁸²⁻⁸⁴

The Gram-stained smear is an essential and necessary part of evaluation of sputum and tracheal aspirates for

determining the quality and acceptability of specimens for bacterial culture^{74,76} and for providing a rapid assessment of the most likely etiologic agent of the pneumonia. Although Gram stains might also suggest the presence of mycobacteria, fungi, and parasites, special stains should be ordered when those pathogens are suspected. The Gram stain also stains squamous epithelial cells, ciliated columnar epithelial cells, neutrophils, and alveolar macrophages, which are used for assessment of specimen quality and inflammatory response. Table 17-7 shows criteria used by the laboratory to interpret findings on Gram stain and report them to the physician. Although it is impossible to correlate every staining pattern to a particular pathogen, several Gram stain patterns are pathognomonic for a particular pathogen or clinical entity (Table 17-8).

The accuracy of Gram stain for detection of infection depends on the stringency of criteria. In assessing patients with acute CAP, Rein and colleagues⁸⁵ found that three or more gram-positive lancet-shaped diplococci (Fig. 17-2) correctly predicted the presence of pneumococci in corresponding cultures in 90% of cases, with a sensitivity and specificity of 62% and 85%, respectively. As expected, improving the sensitivity of the Gram stain examination by lowering the criteria for positivity resulted in reduced specificity in the diagnosis of pneumococcal infection. Similar levels of sensitivity of Gram-stained smears have been reported by others in identifying pneumococci as well as *H. influenzae* (Fig. 17-3) in sputum specimens from patients with acute CAP.^{86,87} For the diagnosis of pneumococcal pneumonia, a combination of Gram-stained smear and

Table 17-7 Laboratory Criteria for Reporting Gram Stain Results to the Ordering Physician

Number of Bacteria Found per Field under Oil Immersion 100× Objective	Bacterial Quantity Reported to Clinician
0	Negative
<1	1+ (rare)
1–5	2+ (few)
6–30	3+ (moderate)
>30	4+ (heavy)

Table 17-8 Pathognomonic Gram Stain Patterns

Pattern Reported	Pathogen or Entity Suggested
Intracellular organisms	Active infection
Gram-positive cocci in pairs (lancet-shaped diplococci) and short chains	<i>Streptococcus pneumoniae</i>
Pleomorphic gram-negative coccobacilli	<i>Haemophilus influenzae</i>
Gram-negative diplococci	<i>Moraxella catarrhalis</i> *
Gram-positive cocci in clusters	<i>Staphylococcus aureus</i>
Mixed morphotypes of gram-positive and gram-negative rods, cocci, and coccobacilli	Aspiration pneumonia
Beaded gram-positive or gram-variable rods	Actinomycetales order, which includes genera <i>Mycobacterium</i> , <i>Actinomyces</i> , <i>Corynebacterium</i>
Filamentous branching gram-positive or gram-variable rods	<i>Nocardia</i> , <i>Actinomyces</i>

*Cannot be distinguished from *Neisseria meningitidis*.

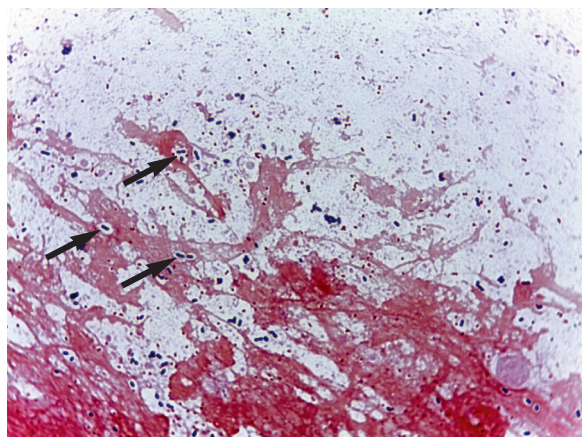


Figure 17-2 Lancet-shaped diplococci in Gram-stained sputum from a case of *Streptococcus pneumoniae* pneumonia. The clear “halo” surrounding some of the diplococci (arrows) is the consequence of the thick polysaccharide capsule. (From Tille P: *Bailey & Scott’s diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 15-1.)

culture of sputum can yield the correct diagnosis in more than 80% of patients who received less than 24 hours of effective antibiotic therapy.⁸⁸

Direct examination of sputum for the identification of other organisms that can either be commensals or causes

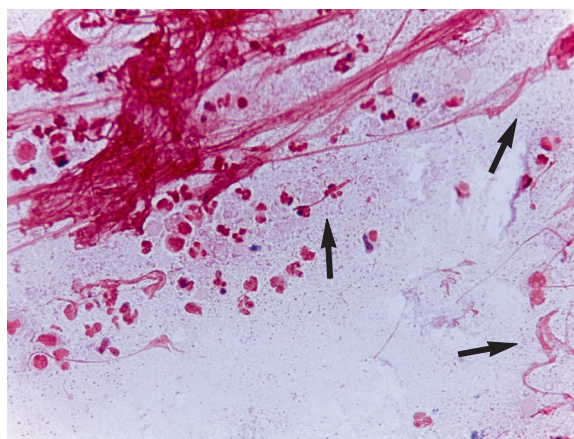


Figure 17-3 Gram stain of *Haemophilus influenzae* in sputum. The small gram-negative bacilli (arrows) can be difficult to distinguish from debris. (From Tille P: *Bailey & Scott’s diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 32-1.)

of acute bacterial pneumonia in adults, such as *H. influenzae*, *M. catarrhalis*, and *N. meningitidis*, may also be problematic.^{7,78,80,89} Their role as etiologic agents of pneumonia is strongly suggested by the finding of large numbers of gram-negative coccobacilli (*H. influenzae*) and diplococci (*M. catarrhalis* and *N. meningitidis*) located within and outside of neutrophils in sputum specimens.^{82–84} Because sputum microscopy (and subsequent culture) can give misleading results, the diagnosis of *Haemophilus*, *Moraxella*, or meningococcal pneumonia can be confirmed only by invasive techniques. Because invasive techniques are infrequently performed to identify the etiologic agents of acute CAP, the sensitivity and specificity of sputum Gram-stained smears cannot be determined reliably in such cases. A similar challenge is faced when trying to distinguish between colonization and infection by gram-negative bacilli. For example, up to 10⁸ CFU of gram-negative bacilli per milliliter may be found in respiratory secretions of patients on mechanical ventilation in intensive care units without evidence of pneumonia.¹²

Acid-fast staining is the method of choice for visualization of mycobacteria in respiratory specimens. Laboratories may use either carbolfuchsin or fluorochrome to stain mycobacteria. Table 17-9 shows criteria used by the laboratory to report findings on the acid-fast stain. In most studies the carbolfuchsin-based stain has a sensitivity of 60% or lower compared to culture.⁹⁰ The fluorochrome stain, which uses fluorescent dye such as auramine or auramine-rhodamine to highlight mycobacteria, is on average 10% more sensitive than carbolfuchsin⁹⁰ and is therefore the method recommended by the World Health Organization for screening sputum smears for mycobacteria. The sensitivity of acid-fast microscopy depends on the bacillary burden, sample volume, host immune status, staining method, and other variables.⁹¹ The major limiting factor is that approximately 10⁴ acid-fast bacilli per milliliter of sputum must be present to be visualized under light microscopy using an acid-fast stain.⁹¹ The insensitivity of smear microscopy for TB therefore necessitates the use of more sensitive methods such as culture and nucleic acid tests.^{92,93}

In addition, although acid-fast stains have high specificity, they cannot distinguish between *M. tuberculosis* complex and nontuberculous mycobacteria, and carbolfuchsin stains also stain *Legionella micdadei* (also known as *Tatlockia micdadei*).⁹⁴ Modified acid-fast stain, a modified carbolfuchsin stain, is used for direct staining of partially acid-fast-positive organisms such as *Nocardia*, *Tsukamurella*, *Rhodococcus*, and *Gordonia*.⁵

Immunofluorescence examination by DFA staining is an alternative method for direct visualization of organisms. The diagnosis of legionellosis is usually made by a combination of direct immunofluorescence examination and culture of respiratory specimens, and antigen and antibody testing. DFA staining can be performed on sputum, endotracheal aspirate, bronchial washing, and lung tissue specimens, with sensitivities ranging from 25% to 66% for the diagnosis of *L. pneumophila* pneumonia and specificities of more than 94%⁹⁵ (Fig. 17-4). Both clinical and technical variables account for the broad range of sensitivity of this test, and the accuracy of this method for detection of pneumonia due to other *Legionella* species is less precisely known. In the absence of other supporting evidence, a positive DFA result is generally not accepted as sufficient for the diagnosis of *Legionella* infection, and other confirmatory measures should be undertaken.

DFA testing has also been found to be sensitive and specific in detecting *Chlamydia trachomatis* in nasopharyngeal

specimens from infants with pneumonia and has also been applied to sputum and BAL for detection of *P. jirovecii*, the causative agent of *Pneumocystis* pneumonia.^{96,97} Silver stain, direct immunofluorescence, indirect immunofluorescence, and Diff-Quik (a modified Giemsa stain) have all been found to have greater than 90% sensitivity for detecting *P. jirovecii* in induced sputum and BAL samples from human immunodeficiency virus (HIV)-infected patients⁹⁸ (Fig. 17-5). All of these staining techniques have lower sensitivity in patients who are not infected with HIV, but DFA is consistently more sensitive than the other staining techniques.^{99,100}

DFA has also been applied to respiratory secretions for the diagnosis of respiratory virus infections. DFA testing can be performed in 1 to 4 hours and is typically more sensitive than rapid antigen tests.^{77,101} However, DFA testing for respiratory viruses requires a high level of technical and interpretive expertise, is difficult to adapt to the high throughput required for pandemic or high-volume testing, and remains less sensitive than real-time polymerase chain reaction (PCR).^{77,102} DFA for viral detection has been phased out in many clinical laboratories as rapid, sensitive, multiplexed molecular diagnostic respiratory virus tests have become available.

The visualization of fungal elements in respiratory secretions requires the use of special stains. Historically, potassium hydroxide was used to degrade host tissue and visualize fungal elements (Fig. 17-6). Calcofluor white stain, a fluorochrome that binds to chitin and cellulose present in the fungal cell wall, is now commonly added to potassium hydroxide or used alone to provide better delineation of fungal elements (Fig. 17-7).^{103,104} Table 17-10 lists staining patterns that are suggestive of certain fungal pathogens. It is important to note that identification of fungi based on microscopic appearance of fungal elements in lung tissue or secretions is subject to error, and definitive identification must be deferred to culture.¹⁰⁵

The identification of pulmonary parasites such as *Strongyloides stercoralis* and *Paragonimus* spp. is typically made by microscopic examination of respiratory secretions. *S. stercoralis* larvae and rarely eggs can be seen on most stains but are sufficiently large that they are more likely to be found using a low-power objective (Fig. 17-12).¹⁰⁶ The diagnosis of microfilariae causing tropical pulmonary eosinophilia requires peripheral blood parasite examination of nightly blood samples because these parasites typically circulate in the blood only at night, which coincides with activity of its

Table 17-9 Laboratory Criteria for Reporting of Acid-Fast Stain Results		
No. of AFB Found under Oil Immersion 100× Objective (Carbolfuchsin Stain)	No. of AFB Found under 10× Objective (Fluorochrome Stain)	Bacterial Quantity Reported to Clinician
0 per 300 fields	0 per 30 fields	Negative
1-2 per 300 fields	1-2 per 30 fields	± (suspicious)
1-9 per 100 fields	1-9 per 10 fields	1+
1-9 per 10 fields	1-9 per field	2+
1-9 per field	10-90 per field	3+
>9 per field	>90 per field	4+

AFB, acid-fast bacilli.
Adapted from David HL: *Bacteriology of the mycobacterioses*, Atlanta, GA, DHEW Publication No. (CDC) 76-8316, 1976:153.

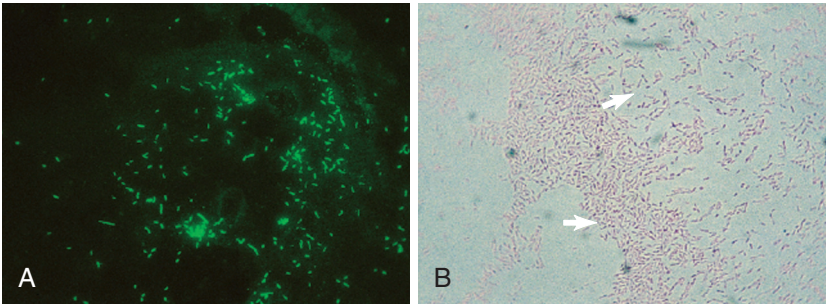


Figure 17-4 *Legionella pneumophila* detection by microscopy. **A**, Direct fluorescent antibody stain. **B**, Gram stain of a colony grown on agar. The organisms are thin gram-negative bacilli (arrows). (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Figs. 35-2 and 35-4.)

insect vector.¹⁰⁷ *Echinococcus* cysts may be detected in pulmonary cyst fluid, and *Entamoeba histolytica* may be seen in association with pleural disease, if an amebic liver abscess erodes through the diaphragm.

CULTURE

Microbiologic culture of respiratory specimens allows definitive identification of the suspected pathogens and permits determination of bacterial, mycobacterial, and yeast susceptibility to antimicrobial agents. For cultivation of particular groups or species of microorganisms, laboratories must inoculate processed samples on one or more culture media supplemented with nutrients suitable for cultivation of the desired microorganisms and inhibitors

for selective inhibition of undesirable organisms. The clinician must therefore be aware that, although many organisms do grow on routine aerobic and anaerobic cultures, a number of respiratory pathogens such as *Mycoplasma*, *Legionella*, *Mycobacterium*, *Nocardia*, *Rhodococcus*, and *Histoplasma capsulatum* require pathogen-specific growth conditions (growth supplements, temperature and carbon dioxide requirements, and incubation times), which have to be specified when fastidious pathogens are part of the differential diagnosis.⁵ For example, *Legionella* species require culture media supplemented with L-cysteine and α -ketoglutarate (buffered charcoal yeast extract),⁹⁵ slow-growing mycobacteria require media enriched with a lipid extract and antimicrobials to limit the growth of oral commensals,⁹¹ and *H. capsulatum* requires extended incubation time up to 4 weeks.¹⁰⁸ Although most *Nocardia* species grow well on mycobacterial culture media as well as on ordinary bacterial and fungal culture media, optimal recovery from clinical specimens is obtained by using the same buffered charcoal yeast extract culture medium as that for the isolation of *Legionella*.¹⁰⁹

Laboratories commonly use a semiquantitative culturing method and report the number of colonies present in consecutive streaked quadrants using a 1+ to 4+ grading system. Table 17-11 lists criteria for reporting of semiquantitative cultures. It is important to note that with the semiquantitative culture method, the volume of specimen cultured is not standardized. Quantitative cultures are also performed on certain respiratory specimens such as protected catheter brush specimens and BAL fluid.¹¹⁰ Nonetheless, a randomized trial found that in mechanically ventilated patients with pneumonia, the use of quantitative BAL and nonquantitative endotracheal aspirate cultures resulted in similar clinical outcomes, although patients known to be colonized or infected with *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* were

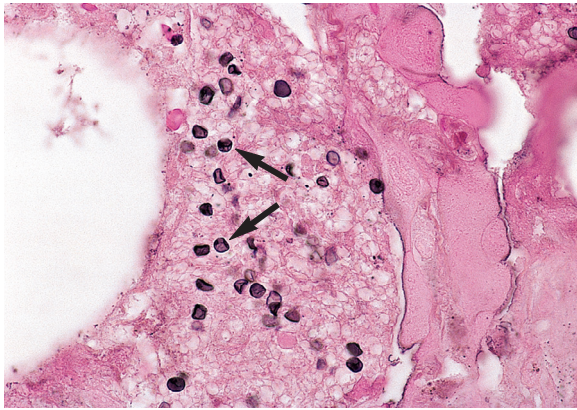


Figure 17-5 Cyst forms of *Pneumocystis jirovecii* (arrows) stained with methenamine silver and hematoxylin and eosin stain ($\times 500$ original magnification). (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 62-1.)

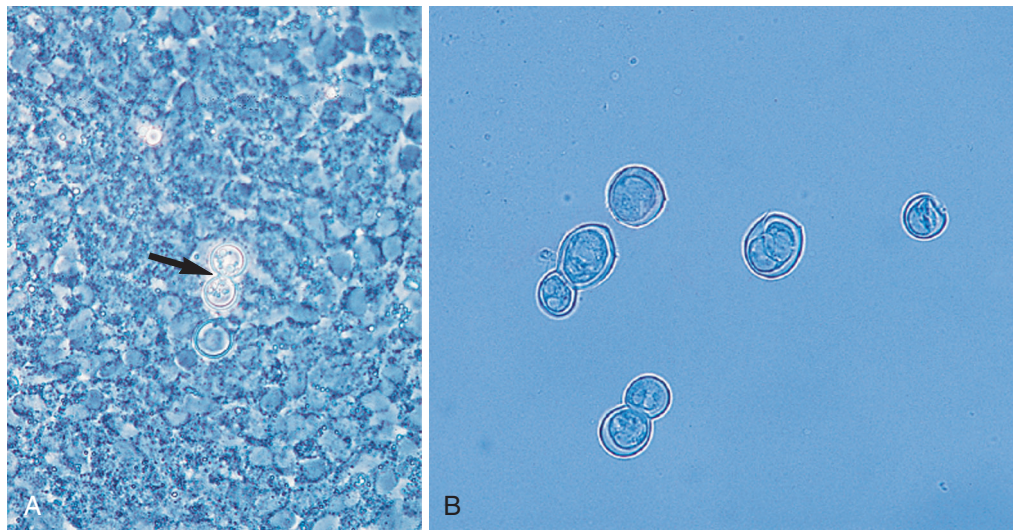


Figure 17-6 *Blastomyces dermatidis*. **A**, Potassium hydroxide preparation of exudate shows a large budding yeast cell with a distinct broad base (arrow) between inflammatory cells (phase-contrast microscopy). **B**, Thick-walled, oval to round, single-budding, yeastlike cells from culture. (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Figs. 60-28 and 60-29.)

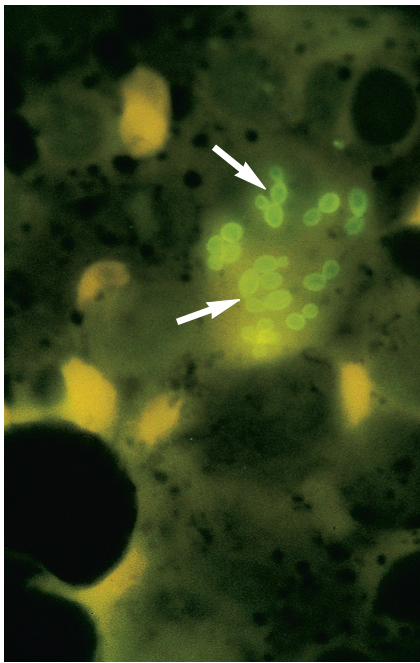


Figure 17-7 Calcofluor white stain of sputum showing 2- to 5-μm-diameter intracellular *Histoplasma capsulatum* (arrows). (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 60-6.)

Table 17-10 Microscopic Descriptions Suggestive of Certain Fungal Pathogens	
Key Patterns Reported from Respiratory Specimens	Pathogens the Findings Suggest
Broad-based budding yeast (see Fig. 17-6)	<i>Blastomyces dermatitidis</i>
Narrow-based budding yeast (Fig. 17-8)	<i>Candida</i> , <i>Cryptococcus</i> , <i>Histoplasma capsulatum</i> , <i>Sporothrix schenckii</i>
Spherule (Fig. 17-9)	<i>Coccidioides immitis</i> , <i>Coccidioides posadasii</i>
Nonseptate hyphal element (Fig. 17-10)	Zygomycetes (cannot be predicted from formalin-fixed paraffin-embedded tissue)
Septate hyphal element (Fig. 17-11)	Monomorphic hyaline and dematiaceous molds, including <i>Aspergillus</i>

excluded and antibiotics were withheld until the results of culture were available.⁵² Bacteria present in quantities greater than 10³ CFU/mL in cultures of protected catheter brushes⁴⁸ and in quantities greater than 10⁴ CFU/mL in cultures of BAL fluids⁵⁰ are defined by the laboratory as positive and identified and tested for their susceptibility to appropriate antimicrobial agents.¹¹¹ The diagnostic value of break points of bacterial growth (i.e., 10³ to 10⁵ CFU/mL) depends not only on the type of microbiologic processing used but also on the relationship of two variables: the concentration of pathogens present in the BAL fluid and the degree of contamination of the bronchoscopic channel through which lavage fluid was injected and aspirated. Other variables affecting the sensitivity of BAL specimens include antibiotic administration and the volume of lavage

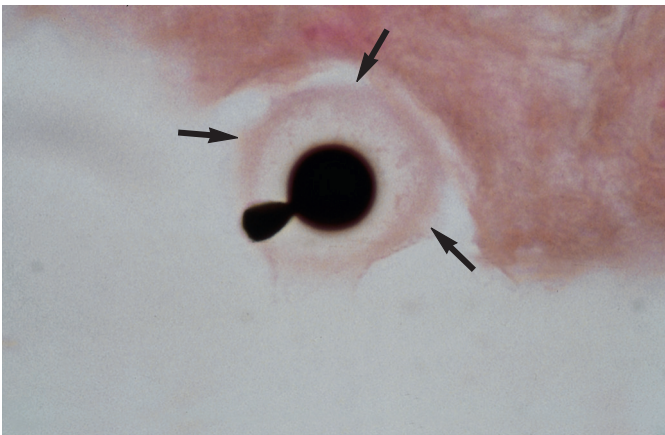


Figure 17-8 *Cryptococcus neoformans* with narrow-based bud; silver stain. The faintly staining capsule is also visible (arrows). (From Mandell GL, Bennett JE, Dolin R: *Principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Churchill Livingstone, Fig. 263-8.)

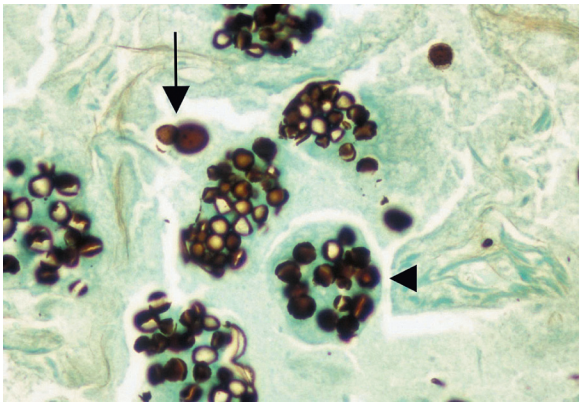


Figure 17-9 *Coccidioides immitis* spherules in a tissue biopsy. Spherules can also be found in fresh sputum samples. The internal endospores stain with silver (arrowhead), whereas the external wall of the spherule does not. The endospores that have been released from a spherule resemble budding yeast (arrow) (GMS stain; ×400 original magnification). (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 60-31.)

fluid injected and the volume of fluid retrieved.¹¹² Diagnostic specificity depends greatly on techniques used to minimize contamination of the specimen by upper respiratory flora, such as discarding the first aliquot of aspirated fluid.¹¹³

Because many pathogens of the lower respiratory tract are also members of the oropharyngeal flora, culture results must be correlated with the Gram stain findings, including the presence or absence of polymorphonuclear leukocytes. Respiratory pathogens seen on Gram stain to be predominant with typical morphologic characteristics both within and outside polymorphonuclear leukocytes are reported and identified to the species level. Upper respiratory colonization with potentially pathogenic microorganisms, such as gram-negative bacilli, may not be related to the actual etiologic agents of lower respiratory tract infection. Sputum specimens contaminated with Enterobacteriaceae or *S. aureus* from oropharyngeal secretions may obscure the diagnosis of pneumococcal pneumonia, anaerobic pleuropulmonary infection, or even TB.¹¹⁴⁻¹¹⁷ Except



Figure 17-10 *Rhizopus* spp. in a potassium hydroxide preparation of sputum showing broad, predominantly nonseptate hyphae (arrows). Phase-contrast microscopy. (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 60-2.)

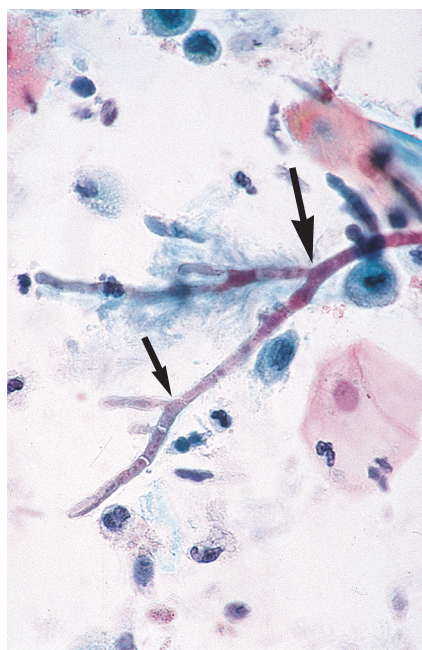


Figure 17-11 Branching septate hyphae (arrows) of *Aspergillus fumigatus*. Papanicolaou staining of sputum. (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 60-17.)

for *Cryptococcus*, yeasts are considered to be of upper respiratory origin and are not routinely identified.¹¹⁷

The sensitivity and specificity of cultures depend on the pathogen burden, specimen type, collection method, the cytologic screening criteria applied to ensure sampling of lower respiratory tract secretions, and the threshold of colony count to distinguish infection from contamination.



Figure 17-12 *Strongyloides stercoralis* rhabditiform larva; iodine stain. When examined under low power, staining of sputum may be unnecessary. Unfixed preparations can also show larval mobility. (From Tille P: *Bailey & Scott's diagnostic microbiology*, ed 13, Philadelphia, 2014, Mosby, Fig. 51-8.)

Table 17-11 Semiquantitative Scheme for Grading Bacterial Growth on Streaked Agar Plates

Grade	NO. OF COLONIES PRESENT IN CONSECUTIVE STREAKED QUADRANTS		
	First	Second	Third
1+	<10	0	0
2+	>10	<5	0
3+	>10	>5	<5
4+	>10	>5	>5

Based on data from Waites KB, Saubolle MA, Talkington DF, et al: *Cumitech 10A: laboratory diagnosis of upper respiratory tract infections* (Sharp SF, coordinating editor), Washington, DC, 2006, ASM Press.

In 1971 Barrett-Connor¹¹⁴ showed that only 45% of patients with bacteremic pneumococcal pneumonia had pneumococci isolated from their sputum cultures, whereas 27% of patients had moderate to heavy growth of another potential pathogen in these cultures. In contrast, fungal cultures of respiratory specimens were positive in approximately 85% of cases with disseminated or chronic pulmonary histoplasmosis.^{118,119} We now better understand how careful specimen collection, cytologic screening of specimens to discard those contaminated with oropharyngeal secretions, and use of the results of the Gram-stained smear to guide identification of isolates in culture all contribute to the diagnostic value of sputum culture in acute pneumococcal pneumonia.

It is important for the clinician to have knowledge of the turnaround time of all tests, including cultures. The time to detection of positive culture results is dependent on the number of organisms in the inoculum and the replication rate of the pathogen.¹⁰⁸ Table 17-12 shows typical turnaround times for lower respiratory tract pathogens.

Fecal culture may be useful in cases of suspected pulmonary involvement with *S. stercoralis* when sputum cytologic

Table 17-12 Time to Detection of Respiratory Pathogens in Culture

Key Respiratory Pathogens	Time to Detection in Culture
<i>Acinetobacter baumannii</i> , <i>Aspergillus</i> , <i>Coccidioides immitis</i> , <i>Coccidioides posadasii</i> , <i>Cryptococcus</i> , <i>Escherichia coli</i> , <i>Haemophilus influenzae</i> , <i>Klebsiella pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>Mycobacterium abscessus</i> group, <i>Mycobacterium chelonae</i> , <i>Neisseria meningitidis</i> , <i>Nocardia</i> ,* <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Zygomycetes</i>	1–3 days
<i>Actinomyces</i> , <i>Legionella</i> ,* <i>Sporothrix schenckii</i>	3–5 days
<i>Blastomyces dermatitidis</i> , <i>Histoplasma capsulatum</i> , <i>Mycobacterium avium-intracellulare</i> complex, <i>Mycobacterium tuberculosis</i> complex, <i>Mycoplasma pneumoniae</i>	1–4 weeks

*May take longer.

Adapted from Hove MG, Woods GL: Duration of fungal culture incubation in an area endemic for *Histoplasma capsulatum*. *Diagn Microbiol Infect Dis* 28:41, 1997.

examination fails to identify larvae. The agar plate method, which looks for tracking of bacteria by the motile larvae, is a useful adjunct to standard microscopic fecal examination and may be up to six times more sensitive.¹²⁰⁻¹²³

Viral culture techniques previously played an important role in the diagnosis of respiratory virus infections.¹²⁴ However, traditional viral culture is laborious, requires significant technical and interpretive expertise, allows the isolation of only a limited range of disease-causing viruses, and has a long turnaround time that limits clinical utility.¹²⁵ Shell vial culture is an improved method in which a sample is centrifuged onto a layer of cells, with subsequent detection of viral antigen. Shell vial cultures, particularly those using a mixture of mink lung and A549 cells, provide equivalent to improved sensitivity compared to traditional culture, with more rapid turnaround time.¹²⁶⁻¹²⁸ Similar to respiratory virus DFA, routine respiratory viral cultures are being phased out in many clinical laboratories with the widespread availability of respiratory virus molecular diagnostic tests. However, in BAL samples from transplant recipients and other immunocompromised patients, shell vial cultures using human fibroblast cell lines may be clinically useful for detection of *cytomegalovirus* (CMV)^{129,130} and traditional viral cultures may be useful for recovery of herpes simplex virus.¹³¹⁻¹³³

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Antimicrobial susceptibility testing is performed to assist clinicians with the selection of appropriate targeted antibiotic therapy to optimize clinical outcomes. There are several aspects of this in vitro testing that are important to understand. First of all, testing methods and interpretation of results must be done according to accepted standards, such as the *Clinical and Laboratory Standards Institute* (CLSI), the U.S. *Food and Drug Administration* (FDA), or the *European Committee on Antimicrobial Susceptibility Testing* (EUCAST)

for the various categories of organism. Second, the selection of antibiotics to test and report is determined in collaboration with CLSI/EUCAST guidelines, the hospital formulary, infectious disease specialists, the pharmacy, and the infection prevention committee. Third, antimicrobial susceptibility testing should not be performed when the pathogen has a predictable susceptibility profile (e.g., all *Streptococcus pyogenes* are currently susceptible to penicillin), nor is susceptibility testing needed for a specific antibiotic when an organism has intrinsic resistance to that antibiotic (e.g., *Enterobacter* spp., *Klebsiella* spp., *Citrobacter* spp., and *Serratia* spp. are all intrinsically resistant to ampicillin). The bacterial pathogens from the lower respiratory tract, for which the susceptibility profile is not predictable and thus antimicrobial susceptibility testing is commonly performed, are *S. pneumoniae*, *S. aureus*, *H. influenzae*, *M. catarrhalis*, the Enterobacteriaceae, *P. aeruginosa*, and other nonfermenting gram-negative rods. Fourth, because antimicrobial susceptibility testing measures in vitro activity, other factors must be considered when determining in vivo activity, including antimicrobial pharmacokinetics and pharmacodynamics and patient-specific factors such as immune status.

Phenotypic susceptibility testing methods used by the clinical laboratory consist of the disk diffusion method, which generates a qualitative result based on the zone size of bacterial growth inhibition, and the dilution method, which generates a quantitative result: the minimum inhibitory concentration. Results generated by each method are reported as: “susceptible,” “intermediate,” or “resistant.” Susceptible implies the organism will likely respond to treatment with the antibiotic at a standard dosage. Intermediate may be effective if higher dosing can be used (e.g., β -lactams) or the antibiotic being used concentrates at the site of infection (e.g., fluoroquinolones for urinary tract infections). Resistant implies the organism is not likely to respond to therapy with that antibiotic. The interpretation criteria (susceptible, intermediate, resistant) are specific to each organism-drug combination as well as to pharmacokinetic (e.g., peak serum levels, protein binding, and clearance rate of the drug) and pharmacodynamic (e.g., whether the rate of bacterial killing is concentration dependent) characteristics of each drug. Therefore, because the measurement of the minimum inhibitory concentration alone does not capture these multiple considerations, simply choosing a drug on the basis of the lowest minimum inhibitory concentration in a susceptibility report is not recommended.

Genotypic susceptibility testing is also possible for certain pathogen-drug combinations when a monogenic mutation accurately predicts a resistant phenotype. Examples include the *mecA* gene for methicillin resistance in *Staphylococcus*,¹³⁴ *vanA* and *vanB* for vancomycin resistance in *Enterococcus*,¹³⁵ and specific *rpoB* mutations in rifampin resistance in *M. tuberculosis*.¹³⁶

Not all pathogens isolated in the laboratory can be reliably tested for antimicrobial susceptibility. For organisms such as *Chlamydia*, *Mycoplasma*, *Legionella*, nontuberculous mycobacteria, and molds, there are currently no standard test methods or interpretive criteria. For these pathogens, clinical experience, use of consensus guidelines, and careful assessment of patient response to antimicrobial therapy is most valuable for optimal patient management.

NUCLEIC ACID TESTS

In recent years, technological advances in *nucleic acid testing* (NAT) and instrument automation have revolutionized the simplicity, speed, and accuracy of detecting fastidious pathogens directly from respiratory specimens.¹³⁶⁻¹³⁸ In many laboratories these tests have replaced conventional, less sensitive, more laborious methods for routine use. With the unique capabilities of molecular diagnostic tests and the need for rapid, sensitive detection of respiratory pathogens, molecular assays will continue to gain an increasing role in the diagnosis and management of patients with opportunistic and community-acquired pneumonia. Most NATs are based on amplification and detection of nucleic acid targets specific to the pathogens of interest. NATs offer several advantages over conventional direct examination, microbiologic cultures, and serologic assays. First, NATs have the ability to detect and identify pathogens rapidly (in hours). Second, NATs provide the only means of detection for some microorganisms that are difficult or impossible to grow in culture. Certain viruses, for example, are very difficult to cultivate by conventional culture-based methods, and NATs enable detection of these organisms in clinical specimens.¹³⁹ Third, NATs make possible detection of pathogens, such as *M. tuberculosis*, in resource-limited settings where laboratory infrastructure for culture is lacking.^{140,141} Finally, for some pathogens, NATs allow determination of antimicrobial susceptibility directly from respiratory tract specimens.

A number of commercial and in-house NATs are available for direct detection of *M. tuberculosis* in sputum. These assays can yield results in 2 to 8 hours. For example, in comparison to conventional cultures for *M. tuberculosis*, NATs have high sensitivities (86% to 97%) and specificities (98%) in smear-positive respiratory samples.⁹¹ In smear-negative, culture-positive specimens, NATs can confirm the presence of *M. tuberculosis* in 33% to 96% of samples, weeks earlier than culture.⁹¹ The sensitivity further improves with smear-negative sputa if the assay is performed on one to two additional samples.¹³⁶ Detection of *M. tuberculosis* susceptibility to first- and second-line drugs can also be accomplished directly from sputum.^{142,143} Commercial NATs detect rifampin and isoniazid resistance with sensitivity of 94% to 99% and 88% to 95%, respectively.^{91,143-145} Based on the improved performance of NATs over smear microscopy and the rapid turnaround time compared to culture, the U.S. Centers for Disease Control and Prevention (CDC) recommended that NAT “testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities.”⁹³ In addition, the World Health Organization has recommended the use of NATs to screen for multidrug-resistant TB. Three such NATs are commercially available in Europe and elsewhere, and one has been approved by the FDA as of 2014.

Diagnostic methods have also been described for detecting the nucleic acids of *C. pneumoniae*,^{7,41,42} *M. pneumoniae*,^{40,44,45} *L. pneumophila*,⁴⁰ dimorphic fungi,¹⁴⁶ monomorphic fungi,¹⁴⁷⁻¹⁵⁰ *P. jirovecii*,^{151,152} *Toxoplasma gondii*,¹⁵³ respiratory viruses,¹³⁹ herpes simplex virus,¹³²

and CMV^{154,155} directly in respiratory specimens of normal and immunocompromised hosts. Accuracy studies have indicated that most of these assays are at least comparable to, if not better than, conventional culture, direct antigen, and/or serologic detection methods, especially when examining respiratory specimens that contain low numbers of pathogens. For example, a rapid PCR assay has been applied for the diagnosis of an outbreak of *Chlamydia psittaci* that resulted from transmission of this infectious agent to humans from birds purchased in stores; in this outbreak, PCR detected 50% more cases than did culture.¹⁵⁶ Compared to culture and serologic tests, PCR was also shown to be the most sensitive method for detection of *C. pneumoniae* during an outbreak of CAP.¹⁵⁷ However, NAT results should be interpreted with caution because NATs currently cannot differentiate between organisms that inhabit the upper airway without causing disease and those that are responsible for the patient's illness. For example, as mentioned, *S. pneumoniae*, *C. pneumoniae*, and *M. pneumoniae* may inhabit the upper airway without causing disease.^{6,10} Similarly, the lowered diagnostic specificity of *P. jirovecii* NATs is likely due to the detection of *P. jirovecii* nucleic acid from cysts that are present in low numbers and in a latent state in pulmonary tissues of asymptomatic patients.¹⁵⁸⁻¹⁶⁰

In patients with culture-negative infection, or when cultures were not performed on a tissue biopsy sample before fixation, a broad-range PCR assay coupled with amplicon sequencing can be used for detection and identification of bacterial and fungal DNA from fresh or *formalin-fixed paraffin-embedded* (FFPE) specimens.¹⁶¹⁻¹⁶⁴ The bacterial 16S ribosomal RNA gene and the fungal ribosomal RNA operon (encoding 5.8S, 18S, 28S ribosomal subunit genes with the internal transcribed spacer regions [ITS1 and ITS2]) are the most reliable and frequently used targets for identifying bacterial and fungal sequences, respectively.¹⁶⁵ As with all NATs, sensitivity is higher from fresh tissue than from FFPE specimens: for example, fungal sequencing was successfully completed on 97% of specimens when performed on fresh specimens compared to 63% to 70% when performed on FFPE specimens.¹⁶³ Despite the many advantages of direct bacterial and fungal identification by sequencing, clinicians must be aware that the success of this method is dependent on the amount of specimen submitted (e.g., open biopsy versus needle biopsy), the pathogen burden, and whether fresh versus FFPE tissue is tested. It is imperative that testing is strictly limited to samples obtained from sterile sources because contamination of the sample with commensal organisms or environmental spores could yield false-positive results and lead to mismanagement of the patient.^{163,164} Sequence results must always be correlated with clinical, histopathologic, and ancillary test results (antibody or antigen detection) to ensure the clinical accuracy of sequence results.

The diagnosis of respiratory virus infections (Table 17-13) has been revolutionized by nucleic acid amplification testing.¹³⁹ These tests are now considered more sensitive than all other current methods of virus detection, including viral culture and DFA testing, discussed earlier, as well as rapid antigen tests, discussed later. Following the 2009 influenza A H1N1 pandemic, there was a tremendous increase in the availability and widespread implementation of real-time PCR assays for influenza and other respiratory

Table 17-13 Respiratory Viruses

STANDARD RESPIRATORY VIRUS TEST PANEL

Influenza A, B
Respiratory syncytial virus
Human *Metapneumovirus*
Parainfluenza 1, 2, 3
Adenovirus

EXPANDED RESPIRATORY VIRUS PANEL (MAY INCLUDE ONE OR MORE)

Rhinovirus
Enterovirus*
Human *Coronavirus* (229E, HKU1, OC43, NL63)
Human bocavirus (HBoV)[†]

ADDITIONAL VIRUSES TO CONSIDER IN THE IMMUNE COMPROMISED

Cytomegalovirus
Herpes simplex virus
Varicella-zoster virus
Human herpesvirus 6

OTHER VIRUSES THAT CAUSE LOWER RESPIRATORY TRACT INFECTION

Hantavirus
Measles virus
Parechovirus
Parainfluenza virus 4
Influenza C
Polyomavirus (BK, WU, K1)

EMERGING SEVERE ACUTE RESPIRATORY VIRUSES

Avian influenza (H5N1, H7N9)
Human coronavirus—severe acute respiratory syndrome
Human coronavirus—Middle Eastern respiratory syndrome

*Commercial multiplex nucleic acid amplification tests may not distinguish between *Rhinovirus* and *Enterovirus*.
[†]Human bocavirus detection in respiratory specimens is of uncertain clinical significance, though this virus is included in several commercial multiplex nucleic acid amplification tests.

viruses. These real-time PCR assays include those endorsed by the CDC, as well as numerous laboratory-developed and commercially produced tests.¹³⁹ However, in-house real-time PCR tests are of high complexity, requiring experienced and highly skilled staff, as well as specialized molecular diagnostic laboratory facilities. Furthermore, these tests are generally batched, thereby prolonging the turnaround time and reducing clinical utility. Finally, real-time PCR allows only a moderate level of multiplexing (i.e., use of primers and probes for detecting multiple targets in the same reaction), a potential issue for detecting a broad range of respiratory viruses with a limited number of reactions. To address these issues, a variety of commercial test systems have been developed, though no single system provides comprehensive detection of clinically relevant respiratory viruses with optimal sensitivity in a format that can be performed at or near the point of care. Three groups of molecular testing now exist, with different levels of technical and personnel demands (referred to as moderate or high complexity, as established by the Clinical Laboratory Improvement Amendments).

One group of molecular tests includes limited respiratory virus panels of moderate complexity on FDA-cleared, sample-to-answer platforms that combine the speed and

simplicity of rapid antigen tests with the sensitivity of nucleic acid amplification. These tests include Xpert Flu (Cepheid; Sunnyvale, CA), which detects influenza A and B in about 1 hour, and Verigene Respiratory Virus Plus (Nanosphere; Northbrook, IL), which detects and subtypes influenza A and B, and detects and types *respiratory syncytial virus* (RSV) in less than 2½ hours. Though more sensitive than traditional respiratory virus diagnostics, Xpert Flu is slightly less sensitive than in-house real-time PCR assays.^{101,166-171} Performance of the Verigene Respiratory Virus Plus appears comparable to in-house real-time PCR.¹⁷² These assays have not yet been compared to each other.

A second group of tests are the high-complexity, FDA-cleared, comprehensive respiratory virus panels that require separate extraction and PCR amplification steps before multiplex nucleic acid detection. These tests include the xTAG Respiratory Virus Panels (Luminex; Austin, TX): xTAG RVPv1 and xTAG RVP FAST, as well as the eSensor Respiratory Virus Panel (GenMark Diagnostics; Carlsbad, CA). The xTAG RVPs achieve high-level multiplexing through the combination of target amplicon labeling with universal, minimally cross-hybridizing, complementary oligonucleotide sequences and flow cytometric detection using a solution-phase array composed of spectrally distinct microspheres.¹⁷³ In approximately 8 hours, RVPv1 detects influenza A, including subtyping H1 and H3, influenza B, RSV A, RSV B, parainfluenza virus 1, 2, and 3, human metapneumovirus, adenovirus, and rhinovirus/enterovirus. Compared to RVPv1, RVP FAST has a shorter time to result (about 6 hours); however, it does not detect the parainfluenza viruses, and it does not distinguish between RSV types. Several studies have compared the clinical performance of the xTAG RVPs and found that both the xTAG RVPv1 and RVP FAST panels are more sensitive than traditional respiratory virus testing methodologies, less sensitive than in-house real-time PCR, and that RVPv1 is more sensitive than RVP FAST.¹⁷⁴⁻¹⁸⁰ Of note, these assays demonstrate low sensitivity for adenoviruses and do not distinguish between the closely related picornaviruses, rhinovirus, and enterovirus.

In this same group the eSensor RVP achieves high-level multiplexing through competitive hybridization and electrochemical detection using a microfluidic device containing an array of single-stranded oligonucleotide capture probes. In approximately 8 hours the eSensor RVP detects influenza A, including H1, 2009 H1, and H3 subtyping, influenza B, RSV A, RSV B, parainfluenza virus 1, 2, and 3, human metapneumovirus, adenovirus C, adenovirus B/E, and rhinovirus. The eSensor RVP demonstrates comparable performance to in-house real-time PCR, including detection of adenovirus and rhinovirus, and at this time appears to be the most sensitive of the multiplex respiratory virus assays.^{180,181} Both the xTAG and eSensor RVP assays have research-only versions or versions approved outside of the United States that offer detection of parainfluenza 4, human coronaviruses 229E, HKU1, OC43, and NL63 and, for xTAG RVP, bocavirus and the severe acute respiratory syndrome coronavirus. Determination of the clinical utility of these expanded panels requires additional study.

The third group of molecular respiratory virus tests are of moderate complexity and combine the simplicity and

speed of rapid antigen testing with the sensitivity and multiplexing capability of the xTAG or eSensor RVP. At present, one assay is available in this category: the FilmArray Respiratory Panel (BioFire Diagnostics; Salt Lake City, UT), which integrates sample preparation, nested-PCR amplification, real-time fluorescent detection, and analysis in a single assay pouch.¹⁸² In about 1 hour, including less than 5 minutes of hands-on time, this assay detects influenza A, including H1, 2009 H1, and H3 subtyping, influenza B, RSV, parainfluenza virus 1, 2, 3, and 4, human metapneumovirus, adenovirus, rhinovirus/enterovirus, and human coronaviruses 229E, HKU1, OC43, and NL63. In addition, it detects three bacterial species: *Bordetella pertussis*, *C. pneumoniae*, and *M. pneumoniae*. Clinical performance is similar to xTAG RVPv1, demonstrating higher sensitivity than traditional respiratory virus testing methodologies and lower sensitivity compared to in-house real-time PCR.^{177,179,180,183-188} The current Film Array Respiratory Panel also has low sensitivity for adenoviruses, does not distinguish between rhinovirus and enterovirus, and has low throughput, because only one test can be performed on an instrument at a time. However, its rapid turnaround and ease of use allows most laboratories to perform multiplexed molecular respiratory virus testing. In the future it is expected that assays in this category will improve sensitivity, specificity, and throughput to create optimal, rapid multiplex molecular respiratory virus tests.

Given the variety of nucleic acid tests that are currently available for the diagnosis of respiratory virus infection and the rapid development of new NATs, it is important to communicate with the laboratory to confirm the viruses included in the local panel, the expected turnaround time, and local test performance characteristics. Furthermore, note that nasopharyngeal swabs and aspirate/washes are the only specimen types that have received FDA clearance so far, so it is also important to verify that the local laboratory has validated the use of lower respiratory tract specimens in their test system before sending such samples for testing.

ANTIGEN TESTING

The diagnosis of lower respiratory tract infections can be aided by detection of pathogen-specific antigens in serum or other body fluids. Antigen detection offers an alternative to direct examination of infected tissue and may play a role in the detection of pathogens that grow poorly, or not at all, in culture.

Urinary antigen assays may have value for adults with *S. pneumoniae* and *L. pneumophila* infections. In a meta-analysis of 27 studies using a composite of culture tests as the reference standard, the pooled sensitivity for direct antigen detection of *S. pneumoniae* in the urine of adults with CAP was 74% (95% confidence interval [CI], 67% to 82%) and specificity was 97% (95% CI, 93% to 100%).¹⁸⁹ In children, pneumococcal antigen in urine is less specific for invasive infection, because it was detected in 43% of children with only nasopharyngeal colonization.¹⁹⁰ Similarly, in children with pneumonia, detection of *H. influenzae* type B antigens in urine is of potential diagnostic value, but transient antigenuria may follow immunization with *H. influenzae* type B conjugate vaccine.¹⁹¹ In the evaluation of adults for

legionnaires' disease, urine *L. pneumophila* serogroup 1 antigen has a high negative predictive value with pooled sensitivity of 74% (95% CI, 68% to 81%) and specificity of 99% (95% CI, 98% to 100%).¹⁹² Urine antigen for *L. pneumophila* is detectable in 80% to 89% of patients with legionnaires' disease beginning with the first 3 days of symptoms and continuing for at least 14 days; the duration of antigenuria was reduced by antibiotic therapy and was detectable for up to 42 days, especially in immunocompromised patients.¹⁹³ The urinary antigen assays are limited to detection of infections due to *L. pneumophila* serogroup 1 and not other *Legionella* serogroups or species.⁹⁴

Detection of fungal antigen in serum, urine, and other body fluids is used as an aid in the diagnosis of infections due to *Cryptococcus neoformans*, *Aspergillus*, *H. capsulatum*, and *P. jirovecii*. Assays to detect capsular polysaccharides of *C. neoformans* in serum or cerebrospinal fluid are essential for rapid diagnosis of cryptococcosis. Commercially available assays show sensitivity ranging from 83% to 97% and specificity from 93% to 100%.¹⁹⁴ Cryptococcal antigen may also be detectable in pleural fluid and BAL fluid of patients with cryptococcal pneumonia.^{195,196} Serial measurement of serum antigen titers over time is not useful for management of patients with pulmonary cryptococcosis.¹⁹⁷ Cryptococcal antigen may be falsely positive due to the presence of rheumatoid factor or heterophile antibodies (i.e., antibodies produced to poorly defined antigens with weak affinity and multispecific activities) and falsely negative due to the prozone effect (antigen excess), localized infection, infection with a poorly encapsulated strain, or low organism burden.¹⁹⁴

Several commercial *H. capsulatum* antigen assays with variable accuracies are available for diagnosis of histoplasmosis.¹⁹⁸ The polysaccharide antigen of *H. capsulatum* can be detected in urine in approximately 90% of patients with disseminated disease and 75% with diffuse acute pulmonary histoplasmosis.^{118,119} A recent multicenter study identified antigenuria in 91.8% of 158 patients with disseminated histoplasmosis, 83.3% of 6 patients with acute histoplasmosis, 30.4% of 46 patients with subacute infection, and 87.5% of 8 patients with chronic histoplasmosis; antigenemia was detected in 100% of 31 patients with disseminated infection.¹⁹⁹ Urinary *Histoplasma* antigen levels persist during ongoing active infection, become undetectable with successful therapy, and rise with relapse of infection. The specificity of the *Histoplasma* antigen assay was 99% in patients with nonfungal infections and in healthy controls¹⁹⁹; however, the assay is known to yield positive results in patients with disseminated infections caused by *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Aspergillus*, and *Penicillium marneffei*.^{200,201} Cross reactivity of the assay has not been observed in patients with invasive candidiasis, cryptococcosis, or other opportunistic systemic mycoses.²⁰⁰

At least one commercial laboratory offers antigen tests for the diagnosis of coccidioidomycosis and blastomycosis, but both tests exhibit significant cross reaction with *H. capsulatum*.²⁰²

Aspergillus galactomannan is a major cell wall component of the fungus, and detection of this antigen has been studied in many different clinical situations. Galactomannan detected in serum by enzyme immunoassay can aid in

the early diagnosis of invasive pulmonary aspergillosis, with pooled diagnostic sensitivity of 71% (95% CI, 68% to 74%) and specificity of 89% (95% CI, 88% to 90%) for proven cases of invasive aspergillosis.²⁰³ The reported sensitivity and specificity range from 40% to 100% and 56% to 100%, respectively, in various patient groups.^{17,147,204-206} The Platelia *Aspergillus* test (Bio-Rad Laboratories, Hercules, CA), a commercially available assay that detects galactomannan from *A. fumigatus*, *A. flavus*, *A. niger*, *A. versicolor*, and *A. terreus*, has been shown to yield positive results at an early stage of infection, with positive and negative predictive values of more than 90% in high-risk patients who were tested biweekly.²⁰⁴ However, this assay may cross react with *Histoplasma*, *P. brasiliensis*, *Penicillium*, *Paecilomyces*, *Alternaria*, and *Cryptococcus*,²⁰⁶⁻²⁰⁸ and false-positive galactomannan antigen assay results can be observed in patients receiving certain foods or intravenous piperacillin-tazobactam, amoxicillin, or ticarcillin.²⁰⁸⁻²¹¹ Cross reactivity with *Listeria monocytogenes* has also been reported.²¹² BAL fluid specimens from lung transplant recipients have also been evaluated for testing by *Aspergillus* galactomannan detection assay, with sensitivity of 82% and specificity of 96%.²¹³ Of note, the Plasma-Lyte (Baxter International Inc., Deerfield, IL) solution commonly used to perform BAL has been found to yield false-positive results with the Platelia *Aspergillus* test.²¹⁴ Overall, assays for galactomannan show promise, but currently a single positive result has limited value and cross reactivity is common.

Another fungal antigen used for the diagnosis of invasive fungal infection is (1→3)- β -D-glucan, which is a component of the outer cell wall of saprophytic and pathogenic fungi except Zygomycetes (*Mucor* and *Rhizopus* species) and *Cryptococcus* species.^{204,215} This antigen has been detected in serum or other body fluids of patients with invasive aspergillosis, invasive candidiasis, and infections caused by *Fusarium*, *Acremonium*, *Trichosporium*, *Scedosporium*, *Saccharomyces*, and *P. jirovecii*.^{149,216,217} A meta-analysis for diagnosis of invasive fungal infection showed a pooled sensitivity of 77% (95% CI, 67% to 84%), and specificity of 85% (95% CI, 80% to 90%).²¹⁸ Use of different assay cutoff values may result in differences in sensitivity and specificity among the various commercially available assays for detecting this antigen.^{215,219} For the diagnosis of *Pneumocystis* pneumonia in HIV-positive patients, the sensitivity of the (1→3)- β -D-glucan assay was 92% and specificity was 65%.²²⁰ In pneumocystis pneumonia, β -D-glucan levels do not correlate with organism burden, *Pneumocystis* pneumonia severity, or response to therapy.²²⁰ Cross reactivity of β -D-glucan assays has been reported with the use of cotton gauzes, swabs, packs, pads, or sponges for wound care or surgery; cellulose filters in hemodialysis patients; and various antimicrobial agents including piperacillin-tazobactam.^{215,221}

Rapid antigen tests for influenza A and B are commonly used in both ambulatory and inpatient settings. Rapid detection of influenza is critical to allow prompt treatment with antiviral agents, to reduce the risk for further transmission through implementation of infection control practices, and to reduce inappropriate use of antibiotics.^{222,223} A meta-analysis evaluating 159 studies and 26 different rapid influenza antigen tests reported a sensitivity of 62% (95% CI, 58% to 67%) and a specificity of 98% (95% CI,

98% to 99%).^{223,224} Because of this low sensitivity, physicians should consider following negative rapid influenza antigen tests with more sensitive testing, particularly if specimens are collected during times of high influenza prevalence.²²⁵ Rapid antigen tests for RSV are also available and may similarly aid in patient triage, infection control, and antibiotic management, particularly in pediatric patients. The sensitivities and specificities of these RSV rapid antigen tests range from 59% to 89% and 93% to 100%, respectively.^{124,226}

SEROLOGIC TESTING AND INTERFERON- γ RELEASE ASSAYS

The cause of lower respiratory tract infections can be suggested by detection and quantitation of humoral (e.g., antibody) responses to pathogens. In addition, *latent TB infection* (LTBI) can be diagnosed by detection of cellular immune responses to *M. tuberculosis* antigens, such as the *interferon- γ release assays* (IGRAs). Serologic testing is used commonly to identify infections due to pathogens that are difficult to detect by other conventional methods, to evaluate the course of an infection, and to determine the nature of the infection (primary infection versus reinfection, acute versus chronic infection). Serologic testing and IGRAs are less sensitive in patients with compromised immune systems and therefore cannot be used to rule out infection.²²⁷⁻²²⁹ When possible, microbiologic culture and NATs on respiratory secretions or lung tissue should be performed to detect and confirm the presence of pathogens in immunosuppressed patients who may not be able to mount antibody or cell-mediated immune responses.

The serologic methods commonly used in diagnostic laboratories include enzyme immunoassay, immunoprecipitation, *immunodiffusion* (ID), *complement fixation* (CF), immunoblotting (including Western blot), agglutination, hemagglutination inhibition, and indirect immunofluorescence assay. Serologic results are often expressed as a titer, which is the inverse of the greatest dilution, or lowest concentration of a patient's serum that retains measurable specific antibody-antigen reactivity (e.g., dilution of 1:16 = titer of 16). A fourfold or greater rise in antibody titer between acute and convalescent sera is usually required for diagnosis. An elevated pathogen-specific IgM antibody titer in a single serum sample suggests recent infection, and a falling titer provides further support for the etiologic significance of this organism. However, false-positive *immunoglobulin* (Ig) M antibody tests are not rare. Thus serologic testing of pathogen-specific IgG antibody in acute and convalescent sera remains the approach to establish a specific microbial cause of the infection.²³⁰

Various commercial assays are available for detection of specific IgM and/or IgG antibodies to respiratory tract pathogens.²³¹ These assays are useful for supporting or confirming the diagnosis of bacterial infections caused by *C. pneumoniae*, *Legionella* species, *F. tularensis*, *Y. pestis*, *C. trachomatis*, *C. pneumoniae*, *C. psittaci*, and *Coxiella burnetii*. Although antibody testing is commonly used for the detection of infection with *M. pneumoniae*, a recent study was unable to distinguish between infection and asymptomatic colonization with this organism.¹⁰ The diagnosis of *C. pneumoniae* infection can also be a problem. In some additional

instances, such as infection with *M. tuberculosis*, commercial serologic tests have been shown to be inconsistent and imprecise, which is the basis of World Health Organization policy statement advising against use of existing serologic tests in TB.²³²

M. pneumoniae infection is often diagnosed by the presence of specific antibodies in serum.²³³ Cold agglutinins, detected by agglutination of type O Rh-negative red blood cells at 4° C, are present in the sera of approximately 50% of patients with *M. pneumoniae* infection, and levels decline to baseline within 6 weeks after acute infection.²³³ However, cold agglutinins are nonspecific. Antibodies to a chloroform-methanol glycolipid extract of *M. pneumoniae* are detected by a CF test in more than 85% of culture-positive patients; a single elevated titer of greater than 80 or a greater than fourfold rise in titer between acute and convalescent sera is required to establish a diagnosis. Enzyme immunoassays to detect IgM and IgA antibodies that specifically recognize *M. pneumoniae* membrane proteins have been developed with improved sensitivity and specificity over the CF assay.²³³ Specific IgM antibodies appear during the first week of illness and reach peak titers during the third week. However, the IgM antibodies to *M. pneumoniae* are not consistently produced in adults because of prior sensitization, so that a negative IgM result does not rule out acute *M. pneumoniae* infection, particularly in older adults. Detection of specific IgA antibodies in the serum has been shown by one group to be a reliable approach for diagnosis, because these antibodies are also produced early in the course of disease and more reliably present in the infected individuals regardless of age.²³³ Others, however, found them of little value.¹⁰

Serologic testing plays an important role in the diagnosis of fungal respiratory tract infections due to *C. immitis* and *H. capsulatum*.²³⁴ For *C. immitis* a diagnosis of infection can be based on detection of antibodies to antigens derived from the coccidioidal mycelia or spherules, although there may be cross reactivity with other yeasts and dimorphic fungi. Antibodies to *C. immitis* can be detected by ID, CF, and enzyme immunoassay. Precipitin-specific IgM antibodies develop in up to 75% of individuals within 2 to 3 weeks after primary *C. immitis* infection and subsequently disappear except in patients with disseminated infection. Complement-fixing IgG antibodies appear later and persist in relation to the severity of disease, but decline with disease remission. Titers of 32 or higher suggest the possibility of disseminated infection.^{235,236} The sensitivity of serologic testing drops 8% to 20% in immunocompromised hosts compared to immunocompetent patients.²³⁷

For *H. capsulatum*, serum antibodies are detected by CF using both yeast and mycelial antigens and an ID assay, which show increased titers in more than 90% of patients with pulmonary histoplasmosis and approximately 80% with disseminated disease.¹¹⁹ The CF test is more sensitive but less specific than the ID test for the diagnosis of subclinical and acute pulmonary histoplasmosis.²³⁸ Antibodies become detectable first by CF at 2 to 6 weeks after *Histoplasma* infection and then by ID 2 to 4 weeks later. However, the ID test remains positive longer than the CF test after resolution of infection, becoming negative 2 to 5 years later. Antibody levels remain high in those with chronic pulmonary infection, progressive disseminated disease, or

mediastinal fibrosis. Commercially available serologic tests for blastomycosis exist but suffer from limited accuracy and are of minimal value in patient care.²³⁹

Serologic testing is also useful for diagnosis of parasitic infections, especially *Paragonimus*, *T. gondii* and *S. stercoralis*,^{240,241} and for diagnosis of extraintestinal *E. histolytica* disease. Serologic testing plays an especially important role for screening prospective organ transplant recipients and other patients considered for immunosuppressive therapies.

Serologic testing plays a limited role as an aid to the diagnosis of respiratory viral infections. Although detection of recent respiratory virus infection, for example with influenza A, may be determined via seroconversion or a fourfold or greater rise in antibody titer in a convalescent relative to an acute serum sample, the requirement for two temporally distinct specimens makes serologic results unlikely to factor in clinical decision making.²⁴² In contrast, routine CMV serologic testing in transplant donors and recipients provides valuable information about the risk for subsequent CMV-related sequelae, including the development of respiratory disease.²⁴³

IGRAs are in vitro assays used to measure T-cell responses to *M. tuberculosis*-specific antigens, such as ESAT-6, CFP-10, and TB7.7.²⁴⁴ Two FDA-approved commercial IGRAs are currently available: the *QuantiFERON-TB Gold In-Tube* assay (QFT-GIT; Qiagen, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom). IGRAs were developed as an alternative to the *tuberculin skin test* (TST) for diagnosis of LTBI.^{245,246} Compared to the TST, IGRAs have improved specificity for distinguishing between the responses due to *bacillus Calmette-Guérin* (BCG) vaccination and latent TB infection, because the antigens used in IGRAs, ESAT-6 and CFP-10, are absent from all strains of BCG. Also, compared to the TST, IGRAs offer logistical advantages because they do not depend on accurate intradermal injection and patients do not have to return to a health facility for the result to be read.²⁴⁴ However, like TSTs, IGRAs cannot distinguish between LTBI and active disease.²⁴⁷ The sensitivity of IGRAs in culture-positive active TB cases has ranged from 65% to 100%,^{244,248,249} and the sensitivity in patients with LTBI who progressed to active TB ranged from 40% to 100%.²⁵⁰ Both IGRAs and the TST have been shown to have similar sensitivity in adults in low- and middle-income countries.²⁵¹ However, the accuracy of IGRA testing appears to falter at the borderline levels of positivity. Studies conducted in health care workers in low-incidence settings have shown highly variable IGRA results with serial testing. The rate of conversions (negative to positive result using the manufacturer- and CDC-recommended cutoff of ≥ 0.35 IU/mL) ranged from 2% to 15%, and the rate of reversions (positive to negative result) ranged from 20% to 40%.^{252,253} Those with borderline results around the assay cutoff are more likely to revert or convert. Finally, there are limitations to the use of IGRAs. IGRA results have not proven useful for monitoring response to TB treatment. Similarly, IGRAs are no more able than the TST to predict which patients with positive results will go on to develop active TB.^{254,255} Currently, therefore, IGRA is most useful as an alternative to the TST, especially in subject populations with a high incidence of BCG vaccination.

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Key Points

- Diagnostic testing should be ordered only if the result will alter treatment decisions.
- The clinician plays a critical role in preventing accidental laboratory exposure by notifying the microbiology laboratory when highly virulent and transmissible agents are suspected as the cause of disease.
- Syndromic order sets can improve the accuracy and efficiency of test selection and thus facilitate accurate diagnosis of infectious diseases.
- Lower respiratory tract secretions collected through the oropharynx are nearly always contaminated with resident microflora of the oral cavity, and therefore microscopy, culture, and nucleic acid test results must be interpreted in the context of other clinical evidence and diagnostic findings.
- Nucleic acid tests can facilitate rapid and accurate diagnosis of lower respiratory tract infections, especially those caused by viruses and pathogens that are difficult to culture.

Complete reference list available at *ExpertConsult*.

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THORACIC RADIOLOGY: NONINVASIVE DIAGNOSTIC IMAGING

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INTRODUCTION

Imaging plays a major role in the detection, diagnosis, and serial evaluation of thoracic disease. The appropriate use of imaging techniques requires some basic understanding of the technical aspects of and abnormal findings visible with different imaging techniques and of the diagnostic accuracy of these techniques. It is not the intent of this chapter to provide a complete description of the techniques involved or an encyclopedic catalogue of radiographic abnormalities of chest diseases. Rather, this chapter is intended to provide a general survey of the imaging methods available, their most common indications, and certain principles concerning their use.

Since the late 1990s, there have been remarkable advancements in the effectiveness of cross-sectional imaging techniques for the diagnosis of thoracic diseases, particularly with the development of multislice *computed tomography* (CT), as well as improvements in *magnetic resonance imaging* (MRI) and ultrasonography. In many instances, cross-sectional methods have supplanted radiography for the diagnosis of chest diseases. As with any imaging method, the decision to utilize cross-sectional imaging should be based on consideration of the patient's clinical problem and the results of other imaging and laboratory testing.

Chest radiography still plays a fundamental role in the diagnosis of thoracic disease. Chest radiography is usually the initial imaging procedure performed when chest disease is suspected, and despite the proliferation of other imaging methods, chest radiography remains one of the most frequently performed radiographic examinations in the United States.

The thorax is difficult to image with radiographic techniques because of large regional differences in tissue density and thickness. For example, with standard radiography, the number of x-ray photons passing through the lungs is more than 100 times greater than the number of x-ray photons penetrating the mediastinum.¹ The dynamic contrast range of conventional film-screen radiography is insufficient to demonstrate this range of x-ray photon transmission properly; with standard radiographic techniques, the use of exposure high enough to display the mediastinum and the subdiaphragmatic regions usually results in overexposure of the lungs (Fig. 18-1A). Conversely, an exposure designed to provide the best visualization of the pulmonary parenchyma (see Fig. 18-1B) is normally too light to visualize mediastinal anatomy. One of the advantages of digital imaging is that displayed contrast and brightness are largely independent of the kilovoltage and milliamperage values used to obtain the examination; both contrast and brightness can be manually adjusted by the user after the image has been obtained.² Furthermore, the dynamic contrast range (latitude) of digital radiographic techniques exceeds that of film-screen methods by a factor of 10 or more.²

Chest radiography has been in use since the discovery of x-rays, and evolutionary developments in radiographic technology have addressed some of the fundamental limitations of radiographic techniques.¹ Whereas film-screen projection radiography was the primary method by which chest radiography was performed for many years, digital radiography has largely supplanted film-screen techniques, providing advantages such as image postprocessing and electronic storage of the radiographic data. The latter is particularly important because it allows for simultaneous

Major Factors Affecting Image Quality in Standard Film-Screen Radiography and Digital Radiography

Bronchography

Pulmonary Angiography

Aortography and Bronchial Angiography

ULTRASONOGRAPHY

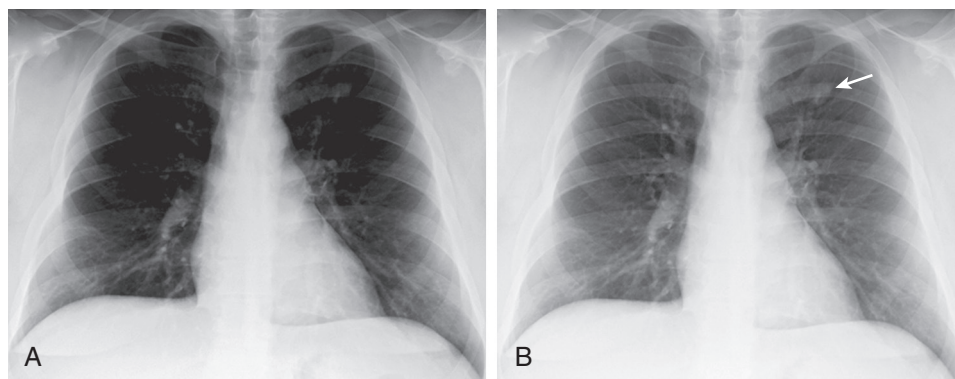


Figure 18-1 Overexposed versus properly exposed chest radiograph. **A**, Frontal chest radiograph performed with overexposed technique shows relatively good visualization of the mediastinum, but the lungs are abnormally “black,” which obscures fine detail. **B**, Repeat frontal chest radiograph performed with proper exposure shows slightly reduced ability to “see through” the mediastinum compared with the overexposed chest radiograph, but lung parenchymal detail is clearly superior in the properly exposed image. The proper exposure allows visualization of a left upper lobe nodule (arrow). (Courtesy Michael Gotway, MD.)

access to imaging studies by multiple providers and transmission of the data over long distances quickly.

Meticulous attention to technique is essential. Regardless of the method of recording the image, whether through standard film-screen radiography, image intensification, or digital recording, poor quality control leads to degradation of diagnostic information. Unfortunately, many technically inadequate radiographs are produced, leading either to repeat studies with additional patient radiation exposure or to interpretation of the poor images, increasing the chance of diagnostic errors.

Indications for the use of chest radiography are protean and include the assessment of both acute (e.g., pneumonia) and chronic (e.g., *chronic obstructive pulmonary disease* [COPD]) lung diseases, assessment of dyspnea or other respiratory symptoms, evaluation of treatment success for patients with acute lung disease, follow-up of patients with a known chronic lung disease, monitoring of patients in *intensive care units* (ICUs), diagnosis of pleural effusion, screening for asymptomatic diseases in patients at risk, monitoring patients with industrial exposure, preoperative evaluation of surgical patients, and as the initial imaging study in patients with known or suspected lung cancer and other tumors, vascular abnormalities, and hemoptysis. Abnormal radiographic findings can be quite subtle, however, and, in many circumstances the sensitivity and specificity of chest radiography is limited. In such situations, other imaging studies, especially chest CT, are performed to investigate abnormalities visible on radiographs or to evaluate patients considered high risk for a particular condition, but with normal chest radiographic results.

The utility of chest radiography has been studied in a number of clinical settings, and the appropriate criteria for their use have been determined by the *American College of Radiology* (ACR, <http://www.acr.org/Quality-Safety/Appropriateness-Criteria/Diagnostic/Thoracic-Imaging>). Although a detailed analysis of the diagnostic accuracy of chest radiographs in all instances is beyond the scope of this chapter, for illustrative purposes their utility and limitations in several specific clinical settings are reviewed.

CHEST RADIOGRAPHY: TECHNIQUES



RADIOGRAPHIC VIEWS AND TECHNIQUES

Routine Examination

A routine chest radiographic examination in an ambulatory patient usually consists of *posteroanterior* (PA) and left lateral projections. The utility of routine lateral radiographs, however, has been questioned. After analyzing more than 10,000 radiographic chest examinations obtained routinely in a hospital-based population, Sagel and associates²⁰ concluded that the lateral radiograph could be safely eliminated in the routine examination of patients 20 to 39 years of age. Conversely, they and others²¹ have concluded that the lateral radiograph should be obtained in patients with suspected chest disease and in screening examinations of patients 40 years of age or older (Fig. 18-2).

Expiratory Views

Conventional radiographs are made at total lung capacity (i.e., full inspiration), thereby permitting the greatest volume of lung to be evaluated for possible pathology and providing the most contrast between intrapulmonary air and normal and abnormal intrathoracic structures (Fig. 18-3). However, localized or generalized air trapping in the lung or pleural space is more easily detected (and sometimes only detected) on a radiograph made during expiration. The normal lung diminishes in volume and increases in density with expiration. Areas of trapping usually retain their lucency and volume regardless of the phase of respiration. With unilateral or localized air trapping, mediastinal shift (Fig. 18-4) and failure of normal elevation of the hemidiaphragm on the affected side are frequently apparent only on expiration. Small pneumothoraces, difficult to visualize and frequently overlooked on inspiratory radiographs, appear larger and more apparent on the expiratory study. As the thorax and underlying lung diminish in volume, the lung becomes denser, whereas the pneumothorax remains

The goal of chest radiography is to maximize diagnostic information through optimal film quality, while limiting radiation exposure to the patient. Although there are minor disagreements among experts, virtually all definitions of image quality include three general factors: radiographic contrast, resolution, and image noise.^{1,3} These are inter-related, and the ultimate quality of the radiograph is determined by the worst of the factors involved in its production.

MAJOR FACTORS AFFECTING IMAGE QUALITY IN STANDARD FILM-SCREEN RADIOGRAPHY AND DIGITAL RADIOGRAPHY

Standard analog film-screen radiography has been employed for the production of chest radiographic images for many years, but has largely been supplanted by digital techniques. With film-screen radiography, an x-ray photon is absorbed in a screen containing a photostimulable coating, resulting in the production of multiple light photons that, in turn, expose the actual film. This method differs from that used by digital radiographic techniques for image creation;⁴ the differences between film-screen and digital radiographic techniques are reviewed below. Nevertheless, the following discussion of technical factors impacting imaging quality applies to both methods.

Radiographic Contrast

Radiographic contrast, or *contrast resolution*, may be defined as the magnitude of signal difference between the imaged object and its surroundings in the displayed image,^{2,4} and it is principally determined by components of the system, chiefly the energy of the x-rays, and the degree to which secondary radiation (scatter) is eliminated. A film-screen combination possessing an intermediate or wide gray scale (latitude) is preferable to one producing extreme contrast^{1,3}; such “wide latitude” is intrinsic to digital radiographic production methods and, as will be discussed shortly, is one of the advantages digital imaging enjoys over older analog film-screen techniques. Although very “white-and-black” radiographs appear to demonstrate excellent detail, differentiation of structures differing slightly in density, such as the pulmonary vessels and the background lung, is better achieved with a wide-latitude film-screen combination or digital radiography. Wide-latitude film-screen combinations or digital radiography also better display the wide range of densities present in the thorax.¹

When an object is radiographed, some photons are absorbed or scattered, whereas others pass unaffected through the object (eFig. 18-1A). If the object is close to the detector, exposure from scattered radiation degrades image contrast and detail.^{1,3} Because production of scatter radiation varies with the volume of tissue being imaged, the use of devices, referred to as “collimators,” to restrict the beam size to the area being studied reduces scatter radiation. The further addition of filtration to the x-ray tube in the area of the collimator prevents low-kilovoltage radiation from reaching the patient, thus reducing the radiation absorbed by the patient without compromising diagnostic information.

Scattered radiation can also be removed by placing an antiscatter grid between the patient and the x-ray cassette

with film-screen systems (eFigs. 18-1B and 18-2A).^{1,3,5,6} Such grids permit the passage of the parallel primary x-ray photons to expose the detector while absorbing radiation scattered at an angle to the primary beam; the grid also absorbs some primary photons, making it necessary to increase the exposure technique to maintain the correct film density. Similarly, an exposure increase is also required when using grids with digital detectors to compensate for attenuation of the primary radiation beam by the grid.^{2,4} Care must be taken to ensure that the grid is of the proper type and is properly aligned to the x-ray beam. Placement off center, angulation, or the use of a grid focused at the wrong distance may affect the symmetry of radiograph exposure or even render it uninterpretable. Scatter radiation may also be reduced by increasing the distance between the detector and the patient, a process referred to as “creating an air gap” (eFigs. 18-1C and 18-2B). Some digital imaging systems, such as scanned-slot digital radiography detectors, have intrinsic scatter rejection capability and therefore do not require the use of a grid.^{2,4}

Spatial Resolution

Spatial resolution reflects the ability of an imaging system to allow two adjacent structures to be visualized as distinctly separate.^{2,4} Spatial resolution of film-screen combinations in common use is 10 to 12 line pairs/mm and is primarily determined by the thickness of the screen employed (thicker screens are associated with poorer spatial resolution).^{2,4} Other technical issues are responsible for limiting spatial resolution in digital radiography systems.^{2,4} A number of other factors may contribute to the reduction of the final resolution achieved on a chest radiograph produced by either film-screen or digital techniques. The use of large focal spots, particularly in thick body parts such as the thorax, degrades resolution by producing “edge unsharpness” or blur due to penumbra effects. Conversely, the limited capacity of a very small focal spot dictates a long x-ray exposure, and body motion can degrade spatial resolution, also causing edge unsharpness. A compromise choice in x-ray focal spot size of 1 mm or less is recommended. Lengthening of exposure duration causes degradation of spatial resolution because of insufficient power of the x-ray generator or deficiency of the heat capacity of the tube. Ideally, exposure duration should not exceed 25 msec and, for frontal projections, should be considerably less. A tube-detector distance of at least 6 feet (1.8 m) is usually used to reduce magnification and image blurring (see eFig. 18-2).

Noise

All imaging systems are limited by noise, which, in radiography, may be defined as fluctuations within the image that do not correspond to variations in x-ray attenuation in the imaged object.^{2,4} In radiography, noise is frequently referred to as “quantum mottle.”³ Noise is primarily determined by the number of x-ray photons used to produce the image, although factors intrinsic to the imaging systems contribute to image noise.^{2,4} The fewer the number of photons, the noisier the image will be. With a given film-screen or digital system, attempts to increase speed generally result in decreased resolution because of mottle.

X-ray screens that employ rare earth phosphors and have the property of converting x-ray photons to light more

efficiently have been developed. When used with properly matched films, these rare earth screens double or triple the speed at which a properly exposed radiograph can be made. They do not increase the noise of the system significantly and they permit reduction of radiation exposure to the patient by one half or more.

American College of Radiology Standards

The ACR standards for performing adult chest radiography (http://www.acr.org/~media/ACR/Documents/PGTS/guidelines/Chest_Radiography)⁷ specify the use of at least a 72-inch tube-film distance, a tube focal spot not to exceed 2 mm (0.6 to 1.2 mm recommended), rectangular collimation and beam filtration, a high-kilovoltage technique (120 to 150 kVp) appropriate to the characteristics of the film-screen combination, a film-screen speed of at least 200, an antiscatter technique (grid or air gap) equivalent to a 10:1 grid (preferably 12:1), and a maximum exposure time of 40 msec. The ACR also specifies a maximum mean skin entrance radiation dose (0.3 mGy/exposure). Guidelines for the production of digital chest radiographs have been published.²

Portable Radiography

The proliferation of ICUs and the increased use of patient monitoring for life-support devices have significantly increased the number of portable radiographs obtained.^{1,8,9} As indicated earlier, these examinations are necessary to determine whether catheters, endotracheal tubes, intra-aortic balloons, and various other devices have been correctly placed (eFigs. 18-3 to 18-7).^{10,11} Portable radiographs are also essential for assessing responses to therapy and for surveying for the presence of new thoracic disease.

Even under ideal circumstances, the quality of the radiographs obtained with portable techniques does not approach the standard of those made in the radiology department (eFig. 18-8). Portable examinations are generally made at a focal spot–detector distance of less than 72 inches, resulting in penumbral blurring, edge unsharpness, and degradation of fine detail.³ The routine use of the *anteroposterior* (AP) projection, with the recording device adjacent to the patient's back, magnifies the cardiac silhouette and other anterior structures. When possible, the radiograph should be obtained with the patient in the sitting position, but this is frequently not feasible. Images obtained with the patient recumbent compromise the detection of pleural effusions and pneumothorax, as well as the assessment of the gravitational distribution of pulmonary blood flow based on vessel size and lung zone opacity.

None of the several different types of mobile generators available is ideal. Exposure duration is difficult to control and is relatively long, and motion blurring degrades the image. Because of these limitations and the frequent need for immediate viewing of chest radiographs, storage phosphor-computed digital units are widely used for ICU radiography (see later discussion).¹¹ The storage plate phosphor's ability to provide relatively even density for overexposed and underexposed films and its ability to adjust the images digitally to visualize mediastinal or pulmonary parenchymal areas are well suited for ICU portable radiography.

The ACR standards for performance of portable chest radiographs (http://www.acr.org/~media/ACR/Documents/PGTS/guidelines/Portable_Chest.pdf) are relatively forgiving.^{7,12} A tube-film distance of 40 to 72 inches is recommended, closer to the latter preferred. From 70 to 100 kVp is recommended if a grid is not used, whereas more than 100 kVp may be used in conjunction with a grid. Exposure times should be as short as feasible to reduce motion artifacts.

Digital (Computed) Radiography

The development of reusable radiation detectors along with advances in electronics and computer technology enabled the development of a new type of radiographic imaging: digital radiography and computed radiography.^{1,13} These systems are fundamentally different from film-screen radiography in that image detection can be completely separated from the method of image display⁴ and, because the images are digital in format, they can be subjected to significant postprocessing to improve diagnostic information.⁴ Also, digital image receptors have a much wider range of sensitivity, or latitude, compared with standard film-screen combinations (10,000:1 rather than 100:1), and their response to radiation is linear over this entire range.^{1,2} Within these large limits, image contrast is independent of exposure. Furthermore, digital images can be displayed, transmitted, and stored electronically,^{2,3} and digital systems allow for faster patient throughput, increased dose efficiency, and possibly reduced x-ray exposure compared with film-screen techniques.^{4,13} These advantages have allowed digital radiography to supplant film-screen radiography in many radiology facilities.¹³

Storage Phosphor Systems

A commonly employed system of digital radiographic imaging, known as *computed radiography* (CR), uses imaging plates that are exposed by conventional radiographic equipment and can be used like any x-ray cassette.^{1,3} The reusable plates are coated with a photostimulatable phosphor that absorbs energy and retains a latent image when exposed to x-rays. The stored energy of the latent image is released as light when the plate is scanned by a laser in an image plate reader.⁴ The light produced is measured and digitized, yielding an image that can be subjected to contrast and spatial frequency enhancement and can be stored on magnetic or optical disks, viewed on monitors, or printed on film with a laser printer (eFig 18-9). The imaging plates are erased by exposure to light and may be reused almost immediately.

The resolution of digital images depends on the matrix size used. Spatial resolution is less than that of film-screen combinations (2.5 to 5 line pairs/mm), depending on the size and type of plate used to capture the image.¹ The unit can be set to perform automatic processing by preprogramming parameters for certain examinations or may be postprocessed manually by the radiologist to enhance various specific image features.¹⁴ The contrast scale can be altered, and the optical density of the entire image, or of various areas, can be changed. Edge enhancement can be obtained by amplifying high frequencies to visualize minute pulmonary detail. For the thorax, the automatic processing can be preset to produce a pair of images: one resembling a

conventional film-screen radiograph and the other exhibiting varying amounts of edge enhancement (eFig. 18-10).

An obvious advantage is that the images can be immediately transmitted electronically and viewed at a workstation in the emergency department, ICU, operating room, or other area where online viewing is required.^{1,3} Because the images are stored electronically, they may be recalled for comparison with subsequent studies, and they may be printed for conventional display at any time. High-resolution display units (2000-line) allow displayed images with excellent spatial resolution.

Clinical Efficacy

A large number of studies have compared digital imaging systems with conventional film-screen radiographs in both measured physical performance and interpretive accuracy. It is generally agreed that the denser portions of the thorax and the lung in front of or behind these dense areas are seen

significantly better with digital systems. There is disagreement concerning visualization of fine lung detail, line shadows, pneumothoraces, and interstitial lung disease.¹⁵⁻¹⁹ An important consideration is that digital recording systems have a very wide exposure latitude, and adequate images can be obtained with a wide range of exposures, which reduces the need for repeat imaging.⁴

Factors other than image quality have played a preeminent role in the dissemination of digital techniques. Among these are immediate availability of the images, ease of storage and retrieval, interaction with hospital electronic information systems, and cost of film and file room operation. CT, MRI, ultrasonography, and nuclear medicine studies already are digital. The completely digital imaging department is now common and will likely be ubiquitous in the near future. Digital imaging also enables the use of computer-aided detection techniques, particularly in the setting of mammography, chest radiography, and chest CT.¹

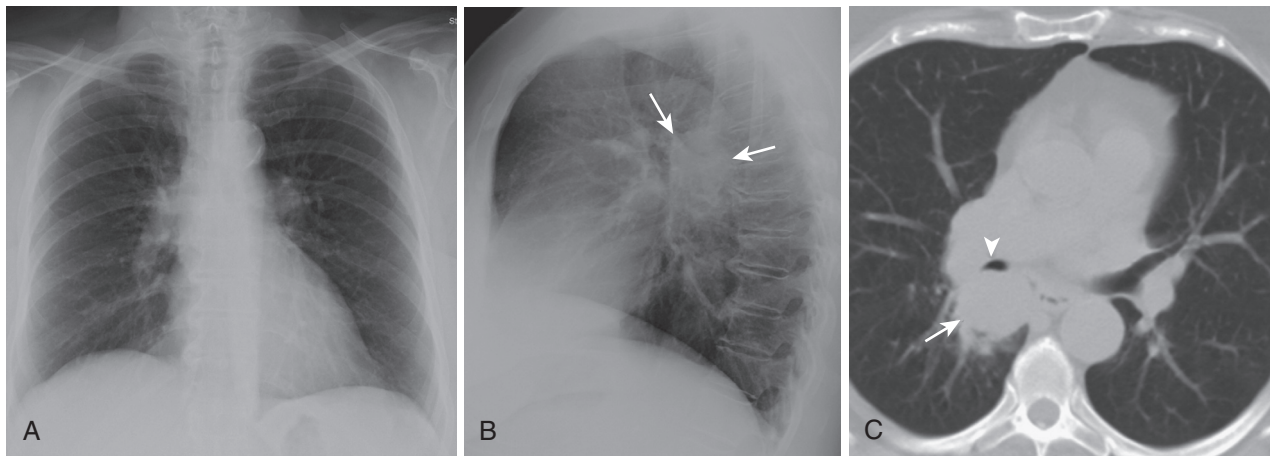


Figure 18-2 The utility of the lateral radiograph. **A**, The posteroanterior radiograph shows no specific abnormalities. **B**, The lateral radiograph identifies a mass (arrows) projected over the hilum. **C**, Axial chest CT confirms the presence of a mass (arrow) in the right lower lobe posterior to the bronchus intermedius (arrowhead). The lesion was found to represent bronchogenic carcinoma. (Courtesy Michael Gotway, MD.)

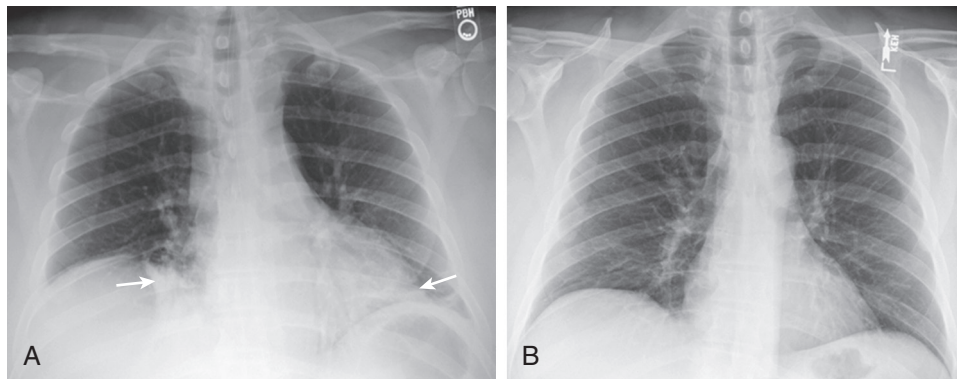


Figure 18-3 Comparison of radiographic appearances of thorax between expiratory and inspiratory radiographic techniques. **A**, Frontal chest radiograph performed with expiratory technique shows basal opacities (arrows) bilaterally. The mediastinum is wide, and the heart size is difficult to assess. **B**, Repeat frontal chest radiograph performed at full inspiratory volume made shortly following (**A**) now shows clearing of the basal opacities; the heart size is clearly normal and the mediastinum now shows normal width. (Courtesy Michael Gotway, MD.)

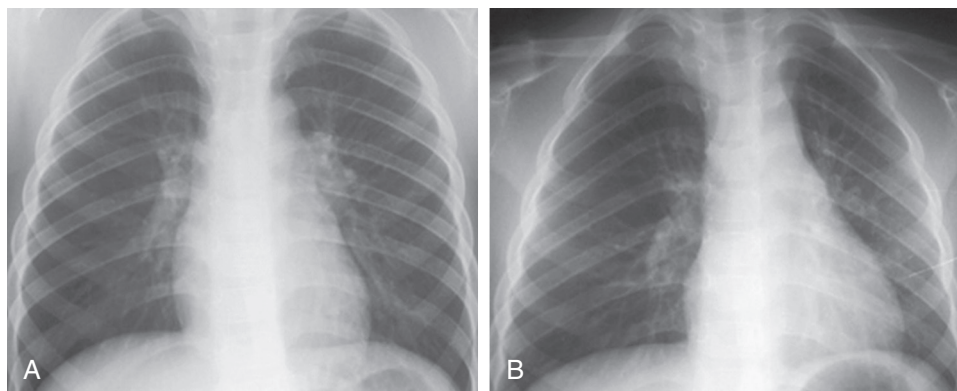


Figure 18-4 Unilateral hyperlucent lung in an 8-year-old boy with a foreign body in the right main-stem bronchus. **A**, The inspiration radiograph shows mild hyperlucency of the right lung. **B**, The expiration film shows that the right hemidiaphragm remains fixed in a low position, the right lung remains lucent, and the mediastinum is shifted to the left (air trapping). A foreign body was removed. (Courtesy Michael Gotway, MD.)

essentially unchanged in size, thus occupying a greater proportion of the deflated hemithorax, thereby being outlined more clearly by denser pulmonary parenchyma (Fig. 18-5).

Other causes of localized or unilateral lucency on the radiograph are differentiated from air trapping by the

expiratory study. Among these are technical causes such as patient rotation (eFig. 18-11), miscentered x-ray beam or grid, and “the anode-heel effect,” an artifact of asymmetrical generation by the anode of the x-ray tube. Chest wall abnormalities, either congenital or postsurgical (Fig. 18-6),

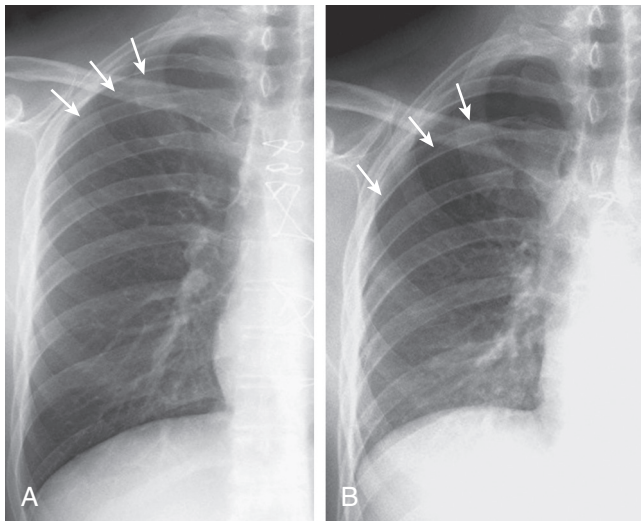


Figure 18-5 Inspiration and expiration chest radiography of pneumothorax. **A**, On the inspiratory image, the right pneumothorax is difficult to visualize but is faintly seen in the right upper thorax (arrows). **B**, On the expiratory image, the right pneumothorax (arrows) is outlined against denser lung and appears larger than on the inspiration (**A**) study. (Courtesy Michael Gotway, MD.)

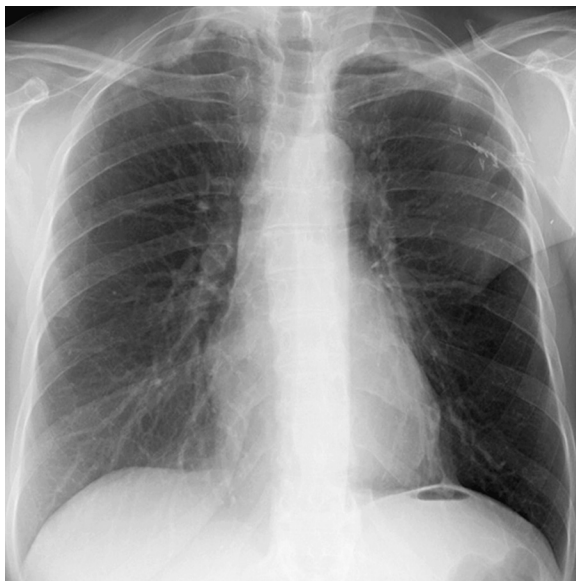


Figure 18-6 “Unilateral hyperlucent lung” simulating air trapping. Frontal chest radiograph shows lucency throughout the left thorax compared with the right, simulating air trapping (compare with Fig. 18-4B). Note, however, that the left thorax shows neither abnormally increased (unlike Fig. 18-4B), nor decreased, lung volume. The left axillary surgical clips are a clue to the cause of left lung hyperlucency: left mastectomy for previous breast malignancy. The removal of left thoracic soft tissue creates less tissue density along the path of travel of the x-ray photons through the patient’s left side relative to the right, resulting in relative lucency of the left thorax compared with the right. (Courtesy Michael Gotway, MD.)

can produce unilateral lucency. Undetected areas of atelectasis with compensatory overexpansion of portions of the lung and primary vascular disease, such as pulmonary embolus (see eFigs. 57-7 and 57-9), may also produce lucency. None of these causes of pulmonary lucency will show trapped air on the expiratory radiograph.

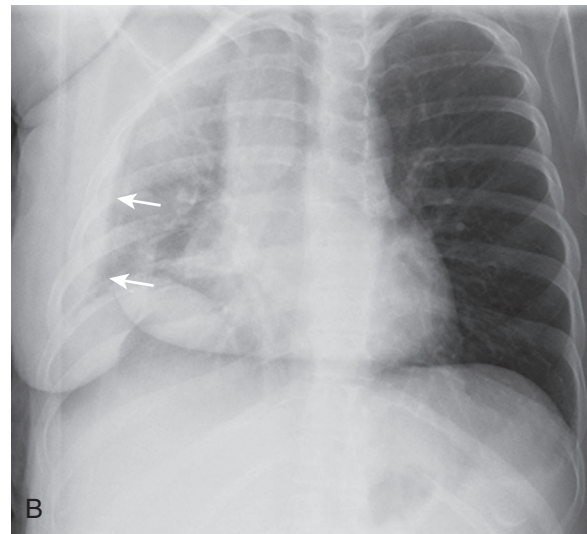
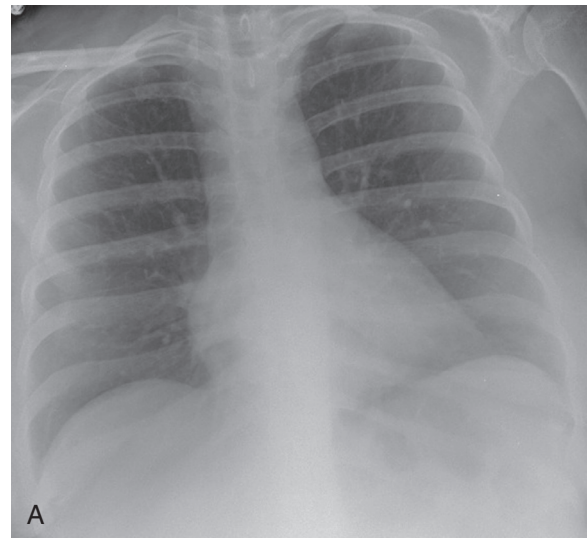


Figure 18-7 The value of decubitus radiography. This patient had right pleuritic chest pain. **A**, A frontal chest radiograph shows no specific abnormalities; the right costophrenic angle is sharp. **B**, A right lateral decubitus radiograph shows a small right pleural effusion (arrows). Note that decubitus imaging causes collapse of the ipsilateral lung. (Courtesy Michael Gotway, MD.)

Decubitus Views

Decubitus radiography is performed by placing the patient in the recumbent position, usually lying on one side and then the other. The x-ray exposure is made with a horizontal beam in either the AP or PA projection.

The technique is useful for determining the presence or absence of free fluid in the pleural space or parenchymal cavities, for estimating the size of effusions, and for diagnosing pneumothorax in patients who are unable to sit or stand. Free fluid gravitates to the dependent portion of the thorax, which in the decubitus patient lies against the lateral rib cage of the dependent hemithorax (Fig. 18-7) or the mediastinum of the contralateral side; pneumothorax behaves in the opposite fashion. In the typical AP supine chest radiograph, free fluid will layer posteriorly and manifest as an increase in density involving the entire hemithorax. Air within the pleural space will collect anteriorly and is often difficult to detect. The proper use of decubitus

radiography will demonstrate the presence of free fluid, pneumothorax, or both (Figs. 18-8 and 18-9). When a portable study must be performed with the patient in bed, it may be technically difficult to obtain high-quality radiographs of the dependent portion of the hemithorax due to the underlying bed, clothes, or other inconveniences. For this reason, bilateral decubitus studies may be obtained. Even in patients in whom PA and lateral erect radiographs can be performed, subpulmonic effusions may be difficult to detect, and no fluid meniscus may be visualized. Unless the fluid is completely loculated, a decubitus study will demonstrate its presence and size (see Fig. 18-9). As little as 20 mL of fluid can be seen in the decubitus position.

Lordotic Views

Radiographs made in the lordotic position can be of value in demonstrating lesions in the immediate subclavicular region or partially hidden by the clavicle (eFig. 18-12). This is particularly true if these lesions are located posteriorly. In the lordotic view, which is most frequently obtained in the AP projection, the clavicle, being an anterior structure, is projected above the lung apex, and the subclavicular lung regions are well visualized (see eFig. 18-12). The lordotic view may also be used to confirm middle lobe or lingular atelectasis. A lordotic view centered over the lower portion of the chest will project the atelectatic lobe or segment so

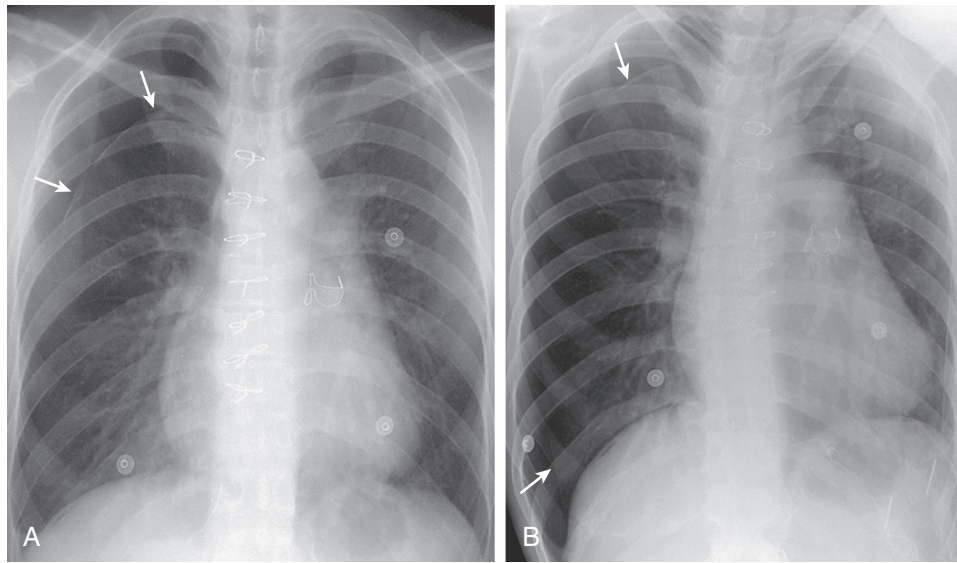


Figure 18-8 Comparison of pneumothorax appearance at upright and lateral decubitus chest radiography. **A**, Upright inspiratory frontal chest radiograph shows the typical appearance of a pleural line (arrows) over the apex of the right lung, representing pneumothorax. **B**, Left lateral decubitus chest radiograph shows the gas in the pleural space has migrated in a nondependent fashion over the entire peripheral right thorax, creating a pleural line (arrows) over both the apical and costophrenic regions. (Courtesy Michael Gotway, MD.)

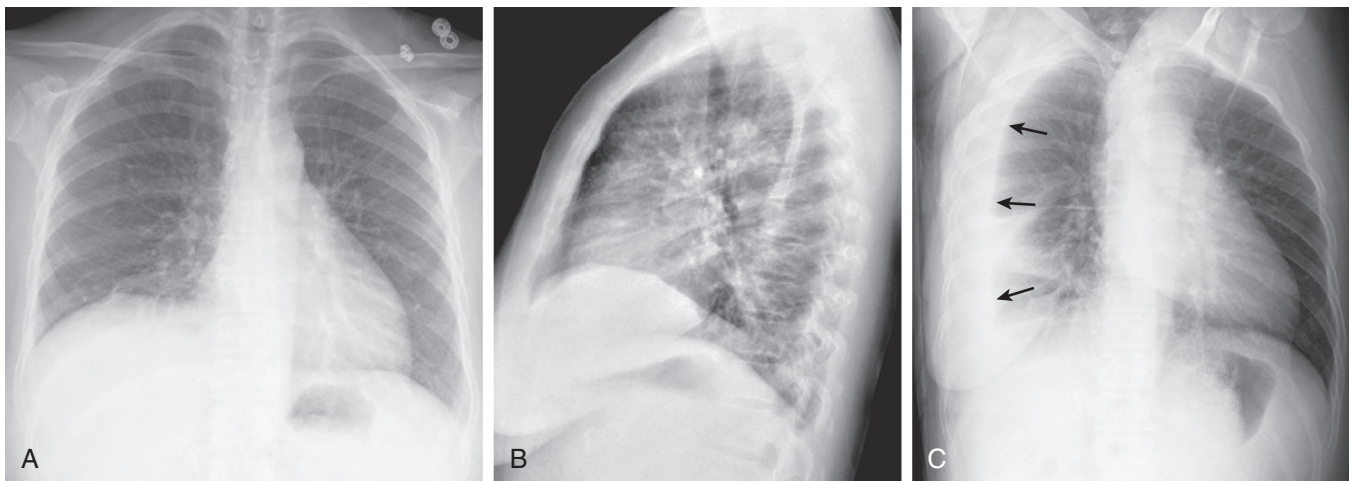


Figure 18-9 The value of decubitus radiography in a patient with right thoracic pain. **A**, Frontal chest radiograph shows apparent elevation of the right hemidiaphragm, but the right costophrenic angle is sharp. **B**, Lateral chest radiograph reveals obscuration of the posterior portion of the right hemidiaphragm, but a clear meniscus indicating right pleural effusion is not seen. **C**, Right lateral decubitus radiograph reveals the presence of a large, free pleural effusion (arrows). The apparent elevation of the hemidiaphragm on the conventional posteroanterior and lateral radiographs is due to subpulmonic effusion. (Courtesy Michael Gotway, MD.)

that it directly faces the x-ray beam, and it will be easily visualized as a dense triangular shadow.

Oblique Views

Occasionally, shallow oblique views are valuable in sorting out superimposed shadows and in visualizing pulmonary parenchymal opacities obscured by superimposition from the heart, mediastinum (eFig. 18-13), or portions of the bony thorax. In general, it is more rewarding to study these opacities with CT.

FLUOROSCOPY

Fluoroscopy at one time was commonly employed either as the primary method of radiologic examination of the chest or as an adjunct study to standard radiographs. Its use over the past several decades has diminished considerably. However, there remain a few situations in which fluoroscopy can provide information that is difficult to obtain by other means, such as for the detection of abnormalities of diaphragmatic motion that result from conditions affecting the phrenic nerve (Video 18-1). The major use of chest fluoroscopy in current medical practice is as a guide for interventional procedures such as catheter angiography and needle or transbronchial biopsies.

An expanded discussion of different radiographic modalities and technique is available online at ExpertConsult.



COMPUTED TOMOGRAPHY

PHYSICAL PRINCIPLES

CT is based on the precise measurement of attenuation of a thinly collimated x-ray beam. Differential x-ray beam attenuation by different tissues forms the basis of image contrast on CT images. The advantages of CT are its axial tomographic (“slicelike”) format and its high sensitivity to differences in density between different tissues.

To obtain CT images, x-rays—produced by a modified standard x-ray tube—are passed through the patient, and the transmitted photons are measured by a series of x-ray detectors. The detectors produce an electric current that is proportional to the intensity of the incident x-ray beam. The strength of this current is measured and digitized by an analog-to-digital converter and thus is available for computer manipulation. The reduction in the intensity of the beam as it passes through the patient’s body is termed “attenuation” and is due to scattering and absorption of the x-ray photons by tissue. The attenuation (more precisely, the linear attenuation coefficient) of each point within the body can be calculated by the scanner’s computer, provided that multiple measurements of x-ray attenuation can be made from different angles. The details of the x-ray beam and detector motion by which these multiple measurements are obtained vary considerably among scanners.

Spiral, or helical, CT scanners, and more recently, multislice CT scanners, use a continuously rotating gantry (containing the tube and detector array) and are capable of imaging the entire thorax in a single breath-hold.

Because the x-ray attenuation measurements are stored in the computer, the image can be enhanced or manipu-

lated mathematically with specific reconstruction algorithms. For example, the technique of *high resolution CT* (HRCT) combines narrow collimation and image reconstruction with a high-spatial-frequency algorithm to produce increased sharpness in the final stage.

IMAGE DISPLAY

The reconstructed CT image is made up of a matrix of picture elements or “pixels.” The x-ray attenuation of each pixel is normalized to that of a test object containing pure water. The CT number is the ratio of tissue attenuation minus water attenuation relative to water attenuation multiplied by 1000 and is expressed in *Hounsfield units* (HU). The CT number for normal lung ranges from −700 to −900 HU, whereas soft tissues have CT numbers ranging from −100 (fat) to +100 HU (blood clot), with water measuring 0 HU and most soft tissues in the 20 to 60 HU range. The range of CT numbers encountered in patients is approximately 2000, ranging from −1000 (air) to +1000 (bone). However, although the computed image contains 2000 number levels, which could correspond to 2000 shades of gray, the human eye can perceive only about 16 to 20 distinct shades of gray. It is thus necessary when displaying CT images to restrict the image display to a small fraction of the actual range of attenuation values.

This restriction is done first by combining similar CT numbers into a single gray shade and second by setting the window width and window level display settings. The window *width* is the range of densities that will be displayed as shades of gray; all higher pixel values are shown as white, and all lower ones are shown as black. The window *level* is simply the median pixel value about which the display range is centered. Thus, to view the lungs, an appropriate window level is −700 HU, with a window width of approximately 1200 HU, which may be adjusted depending on user preference. For viewing soft tissues, pleural space, mediastinum, or hila, a window level of 20 to 40 HU with a width of approximately 400 HU is preferred. These are usually referred to, respectively, as “lung window” and “mediastinal or soft-tissue window” settings, and both should be displayed for a chest CT study.

SPIRAL AND MULTISLICE COMPUTED TOMOGRAPHY

The terms “spiral” and “helical” CT are essentially equivalent; they refer to the path the rotating x-ray beam describes as a result of its continuous rotation around the longitudinal axis of the patient as the patient is transported through the CT gantry on a continuously moving table. In many patients, the entire thorax can be scanned during a single breath-hold. Spiral CT has the advantages of (1) volumetric imaging, which ensures contiguous image reconstruction and allows multiplanar or three-dimensional reconstructions to be performed; (2) more rapid scanning; and (3) more rapid contrast infusion with denser opacification of vessels.

Volumetric CT refers to the ability of modern CT scanners to acquire scan data continuously between two points (in the thorax, typically from the cervico-thoracic junction to the diaphragm), rather than, as with older CT technology,

BRONCHOGRAPHY

Contrast bronchography, formerly a fairly common thoracic examination, has been replaced by fiberoptic bronchoscopy and either CT or *high-resolution computed tomography* (HRCT) of the lung. In patients with suspected bronchiectasis, HRCT and CT are as sensitive and are safer, more easily obtained, and much more pleasant to undergo than bronchography.

PULMONARY ANGIOGRAPHY

Pulmonary angiography has traditionally been employed primarily for the detection or exclusion of pulmonary embolism (eFig. 18-14; see Figs. 57-7, 11, and 16, **Video 18-2**). Although it has been traditionally regarded as the “gold standard” for making the diagnosis of pulmonary embolism, it has limitations and tends to be underutilized.²² Other situations in which pulmonary angiography has been employed include the diagnosis and embolization of pulmonary arteriovenous malformations (eFig. 18-15; see Fig. 19-14; and Chapter 61), pulmonary arterial foreign body retrieval, pulmonary vasculitis (eFig. 18-16; see Chapter 60), and occasionally, the delineation of the anatomy of pulmonary vessels before lung surgery. The study is performed by rapidly injecting intravenous contrast material through a catheter and imaging the lung while the contrast material traverses the arteries and veins. Most frequently, the catheter is inserted into the femoral vein percutaneously and then guided into the pulmonary artery under fluoroscopic control.

Angiograms may be done with the catheter in a main branch of the pulmonary artery or more selectively in distal vessels. The radiographic contrast material is injected at the rate of approximately 10 to 25 mL/sec, depending on the vessel size. The volume of contrast depends on the location of the catheter. Between 40 and 60 mL of contrast material is usually injected into the right or left main pulmonary artery; half this amount of contrast is needed with digital subtraction techniques. Selective injections made within the more distal pulmonary arteries require smaller volumes. If the angiogram is performed for the detection or exclusion of pulmonary embolism after an abnormal but nondiagnostic perfusion scan, the location of the perfusion defect on the scan may act as a “road map” for the angiographer, and selective or superselective injections proximal to the area of perfusion deficit may be performed.

Unless the angiogram is done with a balloon occlusion technique, serial recording is necessary. In the past, rapid film changers were used with an exposure rate of 3 or 4/sec, but such “cut-film” techniques have been replaced by digital subtraction angiography. Filming is usually carried out for several seconds after injection to permit visualization of the pulmonary veins, the left side of the heart, and the thoracic aorta.

It is frequently necessary to image in several different projections to confirm or exclude pulmonary embolism. Oblique or lateral projections may be desirable. If the angiographic suite contains biplane equipment, the number of necessary contrast material injections can be diminished by imaging in two orthogonal planes after a single injection of contrast medium. Magnification angiography may show

emboli in vessels that are too small to be seen clearly on standard studies.

For a definite diagnosis of pulmonary embolism, it is necessary to visualize the embolus as either a filling defect (see eFig. 18-14) within a vessel or the trailing edge of a thrombus. Other abnormalities should not be regarded as diagnostic of embolism.

Complications and death are rare, fortunately. Significant complications are seen in less than 5% of patients, and 0.1% to 0.5% of patients die undergoing angiographic studies to evaluate suspected pulmonary embolism.²³ Minor arrhythmias are not infrequent when the catheter tip traverses the right ventricle. Ventricular fibrillation has been reported, as has refractory shock. Electrocardiographic monitoring and immediate availability of defibrillating equipment are mandatory. Reactions to contrast material are most frequently minor and primarily consist of urticaria and vasovagal responses. However, patients can occasionally suffer major reactions, with bronchospasm and cardiopulmonary collapse. Renal failure after administration of iodinated contrast material is a well-recognized complication, and preexisting renal disease manifested by elevated serum creatinine levels represents a relative contraindication to angiography. In all circumstances, the amount of contrast material injected should be the minimum required to produce diagnostic opacification of the pulmonary vessels. The use of nonionic or low-osmolar contrast material diminishes the number of minor reactions and increases patient comfort during the procedure. It is now routine in most practices.

AORTOGRAPHY AND BRONCHIAL ANGIOGRAPHY

Aortography is generally accomplished by the retrograde passage of a catheter from the femoral artery to the aorta or its branches after percutaneous insertion (eFig. 18-17). The study of the aorta and its branches plays a limited role in diseases of the lung. The imaging modalities of choice for diagnosing suspected aortic abnormalities, including aortic dissection, are CT, MRI, and, in acute cases, transesophageal ultrasonography; aortography is seldom required. The diagnosis of pulmonary sequestration once depended on the demonstration of anomalous systemic blood supply by aortography but, in modern practice, chest CT aortography and *magnetic resonance angiography* (MRA) are often diagnostic and easily demonstrate the abnormal vascular supply (eFig. 18-18). Patients with severe hemoptysis may require bronchial arteriography and embolization of the bronchial artery or arteries supplying the bleeding site (eFig. 18-19). These studies require selective catheterization of the bronchial arteries. Angiographic technique is, for the most part, individualized to fit the particular clinical condition being studied.

Angiography can be performed with a technique termed “digital subtraction angiography.” With digital subtraction angiography, an early image from the angiogram is recorded with an image intensifier and a high-resolution television camera and is digitized and stored. A later image in which vessels are opacified is handled in a similar manner. The first image is then subtracted from the second, and the resulting image is displayed. The background body structures are

subtracted, leaving an image of the contrast-filled vessel (see [eFigs. 18-17](#) and [18-19](#)). Because the body background does not obscure the final image, angiography can be accomplished with smaller amounts of contrast than otherwise necessary. Motion of structures in the area being studied may make subtraction of images difficult.

ULTRASONOGRAPHY

Ultrasonography, which is also discussed in Chapter 20, has limited usefulness in thoracic imaging because the ultrasound beam is reflected at the air-soft-tissue interface around the lungs, but some specific uses have been recognized.²⁴⁻²⁶ It is useful for studying vascular, cardiac, and some mediastinal abnormalities, for the localization of pleural fluid and air collections, and for directing interventions (see Fig. 19-3). Transesophageal sonography can allow imaging of some mediastinal structures and is often performed to assess the thoracic aorta and heart. The use of ultrasonography in lung imaging is largely limited to the pleura and immediate subpleural areas or to areas of consolidated lung or masses contacting (see Fig. 19-3) or invading the chest wall. It is most commonly utilized for the detection, localization, and characterization of pleural effusions and to guide thoracentesis ([eFig. 18-20](#)).

Ultrasonography is also valuable in differentiating effusion from pleural thickening. Effusion is usually anechoic or hypoechoic, whereas pleural thickening results in an echogenic stripe within the enclosing rib margin. When free-flowing or layering fluid is not demonstrated on decubitus radiographs in the presence of a thickened pleural stripe, ultrasound study may show collections of loculated

fluid surrounded by pleural adhesions. Septations may be visualized within pleural collections, and their shape may change during the breathing cycle, confirming the presence of low-viscosity fluid. A complex echogenic fluid collection indicates the presence of exudate, empyema, or hemothorax, but an echo-free collection does not exclude these diagnoses. Ultrasound is also effective in differentiating subphrenic fluid from pleural effusion because the two hemidiaphragms are excellent reflectors of the ultrasound beam and therefore provide a visible boundary distinguishing intrathoracic from subdiaphragmatic spaces ([eFig. 18-21](#)). The presence of a hypoechoic area caudal to the echogenic diaphragmatic stripe but cranial to the liver or spleen indicates ascites.

Ultrasound-guided thoracentesis is frequently performed when loculated fluid is suspected or after attempts at thoracentesis have failed.²⁷ The use of real-time equipment permits the performance of this procedure at the bedside (see [eFig. 18-20](#)). After locating the apparent fluid collection, the appropriate depth to which the needle should be inserted is displayed on the screen, and the aspiration is performed in the usual manner. Placement of catheters for drainage can be accomplished in a similar fashion.

Pleural neoplasms, mediastinal masses, or parenchymal masses that abut the pleural surface may be biopsied under ultrasonic guidance (see Fig. 19-3), provided that no aerated lung intervenes between the lesion and the pleura. The tip of the needle can be guided and identified within the mass, thus confirming appropriate placement before aspiration or biopsy.²⁸ However, CT (see Figs. 19-1, 2, and 6) or fluoroscopic guidance is more frequently employed for this purpose.

using a “stop-and-shoot” method. With the latter technique, individual image “slices” could be summed to create a volume of imaged tissue but were limited by misregistration between the individual image slices, particularly between successive individual breathholds. Owing to the rapid acquisition times of modern CT scanners, the entire thorax can now be imaged completely in a *single breathhold*, leading to a single “block” of tissue data that can be reconstructed into practically any desired slice thickness and imaging plane desired.

Multislice CT (MSCT) markedly improves on the advantages offered by single-slice spiral CT. MSCT scanners acquire information using *multiple channels* during a single tube rotation, thereby dramatically increasing the data acquisition rate. Current MSCT scanners may acquire up to 320 images per tube rotation for a given collimation, whereas routine single-slice spiral CT scanners would only acquire 1 image per tube rotation for a similar collimation. The speed advantage of MSCT scanning is obvious, and this tremendous speed allows for rapid imaging of large volumes of tissue in practically any phase of intravenous contrast enhancement. The image data sets provided by MSCT scanners also allow for improved-quality reformatted images (eFig. 18-22, Videos 18-3 and 18-4). Furthermore, the imaging data acquired with MSCT scanning allow for “retrospective reconstruction” of narrow section images (e.g., “thin sections” or “high-resolution” images) following scan completion.

With MSCT, the ability to reconstruct narrow section images retrospectively has transformed the process of nodule characterization. In the era of single-slice CT scanning, when narrow section imaging was used to characterize a pulmonary nodule, particularly by the detection of calcium or fat within the nodule, either the patient would

be held within the department and the radiologist contacted to review the scan to determine if narrow section imaging was required (with the associated detrimental effect on departmental throughput), or the patient would be called back at a later time for further imaging (with the associated patient and referring physician inconvenience). With MSCT scanning, CT protocols that acquire narrow sections (often on the order of 1 mm or less) are devised but are reconstructed using wider sections (often 5 mm) for routine interpretation, which allows for optimized computer performance and data handling; however, the narrow sections have been acquired and are available for review, if needed. In the foregoing example, if narrow sections are needed for pulmonary nodule characterization, the narrow section data may be retrospectively reconstructed and reviewed (Fig. 18-10). In fact, many radiology departments prospectively reconstruct both wider section widths for routine viewing and narrow section widths for specialized applications and save both series to the picture archiving communication system; such an approach strikes an excellent balance between the need for smaller data sets to facilitate routine data handling, while still allowing for specific questions to be addressed later through the use of thin-section imaging without reimaging the patient.

COMPUTED TOMOGRAPHY SCAN PROTOCOLS

CT scans are obtained with different parameters, depending on the indication for the examination (Table 18-1). Variables include scanning range, patient position, scan section thickness, table transport speed/pitch, and intravenous contrast injection rate, timing, and volume. These parameters are briefly reviewed later. The influence of table transport speed/pitch on CT protocols has evolved with the

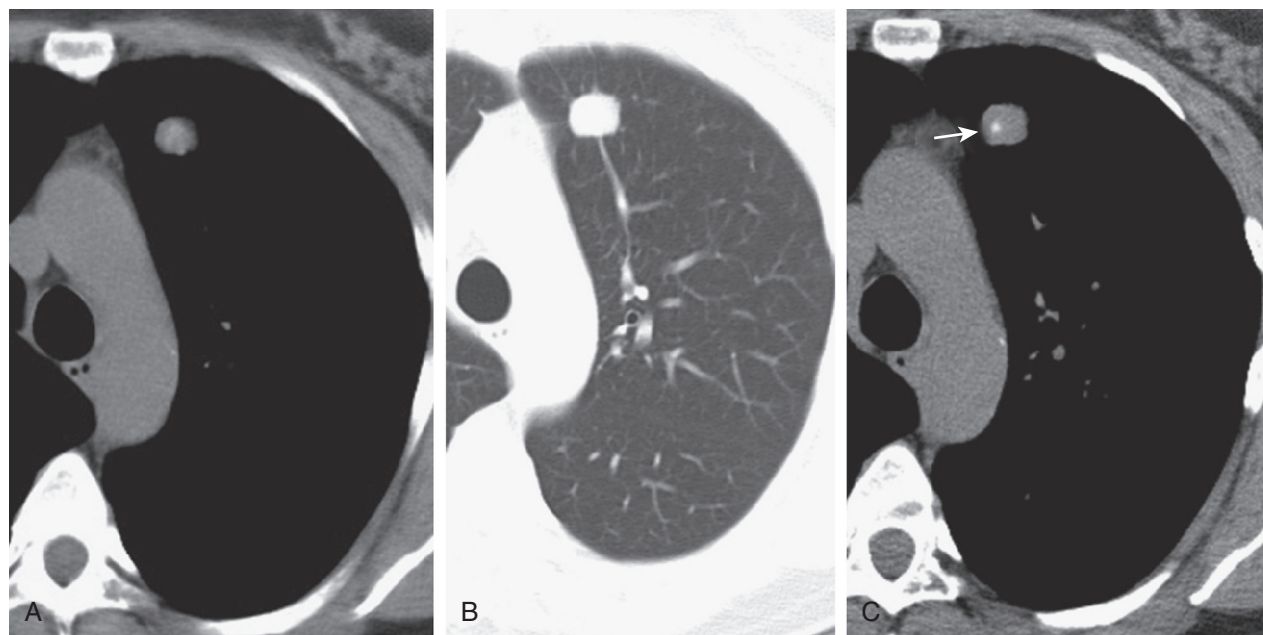


Figure 18-10 Volumetric multislice CT imaging of a pulmonary nodule detected at chest radiography. **A**, “Routine” axial 5-mm CT image shows a soft-tissue nodule in the left upper lobe. Vaguely increased attenuation is seen within the nodule, suggesting calcification, but the finding is not well seen. **B**, Lung window images show that the nodule is circumscribed. **C**, Retrospectively reconstructed thin-section (1-mm) soft-tissue image more clearly shows a small focus of calcification (arrow) within the lesion, suggesting a benign etiology. (Courtesy Michael Gotway, MD.)

Table 18-1 Common Chest CT Scanning Protocols and Indications

Scan Protocol	Intravenous (IV) Contrast Use?	Common Indications	Notes
"Routine" chest CT* (including spiral and multislice technology)	Possibly, depending on specific application	Initial and repeat cancer staging (may be performed with IV contrast, depending on tumor type), nonspecific chest pain, cough, or shortness of breath, pleural disease, mediastinal or chest wall mass evaluation, suspected thoracic lymphadenopathy, investigation of focal chest radiographic abnormalities, suspected infection, lung cancer screening	IV contrast injection often beneficial for suspected lymphadenopathy, pleural disease, bronchogenic malignancy staging. Employed for fever of unknown origin (often when chest radiography is unrevealing, particularly for immunosuppressed patients). Often used for evaluation before solid or hollow organ transplant to assess for asymptomatic findings that could represent malignancy. Aggressive radiation dose reduction frequently employed for lung cancer screening studies
CT pulmonary angiography	Yes	Assessment of suspected acute or chronic thromboembolic disease, pulmonary artery aneurysm, or pulmonary artery anomaly	IV contrast injection timing scaled for optimal pulmonary artery enhancement
CT aortography	Yes	Assessment of suspected aortic dissection or aneurysm	IV contrast injection timing scaled for optimal aortic enhancement
Coronary calcium scoring	No	Evaluation for presence of calcified coronary artery atherosclerosis for heart disease risk stratification	Volume of acquisition limited to heart
Coronary CT angiography	Yes	Evaluation for coronary artery atherosclerosis, aneurysm, or anomaly	Scan performed with ECG gating for motion-free images. Volume of acquisition typically limited to heart
Cardiac CT	Yes	Evaluation for congenital or acquired structural cardiac disease, pericardial disease, or assessment of specific mediastinal or lung pathology impact on heart	Scan performed with ECG gating for motion-free images. Volume of acquisition typically extended slightly beyond heart to include great vessel anatomy. Contrast injection timing may be adjusted to suit particular indications
Pulmonary vein CT	Yes	Assessment for pulmonary venous and left atrial anatomy before electrophysiologic ablation	Contrast injection timing optimized for left heart enhancement
High-resolution CT	Typically not required, although in the case of initial evaluation of suspected sarcoidosis, may be of benefit	Diffuse lung disease at chest radiography or suspected by clinical evaluation—initial diagnostic assessment, biopsy site selection, serial evaluation of treatment efficacy; small airway diseases, bronchiectasis, chronic dyspnea or progressive exercise intolerance, assessment of abnormal pulmonary functions testing, lung transplantation evaluation	Thin-section imaging with prone and postexpiratory imaging as well
Contrast-enhanced chest CT for solitary nodule evaluation	Yes	Evaluation of an indeterminate solitary pulmonary nodule (typically > 1 cm, <3 cm)	Specific, weight-based contrast injection protocol with structured timing of image acquisition to assess for nodule enhancement. Lack of nodule enhancement strongly suggests an indeterminate nodule is benign

*"Routine" chest CT section thickness (collimation) varies depending on scanner manufacturer, but typically approximates 5 mm. Narrower sections are routinely automatically obtained with modern multislice CT scanning protocols (on the order of ≤ 1 mm); however, these images may or may not be reconstructed and archived in the picture archive and communications system (PACS), depending on individual radiology departmental protocols. Even when such images are routinely reconstructed and archived to PACS, often an additional series of images employing a wider reconstruction interval (typically approximately 5 mm) is saved to PACS to facilitate day-to-day interpretation and data handling and storage efficiency.


ECG, electrocardiogram.

proliferation of MSCT scanners. Consideration of these variables is more relevant to cardiovascular imaging and is not discussed here. The interested reader is referred to excellent reviews on the topic of MSCT scan parameters and the technical aspects of MSCT scanning.^{22,23} Owing to MSCT's rapid scan capability and ability to retrospectively reconstruct narrow section data, in recent years there has been some degree of CT protocol "simplification" compared with the single-slice CT era. For example, single-slice high-resolution CT protocols previously included noncontiguous supine and prone 1-mm inspiratory scans, as well as noncontiguous supine expiratory scanning. Using such a protocol, it was not uncommon to mistake a pulmonary vessel for a lung nodule; the inability to review adjacent sections immediately cranial and caudal to the vessel, owing to the noncontiguous nature of single-slice high-resolution CT protocols, often resulted in a pulmonary vessel simulating a nodule. This high-resolution CT protocol was distinct from the "routine" single-slice CT chest protocol, employing contiguous imaging, that was required to clarify the nature of this potential abnormality. Current MSCT high-resolution CT protocols, however, employ contiguous 1-mm supine imaging routinely, supplemented with noncontiguous 1-mm prone inspiratory and supine expiratory imaging, thus alleviating the difficulties associated with noncontiguous imaging techniques while simultaneously maintaining the benefits of thin-section imaging in the characterization of diffuse lung diseases.

Scanning Range

In most instances, a chest CT study should encompass the entire thorax, from the lung apices to the posterior costophrenic angles. This is easily accomplished in a matter of a few seconds with MSCT. In patients with lung cancer, chest CT done for staging purposes may include the adrenal glands and liver, although the liver acquisition should be timed properly to obtain images in the correct phase of liver enhancement. In practice, lung cancer staging studies are typically performed as dedicated examinations of the entire chest, abdomen, and pelvis.


Patient Position

Normally, patients are scanned in the supine position. However, decubitus positioning or prone positioning may be used to elucidate whether pleural fluid collections are free or loculated, to distinguish dependent atelectasis from parenchymal fibrosis, or to position lung lesions optimally for biopsy. Images are normally obtained at total lung capacity to obtain maximum air-tissue contrast and to spread anatomic structures and lesions over a larger area, thus minimizing volume averaging. Prone images are usually obtained with HRCT studies. Technical advances now permit the acquisition of CT images during, rather than after, forced expiratory vital capacity maneuvers (see  [Videos 106-1 to 3](#)).

Scan Section Thickness

In the era of single-slice spiral CT, the thickness of an individual CT section was set to a predetermined value before scanning by setting the x-ray beam to a certain thickness: a process referred to as "collimation." Typical slice thicknesses for single-slice spiral CT ranged from 1 to 10 mm,

with 5- to 7-mm collimation employed for most "routine" chest CT applications. With the development of MSCT systems, although various collimation choices are still possible, most MSCT protocols employ certain detector configurations that either favor narrow detector width (to promote optimal spatial resolution) or wider detector widths (to facilitate rapid volume of coverage). As systems with greater numbers of detectors are developed, the choice of high spatial resolution at the expense of volume of coverage and total length of exposure—an age-old compromise in the era of single-slice spiral CT—is becoming less of a quandary. Modern MSCT systems now allow the entire thorax to be scanned with a narrow detector configuration (1 mm) in a matter of a few seconds. Once such images are acquired, they may be combined in various ways for optimal viewing. For example, a chest CT study obtained on an MSCT system with detector elements arranged in a manner resulting in 1-mm detector configuration would produce several hundred 1-mm images for the thorax of an averaged-sized patient. However, these 1-mm images can be "combined" to generate 5-mm images, and these images can be displayed for routine review; this results in about 50 to 70 images for a typical chest CT. Should the radiologist desire to view the high-resolution, 1-mm images, these images can be reconstructed from the original dataset as long as the original scan data are saved. For example, with single-slice spiral CT scanners, frequently the patient would need to return for additional thin-section (narrow-collimation) imaging to characterize any nodules encountered at the examination. The only way to avoid bringing patients back in this setting was to keep the patient on the scanner while the study was reviewed, but this approach seriously decreases scanner throughput. Even if the patient were held during the scan review, additional nodule characterization with single-slice CT would require repeat scanning with narrow collimation to detect fat or calcium within the nodule, which requires additional radiation exposure. With MSCT, when a nodule is recognized on a study, images may be reconstructed according to the narrowest detector configuration to accomplish this goal long after the patient has left the scanner, without the need for additional scanning.

An additional benefit realized by the development of MSCT is the ability to image using isotropic voxels. The term *isotropic voxel* indicates that the resolution of the scan in the x-, y-, and z-planes is equal. In other words, MSCT scanning using isotropic voxels allows the CT data to be reconstructed in any plane with resolution equal to that of the axial scans. Most single-slice CT examinations did not possess this capability, and therefore nonaxial reformatted images suffered from degraded quality compared with that of the axial scans. MSCT's ability to scan using isotropic voxels allows creation of images in any desired plane that are equal in resolution to the axial scans (see [eFig. 18-22](#), [Videos 18-3](#) and [18-4](#))—this multiplanar capability was previously an advantage enjoyed by MRI and ultrasound over CT. 

Contrast Enhancement

The injection of intravenous iodinated contrast material during chest CT is important in many situations. Administration of contrast material is not routine except for the diagnosis of vascular abnormalities such as aortic dissection, aneurysm, pulmonary embolism, when using

a specific protocol in selected patients with pulmonary nodules, or for examinations performed for lung cancer staging or assessment of pleural or chest wall diseases. If possible, iodinated contrast materials are avoided because they are expensive and associated with a small but definite risk of serious reactions and toxicity. Although contrast infusion can be helpful in distinguishing vessels and soft-tissue masses in the mediastinum and hila, it is not considered necessary for diagnosis by all radiologists. For routine CT of the lungs (e.g., to rule out metastases), contrast material is rarely required.

Nonionic and low-osmolar contrast materials have proved to have a lower incidence of adverse reactions than high-osmolar agents.²⁴ Patients with a prior history of contrast reaction should be treated with extreme care because they are at higher risk for subsequent serious reactions, particularly those rare patients that have experienced contrast reactions despite proper premedication with corticosteroids and antihistamines.^{24,25} If vascular pathology is of interest in such patients, MRI is the preferred modality. If CT with contrast enhancement is necessary, pretreatment with corticosteroids is advisable. Iodinated contrast media reactions (“radiographic contrast-medium-induced leukostasis”) is discussed in Chapter 71.

The technique of intravenous contrast material administration is important. Peak opacification of vascular structures is desirable. To achieve this, a bolus of contrast material must be administered, preferably via a calibrated mechanical injector, and the area of interest must be scanned rapidly during the initial transit of the contrast agent. Timing of the delivery of intravenous contrast should be adjusted to the organ system of interest. For example, chest CT protocols designed for the detection of pulmonary embolism generally use rather short delays from the time of the beginning of contrast injection to the start of imaging (usually ≤ 20 sec), whereas chest CT protocols designed for the evaluation of aortic dissection generally use slightly longer contrast injection delays.

MEDICAL IMAGING AND RADIATION

The major drawback of the increased utilization of CT is radiation exposure. In 1980–1982, radiation from medical imaging accounted for approximately 18% of the per-capita effective radiation dose in the United States, but this value increased to 54% by 2006, due largely to increased radiation doses resulting from CT scanning and, to a much lesser extent, nuclear medicine procedures. It was recently reported that CT represents about 17% of all radiologic procedures in the world but accounts for more than 40% of the collective dose.³² Given the continued increased use of CT since 2006, it is likely that these numbers are now even greater.²⁶



Additional material regarding radiation exposure from medical sources is available online.

Approximate effective doses (scanner outputs) for CT are given in Table 18-2 and compared with nonmedical radiation exposures.²⁹ Of note, the values given are representative measurements but, in fact, there is a wide range of exposures dependent on CT technique and method of estimation. Also, indications such as pulmonary embolism, which require narrower sections, may involve a relatively

Table 18-2 Typical Radiation Doses Associated with Background Sources and Common Thoracic Imaging Applications and Environmental Exposures

Radiation Exposure	Effective Dose (mSv)
U.S. annual per-capita effective radiation dose 2006 (background/medical/total)	2.4/3.0/5.6 ³²
Posteroanterior chest radiograph*	0.02 ²⁹⁸
Ventilation/perfusion scan*	1.4–2 ^{298,299}
Standard chest CT	5–8 ^{298,299}
“Low-dose” chest CT	2
High-resolution chest CT (1-cm noncontiguous intervals)*	1
Catheter pulmonary angiography*	2.3–4.1
Whole-body PET*	14 ²⁹⁹
Coast-to-coast U.S. flight (≈ 3000 miles)†	0.03
Living near coal-fired power plant†	0.0003
Proximity to x-ray luggage inspectors	0.00002
Living within 50 miles of a nuclear power plant†	0.00009
Living in Denver for 1 year	1.8
Airport backscatter device	0.000015–0.00088 ³⁰⁰
Smoking, 1 year‡	2.8

*Values may vary according to individual equipment manufacturers, patient size, duration of study, use of dose-reduction techniques, and individual institutional protocols.

†Data from <http://www.ans.org/pi/resources/dosechart/>

‡Data from <http://web.princeton.edu/sites/ehs/osradtraining/backgroundradiation/background.htm>

CT, computed tomography; PET, [¹⁸F]fluoro-2-deoxy-D-glucose PET. Additional comparisons are available in McCollough CH, Guimaraes L, Fletcher JG: In defense of body CT. *AJR Am J Roentgenol* 193(1):28–39, 2009.

greater amount of radiation exposure compared with “standard” chest CT protocols. In recent years, concerted efforts to curtail medical radiation exposure have resulted in a number of advances that have significantly reduced the amount of radiation delivered to the patient, chiefly through reduction of CT-related exposures. A thorough review of these methods is beyond the scope of this brief discussion but includes increasing public and provider awareness through efforts such as the “ImageGently” campaign conducted by the Alliance for Radiation in Safety in Pediatric Imaging and the ACR’s “ImageWise” (radiation safety in adult medical imaging) effort; technical advances in CT scanner equipment (new reconstruction algorithms and automated exposure controls that more efficiently apply the radiation exposure to the patient, such as automatically reducing tube current through thinner body regions); encouraging the use nonionizing radiation imaging alternatives for selected disorders; and active interventions by radiologists, including limiting scanning range and reducing x-ray tube current and voltage, among other considerations. It is now relatively commonplace that exposures associated with newer CT protocols are significantly less than the values reported in Table 18-2 (Video 18-5).

Considerable controversy regarding the genesis and magnitude of adverse effects resulting from radiation exposure in humans exists and has been the subject of debate for decades.²⁷ The rapid rise in the use of CT scanning in recent



The two primary terms for describing the radiation imparted by a CT scan are *adsorbed* and *effective dose*. The adsorbed dose, measured in *grays* (Gy), is the energy absorbed per unit mass of a specific organ. In other words, it is the radiation imparted to a specific organ and thus accounts for the future risk of developing a malignancy at that site. Effective dose, measured in *sieverts* (Sv), is an overall estimate of total-body radiation exposure; this unit attempts to provide a measure of the overall potential harm caused by radiation exposure. Effective dose is defined as the radiation dose that must be delivered to the whole body to yield the same biologic consequences (specific for cancer induction only) as the dose actually received by the exposed organs.²⁷ This is calculated by summing the individual adsorbed doses to each organ, each of which is multiplied by a weighting factor reflecting individual organ radiosensitivities. Effective dose is useful for gross comparisons between different modalities and techniques. It should be understood that effective dose is *not* an actual measure of the radiation imparted to a patient during a given CT examination, although many published articles use this unit (often expressed as *millisieverts* [mSv] or in the form of the older unit, *millirems* [mrem]) in this fashion.²⁸ This miscon-

ception is compounded by the recording of a “patient dose report” as part of the CT scan report (eFig. 18-23). Rather, the actual radiation dose imparted to a patient during a CT examination depends directly on the size and shape of the actual patient.²⁸ The units reported by the CT scanner, often the *CT Dose Index* (usually expressed as the $CTDI_{vol}$, reported as an absorbed dose, in mGy) or the *Dose-Length Product* (DLP, reported as an effective dose, in mSv, and equal to the $CTDI_{vol}$ multiplied by the irradiated scan length), are measures of *scanner radiation output*, not patient dose. Calculating the radiation dose imparted to a patient during a given CT scan requires complex equations that take into account patient size, shape, body composition, and the organs irradiated, as well as scanning range. With knowledge of the patient size, body region scanned, CT scanner output, and scan length, a reasonable approximation of patient dose for a given CT scan is possible, but it remains imperative to understand that the units of scanner output—the CTDI and DLP—are not measures of patient radiation dose.²⁸ Therefore, these parameters should not be used to estimate potential cancer risk or radiation-related deterministic effects (e.g., skin injury) for individual patients undergoing medical imaging procedures.²⁸

years, as well as several well-publicized patient overexposure events at CT scanning, have fueled this debate.²⁷ Nevertheless, several points can be agreed on by investigators on both sides of this debate:

1. Radiation is potentially harmful to biologic systems and exposure can induce cancer, among its other effects³⁰;
2. There is relatively clear evidence for radiation-induced carcinogenesis for exposures exceeding 100 mSv^{27,31};
3. Radiation is a relatively weak carcinogen, and excess radiogenic cancer risk, if any, is considerably less than spontaneous cancer risk³²;
4. There are no parameters that allow a radiation-induced malignancy to be distinguished from a “naturally occurring” one³³;
5. The risk of radiation-induced malignancy is generally *inversely related to age*³⁰ and relatively higher in women compared with men^{32,34};
6. The risk for radiation-induced carcinogenesis from a CT scan is generally far less than the benefit of the information gained from appropriately indicated CT studies.^{29,35}



Additional detail concerning radiogenic cancer risk is available online.

Although conflicting interpretations are difficult to reconcile and data on both sides of the argument can be compelling, in practice, employing medical radiation only when necessary and substituting nonradiation utilizing procedures and dose-saving methodologies whenever possible should provide an optimal approach to balancing the immediate need for diagnostic information with patient safety.

MAGNETIC RESONANCE IMAGING

PHYSICAL PRINCIPLES

MRI is performed by magnetizing the patient's tissue slightly, generating a weak electromagnetic signal by applying a radiofrequency pulse, and mapping that signal spatially by manipulating its frequency and phase in a location-dependent manner with magnetic field gradients. MRI does not require mechanical motions of the scanner and therefore can image directly in nonaxial planes.

Although MRI uses electromagnetic radiation, the energy levels used in MRI are quite low (i.e., nonionizing). MRI appears to be remarkably free of significant bioeffects. Potential safety hazards in MRI relate to the extremely strong static magnetic field and rapidly switched gradient magnetic fields used and to the possibility of tissue heating from radiofrequency energy absorbed by the body. Tissue heating is a theoretic concern but, in practice, is not significant when conventional MRI techniques are used. Theoretically, the rapidly varying gradient magnetic fields could stimulate electrically excitable tissue, but this is not a problem with routine MRI techniques. In contrast, the powerful static magnetic field is a major safety hazard because the magnetic forces near a whole-body *magnetic resonance* (MR) imager are strong enough to cause significant projectile hazards. For example, an ordinary steel oxygen cylinder brought into an MRI examination room will fly into the bore of the magnet with a terminal velocity of about 45 mph. The possibility of displacements or torques on metallic

implants within patients also must be considered. Although the margin of safety is high, there are rare documented instances of harm to patients from dislodging intracranial aneurysm clips or intraocular metallic foreign bodies. Finally, the magnetic field can operate reed relays in cardiac pacemakers and cause a change in the pacing mode. Accordingly, strict security around MRI facilities is essential to prevent patients with certain types of metallic implants from entering the scanner and to prevent medical personnel from carrying into the scan room objects that could become projectiles.

MRI produces extremely high contrast between different types of soft tissue. This soft-tissue contrast is based on intrinsic properties of the tissues, but it can be modified and exploited by appropriate use of operator-selectable imaging techniques. The tissue properties normally utilized in MRI are as follows: the concentration of protons available to produce an MR signal (“proton density”), the presence of motion or blood flow, and two properties known as T1 and T2, time constants that describe how quickly an MR signal can be generated from a tissue (T1) and how quickly the MR signal, once generated, decays away (T2). In general, pathologic tissues have long T1 times and appear dark on those MR images whose appearance is conditioned primarily by T1 effects (“T1-weighted images”). Usually, pathologic tissues also have long T2 times and appear bright on T2-weighted images. The reason for this opposite behavior is that “T1” and “T2” describe processes that have opposite effects on the intensity of the MR signal. Flowing blood also can appear either bright or dark on MR images, depending on the examination technique used. The art of performing an MRI examination depends on appropriate manipulations of imaging techniques to capitalize on differences in proton density, flow, T1, and T2 between normal and pathologic tissue. In addition, the use of gadolinium-based MRI contrast materials, which alter the T1 and T2 of tissues semiselectively, has become important for numerous clinical applications, particularly *MR angiography* (MRA). MRI also can display other tissue properties such as molecular self-diffusion, temperature, and metabolites (MR spectroscopy), but these are less important for thoracic applications, although diffusion imaging and MR spectroscopy have recently shown some promise in lung cancer evaluation and staging.

TECHNIQUES

Motion during MRI causes artifacts that can degrade image quality severely. Motion compensation techniques, such as electrocardiographic gating and respiratory compensation, are widely used in chest MRI. High-speed techniques permit imaging in a matter of seconds, even fast enough to stop cardiac motion.

Direct MRI in sagittal, coronal, and oblique planes can provide superior depiction of structures that are oriented in the long axis of the body, such as the aorta, and of edges of structures that lie within the axial plane, such as lesions in the aortopulmonary window or lung apex.⁴⁸

Flow has profound effects on the MR image. Two basic effects from flow are seen in MRI; they are called “time-of-flight effects” and “spin-phase effects.” The manifestations of flow effects in MR images strongly depend on the type of

The primary source of controversy between those who believe low-level radiation exposures—exposures less than 100 mSv, which are typical for the exposures associated with medical imaging—may result in the development of malignancy and those who claim no such evidence exists lies with the *linear nothreshold* (LNT) model for radiation-induced carcinogenesis. The LNT theory holds that a straight-line relationship between radiation dose and cancer risk exists, and there is no threshold dose below which radiation is not carcinogenic.^{27,29} Proponents of the LNT theory hold that a linear model best describes the relationship between radiation exposure and cancer induction, and no evidence to support a departure from the LNT model exists^{36,37}; by contrast, critics of the LNT model for radiation-induced carcinogenesis risk prediction insist that the LNT model was developed to establish standards for protection of occupationally exposed individuals and overestimates the incremental risk for cancer development at low-level radiation exposures, and, therefore, it is inappropriate to project individual cancer risks from medical radiation exposures using this model.²⁷ Nevertheless, many of the widely publicized reports^{30,38-40} estimating the number of cancer-related deaths resulting from CT scanning have used the LNT methodology.

Estimates for the risk of radiation-induced carcinogenesis in humans primarily stem from epidemiologic studies of exposed patient cohorts, particularly Japanese survivors of the atomic bombings in 1945; other data sources include occupational radiation exposures and radiation accidents, such as the Three Mile Island and Chernobyl accidents.^{27,29,30,41} The LNT model is often used to extrapolate the elevated rate of malignancy found among these exposed cohorts to patients receiving the relatively low-level radiation exposures, typical of medical imaging, in the effort to estimate individual cancer risks; in addition, both the National Council on Radiation Protection and Measurements and the International Commission on Radiological Protection advise against the use of the effective dose paradigm and LNT theory in this fashion.³⁴ Furthermore, it should be understood that the LNT model does not provide for the ability to “sum” separate radiation exposures from temporally separated radiation-utilizing procedures into a “cumulative” cancer risk. In other words, regardless of the patient’s previous radiation exposures, the imaging study the patient is about to undergo only adds the potential incremental risk for cancer development attributable to that examination³⁴; the radiation exposures from separate examinations are not additive.^{34,42-44} This notion carries significant implications regarding the recent trend toward the development of radiation “dose registries,”⁴⁵ whereby patient medical imaging radiation exposures are tracked in a database with the intention of using such information to make future medical imaging decisions.

Low-Level Radiation-Induced Malignancy: Evidence for and Against

Investigators who assert that low-level radiation has carcinogenic potential cite the elevated incidence of malignancy noted in many large epidemiologic cohorts of exposed patients, particularly the Japanese atomic bomb survivors in the Life Span Study. This argument relies on the LNT

model to extrapolate the experience of these cohorts, exposed at relatively higher rates, to estimate the risks associated with the lower-level radiation exposures typical of medical imaging.³⁷ These investigators assert that a linear relationship (e.g., the LNT model) best describes the relationship between cancer rates and radiation exposures over a wide range of exposures; moreover, this relationship is consistently observed not only in the Life Span Study but in the analysis of other large epidemiologic studies of individuals exposed to radiation,³⁷ and that linearity best describes the responses of biologic systems to radiation exposure. Furthermore, experimental evidence can directly show cellular damage induced by radiation.³⁰ Finally, a recent large epidemiologic study focusing on younger patients undergoing CT scanning has shown a significant linear association between radiation dose to the brain and bone marrow and subsequent development of brain tumors and leukemia, respectively.^{35,46} This study evaluated 180,000 patients younger than 22 years undergoing nearly 280,000 CT scans in the United Kingdom between 1985 and 2002, who were subsequently followed for cancer development; the investigation specifically focused on brain tumors and leukemias, which are the cancers expected to appear first in irradiated pediatric patients^{35,46}; the risks for brain tumor and leukemia development in this patient cohort were small: it was estimated that one head CT may result in one excess brain tumor, for every 10,000 patients undergoing CT, in the first decade following the exposure.^{35,46} However, a recent editorial³⁵ also noted that the relatively short follow-up time in this study (average 10 years)⁴⁶ is insufficient to detect all potentially radiation-induced malignancies in this patient cohort, given that the latency of some radiation-induced malignancies may be as long as 20 to 40 years. Extrapolating the 10-year risk for radiation-induced carcinogenesis for the patients studied to lifetime carcinogenic risks for the exposed individuals yields estimates for cancer induction that are roughly similar to those asserted by the Life Span Study.³⁵ Note that this study⁴⁶ focused on pediatric patients, in whom the individual risks for radiation-induced malignancy are higher than for adults, but more than 90% of CT scans are performed in adult patients.³⁵

Investigators who challenge the notion that low-level radiation poses significant carcinogenic potential note the difficulties resulting from the reliance on the LNT model, as discussed previously, but also point to significant differences among the patients in the Life Span Study compared with those undergoing procedures utilizing medical radiation. Such differences include the following: that cancer incidence in Japan today is substantially different than in the United States, and that cancer incidence in both countries today is likely substantially different than in Japan in 1945.⁴¹ Medical imaging radiation exposure sources include relatively low energy x-rays and gamma rays, whereas atomic bomb explosions exposed patients to high-energy gamma rays, neutrons, and other charged particles⁴¹; medical imaging typically employs *fractionated* doses (radiation doses delivered intermittently over a period of time), whereas atomic bomb blasts exposures are instantaneous⁴¹; and Japanese atomic bomb survivors suffered uniform, whole-body exposures and radioactive fallout, whereas patients undergoing medical-imaging procedures

typically only expose limited body regions in a nonuniform fashion (the exception being some nuclear medicine procedures).⁴¹ Furthermore, the health of Japanese atomic bomb survivors was comparatively compromised, compared with patients undergoing medical imaging, owing to the limited resources for medical care, food, and shelter in Japan following the atomic bomb blasts.⁴¹ Thus, it seems clear that these substantial population differences limit the ability to extrapolate radiation-induced cancer incidence from one cohort to another.

In contrast to other investigators,³⁰ those who challenge the belief that low-level radiation has carcinogenic potential assert that the results of epidemiologic studies of radiation-induced carcinogenesis show no, or much smaller, health effects from radiation exposure than the data from the Life Span Study.⁴¹ Additionally, these investigators have called attention to serious limitations in the manner in which radiation-induced malignancy rates are calculated through the generation of “lifetime attributable risk” modeling.⁴¹

Lines of biologic evidence also call into question the simple notion that the rate of cancer induction is propor-

tional to the amount of radiation exposure. For example, it has been suggested that a 0.1 Sv radiation dose, which is at the upper limit of what is referred to as “low-level radiation,” is estimated to cause 0.004 long-term mutations per cell, which is a minor addition to the 1 mutation per cell per day that results from natural processes.⁴⁷ Furthermore, a number of in vivo experiments have shown a reduced rate of chromosomal aberrations following low-level radiation exposure due to stimulated production of DNA repair enzymes and immune system activation—the so-called “adaptive response.”^{31,47} Finally, the same survival curves plotted for Japanese atomic bomb survivors and other large-scale epidemiologic investigations of radiation effects, interpreted by some investigators as supporting the notion of a linear-dose response relationship between radiation exposure and carcinogenesis, are interpreted by others as showing a threshold effect, below which cancer is not induced, or in some cases, below which cancer risk actually decreases. The latter concept has been referred to as “hormesis” and is thought to be due to upregulation of protective mechanisms within cells and tissues induced by low-level radiation.^{31,47}

flow that is present and on the specific MRI techniques used. The clinical implication of this is that one can make the MR image of blood either bright (“white-blood images”) or dark (“black-blood images”). Most types of vascular pathology can be demonstrated with either white-blood or black-blood images, but there are usually clinical advantages to using one approach or the other in specific situations. Flow velocity can be estimated with MRI techniques, and thus noninvasive estimates of blood flow are potentially available.

Although high-speed imaging techniques are now available with MRI, it still is not an appropriate method to use for wide-ranging screening examinations of the entire trunk for metastatic disease. Such examinations normally should be performed with modern CT scanners. It usually is more rewarding to ask an anatomically focused question when requesting an MRI study.

APPLICATIONS OF CONVENTIONAL CHEST RADIOGRAPHY

SCREENING AND “ROUTINE” CHEST RADIOGRAPHS

It is now generally agreed that screening chest radiographs are not indicated except in specific high-risk populations.³⁷ Estimates as to possible iatrogenic disease caused by ionizing radiation from screening examinations, forecasts of possible genetic consequences, and financial concerns outweigh the medical value of such examinations. In 1973, the Department of Health, Education, and Welfare, in conjunction with the ACR and the American College of Chest Physicians, recommended the discontinuation of screening examinations. In 1985, recommendations of the ACR were more explicit: chest radiographs obtained for routine examination, preemployment screening,⁴⁹ prenatal or obstetric screening, and hospital admission, as well as repeated examinations of patients with positive tuberculin tests and a negative initial chest radiograph, should be eliminated. From their analysis of more than 10,000 chest radiographic examinations obtained in a hospital-based population, Sagel and associates²⁰ concluded that routine screening examinations done solely because of hospital admission or scheduled surgery are not warranted in patients younger than 20. Even in selected high-risk populations, radiographic screening for carcinoma of the lung has failed to significantly increase longevity.

The value of the routine hospital admission chest radiograph is still controversial. Although the yield is low in asymptomatic patients, the examination can be extremely valuable as a baseline study for comparison with radiographs taken during or after the course of hospitalization in patients who develop pulmonary symptoms.

DETECTION OF LUNG CANCER AND ASSESSMENT OF SOLITARY PULMONARY NODULES

Although chest radiographs are clearly useful in the initial evaluation of patients suspected of having lung cancer,

they are of limited accuracy in showing small or early cancers. At the time of their initial diagnosis, it is not uncommon for lung cancers to be visible retrospectively on prior radiographs.⁵⁰ Although additional radiographic studies, such as oblique views, are cost-effective for the initial evaluation of “nodular opacities” (see eFig. 18-13) that do not clearly represent a lung nodule and are often of value in determining that a “nodular opacity” is not a true nodule, studies by CT are superior for the detailed evaluation of a known lung nodule.⁵¹

EVALUATION OF INTENSIVE CARE UNIT PATIENTS

Chest radiography is generally the most common imaging study performed in the most critically ill patients in the hospital—those in the ICU. ICU radiographs are taken with portable and, therefore, suboptimal technique; nonetheless, the information they provide is useful and may alter patient management.⁹

The overall incidence of abnormalities found on chest films in ICU patients is quite high; in a study of more than 1000 consecutive medical or surgical ICU films obtained routinely or after a change in clinical status, malposition of a monitoring device or a marked change in apparent cardiopulmonary status was found in 65%.⁸ In a study of patients in a respiratory ICU,⁵² chest radiographs showed at least one new, clinically unsuspected finding in 35% of patients that, in 29% of these patients, led to a change in management. Significant findings are even more likely when the study is obtained to assess a change in clinical status. In intubated patients in a medical ICU, 43% of radiographs showed significant worsening of a known process or development of a new abnormality.⁵³ The value of obtaining chest radiographs on a daily basis in ICU patients is less clear. Strain and colleagues⁵⁴ found that routine morning radiographs revealed unsuspected abnormalities that led to a change in management in only about 15% of medical ICU patients, although this percentage was considerably higher (57%) in patients with pulmonary or unstable cardiac disease. Graat and coworkers⁵⁵ prospectively assessed the value of 2457 routine chest radiographs performed on patients in a combined medical and surgical ICU and found only 5.8% of routine chest radiographs showed new or unexpected findings; only 2.2% of patients required a change in management. Hall and colleagues⁵⁶ found that 18% of mechanically ventilated patients in a medical/surgical ICU had at least one radiograph that showed a clinically significant and unsuspected finding. The value of daily chest radiography in patients who have undergone thoracotomy and pulmonary resection has also been challenged. Daily chest radiography in nonhypoxic patients who had recently undergone thoracotomy and pulmonary resection changed care in only 27% of patients, whereas chest radiography altered management in 79% of such patients who were hypoxic.⁵⁷ Finally, a meta-analysis of 8 studies totaling 7078 patients found that elimination of daily routine chest radiography did not affect hospital or ICU mortality and there was no difference in length of stay in either the ICU or hospital, or the period required for mechanical ventilation, between patients undergoing routine daily chest radiography and those receiving

“on-demand” imaging.⁵⁸ Similarly, Hejblum and associates⁵⁹ concluded that an on-demand strategy for ordering chest radiographs for mechanically ventilated patients in the ICU is associated with a 32% reduction in the use of chest radiography compared with a routine daily strategy, but both strategies result in a similar rate of therapeutic or diagnostic intervention. On the basis of these results, the ACR has recommended that portable chest radiography should be obtained only for clinical indications, not routine assessment, when monitoring a stable patient or for a patient undergoing mechanical ventilation in the ICU.⁶⁰ Furthermore, routine chest radiography is not recommended for stable patients admitted to the ICU for cardiac monitoring or for stable patients admitted to the ICU for extrathoracic disease only.⁶⁰ Chest radiography is still recommended for the assessment of patients following initial support device placement, including endotracheal intubation, central venous catheter insertion, pulmonary arterial catheter placement, nasogastric tube placement, and thoracostomy tube insertion.⁶⁰

INDICATIONS IN ACUTE LUNG DISEASE

Dyspnea

Two studies suggest that chest radiography should be used routinely in patients with acute or chronic dyspnea.^{61,62} In one study, new, clinically important radiographic abnormalities requiring acute intervention or follow-up evaluation were identified in 35% of 221 symptomatic patients.⁶¹ Another study found that acute dyspnea was a strong predictor of a radiographic abnormality, but mainly in patients older than 40.⁶³ In this group, 86% of dyspneic patients had abnormal chest radiographs, whereas radiographs were abnormal in only 31% of patients younger than 40. Only 2% of patients younger than 40 with a normal physical examination had abnormal radiographs indicative of an acute abnormality. The ACR⁶⁴ recommends chest radiography when dyspnea is chronic or severe or when additional risk factors are present, such as age older than 40; known cardiovascular, pulmonary, or neoplastic disease; or abnormal physical findings.

Acute Respiratory Symptoms

Opinions are also divided about the utility of chest radiographs in patients with suspected acute lung disease and symptoms other than dyspnea. In a study of 1102 outpatients with acute respiratory disease, Benacerraf and coworkers⁶³ found patient age, results of physical examination, and presence or absence of hemoptysis to be important factors in predicting the value of radiographs; only 4% of patients younger than 40, without hemoptysis and without detectable abnormalities on physical examination, had acute radiographic abnormalities, whereas a much higher incidence of radiographic abnormalities was present if the patient was older than 40, had hemoptysis, or had abnormal physical findings. Heckerling,⁶⁵ in a study of 464 patients with acute respiratory symptoms, found a low incidence of pneumonia (3%) in patients with a negative physical examination, except in those with dementia. Whenever pneumonia is suspected in adults, the American Thoracic Society recommends PA (and lateral when possible) chest

radiography although the impact of chest radiography on clinical outcomes in patients with lower respiratory tract infections remains unclear.^{65a} In this setting, chest radiography may be useful to determine which patients should be hospitalized and which patients should be classified as having “severe” pneumonia.⁶⁶ The ACR considers chest radiography appropriate in immunocompetent patients with acute respiratory illnesses when one or more of the following is present: patient older than 40; dementia, positive physical examination findings; hemoptysis, hypoxemia, leukocytosis, and a number of other risk factors, including coronary artery disease, congestive heart failure, or drug-induced respiratory failure.⁶⁷ For patients younger than 40 with an acute respiratory illness but without such additional findings, chest radiography is generally not routinely indicated. Chest radiography is also considered appropriate for any patient clinically suspected of pneumonia.⁶⁷

Acute Asthma

Chest radiography is uncommonly used to make a diagnosis of asthma; radiographs are often normal, and visible abnormalities in this disease are usually nonspecific.⁶⁸ Although Petheram and associates⁶⁹ reported that 9% of 117 patients with severe acute asthma had unsuspected radiographic abnormalities affecting management, the usefulness of radiography in both adult and pediatric^{69a} patients with an established diagnosis of asthma who suffer an acute attack is limited. Correlation between the severity of radiographic findings and the severity or reversibility of an asthma attack is generally poor,⁶⁸⁻⁷⁰ and radiographs provide significant information that alters treatment in 5% or fewer patients with acute asthma.^{65,71,72} Although it is difficult to generalize regarding the role of radiographs in both adults and children with acute asthma, chest imaging should be used to exclude the presence of associated pneumonia or other complications when significant symptoms and/or appropriate clinical or laboratory findings are suggestive.^{68,70,72} The ACR considers chest radiography warranted in adult patients with asthma when a clinical suspicion for pneumonia or pneumothorax is present, or unless one or more of the following is noted: chest pain, edema, leukocytosis, or the patient has a history of either coronary artery disease or congestive heart failure.⁶⁷

Exacerbation of Chronic Obstructive Pulmonary Disease

Chest radiographs are often used in the initial assessment of patients with suspected COPD; however, they are of limited value in patients with known COPD who present with worsening of their disease.^{72,73} In a study of 107 patients with COPD presenting with an exacerbation of symptoms, only 17 (16%) had an abnormal chest radiograph, and in only half of these did the radiographic findings result in a significant alteration in management.⁷² In another study, including patients with both COPD and asthma, the management of 21% of patients was altered by radiographic findings.⁷³ It has been recommended that chest radiographs be obtained in patients with COPD only if certain clinical indicators are present; in various studies, these have included a clinical suspicion for pneumonia or pneumothorax, a history of coronary artery disease or congestive heart failure, leukocytosis, chest pain, peripheral

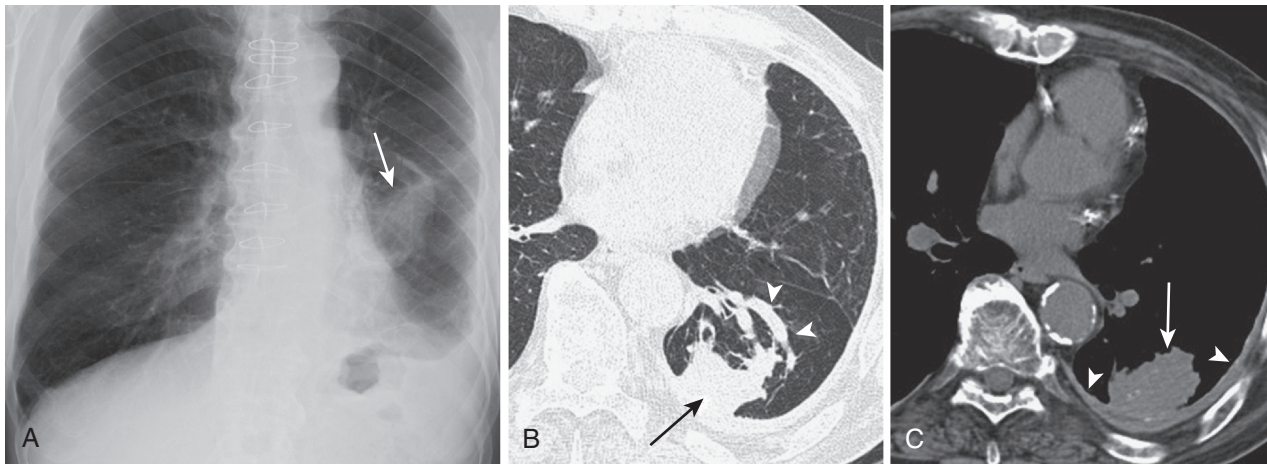


Figure 18-11 Chest CT shows typical findings of rounded atelectasis. **A**, Frontal chest radiograph shows volume loss in the left lower lobe associated with an oblong mass (arrow) and left-sided pleural abnormality. **B**, Axial chest CT in lung windows shows a subpleural left lower lobe mass (arrow) associated with left lower lobe volume loss (posterior displacement of left major fissure, small volume in the left lower lobe). Note “spiraling” appearance of left lower lobe bronchovascular bundles as they extend into the mass (arrowheads); this is the so-called comet-tail sign. **C**, Axial chest CT displayed in soft-tissue windows shows other features consistent with rounded atelectasis including abnormally thickened pleura (arrowheads) and contact of the mass (arrow) with the abnormal pleura. (Courtesy Michael Gotway, MD.)

edema,⁶⁷ intravenous drug abuse, fever, seizure, immunosuppression, and other pulmonary disease. When such indicators are used as a guide, nearly all patients with significant findings will have radiographs performed; moreover, it should be noted that more than two thirds of patients in one study met inclusion criteria for performing radiography.⁷³

In most patients with an established diagnosis of cystic fibrosis, clinical findings and chest radiographs are often sufficient for clinical management. Conversely, it should be recognized that patients with cystic fibrosis can have a significant exacerbation of their symptoms with little visible radiographic change.

APPLICATIONS OF CROSS-SECTIONAL IMAGING TECHNIQUES

SOLITARY PULMONARY NODULES

Assessment of a *solitary pulmonary nodule* (SPN) seen on chest radiographs is a common indication for CT.^{51,74} CT is used to confirm that the SPN is real, to confirm that the SPN is solitary, to attempt further noninvasive characterization of the lesion, to guide percutaneous biopsy of the lesion, and to provide staging information if the SPN is found to represent a carcinoma. The likelihood of malignancy in such nodules varies from less than 10% in mass screenings to about 50% among resected nodules.

In general, CT of a patient with an SPN should be performed with thin-section volumetric imaging to provide detailed analysis of nodule morphology and to allow identification of the presence of fat or calcium (see Fig. 18-10, Video 18-6) within the nodule, and when the latter is present, the pattern of calcification; this is now fairly routine in the era of MSCT technology.



Figure 18-12 Chest CT of bronchogenic carcinoma. Axial CT displayed in lung windows shows a spiculated lesion within the left upper lobe. (Courtesy Michael Gotway, MD.)

In up to 20% of instances, a “lung nodule” visible on chest radiographs actually represents an artifact, chest wall lesion (eFig. 18-24), or pleural abnormality; in some cases, CT is essential to determine the true nature of the opacity. CT can be useful to define the morphology of the SPN and suggest whether it is benign, likely malignant, or indeterminate, in other words, having neither benign nor malignant characteristics. In some patients, a specific diagnosis of lesions such as rounded atelectasis (Fig. 18-11, Video 18-7), a mucous plug, or arteriovenous malformation (Video 18-8) can be made on the basis of CT findings, indicating the benign nature of the lesion.^{51,74} Other CT appearances suggest the presence of malignancy (eFig. 18-25).⁵¹ Malignant features include a spiculated (see eFig. 18-25D) or irregular contour; the presence of air bronchograms within the nodule (see eFig. 18-25A), bubbly air collections (“pseudocavitation”), or cavities; and a diameter larger than 2 cm (Fig. 18-12, see eFig. 18-25A).^{51,74} Benign features include the presence of several patterns of calcification; “benign” patterns include diffuse, central, laminated,

and chondroid, or “popcorn,” calcification (Fig. 18-13).^{51,74} In about 30% of benign nodules, calcium not readily visible on chest radiographs can be seen on thin-section CT (eFigs. 18-26 and eFigs. 18-27). Carcinomas may occasionally show calcification (eFig. 18-28), although often in an eccentric or stippled pattern. The presence of fat within an SPN, indicated by a low CT attenuation coefficient (Fig. 18-14), strongly suggests the presence of hamartoma^{51,74} or lipoid pneumonia (eFig. 18-29); such nodules can be safely followed with serial radiographs.

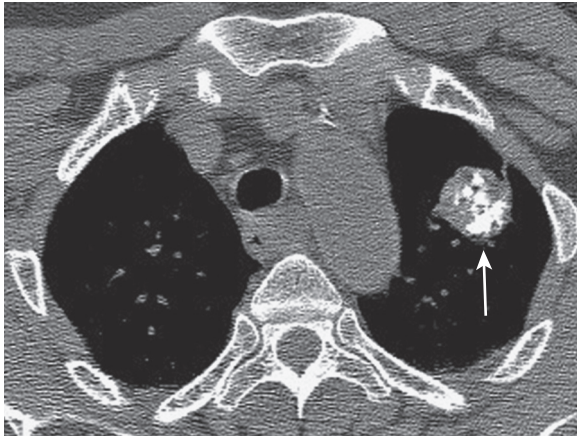


Figure 18-13 Chest CT of hamartoma. Chest CT showing “popcorn” (chondroid) calcification within a left upper lobe nodule (arrow), consistent with hamartoma. (Courtesy Michael Gotway, MD.)



Figure 18-14 Chest CT of a hamartoma. CT image showed low attenuation within the solitary pulmonary nodule (typical CT numbers within the lesion ranged from -90 to -100 HU), consistent with fat. (Courtesy Michael Gotway, MD.)

Malignant tumors tend to show greater enhancement than benign nodules after the rapid injection of iodinated contrast material.⁷⁵⁻⁷⁸ Because the degree of enhancement depends on the amount and rapidity of contrast infusion, it is important to use a consistent technique. Using a specific contrast enhancement CT protocol, a threshold for enhancement of 15 HU or more is typically seen with malignancy, hamartoma, and some inflammatory lesions. Enhancement of less than 15 HU almost always indicates a benign lesion, usually a granuloma. Therefore, whereas positive results (enhancement of >15 HU at any time point during the study) are nonspecific, negative results are quite useful (eFig. 18-30). This technique has been shown to have a sensitivity of 98% and a specificity of 58% in diagnosing carcinoma. More importantly, the negative predictive value of this technique is approximately 96%.⁷⁷ CT nodule enhancement studies are most appropriately used for patients who have indeterminate nodules (i.e., those without typical benign or malignant appearances). A similar use for dynamic, contrast-enhanced MRI has been reported, although data are limited.⁷⁹ The use of *fluorodeoxyglucose positron emission tomography* (PET) imaging (see Chapter 21) has also been shown to be useful for distinguishing benign from malignant nodules (see Fig. 21-1)⁸⁰ and is generally favored over contrast-enhanced CT for additional imaging characterization of indeterminate lung nodules. In a meta-analysis,⁷⁹ PET was shown to be 94% sensitive and 83% specific for the differentiation of benign from malignant solid nodules 1 to 3 cm in size. The addition of PET-CT tends to increase sensitivity with no change in specificity compared with PET alone.⁸¹ False-positive PET results may be seen with inflammatory processes, particularly granulomatous diseases⁷⁹ such as tuberculosis (see eFig. 53-6C and D), histoplasmosis, and sarcoidosis. Tumors that may be ^{18}F PET-negative include minimally invasive adenocarcinoma (see Fig. 21-2, eFig. 53-7A), carcinoid tumors,⁷⁹ and some metastases (e.g., renal cell carcinoma).⁸² In addition, small nodules may not be of a sufficient size to produce a positive result with PET scanning (see eFig. 53-7F). The sensitivity of PET imaging significantly decreases with nodules measuring less than 8 to 10 mm in diameter (see eFig. 53-7F). As with any imaging modality, the correlation of the PET results with morphologic features on CT, prior radiographic examinations, and the clinical presentation will improve the determination of the likelihood of malignancy.

MULTIPLE PULMONARY NODULES

CT is the favored procedure for identifying multiple pulmonary nodules or masses. It detects more and smaller metastases (Fig. 18-15, Video 18-9) than any other imaging technique, and 2- to 3-mm nodules are routinely visible.⁸³⁻⁸⁵ This is most relevant for patients with extrathoracic malignancies, in whom the detection of metastatic disease has a major impact on initial staging and assessment of response to therapy. The major sources of controversy regarding the use of CT for evaluation of possible metastases have been its limited specificity and cost-benefit ratio.⁸⁴

CT is clearly more sensitive than chest radiographs in diagnosing multiple pulmonary nodules in patients with suspected metastasis.⁸³⁻⁸⁵ The sensitivity of CT for detecting

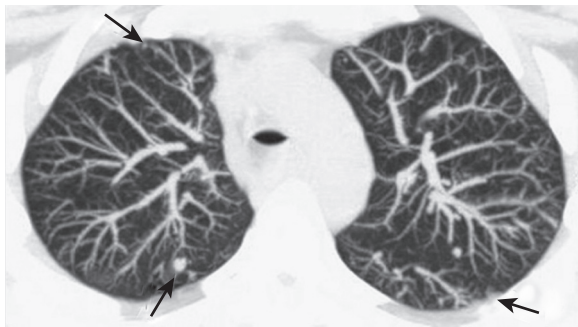


Figure 18-15 Chest CT in a patient with metastatic cervical carcinoma. Maximum-intensity projected CT shows numerous bilateral pulmonary nodules (arrows) that were not visible on the chest radiograph. CT is more sensitive than radiography for detection of small nodules of any cause. (Courtesy Michael Gotway, MD.)

surgically proven nodules ranges from 50% to 75% (i.e., 50% to 75% of all resected nodules are seen on preoperative CT scans), whereas the sensitivity of chest radiographs is about 25%. In some studies, most nodules (55% to 60%) seen on CT and subsequently resected have proved to be benign (granulomas, intrapulmonary lymph nodes, and the like).⁸⁶ In other studies, most CT-detected nodules (80% to 95%) have proved to be metastatic lesions.⁸⁷ In an older study from the pre-MSCT era involving radiologic-surgical correlation, Peuchot and Libshitz⁸⁷ evaluated 84 patients with previously documented extrathoracic malignancies and newly identified pulmonary nodules. These authors noted important limitations in both the sensitivity and specificity of CT. Of a total of 237 nodules resected, CT was able to identify only 173 (73%); 207 (87%) were metastatic tumors, 21 (9%) were benign, and 9 (4%) were bronchogenic carcinomas. Of 65 nodules interpreted as solitary on chest radiographs, CT disclosed multiple nodules in 46%, and 84% of these additional nodules were metastases. Although exquisitely sensitive for small nodule detection, CT is not infallible. In a study of 53 preoperative patients undergoing 60 metastectomy surgeries from 1996-2004, in whom nodules detected at chest CT were compared with pathologically confirmed metastases, 46% to 47% of surgically palpable lung metastases were not reported at preoperative CT.⁸⁸ Although there are intrinsic biases affecting such reports, including the possibility that surgical palpation will detect benign nodules and may overlook some malignant nodules that will subsequently manifest as growing nodules at chest CT, as well as the inherent difficulties correlating the location of nodules detected at chest CT with pathologic specimens, the results of this study nevertheless highlight the limitations of chest CT for small nodule detection and characterization.⁸⁸

Accordingly, CT results must be interpreted in light of the clinical characteristics of the patient. Primary tumors that commonly spread to the lungs, more advanced malignancies, and the absence of any simulators of metastases (sarcoidosis, sarcoidosis, and prior granulomatous infection) would favor malignancy in pulmonary nodules detected by CT. Furthermore, smaller and less numerous nodules are more likely to be benign. The findings on CT are in themselves not specific, however, and follow-up may be necessary to demonstrate the growth or stability of small nodules.

LUNG CANCER STAGING

In patients with lung cancer, accurate anatomic staging is essential for planning the therapeutic approach.^{89,90} CT is used in both assessment of primary tumor extent and detection of lymph node metastases. However, its accuracy in both situations is limited.^{89,90} Lung cancer staging is reviewed in detail in Chapter 53.

Computed Tomography

The primary goal of CT is to help distinguish patients who likely have resectable tumors from those who do not.⁹¹ Pulmonary malignancy is considered to be likely unresectable (stage T4) if the primary tumor (1) involves the trachea (eFig. 18-31) or carina; (2) invades the mediastinum (eFig. 18-32) with involvement of mediastinal structures (eFig. 18-33); (3) invades the chest wall with involvement of great vessels, brachial plexus (see eFig. 53-18), or vertebral column (eFig. 18-34); or (4) results in a malignant pleural effusion or pleural implants (eFig. 18-35, see eFigs. 53-4 and eFig. 53-5).⁹²⁻⁹⁵ Note, however, that acceptable morbidity and mortality have been reported following en bloc vertebral body resection with reconstruction for neoplasms invading the spine, particularly following induction chemotherapy,⁹³ but such extensive surgeries are relatively restricted to larger academic or high-volume centers. The presence of satellite nodules in the same lobe as the primary tumor (see eFig. 53-19) is now designated as T3 in the seventh edition of the TNM Classification of Malignant Tumors and does not preclude surgical resection.^{93,94}

Tracheal (see eFig. 18-31) or carinal invasion (eFig. 18-36) can be suggested with CT but requires biopsy confirmation. The CT diagnosis of chest wall (see eFig. 53-16) or mediastinal (see eFig. 18-32) invasion can be a problem, and many CT scans suggesting chest wall invasion are relatively nonspecific and can be seen with a number of inflammatory disorders. The sensitivity and specificity of CT for diagnosing T4 mediastinal or chest wall invasion are about 60% and 90%,^{96,97} respectively, although some findings (e.g., vertebral body destruction, encasement of mediastinal structures, mediastinal fat infiltration) are virtually diagnostic.⁹³⁻¹⁰¹ Limited chest wall or mediastinal invasion is considered potentially resectable by many surgeons, but knowledge of tumor extent is nonetheless an important factor when planning therapy.

CT findings suggesting mediastinal invasion^{97,99} include (1) replacement of mediastinal fat by soft-tissue attenuation; (2) compression or displacement of mediastinal vessels by tumor; (3) tumor contacting more than 90 degrees of the circumference of a structure such as the aorta or pulmonary artery (the greater the extent of circumferential contact, i.e., 180 degrees, the greater the likelihood of invasion); (4) more than 3 cm of contact between tumor and the mediastinum; and (5) obliteration of the mediastinal fat plane normally seen adjacent to most mediastinal structures (see eFig. 18-32 and eFig. 18-37). However, individually, these findings are unreliable for differentiating mediastinal invasion from anatomic contiguity.⁹⁹

CT is of little value in the diagnosis of malignant pleural effusion because this diagnosis requires cytologic confirmation.¹⁰² However, in some patients, CT may show diffuse or nodular pleural thickening with (see eFig. 53-4) or without

(see eFig. 18-35 and eFig. 53-5) pleural liquid.^{102,103} PET may show tracer uptake in patients with malignant pleural effusion (see eFig. 53-4), even when CT does not show evidence of nodular pleural thickening and when cytologic analysis is negative.¹⁰⁴

The diagnosis of mediastinal lymph node metastasis by CT is determined largely by node size, although the preservation of fat within lymph nodes often reflects the absence of pathologic infiltration, whereas necrosis may imply pathologic infiltration even within normal-sized lymph nodes.⁹⁰ By convention, a nodal short axis diameter of 1 cm or greater is considered to be abnormal in all node stations (Fig. 18-16),^{90,94} except the subcarinal space.^{105,106} In general a tumor cannot be detected in normal-sized lymph nodes by CT, and there are no characteristic appearances allowing benign and malignant causes of nodal enlargement to be distinguished (see eFigs. 53-1 and 53-3).¹⁰⁶⁻¹⁰⁸ Pooled information from 35 studies published between 1991 and June 2006 evaluating the performance of CT scanning for noninvasive staging of the mediastinum has shown that this size threshold has a sensitivity of only about 51% and a specificity of 86% for diagnosing mediastinal lymph node metastases in patients with lung cancer.^{95,109,110} Furthermore, the accuracy of CT for detecting involvement of individual node groups is low, perhaps as low as 40%.¹⁰⁹ In a more recent review⁹⁰ of the accuracy of mediastinal lymph node staging using CT, a combination of studies evaluating 7368 patients found the median sensitivity and specificity for mediastinal lymph node metastases detection at chest CT of 55% and 81%, respectively.

Despite its limited accuracy, CT, particularly in conjunction with PET, is useful in determining the need for preoperative mediastinoscopy. Furthermore, CT may also be useful in deciding on the need for preoperative mediastinoscopy, anterior mediastinotomy (e.g., the Chamberlain procedure), or suggesting alternate procedures for lymph node

staging (e.g., needle biopsy, endoscopic and/or endobronchial ultrasound).

Perhaps the most important potential contribution of CT to intrathoracic staging is precise mapping of nodes likely to be involved by tumor, and to thereby direct additional diagnostic procedures required for accurate lung cancer staging.

Positron-Emission Tomography and Positron-Emission Tomography–Computed Tomography

The role of PET imaging in the staging of bronchogenic malignancy is explored in detail in Chapters 21 and 53. The primary value of PET is to increase the sensitivity for the detection of local and distant malignancy in order to prevent patients with unresectable disease from undergoing unnecessary surgery. PET and PET-CT are most useful for evaluating the N (Fig. 18-17) and M components of staging, although PET activity in the primary tumor (T component) may provide insight into biologic aggressiveness and the chance of future spread of early localized tumors.¹¹¹

Magnetic Resonance Imaging

There are few situations in which MRI is the preferred imaging modality for patients with primary lung cancer. The extent of chest wall invasion adjacent to a lung tumor sometimes may best be shown by MRI, and there may be some advantage to MRI over CT for assessment of mediastinal invasion, vertebral body invasion, and involvement of the chest wall.⁹⁰ Sagittal or coronal MR images can be advantageous in delineating the extent of tumors at the lung apex (see eFig. 53-18B and C).^{90,112} Consequently, MRI is more accurate than CT for determining chest wall involvement in superior sulcus tumors; moreover, involvement of the neurovascular bundle¹¹² is better shown with coronal and sagittal MRI than with axial CT images (see eFig. 53-18B and C).

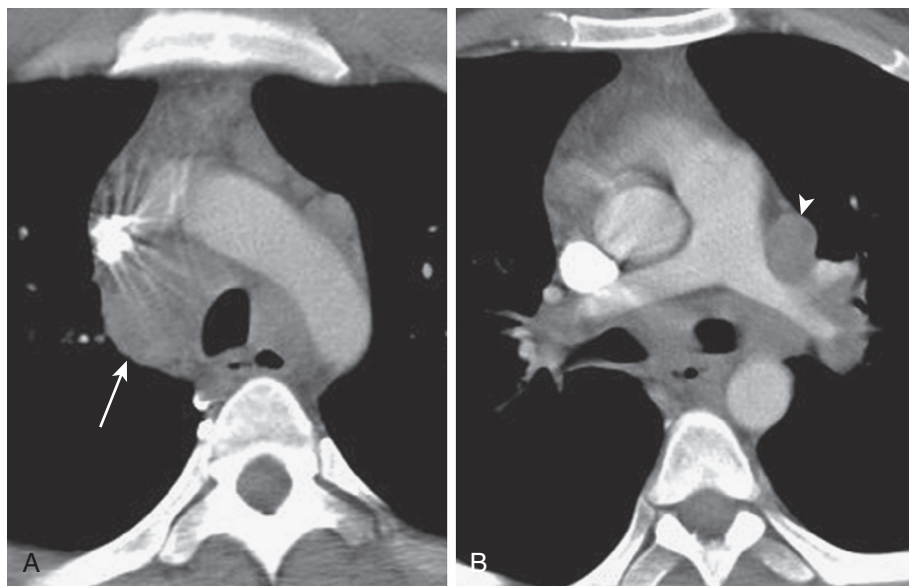


Figure 18-16 Chest CT performed for staging in a patient with non-small cell lung cancer. **A**, The primary tumor was present at another level in the right lung. Right paratracheal lymphadenopathy (arrow) is present; left mediastinal nodes also appear enlarged. **B**, Axial chest CT at a slightly lower level shows left hilar and subaortic (arrowhead) lymph nodes, which measure greater than 1 cm in short axis diameter, the most widely accepted size threshold for abnormality, and would be considered suspicious for metastasis. (Courtesy Michael Gotway, MD.)

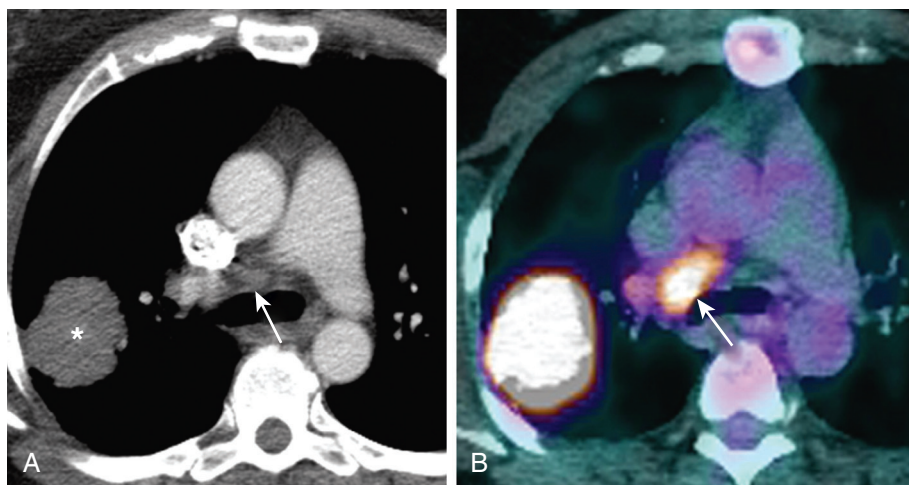


Figure 18-17 PET-CT in the staging of pulmonary malignancy. This patient was diagnosed with non-small cell lung cancer, and CT and PET-CT were performed for staging. **A**, The primary tumor is visible in the peripheral right lung (*). Borderline right paratracheal lymph nodes (arrow) are present. **B**, PET-CT shows intense tracer uptake in the primary right lung neoplasm, as well as within the right paratracheal lymph nodes (arrow). The latter finding prompted mediastinoscopy, which confirmed metastatic nodal disease. (Courtesy Michael Gotway, MD.)

In most patients with primary lung cancer, MRI has no unique information to offer and CT is the preferred imaging procedure.⁹⁰ MRI is similar to CT in its ability to identify mediastinal lymph nodes⁹⁰ and to diagnose mediastinal metastases. Although it has been reported that MRI is more accurate than CT in detecting mediastinal,^{90,95,113} cardiac, or vascular invasion by lung cancer, the reported differences in accuracy are small. In general, the MR properties of benign and tumor-bearing mediastinal lymph nodes do not differ significantly in most patients and, as with CT, node size is usually the main diagnostically useful discriminator. However, recent data with newer MR sequences—particularly diffusion-weighted imaging,¹¹⁴ *short-tau inversion recovery imaging* (STIR),^{115,116} and recent observations regarding findings at T2-weighted chest MRI¹¹⁷—may allow discrimination between benign and malignant lymph node involvement, even for lymph nodes with short axis dimensions less than 1 cm. In addition, in some cases, MRI is able to demonstrate masses better than CT by imaging in the coronal or sagittal plane and, in some cases, MRI may be used as a problem-solving tool.

Brachial Plexopathy

Imaging of the brachial plexus is useful for patients with suspected metastatic disease, radiation injury, primary tumor, or traumatic injury. Clinical evaluation can suggest possible etiologies of brachial plexopathy and whether the neurologic deficit is more likely due to a central or a peripheral lesion.¹¹⁸ However, clinical evaluation cannot demonstrate the pathology and localize precisely the site of involvement.

Metastatic disease and radiation injury are the most common causes of brachial plexopathy, and the clinical distinction between these is difficult, although pain, Horner syndrome, and lower trunk involvement are characteristic of metastatic involvement.^{119,120} CT is of proven value for patients with primary or metastatic tumors,^{118,121} but it may be less useful for patients with radiation fibrosis. CT is superior for the detection of osseous involvement due to

superior sulcus tumors.¹¹² Older data clearly indicated that MR is superior to CT for assessment of brachial plexus involvement by lesions within the superior sulcus, primarily due to the multiplanar capabilities of MR. However, as mentioned previously, advances in CT technology now allow imaging reconstruction in any plane, and it is likely that these improvements have enhanced the diagnostic capabilities of CT for assessment of superior sulcus tumors. Nevertheless, MR possesses inherently superior contrast resolution to CT, which is a valuable property for imaging the superior sulcus region. Therefore, MR is still considered the reference standard for evaluation of tumors within the superior sulcus and for assessment of brachial plexus involvement by tumors in this region.^{90,112}

CT myelography, often in conjunction with conventional myelography and MR imaging, is the optimal imaging modality for the assessment of traumatic brachial plexus injury.¹²²

LUNG CANCER SCREENING

The utility of CT for lung cancer screening was a subject of significant controversy, but with the publication of the results of the *National Lung Screening Trial* (NLST),¹²³ the benefit of CT lung cancer screening for high-risk smokers is no longer in doubt. Before the NLST, a number of cohort studies had suggested significant benefit to lung CT screening in smokers, but these studies were persistently questioned due to various biases, including lead-time bias, length-time bias, and overdiagnosis bias, inherent to non-randomized studies. Many of these screening studies showed a high percentage of early-stage cancers found, suggesting early detection and a greater chance of cure. For instance, in the International ELCAP study,¹²⁴ 85% of cancers detected were stage I. Because none of these studies had a control arm, the mortality benefit from early diagnosis assumes that lung cancer is an invariably fatal disease; however, this is not necessarily true. Despite these encouraging results, the prospect of biases in study design

prevented acceptance of the use of CT for lung cancer screening and highlighted the need for randomized, controlled trials to settle the debate.

A second potential issue with lung cancer screening is the high incidence of nonmalignant pulmonary nodules detected. According to the Mayo Clinic data,¹²⁵ 74% of patients had at least one nodule detected during the 4-year study period and only 2% of noncalcified nodules were found to be malignant. Given that most patients with nodules are followed with CT to demonstrate 2 years of stability, the acceptance of lung cancer screening would undoubtedly result in a large number of subsequent CT scans that would not have otherwise been performed. This could have a significant impact on the cost-effectiveness of lung cancer screening and radiation exposure in this patient population. Ongoing research efforts have been directed at identifying the populations most appropriate to undergo lung cancer screening with CT and how to optimize the approach to abnormalities detected at screening, in particular to limit false-positive results, and to develop strategies for management of nodules detected at CT screening.

Although a number of nonrandomized studies evaluating the ability of screening with CT to reduce all-cause and lung cancer-specific mortality have been published, and several randomized trials are ongoing (particularly in Europe), the NLST data¹²³ represent the largest randomized, controlled trial of lung cancer screening with CT to date. Between August 2002 and April 2004, 53,454 asymptomatic patients, at high risk for pulmonary malignancy, at 33 academic medical centers in the United States, were enrolled and randomized to undergo three annual screenings with low-dose chest CT (26,722 participants) or single-view posteroanterior chest radiography (26,732 patients). “Low-dose” chest CT reduces the effective dose to approximately 2 mSv compared with the 5–8 mSv typical of “standard-dose” chest CT (see Table 18-2). “High-risk” eligible patients were defined as patients 55 to 74 years old, with at least a 30-pack-year smoking history and who were either current smokers or smokers within the previous 15 years. Eight participants had lung cancer and another seven died before the first screening, leaving 26,715 patients in the low-dose CT screening group and 26,724 in the chest radiography screening group.¹²³ Additional baseline patient characteristics of the NLST study group included 59% men with an average age of 61 (± 5) years, and 91% of the patients were Caucasian. The mean smoking duration was 43 pack-years and 48% of patients were current smokers.¹²³

The first scheduled screening was successfully performed in 98.5% ($n = 26,309$) of patients in the low-dose CT group and 97.4% ($n = 26,035$) of patients in the chest radiography group. No difference in compliance with screening was noted between the two groups.¹²³

A “positive” screening result at low-dose CT was defined as the detection of any noncalcified nodule at least 4 mm in any diameter, whereas a positive result at chest radiography was defined as any noncalcified nodule or mass “suspicious for” lung cancer. The presence of lymphadenopathy or pleural effusion could be considered a positive result as well. The proportion of positive screening results was higher in the low-dose CT screening group (24.2%) compared with the chest radiography screening group (6.7%) over all three rounds of screening, and overall, 39.1% of patients

undergoing low-dose screening with CT had at least one positive screening result, whereas 16% of those in the chest radiographic arm had at least one positive result. The proportion of patients with negative screening results, but with significant incidental findings, was over three times higher in the low-dose CT group compared with the group screened with chest radiography (7.5 vs. 2.1%, respectively).¹²³

Across the three rounds of screening, 96.4% of the positive results at low-dose CT and 94.5% of the positive results at chest radiography were false-positive results.

A total of 1060 lung carcinomas (645 per 100,000 person-years) were diagnosed in the low-dose CT screening group, and 941 (543 per 100,000 person-years) lung cancers were diagnosed through chest radiography. The proportion of stage I lung carcinomas among those with positive screening results in the low-dose CT screened group was 63%, whereas this value was 47.6% in the chest radiograph-screened group.¹²³ A preponderance of adenocarcinomas was found in the CT-screened group. A 20% relative reduction in lung cancer-specific mortality was found in the low-dose CT screened group at 6 years following the initial prevalence scan and two rounds of screening, compared with the chest radiography screened group. Similarly, all-cause mortality was decreased by 6.7% in the low-dose CT screened group compared with the group screened by chest radiography.¹²³ It has been noted that the mortality benefit of lung screening with CT is likely greater than the 20% reduction reported in the NLST because this trial was halted early when analysis showed that the target level for lung cancer mortality reduction had been reached.¹²⁶ Although both CT screening and chest radiography were associated with relatively high false-positive rates, most of the false-positive findings underwent serial evaluation, rather than invasive testing, and therefore complications related to invasive diagnostic evaluation were uncommon.

Following the publication of the successful results observed in the NLST, a number of organizations, including the National Comprehensive Cancer Network,^{127,128} the American Lung Association,^{127,129} the American College of Chest Physicians, the American Society of Clinical Oncology,^{127,130} the American Cancer Society,¹³¹ the American Thoracic Society,^{130,132} the American Association for Thoracic Surgeons,^{127,133} and, most recently, the U.S. Preventive Services Task Force^{134–136} have now endorsed low-dose CT screening for lung cancer in high-risk patients. Nevertheless, a number of questions remain unanswered¹³⁷:

1. Will patient populations with risk profiles different from those studied in the NLST benefit from low-dose CT screening?
2. Are less frequent CT screening intervals as effective as yearly screening, and how long should screening continue? A recent evidence-based guideline suggests annual low-dose CT screening in high-risk individuals for 3 consecutive years and, if these studies are negative (defined as no solid nodule ≥ 5 mm or *ground-glass opacity* [GGO] nodule ≥ 8 mm), biannual screening thereafter¹³⁷;
3. How should lung nodules detected at low-dose CT screening, the vast majority of which represent false positive findings, be managed?

4. Would different criteria for a “positive” screening result enhance or detract from the efficacy of CT screening?
5. Can the results of the NLST be extrapolated to community practice? Importantly, the NLST was conducted among centers with recognized excellence in diagnostic imaging and thoracic surgery, and one of the most important factors influencing the success of lung cancer screening—the mortality associated with thoracic surgery—was only 1% in the NLST, which was substantially lower than the 4% mortality rate reported for the population in the United States in general.^{123,138}

Initial studies^{139,140} of the cost-effectiveness of lung cancer screening with CT suggest that low-dose CT performed in high-risk, commercially insured patients, typically using patient selection criteria similar to that used in the NLST, compares favorably with other widely accepted screening programs, such as screening for cervical, colorectal, and breast malignancies.¹⁴⁰ One such analysis suggested that the cost-per-life saved for lung carcinoma screening with low-dose CT is less than \$19,000 and is still less than \$27,000 in the “highest-cost” scenario, with both values less than the costs for screening programs already recommended by the U.S. Preventive Services Task Force.¹³⁹ When approached from the payer perspective, the additional cost per commercial insurance plan member per month for low-dose lung cancer CT screening was \$0.76 in 2012, compared with \$2.50, \$1.10, and \$0.95 for breast, cervical, and colorectal cancer screening, respectively.¹⁴⁰ Adding smoking cessation programs to low-dose CT screening efforts further improves the cost-effectiveness of lung cancer screening with CT.¹⁴⁰

Finally, although the NLST has provided great optimism for the reduction of lung cancer–related mortality, this optimism has been somewhat tempered by the lack of a similar lung cancer mortality reduction from CT screening in several European trials.^{132,141–143} Such results raise the possibility that the magnitude of the benefit of CT screening for lung cancer may not be fully realized in community practice. It has been noted that the lack of mortality reduction from CT screening in these other trials^{132,141–143} may be the result of the smaller sample size of these trials^{132,141–143} compared with the NLST (number of patients randomized to the intervention arm ranging from 1202 to 2052 in the smaller studies^{132,141–143} vs. 26,722 in the NLST), but several peculiar features of the NLST raise questions regarding the generalizability of this trial. Such features include far greater adherence with screening follow-up among NLST patients (>90%) than may be expected in practice and that NLST patients were more highly educated and less likely to be current smokers compared with the general population, suggesting that NLST patients may be healthier than patients in the general population eligible for CT screening.¹³² Additionally, questions regarding the potential harms of CT screening for lung cancer remain when this procedure is applied to individuals in the general population. Taken together, these concerns indicate that programs for lung cancer screening using CT must be implemented in the safest and most effective manner, and future research efforts to identify such methods remains of critical importance.^{132,144}

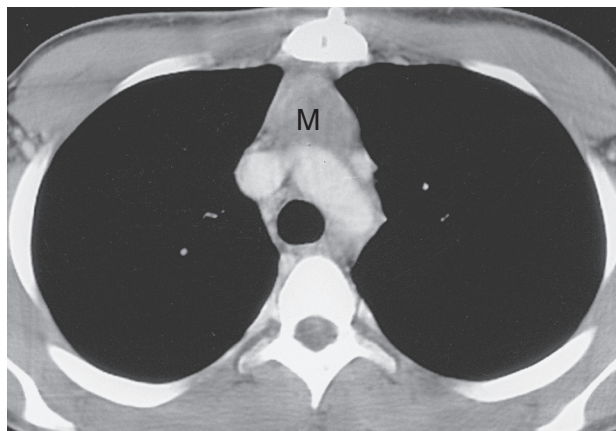


Figure 18-18 Chest CT for localization of mediastinal masses. An axial CT image shows an anterior mediastinal soft-tissue mass (M). There are no characteristic attenuation features (e.g., fat, calcium). The location of the mass, however, is precisely documented, and thus the differential diagnosis was limited and biopsy facilitated. The lesion was a seminoma. (Courtesy Michael Gotway, MD.)

HILAR AND MEDIASTINAL MASSES

CT is indicated as the primary imaging modality in most patients with suspected hilar or mediastinal masses. The cross-sectional display and tissue discrimination of CT have revolutionized diagnostic imaging of the hilum and mediastinum.

Lesions can be detected with high sensitivity and located precisely to their structure of origin or anatomic region (Fig. 18-18). (See Chapter 83.) By localizing a mass to a particular region of the mediastinum,^{145,146} the differential diagnosis can be made more specific, and biopsy procedures can be planned with greater accuracy. In addition to the information gained from the location of the mass, the density discrimination of CT enables soft-tissue abnormalities, fluid collections, and fatty tissue (see Chapter 83 eFigure Image Gallery) to be distinguished accurately (Fig. 18-19).^{147–149} With use of intravenous contrast material, masses and vascular anomalies (see eFigs. 83-47B, 48B-D, 49B, and 50B-D) can be accurately delineated. CT is useful in further evaluating a mass initially detected on chest radiography, for demonstrating pathology that is suspected on the basis of the clinical setting (but not visible on conventional imaging studies), and for precisely delineating the location of lesions for planning therapy.

MRI may be indicated as the primary imaging modality in patients with suspected mediastinal mass in many situations: for determining whether mediastinal abnormalities are vascular, for displaying lesions at the thoracic inlet in the coronal plane, for distinguishing cystic from solid masses (see eFigs. 83-28 and 83-43C and D),¹⁵⁰ for detecting hemorrhagic components within a mediastinal lesion (see eFig. 83-36D and E), for distinguishing between surgical (see eFigs. 83-17D-G and 83-24C and D) and nonsurgical (see eFig. 83-16B-D) mediastinal masses,¹⁵¹ and for evaluation of posterior mediastinal masses (see eFig. 83-41D and E) and neurogenic tumors (see eFig. 83-15), which may have intraspinal components.^{150,152,153} Early experience with mediastinal MRI suggested that this modality may be capable of distinguishing between a tumor mass and a benign fibrous mass^{154–156} following radiation therapy,

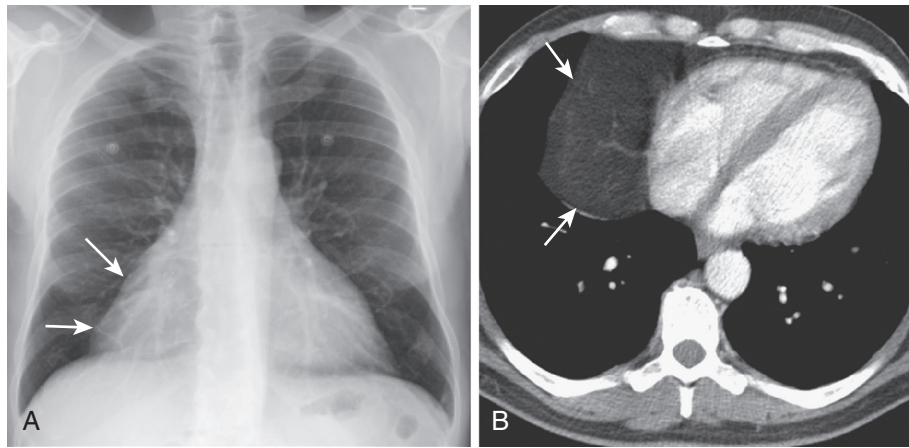


Figure 18-19 Chest CT characterization of fatty mediastinal masses. **A**, Frontal chest radiograph shows a contour abnormality (arrows) along the right inferior mediastinum. **B**, Axial chest CT shows a fatty right paracardiac mass (arrows), consistent with thymolipoma. (Courtesy Michael Gotway, MD.)



Figure 18-20 MRI characterization of cardiac masses. **A**, Axial T1-weighted image shows a soft-tissue intensity mass (arrows) within the right atrium. **B**, Contrast-enhanced axial T1-weighted MRI shows intense enhancement of the mass (arrows), excluding thrombus as the diagnosis and suggesting neoplasm. **C**, Balanced fast-field echo image (obtained for function) shows the mass as a low-signal lesion (arrows) within the right atrium. Resection confirmed right atrial myxoma. (Courtesy Michael Gotway, MD.)

a distinction that can be difficult with CT. However, in practice, the differentiation of tumor from associated inflammation or post-treatment changes is difficult,^{154,155} and PET is generally preferred for this distinction.

MRI is rarely indicated for imaging hilar masses; CT is usually preferred for this application. Traditionally, contrast-enhanced MR would be considered as an alternative to contrast-enhanced chest CT for the assessment of hilar or mediastinal lesions in patients with impaired renal function, but recognition that, in patients with impaired renal function, gadolinium may predispose to fibrosing dermopathy, referred to as nephrogenic systemic fibrosis, gives pause to such an approach.¹⁵⁷ Nevertheless, unenhanced MR, due to its inherent high-contrast resolution (see eFig. 83-14), may still provide valuable information regarding hilar and mediastinal masses.

Primary and metastatic cardiac tumors usually are often detected initially by echocardiography, but MRI is also an accurate method of delineating such lesions.¹⁵⁸⁻¹⁶⁰ It is thus appropriate as a problem-solving technique for patients with inconclusive echocardiographic examinations, but it is also emerging as a first-line examination for a number of cardiovascular applications. Both MRI and CT can specifically demonstrate fat within cardiac lesions and fluid within pericardial cysts (see eFig. 83-43B-D). Intracardiac tumor

(Fig. 18-20) and thrombus frequently can be differentiated by MRI, particularly following contrast administration.

DIFFUSE LUNG DISEASE

The clinical assessment of a patient with suspected *diffuse interstitial lung disease* (DILD) can be a difficult and perplexing problem. Imaging studies are often important in reaching a final diagnosis, suggesting appropriate diagnostic procedures, and assessing the patient's course and prognosis.

In clinical practice, the imaging studies most frequently used to evaluate patients with suspected DILD are chest radiographs and HRCT. HRCT is typically used when the diagnosis is uncertain at chest radiography and clinical evaluation and further assessment is considered warranted, as well as to assess treatment response in patients with established diagnoses.

HRCT findings in a wide variety of parenchymal diseases have been described, including the idiopathic interstitial pneumonias,¹⁶¹ sarcoidosis,¹⁶²⁻¹⁶⁵ diffuse neoplasms, pneumoconioses,¹⁶⁶⁻¹⁷⁰ infections, and numerous other disorders.¹⁷¹⁻¹⁸³ These studies have shown that HRCT delineates both normal anatomic structures (Fig. 18-21) and pathologic alterations in lung morphology more clearly

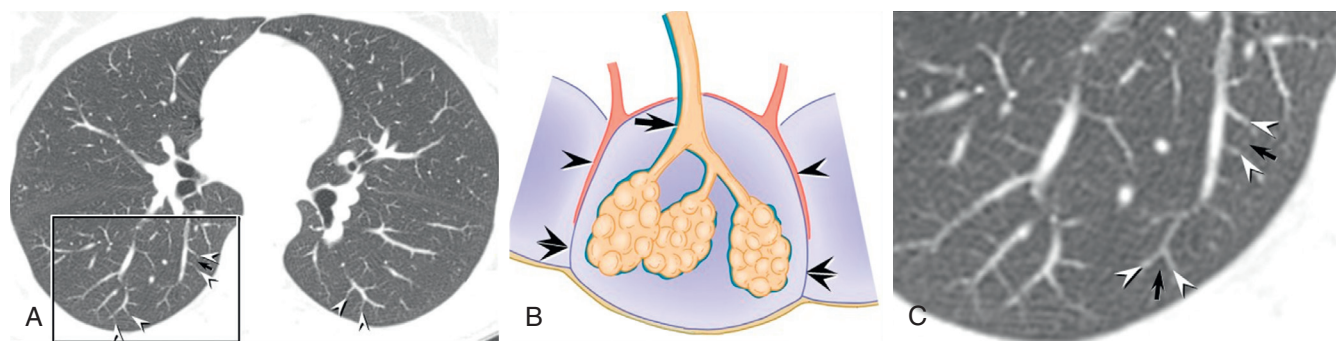


Figure 18-21 Normal high-resolution chest CT (HRCT): lobular anatomy. **A** (**C**, inset detail image of the area of interest in the right lower lobe), Axial HRCT image through the level of the right lower lobe bronchus shows normal major (oblique) fissures, central airways, and pulmonary vessels. Small peripheral pulmonary veins (*small white arrowheads*) are visible. Pulmonary veins travel within interlobular septae and therefore may outline secondary pulmonary lobules (lung parenchyma between *small white arrowheads*). Occasionally the centrilobular artery (*small black arrows*), the arterial structure entering the center of the pulmonary lobule, may be normally visible. An understanding of secondary pulmonary lobular anatomy underlies the anatomic approach for localization of small nodules detected at HRCT, which provides the basis for differential diagnosis of such nodules. **B**, Illustration of the normal secondary pulmonary lobule. Pulmonary veins (*single arrowheads*), travel within interlobular septae (*double arrowheads*). The centrilobular artery and bronchus (*arrow*) enters the secondary lobule and branches sequentially, eventually extending to the level of gas exchange units—respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli and the capillary network associated with these structures. (**A** and **C**, Courtesy Michael Gotway, MD.)

than routine CT or chest radiographs.^{165,179,184,185} Much of the basis of HRCT interpretation rests on recognition of the anatomy of the secondary pulmonary lobule (see Fig. 18-21) as reflected on HRCT images; in particular, the histopathologic patterns of disease involvement of the secondary pulmonary lobule are often reflected in HRCT images, and recognition of the HRCT correlates of these disease facilitates noninvasive diagnosis. This approach is particularly useful for the anatomic localization of small nodules at HRCT, as will be illustrated subsequently.

In general, HRCT findings of lung disease can be divided into increased lung opacity, including reticular, linear, and nodular opacities, consolidation, and GGO, and decreased lung opacities such as cysts, cavities, emphysema, and mosaic perfusion.¹⁸⁶

Increased Lung Opacity

Linear and Reticular Opacities. Thickening of the interstitial fiber network of lung by fluid, fibrous tissue, or interstitial infiltration by cells results in an increase in both linear and reticular opacities as seen on HRCT.¹⁸⁶ Interlobular septal thickening is seen in patients with a variety of interstitial lung diseases, but most typically pulmonary edema, lymphangitic spread of tumor (Fig. 18-22),¹⁸⁶ and sarcoidosis,¹⁶⁴ in addition to a small number of rarer causes.^{169,187,188} Septal thickening is not common in patients with interstitial fibrosis, except for those with sarcoidosis and asbestosis.¹⁸⁹ Honeycombing reflects extensive fibrosis with lung destruction and results in a cystic, reticular appearance on HRCT that is characteristic (Fig. 18-23).^{186,189} When honeycombing is present, normal lung architecture is distorted and secondary lobules are difficult or impossible to recognize. The cystic spaces of honeycombing can range from several millimeters to several centimeters in diameter and are characterized by thick, clearly definable, fibrous walls and are often found stacked in several layers in the subpleural regions of lung.^{190,191}

Nodules. Nodules can be classified according to their distribution as perilymphatic, random, or centrilobular according to their distribution within the secondary pulmonary

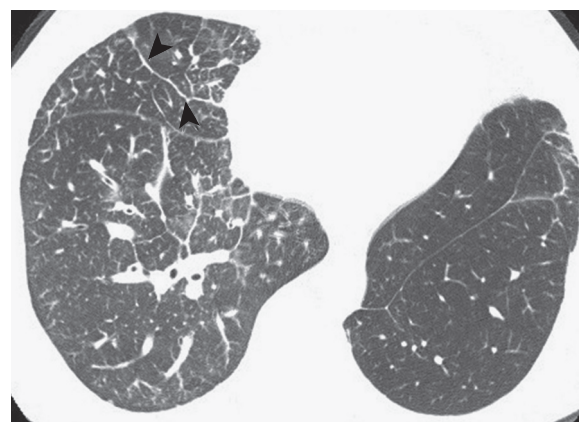


Figure 18-22 This HRCT image in a patient with lymphangitic metastasis from breast carcinoma shows smoothly thickened interlobular septa (*arrowheads*); note asymmetry of the process. (Courtesy Michael Gotway, MD.)

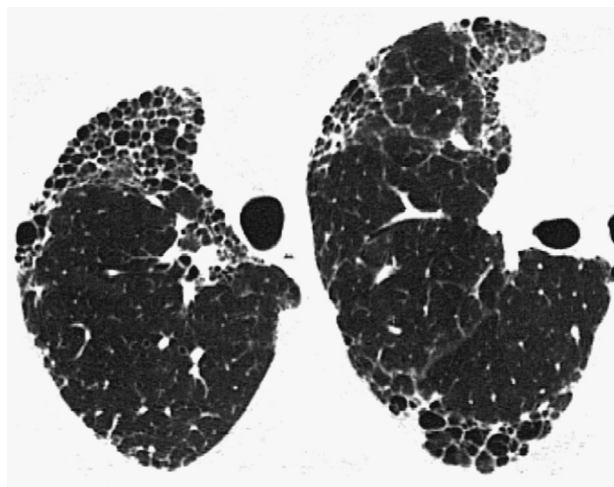


Figure 18-23 HRCT at two levels shows rheumatoid lung disease with honeycombing. The appearance of multiple, contiguous, air-filled cystic structures having a subpleural predominance is typical. (Courtesy Michael Gotway, MD.)

lobule (see Fig. 18-21).^{186,192} Recognition of one of these distributions is fundamental to the generation of differential diagnoses.^{192,193} Perilymphatic nodules affect the peribronchovascular, interlobular septal, subpleural, and centrilobular interstitial compartments and are typical of sarcoidosis, which tends to have a peribronchovascular and subpleural predominance (see Fig. 18-24, Video 18-10)^{164,192-194}; silicosis and coal workers' pneumoconiosis, which predominate in the subpleural and centrilobular regions^{169,174,187}; and lymphangitic spread of tumor, which is usually peribronchovascular and septal.¹⁸⁶ Random nodules are most typical of miliary infections (see Fig. 18-25)¹⁹⁵ and hematogenous metastases.¹⁸⁶ Well-defined centrilobular nodules can be seen in silicosis and coal workers' pneumoconiosis,¹⁶⁷ asbestosis,¹⁶⁶ and Langerhans cell histiocytosis.¹⁹⁶ Poorly defined centrilobular nodules often reflect bronchiolar or peribronchiolar abnormalities¹⁹³ and can be seen in silicosis and coal workers' pneumoconiosis,¹⁶⁷ endobronchial spread of infection,¹⁹⁵ pulmonary

hemorrhage (see Fig. 18-26), hypersensitivity pneumonitis (see Fig. 18-27),^{197,198} and pulmonary edema.¹⁹⁹

Consolidation and Ground-Glass Opacity. Air space consolidation, by definition, is seen when alveolar air is replaced by fluid, cells, or other material.¹⁹¹ On HRCT, consolidation results in an increase in lung opacity associated with obscuration of underlying vessels. Among patients with chronic DILD, common causes of this pattern include chronic eosinophilic pneumonia and cryptogenic organizing pneumonia.^{200,201} The term GGO refers to a hazy increase in lung opacity that is not associated with obscuration of underlying vessels.¹⁹¹ This finding can reflect the presence of a number of diseases and can be seen in patients with either minimal interstitial thickening or minimal air space filling.^{178,180,202-205} It often reflects the presence of active disease, such as pulmonary edema (see eFig. 70-6G); alveolitis associated with some idiopathic interstitial pneumonias (see eFigs. 63-11C-F, 16, 17, 18, 20, 28, 26, and 29);

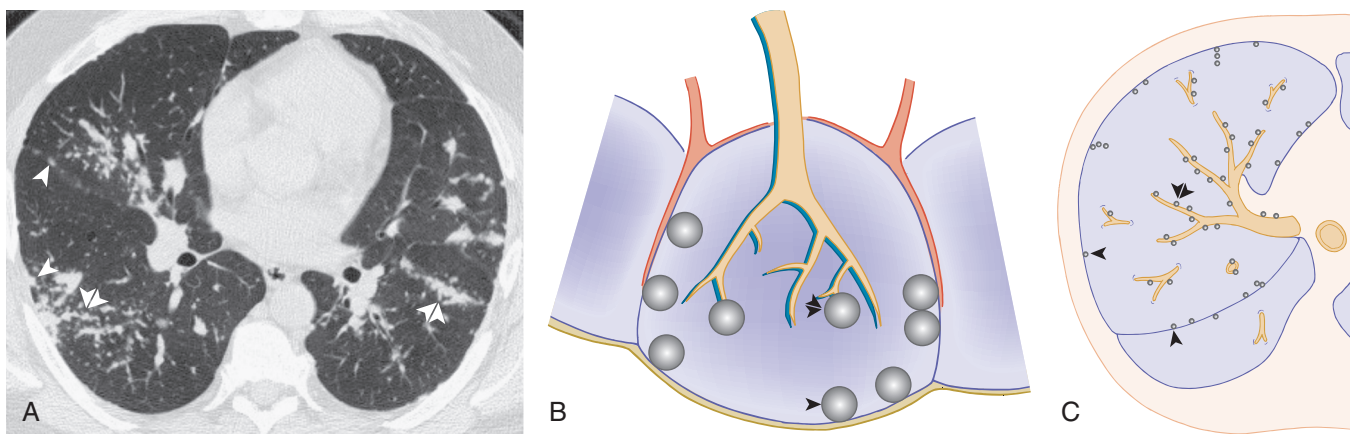


Figure 18-24 HRCT illustration of perilymphatic nodules: sarcoidosis. **A**, Axial HRCT image of a patient with sarcoidosis shows numerous subpleural nodules in relation to costal and fissural visceral pleural surfaces (single arrowheads), and nodules are also clearly visible along bronchovascular bundles (double arrowheads). These findings, along with the patchy distribution of the nodules, are diagnostic of sarcoidosis in the appropriate clinical setting. **B**, Perilymphatic nodule distribution in the secondary pulmonary lobule. Small nodules are primarily distributed along the visceral pleural surfaces (single arrowhead), interlobular septae, and bronchovascular bundles (double arrowhead). **C**, Anatomic localization of small nodules at HRCT. Perilymphatic nodules are primarily distributed along costal and fissural visceral pleural surfaces (single arrowheads), interlobular septae, and bronchovascular bundles (double arrowhead). (A, Courtesy Michael Gotway, MD.)

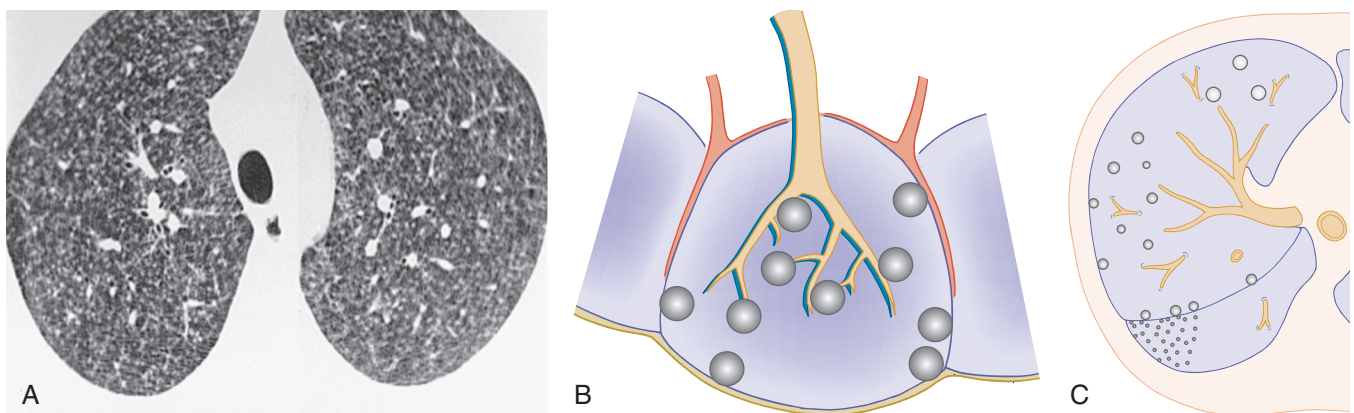


Figure 18-25 HRCT illustration of random nodules: miliary tuberculosis. **A**, Axial HRCT image shows numerous, small, circumscribed nodules equally distributed throughout the lungs bilaterally, with nodules seen in contact with fissural pleural surfaces, as well as sparing the fissural surfaces. **B**, Random nodule distribution in the secondary pulmonary lobule. Small nodules are seen along the bronchovascular bundles, interlobular septae, and visceral pleural surfaces. **C**, Anatomic localization of small nodules at HRCT. Random nodules are distributed along costal and fissural visceral pleural surfaces, interlobular septae, and bronchovascular bundles in a fairly even, diffuse distribution bilaterally. (A, Courtesy Michael Gotway, MD.)

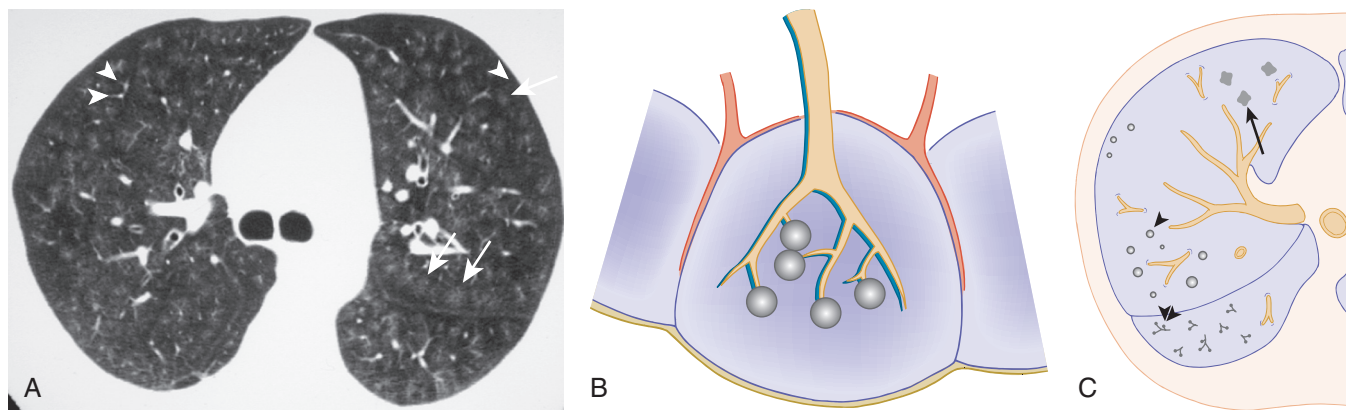


Figure 18-26 HRCT illustration of centrilobular nodules: chronic pulmonary hemorrhage. **A**, Axial HRCT image shows numerous, bilateral, poorly defined ground-glass opacity nodules (arrows). Note that the nodules approach, but generally do not touch, costal and fissural visceral pleural surfaces; this relationship is particularly evident along the left major fissure. Also note that occasionally the relationship of the nodules to adjacent pulmonary veins (single arrowheads, right upper lobe) and interlobular septae (single arrowhead, left upper lobe) is apparent—the nodules have a small amount of “spared” lung separating them from the interlobular septae and small pulmonary veins, a key indicator of the centrilobular distribution. **B**, Centrilobular nodule distribution in the secondary pulmonary lobule. Small nodules are seen primarily in the center of the lobule, along the bronchovascular bundles, largely sparing the interlobular septae, pulmonary veins, and visceral pleural surfaces. **C**, Anatomic localization of small nodules at HRCT. Centrilobular nodules typically approach, but do not contact, the costal and fissural visceral pleural surfaces and interlobular septae. Centrilobular nodules may be round (single arrowhead) and solid, poorly defined and irregular in shape (arrow), or show ground-glass attenuation. When centrilobular nodules show branching configurations (double arrowhead), the nodule morphology is often described as “tree-in-bud” opacity. (A, Courtesy Michael Gotway, MD.)

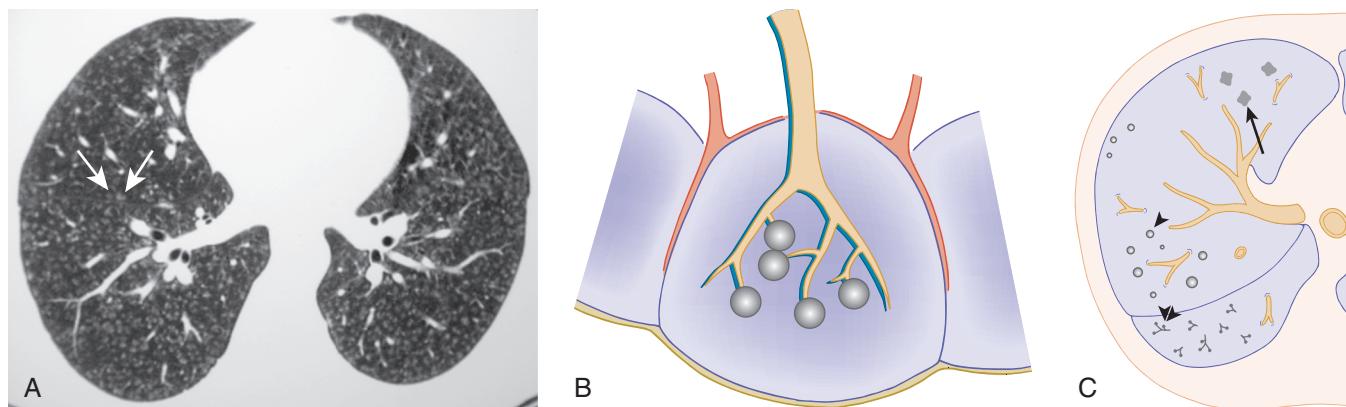


Figure 18-27 HRCT illustration of centrilobular nodules: hypersensitivity pneumonitis. **A**, Axial HRCT image shows numerous, bilateral, poorly defined ground-glass opacity nodules (arrows). Note that the nodules approach, but generally do not touch, costal and fissural visceral pleural surfaces—this appearance is a key indicator of the centrilobular distribution. **B**, Centrilobular nodule distribution in the secondary pulmonary lobule. Small nodules are seen primarily in the center of the lobule, along the bronchovascular bundles, largely sparing the interlobular septae, pulmonary veins, and visceral pleural surfaces. **C**, Anatomic localization of small nodules at HRCT. Centrilobular nodules typically approach, but do not contact, the costal and fissural visceral pleural surfaces and interlobular septae. Centrilobular nodules may be round (single arrowhead) and solid, poorly defined and irregular in shape (arrow), or show ground-glass attenuation. When centrilobular nodules show branching configurations (double arrowhead), the nodule morphology is often described as “tree-in-bud” opacity. (A, Courtesy Michael Gotway, MD.)

pulmonary hemorrhage (see Fig. 18-26, see eFigs. 70-6C, eFigs. 67-1, 2E and F, 3C, 4, 5, 8B, 9B-E); infectious pneumonias (particularly *Pneumocystis jirovecii* pneumonia (see eFigs. 90-12B, 14C, 15B, 18, and 20B and C); lipid pneumonia (see eFig. 70-6B); alveolar proteinosis (see eFigs. 70-4 and 5, 8A-D, 9, and 10); hypersensitivity pneumonitis (see Fig. 64-4), often with a centrilobular nodular appearance (see Fig. 18-27, see eFigs. 64-2C and D, and 64-3C-E); and sarcoidosis.²⁰⁶ However, GGO may reflect the presence of fibrosis below the resolution of HRCT, particularly when the GGO is associated with other findings of fibrotic lung disease, such as coarse reticulation, architectural distortion, traction bronchiectasis, and honeycombing.²⁰³ Because of its potential reflection of active lung

disease, the presence of GGO may lead to surgical lung biopsy, depending on the clinical status of the patient.

Decreased Lung Opacity

Emphysema. Emphysema is accurately diagnosed with HRCT, and HRCT is more sensitive for the detection of emphysema than routine CT or chest radiographs.^{141,181} Emphysema results in focal areas of low attenuation that can be easily contrasted with surrounding, higher-attenuation, normal lung parenchyma (Fig. 18-28). In patients with centrilobular emphysema, areas of lucency can be seen surrounding the centrilobular artery and have a patchy, upper lobe distribution. In panlobular emphysema, focal areas of lucency are not usually present, but a

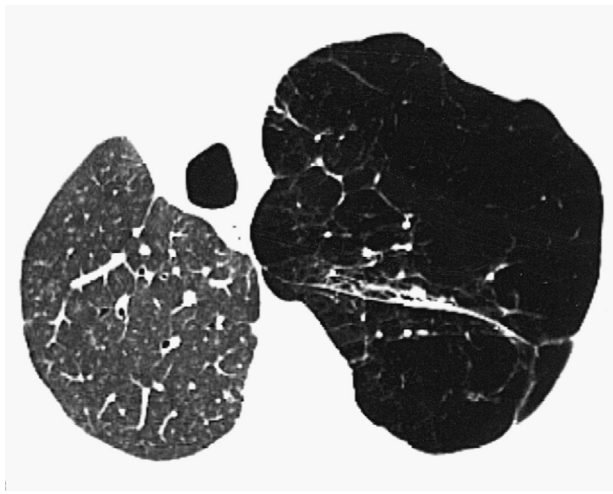


Figure 18-28 HRCT scans for emphysema. This HRCT is from a patient with panlobular emphysema who underwent right lung transplantation. The emphysematous left lung is easily contrasted with the normal-appearing right lung. The emphysematous left lung is less dense, is larger in volume, and contains fewer and smaller vessels. (Courtesy Michael Gotway, MD.)

diffuse simplification of lung architecture and a decrease in lung attenuation are present (see Fig. 18-28). In clinical practice, HRCT is rarely used in an attempt to diagnose emphysema. Usually, the combination of a smoking history, a low diffusing capacity, airway obstruction on pulmonary function tests, and an abnormal chest radiograph showing large lung volumes is sufficient to make the diagnosis. HRCT is useful for evaluating patients with COPD who are being considered as candidates for lung volume-reduction surgery. In addition, some patients with early emphysema can present with clinical findings more typical of infiltrative lung disease or pulmonary vascular disease, namely shortness of breath and low diffusing capacity, without evidence of airway obstruction on pulmonary function tests.²⁰⁷ In such patients, HRCT can be valuable for detecting the presence of emphysema and excluding an interstitial abnormality. If significant emphysema is found on HRCT, no further evaluation is necessary.²⁰⁸

Cystic Pulmonary Diseases. Lymphangioleiomyomatosis (see images associated with Chapter 69, eFig. 56-2, and Fig. 18-29) and Langerhans cell histiocytosis often result in multiple lung cysts (see Fig. 69-3B), which have a distinct appearance on HRCT.^{196,209-215} The cysts have a thin but easily discernible wall, ranging up to a few millimeters in thickness. Associated findings of fibrosis are usually absent or much less conspicuous than they are in patients with honeycombing. In these diseases, the cysts are usually interspersed within areas of normal-appearing lung. In patients with Langerhans cell histiocytosis (see Fig. 69-3B and eFig. 54-37), the cysts can have bizarre shapes and an upper lobe predominance. Numerous causes of cystic and cavitary pulmonary lesions are recognized.²¹⁶

Mosaic Perfusion. Decreased lung attenuation not reflecting the presence of cystic lesions or emphysema can sometimes be recognized on HRCT in patients who have diseases that produce air trapping, poor ventilation, or poor perfusion.^{181,200,202,204-208,211-213,217,218} The areas of decreased

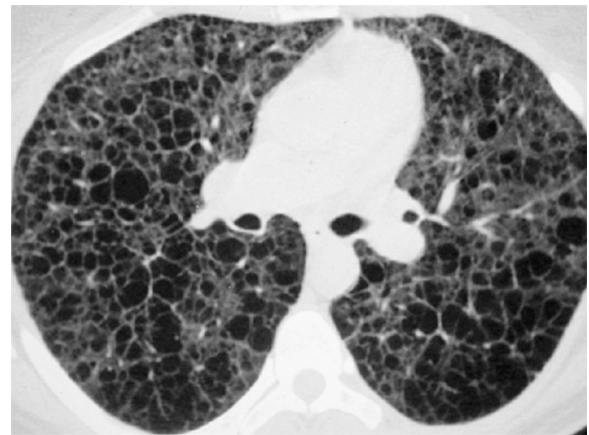


Figure 18-29 HRCT for cystic lesions. An HRCT in a patient with lymphangioleiomyomatosis shows the multiple cystic areas, which have clearly definable walls, in contrast to the appearance of emphysema (see Fig. 18-28). (Courtesy Michael Gotway, MD.)

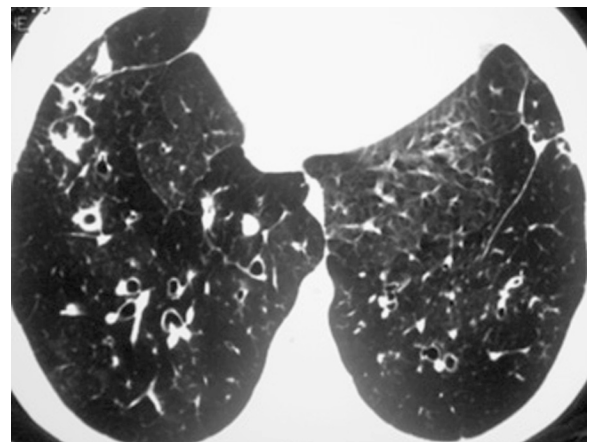


Figure 18-30 HRCT for mosaic perfusion. HRCT in a patient with cystic fibrosis shows inhomogeneous opacity in the lung bases bilaterally, somewhat geographically distributed. The areas of decreased attenuation represent mosaic perfusion in this patient resulting from a combination of regional air trapping due to large airway disease and hypoperfusion in the affected areas of lung. (Courtesy Michael Gotway, MD.)

lung attenuation that are seen on HRCT can be focal, lobular,²¹⁹ lobar, or multifocal. The term *mosaic perfusion* has been used to refer to patchy decreased lung attenuation resulting from perfusion abnormalities (Fig. 18-30).¹⁹¹ In patients with air trapping, this appearance can be enhanced with expiratory HRCT.^{181,218,220,221}

Diagnostic Utility

The utility of chest radiographs and HRCT in the clinical diagnosis of diffuse lung disease relates to their ability to detect the presence of lung disease (sensitivity and specificity), characterize its nature, assess disease activity, and guide lung biopsy.

Sensitivity and Specificity. It is well documented that chest radiographs are limited in both their sensitivity and specificity in patients with DILD.²²²⁻²²⁴ For example, Gaensler and Carrington²²³ reported that nearly 16% of patients with pathologic proof of interstitial lung disease had normal

chest radiographs. The sensitivity of CT for detecting lung disease has been compared with that of chest radiography in a number of studies; without exception, these have shown that CT, and particularly HRCT, is more sensitive than chest radiography for detecting both acute and chronic diffuse lung diseases.^{163,170,175,197,225,226} The average results of several studies show that the sensitivity of HRCT for detecting DILD is approximately 94% compared with 80% for chest radiographs.²²⁴ The sensitivity of HRCT has also proved superior to that of routine CT obtained with wider collimation.^{166,205,206}

It is important to note that the increased sensitivity of HRCT is not achieved at the expense of decreased specificity or diagnostic accuracy.^{171,174,224} A specificity of 96% for HRCT compared with 82% for chest radiographs was reported by Padley and colleagues²²⁴ in patients with DILD. In other studies of patients with suspected DILD on chest radiographs, normal biopsy results have been proven in 10% to 20% of patients.^{222,223} Although HRCT is clearly more sensitive than chest radiographs, its sensitivity in detecting lung disease is not 100%, and a negative HRCT cannot generally be used to rule out DILD. For example, in one study, although HRCT had high sensitivity and specificity values, 4% of subjects with biopsy-proven lung disease were interpreted as having a normal HRCT.²²⁴

Diagnostic Accuracy. Even in the presence of definite abnormalities, chest radiographs have limited diagnostic accuracy for patients with DILD.²²⁷ Numerous reports have shown that HRCT is significantly more accurate than are chest radiographs in diagnosing both acute and chronic diffuse lung disease, usually allows a more confident diagnosis, and is subject to considerably less interobserver variation in its interpretation.^{171,173,174,181,189,205,228-234}

In an attempt to refine diagnostic accuracy, Grenier and coworkers¹⁷² used Bayesian analysis to determine the relative value of clinical data, chest radiographs, and HRCT for patients with chronic DILD. For this study, two samples from the same population of patients with 27 different diffuse lung diseases were consecutively assessed: an initial retrospectively evaluated set of “training” cases ($n = 208$) and a subsequent prospectively evaluated set of “test” cases ($n = 100$) for validation. The results showed that for the test group an accurate diagnosis could be made in 27% of cases based on clinical data only, increasing to 53% ($P < .0001$) with the addition of chest radiographs and to 61% ($P = .07$) with the further addition of HRCT scans. In some situations, HRCT findings are sufficiently diagnostic to obviate biopsy.^{161,186,235} In particular, the presence of an HRCT pattern typical of usual interstitial pneumonia/idiopathic pulmonary fibrosis, seen in more than 50% of patients suspected of this disorder, is sometimes sufficient to bypass surgical lung biopsy when encountered in the context of typical clinical features.^{190,235,236}

Assessing Disease Activity. In addition to being more sensitive, specific, and accurate than chest radiographs, HRCT may also play a critical role in the evaluation of disease activity in patients with diffuse lung disease.^{161,186,235} Available data suggest that, in certain cases, HRCT may be used to determine the presence or absence, and extent, of reversible (acute or active) lung disease compared with

irreversible (fibrotic) lung disease. Furthermore, because HRCT may accurately identify subtle “active” lung disease, it can be used to study patients who are being treated in order to monitor the success or failure of the treatment.^{161,162,186,235,237-240}

Although a number of HRCT findings have been described as being indicative of active or reversible lung disease in patients with different disease entities, most attention has focused on the potential significance of GGO in patients with chronic DILD.^{178,203} This finding has been reported in a wide range of DILDs, including usual interstitial pneumonia, desquamative interstitial pneumonitis, lymphoid interstitial pneumonia, sarcoidosis, hypersensitivity pneumonitis, alveolar proteinosis, cryptogenic organizing pneumonia, respiratory bronchiolitis, and chronic eosinophilic pneumonia.¹⁷⁸ GGO has also been described in patients with premalignant lesions and pulmonary neoplasms, in particular atypical adenomatous hyperplasia and adenocarcinoma in situ (formerly referred to as *bronchoalveolar carcinoma*), respectively, as well as a wide variety of acute lung processes, such as acute interstitial pneumonia; bacterial, fungal, viral, and parasitic infections; pulmonary hemorrhage syndromes; and congestive heart failure and other causes of pulmonary edema.

Although GGO is a nonspecific finding and can reflect various histologic abnormalities, in patients with chronic DILD, GGO may represent active parenchymal inflammation. In a study of 26 patients with DILD in whom histopathologic correlation was obtained, biopsy specimens demonstrated that GGO corresponded to inflammation in 24 cases (65%), and in 8 additional cases (22%), inflammation was present but fibrosis predominated.^{178,203} In only 5 cases (13%) was fibrosis the sole histologic finding. Similarly, Leung and associates,²⁰² in a study of 22 patients with a variety of chronic DILDs and evidence of GGO as either a predominant or an exclusive HRCT finding, showed that 18 (82%) had potentially active disease identified on lung biopsy.

GGO may also be seen in the presence of interstitial fibrosis without active inflammation.^{178,202,203} For GGO to indicate active disease, this finding should generally be unassociated with HRCT findings of fibrosis.^{178,202,203} In patients with idiopathic pulmonary fibrosis, a significant correlation has been found between the presence of HRCT findings of GGO and pathologic findings of active inflammation, the development of pulmonary fibrosis, the patient's prognosis,^{182,237,238,240-247} and the likelihood of response to therapy.^{237,238,240} HRCT has also been used to assess disease activity, as well as the likelihood of response to therapy in patients with sarcoidosis.^{162,165,194,204,239} In most series of patients with sarcoidosis, the main HRCT determinant of disease activity has been the presence and, to a lesser degree, the extent and distribution of small nodules.^{165,204}

Guiding Lung Biopsy. Among the many indications for HRCT, an important one is as a potential guide for surgical lung biopsies. Many “diffuse” lung diseases are quite patchy in distribution, with areas of abnormal lung frequently interspersed among relatively normal areas of lung parenchyma. Furthermore, both active and fibrotic disease can be present in the same lung.^{142,144,161,182,186,194,199-201,235,246,247} To establish a specific diagnosis and assess the clinical

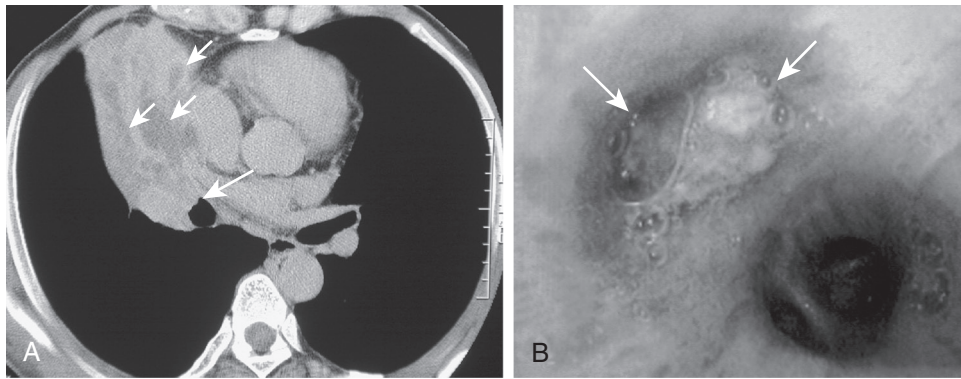


Figure 18-31 Chest CT for airway lesions. **A**, Axial CT image shows a squamous carcinoma occluding the right middle lobe bronchial orifice (*large arrow*), producing complete collapse of the right middle lobe. Low-attenuation tubular foci (*small arrows*) visible within the collapsed right middle lobe represent mucus-impacted bronchi. **B**, Bronchoscopic image shows the carcinoma occluding the right middle lobe bronchus and protruding into the bronchus intermedius (*arrows*). (Courtesy Michael Gotway, MD.)

significance of the abnormalities present, it is critically important to sample those portions of the lung that are the most abnormal and the most likely to be active. Optimal sampling sites can be selected with HRCT. Also, as a direct consequence of its ability to visualize, characterize, and determine the distribution of parenchymal disease, HRCT also provides a unique insight into the likely efficacy of transbronchial or surgical lung biopsy in patients with either acute or chronic diffuse lung disease. Surgical lung biopsy is often diagnostic, with accuracies greater than 90% generally reported,^{186,223,235,248,249} but this procedure is also subject to sampling error. HRCT is of considerable value in determining the most appropriate sites for biopsy.^{161,186,229,235}

INTRATHORACIC AIRWAY DISEASE

Previously, CT was used to evaluate the trachea or central airways, but HRCT is currently more appropriate for imaging the peripheral airways. With the development of MSCT, volumetric HRCT is now possible, which allows simultaneously optimized evaluation of the central airways combined with HRCT technique for evaluation of the peripheral airways in a single examination.¹⁹⁰

Central Airways

CT can effectively evaluate lesions (Fig. 18-31) of the trachea and central airways,²⁵⁰ including strictures and stenoses, inflammatory diseases such as polychondritis (Fig. 18-32), some cases of extrinsic versus intrinsic obstruction,²⁵¹ aspirated foreign objects, tracheobronchomalacia, and neoplasms (Video 18-11).²⁵⁰ MS CT, with its ability to acquire images rapidly with equal resolution in all planes, is particularly useful in this assessment and can provide detailed three-dimensional analysis of the central airways (Video 18-11B). The ability to produce excellent quality three-dimensional images aids in the evaluation of subtle airway stenoses and complex airway lesions, particularly when they are oblique with respect to the imaging plane. In the assessment of tracheal and central bronchial neoplasms, CT does not substitute for bronchoscopy and biopsy, but it can be useful to determine the extent of invasion and to direct the bronchoscopist to a particular

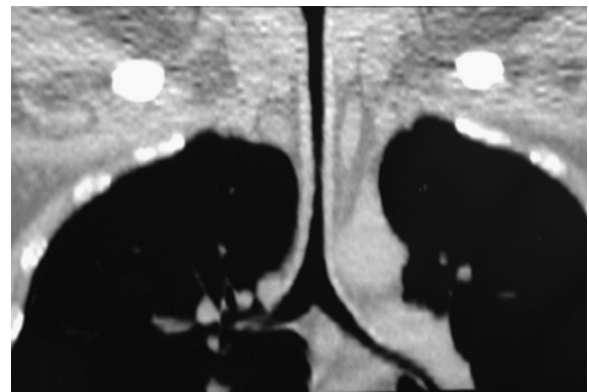


Figure 18-32 Multislice CT for central airway evaluation. With rapid volumetric high-resolution imaging, MSCT allows detailed three-dimensional analysis of the airways. In a patient with relapsing polychondritis, coronally reconstructed image shows diffuse thickening and narrowing of the trachea. (Courtesy Michael Gotway, MD.)

segment or to a precise location of peribronchial disease. The major value of CT imaging is its ability to visualize the luminal contents, the airway wall, and the surrounding soft tissue. Accordingly, the use of CT carries the greatest benefit in circumstances that require all three of these capabilities.

Bronchiectasis

CT should be the initial investigation in all patients with suspected bronchiectasis, as discussed further in Chapter 48.²⁵²⁻²⁵⁵ The sensitivity and specificity of HRCT (scans at 1-mm intervals) for diagnosing bronchiectasis to the segmental level are 95% to 98% (Fig. 18-33), whereas the sensitivity and specificity of thick-section CT are only about 80%. In current medical practice, CT has replaced bronchography, and a review of the CT criteria for diagnosing bronchiectasis and the technical pitfalls that may be encountered has been published.²⁵⁶ MSCT scanning with narrow collimation (on the order of 1 mm) provides a larger volume of coverage with spatial resolution superior to routine single-slice spiral CT yet also allows for volumetric imaging and the creation of exquisite reformatted images, including volume rendering.

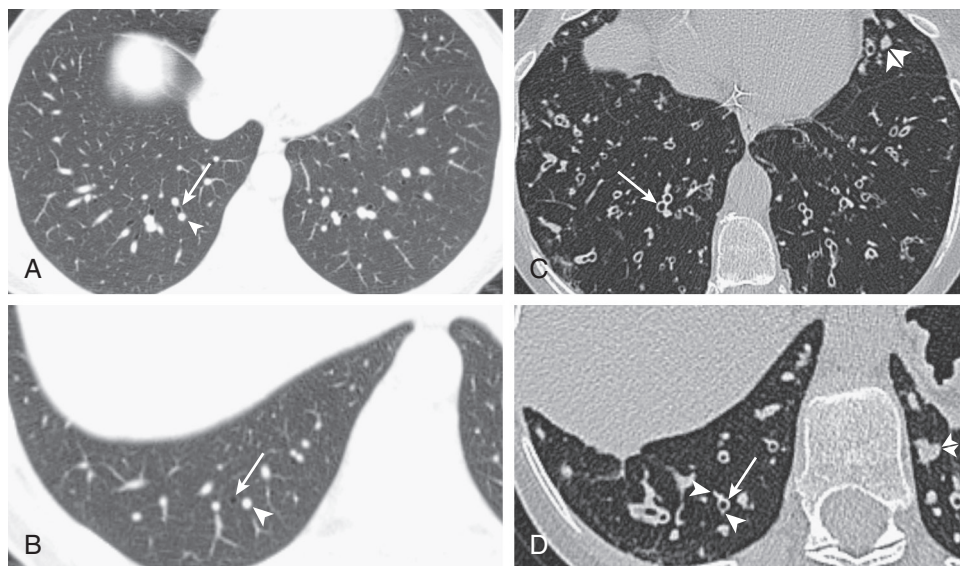


Figure 18-33 Normal appearance of bronchi at chest CT compared with bronchiectasis. **A** and **B**, Axial chest CT images show the appearance of normal peripheral bronchi—the internal diameter of the bronchus (arrows) is similar to the adjacent pulmonary artery (arrowheads), and the bronchi are patent and uniformly thin-walled. **C** and **D**, Detailed images through the lung bases showing CT features of bronchiectasis and large airway disease. The bronchi are abnormally dilated—the internal diameter of the bronchi (arrows) clearly exceeds the size of the adjacent pulmonary arteries (single arrowheads). The bronchi are also clearly visualized more peripherally than is normal (compare with **A** and **B**, where peripheral bronchi are largely not visible). Finally, the bronchi (arrows) are visibly thick-walled, and several airways show intraluminal secretions and impaction (double arrowheads). (Courtesy Michael Gotway, MD.)

Small Airway Disease


HRCT has the ability to demonstrate abnormalities of small airways having a diameter of a few millimeters or less.^{161,193,199,200,218,220,221,235,257} Abnormalities that can be diagnosed include (1) inflammatory forms of bronchiolitis, such as cellular bronchiolitis (usually due to infection [Fig. 18-34A], aspiration, or hypersensitivity pneumonitis [see Figs. 18-27 and 18-34B]), respiratory bronchiolitis (Fig. 18-34C), follicular bronchiolitis, and panbronchiolitis (Fig. 18-34D); and (2) small airway diseases associated with airflow obstruction (e.g., constrictive bronchiolitis [Fig. 18-34E and F]).²⁵⁷ Cryptogenic organizing pneumonia has been previously classified as a disease of the small airways but is now considered an idiopathic interstitial pneumonia.^{161,235,257} The use of postexpiratory HRCT is particularly important in the diagnosis of small airway diseases because air trapping may be visible in the absence of other abnormalities (see eFig. 106-3).^{220,221} Postexpiratory HRCT may be performed by imaging after a forced vital capacity maneuver (Video 18-12, see Videos 106-1 and 106-3)²⁵⁸ or with lateral decubitus CT.²⁵⁹ Available data suggest that postexpiratory CT performed during a forced vital capacity maneuver, called “dynamic expiratory CT,” is a more effective technique for the demonstration of subtle or transient air trapping.^{258,260,261}

CARDIOVASCULAR DISEASE

Pulmonary Thromboembolism

Chest MSCT, performed with intravenous contrast injection using a specific CT pulmonary angiography (CTPA) technique, has emerged as the test of choice for the imaging evaluation

of suspected pulmonary embolism. Ventilation-perfusion scanning has long been used as the initial test for such patients. Its strengths and its limitations are well known and reviewed in Chapter 57. The test is extremely safe, widely available, and exceedingly sensitive: a normal perfusion scan effectively excludes pulmonary embolism. A high-probability scan is quite specific (97% in the *Prospective Investigation of Pulmonary Embolism Diagnosis* [PIOPED] I study).²⁶² However, a substantial fraction of perfusion scans yield results that are abnormal but nonspecific. In addition, it has been recognized increasingly that imaging the lower-extremity veins can be useful and cost-effective for many patients suspected of having acute pulmonary embolism; thus, a single imaging procedure that evaluates both the lower extremity veins and the pulmonary arteries would be quite useful. Owing to these considerations, improved CTPA techniques are being increasingly used to diagnose pulmonary thromboembolism.

Single-slice spiral CTPA, in pooled data from a number of studies, showed an overall sensitivity and specificity approaching 90% and 96%, respectively. Regardless, criticisms regarding the methodology employed in single-slice CTPA studies, as well as the long-held faith in the diagnostic accuracy of catheter pulmonary angiography for suspected pulmonary embolism, led to relatively slow adoption of the use of CTPA for this application in some centers. Once MSCT technology became available, however, it became clear that multislice CTPA scans could demonstrate smaller vessels and therefore, by inference, should be more sensitive than single-slice CTPA for the detection of thromboembolic disease. Several studies investigating the incremental value of multislice CTPA over single-slice CTPA for the diagnosis of thromboembolic disease (Fig. 18-35A, Video 18-13) 

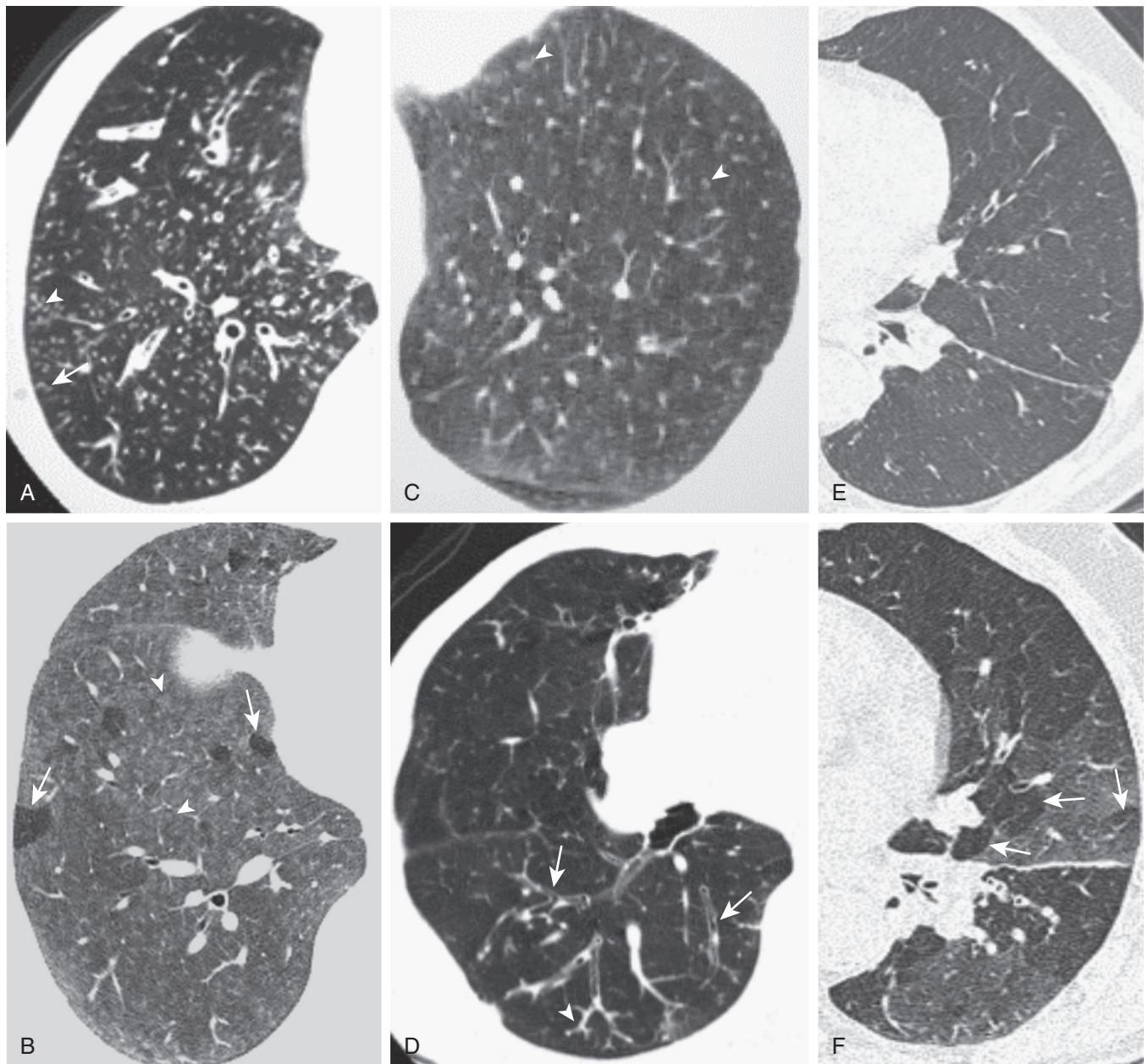


Figure 18-34 HRCT manifestations of small airway disease. **A**, Bronchopneumonia and bronchiolitis. Axial chest CT image through the right lower lobe shows numerous small, solid centrilobular nodules (*arrow*), some with branching configurations (*arrowhead*), the latter consistent with “tree-in-bud” opacity, representing bronchiolar impaction. Compare with diagrams in *Figs. 18-26* and *18-27*. **B**, Cellular bronchiolitis in hypersensitivity pneumonitis. Axial chest CT image through the right lower lobe shows poorly defined ground-glass opacity centrilobular nodules (*arrowheads*). Areas of lobular low attenuation (*arrows*), representing air trapping resulting from inflammatory bronchiolitis, are present. **C**, Respiratory bronchiolitis. Axial chest CT image through the right upper lobe shows faintly detectable ground-glass attenuation nodules (*arrowheads*). **D**, Panbronchiolitis. Axial chest CT image through the right lower lobe shows large airway thickening and dilation (*arrows*), associated with intraluminal material and small airway impaction (*arrowhead*). **E** and **F**, Constrictive bronchiolitis (bronchiolitis obliterans). Axial chest CT image through the left lung shows normal inspiratory scan findings (**E**). Postexpiratory imaging (**F**) shows the development of numerous areas of low attenuation consistent with air trapping, in some areas with a lobular configuration (*arrows*), due to small airway obstruction. (Courtesy Michael Gotway, MD.)

were conducted shortly after the introduction of this technology, including the PIOPED II trial,²⁶³ the results of which were published in 2006. In PIOPED II, the sensitivity of multislice CTPA for the diagnosis of pulmonary embolism was 83% (95% confidence limits, 76% to 92%) and the specificity was 96%. The positive predictive value of a positive multislice CTPA study was 86%, and the negative predictive value was 95%. The sensitivity of multislice CTPA in

the PIOPED II trial has led some investigators to question the utility of CTPA for the evaluation of suspected pulmonary embolism; currently, however, multislice CTPA is widely used as the first-line diagnostic modality for the investigation for such patients all across the world.

Ultimately, the main question that must be answered when patients suspected of thromboembolic disease undergo CTPA is, “Can anticoagulation be safely withheld



Figure 18-35 CT pulmonary angiography (CTPA) and indirect CT venography images demonstrate pulmonary emboli and deep vein thrombosis. **A**, CTPA shows bilateral large filling defects (arrows) consistent with pulmonary emboli. **B** and **C**, Axial indirect CT venography (i.e., without additional contrast material injection) shows filling defects in the right common femoral and iliac veins (arrowheads) consistent with venous thrombi. (Courtesy Michael Gotway, MD.)

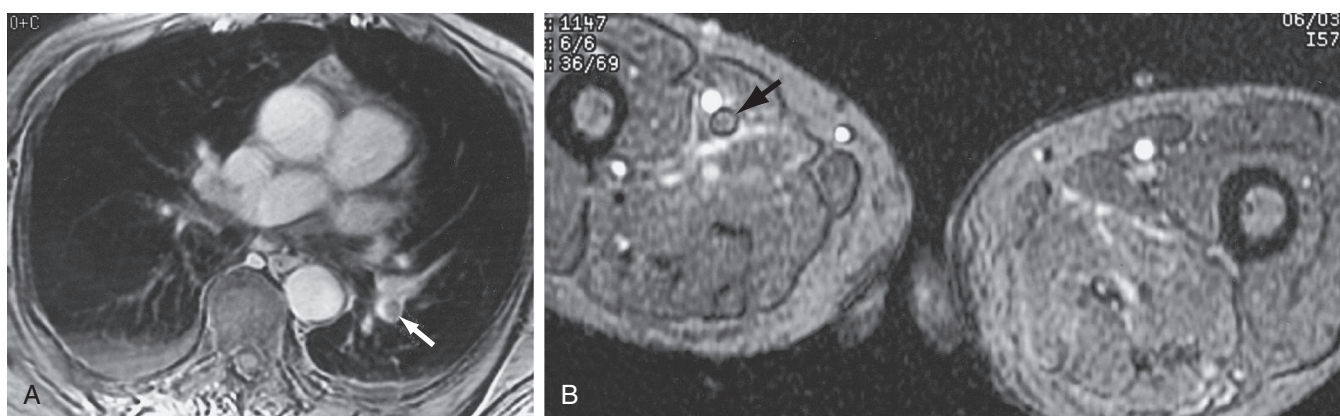


Figure 18-36 MRI demonstrates pulmonary embolism and deep vein thrombosis. **A**, This magnetic resonance angiogram (MRA) image shows a filling defect consistent with pulmonary embolus in the left lower lobe artery (arrow). **B**, This MR image made without contrast material shows a filling defect in the right superficial femoral vein consistent with venous thrombus (arrow), whereas the contralateral vein is patent and without filling defects. (Courtesy Michael Gotway, MD.)

in patients with a negative result?” In other words, what is the negative predictive value of CTPA for thromboembolic disease? Several studies have addressed this question, and the negative predictive value of CTPA ranges from 95% to 99%.^{263,264} Importantly, it has been suggested that further diagnostic testing should be pursued when CTPA results (with or without indirect CT venography, see later) are discordant with the clinical probability for pulmonary embolism, particularly when CTPA results are negative and the clinical probability of pulmonary embolism is considered high.²⁶³

Various investigations also suggest that CTPA may also be able to detect deep venous thrombosis in the proximal leg and pelvic veins without injection of additional contrast material (Fig. 18-35B and C), a technique known as indirect CT venography.²⁶⁵⁻²⁶⁷ The addition of CT venography to CTPA studies obtained for the evaluation of suspected pulmonary embolism allows for the simultaneous evaluation of deep venous thrombosis and pulmonary embolism with a single test. Combining CTPA with CT venography increased the sensitivity for the diagnosis of pulmonary embolism to 90%, and the negative predictive value of the combination of the examinations was 97% in the PIOPED II trial.²⁶³

As for CTPA, MRI can demonstrate pulmonary embolism directly as intravascular filling defects on cross-sectional images (Fig. 18-36 and Video 18-14).²⁶⁸⁻²⁸⁰ Experience with MRI in patients suspected of having pulmonary embolism is far more limited than that with CTPA. The two techniques are probably overall roughly similar in accuracy for the detection of pulmonary embolism, although MRI may show more pronounced interobserver variability than CTPA and may show slightly decreased sensitivity compared with CTPA at the segmental and subsegmental vascular levels.²⁷⁸ The diagnostic accuracy of MRI for pulmonary embolism assessment is enhanced through the use of multiparametric protocols that include a combination of real-time steady-state free precession imaging, perfusion imaging, low flip angle, three-dimensional gradient-echo imaging, and contrast-enhanced MRA (see Video 18-14).^{268,269,272,275,276;} not all studies reporting the diagnostic accuracy of MRI for acute pulmonary embolism diagnosis have used a multiparametric approach.²⁷⁸ In addition, MRI has been shown to be highly accurate for detecting deep venous thrombosis.^{281,282}

The potential advantages of MRI are the lack of need for iodinated contrast material or ionizing radiation, ability to

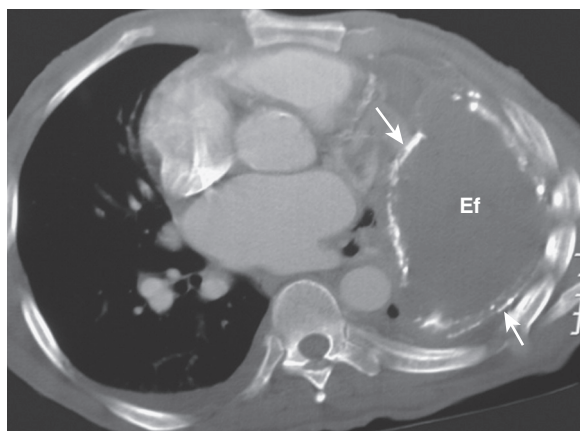


Figure 18-37 Chest CT for pleural disease. Chest CT performed in a patient with a history of tuberculosis shows pleural thickening and calcification (arrows) and a residual pleural effusion (Ef) indicative of empyema. (Courtesy Michael Gotway, MD.)

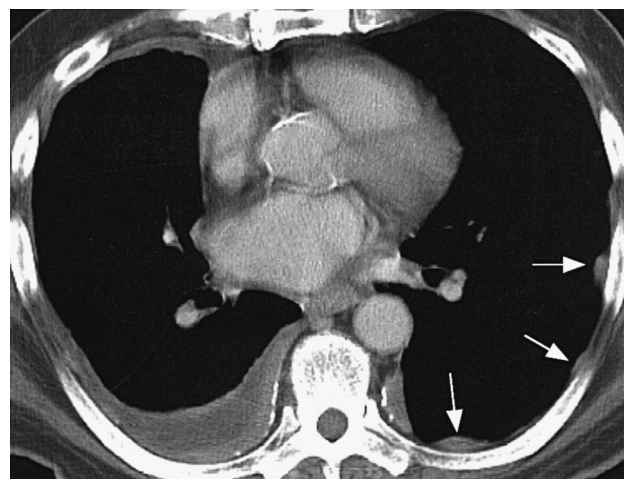


Figure 18-38 Chest CT for pleural disease. A patient with prior asbestos exposure has focal areas of pleural thickening or pleural plaques within the left hemithorax (arrows). Pleural thickening on the right is associated with pleural effusion. This reflected the presence of early malignant mesothelioma. (Courtesy Michael Gotway, MD.)

image the pulmonary arteries and deep venous system in a single examination, ability to assess right ventricular function simultaneously, and ability to perform perfusion imaging. The latter point is of particular significance in light of the imperfect sensitivity of CTPA. The advantages of CTPA are higher spatial resolution, wider availability, fewer artifacts, faster examination time, and simpler, more robust technology, as well as, importantly, the availability of alternative diagnoses for patients with negative results. Currently, CTPA is a realistic option in the clinical management of patients with suspected pulmonary embolism; the clinical use of MRI is limited to medical centers with personnel who are highly skilled with advanced MRI technology.²⁷⁸

See the online version of this chapter for additional discussions on imaging acquired aortic diseases and congenital anomalies of the thoracic great vessels.



PLEURAL DISEASE

Most pleural processes, as discussed further in Chapters 79 to 82, can be imaged accurately and cost-effectively with conventional radiography or ultrasonography. However, CT, including single-slice spiral, multislice, and high-resolution, can be useful in evaluating several clinical problems relating to the pleura.^{102,296,297} These include differentiation of pleural and parenchymal disease (including the distinction between lung abscess and empyema); detection of subtle pleural abnormalities (such as early pleural plaques or small pneumothoraces); location of pleural fluid collections and pleural tumors, including localization for interventional purposes (e.g., tube drainage, biopsy); determination of the extent of pleural tumors (in particular, metastases and mesothelioma); and occasionally, characterization of pleural lesions (Figs. 18-37, 18-38, and Fig. 18-11) or paradiaphragmatic lesions. MRI currently has a limited role in the evaluation of pleural abnormalities.

Type of Fluid

Most effusions are near to water in attenuation; accordingly, CT numbers cannot be used to predict the specific

gravity of the fluid or its cause. One exception, however, is acute or subacute hemothorax. Hemothorax can sometimes appear inhomogeneous in attenuation, with some areas having an attenuation value higher than that of water.

The presence of pleural thickening is often of value in predicting the nature of the effusion. In patients with effusion (see Chapter 79), the presence of pleural thickening on CT indicates that the effusion is an exudate.¹⁰² By definition, the pleura is considered thickened if it is visible on a contrast-enhanced or unenhanced CT. Transudates are not associated with pleural thickening. Conversely, the absence of pleural thickening on contrast-enhanced CT is less helpful. In this case, the effusion can be an exudate or transudate. Only about 60% of exudates are associated with visible pleural thickening. However, the absence of pleural thickening on a contrast-enhanced scan rules out empyema; empyema is always associated with parietal pleural thickening on contrast-enhanced CT.

Pleural versus Parenchymal Disease

Opacities detected at chest radiography can frequently be localized as either parenchymal or extraparenchymal (pleural or chest wall) in location. Chest radiographic features that favor a parenchymal location for a pulmonary opacity include a relative rounded contour; relatively acute angles between the opacity and the chest wall (Fig. 18-39, see eFigs. 33-4B-E, 13B and C, and 26B and C), and air-fluid levels (when present) that are relatively similar in length in both frontal and lateral projections (Fig. 18-40). In contrast, opacities that are extraparenchymal in location often show an elliptical or lenticular contour; the opacity forms obtuse angles at the point of contact with the chest wall (see Fig. 18-39), and air-fluid levels commonly show significantly different lengths in the frontal and lateral projections (see Fig. 18-40). However, occasionally chest radiography may not be able to distinguish between parenchymal disease, pleural disease, and pathology affecting both compartments. CT can be useful in this setting. Pleural lesions

Acquired Aortic Disease

Acquired aortic diseases, such as aortic dissection, can be imaged with aortography, CT aortography, echocardiography, and MRI.^{283,284} Transthoracic echocardiography can assess the ascending aorta, but its limited field of view restricts its utility. Transesophageal echocardiography has produced definitive results,²⁸⁵ but this technique requires sedation and carries the risk of esophageal injury. Catheter aortography has previously been considered the standard method for demonstrating aortic dissection, but it is invasive and can produce both false-positive and (more commonly) false-negative results.²⁸³ It has largely been replaced by cross-sectional imaging methods for the evaluation of aortic pathology.

CT aortography can accurately identify the intimal flap, the true and false lumens (eFig. 18-38), the vessels involved by dissection, and the presence of end-organ perfusion impairment; thus, CT aortography is used routinely for evaluating aortic dissection.²⁸⁶ Complications of dissection, such as mediastinal hematoma, hemothorax, and hemo-pericardium, can also be detected. Limitations of CT aortography include the need for iodinated contrast material and its limited ability to assess aortic valve function (information that some surgeons require and others do not). The latter concern has been alleviated somewhat with the development of retrospectively electrocardiographic-gated CT aortography. With this technique, the imaging acquisition is conducted simultaneously with the electrocardiographic tracing, and data can then be reconstructed at any time during the cardiac cycle. Images reconstructed during late diastole often are motion free and allow assessment of the coronary arteries and aortic valve (eFig. 18-39).

MRI has several advantages in suspected aortic dissection. No iodinated contrast material is required (eFig. 18-40), and MRI does not require ionizing radiation. Fast gradient-echo and steady-state free precession MRI sequences can assess aortic valve and left ventricular function. However, MRI also has limitations in the assessment of dissections. Some patients are excluded from MRI for safety reasons. MRI examinations usually require more time than CT aortography studies for dissection. Artifacts lead to nondiagnostic studies more often with MRI than with CT aortography. Greater experience is required to interpret MR images accurately.

The relative accuracy of aortography, transesophageal echocardiography, CT aortography, and MRI for detecting and characterizing dissections has not been established by definitive prospective clinical trials. For practical reasons, such a trial is not likely to be conducted. Accordingly, which technique is superior is arguable, and judgment is required for individual cases. Aortography is the time-tested gold standard, but it is invasive and known to be inaccurate, particularly in cases with thrombosed false lumina, and has largely been replaced by cross-sectional methods. Extensive data indicate that both CT aortography and MRI are accurate in evaluating dissections.^{286,287} Our experience is that CT aortography and MRI have equivalent accuracy for detecting dissection and that both are more sensitive than aortography. However, no single technique always fulfills all of the requirements for characterization of dissections. Several reports suggest that hemodynamically unstable

patients with suspected aortic dissection should be studied with transesophageal echocardiography, whereas stable patients should be evaluated by CT aortography or MRI.^{285,288} MRI is also recommended for serial studies of patients with chronic dissection.

Both CT aortography and MRI have advantages over aortography for evaluating thoracic aortic aneurysms. Both are noninvasive, can document that a mediastinal mass is an aneurysm, can assess the thickness of the aortic wall, and can measure accurately the diameter and longitudinal extent of the aneurysm.²⁸⁶ In most situations, CT aortography is sufficient for diagnosis, and because it is less expensive and faster than MRI, it is the preferred study. MRI is particularly useful for patients with contraindications to iodinated contrast material.

In suspected traumatic aortic rupture, CT aortography has replaced catheter aortography for initial diagnosis.²⁸⁹ Catheter aortography is generally reserved for indeterminate CT aortography studies, problem-solving cases, or percutaneous interventional therapy, such as during endovascular stent placement. Although MRI has been reported in this setting, it is not normally used because the problems of monitoring and sustaining the trauma patient are greater with MRI; in addition, CT aortography examinations are substantially faster than MR examinations, and time is of the essence in traumatically injured patients. Chronic pseudoaneurysms (eFig. 18-41) in survivors of traumatic or iatrogenic aortic injury can be evaluated with either MRI or CT aortography.

Congenital Anomalies of the Thoracic Great Vessels

Echocardiography, MRI, and angiography are commonly chosen modalities for demonstrating great vessel anomalies, associated cardiac malformations, and their physiologic sequelae in children. CT angiography usefully can demonstrate simple vascular anomalies, such as an aberrant subclavian artery and persistence of the left superior vena cava. The vascular supply of sequestrations can be identified by MRI or CT angiography, and angiography is rarely necessary (see eFig. 18-18). In adults with congenital anomalies of the great vessels, MRI is often the procedure of choice because its field of view is wider than that of echocardiography and it is noninvasive but, in complex lesions, these techniques often are complementary. CT angiography is also an effective tool for the investigation of adult and pediatric congenital cardiovascular abnormalities.

Published experience with MRI in developmental anomalies of the great vessels has focused on aortic coarctation and pulmonary artery obstruction, but extensive investigations of the utility of MR techniques for other vascular abnormalities, including extracardiac shunts and partial anomalous pulmonary venous return, have been performed. Coarctation is detected accurately by MRI (eFig. 18-42) or CT angiography. Complications of treatment, including restenosis and aneurysm, can be detected,^{290,291} and the degree of collateral vascular supply, which affects the risk of surgery, can be established with either technique. The pressure gradient across the coarctation and the relative increase in blood flow distal to the coarctation

may be quantified by MRI. Such calculations also provide quantitative data regarding the efficacy of operative and percutaneous interventions.

MRI is the noninvasive imaging procedure of choice for detecting central pulmonary artery obstruction,²⁹² evaluating the potential for palliative shunts,²⁹³ and assessing the

results of surgery,^{290,294,295} although CT angiography is also highly useful. Comparisons of MRI with transthoracic echocardiography usually have shown MRI to be superior for demonstration of great vessel anomalies. Diagnosis of a variety of other congenital vascular anomalies by MRI and MSCT angiography also has been reported.

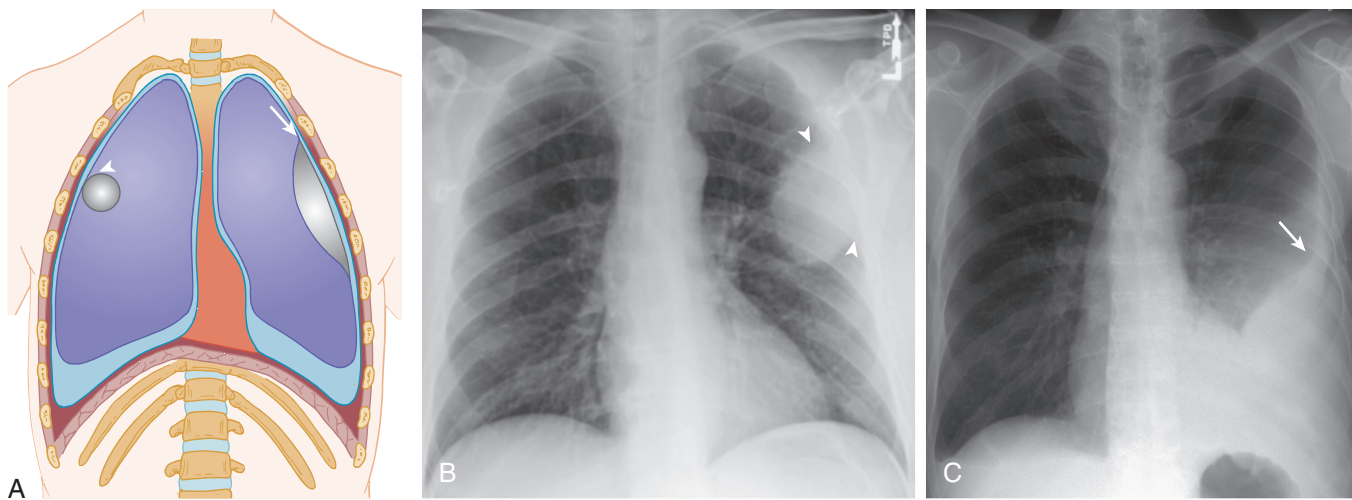


Figure 18-39 Chest radiographic localization of an opacity as parenchymal or extraparenchymal: angle of the opacity with the chest wall. **A**, Illustration showing the typically *acute* angles (arrowhead) formed by a parenchymal process, such as a lung abscess, with the chest wall, compared with the *obtuse* angles (arrow) usually formed with the adjacent chest wall by an *extraparenchymal* process, such as empyema. **B**, Frontal chest radiograph in a patient with a lung abscess shows the typically *acute* angles (arrowheads) formed with the chest wall by a *parenchymal* process. **C**, Frontal chest radiograph in a patient with empyema shows the usual *obtuse* angles (arrow) formed with the chest wall by an *extraparenchymal* process. (B and C, Courtesy Michael Gotway, MD.)

typically have obtuse tapering margins and sharp interfaces with adjacent lung parenchyma (see eFig. 33-7B-E), whereas parenchymal lesions tend to blend with lung parenchyma and have acute, irregular margins (see eFigs. 33-4B-E, 13A, and 26A). One of the more common and therapeutically important problems in this category is differentiating lung abscess from empyema. Empyemas typically have smooth outer and inner margins, a lenticular shape, and a sharp interface with underlying lung; they tend to displace pulmonary vessels around them (see eFig. 33-7B-E) and often display prominent rim enhancement (the “split pleura sign”) with intravenous administration of iodinated contrast material. Lung abscesses are characterized by spherical or polygonal shape, a thick wall with a shaggy or irregular inner margin, and permeation between adjacent pulmonary vessels (see eFigs. 33-4B-E, 12B and C, 26B and C). None of these features is unique, but when considered together, they permit categorization of the abnormality in most cases.

Early Detection

The contrast resolution and cross-sectional format of CT make it highly sensitive and accurate in detecting pleural thickening and early pleural plaques in patients with asbestos-related pleural disease (see Fig. 18-38).^{166,297} Circumscribed plaques often are overlooked on chest radiographs unless they are calcified or attain a thickness of about 5 mm or more. Furthermore, normal extrapleural soft tissues and fat can be misinterpreted as plaques when they are prominent on chest radiography. Both standard CT and HRCT are accurate for detecting pleural plaques, but HRCT may be more accurate for characterizing subtle plaques.

CT has been shown to be accurate and more sensitive than conventional radiographs in detecting pneumothoraces. This can be of particular importance in trauma patients, who may require intubation and positive-pressure ventilation.

Key Points

- After the medical history and physical examination, radiography is the most commonly used technique in the evaluation of patients with known or suspected thoracic disease.
- High-quality frontal and lateral chest radiographs can address many clinical questions. Currently available techniques of digital recording of images offer many interpretive and logistical advantages.
- Spiral (or helical) CT technology allows the entire chest to be scanned during a single breath-hold thereby permitting *volumetric* imaging, which generates a continuous block of data (rather than slices) that can be reconstructed to produce images in different slice thicknesses or orientations. Multislice CT uses *multiple* channels during the spiral acquisition, thereby dramatically increasing the amount of data acquired and the speed of acquisition.
- Multislice CT, with its rapid acquisition time and greatly improved resolution, has become the imaging method of choice for further evaluation of pulmonary nodule(s), lung cancer, mediastinal abnormalities, diffuse lung diseases, airway diseases, and suspected pulmonary embolism.
- Radiation is a relatively weak carcinogen, and the risk for radiation-induced carcinogenesis from a CT scan is generally far less than the information gained from an appropriately indicated study.
- *Magnetic resonance imaging* (MRI) is useful in evaluating superior sulcus lesions, brachial plexopathy, and certain cardiac and mediastinal abnormalities. MRI is also useful, though less often used than multislice CT, for evaluating suspected aortic dissection and pulmonary embolism.
- Further information about the application of imaging techniques and the results of these studies is presented in the chapters concerning specific pulmonary diseases that appear later in this book.

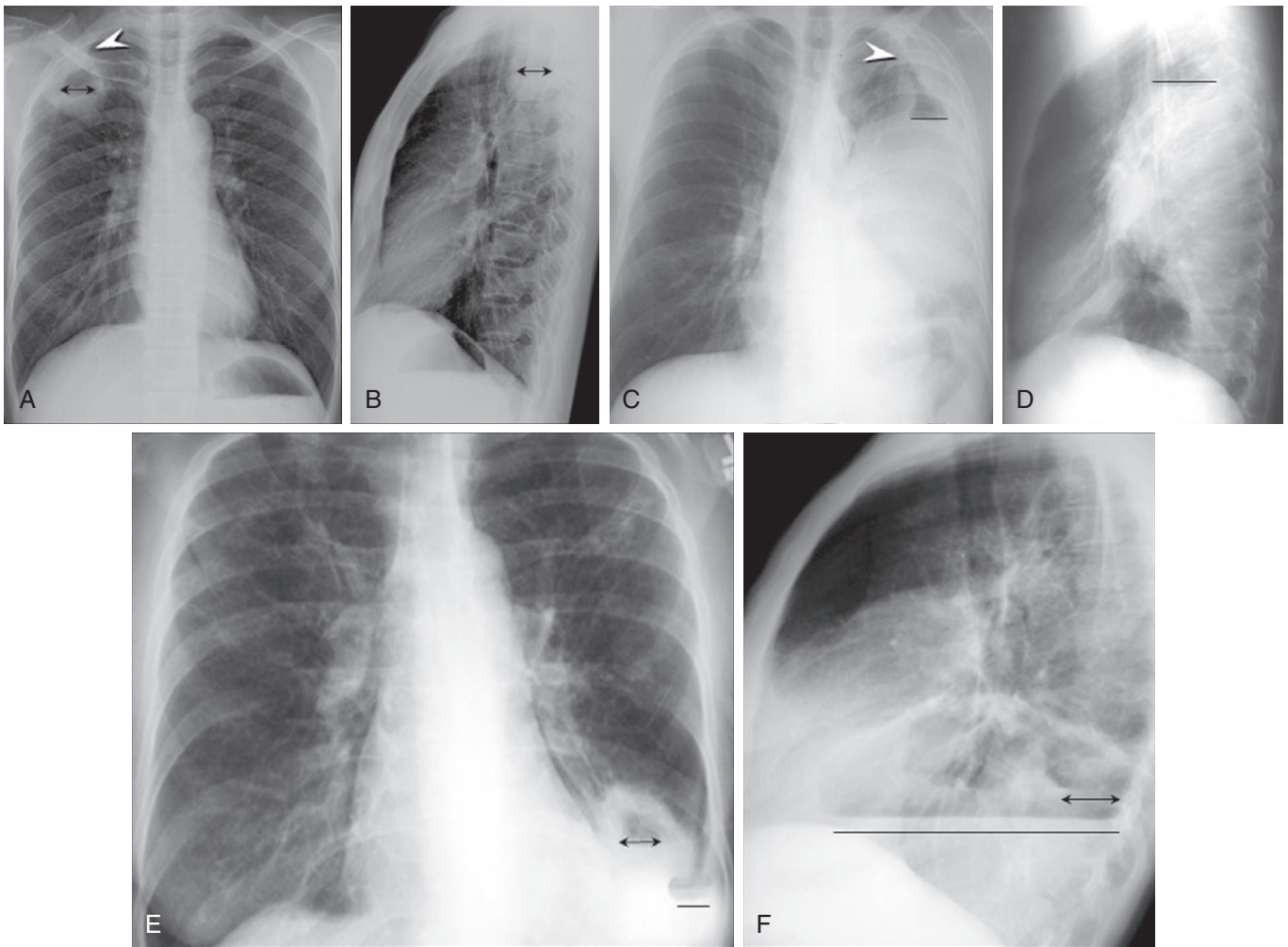


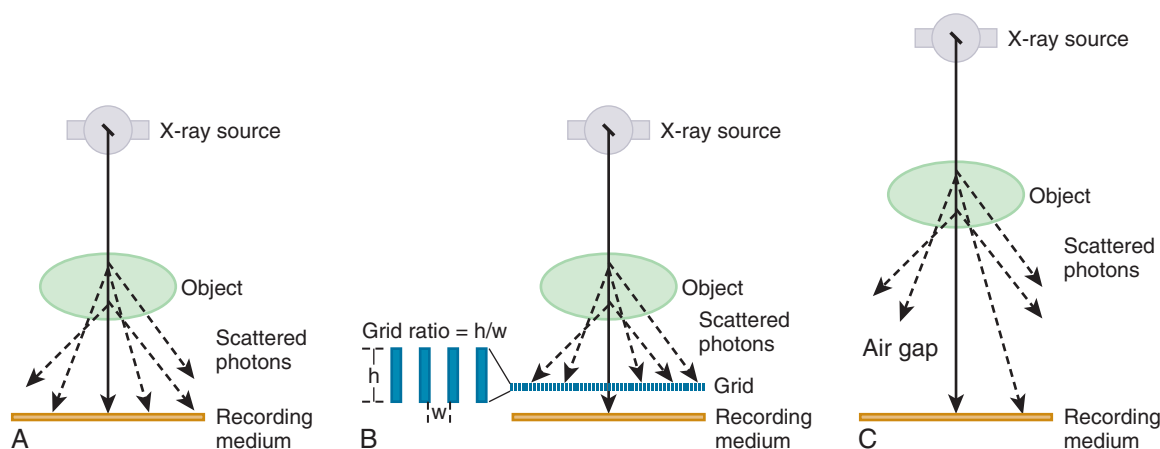
Figure 18-40 Chest radiographic localization of an opacity as parenchymal or extraparenchymal: differential air-fluid length. **A**, Frontal and **B**, lateral chest radiograph in a patient with lung abscess (same patient as eFig. 33-13A) shows an opacity with an air-fluid level (*line*) that is roughly the same length in both the frontal (**A**) and lateral (**B**) projections. The typical acute angle formed by the parenchymal process with the chest wall (*arrowhead*) is evident. **C**, Frontal and **D**, lateral chest radiograph in a patient with empyema shows an opacity creating the obtuse angles with the chest wall characteristic of an extraparenchymal process (*arrowhead*). An air-fluid level is present (*line*) and shows a different length in the frontal (**C**) and lateral (**D**) projections, which suggests extraparenchymal localization of the process. **E**, Frontal and **F**, lateral chest radiograph in a patient with lung abscess creating a broncho-pleural fistula shows an opacity with an air-fluid level (*double arrowhead line*) of roughly the same length in frontal (**E**) and lateral (**F**) projections, representing a lung abscess. Another process with air-fluid levels that differ in length markedly between the frontal (**E**) and lateral (**F**) projections (*line*) represents empyema. (Courtesy Michael Gotway, MD.)

Complete reference list available at **ExpertConsult**.

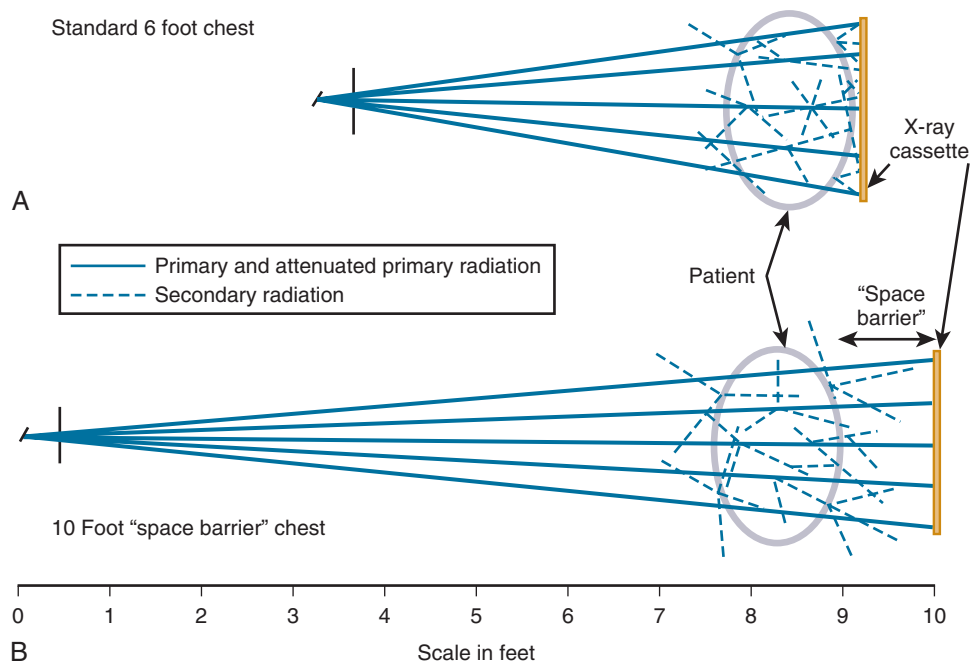
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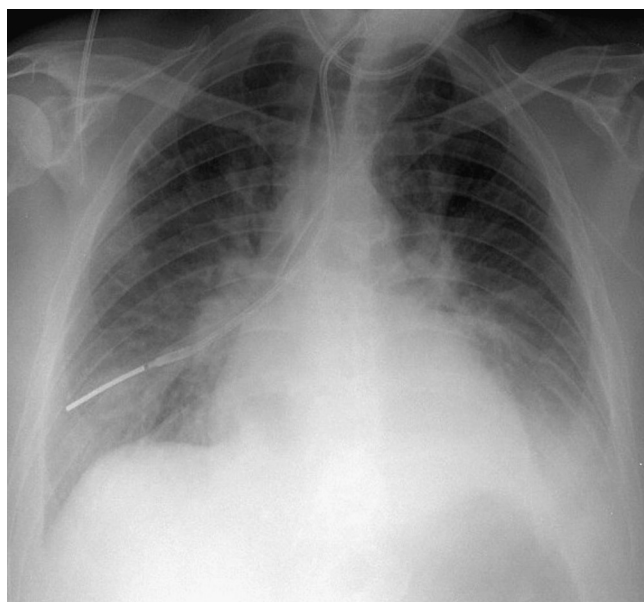
eFIGURE IMAGE GALLERY



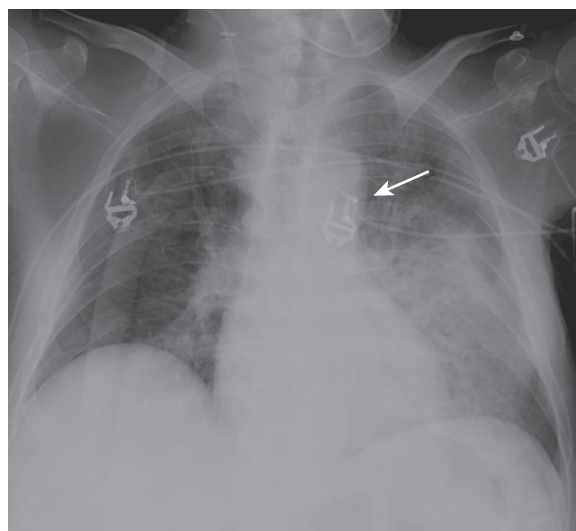
eFigure 18-1 Scattered radiation and scatter reduction. **A**, When an object is radiographed, some photons (the primary x-ray beam) (*solid line*) pass unaffected through the patient. Scattered or secondary radiation (*dashed lines*) arises at various angles to the primary beam and may expose the recording medium, reducing image contrast and detail. **B**, Scatter can be reduced with a grid. An antiscatter grid placed between the object and the recording medium reduces exposure due to scattered radiation. A grid is made of thin layers of radiation absorber (e.g., lead). Scattered radiation traveling at an angle to the grid layers is absorbed, although some scattered radiation at shallow angles may pass through. The grid ratio is equal to the height of the radiation absorber strips divided by the distance between them. **C**, Scatter can be reduced with an air gap. When the distance between the object and the recording medium is increased, an air gap is created. With an air gap, scattered photons at sufficiently great angles miss the recording device.



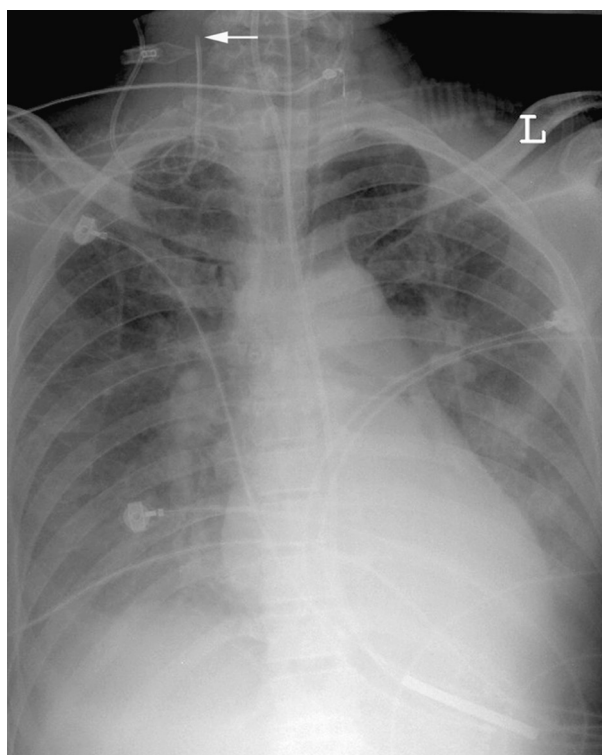
eFigure 18-2 A, The geometry of a standard 6-foot chest radiograph. For beam energies in the recommended range (>120 kVp), a grid is necessary between the patient and the detector to diminish scattered radiation. **B**, A 10-foot air gap or “space barrier” can also be used. The air gap obviates the need for a grid. The 10-foot tube-to-detector distance helps to minimize geometric enlargement. The avoidance of the grid diminishes patient radiation exposure.



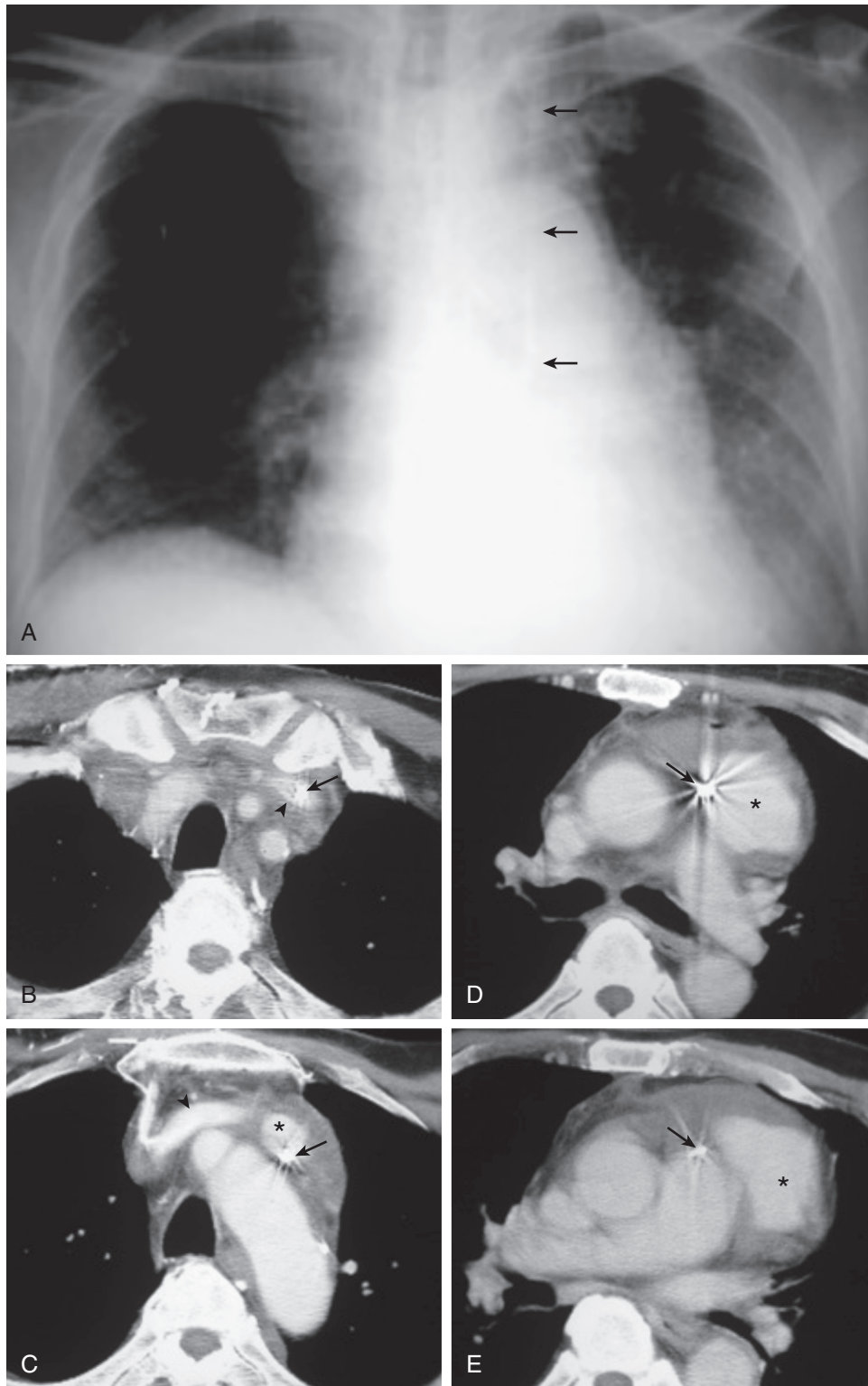
eFigure 18-3 Portable chest radiograph shows malposition of an enteric tube. Frontal chest radiograph shows placement of an enteric tube in the right lower lobe bronchus. (Courtesy Michael Gotway, MD.)



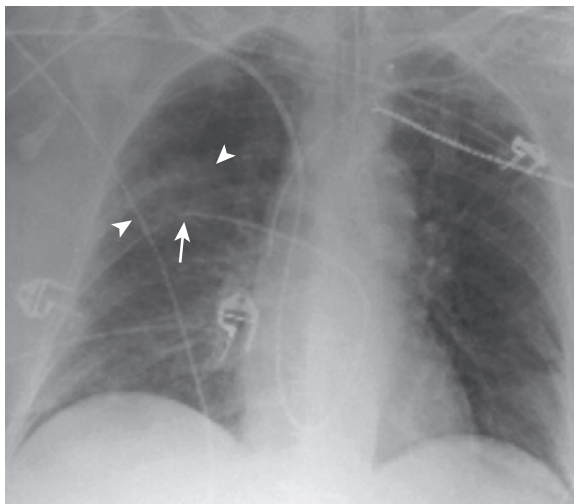
eFigure 18-5 An intensive care unit portable radiograph demonstrates malposition of a right central venous catheter. The catheter has been inadvertently inserted into the right carotid artery; the tip (*arrow*) resides in the aortic arch. A large area of consolidation is seen in the left lung. (Courtesy Michael Gotway, MD.)



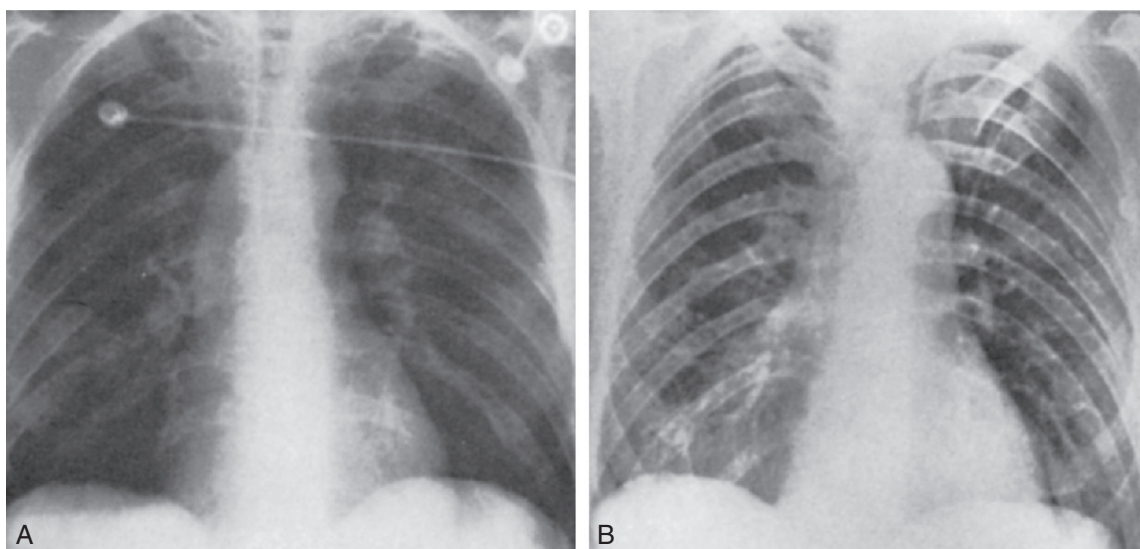
eFigure 18-4 A portable radiograph shows a misplaced central venous line. Note that the right external jugular venous catheter tip (*arrow*) is within the right internal jugular vein, rather than the superior vena cava. Extensive opacities (pulmonary edema) are present in both lungs. (Courtesy Michael Gotway, MD.)



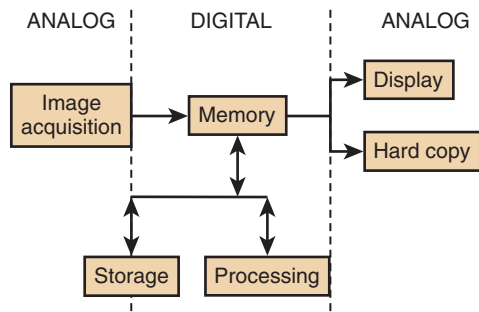
eFigure 18-6 Portable intensive care unit radiography is useful in several situations. **A**, Chest radiograph performed following insertion of a left internal jugular central venous catheter shows the catheter (*arrows*) following a more medial and inferior course than expected for left internal jugular and brachiocephalic vein catheter placement. Sequential axial contrast-enhanced chest CT images near the thoracic apex (**B**), at the thoracic aortic arch (**C**), at the level of the left pulmonary artery (**D**), and at the level of the main pulmonary artery (**E**) shows the catheter (*arrow*) extending through the inferior margin of the left brachiocephalic vein (*arrowhead*, **B** and **C**) into an extravascular location more inferiorly, with surrounding active contrast extravasation (*) and hematoma resulting from venous perforation and pulmonary artery laceration. (Courtesy Michael Gotway, MD.)



eFigure 18-7 Sequelae of a malpositioned pulmonary artery (PA) catheter. The catheter (arrow = tip) extends too far peripherally into the segmental vessels of the right upper lobe artery. The catheter had been in this location for a number of hours. Note the opacity in the right upper lobe (arrowheads), representing pulmonary hemorrhage or infarction secondary to vessel obstruction by the PA catheter. (Courtesy Michael Gotway, MD.)



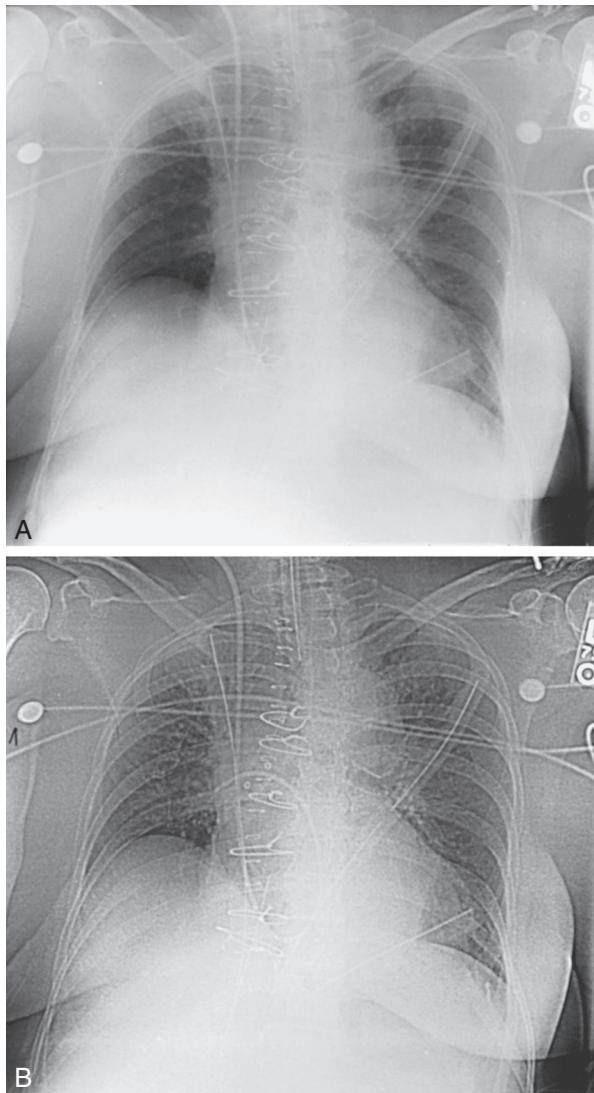
eFigure 18-8 Portable radiography has limitations. **A**, This anteroposterior (AP) supine portable radiograph was made in the intensive care unit. The energy of the beam was 100 kVp, and the focal spot–film distance was 40 inches. The pulmonary markings are poorly visualized because of a long exposure with motion blurring and a short focal spot–film distance with magnification and detail degradation. **B**, This radiograph was obtained from the same patient shortly after that shown in **A**, but in the main radiology department. The patient was sitting in a chair. The energy of the beam was 130 kVp, with a focal spot–film distance of 60 inches. Radiograph in **B** shows much better detail than radiograph **A** and also has less magnification. (Courtesy Michael Gotway, MD.)



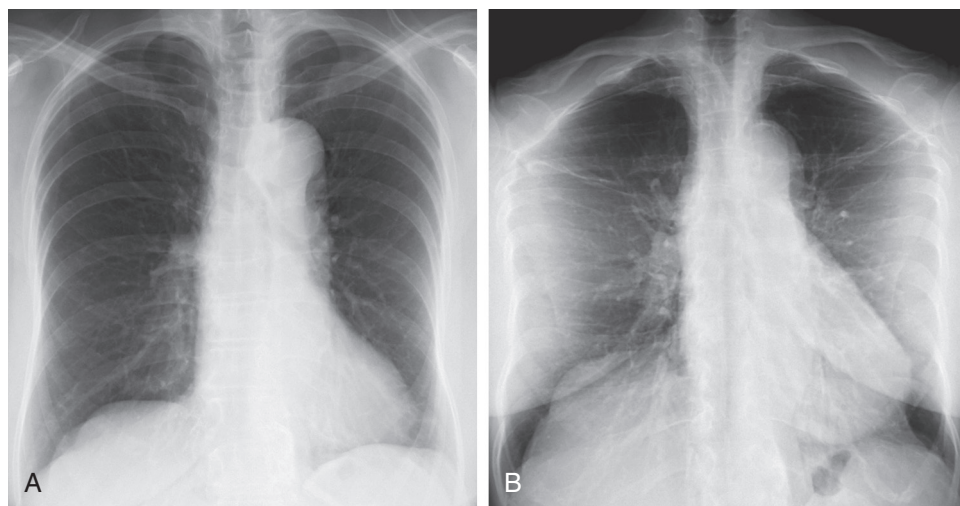
eFigure 18-9 This block diagram shows components of a digital radiographic system. Image manipulation, subtraction, and other such functions are performed during the digital phase. (From Nudelman S: In Digital radiology—physical and clinical aspects: proceedings of meeting held at Middlesex Hospital and Medical School, London, England, March 9, 1983. London, 1984, Institute of Physical Sciences in Medicine, pp 1–43.)



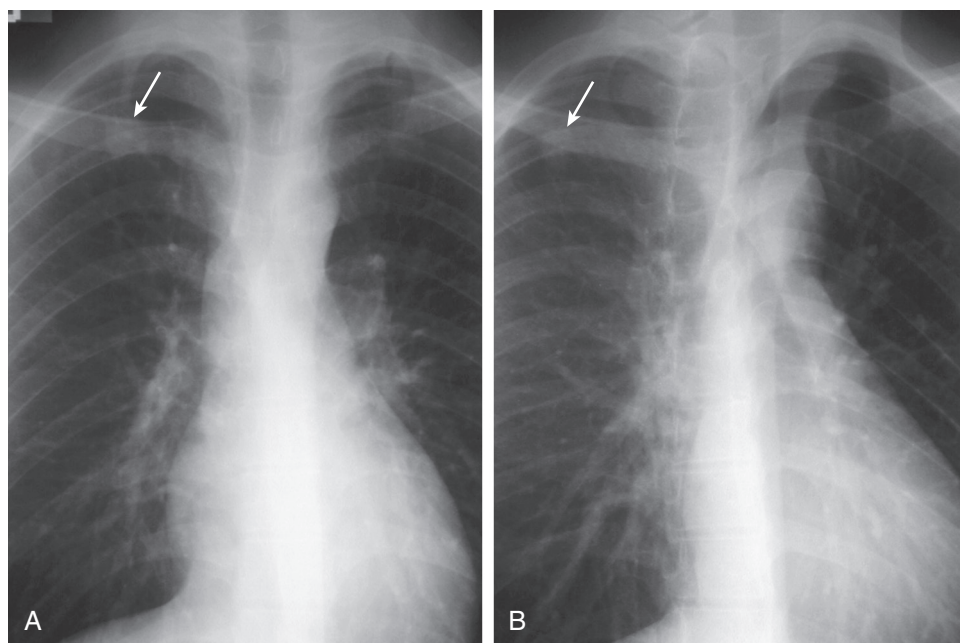
eFigure 18-11 Unilateral hyperlucent lung due to patient rotation. Frontal chest radiograph rotated to a right anterior oblique position shows diffuse lucency affecting the left thorax. Focal lucency can result from air trapping due to obstructive lung disease or endobronchial obstruction, or, rarely, vascular obstruction (see eFigs. 54-15, 57-7, 57-9), or chest wall disorders (such as mastectomy or Poland syndrome), but is most commonly the result of technical factors. (Courtesy Michael Gotway, MD.)



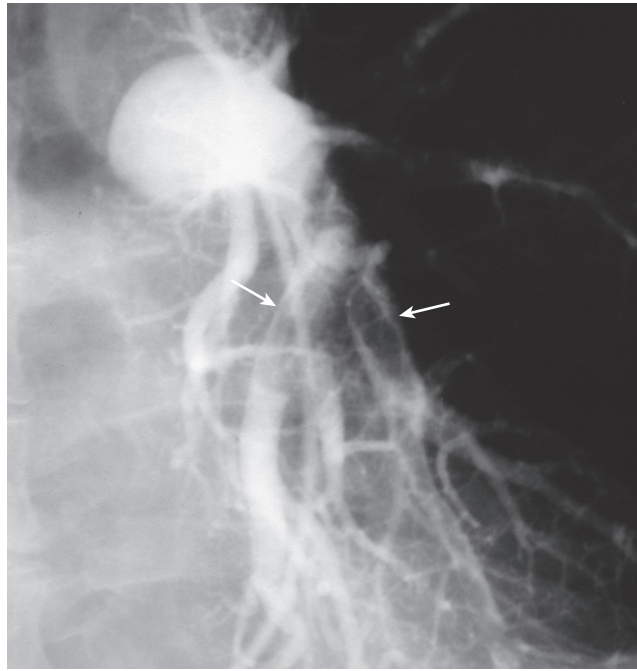
eFigure 18-10 This digital (computed radiographic) study of the chest was made in an intensive care unit. **A**, This view resembles a “conventional” film-screen radiograph. **B**, This view was processed for edge enhancement. (Courtesy Michael Gotway, MD.)



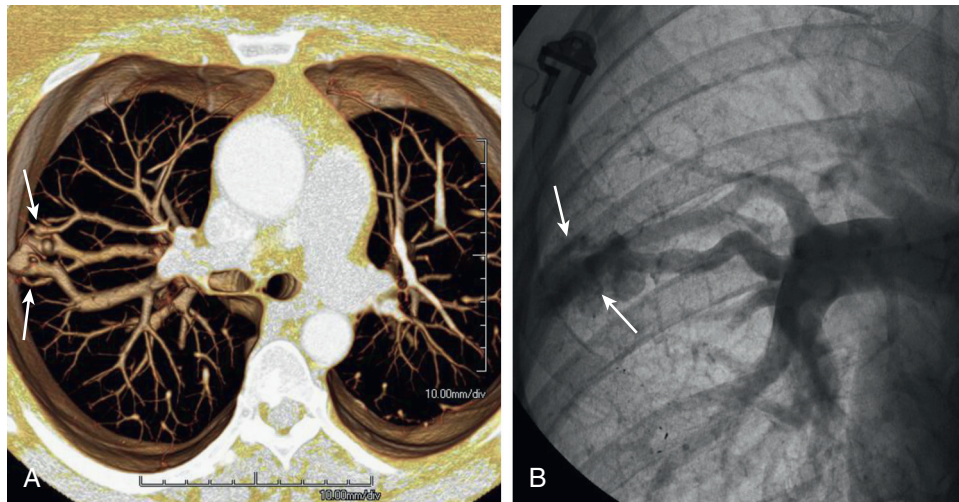
eFigure 18-12 Lordotic chest radiography. **A**, Frontal chest radiograph shows how the anterior and posterior cranial ribs overlap with the clavicles, creating superimposition that often obscures abnormalities in the apices. **B**, Lordotic chest radiograph shows that the clavicles are now projected cranial to the first ribs, and the anterior and posterior portions of the ribs nearly overlap with one another, improving visualization of the pulmonary parenchyma in the lung apices. (Courtesy Michael Gotway, MD.)



eFigure 18-13 Value of oblique chest radiography. **A**, Frontal posteroanterior radiograph shows a possible nodular opacity (*arrow*) at the right apex, obscured by overlap of the right clavicle and anterior first rib. **B**, 5-degree right anterior oblique chest radiograph shows that the possible opacity “moves” relative to the clavicle and first rib, indicating that the lesion is unrelated to the anterior chest wall and resides within the lung. (Courtesy Michael Gotway, MD.)



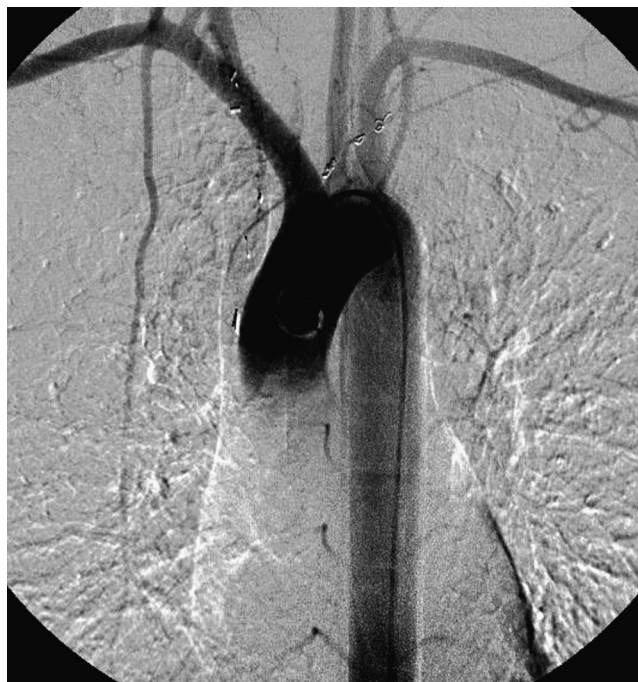
eFigure 18-14 Catheter pulmonary angiography of acute pulmonary embolism. Pulmonary angiography shows multiple emboli. Intraluminal filling defects (*arrows*) are present within the left pulmonary arterial vasculature, consistent with pulmonary emboli. (Courtesy Michael Gotway, MD.)



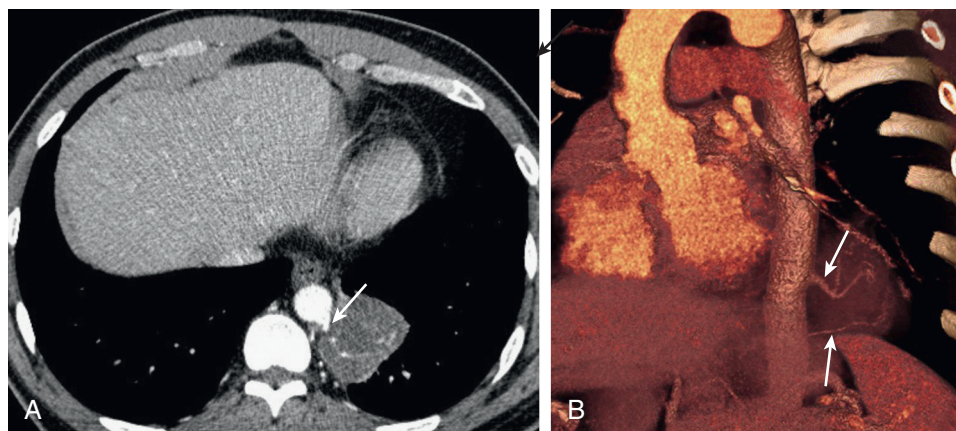
eFigure 18-15 Arteriovenous malformation. **A,** Axial volume-rendered chest CT shows an arteriovenous malformation (*arrows*) in the peripheral right lung. **B,** Coronal pulmonary angiogram before embolization shows the arteriovenous malformation (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 18-16 Catheter pulmonary angiography of pulmonary artery vasculitis. Pulmonary arteriogram in a patient with Takayasu arteritis shows a high-grade stenosis (*arrow*) of the right upper lobe pulmonary artery. (Courtesy Michael Gotway, MD.)



eFigure 18-17 Catheter aortography. Oblique coronal image from an aortogram shows the typical appearance of the aorta and great vessels. (Courtesy Michael Gotway, MD.)



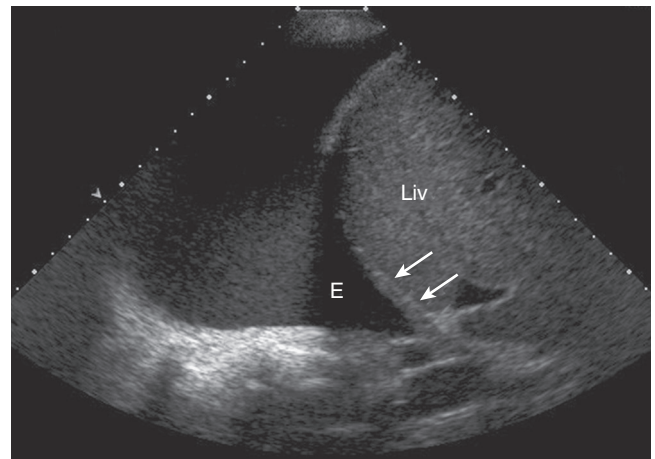
eFigure 18-18 Intralobar bronchopulmonary sequestration. **A**, Axial chest CT in a 24-year-old man with recurrent pneumonia shows a masslike opacity in the posterior basilar left lower lobe. Note the prominent aberrant vessel originating from the descending thoracic aorta (*arrow*) supplying the mass. **B**, Oblique coronal volume-rendered image shows the posterior basilar left lower lobe mass as well as two aberrant vessels (*arrows*) supplying the lesion. (Courtesy Michael Gotway, MD.)



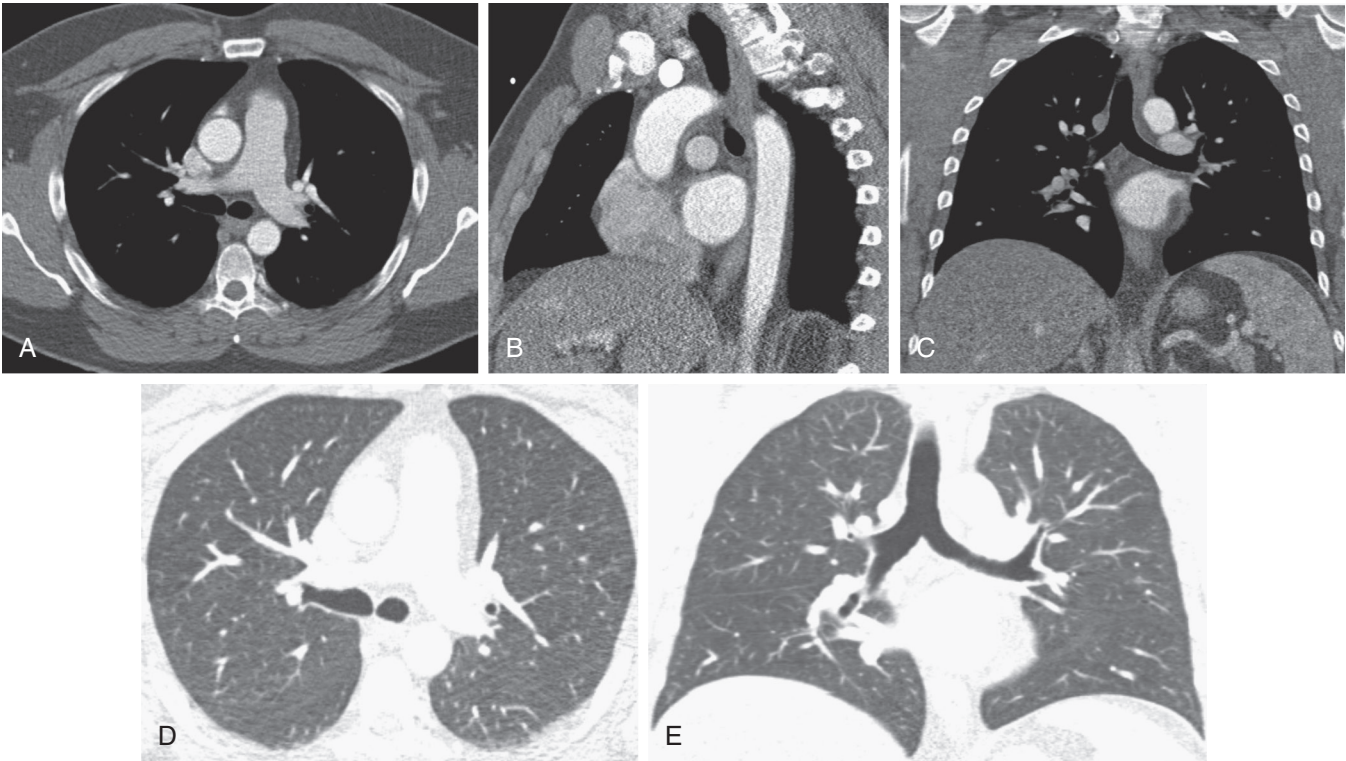
eFigure 18-19 Bronchial arteriography in a patient with right lower lobe bronchiectasis and hemoptysis. **A**, Initial contrast injection into a hypertrophied bronchial artery. **B**, Injection into the same artery as in **A** shows significantly decreased blood flow following coil embolization. (Courtesy Michael Gotway, MD.)



eFigure 18-20 The position of a patient for ultrasound-guided thoracentesis. (Courtesy Michael Gotway, MD.)



eFigure 18-21 Ultrasound of pleural effusion. Ultrasound examination of the lower left chest shows effusion (**E**) cranial to the right hemidiaphragm (**arrows**). **Liv**, liver. (Courtesy Michael Gotway, MD.)



eFigure 18-22 Isotropic multiplanar imaging with multislice CT of the thorax. A–C, Axial (A), sagittal (B), and coronal (C) soft tissue images from a pulmonary CTA study show that the resolution and diagnostic quality of the sagittal (B) and coronal (C) imaging is identical to that of the source axial images (A). D, Axial and E, coronal images displayed in lung windows also show equivalent diagnostic quality. (Courtesy Michael Gotway, MD.)

Dose Report					
Series	Type	Scan Range (mm)	CTDIvol (mGy)	DLP (mGy-cm)	Phantom cm
1	Scout	-	-	-	-
200	Axial	I73.250-I73.250	1.52	0.76	Body 32
201	Axial	I62.250-I62.250	4.55	2.28	Body 32
2	Helical	I28.000-I175.500	7.17	138.97	Body 32
Total Exam DLP:				142.00	
1/1					

eFigure 18-23 CT “dose report.” The total radiation exposure associated with this CT examination is shown as both the CT dose index (CTDI_{vol}) and the dose-length product (DLP). Such dose reports are often recorded as DICOM images and archived as part of the CT examination in the radiology database, typically a PACS (Picture Archiving and Communication System). (Courtesy Michael Gotway, MD.)

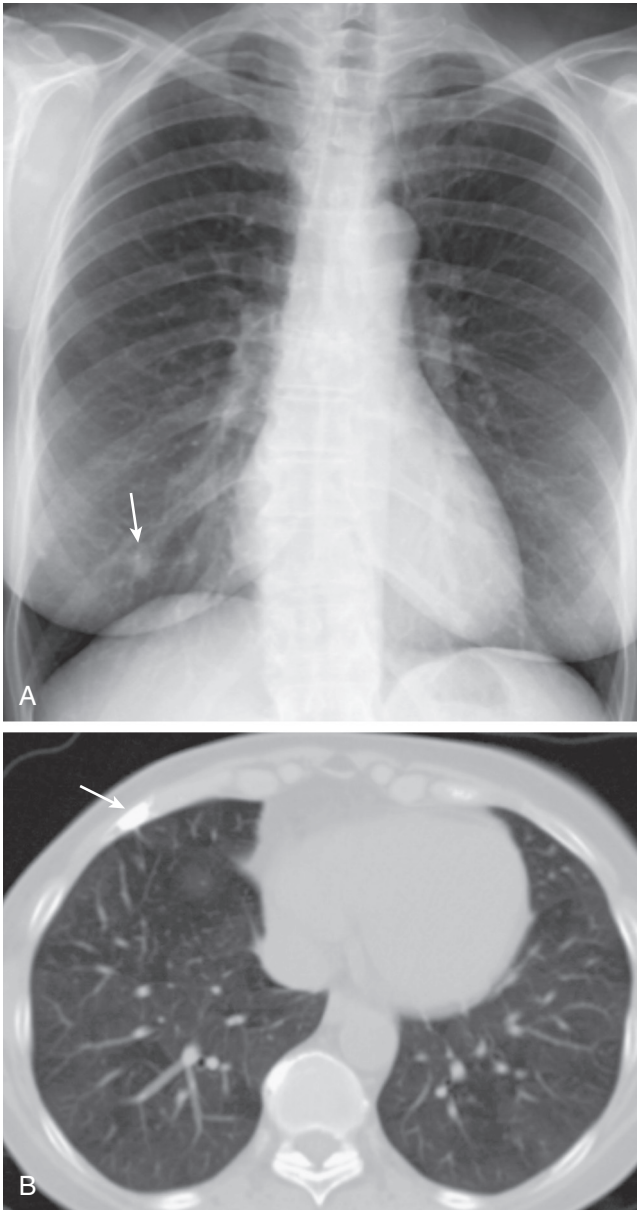
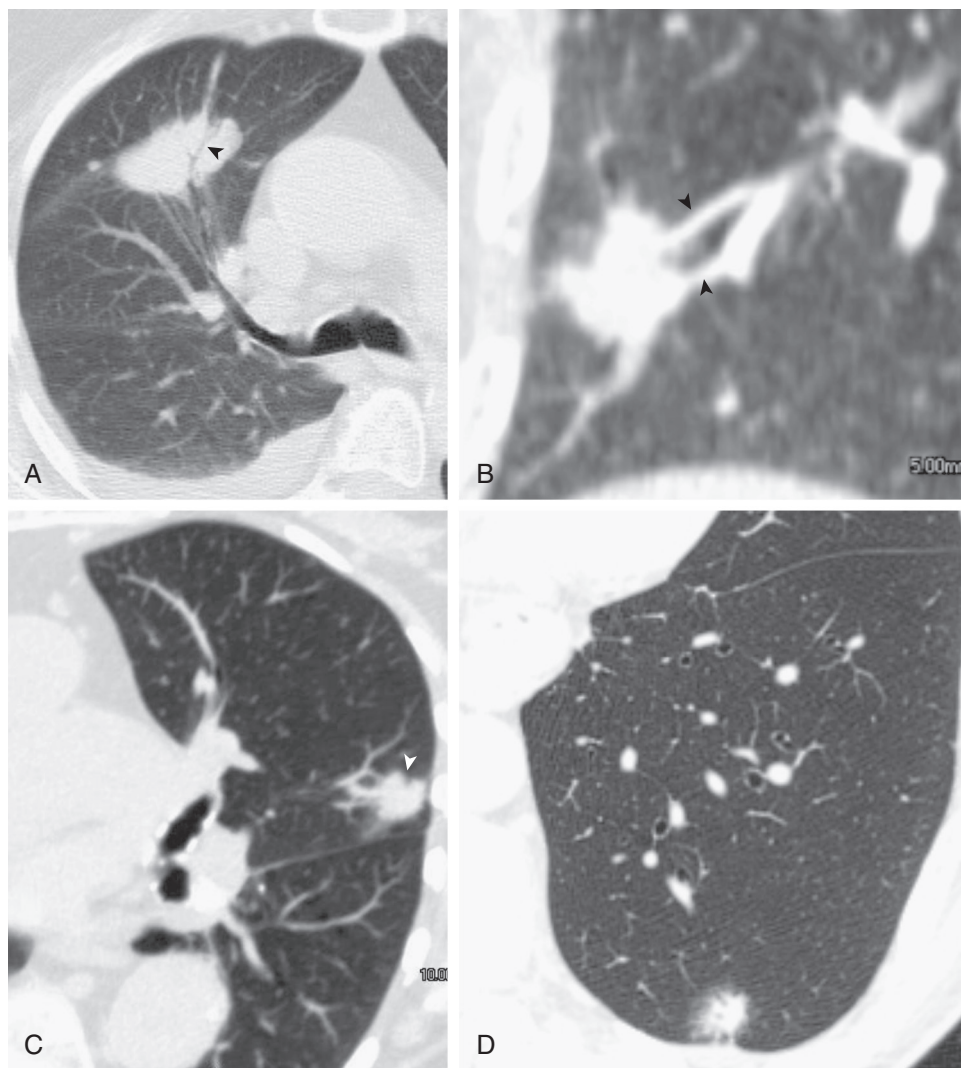
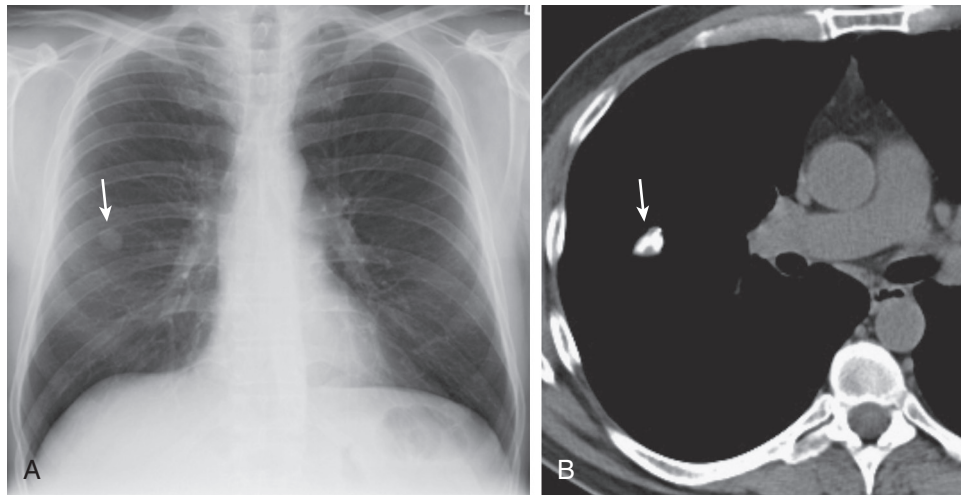


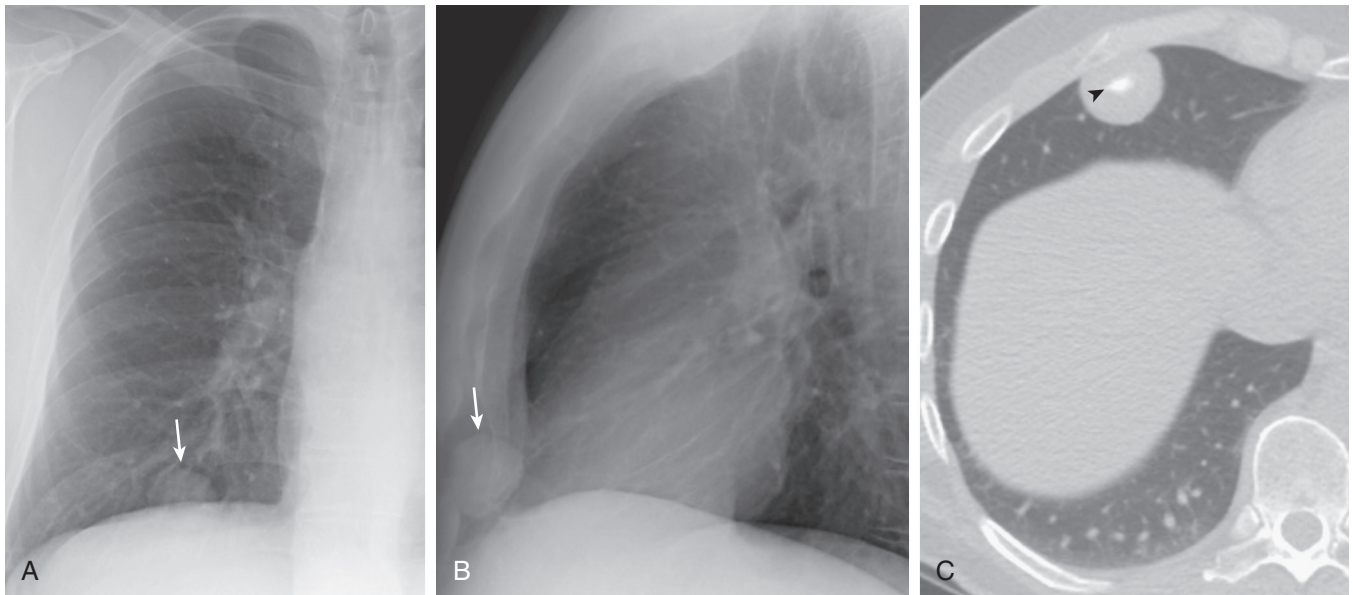
Figure 18-24 Chest wall lesion simulating a solitary pulmonary nodule at chest radiography: value of chest CT. **A**, Frontal chest radiograph shows a right lower lobe opacity (*arrow*) simulating a pulmonary nodule. **B**, Axial chest CT displayed in lung windows shows a sclerotic lesion (*arrow*) within an anterior rib, which accounts for the chest radiographic abnormality; no lung nodule is present. (Courtesy Michael Gotway, MD.)



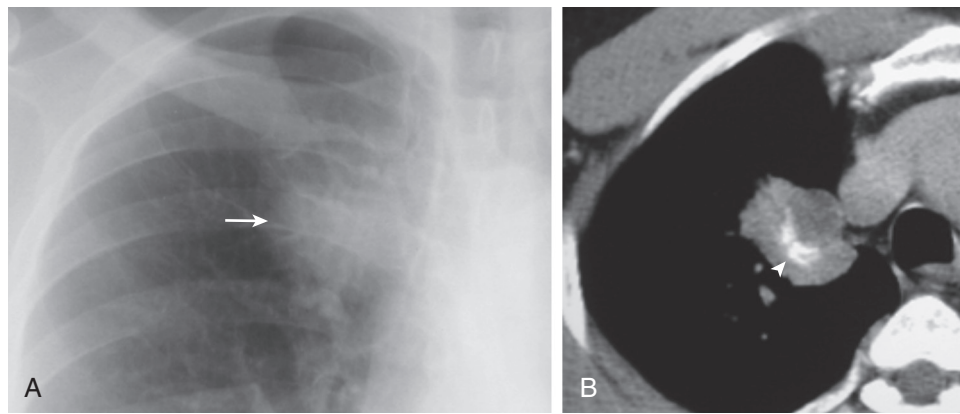
eFigure 18-25 CT features of malignant pulmonary nodules. **A**, Air bronchogram (*arrowhead*) within a solitary pulmonary nodule; **B**, vascular convergence sign—note pulmonary vessels (*arrowheads*) appearing to “converge” on the poorly defined pulmonary nodule; **C**, “notch” sign—note the lucent defect within the anterior portion of the lingular nodule (*arrowhead*), and; **D**, spiculation. Note that this nodule also shows a notch or small air bronchogram anteriorly. All four nodules show a pleural “tail”—linear opacities extending from the nodule to the visceral pleural surface. Once thought to be a feature suggesting a malignant etiology for a solitary pulmonary nodule, the pleural “tail” is actually a nonspecific finding. (Courtesy Michael Gotway, MD.)



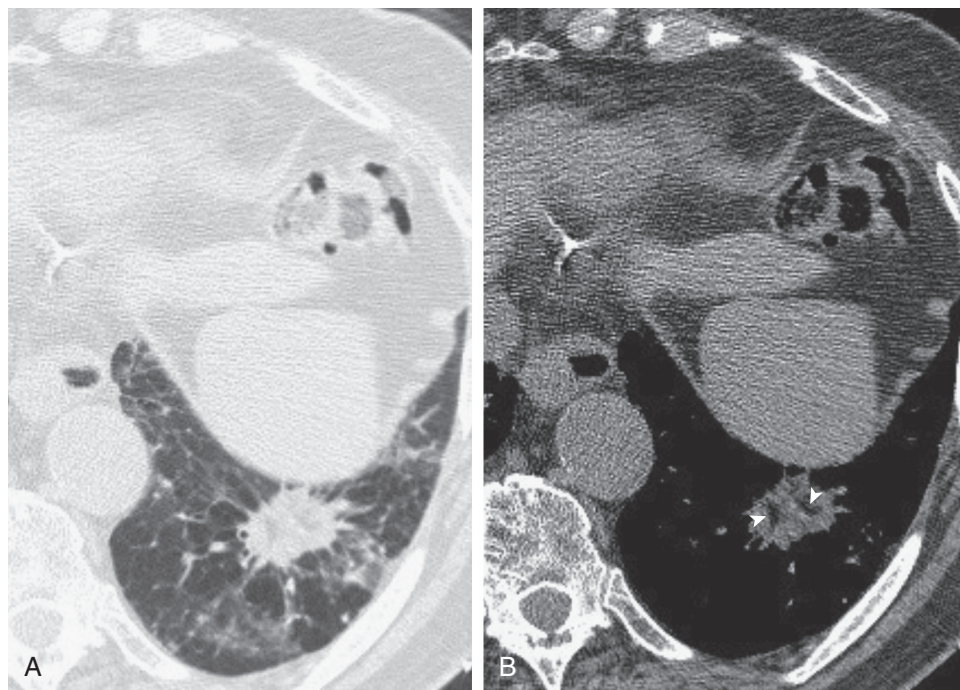
eFigure 18-26 Failure of detection of calcification within a solitary pulmonary nodule at chest radiography: value of chest CT. **A**, Frontal chest radiograph shows a solitary pulmonary nodule (*arrow*) in the right lung. The nodule may be calcified, but the absolute determination of calcification within a nodule at chest radiography can be both difficult and occasionally inaccurate. **B**, Unenhanced chest CT displayed in soft tissue windows shows that the nodule (*arrow*) is almost entirely calcified. (Courtesy Michael Gotway, MD.)



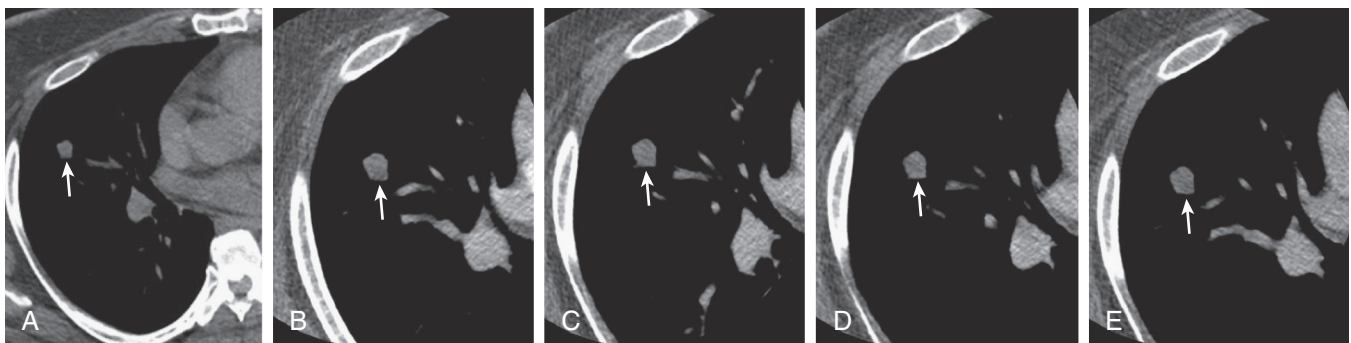
eFigure 18-27 **A**, Frontal and **B**, lateral chest radiograph in a patient with a right middle lobe solitary nodule (*arrow*) does not clearly show calcification within the nodule. **C**, Axial chest CT displayed in lung windows shows a small focus of calcification (*arrowhead*) within the center of the nodule. This lesion was growing slowly and was resected; it proved to be a necrotic granuloma. (Courtesy Michael Gotway, MD.)



eFigure 18-28 Calcification in a bronchogenic carcinoma. **A**, Detail frontal chest radiograph shows a right upper lobe nodule (*arrow*), but calcification is not clearly seen within the lesion. **B**, Unenhanced chest CT displayed in soft tissue windows shows calcification (*arrowhead*) within the nodule. Note the heterogeneous appearance of this nodule; biopsy subsequently confirmed adenocarcinoma. (Courtesy Michael Gotway, MD.)



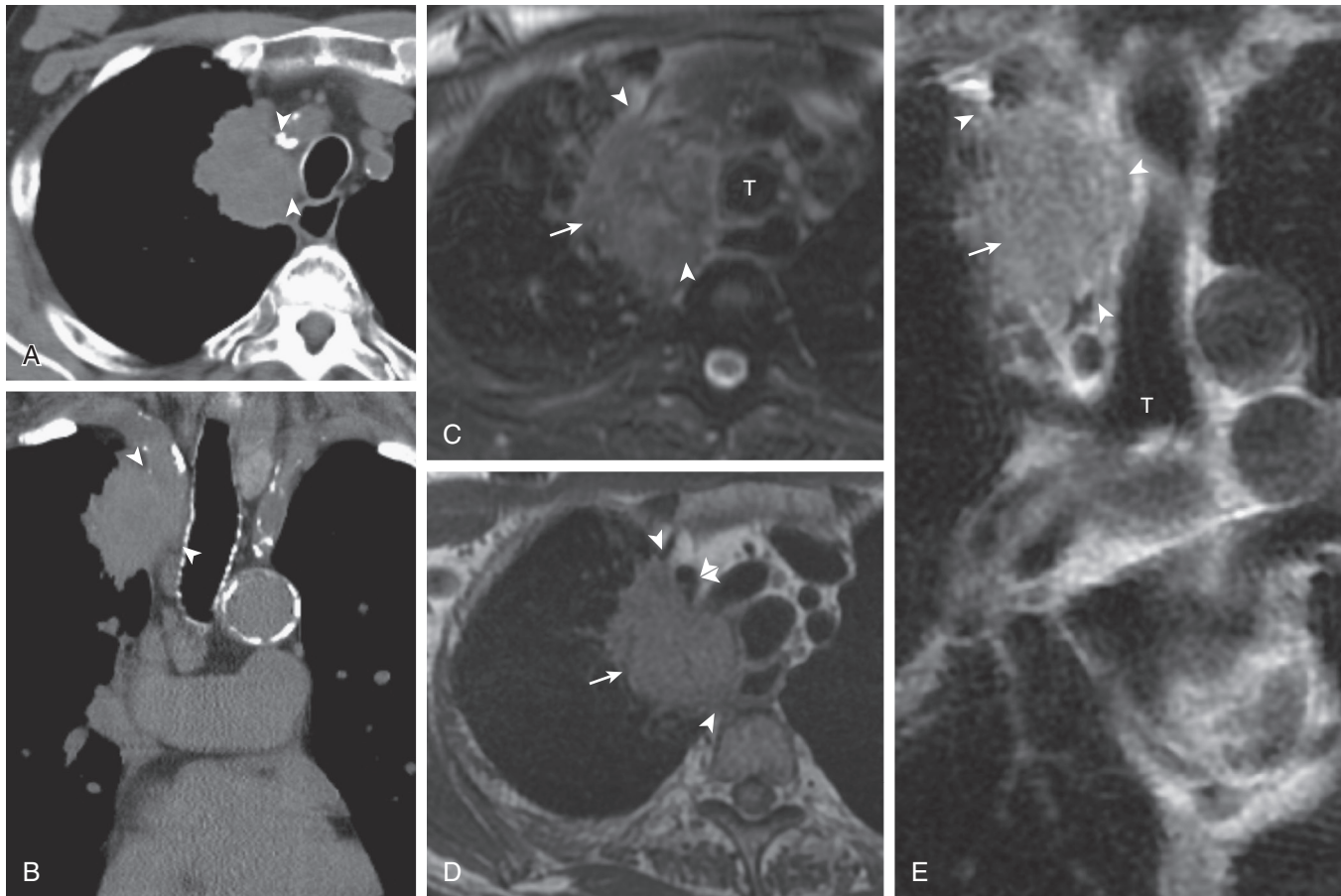
eFigure 18-29 Detection of fat within a nodule at chest CT: lipoid pneumonia. **A**, Axial chest CT displayed in lung windows shows a spiculated left lower lobe opacity associated with surrounding inhomogeneous lung opacity. The appearance resembles bronchogenic carcinoma. **B**, Axial chest CT displayed in soft tissue windows shows that the nodule contains low attenuation material consistent with fat (*arrowheads*), consistent with lipoid pneumonia. The patient was subsequently discovered to be using mineral oil as a laxative. (Courtesy Michael Gotway, MD.)



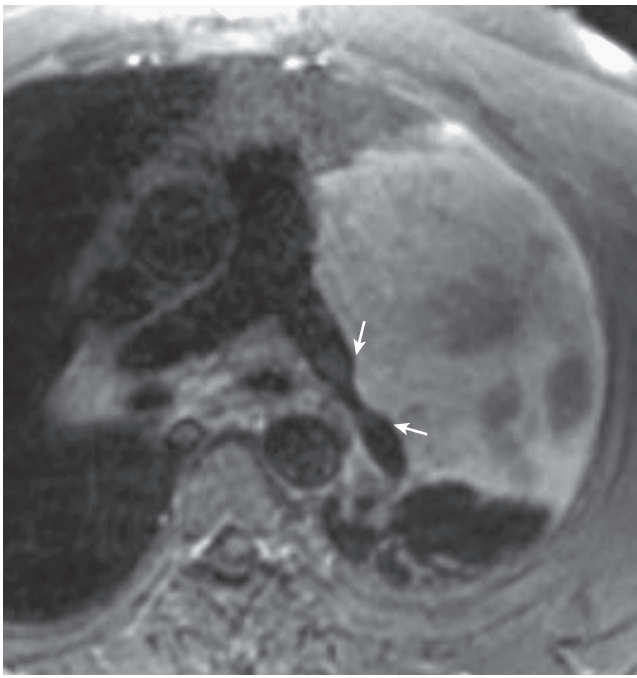
eFigure 18-30 Chest CT solitary nodule enhancement study: negative results. Axial chest CT imaging **A**, before intravenous contrast injection, **B**, at 1 minute, **C**, at 2 minutes, **D**, at 3 minutes and, **E**, at 4 minutes following intravenous contrast injection shows an unenhanced nodule (*arrow*) attenuation coefficient of 18 HU, and following intravenous contrast injection of 20 HU, 24 HU, 21 HU, and 23 HU at 1, 2, 3, and 4 minutes following intravenous contrast injection, respectively. The lack of significant intravenous contrast enhancement (i.e., >15 HU) at any of the 4 time points following intravenous contrast injection strongly suggests that the nodule is benign. (Courtesy Michael Gotway, MD.)



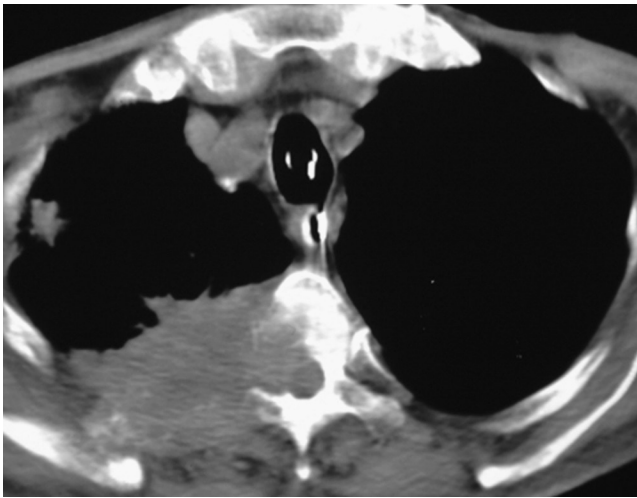
eFigure 18-31 Chest CT for lung cancer staging: tracheal involvement. Enhanced chest CT displayed in soft tissue windows shows a large right lung mass invading the mediastinum and clearly extending into the trachea. (Courtesy Michael Gotway, MD.)



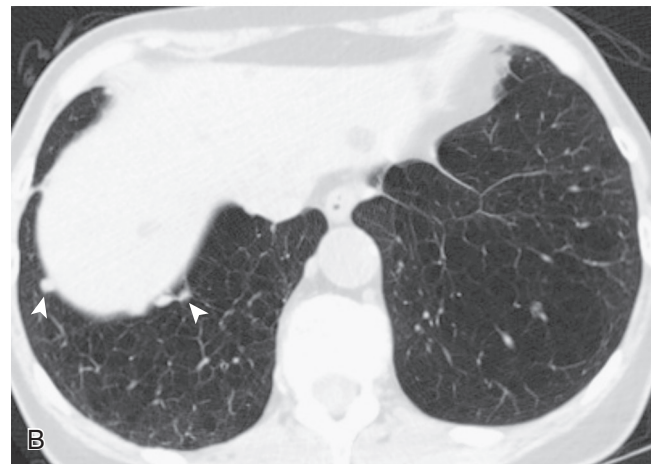
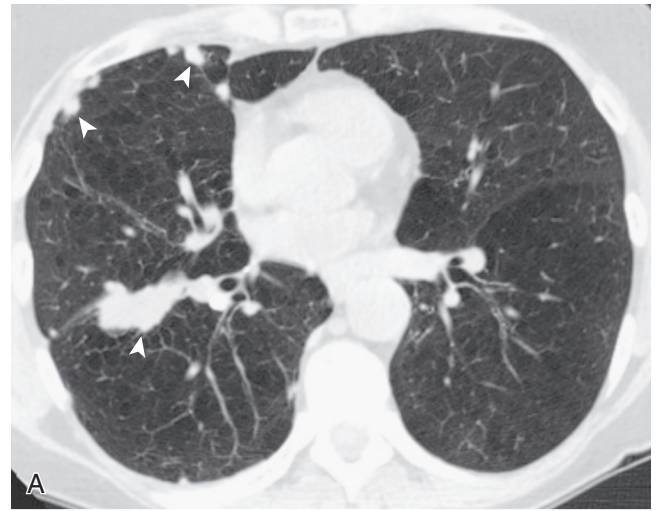
eFigure 18-32 CT and MRI for lung cancer staging: mediastinal invasion. **A** and **B**, Axial (**A**) and coronal (**B**) unenhanced chest CT displayed in soft tissue windows shows a medial right upper lobe bronchogenic carcinoma invading the mediastinum—note the obliteration of mediastinal fat planes by the tumor (*arrowheads*) and the tumor's close approach to the right brachiocephalic artery. **C–E**, Axial T2-weighted (**C**), unenhanced axial T1-weighted (**D**), and enhanced coronal T1-weighted (**E**) MR images show the intermediate-to-low signal intensity tumor (*arrows*) extending into the mediastinal fat (the hyperintense, white stripe between the tumor and the trachea [T] in **C** and **E**). The tumor shows extensive contact with the mediastinum (margins of the tumor—mediastinal contact is indicated by *arrowheads*). The tumor also shows extensive contact with the right brachiocephalic artery (*double arrowheads*, **D**). (Courtesy Michael Gotway, MD.)



eFigure 18-33 Chest MRI for lung cancer staging: mediastinal vascular invasion. Enhanced, T1-weighted fat saturation MRI image shows a heterogeneously enhancing left lung mass clearly invading the left pulmonary artery (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 18-34 CT for lung cancer staging: chest wall and vertebral body invasion. Unenhanced axial chest CT displayed in soft tissue windows shows an extensive right apical neoplasm invading the posterior chest wall and vertebral body. (Courtesy Michael Gotway, MD.)



eFigure 18-35 CT for lung cancer staging: pleural dissemination. A and B, Axial chest CT displayed in lung windows shows extensive pleural nodularity (*arrowheads*) representing pleural metastatic disease from bronchogenic malignancy. (Courtesy Michael Gotway, MD.)

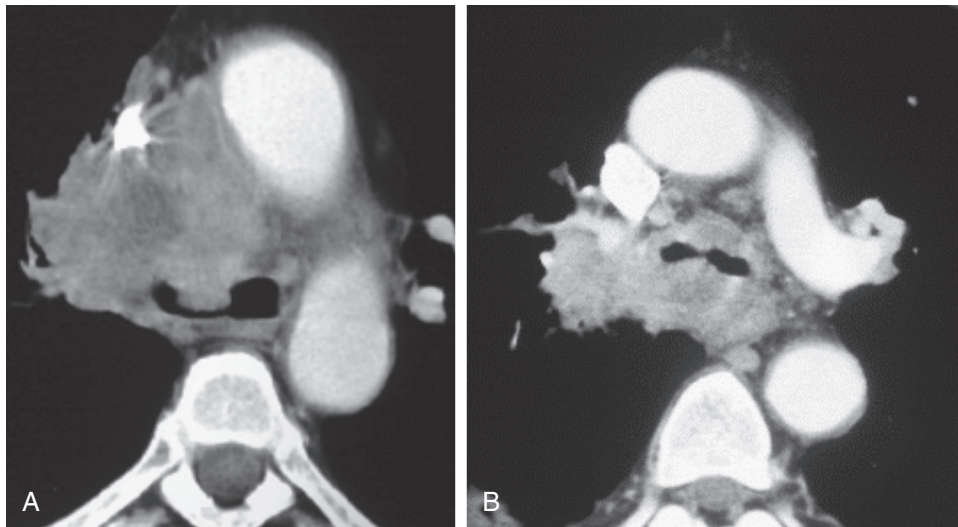


Figure 18-36 CT for lung cancer staging: tracheal carinal invasion. **A,** Axial contrast-enhanced chest CT shows extensive tumor involvement of the mediastinum with invasion of the tracheal carina. **B,** Axial contrast-enhanced chest CT in another patient shows tumor surrounding both mainstem bronchi at the level of the inferior margin of the carina. (Courtesy Michael Gotway, MD.)

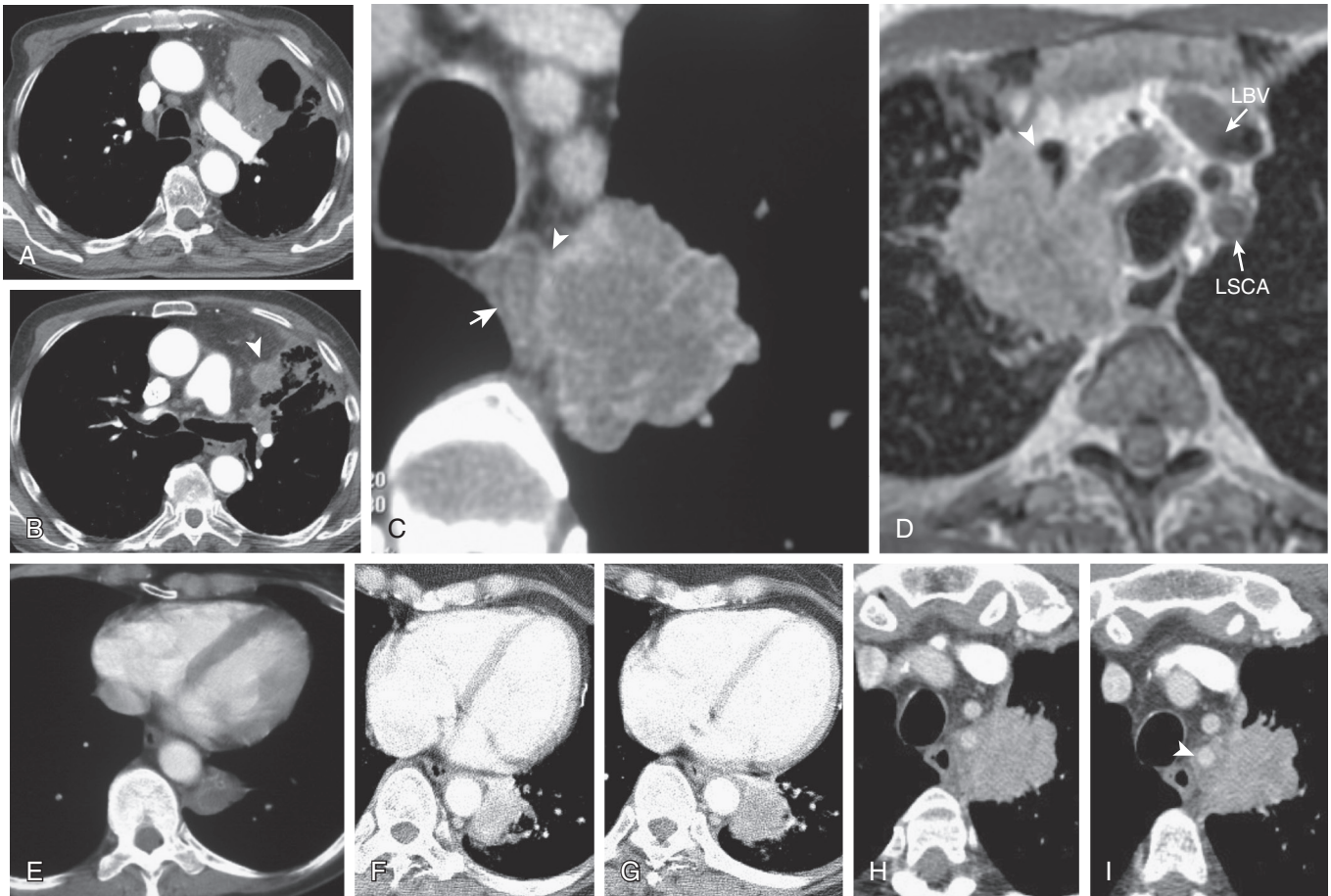
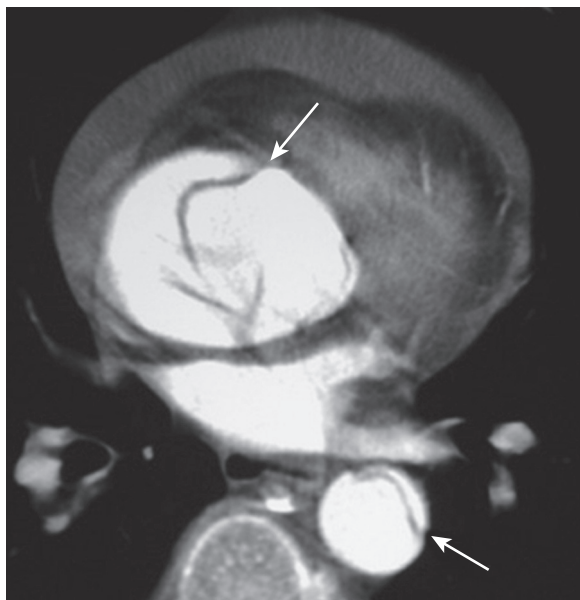
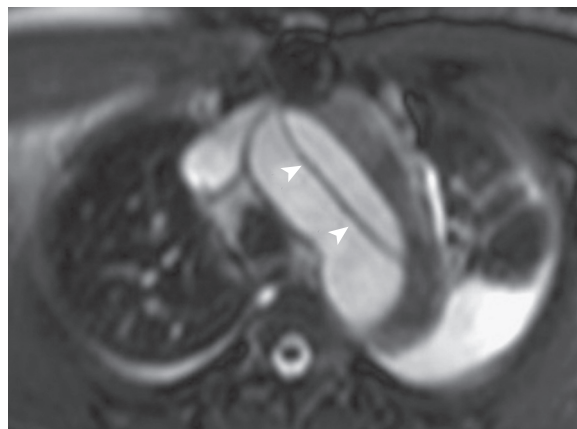


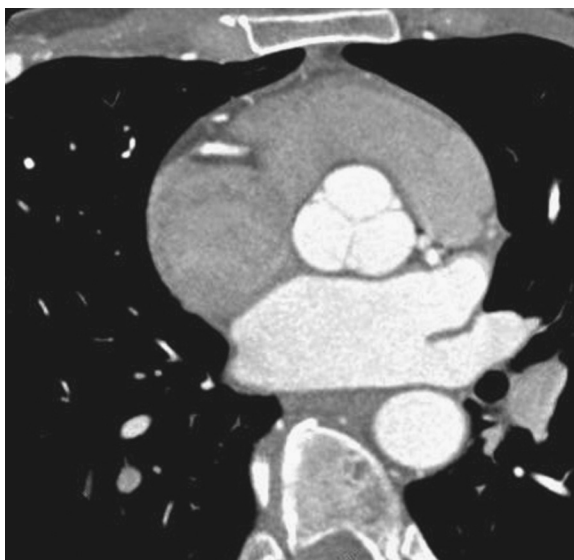
Figure 18-37 Chest CT for lung cancer staging: summary of the CT approach to possible mediastinal invasion by bronchogenic carcinoma. **A and B,** Axial chest CT displayed in soft tissue windows shows extensive mediastinal tumor contact (>3 cm) and clear tumor nodules invading mediastinal fat (*arrowhead*). **C,** Axial enhanced chest CT displayed in soft tissue windows shows a medial left upper lobe neoplasm exerting mass effect on the adjacent mediastinal fat and obliterating the fat plane (*arrowhead*) normally surrounding the esophagus (*arrow*); endoscopic ultrasound confirmed invasion of the esophagus. **D,** Axial enhanced, T1-weighted MRI shows invasion of the hyperintense mediastinal fat (note the signal characteristics of normal mediastinal fat surrounding the left subclavian artery [LSCA] and left brachiocephalic vein [LBV]). The tumor invades the right brachiocephalic artery (*arrowhead*)—note the mass effect deforming this vessel and the small intraluminal soft tissue focus, representing tumor thrombus. **E,** Axial enhanced chest CT displayed in soft tissue windows shows a medial left lower lobe bronchogenic neoplasm contacting the mediastinum and descending thoracic aorta; the tumor contacts less than 90 degrees of the descending thoracic aortic circumference, which generally predicts the *absence* of vascular invasion. **F and G,** Axial enhanced chest CT displayed in soft tissue windows shows a medial left lower lobe bronchogenic neoplasm contacting the mediastinum and descending thoracic aorta; this tumor contacts greater than 90 degrees but less than 180 degrees of the descending thoracic aortic circumference, which is indeterminate as regards vascular invasion. **H and I,** Axial enhanced chest CT displayed in soft tissue windows shows a medial left upper lobe bronchogenic neoplasm contacting the mediastinum and left subclavian artery (*arrowhead*); this tumor contacts greater than 180 degrees of this vessel, suggesting the presence of vascular invasion. (Courtesy Michael Gotway, MD.)



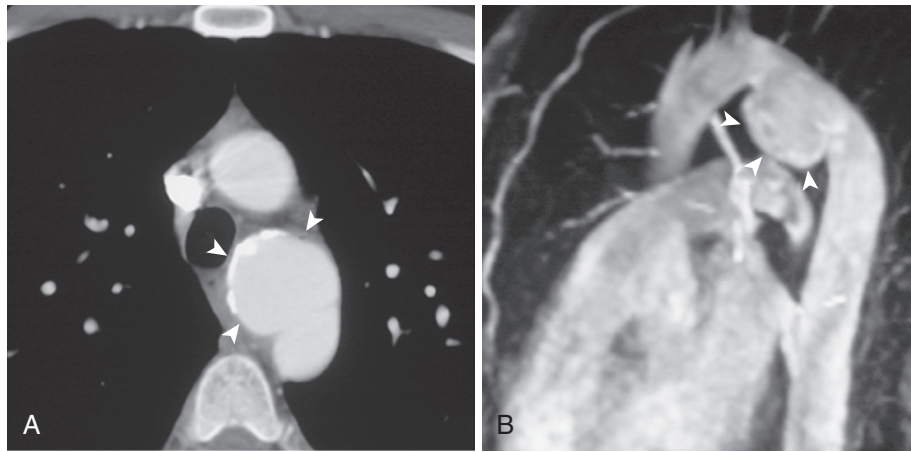
eFigure 18-38 Chest CT aortography. Chest CT aortogram in a patient with Stanford type A aortic dissection shows an intimal flap (*arrows*) in the ascending and descending thoracic aorta. Note dilation of the ascending aorta. (Courtesy Michael Gotway, MD.)



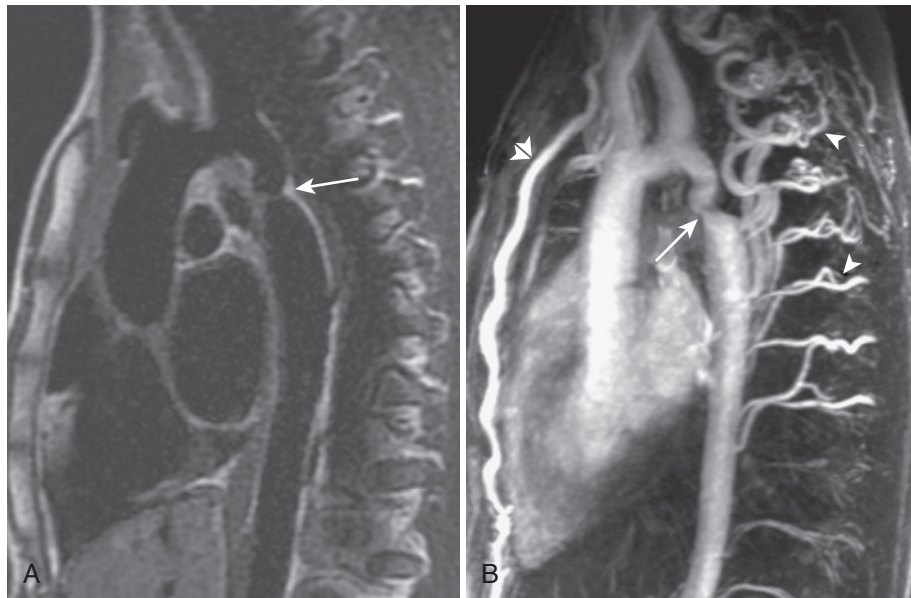
eFigure 18-40 This patient had symptoms classic for aortic dissection. “White blood” cine MR images show an intimal flap within the aortic arch (*arrowheads*), consistent with aortic dissection. (Courtesy Michael Gotway, MD.)



eFigure 18-39 Value of retrospectively gated chest CT aortography for the evaluation of the aorta. Axial CT aortography image obtained with retrospective electrocardiographic gating (image reconstructed during diastole) shows a motion-free image. Note clarity of the aortic valve cusps. Compare with the nongated CT aortography image in [eFig. 18-38](#). (Courtesy Michael Gotway, MD.)



eFigure 18-41 Chronic pseudoaneurysm in a long-term survivor with undiagnosed traumatic aortic injury 17 years earlier. **A**, Chest CT aortogram at the level of the aortic arch reveals a pseudoaneurysm (*arrowheads*); note calcification along the medial wall of the lesion. **B**, Oblique sagittal three-dimensional MRA image shows the pseudoaneurysm (*arrowheads*) to advantage. (Courtesy Michael Gotway, MD.)



eFigure 18-42 Value of MRI in the assessment of congenital cardiovascular diseases: aortic coarctation. **A**, Oblique sagittal T1-weighted spin-echo image of the thoracic aorta shows focal, severe narrowing of the proximal descending thoracic aorta (*arrow*) consistent with aortic coarctation. **B**, Oblique sagittal volume-rendered image shows coarctation (*arrow*), as well as collateral vessel formation. The latter derive from intercostal (*single arrowheads*), internal mammary (*double arrowheads*), and chest wall arteries and indicate the presence of a significant pressure gradient across the coarctation. (Courtesy Michael Gotway, MD.)

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THORACIC RADIOLOGY: INVASIVE DIAGNOSTIC IMAGING AND IMAGE-GUIDED INTERVENTIONS

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INTRODUCTION

Image-guided *transthoracic needle biopsy* (TNB), which is typically performed using *computed tomographic* (CT) guidance under local anesthesia and conscious sedation, is a minimally invasive procedure that can provide a definitive cytologic, histologic, or microbiologic diagnosis in 90% of patients with localized thoracic lesions.¹ The decision to perform TNB in lieu of alternative invasive diagnostic procedures or imaging follow-up, particularly for indeterminate lung lesions, is usually made following a multidisciplinary review of relevant clinical, laboratory, imaging, and pathologic material and requires consideration of local expertise, the availability of alternative invasive diagnostic procedures, including bronchoscopy and *video-assisted thoracic surgery* (VATS), and the needs of the referring physician and patient.

Interventional radiologists also play an important role in the management of intrathoracic air and fluid collections, using cross-sectional imaging to guide catheter placement and monitor response to drainage, and in control of massive hemoptysis by embolization of bronchial or systemic arteries. More recently, CT-guided thermal ablation of early-stage lung cancer and limited pulmonary metastatic disease has shown efficacy as a minimally invasive alternative to surgical management and external beam radiation therapy in select patients with stage IA lung cancer or those with limited pulmonary metastases.

TRANSTHORACIC NEEDLE BIOPSY

INDICATIONS AND CONTRAINDICATIONS

The most common indication for TNB is the diagnosis of a solitary pulmonary nodule (Fig. 19-1).² Additional indications include diagnosis of a mediastinal mass, enlarged

hilar or mediastinal lymph node,³ chest wall mass, or pleural mass or thickening.⁴ Most often the primary diagnostic concern is malignancy, but the diagnosis of opportunistic lung infection producing focal lung lesions in immunocompromised patients is an additional indication for image-guided TNB. In these latter patients, the retrieval of material for microbiologic stains and cultures rather than cytologic analysis for malignancy is the primary purpose for TNB.⁵ In selected patients with known *non-small cell lung cancer* (NSCLC) based on cytologic analysis from prior biopsy, core tissue TNB can be performed for immunohistochemical analysis (e.g., breast cancer metastases assessed for the presence of estrogen and progesterone receptors)⁶ or molecular testing (e.g., epidermal growth factor receptor or *echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase* [EML4-ALK] rearrangement quantification)⁷ to help guide therapy. Occasionally a lesion thought likely to be benign based on clinical and imaging analysis is sampled using TNB to provide a definitive benign diagnosis.

The only absolute contraindication to TNB is the inability of a patient to cooperate for safe and successful sampling of the thoracic lesion in question. Most adults, even those with compromised pulmonary function, can undergo successful image-guided TNB using local anesthesia and either conscious sedation or monitored anesthesia care. For sampling of small lesions (<15 mm in diameter), the patient must be able to hold his or her breath when instructed to allow the operator to position the needle accurately within the lesion for successful retrieval of cytologic material. For larger lesions, particularly those at the lung periphery and those in the upper lobes that are less subject to craniocaudal motion during normal breathing, breath-holding is less important and TNB can be safely performed in most such patients without the need for the patient to respond to verbal commands. TNB can be performed selectively in patients receiving general anesthesia and endotracheal

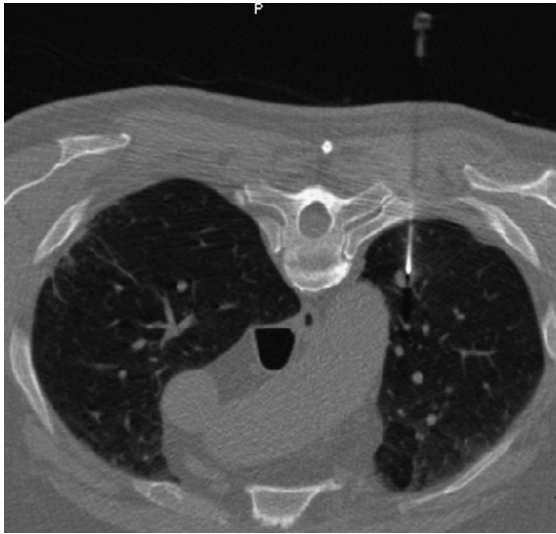


Figure 19-1 Transthoracic needle biopsy of a solitary pulmonary nodule. CT with patient prone during transthoracic needle biopsy showing the vertical course of the coaxial needle with its tip at the edge of a 1-cm left upper lobe nodule.

intubation when necessary. Even patients with severe dyspnea—who are unable to lie recumbent for CT-guided or fluoroscopically guided biopsy and cannot hold their breath—can undergo successful ultrasonographically guided TNB in the sitting position if the lesion to be sampled in the lung or pleura provides an adequate intercostal acoustic window to allow real-time visualization and biopsy. As with superior mediastinal lesions, an ultrasonographically guided suprasternal approach with the patient in the sitting position can be used.

Bleeding diatheses are only a relative contraindication to TNB and if identified can usually be corrected before the procedure. Although no objective data exist showing an increased risk for bleeding from TNB in patients with abnormal clotting parameters, such as elevated international normalized ratio higher than 1.5 or a platelet count lower than 50,000 cells/ μ L, most operators and published guidelines recommend preprocedure correction of abnormal bleeding parameters.⁸ Patients receiving antiplatelet agents, including aspirin and/or clopidogrel (Plavix) for prophylaxis after myocardial infarction, stroke, or recent coronary artery stent placement, who require TNB should have an assessment of the relative risks and benefits of discontinuing these agents compared with the potential bleeding complications induced by TNB. Published guidelines recommend discontinuing antiplatelet agents at least 5 days before TNB.⁸ Those patients who are considered to be at risk for thrombosis if anticoagulation or antiplatelet agents are withdrawn before biopsy can be bridged to receive intravenous heparin, which can be discontinued several hours before TNB, thereby providing a brief periprocedural window without anticoagulation. For large mediastinal masses or large peripheral lung or pleural/chest wall lesions, aspiration biopsy can be safely performed while the patient remains on anticoagulation or antiplatelet agents. If core tissue biopsy is required, typically for the diagnosis of an anterior mediastinal mass such as lymphoma or thymic neoplasm or for molecular analysis of NSCLC (adenocarci-

nomas), antiplatelet agents should ideally be discontinued for 7 days before biopsy. Patients who have had a prior pneumonectomy are at greater risk for respiratory compromise should they develop bleeding or pneumothorax from lung biopsy. However, because these complications can usually be anticipated and managed successfully, prior pneumonectomy does not preclude TNB for evaluation of a suspicious lesion in the residual lung.

PATIENT-LESION SELECTION AND PREPROCEDURE CLINICAL AND IMAGING EVALUATION

The decision to perform a TNB for diagnosis follows a thorough imaging evaluation and clinical assessment of the patient; typically this includes a consultation with a pulmonologist or oncologist who interviews and examines the patient to determine the clinical likelihood of malignancy after a suspicious thoracic lesion has been identified. For patients younger than 35 years without significant risk factors for malignancy who have focal lung lesions, imaging follow-up is almost invariably employed because the likelihood of malignancy in such patients is very low. Conversely, for patients with localized lesions who have a high prebiopsy likelihood of lung cancer, direct referral for surgical consultation is reasonable and more cost-effective, because the result of TNB will be unlikely to obviate resection of the lesion. Nevertheless, biopsy of likely malignant nodules can be of utility in patients who are poor surgical candidates, in whom the lesion is not amenable to VATS resection for intraoperative frozen section diagnosis, and in those with a history of prior malignancy in whom metastatic disease is a consideration and a TNB diagnosis of metastatic disease would not lead to surgical metastasectomy. For anterior mediastinal masses, core biopsy is almost always necessary for the initial diagnosis of lymphoma, particularly if diagnosis would preclude unnecessary sternotomy and resection, because these lesions are treated with radiation therapy and/or systemic chemotherapy.

It is important to determine the following before the procedure: (1) if TNB will alter the therapeutic approach to the lesion in question and (2) if a patient with suspected malignancy would opt for treatment based upon the results of the procedure should it yield malignant material. It is reasonable to refer patients with a high likelihood of NSCLC directly to VATS with sublobar or wedge resection for initial diagnosis because this procedure may provide both diagnostic material and definitive treatment, particularly for smaller, peripheral lung lesions likely to reflect adenocarcinoma as determined by thin-section CT analysis. In patients with stage I NSCLC who are older than 75 years, segmentectomy or extended wedge resection may be offered as an effective and potentially beneficial alternative to lobectomy, particularly if the patients have indolent (i.e., ground-glass or subsolid) lesions or significant medical comorbidities such as severe chronic obstructive pulmonary disease.⁹

All patients referred for image-guided TNB should have a recent (optimally within 4 weeks of the procedure) thin-section (<2 mm slice thickness) CT examination of the lesion to be sampled. For TNB of mediastinal masses, enlarged mediastinal nodes, or pleural and chest wall masses, a recent contrast-enhanced CT or magnetic

resonance imaging study helps determine the vascularity of the lesion and its proximity to critical vascular structures.

Informed consent is obtained on arrival to the radiology department for all patients undergoing TNB by either the individual performing the procedure or a health care professional who is able to describe the procedure accurately and answer questions for the patient and accompanying family members. The informed consent should include a detailed explanation of the TNB procedure itself, the expected length of time in the department (typically 1 hour for the procedure and 3 hours of postprocedure observation), and the benefits of the image-guided transthoracic approach compared with alternative noninvasive diagnostic options, including the option of not undergoing any further diagnostic procedures, once the risks and benefits of TNB have been described. The published incidence of TNB-induced pneumothorax (approximately 20%), chest tube insertion (3%), and hemoptysis (5%)¹⁰ are provided before the patient signs the printed consent form.

CHOICE OF IMAGING GUIDANCE

Although TNB can be performed under fluoroscopic, CT, or ultrasonographic guidance, most operators use CT guidance exclusively or for the majority of their procedures. CT provides rapid and precise information regarding lesion and needle location. It is the only imaging modality that allows access to small, central lesions and safe access to enlarged mediastinal nodes (Fig. 19-2). The ability to visualize intervening structures allows the operator to avoid bullae or large vessels in the projected needle path. Precise needle tip localization allows for a more confident assessment of adequacy of needle placement, particularly within small lesions or those with a necrotic or cavitory center. Complications such as bleeding or pneumothorax are readily identified and expeditiously managed.

Fluoroscopy can be used for biopsy of lesions that are easily seen radiographically.¹¹ Ideally a biplane or C-arm unit that allows orthogonal views to be obtained during

needle placement without rolling the patient from the recumbent position helps assess the accuracy of needle placement into the lesion. Radiation dose to the patient from fluoroscopically guided TNB is generally lower than from CT-guided TNB. Because most radiologists currently performing TNB have been trained to use CT for abdominal and pelvic image guided interventions, most radiologists use CT to perform TNB.

Ultrasonography can be used to guide TNB in select cases.¹² Its primary advantage is real-time visualization during administration of local anesthesia, needle placement into the lesion, and lesion sampling, particularly automated core needle biopsy for histologic analysis. Intervening vascular structures are easily identified using Doppler so that they may be avoided. Although the technique is operator dependent, most radiologists have experience with diagnostic ultrasound probes and biopsy techniques that are easily applied to TNB. The use of ultrasonography to guide TNB is limited to lesions with an adequate acoustic window, such as anterior mediastinal masses and peripheral lung lesions with a broad pleural contact between the lesion and the chest wall (Fig. 19-3).

PROCEDURE

For CT-guided TNB the patient is placed recumbent and positioned to provide the shortest distance from the anticipated skin puncture site to the lesion, typically with the skin puncture site nondependent, allowing a vertical needle trajectory (see Fig. 19-1). For those patients unable to lie prone for the procedure because of breathing difficulties, the patient can be placed in the lateral decubitus position and a posterior puncture performed with the needle horizontally oriented. Most patients receive conscious sedation with relatively short-acting and readily reversible analgesic and amnestic agents, such as fentanyl and midazolam (Versed), respectively; if necessary, though, occasional patients require monitored anesthesia care or general anesthesia. For TNB performed using conscious sedation, a dedicated interventional radiology nurse administers the medications and

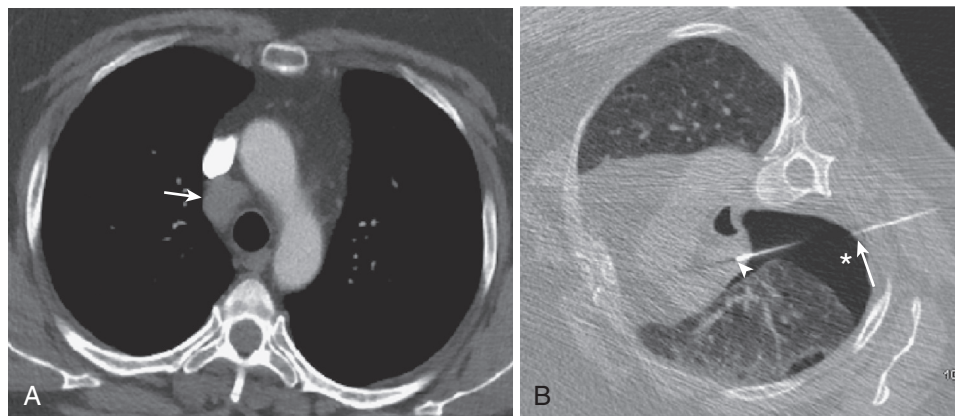


Figure 19-2 Transthoracic needle biopsy of mediastinal lymphadenopathy. **A**, Contrast-enhanced CT just below the level of the aortic arch shows an enlarged right lower paratracheal (4R) node (arrow). The patient had a left upper lobe mass (not shown). **B**, CT with the patient in the right lateral decubitus position showing the coaxial needle tip (arrowhead) within the enlarged right lower paratracheal node. Note the presence of an iatrogenic pneumothorax (asterisk) induced by a second blunt-tipped needle (arrow) that was initially placed into the pleural space with air injected to provide an extravascular pleural access to the node. Aspiration and core biopsy of the nodes confirmed the presence of contralateral (N3) nodal metastases from primary adenocarcinoma of the left upper lobe.

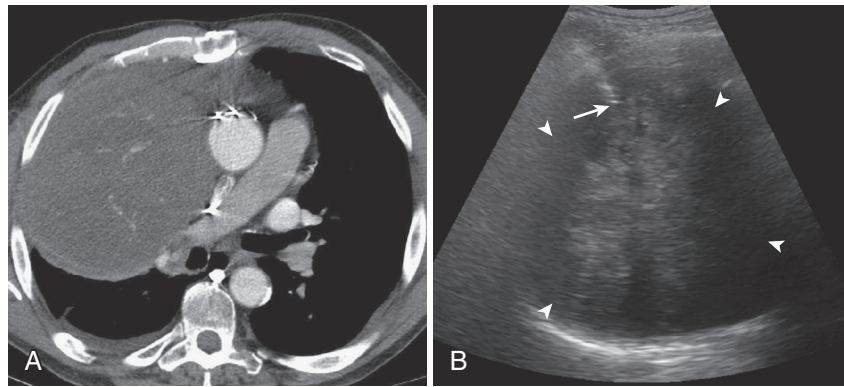


Figure 19-3 Ultrasonographically guided biopsy of large lung mass. **A**, Contrast-enhanced CT at the level of the right pulmonary artery showing a large right chest mass that has a broad area of contact with the pleural surface anteriorly and laterally. **B**, Transverse ultrasonographic image through the right anterior chest during core biopsy shows the mass (arrowheads) with an irregular echogenic region centrally. The biopsy needle is seen with its tip (arrow) within the mass. Histologic diagnosis was rhabdomyosarcoma.

monitors the patient's oxygen saturation, heart rate, respiratory rate, and level of responsiveness throughout the procedure. Ideally the patient should be able to cooperate with consistent breath-holding, which is necessary to position the biopsy needle accurately into small lesions for successful sampling; this is particularly important for lesions near the diaphragm, which show significant craniocaudal movement during even tidal breathing.

Once the patient has been properly positioned, a scout view (a planar image of the thorax analogous to a frontal radiograph that is used to plan for the axial scans) is obtained at functional residual capacity. All scans obtained through the region of interest are likewise obtained at normal end-expiration, which is a comfortable and reproducible lung volume for the patient to achieve, even when sedated. For TNB of small lung nodules, a reconstructed scan thickness of no greater than half of the diameter of the lesion should be obtained for identifying and marking the needle puncture site. This provides a detailed view of the ribs and intercostal space, helps visualize the anticipated needle path and any intervening large vessels or bullae to be avoided, and minimizes partial volume averaging when assessing the position of the needle tip relative to the lesion being sampled. Thin sections are particularly important when sampling lesions with subsolid attenuation, because it is important to identify any solid components within the lesion to target for TNB to provide a more confident cytologic diagnosis of malignancy. Once the thin sections encompassing the lesion have been obtained, an electronic grid is superimposed on the image at the desired level for needle entry at the technologist's console. This grid has major axes that mark the central meridian of the gantry in the coronal (x-axis) and sagittal (y-axis) planes and accurately correspond to laser lights on the CT gantry that project onto the patient's skin at the chosen axial level. Measurements are then made on the console from the axis closest to the desired entry point, and using a ruler on the patient's skin, this point is marked on the skin with an indelible marker.

The area is then prepared and draped with a sterilizing solution such as povidone-iodine (Betadine) or, for those with iodine allergies, chlorhexidine gluconate (Hibiclens). Local 2% lidocaine is administered subcutaneously to the

Table 19-1 Indications for Core Needle Biopsy in the Thorax

Anterior or posterior mediastinal mass
Probable benign lesion (hamartoma, granuloma)
Molecular markers in adenocarcinoma
Mesothelioma
Rapid cytopathologic review unavailable
?Subsolid lung lesions

entry site and deeper, approaching the pleural surface, because the parietal pleura is heavily innervated and is best anesthetized before transpleural placement of the biopsy needle. We and most operators employ a coaxial needle approach, with an outer thin-walled guide needle 18- or 19-gauge in diameter placed through the chest wall and neighboring pleura and positioned with its tip at the edge of the lesion. Samples are obtained by placing a thin 20- to 22-gauge aspiration or core needle through the outer coaxial guide needle. Patient breath-holding during needle placement and repositioning at the same end-expiratory volume as directed for the preliminary scans is key to accurate needle placement. Rapid assessment of needle position following advancement and repositioning can be obtained by repeated axial images through the region or by using CT fluoroscopy, which allows the operator to obtain several quick contiguous low-dose thin-section images through the lesion and needle without having to leave the room.

Once the guide needle is properly positioned at the edge of the lesion to be sampled, aspiration biopsy is performed by using a rapid, rotatory, and to-and-fro motion with the inner needle attached to a syringe with suction applied. The needle-syringe combination is removed and handed to a cytotechnologist who expresses the contents onto a glass slide and then fixes the slide in alcohol. The slides are then stained using toluidine blue O and examined with a microscope kept in an adjoining area. Additional aspiration samples are typically obtained for immunocytochemical analysis, cell block, or stains and cultures when necessary. Core tissue biopsy specimens can be obtained using 20-gauge or larger automated cutting needles and are reserved for situations when histologic analysis is deemed necessary (Table 19-1).

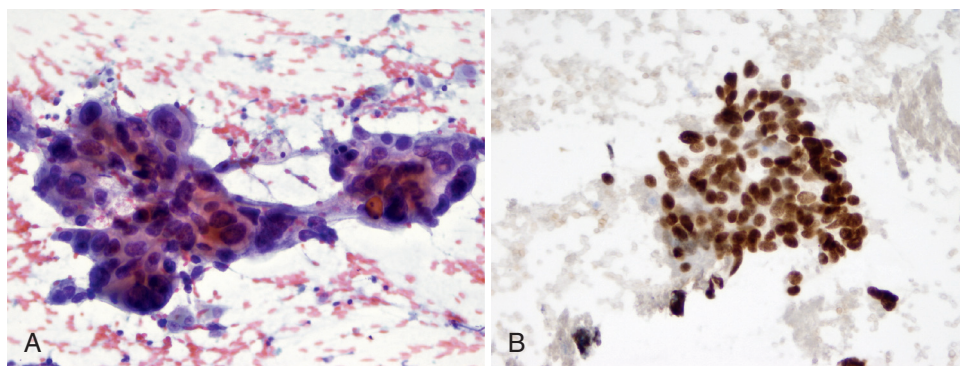


Figure 19-4 Immunocytochemical diagnosis of primary pulmonary adenocarcinoma. **A**, Photomicrograph of aspirated specimen from a 71-year-old with a spiculated 15-mm upper lobe lung nodule showing cohesive clusters of large pleomorphic tumor cells with irregular nuclear contours and somewhat vacuolated cytoplasm (Papanicolaou stain; $\times 20$ original magnification). **B**, Thyroid transcription factor 1 immunocytochemical stain shows strong nuclear positivity, supporting pulmonary origin for this adenocarcinoma ($\times 20$ original magnification). (Courtesy Sharon Mount, MD, University of Vermont College of Medicine, Department of Pathology.)

It is our practice to have a cytopathologist attend each image-guided biopsy procedure performed in the radiology department to provide a rapid interpretation of aspirated material using light microscopy. This feedback helps guide the radiologist to obtain additional aspirated specimens for culture or immunocytochemical analysis or to perform core needle biopsy for histologic analysis.¹³ Ideally the pathologist responsible for processing and interpreting the specimens obtained from the biopsy procedure is consulted before the biopsy; this allows for review of existing pathologic specimens that help in the interpretation of the biopsy specimen. If a core biopsy for histologic material is anticipated, as for a mediastinal mass, or if cultures are likely to be obtained, the pathologist or cytotechnologist can bring the appropriate materials to the site of the biopsy in the radiology department to process the specimens. CytoLyt solution should be used to preserve cellular material for cell block, and Roswell Park Memorial Institute medium is used for flow cytometry when lymphoma is a diagnostic consideration and core needle biopsy is not possible. Culture medium should be used for processing aspirates for microbiologic stains and cultures, even when infection is remotely suspected.

The initial approach to the pathologic evaluation of a TNB specimen obtained from a lung nodule or mass is to determine whether the lesion represents a *small cell lung cancer* (SCLC) or an NSCLC. This distinction is typically made on the basis of light microscopic examination of the stained specimen.¹⁴ In the majority of biopsy specimens showing an epithelial malignancy, additional immunocytochemical tests performed on aspirated specimens are needed for definitive determination of the primary site of disease. Immunocytochemistry involves the binding of monoclonal or polyclonal antibodies to specific antigens within tumor cells that render these antigenic proteins visible under light microscopy.⁶ The technique is versatile, because it can be performed on cytologic material obtained fixed on slides, on a cell block, or on histologic specimens that are embedded in paraffin. By using positive and negative controls and assessing for nuclear, cytoplasmic, or membranous staining, the pathologist can incorporate the results of the immunocytochemical stains into the diagnostic algorithm

to render an impression regarding the specific cause of the sampled lesion.

Neuroendocrine markers, including chromogranin, synaptophysin, and CD56, are used to help confirm the diagnosis of small cell carcinoma, typical and atypical carcinoid tumors, and large cell neuroendocrine carcinoma. The markers most often used to determine the primary site of adenocarcinoma include thyroid transcription factor 1 (positive in lung and thyroid carcinoma) (Fig. 19-4), cytokeratin 7 and 20 (positive in lung and colorectal carcinoma, respectively, and helpful in distinguishing the two), CDX2 (positive in colorectal carcinoma) (Fig. 19-5), and estrogen receptors and HER2neu (positive in some breast carcinomas).¹⁵ Increasingly, core specimens for *EGFR* and *ALK* mutational analysis in patients with NSCLC thought to reflect adenocarcinoma should be obtained in patients who might benefit from such information (Fig. 19-6).

POSTPROCEDURE PATIENT MANAGEMENT

Once the biopsy has been completed, the patient is monitored and precautions are instituted to minimize delayed complications. Typically, patients are kept recumbent, ideally with the biopsy side down) in an effort to reduce the likelihood of air leak from the lung puncture site^{16,17} and to decrease the likelihood that any alveolar hemorrhage induced by the biopsy will be aspirated into the uninvolved lung and produce respiratory compromise. After the biopsy has been completed, the coaxial needle is withdrawn and the patient is immediately moved by radiology personnel from the biopsy table to a stretcher with the biopsy side placed dependently; this avoids straining that would produce an increase in intrathoracic pressure that would promote air leak. Some radiologists inject autologous blood clot or saline upon withdrawal of the outer guide needle of a coaxial system in an attempt to seal the visceral pleural surface to prevent an air leak and pneumothorax following the biopsy. The patient receives supplemental oxygen as a precaution while recovering from conscious sedation and also to help promote resorption of any pneumothorax.

An upright chest radiograph is obtained 2 to 3 hours following the completion of the biopsy to assess for

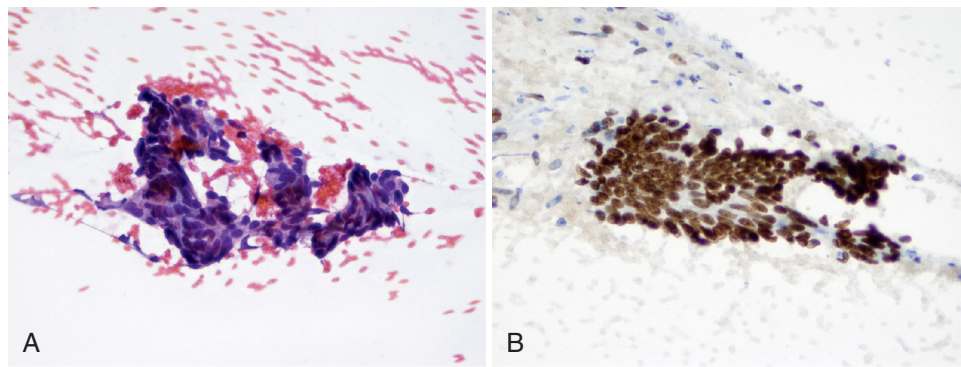


Figure 19-5 Immunocytochemical diagnosis of metastatic colorectal adenocarcinoma to lung. **A**, Photomicrograph of aspirated specimen from a patient with a history of stage III colorectal carcinoma and a solitary pulmonary nodule showing a cohesive cluster of tumor cells with rather uniform oval-shaped nuclei and delicate cytoplasm. (Papanicolaou stain; $\times 20$ original magnification). **B**, Immunocytochemical stain for CDX2 shows nuclear immunoreactivity, supporting the diagnosis of metastatic adenocarcinoma of gastrointestinal origin ($\times 20$ original magnification). (Courtesy Sharon Mount, MD, University of Vermont College of Medicine, Department of Pathology.)

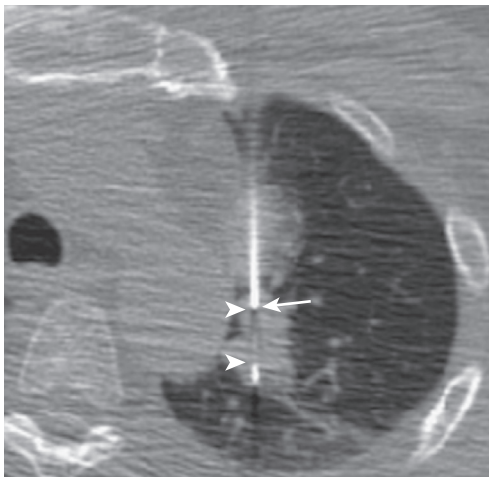


Figure 19-6 Core biopsy for molecular analysis. CT performed at the level of the aortic arch shows the coaxial guide needle (arrow) with its tip at the anterior edge of a lobulated left upper lobe nodule, with the receptacle stylet of the inner cutting needle (between arrowheads) within the nodule. Core specimens were obtained for subsequent molecular analysis of this known pulmonary adenocarcinoma.

intraparenchymal or pleural hemorrhage and to exclude a pneumothorax. If no pneumothorax is detected, the patient can be safely discharged to home.¹⁸ If a small (< 2 cm from chest apex to pleural line of upper lobe) pneumothorax is present and the patient is asymptomatic, the patient can be discharged safely if the pneumothorax was detected on CT during the biopsy. Otherwise, the patient is observed for an additional 2 hours to confirm that the pneumothorax is stable; if it enlarges, a pleural drainage catheter is placed under fluoroscopic or CT guidance, and the patient is admitted for observation and management. Any symptomatic, moderate-sized (2 to 4 cm), large (> 4 cm), or enlarging pneumothorax is evacuated, and the patient is admitted for management. Select patients who undergo evacuation of a biopsy-induced pneumothorax with a catheter attached to a Heimlich valve can be safely managed on an outpatient basis, provided they have family or friends who can monitor them and if they live within short distance of a health care facility that can assess and manage them should their shortness of breath redevelop. Patients undergoing catheter

drainage have underwater seal and suction until the pneumothorax has resolved and no air leak can be demonstrated, at which time the catheter can be safely removed.

RESULTS

TNB has proven highly sensitive for the cytologic diagnosis of malignancy, with sensitivities exceeding 90% in the largest series published.^{1,2} The distinction between NSCLC and SCLC is made with high accuracy ($> 85\%$).¹⁴ A variety of factors have been shown to affect sensitivity, including the patient's ability to lie still and cooperate sufficiently, the presence of underlying emphysema, operator experience, lesion size and location, lesion density, and availability of expert cytopathologic analysis; all these factors affect the TNB success rate. Even for lesions smaller than 10 mm, the sensitivity rate of TNB is high.¹⁹ Certain lesions, particularly large mediastinal lymphomas, such as nodular sclerosing Hodgkin lymphoma, and certain forms of non-Hodgkin lymphoma that contain significant fibrosis, localized fibrous tumors of pleura, and neurogenic lesions can be more difficult to diagnose cytologically; core needle biopsies are typically obtained for definitive diagnosis of these lesions. TNB samples of subsolid adenocarcinomas can be difficult to distinguish cytologically from atypia or adenomatous hyperplasia, although our experience suggests that the yield of TNB from these lesions is similar to that for solid nodules.

Precise cytologic diagnosis of benign pulmonary lesions, such as granulomas, is more difficult than that of malignant lesions because their relatively small size and typically hypocellular, fibrotic matrix makes retrieval of diagnostic material from TNB difficult. Core needle biopsy as an adjunct to cytologic analysis alone can increase the diagnostic yield from TNB of benign lesions to approximately 80%.²⁰ Pulmonary hamartomas, particularly those with a significant cartilaginous component, can be difficult to aspirate, and core needle biopsy may be necessary for these lesions. Nevertheless, a skilled cytopathologist can make the diagnosis of a pulmonary hamartoma if provided adequate cytologic material (Fig. 19-7).

The diagnostic yield of TNB for infection is somewhat lower than for malignancy. However, TNB can identify the

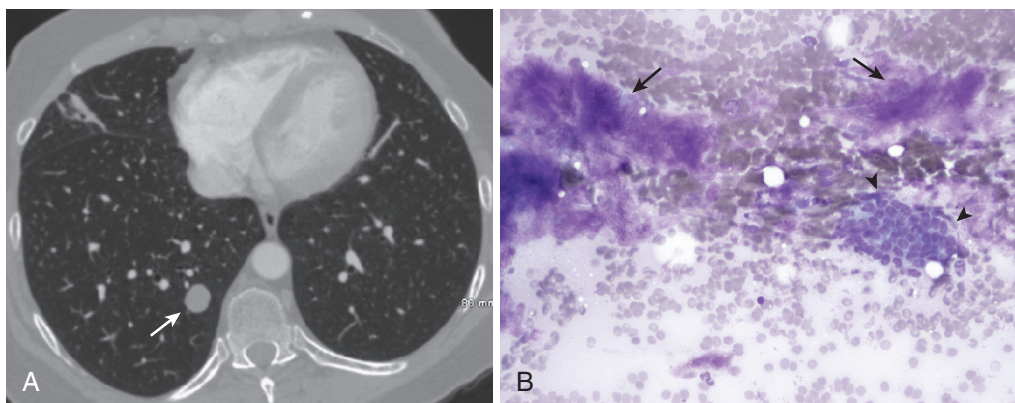


Figure 19-7 Pulmonary hamartoma on transthoracic needle biopsy. **A**, CT scan through the lower lobes displayed in bone windows showing a lobulated 13-mm right lower lobe nodule without obvious fat or calcium (arrow). **B**, Photomicrograph of aspirated specimen shows chondroid fragments (arrows) with adjacent normal bronchial epithelial cells (arrowheads), consistent with a chondroid hamartoma (Giemsa stain; $\times 20$ original magnification). (Courtesy Gladwyn Leiman, MD, University of Vermont College of Medicine, Department of Pathology.)

causative microorganisms producing focal lesions in 80% of immunocompromised patients with suspected lung infection.²¹

COMPLICATIONS

The most common complications of TNB include pneumothorax and bleeding. Pneumothorax develops in approximately 20% of patients undergoing TNB, of whom 3% require catheter or tube drainage.¹⁰ Factors that may be associated with an increased rate of TNB-induced pneumothorax include operator inexperience, advanced patient age, smaller lesion size, greater lesion depth from the pleural surface, the presence of underlying emphysema or obstructive lung disease, larger outer coaxial needle diameter, prolonged needle dwell time, and greater obliquity of the angle between the biopsy needle and the transgressed visceral pleural surface.²²⁻²⁴

Hemorrhage (eFig. 19-1) with or without hemoptysis develops in approximately 5% of patients undergoing TNB but is rarely the cause of prolonged observation, hospitalization, or need for transfusion. Biopsy-induced hemorrhage can preclude successful completion of TNB if it leads to intractable coughing or if blood at the biopsy site in the lung obscures the lesion being sampled, thereby rendering further attempts at accurate sampling impossible.

Rare complications of TNB include hemothorax from intercostal artery damage (see eFig. 19-1), air embolism (eFig. 19-2), malignant seeding of the biopsy path, and, rarely, death.

CATHETER DRAINAGE OF INTRATHORACIC COLLECTIONS

Image-guided catheter or tube drainage of intrathoracic collections is an effective, minimally invasive method for treating a spectrum of intrapleural and intrapulmonary collections (see additional discussion in Chapter 79). This section will review the common indications, imaging considerations, catheter placement, and postprocedure man-

Table 19-2 Indications for Catheter Drainage of Parapneumonic Effusion

Small- to moderate-sized free-flowing collection lacking septations on ultrasonography
Unilocular collections lacking septations on ultrasonography
Selected multilocular or septated collections in nonsurgical candidates

agement of intrathoracic collections with a review of complications and results in selected patients.

PARAPNEUMONIC EFFUSIONS—EMPYEMA

Intrapleural collections amenable to image-guided drainage include a wide spectrum of common causes of pleural effusions (see additional discussion in Chapter 80). Selected patients with complicated parapneumonic effusions, defined as those unlikely to resolve spontaneously with treatment of the underlying pulmonary infection, or frank empyema can benefit from image-guided drainage, thereby avoiding prolonged hospitalization and open surgical drainage and/or decortication procedures (Table 19-2).

According to the American College of Chest Physicians consensus statement on the medical and surgical management of parapneumonic effusions, the anatomy of infected pleural fluid collections, the presence or absence of bacteria within the parapneumonic effusion, and pleural fluid chemistry have prognostic utility for predicting patient morbidity and mortality.²⁵ Ultrasonography can detect very small parapneumonic effusions and helps guide safe, diagnostic sampling of these collections when necessary. Ultrasonographic findings that predict the likelihood of successful catheter or tube drainage, corresponding to early exudative stage parapneumonic collections, include small- to moderate-sized free-flowing, nonloculated collections lacking internal echoes or septations. Alternatively, ultrasonographically detected septations within complicated parapneumonic collections and empyemas make it more likely that a longer duration of chest tube drainage and longer hospital stay will be necessary.

Because these collections are likely to require fibrinolytics (see subsequent discussion) and ultimately surgical intervention, primary surgical treatment may be warranted in this subgroup of patients.²⁶ Analysis of the entire extent of the pleural fluid collection and characterization of underlying lung and adjacent chest wall disease is best demonstrated on contrast-enhanced multidetector CT, which provides axial, sagittal, and coronal reformatted images that offer important information when considering therapeutic options for parapneumonic effusions. Similarly, early-stage exudative or fibrinopurulent effusions characterized on CT as dependent meniscoid or unilocular collections are best suited to small-bore image-guided catheter placement, with case series reporting success rates as high as 93%.²⁷ The presence of enhancing visceral and parietal pleural layers encompassing a loculated pleural fluid collection is relatively specific for the presence of an empyema, although the identification of this split pleura sign does not preclude successful catheter drainage. Selected patients with unilocular empyemas or multiloculated collections who are poor surgical candidates for open management of infected pleural collections can be successfully managed with one or more image-guided catheters, either as definitive therapy or as a bridge to definitive surgical treatment.

After ultrasonographic localization for small-bore image-guided catheter treatment of parapneumonic effusions, we prefer a trocar catheter placement technique using a 14- or 16-French drainage catheter) for free-flowing or unilocular, nonseptated parapneumonic collections that have an adequate area of contact with the costal pleural surface and sufficient width to allow safe placement of the sharp-tipped trocar-catheter combination into the dependent part of the collection (Fig. 19-8). For treatment of frank empyemas or large collections with ultrasonographically or CT-detected septations in nonsurgical patients, we prefer a large 28-French tube placed using a Seldinger technique, which involves placement of an 18-gauge needle followed by a guidewire and sequential dilation to 30-French diameter before tube insertion. If necessary, multiple catheters or tubes can be employed to drain different locules within the

chest as depicted on CT, particularly for those patients felt to be poor candidates for primary surgical drainage.²⁷

Once catheters and tubes have been placed under imaging guidance, the patient's clinical status, tube output, and radiologic studies are reviewed daily to determine the effectiveness of drainage. The tube or catheter should be flushed with saline three times a day to maintain patency of the lumen and prevent occlusion of the drainage holes located in the distal aspect of the device by fibrin and debris. An inadequate response to treatment is defined as a lack of improvement in fever, peripheral white blood cell count, and oxygenation, with persistent dyspnea or pain; importantly, a persistent or enlarging collection on radiography or CT warrants a reevaluation of the patient with consideration of additional maneuvers to improve drainage or proceeding to surgical management. Assuming radiologic evaluation and management demonstrates adequate positioning and functioning of the drainage catheter or tube within the collection(s), inadequate drainage may require increasing the size of the tube and/or the use of intrapleural fibrinolytic agents to promote drainage. Contrast-enhanced chest CT evaluation is helpful for patients who have failed to improve following adequate tube placement to detect undrained locules and to guide tube exchange when necessary; CT can also assess the status of the underlying pneumonia or abscess to determine if lack of clinical improvement is more a result of progressive pulmonary infection than inadequate pleural drainage. Once there has been clinical and radiographic resolution of the collection and drainage has diminished to less than 100 mL/day, the catheter is removed.

The use of intrapleural fibrinolytic agents as an adjunct to catheter or tube drainage can aid in the successful management of complicated parapneumonic effusions and empyemas, particularly those collections in the fibrinopurulent or organizing stages of empyema formation.²⁸ Multiple case series assessing the use of intrapleural streptokinase, urokinase, or recombinant tissue plasminogen activator have shown radiographic resolution of infected pleural fluid collections (see Fig. 19-8), obviating the need

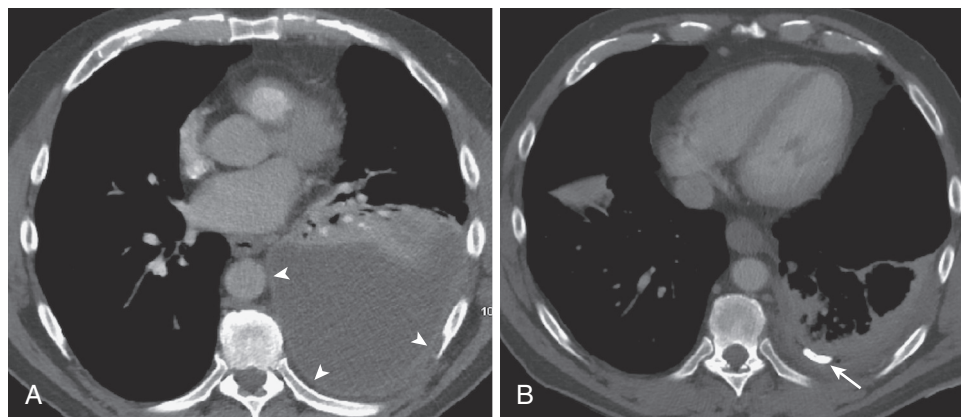


Figure 19-8 CT-guided catheter drainage of loculated empyema treated with intrapleural fibrinolytics. **A**, Contrast-enhanced CT displayed in mediastinal windows through the level of the left atrium showing a unilocular collection in the lower posterior left pleural space. Note subtle enhancement of the parietal pleural surface (arrowheads), suggesting presence of an exudative effusion. **B**, Repeat contrast-enhanced CT scan displayed in mediastinal windows performed through the lower lobes following placement of a 14-French pigtail drainage catheter and intrapleural instillation of recombinant tissue plasminogen activator for 5 days shows the catheter (arrow) in the posterior pleural space with evacuation of the pleural fluid.

for surgical drainage. Given problems with allergic reactions to streptokinase and the limited availability of urokinase, most centers, including ours, use recombinant tissue plasminogen activator for intrapleural fibrinolysis. Although there is literature to indicate that intrapleural fibrinolytics provide no added benefit compared with drainage alone in terms of survival, length of hospital stay, or need for open surgical drainage,²⁹ methodologic limitations of these studies have been identified.³⁰

Specifically, the largest randomized controlled trial, the MIST1 study, used only chest radiography to assess pleural fluid morphologic characteristics, which is not as accurate as CT or ultrasonography to assess for septations, loculations, and intrafissural and medial pleural locules.²⁹ In support of the use of intrapleural fibrinolytics in the adult population is a recent meta-analysis published in 2012 of seven randomized controlled studies, conducted primarily in Europe, comparing fibrinolytics with placebo using data collected through October 2011.³¹ This study showed that fibrinolytics are potentially beneficial for the management of parapneumonic effusions and empyemas in adults.

The most recent evidence supporting intrapleural therapy for the treatment of pleural infection is a randomized controlled trial comparing intrapleural recombinant tissue plasminogen activator in combination with DNase or with either agent alone versus no intrapleural treatment, which showed a significant change in mean pleural opacity on radiography 1 week after 3 days of twice-daily intrapleural administrations of both agents.³² Subgroup analysis showed no differences in treatment effect between use of large- or small-bore tubes, purulent or nonpurulent pleural fluid, or presence or absence of loculations. In addition, frequency of referral for surgery and length of hospital stay were reduced for patients receiving the combined intrapleural treatment compared with those receiving either agent or no agent alone, and there was no difference in adverse events among all groups. Although further study of intrapleural treatment for infected pleural collections is needed, this latter study suggests that the combination of recombinant tissue plasminogen activator for fibrinolysis and DNase to

cleave extracellular DNA and reduce pleural fluid viscosity may become the standard of treatment for selected patients with infected pleural fluid collections. However, the potential cost-effectiveness of intrapleural fibrinolytic treatment has not been well delineated.

MALIGNANT PLEURAL EFFUSIONS

A malignant pleural effusion is defined by the presence of positive cytologic results on pleural fluid analysis or positive pleural biopsy in a patient with malignancy. Malignant pleural effusion is most commonly due to lung or breast cancer, although in 10% to 15% of patients with malignant effusions, no primary tumor can be identified.³³ Catheter drainage of a malignant effusion, followed by either chemical pleurodesis or the use of an indwelling tunneled catheter, can be used to provide extended drainage of symptomatic malignant effusions in patients with a limited life expectancy and is a reasonable alternative to thorascopic or open surgical drainage and sclerosis (Fig. 19-9).³⁴

Because the majority of symptomatic and recurrent malignant effusions are large and free flowing, catheter placement for drainage and subsequent talc pleurodesis is typically performed using ultrasonographic guidance with the patient in the sitting position. A diagnostic ultrasonographic examination is performed to confirm the size and dependent location of the collection. A lower intercostal approach is used to place the catheter tip in a dependent location to facilitate drainage of dependent fluid no matter what position (i.e., supine or upright) the patient maintains. Optimally the catheter is placed through the junction of the serratus anterior and latissimus dorsi muscles along the lower posterolateral chest wall where it traverses the least amount of muscle and will not be compressed or kinked when the patient lies on his or her back. For serous or thin serosanguineous effusions a 10- or 12-French catheter allows for adequate drainage, whereas a larger diameter (12- or 14-French) is employed if talc slurry is to be administered for subsequent pleurodesis following adequate drainage of the pleural space and reexpansion of the

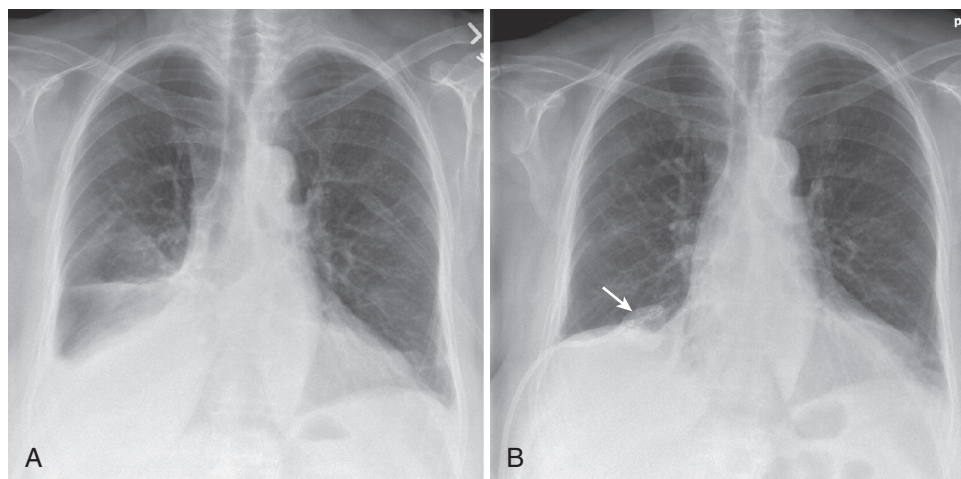


Figure 19-9 Ultrasonographic-guided drainage of a malignant pleural effusion. **A**, Frontal chest radiograph in a 68-year-old woman with a malignant right pleural effusion from metastatic ovarian carcinoma showing a right pleural effusion with passive right lower lobe atelectasis. **B**, Repeat radiograph after ultrasonographically guided placement of a 10-French pigtail catheter shows the catheter (arrow) in the dependent aspect of the right pleural space with evacuation of the effusion and reexpansion of the lower lobe.

underlying lung. Loculated collections can benefit from intrapleural fibrinolytics to lyse adhesions before attempts at chemical sclerosis.

If talc slurry is used for chemical pleurodesis, 4 g of talc mixed with 50 mL of normal saline is injected into the evacuated pleural space and left to dwell for 1 hour. Suction is then reinstituted, with the catheter removed once drainage has diminished to less than 150 mL/day and the patient has shown symptomatic and radiographic improvement. Complete response rates of 70% and higher have been reported for use of small-bore catheters and talc pleurodesis in selected patients.³⁵

PNEUMOTHORAX

Fluoroscopy- or CT-guided small-bore (<12-French) catheter drainage of pneumothorax can be employed for management of moderate-to-large or enlarging pneumothoraces, or any size pneumothorax that is symptomatic (see additional discussion in Chapter 81). Today, most often image-guided catheter drainage of pneumothorax is performed for pneumothorax that develops as a complication of TNB or thermal ablation of localized thoracic malignancy, although catheter drainage has been traditionally used to treat spontaneous pneumothorax and pneumothorax related to traumatic causes (Fig. 19-10).³⁶

For pneumothorax resulting from a CT-guided procedure, catheter placement is typically performed using CT. Otherwise, fluoroscopy provides real-time visualization of catheter placement and is the preferred guidance modality. An approach via the anterior 2nd intercostal space in the midclavicular line is typically used, although in women a lateral approach via the 5th to 6th intercostal space in the midaxillary line can be employed to avoid traversing breast tissue. Conscious sedation and local anesthesia are used, with adequate numbing of the heavily innervated parietal pleura with lidocaine being the key to patient comfort during catheter placement. We employ a trocar technique in which, following successful pleural anesthesia, a drain-

age catheter with a self-retaining pigtail tip configuration loaded onto a stiffening cannula and inner sharp-tipped trocar is placed into the pleural space and positioned into the pleural apex under direct visualization. Once the catheter tip is confirmed to lie within the apex of the pleural space, the pigtail tip is “locked” into position by use of a string that opposes the catheter tip to a more proximal portion of the catheter, and lidocaine is injected through the catheter lumen to provide local anesthesia to the apical pleura, which if contacted by the catheter can produce significant ipsilateral shoulder pain. Alternatively, the catheter can be introduced into the pleural space in a stepwise fashion, whereby a hollow needle is initially used to access the pleural space, followed by placement of a guidewire and then progressive dilation of the track to the diameter of the catheter to be placed for drainage.

Once the catheter has been successfully placed, it is affixed to the skin using an adhesive ostomy-type dressing with ties surrounding the catheter and is attached to a Pleur-evac device for suction drainage. The catheter should be flushed two to three times a day to prevent fibrin deposition that can occlude the drainage holes situated in the distal pigtail-shaped component of the catheter.

Success rates for small-bore catheter drainage of iatrogenic pneumothorax exceed 85% in multiple series,^{36,37} but drainage is also successful in the majority of patients when used in emergency settings for noniatrogenic traumatic and spontaneous pneumothoraces.³⁸

LUNG ABSCESS

Although postural drainage and antibiotics are the standard methods for medical management of lung abscess, those collections that do not readily communicate with an airway or for which medical management is unsuccessful can be treated with catheter drainage under CT guidance, as discussed in Chapter 33. Because most of these collections are pleural based, with intrapleural adhesions typical at the site of pleural contact, the risk for development of a

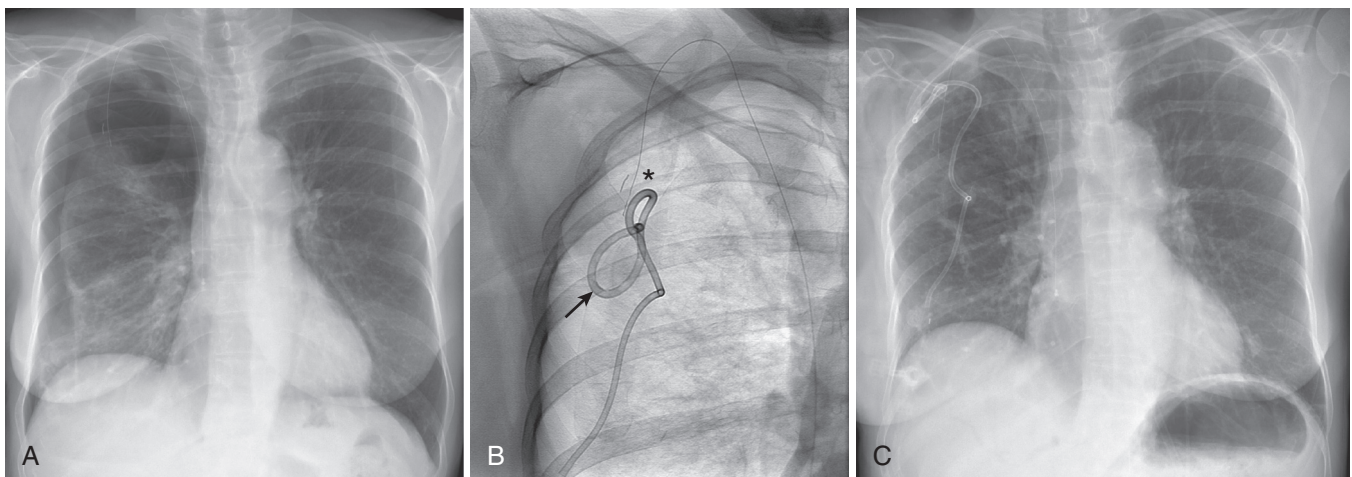


Figure 19-10 Catheter drainage of a biopsy-induced pneumothorax. **A**, Upright frontal chest radiograph obtained 2 hours after CT-guided biopsy of a cavitary metastasis to the right lung showing a large right pneumothorax. **B**, Spot radiograph during drainage catheter placement shows the catheter (arrow) placed via the second anterior intercostal space with the catheter coursing over the right pleural apex (asterisk). **C**, Repeat frontal radiograph obtained the following morning shows the catheter over the right lung apex and complete evacuation of the pneumothorax.

bronchopleural fistula is minimal. As with drainage of complex pleural collections, image-guided catheter drainage can be definitive or can be used as a bridge to surgical management.³⁹

Drainage of lung abscess or an infected bulla is best performed under CT guidance, because this provides direct visualization of the catheter course and helps minimize traversal of normal intervening lung by the drainage catheter. The principles of catheter placement are similar to those for drainage of abscesses elsewhere in the body. The patient is positioned to allow access to that part of the abscess that is closest to a pleural surface. If possible, it is best to avoid placing the patient in the decubitus position with the unaffected side dependent, because pus or blood can spill from the abscess cavity into the dependent lung during catheter placement, producing respiratory compromise. We typically use a trocar technique for catheter placement into larger abscesses, whereby the drainage catheter (typically 12- or 14-French) is loaded over both a stiffening cannula and a sharp-tipped trocar that allows puncture of the cavity wall. Alternatively, for smaller collections, a needle can be placed into the cavity, its position confirmed on repeat CT imaging or aspiration of pus through the needle, followed by placement of a guidewire into the cavity and progressive dilation until the desired catheter diameter is achieved. The catheter is then placed directly into the abscess cavity over the guidewire. The pigtail-shaped tip should be placed into the dependent part of the collection to facilitate dependent drainage of the infected fluid. Once properly positioned, the drainage catheter is affixed to the skin and attached to suction drainage until fluid drainage ceases and there is evidence of clinical and radiologic improvement (Fig. 19-11).

There are only limited case series describing the success rate and complications from percutaneous catheter drainage of lung abscess. A recent update summarizing the results of 21 studies showed a success rate of 84%, with a complication rate of 16%.⁴⁰ Clogging of smaller drainage tubes, pneumothorax, hemothorax, hemoptysis, and bron-

chopleural fistula formation are the most frequent complications following catheter abscess drainage.

BRONCHIAL ARTERIOGRAPHY

INDICATIONS AND CONTRAINDICATIONS

The most common indication for urgent or emergent bronchial arteriography is massive hemoptysis. The most commonly used criterion for massive hemoptysis is 500 mL of expectorated blood in a 24-hour period, although it has been defined variably from as low as expectoration of 100 mL to greater than 1000 mL of blood in a 24-hour period.⁴¹ The need for emergent intervention is most commonly determined by the patient's sudden onset of severe hypoxemia from intrapulmonary bleeding and retention of blood; hemoptysis rarely causes life-threatening exsanguination. For practical purposes, any amount of hemoptysis that causes life-threatening inability to maintain a patent airway should be considered emergent.

Massive hemoptysis most commonly results from chronic inflammatory lung diseases due to bronchiectasis, cystic fibrosis (Fig. 19-12), or complicating fungal infection.⁴¹ Neoplasm, such as bronchogenic carcinoma or vascular metastatic disease, can also cause hemoptysis. Less common causes of hemoptysis include lung abscess, pneumonia, chronic bronchitis, ruptured bronchial artery aneurysm, pulmonary arteriovenous malformations, and traumatic or inflammatory pulmonary artery aneurysms. In resource-poor countries, pulmonary tuberculosis is by far the most common cause of massive hemoptysis.

Indications for nonemergent bronchial arteriography and intervention include patients with non-life-threatening chronic hemoptysis that is unresponsive to medical therapy.⁴² Less frequent indications for bronchial arteriography include bronchial artery aneurysms or pseudoaneurysms and arteriovenous fistulas. A failure of a thoracic stent graft caused by bronchial arterial collateral flow into

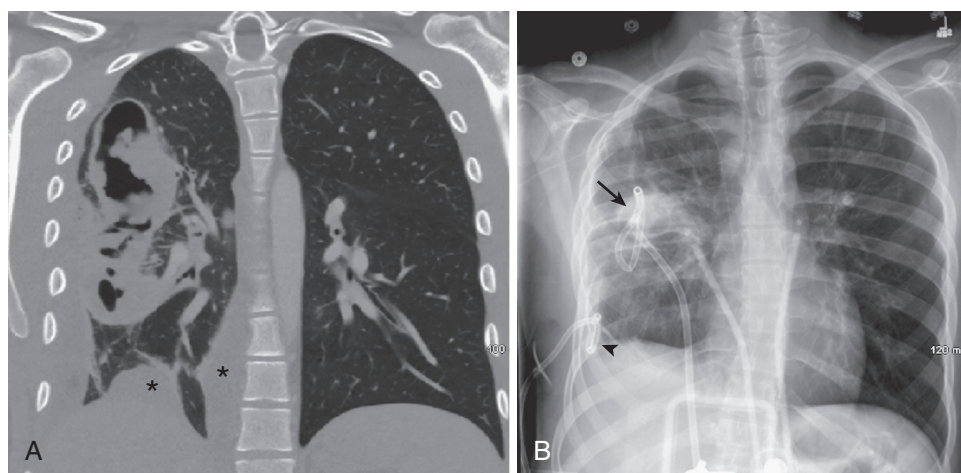


Figure 19-11 CT-guided drainage of right lung abscess. **A**, Coronal-reformatted CT scan displayed in bone windows through the posterior thorax in a 19-year-old man showing a large cavitary lesion extending from the upper to the lower lobe, representing an abscess. There is a multiloculated right paraneumonic effusion (asterisks). **B**, Upright frontal chest radiograph following CT-guided placement of a 16-French curved drainage catheter (arrow) into the abscess and a 12-French pigtail catheter (arrowhead) into the lower lateral right pleural fluid collection shows improvement in the abscess and pleural collection. The patient showed significant clinical improvement following the drainage.

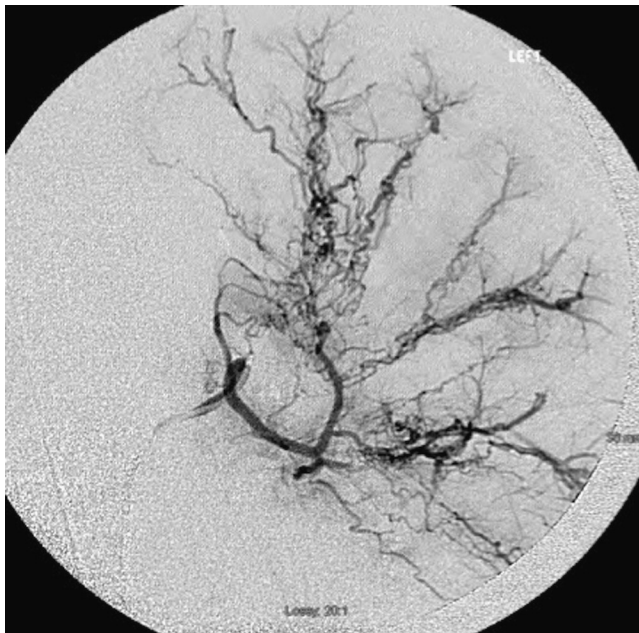


Figure 19-12 Left bronchial arteriogram in a patient with cystic fibrosis and massive hemoptysis. A selective left bronchial arteriogram demonstrates abnormally enlarged and tortuous left bronchial arteries. Bronchoscopy diagnosed acute hemorrhage from the apicoposterior segment of the left upper lobe.

the aneurysm sac (a type II endoleak) is an additional rare indication for bronchial arteriography and intervention. Bronchial arteriography and intervention has been used for patients with lung cancer and other intrathoracic malignancies that can produce significant bleeding, such as hypervascular metastases to the chest. Relative contraindications to bronchial arteriography include severe iodinated contrast allergy and acute or chronic renal disease. Severe aortoiliac or upper extremity occlusive disease may also pose a challenge in accessing the origins of the bronchial arteries.

Conservative management of massive hemoptysis is associated with a mortality rate of 50% to 100%.⁴³ Moreover, reported mortality rates for surgery performed for massive hemoptysis are as high as 35%. Bronchial artery embolization is a safe and effective alternative to medical or surgical management of hemoptysis with successful control of acute life-threatening hemoptysis in 73 to 98% of patients, although hemoptysis may recur.⁴²⁻⁴⁴

The bronchial arteries have variable anatomy with multiple different combinations of origins, branching patterns, and vessel course. The bronchial arteries most commonly originate from the descending thoracic aorta between the levels of the T5 and T6 vertebral bodies (eFig. 19-3) but can originate anywhere from T3 through T7 levels. Eighty percent of individuals will have a right bronchial artery that arises as a common *intercostobronchial trunk* (ICBT) from the posterolateral aspect of the thoracic aorta. The other bronchial arteries arise from the anterolateral aspect of the thoracic aorta. Four classic branching patterns have been described: two on the left and one on the right arising as an intercostobronchial trunk (40%); one on the left and one intercostobronchial trunk on the right (20%); two on the left and two on the right (20%); and one on the left and

two on the right (10%) (Fig. 19-13).^{41,43} Right and left bronchial arteries can originate from the thoracic aorta as a common trunk.

Anomalous bronchial arteries, which may be found in up to 35% of individuals, may arise from the aortic arch, intercostal arteries, internal mammary arteries, thyrocervical trunk, costocervical trunk, brachiocephalic artery, subclavian artery, or inferior phrenic artery. Anomalous bronchial vessels follow the course of the major bronchi. The arteries supplying the chest wall and diaphragm can also be recruited as systemic nonbronchial collaterals in the setting of pleural or parenchymal disease. These collaterals typically supply the lung after directly crossing diseased pleura (eFig. 19-4) or via the pulmonary ligament. Unlike the bronchial artery collaterals, these systemic collaterals do not follow the course of the bronchi. Assessing the presence of anomalous or collateral blood supply is important when evaluating hemoptysis, but, when the bronchial artery supply to a known parenchymal abnormality is not demonstrated during angiography of the conventional bronchial arterial branches, the procedure can become difficult and time consuming.

PULMONARY ARTERIOGRAPHY

INDICATIONS AND CONTRAINDICATIONS

Multidetector *CT pulmonary angiography* (CTPA) has largely replaced conventional pulmonary angiography in the localization and diagnosis of pulmonary arterial pathologic conditions, particularly for pulmonary embolism (see Chapter 57). Therefore diagnostic CTPA is rarely performed in modern practice for purely diagnostic purposes but is more commonly employed as a navigating tool before transcatheter pulmonary artery intervention. Nevertheless, the most common indications for conventional CTPA are acute pulmonary embolism and diagnosis of pulmonary arteriovenous malformations (Fig. 19-14) as discussed further in Chapter 61. Less common indications for pulmonary arteriography include chronic pulmonary embolism, pulmonary sequestration, pulmonary artery stenosis, pulmonary aneurysm or pseudoaneurysm, and pulmonary artery neoplasms.⁴⁵⁻⁴⁷ Relative contraindications for pulmonary arteriography include severe contrast allergy, severe pulmonary hypertension, and left bundle-branch block.

The main pulmonary artery is intrapericardial. It starts anteriorly at the pulmonic valve then runs in a posterior and cranial direction until it divides into the right and left main pulmonary arteries. The right main pulmonary artery crosses the mediastinum posterior to the ascending aorta and superior vena cava and anterior to the carina and right main bronchus. Leaving the right lung hilum and lateral to the mediastinum, the artery branches into upper and lower trunks and then into lobar and segmental arteries that generally parallel the bronchi. The left main pulmonary artery continues superiorly and then crosses anterior to the left main bronchus and just inferior to the aortic arch before coursing posteriorly to the left lung hilum. At the left lung hilum, the left main pulmonary artery provides segmental arterial branches to the upper lobe before continuing as a single trunk to supply the lower lobe. Blood supply to the

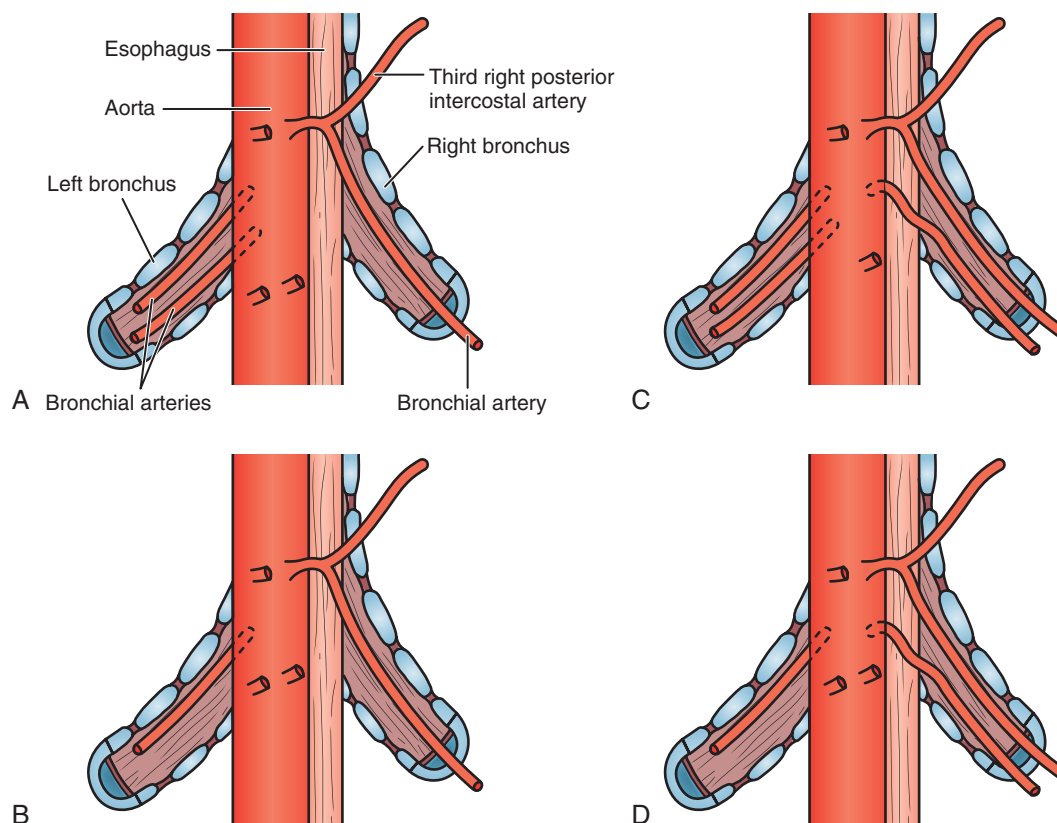


Figure 19-13 The four most common bronchial artery branching patterns (viewed from posterior). **A**, Two left vessels and one right vessel that represents an intercostobronchial trunk. **B**, One left vessel and one intercostobronchial trunk vessel on the right. **C**, Two left and two right (one intercostobronchial trunk and one bronchial artery) vessels. **D**, One left and two right (one intercostobronchial trunk and one bronchial artery) vessels. (Redrawn from Cauldwell EW, Siekert RG, Lininger RE, Anson BJ: The bronchial arteries: an anatomic study of 105 human cadavers. *Surg Gynecol Obstet* 86:395–412, 1948.)

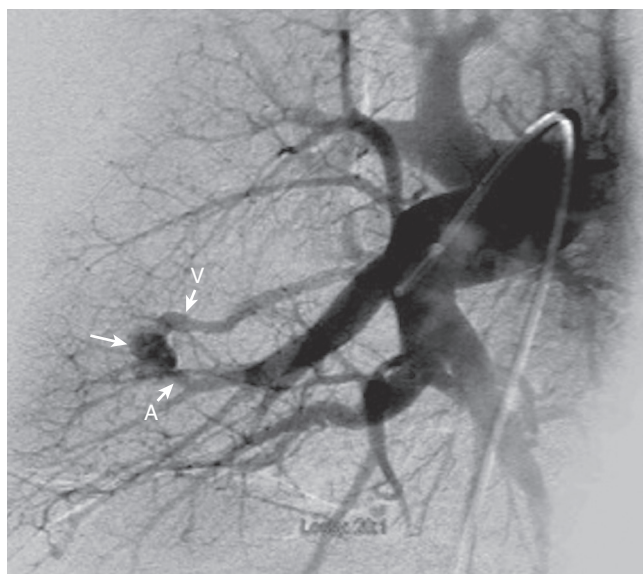


Figure 19-14 Pulmonary arteriovenous malformation on pulmonary angiography. A selective right descending pulmonary arteriogram in a 64-year-old woman with hereditary hemorrhagic telangiectasia demonstrates a pulmonary arteriovenous malformation (arrow) in the middle lobe. Note characteristic feeding artery (A) and early draining vein (V).

lingula is variable but usually arises from the lingular branch of the left upper lobe. As with the right lung, the left pulmonary artery lower lobe trunk then branches into segmental vessels that follow the bronchi.

THERMAL ABLATION OF LOCALIZED LUNG CANCER AND PULMONARY METASTATIC DISEASE

INDICATIONS AND CONTRAINDICATIONS

Thermal ablation of lung nodules using *radiofrequency* (RF) waves, microwaves, or a cryoprobe has been used to obtain local control of malignancy in the chest for over 10 years.⁴⁸⁻⁵⁰ All three minimally invasive techniques involve image-guided targeting of lung nodules or masses using needles that induce tumor necrosis via either coagulation necrosis (RF ablation, microwave) or freezing and thawing of tissues (cryoablation). Although all three techniques have been used in the treatment of localized thoracic malignancy, the most extensive experience has been with RF ablation. When used in the chest, the needle probes are usually placed via CT guidance with the patient under conscious sedation as with TNB.

Table 19-3 Indications for Thermal Ablation of Lung Tumors

Stage IA (T1a or T1b) non-small cell lung cancer in nonsurgical candidate
Limited (<4) pulmonary metastases; all < 3 cm diameter; primary tumor controlled
Control of localized recurrence of lung cancer in patient with previous advanced-stage lung cancer
Selected patients with unresectable carcinoid tumor of lung

Two primary groups of patients are considered for thermal ablation of the lung: (1) those with small, stage IA (<3 cm) NSCLC in whom surgery is contraindicated or refused and (2) patients with malignancy and limited (fewer than four) pulmonary metastases who are not candidates for surgical metastasectomy and have documented control of their primary tumor. For those with limited pulmonary metastases, a potential survival benefit from successful treatment of their metastases should exist to consider these patients for thermal ablation. Because many of these same patients are also candidates for external beam radiation using stereotactic techniques, the decision for nonsurgical candidates to use one or both techniques, if available, is made by a multidisciplinary group in consultation with the patient. Additional, less common indications for thermal lung ablation are listed in [Table 19-3](#).

There are several relative or absolute contraindications to performing image-guided thermal ablation of the lung. A patient's inability to cooperate for a prolonged (1½ hours) procedure on the CT table, despite the use of conscious sedation, can be managed by the use of general anesthesia with airway maintenance. Coagulopathy is a particular concern with cryoablation, which tends to induce local bleeding as a result of the freezing and thawing of tissue inherent to this technique. For these reasons any bleeding diathesis should be corrected before thermal ablation. Lesions that are immediately adjacent to the heart, aorta, superior vena cava, trachea, or esophagus are not amenable to thermal ablation, due to concern for damage to these structures.

Additionally, thermal ablation of lesions adjacent to larger intrathoracic vessels may not be adequately heated (RF ablation, microwave) or frozen (cryoablation) because flowing blood in these vessels produces a "heat sink" effect, whereby the temperatures in the part of the lesion nearest the flowing blood does not reach the temperature required to produce a cytotoxic effect and coagulative necrosis, and therefore the perivascular component of the tumor remains viable following ablation. Patients with pacemakers or implantable cardioverter-defibrillators are able to undergo RF ablation, but due to possible electromagnetic interference from the RF waves emitted from the ablation probe, these patients should be reprogrammed by an electrophysiologist for the duration of the procedure to avoid possible cardiac device malfunction.

The procedure of performing RF ablation is similar to the other two approved thermal treatment methods. The patient is positioned as if undergoing CT-guided TNB, with the anticipated puncture site placed nondependently. Because RF ablation involves electrical current extending from the probe into the surrounding tissues and through the body,

grounding pads are placed on the patients' thighs before the procedure to prevent the potential for skin burns by allowing for safe egress of electrical current from the body. For most lung lesions, a single needle probe is used and placed through the meridian of the lesion along its long axis. For treatment of lesions smaller than 2.5 cm, a standard 14-gauge probe ablates approximately a 3- to 4-cm zone of tissue, which provides for effective treatment of the lesion, and a 1-cm zone of normal lung surrounding the lesion, which should treat any microscopic disease at the margin of the tumor. For lesions larger than 2.5 cm, or for irregularly shaped lesions that cannot be effectively treated using a single ablation application, multiple overlapping ablation zones with repositioning of the needle between applications can be performed, although some radiologists prefer multi-tined probes or clustered electrodes that are designed to provide a larger ablation zone.

For RF ablation using a feedback algorithm to monitor impedance, intratumoral temperature, and electrical current, the needle is attached to a generator and conducts an alternating current at the frequency of radio waves (460 to 500 kHz) through the distal 3 cm that has been placed through the lesion to be treated. A 12-minute cycle is typically administered, during which current flows intermittently through the distal 3 cm of the needle. Impedance is monitored, and temperatures are measured to confirm adequate heating of tissues to ensure tumor death and a surrounding zone of lung necrosis. Ideally the temperature measured by the electrode within the tumor following the ablation cycle exceeds 50° C, a temperature at which cells die within minutes. Successful RF ablation produces a zone of ground-glass opacity surrounding the lesion and needle electrode on CT scans obtained immediately following ablation ([Fig. 19-15](#)). After one or more cycles have produced an adequate ablation zone as determined on CT, the needle is removed and the patient is managed as for TNB.

Multiple series detailing CT-guided RF ablation of unresectable early-stage lung cancer and limited pulmonary metastatic disease have shown the procedure to be safe with an acceptable complication rate.⁴⁸⁻⁵⁰ The most common complications include pneumothorax in 30% to 50% of patients, with 10% to 20% requiring catheter drainage.⁵¹ For lesions situated along the outer edge of lung, pain typically develops either during the ablation procedure or within 5 days of treatment, because RF ablation induces significant tissue infarction and secondary parietal pleural irritation. Twenty percent of patients will develop a pleural effusion, again most commonly when treating peripheral lesions, although most remain small and do not produce respiratory compromise or require drainage.

Although no randomized controlled trials have yet compared RF or other thermal ablation procedures to standard treatment therapies, such as surgery and radiation therapy, several series have shown 2-year survival rates of 50% to 60% for treatment of stage I NSCLC ([Fig. 19-16](#)) and approximately 70% for RF-treated colorectal metastases in selected patients, when lesions are 3 cm or smaller in diameter.⁵²⁻⁵⁴ The majority of recurrences are local and are directly related to mean tumor diameter, with lesions larger than 3 cm showing significantly higher recurrence rates and lower overall and disease-specific patient survival than those less than 3 cm in diameter.⁵⁵

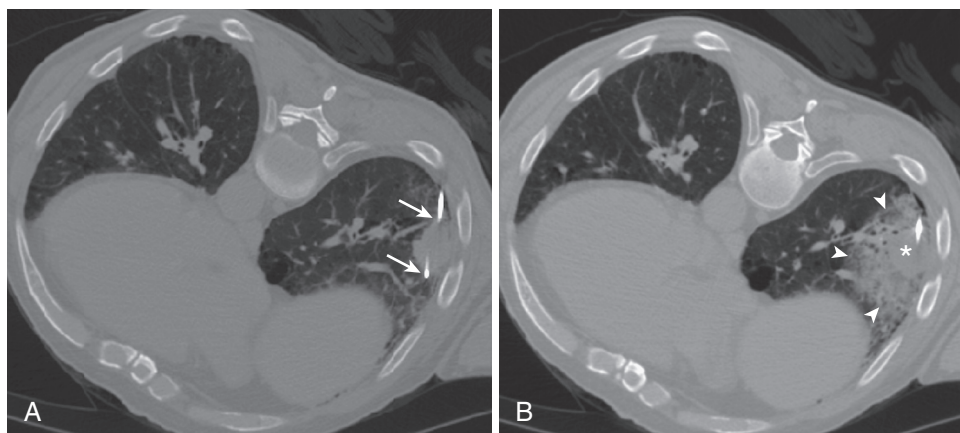


Figure 19-15 CT appearance immediately following radiofrequency ablation of a pulmonary lesion. **A**, Chest CT displayed in bone windows with the patient prone during radiofrequency ablation of a solitary 3.5-cm metastasis from urothelial carcinoma shows two ablation probes (*arrows*) used to create a large ablation zone. **B**, Repeat CT scan following ablation shows a large halo of ground-glass opacity (*arrowheads*) encompassing the treated lesion (*asterisk*).

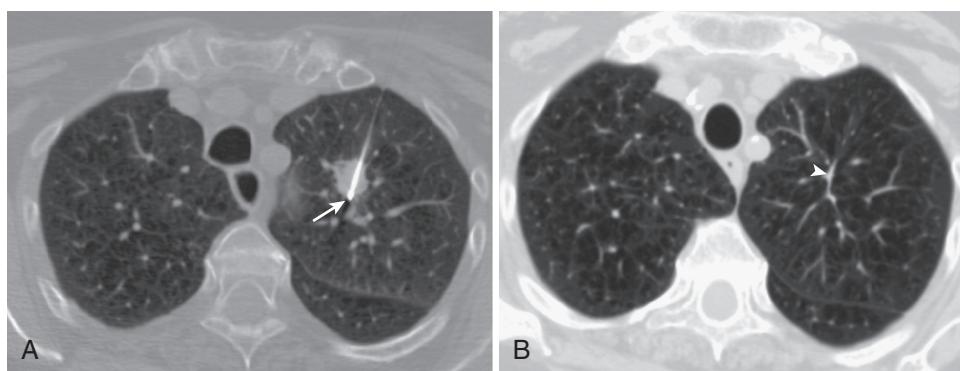


Figure 19-16 Long-term success of radiofrequency ablation for T1a non-small cell carcinoma of lung. **A**, Unenhanced CT displayed in bone windows performed through the upper lobes during radiofrequency ablation shows the electrode (*arrow*) placed through the left upper lobe nodule known to reflect a non-small cell lung carcinoma. **B**, CT scan 5 years following ablation shows a linear scar (*arrowhead*) at the site of the previous nodule.

PREOPERATIVE CT-GUIDED LOCALIZATION FOR VIDEO-ASSISTED THORACIC SURGERY NODULE RESECTION

INDICATIONS AND CONTRAINDICATIONS

With the increased detection of small pulmonary nodules on multidetector chest CT examinations, there is a concomitant increase in the need for pathologic diagnosis of those lesions too small to characterize as definitively benign or to sample accurately with TNB. The most common clinical scenario is the patient with a small lung nodule or nodules and a known primary thoracic or extrathoracic malignancy in whom the diagnosis of metastatic disease must be excluded. A patient with a solitary small lung nodule in whom wedge resection would provide both diagnostic information and potential therapeutic benefit may also be considered for VATS resection.

Most solid nodules 1.5 cm or smaller in the lung periphery (i.e., within 1.5 cm of the costal or diaphragmatic

pleural surface) can be successfully identified and resected at VATS. In certain patients with lesions smaller than 10 mm or with subsolid nodules, preoperative needle localization may aid the surgeon in identifying nodules intraoperatively. This facilitates successful intraoperative resection of these lesions, particularly if the nodule is greater than 1 cm from the visceral pleural surface and will be difficult to identify intraoperatively.

The preoperative patient preparation and basic technique of marking subpleural nodules for VATS resection is similar to that for TNB. The procedure is typically performed under CT guidance and is coordinated with the operating room so that the patient proceeds directly from radiology to the preoperative holding area and operating room immediately following image-guided localization.

The patient is positioned as if for performance of a CT-guided TNB, with the planned needle approach being the shortest distance between the nodule and the costal pleural surface. This aids the surgeon in using the localizing needle or wire to palpate the subpleural nodule intraoperatively and resect the least amount of normal lung along with the lesion to be removed. Rarely, a biopsy of a small

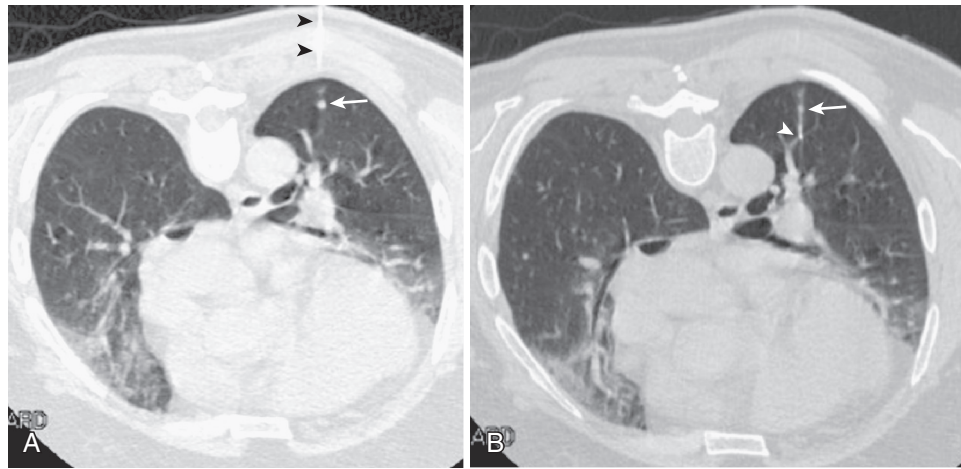


Figure 19-17 CT-guided needle localization of small peripheral nodule for video-assisted thoracic surgery resection. **A**, CT displayed in lung windows performed through the mid chest with the patient in prone position shows a 3-mm left lower lobe nodule (arrow) with the guide needle in the posterior chest wall (black arrowheads). **B**, Repeat scan following deployment of hook wire shows the wire with its tip (arrowhead) deep to the nodule (arrow). The lesion was successfully identified and resected intraoperatively.

nodule is attempted before the localizing procedure so that a VATS planned for diagnosis can be canceled if the TNB recovers a specimen with positive cytologic results or can proceed if the TNB is nondiagnostic. For patients in whom the VATS resection will be performed regardless of the preoperative diagnosis, only a localization procedure is performed. Ordinarily, conscious sedation is used as for TNB.

Although several differential techniques have been detailed for marking small peripheral nodules to aid VATS resection, most describe placing a needle through the nodule with a hook wire deployed through the needle and positioned with the hook deep to the nodule and left in position to aid resection in the operating room (Fig. 19-17).⁵⁶ A dressing is then applied to the skin and the patient transferred to the operating room for VATS.

Published success rates from multiple series detailing preoperative localization before successful VATS resection of peripheral nodules are generally around 90%.^{56,57} Even when a wire becomes displaced following deployment, the puncture site at the visceral pleura is usually visible intraoperatively and helps guide the surgeon to successful resection. Pneumothorax develops in approximately 10% of patients but rarely leads to wire displacement and is easily managed because the patients invariably proceed to thoracoscopy where a pneumothorax is induced as part of the operative procedure.

Key Points

- The most common indications for performing trans-thoracic needle biopsy include the definitive pathogenic diagnosis of a solitary pulmonary nodule, mediastinal mass, enlarged lymph node, chest wall mass, or pleural mass or thickening.
- Early-stage parapneumonic effusions, particularly those that are free flowing or unilocular, are amenable to successful image-guided catheter drainage using computed tomographic or ultrasonographic guidance, often with use of intrapleural fibrinolytic agents.

- Catheter drainage, with or without pleural sclerosis, provides effective treatment of symptomatic, recurrent malignant pleural effusions.
- Small-bore catheter drainage is a particularly effective treatment for iatrogenic pneumothorax, with success rates exceeding 85%.
- When indicated, catheter drainage for lung abscesses should be performed under computed tomographic guidance, placing the catheter in that part of the abscess closest to the pleural surface, ideally avoiding traversal of normal lung.
- Image-guided radiofrequency ablation of lung tumors is most effective for lesions less than 3 cm in diameter, with higher recurrence rates and lower overall survival for patients with lesions exceeding 3 cm.
- Needle-wire localization of lung nodules before video-assisted thoracoscopic surgical resection is most useful for lesions 1 cm or smaller and more than 1 cm from the pleural surface.

Complete reference list available at ExpertConsult.

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eFIGURE IMAGE GALLERY

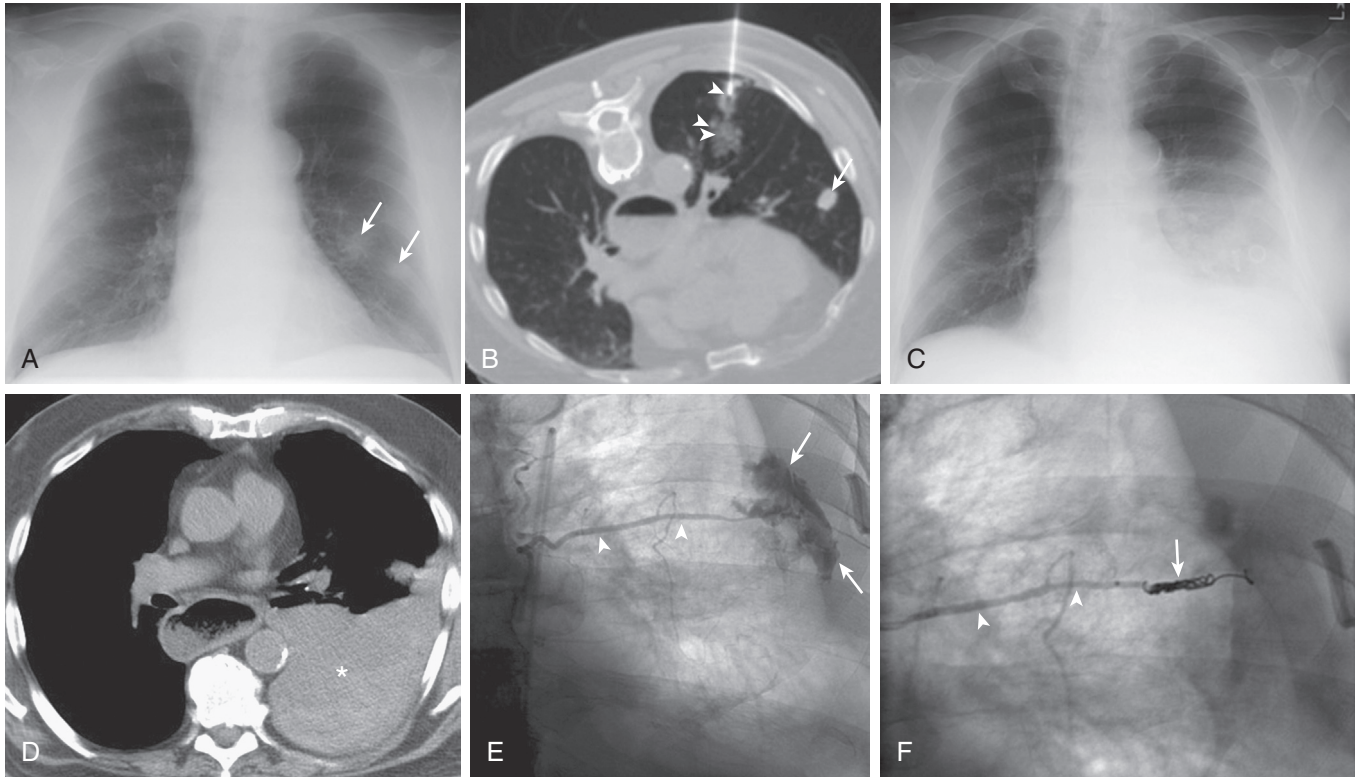
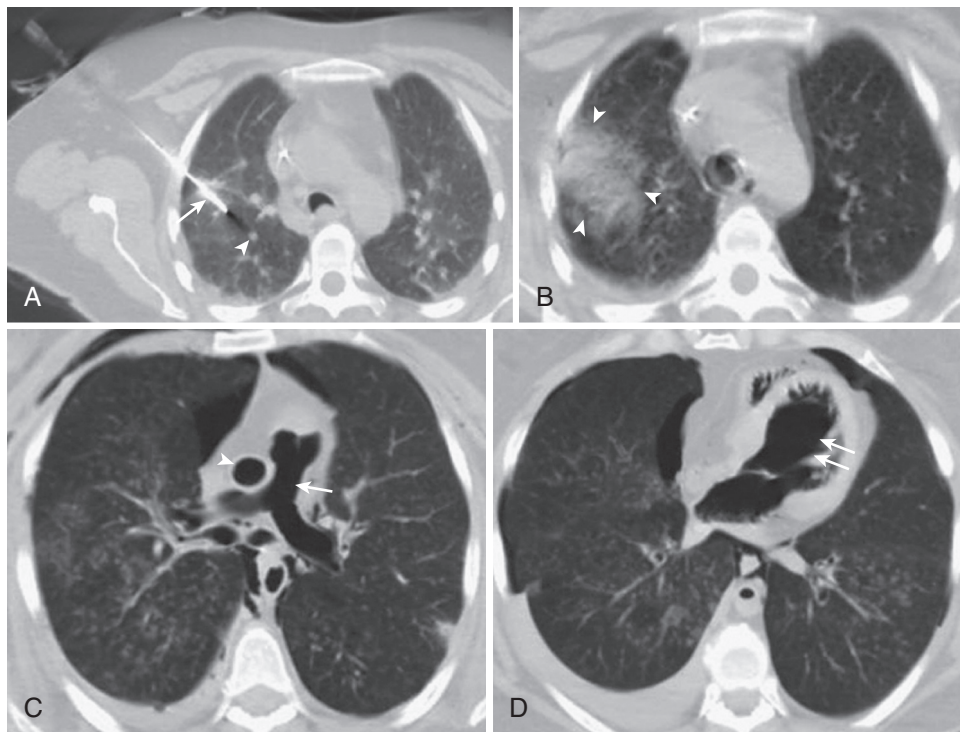
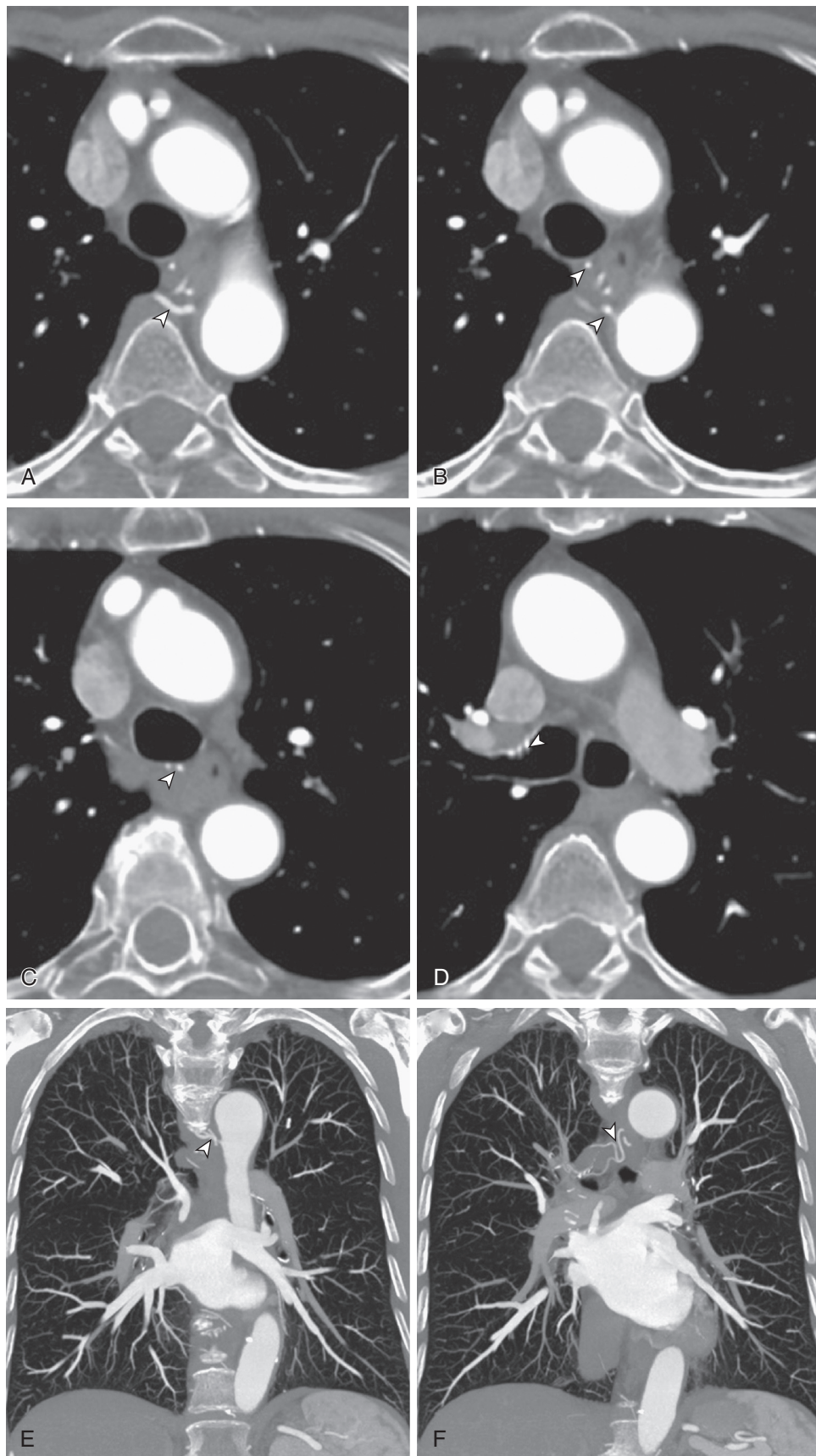


Figure 19-1 Transthoracic needle biopsy complication: intercostal artery laceration resulting in hemothorax. Frontal chest radiograph (A) shows two nodular opacities (arrows) projected over the left lung base. Axial prone chest CT during percutaneous needle biopsy (B) shows the needle tip within a left lower lobe nodule (single arrowhead). The other nodule seen at chest radiography (also in A) is visible in the lingula (arrow). Hemorrhage is seen (arrowheads) deep to the lesion undergoing biopsy. Note that the point of needle entry into the thorax is inferior to the rib. Frontal chest radiograph performed several hours after the biopsy was completed (C), when the patient began to complain of chest pain and shortness of breath, shows extensive new left base opacity consistent with a combination of pleural effusion and adjacent consolidation. Axial unenhanced chest CT performed to assess the new chest radiographic findings (D) shows high-attenuation material in the left posterior thorax (asterisk), consistent with hemothorax. These findings suggested the possibility of intercostal artery laceration. Selective intercostal artery angiogram (E) shows the intercostal artery (arrowheads) that was injured and documents the presence of active extravasation (arrows) from this vessel. A pigtail catheter is visible at the far image right, and the catheter in the aorta is visible at the far image left, projected over the left paraspinal region. Note the relationship of the intercostal artery on this image—midway between the posterior thoracic ribs. Selective intercostal artery angiogram (F) following intercostal artery coil embolization (arrow) shows cessation of active extravasation from the injured vessel (arrowheads). (Courtesy Michael Gotway, MD.)



eFigure 19-2 Transthoracic needle biopsy complication: massive air embolism. **A**, Axial chest CT during percutaneous needle biopsy shows the biopsy needle tip (*arrow*) slightly short of the targeted small nodule (*arrowhead*). **B**, Axial chest CT performed following the development of severe cough shows rounded ground-glass opacity (*arrowheads*), representing pulmonary hemorrhage. Axial chest CT performed after cardiopulmonary collapse (**C** and **D**) shows extensive air embolism, with gas lucency now occupying the ascending aorta (*arrowhead*, **C**), main pulmonary artery (*arrow*, **C**), and left ventricle (*double arrows*, **D**). Numerous small centrilobular nodules bilaterally represent aspirated blood following pulmonary hemorrhage. The patient subsequently died. (Courtesy Michael Gotway, MD.)



eFigure 19-3 Hypertrophied bronchial arteries. Axial (**A-D**) and coronal maximum intensity projected (**E** and **F**) enhanced chest CT images show enlarged intercostobronchial trunk (*arrowheads*). The origin of the intercostobronchial trunk from the aorta is visible in **A** and **E**. Note the close association of the bronchial artery branches with the airways (*arrowheads*; **B-D**). (Courtesy Michael Gotway, MD.)

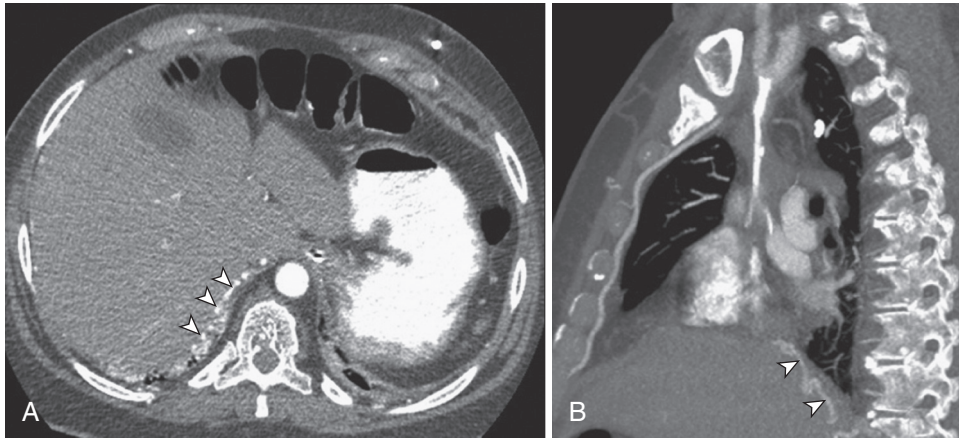


Figure 19-4 Transpleural systemic-to-pulmonary collateral vessels. Axial (**A**) and sagittal maximum intensity projected (**B**) contrast-enhanced chest CT images from a patient with chronic right pleural inflammation show prominent transpleural collateral vessels (*arrowheads*). (Courtesy Michael Gotway, MD.)

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INTRODUCTION**BASICS OF ULTRASONOGRAPHY**

Ultrasound Physics
 Ultrasonographic Modes
 Transducers

Doppler Ultrasonography

ULTRASONOGRAPHIC IMAGE ACQUISITION

Positioning of Patients and Probe
 Scan/Probe Orientation

Probe Handling

Image Acquisition

Image Interpretation

LUNG ULTRASONOGRAPHY

Normal Lungs

Pneumothorax

Lung Consolidation/Atelectasis

Alveolar Interstitial Pattern

Other Diagnoses

Algorithmic Evaluation of Acute
 Dyspnea

PLEURAL ULTRASONOGRAPHY

Pleural Effusions

Solid Pleural Lesions

Thoracic Procedure Guidance

DOCUMENTATION**TRAINING****ADVANTAGES AND DISADVANTAGES****INTRODUCTION**

Thoracic application of ultrasonography can be broadly divided into lung and pleural imaging. Additional applications designed for the evaluation of patients with dyspnea include vascular scanning for the diagnosis of lower limb deep venous thrombosis and basic ultrasonography of the heart. Furthermore, ultrasonography provides visual guidance for interventions in the pleural space. Instead of being considered as an optional thoracic imaging modality, bedside ultrasonography is increasingly seen as an extension of physical examination in the clinical evaluation and management of patients.¹

Ultrasonography continues to revolutionize pulmonary medicine by extending bedside diagnostic capabilities. Concerns remain regarding the medicolegal implications of errors in image interpretation. However, the utility of ultrasonography is gradually making the converse true as well: it is increasingly inexcusable not to use ultrasonography.^{2,3} Therefore it appears inevitable that ultrasonography will become established in the standard curriculum of pulmonary training.

BASICS OF ULTRASONOGRAPHY**ULTRASOUND PHYSICS**

Ultrasound is nonaudible sound energy used for medical applications in a frequency range of 2 to 20 MHz, frequencies that have been found to provide the best combination of penetration and resolution in the body. These frequencies are more than 1000 times greater than the audible range of sound, which ranges up to only 20 kHz. As ultrasound waves travel through tissue, they undergo attenuation and are also deflected by scattering, refraction, and reflection; it is the reflection of the waves that forms the basis of the ultrasonographic images. Reflection depends on the difference in sound transmission characteristics of the tissue, or the impedance, which is a measure of the resistance to propagation of sound waves from one medium to another.

At the boundary between two tissue structures with different impedance (i.e., an impedance mismatch), an ultrasound pulse is partially reflected. The greater the difference in acoustic impedance, the greater the strength of the reflected ultrasound signal will be. The difference in impedance between air and tissue is greatest, and thus almost all energy is reflected back; a coupling gel is necessary to remove all air from between the transducer and the skin to allow ultrasound energy to enter the body. The more minor differences in impedance between different body tissues allow partial reflection of waves that impart information about the location and characteristics of the tissues. Signal processing of the reflected energy into a gray-scale image on a screen forms the basis of ultrasonographic technology. (Table 20-1 provides a glossary of ultrasonographic terminology.)

The ultrasound pulse is generated by the piezoelectric crystals within the transducer probe. When an alternating current is applied, these crystals vibrate to convert electrical energy into mechanical energy and produce an emitting pulse. After the pulse is transmitted, the system awaits the return of reflected signals, which are received by the same piezoelectric crystals in the transducer. Returning ultrasound energy provides two types of information: the amplitude of the signal, which indicates how much energy is reflected, and the timing of the returning signal, which is related to the distance of the target from the emitting probe.

ULTRASONOGRAPHIC MODES

The processing of the reflected signals determines the type of image seen. In the A-mode (or *amplitude* mode), the received amplitude of energy from the transducer is displayed as peaks or waves shown at the distance determined by the depth of the image. This mode is not used currently in thoracic ultrasonography. With the B-mode (or *brightness* mode), the amplitude of energy is instead displayed as spots of different brightness, so that a series of B-mode images can be used to produce a conventional two-dimensional ultrasonographic image. In the M-mode (or *motion* mode), the image of a particular object is traced by capturing a

Table 20-1 Glossary of Ultrasonographic Terminology

Acoustic enhancement	An artifact showing an increase in echogenicity in a region distal to a fluid collection.
Acoustic impedance	Defined as the ratio of sound pressure to flow. A measure of the “resistance” of the medium to the transmission of sound waves from one tissue to another. The difference in acoustic impedance (mismatch) between two tissues determines the reflection of waves at the interface.
Acoustic shadow	Anechoic area behind bony structures.
Acoustic window	Pathway of an ultrasound beam between the probe and the target.
Alveolar interstitial pattern (or syndrome)	Multiple B-lines that signify the presence of thickened interlobular septa. This sign is defined by at least three B-lines in any single intercostal space and in at least two scanning zones of the thorax.
Attenuation	The progressive reduction of amplitude and intensity of a transmitted signal as it moves through a medium.
Artifacts	Images created by physical effects on sound wave propagation not reflecting the presence of actual tissues.
Artifact lines	
Comet-tail artifacts	Vertical hyperechoic lines arising from the pleural line (include B- and Z-lines).
B-lines	Comet-tail artifacts that spread all the way to the edge of the screen without fading.
Z-lines	Comet-tail artifacts that fade quickly without reaching the edge of the screen.
Other Lines	
A-lines	Horizontal hyperechoic echoes of the pleural line.
Doppler	Technique for imaging moving particles by the detection of a change in the frequency of the reflected ultrasound energy.
Echogenicity	
Hyperechoic	An appearance that is brighter or more white than that of normal solid organ structures such as the liver or spleen, which are considered isoechoic.
Hypoechoic	An appearance that is darker or more black than that of normal solid organ structures.
Anechoic	An appearance that is black and without echoes.
Lung sliding	The “to-and-fro” twinkling movement of the lung during respiration as it slides past the chest wall at the pleural line.
Modes	The means by which reflected ultrasound energy is displayed on the screen. In each case, the time for the energy to be reflected from an object determines the depth of the resultant image on the screen.
A-mode	Amplitude mode—reflected energy is shown as peaks of different size; not currently used in thoracic ultrasonography.
B-mode	Brightness mode—reflected energy is displayed as areas of different brightness; used to generate the standard two-dimensional ultrasonographic image.
M-mode	Motion mode—reflected energy is shown as areas of brightness traced from left to right on screen with time on the x-axis, used as an adjunct to B-mode.
M-mode signs	
Sinusoid sign	A hyperechoic sinusoidal line deep to a pleural effusion that represents movement of the visceral pleura with respiration adjacent to a pleural effusion.
Seashore sign	A grainy “sandy” image with a few horizontal lines denoting the “sea” at the top, a sign that represents aerated lung.
Stratosphere sign	A series of prominent horizontal lines that represents a pneumothorax.
Lung point	A sudden transition from a seashore to a stratosphere sign, representing the fleeting appearance of aerated lung expanding in inspiration into a pneumothorax. A positive ultrasonographic sign for pneumothorax.
Phased array probes	Probes that can steer ultrasound beams electronically by pulsing of transducer elements in sequence (phases). This allows a highly focused ultrasound beam to scan like a searchlight through tissue before a composite B-mode image is assembled.
Pleural line	Horizontal hyperechoic line that corresponds to the interface between the lung and the chest wall.
Resolution	The ability to display two tissue interfaces that are close to each other as separate images by ultrasonography.
Time-variable gain	An amplification of reflected ultrasound energy proportional to the timing of the returning signals to enable deeper objects to be as bright as those closer.

B-mode image as it sweeps across the screen against a time axis. This provides a single image in which relative positions of images are shown against time on the x-axis. The B-mode is the standard mode for all studies, and the M-mode is usually used as an adjunct, especially when B-mode findings are equivocal.

TRANSDUCERS

Thoracic ultrasonography typically uses the 3.5- to 5-MHz frequency range, which provides the optimal compromise between spatial resolution and depth of penetration for thoracic indications. Higher frequencies improve resolution but limit the depth of imaging; lower frequencies visualize with less resolution but to a greater depth. Thoracic ultrasonography generally uses curvilinear, or microconvex,

probes, which employ a curved surface to create a scanned field that is wider than the footprint of the probe, producing a sector or fan-shaped image; small footprints can also be achieved with phased array probes with electronic steering. Small footprints enable better access through the narrow acoustic windows available between ribs through which the beam can access deeper tissues. Compared to linear probes, curvilinear transducer probes have reduced lateral resolution; however, the resolution is acceptable for discriminating the relative sizes of structures imaged in the chest.

DOPPLER ULTRASONOGRAPHY

Doppler imaging is used to detect motion. Doppler imaging is based on the principle that the frequency of sound increases as the source of sound moves toward an observer

and decreases as the source of sound moves away. In pulsed wave Doppler, a pulse is transmitted and the change in frequency of the returning echo is measured at a certain time. Traditionally, red denotes objects moving toward the probe and blue on the screen denotes objects moving away from the probe. Optimal imaging for color Doppler is obtained when the transducer is directed *parallel* to the flow of the target; in contrast, for B-mode and M-mode ultrasonography, optimal imaging is produced when the transducer is directed *perpendicular* to the target.

ULTRASONOGRAPHIC IMAGE ACQUISITION

POSITIONING OF PATIENTS AND PROBE

In a free pleural space without septations, effusions will collect in the dependent parts of the thorax, whereas free air will collect in superior, nondependent locations. Therefore the positions of the patient and ultrasonographic probe are crucially important to evaluating these indications. In most thoracic evaluations the patient is examined sitting upright. Patients who are ill may be examined in the supine or lateral decubitus position, but this must be taken into consideration when images are interpreted. By abducting the arm, the intercostal space distance can be increased to provide a larger acoustic window. For a systematic evaluation, the hemithorax should be examined in each of the four zones demarcated by the parasternal, anterior axillary, and posterior axillary line^{4,5} (Fig. 20-1). The patient is then asked to sit upright and is scanned along the posterior paravertebral line. Every scan must visualize the diaphragm inferiorly. For better access to the posterior thorax, supine patients who cannot sit up can be moved to the lateral edge of the bed.

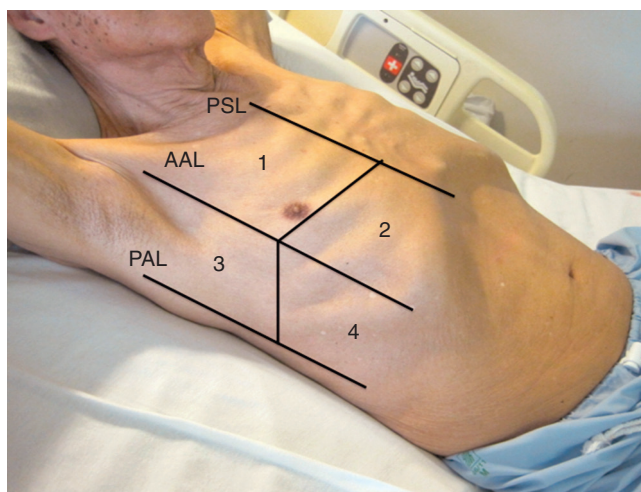


Figure 20-1 Four zones of chest ultrasonography. Systematic approach to ultrasonography of the chest begins by evaluating the hemithorax in each of the four zones demarcated by the parasternal (PSL), anterior axillary (AAL), and posterior axillary (PAL) lines.² The operator should obtain at least one representative intercostal scan from each region. The patient is then asked to sit upright and is scanned along the posterior paravertebral line (not shown).

SCAN/PROBE ORIENTATION

Longitudinal scans through the intercostal spaces (i.e., parallel to the long axis of the body) are preferred to transverse scanning both because of convention and because a longitudinal image will include the diaphragm for ease of reference. To maintain orientation of the probe and the resulting image, the transducer probe has a ridge or groove. With the groove oriented toward the head of the patient, the resultant image will show the cranial direction to the left of the screen. Superficial structures will be at the upper part of the screen and deep structures at the bottom of the screen (Fig. 20-2).

PROBE HANDLING

The probe is held in the dominant hand as one would hold a pen, with the forefinger on the orientation groove. The examiner's hand rests against the patient's skin as a support to stabilize the transducer. The probe is moved from intercostal space to intercostal space and moved transversely within intercostal spaces. For this movement, called "transducer movement," the probe is held perpendicular to the skin. For two other movements, the probe is tilted: "transducer tilt" describes the rocking movement of the probe at any particular position to obtain images along the same tomographic plane and "transducer angulation" to obtain images in adjacent planes. Tilt and angulation are fine movements, and too much of either can result in loss of contact with the skin, causing a poor image. Because air forms an almost impermeable barrier to ultrasound, air trapping is minimized by using a water-based coupling gel and by holding the probe firmly against the skin. The probe must be kept still during image acquisition to prevent confusion between the movement of the probe and dynamic signs within the thorax.

IMAGE ACQUISITION

Two parameters need to be adjusted for optimal acquisition of the images: depth and gain. The depth of the field is set according to the needs of the ultrasonographic

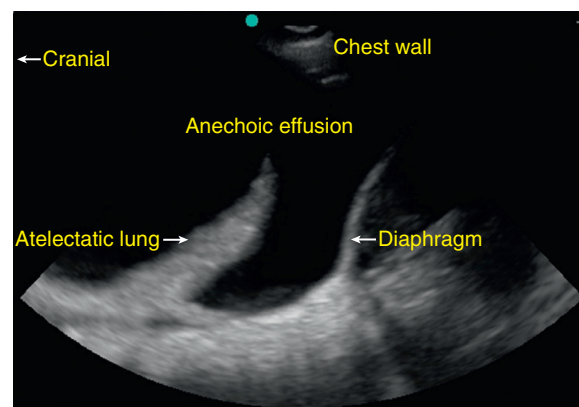


Figure 20-2 Pleural effusion. In this B-mode image, an anechoic pleural effusion is bordered by the hyperechoic diaphragm and an isoechoic atelectatic lung. The green dot at the top of the screen indicates that the cranial orientation is to the left of the screen.

examination: a 10-cm depth will usually suffice for most thoracic investigations. Less depth magnifies the image and allows clearer visualization of the near field, as, for example, for evaluating the pleural surface for lung sliding. Deeper penetration may sometimes be needed to define boundaries of the image of interest. The gain is set to amplify signals relative to background noise. Increasing the gain makes an image whiter, whereas decreasing the gain makes the image blacker. Time-variable gain enables the operator to amplify ultrasound signals proportional to the depth to make deeper structures appear as bright as more superficial structures. Because solid organs such as the normal liver are considered to be of intermediate density (isoechoic), gain can be adjusted with reference to the liver image to make it gray on the screen; other tissues can then be evaluated in comparison to this standard gray image. Although noise filters can improve the quality of imaging solid and liquid structures, the use of such filters can also obliterate the signal artifacts that are crucial to diagnostic analysis of aerated lung.

IMAGE INTERPRETATION

Two types of images are visualized by ultrasonography, either anatomic structures or artifacts.⁶ Anatomic structures are identified based on their location and echogenicity. Echogenicity of body structures can be referenced to solid organs such as the liver, which are made to appear gray or isoechoic on the screen. Uncomplicated fluid collections appear darker than these solid organs and are termed “hypoechoic”; if they appear black, they are termed “anechoic.” Air appears white and is hyperechoic. The homogeneity or heterogeneity of echoes also contributes to the recognition of different tissues.

Artifacts are images that do not correspond to specific anatomic structures but provide useful information if properly recognized. Examples of artifacts are acoustic shadows, acoustic enhancement, and reverberation echoes (see [Table 20-1](#)). Unlike anatomic structures, artifacts tend to move with the movement of the probe and converge toward the near field at the top of the screen. *Acoustic shadows* are anechoic regions that lie behind bony structures such as ribs. Because acoustic shadows provide no ultrasound information, the transducer probe should have an appropriately small footprint to transmit ultrasound pulses between the bony structures and thus avoid them. *Acoustic enhancement* is a hyperechoic region (lighter than liver) located distal to a fluid collection; the enhanced region distal to the fluid should not be mistaken for another tissue structure. *Reverberation echoes* are alternating dark and white lines produced when ultrasound beams reflect back and forth between two surfaces, often at an air–soft tissue interface. These echoes produce multiple-copy images seen at different depths depending on the number of times the beam was reflected ([Fig. 20-3](#)).

LUNG ULTRASONOGRAPHY

Competence in lung ultrasonography involves knowledge of terminology of ultrasound signatures in the thorax, as well as identification of consolidated lung and air artifacts.⁷

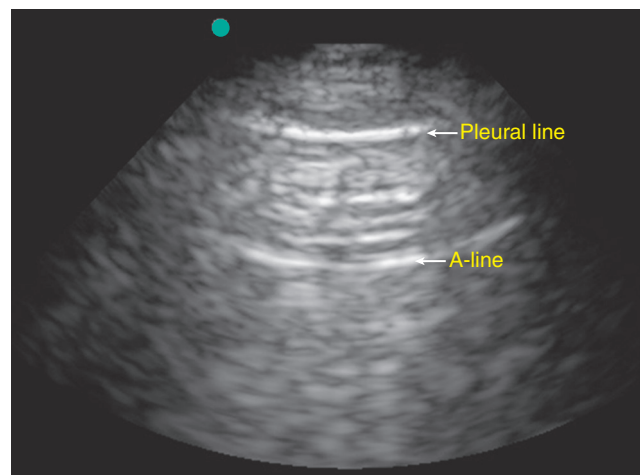


Figure 20-3 Normal lung. In this B-mode image of normal lung, the pleural line and A-lines are indicated. A-lines are echoes of the pleural line and indicate the presence of an air–pleural interface, whether the air is in aerated lung or free in the pleural space (e.g., pneumothorax).

([Table 20-2](#) lists lung ultrasonographic signs, and [Table 20-3](#) compares lung and pleural ultrasonographic competencies.) Key diagnoses that can be made include pneumothorax, pulmonary consolidation, and pulmonary edema.

NORMAL LUNGS

“Lung sliding” is the key sign used to identify normal lungs.⁶ To identify lung sliding, one first identifies the “pleural line” as a horizontal hyperechoic line located approximately 0.5 cm below the skin surface corresponding to the interface between the lung and the chest wall.⁸ The pleural line is framed by anechoic shadows caused by the ribs. A-lines are deeper horizontal lines that are reverberation echo artifacts of the pleural line⁸ (see [Fig. 20-3](#)). Once these lines are identified, lung sliding is seen as the to-and-fro twinkling and movement of the lung adjacent to the pleural line in rhythm with inspiration and expiration ([Video 20-1](#)). The image above the pleural line on the screen is motionless. Therefore lung sliding identifies visceral pleura sliding over parietal pleura. An M-mode image of this view will show up as a grainy pattern that recedes distally and is termed the “seashore sign”⁹ ([Fig. 20-4A](#)).

Lung sliding is an important sign for identifying normal lung, but it is dependent on technical issues and interpretation. For example, the sign may not be detected with low-frequency probes below 2.5 MHz or if the depth is set too deep.⁹ In addition, the amplitude of lung sliding will decrease at the apex of the lung, where movement of the lung is less. Lung sliding can be mimicked by accessory respiratory muscle contractions, although, unlike lung sliding, muscle movement will appear superficial to the pleural line. Lung sliding can also be absent in pathologic conditions in which lung motion is impaired, such as pleurisy, pleurodesis, pneumothorax, subcutaneous emphysema, apnea, jet ventilation, extreme bronchospasm, extensive pneumonia, and the *acute respiratory distress syndrome* (ARDS).⁸ Thus the absence of lung sliding may not be useful, whereas its presence is effective in ruling out many of the abnormalities of the lung.

Table 20-2 Ultrasonographic Signs of Normal Lungs and Pulmonary Pathologic Conditions

Condition	Ultrasonographic Findings
Normal lungs	Lung sliding A-lines 1-2 B-lines Seashore sign on M-mode
Pneumothorax	Absence of lung sliding sign A-lines Absence of B-lines Stratosphere sign and lung point on M-mode
Lung consolidation/atelectasis “Alveolar pattern”	Isoechoic hepatization of lung with white linear or branched air bronchograms Vascularity within consolidation preserved on color Doppler Atelectasis may present with elevated hemidiaphragm and black (fluid-filled) bronchograms
Pulmonary edema	Diffuse and multiple B-lines with homogeneous distribution Lung sliding present Normal pleural line Bilateral anechoic pleural effusions Evidence of left ventricular dysfunction on echocardiography
ARDS/pulmonary fibrosis “Alveolar interstitial pattern”	Diffuse and multiple B-lines with heterogeneous distribution Reduced or absent lung sliding Abnormal pleural line (irregular thickening or fragmentation)
Diaphragm paresis or paralysis	Diaphragm moving < 5 mm or paradoxically in inspiration Thinning of the diaphragm or loss of normal thickening with inspiration Loss of lung sliding sign
Pulmonary embolism	Pulmonary infarcts appearing as peripheral wedge-shaped consolidation with diminished vascularity on color Doppler Ipsilateral hyperechoic (hemorrhagic) effusion Supportive signs from ultrasonography of the heart (acute cor pulmonale) and compression vascular sonography of lower limbs (proximal deep venous thrombosis)

ARDS, acute respiratory distress syndrome.

Table 20-3 Required Competencies for Lung and Pleural Ultrasonography⁴⁸

Lung Ultrasonography	Pleural Ultrasonography
1. Knowledge of ultrasonographic signs: lung sliding, A-lines, B-lines, lung point 2. Identification of normal lung 3. Identification of signs that rule out and rule in pneumothorax 4. Identification of consolidated lung 5. Identification of alveolar interstitial pattern 6. Recognition that the absence of lung sliding and B-lines is a sensitive, but not specific, sign for pneumothorax	1. Identification of a pleural effusion as defined by typical anatomic boundaries 2. Identification of dynamic signs of pleural effusions 3. Identification of ascites and adjacent organs such as the liver, spleen, kidney, and heart 4. Characterization of pleural fluid based on echogenicity, homogeneity, and presence of debris/septations 5. Semiquantitative assessment of volume of pleural effusion 6. Identification of solid pleural lesions and pleural thickening 7. Recognition of limitations of ultrasonography in identifying pleural fluid

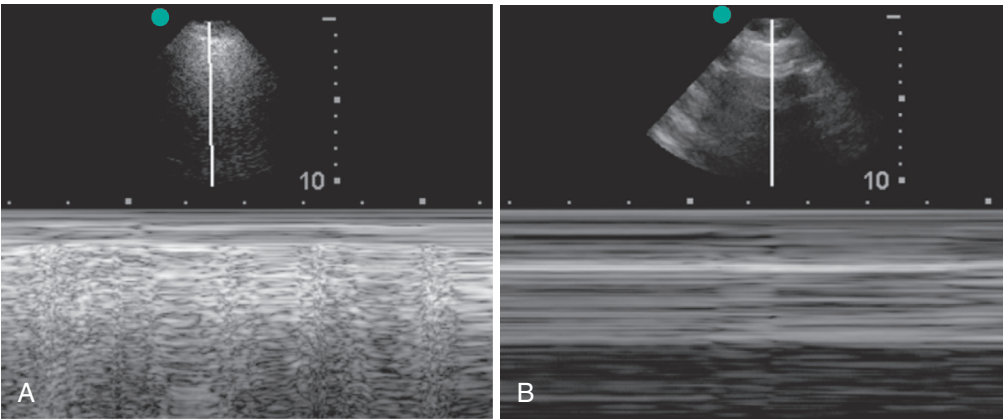


Figure 20-4 Normal lung compared to a pneumothorax. In these M-mode images, a normal lung is seen showing the seashore sign (A) next to a pneumothorax showing the stratosphere sign (B). The seashore sign is recognized by the grainy texture and is distinguished from the stratosphere sign, in which the grainy quality is absent and only the horizontal lines are seen. Top, The B-mode images from which the M-mode images were generated.

PNEUMOTHORAX

Ultrasonography is more accurate than supine anteroposterior chest radiographs in the diagnosis of pneumothorax.¹⁰ Pneumothorax itself has few positive findings; it is generally identified by the absence of the signs of normal aerated lung. As described earlier, aerated lung is noted by the presence of the lung sliding sign; the lung is also noted by artifacts called “comet tails,” including B-lines and Z-lines, which are vertical hyperechoic lines that arise from the pleural line and move in synchrony with lung sliding.⁹ B-lines spread from the pleural line all the way to the edge of the screen without fading.⁹ These lines are the most important of the comet tails, and their presence or absence can help guide the diagnostic value of ultrasonography (Video 20-2). Z-lines are similar but, unlike B-lines, fade quickly and do not reach the periphery of the screen.⁹

In any ultrasonographic examination for pneumothorax, the nondependent part of the hemithorax needs to be scanned. In a pneumothorax, A-lines representing reverberation echoes of the pleural line will still be seen, showing that an air-tissue interface is present, but there will be no movement of the lung sliding at the pleural line and no evidence of B-lines^{11,12} (Video 20-3). In the appropriate clinical context, the absence of lung sliding and B-lines indicates the presence of pneumothorax with a reported 100% sensitivity and 96.5% specificity.¹³ On the other hand, the presence of the lung sliding sign basically excludes a pneumothorax, with a reported 100% negative predictive value.¹¹ In a pneumothorax, multiple accentuated A-lines may be seen, and this can be captured on M-mode as a series of stratosphere-like horizontal lines (i.e., the stratosphere sign)⁹ (Fig. 20-4B). The horizontal lines seen in the stratosphere sign, which are characteristic of free air, can be contrasted with the grainy pattern prominent in the seashore sign of normal aerated lung (see Fig. 20-4A). A pneumothorax can be grossly quantified as large if the loss of both lung sliding and comet tails extends to dependent parts of the thorax. The sudden and fleeting appearance of lung sliding and B-lines in an area where they were previously absent may indicate aerated lung expanding intermittently into a moderate-sized pneumothorax. This fleeting appearance if captured on M-mode is termed the “lung point” and has been reported to have 66% sensitivity and 100% specificity for the diagnosis of a pneumothorax.¹⁴ These ultrasonographic signs when used in combination may diagnose occult pneumothoraces not detected on supine chest radiographs¹⁵ and are useful in the evaluation of patients after procedures such as central venous catheter placement, transbronchial lung biopsy, and chest tube clamping. The presence of a pneumothorax must be strongly suspected if B-lines that were present before the procedure are not detected after the procedure.

Errors that can lead to a failure to diagnose pneumothorax include failure to scan in the nondependent parts of the thorax, failing to scan longitudinally, excessive use of noise filters, and an unsteady scanning hand that may give the false impression of lung sliding. A false diagnosis of pneumothorax may arise in patients with *chronic obstructive pulmonary disease* (COPD), lung bullae, and adhesions, which may mimic pneumothorax on ultrasonography.⁴ In patients

with COPD the specificity of the diagnosis of pneumothorax is reduced to 71% even among experienced operators, indicating that additional imaging studies are required to confirm a pneumothorax in such patients.¹⁶

LUNG CONSOLIDATION/ATELECTASIS

Alveolar consolidation can be identified on ultrasonography if the area of consolidation extends to the visceral pleura; if not, the intervening aerated lung will generate artifacts that make the diagnosis difficult. In alveolar consolidation, lung sliding will be abolished and a tissue pattern similar to the liver will develop because of the consolidation and “hepatization” of the lung. This sign, which has been termed the “alveolar syndrome” in some studies¹⁷ and is here referred to as the “alveolar pattern,” can be due to a variety of causes, including pneumonia, atelectasis, contusion, malignancy, and infarction. Discrimination between these diagnoses may be attempted with further ultrasonographic analysis, including assessment of the deep margins of consolidation, identifying air or fluid bronchograms, and evaluating the vascular pattern within the consolidation using color Doppler.⁴

In patients who have pneumonia, the superficial boundary of consolidated lung is usually regular and conforms to the visceral pleura, whereas the deep border is irregular and faded and varies with respiration.^{17,18} Comet-tail artifacts may also be seen at this far-field border.¹⁸ Air bronchograms may be seen as hyperechoic (white) branched or linear shadows that may vary with respiration^{19,19a} (Fig. 20-5). Air trapped in the distal airways shows up as punctate white spots.²⁰ On color Doppler, branching pulmonary blood vessels may be visualized within the area of consolidation.²¹ These signs together with the absence of a sinusoidal pattern on M-mode that would indicate lung motion give ultrasonography a diagnostic sensitivity of 90% and specificity of 98% in detecting consolidation when compared to *computed tomography* (CT) scans.²² A false-positive diagnosis of consolidation may result when complex echogenic pleural effusions or intrathoracic fat are mistaken for consolidation. The size of consolidation is typically smaller on ultrasonographic images than on chest radiographs because the peripheries of a pneumonic area are usually partially air filled.²³

Atelectasis is imaged by ultrasonographic scanning in a way similar to that for consolidation. In addition, intercostal spaces may be narrowed and the hemidiaphragm elevated. If air bronchograms are seen, they do not change size with respiration. If the bronchi are filled with fluid in a postobstructive atelectasis, then fluid bronchograms may be seen as anechoic linear shadows within the area of consolidation.²⁴ The features of peripheral lung malignancies with chest wall invasion and infarctions associated with pulmonary embolism are described in subsequent sections.

ALVEOLAR INTERSTITIAL PATTERN

The alveolar interstitial pattern (or syndrome) is a term used to describe multiple B-lines in multiple scanning zones of the thorax, a pattern that can be seen in various pathologic conditions such as pulmonary edema, ARDS,

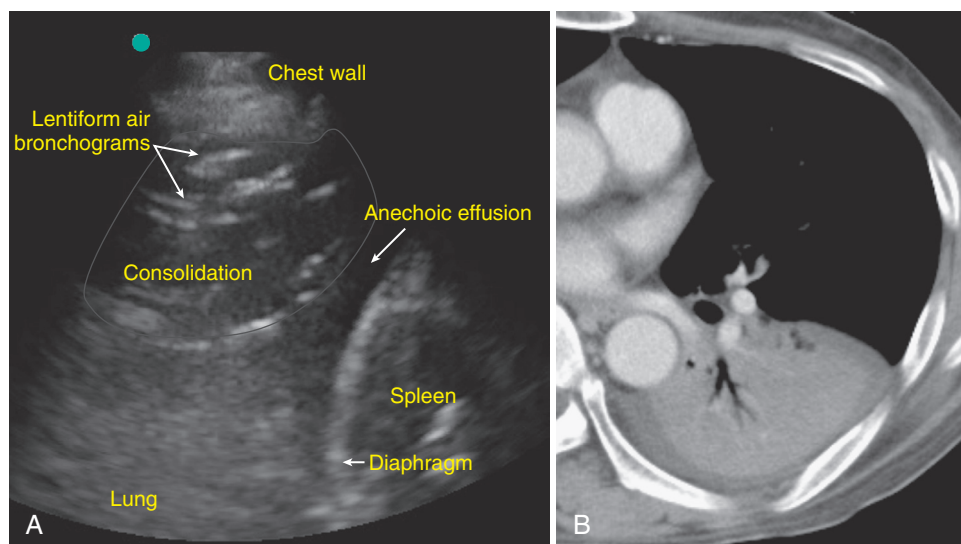


Figure 20-5 Consolidated lung. In this B-mode image (A), subpleural consolidation with hyperechoic branched shadows (arrows) are shown that correspond to the air bronchograms seen on the adjacent CT scan of the same patient (B).

and pulmonary fibrosis. Whereas single B-lines are found in normal lungs as described, multiple B-lines have been shown to correlate to thickened interlobular septa.²⁵ To identify an alveolar interstitial pattern, one must see at least three B-lines in any single intercostal space and in at least two scanning zones of the thorax (see Fig. 20-1).^{4,26} Finding bilateral and diffuse multiple B-lines has a diagnostic sensitivity and specificity of 93% when compared to chest radiographs in the diagnosis of pulmonary edema.^{27,27a} The diagnosis can be confirmed by the disappearance of this finding with appropriate treatment of heart failure. This ultrasonographic pattern has been shown to correlate with N-terminal pro-brain natriuretic peptide levels.²⁸ The total number of B-lines in the anterior and lateral chest of supine patients has also been shown to correlate with both oxygenation levels and pulmonary artery wedge pressure.^{29,30}

The presence of bilateral anechoic pleural effusions can contribute to the diagnosis of pulmonary edema. Echocardiography at the same setting can assess left ventricular size and function to confirm the diagnosis and cause. A dilated left ventricle suggestive of volume overload can be identified on the parasternal long axis view at the left sternal border in the third to fifth intercostal space with the orientation groove pointing at the right shoulder. If there is a 5-mm or lower approximation of the anterior mitral valve toward the interventricular septum, the ejection fraction is likely to be normal. Rotation of the probe 90 degrees to point toward the left shoulder should produce the parasternal short axis view at the papillary muscle midsection. This view helps identify heterogeneous contractility suggestive of myocardial ischemia/infarction. Both long- and short-axis views also help the physician look at global left ventricular function. These are examples of qualitative assessments that can be made by physicians who have received the appropriate training and can provide accurate point-of-care diagnoses.³¹

Pulmonary fibrosis and ARDS can be mistaken for pulmonary edema because ultrasonography cannot distinguish between interlobular thickening due to edema and interstitial thickening due to inflammation or infiltration.²⁷ However, in ARDS and pulmonary fibrosis, lung sliding is

reduced or absent, the B-line pattern is inhomogeneous, and pleural line abnormalities such as irregular thickening and fragmentation may be detected.^{4,32} In addition, ARDS presents with patchy anterior consolidation and spared areas representing regions of normal lung.³² If a unilateral or focal alveolar interstitial pattern is found, the differential diagnoses include pneumonia, pneumonitis, atelectasis, contusion, infarction, and malignancy.^{4,33}

OTHER DIAGNOSES

Diaphragmatic function can be assessed via ultrasonography. This can be especially useful in evaluating patients with difficulties in weaning from mechanical ventilation. For such studies, to ensure diaphragm recruitment and avoid false-negative study results, patients should be placed on a spontaneous breathing trial. With inspiration the normal diaphragm moves caudally 10 to 15 mm.¹⁸ In the setting of diaphragmatic dysfunction, the movement of the diaphragm on inspiration may be less than 5 mm, and signs of lung motion such as lung sliding may be lost.¹⁸ Paradoxical movement of the diaphragm moving cranially during inspiration may also be seen. The normal diaphragm should be more than 2 mm thick at the zone of apposition with the rib cage and should thicken by more than 20% with inspiration³⁴ (Video 20-4). Thinning of the diaphragm at rest or a reduced thickening with inspiration suggests paralysis.³⁵ Normal thickening may predict success of weaning from ventilation.^{35a}

Pulmonary embolism is suggested by peripheral consolidation representing pulmonary infarction and by the detection of a unilateral pleural effusion, which may be hyperechoic due to hemorrhage. Pulmonary infarcts typically appear as round or triangular pleural-based lesions³⁶ with evidence of reduced vascularity on color Doppler.²³ Thoracic ultrasonographic findings can be supplemented by compression vascular sonography of the lower limbs to identify deep venous thrombosis, which can be detected in over 50% of patients with symptomatic pulmonary embolism.^{37,37a,37b} Venous ultrasonography is performed using a 5- to 10-MHz linear probe, which has higher

resolution than a thoracic probe. The supine patient is positioned with the thigh externally rotated and the knee flexed at 45 degrees. Transverse scanning starts at the common femoral vein proximal to the junction of the great saphenous vein and moves distally at 2-cm intervals along the superficial femoral vein and then the popliteal vein until its trifurcation into calf veins. Chronic, organized thrombus is echogenic and is seen lying within the vein (Video 20-5). Acute thrombus is hypoechoic and requires a compression maneuver for identification. Using the adjacent artery as a reference, the operator applies compression to the tissues overlying the vascular structures. In the normal setting the vein can be completely compressed, with the anterior and posterior walls apposing and the lumen obliterated, whereas there is only minimal deformation of the adjacent artery (Video 20-6). In the presence of thrombus, the vein will not compress or will compress only partially (Video 20-7). Compression ultrasonography performed by intensivists has a diagnostic sensitivity and specificity of 86% and 96%, respectively.³⁸ If the compression ultrasonographic diagnosis remains uncertain, then Doppler evidence of absence of flow, especially during augmentation by calf compression, can be used.³⁹

Acute cor pulmonale caused by pulmonary embolism can be diagnosed by identifying right ventricle dilatation and pressure overload.⁴⁰ When ultrasonography is used to evaluate the heart, the operator must be trained in the recognition of ventricle size and function in different views. On the apical four-chamber view, in normal patients the left ventricle forms the apex of the heart and the right ventricle is about 60% the size of the left. Right ventricular dysfunction can be identified by a dilatation of the right ventricle relative to the left and by identifying a dyskinesia of the interventricular septum caused by pressure overload. On the parasternal short-axis view, the septum flattens out and the right ventricle loses its normal crescent shape, instead taking on a D-shaped configuration. McConnell's sign (i.e., regional right ventricular dysfunction with akinesia of the mid-free wall but normal wall motion at the apex) is very specific for acute pulmonary embolism but has limited sensitivity⁴¹ (see Video 57-1).

Chest wall invasion by lung cancer may be assessed more accurately by ultrasonography than by CT scans, with sensitivity and specificity of 89% and 95%, respectively.⁴² Chest wall invasion is diagnosed by finding tumor growth across the pleura, invasion of the ribs, and absence of lung sliding. A high-frequency vascular probe may be needed to identify tumor invasion.¹ Subpleural tumors typically have heterogeneous echogenicity and distorted vascularity as seen on color Doppler imaging.^{23,43}

Airway diseases are not generally evaluated using ultrasonography. Although ultrasonography is of little diagnostic value in airway diseases, bronchospasm can be suspected in a breathless patient based on prominent A-lines and preserved lung sliding.^{44,44a} Unilateral main-stem bronchus intubation results in cessation of ventilation to one lung and consequently causes lung sliding on that side to be abolished. However, the lung may still be aerated, causing A-lines and the lung pulse sign of transmitted cardiac contractions to be retained.⁴⁵

Lung abscesses present as hypoechoic fluid collections within an area of consolidation with well-defined walls.⁴⁶ The irregular borders of consolidation about the pleura at an acute angle, and, in the center of the abscess, swirling fluid may be seen. Air-filled cavities will have echogenic foci within the abscess.¹ It may be difficult to distinguish a lung abscess from a pleural empyema, and a distinction between the two diagnoses can be important because of the implications for pleural drainage. Identification of vessels in the pericavitary consolidation using color Doppler has a specificity approaching 100% for peripheral lung abscesses. Conversely, the presence of septations and passive atelectasis are common findings in empyema.⁴⁷

ALGORITHMIC EVALUATION OF ACUTE DYSPNEA

Ultrasonography can be used in the evaluation of a patient with severe, new-onset dyspnea using an algorithmic approach called the *Bedside Lung Ultrasound in Emergency* protocol (i.e., the "BLUE" protocol) (Fig. 20-6). For this protocol the anterior chest is first scanned with the patient in

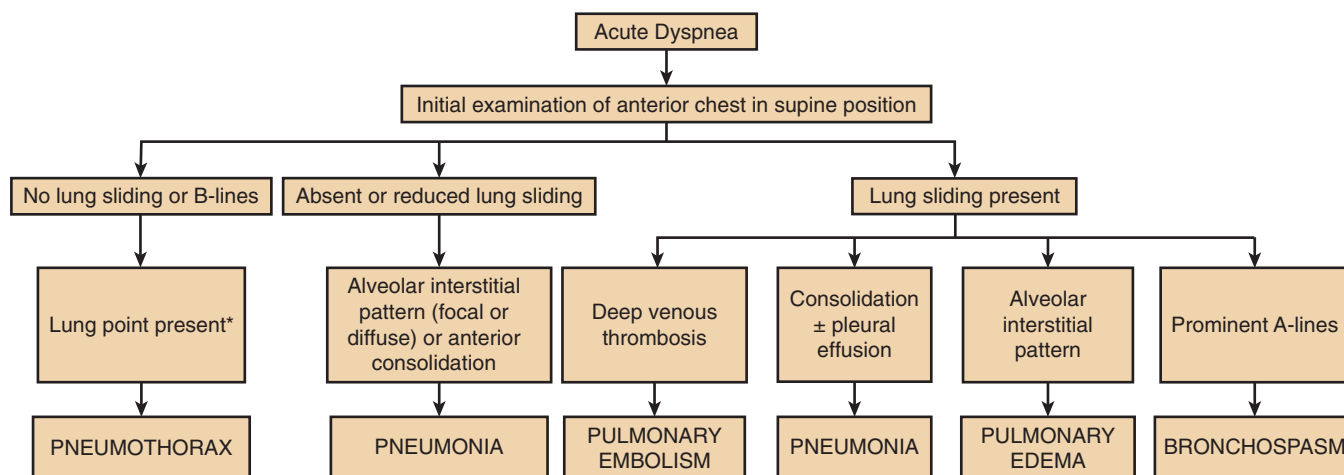


Figure 20-6 Algorithmic evaluation of acute onset, severe dyspnea showing possible diagnoses.⁴⁴ This stepwise approach has been termed the *Bedside Lung Ultrasound in Emergency* (BLUE) protocol. *If a lung point is not identified, other diagnostic approaches are advised to confirm or exclude pneumothorax.

the supine position.⁴⁴ Lung sliding is assessed, and then four patterns are sought: bilateral A-lines, bilateral alveolar interstitial pattern, and either unilateral alveolar interstitial pattern or consolidation. The diagnosis is then refined depending on the concomitant presence of pleural effusion, posterior consolidation, or deep venous thrombosis.⁴⁴ In patients presenting to the emergency department with acute dyspnea, there is a high degree of concordance between ultrasonography and chest radiographs for diagnoses such as pulmonary edema ($\kappa = 95.0\%$), pneumothorax ($\kappa = 85.5\%$), and consolidation ($\kappa = 70.0\%$).¹⁷ Goal-directed ultrasonography of the heart can supplement the evaluation by assessing cardiac causes of dyspnea. Right or left ventricular dysfunction as well as pericardial effusion can be excluded. Pericardial effusions are distinguished from pleural effusions on the parasternal long-axis view by location with respect to the aorta: pericardial effusions are situated anterior to the descending aorta (Video 20-8). Tamponade physiologic characteristics are identified by early diastolic collapse of the right ventricle, which is best seen on either the apical four-chamber or subcostal view. Certainly such diagnostic use of ultrasonography has great potential but also demands adequate training for proper interpretation.

PLEURAL ULTRASONOGRAPHY

Ultrasonography is extremely valuable for a variety of pleural indications (Table 20-4). Ultrasonography is more sensitive than chest radiography in diagnosing small pleural effusions and is especially effective in distinguishing effusions from lung atelectasis.⁷ Competence in pleural ultrasonography involves identification of a hypoechoic region surrounded by the appropriate anatomic boundaries, iden-

tification of the liver/spleen and other abdominal organs, recognition of dynamic features of pleural effusions, characterization of pleural fluid, semiquantitative assessment of effusion volume, and identification of pleural-based masses, as well as an understanding of the limitations of ultrasonographic scans of the pleura (see Table 20-3).⁷

PLEURAL EFFUSIONS

Pleural effusions are diagnosed either by using longitudinal scanning through the intercostal spaces or by using subcostal abdominal scanning to visualize the diaphragmatic pleura through the liver or spleen. Subcostal scans, which identify effusions in relation to the position of the diaphragm, spleen/liver, and atelectatic lung, are particularly useful when intrathoracic air (e.g., hydropneumothorax) prevents image acquisition via intercostal scans. Pleural effusions can be identified by using both static and dynamic signs.

Static signs for identifying pleural effusions are finding a hypoechoic region within the anatomic boundaries of the diaphragm caudally, the chest wall superficially, and the atelectatic lung at the bottom of the screen (see Fig. 20-2). Although the effusion is usually hypoechoic, echogenicity cannot be the sole criterion for identifying a pleural effusion. For example, whereas all transudative effusions and some exudative effusions are anechoic, anechoic regions can also be seen because of pleural thickening⁴⁸ or abdominal ascites. Alternatively, echogenic regions can be seen with complex pleural effusions such as hemothorax or empyema.

Dynamic signs used to identify pleural effusions include movement of the diaphragm adjacent to the effusion and of the lung within the effusion. The diaphragm is identified as a hyperechoic concave structure that descends with

Table 20-4 Ultrasonographic Signs of Pleural Pathologic Conditions

Pathologic Condition	Ultrasonographic Findings
Pleural effusion (free flowing)	Static signs show a usually anechoic collection that is bordered by the diaphragm, atelectatic lung, and the chest wall Dynamic signs include flapping of atelectatic lung in the effusion and diaphragm movement with respiration, allowing an effusion to be distinguished from ascites B-mode curtain sign showing intermittent appearance of lung expanding into the pleural effusion M-mode sinusoid sign showing visceral pleura motion adjacent to an effusion
Transudates	Anechoic collection
Exudates	Anechoic or echogenic collection If echogenic, can be homogeneous or heterogeneous
Complicated parapneumonic effusions/empyema	Heterogeneously echogenic collection Presence of septations Hematocrit sign
Malignant effusions	Heterogeneously echogenic collection Swirling debris Hematocrit sign Pleural thickening > 10 mm Diaphragmatic thickening > 7 mm Presence of pleural nodules
Mesothelioma	Hypoechoic and irregular thickening that covers large areas of pleura with indistinct borders
Pleuritis	Thick peel of tissue No mobile components (i.e., Doppler negative) Variable echogenicity Calcification seen as hyperechoic spots Visceral pleural inflammation associated with consolidation Any associated effusion tends to be multiloculated

inspiration and is bordered caudally by either the liver or the spleen, both isoechoic structures. The position of the diaphragm helps distinguish a pleural effusion from ascites in the hepatorenal recess, where the diaphragm and its movement will not be seen. Of note, caution must be used in interpreting subcostal images because the concave diaphragm has high reflective properties that can lead to acoustic enhancement artifacts that can be mistaken for consolidation.⁹ Another dynamic sign of pleural effusions that can help avoid these misdiagnoses includes the movement of the atelectatic lung seen as a “flapping” within the effusion (Video 20-9). In addition, sometimes on B-mode a “curtain” of aerated lung slides into and out of small effusions. If the diagnosis is equivocal on B-mode, additional information can be gained by using M-mode; in M-mode a pleural effusion can be identified by seeing the respiratory movement of the visceral pleura toward the chest wall as a sinusoidal pattern.⁹

Ultrasonographic characterization of pleural fluid is based on echogenicity and homogeneity. However, thoracentesis is still needed to distinguish transudates from exudates. In heterogeneous effusions the presence of internal echoes such as swirling debris or septations is highly predictive of either complicated parapneumonic effusions or malignancy^{49,50} (Videos 20-10 and 20-11). In immobile patients the cellular components may settle to create a bilayer with a more echogenic dependent component. This has been termed the “hematocrit sign” and can be seen in either hemothorax or empyema⁴⁸ (Video 20-12). During scanning, the pleura should also be carefully examined because pleural thickening of greater than 10 mm, pleural nodularity, and diaphragmatic thickening of greater than 7 mm have all been found to be highly suggestive of a malignant effusion⁵¹ (Video 20-13).

The use of ultrasonography to quantify the volume of pleural effusions has yet to be established in clinical practice. The size of the thoracic cavity, presence of loculations, position of the diaphragm, and degree of lung collapse all affect ultrasonographic measurements.⁵² Despite these limitations, in supine patients the distance of maximum separation of parietal and visceral pleura on ultrasonography has been shown to correlate better with the volume of thoracentesis drainage than measurements on lateral decubitus chest radiographs.^{52,53} For comparison of the size of the same effusion over time, the transducer and the patient must be in exactly the same position for each measurement.

SOLID PLEURAL LESIONS

Pleuritis is visualized as a thick and hypoechoic peel of tissue with no mobile components (i.e., Doppler negative).⁵⁴ Calcification within pleural fibrosis, indicating chronic inflammation such as previous tuberculosis, may be seen as hyperechoic spots but is usually challenging to detect because of adjacent aerated lung. Visceral pleural inflammation and thickening is associated with underlying consolidation.⁴⁸

Pleural carcinomatosis is visualized through the acoustic window provided by the adjacent effusion as either thickening or echogenic nodules of various shapes and sizes.⁵⁵ Malignant mesothelioma is seen as hypoechoic and irregular thickening that covers large areas of pleura with

indistinct borders. Nodules and chest wall invasion may also be detected in mesothelioma.⁴⁸ Benign pleural tumors such as chondromas and lipomas are both rare and more difficult to diagnose. They display varying ultrasound echogenicity, have distinct capsules, do not invade adjacent tissue, and have no associated pleural effusion.⁴⁸

THORACIC PROCEDURE GUIDANCE

Ultrasonographic guidance can be valuable in increasing the success and safety of thoracentesis. Ultrasonographically guided thoracentesis can obtain fluid in up to 88% of previously unsuccessful “blind” or nonguided cases.⁵⁶ In the majority of failed blind pleural taps, subsequent examination by ultrasonography has shown that the needle had been inserted subdiaphragmatically.^{56,57} By using ultrasonographic guidance, operators can avoid puncturing organs such as the lungs, liver, spleen, and heart. Ultrasonographic guidance can reduce the incidence of iatrogenic pneumothorax from 5% to 39% following blind thoracentesis to as low as 0% to 5.4%.⁵⁸⁻⁶³ With ultrasonographically guided thoracentesis, the rate of pneumothorax can be kept to as low as 1.3% even in patients on positive-pressure ventilation.⁶⁴

An ultrasonographically directed thoracentesis is performed by first identifying and marking the target site with the patient positioned comfortably. To reduce the risk for complications, the operator should position the transducer probe so that the thickest portion of the target fluid collection is in the center of the screen. A separation of 10 mm between the visceral and parietal pleura is usually deemed adequate to tap safely.⁶⁵ Areas with the curtain sign representing intermittently appearing lung or with incursion of the diaphragm during respiration are relatively contraindicated. All intervening structures along the trajectory of the needle must be identified. If free air is present in the thorax due to hydropneumothorax, visualization is lost; in that case, ultrasonographic guidance must be limited to identifying the position of the diaphragm.⁴⁸ The depth of needle insertion can be estimated on the ultrasonography screen, but, because the probe compresses near-field soft tissues, this distance can be misjudged; the problem in estimating distance is exacerbated in edematous or obese patients.

The timing of the procedure can be concurrent with the ultrasonography (i.e., real-time) or at a later time. In a real-time procedure, the needle is usually directed at a downward angle of 45 degrees to the long-axis of the probe over the rib; the operator attempts to keep the entire length of the needle in view along its trajectory. Real-time thoracentesis requires a sterile probe sheath and an assistant to hold the probe during needle insertion. This unnecessarily complicates the procedure without any evidence of improving either safety or success.⁴⁸ If the site is marked for a thoracentesis that will be performed at a later time, the patient position must be kept constant to avoid a change in location of the pleural fluid. The patient is then cleaned, draped, and anesthetized, and the needle is placed at the same angle as the probe, usually perpendicular, at the target site. The point of entry is ideally superior to the rib to avoid injury to the neurovascular bundle. If catheters are inserted, ultrasonography can be used to confirm the position of catheters (Video 20-14). The pleural catheter will appear as

a hyperechoic linear structure within an anechoic fluid collection. Postprocedure ultrasonographic scans of the non-dependent chest wall to identify lung sliding and comet-tail artifacts exclude an iatrogenic pneumothorax.^{12,13}

Despite ultrasonographic guidance, taps can occasionally be unsuccessful. Reasons include plugging of the aspiration needle or the presence of loculations or septations preventing free drainage. Operator error due to compression artifacts may result in misjudging the depth of the effusion. The patient may have moved in the time between the scan and the tap. If a tap is dry, the thoracentesis needle should be withdrawn immediately and the patient rescanned. Repeat scanning enables repositioning of the entry point as well as exclusion of complications such as pneumothorax.

Ultrasonographic scanning can also assess the result of prior interventions. A successful pleurodesis resulting in pleural symphysis can be determined by the absence of lung sliding.⁶⁶ Successful resolution of pneumothorax by aspiration or chest tube drainage can be assessed by ultrasonography; in fact, ultrasonography can identify residual pneumothorax better than chest radiographs.⁶⁷

Ultrasonographic guidance can be used to guide the biopsy of peripheral lung lesions, pleural masses, and anterior mediastinal tumors. Closed pleural biopsies with an Abrams needle when guided by ultrasonography have been shown to contain pleura in 91% and be diagnostic for tuberculosis in 82% of cases.⁶⁸ Because it can distinguish solid from liquid components, ultrasonography is especially useful in avoiding necrotic areas. However, transthoracic needle biopsy of a lung or mediastinal lesion should only be performed by pulmonologists with expert knowledge of both ultrasonography and needle biopsy techniques,⁶⁹ because real-time needle visualization is necessary and the potential for complications is increased.

Prerequisites for ultrasonographically guided transthoracic needle biopsy are the presence of an acoustic window and the absence of overlying structures such as bone or aerated lung. Absolute contraindications include inability of patients to cooperate, to maintain an optimum position, or to control coughing. Uncorrected coagulopathy, thrombocytopenia (platelet count $< 50 \times 10^9/L$), uremia, and severe pulmonary hypertension are relative contraindications. Bronchiectatic and chronic cavitory lesions are considered poor candidates for biopsy because of the limited capacity for local tamponade of any bleeding.⁶⁹

The preferred method of biopsy is by the coaxial technique, in which a stylet with an introducer is inserted and biopsies are taken through the introducer when the stylet is removed. Patients are asked to hold their breath when the needle is advanced, during biopsy, and whenever the introducer is not occluded by the stylet. The needle should be visualized throughout its path, and failure to do so is usually the result of poor angulation. Any undue resistance should raise the suspicion of poor placement. Needle aspirates yield cytologic material; core biopsies for a tissue diagnosis are needed if tumors such as mesothelioma, lymphoma, teratoma, or thymoma are suspected. Core biopsies are also preferred for lung cancer tumor markers such as epidermal growth factor receptor mutation analysis.

Complications of biopsy include pneumothorax, hemoptysis, air embolism, and perforation of other organs. The

pneumothorax rate in needle biopsy of lung lesions has been reported in less than 4%,⁷⁰⁻⁷³ a low rate probably because most of the biopsied lesions were abutting the pleura. Air embolism can result when a swing in intrathoracic pressure draws air into the pulmonary veins via the introducer.

DOCUMENTATION⁷⁴

Appropriate documentation of ultrasonographic findings and interventional procedures is essential for research, reimbursement, and communicating medical information. Capturing of images or video clips enables comparisons with future scans and assessment of a patient's progress. Standard documentation should include patient identification, time and date of procedure, operator identification, patient position, transducer type and location, and indications and anatomic extent of the study. Reports should comment on normal findings, pathologic conditions, subjective measures of certainty (probable versus possible), and changes compared with previous scans. Reports on pleural effusions should mention location, echogenicity, degree of homogeneity, and estimated size. A comment should also be made on the pleural surface characteristics and the presence of any nodules or septations if applicable. Any limitations of the study should also be noted. If interventional procedures were performed, documentation usually includes the site, anesthesia, specimens obtained, complications, and follow-up instructions.

TRAINING

The American College of Chest Physicians and La Société de Réanimation de Langue Française have listed the competencies required for lung and pleural ultrasonography⁷ (see Table 20-3). The European Society of Intensive Care Medicine has agreed to use this as a foundation document in determining training standards.³ The basic principles necessary before acquiring these specific competencies include knowledge of ultrasound physics, machine settings, and manipulation of the probe to acquire adequate images. An understanding of ultrasonographic anatomy and image interpretation is also necessary.⁷ For patient safety, self-awareness is needed of the limitations of capability when embracing new technology. Pulmonologists need to identify poor-quality or complex images that require further consultation with experienced colleagues or referral to a radiologist. In addition, when scans do not correlate with clinical findings, the scans should not be acted upon until either expert opinion is sought or an alternative imaging method such as CT is obtained.

Current recommendations for general critical care ultrasonography require a theoretical program with image-based learning before moving to proctored procedures.³ Hands-on training on normal volunteers facilitates teaching of probe manipulation, spatial orientation, and normal anatomy. This helps perfect psychomotor skills and the proper use of buttons on the ultrasonography machine. For proctored procedures on patients, a logbook is recommended in which trainees should write detailed

interpretation reports for verification by trainers.³ There is no consensus on the number of procedures required for credentialing. However, based on echocardiography and emergency medicine standards, proctored examinations in 25 to 30 cases for each single application is a reasonable target to achieve competence in image acquisition.^{3,75,76}

ADVANTAGES AND DISADVANTAGES

The advantages of ultrasonographic imaging include bedside availability and the relative ease of performing repeated examinations. Imaging is real-time and free of harmful radiation. There are no documented side effects, and discomfort is minimal. Ultrasonography also provides excellent delineation of solid and liquid tissue structures. Furthermore, this modality is easily mastered once the image acquisition, interpretation, and the technical jargon (see Table 20-1) are learned. Despite the absence of randomized controlled trials, ultrasonographically guided interventional procedures in the thorax are likely to improve diagnostic yield and reduce complications by providing visual guidance.⁷⁷ Bedside ultrasonography enables clinicians who understand the clinical context of patients to perform the most appropriate scans directed to address clinically relevant questions.

The disadvantages of ultrasonography are primarily related to the fact that it is heavily operator dependent. Retrospective review of images provides only limited quality control. There is no scout scan to give a global picture for orientation. In addition, the basic ultrasonographic evaluation cannot determine the exact position of devices such as the endotracheal tube, central lines, and feeding tubes in the body. Image quality is degraded in patients who are edematous, muscular, or obese. Chest wounds or dressings prevent optimal probe placement, and subcutaneous emphysema can reflect so much signal that imaging is not possible. The bedside nature of ultrasonography raises issues of infection control. Portable machines should never be placed on patients' beds and should ideally have independent stands. Sterile sheaths should be employed in all real-time interventional procedures together with standard aseptic techniques. Ultrasonography gel can be a culture medium for bacteria,⁷⁸ and it is common courtesy to clean off all gel from the patient's body at the end of the procedure. The ultrasonography machine should also be wiped clean between studies with special attention given to components that may contribute to nosocomial transmission of infection: the transducer probe, cable, and keyboard.

Key Points

- Ultrasonography offers the advantages of real-time, bedside, radiation-free imaging that extends the possibilities for diagnosis and treatment by pulmonary and critical care physicians.
- The choice of transducer probes depends on frequency (compromising between spatial resolution and depth

of scan) and footprint (determining acoustic window size).

- Patient and probe position must be considered when assessing gravitationally dependent pathologic conditions such as pneumothorax and pleural effusion.
- Anatomic structures are identified based on their location and echogenicity.
- Ultrasonographic guidance for thoracentesis and pleural catheter placement increases the success of these procedures and reduces complications.
- A key disadvantage of ultrasonography is that it is operator dependent, thereby limiting retrospective analysis of previously acquired images.

Complete reference list available at ExpertConsult.

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POSITRON EMISSION TOMOGRAPHY

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INTRODUCTION

Positron emission tomography (PET) with ^{18}F -fluorodeoxyglucose (FDG) is a noninvasive imaging technique with several important applications in respiratory medicine. PET has long been used to evaluate inflammatory conditions such as sarcoidosis or idiopathic pulmonary fibrosis; for example, in small series of about 20 patients, the extent and/or activity of these diseases could be assessed more precisely by PET/computed tomography (CT) than by ^{67}Ga single-photon emission computed tomography scintigraphy.¹⁻³ PET has also been studied in patients with posttransplantation lymphoproliferative disease, in which a possible role in staging and follow-up was suggested.^{4,5}

The vast majority of data and clinical applications of PET, however, pertain to patients with respiratory malignancies, such as lung cancer or mesothelioma, and these are the main subjects of discussion in this chapter. Because FDG is by far the most commonly used tracer for this purpose, the term *PET* refers to FDG-PET unless stated otherwise.

PRINCIPLES

PET CAMERA

A PET camera produces three-dimensional images that represent the distribution of radioactivity within the body of a patient. Any molecule labeled with a positron-emitting radioisotope can be used to generate PET images. The PET camera consists of a full ring of several thousand scintillation detectors to generate the image, resulting in higher sensitivity to radioactivity and better spatial resolution than the conventional gamma camera. The spatial resolution of contemporary PET cameras is around 4 mm, allowing accurate characterization of lesions larger than 8 mm.

Modern PET cameras are hybrid systems in which a PET camera is combined with either a CT⁶ or magnetic resonance camera. Hybrid PET/CT cameras are now considered standard, whereas PET/magnetic resonance is an emerging technology. Compared to PET alone, hybrid PET/CT cameras provide three main advantages: (1) CT-based *attenuation*

correction (AC) is applied to the PET image to correct for absorption by the body of the patient; (2) there is increased accuracy of the exact position of the lesion and morphologic characterization of the underlying correlate, reducing equivocal findings; and (3) the combined image increases the confidence of the reporting physician.

Typical scan times for modern PET/CT are in the order of 15 minutes for a skull-to-thigh, “whole body,” image. Unless a separate dedicated contrast-enhanced CT scan is already available, PET/CT is preferably combined with high-dose, contrast-enhanced diagnostic CT than with low-dose CT; with high-dose CT, the PET/CT is more precise for *tumor-node-metastasis* (TNM) staging because of better AC and localization.⁷ It has been demonstrated that the use of oral or intravenous contrast agents does not induce clinically significant changes in the PET images.⁸

METABOLIC TRACER: FDG

For clinical cancer imaging the glucose analogue FDG is by far the most common tracer. Its use is based on the increased cellular uptake of glucose, due to both an increased expression of glucose transporter proteins and a much higher rate of glycolysis of cancer cells.⁹ FDG, a glucose analogue in which the oxygen molecule in position 2 is replaced by a positron-emitting fluorine-18 atom, undergoes the same uptake as glucose but is metabolically trapped and sequestered in neoplastic cells after phosphorylation by hexokinase.¹⁰ The radiation dose for a typical examination is in the order of 5 to 8 mSv,¹¹ comparable to the effective dose of a diagnostic chest CT (7 to 7.5 mSv). The FDG uptake is generally expressed as the *standardized uptake value* (SUV), a semiquantitative measure of FDG-uptake that expresses the uptake of a lesion as a function of the total injected dose.

INTERPRETATION OF PET IMAGES

For diagnosis and staging, visual analysis relies on the detection of foci with activity higher than background not caused by physiologic processes, both for the discrimination of nodules and for the evaluation of mediastinal involvement. Non-AC images should be examined to detect

small lung lesions, because non-AC images have better contrast for such nodules than AC images.¹² High physiologic FDG uptake is present in the brain, kidney, and urinary tract (urinary excretion) and can be present in the heart.¹³ The high uptake in the brain interferes with lesion detection. There is a low degree of physiologic uptake of FDG in the other intrathoracic structures.

False-positive findings are possible, because FDG uptake is not tumor specific and can be found in all active tissues with high glucose metabolism, particularly in sites of inflammation. Therefore FDG-positive findings, especially if isolated and decisive for patient management, require confirmation. The differentiation between metastasis, a benign or inflammatory lesion, and even an unrelated second malignancy should be established by other tests or tissue biopsy.¹⁴ The major causes of false-positive results in chest pathologic conditions are infectious, inflammatory, and granulomatous disorders (Table 21-1)¹⁵ and recent medical procedures.^{16,17}

False-negative findings are less common and may be due to lesion-dependent or technical factors (see Table 21-1). A critical mass of metabolically active malignant cells is

required for PET detection. Therefore careful interpretation is warranted in tumors with low FDG uptake, such as small-sized very well differentiated adenocarcinoma, adenocarcinoma with lepidic growth, or carcinoid tumors. In addition, even in tumors with high FDG uptake, lesions less than 8 mm may prove falsely negative due to the limitations in spatial resolution; in the lower lung fields, due to the greater respiratory motion there, the detection limit may even be 10 mm.¹⁸ One interfering factor inherent to the technique is a high blood glucose level, which should be checked and be within an acceptable range (typically 60 to 180 mg/dL) before tracer injection.

DIAGNOSIS

Noncalcified *solitary pulmonary nodules* (SPNs) are common findings on chest radiograph or CT examination in clinical practice and have become even more frequent with the recent interest in low-dose chest CT for early lung cancer detection.¹⁹ Initially, PET studies in the diagnosis of SPNs used a threshold *maximum SUV* (SUV_{max}) above 2.5 for the diagnosis of malignancy. Applying this criterion, overall sensitivity, specificity, and positive and negative predictive values of 96%, 78%, 91%, and 92%, respectively, were reported in a meta-analysis based on series with nodules larger than 1 cm²⁰ (Fig. 21-1).

However, more recently the use of an SUV_{max} level below 2.5 to exclude malignancy has been challenged as too restrictive.²¹ It is true that solid malignant lesions of at least 1 cm will usually have an SUV_{max} above 2.5, but smaller cancers, lesions with ground-glass appearance on CT (e.g., the lepidic type of adenocarcinoma^{22,23}) (Fig. 21-2), or tumors with low metabolism (e.g., carcinoid tumors^{24,25}) may have an SUV_{max} below 2.5. In a large prospective study of PET/CT scans of indeterminate lesions, SPNs smaller than 2.5 cm were found to have a 24% chance of being malignant when the SUV_{max} was between 0 and 2.5, 80% if between 2.6 and 4.0, and 96% if 4.1 or more.²⁶

Rather than using a fixed SUV_{max} criterion as a threshold, the visual information from PET images—lesions with any increased FDG uptake being potentially malignant—should be added to a comprehensive nodule assessment based on clinical characteristics such as smoking and age, CT imaging characteristics such as appearance (ground glass, semi-solid, or solid) and margins, and growth pattern if available. Using this approach, the chance of identifying an SPN as malignant is improved compared with just using the information from PET alone. The benefit of PET in this setting was confirmed in a series of 106 radiologically indeterminate SPNs, of which 61 were malignant²⁷; PET improved the accuracy over a prediction model that did not incorporate PET data²⁸ by 13.6%.

STAGING

TNM STAGING

The TNM staging system classifies malignant tumors according to the extent of the primary *tumor* (T), the spread to locoregional *lymph nodes* (N), and the presence of distant

Table 21-1 Causes of False-Negative and False-Positive Findings on PET Scanning

FALSE-NEGATIVE FINDINGS

- Lesion dependent
 - Small tumors (<8-10 mm)
 - Ground-glass opacity neoplasms (adenocarcinoma with lepidic pattern)
 - Carcinoid tumors
- Technique dependent
 - Hyperglycemia
 - Paravenous FDG injection
 - Excessive time between injection and scanning

FALSE-POSITIVE FINDINGS

- Infectious-inflammatory lesions
 - (Postobstructive) pneumonia—abscess
 - Mycobacterial or fungal infection
 - Granulomatous disorders (sarcoidosis, granulomatosis with polyangiitis [Wegener granulomatosis])
 - Chronic nonspecific lymphadenitis (Rheumatoid) arthritis
 - Occupational exposure (anthracosis/silicosis)
 - Bronchiectasis
 - Organizing pneumonia
 - Reflux esophagitis
- Iatrogenic causes
 - FDG embolus
 - Invasive procedure (puncture, biopsy)
 - Talc pleurodesis
 - Radiation esophagitis and pneumonitis
 - Bone marrow expansion after chemotherapy
 - Colony-stimulating factors
 - Thymic hyperplasia after chemotherapy
- Benign mass lesions
 - Salivary gland adenoma (Warthin)
 - Thyroid adenoma
 - Adrenal adenoma
 - Colorectal dysplastic polyps
- Focal physiologic FDG uptake
 - Gastrointestinal tract
 - Muscle activity
 - Brown fat
 - Unilateral vocal cord activity
 - Atherosclerotic plaques

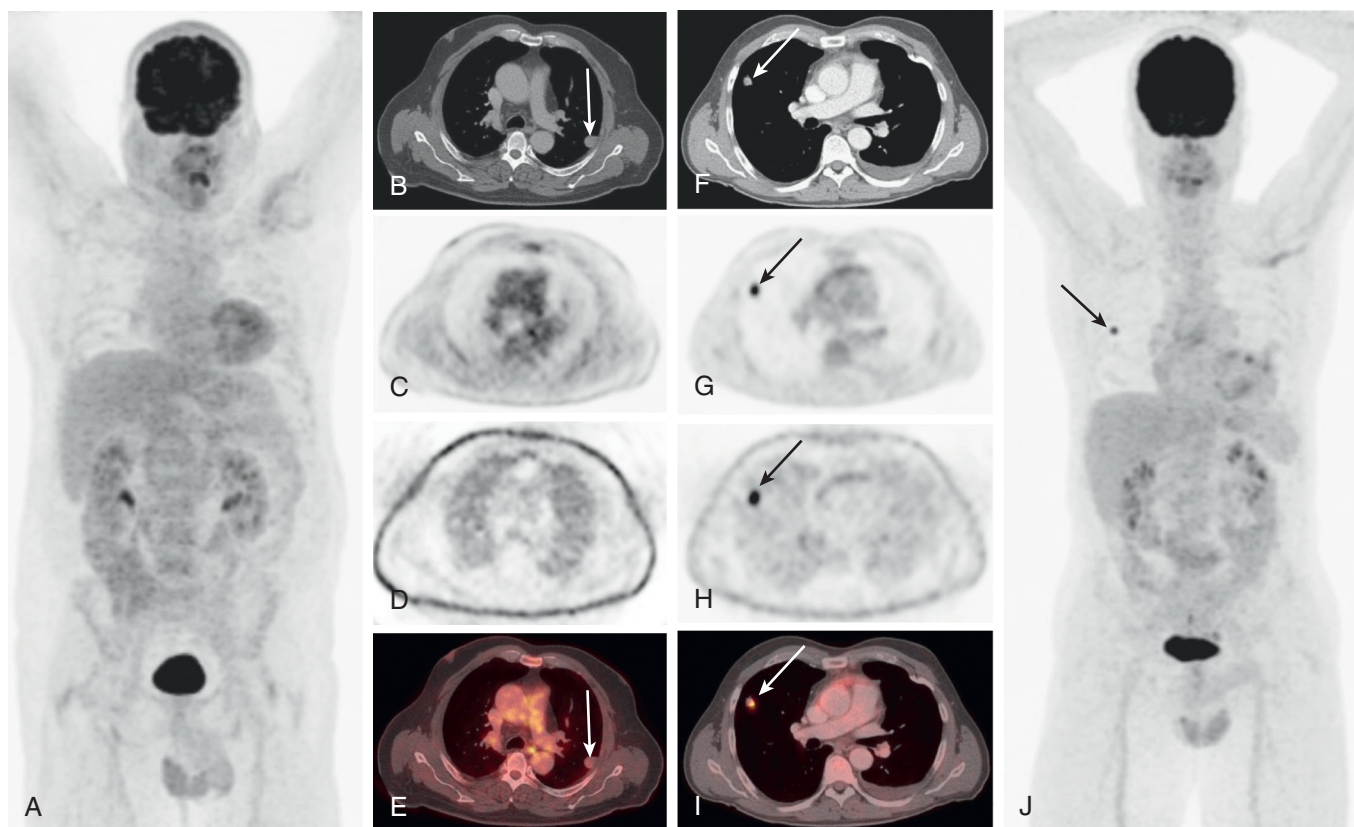


Figure 21-1 Two 60-year-old men with solitary pulmonary nodules differentiated by PET/CT. The first patient (A–E) presented with a 19-mm smooth nodule (arrows, B and E) in the left upper lobe on CT (B), with limited growth over a 4-month period. Both the coronal, attenuation-corrected (A) and non-attenuation-corrected transverse (C and D) PET images show no increased ^{18}F -fluorodeoxyglucose (FDG) uptake within the nodule, with a maximum standardized uptake value (SUV_{max}) of 2.1. The fusion image (E) shows uptake in the lesion lower than in the mediastinal vessels. Histologic analysis following wedge resection demonstrated a pulmonary fibrous hamartoma. The second patient (F–J) presented with a more irregular 15-mm nodule (arrows) in the right upper lobe. There is intense focal uptake in the right lung on the maximum-intensity projection image (J) and on both the attenuation-corrected (G) and non-attenuation corrected (H) transverse images, corresponding to the site of the nodule (I). The SUV_{max} was 6.4, and the lobectomy specimen showed moderately to poorly differentiated pulmonary adenocarcinoma.

metastasis (M); as a result, lung cancer patients of different TNM subsets with similar prognoses can be grouped into stages. Stage is the most important factor in prognosis and choice of treatment,²⁹ which means that reliable noninvasive methods for accurate staging are extremely important. CT scans, endoscopic techniques, and surgical staging procedures are key factors, but the addition of PET to these conventional methods has been shown to improve the staging process substantially; PET greatly aids in distinguishing patients who are candidates for therapy with curative intent, such as surgical resection or intense multimodality treatment, from those who are not.³⁰

The T Factor

Modern multislice CT images allow detailed evaluation of the anatomic relationships among the tumor and the lung fissures, which may determine the type of resection, and among the tumor and both the mediastinal structures and the pleura and chest wall. In addition, integrated PET/CT images may enhance precise definition of chest wall and mediastinal infiltration or correct differentiation between tumor and peritumoral inflammation or atelectasis^{31–33} (Fig. 21-3).

The N Factor

It has been clear since the initial studies^{34,35} that the addition of PET to CT results in more accurate lymph node

staging than CT alone, with an overall sensitivity of 80% to 90% and a specificity of 85% to 95% for the detection of pathologic nodes.^{36–38} In addition, the absence of mediastinal lymph node disease on PET/CT has a high negative predictive value, so that invasive lymph node staging tests can often be omitted, allowing these patients to proceed straight to surgical resection. However, there are limitations to relying on negative PET results; one should have less confidence in negative PET results in cases of a primary tumor larger than 3 cm, insufficient FDG uptake in the primary tumor, a centrally located tumor, or concurrent hilar nodal disease that may obscure coexisting N2-disease on PET. On the other hand, positive PET/CT findings determine the location of suspect lymph nodes and thereby help to direct tissue-sampling procedures, such as endobronchial ultrasonographically-guided transbronchial needle aspiration or cervical mediastinoscopy. Because of false-positive images in lymph nodes—based on the conditions listed in Table 21-1—proof of lymph node involvement in pathologic processes should be sought in most patients with positive mediastinal nodes on PET, except those with obvious bulky nodes on imaging.

The M Factor

PET added to CT is almost uniformly superior to CT alone, except for brain imaging, where the sensitivity for detecting lesions is unacceptably low due to the high glucose uptake

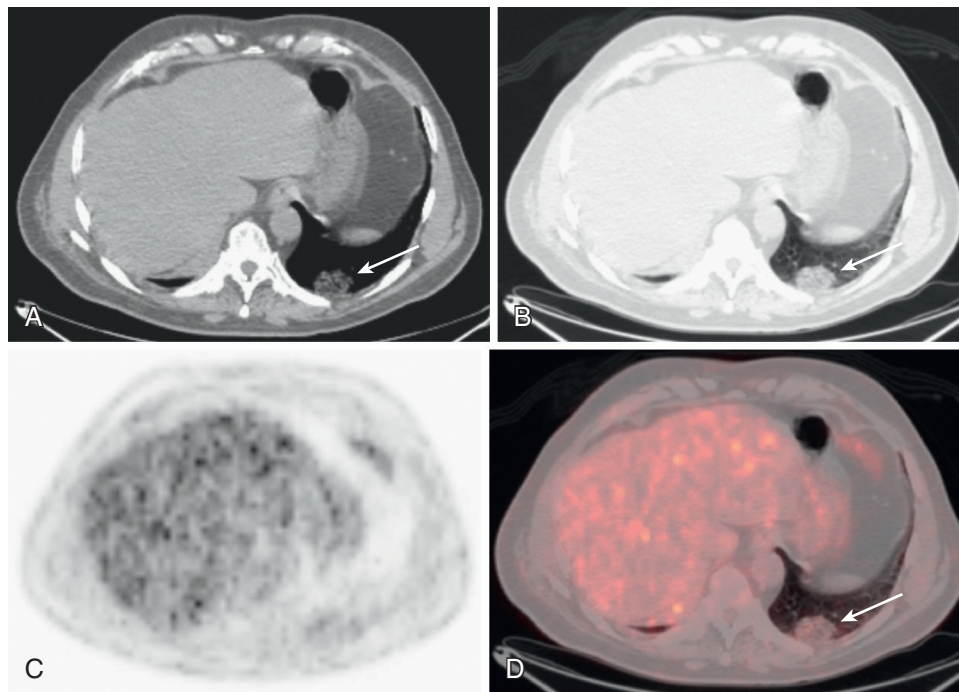


Figure 21-2 False-negative ^{18}F -FDG-PET finding. Axial chest CT displayed in soft tissue (A) and lung (B) windows in a 69-year-old man shows a pulmonary ground-glass opacity persisting for 1 year (arrow). There is no increased FDG uptake on the attenuation-corrected images (C), and the lesion has low FDG uptake comparable to the surrounding lung tissue on the fusion images (arrow, D). The maximum standardized uptake value was 1.5. Histologic analysis demonstrated pulmonary adenocarcinoma with lepidic growth pattern.

of normal surrounding brain tissue. For detecting extrathoracic metastases, the pooled sensitivity and specificity for PET/CT were 77% (95% confidence interval [CI], 47% to 93%) and 95% (95% CI, 92% to 97%), respectively, in a recent meta-analysis.³⁹ CT and especially magnetic resonance imaging remain the methods of choice for brain imaging.

For bone metastases, PET is more accurate than $^{99\text{m}}\text{Tc}$ methylene diphosphate bone scanning: sensitivity is at least as good (90% to 95%) and specificity is far better (95% versus 60% for bone scan).^{40,41} Limitations are that PET only images from the head to just below the pelvis and thus will miss lesions outside this range and that PET may not detect osteoblastic lesions, which nonetheless are rare in untreated lung cancer. For adrenal gland metastases, PET has a high sensitivity, so that an equivocal lesion on CT without FDG uptake will usually not be metastatic. PET can also be of help in differentiating hepatic lesions that remain indeterminate by conventional studies. PET may also reveal metastases in sites that escape attention in conventional staging (Fig. 21-4), including soft tissue lesions, retroperitoneal lymph nodes, barely palpable supraclavicular nodes, and painless bone lesions. Exclusion of malignancy requires caution when smaller lesions (<1 cm) are present (see Table 21-1). A particular example is a small contralateral lung nodule—a common finding in the era of chest multislice CT imaging—where negative PET/CT results often do not guarantee certainty, so that invasive sampling (e.g., thoracoscopy) is still needed to exclude malignancy.

PET/CT has long been used to assess pleural involvement, initially with promising results,^{42,43} but recently with more variable results.⁴⁴ Small pleural deposits can be missed on PET/CT, because of their low tumor load and/or partial

volume effects, whereas false-positive findings may be caused by inflammatory pleural lesions. If the diagnosis of pleural abnormalities will determine the chance for treatment with curative intent, verification of a pathologic process with cytologic analysis or thoracoscopy is often needed.

INFLUENCE ON TREATMENT CHOICES AND PLANNING WITH CURATIVE INTENT

PET has a significant complementary role to CT for two reasons. First, PET can detect unexpected lymph node involvement or distant organ metastatic spread (see Fig. 21-4). After a negative conventional staging, previously unknown metastases are found on PET/CT in 5% to 20% of patients, in increasing numbers from clinical stages I–III tumors.^{45–54} Second, PET is able to determine the nature of some lesions that are equivocal on conventional imaging.^{45–47,49} There is no problem of interpretation when whole-body PET shows metastases in many sites, but an isolated suspect lesion that determines radical treatment intent should always be verified by other tests or tissue sampling, because of the risk for a false-positive finding (see Table 21-1) or a second primary tumor. In one large retrospective series, solitary extrathoracic lesions were documented in about 20% of the patients; about half of these were metastatic, whereas the other half were either unrelated to lung cancer (inflammatory or other benign lesions) or second primary tumors.⁵⁵

The effect of adding PET or PET/CT to a standard staging algorithm has been investigated in several randomized controlled trials. Two earlier trials looked at the advantages of stand-alone PET and reported seemingly contradictory

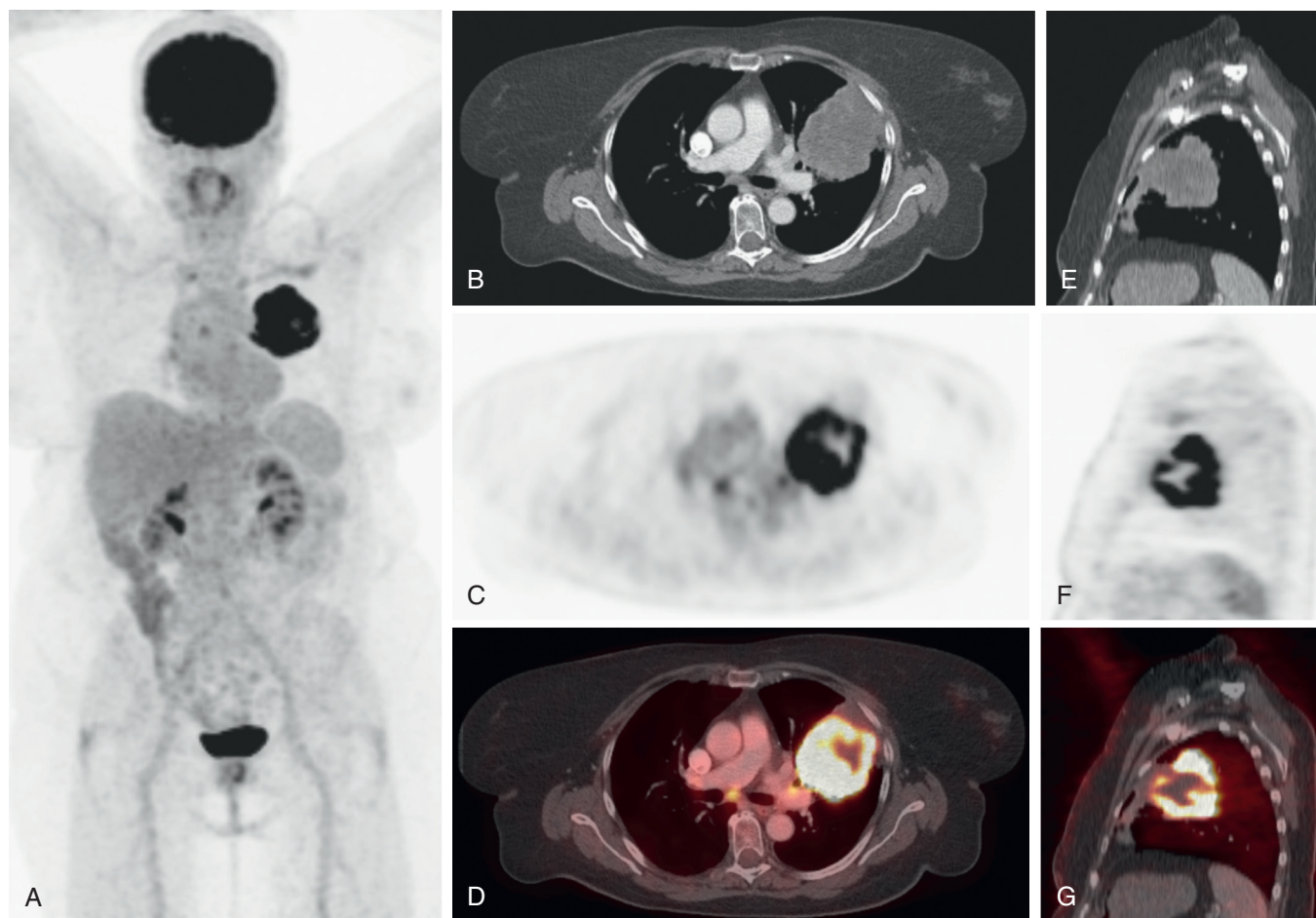


Figure 21-3 Use of ^{18}F -FDG-PET/CT to determine tumor stage. A 76-year-old woman presented with a large tumor mass in the left upper lobe that showed intense FDG uptake (A). On both the transverse (B) and sagittal (E) CT images the consolidation extends to the chest wall. The corresponding PET images show intense uptake in the viable rim, with central photopenia in the necrotic part of the tumor (C and F). The fusion images demonstrate that the metabolically active tumor component does not reach the chest wall (D and G) and is surrounded by postobstructive atelectasis.

results, perhaps because of differences in trial design. In the Dutch trial,⁵⁶ which found value in adding PET to the standard workup, the end point—“futile thoracotomy”—was clearly defined as indicating benign disease, explorative thoracotomy, pathologic stage IIIA-N2/IIIB, or postoperative relapse or death within 12 months. In contrast, in the Australian study,⁵⁷ which found less value in adding PET, there were no benign lesions, surgery was considered to be of use in some stage IIIA-N2 patients, and no strict follow-up terms were predefined. The Australian trial also focused on clinical stage I and II patients only, from which less additional benefit of PET was expected based on previous non-randomized accuracy studies.

Three later trials used PET/CT imaging in addition to standard workup, two of which took place in the surgical setting (Table 21-2). The study of Fischer et al⁵⁸ largely reproduced the Dutch experience, in which addition of PET led to a significant reduction of futile thoracotomies. The study of Maziak et al⁵⁹ mainly looked at improved correct upstaging in resectable stages I–III *non-small cell lung cancer* (NSCLC) and met this primary end point. Overall, in the two studies there was a 4% to 11% increased detection rate of stage IV disease,^{58,59} and the use of PET/CT led to a change in patient management, both in intent (curative versus pal-

liative) and modality (chemotherapy versus other modalities). In a study of unresectable stage III NSCLC, 21/140 (15%) patients were correctly upstaged with PET/CT versus 4/149 (2.7%) with CT alone.⁶⁰ Thus the overall evidence points to significantly more accurate TNM staging with PET/CT than with conventional imaging alone. This leads to true benefits, such as stage migration,⁶¹ better treatment choices, and perhaps better outcome,⁶² although the latter still needs to be proven, because randomized controlled trials have been underpowered to assess this end point.

It has been shown in many radiotherapy planning studies that PET/CT influences the accurate delineation of target volumes for radiotherapy. In general the PET-based volume delineations are smaller than those with CT alone, mainly due to more accurate nodal staging⁶³; the lower tumor volume permitted radiation dose escalation to the tumor in a substantial number of patients. Prospective clinical trials using selective nodal irradiation based on PET/CT scanning reported isolated nodal failures in fewer than 5% of patients treated with chemoradiotherapy,^{64,65} which is lower than the 13% rate of false-negative PET results reported in CT-positive lymph nodes.⁶⁶ The lower recurrence rate than expected might be explained by the incidental irradiation of lymph nodes adjacent to the planning target volume. In

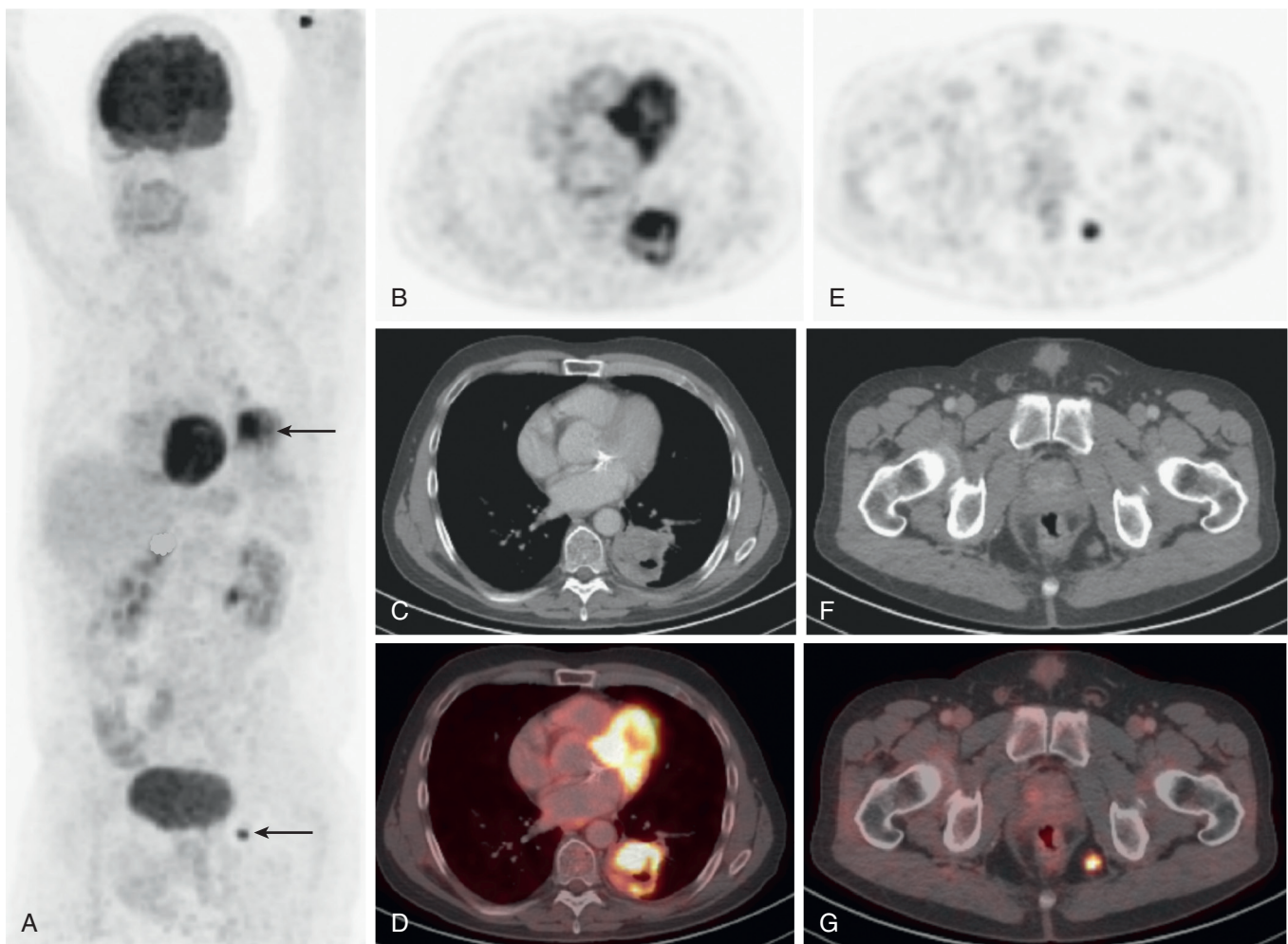


Figure 21-4 Detection of distant metastasis (M1b) outside the traditional scanning range of CT for lung cancer staging. ^{18}F FDG-PET/CT was performed in a 54-year-old man with a primary pulmonary adenocarcinoma. The maximum-intensity projection image shows two sites with intense pathologic uptake (**A**, arrows). Note intense uptake at the primary tumor with central photopenia (**B–D**) due to necrosis (maximum standardized uptake value [SUV_{max}] 13.7). In addition, there is strong focal uptake (**E–G**) in the left ischiorectal fossa (SUV_{max} 8.4). This lesion would have been undetected with the conventional approach of performing CT through the chest and upper abdomen for lung cancer staging. A biopsy of the lesion was performed under ultrasonographic guidance, and the lesion was found to represent metastasis from the lung adenocarcinoma.

Table 21-2 Randomized Controlled Studies Comparing Conventional Staging to Integrated PET/CT Staging in Patients with NSCLC

Study and year	N	Population	Proportion Stages I–II	Primary Outcome
Fischer et al ⁵⁸ 2009	189	Stages I–III	33%	Futile thoracotomy 52% vs. 35% ($P = 0.05$)
Maziak et al ⁵⁹ 2009	337	Stages I–IIIA	90%	Correct upstaging 6.8% vs. 13.8% ($P = 0.046$)
Ung et al ⁶⁰ 2009	304	Stage III	0%	Correct upstaging 2.7% vs. 15% ($P = 0.002$)

N, number of patients; NSCLC, non-small cell lung cancer.

addition, PET/CT-based delineation might be crucial to avoid geographic misses leading to treatment failures. Because of the possibility of false-positive lymph nodes on PET, invasive nodal staging using endosonography (endobronchial ultrasonography or endoscopic ultrasonography) or mediastinoscopy may be warranted if the nodes concerned would have a major impact on defining the radiation treatment field (see Chapter 22).

PET-based delineation of the primary tumor usually does not add significantly to that of CT-based delineation, except in situations with postobstructive atelectasis. The optimal method of delineation still remains to be defined. An automated PET/CT delineation may reduce the interobserver variability in treatment planning compared to CT alone.⁶⁷ PET may also identify high FDG-uptake regions within the primary tumor as being more radioresistant.⁶⁸ Work is in progress to plan higher radiation doses to these potentially radioresistant areas. Radiation dose escalation using an integrated boost to high FDG-uptake regions within the

primary tumor proved to be safe and feasible in a small randomized phase II study.⁶⁹

PROGNOSIS

Several PET staging studies have clearly demonstrated TNM stage migration. The possible effect of stage migration may in part account for an apparent improvement in survival of treated patients in both early and advanced disease stage cohorts. The artifactual improvement seen with stage migration is widely referred to as the “Will Rogers phenomenon,” in which patients that move from one stage to another can improve the apparent survival in both stages.^{61,70} (Will Rogers, the American comedian, observed: “When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”) As mentioned earlier, the randomized controlled trials to date have been underpowered to evaluate the potential individual patient survival benefit due to TNM stage migration brought about by PET.

PET has also been shown to predict the prognosis of patients with NSCLC.⁷¹ In a recent systematic review and meta-analysis, the SUV of the primary tumor at diagnosis was found to predict outcome in NSCLC, especially in the earlier stages.⁷² These studies almost uniformly found a better overall survival among patients with a metabolic activity lower than the threshold SUV value, calculated from either the most discriminative log-rank SUV value or the median SUV. However, although SUV may be a way to assess prognosis, there is no true cutoff point suitable for broad clinical use. Instead of a true cutoff point, there may rather be a continuous SUV spectrum of a gradually worsening prognosis. When baseline SUV was incorporated as a continuous variable in a Cox proportional hazards model, a one-unit increase in SUV was associated with a 7% increase in hazard of death in resected stages I–III NSCLC⁷³ and a 6% increase in hazard of death in inoperable NSCLC patients treated with radiotherapy.⁷⁴

HEALTH ECONOMICS

As respiratory oncologists, we aim for the best-quality health care for our patients but acknowledge the need for financial prudence. The major cost of modern oncology practice, however, does not lie in the baseline diagnostic process, but in the delivery of expensive treatments and the morbidity related to possible side effects. Therefore application of economic modeling to the use of PET has to be based on both diagnostic and therapeutic aspects of health care expenditure within a daily clinical setting.

In a recent overview of all economic evaluations of PET in oncology performed between 2005 and 2010, it was concluded that the strongest evidence for cost-effective use of PET was for the staging of NSCLC, where there may be benefits both for patients in terms of a possible increase in life expectancy and for the health care system in terms of cost savings resulting from the number of invasive procedures avoided.⁷⁵ Taking into account the superior accuracy of PET/CT compared to PET alone in lung cancer staging, the health economic impact in terms of cost-effectiveness can most probably be extended to PET/CT. Since the

introduction of PET/CT technology into clinical medicine in 2001, additional studies in respiratory oncology have confirmed the cost-effectiveness of this integrated scanning method.^{76,77} Furthermore, PET has been shown to be cost-effective for characterizing SPNs and to be the most cost-effective diagnostic strategy for nodules of low to moderate pretest probability of malignancy on CT.⁷⁸

LESS CLASSIC INDICATIONS

SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) typically shows very high FDG accumulation; however, the value of PET for SCLC is not as well established as for NSCLC. For management of SCLC, the data on the use of PET are less robust than for NSCLC, because the emphasis on systemic and radiation therapy as opposed to surgical resection provides less histologic data to serve as the gold standard. Furthermore, most studies were rather small (mean $n = 40$) and retrospective in nature. A review of 14 studies comparing FDG-PET with conventional staging procedures found an overall cumulative staging concordance between PET and conventional imaging in 84%.⁷⁹ Based on PET, limited stage SCLC was upstaged to extensive stage SCLC in 18% of patients, and extensive stage SCLC was downstaged to limited stage in 11%. The information on PET might result in considerable changes in patient management, ranging from 27%⁸⁰ to 47%⁸¹ across studies. The use of PET/CT resulted in changes to the three-dimensional conformal radiation therapy plan in 58% of patients, mainly by decreasing the target volume (in the setting of atelectasis) or detecting unsuspected nodal or pulmonary foci.⁸² For prognostic predictions, pretreatment PET values had no value for stages I–III SCLC, but a complete metabolic response on posttreatment PET/CT was associated with better outcome in retrospective analyses.^{83,84}

MESOTHELIOMA

Integrated PET/CT imaging is playing an increasing role in the assessment of suspected or known *malignant pleural mesothelioma* (MPM, Fig. 21-5). PET/CT could be an effective tool in the correct differentiation of malignant (mainly MPM) and benign pleural diseases in asbestos-related CT findings, with an overall accuracy of higher than 90% and a negative predictive value of above 90%.^{85,86} Compared to CT alone, PET/CT is significantly more accurate in baseline TNM staging of patients who are considered appropriate candidates for multimodal therapy.⁸⁷⁻⁸⁹ Although PET/CT does not provide additional information about the primary tumor compared to CT alone, it identifies a higher number of metastatic mediastinal lymph nodes and/or unknown distant metastatic disease in up to two thirds of patients, with a significant clinical impact on treatment planning. Early evidence also suggests that PET/CT may have a role in evaluating response to therapy in MPM,⁹⁰ which is interesting because the assessment of response in patients with MPM according to standard response criteria on CT is far from simple. More work to define response criteria for MPM on PET is needed. Furthermore, a prospective study in

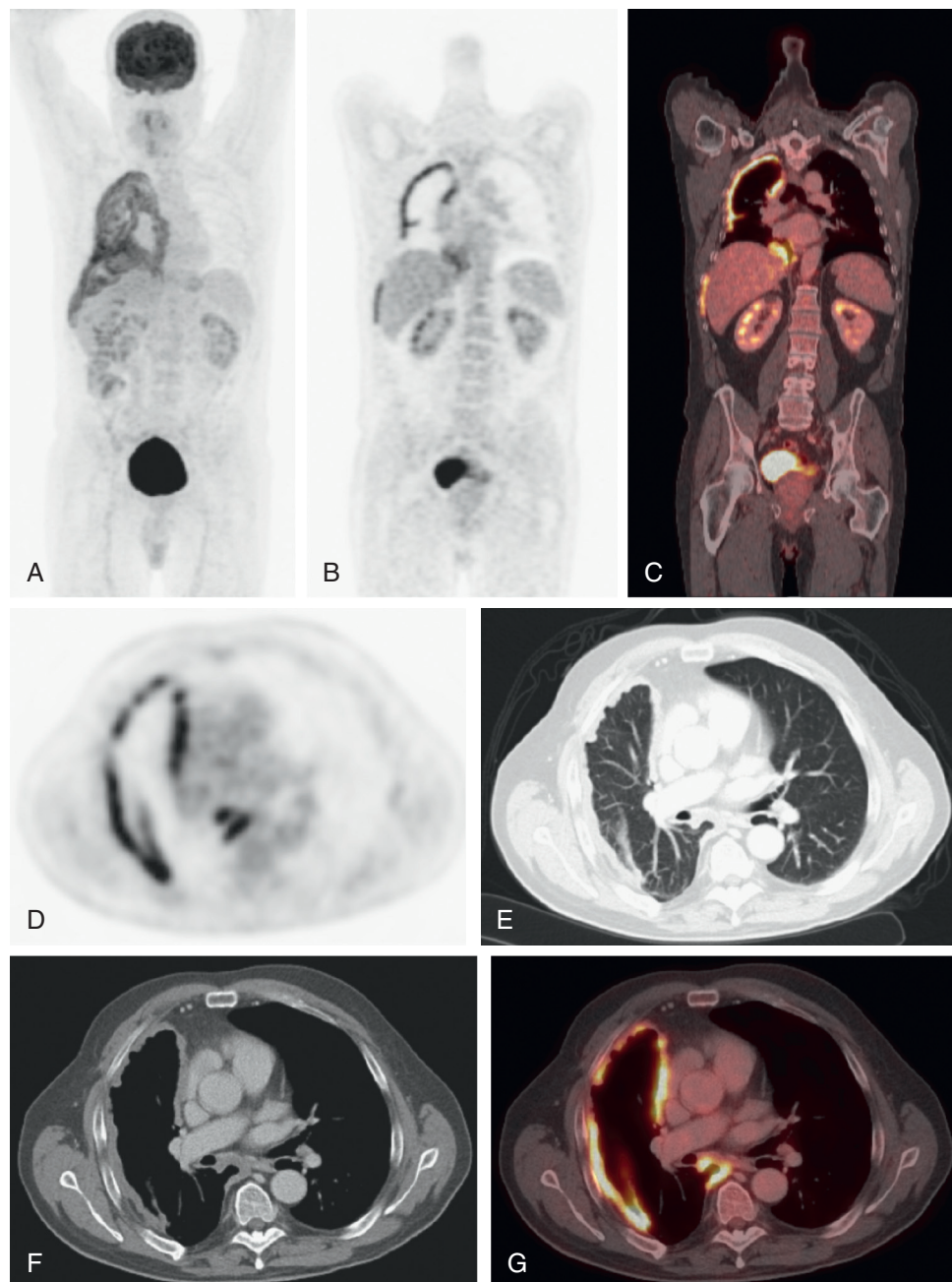


Figure 21-5 ^{18}F -FDG-PET/CT in mesothelioma. A 67-year-old patient underwent FDG-PET/CT for staging of a primary epithelioid pleural mesothelioma. The maximum-intensity projection images (**A**) show diffuse, intense uptake corresponding to the right pleural surface. Coronal (**B** and **C**) PET images show linear intense uptake involving a large portion of the lateral and medial pleura, with a small area on the lateral side without increased uptake. Transverse PET images show increased uptake involving nearly 330 degrees of the pleural circumference (**D** and **G**), corresponding to the neoplastic irregular thickening of the pleura on the corresponding CT images (**E** and **F**).

patients with nonsarcomatoid MPM observed that baseline total glycolytic volume on PET was more predictive of survival than CT-assessed TNM stage in a multivariate analysis.⁹¹ These observations of prognostic capability still require prospective validation.

NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) arise in cells of the amine precursor uptake and decarboxylation system. NETs of the lung are divided in four categories: typical carcinoid,

atypical carcinoid, large cell neuroendocrine carcinoma, and small cell neuroendocrine carcinoma.⁹² FDG uptake is often low in typical carcinoid—a well-known cause of potentially false-negative results—whereas in higher-grade NETs the FDG uptake can be similar to that of NSCLC and SCLC.⁹³ Alternative tracers have been studied for detection and staging of NET with low FDG avidity. Neuroendocrine cells synthesize and secrete a range of peptide hormones. The molecular features of this hormone production have been harnessed to provide imaging targets. The most studied target is the *somatostatin receptor* (SSTR), a

seven-transmembrane G-coupled peptide receptor, which plays a role in the control of hormone secretion and cell growth⁹⁴ and is internalized upon ligand binding.⁹⁵

Synthetic peptides derived from the somatostatin hormone have been coupled with chelators and radiolabeled with a range of different radionuclides, of which the most interesting for PET are the so-called ⁶⁸Ga-DOTA-peptides labeled with the generator-derived gallium-68. These tracers consist of a vector molecule binding the SSTR (e.g., TOC, TATE, NOC), a chelator (DOTA), and a positron-emitting radionuclide (gallium-68). Three of these tracers are currently in clinical use: ⁶⁸Ga-DOTATOC, ⁶⁸Ga-DOTATATE, and ⁶⁸Ga-DOTANOC, all with a high affinity for subtype 2 of the SSTR (low nanomolar range), varying affinity for subtypes 3 and 5, and low affinity for subtypes 1 and 4.⁹⁶ There have been many studies documenting the increased diagnostic performance of these ligands for detection of NETs.^{97,98}

A recent study documented expression of SSTR2A, the prime target for these radioligands, in more than 80% of patients with bronchial carcinoid, with expression by immunohistochemistry similar for typical and atypical carcinoid.⁹⁹ This results in very high uptake rates in typical and atypical bronchial carcinoid, with median SUV_{max} around 15, 20, and 25 for ⁶⁸Ga-DOTATATE,⁹³ ⁶⁸Ga-DOTATOC,¹⁰⁰ and ⁶⁸Ga-DOTANOC,¹⁰¹ respectively (Fig. 21-6). In most cases, bronchial NETs will show an uptake either of an SSTR ligand or of FDG, with virtually no tumors showing uptake of both or neither tracer⁹³; typical carcinoids show

more avidity for the SSTR ligand, whereas atypical carcinoids and higher-grade lesions show more avidity for FDG.^{101a} Comparing FDG and ⁶⁸Ga-DOTATATE uptake, an interesting observation has been made regarding central bronchial carcinoids,¹⁰² which often present with postobstructive atelectasis. ⁶⁸Ga-DOTATATE consistently showed low uptake in these tumors, whereas FDG showed moderate to very high uptake because of postobstructive inflammation or infection with low uptake in the primary tumor.⁹³

RESPONSE TO THERAPY

FDG uptake in tumors is related to (1) the number of viable cancer cells, (2) their metabolic activity and proliferation capacity, and (3) the presence of inflammatory cells.¹⁰³ In many clinical settings the metabolic changes caused by cancer therapy precede the morphologic changes. This discrimination of viable tumor from nonviable tumor is the basis for the use of PET for the determination of response to therapy. Whenever PET scans are to be compared at different time points, it is crucial to perform each PET procedure according to a similar methodology, by standardizing the interval from last therapy, patient preparation, camera setting, reconstruction parameters, and image analysis.^{104,105}

For *early stage* NSCLC treated with *stereotactic ablative radiotherapy* (SABR), the prediction of outcome and assessment of response has become very important.¹⁰⁶ For the prediction of response to SABR, retrospective data

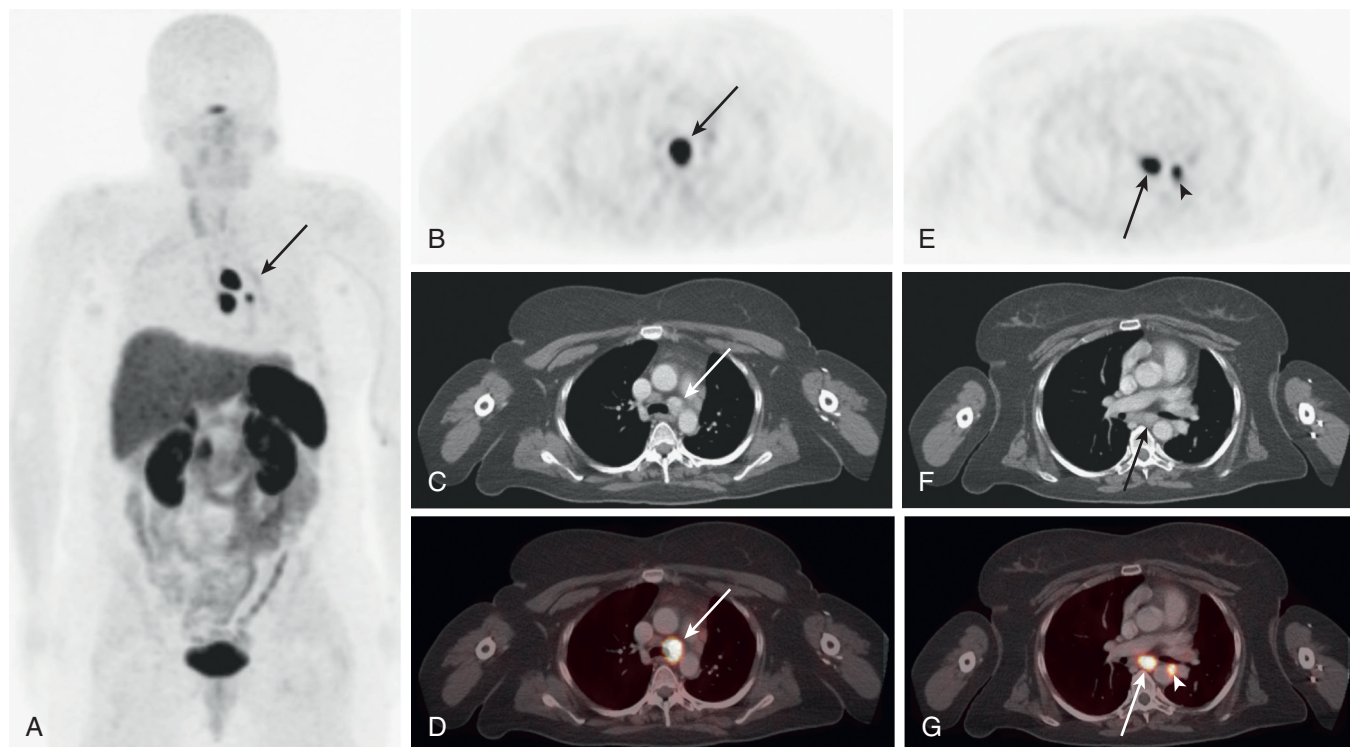


Figure 21-6 ⁶⁸Ga-DOTATATE PET in a patient with typical carcinoid. A 45-year-old woman with a history of a left lower lobectomy for a typical bronchial carcinoid underwent ⁶⁸Ga-DOTATATE PET/CT for a rising serum chromogranin level. The maximum-intensity projection images (A) show physiologic uptake in the pituitary gland, liver, and adrenal gland as well as particularly intense uptake in the spleen, kidneys, and bladder. There are three foci of intense pathologic uptake in the mediastinum (arrow, A). The transverse sections show increased tracer uptake in the left tracheobronchial angle and periesophageal lymph nodes (arrows, B–G) and nodes posterior to the left main bronchus (arrowheads, E and G). After a thorough surgical mediastinal lymph node dissection, these three nodes were confirmed as the only nodes with metastases from her typical carcinoid.

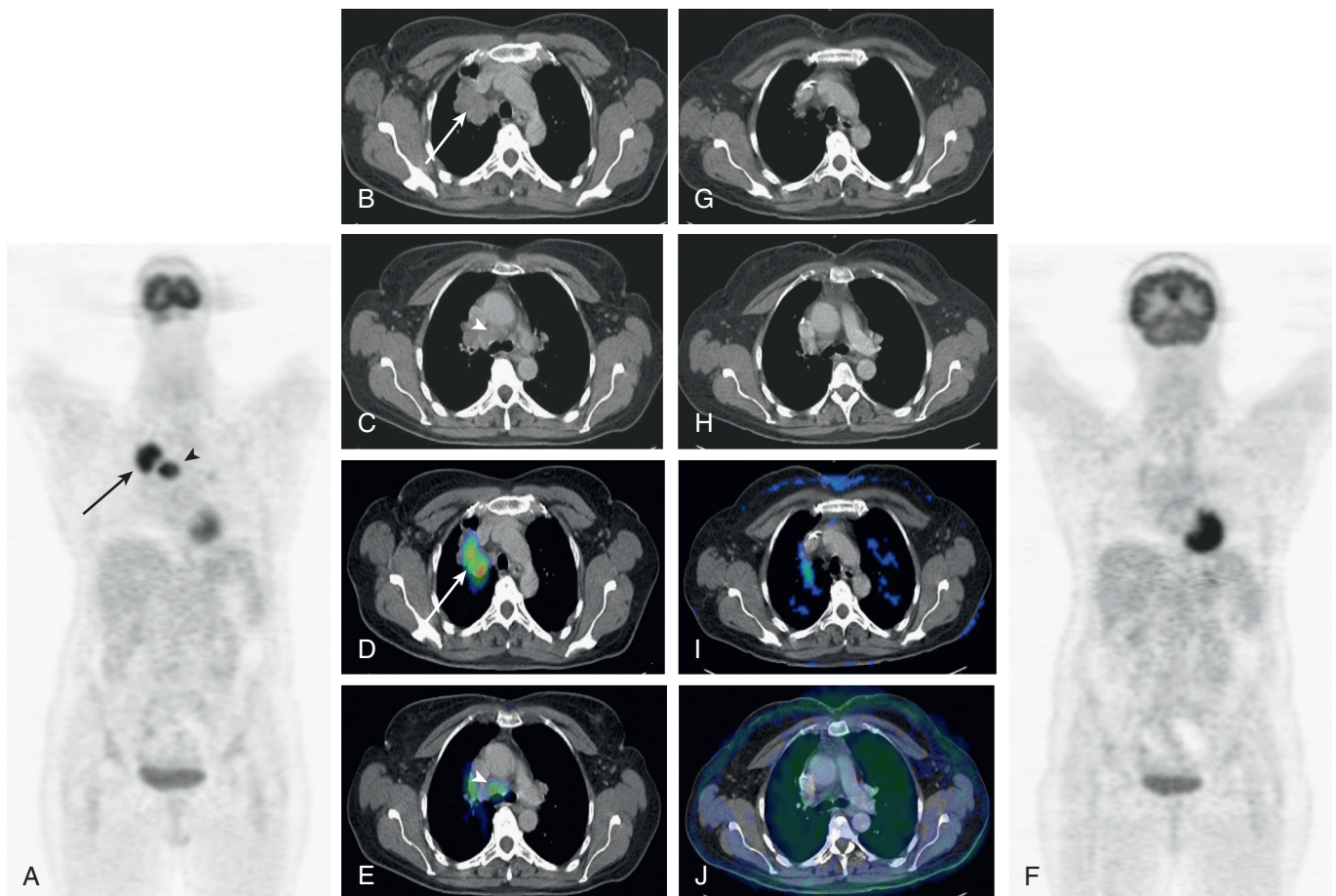


Figure 21-7 ^{18}F -FDG-PET/CT before and after induction chemotherapy. Patient with right upper lobe large cell carcinoma (arrow) with right hilar and right paratracheal adenopathy (arrowhead) (A, coronal PET image; B, C, CT scan; D, E, fusion images). After induction chemotherapy, a major decrease in the metabolic activity of the primary tumor and absence of FDG uptake in the mediastinum is noted (F–J). Surgical findings after induction chemotherapy indicated pT1N0.

regarding the value of pretreatment FDG uptake are too conflicting to be used in clinical practice.^{107,108} On the other hand, the assessment of response using a quantitative FDG uptake on PET at 3, 6, and 9 months after SABR for stage I NSCLC has been more promising. A systematic literature review suggests that changes on CT commonly seen following SABR are unlikely to be recurrence if the SUV_{max} is below 5 (i.e., a negative predictive value of 100%).¹⁰⁹ Further studies are needed, however, to validate these findings.

For *potentially resectable stage III NSCLC*, the evaluation of eligibility for resection after induction chemoradiotherapy is crucial, and restaging after induction therapy has been addressed in several studies (eTable 21-1). When mediastinal lymph nodes are restaged, integrated PET/CT has a sensitivity of up to 70% with a specificity of up to 90%. Mediastinal restaging with PET/CT thus reaches an accuracy level of some clinical value, but tissue confirmation is still mandatory to certify the real nodal status. New positive lesions, especially lymph nodes, need to be interpreted carefully because these new findings have a high false-positive rate.¹¹⁰ The findings on prediction of outcome in this setting are even more interesting. The classic prognostic parameters for surgery in these patients are obtained from the resected specimen(s) that demonstrate (1) downstaging of

mediastinal nodes and (2) the pathologic response in the primary tumor. These parameters are poorly predicted by the clinical or CT-graphic evolution during therapy. However, in prospective studies, both the residual FDG uptake in the primary tumor after induction and the change in FDG uptake when comparing preinduction and postinduction values had strong power to predict pathologic response and outcome after combined modality treatment (Fig. 21-7). In a recent meta-analysis, PET had a sensitivity of 83% and a specificity of 84% in the prediction of pathologic response.¹¹¹ With the advent of endoscopic baseline mediastinal staging to confirm N2/N3 disease, the postinduction assessment can be based on primary tumor response by serial PET and lymph node assessment by a mediastinoscopy after induction therapy. In one model the combination of lymph node involvement and primary tumor response on PET could discriminate “good prognosis” patients (5-year survival 62%) from “poor prognosis” patients (only 6%, hazard ratio 0.18).¹¹² In the setting of induction chemoradiotherapy, there was a separation in prognosis as well, with a 5-year survival of 70% in the group with good PET response and 22% in the group with poor PET response.¹¹³

For *nonresectable stages I–III NSCLC* treated with radical radiotherapy, the data are in line with the findings in

eTable 21-1 Results of PET and Integrated PET/CT in Restaging after Induction Treatment for Locally Advanced NSCLC

Study	N	Stage	Chemotherapy (RT%)*	Imaging	Sensitivity (%)	Specificity (%)
Vansteenkiste et al ¹⁴³ 2001	31	IIIA-N2	0	PET and CT	71	88
Akhurst et al ¹⁴⁴ 2002	56	I–III	29	PET and CT	67	61
Ryu et al ¹⁴⁵ 2002	26	III	100	PET and CT	58	93
Cerfolio et al ¹⁴⁶ 2003	34	IB–IIIA	21	PET and CT	71	77
Hellwig et al ¹⁴⁷ 2004	37	III	70	PET and CT	50	88
Port et al ¹⁴⁸ 2004	25	I–IIIA	0	PET and CT	20	71
Hoekstra et al ¹⁴⁹ 2005	25	IIIA-N2	0	PET and CT	50	71
Yamamoto et al ¹⁵⁰ 2006	26	III	100	PET and CT	88	89
Eschman et al ¹⁵¹ 2007	70	III	100	PET and CT	77	68
Cerfolio et al ¹⁵² 2006	93	IIIA-N2	100	Integrated PET/CT	62	88
Pottgen et al ¹⁵³ 2006	37	III	100	Integrated PET/CT	73	89
De Leyn et al ¹⁵⁴ 2006	30	IIIA-N2	0	Integrated PET/CT	77	92

*All patients received induction chemotherapy; the RT% indicates what percentage received radiotherapy in combination. CT, Computed tomography; N, number of patients; NSCLC, non-small cell lung cancer; PET, positron emission tomography; RT, radiotherapy.

operable disease. Indeed, early PET responses in the third week of radiotherapy correlated with prognosis after radiotherapy alone, or sequential or concurrent chemoradiotherapy: 2-year survival was 92% for responders versus 33% for nonresponders.^{114,115} PET obtained after completion of chemoradiotherapy also could discriminate prognosis, with complete metabolic responders having a median of 31 months versus 11 months for incomplete metabolic responders, and outperformed CT response, stage, or pretreatment performance.^{116,117} In patients with locally advanced disease treated with concurrent chemoradiotherapy, after completion of treatment, PET has an accuracy of about 90% for predicting tumor response.¹¹⁸ PET has also been used to predict tumor control during radiation treatment, with a sensitivity of 100% and specificity of 63%, and a tumor control detection probability of 80%.¹¹⁹ One study suggested that, compared to CT, PET better identified relapse after definitive chemoradiotherapy and that patients evaluated by PET had a better outcome when referred to salvage surgery, with a median overall survival of 12 months in patients operated for relapse on CT versus 43 months for patients operated for relapse on PET.¹²⁰

In patients with *stage IV* NSCLC, effective systemic chemotherapy causes a rapid decrease in FDG uptake on PET during the first cycle, and therefore PET could identify chemotherapy responders and nonresponders at an early treatment stage.^{121,122} Targeted therapies are advancing at a rapid pace in the treatment of NSCLC, and conceptually PET might be of great interest in the assessment of response to these therapies. Two independent studies have shown that early PET can predict progression-free and overall survival in patients treated with erlotinib, even in the absence of a CT response.^{123,124}

FOLLOW-UP

After therapy of NSCLC, early detection of recurrence is important because salvage therapies can be useful, especially in asymptomatic locoregional recurrences.

Selective use of PET can be recommended for the evaluation of a suspected local recurrence on conventional radiologic imaging in lung cancer patients previously treated for early-stage NSCLC with curative intent. Two prospective studies compared the differential diagnostic performance of PET and CT in the early detection of local recurrence^{125,126}; in both, the accuracy of PET was better than that of CT (93% versus 82%; 96% versus 84%). Several prospective series in patients with a residual thoracic abnormality after treatment addressed the value of PET to differentiate between local recurrence and residual nonspecific post-treatment changes.¹²⁵⁻¹³² An SUV cutoff of 2.5, differentiating benign from malignant lesions, as suggested for newly diagnosed lung lesions, had a sensitivity ranging from 97% to 100% and a specificity ranging from 62% to 100%.

Surveillance by PET/CT every 6 to 12 months after a treatment with curative intent (surgery or SABR) for early-stage NSCLC cannot be recommended. Despite several reports of a better sensitivity to detect disease recurrence on PET/CT in asymptomatic patients compared to chest CT scan alone, no survival benefit has been demonstrated in the postoperative follow-up setting. Moreover, false-positive findings are not infrequent after SABR.^{109,133-135}

NEW TRACERS

PET tracers have been developed for a whole range of biologic and pathophysiologic processes. One area of great interest has been the imaging of proliferation, a key hallmark of cancer cells. ¹⁸F-fluorodeoxythymidine (FLT) is a thymidine analogue labeled with the positron emitter fluorine-18.¹³⁶ Upon cell entry, FLT is phosphorylated by thymidine kinase type 1 but is not further metabolized and thus also not incorporated into newly synthesized DNA. Thymidine kinase type 1 is a major enzyme within the DNA salvage pathway, and its activity is strongly correlated with cellular proliferation, because it is upregulated before and during DNA synthesis. A recent meta-analysis provides strong evidence for the relation between FLT uptake and KI-67 score in a range of tumor types, including lung cancer.¹³⁷ FLT uptake in malignant tumors is lower than FDG uptake, resulting in a decreased sensitivity for diagnosis and staging.¹³⁸ For the assessment of response to anti-epidermal growth factor receptor therapy, initial results with FLT were encouraging because changes in FLT uptake early in the course of therapy predicted progression-free survival.¹³⁹ More recent studies comparing FLT and FDG in a similar therapeutic setting confirmed the potential of FLT, but nonetheless FDG was shown to be a better predictor of response.^{123,124}

Hypoxia within lung tumors can be depicted using tracers that accumulate in tissue having low oxygen tension, such as ¹⁸F-fluoromisonidazole and ⁶⁴Cu-diacetyl-bis(N4-methylthiosemicarbazone).¹⁴⁰ Both tracers undergo reduction under hypoxic conditions and subsequently bind to intracellular macromolecules. Because tumor hypoxia is an important component of resistance to radiotherapy, noninvasive measurement of hypoxic areas could direct increased radiation doses to hypoxic areas and perhaps improve locoregional tumor control.

Another interesting potential avenue is the use of radiolabeled drugs to determine biodistribution and tumor targeting.¹⁴¹ Tyrosine kinase inhibitors and chemotherapeutic agents can be labeled using carbon-11 and fluorine-18, resulting in ¹¹C-gefitinib, ¹⁸F-gefitinib, ¹¹C-erlotinib, and ¹¹C-docetaxel. ¹¹C-docetaxel has been studied in lung cancer patients, and the uptake of the tracer was predictive of response measured on subsequent CT.¹⁴² Monoclonal antibodies such as bevacizumab can also be labeled using zirconium-89, which has a half-life of 78 hours with kinetics matching those of monoclonal antibodies.

Key Points

- PET improves the accuracy of diagnosis of solitary pulmonary nodules, because their FDG-uptake pattern improves the comprehensive assessment of the probability of malignancy when combined with demographic, clinical, and CT characteristics.
- Combination PET/CT more accurately stages lung cancer than conventional imaging alone and leads to better treatment choices in a substantial proportion of patients with *non-small cell lung cancer* (NSCLC).

- The uptake of FDG may correlate with the aggressiveness and prognosis of NSCLC.
- The use of PET for diagnosis or staging is cost-effective in NSCLC patients with a potential for cure.
- PET has been shown to be most useful in guiding decisions about combined modality treatment in patients with locally advanced NSCLC.
- PET/CT is not indicated for standard patient follow-up after curative treatment for malignancy but is useful to characterize abnormal findings detected on conventional imaging.
- PET appears to be as useful in the assessment of small cell lung cancer and mesothelioma as in NSCLC but is supported by less abundant data; PET using special neuroendocrine tracers is helpful in patients with bronchial carcinoid tumors.
- Current research with PET is focusing on PET/magnetic resonance applications and on new tracers for molecular imaging and response prediction, which may guide targeted therapies and individualized radiotherapy.

Complete reference list available at ExpertConsult.

Key Readings

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INTRODUCTION AND HISTORICAL BACKGROUND**INDICATIONS****PROCEDURE**

Sedation and Anesthesia

Local Anesthesia

MONITORING**BASIC DIAGNOSTIC BRONCHOSCOPY**

Bronchoalveolar Lavage

Bronchial Washings

Bronchial Brushings

Endobronchial Biopsy

Transbronchial Biopsy

Transbronchial Needle Aspiration

Endobronchial Ultrasonography

ADVANCED DIAGNOSTIC BRONCHOSCOPY

Ultrathin Bronchoscopy

Confocal Bronchoscopy

Electromagnetic and Virtual Bronchoscopic Navigation

Autofluorescence Bronchoscopy

Narrow-Band Imaging

INTRODUCTION AND HISTORICAL BACKGROUND

Flexible bronchoscopy (FB) is one of the prime examples of an area of pulmonary medicine transformed by technological advances. Today it has become one of the most frequently performed invasive procedures in pulmonary medicine. The use of bronchoscopy for *diagnosis* is covered in this chapter, and the use of bronchoscopy for *therapy* is covered in Chapter 23. Diagnostic bronchoscopy can also be divided into *basic* procedures, those available to most facilities and with significant evidence to support their use, and *advanced* procedures, those available only in some centers and still undergoing investigation to determine their most appropriate uses.

Gustav Killian performed the first bronchoscopy in 1897 to extract a piece of a pork bone from the right main bronchus.¹ From that meager beginning, the technology in bronchoscopy has advanced exponentially. In 1966 the flexible bronchoscope was introduced into clinical practice by Shigeto Ikeda.² Currently this instrument is one of the most important tools for diagnosis and treatment of pulmonary diseases.

Bronchoscopy can be easily performed in an outpatient setting, under moderate sedation and local anesthesia. Compared with FB, rigid bronchoscopy is now primarily used for selective indications such as massive hemoptysis and therapeutics (see Chapter 23).³⁻⁶

INDICATIONS

The indications for diagnostic FB are broad and growing (Table 22-1). Nonetheless, certain conditions are not considered indications for FB. For example, FB is not indicated to evaluate patients with cough unless the cough fails to respond to conventional treatment or if there is a change in its character. Similarly, bronchoscopy is not indicated to evaluate patients with isolated pleural effusion or atelectasis,⁷⁻⁹ and its use to remove secretions during acute exacerbations of chronic obstructive lung disease is also considered inappropriate.¹⁰ FB also has little role in finding synchro-

nous lesions in patients undergoing lung resection of a solitary pulmonary nodule suspected to be primary bronchogenic carcinoma.¹¹ Absolute and relative contraindications to performing FB are presented in Table 22-2.

PROCEDURE

FB is usually performed via the oral or the nasal route.¹² Either route provides excellent access to the lower airways. By either route, attention should also be given to the upper airway. In particular, bronchoscopy performed for the evaluation of hemoptysis or wheezing should include a careful evaluation of the upper airway, including the nasopharynx and oropharynx and vocal cords.

SEDATION AND ANESTHESIA

The need for sedation during FB remains a matter of some debate in the literature.¹³⁻¹⁵ The purpose of sedation is to improve patient comfort and add to the ease of the procedure for the bronchoscopist.^{16,17} Although bronchoscopy can be carried out without sedation,^{18,19} most are performed under moderate sedation.²⁰⁻²³

Intravenous preparations of various sedatives such as diazepam, midazolam, lorazepam, morphine sulfate, fentanyl, and hydrocodone have been used either alone or in combination based on the bronchoscopist's preference and the availability of the drug.²⁴⁻²⁹ Fentanyl has a greater analgesic potency than morphine.²⁵ Hydrocodone has a greater antitussive property than codeine but less than that of morphine.³⁰ Due to its rapid onset and anxiolytic and amnestic properties, midazolam is one of the most commonly used sedatives; sedation with midazolam in FB improves the patient's comfort and decreases complaints, without causing significant hemodynamic compromise. It should be offered to the patient on a routine basis.^{31,32}

The combination of a benzodiazepine and an opioid has been shown to be safe and synergistic for the purposes of sedation during FB.^{28,33} Because the combination of benzodiazepines and opiates may cause hypoventilation, particularly in patients with preexisting respiratory failure, patients should be appropriately monitored.³⁴ The combination of

Table 22-1 Indications for Diagnostic Flexible Bronchoscopy (Adult)

Hemoptysis
Wheeze and stridor: suspected stricture, upper airway obstruction
Lung opacities of unknown cause
■ Suspected pulmonary infections not responding to conventional treatment
(a) Localized
(b) Diffuse
■ Lung opacities in an immunocompromised host
■ Recurrent or unresolved pneumonia
■ Cavitory lesion
■ Interstitial opacities
■ New pulmonary nodule
Unexplained lung collapse
Suspected or known bronchogenic carcinoma
■ Positive or suspicious sputum cytologic findings
■ Staging
■ Follow-up after endobronchial treatments
Mediastinal and hilar lymphadenopathy and masses
Lung transplantation
■ Inspect airway anastomosis
■ Rejection surveillance
Esophageal cancer evaluation
Endotracheal intubation
■ Confirm tube position
■ Evaluate for tube-related injury
Evaluation for foreign body aspiration
Chest trauma
■ Rule out rupture of central airways
■ Examine for aspirated contents
Evaluation following burns or chemical injury to the airways
Unexplained superior vena cava syndrome
Unexplained vocal cord paralysis or hoarseness
Suspected fistulas
■ Bronchopleural
■ Tracheoesophageal and bronchoesophageal
■ Tracheoarterial or bronchoarterial
■ Iatrogenic (postsurgical)

Table 22-2 Contraindications for Flexible Bronchoscopy**ABSOLUTE**

Uncorrectable hypoxemia
 Lack of patient cooperation
 Lack of skilled personnel
 Lack of appropriate equipment and facilities
 Unstable angina
 Uncontrolled arrhythmias

RELATIVE

Unexplained or severe hypercarbia
 Uncontrolled asthma
 Uncorrectable coagulopathy
 Unstable cervical spine
 Need for a large tissue specimen for diagnosis
 Debility, advanced age, malnutrition

hydrocodone and midazolam reduces cough during FB without causing significant desaturation and improves the patient's tolerance for the procedure.^{28,33}

Dexmedetomidine (Precedex, Dexdomitor) also has favorable properties of sedation, sympatholysis, analgesia, and a low risk for apnea. These properties suggest that dexmedetomidine may be useful in procedural sedation. However,

it has been shown that dexmedetomidine as a sole agent is unable to provide adequate sedation for awake diagnostic FB without the need for rescue sedation in a large proportion of patients.³⁵

Dextromethorphan can also be given orally 90 minutes before the procedure to improve cough suppression during the procedure.³⁶

Interestingly, according to some surveys, 16% to 21% of physicians use deep sedation or general anesthesia for FB.^{20,22} Use of propofol alone is as effective and safe as combined sedation in patients undergoing FB under conscious sedation, thus representing an appealing option if timely discharge is a priority.³⁷ Deep sedation with propofol for bronchoscopy has gained popularity in recent years, although concern has been raised regarding its potential ability to induce severe respiratory depression. In one prospective study the use of small boluses of propofol at short intervals with monitoring of transcutaneous carbon dioxide level was found to be safe; the authors concluded that propofol used in this manner does not cause excessive respiratory depression and represents an excellent alternative to traditional sedation agents.³⁸ In another prospective study the combination of propofol and hydrocodone was safe and better for cough suppression than propofol alone in FB.³⁹

Fospropofol disodium is a water-soluble prodrug of propofol. A subset analysis was undertaken among elderly patients (≥ 65 years) undergoing FB; fospropofol provided safe and effective sedation, rapid time to fully alert status, and high satisfaction, which were comparable with outcomes in younger patients.⁴⁰

Patients with *human immunodeficiency virus* (HIV) infection, recipients of stem cell transplantation, lung transplant recipients for cystic fibrosis, and drug users usually require higher doses of sedatives than other patients.³¹⁻⁴³ Additionally, because protease inhibitors used in patients with HIV infection have been shown to extend the half-life of benzodiazepines significantly, many institutions in the United States encourage the use of deep sedation in these patients instead.

LOCAL ANESTHESIA

Although nerve blocks can be used to provide excellent analgesia to the airway, physicians generally rely on topical administration of local anesthetic agents. Lidocaine is the most commonly used drug for providing topical anesthesia.⁴⁴ It offers a relatively wide margin of safety with a rapid onset and sufficient duration of action to allow completion of most bronchoscopic procedures. The gel preparation of lidocaine is preferred over the spray for nasal anesthesia.⁴⁵⁻⁴⁷ Given that sensory anesthesia is not dependent on the concentration of lidocaine, 1% is preferred because larger volumes can be instilled to cover a greater surface area of the mucosa before toxic dosages are reached.^{48,49} The oropharynx can be anesthetized with 2% to 4% lidocaine applied as a spray, nebulized solution, or gargles.

The vocal cords as well as the endobronchial tree are anesthetized by direct instillation of lidocaine via the working channel of the bronchoscope. The total dose of lidocaine should be limited to 8.2 mg/kg in adults, with extra caution in older adults or those with liver, renal, or cardiac impairments.²⁴

Anticholinergic agents such as atropine and glycopyrrolate have been commonly used as premedication for FB^{50,51} with the aim to reduce the bronchial secretions and suppress vagal overactivity. Several studies have shown that anticholinergics offer little advantage as premedications, and their use should be abandoned.⁵²⁻⁵⁴

MONITORING

To ensure adequate oxygenation (oxygen saturation of >92%) and hemodynamic stability, pulse oximetry, heart rate, and blood pressure are monitored throughout the procedure. There should be intravenous access and equipment for resuscitation. Supplemental oxygen should be available. At many institutions, continuous end-tidal carbon dioxide monitoring is used to assess ventilation. All FB procedures are performed observing universal precautions. Following each procedure, the instrument is thoroughly disinfected or sterilized according to recently published consensus statements.^{55,56,56a}

BASIC DIAGNOSTIC BRONCHOSCOPY

The standard procedure for FB involves a thorough examination of the entire tracheobronchial tree in a systematic fashion, from the upper airway and vocal cords to the trachea and carina, major bronchi, and the segmental bronchi in each of the five lung lobes. A thorough understanding of normal features can allow detection of abnormalities in anatomy (e.g., missing or duplication of bronchi), shape (e.g., narrowing or distortion), changes in the anatomy with breathing (e.g., collapse), or endobronchial mucosa (e.g., induration, friability, erythema, lesions). A bronchoscopy of a patient with a relatively normal tracheobronchial tree is shown in [Video 22-1](#).

Examination of the upper airway can be instructive. The vocal cords may be involved with infections ([Fig. 22-1](#)) or malignancy; the cords may be paralyzed as a result of interruption of the recurrent laryngeal nerve or erythematous or edematous due to gastroesophageal reflux. The trachea may be abnormal owing to either congenital or acquired

conditions ([Fig. 22-2A and B](#)). The endobronchial mucosa exhibits characteristic changes due to infiltrative or systemic conditions (see [Fig. 22-2C and D](#)). Endobronchial lesions may be caused by a multitude of conditions, including inflammatory, malignant, or infectious disease, or by foreign bodies ([Fig. 22-3](#)). Attention should also be paid to the normal expiratory collapse of the central airway as well as to the presence of excessive dynamic airway collapse/tracheobronchomalacia.^{57,57a-e}

BRONCHOALVEOLAR LAVAGE

Bronchoalveolar lavage (BAL) has become an important clinical and investigational tool.^{58,59} It is a standard diagnostic procedure in all patients with diffuse lung abnormalities of unknown cause whether an infectious, noninfectious, immunologic, or malignant cause is suspected.^{60,61} BAL allows the recovery of both cellular and noncellular components of the epithelial (alveolar) lining fluid and epithelial surface of the lower respiratory tract. Components of the BAL fluid represent the inflammatory and immune status of the lower respiratory tract and the alveoli^{58,62} ([Fig. 22-4](#)). BAL, which samples the distal air spaces, differs significantly from a bronchial washing, which samples the large airways via aspiration of small amounts of instilled



Figure 22-1 Vocal cord candidiasis in an immunocompromised host.

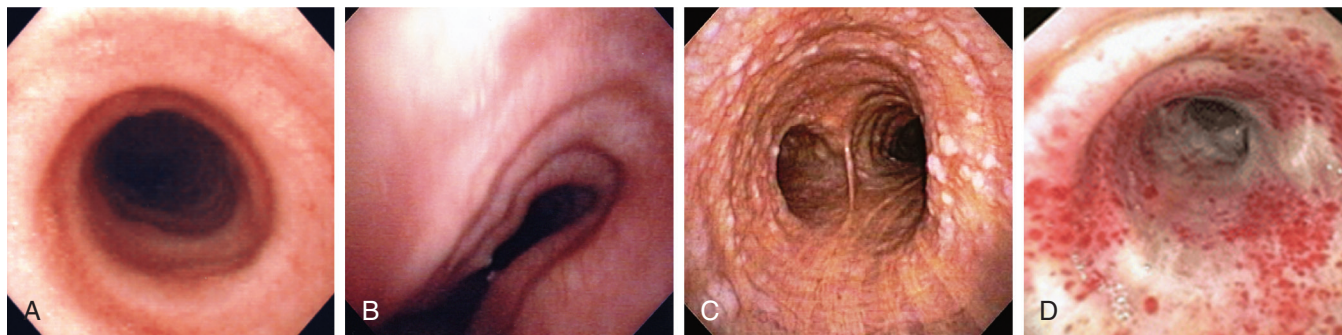


Figure 22-2 **A**, Complete tracheal ring, also called a “stovepipe trachea.” Note the absence of the posterior membrane. **B**, A “saber-sheath” trachea in a patient with emphysema. **C**, Diffuse “pebbly mural” appearance of endobronchial sarcoidosis. **D**, Endobronchial petechiae in a patient receiving clotidogrel. (A, Courtesy Dr. James Stoller.)

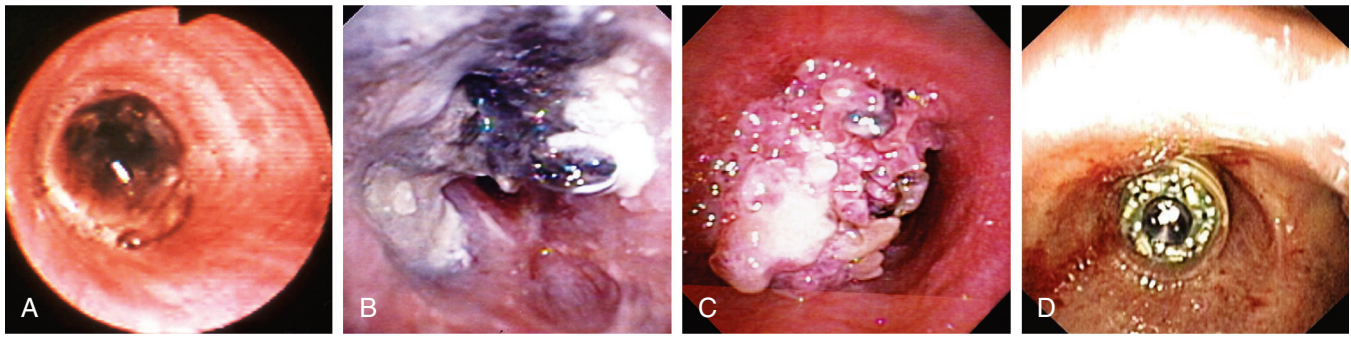


Figure 22-3 Endobronchial lesions. **A**, Metastatic melanoma involving the left main bronchus. Note the black pigmentation of the tumor. **B**, *Aspergillus niger* infection in a lung transplant recipient. The black pigment indicates the fungus and the white pigment indicates calcium oxalate crystals produced by the fungus. **C**, Recurrent respiratory papillomatosis involving the trachea. Note the typical mulberry appearance. **D**, A foreign body in the left main bronchus. The object is a camera used for capsule endoscopy that was aspirated into the lungs. (D, Courtesy Dr. Thomas Gildea.)

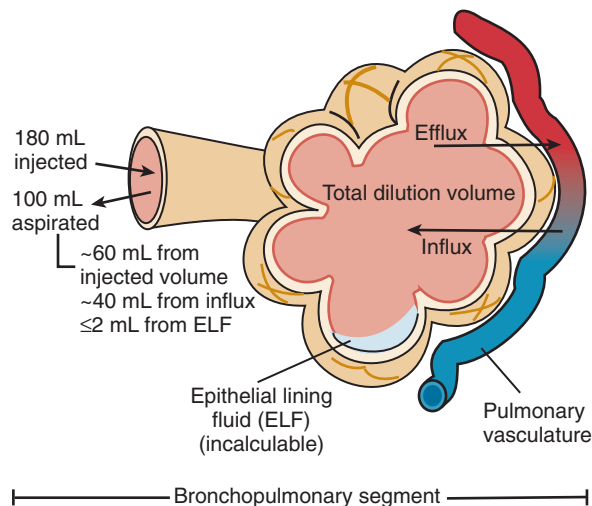


Figure 22-4 Schematic presentation of the constituents of the bronchoalveolar lavage fluid. (From Kuvuru MS, Dweik RA, Thomassen MJ: Role of bronchoscopy in asthma research. *Clin Chest Med* 20(1):153-189, 1999; modified, with permission, from Walters EH, Ward C, Xun Li: Bronchoalveolar lavage in asthma research. *Respirology* 1:233-245, 1996.)

saline.^{61,63,64} BAL should be considered a standard procedure in the evaluation of diffuse lung diseases, suspected infection, or malignancy, especially when the bleeding risk prohibits either bronchial brushing, *transbronchial biopsy* (TBB), or *transbronchial needle aspiration* (TBNA).

For diffuse opacities, any area can be chosen for BAL; however, in such cases, either the right middle lobe or the lingula is preferred because, in a supine patient, gravity assists the recovery of a maximal amount of BAL fluid return.^{59,60,65} In the case of localized disease, lavage should be performed in the area of focal radiographic abnormality,^{61,63,65} and for maximal recovery, the patient can be positioned appropriately to improve recovery from the desired segment. “Good wedge” position usually means that the bronchoscope is advanced as far as possible without losing the view of the distal lumen. In this optimal position, a slow, manual gentle aspiration, without allowing the airway walls to collapse, tends to maximize the lavage return.

BAL has significantly improved the diagnostic workup of lung diseases, whether diffuse or localized. In pulmonary alveolar proteinosis, it has both diagnostic and therapeutic value.^{60,66-69} In an international statement on the major

interstitial lung diseases, BAL is considered to be helpful in strengthening the diagnosis of sarcoidosis in the absence of a tissue diagnosis, by finding a lymphocytosis (>25%) and a CD4/CD8 ratio greater than 4.^{70,71} BAL may be a useful tool in the diagnosis of peripherally located primary lung cancer, with an overall diagnostic yield range of 33% to 69%, being exclusively diagnostic in 9% to 11% of cases.⁷²⁻⁷⁹ Numerous case reports confirm the ability of BAL to diagnose leukemia and lymphomatous pulmonary involvement as well as plasma cell dyscrasia.⁸⁰⁻⁸² Finding asbestos bodies in BAL fluid may correlate with occupational exposure, yet in itself, it is not proof of an asbestos-related disease.^{83,84} The presence of more than 25% eosinophils in the BAL fluid confirms the diagnosis of eosinophilic lung diseases, and the presence of more than 4% CD1⁺ Langerhans cells confirms a diagnosis of Langerhans cell histiocytosis, albeit with low sensitivity.⁸⁵ In chronic beryllium disease, lymphocytes from the BAL proliferate when stimulated in vitro with soluble beryllium salts, with a sensitivity and specificity approaching 100%; this lymphocyte test has become a valuable diagnostic tool for this condition and has replaced open-lung biopsy.^{86,87}

In patients with ventilator-associated pneumonia, a positive quantitative culture (>10⁴ colony-forming units (CFU)/mL) on BAL fluid may be clinically useful with a sensitivity of 22% to 93% and a specificity of 45% to 100%, depending upon the clinical status of the patient.⁸⁸⁻⁹⁵ BAL is also a useful tool in the diagnosis of pulmonary infections in immunocompromised patients, with the reported yield as high as 93%⁹⁶⁻¹⁰³ (Fig. 22-5). Thus, in certain conditions, BAL findings can be diagnostic and thereby avoid the need for either TBB or open-lung biopsy (Table 22-3). In other settings, although not diagnostic, BAL can be used as an adjunct to the diagnosis when interpreted in the context of the entire clinical picture.

While performing BAL in an immunocompromised host and if invasive *Aspergillus* infection is suspected, the fluid should be submitted for galactomannan cell wall antigen detection using an enzyme immunoassay. The sensitivity and specificity of elevated galactomannan levels in BAL fluid are of value in immunocompromised patients. According to a recent meta-analysis, the sensitivity, specificity, and accuracy are reported to be 79%, 86%, and 89%, respectively. It needs to be pointed out that concomitant use of certain antibiotics such as piperacillin-tazobactam,



Figure 22-5 Bronchoalveolar lavage specimen reveals a larva of *Strongyloides stercoralis*. (Courtesy Dr. Suhail Raoof.)

Table 22-3 Diseases in Which Bronchoalveolar Lavage Can Be Diagnostic

Opportunistic infections (<i>Pneumocystis jirovecii</i> , fungi)
Invasive aspergillosis (via galactomannan levels)
Pulmonary alveolar proteinosis
Alveolar hemorrhage syndrome
Malignant opacities (solid tumors, lymphoma, leukemia)
Eosinophilic lung disease
Chronic beryllium disease
Langerhans cell histiocytosis

amoxicillin, or amoxicillin-clavulanate and all fermentation products of *Penicillium* species may produce false-positive results. Besides, the test may also have cross reactivity with *Histoplasma capsulatum* cell wall antigen. Hence the results should be interpreted in the context of the total clinical picture and rechecked periodically.¹⁰⁴

The most common complications associated with BAL are fever, which can be seen in up to 30% of patients, and transient hypoxemia, which is readily handled with supplemental oxygen.

BRONCHIAL WASHINGS

Bronchial washings are obtained by advancing the bronchoscope into an airway, instilling 10 to 20 mL of sterile saline, and then quickly aspirating the instilled saline into a specimen trap. The utility of bronchial washings is largely for the diagnosis of airway diseases, including primary or metastatic lung carcinoma and fungal or mycobacterial infection. Of the various bronchoscopic procedures, bronchial washing is the easiest to perform but has the lowest yield (sensitivity, 27% to 90%),¹⁰⁵⁻¹¹⁰ with a higher yield for central lesions.^{108,111-113} Bronchial washings are an inexpensive adjunct and should be collected during a diagnostic bronchoscopy when appropriate because, even though by a small percentage, they can increase the overall diagnostic yield of the procedure.^{108,114,115}

BRONCHIAL BRUSHINGS

Bronchial brushings were analyzed for the first time in 1973 and showed highly suspicious cytologic findings in most cases with lung cancer.¹¹⁶ In general, bronchial

brushings provide diagnostic material in 72% (44% to 94%) of patients with central lung cancers and 45% of patients with peripheral lesions, when obtained under fluoroscopic guidance.¹¹⁷ When bronchial brushing is combined with *endobronchial biopsy* (EBB) of central lesions, the diagnostic yield of FB increases to between 79% and 96%.¹¹⁸ We usually perform brushing after obtaining all the other bronchoscopy specimens to avoid bleeding or cell distortion interfering with obtaining or interpreting subsequent samples. The diameter or the length of the brush has not been shown to affect the diagnostic yield from the bronchial brushing.

Protected Specimen Brush

Protected specimen brush was first described in 1979 by Wimberley and coworkers¹¹⁹ as a technique to establish an accurate diagnosis in patients with suspected pneumonia. Brushing specimens are collected using a special brush that is enclosed within a double catheter sheath. The catheter is closed off at its distal end by a wax plug, which can be easily dislodged before obtaining the specimen. The purpose of the catheter sheath and wax plug is to prevent contamination of the brush with oropharyngeal flora that remain inside the working channel of the bronchoscope.

In patients with ventilator-associated pneumonia, the sensitivity of protected specimen brush ranges from 58% to 86% and the specificity from 71% to 100%.^{120,121} For now, the procedure appears to have lost popularity against empiricism for the diagnosis of ventilator-associated pneumonia; however, when it is used, quantitative cultures with a cutoff value of greater than 10^3 CFU/mL should be obtained to optimize its accuracy (see also Chapter 34).

ENDOBONCHIAL BIOPSY

EBB is an essential and technically simple tool in the diagnosis of endobronchial neoplasms as well as for inflammatory conditions such as sarcoidosis and amyloidosis. When the forceps are open, they are advanced onto the target and closed, thereby gripping the target. The forceps are briskly pulled back, taking a sample of the endobronchial lesion 2 to 4 mm in diameter. The forceps and biopsy specimen are then pulled out through the working channel, and the tissue sample is collected in saline or fixative. EBB is used for lesions directly visualized during bronchoscopy. It provides histologic specimens, whereas bronchial washing provides only cytologic samples. The reported diagnostic yield of EBB is 80% with a range of 51% to 97% depending upon the patient population.^{105,106,117,122-124} The number of biopsy specimens required for optimal diagnostic yield varies according to the suspected diagnosis. Three biopsy specimens of an endobronchial lesion suspected to be bronchogenic carcinoma can provide a diagnostic yield of over 97%.¹²⁵ Biopsy of the surface of endobronchial tumors may be falsely negative if there is surface necrosis; in such circumstances, needle sampling deeper into the mass may be diagnostic.

TRANSBRONCHIAL BIOPSY

TBB is the technique by which a piece of lung parenchyma is obtained by using flexible forceps positioned distally via

FB. TBB specimens can be obtained blindly or with guidance by fluoroscopy, *computed tomography* (CT), or radial-probe endobronchial ultrasonography. In many instances TBB can obviate the need for an open-lung biopsy; however, certain diagnoses such as idiopathic pulmonary fibrosis generally require larger tissue samples than those that can be obtained bronchoscopically. TBB is diagnostically useful in 38% to 79% of patients (average sensitivity, 52%) depending upon the underlying disease.¹²⁶⁻¹³⁰ For example, in sarcoidosis, TBB has a diagnostic yield of 40% to 90%,^{131,132} although recent studies indicate that *endobronchial ultrasonography-guided TBNA* (EBUS-TBNA) of mediastinal/hilar nodes may have a greater diagnostic yield.¹³³ TBB has also been shown to be diagnostic in up to 10% to 40% of cases of Langerhans cell histiocytosis,¹³⁴ 88% to 97% in *Pneumocystis jirovecii* pneumonia,^{98,135} and 57% to 79% in lung infections caused by *Mycobacterium tuberculosis*.¹³⁶ In patients suspected of having pulmonary alveolar proteinosis, its diagnostic yield has been reported to be as high as 100% (Fig. 22-6).

The diagnostic yield of TBB increases with the number of biopsy specimens obtained.¹³⁷ Usually 6 to 10 biopsy specimens are obtained under fluoroscopic guidance. However, the use of fluoroscopy is not mandatory in patients with diffuse parenchymal disease, and biopsy specimens can be obtained by assessing the proximity to the pleura as guided by the patient's perception of chest pain. The yield of TBB for malignant peripheral lesions more than 2 cm in diameter was also reported to be 70% in a recent study, even without fluoroscopic guidance.¹³⁸ When performed in association with bronchial brushings and TBNA, TBB adds to the diagnostic yield of FB for peripheral lung cancers.^{112,117,139-144}

The success of lung transplantation cannot be imagined without the contributions from FB and especially TBB. In lung transplant recipients, TBB helps in diagnosing or ruling out acute cellular rejection. It also helps establish the diagnosis of antibody-mediated rejection as well as that of chronic rejection, albeit with lower yield. To date, however, there are no gold standard findings for diagnosing rejection in the lung transplant population.

Pneumothorax and hemorrhage are the most feared complications following TBB, with an incidence of up to 5%

of cases. Renal insufficiency (*blood urea nitrogen* [BUN] level > 30 mg/dL [10.7 mmol/L] and creatinine level of >3 mg/dL [265 μ mol/L]) and other coagulopathies are considered risk factors for bleeding following TBB.^{145,146} TBB can be safely performed while patients are receiving aspirin or non-steroidal anti-inflammatory drugs; however, clopidogrel bisulfate should be withheld for at least 5 to 7 days before the procedure.^{147,148}

TRANSBRONCHIAL NEEDLE ASPIRATION

TBNA is a sensitive, accurate, safe, and cost-effective technique in the diagnosis and staging of lung cancer,^{144,149-154} and it can also be applied for the diagnosis of nonmalignant diseases such as sarcoidosis¹⁵⁵⁻¹⁵⁹ (Video 22-2). Despite proven advantages, the practice of TBNA remains underutilized.¹⁶⁰⁻¹⁶² There are no absolute, specific contraindications for TBNA.

Diagnosis and staging of bronchogenic carcinoma, lymphoma, and sarcoidosis can be established using 21- or 22-gauge cytology needles.^{133,161,163,164} For the diagnosis of lung cancer, the reported sensitivity, specificity, and accuracy of TBNA are 60% to 90%, 98% to 100%, and 60% to 90%, respectively.¹⁶³⁻¹⁷⁰ For mediastinal staging, the overall sensitivity, specificity, and accuracy of TBNA are 50%, 96%, and 78%, respectively.¹¹⁷ Judicious use of TBNA can thus reduce the need for surgical staging. In the diagnosis of involvement of mediastinal or hilar lymph nodes by sarcoidosis or tuberculosis, TBNA can be useful as well.¹⁵⁵⁻¹⁵⁹ (Fig. 22-7). In cases with pulmonary nodules, TBNA increases the diagnostic yield of FB by 25%.¹³³ TBNA can also be safely performed in mechanically ventilated patients.¹⁶⁸

The procedure of TBNA is safe, with an overall major complication rate of approximately 0.26%. Complications include damage of the working channel of the bronchoscope, fever, bacteremia, and bleeding from the puncture site (Fig. 22-8).^{139,144,161} Use of CT, fluoroscopy, and ultrasonographic guidance has been shown to improve the yield of TBNA.^{171,172,172a-d}

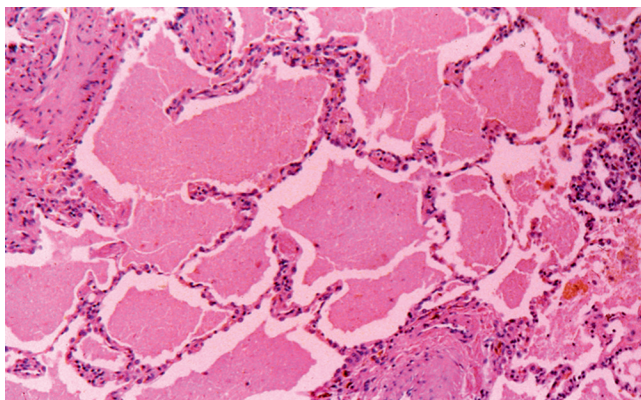


Figure 22-6 Transbronchial biopsy specimen confirms the diagnosis of pulmonary alveolar proteinosis. Note periodic acid-Schiff stain-positive material filling up the alveolar spaces.

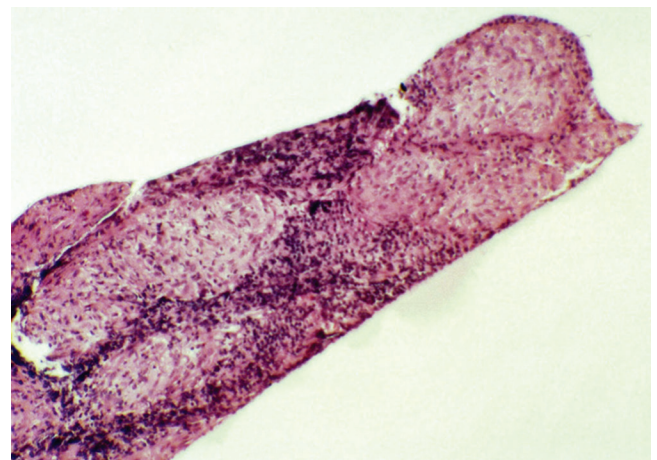


Figure 22-7 Transbronchial needle aspiration specimen obtained using a 19-gauge histology needle reveals noncaseating granulomas under high-power magnification ($\times 200$ original magnification) following hematoxylin and eosin stain.

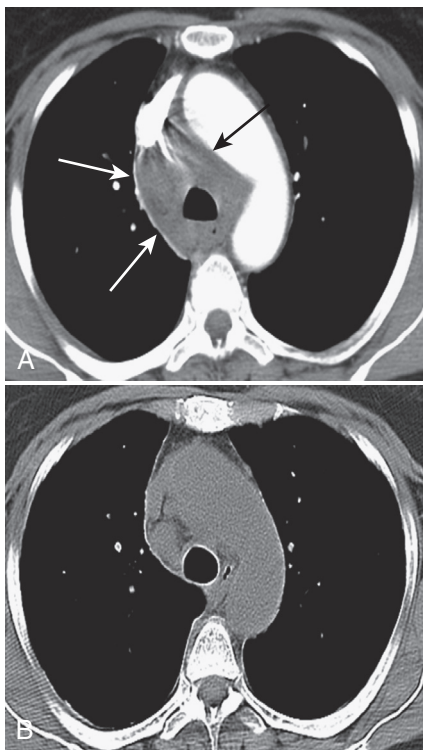


Figure 22-8 Complication of transbronchial needle aspiration. **A**, On day 1, mediastinal hemorrhage is noted (arrows). **B**, By day 6, the abnormality has resolved. (Courtesy Dr. Stefano Gasparini)

ENDOBONCHIAL ULTRASONOGRAPHY

Endobronchial ultrasonography (EBUS) is a bronchoscopic technique that uses ultrasound to visualize structures within and adjacent to the airway wall. There are two types of EBUS device: *radial-probe EBUS* (RP-EBUS) (Fig. 22-9A–C) and *convex-probe EBUS* (CP-EBUS) (Fig. 22-9D).^{173,174}

RP-EBUS is a technique in which a small ultrasound probe (1.4 to 2.8 mm diameter, 20 MHz) is introduced into the airways through the working channel of the FB to obtain ultrasonographic images of the peribronchial tissues. Because the RP-EBUS is placed in the endobronchial tree through the working channel of the conventional bronchoscope, it precludes real-time sampling. Using a fluid-filled balloon around the probe, the structure of the airway wall can be studied as, for example, to determine the depth of tumor invasion or to assess the structure of the bronchial wall in diseases such as tracheobronchomalacia. RP-EBUS provides a 360-degree view of the peribronchial tissue with high-resolution ultrasonographic views of the tissue layers in close contact with the probe or the fluid balloon (see Fig. 22-9C).

For obtaining samples using the RP-EBUS, the RP-EBUS is introduced via a guide sheath and is advanced into the peripheral pulmonary lesion under bronchoscopic guidance. Once the lesion is identified with ultrasonographic images, the probe is removed leaving the guide sheath in place; endobronchial accessories are inserted through the sheath to the peripheral lesion to obtain diagnostic specimens (see Fig. 22-9B and C). Using this technique, the diagnostic yield of FB for peripheral lung lesions less than 3 cm in size has been improved to nearly 75%.¹⁷⁵ During the early

years of EBUS application, the radial probe was also used to guide TBNA in the diagnosis of mediastinal disease and for the staging of non-small cell carcinoma. However, because real-time guidance is not possible with the RP-EBUS, in recent years, sampling of mediastinal pathologic conditions has been carried out with CP-EBUS bronchoscope (see Fig. 22-9D).

CP-EBUS is an endobronchial ultrasonographic technique that allows real-time imaging during sampling. A 7.5-MHz curved ultrasound transducer integrated into the distal tip of the bronchoscope delivers sound waves in a linear or longitudinal fashion encompassing a 55-degree area. The scope has an outward diameter of 6.9 mm and a 30-degree forward endoscopic oblique view.^{176,177} While the site is being imaged ultrasonographically, the TBNA specimen is obtained with a specially designed 21- to 22-gauge needle inserted through the working channel of the scope to obtain a cytologic examination (Video 22-3). The procedure is performed either under moderate sedation or general anesthesia.

The primary role of CP-EBUS is in the nodal staging of non-small cell lung cancer. When mediastinal/hilar lymph nodes less than 20 mm in short axis, especially in the 4L station, need to be sampled, CP-EBUS-TBNA should be the preferred sampling method. For lesions that are paraesophageal, in the inferior mediastinum, or involve the left adrenal gland, *endoscopic* ultrasound-guided fine-needle aspiration may be a more appropriate initial sampling method. The combined use of EBUS-TBNA with endoscopic ultrasound-guided fine-needle aspiration has been shown to reduce the need for surgical sampling and, by accurately staging unresectable patients, to avoid “unnecessary thoracotomies.”^{172,178-180} In various reports of its value in staging for lung cancer, EBUS-TBNA has excellent sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 95%, 100%, 100%, 90%, and 96%, respectively.^{179,181} Despite the cytologic nature of the EBUS-TBNA specimen, adequate tissue is easily obtained for molecular studies and genetic mutation analysis for personalized treatment for unresectable adenocarcinoma of the lung.¹⁸² Compared to that for conventional FB, the procedure for EBUS-TBNA takes longer and requires additional training. EBUS-TBNA is more expensive than conventional TBNA but could reduce expenses by limiting the number of more costly surgical procedures (Table 22-4). In the future EBUS-TBNA may have applications in the diagnosis of airway as well as pulmonary vascular disease.¹⁸³

Compared to mediastinoscopy, EBUS-TBNA was as effective in determining the pathologic lymph node state in prospective studies involving patients with potentially resectable lung cancer.¹⁸⁴ The specificity and positive predictive value for both techniques was 100%, whereas the sensitivity, negative predictive value, and diagnostic accuracy were 81%, 91%, and 93%, respectively, for EBUS-TBNA and 79%, 90%, and 93%, respectively, for mediastinoscopy. These studies suggest that, when performed under general anesthesia, with rapid on-site cytologic examination, and using different needles for each lymph node station, EBUS-TBNA can replace mediastinoscopy for lymph node staging.¹⁸⁴

To determine whether an endobronchial lesion is invasive or resectable, we recommend use of RP-EBUS^{172,185,186} with a balloon sheath catheter. For sampling endobronchial

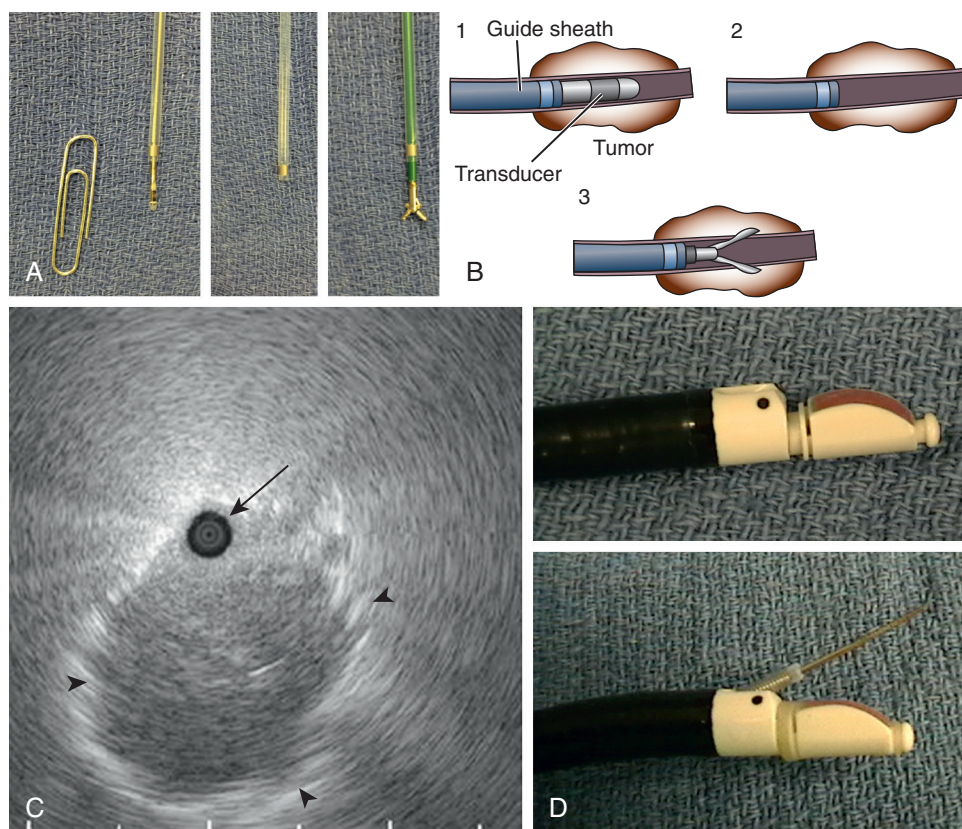


Figure 22-9 Endobronchial ultrasonography (EBUS) using radial probe (RP) or convex probe (CP). **A,** On the *left*, a radial probe is shown extending through a guide sheath. A paper clip is shown for scale. In the *middle* image, the sheath is shown with the probe removed. In the image on the *right*, a forceps is now extended through the guide sheath. **B,** Schematic representation of the technique of sampling a peripheral tumor using RP-EBUS through a guide sheath. Within the guide sheath, the probe is advanced to obtain ultrasonic images and position the guide sheath within the tumor (1); the probe is then withdrawn (2); the forceps is then advanced to the site of the tumor for sampling (3). **C,** Peripheral lung lesion through the eyes of the RP-EBUS. The lesion is indicated by a paucity of the ultrasonic pattern (arrowheads) shown below the dark bronchus (arrow). The “snowstorm” pattern above the bronchus is seen with normal lung parenchyma. **D,** Distal end of CP-EBUS bronchoscope before and after the sampling needle is extended.

Table 22-4 Endobronchial Ultrasonography

Advantages	Disadvantages
Outpatient procedure using local anesthesia and conscious sedation. Sampling of the high mediastinal, paratracheal, and subcarinal lymph nodes possible, similar to mediastinoscopy. Also allows sampling of hilar lymph nodes. High diagnostic yield. More invasive diagnostic procedures (e.g., mediastinoscopy) are frequently rendered unnecessary. Complications are uncommon, while sampling is performed in real time. Real-time imaging permits the sampling of lymph nodes that are smaller than 10 mm in short axis and/or near major blood vessels.	Cannot image or sample para-aortic and lower paroesophageal lymph nodes. Technically challenging. Not widely available. Only small (i.e., 21- and 22-gauge) needles can be used for EBUS-guided transbronchial needle aspiration. Benign condition may require histologic specimen.

EBUS, endobronchial ultrasonography.

lesions, EBUS-TBNA is seldom required, and EBB and conventional TBNA should be performed instead. To sample a peripheral pulmonary nodule, we suggest that RP-EBUS-guided TBB should be the first sampling procedure. RP-EBUS-guided TBB of peripheral pulmonary nodules detects malignant disease with a sensitivity and specificity of 73% and 100%, respectively.¹⁸⁷ The diagnostic yield of RP-EBUS-guided TBB is also higher than that of conventional TBB.^{172,180,188}

ADVANCED DIAGNOSTIC BRONCHOSCOPY

The following techniques are advancing the field of bronchoscopy using new technology either to improve imaging or to improve navigation to peripheral lesions. Their specific applications and benefit are still being determined, but they hold promise for extending the range of bronchoscopy for diagnosis of central or peripheral lesions.

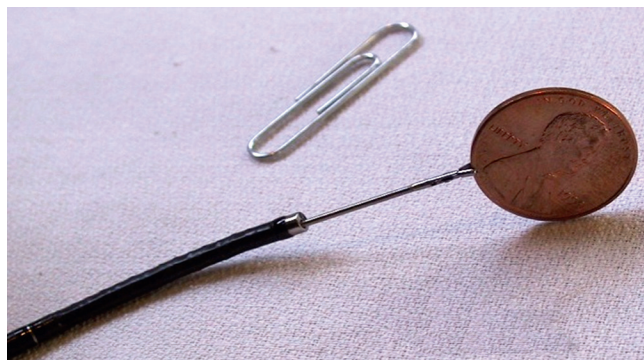


Figure 22-10 Ultrathin bronchoscope with a flexible forceps inserted through the working channel. (Courtesy Dr. Rex Yung.)

ULTRATHIN BRONCHOSCOPY

The ultrathin bronchoscope currently being studied has an outer diameter of 2.8 mm and an inner channel diameter of 1.2 mm and is made up mainly of fiberoptic bundles (Fig. 22-10). This device has been developed to overcome the low diagnostic yield of FB for lesions less than 20 mm in diameter.¹⁸⁹⁻¹⁹² Complexities of the distal airway anatomy require fluoroscopic or CT guidance to maneuver the scope to peripheral lesions.¹⁹³ These bronchoscopes also can be used with ease in mechanically ventilated patients with small endotracheal tubes. Ultrathin bronchoscopes help in evaluating the nature and the extent of upper airway obstruction where there is a risk for completely compromising the airways with standard bronchoscopes.¹⁹² An ultrathin bronchoscope is also useful for defining the distal extent of an endobronchial tumor when it is causing significant airway obstruction.¹⁹⁴

CONFOCAL BRONCHOSCOPY

Fiberoptic confocal fluorescence microscopy is a new technique that produces microscopic imaging of a living tissue via a 1-mm fiberoptic probe that can be introduced through the working channel of the conventional bronchoscope. Confocal endomicroscopy is a feasible method for analyzing human airway wall architecture and endobronchial abnormalities in histologic detail in vivo. In a recent study, bronchial fiberoptic confocal fluorescence microscopy was performed at 488-nm excitation wavelength on two bronchial specimens ex vivo and in 29 individuals at high risk for lung cancer in vivo; the alterations in fluorescent signal appeared to originate from the elastin component of the basement membrane zone.¹⁹⁵ Alterations of the autofluorescence microstructure were observed in 19 of 22 metaplastic or dysplastic samples, 5 of 5 carcinomas in situ, and 2 of 2 invasive lesions, representing a minimally invasive method of studying specific basement membrane alterations associated with premalignant bronchial lesions in vivo. In the future the technique may be used to study bronchial wall remodeling in nonmalignant chronic bronchial diseases.

ELECTROMAGNETIC AND VIRTUAL BRONCHOSCOPIC NAVIGATION

Electromagnetic navigation (EMN) and virtual bronchoscopic navigation can be used to guide the bronchoscopist to

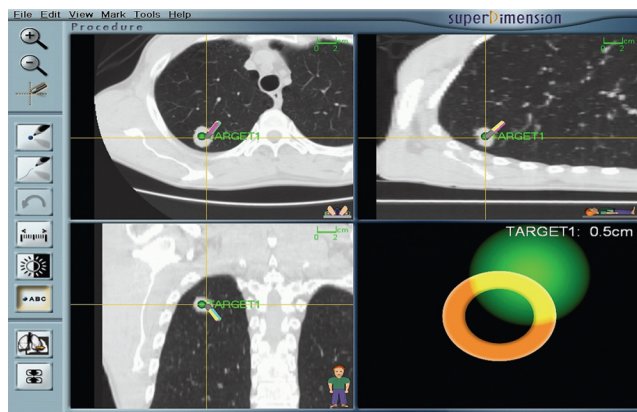


Figure 22-11 Electromagnetic navigation monitor. A pulmonary nodule is depicted in three different views. Right lower quadrant image exhibits the position of the microsensor (orange ring) in relation to the virtual pulmonary nodule (green circle).

lesions that cannot be visualized in the airways, because they are either distal or paratracheal. EMN creates an electromagnetic field around the chest of a patient undergoing FB, superimposes the field upon previously acquired three-dimensional CT images, and determines the position of a locatable guide containing sensors within the endobronchial tree.¹⁹⁶ Once steered into position, the guide is withdrawn, and biopsy tools are advanced through the guide sheath to obtain biopsy specimens at the site. In principle, the navigation system is similar to the global positioning system used in automobiles and airplanes. Virtual bronchoscopic navigation, on the other hand, creates a virtual bronchoscopic map from existing CT data and then suggests the best path to the target lesion.

EMN may improve the otherwise limited diagnostic yield of FB for peripheral lung lesions and solitary pulmonary nodules.¹⁶⁸ Recent studies have shown that EMN increases this yield to the range of 63% to 90%.¹⁹⁷⁻²⁰⁷ EMN and virtual bronchoscopic navigation are well tolerated and have proved to be both safe and useful in localizing small or fluoroscopically invisible lung lesions with a sufficient level of accuracy (Fig. 22-11).^{208,209} The ultimate value of these navigational aids and whether their benefits will justify their cost is not known.

AUTOFLUORESCENCE BRONCHOSCOPY

In the treatment of lung cancer, the best outcome is achieved if the lesion is discovered in the intraepithelial stage. However, intraepithelial neoplastic lesions are difficult to localize by conventional *white-light bronchoscopy* (WLB). *Autofluorescence bronchoscopy* (AFB) has been in use since 1988 as an aid to the diagnosis of bronchial precancerous lesions and early lung cancers.²¹⁰⁻²¹⁵ In this method, airways are illuminated by blue light. Fluorescence emitted from the mucosal surface is partially quenched in areas of dysplasia, a result that can be enhanced by video signal processing. Normal areas are usually exhibited in a green color, whereas the suspicious areas appear with reddish to brown discoloration (Fig. 22-12). Lesions detected by AFB include squamous cell cancer and the “pre-malignant” dysplasias of the squamous epithelium.²¹⁶ AFB can also capture the

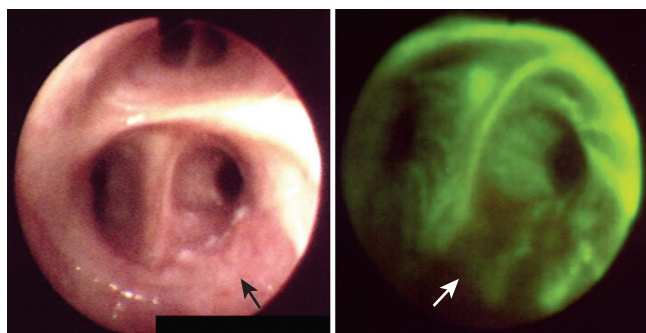


Figure 22-12 Autofluorescence bronchoscopy. White-light image (left) versus autofluorescent image (right). A lesion that is poorly seen using white light (black arrow, left) becomes more evident under fluorescent light (white arrow, right). The brownish discoloration involving the posterior airway wall depicts an area suspicious for early lung cancer.

endobronchial extent of tumor; thus it can be helpful for deciding the line of resection preoperatively or planning endobronchial therapies.

Discrimination between cancerous or precancerous lesions and inflammation is not possible by endoscopic images alone, and a histologic diagnosis is still necessary.²¹⁰ In a multicenter study the combination of WLB and AFB had greater sensitivity (82.3%) for detecting dysplasia than WLB (57.9%) alone, although the benefit for detecting carcinoma *in situ* was not significant.²¹³ In various studies, although the specificity of AFB together with WLB is lower than that of WLB alone, AFB plus WLB seems to improve the sensitivity for detection of intraepithelial neoplasia. However, both techniques are similar for detecting invasive lung cancer.^{217,218}

The low specificity of AFB, the lack of evidence for a decrease in disease-specific mortality, and the lack of cost analyses are some of the drawbacks of this technique.²¹⁶ Therefore AFB is not yet considered a screening tool for lung cancer and is primarily being used as a research tool^{213,216} (Fig. 22-13).

NARROW-BAND IMAGING

Visualizing the vascular pattern of the bronchial epithelial surface promises to advance the understanding of angiogenesis in the early phases of carcinogenesis of lung tissue and to advance the diagnosis of premalignant lesions. *Narrow-band imaging* (NBI) is a new, alternative light-wavelength capture system that can be used to detect the altered blood vessel morphology of bronchial dysplasia. Wavelengths of light in the visible spectrum (400 to 700 nm) are filtered to narrow the wavelength to bands in the blue and green spectrum (415 and 540 nm), coinciding with the peak absorption spectrum of oxyhemoglobin and thereby enhancing detection of blood vessels. It may be helpful to detect severely dysplastic lesions; it is estimated that invasive carcinoma will develop in 40% to 83% of patients with severely dysplastic lesions.^{219,220} NBI in combination with high-magnification bronchoscopy can be useful in characterizing capillary loop patterns of dysplastic airway lesions.^{221,222}

NBI may be more specific than AFB for detecting dysplasia when used as an adjunct to AFB to evaluate the vascular

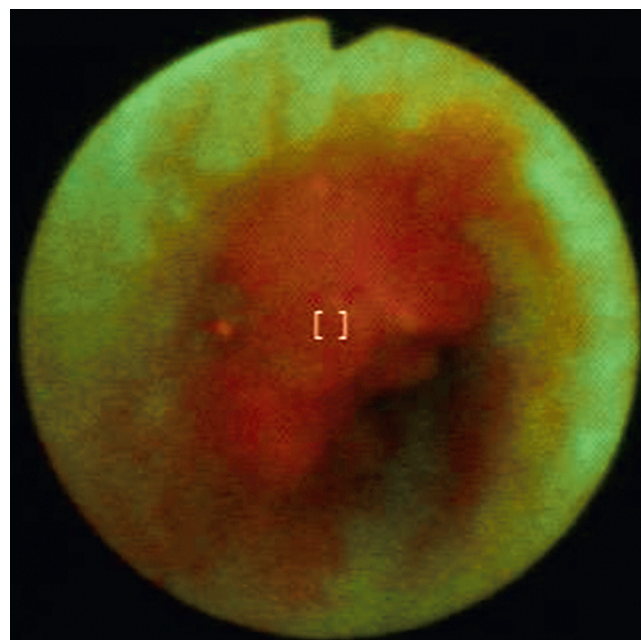


Figure 22-13 False-positive autofluorescence bronchoscopy image in patient with recurrent respiratory papillomatosis involving the trachea. All endobronchial biopsy specimens from the suspicious areas were negative for malignancy.

patterns visualized on areas with abnormal autofluorescence.²⁰³ When NBI is used with WLB, detection of bronchial dysplasia is significantly improved compared with WLB alone. At the same time, NBI requires closer examination both as a stand-alone technology and in comparison with other imaging strategies, including AFB, in the setting of clinical trials.²²³

Because both AFB and NBI are “technologies in search of an indication,” they remain largely research tools and should not be routinely performed outside well-designed clinical trials or special clinical circumstances.^{216,223} In one study, high-magnification bronchovideoscopy combined with NBI was found useful in the detection of capillary blood vessels in angiogenic squamous dysplasia at sites of abnormal fluorescence. Such combined approaches may enable the discrimination between angiogenic squamous dysplasia and other preinvasive bronchial lesions.²²¹

Key Points

- Since its introduction in 1966, flexible bronchoscopy has replaced rigid bronchoscopy for most diagnostic and therapeutic indications; rigid bronchoscopy has a continued role for a few indications such as massive hemoptysis and removal of large foreign bodies, especially in the pediatric population.
- Bronchoalveolar lavage, which samples the distal air spaces, can diagnose several diseases that involve the air spaces, including opportunistic infections, eosinophilic pneumonia, and pulmonary alveolar proteinosis.
- *Transbronchial biopsy* (TBB) has value in the diagnosis of infiltrative diffuse pulmonary diseases. With the advent of novel guidance techniques, such as

electromagnetic navigation, TBB may become accurate at sampling distal focal lesions.

- **Endobronchial ultrasonography (EBUS)** represents a major advance in diagnostic bronchoscopy, allowing ultrasound-guided biopsies from beyond the confines of the tracheobronchial tree. Its major indication today is the sampling of lymph nodes to assess the tumor-node-metastasis staging of non-small cell lung cancer.
- The combination of EBUS and endoscopic ultrasonography is as accurate as mediastinoscopy in the staging of non-small cell lung cancer.
- Advances in confocal bronchoscopy, autofluorescence bronchoscopy, and narrow-band imaging may prove valuable in detecting early malignant lesions of the lung parenchyma and large airways in the future; yet, for now, they remain research tools.

Complete reference list available at ExpertConsult.

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INTRODUCTION AND HISTORICAL BACKGROUND
THERAPEUTIC BRONCHOSCOPY
EVALUATION AND MANAGEMENT OF CENTRAL AIRWAY OBSTRUCTION
 Foreign Body Removal
 Electrocautery

Argon Plasma Coagulation
 Laser Photoresection
 Stent Placement
 Microdébrider
 Cryotherapy
 Photodynamic Therapy

Brachytherapy
EMERGING TECHNOLOGIES
 Bronchoscopic Lung Volume Reduction
 Bronchial Thermoplasty
 Endobronchial Valve Placement for Prolonged Air Leaks

INTRODUCTION AND HISTORICAL BACKGROUND

Gustav Killian performed the first rigid bronchoscopy in 1897 to extract a piece of a pork bone from the right main bronchus.¹ This innovation resulted in a dramatic decrease in the mortality from aspiration pneumonia. In 1966, the flexible bronchoscope was introduced into clinical practice by Shigeto Ikeda.² Currently, the majority of pulmonologists are trained in *flexible bronchoscopy* (FB), whereas only a minority have been trained in rigid bronchoscopy.^{3,4} With the advent of formalized fellowship training programs in interventional pulmonology, training in rigid bronchoscopy is making a comeback and is an extremely valuable instrument in the management of central airway obstruction⁵ (Video 23-1). Whereas FB remains invaluable for the diagnosis of lung masses, parenchymal disease, and mediastinal/hilar adenopathy, the rigid bronchoscope offers the ability to provide an airway allowing oxygenation and ventilation, as well as the passage of large-bore suction catheters and a variety of tools that can aid in the destruction and excision of tumor. Additionally, silicone stents can be placed only via the rigid bronchoscope, thus allowing the physician to place the “best” stent in a selected patient as opposed to being limited to stents that can be placed solely via FB.

THERAPEUTIC BRONCHOSCOPY

Central airway obstruction, from both malignant and non-malignant causes (Table 23-1), is associated with significant morbidity and mortality and often presents a great challenge to physicians. It is estimated that 20% to 30% of patients with lung cancer will develop complications associated with airway obstruction, and the incidence of nonmalignant causes such as postintubation/posttracheostomy stenosis is likely to increase due to the increasing use of artificial airways in an ever-aging population.⁶

It should be noted that designing large randomized trials to investigate comparative efficacy is extremely difficult in patients with central airway obstruction. Limitations

include selecting patients with comparable disease and comorbidities, as well as the fact that many of these patients present in respiratory distress. Double blinding is also clearly impossible. Therefore the literature supporting therapeutic bronchoscopy is primarily based on large case series and retrospective analyses. That being said, the impact of therapeutic bronchoscopy on quality and length of life is impressive.⁷⁻¹⁰ Therapeutic bronchoscopy has also been associated with immediate reductions in the level of care required for patients with acute respiratory failure from central airway obstruction.¹¹

Training in advanced diagnostic and therapeutic bronchoscopy tends to be limited and is more common in centers that have dedicated interventional pulmonology training programs.¹² Over the last several years, dedicated training in interventional pulmonology has become more popular, with 26 dedicated programs currently available in the United States (www.aabronchology.org) and the development of standardized curricula and in-service examinations.^{5,13} The first board examination for IP was administered in 2013.

Even with the recent increase in training in rigid bronchoscopy, the flexible bronchoscope remains an essential tool in therapeutic bronchoscopy. It is used in almost every rigid bronchoscopic procedure and, when rigid bronchoscopy is not available, can also be used as the only bronchoscope for foreign body removal, tumor excision/tumor destruction, and balloon dilation. There are several therapeutic techniques, each with its own associated risks and benefits, advantages and disadvantages (Table 23-2). Because comparative data are lacking, the technique of choice often depends on equipment availability and the bronchoscopist's expertise. Two of the most important considerations in the care of patients with central airway obstruction is assessing the stability of the patient for the planned procedure and having a realistic understanding of the local resources and skill set. Clearly, all efforts should be made to ensure that a patient with a relatively stable airway does not develop an unstable airway during the procedure because these patients can deteriorate quickly. These patients are often best cared for in a multidisciplinary approach in “centers of excellence” that routinely evaluate and manage such problems.⁶

Table 23-1 Causes of Central Airway Obstruction

Nonmalignant	Malignant
Vascular	Primary airway tumors
Sling	Bronchogenic
Cartilage	Mucoepidermoid
Relapsing polychondritis	Adenoid cystic
Lymphadenopathy	Carcinoid
Infectious (e.g., histoplasmosis, tuberculosis)	Tumors metastatic to the airway
Sarcoidosis	Bronchogenic
Granulation tissue associated with:	Renal cell
Artificial airways	Breast
Airway stents	Melanoma
Aspirated foreign bodies	Thyroid
Surgical anastomosis	Colon
Inflammatory lesions	Esophageal carcinoma
Granulomatosis with polyangiitis (Wegener granulomatosis)	Lymphadenopathy from any malignancy
Amyloidosis	Mediastinal tumors
Papillomatosis	Thyroid
Tracheobronchomalacia	Thymus
Other:	Germ cell
Goiter	Lymphoma
Secretions/blood clot	

EVALUATION AND MANAGEMENT OF CENTRAL AIRWAY OBSTRUCTION

FOREIGN BODY REMOVAL

Indications

Foreign body aspiration is one of the most common indications for therapeutic bronchoscopy. There is a bimodal incidence of airway aspiration, peaking in children 1 to 2 years old and in adults older than 70. Risk factors for aspiration in adults include alcohol intoxication, sedative and hypnotic drug use, poor dentition, senility, seizure, trauma, swallowing impairment, parkinsonism, and general anesthesia. In adults, foreign bodies are most commonly found in the right-sided airways but, in children, are found equally in the left and right owing to the equal size and angulation of the main bronchi. Because a history of aspiration is obtained in less than 50% of patients, and visible foreign bodies can be identified on chest radiography in less than 10% of cases, a high index of suspicion is required.¹⁴⁻¹⁷

Contraindications, Procedure, Results, and Complications

All contraindications that apply to routine FB also apply to the removal of a foreign body. Lack of experience and lack of availability of all necessary endobronchial accessories are the more important considerations. Removal of a foreign body using FB should be attempted only by or under the supervision of an expert bronchoscopist. The removal

Table 23-2 Advantages and Disadvantages of Therapeutic Modalities

Modality	Time to Achieve Results	Advantages	Disadvantages	Cautions
Electrocautery	Immediate	Inexpensive Multiple accessories	Often need to couple with mechanical débridement	Need to deactivate pacemaker/AICD Keep $\text{FI}_2 < 0.4$
Argon plasma coagulation	Immediate	Inexpensive Can treat at an angle to electrode	Risk for gas embolization with higher flow rates Often need to couple with mechanical débridement	Need to deactivate pacemaker/AICD Depth of penetration 2-3 mm Keep $\text{FI}_2 < 0.4$
Laser	Immediate	Extensive data supporting its use	Need laser safety precautions	Depth of penetration up to 10 mm Keep $\text{FI}_2 < 0.4$
Stent	Immediate	Only bronchoscopic modality for extrinsic compression	All stents have associated complications of granulation tissue formation, infection, and migration	Metallic stents should be used with caution in patients with nonmalignant disease
Microdébrider	Immediate	Can use in high- FI_2 environments	May need additional tools to provide hemostasis	Cannot reach distal airways
Cryotherapy	48-72 hr	Normal airway is cryoresistant Can use in high- FI_2 environments	Delayed maximal effect, requiring "cleanout" bronchoscopy	Cryo-adhesion can remove organic foreign bodies
Photodynamic therapy	48-72 hr	Can destroy submucosal tumor Can use in high- FI_2 environments	Delayed maximal effect, requiring "cleanout" bronchoscopy Systemic photosensitivity Need laser safety precautions	Swelling of tumor can cause obstruction
Brachytherapy	Delayed: days—weeks	Can destroy submucosal tumor	Coordination with radiation oncology	Radiation bronchitis Risk for erosion into vessels Swelling of tumor can cause obstruction

AICD, automatic internal cardiac defibrillator.

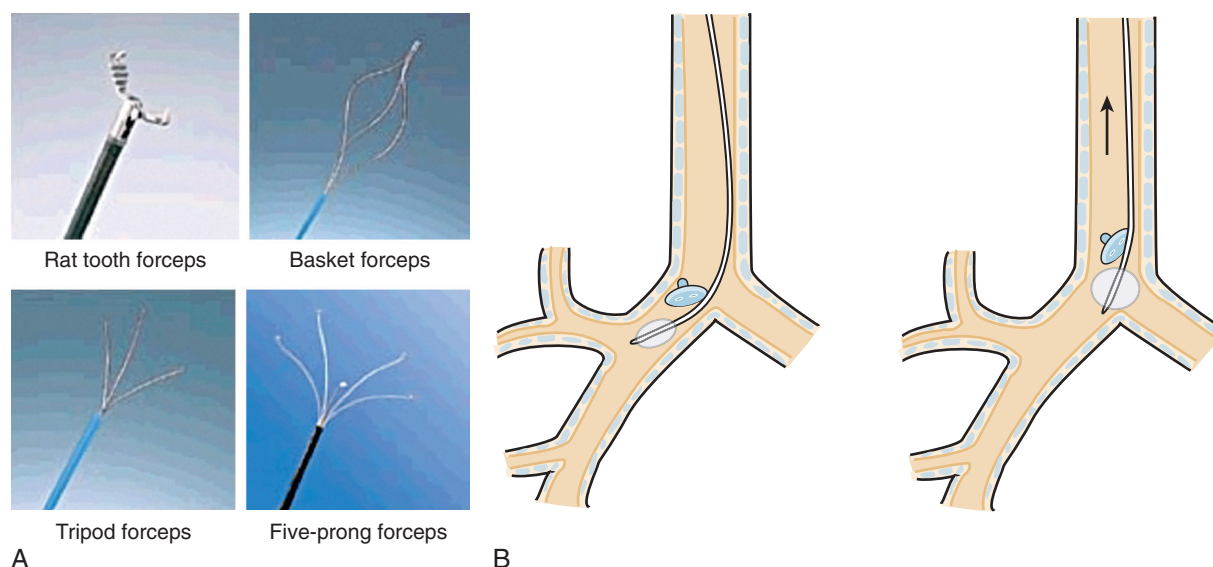


Figure 23-1 **A**, Examples of foreign body retrieval tools: rat tooth forceps, basket forceps, tripod forceps, five-prong forceps. **B**, Schematic representation of the use of a balloon catheter for dislodging a foreign body by a retrograde pull. (**B**, Courtesy Dr. Eric Folch.)

of foreign bodies can be performed successfully with either the flexible or rigid bronchoscope. Flexible bronchoscopy is successful in 86% to 91% of cases, whereas rigid bronchoscopy is successful in 99.9%.^{15,16,18-24} If available, rigid bronchoscopy should be used in all cases of acute respiratory distress caused by foreign body aspiration given the near 100% success rate and the speed at which the procedure can be performed. The benefits of FB include its widespread availability and its lack of a requirement for general anesthesia.

Foreign body removal using FB is carried out in stages: first, dislodging the foreign body; then, grasping or securing the object; and finally, removing it along with the flexible bronchoscope as a single unit. A variety of ancillary accessories (forceps, grasping claws, snares, baskets, and magnets) are available for foreign body extraction (Fig. 23-1). A cryoprobe passed through the flexible bronchoscope can be especially useful for the removal of blood clots, mucous plugs, and organic material, because the extreme cold can cause immediate and strong adherence (“cryoadherence”) to the biologic materials. Once the object is grasped and secured, care must be taken to avoid losing it in the subglottic area or at the level of the vocal cords. If necessary, the patient can also be asked to cough to expel the foreign body once it has been brought into the mid-upper trachea.

Serious complications can accompany removal of a foreign body, including central airway obstruction, hypoxemia, bronchospasm, and bleeding. Objects can also migrate, and their fragments can impact in distal airways.

ELECTROCAUTERY

Endobronchial electrocautery is the application of heat produced by high-frequency electrical current to treat tumor tissue. It involves the use of special accessories such as blunt probes, hot forceps, knives, and snares introduced through a bronchoscope. The probe functions as an active electrode that focuses heat at the point of contact, leading to tissue

coagulation or vaporization. The electrical current can also cut or combine cutting with coagulation. The degree of tissue destruction depends on the power used, duration of contact, surface area of contact, and water content of the tissue. Use of the snare device is especially suited to the removal of a pedunculated airway lesion because cauterization of the stalk can allow removal of the majority of the tumor for pathologic review (Video 23-2).

To avoid endobronchial ignition, the *fractional concentration of oxygen in inspired gas* (FIO₂) should be kept below 0.4. Insulated bronchoscopes, compatible with electrocautery, are used to prevent leakage of electrical current, avoiding burns or electrical shock to the patient and the bronchoscopist.

Indications and Contraindications

Electrocautery is used for either coagulation or vaporization of malignant or nonmalignant disease within the airways and has been shown to be potentially curative in patients with carcinoma in situ. Coagulation is achieved by gently touching the tumor tissue and applying 1- to 2-second bursts of 20- to 40-W energy until blanching or destruction of the mucosa becomes apparent. Additional contact time can result in vaporization of the tissue as desired. The tumor area should be kept free of blood or mucus by continuous suctioning, or the electrical current will be dissipated through these liquids. The coagulated tissue can then be removed using biopsy forceps or suction. The use of electrocautery is contraindicated in patients with pacemakers and/or defibrillators to avoid electrical interference with these devices.²⁵

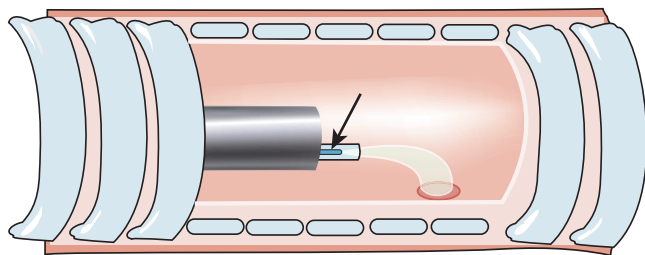
Results and Complications

Electrocautery has been used effectively and safely as an ablative modality in both malignant and nonmalignant airway obstruction. In several studies, electrocautery has been shown to achieve luminal patency and symptomatic improvement at rates similar to *laser* (light amplification by stimulated emission of radiation) and other ablative airway

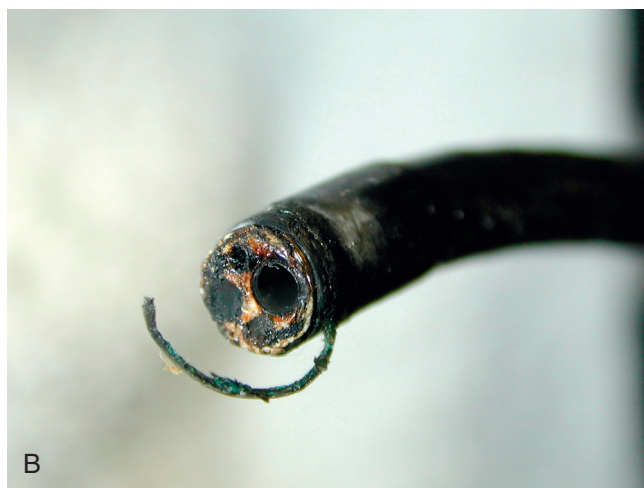
modalities.²⁶⁻³⁰ Moreover, electrocautery is a cost-effective bronchoscopic intervention due to the low cost of the machine and the reusable nature of its accessories.²⁶ In a selected group of patients with small, polypoid endobronchial lesions, Coulter and Mehta³¹ showed that electrocautery had a high success rate (89%) under local anesthesia, thereby eliminating the need for the more costly laser therapy. Complications are rare in experienced hands: the most common ones are bleeding (2% to 5%), endobronchial fire in a high-FiO₂ environment, and electrical shock to the operator should the cautery probe touch an ungrounded bronchoscope.

ARGON PLASMA COAGULATION

Argon plasma coagulation (APC) is a noncontact form of electrocautery that uses ionized argon gas (plasma) to conduct electrical current from the probe to the tissue. Because positively charged argon gas flows toward the negatively charged tissue, treatment can be directed in an axial or tangential fashion (Fig. 23-2A). As the tissue becomes desiccated, it offers more resistance to the electrical current, limiting its penetration to approximately 2 to 3 mm.^{25,26} APC probes can be passed via a rigid or flexible bronchoscope.



A



B

Figure 23-2 **A**, Schematic presentation of argon plasma coagulation. Arrow shows the tungsten carbide electrode. Positively charged argon gas automatically flows radially to the negatively charged bleeding tissue. **B**, Damage to the tip of the bronchoscope caused during argon plasma coagulation by having the catheter too close to the tip of the bronchoscope during activation. Note the charred tip along with the frayed rubber sheath. (A, Courtesy Dr. Eric Folch.)

Indications and Contraindications

APC is frequently used for palliation of malignant airway obstruction as part of multimodality therapy, including mechanical débridement; mechanical débridement is needed to remove the cauterized tissue because, unlike laser, APC and other forms of electrocautery do not vaporize tissue. APC is also extremely useful for control of bleeding in the central airways and has been used for the treatment of excess granulation tissue (including stent-related granuloma), postinfectious airway stenosis, and endobronchial papillomatosis (Video 23-3).^{25,26} The most important advantages of this technique are the ability to treat lesions at sharp angles from the tip of the electrode, to treat lesions in close proximity to airway stents, and to achieve superior hemostasis. Its major limitation is the depth of penetration of less than 3 mm; however, this also may reduce the risk for airway perforation. Its only absolute contraindication is the presence of a pacemaker or implantable defibrillator susceptible to electrical interference. As with electrocautery and laser use in the airway, APC requires that the FiO₂ be < 0.4.

Results and Complications

In properly selected cases, APC provides symptomatic relief in almost 90% of patients. It is also portable, less expensive than laser, and typically available in most operating rooms (though bronchoscopic fibers may need to be purchased). Potential complications include gas embolization,³² airway fire, postprocedure stenosis, and injury to deeper structures or to the flexible bronchoscope (see Fig. 23-2B). The observed mortality and overall complication rates are 0.4% and 3.7% of cases, respectively.^{33,34}

LASER PHOTORESECTION

Laser light has three unique characteristics—monochromaticity, coherence, and collimation—that permit controlled delivery of a well-defined energy. Laser light causes thermal, photodynamic, and electromagnetic changes in living tissue. Laser energy can cut, coagulate, or vaporize endobronchial lesions in a predictable manner, depending on the wavelength used. Although many types of laser systems exist, the *neodymium:yttrium-aluminum-garnet* (Nd:YAG) and *neodymium:yttrium-aluminum-perovskite* (Nd:YAP) lasers are most commonly used in the airways because of their ability to coagulate and vaporize tissue, with a depth of penetration of 5 to 10 mm.²⁶ Though the carbon dioxide laser provides minimal hemostasis, it is extremely precise (depth of penetration of <1 mm). Such precision can permit fine procedures such as those needed to incise weblike stenoses or to remove granulation tissue surrounding airway stents.

Indications

The main indications for *laser photoresection* (LPR) are relief of central airway obstruction from exophytic obstructive neoplasms and from tracheal stenosis (Video 23-4). An ideal lesion for the LPR is an endobronchial tumor that arises from a single wall of a central airway and has a visible distal lumen, with a duration of lung collapse of less than 4 to 6 weeks. LPR can be performed using either a rigid or

flexible bronchoscope. The end results and the complication rates are similar with both types of instruments. The selection of the scope mainly depends upon personal preference, availability of the instruments, and training. Bronchoscopists proficient in rigid bronchoscopy prefer to use the rigid scope because of the ease of mechanical debulking and superior suction capabilities.

Contraindications

Lesions not amenable to LPR are extrinsic or submucosal, primarily involving lobar or segmental bronchi, and those for which the operator is unable to identify a patent airway distal to the obstruction. As with other forms of heat therapy, laser is contraindicated in patients with a high oxygen requirement.²⁶

Results and Complications

LPR can restore airway patency with immediate symptomatic improvement in 93% of cases (Fig. 23-3).^{26,35} It can be combined with other techniques such as APC and stent placement to achieve full patency of major airways. This technique palliates symptoms of cough, dyspnea, and hemoptysis along with documented benefits in radio-

graphic, spirometric, and quality of life parameters. Studies have shown a small survival benefit when emergent LPR is compared with emergent radiotherapy. LPR is associated with the following complications (range, 0% to 2.2%): exsanguination (2%), endobronchial ignition, pneumothorax or barotrauma, bronchopleural or bronchoesophageal fistula, and hypoxemia.³⁶ Extensive knowledge of the anatomy of the tracheobronchial tree is mandatory before performing the procedure. Accumulation of blood and secretions can lead to rapid desaturation. Tracheobronchial tree perforation can be fatal owing to the close proximity of the great vessels. While performing the procedure, one must take precautions to avoid airway fires, activating the laser only when the FiO_2 is < 0.4 . Laser safety precautions for the bronchoscopist and operating room personnel are also required.³⁶

STENT PLACEMENT

Stents are devices used for the internal splinting of luminal structures. The first stents that were used in the trachea were the T tubes developed by Montgomery.³⁷ Though they require a tracheostomy for their placement, these silicone

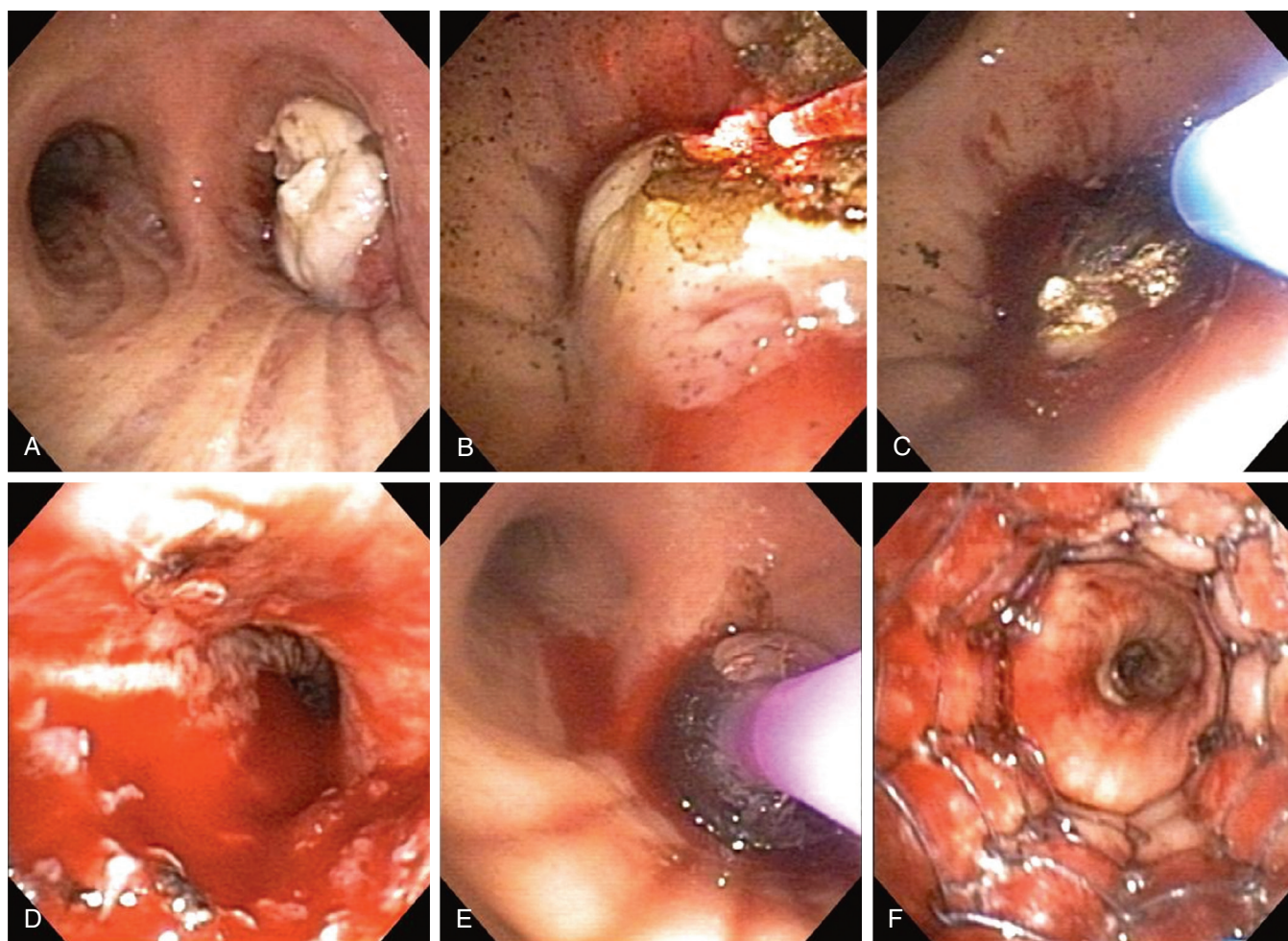


Figure 23-3 Multimodality palliative therapy for a patient with a malignant lesion obstructing the right main-stem bronchus. A, Pretreatment. B, Laser photoresection (note the laser fiber). C, Argon plasma coagulation (note the blue argon plasma coagulation catheter). D, After mechanical débridement. E, Balloon dilation. A silicone balloon is fully inflated in the right main-stem bronchus location. F, Stent placement. Note the self-expanding metallic stent in place. (A–F, Courtesy Dr. Eric Folch.)

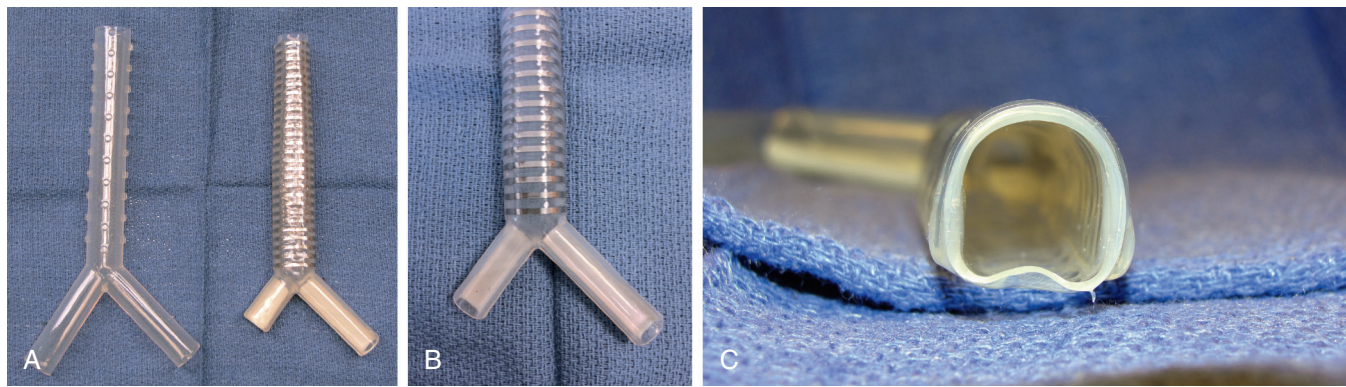


Figure 23-4 **A**, Silicone Y stent and Rusch Y stent. **B**, Rusch Y stent (with metal anterior rings to mimic the normal trachea). **C**, Rusch Y stent on end. Note the dynamic nature of the stent with a “posterior membrane.”

stents are still widely used, primarily in patients with high tracheal stenosis and/or malacia. Westaby and colleagues modified this stent and designed a T-Y prosthesis, which enabled splinting of the distal trachea and carina. Dumon³⁸ later developed the first stents that could be inserted through a bronchoscope without a tracheostomy. Over the years, several other stents have been developed, including “dynamic” stents made to mimic the airway with a “posterior longitudinal membrane,” stents made of steel or nitinol (a nickel-titanium alloy), as well as newly developed (though not commercially available) bioabsorbable and drug-eluting varieties (Fig. 23-4).³⁹ Unfortunately, there is no perfect stent. The ideal stent would be easy to insert and remove, strong enough to support the airway yet flexible enough to mimic normal airway physiology and promote secretion clearance, biologically inert to minimize the formation of granulation tissue, and available in a variety of sizes and shapes. Whereas self-expanding metallic stents can be placed with flexible bronchoscopy, silicone stents require rigid bronchoscopy. Many bronchoscopists who perform rigid bronchoscopy feel it is significantly easier to place metallic stents via the rigid bronchoscope due to the fact that patients are under general anesthesia and the larger rigid forceps allow for easier stent manipulation. All currently available stents have their own advantages and disadvantages, and thus it is most important to select the best stent for the individual patient. This requires the bronchoscopist to be familiar with and able to place a variety of stents.

Indications and Contraindications

Indications for airway stent placement include (1) counteracting extrinsic compression from tumors or lymph nodes (Video 23-5); (2) preventing regrowth of intraluminal tumor that will compromise an airway, (3) maintaining airway patency in patients with significant and symptomatic malacia, and (4) sealing malignant fistulas.²⁶ Because one of the major complications of metallic stents is epithelialization, which makes removal extremely difficult, the U.S. Food and Drug Administration has issued a warning against the use of metallic stents in patients with benign conditions until all therapeutic options, including use of silicone stent and surgery, have been explored. Though many of the other modalities described in this chapter can be used to treat patients with intraluminal or transmural

disease, airway stents are the only bronchoscopic modality that can treat extrinsic airway compression.

Results and Complications

Airway stenting has been associated with improved quality and length of life in patients with malignant airway obstruction,^{26,40,41} improved quality of life in patients with tracheobronchomalacia,⁴² an increased ability to be liberated from the ventilator, even in patients with nonmalignant disease,⁴³ and improved lung function and pulmonary infection rates in patients with airway stenosis following lung transplantation.⁴⁴

Retained secretions, bacterial colonization, migration, stent fractures, and development of granulation tissue are frequent complications, and all can be seen with any type of stent. Silicone stents tend to have a higher incidence of migration, whereas covered metallic stents are more prone to infection.⁴⁵ Silicone stents and the presence of lower respiratory tract infections were also found to increase the risk for granulation tissue formation. Though typically requiring rigid bronchoscopy, removal of silicone stents is a relatively easy procedure. Removal of metallic stents on the other hand, especially the uncovered/partially covered varieties, can be extremely difficult and associated with significant complications and cost.^{46,47} As such, it is our practice to perform surveillance bronchoscopy to assess for stent-related complications at approximately 6 weeks following stent placement because the complications, if present, are often easier to manage earlier rather than later, once the patient develops symptoms.

MICRODÉBRIDER


The microdébrider is a form of “powered instrumentation” that uses a spinning blade contained within a rigid suction catheter to cut tissue while providing suction to remove blood and tumor/granulation tissue^{48,49} (Video 23-6). We generally use a 45-cm-long, 4-mm-wide angle-tip blade, allowing it to reach lesions in the trachea, main-stem bronchi, and bronchus intermedius. Advantages of the microdébrider are that it can be used in high-FiO₂ environments, and, because it does not vaporize tissue, a specimen trap can be connected in line so that tissue can undergo pathologic analysis. The continuous suction also provides a clean operating environment. Because the microdébrider

does not use any thermal energy, it is often necessary to use additional modalities such as APC to achieve complete hemostasis. When used by skilled operators, adverse events are rare but can include airway perforation and bleeding.

CRYOTHERAPY

Cryotherapy relies on repeated freeze-thaw cycles to cause tissue damage. Maximal cellular damage results from rapid and deep cooling and a relatively slow thaw. The Joule-Thompson effect describes the drop in temperature that develops as a gas expands from a high-pressure to a low-pressure environment. The most commonly used cooling agents (cryogenes) available are nitrous oxide and carbon dioxide. The cryoprobe can be used through rigid or flexible bronchoscopes. When nitrous oxide is used, the temperature at the tip of the probe falls to -89°C within several seconds. The temperature increases approximately 10°C per mm from the tip (“warming effect”), so the effective killing zone is approximately 5 to 8 mm. Because freezing and recrystallization depend on cellular water content, cartilage and fibrous tissue are relatively cryoresistant, making it more difficult to damage the normal airway with this therapy than with other forms of thermal energy. Repeated cycles of freezing and thawing are applied to the endobronchial tissue in a contiguous fashion to cover the entire surface of the lesion. Tissue necrosis and sloughing takes place within 24 to 48 hours, and a “cleanup” bronchoscopy is usually required to remove necrotic tissue. This delayed tissue effect is one of the shortcomings of cryotherapy.⁵⁰

Indications and Contraindications

 Cryotherapy has been used for the destruction of endobronchial lesions when immediate results are not mandatory and “hot” therapies are contraindicated (Video 23-7). For example, cryotherapy is ideal for treating stent-related granulomas when the stent is made of a flammable material.^{26,50} Cryotherapy can be used with excellent results in removing organic foreign objects, blood clots, and mucous plugs by cryoadhesion, as described earlier. Advantages of cryotherapy include its ability to be used in a high-oxygen environment and its limited bronchial wall damage.⁵⁰ A newer form of cryotherapy, cryoextraction, has also been described recently, in which tumor in the central airways is frozen to the cryoprobe and removed en bloc with the bronchoscope in a similar manner as removing a foreign body.⁵¹

Results and Complications

In most cases, cryotherapy offers a safe and inexpensive alternative for ablation of endobronchial tumor, with success rates up to 80%.^{52,53} As mentioned, tumor sloughing requiring a repeat bronchoscopy and delayed maximal effect are the two major downsides of using cryotherapy for tumor excision. Moderate bleeding, mediastinitis, and fistula formation following cryotherapy have also been encountered in few cases, though the risk for bleeding is likely less than with other therapies due to the vasoconstrictive and platelet-aggregating properties of cryotherapy.⁵⁰ Likewise, the risk for airway fire is nonexistent. It should be noted that the risk for bleeding with cryoextraction may be higher than when cryotherapy is used for tumor destruction.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) refers to a process by which a photosensitizing drug is activated by a nonthermal laser light to induce a phototoxic reaction leading to cell death. PDT is a three-step process. On day 1, a photosensitizing agent such as porfimer sodium) is administered intravenously. Forty-eight hours after injection, the drug is preferentially retained by tumor cells and cleared from most healthy tissues, and the tumor is then exposed to a nonthermal laser light introduced via a flexible bronchoscope. Exposure of the drug to light of 630 nm results in a photochemical reaction, including generation of oxygen radical species, direct damage to cells and organelles, indirect ischemic effects, apoptosis, and inflammatory effects. One to two days later, a cleanup bronchoscopy is then necessary to remove the devitalized tissue, which is difficult to expectorate and can cause complications such as postobstructive pneumonia, respiratory distress, or respiratory failure.²⁶

Indications and Contraindications

PDT is indicated for the palliation of advanced non-small cell lung cancer obstructing the tracheobronchial tree and appears to be effective for superficial as well as submucosal disease. Curative treatment for early lung cancer/carcinoma in situ is another indication for PDT. Occasionally it is also used preoperatively to reduce the extent of surgical resection by rendering the line of resection free of disease.

Owing to its delayed effect and to the possible swelling of the lesion following the therapy, PDT is relatively contraindicated for treatment of tracheal and carinal lesions or lesions in postpneumonectomy patients (i.e., lesions for which any swelling might precipitate total lung obstruction). PDT is also contraindicated if the tumor invades vascular structures or if there is a history of porphyria and/or porphyrin hypersensitivity.

Results and Complications

PDT has been used to treat advanced lung cancer,⁵⁴ to treat multiple malignancies alone or in combination with surgery,⁵⁵ and to pretreat to reduce the extent of the surgical resection.⁵⁶ In superficial tumors a complete remission rate between 64% and 98% with PDT has been described, and balloon-sheath endobronchial ultrasonography can be invaluable in determining lack of transmural spread.^{54,55,57}

Compared to other therapies, PDT is not immediately effective and therefore should not be used for acute central airway obstruction. Additionally, cleanup bronchoscopy is required, and the induced systemic photosensitivity mandates that the patient avoid sunlight for 4 to 6 weeks, a potentially major drawback for those with limited life expectancy.⁵⁸ The most common complications include skin photosensitivity, local airway edema, strictures, hemorrhage, and fistula formation.²⁶

BRACHYTHERAPY

Brachytherapy refers to a technique in which the radiation source is placed within or in close proximity to the target to deliver the maximum dose of radiation to the tumor while sparing the normal surrounding tissues. The radiation dose

to the surrounding tissue is dictated by the inverse square law, according to which the radiation dose decreases as a function of the inverse square of the distance from the center of the source. Thus this mode of radiation therapy allows the tumor to receive significantly higher radiation doses than the surrounding healthy tissues such as lung parenchyma and mediastinal vasculature.

For central airway lesions, a polyethylene catheter is placed adjacent to the lesion via FB and its position verified by fluoroscopy. The catheter is then loaded with the radioactive source. Low-dose-rate, intermediate dose rate, and high-dose-rate treatments imply a dose of less than 2 Gy/hr, 2 to 12 Gy/hr, and greater than 12 Gy/hr, respectively, to a target at a distance of 10 mm. High-dose-rate brachytherapy, which uses Iridium-191 as the radiation source, is the most common form of brachytherapy and is typically applied in three treatment sessions over a week in the outpatient setting.⁵⁹ Brachytherapy requires close collaboration between the bronchoscopist and the radiation oncologist. The role of the bronchoscopist is to identify appropriate patients and place a catheter into the tracheobronchial tree, whereas the radiation oncologist calculates the radiation dose and guides the actual delivery of radiation to the tumor.

Indications

Brachytherapy is most useful for endobronchial tumors with a component of submucosal/peribronchial disease. Brachytherapy is also useful for recurrent tumors following maximally tolerated external beam radiation. The primary goal of brachytherapy is palliation of tumor symptoms such as cough, dyspnea, and hemoptysis. Because it requires up to 3 weeks for the tumor to regress, brachytherapy is not suitable for immediate relief of obstructive symptoms.⁵⁹ Brachytherapy is a therapeutic option for occult early-stage central lung cancers when surgery cannot be performed. Brachytherapy has also been used in management of excessive granulation tissue at the site of anastomosis in lung transplant recipients.⁶⁰

Contraindications

A few absolute contraindications for endobronchial brachytherapy exist, such as known fistulas involving the airways. To avoid life-threatening complications, one should exclude tumors directly involving the major vessels. Patients with endotracheal carcinoma causing high-grade obstruction should not be treated with brachytherapy because of the delayed effects and potential postradiation edema that could lead to total airway obstruction.

Results and Complications

The studies that combined external radiation with brachytherapy showed that, even if quick airway response was gained, there was no survival benefit; thus its role is mainly for palliation. Brachytherapy is reported to improve cough in 20% to 70%, dyspnea in 25% to 80%, and hemoptysis in 70% to 90% of patients. For patients who have not yet received radiation, external beam radiation therapy offers improved duration of response and survival compared with brachytherapy alone; thus external beam radiation therapy should be selected as first-line therapy instead of brachytherapy for lung cancer patients with central lesions.⁶¹ In patients with inoperable early-stage cancer of the central

airways, brachytherapy has been reported to produce a complete endoscopic response in up to 60% to 90% with 5-year survival rates of 30% to 80%.^{59,62,63}

Complications include respiratory compromise, massive hemoptysis, fistula formation, radiation bronchitis, and airway stenosis. Fatal hemoptysis has been reported in up to 5% to 10% of patients. The risk for late exsanguination has been found to be highest in patients receiving brachytherapy to the right upper lobe, owing to its close proximity to the pulmonary artery.^{59,62}

EMERGING TECHNOLOGIES

BRONCHOSCOPIC LUNG VOLUME REDUCTION

To date the only options for patients with advanced emphysema are lung volume-reduction surgery and lung transplantation. The National Emphysema Treatment Trial demonstrated that, in patients with heterogeneous emphysema with upper lobe predominance and low exercise capacity, lung volume-reduction surgery significantly improves lung function, exercise tolerance, quality of life, and survival.⁶⁴ Unfortunately, the associated morbidity and mortality of the procedure have limited its widespread application.

Indications and Contraindications

Endobronchial treatment of severe emphysema has been studied for over a decade and has been approved in several countries around the world. Incidentally, it still remains a matter of research in the United States at the time of writing this chapter. Various devices and chemical agents have been used via the endobronchial route to reduce lung volumes in a relatively noninvasive fashion.⁶⁵⁻⁷⁰ The majority of studies have focused on patients with heterogeneous (i.e., upper lobe predominant) emphysema, though some have also investigated patients with homogenous disease. Because all of these techniques are relatively new, the ideal patient population for each specific approach will need to be defined. The following section provides a brief review of current knowledge related to concepts of bronchoscopic lung volume reduction.

Endobronchial Valves

Endobronchial valves are one-way valves designed to allow air to exit the targeted lung segment without allowing reentry of the inspired air, thus leading to deflation of the emphysematous portion of the lung and volume reduction. Two different types of valves, the Zephyr (Pulmonx Corporation) and the IBV (Olympus Corporation) have been evaluated. The Endobronchial Valve for Emphysema Palliation Trial (VENT), a randomized, prospective, multicenter study, examined the safety and efficacy of the Zephyr endobronchial valve in comparison to optimal medical care in patients with advanced heterogeneous emphysema.⁶⁶ Primary efficacy end points were percent changes in FEV₁ and 6-minute walk test. Though there were modest improvements in these end points, they did not reach clinical significance, and the U.S. Food and Drug Administration did not approve the valve for use in the United States. Optimal valve placement to achieve total lobar exclusion and the presence of a complete fissure separating the treated lobe were two

determinants of significant improvement. A bronchoscopic system (Chartis; Pulmonx Corporation) to detect collateral ventilation has been developed that has an effectiveness of approximately 75% in predicting clinical improvement after lobar occlusion with valves.⁷⁰ Studies of the IBV in patients with upper lobe predominant emphysema also reported improvements in health-related quality of life but did not find improvement in pulmonary function or exercise capacity.⁶⁹

Bronchial Lung Volume-Reduction Coils

The bronchial lung volume-reduction coil (PneumRx) is made of nitinol wires that, when deployed by advancing into the bronchus via the bronchoscope, retract and fold the parenchyma, thus reducing lung volume in abnormal areas with the goal of restoring elasticity to the normal areas. The virtue of this approach is that the presence of collateral ventilation does not affect its efficacy. Preliminary studies using lung volume-reduction coils have been shown to improve quality of life, pulmonary function, and the 6-minute walk test.⁷¹

Biologic Sealant

Bronchoscopic lung volume reduction using direct application of a biologic sealant to collapse areas of emphysematous lung has been reported. Initial tests of a synthetic polymeric foam sealant (emphysematous lung sealant, AeriSeal) have shown improvements in pulmonary function, exercise capacity, and quality of life.⁶⁸ It should be noted that fissure integrity may not be as important with this method of achieving bronchoscopic lung volume reduction.⁷²

Bronchoscopic Thermal Vapor Ablation

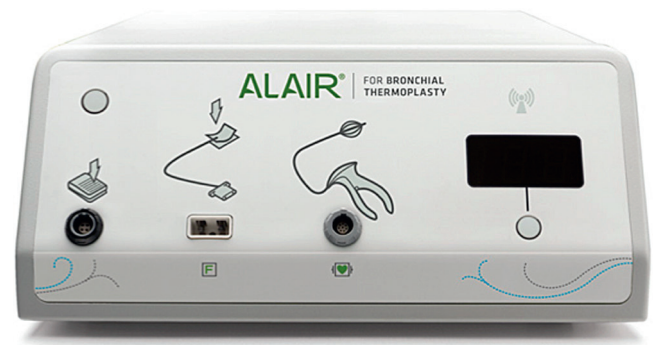
Bronchoscopic thermal vapor ablation involves delivery of a precise amount of steam water vapor at a precise temperature directly into the targeted lung segments via a specialized catheter. The thermal reaction produces a localized inflammatory response leading to fibrosis and atelectasis. This results in complete and permanent lung volume reduction. Improvements in pulmonary function and quality of life have been reported with this technique in preliminary studies.⁷³ As with the reduction coils and biologic sealants, a potential advantage of bronchoscopic thermal vapor ablation is that success is independent of the presence or absence of collateral ventilation.⁷⁴

Complications

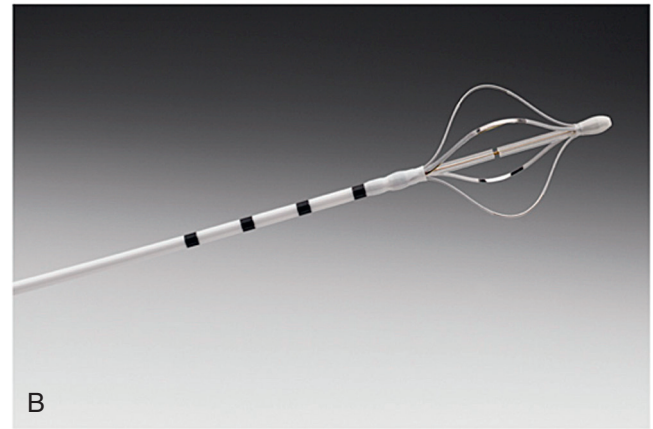
Because these procedures are performed in patients with severe underlying emphysema, complications can be expected. The more common complications include transient reductions in lung function, flares of bronchitis or pneumonia, and pneumothorax. Whereas placement of valves is reversible, the placement of coils, instillation of sealant, and ablation via bronchoscopic thermal vapor are irreversible procedures.

BRONCHIAL THERMOPLASTY

Bronchial thermoplasty (BT) is a novel bronchoscopic treatment for patients with severe asthma aiming to reduce the airway smooth muscle mass, therefore diminishing bronchial constriction and improving asthma symptoms.⁷⁵ This



A



B

Figure 23-5 A, The radiofrequency ablation catheter used for bronchial thermoplasty. B, The disposable catheter contains a four-electrode basket that delivers controlled heat to the airways.

is accomplished by delivering controlled heat to the airway walls via a radiofrequency electrical generator and a disposable catheter with an expandable four-electrode basket at its distal tip (Fig. 23-5). BT is performed in three bronchoscopy sessions, 2 to 3 weeks apart. The first two sessions treat each lower lobe separately, and the third session treats both upper lobes (the right middle lobe is not treated, because it was not included in recent study protocols). Radiofrequency energy is delivered in a systematic fashion at 5-mm intervals starting from just beyond the endoscopic visual limit to the proximal lobar bronchi.

Indications and Contraindications

BT is indicated in adult patients with severe persistent asthma who remain symptomatic despite maximal medical treatment. Concomitant medical conditions that can contribute to asthma symptoms should be sought and treated before resorting to this treatment. In addition, BT should not be used as a substitute for medication compliance. Contraindications for BT include the presence of an implantable electronic device, severe comorbid conditions that increase the risk of the procedure, and FEV₁ of greater than 65% predicted. In children (age < 18 years), the procedure has not been studied and is not approved.

Results and Complications

In multiple studies performed in patients with asthma of various severity, BT has been shown to reduce asthma exacerbations and improve quality of life. Adverse events were

limited to an increase in asthma exacerbations in the perioperative period.⁷⁶⁻⁸⁰

The definitive study of BT, which led to Food and Drug Administration approval, used a randomized double-blind, sham-controlled design of 288 subjects with severe persistent asthma. Patients receiving BT had improvement in quality of life based on a questionnaire but, most importantly, had a 30% reduction in severe exacerbations, an 80% reduction in emergency department visits, and a decrease in days missed from work or school.⁸⁰ The short-term adverse events included airway inflammation and upper respiratory infections that resolved with conventional treatment. There was a higher rate of hospitalization in the BT group in the postprocedure period. A recent study reported on the 5-year follow-up of 162 patients enrolled in the study just described and demonstrated durability of the benefits of BT and safety up to 5 years.⁸¹

ENDOBONCHIAL VALVE PLACEMENT FOR PROLONGED AIR LEAKS

Prolonged air leaks following thoracic surgery are a common complication, reported in up to 18% of patients undergoing lobectomy or lesser resections, and are associated with prolonged hospitalizations, morbidity, and considerable health care costs.⁸²⁻⁸⁴ The usual management of these patients includes prolonged tube thoracostomy drainage, pleurodesis, or attempts at surgical repair. The IBV (Olympus), initially developed as an approach to achieve bronchoscopic lung volume reduction in patients with emphysema, has received Food and Drug Administration approval as a humanitarian use device for the treatment of prolonged leak following lobectomy, segmentectomy, or lung volume-reduction surgery. The procedure is performed under deep sedation/general anesthesia and begins with selective balloon occlusion of the suspected airways. When the culprit airway is occluded, a significant reduction or cessation of the leak can be visualized in the water-seal chamber of the chest drainage system. A calibrated balloon is used to select the proper-sized valve, which is then placed under bronchoscopic control. It is common that multiple valves are used in each case because many patients have a degree of collateral ventilation. After 6 weeks the valves are removed. IBV use in this patient population has been associated with cessation of the air leak in as little as 1 day following placement and hospital discharge within 3 days in the majority of patients. Though complications can theoretically include postobstructive pneumonia, hypoxemia, and valve migration, these seem to be quite rare. More data are required before the use of endobronchial valves can be recommended for other causes of prolonged air leaks such as in the setting of secondary spontaneous pneumothorax.

Key Points

- Rigid and flexible bronchoscopy are essential tools for the interventional pulmonologist.
- Therapeutic bronchoscopy can improve quality and length of life in patients with central airway obstruction.

- Each therapeutic bronchoscopic modality has its own advantages and disadvantages; it is hoped that, with ongoing research, the best use of these techniques will be determined.
- Patients with central airway obstruction are best served by a multidisciplinary team of an interventional pulmonologist, thoracic surgeon, head and neck surgeon, anesthesiologist, and medical and radiation oncologist.
- Central airway obstruction with tumor can be approached by immediate (e.g., laser, stent) or delayed approaches (e.g., cryotherapy, photodynamic therapy). Techniques with immediate action should be selected when urgent therapy is needed or when any swelling would compromise ventilation.
- The hot techniques (electrocautery, argon plasma coagulation, laser photoresection) have immediate effects but cannot be used in a high-FiO₂ environment because of the risk for fire. For immediate therapy in a high-FiO₂ setting, a stent or microdebrider can be considered.
- Stent placement is the only technique that can treat extrinsic airway compression.
- Lung volume reduction can now be achieved via bronchoscopic techniques, including one-way endobronchial valves; however, these are not yet approved in the United States. One-way valves are reversible and affected by collateral flow; lung volume-reduction coils, biologic sealants, and thermal vapor ablation are irreversible and are useful even in the presence of collateral air ventilation.

Complete reference list available at [ExpertConsult](#).

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INTRODUCTION**THORACOSCOPY (PLEUROSCOPY/
MEDICAL THORACOSCOPY)**

Historical Development

Techniques

Equipment

Indications

Contraindications

Complications

Patient Preparation

Access to the Pleural Space

Anesthesia

Thoracoscopic Technique

Talc Pleurodesis

Results

**DIFFERENCES BETWEEN
THORACOSCOPY AND VIDEO-
ASSISTED THORACIC SURGERY****INTRODUCTION**

Biopsy procedures play an essential role in the diagnostic evaluation of patients with respiratory diseases. Most of the basic techniques we use today were mainly developed and refined during the 20th century. Recently, significant advances in endoscopic technology have provided sophisticated endoscopic instruments and endoscopic telescopes with extremely high optical resolution and small diameters. In addition, developments in anesthesiology offer a wide range of alternatives, from procedures performed under local anesthesia to selective double-lumen intubation under general anesthesia.

As with all medical procedures, the risk-benefit ratio of more invasive methods has to be considered for each individual patient, weighing the risk for morbidity and mortality against the benefit of obtaining an early diagnosis to guide correct therapy. Usually the more invasive procedures are used if simpler, less invasive methods have failed, if the latter are not very promising for obtaining a reliable diagnosis, or if additional therapeutic options can be combined with the diagnostic approach.

This chapter reviews these more invasive thoracoscopic procedures as performed by pulmonologists. Other biopsy methods, such as bronchoscopic biopsies, thoracentesis, needle biopsy of lung lesions, and closed-needle biopsy of the pleura, are described in other chapters.

**THORACOSCOPY (PLEUROSCOPY/
MEDICAL THORACOSCOPY)****HISTORICAL DEVELOPMENT**

Thoracoscopy was introduced together with laparoscopy in 1910 by Hans-Christian Jacobaeus, who at that time worked as an internist in Stockholm, Sweden. He published his first experiences in a paper entitled "On the Possibility to Use Cystoscopy in the Examination of Serous Cavities."¹ It was recently reported that, as early as 1866, F.R. Cruise in Ireland had possibly been the first to perform a thoracoscopy, examining the pleural space of a girl with empyema through a pleurocutaneous fistula that had developed after spontaneous pleural drainage.² Jacobaeus, in his pioneering

paper,¹ mentions two cases of pleuritis exudativa (tuberculous pleurisy), in which he studied the pleural surfaces after replacing the fluid with air. Although not able to get a clear impression of the pleural changes, he was confident that the method would be successful in the future and might eventually yield prognostic information. Jacobaeus³ himself initiated the therapeutic application of thoracoscopy for lysis of pleural adhesions by means of thoracocautery to facilitate pneumothorax treatment of tuberculosis ("Jacobaeus operation"). During the ensuing 40 years, his technique of using a single entry site for the thoracoscope and another for the electrocautery device under local anesthesia was applied worldwide for this specific therapeutic purpose, until antibiotic therapy of tuberculosis was introduced and made the procedure obsolete.⁴ Between 1950 and 1960, a generation of chest physicians familiar with the therapeutic application of thoracoscopy began to use the technique for biopsy diagnosis of pleural and even pulmonary disease.⁵ Today, thoracoscopy is considered as an integral part of interventional pulmonology.⁶

At the same time, the excellent results of laparoscopic surgery and the tremendous advances in endoscopic technology stimulated many thoracic surgeons almost simultaneously in Europe and the United States to develop minimally invasive techniques, which were termed "therapeutic" or "surgical thoracoscopy," as well as video-controlled or videothoracoscopic surgery, or *video-assisted thoracic surgery* (VATS).⁷⁻¹⁰

To clarify the difference between the two methods, the term *medical thoracoscopy* was introduced.¹¹ This is performed using the Jacobaeus technique under local anesthesia or conscious sedation, via a single or two sites of entry, by the pulmonary physician in an endoscopy suite using nondisposable rigid instruments.¹² Its main indications are the diagnosis and treatment of recurrent pleural exudative effusions and the treatment of spontaneous pneumothorax. However, because the term *thoracoscopy* is used for both the medical and the surgical procedures, a degree of uncertainty has arisen, which may lead to unnecessary surgical interventions for what are, in fact, medical indications. Recently the old term *pleuroscopy*⁴ has been reintroduced mainly for thoracoscopy with the semirigid (semiflexible) instrument called a pleuroscope.

Finally, in some countries, interventional pulmonologists have broadened their field of expertise to include more

elaborate interventions (e.g., sympathectomy, splanchnicectomy, treatment of empyema)¹³⁻¹⁵ and to perform thoracoscopy in the operating theater, under total intravenous anesthesia and spontaneous ventilation (with a laryngeal mask or simple endotracheal tube protecting the airway) or mechanical ventilation.

In fact, the terms *thoracoscopy*, *medical thoracoscopy*, and *pleuroscopy* are used interchangeably in the literature. To avoid confusion, in this chapter we will use the term *thoracoscopy* for the procedure performed by the pulmonologist, and consequently also the terms *thoracoscopist* and *thoracoscope*. For the thoracoscopic procedure performed by a surgeon, we will use the term *VATS*.

In Europe thoracoscopy is part of the training program of pulmonary medicine,¹⁶ and it is becoming more popular in the United States. According to a national survey in 1994, thoracoscopy was used frequently by 5% of all pulmonary physicians.¹⁷ Although newer data are not yet available, the interest in the technique seems to be increasing.¹⁸ However, training is lagging: in an American College of Chest Physicians' survey of U.S. pulmonary/critical care fellowship programs in 2002–2003, only 12% of the directors stated that thoracoscopy was offered in their programs.¹⁹ In the United Kingdom, where thoracoscopy has been underutilized compared with the rest of Europe, there is also growing interest.²⁰⁻²³ The British Thoracic Society published a guideline on thoracoscopy (using local anesthetic) in 2010.²⁴ In this guideline, three levels of competence in thoracoscopy are defined, of which level 1 includes basic diagnostic and therapeutic techniques and level 2 the more advanced techniques, whereas level 3 covers all VATS techniques (e.g., lung resection) and is the province of the thoracic surgeon.²⁵

Meanwhile, the technique has been introduced successfully in many Asian countries and in other parts of the world, particularly with the introduction of the semirigid (semiflexible) thoracoscope, called a *pleuroscope*.²⁶⁻²⁸

TECHNIQUES

Thoracoscopy is an invasive technique that should be used to obtain a diagnosis when other, simpler methods are non-diagnostic (in case of pleural exudates) or to achieve pleurodesis (in case of recurrent pleural effusion or pneumothorax).^{25,29} As with all technical procedures, there is a learning curve before full competence is achieved.^{30,31} Appropriate training is therefore mandatory.^{12,31,32,33} The technique of insertion by means of a trocar is actually very similar to that of chest tube insertion. Once the pleuroscope is in the pleural space, the thoracoscopist can visualize and obtain a biopsy specimen from all areas of the pleural cavity, including the chest wall, diaphragm, mediastinum, and lung under direct visual control. When indicated, talc pouddage can be performed. In general, thoracoscopy is easier to learn than flexible bronchoscopy if sufficient expertise in thoracentesis and chest tube placement has already been gained.¹²

There are two different techniques of diagnostic and therapeutic thoracoscopy, as performed by the pulmonary physician (Video 24-1³⁴).^{12,25,35,36} In the first method, as first described by Jacobaeus for diagnostic purposes, a single entry site is usually produced with a 7- or 9-mm trocar for

a thoracoscope with a working channel for accessory instruments and optical biopsy forceps; for this technique, local anesthesia is usually employed.⁵ This approach can be modified for use of a semirigid thoracoscope (also called *pleuroscope*).²⁶⁻²⁸ In the other technique, as used by Jacobaeus for lysis of adhesions, two entry sites are used: one with a 7-mm trocar for the examination telescope and the other with a 5-mm trocar for accessory instruments, including the biopsy forceps. For this technique, conscious sedation or general anesthesia is preferred.³⁵

EQUIPMENT

Rigid instruments are still in use, as they were from the beginning.²⁵ Compared with the rigid thoroscopes, flexible bronchoscopes or other flexible endoscopes have several disadvantages, mainly less adequate orientation within the pleural cavity and small channels that limit the size of biopsy forceps, which may result in inadequate biopsy specimens. A recently modified semirigid pleuroscope with a flexible tip has become an attractive alternative.^{26-28,28a} As mentioned, the single-entry-site technique is usually performed via a 7- or 9-mm diameter trocar and a cannula with valve. Trocars are also available with diameters of 5 and 3.75 mm for performing thoracoscopy in children. Optical devices exist with various fields of view (0, 30, and 90 degrees) (Fig. 24-1). Recently mini-thoracoscopy has been introduced, with the use of a rigid optical telescope of 3 mm and a trocar with a diameter of 4 mm.³⁶ The indication for minithoracoscopy is for the evaluation of a small pleural effusion or the presence of a narrow intercostal space. A second port of entry is necessary to obtain biopsy specimens. In infants, smaller rigid equipment (3.5 mm), also used for minithoracoscopy, or instruments similar to those used in rigid bronchoscopy are employed. Biopsy forceps with the feature of viewing straight ahead to the biopsy site as well as accessory instruments such as puncture needle, cautery electrode, probe, combined suction, cautery cannula with valves, and various biopsy forceps and scissors are available. For talc pleurodesis, a talc atomizer is used.³⁵

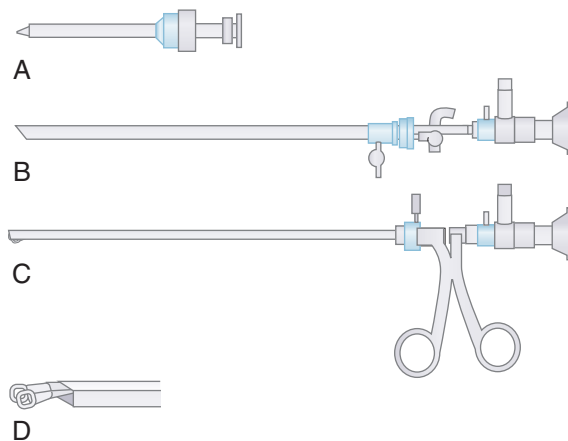


Figure 24-1 Instruments for thoracoscopy. A, Trocar and cannula with valve. B, Single-incision thoracoscope (9 mm diameter). C, Biopsy forceps with straight optics. D, Magnified view of optical device and forceps in the thoroscope shaft ready for biopsy. (Redrawn from Loddenkemper R: Thoracoscopy—state of the art. *Eur Respir J* 11:213–221, 1998.)



Figure 24-2 The semirigid (semiflexible) pleuroscope (Olympus Corporation). Control section allows handling as with the flexible bronchoscope. (Copyright Olympus SE & Co. KG.)

The two-entry-site technique uses a 7-mm trocar for the first site of entry for appropriate telescopes and forceps and similar accessory instruments. For the second site of entry, a 5-mm trocar is used for insertion of instruments designed for its smaller bore, including a loop for dividing adhesions and a double-lumen insufflator.³⁵

As stated earlier, the semirigid (semiflexible) pleuroscope, was developed recently.²⁶⁻²⁸ The design, including the handle, is similar to that of a standard flexible bronchoscope; however, the proximal 22 cm is stiff and the distal 5 cm is bendable with an angulation of 160 and 130 degrees (Fig. 24-2). The outer diameter of the shaft is 7 mm, and a working channel of a diameter of 2.8 mm allows the use of standard instruments available for flexible bronchoscopy. The semirigid pleuroscope has several advantages. The skills involved in operating the instrument are already familiar to the practicing bronchoscopist. Because the shaft is rigid, it can be moved like the rigid thoracoscope without losing the orientation, and it is compatible with the video processors and light sources of the same manufacturer. Finally, the flexible tip permits easier visualization of the entire pleural cavity and permits a homogeneous distribution of talc on all surfaces.²⁵ Compared with rigid thoracoscopic instruments, the disadvantages of the flexible pleuroscope are the costs, the vulnerability of the scope, and the smaller biopsy specimens, although its diagnostic yield in pleural disease has been shown to be comparable with that of the conventional rigid thoracoscope.^{25,28} In addition, the flexible forceps used with the pleuroscope may not have the mechanical strength to obtain pleural biopsy specimens of sufficient depth, which may reduce the diagnostic yield in mesothelioma. This technical problem can be overcome by the use of a diathermic knife, which is also useful for the cutting of pleuropulmonary adhesions.²⁷

The procedure suite should be equipped with monopolar and, if possible, bipolar electrocoagulation as well as equipment for resuscitation and assisted ventilation, electrocardiography, and blood pressure monitoring, and a defibrillator, an oxygen source, and vacuum generators.^{5,35}

Thoracoscopy can be performed in the operating room or in an environment dedicated to invasive procedures (see Video 24-1³⁴).^{11,12,27} The personnel required to perform

thoracoscopy include an endoscopy nurse (or an endoscopy assistant) to assist with the instrumentation, an additional assistant outside the sterile field to bring necessary equipment, and the physician performing the thoracoscopy.³¹ Ideally an additional person sits at the patient's head and monitors his or her overall condition. In an emergency, thoracoscopy can be performed with only a physician and a nurse, but this is less efficient and prolongs the procedure.⁵ Medical thoracoscopy can also be performed safely in an entirely outpatient setting.^{36a}

INDICATIONS

Thoracoscopy today is primarily a diagnostic procedure, but it can also be applied for therapeutic purposes (Table 24-1).^{11,12,15,25} Thoracoscopy is mainly used for diagnosis of exudates of unknown cause, for staging of diffuse malignant mesothelioma or lung cancer, and for treatment by talc pleurodesis of malignant or other recurrent effusions.^{37,38} Thoracoscopy is also useful for evaluation and possible treatment of spontaneous pneumothorax and empyema.¹¹ For those familiar with the technique, thoracoscopy is also indicated for diagnostic biopsies from the diaphragm, lung, mediastinum, and pericardium and for more elaborate procedures.¹³⁻¹⁵ As mentioned earlier, there is an overlap of indications between thoracoscopy and VATS (see later discussion and Table 24-1). In addition, thoracoscopy offers a remarkable tool for research as a gold standard in the study of pleural effusions.

The diagnosis of pleural effusions is the main and oldest indication for thoracoscopy, as described by Jacobaeus himself in his earliest articles.^{1,4} However, even in the therapeutic era, publications from many countries emphasized the diagnostic value of thoracoscopy in spontaneous pneumothorax, focal pulmonary disease, diseases of the chest wall, mediastinal tumors, diseases of the heart and great vessels, and thoracic trauma.⁴ Later, these indications were expanded to include performing biopsies for localized and diffuse lung diseases.^{11,12} Today, the use of thoracoscopy for diagnosis of lung diseases has decreased owing to the improvements in less invasive pulmonary biopsy techniques such as flexible bronchoscopic biopsy and computed tomography (CT)-guided biopsy.^{4,12}

In the past, therapeutic thoracoscopy was used extensively for collapse treatment of tuberculosis to sever adhesions that prevented a complete artificial pneumothorax.³ This indication disappeared after the successful introduction of chemotherapy for tuberculosis.⁴ Today, the main indication for therapeutic thoracoscopy is talc poudrage in malignant or other chronic and recurrent pleural effusions.³⁸ The first report on *talcage* was published in 1935,³⁸ and in 1963 it was first used for treating recurrent effusions.⁴ Since then, talc poudrage performed during thoracoscopy for pleurodesis in malignant pleural effusions has been widely applied, especially in Europe.⁴ Talc pleurodesis via thoracoscopy has several advantages over pleurodesis via a thoracostomy tube: simultaneous drainage of pleural fluid, visualization of the visceral pleura to ensure that the lung is not encased by pleural thickening or tumor that could prevent reexpansion (Video 24-2), and guidance of chest tube placement.³⁹ In addition, talc pleurodesis can also be used to prevent recurrent pneumothorax.⁴⁰

Table 24-1 Indications for Thoracoscopy (Medical Thoracoscopy) versus VATS (Surgical Thoracoscopy)

Thoracoscopy	Thoracoscopy or VATS (Gray Area)	VATS
PLEURAL EFFUSIONS <ul style="list-style-type: none"> ■ Pleural effusions of unknown cause ■ Staging of lung cancer ■ Staging of diffuse malignant mesothelioma ■ Pleurodesis by talc poudrage 	SPONTANEOUS PNEUMOTHORAX <ul style="list-style-type: none"> ■ Staging ■ Pleurodesis by talc poudrage EMPHYEMA (STAGE I/II) <ul style="list-style-type: none"> ■ Drainage DIFFUSE PULMONARY DISEASES <ul style="list-style-type: none"> ■ Biopsy LOCALIZED LESIONS <ul style="list-style-type: none"> ■ Chest wall, diaphragm ■ Sympathectomy ■ Splanchnicectomy 	LUNG PROCEDURES <ul style="list-style-type: none"> ■ Lung biopsy ■ Lobectomy ■ Lung volume reduction surgery PLEURAL PROCEDURES <ul style="list-style-type: none"> ■ Pleurectomy (pneumothorax) ■ Drainage/decortication (empyema stage III) ESOPHAGEAL PROCEDURES <ul style="list-style-type: none"> ■ Excision of cyst, benign tumors ■ Esophagectomy ■ Antireflux procedures MEDIASTINAL PROCEDURES <ul style="list-style-type: none"> ■ Resection of mediastinal mass ■ Thoracic lymphadenectomy ■ Thoracic duct ligation ■ Pericardial window ■ Sympathectomy

VATS, video-assisted thoracic surgery.

Other indications for therapeutic thoracoscopy are the drainage of empyema¹⁵ or dorsal sympathectomy in hyperhidrosis patients.^{13,14} Anecdotal reports describe its use for removal of foreign bodies, for removal of benign tumors, and for production of pericardial fenestrations.¹²

CONTRAINDICATIONS

Contraindications to thoracoscopy are few and rarely absolute.²⁵ The main limitation is the size of the free pleural space, which must be at least 6 to 10 cm in width.¹² If extensive adhesions prevent the lung from collapsing away from the chest wall, thoracoscopy can still be performed (extended thoracoscopy), but this requires special skill and should not be undertaken without appropriate training.⁴¹

Several factors may make it necessary to postpone thoracoscopy but are rarely prohibitive; these include a persistent cough, hypoxemia, hypocoagulability (prolonged international normalized ratio or platelet count <40,000 to 60,000/ μ L), and cardiac abnormalities. Hypercarbia indicative of respiratory failure may prove to be an absolute contraindication, except in patients with a tension pneumothorax or massive pleural effusion, in whom it can be anticipated that thoracoscopy would provide therapeutic benefit in addition to a possible diagnosis. Under these conditions, premedication should be administered judiciously to minimize respiratory center depression. Even in very ill patients on a ventilator, diagnostic thoracoscopy has been carried out without significant complications.^{5,35}

Contraindications for pulmonary biopsy are suspicion of arteriovenous pulmonary aneurysm, vascular tumors, hydatid cysts, and a stiff fibrotic lung.^{30,42} Relative contraindications for pulmonary biopsy would include previous systemic steroid or immunosuppressive therapy because, under these circumstances, bronchopleural fistulas resulting from lung biopsy may heal poorly.

The thoracoscopist must consider the risk-benefit ratio in each case. Thoracoscopy should be performed only after careful evaluation aimed at answering specific questions.

COMPLICATIONS

Thoracoscopy is a safe and effective modality in the diagnosis and treatment of several pleuropulmonary diseases if certain standard criteria are fulfilled.^{5,25,35,43} In the most thorough review, there was only 1 death among 8000 cases, for a mortality rate of 0.01%.⁴² In another series reviewing 4300 cases, the mortality rate was 0.09%.³⁵ The reported mortality rate of thoracoscopy is thus roughly equivalent to or less than that of transbronchial biopsies. In another report of 817 thoracoscopy procedures using conscious sedation and local anesthesia, the complications were persistent air leak of more than 7 days' duration in 2%, subcutaneous emphysema in 2%, and postoperative fever in 16%.⁴⁴ The major complication rate in a series of 102 patients was 1.9% and included ventricular tachycardia responding to resuscitation, subcutaneous emphysema, and persistent air leak.⁴⁵ The minor complication rate was 7.5%, including transient air leak, fever, and minor bleeding at a biopsy site. Another large series including 360 patients reported morbidities of fever in 9.8%, empyema in 2.5%, pulmonary infection in 0.8%, and malignant invasion of the scar in 0.3%.⁴⁶ Major uncontrollable bleeding requiring thoracotomy was not reported in any of these large series and appears to be extremely rare. Many complications such as benign arrhythmias, low-grade hypotension, and hypoxemia can be prevented by administration of oxygen.⁴⁷ In case of persistent bleeding, electrocoagulation may become necessary.³⁵

Reexpansion pulmonary edema from the removal of large pleural effusions is infrequent, perhaps because immediate equilibration of the pleural pressure is provided by direct entrance of air through the cannula into the pleural

space. Bronchopleural fistulas may follow lung biopsies; if the lungs are stiff, a fistula may require longer to heal than the usual 3- to 5-day period of chest tube drainage with applied pleural suction.³⁵ Local site infection is uncommon, and empyema has been reported only very rarely.⁴² In cases of mesothelioma the late complication of tumor growth at the site of entry has been observed after thoracoscopy and also after thoracentesis or closed-needle biopsy. Radiation therapy 10 to 12 days after thoracoscopy has been reported to prevent this late complication,⁴⁸ although the standard use of prophylactic radiation therapy in these cases is controversial.⁴⁹ After talc poudrage, any postprocedure fever, as a nonspecific inflammatory reaction, and pain can be treated symptomatically. In conclusion, the overall mortality rate with thoracoscopy is extremely low. Morbidity, which is mainly due to benign postprocedural fever, is also minimal. Thoracoscopy in the hands of the appropriately trained pulmonologist is safe.⁴³

PATIENT PREPARATION

Before thoracoscopy, radiologic evaluation should routinely include a posteroanterior and a lateral chest radiograph.²⁵ Ultrasonography for localization of the pleural fluid and for diagnosis of potential fibrinous membranes or adhesions in the pleural space is helpful (see Chapter 20). In a British observational study, thoracic ultrasonography localized a safe site for thoracoscopy when not clinically apparent in 11 out of 80 cases (14%) and detected unexpected septations in 7 (9%).⁵⁰ According to the guidelines of the British Thoracic Society on pleural procedures and ultrasonography, thoracic ultrasonography is strongly recommended for all pleural procedures to localize the site of pleural fluid.⁵¹ A CT scan is not mandatory but can be helpful to localize abnormalities such as loculated empyema or localized lesions (tumors) of the chest wall or diaphragm.

Evaluation of the patient's respiratory status requires, at a minimum, arterial or capillary blood gas analysis. An electrocardiogram should be obtained to exclude recent myocardial infarction or significant arrhythmia. The clinical laboratory will provide the coagulation parameters, serum electrolyte levels, and blood glucose level as well as blood group typing, platelet count, results of liver function studies, and serum creatinine level.

The planned technique, the management of possible postoperative complications, and the expected diagnostic or therapeutic results should be explained to the patient. It is only then that the patient can truly provide informed consent.⁵

The site of introduction of the thoracoscope depends in part on the location of abnormalities to access and the location of potentially hazardous areas to avoid. Thoracoscopy is usually performed with the patient in the lateral decubitus position with the intended procedural site facing upward.^{5,11,35,52} A pillow is placed under the patient's flank, causing the spine to flex laterally and widening the intercostal spaces at the procedural site.

ACCESS TO THE PLEURAL SPACE

Because it is impossible to perform the procedure if the pleural cavity is completely obliterated, a sufficiently large

pleural space is an essential prerequisite, allowing the introduction of the trocar and thoracoscope without injuring the lung or other organs (see [Video 24-1](#)³⁴).²⁵

The simplest access is available in the setting of a preexisting complete pneumothorax or large pleural effusion, in which the trocar can be introduced directly into the pleural space without risk for injuring the lung. In the setting of a small or moderate-size pleural effusion, a needle puncture should be performed at the level of greatest opacification/dullness or, ideally, under ultrasonographic or fluoroscopic guidance. When pleural fluid is aspirated, the syringe is removed from the needle, and air enters the pleural space either spontaneously or after the patient takes a few deep breaths. The entry of air causes the lung to collapse away from the chest wall and creates a pleural space for safe trocar insertion. Alternatively, if one is certain that the needle is well positioned in the pleural fluid (e.g., not in the lung), air can be injected into the pleural space by means of a syringe. Most often, a few milliliters of air is sufficient to create a good separation of the lung from the chest wall. Greater safety is provided under ultrasonographic guidance, which allows the operator to localize the pleural effusion and to exclude thick septations/adhesions, which may prevent a sufficient collapse of the lung and thus may cause possible complications such as bleeding and injury to the lung, diaphragm, and other thoracic structures when introducing the trocar at the site of the septations/adhesions.⁵³ Another option is fluoroscopy "on the table," which can show the air-fluid level caused after injection of air, as well as the presence of any adhesions.

If neither effusion nor pneumothorax is present, an artificial pneumothorax must be created either by the blunt dissection technique using the finger⁴¹ or by the technique of pneumothorax induction. The blunt dissection technique (extended thoracoscopy) involves gentle dissection of the pleural adhesions with a finger to advance the thoracoscope into the pleural space.^{41,52} Some operators introduce carbon dioxide, instead of air, to maximize absorption rates in the unlikely event of air embolism. If so, the pneumothorax should be induced immediately before undertaking thoracoscopy, because the pneumothorax will be absorbed rapidly.^{5,12} Some thoracoscopists induce the pneumothorax the day before the procedure, allowing more time to obtain pressure measurements and to determine if the pleural space is patent, as indicated by a fluctuation of pressure with breathing between -15 and -5 cm H₂O (1 cm H₂O \cong 1 mbar).

However, some experienced teams regularly perform thoracoscopy without any form of image-guided induction of a pneumothorax. In one series of more than 700 thoracoscopies conducted without preprocedural imaging of the entry site, induction of a pneumothorax was impossible in only 10 patients, due to extensive adhesions.⁵⁴ In this series, no major complications such as bleeding were observed.

ANESTHESIA

Thoracoscopy by the single-entry-site technique is usually done under local anesthesia with premedication, together with an antianxiolytic, a narcotic, or both (e.g., midazolam and hydrocodone).²⁵ If necessary, additional pain medication should be given during the procedure, as required.

With this conscious sedation, an anesthetist is not needed. Exceptions are rare idiosyncratic or allergic sensitivities to typical anesthetics, very anxious or uncooperative patients, including children, and severe hypercarbia. An excellent alternative today is sedation by propofol with or without premedication⁵⁵; however, the use of propofol for moderate sedation is not approved in some countries, including the United States, without the supervision of an anesthesiologist.⁵⁶ General anesthesia with intratracheal intubation and ventilation is used in some centers,⁵⁷ as it is for VATS, but is not generally necessary for thoracoscopy.^{12,52}

Monitoring devices such as a cardiac monitor, oxygen saturation monitor, and automatic blood pressure monitor are applied. Some advocate the simultaneous measurement of cutaneous or exhaled carbon dioxide tension, because sedation may lead to significant hypoventilation.⁵⁸ An intravenous line is maintained, both for intravenous sedation and for possible resuscitation medications.

THORACOSCOPIC TECHNIQUE

The site of introduction of the thoracoscope should be chosen to access the location of presumed abnormalities and to avoid potentially hazardous areas such as the midanterior line, where one finds the internal mammary artery, the axillary region with the lateral thoracic artery, and the infraclavicular region with the subclavian artery (see **Video 24-1**³⁴). The region of the diaphragm is unsuitable, not only because adhesions are frequent but also because the liver or spleen may be injured.^{5,12,25,52} For general applications the trocar is introduced in the lateral thoracic region between the midaxillary and the anterior axillary line in the 4th to 7th intercostal space ("safety triangle"); for pleural effusions, in the 6th or 7th intercostal space; and for pneumothorax, in the 4th intercostal space. Following preparation with a surgical disinfectant and local anesthesia using 1% or 2% lidocaine, a small skin incision is made, and the trocar is advanced with a fairly forceful corkscrew motion until the detectable resistance of the internal thoracic fascia has been overcome. The cannula of the trocar should lie at least 0.5 cm within the pleural space. Pleural effusions should be removed by using a suction tube that does not occlude the cannula, so that air may rapidly enter the pleural space to equalize pressures. After complete removal of the effusion, or in cases without effusion, the optical device is introduced through the cannula, and the pleural space is then inspected (see **Video 24-1**³⁴) (**Fig. 24-3**).

The pleural space can be inspected directly through the thoracoscope or indirectly by viewing the image on a screen via videothoracoscopy, the standard procedure today. The advantages of videothoracoscopy over direct thoracoscopy are multiple: The view is better when projected on a screen, the other participants of the procedure (fellow, nurse, anesthesiologist) can watch the thoracoscopy, which is also important for teaching purposes, and indirect viewing provides greater sterility.

Anatomic relationships and intrathoracic structures are usually well recognized (**Video 24-3**). Biopsies of the pleura and, if needed, of the lungs, can be performed easily and safely by means of the lung biopsy forceps (**Video 24-4**). In the presence of undiagnosed pleural effusions, biopsy specimens should be taken from macroscopic lesions at the

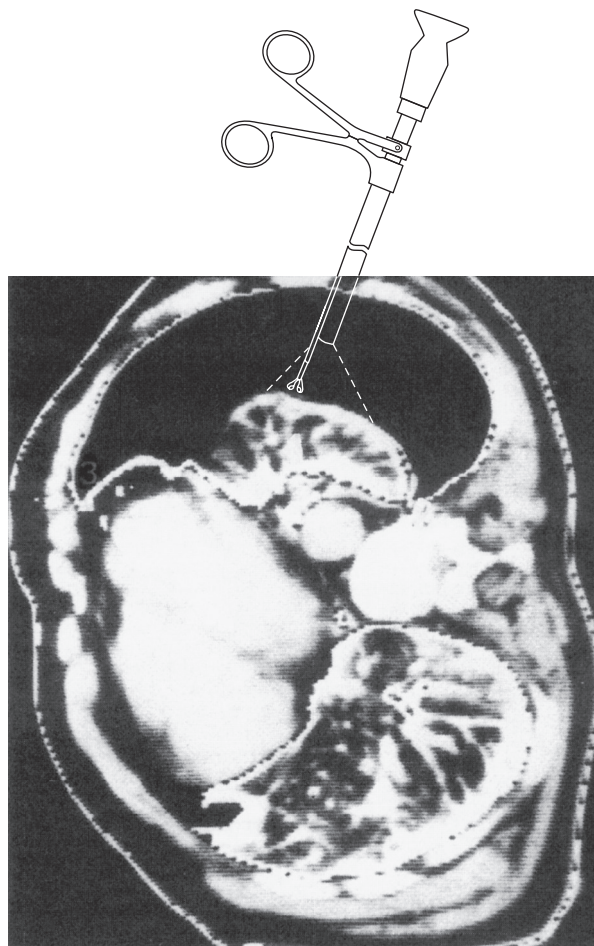


Figure 24-3 CT representation of pleuroscopy in the right thoracic cavity with the patient in the left lateral decubitus position. Visualization of the chest wall, pleura, diaphragm, lung, and anterior (and part of posterior) mediastinum is possible. (From Loddenkemper R: Thoracoscopy—state of the art. *Eur Respir J* 11:213–221, 1998.)

anterior chest wall, the diaphragm, and the posterior chest wall for histologic evaluation and, if there is suspicion of tuberculosis, for mycobacterial culture. If no macroscopic abnormalities are visible, several biopsy specimens should be taken from different sites of the parietal pleura. Biopsy specimens from the lung are not taken routinely because of the risk for creating a fistula but may be necessary when the abnormalities are seen only on the lung surface. The likelihood of creating a bronchopleural fistula can be reduced by the use of an electrocautery biopsy forceps.⁵⁹ In cases of inflammatory pleural exudates or when several therapeutic thoracenteses have already been performed, fibrinous membranes or adhesions may be present that hinder examination. If so, these can be severed by using a blunt forceps or by cutting with electrocautery.

Although a single site of entry is generally sufficient, a second site may be useful for biopsies or to coagulate.³⁵ A second port of entry is mandatory to introduce a biopsy forceps in case of mini-thoracoscopy, in which the scope is too small to accommodate a forceps.³⁶ The position of the second site of entry can be determined by viewing through the 50-degree scope while depressing the possible entry site with the index finger. It is sometimes helpful to insert a

needle through the same site while viewing its precise location through the thoracoscope. After administration of a local anesthetic, a 5-mm incision is made and the 5-mm trocar is inserted directly. Its cannula will accommodate many instruments designed for its smaller bore.

TALC PLEURODESIS

Talc poudrage is the most widely reported method of talc instillation into the pleural space.³⁸ It is mainly used for pleurodesis in malignant or recurrent pleural effusions^{27,38,42} but is also used in persistent or recurrent spontaneous pneumothorax.⁴⁰ Thoracoscopic talc pleurodesis can be performed under local anesthesia but generally requires additional pain medication.²⁵

Before the procedure it is important to confirm that the lung can completely expand because contact of the lung with the chest wall will be necessary for a successful pleurodesis.^{38,39} Failure to expand fully may indicate a trapped lung caused by thickening of the visceral pleura (which can be confirmed at thoracoscopy) or a main-stem bronchial occlusion by tumor. If the chest radiographs fail to show a contralateral mediastinal shift in the presence of a large pleural effusion, an endobronchial obstruction should be suspected and, if possible, removed by bronchoscopy before the thoracoscopy.

During the procedure, in cases of pleural effusion it is important to remove all pleural fluid before spraying with talc. Complete collapse of the lung is desirable, because it permits wide and uniform distribution of the talc.

The optimal dose of talc for poudrage is not known, but usually a dose of approximately 5 g is recommended for malignant or recurrent effusions,³⁹ whereas for pneumothorax patients 2 g is usually sufficient.⁴⁰ The pleural cavity should be inspected during talc insufflation to ensure that the talc is uniformly distributed (Video 24-5). For this purpose one can use a thoracoscope with an angled optical device and a flexible suction catheter that is connected to a small bottle containing talc and to a pneumatic atomizer introduced through the working channel of either the thoracoscope^{35,52} (Fig. 24-4) or the semirigid pleuroscope.²⁷

After talc poudrage a 10- to 24-French chest tube should always be inserted and pointed toward the posterior costo-

vertebral gutter in patients with effusions or toward the apex in patients with pneumothorax. It is questionable if suction is necessary. If suction is applied, the use of high-volume, low-pressure systems is recommended, with a gradual increment in pressure to about -20 cm H₂O.⁶⁰ Following the procedure, chest tube removal has been recommended when the daily amount of fluid production is less than 150 mL, but there is little evidence to support this practice.⁶⁰ One report suggests that the chest tube can be removed within 24 hours without regard to daily fluid production.⁶¹ A potential advantage of talc poudrage via thoracoscopy compared with slurry delivered via chest tubes is the more even distribution of talc over the whole pleural surface.³⁹ In three head-to-head studies⁶²⁻⁶⁴ comparing talc poudrage with talc slurry instillation, talc poudrage was at least equally, and in some studies significantly more, effective, than talc slurry; slurry has never been shown to be superior to poudrage. In patients undergoing thoracoscopy, talc poudrage should therefore be the preferred method. In patients with a poor Karnofsky index, or when thoracoscopy is refused or impossible, talc slurry represents a valid alternative.

Talc is inexpensive and highly effective.⁶⁵ Its most common short-term adverse effects include fever and pain. Cardiovascular complications such as arrhythmias, cardiac arrest, chest pain, myocardial infarction, and hypertension have been noted⁶⁶; whether these complications result from the procedures or are related to talc per se has not been determined.⁶⁷ Acute respiratory distress syndrome, acute pneumonitis, and respiratory failure have also been reported after talc poudrage and slurry, especially in the United States. The development of respiratory failure is most likely due to the dose and especially to smaller particle sizes of talc,⁶⁸ which can distribute via the pleural stomata (which are the openings to the lymphatics) to the lung.⁶⁹ Ferrer and associates⁶⁹ demonstrated that the particle size of the talc used in the United States is significantly smaller than the French talc that is used in Europe (10th percentile diameter 2.4 to 3.1 μ m in the United States versus 10.5 μ m for French talc). In a review it was demonstrated that a small particle size of talc plays a key role in the development of complications after talc pleurodesis⁷⁰ via the pleural lymphatics to the rest of the body. The use of size-calibrated, larger-size talc appears to be absolutely safe in the treatment of recurrent pleural effusions and spontaneous pneumothorax.⁷¹⁻⁷⁴ Unfortunately, the large-particle size-calibrated French talc has not yet been approved for use in the United States.

RESULTS

Pleural Effusions

Even after extensive diagnostic workup of the pleural fluid, the cause of a number of pleural effusions may remain undetermined.^{12,75} Blind needle biopsies may establish the diagnosis in some additional cases, particularly in tuberculous pleurisy. In a series by Boutin and colleagues³⁰ of 1000 consecutive patients with pleural effusion, 215 cases remained undiagnosed after repeated pleural fluid analysis and performance of pleural biopsies. This is in agreement with the results of several other authors who, without the

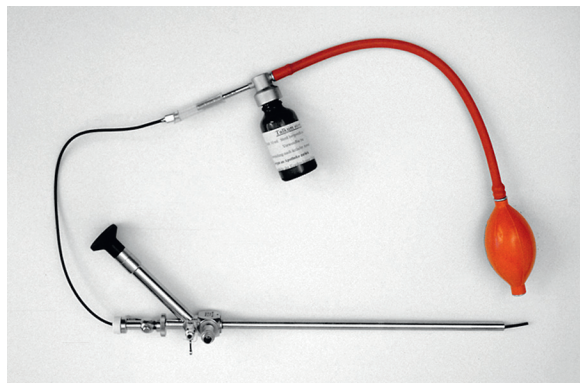


Figure 24-4 The flexible catheter, connected to a small bottle containing talc and to a pneumatic atomizer (manual insufflator), is introduced through the working channel of the rigid thoracoscope.

use of thoracoscopy, report that at least 20% to 25% of pleural effusions remain undiagnosed, although this certainly depends strongly on the particular patient populations.¹² Because of the higher diagnostic yield and ability to induce pleurodesis in a single setting, it has been estimated in a theoretical cost analysis in the United Kingdom that medical thoracoscopy may save considerable costs in the evaluation of unexplained pleural effusions compared with other tests, including image-guided pleural biopsy.⁷⁶

Several studies have tried to determine the diagnostic accuracy of thoracoscopy in the setting of undiagnosed pleural effusion, but the results vary widely, with a range of 60% to 90%.^{30,45,77} Closer evaluation of the study designs reveals that the duration of follow-up was occasionally short and frequently not mentioned at all. One well-designed study of thoracoscopy in 102 patients reported by Menzies and Charbonneau,⁴⁵ with follow-up periods between 1 and 2 years, found a sensitivity of 91%, a specificity of 100%, accuracy of 96%, and a negative predictive value of 93%. Boutin and colleagues³⁰ reported a false-negative rate of 15% within 1 year of follow-up. In a retrospective study of 709 patients who underwent thoracoscopy for diagnosis of unexplained exudative effusions, Janssen and coworkers⁷⁷ also found a 15% false-negative rate in a long-term follow-up (minimum, 24 months) of 208 patients with initial negative results; the overall sensitivity of thoracoscopy was 91%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 92%.⁷⁷ Of note, even thoracotomy can miss the diagnosis. In a study of the results of thoracotomy in patients with pleural effusion of undetermined cause, even after a pathologic diagnosis of a benign pleural process, 25% of patients were diagnosed with a malignancy.⁷⁸ The diagnoses most often missed were malignant pleural mesothelioma and lymphoma (mesothelioma in 10 and lymphoma in 4 out of 31 cases,⁷⁷ and lymphoma in 6 and mesothelioma in 4 of 13 cases⁷⁸). Autofluorescence videothoracoscopy may help in the future to avoid some of the false-negative results.⁷⁹

Because of its high diagnostic accuracy, diagnostic thoracoscopy is an excellent option in cases of exudates in which the cause remains undetermined after pleural fluid analysis.^{27,39,42} The procedure allows fast and more definite biopsy diagnosis, including a high yield for tuberculosis cultures, and determination of hormone receptors in some malignancies. Furthermore, staging in lung cancer and diffuse mesothelioma is possible. The exclusion of an underlying malignancy or of tuberculosis is provided with high probability. Surgery, including surgical thoracoscopy, not only is more invasive and expensive but also does not produce better results than thoracoscopy and should therefore be reserved for very selected cases.

Malignant Pleural Effusions

Diagnosis. Malignant pleural effusions are today the leading diagnostic and therapeutic indication for thoracoscopy^{12,27,80} (Figs. 24-5 and 24-6). In a prospective comparison of different diagnostic tests, the diagnostic yield of nonsurgical biopsy methods in malignant pleural effusions was studied simultaneously in 208 patients, including 116 metastatic pleural effusions (from 28 breast cancers, 30 cancers of various other organs, and 58 cancers of unde-

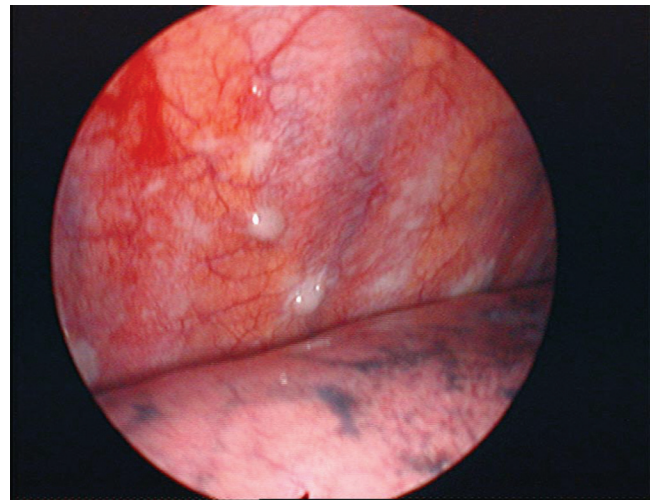


Figure 24-5 View through the thoracoscope in a patient with a malignant pleural effusion due to breast cancer. One can see small whitish tumor nodules on the parietal (chest wall) pleura (*upper part of photo*). The lung surface (*lower part of photo*) demonstrates some anthracosis. (From Loddenkemper R, Mathur PN, Noppen M, Lee P: *Medical thoracoscopy/pleuroscopy: manual and atlas*, New York, 2011, Thieme.)

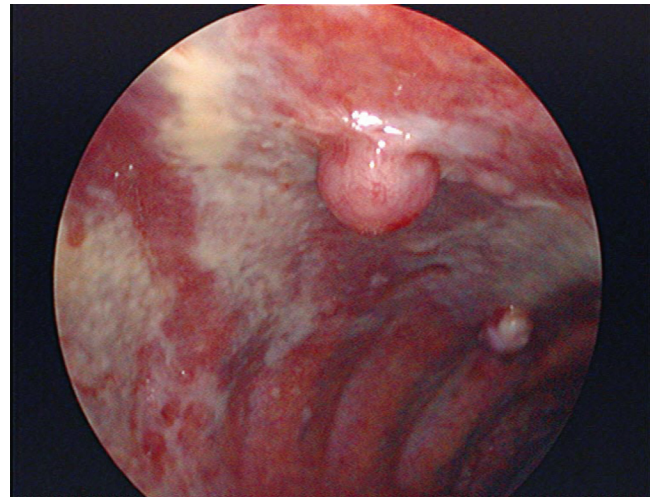


Figure 24-6 View through the thoracoscope in a patient with diffuse malignant mesothelioma following occupational asbestos exposure. One can see tumor nodules and whitish areas with pleural thickening on the parietal (chest wall) pleura (*upper part of photo*). Histologic examination revealed a sarcomatoid cell type. (From Loddenkemper R, Mathur PN, Noppen M, Lee P: *Medical thoracoscopy/pleuroscopy: manual and atlas*, New York, 2011, Thieme.)

termined origin); 29 cancers of the lung; 58 diffuse malignant mesotheliomas; and 5 malignant lymphomas.⁴² The diagnostic yield of pleural fluid cytologic examination was 62%, of closed pleural biopsy was 44%, and of thoracoscopy was 95%. The sensitivity of thoracoscopy was higher than that of cytologic examination and closed pleural biopsy combined (95% vs. 74%, $P < 0.001$). The combined methods were diagnostic in 97% of malignant pleural effusions (Fig. 24-7). In 6 of the 208 cases (2.9%), an underlying neoplasm was suspected at thoracoscopy but confirmed only by thoracotomy or autopsy. Similar results have been reported by a number of other investigators.^{21,29,77}

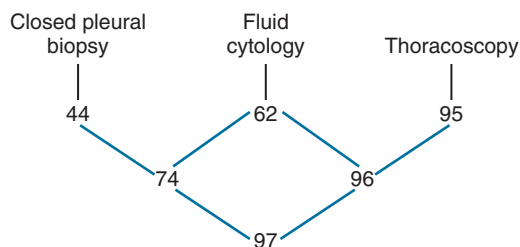


Figure 24-7 Sensitivity of different biopsy methods (cytologic and histologic results combined) for the diagnosis of malignant pleural effusions. Numbers represent sensitivity (%) of tests, either alone or combined, in a prospective inpatient comparison of 208 patients. It shows that thoracoscopy alone has 95% sensitivity for the diagnosis of malignancy; cytology and closed pleural biopsy contribute little to the total sensitivity for all three tests of 97%. (Redrawn from Loddenkemper R, Boutin C: Thoracoscopy: present diagnostic and therapeutic indications. *Eur Respir J* 6:1544–1555, 1993.)

The reasons for false-negative results of thoracoscopy include insufficient and nonrepresentative biopsy specimens, probably due to lack of experience of the thoracoscopist or the presence of fibrous adhesions preventing access to neoplastic tissue.^{35,42}

The diagnostic sensitivity of thoracoscopy is similar for all types of malignant effusion. In one study the overall yield in 287 cases was 62% for cytologic examination and 95% for thoracoscopy; the relative yields for cytologic examination and thoracoscopy did not vary greatly for lung carcinomas ($n = 67$), at 67% and 96%, respectively, for extrathoracic primaries ($n = 154$), at 62% and 95.5%, or for diffuse malignant mesotheliomas ($n = 66$), at 58% and 92%.¹²

Staging. Thoracoscopy may be useful in staging lung cancer, diffuse malignant mesothelioma, and metastatic cancer. In lung cancer patients, thoracoscopy can help to determine whether the effusion is malignant or paramalignant.⁴² As a result, it may be possible to avoid exploratory thoracotomy for tumor staging. Canto and associates⁸¹ found no thoracoscopic evidence of pleural involvement in 8 of 44 patients with lung cancer and pleural effusion; 6 proceeded to resection, where the lack of pleural involvement was confirmed. The new American College of Chest Physicians Clinical Practice Guidelines recommend that patients suspected of having lung cancer who have an accessible pleural effusion and a negative pleural fluid cytology should have a pleural biopsy, either by image-guided techniques or by thoracoscopy.^{81a}

In diffuse malignant mesothelioma (Videos 24-6 and 24-7), thoracoscopy can provide an earlier diagnosis and better histologic classification than closed pleural biopsy because of larger and more representative biopsy specimens and more accurate staging.^{82,83} Earlier diagnosis and staging may have important therapeutic implications either for surgery or for local immunotherapy or local chemotherapy, because better clinical outcomes have been observed for patients detected in the early stages (I and II).⁸²

Thoracoscopy is also helpful in the diagnosis of benign asbestos-related pleural effusion by excluding mesothelioma or malignancies. Fibrohyaline or calcified, thick, and pearly white pleural plaques may be found (see as a small part of Video 24-8), indicating possible asbestos exposure.⁸²

Thoracoscopic pulmonary biopsy specimens and even biopsy specimens from special lesions on the parietal pleura may demonstrate high concentrations of asbestos fibers and thereby provide further support for a diagnosis of asbestos-induced disease.⁸⁴

A further advantage of thoracoscopy in metastatic pleural disease is that biopsies of the visceral and diaphragmatic pleura are possible under direct observation. In addition, the larger size of thoracoscopic biopsy specimens may provide easier identification of primary tumor, including hormone receptor determination in breast cancer,⁸⁵ and improved morphologic classification in lymphomas.^{86,87} In addition, the extent of intrapleural tumor spread can be described using a scoring system that has been shown to correlate well with survival⁸⁸ and with response to talc poudrage.⁸⁹

Of recent interest is the assessment of specific mutations in lung cancer cells that can direct targeted therapy. In pleural biopsy specimens, Guo et al⁹⁰ found a rate of 70% of epidermal growth factor receptor mutations and concluded that pleural biopsy specimens, in this case obtained by VATS, provided better material than other techniques, even including surgical resection. Adequate tissue appears to be important for these assays; the reliability of cytologic examination for demonstration of epidermal growth factor receptor mutations is subject to further research.⁹¹ Direct comparative studies on epidermal growth factor receptor mutation rate of histologic and cytologic specimens are not available.

Therapy. In malignant pleural effusions, talc pleurodesis achieves success rates of more than 90% as reported in several series.³⁹ Although there is a lack of randomized controlled studies, talc poudrage seems to be the most efficient method of pleurodesis.³⁹ Diacon and colleagues,⁹² in a prospective randomized trial, compared thoracoscopic talc poudrage under local anesthesia to bleomycin instillation. In 36 patients they found much lower recurrence rates of effusion after talc poudrage (13% and 65%, respectively, after 180 days). A cost estimation also favored talc poudrage, both for initial hospitalization and with regard to recurrences. Boutin and associates³⁵ randomly compared talc poudrage and tetracycline instillation in 40 patients: after 1 month, the success rate was 90% for talc and 80% for tetracycline; however, after 9 months, talc pleurodesis persisted, whereas half had recurred after tetracycline. Fentiman and coworkers⁹³ found talc superior to tetracycline for control of pleural effusions secondary to breast cancer. Viallat and associates,⁴⁶ in a retrospective study of over 300 patients, found that talc poudrage achieved a 90% success rate at 1 month and, in 82%, produced a lifelong symphysis. The success rate in metastatic adenocarcinoma cases was higher than in mesothelioma cases. Weissberg and BenZeev⁹⁴ reported similar results in another large series with 360 cases. Aelony,⁹⁵ in a case series, observed prolonged survival averaging 22.4 months after treatment with talc poudrage pleurodesis. In vitro studies suggest that talc produces apoptosis in human malignant mesothelioma cells and might therefore have an antitumor,⁹⁶ as well as an antiangiogenic, effect.⁹⁷

In chylothorax due to lymphoma, Mares and Mathur⁹⁸ showed excellent results of talc poudrage, all in cases

refractory to chemotherapy or radiation therapy. All 19 patients with 24 hemithoraces involved had no recurrence after 30, 60, and 90 days (8 patients died during the 90 days of follow-up).

The recent development of indwelling (also called “tunneled”) pleural catheters has challenged the position of talc pleurodesis as the first option of treatment for malignant pleural effusion.⁹⁹⁻¹⁰¹ The primary goal of an indwelling pleural catheter is symptom relief by repeated drainage of pleural fluid in the home setting. The indwelling pleural catheter can induce a spontaneous pleurodesis, at a rate reported to range from 26% to 70%,¹⁰¹⁻¹⁰⁴ with a mean rate of 46%.¹⁰⁵ The spontaneous pleurodesis has been observed between 29 to 59 days.¹⁰²⁻¹⁰⁴ For daily drainage, dedicated disposable vacuum bottles are provided by the manufacturer of the drainage system. These bottles are expensive, and reimbursement by health insurance companies is not provided in many countries. Reported complications are malfunctioning of the catheter (9.1%), pneumothorax requiring chest tube (5.9%), pain (5.6%), and blocked catheter (3.7%). Less common complications are catheter fracture, empyema, cellulitis, and tumor metastasis along the catheter tract.¹⁰⁵

No randomized studies are yet available that compare thoracoscopic talc *poudrage* and indwelling pleural catheter placement. In a randomized controlled trial, talc *slurry* pleurodesis and an indwelling pleural catheter were compared with a primary end point of patient-reported relief of dyspnea; in this study no significant difference between the two methods was found in dyspnea or in quality of life. Twelve patients (22%) in the talc slurry group required further pleural procedures, which was significant compared to 3 patients (6%) in the indwelling pleural catheter group. On the other hand, significantly more patients (40%) experienced adverse events in the indwelling pleural catheter group versus 13% in the talc group.¹⁰⁶ In a cost-analysis study, talc slurry pleurodesis was found to be more cost-effective than the indwelling pleural catheter if the patient survived for more than 6 weeks.¹⁰⁷

In another study, thoracoscopic talc *poudrage* and indwelling pleural catheter placement were combined in 30 patients.¹⁰⁸ Successful pleurodesis was obtained in 92%; the indwelling pleural catheter could be removed at a median of 7.54 days. The authors stated that both length of hospital stay and duration of indwelling pleural catheter use could be reduced significantly compared to either procedure alone.

An indwelling pleural catheter placement is most likely the best treatment option in patients with a trapped lung. For all other patients the advantage of placement of an indwelling pleural catheter as opposed to thoracoscopic talc pleurodesis (or the combination of both) remains to be established. A major advantage of thoracoscopic talc pleurodesis is the possibility of obtaining a histologic diagnosis of the pleura in the same session. In future studies comparing indwelling pleural catheter and thoracoscopic talc pleurodesis, this important fact should be included in the design of the study.

❏ **Tuberculous Pleural Effusions (Video 24-8).** Although the diagnostic yield of pleural fluid culture combined with closed-needle biopsy for the diagnosis of tuberculosis is

quite high, there may be indications for thoracoscopy in otherwise uncertain pleural effusions^{12,37} (Fig. 24-8). The diagnostic accuracy of thoracoscopy is almost 100% because the pathologist is provided with multiple selected biopsy specimens, and there is a higher likelihood of obtaining the tubercle bacilli on culture.^{12,42} In this prospective inpatient comparison, an immediate diagnosis of *M. tuberculosis* infection in 100 cases was established histologically in 94% with thoracoscopy, but in only 38% with needle biopsy.^{12,42} This may be of clinical importance, because a proper histopathologic diagnosis allows antituberculous chemotherapy to be started without delay. The combined yield of histologic diagnosis and bacteriologic culture was 99% for thoracoscopy and 51% for needle biopsy, increasing to 61% when culture results from effusions were added (Fig. 24-9). The percentage of positive *M. tuberculosis* cultures from thoracoscopic biopsies (78%) was twice as high as that from pleural fluid and needle biopsies combined (39%), allowing bacteriologic confirmation of

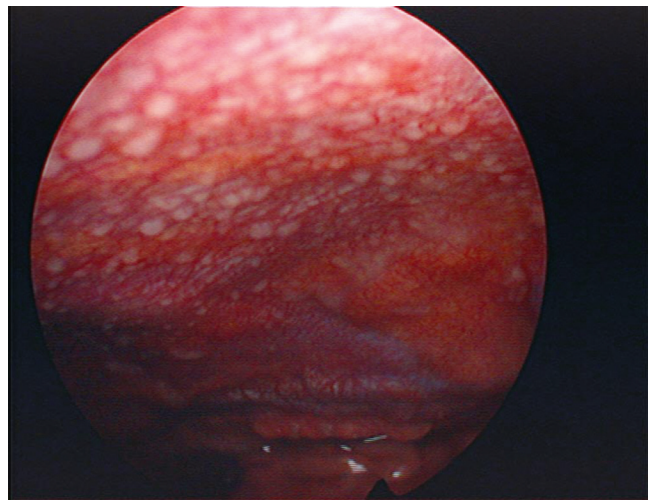


Figure 24-8 View through the thoracoscope in a patient with a tuberculous pleural effusion. Note the numerous small whitish nodules on the parietal (chest wall) pleura (upper part of photo). The histologic examination revealed florid exudative tuberculous pleurisy with epithelioid cell granulomas, numerous multinucleated giant cells of the Langerhans type, and necrosis. *Mycobacterium tuberculosis* cultures from the biopsy specimens were positive, whereas those from the effusion were negative. (From Loddenkemper R, Mathur PN, Noppen M, Lee P: *Medical thoracoscopy/pleuroscopy: manual and atlas*, New York, 2011, Thieme.)

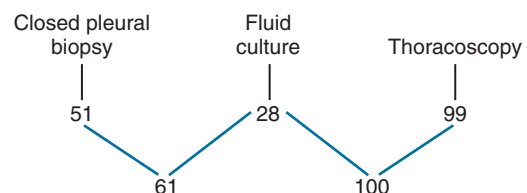


Figure 24-9 Sensitivity of different biopsy methods (histologic and bacteriologic results combined) for the diagnosis of *Mycobacterium tuberculosis* infection. Numbers represent sensitivity (%) of tests, either alone or combined, in a prospective inpatient comparison of 100 patients. Thoracoscopy alone has 99% sensitivity for the diagnosis of tuberculosis. (Redrawn from Loddenkemper R, Boutin C: Thoracoscopy: present diagnostic and therapeutic indications. *Eur Respir J* 6:1544–1555, 1993.)

the diagnosis and, importantly, drug susceptibility testing. In 5 of the 78 positive cases (6.4%), resistance to one or multiple antituberculous drugs was found and influenced therapy and prognosis.

Closed-needle biopsy can have high yield in areas with a high prevalence of tuberculosis, but even then thoracoscopy can have other benefits.¹⁰⁹ In a prospective study of 40 cases from South Africa, thoracoscopy had a diagnostic yield of 98% in comparison with an 80% diagnostic yield from pleural biopsies performed with an Abrams needle.¹¹⁰ In addition, thoracoscopy can lead to complete drainage of the effusion; initial complete drainage of the effusion, performed during and after thoracoscopy, was associated with greater symptomatic improvement than any subsequent therapy.¹¹¹ The positive role of early removal of the pleural fluid has also been shown recently in a double-blind, randomized, placebo-controlled trial from Taiwan.¹¹² No studies are known that compare the potential benefits of thoracoscopy, allowing early diagnosis, complete drainage, and early drug treatment, with those of drug treatment alone.

It is debatable whether to treat patients with antituberculous drugs merely on the suspicion of tuberculous pleurisy if they present with a high lymphocyte count in the pleural fluid and a positive skin test. At least in countries with a low prevalence of tuberculosis, where other laboratory tests such as adenosine deaminase may not be specific, thoracoscopy may be indicated instead of blind needle biopsies, to prove or exclude tuberculosis.¹¹³ In addition, the high yield for *M. tuberculosis* cultures from thoracoscopic biopsy specimens increases the possibility of obtaining susceptibility tests, which, in cases of drug resistance, may influence therapy and prognosis.^{12,109}

Other Pleural Effusions. For diagnosis, in cases with effusions that are neither malignant nor tuberculous, thoracoscopy may give visual clues to the cause, such as by revealing the thick white fibrin deposits seen in rheumatoid effusions, calcifications in effusions following pancreatitis, dilated veins in liver cirrhosis, or signs of trauma.^{5,42} Although for these entities the history, pleural fluid analysis, and physical and other examinations are usually helpful, thoracoscopy may be indicated to confirm the clinical suspicion.⁷⁵ If pleural effusion is secondary to underlying lung diseases such as pulmonary infarct or pneumonia, the diagnosis can frequently be made on visual examination and be confirmed by biopsy of the lung.^{5,35,42} As already mentioned, thoracoscopy is well suited for determining that a patient with a history of asbestos exposure likely has benign asbestos-related pleural effusion, which, by definition, is a diagnosis of exclusion of other causes, in particular malignancies.⁸²

For diagnosis, in the setting of other undiagnosed pleural effusions, the main diagnostic value of thoracoscopy lies in its ability to exclude malignant and tuberculous disease.^{12,75} By means of thoracoscopy, the proportion of so-called idiopathic pleural effusions usually falls below 10%, whereas in studies that have not used thoracoscopy, failure to obtain a diagnosis can exceed 20% of cases.⁷¹ However, this certainly also depends on the selection of patients and on the definition of “idiopathic.” Even after surgical exploration—the gold standard—there are still undiagnosed effusions.^{78,114}

For treatment, talc pleurodesis can be considered in some cases of nonmalignant pleural effusions that are recurrent and symptomatic and do not respond to medical therapy (Video 24-9). Such effusions may include those due to hepatic and renal hydrothorax, chylothorax, yellow nail syndrome, and systemic lupus erythematosus.¹¹⁵⁻¹¹⁷ In such patients with recurrent benign undiagnosed effusions, Vargas and colleagues¹¹⁸ achieved successful pleurodesis in 20 of 22 by talc insufflation using a thoracoscopic technique with a mediastinoscope performed under general anesthesia.

Empyema

Thoracoscopy can also be used in the management of early empyema, mainly to achieve early and complete drainage^{15,35,119,120} (Video 24-10). As a procedure intermediate between tube thoracostomy and VATS, thoracoscopy is effective and, when compared with surgical drainage, costs significantly less and avoids general anesthesia. It is particularly advisable for frail patients at high surgical risk.^{15,121} In cases with multiple loculations, it is possible to open these spaces to remove the fibrinopurulent membranes by forceps and to create a single cavity that can then be successfully drained and irrigated.¹²² If performed for this indication, thoracoscopy should be carried out early in the course of empyema, before the adhesions become too fibrous and adherent to perform thoracoscopy. Adhesions can be evaluated before the procedure by ultrasonography; thick dense adhesions may preclude thoracoscopy or talc pleurodesis.¹²³ In fact, ultrasonographic imaging before thoracoscopy significantly reduces the number of pleural access failures: it helps locate the optimal site for thoracoscopy and, in case of complete adhesion of the pleura, indicates the need for another procedure such as VATS or a CT-guided biopsy.¹²³

Thus, if the indication for placement of a chest tube is present and if the facilities are available, thoracoscopy can be performed at the time of chest tube insertion. Overall, thoracoscopy is a procedure similar to chest tube placement but one that enables the creation of a single pleural cavity, allowing much better local treatment.^{119,122,123} In a retrospective study of 41 patients, thoracoscopy was successful without further intervention in 35 (85%).¹²⁴ It was mainly successful in patients with free-flowing fluid (100%) and multiloculated empyema (92%), but in only 4 of 8 patients with an empyema in the organizational stage. However, prospective studies on the role of thoracoscopy in the treatment of early empyema in adults have not yet been published.

Spontaneous Pneumothorax

In spontaneous pneumothorax, thoracoscopy has both diagnostic and therapeutic purposes^{5,35,40,42,125-127,127a} (Fig. 24-10). Whenever a chest tube is introduced by the trocar technique, it is easy to use an optical device for visual inspection of the lung and pleural cavity before insertion of the chest tube. Special techniques, including fluorescence thoracoscopy, have been used to identify blebs and other porosities (Video 24-11).¹²⁸ By inspection during thoracoscopy, the underlying lesions can be directly assessed according to the classification of Schramel and coworkers¹²⁶: stage I, with an endoscopically normal lung; stage II, with

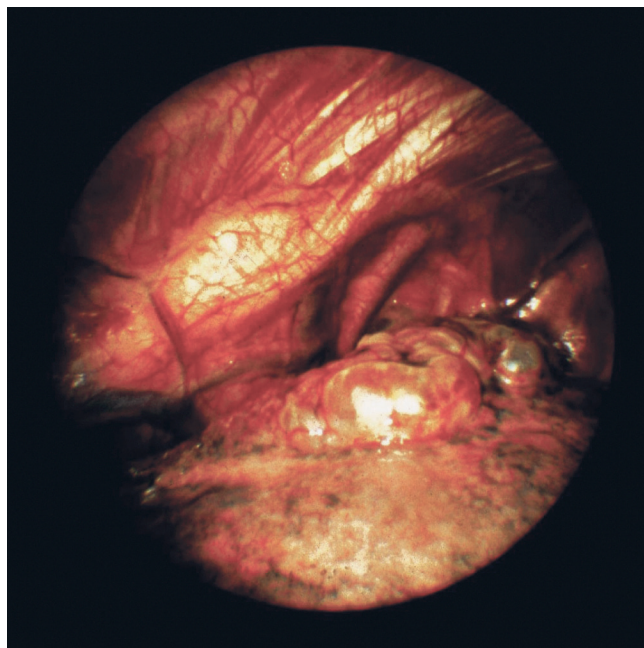


Figure 24-10 View through the thoracoscope in a patient with a spontaneous pneumothorax. On the surface of the lung (lower part of photo), large apical blebs are visible.

pleuropulmonary adhesions; stage III, with small bullae and blebs (<2 cm in diameter); and stage IV, with numerous large bullae (>2 cm in diameter). In 1047 cases of pneumothorax in which thoracoscopy was used by three different teams, pathologic lesions were detected in approximately 70%, with similar percentages for stages II, III, and IV.¹² In this study, blebs and bullae were detected in 45% to 62% of cases. Although the detection rates of blebs and bullae are reported to be higher (76% to 100%) in series using VATS or thoracotomy,¹²⁶ it is unlikely that large bullae and blebs or fistulas would be overlooked during thoracoscopy.

Treatment by thoracoscopy may include electrocautery of blebs and bullae (if the site of the air leak is visible) and pleurodesis using talc poudrage (Video 24-12).^{40,125} The first use of thoracoscopy for treatment of pneumothorax was in Vienna in 1937 by Sattler, who cauterized adhesions that prevented the closure of bronchopleural fistulas.⁴ Talc poudrage achieves excellent results, with recurrence rates reported below 10%.⁴⁰ A prospective study showed that, for complicated pneumothorax, defined as recurring or persistent pneumothorax, simple talc poudrage under local anesthesia prevented a recurrence of pneumothorax.¹²⁹ In a prospective, randomized, multicenter comparison, talc poudrage for primary spontaneous pneumothorax proved more efficient (only 1 of 61 patients with talc poudrage had a recurrence, compared with 10 of 47 with simple pleural drainage) and more cost-effective than drainage alone.¹³⁰ The recurrence rate after thoracoscopic talc poudrage is 5%, which is similar to the recurrence rate after VATS.¹³¹ An important disadvantage of VATS is long-term postoperative pain, which may develop in more than 30% of patients and may last for 3 to 18 months.¹³² Currently there is no

study directly comparing efficacy and complication rates of VATS and thoracoscopy.¹³¹

Other types of pneumothorax treated successfully by thoracoscopy have included those due to *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia, metastatic osteosarcoma, pleural endometriosis, lymphangioleiomyomatosis, and cystic fibrosis.⁷⁵

In talc poudrage for pneumothorax, a mere 2 to 4 mL of talc can be sufficient for effective pleurodesis.⁴⁰ The short-term safety of insufflation of large particle size talc in patients with spontaneous pneumothorax has recently been proven in a prospective multicenter study.⁷² In a study of patients 22 to 35 years after talc poudrage, there were no long-term sequelae; total lung capacity averaged 89% of the predicted value in 46 patients, whereas it was 97% of the predicted value in 29 patients treated with tube thoracostomy alone.¹³³ In this long-term follow-up, none of the poudrage group developed mesothelioma. Although talc poudrage may result in minimally reduced total lung capacity, as well as pleural thickening on chest radiography, these changes appear to be clinically unimportant.^{72,134} Talc poudrage may be relatively contraindicated for patients who may become candidates for lung transplantation, although currently it is not considered an absolute contraindication to lung transplantation.¹³⁵

In the United States, where large particle size talc is not yet available, apical bullectomy followed by mechanical abrasion or resection of the pleura is sometimes considered to be the procedure of choice for treatment of recurrent spontaneous pneumothorax, if apical blebs or bullae are present. It is important to add pleurodesis (chemical or mechanical) to a VATS procedure because the recurrence rate after bullectomy alone is unacceptably high, 27.5% after 10 years' follow-up in one study.¹³⁶ Mechanical pleurodesis can include abrasion or a partial parietal pleurectomy. There are a few studies comparing these approaches. When talc pleurodesis was added to the VATS procedure, Bridevaux and colleagues⁷³ found a significantly lower recurrence rate of 1.8% compared to 9.2% after partial parietal pleurectomy. In a review by Sepehrpour and associates,¹³⁷ recurrence rate after VATS pleurectomy was demonstrated to be lower than after pleural abrasion; however, there was slightly better results with talc pleurodesis than with either of the mechanical techniques.

Therefore, if the facilities are available, thoracoscopy may be performed in all patients with spontaneous pneumothorax in whom tube drainage is indicated. Several advantages are offered: precise assessment of underlying lesions under direct visual control, choice of best (conservative or surgical) treatment measures, direct treatment by electrocautery of small blebs and bullae, and severing of adhesions, if necessary, followed by talc poudrage, as well as selection of the best location for subsequent chest tube placement.⁴²

Diffuse Pulmonary Diseases

Diffuse lung diseases provide a good indication for diagnostic thoracoscopy.^{5,35,42,135,138,139} (Fig. 24-11). An overview of the entire lung surface, assisted by the magnification of the thoracoscope, allows harvesting of representative samples of abnormal areas of parenchyma. In a review of

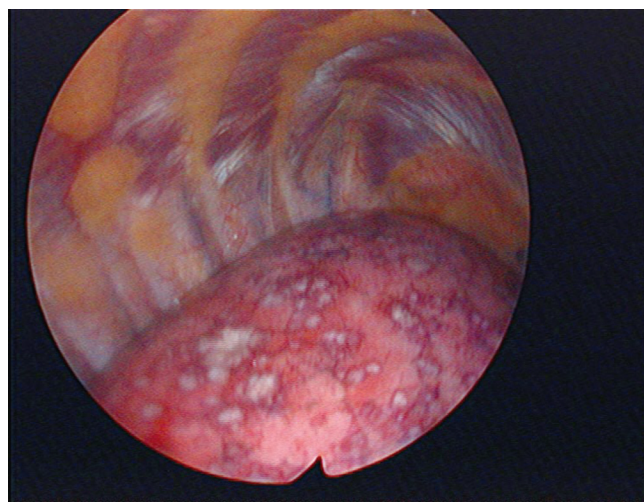


Figure 24-11 A view through the thoracoscope in a patient with multiple pulmonary metastases due to ovarian cancer (lower part of photo).

the literature, the sensitivity of thoracoscopic lung biopsy specimens was 93% in 1031 cases with varying causes.³⁵ In a large series of 419 patients with diffuse lung diseases, the overall sensitivity was 85% with different yields depending upon the underlying disease: 98% in sarcoidosis stage II and III, 88% in malignant diseases, 85% in diffuse pulmonary fibrosis/interstitial pneumonia, and 42% in histiocytosis X.⁴² Thoracoscopy has also been used with a high diagnostic yield in immunocompromised patients.¹³⁸

In comparison with bronchoscopy, thoracoscopy is more invasive (see “[Contraindications](#)” section) but presents several advantages. It provides significantly larger samples and allows the physician to choose the biopsy site. Unlike transbronchial biopsy, thoracoscopy enables electrocautery, so that bleeding following a thoracoscopic parenchymal biopsy can be managed without difficulty. In cases where a prolonged bronchopleural fistula after biopsy can be anticipated, as in end-stage pulmonary fibrosis, thoracoscopic biopsies should be avoided in favor of a VATS biopsy with suturing or stapling. Vansteenkiste and coworkers¹³⁹ found that the required pleural drainage time (on average 5.3 ± 4.7 days) was related to the total lung capacity, which mirrors the severity and stiffness of interstitial lung disease.

With regard to sensitivity and invasiveness, thoracoscopy ranks between transbronchial biopsy and open-lung biopsy.⁴² In a recent experimental animal study, subpleural and deep lung biopsy specimens were taken during thoracoscopy in six sheep.¹⁴⁰ No significant differences were found between subpleural and deep biopsies regarding the mean quality scores of the tissue obtained. According to this study, subpleural biopsy specimens obtained during thoracoscopy might be sufficient for establishing an accurate diagnosis in diffuse parenchymal lung disease, where the subpleural layers are involved.

Localized Diseases

Localized abnormalities of the chest wall, diaphragm, and thoracic spine may be diagnosed using thoracoscopy if the

pleural space is not obliterated.^{5,42} Hyaline pleural plaques, localized pleural mesothelioma, lipoma, neurinoma, rib metastasis, rib erosions, and the like can be examined and, if necessary, biopsied. Very discrete metastases are sometimes found in the region of the diaphragm and the posterior chest wall, with or without associated pleural effusion. Chest wall lesions may be easier to diagnose than lung lesions: in a retrospective study in which 109 cases with chest wall lesions of different causes were analyzed, the diagnostic sensitivity was 83%,⁴² whereas, in solitary lung lesions, the overall diagnostic sensitivity was only 46%.

Currently the application of thoracoscopy has decreased substantially for localized disease because of better imaging techniques such as CT, magnetic resonance imaging, and ultrasonography, which allow image-guided biopsies. For example, such biopsies have proved useful for diagnosis of pleural plaques, lipomas, and cysts.¹² Alternatively, surgical thoracoscopy (VATS) will now be used for these indications, because the technique not only is diagnostic but also allows the removal of benign or malignant lesions.

DIFFERENCES BETWEEN THORACOSCOPY AND VIDEO-ASSISTED THORACIC SURGERY

As described in the preceding sections, thoracoscopy is used mainly for diagnosis of pleural diseases. The most common indications for thoracoscopy are diagnosis of pleural effusion with inspection of the pleural cavity, combined with biopsy specimens from the parietal and visceral pleura, as well as treatment of malignant or other therapy-refractory effusions by talc pleurodesis (poudrage). It is a relatively simple and inexpensive technique because it can be performed in an endoscopy room, under local anesthesia or conscious sedation, through a single entry site with nondisposable instruments.

VATS, conversely, which takes its roots from thoracoscopy, has now been technically developed to the point that it can replace thoracotomy for most indications, if certain limitations such as dense pleural symphysis are not present. VATS requires an operating room, general anesthesia with single-lung ventilation, more than two (usually three) entry sites, and complex instruments. Overall, it is a more invasive and expensive technique with a higher risk than thoracoscopy; however, in experienced hands and in the proper setting, VATS is less invasive, is less expensive, and has a lower risk than open procedures.

The different clear-cut indications for either thoracoscopy or VATS are listed in [Table 24-1](#). However, there remains a gray area of indications for which either method can be used (see [Table 24-1](#)). Gray areas include treatment of pneumothorax stages I to III, drainage of empyema stages I and II, biopsies in diffuse parenchymal lung diseases, and sympathetic nerve interventions. For these indications the choice of the medical or the surgical approach depends on local expertise, availability of the technique, and performance status and prognosis of the patient. More details are given in the book *Medical Thoracoscopy/Pleuroscopy: Manual and Atlas*.²⁵

Key Points

- Thoracoscopy (medical thoracoscopy/pleuroscopy) is less invasive than video-assisted thoracic surgery (surgical thoracoscopy) because it is performed under local anesthesia and conscious sedation, most commonly through a single entry. It is also less expensive because it can be performed in an endoscopy suite, using nondisposable rigid or semirigid endoscopes, and usually does not require an anesthesiologist.
- Thoracoscopy is used today mainly for diagnostic purposes, in particular in pleural effusions of otherwise indeterminate origin, owing to its high sensitivity and specificity for the diagnosis of malignancy and tuberculosis.
- Thoracoscopy is useful in staging diffuse malignant mesothelioma and lung cancer with pleural effusion.
- Thoracoscopy allows talc poudrage, which is a highly successful conservative method for pleurodesis in malignant and recurrent pleural effusions.
- Thoracoscopy can be useful for treatment of spontaneous pneumothorax; the introduction of the scope by the trocar technique is similar to the introduction of a chest tube, and an optical device can be used to inspect the pleural space followed by coagulation of blebs and bullae and talc poudrage.
- Thoracoscopy can be used in the management of early empyema, for biopsy diagnosis of diffuse pulmonary diseases, and for sympathectomy in hyperhidrosis patients. As an invasive procedure, it should be used only if other, simpler methods fail or are not available.
- Thoracoscopy is a safe procedure that is even easier to learn than flexible bronchoscopy if sufficient expertise in thoracentesis and chest tube placement has already been gained. As part of interventional pulmonology, it should be included in the training program of pulmonologists.

Complete reference list available at *ExpertConsult*.

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EVALUATION

25

PULMONARY FUNCTION TESTING

WARREN M. GOLD, MD • LAURA L. KOTH, MD

INTRODUCTION

MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Measurements of Ventilatory Function

Clinical Applications of Flow-Volume Relationships

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An expanded version of this chapter is available online at ExpertConsult.

INTRODUCTION

Pulmonary function tests permit accurate, reproducible assessment of the functional state of the respiratory system. It is worth emphasizing that pulmonary function tests do not diagnose specific diseases. Different diseases cause different patterns of abnormalities in a battery of pulmonary function tests. These patterns allow us to quantify the severity of respiratory disease, which enables us to detect disease early and characterize the natural history and response to treatment. It is important to remember, however, that these conclusions are based on inferences, not specific proofs. The accuracy of our inferences depends on a complete knowledge of the physiologic basis of the functions tested, properly validated equipment, and appropriate protocols. The purpose of this chapter is to describe these pulmonary function tests, reviewing briefly their physiologic basis, their

equipment and protocol requirements, and their clinical results.

This chapter has an extended online version. A wealth of details of procedures, normal and predicted values, equations, and descriptions of techniques can be found in the online chapter.

MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

MEASUREMENTS OF VENTILATORY FUNCTION

The physiologic determinants of airflow during quiet breathing, maximal airflow, lung volumes, and elastic recoil are reviewed in detail in Chapter 5. [Figure 25-1](#) reviews the mechanisms involved in determining maximal airflow.

Flow

Forced Spirometry

Spirometry requires recording the volume of air inhaled and exhaled, plotted against time, during a series of ventilatory maneuvers. The resulting curves permit the

ARTERIAL BLOOD GASES

Measurements of Arterial Blood Gases

INDICATIONS. There are several reasons for performing spirometry:

1. In any occupation that is potentially hazardous to the lungs, individual workers should be monitored periodically by spirometry to detect and quantify evidence of pulmonary problems.
2. Spirometry appears to be the best method to identify smokers at risk for developing severe chronic airflow obstruction.¹
3. Spirometry can indicate the statistical risk of specific surgical procedures for a group of patients but is probably not useful for the individual patient. Arterial oxygen desaturation is a much better indicator of the probability of a high risk associated with a surgical procedure (e.g., the need for prolonged postoperative mechanical ventilation) than is spirometry.²
4. Many government agencies (e.g., the Social Security Administration) require results of spirometry to quantify impairment in patients who claim disability caused by chronic bronchitis or emphysema, as well as pneumoconioses, pulmonary fibrosis, and other pulmonary disorders.
5. Spirometric results, including peak flow rates, are extremely useful in assessing the effectiveness of treatment in asthmatic patients. These simple tests are equally valuable for quantifying the effects of treatment in patients with other forms of chronic airflow obstruction, as well as many forms of restrictive disorders.
6. Spirometry can be very sensitive for evaluating progression of disease, especially if baseline values, or results obtained early in the course of the illness, are available for comparison. Variation in the range of normal is so large that changes in serial test results are much more sensitive than a single value for detecting abnormal function. For example, changes in forced vital capacity were found to be predictive of survival time in idiopathic pulmonary fibrosis.³
7. Spirometry is an excellent screening test for detection of chronic airflow obstruction, localizing and grading a critical orifice in the central airways, but may also be useful in detecting restrictive disorders.

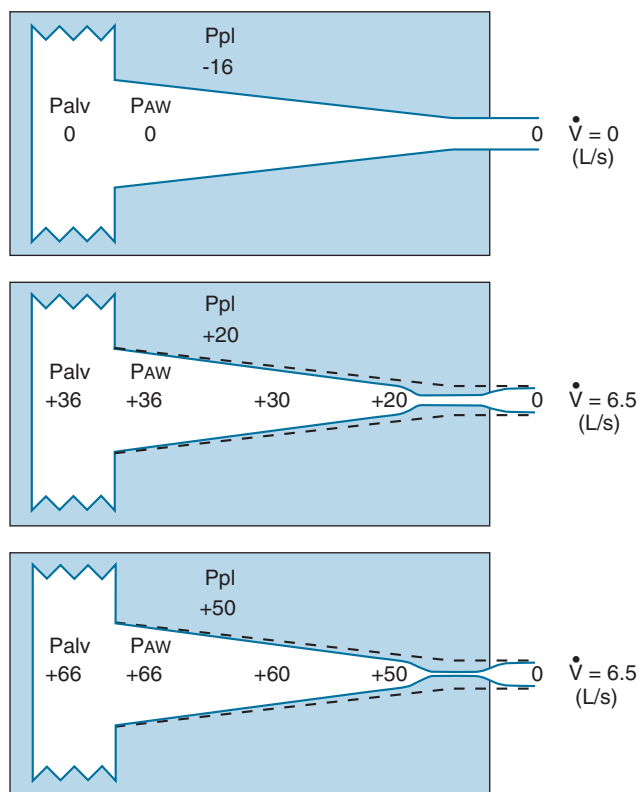


Figure 25-1 Model of expiratory flow limitation. *Top*, The static relationships of pleural pressure (Ppl), alveolar pressure (Palv), and intraluminal airway pressure (PAW), and airway dimensions at a fixed lung volume. *Middle and bottom*, Conditions at the onset of maximal flow and with increased expiratory effort, respectively. *Dotted lines* show static airway dimensions for comparison with the dynamic state. All three panels show pressures (cm H₂O) at the same lung volume: 60% of total lung capacity where lung elastic recoil pressure is +16 cm H₂O and equals the transpulmonary pressure (PL) (PL = Palv – Ppl). *Top*, When conditions are static, Palv is zero (i.e., atmospheric) and flow (\dot{V}) at the mouth is zero. *Middle*, The subject makes a forced expiratory effort at the same lung volume. Now \dot{V} is 6.5 L/sec driven by Palv of +36 cm H₂O. Because of the resistances down the airways from alveolus to mouth, the PAW decreases to the point where PAW = Ppl (+20 cm H₂O, which is called the *equal pressure point* [EPP] because Ppl = PAW). Between the alveolus and the EPP, the airways are not compressed, but distal to the EPP there is compression and airway narrowing, because Ppl exceeds the pressure within the airways. For this lung volume, 6.5 L/sec is the maximal flow possible (see discussion of *bottom panel*, next). *Bottom*, The subject makes a forced expiratory effort starting at the same volume as in the top and middle panels (PL = Palv – Ppl = +16). In this instance, the expiratory effort is markedly increased, reflected by the increased Ppl (+50 cm H₂O) and Palv (+66 cm H₂O). However, the flow generated is still only 6.5 L/sec because the increased effort succeeds only in compressing the airways more, dissipating the increased driving pressure across the increased resistance offered by the more narrowed airways; thus flow is maximum for this particular lung volume. (Modified from Rodarte JR: Respiratory mechanics. In *Basics of RD*, New York, 1976, American Thoracic Society.)

determination as to whether the subject has a normal ventilatory reserve or an abnormal pattern characteristic of obstructive, restrictive, or mixed ventilatory abnormalities. None of these patterns is specific, although most diseases cause a predictable type of ventilatory defect. Spirometry alone cannot establish a diagnosis of a specific disease, but it is sufficiently reproducible to be useful in following the course of many different diseases. In addition, the results of spirometry make it possible to estimate the degree of exercise limitation due to a ventilatory defect (e.g., *maximal*

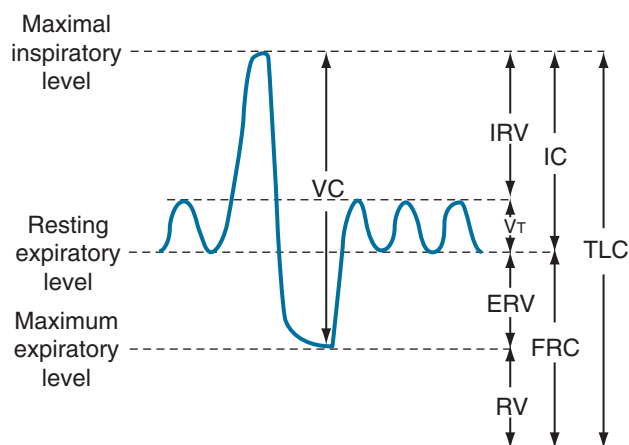


Figure 25-2 Lung volume and capacity. *Volumes*: There are four volumes, which do not overlap: (1) tidal volume (VT) is the volume of gas inhaled or exhaled during each respiratory cycle; (2) inspiratory reserve volume (IRV) is the maximal volume of gas inspired from end-inspiration; (3) *expiratory reserve volume* (ERV) is the maximal volume of gas exhaled from end-expiration; and (4) residual volume (RV) is the volume of gas remaining in the lungs following a maximal exhalation. *Capacities*: There are four capacities, each of which contains two or more primary volumes: (1) total lung capacity (TLC) is the amount of gas contained in the lung at maximal inspiration; (2) vital capacity (VC) is the maximal volume of gas that can be expelled from the lungs by a forceful effort following maximal inspiration, without regard for the time involved; (3) inspiratory capacity (IC) is the maximal volume of gas that can be inspired from the resting expiratory level; and (4) functional residual capacity (FRC) is the volume of gas in the lungs at resting end-expiration.

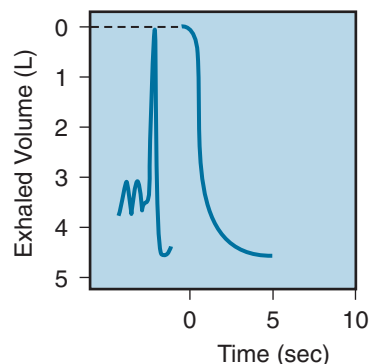


Figure 25-3 Spirogram obtained in a normal subject showing maneuvers to determine vital capacity and forced vital capacity. On the tracing shown on the *left*, the subject breathes quietly (slow recording speed), then takes a maximal inspiration followed by a maximal expiration without concern for time (vital capacity). On the tracing shown to the *right*, after a maximal inspiration (not shown), with a rapid recording speed, the subject then exhales completely, forcefully, and as rapidly as possible (forced vital capacity).

voluntary ventilation [MVV] can be predicted from the *forced expiratory volume in 1 second* [FEV₁]⁴ and to identify the type of patient likely to develop ventilatory failure after pneumonectomy.^{5,6}

The volumes of air inhaled and exhaled with relaxed and maximal effort can be measured easily with standard equipment. Lung volumes and capacities are defined in Figure 25-2. The results are obtained and displayed in a standardized manner as a spirogram (Fig. 25-3). Tests can be performed with a simple recording spirometer, which is inexpensive enough to be standard equipment in a physician's office or the diagnostic laboratory of a small clinic or

Table 25-1 Terms Used for Spirometric Measurements

Term	Previously Used Terms	Description
Vital capacity (VC)		Largest volume measured on complete exhalation after full inspiration
Forced VC (FVC)	Timed VC, fast VC	VC performed with forced expiration
Forced expiratory volume with subscript indicating interval in seconds (FEV_t) (e.g., FEV_1)	Timed VC	Volume of gas exhaled in a given time during performance of FVC
Percentage expired in t seconds ($FEV_t\%$) (e.g., $FEV_1\%$)	Timed VC	FEV_t expressed as percentage of FVC
Forced midexpiratory flow ($FEF_{25\%-75\%}$)	Average flow rate during middle 50% of the FVC	Maximal midexpiratory flow
Forced expiratory flow with subscript indicating volume segment (FEF_{V1-V2}) (e.g., $FEF_{200-1200}$)	Maximal expiratory flow rate	Average rate of flow for a specified segment of FVC, most commonly 200–1200 mL in adults
Maximal voluntary ventilation (MVV)	Maximum breathing capacity (MBC)	Volume of air a subject can breathe with voluntary maximal effort for a given time

Modified from Kory RC: Clinical spirometry: recommendation of the Section on Pulmonary Function Testing, Committee on Pulmonary Physiology, American College of Chest Physicians. *Dis Chest* 43:214, 1963.

hospital. Recommended criteria for acceptable performance standards for equipment have been published.⁷ Although normal values have been established in a spectrum of subjects of different sex, age, size, and ethnic background, few have been reported using the standards of the *American Thoracic Society* (ATS).⁸⁻¹¹ Many samples are deficient in older subjects. Almost no data exist concerning the proper prediction equations to use in individuals of foreign extraction after the family has lived in the United States for several generations. Some regression equations that include “weight” as a determinant yield absurd values in very obese subjects.¹² All these measurements depend heavily on patient understanding and cooperation and must be conducted by a well-trained technician able to communicate instructions clearly.

MAXIMAL-EFFORT EXPIRATORY VITAL CAPACITY. To obtain a maximal-effort expiratory vital capacity (VC), the subject inhales maximally to *total lung capacity* (TLC) and then exhales as rapidly and forcefully as possible. When volume is recorded on the y-axis and time on the x-axis, the resulting curve is called the *forced vital capacity* (FVC) curve. Analysis of this curve permits computation of the volume exhaled during the time following the start of the maneuver (*forced expiratory volume over time*, or FEV_t), the ratio of FEV_t to total FVC, and average flow rates during different portions of the curve. The terms used in clinical spirometry, including these different components, are summarized in Table 25-1.¹³

Several useful variables may be derived from the maximal-effort FVC.

FORCED EXPIRATORY VOLUME OVER TIME. The FEV_1 is the measurement of dynamic volume most often used in conjunction with the FVC in analysis of spirometry (Fig. 25-4). The measurement incorporates the early, effort-dependent portion of the curve and enough of the midportion to make it reproducible and sensitive for clinical purposes. *Forced expiratory volume* (FEV) measurements taken at 0.5, 0.75, 2.0, and 3.0 seconds add little information to the FEV_1 measurement. The *forced expiratory volume exhaled in 6 seconds* (FEV_6) is useful, however, because it closely approximates FVC, has been shown to be a valid alternative to the conventional FEV_1/FVC , and is easier for patients with severe airflow obstruction to attain.¹⁴ In addition, the end of the

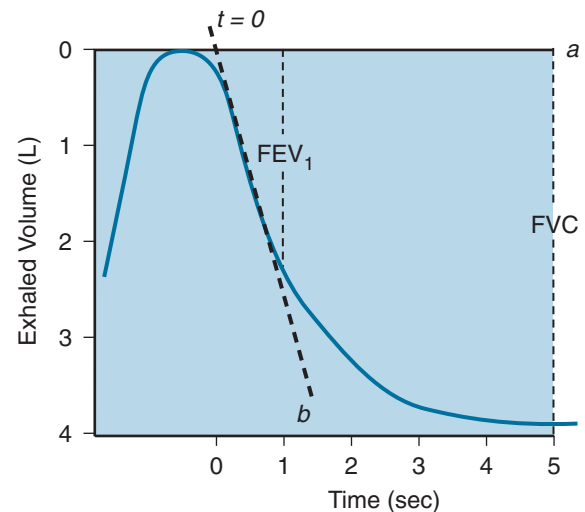


Figure 25-4 Measurement of forced expiratory volume in 1 second. This diagram illustrates measurement of forced expiratory volume in 1 second (FEV_1) using the back-extrapolation method to define time zero (i.e., the point during the forced vital capacity [FVC] maneuver when the subject began to blow as hard and as fast as possible). A solid horizontal line (a) indicates the level of maximal inhalation. A heavy dashed line (b) passes through the steepest portion of the volume-time tracing. The intersection point of these two lines becomes time zero, from which timing is initiated, as indicated; 1 second after time zero, the vertical dashed line is drawn, indicating FEV_1 , and 5 seconds later, another vertical dashed line is drawn, indicating FVC.

test is more clearly defined, permitting more reliable correspondence between measured and referenced values.¹⁵ Furthermore, as demonstrated by Swanney and associates,¹⁵ the degree of airflow obstruction, reflected in the FEV_1/FEV_6 obtained from spirometry, can serve as an independent predictor of subsequent decline in lung function; it may therefore be used to detect smokers at higher risk for developing *chronic obstructive pulmonary disease* (COPD).¹⁵

FORCED EXPIRATORY VOLUME OVER TIME AS A PERCENTAGE OF FORCED VITAL CAPACITY. The ratio of FEV_t to total FVC has been defined precisely in healthy subjects.¹⁶ It declines with age, but abnormally decreased ratios indicate airway obstruction; normal or increased ratios do not reliably exclude airway obstruction, particularly in the presence of

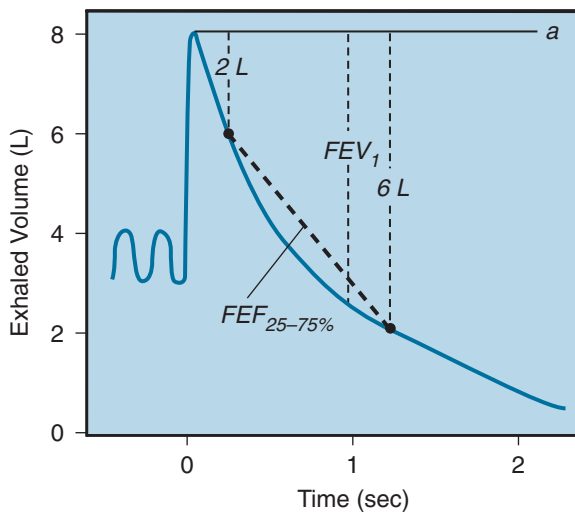


Figure 25-5 Determination of forced expiratory flow between 25% and 75% of total lung capacity ($FEF_{25-75\%}$). A heavy dashed line connects two points on the volume-time curve of the forced vital capacity (FVC) maneuver. One point is marked when 25% of the FVC has been exhaled (2 L); the other point is marked when 75% of the FVC (6 L) has been exhaled from the level of maximal inhalation indicated by the solid line (a). In this example, the elapsed time between these two points is 1 second; thus the calculated $FEF_{25-75\%}$ is 4 L/sec. FEV_1 , forced expiratory volume in 1 second.

a decreased FVC. When the FVC is decreased by an interstitial process or by chest wall restriction, and the airways are normal, the FEV_1/FVC ratio is increased. (The FEV_1/FVC ratio may also be increased in subjects who fail to make a maximal effort throughout the expiratory maneuver.) The absence of an increased ratio in patients in whom one would expect the ratio to be increased suggests the presence of concomitant airway obstruction. Absolute flow may be increased initially, probably because of outward traction of increased elastic forces on airway walls. However, because flow is volume dependent, it eventually decreases in restrictive disorders without airway obstruction, although precise quantification for the various types of pure restrictive disorders is not available. Examining exhaled volumes and flows as a percentage of predicted values may facilitate interpretation of the spirogram in patients with mixed ventilatory defects.

AVERAGE FORCED EXPIRATORY FLOW. The $FEF_{25-75\%}$, or forced expiratory flow between 25% and 75% of FVC, was introduced as the maximal midexpiratory flow rate (Fig. 25-5). This measurement was intended to reflect the most effort-independent portion of the curve and the portion most sensitive to airflow in peripheral airways, where diseases of chronic airflow obstruction are thought to originate.¹⁷ These properties have gained support from clinical experience and theoretical analysis,¹⁸ and the $FEF_{25-75\%}$ is widely used currently. However, the $FEF_{25-75\%}$ shows marked variability in studies of large samples of healthy subjects, and the 95% confidence limits for normal values are so large that they limit its sensitivity in detecting disease in an individual subject.^{6,19}

Flow-Volume Relationships

GENERAL PRINCIPLES. The widespread availability of computer-based electronic pulmonary function test appa-

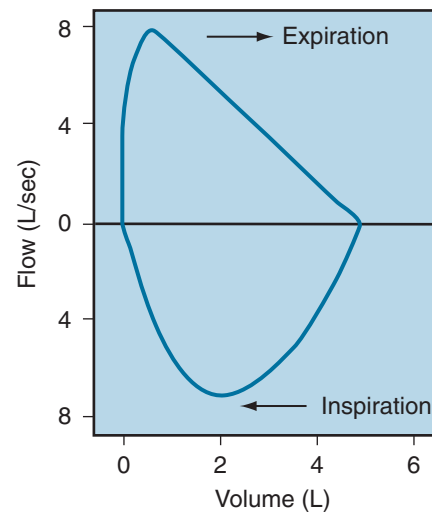


Figure 25-6 The flow-volume curve. The tracing of the flow-volume curve is recorded during maximal inspiration and expiration in a normal subject.

ratus permits flow-volume curves to be as readily available in the physician's office as spirometry. All of the indications for spirometry probably apply equally to the flow-volume curve. This maneuver requires the subject to inspire and expire fully with maximal effort into an instrument that measures flow and volume simultaneously. These values are plotted on the two axes of an x-y recorder or computer monitor (Fig. 25-6). As summarized in Figure 25-1, analysis of these curves has contributed to the basic understanding of the mechanical events that limit maximal exhalation. Maximal flow clearly depends on lung volume: for every point on the lower two thirds of VC, a maximal flow exists that cannot be exceeded regardless of the effort exerted by the subject. Thus maximal flow must depend on mechanical characteristics of the lungs. Flow-volume curves also provide a useful way to display ventilatory data for diagnostic purposes.

By superimposition of repeated curves using graphic means or a computer, a maximal flow-volume envelope can be constructed for any subject. This envelope represents the maximal flow values of which the respiratory system is capable, and it may exceed the airflow rates achieved in any single maneuver. As illustrated in Figure 25-7, the maximal flow-volume envelope can be approximated by having the subject make repeated trials of increasing effort or by having the subject cough repeatedly while flow-volume relationships are recorded. The flow-volume curve and FEV -time curve are mathematically interchangeable; either one can be derived graphically, or by computer analysis, from the other. This relationship can provide an internal check on the accuracy of the tests. Spirometric values can be computed from flow-volume curves. Thus values for both forced expiratory tests can be obtained with fewer efforts while still defining the maximal capacity of the respiratory system accurately. From a practical point of view, this means that the subject can generate the needed data with fewer maximal efforts and in a shorter time.

On forced exhalation, the flow-volume curve has a characteristic appearance. The curve shows a rapid ascent to peak flow and subsequently a slow linear descent proportional to volume. The initial portion of the curve (the first

Peak Expiratory Flow Rate. Expiratory flow reaches a transient peak early in the forced expiratory maneuver. Peak flow manifests during the most effort-dependent portion of the expiratory maneuver, so decreased values can result from even slightly submaximal effort rather than from airway obstruction. Nevertheless, the ease of measuring peak flow with an inexpensive, small, portable device²⁰ has made it a popular means of following the pattern of airflow obstruction on an ambulatory basis. For example, the test is used to monitor patients suspected of having occupational asthma and those who seem insensitive to the severity of bronchospasm. When a maximal effort is made, peak flow is largely a function of the caliber of large airways; it is also influenced by the transient flow caused by expulsion of air from compressed central airways. For these reasons, peak flow is abnormally decreased only in moderate to severe airway obstruction.

The national program to improve the management of patients with asthma based on the National Heart, Lung, and Blood Institute expert panel report^{21,22} depends heavily on spirometry as well as the informed use of peak flowmeters for proper patient care. These devices are sufficiently accurate that peak flow measurements made in the morning and evening (before and after bronchodilator treatments) enable patients to participate effectively in their own care. The test provides a quantitative estimate of airway lability (change in peak flow > 20%) that correlates well with more sophisticated measures of airway hyperresponsiveness obtained by provocation testing. It also provides correlation of the clinical course with pulmonary function on a daily basis, provides an early warning that pulmonary function is deteriorating, and may be used as the basis of an action plan of treatment carried out by the patient.

Maximal Voluntary Ventilation. The *maximal voluntary ventilation* (MVV) measurement is defined as the maximal volume of air that can be moved by voluntary effort in 1 minute. Subjects are instructed to breathe rapidly and deeply for 15 to 30 seconds, ventilatory volumes are recorded, and the maximal volume achieved over 15

consecutive seconds is expressed in liters per minute. Lung volumes are reported at the largest size possible within the chest and at body temperature (37°C) and standard pressure fully saturated with water vapor (760 mm Hg).

The observer should demonstrate the test; then the subject should choose his or her own respiratory rate and perform several practice runs. The respiratory frequency used in the MVV should be noted and recorded as a subscript (e.g., MVV₉₀ or MVV₁₁₀). Maximal levels are usually achieved between 70 and 120 breaths/min, but the choice of frequency does not greatly affect the test.²³

This test is heavily dependent on subject cooperation and effort. Loss of coordination of respiratory muscles, musculoskeletal disease of the chest wall, neurologic disease, and deconditioning from any chronic illness, as well as ventilatory defects, decrease MVV, so the test is nonspecific. The MVV is decreased in patients with airway obstruction, but less so with mild or moderate restrictive defects because rapid, shallow breathing can compensate effectively for the decreased lung volume.

Despite these caveats, MVV can be useful in special circumstances. It correlates well with subjective dyspnea and is useful in evaluating exercise tolerance. It appears to have prognostic value in preoperative evaluation, possibly because the extrapulmonary factors to which it is sensitive are also important for recovery from a surgical procedure.²⁴ It also provides a measure of respiratory muscle endurance that may be important in the evaluation of respiratory muscle fatigue, whether from obstructive or restrictive ventilatory defects or from specific neuromuscular diseases.²⁵ In myasthenia gravis, for example, the patient can often produce maximal efforts for a short time, so that FVC and maximal inspiratory and expiratory pressures are normal. However, the effort cannot be sustained, so the MVV or repeated FVC values decrease, even within 12 to 15 seconds. The respiratory crisis of myasthenia gravis may happen rapidly and lead to respiratory failure. As a result, some investigators have suggested that MVV should never be measured in patients with myasthenia gravis, except under carefully controlled circumstances when it may be useful in evaluating treatment.⁶

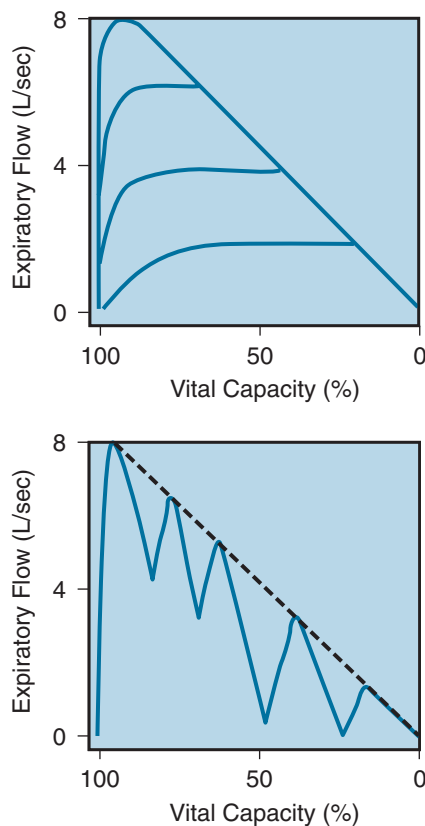


Figure 25-7 Flow-volume curves created by increasing effort and by coughing. Top, Expiratory flow-volume curve recorded during a series of expirations with increasing efforts, finally producing a maximal flow-volume envelope. Bottom, Expiratory flow-volume curve recorded during coughing (solid line), approximating the maximal flow-volume envelope (dashed line).

25% to 33% of the VC exhaled) depends on effort. As a subject exerts increasing effort during exhalation, associated with increasing intrathoracic pressure, increasing flow is generated. This portion of the curve has limited diagnostic use because its appearance depends primarily on the subject's muscular effort and cooperation rather than on the mechanical characteristics of the lung.

Shortly after development of peak flow, the curve follows a remarkably reproducible, effort-independent envelope as flow diminishes in proportion to volume until *residual volume* (RV) is reached. For each point on the volume axis, a maximal flow exists that cannot be exceeded regardless of the pressure generated by the respiratory muscles. Although this portion of the curve is very reproducible in a given subject from time to time, it is altered in a characteristic manner by the effect of diseases on the mechanical properties of the lungs. In most subjects older than age 30 and in patients with pulmonary disease, RV is determined by airway closure, so the flow-volume curve shows a progressive decrease in flow until RV is reached. In some young individuals, however, and perhaps in some patients with chest wall disease, RV is determined by chest wall rigidity, which limits maximal exhalation. In such cases, expiratory flow abruptly decreases to zero at low lung volumes.

On forced *inhalation*, the flow-volume curves are normally entirely effort dependent. The shape of the inspiratory portion is symmetrical with flow, increasing to a

maximum midway through inspiration and then decreasing as inhalation proceeds to TLC. It is less influenced by diffuse airway or parenchymal disease. When central airway obstruction is suspected, the inspiratory limb of the flow-volume curve has great diagnostic usefulness, whereas ordinary spirometry reveals a nonspecific pattern.

OBSTRUCTIVE VENTILATORY DEFECTS. Some studies suggest that early asymptomatic airway obstructive disorders may be associated with decreased maximal flow at low lung volumes,²⁶ but sufficient numbers of anatomic studies that correlate findings in patients with emphysema and with central and peripheral airway lesions are not available.^{17,27} The variability of the flow-volume curve at low lung volumes has made it difficult to interpret individual curves even when compared with studies of large populations.²⁸

In patients with obstructive ventilatory patterns, peak flow is diminished. However, it is probable that abrupt emptying of large central airways associated with vigorous exhalation causes these central airways to be compressed, generating a brief period of relatively high flow, which preserves peak flow relative to flow at lower lung volumes. Furthermore, the usual linear descent of the flow-volume curve is disrupted by an exaggerated concavity of the descending limb of the curve. This curvilinear portion of the lower half of the flow-volume curve is characteristic of obstructive ventilatory patterns and suggests the presence of airflow obstruction even when the FVC, FEV₁, and FEV₁/FVC ratio are well preserved.^{29,30,30a}

This loss of linearity relates to the severity of the obstruction as well as the type of disease. A decrease in volume is seen in conjunction with both obstructive and restrictive ventilatory defects, reflecting decreased VC. The decrease is relatively less in airway obstruction than in restrictive ventilatory defects, so the characteristic flow-volume curve in obstructive ventilatory defects tends to have its major axis oriented along the horizontal (volume) axis; in restrictive defects, the major axis appears to be along the vertical (flow) axis (see “[Pathophysiologic Patterns](#)” section).

When the tidal volume loop is superimposed on the flow-volume curve, comparison of the two may be useful in clinical evaluation. The difference between flow during tidal breathing and flow during maximal effort is a measure of pulmonary reserve. As the severity of airflow obstruction increases, the expiratory flow during the two maneuvers becomes superimposed, at first low in the lung volume, and then, as the disease becomes more severe, at higher lung volumes.

“Negative effort dependence” is present when expiratory airflow rates during quiet breathing exceed those during maximal effort. When present, this phenomenon suggests that the airways are less stable than normal, as may be seen in emphysema and in some forms of chronic bronchitis. (See later discussion of obstructive ventilatory defect in “[Pathophysiologic Patterns](#)” section for further details about this phenomenon.)

Finally, the relative position of the two curves on the volume axis is a graphic measure of the amount of expiratory volume in reserve. As this reserve decreases due to obesity, pregnancy, or ascites, the tidal volume loop moves closer to the RV.

Two other factors that affect flow-volume curves are upper airway obstruction and gas density.

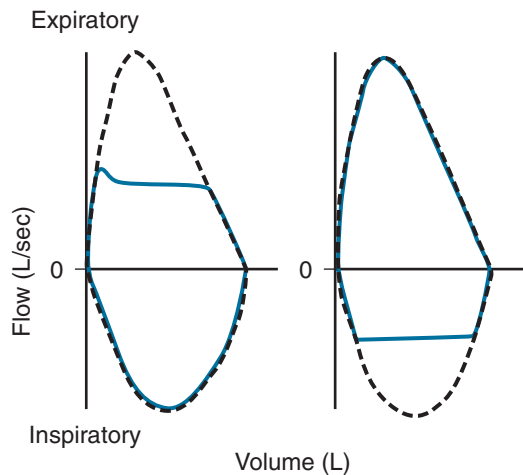


Figure 25-8 Flow-volume curves obtained from patients with upper airway obstruction. Dashed line represents a curve obtained from a normal subject with the same vital capacity as that observed in the patients. Solid line indicates a curve obtained from a patient with intrathoracic obstruction (left) and from another patient with extrathoracic obstruction (right).

UPPER AIRWAY OBSTRUCTION: STENOSIS AND MALACIA. Flow-volume curves may be especially helpful in identifying tracheal or other upper airway lesions as a cause of obstruction.³¹ Central airway obstruction (i.e., proximal to the tracheal carina) that is located within the thorax produces a plateau during forced exhalation instead of the usual rise to and descent from peak flow (Fig. 25-8). When more than 50% of the VC has been exhaled, the curve then follows the usual flow-volume envelope to RV. In patients with stridor, particular attention should be paid to the configuration of the inspiratory portion as well as the expiratory portion of the flow-volume curve. Lesions located in the trachea within the thorax cause decreased airflow particularly during exhalation; during inhalation, the posterior tracheal membrane is pulled out by negative intrathoracic pressure, so increased effort increases airflow rates and the inspiratory limb of the flow-volume curve can appear normal. Conversely, tracheal lesions located outside of the thorax cause decreased airflow during inhalation; during inhalation, the tracheal membrane is sucked in and is usually associated with stridor. It is possible to estimate the diameter of a stenotic lesion by analysis of the flow-volume curve with an accuracy of ± 1 mm (eFig. 25-1), but the length of the flow-limiting segment must be confirmed by *computed tomography* (CT) scan to plan surgical correction, if required. Because a critical orifice located at the thoracic outlet is not affected by pressure above or below the lesion, airflow is limited equally during both inhalation and exhalation.³² Similarly, if a lesion is fixed and not altered by surrounding pressures, whether intra- or extrathoracic, airflow should be limited equally during inhalation and exhalation.

RESTRICTIVE VENTILATORY DEFECTS. The increase in lung elastic recoil that accounts for the decrease in VC seen with restrictive defects also increases the force driving expiratory flow and pulling outward on airway walls; thus, the usual flow-volume curve in restrictive ventilatory defects is tall and narrow. Peak expiratory flow is relatively preserved, and the descending portion of the expiratory limb is linear, decreasing rapidly from peak flow to RV. The loop often

maintains a nearly normal shape but appears miniaturized in all dimensions.

Lung Volumes

Vital Capacity and Other Static Lung Volumes. The measurement of VC requires the subject to inhale as deeply as possible and then to exhale fully, taking as much time as required. Figure 25-2 illustrates the subdivisions of lung volume.³⁷ The measurement can also be obtained by adding two of its components: the expiratory reserve volume, obtained by having the subject exhale maximally from the resting end-tidal level; and the inspiratory capacity, obtained by having the subject inspire fully from the resting end-tidal level. The sum of these two measurements yields the “combined VC”; as long as the resting end-tidal lung volume is the same for the two component maneuvers, the combined VC and the VC are equal. In patients with severe airflow obstruction the combined VC appears to be larger than the VC, suggesting the presence of poorly ventilated regions of lungs, or so-called trapped gas. This result probably reflects increased transmural pressure, which tends to cause airway closure during a large portion of the single maneuver—but only in the portion near RV during the combined VC maneuver.

A similar inference can be made by comparing the “slow VC” (performed without regard to time) and FVC, or by comparing inspired VC (maximal volume inhaled from RV to TLC) with the expired VC maneuver just described. Except for those subdivisions involving RV, each of the defined volumes can be recorded and measured by simple spirometry. The RV can be measured only by indirect methods (e.g., nitrogen washout, helium dilution, or body plethysmography). Figure 25-2 illustrates the fact that VC can be decreased in two different ways: by a decrease in TLC or by an increase in RV. Only measuring RV and TLC can differentiate these two causes.

The cause of a reduction in VC can often be inferred by analysis of maximal expiratory flow. Abnormally decreased flows support the diagnosis of an obstructive ventilatory defect, suggesting that the decreased VC is due to an increased RV (as in asthma, chronic bronchitis, and emphysema). Normal values for airflow make an obstructive ventilatory defect unlikely and suggest that a decrease in VC may be due to a decreased TLC. Restrictive ventilatory defects (e.g., pulmonary fibrosis, resection of lung tissue) decrease VC by decreasing TLC. Thus the finding of decreased VC alone is inadequate and nonspecific to assess decreased ventilatory reserve. Performance of complete spirometry (i.e., FVC and its subdivisions as well as VC) adds clarification of the mechanism and the severity of a ventilatory defect. Measurement of RV provides convincing proof of the presence or absence of overinflation or underinflation of the lungs.

Gas Dilution Methods. The two most commonly used gas dilution methods for measuring lung volume are the *open-circuit nitrogen* (N_2) method and the *closed-circuit helium* (He) method. Both methods use a physiologically inert gas that is poorly soluble in alveolar blood and lung tissues, and both are most often used to measure *functional residual capacity* (FRC), the volume of gas remaining in the lung at the end of a normal expiration. In the *open-circuit* method,

GAS DENSITY. Comparison of flow-volume curves obtained when the subject is breathing air and breathing low-density gas mixtures such as “heliox” (80% helium, 20% oxygen) has been advocated to detect early airway obstruction³³ or localize the site of obstruction.¹⁴ During a forced exhalation, when flow limitation develops in large central airways where flow is turbulent, a low-density gas such as heliox increases maximal flow (defined by the increased maximal flow at 50% VC, or $\Delta\dot{V}_{\max_{50\%}}$). As lung volume decreases, the flow-limiting segment moves into small peripheral airways, where flow is laminar and density independent. At this lung volume, air and heliox flow-volume curves can be superimposed; the lung volume at which flow becomes density independent is called the volume of isoflow. Clinical application of heliox in detecting airflow obstruction is generally not performed because a number of controversial issues have not been resolved.³⁴⁻³⁶

all exhaled gas is collected while the subject inhales pure oxygen. By assuming values for the initial concentration of nitrogen in the lungs (alveolar nitrogen fraction varies slightly with the respiratory quotient but is assumed to be approximately 0.81) and, for the rate of nitrogen elimination from blood and tissues (about 30 mL/min), measurement of the total amount of nitrogen washed out from the lungs permits the calculation of the volume of nitrogen-containing gas present at the beginning of the maneuver (Fig. 25-9). In the *closed-circuit* helium dilution method

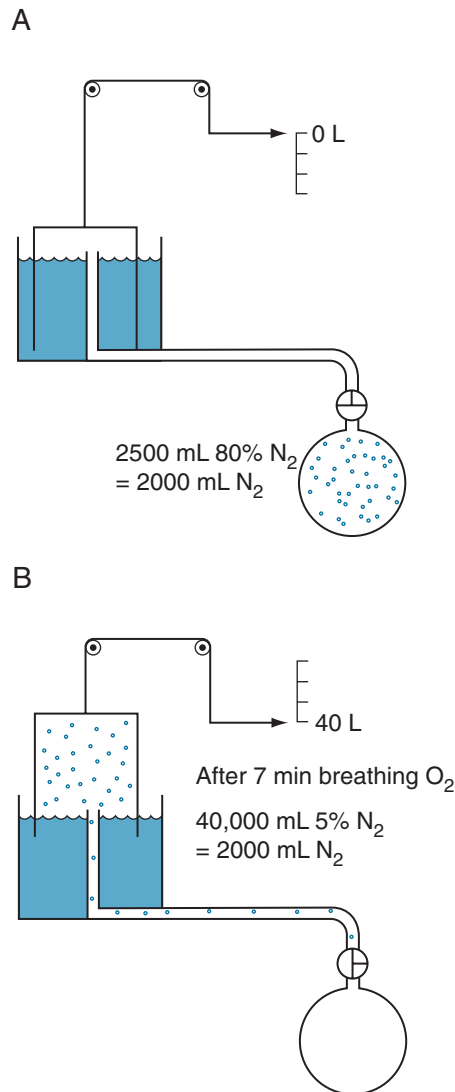


Figure 25-9 Open-circuit nitrogen method to measure functional residual capacity. Dots represent nitrogen (N_2) molecules. **A**, Initially all the N_2 molecules are in the lungs (as 80% N_2). **B**, When N_2 -free oxygen ("pure O_2 ") is breathed, the N_2 molecules are washed out of the lungs and collected with the O_2 as expired gas in the spirometer. The spirometer contains 40,000 mL of mixed expired gas with a N_2 concentration of 5%. Thus the spirometer contains $0.05 \times 40,000 = 2000$ mL of N_2 ; the remaining 38,000 mL of gas is mainly O_2 used to wash the nitrogen out of the lungs, plus some carbon dioxide. The 2000 mL of N_2 was distributed within the lungs at a concentration of 80% N_2 when the washout began; therefore the alveolar volume in which the N_2 was distributed was $2000/0.8 \text{ mL} = 2500 \text{ mL}$. Corrections must be made for the small amount of N_2 washed out of the blood and tissue when O_2 is breathed and for the small amounts of N_2 in "pure O_2 ."

(Fig. 25-10), the theory is similar. The subject rebreathes a gas mixture containing helium, a physiologically inert tracer gas, in a closed system until equilibration is achieved. If the volume and concentration of helium in the gas mixture rebreathed are known, measurement of the final equilibrium concentration of helium permits calculation of the volume of gas in the lungs at the start of the maneuver.

Body Plethysmography

TYPES OF PLETHYSMOGRAPHS. There are three types of plethysmographs: pressure, volume, and pressure-volume.

PRESSURE (CLOSED-TYPE) PLETHYSMOGRAPH. This type of plethysmograph has a closed chamber with a fixed volume

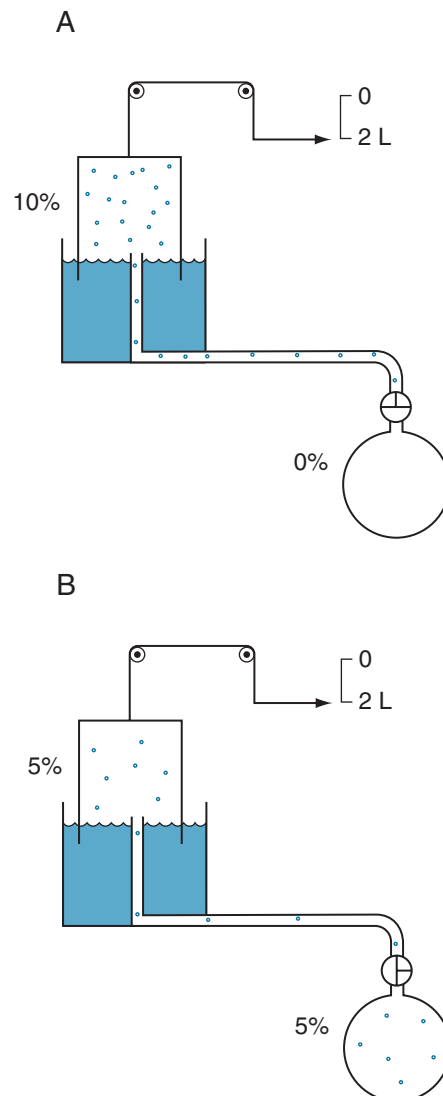


Figure 25-10 Closed-circuit helium method to measure functional residual capacity. Dots represent molecules of helium (He). **A**, Initially, all He molecules are in the spirometer (as 10% He), and no molecules are in the lungs. If the spirometer contains 2000 mL of gas, of which 10% is He, then $2000 \text{ mL} \times 0.1$, or 200 mL, of He is present in the spirometer before rebreathing. **B**, Rebreathing results in redistribution of the He molecules until equilibrium develops, at which time lung volume can be calculated. At the end of the test, the same amount of He (200 mL) must be redistributed in the lungs, tubing, and spirometer, assuming that He is inert and not soluble in blood or tissues.

An advantage of the open-circuit method is that it also permits an assessment of the uniformity of ventilation of the lungs by analyzing the slope of the change in nitrogen concentration over consecutive exhalations, by measuring the end-expiratory concentration of nitrogen after 7 minutes of washout,³⁸ or by measuring the total ventilation required to reduce end-expiratory nitrogen to less than 2%.³⁹ The open-circuit method is sensitive to leaks anywhere in the system (especially at the mouthpiece) and to errors in measurement of nitrogen concentration and exhaled volume. If a pneumotachygraph is used to measure volume, attention must be paid to the effects of viscosity changes in the exhaled gas, because it contains a progressively decreasing concentration of nitrogen. The open-circuit method shares several disadvantages with the closed-circuit method: it does not measure the volume of gas in poor communication with the airways (e.g., lung bullae); it assumes that the volume at which the measurement was made corresponds to the end-expiratory point on the spirometry tracing used to calculate expiratory reserve volume and inspiratory capacity (needed for the computation of RV and TLC from the measured FRC); and it requires a long period of reequilibration with room air before the test can be repeated. Measuring spirometric volumes immediately before measuring FRC as a combined, continuous sequence can eliminate the assumption of a constant or reproducible end-expiratory volume. This can be achieved with appropriate valves connected to the mouthpiece, which are available in many commercial systems.

Closed Circuit Methods. The closed-circuit helium dilution method (see Fig. 25-10) is similar in its basic theory. It involves having the subject rebreathe a gas mixture containing helium, a physiologically inert tracer gas, in a closed system until equilibration is achieved. If the volume and concentration of helium in the gas mixture rebreathed are known, measurement of the final equilibrium concentration of helium permits calculation of the volume of gas in the lungs at the start of the maneuver.

In a closed-circuit method, a thermal-conductivity meter measures the helium concentration continuously, permitting return of the sampled gas to the system. Because the meter is sensitive to carbon dioxide, and because carbon dioxide must in any case be removed from a closed system, a carbon dioxide absorber is added. The removal of carbon dioxide results in a constant fall in the volume of gas in the closed circuit, as oxygen is consumed and the subject produces carbon dioxide. An equivalent amount of oxygen is therefore introduced as an initial bolus or as a continuous flow. In either case, it is important that the subject be

“switched into” the system at the end-tidal point. It is possible to calculate the correction for an error in this point, but only if the subject is able to relax and exhale reproducibly to the actual end-tidal point while breathing from the circuit. In a cooperative subject the closed-circuit method also permits the measurement of inspiratory capacity, expiratory reserve volume, and VC from maneuvers recorded on the spirometer while the subject is switched into the system. This eliminates dependency on the identity of the value of end-tidal lung volume (FRC) at the time that the closed-circuit measurement is made and at the time that the subdivisions of spirometric volumes are measured.

Like the open-circuit method, the closed-circuit method is sensitive to errors caused by gas leaks and alinearity of the gas analyzer. It also fails to measure the volume of gas in lung bullae, and it cannot be repeated at short intervals. The test nevertheless gives reproducible results (the *standard deviation* [SD] of repeated measurements is 90 to 160 mL),⁴⁰ and normal values are available from several studies of healthy subjects.^{6,41}

Two other measurements of lung volume can be obtained from the dilution of gases used in standard tests of lung function. One involves measurement of the mean concentration of nitrogen in the air exhaled after the VC inspiration of pure oxygen in the single-breath nitrogen washout test of the distribution of ventilation.⁴² The other involves measuring the change in concentration of the neon, helium, or methane used as the inert tracer gas in the single-breath measurement of the *diffusing capacity for carbon monoxide* (DL_{CO}).⁴³ Indeed, the alveolar volume achieved during performance of the standard diffusing capacity maneuver is approximately TLC and must be calculated in order to measure DL_{CO} . Although the lung volume calculated from the single-breath nitrogen washout test of distribution is reported rarely, the TLC calculated from measurement of DL_{CO} is used commonly in many pulmonary function laboratories. Because the time for dilution of the tracer gas is short (10 seconds), true TLC is underestimated in patients with severe airway obstruction or uneven distribution of ventilation. FEV_1 /FVC must be less than 0.40 for TLC measured by single-breath dilution to be underestimated significantly. In healthy subjects and in patients with mild airflow obstruction, the values obtained correspond well with those obtained by body plethysmography.^{6,44}

Radiographic Methods. TLC and FRC can be estimated from chest radiographs, although what is measured is the combined air and tissue volume of the lungs; this is in contrast to the communicating gas volume that is measured by gas dilution methods and the compressible gas volume that is measured by body plethysmography.⁴⁵

in which the subject breathes the gas in the plethysmograph (or body box) (Fig. 25-11). Volume changes associated with compression or expansion of gas within the thorax are measured as pressure changes in gas surrounding the subject within the box. Volume exchange between lung and box does not directly cause pressure changes, although thermal, humidity, and carbon dioxide–oxygen exchange differences between inspired and expired gas do cause pressure changes. Thoracic gas volume and airway resistance are measured during rapid maneuvers, so small leaks are tolerated or are introduced to vent slow thermal-pressure drift. This device is best suited for measuring small volume changes because of its high sensitivity and excellent frequency response. It need not be leak-free, absolutely rigid, or refrigerated because the measurements are usually brief and are used to study rapid events.

THORACIC GAS VOLUME. The thoracic gas volume is the compressible gas in the thorax, whether or not it is in free communication with airways. By Boyle's law, pressure times the volume of the gas in the thorax is constant if its temperature remains constant ($PV = P'V'$). At end-expiration, *alveolar pressure* (P_{alv}) equals *atmospheric pressure* (P) because there is no airflow; V (thoracic gas volume) is unknown (eFig. 25-5). Then, the airway is occluded and the subject makes small inspiratory and expiratory efforts against the occluded airway. During inspiratory efforts, the thorax enlarges (ΔV) and decompresses intrathoracic gas, creating a new thoracic gas volume ($V' = V + \Delta V$) and a new pressure ($P' = P + \Delta P$). A pressure transducer between the subject's mouth and the occluded airway measures the new pressure (P'). It is assumed that the *mouth pressure* (P_{mouth})

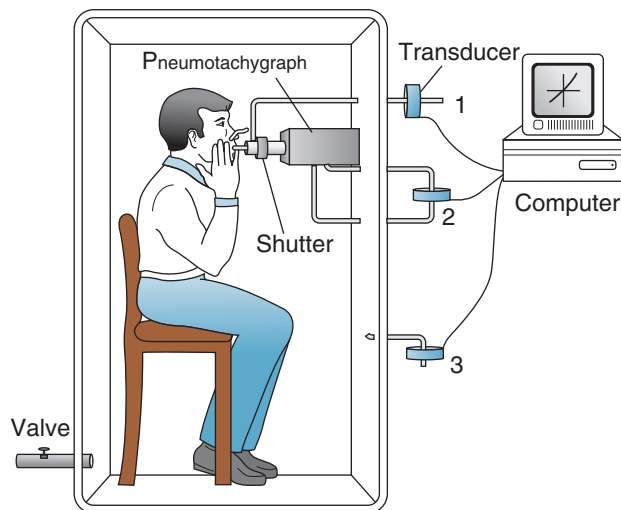


Figure 25-11 Pressure (closed-type) plethysmograph. The subject breathes through a shutter/pneumotachygraph. The shutter is open during tidal breathing and for measurements of airway resistance, and closed for measurements of thoracic gas volume. When the shutter is closed, mouth pressure (equal to alveolar pressure at no flow) is measured by a pressure transducer (1). The pneumotachygraph measures airflow with another transducer (2), and the flow signal is integrated to volume electronically. The plethysmograph pressure is measured by a third transducer (3). The signals from the three transducers are processed by a computer. Excess box pressure caused by temperature changes when the subject sits in the closed box is vented through a valve.

equals P_{alv} during compressional changes while there is no airflow at the mouth, because pressure changes are equal throughout a static fluid system (Pascal's principle). Accordingly,

$$PV = P'V' = (P + \Delta P)(V + \Delta V) \quad (2)$$

$$0 = P\Delta V + \Delta PV + \Delta P\Delta V \quad (3)$$

$$\text{If } \Delta P \ll P, \text{ then } \Delta P\Delta V \approx 0 \quad (4)$$

$$V = -\frac{\Delta V}{\Delta P}P \quad (5)$$

where P equals atmospheric pressure minus water vapor pressure (in mm Hg), assuming that alveolar gas is saturated with water vapor at body temperature; ΔV equals change in thoracic gas volume; and ΔP_{mouth} equals change in P_{mouth} , which is equal to the change in alveolar pressure (ΔP_{alv}). Then the thoracic gas volume is calculated as follows:

$$V = -\frac{\Delta V(\text{mL})}{\Delta P_{alv}(\text{cm H}_2\text{O})} \times (P - 47 \text{ mm Hg})(1.36 \text{ cm H}_2\text{O}/\text{mm Hg}) \quad (6)$$

If a closed plethysmograph is used, ΔV is detected measuring increased plethysmographic pressure with a sensitive pressure transducer. If plethysmographic pressure is displayed on the x-axis and P_{mouth} P_{alv} is displayed on the y-axis of an oscilloscope (Fig. 25-12), the slope of the line

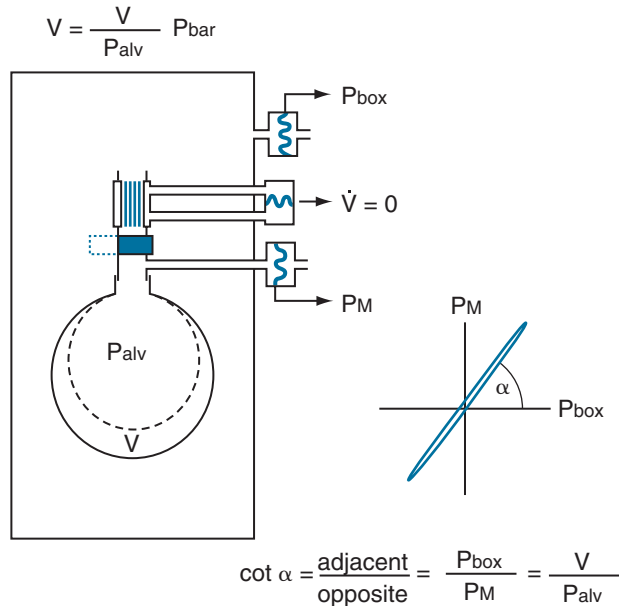


Figure 25-12 A closed, constant-volume, variable-pressure whole-body plethysmograph. As described in eFigure 25-5, at end-expiration airflow is zero, thoracic gas volume (V) = functional residual capacity, and alveolar pressure (P_{alv}) = mouth pressure (P_M) = barometric pressure (P_{bar}). The rectangle represents the plethysmograph. When the subject inhales against an occluded shutter in the airway, airflow remains zero, but V increases by ΔV to V' and $P_M (= P_{alv})$ increases by ΔP ($P + \Delta P$) to equal P' . When P_M is plotted against box pressure (P_{box}), the slope of the line (α) yields $\Delta V/\Delta P_{alv}$, and $V = \Delta V/\Delta P_{alv} \times P_{bar}$, as indicated in the text. \dot{V} , airflow. (Modified from Comroe JH Jr, Forster RE II, DuBois AB, et al: *The lung: clinical physiology and pulmonary function tests*, ed 2, Chicago, 1962, Year Book.)

VOLUME (OPEN-TYPE) PLETHYSMOGRAPH. This type of plethysmograph (eFig. 25-2) has constant pressure and variable volume. When thoracic volume changes, gas is displaced through a hole in the box wall and is measured either with a spirometer or by integrating the flow through a pneumotachygraph (or flowmeter). This device is suitable for measuring small or large volume changes. To attain good frequency response, the impedance to gas displacement must be very small. This requires a low-resistance pneumotachygraph, a sensitive transducer, and a fast, drift-free integrator, or meticulous use of special spirometers; consequently this form of plethysmography is challenging and is used in the research setting only.

PRESSURE-VOLUME PLETHYSMOGRAPH. This device (eFig. 25-3) combines features of both the closed and open types. As the subject breathes from the room, changes in thoracic gas volume compress or expand the air around the subject in the box and also displace it through a hole in the box wall. The compression or decompression of gas is measured as a pressure change; the displacement of gas is measured either by a spirometer connected to the box or by integrating airflow through a pneumotachygraph in the opening. At every instant, all of the change in thoracic gas volume is accounted for by adding the two components (pressure change and volume displacement). This combined approach has a wide range of sensitivities, permitting all types of measurements to be made with the same instrument (i.e., thoracic gas volume and airway resistance, spirometry, and flow-volume curves). The box has excellent frequency response and relatively modest requirements for the spirometer. The integrated flow version dispenses with water-filled spirometers and is tolerant of leaks.

In this type of plethysmograph, changes in lung volumes are computed from measurements of both *box pressure* (P_{box}) and volume displacement to determine accurately

the true volume change regardless of amplitude or frequency. P_{box} is multiplied by a *constant* (K_{box}) proportional to the gas volume in the box (i.e., by total box volume minus patient volume). P_{box} is also divided by the *box flowmeter resistance* (R_{box}) and multiplied by the integral of box flow to obtain the *box volume* (V_{box}). These two signals are added together to yield the change in lung volume (ΔV):

$$\Delta V = P_{box}K_{box} + \frac{P_{box}}{R_{box}} \int \dot{V} \quad (1)$$

The physical principles underlying this type of plethysmograph are illustrated in eFigure 25-4. The displacement volume, $\int \dot{V}$, is added to the plethysmograph compression volume, $P_{box}K_{box}$, to produce the “true” volume. If the volume change were instantaneous, the “true” volume event would be as illustrated in eFigure 25-4A. During this rapid inspiration, pressure in the plethysmograph increases abruptly and then decays exponentially (see eFig. 25-4B). If the plethysmograph flowmeter has a linear response, the plethysmograph flow signal (see eFig. 25-4C) will have a shape similar to that of the pressure signal (see eFig. 25-4B). The plethysmograph flow signal is integrated to determine volume (see eFig. 25-4D). The integrated flow signal attains the same level as that of the “true” volume event, but the shape of the integrated flow signal does not conform to that of the “true” volume event. The difference between the two waveforms is due to compression of the large volume of gas in the plethysmograph and is directly proportional to plethysmograph pressure. Thus, by adding a portion of the plethysmograph pressure to the integrated plethysmograph flow, the “true” volume event may be reconstructed accurately (see eFig. 25-4E) using Equation 1. The relative contributions of these two variables vary with frequency, but when added together, they always yield the total ΔV .

(α) can be measured during panting efforts against the closed airway:

$$V = \frac{(P - 47 \text{ mm Hg})(1.36 \text{ cm H}_2\text{O/mm Hg}) \times \text{box calibration (mL/cm)}}{\alpha \times \text{pressure calibration (cm H}_2\text{O/cm)}} \quad (7)$$

$$V = \frac{970 \times \text{box calibration}}{\alpha \times \text{pressure calibration}} \quad (8)$$

The thoracic gas volume usually measured is slightly larger than FRC unless the shutter is closed precisely after a normal tidal volume is exhaled. Connecting the mouthpiece assembly to a valve and spirometer (or pneumotachygraph and integrator), or using a pressure-volume plethysmograph, makes it possible to measure TLC and all its subdivisions in conjunction with the measurement of thoracic gas volume.

TECHNICAL PROBLEMS. As might be expected, several problems may complicate these measurements. The most important are the following.

EFFECTS OF HEAT, HUMIDITY, AND RESPIRATORY GAS EXCHANGE RATIO. Effects of heat, humidity, and respiratory gas exchange ratio cause difficulties in obtaining stable baselines.

CHANGES IN OUTSIDE PRESSURE. Outside pressure changes can make it difficult to detect the “signal” relative to “noise.”⁴⁶

COOLING. Refrigeration is required for many of these boxes, but it can cause a variety of problems related to vibration and localized cooling (e.g., a cool body and a warm head may result because of poor circulation currents).

UNDERESTIMATION OF MOUTH PRESSURE. Stanescu and colleagues⁴⁷ have reported that, in patients with asthma, lung volume measured by plethysmograph may be overestimated owing to an underestimation of P_{alv} by measurements of P_{mouth} .

COMPRESSION VOLUME. Commercial plethysmographs are now available that correct for these problems; some of these devices also take into account the compression of thoracic gas during a forced expiration.

Airway Resistance

GENERAL PRINCIPLES. Airway resistance (RAW) is easy to measure and is always related to the lung volume at which it is measured. It is useful to detect diseases such as asthma that are associated with increased airway smooth muscle tone. This can be accomplished by demonstrating that RAW is abnormally increased relative to lung volume, or by inducing significant relaxation of bronchomotor tone by administration of bronchodilator drugs. The test is very sensitive in detecting increased airway smooth muscle tone induced by provocative stimuli. This approach is useful in the assessment of nonspecific hyperirritability in response to pharmacologic agents, exercise, or cold air, or in response to specific agents such as allergens or chemicals (e.g., isocyanates) that are associated with occupational asthma (see “Bronchial Provocation” section). Measurements of RAW may also be useful in differential diagnosis of the type of airflow obstruction or localization of the major site of obstruction.

RAW is measured during airflow and represents the ratio of the driving pressure (between the alveoli [P_{alv}] and mouth [P_{mouth}]) and instantaneous airflow (\dot{V}). In a closed plethysmograph, inspiration of 500 mL of gas from the box into the lungs increases plethysmographic pressure. At the start of inspiration, thoracic gas volume enlarges, and P_{alv} (previously at atmospheric pressure) becomes subatmospheric throughout inspiration; thus alveolar gas occupies a larger volume. This decompression of thoracic gas is equivalent to adding a small volume of gas to the plethysmograph, so its pressure increases (as measured by a sensitive pressure transducer). The reverse results during exhalation, when alveolar gas is compressed. Thus \dot{V} is measured continuously with a pneumotachygraph, P_{mouth} is measured with a pressure transducer connected to a side tap in the mouthpiece, and P_{alv} is estimated continuously with the body plethysmograph (Fig. 25-13).

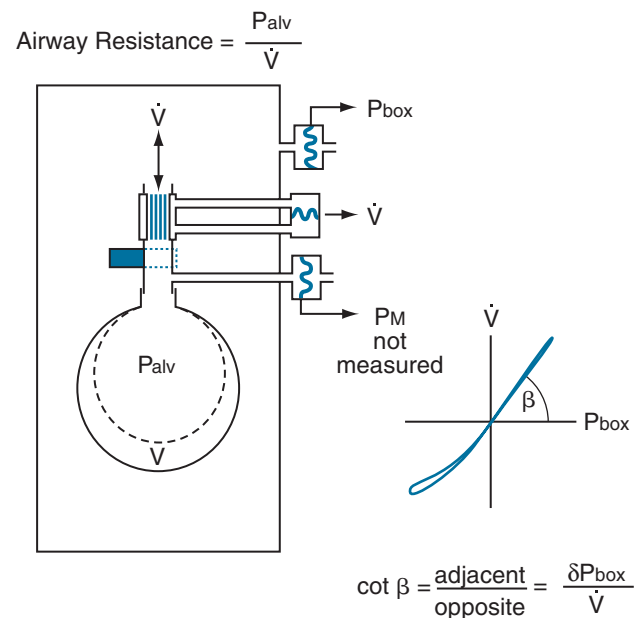


Figure 25-13 Measurement of airway resistance by plethysmography. The rectangle represents a closed, constant-volume, variable-pressure, whole-body plethysmograph, as in eFig. 25-5. The subject is represented by a single alveolus and its conducting airway. The top pressure transducer measures pressure within the plethysmograph, or box pressure (P_{box}). The middle pressure transducer measures the pressure drop across the pneumotachygraph connected in series with the open shutter to the airway, which yields airflow (\dot{V}). The bottom pressure transducer measures airway pressure (alveolar pressure during no flow, or P_{alv}). During inspiration, the alveolus enlarges by ΔV from the original volume (broken line) to a new volume (solid line); during expiration, the alveolus returns to its original volume. Throughout inspiration, alveolar gas (previously at atmospheric pressure) is subatmospheric and therefore occupies more volume. This is the same as adding this increment of gas volume resulting from decompression of the alveolar gas to the plethysmograph, so P_{box} increases and is recorded by the sensitive P_{box} transducer. The reverse happens during expiration when alveolar gas is compressed. Thus alveolar pressure can be monitored throughout the respiratory cycle. When \dot{V} is plotted against P_{box} , the slope of the line (β) yields the ratio of $\Delta P_{\text{box}}/\dot{V}$ as indicated in the text. (Modified from Comroe JH Jr, Forster RE II, DuBois AB, et al: *The lung: clinical physiology and pulmonary function tests*, ed 2, Chicago, 1962, Year Book.)

In practice, RAW is determined by measuring the slope (β) of a curve of plethysmograph pressure (x-axis) displayed against airflow (y-axis) on a computer monitor during rapid, shallow breathing through a pneumotachygraph within the plethysmograph. Then, a shutter is closed across the mouthpiece, and the slope (α) of plethysmographic pressure (x-axis) displayed against Pmouth (y-axis) is measured during panting under static conditions. Because Pmouth equals Palv in a static system, the second step serves two purposes. First, it relates changes in plethysmographic pressure to changes in Palv in each subject. Palv is effectively measured during flow, provided that the ratio of lung to plethysmographic gas volume is constant, because Palv for a given plethysmographic pressure is the same whether or not flow is interrupted. Second, it relates RAW to a particular thoracic gas volume:

$$RAW = \frac{\alpha}{\beta} \times \frac{PM \text{ calibration}}{\dot{V} \text{ calibration}} - R_{EXT} \quad (9)$$

$$RAW = \frac{PM}{\Delta V} \times \frac{\Delta V}{\dot{V}} - R_{EXT} \quad (10)$$

$$RAW = \frac{PM}{\dot{V}} - R_{EXT} \quad (11)$$

$$RAW = \frac{Palv}{\dot{V}} - R_{EXT} \quad (12)$$

where PM calibration is Pmouth calibration (cm H₂O per cm), \dot{V} calibration is pneumotachygraph calibration (L·sec per cm), and R_{EXT} is resistance of breathing through mouthpiece and pneumotachygraph (cm H₂O per L/sec).

Physiologic Factors. Several physiologic factors affect the values obtained during plethysmographic measurement of RAW.

AIRFLOW. RAW relates to a particular flow rate during continuous pressure-flow curves, so the slope may be read at any desired airflow rate. In general, RAW is measured at low flows, at which transmural compressive pressures across the airways are small and the relation to Palv is linear. RAW will be increased transiently with forced respiratory maneuvers in which airflow rates become limited by large transmural compressive pressures across the airways, by maximal dynamic airway compression, and by possible alterations in airway smooth muscle tone. Thus, to avoid artifacts, the standard approach is to measure RAW at low flows.

VOLUME. Near TLC, resistance is small, but, near RV, resistance is large. Lung volume may be changed voluntarily to evaluate RAW at larger or smaller volumes in health and disease.

TRANSPULMONARY PRESSURE. RAW is related directly to lung elastic recoil pressure at any lung volume. Subjects with increased lung elastic recoil have a lower RAW at a given lung volume than normal subjects because of increased tissue tension pulling outward on airway walls. In contrast, loss of elastic recoil results in loss of tissue tension and decreased traction on airway walls, so RAW is increased. This relationship may be used to analyze the mechanism of airflow limitation in various obstructive ventilatory defects (e.g., bullous lung disease).^{48,49}

AIRWAY SMOOTH MUSCLE TONE. The airways are affected markedly by smooth muscle tone, depending on the state of inflation and the subject's previous pattern of breathing (referred to as "volume history").⁵⁰ These relationships are relevant to diseases in which smooth muscle tone is increased (e.g., asthma) or low lung volumes are encountered (e.g., during cough). Thus, bronchoconstriction is not demonstrable temporarily after a deep breath or at TLC in healthy subjects. Similarly, RAW in healthy subjects may be greater when a given lung volume is reached from RV than from TLC.

PANTING. Panting minimizes changes in the plethysmograph caused by thermal, water saturation, and carbon dioxide-oxygen exchange differences during inspiration and expiration; hence these factors may be neglected if measurements are made during panting. Panting also improves the signal-to-drift ratio, because each respiratory cycle is completed in a fraction of a second; gradual thermal changes and small leaks in the box become insignificant compared with volume changes attributable to compression and decompression of alveolar gas. The glottis stays open, rather than varying its position as it does during tidal breathing. Abdominal pressure changes are also minimized.

QUIET BREATHING. Increasingly laboratories are using commercial plethysmographs that estimate RAW during so-called quiet breathing, relying on computer software rather than panting to compensate for the effects of humidity, temperature, and gas exchange. In fact, the subject must breathe at higher than normal frequencies and tidal volumes to estimate RAW using this software. The limitation to this approach is that the average resistance values tend to be slightly higher than those observed during

panting because the glottis is often partially closed during the measurement. Nonetheless, more and more laboratories are switching to this approach.

Stanescu and Rodenstein⁵¹ have demonstrated that, to avoid overestimation of thoracic gas volume, as described previously, panting must be done at 1 Hz; however, to measure RAW and avoid the temperature artifact, panting must be done at approximately 2 Hz, as advocated originally by DuBois and colleagues.⁵² This difference in the panting rates necessary for accurate measurements may prove impractical for clinical use. Alternatively, both artifacts may be avoided if the subjects breathe quietly at *body temperature* (37°C) and *standard pressure fully saturated with water vapor* (760 mm Hg) (BTPS) or may be compensated for electronically.⁵³

RAW measured plethysmographically is not the average of unequal resistances throughout the lungs; rather, it is the average Palv per unit volume divided by average airflow rate at the mouth. It corresponds to average *airway conductance* (GAW). $GAW = G_1 + G_2 + \dots + G_n$, which is equivalent to adding resistances in parallel according to reciprocals: $1/RAW = (1/R_1) + (1/R_2) + \dots + (1/R_n)$. The control of these physiologic influences is often critical in determining specific factors that influence GAW (or RAW) in a particular subject (e.g., loss of lung elastic recoil, airway smooth muscle spasm).

Lung Elastic Recoil

General Principles. Lung elastic recoil is an important physiologic characteristic of the lungs, which may change in qualitatively different ways in various diseases. In general, elastic recoil is increased in a restrictive ventilatory defect associated with decreased lung volumes. Conversely, in almost all forms of airflow obstruction, elastic recoil is decreased. Testing for elastic recoil is time-consuming, difficult to perform, expensive, and invasive. Thus the test may not be practical for the routine evaluation of patients with restrictive ventilatory defects but may be of great value in the assessment of various obstructive ventilatory defects, including those with isolated bullae or advanced emphysema, to determine whether patients will benefit from resection of nonfunctioning or very poorly functioning lung tissue. In other patients, it may be useful to differentiate emphysema from asthma or bronchitis. In evaluating patients with mixed ventilatory defects (e.g., emphysema plus fibrosis), the test may confirm the presence of both disorders.

Lung elastic recoil pressure, or *transpulmonary pressure* (PL), is the difference between the pressure inside the lungs (the alveolar pressure) and the pressure outside the lungs (the *pleural pressure* [Ppl]): $PL = Palv - Ppl$. To maintain a sustained inspiration at a volume of three fourths of TLC with the mouth and glottis open, the muscles of inspiration must maintain a pleural pressure of approximately 12 cm H₂O below atmospheric pressure ($Ppl = -12$ cm H₂O). Under conditions of no flow and pressures at the mouth, alveoli, and atmosphere are equal: $PL = 0 - (-12$ cm H₂O). If the muscles of inspiration relax, allowing the chest wall to recoil inward, Ppl rises from -12 to 0 cm H₂O and Palv from 0 to +12 cm H₂O at the instant before flow begins. This example illustrates two of the principles that underlie measurement of lung recoil: (1) the pressure required to expand

Impulse Oscillometry and Forced Oscillation Methods to Measure Respiratory Resistance (Rather Than Airway Resistance).^{54,55} DuBois and colleagues⁵² described an oscillatory method to measure the mechanical properties of the lung and thorax. In contrast to the methods already described, the oscillation techniques use an external loudspeaker or similar device to generate and impose flow oscillations on spontaneous breathing, rather than using the respiratory muscles. Impulse oscillometry measures RAW and lung compliance independently of respiratory muscle strength and patient cooperation. Sound waves at various frequencies (3 to 20 Hz) are applied to the entire respiratory system (airways, lung tissue, and chest wall); a piston pump can be used to apply such pressure waves around the body in a whole-body respirator. With modern computer methods, the slow frequency changes in pressure, flow, and volume generated by the respiratory muscles during normal breathing are subtracted from the raw data, permitting analysis of the pressure-flow-volume relationships imposed by the oscillation device (eFig. 25-6).

The elastic forces (pressures) of the lungs and chest wall oppose the volume changes induced by the applied pressure, which decrease as the frequency of oscillation increases. The total force or pressure that opposes the driving pressure applied by the loudspeaker, which can be measured as peak-to-peak pressure difference divided by peak-to-peak flow, is a combination of the resistance and reactance, which itself has elastic and inertial components. The reactance reaches a minimum at loudspeaker frequencies of approximately 3 to 8 Hz, where the resistance produces the only opposing force. This resistance is proportional to the RAW in healthy subjects and patients, although it does include a small component of lung tissue and chest wall resistance, as well as the resistance of the airways.

Values for the pulmonary resistance and total respiratory resistance primarily reflect RAW. The portion due to lung tissue resistance is about one fifth of the pulmonary resistance in healthy subjects. It is increased in patients with pulmonary fibrosis or kyphoscoliosis,⁵⁶ but rarely to a level of clinical importance where it becomes the limiting resistance. The total resistance of the respiratory system (airway + lung + chest wall, or $R_T = R_{AW} + R_L + R_{CW}$) usually is about 25% greater than the resistance of the airways in healthy subjects, or not much greater than pulmonary resistance. Again, although the chest wall resistance may be elevated in conditions such as kyphoscoliosis or parkinsonism, it rarely attains a level of clinical significance.

If the airways, lungs, and chest wall behaved as if they were a single bellows with frictional resistance, elasticity, and inertia, then the oscillations in airflow into and out of the lungs caused by the driving pressure produced by the loudspeaker across the respiratory system could be described as a function of the applied frequency by the following equations. At any frequency, the magnitude and phase shift of the reflected waves give a measure of impedance (Z) and reactance (X). The impedance is described by

$$Z = \sqrt{R^2 + \left(2\pi fL - \frac{1}{2\pi fC}\right)^2} \quad (13)$$

where Z is mechanical impedance (cm H₂O per L/sec) and is analogous to electrical impedance, R is resistance (cm H₂O per L/sec), L is electrical inductance (cm H₂O per L/sec²) and is analogous to electrical inductance, C is compliance (L/cm H₂O) and is analogous to electrical capacitance, and

f is the frequency of the driving pressure applied by the loudspeaker (Hz, or cycles per second).

The second equation describes the phase angle or lag (Θ) of the flow with respect to the applied pressure wave:

$$\tan \Theta = \frac{X}{R} = \frac{2\pi fL - \frac{1}{2\pi fC}}{R} \quad (14)$$

The inertial reactance ($2\pi fL$) corresponds to the electrical inductive reactance, which increases with frequency. The elastic reactance ($2\pi fC$) corresponds to the electrical capacitance, which decreases with increasing frequency.

The frequency at which the absolute values of these reactances are equal is called the resonant frequency. According to the Equation 14, the impedance (Z) becomes equal to the resistance of the respiratory system at the resonant frequency, which can be calculated from the following equation:

$$\text{Resonant frequency} = \frac{1}{2\pi\sqrt{LC}} \quad (15)$$

Landser and coworkers⁵⁷ developed a device based on multiple frequencies (pseudorandom noise) in contrast to Dubois and colleagues⁵² and Michaelson and coworkers,⁵⁸ who used a random noise signal. The technique requires little of the subject but to simply breathe quietly on a mouthpiece for 30 seconds; the computer does the complete analysis, yielding values for respiratory resistance at different frequencies. (The same device simultaneously estimates respiratory inductance and dynamic compliance.) This approach has been used extensively in Europe because it is fast, noninvasive, and reproducible; moreover, it seems to yield clinically meaningful results in healthy subjects before and after use of a bronchodilator, as well as in the evaluation of airflow obstruction in COPD, asthma, and congestive heart failure.⁵⁹⁻⁶¹

It should be noted that the lungs and chest wall rarely respond to a driving pressure with diverse frequencies in the same way as a simple model assumed to be composed of single values of resistance, compliance, and inductance, as described earlier. The resonant frequency of the ribs is 7 to 10 Hz, whereas the resonant frequency of the abdomen and diaphragm is about 3 Hz. The air in the trachea, bronchi, and bronchioles has an inertial reactance that is significant at relatively high frequencies (≈ 6 Hz or greater). Consequently, when the whole system appears to be at resonant frequency, the impedance is probably not a pure resistance at all, but rather an admixture of other forces of the lungs and chest wall, as described earlier.⁶²⁻⁶⁵

Bijaoui and colleagues⁶⁶ have taken advantage of the impact of cardiogenic oscillations on the adjacent lungs to estimate mechanical output impedance of the lung. They observed that the beating heart creates small oscillations in flow that can be measured at the mouth when the glottis is open. Using the Fourier-domain ratio of these oscillations in pressure and flow, Bijaoui and coworkers calculated the respiratory impedance to be between 1.5 and 10 Hz. The real portion was similar to or smaller than the resistance measured simultaneously by the forced oscillation method. They suggested that they are measuring the flow resistance of the central and upper airway. This approach may prove to be useful to obtain information about the mechanical properties of the lungs without the need for an external source of applied flow.

a lung to any volume is equal to the recoil pressure at that volume, and (2) under conditions of no flow, with the glottis open, P_{alv} and P_{mouth} are identical. It is easy to measure P_{mouth} ; absolute lung volume can be measured by any of a variety of methods already discussed; and the change in volume can be measured easily with a spirometer. All that is needed to measure lung elastic recoil pressure and lung compliance is a measurement of P_{pl} in relation to lung volume.

Because the esophagus passes through the pleural space, it seems reasonable to assume that pressure within the esophagus approximates P_{pl} . This assumption works as long as the sphincters of the upper and lower esophagus are competent and there is no force compressing the esophageal lumen, such as active contraction of the esophageal muscles or passive compression by surrounding mediastinal structures. Most of these conditions are met in subjects without esophageal disease who are sitting or standing upright.

Analysis

COMPLIANCE. When the balloon is in place, the relationship between changes in lung volume and changes in P_{pl} can be measured.

Dynamic lung compliance refers to the ratio of the change in volume to the change in pressure over a tidal breath, with the pressure measured at moments of zero flow during breathing. Measurement of dynamic lung compliance at increasing respiratory frequencies allows estimation of the frequency dependence of compliance. A fall in dynamic lung compliance as frequency increases implies narrowing of some of the airways subtending alveoli. Thus, in the absence of abnormalities in total RAW or FEV_1 (which, as described previously, are largely determined by resistance in large airways), decreased dynamic lung compliance suggests possible narrowing of small, peripheral airways.⁶⁸

Static lung compliance is the slope of the pressure-volume curve of the lung obtained during deflation from TLC.

The data obtained are conveniently expressed in terms of lung compliance, the ratio of the change in lung volume to the change in P_{pl} . However, it is clear that lung compliance changes with lung volume, with the highest values observed at volumes around FRC and lower values prevailing as the lungs are expanded more nearly to TLC (Fig. 25-14). Compliance therefore is usually reported as the slope of the curve at the point 0.5 L above FRC. However, when this convention is used, the value expressed for lung compliance is influenced by the determinants of FRC, rather than simply by the relationship between lung volume and distending pressure. Another value commonly calculated is the *coefficient of retraction* (lung elastic recoil pressure at TLC divided by TLC). Normal values are available for both compliance and the coefficient of retraction, although the great variability of these measurements limits their utility in individual patients. Because lung compliance is so dependent on lung volume (compliance can fall by 50% with resection of one lung, for example, even though the elastic properties of the remaining lung are unaltered), its variability can be somewhat reduced by correcting it for height, predicted TLC, or measured FRC.⁶⁹

Maximum information about lung elastic recoil can be derived by analyzing the whole curve, when, for example,

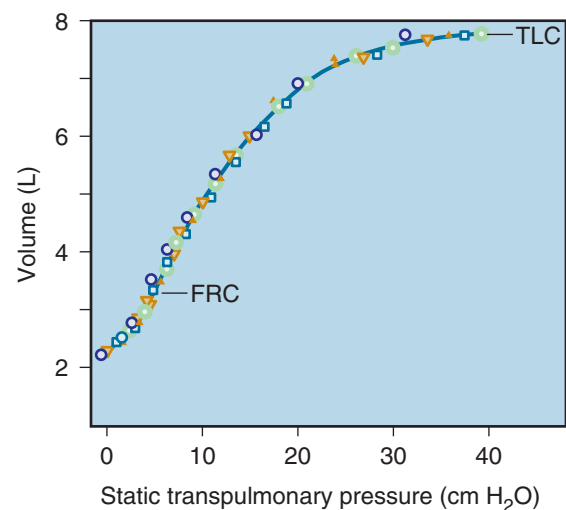


Figure 25-14 Static pressure-volume curve of the lungs during deflation in a normal subject. Measurements were obtained during five different maneuvers. FRC, functional residual capacity; TLC, total lung capacity.

static lung elastic recoil pressure is plotted against lung volume expressed as a percentage of *predicted* TLC.⁷⁰ Such a plot often makes it obvious whether a reduction in TLC is a function of the inability to generate an adequate lung elastic recoil pressure due to neural, muscular, or chest wall disease or is caused by a true loss of lung compliance. If lung compliance is reduced, it can still be difficult to determine whether the abnormality is due to a true increase in elastic forces or to a decrease in the number of alveoli communicating with the airways (see later discussion).

CLINICAL APPLICATIONS OF FLOW-VOLUME RELATIONSHIPS

Normal Values

Spirometric values vary with height, gender, age, and ethnicity. Publications describing reference populations should include not only the prediction equations but also a means to define their lower limits. A lower limit can be estimated from a regression model: for spirometry, values below the 5th percentile are taken as below the “lower limit of normal.”²⁸ There is no statistical basis for the common practice of using 80% of the predicted normal values for FEV_1 and FVC as the lower limit of normal in adults. In fact, Miller et al⁷¹ studied 11,413 patients and found that using fixed cut points to determine whether lung function is abnormal could misdiagnose more than 20% of patients, which they found could be avoided by using the lower limit of normal based on the 5th percentile values.

Changes in Function over Time. Changes in spirometric measurements can represent a true change or merely variability. A real change is more likely when a series of tests shows a consistent trend. A change varies in significance depending on the variable measured, the time period, and the type of patient. When the FVC and VC are followed in healthy, normal subjects, within-day changes of 5% or more, between-weeks changes of 11% to 12% or more, and

Protocol for Measurement of Lung Elastic Recoil.

To preserve the patency of a tube placed in the esophagus to measure esophageal pressure, it is necessary to cover the end of the tube with a balloon. This complicates the situation, for now intraballoon pressure is assumed to reflect intraesophageal pressure, which in turn is assumed to reflect the surrounding Ppl. The artifacts caused by the balloon generally cause the measured pressure to be too positive, owing to the compression of the balloon by the walls of the esophagus (eFig. 25-7). A long (10 cm), narrow (2.5-cm perimeter), thin-walled (0.04 cm), highly compliant latex balloon containing a small amount (0.2 to 0.4 mL) of air can reduce these artifacts. The volume of air that minimizes this artifact varies slightly for different balloons. The volume can be determined for each balloon by suspending it vertically in water, with the top (proximal end) of the balloon at the surface, allowing it to empty before the tube is closed with a stopcock.⁶⁷

Ppl changes along a vertical gradient, with pressures being most negative at the base of the thoracic space. It is customary to measure pressure in the lower third of the esophagus, to estimate the pressure necessary to expand the greater proportion of the lungs. The balloon is advanced to the gastroesophageal junction (identified easily by the positive pressure caused by an inspiratory sniff) and then pulled back 10 cm.

Having the subject inhale to TLC three times standardizes the volume history and ensures minimization of the changes due to the dynamics of entry of surface-active material into the air-liquid interface. On the third inhalation the subject pauses at TLC for 3 to 5 seconds and then exhales slowly, while flow is interrupted by closing the mouth shutter for 2 to 3 seconds at each of several volumes. Repeating this maneuver four or five times provides enough data to characterize the relationship between the change in lung volume and the change in PL over the entire VC (see Fig. 25-14). To fix the resultant curve on the volume axis requires knowing absolute lung volume at some PL. This is easily measured directly if the curve is obtained with the subject in a body plethysmograph. Alternatively, but less accurately, lung volume (TLC, FRC, or RV) measured at another time by a gas dilution technique, for example, may be assumed to be the same at the time of measurement of lung compliance.

Exponential Analysis. Gibson and Pride⁷⁰ suggested that exponential analysis of the lung pressure-volume curve is superior to other approaches because it is less affected by patient effort and lung size, uses a greater range of the pressure-volume data, and mathematically describes the whole lung^{70a}:

$$V = V_{\max} - Ae^{-KP} \quad (16)$$

where V is the lung volume and V_{\max} is the maximal or extrapolated lung volume at infinite distending pressure. K is a constant describing the shape of the pressure-volume curve.

EXPONENTIAL ANALYSIS OF PRESSURE-VOLUME CURVE. K is related to the incremental compliance (dV/dP) such that

$$\frac{dV}{dP} = AK e^{-KP} = K(V_{\max} - V) \quad (17)$$

where P is the lung elastic recoil pressure. When P is measured in centimeters of water, K has the dimensions of

1/cm H₂O. To describe the curve fully requires the two parameters V_{\max} and A , which both have the dimensions of volume. $A = V_{\max} - V_0$, where V_0 equals the volume extrapolated to $P = 0$. A number of investigators have now used the approach in the evaluation of both restrictive and obstructive ventilatory defects (see later discussion).^{6,70b,70c}

FIBROSIS. Exponential analysis of the pressure-volume curve appears to differentiate restriction due to loss of volume from that due to increased elastic properties.^{70b} Gibson and colleagues^{70b} reported that the elastic properties of the lungs in patients with diffuse interstitial fibrosis can be accounted for almost entirely by a loss of alveoli. This implies that the lungs of such patients consist of a population of completely obliterated, unventilated alveoli and a population of surrounding normal alveoli. Thompson and Colebatch^{70d} confirmed these findings.

EMPHYSEMA. Colebatch and associates³⁰⁹ reported that the constant K (describing the shape of the curve) falls outside the normal range in patients with pulmonary diseases (increased K in emphysema; decreased K in fibrosis). These results were confirmed by others.^{70b}

Other researchers have examined this issue, and the results are more controversial. Gugger and coworkers^{70e} found a significant correlation between elastic recoil pressure and both the FEV₁ and the DL_{CO}. Lung density (measured by CT scans, which, in turn, correlate with the amount of emphysema measured by panel grading) correlated with both the natural logarithm of K and elastic recoil pressure of the lungs at 90% of TLC. Because elastic recoil pressure correlated with emphysema and with FEV₁, their results suggest that loss of elastic recoil is one determinant of airflow limitation in patients with COPD.

Macklem and Eidelman^{70f} and others¹⁶⁵ have reexamined the effect of the elastic properties of emphysematous lungs on airflow obstruction. From published data in normal lungs and in patients with emphysema, they calculated specific lung elastance (change in lung elastic recoil pressure to produce a given fractional change in lung volume) for normal and emphysematous lungs. They found that specific lung elastance and the change in specific elastance with lung elastic recoil were increased in patients with emphysema compared with normal subjects. They speculated that this finding probably represents two distinct abnormalities in the elastic properties of emphysematous lungs: (1) an increase in resting length of alveolar walls, accounting for hyperinflation (TLC); and (2) a decrease in extensibility of alveolar walls once they become stressed (specific lung elastance). Surprisingly, these studies found no correlation between either of these factors and FEV₁. They concluded that the change in elastic properties of the lungs in emphysema does not appear to account for flow limitation in this disease. Furthermore, because of the decreased extensibility of emphysematous lungs, they also suggested that these emphysematous regions are not only poorly perfused but also poorly ventilated; therefore they speculated that emphysema per se may not seriously disturb ventilation-perfusion relationships.^{70f}

An equally surprising study of patients with severe expiratory airflow obstruction was reported by Gelb and colleagues.^{70g} They documented that marked loss of lung elastic recoil, causing hyperinflation with increased TLC, associated with decreased DL_{CO}, can be present despite the absence of or only trivial emphysema on lung CT scans and

in morphologic studies. These authors attributed the decreased DL_{CO} to errors related to inhomogeneity of ventilation and increased physiologic dead space. They attributed the severe, fixed expiratory airflow limitation to intrinsic disease of the bronchioles. They speculated that bronchiolar obstruction caused dynamic hyperinflation and gas trapping, leading to chronic loss of lung elastic recoil through unknown mechanisms, despite the absence of macroscopic emphysema. Thus the combination of increased TLC plus spuriously reduced DL_{CO} may be mistaken for emphysema; in such cases high-resolution lung CT scanning may help to clarify the source of lung hyperinflation as resulting from bronchiolar disease.

Sources of Variability. The ATS has published a formal recommendation on the selection of reference values and interpretative strategies for lung function tests, including FVC, FEV_1 , FEV_1/FVC , FEV_1/VC , and criteria defining a significant response to a bronchodilator for adult white and black men and women.⁶ This statement recommends reference values derived from the *National Health and Nutrition Examination Survey* (NHANES) III, which included whites, blacks, and Mexican Americans.⁷²⁻⁷⁴ In 2010 the Multi-Ethnic Study of Atherosclerosis lung study assessed the performance of the NHANES III reference equations in 3893 participants, of which approximately one third were Asian Americans. This study found the equations to be valid for the previously mentioned ethnic groups and, in addition, the investigators suggested that a correction factor of 0.88 be applied to the predicted and lower limits of normal values when comparing whites and Asian Americans.⁷⁵

The ATS statement also emphasizes the importance of laboratory control of technical sources of variation, including strict adherence to ATS guidelines for equipment performance and calibration, minimizing temperature-related errors, careful validation of computer calculations when purchasing or changing equipment or software, and proper performance of the tests. Although certain within-individual sources of variation fall within the control of each laboratory, between-individual sources of variation are critical to the choice of appropriate reference values. Furthermore, environmental sources of variation pertinent to a given patient (in addition to other relevant clinical data) are likely to be known by the referring clinician. This information should be provided to the laboratory director, who should use it to evaluate the clinical relevance in a given lung function report. When short-term variation

caused by disease, drugs, environment, smoking, laboratory instruments, or submaximal efforts is excluded, body position, head position, effort dependency of maximal flows, and circadian rhythms cause the primary residual sources of variation.⁶ Host factors (e.g., sex, size, aging, race, and past and present health), environmental factors, geographic factors, pollution, and socioeconomic factors cause variability among subjects.

Statistical Considerations. Distributions of FEV_1 and FVC in population studies are close to gaussian in the middle age range but not at the extremes. Furthermore, distributions of flow rates and ratios (FEV_1/FVC) are not symmetrical.²⁸ Therefore publications describing reference populations should include not only the prediction equations but also a means to define their lower limits. A lower limit can be estimated from a regression model. For spirometry, values below the 5th percentile are taken as below the "lower limit of normal."²⁸ If there are sufficient measurements within each category, percentiles can be estimated directly from the data. If the distribution of individual observations is close to gaussian, as it sometimes is in children, the value of the 5th percentile can be approximated.

However, comparisons of spirometric prediction equations indicate that there is good agreement using the 5th percentile. Furthermore, as stated previously, there is no statistical basis for the common practice of using 80% of the predicted normal values for FEV_1 and FVC as the lower limit of normal in adults. For $FEF_{25\%-75\%}$ and for instantaneous airflow rates, this practice causes significant errors because the lower limits of normal for these values are close to 50% of predicted normal values. Using a fixed FEV_1/FVC ratio as a lower limit of normal in adults also causes significant errors because this ratio is inversely related to age and height.²⁸ However, using a fixed percentage of the predicted value as a lower limit of normal may be acceptable in children when the SD is proportional to the predicted mean value. In general, the lowest 5% of the reference populations may be considered as being below the lower limit of normal for any spirometric value.

The ATS suggests that individual laboratories use published reference equations that most closely describe the populations tested in their laboratories. It is useful to compare the results observed in 20 to 40 local subjects with those provided by the intended reference equations. These local subjects should be lifetime nonsmokers selected by age, ethnic group, and sex to match the population usually studied in the laboratory.⁷⁵⁻⁷⁹

yearly changes of 15% or more are probably clinically significant. In a classic epidemiologic study of the changes of FEV₁ over time, normal men were found to have approximately a 40- to 50-mL decrease in FEV₁ per year; the rate of loss increased in smokers, who were susceptible to the damaging effect of cigarette smoke and could return to a normal rate of loss with smoking cessation.^{79a} More recent studies using data from the Framingham Offspring cohort have expanded this analysis to include women, to enlarge the age range, and to standardize the spirometric measurements. In this study, both men and women nonsmokers were found to have an equivalent gradual loss of FEV₁ with age (approximately 20 mL/year in men, 18 mL/year in women).⁸⁰ There was an increase in loss with smoking (38 mL/year in men, 24 mL/year in women) and a benefit from quitting.

Flow-Volume Curves. The range of normal for measurements derived from flow-volume curves has been even more difficult to define than that for spirometry. Correlations with sex, age, and height are poor and do not appear to decrease variability. Most published studies provide prediction equations for mean values only; a few report standard deviation or some other estimate of population variance, but this is of little use in predicting the lower limit of normal. Several investigators have analyzed this problem and have provided predicted mean values and estimates of the lower limit of normal values.^{6,28}

This wide range of normal values limits the interpretation of spirometric and flow-volume curves.⁸¹ If a subject has values in the very low normal range at a given time, the results may be normal for that person or may be significantly abnormal in a person whose VC or flow rates were much higher than average before the onset of the disease. In such cases a discrepancy between static and dynamic measurements, expressed as a percentage of predicted value, may yield a clue to this situation. For example, it would be unusual for a normal person to have a VC that is 115% of the predicted value and a FEF_{25%-75%} that is 85% of the predicted normal value. These findings suggest the possibility of some form of airway obstruction. As with all laboratory tests, evaluation of the results in the clinical context may be helpful in interpretation.

Although the range of predicted values is large, the same pulmonary function tests tend to have reproducibility in the same subject. If variability is limited by careful standardization of pulmonary function testing, spirometry should be reproducible within 5% of the initial values obtained. In addition, if the patients are highly cooperative, the variability can be as small as 2% to 3%.⁸² Thus, repeated measurements of spirometry over time provide a sensitive way of monitoring disease. This reproducibility also accounts for the utility of performing spirometry initially in workers entering a job that will expose them to risks of obstructive or restrictive ventilatory defects.⁸³

Pathophysiologic Patterns

The diagnosis and quantitation of airway obstruction are among the most common uses of pulmonary function tests. RAW, however, is not measured directly by spirometry. Variables derived from spirometry and flow-volume curves may be used to infer increased RAW from measurements of

expiratory airflow achieved with a maximum effort by the subject. Because this maximum effort is not quantitated, the observer can only presume that the decreased flow is due to increased resistance, rather than a decreased effort to produce the flow. If necessary, the degree of effort can be determined using an intraesophageal balloon to estimate pleural pressure or, noninvasively, by estimating compression volume in a pressure-volume plethysmograph (see earlier discussion).

Obstructive Ventilatory Defect. Despite the dependence on effort, reproducible patterns are obtained in normal subjects and in patients with obstructive ventilatory defects (Fig. 25-15). An inference of increased RAW can be made with reasonable assurance, and correlation with measurements made by body plethysmography is good.

In patients with emphysema, most authors suggest that decreased maximal expiratory flow is thought to be due to the effect of loss of lung elastic recoil on airway dimensions, which results in an increased resistance to flow owing to increased compliance and collapse of airway walls.

In emphysema and other diffuse obstructive disorders, the decrease in expiratory flow is usually associated with decreased VC. The decreased VC results from “gas trapping” associated with increased RV. Actual measurement of RV

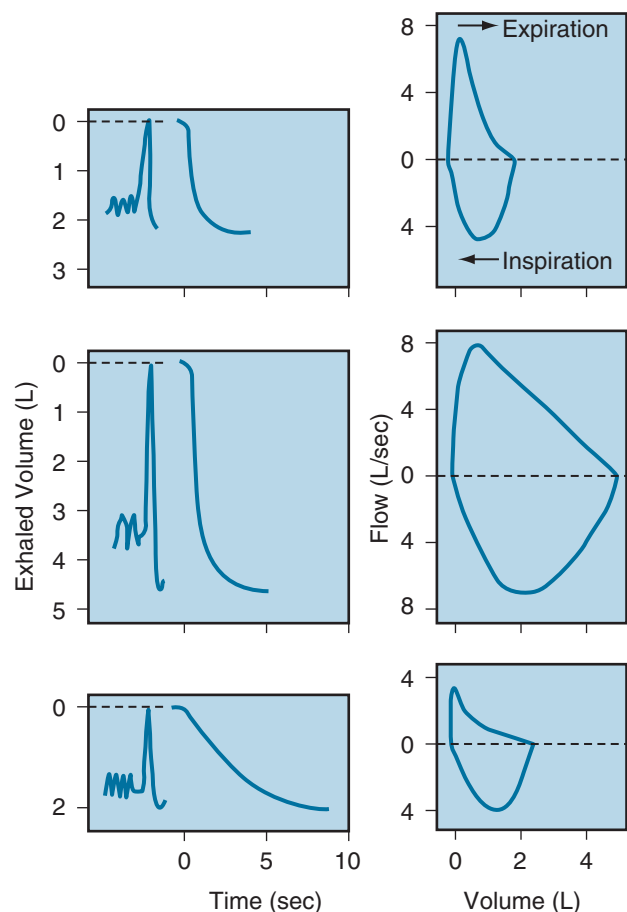


Figure 25-15 The three major patterns of flow. Spirograms and flow-volume curves are shown which were obtained in a patient with a restrictive ventilatory defect (*top*), a normal subject (*middle*), and a patient with an obstructive ventilatory defect (*bottom*).

may be necessary to document this phenomenon and to rule out a mixed restrictive and obstructive ventilatory defect. Expressed as percentages of predicted values, the decrease in VC in patients with obstructive ventilatory defects is relatively less severe than the decrease in airflow.

The pulmonary ventilation is limited ultimately by the highest flows that can be generated by the subject. Even during high-intensity exercise, most healthy subjects do not experience expiratory flow limitation.⁸⁴ However, patients with COPD may experience expiratory flow limitation at low work rates during exercise or even at rest, as first suggested by Potter and colleagues.⁸⁴ Potter's group reported that patients with advanced COPD often breathe on their maximal expiratory flow-volume curves during tidal breathing. They suggested that this phenomenon develops because of expiratory flow limitation (i.e., inability to increase flow beyond a limit at a given lung volume). The phenomenon of expiratory flow limitation has been studied extensively in COPD patients both at rest and during exercise.^{85,86} Flows observed during tidal breathing in COPD patients often exceed the maximal expiratory flow-volume envelope.^{84,85} This pattern has been termed "negative-effort dependence" and is attributed to abnormal compressibility or collapse of the airway walls; in this situation, tidal breathing involves less expiratory force, less collapse of highly collapsible airways, and slightly greater flow than seen with a maximal forced expiratory maneuver.

Restrictive Ventilatory Defects. A restrictive ventilatory defect is suggested by a decreased VC, reflecting limitation in chest excursion (which, according to the ATS expert panel, requires confirmation by a decreased TLC). Typical results consist of a decreased VC, little or no reduction in expiratory airflow, and relative preservation of MVV. Early in the development of an interstitial lung disease, before development of decreased lung volumes, *volume-corrected* flow (i.e., flow divided by the total lung capacity, to account for lung size) and FEV₁/FVC ratios are increased. These increased airflow rates result from the increased force causing outward traction on airway walls. Thus airway diameters become larger than normal relative to lung volume, so airflow rates are increased. Because of the increased flows relative to lung volume, the usual flow-volume curve in restrictive defects is tall and narrow (see Fig. 25-15). With time, as the disease becomes more severe, lung volumes decrease, as reflected by a decreased VC. If the disease can be reversed, volumes return to normal first, then volume-corrected flows, and then the FEV₁/FVC ratio.⁹⁸⁻¹⁰⁰

DISTRIBUTION OF VENTILATION

For discussion of ventilation, blood flow, and gas exchange, see Chapter 4

Tests that measure distribution of ventilation are very sensitive to abnormalities in lung structure and function but are nonspecific. Thus they are useful for detecting the presence of abnormal function early, when other test results are normal, or to confirm the presence of airflow obstruction when other test results are only mildly abnormal. They are particularly important in the evaluation of patients

with suspected upper airway obstruction to determine if there is associated disease of the airways distal to the trachea. They may be very useful in epidemiologic studies, such as evaluation of the effects of smoking or air pollution in large populations.

MEASUREMENTS OF DISTRIBUTION OF VENTILATION

The physiologic determinants of distribution of ventilation are reviewed in Chapter 4. eFigure 25-9 illustrates the concept of uneven distribution of inspired gas.

Resident Gas, Single-Breath Test

The single-breath nitrogen washout test (sometimes called the single-breath oxygen test) is designed to assess the uniformity of gas distribution in the lungs and the behavior of the dependent airways.¹⁰¹ At present, the most clinically useful aspect of the test is the measurement of the slope of phase III (alveolar gas plateau) to determine the uniformity of gas distribution.

A lung clearance index can be measured not only by resident N₂ but also by exogenous tracer gas using a mass spectrometer or, more recently, a novel gas analyzer (Innocor), thus providing a potentially useful clinical tool as an early marker for disease in children and adults.¹¹⁰ With the use of exogenous tracer gases not found in normal air, patients can perform the washout tests while breathing air and not pure oxygen, as is needed for nitrogen washout. By breathing air, the patient avoids the unwanted changes in ventilation related to oxygen breathing. Sulfur hexafluoride, an inert gas, is a tracer used for this purpose.¹¹¹

CLINICAL APPLICATIONS

Tests of distribution of ventilation have been used widely in epidemiologic studies. Studies of cigarette smokers and studies of patients with mild airway obstruction have suggested that the single-breath nitrogen washout test (phase III) often has the most abnormal test results of lung function, and sometimes the only abnormal test results. The sensitivity of these tests of distribution may also prove useful in the field of occupational health for early detection of the effects of occupational hazards, but the practical value of these tests for occupational screening remains to be established.

The usefulness of tests of distribution of ventilation in clinical evaluation is well established. The single-breath nitrogen washout test has abnormal results in both restrictive and obstructive ventilatory defects. Presumably, this reflects its sensitivity to abnormalities in the mechanical properties of the lungs. Even though interstitial pulmonary fibrosis or emphysema may affect the lung diffusely, the process is never distributed homogeneously. Thus some regions of lung fill and empty more slowly than others, resulting in abnormal single-breath nitrogen test results. Why, then, is a test of distribution indicated in clinical evaluations? First, in mild disease, spirometry and clinical evidence may be equivocal, but tests of distribution may provide a more sensitive indicator of the presence of disease and the response to treatment. Second, not only is the test sensitive, but the degree of abnormality of the single-breath

Expiratory Flow Limitation Assessed by Comparison of Tidal and Maximal Flow-Volume Curves

1. Tidal and maximal flow curves are usually aligned on the assumption that TLC does not change during exercise and hence that changes in inspiratory capacity reflect changes in end-expiratory lung volume. Most reports indicate that TLC does not change with exercise,^{86,87} but others have found that TLC does increase.⁸⁸ In addition, this approach assumes that the patients can make a truly maximal inspiratory effort during exercise. In fact, some COPD patients are not able to perform these maneuvers during exercise.
2. Maximal expiratory airflow depends on the volume and time history of the preceding inspiration.^{89,90} However, the previous volume and time history always differ between tidal breathing and maximal inspiration. Therefore assessment of flow limitation by comparison of tidal and maximal flow-volume curves may lead to erroneous assumption of abnormal airway collapsibility, even if the measurements are made plethysmographically.
3. In nearly all reports, the tidal and forced flow-volume loops were obtained from measurements of expired gas volume at the mouth. The assumption is made that both loops develop at the same lung volume when, in fact, the forced loop may be at a smaller volume due to gas compression during the forced maneuver. Such gas compression artifacts can be avoided by measuring volume with a body plethysmograph, as suggested by Ingram and Schilder.⁹¹
4. Exercise may result in bronchodilation and other changes in the mechanical properties of the lungs, which may affect both the tidal and maximal flow-volume curves.⁸⁶
5. Evaluation of expiratory flow limitation has also been studied by comparison of tidal flow-volume curves with partial flow-volume curves, thereby keeping the previous volume history constant. Although theoretically appealing, this approach often neglects the effect of the previous time history (which affects both partial and maximal forced flow-volume curves)^{89,92} and is not practical in most patients with COPD at rest, let alone during exercise.

Thus it appears that study of expiratory flow limitation on the basis of comparison of tidal with maximal flow-volume curves can be problematic. An alternative approach, called the negative expiratory pressure method, has been developed by Koulouris and associates⁹³ (eFig. 25-8). This method does not require flow-volume maneuvers by the subject, nor must it be performed in a body plethysmograph. A negative pressure is applied at the mouth during a tidal expiration, and the ensuing expiratory flow-volume curve is compared with that of the previous control tidal expiration. With this method the volume and time history of the control and test breath are the same. The negative expiratory pressure method has been validated in mechanically ventilated patients by direct comparison with isovolume pressure-flow curves.⁹⁴ It has also been used to study stable COPD patients at rest and during exercise.^{95,96}

Ninane and associates⁹⁷ have offered another approach to the technical issues associated with comparing tidal breathing with maximal flow curves. They described a

method to detect expiratory flow limitation by manual compression of the abdominal wall. In healthy subjects, abdominal compression causes decreased abdominal diameter, increased gastric and pleural pressures, and increased expiratory flow. This method has been used successfully to study expiratory flow limitation in neonates, but in adults with COPD abdominal compression fails to increase expiratory flow despite increased gastric and pleural pressures.⁹⁷

Protocol. The single-breath nitrogen washout test (sometimes called the single-breath oxygen test) is designed to assess the uniformity of gas distribution in the lungs and the behavior of the dependent airways.¹⁰¹ At present the most clinically useful aspect of the test is the measurement of the slope of phase III (alveolar gas plateau) to determine the uniformity of gas distribution. The subject inspires a single breath of pure oxygen from RV to TLC (inspiratory VC maneuver); nitrogen concentration at the mouth during exhalation is measured with a nitrogen analyzer or mass spectrometer. At end-inspiration, the dead space is filled with oxygen that has just been inspired (see eFig. 25-9). At the beginning of the subsequent expiratory VC maneuver, the nitrogen meter continues to record 0% nitrogen, because the first gas to leave the lungs is from conducting airways—the so-called anatomic dead space (phase I) (see eFig. 25-9). Subsequently, the nitrogen concentration increases in a sigmoid curve upward and reflects mixing of gas from dead space and alveoli (phase II). The slightly sloping plateau in phase III reflects the almost constant nitrogen concentration in alveolar gas. If inspired oxygen is distributed evenly to all alveoli so each has the same nitrogen concentration, then phase III of the nitrogen tracing is almost horizontal (alveolar plateau). However, if inspired oxygen is distributed unevenly (as happens to a small extent even in healthy subjects), then the end-inspiratory nitrogen concentrations are not equal throughout the lung. The concentrations of exhaled nitrogen from different alveoli are not recorded as a horizontal line; the first portion of phase III usually contains a lower nitrogen concentration than the last portion.

The analysis of these curves is not entirely objective. When the same observer reads such curves twice under “blind” conditions, agreement between the two measurements is poor. This variability appears to be due to differences between individual lungs; when a subject generates such a curve, usually all curves produced by that subject are difficult to analyze. On the other hand, if a subject generates a curve that is easy to analyze, most curves produced by that subject are reproducible. Obviously, analysis of these curves requires good judgment; some curves, although conforming to the criteria of acceptability, are unreadable and therefore should be ignored. It appears difficult, if not impossible, at present to establish a uniform set of criteria for this analysis.¹⁰²

Normal Values. The slope of phase III (percentage of nitrogen per liter) is determined as the line of best fit (by least-squares linear regression) between 70% of VC and the onset of phase IV. In most cases, the range about the mean of three measurements of the slope of phase III should not be greater than $\pm 0.5\%$ N₂/L.¹⁰³ The variations appear to be independent of the time of day at which the test is

performed, but the slope of phase III does depend on inspiratory flow.¹⁰⁴

The TLC measured by the single-breath nitrogen test correlates well with that measured by helium dilution in a population of men and women free from abnormalities of gas distribution, for both smokers and nonsmokers with and without symptoms.¹⁰³ As expected, the measurement of TLC underestimates lung volume in patients with airway obstruction.^{6,103}

Other Tests

The methods just described use the resident-gas technique. Similar measurements made by bolus techniques and resident-gas techniques have been compared, and they show either close similarities in results or a systematic tendency for measurements of phase IV determined by the resident-gas technique to be slightly lower than those determined by the bolus technique.¹⁰⁵

Other methods used to assess uniformity of distribution of ventilation include measurement of residual nitrogen following multiple-breath, open-circuit nitrogen washout¹⁰⁶ and determination of helium mixing time during closed-circuit equilibration. In the multiple-breath nitrogen washout, for example, continuous breath-by-breath measurement of nitrogen concentration at the mouth during tidal breathing of pure oxygen is performed until end-tidal nitrogen concentration falls to less than 1%. The fall in end-tidal nitrogen concentration on a breath-by-breath basis is

related to the cumulative volume of ventilation or breath number. By extending the nitrogen washout time to 30 minutes or more in subjects with severe chronic airway obstruction, estimates of lung volume may be obtained that compare favorably with those calculated by plethysmographic or radiographic methods.¹⁰⁷

Exponential analysis of the end-tidal nitrogen concentration with time, cumulative ventilation, or breath number reveals that in normal subjects nitrogen concentration decreases in a single exponential curve. In the presence of uneven distribution of ventilation, the curve can be described by two or more exponentials. This analysis can be extended to estimate the size of poorly ventilated regions of the lung, but these multiple-breath tests are cumbersome and time-consuming, may have no anatomic correlates, and cannot be repeated rapidly (i.e., until all the added oxygen is washed out).

With the advent of rapidly acting infrared analyzers in commercial pulmonary function equipment, in which various filters are used in conjunction with an infrared analyzer to analyze methane, carbon monoxide, and acetylene to measure diffusing capacity and pulmonary blood flow, the opportunity has developed to assess distribution of ventilation using added inert gases, such as methane. The principle is the same as that for resident gases, but the modeling and mathematics are slightly altered. Reference equations have been published for values expected in healthy normal subjects.^{108,109}

nitrogen washout test results is generally proportional to the amount of underlying lung disease. Third, the degree of abnormality of the test results may give an indication of the difficulties to be expected in gas exchange. When the closing volume (phase IV) is elevated above FRC, it is likely to be associated with atelectasis and hypoxia, particularly when narcotics or hypnotic drugs depress the drive to ventilation. Finally, in patients with suspected upper airway obstruction, a test of distribution of ventilation (e.g., single-breath nitrogen washout) may be the only way to assess whether there is associated disease of the airways distal to the carina.

DIFFUSION

Physiologists have devised a variety of methods to study the diffusion of gases across the alveolar-capillary membranes; many of these methods are useful clinically, and their physiologic foundations are discussed in Chapter 4. The advantages of physiologic tests for measuring diffusing capacity are that they permit diagnosis of an impaired surface area for the transfer of gases from the alveoli to the pulmonary capillaries, sometimes even during early stages of disease. Many pulmonary diseases are manifested by a diffusion defect when there is no abnormality apparent in other routine pulmonary function tests. These diseases include all interstitial lung diseases, asbestosis, scleroderma, lupus erythematosus, emphysema, pulmonary thromboembolism, diffuse metastatic cancer of the lungs,¹¹² *Pneumocystis jirovecii* pneumonia, and rejection of a transplanted lung. There is now considerable evidence correlating the diffusing capacity and its subdivisions (*membrane diffusing capacity* [DM] and *pulmonary capillary blood volume* [VC]) with the morphometric study of normal lungs.¹¹³ Similar correlative studies of the lungs of patients with emphysema⁴⁸ document the structural basis for the abnormal alveolar-capillary interface as a result of decreased numbers of patent pulmonary capillary segments.¹¹⁴ Finally, the tests are relatively simple (as far as the patient is concerned) and easy to repeat, making it practical to study the diffusing capacity frequently and to evaluate the effects of therapy or the natural history of the disease.

MEASUREMENTS OF PULMONARY DIFFUSING CAPACITY (TRANSFER FACTOR)

General Principles

The measurement of pulmonary *diffusing capacity* (also known as *transfer factor*) requires the use of a gas that is more soluble in blood than in lung tissues. Oxygen and carbon monoxide are the only two such gases known, and their chemical reaction with hemoglobin is responsible for this unusual pattern of “solubility.” Both molecules measure the same process, and estimates of DL_{O_2} can be made by multiplying the DL_{CO} by 1.23. However, the more difficult and time-consuming method of measurement by oxygen has been largely displaced by the carbon monoxide method.

For the standard DL_{CO} method, a low concentration of carbon monoxide is delivered to the lungs by adding about 0.3% carbon monoxide to inspired air. The mixed venous carbon monoxide concentration is assumed to be zero for

all practical purposes (unless the test is repeated frequently over a short time). Molecules of carbon monoxide diffuse across the membrane, dissolve in the plasma, and then combine with hemoglobin. Carbon monoxide has a high affinity for hemoglobin, 210 times that of oxygen; thus carbon monoxide in the vicinity of a hemoglobin molecule binds avidly to it, and the partial pressure of dissolved carbon monoxide remains very low. Except in a patient with severe anemia, the available binding sites for carbon monoxide are so numerous that they cannot be saturated by the number of carbon monoxide molecules that diffuse from the air spaces to the capillary blood at the low concentrations of carbon monoxide used in the test. Therefore carbon monoxide transfer is not limited by pulmonary blood flow; instead, it is limited primarily by the alveolar-capillary diffusion rate and, to a lesser extent, by the red blood cell membrane diffusion rate and the chemical reaction rate between hemoglobin and carbon monoxide. The carbon monoxide transfer therefore can be considered a measure of the capillary surface area available for gas exchange.

In contrast, gases such as Freon, nitrous oxide, and acetylene are equally soluble in lung tissues and blood because they do not combine chemically with blood components. These gases diffuse across the alveolar-capillary membranes and quickly saturate the plasma; further diffusion is prevented until fresh blood enters the pulmonary capillaries. Thus these gases can be used to estimate pulmonary capillary blood flow to ventilated lung units.

There are some important differences in the transfer of carbon monoxide and oxygen. Both plasma and hemoglobin contain oxygen (but not carbon monoxide) when mixed venous blood enters the pulmonary capillaries. The rate of oxygen diffusion into blood depends on the alveolar-capillary PO_2 difference. As oxygen crosses the alveolar-capillary membranes, capillary PO_2 increases, narrows the alveolar-capillary PO_2 difference, and slows diffusion. Thus, before calculating a diffusing capacity for oxygen, blood PO_2 must be known at every point along the capillary and can be obtained by a combination of certain measurements and mathematical computations.¹¹⁵

Carbon Monoxide Methods for Clinical Measurement of Pulmonary Diffusing Capacity. The DL_{CO} is calculated as follows:

$$DL_{CO} = \frac{\text{CO transferred from alveolar gas to blood (mL/min)}}{\text{Mean alveolar CO pressure} - \text{Mean capillary CO pressure (mm Hg)}} \quad (18)$$

To determine the amount of carbon monoxide transferred from alveolar gas to blood per minute, it is necessary to measure the mean alveolar carbon monoxide pressure and the mean pulmonary capillary carbon monoxide pressure. There are several tests available.

The *standard single-breath* DL_{CO} test is probably the most widely used and the best standardized of the various methods described. It has been used in the largest number of normal subjects and has been corrected for the effects of age, body size, sex, ethnic background, cigarette smoking, and physiologic factors.

The *intra-breath* method requires a special, very rapid infrared analyzer, but this is also commercially available. Because this method does not require a breath-hold and

expiratory flow can be controlled by a critical orifice, the intrabreath method is probably the easiest of the four methods for sick patients to perform. With proper filters the same analyzer can be used to measure methane, acetylene, and carbon monoxide simultaneously. Diffusing capacity can be measured during exercise to define distensibility of the capillary bed using the intrabreath or three-gas iteration method, but this also requires extensive validation and establishment of predicted normal values.¹¹⁶⁻¹¹⁸

The *three-gas iteration* method may be more reproducible and is unaffected by a wide variety of factors that alter the single-breath or intrabreath methods, especially abnormalities in distribution of ventilation. More normal data are needed, as is validation in other laboratories, but the method is commercially available.

The *steady-state*, or rebreathing method, can also be measured during exercise, but is not widely used because its results are markedly affected by uneven distribution of ventilation or ventilation-perfusion abnormalities. The rebreathing method is more variable than the single-breath method and requires considerable patient cooperation to attain the rapid respiratory rate required.

SINGLE-BREATH METHOD. In the single-breath method, the patient inhales a gas mixture containing 0.3% carbon monoxide and a low concentration of inert gas (0.3% neon, 0.3% methane, or 10% helium), then holds his or her breath for approximately 10 seconds. During the breath-hold, carbon monoxide leaves the air spaces and enters the blood. The larger the diffusing capacity, the greater the amount of carbon monoxide that enters the blood in 10 seconds.

The equation used in the single-breath method is as follows:

$$DL_{CO} = \frac{V_A \times 60}{(P_{bar} - 47) \times t} \ln \frac{F_{ACO_0}}{F_{ACO_t}} \quad (19)$$

where F_{ACO_t} is *fractional alveolar carbon monoxide concentration* at time (t), t is breath-hold time in seconds, P_{bar} is *barometric pressure* (in mm Hg), V_A is *alveolar volume* (in mL) obtained from the ratio of inspired and expired inert gas concentrations and inspired volume, F_{ACO_0} is the inspired carbon monoxide concentration corrected for dilution by the RV as estimated by the ratio of inspired and expired inert gas concentrations, and 60 is the conversion factor for seconds to minutes.

In the single-breath test, alveolar PCO is not maintained at a constant concentration, because carbon monoxide is absorbed during the period of breath-holding. Furthermore, the mean alveolar PCO is not the average of the PCO at the beginning and end of the breath-holding period. However, the mean alveolar PCO can be estimated and diffusing capacity measured. The single-breath test requires little time or cooperation from the patient except to inhale and to hold the breath for 10 seconds. Analyses are performed with an infrared analyzer or gas chromatograph, and no blood samples are needed. The test can be repeated a number of times rapidly, if desired. However, a measurement of the patient's RV is required, because a value for total alveolar volume during breath-holding must be calculated to measure carbon monoxide uptake. Furthermore, an inert gas such as helium, methane, or neon must be inhaled with carbon monoxide to correct for dilution of inspired

carbon monoxide. This method has the disadvantages that carbon monoxide is a nonphysiologic gas, breath-holding is not a normal pattern of breathing, and breath-holding for 10 seconds may not be possible for patients with severe dyspnea or during exercise.

Factors such as inhalation time, breath-holding time, breath-holding lung volume, exhalation time, and the size and portion of alveolar gas sampled have all been shown to affect the single-breath DL_{CO} . Ogilvie and colleagues¹¹⁹ recognized that these discrepancies could exist either because diffusing capacity is not distributed homogeneously within the lung or because the single-breath equation ignores the fact that carbon monoxide uptake takes place during inhalation and exhalation as well as during breath-holding. They tried to circumvent these problems by standardizing the test.

Jones and Mead¹²⁰ showed that, because the diffusion equation was valid only for breath-holding, there are errors in calculation of single-breath DL_{CO} owing to the nature of carbon monoxide uptake during inhalation and exhalation. Because delay in collection of the alveolar sample has been shown to cause an apparent increase in DL_{CO} , the ATS epidemiology standardization project²³ developed a variation of the Jones and Mead method that took this problem into account and placed strong emphasis on an automated system, which standardized the procedure and is available in most modern commercial systems.

INTRABREATH METHOD. In the intrabreath (within-breath or exhaled) DL_{CO} method, DL_{CO} is measured at increments of the exhaled volume using a method devised by Newth and associates¹²⁷ and modified by Hallenborg and colleagues.¹²⁸

Although more complicated than the standard single-breath method, this technique makes no assumptions about the initiation of carbon monoxide uptake or the volume at which carbon monoxide uptake manifested, measures carbon monoxide uptake directly during the entire maneuver, and can be used during exercise as well as at rest. The method does require a rapidly responding carbon monoxide meter or special modification of a mass spectrometer (to measure $C^{18}O$) to make the number of measurements of carbon monoxide concentration required during the single exhalation. The intrabreath method has been useful in detecting pulmonary hemorrhage¹²⁸ and pulmonary vascular obstruction.¹³⁰ The method is now available commercially using a rapidly responding infrared analyzer. With appropriate filters, the device can measure not only carbon monoxide but also methane (to measure tracer gas dilution) and acetylene (to measure pulmonary capillary blood flow to ventilated lung units), and the response to all three gases is linear.^{109,131-133}

Indications

The diffusing capacity is affected by those physiologic and pathophysiologic conditions that change the surface area of pulmonary capillaries available for gas exchange. For most purposes, one can think of DL_{CO} as a measure of the blood-filled capillaries in the lung.

It is interesting to consider the conditions that can increase the DL_{CO} . Indeed, many processes can increase the capillary blood surface area by increasing the blood volume in the lung, including recumbent posture, pregnancy, and obesity. Many pathologic processes that do not involve lung disease

Diffusing Capacity

STEADY-STATE METHOD. In the steady-state method, the patient breathes a mixture of 0.1% carbon monoxide in air for several minutes through a one-way valve system. During the last 2 minutes, exhaled gas is collected in a plastic bag and analyzed for oxygen, carbon dioxide, and carbon monoxide concentrations (requiring rapidly responding gas analyzers). During collection, an arterial blood sample is drawn and analyzed for PCO_2 .¹²¹ The amount of carbon monoxide transferred from the air spaces to capillary blood per minute ($\dot{V}CO$) can be calculated from the inspired and expired gas concentrations and the volume of gas exhaled ($\dot{V}E$) at standard conditions (i.e., STPD, where the “ideal gas” is corrected to standard pressure dry [760 – 47 mm Hg] and 0°C or 273°K, where 1 mole of ideal gas occupies 22.4 L.). The mean alveolar fractional concentration of carbon monoxide (FACO) is estimated from the Bohr equation for dead space volume divided by tidal volume (V_D/V_T). Assuming that V_D/V_T for carbon dioxide and carbon monoxide are the same, FACO can be calculated with the following equation, using the fractional concentrations of mixed expired carbon monoxide (FECO), mixed expired carbon dioxide (FECO₂), alveolar carbon dioxide (FACO₂), and inspired carbon monoxide (FICO):

$$FACO = FICO - \frac{FACO_2(FICO - FECO)}{FECO_2} \quad (20)$$

$$PACO = FACO(Pbar - 47) \quad (21)$$

This value (alveolar carbon monoxide [PACO]) can now be used to calculate pulmonary diffusing capacity:

$$DL_{CO} = \frac{\dot{V}CO}{PACO} \quad (22)$$

Steady-state DL_{CO} can be measured during tidal breathing, anesthesia, sleep, and exercise. Nevertheless, the method is not used widely because its results are more subject to error than those of the single-breath technique, especially in patients with uneven distribution of ventilation or with ventilation-perfusion abnormalities. In these conditions, a decreased DL_{CO} (steady state) may reflect impairment of the ventilation-perfusion ratio $\dot{V}A/\dot{Q}C$, where $\dot{V}A$ is alveolar ventilation and $\dot{Q}C$ is pulmonary capillary blood flow, or an alteration of pulmonary gas transfer. A major problem is the estimation of alveolar carbon monoxide concentration. In addition, the method requires obtaining an arterial blood sample and is extremely sensitive to changes in breathing pattern. The “end-tidal” modification¹¹² of the steady-state method does not require arterial blood samples but suffers from even more sources of error. Both approaches to the estimation of diffusing capacity really reflect ventilation-perfusion abnormalities in the lungs more than characteristics of the alveolar-capillary surface and functioning pulmonary capillaries. Marshall¹²² has reported another modification of this method, in which mixed venous PCO_2 was computed by an equilibration method that avoids arterial puncture but may be too imprecise for use in the Filley equations (Equations 21 and 22) at rest.

REBREATHING METHOD. In the rebreathing method,¹²³ the patient rebreathes the test gas (air plus a low concentration of carbon monoxide) from a reservoir, the volume of which equals the patient's FEV₁. The patient exhales to RV before a valve is turned, then rebreathes from the reservoir, which should be emptied with each inspiration. Rebreathing

continues for 30 to 45 seconds at a controlled rate of 30 breaths/min (to ensure mixing between lung and reservoir). The volume of RV plus reservoir, multiplied by the change in carbon monoxide concentration, equals the carbon monoxide volume transferred. Mean capillary PCO is neglected. Mean alveolar PCO is calculated from the same equation used in the single-breath method. The rebreathing method for measuring DL_{CO} is more variable and requires considerable patient cooperation, but it is less influenced by abnormalities in distribution of ventilation and is easier to use during exercise than the steady-state or single-breath technique. The rapid respiratory rate may be difficult for some patients to maintain and is not physiologic.

THREE-GAS ITERATION METHOD. Graham and associates¹²⁴ have described a method of calculating DL_{CO} that uses separate equations for the inhalation, breath-hold, and exhalation phases of the single-breath maneuver rather than trying to force them to fit the breath-hold equation. The method is now available commercially using a rapidly responding infrared analyzer. This method has been reported in a theoretical paper,¹²⁵ analyzed in a lung model, and compared with the standard Ogilvie method,¹¹⁹ the Jones-Mead modification,¹²⁰ and the ATS epidemiology standardization modification of the Ogilvie method.²³ It has also been reported during exercise.¹¹⁶⁻¹¹⁸

Although DL_{CO} values calculated using the three conventional methods showed large changes with variations in inspiratory flow rates, inspiratory volumes, and collection times, the three-equation method yielded calculations of DL_{CO} that were minimally affected by these changes.¹²⁴ These results agree with previous results obtained in the lung model, support the hypothesis that diffusing capacity is independent of lung volume, and indicate that the three-gas iteration method significantly improves the accuracy and precision of single-breath measurements.¹²⁶

PROTOCOL. As originally described, the subject performs two VC maneuvers, then exhales to RV and rapidly inhales a mixture containing 0.3% carbon monoxide, 15% helium, 21% oxygen, and the remainder nitrogen from a bag-in-box. After a 3-second breath-hold, the subject exhales while watching a flow signal to maintain a constant flow of 0.5 L/sec. Carbon monoxide concentrations are measured continuously with a rapidly responding infrared meter, and helium concentrations are measured with a mass spectrometer. Airflow is measured with a pneumotachygraph and integrated electrically to obtain volume. Data are converted from analog to digital form at 30 points per second and recorded by a digital computer to adjust carbon monoxide and helium recordings for time lags and to remove cardiac oscillations using a sliding, 30-point curve-averaging technique. The exhaled VC is divided into 2% decrements, and the corresponding exhaled carbon monoxide and helium values are used for calculations. The initial part of the VC, until the onset of phase III of the helium curve, is discarded as dead space. The lower portion of the VC, after the onset of phase IV of the helium curve, is also discarded because of uncertainties regarding contributions by dependent regions to expired gas concentrations. Approximately 40 data points are obtained over the lower 80% of the exhaled VC, and the rate of carbon monoxide uptake is calculated over 10% intervals of the exhaled VC (e.g., 20% to

30%, 22% to 32%). Alveolar volume is calculated at the midpoint of each 10% interval by subtracting the exhaled volume from TLC (measured by the single-breath helium

dilution method). Intradbreath DL_{CO} is calculated in each interval by the Krogh equation¹²⁹ and plotted against exhaled volume.

can also increase blood volume in the lung, such as congestive heart failure. Lung diseases that can increase blood volume are thought to include asthma, perhaps by increased intrathoracic negative pressures, and diffuse alveolar hemorrhage.

Most pathologic processes that involve the pulmonary capillaries *decrease* the DL_{CO} . Therefore the most common clinical indications for measuring DL_{CO} include evaluation of patients with diffuse interstitial lesions such as sarcoidosis and asbestosis,¹³⁴ evaluation of patients suspected of having emphysema, for which several structure-function studies are now available,⁴⁸ and assessment of patients with pulmonary vascular obstruction.¹³⁵ It is important to recognize that the DL_{CO} depends on hemoglobin concentration; decreased DL_{CO} caused by severe anemia must not be misinterpreted as secondary to nonexistent lung disease. Thus DL_{CO} is routinely corrected for hemoglobin concentration, if known.

Standardization of the Single-Breath Methods

The ATS has recommended standardization of the test using criteria including rapid inspiration, inspired volume at least 90% of largest VC, breath-hold time between 9 and 11 seconds, and adequate washout and sample volumes. The mean of the acceptable tests is reported; if more than two tests are performed, the mean of all acceptable tests is reported. Calculations are standardized for breath-hold time and adjusted for dead space, gas collection conditions, and carbon dioxide concentration. Reproducibility of the two acceptable tests should be within 10% or 3 mL/min per mm Hg (at *standard temperature, pressure, and dry* [conditions] [STPD]), whichever is larger. When the ratio of DL_{CO} to alveolar volume (DL_{CO}/VA) is reported, DL_{CO} is at STPD and VA is at BTPS.

Interpretation

Subdivisions of the Total Diffusing Capacity. It is possible to separate the pulmonary diffusing capacity into its two components: the *membrane diffusing capacity* (DM) and the component related to the pulmonary capillaries (Vc). Nonetheless, it has been shown that almost all decreases in diffusing capacity are due to decreases in the capillary component (Vc).

$$1/DL_{CO} = 1/\theta VC + 1/DM \quad (31)$$

The method of separation depends on measurement of DL_{CO} at different alveolar oxygen pressures. When alveolar oxygen is increased by breathing enriched oxygen mixtures, oxygen molecules compete with carbon monoxide molecules for reactive sites on hemoglobin, thereby decreasing carbon monoxide uptake by the red blood cells. However, even at the higher oxygen concentration, transfer of carbon monoxide across the alveolar-capillary membranes is presumed to be unaffected. Thus measurements of DL_{CO} at 21% oxygen and at several higher concentrations of oxygen permit separation of the two components of the DL_{CO} (eFig. 25-11).¹⁵⁰

Diffusing Capacity for Nitric Oxide

The *diffusing capacity of the lung for nitric oxide* (DL_{NO}) is a relatively new pulmonary function test and similar in many ways to the more established DL_{CO} .¹⁵¹ It differs from the

latter in being independent of P_{O_2} and the hematocrit. It has been suggested that DL_{NO} can be used to describe pulmonary DM directly.^{151a}

CLINICAL APPLICATIONS

The single-breath DL_{CO} can be used to differentiate airflow obstruction associated with intrinsic airway disorders from obstruction related to emphysema. A normal single-breath diffusing capacity in the setting of an obstructive pattern argues against the presence of emphysema.⁴⁸ In fact, a normal or increased single-breath DL_{CO} associated with airflow obstruction is often associated with asthma.¹⁶⁰ The single-breath DL_{CO} may be abnormal in patients with emphysema when there is no evidence of airflow obstruction, and it may become progressively more abnormal much more rapidly than tests of airway function, even when they do become abnormal.¹⁶¹ Several studies have demonstrated a correlation not only with the presence of emphysema but also with the amount of emphysema.^{134,162-165}

DL_{CO} has also been used to study the earliest stages of emphysema. For example, some studies suggest that alveolar septal destruction may be seen in cigarette smokers before the development of either increased air space size or anatomic evidence of emphysema.¹⁶⁶ In our laboratory, single-breath DL_{CO} was found to correlate with emphysema grade by panel grading¹⁶⁷ from grade 1 to 100 ($r = -0.73$) in 50 patients whose lungs were studied at surgical resection, which was performed within 1 week of their pulmonary function tests (eFig. 25-12). However, for the milder, early emphysema at grade 30 or less, the intrabreath DL_{CO} appeared to be more sensitive and specific than the single-breath DL_{CO} .¹²⁷

Pulmonary Vascular Obstruction

The changes in DL_{CO} in the setting of pulmonary vascular obstruction can be complex, making it difficult to make a straightforward diagnosis. If pulmonary *capillaries* are occluded, single-breath DL_{CO} is decreased.¹¹⁴ In the presence of *precapillary* vascular obstruction, with the obstruction upstream of the capillaries, the single-breath DL_{CO} may be decreased,¹⁶⁸ normal,¹⁶⁹ or even increased, depending on the effect on pulmonary capillary blood volume. The capillary blood volume in turn depends on the relationship between pulmonary arterial pressure, pulmonary venous pressure (or left atrial pressure), and bronchial collateral blood flow. For example, bronchial arterial pressure may distend capillaries via collateral channels so that, even if pulmonary arteries are obstructed, a normal DL_{CO} may be maintained. In our laboratory, every patient with pulmonary vascular obstruction who had decreased single-breath DL_{CO} had a decreased pulmonary capillary blood volume.

Finally, capillary distention may vary in different parts of the lung (Fig. 25-16). According to the model of the zones of lung perfusion presented by West and colleagues,¹⁷⁰ at the lower zone at the lung base, capillaries are distended by pulmonary arterial and pulmonary venous pressures. Even if the pulmonary arteries are obstructed, the capillaries are distended by pulmonary venous pressure and the DL_{CO} is maintained. DL_{CO} is decreased in this zone if the capillaries are occluded or if pulmonary venous pressure is decreased.

Interpretation of Diffusing Capacity

HEMOGLOBIN. Adjustment for hemoglobin is not mandatory but is desirable. Unadjusted values must always be reported even if the adjusted values are also reported. The adjustment should be made on the observed, not the predicted, value. Hemoglobin is reported in grams per deciliter, and the method of Cotes and associates¹³⁶ should be used to make the adjustment:

$$\text{Hemoglobin-adjusted } DL_{CO} = \text{measured } DL_{CO} \times \frac{(14.6 \times DM/Vc) + \text{hemoglobin}}{\text{hemoglobin} \times (1 + DM/Vc)} \quad (23)$$

where DM is the membrane diffusing capacity and Vc is the pulmonary capillary blood volume.

CARBOXYHEMOGLOBIN. Heavy smokers may have as much as 10% to 12% carboxyhemoglobin in their blood, and therefore the back-pressure of carbon monoxide in mixed venous blood entering the pulmonary capillaries cannot be assumed to be zero in such individuals. The steady-state method is more sensitive to errors caused by this problem than the single-breath technique. Carbon monoxide back-pressure may be estimated, and DL_{CO} calculations may be corrected for back-pressure of carbon monoxide using the Haldane equation.^{136,137} Alternatively, carboxyhemoglobin may be measured directly.¹³⁸ In either case, the measured DL_{CO} is adjusted, and both the unadjusted and the adjusted values are reported. DL_{CO} measurements should not be performed on patients who have been breathing oxygen-enriched mixtures immediately before the test; at least 20 minutes of breathing room air should be allowed before measurement of DL_{CO} .

Graham and associates demonstrated that carbon monoxide back-pressure has a more complex effect than suggested in the ATS standardization statement. To adjust properly for the effect of carbon monoxide on the diffusing capacity, not only must the direct effect of carbon monoxide back-pressure build-up be corrected, but also the indirect anemia effect of increasing carboxyhemoglobin.¹³⁹ The original ATS statement on this issue should be updated to account for both necessary adjustments.

ALTITUDE. As altitude increases and fractional concentration of inspired oxygen (FI_{O_2}) remains constant, pressure of inspired oxygen (PI_{O_2}) decreases and DL_{CO} increases approximately 0.35% for every 1 mm Hg decrease in alveolar PO_2 :

$$\text{Altitude-adjusted } DL_{CO} = \text{measured } DL_{CO} \times [1.0 + 0.0035(PA_{O_2} - 120)] \quad (24)$$

If alveolar PO_2 is not available, adjustments may be made for interpretative purposes, assuming a mean PI_{O_2} of 150 mm Hg at sea level:

$$\text{Altitude-adjusted } DL_{CO} = \text{measured } DL_{CO} \times [1.0 + 0.0031(PI_{O_2} - 150)] \quad (25)$$

assuming $PI_{O_2} = 0.21(P_{bar} - 47)$.

Normal Values for Pulmonary Diffusing Capacity

BODY SIZE. Body size is one of the factors that probably affect normal values⁶; diffusing capacity has been found to vary with body surface area (BSA, in square meters) according to the following equation, derived by Ogilvie and colleagues¹¹⁹:

$$DL_{CO} = 18.85 BSA - 6.8 \quad (26)$$

A better prediction¹⁴⁰ is based on height (H, in centimeters) and age (A, in years):

$$\text{Males: } DL_{CO} = 0.416(H) - 0.219(A) - 26.34 \quad (27)$$

$$\text{Females: } DL_{CO} = 0.256(H) - 0.144(A) - 8.36 \quad (28)$$

Values for DL_{CO} measured by analyzing the gases with a chromatograph are approximately 6% higher than values obtained with infrared meters.¹⁴¹

AGE. Maximal DL_{O_2} (i.e., DL_{O_2} during maximal exercise) has been found to decrease with increasing age according to the following equation:

$$\text{Maximal } DL_{O_2} = 0.67(H) - 0.55(A) - 40.9 \quad (29)$$

Age also affects DL_{CO} at rest (see previous discussion).

LUNG VOLUME. Diffusing capacity determined by the single-breath technique measured between FRC and TLC is relatively independent of lung volume in the same individual, although the diffusing capacity varies with lung volume among individuals, reflecting differences in alveolar-capillary surface with lung volume.⁴⁸

$$DL_{CO} = 13.67 + 4.36 \text{ BTPS}(TLC) - 0.2(A) \quad (30)$$

EXERCISE. Exercise raises DL_{CO} and DL_{O_2} by enlarging the surface area of functioning alveoli in contact with pulmonary capillaries (eFig. 25-10). This is due primarily to recruitment of capillaries. Exercise causes an approximate doubling of pulmonary diffusing capacity and pulmonary capillary blood volume.^{142,143} Huang and coworkers¹⁰⁹ studied 105 healthy subjects with the intrabreath method and reported reference equations for diffusing capacity at rest and during exercise based on age, sex, and height. Hsia and associates¹⁴³ found that DL_{CO} increased normally as cardiac output increased during exercise in patients who had undergone pneumonectomy compared with normal subjects. Although an upper limit to DL_{CO} with respect to oxygen uptake during exercise was observed by Stokes and colleagues,¹⁴⁴ using the intrabreath carbon monoxide method, our group and Hsia et al found no upper limit to DL_{CO} in normal subjects or in pneumonectomy patients with respect to cardiac output during exercise.^{116,145} Maximal values attained during exercise in patients who had undergone pneumonectomy were less than those attained by normal controls, as might be expected because the patients had been chronic smokers and probably had emphysema in the remaining lung.

As reviewed by Ceretelli and DiPrampo,¹⁴⁶ whether DL_{CO} reaches a true plateau during exercise appears to depend on the method used and the level of exercise attained by the subjects. Kinker and associates¹⁴⁷ used a modified steady-state method to determine breath-by-breath DL_{CO} during exercise. They found that the rise of DL_{CO} with increasing work was attenuated at high levels of exercise (maximal oxygen uptake, or $\dot{V}O_{2\max}$, approximately 4 L/min) in most subjects, suggesting that alveolar-capillary surface area tends to approach a maximum.¹⁴⁷ These findings are consistent with studies of capillary perfusion patterns in single alveolar walls visualized through a transparent thoracic window implanted in anesthetized dogs.¹⁴⁸ Results of this study agreed with a computer model of capillary flow developed by West and associates.¹⁴⁹

BODY POSITION. DL_{CO} is 15% to 20% greater in the supine than in the sitting position and 10% to 15% greater in the

sitting than in the standing position, because of the effects of changes in posture on pulmonary capillary blood volume.

ALVEOLAR OXYGEN PRESSURE. Alveolar PO_2 affects DL_{CO} because of the former's effect on the carbon monoxide reaction with hemoglobin. For example, diffusing capacity values measured at alveolar PO_2 values of 40 and 600 mm Hg are approximately 45 and 18 mL/min per mm Hg, respectively (see Fig. 25-11). Changes in DL_{CO} caused by variations in alveolar PO_2 in the physiologic range are much smaller. In patients with severe hypoxia (arterial $PO_2 < 40$ mm Hg), increased pulmonary blood flow and dilation of the pulmonary capillaries may increase the DL_{CO} . Hypoxia may also increase DL_{CO} as a result of its effect on the reaction rate between carbon monoxide and hemoglobin.

Diffusion properties of nitric oxide are similar to those of carbon monoxide; however, its rate of reaction with red blood cells is much greater.¹⁵² DL_{NO} primarily reflects DM, whereas DL_{CO} depends on both DM and Vc.^{151,152} In combination with DL_{CO} , Vc and DM can be determined in a single maneuver, based on the equation for the serial connection of resistances.¹⁵³ Using the combined DL_{NO} – DL_{CO} method, patients with COPD,¹⁵⁴ pulmonary arterial hypertension,¹⁵⁵ and parenchymal lung diseases^{156,157} have been studied, as well as the effects of exercise.^{152,153,158} In addition, reference values have been published.¹⁵⁹ The clinical utility of the DL_{NO} – DL_{CO} method remains to be determined by studies of healthy subjects under various experimental conditions and by studies of diverse patients by various laboratories.

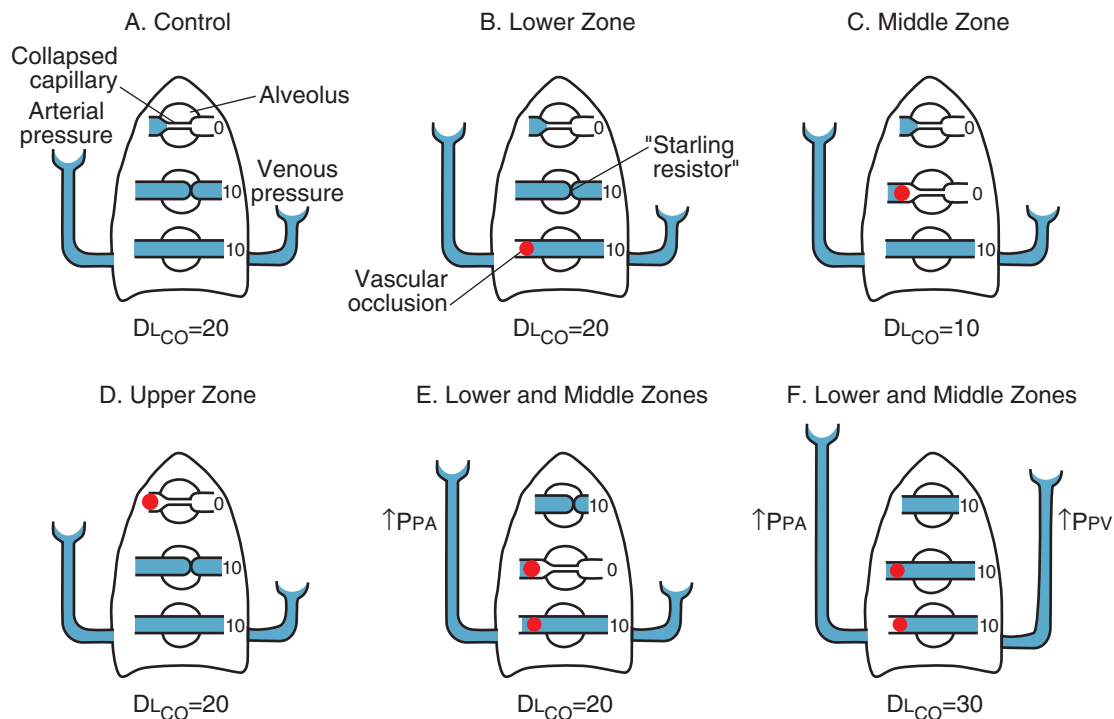


Figure 25-16 Theoretical model showing the effect of pulmonary arterial pressure (PPA) and pulmonary venous pressure (PPV) on pulmonary capillaries at different levels of the lungs. The magnitude of PPA or PPV is indicated by the height of the fluid columns. For simplicity, the pressure in alveoli (Palv) is assumed to be equal to atmospheric pressure. Single-breath carbon monoxide diffusing capacity (DL_{CO}) is given in arbitrary units indicating the relative contribution of various zones of the lung. **A**, In the control state, at the bottom of the lung, both PPA and PPV are greater than Palv, and both keep the capillaries open. In the middle zone, PPA is greater than Palv and PPV, so PPA holds capillaries open. (The exact anatomy of capillaries in the zone in which Palv is greater than PPV is unknown; in the diagram, the compressed segment at the end of the capillary is meant to suggest a “Starling resistor” effect.) In the upper zone, Palv is greater than PPA and PPV, and capillaries are “collapsed.” **B**, When arterial inflow is occluded to the lower zone (indicated by red solid sphere), PPV is greater than Palv, so the capillaries in this zone remain distended and DL_{CO} is unchanged. **C**, When arterial inflow to the middle zone is occluded, Palv is greater than PPV and capillaries in this area are collapsed, so there is a decrease in DL_{CO} . **D**, When arterial inflow to the upper zone is occluded, the capillaries are already collapsed, so there is no change in DL_{CO} . **E**, When arterial inflows to the lower and middle zones are occluded simultaneously, capillaries in the middle zone may collapse. However, if PPA increases, capillaries in the upper zone may become distended, and the net result may be no change in DL_{CO} . Under these circumstances, if PPV also increases (**F**), DL_{CO} may actually increase. (Modified from Nadel JA, Gold WM, Burgess JH: Early diagnosis of chronic pulmonary vascular obstruction: value of pulmonary function tests. *Am J Med* 44:16–25, 1968.)

In the middle zone of the lung, capillaries are distended by pulmonary arterial pressure only; they are not affected by pulmonary venous pressure. DL_{CO} would be decreased by pulmonary vascular obstruction alone; however, DL_{CO} would be normal if the obstruction led to an increase in pulmonary arterial pressure that then distended apical capillaries that were not perfused previously. In addition, the DL_{CO} would increase if the pulmonary venous pressure increased, as long as the pulmonary capillaries remained patent despite pulmonary artery occlusion in this zone.

In the upper zone at the lung apex, pulmonary capillaries may be nondistended because Palv exceeds both pulmonary arterial and venous pressures (assuming the lung is ever in this condition). In this situation, obstruction of pulmonary arteries would not affect DL_{CO} . Changes in Palv would affect the analysis of the test and thus might affect DL_{CO} .¹⁷¹ In conclusion, a decreased DL_{CO} may support the diagnosis of pulmonary vascular obstruction, but a normal DL_{CO} does not rule out this diagnosis.¹³⁵

Restrictive Ventilatory Defects

DL_{CO} is reduced in interstitial pulmonary fibrosis and correlates with anatomic findings in resected lung tissue or on high-resolution CT scans. Although DL_{CO} is reduced in

at least half of these patients, the test may be normal in at least one third more who have abnormal responses to exercise and have documented fibrosis by lung biopsy or CT scan.¹⁷² DL_{CO} is often decreased in patients with many other forms of pulmonary restriction. DL_{CO} (expressed as percentage of predicted normal) best reflects the extent of interstitial fibrosing alveolitis on chest CT scan associated with systemic sclerosis.¹⁷³ DL_{CO} (expressed as percentage of predicted normal) also correlates closely with arterial oxygen desaturation during exercise in these patients. DL_{CO} is usually decreased in patients with asbestos-induced pleural fibrosis, who have a restrictive ventilatory defect without evidence of associated parenchymal abnormalities as documented by chest radiograph, bronchoalveolar lavage, and high-resolution CT scan.¹⁷⁴ In interstitial pulmonary fibrosis, DL_{CO} may better define pulmonary gas exchange impairment than resting arterial PO_2 , exercise alveolar-arterial PO_2 ((A-a) PO_2) differences, or 6-minute walk test arterial oxygen saturation.^{175,176}

When the diffusing capacity is reduced in patients with interstitial lung diseases, it is usually decreased out of proportion to the lung volumes; thus the DL_{CO}/VA ratio is also decreased. However, this may not be the case in all patients with a restrictive defect. A patient with sarcoidosis, for

example, may present with a TLC 50% of predicted normal, associated with a DL_{CO} that is also 50% of predicted normal, in which case the DL_{CO}/VA ratio is normal. Following treatment with systemic corticosteroids, the lung volume may return to normal, but diffusion may not, in which case the DL_{CO} and DL_{CO}/VA ratio may both be 50% of the predicted normal. In such cases, it is thought that the granulomas and fibrosis cause lasting damage to the alveolar membranes and capillaries, even though the lung volumes return to normal levels. Therefore clinical interpretation of the DL_{CO} corrected for alveolar volume in patients with interstitial lung diseases is limited. It should not be assumed that a normal DL_{CO}/VA ratio indicates that the capillary beds are functioning normally.

Rejection of Transplanted Lungs

Lung transplantation provides special challenges for physiologic evaluation. DL_{CO} is reported to be decreased abnormally in most patients with single-lung, double-lung, or heart and lung transplants. Great emphasis has been placed on the importance of detection of bronchiolitis obliterans in these patients as a potentially reversible manifestation of rejection that is lethal if treated inadequately or too late.¹⁷⁷ Given the frequency of diffusion defects in patients with lung transplants, and given that rejection is mediated via the vascular bed, it is surprising that little emphasis has been placed on the potential value of serial evaluation of DL_{CO} to detect rejection early.^{178,179}

A major limitation to the use of simple lung function monitoring in single-lung transplant patients is the bias caused by the contribution of the native lung. Ikonen and associates used relative ventilation, perfusion, and ventilation-perfusion ratio of the transplanted lung, as determined with multidetector *xenon-133* (^{133}Xe) radiospirometry, to assess function of the graft specifically. Fractions of FEV₁, FVC, and single-breath DL_{CO} were also determined using corresponding radiospirometric parameters to calculate their distribution between the lungs. This approach may have potential for distinguishing between acute rejection and infection.¹⁷⁸

REGULATION OF VENTILATION

MEASUREMENTS OF REGULATION OF VENTILATION

Ventilatory regulation may be assessed by measuring the ventilator response to hypoxia or hypercapnia or by measuring the overall respiratory drive. The response to hypoxia and hypercapnia has been assessed using rebreathing methods, which are less time-consuming and tiring than classic steady-state methods. In one rebreathing method described by Severinghaus and associates,¹⁸⁰ rapid step changes in the patient's PO_2 while PCO_2 is stabilized offer the advantage of a brief stable period of hypoxia. Respiratory drive can be assessed by measuring the inspiratory occlusion pressure at 100 msec (0.1 second), which is thought to reflect the entire neural output of the respiratory center. It is not influenced by conscious muscle effort and is less influenced by abnormal mechanical properties of the respiratory system than is measurement of ventilation. Other

methods, including electromyographic measurements of the diaphragm, the measurement of isometric inspiratory loads, and the use of drugs that stimulate the carotid body, have not been used often enough to establish their clinical utility.¹⁸¹

CLINICAL APPLICATIONS

Carbon Dioxide Responses

In general there are three clinical conditions associated with abnormal carbon dioxide responses: decreased central chemoreceptor response to carbon dioxide, neuromuscular disease preventing a normal response to carbon dioxide, and abnormalities of the mechanical properties of the respiratory system.

Patients with decreased central chemoreceptor response to carbon dioxide may have varied defects. Decreased responsiveness may result from congenital abnormalities or may be acquired following trauma or inflammatory lesions in the central nervous system. Decreased responsiveness may also result from chronic carbon dioxide retention with associated increased bicarbonate levels and increased buffer capacity of blood and other tissue fluids.

Patients with neuromuscular disease have normal chemoreceptor responses from the ventilatory centers but an inadequate peripheral response. Thus patients with myasthenia gravis cannot respond because of the defective neuromuscular junction, and patients with poliomyelitis cannot respond because of damaged anterior horn cells. These patients have decreased inspiratory work and diminished maximal inspiratory force in response to inhaled carbon dioxide and can be diagnosed using tests of respiratory muscle strength.

Patients with chronic airflow obstruction, pulmonary restriction, or deformities of the chest wall have mechanical limitations to thoracic expansion in response to inhaled carbon dioxide. These patients have normal chemoreceptor responses from the ventilatory centers, a normal peripheral response, but a mechanical limitation that prevents the respiratory muscles from increasing ventilation normally. Thus the ventilatory response to inhaled carbon dioxide may be reduced, but the response reflected by diaphragmatic *electromyography* (EMG), the $P_{0.1}$, is appropriate for the carbon dioxide.

Hypoxic Responses

There are few clinical indications for evaluation of hypoxic responses. The response to alveolar hypoxia has been used in patients with carotid body denervation to test the degree of depressed sensitivity to oxygen. Patients born at high altitude and patients with cyanotic congenital heart disease may have diminished response to hypoxia. The degree of abnormality can be assessed by administration of low-oxygen mixtures to breathe, but this is largely a research procedure.

In patients with chronic carbon dioxide retention, it may be worthwhile to test hypoxic responses because ventilation may be driven primarily by hypoxia. This possibility can be assessed by measuring the level of ventilation when the patient breathes room air and again with oxygen. Whereas normal subjects show a small decrease in ventilation, some

The subject should be prepared for these tests according to the recommendations of the ATS Workshop on Assessment of Respiratory Control in Humans.¹⁸² To minimize distractions, the subject should be positioned so as to be screened from the meters, monitors, and manipulators; preferably, the subject's eyes should be closed during the test procedure.

The ventilatory responses to hypoxia and hypercapnia vary considerably even in normal individuals. To prevent extraneous influences from further increasing this variability, the following recommendations are made: (1) studies should be performed in the fasting state with the bladder empty, (2) the subject should be comfortable and should rest for at least 30 minutes before the test, (3) the room should be quiet, (4) body temperature should be determined, (5) tests may be performed in either the sitting or semisupine position, (6) consideration should be given to preliminary evidence suggesting that normal subjects may have greater hypoxic responses when using a nose clip and mouthpiece than when using a mask, and (7) tests should be performed in duplicate with at least 10 minutes of rest between tests.

Ventilatory responses to hypoxia and hypercapnia are potentially hazardous. The clinical condition of the patient should be considered when evaluating the potential hazardous effects of the test procedure, and the usual precautions for safety of the patient used in any stress test should be taken.

Breath-Holding Time

With nose clips in place, the subject exhales to RV, inhales to TLC, and holds his or her breath as long as comfortably possible. Analyses of expired gases can be made to estimate end-tidal carbon dioxide concentrations. Breath-holding time equals the average time in seconds from the end of inspiration to TLC until the first expiration. The test is repeated until the breath-holding times or end-tidal carbon dioxide concentrations are reproducible. The mean value for predicted breath-holding at TLC is 78 seconds.¹⁸³ In six normal subjects studied by Davidson and colleagues,¹⁸⁴ reproducibility of the test at TLC was 75 ± 3 seconds at sea level (mean \pm standard error [SE]); subjects were trained until the expired end-tidal carbon dioxide was reproducible within 2 mm Hg.

Hypercapnic Response

As suggested by Read,¹⁸⁵ a reservoir bag is filled with a volume equal to the subject's VC plus 1 L with a mixture containing 7% carbon dioxide and 93% oxygen. The subject breathes room air and exhales into the room. Expired flow and end-tidal carbon dioxide are recorded. After a period to establish a stable baseline, valves are turned so the subject breathes in and out of the reservoir bag. The test is continued until the subject stops because of dyspnea, until the end-tidal PCO_2 equals 9%, or until 4 minutes have elapsed.

The ventilation in liters per minute (BTPS), either breath-by-breath or averaged over 5 to 10 breaths, is plotted on the ordinate, and the mean end-tidal carbon dioxide (in mm Hg) is plotted on the abscissa for the same periods (eFig. 25-13). The slope change in \dot{V}_E ($\Delta\dot{V}_E/\text{change in end-tidal } \text{PCO}_2$) is determined for all of the periods, preferably by linear least-squares regression analysis, eliminating the first 30 seconds of rebreathing.

The variability among normal subjects is large.^{6,185} The hypercapnic response has been shown to correlate with weight, height, and VC.¹⁸⁶ In subjects studied on two occasions 15 minutes apart, the mean \pm SE of the slope of the first test was 2.60 ± 0.11 , and that of the second test was 2.46 ± 0.10 . The mean \pm SE of the intercept on the carbon dioxide axis was 32.42 ± 0.67 mm Hg for the first test and 31.17 ± 0.71 mm Hg for the second test. When 10 of the same subjects were retested as long as 2 years later, the differences in slopes from earlier values varied from 0.04 to 3.57 L/min per mm Hg, and the differences in intercepts on the abscissa varied from 0 to 7.6 mm Hg.

Hypoxic Response

Following the method of Rebuck and Campbell,¹⁸⁷ a reservoir bag is filled with a volume equal to the VC of the subject plus 1 L with a mixture containing approximately 7% carbon dioxide, 70% nitrogen, and the balance oxygen. The subject breathes from and exhales into the room. Values for expired volume, end-tidal PO_2 , end-tidal PCO_2 , and oxygen saturation are recorded. When the end-tidal PCO_2 values become stable, appropriate valves are then turned so the subject rebreathes from the bag. The subject then takes three deep breaths to facilitate mixing; after these three breaths, the carbon dioxide value is recorded. Carbon dioxide is maintained at this level by manually adjusting flow through the carbon dioxide absorber. Rebreathing is continued until end-tidal PO_2 decreases to 45 mm Hg, oxygen saturation decreases to 75%, or the subject becomes distressed. If ventilation increases too rapidly, addition of oxygen at a rate of 125 to 200 mL/min will slow the rate of change.

Ventilation, in liters per minute BTPS (breath-by-breath or averaged over 5 to 10 breaths), is plotted on the ordinate, and the mean oxygen saturation (percentage) on the abscissa for the same periods (eFig. 25-14). The slope ($\Delta\dot{V}_E/1\%$ desaturation) is calculated, preferably by linear least-squares regression analysis. These values are reported in terms of the mean end-tidal PCO_2 during the test.

The variability of the hypoxic response during eucapnia in normal subjects is large. The difference in slopes indicates that the hypoxic response is very sensitive to the level of end-tidal PCO_2 selected. According to Rebuck and Campbell,¹⁸⁷ repeated measurements in five subjects from day to day showed a variance within individuals of 0.76 and between individuals of 7.75.

Inspiratory Occlusion Pressure

When the patient is breathing room air or while the hypercapnic or hypoxic response is being tested, P_{mouth} at 100 msec (0.1 second), $P_{0.1}$, or the *maximum rate of inspiratory pressure change* ($[dP/dt]_{\text{max}}$), can be measured. Brief inspiratory occlusion should be performed randomly, always preceded by three or more tidal breaths.¹⁸⁸ Out of view of the subject, the operator uses a syringe during expiration to close a Starling resistor arranged in series with the inspiratory channel so the channel is occluded. The syringe is decompressed as soon as possible after the inspiratory attempt is initiated. Recorder speed should be 50 mm/sec during the subject's inspiratory attempt. Alternatively, P_{mouth} and its differential (the change in pressure) can be

measured in the 10 to 50 msec before the inspiratory valve opens. This approach takes advantage of the inherent resistance of the valve and can be measured at a slow recording speed for every breath without requiring use of a Starling resistor or other maneuvers by the operator.¹⁸⁹ $P_{0.1}$ should be measured every minute and at the same time after the inspiratory effort begins (e.g., 100 ± 10 msec).

The $P_{0.1}$ measured during single partially occluded breaths, or the average (dP/dt)max of several breaths, is determined directly from the recording and plotted on the ordinate. Mean \dot{V}_E calculated from three or more breaths preceding inspiratory occlusion, end-tidal PCO_2 , or arterial oxygen saturation is displayed on the abscissa (eFig. 25-15).

Kryger and colleagues¹⁹⁰ found a mean $P_{0.1}$ of 2.6 cm H_2O (range, 1.5 to 5.0 at an arterial PCO_2 of 39 to 42 mm Hg). Gelb and coworkers¹⁹¹ found a mean \pm SD increase of 0.52 ± 0.19 cm H_2O /mm Hg PCO_2 during increasing hypercapnia. Matthews and Howell¹⁸⁹ found (dP/dt)max to vary during quiet breathing from 12.5 to 25 cm H_2O /sec. During hypercapnia the increase in (dP/dt)max ranged from 0.6 to 4.6 cm H_2O /sec per mm Hg carbon dioxide, and end-tidal PCO_2 increased from 50 to 60 mm Hg. Whitelaw and associates¹⁸⁸ found a mean $P_{0.1} \pm$ SD of 13.2 ± 0.76 cm H_2O during constant hypercapnia (end-tidal PCO_2 of 56 mm Hg). Matthews and Howell¹⁸⁹ found that individual breath-to-breath (dP/dt)max varied up to 20%.

patients with chronic carbon dioxide retention show a marked decrease in ventilation. Although this decreased response is unusual in patients with chronic airflow obstruction who are treated with oxygen, it is important to be aware that such a response can be seen in some patients, who may require assisted ventilation.

VENTILATION-PERFUSION RELATIONSHIPS

For discussion of ventilation, blood flow, and gas exchange, see Chapter 4.

MEASUREMENTS OF VENTILATION-PERFUSION RELATIONSHIPS

Inhaled air and pulmonary capillary blood flow are not distributed uniformly or in proportion to each other, even in the normal lung. Distributions of ventilation and blood flow are altered by posture, lung volume, and exercise not only in healthy subjects but even more so in patients with respiratory disease. The most common cause of arterial hypoxemia is increased mismatching of ventilation and perfusion, resulting in regional hypoventilation relative to perfusion (eTable 25-1). Whereas samples of alveolar gas and pulmonary capillary blood cannot be obtained to analyze gas exchange, inspired and expired gas (gas entering and leaving the alveoli) and mixed venous (blood entering the pulmonary capillaries) and arterial blood can be obtained and analyzed.

CLINICAL APPLICATIONS

The various methods of measuring ventilation-perfusion relationships have been used widely in the diagnosis and management of patients with various pulmonary disorders. This is not surprising because almost every pulmonary disease affects the delicate match between ventilation and perfusion early in the process, with the matching becoming worse as the disease progresses.

Understanding ventilation-perfusion mismatching may be essential to proper diagnosis and management. For example, measurement of physiologic dead space has provided insights into the gas exchange defects of the patient in the intensive care unit and of the patient with chronic pulmonary embolism who presents with the complaint of exertional dyspnea. Measurement of intrapulmonary shunts by having a patient breathe pure oxygen can be used to estimate the size of shunts and assess efficacy of therapeutic embolization of shunt vessels.

Although the measurement of distribution of ventilation-perfusion ratios has taught us a great deal about the pathophysiology of ventilation-perfusion matching in pulmonary disease, it has not been useful as a clinical tool. On the other hand, radioisotope lung scans are critically important in the management of many of our patients, not only those with pulmonary vascular problems, but also patients who have undergone a single-lung transplant, in whom we can understand the role played by the native lung as well as the graft.

APPLICATIONS OF PULMONARY FUNCTION TESTS

SCREENING STUDIES

As suggested by Comroe and Nadel,²⁵² screening pulmonary function tests should separate subjects who have normal lungs from those who have abnormal lungs in a few minutes of the patients' time, with little or no discomfort. The apparatus should be inexpensive and portable and should require little or no technical training to operate. Tests should be free from error and should pinpoint the specific functional abnormality and its location in a quantitative manner.

The single test that best fits this definition is spirometry. Spirometry is generally able to separate those with normal lungs from those with abnormal lungs; it is inexpensive, can be portable, and requires less training. Screening tests always include spirometry, with the understanding that the major limitation of spirometry is the inability to measure total lung volume. Additional tests may be added for screening pulmonary function as the situation demands.

Screening tests are useful for early detection of pulmonary or cardiopulmonary disease (e.g., emphysema, pulmonary fibrosis, pulmonary vascular disease); differential diagnosis of patients with dyspnea; detection of the presence, location, and extent of regional disease; evaluation of patients before surgical procedures; determination of the risk of certain diagnostic procedures; early detection of respiratory failure and monitoring of treatment in critical care units; quantitative evaluation of specific treatment in patients with known pulmonary disease; periodic examination of pulmonary function in workers whose occupations are associated with known pulmonary hazards; and epidemiologic studies of populations to provide clues regarding the pathogenesis of pulmonary disease.

In obstructive ventilatory defects, screening pulmonary function tests permit the diagnosis in asymptomatic patients on the basis of decreased $FEF_{25\%-75\%}$ from spirometry and decreased maximal flow at low lung volumes from flow-volume curves. In more advanced obstruction, FEV_1 , FEV_1/FVC ratio, and maximal flows at all lung volumes may be abnormally decreased. The evidence of airway obstruction may be associated with uneven distribution of ventilation, as reflected by an abnormal single-breath nitrogen washout test, and associated hyperinflation, as reflected by increased RV and FRC. If the airway obstruction is severe (FEV_1/FVC ratio < 0.4), the TLC measured by single-breath dilution may be underestimated significantly.^{43,44}

In restrictive ventilatory defects, if airway function is normal, screening pulmonary function tests permit an early diagnosis by the finding of an increased FEV_1/FVC ratio associated with increased maximal expiratory airflow. With more advanced disease, TLC, VC, and associated lung volumes are decreased, with evidence of uneven distribution of ventilation. In mixed ventilatory defects, the interpretation of the spirogram may be aided by examining FEV_1 as a percentage of predicted normal rather than as a percentage of FVC; however, mixed defects are more easily defined by measurement of TLC using a multiple-breath dilution technique or, preferably, body plethysmography.

eTable 25-1 Causes of Hypoxemia: The Effect on Alveolar-Arterial PO_2 Differences and Arterial PCO_2

Cause	Effect on Alveolar PO_2	Effect on (A-a) PO_2	Effect on Arterial PCO_2
Normal lungs/inadequate oxygenation			
Deficiency of oxygen in atmosphere	↓	↔	↓
Hypoventilation (neuromuscular disorder)	↓	↔	↑
Pulmonary disease			
Hypoventilation (airway/parenchymal disorder)	↓	↔	↑
Diffusion abnormality	↓* [†]	↑* [†]	↓
Ventilation-perfusion imbalance	↓ [†]	↑ [†]	↓ ↔, or ↑
Right-to-left shunts	↓	↑	↓, ↔, or ↑
Inadequate transport/delivery of oxygen			
Anemia	↔	↔	↔
General/localized circulatory insufficiency	↔		↔
Inadequate tissue oxygenation			
Abnormal tissue demand/poisoned enzymes/edema	↔	↔	↔

*Infrequently observed at rest but more likely during exercise.

[†]Unless patient is hyperventilating.

↑, increased; ↔, no change; ↓, decreased.

Adapted from Comroe JH Jr, Forster RE II, DuBois AB, et al: Arterial blood oxygen, carbon dioxide and pH. In Comroe JH Jr, Forster RE II, DuBois AB, et al: *The lung: clinical physiology and pulmonary function tests*, ed 2, Chicago, 1962, Year Book, pp 140–161.

Resting Ventilation

Minute ventilation under resting conditions is defined as the amount of air exhaled per minute (\dot{V}_E). It can be measured readily using a recording spirometer equipped with a carbon dioxide absorber. (The measured expired volume must be corrected for the amount of absorbed carbon dioxide.) Many laboratories use a mouthpiece equipped with valves that separate inhaled and exhaled gases, permitting collection of exhaled air in a plastic bag or meteorologic balloon in preference to the use of a spirometer. Most commercial devices now direct expired gas through a pneumotachygraph and use a computer to integrate the flow signal to calculate expired volume. The volume of exhaled gas collected is then measured with a 120-L (Tissot) spirometer or with a dry-gas meter. For use at the bedside, a Wright spirometer¹⁹² is preferred; it is used commonly in surgical recovery rooms and critical care units. From \dot{V}_E , it is possible to estimate alveolar ventilation (see discussion later), using an assumed value for *dead space* (V_D):

$$V_D (\text{mL}) = \text{subject's body weight (lb)} \quad (32)$$

Measurement of resting \dot{V}_E usually plays a minor role in routine assessment of pulmonary function, because patients with advanced disease of the lungs often breathe with a normal tidal volume and respiratory frequency. The attending physician may wish to obtain an accurate record of resting \dot{V}_E if hypoventilation or an abnormal respiratory pattern is suspected, such as that associated with central nervous system lesions or psychogenic disorders. Resting \dot{V}_E in normal subjects has been studied in detail: men breathe at an average rate of 16 breaths/min, women breathe at 19 breaths/min with much individual variation, and sighs happen at an average of 9 per hour in men and 10 per hour in women.¹⁹³

Because the attempts to measure \dot{V}_E change an automatic, unconscious process to one of concern to the subject, it is difficult to obtain accurate measurements of the rate and pattern of resting ventilation. In addition to making measurements when the subject is unaware, investigators have used magnetometers attached to the chest wall and impedance plethysmography¹⁹⁴ to measure ventilation and the pattern of breathing accurately.

Measurement of resting \dot{V}_E plays an important, but previously neglected, part in management of patients in danger of developing respiratory failure from hypoventilation (e.g., patients with obesity and sleep disorder syndromes). In such patients, and in patients in postoperative states, with drug intoxication, or with neuromuscular disease, measurement of \dot{V}_E is as important as measurement of the usual vital signs (heart rate and blood pressure) and should be obtained at frequent intervals.

The Bohr Equation for Respiratory Dead Space

The Bohr equation, applied to a particular gas X, is as follows. Expired gas is the total volume of gas leaving the nose and mouth between the beginning and the end of a single exhalation (V_E). V_A indicates the volume of alveolar gas contributed to the exhaled gas and does *not* refer to the total volume of gas in the alveoli. The amount of gas X in V_E , V_A , or V_D is the product of its fractional concentration

(F_X) and the volume in which gas X is contained. Therefore,

$$F_{E_X} V_E = F_{A_X} V_A + F_{D_X} V_D \quad (33)$$

If the gas in question is carbon dioxide, this equation is simplified, because inspired air contains practically no carbon dioxide ($F_{ACO_2} = 0.0005$), and the Bohr equation becomes

$$V_D = \frac{[F_{ACO_2} - F_{ECO_2}]}{F_{ACO_2}} V_E \quad (34)$$

“Physiologic” Dead Space (also called Wasted Ventilation)

In the Bohr equation for respiratory dead space, F_{ECO_2} and V_E can be measured easily, but F_{ACO_2} is difficult to obtain, and V_D cannot be calculated unless the correct value for F_{ACO_2} is known. Because there is almost always complete equilibrium between alveolar PCO_2 and end-pulmonary capillary PCO_2 , arterial PCO_2 represents a mean alveolar PCO_2 over several respiratory cycles, provided that arterial blood is sampled over this same period and the patient does not have a significant venous-to-arterial shunt. Thus arterial PCO_2 can replace alveolar PCO_2 , and the Bohr equation becomes

$$V_D = \frac{[P_{aCO_2} - P_{ECO_2}]}{P_{aCO_2}} V_E \quad (35)$$

In the ideal case, anatomic and “physiologic” dead spaces are equal. However, in patients with uneven ventilation–blood flow ratios in the lung, the physiologic dead space is larger than the anatomic dead space, because regions with decreased blood flow in relation to ventilation act as regions of wasted ventilation or respiratory dead space.¹⁹⁵

By substituting arterial PCO_2 for alveolar PCO_2 in the Bohr equation, it is possible to calculate physiologic dead space. This includes anatomic dead space and alveolar dead-space ventilation. The latter includes ventilation of alveoli without perfusion; alveoli with decreased perfusion and increased, normal, or slightly decreased ventilation; and alveoli with normal perfusion and marked overventilation. Because it is technically impossible to distinguish the various types of increased \dot{V}_A/Q_C ratios, we assume that part of alveolar ventilation to regions with diminished perfusion goes to regions without any blood flow. That is, the physiologist assumes two compartments: one with and one without perfusion. Overventilation relative to perfusion wastes ventilation with respect to oxygen transfer because of the shape of the oxygen-hemoglobin dissociation curve. Little oxygen is added to blood by increasing alveolar PO_2 from 100 to 140 mm Hg. This excess ventilation is not wasted with respect to carbon dioxide elimination, because increased ventilation decreases arterial carbon dioxide. Regions with excess ventilation are usually accompanied by other regions with diminished ventilation and increased PCO_2 . Ventilation is still “wasted” with respect to carbon dioxide, because it is not distributed proportionately to perfusion. Assessment of wasted ventilation is essential for the proper management of critically ill patients in the intensive care unit and for the diagnosis of patients with pulmonary vascular obstruction in the pulmonary exercise laboratory.

Alveolar Air Equation

The measurement of alveolar PO_2 and PCO_2 from analysis of a single sample of exhaled alveolar gas is subject to considerable error, but mean alveolar PO_2 can be calculated accurately. The underlying principle is based on the concept that at sea level the total pressure of gases (oxygen, carbon dioxide, nitrogen, and water) in the alveoli equals 760 mm Hg, and that if the partial pressures of any three of these four are known, the fourth can be obtained by subtraction. As derived in Chapter 4,

$$760 \text{ mm Hg} = PO_2 + PCO_2 + PN_2 + PH_2O \quad (36)$$

In general, water vapor pressure at 37°C is approximately 47 mm Hg, and this presents no problem. Arterial PCO_2 is used to represent mean alveolar PCO_2 , because arterial blood coming from all the alveoli approaches an integrated value of alveolar PCO_2 with respect to different regions of the lung and to different times during the respiratory cycle. It is also assumed that $PN_2 = 563$ mm Hg. This would be true if the *respiratory gas exchange ratio* (R) were 1 (i.e., the amount of carbon dioxide added to the alveoli equals the amount of oxygen removed from the alveoli per minute). Actually, the amount of oxygen removed per minute is greater than the amount of carbon dioxide added:

$$R = \frac{200 \text{ mL } CO_2/\text{min}}{250 \text{ mL } O_2/\text{min}} \cong 0.8 \quad (37)$$

With an R of 0.8, the nitrogen molecules are slightly more concentrated, because the same number of nitrogen molecules is present in a smaller volume. If the alveolar nitrogen concentration increases to 81%, alveolar PN_2 increases to 577 mm Hg and alveolar PO_2 falls to 96 mm Hg. It is therefore essential to measure R to calculate alveolar PN_2 accurately. The precise formula (assuming inspired PCO_2 is zero) is

$$PAO_2 \cong \left(\begin{matrix} \text{(unknown)} \\ \text{(known)} \end{matrix} \right) (PIO_2 - PACO_2) \times \left(\begin{matrix} \text{(measured)} \\ \text{(correcting factor)} \end{matrix} \right) \left(FIO_2 + 1 - \frac{FIO_2}{R} \right) \quad (38)$$

where PIO_2 (moist) at sea level is calculated as 20.93% of $(760 - 47) = 149$ mm Hg, and alveolar carbon dioxide pressure ($PACO_2$) is assumed to be equal to the arterial PCO_2 , which can be measured accurately.

The *alveolar air equation* is often approximated to estimate alveolar-arterial oxygen differences for clinical purposes (assuming $PACO_2 = PaCO_2$):

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R} \quad (39)$$

The *alveolar-arterial PO_2 difference* ($(A-a)PO_2$) has been shown to be larger in older subjects than in younger ones.¹⁹⁶ According to Mellemaard,¹⁹⁷ the regression with age is expressed as $(A-a)PO_2 = 2.5 + 0.21 \times \text{age (in years)}$. Mellemaard's study was performed on 80 healthy, seated subjects whose ages ranged from 15 to 75 years.

Calculation of Alveolar Ventilation

Carbon dioxide in exhaled gas must all come from alveolar gas. As derived in Chapter 4, this equation is as follows:

$$\dot{V}_A(\text{mL}) = \frac{\dot{V}_{CO_2}(\text{mL}) \times 863}{PACO_2} \quad (40)$$

Relation of Alveolar Ventilation to Pulmonary Blood Flow

Equation 41, derived in Chapter 4, relates the factors that determine the adequacy of alveolar ventilation:

$$\frac{\dot{V}_A}{\dot{Q}_C} = \frac{863(C\bar{V}CO_2 - Cc'CO_2)}{PACO_2} \quad (41)$$

where \dot{Q}_C is pulmonary capillary blood flow, $C\bar{V}CO_2$ is the carbon dioxide concentration in mixed venous blood, $Cc'CO_2$ is the carbon dioxide concentration in the end-pulmonary capillary blood, \dot{V}_A is alveolar ventilation, $PACO_2$ is alveolar carbon dioxide tension, and 863 is a constant to correct for changes from alveolar fraction to alveolar pressure of carbon dioxide. In any individual the mixed venous blood distributed to all pulmonary capillaries has the same carbon dioxide concentration, and end-pulmonary capillary blood has the same PCO_2 as alveolar gas; therefore alveolar PCO_2 is determined by the ratio \dot{V}_A/\dot{Q}_C .

Calculation of Quantity of Venous-to-Arterial Shunt

For a more detailed discussion of pulmonary shunts, see Chapter 61 which discusses pulmonary arteriovenous malformations and other pulmonary vascular abnormalities.

When a patient has a venous-to-arterial shunt, arterial blood contains some mixed venous blood that has bypassed the lungs and some well-oxygenated blood that has passed through the pulmonary capillaries. The equation that expresses this relationship for blood is analogous to the Bohr equation for calculation of respiratory dead space:

$$\dot{Q}_S = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - C\bar{V}O_2} \times \dot{Q} \quad (42)$$

where \dot{Q}_S is shunt blood flow, $Cc'O_2$ is the oxygen content of end-capillary blood, CaO_2 is the oxygen content of arterial blood, $C\bar{V}O_2$ is the oxygen content of mixed venous blood, and \dot{Q} is total blood flow.

Arterial and mixed venous blood can be obtained, so the arterial concentration of oxygen and $C\bar{V}O_2$ can be measured. The quantity of blood flowing through the shunt can be determined by having the patient breathe pure oxygen for a sufficient time to wash all of the nitrogen from the alveoli. Alveolar PO_2 is then equal to 760 – alveolar PH_2O – alveolar PCO_2 , or approximately 673 mm Hg. Under these conditions, there is no alveolar-to-end-capillary difference, and end-capillary blood can be assumed to contain an amount equal to the oxygen capacity of hemoglobin plus 2.0 mL of dissolved oxygen per 100 mL.

“Venous admixture” or “physiologic shunt” can be estimated by the method of Lilienthal and associates.¹⁹⁸ “Shunt” means decreased \dot{V}_A/\dot{Q}_C ratios and includes perfused alveoli without ventilation; very poorly ventilated alveoli with normal, increased, or slightly decreased perfusion; and ventilated alveoli with markedly increased perfusion. In this situation, the physiologist assumes two compartments: one with and one without a complete shunt.¹⁹⁹

If a patient is given pure oxygen to breathe, it is possible to distinguish a right-to-left shunt from a ventilation-perfusion abnormality. Alveolar and arterial PO_2 values expected in an ideal lung, with \dot{V}_A/\dot{Q}_C ratio imbalance, and with right-to-left shunt are given in eTable 25-1.

Pure oxygen replaces nitrogen with oxygen in all gas-exchange units that have patent airways, even in the presence of severe airway obstruction or pulmonary restriction; this leaves only oxygen, carbon dioxide, and water in the air spaces. Under these conditions,

$$PAO_2 = PA_{TOTAL} - PACO_2 - PAH_2O \quad (43)$$

Total pressure (PA_{TOTAL}) and water vapor pressure (PAH_2O) are the same in all patent gas-exchange units; thus alveolar PO_2 differences between units exist only when there are differences in PCO_2 . In ideal lungs or lungs with a \dot{V}_A/\dot{Q}_C imbalance, the high alveolar PO_2 corrects the ventilation-perfusion imbalance; arterial PO_2 values are also high, provided all nitrogen is washed out of communicating units by oxygen.

In most normal subjects, the right-to-left shunts are distal to the gas-exchange units (so-called postpulmonary shunts). These shunt vessels include bronchial veins, mediastinal-to-pulmonary veins, and thebesian vessels (left ventricular muscle to left ventricular cavity). In some patients, intracardiac shunts, pulmonary arteriovenous malformations, or perfusion of nonventilated alveoli produce pulmonary shunts. Most shunts in patients with pulmonary disorders involve perfusion of nonventilated alveoli. For clinical purposes the amount of right-to-left shunt may be estimated from the fall in arterial PO_2 below the expected value of 673 mm Hg, as long as the PO_2 is sufficient to saturate hemoglobin (i.e., more than 200 mm Hg). For every 2% shunt, PO_2 decreases 35 mm Hg.

Measurement of Ventilation-Perfusion Relationships Using Insoluble Gases

For a more detailed discussion of ventilation-perfusion relationships, see Chapter 4.

^{133}Xe is a relatively insoluble gas with a blood-gas partition coefficient of approximately 0.13.²⁰⁰ When it is inhaled, ^{133}Xe can be used to measure regional ventilation per unit lung volume, and when it is dissolved in saline and injected intravenously, it can be used to measure regional blood flow.²⁰¹ When either of these procedures is followed by rebreathing in a closed circuit, a plateau is obtained that reflects the product of lung volume detected by the counter and the geometric factor for ^{133}Xe ; for this purpose, the subject is switched into a closed circuit at the end of the injection. Measurements that can be obtained are illustrated in eFigure 25-16. Following intravenous injection, peak activity reflects the appearance of the isotope distributed in proportion to pulmonary blood flow; because of its low blood-gas partition coefficient, about 85% of the isotope passes into the alveolar gas, where it remains as long as the subject holds his or her breath. On resumption of breathing, the distribution reflects ventilation of perfused tissue. A slow clearance implies units with a relatively low \dot{V}_A/\dot{Q}_C ratio. Because of the overlap of many units (at least 10^7) with a single counting field, a functional definition of the \dot{V}_A/\dot{Q}_C ratio in this manner is more closely related to pulmonary gas exchange than a ratio obtained by dividing a measurement of regional ventilation by a separate measurement of regional perfusion.

The lower graph of eFigure 25-16 shows a wash-in of ^{133}Xe in a closed circuit followed by a washout. The equi-

libration plateau is evidence that the isotope concentration is the same in all alveoli. Local count rates then reflect the volume of alveolar gas in the counting fields. Perfusion per unit volume is obtained by dividing the peak counts for any region by the counts at equilibrium after intravenous injection. Both measurements should be made at the same lung volume, so geometric factors in the chest wall and differences in detector sensitivity do not influence the results.

If several VC breaths are taken at the beginning of the test, healthy subjects reach equilibration after rebreathing for 1 to 2 minutes or less. Patients with airway obstruction may not reach full equilibration in 20 minutes because isotope is accumulated in the blood and chest wall; rebreathing may then be terminated at 4 minutes. Ventilation per unit of lung volume may be obtained from the initial slope or half-time of the wash-in or washout of ^{133}Xe (see eFig. 25-16). Beyond the half-time, the washout curve cannot be interpreted because of activity in the chest wall and in the recirculating blood. Ventilation per unit of lung volume may also be obtained from the activity during a breath held subsequent to taking in a tidal volume of ^{133}Xe ; activity is divided by the plateau level at the same lung volume.

Alternatively, a bolus of ^{133}Xe may be injected close to the mouthpiece just before the start of inhalation, which is then continued until full inhalation. Under these circumstances the bolus is distributed in a pattern reflecting the early phase of inspiration starting at end-expiration. Because ventilation tends to be sequential, it is preferable to label the whole tidal breath. A bolus given at the beginning of inspiration after a maximal exhalation to RV is distributed preferentially to the lung apex. An inspiratory capacity breath of ^{133}Xe reflects regional compliance, not regional ventilation, and measures the regional inspiratory capacity. Thus it is possible to use the gas dilution principle to calculate regional inspiratory capacity or regional VC using a variety of radioisotopes.²⁰²

The most widely used radioisotope study of the lung is the perfusion scan following intravenous injection of human serum albumin microspheres or microaggregates labeled with technetium-99m (^{99m}Tc).²⁰³ Particles are 20 to 50 μm in diameter and impact in small pulmonary vessels in proportion to local perfusion. Regional perfusion is measured, not perfusion per unit volume, so the volume of lung in the counting field influences the measurement. Calculations suggest that from 1 mg of protein, particles of 500, 100, and 30 μm in diameter obstruct, respectively, 0.12%, 0.31%, and 0.26% of the vascular bed.²⁰⁴ On this basis, injection is potentially hazardous in patients with severe pulmonary vascular disease, and deaths in this situation have been recorded. However, with reasonable precautions, the risk is minimal. Passage of particles into the systemic circulation through right-to-left intrapulmonary or intracardiac shunts does not appear to be accompanied by side effects. The radiation dose from most pulmonary isotopic procedures is low and confined primarily to the lungs. A typical ^{133}Xe or ^{99m}Tc study yields 0.2 to 0.4 rad (the annual permitted dose is 5 rad).

Distribution of Ventilation-Perfusion Ratios

Distribution of perfusion in relation to ventilation of the lung may be analyzed on the basis of a region or lobe or for the lung as a whole and expressed in terms of physiologic

shunt, physiologic dead space, and other compartments or in terms of ventilation-perfusion ratios. In an approach developed by Wagner and colleagues,²⁰⁵ the lung is assumed to consist of a large number of homogeneous compartments in parallel, each with its own ventilation, blood flow, and appropriate gas concentrations. Distribution of ventilation-perfusion ratios is evaluated with six inert gases of varying solubility dissolved in saline and infused intravenously and concurrently at a constant rate. Under these circumstances in the steady state, the amount of any gas exchanging between alveoli and pulmonary capillary blood is identical to that exchanging between alveoli and atmosphere. For each compartment, the quantity of gas is a function of the ventilation-perfusion ratio and the blood-gas partition coefficient for the gas in question, expressed as a fraction of that in the mixed venous blood. For the lung as a whole, the mixed arterial concentration is a blood flow-weighted mean of the values for several compartments, and the mean expired level is similarly a ventilation-weighted mean of the compartmental values. These parameters are measured directly, together with the cardiac output and the minute volume of ventilation. They are used to calculate the corresponding mixed venous and alveolar concentrations and then a distribution of ventilation-perfusion ratios that is compatible with the arterial and alveolar concentrations of all gases concurrently (eFigs. 25-17 and 25-18).

The limitations of the method include the limited accuracy of current chromatographic techniques for gas analysis. In addition, it does not provide a unique solution, because the same arterial and alveolar gas concentrations could result from other distributions of ventilation and perfusion in the lung. Wagner and associates²⁰⁶ also reported a modification of the multiple inert gas method that permits estimation of the levels of inert gases in peripheral venous blood, rather than arterial blood, which may prove to be of considerable clinical interest.

ARTERIAL BLOOD GASES

MEASUREMENTS OF ARTERIAL BLOOD GASES

The physiologic determinants of arterial oxygen levels and acid-base balance are reviewed in detail in Chapter 4 and Chapter 7, respectively.

Invasive Measurements

pH. The pH of blood is now measured almost entirely by the use of the pH electrode (eFig. 25-19). This device takes advantage of the discovery that an electrical potential difference exists across some types of glass membranes placed between solutions of different pH. By maintaining one side of the membrane at a known pH with a buffer solution (pH = 6.84), the pH of the solution placed on the other side of the membrane can be calculated from the potential difference generated, using the Nernst equation. The modern pH electrode is made up of two cells. The measurement half-cell consists of a fine capillary tube of pH-sensitive glass separating the introduced sample (as little as 25 μ L) from the buffered solution, and a silver/silver chloride electrode to conduct the generated potential difference to the

electronic circuitry. The reference half-cell usually contains a calomel (mercury/mercurous chloride) electrode in an electrolyte solution to provide a constant reference voltage and is connected to the measurement half-cell by a contact bridge to complete the circuit. These two cells are enclosed together in a sealed jacket and are maintained at a constant temperature (see eFig. 25-19).

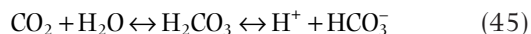
The potential difference generated across the glass membrane is a linear function of the pH. Thus it is usually adequate to calibrate the electrode with two buffered solutions of known pH that span a significant portion of the range expected in the samples to be measured. The normal range for arterial pH at sea level is 7.35 to 7.45 units. Even preliminary deviations from this range can be interpreted only by also examining the PCO₂, making use of the Henderson-Hasselbalch equation,

$$\text{pH} = 6.10 + \frac{\log(\text{HCO}_3^-)}{0.03 \times \text{PCO}_2} \quad (44)$$

to infer whether the deviation in pH is due primarily to a metabolic or a respiratory cause and whether it is due to an acute or chronic disturbance. In clinical use the pH meter has proved to be a rugged, dependable device. Repeated measurements of a single sample by the same instrument fall within a narrow range of ± 0.02 unit (± 2 SD). Generally there is good agreement among the values obtained on unknown samples by the different instruments used by laboratories enrolled in quality-control programs (SD = 0.014 pH unit has been obtained in more than 800 laboratories).²⁰⁷ This remarkable accuracy depends on the integrity of the differential permeability of the glass membrane to hydrogen ions. The permeability may be altered by the deposition of protein or by the development of cracks on the membrane surface. Proper quality control requires that pH calibration be checked at one point before each series of pH determinations and at two major points every 4 hours. A number of standard phosphate buffer solutions are suitable for routine calibrations and are available commercially. Protein contamination of the membrane can be minimized by flushing the electrode with a cleaning solution at regular intervals (every 10 samples) and by taking care to follow injections of blood with injections of saline (not distilled water).

Carbon Dioxide. Early chemical methods for measuring gas concentrations in blood were laborious and demanding. They involved liberating chemically bound oxygen and carbon dioxide in blood by adding chemical agents to a sample kept in a closed vessel. The quantity of gas released was then measured by a manometric²⁰⁸ or volumetric²⁰⁹ method. Carbon dioxide was then selectively absorbed, and the change in volume permitted calculation of the content of the blood sample of the two gases. These tedious and technically demanding methods gave accurate values for the content of the two gases in blood. Determination of pressure required measurement of the content of the gases in plasma alone, after separating plasma from red blood cells in a closed system. Alternatively, back-calculation of pressure could be made by measurement of blood hemoglobin content combined with measurements and calculations of the quantities of the gases transported in the cells and proteins of blood.

The breakthrough in the measurement of carbon dioxide came with the development of the membrane-covered carbon dioxide electrode (eFig. 25-20). This device exploits the principles of the pH electrode and the known relationship between PCO_2 and pH in a buffered solution. The sample to be analyzed is separated from a buffer solution by a membrane permeable to carbon dioxide. The carbon dioxide molecules that diffuse through the membrane alter the concentration of carbonic acid and therefore the concentration of hydrogen ion in the buffered solution:



A pH meter reads the resulting change in pH with the output scaled in terms of PCO_2 . The time for response of the carbon dioxide electrode depends on the concentration and volume of the buffered solution, the diffusion properties of the artificial membrane, and the thickness of a second “stabilizing membrane” placed over the pH-sensitive glass. With silicone-rubber membranes, the 95% response time has been reduced to as little as 10 seconds (see eFig. 25-20).

Perhaps because it incorporates a pH electrode in its design, the PCO_2 electrode also has the advantages of precision and dependability if calibrated regularly. As with the pH electrode, a one-point calibration should be checked before each series of blood-gas measurements, and two-point calibrations every 4 to 8 hours or whenever the one-point calibration indicates the need for readjustment of more than 2 mm Hg PCO_2 . The range of repeated measurements of samples of blood equilibrated under controlled conditions to PCO_2 of 20 to 60 mm Hg is ± 3.0 mm Hg, and tests with commercially available, sealed buffer solutions with different PCO_2 values show similar reproducibility with a variety of blood-gas measuring devices. The agreement among devices of laboratories enrolled in quality-control programs is also good.

The normal range of values for PCO_2 varies with altitude. At sea level, it ranges from 36 to 44 mm Hg.²¹⁰ In Salt Lake City, Utah (elevation 1340 to 1520 m), the range is reported to be 30 to 40 mm Hg.²¹¹

Oxygen

OXYGEN PRESSURE. As with the measurement of PCO_2 , the development of an accurate, stable electrode has almost entirely supplanted the use of older chemical methods for measuring total blood oxygen content and then back-calculating PO_2 . The principle of the oxygen electrode differs from that of the pH and PCO_2 electrodes in that the oxygen electrode measures a current generated by the presence of the relevant molecule, rather than a potential difference. The device consists of platinum and silver electrodes placed in potassium chloride solutions, a polarizing voltage of 0.5 to 0.6 volt, and an electrolyte bridge to complete the circuit. Oxidation takes place at the silver electrode, where silver reacts with chloride ions to form silver chloride. This reaction produces electrons, which are consumed by the reduction of oxygen at the platinum electrode. The flow of electrons (current) is thus proportional to the concentration of oxygen at the platinum electrode (eFig. 25-21).

Clark²¹² developed a useful electrode based on this principle. The important features of the Clark electrode are that it minimizes oxygen consumption by the use of a thin platinum electrode and ensures a constant diffusion distance

between the surface of the electrode and the sample by covering the electrode with an oxygen-permeable membrane. The surface area of the platinum electrode and the permeability of the membrane to oxygen determine the sensitivity and response time of the electrode. However, the larger the electrode and the more permeable the membrane, the more rapidly oxygen is consumed, causing PO_2 to fall in small samples as the measurement is made. For most available devices, the compromises made result in a 95% response time of about 50 seconds.

A peculiarity of the oxygen electrode is that slightly different currents are generated when gases and liquids at the same PO_2 are introduced. The magnitude of the difference is usually 3% to 4%, depending on the electrode diameter, the nature and thickness of the membrane, and the flow of the sample around the electrode. A correction factor is sometimes introduced into the calculation of arterial PO_2 when gases are used for calibration. These factors, however, may not be related linearly to PO_2 , resulting in errors when high oxygen pressures are measured, as in samples obtained from a patient to whom pure oxygen is given to estimate the magnitude of a right-to-left shunt. The simplest approach would seem to be calibration of the electrode with solutions, rather than gases. This is probably true, but large differences have been found for the same instrument using samples of different test solutions equilibrated to the same PO_2 .²¹³ In general, the more the oxygen-carrying capacity of the solution approximates that of blood, the smaller is the error. Thus the large interinstrument variability of oxygen pressure values reported for blind samples tested in a quality-control program may not reflect the variability that would be achieved if all tests were run with blood equilibrated to the appropriate oxygen tensions. For a single machine, the range of repeated measurements of PO_2 in blood is 3.0 mm Hg for PO_2 values from 20 to 150 mm Hg.²¹⁰ In normal seated adult subjects, the predicted arterial PO_2 can be obtained from Mellemaard's data¹⁹⁷ with a SD around the regression line of approximately 6.0 mm Hg:

$$\text{PO}_2 = 104.2 - 0.27 \times \text{age (years)} \quad (46)$$

A final problem for some highly automated blood-gas machines appears only when samples of very high or very low PO_2 are tested. This is due to the error introduced by “contamination” of the sample chamber by the rinsing fluid.¹⁸⁵ If the PO_2 of the rinsing fluid is similar to that of room air, then the persistence of a small amount of fluid does not much alter the PO_2 measured for blood samples with oxygen pressures between 60 and 100 mm Hg. The PO_2 of the rinsing fluid affects the values recorded for samples with oxygen pressures at either extreme. If the design of the machine permits, this source of error can be reduced by flushing the sample chamber with a fluid that has a PO_2 near the estimated value of the sample or by introducing consecutive specimens without flushing the chamber.

OXYGEN CONTENT. Assessment of the adequacy of oxygen delivery requires not only measurement of the PO_2 in plasma but also measurement of the oxygen content in blood. Oxygen content, the sum of the oxygen bound to hemoglobin and that dissolved in plasma, can be measured directly by chemical or galvanic cell methods and can be estimated from the PO_2 , the total hemoglobin

concentration, and the percentage of oxyhemoglobin. The measurement or estimation of oxygen content of arterial and venous blood is required for calculating cardiac output by the Fick equation and for estimating the “shuntlike effect” in hypoxemic patients.

The chemical method for measuring total oxygen content involves liberating chemically bound oxygen and carbon dioxide from blood by adding ferricyanide, measuring the total quantity of gas displaced, and then absorbing the carbon dioxide with sodium hydroxide. This is the basis of the Van Slyke method, which served as the reference method for many years but is now used infrequently because of its demands on time and technical skill.²⁰⁸

Another method is the galvanic cell method, in which oxygen is chemically liberated from blood and transferred to a fuel cell, where a current is generated in proportion to the amount of oxygen delivered. This device yields values with an accuracy and precision similar to those obtained by the Van Slyke method.²¹⁴

The method used most commonly for calculating oxygen content is measurement of the total hemoglobin concentration by the cyanmethemoglobin method,²¹⁵ the percentage of oxyhemoglobin by a spectrophotometric method, and the dissolved oxygen as the product of arterial PO_2 and oxygen's solubility coefficient (0.003 mL per 100 mL blood).

Spectrophotometry is based on the discovery that substances differentially absorb various wavelengths of light. In the absence of other materials that absorb light at the same wavelength, the concentration of a substance in a solution is proportional to the amount of light absorbed. This method is especially applicable to hemoglobin analysis, because the various forms of hemoglobin (e.g., oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin, sulfhemoglobin, methemoglobin) have characteristic spectra of light absorption. A simple two-wavelength spectrophotometer developed in 1900 could relate the amount of oxyhemoglobin to total hemoglobin but gave falsely high values when carboxyhemoglobin or methemoglobin was present. Three-wavelength instruments can simultaneously measure total hemoglobin, oxyhemoglobin, and carboxyhemoglobin; and a four-wavelength device is now marketed that enables measurement of methemoglobin as well.²¹⁵

The importance of measuring carboxyhemoglobin lies not just in quantifying correctly the proportion of nonreduced hemoglobin that is actually available for carrying oxygen but also in identifying a cause of a shift in the position of the oxygen-hemoglobin dissociation curve. The presence of carboxyhemoglobin increases the affinity of adjacent hemoglobin molecules for oxygen, so the curve is shifted to the left (i.e., less oxygen is unloaded from oxyhemoglobin at normal tissue PO_2). Similar disorders may result from inherited abnormalities in hemoglobin structure, as with hemoglobin Chesapeake, for which 50% desaturation does not develop until the PO_2 is lowered to 19 mm Hg, as opposed to the normal 50% unloading point of 27 mm Hg.

Direct measurement of the PO_2 at which 50% of the binding sites on hemoglobin are saturated (P_{50}) requires measurement of hemoglobin saturation after the blood sample is equilibrated at three oxygen pressures spanning the expected range (PO_2 values from 20 to 35 mm Hg are typical). Alternatively, a close estimate of PO_2 can be

drawn from single measurements of PO_2 and hemoglobin saturation.²¹⁵

Measurement of P_{50} is rarely needed in clinical practice. With the important exception of conditions in which carboxyhemoglobin is likely to be present in appreciable quantities (as in victims of fires or of exposure to closed-space combustion, or in heavy cigarette and cigar smokers), the estimation of blood oxygen content from measurements of arterial PO_2 and hemoglobin concentration usually provides sufficient information for decisions about clinical management.

Errors in the values used for such decisions arise most often from failures in the methods used for obtaining, transporting, and storing the sample of blood to be analyzed. For validity of the measurement, care must be taken to avoid contamination with room air or an excessive amount of anticoagulant when the sample is obtained, as well as leakage, diffusion, or consumption of gases while the sample is being transported and stored. For clinical utility, it is important that the sample be obtained with minimal discomfort and hazard. Syringes for *arterial blood gas* (ABG) collection are now designed to reduce the chance of a needle stick and to contain the optimal concentration of heparin.

Because of the adequacy of collateral flow in the event of occlusion of the sampled artery, the radial artery is the preferred site for obtaining the blood sample. However, in elderly patients and in patients with arteriosclerotic vascular disease, the adequacy of ulnar flow should be confirmed by the Allen test (appearance of palmar flush when the radial artery alone is decompressed). In infants, samples are most safely collected from the temporal or umbilical arteries. If radial and femoral arterial cannulation cannot be accomplished, then the brachial, axillary, and dorsalis pedis arteries should be considered. Sometimes physicians have been advised to avoid percutaneous cannulation of the brachial artery because of a lack of collateral vessels and the anatomic proximity to the median nerve. Aneurysm formation, thrombosis with loss of radial arterial pulse, and permanent median nerve neuropathy caused by hematoma have all been reported as complications of brachial cannulation. On the other hand, the literature associated with left heart catheterization states that percutaneous cannulation of the brachial artery is as “safe and effective” as surgical cutdown and arteriotomy.²¹⁶

Venous blood gases (VBG) are increasingly used as alternative samples to estimate systemic carbon dioxide and pH that do not require ABG sampling. Using VBG in the intensive care unit is particularly attractive because most critically ill patients have a central venous catheter from which it is easy to obtain VBG quickly.

VBG analysis can be performed on a central venous sample (central venous catheter), mixed venous sample (pulmonary artery catheter), or peripheral venous sample (venipuncture).

Central venous samples have been well correlated with ABGs. Venous pH, serum HCO_3^- , and PCO_2 are used to assess ventilator and acid base status; arterial oxygen saturation to guide resuscitation during septic shock; but partial oxygen pressure in mixed venous blood has no practical value because the tissues have already extracted oxygen before reaching the venous system.

The difference between VBG and ABG depends on the site of venous sampling; central venous pH is usually 0.03 pH units lower than ABG, PCO_2 4 to 5 mm Hg higher than ABG, and little or no difference in serum HCO_3^- .^{217,218} Mixed venous blood results are similar to central venous blood samples.^{219,220} Similar comparisons have been published for peripheral venous pH and ABG.²²¹⁻²²⁵

In clinical studies there is good agreement for pH and HCO_3^- between ABG and VBG in COPD patients, but not for PCO_2 or PO_2 . To avoid misleading results, clinicians should avoid VBG in hemodynamically unstable patients and rely on ABGs instead.²²⁶⁻²²⁸ If serial monitoring of critically ill patients is done routinely, VBG and ABG should be compared periodically. Widespread clinical use of VBG is limited because of the lack of validation studies on clinical outcomes.²²⁹

An alternative to arterial puncture is to obtain a sample of “arterialized” capillary or venous blood. The assumption is that the vasodilation produced by heat or by application of vasodilator cream to a region with low metabolic activity will result in delivery of such an excess of arterial blood that local metabolism causes only small changes in PO_2 , PCO_2 , and pH. Under these circumstances, analysis of capillary or venous blood should provide close estimates of arterial values. The sites most commonly used for capillary sampling are the earlobe in adults and children and the lateral margin of the foot in infants; for sampling of arterialized venous blood, a dorsal hand vein is most commonly used. From any of these sites, the values obtained correlate well with arterial pH and PCO_2 .²³⁰ The values for PO_2 are also accurate, except in patients with arterial hypotension or local reductions in flow to the sample site (as may develop with the vasoconstrictive response to severe hypoxemia), in newborns, and in patients with high arterial PO_2 (i.e., breathing oxygen-enriched gas mixtures).

Once the sample is obtained, it should be analyzed promptly or placed on ice to minimize the effects of continued cell metabolism on oxygen consumption. This is especially important for samples with very high white blood cell or platelet counts and in samples with PO_2 greater than 100 mm Hg.

However the sample is obtained, clinical interpretation of blood-gas values is possible only if the condition of the patient at the time of sampling is noted. Most important is a description of the oxygen pressure of the inspired gas mixture, but position, activity level, habitus, diet, and other factors can also influence arterial blood-gas values. Clearly, an excited or frightened patient may hyperventilate or breath-hold during arterial puncture. However, comparison with the values obtained from indwelling catheters shows that pain caused by arterial sampling does not routinely cause a change in alveolar ventilation.

Noninvasive Measurements

The appeal of an accurate, noninvasive means of assessing arterial blood-gas pressures is compelling, and several devices have been developed for transcutaneous measurement of oxygen saturation and pressure. Some devices already provide sufficiently accurate data on oxygen pressure to have been put into widespread clinical use. However, important physiologic and technologic barriers must be

overcome for the development of a useful device for measuring carbon dioxide content and pressure.

Oxygen

OXIMETRY. It was recognized more than 50 years ago that the principles of spectrophotometry could be applied to transcutaneous measurement of oxygen saturation in capillary blood by measuring the quantities of light at different wavelengths transmitted through or reflected from the earlobe. With dilation of local arterial vessels through application of heat or a vasodilating chemical (e.g., nicotine, alcohol), capillary oxygen saturation should approximate arterial oxygen saturation. Early ear oximeters were reported to give accurate data but were not widely accepted because of the practical difficulties in operating cumbersome instruments that were hard to calibrate, sensitive to changes in position, and likely to give unpredictable, unstable values.

The principle of oximetry depends on Beer's law, by which the amount of light absorbed by a solute in solution is related to the concentration of the unknown solute:

$$\text{Log} \frac{I_{\text{IN}}}{I_{\text{TR}}} = C_A \times d \times \epsilon_A \quad (47)$$

where I_{IN} is the quantity of incident light, d is the distance through which light passes, C_A is the concentration of the solute (e.g., hemoglobin), ϵ_A is the absorption coefficient, and I_{TR} is the amount of light transmitted through A , the substance containing the solute.

When light is passed through tissue from the oximeter, the tissues absorb most of the light, and the amount of light absorbed does not vary with the cardiac cycle. During the cardiac cycle, however, there is a small increase in arterial blood, causing an increase in absorption of light. By comparing absorption at the peak and trough of the arterial pulse, the nonarterial sources of absorption become irrelevant (eFig. 25-22).

The probe consists of two light-emitting diodes that emit light at specific wavelengths, usually 660 nm and 940 nm (eFig. 25-23). At these wavelengths the light absorption by oxyhemoglobin and by reduced hemoglobin is markedly different. A photodetector is placed across a vascular bed (finger, nose, or earlobe) from the light source. When the *ratios* (R) of pulsatile and baseline light absorption are compared at these two wavelengths, the ratio of oxyhemoglobin to reduced hemoglobin may be calculated:

$$R = \frac{\text{pulsatile absorbance (660)}}{\text{baseline absorbance (660)}} \div \frac{\text{pulsatile absorbance (990)}}{\text{baseline absorbance (990)}} \quad (48)$$

The relationship between R and oxygen saturation was determined experimentally because there is no known function relating these two variables. A calibration curve was created by having healthy subjects with previously measured amounts of methemoglobin and carboxyhemoglobin breathe various hypoxic gas mixtures designed to produce oxygen saturations between 70% and 100%.²³¹ A sample of arterial blood was obtained with each gas mixture, oxygen saturation was measured using a carbon monoxide oximeter (spectrophotometric hemoximeter), and the R value measured by the pulse oximeter was compared.

Because only two wavelengths are used, the pulse oximeter can measure only two substances, so it determines “functional saturation”:

$$\text{Functional saturation} = \frac{\text{oxyhemoglobin}}{\text{oxyhemoglobin} + \text{reduced hemoglobin}} \quad (49)$$

Pulse oximeters are accurate when oxygen saturation is between 70% and 100%,²³² but they may be inaccurate below that range. These devices may be misleading in the presence of abnormal hemoglobins (methemoglobin, carboxyhemoglobin, fetal hemoglobin), dyes (methylene blue, indocyanine green), increased bilirubin level, low perfusion states, anemia, increased venous pulsations, and external light sources.²³³

Continuous monitoring of oxygen saturation is considered the standard of care in operating rooms and recovery rooms.²³⁴ The limitation of oximetry is that it measures oxygen saturation, and the flattened shape of the upper portion of the oxygen-hemoglobin dissociation curve means that large changes in PO_2 result in small changes in arterial oxygen saturation. Oximetry is thus inherently insensitive to changes in PO_2 from the normal range that have diagnostic and clinical significance even if they do not result in important falls in oxygen delivery. The actual 95% confidence limits of $\pm 5\%$ for arterial oxygen saturation reported for oximetry make this limitation all the more important.

TRANSCUTANEOUS OXYGEN ELECTRODE. The basic idea of the transcutaneous electrode is that a small polarographic electrode can measure the oxygen pressure in a bubble of gas trapped over the skin. Because the PO_2 at the surface of unwarmed skin is near zero, the success of the transcutaneous oxygen electrode depends on producing enough local vasodilation to compensate for the arterial-capillary gradient and also for the further loss of oxygen due to skin metabolism and imperfect diffusion of oxygen through the skin layer. This degree of vasodilation is achieved by warming the skin to 42°C . The increase in temperature causes local vasodilation and displaces the hemoglobin dissociation curve to the right. Thus the oxygen pressure is increased for any blood oxygen pressure, partially correcting for the losses of oxygen between the arterioles and the skin surface.

The skin surface electrode developed by Huch and associates²³⁵ in 1973 has proved accurate in continuous measurement of transcutaneous PO_2 in both healthy and sick newborns. Not surprisingly, transcutaneous PO_2 most severely underestimates arterial PO_2 when skin perfusion is decreased from hypotension. Arterial PO_2 was also underestimated in infants treated with tolazoline for pulmonary hypertension, possibly because the general peripheral vasodilation caused by the drug exceeded the effect of the preferential local vasodilation intended from local heating of the skin. These problems have not prevented the application of this noninvasive device for regulating oxygen therapy or ventilatory assistance to infants with neonatal respiratory distress syndrome, for monitoring apnea, for sleep studies, or for analyzing the impact of nursery procedures on oxygenation. The technique is not as well accepted for estimating PO_2 in adults, in whom the greater thickness of skin impairs oxygen diffusion. Carter and Banham²³⁶ reported

that transcutaneous electrodes for measuring PO_2 and PCO_2 during exercise in adults with a variety of pulmonary disorders were reliable, provided the electrodes were kept at a slightly higher temperature (45°C) and the work rate intervals were gradual to allow for the slow response time. Unfortunately, most other workers have failed to confirm these findings,²³⁷ although the technique appears reliable for measuring the direction of change in arterial PO_2 in adult patients performing exercise^{238,239} or during sleep studies.

Carbon Dioxide

CAPNOGRAPHY. The noninvasive measurement of PCO_2 is as important as the measurement of PO_2 , especially in critical care units and operating rooms. The measurement of carbon dioxide during the respiratory cycle is called *capnometry*, and the display of the analog waveform is called a *capnogram* (eFig. 25-24). This measurement can be made using an infrared spectrometer, which is widely available. Care must be taken to calibrate the instrument regularly and to avoid interference by nitrous oxide, acetylene, and carbon monoxide.²⁴⁰ A mass spectrometer can be used to measure all the respiratory gases (carbon dioxide, oxygen, and nitrogen) as well as many anesthetic gases. This device is very rapid but very expensive. It is used most commonly in pulmonary and exercise laboratories and in operating rooms where sample gases from several patients may be tested in sequence. Capnography is valuable in detecting successful tracheal intubation versus esophageal intubation and in monitoring cardiopulmonary resuscitation. Capnography is also useful in detecting a variety of problems in ventilated patients, including an obstructed endotracheal tube, a disconnected airway, ventilator malfunction, severe pulmonary hypoperfusion, and pulmonary embolism.²⁴¹⁻²⁴³

The end-tidal carbon dioxide may decrease suddenly in a life-threatening situation such as ventilator malfunction or a disconnected airway, as illustrated in eFigure 25-25. The end-tidal carbon dioxide data may be misleading when dead space is increased (increased anatomic dead space, dead space added in series to the airway of the patient, abnormally increased respiratory rate). In these situations there is an increased difference between arterial and end-tidal carbon dioxide, and the end-tidal level does not plateau. When wasted ventilation is increased because of regional increased ventilation relative to perfusion (e.g., restrictive or obstructive ventilatory defects, parallel dead space, or pulmonary vascular obstruction), differences between arterial and end-tidal carbon dioxide are also increased. In these situations the alveolar plateau is present but abnormally reduced. The shape of the waveform may be diagnostic of pulmonary vascular obstruction (eFig. 25-26).

COLORIMETRIC END-TIDAL CARBON DIOXIDE. In some centers, colorimetric measurement is used instead of capnography or other devices to monitor end-tidal carbon dioxide in critical care units, recovery rooms, and operating rooms. The method appears to be as accurate and sensitive as capnography. Both techniques appear useful in the management of critically ill patients.²⁴⁴

TRANSCUTANEOUS CARBON DIOXIDE ELECTRODE. A device for transcutaneous measurement of PCO_2 has been developed. It also involves trapping gas above the skin layer, and

measuring carbon dioxide pressure by photometric analysis with infrared light.²⁴⁵ The device has a long time-constant, and skin preparation requires stripping of the stratum corneum. Although the values for transcutaneous PCO₂ correspond closely to those for arterial PCO₂ in healthy subjects, erroneous values manifest with decreased skin perfusion, edema, and obesity.²³⁶ This electrode does appear useful in long-term monitoring,²⁴⁶ but its use in evaluating carbon dioxide transfer during exercise in adults is still controversial.²³⁷

New Technologies

Even at the bedside, in vitro blood-gas analysis requires limitation of the frequency of serial blood-gas measurements for two major reasons: blood loss and cost. Therefore a second major area of development involves in vivo or ex vivo blood-gas analyzers.²⁴⁷ These analyzers make it possible for the measurements to be made continuously, or as frequently as deemed desirable, without permanently removing blood or adding cost.²⁴⁸

So-called on-demand blood-gas monitors locate the sensors extravascularly but within the radial artery line, thereby avoiding the problems associated with intravascular measurements. Extravascular on-demand blood-gas analysis appears accurate, allows monitoring of trends of blood-gas changes, and decreases the risk for infection, the therapeutic decision time involved, and blood loss. However, until large patient studies are available, the clinical role of online blood-gas analysis cannot be clearly delineated.²⁴⁹

The successful relocation of blood-gas measurements from the standard clinical laboratory to a combination of blood-gas monitors and point-of-care analyzers at the bedside could change the practice of acute care medicine as did the introduction of laboratory-based blood-gas analysis more than 30 years ago. Therefore it is crucial for pulmonologists, intensivists, and their colleagues to be certain that these devices are accurate, reliable, and cost beneficial to avoid widespread application of yet another set of new technologies that provide more data, greater costs, and only questionable patient benefits.^{250,251}

Table 25-2 Severity of Pulmonary Impairment²²⁹

Impairment	FEV ₁ [*]	TLC [†]	VC [†]	DL _{CO}
Normal	±95% CI	±95% CI	±95% CI	±95% CI
Mild	<LLN and ≥70	<LLN and ≥70	<LLN and ≥70	<LLN and ≥60
Moderate	60–69	<70 and ≥60	<70 and ≥60	<60 and ≥40
Moderately severe	50–59		<60 and ≥50	
Severe	35–49	<60	<50 and ≥35	<40
Very severe	<35		<35	

*Airflow obstruction is based on a decreased FEV₁/VC ratio. If the ratio is decreased below the lower 95% confidence interval (CI), the severity of airflow is graded on the percent predicted FEV₁.

†Pulmonary restriction is based on decreased TLC. If TLC is not available, a reduction in VC without a reduction in the FEV₁/VC ratio is a "restriction of the volume excursion of the lung."

CI, confidence interval; DL_{CO}, carbon monoxide diffusion in the lung; FEV₁, forced expiratory volume in 1 second; LLN, lower limit of the 95% confidence interval; TLC, total lung capacity; VC, vital capacity.

In patients with neither a restrictive nor an obstructive ventilatory defect, the finding of an isolated decreased single-breath DL_{CO} may be the first clue to the presence of an interstitial process, emphysema, or pulmonary vascular obstruction. In general the degree of severity of a particular pulmonary pattern is indicated by the decrease in percentage of predicted values, illustrated in Table 25-2.

If the screening test results are normal but the patient has symptoms, more complete pulmonary function studies are indicated. Such a diagnostic approach is essential if the ABG levels reveal evidence of chronic hyperventilation. Chronic hyperventilation (decreased arterial PCO₂ with evidence of renal compensation and a near-normal arterial pH) is observed in several major pulmonary disorders, probably reflecting an abnormal ventilatory drive.^{253–255} In patients with cough or with a history of wheezing with respiratory tract infections, bronchial provocation testing can determine whether the patient has abnormal airway responsiveness. If the patient complains of effort dyspnea or fatigue, particularly if the symptoms have caused a significant change in lifestyle and the screening tests do not explain the symptoms, an exercise test is indicated (see Chapter 26).

PATTERNS OF RESPONSE

Obstructive Ventilatory Defects

Airway obstruction is characterized by a decrease in flow (Table 25-3). Supplementary data confirming obstruction include increased RV and RAW, uneven distribution of ventilation, and significant reversibility of airway obstruction, with or without decreased diffusing capacity. It is noteworthy to point out that some patients with normal lungs may have a decrease in the lower limits of normality for the FEV₁/FVC ratio with a normal FEV₁, and all other measured parameters may be normal. In this situation, this would be considered a normal variant.²⁵⁶ Alternatively, if this pattern

Table 25-3 Obstructive Ventilatory Defect

CHARACTERISTICS OF OBSTRUCTIVE VENTILATORY DEFECT
Decreased maximum expiratory airflow
Decreased MVV
Normal or decreased VC
SUPPLEMENTAL DATA CONFIRMING OBSTRUCTION
Increased RV
Increased airway resistance
Abnormal distribution of inspired gas
Significant response to bronchodilator
Decreased DL _{CO}
Decreased lung elastic recoil

DL_{CO}, diffusing capacity of the lung for carbon monoxide; MVV, maximal voluntary ventilation; RV, residual volume; VC, vital capacity.

Adapted from Welch MH: Ventilatory function of the lungs. In Guenter CA, Welch MH, editors: *Pulmonary medicine*, Philadelphia, 1977, JB Lippincott, pp 72–123.

is observed in a subject with curvilinearity of the flow-volume curve, accompanied by other patterns suggesting airway obstruction, this could suggest early airway obstruction.

Because of the increased incidence of obesity in the United States, it is important to be aware of the deleterious effect of obesity on patients with airflow obstruction. In addition, the increased mass of the chest wall decreases expiratory reserve volume, subsequently FRC, and then TLC. As the expiratory volume in reserve diminishes, tidal volume is shifted toward RV, graphically depicted when the tidal volume loop is superimposed on the flow-volume loop. As the patient breathes at lower lung volumes, RAW increases, (A–a)PO₂ differences increase, and respiratory symptoms increase. This situation is worsened in the supine posture. These effects of obesity are particularly limiting in patients with airflow obstruction. (see Chapter 98)

Reversibility. Another approach to the differential diagnosis of the obstructive pattern is the assessment of reversibility of impaired expiratory airflow. Reversibility may appear acutely in response to administration of bronchodilator aerosols, chronically in response to a variety of airway treatments, or spontaneously during remission of bronchial asthma. Reversibility implies a better prognosis than fixed obstruction and may have considerable significance in planning a treatment program.

The ATS recommends that VC (slow or forced) and FEV₁ be the primary spirometric indices used to determine bronchodilator response.⁶ Total expiratory time should be considered when using FVC to assess the dilator response because, in obstructed patients, FVC increases when expiratory time increases. A 12% increase above the prebronchodilator value and a 200-mL increase in either FVC or FEV₁ indicate a positive bronchodilator response in adults. FEF_{25%–75%} and instantaneous flow rates should be considered only secondarily in evaluating reversibility. They must be volume-adjusted, or the effect of changing FVC must be considered in the interpretation (Fig. 25-17). Ratios such as FEV₁/VC should not be used to evaluate reversibility.

Eliasson and Degraff²⁵⁷ reported that these conventional criteria may still be misleading. In their study these criteria were not useful for distinguishing patients with asthma from those with other forms of chronic airway obstruction

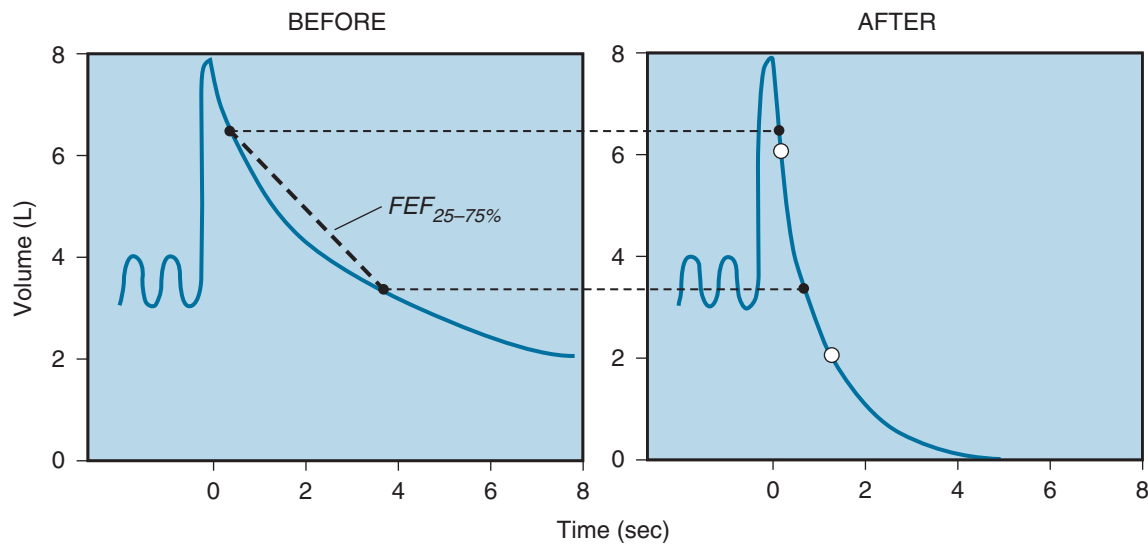


Figure 25-17 Schematic illustration of volume adjustment to calculate the isovolume $FEF_{25-75\%}$ or forced expiratory flow between 25% and 75% of forced vital capacity. Left, Before administration of bronchodilator, the $FEF_{25-75\%}$ is calculated from a line connecting two points on the volume-time curve of the forced vital capacity (FVC). One solid circle indicates when 25% of the FVC is exhaled (6.5 L), and the other solid circle indicates when 75% of the FVC is exhaled (3.5 L). This volume change (3.0 L) develops in 3.4 seconds, so the $FEF_{25-75\%}$ is 0.88 L/sec. Right, After administration of bronchodilator, one open circle indicates when 25% of the FVC is exhaled (6.0 L), and the other open circle indicates when 75% of the FVC is exhaled (2.0 L). This volume change develops in 1.3 seconds, so the $FEF_{25-75\%}$ is 3.0 L/sec. The values based on the “before” volumes from the pretreatment curve (solid circles) have been extended to the posttreatment (“after”) curve. The volume-adjusted or isovolume $FEF_{25-75\%}$ is determined from a line connecting the solid circles on the “after” graph. In this case the volume change is the same as that observed in the “before” graph, or 3.0 L, but it took place in only 0.6 second, so the isovolume $FEF_{25-75\%}$ is 5.0 L/sec, a marked improvement induced by the bronchodilator. This approach was developed because early reports indicated that some patients appeared to have significant improvement in forced expiratory volume in 1 second (FEV_1) but not in $FEF_{25-75\%}$ when no volume adjustment was made in the calculation of $FEF_{25-75\%}$. When a volume adjustment was made in the calculation of $FEF_{25-75\%}$ there was improvement in both FEV_1 and $FEF_{25-75\%}$ as illustrated.

in a clinically defined population. Furthermore, when applied to a patient population, they resulted in selection of the most obstructed patients (a contradiction of the definition of reversibility). Instead, these authors suggested that the difference in FEV_1 before and after bronchodilator administration (expressed either as an absolute value or as a percentage of predicted FEV_1) appeared more appropriate as an expression of reversibility. Their study indicated that, when one compares results from two different bronchodilator studies, careful attention must be paid to the definitions of patient populations, the definitions of obstruction and reversibility, the degree of obstruction present, and the methods used to calculate bronchodilator response. Jain et al²⁵⁸ studied 321 physician-diagnosed asthmatic patients and found a significant proportion had increased RV and abnormal RV/TLC ratio in the presence of normal FEV_1 /FVC ratio and no significant bronchodilator response.

Failure to demonstrate significant responses to acute bronchodilator therapy does not rule out reversible airway obstruction. Many reports confirm that asthmatic patients with completely reversible airway obstruction may initially fail to respond to inhaled bronchodilators.²⁵⁹

In fact, one of the pharmacologic benefits attributed to corticosteroids in this situation is that they enhance responsiveness to β -adrenergic agonists.²⁶⁰ We have observed that many patients with severe chronic airflow obstruction are undertreated with the usual treatment regimens. These patients show significant bronchodilation during exercise and in response to increased β -adrenergic treatment.

Bronchial Provocation. Provocation tests may be extremely useful in the diagnosis and management of

patients with asthma or occupational asthma and in the differential diagnosis of patients with chronic cough, wheezing, or intermittent dyspnea. Although many laboratories use spirometry to evaluate the airway response, measurement of RAW in a body plethysmograph is more sensitive, more specific for abnormalities in airway tone, and usually easier for the patient to perform than tests that depend on inspiration to TLC followed by a forced exhalation. In limited numbers of patients, tests with specific allergens may be helpful in the evaluation of allergic asthma. Similarly, in a small number of patients suspected of having occupational asthma, specific challenge with agents found in the workplace may be useful in the diagnosis. However, the referring physician should be aware that these challenge tests are dangerous and tedious, usually require hospitalization for observation, and may not be useful if the patient is exposed to multiple agents in the workplace. (When multiple agents are involved, provocation testing for each agent is usually not practical because it would require many weeks and repeated hospitalizations at great expense to assess each and every agent at multiple concentrations or doses [see Chapter 72].)

Tests of Nonspecific Airway Responsiveness. Abnormal airway responsiveness is viewed by many as a characteristic feature of asthma. It may also be found in patients with chronic bronchitis and cystic fibrosis. Although a variety of stimuli have been used, including exercise and eucapnic ventilation, the most common stimuli are histamine and methacholine. Responses to these stimuli have good correlation and reproducibility.²⁶¹ These agents are delivered in incremental concentrations until a desired

Obstructive Ventilatory Defects

Reversibility. Inhalation of albuterol (180 µg) 10 to 20 minutes before spirometry testing is used in many laboratories to test reversibility. Because many patients with asthma or other forms of airway disease do not respond initially to β -adrenergic agonists, particularly at low doses, it is worth considering evaluation of reversibility after administration of ipratropium bromide aerosol (36 µg). However, the maximal effect of ipratropium bromide may take 30 to 45 minutes. Furthermore, many patients with reversible airway obstruction do not respond to a standard clinical dose of either class of dilator, but airway obstruction still reverses completely if they are treated with larger doses. Thus, in some patients with airway obstruction who have never been treated before and who do not respond to a standard clinical dose of inhaled dilator, we often administer a cumulative dose-response protocol. Spirometry is measured before (baseline) and 15 minutes after administration of progressively increasing doses of albuterol (180 µg) or ipratropium bromide (36 µg) aerosol. The aerosol is administered every 15 minutes until a maximal increase in FEV₁ or FVC is attained or limiting symptoms are reached. In this time interval, both agents produce at least 80% of their maximal response, and most patients respond maximally after receiving 8 to 10 puffs.

effect on pulmonary function is achieved; usually, less than 0.1 mg/mL is the initial concentration to avoid inducing an inordinately severe reaction.

FEV₁ is the most common test used to evaluate the outcome of this procedure, although specific RAW may be more sensitive. Medications, baseline airway function, respiratory infections, and exposure to specific allergens and chemical sensitizers influence responses. Bronchodilators, antihistamines, and other agents that decrease bronchial responsiveness should be withheld before the test.²⁶²

Compared to methacholine and histamine, which have *direct* effects on airway smooth muscle to cause airway narrowing, so-called *indirect* challenge tests (which cause airway narrowing indirectly by triggering mast cell degranulation by osmotic stimuli, or mediator release from inflammatory cells) may have an important place in the assessment of asthma. Such indirect challenge tests (including exercise-induced bronchoconstriction, eucapnic voluntary hyperpnea, hypertonic and hypotonic aerosols, and mannitol) are useful for monitoring treatment with inhaled corticosteroids.²⁶³ Indirect tests identify subjects with the potential for exercise-induced bronchoconstriction and therefore are useful for members of the armed services, firefighters, police, and elite athletes. A positive indirect test result suggests that inflammatory cells and their mediators are present in sufficient numbers and concentration to indicate that asthma is active at the time of the test. A negative test result in a known asthmatic patient means good control or mild disease. Healthy subjects do not experience bronchoconstriction during the indirect tests.²⁶³

Although histamine and methacholine are well-established agents for identifying airway hyperresponsiveness, the response to these agonists is not specific for the diagnosis of asthma. Both agents are better at excluding the diagnosis of asthma than making the diagnosis. Furthermore, neither agonist can establish or exclude the diagnosis of exercise-induced asthma, so they are not appropriate for assessment of persons at occupational risk or of athletes. Identification of airway hyperresponsiveness by pharmacologic agents does not indicate who will respond to inhaled corticosteroids, nor does it distinguish between the effects of different doses of steroids. Many asthmatic patients remain reactive to histamine and methacholine long after treatment, so airway hyperresponsiveness is not useful as a guide to withdrawal from steroid treatment.

According to Anderson and Brannan,²⁶³ dry powder mannitol can identify those patients with exercise-induced asthma who will respond to inhaled corticosteroids. A positive response to mannitol depends on activation of mast cells secondary to osmotic changes in the airways, release of leukotrienes and other mediators, and development of active inflammation in the airways.²⁶³ If the mannitol response is positive, sufficient numbers of inflammatory cells are present to release enough mediators to cause bronchoconstriction. The response to mannitol is reduced by corticosteroid therapy and may disappear within 6 to 8 weeks. Thus mannitol responsiveness may be able to predict the risk for a clinical flare during reduction of the corticosteroid dose. Mannitol alone may be able to identify those patients who will respond to inhaled corticosteroids and also (in patients already treated with corticosteroids) serve to guide the reduction of the steroid dose.²⁶⁴⁻²⁶⁸

Tests of Specific Airway Responsiveness. Incremental allergen concentrations are given sequentially until the desired pulmonary function change develops. The response to inhaled allergen depends on both allergic sensitivity, as reflected by skin test, and nonspecific airway responsiveness, as reflected by histamine or methacholine responsiveness.

Objective Evaluation of Lung Function in Management of Asthma. Peak flowmeters play a very important role in National Institutes of Health–based guidelines for proper asthma management. Peak flowmeters offer advantages of convenience and portability; however, peak flowmeters are also less reproducible than standard spirometry. Thus it is critical that physicians recognize the importance of the use of spirometers in the initial assessment of the patient suspected of having asthma and in periodic monitoring of the management program.

According to the National Institutes of Health guideline for the diagnosis and management of asthma (Expert Panel Report No. 2, 1977), “spirometry measurements (FEV₁, FVC, FEV₁/FVC) before and after the patient inhales a short-acting bronchodilator should be undertaken for patients in whom the diagnosis of asthma is being considered.”²⁷¹ Office-based physicians caring for asthma patients should have access to spirometry, which is useful both in diagnosis and in periodic monitoring of airway function. When office spirometry shows severe abnormalities or if questions arise regarding test accuracy or interpretation, the Expert Panel recommends further assessment in a specialized pulmonary function laboratory.

These objective measurements of pulmonary function (e.g., peak flow, spirometry) are necessary for the diagnosis of asthma because the medical history and physical examination do not reliably exclude other diagnoses or characterize the lung impairment. Physicians seem to be able to identify the presence of airflow obstruction,²⁷² but they have a limited ability to assess the degree of obstruction²⁷³ or to predict whether it is reversible.²⁷² Furthermore, large segments of our population, particularly older adults, appear to have undiagnosed airflow obstruction and also undiagnosed asthma. These patients are neither detected nor diagnosed properly without spirometric assessment.^{274,275,275a}

Bullous Lung Disease. In certain obstructive ventilatory defects, a variety of specific tests may prove useful. For example, in a patient with a localized bulla who is being considered for surgical resection of the lesion, it is important to show that the bulla, and not intrinsic airway disease or emphysema, is responsible for the pulmonary function abnormalities and disability. An exercise study can quantify the disability caused by the bulla or associated disease. Physiologic studies relating RAW and V_{max} to static PL can differentiate the effects of loss of lung elastic recoil from those of intrinsic airway disease. Radioisotope perfusion lung scans, pulmonary angiograms, and thin-section CT scans can determine whether the vascular defects are localized (i.e., bullae) or diffuse (i.e., emphysema). These studies may also indicate whether the bulla is compressing normal lung tissue. This possibility can be confirmed by a shunt study to determine whether compression of normal lung

The nonspecific airway challenge begins with a diluent control aerosol, and responses are reported relative to the diluent value. The dose of agonist is expressed on the logarithmic abscissa as (1) cumulative inhalation breath units (the equivalent of one breath of a concentration containing 1 mg/mL); (2) cumulative amount of agonist (in micro-moles) delivered from the nebulizer; and (3) the concentration inhaled (in milligrams per milliliter). The end point is the dose causing a decrease in FEV₁ of 20% or a decrease in specific airway conductance of 40%. Pulmonary function measurements should be made 3 to 5 minutes after delivery of the aerosol and repeated in 5 minutes.

Most commercial allergens are obtained as lyophilized extracts or as concentrated solutions. These retain potency indefinitely when stored at -20°C . Thus the original guidelines of a starting concentration of *ragweed pollen extract* (AgE) that produces a 2+ reaction (larger than a 5-mm

wheal) after intradermal injection is probably safe but may result in many doses having to be delivered in some patients. With a 2+ skin test at 0.0005 μg AgE/mL, an aerosol of 0.025 μg AgE/mL is used; with a 2+ skin test at 0.005 μg AgE/mL, an aerosol of 0.05 μg AgE/mL is used; and with a 2+ skin test at 0.05 μg AgE/mL, the same concentration of AgE is used in the aerosol challenge.

Aerosol delivery in North America is usually by (1) intermittent generation of aerosol during inspiration from a DeVilbiss 646 nebulizer connected to a dose-metering device that controls flow of compressed air at 20 psi for a fixed time, at a flow rate of 750 mL/min or less²⁶⁹; or (2) by a Wright nebulizer with aerosol delivered to a face mask with a nebulizer output of 0.13 to 0.16 mL/min.²⁷⁰ Respiratory rate, tidal volume, and inspiratory flow rate are kept constant for a fixed time interval, and the volume of aerosol solution administered is 3 mL.

tissue by the bulla is having a shuntlike effect on arterial PO_2 . Radioisotope ventilation lung scans also help determine whether the ventilatory defects are localized (i.e., bullae) or diffuse (i.e., emphysema). The single-breath DL_{CO} is useful for detecting decreased numbers of pulmonary capillaries, reflecting the presence of pulmonary emphysema. Measurement of “trapped gas” by comparison of TLC measured by single-breath gas dilution and by body plethysmography should provide an estimate of the size of the bulla. This same multipronged approach may be useful for evaluating patients with advanced emphysema before consideration for possible surgical treatment (see later discussion).

Emphysema: Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) for emphysema, first introduced by Brantigan²⁷⁶ in 1954, is based on the theory that reduction in lung volume in patients with diffuse emphysema improves lung elastic recoil, increases radial traction on bronchi, and thus increases expiratory flow and relieves dyspnea. After initial disappointing results, this approach was revived as a therapy for COPD in the early 1990s, but it was not until Cooper and Patterson²⁷⁷ reported their first 20 operations using the sternotomy approach in 1995 that enthusiasm for LVRS increased dramatically.

The conventional explanations for the beneficial effects of LVRS are the increased elastic recoil at TLC²⁷⁸ and increased ability of inspiratory muscles to generate force.²⁷⁹ An important concept concerning the mechanism of LVRS was proposed by Fessler and Permutt.²⁸⁰ They developed a mathematical analysis and graphic model of the mechanism of improvement in both VC and expiratory airflow, based on their concept of the interaction between lung function and respiratory muscle function. They extended their analysis from LVRS to previously published data on mechanical properties of the lungs in patients with α_1 -antitrypsin deficiency, COPD, and asthma. In each of these diseases, a major determinant of airflow limitation is the ratio of *residual volume to total lung capacity* (RV/TLC). Their analysis suggested that RV/TLC determines the improvement in pulmonary function following surgical treatment of emphysema. Regardless of the underlying disease, impaired airflow appears to be due to the mismatch between the size of the lung and the size of the chest wall; surgical resection of lung tissue improves the matching. Fessler and Permutt also suggested that their analysis can be used to guide patient selection for LVRS.

Thus, when LVRS improves airflow limitation, it does so by improving the fit between lungs and chest wall by decreasing RV more than TLC. Although increased elastic recoil at TLC and increased ability of inspiratory muscles to generate force are the conventional explanations for the beneficial effects of LVRS, neither of these factors would necessarily increase VC as well as FEV_1 .

This analysis demonstrates that, regardless of the cause of increased RV (emphysema, increased airway closing pressure, or a normal lung contained in a chest wall that is too small), LVRS improves FEV_1 . The level of RV/TLC is of greater importance than the specific cause of the increased RV/TLC ratio. Furthermore, there is little difference in improvement in FEV_1 whether the surgeon removes completely nonfunctional lung tissue or tissue with the same

function as the lung left behind. The implications for selection criteria are straightforward: if increased FEV_1 is the goal of LVRS, then the optimal candidates are those with the highest RV/TLC. Finally, the critical factor in comparing outcomes among patients, procedures, or centers is the amount of lung removed, which cannot be estimated accurately by weighing the resected specimens. Fessler and Permutt²⁸⁰ suggested that the best measurement of the fraction of lung resected may be derived from the ratio of residual volumes: $1 - RV_A/RV_B$, where RV_A is the residual volume before LVRS and RV_B is the residual volume after LVRS. Several studies have examined the mechanisms responsible for improved function in these patients. Fessler and associates²⁸¹ studied 78 patients and found that the results supported their model, as discussed previously; that is, RV/TLC is an important predictor of improvement in FVC because it reflects the mismatch in size between the hyperinflated lungs and the surrounding chest, and increased FVC is an important determinant of increased FEV_1 after LVRS. Ingenito and associates²⁸² performed an elegant study of 37 patients undergoing LVRS and found that increased FEV_1 (increased by $28\% \pm 44\%$) correlated closely with increase in maximal flow of $78\% \pm 132\%$. The increased expiratory flow was largely due to increased lung recoil pressure, and FEV_1 improved without changes in small airway conductance, airway closing pressure, or lung compliance. These results support the Fessler and Permutt concept that “resizing of the lung to the chest wall” is the primary mechanism by which LVRS improves function. In another study, Mineo and colleagues²⁸³ showed dramatic improvement in right heart function during exercise following LVRS; furthermore, the improvement in right ventricular ejection fraction during exercise correlated closely with the change in RV/TLC ratio, also supporting the Fessler and Permutt theory.

In a review of respiratory muscles, Laghi and Tobin²⁸⁴ strongly supported the Fessler and Permutt concept. They argued that an imbalance between hyperinflated lungs and a relatively small rib cage was primarily responsible for abnormal respiratory muscle function in patients with COPD; therefore reducing the volume of the lungs improves the match between the lungs and rib cage, and thereby the capacity of the respiratory muscles to generate pressure. They noted that most patients undergoing LVRS show improved expiratory flow and less hyperinflation and air trapping. These effects result from increased lung elastic recoil and better matching of lung and rib cage size, which also leads to decreased respiratory pressure required for tidal breathing and decreased cost of carbon dioxide removal. The mechanisms responsible for these benefits include improved alveolar ventilation, decreased operating lung volumes, decreased dynamic positive end-expiratory pressure, and decreased dynamic lung and chest wall stiffness. According to Laghi and Tobin, the surgery also improves the length-tension relationship of the respiratory muscles. They also noted improved coupling between inspiratory effort and output of the diaphragm, which correlated closely with improved 6-minute walk test results.

Long-term benefits are more difficult to identify. Improved FEV_1 appears to peak at 3 to 6 months and then declines 100 to 150 mL or more over the subsequent year. Improvement in TLC and RV may be more stable in the first year.

Table 25-4 Restrictive Ventilatory Defect

CHARACTERISTICS OF RESTRICTIVE VENTILATORY DEFECT

Decreased VC
Relatively normal expiratory flow rates
Relatively normal MVV

SUPPLEMENTAL DATA CONFIRMING RESTRICTIVE PATTERN

Decreased TLC
Decreased lung compliance
Chronic alveolar hyperventilation
Increased (A-a)PO₂
Abnormal distribution of inspired gas

(A-a)PO₂, alveolar-arterial PO₂ difference; MVV, maximal voluntary ventilation; TLC, total lung capacity; VC, vital capacity.

Adapted from Welch MH: Ventilatory function of the lungs. In Guenter CA, Welch MH, editors: *Pulmonary medicine*, Philadelphia, 1977, JB Lippincott, pp 72-123.

Gelb and associates²⁸⁵ reported that FEV₁ decreased 141 ± 60 mL per year over 3.8 ± 1.2 years following surgery. Obviously, many more long-term data are needed before it is clear whether this procedure is useful in treatment of COPD.^{286,287}

Restrictive Ventilatory Defects

A parallel decrease in FEV₁ and FVC with a normal or increased FEV₁/FVC ratio suggests a restrictive defect, but this diagnosis requires a decreased TLC by plethysmograph or multiple-breath dilution method. Supplementary data confirming restriction include decreased single-breath DL_{CO}, uneven distribution of ventilation, chronic alveolar hyperventilation, and increased (A-a)PO₂ (Table 25-4). Because static lung elastic recoil pressure depends on lung volume, the diagnosis of a restrictive ventilatory defect does not usually require measurement of pressure-volume curves of the lung. In patients with mixed disease or in whom poor cooperation is suspected, measurement of pressure-volume curves may be helpful.

Pulmonary function tests have been widely accepted and used in the management of interstitial lung diseases. Although the tests performed have changed little over the past several decades, extensive literature has been published highlighting their clinical role in the diagnosis, staging, prognosis, and follow-up of patients with a wide variety of interstitial lung diseases. Pulmonary function testing aids in the evaluation and management of patients with interstitial lung disease. Such function tests can provide a baseline estimation of prognosis and can be used to monitor disease progression and response to therapy. The FVC and DL_{CO} are the most valuable serial measurements,^{288,289} but further data are required to examine composite scoring and exercise gas exchange.²⁹⁰

Two groups have tried to develop a systemic approach to improving the initial evaluation of these patients. Wells and colleagues²⁹¹ of Brompton Hospital developed a composite physiologic index using DL_{CO}, FVC, and FEV₁, which is designed to reflect the morphologic extent of pulmonary fibrosis, with the goal of excluding confounding emphysema in patients with pulmonary fibrosis. Survival of 106 patients with pulmonary fibrosis was predicted more closely by the composite index than any single pulmonary function test. King and associates²⁹² collated their extensive

experience with interstitial lung disease at the National Jewish Medical and Research Center in a new scoring system and survival model for interstitial lung disease. They reviewed 238 patients with usual interstitial pneumonia confirmed by biopsy to develop a scoring system that would predict survival in newly diagnosed patients, based on clinical, radiologic, and physiologic data. In contrast to the Brompton index, the National Jewish Medical and Research Center system found that pulmonary function data contributed 45% of the score as follows: DL_{CO}/VA, 5%; (A-a)PO₂ at rest, 10%; and gas exchange during exercise, 30% (of which arterial PO₂ during exercise contributed 10.5%). Thus King and colleagues found that arterial hypoxemia is the most important single factor limiting exercise in these patients.

Three large referral centers have published qualitatively similar observations: a decrease in pulmonary function, especially FVC, with elapsed time after referral to the tertiary center predicts decreased survival in patients with idiopathic pulmonary fibrosis.^{290,293-295} Apparently, the changes in pulmonary function as early as 6 months after referral, rather than baseline pulmonary function or histopathologic characteristics, are of critical importance with respect to ultimate outcome. Future studies are essential to determine the specific features of patients with idiopathic pulmonary fibrosis who experience varying rates of deterioration with time, hopefully to understand the mechanisms involved and to improve treatment. (For comparison with other patterns of abnormal function, see Table 25-5.)

Mixed Obstructive and Restrictive Ventilatory Defects

This pattern of pulmonary function defect is not common; however, the ATS guidelines do not provide suggestions for how to assess the components of a mixed ventilatory defect separately. It is logical to assume that using the FEV₁ percentage predicted to grade the severity of obstruction in a mixed disorder will overestimate the severity due to the concomitant loss of volume contributed by restriction. A study by Gardner²⁹⁶ and coworkers has begun to address this issue by adjusting the FEV₁ percentage predicted for the degree of restriction. They accomplished this by dividing the FEV₁ percentage predicted by the TLC percentage predicted. In their cohort of 199 subjects with a mixed ventilatory defect, using the *adjusted* FEV₁ percentage predicted, they classified 33% with severe or very severe obstruction, whereas, using the *unadjusted* FEV₁ percentage predicted, they classified 76% in this category.²⁹⁶ They also showed that the correlation between the adjusted FEV₁ percentage and RV/TLC was better than with the unadjusted FEV₁ percentage. Because this work has not been validated, there is no widespread consensus on its use in clinical practice; however, it is important for the clinician to be cognizant of the possibility of overestimating the severity of obstruction in a patient with a mixed physiologic defect.

Pulmonary Vascular Obstruction

Patients who have dyspnea during exertion, especially those with decreased DL_{CO} without evidence of obstructive or restrictive ventilatory defects, deserve detailed pulmonary function studies of the pulmonary circulation. These studies should include exercise tests, especially when signs of

Table 25-5 Patterns of Abnormal Function for Various Pulmonary Disorders

Test	Emphysema	Chronic Bronchitis	COPD	Asthma	RESTRICTION		Neuromuscular	PVO	CHF
					Parenchymal	Chest Wall			
FVC (L)	(N)⇒↓	(N)⇒↓	(N)⇒↓	(N)⇒↓	↓	↓	N⇒↓	N	↓
FEV ₁ (L)	↓	↓	↓	↓	↓	↓	N⇒↓	N	↓
FEV ₁ /FVC (%)	↓	↓	↓	N⇒↓	N⇒↑	N	N	N	N⇒↓
FEF (L/sec)	↓	↓	↓	↓	N⇒↓	↓	N⇒↓	N	↓
PEF (L/sec)	↓	↓	↓	↓	N⇒↓	↓	N⇒↓	N	↓
MVV (L/min)	↓	↓	↓	↓	N⇒↓	↓	N⇒↓	N	↓
FEF ₅₀ (L/sec)	↓	↓	↓	↓	N⇒↓	↓	N⇒↓	N	↓
TLC (L)	↑	N⇒↑	↑	N⇒↑	↓	↓	N⇒↓	N⇒↓*	↓
RV (L)	↑	↑	↑	↑	↓	↓	N⇒↑	N	↑⇒N⇒↓
RV/TLC (%)	↑	↑	↑	↑	N	N⇒↑	N⇒↑	N	↑⇒N⇒↓
DL _{CO} (mL/min/mm Hg)	↓	N⇒↓	N⇒↓	↑⇒N	↓	N⇒↓	N⇒↓	↓⇒N⇒↑	↓
PaO ₂ (mm Hg)	N⇒↓	↓	N⇒↓	N⇒↓	↓	N	N⇒↓	N⇒↓	N⇒↓
SaO ₂ (%)	N⇒↓	↓	N⇒↓	N⇒↓	↓	N	N⇒↓	N⇒↓	N⇒↓
PaCO ₂ (mm Hg)	N⇒↑	↑	N⇒↑	N⇒↓	N⇒↓	N	N⇒↑	↓	N⇒↓
pH (−log[H ⁺])	N⇒↓	N⇒↓	N⇒↓	N⇒↑	N⇒↑	N	N⇒↓	N	N⇒↑
RAW (cm H ₂ O/L/sec)	↑	↑	↑	↑	↓⇒N⇒↑	N⇒↑	N⇒↑	N	N⇒↑
Cst _L (L/cm H ₂ O)	↑	N	N⇒↑	N⇒↑	↓	N	N	N	N⇒↓
Cdyn _L (L/cm H ₂ O)	↓	N⇒↓	N⇒↓	N⇒↓	↓	N	N	N	N⇒↓
Pst _{max} (cm H ₂ O)	↓	N	N⇒↓	↓	N⇒↑	N⇒↓	N⇒↓	N	N⇒↓
Phase III (% N ₂ /L)	↑	↑	↑	↑	N⇒↑	N	N	N	N⇒↑
Phase IV (% VC)	A	↑⇒A	↑⇒A	↑⇒A	N⇒↑	N	N	N	N⇒↑
MEP (cm H ₂ O)	N⇒↓	↑	↓⇒N⇒↑	N	N⇒↓	N⇒↓	↓↓	N	N
MIP (cm H ₂ O)	↓	N	N⇒↓	N	N⇒↑	N⇒↑	↓↓	N	N

*Volumes are decreased in the presence of primary pulmonary hypertension but not chronic thromboemboli.

A, often absent; N, normal; (N), occasionally normal; ⇒, to; ↑, increased; ↓, decreased. Cdyn_L, dynamic compliance of the lung; CHF, congestive heart failure; Cst_L, static compliance of the lung; DL_{CO}, diffusing capacity of the lung for carbon monoxide; DLVA, diffusing capacity of the lung/alveolar volume; FEF, forced expiratory flow; FEF₅₀, forced expiratory flow after 50% of vital capacity exhaled; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MVV, maximal voluntary ventilation; PaCO₂, arterial PCO₂; PaO₂, arterial PO₂; PEF, peak expiratory flow; Pst_{max}, maximal static pressure; PVO, pulmonary vascular obstruction; RAW, airway resistance; RV, residual volume; SaO₂, arterial oxygen saturation; TLC, total lung capacity.

pulmonary hypertension are absent and radiographic methods fail to demonstrate obstruction of large pulmonary arteries. In fact it is important to make the diagnosis of pulmonary vascular obstruction before the development of pulmonary hypertension if possible. Measurements of V_D/V_T may be normal at rest but increased during exercise, indicating ventilated but poorly perfused regions of lung. The diagnosis of pulmonary vascular obstruction may be made by V_D/V_T measurements during exercise provided that no V_A/Q̇ abnormalities exist as a result of restrictive or obstructive ventilatory defects. Pulmonary vascular obstruction may cause abnormalities in V_D/V_T *only* during exercise, for several reasons. At rest, poorly perfused regions may be poorly ventilated; during exercise, ventilation may increase if deep breaths overcome smooth muscle constriction in peripheral airways.²⁹⁷ At rest, bronchial blood flow may maintain normal carbon dioxide output from a poorly perfused region; during exercise, the collateral blood flow may not be able to increase proportionately to ventilation. At rest, narrowed pulmonary arteries may perfuse poorly ventilated regions; with exercise, blood flow may fail to increase as much as the ventilation.

ABGs should be studied because most patients with pulmonary vascular obstruction appear to have an abnormal drive to ventilation, resulting in tachypnea and alveolar hyperventilation at rest and during exercise.^{297a} This abnormal drive results in decreased arterial PCO₂ and partially compensated respiratory alkalosis. Arterial PO₂ should be measured; in many patients with pulmonary vascular obstruction, arterial PO₂ may be normal at rest but decreased during exercise (eTable 25-2). Breathing pure oxygen allows the determination of the presence of a right-to-left shunt, which is often dependent on posture or exercise. The shunt tends to increase under conditions that increase right-sided pressures relative to left-sided pressures, as during increased venous return during exercise, in the supine posture, or at high versus low lung volumes.

“Poor Cooperation” Pattern

Pulmonary function tests in general depend heavily on the cooperation of the subject being tested. If a competent technician performs the procedures and recordings of the test tracings accompany the measurements, it is usually possible to determine the validity of the data. In some instances,

eTable 25-2 Effects of Exercise, Respiratory Maneuvers, and Posture on Arterial PO₂ (mm Hg) During Inhalation of Pure Oxygen

Case no.	SITTING ARTERIAL PO ₂				SUPINE ARTERIAL PO ₂	
	Rest	Slow Maximal Inspiration	Slow Maximal Expiration	Exercise	Rest	Slow Maximal Inspiration
1*	410	370	512	122		
3 [†]	615 (105)	620	605	605 (83)	490	375
5 [‡]	410	240		480	440	
7 [§]	389				487 (58)	384
9	572	395	463	96	520	
10 [¶]	426 (72)			130	330 (62)	
11 [‡]	350	120	390	180		

Numbers in parentheses indicate arterial PO₂ during inhalation of room air.

*Patent foramen ovale.

[†]Abnormal pleural-pulmonary vessels.

[‡]No shunt at cardiac catheterization.

[§]No abnormal vessels.

^{||}PO₂ 73 mm Hg during exercise while supine breathing pure oxygen.

[¶]Orthopnea relieved by breathing oxygen or sitting up.

Table 25-6 Poor Cooperation

CHARACTERISTICS OF POOR COOPERATION

Decreased vital capacity
Relatively normal expiratory airflows (increased FEV₁/FVC ratio)

SUPPLEMENTARY RESULTS CONFIRMING PATTERN

Decreased total lung capacity
Decreased maximal static transpulmonary pressure
Uneven, slurred, irregular recording of spiograms

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.
Adapted from Welch MH: Ventilatory function of the lungs. In Guenter CA, Welch MH, editors: *Pulmonary medicine*, Philadelphia, 1977, JB Lippincott, pp 72–123.

particularly in cases involving financial compensation, the pulmonary function tests must be carried out as part of a complete clinical evaluation, and the evaluating physician involved must observe the test results generated. Nevertheless, “poor cooperation” can usually be identified on the basis of the features listed in Table 25-6. The VC is decreased and does not show a smooth curve, reaching a maximum value. The decreased VC is often accompanied by relatively normal expiratory airflow, increased FEV₁/FVC ratio, and decreased MVV. Supplemental data confirming invalid test results include uneven, slurred, or notched curves on inspection; poor reproducibility on repeated testing; and decreased maximum lung elastic recoil pressure. A valid restrictive pattern differs from a test with poor effort in that it is reproducible and shows smooth expiratory curves on direct examination, increased lung elastic recoil, and a normal or nearly normal MVV.

“Nonspecific” Pattern

In a study of 80,929 pulmonary function test results, what has been termed the “nonspecific” pattern was described, which consists of a reduced FEV₁ and/or FVC with a normal FEV₁/FVC and normal TLC. This pattern was identified in 7702 subjects (or ≈10%).²⁹⁸ The ATS/European Respiratory Society consensus statement considers this pattern as representing incomplete inhalation and/or exhalation and ultimately classified this pattern as obstructive.²⁹⁹ The original study was followed up with a longitudinal study of 1284 subjects who had one or more pulmonary function tests performed 6 months or more after initial testing, with a median follow-up of 3 years. The authors used a multivariate, multinomial logistic regression model to study the association between different variables and the final pulmonary function pattern. Their findings revealed that the nonspecific pattern was reproduced in 64% of subjects. Roughly equal numbers of subjects (≈15%) went on to develop a restrictive or obstructive pattern, whereas 3% normalized and 2% showed a mixed pattern.³⁰⁰ These data highlight the importance of longitudinal follow-up in patients with conflicting pulmonary function patterns.

Role of Obesity

Obesity is common in the United States and contributes to increased risk for death from heart disease and diabetes. It also increases the risk from anesthesia and surgical procedures, especially for procedures involving the upper abdomen and thorax. Obesity also complicates life for

individuals with pulmonary disease because it increases the work of breathing. Obesity also increases the symptoms and adverse physiologic consequences of airway obstruction. Because of the increased extrathoracic mass, these patients are forced to breathe at low lung volumes, where airway diameters are decreased. The increased work of breathing at low lung volumes and reduced airway diameters interacts with the increased work of breathing due to increased extrathoracic mass. These factors are particularly troublesome, especially if the obese patient develops even mild airflow obstruction.³⁰¹ Obesity is also often associated with sleep disorders and impaired regulation of ventilation. In general, obesity limits exercise tolerance, and it makes physical conditioning more difficult to attain and maintain. (For a summary of the effects of mild obesity on lung function, see eTable 25-3).

The increased mass of the chest and abdominal walls and their contents results in decreased outward recoil of the chest wall and increased pressure within the abdomen. Expiratory reserve volume and FRC are decreased, especially when the obese subject is recumbent.³⁰² The single-breath nitrogen washout test results are abnormally increased, and perfusion is increased to poorly ventilated, dependent lung zones at the bases.³⁰³ This results in airway closure, often at lung volumes greater than FRC, with associated arterial hypoxemia.³⁰⁴ DL_{CO} is often increased in mild to moderate obesity and is associated with an increased red blood cell mass, cardiac output, and central blood volume. On the other hand, in morbid obesity DL_{CO} is usually decreased secondary to airway closure and atelectasis.³⁰⁵ Ventilatory response to carbon dioxide is often reduced; in some subjects the ventilatory responses to both hypoxia and hypercapnia are abnormal.³⁰⁶ Fatty infiltration of respiratory muscles may decrease maximum respiratory pressures, aggravate the abnormal lung volumes, and inhibit the capacity to maintain the increased work of breathing. As mentioned, obese patients who also have asthma or other forms of obstructive ventilatory defects usually have increased symptoms relative to the severity of the airway obstruction because they are forced to breathe at low lung volumes, where airflow resistance is increased.^{306a}

A large study of almost 1500 adults in the general population who were followed for 8 years revealed that the detrimental effect of weight gain might be reversible because lung function improved in all those who lost weight. Obese patients with ventilatory impairment should therefore be encouraged to lose weight.^{307,308,308a}

Aging Lung

Aging is associated with a decrease in lung elastic recoil pressure at TLC and at all lower lung volumes. Colebatch and coworkers³⁰⁹ showed that the index of curvature in the exponential expression of lung elastic recoil (see “Lung Elastic Recoil” section) increases with age. They concluded that this change was related to increased alveolar size. These findings were confirmed by Knudson and Kaltenborn,³¹⁰ and morphologic studies have confirmed the increased alveolar dimensions. The effect of age on airflow rates depends on whether the data are based on cross-sectional studies or longitudinal studies. Burrows and associates³¹¹ found that the progressive decline in FVC and FEV₁ did not begin until the middle 30s, and that the subsequent

eTable 25-3 Effects of Mild Obesity on Lung Function
(Mean \pm SD)

Parameter	Grade 0	Grade I	Grade II
BMI (kg/m ²)	20–24.9	25–29.9	30–40
Smoking history (pack-years)	29 (1–82)*	26 (1–123)*	27 (3–90)*
FRC (L)	3.45 \pm 0.71	3.17 \pm 0.69	2.66 \pm 0.74
ERV (L)	1.10 \pm 0.50	0.77 \pm 0.37	0.59 \pm 0.34
RV (L)	2.32 \pm 0.48	2.36 \pm 0.52	2.13 \pm 0.54
TLC (L)	6.74 \pm 0.97	6.58 \pm 1.02	6.33 \pm 0.91
FEV ₁ (L)	3.15 \pm 0.68	2.91 \pm 0.56	3.14 \pm 0.49
FVC (L)	4.12 \pm 0.17	3.84 \pm 0.71	3.94 \pm 0.69
PEF (L/min)	456 \pm 104	458 \pm 98	470 \pm 100

*Median (range).

BMI, body mass index; ERV, expiratory reserve volume; FEV₁, forced expiratory volume in 1 second; FRC, functional reserve capacity; FVC, forced vital capacity; PEF, peak expiratory flow; RV, residual volume; SD, standard deviation; TLC, total lung capacity.

Modified from Jenkins SC, Moxham J: The effects of mild obesity on lung function. *Respir Med* 1991;85:309–311.

decline in FEV_1/FVC was linear with age, independent of FVC, similar in men and women, and much less severe than that described in cross-sectional studies. Gelb and Zamel³¹² reported decreased maximal flows but no change in lung elastic recoil pressure or RAW with age, suggesting that airway collapsibility increased with age. More recently, Babb and Rodarte³¹³ confirmed work by Janssens and coworkers,³¹⁴ indicating that decreases in maximal expiratory airflow and in the minimum pressure needed to generate maximal flow in older subjects were due to decreased static lung elastic recoil compared with that in younger subjects. VC decreases with age, whereas RV and closing volume increase with age,³¹⁵ suggesting that lung emptying is limited with increasing age because of airway closure (see earlier discussion).³¹⁶ MVV decreases approximately 30% between 30 and 70 years of age, probably as a consequence of decreased maximal respiratory pressures, decreased distensibility of the total respiratory system, decreased lung elastic recoil, and impaired coordination of the respiratory muscles.

The slope of the alveolar plateau measured in the single-breath nitrogen washout test increases with age. Although arterial PCO_2 does not change with age, arterial PO_2 declines³¹⁶ and the $(A-a)PCO_2$ widens with age.³¹⁷ These changes probably reflect the increase in closing volume relative to expiratory reserve volume. Georges and coworkers³¹⁸ reported that DL_{CO} decreases because membrane diffusing capacity decreases after 40 years of age; pulmonary capillary blood volume is maintained until the seventh decade and then decreases rapidly. The accelerated decline in DL_{CO} over the age of 40 years was confirmed by Viegi and colleagues.³¹⁹ These changes appear to be consistent with the results of morphologic studies of the aging lung, which show a decrease in the surface area of the alveoli and the capillary bed.

Abnormal Respiratory Muscle Function

Increasing attention has been focused on the evaluation of respiratory muscles to detect abnormal function as a cause of unexplained dyspnea or respiratory failure. Inspiratory muscles may become fatigued and fail to contract adequately despite effective neural stimulation. If not detected and treated adequately, respiratory failure may result. This problem may develop in patients with obstructive or restrictive ventilatory defects, neuromuscular disorders such as myasthenia gravis, cardiogenic shock, or sepsis.²⁸⁴

Inspiratory Muscle Function Tests. Inspiratory muscle function may be tested clinically by measuring muscle strength or endurance. Common measurements include maximally negative airway pressure, *maximum transdiaphragmatic pressure* ($P_{di,max}$), MVV, diaphragmatic EMG, and fluoroscopy.

For more details about these measurements of muscle function, please see the online version of the chapter.

Events Precipitating Respiratory Failure. Any one of three events may precipitate respiratory failure: increased work of breathing, decreased energy supply, and decreased muscular efficiency.

INCREASED WORK OF BREATHING. Higher airflow resistance or greater elastic recoil of lung or chest wall, or both, may

increase the work of breathing and the energy required of the respiratory muscles.

DECREASED ENERGY SUPPLY. Reduction in the supply of vital metabolic substrates may limit the efficiency of respiratory muscles under certain circumstances. Reduction in cardiac output, arterial oxygen content, or extraction of oxygen from the blood (or a combination of these factors) may impair aerobic metabolism and compromise respiratory muscle function. Decreased oxygen delivery may be critically important under conditions that increase respiratory work. Oxygen consumption by respiratory muscles may rise 25-fold above baseline under conditions of high ventilatory requirement and increased RAW, and it may exceed supply. Forceful muscle contraction alone impedes blood flow to respiratory muscles in animals breathing against increased respiratory workloads. Other variables related to metabolism (e.g., hypercapnia, malnutrition, acidosis, electrolyte disorders) may also limit endurance.

DECREASED MUSCULAR EFFICIENCY. The number and distribution of fiber types determine inspiratory reserve. Disease processes and inactivity may alter the number and relative proportions of fibers in the diaphragm. Under certain conditions, changes in the distribution of fiber types or the loss of fibers may play an important role in the development or maintenance of respiratory failure. For example, atrophy of respiratory muscles is a potentially important problem in patients undergoing long-term mechanical ventilation.³²⁶

Muscular efficiency depends on mechanical factors as well as on structure.²⁸⁴ The position and configuration of the diaphragm at the beginning of inspiration determines the resting length of the muscle fibers. As FRC increases, the contour of the diaphragm flattens, and muscle fibers are not stretched to their optimal length. Acute hyperinflation (as in asthma) may cause a mechanical disadvantage of the diaphragm by shortening muscle fibers. In addition to changing muscle fiber length, hyperinflation also causes a mechanical disadvantage by changing the shape of the diaphragm. The $P_{di,max}$ is determined by the radius of curvature of the diaphragm at any value of muscle tension (Laplace's law). Thus, increasing the radius of curvature of the diaphragm (i.e., flattening the diaphragm) greatly reduces its capacity to develop P_{di} and to change lung volume.

Although abdominal muscles are usually regarded as expiratory, abdominal muscle tone may be needed to maintain the mechanical advantage of the diaphragm. Thus flaccidity of abdominal muscles contributes to the inefficient ventilation seen in paraplegic patients, especially when these patients are in the upright position.

VC is a useful test of respiratory muscle weakness because normally a small fraction of the muscle strength is required to inflate the lung. Furthermore, the curvilinear relationship between pressure and volume means that a greater loss of muscle strength (pressure) is required to produce a loss of volume; for example, a 50% decrease in MIP is associated with only a 15% decrease in VC. Although MIP may be reduced markedly before lung volume decreases, most patients with respiratory muscle weakness have decreased VC and decreased lung compliance. The latter finding is thought to result from atelectasis, which may be detectable in chest radiographs. FRC, inspiratory capacity, expiratory reserve volume, and TLC may also be decreased in



MAXIMALLY NEGATIVE AIRWAY PRESSURE. The maximally negative airway pressure measures the maximally negative airway pressure generated by an inspiratory effort against an occluded airway. In this test the subject inspires maximally from RV against an obstructed mouthpiece with a small leak (1 mm in diameter) to prevent closure of the glottis or development of pressure above the glottis by the muscles of the cheeks. A plateau pressure should be maintained for at least 1 second. Reproducible maximal values are difficult to obtain; the coefficient of variation is about 9% for duplicate tests for the *maximal inspiratory pressure* (MIP) and the *maximal expiratory pressure* (MEP).³²⁰

MAXIMUM TRANSDIAPHRAGMATIC PRESSURE. $P_{di_{max}}$ is measured during the same maneuver by determining the difference between intragastric and esophageal pressures. These pressures should be measured at RV because maximally negative airway pressure is reduced at larger lung volumes. Conversely, MEPs are greatest at TLC. Because it is difficult to obtain cooperation from patients to exhale to RV, MIP, MEP, and $P_{di_{max}}$ are often measured at FRC (which probably accounts in part for the reported variability). Healthy persons can sustain respiratory patterns requiring 40% of $P_{di_{max}}$ for long periods without fatigue. When a patient must increase the $P_{di}/P_{di_{max}}$ ratio to overcome a resistive load, endurance decreases in proportion to the resistive load (eFig. 25-27). Normal subjects can inspire with varying degrees of diaphragm and rib cage contraction. Thus $P_{di_{max}}$ may be decreased because of marked recruitment of the rib cage during the test. The range reported is accordingly large: 18 to 137 cm H₂O. Training results in improved coordination and reproducible values with a coefficient of variation of 19%.³²¹

Similowski and colleagues³²² have reported the use of *cervical magnetic stimulation* (CMS) as a method of phrenic nerve stimulation. They reported the results of comparisons of stimulated Pdi with the maximal Pdi obtained during the static combined expulsive-Mueller maneuver ($P_{di_{max}}$) and with the Pdi generated during a sniff test. Their results were comparable to those obtained in other studies using transcutaneous phrenic stimulation. They were highly reproducible in all the subjects. EMG data provided evidence of bilateral maximal stimulation. CMS is a nonspecific method and may stimulate various nervous structures. Co-contraction of neck muscles, including the sternomastoid, was present, but its influence in the CMS-induced Pdi appeared minimal. The method appears to avoid the pain of transcutaneous phrenic stimulation and the potential danger of needle stimulation of the phrenic nerves. However, subsequent studies showed that CMS stimulated many muscles of the upper thoracic cage as well as the

diaphragm. Investigators have used chest wall electrodes to record the diaphragm compound action potential to assess the extent of stimulation of other muscles.³²³

Although initially promising, these studies have demonstrated difficulty in obtaining surface signals of acceptable quality.³²⁴ The variable shape and latency of the action potential induced by magnetic stimulation plus the shorter phrenic nerve conduction times with CMS compared with electrical stimulation indicate that diaphragm EMG after CMS is potentially unreliable, perhaps because chest wall electrodes also record electrical activity from other muscles. As demonstrated by Luo and associates,³²⁵ the method also appears unreliable for the measurement of phrenic nerve conduction time.

MAXIMUM VOLUNTARY VENTILATION. MVV measurements can also be used to assess endurance. Endurance decreases as VE/MVV increases in a pattern similar to that observed with increasing $P_{di}/P_{di_{max}}$ ratio. In the absence of an external resistance, the largest ventilation that can be sustained more than 15 minutes is approximately 60% of the MVV.

DIAPHRAGMATIC ELECTROMYOGRAPHY. This is another technique used to evaluate respiratory muscle strength and endurance. Changes in respiratory muscle electrical activity appear to reflect closely other aspects of muscle contraction. Normally the phrenic nerve stimulates the diaphragm at a mixture of frequencies between 20 and 400 Hz. A graphic display of the EMG signal strength against frequency is called the *power spectrum*. When the EMG is analyzed over two limited frequency ranges (<50 Hz and >150 Hz), the power spectrum shifts to the low-frequency range as the diaphragm fatigues. This change precedes failure of contraction, and it therefore may be useful to predict decompensation of the respiratory muscles. Phrenic nerve conduction time may also be used to assess diaphragmatic paralysis or weakness. With recording electrodes placed over the rib cage above the diaphragm, the phrenic nerve is stimulated in the neck. Normal conduction time is 7.7 ± 0.8 msec.

FLUOROSCOPY. Fluoroscopy may be used to evaluate diaphragmatic function. Decreased excursion should be evaluated with a lateral view using the "sniff test." Decreased excursion alone is nonspecific, but decreased excursion associated with paradoxical motion during the sniff test is very specific. False-negative findings may result during spontaneous breathing because of contraction of abdominal muscles during exhalation, which produces downward motion of the diaphragm when the abdominal muscles relax at the beginning of inspiration. False-positive results may be produced by paradoxical motion limited to the anterior portion of the diaphragm.

association with decreased lung elastic recoil, suggestive of decreased outward recoil of the chest wall.

According to Rochester and Esau,³²⁷ substantial respiratory muscle strength can be lost without a change in spirometric values or ABG levels. There is a moderate decrease in MVV and increased RV, and MIP and MEP may be 50% of predicted normal. In advanced chronic disease, patients still may not have symptoms because they are not exercising. When patients reach the stage of poor cough, scoliosis, absent gag reflex, and MIP and MEP less than 50% of predicted normal, MVV is decreased more and RV enlarges further. Overt respiratory failure may develop abruptly, so it is important to follow these patients serially with VC and MIP/MEP studies.

Lung Transplantation

Lung transplantation can improve the quality of life and the capacity to exercise in patients with end-stage emphysema or interstitial lung disease, but it is not clear if it prolongs life.^{328,328a} In single-lung transplantation for emphysema, the radius of curvature of the dome of the diaphragm and the zone of apposition of the diaphragm with the chest wall on the side of the graft return to normal. The surface area of the dome also becomes smaller on the side of the graft compared with controls.³²⁹ This effect results from mediastinal displacement toward the graft, due to the lesser lung elastic recoil of the native (emphysematous) lung and greater lung elastic recoil of the graft. The disparity in elastic recoil may be increased if the graft is infected or undergoes rejection. It has also been suggested that mediastinal shift toward the graft may reflect dynamic hyperinflation of the native lung. Such dynamic hyperinflation seems unlikely because single-lung transplants do not show flow limitation during tidal breathing except during maximal exercise.³³⁰ Mediastinal displacement is usually counterbalanced by equal expansion of the rib cage on the side of the graft. Compensatory expansion of the rib cage on the graft side is not always sufficient to accommodate expansion of the contralateral hyperinflated lung. In rare cases the mediastinal shift can compromise function of the graft. This risk depends on the severity of obstruction and air trapping preoperatively.

When patients with a single-lung transplant inhale to TLC, they attain only 78% of the volume of matched controls. The smaller volume is due to mediastinal shift, mismatch in sizing the graft relative to the native lung and rib cage, and reduced capacity of inspiratory muscles to generate required pressures. Smaller inspiratory pressures may result from shorter operating length of the inspiratory muscles, steroid myopathy, or the respiratory myopathy caused by the vehicle used with cyclosporine.³³¹

Transplantation of two lungs results in a normal TLC in patients with chronic hyperinflation (FRC about 1 L above predicted levels).³³² Electrical stimulation and sniff-induced Pdi are not affected by single-lung transplantation. However, after bilateral lung transplantation, increased resting length of muscle fibers and normalization of the radius of curvature of the diaphragm lead to improved sniff pressure and normal MIP.³³³ It is still uncertain why MEP is only 70% of normal, even after double-lung transplantation. The fact that weakness of expiratory respiratory muscles and ankle dorsiflexors is equivalent suggests that these muscles may

be vulnerable to a factor that does not affect the diaphragm, perhaps because the diaphragm is active continuously.³³⁴ Inspiratory muscle endurance does not change after single-lung or double-lung transplantation.

A major problem, well recognized by transplant surgeons, is the need to obtain a proper fit of the donor graft within the chest cavity of the recipient. As suggested by Fessler and Permutt (see earlier discussion of lung volume resection surgery), a mismatch in size of the single-lung (or double-lung) graft and the size of the surrounding chest, as reflected by RV/TLC, has a profound effect on pulmonary function. If the donor graft is too large for the chest cavity, regardless of how healthy the graft is, the respiratory muscles of the recipient are unable to generate sufficient pressures to improve expiratory airflow and reduce hyperinflation and air trapping.

In patients with a single-lung or double-lung transplant, maximal exercise capacity is about half normal. This is not the result of ventilatory limitation, as it is in COPD patients without transplantation. The ventilatory reserve during maximal exercise is similar in transplant patients and matched controls. Evidence suggests that exercise limitation after transplantation results from decreased strength and endurance of locomotor muscles. Compared with healthy controls, transplant patients have shorter time to exhaustion, greater acidosis in quadriceps during knee-extension exercise, decreased type I fibers, and markedly decreased mitochondrial oxidative capacity.^{335,336}

AIRLINE TRAVEL

The increase in air travel makes it important for family physicians and specialists to be able to advise patients concerning the medical risks involved. Cardiovascular and pulmonary problems are the most common reasons for excluding air travel. Hypoxia in the aircraft, despite pressurization to the equivalent of 6000 to 8000 feet altitude, may be dangerous for patients with unstable angina, severe congestive heart failure, or chronic airway obstruction.³³⁷ Patients with severe lung disease associated with arterial oxygen desaturation should be evaluated at sea level for the risk for hypoxia during air travel or during travel to high altitude. Measurement of arterial PO₂ at ground level (as close to departure as possible) is a good predictor of tolerance to altitude, because hypoxia is the most important stress for patients with pulmonary disease at high altitude. If arterial PO₂ at altitude is 55 mm Hg or greater with a saturation of 85% to 90% or greater, the patient should tolerate air travel reasonably well.

Using altitude *simulation* (using low-oxygen mixtures or hypobaric chambers), it is possible to assess symptoms, tolerance to exercise, amount of supplemental oxygen required, and effects of controlled hypoxia on associated hematologic, cardiac, and neurologic disorders. Such information cannot be obtained from the prediction of altitude arterial PO₂ alone. Furthermore, the equations for estimation of hypoxia at altitude are relatively population-specific (i.e., limited to COPD patients) and only deal with the effects of altitude on arterial oxygenation.

Thus, although predictions may be useful in patients with COPD, they may be misleading in patients with other conditions. For example, in children with cystic fibrosis,

The arterial PO_2 at altitude in patients with chronic airflow obstruction may be estimated from the following equation³³⁸:

$$\text{PaO}_2 = 22.8 - 2.74(\text{altitude}) + 0.68(\text{PaO}_2 \text{ at sea level}) \quad (50)$$

where altitude is given in thousands of feet. The use of FEV_1 may enhance the accuracy of prediction of the arterial PO_2 at 8000 feet in patients with chronic airflow obstruction³³⁹:

$$\text{PaO}_2 = 0.453(\text{PaO}_2 \text{ at sea level}) + 0.386(\text{FEV}_1) + 2.440 \quad (51)$$

where FEV_1 is given as percentage of predicted normal.

As suggested by Gong and associates,³³⁸ while the patient breathes hypoxic gas mixtures equivalent to the atmospheric oxygen at 8000 feet (15.1% oxygen, representing “worst case” cabin pressurization excluding accidental depressurization), measurements can be made of pulse oximetry or ABG levels combined with electrocardiographic monitoring at rest and during exercise. Although measurements of ABGs may be used to predict the likely oxygenation of pulmonary patients at altitude, more objective information may be obtained from a hypoxia-altitude

simulation test. Berg and associates³⁴⁰ approached altitude simulation directly and studied patients with COPD [FEV_1 0.97 L ($\pm 31.3\%$)] in a hypobaric chamber to simulate a commercial jet aircraft cabin at the equivalent of 8000 feet altitude. When breathing supplemental oxygen by nasal cannula at 4 L/min, the mean arterial PO_2 increased from 47.4 ± 6.3 mm Hg to 82.3 ± 14 mm Hg ($n = 18$). Supplementation of oxygen by 24% Venturi mask caused arterial PO_2 at 8000 feet to increase by 12.7 ± 3.8 mm Hg; a 28% Venturi mask caused arterial PO_2 at 8000 feet to increase by 19.7 ± 8.2 mm Hg. Compared with ground level, oxygen at 4 L/min (by nasal cannula) increased mean arterial PO_2 by 9.9 ± 12.6 mm Hg; 24% and 28% Venturi masks did not cause mean arterial PO_2 to increase above ground-level values. These changes could be evaluated accurately using a transmittance ear oximeter and less accurately using a reusable digital pulse oximeter.³⁴¹

These results suggest that altitude simulation studies may be more accurate in assessing hypoxemia and the effect of treatment with supplemental oxygen than predictions of altitude arterial PO_2 based on studies at ground level.

simple spirometry and baseline arterial PO_2 may underestimate the individual response to air travel or altitude.³⁴² In a study of 17 patients with restrictive ventilatory defects, Christensen and colleagues³⁴³ reported the effect of simulated air travel in a hypobaric chamber on ABGs, blood pressure, and cardiac frequency during rest and mild exercise, and the response to supplementary oxygen. They found that resting arterial PO_2 was much lower than predicted by an equation, and that arterial PO_2 fell further with light exercise. Thus, for patients with diseases other than COPD, it is probably prudent to use some form of altitude simulation to estimate the possible physiologic and clinical effects of altitude or air travel on patients with pulmonary disease.³⁴⁴⁻³⁴⁶

INFECTION CONTROL AND SAFETY

When patients with communicable infectious diseases are referred for pulmonary function tests, they always present a potential risk for transmission of infectious diseases to the technical and administrative staff of the laboratory, as well as to other patients who may be in the laboratory for studies at the same time. Pulmonary laboratory directors are familiar with the risk for spreading tuberculosis by aerosols produced by sputum-positive patients. There has also been the more theoretical possibility of transmitting tuberculosis from one patient to another via infected secretions, which may contaminate pulmonary function equipment. The increasing number of immunosuppressed patients in cancer treatment and transplantation programs has raised the possibility of increased risk for transmission of infection to such patients.

Key Points

- There are two main ventilatory patterns measured by pulmonary function tests: obstruction and restriction. Categorization of these patterns is dictated by the lung volumes, both static and forced, as well as the interpretation of the flow-volume loop.
- Because pulmonary function testing is effort dependent, technicians must be trained sufficiently and laboratories must adhere to high standards to obtain the most accurate and reproducible results possible.
- Measurements from spirometry alone can be useful in patients whose main physiologic impairment is airway obstruction. The findings from spirometry can provide clues that concomitant restriction is present; however, for assessment of restriction, lung volumes must be measured.
- In patients with reversible mild airway disease, the results of pulmonary function tests may be normal because the disease is dynamic and patients with mild airflow obstruction may spontaneously return to normal.
- The diffusing capacity measurement is used to determine defects of the alveolar-pulmonary capillary unit. A defect in the diffusing capacity alerts the physician that oxygen transfer, the alveolar-capillary membranes, and/or pulmonary capillaries may not be normal, and further evaluation of the underlying cause of this defect should be pursued.
- Methacholine provocation testing is used to identify whether abnormal airway responsiveness is present. Usually this indicates a diagnosis of asthma, but the clinician must understand that other conditions that involve airway inflammation, such as sarcoidosis, may also show abnormal airway responsiveness.

Complete reference list available at ExpertConsult.

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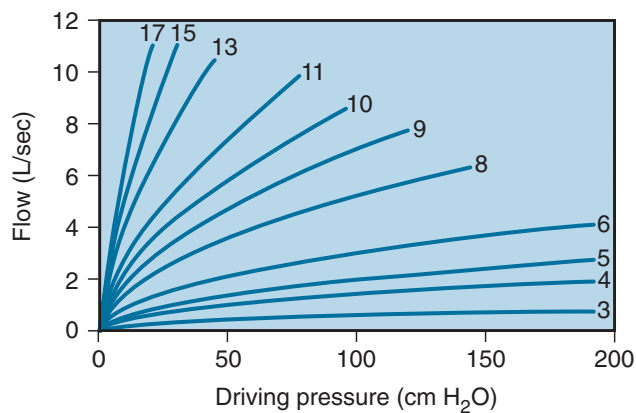
With the *human immunodeficiency virus* (HIV) epidemic and the recent severe acute respiratory syndrome epidemic and the possible risk for transmission of a lethal virus, this issue has been rigorously reassessed. It is not possible to screen everyone studied in a laboratory for HIV infection or the *acquired immunodeficiency syndrome* (AIDS) before testing. Furthermore, in hospitals in which large numbers of patients with chronic liver disease are evaluated for possible liver transplantation, there is a high prevalence of diverse hepatitis viruses, which are also difficult if not impossible to screen out before pulmonary function testing.

For these reasons, on the advice of the Infectious Disease Control Committee and the AIDS Advisory Committee at University of California, San Francisco, the laboratory with which I am affiliated has adopted a uniform protocol designed to protect all patients and technical staff from possible infectious diseases. When a patient is sent to the laboratory, the administrative assistant responsible for the schedule makes certain the requisition is completed. The requisition is designed to screen for possible HIV, tuberculosis, and other infectious diseases. The administrative assistant also checks for these possibilities with the referring physician when the study is scheduled. When the patient arrives at the laboratory for the study, the technicians check for possible communicable infectious diseases on the requisition, the medical record, and the questionnaire completed by the patient. If this review is negative, studies are

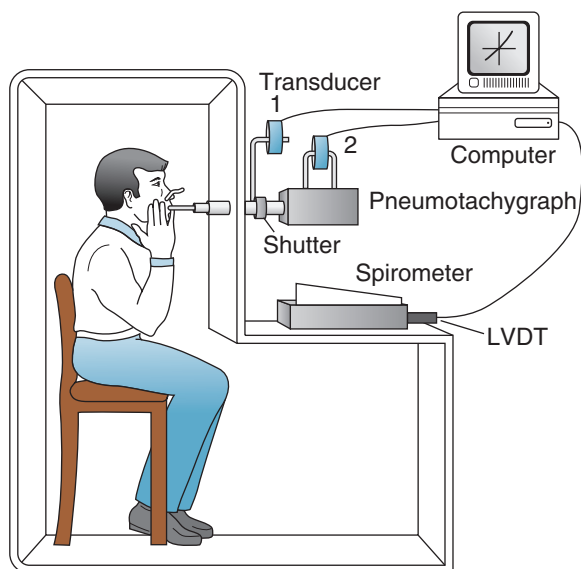
performed. All patients are studied on the same equipment. All studies are performed with the patient breathing through a filter that traps particles as small as 0.2 μm in diameter and does not affect the results of the physiologic tests performed. It is assumed that infectious particles, whether bacterial, fungal, parasitic, or viral, will be carried in respiratory secretions of such a large size that all of them will be trapped by these filters. No infectious diseases have been transmitted from the equipment in this laboratory, a fact that reinforces these assumptions. The fact that the Centers for Disease Control and Prevention has not reported transmission of HIV or hepatitis virus via pulmonary function equipment also reinforces the assumptions.

Because of the expense of effective filters, an alternative and conservative policy might include the following: careful screening of patients before testing; use of disposable mouthpieces that are discarded after single-patient use or rubber mouthpieces that are changed between each patient and cleaned with high-level disinfection procedures; replacing external spirometer tubing between patients, with high-level disinfection and drying of the tubing between each use; replacing nose clips between each patient and discarding used nose clips or cleaning them with high-level disinfection procedures; changing the water in water-sealed spirometers at least monthly; and washing hands thoroughly before and after pulmonary function testing, with appropriate use of gloves when blood samples are to be collected.

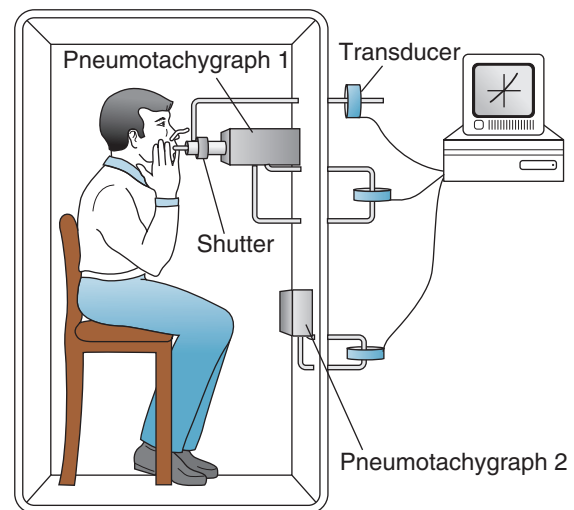
eFIGURE IMAGE GALLERY



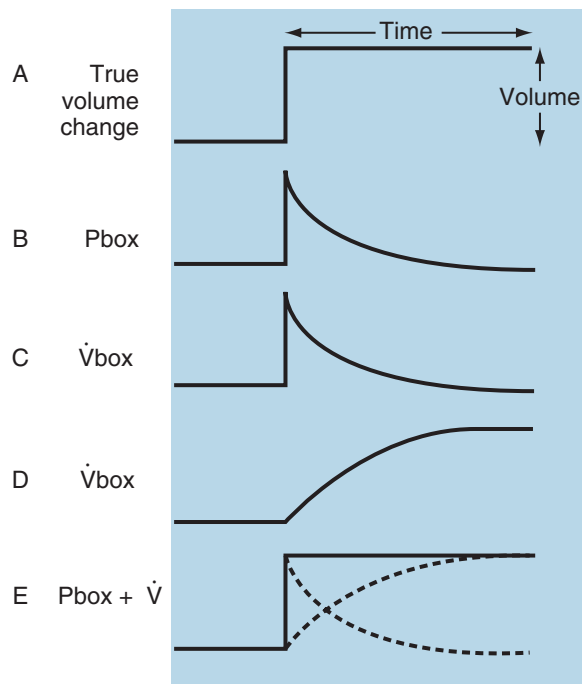
eFigure 25-1 Relationship between driving pressure (x-axis) and airflow (y-axis) through a series of critical orifices of varying diameters (in mm). Using this family of curves, it is possible to determine the diameter of a critical orifice in a patient with upper airway obstruction. Assuming a driving pressure of 100 cm H₂O, the diameter is given by the curve closest to the maximum flow observed in the flow plateau obtained from the flow-volume loop obtained from the patient. Curves were constructed by using graded external resistances in a normal subject.



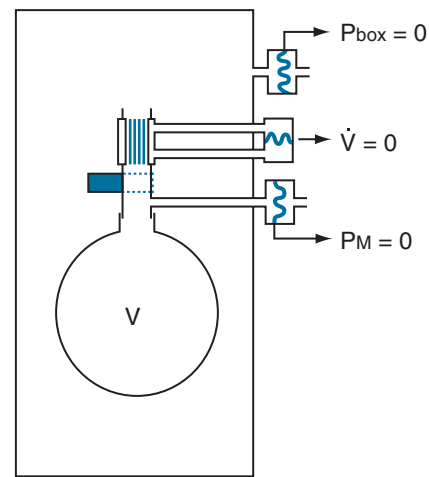
eFigure 25-2 Volume (open-type) plethysmograph. In this constant-pressure, variable-volume type of plethysmograph, the subject also breathes through a shutter/pneumotachygraph apparatus, which usually is located outside the plethysmograph itself. The shutter is open for tidal breathing, measurement of airway resistance, and spirometry. It is closed for measurement of thoracic gas volume. In the closed-shutter mode, mouth pressure is measured by a transducer (1) and approximates alveolar pressure with no flow and small volume changes. The pneumotachygraph measures flow via another transducer (2, above the pneumotachygraph). Flow is integrated electronically to obtain volume. Changes in volume of the plethysmograph, reflecting movement of the chest wall, are measured with a spirometer and a linear volume-displacement transducer (LVDT). The spirometer illustrated is a Krogh water-sealed spirometer with good frequency response and very small impedance to gas displacement. A low-resistance pneumotachygraph (flowmeter) with a fast, drift-free integrator may be used instead. Processing is usually performed by computer and permits slow and forced vital capacity maneuvers as well. However, neither approach is routine.



eFigure 25-3 Pressure-volume (or flow) plethysmograph. This type of plethysmograph combines features of the closed and open types. The subject breathes through a shutter/pneumotachygraph apparatus. The shutter is open for tidal breathing, measurement of airway resistance, and spirometry. It is closed for measurement of thoracic gas volume. In the closed position, mouth pressure (alveolar pressure) is measured by a transducer (top). The pneumotachygraph at the mouth (pneumotachygraph 1) measures airflow with another transducer (middle). This airflow at the mouth is integrated to obtain volume inhaled and exhaled at the mouth. Changes in plethysmograph or box volume resulting from movements of the chest wall are measured by a pneumotachygraph in the wall of the plethysmograph (pneumotachygraph 2) with a third transducer (bottom), and this signal is integrated to obtain volume change of the thorax. The signals from all three transducers usually are processed by computer to obtain slow and forced vital capacities as well as resistance and thoracic gas volumes.



eFigure 25-4 Physical principles underlying pressure-volume plethysmography. **A**, The theoretical “true” instantaneous volume event. During this event, plethysmographic pressure increases rapidly and then decays exponentially (**B**). If the plethysmographic pneumotachygraph is linear, the flow signal has a shape similar to that of the pressure transducer (**C**). This flow signal is integrated to obtain volume (**D**), which reaches the same level as the true volume event, but the shape does not conform to the “true” event. The difference is a result of the compression of a large volume of gas in the plethysmograph and is directly proportional to the plethysmograph pressure. Therefore, by adding a portion of the plethysmograph pressure to the integrated plethysmograph flow (**E**), the true volume event is reconstructed accurately: $\Delta V = P_{box} + \int \dot{V}_{box}$. Thus the true volume is obtained by adding the plethysmographic compression volume (P_{box}) and the displacement volume ($\int \dot{V}_{box}$). More precisely, (1) box pressure (P_{box}) is multiplied by a constant (K_{box}), a factor to correct pressure to volume that is proportional to the gas volume in the box (total box volume – patient volume); and (2) P_{box} is also divided by the box flowmeter resistance (R_{box}) to yield box flow (\dot{V}_{box}), and integrated to obtain volume (V_{box}). These two signals are added together to yield the change in lung volume: $\Delta V = P_{box}K_{box} + P_{box}/R_{box} \int \dot{V}_{box}$.



eFigure 25-5 The rectangle represents a closed, constant-volume, variable-pressure whole-body plethysmograph. As described in eFigure 25-4, at end-expiration airflow is zero, thoracic gas volume (V) = functional residual capacity, and alveolar pressure (P_{alv}) = mouth pressure (P_M) = barometric pressure (P_{bar}). When the subject inhales against an occluded shutter in the airway, airflow remains zero, but V increases by ΔV to V' and P_M (= P_{alv}) increases by ΔP ($P + \Delta P$) to equal P' . When P_M is plotted against P_{box} , the slope of the line (α) yields $\Delta V/\Delta P_{alv}$, and $V = \Delta V/\Delta P_{alv} \times P_{bar}$, as indicated in the text. \dot{V} , airflow. (Modified from Comroe JH Jr, Forster RE II, DuBois AB, et al: *The lung: clinical physiology and pulmonary function tests*, ed 2, Chicago, 1962, Year Book.)

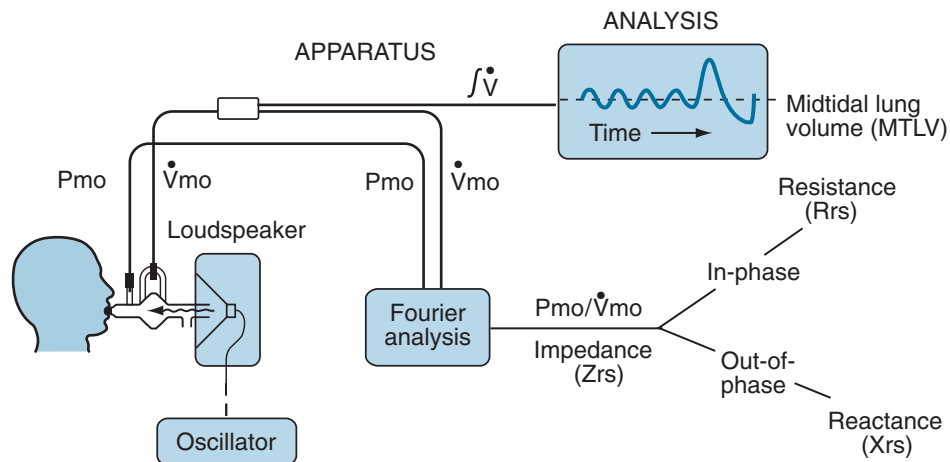


Figure 25-6 Measurement of respiratory resistance by forced oscillation. A loudspeaker may be driven to produce a sinusoidal oscillation at a single frequency, a sequence of sinusoidal oscillations at diverse single frequencies, or a random noise signal. The flow signal is integrated to yield tidal volume or, at the end of the study, inspiratory capacity. The recorded signals for mouth pressure (P_{mo}) and flow (\dot{V}_{mo}) are directed to a Fourier analyzer, and the component of each signal caused by the applied oscillation is differentiated from changes caused by tidal breathing. Impedance (Z_{rs}) is calculated over a wide range of frequencies. The impedance is subdivided into the in-phase and out-of-phase components of the primary signals. The in-phase signal is the resistance of the total respiratory system (R_{rs}), and the out-of-phase signal is the reactance (X_{rs}), sometimes called the imaginary part of the impedance. The reactance is related to the compliance and inertance of the respiratory system (see text). (Modified from Hughes JMB, Pride NB: *Lung function tests*, London, 1999, WB Saunders, p 35.)

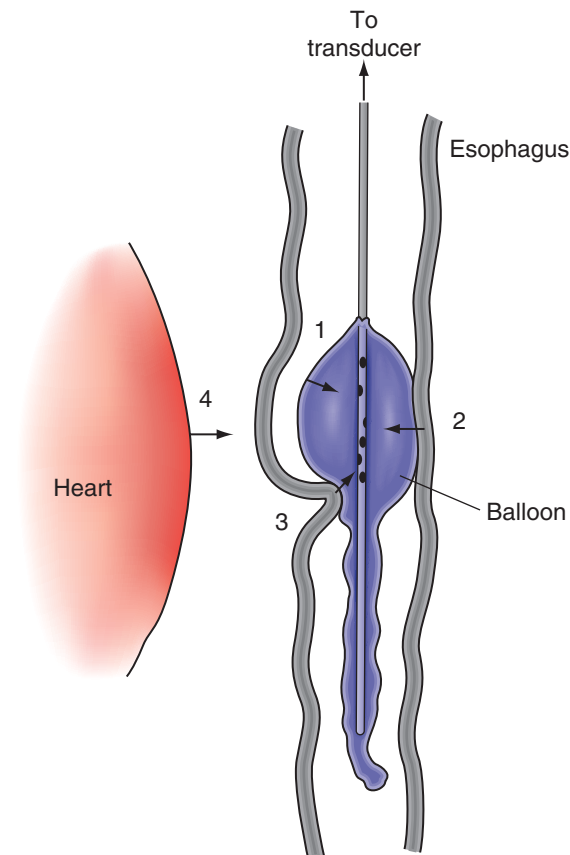


Figure 25-7 Schematic drawing illustrating the position of an esophageal balloon in relation to adjacent structures. The balloon is made of latex (wall thickness, 0.06 mm; length, 10 cm; circumference, 3.5 cm). The tubing is polyethylene (inner diameter, 0.14 cm; outer diameter, 0.19 cm) with holes placed in a spiral arrangement in the portion inside the balloon. The balloon is filled with 0.2 to 0.4 mL of air and positioned in the lower third of the esophagus. Intraesophageal pressure recorded from the catheter within the balloon is affected by the following factors in addition to static transpulmonary pressure: retractile pressure of balloon wall (1), pressure caused by resting esophageal tension (2), and pressure caused by mediastinal structures (3), including pulsations of the heart (4).

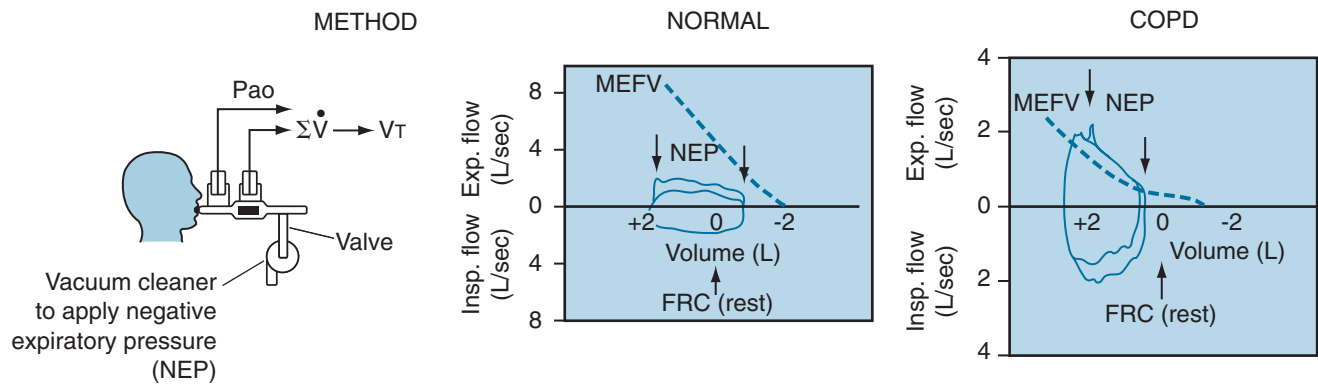


Figure 25-8 Measurement of expiratory flow limitation by negative expiratory pressure (NEP) method. *Left*, The experimental setup. The subject breathes tidally through a pneumotachygraph that records flow (\dot{V}), which is integrated to yield tidal volume (V_T). After recording baseline V_T , a negative expiratory pressure of -5 cm H_2O is applied to the subsequent V_T , in which the pressure at the airway opening (P_{ao}) is reduced by 5 cm H_2O . *Right and center*, Examples of tidal flow-volume curves. Both results were obtained during exercise. In the normal subject (*center*), expiratory flow increases, but except for a transient spike of flow, there is no change in flow in a patient with COPD (*right*). Note that the flow and volume scales are different in the two panels, as are the shapes of the curve in the normal individual (rectangular) and in the COPD patient (*right*). The change in volume during exercise is referred to as the functional residual capacity (FRC) at rest. Note the decrease in volume in the normal lung and the increase in volume in the COPD lung during exercise. The *dashed lines* indicate the full maximal flow-volume curves in both subjects. There is a large reserve of expiratory flow in the normal subject, whereas tidal expiratory flow exceeds the full flow-volume envelope at the same volume in the COPD patient. MEFV, maximal expiratory flow-volume. (Modified from Koulouris NG, Dimopoulou I, Volta P, et al: Detection of expiratory flow limitation during exercise in COPD patients. *J Appl Physiol* 82:723–731, 1997.)

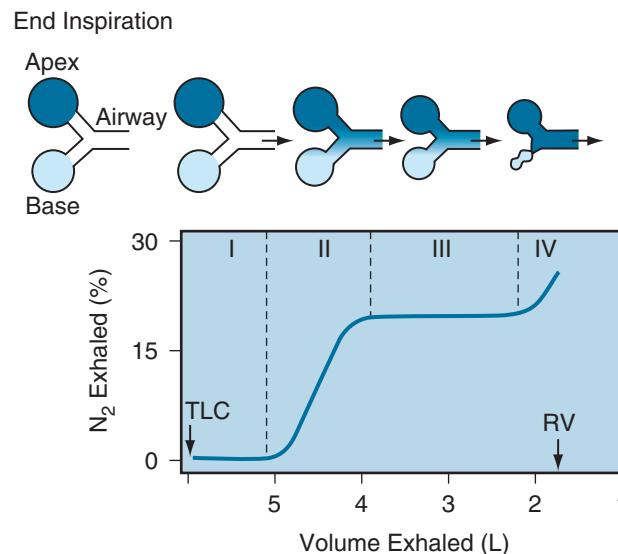


Figure 25-9 Relationship between nitrogen (N_2) concentrations in different regions of lung (top) and the single-breath N_2 washout test of distribution of ventilation (bottom). *Top*, Schematic illustration of a ventilatory unit near the lung apex (*dark blue*) and a ventilatory unit near the base (*light blue*) subtended by a common airway. The intensity of color reflects the end-inspiratory concentration of the resident gas (N_2) at the end of a single maximal inspiration of pure oxygen (O_2) (at total lung capacity [TLC]). The differences in N_2 concentration in each unit result from the effect of differences in regional residual volume (RV) and the distribution of inspired gas (see text). *Bottom*, At the start of exhalation, the gas (pure oxygen) in the conducting airway empties first, and 0% N_2 is recorded (phase I). As exhalation continues, gas from both ventilatory units mixes in the airway, and the N_2 concentration increases rapidly (phase II). With continued exhalation, mixed alveolar gas is recorded by the N_2 analyzer (phase III). Finally, dependent airways at the base of the lungs close near RV (closing volume), and exhalation continues from the apical ventilatory unit of the lung only, which contains a higher N_2 concentration than the basal unit (phase IV).

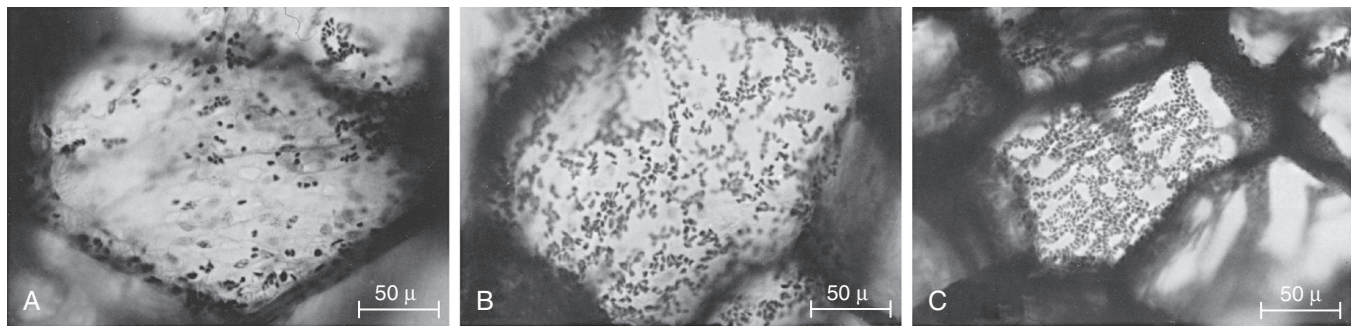


Figure 25-10 Face-on views of freeze-dried, stained alveolar walls (200- μ m-thick section) showing the distribution of the pulmonary capillary bed in anesthetized cats. A, Zone I lobe. B, Zone II lobe. C, Zone III lobe. Morphometric analysis showed that 21% of the alveolar walls were occupied by red blood cells in zone I lobes, 43% in zone II lobes, and 61% in zone III lobes. Independent changes in pulmonary arterial or venous pressure were associated with changes in the pulmonary capillary blood volume over a threefold range. (From Vriem CE, Staub NC: Pulmonary vascular pressures and capillary blood volume changes in anesthetized cats. *J Appl Physiol* 36:275–279, 1974.)

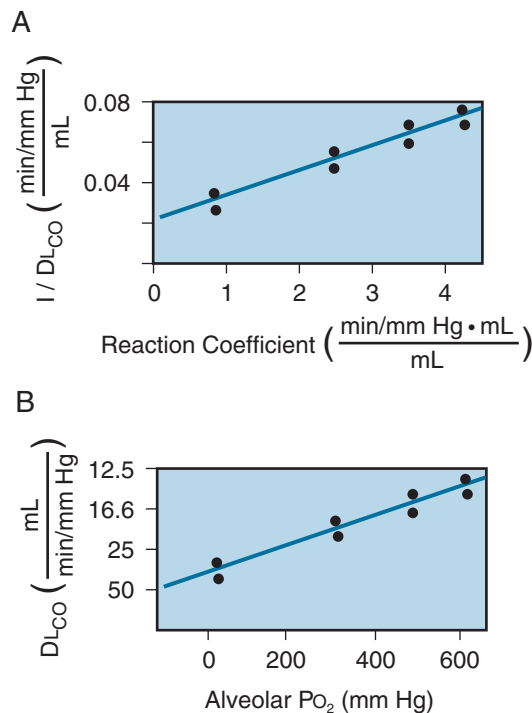


Figure 25-11 Subdivisions of the DL_{CO} . Experimental values of the diffusing capacity for carbon monoxide (DL_{CO}) obtained at different alveolar PO_2 values (x-axis in **B**) can be analyzed mathematically to obtain the subdivisions of total DL_{CO} : the diffusing capacity of the membrane (DM) and pulmonary capillary blood volume (VC). As the alveolar PO_2 was increased from 40 mm Hg to 600 mm Hg, the duplicate measurements of DL_{CO} decreased from approximately 45 to 15 mL/min per mm Hg. Changing alveolar PO_2 changes the reaction coefficient (θ), reflecting the change in hemoglobin affinity for carbon monoxide. The reaction coefficient is plotted against $1/DL_{CO}$ in **A**. There is a linear relationship between $1/DL_{CO}$ and $1/\theta$ such that $1/DL_{CO} = 1/\theta VC + 1/DM$. Under these conditions, DM is derived from the value of the y-intercept and VC from the slope of the line.

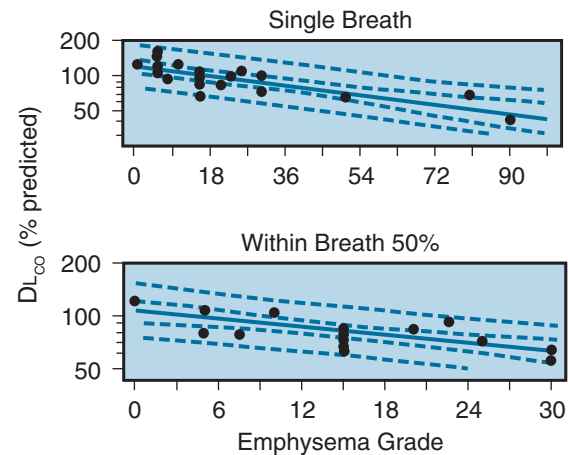
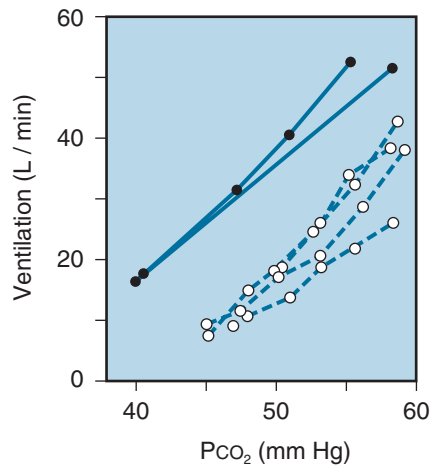
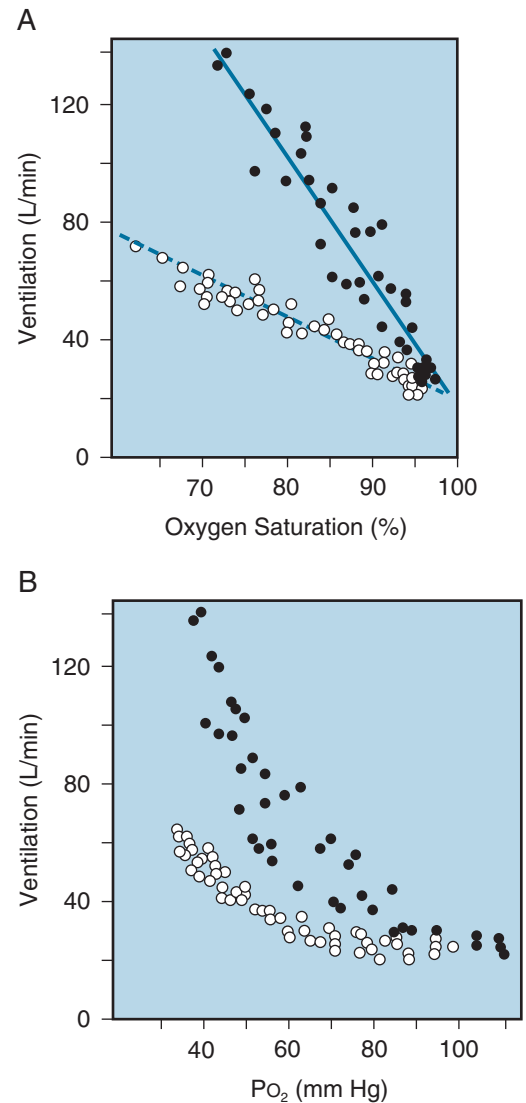


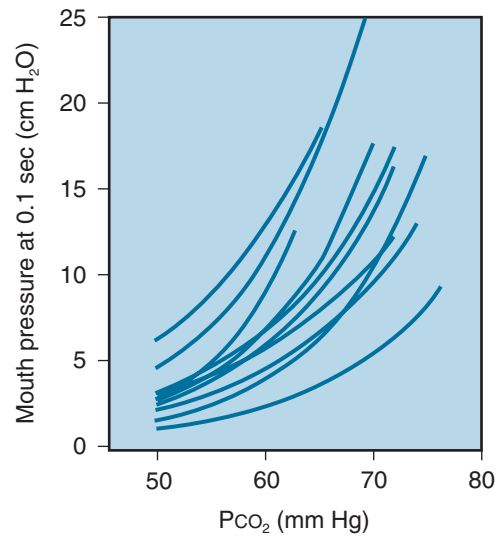
Figure 25-12 Correlation between diffusing capacity for carbon monoxide (DL_{CO}) and emphysema grade. *Top*, The single-breath DL_{CO} , expressed as the percentage of predicted normal, is displayed on the ordinate. Emphysema grade is displayed on the abscissa and was determined by the panel grading method on lung tissue resected from these patients within 1 week of pulmonary function testing. The *solid line* is the line of best fit ($r = -0.73$), the *outer dashed lines* show the 95% confidence limits for the points, and the *inner dashed lines* show the 95% confidence limits for the line. The single-breath DL_{CO} correlates with the presence and amount of emphysema except when emphysema is mild (grades 0 to 30); when single-breath DL_{CO} was plotted against emphysema for patients with minimal disease (grades 0 to 30), there was no significant correlation. *Bottom*, The intrabreath DL_{CO} , expressed as the log of the percentage of predicted normal at 50% exhaled vital capacity, is displayed on the ordinate. Emphysema grade is displayed on the abscissa and was determined by the panel grading method on lung tissue resected from these patients within 1 week of pulmonary function testing. The *solid line* is the line of best fit ($r = -0.77$), the *outer dashed lines* show the 95% confidence limits for the points, and the *inner dashed lines* show the 95% confidence limits for the line. Thus the intrabreath DL_{CO} correlates with the presence and amount of emphysema even when emphysema is mild (grades 0 to 30) and cannot be detected or quantified by the single-breath method.



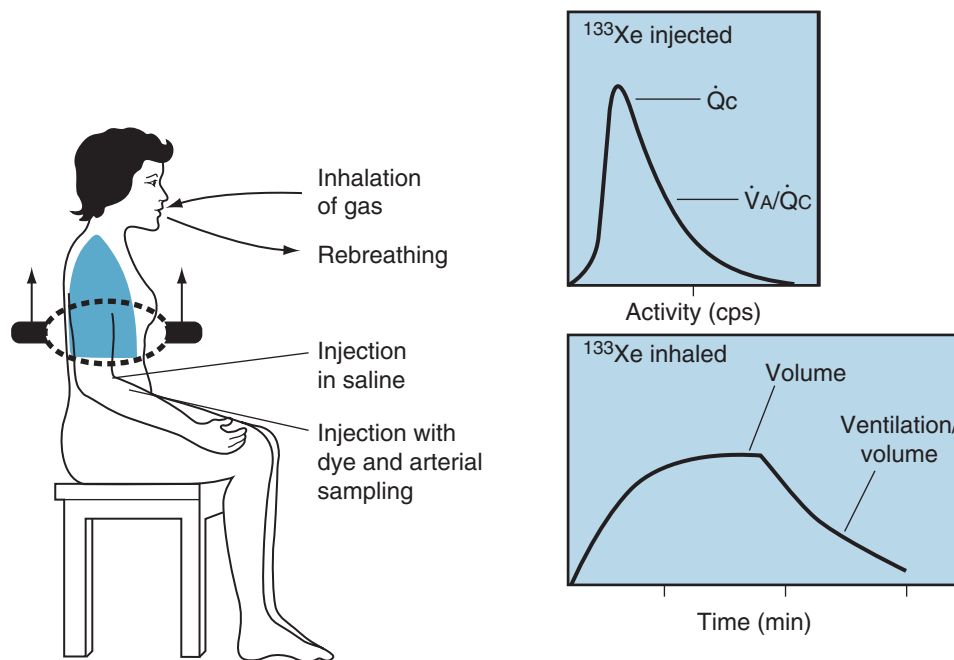
eFigure 25-13 Comparison of rebreathing and steady-state hypercapnic response curves. Response lines defined by the steady-state method (solid symbols) and by the rebreathing method (open symbols) are shown for two experiments on the same subject. In one experiment, the steady-state points were defined by inhalation of each of four carbon dioxide mixtures for 20 minutes without intervening periods of air breathing. In the other experiment, the steady-state points were defined by inhalation of each carbon dioxide mixture for 30 minutes, with an intervening rest period of 30 minutes. The figure illustrates a difference in position of the response lines due to a smaller PCO_2 gradient between arterial blood and chemoreceptor tissue during the rebreathing method. The close agreement in slope implies that the ratio of change in end-tidal PCO_2 to change in chemoreceptor PCO_2 is the same in the two methods. (Modified from Read DJC: A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med* 16:20–32, 1967.)



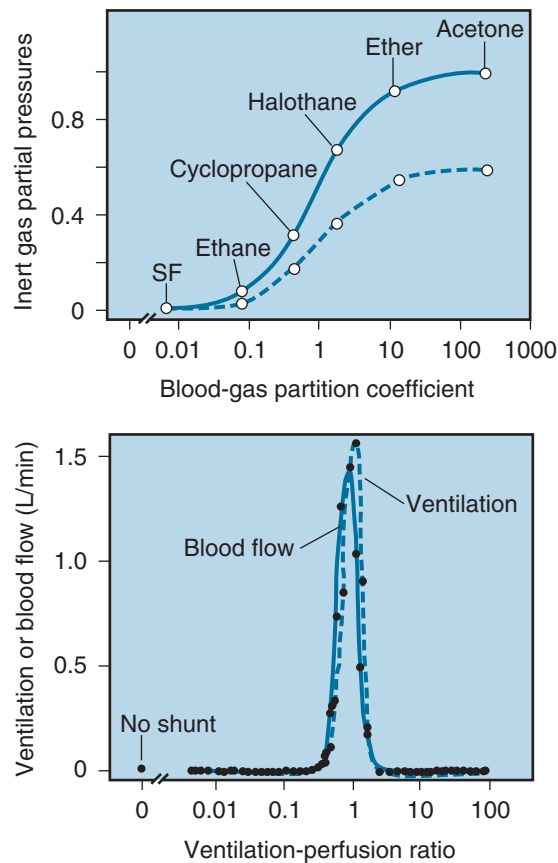
eFigure 25-14 Hypoxic response curves, representing pooled results of four studies in two subjects. **A**, Ventilation is plotted against oxygen saturation, producing linear responses. **B**, The more traditional hyperbolic relationship is obtained by plotting ventilation against alveolar PO_2 . (Modified from Rebuck AS, Campbell EJM: A clinical method for assessing the ventilatory response to hypoxia. *Am Rev Respir Dis* 109:345–350, 1974.)



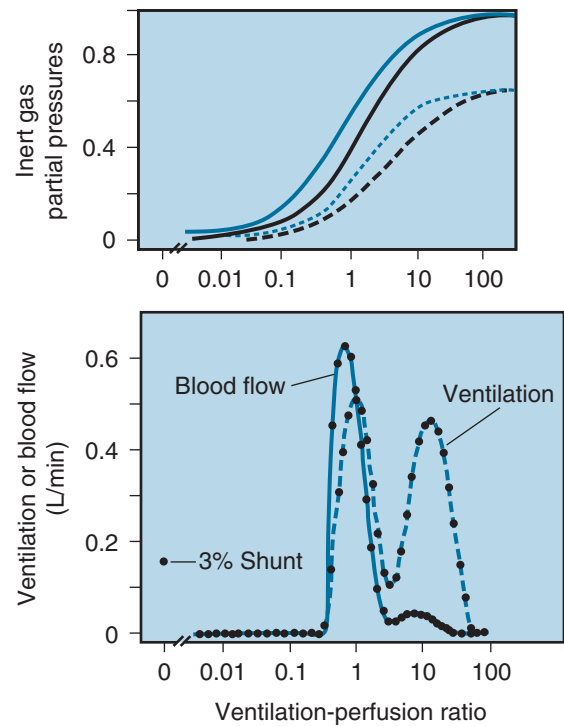
eFigure 25-15 Inspiratory occlusion pressure at 100 msec (0.1 second) in response to hypercapnia. Each curve is the mean regression of mouth pressure at 0.1 second against PCO_2 for one subject. Inspiratory occlusion pressure may be used to measure the output of the respiratory center in response not only to hypercapnia, but also to hypoxia, exercise, and other factors. (Modified from Whitelaw WA, Derenne J, Milic-Emili J: Occlusion pressure as a measure of respiratory center output in conscious man. *Respir Physiol* 23:181–199, 1975.)



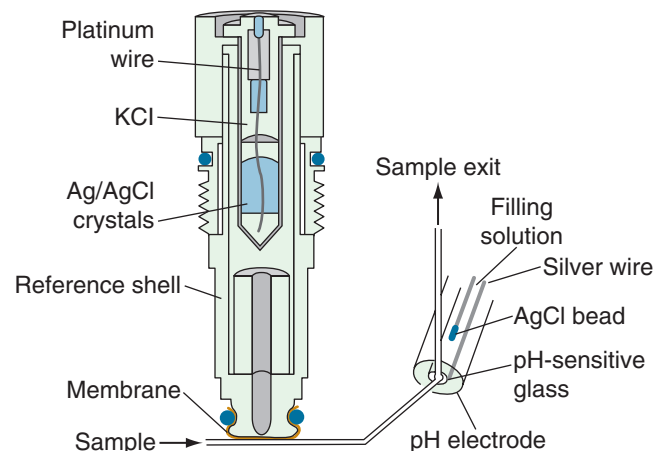
eFigure 25-16 Assessment of regional lung function using xenon-133 (^{133}Xe). *Top*, After injection, the initial peak reflects the regional blood flow (\dot{Q}_c); the isotope then passes into the gas phase, in which the clearance during normal breathing reflects the ventilation of lung tissue that is perfused. A slow washout indicates a low ventilation-perfusion ratio (\dot{V}_A/\dot{Q}_c). *Bottom*, During rebreathing, the plateau count rate when mixing is complete reflects the volume of lung gas in the field of counting. The slopes of the wash-in and washout curves indicate the ventilation per unit volume. (Modified from Cotes JE: *Lung function*, ed 4, Oxford, 1979, Blackwell Scientific.)



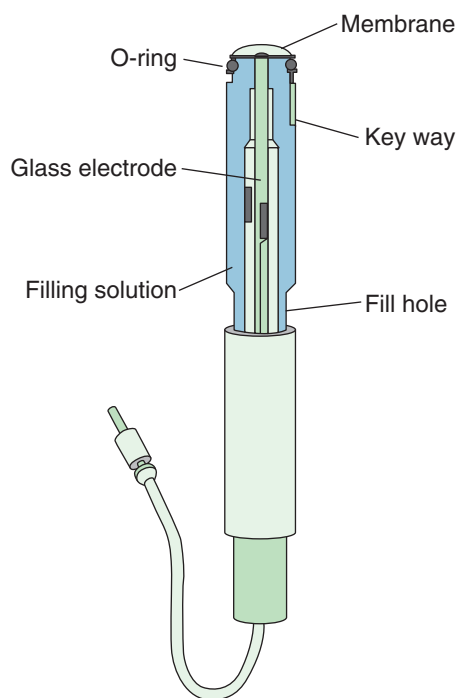
eFigure 25-17 Distribution of ventilation-perfusion ratios in a normal person. *Top*, The retention (arterial/venous, *solid line*) and excretion (expired/venous, *dashed line*) data points together with the curves for a homogeneous lung. *Bottom*, Continuous distribution of ventilation-perfusion ratios as found in a semirecumbent young (22-year-old) normal subject by means of the inert gas elimination method. Note the narrow dispersion and the absence of shunt. The *dashed line* indicates ventilation, and the *solid line* indicates blood flow. SF, sulfur hexafluoride. (Modified from West JB: *Ventilation/blood flow and gas exchange*, ed 3, Oxford, 1977, Blackwell Scientific.)



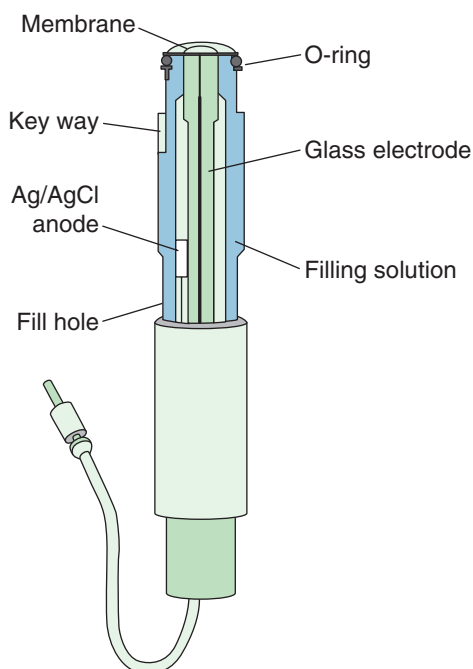
eFigure 25-18 Distribution of ventilation-perfusion ratios in a COPD patient. *Top*, Retention and excretion-solubility curves. *Black lines* indicate data from the patient; *blue lines* indicate data from the normal subject depicted in eFigure 25-17. *Bottom*, Continuous distribution of ventilation-perfusion ratios in a 60-year-old patient with chronic airway obstruction, predominantly emphysema. The *dashed line* indicates ventilation and the *solid line* indicates blood flow. Note the broad bimodal distribution with the large amount of ventilation going to lung units with very high ventilation-perfusion ratios. (Modified from West JB: *Ventilation/blood flow and gas exchange*, ed 3, Oxford, 1977, Blackwell Scientific.)



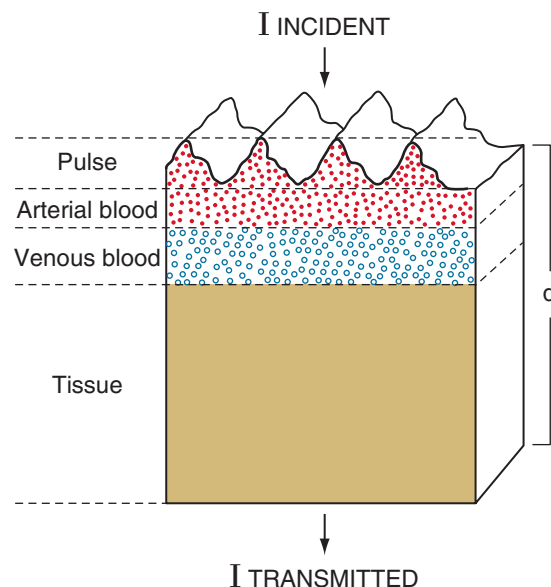
eFigure 25-19 The structure of a pH electrode, which comprises two cells. The measurement half-cell consists of a fine capillary tube of pH-sensitive glass separating the introduced sample of 25 μ L from the buffered solution and a silver/silver chloride (Ag/AgCl) electrode to conduct the generated potential difference to the electronic circuitry. The reference half-cell usually contains a calomel (mercury/mercurous chloride) electrode in an electrolyte solution to provide a constant reference voltage and is connected to the measurement half-cell by a contact bridge to complete the circuit. Both cells are enclosed in a sealed jacket and maintained at a constant temperature. KCl, potassium chloride.



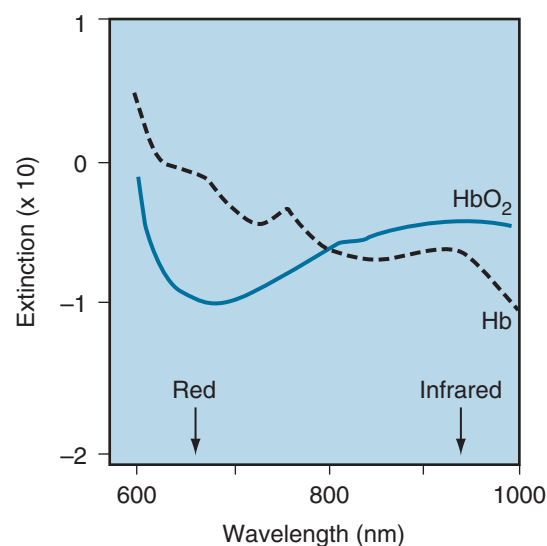
eFigure 25-20 The structure of a carbon dioxide electrode. This electrode uses the combination of the relationship between PCO_2 and pH in a buffered solution and the design of a pH electrode. The sample is separated from a buffer solution by a membrane permeable to carbon dioxide. The carbon dioxide molecules diffuse through the membrane, altering the concentration of carbonic acid, and therefore the hydrogen ion concentration in the buffered solution. The change in pH is read by a pH meter with output scaled in terms of PCO_2 .



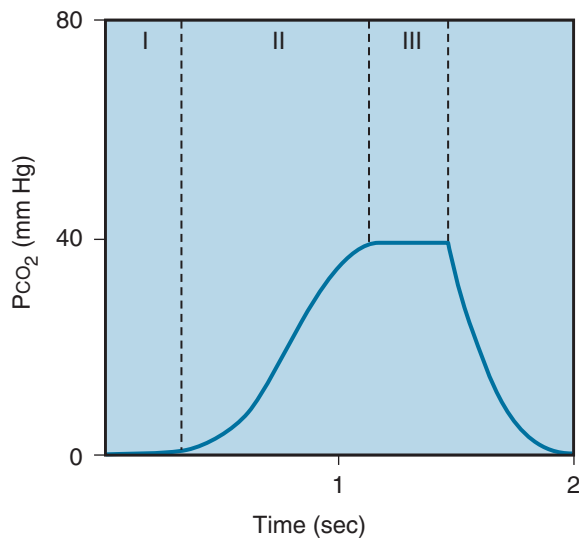
eFigure 25-21 The structure of an oxygen electrode. This electrode consists of platinum and silver electrodes placed in potassium chloride solutions, a polarizing voltage of 0.5 to 0.6 volts, and an electrolyte bridge to complete the circuit. Oxidation at the silver (Ag) electrode secondary to silver reacting with chloride ions to form silver chloride (AgCl) produces electrons that are consumed at the platinum electrode by reduction of oxygen. The flow of electrons (the current) is thus proportional to the concentration of oxygen at the platinum electrode.



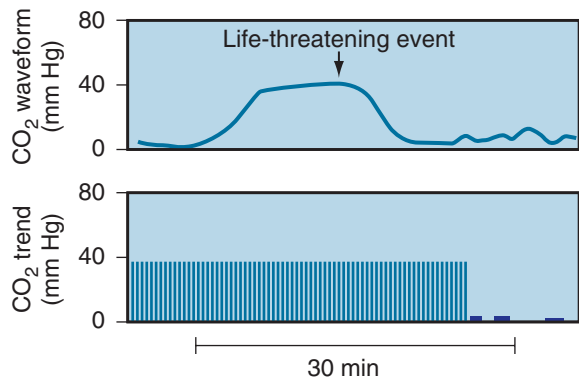
eFigure 25-22 Factors influencing detection by pulse oximetry of light absorption through a pulsatile vascular bed. Solid circles represent light absorption by hemoglobin in arterial blood and by the pulse of arterial blood; open circles represent light absorption by hemoglobin in venous blood; shaded zone represents absorption by tissue that absorbs incident light. d , distance through tissue that absorbs incident light.



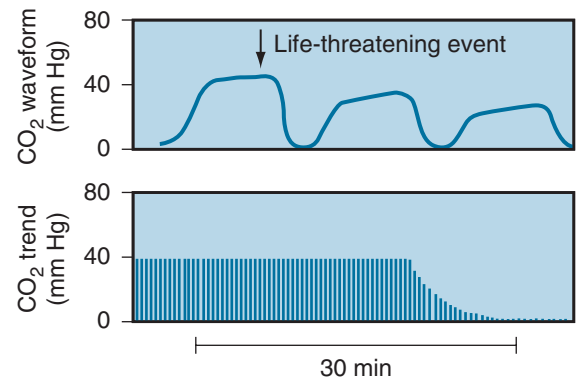
eFigure 25-23 Absorption spectrum of reduced hemoglobin (Hb) and oxyhemoglobin (HbO₂). Readings are made at 660 nm (red) and 940 nm (infrared) wavelengths.



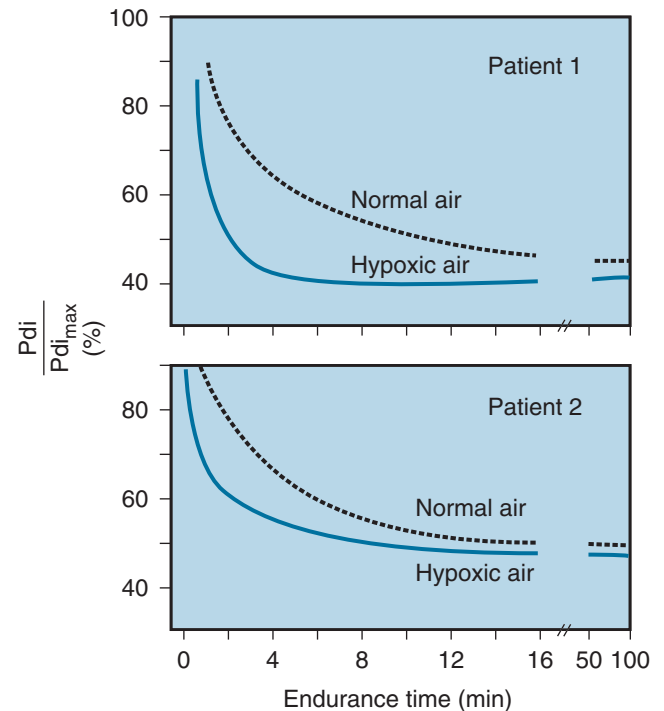
eFigure 25-24 Normal capnogram. During inspiration, PCO_2 is zero. At the start of exhalation, PCO_2 remains zero as gas from the anatomic dead space leaves the airway (comparable to phase I in the single-breath nitrogen washout test). Next, PCO_2 rises rapidly as alveolar gas mixes with gas from the dead space (comparable to phase II in the single-breath nitrogen washout test), and then the PCO_2 level stabilizes as gas from the dead space decreases and all the gas comes from alveoli containing carbon dioxide. The PCO_2 at the end of the “alveolar plateau” is called the end-tidal PCO_2 (comparable to phase III in the single-breath nitrogen washout test).



eFigure 25-25 Abnormal capnogram. The sudden decrease in end-tidal PCO_2 suggests a life-threatening situation in which the capnograph no longer detects carbon dioxide in the exhaled gas. This capnogram suggests the possibility of esophageal intubation, obstructed endotracheal tube, disconnected airway, or ventilator malfunction; these possibilities must be excluded before it can be assumed that the capnograph is malfunctioning.



eFigure 25-26 Abnormal capnogram with an exponential decrease in end-tidal PCO_2 . Note the progressively more sloping alveolar plateau, reflecting not only abnormal distribution of ventilation but also uneven perfusion relative to ventilation. This pattern suggests a potential life-threatening situation such as cardiac arrest, severe pulmonary hypoperfusion, or pulmonary embolism, as discussed in the text.



eFigure 25-27 Diaphragmatic endurance in two patients in normal and hypoxic conditions. The relationship between endurance and transdiaphragmatic pressure (Pdi) is expressed as a percentage of maximal transdiaphragmatic pressure (Pdi_{max}). Data from two patients breathing normal and hypoxic air are shown. Added resistance leads to an increased $\text{Pdi}/\text{Pdi}_{\text{max}}$ ratio and increases the work of breathing. As the $\text{Pdi}/\text{Pdi}_{\text{max}}$ ratio increases, endurance rapidly decreases. This effect is more pronounced when the respiratory muscles are hypoxic. (Modified from Roussos CS, Macklem PT: Diaphragmatic fatigue in man. *J Appl Physiol* 43:189–197, 1977.)

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INTRODUCTION**PHYSIOLOGIC RESPONSES TO EXERCISE**

Exercise as a Multisystem Process
Normal Individuals
Individuals with Underlying
Cardiopulmonary Disease

CARDIOPULMONARY EXERCISE TESTING

Indications and Contraindications
Safety Considerations and
Contraindications to Cpet
Conducting Exercise Tests

Interpreting Cardiopulmonary Exercise Tests

Alternative Methods of Assessing Exercise Performance

INTRODUCTION

Sustained exercise requires tight integration of multiple physiologic systems including the cardiac, neuromuscular, and respiratory systems. Diseases affecting any of these systems can manifest as dyspnea or exercise limitation. In addition to other modalities commonly used in the assessment of patients with these complaints, *cardiopulmonary exercise testing* (CPET) provides a systematic means to assess exercise responses, unravel the different interacting components, and understand which system is contributing the most to the perceived limitation. Beyond this primary role, CPET has other important uses including (1) quantifying maximal exercise capacity and generating data that can be used to assess functional limitation, (2) prescribing appropriate rehabilitation and training regimens, and (3) guiding clinical decisions about fitness for planned procedures.

The goals of this chapter are to describe the application of CPET in clinical practice and assist the reader in understanding who would benefit from CPET and how it can be used to evaluate dyspnea and exercise limitation. Because CPET interpretation requires a solid understanding of the physiologic responses to exercise, the chapter begins with a review of exercise physiology that sets the foundation for the balance of the chapter. The review includes exercise responses in normal individuals and those with various forms of cardiopulmonary disease, including heart failure, *chronic obstructive pulmonary disease* (COPD), pulmonary vascular disease, *interstitial lung diseases* (ILDs), and adult congenital heart disease. The chapter then describes the primary indications and contraindications of CPET, reviews the various options for conducting exercise tests, and presents an approach to test interpretation. It concludes by describing alternative modalities for assessing exercise responses that are used in clinical practice.

PHYSIOLOGIC RESPONSES TO EXERCISE**EXERCISE AS A MULTISYSTEM PROCESS**

The ability to perform vigorous aerobic exercise requires tight integration of multiple systems. The respiratory

system serves as a ventilatory pump to move *oxygen* (O_2) from the atmosphere to the alveoli, where it efficiently moves across the alveolar walls to bind to hemoglobin. The heart must then pump the oxygenated blood to the exercising muscles, which extract oxygen to support adenosine triphosphate generation and muscle contraction. Muscle activity leads to production of *carbon dioxide* (CO_2), which must be delivered by the circulatory system to the lungs, where it diffuses across the alveolar walls and is eliminated via the ventilatory pump. The nervous system contributes at multiple stages in this process, providing important signals to increase ventilation and drive muscular contraction. All of these systems work in a highly coordinated manner to support exercise, and problems in one or more of these systems may manifest as dyspnea or exercise limitation.

NORMAL INDIVIDUALS

To appreciate changes in exercise performance associated with cardiopulmonary diseases, it is helpful to examine the normal physiologic responses to progressive exercise in four major areas—metabolic activity, hemodynamic responses, ventilatory responses, and gas exchange.

Metabolic Activity

Oxygen Consumption. Of all the parameters followed in clinical exercise testing, oxygen consumption, denoted as $\dot{V}O_2$ (a volume per time, e.g., mL/min), is perhaps the most useful for assessing overall exercise capacity. In essence, $\dot{V}O_2$ is the amount of fuel consumed in conducting work; the bigger or better the motor, the greater the maximum fuel consumption. To understand its utility in this regard, consider the determinants of $\dot{V}O_2$ using the Fick equation:

$$\dot{Q} = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2} \quad (1)$$

where \dot{Q} = cardiac output (mL/min), CaO_2 = arterial oxygen content (mL/dL), and $C\bar{v}O_2$ = mixed venous oxygen content (mL/dL). Rearranging the relationship as follows,

$$\dot{V}O_2 = \dot{Q}(CaO_2 - C\bar{v}O_2) \quad (2)$$

demonstrates that oxygen consumption is dependent on cardiac output; oxygen content, which is related to the

amount of hemoglobin and the partial pressure of oxygen; and the ability of the tissues to utilize oxygen. As a result, $\dot{V}O_2$ provides useful information about many of the systems necessary to perform sustained high-level exercise.

In addition to providing a sense of overall exercise capacity, the *maximum oxygen consumption* ($\dot{V}O_{2\max}$) achieved during progressive exercise is particularly useful for assessing cardiac function. Given that the arteriovenous oxygen content difference at maximum exercise is largely the same in normal individuals and those with cardiac disease,¹ the wide variation in $\dot{V}O_{2\max}$ across individuals is primarily determined by the variation in cardiac output. The greater the $\dot{V}O_{2\max}$, the greater an individual's cardiac output and vice versa.

Oxygen consumption can also be used to estimate stroke volume at maximum exercise. To understand this, [equation \(2\)](#) can be rewritten:

$$\dot{V}O_2 = HR \times SV(CaO_2 - C\bar{v}O_2) \quad (3)$$

and then rearranged as:

$$\frac{\dot{V}O_2}{HR} = SV \times (CaO_2 - C\bar{v}O_2) \quad (4)$$

The constancy of the arteriovenous oxygen content difference across normal individuals at maximum exercise means that the term $\dot{V}O_2/HR$, referred to as the *oxygen pulse* or *O₂ pulse*, can be used as a surrogate marker for stroke volume. The expected changes in normal individuals for this parameter, as well as cardiac output, are described as follows.

During progressive exercise to a symptom-limited maximum, $\dot{V}O_2$ increases linearly from resting values near 250 mL/min for an average-sized person until a plateau is reached at $\dot{V}O_{2\max}$. If a plateau is not identified, the term $\dot{V}O_{2\text{peak}}$ is often applied instead to denote that it may not represent the individual's potential maximum. In average sedentary individuals, $\dot{V}O_{2\max}$ is roughly 30 to 40 mL/kg/min at end-exercise, whereas fit athletes can attain values as high as 80 to 90 mL/kg/min. An individual's $\dot{V}O_{2\max}$ is influenced by a variety of factors including age and gender, which are discussed further later. With intensive training, unfit subjects can increase $\dot{V}O_{2\max}$ by 15% to 25%,^{2,3} but it is not possible to raise $\dot{V}O_{2\max}$ from an average level to an elite level. What tends to improve with training is the efficiency of work and ability to sustain high levels of power output. Genetic factors also play an important role in determining an individual's $\dot{V}O_{2\max}$ in the sedentary state,⁴ as well as in their response to training regimens.⁵ In clinical exercise testing, an individual's $\dot{V}O_{2\max}$ is typically expressed in reference to what would be predicted for their age and gender on the basis of data from large population studies. Numerous reference values have been published, but methodologic issues limit the wide applicability of many of them.⁶ As with all reference values, the normal range is dependent on the population studied. For example, Hansen and colleagues⁷ used studies from ex-shipyards workers who tended to be primarily older men while Nader and colleagues⁸ randomly selected their subjects to include equal numbers of men and women uniformly drawn across ages 20 to 80.

Carbon Dioxide Output. With increasing work, *carbon dioxide output* ($\dot{V}CO_2$) increases linearly from resting values,

which are near 200 mL/min for an average-size person, at about the same rate as oxygen consumption. Above the ventilatory threshold, an important exercise time point described further later, the rate of $\dot{V}CO_2$ output steepens as bicarbonate buffering of increasing lactate production leads to $\dot{V}CO_2$ production beyond that generated by aerobic metabolism.⁶

Respiratory Exchange Ratio. Defined as $\dot{V}CO_2/\dot{V}O_2$, the respiratory exchange *ratio* (R) remains largely stable between 0.8 and 0.9 in early to mid-exercise, with slight variation between individuals depending on the balance of dietary fats and carbohydrates. Just before and in the early stages of exercise, R can transiently increase due to anticipatory hyperventilation. Above the ventilatory threshold, $\dot{V}CO_2$ increases markedly and R increases above 1.0. With cessation of exercise, $\dot{V}O_2$ decreases abruptly while $\dot{V}CO_2$ remains elevated as tissue CO_2 stores continue to be eliminated. R can subsequently increase over 1 to 2 minutes to values as high as 1.3 to 1.5 before returning to baseline levels.

Ventilatory Thresholds. Normal individuals demonstrate a phenomenon termed the ventilatory threshold at about 50% to 60% of the $\dot{V}O_{2\max}$, although there is considerable interindividual variability in the timing of this phenomenon.^{6,9} This threshold marks a critical point in progressive exercise where blood flow to the exercising muscle is no longer sufficient to meet metabolic demands and the individual is transitioning from light-moderate to moderate-high-intensity exercise.¹⁰ Alternatively referred to as the *lactate threshold*, *gas exchange threshold*, or *anaerobic threshold*, the phenomenon is temporally related to an increase in lactic acid production and a decrease in pH, with considerable debate regarding the mechanisms for the increased lactate production^{11,12} and whether it happens suddenly or in a more continuous manner throughout exercise.¹³⁻¹⁵ As lactic acid dissociates, hydrogen ions are buffered by intracellular bicarbonate leading to further CO_2 generation beyond that associated with aerobic metabolism.^{10,16} This leads to a steep rise in the $\dot{V}CO_2$ versus work relationship, as well as the $\dot{V}CO_2$ versus $\dot{V}O_2$ relationship ([Fig. 26-1](#)). Identifying the change in slope of the latter relationship is referred to as the *V-slope method* and is a key step in CPET interpretation described later in this chapter.

With further increases in work beyond the ventilatory threshold, many individuals demonstrate a second ventilatory threshold, sometimes referred to as the *respiratory compensation point*, at which rising lactate concentrations cannot be buffered by intracellular bicarbonate, and *minute ventilation* ($\dot{V}E$) increases beyond that expected for the increase in $\dot{V}CO_2$, thereby leading to a respiratory alkalosis.^{10,16} This point, which may not be visible in all individuals due to interindividual variation in ventilatory responses to metabolic acidosis, can be identified by finding threshold responses in several ventilatory parameters described further later.

Further information on how to identify various thresholds is provided in "Interpreting Cardiopulmonary Exercise Tests" later.

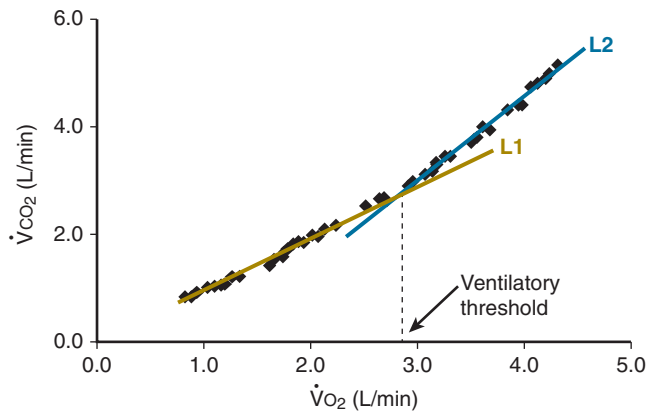


Figure 26-1 The “V-slope” method for identifying the first ventilatory threshold. Before the threshold, oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) rise at the same rate. A best-fit line through these points is labeled L1 and is denoted in brown. After the threshold, $\dot{V}CO_2$ rises faster than $\dot{V}O_2$. A best-fit line through these points is labeled L2 and is denoted in blue. The point at which the two lines intersect denotes the $\dot{V}O_2$ at which the ventilatory threshold is reached.

Hemodynamic Responses

Cardiac Output. Cardiac output (mL/min), which can be either estimated from oxygen uptake using the Fick principle, measured invasively with a pulmonary artery catheter, or estimated noninvasively using inert gas rebreathing techniques,¹⁷ increases linearly with workload before reaching a plateau near peak exercise. The initial increase is a function of increasing stroke volume and heart rate, whereas the changes seen near peak exercise are driven primarily by increases in heart rate.¹⁸

Heart Rate. Due initially to decreased vagal tone and later to increases in sympathetic activity, heart rate (beats/min) increases linearly with increasing oxygen consumption. The heart rate reserve, defined as the difference between the maximum predicted heart rate and the heart rate achieved at peak exercise, is typically small or nonexistent in normal individuals (<20 beats/min), but this parameter is difficult to use in exercise test interpretation due to significant variability in maximum heart rates in normal age-matched individuals.^{6,19} Another measure of heart rate response, also termed the *heart rate reserve*, is the difference between the resting and maximal heart rate. This review uses the former definition.

Pulmonary Artery Pressure. Pulmonary artery pressure rises only modestly with progressive exercise in normal individuals, due to recruitment and distention of the pulmonary vasculature and the subsequent decrease in pulmonary vascular resistance. There is interindividual variability in observed responses,²⁰ with greater variability seen in older individuals.²¹ (For physiologic implications of pulmonary vascular recruitment see Chapter 4).

Stroke Volume. Characterized during CPET by the O_2 pulse (described earlier), stroke volume increases in early exercise before leveling off and possibly decreasing slightly at high levels of exercise.¹⁸ The initial increases are driven largely by mobilization of blood from lower extremity

venous capacitance vessels, whereas later, smaller increases result from increased inotropic activity.

Systemic Blood Pressure. Due to increases in cardiac output and vascular resistance in the skin and renal and splanchnic circulations, systemic blood pressure (mm Hg) increases with progressive exercise. Although vasodilation in exercising muscle beds limits the rise in diastolic pressure, systolic pressure rises significantly, particularly following the ventilatory threshold, and may reach values over 200 mm Hg at peak exercise.

Ventilatory Responses

Minute Ventilation. Due to an increase in both the respiratory rate and tidal volume, *minute ventilation* (\dot{V}_E , mL/min) rises throughout exercise with large increases seen following the ventilatory threshold. The tidal volume plateaus at about 50% to 60% of vital capacity, after which further increases in \dot{V}_E are driven solely by increases in respiratory rate.^{22,23} At peak exercise, \dot{V}_E is typically less than 80% of the predicted maximum, as estimated by the *maximum voluntary ventilation* (MVV) or *forced expiratory volume in 1 second* ($FEV_{1\text{ s}}$) $\times 40$.²⁴

Ventilatory Equivalents for Oxygen and Carbon Dioxide. The ventilatory response can be expressed as a function of the amount of ventilation per liter of oxygen consumed ($\dot{V}_E/\dot{V}O_2$, unitless) or per liter of exhaled carbon dioxide ($\dot{V}_E/\dot{V}CO_2$, unitless). Both ratios remain relatively steady (~24 to 30) through early exercise as ventilation rises proportionately with $\dot{V}O_2$ and $\dot{V}CO_2$. Due to the large increases in \dot{V}_E noted earlier, both parameters rise following the ventilatory threshold, peaking at around 35 to 40, with slightly greater increases seen in the $\dot{V}_E/\dot{V}O_2$.⁶ Both parameters may be elevated in early exercise in highly fit or anxious individuals but typically return to the normal range as exercise progresses and reach their nadir just before the ventilatory threshold. The range of ventilatory equivalents seen across normal individuals reflects the variability in respiratory drives in the population.

Dead Space Fraction. Because of increased tidal volumes and recruitment of the pulmonary vasculature resulting from increased pulmonary blood flow, the dead space fraction (V_D/V_T , unitless) normally decreases from 0.3 to 0.4 at rest to less than 0.2 at peak exercise, with the lowest values seen in younger individuals.⁶

Gas Exchange

Arterial and End-Tidal Partial Pressures of Carbon Dioxide. Despite increasing $\dot{V}CO_2$, the *arterial* (P_{aCO_2} , mm Hg) and *end-tidal partial pressure* (P_{ETCO_2} , mm Hg) of carbon dioxide remain near normal through early exercise due to the fact that alveolar ventilation rises proportionally with increasing $\dot{V}CO_2$. Low values may be seen in normal individuals who hyperventilate at the start of exercise, but these values typically normalize over the first few minutes of work. Following the ventilatory threshold, minute and alveolar ventilation rise out of proportion to the increase in $\dot{V}CO_2$ and, as a result, both arterial P_{CO_2} and P_{ETCO_2} decrease so that both values are nearly always less than 40 mm Hg at $\dot{V}O_{2\text{ max}}$.²⁵

Arterial and End-Tidal Partial Pressures of Oxygen and the Alveolar-Arterial Oxygen Difference. Below the ventilatory threshold, both the *end-tidal partial pressure of oxygen* (P_{ETO_2} , mm Hg), which is used as a surrogate measure of alveolar oxygen tensions, and the arterial (PO_2 , mm Hg) remain in the normal range, as do both the *arterial oxygen saturation* (SaO_2 , %) and the *alveolar-arterial oxygen difference* ($(A-a)PO_2$, mm Hg). As normal individuals pass their ventilatory threshold and approach maximum exercise, P_{ETO_2} increases due to alveolar ventilation that increases out of proportion to $\dot{V}O_2$.

While the alveolar PO_2 increases, the arterial PO_2 remains unchanged due to a lower $\dot{C}\bar{V}O_2$ and normal physiologic shunting. As a result, the $(A-a)PO_2$ increases slightly with heavy exercise. In a minority of highly fit individuals with high $\dot{V}O_{2max}$, arterial PO_2 and arterial SO_2 can decline in late exercise, a phenomenon referred to as *exercise-induced arterial hypoxemia*.^{26,27}

In CPET, the changes in many of the parameters described earlier can be identified from tabular data but are often best appreciated graphically using an approach developed by Wasserman and colleagues²⁸ in which nine separate graphs are displayed in a standardized format. The exercise responses in normal individuals described earlier are depicted in this manner in [Figure 26-2](#).

Changes with Age

Perhaps the most important change in exercise responses with aging is the decrease in maximum exercise capacity, which has been consistently reported in both cross-sectional^{29,30} and longitudinal studies.^{31,32} The expected rate of decline in $\dot{V}O_{2max}$ is unclear because documented rates vary from as low as 0.28 mL/kg/min/yr³¹ to as high as 1.04 mL/kg/min/yr,³³ with much of the variation attributable to differences in study design such as participant age, activity levels at the time of enrollment, and time intervals over which the study took place.³² Although some studies demonstrate a slower rate of decline in active individuals compared with sedentary individuals,³¹ others³⁴ have reported no effect of activity level on age-related declines in $\dot{V}O_{2max}$. Training programs in older sedentary individuals may be able to reverse much of the age-related decline in $\dot{V}O_{2max}$,³⁵ which accelerates in the later stages of life.³⁶

The etiology of the decrease in $\dot{V}O_{2max}$ varies depending on the time period examined. Between 20 and 50 years of age the decline in $\dot{V}O_{2max}$ is largely attributable to impaired peripheral oxygen extraction,³² whereas later changes relate to impaired peripheral extraction and decrements in maximum cardiac output due to an inability to raise stroke volume at maximum exercise.³⁷ Impairment in peripheral extraction may be due to decreases in lean body mass, age-related changes in skeletal muscle, or blood flow distribution at peak-exercise³²; the decline in cardiac output may represent the increasing incidence of comorbid conditions affecting cardiac performance.³⁷

Gender Differences

Comparisons of exercise responses in men and women are difficult because the majority of studies of physiologic responses to exercise have been performed in men. The available evidence shows that women have the same qualitative responses to exercise as men but have lower $\dot{V}O_{2max}$,

even after accounting for differences in lean body mass and training status.³⁸⁻⁴⁰ The mechanism for the observed differences remains unclear but may relate to differences in blood volume, heart size, hormonal and metabolic status, as well as autonomic nervous system regulation of the heart and vascular system.³⁸ Although some studies report slower age-related rates of decline in $\dot{V}O_{2max}$ in women compared with men, a recent large, cross-sectional study found no differences in this regard.³⁶

Ventilatory responses and gas exchange may also differ by gender, with some studies noting higher $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ in women^{36,39,41} and others reporting higher $(A-a)PO_2$ in fit women at high levels of oxygen consumption.⁴² At high exercise intensities, women may also rely more heavily than men on fat oxidation as a fuel source and, as a result, may have a lower respiratory exchange ratio.^{43,44}

Obesity

Obese individuals lacking underlying cardiac or pulmonary disease display $\dot{V}O_{2max}$ lower than predicted for age and gender when expressed per kilogram of actual body weight but normal values when adjusted for ideal body weight. Because of the increased metabolic requirements resulting from their increased weight, however, several important differences are observed relative to nonobese individuals. $\dot{V}O_2$ for any given level of work is higher than in the nonobese, although the *rate of change in oxygen consumption per given change in work rate* ($\Delta\dot{V}O_2/\Delta WR$) remains the same.^{45,46} Obese individuals also have markedly increased $\dot{V}O_2$ when pedaling without resistance (unloaded pedaling) due to the energy demands of moving heavier legs against gravity⁴⁷ that is not reflected in the work rate reported on the cycle ergometer.

Another consequence of the increased metabolic requirements is an increase in $\dot{V}E$ for a given work rate compared with the nonobese due to the added CO_2 production from the additional tissues.⁴⁵ This is typically achieved by increasing respiratory rate rather than tidal volume, which some data suggest is decreased during exercise relative to normal individuals,^{48,49} possibly due to the increased inspiratory load associated with extra chest wall soft tissue. Obese individuals also have difficulty decreasing end-expiratory lung volume during exercise, likely as a result of expiratory flow limitation and air trapping.^{49,50}

The presence and magnitude of observed differences in these parameters may be a function of the degree of obesity, with greater differences seen in heavier individuals. The presence or absence of comorbid conditions may also be important, as demonstrated by Vanhecke and colleagues,⁵¹ who showed that obese individuals (average body mass index 49 ± 9 kg/m²) with *obstructive sleep apnea* (OSA) have lower $\dot{V}O_{2max}$, increased systolic and diastolic blood pressure, and impaired heart rate recovery compared with obese patients lacking OSA.

INDIVIDUALS WITH UNDERLYING CARDIOPULMONARY DISEASE

The physiologic responses to exercise described earlier are altered by the presence of underlying cardiopulmonary disease with different responses seen depending on the particular disease process.

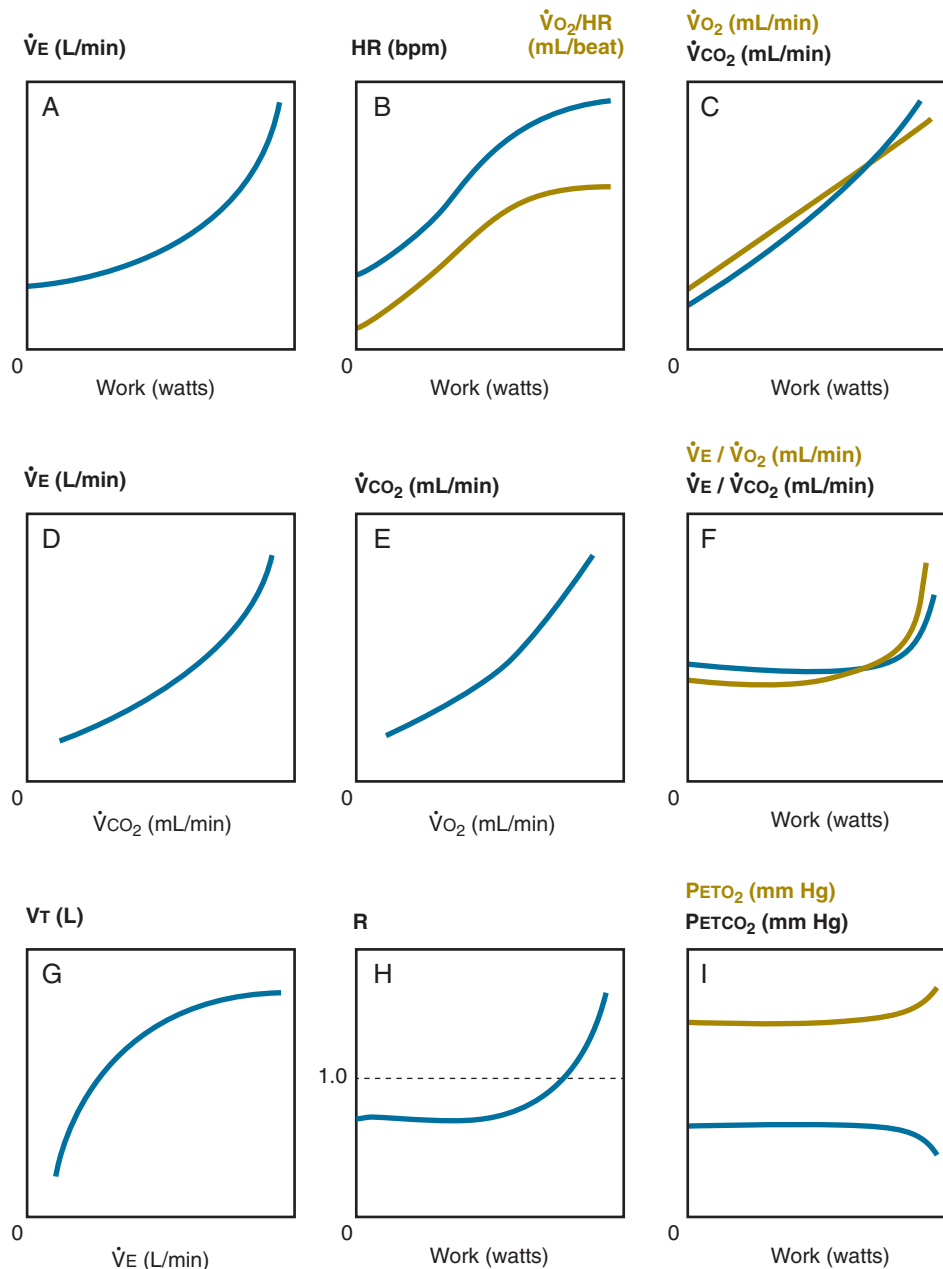


Figure 26-2 Nine-box plot displaying the expected responses to exercise in normal individuals. A, Minute ventilation (\dot{V}_E) versus watts; B, heart rate and oxygen pulse ($\dot{V}O_2/HR$) versus watts; C, oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) versus watts; D, \dot{V}_E versus $\dot{V}CO_2$; E, $\dot{V}CO_2$ versus $\dot{V}O_2$; F, ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and ventilatory equivalents for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) versus watts; G, tidal volume (V_T) versus \dot{V}_E ; H, respiratory exchange ratio (R) versus watts; I, end-tidal partial pressure of oxygen ($PETO_2$) and end-tidal partial pressure of carbon dioxide ($PETCO_2$) versus watts. Labels for the y-axis variables are presented on the top of each graph. Note that for the variables on the x- and y-axes the lowest values are in the lower left-hand corner of each plot. (Modified from Luks AM, Glenny RW, Robertson HT: Introduction to cardiopulmonary exercise testing. New York, 2013, Springer, Fig. 3-1.)

Heart Failure

As in normal individuals, maximum exercise in patients with heart failure is limited by the amount of blood that can be delivered to exercising muscle (i.e., they have a cardiac limitation to exercise). As a result, patients with heart failure demonstrate the same patterns of physiologic responses during progressive exercise to a symptom-limited maximum, albeit with significant differences in the magnitude of many of the observed responses.

The most important difference is the decrease in $\dot{V}O_{2max}$ and peak work rate relative to normal individuals. The

decrease in $\dot{V}O_{2max}$, which does not vary in magnitude between patients with systolic or diastolic dysfunction,^{52,53} results from an inability to raise cardiac output adequately due to impaired stroke volume responses with progressive exercise, denoted by the decreased $\dot{V}O_2/HR$. The ventilatory threshold is still usually reached at 50% to 60% of $\dot{V}O_{2max}$, but because $\dot{V}O_{2max}$ is decreased, the threshold is at a lower $\dot{V}O_2$ compared with normal individuals.

Many patients with heart failure compensate for the decreased stroke volume with an increase in heart rate for any given level of work. As a result, the heart rate reserve

at peak exercise is usually small (<20 beats/min). There is considerable variability in these responses, however, with some patients manifesting an inability to raise heart rate with progressive exercise, a phenomenon referred to as *chronotropic incompetence*, that persists even following discontinuation of β -blockers.⁵⁴ Patients with heart failure also may demonstrate an abnormal decline in heart rate on stopping exercise. In particular, heart rate recovery, which takes place as a result of reactivation of vagal tone⁵⁵ and is defined as the difference between peak heart rate and heart rate 1 minute into the recovery period, is decreased compared with normal individuals.

Altered ventilatory responses have also been described in patients with heart failure including increased airway resistance,⁵⁶ expiratory flow limitation at low work rates,⁵⁷ and an increased ventilatory reserve due to the fact that they are not able to do as much work and therefore do not require a high \dot{V}_E . Perhaps the most important difference, however, is the increased ventilatory inefficiency in patients with moderate to severe systolic or diastolic dysfunction, as indicated by an increased \dot{V}_E/\dot{V}_{CO_2} at the ventilatory threshold or an increased slope of the relationship between these parameters ($\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$).^{52,53} The most likely cause of this phenomenon is an increase in physiologic dead space due to impaired lung perfusion. Studies have shown, for example, that ventilatory inefficiency is related to abnormal pulmonary vascular tone⁵⁸ or right ventricular dysfunction⁵⁹ and actually improves following treatment with phosphodiesterase inhibitors and improvements in right ventricular function even when left ventricular function is unchanged.⁶⁰ Abnormal peripheral and central chemoreceptor sensitivity may also play a role in augmenting ventilation above that necessary for a given level of CO_2 production.⁶¹

Between 13% and 50% of patients with heart failure demonstrate another abnormal ventilatory response, referred to as *exercise oscillatory ventilation*, in which exercise ventilation is marked by periodicity similar to that seen in central sleep apnea.⁶²⁻⁶⁴ The mechanism for this is not clear but may relate to increased circulatory times, increased peripheral chemoreceptor sensitivity, increased ventilatory responses related to pulmonary congestion, and increased ergoreflex signaling (a peripheral reflex originating in skeletal muscle) related to muscle metabolic abnormalities.⁶⁴ Exercise oscillatory ventilation may be a marker of reduced cardiac index both at rest and during exercise⁶⁵ and may also improve following therapeutic interventions directed at the underlying heart failure such as treatment with sildenafil⁶⁶ or an exercise training program.⁶⁷ Despite these altered ventilatory responses, patients with heart failure have a normal (A-a)PO₂ and do not develop hypoxemia during exercise even though pulmonary artery occlusion pressure is elevated.^{68,69}

The pattern of exercise responses seen in patients with heart failure is displayed graphically in Figure 26-3.

Pulmonary Vascular Disease (for discussion of clinical aspects of pulmonary vascular disease, see Chapter 58)

In many respects, patients with pulmonary vascular diseases such as *pulmonary arterial hypertension* (PAH) and chronic thromboembolic pulmonary hypertension demonstrate physiologic responses to progressive exercise similar to those seen in patients with heart failure. Relative to

normal individuals, $\dot{V}_{O_{2max}}$, peak work rate and \dot{V}_{O_2}/HR are decreased while the ventilatory threshold is reached at a lower \dot{V}_{O_2} . Similar to patients with heart failure, the observed decline in $\dot{V}_{O_{2max}}$, which correlates inversely with mean pulmonary arterial pressure,⁷⁰ is due to an inability to raise cardiac output in response to exercise. The decreased cardiac output in patients with pulmonary hypertension exists because the right ventricle is unable to adequately preload the left ventricle due to high pulmonary vascular resistance.⁷¹ The fact that treatment with a pulmonary vasodilator such as sildenafil over a several-month period leads to improvements in both $\dot{V}_{O_{2max}}$ and \dot{V}_{O_2}/HR provides support for this concept.⁷²

These patients also demonstrate abnormal ventilatory responses including increases in \dot{V}_E/\dot{V}_{O_2} and \dot{V}_E/\dot{V}_{CO_2} ^{73,74} of greater magnitude than those seen in patients with heart failure of similar *New York Heart Association* (NYHA) functional class.⁷⁵ This ventilatory inefficiency can be attributed to increased physiologic dead space, as well as increased peripheral chemoreceptor stimulation from exercise-induced hypoxemia, and improves following several months of treatment with sildenafil.⁷² Depending on the extent of vascular occlusion and subsequent differences in physiologic dead space, the degree of ventilatory inefficiency, as measured by $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$, may vary in magnitude between classes of pulmonary vascular disease patients, with higher values seen in patients with chronic thromboembolic pulmonary hypertension compared with PAH.⁷⁶

Aside from these similarities, an important difference between heart failure and pulmonary vascular disease is seen in the pulmonary artery pressure responses. Unlike in normal individuals or patients with heart failure where pulmonary artery pressure rises only modestly with increasing exercise, pulmonary vascular disease patients experience large rises in their pulmonary artery pressure with increasing blood flow due to impaired recruitment and distention of the pulmonary vasculature.^{77,78}

Physiologic dead space also changes in a different manner. Whereas V_D/V_T decreases from 0.3 to 0.4 at rest to less than 0.2 at peak exercise in normal individuals and patients with heart failure, it decreases only mildly and may even increase in patients with pulmonary vascular disease.⁷⁹ For example, Zhai and colleagues⁷⁶ reported V_D/V_T of 0.42 ± 0.13 and 0.53 ± 0.08 at peak exercise in patients with PAH and chronic thromboembolic pulmonary hypertension, respectively. This response is abnormal because perfusion of many lung units does not increase proportionately with alveolar ventilation due to impaired recruitment and distention. In addition, if patients develop right-to-left shunt by opening a patent foramen ovale during exercise, mean expired CO_2 decreases, leading to higher calculated V_D/V_T . As a result of the abnormal physiologic dead space, $PETCO_2$ is decreased relative to normal individuals at all stages of exercise in proportion to the patient's functional limitation.⁷⁰

A final important difference is the fact that patients with pulmonary vascular disease develop hypoxemia with progressive exercise even in the absence of resting hypoxemia. For example, Deboeck and colleagues⁷⁵ reported an oxygen saturation by pulse oximetry of $86 \pm 2\%$ at peak exercise in PAH patients compared with $96 \pm 3\%$ in patients with heart failure with similar NYHA functional class and D'Alonzo and colleagues⁷⁹ reported a mean (A-a)PO₂ of $45 \pm$

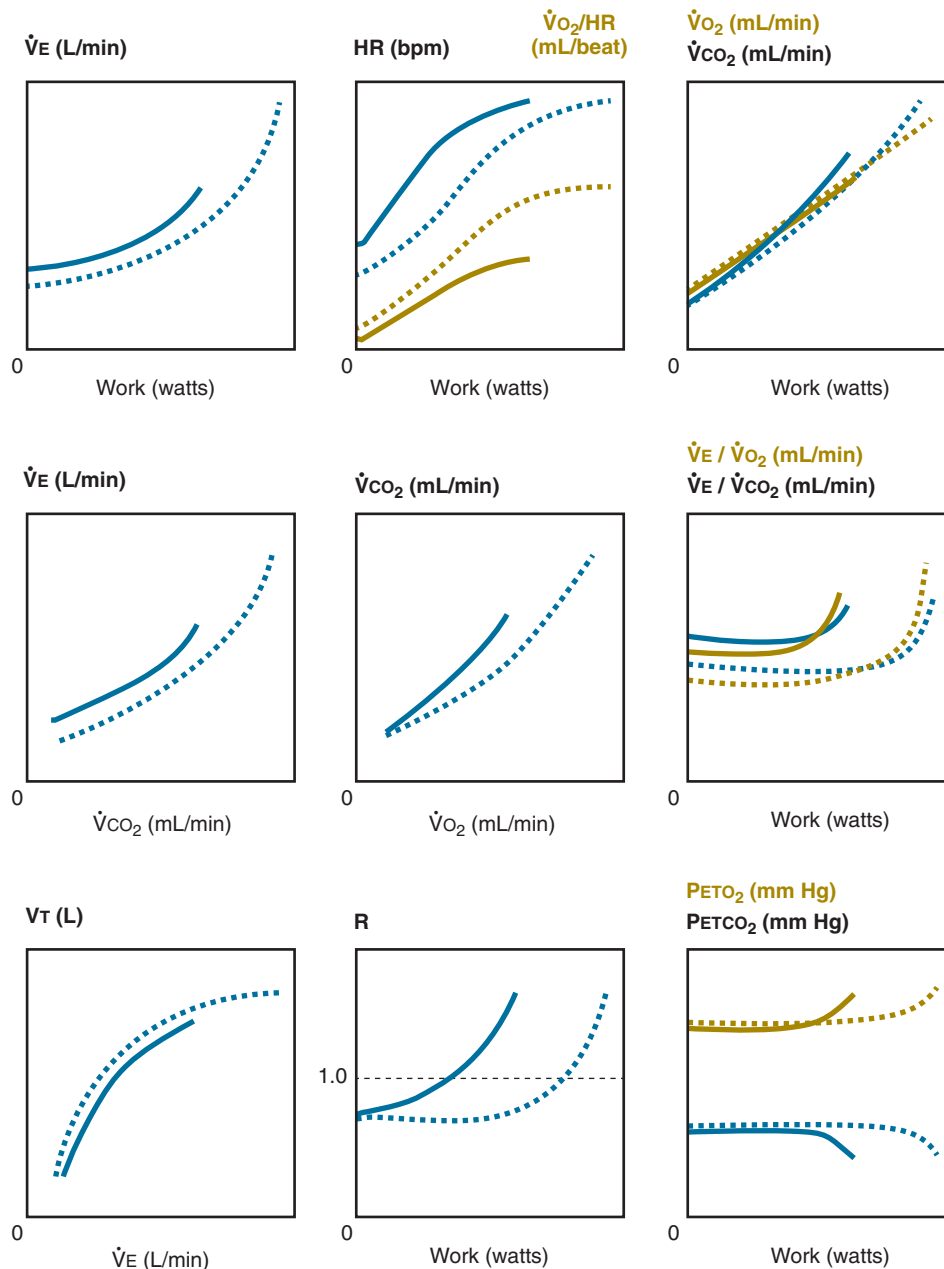


Figure 26-3 Heart failure compared to normal. Nine-box plot demonstrating expected physiologic responses to exercise in patients with cardiac limitation due to underlying heart failure (solid lines) compared with normal individuals (dotted lines). The layout of the graphs is the same as in Figure 26-2. (Modified from Luks AM, Glenn RW, Robertson HT: Introduction to cardiopulmonary exercise testing. New York, 2013, Springer, Fig. 3-3.)

17 mm Hg at peak exercise in idiopathic PAH patients, a higher value than typically seen in normal individuals.²⁵ In some patients, hypoxemia develops due to right-to-left shunting through an existing right-to-left communication or through a foramen ovale that opens during exercise due to the rise in pulmonary artery pressure, a finding that is predictive of death or need for transplant.⁸⁰ In other cases, hypoxemia may be due to diffusion limitation; red blood cell capillary transit time decreases with increasing pulmonary blood flow and may no longer be sufficient to ensure full equilibration between the capillary and alveolar P_{O_2} in the setting of the decreased functional capillary bed.⁸¹ This latter phenomenon is further accentuated by the low $\dot{C}\bar{V}O_2$ that exists due to the low cardiac output in this patient

population. (For clinical discussion of mechanisms of hypoxemia, see Chapter 4.)

The findings noted earlier pertain to patients with PAH at rest. Recent work suggests that measurement of hemodynamic variables during exercise may identify an intermediary phenotype between healthy individuals and overt PAH in which individuals develop mean pulmonary artery pressure greater than 30 mm Hg during exercise.⁸²⁻⁸⁴ This group may represent an early form of PAH. Standardized protocols to guide clinical practice regarding these patients are lacking at this time.⁸²

The pattern of exercise responses seen in patients with pulmonary vascular disease is displayed graphically in Figure 26-4.

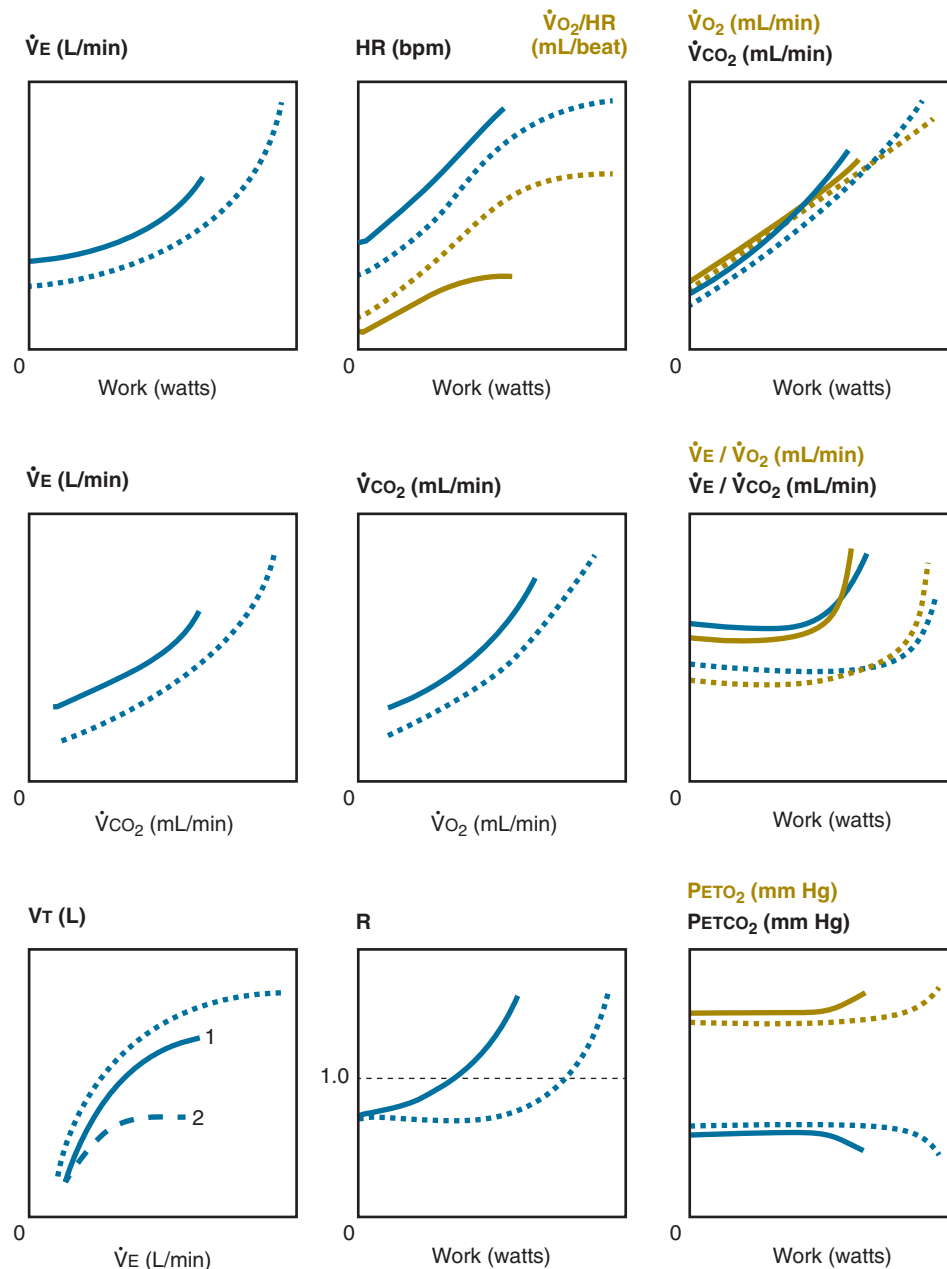


Figure 26-4 Pulmonary vascular or interstitial lung disease compared to normal. Nine-box plot demonstrating expected physiologic responses to exercise in patients with pulmonary vascular or interstitial lung disease patterns of limitation (solid lines) compared with normal individuals (dotted lines). Because the patterns of responses to exercise in each disease are similar, they are represented together above. In the graph in the lower left-hand corner, tidal volume (V_T) versus minute ventilation (\dot{V}_E), the solid blue line (Line 1) represents the expected response for a patient with pulmonary vascular disease while the dashed blue line (Line 2) represents the expected response for a patient with interstitial lung disease. (Modified from Luks AM, Glenn RW, Robertson HT: Introduction to cardiopulmonary exercise testing. New York, 2013, Springer, Fig. 3-6.)

Interstitial Lung Diseases (for discussion of clinical aspects of interstitial lung diseases, see Chapters 63–66)

Patients with *interstitial lung disease* (ILD) manifest physiologic responses during progressive exercise similar to those seen in patients with pulmonary vascular disease. In particular, they demonstrate reduced $\dot{V}O_{2max}$ and *maximum work rate* (W_{max}), increased $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$, reduced tidal volumes and increased respiratory rates, stable or increased V_D/V_T at end-exercise, and hypoxemia with reduced arterial PO_2 and increased $(A-a)PO_2$. Although patients with ILD may not have a decreased $\dot{V}O_2/HR$ and

the ventilatory threshold may not be decreased relative to their $\dot{V}O_{2max}$, these differences are usually not sufficient to distinguish between these two classes of patients on the basis of CPET alone and further studies such as *pulmonary function tests* (PFTs) and *computed tomography* (CT) imaging are necessary. Of note, when ILD develops in the setting of a collagen vascular disease, some of these responses can be observed before pulmonary involvement is evident on PFTs.⁸⁵

Debate exists regarding the underlying mechanism for the reduction in maximum exercise capacity. Hansen and

Wasserman,⁸⁶ for example, demonstrated that abnormal cardiac function due to pulmonary vascular pathology was more important than respiratory system factors in limiting exercise while Marciniuk and colleagues⁸⁷ used dead space loading during exercise to show that abnormal respiratory mechanics were the more important factor. Ventilatory equivalents are increased due to the increased dead space and the hypoxic ventilatory response, whereas exercise-induced hypoxemia, for which risk is increased in patients with a low *diffusion capacity for carbon monoxide* (DL_{CO}) on PFTs,⁸⁸ is due to a combination of *ventilation-perfusion* (\dot{V}_A/\dot{Q}) inequality and diffusion limitation.⁸⁹

Because the term *interstitial lung disease* represents a heterogeneous group of disorders, the physiologic responses to exercise vary on the basis of the specific disease process. Wells and colleagues,⁹⁰ for example, found increased dyspnea and hypoxemia in idiopathic pulmonary fibrosis compared with systemic sclerosis with ILD, while other studies have also shown worse hypoxemia, as well as increased pulmonary artery pressure responses in patients with idiopathic pulmonary fibrosis compared with sarcoidosis and other forms of ILD.^{91,92} The onset of pulmonary hypertension as a complication of ILD or an underlying systemic illness is associated with worse exercise tolerance, hypoxemia, and ventilatory inefficiency compared with otherwise similar patients with normal pulmonary artery pressures.^{93,94}

The pattern of exercise responses seen in patients with interstitial lung disease is displayed graphically in Figure 26-4.

Adult Congenital Heart Disease

With improvements in medical care, many patients with congenital heart disease are living into adulthood⁹⁵ and the increasing use of CPET in disease management has enhanced the understanding of their physiologic responses to exercise. Similar to that seen in patients with heart failure, patients with congenital heart disease demonstrate reductions in $\dot{V}O_{2max}$, peak work rate, and maximum heart rate and increases in $\dot{V}_E/\dot{V}CO_2$ compared with normal individuals.⁹⁶ In contrast, however, many congenital heart disease patients develop hypoxemia at end-exercise.⁹⁷ Given that many have coexisting pulmonary hypertension, one might also expect stable or increased \dot{V}_D/\dot{V}_T at end-exercise in many patients but this variable has not been reported in major series.

Owing to the diversity in the type and severity of congenital lesions, there is significant variability in the magnitude of observed changes in $\dot{V}O_{2max}$ and $\dot{V}_E/\dot{V}CO_2$ with the most serious abnormalities seen in those patients with Eisenmenger syndrome and complex lesions such as double-outlet ventricle or univentricular physiology.^{96,98} Patients with cyanosis and/or pulmonary hypertension also demonstrate greater reductions in these parameters when compared with patients lacking these problems.^{98,99} Importantly, functional impairment is not limited to those with significant lesions because even patients who are reportedly asymptomatic¹⁰⁰ or those with mild lesions such as repaired coarctation of the aorta demonstrate decreased $\dot{V}O_{2max}$ and increased $\dot{V}_E/\dot{V}CO_2$ compared with normal individuals.⁹⁶ Surgical repair is associated with improvements in exercise capacity,^{101,102} with the degree of improvement related in

some cases to whether the abnormality is repaired when the patient is a child or an adult.¹⁰³

Although much of the decrement in exercise capacity in these patients is attributable to cardiac and pulmonary vascular dysfunction related to the underlying defect or its repair, some patients are also limited by abnormal respiratory mechanics. Up to 50% of patients who have undergone surgical repairs have findings suggestive of restriction on spirometry,^{104,105} perhaps due to their often multiple thoracotomies and sternotomies. Those with abnormal spirometry show worse exercise capacity and NYHA functional class compared with those with normal spirometry.¹⁰⁵

Chronic Obstructive Pulmonary Disease

(for clinical discussion, see Chapters 43 and 44)

Patients with mild COPD may actually have normal exercise capacity while patients with moderate to severe COPD demonstrate decrements in $\dot{V}O_{2max}$ and peak work rate proportional to the severity of their disease as measured by *Global Initiative for Obstructive Lung Disease* (GOLD) stage.^{106,107} Beyond this decrease in exercise capacity, the pattern of physiologic responses to progressive exercise in COPD is different from that seen in patients with heart failure. Whereas exercise is limited in heart failure by an inability to deliver oxygen-rich blood to exercising muscles, patients with moderate-severe COPD are limited by altered respiratory mechanics; their ventilatory pump fails before the heart does.

The hallmark of ventilatory limitation in moderate to severe COPD is the fact that both arterial PCO_2 and $PETCO_2$ remain stable or increase at end-exercise due to an inability to raise minute and alveolar ventilation in response to increasing $\dot{V}CO_2$ and, when present, a metabolic acidosis. This phenomenon, which is present to a greater extent at higher GOLD stages of disease,¹⁰⁷ results from mechanical constraints due to dynamic hyperinflation during exercise (discussed further later) and altered ventilation-perfusion relationships.^{108,109}

In addition, \dot{V}_E at peak exercise will be at or close to the maximum predicted ventilation as measured by the MVV or $FEV_1 \times 40$, a marked contrast from normal sedentary individuals and those with heart failure in whom \dot{V}_E/MVV is normally less than 75% to 80%. Ventilation is typically higher for any given work rate and is usually marked by a high respiratory rate, low tidal volume, higher end-expiratory volume, and lower inspiratory capacity compared with normal individuals.¹¹⁰ Still another manifestation of ventilatory limitation is the absence of a ventilatory threshold in most patients with severe disease. Although patients with mild disease may still develop a metabolic acidosis¹¹¹ and even manifest a ventilatory threshold at lower levels of $\dot{V}O_2$ than normal individuals,¹¹⁰ patients with severe disease will not manifest such changes.¹¹² Along with the fact that peak heart rate is typically well below the maximum predicted heart rate in severe disease, the absence of the ventilatory threshold is strongly indicative of the fact that the ventilatory pump is failing before the circulatory pump.

Perhaps the most important reason for these manifestations of ventilatory limitation is a phenomenon referred to as *dynamic hyperinflation*. Due to expiratory flow limitation that develops even at low-moderate levels of exercise,

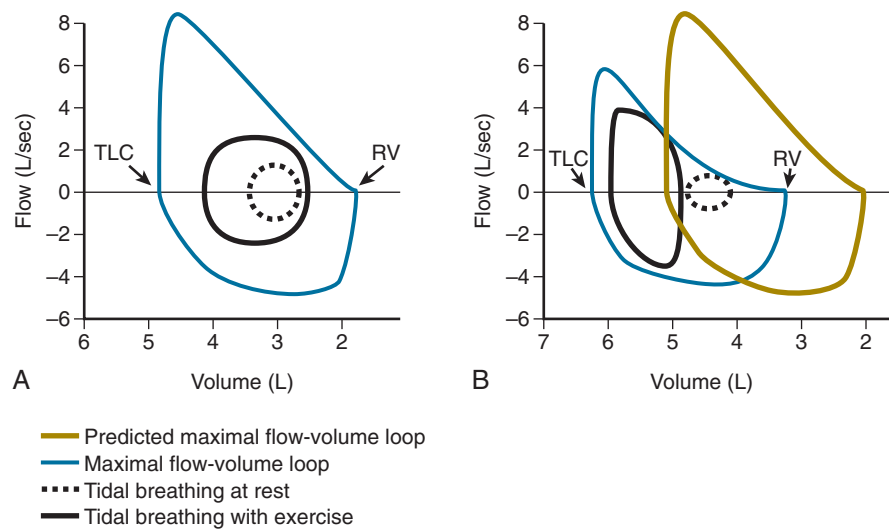


Figure 26-5 Expiratory flow limitation during exercise in patients with COPD. **A**, Typical pattern in normal individuals. During exercise, expiratory flow (black line) remains below the expiratory flow obtained in a forced vital capacity maneuver (blue line). **B**, Similar schemata for a patient with COPD. The flow-volume curve obtained in a forced vital capacity maneuver (blue line) is shifted to the left (higher volumes) and curvilinear, especially at low lung volumes, relative to the normal individual (brown line). With exercise, expiratory flow (black line) is equal to maximum expiratory flow over a portion of exhalation. RV, residual volume; TLC, total lung capacity.

patients with COPD must increase end-expiratory lung volumes and encroach on their inspiratory reserve volume in order to raise \dot{V}_E as metabolic activity increases (Fig. 26-5). The hyperinflation that results causes flattening of the diaphragm, which limits contractile strength, increases respiratory muscle fatigue, and causes increased dyspnea for any given level of ventilation.¹¹³ Interestingly, patients with dynamic hyperinflation have less locomotor muscle fatigue with exercise¹¹⁴ because the ventilatory pump fails before the nonrespiratory muscle groups face significant loads.

Dynamic hyperinflation also has significant hemodynamic effects, including alterations in cardiac preload and afterload that subsequently impair cardiac function and manifest as a decrease in $\dot{V}O_2/\text{HR}$. The magnitude of this problem inversely correlates with the increase in end-expiratory lung volumes,¹¹⁵ and improvement can be seen following interventions that decrease dynamic hyperinflation such as *lung volume reduction surgery* (LVRS).¹¹⁶ Impaired right ventricular function may also result from increased pulmonary vascular resistance due to hypoxic pulmonary vasoconstriction and structural changes in the pulmonary circulation.¹¹⁷ In fact, in patients whose COPD is complicated by pulmonary hypertension (mean PAP ≥ 40 mm Hg), impaired circulatory function is the primary factor limiting exercise rather than the ventilatory constraints.¹¹⁸ Some patients with COPD also manifest chronotropic incompetence,¹¹⁹ which may limit the cardiac response to exercise. The increased work of breathing may also contribute to exercise limitation by limiting blood flow to locomotor muscles.¹²⁰

Another important feature of progressive exercise in patients with COPD is the onset of hypoxemia with a widened (A-a) PO_2 . This problem correlates with reductions in diffusing capacity,¹²¹ is more common when the COPD is due to emphysema rather than to chronic bronchitis, is more severe in patients with pulmonary hypertension,¹²² and is more prominent with walking as opposed to cycling.¹²³

The predominant mechanism is \dot{V}_A/\dot{Q} inequality, the effects of which are magnified by reductions in $\text{C}\dot{V}O_2$ during exercise.⁸⁹ Depending on the distribution of blood flow and ventilation, however, \dot{V}_A/\dot{Q} inequality may actually improve during exercise, which accounts for the observation that some patients with COPD actually see improvement in arterial PO_2 during exercise testing.^{124,125}

The pattern of exercise responses seen in patients with ventilatory limitation due to COPD is displayed in Figure 26-6.

CARDIOPULMONARY EXERCISE TESTING

INDICATIONS AND CONTRAINDICATIONS

The indications for CPET sort into five general areas: determining the etiology of exercise limitation, assessing functional status, stratifying risk for surgery, prognosticating outcomes related to specific diseases, and creating individualized exercise prescriptions for rehabilitation programs. The list of indications for CPET (Table 26-1) is largely compiled from expert opinions, and the evidence for the utility of CPET varies by indication, each of which is reviewed later.

Determining Etiology of Dyspnea and Exercise Limitation (for discussion of dyspnea see Chapter 29)

Evaluating Dyspnea. Dyspnea with exercise is a subjective complaint that is the end result of various diseases. When the cause of dyspnea is not apparent from history, physical examination, laboratory testing (including a hemoglobin concentration and resting arterial blood gas), chest imaging, and PFTs, CPET can be used to quantify a patient's exercise limitation and determine which system is limiting exercise. Although CPET on occasion can narrow the differential list down to a single limiting system, such as

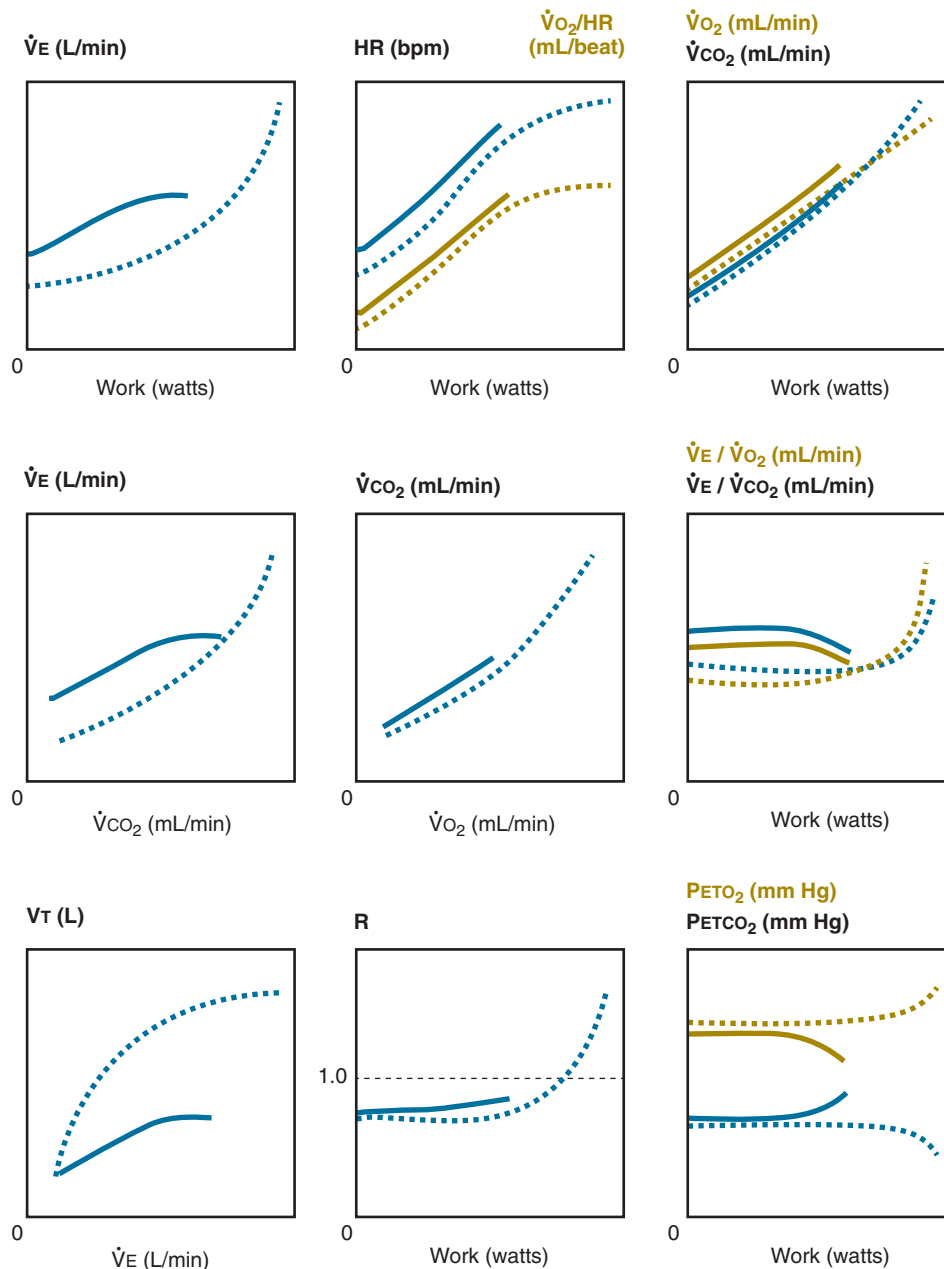


Figure 26-6 COPD compared to normal. Nine-box plot demonstrating expected physiologic responses to exercise in patients with ventilatory limitation due to COPD (solid lines) compared with normal individuals (dotted lines). (Modified from Luks AM, Glenn RW, Robertson HT: Introduction to cardiopulmonary exercise testing. New York, 2013, Springer, Fig. 3-4.)

in patients with chronotropic incompetence or myocardial ischemia, it is most useful in identifying the next best studies to pursue in making a definitive diagnosis.

The first step in using CPET to evaluate dyspnea is to determine if the patient's subjective complaints and description of their limitations are appropriate for the degree of work they are able to perform. It is therefore imperative that the patient gives a maximal effort during the CPET. An arterial blood gas at the end of exercise can be helpful in this setting to determine if the individual gave a good effort, was ventilatory limited, had excess dead space, or was hyperventilating. It can also be helpful to use a dyspnea scale¹²⁶ during a ramped exercise protocol to

quantify and link a patient's sense of dyspnea with the level of work being performed. It is also important to ask the patient if the CPET protocol reproduced the patient's symptoms of dyspnea. This postexercise questioning often helps define the subjective complaints and narrow the differential diagnosis.

As described earlier, the pattern of response to exercise can be used to determine which system is limiting exercise and likely creating the sense of dyspnea. In a group of 50 patients referred for CPET with unexplained dyspnea,¹²⁷ for example, broad diagnoses of cardiac limitation, pulmonary limitation, obesity and/or deconditioning, and psychogenic dyspnea were identified.

Table 26-1 Indications and Contraindications for Cardiopulmonary Exercise Testing

Indications	Contraindications
Determining the etiology of dyspnea and exercise limitation Evaluating dyspnea Evaluating exercise limitation Evaluating combined cardiac and pulmonary disorders Diagnosing exercise-induced bronchoconstriction Assessing functional status and quantifying impairment Risk stratification Assessment for thoracic surgery Evaluation for lung volume reduction surgery Assessment for major general surgery Prognosticating outcomes Evaluation of heart failure and prognostication for transplantation Assessment of adult congenital heart disease Assessment of pulmonary arterial hypertension Exercise prescriptions for rehabilitation programs	ABSOLUTE Active myocardial ischemia (unstable angina, myocardial infarction within 30 days) Acute heart failure exacerbation Exercise-induced syncope Uncontrolled arrhythmias Severe aortic stenosis Acute endocarditis, myocarditis, pericarditis Acute aortic dissection or suspected dissecting aortic aneurysm Acute pulmonary embolism or lower extremity deep venous thrombosis Active COPD exacerbation or uncontrolled asthma Active pulmonary edema Oxygen saturation < 85% breathing air at rest Acute respiratory failure RELATIVE Severe pulmonary hypertension Left main coronary artery stenosis Moderate stenotic valve disease Severe hypertension (SBP > 200 mm Hg, DBP > 120 mm Hg) Hypertrophic cardiomyopathy High-degree atrioventricular block Severe electrolyte abnormalities Tachyarrhythmias or bradyarrhythmias Advanced or complicated pregnancy Implanted cardiac defibrillator that cannot be interrogated or temporarily reset due to inaccessibility of an individual qualified to do this (e.g., device manufacturer representative)

DBP, diastolic blood pressure; SBP, systemic blood pressure.

Table 26-2 Estimating $\dot{V}O_{2\max}$ from the History

Activity Limitations	Approximate $\dot{V}O_{2\max}$ (mL/kg/min)
Participates in competitive sports with sustained activity like rowing, basketball, and soccer.	>40
Engages in regular endurance training. Tolerates sustained heavy labor well; can play recreational soccer or full-court basketball without slacking or run at an 8-minute/mile pace	
Tolerates sustained heavy labor well; can play recreational soccer or full-court basketball	35–40
Participates in recreational cross-country skiing or half-court basketball with minimal limitation	30–35
Performs heavy labor with difficulty; downhill skiing somewhat limited by fatigue	25–30
Heavy housework or yard work causes dyspnea; cannot play singles tennis	20–25
Dyspnea with two flights of stairs at own pace; cannot play golf while carrying bag or pulling a cart	17–20
Unable to vacuum average room or change sheets without rest	14–17
Difficulty walking slowly with peers in shopping mall	12–14
Dyspnea while brushing hair, dressing, showering	<12

Adapted with permission from Luks A, Glenny R, Robertson H: *Introduction to cardiopulmonary exercise testing*. New York, 2013, Springer.

Evaluation of Exercise Limitation. Patients presenting with exercise limitation rather than dyspnea as a complaint state that they just cannot perform the amount of work that they could do in the past. These complaints tend to be more vague and difficult to sort out by the usual history and standard studies. CPET is useful in this setting to quantify the amount of work that an individual can perform in a supervised test and compare it with what they say they can do during the activities of daily living. Table 26-2 provides a rough estimate of the maximal oxygen consumption that correlates with the level of exercise a patient states he or she can perform.¹²⁸ It is important to keep in mind that there is a broad spectrum of exercise capabilities across the normal population. Although an individual may have a “normal” exercise study as judged by the maximal oxygen

consumption, the observed response for any individual may represent a significant decline in his or her exercise performance from a previous supranormal level.

Evaluating Combined Cardiovascular and Pulmonary Disorders. When individuals have underlying diseases in more than one system, CPET can help determine which system is primarily responsible for their exercise limitation and guide patient management. For example, in a patient with both aortic stenosis and COPD, CPET can help determine whether or not to proceed with valve repair. Were such a patient to be primarily limited by his or her ventilatory capacity, repairing the aortic valve may not be indicated, because following surgery the individual would still be significantly limited by his or her ventilatory

capacity. While assisting in identifying the primary limiting system, CPET cannot quantitatively partition the degree of limitation due to each of the affected systems.

Diagnosing Exercise-Induced Bronchoconstriction. CPET can be used to diagnose exercise-induced bronchoconstriction, a transient, reversible bronchoconstriction that develops during or after strenuous exercise, which is present in more than 10% of the general population and up to 90% of persons previously diagnosed with asthma.¹²⁹ Although administration of inhaled bronchoprovocatory agents such as methacholine or mannitol can be used to make the diagnosis (see Chapter 25), exercise challenge using free running, treadmill, or cycle ergometry has been used to elicit exercise-induced bronchoconstriction since the 1970s¹³⁰ and, along with eucapnic voluntary hyperventilation, is a more sensitive and specific testing modality.¹³¹ Exercise testing for this purpose requires specialized equipment, personnel, and the ability to exercise at 85% to 95% maximum heart rate with dry medical grade air and high flow rates (>100 L/min)¹³² and should be performed according to published guidelines.^{133,134}

Due to the logistical issues associated with exercise challenges, the International Olympic Committee Medical Commission recommends eucapnic voluntary hyperventilation¹³¹ as the initial testing modality followed by CPET if eucapnic voluntary hyperventilation is nondiagnostic.¹³⁵

Assessing Functional Status and Degree of Impairment

Quantitative measures of exercise capacity are also useful in determining eligibility for disability because static tests such as PFTs and cardiac ejection fraction by echocardiography do not correlate well with exercise capacity.¹³⁶⁻¹³⁸ For example, in a heterogeneous population of subjects, the variables FEV₁ and DL_{CO} poorly predicted the maximal O₂ consumption,¹³⁹ likely due to the fact that many individuals have cardiovascular limitations not captured by either of these PFT parameters. Despite these issues, the American Thoracic Society statement on the evaluation of impairment and disability¹⁴⁰ states that impairment can be determined from standard pulmonary functions studies in most cases and that further testing with CPET may be helpful in selected situations. Importantly, quantifying impairment informs but does not define disability because disability assessment requires social, economic, environmental, and other input.¹⁴¹ Largely on the basis of empirical knowledge, rough estimates of the work that an individual should be able to perform have been proposed (Table 26-3).

Risk Stratification

Risk Assessment for Thoracic Surgery. A number of studies have looked at preoperative CPET to determine whether patient outcomes can be predicted on the basis of exercise capacity.¹⁴²⁻¹⁴⁵ Although the available studies have not used randomized, controlled designs and generally involve small numbers of patients from single centers, they do show an association between exercise capacity and clinical outcomes following major surgery. Drawing on this evidence, an expert panel of the American College of Chest Physicians¹⁴⁶ devised an algorithm that incorporates CPET along with the Thoracic Revised Cardiac Risk Index,¹⁴⁷

Table 26-3 Impairment Determined by Cardiopulmonary Exercise Testing

Vo _{2max} (mL/kg/min)	Description of Work
>25	Capable of all but most physically demanding jobs
15–25	Able to work at the specific job that does not require frequent and extended work above 40% of maximum Vo ₂
<15	Unable to perform most jobs

Based on recommendations from the American Thoracic Society: Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis* 133(6):1205–1209, 1986.

spirometry, DL_{CO}, and performance on stair climbing or shuttle walk testing to guide selection of the appropriate therapeutic approach in lung cancer patients (Fig. 26-7). The general approach can probably be used as a foundation for any lung resection surgery. Patients who require CPET as part of this algorithm are deemed low risk (expected risk of mortality < 1%) if the Vo_{2max} is greater than 20 mL/kg/min or more than 75% of predicted. They are considered high risk (expected mortality > 10%) if their Vo_{2max} is less than 10 mL/kg/min or less than 35% of predicted. The expert panel gave this algorithm a strong recommendation on the basis of their experience, although it should be recognized there are no data demonstrating the utility of this approach or comparing it with other risk stratification algorithms that do not use CPET.¹⁴⁸

In addition to risk stratification, CPET provides a wealth of information that helps identify those systems responsible for reduced aerobic capacity. Once those systems are identified, corrections can be implemented to improve patient fitness and minimize surgical risk.¹⁴⁹ Such steps might include, for example, coronary revascularization, medical treatment, or physical rehabilitation.

Evaluation for Lung Volume Reduction Surgery. The landmark National Emphysema Therapy Trial¹⁵⁰ demonstrated that LVRS was clearly of benefit, but only for the subset of patients defined by their reduced exercise capacity, when using a modified but formalized exercise protocol. The study participants underwent a maximal CPET on a cycle ergometer while wearing a face mask delivering an FiO₂ of 0.30 and pedaling for 3 minutes without resistance, followed by progressive increases in work rate by 5 or 10 watts/min. Those patients with a low exercise capacity, here defined as less than 25 W for women and 40 W for men, were found to benefit from LVRS.

Risk Assessment for Extrathoracic Surgery. A number of studies have investigated the utility of performing CPET for risk stratification or identification of other comorbidities that could be addressed in the perioperative period. Such an approach has been investigated in a variety of groups undergoing major surgery including those undergoing abdominal-aortic repair,^{151,152} hepatic transplantation,¹⁵³ upper gastrointestinal surgery,¹⁵⁴ as well as elderly patients undergoing intra-abdominal surgery.¹⁵⁵ Seven of the nine studies included in a review of this issue¹⁵⁶ found higher mortality in patients with lower Vo_{2max}. In one of the

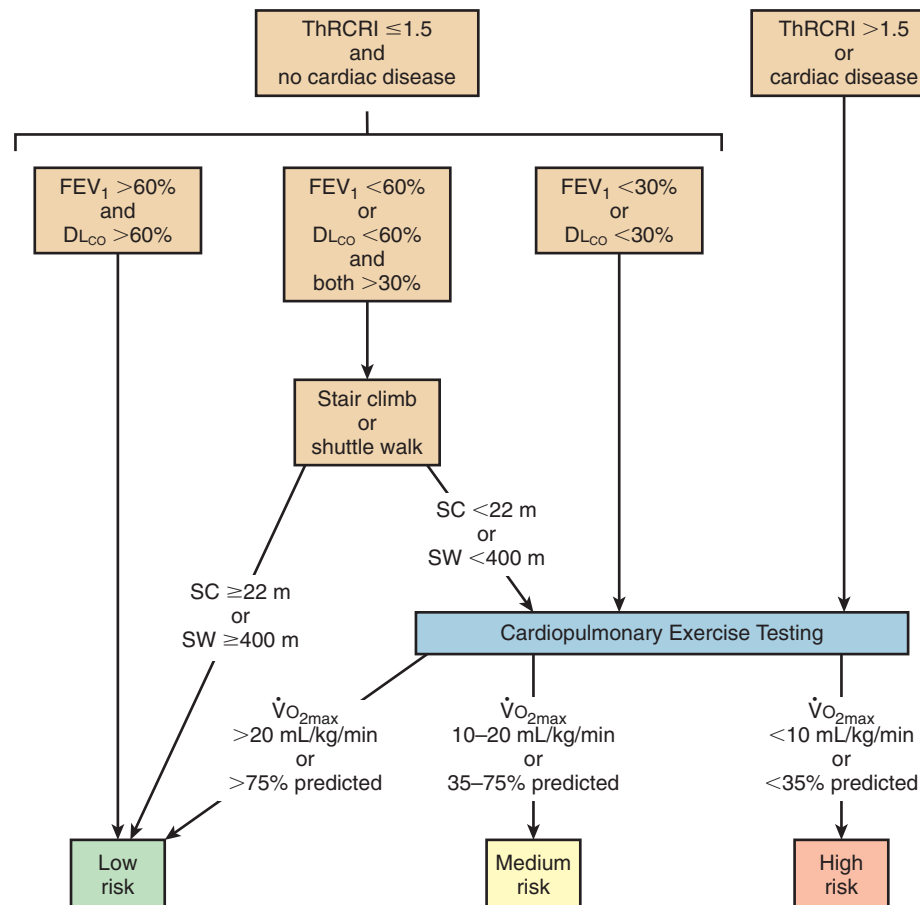


Figure 26-7 Algorithm for risk stratification for thoracic surgery in patients with lung cancer. The Thoracic Revised Cardiac Risk Index (ThRCRI) uses a point system in which a pneumonectomy, previous heart disease, and prior stroke or transient ischemic attack receive 1.5 points each and a creatinine greater than 2 mg/dL is given 1 point. The forced expiratory volume in 1 second (FEV₁) and diffusion capacity for carbon monoxide (DL_{CO}) cutoffs are based on the predicted postoperative values that are calculated by multiplying the preoperative measured values by the fraction of lung remaining after resection. SC, stair climb; SW, shuttle walk.

studies,¹⁵⁵ $\dot{V}O_2$ at the ventilatory threshold measured preoperatively was used to determine the appropriate hospital location for postoperative care; a $\dot{V}O_2$ less than 11 mL/kg/min was the cutoff in the postoperative intensive care unit and a marker of increased mortality. Despite this evidence, there are no prospective studies documenting survival benefit or cost-effectiveness for using CPET in this manner.

Prognosticating Clinical Outcomes

In normal subjects without specific diseases and in general among individuals with disease, survival is associated with a higher exercise capacity.^{157,158} However, interventional studies have not been conducted to determine whether training to improve $\dot{V}O_{2max}$ increases life expectancy. Some of the patient populations for whom $\dot{V}O_{2max}$ and other data derived from CPET provide prognostic information are described as follows.

Heart Failure. $\dot{V}O_{2max}$ is the most objective data available for assessing exercise capacity in individuals with heart failure. When the contribution of heart failure to exercise limitation is uncertain, the American College of Cardiology and the American Heart Association recommend CPET in patients presenting with heart failure to guide management and determine whether heart failure is the cause of exercise

limitation.¹⁵⁹ A number of early studies¹⁶⁰⁻¹⁶² documented a progressive decline in survival with decreasing $\dot{V}O_{2max}$. More recent studies have shown similar relationships between $\dot{V}O_{2max}$ and mortality.^{163,164} Importantly, the inclusion of patients treated with β -blockers in recent series¹⁶⁵⁻¹⁶⁷ now suggests that a threshold of less than 14 mL/kg/min should be considered for heart transplantation. Most studies investigating the utility of $\dot{V}O_2$ for prognostication in heart failure use the traditional weight normalized values (mL/kg/min), but due to the obesity “epidemic,” the reported oxygen consumption data may be inappropriately low and decisions for heart transplantation may be skewed toward the obese. Correcting $\dot{V}O_2$ for lean body mass may improve prognostication.^{168,169}

Other CPET variables may be better predictive tools than $\dot{V}O_{2max}$. For example, a series of studies show that $\dot{V}E/\dot{V}CO_2$ or the $\dot{V}E/\dot{V}CO_2$ slope¹⁷⁰⁻¹⁷⁵ is an accurate predictor of mortality and may improve predictive capabilities of models used to guide heart failure management.¹⁷⁶ Although most of these studies identify a single threshold above which the $\dot{V}E/\dot{V}CO_2$ indicates a higher mortality in patients with heart failure, a more recent analysis by Arena and colleagues¹⁷⁰ created four classes on the basis of the $\dot{V}E/\dot{V}CO_2$ slope and reported that event-free survival was significantly different across the four classes. When combined with the peak

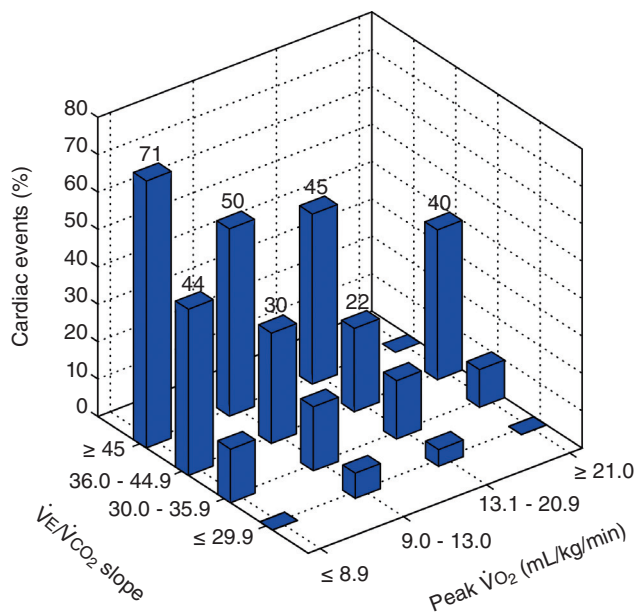


Figure 26-8 Cardiac events associated with exercise test results. The likelihood of a major cardiac event was higher in those with a low peak oxygen consumption ($\dot{V}O_2$) and high slope of ventilatory equivalents for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) from a cardiopulmonary exercise test. Patients with a peak $\dot{V}O_2$ of less than 8.9 mL/kg/min and a $\dot{V}E/\dot{V}CO_2$ slope greater than 45 had a greater than 70% chance of having a cardiac event over a 2-year period. (From Arena R, Myers J, Abella J, et al: Development of a ventilatory classification system in patients with heart failure. *Circulation* 115(18):2410–2417, 2007.)

$\dot{V}O_2$, the $\dot{V}E/\dot{V}CO_2$ slope further differentiates which patients are at risk for major cardiac events (Fig. 26-8). On the basis of the most recent literature, individuals with a $\dot{V}O_{2max}$ less than 10 mL/kg/min or a $\dot{V}E/\dot{V}CO_2$ slope greater than 40 have the poorest prognosis.¹⁷⁷

Other parameters shown to be associated with outcomes such as mortality, need for transplantation, or need for device implantation in patients with heart failure include heart rate recovery,¹⁷⁸⁻¹⁸¹ oxygen uptake efficiency,¹⁸²⁻¹⁸⁴ exertional oscillatory ventilation,^{63,64,185} heart rate variability,^{186,187} and blood pressure response.^{188,189} A number of different groups have attempted to use multiple CPET parameters¹⁹⁰⁻¹⁹² or combined CPET parameters with other medical information (renal function, echocardiography, questionnaires)^{164,193} to guide prognostication as an alternative to the traditional strategy of using a single parameter.

Adult Congenital Heart Disease. CPET has emerged as a valuable tool in the management of patients with congenital heart disease.⁹⁶ It aids in risk stratification and determining the need and timing of therapeutic interventions. CPET is thought to be of special importance in this patient population because self-reported exercise capacity has been shown to be of poor predictive value¹⁹⁴ and functional limitation can be documented in those who are asymptomatic.¹⁰⁰ Similar to patients with heart failure described earlier, $\dot{V}O_{2max}$ ¹⁰⁰ and $\dot{V}E/\dot{V}CO_2$ ¹⁹⁵ are strong predictors of mortality. Due to a variety of factors, including the significant heterogeneity of adult congenital heart disease, the decision of when to consider heart transplantation in the adult patient with congenital heart disease is particularly complex but CPET can be useful.^{98,196}

Pulmonary Arterial Hypertension. Assessment of exercise capacity can also be used to assess prognosis and response to treatment in PAH patients. For example, Sun and colleagues⁷⁴ found that peak work rate, $\dot{V}O_{2max}$, ventilatory threshold, O_2 pulse, and slope of $\dot{V}E/\dot{V}CO_2$ were all correlated with NYHA class. Yasunobu and colleagues⁷⁰ reported that $PETCO_2$ progressively decreased as the disease severity increased and directly correlated with changes in mean pulmonary artery pressure. Other studies have demonstrated a relationship between survival and $\dot{V}O_{2max}$ and $\dot{V}E/\dot{V}CO_2$ ^{71,197,198} and that persistent exercise-induced right-to-left shunt and poor ventilatory efficiency during serial assessments were highly predictive of poor outcomes in patients with PAH.⁸⁰

Although CPET is a safe^{74,199} and effective means to grade the severity of exercise limitation, assess prognosis, and measure response to therapy,²⁰⁰ the use of CPET is limited in most PAH trials due to a number of practical issues. Instead, most trials rely on the simple, less expensive, and reproducible 6-Minute Walk Test (6MWT, described in greater detail later), which, like CPET, provides prognostic information.^{201,202} Improvement in the 6MWT following therapeutic intervention may also be associated with a decrease in mortality,^{203,204} although not all studies have validated this finding.²⁰⁵

Exercise Prescriptions for Cardiac and Pulmonary Rehabilitation Programs (for discussion of clinical

aspects of rehabilitation, see Chapter 105)

Given that the intensity of aerobic exercise is linked to both the improvement in exercise capacity and the risk of adverse events during exercise, a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation stressed the importance of functional evaluation using exercise testing before starting an aerobic training program.¹⁰ Although there are many methods for creating individualized training programs, these guidelines propose that CPET be the gold standard for assessment and prescription of exercise intensity. The committee's goal is to shift from a "range-based" to a "threshold-based" aerobic exercise intensity prescription to maximize the benefits obtainable by the use of aerobic exercise training in cardiac rehabilitation.¹⁰

Similarly, the American Thoracic Society and the European Respiratory Society statement on pulmonary rehabilitation²⁰⁶ states that before initiating rehabilitation for COPD, CPET should be considered as part of a thorough assessment to identify factors contributing to exercise limitation, to determine the exercise prescription, and to evaluate safety by monitoring ECG and blood pressure for potential risks.²⁰⁷ Casaburi and colleagues,²⁰⁸ for example, have shown that high-intensity training programs (80% of W_{max} in the incremental test) are more effective than less intense programs (50% of W_{max}) in patients with COPD. In the absence of cardiovascular limitation, the training program in these individuals may begin at or above the intensity of the ventilatory threshold, with progressive increase in the limits of tolerance.^{208,209} In patients who cannot reach the ventilatory threshold during incremental testing, training can begin at a level closer to the maximum

intensity obtained.¹¹² Using the ventilatory threshold as a landmark when it is reached or knowing that it has not been reached during standardized testing facilitates higher-intensity targets and more efficient training.²⁰⁷

From a practical standpoint, a formal CPET study may not be necessary to build a tailored exercise program and others have used variables obtained in the 6MWT, such as peak heart rate,²¹⁰ to target exercise levels. Despite the expert opinions that CPET or 6MWT should be used to create individualized training programs, there are no data showing that the exercise prescription derived by these means improves quality of life or survival.

SAFETY CONSIDERATIONS AND CONTRAINDICATIONS TO CPET

Performing a CPET is not without risk, and the decision to conduct the test must reflect consideration of those risks relative to the benefits in terms of information gained. Multiple contemporary surveys indicate that the risks of complications that require hospitalization are low; the risk of serious arrhythmias, acute myocardial infarction, or sudden cardiac death during or immediately after an exercise test are less than 0.2%, 0.04%, and 0.01%, respectively.²¹¹ This estimate captures the risk for the entire population of individuals performing CPET and is likely to vary in a given patient on the basis of his or her underlying disease. Unfortunately, risk estimates are not available for every possible condition, and the clinician must use clinical judgment in assessing the risk and informing each individual.

Some diseases do carry significantly higher risks and represent absolute or relative contraindications to performing CPET (see Table 26-1). Patients with *implantable cardiac defibrillators* (ICDs) also require special attention. Documentation of the defibrillator settings should be reviewed before exercise to ensure that the peak heart rate during the test does not encroach on the rate at which the defibrillator is set to discharge. The defibrillator function should not be entirely disabled, however, as one needs maintain the ability to defibrillate patients who develop arrhythmias during the exercise test.

CONDUCTING EXERCISE TESTS

Exercise Equipment

A number of commercially available exercise monitoring systems allow breath-by-breath measurements of exhaled gases. The general components of these systems include an airflow transducer to measure the volumes of each inhalation and exhalation and rapid gas analyzers to measure the O₂ and CO₂ during inspiration and expiration. As technologies have improved, these components have become more reliable but still require strict and daily calibration tests to assure accurate data. Multiple resources are available with recommendations for calibration procedures and quality control.^{6,9,177} Gas exchange measurements during exercise should be reproducible, and therefore it is a good practice to have one or two individuals in the exercise laboratory perform monthly CPET to confirm that their data remain stable over time. Both maximal and submaximal tests can

be used for this purpose because reproducible data are generated in either case.

Exercise Modalities and Protocols

Cycle Ergometer versus Treadmill. Functional capacity is usually assessed in CPET by having the individual exercise on a stationary cycle ergometer or motorized treadmill. Either modality can be used to elicit progressively increasing work rates in subjects. Progressive work is produced on the cycle ergometer by increases in the resistance to pedaling. Through electronic braking and sensors, it is possible to gauge the work being done by the individual and quantify work over time as a rate in *watts* (W). Progressive work is produced on the treadmill by increases in the grade and speed of the treadmill. Because arm movement and the uplift of body weight while walking/running on the treadmill add to the work being performed, work on a treadmill is more dependent on an individual's weight and, as a result, is harder to quantify than with cycle ergometry, in which leg muscles do the vast majority of the work and the individual's weight is supported by the bicycle. Treadmill work is measured relative to each individual's resting energy expenditure and is typically expressed in terms of *metabolic equivalents* (METs). One MET represents the amount of oxygen consumed at rest and each successive stage achieved in a given treadmill protocol corresponds to a higher level of METs that can, in turn, be related to the individual's oxygen consumption (1 MET = 3.5 mL O₂/kg/min in the average adult).²¹² As discussed previously, oxygen consumption is also tightly linked with work rate on a cycle ergometer, with $\dot{V}O_2$ increasing at a rate of 10 mL/min/watt above the resting value. Hence watts and METs can be roughly compared through the shared $\dot{V}O_2$ and are dependent on the individual's weight. Table 26-4 provides examples of watts, oxygen consumption, and METs for two individuals of different weights to give the reader a general idea of how these measures of work compare.

Both exercise modalities can impose progressively increasing work rates that provide a range of oxygen consumptions to identify exercise patterns described earlier in this chapter. The resistance and, therefore, watts in cycle ergometry can be increased in either a continuous or stepwise manner over time. Treadmill work rates are usually increased according to specific protocols such as the

Table 26-4 Comparison of Oxygen Consumption and Metabolic Equivalents (METs) at Different Levels of Work in Individuals of Different Weights

Watts	70-kg PERSON		100-kg PERSON	
	$\dot{V}O_2$ (mL/min)	METs	$\dot{V}O_2$ (mL/min)	METs
0 (rest)	250	1.0	350	1.0
25	500	2.0	600	1.7
50	750	3.1	850	2.4
100	1250	5.1	1350	3.9
200	2250	9.2	2350	6.7
300	3250	13.3	3350	9.6
400	4250	17.3	4350	12.4

$\dot{V}O_2$ increases at a rate of 10 mL/min/watt above the resting value. One MET represents the amount of oxygen consumed at rest.

Bruce,²¹³ Balke,²¹⁴ or Naughton²¹⁵ that define how to change the speed and inclination of the treadmill over time. The work rate ramp or steps should be chosen so that subjects can perform 10 to 12 minutes of exercise before reaching their $\dot{V}O_{2\max}$, because this time frame usually provides the temporal resolution necessary to identify patterns of exercise responses. $\dot{V}O_{2\max}$ estimates tend to be 10% to 15% higher using a treadmill compared to a cycle ergometer due to the extra work being performed by the arms when walking or running. Each modality may offer advantages depending on the patient and goals of the test. Whereas cycle ergometry tends to be better for patients who are obese or have gait problems and is more suited for drawing arterial blood gases, treadmill testing may be preferred in patients whose symptoms are elicited with walking and running or in patients with exercise-activated pacemakers that sense arm movement.

Invasive Cardiopulmonary Exercise Testing. When competing comorbidities in a given patient make it difficult to determine the primary cause of exercise limitation, exercise with a right heart catheter can provide additional data to help (1) separate out the cardiac and pulmonary systems, (2) further differentiate the broad category of “cardiac limitation” as either right or left heart failure, and (3) identify a component of muscle deconditioning. The data available from the right heart catheter include mixed venous oxygen saturation and content, pulmonary artery pressure, pulmonary artery occlusion pressure, and thermomodulation cardiac output. With increasing exercise to exhaustion in a normal individual, cardiac output should increase fourfold to fivefold, but the mean pulmonary arterial pressure should remain less than 30 mm Hg.²¹⁶ In patients with left heart failure or pulmonary vascular disease, the mean pulmonary arterial pressure may increase above this level and, if associated with symptoms of dyspnea, may give a clue to underlying mechanisms. Pulmonary vascular resistance can be calculated to determine if elevated pulmonary artery pressures are due to left-sided heart failure or pulmonary vascular disease. Because intrathoracic pressure affects right-heart catheterization measurements, the pulmonary artery occlusion pressure must be measured at end-exhalation, which may be difficult to achieve without asking patients to temporarily alter their breathing patterns during measurements. Stroke volume can be calculated from the heart rate and cardiac output rather than assessed through a surrogate measure, the O_2 pulse. Placement of an arterial line with the right heart catheter allows calculation of cardiac output using the Fick equation and determination of the arteriovenous oxygen content difference, with narrow values of the latter providing evidence of deconditioning as a cause of exercise limitation.

Noninvasive Estimates of Cardiac Output during CPET. A number of noninvasive commercial methods are also available for estimating the cardiac output during exercise. They rely on a variety of different technologies, including CO_2 rebreathing,²¹⁷ pulse contour analysis,²¹⁸ chest bioreactance,²¹⁹ echocardiography,²²⁰ and inert gas rebreathing.²²¹ The technology that has been most rigorously evaluated in exercise²²² is the inert gas rebreathing

method. Although the available evidence indicates that these measurements are feasible and that cardiac output and $\dot{V}O_2$ are tightly correlated in both normal subjects and individuals with heart failure,²²³ their clinical utility remains unclear.²²¹

Indications for Arterial Blood Gases

Arterial blood gases provide additional data that assist in differentiating the causes of exercise limitation and dyspnea. In particular, they allow the determination of the (1) (A-a) PO_2 to evaluate gas exchange; (2) arterial PCO_2 as the gold standard for identifying ventilatory limitation; (3) V_D/V_T as an indicator of pulmonary vascular disease; and (4) base deficit as a surrogate for lactic acidosis. Arterial blood gases can be measured either once immediately following conclusion of the exercise test or at repeated intervals through the test. Both sampling methods permit determination of the dead space fraction at end-exercise while the latter method also allows one to roughly estimate the position of the ventilatory threshold. The latter approach requires an arterial line while a single needle puncture can be used for the former. The operator should be aware that arterial puncture following maximal exertion can cause a vagal reaction and hypotension, especially in younger subjects.

INTERPRETING CARDIOPULMONARY EXERCISE TESTS

In [Figure 26-9](#), a basic approach is shown for interpreting the results of cardiopulmonary exercise tests. Because CPET interpretation is highly dependent on data quality, the reader should first ensure that there are no systematic data collection errors and that the patient gave a full effort. Several key aspects of the interpretation process are considered as follows.

Identifying the Ventilatory Threshold

One of the critical steps in CPET interpretation is identifying whether the patient reached a ventilatory threshold, because it is one of the primary means of distinguishing between cardiac or pulmonary vascular limitation, on the one hand, and ventilatory limitation, on the other. As indicated earlier, there are actually two distinct ventilatory thresholds but, for the majority of CPET interpretations, it is less important to identify the specific threshold and more important to identify whether the range of expected responses is consistent with either threshold.

The ventilatory threshold can be identified by invasive and noninvasive means. The former involves measurement of arterial lactate or bicarbonate concentrations. A single measurement at end-exercise is sufficient for a binary decision as to whether the threshold was reached, whereas serial measurements every other minute during exercise can be used as part of several different techniques to determine the $\dot{V}O_2$ at which the threshold was reached.^{13,224} Several noninvasive methods can also be used, including the V-slope method described earlier (see [Fig. 26-1](#)), identification of the point at which $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ reach their nadir and begin to increase, or identification of the point at which the $PETO_2$ starts to rise or $PETCO_2$ starts to decrease ([Fig. 26-10](#)). The accuracy of the different methods varies on the basis of operator experience, the testing

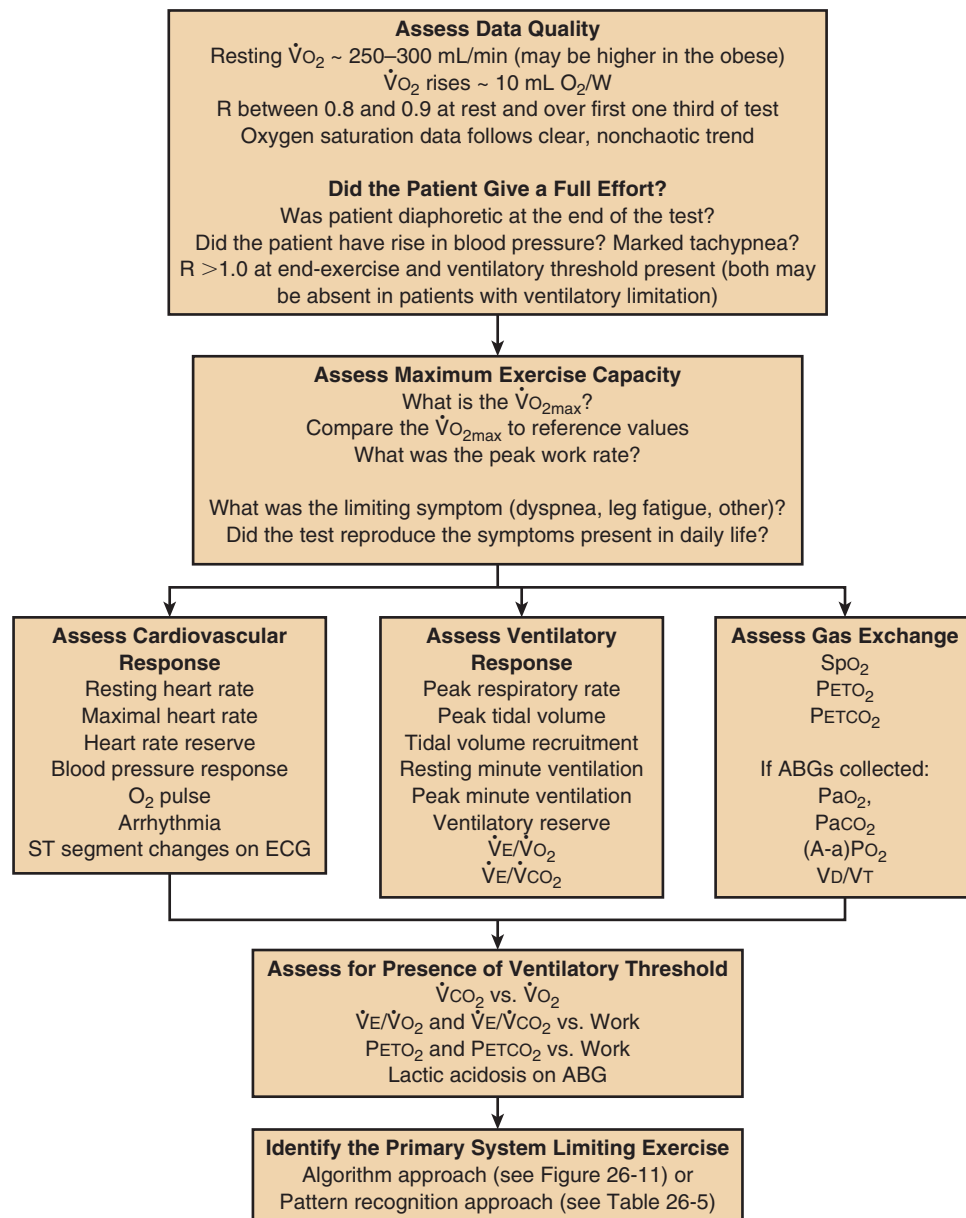


Figure 26-9 A general approach to cardiopulmonary exercise test interpretation. Because data interpretation is highly dependent on the quality of the data, the initial steps involve ensuring there are no systematic data errors and that the patient gave a complete effort. Once this is done, the next tasks are to assess maximum exercise capacity and the cardiovascular, ventilatory, and gas exchange responses and then identify whether a ventilatory threshold is present and determine the primary system limiting exercise. ABG, arterial blood gas; ECG, electrocardiogram; R, respiratory exchange ratio; SpO_2 , oxygen saturation by pulse oximetry; W, watt.

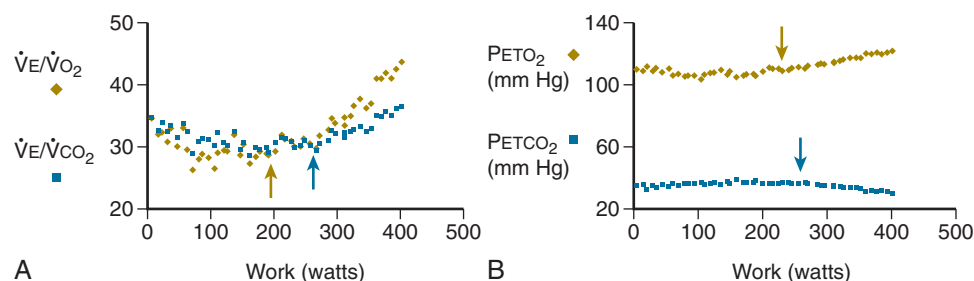


Figure 26-10 A, Analysis of ventilatory equivalents to identify whether a ventilatory threshold is present. Following the increase in minute ventilation at the ventilatory threshold, ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$, denoted in brown) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$, denoted in blue) begin a steady rise. The point at which each variable starts to rise is marked by an arrow in the respective colors. The start of the rise in $\dot{V}_E/\dot{V}O_2$ is associated with the first ventilatory threshold and is expected to take place before the rise in $\dot{V}_E/\dot{V}CO_2$. **B**, Using changes in end-tidal partial pressure of oxygen ($PETO_2$) and carbon dioxide ($PETCO_2$) to identify whether a ventilatory threshold is present. At the ventilatory threshold, minute ventilation (\dot{V}_E) increases out of proportion to the changes in oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). As a result, $PETO_2$ (denoted in brown) begins a steady rise (brown arrow), while $PETCO_2$ (denoted in blue) begins a steady decrease (blue arrow).

protocol, and the data collection system,⁶ and there is no evidence that any particular noninvasive method is superior to the others.^{225,226} This is not a critical issue in most CPET interpretations because the key question is whether or not the threshold is reached rather than when it is reached. When the specific $\dot{V}O_2$ at the ventilatory threshold must be known, as in devising exercise prescriptions or training protocols, the key factor will be application of a consistent approach from test to test.

Identifying the Primary System Limiting Exercise: Algorithmic versus Pattern Recognition Approaches

Perhaps the most important aspect of CPET interpretation is identifying the primary reason for exercise limitation. One approach to this task, first introduced by Wasserman

and colleagues,²⁸ employs a binary tree algorithm and flow charts that direct the interpretation through a series of decision points to specific causes of exercise limitation. A simplified flow chart is shown in Figure 26-11 to demonstrate the concept. The advantages of this approach are that the decision points and values are well defined so that there is no ambiguity in the direction to branch in the flow chart. This strategy is probably easier to follow for the novice interpreter than the pattern recognition approach outlined later. The primary disadvantage is that the interpretation is entirely dependent on a single data point at each bifurcation. Any error in data collection or misinterpretation at one bifurcation can direct the interpretation down a wrong pathway and an incorrect diagnosis. A secondary disadvantage is that CPET interpretation by this method requires an extensive array of flow charts.

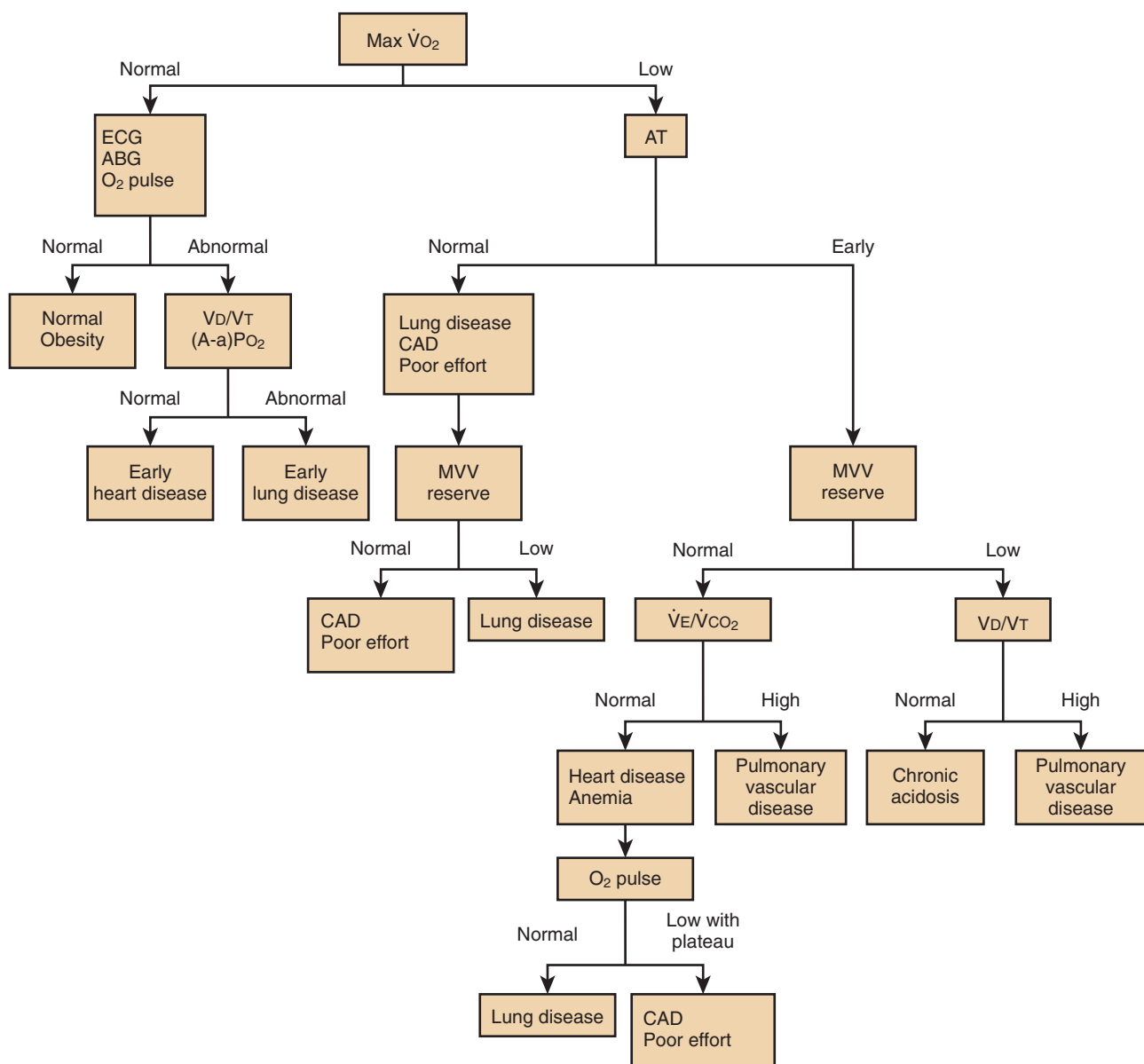


Figure 26-11 Simplified flow chart demonstrating decision making in cardiopulmonary exercise test interpretation. The decision tree begins at the top with the maximum oxygen consumption ($\dot{V}O_{2max}$) compared with predicted values. ABG, arterial blood gas; AT, anaerobic threshold; CAD, coronary artery disease; ECG, electrocardiogram; MVV, maximum voluntary ventilation; (A-a)PO₂, alveolar-arterial oxygen difference; V_D/V_T, dead space fraction; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide. (Modified from Wasserman K, Hansen JE, Sue DY, et al: Principles of exercise testing and interpretation, ed 5. Philadelphia, 2012, Lippincott Williams & Wilkins.)

Table 26-5 Identifying the Pattern of Limitation on Cardiopulmonary Exercise Testing

Observation	PATTERN OF LIMITATION		
	Cardiac	Pulmonary Vascular and Interstitial Lung Disease*	Ventilatory
Clear ventilatory threshold	⊙	⊙	
Plateau in O ₂ pulse late in exercise	⊙	⊙	⊙ [†]
High \dot{V}_E/\dot{V}_{CO_2}	⊙	⊙	
High \dot{V}_E/\dot{V}_{O_2}	⊙	⊙	
\dot{V}_{Emax} far below maximum voluntary ventilation (MVV)	⊙		
Metabolic acidosis by arterial blood gas late in exercise	⊙	⊙	
Decreasing PETCO ₂ late in exercise	⊙	⊙	
R clearly rises above 1.0	⊙	⊙	
Stop exercising due to leg fatigue	⊙	⊙	
Heart rate near predicted maximum late in exercise	⊙		
ST changes on electrocardiography	⊙		
Inappropriate blood pressure response	⊙		
Increasing or unchanged VD/VT by arterial blood gas late in exercise		⊙	
Absent ventilatory threshold			⊙
Decrease in oxygen saturation		⊙	⊙
Heart rate far below predicted maximum late in exercise			⊙
Increasing or unchanged PETCO ₂ late in exercise			⊙
PaCO ₂ > 40 mm Hg by arterial blood gas (end-exercise)			⊙
\dot{V}_{Emax} near MVV			⊙
Decreasing tidal volume			⊙
R does not increase above 1.0			⊙
Stop exercising due to dyspnea			⊙

*Pulmonary vascular and interstitial lung diseases share many common features on CPET, and additional resting, such as echocardiography, pulmonary function testing, and imaging, is often necessary to distinguish between the two forms of disease.

[†]Can be seen if “air trapping” affects cardiac function.

The size of the marker indicates the relative importance of the observation.

Modified and reprinted with permission from Luks A, Glenney R, Robertson H: Introduction to cardiopulmonary exercise testing. New York, 2013, Springer.

An alternative method is one of pattern recognition that uses the expected trends for multiple variables over the course of progressive exercise to identify the organ system limiting exercise. As discussed earlier, general disease categories such as heart failure, pulmonary vascular disease, or ventilatory insufficiency have expected patterns of exercise responses (Table 26-5). These patterns can be weighted by their relative specificity for each organ system and then examined in sum to suggest the most likely organ system limiting exercise. Patients with cardiac limitation, for example, will demonstrate a ventilatory threshold, a decreased PETCO₂ and arterial PCO₂, and an increased ventilatory \dot{V}_E/\dot{V}_{O_2} and \dot{V}_E/\dot{V}_{CO_2} at end-exercise. Patients with pulmonary hypertension demonstrate many similar findings but will manifest hypoxemia and a fixed VD/VT in late exercise. Other temporal trends that are specific for an organ system failure can be seen with exercise but not regularly enough to warrant listing in Table 26-5. Patients with severe heart failure, for example, may have exercise oscillatory ventilation^{64,65} that can be readily seen when the \dot{V}_E is plotted as a function of time or work rate.

Because the various observations listed in Table 26-5 are not necessarily present in every patient, a useful approach in the pattern recognition method is to conceptualize it as a scale on which the different observations are blocks that

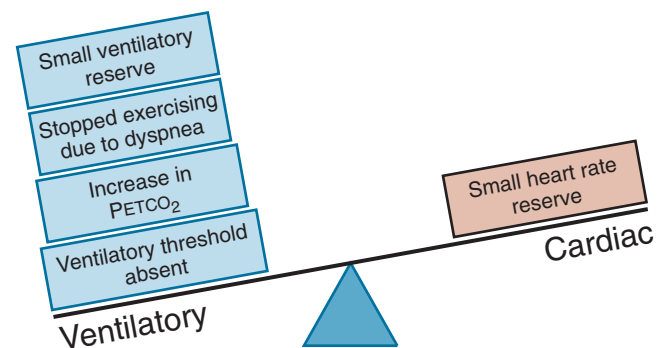


Figure 26-12 The “balance” approach to identifying the pattern of exercise limitation. In this example, the patient has many features consistent with ventilatory limitation due to COPD and only one aspect of the data consistent with a cardiac limitation. Because the preponderance of data favors the left side of the balance, this patient would be best labeled as having a ventilatory limitation pattern.

are placed on the side of the scale representing the potential limiting pattern (Fig. 26-12). Each block may be of different size representing the relative weight placed on that particular factor. The presence or absence of a ventilatory threshold would be the biggest block in this method. The side of the scale with the greatest weight (number of blocks)

is most likely to be the limiting organ system. By being less dependent on single parameters to make a decision throughout a binary tree, pattern recognition may be less prone to misclassifications of the limiting organ system. The disadvantage of the pattern recognition approach is that it requires some expertise to recognize the patterns.

Each of these approaches to data interpretation has strengths and weaknesses, and neither has been demonstrated to be superior to the other. Regardless of the interpretation method used, the CPET data are more useful for determining the primary system limiting exercise and less effective at identifying the specific disease process at work.

ALTERNATIVE METHODS OF ASSESSING EXERCISE PERFORMANCE

In addition to the symptom-limited progressive work exercise test, there are several other means for assessing exercise responses in clinical practice.

The 6-Minute Walk and Shuttle Walk Tests

The 6MWT is a widely available, inexpensive, and reproducible submaximal exercise test during which subjects walk back and forth along a flat indoor course varying in length between 30 and 100 m for a period of 6 minutes under the supervision of a trained technician following a specified testing protocol.²²⁷ Individuals move at their own pace, can use supplemental oxygen, and, unlike in a cardiopulmonary exercise test, may stop to rest if necessary. The primary measurements obtained during the test include the distance walked, as well as heart rate, oxygen saturation, blood pressure, and subjective ratings of dyspnea and leg fatigue. The test is usually performed only once during a given testing period, although some have argued that addition of a second trial improves the yield of the study.²²⁸

The 6MWT is used for two general purposes. The first of these is to monitor response to interventions or follow disease activity over time as demonstrated by the extensive use of the distance walked as an outcome in pulmonary hypertension²²⁹ and idiopathic pulmonary fibrosis trials,²³⁰ while the other is to assess patient prognosis. Studies done in patients with COPD,²³¹ pulmonary hypertension,²³² and idiopathic pulmonary fibrosis^{233,234} have shown relationships between the distance walked or development of hypoxemia during the test and outcomes such as mortality risk. Such information can be used to guide management decisions, such as when to list a patient for transplantation. Whether the distance walked is an adequate surrogate for $\dot{V}O_{2\max}$ remains unclear, however, because studies have reported varying degrees of correlation between these two variables.²³⁵ Importantly, due to the limited nature of the data available from the test, the 6MWT cannot be used to determine the etiology of exercise limitation. In addition, it is generally only relevant to patients or elderly individuals who are unable to maintain a normal or brisk walking pace and has little role in the assessment of exercise responses in fit individuals.

Use of the test for the purposes noted earlier requires recognition of several important issues. First, although reference values for normal individuals have been published,^{236,237} their utility is limited by the fact that test results vary on the basis of differences in testing methodology and the popula-

tion under consideration. Second, subject performance can be affected by learning, verbal encouragement, and course layout, necessitating strict adherence to published guidelines for conducting the test.²²⁷ Finally, when using the 6MWT to assess response to therapy or change over time, clinicians must understand the minimal clinically important difference, the threshold at which a change in 6MWT is recognized as either important by the patient or associated with other outcomes. Minimal clinically important difference values have been published but vary depending on the patient population and outcome in question.^{238,239}

The incremental *Shuttle Walk Test* (SWT) is a less widely used alternative to the 6MWT, which requires the patient to walk at a specified pace that increases over time until the individual can no longer maintain the pace or stops due to symptoms. Designed as a less invasive assessment of maximum exercise capacity, the test correlates reasonably well with $\dot{V}O_{2\max}$ ²⁴⁰ and can be used to monitor responses to therapeutic interventions.²⁴¹ Reference values for normal individuals are lacking, and its use is largely limited to following changes over time in a given patient or to making comparisons between patient groups.

More thorough reviews of the clinical utility and limitations of these tests are available elsewhere.^{242,243}

Exercise Treadmill Testing

In addition to its role in cardiopulmonary testing described earlier, *exercise treadmill testing* (ETT) is also commonly performed without exhaled gas collection. Because data collection is limited in such cases to assessment of symptoms, blood pressure, heart rate, oxygen saturation, electrocardiography, and exercise duration, ETT cannot be used to determine which system is limiting exercise but does provide information for assessing exercise responses and guiding management.

The primary use of ETT is to identify coronary artery disease in low- to intermediate-risk individuals capable of exercise who have normal baseline electrocardiograms (absence of left bundle branch block, left ventricular hypertrophy with any repolarization abnormalities, or ST segment depression). The test can be performed in the outpatient setting, as well as part of diagnostic protocols for low-risk patients admitted to chest pain units from the emergency department.²⁴⁴ Myocardial perfusion imaging is combined with ETT for patients with abnormal baseline electrocardiograms and is often necessary when evaluating female patients because the predictive capability of routine ETT is limited by the lower pretest probability of *coronary artery disease* (CAD) in this patient group.²⁴⁵

Using the concept of *metabolic equivalents* (METs) rather than direct measurement of $\dot{V}O_{2\max}$, ETT can also be used to assess exercise capacity. Although this approach is less precise than measurements using exhaled gas collection, various studies have demonstrated its utility in patient assessment and prognostication. Higher exercise capacity on ETT is associated with less significant coronary artery disease on left heart catheterization, for example,²⁴⁶ while decrements in exercise capacity measured by ETT predict mortality in both men and women.^{157,158} Consideration of exercise capacity may also improve the predictive ability of risk models on the basis of traditional clinical CAD risk factors.²⁴⁷

Other variables measured during ETT can also be related to mortality risk or the severity of coronary artery disease. For example, decreased heart rate recovery following exercise (<25 beats/min) is associated with increased risk of sudden death from myocardial infarction,²⁴⁸ whereas impaired heart rate response to increasing work rates is an independent predictor of mortality in asymptomatic women²⁴⁹ and impaired blood pressure responses are useful for identifying patients with three-vessel coronary disease.²⁵⁰ More complete reviews of the utility of ETT can be found elsewhere.^{251,252}

Key Points

- The ability to perform sustained exercise requires tight integration of multiple systems. Disease within any of these systems can manifest as dyspnea during exertion or as exercise limitation.
- Assessment of maximal oxygen consumption provides valuable insight into maximum exercise capacity, as well as important aspects of cardiac function including cardiac output and stroke volume.
- Normal individuals demonstrate a characteristic pattern of responses to progressive exercise to a symptom-limited maximum. Characteristic patterns of deviation from these normal responses are seen in various disease states such as heart failure, pulmonary vascular disease, interstitial lung disease, and COPD.
- Cardiopulmonary exercise testing can be used to characterize the pattern of responses to progressive exercise and to identify the primary organ system limiting exercise capacity.

- Beyond assessing exercise capacity, cardiopulmonary exercise testing can be used to gather prognostic information and guide management in certain patient groups, guide perioperative management in thoracic and other major surgical procedures, assess disability, and develop exercise prescriptions as part of rehabilitation programs.

Complete reference list available at ExpertConsult.

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INTRODUCTION

Definition and Impact of Postoperative Pulmonary Complications in Thoracic Surgery

Morbidity and Mortality in Thoracic Surgery: Can We Identify Patients at the Highest Risk for Adverse Outcomes?

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INTRODUCTION

Patients undergoing thoracic surgeries are different from those undergoing most noncardiac surgeries. Although the risk for perioperative major cardiac complications is significant, *postoperative pulmonary complications* (PPCs) contribute equally, if not more, to perioperative morbidity and mortality in this group of patients. Almost by definition, lung resection leaves patients with impaired pulmonary function (with some important exceptions, see later). The purpose of preoperative assessment of thoracic surgery patients is to identify high-risk patients (including those in whom the risk may preclude surgery), to plan the intraoperative and postoperative management, and to treat concomitant medical issues, with the goal of optimizing patient outcomes.

In this chapter we will provide an approach to the preoperative evaluation of patients undergoing thoracic surgery in light of the most recent evidence about the physiologic demands that these surgeries impose on patients. We will also briefly touch upon important issues during the intraoperative and immediate postoperative period that may influence outcome and may be of interest to pulmonologists who are involved in managing this interesting and challenging group of patients.

DEFINITION AND IMPACT OF POSTOPERATIVE PULMONARY COMPLICATIONS IN THORACIC SURGERY

Unsurprisingly, postthoracic surgery patients have a higher risk for PPCs (Table 27-1) than patients having upper or lower abdominal surgeries (19% to 59% compared to 16% to 17% and 0% to 5%, respectively¹).

One reason for the wide variability in the reported incidence of PPCs is the variability in defining what constitutes a PPC. For the purposes of this chapter we will define PPCs as shown in Table 27-1. PPCs after lung resection are a major cause or contributing factor to postoperative deaths, accounting for up to 84% of all deaths.¹ PPCs have a disproportionate impact on hospital costs as well,

with one study finding that PPCs (defined by the authors as pneumonia, unplanned intubation, and failure to wean from mechanical ventilation) added more to hospital costs than either cardiovascular, infectious, or thromboembolic complications.² An important study using data from the prospectively collected National Surgical Quality Improvement Program showed that a postoperative complication within the first 30 days after eight common surgeries (including lung resection) was independently associated with increased short-term (30-day) and long-term (1- and 5-year) mortality.³ Compared to wound complications, the other most common postoperative complication, PPCs had a disproportionate adverse impact on survival, as shown in Figure 27-1.

MORTALITY AND MORBIDITY IN THORACIC SURGERY: CAN WE IDENTIFY PATIENTS AT THE HIGHEST RISK FOR ADVERSE OUTCOMES?

Lung cancer is the most common indication for lung resection in the Western world,⁴ and, for patients with localized cancer, lung resection provides the best chance of a cure.⁵ The poor outcomes associated with nonoperative management of lung cancer together with improvements in surgical technique, anesthetic management, and postoperative management have resulted in larger numbers of sicker patients being offered surgery. It is now well established that the operative volume of the hospital where lung resection is performed has an important impact on outcomes.⁶⁻⁸ Mortality has also been reported to be lower when surgeries are performed by board-certified thoracic surgeons compared to nonspecialists, even though the board-certified thoracic surgeons often operate on patients with a higher burden of comorbid disease.⁹

Consequently, there is significant interest in the ability of clinicians to be able to predict the risk for mortality and major morbidity following thoracic surgery, both to ensure quality and to provide patients with a reasonable estimate of the risk involved before undertaking surgery.¹⁰ Currently available tools are limited in their utility by the quality of the databases that are used to generate them.

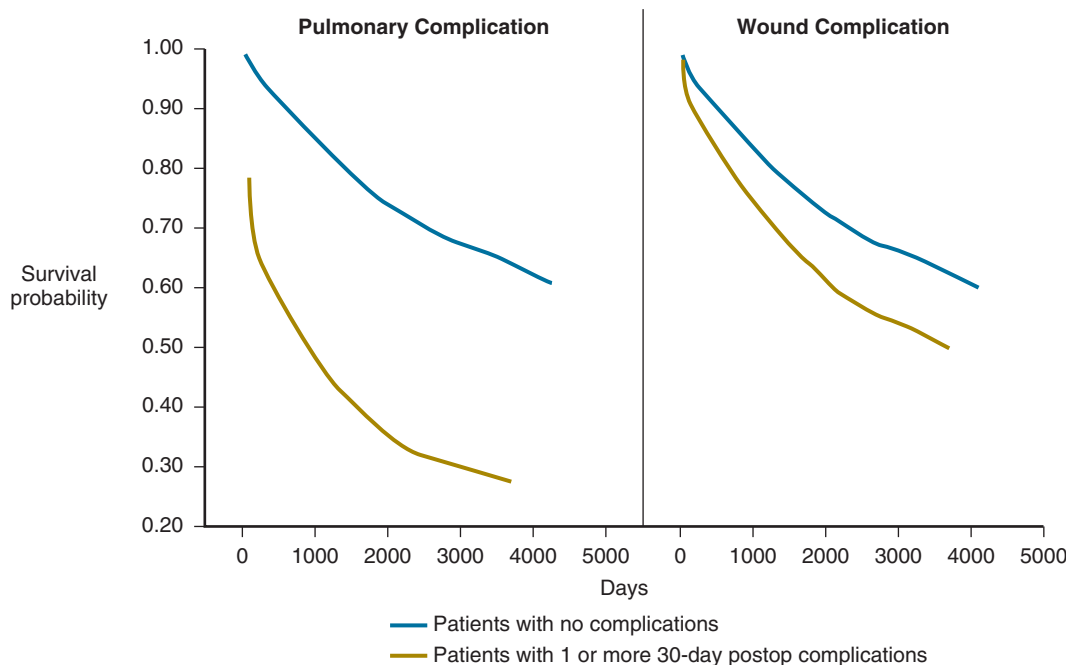


Figure 27-1 Postoperative pulmonary complications (PPCs) have a significant influence on long-term mortality. Cox survival curves of study patients stratified as to whether or not the patients had sustained a PPC (*left*) or wound complication (*right*) in the first 30 postoperative days. Compared to wound complications, pulmonary complications had a disproportionate impact on survival. (From Khuri SF, Henderson WG, DePalma RG, et al: Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 242[3]:326–341; discussion 341–343, 2005.)

Table 27-1 Definition of Postoperative Pulmonary Complications

1. Nosocomial pneumonia (bacteriologically confirmed)
2. Lobar or whole lung atelectasis on chest radiograph
3. Acute respiratory failure: mechanical ventilation for > 24 hr OR reintubation
4. Prolonged air leak requiring > 7 days of chest tube drainage
5. Pulmonary embolism (confirmed radiographically or on autopsy)
6. Acute respiratory distress syndrome
7. Pneumothorax
8. Bronchospasm
9. Aspiration pneumonitis

From Stephas F, Boucheseiche S, Hollande J, et al: Pulmonary complications following lung resection: a comprehensive analysis of incidence and possible risk factors, *Chest* 118:1263–1270, 2000.

The Thoracoscore was developed in France using data obtained from more than 15,000 patients who were enrolled in a nationally representative thoracic surgery database (Epithor, developed by the French Society of Thoracic and Cardiovascular Surgery). The authors identified nine factors that predicted increased mortality: age, sex, dyspnea score, American Society of Anesthesiologists status, performance status, priority of surgery, diagnosis, procedure class, and comorbid disease.¹¹ The model was subsequently validated in the United States¹² and incorporated into the British Thoracic Society guidelines for risk assessment of patients with lung cancer¹³; it is available in a Web-based calculator (http://sfctcv.fr/pages/epithor/thoracoscore_engl.php). However, more recent studies have found the Thoracoscore to have a lower predictive power than reported earlier.^{14,15} Recently Kozower and colleagues¹⁶ reported on a model of perioperative risk for mortality and major morbidity from a

database of more than 18,000 patients—the *Society of Thoracic Surgeons* (STS) General Thoracic Database. They found 12 risk factors to be associated with mortality, including American Society of Anesthesiologists status, the Zubrod functional status scale, renal dysfunction, induction chemotherapy, *forced expiratory volume in the first second* (FEV₁), body mass index (an increase was protective), male sex, and importantly, the type of surgery (pneumonectomy and bilobectomy had significantly higher mortality risks).¹⁶ An important limitation of both the Thoracoscore and the STS models is the lack of incorporation of *diffusing capacity for carbon monoxide* (DL_{CO}) data into their models because the majority of the patients in this database did not have measurement of diffusion capacity. In a subset of the STS database patients that did have DL_{CO} values (almost 7900 patients), DL_{CO} was found to be a strong independent predictor of mortality, in addition to the factors mentioned previously.¹⁷ Although these and other predictive models are still far from ideal, they do provide the clinician with objective data that may help supplement individual judgment in planning the best course of action for complex patients.

ASSESSMENT OF CARDIAC RISK IN PATIENTS WITH LUNG DISEASE

Patients with lung cancer often have cardiovascular disease, because cigarette smoking is a shared risk factor for both diseases. The revised guidelines from the *American College of Cardiology and the American Heart Association* (ACC/AHA) are particularly helpful in evaluating cardiac risk¹⁸ (Fig. 27-2).

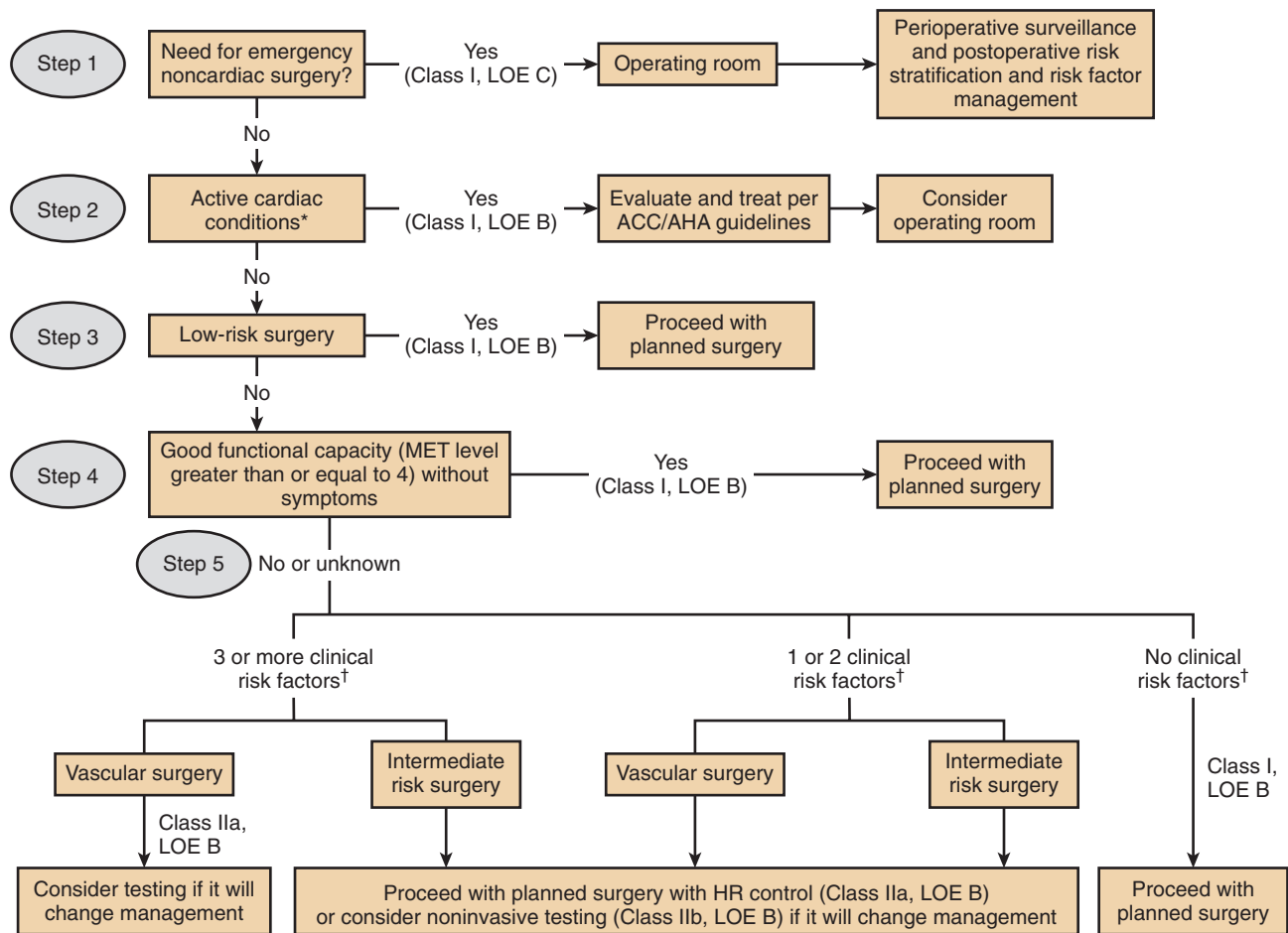


Figure 27-2 Cardiac evaluation and care algorithm for noncardiac surgery based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or greater. *Active cardiac conditions include unstable coronary syndromes, decompensated heart failure, significant arrhythmias, and severe valvular disease. †Clinical risk factors include ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease. ACC, American College of Cardiology; AHA, American Heart Association; LOE, level of evidence; MET, metabolic equivalent; HR, heart rate. (From Fleisher LA, Beckman JA, Brown KA, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *Circulation* 116[17]:e418–e499, 2007.)

The pathway for both emergent and elective surgeries in patients with active cardiac conditions (a *myocardial infarction* [MI] < 30 days ago, unstable angina, decompensated heart failure, significant arrhythmias, or severe valvular disease) is relatively straightforward. Most thoracic procedures fall into the intermediate risk category (with a combined risk for cardiac death and nonfatal MI between 1% and 5%), and will need a cardiac workup if they have *both* a poor functional capacity—defined as an exercise capacity of less than 4 metabolic equivalents (METs; 1 MET is approximately the level of effort required to climb up a flight of stairs) *and* more than one risk factor on the Revised Cardiac Risk Index¹⁹ (comprising a history of ischemic heart disease, cerebrovascular disease, heart failure, diabetes mellitus, and renal insufficiency). Most thoracic surgery patients in this group are likely to benefit from perioperative heart rate control. The ACC/AHA guidelines recommend noninvasive stress testing in this group of patients only if it is likely to change clinical management. Some patients may fall into relatively ill-defined areas in the guidelines, and they benefit from the opinion of an experienced cardiologist. A few specific situations are examined in the following section.

INDICATIONS FOR CORONARY REVASCULARIZATION

There has been a consensus over the last decade that invasive testing and coronary revascularization (either with bypass surgery or percutaneous coronary intervention) are unlikely to improve outcomes in noncardiac surgery unless the intervention is independently indicated for an acute coronary syndrome. In the Coronary Artery Revascularization Prophylaxis trial for patients undergoing vascular procedures, McFalls and associates²⁰ randomly assigned 510 patients with significant coronary artery stenosis from among 5859 patients to either coronary artery revascularization or no revascularization before surgery. The short-term risk for death or MI or long-term outcomes was similar in both groups. It is important to remember that the study excluded patients with more than 50% left main vessel disease, a left ventricular ejection fraction of less than 20%, and severe aortic stenosis.²⁰ Subsequent studies have supported these conclusions.^{21,22} (These studies were performed in the vascular surgery population, because this group of patients is at the highest risk for perioperative cardiac death/nonfatal MI.¹⁸) Although prospective data in

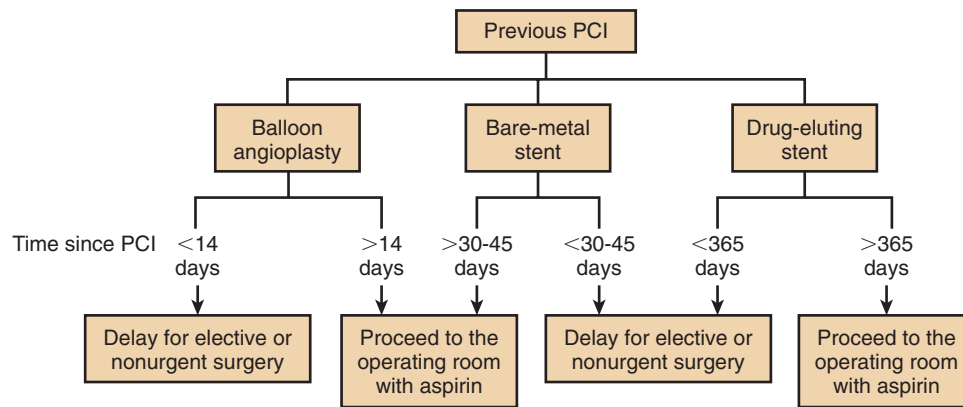


Figure 27-3 Proposed approach to the management of patients with previous percutaneous coronary intervention (PCI) who require noncardiac surgery, based on expert opinion. (From Fleisher LA, Beckman JA, Brown KA, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery]: developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation* 116[17]:e418-e499, 2007.)

thoracic surgery patients are lacking, it is not unreasonable to extrapolate these data to the thoracic surgery population. A number of retrospective studies show a higher incidence of major cardiac adverse events in patients who undergo lung surgery after the placement of either a bare metal stent or a drug-eluting stent.²³⁻²⁵ The difficult problem of a patient who needs both coronary revascularization and lung resection for cancer is best resolved on a case-by-case basis. The ACC/AHA recommended approach to nonemergent surgery in patients who have had a percutaneous coronary intervention is laid out in Figure 27-3.

β-BLOCKADE

The publication of the POISE (*PeriOperative ISchemic Evaluation*) trial in 2008 resulted in significant changes to the ACC/AHA recommendations on perioperative β-blockade that were laid out in the 2009 focused update on perioperative β-blockade.²⁶ The POISE investigators randomized 8351 patients with or at risk for atherosclerotic disease to a fixed, relatively high dose of extended-release metoprolol (200 mg/day) compared to placebo, beginning with 100 mg 2 to 4 hours before surgery and continuing for 30 days. Fewer patients in the metoprolol group had an MI. However, more patients died in the metoprolol group than in the placebo group. These deaths were attributed to a higher incidence of strokes in the metoprolol group, perhaps secondary to a higher incidence of hypotension and bradycardia in these patients.²⁷ The POISE study therefore raised the possibility that initiating β-blockers perioperatively in β-blocker-naïve patients *without titrating the dose to heart rate and blood pressure parameters* may be associated with worse outcomes. Consequently, although continuing β-blockers for patients who are already on these medications remains a class I recommendation, the ACC/AHA has downgraded its recommendation for initiating β-blockers in high-risk vascular surgery patients from class I to class IIa and added the proviso that β-blockers should be titrated to heart rate and blood pressure. A similar recommendation applies to high-risk thoracic surgical patients. A new recommendation has been added advising against the initiation of high-

dose β-blockers in the absence of titration (class III).²⁶ Another issue with perioperative β-blockade is that clinicians are sometimes reluctant to use these drugs on elderly patients and in patients with *chronic obstructive pulmonary disease* (COPD) for fear of exacerbating airway obstruction. However, the data suggest that, not only is it safe to administer β-blockers to such patients, but that failing to use these drugs may be associated with worse outcomes.²⁸⁻³⁰

ATRIAL FIBRILLATION PROPHYLAXIS

Atrial fibrillation (AF), the most common arrhythmia following general thoracic surgical procedures, develops in 12% to 44% of patients after lung resection and esophageal surgeries.^{31,32} Patients with postoperative AF have increased lengths of hospital stay, increased medical costs, and increased risks for stroke, cognitive dysfunction, and death.^{31,33} Consequently, effective prophylaxis to prevent postoperative AF is an important goal. The recommendations in this section are derived from clinical practice guidelines on AF prophylaxis by the STS.³⁴ As in the ACC/AHA guidelines regarding perioperative β-blockade, it is important to continue β-blockers in patients already taking them to reduce the risk for β-blocker withdrawal. The data here come chiefly from the cardiac surgery literature, where propranolol withdrawal has been associated with new-onset AF.^{35,36} The dose of β-blockers in these patients should be adjusted, and “hold-parameters” should be in place because many of them are likely to have epidural catheters in place for analgesia, increasing the risk for hypotension and bradycardia. In patients not taking β-blockers preoperatively and who do not need to be started on them based on the ACC/AHA recommendations described earlier, calcium channel blockers such as diltiazem have proven to be effective at AF prophylaxis.^{37,38} Amiodarone is effective at AF prophylaxis^{39,40}; however, in one study, amiodarone was associated with an increase in the incidence of acute respiratory distress syndrome—particularly if given after a pneumonectomy.³⁹ The use of amiodarone may also be associated with a higher incidence of postoperative acute respiratory distress syndrome^{41,42} and, if there is

preexisting pulmonary disease, a higher risk for amiodarone-induced pulmonary toxicity.⁴³ On the other hand, two more recent studies by Tisdale and coworkers in patients after pulmonary resection⁴⁰ and after esophagectomy⁴⁴ did not find increased pulmonary toxicity with amiodarone, although the doses used were lower. For the present the STS recommends the use of amiodarone only in very limited circumstances and in carefully controlled doses. It recommends against the use of amiodarone for AF prophylaxis in patients undergoing pneumonectomy. Digitalis and flecainide should not be used for the prophylaxis of AF.^{37,45} Therefore the current recommendations for AF prophylaxis are to continue β -blockade throughout the perioperative period if the patient is already taking β -blockers. If the patient is not taking them, then calcium channel blockers would be recommended for prophylaxis.

SPECIAL PATIENT POPULATIONS

PATIENTS WHO SMOKE

Smoking is one of the most important causes of preventable death in the world. Studies suggest that smoking is responsible for almost half a million deaths and more than \$200 billion in health care costs and lost productivity in the United States alone.⁴⁶ At the time of diagnosis of lung cancer, it is estimated that up to 18% of patients have never smoked, 58% are former smokers, and 24% to 40% are current smokers.⁴⁷ About 20% of patients smoke at the time of cancer surgery, and half of these continue to smoke afterward.⁴⁷ There are extensive data documenting the adverse effects of smoking on both pulmonary function and clinical outcomes. Smoking decreases macrophage function, impairs vascular endothelial function, decreases coronary reserve, and places patients at increased risk for tachycardia, hypertension, and ischemia.^{48,49} In addition, smoking increases the risk for arterial desaturation and laryngospasm during anesthesia.⁵⁰ Smokers also have increased levels of carboxyhemoglobin (between 3% and 15%) that both compromise the total oxygen content of blood and impairs oxygen release at the tissue level by shifting the oxygen dissociation curve to the left.⁵¹ Recent multicenter outcome studies have confirmed the association between smoking and worse perioperative outcomes. Using data from the American College of Surgeons National Surgical Quality Improvement Program database, Turan and colleagues⁵² showed that smokers had an approximately 30% higher adjusted odds of postoperative mortality and major complications compared to nonsmokers. Another large database analysis using the Veterans Affairs Surgical Quality Improvement Program (with more than 390,000 patients) showed that past smokers have an approximately 20% higher odds of postoperative mortality or major complication.⁵³ In an STS database with almost 8000 patients undergoing lung resection surgery for cancer, Mason and associates⁵⁴ showed that smokers have a significantly increased risk for hospital mortality and pulmonary complications (hospital mortality 1.5% in smokers compared to 0.39% in nonsmokers), and that smoking cessation gradually mitigated these risks. However, they could not identify an optimal interval for smoking cessation.

There is some controversy over the timing of smoking cessation because some studies suggested an increase in PPCs in patients who quit smoking less than 8 weeks before surgery.^{55,56} The risk seemed to be higher in patients who quit closest to the day of surgery. However, more recent studies have not been able to show this increased risk in recent quitters. It does seem that the benefits increase with the duration of smoking cessation. A meta-analysis of 6 randomized trials and 15 observational studies of smoking cessation demonstrated a relative risk reduction of 41% in PPCs. In addition, each week of cessation increased the magnitude of the effect by 19%.⁵⁷ Another recent meta-analysis examined postoperative outcomes in patients who quit smoking less than 8 weeks before surgery compared to those who continued to smoke. They reported that there was no evidence of any positive or negative effect of late smoking cessation on PPCs.⁵⁸ Given these data, it seems prudent to encourage smoking cessation irrespective of surgical timing. The U.S. Public Health Service recommends that physicians strongly advise smokers to quit smoking because physicians' advice to quit has been associated with increased abstinence rates. Effective interventions include medical advice and pharmacotherapy such as nicotine replacement (which is generally safe in the perioperative period) and non-nicotine options such as bupropion and varenicline. Varenicline seems to be the most effective pharmacologic intervention to promote abstinence from smoking.^{59,60} It is important to note that the Food and Drug Administration has issued boxed warnings for both drugs because of reports of increased psychiatric symptoms or suicidal ideation.⁶¹

ASTHMA

Well-controlled asthma is unlikely to be a risk factor for either intraoperative or postoperative complications (for clinical aspects of asthma, see Chapter 42). However, poorly controlled asthma, evidenced by active wheezing, can increase PPCs.⁶² The combination of inhaled β -agonists such as albuterol and inhaled steroids with long-acting β -agonists is often very useful to achieve control of symptoms before surgery. If bronchospasm persists, a short course of low-dose systemic steroids may be considered and does not seem to have an impact on postoperative wound healing.⁶³ It is important to keep in mind that symptoms suggestive of asthma could in fact be due to other pathologic conditions such as pulmonary carcinoid,⁶⁴ tracheal stenosis,⁶⁵ and other endobronchial tumors,⁶⁶ and difficult-to-treat asthma should prompt a workup for these rarer conditions.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is increasingly being recognized as a disorder with both pulmonary and extrapulmonary manifestations, including an increased incidence of lung cancer⁶⁷ (for clinical aspects of COPD, see Chapter 44). Between 50% and 80% of patients with lung cancer have COPD, and the association is independent of the intensity of smoking.⁶⁸ Unlike well-controlled asthma, COPD is associated with an increased risk for PPCs.⁶⁹ As a general rule, the management of COPD before surgery is the same as for patients who

will not have surgery. The optimal management of COPD, including surgical approaches such as lung volume-reduction surgery, is discussed elsewhere in this textbook. (For clinical discussion of lung volume-reduction surgery, see Chapter 44.) Preoperative pulmonary rehabilitation may improve perioperative outcomes in these patients⁷⁰ (see later).

OBSESITY AND OBSTRUCTIVE SLEEP APNEA

More than 65% of Americans are overweight or obese. Obesity is associated with multiple comorbidities, including diabetes and heart disease. There is evidence that obesity is an independent risk factor for worse perioperative outcomes in many types of surgery⁷¹—however, in thoracic surgeries, the effect of obesity on outcome is less clear. As mentioned earlier, a high body mass index appeared to be protective in the STS database risk model study by Kozower and coworkers.¹⁶ A recent propensity-matched comparison of survival after lung resection in high versus low body mass index groups also suggested a protective effect of obesity in the setting of lung cancer.⁷² In another retrospective study, Dhakal and associates⁷³ did not find any adverse effect of obesity on postoperative morbidity or mortality following lung resection. It is unclear why obesity has no harmful or even a protective effect for perioperative outcomes—it is tempting to speculate that, in the setting of lung cancer, obesity is a marker of better nutritional and immune status, leading to better outcomes.

In contrast, patients with *obstructive sleep apnea* (OSA) have a higher incidence of (mainly respiratory) PPCs than those without OSA⁷⁴ (for discussion of OSA, see Chapter 88). In those undergoing hip or knee replacements, 39% of patients with OSA developed PPCs or cardiac complications compared to 18% of patients without OSA; 24% of the patients with OSA required intensive care unit admissions compared to 9% of patients without OSA.⁷⁵ Few investigations have identified the perioperative risks for OSA surgical patients,⁷⁶ but left heart failure or right heart dysfunction due to pulmonary hypertension could be responsible and should be sought. In particular, pulmonary hypertension is associated with significant perioperative risk.⁷⁷⁻⁷⁹ Because cardiovascular dysfunction in OSA patients can be modified by treatment,⁸⁰⁻⁸² it is important to identify patients with OSA and begin treatment. The use of standardized questionnaires such as the STOP (*Snoring, Tiredness during daytime, Observed apnea, high blood Pressure*) and STOP-Bang (*Body mass index, Age, Neck circumference, Gender*) forms have been validated in the perioperative setting and provide a simple and useful screening tool for OSA.⁸³ Current studies suggest that diagnosis and treatment of OSA can improve postoperative outcomes.^{83a}

LUNG RESECTION

The preoperative evaluation of patients for lung surgery differs from that for other surgeries. Not only are these patients more likely to have pulmonary disease, but the postoperative function may be impaired permanently because of the effects of the operation. In most other operations, the evaluation is primarily to optimize the anesthetic

Table 27-2 Resections That May Change Postoperative Pulmonary Function

Worse Function	Better Function
<ul style="list-style-type: none"> ■ Sublobar resection ■ Lobectomy ■ Pneumonectomy 	<ul style="list-style-type: none"> ■ Decortication/pleurodesis ■ Bleb resection ■ Volume reduction ■ Lung transplantation

and surgical plan and to prepare the patient, but in pulmonary resection, the evaluation determines whether or not the surgery can proceed.

PREDICTING POSTOPERATIVE FUNCTION

The challenge in assessing patients for pulmonary resection is predicting the postoperative course, both for the acute changes and postoperative morbidity, and for the final postoperative status. Depending on the type of operation, the eventual status may be better or worse than the current status (Table 27-2).

The typical method used to predict postoperative function is to use a regional ventilation-perfusion scan (V/Q scan using a radioactive gas) to estimate the proportion of lung function expected to be lost. This assessment was based on older studies that showed an excellent correlation.⁸⁴ More recent work, however, shows the nuances of postoperative functional prediction. For example, in one prospective study, the immediate postoperative function was significantly worse than the predicted postoperative FEV₁, and, although there was recovery in the first week, the FEV₁ did not reach the level predicted⁸⁵ (Fig. 27-4). In a study that followed patients over 3 months after discharge for lobectomy, pulmonary function was found to reach predicted levels at 1 month and in fact to surpass them at 3 months by approximately 10%⁸⁶ (Fig. 27-5).

In an STS report on their large registry of pulmonary resections (18,000 operations, 111 centers), pulmonary resection was associated with a 2% overall mortality.¹⁶ Significant predictors of morbidity and mortality included low preoperative FEV₁, renal failure, high American Society of Anesthesiologists class, steroid use, induction chemoradiation, and especially the type of resection, with pneumonectomy carrying more risk than lobectomy. Thoracoscopic surgery was somewhat protective.¹⁶

GUIDELINES FOR LUNG RESECTION

There are several consensus published guidelines for assessing a patient's suitability for pulmonary resection. Typically some measure of pulmonary function is used. Especially for more extensive resection (e.g., pneumonectomy), the possibility that the diseased lung may not be contributing a proportional share of function and thus may be safely resected is addressed by *predicted postoperative* (PPO) values. The estimate is usually calculated using ventilation-perfusion scans.

The American Thoracic Society/American College of Chest Physicians guidelines review cardiopulmonary exercise testing in detail but touch on preoperative evaluation only briefly. They recommend FEV₁ and DL_{CO} criteria as the

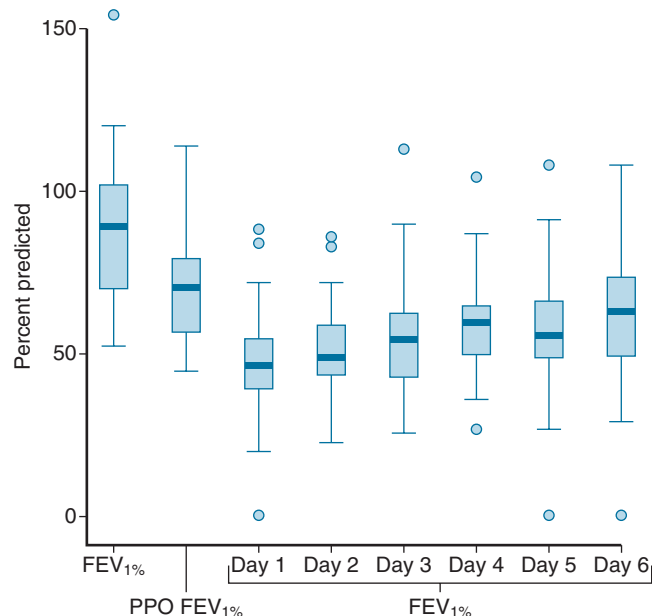


Figure 27-4 The actual FEV₁% measured in the first week after lobectomy compared to the predicted postoperative FEV₁%. In a prospective study of 125 patients undergoing lobectomy, the actual FEV₁% after surgery was lower than the predicted postoperative FEV₁% (PPO FEV₁%). Although the actual FEV₁% increased over 6 days, it remained below the level predicted (PPO FEV₁%). FEV₁% = FEV₁/FVC. (From Varela G, Brunelli A, Rocco G, et al: Predicted versus observed FEV₁ in the immediate postoperative period after pulmonary lobectomy. *Eur J Cardiothorac Surg* 30[4]:44–648, 2006.)

primary measures and, when these values are borderline, cardiopulmonary exercise testing has utility.⁸⁷ The British Thoracic Society recommends an initial FEV₁ evaluation and more detailed analysis in marginal cases.⁸⁸

PRINCIPLES OF CARDIOPULMONARY EXERCISE TESTING—STRENGTHS AND WEAKNESSES

(see Chapter 26)

Cardiopulmonary testing increases the demands of both the cardiovascular and respiratory system, but, given that the respiratory capacity is utilized only at peak exercise in healthy patients, exercise is usually limited by cardiac factors before respiratory function limits exercise capacity in normal individuals.⁸⁹ Exercise testing in patients is associated with severe complications in 1:10,000, and testing is contraindicated in patients with severe cardiac disease (e.g., cardiomyopathy, unstable angina, arrhythmias), uncontrolled asthma, significant infections, metabolic derangements, and uncooperative patients.⁹⁰

Not all investigations have found an association between exercise performance and a risk for perioperative complications.⁹⁰ Some of the issues with oxygen consumption measurements are that they are affected by muscle mass, body size, and level of fitness.⁸⁹ Therefore using *maximum oxygen consumption* ($\dot{V}O_2\text{max}$) may bias the preoperative assessment against older and obese individuals.⁸⁹

Some other issues that need to be considered are that $\dot{V}O_2/\text{kg}$ predictions based on preoperative measurements have significantly *overestimated* the degree of exercise capacity loss after an operation.⁹¹ Although the PPO $\dot{V}O_2/\text{kg}$ did not accurately predict postoperative exercise capacity, it was

nonetheless the best predictor for postoperative morbidity and mortality.⁹¹

It is also unclear whether preoperative exercise performance has any influence on long-term clinical outcomes. In one report, 68 of 86 patients categorized as high risk, with preoperative measured $\dot{V}O_2/\text{kg}$ less than 15 as well as having PPO FEV₁ of less than 33%, underwent lung resections. Although they had higher morbidities, the high-risk group had a low mortality of only 4% (3/68).⁹² Furthermore, the 68 high-risk patients who underwent resection had better 5-year outcomes than similar high-risk patients who were denied surgery.⁹² Patient outcomes after surgery are influenced by improvements in surgical techniques and postoperative care, as well as nonsurgical therapies for early-stage lung cancer, so that guidelines and other recommendations need to be revisited on a regular basis.⁸⁹

PREOPERATIVE PREDICTORS

Although a variety of testing schemes have been used for predicting postoperative complications after lung resection, $\dot{V}O_2\text{max}$ is currently considered the best predictor. In a 2007 meta-analysis of $\dot{V}O_2\text{max}$ as a predictor that pooled 14 studies and nearly 1000 patients, a higher $\dot{V}O_2\text{max}$ (20 versus 16 mL/kg/min) was found in the group without PPCs. DL_{CO} and FEV₁ were also somewhat higher in the group without complications; however, they were found to be less useful clinically than the $\dot{V}O_2\text{max}$.⁹³ $\dot{V}O_2\text{max}$ was also evaluated in a Cancer and Leukaemia Group B study that included 400 patients and a two-tier resectability evaluation. The first group based on FEV₁ and FEV₁-PPO criteria were considered “low risk.” Patients failing FEV₁ criteria were further stratified by a value of $\dot{V}O_2\text{max}$ greater than 15 mL/kg/min into “high risk” and “only at physician discretion.” The mortality and morbidity rate was higher for the high-risk group compared to the low-risk group, but overall survival was much better in all operative patients. There was also a tendency for the higher-risk patients to get a less extensive resection.⁹²

RECENT GUIDELINES FOR PREOPERATIVE TESTING IN LUNG CANCER PATIENTS

A recent evidence-based clinical practice guideline supported by the American College of Chest Physicians was published in the third edition of their supplement concerning the diagnosis and management of lung cancer.⁹⁴ Twelve recommendations were made and given grades for the level of existing evidence.⁹⁴ These recommendations for patients with lung cancer being considered for surgery are listed with our comments:

1. The preoperative assessment should be conducted by a multidisciplinary team. [This is reasonable, given that the patient will be cared for by a pulmonologist before and after surgery but will be cared for intraoperatively and perioperatively by an anesthesiologist and a surgeon.]
2. Evaluations should be done for patients regardless of age. [Many perioperative outcome studies have documented that the physiologic age is more important than the duration of life.]

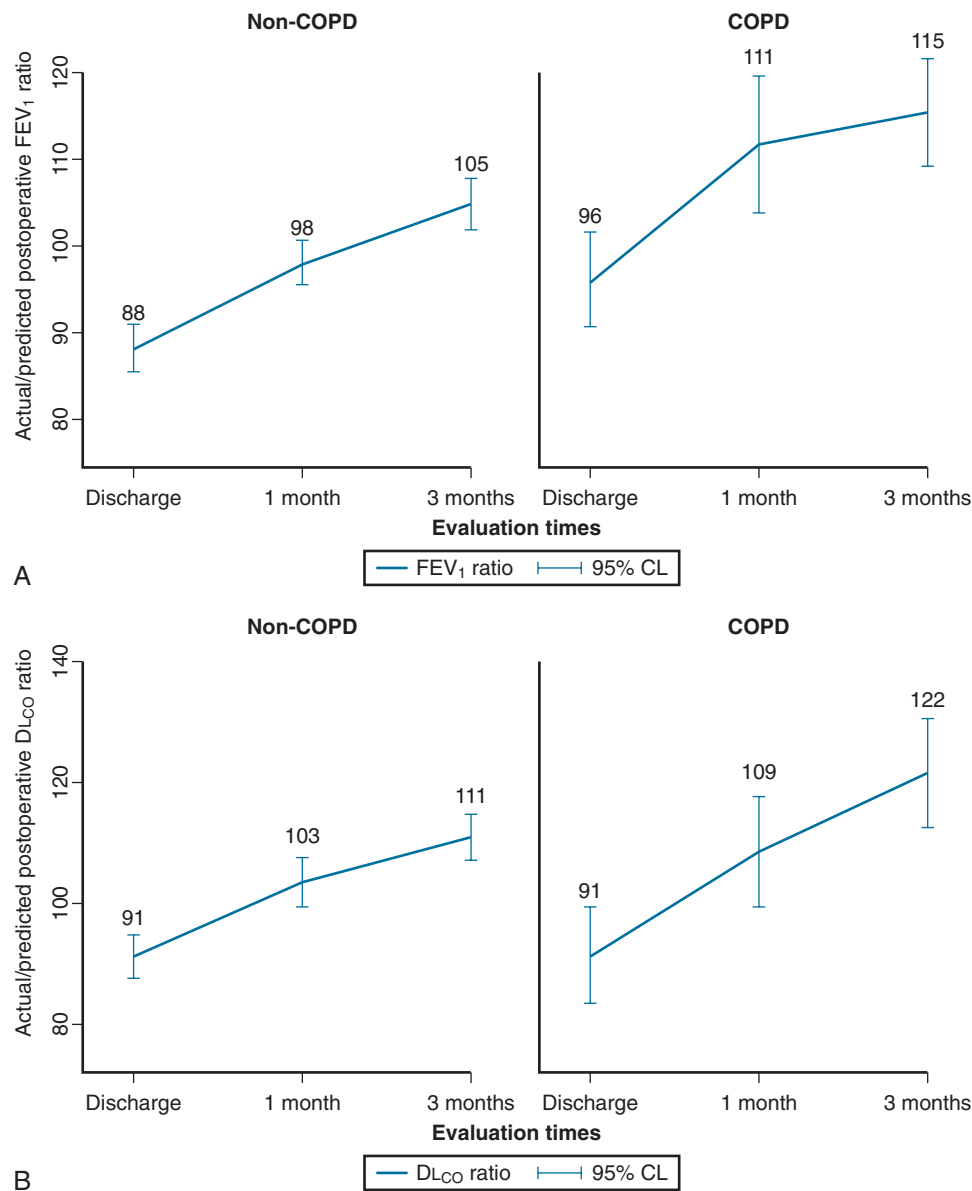


Figure 27-5 The ratios of actual to predicted postoperative values in patients with chronic obstructive pulmonary disease (COPD) or without COPD after lobectomy shown for FEV₁ (A) and DL_{CO} (B). COPD was defined as FEV₁ at or less than 80% and FEV₁/FVC less than 0.7. The predicted values were fairly accurate at 1 month in predicting the actual FEV₁ or DL_{CO} but underestimated the actual values at 3 months, especially in patients with COPD. CL, confidence limit. (From Brunelli A, Refai M, Salati M, et al: Predicted versus observed FEV₁ and DL_{CO} after major lung resection: a prospective evaluation at different postoperative periods. *Ann Thorac Surg* 83(3):1134–1139, 2007.)

- Cardiovascular risk should be managed according to existing guidelines for noncardiac surgery. [See earlier discussion of indications for coronary revascularization.]
- FEV₁ and DL_{CO} should be measured, and both PPO FEV₁ and PPO DL_{CO} should be calculated. If both of these PPO measurements are greater than 60% predicted, no further tests are recommended.
- However, if they are less than 60% predicted but above 30% predicted, a low-technology exercise test should be performed.
- If either of the PPO FEV₁ or the PPO DL_{CO} are less than 30% predicted, a formal cardiopulmonary exercise test should be done with measurement of the $\dot{V}O_2\text{max}$.
- Similarly, if a patient is considered for surgery who walks less than 25 shuttles [<400 m] on the shuttle walk test or climbs less than 22 m on a stair-climbing test, a formal cardiopulmonary exercise test with measurement of $\dot{V}O_2\text{max}$ is also recommended.
- If patients with lung cancer being considered for surgery have a $\dot{V}O_2\text{max}$ less than 10 mL/kg/min or less than 35% predicted, they should be counseled about minimally invasive surgery, sublobar resections, or nonsurgical treatment options. [See earlier comments regarding patients who were deemed high risk due to their exercise test results but had low perioperative mortality.⁹²]
- In patients with lung cancer who are being considered for surgery who undergo neoadjuvant therapy, it is

suggested that repeat pulmonary function testing with diffusing capacity be performed after completion of the neoadjuvant therapy. [These patients may be more prone to problems with drugs such as amiodarone—see earlier discussion.]

10. In patients with lung cancer in an area of upper lobe emphysema who are candidates for lung volume-reduction surgery, combined lung volume-reduction surgery and lung cancer resection is suggested.
11. In all patients with lung cancer being considered for surgery who are actively smoking, tobacco dependence treatment is recommended.
12. In patients with lung cancer being considered for surgery and deemed at high risk [PPO FEV₁ or the PPO DL_{CO} less than 60% predicted and $\dot{V}O_2$ max less than 10 mL/kg/min or less than 35% predicted], preoperative or postoperative pulmonary rehabilitation is recommended.⁹⁴

RISK MODIFICATIONS

Smoking Cessation

The most obvious risk modification available to patients is smoking cessation (see “Patients Who Smoke,” earlier). Interestingly, there had been a concern that there would be increased secretions and reactivity in the immediate withdrawal period. In the most relevant study of the timing of cessation before thoracotomy, Barrera and coworkers⁹⁵ found no difference in mortality or morbidity based on the duration of cessation and thus found no evidence of a paradoxical increase in complications among recent quitters. Smoking cessation is always to be encouraged before thoracotomy.

Surgical Approach

The surgical approach has implications for postoperative outcome. Based on the STS database of over 1000 patients undergoing lobectomy, a thoracoscopic approach had improved outcomes, including less AE, need for transfusion, and prolonged air leaks and shorter length of stay.⁹⁶ Similar findings have recently been found in a propensity score-matched study in which video-assisted thoracoscopic lobectomy was associated with a lower incidence of pulmonary complications (1.1% versus 12.1%), a shorter length of stay, and shorter operation time than lobectomy via thoracotomy.⁹⁷ Studies are now also showing that video-assisted thoracoscopic lobectomy offers similar long-term outcomes: in a study of patients with clinical stage I non-small cell lung cancer, video-assisted thoracoscopic lobectomy offered similar overall survival and disease-free survival as lobectomy by thoracotomy.⁹⁸

Exercise Training (For Clinical Exercise Testing, see Chapter 26)

It is interesting that $\dot{V}O_2$ max is a modifiable measurement. Preoperative interventions can improve exercise capacity in lung resection candidates. For COPD patients about to undergo lobectomy, Stefanelli and colleagues⁹⁹ found that “high-intensity training” improved $\dot{V}O_2$ max by 20%, an improvement that persisted for at least 2 months postoperatively. Static measures of lung function (DL_{CO} and FEV₁)

were unchanged by the training and decreased after surgery, as expected. In another study of 27 COPD patients facing lung resection, pulmonary rehabilitation improved $\dot{V}O_2$ max (from 13 to 19 mL/kg/min), arterial PO₂, and even FEV₁ to resectable levels, and subsequent resection was tolerated with only a 15% short-term morbidity.¹⁰⁰

Even if rehabilitation was not initiated before resection, there is evidence that postoperative exercise function can be improved with pulmonary rehabilitation after lung resection.¹⁰¹ Of course, merely improving the $\dot{V}O_2$ max does not guarantee better outcomes. The hope is that better function will allow a safer perioperative course in marginal patients¹⁰² and will improve overall postoperative function. However, the current literature is not yet sufficient to reach this conclusion. Certainly there is no hint of harm from pulmonary rehabilitation in this population, and the therapy matches recommendations for those in the general population with impaired pulmonary function.

Intraoperative Management

There is increasing recognition that intraoperative management can affect postoperative outcomes. Lung-protective ventilation, specifically smaller tidal volumes, use of positive end-expiratory pressure, and periodic recruitment maneuvers have significantly reduced postoperative pulmonary complications, need for reintubation, and length of stay in elective abdominal surgery.¹⁰³ The extension of these protective maneuvers to thoracic surgery is not simple. Pulmonary surgery usually benefits from one-lung ventilation, with the lung on the operative side deflated. However, because the pulmonary circulation is not routinely occluded, there is an obligatory pulmonary shunt and a real chance of hypoxemia during surgery. Traditionally, large tidal volumes, no positive end-expiratory pressure, and high fractional concentration of oxygen in inspired gas were used to combat hypoxemia.¹⁰⁴ However, there is now evidence that such management can cause postoperative pulmonary complications.¹⁰⁵ In a study designed to test different ventilatory strategies during one-lung ventilation for lung resection surgery, a protective lung ventilatory strategy was associated with significantly less postoperative lung dysfunction¹⁰⁵ (Fig. 27-6).

The choice of anesthetic agent also appears to influence the development of lung injury. For instance, in patients undergoing one-lung ventilation for thoracic surgery, the inhaled agents sevoflurane and desflurane suppressed the increase in a number of inflammatory markers (tumor necrosis factor, interleukin-1 β , interleukin-8) in bronchoalveolar lavage fluid as compared to intravenous propofol.¹⁰⁶

What factors predict hypoxia while performing one-lung ventilation? Patient position has a strong effect, with gravity improving flow to the dependent, ventilated lung.^{107,108} More disease in the non-ventilated lung, for instance as measured by end-tidal to arterial CO₂ gradient, predicts better tolerance of one-lung ventilation.¹⁰⁸ Overall, most thoracic anesthesiologists understand and work to minimize injury to the lungs during one-lung ventilation but also to preserve gas exchange.

Pain Management

A thoracotomy incision is considered to be one of the most painful surgical incisions and can significantly impair

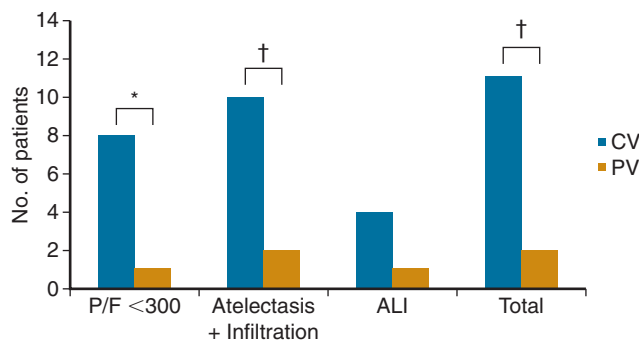


Figure 27-6 Pulmonary complications seen after two ventilatory strategies in one-lung ventilation for lung resection. Fifty patients were ventilated with conventional ventilation (CV, blue) and 50 with protected lung ventilation (PV, brown). The pulmonary complications within 72 hours of the operation include arterial PO_2 /fractional concentration of oxygen in inspired gas (P/F) less than 300 mm Hg, new lung infiltrates, or acute lung injury (ALI). Note that fewer of the postoperative patients developed complications after protective ventilation for all complications except ALI. * $P < 0.05$ by Fisher exact test; † $P < 0.05$ by χ^2 test. (From Yang M, Ahn HJ, Kim K, et al: Does a protective ventilation strategy reduce the risk of pulmonary complications after lung cancer surgery?: a randomized controlled trial. *Chest* 139[3]:530–537, 2011.)

postoperative respiratory function¹⁰⁹ (for discussion of chest pain, see Chapter 31). In addition, inadequate relief of postoperative pain has been linked to a higher incidence of chronic postthoracotomy pain,¹¹⁰ poorer functional status,¹¹¹ and an adverse effect on quality of life.¹¹² Effective postoperative pain management is therefore a critical component of the perioperative management of thoracic surgery patients. The most common modality of pain management for patients undergoing thoracotomies (as opposed to thoroscopic procedures) has been *thoracic epidural analgesia* (TEA), which is commonly considered the gold standard for pain management in this patient population.¹¹³ In TEA, continuous infusion of a combination of local anesthetic and opioid into the epidural space selectively blocks pain fibers and sympathetic nerve fibers from the surgical site; the sympathectomy may reduce stress responses postoperatively. In a meta-analysis of 100 randomized trials comparing continuous epidural analgesia to parenteral opioids in thoracic, abdominal, and lower extremity surgery, Block and associates found that epidural analgesia provided significantly superior pain relief in all categories of surgery compared to parenteral opioids from the day of surgery through postoperative day 3¹¹⁴ (Fig. 27-7).

However, epidural analgesia is associated with a small but significant risk for major complications, including epidural hematoma formation, nerve damage (both via direct trauma and via drug toxicity), infection, and respiratory depression when opioids are used along with local anesthetics. Less serious but more frequent complications include hypotension, pruritus, nausea, and urinary retention. An emerging alternative to TEA in recent years has been the ultrasound-guided continuous thoracic *paravertebral block* (PVB). The PVB may be easier to place than a thoracic epidural, is unilateral (therefore less likely to cause complete sympathetic block and hypotension), and is less likely to cause significant bleeding or nerve damage.¹¹⁵ A number of studies have compared the two techniques in thoracotomy

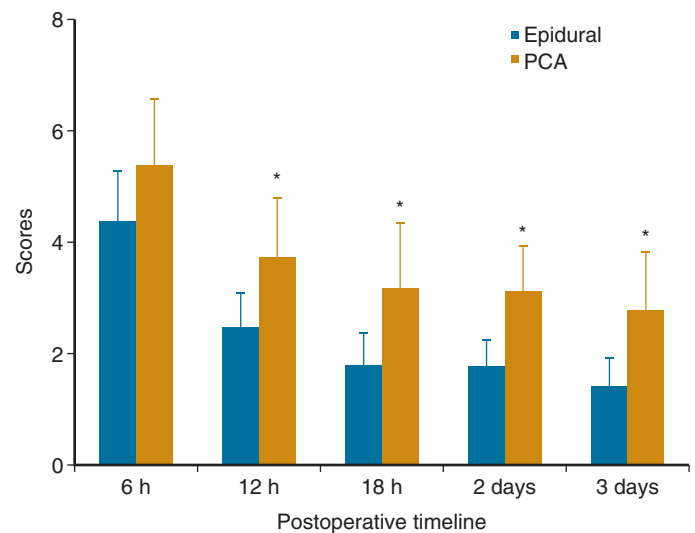


Figure 27-7 Main pain scores for the epidural and PCA groups. Values represent means with 95% confidence intervals. Epidural anesthesia is more effective than PCA from 12 h on. (From Ali M, Winter DC, Hanly AM, et al: Prospective, randomized, controlled trial of thoracic epidural or patient-controlled opiate analgesia on perioperative quality of life. *Br J Anaesth* 104:292–297, 2010, Fig. 2.)

patients and have found analgesic efficacy to be equivalent in both TEA and PVB modalities, with an improved short-term side effect profile with PVB.^{115–118} Continuous PVB analgesia is therefore increasingly being employed in thoracic surgery. In the absence of an adequately powered, prospective, randomized trial, however, it remains difficult to endorse one technique unequivocally over the other.

Key Points

- Postoperative pulmonary complications are very common after thoracic surgery and contribute to poor outcomes for patients and increased costs.
- Increased risk for pulmonary complications and mortality are associated with patients who have higher American Society of Anesthesiologists status classification, induction chemoradiation, lower DL_{CO} , lower FEV_1 , and the need for a large resection (i.e., pneumonectomy or bilobectomy).
- Atrial fibrillation is very common after thoracic operations, and effective prophylaxis should be the goal.
- Patients who are smoking preoperatively should be encouraged to quit and should be given help to abstain from smoking.
- Preoperative pulmonary rehabilitation may improve perioperative outcomes in patients with COPD and may enable patients with marginal maximum oxygen consumption to improve and thus qualify for resection. Changes in surgical techniques and chemotherapies may also improve perioperative outcomes for these patients.
- Continuous epidural analgesia via a thoracic epidural using opioids and local analgesia provides optimal pain relief for up to 3 days after a thoracotomy.

Complete reference list available at ExpertConsult.**Key Readings**

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EVALUATION OF RESPIRATORY IMPAIRMENT AND DISABILITY

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INTRODUCTION

Respiratory impairment refers to an alteration in lung structure and/or lung function that results in decreased or limited functional ability and is usually manifested by dyspnea on exertion. Many respiratory diseases may cause impairment, from airway disease such as asthma and *chronic obstructive pulmonary disease* (COPD) to interstitial lung diseases. A pulmonary physician may be asked to evaluate impairment and/or disability, either for his or her own patients or for others in the context of an independent medical examination through a benefits or compensation program and/or to provide a statement about ability to work.

This chapter reviews the elements of an impairment evaluation. An overview of the major programs in the United States is presented. The program details, including how disability and/or impairment is determined under specific programs, is contained in the online version of the chapter. Impairment ratings are described using the framework for the assessment of respiratory impairment set forth by the *American Thoracic Society* (ATS)^{1,2} along with an overview of the most commonly used impairment rating methodology contained in the *American Medical Association* (AMA) *Guides to the Evaluation of Permanent Impairment*, hereafter referred to as the *AMA Guides*. However, the *AMA Guides* are not used by every benefit and compensation system. The evaluating physician must understand and follow the rules and specific requirements of the program under which the patient is being evaluated. The final determination on the award is usually made by personnel in the program or a judge, but the thoroughness of the medical report and its consistency with the program requirements will increase the weight given to the physician's medical

opinion. Finally, an overview of workplace protections for workers with lung disease is covered.

DEFINITIONS

There is a critical distinction between the terms *impairment* and *disability*. The terms *impairment* and *disability* are often used interchangeably, perhaps made more confusing by the fact that different benefits and compensation programs may use both terms but focus on one more than the other. *Impairment* occurs at the organ or organ system level. *Whole-person impairment* refers to the loss relative to the functioning of the body as a whole. *Disability*, in contrast, refers to the person in terms of limitation in the ability to perform normal activities, including personal, social, and work activities.

Physicians should understand that such determinations are medicolegal decisions, and they can have additional ramifications for the patient beyond that of providing a diagnosis. The physician may be asked to address causation (i.e., the physician may need to opine whether the respiratory condition was caused or at least aggravated by a certain factor, most commonly work, on a more-likely-than-not basis).

Although the terms "impairment" and "disability" are related, it is important that each term be applied in accordance with its precise definition. The definitions used in most existing benefits and compensation programs in the United States are based on the *World Health Organization's* (WHO's) *International Classification of Impairment, Disability, and Handicap* (ICIDH) model from 1980.³ This model was replaced by the *International Classification of Functioning, Disability, and Health* (ICF)⁴ in 2001, which uses different

APPORTIONMENT AND FUTURE MEDICAL TREATMENT

Apportionment

Expected Future Medical Treatment

Programs in Which Physicians Primarily Determine Disability

Programs in Which Physicians Primarily Determine Impairment

Energy Employees Occupational Illness Compensation Program

definitions of these words. To avoid confusion, the definitions from the ICIDH are presented here. The ICF model and the framework for disability put forth by the *Institute of Medicine* (IOM) are presented in the “Future Directions” section.

IMPAIRMENT

Impairment refers to the degree of loss of normal use or function of a body part or organ. It was defined by the WHO as “any loss or abnormality of psychological, physiologic, or anatomic structure or function.”³ It was defined by the AMA as “a loss, loss of use, or derangement of any body part, organ system or organ function.”⁵

The essential elements that make up an impairment evaluation will vary to some degree according to the program or system through which the evaluation is being performed. Standard components typically include history, with occupational and environmental history and description of limitations in *activities of daily living* (ADLs); physical examination; and review of medical records and diagnostic test results that establish the respiratory condition.

Although *pulmonary function test* (PFT) results are the primary factor that determine the presence and degree of pulmonary impairment, some systems will specify that particular tests should be used for assessment of impairment or disability, whereas others allow physician discretion in choosing another test if he or she believes it to be a more accurate reflection of the patient’s true respiratory impairment. Some programs will only allow physicians with certain qualifications to perform impairment ratings. Additional elements that may need to be addressed can include delineation of permanent work restrictions, outline of future medical treatment requirements, and/or consideration of apportionment.

Before a physician can determine that a condition has resulted in permanent impairment or disability, the diagnosis should be well defined, the condition stable, and medical treatment either optimized or reasonable options exhausted. When these criteria are met, this is termed *maximum medical improvement* (MMI).

DISABILITY

Disability refers to any resulting alteration in the individual’s capacity to perform customary activities. It was defined by the WHO as “any restriction or lack of ability to perform any activity within the range considered normal for a human being.”³ The AMA defined *disability* as an “alteration of an individual’s capacity to meet or perform personal, social, or occupational demands or statutory or regulatory requirements because of an impairment.”⁵

Although the degree of impairment frequently correlates with the degree of disability, this is not always the case. The classic example of this is the loss of the fifth finger of the nondominant hand. Under the typical impairment rating system, the loss of this finger would be associated with a small impairment of the whole person. For the average person, this small impairment would result in a correspondingly small disability. For a concert pianist, this small impairment would be associated with significant disability, particularly in the context of work activities.

ADDITIONAL TERMS

Temporary impairment refers to impairment that exists only for a limited period of time after an injury or illness.

Temporary disability insurance covers partial compensation for loss of wages due to a non-work-related injury or illness. Partial compensation for lost wages, as well as medical benefits, are covered by workers’ compensation for work-related injuries and illness.

Permanent impairment can be assessed only once the patient has reached MMI. MMI is defined in the *AMA Guides*, Sixth Edition,⁶ as the “point in time in the recovery process ... when further formal medical or surgical intervention cannot be expected to improve the underlying impairment” and “symptoms can be expected to remain stable with the passage of time, or can be managed with palliative measures that do not alter the underlying impairment substantially.” This is termed “permanent and stationary” in some systems.

Whole-person impairment refers to the alteration in the functioning of the body as a whole and therefore can range from 0% (no impairment) to 100% (essential cessation of all body functions).

Permanent partial impairment is the numeric percentage of the loss of body functioning due to the loss or limitation in the functioning of the organ or organ systems affected. For most respiratory conditions, the primary organ involved is the lung, but at times, the pulmonary arteries or nose and throat may be affected.

Permanent total disability is the medicolegal determination that a person’s impairment precludes future gainful employment.

Handicap refers to the societal disadvantage caused by an impairment or disability. It was defined by the WHO in the ICIDH model as “a disadvantage for a given individual that limits or prevents fulfillment of that person’s normal role depending on sex, age, social and cultural factors.”³

CLINICAL APPROACH TO IMPAIRMENT EVALUATIONS

Although the term *impairment rating* is sometimes used interchangeably with the term *impairment evaluation*, the impairment rating itself is but a small part of what should be a comprehensive medical evaluation⁷ (Table 28-1). The physician must first fully understand the purpose and requirements of the program for which the evaluation is being conducted. The initial goal of the impairment evaluation should be to confirm the medical diagnosis,² through a thorough, detailed patient history, physical examination, and review of diagnostic testing results that established the diagnosis. The diagnosis or diagnoses should be clearly stated, along with extrapulmonary conditions that may be contributory to symptoms, limitations in ADLs, and/or impairment. A statement of MMI is often required. Factors important to the impairment rating itself include items from history, physical examination, and diagnostic testing results that reflect disease severity, including impact on normal ADLs,⁵ and current treatment requirements. The physician may be asked to make a statement on causation

Table 28-1 Components of a Respiratory Impairment Evaluation

1. Clear understanding of the rules and specific requirements of the program under which the individual is being evaluated.
2. Complete medical history
 - a. Complete occupational and environmental exposure history
 - b. Limitations in activities of daily living (ADLs)
3. Physical examination
4. Diagnostic testing
 - a. Tests that establish the diagnosis
 - b. Tests that identify extrapulmonary conditions contributing to impairment
 - c. Results used in the assessment of impairment
 - i. Pulmonary function tests
 - A. Spirometry
 - B. Single-breath diffusing capacity (DL_{CO})
 - ii. Cardiopulmonary exercise test (when indicated)
 - iii. Arterial blood gas measurement (when indicated)
5. Diagnosis
 - a. Assessment of causation, usually relationship to work (when indicated)
6. Impairment assessment
 - a. Statement of maximum medical improvement (MMI)
 - b. Impairment rating
 - c. Ability to work/work restrictions (when indicated)
 - d. Apportionment (if requested)
 - e. Future medical treatment

or apportionment. An outline of reasonably anticipated future medical course and treatment requirements should be given. The following sections describe the various aspects of an impairment evaluation, including the history to be taken, the examination to be conducted, and the testing to be obtained depending on the diagnosis considered and the type of evaluation being performed.

HISTORY

The *history of present illness* (HPI) is the standard, detailed respiratory history used by most pulmonologists, including symptoms of cough, cough with phlegm, wheeze, chest tightness, and shortness of breath. If present, details should be provided that include when the symptom started, exacerbating and alleviating factors along with temporal relationship, progression over time, and current status including frequency, severity, and response to any medication that is used. A scale for the rating of dyspnea is suggested in the *AMA Guides*, based on the Epidemiology Standardization Project,⁸ which also provides standardized questions for the assessment of other symptoms. Questions about conditions such as chronic rhinitis, postnasal drip, gastroesophageal reflux disease, cardiac disease, and other lung diseases, including smoking-related lung disease, may help the physician understand other possible contributors to respiratory symptoms. Although dyspnea is the primary limiting symptom of respiratory impairment, dyspnea can also result from nonpulmonary causes including cardiovascular disease, obesity, and deconditioning. Frequency, severity, treatment requirements, and duration of periodic exacerbations of diseases such as asthma and bronchiectasis should be well documented. Medications used or tried in the past for the treatment of the respiratory conditions should be described, along with a description of the relief afforded.

Constitutional symptoms are relevant in the HPI in patients with certain diseases, such as fever, sweats, chills, and fatigue in patients with hypersensitivity pneumonitis; chest pain, weight loss, and malaise in patients with asbestos-related lung disease; and night sweats and fatigue in patients with chronic beryllium disease.

A standard detailed past medical and surgical history, list of medications and allergies, family history, and review of systems will provide a good understanding of the patient as a whole. It will also allow the physician to identify other possible diseases that may be contributory to the patient's current status, as well as to assess potential treatment-related side effects. The standard social history should include smoking history, including amount, duration, and current smoking status.

An element that may be new to most pulmonologists is the need to obtain a detailed occupational and environmental history. This is necessary to help the physician address whether there is a relationship between a respiratory condition and past or ongoing workplace exposures. The occupational history is most easily performed in chronological order starting from childhood. Details about the period of time spent at each job, the job title, description of the work performed, and details about jobs or processes that may have produced dust, fumes, gas, or smoke should be described, including estimation of intensity, frequency, and duration of exposure. Questions about ventilation and use of respiratory protection can provide helpful clues, as well as whether or not there were any immediate symptoms noted. Chemical exposures, particularly any heavy exposures or exposures that resulted in symptoms, should be detailed. If available, the *Safety Data Sheet* (SDS), formerly called *Material Safety Data Sheet* (MSDS), may be reviewed because it can provide helpful information on the components of the chemicals used in the workplace and potential associated health effects. Unfortunately, MSDSs are not required to provide complete information, and thus some are more reliable than others.

An environmental history includes questions about heating, cooling, and humidification sources; pets including birds; hot tubs; water-damaged areas; and exposures from hobbies should also be obtained to determine whether there is a relationship between the disease and any environmental exposures.

In addition to the just-discussed components, the history should also include a description of how the condition affects the person's ability to perform normal ADLs. Questions most relevant to patients with pulmonary disease include ability to perform basic self-care such as showering; ability to walk, including estimated distance at own pace and at a fast pace or up a hill, estimated pace compared with others one's own age, and number of flights of stairs that can be climbed; and ability to perform indoor and outdoor home maintenance chores, as well as customary hobby, exercise, and job-related activities. There are a number of standardized methods by which to assess ability to perform ADLs, some of which are disease specific. A list of ADLs suitable for all conditions is outlined in the *AMA Guides*.^{5,9} Symptoms and limitations in ADLs that are consistent with the lung disease and objective testing data provide useful supporting information for the impairment rating. Dyspnea scales are often used and can be a helpful way to summarize

the relative degree of symptomatology or activity limitation.⁸ However, the degree to which dyspnea correlates with objective measures of pulmonary function and exercise performance is variable.¹⁰⁻¹³

PHYSICAL EXAMINATION

A complete physical examination should be performed, with focus on the respiratory and cardiovascular systems.^{2,7} A detailed description of the chest should be made, including any deformities or scars, abnormal motion, respiratory rate and effort, breath sounds, and percussion, which can help support the diagnosis. Vital signs should be documented including blood pressure and heart rate, which may affect ability to perform pulmonary function and exercise tests, as well as height and weight, because obesity can cause PFT and exercise test abnormalities and contribute to pulmonary symptoms. Signs of hypoxemia, such as cyanosis and clubbing, should be documented. Signs of cor pulmonale, such as jugular venous distention, right ventricular heave, and liver engorgement, and peripheral edema provide evidence of severe respiratory impairment in patients with respiratory disease.²

DIAGNOSIS, CAUSATION, AND MAXIMUM MEDICAL IMPROVEMENT

Any available or provided medical records should be summarized, with focus on the results of the diagnostic testing that help establish the diagnosis and/or severity of the condition. Medicolegal cases may often involve the review and summarization of large volumes of records. Some independent medical examinations require that only the records provided through the program be reviewed.

The list of medical diagnoses should start with the diagnosis of the condition for which the patient is being evaluated, including disease severity. The diagnosis of asthma associated with workplace exposures may fall under one of three different diagnoses: occupational asthma (new-onset asthma caused by a workplace exposure), work-aggravated asthma (existing asthma aggravated by a workplace exposure), and *reactive airways dysfunction syndrome* (RADS), which can result from a single high-level irritant exposure. Other diagnoses that may be contributory to symptoms, limitations in ADLs, or testing abnormalities should be clearly delineated.

If relevant, the diagnosis should also include a statement on *causation*, the physician's opinion as to whether or not a given workplace exposure has caused or aggravated an illness. This is a medicolegal determination, also known as *attribution*, made on a medically probable basis, also known as a "more-likely-than-not" basis. That is, the physician should be able to opine with greater than 50% certainty that the exposure(s) in the workplace caused the respiratory condition or worsened an underlying condition on the basis of objective criteria, such as change in treatment requirements. This criterion is less rigorous than would be required for scientific proof of a hypothesis (i.e., 95% certainty). This is important because in cases of respiratory illness, there may be multifactorial causation, frequently a long latency between initial exposure and clinical onset of disease, nonspecific clinical manifestations, incom-

plete understanding of dose-response relationships from epidemiologic studies, and lack of individual exposure data. Although recognition of these limitations is necessary, causation can be attributed in most cases on a more-probable-than-not basis by simply applying reasonable judgment. This process is easier when the exposure is known, the dose-response relationship is well characterized, and competing diagnoses are unlikely. The physician should clearly describe the specific substances at the workplace; their known health effects according to the medical literature; the relative dose, in terms of estimated intensity, frequency, and/or duration of exposure; and finally, why it is medically probable that the exposure(s) caused or resulted in permanent aggravation of the diagnosed medical condition in this worker. When one or more of these conditions are not met, attribution should be based on the answers to the following questions.

- Is the diagnosis clearly established, and is it biologically plausible (or consistent with the available epidemiologic data) that the disease could have been caused or aggravated by the exposure in question?
- Have competing diagnoses been adequately considered?
- Is the exposure of sufficient intensity and duration to have caused or aggravated the disease?
- Has there been an adequately long latent period, or is there a temporal relationship between onset of exposure and clinical manifestation of disease?

Some systems, such as most state workers' compensation and a Department of Labor Program, the *Energy Employees Occupational Illness Compensation Program* (EEOICP), require the physician to make a statement that the patient has reached MMI before performing an impairment rating. If the examining physician believes the condition is not stable or believes that there may be additional treatment reasonably likely to improve the condition, it is medically prudent to state this. What will happen logistically following determination of the MMI will depend on the specific program requirements. The examining physician should be aware of the ramifications of making these medicolegal determinations. For example, in the state workers' compensation system, determination of MMI will allow the worker to be awarded permanent impairment but will also result in the cessation of temporary benefits such as compensation for lost wages, as the case is closed by the workers' compensation insurance company.

GUIDES TO RESPIRATORY IMPAIRMENT RATINGS

AMERICAN THORACIC SOCIETY GUIDELINES FOR EVALUATION OF IMPAIRMENT OR DISABILITY

A number of systems have been used to determine respiratory impairment. Most base impairment primarily on lung function. In their "Guidelines for the Evaluation of Impairment/Disability Secondary to Respiratory Disorders," the ATS recommends that impairment due to most lung diseases be rated on the basis of *pulmonary function test*

Table 28-2 American Thoracic Society Impairment Categories, with Corresponding Description of Ability to Perform Job Demands

Category	Criteria	Ability to Perform Job Demands
Normal	$FVC \geq 80\%$ of predicted <i>and</i> $FEV_1 \geq 80\%$ of predicted <i>and</i> $FEV_1/FVC \times 100 \geq 75\%$ <i>and</i> $DL_{CO} \geq 80\%$ of predicted	
Mildly impaired	FVC 60–79% of predicted <i>or</i> FEV_1 60–79% of predicted <i>or</i> $FEV_1/FVC \times 100$ 60–74% <i>or</i> DL_{CO} 60–79% of predicted	Usually not correlated with diminished ability to perform most jobs
Moderately impaired	FVC 51–59% of predicted <i>or</i> FEV_1 41–59% of predicted <i>or</i> $FEV_1/FVC \times 100$ 41–59% <i>or</i> DL_{CO} 41–59% of predicted	Progressively lower levels of lung function correlated with diminishing ability to meet the physical demands of many jobs
Severely impaired	$FVC \leq 50\%$ of predicted <i>or</i> $FEV_1 \leq 40\%$ of predicted <i>or</i> $FEV_1/FVC \times 100 \leq 40\%$ <i>or</i> $DL_{CO} \leq 40\%$ of predicted	Unable to meet the physical demands of most jobs, including travel to work

DL_{CO} , single-breath carbon monoxide diffusing capacity; FEV_1 , forced expiratory volume in 1 second; FVC , forced vital capacity.

From American Thoracic Society (ATS): Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. *Am Rev Respir Dis* 133:1205–1209, 1986.

(PFT) results.² Pulmonary function testing is described in Chapter 25. The results of the ATS impairment system, based on PFTs, place individuals into four impairment categories. Each of these categories provides a corresponding description of the associated ability to perform job demands (Table 28-2). The ATS did not include a system by which to assign an associated numerically derived percentage of whole-person impairment, on which monetary awards are typically based. Therefore the ATS guidelines did not lend themselves to use in most compensation systems.

AMERICAN MEDICAL ASSOCIATION GUIDES TO THE EVALUATION OF PERMANENT IMPAIRMENT

The *AMA Guides*, Fifth Edition, adapted the ATS Guidelines by adding a system through which to assign a numerically derived percentage of whole-person impairment within each of the four impairment classes.¹⁴ Although the *AMA Guides*, Fifth Edition, is no longer the most current edition, the methodology is presented here because it is directly based on ATS Guidelines and because many compensation systems have not yet adopted the Sixth Edition. The *AMA Guides*, Fifth Edition, assigned the following associated ranges of whole-person respiratory impairment to each of the four ATS classes: class 1 impairment is equal to 0% whole-person impairment, class 2 (mild) impairment ranges from 10% to 25% impairment, class 3 (moderate) ranges from 26% to 50% impairment, and class 4 (severe) ranges from 51% to 100% whole-person impairment. After determining the class of impairment based on *forced vital capacity* (FVC), *forced expiratory volume in the first second* (FEV_1), FEV_1/FVC , *single-breath diffusing capacity* (DL_{CO} , or $\dot{V}O_2$, the physician determines the final numeric percentage whole-person impairment on the basis of where the test results fall within that range of impairment, as well as other factors, including impact of the respiratory condition on the ability to perform ADLs.

The *AMA Guides*, Sixth Edition, adopts a different methodology, defining 4 classes of impairment: class 0: 0% whole-person impairment, class 1 (minimal) ranges from 2% to 10% impairment, class 2 (mild) ranges from 11% to 23% impairment, class 3 (moderate) ranges from 24%

to 40% impairment, and class 4 (severe) ranges from 45% to 65% whole-person impairment.¹⁵ The “key factor” is the objective test data, FVC, FEV_1 , FEV_1/FVC , and DL_{CO} , using the measurement most relevant to the disease process.¹⁵ $\dot{V}O_2$ may be considered as the key factor if one of the other pulmonary function test results is abnormal. The specific value within the impairment class is determined by the physical examination findings, dyspnea, and treatment requirements. The maximum whole-person impairment in the *AMA Guides*, Sixth Edition, for most respiratory disorders is 65% whole-person impairment, rather than 100% whole-person impairment in previous editions, although this rating may still be combined with impairment in other organ systems.

Because a person can never have more than 100% impairment of the body, impairment in any additional organ system needs to be combined rather than added to the respiratory impairment. Each edition of the *AMA Guides* contains a special combining table for this purpose.

CLASSIFICATION OF IMPAIRMENT RESULTING FROM SPECIFIC PULMONARY DISEASES

Regardless of the rating system used, the greatest weight should be placed on objective data.

Asthma (for details concerning diagnosis and management of asthma, see Chapter 42)

Rating asthma according to the standard respiratory disorder methodology can both underestimate and overestimate impairment, given the episodic and variable nature of airflow limitation and bronchial hyperresponsiveness.¹⁶ The ATS developed “Guidelines for the Evaluation of Impairment/Disability in Patients with Asthma” in 1993 to reflect the true impairment due to this condition.¹ First, a worker with objectively confirmed asthma must be determined to be at MMI or to have achieved optimal therapeutic goals (i.e., minimum medication that obtains the best overall outcome).¹⁵ To rate asthma impairment according to ATS methodology (Table 28-3), the postbronchodilator FEV_1 , reversibility (% change with bronchodilator), or methacholine challenge results (provocative concentration of methacholine inducing a 20% drop in FEV_1 [PC_{20} in mg/mL]), and minimum medications required to maintain

Table 28-3 American Thoracic Society Impairment Rating Guidelines for Asthma**A. Postbronchodilator FEV₁**

Score	FEV ₁ (% predicted)
0	> lower limit of normal
1	70– lower limit of normal
2	60–69
3	50–59
4	<50

B. Reversibility of FEV₁ or Degree of Airway Hyperresponsiveness*

Score	% FEV ₁ change	PC ₂₀ (mg/mL or equivalent)
0	<10	>8
1	10–19	8–>0.5
2	20–29	0.5–>0.125
3	≥30	≤0.125
4	—	—

C. Minimum Medication Need†

Score	Medication
0	No medication
1	Occasional bronchodilator, not daily, and/or occasional cromolyn,‡ not daily
2	Daily bronchodilator and/or daily cromolyn‡ and/or daily low-dose inhaled steroid (<800 µg beclomethasone or equivalent)
3	Bronchodilator on demand and daily high-dose inhaled steroid (>800 µg beclomethasone or equivalent) or occasional course (1–3/year) systemic steroid
4	Bronchodilator on demand and daily high-dose inhaled steroid (>1000 µg beclomethasone or equivalent) and daily systemic steroid

D. Summary of Impairment Rating Classes‡

Impairment Class	Total Score
0	0
I	1–3
II	4–6
III	7–9
IV	10–11
V	Asthma not controlled despite maximal treatment (i.e., FEV ₁ remaining < 50% despite use of ≥ 20 mg prednisone/day)

*When FEV₁ is above the lower limit of normal, the PC₂₀ value should be determined and used for rating of impairment; when FEV₁ is < 70% predicted, the degree of reversibility should be used; when FEV₁ is between 70% predicted and the lower limit of normal, either reversibility or the PC₂₀ can be used.

Reversibility with bronchodilator is calculated as

$$\frac{\text{FEV}_1 \text{ postbronchodilator} - \text{FEV}_1 \text{ prebronchodilator}}{\text{FEV}_1 \text{ prebronchodilator}} \times 100\%$$

Airway responsiveness is expressed as that concentration of bronchoconstrictor agents that will provoke a fall in FEV₁ of 20% from the lowest postsaline value. Plot the concentration of methacholine or histamine against the fall in FEV₁ using a logarithm scale for the doubling concentrations. The PC₂₀ is obtained by interpolation between the last two points. The formula for linear interpolation of the PC₂₀ from the log dose response curve is as follows:

$$\text{PC}_{20} = \text{antilog } C1 + \frac{(\log C2 - \log C1)(20 - R1)}{(R2 - R1)}$$

Where C1 = second last concentration (<20% FEV₁ fall)

C2 = last concentration (>20% FEV₁ fall)

R1 = % fall FEV₁ after C1

R2 = % fall FEV₁ after C2

†The need for minimum medication should be demonstrated by the treating physician, e.g., previous records of exacerbation when medications have been reduced.

‡Very limited current use.

§The impairment rating is calculated as the sum of the patient's scores from Tables A, B, and C.

From the American Thoracic Society, Medical Section of the American Lung Association: Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Respir Dis* 147:1056–1061, 1993.

this status are assigned scores using Tables 28-3A, B and C. The class of impairment is defined by the sum of the asthma scores based on Table 28-3D. The *AMA Guides*, Fifth Edition, adopted the ATS methodology and assigned a numeric range of whole-person impairment for each impairment class that is equivalent to the impairment assigned for general respiratory conditions.¹⁴ Additionally, ATS added a fifth class of impairment, defined as asthma not controlled despite maximal treatment (i.e., FEV₁ remaining <50% despite use of ≥20 mg of prednisone daily). The *AMA Guides*, Sixth Edition, additionally recommends that an impairment rating be performed after the patient has achieved optimal therapeutic goals, and that it is prudent to wait at least 2 years after diagnosis and removal from exposure in cases of occupational asthma.¹⁵ In the *AMA Guides*, Sixth Edition, PC₂₀ mg/mL is used as the primary “key factor” by which to determine the class of asthma impairment, although postbronchodilator FEV₁ may be used as an alternative. Minimum medication requirements and frequency of attacks are used to determine the specific numeric rating within the class.¹⁵

Bronchiectasis (for further discussion, see Chapter 48)

Rating conditions such as bronchiectasis by the standard pulmonary function testing methods also can underestimate impairment because it is the recurrent episodes of infection and inflammation that cause intermittent respiratory symptoms, respiratory dysfunction, and limitations in ADLs, often with normal lung function in between episodes. The *AMA Guides*, Fifth Edition, acknowledge that this method will be applicable only in “limited cases,” but they will allow the physician to assign a rating on the basis of the extent and severity of these episodes and their impact on ADLs, with objective supporting evidence documented.¹⁴ The *AMA Guides*, Sixth Edition, does not delineate a specific methodology for this condition.¹⁵

Sleep Disorders (for further discussion, see Chapters 85–89)

Sleep disorders are recognized in the *AMA Guides*, Sixth Edition, as a condition that may cause impairment not well estimated by standard pulmonary function testing or exercise testing.¹⁵ Both the *AMA Guides*, Fifth and Sixth Editions, describe the importance of obtaining sleep testing in an accredited laboratory, and grading severity based on the number of apnea and hypopnea episodes observed during polysomnography and the severity of hypoxia.^{14,15} However, as there are no standardized, well-documented criteria for determining level of impairment, the rating should be performed by a sleep specialist. The *AMA Guides*, Sixth Edition, specifies that the rating should not exceed 3% whole-person impairment.

Lung Cancer (for discussion of clinical aspects of lung cancer, see Chapter 53)

The *AMA Guides*, Fifth and Sixth Editions, recommend one of two methods be used for rating permanent impairment due to lung cancer.^{14,15} All individuals with lung cancer are considered severely impaired at the time of diagnosis. At 1 year after diagnosis, if there is still evidence of tumor or tumor recurrence, the person is considered to be severely impaired. If there is no residual tumor or recurrence, the

impairment rating is performed according to the standard rating methodology for respiratory diseases.

Diseases of the Pulmonary Arteries (for discussion of disorders of the pulmonary vascular bed, see Chapters 57–61)

Diseases rated by this methodology include pulmonary artery hypertension, cor pulmonale, and pulmonary emboli. In the *AMA Guides*, Fifth Edition,¹⁷ the rating is determined by the presence or absence of physical examination signs (right ventricular heave, increased *pulmonic component* [P₂] of the *second heart sound* [S₂], peripheral edema) and symptoms of right heart failure (dyspnea), as well as the observed *pulmonary artery pressure* (PAP). In the *AMA Guides*, Sixth Edition,⁹ the objective findings including PAP, B-type natriuretic peptide, and $\dot{V}O_2$ are the “key factors” that determine the class of impairment. The specific percentage assigned within the class is determined by history (dyspnea and activity limitations) and physical examination findings (signs of right heart failure).

Conditions of the Upper Airways

(for further discussion, see Chapter 49)

The *AMA Guides*, Fifth Edition,¹⁸ contain methodology by which to assign impairment due to obstruction of the upper airway, larynx, trachea, and/or bronchi, based on degree and location(s) of the obstruction, nature of the activities that trigger dyspnea, as well as need for ventilation. The *AMA Guides*, Sixth Edition, uses the nature of the activities that trigger dyspnea as the “key factor” in determining impairment class and physical examination findings and objective test results, such as sinus CT or findings on laryngoscopy determine the final numeric rating.¹⁹ There are also methods for the rating of voice/speech impairment, based on audibility, intelligibility, and functional efficiency in the *AMA Guides*, Fifth Edition. These factors are also used to define the “key factor” for impairment class in the *AMA Guides*, Sixth Edition, as well as consideration of stroboscopy, objective voice and speech measures, and Voice Handicap Index. It is important to note that there are differences in what defines impairment within a given class in the two editions.

ROLE OF DIAGNOSTIC TEST RESULTS IN IMPAIRMENT RATINGS

RADIOGRAPHIC DATA

Documentation of chest radiograph or *computed tomography* (CT) scan abnormalities consistent with the lung disorder is frequently required to establish evidence of disease, particularly for diseases such as pneumoconiosis. The chest imaging findings may correlate poorly with the physiologic findings, especially in patients with obstructive lung disease.

Some programs require that chest radiographs be read by a *National Institute of Occupational Safety and Health* (NIOSH)-certified B-reader and classified according to the *International Labour Organization's* (ILO's) classification system.²⁰ This radiographic interpretation system was devised in an attempt to report the presence, appearance, and extent of

radiographic changes consistent with pleural and parenchymal evidence of pneumoconiosis in an objective and consistent manner. Chest radiographic findings of opacities with an ILO profusion score of at least 1/0 are “consistent with” asbestosis and will be accepted for compensation purposes by programs such as the Department of Labor for that condition. If the opacities are small and irregular (classified as “s” and “t”) and are found predominantly in the middle and lower lobes or are found in conjunction with pleural plaques, these findings are highly consistent with a diagnosis of asbestosis.

Whereas the ILO interpretation may help raise suspicion of pneumoconiosis, or provide sufficient evidence of disease in the correct clinical situation, the physician needs to determine on a clinical basis whether additional testing is necessary to establish a medical diagnosis and determine whether treatment is necessary. The physician should note that additional testing may or may not be covered by the benefits or compensation program. Because of the variability in the extent of radiographic findings and the degree of physiologic impairment, none of the major programs or rating systems uses radiographic findings in the assessment of impairment due to lung disease. The NIOSH website provides a search tool by which to find certified B-readers by state and country.²¹

A standardized CT classification system similar to the ILO system called the *International Classification of High-Resolution Computed Tomography for Occupational and Environmental Disease* has been proposed.²² Although this CT classification system was found to have satisfactory inter-reader reliability by an international panel of experts,²³ the assessment mainly focused on one lung disease, asbestos-related lung disease, so the generalizability of this system is not clear. Neither this nor any other standardized system for reporting CT findings of pneumoconiosis is currently in widespread use.

PULMONARY FUNCTION TESTING

(for further discussion, see Chapter 25)

PFTs are the most important tests, both from a diagnostic standpoint and in their use to determine impairment for most respiratory conditions. Both the ATS² and the *AMA Guides* specify the use of FVC, FEV₁, FEV₁/FVC, and DL_{CO}. Some programs mandate that pulmonary function testing be performed pre- and post-bronchodilator and should be done in patients with low FEV₁ or diagnoses of reversible airflow limitation. The ATS specifies that individuals should be evaluated only after they have received an accurate diagnosis and while they are receiving optimal therapy.² This is consistent with the *AMA Guides'* requirement that the patient be at MMI, as described previously. Measurement of height in stocking feet is recommended, as is measurement of arm span (distance between the tips of the middle fingers with arms outstretched) in cases of spinal deformity.^{2,24}

Both ATS and the *AMA Guides* emphasize the importance of only using test results that meet the quality standards defined in the latest ATS statement “Standardization of lung function testing.”²⁵ This document governs the equipment, quality assurance, and techniques that should be used to perform lung function testing, in addition to the assessment of the quality of the test and the method of

interpretation. If a physician has concern that the PFTs were not performed in a manner consistent with the ATS Guidelines, including acceptability and reproducibility, then the physician should request repeating the test. An exception happens when the patient has consistently demonstrated less than optimal technique on past tests despite language-appropriate education and encouragement. This consistent, unacceptable test performance may be due to overall debilitation, pain, or language barrier and when it is unlikely that repeating the test will yield improved results. Test results that are markedly worse than those of prior tests raise concern that there has been an exacerbation of the underlying condition and that the patient is not at MMI, or it may be that the patient gave less than full effort; regardless, such results would not be considered to reflect the patient's permanent impairment status. Options include informing the subject of the discrepancy and repeating the test or using the results "as a subsidiary and not the main criterion."²⁶

When evaluating PFTs for impairment, the normal values of the laboratory performing the test should not be used, but rather the normal values of the impairment rating system. For example, the ATS and *AMA Guides*, Fifth Edition, reference population normal values derived from Crapo and coworkers,²⁷ while the *AMA Guides*, Sixth Edition, reference *National Health and Nutrition Examination Survey* (NHANES) III-derived prediction equations.²⁸

DL_{CO} , measured by the single-breath method of Ogilvie and colleagues²⁹ and interpreted according to Crapo and Morris,³⁰ is suggested by both ATS and the *AMA Guides*. Both recommend correction by the methodology of others for factors including hemoglobin, carboxyhemoglobin,^{2,14} and altitude and alveolar volume,² but correction methodology and interpretive strategies are not explicitly described in the rating criteria. The most recent ATS statement on DL_{CO} describes explicit criteria for evaluating acceptability and repeatability, as well as adjustment for hemoglobin, supplemental oxygen, altitude, and carboxyhemoglobin, while noting that further study is necessary before specific recommendations for lung volume adjustment can be made.³¹ In a separate statement, the ATS has noted that low DL_{CO} along with low DL_{CO} corrected for alveolar volume (DL_{CO}/VA) suggests parenchymal abnormalities as the cause of the impairment but recommends examining the two separately.²⁵ Neither the ATS nor the *AMA Guides* utilize DL_{CO}/VA in assessing impairment.

Maximal voluntary ventilation (MVV) and $FEV_{25\%-75\%}$ are not recommended for use by ATS or the *AMA Guides* in impairment evaluation. ATS defines a restrictive ventilatory defect as a reduction in total lung capacity (TLC) below the lower limit of normal (i.e., below the fifth percentile of the predicted value), with a normal FEV_1/FVC ratio.²⁵ TLC is not included in the standard rating criteria in either the ATS or the *AMA Guides*. Although the *AMA Guides*, Sixth Edition, caution that a true restrictive defect may not be present even with a reduced FVC in the setting of a normal or increased FEV_1/FVC , FVC continues to be the test used in the rating of impairment. Low FVC can be caused by submaximal inspiratory or expiratory effort and/or peripheral airflow obstruction.²⁵ One study showed the predictive value of reduced FVC to be less than 60% for the presence of true restrictive deficit.³² Others report concern about

reduced lung function test results, including FVC, in obesity,^{33,34} but there are no established criteria by which to account for obesity in testing.

CARDIOPULMONARY EXERCISE TESTING

(see Chapter 26 for details)

Neither the ATS nor the *AMA Guides* recommend the routine use of exercise test results in the determination of permanent impairment, but maximal exercise test results, specifically $\dot{V}O_2$, should be used in specific circumstances. ATS recommended that exercise test results be used in cases where the resting PFTs do not reflect the true impairment present.² For example, studies have demonstrated that alveolar-arterial oxygen pressure difference ($A-a$) PO_2 during exercise is a better reflection of impairment due to gas exchange abnormality than DL_{CO} .³⁵ Although exercise limitation does not necessarily correlate with resting lung function testing,^{36,37} exercise testing can be helpful in cases where there is a large discrepancy between symptoms and resting physiology,³⁵ providing a more precise measurement of work capacity.³⁸

Airflow limitation and gas exchange abnormality help define the relative degree to which respiratory disease is contributing to exercise limitation. When exercise limitation is present, nonrespiratory causes of exercise limitation should be considered as well, including cardiovascular disease, deconditioning, and neuromuscular disease.³⁹ The ATS guidelines for respiratory impairment note that exercise testing can be used as a valid measure of respiratory impairment when the following criteria are met: (1) if exercise testing is not terminated for other nonpulmonary reason, (2) if there is low breathing reserve at termination, and (3) if there is absence of erratic overventilation at submaximal levels with failure to achieve anaerobic threshold. However, there are no details provided on how these criteria should be met and the *AMA Guides* do not delineate a specific methodology. The reason for test termination should be noted because tests terminated early due to nonrespiratory causes such as excessive blood pressure, cardiac abnormality, or leg pain do not reflect maximum exercise tolerance.

To determine work capacity, and thus impairment, ATS requires use of $\dot{V}O_{2max}$ to place workers into one of three categories of work tolerance, assuming that workers can comfortably perform sustained work at 40% of $\dot{V}O_{2max}$ and that O_2 requirements of the workers' jobs are known (Table 28-4). Major limitations to this approach include the following: (1) little published data that substantiate its use; (2) heterogeneous methods of assessing maximal oxygen uptake⁴⁰; (3) the fact that actual work performed by workers with the same job title can vary markedly from employer to employer or among employees with differing seniority at the same employer; (4) the questionable relationship between exercise tolerance on the treadmill or bicycle and performance on the job⁴¹; and (5) the lack of consideration of modifying factors such as the need to talk or use *personal protective equipment* (PPE) while performing the work.⁴² The average energy requirements of a number of jobs are listed in Table 28-5. The *AMA Guides*, Fifth and Sixth Editions, both consider a $\dot{V}O_{2max}$ greater than 25 mL/kg/min to place one into the lowest (least) category of impairment (class 1 and class 0, respectively) and a $\dot{V}O_{2max}$ less than

Table 28-4 American Thoracic Society Interpretation of Exercise Test Results Using $\dot{V}O_{2\max}$

$\dot{V}O_{2\max}$	METS	Estimated Work Ability
≥ 25 mL/kg/min	≥ 7.1	Continuous heavy exertion throughout an 8-hour day in all but the most physically demanding jobs
15–25 mL/kg/min and Metabolic demands of the work $\leq \dot{V}O_{2\max}$		Able to perform that job comfortably, assuming there are no frequent or extended periods (5 min) requiring exertion substantially $>40\%$ $\dot{V}O_{2\max}$
≤ 15 mL/kg/min	≤ 4.3	Unable to perform most jobs because they would be uncomfortable traveling back and forth

METS, the energy demand in liters of oxygen consumption per minute/basal oxygen consumption (3.5 mL/kg/min); $\dot{V}O_{2\max}$, maximal oxygen consumption.

From American Thoracic Society (ATS): Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis* 133:1205–1209, 1986.

Table 28-5 Energy Requirements Expressed as Oxygen Uptake ($\dot{V}O_2$) of Various Types of Work

Level of Work	$\dot{V}O_2$ (APPROXIMATE)		
	mL/kg/min	L/min	METS
Light to moderate work (sitting)			
Clerical	5.6	0.42	1.6
Using repair tools	6.3	0.47	1.8
Operating heavy equipment	8.8	0.66	2.5
Heavy truck driving	12.6	0.95	3.0
Moderate work (standing)			
Light work, own pace	8.8	0.66	2.5
Janitorial work	10.5	0.79	3.0
Assembly line (lifts > 45 lb)	12.3	0.92	3.5
Paper hanging	14.0	1.05	4.0
Standing and/or walking (arm work)			
General heavy labor	15.8	1.19	4.5
Using heavy tools	21.0	1.58	6.0
Lift and carry 60–80 lb	26.2	1.97	7.5

METS, the energy demand in liters of oxygen consumption per minute/basal oxygen consumption (3.5 mL/kg/min).

Adapted from Becklake M: Organic or functional impairment. *Am Rev Respir Dis* 129:S96–S100, 1984.

15 mL/kg/min to place one into the highest (greatest) category of impairment (class 4). The use of exercise testing and $\dot{V}O_{2\max}$ overestimates impairment in older workers. As an alternative, it has been proposed that $\dot{V}O_{2\max}$ be expressed as percent of predicted,⁴³ although this is not in standard use at this time. Although advances have been made, the recent ATS Statement on Cardiopulmonary Exercise Testing³⁹ noted that a comprehensive updated framework for impairment/disability is needed urgently.

BLOOD GAS ANALYSIS

Arterial blood gas analysis is not used for impairment rating purposes on a routine basis. Resting arterial PO_2 does not

correlate with exercise capacity. As a result, arterial hypoxemia at rest is, by itself, not evidence of severe impairment in exercise tolerance. ATS recommends it only be used in “selected patients” under “rigidly controlled laboratory conditions” and should be documented on at least two occasions separated by at least 4 weeks.² They consider hypoxemia to be evidence of severe impairment only when accompanied by evidence of cor pulmonale. Arterial blood gas analysis was also considered to be a test infrequently indicated in the evaluation of impairment in the *AMA Guides*, Fifth Edition.¹⁴ It is not included in the Sixth Edition.¹⁵

ADDRESSING DISCREPANCIES BETWEEN OBJECTIVE AND SUBJECTIVE DATA

A description of the severity of the disease or condition should be given. This can be difficult when there is a discrepancy between the severity reported by the patient and the severity of the disease based on the results of the diagnostic testing. It is important that the physician distinguish between data that are *objective* (findings evident to the examiner in a reproducible manner and not dependent on only the patient’s perceptions), including physical signs and diagnostic testing results, and *subjective* data, which are reported by the patient, such as symptoms perceived by the patient only and not evident to the examiner. Normally, the two will be similar, making the history, physical examination, and diagnostic testing findings all helpful in the assessment of true functional impairment. If the subjective complaints are not consistent with the objective findings, the physician should first be sure there is no coexisting disease process responsible for the symptoms. For example, dyspnea may also be caused by nonrespiratory disorders such as cardiac disease and anemia. *Organic impairment* refers to the presence of objective findings of respiratory dysfunction or disease. *Functional impairment* refers to dyspnea for which an objectively measured abnormality of organ function cannot be identified. Recognizing that tests for organic impairment are not perfectly sensitive, the contribution of functional impairment can range from “negligible” to “perhaps accounting for the entire extent of a patient’s dyspnea.” When there is a discrepancy between the subjective and the objective data, and other medical conditions have been excluded as possible contributors to the subjective complaints, several steps should be taken. The first and foremost is to review the purpose of the evaluation with the patient to ensure that a lack of comprehension of either questions or performance of PFTs does not exist. Second, an evaluation of test performance, including cooperation and the results of effort-independent tests such as functional residual capacity, may be of some use. Examination of test results for comparability over time may show evidence of consistency or the lack thereof. Finally, exercise testing may shed considerable light on a patient’s level of effort by demonstrating the relationships of heart rate and ventilatory rate at workloads actually achieved to the predicted maximal values.

Dyspnea due to functional impairment may result from subconscious effects on the perception of symptoms or from outright malingering. Because of the inability of PFTs and other tests to be perfectly sensitive in diagnosing organic

causes of impairment, the diagnosis of malingering should be made with caution. The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, (DSM-5), classifies malingering as a condition “that may be a focus of clinical attention.”⁴⁴ Furthermore, malingering is described as “the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives.” Specific listed examples of these external incentives include avoiding work and obtaining financial compensation. The DSM-5 recommends that malingering should be strongly suspected if any combination of the following is noted: (1) there is a medicolegal context of presentation, (2) a marked discrepancy between the person’s claimed stress or disability and the objective findings is noted, (3) a lack of cooperation during the diagnostic evaluation and compliance with the prescribed treatment regimen are observed, and (4) there is the presence of anti-social personality disorder. Malingering is differentiated from a factitious disorder in that the motivation for the symptom production is external, rather than an intrinsic need to maintain the sick role. Malingering may also be differentiated from conversion disorder and other somatoform disorders by the intentional production of symptoms and the obvious external incentives associated with it.

Although it is important to identify frank malingering, which represents fraud, it must be emphasized that malingering is relatively rare and should remain a diagnosis that is made through exclusion and with extreme caution.

MAJOR STATE AND FEDERAL BENEFIT AND COMPENSATION PROGRAMS

Most impairment and disability evaluations will be performed under the context of a particular state or federal program. A number of different programs exist for individuals and workers in specific employment settings. Some of the larger programs include the Federal Black Lung Program for coal mine workers, Social Security Disability for disabled workers, Workers’ Compensation for ill and injured workers through their employers, the Veterans Administration for veterans with service-related conditions, the Energy Employees Occupational Illness Compensation program for Department of Energy workers, with special provisions for workers with chronic beryllium disease and certain workers with silicosis and a defined set of cancers. The *Radiation Exposure Commission Act* (RECA) provides compensation to individuals who develop specific cancers and other serious diseases as a result of exposure to radiation during above-ground nuclear weapons testing or during work as uranium miners, millers, and ore transporters. Most of these programs refer to both impairment and disability. In some programs, the primary determination to be made by the physician is disability, usually in the context of making the dichotomous determination of “disabled” or “not disabled,” and in others the primary determination is impairment. Each system has its own rules by which to establish patient eligibility and rules for assignment of disability and/or impairment. Most major compensation systems require physicians to undergo special training and/or approval

before they are permitted to perform these evaluations for benefits programs.

Detailed descriptions of these programs are contained in the online version of this chapter on ExpertConsult.



WORKPLACE PROTECTIONS

RESPIRATORY PROTECTION

In considering whether respiratory protection may be required in the workplace, it is important to consider NIOSH’s recommended hierarchical approach to reducing workplace exposures including (1) elimination; (2) substitution; (3) engineering controls, such as improving ventilation or enclosing exposures; (4) administrative controls; and (5) as a last resort, personal protective equipment such as respirators.⁵⁶ Medical clearance for the use of respirators is mandated by the OSHA, either through use of their standard questionnaire or through a comparable medical examination.⁵⁷ Before using a respirator, the worker should undergo tests with the specific make and model of the respirator to be used to ensure proper fit and protection. Fit testing is also regulated by OSHA.

WORK RESTRICTIONS

Some compensation systems, such as workers’ compensation, require a statement on ability to work and whether there are any physical activities or exposures the worker should avoid. Treating physicians may recommend temporary work restrictions for their patients during exacerbations of illness; these restrictions may or may not be accommodated by the workplace because there is no requirement for them to do so. Physicians may also assign permanent work restrictions, which employers are obligated to consider for reasonable accommodation under the *Americans with Disabilities Amendments Act* (ADAAA).⁵⁸ Restrictions may include limitations in the ability to perform a specific physical activity, perform it safely on a sustained or repeated basis, and/or to be able to work in the presence of certain dust, fume, gas, chemical, and/or antigen exposures, as in the case of occupational allergic asthma and hypersensitivity pneumonitis.

In order for the physician to determine whether or not the worker can perform job tasks and if restrictions are needed, both the physical requirements of the job and the worker’s capabilities need to be ascertained. Exercise testing, with its limitations noted previously, is a standard approach used in this assessment. Although submaximal testing has been used and does have some advantages in terms of administration and merits in terms of demonstrating a worker’s ability to sustain activity at a predetermined level of exertion, maximal exercise testing is normally used. Accuracy of exercise testing to predict functional performance can be increased by combining exercise testing with measures of pulmonary function³⁶ and with heart rate monitoring during the performance of work activities.⁵⁹ Actual simulation of work may be performed by a physical or occupational therapist, called a *functional capacity evaluation* (FCE). Interpretation of results and formulation of formal work restrictions should be performed in a manner

APPORTIONMENT AND FUTURE MEDICAL TREATMENT

APPORTIONMENT

When multiple disease processes are present that may contribute to respiratory impairment, the physician may be asked to apportion, or make a statement of the relative contribution of each disease process to the total impairment. This is usually performed in the context of workers' compensation in an effort to limit the amount of the monetary award to that specifically attributed to the workplace exposure or event. It does not typically reduce medical treatment benefits or wage compensation. Unfortunately, the scientific basis for this level of precision is rarely present and thus must be acknowledged as arbitrary even if required by the entitlement system.

Cigarette smoking and its sequelae is the most common condition taken into account when considering apportionment of respiratory impairment. For example, much has been written about the difference in symptoms and physical limitations in smoking compared with nonsmoking asbestos workers,⁴⁵ and the observation that the most common cause of exercise limitation in one group studied was the cardiovascular system rather than the respiratory system.⁴⁶ Specific methods for apportionment have been proposed,⁴⁷ but none has been validated scientifically or considered generally accepted. If objective evidence of prior impairment exists, such as diagnostic testing results performed before the work-related exposure or development of disease, some states will allow apportionment to be performed by subtracting the preexisting impairment from the current total impairment.

EXPECTED FUTURE MEDICAL TREATMENT

A description of the expected natural history of the condition, that is, if the condition is expected to remain stable or potentially to deteriorate over time, should be provided. In addition, the recommended medical follow-up and anticipated treatment requirements can provide a helpful measure of reasonably anticipated future medical expenses. This is of value to the worker, as well as insurance adjusters and attorneys.

Most programs include both impairment and disability. In some programs, the primary determination to be made by the physician is disability, usually in the context of making the dichotomous determination of "disabled" or "not disabled." Other systems require the physician to determine impairment. Most major compensation systems require physicians undergo special training and/or approval before they are permitted to perform these evaluations for benefits programs. A few of the larger programs are reviewed in the following sections.

PROGRAMS IN WHICH PHYSICIANS PRIMARILY DETERMINE DISABILITY

Some programs provide benefits to individuals who are determined to be unable to work due to a medical condition. The role of the physician is to determine if there is evidence

of an illness and, if so, to provide medical evidence that supports the determination that the worker cannot engage either in a particular occupation or in any type of gainful employment. These are typically all or none systems; either the worker is totally disabled due to the condition or he or she is not. No benefits are awarded unless the worker is determined to be totally disabled.

Federal Black Lung Program

The Federal Black Lung Program is a medical treatment program for miners, administered through the *Department of Labor* (DOL).⁴⁸ It arose out of the Federal Coal Mine and Safety Act of 1969, with amendments made in 1977, 1981, and 2000. The Act established mandatory safety and health standards in mines and included provisions for research and training. Title IV of the Act established black lung benefits, recognizing that there are many coal miners who are disabled or deceased because of mining-related lung disease, primarily pneumoconiosis. The amendments that followed the initial act broadened the scope of workers covered and the breadth of lung diseases covered. A *miner* is now defined as "any person who works or has worked in or around a coal mine or coal preparation facility in the extraction, preparation or transportation of coal, and any person who works or has worked in coal mine construction or maintenance in or around a coal mine or coal preparation facility." In addition, the amendments also broadened the disease covered, so *pneumoconiosis* is now defined as any "chronic dust disease of the lung and its sequelae including respiratory and pulmonary impairments, arising out of coal mine employment." Thus, the Federal Black Lung program covers not only coal miners with silicosis or coal workers' pneumoconiosis but also airway disease due to coal mining, such as chronic airway obstruction.

Benefits are awarded to the miners or to their *surviving dependents*, defined as the wife or dependent child, parents, or siblings of the miner. Each miner who applies for benefits is afforded the opportunity to undergo a medical evaluation paid for by the DOL to ascertain if she or he is eligible for benefits. The testing must be performed in the manner outlined in the Federal regulations. Only physicians who have been approved by the DOL may perform the examination; they cannot be related to the miner or have examined or treated the miner within the preceding 12 months. Miners may apply for benefits under state workers' compensation as well.

There are strict eligibility requirements. This normally requires the miner to have been employed for a minimum of 10 years in underground mine work. Once determined to be eligible to perform the examination, the physician must then determine if the miner has lung disease due to mining, as defined by the statute. This is most commonly determined on the basis of chest radiograph findings of pneumoconiosis, specifically large or small opacities of profusion 1/0 or greater, read by a NIOSH-certified B-reader, and classified according to the ILO's classification system.²⁰ A determination may also be made by biopsy or autopsy evidence of pneumoconiosis, or through a reasoned medical opinion that there was a condition that would be reasonably expected to yield the previously discussed chest radiograph or pathology findings. The regulations also specify criteria for posthumous determinations.

The physician then determines if the miner meets the definition of *totally disabled*, defined as being unable to work

as a miner or perform comparable work due to respiratory impairment. The medical criteria that establish total disability are pulmonary function test results with FVC, FEV₁, or MVV below values listed in the tables contained in the regulations (60% of predicted), FEV₁/FVC ratio 55% or less, or arterial blood gas analysis based on a PO₂ at or below a value specified for concurrently measured PCO₂, listed in one of three tables provided for different ranges of altitude. If these criteria are met, the physician must also establish that the miner is unable to perform his or her usual job in the coal mine or is unable to be employed in the area of their residence with the skills used in the mines over a period of time. The specific tables noted previously may be accessed at the U.S. DOL's Division of Coal Mine Workers' Compensation page⁴⁹ through the Pulmonary Functions Standards and Tables link. This website also contains a link to the specific standards that must be used for the administration and interpretation of PFTs contained in the legislation.

If not covered under state workers' compensation, medical treatment expenses for black lung–related conditions, including medication, will be covered. Home oxygen, pulmonary rehabilitation, and home health care may be covered after special approval.

Social Security Disability

Amendments to the Social Security Act in 1950 established the first legislation for financial assistance “to aid the permanently and totally disabled.” Numerous changes in this

system have been implemented since that time. The *Social Security Administration* (SSA) oversees two programs: the *Social Security Disability Insurance* (SSDI) program, which pays monthly cash benefits to former workers now unable to work for at least a year due to disability; and the *Supplemental Security Income* (SSI) program, which provides benefits to disabled persons who meet financial need criteria. Former workers are eligible for SSDI if they have earned a sufficient number of work credits while working in the past, based on past contributions made to Social Security. What constitutes a credit is variable, as is number of credits required, and with workers aged 62 years or older requiring the greatest number of credits to qualify.

In this program, the physician must first determine whether an applicant is disabled. *Disability* is defined as not being able to do any substantial gainful work activity because of a medically determined physical or mental impairment, which is expected to last at least 12 months or which may result in death. The determination may be made on the basis of information submitted by treating physicians and/or through an evaluation by an approved physician. There are strict eligibility criteria. The categories of impairments of the respiratory system and an overview of the impairment criteria are listed in [eTable 28-1](#). The SSA outlines the specific tests and testing criteria, including quality considerations, which form the basis for the determination as to whether or not the degree of impairment would be expected to prevent an individual from

eTable 28-1 Social Security Administration Respiratory System Impairment Categories and Criteria by Which to Establish Sufficient Impairment to Result in Disability

Category		Impairment Rating Criteria to Establish Disability
Chronic pulmonary insufficiency	Obstructive disease, any cause	Based on FEV ₁ in liters (BTPS) and height without shoes (Table I)*
	Restrictive disease, any cause	Based on FVC in liters (BTPS) and height without shoes (Table II) [†]
	Pulmonary disease causing gas exchange abnormality	DL _{CO} <10.5 mL/min/mm Hg, or DL _{CO} <40% predicted, or ABG result based on PO ₂ for a specified PCO ₂ , at rest or steady state exercise ≤5 METS [‡]
Asthma		Based on Table I criteria or based on frequency of attacks [§]
Cystic fibrosis		As per COPD or based on frequency of infections or exacerbations or based on infection treatment requirements
Pneumoconiosis		Based on Table II criteria
Bronchiectasis		Based on Table II criteria or based on frequency of infections or exacerbations [§]
Mycobacterial, mycotic, or other chronic infection		Based on Table II criteria
Cor pulmonale	Secondary to pulmonary vascular hypertension	Mean pulmonary artery pressure > 40 mm Hg Arterial hypoxemia [‡] or based on Section 4.02 (chronic heart failure)
Sleep disorders Lung transplant		As per cor pulmonale

ABG, arterial blood gas; BTPS, body temperature, ambient pressure, saturated with water vapor; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PCO₂, pressure of carbon dioxide; PO₂, pressure of oxygen.

Adapted from the Social Security Administration: Updated Blue Book information can be obtained on the SSA website (<http://www.ssa.gov/disability/professionals/bluebook/>) under the links to the Adult Listings, and the link to Section 3.00 Respiratory system.

*SSA Blue Book Section 3.02 Table I.

[†]SSA Blue Book Section 3.02 Table II.

[‡]SSA Blue Book Section 3.02 Table III-A, III-B, or III-C, depending on altitude.

[§]Frequency of attacks, defined as occurring every 2 months or at least 6 times a year despite treatment. Attacks requiring inpatient hospitalizations are counted as 2 attacks.

^{||}Infection treatment requirements, defined as persistent infection accompanied by bacterial infections occurring at least once every 6 months requiring intravenous or nebulization antimicrobial therapy.

[¶]Frequency of infections or exacerbations, defined as number of episodes of bronchitis, pneumonia, hemoptysis, or respiratory failure requiring treatment occurring at least every 2 months or 6 times per year. Inpatient hospitalizations are counted as 2 episodes.

working. Up-to-date Blue Book information can be accessed freely at the SSA website (<http://www.ssa.gov/disability/professionals/bluebook/>).

PROGRAMS IN WHICH PHYSICIANS PRIMARILY DETERMINE IMPAIRMENT

In addition to the programs outlined previously, some programs compensate workers for permanent impairment remaining after treatment of a medical condition that developed as a direct result of a workplace exposure or activity. A description of a few of these programs follows.

Workers' Compensation

State workers' compensation systems are state specific because they are governed by the rules and laws of each individual state. States began to adopt this European "no-fault" model in the early 1900s in a piecemeal manner.⁵⁰ This system affords employees the right to guaranteed treatment and benefits for an injury or illness that happens "in the course and scope" of their work, regardless of fault, but in exchange for the ability to sue their employers for negligence.⁵¹ The determination that a worker has a work-related condition is usually made by a physician on a medically probable basis (i.e., it is at least 51% likely that work event caused or substantially worsened the condition or illness). Whereas the state workers' compensation systems remain highly variable from state to state, commonalities include employer funding of the system; coverage of medical treatment expenses; temporary wage replacement compensation, usually about two thirds of salary; vocational rehabilitation training (some states only); and compensation for permanent impairment that remains after the worker has completed medical treatment (i.e., is at MMI). There is usually a statute of limitation, or a time period that a claim must be made after the worker has received a diagnosis of a work-related disease. In many states, the statute of limitations is 2 years.

The monies a worker may be paid in compensation for persistent permanent impairment of the respiratory system are usually based on the impairment rating provided by the physician. Most states designate the specific system by which permanent impairment is to be determined. Forty-four states and two commonwealths use the *AMA Guides*.⁶ Some states mandate the use of the "most recent" or "most current" edition, whereas others specifically mandate that a specific edition of the *AMA Guides* be used. Some states, such as Minnesota, have developed their own guidelines for the rating of permanent impairment. Some states, such as Colorado, require that a physician has undergone training and become "accredited" before performing impairment evaluations. Because of the variability of the systems used, as well as concerns for validity and internal consistency within some editions of the *Guides* themselves,⁵² significant variability exists in impairment ratings performed across the country.⁵³ Physicians should consult their state regulations or workers' compensation agencies to learn about the system and statutes used in their state.

There are other workers' compensation programs that cover specific groups of workers. For example, the *Office of Workers' Compensation* (OWCP) administers medical treatment and benefits to current federal workers through the

Federal Employees' Compensation Program, *Department of Energy* (DOE) workers through the EEOICP (as described in the next section), and through the Longshore and Harbor Workers' Compensation Program for workers in these industries. Under the *Federal Employers' Liability Act* (FELA), enacted in the beginning of the 20th century, federal railroad workers must establish that negligence of the railroad or other railroad personnel contributed to the injury or illness through a legal claim before full treatment and other benefits are awarded. If there is "contributory negligence" on the part of the worker, partial benefits are awarded. The Merchant Marine Act (Jones Act) describes a similar system.

Veterans Administration

Department of Veterans Affairs provides medical care for military personnel who have a service-connected condition. Veterans who meet the service requirements and were discharged under other than dishonorable conditions may apply for compensation for disability due to service-connected conditions, defined as injury or illness incurred or aggravated during active military service. Veterans with disabilities can qualify for severance with disability pay or monthly disability compensation. Those veterans who are permanently and totally disabled or 65 years of age and older, had wartime service, and meet the financial eligibility requirement may receive a monthly pension.

Disability ratings are performed according to the Rating Schedule, which contains more than 700 diagnostic codes under 14 different body systems.⁵⁴ Although it is called a disability rating, the listed criteria reflect symptoms, impairment, and treatment requirements by which the rater determines the rating, given in 10% increments ranging from 0% to 100%, rather than a determination of ability or inability to work.

The respiratory system is divided into diseases of the nose and throat, diseases of the trachea and bronchi, and diseases of the lung and pleura. Veterans Affairs-affiliated and Veterans Affairs-designated physicians review medical records and are asked to provide medical history, including current treatment requirements, physical examination findings, and results of diagnostic and clinical tests that support the diagnosis along with any associated conditions, and PFT results. The major criteria that the raters use in the determination of the disability rating for the specified respiratory diseases are shown in [eTable 28-2](#), adapted from the U.S. Department of Veterans Affairs *Web Automated Reference Materials Systems* (WARMS) website, which contains the up-to-date Book C Schedule for Rating Disabilities.⁵⁴ Specific illnesses and medical conditions are presumed to be service connected for select groups of veterans, including prisoners of war, veterans exposed to radiation, Vietnam veterans exposed to agent orange or other herbicides, and Gulf War veterans. These veterans are eligible for disability compensation for those conditions without burden of proof.

ENERGY EMPLOYEES OCCUPATIONAL ILLNESS COMPENSATION PROGRAM

This is a federal program available as an adjunct or alternative to state workers' compensation for workers who were or are employed by or were subcontractors at DOE sites or

eTable 28-2 Veterans Administration: Specific Lower Respiratory Diseases for Which Veterans May Be Eligible for Service-Related Disability and General Criteria Used

Disease	Rating Based on the Following Criteria
Bronchitis, chronic	FEV ₁ , FEV ₁ /FVC, DL _{CO}
Bronchiectasis	Cough frequency, number and frequency of infections requiring antibiotics and incapacitating episodes per year
Bronchial asthma	Frequency and type of treatment, physician visits, severity of attacks, FEV ₁ , FEV ₁ /FVC
COPD, emphysema	FEV ₁ , FEV ₁ /FVC, DL _{CO} , $\dot{V}O_{2max}$ (with cardiorespiratory limit), use of oxygen, evidence of secondary cardiovascular dysfunction*
TB	Active vs. inactive disease, respiratory status, x-ray findings, residual lung disease, thoracoplasty
Pulmonary vascular disease	Pulmonary embolism with residual symptoms, ongoing treatment needs, IVC surgery, evidence of secondary cardiovascular dysfunction*
Neoplasm	If in remission 6 months after ending treatment, rating will be reassessed and may decrease from 100% on the basis of residuals.
ILD†	FVC, DL _{CO} , $\dot{V}O_{2max}$ (with cardiorespiratory limit), evidence of secondary cardiovascular dysfunction,* use of oxygen
Mycotic lung disease‡	Active vs. inactive disease, respiratory symptoms, constitutional symptoms
Restrictive lung diseases§	FEV ₁ , FEV ₁ /FVC, DL _{CO} , $\dot{V}O_{2max}$ (with cardiorespiratory limit), use of oxygen, evidence of secondary cardiovascular dysfunction*
Sarcoidosis	Radiographic involvement, frequency and type of treatment, cardiac involvement, respiratory and systemic symptoms
Sleep apnea	Sleep study results, symptoms, CPAP treatment, respiratory failure

*Evidence of secondary cardiovascular dysfunction: evidence of cor pulmonale, RVH, or pulmonary hypertension.

†ILD: diffuse interstitial fibrosis, DIP, pulmonary alveolar proteinosis, drug-induced pulmonary pneumonitis and fibrosis, radiation-induced pulmonary pneumonitis and fibrosis, HP, pneumoconiosis (silicosis, anthracosis), asbestosis.

‡Mycotic lung disease: histoplasmosis, coccidioidomycosis, blastomycosis, cryptococcosis, aspergillosis, mucormycosis.

§Restrictive lung diseases: diaphragm paralysis/paresis, spinal cord injury with respiratory insufficiency, chest wall deformities, postsurgical residua, chronic pleural fibrosis or effusions.

COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DIP, desquamative interstitial pneumonia; DL_{CO}, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IVC, inferior vena cava; RVH, right ventricular hypertrophy; TB, tuberculosis; $\dot{V}O_{2max}$, maximal oxygen consumption.

Veterans Affairs Web Automated Reference Materials Systems (WARMS) website: http://www.warms.va.gov/regs/38CFR/BOOKC/PART4/S4_97.DOC (Accessed June 15, 2008).

who worked for businesses that functioned as vendors providing services or goods for the DOE. The compensation program is outlined in the EEOICP Act of 2000, as amended (EEOICPA or Act), which also established the DOL's responsibility for the administration of this program.⁵⁵ Part B of the Act provides compensation to current and former workers who meet DOL criteria for beryllium sensitization, *chronic beryllium disease* (CBD) and silicosis (eTable 28-3). Individuals with beryllium sensitization are awarded medical monitoring for possible progression to CBD, whereas those with CBD and silicosis are awarded medical evaluation to follow up and monitor disease, as well as coverage of medications and consequential illness evaluation and treatment as needed, along with a one-time lump-sum payment of \$150,000.

DOE employees, contractors, and subcontractors and atomic weapons employees diagnosed with cancer are compensated in a manner similar to that of CBD and silicosis, if that cancer is determined to have developed as a result of working at a covered facility, based on DOL criteria. Members of special cohorts, composed of workers at specific sites during certain time periods, are afforded compensation for specific cancers without further burden of proof. The *Radiation Exposure Commission Act* (RECA) provides compensation to individuals who develop these specific cancers and other serious diseases as a result of exposure to radiation during above-ground nuclear weapons testing or during work as uranium miners, millers, and ore transporters.

Eligibility is largely determined on the basis of having worked in certain locations during specified periods of time, a minimum duration of exposure, and having a specific type of cancer. A lump-sum payment and medical expenses will be awarded to individuals who have been awarded compensation by the *Department of Justice* (DOJ). Because the DOL makes the final determination as to whether or not the worker meets the requirements for the diagnosis, the evaluating physician should clearly document the history of the claimed illness(es), physical examination findings, the clinical testing data supporting the diagnosis, and the date the illness was first documented. Consequential illness or injury may be accepted if sufficient medical documentation of its relationship to the covered illness is submitted. There are provisions for survivor eligibility provided as part of this compensation program.

The EEOICP Act established Part E and replaced Part D, a program that had been administered by the DOE in which panels of physicians made medical determinations as to whether or not a particular illness was related to DOE work. Under Part E, DOE employees, contractors, and subcontractors, as well as eligible RECA claimants, are awarded payment of medical expenses, as well as a maximum of \$250,000 compensation for permanent impairment and loss of wages, if they are determined to have developed an illness as a result of occupational exposure to a toxic substance at a covered DOE facility. Workers with conditions accepted under Part B will be automatically accepted under

eTable 28-3 EEOICPA Part B Requirements for Eligibility and Diagnosis under the Act for Beryllium-Related Illness and Silicosis*

Condition	Eligible Workers	Requirements for Diagnosis under Part B
Beryllium sensitization	See chronic beryllium disease	Abnormal <i>Beryllium Lymphocyte Proliferation test</i> (BeLPT) performed on blood or BAL cells
Chronic beryllium disease	Employees of the DOE, its predecessor agencies, contractors, and subcontractors; designated atomic weapons workers; and beryllium vendors	For diagnoses made on or after 1/01/1993 [†] An abnormal BeLPT and at least 1 of the following: 1. Lung biopsy showing a process consistent with CBD 2. A CT scan showing changes consistent with CBD 3. A pulmonary function or exercise tolerance test showing pulmonary deficits consistent with CBD
Chronic silicosis	DOE employee or contractor who worked at least 250 days in underground tunnel operations at the Nevada or Alaska nuclear test sites	One of the following: 1. A chest radiograph B-reading confirming pneumoconiosis with a profusion score of 1/0 or greater 2. Results from a CT or other imaging study consistent with silicosis 3. A lung biopsy consistent with silicosis

*The final decision as to whether or not the patient meets the requirements is made by the Department of Labor.

[†]If the diagnosis was made before 1/01/1993, at least 3 of the following must be documented: characteristic chest radiograph or CT scan denoting abnormalities; a test showing restrictive, obstructive, or diffusion abnormality; lung pathology consistent with CBD; a clinical course consistent with a chronic respiratory disorder; an immunologic test showing beryllium sensitivity (skin patch test or beryllium test preferred).

BAL, bronchoalveolar lavage; CBD, chronic beryllium disease; CT, computed tomography; DOE, U.S. Department of Energy; EEOICPA, Energy Employees Occupational Illness Compensation Program Act.

Adapted from U.S. Department of Labor Medical Requirements under the Energy Employees Occupational Illness Compensation Program Act OMB No. 1215-0197 Expiration date: 08/31/2010 Form EE-7 April 2005.

Part E for compensation for impairment. Unfortunately, DOE vendors are eligible under Part B but are not eligible for compensation under Part E. There is survivor eligibility provided under Part E. Impairment ratings may be performed by physicians who are certified by the *American Board of Independent Medical Examiners* (ABIME) or *American Academy of Disability Evaluating Physicians* (AADEP) or who are otherwise considered by the DOL to have the requisite experience or knowledge. Not all physicians approved to provide care for workers under Part B of the program are eligible to provide impairment ratings under Part E.

Physicians will be asked to submit such credentials for approval by the DOL to confirm their ability to provide impairment ratings. Alternatively, medical consultants to the DOL may perform the ratings. Currently, the ratings are still performed under the *AMA Guides*, Fifth Edition, which had been the most recent edition at the time the legislation was passed. Each percent whole-person impairment determined through an impairment rating is compensated \$2500. Compensation for lost wages is based on the number of years that the employee was unable to work or sustained a reduction in wages because of the illness up to age 65.

consistent with the ADAAA considerations, including suggesting possible methods of reasonable accommodation in the workplace.

AMERICANS WITH DISABILITIES ACT AMENDMENTS ACT

The *Americans with Disabilities Act* (ADA) of 1990 and the *Americans with Disabilities Act Amendments Act* (ADAAA) of 2008 prohibit discrimination against a qualified individual with a *disability*, defined as “a physical or mental impairment that substantially limits a major life activity.”^{58,60} The Act applies to individuals who have, have a record of, or are regarded as having a physical or mental impairment. Initially, determination of whether cases met the ADA criteria focused on whether or not the individual met the definition of disabled. More recently, by retaining the original definitions of disability, the ADAAA expanded the definition of “major life activities” to include activities such as sleeping, standing, lifting, bending, concentrating, communicating, thinking, and working and effectively expanded the number of workers who qualify for coverage under the Act.⁵⁸ A list of “major bodily functions” is also now covered by the ADAAA, such as functions of the immune system, normal cell growth, and respiratory. A disease that causes intermittent impairment or that is in remission is considered a disability if it would substantially limit a major life activity when active. The goal of these changes was to focus workplace accommodation for “qualified individuals.” A qualified individual is a person who has the requisite skills and experience to do the job and “can perform the essential job tasks with or without reasonable accommodation” without risk of direct threat to self or others. Knowing what the essential job tasks are and what is required to do them physically is essential for the physician to be able to make this determination. This information is often contained in the workers’ position description. The worker’s job title typically provides insufficient information.

Essential job tasks are defined as the specific functions that an individual in that position must be able to perform without aid or with the assistance of reasonable accommodation. Factors involved in determining whether or not a job activity is an “essential function” include whether or not all employees in the position are required to perform the task, the position exists to perform the function, the frequency and duration of the job function, and whether or not there are other employees available and qualified to perform the function. A “preemployment” physical is not permitted under the ADA; an employer may not ask questions about disability or require a medical examination until after a conditional job offer has been made. A postoffer, preplacement medical evaluation is permitted, as long as the employer does this for all employees entering the same job category; if doing so is job related and consistent with business necessity on the basis of objective evidence that a worker will be unable to perform essential job functions or will pose a direct threat because of a medical condition; or when an employer receives a request for reasonable accommodation and the disability or the need for the accommodation is not obvious.

Reasonable accommodation is defined as a modification or adjustment to the job, work environment, or way things are

usually done that enables a person with a disability to perform the essential job function. Physicians may suggest means by which reasonable accommodation may be made, but the employer decides whether or not the accommodation is reasonable on a case-by-case basis. Examples of reasonable accommodation for individuals with respiratory impairment can include modification of the workstation to allow use of a wheelchair, scooter, or oxygen equipment; decreasing the need to travel distances, lift or push objects; and/or allowing written rather than lengthy verbal communication. A direct threat exists when an individual poses a significant risk of substantial harm to the health or safety of herself, himself, or others and the risk cannot be reduced to an acceptable level with reasonable accommodation. The risk needs to be defined in terms of the specific behavior or physical limitation that would pose the direct threat, the duration of the risk, the nature and severity of the potential harm, and the likelihood and imminence of the potential harm. An example of direct threat would be use of oxygen in an area with open flames or sparking materials.

FAMILY AND MEDICAL LEAVE ACT

The *Family Medical Leave Act* (FMLA) entitles eligible employees up to 12 weeks of unpaid leave with benefits per year due to a serious health condition of their own or to care for a spouse, child, or parent with a serious health condition.⁶¹ There are additional provisions for child care and service members and their families. Eligibility is based on the number of hours the patient has worked for the employer and the size of the employer. Physicians must complete a standardized form indicating the condition and the expected frequency and duration of the work absences.

FUTURE DIRECTIONS

DEVELOPING AN IMPROVED FRAMEWORK OF DISABILITY

International Classification of Functioning, Disability, and Health

The WHO’s ICIDH model was recognized as problematic in a number of respects, including an implied unidirectional relationship from impairment to handicap, limited definition of the role of the environment, and focus on the disability, rather than the factors that may enable functional ability. The WHO put forth the *International Classification of Functioning, Disability, and Health* (ICF) in 2001 in two parts,⁴ designed to be used in conjunction with the *International Classification of Diseases* (ICD)-10 codes as a uniform description of health and well-being.

The first part of the ICF is most relevant to most physicians, combining consideration of body structure and function, activities, and participation into a unified concept. The term *functioning* according to the ICF combines the positive aspects of body functions, activities, and participation, whereas the term *disability* is used to describe the combination of the negative aspects of functional loss (impairment), activity limitation (disability), and participation restriction (handicap). Part 2 of the ICF describes Contextual Factors,

divided into personal factors, such as age, education, attitudes, and environmental factors. *Facilitators* are contextual factors that enhance functioning and *barriers* are contextual factors that restrict or limit functioning.

This model was developed as a method to describe functioning and disability in a uniform manner across a wide range of medical disorders on an international level. *The World Health Organization Disability Schedule 2.0* (WHODAS 2.0) is an interviewer-administered questionnaire designed to measure functioning and disability within the conceptual framework of the ICF.⁶² It measures six domains (cognition, mobility, self-care, getting along, life activities, and participation). The data are subjective and many of the questions relate to basic ADLs. This tool is not in use in the occupational setting at this time.

INSTITUTE OF MEDICINE FRAMEWORK

An alternative framework to the WHO's ICIDH and ICF models was based on an *Institute of Medicine* (IOM) model that includes pathology, impairment, functional limitation, and disability.^{63,64} The IOM's most recent report *Future of Disability in America* (2007) indicates that the model is still in the process of refinement,⁶⁵ incorporating concepts from other models to emphasize that enablement/disability is a multistage and bidirectional process and that the patient's environment plays a critical role in either facilitating or obstructing functioning and participation.⁶³⁻⁶⁶ In addition, this model incorporates the notion that prevention of conditions arising secondary to the primary condition can improve quality of life.⁶⁵ In the current IOM framework, *pathology* is defined as the "interruption or interference of normal bodily processes or structures caused by disease, trauma, or other conditions." *Impairment* is defined as "loss and/or abnormality of mental, emotional, physiological, or anatomical structure or function." *Functional limitation* is defined as the "restriction or lack of ability to perform an action or activity in the manner or within the range considered normal that results from impairment." *Disability* is defined as the "inability or limitation in performing socially defined activity and roles expected of an individual within a social and physical environment" and expands the definition to the "gap between a person's capacities and the demands of relevant, socially defined roles and tasks in a particular physical and social environment."⁶³ The IOM has indicated that priority should be given to disability research, improving access to health care and support services, reducing barriers to health insurance, making needed assistive services and technologies more available, and developing educational programs and public health campaigns to increase public and health care professionals' awareness of available assistive and accessible technologies.⁶⁵

DISEASE-SPECIFIC IMPAIRMENT

There is increasing recognition that some diseases not only alter lung structure and/or function but also impair other organ systems that in turn contribute to whole-person impairment and disability.^{67,68} COPD is one of the major causes of respiratory impairment and disability,⁶⁹ and the disease has major economic and societal impact world-

wide.⁷⁰ In addition to lung function, COPD impairs lower extremity strength,^{71,72} balance,^{71,73} and cognition⁷⁴ and increases anxiety and depression.^{75,76} This multisystem impairment may arise independent of lung function,⁷⁷ and contribute to decreased global functioning.^{77a} Although this bidirectional relationship is consistent with the IOM framework, it adds considerable complexity to the development of a model through which to estimate impairment and disability caused by a work-related lung disease.

Key Points

- *Impairment* refers to the degree of loss of normal use or function of a body part or organ.
- *Disability* refers to any resulting alteration in the individual's capacity to perform customary activities. That definition has been expanded by the Institute of Medicine to include the "gap between a person's capacities and the demands of relevant, socially defined roles and tasks in a particular physical and social environment," emphasizing the bidirectional nature of the model and the importance of factors in the environment that facilitate or present obstacles to functioning and participation.
- *Maximum medical improvement* (MMI) is the time at which permanent impairment can be assessed. It is achieved when the diagnosis has been well defined, the condition is stable, and medical treatment has either optimized or reasonable options have been exhausted.
- The *Americans with Disabilities Amendments Act of 2008* greatly expanded the definition of disability to focus on workplace accommodation of "qualified individuals." A qualified individual is a person who has the requisite skills and experience to do the job and "can perform the essential job tasks with or without reasonable accommodation" without risk of direct threat to self or others.
- *Reasonable accommodation* is defined as a modification or adjustment to the job, work environment, or the way things are usually done that enables a person with a disability to perform an essential job function.
- An *impairment evaluation* is a medical evaluation that typically includes history, including a detailed occupational and environmental history and description of limitations in activities of daily living; physical examination; and review of medical records and diagnostic test results that establish the respiratory condition. If the worker is at MMI, a permanent impairment rating can be performed. The physician may be asked to address causation, which is usually the disease relationship to workplace exposures, the need for work restrictions, future medical needs, and possibly apportionment of impairment.
- An *impairment rating* is a numeric value from 0% to 100% that represents the percent loss of total body function due to the respiratory system. This numeric value helps form the basis for the monetary award given to workers with permanent impairment that remains after reaching MMI.

- In addition to state and federal workers' compensation programs, other special benefit and compensation programs exist for certain groups of workers, including miners, Department of Energy workers, veterans, and radiation-exposed workers.

Complete reference list available at *ExpertConsult*.

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SYMPTOMS OF RESPIRATORY DISEASE AND THEIR MANAGEMENT

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DYSPNEA

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INTRODUCTION

Dyspnea (Greek *dys*, meaning “painful,” “difficult,” and *pneuma*, meaning “breath”) is a clinical term for the sensation of breathlessness or shortness of breath experienced by both normal subjects and patients with diseases affecting the respiratory system. Its importance has been recognized by the release of an updated American Thoracic Society Statement.¹ Dyspnea assumes clinical significance when it is felt at a level of exertion that is unacceptably low for the individual or modifies a patient’s lifestyle dramatically in an effort to avoid breathing discomfort. It is increasingly regarded as an important outcome for both prognostic and therapeutic purposes across a wide range of clinical conditions, principally *chronic obstructive pulmonary disease* (COPD),² heart failure,³ advanced cancer,⁴ and interstitial lung diseases.⁵

There are no precise data on the prevalence of dyspnea.⁶ A meta-analysis suggests a worldwide prevalence of 10% for COPD in adults older than 40 years,⁷ making its cardinal symptom, dyspnea, a substantial cause of morbidity, espe-

cially in older people. A high prevalence of dyspnea due to all causes is indicated by a survey of 4900 middle-aged and older adults in which 27.2% reported having dyspnea, whereas only 12.5% reported having COPD.⁶ In a survey of 1556 seriously ill patients admitted to hospital, 49% reported having dyspnea compared with 51% who reported pain.⁸ Morbidity associated with dyspnea is variable, ranging from minor annoyance to functional incapacity.⁹ Moreover, dyspnea is a strong independent predictor of mortality in COPD,¹⁰ heart failure¹¹ and aging.¹² Compared with pain, dyspnea is relatively refractory to effective symptom management, likely affecting not only patients but also their care providers (including health professionals) during terminal or severe chronic conditions.¹³

Dyspnea encompasses a variety of sensations experienced when breathing feels uncomfortable, labored, and unsatisfying,¹ sensations likely to be linked to discrete physiologic mechanisms.¹⁴ As a symptom, dyspnea can be reported only by the patient and is distinct from objective findings or signs associated with physical examination, such as tachypnea, hyperinflation, and cyanosis. Dyspnea

is multifactorial and, although it results from pathophysiologic events, is likely to be influenced by such factors as psychological state, bodily preoccupation, level of awareness, usual level of physical activity, body weight, state of nutrition, and medications. These many modifying factors may explain the variable correlation between dyspnea ratings and airflow limitation or exercise performance.¹⁴ Because most diseases for which dyspnea is a common symptom are essentially irreversible (e.g., chronic lung disease, heart failure, cancer), effective management of the dyspnea symptom to improve quality of life is a desirable goal.

DEFINITION OF DYSPNEA

Over the years there have been many attempts to define dyspnea, and these have shared a common theme of an uncomfortable perception associated with the act of breathing. However, the more formalized definition given in the consensus statement of the American Thoracic Society is now widely accepted and has provided a sound basis for researchers and clinicians concerned with understanding and managing this symptom.¹ This states: “*Dyspnea* is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and it may induce secondary physiological and behavioral responses.” The American Thoracic Society dyspnea statement also emphasizes that “distinct sensations most often do not occur in isolation,” and that the sensations “vary in their unpleasantness and their emotional and behavioral significance.”¹

LANGUAGE OF DYSPNEA

The breathing discomfort associated with various cardiopulmonary derangements is characterized by a range of words and phrases used to describe the sensation and can trigger strong affective responses. Studies of the language of dyspnea provide insights into the patient's perception of the problem, and these descriptors often offer clues to the underlying physiologic derangements. A multidimensional model for dyspnea, which includes sensory intensity, qualitative descriptors, and affective elements has been proposed.¹⁵

QUALITATIVE PHRASES—THE DESCRIPTIVE DIMENSION OF DYSPNEA

When patients complain of being short of breath, they are usually reporting familiar sensations that have become noticeable at lower levels of exertion. When questioned further, patients may volunteer comments such as “hard to breathe,” “can’t get enough air,” or “feeling tight” but often have difficulty being more specific. Overlaying this, cultural or language differences may result in patients using different words to describe the same sensory experience.¹⁶ Modeled on the proven clinical utility of evaluating the language of pain (e.g., assessing ischemic heart disease),

researchers have asked if the language of dyspnea might be similarly useful.

Since the early 1980s, studies in healthy subjects and dyspneic patients have identified distinctive clusters of descriptors from commonly used expressions of breathing discomfort. In general, four primary categories of breathing discomfort can be identified by the following descriptors: “tightness,” “need or urge to breathe,” (often labeled “air hunger”), “work or effort of breathing,” and “depth and frequency of breathing.” In patient populations, “tightness” appears to be clearly associated with bronchoconstriction, whereas “urge to breathe” is associated with enhanced central drive and/or limitations of tidal volume, and “effort of breathing” is seen in conditions characterized by alterations in the respiratory pump (e.g., ventilatory muscle weakness or increased airway resistance). The “depth and frequency of breathing” descriptor, typically associated with activity or exercise, probably relates more to awareness of chest wall movement than to awareness of breathing discomfort but may nonetheless be worrisome to the patient.

Although there are few cross-cultural studies of the language of dyspnea, the basic categories of phrases noted previously appear consistent across countries.¹⁴ In addition, children use qualitative descriptors to describe the respiratory discomfort associated with asthma in a manner quite similar to adults, and their use of language is reliable over time.¹⁷ Other factors, such as obesity, may be associated with different sensory qualities that relate to the intensity of the breathlessness.^{17a} The primary studies that have defined and explored the utility of qualitative descriptors have been summarized.¹⁴

EMOTIONAL PHRASES—THE AFFECTIVE DIMENSION OF DYSPNEA

The pain model of symptom attributes has been further applied to explore the importance of the affective component (e.g., unpleasantness, fear, anxiety) of dyspnea in addition to its intensity and quality.¹⁵ One study reported that for a given intensity of dyspnea, a stimulus with a greater “air hunger” component is perceived as a substantially more unpleasant experience than one with a strong “work/effort” component.¹⁸ These authors have developed a multidimensional profile for dyspnea, based on an analogous instrument for pain, which should provide a better understanding of the affective component of dyspnea with a view to developing more-targeted therapeutic approaches; reliability and validity of the instrument have been demonstrated.^{18,19} Similar efforts have produced a single dyspnea tool that incorporates both the descriptive and affective dimension into one instrument.^{20,21}

In patients with COPD, those with more severe degrees of respiratory system dysfunction, as evidenced by the BODE (*body mass index, airflow obstruction, dyspnea, and exercise capacity*) index, volunteered more extreme affective phrases, such as “frightening” and “worried.”²² Furthermore, those patients expressing higher dyspnea-related fear may have greater improvements in dyspnea with a pulmonary rehabilitation program.²³ Interestingly, there appears to be no difference in the affective response in patients with COPD when they have dyspnea at home compared to when dyspnea is stimulated in a laboratory setting,²⁴ which

suggests that the ability to control dyspnea by reducing activity may mitigate the emotional dimension in a manner similar to telling an investigator to stop the experiment.

A more careful consideration of the language and emotional impact of dyspnea by health practitioners might yield important diagnostic insights or improved management of breathless patients and is increasingly becoming a marker of quality of care for evaluating dyspnea.²⁵

MECHANISMS OF DYSPNEA

The neurophysiologic mechanisms that give rise to the perception of dyspnea are incompletely understood (Fig. 29-1). Current thinking suggests that the discomfort of dyspnea comprises two primary components: (1) an “urge to breathe” (referred to as “air hunger”) and (2) a “sense of excessive effort” associated with breathing. Although sensations of urge to breathe and effort increase together with exertion, they can be separated experimentally²⁶ with the former being reported as more unpleasant in healthy subjects.²⁷ A third quality of respiratory discomfort, “chest tightness,” is commonly reported by asthmatics.²⁸ Dyspnea in an individual patient may well represent a combination of these component sensations and account for the different qualities of dyspnea mentioned previously.

As with all sensations, the experience of dyspnea must result from changes in neural activity within the cortical and subcortical structures of the brain involved in perception. Respiratory-related afferent information from the upper airway, lungs, thoracic cage, and chemoreceptors as well other signals from, for example, exercising limbs and the cardiovascular system provide numerous peripheral inputs relating to cardiorespiratory function. Such information may integrate with central neural respiratory networks, notably in the cerebral cortex, limbic system, and

brain stem to generate a range of respiratory sensations.²⁹ Moreover, these experiences are likely to be modulated by neural traffic related to cognitive, emotional, and nonrespiratory sensory input. The fact that clinical dyspnea can arise with or without deficiencies in gas exchange and in the presence or absence of impaired respiratory mechanics underscores the complexity of this symptom. As indicated earlier, the use of language to identify qualitative variations in dyspnea, perhaps related to different patterns of central neural activation, may lead to a more comprehensive understanding of the origin of dyspnea and better therapeutic strategies for its management in individual patients.

Because dyspnea is a perception, studies on its mechanisms must be confined to humans and are limited by the difficulty of measuring a subjective experience and the neural activity that underlies it. Neuroimaging technologies, principally PET and functional magnetic resonance imaging, allow imaging of brain function associated with sensory, motor, and cognitive processes, and these have been applied to study the neural basis of dyspnea in healthy subjects. Different investigators have induced dyspnea in different ways, with varying degrees of “urge to breathe” and “sense of effort.” Despite this, a consistent pattern of neural activity associated with dyspnea perception is emerging from these studies. Of particular note is the activation of limbic and paralimbic structures, especially the anterior insular cortex, anterior cingulate gyrus, amygdala, and cerebellum. Activation of these phylogenically ancient regions of the brain has been seen in brain imaging studies of pain,³⁰ thirst,³¹ and hunger³² and is consistent with the idea that dyspnea is a primal experience associated with behaviors intended to counteract a threat to survival.³³⁻³⁵ Such studies are difficult to interpret definitively and are not easily generalizable to clinical populations. Nonetheless, neuroimaging techniques are rapidly becoming more sophisticated, and future studies in symptomatic populations offer the potential of a clearer picture of the neural basis of clinical dyspnea.

There is good evidence that the “urge to breathe” component of the dyspnea sensation depends to a large extent on the degree to which respiratory-related neurons in the brain stem are stimulated. Stimulation of ventilation with exercise, hypoxia, hypercapnia, and metabolic acidosis induces dyspnea,^{36,37} whereas a voluntary increase in ventilation induces little dyspnea, even in patients with respiratory mechanical limitation.³⁸ Moreover, dyspnea is felt strongly when the respiratory neurons are stimulated in the absence of a possible ventilatory response, as with spinal transection and experimental respiratory muscle paralysis.^{39,40} The role of afferent feedback from the lungs and chest wall in the genesis of dyspnea is complex. Conditions thought to activate lung irritant receptors and/or pulmonary C fibers (e.g., pulmonary edema, atelectasis, congestive heart failure) may well contribute to dyspnea via vagal nerve afferents either directly or by modulating other sensory inputs that give rise to dyspnea.^{40,41} Conversely, physiologic activation of slowly adapting stretch receptors during lung inflation may inhibit the central respiratory drive and in this way ameliorate dyspnea. When the desired ventilation and the achieved ventilation are not matched, based on feedback from mechanical and flow (temperature) receptors in the lungs, airways, and chest wall, the intensity

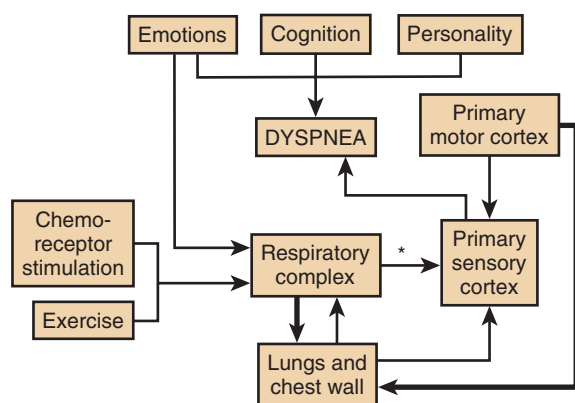


Figure 29-1 The respiratory complex in the brain stem is central to our understanding of dyspnea. Activation of the respiratory complex by afferent input from a variety of receptors or by emotions, with input from the lungs and chest wall, determines the efferent command to the lungs and chest wall to breathe. The brain is made aware of this as dyspnea by a simultaneous corollary discharge (*) to the primary sensory cortex. Alternatively, the primary motor cortex can initiate voluntary efferent commands to the lungs and chest wall to control breathing, with coactivation of the primary sensory cortex, which contributes to dyspnea. The primary sensory cortex also receives input from the lungs and chest wall that may affect the perception of dyspnea. The central experience of dyspnea may also be affected by emotions, cognition, and personality. (Bold lines indicate efferent output commands to the lungs and chest wall to breathe.)

of dyspnea increases. The immediate relief of dyspnea observed with thoracic movements following breath-holding but without improvements in blood gas status is consistent with this concept.⁴²

In their review of the roles of airway nerves in inflammatory airway disease, Undem and Nassenstein⁴⁰ implicate vagal mechanisms in the production of dyspnea, both directly by neural signaling and indirectly by increasing the work of breathing via the release of acetylcholine (which stimulates airway smooth muscle contraction and mucus secretion). Nishino⁴³ suggested that vagal mechanisms associated with coughing affected the sensation of dyspnea, although the author agreed that other neural mechanisms could play roles. Further support for this comes from the observation in quadriplegic patients, who lack afferent information from the chest wall, that increases in tidal volume reduce the dyspnea from carbon dioxide inhalation without any change in blood gas levels.⁴⁴ Moreover, inhaled furosemide, which potentiates slowly adapting stretch receptor activity in an animal model, has been shown to ameliorate the sensation of experimental dyspnea in healthy subjects⁴⁵ and exertional dyspnea in COPD patients.⁴⁶ With respect to “sense of effort,” proprioceptive feedback from muscle, joint, and metaboreceptors (peripheral afferent nerves that respond to metabolic by-products of skeletal muscle metabolism) probably integrates with the motor cortical output in the genesis of this perception.¹⁴

In light of the previous discussion, exertional dyspnea in patients with lung disease can be considered a manifestation of the increased central respiratory drive necessary to achieve adequate ventilation by a mechanically constrained respiratory apparatus. This concept fits with the observation that, in COPD patients, progressive hyperinflation is associated with increasing dyspnea because ventilatory demands require greater respiratory muscle activity to overcome increased elastic work at high lung volumes and to offset the foreshortening of inspiratory muscles that places them at a mechanical disadvantage.^{14,47} Furthermore, to the extent that inspiratory capacity is compromised by increases in end-expiratory lung volume in these patients, expected tidal volume and achieved tidal volume are not matched, and dyspnea intensity increases.^{14,47} Following from this, the lessening of dyspnea that follows successful lung volume-reduction surgery, as well as pharmacologic lung volume reduction,⁴⁷ is consistent with improvement in both lung and respiratory muscle mechanics. Support of this concept comes from a study showing that a decrease in dyspnea after volume reduction was associated with alleviation of hyperinflation of the lungs and a decrease in neural drive to the diaphragm.⁴⁸ Moreover, the concept is supported by the observation that noninvasive ventilatory support during exercise relieves dyspnea in patients with COPD,⁴⁸ presumably by reducing the work of breathing and consequently the efferent neural activity to respiratory muscles.

The utility of this concept of dyspneogenesis extends to conditions in which lung disease is not the primary problem. In particular, the dyspnea of heart failure might be accounted for in terms of a heightened respiratory drive secondary to expiratory flow limitation⁴⁹ or peripheral muscle dysfunction.⁵⁰ A similar phenomenon may arise with deconditioning. The benefits of exercise training for

those with dyspnea may be mediated in part by changes in peripheral muscle function. Other conditions in which dyspnea in the absence of lung disease could be accounted for by increased respiratory drive include motor neuron disease/respiratory muscle weakness,⁵¹ late-stage pregnancy,⁵² anemia,⁵³ thyroid disorders, panic disorder, and anxiety.⁵⁴

The sensation of dyspnea, like pain, has a psychological dimension.⁵⁵ An individual's emotional state, personality, previous experience, and cognitive function are likely to influence the experience and reporting of dyspnea. Dyspnea is worse when it is unexpected, when it happens in inappropriate situations, and when it is perceived by the patient to be dangerous.⁵⁶ Studies in healthy subjects and in patients with underlying disease have suggested that perception of the intensity of breathlessness may be influenced by prior experience of the sensation.^{57,58} Moreover, both auditory distraction⁵⁹ and experimentally induced changes in mood⁶⁰ have been shown to increase the unpleasantness of exertional dyspnea in COPD patients. Whether such observations are related to the frequency of prior experience of dyspnea (e.g., with exercise) or to some ill-defined psychological factor is unknown. In patients with the hyperventilation syndrome, both dyspnea and ventilation may dramatically increase in the absence of any known physiologic stimulus to breathe.⁵⁴ Dyspnea is a particular problem in patients with panic attacks. An Internet-based survey found that 95% of the respondents reported breathing problems during panic attacks, and 68% reported “remarkable” dyspnea.⁶¹ An interesting example of clinically significant activity-related breathlessness in healthy human pregnancy is reported by Jensen and colleagues.⁶² They observed that variability in the perceptual response to exercise could not be explained by variation in central ventilatory drive or in respiratory mechanical/muscular factors, but ultimately reflected a difference in awareness of increased ventilation. The source of that variation in perception is not clear. O'Donnell and coworkers⁶³ have reviewed the role of “higher center” neural processing on dyspnea perception and its relevance to self-management of this symptom.

In sum, dyspnea may develop when there is (1) increased central respiratory drive secondary to exercise, hypoxia, hypercapnia, or other afferent input; (2) augmented requirement for the respiratory drive to overcome mechanical constraints or weakness; and (3) altered central perception.

ASSESSMENT OF DYSPNEA

Clinicians generally rely on a combination of patients' reports and physiologic measurements (e.g., *forced expiratory volume in 1 second* [FEV₁]) to evaluate the presence and intensity of dyspnea and its pathologic origins. By assessing the nature and severity of symptoms, such as dyspnea, physicians quickly gain an advantage in the decision-making process. With a better understanding of the physiologic basis of symptoms, physicians can target the types and extent of diagnostic testing as well as the urgency with which a diagnosis must be made. Understanding the mechanisms of dyspnea or the responses to interventions, however, requires objective measurement of the symptom.

Although primarily used for clinical investigation, there is increasing interest in applying dyspnea measurements to clinical practice.⁶⁴ For a review of factors that limit exercise performance in COPD and the identification of factors that contribute to the variability of dyspnea during exercise, see Stendardi and associates.⁶⁵ O'Donnell and coworkers¹⁴ present a hypothetical model for exertional dyspnea based on current neurophysiologic concepts that were developed to explain the origins of “effort,” “air hunger,” and the accompanying affective “distress” response.

EXERCISE PERFORMANCE AS AN INDICATION OF DYSPNEA

Exercise testing is commonly used to understand dyspnea better,⁶⁶ although there are discrepancies in the available diagnostic algorithms.⁶⁷ This form of testing focuses more on physiologic limitations than on the symptoms that limit exercise and might not be necessary for all patient groups. Two widely used field tests are the 6-minute walk distance and shuttle walking tests,⁶⁸ which are easy to perform and require minimal equipment; more sophisticated cardiopulmonary exercise testing can be particularly helpful when it is unclear whether the patient is limited by the respiratory or the cardiovascular system.^{69,69a} When an exercise test is limited by symptoms, it is important to ask the patient the exact reason for stopping. Although the patient may appear to be in respiratory distress, it is not uncommon that joint pain, leg fatigue or discomfort, or generalized weakness is the actual limiting factor.

EXERCISE LIMITATION DUE TO DYSPNEA

Early attempts to evaluate the severity of dyspnea involved patient assessments of their own exercise tolerance (e.g., the five-point Medical Research Council scale⁷⁰ and its modified version, the American Thoracic Society scale). Although such scales are simple, they are insensitive, require individuals to make comparisons with others, and cannot readily measure changes following therapeutic interventions. The Baseline Dyspnea Index, a rater-administered test, was developed to rate patients with regard not only to the “magnitude of the task” that elicits dyspnea (e.g., hills compared with level ground) but also to the impact of dyspnea on activities of daily living and the effort required to produce dyspnea.⁷¹ Measurements can be repeated over time or in response to interventions. A number of easy-to-use self-administered questionnaires to assess functional limitation due to dyspnea have been developed but in general have not found widespread use.⁷²

QUALITY OF LIFE AND DYSPNEA

The negative impact of dyspnea on an individual's quality of life has been increasingly recognized since the mid-1980s and now is an important outcome measure in studies of therapeutic intervention for COPD/dyspnea. Two questionnaires, the Chronic Respiratory Disease Questionnaire and the St. George's Respiratory Questionnaire, are used most often. The Chronic Respiratory Disease Questionnaire is a rater-administered questionnaire with 20 items that focus on four aspects of illness: dyspnea, fatigue, emotional function, and the patient's feeling of control over the disease.⁷³ Dyspnea is evaluated on a seven-point scale in relation to the five most important activities provoking dyspnea during the previous 2 weeks. In effect, the Chronic Respiratory Disease Questionnaire assesses how breathing sensations alter the quality of the patient's life. The St. George's Respiratory Questionnaire is a self-administered questionnaire with 76 items addressing symptoms, activity, and the impact of disease on daily life. Dyspnea is not evaluated specifically but is included with other respiratory symptoms such as cough, sputum, and wheezing.⁷⁴ These instruments have been shown to be reproducible, to correlate with each other, and to relate appropriately to physiologic measurements.⁷⁵⁻⁷⁷ Although important for clinical investigation, these tools are somewhat demanding to use, often requiring trained health personnel, and are of unproven value for routine clinical care.

PSYCHOMETRIC MEASUREMENT OF DYSPNEA

Several instruments are available for rating the symptom dyspnea directly; they allow reasonably reproducible rating of the intensity of dyspnea on a simple linear or numeric scale during exercise or in response to specific questions. The *visual analogue scale* (VAS) is a horizontal or vertical line, usually 10 cm long, anchored at either end with words such as “no dyspnea” and “maximal dyspnea” (Fig. 29-2). In response to a question (e.g., “How short of breath are you?”), the subject marks a point along the line so the length reflects the intensity of the sensation. The Borg scale is a 10-point scale with extremes of “nothing at all” and “maximal.”⁷⁸ Unlike the visual analogue scale, the Borg scale (Table 29-1) includes verbal descriptors (e.g., “slight,” “severe”) to assist in rating the symptom. Both scales demonstrate good reproducibility,^{79,80} but the proximity of the terms “slight” and “severe” on the Borg scale may reduce its sensitivity and discourage subjects from using the whole scale as they do with the visual analogue scale.⁸¹ A valid approach, which has perhaps better clinical utility, has been

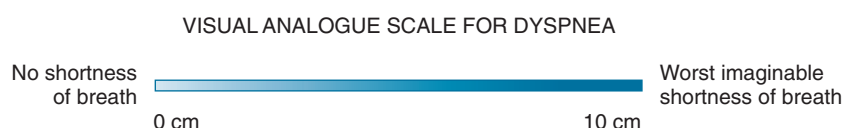


Figure 29-2 Visual analogue scales, such as the horizontal one shown here, can be used for measuring dyspnea during an activity (e.g., exercise testing) or in response to questions. Such scales may be depicted vertically as well. On request, the subject marks a point on the line in response to a question (e.g., How short of breath are you right now?). The score is determined by the length of the line from “no shortness of breath” to the point marked by the patient. The scales are usually 10 cm long to facilitate scoring, and electronic scales may be used to allow online scoring (e.g., during exercise testing). Instructions about what is meant by the terms used to describe a sensation (e.g., “extremely breathless”) must be clear and must be presented in a uniform fashion to provide meaningful results. The description of the “anchors” at each end of the scale must also be clearly defined in terms that are meaningful to the patient or research subject.

Table 29-1 Modified Borg Category Scale for Rating Dyspnea

Rating	Intensity of Sensation
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

to employ a simple numeric rating scale ranging from 0 to 10.⁸² Additional scales continue to be developed.⁷² Any of these validated instruments may be appropriate when designing research studies, but it is critical that they be administered in a standardized way.

MULTIDIMENSIONAL ASSESSMENT OF DYSPNEA

There has been a growing focus on extending the assessment of dyspnea beyond the intensity domain to include the qualitative and affective components of this complex symptom. Using a multidimensional approach (modeled on those widely used in pain research), there are now a number of validated instruments that are being used in research and clinical studies. A number of these are referenced in the “Language of Dyspnea” section¹⁹⁻²¹ and have been comprehensively reviewed, in the overall context of dyspnea assessment.⁸³

DIAGNOSTIC APPROACH TO THE PATIENT WITH DYSPNEA

OVERVIEW: PHYSIOLOGIC CATEGORIES OF DYSPNEA

The differential diagnosis of dyspnea includes neuromuscular, renal, endocrine, rheumatologic, hematologic, and psychiatric diseases, as well as diseases of the lungs, heart, and chest wall. The diagnostic approach is determined by the acuity of the problem. For acute dyspnea, the differential diagnosis is relatively narrow, and the cause is generally easily identified (e.g., pneumonia, pulmonary embolism, congestive heart failure, asthma), although psychogenic dyspnea or hyperventilation syndrome can pose a diagnostic challenge.⁸⁴ For subacute or chronic dyspnea, a systematic, physiologically based approach enables one to make sense of what otherwise becomes a long list of potential diagnoses.

At its core, the goal of the respiratory and cardiovascular systems is to take oxygen from the air we breathe, transfer it to hemoglobin, deliver it to metabolically active tissue, and transport carbon dioxide, the primary product of

metabolism, back to the lung, where it can be eliminated. Dyspnea arises (1) when this goal has not been met and the patient becomes hypoxemic, hypercapnic, and/or acidemic with consequent stimulation of the chemoreceptors; (2) when achieving this goal produces stress within the cardiorespiratory system (e.g., increased work of breathing, inappropriately small tidal volume for a given level of respiratory drive, or elevated left ventricular and pulmonary capillary pressures, secondary to pathologic abnormalities); or (3) when pulmonary receptors (e.g., irritant receptors, again resulting from a pathologic process) are stimulated. Ultimately, one can consider dyspnea as originating from the respiratory or cardiovascular systems, which includes derangements in oxygen delivery, such as in anemia, and problems with uptake and utilization of oxygen, such as in mitochondrial disorders.

To facilitate a systematic approach to this problem, one can divide the process of respiration into three components (Table 29-2):

1. A controller, which determines the rate and depth of breathing;
2. A ventilatory pump, which facilitates the movement of gas into and out of the alveolus; and
3. A gas exchanger, which consists of the pulmonary vasculature and the alveolus.

Abnormalities in any one of these elements can lead to dyspnea. Similarly, one can consider the derangements of the cardiovascular system within three categories: conditions characterized by high cardiac output, normal cardiac output, and low cardiac output.

Abnormalities of the *controller*, such as any stimulus of ventilation (e.g., exercise, hypoxia, acidosis, interstitial edema, pulmonary hypertension), may provoke the sensation of dyspnea. Diseases that interfere with the *ventilatory pump* increase the effort of breathing, whether because of narrowing of the airway or because of a change in the elastic properties of the lungs or chest wall. If the respiratory muscles are weakened, the effort of breathing seems greater because a larger fraction of maximal available muscle force is required. (This is analogous to peripheral muscle function, in which, for example, it would be more difficult to lift a weight after an arm has just been liberated from being in a cast.) Mechanical derangements of the pump also frequently result in inappropriately small tidal volumes. Patients with reduced chest wall compliance or dynamic hyperinflation, which reduces inspiratory capacity as end-expiratory lung volume approaches total lung capacity, commonly complain of air hunger or an unsatisfied inspiration as a consequence of the limited tidal volume.^{63,85} One study described a change in the qualitative descriptors used by patients with COPD from “work and effort” to “unsatisfied inspiration” as dynamic hyperinflation led to increasingly small tidal volume.⁸⁶ Abnormalities in the *gas exchange* functions can lead to increased respiratory drive and resultant dyspnea. Psychological dysfunction may cause or exaggerate dyspnea and is thought to be an alteration in behavioral control of breathing.⁸⁷ In many conditions the origin of dyspnea is only partially understood (e.g., pulmonary embolism without hypoxemia) or is due to multiple factors (e.g., abnormalities of the ventilatory pump and gas exchange in a patient with COPD).

Table 29-2 Diseases That Cause Dyspnea Grouped by Physiologic Mechanism of Action***VENTILATORY CONTROLLER AND GAS EXCHANGE—INCREASED RESPIRATORY DRIVE****Simulation of Chemoreceptors**

Conditions leading to acute hypoxemia

Impaired gas exchange (e.g., asthma, pulmonary embolism, pneumonia, congestive heart failure[†])

Environmental hypoxia (e.g., altitude, contained space with fire)

Conditions leading to increased dead space and/or acute hypercapnia

Impaired gas exchange (e.g., acute, severe asthma, exacerbations of COPD, severe pulmonary edema)

Impaired ventilatory pump (see below) (e.g., muscle weakness, airflow obstruction)

Metabolic acidosis

Renal disease (renal failure, renal tubular acidosis)

Decreased oxygen-carrying capacity (e.g., anemia)

Decreased release of oxygen to tissues (e.g., hemoglobinopathy)

Decreased cardiac output

Stimulation of Pulmonary Receptors (Irritant, Mechanical, Vascular)[‡]

Interstitial lung disease

Pleural effusion (atelectasis)

Pulmonary vascular disease (e.g., thromboembolism, idiopathic pulmonary hypertension)

Congestive heart failure

Mild asthma

Inhalation of toxic gases

Behavioral Factors

Hyperventilation syndrome, anxiety disorders, panic attacks

VENTILATORY PUMP—INCREASED EFFORT OR WORK OF BREATHING**Muscle Weakness**

Myasthenia gravis, Guillain-Barré syndrome, spinal cord injury, myopathy, postpoliomyelitis syndrome

Decreased Compliance of the Chest Wall

Severe kyphoscoliosis, obesity, pleural effusion

Airflow Obstruction (Includes Increased Resistive Load from Narrowing of Airways and Increased Elastic Load from Hyperinflation)

Asthma, COPD, laryngospasm, aspiration of foreign body, bronchitis

*Some diseases appear in more than one category. They act via several physiologic mechanisms.

[†]Heart failure includes both systolic and diastolic dysfunction. Systolic dysfunction may produce dyspnea at rest and with activity. Diastolic dysfunction typically leads to symptoms primarily with exercise. In addition to the mechanisms noted above, systolic heart failure may also produce dyspnea via metaboreceptors; these are receptors that are postulated to lie in muscles and are stimulated by changes in the metabolic milieu of the tissue that result when oxygen delivery does not meet oxygen demand.

[‡]These conditions probably produce dyspnea by a combination of increased ventilatory drive and primary sensory input from the receptors. COPD, chronic obstructive pulmonary disease.

HISTORY

A comprehensive medical history is important for uncovering the diagnosis responsible for dyspnea.⁸⁸ It is important to identify activities that precipitate it and to understand its impact on the patient's life. Because decreased exercise tolerance may go unrecognized by the patient owing to alterations in lifestyle that do not tax the respiratory and cardiovascular systems (e.g., a patient who develops

dyspnea climbing stairs may move from a two-story house to a single-level apartment), input from close acquaintances may be helpful. Although most patients with severe lung disease report that their activities are limited by dyspnea, some patients are actually more limited by fatigue, weakness, joint pain, or chest pain than by dyspnea. Key questions to ask your patient to localize the cause of exercise limitation include the following: "At the moment you feel you need to stop (walking, jogging, etc.), what is making you stop?" or "If I could fix one thing to enable you to walk more, what would that be?"

The key areas of inquiry are (1) quality of the symptom, (2) persistence or variability of the symptom, and (3) aggravating or precipitating factors leading to the symptom. As noted previously (in "Mechanisms of Dyspnea"), the sensation of "chest tightness" is commonly associated with bronchoconstriction, an increased sense of "effort or work of breathing" is typical of derangements of the ventilatory pump, and a sense of "air hunger" or "urge to breathe" is characteristic of problems that stimulate the respiratory controller (often exacerbated by inappropriately small tidal volume). The sense of difficulty getting a deep breath may be associated with hyperinflation due to obstructive lung disease or with the hyperventilation syndrome.

Intermittent dyspnea is probably due to reversible conditions (e.g., bronchoconstriction, congestive heart failure, pleural effusion, acute pulmonary embolism, hyperventilation syndrome), whereas persistent or progressive dyspnea is more characteristic of chronic conditions (e.g., COPD, interstitial fibrosis, chronic pulmonary embolism, dysfunction of the diaphragm or chest wall). Nocturnal dyspnea may be brought on by asthma, congestive heart failure, gastroesophageal reflux,⁸⁹ obstructive sleep apnea, or even nasal obstruction. Dyspnea in the recumbent position (i.e., orthopnea) is classically associated with left ventricular failure but may also be seen with abdominal processes (e.g., ascites) or diaphragmatic dysfunction. Dyspnea that worsens in the upright position (i.e., platypnea) may be related to orthodeoxia, a decrease in arterial PO_2 in the upright position, seen with cirrhosis, pulmonary arteriovenous malformations, or interatrial shunts.⁹⁰⁻⁹³ Physical activity generally accentuates dyspnea of physiologic origin, as when ventilation is stimulated by lactic acid production at relatively low levels of exercise (e.g., anemia, cardiac disease, deconditioning). Dyspnea after exercise may be affected by a number of factors (e.g., activity, time of day, position, exposures, meals, medications). To the extent that postexercise dyspnea may be mitigated by warm-up activities or use of inhaled bronchodilators, exercise-induced asthma should be considered. Although emotional states may affect dyspnea of any cause,⁸⁴ psychogenic dyspnea should be suspected when dyspnea varies on a daily or hourly basis, especially when it is unrelated to exertion or if litigation is involved.⁸⁷

Recognition of factors that may precipitate (e.g., cigarettes, allergens, smog) or relieve (e.g., position, medications) breathlessness is helpful. Obesity may aggravate dyspnea because of increased metabolic and ventilatory demands as well as mechanical interference with chest movement.⁹⁴ Severe weight loss may weaken the respiratory muscles.⁹⁵ Symptoms of right ventricular failure (e.g., abdominal swelling, edema of the extremities) suggest

hypoxemia, pulmonary vascular problems (e.g., pulmonary hypertension of any cause, obstructive sleep apnea), or left ventricular failure. Neuromuscular diseases, such as amyotrophic lateral sclerosis, may present with dyspnea as a result of respiratory muscle weakness.⁹⁶ Raynaud phenomenon alone or in combination with skin, joint, or swallowing problems suggests collagen vascular disease.

PHYSICAL EXAMINATION

Pattern of breathing (e.g., splinting, use of pursed lips or accessory muscles), body habitus (e.g., cachexia, obesity), posture (e.g., leaning forward on elbows to recruit pectoralis muscles as ventilatory muscles, as in COPD), skeletal deformity, and emotional state may be important clues to the underlying diagnosis. Cough on deep inspiration or expiration suggests asthma or interstitial lung disease. A generalized decrease in the intensity of breath sounds suggests emphysema or moderate to severe bronchoconstriction, whereas a localized decrease may result from pneumothorax, pleural effusion, localized airway obstruction, or elevated hemidiaphragm of any cause. Forced expiratory maneuvers may elicit focal or diffuse wheezing. Cardiac examination may suggest pulmonary hypertension (e.g., right ventricular heave or prominent P₂) or right ventricular failure (e.g., jugular venous distention, right-sided S₃ gallop). Clubbing of the digits is an easily overlooked sign of many processes, notably cancer or purulent lung disease (e.g., bronchiectasis). Cyanosis, a bluish coloration of the perioral region or nails, indicates there are at least 5 g of deoxygenated hemoglobin per 100 mL of blood (note: hypoxemia in the presence of significant anemia may not cause cyanosis because of insufficient hemoglobin). Edema of the lower extremities suggests congestive heart failure if symmetrical and thromboembolic disease if asymmetrical. Assessment of the patient's emotional status may be helpful.⁸⁴

If a patient's history includes a report that he or she develops dyspnea walking a short distance (e.g., <200 yards), one should consider walking the patient in a corridor or up a flight of stairs near the examination room to provoke his or her symptoms. When the patient becomes dyspneic, observe the patient, repeat the vital signs, reexamine the chest and heart, and check the oxygen saturation with pulse oximetry. The development of an abrupt increase in heart rate and blood pressure (e.g., pulse pressure product) or onset of basilar crackles or acute wheezing suggests a rapid increase in pulmonary capillary pressure and interstitial edema. Rapid shallow breathing may be a sign of stiff lungs or chest wall. Occasionally the patient will walk farther than one would expect from the history; motivation and the inability of the patient to tolerate any respiratory discomfort may, in fact, be the cause of the patient's limitation. It is not uncommon for patients who lead extremely sedentary lives, especially if they have been told they have a condition that may cause shortness of breath, to interpret any increase in ventilation as pathologic.

LABORATORY ASSESSMENT

The laboratory is only occasionally of help in the diagnosis of dyspnea. Anemia of any cause may contribute to

dyspnea. Polycythemia may be the only clue to chronic hypoxemia. Elevation of the erythrocyte sedimentation rate may suggest occult infection or autoimmune disease. A chemistry panel may reveal occult renal disease or acid-base derangement; elevated serum bicarbonate level may be a clue to the presence of hypercapnia. More elaborate screening may uncover collagen vascular or thyroid disease. Measurement of B-type natriuretic peptide level is finding wide acceptance in refining the differential diagnosis of acute dyspnea,^{97,98} primarily in the emergency department setting,⁹⁹ where its use has been shown in a meta-analysis to reduce the duration of hospitalization but not to change other clinical outcomes.¹⁰⁰ The ventricle secretes B-type natriuretic peptide in response to elevated pressure. Therefore it is usually elevated in patients with left ventricular failure or cor pulmonale but not in patients with exacerbations of obstructive lung disease. It has been shown to be more accurate than echocardiography in recognizing left ventricular dysfunction as a cause of acute dyspnea.¹⁰¹

The clinical database should include chest radiography, spirometry, and possibly electrocardiography. Chest radiographs are useful when abnormal but are insensitive for detecting early obstructive and interstitial diseases; approximately 10% of patients with interstitial disease will have a normal chest radiograph. *Computed tomography pulmonary angiography* (CTPA) has become the standard modality for assessment of suspected thromboembolic disease. Although it is not recommended as a general screening test, it can be used to assess for both occult interstitial lung disease and thromboembolic disease in patients with evidence of gas-exchange abnormalities, for example, low diffusing capacity and/or hypoxemia at rest or with exercise (desaturation on exercise oximetry), or pulmonary hypertension on echocardiography.

Spirometry is a useful screening test for both airway and parenchymal disease. Because airway obstruction in asthma may be intermittent, monitoring peak flow at home or in the workplace may be productive. The yield of routine electrocardiography is low, although it may reveal previously unsuspected coronary artery disease, occult valvular disease, or diastolic dysfunction and can suggest pulmonary hypertension (i.e., if signs of right ventricular hypertrophy or tricuspid regurgitation are present). As ultrasound technology has advanced, small hand-held ultrasound machines are increasingly being employed by nonradiologists at the bedside, particularly to assess left ventricular function, central venous pressure, alveolar filling, and pleural effusion.^{102,103}

SPECIAL STUDIES (INCLUDING PULMONARY FUNCTION TESTS)

An array of special studies may be required for the diagnosis of conditions causing dyspnea (Table 29-3). Pulmonary function tests are useful but correlate only moderately with the severity of the dyspnea.¹⁰⁴ In the patient with episodic dyspnea but with normal spirometry results, methacholine inhalation testing can aid in the diagnosis of asthma. Patients who characterize their dyspnea as "chest tightness" are most likely to have positive study results.¹⁰⁵

Pulse oximetry may reveal previously unrecognized hypoxemia, a possible clue to many diseases. Because the

Table 29-3 Special Studies for Evaluation of Dyspnea**PULMONARY FUNCTION STUDIES**

Lung volumes and flow rates
 DL_{CO}
 Arterial blood gases
 Cardiopulmonary exercise testing
 Bronchial challenge (e.g., methacholine)
 Maximal inspiratory pressure

IMAGING TECHNIQUES

Bedside ultrasonography
 Ventilation-perfusion lung scanning
 Chest CT scanning (high-resolution)
 Chest CT pulmonary angiography
 Gallium scanning
 Diaphragmatic fluoroscopy

CARDIAC EVALUATION

Echocardiographic or radionuclide ventriculography
 Thallium scan
 Holter monitoring (for occult ischemia or arrhythmia)
 Cardiac catheterization (preferably with exercise for assessment of left atrial and pulmonary artery pressure)

ESOPHAGEAL EXAMINATION OR pH MONITORING**OTOLARYNGOLOGIC ASSESSMENT****SLEEP STUDIES****PSYCHOLOGICAL ASSESSMENT**

CT, computed tomography; DL_{CO} , diffusing capacity for carbon dioxide.

lungs have significant reserve capacity at rest, exercise oximetry may be necessary to elicit hypoxemia in patients with abnormalities of gas exchange. Oximetry should always be assessed in patients with a low diffusing capacity, which may be seen in individuals with emphysema, pulmonary vascular disease, and interstitial lung disease. Orthodeoxia (i.e., hypoxemia worse in the upright position) leads to a search for one of the many causes of this unusual condition.^{92,93,106}

If ventilatory muscle weakness is suggested by the patient's history, physical examination, or measurement of lung volumes, ventilatory muscle strength should be assessed. Maximal inspiratory and expiratory pressures can be measured easily and followed sequentially over time.

Cardiopulmonary exercise testing helps determine whether exercise is limited by the pulmonary, cardiovascular, or musculoskeletal system.⁶⁹ To the extent that patients with lung disease are frequently at risk for or have concurrent cardiac problems due to cigarette smoking, cardiopulmonary exercise testing can be very useful. Unfortunately, exercise testing is insensitive for distinguishing cardiac disease from deconditioning.¹⁰⁷ Therefore additional cardiac evaluation may be required. CTPA has replaced ventilation-perfusion lung scanning as the screening procedure of choice for the diagnosis of pulmonary embolic disease.^{108,109} One should remember that patients with chronic thromboembolic disease often present with gradually worsening dyspnea in the absence of episodic breathlessness characteristic of acute pulmonary embolism.

If exercise testing suggests cardiac dysfunction, echocardiography, radionuclide scanning, measurement of B-type natriuretic peptide, or even cardiac catheterization (preferably combined with supine exercise) may identify

unsuspected ventricular dysfunction, valvular disease, or pulmonary hypertension.^{101,110} Diastolic dysfunction, characterized by normal ventricular pressures at rest but elevations during exercise, is a common cause of heart failure but is frequently missed as the cause of exertional dyspnea. In a patient with a history of hypertension and/or left ventricular hypertrophy, diastolic dysfunction should be considered, even in the presence of normal systolic function on an echocardiogram. Stage III cardiopulmonary exercise testing (with pulmonary artery catheter in place) might be necessary to confirm the role of diastolic dysfunction in the patient's symptoms.

Gallium and high-resolution CT scanning are sensitive but not specific for occult infectious and inflammatory lung disease.¹¹¹

It is clear that a cascade of special studies might be necessary before reaching a specific diagnosis. If extensive testing is unrevealing, psychiatric evaluation may be valuable, especially if there is a strong emotional or behavioral component. However, it is more likely that the patient has an early stage of an as-yet-undiagnosed condition that may be revealed by serial testing.

SYMPTOMATIC TREATMENT OF DYSPNEA

Dyspnea can be most effectively alleviated by treatment of the underlying disease and its complications. The focus should be on alleviating symptoms as well as improving pulmonary function.^{112,113} Lung volume-reduction surgery for relief of dyspnea in advanced emphysema deserves special mention. Removal of multiple bullous or emphysematous portions of the lungs reduces hyperinflation and improves lung recoil, potentially leading to dramatic improvement in pulmonary function and dyspnea for some individuals.¹¹⁴ Because of the morbidity associated with surgical approaches to lung volume reduction, however, bronchoscopic approaches that employ endobronchial valves, coils, and biologic and polymer glues to block ventilation of bullous regions, thereby leading to volume reduction as air in the bullae is absorbed, are being studied.^{115,116}

When dyspnea persists despite optimal treatment of the underlying disease, treatment should focus on the symptom rather than the disease and particularly on the specific mechanisms contributing to an individual's dyspnea (e.g., respiratory muscle dysfunction, hypoxemia, anxiety).^{1,113} Until guidelines for specific therapy are established, one must take a generic approach to treatment, with a focus on improving respiratory muscle function, decreasing respiratory drive, altering the central nervous system experience of dyspnea, and instituting exercise training (Table 29-4 and Fig. 29-3).

REDUCING RESPIRATORY EFFORT AND IMPROVING RESPIRATORY MUSCLE FUNCTION

Energy conservation techniques reduce physical effort (e.g., by walking more slowly) and thereby reduce the necessary ventilatory effort. Breathing techniques (e.g., pursed lips) may reduce respiratory discomfort by slowing breathing,

Table 29-4 Symptomatic Treatment of Dyspnea**REDUCE SENSE OF EFFORT AND IMPROVE RESPIRATORY MUSCLE FUNCTION**

Energy conservation (e.g., pacing)
 Breathing strategies (e.g., pursed-lip breathing)
 Position (e.g., leaning forward)
 Correct obesity or malnutrition
 Inspiratory muscle exercise
 Respiratory muscle rest (e.g., cuirass, noninvasive ventilation, transtracheal oxygen)
 Medications (e.g., theophylline)

DECREASE RESPIRATORY DRIVE

Oxygen
 Opiates and sedatives
 Exercise conditioning
 Vagal nerve section (not done)
 Carotid body resection (not done)

ALTER CENTRAL NERVOUS SYSTEM FUNCTION

Education
 Psychological interventions (e.g., coping strategies, psychotherapy, group support)
 Opiates and sedatives

USE EXERCISE TRAINING ALONE OR WITH PULMONARY REHABILITATION

Enhance self-esteem and self-confidence in ability to perform
 Improve efficiency of movement
 Improve oxygen delivery and utilization by skeletal muscles
 Desensitization to dyspnea (e.g., from repeated exercise)

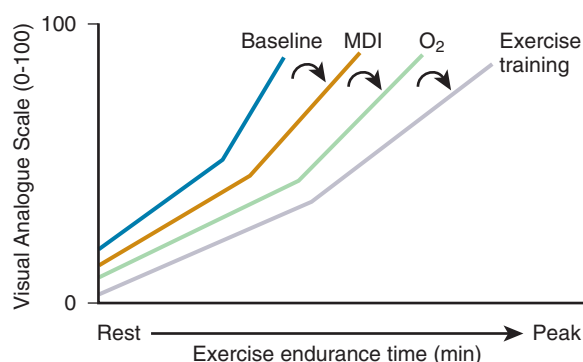


Figure 29-3 The cumulative benefits of treatment on time of exercise endurance at a set workload and dyspnea as measured by a visual analogue scale. The endurance time gradually improves with cumulative treatment using a bronchodilator metered-dose inhaler (MDI), oxygen (O₂), and exercise training. Dyspnea relative to the workload is relieved both at rest and during exercise, even though maximum dyspnea remains about the same. Improvement on exercise testing should translate into improvement with activities of daily living so the patient should experience less dyspnea with activities of daily living.

reducing hyperinflation, and improving oxygen saturation.^{117,118} In a Cochrane systematic review, breathing exercises over 1 to 4 months were shown to improve functional capacity in patients with COPD¹¹⁹; effects on dyspnea, however, were inconsistent, perhaps due to the variable causes of dyspnea within this population. If ventilation limits exercise, strengthening the respiratory muscles should improve maximal ventilation and exercise performance, thereby alleviating the dyspnea. Unfortunately, the

results of this approach have been inconsistent,^{120,121} although one meta-analysis concluded that it can be of value especially in patients with documented respiratory muscle weakness.¹²² Efforts to reduce turbulent flow and the consequent work of breathing by having the patient inhale a mixture of helium and oxygen (i.e., heliox, low-density gas relative to oxygen alone, or oxygen plus nitrogen) have been effective in cases of upper airway narrowing,¹²³ but data in asthma¹²⁴ and COPD¹²⁵ have been mixed; exercise function may be improved in patients with COPD who exercise while inhaling heliox, but changes in dyspnea are inconsistent.¹²⁵

Nutritional repletion of cachectic patients can improve respiratory muscle strength and decrease dyspnea, although the clinical effectiveness of this therapy is unclear.^{120,126} It is intuitively appealing to “rest” chronically “fatigued” respiratory muscles with mechanically assisted ventilation (positive or negative pressure) so they perform better with less dyspnea; although not all studies have shown much benefit,¹²⁷ there is increasing evidence in support of this management strategy in patients with exacerbations of chronic diseases¹²⁸ or respiratory failure.¹²⁹ In less acute circumstances, a meta-analysis concluded that acute non-invasive ventilatory support during exercise does relieve dyspnea and improves exercise performance in COPD.⁴⁸ Studies of medications to relieve dyspnea by increasing muscle contractility have been unconvincing.¹³⁰

DECREASING RESPIRATORY DRIVE

Because many forms of dyspnea are closely related to the respiratory drive, treatments that reduce the drive should reduce dyspnea. Supplemental oxygen can reduce carotid body activation and decrease dyspnea by decreasing ventilation and reducing hyperinflation during exercise.¹³¹ Oxygen may also decrease dyspnea by improving ventilatory muscle function,¹³² enhancing left ventricular contractility, and reducing pulmonary artery pressure.¹³³ Supplemental oxygen administered via nasal cannula may reduce dyspnea in large part by stimulating flow receptors in the nasopharynx, which reduces the drive to breathe.¹³⁴ The amount of oxygen should be titrated to prevent desaturation below 90%, although even higher amounts may be advantageous for preventing dyspnea and improving exercise performance. Indeed, oxygen supplementation can improve exercise capacity in individuals without exercise hypoxemia.¹³⁵ Oxygen supplementation is recommended for use during pulmonary rehabilitation programs.¹²¹

Treatments aimed at peripheral receptors or reflex pathways have shown some positive results. In healthy subjects, topical anesthesia of airway receptors¹³⁶ or buccal mucosa¹³⁷ reduced experimentally induced breathlessness. Inhalation of furosemide, proposed to potentiate activity of slowly adapting stretch receptors in the lungs, has been shown to reduce dyspnea in some individuals with COPD.^{45,46} In studies in COPD patients, a fan blowing air on the face has been shown to decrease dyspnea,¹³⁸ and chest wall vibration¹³⁹ has been shown to reduce exertional dyspnea, raising hope for treatments directed at peripheral receptors. More drastic surgical approaches, including vagal nerve section and carotid body resection, have always been controversial and are not currently available.

ALTERING CENTRAL PERCEPTION

The experience of dyspnea is affected by many factors, including education, cultural background, knowledge, emotional state, bodily preoccupation, and prior experience. Some recent studies of dyspnea relief emphasize the importance of central processes in decreasing dyspnea.¹⁴⁰ Individuals with dyspnea that cannot be explained by cardiopulmonary disorders appear to be particularly sensitive to the unpleasantness of dyspnea associated with acute hypercapnia.¹⁴¹ Altering the central experience of dyspnea may be helpful even when physiologic approaches are inadequate.¹ Education, including specific coping strategies (e.g., muscle relaxation¹⁴²), helps patients understand their disease and develop feelings of mastery over it.¹⁴³ Sharing experiences with others or psychotherapy may reduce the intensity of the dyspnea and the distress associated with it.^{144,145} These educational and psychosocial strategies for symptom management have been comprehensively reviewed, and their use, in conjunction with exercise training, is recommended.¹²¹

Most discussions of centrally acting drugs for dyspnea focus on opiates. Opiates do have pharmacologic effects that should reduce the severity of the dyspnea (including reduction in ventilation), and it is likely that opiates can affect an individual's experience of dyspnea as they do for pain.^{146,147} However, fear of side effects, especially respiratory depression, has discouraged their use in patients with COPD.¹⁴⁸⁻¹⁵¹ Some of these fears may be unwarranted. In a study of normal individuals in whom dyspnea was induced in a laboratory environment, small doses of morphine relieved dyspnea with relatively minor effects on minute ventilation.¹⁵² Furthermore, in laboratory studies in COPD patients, opiates have produced modest improvement in exercise performance and dyspnea scores and only slight and infrequent side effects (e.g., drowsiness) with benefits that have been related both to decreases in ventilatory requirements for a given workload and to reductions in the perception of breathlessness at each level of ventilation.^{146,153} Conversely, placebo-controlled outpatient studies have shown inconsistent benefits and frequent side effects.^{148,150,154,155} For example, in a 14-week controlled crossover study of 16 patients with severe stable COPD,¹⁵⁴ long-acting morphine produced no relief of the dyspnea as measured by the Chronic Respiratory Disease Questionnaire or during walking. However, the authors emphasized that one subject had a "spectacular" response and continued treatment. Almost all of the subjects experienced significant, although not life-threatening, side effects. Thus opiates may be appropriate for dyspnea in an occasional carefully selected patient with far-advanced disease.¹⁵⁶

Opiates are less controversial for palliation of dyspnea in terminal malignant disease or chronic respiratory failure. Patients with severe COPD fear suffocating,¹⁵⁷ and, in this setting, the importance of relieving suffering despite the risk for shortening life is more widely accepted. Several systematic reviews clearly demonstrate the efficacy of this approach in the palliation of refractory dyspnea,^{158,159} and several major national professional societies include opiates for consideration in the palliation of dyspnea.¹⁶⁰⁻¹⁶²

Based on the concept that there are opiate receptors in the airways, inhalation of opiates has been examined as a

way of relieving dyspnea without the side effects seen with systemic administration. Despite earlier reports that inhaled opiates increased submaximal exercise endurance time in patients with severe COPD¹⁶³ and reduced dyspnea in patients with terminal lung disease and heart failure,¹⁶⁴ recent systematic reviews based on controlled trials have failed to demonstrate any real benefit of administering opiates by this route.^{158,159}

Centrally-acting pharmacologic agents have a limited role in the treatment of dyspnea, although controlled studies of unselected COPD patients have shown no benefit of anxiolytics on dyspnea.^{148,165} Similarly, there is little experimental evidence to support the use of antidepressants in the management of dyspnea, although positive results have been reported in case studies.^{166,167} Despite a lack of evidence, there is widespread recognition that there are clear clinical associations between dyspnea, anxiety, and depression. It is thought that individual patients with chronic dyspnea can benefit by targeting psychological morbidities with appropriate therapies.^{168,169}

ROLE OF EXERCISE TRAINING IN RELIEVING DYSPNEA (see Chapter 105)

There is now convincing evidence that pulmonary rehabilitation programs, along with improving exercise capacity and health-related quality of life, improve the symptom of dyspnea in patients with COPD.¹²¹ Exercise training appears to be a critical part of pulmonary rehabilitation programs for reduction of dyspnea, and, although one randomized, controlled study reported a better outcome with high-intensity compared with moderate-intensity training,¹⁷⁰ further studies are needed to clarify the impact of training intensity on dyspnea outcomes. Although most studies have employed endurance training using treadmills or cycles in supervised clinical environments, there is accumulating evidence that pulmonary rehabilitation programs can yield dyspnea-related benefits with (1) interval training,¹⁷¹ (2) strength training,¹⁷² and (3) home-based exercise training.¹⁷³ Individuals who report high levels of anxiety and fear related to dyspnea may be particularly responsive to the benefits of exercise programs.²³ It is not certain how important the educational component of pulmonary rehabilitation is in relieving dyspnea. A program of dyspnea management (including relaxation, breathing retraining, pacing, self-talk, and panic control) without an exercise component was compared with general health education; neither measure alleviated the dyspnea or improved the 6-minute walking distance.¹⁷⁴ By contrast, it has been shown that treadmill training with or without nurse coaching is equally effective in reducing dyspnea during exercise testing and activities of daily living.¹⁷⁵ Despite uncertainty about the impact of education per se on dyspnea outcomes, current recommendations strongly endorse the inclusion of an educational component as part of a pulmonary rehabilitation program.¹²¹

Exercise training may relieve dyspnea by many mechanisms. Neither pulmonary mechanics nor respiratory muscle strength is usually affected.^{121,176} True conditioning may decrease lactate production and decrease stimulation of ventilation even in patients with severe disease.¹⁷⁷ Relaxation and increased mechanical efficiency (e.g.,

longer stride length¹⁷⁸) may lower oxygen consumption and ventilation for a given activity.¹⁷⁹ Exercise training may improve self-confidence, thereby reducing anxiety and dyspnea.^{23,180,181} Repeated exercise may result in desensitization to the symptom (i.e., the same ventilatory stimulus results in less dyspnea^{57,175,182,183}). In any one patient, it is difficult to know which of these mechanisms is operant, but for clinical purposes, it may not matter.

RELIEF OF DYSPNEA IN END-STAGE LUNG DISEASE

Dyspnea is one of the most devastating symptoms known to human beings. In no area of medicine is relief more important than when dealing with dyspnea in end-stage lung disease. The severity of this symptom is well recognized in terminal malignancy, interfering with both physical and psychological function.¹⁸⁴ This awareness is lacking in other areas of terminal lung disease, where most information is anecdotal.^{185,185a} One exception is the treatment of the terminal phase of amyotrophic lateral sclerosis. The value of opiates and anxiolytics for relief of symptoms (especially dyspnea) in the last 24 hours of life of patients with amyotrophic lateral sclerosis has been documented by postmortem telephone interviews with family members in both the United Kingdom and Germany.¹⁸⁶

Although patients with chronic lung disease are normally encouraged to exercise to maintain their state of fitness, there comes a time when a different approach is required and the focus shifts from prolongation of life to relief of distress.^{160,161,185} When dyspnea with exertion is extreme, it may be more appropriate to restrict activity and to focus on treatments such as oxygen, opiates, and anxiolytics. Palliative treatment may include partial ventilatory support or, under rare circumstances, a tracheostomy with mechanical ventilation. Such dramatic steps to relieve dyspnea must be taken with full understanding of the ramifications and complications. As mentioned, many patients with end-stage COPD fear suffocation at the end of life.^{157,187} Some patients might choose a morphine drip to allow a comfortable death, whereas others might choose an aggressive approach focused on prolongation of life as well as relief of discomfort. It is up to the health care provider to help the individual patient understand these choices.

Key Points

- Dyspnea is a complex symptom arising from the central processing of information relayed from the respiratory complex, with modifying information from numerous afferent sources.
- The sensory information is integrated within the context of the psychological and intellectual makeup of the individual. It is still unclear whether there is a final common pathway for the sensation.
- Dyspnea is increasingly viewed as a multidimensional symptom, with qualitative and affective components in addition to sensation intensity components.
- Dyspnea may be due to diseases in virtually any organ system, whether caused by interference with breathing, increased demand for breathing, or weakening of the respiratory pump. In most cases, however, one is

dealing with a disorder of the respiratory or cardiovascular system.

- Diagnosis of the underlying condition causing dyspnea requires a comprehensive database. Cardiopulmonary exercise testing may be particularly useful when a patient has concomitant cardiopulmonary diseases or when cardiovascular deconditioning is suspected.
- When the cause of dyspnea is not obvious, a series of studies analyzing cardiopulmonary function at rest and with exercise usually uncovers a specific diagnosis. Sophisticated studies of the heart, pulmonary vascular bed, lung parenchyma, and even esophagus may be necessary.
- Treatment of dyspnea is most effective when it is based on a specific diagnosis. When treatment of the underlying disease is inadequate, treatment should focus on relieving the intensity and/or the unpleasantness of the symptom.
- A combination of education, exercise training, oxygen, and muscle strengthening aids most patients; in far-advanced disease, compassion may require the use of agents that directly blunt the often frightening and debilitating sense of breathing discomfort even though they may shorten life.

Complete reference list available at [ExpertConsult](#).

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INTRODUCTION

Cough is a symptom that has been experienced by every human and is an essential innate protective mechanism that ensures the removal of mucus, noxious substances, and infections from the larynx, trachea, and large bronchi. Cough also minimizes the inhalation of toxic material. Impairment or absence of coughing can be harmful or even fatal in disease. Cough may also be a sign of disease in or outside the airways and lungs and a useful indicator for both patient and physician for initiating diagnosis and treatment of disease processes. When cough itself is persistent and excessive, it can be harmful and deleterious and may need to be suppressed directly.

Because cough is a normal defensive mechanism, it is a symptom experienced by healthy individuals. Epidemiologic surveys have shown that between 11% to 18% of the general population report a persistent cough,¹⁻³ but it is not known how much this cough is "normal" or is associated with disease. Reports of chronic cough in these surveys may be due to the presence of cigarette smokers; the exposure of an urbanized population to environmental indoor and outdoor irritants and air pollution; or undiagnosed illnesses associated with cough. The potential contribution of irritants to cough is illustrated by the report of excessive cough in New York firefighters who worked in the dust fallout of the World Trade Center attacks on September 11, 2001.⁴ Cough is also a common presenting symptom to the clinician. In the United States, cough is the most common complaint for which patients seek medical attention and the second most common reason for a general medical consultation; patients with persistent cough constitute about 10% to 38% of a chest specialist outpatient practice. In the United Kingdom, about 3 million prescriptions are written annually for cough preparations by general practitioners, representing a cost of \$3 million; this is an underestimate

because a vast number of cough mixtures are also bought over the counter without a medical prescription. In the United States, cough and cold medicines sold over the counter between 2007 and 2012 amounted to \$2.3 billion.

DEFINITION OF COUGH

Cough is initiated as a series of respiratory maneuvers that leads to a sudden expulsion of air creating a characteristic cough sound. It usually starts as a deep inspiration, followed by a strong expiration against a closed glottis, which then opens with an expulsive flow of air, followed by a restorative inspiration; these are the inspiratory, compressive, expulsive, and recovery phases of cough (Fig. 30-1). The cough sound in the first of three phases is an explosive sound heard during the expulsive phase consisting of a noiselike waveform. This is followed by an intermediate phase when there is decreased airflow associated with a decreasing sound amplitude. Finally, there is often a third phase called the *voiced* or *glottal* phase, that constitutes the second sound, produced by the vibration of a partly closed glottis, which produces a regular periodic noise (Fig. 30-2; listen to the associated Audios 30-1 and 30-2).

The initial inspiration of cough may be followed by a series of expiratory efforts, with closures of the glottis but not intervening inspirations—a "cough bout" or an "epoch" (see Fig. 30-2). Punctate mechanical stimulation of the trachea or larynx causes a brief but strong expiratory effort—the "expiration reflex"—rather than a true cough and, in the case of the glottis, reflex glottal closure⁵⁻⁷; these reflexes presumably act to prevent or minimize entry of foreign material into the trachea and lungs. Throat clearing, as in postnasal drip, consists more of this expiration reflex or "huff" than a full cough. Not only are there different patterns of "cough," but these patterns may be

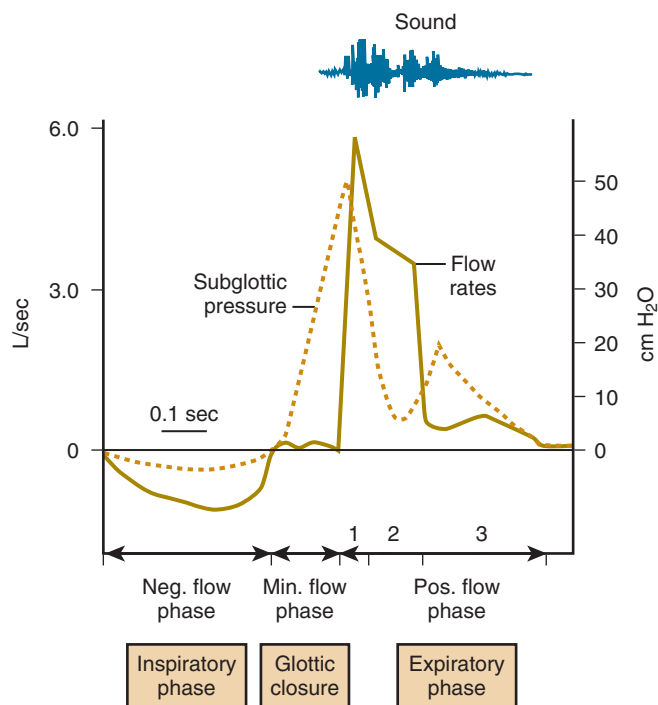


Figure 30-1 Diagrammatic representation of the changes of the following variables during a representative cough: sound, flow rate, subglottic pressure. During inspiration, the flow rate is negative; at the glottic closure, the flow rate is zero; and during the expiratory phase, the flow rate is positive. The expiratory phase can be divided into three parts: during the *first* expulsive phase (1), there is an explosive cough sound, the first cough sound; during the *second* phase (2), as the expulsive airflow diminishes, the sound amplitude diminishes; and during the *third* phase (3), the vibration of a partly closed glottis produces a regular periodic sound, the second sound. Refer to [Figure 30-2](#) for a representation of the cough waveform. (From Bonica JJ: *Obstetric analgesia and anesthesia*. World Federation of Societies of Anaesthesiologists, Amsterdam, 1980.)

differently affected by pharmacologic and physiologic inputs.⁵⁻⁷ Cough sounds may have clear harmonic patterns,⁸ but the basis of these patterns has been little analyzed and their significance, if any, has not been established. *Induced cough* is usually preceded by an awareness of airway irritation and an “urge-to-cough,”⁹ involving activation of sensory processing and limbic regions in the cerebral cortex.^{10,11} *Evoked cough* may be either involuntary (reflexively evoked) or voluntary (a behavioral outcome in response to the urge-to-cough), the former mediated by sensory inputs at a brain-stem level and the latter originating in motor regions of the cerebral cortex.^{12,13} It is unclear what proportion of cough in disease is reflexive versus behavioral. *Habit cough* is a variant of voluntary cough, which may or may not be associated with an urge-to-cough. Once a cough has been induced, there will be secondary feedbacks from both the lungs and the higher parts of the brain, which do not seem to have been analyzed.

Thus, the definition of cough may need to be extended to embrace, or at least consider, these different patterns and neural circuits. This consideration is not a semantic quibble. The various defensive respiratory patterns defined as cough have different afferent and central nervous pathways, but clinical descriptions of cough have seldom differentiated between them. Antitussive drugs could have selective

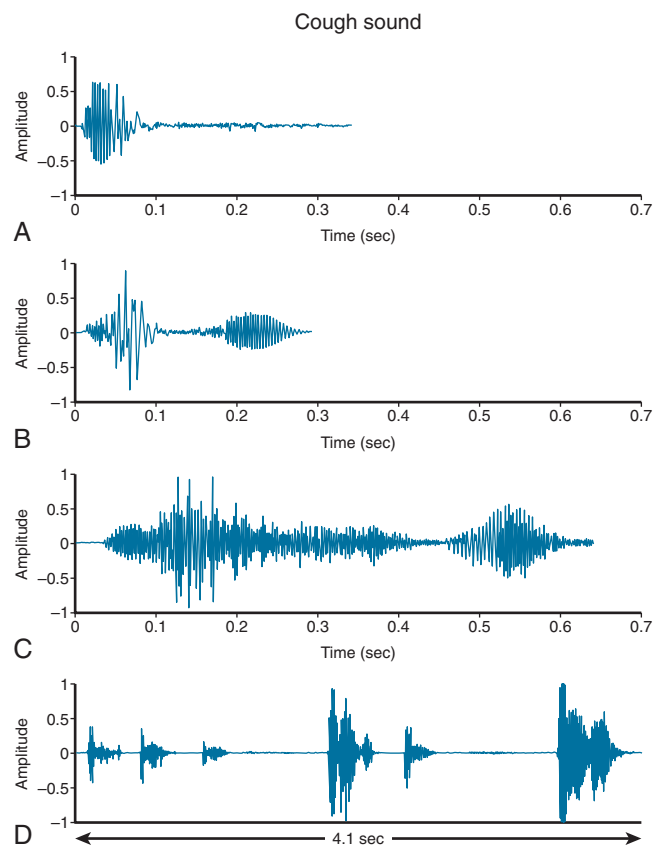


Figure 30-2 Cough sound waveforms from patients with a chronic cough. **Panel A** shows two phases with an initial expulsive phase that is the first cough sound, followed by an intermediate phase with decreasing sound. **Panel B** (from an “idiopathic” chronic cough) and **C** (from a patient with pulmonary tuberculosis) show an additional third phase called *voiced* or *glottal phase*, which gives rise to a second cough sound (refer to [Audio 30-1](#)). **Panel D** shows an epoch of six coughs in succession in a female subject with chronic idiopathic cough (refer to [Audio 30-2](#)). (Courtesy Sergio Matos and Surinder Biring, Kings College Hospital, London, and Richard Turner, Homerton University Hospital, London.)

actions on the different neural pathways and therefore have different indications in the clinic.

PHYSIOLOGY

Experimentally, involuntary coughing appears to be initiated only from those structures innervated by the vagus nerve and its branches.^{5,14} These are predominately the larynx and the proximal tracheobronchial tree, but they also include the lower part of the oropharynx and the smaller bronchi, as well as the tympanic membrane and the external auditory meatus. Irritation of all these sites can cause coughing. The one clear exception to vagally mediated coughing is that caused voluntarily^{15,16} ([Fig. 30-3](#)); of all the highly complex defense mechanisms, cough is the only one that we can mimic voluntarily and accurately. We can also inhibit it voluntarily. Most patients can suppress their cough for 5 to 20 minutes if they try hard.¹⁵

Spontaneous coughing can be initiated by a wide variety of inflammatory or mechanical changes in the airways and by inhalation of a large number of chemical and mechanical irritants. Rapid and large changes in lung volume can

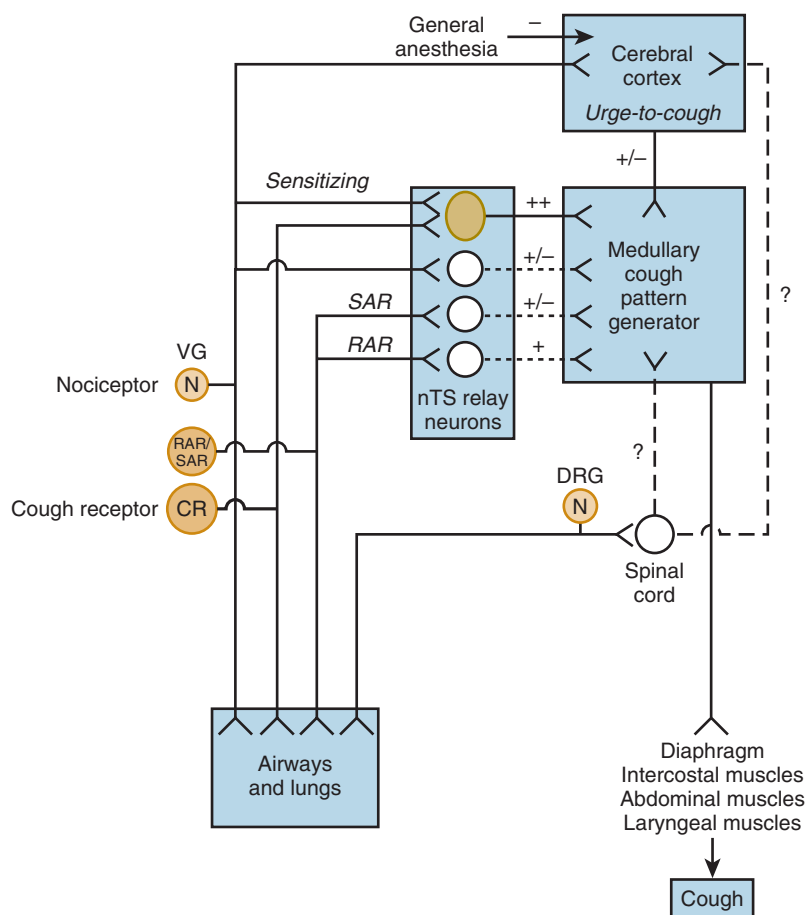


Figure 30-3 Model illustrating the afferent and efferent pathways in the control of cough. Rapidly adapting receptors (RARs), slow-adapting receptors (SARs), and nociceptors (N) may modulate the cough responses, and a distinct set of cough receptors (CR) has been described in the guinea pig. There may be promotion of coughing through interactions with cortical and brain-stem structures, in addition to putative contributions via spinal airway afferents. The cough pattern generator coordinates the output to muscles and effectors that results in the cough response. However, voluntary cough pathways arising from the cortex may bypass the brain-stem respiratory centers and directly regulate spinal respiratory motor neurons (not shown). DRG, dorsal root ganglion; nTS, nucleus tractus solitarius; +, enhancing; -, inhibitory; ?, putative, +/-, evidence for both enhancing and inhibiting exists. (Adapted and updated from Mazzone SB: Sensory regulation of the cough reflex. *Pulm Pharmacol Ther* 17:361–368, 2004.)

cause cough, as can psychological effects such as laughter. The extremely wide variety of stimuli that can trigger cough points to a similarly wide range of properties of the sensory receptors that are the starting point of the cough reflex.^{5,14,17}

SENSORY RECEPTORS FOR THE COUGH REFLEX

The most sensitive sites for initiating cough are the larynx and tracheobronchial tree, especially the carina and points of bronchial branching.^{5,14,17–19} Inhaled materials impinge on these points. In experimental animals and humans, it is difficult or impossible to induce coughing from the smaller airways and alveoli. This is teleologically understandable because in the smaller airways even a vigorous cough would not move gas fast enough to cause turbulence and shearing forces at the airway wall, so the cough would be ineffective. In view of the wide range of stimuli for coughing, one would expect that there would be several types of cough-evoking sensory nerves and that the sensory nerve receptors would be “polymodal” (i.e., to respond to a variety of chemical, physical, and pharmacologic mediators). Indeed, at least two types of airway sensory nerve subtypes for initiating cough have been described and these each respond to a range of different stimuli.²⁰ However, broadly speaking these sensory subtypes can be categorized as either nociceptors, which detect a range of noxious chemical irritants but are relatively insensitive to mechanical stimuli, or mechanoreceptors, which have some (but

limited) chemosensory properties but are exquisitely sensitive to punctate (touchlike) mechanical stimuli.

Larynx and Pharynx

Nerve receptors (or perhaps better termed “sensors,” which is used in this chapter) in the laryngeal mucosa are activated by the mechanical and chemical stimuli for cough; their fibers run mainly in the superior and recurrent laryngeal nerves before joining the vagus nerves. Many studies of laryngeal afferent innervation suggest that the sensors for cough belong to the broad group of *rapidly adapting receptors* (RARs), albeit a different class to the classic RARs described in the intrapulmonary airways and lungs.^{21–24} Laryngeal and pharyngeal mechanosensors are normally silent, as would be expected and, when activated, cause rapidly adapting discharges with an irregular pattern that are conducted in fast-velocity vagal myelinated (A δ) fibers. Their many stimuli include cigarette smoke, ammonia, ether vapor, acid and alkaline solutions, hypotonic and hypertonic saline, and punctate mechanical stimulation by catheter, mucus, or dust (but not stretch or bronchospasm); all these stimuli can provoke cough. The larynx and pharynx are also innervated by cough-evoking nociceptors. These are unmyelinated slow conducting C-fibers that are characterized by their responsiveness to the chemical capsaicin, the active ingredient in hot chili peppers. Nociceptors are also responsive to a wide range of proinflammatory molecules, which notably include bradykinin, prostaglandins,

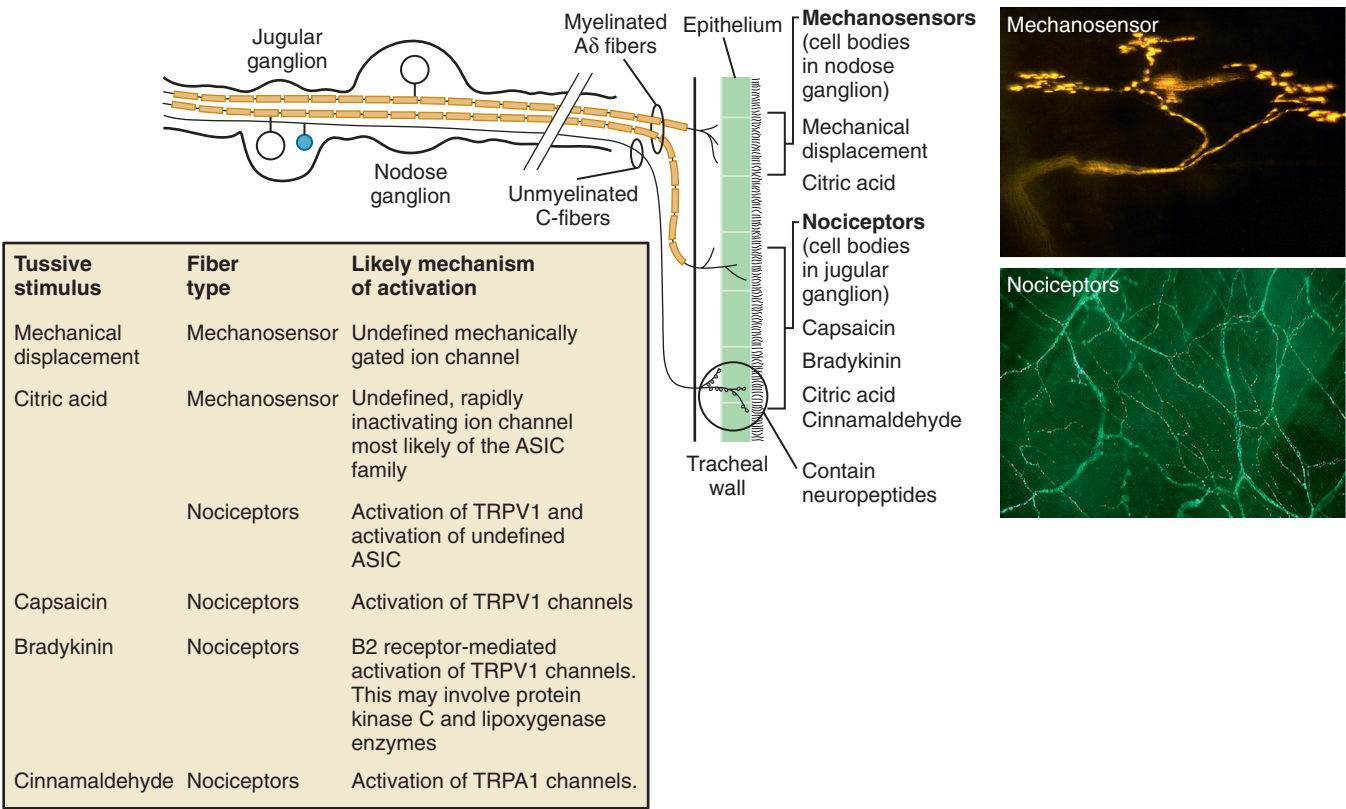


Figure 30-4 Vagal afferent innervation of guinea pig trachea. Mechanism of sensory nerve stimulation by various cough-inducing stimuli (table inset). The micrographs show the structure of airway mechanosensors (upper) and nociceptors (lower). ASIC, acid-sensing ion channel; TRPA1, transient receptor potential cation channel, subfamily A, member 1; TRPV1, transient receptor potential vanilloid-1 receptor. (Redrawn and modified from Undem BJ, Carr MJ, Kollarik M: Physiology and plasticity of putative cough fibers in the guinea pig. *Pulm Pharmacol Ther* 15:193–198, 2002.)

leukotrienes, proteases, and cytokines, as well as noxious irritants such as capsaicin, acid, nicotine, and acrolein.²⁵ Laryngeal nociceptor activation during anesthesia has been shown to induce apnea rather than cough, which might indicate that these sensory fibers are inhibitory to cough. However, studies in conscious animals show laryngeal nociceptor activation to be a powerful stimulus for coughing, suggesting that anesthesia confounds the role of laryngeal nociceptors in generating cough responses.

Although strong cough can be induced from the larynx, its denervation or bypass makes little difference to the strength of cough caused by inhaled irritants. As with many protective/defensive mechanisms, the cough reflex displays much “redundancy”—that is, a doubled sensory input for cough does not result in a doubling of the motor response. Activation of sensors in the larynx or pharynx may cause either a “typical” cough, starting with an inspiration, or the expiration reflex, starting with an expiratory effort.^{5–7} The difference is presumably due to various types of cough sensors in the mucosa or the timing of the sensory input to the brain stem relevant to the respiratory cycle. Although cough induced from the pharynx may seem to be the exception to the vagal rule, in that the pharynx is supplied mainly by the glossopharyngeal nerve, there is a small pharyngeal branch of the superior laryngeal (vagal) nerve that could mediate cough, and this seems to be especially active in humans.²⁶ For example, postnasal drip associated with inflammation due to nasopharyngitis and sinusitis can

induce cough possibly due to spread of inflammatory mediators into the larynx.

Tracheobronchial Tree

Touch-sensitive (stretch-insensitive) mechanosensors are also found in the trachea and large bronchi of those species that cough. These sensors have nerve terminals under or within the epithelium (Fig. 30-4), concentrated at points of airway branching; some of them lie close (1 μm) to the epithelium.^{27–29} Their appearance and location suggest that they might be sensitive to intraluminal irritants or particulate matter that physically displaces the epithelium. They are comparable with those in the larynx in their sensitivity to chemical and mechanical irritants. Farther along the bronchial tree in the intrapulmonary airways and lungs, the mechanoreceptors change functionally in that they gain sensitivity to stretch stimuli, as well as additional chemosensitivity (notably becoming sensitive *adenosine triphosphate* (ATP) analogues that activate purinergic receptors).²¹ These sensors represent the classic RARs known to be involved in the Hering-Breuer deflation reflex. In experimental animals, intrapulmonary RAR activity is enhanced by pulmonary congestion, atelectasis, bronchoconstriction, and decreases in lung compliance, all of which can contribute to cough in patients. However, whether intrapulmonary RARs can directly initiate coughing is unclear. The other type of intrapulmonary mechanoreceptor (*slowly adapting stretch receptors* [SARs] involved in the

Hering Breuer inflation reflex) may inhibit cough through central mechanisms.

C-fiber sensors are also found in the tracheal, bronchial, and alveolar walls. They are activated by much the same range of stimuli as are those in the larynx, but their evoked responses are not homogeneous and, at least for those in the alveolar walls, do not include cough.^{17,29,30} In some species the C-fiber sensors may release tachykinins, such as substance P, by an axon reflex, which in turn causes neurogenic inflammation. This may explain the effect of tachykinin antagonists in inhibiting cough, although axon reflexes do not appear to be prevalent in human airways. C fibers are also responsible for generating the urge-to-cough, which may trigger behavioral coughing in an attempt to relieve the urge.³¹ Indeed, there is no convincing evidence that C-fiber receptors can be a primary sensory input for reflexive cough. Airway C-fiber sensors have been differentiated into two groups^{28,32} and, in the guinea pig, a new group of A δ -nociceptors has been identified. Jugular ganglia C fibers can initiate coughing, whereas nodose ganglia C fibers do not and may even be inhibitory to cough.^{33,38} The role of A δ -nociceptors in cough has not been defined. Thus, the fact that multiple sensory nerve subtypes can elicit or modify cough suggests that the total pattern of cough may be due to the interaction of several reflexes. This view, together with the variety of physiologic patterns of sensitivities and responses of mechanosensors and nociceptors in various parts of the respiratory tract, could explain the great divergence of cough patterns in different conditions and in different patients. The effectiveness of antitussive drugs that act at peripheral sites (e.g., by the inhalation of anesthetic aerosols) may depend on their relative actions on the different groups of receptors that affect cough or on their central connections.

Membrane Receptors/Channels on Sensory Endings for Cough

The past decade has seen extensive studies on the membrane/channel receptors in sensory nerves involved in coughing.^{29,34-37} The details are complex, so they are summarized only briefly; however, the results are of considerable importance in not only indicating how coughing may be induced but also by pointing to possible future targets in antitussive therapy.

Mechanically-activated cough sensors are stimulated by touch but not stretch and are thought to express mechanically gated membrane channels that are unique to this class of airway sensory neuron.²¹ These channels have yet to be identified. In addition, they have other channels that can be activated by acid and belong to the *acid-sensing ion channel* (ASIC) family and the NaV1.7 subtype of voltage gated sodium channels,³⁸ characterized by their sensitivity to the neurotoxin, tetrodotoxin. However, the mechanosensor membranes normally lack several *transient receptor potential* (TRP) channels, which are found in C- and A δ -nociceptors, namely the temperature-sensitive *transient receptor potential vanilloid-1* (TRPV1) and *transient receptor potential cation channel, subfamily A, member 1* (TRPA1) receptors, although the expression of these TRP channels on mechanosensors may be induced during inflammation.³⁹ TRPV1 receptors are directly activated by capsaicin, much used as a tussive agent, and are sensitized or indirectly activated by heat,

protons, bradykinin, arachidonic acid derivatives, ATP, and phosphokinase C. TRPA1 is coexpressed with TRPV1 on many vagal C fibers in the airways⁴⁰ and is activated by allyl isothiocyanate (mustard oil), cinnamaldehyde (from cinnamon), and acrolein (from cigarette smoke). TRPA1 has been shown to mediate a myriad of sensory nerve dependent processes and may interact functionally with TRPV1. C fibers also express tetrodotoxin-insensitive voltage-gated sodium channels.⁴¹

Thus, the way in which a large variety of tussive stimulants activate the sensory nerves responsible for cough and the urge-to-cough is beginning to be clarified, and it is now recognized that stimuli must produce the correct pattern of action potential firing in order to encode for coughing.⁴² Of note, the membrane receptors on cough sensors have been studied mainly in experimental animals,^{25,34} and their relevance to human cough is still unclear.

CENTRAL NERVOUS SYSTEM CONTROL

A (possible) circuit diagram for the interaction of cough inputs and outputs and the respiratory rhythm generator in the brain stem has been proposed.⁴⁴⁻⁴⁷ Reflex coughing is integrated in the medulla oblongata, where the afferent fibers for coughing first relay in or near the nucleus of the tractus solitarius; the motor outputs are in the nucleus retroambigualis, sending motoneurons to the respiratory muscles, and in the nucleus ambiguus, sending motoneurons to the larynx and bronchial tree. In the cat, brain-stem pathways for the expiration reflex differ from those for a typical cough,^{47,48} and pathways for cough from the larynx differ from those from the tracheobronchial tree.⁴⁹ These observations, if true for humans, may point to different antitussive agents appropriate to the two sites.

Afferent inputs to the brain stem are relayed to higher brain regions where inputs are integrated in pontine, subcortical, and cortical nuclei.³¹ However, these ascending pathways may be different for sensors innervating the upper versus lower airways.^{49a} Studies with functional magnetic resonance imaging of the human brain during induced cough are delineating those areas involved and have shown them to be important for the different sensory discriminative and motor aspects of noxious airway stimulation^{10-12,49b} (Fig. 30-5). For example, the anterior insula cortex is activated in a stimulus-dependent manner, suggesting that it plays a role in monitoring the amount of sensory input arising from the airways. The primary sensory cortex, on the other hand, is activated in a perception-dependent manner, suggesting that it is intimately involved in assimilating sensory inputs and coding for the urge-to-cough intensity. The posterior parietal and prefrontal cortices provide spatial awareness (i.e., where is the stimulus located), and parts of the limbic system (e.g., the orbitofrontal cortex) help shape emotive responses to the irritation. Cough can also be initiated voluntarily, a process that originates in motor and premotor cortical brain regions. These voluntary descending pathways can probably bypass brain-stem integrative centers^{15,16} (see Fig. 30-4) because some patients with brain-stem damage lack a spontaneous cough reflex but can consciously induce coughing to clear the airways.⁵⁰ The motor cortex and inferior frontal gyrus

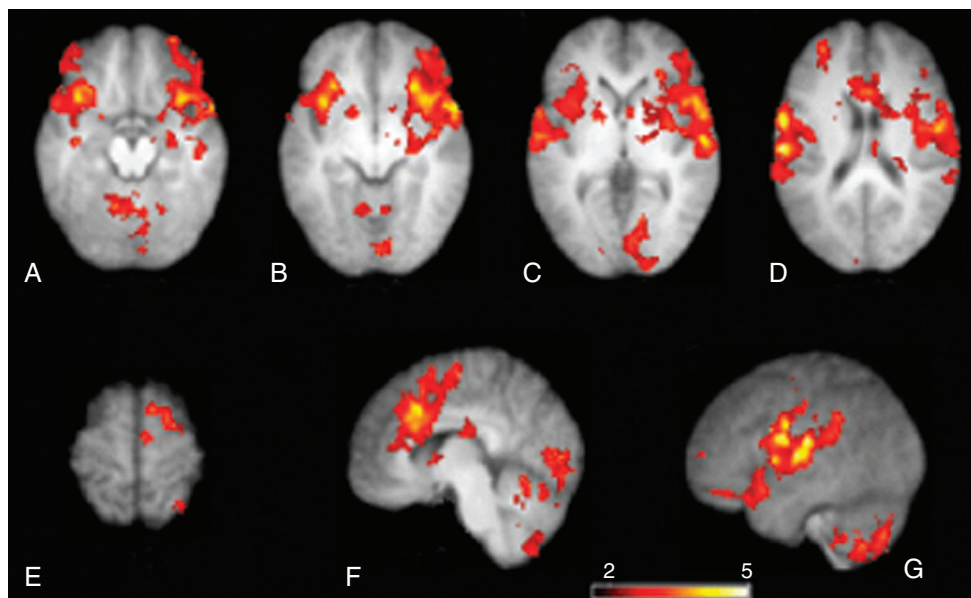


Figure 30-5 Activation of brain pathways associated with inhalation of capsaicin to cause an “urge-to-cough” shown by functional magnetic resonance imaging in normal subjects. The images show activity combined from the different subjects at different levels of the brain. The majority of regional activations were distributed in both hemispheres, including the orbitofrontal cortex (A), inferior frontal gyrus (A and B), anterior insula (B and C), superior temporal gyrus (C), and primary motor and somatosensory cortices (D and G). Midline capsaicin activations include the supplementary motor area (E) and the anterior midcingulate cortex (F). The locations of capsaicin activations in the primary motor and somatosensory cortices were at the caudal end of the central sulci in both hemispheres (D) and are clearly discernible on the three-dimensional rendering of the left hemisphere. (A–G, From Mazzone SB, McLennan L, McGovern AE, et al: Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med* 176:327–332, 2007.)

can also generate cough suppression, which inhibits brain stem–mediated cough via poorly defined pathways.^{13,50a} Greater understanding of the central control of coughing is desirable because most antitussive drugs act centrally, and we know little about how they do this. However, research has shown that central nervous membrane receptors for cough include those that respond to serotonin, gamma-aminobutyric acid, *N*-methyl-*D*-aspartate (NMDA), neurokinins, and dopamine, results that could have considerable therapeutic implications.^{44,51}

The central nervous pathways for cough show interactions and plasticity, as do the peripheral mechanisms already described.^{52–54} For example, afferent fibers from mechanosensors and C-fiber receptors converge in the nucleus of the solitary tract. Neurokinins released from the latter potentiate the activity of the former, especially cough and reflex bronchoconstriction, and this potentiation is enhanced by continued C-fiber activity. Ongoing activity of peripheral afferents may therefore lead to central plasticity of cough circuits,⁵⁵ thereby reducing the need for peripheral inputs to elicit coughing. This is likely important for chronic cough in respiratory disease but may also be seen in some cases of *gastroesophageal reflux disease* (GERD), where activity in esophageal afferents, which do not normally cause cough, may activate the cough reflex when sensitization takes place.

MOTOR OUTPUTS

Although glottic closure is usually regarded as an essential and definitive component of cough, in both human and experimental animals, the closure may be incomplete or even absent, and this does not seem to impair the effectiveness of the cough in terms of airway clearance. In addition,

the glottal closure reflex has a lower threshold to irritants than does the expiration and cough reflexes and may therefore depend on different pathways.^{18,19}

Coughing is associated with respiratory actions other than those of the respiratory skeletal muscles.^{5,14,17} There is usually bronchoconstriction, although this may be masked or reversed by the dramatic changes in lung volume. The afferent mechanisms for reflex cough and reflex bronchoconstriction may be different, even though the initial stimulus is the same. Thus, extrapulmonary mechanosensors and jugular ganglia–derived C fibers may evoke cough, whereas the bronchoconstriction is mainly by intrapulmonary RARs and nodose ganglia–derived C-fiber sensors. Bronchoconstriction would increase linear velocity of airflow and lessen the inflow of irritant material to deeper parts of the airways.

The afferent sensors for cough also cause reflex secretion of mucus from airway submucosal glands.^{5,14,17,56} Mucus entraps inhaled particles and irritant chemicals, and the material is thus cleared from the airways by mucociliary transport and by the cough itself. Mucus could also act as a physicochemical barrier between the luminal irritants and the airway wall. However, an increase in mucus secretion in conditions associated with cough has never been accurately measured, perhaps because of lack of appropriate methods.

MECHANICS OF COUGHING

The inspiratory phase of cough consists of a deep inspiration through a widely opened glottis. The inhaled volume varies greatly, from a low to a nearly complete vital capacity. The inspiration may draw material into the lungs; however, the large lung volume provides a better mechanical

efficiency for the expiratory muscles of cough because they are stretched, their stretch reflex is activated, and there is a stronger elastic recoil of the lung to aid expiration. Furthermore, the deep inspiration opens the airways in preparation for their clearance during the expiratory phase.⁵³

In the compressive phase of cough, which lasts about 200 ms, the glottis closes while the expiratory muscles contract, and the intrapleural and intra-alveolar pressures rise rapidly to a range of values that can vary from 40 to 400 cm H₂O, which can be used as an index of the intensity of the cough.^{53,57} The expulsive phase follows when the glottis opens. The expiratory flow rate depends on both air leaving the central airways during dynamic collapse as a result of the high intrathoracic pressure and the effect of high alveolar pressure, increased during the compressive phase and maintained at a high level by the contraction of the expiratory muscles. The expulsive phase of coughing may be long-lasting, with a large expiratory tidal volume, or it may be interrupted by glottic closures into a series of short expiratory efforts, each having a compressive and an expulsive phase. What determines the pattern of coughing has not been established but may depend on the anatomic site of origin of the cough, on the different nerve types of receptor activated, and on the strength of their activation.

Maximum expiratory flow is effort independent because it is limited by dynamic compression of the airways.⁵³ This compression starts immediately downstream from the “equal pressure point” at which intraluminal and extraluminal pressures around the bronchial wall are equal so that transbronchial pressure is zero. The effectiveness of cough depends on peak airflow and will therefore be greater with a larger elastic recoil of the lung and a greater stiffness of the central airways. Dynamic compression of the airways downstream from the equal pressure point increases velocity, kinetic energy, and turbulence of the air passing through the proximal airways. Thus, the clearing capacity of the cough is improved. If cough consists of a series of expiratory efforts, with lung volume decreasing with each effort, dynamic compression is predicted to move into the more peripheral bronchi, which will be progressively cleared of intraluminal material. However, at present this description is largely theoretical and needs to be established experimentally.

Whereas mucociliary transport is the major method of clearing the airway lumen in healthy subjects, cough is an important reserve mechanism, especially in patients with lung disease. In many lung diseases, mucociliary clearance is impeded and cough is necessary to remove the increased amount of secretions and debris. Healthy subjects have twice the mucociliary clearance rate of that in patients with chronic bronchitis, but when cough is permitted or encouraged, the patients increase their clearance by 20%, whereas healthy subjects increase their clearance by only 2.5%. As would be expected, all studies point to the fact that cough is effective in causing clearance if there is hypersecretion of mucus; by definition, a dry cough is an unproductive one.

NEURAL MECHANISMS OF COUGH HYPERSENSITIVITY

In disease, the sensory receptors for cough can show an exaggerated response to stimuli that would normally be

harmless or mildly irritating. This increase in sensitivity of mechanosensors and C-fiber receptors can be caused by stimuli including allergen challenge, viral infections, ozone, cigarette smoke, and a variety of inflammatory mediators.³⁴ Mechanosensors can also be sensitized by mucus in the airways, smooth muscle contraction, and mucosal edema.^{29,30,35,52,58} Increases in sensitivity have been related to structural changes in the nervous receptors, in particular in their intracellular mediators, and in the nerve cell bodies in the jugular and nodose ganglia and in the afferent pathways entering the brain stem. These effects lead to central sensitization, a neural mechanism in the *central nervous system* (CNS) that amplifies incoming sensory inputs and produces hyperreflexic states.⁵⁹

The alterations in the structure and function of vagal sensory neurons and central processing pathways seen in disease models of *hypertussia* (increased cough sensitivity to known stimuli) reflect cough neuropathy (Fig. 30-6). The concept of a vagal sensory neuropathy producing airway hypersensitivity is comparable with the well-known role of peripheral sensory neuropathy leading to chronic pain syndromes.⁵⁵ In patients with neuropathic pain, damage or disease of the peripheral sensory nervous system or its central projection pathways underpins pain hypersensitivity, characterized by the clinical pain symptoms of hyperalgesia (an elevated sensitivity to painful stimuli) and allodynia (pain in response to nonpainful stimuli). Neuropathic pain may act in tandem with inflammatory pain mechanisms in which altered nerve fiber activity is associated with both local tissue inflammation, as well as damage or disease of the nervous system.^{60,61} Indeed, a host of inflammatory mediators released from resident and infiltrating cells can sensitize or damage the airway nervous system to alter its normal functions.^{25,41,62} Although the nerve damage in neuropathic pain may be easy to recognize (e.g., the crushing or severing of peripheral nerves associated with major trauma), neuropathies can manifest as a result of less apparent insults including viral infection, metabolic diseases (e.g., diabetes), and other causes of neuroinflammation.

APPROACH TO THE PATIENT WITH COUGH

As emphasized in all national guidelines,^{63,64} the approach to the management of a patient with cough is first to identify the cause(s) of the cough and then to treat the cause(s). Cough may be indicative of trivial or serious airway or lung diseases and also of extrapulmonary processes. Often, the cause may not be found, the treatment of the putative cause may not suppress or improve the cough, or the cause may have no effective treatment. In those cases, therapy that suppresses cough by inhibiting the cough pathway without treating the cause (“symptomatic,” “nonspecific,” or “indirect” antitussives) is necessary.

The differential diagnosis of cough is extensive and includes infections, inflammatory and neoplastic conditions, and many pulmonary, as well as extrapulmonary, conditions (Table 30-1). The protocol for investigating a chronic cough—defined as a cough that has persisted for

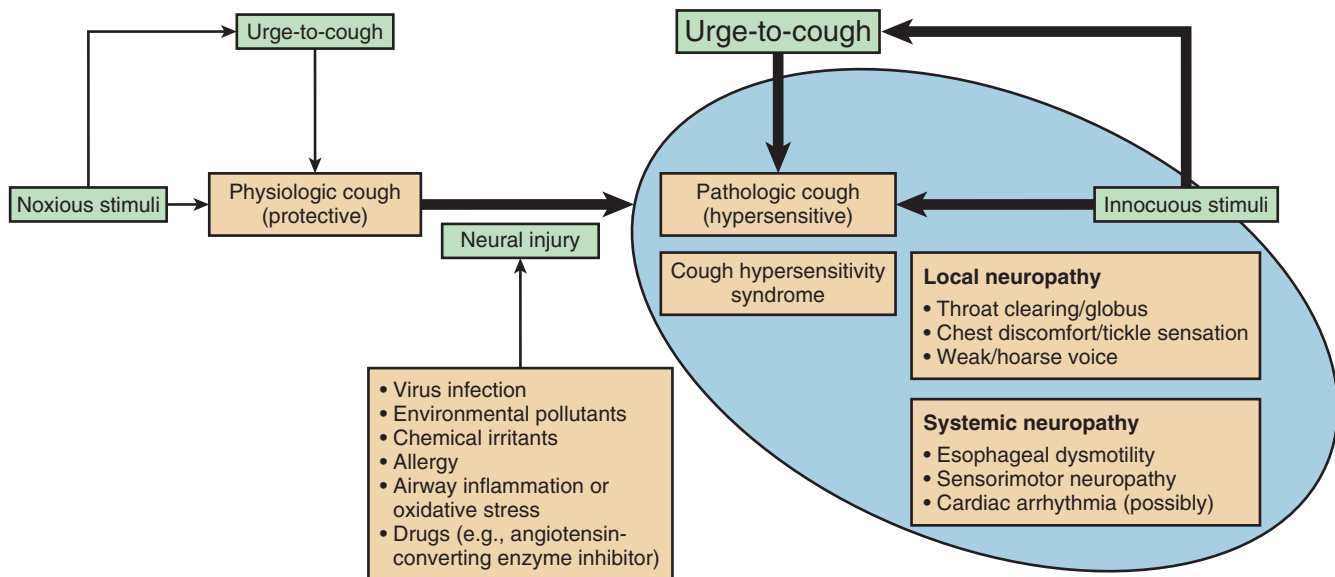


Figure 30-6 Cough hypersensitivity syndrome. The proposed effect of vagal nerve injury arises from inflammation caused by airway exposure to infective, physical, chemical, and allergic insults. The blue oval emphasizes the pathology (neuropathy) of the cough hypersensitivity syndrome. (From Chung KF, McGarvey L, Mazzone S: Chronic cough as a neuropathic disorder. *Lancet Respir Med* 1:414–422.)

Table 30-1 Common Causes of Cough	
ACUTE INFECTIONS Tracheobronchitis Bronchopneumonia Viral pneumonia Acute-on-chronic bronchitis Pertussis	TUMORS Bronchogenic carcinoma Alveolar cell carcinoma Benign airway tumors Mediastinal tumors
CHRONIC INFECTIONS Bronchiectasis Tuberculosis Cystic fibrosis	ASPIRATED FOREIGN BODIES
AIRWAY DISEASES Asthma Eosinophilic bronchitis Cough variant asthma Chronic bronchitis COPD Chronic postnasal drip	MIDDLE EAR PATHOLOGY
PARENCHYMAL DISEASES Interstitial pulmonary fibrosis Emphysema Sarcoidosis	CARDIOVASCULAR DISEASES Left ventricular failure Pulmonary infarction Aortic aneurysm
	OTHER DISEASES Gastroesophageal reflux disease Laryngopharyngeal reflux Recurrent microaspiration Endobronchial sutures Obstructive sleep apnea Laryngeal dysfunction
	DRUGS Angiotensin-converting enzyme inhibitor medications

more than 3 weeks—takes into account several factors pertaining to the pathophysiology of cough and to the most common causes of cough. Persistent cough may be due to the presence of excessive secretions, airway damage and infection, or the establishment of a hypersensitive cough reflex. A protocol based on systematic evaluation using history, examination, and laboratory investigations focusing on the anatomic sites of cough receptors that constitute the afferent limb of the cough reflex is a most widely advocated approach to diagnosis and treatment.

The foremost consideration for the clinician at the first visit is to (1) determine the severity, (2) assess the cause(s)

of the cough, and (3) plan investigations and treatment. Various indicators in the history and examination of the patient may provide clues to the diagnosis, although these may not be entirely reliable or specific and may be absent in many cases.

An acute cough due to an upper respiratory virus infection generally lasts for no more than 3 weeks, although some postviral coughs may persist for many weeks or months. Thus, a chronic cough is considered to be one that persists longer than 3 weeks. The one caveat is that many patients with an “idiopathic” cough often state that their cough originated during an upper respiratory tract infection. Nonetheless, a cough that has lasted for more than 2 to 3 months is unlikely to be due to an upper respiratory tract infection, and other associated causes must be investigated.

Cough with sputum production usually points toward conditions such as chronic bronchitis and bronchiectasis or other causes of bronchorrhea. The diagnostic value of knowing that the cough is productive is probably limited because similar causes are often found for both productive and dry cough.⁶⁵ In addition, the volume of sputum produced is difficult to estimate accurately (usually depending on sputum cups and block of salivary contamination), and coughing itself leads to sputum production. The concept of a dry versus a productive cough as delineating a cough secondary to an increased cough reflex for the former and a cough secondary to excessive mucus production for the latter is not entirely correct. An enhanced cough reflex may be present in both productive and nonproductive cough. Features that are associated with an increased cough reflex include cough triggered by taking a deep breath, laughing, inhaling cold air, and prolonged talking. Therefore, the diagnostic approach remains similar whether or not the cough is productive.

The characteristics of the cough, however, may sometimes help direct the diagnostic evaluation. Throat clearing

may be associated with a postnasal drip, a predominantly nocturnal cough may be attributed to asthma, or coughing after meals may be related to coexistent GERD. However, the predictive value of these characteristics is low.⁶⁶ A cough with a “honking” or “barking” quality, particularly in a child, has been associated with a psychogenic or habit cough.

Many cigarette smokers have a chronic cough but rarely seek medical advice regarding their cough because they expect that the irritant effect of cigarette smoke is the cause of their cough. However, chronic smokers may actually have a reduction in their cough reflex sensitivity, perhaps due to desensitization or damage of the epithelial nerve endings. A change in the pattern or characteristics of their cough, such as an increase in intensity (usually after an upper respiratory tract infection), or accompanying hemoptysis may force a smoker to seek medical attention. A chest radiograph is mandatory in this situation.

MEASURING COUGH

Assessment of cough frequency and severity rests mainly on the history. In very severe cough, patients may experience complications such as vomiting, rib fractures, tiredness, incontinence, and syncope (Table 30-2), and their presence indicates that the chronicity and intensity of the cough are severe. The effect of cough on the patient's lifestyle and psychological well-being may also provide an idea of the severity of the cough. Questionnaires that are specifically devised to measure these effects have been developed and validated.^{67,68} Direct measurement of the frequency and severity of cough has also been developed.^{8,69} In many published studies, the effectiveness of particular interventions on cough has been determined qualitatively in the clinic, but the use of more quantitative tools is now gradually being introduced (see later).

Cough can be measured in several ways: (1) cough severity can be judged by the patient recording her or his perception on a visual analogue scale ranging from mild to severe or on a nominal line from 0 to 10; (2) the cough reflex can be measured by counting the cough responses to inhalation of tussive agents such as capsaicin, the pungent extract of

peppers, or citric acid— or low-chloride-content solutions; (3) cough frequency and intensity can be measured by quantitative ambulatory recording; and (4) cough-specific, health-related quality of life questionnaires can provide a quantitative measure of the impact of chronic cough on the patient.^{67,68,70} There is a correlation between the various measures of cough as, for example, between objectively measured cough frequency and subjective scoring systems measured by the cough visual analogue scale or the Leicester Cough questionnaire, although this correlation remains weak.⁷¹ This means that subjective scoring systems may be responsive to not only cough frequency but also other factors related to the cough. Therefore, a combination of both subjective and objective measurements should ideally be used. All these features are of concern to the patient.

MEASUREMENT OF THE COUGH REFLEX

Persistent cough may result from an increase in the sensitivity of the cough sensors. Most patients with a persistent cough, due to a range of causes, have an enhanced cough reflex to inhalation of an aerosol of capsaicin or of citric acid when compared with healthy noncoughing subjects.⁷² Successful treatment of the primary condition underlying the chronic cough (specific or disease-specific treatment) sometimes leads to a normalization of the cough reflex.⁷³ The degree of the cough responsiveness to inhaled capsaicin may contribute to the severity of the cough. Of relevance to the evaluation and treatment strategies for persistent dry cough is the fact that the cough response can be augmented by various mediators of inflammation such as the *prostaglandins* PGE₂ and PGF_{2α} and bradykinin through a process of sensitization.^{74,75} Measurement of the cough reflex response to such agents may be useful in confirming the presence of a persistent cough or in assessing the response to treatment. At the moment, only centers with an interest in cough use it for clinical and research purposes.

MEASUREMENT OF COUGH FREQUENCY AND INTENSITY

Advances in computer technology and digital sound recording have led to the development of ambulatory systems for audio or audiovisual recording of cough, with the ultimate objective of automatically obtaining cough counts and possibly intensity in a real-life setting. Several devices have been described.^{8,76} The number of cough sounds and the cough seconds, a measurement of the time of coughing, have been shown to correlate with scores on a *Leicester Cough Questionnaire* (LCQ) and on a cough visual analogue scale.⁸

Although the methods are valuable in counting the number of expiratory efforts associated with cough, they do not allow assessment of cough intensity (because this need not correlate with intensity of expiratory sound). They can be used to differentiate between individual coughs and those associated with a cough epoch, although the definition of the distinction is arbitrary. Both the frequency and intensity of cough efforts are features of importance to the patient. Current methods do not allow a distinction between a “true” cough and an expiration reflex, a feature

Table 30-2 Potential Complications from Excessive Cough

RESPIRATORY	MUSCULOSKELETAL
Pneumothorax	Intercostal muscle pain
Subcutaneous emphysema	Rupture of rectus abdominis muscle
Pneumomediastinum	Increase in serum creatine phosphokinase
Pneumoperitoneum	Cervical disc prolapse
Laryngeal damage	
CARDIOVASCULAR	GASTROINTESTINAL
Cardiac dysrhythmias	Esophageal perforation
Loss of consciousness	
Subconjunctival hemorrhage	
CENTRAL NERVOUS SYSTEM	OTHER
Syncope	Social embarrassment
Headaches	Depression
Cerebral air embolism	Urinary incontinence
	Disruption of surgical wounds
	Petechiae
	Purpura

that might seem trivial to a patient but should be important to the investigator because it might provide insight into the location of the cough trigger.

QUALITY OF LIFE QUESTIONNAIRES

Quality of life questionnaires specific for the evaluation of the impact of chronic cough^{67,68} provide subjective measurements that are likely to reflect the severity of cough from the viewpoint of the patient. Such measurements integrate both the impact of frequency and the intensity of cough. The LCQ uses a seven-point Likert response scale for 19 items from three domains (physical, psychological, and social) and is shown to be repeatable and sensitive in patients with chronic cough.⁷⁷ This is increasingly becoming a useful clinical tool.

DIAGNOSIS AND INVESTIGATIONS OF CHRONIC COUGH

The history and examination will sometimes indicate the likely associated diagnosis or diagnoses, and the timing of various investigations may vary according to presentation (Table 30-3). Initial investigations may be limited to a chest radiograph, particularly in a cigarette smoker. Abnormalities have been reported in 10% to 30% of chest radiographs of cigarette smokers, although the yield of tumors is likely to be lower. Further investigations (e.g., *computed tomography* [CT] or fiberoptic bronchoscopy) may be pursued despite a “normal” chest radiograph.

Patients on *angiotensin-converting enzyme* (ACE) inhibitor therapy should discontinue such therapy, with replacement by other appropriate treatments. Patients who provide a good history of an upper respiratory tract infection may be observed for 3 to 4 weeks before further investigation or therapeutic trial, although institution of an anti-inflammatory therapy such as inhaled corticosteroids can be useful in controlling this type of cough.

Table 30-3 Diagnostic Evaluation of Chronic Cough

1. History and physical examination.
2. Chest radiograph, particularly in smokers.
3. Initial evaluation may lead to diagnosis of chronic bronchitis in cigarette smokers and of angiotensin-converting enzyme inhibitor cough. Discontinue cigarette smoking and offending drug.
4. Further diagnostic evaluation on basis of initial evaluation:
 - i. If suggestive of postnasal drip, order a CT scan of sinuses, and allergy tests.
 - ii. If suggestive of asthma, request a record of peak expiratory flow measurements at home for 2 weeks and a bronchoprovocation test with histamine or methacholine and/or a trial of antiasthma treatment.
 - iii. If suggestive of gastroesophageal reflux disease, request 24-hour pH monitoring and, if necessary, an endoscopic examination of the esophagus or a barium swallow series.
 - iv. If the chest radiograph is abnormal, consider examination of sputum and a fiberoptic bronchoscopy. A high-resolution CT scan of the thorax and further lung function evaluation may be necessary.
5. Treat specifically for associated conditions. The cause(s) of cough is (are) determined when specific therapies eliminate or improve the cough. There may be more than one associated cause for the cough.

After these initial steps, investigation of the major causes of cough should be considered. Postnasal drip (“nasal catarrh” or “upper airway cough syndrome”), asthma, and GERD are the three most common conditions associated with a chronic cough, and a diagnostic approach to exclude these conditions is sensible. Postnasal drip, secondary to rhinosinusitis, is an often overlooked condition. If there is a history of postnasal drip or rhinosinusitis, examination of the nose and sinuses with a computed axial tomogram of the sinuses may be indicated. Treatment consists of corticosteroid nasal drops together with an antihistamine, with the possibility of adding antibiotic therapy and a short period of treatment with a nasal decongestant. An asthma diagnosis is supported by the presence of diurnal variation in peak flow measurements, bronchial hyperresponsiveness to histamine or methacholine challenge, and the presence of eosinophils in sputum. Under the umbrella of “asthma” would also be included cough-variant asthma and eosinophilic bronchitis. However, a therapeutic trial with inhaled corticosteroids may be the best initial approach, particularly when the history and examination provide supportive clues. It is important that effective doses of medication over a sufficient period of time are given. Often, a longer-than-usual period of treatment is necessary to control the cough, and GERD may be initially evaluated with ambulatory esophageal pH monitoring.

Often, more than one of these conditions may coexist and cough may respond only with concomitant treatment of these. For example, inhaled steroid therapy and gastric acid suppression with a proton pump inhibitor or H₂-histamine blockers would be indicated for the coexistence of asthma and GERD, respectively.

Bearing in mind that there are a myriad of other less common causes of a chronic cough, investigations must proceed further if the common causes have been excluded. Lung function tests to include lung volumes and diffusing capacity, as well as a CT of the lungs, should be considered in case of bronchiolar or parenchymal disease or unsuspected bronchiectasis. Fiberoptic bronchoscopy should be considered and, apart from excluding small central tumors, provides mucosal biopsies for histologic diagnosis (e.g., to diagnose eosinophilic bronchitis).

CAUSES AND TREATMENT OF ACUTE AND CHRONIC COUGH

ACUTE COUGH

Acute cough is usually due to a viral or bacterial upper respiratory tract infection. The cough of the common cold is usually self-limiting and accompanies the cold in the majority of sufferers within the first 48 hours.⁷⁸ Other symptoms of postnasal drip, throat-clearing, irritation of the throat, sore throat, nasal obstruction, and nasal discharge also accompany the cough, which usually resolves within 2 weeks, although it can be sometimes prolonged. Pertussis should be considered in the differential diagnosis, particularly with a whooping characteristic of the cough (Audios 30-3 and 30-4), and is often associated with vomiting. About 20% of adolescents and adults with cough

lasting for 2 weeks or more have evidence of recent whooping cough.⁷⁹ Other causes of acute cough are pneumonia, congestive cardiac failure, exacerbation of *chronic obstructive pulmonary disease* (COPD), aspiration, or pulmonary embolism. These conditions are usually accompanied by other symptoms such as shortness of breath and fever, but cough may remain the predominant or, rarely, the only symptom.

Patients with the common cold usually self-medicate with over-the-counter antitussive preparations. A Cochrane review reported no good evidence for or against the effectiveness of over-the-counter medicines such as antitussives and antihistamines in acute cough. “Satisfactory” responses to pediatric cough syrups were reported in 46% and 56% of children compared with 21% of children in the placebo group.⁸⁰ Codeine was ineffective compared with placebo against the acute cough of the common cold,⁸¹ while dextromethorphan had some effect in a meta-analysis,⁸² but not in two smaller studies.^{83,84} In a study of 100 children, dextromethorphan or diphenhydramine given as a single dose before bedtime was found to be no better than placebo in providing nocturnal symptom relief for children with cough and sleep difficulty from an upper respiratory tract infection.⁸⁵ Instead, a subsequent study showed that buckwheat honey provided symptomatic relief,⁸⁶ but a placebo effect was not excluded. The American Academy of Pediatrics has highlighted the fact that the efficacy of antitussive preparations in children is lacking and that these medications may be potentially harmful.⁸⁷ Their recommendation is that cough due to acute viral airway infections is self-limiting and should be treated only with fluids and humidity.

A first-generation antihistamine and decongestant has been proposed for the treatment of cough associated with a postnasal drip in acute cough,⁷⁸ but a study using a newer-generation antihistamine, loratadine, in combination with a decongestant showed no effect.⁸⁸ The rhinitis associated with the common cold may become mucopurulent, but this is not an indication for antibiotic therapy unless this persists for more than 10 to 14 days.

CHRONIC COUGH

Chronic cough (cough that persists for more than 3 weeks) can be caused by many diseases, but according to several series, it is most commonly due to postnasal drip, asthma, GERD, chronic bronchitis, and bronchiectasis.^{73,89} A recent worldwide survey revealed a striking gender and age demographic of chronic coughers, most of whom are female aged between 60 and 69 years.^{89a}

Postnasal Drip (Rhinosinusitis, Upper Airway Cough Syndrome)

Postnasal drip has been reported as being the most common cause of chronic cough.^{89,90} The *upper airway cough syndrome* (UACS) has been coined as a better term than postnasal drip to denote chronic cough related to upper airway abnormalities. The strong association between postnasal drip and chronic persistent cough is based on epidemiologic evidence and on a prospective study in adults. Postnasal drip (“nasal catarrh”) is characterized by a sensation of nasal secretions or of a “drip” at the back of the throat,

accompanied often by frequent need to clear the throat (“throat-clearing”). There may be a nasal quality to the voice due to concomitant nasal blockage and congestion, and there may be hoarseness of the voice. Physical examination of the pharynx is often unremarkable, although a “cobblestoning” appearance of the mucosa and draining secretions may be observed. CT of the nasal passages and sinuses may reveal rhinosinusitis with mucosal thickening or sinus opacification and air-fluid levels. Extrathoracic variable upper airway obstruction is not always present.⁹¹ Testing for allergens may be helpful, and the presence of allergy to pollens supports the presence of seasonal allergic rhinitis.

The best treatment is topical administration of corticosteroid drops in the head-down position, often with the concomitant use of antihistamines. Topical steroids offer a local effect with the minimum of side effects. Occasionally, severe symptoms may be controlled initially by a short course of oral steroids, followed by topical therapy. A topical anticholinergic spray to the nose (such as ipratropium bromide) to dry excessive nasal secretions may provide additional benefit. A combination of topical corticosteroid, antihistamine, and anticholinergic treatments has been shown to benefit the chronic cough accompanying postnasal drip associated with an improvement in nasal discharge and endoscopic appearances.⁹² Topical decongestant vasoconstrictor sprays may be useful adjunct therapy for a few days, but rebound nasal obstruction may develop after prolonged use. Antibiotic therapy is necessary in the presence of acute sinusitis involving bacterial infection with the presence of mucopurulent secretions that has persisted for at least 10 days.

Asthma and Associated Eosinophilic Conditions

Asthma may lead to chronic cough under different clinical settings. Asthma may present predominantly with cough, often nocturnal, and the diagnosis is supported by the presence of reversible airflow limitation and bronchial hyperresponsiveness.⁹³ This condition of “cough-variant” asthma is a common type of asthma in children. Elderly asthmatics may also give a history of chronic cough before a diagnosis of asthma. Cough as the only presenting symptom of asthma has been reported in up to 57% of patients and is often its most prominent symptom.⁹⁴ Cough may also arise as a first sign of worsening of asthma; the cough usually presents first at night, associated with other symptoms such as wheeze and shortness of breath with drops in early morning peak flows. Some patients with asthma may also develop a persistent dry cough despite good control of their asthma.

Atopic cough is recognized in Japan as an isolated chronic cough characterized by an atopic background, sputum eosinophilia, cough hypersensitivity, normal pulmonary function, and airway hyperresponsiveness.⁹⁵ On the other hand, eosinophilic bronchitis is characterized by cough without asthma symptoms or bronchial hyperresponsiveness but with eosinophilia in sputum.⁹⁶

An enhanced cough reflex, although not usually found in patients with asthma, may be seen in a subgroup of asthmatics with a persistent cough.⁹⁷ In these patients, cough sensors may be sensitized by inflammatory mediators such as bradykinin, tachykinins, and prostaglandins. Cough

in asthma may also be due to bronchial smooth muscle contraction, which may activate cough receptors through physical deformation. Indeed, in some patients with cough-variant asthma, β -adrenergic bronchodilators are effective antitussives.⁹⁸ A predominance of eosinophils in induced sputum and bronchial biopsies, together with a thickened basement membrane and bronchial hyper-responsiveness, is present in cough-variant asthma. In eosinophilic bronchitis, conversely, cough responsiveness to capsaicin is increased without bronchial hyper-responsiveness, but the immunopathologic abnormalities are similar to those of asthma.⁹⁹

Cough associated with asthma should be treated with antiasthma medication including inhaled corticosteroid therapy and bronchodilators such as β_2 -adrenergic agonists. Such treatment should be given over a prolonged period of time (3 to 6 months) at the lowest dose that controls the cough. Often, a trial of oral corticosteroids (e.g., prednisolone 40 mg/day for 2 weeks) may be recommended, particularly in those asthmatics who have had a cough despite being on adequate antiasthma medication. A combination of inhaled corticosteroids and a long-acting β -agonist is now the best available maintenance treatment for moderate-to-severe asthma. Leukotriene receptor antagonists may also control cough-variant asthma.¹⁰⁰ Eosinophilic bronchitis responds well to inhaled or oral corticosteroid therapy.

Gastroesophageal Reflux Disease

GERD, the movement of acid and other components of gastric contents from the esophagus into the larynx and trachea, is one of the most commonly associated causes of chronic cough in all age groups. GERD may lead to symptoms such as heartburn, chest pain, a sour taste, regurgitation, and a chronic persistent cough. Prolonged exposure of the lower esophagus to acid may lead to esophagitis, Barrett esophagus, esophageal ulceration and stricture, and bleeding. However, there may also be no symptoms associated with GERD or with the exposure of the esophagus to acid. An esophageal-tracheobronchial cough reflex mechanism has been proposed on the basis of studies in which perfusion of the distal esophageal with acid induced coughing episodes that could be suppressed by local distal esophageal perfusion of lidocaine and by an inhaled anticholinergic agent, ipratropium bromide.¹⁰¹ More than 90% of the cough episodes have been shown to be temporally related to reflux episodes. Significant reflux happens in both supine and upright positions. Given the poor response of cough to treatment with gastric acid suppressors such as proton pump inhibitors,^{102,103} there is a possibility that non-acid reflux factors such as the liquid, gas, pepsin, or other enzymes may be important in stimulating cough. A high proportion of patients with GERD also appear to have laryngopharyngeal reflux,¹⁰⁴ which may represent a direct effect of gastroesophageal reflux on cough receptors in the larynx and trachea. However, one study showed no differences in non-acid reflux events in the proximal or distal esophagus between patients with chronic cough and normal subjects.¹⁰⁵ Coughing itself may precipitate reflux, creating a vicious circle of acid-inducing cough that in turn induces acid reflux. Continuous monitoring of tracheal and

esophageal pH in patients with symptomatic GERD has demonstrated significant increases in tracheal acidity with a fall in the pH to 4 or less during episodes of reflux.¹⁰⁶ Other components of the refluxate, apart from acid, such as pepsin or other enzymes may also contribute to cough.

There is no particular pattern of the cough caused by GERD. The cough may be long-standing and productive. In the presence of reflux and microaspiration, laryngeal symptoms may be present with dysphonia, hoarseness, frequent throat clearing, a globus sensation (e.g., a feeling of a lump in the throat), and sore throat; often, posterior vocal cord laryngeal inflammation with edema, erythema, contact ulceration, pachydermia, and/or granuloma is visible. There may be associated esophageal dysmotility characterized by heartburn, water brash, and oral regurgitation, which can be worse in the supine position. Ineffective esophageal peristalsis has been reported in chronic cough, and this may increase the exposure time of the larynx and pharynx to any refluxate.^{107,108}

Monitoring of 24-hour ambulatory pH, examining for episodes of pH below 4, together with monitoring of non-acid reflux in the proximal and distal esophagus with analysis of the temporal relationship between cough and reflux episodes, are the most specific tests for GERD. In one study of patients with chronic cough, however, acid reflux preceded cough in only up to 13% of coughs; however, many of the patients did have reflux, suggesting that the association may be more indirect.¹⁰⁹ Positive predictive values for the use of esophageal pH monitoring are reported to be between 68% and 100%, and a negative test nearly excludes GERD as the cause of cough. However, there has been a greater association of a cough event with a non-acid reflux episode in chronic cough patients.¹¹⁰ In half of an unselected cohort of patients with chronic cough, a positive association for acid reflux detected by esophageal pH testing and for non-acid reflux detected by intraluminal impedance and cough sounds on an ambulatory cough counter was reported. This was associated with a heightened cough reflex sensitivity.¹¹¹ Other tests that may be used are esophageal manometry to measure dysmotility, particularly associated with reflux episodes; upper gastrointestinal contrast series to detect reflux of barium into the esophagus; or an upper gastrointestinal endoscopy. A trial of antireflux treatment with a proton pump inhibitor or a histamine H_2 -antagonist may be used in patients as a diagnostic measure where ambulatory 24-hour pH esophageal monitoring is not available. This may also be indicated in patients with chronic cough that remains unexplained after diagnostic workup or exclusion of other associated causes.

The aim of treatment of GERD is to decrease the frequency and duration of the events. Conservative measures such as weight reduction, a high-protein, low-fat diet, elevation of the head of the bed, and avoidance of coffee and smoking should be advocated. Reduction of acid production by the stomach can be achieved with either H_2 -histamine blockers or proton pump inhibitors, although they have not been compared. Given the increasing use of proton pump inhibitors and their superior effect in acid suppression and in treating GERD, these drugs will remain the preferred choice. Although initial uncontrolled studies

have provided optimistic effects of histamine H₂-receptor antagonists or proton pump inhibitors in controlling the cough associated with GERD, double-blind placebo-controlled studies^{103,112} report more limited effects. Nevertheless, treatment for 3 months, at the highest recommended dose of a proton pump inhibitor, is usually advocated. It has been reported that those with evidence of a pathologic acid reflux may profit more from PPI therapy.¹¹³ The effect of specific treatments for esophageal dysmotility is not known. A case report of successful treatment of cough in 3 patients with GERD unresponsive to PPI using baclofen was reported,¹¹⁴ with baclofen perhaps working through reducing both acid and non-acid reflux. The use of domperidone to increase gastric emptying in GERD remains unclear.

One of the reasons for failure of an antacid strategy may be the continued effect of the nonacid refluxate. Antireflux surgery such as laparoscopic fundoplication may be considered for patients with proven GERD disease whose cough has failed to respond to medical therapy.¹¹⁵ Complete resolution of the cough has been reported in about 60% of subjects,¹¹⁶ but predictors of a good response to surgery have not been defined.

Chronic Bronchitis/Chronic Obstructive Pulmonary Disease

Chronic bronchitis should be considered in a patient who produces sputum on most days over at least 3 consecutive months, particularly during the winter months, over at least 2 consecutive years. Although 30% to 40% of the community smokes tobacco, chronic bronchitis is only reported in 5% of the patients seeking medical attention for cough. In a smoker, the presence of chronic bronchitis may be predictive of progressive irreversible airflow obstruction, leading to COPD.¹¹⁷ In addition, the presence of cough and sputum in COPD identifies patients at greater risk of subsequent exacerbations.¹¹⁸

The cough of chronic bronchitis may result from excessive sputum production associated with mucus cell hyperplasia and bronchiolar inflammation. In addition, there is evidence of an increase in capsaicin cough hypersensitivity in patients with COPD,^{97,119} which may result from the airway inflammatory process. The presence of airflow obstruction diagnosed on the basis of a ratio of *forced expiratory volume in 1 second* to *forced vital capacity* (FEV₁/FVC) of less than 70% or of an FEV₁ of less than 70% of the predicted value indicates the presence of COPD.¹²⁰

The productive cough in chronic bronchitis is exacerbated by upper respiratory infections with common viruses or respiratory bacteria or by exposure to irritating dusts or environmental pollutants. Other causes of productive cough such as bronchiectasis or postnasal drip should be excluded. It is important to exclude also the presence of lung tumors. Cessation of cigarette smoking is usually accompanied by a reduction in cough, most often within 4 to 5 weeks.¹²¹ Smoking cessation may be aided by various adjuncts such as nicotine replacement or bupropion or varenicline, a nicotine receptor partial agonist.¹²² Treatment of any associated chronic airflow obstruction with short-acting and/or long-acting β_2 -adrenoceptor agonists and anticholinergic agents should be considered, particularly in

the presence of dyspnea. Suppression of the inflammatory process in the small airways may be tried with the combination of inhaled corticosteroids and long-acting β -agonists. Oral or systemic corticosteroids are effective in the treatment of exacerbations of COPD. Mucolytic therapy may reduce the incidence of exacerbations. Indirect (symptomatic) antitussive therapies are not recommended but may be needed in patients with excessive coughing that is impairing their quality of life.

Bronchiectasis

The cough of bronchiectasis is associated with overproduction of airway secretions together with a reduced clearance, often within a vicious circle of recurrent bacterial infections. Usually, the patient produces 30 mL or more of mucoid or mucopurulent sputum per day, sometimes accompanied by fever, hemoptysis, and weight loss. Early on, bronchiectasis may present solely as a persistent, productive cough. Bronchiectasis may be associated with postnasal drip and rhinosinusitis, asthma, GERD disease, and chronic bronchitis. Common pathogens cultured from sputum include *Haemophilus influenzae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The chest radiograph may show increased bronchial wall thickening, particularly in the lower lobes in advanced cases, but thin-section CT of the chest can reveal early changes of airway wall thickening, dilation, and distortion, with mucus plugging, and evidence of bronchiolitis.¹²³

Cough in bronchiectasis is the most effective mechanism for clearing airway secretions. Chest physiotherapy to improve airway clearance remains essential. In addition, there is an increased capsaicin cough response in bronchiectasis.¹²⁴ Cough during infective exacerbations of bronchiectasis may become a tiring symptom. Long-term macrolide therapy may lead to an improvement in exacerbations and lung function. The cough due to bronchiectasis may be controlled by the use of inhaled β_2 -agonists to improve mucociliary clearance and reverse any associated bronchoconstriction, by postural drainage of airway secretions, and by the use of intermittent antibiotic therapy. Use of antitussives is not recommended but, in the context of severe cough, some suppressive effect may be clinically beneficial.

Angiotensin-Converting Enzyme Inhibitor Cough

ACE inhibitors are often prescribed for the treatment of hypertension and heart failure, and cough has been observed in 2% to 33% of patients.^{125,126} The cough is typically described as "dry," associated with a tickly irritating sensation in the throat. It may appear within a few hours of taking the drug, but it may also become apparent only after taking the drug for weeks or even months. The cough disappears within days or weeks following withdrawal of drug. Patients with ACE inhibitor cough demonstrate an enhanced response to the capsaicin inhalation challenge. Accumulation of bradykinin and prostaglandins, which sensitize cough receptors directly, has been implicated. The best course of action for ACE inhibitor cough is to discontinue the treatment and replace it with alternative therapies such as angiotensin II receptor antagonists, which are not usually associated with cough.

Postinfectious Cough

Postinfectious cough has been reported in 11% to 25% of patients with chronic cough.^{127,128} A persistent cough develops in 25% to 50% of patients following *Mycoplasma* or *Bordetella pertussis* infection.¹²⁹ *B. pertussis* infection has now been increasingly recognized as a cause of both acute and chronic cough, particularly in older children and adults.¹³⁰ In children, other respiratory infections associated with chronic cough include viruses (respiratory syncytial virus and parainfluenzae), *Mycoplasma*, and *Chlamydiae*.¹³¹ The cough of *B. pertussis* usually lasts for only 4 to 6 weeks (but can last longer) and is spasmodic with a typical whoop. In most patients with a postinfectious cough, the initial trigger is usually an upper respiratory tract infection, and cough that would have been expected to last for only a week persists for many months. Such patients are often referred to a cough clinic and are usually investigated for the more commonly associated cause of cough. It is assumed that the initial infection may have induced persistent airway inflammation or epithelial damage that then allowed irritants to penetrate more easily, thereby setting up a vicious circle of events that maintains and triggers further cough.

Inhaled corticosteroids are often prescribed, but with variable success. Oral steroids may be successful.¹²⁷ Inhaled ipratropium bromide was reported to be effective in a small study.¹³² Macrolide antibiotics or trimethoprim/sulfamethoxazole are effective in eliminating *B. pertussis* but do not alter the subsequent clinical course.¹³³

Other Conditions

Other conditions causing cough include bronchogenic carcinoma, metastatic carcinoma, sarcoidosis, chronic aspiration, interstitial lung disease, or left ventricular failure, conditions that can usually be excluded with a normal chest radiograph. More recently, associations of chronic cough with obstructive sleep apnea, chronic tonsillar enlargement, and laryngeal dysfunction have been reported. Psychogenic or habit cough is common, particularly in children, and is usually a diagnosis arrived at after exclusion of other causes. Habit cough is a throat-clearing noise made by a person who is nervous and self-conscious. Cough may be associated with a depressive illness, and long-standing cough may cause depression. In the pediatric population, other cough etiologies specific for this age group need to be considered: congenital abnormalities including vascular rings and tracheobronchomalacia (eFig. 30-1), pulmonary sequestration or mediastinal tumors, foreign bodies in the airway (eFig. 30-2) or esophagus, aspiration due to poor coordination of swallowing or esophageal dysmotility, and heart disease.

Chronic Persistent Cough of Unknown Cause ("Idiopathic" Cough)

Identification of a potential cause of cough has been reported in 78% to 99% of patients presenting at a cough clinic, and specific treatment of identifiable causes has also been reported to be successful in up to 69% to 99% of cases.^{89,134} However, more recent series have identified 7% to 46% of patients with chronic cough as having idiopathic cough, despite undergoing thorough diagnostic evaluation.

These differences may relate to the definition of successful treatment and the case mix. The patient with idiopathic cough should be diagnosed as such only after an intensive diagnostic evaluation and empirical trial of therapy(ies) have been carried out. In one report, patients with idiopathic cough tended to be middle-aged women who frequently gave a history of cough onset at menopause and had associated autoimmune disorders such as autoimmune hypothyroidism.¹³⁵ Patients with an enhanced cough reflex often complain of a persistent tickling sensation in the throat that leads to paroxysms of coughing. This sensation can be triggered by factors such as changes in ambient temperature, taking a deep breath, laughing, talking over the phone for a few minutes, and exposure to cigarette smoke or other irritants such as aerosol sprays or perfumes or to certain odors. Mucosal biopsies taken from a group of nonasthmatic patients with idiopathic cough showed increased mast cell numbers and features of airway wall remodeling such as increased sub-basement membrane thickening, increased airway smooth muscle mass, goblet cell hyperplasia, and increased blood vessels.¹³⁶ These changes could represent the sequelae of chronic trauma to the airway wall following intractable cough and could in turn lead to sensitization of the cough reflex. There is an increase in neural profiles that express the neuropeptide, *calcitonin gene-related peptide* (CGRP), and the calcium channel, TRPV1, in the airway epithelium of chronic coughers that could contribute to the increased cough reflex.^{137,138}

Cough Hypersensitivity Syndrome

The concept of a *cough hypersensitivity syndrome* (CHS) has been introduced to encompass most chronic coughs, particularly those with a definition of an idiopathic cough.^{55,139,139a} This concept focuses on the pathogenesis of the cough itself and may be defined as a neuropathic syndrome presenting with a chronic persistent cough that has lasted for more than 8 weeks and is associated with characteristic trigger symptoms and sensations indicating the presence of an enhanced cough reflex (see Fig. 30-6). Patients with CHS often complain of a persistent tickling or irritating sensation in the throat (feeling of an itch) or a choking sensation, and it may sometimes be felt in the chest, which often leads to paroxysms of uncontrollable coughing. Other symptoms associated with chronic cough patients include clearing of the throat, chest tightness, hoarse voice and dysphonia, vocal cord dysfunction symptoms, sensation of globus, acid reflux symptoms, sense of effort, and air hunger. Triggers such as lying down, eating, singing, talking, laughing, and taking a deep breath (through mechanoreceptors); changes in ambient temperature (through thermoactivation); aerosols, scents, odors, and cigarette smoke (through chemoactivation) are common.¹⁴⁰ In addition to these symptoms, patients with chronic cough demonstrate cough hypersensitivity with inhaled citric acid or capsaicin challenge.

Within CHS, the sensory laryngeal neuropathy described by laryngologists can be included as a condition presenting with chronic cough, laryngospasm, or paradoxical vocal cord dysfunction.¹⁴¹ This has been described after an upper respiratory virus infection affecting the superior or recurrent laryngeal nerves. An irritable larynx measured as laryngeal hyperresponsiveness with histamine inhalation is

present in the majority of chronic cough patients associated with postnasal drip, GERD, and asthma, and with unexplained cough.¹⁴² Paradoxical vocal cord movement present in chronic cough is also associated with extrathoracic airway hyperresponsiveness.¹⁴³

COUGH SUPPRESSION THERAPIES

NONPHARMACOLOGIC APPROACH: SPEECH PATHOLOGY MANAGEMENT

In patients with chronic cough refractory to medical treatment, speech pathology management or cough suppression therapy consisting of an educational component about cough, cough suppression therapy, vocal hygiene training, and psychoeducational counseling has been shown to be effective in improving cough symptom scores, as well as breathing, voice, and upper airway symptoms.¹⁴⁴ In addition, this therapy also reduced capsaicin cough sensitivity.¹⁴⁵ Improved cough and breathing symptoms were also observed in patients with chronic cough and paradoxical vocal cord movement after a combination of proton pump inhibitor therapy and a speech pathology intervention.¹⁴⁶ This treatment administered by a voice and speech and language specialist or respiratory physiotherapist should be considered for patients with refractory chronic cough.¹⁴⁷

“SYMPTOMATIC,” “INDIRECT,” OR “NONSPECIFIC” ANTITUSSIVES

When the treatment of the cause of cough is not effective or not available, therapies directed at eliminating the symptom of cough irrespective of the cause of the cough may be tried¹⁴⁸ (Table 30-4). These therapies are also termed “symptomatic,” “indirect,” or “nonspecific” antitussives. This is particularly relevant to patients with lung cancer with a persistent cough, of whom 50% rate their cough as moderate to severe.¹⁴⁹ Drugs that affect the complex mechanism of the cough reflex may work by inhibition of central mechanisms within the brain stem or of peripheral mechanisms on the cough sensors in the airways. Alternatively, antitussive activity of some drugs may not be a result of pharmacologic means because cough exhibits an unusually robust sensitivity to placebo suppression.^{16,150} Because of the relative low efficacy of current antitussives, several new classes of antitussives are being developed on the basis of our understanding of the cough reflex and of the membrane receptors and channels on cough sensors.^{151,152} An ideal cough therapy would be one that suppresses excessive cough in disease yet allows for protective cough to be maintained. No such compounds have been identified to date. A summary of the existing direct and indirect antitussives and their potential modes and sites of actions is shown in Figure 30-7.

NARCOTIC AND NON-NARCOTIC ANTITUSSIVES

Opiates including morphine, diamorphine, and codeine are the most effective antitussive agents. (Diamorphine is not prescribed in the United States.^{152a}) At their effective doses, they cause physical dependence, respiratory depression,

Table 30-4 Treatments for Cough

1. TREATING THE SPECIFIC UNDERLYING CAUSE(S)	
Asthma, cough-variant asthma	Bronchodilators and inhaled corticosteroids
Eosinophilic bronchitis	Inhaled corticosteroids; leukotriene inhibitors
Allergic rhinitis and postnasal drip	Topical nasal steroids and antihistamines Topical nasal anticholinergics (with antibiotics, if indicated)
Gastroesophageal reflux	Conservative measures Histamine H ₂ antagonist or proton pump inhibitor
Angiotensin-converting enzyme inhibitor	Discontinue and replace with alternative drug such as angiotensin II receptor antagonist
Chronic bronchitis/COPD	Smoking cessation Treat for COPD
Bronchiectasis	Postural drainage Treat infective exacerbation and airflow obstruction
Infective tracheobronchitis	Appropriate antibiotic therapy Treat any postnasal drip
2. SYMPTOMATIC TREATMENT (ONLY AFTER CONSIDERATION OF CAUSE OF COUGH)	
Acute cough likely to be transient (e.g., upper respiratory viral infection)	Simple linctus (cough syrup)
Persistent cough, particularly nocturnal	Opiates (codeine or pholcodeine)
Persistent intractable cough due to terminal incurable disease	Opiates (morphine or diamorphine) Local anesthetic aerosol
Cough in children	Simple linctus (pediatric)

and gastrointestinal colic. Morphine and diamorphine are reserved for the control of cough and pain of terminal bronchial cancer patients, but codeine, dihydrocodeine, and pholcodeine can be tried in other cases of chronic cough. Codeine is the methylether of morphine and has long been the standard centrally acting antitussive drug against which the pharmacologic and clinical effects of newer drugs have been measured. Codeine is probably the most commonly prescribed antitussive. It has some antitussive activity, compared with placebo when given orally. Although codeine possesses antitussive activity against pathologic cough¹⁵² and against induced cough in normal volunteers,¹⁵³ a recent study suggested, contrary to earlier evidence, that it had little effect on cough in selected COPD patients¹⁵⁴ or against acute cough of the common cold⁸¹ compared with placebo.

Codeine should be used cautiously in patients with reduced hepatic function but can be used without dose modification in patients with renal failure. Drowsiness may be an incapacitating side effect, together with nausea, vomiting, and constipation. Rarely, allergic cutaneous reactions such as erythema multiforme have been described. Codeine can cause physical dependence, but on a smaller scale than morphine. Dihydrocodeine has no particular advantage over codeine and may cause more addiction than codeine. Pholcodeine is also as effective as codeine but has little or no analgesic effect.

Morphine and diamorphine (diamorphine is not prescribed in the United States) should be used only for severe

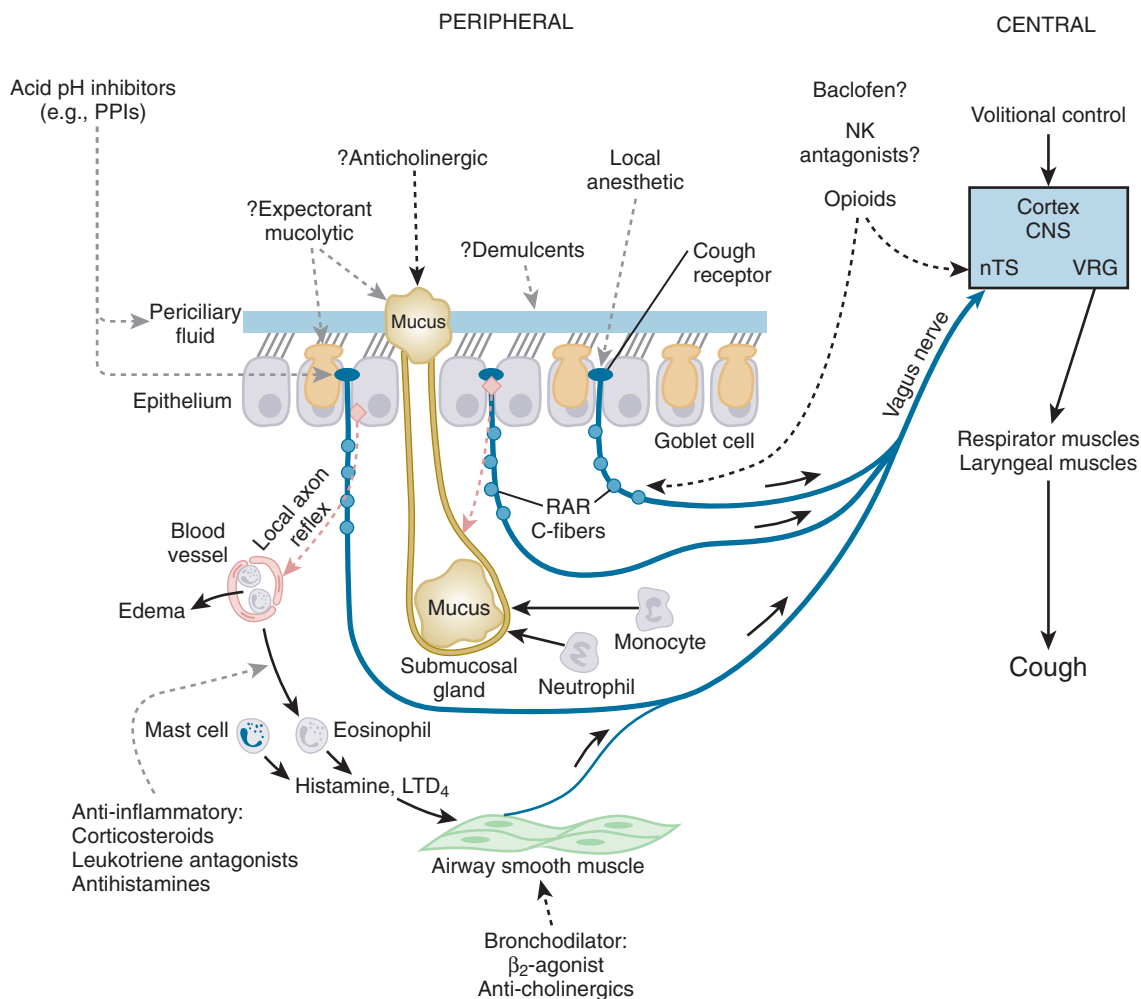


Figure 30-7 Afferent pathways of the cough reflex and some potential sites of action of direct and indirect antitussive therapies. Drugs may be divided according to their peripheral effects on airways or their central effects in the central nervous system (CNS). LTD₄, leukotriene D₄; NK, neurokinin; nTS, nucleus tractus solitarius; PPI, proton pump inhibitor; RAR, rapidly adapting receptors; VRG, ventral respiratory group. (Redrawn and modified from Chung KF: Management of cough. In Chung KF, Widdicombe JG, Boushey HA, editors: Cough: causes, mechanisms and therapy. Oxford, 2003, Blackwell, pp 283–297.)

distressing cough that cannot be relieved by other less potent antitussives and are therefore usually confined to patients with terminal illness such as bronchial carcinoma.¹⁴⁹ Slow-release morphine has been shown to be partially effective in controlling severe chronic cough without altering the cough reflex response.¹⁵⁵ These opioids also relieve anxiety and pain. They cause sedation, respiratory depression, and constipation. Opioids can exacerbate wheezing through the release of histamine, but this is rare. Diamorphine may be preferred to morphine because of its lower incidence of nausea and vomiting.

Dextromethorphan is a non-narcotic antitussive, a synthetic derivative of morphine with no analgesic or sedative properties, and is usually included as a constituent of many compound cough preparations sold over the counter. It is as effective as codeine in suppressing acute and chronic cough when given orally,^{152a,156,157} with one study showing its superiority over codeine.¹⁵⁸ Antitussive efficacy of a single 30-mg dose has been demonstrated against cough associated with upper respiratory tract infections in adults.⁸² However, in children, dextromethorphan has been shown to be ineffective in cough due to upper respiratory tract

infections.^{85,86} It is commonly used as a constituent of many compound cough preparations that are sold over the counter. Side effects are few at the usual dose but, at higher doses, dizziness, nausea, vomiting, and headaches may be reported. It should be avoided in patients with hepatic insufficiency because metabolic degradation takes place in the liver. The American Academy of Pediatrics has highlighted the potential adverse effects and overdosage associated with antitussive preparations containing dextromethorphan in children,⁸⁷ where it is not effective in cough due to upper respiratory tract infections.^{85,86} Dextromethorphan should be used with caution in patients on monoamine oxidase inhibitors in whom central nervous depression and death has been reported.

Other non-narcotic preparations include noscapine and levopropoxyphene, although their antitussive efficacy has not been proved. Levodropropizine, a nonopioid antitussive with peripheral inhibition of sensory cough receptors, has a favorable benefit/risk profile compared with dextromethorphan.^{152a,159} Other drugs acting on cough receptors include benzonatate, which inhibits vagal stretch lung receptors, with a possible central effect.

OTHER NON-NARCOTIC ANTITUSSIVES

Amitriptyline and gabapentin have been used as antitussives. A prospective, randomized, controlled open trial comparing the effectiveness of amitriptyline versus codeine/guaifenesin for chronic cough following an upper respiratory tract infection showed that amitriptyline led to a complete response of the cough in most subjects while none of the codeine/guaifenesin group had a complete response.¹⁶⁰ Gabapentin was effective in reducing cough in chronic cough patients in a randomized double-blind trial, suggesting that there is a central reflex sensitization in refractory chronic cough.¹⁶¹ Both amitriptyline and gabapentin have central antinociceptive actions, and both have been used successfully in the treatment of neuropathic pain. Gabapentin may reduce pain via an action on gamma-aminobutyric acid neurotransmission or voltage-gated ion channels in the spinal cord, midbrain, thalamus, and insular cortices in the brain. The success of these agents in controlling chronic cough may indicate that chronic cough is a neuropathic condition.⁵⁵

LOCAL ANESTHETICS

Lidocaine aerosol inhaled from a nebulizer has been administered to cases of intractable cough with variable results and should be reserved for selective individual cases.¹⁶² It works by inhibiting sensory neural activity but also removes reflexes that protect the lung from noxious substances. Its effects are transient and should be avoided in patients with asthma or a past history of asthma because they can induce severe bronchoconstriction. There have been no controlled trials of local anesthetics, but their efficacy in controlling cough is not ideal because of their short duration of effect. A retrospective analysis suggests that nebulized lidocaine may be a safe option and that a 2-week trial may identify those patients who will derive most therapeutic benefit.¹⁶³

EXPECTORANTS AND MUCOLYTICS

Expectorants and mucolytics may alter the volume of secretions or their composition. Despite the lack of proof, mucolytic agents such as acetylcysteine, carbocysteine, bromhexine, and methylcysteine are often used to facilitate expectoration by reducing sputum viscosity in patients with chronic bronchitis. A small reduction in the exacerbation of bronchitis has been reported with oral acetylcysteine, accompanied by small improvement in cough, a decrease in volume of sputum, and some ease of expectoration. Aromatic agents such as eucalyptus and menthol have decongestant effects in the nose and can be useful in short-term relief of cough. Menthol inhibits capsaicin-induced cough in normal volunteers¹⁶⁴ and acts on a cold-sensitive receptor. Demulcents also form an important component of many proprietary cough preparations and may be useful because the thick sugary preparation may act as a protective layer on the mucosal surface.

POTENTIAL NEW ANTITUSSIVES

New cough suppressants in development include new opioids or blockers of ion channels on vagal afferent

endings,¹⁶⁵ but as yet few have been tested in humans. An orally active selective NOP1 (*nociceptin opioid 1*) receptor agonist was tested in subacute cough with no significant subjective or objective efficacy compared with placebo.¹⁶⁶ Preclinical studies have identified TRP channels as an exciting target for cough suppression. TRPV1 agonists are potent inducers of cough,¹⁶⁷ and patients with chronic cough have increased TRPV1-positive nerve fibers in their airways. TRPV1 antagonists are currently being developed for control of pain, and several compounds have been examined in man.¹⁶⁸ However, early trials with TRPV1 blockers in cough patients have been disappointingly negative.^{168a} Hyperthermia and noxious heat sensation are among the adverse effects of these TRPV1 antagonists, which has limited their use. Agonists acting at TRPA1, such as cinnamaldehyde, acrolein, and allyl isothiocyanate (aka mustard oil), can also cause cough, including in humans,¹⁶⁹ and TRPA1 antagonists are currently being tested in cough. Voltage-gated sodium channels are channels that initiate and conduct action potentials. Lidocaine is a nonselective blocker of this family of sodium channels. The NaV1.7 subunit has been found to be specifically involved in the control of cough responses to citric acid in guinea pigs,¹⁷⁰ but as yet there are no specific blockers of NaV1.7. Memantine, the uncompetitive NMDA channel blocker developed for use in Alzheimer disease, inhibits cough in guinea pigs¹⁷¹ and is currently being tested in humans.

Key Points

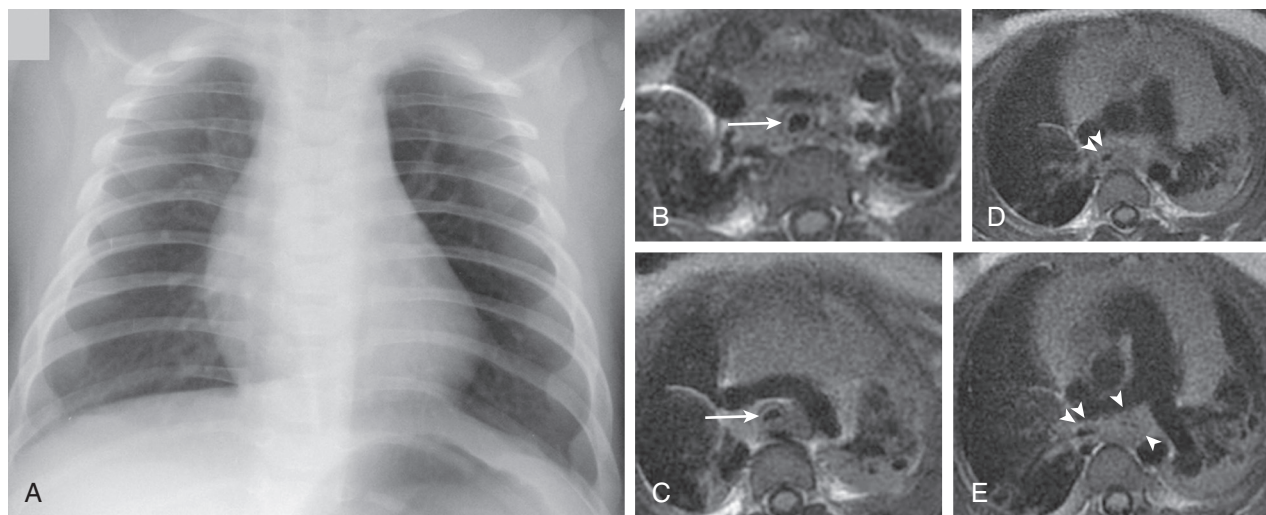
- Cough may be a sign of disease in or outside the airways and lungs and a useful indicator for both patient and physician for initiating a diagnostic evaluation and treatment of disease processes.
- Impairment or absence of coughing can be harmful or even fatal in disease. On the other hand, when cough itself is persistent and excessive, it can also be harmful and deleterious and may need to be suppressed directly.
- The most sensitive sites for initiating cough are the larynx and tracheobronchial tree.
- In the management of a patient with cough, the first step is to identify the cause(s) of the cough and then treat the cause(s).
- Postnasal drip, asthma, and gastroesophageal reflux are the three most common conditions associated with a chronic cough, and a diagnostic approach to exclude these conditions early on is sensible.
- Many cigarette smokers have a chronic cough, but a change in the pattern or characteristics of their cough, such as an increase in intensity or an accompanying hemoptysis, should force a smoker to seek medical attention. A chest radiograph is mandatory in this situation.
- Patients with chronic cough while on angiotensin-converting enzyme inhibitor therapy should discontinue such therapy, with replacement by other appropriate treatments.
- When the treatment of the cause of cough is not effective, therapies directed at eliminating the symptom of cough irrespective of the cause of the cough may be tried (see Table 30-4).

Complete reference list available at *ExpertConsult*.

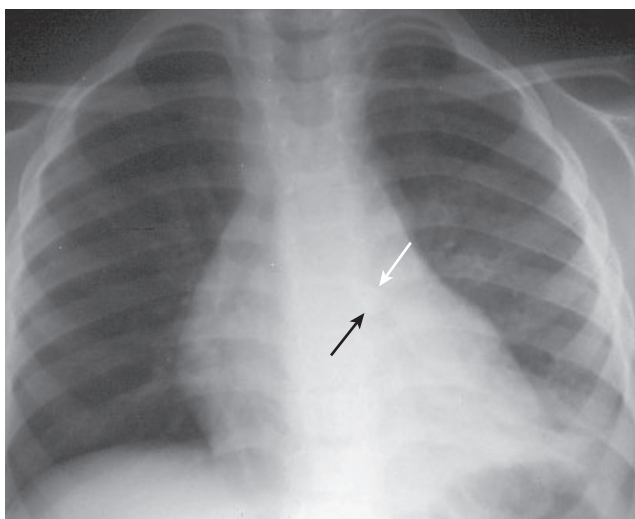
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eFIGURE IMAGE GALLERY



eFigure 30-1 **A**, Frontal chest radiograph in a pediatric patient with tracheobronchial malacia and cough shows diffusely decreased left lung attenuation compared with the right lung, suggesting diffuse air trapping. **B–E**, Axial thoracic double inversion recovery T1-weighted MR images show a circumferentially thickened tracheal wall (*arrows*, **B** and **C**) with a thickened and narrowed right mainstem bronchus (*double arrowheads*, **D** and **E**). The left mainstem bronchus (between *single arrowheads*, **E**) is severely thickened and narrowed, which resulted in the diffuse left lung air trapping seen in **A**. (Courtesy Michael Gotway, MD.)



eFigure 30-2 Frontal chest radiograph in a pediatric patient with unexplained cough shows an aspirated tooth (*arrow*) in the left mainstem bronchus. (Courtesy Michael Gotway, MD.)

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INTRODUCTION**EPIDEMIOLOGY****NEUROBIOLOGY OF PAIN**

Somatic Pain

Visceral Pain

HYPERALGESIA**MEASURING PAIN****CHEST PAIN SYNDROMES**

Pleuropulmonary Disorders

Tracheobronchitis

Inflammation or Trauma of the Chest

Wall

Cardiovascular Disorders

NONCARDIAC CHEST PAIN

Musculoskeletal Disorders

Gastrointestinal Disorders

Psychological Factors

Miscellaneous Causes of Chest Pain

EVALUATION AND TREATMENT OF CHEST PAIN

Cardiac Ischemia

Pulmonary Embolism

Pericardial Disease

Cardiac Tamponade

Pulmonary Arterial Hypertension

Thoracic Aortic Dissection

Pneumothorax

Tension Pneumothorax

Pancoast Tumors

Chest Trauma

Gastroesophageal Reflux

Pancreatitis

INTRODUCTION

Pain is a complex subjective experience that varies from person to person in its quality, intensity, duration, location, frequency, and associated features. Its perception is influenced by a subject's culture, emotional and cognitive contributions, socioeconomic status, familial background, prevailing psychological factors, anticipation and previous experience, and the clinical context.

Chest pain is characterized by an unpleasant sensation that is either localized to the thorax or believed to originate from structures located there. It may announce the presence of severe, occasionally life-threatening, disease. Diagnosis of chest pain is often complicated by the vague presentations and indistinct anatomic localization of many of its causes.

EPIDEMIOLOGY

There are uncertainties about the exact prevalence of chest pain. In a study of 500 randomly selected households in Burlington, Canada, 16% of 827 respondents reported experiencing pain within the 2 weeks preceding the survey.¹ Persistent pain was approximately twice as common as temporary pain, and chest pain was the fifth most common type of temporary pain. In studies of acute pain that was sufficient to warrant medical attention, chest pain is always an important factor.

A survey of 1016 randomly selected enrollees of a health care plan in Seattle, Washington, revealed that they reported a high incidence of pain lasting a whole day or more several times during the previous 6 months²; the most common complaint was back pain, followed by headache, abdominal pain, facial pain, and chest pain. Chest pain accounted for 12% of the reported cases but was the most common site of pain that prompted respondents (35%) to seek medical attention. Pain is also a common reason for persons to visit hospital emergency departments. In a survey of 36,271 random evaluations, stomach pain, other abdominal pain,

and chest pain were the most often cited reasons; they presented with almost equal frequency and, together, accounted for 10.7% of all emergency department visits.³

NEUROBIOLOGY OF PAIN

Pain is not a simple sensation. The neurobiologic and functional components of the sensory channels for pain are neither fixed nor immutable. The nervous system, from the level of the nociceptor (the receptor that responds to noxious stimuli) to the supraspinal sites of integration, is characterized by its dynamic response (plasticity) to tissue insult.

Pain arising from *visceral* organs (e.g., heart or gastrointestinal tract) differs in many ways from that arising from *somatic* structures, such as the skin. Visceral pain is difficult to localize, is diffuse in character, and is typically referred to somatic structures. In addition, it is often associated with greater autonomic and motor responses than is somatic pain. These differences between visceral and somatic pain are associated with characteristic features of sensory innervations that are unique to the viscera.

SOMATIC PAIN

Somatic structures, such as the skin, are invested with a wide variety of nociceptors, each with selective sensitivities to mechanical, thermal, or chemical stimuli, in addition to the polymodal nociceptor that responds to multiple modalities of noxious stimuli.^{4,5} Cutaneous nociceptors are characterized by very infrequent or no spontaneous discharges, an ability to encode stimulus intensities in the noxious (but not innocuous) range, and most importantly, sensitization. *Sensitization* refers to an increase in the magnitude of response after tissue insult, sometimes associated with an increase in spontaneous activity as well as a decrease in response threshold. This attribute of nociceptors contributes to development of hyperalgesia, or an increased response to a stimulus that is normally painful.

When a tissue is injured, a host of sensitizing chemicals are synthesized at the site of injury or released from circulating cells that are attracted to the site of injury. These include amines (e.g., histamine and serotonin), peptides (e.g., substance P and calcitonin gene—related peptide), kinins (e.g., bradykinin), neurotrophins, cytokines, prostaglandins, leukotrienes, excitatory amino acids (e.g., glutamate), and free radicals. However, it is unlikely that any one putative chemical mediator is responsible for nociceptor sensitization. Although substance P, for example, is contained in most nociceptor cell bodies, it is also present in a significant number of non-nociceptor cell bodies. Similarly, other neuropeptides, such as calcitonin gene—related peptide, somatostatin, and galanin, are found more commonly in small- to intermediate-sized dorsal root ganglion cell bodies.

VISCERAL PAIN

Input to the central nervous system from aortic baroreceptors, gastric chemoreceptors, and pulmonary stretch receptors is rarely perceived. Nevertheless, it is evident that visceral afferents possess many of the characteristics of nociceptors.

All viscera possess a dual innervation. Organs of the thoracic cavity are innervated by vagal afferent fibers with cell bodies in the nodose and jugular ganglia as well as by spinal afferent fibers with cell bodies in thoracic dorsal root ganglia. Unlike their somatic counterpart, spinal visceral afferent fibers typically traverse either or both prevertebral and paravertebral ganglia en route to the spinal cord. Thus, in contrast to somatic input to the central nervous system, which has a single, usually spinal, destination, input to the central nervous system from organs in the thoracic cavity arrives at two locations, namely the brain-stem nucleus tractus solitarius (vagal afferent input) and the thoracic spinal cord. Accordingly, the potential exists for interaction in the central nervous system of inputs from the same thoracic organ. The esophagus and heart also possess an intrinsic nervous system with cell bodies in the organ wall or in ganglia in the epicardial fat.⁶

Further differences between somatic and visceral innervation relate to the density of innervation and spinal pattern of termination. In general, the number of visceral afferent fibers is disproportionately less than the number of somatic afferent fibers, although the rostrocaudal spread of visceral afferent fiber terminals in the spinal cord is considerably greater than the spread of central terminals from somatic afferent fibers. Although this means that there are fewer central visceral terminals in the spinal cord, visceral afferent fiber terminals have many more terminal swellings (suggestive of synapses) than somatic nociceptor terminals and they spread over several spinal cord segments.⁷ The obvious consequence of the low number of visceral afferents and greater intraspinal spread is loss of spatial discrimination, consistent with the diffuse, difficult-to-localize, nature of visceral pain.

The axons of visceral sensory neurons are, with rare exception, either thin, myelinated A δ fibers or unmyelinated C fibers. In general, A δ fibers, having some myelin, carry moderately fast impulses, usually of acute or sharp pain but also temperature. C fibers, without myelin, carry

slow impulses, usually of burning pain. Generally the proportion of A δ fibers in visceral sensory nerves is less than the proportion of C fibers. In addition, A δ fibers are fibers with a low threshold for response to mechanical stimulation, whereas C fibers have high thresholds; however, this is not universal.

Unlike tissue-damaging stimuli that produce pain in somatic structures, tissue injury is not required for production of pain in the viscera. For the lower airways, irritants contained in smoke, ammonia, and other inhaled substances are capable of producing discomfort and pain. For the heart and mesentery, ischemia can be an adequate stimulus.⁸ For hollow organs of the gastrointestinal tract, distention of the lumen of the organ, which activates stretch and tension receptors in the smooth muscles, is typically adequate.

Hollow viscera, including the esophagus, are innervated by two populations of mechanosensitive afferent fibers, namely a larger group (70% to 80%) of fibers that have low thresholds for response (i.e., within the physiologic range), and a smaller group (20% to 30%) of fibers that have thresholds for response that fall in the noxious range.⁹ All mechanosensitive visceral afferent fibers may function in some circumstances as nociceptors, and low- and high-threshold mechanosensitive fibers contribute to discomfort and pain that arise from the viscera.

Silent nociceptors, a relatively new category of receptor/afferent fibers, may also contribute to altered sensations from visceral structures.¹⁰ Silent nociceptors, more appropriately termed “mechanically insensitive afferents” have no spontaneous activity and do not respond to acute, high-intensity mechanical stimulation in normal circumstances. After tissue insult, mechanically insensitive afferents typically begin to discharge spontaneously and acquire sensitivity to mechanical stimulation. However, the contribution of such “silent” or “sleeping” afferent fibers to altered sensations that arise from the viscera is uncertain at present.^{11,12}

HYPERALGESIA

Some individuals are uniformly more sensitive (i.e., have lowered thresholds for stimulus-produced pain) than others. *Hyperalgesia*, the enhanced response to a stimulus that is normally noxious, consists of primary and secondary components. *Primary hyperalgesia* refers to enhanced sensitivity to stimuli applied at the site of tissue injury (e.g., an incision). *Secondary hyperalgesia*, conversely, pertains to enhanced sensitivity to stimuli applied to uninjured tissue adjacent to and occasionally distant from the site of injury. Peripheral mechanisms (sensitization of nociceptors and afferent fibers innervating the insulted tissue) and central mechanisms (changes in the excitability of spinal and supraspinal neurons) contribute to primary and secondary hyperalgesia, respectively. Afferent fibers that innervate the pelvic viscera have been shown to sensitize when organs are experimentally inflamed. After inflammation, both low-threshold and high-threshold mechanosensitive afferent fibers in the pelvic nerve exhibit exaggerated responses to distention relative to responses of the same afferent fibers before inflammation. This change in neuron excitability is believed to arise principally through the action of

glutamate at the *N*-methyl-D-aspartate receptor. Contributions of non-*N*-methyl-D-aspartate receptors, AMPA or kainate, and of the receptor at which substance P acts (neurokinin 1 receptor) are also likely.¹³ Glutamate and substance P are co-contained in many small-diameter dorsal root ganglion cells and presumably are concurrently released in the spinal dorsal horn, where *N*-methyl-D-aspartate receptors on nociceptor terminals may act as autoreceptors to facilitate the further release of both glutamate and substance P.¹⁴ In addition, there is evidence that substance P can act synergistically with glutamate to enhance the responses of spinal neurons.¹⁵

Virtually all spinal cord neurons that receive a visceral input also receive input from somatic structures, including the skin, muscle, and joints. This convergence of inputs in the spinal dorsal horn includes both viscerosomatic and viscerovisceral pathways and is believed to be the basis of the referred sensation that characterizes visceral pain. Such convergence suggests that injury to somatic tissue could lead to visceral hyperalgesia and, conversely, that injury to a viscus could lead to somatic hyperalgesia.

Spinal nociceptive transmission can be modulated by electrical or chemical stimulation in the midbrain or medulla.¹⁶ Both facilitatory and inhibitory influences on spinal nociceptive transmission are present and likely play an important role in the maintenance of secondary hyperalgesia.¹⁷ Electrical activation of vagal afferent fibers similarly engages descending facilitatory and inhibitory modulation of spinal nociceptive transmission. Responses of neurons in the thoracic dorsal horn to either esophageal distention¹⁸ or lower airway irritation caused by ammonia or smoke¹⁹ are altered when the cervical spinal cord is blocked or transected or when the vagi are cut. Responses to esophageal or respiratory stimulation would be expected to increase when the cervical spinal cord was blocked because tonic descending inhibitory influences are usually present; unexpectedly, responses were more commonly reduced, suggesting the presence of a descending facilitatory influence that is associated with vagal input to the brain stem. In a related work, both vagal afferent input and spinal cardiac nerve afferent inputs contribute to the sensation of cardiac pain, particularly referral of such pain to the neck and jaw.²⁰

MEASURING PAIN

Pain has proved to be both hard to define and difficult to measure. Because pain can be quantified only indirectly, it has been difficult to determine the optimal measuring tool for all types of pain sensations. Two widely used techniques, namely rating scales and questionnaires, are often used in clinical and epidemiologic studies of chest pain.

Rating scales constitute the simplest measurement of pain. One of the easiest to use is the quantification of pain intensity by a graded rating scale, such as the popular visual analogue scale.²¹ However, the sensation of pain has many more components than just its intensity; thus a single-dimensional rating scale leaves many aspects of the sensation undocumented.

To address the multidimensional qualities of pain, questionnaires have been developed.²² The McGill Pain Ques-

tionnaire, the most widely used method in the English language for studying the epidemiology of pain, was developed in the 1970s²³ and has been shown to be reliable and useful.²⁴ Although questionnaires are a powerful way of obtaining data on both the qualitative and the quantitative aspects of pain, it is not always possible to compare the results of studies with the same questionnaire because of differences in the way they have been employed.

CHEST PAIN SYNDROMES

Pain arising from the various viscera in the thoracic cavity and from the chest wall is often qualitatively similar and exhibits overlapping patterns of referral, localization, and quality, given the proximity of the various organs and the vagaries of perception of pain of visceral origin. This leads to difficulty in the differential diagnosis of chest pain (Table 31-1). Nevertheless, many chest pain syndromes are sufficiently distinctive clinically that diagnostic efforts often rely on accurate description of the characteristic pattern of pain. The importance of the medical history in unraveling the various causes of chest pain cannot be overemphasized. The locations to which various pain syndromes are referred in the chest are illustrated in Figure 31-1.

PLEUROPULMONARY DISORDERS

Although the lung parenchyma and visceral pleura are considered to be insensitive to ordinary noxious stimuli, immunohistochemical studies from vagal denervation and talc-pleurodesis animal models indicate the presence of nerve fibers in the visceral pleura that may be capable of conducting pain stimuli.^{25,26} Pain does arise from stimulation of the mucosa of the trachea and main bronchi.²⁵ The lungs and bronchi are innervated with mechanoreceptors that respond to stretch (inflation or deflation of the lungs) as well as chemoreceptors called J receptors that respond to a variety of pain-inducing chemicals, including bradykinin, prostaglandins, serotonin, and capsaicin.^{27,28} Inhalation of irritant substances, such as ammonia, can trigger a cough reflex and can produce a sense of rawness, tightness in the chest, and pain. In addition, rapidly adapting mechanoreceptors that respond to lung deflation are also "irritant receptors" and signal respiratory pain. J receptors have been proposed to contribute to discomfort and pain that accompanies breathlessness.²⁷⁻²⁹

These receptors are, in turn, innervated by vagal and spinal splanchnic afferent fibers. Nerve fibers that travel in the vagus nerves, including myelinated axons that carry impulses from slowly adapting stretch receptors in the conducting airways, myelinated axons that lead from rapidly adapting irritant cough receptors in the trachea and bronchi, and unmyelinated axons that subserve the extensive network of C fiber receptors (e.g., "pulmonary" J receptors and "bronchial" C fibers), are most important.³⁰

The pulmonary causes of chest pain may be related to the pleural tissue, pulmonary vessels, or lung parenchyma. Causes of chest pain related to the lung parenchyma include infection, cancer, or chronic diseases such as sarcoidosis. These are discussed in more detail elsewhere in the textbook.

Table 31-1 Common Causes of Chest Pain

PLEUROPULMONARY DISORDERS

Pleurisy
Infection
Pulmonary embolism
Spontaneous pneumothorax
Collagen vascular disease
Sickle cell disease
Familial Mediterranean fever
Malignancy (e.g., mesothelioma)
Pulmonary hypertension
Pulmonary embolism
Primary pulmonary hypertension
Eisenmenger syndrome

TRACHEOBRONCHITIS

Infection
Inhalation of irritants
Malignancy

INFLAMMATION OR TRAUMA OF THE CHEST WALL

Rib fracture
Muscle injury (myalgia)
Infection
Malignancy
Sickle cell disease
Neuritis-radiculitis
Herpes zoster infection

CARDIOVASCULAR DISORDERS

Angina pectoris
Variant angina
Myocardial infarction
Aortic valve disease
Mitral valve prolapse
Hypertrophic cardiomyopathy
Pericarditis
Cocaine toxicity

DISORDERS OF THE AORTA

Aortic dissection

GASTROINTESTINAL DISORDERS

Reflux esophagitis
Esophageal motility disorders
Cholecystitis
Peptic ulcer disease
Pancreatitis
Disorders of intestinal motility

MISCELLANEOUS CAUSES OF CHEST PAIN

Thoracic outlet obstruction
Mediastinal emphysema
Iatrogenic

Pleurisy

Pleurisy results from inflammation of the parietal pleura. Inflammatory processes in the periphery of the lung that involve the overlying visceral pleura (e.g., pneumonia) frequently cause inflammation of the adjacent parietal pleura that, in turn, provokes pleuritic pain conveyed by somatic nerves. The parietal pleura that lines the interior of the rib cage and covers the outer portion of each hemidiaphragm is innervated by the neighboring intercostal nerves; when pain fibers in these regions are stimulated, pleuritic pain is localized to the cutaneous distributions of the involved neurons over the chest wall. In contrast, the parietal pleura that lines the central region of each hemidiaphragm is innervated by fibers that travel with the phrenic nerves; when this portion of the diaphragm is stimulated (e.g., by

contiguous inflammation), the resulting pain is referred to the ipsilateral shoulder or neck. This pain referral likely arises because visceral afferent input carried by the phrenic nerve converges with somatic input carried by the supraclavicular nerves that innervate the skin of the shoulder onto C3-5 spinal dorsal horn neurons (i.e., viscerosomatic convergence, a common feature of visceral pain leading to referred sensations). Thus, when this portion of the diaphragm is stimulated (e.g., by contiguous inflammation), the resulting pain is referred to the ipsilateral shoulder or neck.

Because of the somatic innervation of the parietal pleura, as well as the localization of most diseases of the lungs or chest wall to one hemithorax or the other, pleuritic pain tends to be limited to the affected region rather than be diffuse, with the exception of referral to the ipsilateral neck or shoulder. Pain may be variously described as “sharp,” “dull,” “achy,” “burning,” or simply a “catch.” There is a distinctive and unmistakable relationship to breathing movements, and taking a deep breath typically aggravates pleuritic pain.³¹ Coughing and sneezing can cause intense distress. Movements of the trunk, such as bending, stooping, or turning in bed, worsen pleuritic pain, so much so that patients often prefer the body position in which motion of the affected region is least.

An immediate onset of pleuritic pain suggests traumatic injuries or spontaneous pneumothorax. A sudden onset, often associated with dyspnea and tachypnea, also characterizes the clinical presentation of pulmonary embolism.³² A slower but still acute onset over minutes to a few hours often heralds the development of community-acquired bacterial (typically pneumococcal) pneumonia, especially when accompanied by fever and chills. Recurrent acute pleuritic pain is a feature of familial Mediterranean fever.³³ Finally, a gradual onset over days or weeks, often associated with features of chronic illness, such as low-grade fever, weakness, and weight loss, suggests tuberculosis or malignancy.

Pulmonary Hypertension

Persons with pulmonary hypertension may experience crushing or constricting substernal pain that at times radiates to the neck or arms, thus resembling the pain of myocardial ischemia.³⁴ Pain from pulmonary hypertension has been reported in patients with conditions that are acute (e.g., multiple or massive pulmonary emboli) and chronic (e.g., Eisenmenger syndrome, pulmonary vasculitis, or mitral stenosis). In addition, approximately half of the patients with primary pulmonary hypertension may have precordial chest pain.³⁵

In acute pulmonary hypertension resulting from massive pulmonary embolism, the pain may be caused by sudden distention of the main pulmonary artery and stimulation of mechanoreceptors.

In primary pulmonary hypertension, chest pain may be related to either (1) right ventricular ischemia because coronary blood flow is unable to meet the metabolic needs of the overloaded right ventricular muscle mass as the latter strives to maintain sufficient systolic and diastolic pulmonary arterial pressures³⁶ or (2) compression of the left main coronary artery by the dilated pulmonary artery trunk.³⁷

Although precordial pain related to the sudden onset of pulmonary hypertension can develop in cases of acute

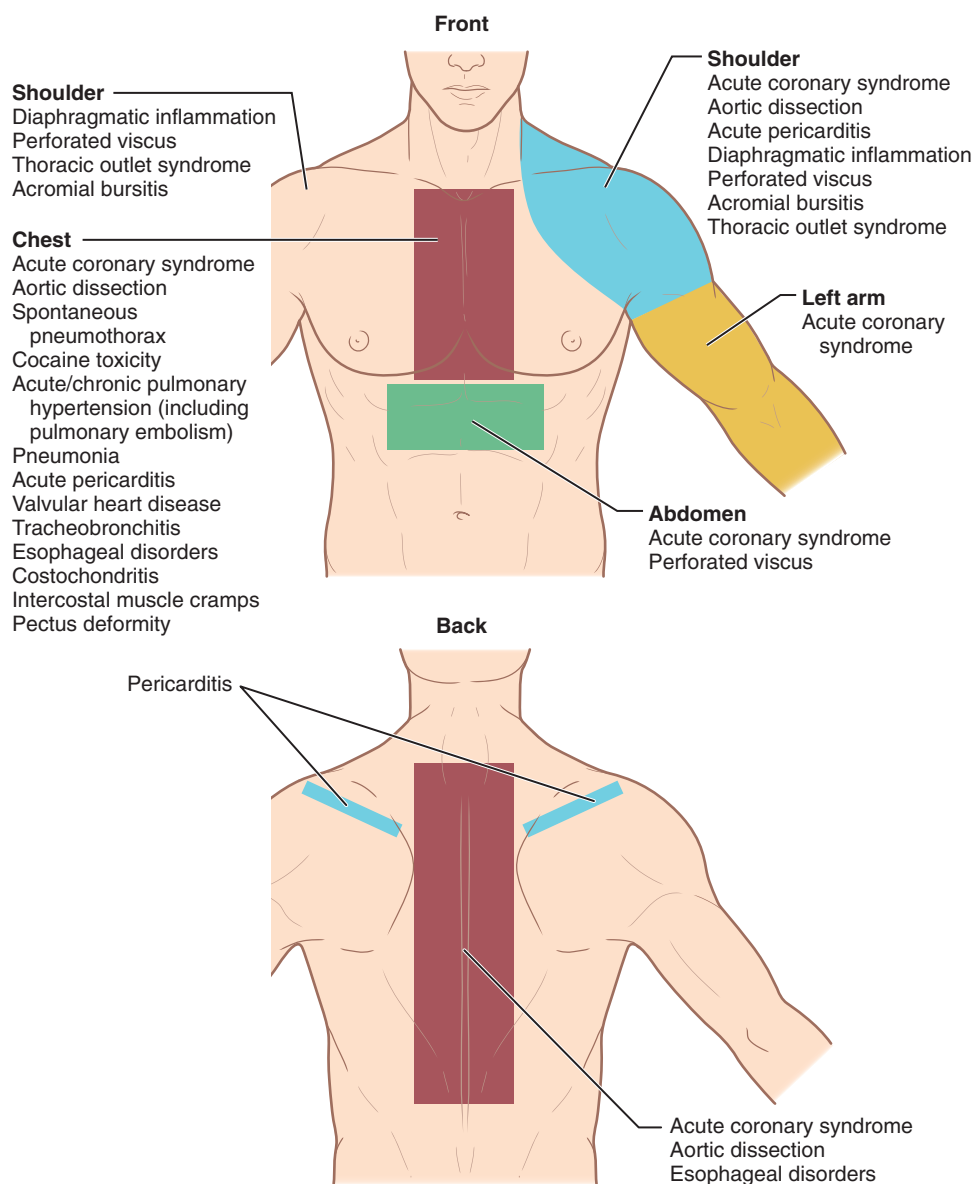


Figure 31-1 Sites of referred pain in the chest. Some conditions are shown that should be considered as sources of referred pain in certain locations of the chest. Potential sources are listed in order of severity. Referred pain is generally due to viscerosomatic convergence, in which spinal cord neurons receive input from both visceral and somatic sources so that visceral pain can be interpreted as coming from a somatic source. Not shown are psychological causes of pain, which may constitute one of the most common entities, although it should remain a diagnosis only after considering and excluding these sources of pain.

pulmonary embolism, embolism-associated pain is much more likely to be pleuritic in character, whether or not there is pulmonary infarction.³⁸

Pulmonary artery stenosis may also cause substernal pain, presumably by the same pressure-overload mechanism through which pulmonary hypertension with right ventricular hypertrophy provokes pain.³⁹

TRACHEOBRONCHITIS

Pain of tracheal origin is generally felt in the midline, anteriorly, from the larynx to the xiphoid. Conversely, pain from either main bronchus is felt in the ipsilateral anterior chest near the sternum or in the anterior neck near the midline.⁴⁰ Whatever its origin, pain related to tracheobronchitis is typically described as “raw” or “burning” but may be “dull”

or “achy,” and exaggerated by deep breathing. This type of discomfort usually denotes the presence of viral or bacterial tracheobronchitis or, less often, a malignancy but can also be experienced during exposure to noxious gases. Tracheobronchial pain is thought to be mediated by bronchial C fibers. Experimentally induced tracheal pain can be abolished by vagal blockade⁴¹ or by vagotomy.⁴²

INFLAMMATION OR TRAUMA OF THE CHEST WALL (see Chapter 98)

Inflammation of, or trauma to, the joints, muscles, cartilages, bones, and fasciae that constitute the thoracic cage can cause chest pain.⁴³⁻⁴⁵ Fibromyalgia, fibrositis, and other rheumatologic disorders of the thoracic cage, such as ankylosing spondylitis, are known to cause pain and discomfort

in the chest.⁴⁶ Acute or chronic inflammation of the xiphoid process (xiphodynia)⁴⁷ and superficial thrombophlebitis of the chest wall (Mondor syndrome)⁴⁸ may also be uncommon sources of chest pain. Occasionally pain related to respiration may be experienced along the costal margins after vigorous exercise.⁴⁹ In addition, metastatic malignancy may present as painful lesions of the chest wall, sometimes with spontaneous rib fractures. Another confusing source of chest pain is infectious arthritis of the sternoclavicular joint or costochondral junctions, which is an increasing problem among injection drug users.⁵⁰

With *costochondritis*, chest wall pain arises from the costochondral cartilaginous junctions. It is usually described as “dull with a gnawing, aching quality.” There is little, if any, relationship to respiratory or other body movements. Tenderness to palpation is clearly localized to one or more of the costal cartilages.⁵¹ There may be redness, swelling, and enlargement of the costal cartilages (Tietze syndrome). The most common sites of costosternal perichondritis are the second, third, and fourth cartilages, but any part of the large cartilaginous shield along the central and lower portions of the anterior thoracic cage may be involved.

The pain of *intercostal neuritis* or *radiculitis*, which often originates from disorders of the cervicodorsal spine or nerve roots, is usually perceived in the rib cage. The superficial, spontaneous lancinating or electric shock–like pain of intercostal neuritis is typically felt over the cutaneous distribution of the involved nerves and may be worsened by taking deep breaths, coughing, and sneezing. Unlike pleurisy, neuritic pain is usually not aggravated by ordinary breathing; the diagnosis is supported by the presence of hyperalgesia or anesthesia on examination of the skin. In some patients with neuritis/radiculitis, the diagnosis becomes evident 2 or 3 days later with the development of the characteristic vesicular rash of herpes zoster over the involved dermatome. Painful radiculitis is also recognized as an important early manifestation of Lyme disease.⁵²

Injuries to the ribs (fracture) and thoracic cage muscles (strain, tears, or hematoma) are common causes of localized chest pain. The relationship of the pain to trauma is obvious in most instances, but diagnosis may be elusive, particularly if the inciting event is relatively minor (e.g., unnoticed episode of coughing) or when the onset of pain is delayed.

CARDIOVASCULAR DISORDERS

Mechanosensitive and chemosensitive afferent fibers are present in the myocardium.^{27,53} Chemical stimuli are believed to be the most important causes of cardiac pain, but mechanical distention or distortion may also play a role.⁵⁴ Sensory fibers travel from the heart to the spinal cord through the several cardiac nerves, the upper five thoracic sympathetic ganglia, and finally, the upper five thoracic dorsal roots; afferent fibers also reach the brain through the vagus nerves.⁵⁵ Cardiac pain is likely associated with activity in afferent fibers contained in the spinal afferent innervation of the heart.

Acute Coronary Syndrome

Acute coronary syndrome includes all conditions with myocardial ischemia caused by obstruction to coronary blood

flow. *Angina pectoris* due to myocardial ischemia is typically described as severe “pressure,” “squeezing,” or “constriction” with maximal intensity retrosternally or over the left parasternal border. Radiation to the neck, jaw, shoulder, or down the inner aspect of one or both arms may be present. It is usually induced by exercise but may be provoked by heavy meals, excitement, or extreme emotion. Pain tends to recur with repeated provocation, although its severity may vary. Pain usually subsides within 2 to 10 minutes with rest, and relief is accelerated by treatment with sublingual nitroglycerin.⁵⁶ A majority of patients with stable angina pectoris have significant reduction of at least one major coronary artery.⁵⁷ Prinzmetal or variant angina is similar in quality and location to typical angina pectoris but appears at rest rather than during exercise or increased myocardial oxygen needs.⁵⁸ In this syndrome the imbalance between myocardial oxygen supply and demand is postulated to arise from epicardial coronary artery vasospasm, usually superimposed on noncritical atheromatous vessel narrowing. Pain does not always accompany myocardial ischemia, and many electrocardiographically detectable episodes of ischemia in patients with stable angina pectoris are asymptomatic (“silent” ischemia).⁵⁹ Conversely, many individuals with angina-like chest pain have normal or nearly normal coronary arteries when studied by arteriography. As many as 30% of these noncoronary cases are classified as “syndrome X,”⁶⁰ with the development of chest pain attributed to either coronary microvascular spasm or heightened pain perception.^{60,61}

The pain of *acute myocardial infarction* is similar in location to that of angina pectoris but is typically much more severe in intensity, is not relieved by rest or nitroglycerin, often requires large doses of opiates for control, and is frequently associated with profuse sweating, nausea, dyspnea, and profound weakness.⁵⁶ During episodes of myocardial ischemia, the involved myocardium stiffens; when severe, this decrease in compliance may increase left ventricular end-diastolic filling pressure sufficiently to raise left atrial and pulmonary vascular pressures and cause pulmonary edema. Massive myocardial infarction may also lead to intractable hypotension and shock. Acute myocardial infarction may also be silent,⁶² especially in patients with diabetes mellitus.⁶³

Valvular Heart Disease

Chest pain can also arise from other *non-coronary artery disorders*, including mitral valve prolapse, myocarditis,⁵⁶ pericarditis, and hypertrophic cardiomyopathy.⁶⁴ It can also be related to cocaine use.

Patients with aortic stenosis may complain of angina-like pain on exertion. The frequency of chest pain is higher with aortic stenosis than with any other valvular heart disease and is found in two thirds of patients with severe disease.⁵⁶ Whenever a patient presents with progressive angina, dyspnea, or syncope, aortic stenosis should be considered. In contrast, patients with mitral stenosis or pulmonic stenosis infrequently experience chest pain.

Pericarditis

The pain of *pericarditis* is most commonly pleuritic and arises from spread of the inflammatory process across the pericardium to the adjacent parietal pleura. Typically pain

is worse in the recumbent position and while lying on the left side and is partially or completely relieved by sitting up, leaning forward, or lying on the right side. Occasionally, pericardial pain may be confused with anginal pain, but radiation to the arms is uncommon. Although there are few nociceptors in the pericardium, there appear to be nociceptors in the diaphragmatic portion of its parietal layer, which is innervated by sensory axons that travel in the phrenic nerves.⁶⁵ Stimulation of these fibers causes pain that may be sharp and steady and referred to the margins (ridge) of the trapezius muscles. Pain in this location is claimed to be specific for pericarditis because other diseases seldom cause discomfort in that area⁵⁶ (see Figure 31-1).

Pericardial friction rubs, presumably indicating underlying pericarditis, are more common than pericardial pain during the first few days after acute myocardial infarction and with worsening uremia.^{56,66} Other causes of pericarditis, usually associated with pericardial pain, are infections, often viral but also bacterial,⁶⁷ and connective tissue diseases (e.g., lupus erythematosus). Pericarditis, usually with fever, also can develop after open heart surgery (post-pericardiotomy syndrome) and after myocardial infarction (Dressler syndrome), both of which are considered to be autoimmune disorders.⁶⁸ Often, no diagnosis can be made, and pericarditis is considered idiopathic.

Cocaine Toxicity

Cocaine toxicity is associated with more visits to the emergency department for adverse reactions than any other illicit drug, and chief among the presenting complaints is chest pain.⁶⁹ Cocaine-associated chest pains typically begin approximately 60 minutes after injection or inhalation of the substance and last for 120 minutes.⁷⁰ The pain is most frequently substernal in location and pressure-like in character; it may be accompanied by shortness of breath and diaphoresis. Interestingly, clinical presentation may not differ among persons who develop myocardial infarction documented by biochemical markers and those who do not.

Cocaine-induced chest pain is undoubtedly provoked by the combined effects of an increase in myocardial oxygen demand owing to an increase in heart rate and in systolic and mean arterial pressures and a decrease in myocardial oxygen supply due to vasoconstriction of the epicardial coronary arteries.⁷¹

Despite the widespread use of cocaine and the frequent causal association (even among casual users) with chest pain, patients with chest pain who are seeking medical assistance are seldom queried about recent use of cocaine. Consequently, in the setting of cardiac symptoms, identification of cocaine exposure is a legitimate goal of cardiovascular history taking. In addition, this is an important question to ask because there is consensus that β -adrenergic blocking agents, which are indicated in acute coronary artery syndromes, may aggravate cocaine-induced myocardial ischemia by leaving the α -adrenergic system unopposed and potentially aggravating hypertension and coronary vasoconstriction. Thus, for cocaine-induced chest pain, nitroglycerin and calcium-channel blocking drugs (e.g., verapamil) constitute the treatments of choice. Cessation of cocaine use is essential for secondary prevention.

Disorders of the Aorta

Dissection of the aorta is usually associated with pain that is nearly always sudden and extremely severe at onset. Pain may be described, aptly, as “tearing” or “ripping” and often spreads widely, to the neck, throat, jaw, back, or abdomen, as the dissection extends from its point of origin.⁷² Frequent associated features are drenching sweats, nausea and vomiting, and light-headedness. Angina-like chest pain can also arise secondary to reduced coronary artery blood flow as a result of syphilitic aortitis or Takayasu vasculitis.

NONCARDIAC CHEST PAIN

The term *noncardiac chest pain* is used to describe an entity resembling angina. Noncardiac chest pain in the United States has an estimated annual incidence as high as 450,000 cases and causes considerable long-term morbidity as well as health care utilization. There are three main categories of extracardiac disease that cause angina-like chest pain: (1) musculoskeletal disorders of the chest wall, which may account for 10% to 20% of cases; (2) a variety of esophageal disorders, particularly gastroesophageal reflux, which may cause 30% to 40%; and (3) psychological factors, which may explain up to 50% of the total.

MUSCULOSKELETAL DISORDERS

Of the musculoskeletal causes of chest pain, the ones most commonly confused with angina are cervical neck disease, costochondritis, subacromial bursitis, intercostal muscle cramps, or congenital malformations such as pectus excavatum or carinatum. The best way to distinguish musculoskeletal pain from true angina is by reproduction of the pain with palpation or manipulation of the affected area. A history of recent trauma, chest infection, or cough can also support this diagnosis.

GASTROINTESTINAL DISORDERS

Receptors are present in the esophagus and may cause pain when activated by mechanical (spasm), chemical (acid reflux), or thermal (hot liquids) stimuli. Afferent nerves travel in both vagal and spinal (T3-T12) pathways.⁷³ Pain originating from the esophagus is usually referred to midline structures, such as the throat, neck, and sternal regions but may involve the arms as well. Stimulation of the distal end of the esophagus can cause pain directly over the heart.

Chest pain may arise either from esophageal reflux (the most common identifiable esophageal cause of chest pain) or from disorders of esophageal motility, such as diffuse esophageal spasm, achalasia, hyperactive lower esophageal sphincter, or nutcracker esophagus (a dysmotility disorder with high peristaltic pressures).^{74,75} Esophageal pain may mimic angina pectoris by its radiation to the neck and arms as well as relief by nitroglycerin.⁵⁶ Chest discomfort that lasts an hour or more, that leaves a residual dull achy discomfort, or that is associated with heartburn, odynophagia, or dysphagia should suggest pain of esophageal origin. Clinical history alone, however, cannot reliably distinguish pain originating from the esophagus from cardiac pain.

Lastly, other gastrointestinal disorders, such as cholecystitis, peptic ulcer disease, and acute pancreatitis, may present with pain that is perceived in the lower thorax.⁶⁵

PSYCHOLOGICAL FACTORS

Many patients experience chest pain for which no cause is ever found even after careful and thorough evaluation. Psychological factors clearly affect each person's interpretation of bodily sensations, and a psychiatric cause should be excluded in undiagnosed cases of chest pain.

An association between noncardiac chest pain and anxiety disorders, particularly panic disorder, has been reported. This is particularly well described in patients with mitral valve prolapse.⁷⁶ Patients with demonstrable heart disease may also have panic attacks. Alternatively, persons with chest pain may have psychological distress that is related to the panic syndrome and not the cardiac condition.

MISCELLANEOUS CAUSES OF CHEST PAIN

Obstructive lesions at the thoracic outlet may compress the brachial plexus and subclavian artery and can cause pain in the anterior chest and arms. *Thoracic outlet syndrome* is usually caused by compression of the neurovascular bundle by a cervical rib or a structural abnormality of the 1st rib or clavicle. Associated neuronal abnormalities have been described,⁷⁷ and electrophysiologic studies are useful not only to assist with the diagnosis but also to define which patients will respond to surgical decompression.⁷⁸ Chest pain may also arise from *iatrogenic causes*, such as pneumothorax following bronchoscopy or central venous catheter malposition.⁷⁹

EVALUATION AND TREATMENT OF CHEST PAIN

Given the wide variety of causes and seriousness of chest pain, considerable clinical judgment is required to decide which patients should be thoroughly evaluated and which tests should be used in the workup. In many instances, empirical therapy may need to be initiated even as evaluation proceeds, with subsequent readjustments in treatment protocols as more information is obtained that clarifies the clinical picture.

The evaluation of chest pain begins with a complete medical interview. The history may reveal nuances in the quality, location, duration, provoking events, and relieving measures, which serve to focus the subsequent evaluation. However, with few exceptions, such as evident injury to the chest wall, a specific diagnosis cannot be made with complete confidence from the clinical history alone. Physical examination may reveal evidence of pleural, lung parenchymal, or airway disease; localized chest wall involvement; or signs of mitral valve prolapse, aortic valve stenosis, or other cardiac abnormalities.

For adults who present to the emergency department with new-onset chest pain, the immediate concern is to identify and characterize potentially life-threatening

conditions, such as myocardial infarction, acute pulmonary embolism, or tension pneumothorax, requiring urgent management. Some diagnostic features are listed in [Table 31-2](#).

A standard 12-lead *electrocardiogram* (ECG), appropriate chest imaging, measurement of oxygen saturation and arterial blood gas levels, and blood chemistry profiles (e.g., troponin, D-dimer) often provide important data. In the appropriate clinical setting, some patients may require echocardiography or pulmonary function testing. Many other noninvasive or invasive tests are available for the evaluation of pain believed to be of respiratory, cardiac, or gastrointestinal origin. If the diagnosis remains uncertain, admission to chest pain observation units that offer a safe and effective means of care for patients with possible unstable angina who are considered to be at intermediate risk for cardiovascular events may be considered.

The most definitive treatment of chest pain, whatever its origin, is to find its cause and to cure it. The general principles of therapy for respiratory, cardiac, musculoskeletal, esophageal, and panic disorders are available, and the clinician is encouraged to refer to them. Chronic noncardiac chest pain is more difficult to manage, especially when its trigger cannot be found. Because of the complexities and difficulties in dealing with those few patients who have chronic, severe, and often refractory pain, referral to special pain centers staffed by a multidisciplinary team of specialists is recommended. At times, psychiatric consultation for specific treatment may be helpful.

CARDIAC ISCHEMIA

Initial evaluation of patients with suspected acute coronary syndrome including unstable angina or non-ST elevation myocardial infarction should always include a 12-lead ECG. Serial ECGs may be considered if the initial ECG is not diagnostic or if the patient is thought to have evolving myocardial ischemia or injury. Biomarker assessment for myocardial injury should include creatine kinase-MB, myoglobin, and cardiac-specific troponin. Patients who are chest pain-free and have no ischemic ECG changes or cardiac biomarker elevation should be considered for risk stratification with a cardiac functional study including exercise stress electrocardiography, stress echocardiography, or myocardial single-photon emission computed tomography imaging.⁸⁰⁻⁸² The indication for stress echocardiography has recently been clarified and includes the evaluation of acute chest pain and other chest pain syndromes, such as anginal equivalent, with or without heart failure, as well as risk assessment in symptomatic patients following revascularization procedures.^{81,82}

Acute ECG changes, such as ST segment deviations or deep T wave inversions, positive cardiac biomarkers or stress test results, or hemodynamic instability should prompt admission to an intensive care unit. Hospital admission may also be considered if the diagnosis remains uncertain despite initial limited evaluations. Available risk stratification models, such as the Thrombolysis in Myocardial Infarction score, may aid diagnosis and management.⁸³ Aspirin, preferably non-enteric-coated formulations, should be provided unless contraindicated or already taken by the patient. Other medications that may be useful in the management

Table 31-2 Differential Diagnosis of Chest Pain

Diagnosis	Pain	Characteristics	ECG	CXR	Associated Features
Angina pectoris	Substernal, constricting	Transient, effort-related	Local ST depression; occasional elevation	Normal	Relief with NTG
MI	Substernal, crushing	Persistent, severe	Local ST elevation or depression	Possible vascular congestion or cardiomegaly	Relief with opiates; possible hypotension; ↑ troponin
Pulmonary embolism	Pleuritic	Sudden onset with dyspnea	Nonspecific; occasional RV strain	Normal or opacities ± small pleural effusion	Risk factor/s for venous thrombosis
Pulmonary artery hypertension	Gradual onset	Associated with dyspnea, fatigue, and edema	Tall right precordial R waves, right axis deviation, RV strain	Prominent pulmonary arteries	Exclude pulmonary thromboembolism and interstitial lung disease
Bacterial pneumonia	Pleuritic	Onset in minutes to hours	Normal	Consolidation	Fever, productive cough
Pneumothorax	Sharp, unilateral	Sudden onset with dyspnea	Normal	Collapsed lung	Asthenic habitus, recurrence
Pericarditis	Pleuritic	Either side; gradual onset; pain referred to trapezius	Generalized ST elevation	Possible enlarged silhouette	Friction rub
Aortic dissection	Substernal, severe	Radiation to the back	Nonspecific; LVH or inferior MI	Widened mediastinum	Prostration, loss of pulse, aortic insufficiency
Esophageal spasm/reflux	Substernal	May mimic angina; burning	Normal or ST-T changes	Normal	Relief with NTG or antacids
Costochondritis	Dull-achy, localized	↑ by cough or deep breath	Normal	Normal	Localized tenderness
Herpes zoster	Sharp, unilateral	Dysesthesia	Normal	Normal	Vesicular rash

LVH, left ventricular hypertrophy; MI, myocardial infarction; NTG, nitroglycerin; RV, right ventricular.

of ischemic heart disease include nitroglycerin (sublingual or intravenous), β -blockers, angiotensin-converting enzyme inhibitors, nondihydropyridine calcium channel blockers, morphine sulfate (for persistent chest discomfort), antiplatelet agents (clopidogrel, prasugrel, ticagrelor, or glycoprotein IIb/IIIa inhibitor), and anticoagulant therapy (e.g., unfractionated heparin, enoxaparin, or fondaparinux).⁸⁴ Patients should be placed on strict bed rest, and supplemental oxygen should be provided, particularly if the patient is in respiratory distress or if oxygen saturation is less than 90%. Every patient with acute coronary syndrome should be evaluated for possible revascularization, preferentially percutaneous coronary intervention.⁸⁵ Management of non-ST segment elevation acute coronary syndromes by early invasive therapy improves long-term survival and reduces adverse cardiovascular events (late myocardial infarction and rehospitalization for unstable angina) compared with a more conservative approach.⁸⁶ Reperfusion therapy with fibrinolytic agents should be reserved for ST elevation myocardial infarction patients presenting to centers without angioplasty capability when anticipated delay to performing angioplasty is greater than 120 minutes from first medical contact. Urgent coronary artery bypass grafting surgery should be considered in acute coronary syndromes or ST elevation myocardial infarctions when primary angioplasty has failed or coronary anatomy is not amenable to percutaneous coronary intervention and high-risk features are present—including ongoing symptomatic ischemia, cardiogenic shock, heart failure, ischemic mitral regurgitation, ventricular septal defect, ventricular free wall perforation, or life-threatening arrhythmias.⁸⁷

Evaluation and management of variant or Prinzmetal angina consists of coronary angiography in patients with chest pain accompanied by transient ST segment elevation. Nitrates and calcium channel blockers may be given if no obstructive coronary artery lesions are evident on coronary angiography, with percutaneous coronary intervention reserved for those with significant coronary artery stenosis. Provocative testing may be considered in cases of diagnostic uncertainty if no contraindications exist.

For cardiac ischemic chest pain related to the use of cocaine or methamphetamine, nitroglycerin and calcium channel blockers may be considered as is immediate coronary angiography (preferred) or fibrinolytic therapy (if coronary angiography is not possible) if electrocardiographic ST elevation (or new ST segment depression or T wave changes) persists despite pharmacologic intervention. A combined α - and β -blocking agent, such as labetalol, may be helpful in patients with sinus tachycardia related to cocaine use if a vasodilator (nitroglycerin or calcium channel blocker) has been administered within the previous hour.

Patients with cardiovascular syndrome X may also benefit from medical intervention with nitrates, calcium channel blockers, and/or β -adrenergic blockers. Intracoronary ultrasonography, coronary angiography, 24-hour ambulatory ECG, provocative testing, or coronary flow reserve measurement may be considered to aid with diagnosis.

Risk stratification with exercise ECG (using the Bruce protocol or Duke treadmill score), exercise perfusion imaging, or exercise echocardiography should be considered for patients with symptomatic chronic stable angina who are able to exercise and have no contraindications to such testing. For those who are unable to exercise,

pharmacologic stress testing with dipyridamole, adenosine, dobutamine, or regadenoson nuclear myocardial perfusion imaging or dobutamine echocardiography is recommended unless contraindications to such testing exist.⁸⁸

PULMONARY EMBOLISM (see Chapter 57)

Pulmonary embolism is a life-threatening feature of venous thromboembolism and most frequently originates from deep venous thrombosis in the lower extremities.

Patients with acute pulmonary embolism who have elevated levels of troponin are at high risk for short-term mortality and adverse outcome events.⁸⁹ A recent meta-analysis of the different diagnostic strategies for suspected pulmonary embolism disclosed the positive likelihood ratios for high-probability ventilation-perfusion lung scan (18.3), computed tomography pulmonary angiography (CTPA) (24.1), and lower extremity venous ultrasonography (16.2).⁹⁰ The corresponding negative likelihood ratios were 0.05 for a normal or near-normal lung scan, 0.04 for a negative result on CTPA along with a negative result on ultrasonography, and 0.08 for a D-dimer concentration less than 500 µg/L by quantitative enzyme-linked immunosorbent assay. Using these tests, patients with a moderate or high pretest probability had a posttest probability of greater than 85%, while patients with a low or moderate pretest probability had a 5% posttest probability. Because of higher negative likelihood ratios, CTPA alone, a low-probability ventilation-perfusion lung scan, magnetic resonance angiography, a quantitative latex D-dimer test, and hemagglutination D-dimers can only exclude pulmonary embolism in those with a low pretest probability.⁹⁰

Patients with pulmonary embolism can be treated with either unfractionated heparin or low-molecular-weight heparin. Dabigatran, a direct thrombin inhibitor, was recently shown to be noninferior to warfarin for the treatment of venous thromboembolism and may be adopted as an acceptable treatment of pulmonary embolism in the future.⁹¹ Anticoagulation is maintained either for 3 to 6 months for events related to a transient risk factor or for greater than 12 months for recurrent venous thromboembolism.⁹²

PERICARDIAL DISEASE

Acute pericarditis is often associated with a pericardial effusion, diffuse concave ST segment elevation, and/or PR segment depression. Therapy for acute pericarditis involves identification and management of any underlying cause of the condition (e.g., infection or malignancy). In constrictive pericarditis, echocardiography can demonstrate the presence of pericardial thickening and calcification that limits diastolic filling of the ventricles and causes a characteristic biphasic pattern of venous return with a diastolic component that is equal to or greater than the systolic component. In selected patients, pericardectomy is a highly effective treatment of constrictive pericarditis.⁹³

CARDIAC TAMPONADE

Cardiac (or pericardial) tamponade is the presence of fluid within the pericardial sac leading to cardiac compression.

This, in turn, impairs ventricular diastolic filling and gives rise to the sensation of chest pain, dyspnea, tachycardia, falling systemic blood pressure, elevated venous pressure (characteristic loss of the atrial Y descent with maintenance of both the systolic atrial filling wave and the X descent), and pulsus paradoxus (an exaggerated inspiratory decrease in arterial systolic pressure > 10 mm Hg). Cardiac tamponade should be suspected whenever a patient presents with unexplained hypotension and/or pulsus paradoxus following myocardial infarction, chest trauma, percutaneous coronary intervention, or cardiac surgery. Other risk factors include anticoagulation therapy, malignancy, or an underlying connective tissue disease. A pericardial rub may be appreciated during physical examination. ECG changes compatible with acute pericarditis may be present as is an enlarged cardiac silhouette on chest films. Diagnosis is generally determined by two-dimensional echocardiography that demonstrates an inspiratory increase of right ventricular dimensions and decrease of left ventricular dimensions, compression of the right atrium, right ventricular diastolic collapse, and a heart that swings with cardiac contractions. Left atrial collapse is less common than right atrial collapse but is very specific for cardiac tamponade. There is commonly also an abnormal inspiratory increase of blood flow velocity through the tricuspid valve accompanied by a decrease in mitral valve flow velocity as well as dilation of the inferior vena cava with lack of inspiratory collapse. Aggressive volume loading and percutaneous or surgical pericardial fluid drainage leads to immediate relief of chest discomfort, dyspnea, venous hypertension, and pulsus paradoxus.^{93,94}

PULMONARY ARTERIAL HYPERTENSION

(see Chapter 58)

Initial evaluation of suspected pulmonary arterial hypertension generally consists of ECG, determination of arterial blood gas levels, a chest radiograph, pulmonary function testing, exercise capacity (6-minute walk test), brain natriuretic peptide or N-terminal brain natriuretic peptide, and noninvasive Doppler echocardiography with and without saline contrast.⁹⁵ Chronic thromboembolic disease is evaluated with ventilation-perfusion scanning and chest CTPA. Ultimately, right heart catheterization is required both to confirm the diagnosis and to assess the severity of the pulmonary hypertension. Testing for connective tissue disease or human immunodeficiency virus infection may be considered in patients with suggestive clinical histories for these disorders.⁹⁶ Acute vasoreactivity testing using inhaled nitric oxide (or other pulmonary vasodilators, including epoprostenol, adenosine, or sodium nitroprusside) should be performed for patients with pulmonary arterial hypertension to guide therapy.^{96a} Polysomnography is indicated for patients with a clinical history suggestive of obstructive sleep apnea. Treatment of pulmonary arterial hypertension includes potent vasodilators such as intravenous prostacyclin and the prostacyclin analogue treprostinil, inhaled iloprost or treprostinil, endothelin receptor antagonists (bosentan and ambrisentan), and cyclic guanosine monophosphate-specific phosphodiesterase type 5 inhibitors (sildenafil and tadalafil).^{96b} Calcium channel blocker therapy is reserved for those patients who demonstrate vasoreactivity at the time

of right heart catheterization. Pulmonary thromboendarterectomy may benefit patients with chronic thromboembolic pulmonary hypertension. Lung (preferably bilateral) transplantation or heart-lung transplantation may be considered for selected patients with New York Heart Association functional class III and IV symptoms.⁹⁷

THORACIC AORTIC DISSECTION

Rapid diagnosis and management are critical for patients with thoracic aortic dissection. Invasive aortography for the diagnosis of thoracic aortic dissection has been replaced by less invasive imaging techniques, including transesophageal echocardiography, contrast-enhanced chest *computed tomography* (CT) scan, and magnetic resonance imaging. All of these modalities yield clinically reliable data for both confirming and ruling out this condition. In one review, pooled sensitivity (98% to 100%) and specificity (95% to 98%) from 16 studies involving 1139 patients were comparable for these three less invasive imaging tools.⁹⁸ Pooled positive likelihood ratio was higher for magnetic resonance imaging than for transesophageal echocardiography or CT. In this review if the patient had a high-risk pretest probability (i.e., 50%), the posttest probability of thoracic aortic dissection following a positive result for each of these imaging tests was 93% to 96%; if the patient had a low-risk pretest probability (i.e., 5%), the posttest probability following a negative result from each of the imaging tests dropped to 0.1% to 0.3%.⁹⁸

PNEUMOTHORAX (see Chapter 81)

Spontaneous pneumothorax can be either primary or secondary. Patients with small primary pneumothoraces may be observed closely for either progression or resolution if they are clinically stable. Chest catheter or tube insertion is indicated if the pneumothorax enlarges or if the patient's clinical situation deteriorates, as well as in patients with large primary or secondary pneumothoraces. Patients with small secondary spontaneous pneumothoraces who are clinically stable may be either observed or managed with a chest tube depending on clinical severity and course of the pneumothorax.^{99,100}

TENSION PNEUMOTHORAX

A tension pneumothorax is a life-threatening condition that requires urgent management. High intrathoracic pressures develop because of ingress of air into the pleural space via a one-way valve process, which, in turn, prevents egress of air; this gives rise to vena caval compression, reduction in venous return, and diminished cardiac output. Radiographically, a tension pneumothorax presents as a complete collapse of the ipsilateral lung, depression/flattening of the ipsilateral hemidiaphragm, and shift of the mediastinum to the contralateral hemithorax. Therapy consists of emergency percutaneous aspiration or chest tube insertion.¹⁰⁰

PANCOAST TUMORS

Pancoast (superior sulcus) tumors require a definitive tissue diagnosis before initiation of therapy, which may, in selected

patients, include resection and/or chemoradiotherapy. Magnetic resonance imaging, both mediastinal and extrathoracic, is frequently performed to rule out involvement of adjacent neurovascular structures (brachial plexus, vertebral column, or subclavian vessels) that will influence surgical approaches.¹⁰¹

CHEST TRAUMA (see Chapter 76)

Blunt and penetrating chest trauma can give rise to chest pain related to hemothorax (bleeding into the pleural space); pneumothorax; rib, sternal, or clavicular fractures; or injury to the chest wall musculature.

As little as 5 mL of hemothorax can be appreciated on a decubitus chest radiograph, but a size of approximately 200 mL is required for it to be readily identified on an upright chest radiograph, where it will appear as blunting or, with greater volume of bleeding, a concave upward sloping of the fluid, in the ipsilateral costophrenic angle. The presence of an air-fluid level indicates a hemothorax. Chest CT is more sensitive than chest radiographs in detecting a small hemothorax; in addition, it may occasionally offer clues to the origin of the bleeding.

Rib fractures may be associated with injuries to the brachial plexus and subclavian veins (upper rib fractures) or spleen and liver (lower rib fractures). A flail chest resulting from at least two fracture sites on at least three consecutive ribs can create regional chest wall instability and respiratory distress. The sternum fractures most commonly at the body or manubrium, generally following direct trauma to the anterior chest or from deceleration. Significant posterior displacement of the sternum may be associated with trauma to the underlying cardiovascular structures. Chest CT is more sensitive than plain chest radiographs for detecting rib and sternal fractures.¹⁰⁰

GASTROESOPHAGEAL REFLUX (see Chapter 93)

Dyspepsia secondary to gastroesophageal reflux can be managed with proton pump inhibitors, histamine₂ receptor antagonists, or prokinetic agents. An empirical trial with these medications may be considered if the clinical history strongly supports the diagnosis of gastroesophageal reflux and if the patient is not at high risk for a gastrointestinal malignancy. Risk factors, such as use of nonsteroidal anti-inflammatory agents, should be investigated. Endoscopy may be necessary in some patients with unexplained dyspepsia and persistent symptoms. Recommendations for eradication therapy for *Helicobacter pylori*-positive dyspepsia have been published.¹⁰²

PANCREATITIS

Common causes of acute pancreatitis include gallstone disease (approximately 50% of cases) and alcohol abuse (20% to 25%). Patients typically complain of abdominal pain and vomiting, but chest pain may develop as well. Elevation of lipase has a higher sensitivity and specificity for pancreatitis than elevation of amylase perhaps because, compared to amylase, lipase is produced only by the pancreas. In addition, the half-life of lipase is longer than that

of amylase. Thus measurement of lipase is preferred. Other helpful laboratory tests include liver chemistry determinations, triglyceride level, and calcium level. When diagnostic doubt exists, abdominal imaging by contrast-enhanced CT may be beneficial. In addition to supportive measures, therapeutic endoscopic retrograde cholangiopancreatography may be considered, particularly if the acute pancreatitis is severe, due to gallstones, or when cholangitis, jaundice, or a dilated common bile duct is present. The presence of cholangitis is an indication for endoscopic sphincterotomy or duct drainage by stenting. Image-guided fine-needle aspiration is recommended for patients with significant pancreatic necrosis, who may require débridement if infection is present.^{103,104}

Key Points

- Chest pain is characterized by an unpleasant sensation that is either localized to the thorax or believed to originate from structures located there. It may announce the presence of severe, occasionally life-threatening disease.
- Pain arising from *visceral* organs (e.g., heart or gastrointestinal tract) differs in many ways from that arising from *somatic* structures, such as the skin. Visceral pain is difficult to localize, is diffuse in character, and is typically referred to somatic structures. Visceral pain is also often associated with greater autonomic and motor responses than is somatic pain.
- Visceral and somatic innervations differ in relation to the density of innervations and spinal pattern of termination. In general, the number of visceral afferent fibers is less than the number of somatic afferent fibers, and the rostrocaudal spread of visceral afferent fiber terminals in the spinal cord is considerably greater than the spread of central terminals from somatic afferent fibers. The low number of visceral afferents and greater intraspinal spread is responsible for loss of spatial discrimination, consistent with the diffuse, difficult-to-localize nature of visceral pain.
- Pain is both hard to define and difficult to measure. Two widely used techniques, namely rating scales and questionnaires, are often used in clinical and epidemiologic studies of chest pain. Although rating scales constitute the simplest measurement of pain, the sensation of pain has many more components than just its intensity; thus, a single-dimensional rating scale leaves many aspects of the sensation undocumented.
- Because of the proximity of the various organs and the vagaries of perception of pain of visceral origin, pain arising from the various viscera in the thoracic cavity and from the chest wall is often qualitatively similar and exhibits overlapping patterns of referral, localization, and quality. This leads to difficulty in the differential diagnosis of chest pain.

Complete reference list available at *ExpertConsult*.

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INFECTIOUS DISEASES OF THE LUNGS

32

VIRAL INFECTIONS

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Common Cold
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Croup
Bronchiolitis
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MAJOR VIRAL PATHOGENS

Adenoviruses
Coronaviruses
Cytomegalovirus
Hantaviruses
Herpes Simplex Virus

Influenza Virus
Measles Virus
Metapneumoviruses
Parainfluenza Viruses
Respiratory Syncytial Virus
Rhinovirus
Varicella-Zoster Virus

INTRODUCTION

Viral infections are important causes of disease of the respiratory tract. The common cold is the most frequently encountered infectious syndrome of humans, while influenza continues to be a major cause of mortality and serious morbidity worldwide. Respiratory viral infections frequently complicate the course of patients with *chronic obstructive pulmonary disease* (COPD) and asthma. As the number of immunocompromised persons in the population has increased, infections due to cytomegalovirus and other herpes viruses, adenoviruses, and paramyxoviruses have assumed increasing importance in pulmonary medicine. Finally, recent years have seen the emergence of new viral respiratory pathogens, including hantaviruses, human metapneumovirus, avian influenza A viruses, and the *severe acute respiratory syndrome* (SARS) and *Middle East respiratory syndrome* (MERS) coronaviruses. This introductory section outlines general concepts of respiratory viral infections and their associated clinical syndromes. The following sections then provide a review of the major viral pathogens infecting the respiratory tract.

CLASSIFICATION

Viruses of importance in the respiratory tract ([Table 32-1](#)) include those considered to be principal respiratory viruses,

the replication of which is generally restricted to the respiratory tract, and others in which respiratory involvement is part of a generalized infection. Virus classification depends in part on the type and configuration of the nucleic acid in the viral genome, the characteristics of the viral structural proteins, and the presence or absence of an envelope surrounding the virus particle. The number of distinct antigenic types within each of the virus families also varies.

TRANSMISSION

The routes by which the different respiratory viruses spread from person to person are variable and include combinations of contact, droplet, and aerosol transmission. For example, rhinovirus and *respiratory syncytial virus* (RSV) are primarily spread by direct contact with contaminated skin and environmental surfaces followed by self-inoculation of virus onto the nasal mucosa or conjunctiva. Other viruses, such as measles and varicella-zoster viruses, spread as small-particle aerosols. Other viruses may spread by means of larger-particle aerosols over short distances (1 m). The relative importance of the various transmission routes under natural conditions for each virus varies and in many cases is unknown.

Table 32-1 Viral Infections of the Respiratory Tract

Group	Nucleic Acid	Envelope	Types	Disease/Syndrome*
Adenovirus	DNA	No	1–47	Common cold; bronchitis; bronchiolitis; pharyngoconjunctival fever; acute respiratory disease (ARD) in military recruits; pneumonia
Coronavirus	RNA	Yes	229E, OC43, SARS-CoV, MERS-CoV	Common cold, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS)
Hantavirus	RNA	Yes	Multiple	Acute respiratory distress, pneumonitis
Orthomyxovirus Influenza virus	RNA	Yes	A, B, C	Influenza; common cold; pharyngitis; croup; bronchitis; bronchiolitis; pneumonia
Paramyxoviruses Measles virus Parainfluenza virus Respiratory syncytial virus Human metapneumovirus	RNA	Yes	1–4 A, B A, B	Measles; pneumonia; bronchiectasis Common cold; croup; bronchitis; bronchiolitis; pneumonia Common cold; croup; bronchitis; bronchiolitis; pneumonia Bronchiolitis, common cold
Picornaviruses Enterovirus Coxsackievirus	RNA	No	1–24	Type A21 colds and ARD; others (types 2, 4, 5, 6, 8, 10); herpangina
Echovirus Rhinovirus			1–34 1–100	Common cold (importance uncertain) Common cold
Herpes viruses Herpes simplex virus	DNA	Yes	1, 2	Acute pharyngitis in normal persons; chronic ulcerative pharyngitis; tracheitis; pneumonia in immunosuppressed patients
Cytomegalovirus			1	Mononucleosis; acute and chronic pharyngitis; pneumonia in immunosuppressed patients
Varicella-zoster virus			1	Pneumonia in normal persons and immunosuppressed patients
Epstein-Barr virus			1	Mononucleosis; acute and chronic pharyngitis
Human herpesvirus 6			1	Pneumonia in immunosuppressed patients
Filovirus	RNA	Yes	Marburg; Ebola 1, 2	Pharyngitis as an early manifestation of hemorrhagic fever
Human immunodeficiency virus	RNA	Yes	1, 2	Pharyngitis with primary infection; secondary pulmonary infections due to immunodeficiency
Papillomavirus	DNA	No	>60	Laryngeal and tracheobronchial papillomatosis

*Bacterial infections, including sinusitis, otitis media, and pneumonia, complicate respiratory virus infection. Also, infection with the respiratory viruses may precipitate attacks of asthma and cause exacerbations in patients with chronic obstructive pulmonary disease.

PATHOGENESIS OF INFECTION

The initial sites of infection and pathogenesis differ for the various virus groups. Some, such as rhinovirus, are associated mainly with upper respiratory tract involvement. Others, such as influenza, commonly invade the lower airways and sometimes pulmonary parenchyma in addition to causing upper airway disease. The viruses also differ in the relative contributions to the clinical manifestations of disease from damage due to direct viral mechanisms and damage due to host immune responses and inflammation.

An additional important feature of respiratory virus infections is their effect on the resident bacterial flora of the upper airways. Respiratory virus infections alter bacterial colonization patterns, increase bacterial adhesion to respiratory epithelium, and reduce mucociliary clearance and phagocytosis. These impairments of host defenses by viruses allow colonization by pathogenic bacteria and invasion of normally sterile areas, such as the paranasal sinuses, middle ear, and lower respiratory tract, resulting in secondary infection.

CLINICAL SYNDROMES

As shown in [Table 32-1](#), infection by one of the respiratory viruses may result in more than one clinical syndrome. Similarly, a particular syndrome can result from infection with different viruses. The poor correlation of agent and syndrome makes specific etiologic diagnosis on clinical grounds inaccurate, although knowledge of the seasonal patterns of infection may be helpful. Moreover, infection with a single virus may cause disease at multiple levels of the respiratory tract.

COMMON COLD

There is no universally accepted, standard definition of a cold, but the term is usually used to refer to acute rhinitis with variable degrees of pharyngitis. Systemic complaints are absent or modest in severity and fever is unusual. Allergic diseases of the upper airway often have clinical manifestations similar to those of colds. Colds are frequently associated with involvement of the middle ear, likely due to

Table 32-2 Viruses Associated with the Common Cold

Virus	Percentage of Cases*
Rhinovirus	40
Coronavirus	10
Parainfluenza virus	10–15
Respiratory syncytial virus	
Influenza virus	
Adenovirus	
Other viruses (enterovirus, rubeola, rubella, varicella)	5
Presumed undiscovered viruses	20–30
Group A β -hemolytic streptococci†	5–10

*Estimated percentage of colds annually.

†Included because differentiation of streptococcal and viral pharyngitis is not possible by clinical means.

eustachian tube dysfunction. Colds are associated with symptomatic otitis media in approximately 2% of cases in adults and in a higher proportion in young children. Colds are frequently associated with sinus mucosal thickening or secretions on computed tomography scans but rarely result in symptomatic sinusitis. Vertigo associated with viral labyrinthitis may also be seen.

The common cold syndrome is caused by any one of a large number of antigenically distinct viruses found in four principal groups (Table 32-2). Epidemiologic studies have indicated that on an annual basis, any one antigenic type of virus is responsible for less than 1% of all colds. Since the discovery of the respiratory viruses in the 1960s, rhinovirus has emerged as the prototype common cold virus (Fig. 32-1).

The recommended approach to colds is to use individual remedies to treat specific symptoms. Nasal sprays containing decongestants should be used for no more than 3 days, to avoid a rebound vasomotor rhinitis. Cough syrups containing expectorants are of unproven value in common colds. Symptoms of sneezing and rhinorrhea can be alleviated with nonselective antihistamines such as brompheniramine, chlorpheniramine, or clemastine fumarate,¹ but treatment with selective H₁ inhibitors is not effective. Studies of pseudoephedrine have demonstrated measurable improvements in nasal air flow consistent with a decongestant effect.² Nonsteroidal anti-inflammatory drugs such as naproxen moderate the systemic symptoms of rhinovirus infection. However, the use of the decongestant phenylpropanolamine has been shown to be associated with an increased risk of hemorrhagic stroke.³ Topical application of ipratropium, a quaternary anticholinergic agent that is minimally absorbed across biologic membranes, reduces rhinorrhea significantly in naturally occurring colds. This agent probably exerts its major effect on the parasympathetic regulation of mucous and seromucous glands. Importantly, most over-the-counter cough and cold remedies have not been studied in pediatric populations, where they may be associated with significant side effects.⁴

PHARYNGITIS

Pharyngitis most often presents as part of the common cold syndrome and thus is usually associated with the same

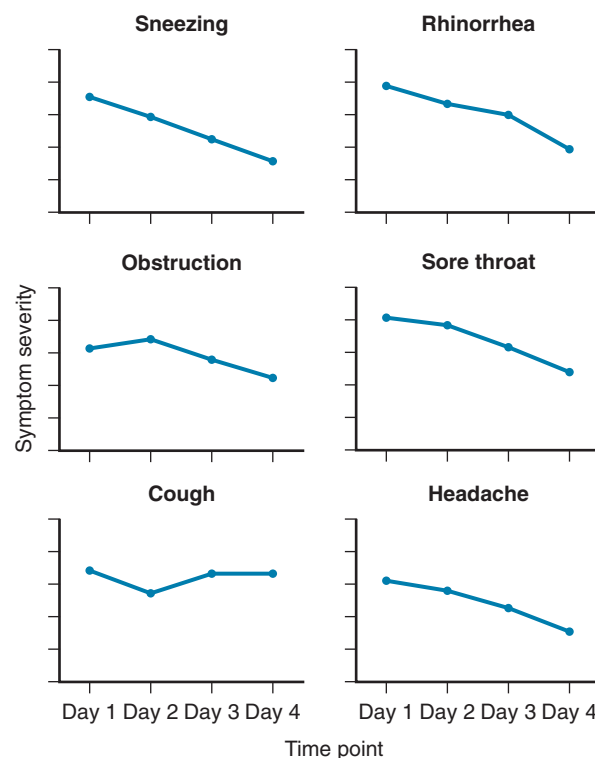


Figure 32-1 Some common clinical features of rhinovirus colds (105 natural infections). Graphs show symptom severity by time point. (Adapted from Gwaltney JM Jr, Hendley JO, Patrie JT: Symptom severity patterns in experimental common colds and their usefulness in timing onset of illness in natural colds. *Clin Infect Dis* 36:724–723, 2003, Fig. 2.)

Table 32-3 Important Microbial Agents Associated with Acute Pharyngitis

Pharyngitis with colds and influenzal illness (no exudate)	Rhinovirus Influenza virus Coronavirus Respiratory syncytial virus
Exudative pharyngitis (exudate is not present in all cases)	<i>Streptococcus pyogenes</i> (group A β -hemolytic streptococcus) Mixed anaerobic infection (Vincent angina and peritonsillar abscess) Adenovirus Herpes simplex virus Epstein-Barr virus <i>Corynebacterium diphtheriae</i> (pseudomembrane)

viruses that cause colds. In some cases, pharyngeal symptoms predominate to a degree that overshadows other complaints. The kinins are potent stimulators of pain nerve endings, and high levels of bradykinin and lysylbradykinin are present in nasal secretions of patients with rhinovirus-induced colds. Intranasal application of bradykinin promotes sore throat and nasal symptoms in volunteers, supporting a role for these agents in the pathogenesis of cold symptoms.⁵

The respiratory viruses causing pharyngitis can be divided into two groups: those associated with a pharyngeal or tonsillar exudate and those without such an exudate (Table 32-3). Pharyngitis is often a prominent complaint with adenovirus and influenza virus infection. Also, some

viruses are associated with other types of *enanthems*, meaning lesions on the mucous membranes, such as vesicles and ulcers. Coxsackie A viruses are associated with the condition herpangina, a painful, often febrile pharyngitis of children and young adults characterized by vesicular lesions of the soft palate.

Viruses in the herpes family cause a small proportion of cases of pharyngitis. Primary infection with herpes simplex virus manifests as an acute vesiculoulcerative pharyngitis or gingivostomatitis that may have an exudative character. In immunocompromised patients, herpes simplex virus causes large, shallow ulcers of the mucosa that are chronic and progressive if untreated. Epstein-Barr virus mononucleosis characteristically has an acute exudative pharyngitis. Mononucleosis due to cytomegalovirus infection may have a nonexudative pharyngitis that is acute or chronic, and rarely, cytomegalovirus causes oral ulcerations in immunosuppressed patients. Pharyngitis can arise during primary infection with *human immunodeficiency virus* (HIV). Viruses in the hemorrhagic fever group produce an acute pharyngitis early in the disease, before skin lesions appear. Exudative pharyngitis is a common clinical manifestation in Lassa fever.

Typically, sore throat accompanied by nasal symptoms is more likely to be viral in nature. Infection with mixed anaerobic bacteria (Vincent angina) or *Corynebacterium diphtheria* is also in the differential diagnosis of exudative pharyngitis. The treatment of most cases of viral pharyngitis is symptomatic.

ACUTE BRONCHITIS

The diagnosis of acute bronchitis is usually applied to cases of acute respiratory disease with severe and prolonged cough that continues after other signs and symptoms of the acute infection have subsided. Cough appears during the first week of illness in 30% of rhinovirus colds in young adults and in 80% or more of cases of influenza A virus infection, in which it is often prolonged. Adenovirus infections characteristically involve the tracheobronchial tree, with resultant bronchitis that, in military populations, is part of the syndrome of acute respiratory disease.

The mechanisms of cough production in viral infection are not well understood but may include direct damage to the respiratory mucosa, release of inflammatory substances in response to the infection, increased production and/or decreased clearance of respiratory secretions, and stimulation of airway irritant receptors. Intranasal application of several prostaglandins also produces cough in uninfected volunteers.⁵ Infection may also enhance airway reactivity, leading to increased sensitivity to cold air and pollutants such as smoke.

The differential diagnosis of acute bronchitis includes nonviral infections and noninfectious etiologies such as cough-variant asthma. *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* infections cause prolonged cough. In otherwise healthy persons, workup of acute cough should be directed toward determining the presence of pneumonia and, if this is not present, then treatment with antibacterial agents is of no benefit.⁶ Symptomatic treatment is directed at the suppression of cough. In children, a single nocturnal dose of honey is as effective

as dextromethorphan in suppressing night time coughing,⁷ but honey should not be administered to infants younger than 1 (due to risk of infant botulism).

INFLUENZA-LIKE ILLNESS

The clinical syndrome of influenza is characterized by the rapid onset of constitutional symptoms, including fever, chills, prostration, muscle ache, and headache, concurrent with or followed by upper and lower respiratory tract symptoms. Systemic symptoms tend to dominate for the first several days of illness, whereas respiratory complaints, particularly cough, predominate later in the first week of illness. Photophobia, excess tearing, and pain with eye movement are common early in the illness. Mild conjunctivitis, clear nasal discharge without obstruction, pharyngeal injection, and small tender cervical lymph nodes are frequently present. Fever may peak at 39° C to 40° C or higher and can last for 1 to 5 days. Persistent nonproductive cough, easy fatigability, and asthenia are common in the second week of illness.

Influenza type A and B viruses are the most important causes of the influenza syndrome, particularly when the illness presents in an epidemic form. However, the syndrome can also be seen in association with infection by other viruses, including adenovirus, parainfluenza, and RSV. The characteristic clinical features of influenza and its epidemic nature usually permit the practitioner to make an accurate diagnosis during recognized epidemics of influenza virus infection, particularly if cough and fever are present.⁸ Specific antiviral therapy is effective if given early in the course of the illness (see the section on [influenza virus](#)). Symptomatic treatment (bed rest, oral hydration, antipyretics, and antitussives) is also beneficial. Fever should be treated in certain clinical situations, such as in children with previous febrile convulsions or patients with preexisting cardiac disease. Because of its possible association with Reye's syndrome, aspirin must be avoided in pediatric patients.

CROUP

The croup syndrome of children is characterized by an unusual brassy or barking cough (see [Audio 30-3](#)) that may be accompanied by inspiratory stridor, dyspnea, and hoarseness.^{8a} The symptoms are often preceded by several days of upper respiratory illness and are typically worse at night. Croup is seen primarily in children younger than 6. The term *acute infectious croup* or *laryngotracheobronchitis* is applied to a contagious disease that affects otherwise healthy children, often associated with a respiratory illness in the family. The term *acute spasmodic croup* is applied to a similar syndrome that is most common in young children prone to recurrent attacks precipitated by respiratory viral infections and possibly allergic or other factors. In these children, fever is frequently absent and symptoms often abate within several hours.

Most children with acute laryngotracheobronchitis have symptoms of decreasing intensity over several days and can be managed at home. However, increasing laryngeal obstruction can be associated with respiratory insufficiency. This is manifested by restlessness, air hunger, stridor

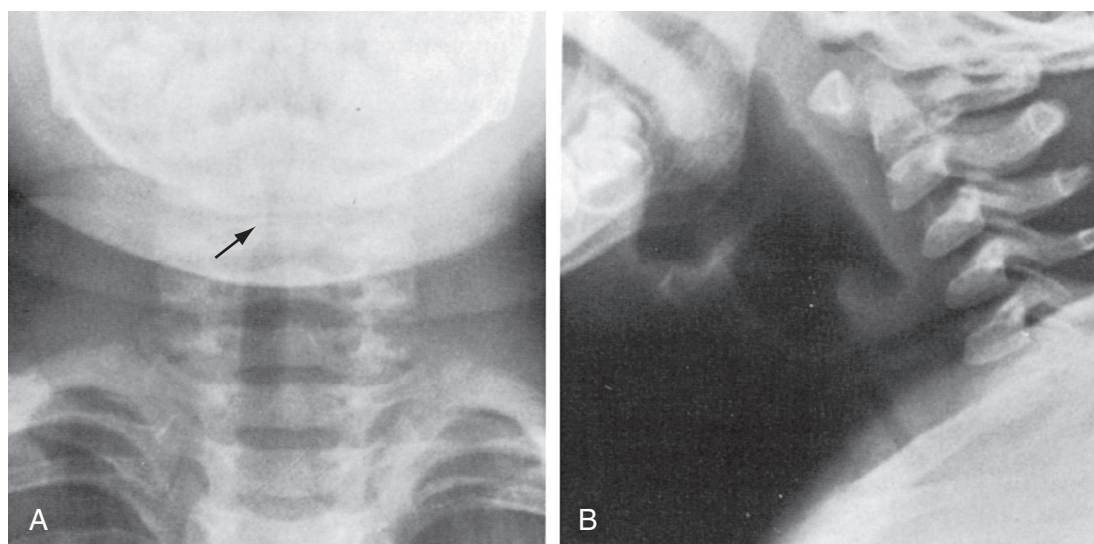


Figure 32-2 Laryngotracheobronchitis. Anteroposterior (A) and lateral (B) neck radiographs of a 2-year-old child with croupy cough, inspiratory stridor, and fever. The anteroposterior view shows subglottic narrowing, referred to as the “steeple” sign (arrow), characteristic of laryngotracheobronchitis. Lateral view shows ballooning of hypopharynx resulting from laryngeal obstruction. (Courtesy Joan McIlhenny, MD, Department of Radiology, University of Virginia Medical Center.)

at rest, use of accessory muscles, and intercostal retractions and may be followed by development of exhaustion with severe hypoventilation, cyanosis, and cardiovascular collapse. A fluctuating course is typical.

Radiologic examination of the upper airway shows glottic and subglottic edema (Fig. 32-2, eFig. 32-1) and helps to differentiate the disorder from acute bacterial epiglottitis. However, radiographs are limited in accuracy and, when the diagnosis is uncertain, radiologic and pharyngeal examination should be avoided because of the risk of cardiorespiratory arrest in acute epiglottitis. Emergency assessment by an otolaryngologist or an anesthesiologist is indicated in this situation.

The acute infectious croup syndrome has been associated principally with infection by one of the parainfluenza viruses, as well as RSV, influenza A and B viruses, adenoviruses, and rhinovirus. Measles is an important cause of severe croup in the developing world, and influenza A epidemics also are associated with severe croup. The differential diagnosis of croup includes acute bacterial epiglottitis, diphtheritic croup, asthma, and intrinsic or extrinsic upper airway obstruction related to an aspirated foreign body, allergic angioedema, and retropharyngeal abscess.

Because the majority of hospitalized children are hypoxicemic, oxygen is the mainstay of treatment for severe disease. Humidified air, or mist therapy, is commonly used, but the value of mist therapy has not been proven, and removal of the child from the parents and placement in a mist tent can be more distressing than beneficial to the child.

Administration of nebulized racemic epinephrine is commonly used for symptomatic relief in croup. It is believed that α -adrenergic stimulation by this drug causes mucosal vasoconstriction, leading to decreased subglottic edema. The onset of action is rapid, often within minutes, but the duration of relief is also limited, lasting 2 hours or less. Therefore, treated subjects should be observed closely for clinical deterioration. Although symptomatic relief is considerable, use of epinephrine is not associated with improve-

ments in oxygenation. Steroids have been shown to confer significant benefits in the management of mild, moderate, and severe croup, including more rapid improvement in symptoms, reduced length of hospital stay, and reduced rates of intubation. Administration of single-dose steroid therapy in this setting has not been associated with significant side effects and should probably be used in any patient ill enough to require an emergency department or clinic visit.⁹

Antiviral agents have not been tested for efficacy in this situation, although the potential benefit of antiviral therapy in the typical self-limited course of croup would likely be limited. Since croup is a viral illness, antibiotic therapy is of no benefit.

BRONCHIOLITIS

Bronchiolitis is an acute inflammatory disorder of the small airways characterized by obstruction with “air trapping,” hyperinflation of the lungs, and atelectasis typically seen in children younger than 2. After a several-day prodrome of mild upper respiratory tract symptoms, patients typically present with inspiratory and expiratory wheezing. The clinical features, which include tachypnea, intercostal and suprasternal retractions, nasal flaring, hyperresonant chest, wheezing, and inspiratory rales, usually lead to an accurate clinical diagnosis. The infant is often afebrile and, in mild cases, symptoms resolve within several days. Chest radiographs show increased lung volumes with flattening of the diaphragms, peribronchial thickening (eFig. 32-2), and often atelectasis or parenchymal consolidation indicative of concurrent bronchopneumonia (Fig. 32-3). Chest computed tomography (CT) may show bronchial wall thickening and areas of increased attenuation representing atelectasis mixed with areas of decreased attenuation due to small airway inflammation and obstruction producing air trapping (eFig. 32-3). The white blood cell count and differential count are usually within normal limits.

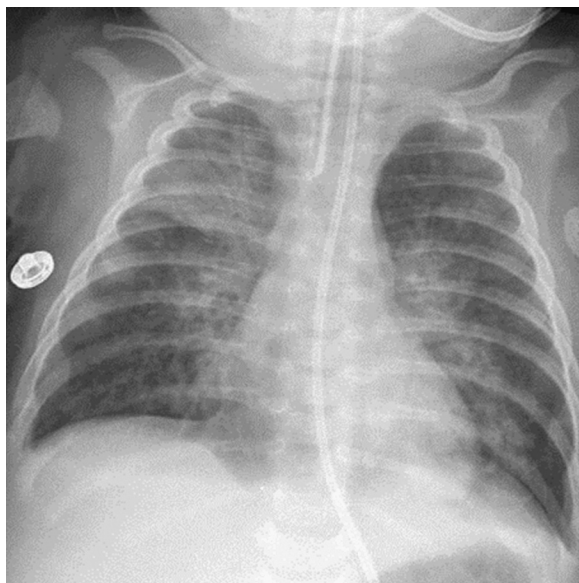


Figure 32-3 Respiratory syncytial virus pneumonia. Frontal chest radiograph in an intubated infant shows bilateral peribronchial interstitial thickening and right upper and left lower lobe consolidation; the right upper lobe opacity is associated with mild volume loss. (Courtesy Michael Gotway, MD.)

The majority of cases in which an etiologic agent has been identified are associated with RSV. Other viruses associated with bronchiolitis include human metapneumovirus, bocavirus, parainfluenza virus, influenza A and B viruses, adenovirus, measles, and rhinoviruses. The major differential diagnostic consideration is asthma, which is uncommon in children younger than one year old.

Correction of hypoxemia is the most important aspect of managing lower respiratory tract disease. Studies of corticosteroid therapies have found no consistent benefit. Studies of bronchodilators have reached conflicting results, and bronchodilating drugs may contribute to increased restlessness and cardiovascular stress, so guidelines do not suggest that bronchodilators be used routinely. One recent randomized trial suggests that “on-demand” use of inhaled racemic adrenaline may result in decreased length of stay in infants hospitalized with bronchiolitis.¹⁰ Because of the dehydrating effect of tachypnea and reduced oral intake in some hospitalized infants, parenteral rehydration is often necessary, but care must be taken to avoid inducing hyponatremia. Aerosol treatment with the synthetic nucleoside ribavirin has been associated with reductions in virus titers but inconsistent clinical benefits. Antibacterial drugs, including azithromycin, are of no benefit.¹¹

PNEUMONIA

Viruses are important causes of pneumonia in both adults and children. They have been associated with up to 40% of radiographically proven pneumonias in hospitalized adults and are estimated to cause 16% of total pneumonias in pediatric outpatients and up to 49% in hospitalized infants. These figures may underestimate the importance of viral infections as a cause of pneumonia, particularly in outpatients, because of the insensitivity of viral diagnostic methods and because of the lack of chest radiographs in

many patients with acute viral infections. Also, because viral infections may be complicated by secondary bacterial pneumonias, invasive procedures would be necessary to differentiate among pure viral pneumonias, secondary bacterial pneumonias, and mixed viral and bacterial infections.

Normal Host

The relative importance of the different viruses as causes of pneumonia depends on the season and the age distribution of the population under study. During outbreaks, influenza virus accounts for more than 50% of viral pneumonia in adults. In addition, RSV, adenovirus, parainfluenza virus, and varicella virus cause pneumonia in normal adults. Unusual viruses continue to emerge in epidemics of severe acute pneumonitis, including hantavirus, coronavirus (SARS), and avian influenza A viruses.

In children, RSV, parainfluenza virus, and adenovirus, in addition to influenza viruses, are the most important causes of pneumonia. Measles virus pneumonia affects children and adults during epidemics in susceptible populations. There are reports of cases of pneumonia in adults and children attributable to rhinovirus, but the evidence that these viruses are definite causes of pneumonia is circumstantial.

The clinical and radiographic features of sporadic cases of viral pneumonia are usually not sufficiently characteristic to permit specific viral diagnosis or differentiation from bacterial pneumonias on clinical grounds alone. Exceptions include measles (eFig. 32-4) and varicella pneumonia, in which the associated rash establishes the diagnosis. Therefore, attention is first directed at excluding primary or secondary bacterial pneumonia. Tests to detect viral antigens or nucleic acid are increasingly available and are rapidly being adopted as the preferred approaches for establishing the etiologic diagnosis^{11a,b} (see Chapter 17).

Treatment of viral pneumonia in the normal host is supportive in nature and directed at early antimicrobial therapy of secondary bacterial infections, if present. Specific antiviral therapy may be beneficial and is discussed with the individual pathogens. Viral pneumonias with extensive involvement of lung tissue may require prolonged ventilatory assistance and pulmonary rehabilitation. Some cases of viral pneumonia have a rapid and relentless fatal course, with generalized alveolar and interstitial opacities, development of the *adult respiratory distress syndrome* (ARDS), and progressive respiratory failure.

Immunocompromised Host

Viral pneumonia can be an important problem for the increasing number of persons in the population who have deficiencies in immunity as the result of cytotoxic chemotherapy, organ transplantation, and the *acquired immunodeficiency syndrome* (AIDS). The major respiratory viruses that affect normal persons may also cause pneumonia in impaired hosts; severe and prolonged pneumonias due to adenovirus, respiratory syncytial, influenza, measles, or parainfluenza virus can develop in such patients. Immunocompromised patients can also shed respiratory viruses for prolonged periods and thus be responsible for extensive transmission of infection to others. In addition, these individuals may develop pneumonia due to viruses, such as cytomegalovirus, that rarely cause lower respiratory tract

disease in normal hosts. Cytomegalovirus causes severe primary viral pneumonia (see eFigs. 91-3, 91-4, and 91-5), as well as predisposing patients to bacterial and fungal superinfections because of its immunosuppressive effects.^{11c,d} Varicella-zoster and herpes simplex virus pneumonias are relatively uncommon but serious infections in immunosuppressed patients.

MAJOR VIRAL PATHOGENS

ADENOVIRUS

Adenovirus is a medium-sized (65 to 80 nm), nonenveloped virus with a genome composed of linear double-stranded DNA¹² (Fig. 32-4). Currently, 47 antigenic types of adenovirus are associated with human infection, although not all types have been associated with human disease. The protein coat of the virus is composed of 252 hexagonal and pentagonal capsomeres in an icosahedral array with long projecting fibers at each vertex. These fibers are thought to be the site of host cell attachment. Adenoviruses type 2 and 5 and coxsackie B viruses use the same receptor, designated the *coxsackie virus and adenovirus receptor* (CAR), whose usual function is to mediate cell interactions with extracellular matrix proteins. Some adenoviruses use the complement regulatory protein CD46 as a cellular receptor. Virus entry into the cell is also promoted by interaction of the penton base of the virus with alpha-V integrins. Viral type-specific antigens, which give rise to neutralizing antibody, are present on the hexons and fibers of the capsid. The hexons also contain a complement-fixation antigen with cross-reactivity among the mammalian adenoviruses.

Epidemiology and Transmission

The adenoviruses that cause human disease do not have nonhuman reservoirs, although nonhuman adenoviruses are found in other species. Some serotypes, especially types

1 and 2, routinely infect infants and young children, who then have prolonged asymptomatic viral shedding from the respiratory and *gastrointestinal* (GI) tracts. Other types, including those that have been most often implicated in respiratory disease (e.g., types 3, 4, and 7), are acquired later in life, characteristically in epidemic settings. In most instances, viral transmission probably takes place by direct contact with infectious secretions. However, the explosive nature of adenoviral acute respiratory disease in military recruits probably reflects airborne spread.

Most community adenovirus respiratory disease has been recognized in the summer months in association with outbreaks or sporadic cases of febrile pharyngitis or bronchitis. Nosocomial outbreaks of adenovirus infection have arisen in hospital wards, special care units, and psychiatric facilities. New variants of adenovirus have occasionally emerged and have been associated with outbreaks worldwide. Since 1996, a specific variant of *adenovirus type 7* (Ad7d2) has been responsible for several civilian outbreaks and a large military outbreak.¹³ More recently, *adenovirus type 14* (Ad14), a previously rare serotype, has been responsible for outbreaks of disease both in the military and in civilian populations.¹⁴⁻¹⁶ Most cases have been relatively mild febrile respiratory illnesses, but some cases have been seen with severe pneumonia requiring hospitalization. Infection with adenovirus type 36 is associated with weight gain in mice,¹⁷ and serologic positivity for this serotype appears to be more common in adults and children with obesity.¹⁸

Pathogenesis

Adenoviruses have been isolated from the upper airway, eye, urine, stool, and rarely, blood. The incubation period for naturally acquired adenovirus disease of the respiratory tract is usually 4 to 7 days but may be up to 2 weeks.

Cytopathologic changes have also been observed in bronchial epithelial cells,¹⁹ and crystalline arrays of virus particles have been found in alveolar lining cells of infected persons with severe illness.²⁰ The extent of damage to the respiratory tract in nonfatal adenovirus respiratory disease is not well defined but may result from a combination of direct viral mechanisms and host-related inflammatory responses to infection. In cases of fatal adenovirus pneumonia, bronchial epithelial necrosis, bronchial obstruction, and interstitial pneumonia have been seen.²¹ Cells containing large basophilic, intranuclear inclusions, so-called “smudge cells,” appear to be characteristic (Fig. 32-5). In lung transplant recipients, necrotizing bronchocentric pneumonia with diffuse alveolar damage has been reported.²²

Clinical Illness

Adenovirus Respiratory Disease. The nonpneumonic respiratory syndromes associated with adenovirus infection include acute respiratory disease of military recruits and pharyngoconjunctival fever of civilians, which have similar characteristics (Fig. 32-6). Adenovirus respiratory disease typically involves the pharynx as a moderate to severe, sometimes purulent, pharyngitis. Also characteristic of this disease is marked tracheitis, bronchitis, or tracheobronchitis, as well as rhinitis and conjunctivitis. Conjunctivitis is not a feature of infection with the other major respiratory

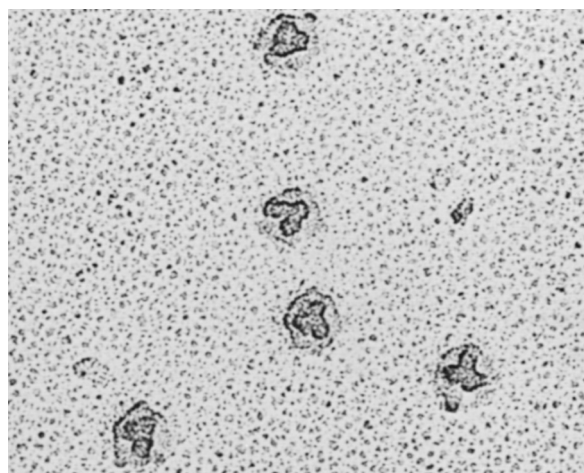


Figure 32-4 Photoelectron micrograph showing human adenovirus type 2. Each virion contains a lobulated group of three adenosomes, which are composed of DNA and protein. Full virion particles contain a total of 12 adenosomes, each of which is found below one vertex of the icosahedral capsid. (Courtesy J. Brown and W. Newcomb, University of Virginia.)

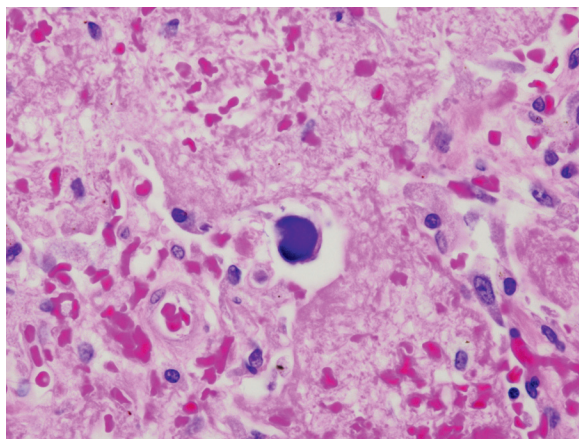


Figure 32-5 Adenovirus causing necrotizing pneumonia. Focal necrosis is apparent; the prominent cell in the center of the field is an adenovirus-infected "smudge cell," with an enlarged nucleus with basophilic inclusions surrounded by a thin rim of cytoplasm (H&E, $\times 80$ original magnification). (Courtesy William D. Travis, MD, Memorial Sloan Kettering Cancer Center, New York, NY.)

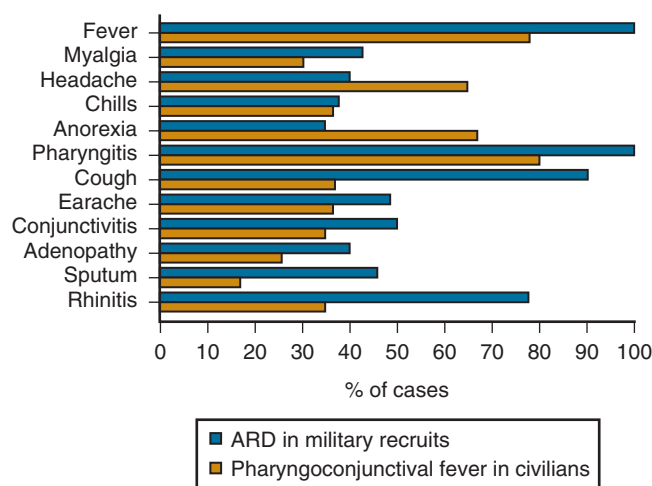


Figure 32-6 Graph showing comparison of the clinical characteristics of acute respiratory disease (ARD) of military recruits and pharyngoconjunctival fever of civilians. (Adapted from Dascomb HE, Hilleman MR: Clinical and laboratory studies in patients with respiratory disease caused by adenoviruses. *Am J Med* 21:161–174, 1956, and Martone WJ, Hierholzer JC, Keenlyside RA, et al: An outbreak of adenovirus type 3 disease at a private recreation center swimming pool. *Am J Epidemiol* 111:229–237, 1980.)

viruses and therefore, when present, is a useful diagnostic finding in adenovirus respiratory disease. With adenovirus respiratory disease, the conjunctivitis is typically mild and follicular, although some adenovirus types also cause the more severe condition, epidemic keratoconjunctivitis. Fever, chills, myalgia, and prostration are prominent features of adenovirus infection, so it is often perceived by the patient as a "flu-like" illness or an unusually severe cold.

Cases of acute respiratory disease tend to have more tracheobronchitis, perhaps reflecting acquisition of infection by the airborne route. Conversely, in pharyngoconjunctival fever, the infrequency of cough and other tracheobronchial complaints in some outbreaks may reflect infection contracted by pharyngeal and/or conjunctival inoculation with virus from contaminated water. The two syndromes are associated with the same viral serotypes and, in civilian

populations, both can be seen as sporadic cases. In young children, adenovirus infection has been associated with both mild and febrile respiratory illness, with an associated otitis media in approximately 40% of these cases.

Adenovirus Pneumonia. Adenovirus was first recognized as a cause of viral pneumonia in military recruits and has since been recognized as a rare cause of pneumonia in civilian adults (eFig. 32-5) and children. The clinical characteristics of adenovirus pneumonia are similar to those of other pneumonias, so it is difficult to make an accurate etiologic diagnosis on the basis of clinical features. In fatal cases, there has been extensive pulmonary damage, with death intervening 2 to 3 weeks into the illness. Intravascular coagulopathy has also been a late feature of some cases, and a septic shock picture has been described.²³ Adenoviruses cause a particularly aggressive form of pneumonia in neonates, characterized by necrotizing bronchiolitis and alveolitis.²⁴ The virus may be acquired from the mother, perhaps via the birth canal. Long-term sequelae of adenovirus infection may include persistent radiographic abnormalities, abnormal pulmonary function tests, bronchiectasis, and bronchiolitis obliterans.

Adenovirus Infection in Persons with Impaired Immunity. Adenoviruses can cause fatal pneumonia and disseminated infection, with hepatitis, hemorrhagic cystitis, and renal failure, in transplant patients and other immunodeficient persons.²⁵ Various immunotypes have been recovered from these patients (eTable 32-1), including higher numbered serotypes that are only seen in such patients. Types seen with particular frequency include 1, 2, 5, 6, 7, 11, 21, 31, 34, and 35. The clinical importance of the recovery of an adenovirus from these patients, particularly from stool samples, is often difficult to determine, because immunodeficient patients may shed adenoviruses in the absence of overt disease caused by them.

Diagnosis

Although diagnosis was traditionally achieved by virus culture, viral antigens or nucleic acid can be detected directly from appropriate specimens of respiratory secretions, conjunctival swabs, stool, or urine, depending on the clinical syndrome. Rapid detection of viral antigens in clinical specimens by ELISA or immunofluorescence and of viral DNA by nucleic acid amplification techniques is increasingly used instead of viral culture because of the fastidiousness of some serotypes and slow rate of isolation^{25a} (see Chapter 17). Quantitative measurement of adenovirus DNA levels in plasma may be useful for diagnosis and response to therapy.²⁶

Frozen specimens (-70°C) are satisfactory for testing because of the relative stability of adenoviruses. In cell culture, cytopathic effect usually appears in 3 to 7 days but may take several weeks, thus limiting the utility of viral culture in guiding clinical management. The time required to detect virus in cell culture can be shortened to as little as 2 days by employing centrifugation culture systems. Serodiagnosis has relied primarily on testing for a group-specific complement-fixation antibody response, using acute and convalescent serum specimens; however, infection with some adenovirus types is not detected by the

eTable 32-1 Adenoviruses Associated with Respiratory Tract Disease in Immunocompromised Patients***PRIMARY IMMUNODEFICIENCIES**

Upper Respiratory Tract Infection	
Group B	Type 34
Bronchitis	
Group C	Type 1
Bronchiolitis	
Group C	Type 2
Pneumonia	
Group A	Type 31
Group B	Types 7, 11, 35
Group C	Type 2

ORGAN TRANSPLANT RECIPIENTS

Upper Respiratory Tract Infection	
Group B	Type 7
Group C	Type 2
Pneumonia	
Group A	Type 31
Group B	Types 7, 11, 34, 35
Group C	Types 1, 2, 5, 6
Group E	Type 4

CANCER IMMUNOSUPPRESSION PATIENTS

Upper Respiratory Tract Infection	
Group A	Type 31
Group B	Type 35
Pneumonia	
Group B	Type 21
Group C	Types 1, 2
Group E	Type 4

AIDS PATIENTS

Upper Respiratory Tract Infection	
Group A	Type 31
Group D	Type 29
Pneumonia	
Group B	Types 3, 11, 16, 21, 34, 35
Group C	Types 1, 2, 5
Group D	Types 8, 22, 29, 30, 37, 43, 44, 45, 46, 47

*Adapted from Hierholzer JC: Adenoviruses in the immunocompromised host. *Clin Microbiol Rev* 5:262–274, 1992.

complement-fixation test. In biopsy specimens, the appearance of characteristic intranuclear basophilic inclusion bodies seen by light microscopy or of crystalline arrays of virus seen by electron microscopy is useful in histopathologic diagnosis.

Treatment and Prevention

Antiviral treatment of adenovirus infection does not have proven value. Ganciclovir and cidofovir are active in vitro, and an increasing number of reports indicate that intravenous ganciclovir may be useful in seriously ill patients, although at the expense of significant renal toxicity.²⁷ Cidofovir has also been used for treatment and for presumptive therapy of adenovirus infection in high-risk immunocompromised patients.²⁸ Although intravenous ribavirin (which is active for group C adenoviruses in vitro)²⁹ or ribavirin combined with immunoglobulin³⁰ has been used in individual patients, failures are common.³¹

Because of the prominent fever and systemic complaints associated with adenovirus respiratory disease, analgesics, such as aspirin and acetaminophen, are needed more often than with a milder coryzal illness such as a rhinovirus cold. Warm saline gargles are helpful for relieving throat pain, which does not usually require narcotics. The presence of pharyngeal exudate may sometimes lead to an incorrect diagnosis of streptococcal pharyngitis, resulting in the initiation of antimicrobial therapy.

Effective and safe live oral vaccines for adenovirus types 4 and 7 were developed for military use and, when delivered in enteric-coated capsules, have controlled acute respiratory disease in recruit populations. Use of these vaccines was not associated with replacement by nonvaccine serotypes. When manufacturing of these vaccines was discontinued, adenoviruses reemerged as important causes of acute respiratory disease in this population. A new vaccine for Ad4 and Ad7 has subsequently been introduced.³²

CORONAVIRUSES

Coronaviruses are enveloped viruses containing a single-stranded, positive-sense *ribonucleic acid* (RNA) genome of approximately 29,000 nucleotides. Distinctive club-shaped projections are present on the virus surface, giving the appearance of having a crown or corona, from which it derives its name. Coronaviruses are classified into four genera: alpha, beta, gamma, and delta. The beta genus is further subdivided into four lineages, A-D. The human coronavirus strains 229E (HCoV 229E) and HCoV NL63 are members of the alpha genus, while the human strains HCoV OC43 and HKU1 are members of the beta genus. The novel coronaviruses, SARS-CoV and MERS-CoV, are also members of the beta genus, in lineages B and C, respectively.³³

The virus contains five structural proteins: *spike* or S protein, *hemagglutinin-esterase* (HE), M (*matrix*), E (*envelope*), and N (*nucleocapsid*). The spike protein is the major envelope glycoprotein and mediates both attachment to cells and fusion with the cell membrane; antibodies to the spike protein are thought to be associated with protection and thus are candidates for therapeutic and vaccine targets. The second envelope protein, HE, is only found in some coronavirus strains. Nonstructural proteins such as the

viral replicases and proteinases, particularly the 3C-like proteinase, are also antiviral drug targets.

Epidemiology and Transmission

Human coronaviruses OC43 and 229E have been recognized as causes of the common cold for many years and cause frequent reinfections throughout life. In adults, these viruses account for 4% to 15% of acute respiratory disease annually and up to 35% during peak periods. Annual illness rates in children reach 8%, with peak rates up to 20%.³⁴ When *polymerase chain reaction* (PCR) techniques were applied to samples collected over 20 years from children younger than 5, coronaviruses were associated with 11.4 lower respiratory tract episodes and 67.3 upper respiratory tract illnesses per 1000 person-years.³⁵ The reported frequency of infection in adults for 229E and OC43 viruses has ranged from 15 to 25 per 100 persons per year, with up to 80% of infections seen in persons with prior antibody to the infecting virus.³⁶ Coronaviruses usually circulate during winter and early spring but can be detected year-round.³⁷

Novel coronaviruses have recently been associated with severe respiratory disease in outbreaks around the world. SARS emerged in southern China in 2003 and quickly spread globally.³⁸ The causative virus was subsequently named SARS-CoV. Ultimately, at least 8098 probable cases of severe respiratory disease and 774 deaths in all ages were attributable to SARS worldwide before the outbreak terminated in 2004. The source of this outbreak is believed to have been from an animal reservoir, the civet cat. More recently, a second outbreak of coronavirus severe respiratory illness has been recognized, with cases primarily found in Middle Eastern countries.^{39,39a,39b} In May 2014, the first case of MERS was confirmed in a traveler from Saudi Arabia to the United States. A second case was identified in a traveler from Saudi Arabia to Florida. The two cases were not linked.^{39c} The virus responsible for MERS has been named MERS-CoV. It is genetically closely related to coronaviruses found in bats, and evidence indicates that MERS-CoV also infects camels, but the role of each of these in transmission to humans remains to be defined.^{40,41} Information on MERS-CoV is actively evolving; current information can be found at <http://www.cdc.gov/coronavirus/mers/>.

For all coronaviruses, transmission likely involves close contact and inoculation of the respiratory tract with infectious secretions via large droplets as demonstrated in human challenge experiments for OC43⁴² and animal studies for SARS-CoV.⁴³ For SARS-CoV, virus shedding peaked at day 10 of symptom onset, which was at the height of disease severity.⁴⁴ This phenomenon accounted for the preponderance of transmission in hospitals, a feature that allowed the outbreak to be controlled with infection control procedures. The incubation period for SARS is estimated from 2 to 10 days, and for conventional human coronaviruses 3 to 4 days.

Pathogenesis

Conventional coronavirus antigen has been detected in epithelial cells shed from the nasopharynx of infected volunteers⁴⁵ and, during experimental infection, nasal airway resistance, mucosal temperature, and the albumin content of nasal secretions increase.⁴⁶ However, relatively little is

known about the pathogenesis of the common cold induced by conventional human coronaviruses.

The hallmark of pulmonary pathology in fatal cases of SARS was diffuse alveolar damage,⁴⁷ type II pneumocyte hyperplasia, squamous metaplasia, and multinucleated giant cells. Hemophagocytosis, or the phagocytosis of erythrocytes, leukocytes, and platelets by histiocytes, was reported, potentially as a consequence of cytokine dysregulation.⁴⁸ Furthermore, virus was detected within pulmonary epithelial cells.⁴⁹ From these findings, it is postulated that disease pathogenesis involves both direct damage to pulmonary epithelia by the virus in combination with an excessive or dysregulated host immune response.

Clinical Illness

Conventional human coronaviruses produce a typical coryzal illness that is indistinguishable from colds due to other viruses. Coronaviruses have also been linked with acute otitis media, exacerbations of asthma in children, and with exacerbations of chronic bronchitis and pneumonia in adults.

In contrast, SARS has a nonspecific presentation that is difficult to distinguish from other viral acute respiratory illnesses, particularly influenza. Common symptoms on presentation are fever, chills and/or rigors, myalgias, and occasionally diarrhea. Cough and dyspnea are the predominant respiratory symptoms but may not be present initially. Respiratory disease becomes more severe over 4 to 7 days, and about 20% of patients require respiratory support. MERS has had a similar presentation, although GI symptoms may be more prominent.⁵⁰ SARS fatality rates were 9.6% for all ages but higher in older adults,⁵¹ and children had milder disease.⁵² Similarly, the majority of recognized cases of MERS to date have been in individuals with comorbidities.⁵³ SARS laboratory abnormalities include elevations in lactate dehydrogenase, transaminases, and creatine kinase, as well as hematologic abnormalities, particularly lymphopenia (depletion of CD4 and CD8 T cells) and thrombocytopenia.

Diagnosis

Common findings on chest CT include unilateral or bilateral areas of ground-glass opacifications and interlobular septal and intralobular interstitial thickening. In most patients, peripheral involvement in the lower lung zones has been observed. In some cases, after recovery from acute illness, pulmonary fibrosis has developed.⁵⁴ Clinical features predictive of poor outcomes included the presence of bilateral disease at presentation, markedly elevated lactate dehydrogenase, older age, and other comorbid conditions.

The main site of viral replication of SARS-CoV appears to be the lower respiratory tract.⁴⁹ PCR detection is most reliable in the sputum, but viral RNA can also be detected in the blood and stool.⁵⁵ Serum antibodies rise within 2 to 3 weeks of illness, although measurements at 4 weeks have become the standard to exclude SARS.

Treatment and Prevention

Immunity against coronaviruses appears to be short-lived. Epidemiologic studies of coronavirus infection have demonstrated high reinfection rates.⁵⁶ In human volunteer experiments, infection with a 229E-like coronavirus only induced

effective immunity short-term because rechallenge with homotypic virus, the 229E serotype, resulted in infection and illness.⁵⁷ In addition, under certain circumstances, vaccines against animal coronaviruses have led to enhanced disease.⁵⁸ This is being taken into consideration but is not deterring efforts to develop an efficacious SARS-CoV vaccine.⁵⁹

There are no currently available antiviral agents with demonstrated clinical activity against coronaviruses in humans. Agents with potential activity against SARS-CoV include chloroquine, protease inhibitors, ribavirin, type I interferons, niclosamide, and anti-inflammatory agents such as indomethacin.⁶⁰⁻⁶² Ribavirin in combination with lopinavir/ritonavir (protease inhibitors used in HIV disease) was associated with a lower incidence of adverse outcomes compared with historical controls of ribavirin alone in one study. Nelfinavir, another protease inhibitor, has also demonstrated in vitro antiviral activity. Other targets for controlling SARS viral replication have included interferons. Although the mechanisms are unknown, chloroquine, niclosamide, and indomethacin all inhibit SARS-CoV in vitro.⁶³⁻⁶⁵

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is a member of the gammaherpesvirus subfamily of the herpes viruses and has the same structural and biochemical characteristics, which include an internal core containing linear double-stranded DNA, an icosahedral capsid containing 162 capsomeres, and an envelope derived from the host-cell nuclear membrane. However, the large size of the CMV virion (200 nm) and larger genome (>200,000 bp) distinguish it from other human herpes viruses. There is approximately 80% homology between the genomes of various strains of CMV, but sufficient differences exist to permit strain identification by restriction endonuclease analysis. The CMV genome codes for approximately 33 structural proteins, the functions of many of which are currently unknown. In addition, clinical isolates often encode multiple gene products not seen in laboratory strains. Envelope glycoproteins B and H have been identified as major antigens eliciting neutralizing antibody. Glycoprotein B may also be a target for cytotoxic T lymphocyte responses,⁶⁶ while multiple proteins also serve as targets for T-cell responses. CMV-specific, cytotoxic T-cell responses are an important host defense mechanism that is associated with survival from CMV infection in bone marrow transplant recipients.⁶⁷ However, CMV uses multiple mechanisms, including down-regulation of HLA class I on the cell surface and interference with antigen processing, to evade recognition by the host.

Epidemiology and Transmission

Infection with CMV, whether symptomatic or not, is followed by prolonged excretion of virus in urine, saliva, stool, tears, breast milk, vaginal secretions, and semen. Thus, the major reservoir for CMV is asymptomatic infected persons. Virus shedding persists for years in children with congenital and perinatal CMV infections. The virus is believed to be transmitted by direct contact, especially under conditions of intimacy such as found in child care centers⁶⁸ and the family setting. Thus, the rate of acquisition of infection is

greater in populations with high density, leading to infection at an early age. In addition to transmission by sexual intercourse, passage through a contaminated birth canal, and ingestion of breast milk, CMV infection can be acquired from transfused blood products and from transplanted organs. No seasonal patterns of CMV infection have been observed.

Pathogenesis

In human fibroblast cell cultures, CMV produces a slowly progressive lytic infection. Infected cells contain large irregular basophilic intranuclear inclusions and also eosinophilic inclusions in paranuclear areas. The intranuclear inclusions are a hallmark of CMV infection and have been found in cells of a number of organs, including kidney, liver, and the GI tract, as well as the lung (Fig. 32-7). In the lung, fibroblasts, epithelial cells, endothelial cells, and smooth muscle cells are all targets for CMV infection.⁶⁹

In immunocompetent persons, most infections are subclinical. If symptoms arise, the most typical manifestation is that of acute pharyngitis with features similar to mono-

nucleosis. In immunocompromised hosts, there may be a variety of clinical syndromes, the severity of which is impacted by whether infection is acquired *de novo* or represents reactivation of endogenous virus. The risk of severe disease is particularly high in transplant patients when a CMV-seronegative recipient receives an organ from a seropositive donor.

The pathogenesis of CMV pneumonia is partly related to viral replication but also thought to have an immunopathologic basis.⁷⁰ The development of CMV pneumonitis reflects a complex interaction between viral infection and graft-versus-host disease, particularly in marrow transplant recipients^{71,72,72a} (see Chapter 91). Two patterns of histopathology have been described in the lung tissue of bone marrow transplant patients with serious pneumonia.⁷³ One is a military pattern, with multiple focal lesions showing extensive cytomegaly with localized necrosis, alveolar hemorrhage, fibrin deposition, and neutrophilic response (see Fig. 32-7). The other is an interstitial pattern, with alveolar cell hyperplasia, interstitial edema, lymphoid infiltration, and diffusely distributed cytomegalic cells.

Clinical Illness

Cytomegalovirus causes a variety of human diseases, including congenital and perinatal infections, infectious mononucleosis, hepatitis, posttransfusion infection, and invasive infection in patients with impaired immunity. In transplant populations, CMV infection often involves multiple organ systems in conjunction with other opportunistic infectious agents.

Because the virus rarely causes pneumonia in healthy hosts, the main impact of CMV as a respiratory pathogen is in immunocompromised patients. In recipients of allogeneic bone marrow transplants, CMV is the most common infectious cause of interstitial pneumonia and, if untreated, is responsible for the highest fatality rate. The risk of CMV pneumonia is greatest between 30 and 90 days after bone marrow transplant. However, late-onset CMV syndromes, at more than 180 days posttransplantation, have been increasingly recognized with effective control of earlier-onset disease.

Risk factors for the disease include advanced age, the presence of acute graft-versus-host disease, intensive conditioning regimens, and allografts. CMV infection and pneumonitis also develop in the majority of lung transplant recipients who are seronegative and, if infection develops in a single-lung recipient, disease is especially marked in the transplanted lung.⁷⁴ In these patients, CMV pneumonitis may be a factor in the development of bronchiolitis obliterans. CMV can also be a primary pathogen in persons with AIDS, although it is more often encountered in conjunction with other pulmonary pathogens^{74a} (see Chapter 90). Characteristically, patients with CMV pneumonia have sustained fever, nonproductive cough, and dyspnea. Rales and tachypnea are often present, and marked hypoxemia is an indicator of life-threatening infection. Pneumonitis may be accompanied by mild neutropenia, thrombocytopenia, and elevated liver enzymes, which may be helpful in differential diagnosis.

Recently, CMV reactivation has been demonstrated to play a role in critically ill, previously immunocompetent patients. During the critical illness, some evidence suggests

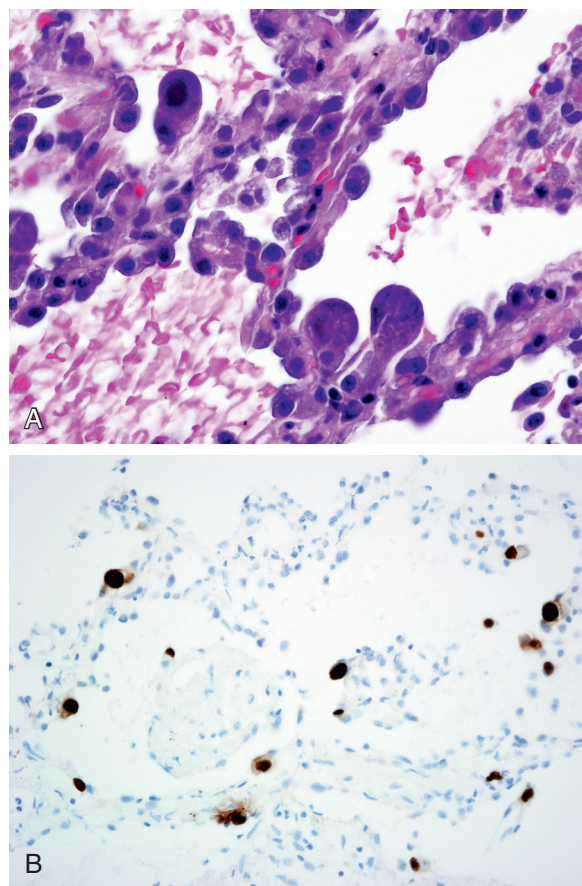


Figure 32-7 Cytomegalovirus infection. **A**, CMV pneumonitis with mild alveolar wall thickening and hyperplastic type II pneumocytes, some of which are infected, showing cytomegaly, nucleomegaly, thickened basophilic nuclear membranes and nuclear inclusion and small basophilic cytoplasmic inclusions (hematoxylin and eosin x80 original magnification). **B**, CMV pneumonitis with infected cells highlighted by immunohistochemistry with a brown color (CMV immunohistochemistry, x40 original magnification). (Images courtesy William D. Travis, MD, Memorial Sloan Kettering Cancer Center, New York, NY.)

a transient and vulnerable period of “immunoparalysis,” making reactivation and not exogenous infection of CMV more likely. In these patients, CMV viremia was found in 33% and was associated with prolonged hospitalization and death.⁷⁵ It is currently unclear whether CMV prophylaxis would be beneficial in this setting.

Diagnosis

Cytomegalovirus pneumonia should be in the differential diagnosis for any immunosuppressed patient with unexplained lower respiratory complaints or pulmonary opacities. However, the clinical assessment of patients with suspected CMV pneumonia is complicated because there are often simultaneous pulmonary infections with other microbes^{76,77} and because the clinical features and radiographic appearance of CMV pneumonia are not sufficiently characteristic to permit an accurate etiologic diagnosis. In addition, noninfectious pulmonary conditions are also common in the population at risk for CMV pneumonitis, including pulmonary malignancy or hemorrhage and post-transplant lymphoproliferative disorder (see eFigs. 91-16 and 91-17).

Chest radiographic changes (see eFig. 91-5A) are usually bilateral, with diffuse or focal haziness involving the mid and lower lung fields. Both miliary and interstitial radiographic patterns have been described. Patients with a miliary pattern may have a sudden onset of tachypnea, severe respiratory distress, and hypoxemia resulting in a rapidly fatal course,⁷⁸ whereas patients with an interstitial pattern of disease often have an insidious onset of pneumonia with slowly progressive hypoxemia. In these patients, pulmonary opacities may be initially localized, with bilateral spread over days or weeks. Often the perihilar distribution of the opacity is suggestive of pulmonary edema.⁷⁴ Common chest CT scan findings include small nodules (see eFigs. 91-3B, 91-4, 91-5), consolidation (see eFig. 91-2), and ground-glass attenuation (see eFigs. 91-3 and 91-5).⁷⁹

In patients with possible CMV pneumonia, the preferred approach to diagnosis is quantitative PCR in serum or *bronchoalveolar lavage* (BAL) fluid.⁸⁰ Culture and pathologic examination of specimens obtained by BAL and transbronchial biopsy may also be diagnostic, although these specimens are less suitable for making management decisions in acutely ill patients. The detection of virus in respiratory secretions, urine, or blood does not establish with certainty that CMV is responsible for a particular clinical syndrome. This is particularly true in patients with AIDS, in whom detection of CMV in BAL is often not associated with pulmonary pathology. However, in transplant recipients, the presence of CMV in blood does increase the risk of subsequent development of CMV pneumonia and is used in guiding preemptive therapy. Serologic testing has no role in diagnosis of acute infection and is used only to determine the serologic status of donors and recipients before transplantation.

Treatment and Prevention

Once CMV pneumonitis is established, particularly in allogeneic bone marrow transplant patients, poor outcomes are common. Ganciclovir is highly active against CMV *in vitro*, but monotherapy is not effective in pneumonitis in bone

marrow/stem cell transplant recipients. The combination of ganciclovir therapy and intravenous CMV immune globulin⁸¹ can reduce mortality from approximately 90% to 50% or lower in these patients. The effect of the immune globulin in this situation may mostly be to ameliorate graft-versus-host disease. Whether combination therapy is required in solid organ transplant recipients with CMV pneumonia is uncertain. Cidofovir and foscarnet are other antiviral drugs with activity against CMV. Both have been used successfully to treat CMV retinitis, but their effectiveness for treating CMV pneumonia has not been established. All of the available CMV antivirals have the potential for serious side effects that require close monitoring.

Guidelines for reducing the risk of CMV disease in stem cell transplant recipients have been published.⁸² Transplant candidates should be screened for evidence of CMV immunity, and CMV-seronegative recipients of allogeneic stem cell transplants from CMV-seronegative donors should receive only leukocyte-reduced or CMV-seronegative RBCs and/or leukocyte-reduced platelets. In mismatched solid organ transplant recipients (seronegative recipient/seropositive donor), posttransplant prophylaxis with oral ganciclovir or its prodrug valganciclovir significantly reduces the risk of CMV disease, although late-onset disease still happens.⁸³ Another strategy is preemptive therapy with ganciclovir or another anti-CMV agent when screening detects infection, but before clinically detectable disease develops. This strategy requires the use of rapid, sensitive, and specific laboratory tests for diagnosis.

No vaccines are available for the prevention of CMV infection or disease, although several strategies are being actively pursued, including live attenuated and inactivated subunit vaccines.

HANTAVIRUSES

Hantaviruses are members of the Bunyavirus family and include a number of genetically diverse viruses. The hantavirus responsible for an outbreak of severe pulmonary disease in the southwestern United States, Sin Nombre virus, is roughly spherical, with a mean diameter of 112 nm. The virions contain a dense envelope, surrounded by fine surface projections. Filamentous nucleocapsids are present within the virions. The genome consists of negative-sense single-stranded RNA arranged in three physically discrete gene segments. The *smallest segment* (S) encodes the nucleoprotein, the *middle-sized segment* (M), the two envelope glycoproteins, G1 and G2, and the *largest* (L), the putative polymerase protein.⁸⁴

Viral entry into the cell is mediated by a variety of cell surface integrins,⁸⁵ which may be related to the patterns of pathogenicity of the virus. The genome is segmented, and genetic reassortments in dually infected cells are common. It is believed that new pathogenic strains arise by this mechanism.

Epidemiology and Transmission

The *hantavirus pulmonary syndrome* (HPS) is a zoonosis in which humans experience severe, often fatal disease. Each of the individual hantavirus strains appears to be associated with a specific rodent host (e.g., Sin Nombre virus with the deer mouse, Bayou virus with the rice rat, *Black Creek*

Canal virus (BCCV) with the cotton rat, and New York virus with the white-footed mouse). The rodent hosts experience prolonged asymptomatic infection, but the features that are associated with maintenance of these viruses in rodent populations and with rodent-to-rodent transmission are unclear. Serologic studies suggest that hantaviral infection of feral rodents is widespread throughout North America.⁸⁶

Transmission to humans is presumed to result from contact with infected rodent excreta. Hantaviruses are stable and can persist in the environment for 10 to 15 days without loss of viability.⁸⁷ Risk factors for acquisition of HPS include high densities of rodents in the household, cleaning of contaminated environments, agricultural activities, and other forms of occupational exposure to rodent droppings. In the Four Corners region of the southwestern United States, El Niño–southern oscillation events have been linked to increased rainfall, high rodent population densities, and increased numbers of cases of HPS.⁸⁸

Person-to-person transmission was not seen in the North American outbreaks.⁸⁹ In contrast, a recent outbreak of HPS in South America has suggested that, under certain circumstances, person-to-person transmission can take place.⁹⁰ This feature appears to be unique to the particular hantavirus implicated in that outbreak (Andes virus) and has not been a major component of other outbreaks. Currently, approximately 11 to 48 cases of HPS per year are reported in the United States,⁹¹ with a case fatality rate of 35%.

Pathogenesis

Infection with Sin Nombre virus or other agents of HPS have relatively long incubation periods (median 14 to 17 days; range 1 to 51 days),⁹² and antibody and cellular responses in humans are usually detectable at the time of presentation.⁹³ Neutralizing antibody is directed against the surface glycoproteins G1 and G2, and lower titers on presentation correlate with greater disease severity.⁹⁴ Viremia is detectable at presentation and declines promptly after resolution of fever.

Pathologic findings in fatal cases include pleural effusions, alveolar edema and fibrin, and interstitial mononuclear cell infiltrate⁹⁵ with little necrosis or neutrophil infiltration. These findings are felt to be most consistent with a capillary leak syndrome with subsequent noncardiogenic pulmonary edema. Immunopathologic responses play a major role in HPS.⁹⁶ Infection of humans with Sin Nombre virus and other hantaviruses results in widespread expression of viral antigens in endothelial cells of pulmonary and cardiac tissues,⁹⁷ and CD8 T cell responses peak at the time of maximal clinical symptoms, implicating these responses in the pathogenesis of disease.⁹⁸ Myocardial depression has also been ascribed to induction of nitric oxide and locally secreted cytokines in response to infection.⁹⁹ Another pathogenic mechanism may be antagonism of the host innate immune response by the hantavirus G1 tail.¹⁰⁰

Clinical Features

Presentation of HPS begins with a prodrome of fever, chills, and myalgias, occasionally accompanied by abdominal discomfort and GI symptoms, and generalized malaise. Upper respiratory symptoms are usually absent. After a variable

period of several days, the patient presents with a mild, nonproductive cough and progressive dyspnea resulting from leakage of high-protein edema fluid into the alveoli. On physical examination patients are febrile, with tachypnea and tachycardia with mild hypotension. Examination of the chest may reveal fine crackles but is otherwise unremarkable.

Laboratory studies generally reveal hemoconcentration, mild thrombocytopenia, and mildly elevated liver function tests. The triad of thrombocytopenia, left shift with circulating myeloblasts, and circulating immunoblasts is highly suggestive of HPS.¹⁰¹ Multivariate analysis has identified dizziness, nausea, and the absence of cough as clinical symptoms predictive of HPS, as well as thrombocytopenia, elevated hematocrit, and decreased serum bicarbonate as features that help distinguish HPS from other causes of acute respiratory distress such as pneumococcal pneumonia and influenza.¹⁰² Mild renal abnormalities may be detected but, unlike the situation with another hantaviral illness, hemorrhagic fever with renal syndrome, do not progress to renal failure. Renal dysfunction may be more common in HPS associated with the Bayou hantavirus.¹⁰³

Pleural effusions are present in most cases. Early in the course of HPS, these effusions are transudative, while later they develop higher fluid protein content and in severe cases have the protein characteristics of plasma.¹⁰⁴ Cardiopulmonary manifestations in severe cases include a shock state with low cardiac index, low stroke volume index, and high systemic vascular resistance.¹⁰⁴ Progression is associated with worsening cardiac dysfunction and development of lactic acidosis. In those patients who survive, exertional dyspnea and reduced expiratory flow are common in early convalescence and resolve in most patients.¹⁰⁵ However, some patients have manifested long-term pulmonary and cognitive dysfunction.¹⁰⁶

Diagnosis

Chest radiographs are typical of pulmonary edema, without consolidation. In the absence of immunodeficiency, patients universally have detectable serum *immunoglobulin M* (IgM) and IgG antibody at the time of admission, and serologic techniques are the mainstay of diagnosis. In low-prevalence areas, a positive IgM is diagnostic.¹⁰⁷ Virus can also be detected in blood by *reverse transcriptase polymerase chain reaction* (RT-PCR) during the first 10 days of illness.¹⁰⁸ In contrast, hantaviruses are difficult to isolate from clinical material in cell culture and grow slowly. Isolation of virus from tissue is laborious and time consuming and must be undertaken in suitable containment facilities, so it is not useful for diagnosis.

Treatment and Prevention

Treatment is supportive and requires careful management of fluid status to maintain perfusion without exacerbating pulmonary edema. It has been suggested that high-dose steroid therapy may be useful⁹⁶ because of the pathogenesis of the disease and potential utility of steroids in systemic capillary leak syndrome. In severe cases, extracorporeal membrane oxygenation may be beneficial.^{109,110} The broad-spectrum antiviral agent ribavirin is active against hantavirus in vitro and was demonstrated to be effective against hantavirus-induced hemorrhagic fever with renal

syndrome in Korea.¹¹¹ However, trials of ribavirin in HPS have not shown efficacy.¹¹²

HERPES SIMPLEX VIRUS

Both *herpes simplex virus* (HSV) types 1 and 2 belong to the alphaherpesvirus subfamily of herpesviruses and share the same basic structural features. HSV-1 is most commonly associated with respiratory infection, whereas HSV-2 is more commonly associated with genital infection. The two HSV types were originally differentiated by neutralization assay and have been found to differ in a number of biologic and biochemical properties as well. Infection with either type results in production of both type-specific and cross-reactive antibodies, with higher concentrations of antibodies being produced against the homologous type.

Epidemiology and Transmission

Humans are the reservoir for HSV-1 and HSV-2 viruses. With primary infection, infectious virus is produced in the skin and mucous membranes, being present in vesicle fluid and cellular debris from herpetic ulcers. After establishment of latency in nerve ganglia, virus is intermittently shed in respiratory, vaginal, and urethral secretions in the absence of clinical disease. Asymptomatic respiratory tract shedding can be detected in about 1% to 2% of seropositive children and adults.

HSV-1 spreads by means of transfer of virus-containing respiratory secretions, vesicle fluid, and cell debris under conditions of close personal contact. The portals of entry for primary infection are the mucous membranes of the oropharynx and possibly the eye. Virus deposited onto areas of burned or abraded skin, and exogenous inoculation or autoinoculation of virus, also lead to clinical lesions. Cases of HSV-1 arise sporadically throughout the year, occasionally in small clusters. HSV-1 infection is usually acquired in childhood or adolescence, with epidemiologic surveys showing a prevalence of antibody to HSV-1 in 30% to 100% in adults.

Pathogenesis

Primary HSV infection has a mean incubation period of approximately 1 week. Primary infection begins at a local site, with viral replication in parabasal and intermediate epithelial cells and resultant cell destruction and initiation of host inflammatory responses. Cells containing characteristic nuclear inclusions and sometimes multinucleation may be observed in lesions. In immunocompetent individuals, regional lymph nodes may be involved during primary infection, but the disease is usually contained at the primary site by innate antiviral responses. In neonates and others with deficient or impaired immune systems, local infection may be followed by viremic spread to multiple organs, including skin, liver, brain, adrenals, and lungs. Disease may also disseminate in such individuals following reactivation of latent infection. Visceral infection is characterized by a highly destructive coagulation necrosis of involved sites.¹¹³ In a series of fatal cases of HSV pneumonia, inflammatory infiltrates, parenchymal necrosis, and hemorrhage were found at autopsy.¹¹⁴ Patients with associated herpetic laryngotracheitis have necrotizing lesions in these areas.

Latent infection is established in sensory nerve ganglia and is followed by life-long recurrences of virus shedding and often lesions on skin and mucous membranes of the involved dermatomes. Cellular immunity is of primary importance in controlling HSV infection; studies in patients with AIDS and severe mucocutaneous HSV indicate that both CD4 and CD8 T cells contribute to control of viral replication and spread.¹¹⁵

Clinical Illness

Acute Gingivostomatitis and Pharyngitis. Herpetic disease of the oral cavity and pharynx is the most common overt manifestation of primary infection with HSV-1. Scattered or clustered vesicles and ulcers of various sizes (3 to 7 mm) are located on the buccal mucosa, tongue, gingiva, or floor of the mouth. Individual lesions usually appear as a shallow, white-based ulcer surrounded by a thin rim of erythema. Pain is prominent in involved areas of the mouth and pharynx, and regional nodes are tender and enlarged, particularly with the pharyngitis. Fever, malaise, and reduced oral intake may add to the overall severity of these illnesses, which last up to 2 weeks.

Chronic Ulcerative Pharyngitis and Laryngotracheitis. In immunocompromised patients, including those with AIDS, both primary and recurrent HSV infection may manifest as a chronic erosive process of the mucous membranes of the oral cavity and upper airway. Characteristically, the lesions appear as large (5 to 15 mm) individual ulcerations that are slowly progressive and may coalesce when present in adjacent sites. The base of the ulcer is white or gray. Although shallow, the lesions are usually painful and may reduce oral intake. Herpetic lesions are sometimes present on the lip and skin of the face. Infection may spread to the esophagus and lower airway, possibly facilitated by instrumentation such as orotracheal intubation or bronchoscopy, resulting in the development of similar lesions at these sites. Clinical features of herpetic tracheobronchitis include dyspnea, cough, fever, chills, diaphoresis, chest pain, wheezes, hypotension, and hypoxemia.¹¹⁶ Herpetic tracheobronchitis has also been reported in elderly patients presenting with bronchospasm who did not have histories of chronic lung disease or of immunosuppression.¹¹⁷

Pneumonia. Herpes simplex virus causes pneumonia in neonates with congenital and peripartum infections and in patients with malignancy, burns, organ transplantation, and other conditions associated with impaired immunity. Herpes simplex pneumonia has been reported in neonates between the third and 14th days of life and to be associated with prominent hila and central interstitial opacity on chest radiography.¹¹⁸ Other associated findings include thrombocytopenia, disseminated intravascular coagulation, abnormalities in liver function, vesicular skin lesions, and deterioration during antimicrobial treatment. The pathologic findings in infants, children, and adults suggest that the disease may be the result of direct extension of infection from the tracheobronchial tree to the lung or as the result of hematogenous dissemination of virus from mucocutaneous lesions of the upper airway or genitourinary tract. CT scan findings include multifocal segmental and subsegmental ground-glass opacities but are not

distinctive.¹¹⁹ In one study, more than one half of the patients had concomitant pulmonary infection with other microorganisms, including bacterial, candidal, and *Aspergillus* species and cytomegalovirus.¹¹⁴ Histologic evidence of herpetic esophagitis was present in 10 of 16 patients with herpes pneumonia in whom esophageal examination was performed. Some cases are nosocomially acquired.¹²⁰

Herpes simplex virus infection of the lower airway has also been found in association with ARDS. The relationship of HSV infection to ARDS is unclear, but the presence of HSV in the lower respiratory tract was associated with the need for prolonged respiratory support and an increased late mortality. Isolation of HSV from lower respiratory tract secretions has also been common in mechanically ventilated patients and may be associated with a poor outcome,^{121,122} although it is unclear whether this represents reactivation as a consequence of severe illness or whether the virus plays a direct role in mortality.^{123,124}

Diagnosis

The clinical features of herpetic gingivostomatitis are sufficiently characteristic to permit accurate diagnosis in most cases. Other conditions with similar oral lesions are limited and include herpangina, aphthous stomatitis, Steven-Johnson syndrome, and other enanthems resulting from infection and drug sensitivities. In herpangina, the lesions are smaller (1 to 3 mm), more often vesicular, and usually localized to the soft palate. The ulcers in aphthous stomatitis are few, relatively deep, and circumscribed. Aphthosis is characterized by periodic recurrence, whereas acute herpetic gingivostomatitis and pharyngitis are limited to a single occurrence. Herpetic pharyngitis, when exudative, must be distinguished from pharyngitis due to *Streptococcus pyogenes*, adenovirus, Epstein-Barr virus, and diphtheria. The diagnosis of acute herpetic disease of the oropharynx can be confirmed by examination of Giemsa- or Wright-stained smears of scrapings from the base of a fresh lesion (Tzanck test) and by culture of scrapings or swab specimens. Techniques for the rapid detection of viral antigens or DNA are widely available.

Chronic ulcerative pharyngitis due to HSV has a characteristic clinical appearance that is highly suggestive of the diagnosis. The white color of the lesions may lead to confusion with candidiasis, but the lesion of thrush is an easily removable plaque, not an ulcer. Thrush and chronic herpetic pharyngitis may coexist in the same patient. The lesions of aphthous stomatitis are not characteristically found in the back of the oropharynx and are relatively small (2 to 5 mm) with a fixed diameter.

The diagnosis of herpetic laryngotracheitis may be difficult because of the inaccessibility of the lesions. The disease should be suspected in any immunocompromised patient with herpetic lesions of the mouth, upper airway, or skin of the face, especially if endotracheal intubation has been performed. In such patients, bronchoscopic examination is indicated for sampling of suspected areas for cytology and viral culture.

The diagnosis of HSV pneumonia should be suspected in any immunocompromised patient with unexplained pulmonary opacities, especially in the presence of herpetic laryngotracheitis or herpetic lesions of other mucocutaneous sites, including the genital area. Definitive diagnosis of

HSV pneumonia depends on obtaining a sample of involved lung for viral culture and testing for HSV antigen or nucleic acid. Limited experience with lung biopsy in patients with HSV pneumonia suggests that obtaining adequate samples for culture and histologic examination may be a problem¹¹⁴ and that, when possible, generous biopsy specimens should be obtained.

Treatment and Prevention

No vaccines of proven value are currently available. Primary HSV gingivostomatitis in immunocompetent persons responds to oral acyclovir treatment. Specific therapy of herpes simplex pneumonia has not been evaluated in controlled trials, but most clinicians would use intravenous acyclovir. In immunosuppressed patients with chronic mucocutaneous HSV infection, including pharyngitis and laryngotracheitis, prompt treatment with acyclovir is recommended to control the local infection and prevent possible dissemination to the lung. Valacyclovir, the valine ester prodrug of acyclovir, and famciclovir, the prodrug of penciclovir, are orally administered drugs that are also effective for mucocutaneous HSV.

Antiviral susceptibility testing should be considered in patients with serious HSV infection who do not respond to initial treatment with oral valacyclovir or intravenous acyclovir. Foscarnet is probably the best available alternative therapy. Prophylactic intravenous and oral acyclovir regimens have been shown to be effective in preventing recurrences of mucocutaneous HSV infection in seropositive patients undergoing intense periods of immunosuppression, such as bone marrow transplant recipients or patients receiving combination chemotherapy for leukemia.

INFLUENZA VIRUS

Influenza viruses belong to the family Orthomyxoviridae and are classified into three distinct types: influenza A, influenza B, and influenza C virus. All three viruses share the presence of a host cell-derived envelope, envelope glycoproteins important for entry and egress from cells, and a segmented negative-sense, single-stranded RNA genome. The standard nomenclature for influenza viruses includes the influenza type, place of initial isolation, strain designation, and year of isolation. For example, an influenza A virus isolated from a patient in Puerto Rico in 1934 is given the strain designation A/Puerto Rico/8/34.

The envelope glycoproteins are the *hemagglutinin* (HA) and *neuraminidase* (NA). HA mediates binding of the virus to sialic (also known as *neuraminic*) acid residues on host cell glycoproteins and glycolipids and is essential for viral entry. NA cleaves terminal sialic acid (neuraminic acid) residues from host cell molecules, thereby releasing new viral particles from the cell in which they replicated. At least 16 highly divergent, antigenically distinct HAs (H1 to H16), and at least 9 distinct NAs (N1 to N9), have been described in influenza A viruses. Influenza A viruses are therefore further divided into subtypes on the basis of the *hemagglutinin* (H) and *neuraminidase* (N) (e.g., H1N1 or H3N2). Infection with influenza virus results in long-lived resistance to reinfection with the homologous virus. Infection induces both systemic and local antibodies, as well as cellular

responses, each of which plays a role in recovery from infection and resistance to reinfection.

Epidemiology and Transmission

Influenza virus infection is acquired by transfer of virus-containing respiratory secretions. Both small particle aerosols and droplets probably play a role in this transmission, but for infection control purposes influenza is generally considered to be transmitted by droplets. In temperate climates in either hemisphere, epidemics are seen almost exclusively in the winter months (generally October to April in the Northern hemisphere and May to September in the Southern hemisphere), whereas in the tropics, influenza may be seen throughout the year.

Influenza epidemics are regularly associated with morbidity and mortality, usually expressed in the form of excess rates of pneumonia and influenza-associated hospitalizations and deaths, with as many as 51,000 deaths annually in the United States.¹²⁵ Attack rates are generally highest in the young, whereas mortality is generally highest in the elderly. Excess morbidity and mortality are particularly high in those with medical conditions including pulmonary conditions such as asthma or COPD. Rates of influenza-related hospitalizations are particularly high in healthy children younger than 2, where rates approach those of older children with high-risk conditions.^{126,127}

A high frequency of antigenic variation is a unique feature of influenza virus that helps explain why this virus continues to cause epidemic disease. Antigenic variation principally involves the two external glycoproteins of the virus, the HA and NA, and is referred to as antigenic drift or antigenic shift, depending on whether the variation is small or great. Antigenic *drift* refers to relatively minor antigenic changes that result from amino acid changes in one or more of the five identified major antigenic sites on the HA molecule.¹²⁸ Antigenic *shift* refers to the complete replacement of the HA or NA with a novel HA or NA. These viruses are “new” viruses to which the population has no specific immunity. When such a new virus is introduced into a population, a severe, worldwide epidemic, or pandemic, of influenza can result. Influenza pandemics in the 20th century include the H1N1 pandemic of 1918, the H2N2 pandemic of 1957, and the H3N2 pandemic of 1968. Extensive surveillance and sequence information suggests that these new HA and NA genes are introduced into viruses circulating in humans from resident populations of influenza A viruses in birds.¹²⁹

Since 1997, sporadic outbreaks of influenza in humans caused by direct transmission of avian viruses from bird to human have been reported. Although sustained human-to-human transmission has not been seen, avian subtypes such as H5N1¹³⁰ and H7N9¹³¹ continue to pose a potential pandemic threat. In the spring of 2009, a novel H1N1 virus containing genes from viruses of swine, avian, and human origin emerged. Importantly, the HA gene of this virus was derived from swine influenza virus. Although still an H1N1 virus, the novel, or *pandemic H1N1* (pH1N1) was antigenically distinct from the human H1N1 viruses in circulation since 1977. Instead, the HA was closely related to human H1 viruses from the early 20th century that had been introduced into pigs in approximately 1918 and had not undergone significant antigenic evolution in these animals since

that time. Perhaps for this reason, older adults were relatively spared, and the pandemic disease affected mainly children, adolescents, and adults younger than 50.

Although the circulation of multiple antigenic subtypes is confined to influenza A viruses, influenza B viruses undergo significant antigenic variation as well. Currently, two antigenically distinct lineages of influenza B have co-circulated, designated the “Yamagata” and the “Victoria” lineages. Because antibodies to viruses in one lineage do not provide substantial protection against the other, recent influenza vaccines have included examples of both (see later).

Pathogenesis

Infection with influenza virus in humans is generally limited to the respiratory tract. After inoculation, the incubation period is thought to be from 18 to 72 hours depending in part on the inoculum dose. Virus shedding is maximal at the onset of illness and may continue for 5 to 7 days or longer in children. In immunocompromised patients, especially recipients of solid organ or hematopoietic stem cell transplants, viral shedding can be prolonged for weeks to months.¹³²

Bronchoscopy of individuals with influenza typically reveals diffuse inflammation of the larynx, trachea, and bronchi, as well as a range of histologic findings, from vacuolization of columnar cells with cell loss, to extensive desquamation of the ciliated columnar epithelium down to the basal layer of cells.^{133,134} Generally, the tissue response becomes more prominent as one moves distally in the airway. Recovery is associated with rapid regeneration of the epithelial cell layer and pseudometaplasia. Fatal influenza pneumonia exhibits diffuse alveolar damage with hyaline membranes lining the alveoli, and the alveolar air spaces contain edema fluid, strands of fibrin, desquamated epithelial cells, and inflammatory cells (Fig. 32-8A-D).

Abnormalities of pulmonary function are frequently demonstrated in otherwise healthy, nonasthmatic young adults with uncomplicated (non-pneumonic) acute influenza. Demonstrated defects include diminished forced expiratory flow rates, increased total pulmonary resistance, and decreased density-dependent forced expiratory flow rates consistent with generalized increased resistance in airways less than 2 mm in diameter,^{135,136} as well as increased responses to bronchoprovocation.¹³⁵ In addition, abnormalities have been seen in the carbon monoxide diffusing capacity¹³⁷ and the alveolar-arterial oxygen difference.¹³⁸ Pulmonary function defects can persist for weeks after clinical recovery. Influenza in asthmatics or patients with chronic obstructive disease with influenza may result in acute declines in forced vital capacity or FEV₁. Individuals with acute influenza may be more susceptible to bronchoconstriction from air pollutants such as nitrates.¹³⁹

Clinical Illness

Typical uncomplicated influenza often begins with an abrupt onset of symptoms after an incubation period of 1 to 2 days. Systemic symptoms include feverishness, chilliness, or frank shaking chills, headaches, myalgia, malaise, and anorexia. Typical respiratory symptoms include dry cough, severe pharyngeal pain, and nasal obstruction and discharge. Elderly individuals may simply present with

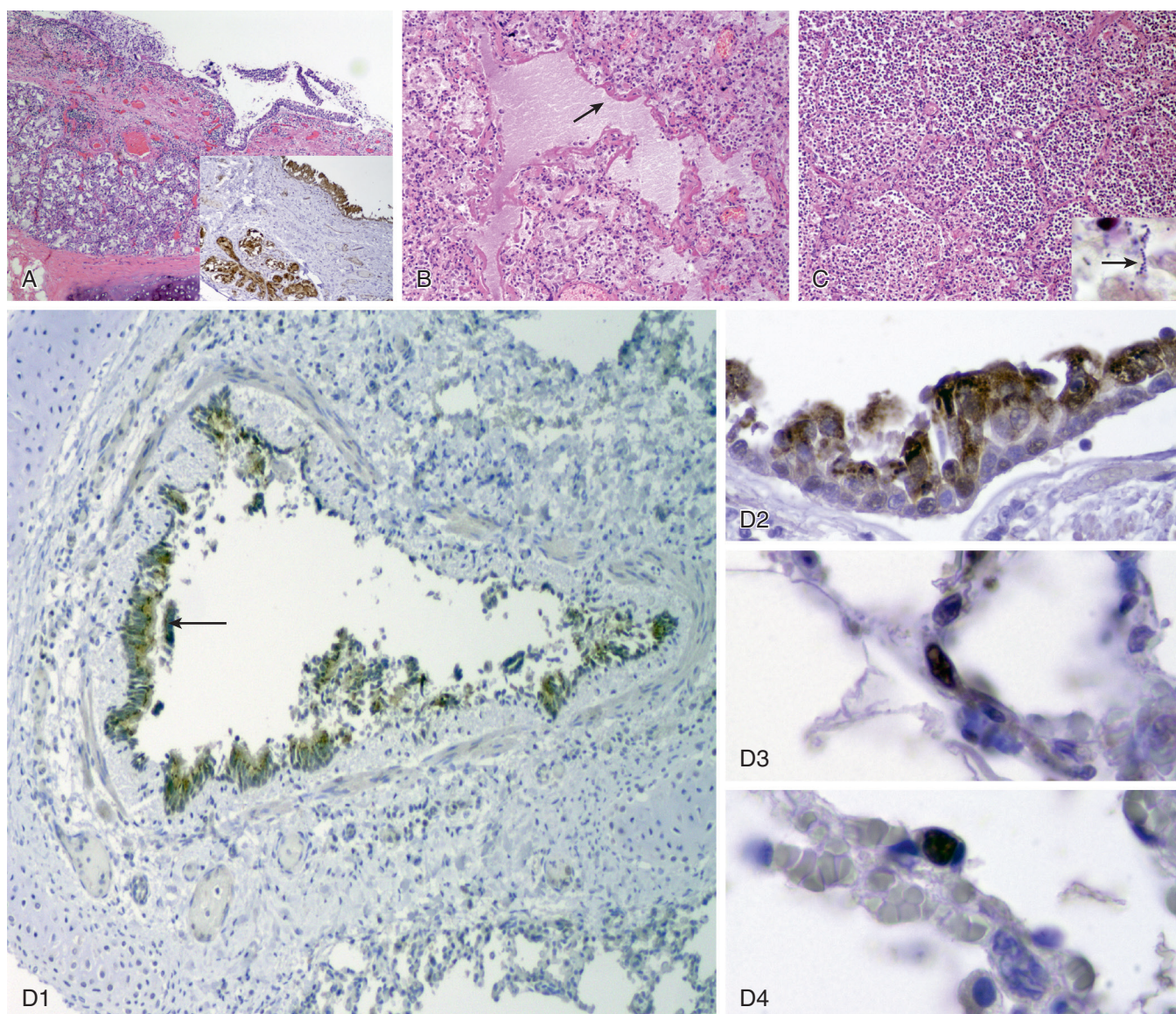


Figure 32-8 Pulmonary involvement in 2009 H1N1 influenza. **A.** Acute necrotizing tracheitis and inflammation of the submucosal tracheal mucous glands (H&E, $\times 400$ original magnification). *Inset:* Immunohistochemical stain for influenza. Viral antigen is stained red-brown on a hematoxylin-stained background, with prominent staining of the respiratory epithelium and underlying mucous glands. **B.** Postmortem lung section showing diffuse alveolar damage with hyaline membranes (*arrow*) lining an alveolar duct and adjacent alveoli. The alveolar air spaces contain edema fluid, strands of fibrin, desquamated epithelial cells, and inflammatory cells (H&E, $\times 100$ original magnification). **C.** Massive infiltration of neutrophils in the airspaces of alveoli associated with secondary bacterial bronchopneumonia (H&E, $\times 100$ original magnification). *Inset:* Brown and Hopps modified tissue Gram stain showing chains of bacteria morphologically compatible with streptococci or pneumococci (*arrow*) ($\times 1000$ original magnification). **D1,** Immunohistochemical staining for influenza in bronchus. Viral antigen is stained red-brown on a hematoxylin and eosin-stained background. *Arrow* shows influenza antigen-positive cells in the bronchial epithelium. **D2,** The section shows an acute necrotizing bronchitis with transmural infiltration of inflammatory cells ($\times 100$ original magnification). **D3** and **4,** Immunohistochemical staining for influenza in a bronchiole. Influenza antigen-positive cells are seen in the bronchiolar epithelium, including ciliated cells, and in the nuclei of some basilar cells ($\times 400$ original magnification). Immunohistochemical staining for influenza in alveolar cells, both type I (**D3**) and type II (**D4**) ($\times 1000$ original magnification). (Adapted from Gill JR, Sheng ZM, Ely SF, et al: Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. *Arch Pathol Lab Med* 134(2):235–243, 2010. Fig 1).

fever, lassitude, and confusion without any of the characteristic respiratory complaints. There may be a wide range of symptoms, but the presence of fever plus either sore throat or cough is predictive of positive culture results for influenza in adults.

The syndrome of primary influenza viral pneumonia was first well documented in the 1957–1958 outbreak. The illness begins with a typical onset of influenza, followed by a rapid progression of fever, cough, dyspnea, and cyanosis. Physical examination and thoracic imaging studies reveal

bilateral abnormalities (Fig. 32-9, eFigs. 32-6 and 32-7), sometimes suggestive of an acute lung injury pattern or ARDS (eFig. 32-8). H1N1 (“swine-origin”) influenza infection has a relatively nonspecific appearance, ranging from normal or nearly normal chest radiography at presentation to multifocal bilateral opacities resembling multifocal pneumonia (eFig. 32-9) or a noninfectious acute lung injury pattern. Chest CT often shows multifocal areas of ground-glass opacity and consolidation, which may show a peripheral distribution, resembling organizing pneumonia

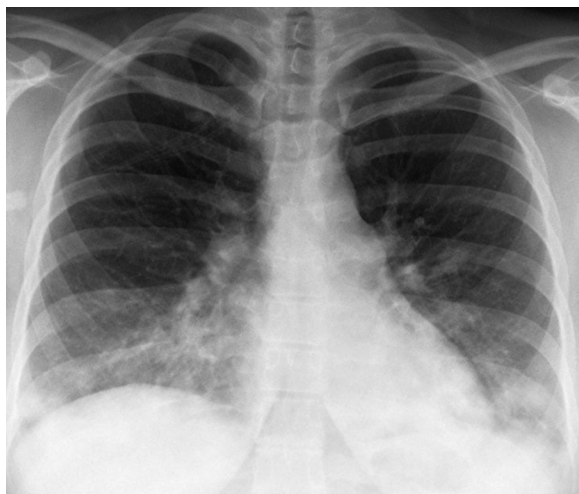


Figure 32-9 Seasonal influenza A. Frontal chest radiograph shows multi-focal, bilateral, perihilar, and lower lobe predominant bronchovascular thickening and somewhat nodular consolidation. (Courtesy Michael Gotway, MD.)

(eFig. 32-9B-E), although other patterns, including small nodules (eFigs. 32-10A and B), ground-glass opacity associated with linear and reticular abnormalities without a clear zonal distribution (eFig. 32-10C), and lobar consolidation (eFig. 32-10D), may be observed. Gram stain of the sputum fails to reveal significant bacteria, and bacterial culture yields sparse growth of normal flora, whereas viral cultures yield high titers of influenza A virus. Such patients do not respond to antibacterial drugs and the mortality is high.

Secondary bacterial pneumonia is an important complication of influenza (Fig. 32-8C) (eFig. 32-11). The classic description is of an influenza illness followed by a period of improvement, usually lasting 4 to 14 days. Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and an area of consolidation detected on physical examination and chest radiography. The most common bacteria implicated are *Streptococcus pneumoniae*, with a significantly increased frequency of *Staphylococcus aureus*,^{140,141} including methicillin-resistant *staphylococcus* (MRSA). Patients may present with mixed viral and bacterial pneumonia. Bacterial superinfections of influenza have been postulated as a major cause of death during the pandemic of 1918.¹⁴²

Patients with a wide range of preexisting conditions are well recognized to be at higher risk for the development of pneumonia and other complications of influenza leading to hospitalization or death (Table 32-4). In recent years, new conditions leading to increased risk have been recognized, including the presence of neuromuscular conditions that compromise respiration¹⁴³ and, in the 2009 pandemic, the presence of obesity.^{144,145} In addition, the 2009 pandemic reemphasized the known increased risk of hospitalization or death in women in all stages of pregnancy or in the immediate postpartum period.^{146,147}

Diagnosis

Immunologic detection of influenza antigens in respiratory samples can be used for rapid diagnosis, and a large number of such tests are commercially available^{147a} (see Chapter

Table 32-4 Target Groups for Influenza Immunization*

PERSONS AT INCREASED RISK FOR COMPLICATIONS

- All children aged 6 through 59 months
- All persons aged ≥ 50 years
- Adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Persons who have immunosuppression (including immunosuppression caused by medications or by HIV infection)
- Women who are or will be pregnant during the influenza season
- Children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection
- Residents of nursing homes and other long-term care facilities
- American Indians/Alaska Natives
- Persons who are morbidly obese (BMI ≥ 40)

PERSONS WHO CAN TRANSMIT INFLUENZA TO THOSE AT HIGH RISK

- Health care personnel
- Household contacts (including children) and caregivers of children aged ≤ 59 months (i.e., aged < 5 years) and adults aged ≥ 50 years, with particular emphasis on vaccinating contacts of children aged < 6 months
- Household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

*Routine annual influenza vaccination is recommended for all persons aged ≥ 6 months who do not have contraindications.

Adapted from Summary Recommendations: Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—(ACIP)—United States, 2013-14. Influenza Prevention and Control Recommendations <http://www.cdc.gov/flu/professionals/acip/2013-summary-recommendations.htm>

17). The reported sensitivities of each test in comparison to cell culture or nucleic acid amplification varies between 40% and 80% and depends on the nature of the samples tested and the viral strain. In general, sensitivities in adults and elderly patients tend to be lower than those reported in young children, who shed much larger quantities of virus and higher concentrations of antigen in their samples.¹⁴⁸ Similarly, sensitivity is likely to be higher early in the course of illness, when viral shedding is maximal.

Molecular diagnostic techniques have recently emerged as the diagnostic modality of choice in most laboratories. Real-time RT-PCR methods have been developed and licensed and are discussed in greater detail in Chapter 17. Many of these tests are designed to detect multiple respiratory pathogens simultaneously and are leading to a growing recognition of the role of respiratory viruses and coinfection in diverse respiratory infections.^{148a} Most cases of influenza, in otherwise healthy individuals with typical symptoms during the course of a recognized influenza epidemic, do not need specific viral confirmation. However, diagnostic testing should be used if the results of the test will influence subsequent clinical management, such as the use of antiviral agents, the need for antibacterial drugs, and the use of infection control.¹⁴⁹

Virus can also be isolated readily from nasal swab specimens, nasal aspirates, combined nose and throat swabs, sputum, or endotracheal aspirate specimens. More than 90% of positive influenza cultures can be detected within 3 days of inoculation.¹⁵⁰

Treatment and Prevention

Vaccines. Two types of vaccine are available for prevention of influenza. Inactivated vaccines consist of partially purified HA and NA preparations derived from virions produced in eggs or in cell culture or, in one case, purified recombinant HA produced in insect cells. Current vaccines contain one example of H1N1, one example of H3N2, and either one or both lineages of influenza B. Inactivated vaccines are administered intramuscularly or intradermally and are primarily designed to induce systemic antibody, although they also induce cellular immune responses that may be associated with protection. Inactivated vaccines are well tolerated in all age groups, although hypersensitivity to hens' eggs is a relative contraindication to use of egg-produced vaccines. Generally, if persons can eat eggs or egg-containing products, vaccination is safe. If necessary, individuals with anaphylaxis can be desensitized and safely vaccinated,¹⁵¹ or vaccines free of egg products can be used.

Increases in hemagglutination-inhibition antibody are seen in about 90% of healthy adult recipients of vaccine. Only a single dose of vaccine is required in individuals who have been previously vaccinated or who have experienced prior infection with a related subtype, but a two-dose schedule is required in unprimed individuals. This includes children up to age 9 who have not previously been vaccinated or who were vaccinated for the first time with only a single dose in the previous season.¹⁵² Diminished responses and diminished efficacy are seen in elderly and immunocompromised populations.

The protective efficacy of inactivated influenza vaccine is estimated to be in the range of 70% to 90% in healthy adults when there is a good antigenic match between vaccine and epidemic viruses.^{153,154} Few prospective trials of protective efficacy have been conducted in high-risk populations. In one placebo-controlled prospective trial, inactivated vaccine was approximately 58% effective in preventing influenza among adults older than 60 and 29% in those older than 70.¹⁵⁵ However, this study used a serologic definition of influenza infection, possibly biasing results in favor of vaccine efficacy.

Observational studies have suggested that in practice the effectiveness of inactivated vaccine in prevention of acute respiratory illness due to influenza ranges between 40% and 60%, with even lower effectiveness in older adults and in seasons with antigenic mismatch. Attempts to improve the effectiveness of inactivated vaccines have included the use of higher doses and adjuvants.

The live attenuated vaccine, administered intranasally, induces a limited, asymptomatic infection of the upper respiratory tract and induces a variety of immune responses designed to mimic the protective immunity induced by natural infection.^{156,157} The vaccine is well tolerated and highly effective in children but is associated with an increased frequency of wheezing in children younger than 2 years of age. Live vaccine is protective in adults as well, resulting in decreased laboratory-confirmed influenza in challenge studies and reduced frequencies of influenza-like illness in the field.¹⁵⁸ Although the vaccine is well tolerated in the elderly and in those with chronic lung disease, immune responses are less frequent in older recipients and the vaccine is not licensed for use in those older than 49.

Although vaccine virus can be recovered from vaccinated individuals, particularly children, for several days following vaccine, transmission is extremely unusual.¹⁵⁹ Live vaccine can be administered safely to health care workers except for those caring for immunosuppressed individuals requiring barrier precautions.

Randomized controlled comparisons of the efficacy of inactivated and live attenuated vaccine in children have consistently shown that live vaccine provides superior efficacy in this population, with an approximately 50% lower cumulative incidence of influenza in those receiving live vaccine.¹⁶⁰ Similar comparisons in adults have suggested slightly superior efficacy of inactivated vaccine,¹⁶¹ and large cohort studies are also consistent with the interpretation that inactivated vaccine has slightly better efficacy than live vaccine in adults, particularly in those who have received vaccines in previous years.¹⁶²

Previous strategies for prevention of influenza in the United States and other countries have focused on targeting vaccines to persons at higher risk for influenza-related complications (see Table 32-4) and on individuals in close contact with these high-risk individuals. Such recommendations were complex and in some ways difficult to implement, leading to lower than desired vaccine uptake. In addition, it was recognized that more universal vaccination strategies, particularly of children, might be able to impact the spread of influenza in the community. Currently, the United States and many other countries have adopted a universal vaccination strategy with annual vaccination of all members of the population. This, of course, includes health care providers, and most institutions have adopted a policy of mandatory vaccination of individuals in contact with patients.

Antibody responses to influenza A virus, whether induced by vaccination or natural infection, are predominantly directed at the "globular head" domain of the HA protein, which is involved in binding host cells. This domain of HA mutates frequently, and amino acid substitutions in this domain allow the new viral variant to escape recognition by antibodies that developed in response to the original virus. Thus, new antigenic variant viruses emerge regularly, and this necessitates development and administration of new influenza vaccines each year. The costly and logistically complex requirement for a distinct influenza vaccine each year has stimulated efforts to develop a vaccine that targets conserved domains of the influenza virus hemagglutinin, rather than the variable globular head domain. Although these efforts have revealed evidence for broadly neutralizing antibodies produced by certain subjects, a clear strategy for production of a vaccine that induces broadly neutralizing antibodies has not yet emerged.¹⁶³⁻¹⁶⁵

Antivirals. Two classes of antiviral agents are currently available for the treatment and prevention of influenza: the *M2 inhibitors* (M2Is) amantadine and rimantadine (adamantanes) and the *neuraminidase inhibitors* (NAIs) oseltamivir and zanamivir. The M2 protein is located in the viral envelope, where it functions as a proton channel and is essential for viral escape into the host cell cytoplasm, where viral replication takes place. The M2-inhibiting adamantanes specifically block the ion channel function of the influenza A M2 protein and are not active against influenza

B viruses. Resistance to these drugs emerges readily in treated individuals, particularly children,¹⁶⁶ and there may be prolonged shedding of resistant viruses in immunocompromised patients even after therapy is terminated.¹⁶⁷ For reasons that remain unclear, the first decade of this century has seen the emergence and spread of adamantane-resistant influenza A (H3N2) viruses,¹⁶⁸ and pH1N1 viruses are also uniformly resistant. Therefore, the adamantane M2I drugs do not have utility against current influenza viruses but might be used if susceptible strains emerge in the future.

NAIs are potent inhibitors of influenza virus in vitro and in vivo because neuraminidase activity is essential for viral release, a necessary step for viral spread to other cells. Influenza B viruses are somewhat less sensitive than influenza A viruses but are well within clinically achievable concentrations. Avian viruses with all nine known neuraminidase subtypes are also sensitive. Although zanamivir and oseltamivir have an identical mechanism of action and similar profile of antiviral activity, they have differing pharmacologic properties. Zanamivir is not orally bioavailable and is administered as a dry powder for oral inhalation, using the so-called “diskhaler” device. Oseltamivir phosphate is an orally bioavailable ethyl ester prodrug that is rapidly absorbed from the GI tract and converted in the liver by hepatic esterases to the active metabolite, oseltamivir carboxylate. The metabolite is excreted unchanged in the urine by tubular secretion, with a serum half-life of 6 to 10 hours.

The major adverse effects reported for oseltamivir have been GI upset in about 10% to 15% of recipients, probably due to irritation caused by rapid release of the drug in the stomach. Rates of nausea can be substantially reduced if the drug is taken with food. Adverse effects reported for zanamivir have been at essentially the same rate as in placebo recipients. However, postmarketing surveillance has found that inhaled zanamivir may be uncommonly associated with bronchospasm in influenza patients, particularly those with underlying airways disease; this acute bronchospasm has sometimes been severe or fatal.

The dose of oseltamivir should be reduced to 75 mg once daily in individuals with renal impairment (i.e., with creatinine clearance 15–30 mL/min and 75 mg every other day in prophylactic treatment). No data are available regarding the use of the drug in individuals with more significant levels of renal impairment. Likewise, no information is available regarding the use of oseltamivir in individuals with hepatic impairment. Clinically significant drug interactions have not been reported. Because the drug is eliminated by tubular secretion, probenecid increases serum levels of the active metabolite approximately twofold. However, dosage adjustments are not necessary in individuals taking probenecid. Coadministration of cimetidine, amoxicillin, or acetaminophen has no effect on serum levels of oseltamivir or oseltamivir carboxylate.¹⁶⁹ Because zanamivir has no significant systemic absorption, there are no recommended dosage reductions.

Both NAIs are effective in the treatment of influenza due to either influenza A or B virus if administered within the first 48 hours of symptom onset, with reduced duration of illness and earlier return to work or normal activities. Meta-analysis of results of these trials has also suggested that early treatment may reduce the frequency of influenza-

related complications, with reductions in the use of antibacterials and in hospitalization.¹⁷⁰ Only oseltamivir is currently licensed for use in children younger than 5 years of age. Administration of oseltamivir liquid at a dose of 3 mg/kg in children 0 to 8 months of age, and 3.5 mg/kg in children 9 to 11 months of age, twice daily for 5 days reached target ranges. Earlier studies showed that they were well tolerated and resulted in a 36-hour reduction in the duration of symptoms in children with influenza A.^{170a,171} NAIs have also been used successfully for seasonal or contact prophylaxis.

Initial placebo-controlled trials of NAI therapy conducted primarily in otherwise healthy adults did not capture substantial numbers of influenza complications. However, pooled analyses of these studies of early therapy with zanamivir¹⁷² and oseltamivir^{170,173} demonstrated a significant reduction in the rate of influenza complications in treated individuals. Subsequent experience in the emerging epidemic of pH1N1 virus has also suggested a beneficial effect of early therapy on complications. These include observations in hospitalized patients^{174,175} and surveillance data suggesting that therapy as late as 5 days improved survival of hospitalized patients.¹⁷⁶ Surveillance data have also suggested that treated children had lower rates of complications.¹⁷⁷

Mutations within the catalytic framework of the NA that abolish binding of the drugs have been described.^{178,179} Depending on the location of the mutation, these viruses may be specifically resistant to only one of the inhibitors.¹⁸⁰ Resistance mutations in the NA may also be associated with altered characteristics of the enzyme with significantly reduced activity.^{181,182} Drug-resistant viruses are most commonly isolated from treated children.¹⁸³ Viral fitness appears to be less compromised by oseltamivir resistance mutations in the N1 neuraminidase,¹⁸⁴ and resistance was common among seasonal H1N1 viruses before the pH1N1 pandemic. Currently, the majority of seasonal influenza viruses are susceptible to both drugs, but N1 resistance is being sporadically reported and it is important to continue to monitor susceptibility patterns.

Although the benefits of antiviral therapy were initially demonstrated as a shortening of illness duration in healthy adults with uncomplicated influenza, this is generally not considered the priority target group for antiviral therapy. Current recommendations include the use of antivirals in individuals at risk for more severe influenza, or in individuals with severe disease or requiring hospitalization.¹⁴⁹ Treatment should be started as early as possible, but even delayed therapy can be of benefit in hospitalized patients.

Treatment of patients requiring mechanical ventilation can be challenging. Administration of oseltamivir by nasogastric tube is effective, and intravenous preparations of zanamivir and the experimental NAI peramivir are available under compassionate use protocols.

MEASLES VIRUS

Measles virus is classified in the *Morbillivirus* genus of the Paramyxoviridae family and is structurally similar to parainfluenza virus and RSV. Its surface glycoproteins include a hemagglutinin responsible for attachment to cells, a *fusion* (F) protein responsible for cell membrane fusion and virus

penetration of cells, but no neuraminidase. The cell surface molecule SLAM (*Signaling Lymphocyte Activation Molecule*) serves as a receptor for entry of the virus into susceptible cells.¹⁸⁵ In addition, the complement regulatory protein CD46 can also serve as a receptor, particularly for the vaccine strain.¹⁸⁶ Only one serotype of wild measles virus is recognized, although minor antigenic differences are detectable by monoclonal antibodies. The human is the sole natural host for measles virus.

Epidemiology and Transmission

Measles is found worldwide, but epidemic patterns vary depending on population density and levels of acquired immunity. Before vaccine use, measles arose in epidemics of 3 to 4 months in duration every 2 to 5 years in temperate regions.¹⁸⁷ Except in isolated areas, most people experienced infection by 20 years of age, and 90% of reported cases were seen in those younger than 10. Infection confers life-long protection against measles, although asymptomatic reinfections may develop.

Measles virus infection is highly contagious and can spread despite high levels of acquired immunity in the population. Airborne transmission via small-particle aerosols and possible spread by fomites appear to account for its high communicability. The virus remains infectious in small-particle aerosols for several hours at low relative humidity and has caused secondary infections in the absence of face-to-face contact with an index case.¹⁸⁸ The incubation period is usually 9 to 14 days but may be longer in adults. Patients are most infectious during the late prodrome, when respiratory involvement contributes to creation of infectious aerosols. The virus may be shed for several days after the onset of rash in normal hosts.

Measles-associated mortality in developed countries is usually 0.1% or less but approaches 2% of cases in the developing world. Case fatality rates have been as high as 25% in some areas. Most deaths result from respiratory tract involvement, neurologic complications, or both, and are related to various combinations of malnutrition, young age, and complications of the immunosuppression induced by measles virus infection itself.

Pathogenesis

The respiratory tract and possibly the conjunctival epithelium are the portals of entry and initial sites of replication of measles virus, as well as subsequent target organs of disease expression. An initial viremic phase leads to infection of mononuclear phagocytes including dendritic cells, and a second phase of viremia, corresponding to the prodromal stage of illness, results in dissemination of virus to the epithelial cells of the skin, respiratory tract, gut, bile duct, and bladder and to lymphoid organs.

Measles virus-induced giant cells may be present in the tonsils, appendix, other lymphoid organs, and various epithelial surfaces, including those of the respiratory tract. The effects of infection on the lymphoid system include leukopenia and immune suppression manifested by cutaneous anergy and depressed natural killer cell activity¹⁸⁹ for weeks after rash onset. The mechanisms by which measles induces immunosuppression are incompletely understood, but infection of dendritic cells and suppression of IL-12 production are thought to play an important role.¹⁹⁰

The onset of the rash correlates temporally with the development of host immune responses and subsequent termination of virus shedding. Skin rash develops in agammaglobulinemic patients with measles, whereas progressive giant cell (measles virus) pneumonia without rash may develop in those with deficient cell-mediated immune function. The pathologic changes in involved organs include lymphoid hyperplasia, mononuclear cell infiltration, and the presence of multinucleated giant cells. Lower respiratory tract involvement may be associated with the destruction of ciliated respiratory epithelium, interstitial pneumonia, epithelial cell hyperplasia, and syncytial cell formation.

Clinical Illness

Typical Measles. The typical prodrome of measles lasts 2 to 8 days and is characterized by fever, malaise, anorexia, cough, coryza, and conjunctivitis. Koplik spots, which are erythematous macular lesions with central white-yellow or gray puncta, appear on the buccal or labial mucous membranes toward the end of the prodromal period. The maculopapular, erythematous eruption begins about the face and neck and progresses to involve the upper body, trunk, and extremities. The rash typically resolves after 5 to 6 days in the order in which it appeared. The fever abates and symptoms improve several days after the appearance of the rash, although persistent cough is common. Leukopenia is common during the prodromal and early exanthematous stages of measles. Pronounced leukopenia (<2000 cells/ μ L) is associated with a poor prognosis. The development of neutrophilic leukocytosis suggests the possibility of bacterial superinfection or other complications.

Lower respiratory tract complications develop in 4% to 50% of patients. These include bronchitis, pneumonia, and, less often, croup or bronchiolitis. In young adults, a multilobar reticulonodular opacity is the most common radiographic abnormality (see eFig. 32-4).¹⁹¹ In the absence of bacterial superinfection or atypical measles, pleural effusion or lobar consolidation is uncommon. In patients with altered cell-mediated immune function, and rarely in apparently normal persons, infection by wild measles virus can cause a lethal giant cell pneumonia with or without rash.¹⁹² Severe virus-induced pneumonia has been recognized during measles in pregnant women¹⁹³ and in those infected with HIV.¹⁹⁴ In hospitalized patients, mortality rates are approximately 70% in oncology patients and 40% in HIV-infected patients.¹⁹²

Secondary bacterial infection has been found in 30% to 50% of young adults with measles-related pneumonia. Symptoms and signs indicative of bacterial infection usually begin 5 to 10 days after onset of the rash. One study employing transtracheal aspiration found a range of bacterial pathogens in adults, most commonly *Haemophilus influenzae*, *Neisseria meningitidis*, and *S. pneumoniae*.¹⁹¹ Up to 30% of cases are complicated by otitis media or sinusitis. Acute nonrespiratory complications include hepatitis, encephalitis, keratitis, mesenteric adenitis, as well as a high rate of severe diarrheal disease in children in developed countries. Measles infection or vaccination may be accompanied by conversion of the tuberculin skin reaction from positive to negative for weeks. Measles may exacerbate active

tuberculosis, but whether measles reactivates dormant tuberculosis is unresolved.¹⁹⁵

Atypical Measles. An unusual clinical syndrome has been recognized in adolescents and young adults who received the inactivated measles vaccine between 1963 and 1968 and who were subsequently re-exposed to the wild virus. The illness begins abruptly, with high fever, headache, myalgia, vomiting, abdominal pain, and nonproductive cough. Respiratory symptoms, including dyspnea, coryza, sore throat, and pleuritic chest pain, are common. A polymorphous eruption, which may include vesicles, petechiae, purpura, and urticarial lesions, begins typically on the distal extremities and spreads proximally over 3 to 5 days. Although Koplik spots are absent, conjunctivitis and glossitis with strawberry tongue have been described.

Pulmonary abnormalities are found in most cases, and acute respiratory failure has been described. Chest radiographic changes include patchy, diffuse, or dense lobar opacities, pleural effusions, and hilar lymphadenopathy.¹⁹⁶ Residual nodular pulmonary opacities may persist for years and lead to diagnostic confusion. The fever and other symptoms usually resolve in 1 to 3 weeks. The pulmonary function changes in atypical measles include transient hypoxemia and significantly reduced lung volumes.

Diagnosis

The diagnosis of measles is most readily confirmed in immunocompetent patients by detecting measles virus-specific IgM by ELISA. In immunodeficient patients, detection of measles virus by nucleic acid amplification of urine or of samples obtained by throat or nasopharyngeal swab is sensitive and specific; samples can be sent to the U.S. Centers for Disease Control (<http://www.cdc.gov/measles/lab-tools/rt-pcr.html>). Measles virus may also be isolated from the blood, urine, or respiratory secretions during the prodrome and up to several days after the exanthem appears. Isolation of virus from clinical specimens has been performed in several types of human and monkey cell cultures but is slow and inefficient. Respiratory and conjunctival secretions or urine sediment stained by various techniques reveals multinucleated giant cells in most cases. Immunofluorescent staining of skin biopsy specimens, cells from combined nasopharyngeal and throat swab samples, and, less often, exfoliated cells in the urine demonstrates measles virus antigens early in the disease.

Treatment and Prevention

The treatment of measles involves supportive care and specific therapy for bacterial complications. No antiviral agents have proven clinical value, but aerosol and intravenous ribavirin and immunoglobulin have been used in treating measles pneumonia.^{193,197} Vitamin A therapy reduces morbidity and mortality in severe measles in children.¹⁹⁸ Patients suspected of having measles should be placed in respiratory isolation.

The live attenuated measles vaccine currently used in the United States provides durable immunity in more than 90% of recipients. Recent outbreaks have seen cases in adolescent and adult recipients of two doses of measles vaccine, but the illness has been mild and not associated with trans-

mission.^{199,200} The vaccine is safe, and it has been conclusively shown to have no association with autism.^{201,202} There have been recent outbreaks of measles in undervaccinated communities in the United States, often introduced by an imported case in an immigrant or traveler.^{202a}

METAPNEUMOVIRUSES

The *human metapneumoviruses* (hMPVs) are pleomorphic particles with short envelope projections, resembling other paramyxoviruses.²⁰³ These viruses are closely related to the pneumoviruses (of which RSV is the human example), differing only by the absence of two nonstructural proteins and a slightly different arrangement of gene order on the negative-sense, single-stranded RNA genome. The basic virology of these viruses closely resembles that of RSV. Envelope glycoproteins include the SH (*sulfhydryl*), F (*fusion*), and G (*attachment*), although there is little sequence homology in these genes between RSV and hMPV.²⁰⁴ By analogy, it is expected that antibody to the F and G proteins of hMPV would play a role in protection against reinfection. At least two major genetic groups have been identified, roughly corresponding to subgroups A and B of RSV.²⁰⁵ Sequential infections of the same individual tend to involve different genogroups. The role of cell-mediated immunity in this infection is largely unexplored.

Epidemiology and Transmission

hMPV infections are distributed worldwide and have been documented in both the outpatient²⁰⁶ and inpatient setting.²⁰⁷ Recent estimates of disease burden based on PCR diagnostics suggest that hMPV results in 1 to 1.2 hospitalizations, 13 emergency department visits, and 55 outpatient visits per 1000 children younger than 5.^{208,209} Children younger than 6 months are at the highest risk. As with many other respiratory viruses, infection is linked to day care attendance.²¹⁰ Serologic studies suggest that essentially all children have been infected by age 5.²⁰³

Similar to the case with RSV, disease has also been documented in adults and in the elderly,²¹¹ although asymptomatic infection is also common in adults. Outbreaks of severe disease have been documented in residential care facilities in older adults.^{212,213} Severe disease may also be seen in immunocompromised subjects such as hematopoietic stem cell transplant recipients (see eFig. 91-6).^{214,215} The mode of transmission has not been documented but is likely to be via droplet spread as with RSV. There is a clear seasonal variation in incidence, with the majority of cases appearing during the winter months.²⁰⁶

An interesting feature of the epidemiology of these viruses is that children with hMPV are often coinfecting with other respiratory viral pathogens, especially RSV.²¹⁶ Dual infections with both viruses may result in more intense bronchiolitis in some infants.²¹⁷ hMPV was also detected in many cases of SARS but did not appear to exacerbate this illness.²¹⁸

Clinical Features

Human metapneumoviruses appear to be responsible for a spectrum of acute respiratory illnesses ranging from mild or asymptomatic infection to severe bronchiolitis and pneumonia. The clinical picture most closely resembles that

of RSV, and bronchiolitis is the major manifestation in children.^{206,219} Clinical features in hospitalized children include wheezing and hypoxia.²²⁰ A variety of other lower and upper respiratory tract syndromes are also associated with hMPV infection, including croup and pneumonitis.^{206,207} There are no clinical features that can distinguish between disease caused by hMPV and RSV, although RSV may be more severe.

Symptomatic infection in adults and in the elderly has also been described.²¹¹ hMPV infections of young adults had features of the common cold, with nasal congestion, rhinorrhea, cough, and hoarseness predominating. Frail elderly and high-risk adults had lower rates of hMPV infection but more severe clinical symptoms, with significantly higher frequencies of dyspnea and wheezing, and more prolonged illness.²¹¹ Elderly patients with hMPV infection were hospitalized with diagnoses of COPD, bronchitis, and pneumonia. hMPV appears to be a leading cause of respiratory tract infection in lung transplantation patients.²²¹ In one study, hMPV was the most commonly detected RNA virus in BAL samples from immunocompromised patients.²²²

Pathogenesis

Relatively little is known regarding the pathogenesis of this disease. In hospitalized children with hMPV, levels of nasal secretion RANTES have been reported to be suppressed, while levels of nasal IL-8 were increased.²²³ The immune responses elicited by hMPV are similar to those of RSV but often not as vigorous.²²⁴

Diagnosis

Viral culture is slow and has low sensitivity. Most infections have been detected by nucleic acid amplification techniques, which are available in panels to detect and identify respiratory viruses^{224a-d} (see Chapter 17).

Prevention and Treatment

Treatment is supportive. No antiviral agents or vaccines are currently licensed for treatment or prevention of hMPV infections, and this is unlikely to change in the near future. Ribavirin is as active in vitro against hMPV as it is against hRSV,²²⁵ but there are no data to support the therapeutic efficacy of this drug. There are no specific monoclonal antibodies available for clinical use, although intravenous immunoglobulin has been suggested as a possible therapeutic agent in immunocompromised hosts.²²⁶

PARAINFLUENZA VIRUSES

Parainfluenza viruses belong to the *Paramyxovirus* genus of the Paramyxoviridae family, which includes mumps virus and important veterinary pathogens. This group of medium-sized (150 to 200 nm), pleomorphic, enveloped viruses has a nonsegmented, single-stranded RNA genome contained in a helical nucleocapsid. The human parainfluenza viruses are separated into types 1 to 4, and type 4 is further divided into subtypes A and B, on the basis of antigenic differences. One envelope glycoprotein (HN) has both hemagglutinin and neuraminidase activity and mediates adsorption of virus to host cell receptors for entry into host cells, as well as subsequent release of new virions from

infected cells after viral replication. The F glycoprotein has membrane-fusing activity and is responsible for viral penetration into cells and for the formation of multinucleated syncytial cells. Antibodies against the HN and F are involved in protective immunity.

Epidemiology and Transmission

Parainfluenza viruses have a worldwide distribution, and almost all persons are infected initially during childhood. Parainfluenza type 3 virus may cause infection in infancy, whereas infections by type 1 and 2 viruses appear to be prevented by maternal antibody and usually arise later. National surveillance has demonstrated distinct seasonality for type 1 viruses, with biennial outbreaks in the fall of odd-numbered years. In contrast, yearly outbreaks of type 3 virus take place in the spring, with smaller autumn outbreaks in those years without type 1 outbreaks. Type 2 viruses are detected much less frequently but appear to be more prevalent in the autumn; type 4 does not exhibit notable seasonality.²²⁷

Parainfluenza viruses appear to be transmitted from person to person by direct contact with infectious respiratory secretions or by large-particle aerosols. The incubation period is approximately 3 to 6 days. Virus is transmitted readily in families. Outbreaks of infection have been seen in closed populations, such as nurseries, day care centers, and hospitals, in which susceptible populations have high attack rates (40% to 80%).

Parainfluenza virus infections, most commonly type 1 virus, are associated with approximately 40% of croup cases and up to 75% of those with a documented viral cause, with smaller proportions of pneumonia or bronchiolitis cases in children. The incidence of croup and lower respiratory tract disease due to type 1 or 2 infections is highest between 6 months and 3 years of age, whereas parainfluenza type 3 is an important cause of bronchiolitis or pneumonia in infants younger than 6 months. Reinfections with parainfluenza viruses are common and, in young children, may arise within several months of each other. Recent population-based disease burden estimates suggest that 1 in 1000 children younger than 5 experience parainfluenza virus-related hospitalization, and that about 6.8% of hospitalizations for fever or respiratory illness in this age group can be attributed to parainfluenza virus.²²⁸

Pathogenesis

Although viremia has been described, replication of the virus is generally restricted to the respiratory tract mucosa. The quantity of virus shed in respiratory secretions tends to parallel the severity of illness.²²⁹ Virus shedding commonly continues for periods of 8 to 10 days in initial infections but may last for 3 weeks or longer. Prolonged shedding (months) of parainfluenza virus type 1 or 3 has been reported in apparently normal hosts,²³⁰ as well as in immunodeficient children.²³¹

The pathologic findings in fatal cases are typical of other viral pneumonias and include peribronchiolar and alveolar lymphocytic infiltration.²³² Infection of the tracheal epithelium with localized edema and fibrinous exudate contributes to airway narrowing in croup. The mechanisms that account for the laryngotracheal localization of parainfluenza virus-induced disease are unresolved. Virus-host cell

interactions (specifically cleavage of the F protein) and other host factors, including the nature of the immune response, are postulated to play contributory roles in the pathogenesis of croup. The nasopharyngeal secretion concentrations of parainfluenza virus–specific IgE and of histamine and leukotriene C4, as well as cellular responses to viral antigen, are higher in patients with wheezing than in those with upper respiratory tract illness alone.²³³

Clinical Illness

Primary infections are usually symptomatic and are associated with the most severe forms of illness. Initial infections with parainfluenza virus types 1 to 3 cause febrile rhinitis, pharyngitis, laryngitis, and bronchitis in children. Depending on the serotype causing infection, 50% to 80% of primary infections are associated with fever, and up to one third of children have evidence of lower respiratory tract involvement. In parainfluenza virus type 1 and 2 infections, lower respiratory disease is principally manifested as croup, whereas type 3 infection has been associated with croup, bronchiolitis, and pneumonia.

In adults and older children, reinfections are frequently asymptomatic. Symptomatic infections are manifested as common colds, usually without fever, and less often pharyngitis, tracheobronchitis, or influenza-like illness. Pneumonia and exacerbations of chronic airway disease have been described following parainfluenza virus infection in adults and in the elderly.²³⁴

Although uncommon, parainfluenza viruses can cause serious lower respiratory tract disease, including fatal pneumonia with or without giant cells, in children with immunodeficiency or leukemia, and in pediatric and adult stem cell transplant recipients.²³⁵ Nosocomial outbreaks in immunosuppressed patients have been reported.²³⁶ Because upper respiratory illness may be absent and nasopharyngeal cultures negative, BAL is often required for diagnosis.

Diagnosis

Rapid diagnosis of parainfluenza infection can be made by detection of viral antigen or RNA in respiratory secretions obtained using throat or nasopharyngeal swabs. Detection of parainfluenza RNA is performed in multiplex nucleic acid amplification panels for respiratory viruses^{224a-d} (see Chapter 17), which may be more readily available than rapid antigen detection assays. Respiratory secretions contain the virus at the time of symptom onset. Viral culture is also sensitive, and parainfluenza viruses can be isolated as early as 3 days and usually within 10 days after inoculation of cell culture with specimens from infants and children. Virus replication in cell culture is usually detected by hemadsorption of guinea pig erythrocytes or immunofluorescence.

Treatment and Prevention

There are currently no available antiviral agents of proven effectiveness against parainfluenza virus. Ribavirin is active against parainfluenza viruses in vitro and would theoretically be expected to be active in vivo as well. Anecdotal reports in immunodeficient children with severe parainfluenza virus infections suggest that aerosolized ribavirin may be associated with antiviral effects and clinical benefit,²³⁷ although delayed treatment with aerosol ribavirin was

not associated with improved survival in bone marrow transplant recipients.²³⁸ The combination of aerosolized ribavirin and intravenous immunoglobulin is frequently used in immunocompromised patients,²³⁹ but there is no direct evidence of efficacy. The sialidase DAS-181 is active in vitro and in small clinical studies^{240,240a} but is not currently available for clinical use.

Initial attempts to develop vaccines for the prevention of parainfluenza viruses involved use of formalin-inactivated virus. However, these vaccines failed to provide protection in field trials carried out in the 1960s, despite being modestly immunogenic. In contrast to RSV vaccines, the use of formalin-inactivated parainfluenza vaccine was not associated with enhanced disease on subsequent infection. Several approaches have been explored subsequently, including use of live attenuated viruses and recombinant subunit vaccines. Clinical trials of these are ongoing.

RESPIRATORY SYNCYTIAL VIRUS

RSV is classified in the *Pneumovirus* genus of the Paramyxoviridae family. Similar in structure to parainfluenza viruses, RSV is a pleomorphic (150 to 300 nm), enveloped virus with a single-stranded, nonsegmented RNA genome. The surface proteins include the F protein responsible for fusion of the viral envelope with the host cell membranes and formation of syncytium, and the G protein, a heavily glycosylated protein responsible for attachment to cells. Antibodies against the F and G protein neutralize RSV in vitro, but antibodies against the G do not prevent syncytium formation. Two major antigenic groups (designated A and B)²⁴¹ are distinguished primarily by differences in the G glycoprotein. The clinical and epidemiologic importance of strain variation are under study, but infections by group A strains appear to be more severe.²⁴² Further antigenic subgroups and genomic heterogeneity are recognized among circulating RSV strains.

Epidemiology and Transmission

RSV is worldwide in distribution and, in temperate climates, causes annual outbreaks of infection in the late fall, winter, or spring. Epidemics are associated with increases in pediatric hospitalizations and deaths due to lower respiratory tract illness in infants and young children.²⁴³ Nearly 50% of children are infected within the first year of life, and almost all have been infected by 3 years of age. Reinfections in children and adults are quite common even with the same strain,²⁴⁴ suggesting immunity is only partial. Epidemiologic factors related to serious illness in infected infants include low socioeconomic status, crowding, maternal smoking, lack of breast feeding, day care center attendance, and history of allergic disease. RSV is also recognized as a cause of severe disease in older adults²⁴⁵ and may result in a greater total burden of mortality in the elderly than in infants.¹²⁵

RSV spreads by large-particle aerosols during close personal contact and by hand contamination with infectious secretions and subsequent self-inoculation of the eye or nose. RSV is a major nosocomial pathogen on pediatric wards, and there can be high attack rates during outbreaks in hospitals, transplantation units, day care centers, and geriatric homes. Attack rates in children have approached

100% during outbreaks in day care centers and are commonly 20% to 50% in hospital staff and patients during epidemic periods. In the family setting, secondary infection develops in approximately one half of infants and up to one third of adult contacts after introduction of virus by an older sibling.²⁴⁶

Pathogenesis

Viral replication generally begins in the upper respiratory tract with gradual (4- to 5-day) progression to involve the lower respiratory tract. In children with normal immunity, the duration of viral shedding ranges from 1 to 3 weeks. Clinical signs of bronchiolitis include airway trapping and wheezing. Pathologic findings in RSV bronchiolitis include necrosis of bronchiolar epithelium, loss of ciliated epithelial cells, and marked peribronchiolar mononuclear inflammation.²⁴⁷ Virus-induced cytopathology and associated submucosal edema lead to obstruction of smaller bronchioles, particularly in infants, with distal collapse or air trapping.

Both serum and mucosal antibody responses are seen but are associated with limited protection. The magnitude of the antibody response is related to the age at primary infection, with infants younger than 8 months having approximately 10-fold lower antibody levels than older ones.²⁴⁸ Reinfection may take place within weeks after primary infection.²⁴⁴ Circulating and mucosal antibody levels increase with each successive infection and appear to be associated with milder illness. High titers of serum neutralizing antibody are generally associated with a lower risk of severe illness in infants and children.²⁴⁹

Cell-mediated immunity appears to be important in viral clearance and may also be involved in pathogenesis. For example, adult bone marrow transplant patients are at high risk of severe lower respiratory disease from RSV which is likely due to prolonged periods of decreased cellular immunity.^{250,251} In contrast, AIDS patients with decreased cellular immunity may suffer only mild disease, but viral shedding can continue for up to 6 months.²⁵²

Studies investigating the association of severe RSV disease in infants with genetic polymorphisms have implicated several candidate innate and adaptive immune genes including surfactants, TLR4, and several cytokine and chemokine genes as modulating the severity of RSV disease.

Clinical Illness

The clinical manifestations of infection depend on both the age and immunologic state of the host. In infants and young children, upper respiratory illness accompanied by fever and otitis media is common. RSV is the major cause of lower respiratory tract illness in infants and young children and accounts for 45% to 90% of bronchiolitis, up to 40% of pneumonia, and smaller proportions of croup and bronchitis cases in this age group. Most severe infections are seen in infants younger than 6 months, and almost all primary infections are symptomatic, with 40% or more associated with bronchiolitis or pneumonia. Approximately 1% to 2% of infections result in hospitalization, and about one in ten hospitalized infants require mechanical ventilatory support.

The risk of hospitalization and severe bronchiolitis is particularly high in infants with congenital heart disease, chronic lung disease, or immunodeficiency. In addition,

infants born prematurely are also at risk for severe disease, perhaps because they lack maternal antibody. Mortality is usually 0.5% to 1.5% in previously healthy infants hospitalized with RSV disease but is 15% to 40% in those with primary immunodeficiency, cancer chemotherapy, or pulmonary and heart disease. Pulmonary hypertension is associated with a particularly high frequency of poor outcomes. Severe disease has also been associated in children with a family history of asthma and those exposed to cigarette smoke in the household.²⁵³ However, it is important to recognize that the majority of those hospitalized with RSV are previously healthy young children.²⁴³

Chest radiographic findings in lower respiratory tract disease include bronchial wall thickening, peribronchial shadowing, air-trapping (eFig. 32-12A), and, in pneumonia, multilobar patchy shadowing or poorly defined nodularity (Fig. 32-3, eFig. 32-12B). Although no radiographic pattern is specific, air trapping, alone or with other abnormalities, is highly associated with RSV infection in hospitalized children.²⁵⁴ Chest CT findings (eFig. 32-13) are relatively nonspecific, often resembling other viral pulmonary infections, including multifocal areas of ground-glass opacity, consolidation, and small nodules, which may show branching configurations ("tree-in-bud" opacity).

The most common physiologic abnormality is hypoxemia that may persist for weeks after apparent recovery.²⁵⁵ Prolonged pulmonary function abnormalities, including increased airway resistance, peripheral airway obstruction, and decreased arterial oxygen saturation, have been detected in children years after bouts of bronchiolitis.²⁵⁶ Bronchiolitis in infancy has also been associated with an increased risk of subsequent recurrent wheezing and cough and airway hyperreactivity.

In adults, one half or more of recurrent infections are associated with upper respiratory tract illness. Adults typically experience coryza, pharyngitis, and cough, sometimes accompanied by low-grade fever. Bronchitis, influenza-like illness, pneumonia, and exacerbations of asthma and chronic bronchitis have also been described in adults with RSV infection. In the United States, approximately 170,000 hospitalizations and more than 10,000 deaths are associated with RSV annually in adults older than 65.¹²⁵ In elderly adults, the clinical features of RSV infection can mimic those of influenza, although fever is less frequent and wheezing is more frequent.²⁵⁷ In one study, RSV infection was seen in 3% to 7% of healthy elderly and 4% to 10% of high-risk adults annually. Compared with influenza, ICU admissions were higher, and mortality was similar, at 7% to 8%.²⁴⁵ RSV also contributes to 5% to 10% of COPD exacerbations.²⁵⁸ Older patients with severe RSV infection had a longer period of viral shedding, higher levels of mucosal IL-6, and a higher frequency of circulating activated T cells compared with young patients with mild disease,²⁵⁹ suggesting viral loads and inflammation may play a role in disease severity.

In immunosuppressed children and adults, RSV, often nosocomially acquired, causes severe lower respiratory tract disease. Upper respiratory tract illness usually precedes the development of pneumonia, and complicating sinusitis and otitis media are common. Two thirds or more of the bone marrow transplant recipients that develop RSV pneumonia will die of the infection.

Diagnosis

The most rapidly and readily available approach to establishing RSV infection is by rapid antigen detection. The sensitivity of such techniques is dependent on the quality of the nasopharyngeal specimen, with nasopharyngeal aspirates superior to brushings or swabs.²⁶⁰ In addition, sensitivity is related to the amount of antigen being shed, so it is generally greater in children than adults. In transplant patients with suspected RSV pneumonia, samples of the lower respiratory tract by BAL are more sensitive than throat swabs for detection of RSV antigens.²⁶¹ PCR-based respiratory viral multiplex assays for detection of RSV and other respiratory viruses have also been approved by the U.S. Food and Drug Administration and are becoming widely available^{224a-d} (see Chapter 17). RSV grows well in several human cell lines, in which it causes formation of characteristic syncytia. Virus can be detected as early as 2 days and usually within 7 days on primary isolation from specimens collected from children.

Treatment and Prevention

Correction of hypoxemia is the most important aspect of managing RSV lower respiratory tract disease. Ribavirin is highly active against RSV in vitro, and aerosolized ribavirin has been shown to reduce viral shedding and shorten the course of illness in some but not all studies. Aerosolized ribavirin is currently recommended for use only in selected infants and young children who are at high risk for serious RSV disease.²⁶²

In immunosuppressed patients, particularly hematopoietic stem cell transplant recipients, both aerosolized ribavirin and high-dose oral ribavirin have been used for early treatment to prevent progression to pneumonia.²⁶³ Recent studies suggest that intermittent aerosolized ribavirin is as effective as continuous aerosolized ribavirin in these patients.²⁶⁴ Once RSV pneumonia has developed, intravenous ribavirin alone is ineffective but, if treatment is initiated before the onset of respiratory failure, combinations of aerosolized ribavirin with intravenous immunoglobulin, and particularly palivizumab (see later) may be beneficial.^{265,266} In adults, short courses of systemic corticosteroids for RSV-related wheezing did not affect viral loads or shedding and only mildly diminished antibody responses.²⁶⁷

An effective vaccine for prevention of RSV has not yet been developed. In a study of formalin-inactivated RSV vaccine conducted in the 1960s, vaccinated infants developed more severe disease compared with unvaccinated children.²⁶⁸ The mechanisms of this enhancement remain uncertain, although studies in those vaccine recipients and in rodent models have implicated low levels or low affinity of the antibodies induced by the formalin-inactivated vaccine, which permitted excessive cytolytic T-cell responses to develop and cause tissue damage. Low-affinity antibodies may also have contributed to immune complex formation and deposition, leading to local inflammation.^{269,270} Formalin-inactivated RSV also primes a T helper 2 response, with high levels of interleukin 4 and interleukin 5, which can promote inflammation of small airways.²⁷¹ Although this adverse experience has prompted extra caution, current RSV vaccine development efforts are ongoing and focus on live attenuated and recombinant subunit vaccines.

In contrast to the earlier vaccine experience, passive transfer of antibody to the RSV F protein has been shown to be a highly effective means to prevent RSV morbidity in high-risk children. The currently commercially available product, palivizumab, is a humanized monoclonal antibody to the F protein.²⁷² Administration of palivizumab to infants with prematurity or bronchopulmonary dysplasia resulted in a 55% reduction in RSV-related hospitalizations and a lower incidence of ICU admissions.²⁷³ In a second trial, administration of palivizumab to infants and children with hemodynamically significant congenital heart disease was well tolerated and resulted in a 45% decrease in RSV-associated hospitalizations.²⁷⁴

Prophylaxis with palivizumab should be considered for infants younger than 24 months with chronic lung disease severe enough to require medical therapy within 6 months of the anticipated start of the RSV season.²⁷⁵ Prophylaxis with palivizumab (and not RSV-IVIG) should be given to infants with hemodynamically significant congenital heart disease and infants born before 32 weeks of gestation. Prophylaxis for infants between 32 and 35 weeks of gestation depends on the presence of other RSV risk factors, such as exposure to tobacco smoke, attendance at day care, school-aged siblings in the household, and congenital airway abnormalities. Palivizumab has not been shown to be effective in the therapy of established RSV disease.

Recommendations for interruption of nosocomial transmission include handwashing, decontamination of surfaces and inanimate objects, and isolation of infected patients. Use of disposable eye-nose goggles by pediatric staff reduces the risk of nosocomial RSV infection in both staff and patients.²⁷⁶ Regular use of gowns, gloves, and possibly masks by hospital staff caring for infected children may also reduce the risk of nosocomial RSV spread. Protective isolation of high-risk infants or deferring their elective admission has been recommended during institutional outbreaks of RSV.

RHINOVIRUS

Rhinoviruses (RVs) are species in the *Enterovirus* genus in the Picornaviridae family. The RV virion is a nonenveloped particle 30 nm in diameter with four major structural proteins. The genome of RV consists of single-stranded RNA of approximately 2.5×10^6 daltons and codes for a 240 kD protein that is cleaved into the structural units of the virion. RV genomes have been found to have 45% to 62% homology with poliovirus genomes. Poliovirus and RV differ, however, in the construction of their protein shells: that of RV being loosely packed with a resultant sensitivity to inactivation at low pH and that of poliovirus being tightly packed, providing the virion with resistance to acid inactivation. The acid sensitivity of RV and its optimum growth at 32°C to 34°C are thought to account for its replication in the nasal passages (and possibly large airways) but not in the GI tract.

On the basis of sequence data, rhinovirus are grouped into three genogroups: A, B, and C.²⁷⁷ In addition, three of the four proteins in the RV shell (VP1, VP2, and VP3) react with neutralizing antibody, forming the basis on which more than 100 antigenic types have been numbered. The presence of neutralizing antibody in serum and nasal

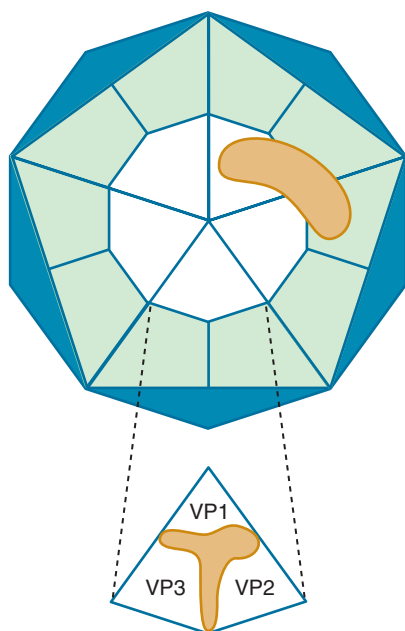


Figure 32-10 View of one side of rhinovirus shell drawn to scale with attached antibody molecule. *Top*, The protein shell is built of 12 pentamers, one of which is shown (white). Each of the five wedge-shaped subunits of the pentamer (white) is called a "protomer." The antibody binding site (brown) bridges protomers of two adjacent pentamers. *Bottom*, Surface organization of the protomer. Three of the polypeptide chains (VP1, VP2, VP3) making up each protomer are exposed on the virus surface, while the smallest polypeptide (VP4) is buried at the bottom of the protomer. The host-cell receptor is thought to bind near the base of the cleft formed by antigenic plateaus forming VP1, VP2, and VP3. The blunt-nosed binding site of the antibody is too wide to fit into the base of the cleft. (Courtesy Dr. Roland Rueckert, University of Wisconsin.)

secretions correlates with protection from infection. X-ray diffraction studies of RV have disclosed the presence of a large depression on the surface of the virus shell at a junction between the plateaus of the three proteins (Fig. 32-10).²⁷⁸ This depression contains the recognition site for the host cell receptor, *intercellular adhesion molecule-1* (ICAM-1), which binds 91 of the 102 known rhinovirus serotypes.²⁷⁹ RV serotypes that do not bind to ICAM-1 are referred to as the *minor receptor group viruses* and appear to utilize the low-density lipoprotein receptor.²⁸⁰ Manipulation of these receptor proteins has been explored as a potential control measure for rhinovirus infection.

Epidemiology and Transmission

RVs are worldwide in distribution. In the United States, RV has been observed to cause 0.74 to 0.77 infections per person per year in adults. RV is believed to produce even higher infection rates in children, leading to acquisition of antibody to the different RV types throughout childhood and adolescence, with peak antibody prevalence in young adults. Immunity to RV is type specific and confers long-lived protection following infection, although there may be second infections with the same virus type. The different immunotypes circulate in a given population in an apparently random manner. In the United States, RV infections are most prevalent in the early fall and late spring.

The major reservoir for RV is school children, who transmit RV infection among their peers in the classroom and

introduce it into their homes, infecting other family members. Studies of experimental RV colds in volunteers have shown that RV is most efficiently spread by contaminated fingers accidentally depositing virus into the nose or eye. Experimental RV transmission has also been achieved by the airborne route, presumably by large-particle aerosol. The relative importance of these two routes of RV transmission under natural conditions has not been determined.

Pathogenesis

Approximately two thirds of both natural and experimental RV infections result in overt illness. The incubation period of RV colds is usually 2 days but may be up to a week. Symptoms begin within 1 day following experimental infection. Small doses of RV instilled into the nose or eye of susceptible volunteers regularly lead to infection, indicating that mucociliary clearance is not effective against the virus. During the period of illness, sloughed ciliated epithelial cells containing viral antigen are present in nasal secretions.²⁸¹

In general, the number of RV-infected cells in the nasopharynx appears to be limited,²⁸² and infection does not lead to detectable damage to the epithelium of the nasal passages. These results have suggested that virus-induced cellular injury is not the direct cause of symptoms in RV colds and that inflammatory mediators play an important role. Nasal secretions during the initial response to RV infection are predominantly the result of increased vascular permeability, as demonstrated by elevated levels of plasma proteins in nasal secretions.²⁸³ Glandular secretions (lactoferrin, lysozyme, and secretory IgA) predominate late in colds.²⁸³ In contrast to the situation in allergic rhinitis, histamine does not appear to play a role in the induction of symptoms in colds. Nasal secretion kinin levels correlate with symptoms in natural and experimental colds, and intranasal administration of bradykinin causes increased nasal vascular permeability, rhinitis, and sore throat.²⁸⁴ *Interleukin* (IL)-1, IL-6, and IL-8 concentrations also increase in experimental RV colds and correlate well with symptom severity.²⁸⁵ Enhanced synthesis of proinflammatory cytokines and cell adhesion molecules in the middle ear may also contribute to the pathogenesis of otitis media associated with colds.²⁸⁶ Polymorphisms in the IL-6 gene affect the symptomatic response to experimental RV challenge in adults.²⁸⁷

Clinical Illness

RV colds vary in severity from mild episodes characterized by 1 to 2 days of coryza or scratchy throat to full-blown illnesses with profuse and prolonged rhinorrhea, pharyngitis, and bronchitis. The profile of a typical RV cold, based on composite results from young adults with natural infection, is shown in Figure 32-1. The median length of illness is 1 week, with symptoms lasting up to 2 weeks in one quarter of cases. Peak symptoms are usually seen on the second and third days of illness. The characteristics of RV illness are not distinctive enough to permit their differentiation from colds due to other respiratory viruses. RV is among the respiratory viruses implicated in the development of acute sinusitis and represents about half of all viruses recovered from middle ear effusions in children with acute otitis media.²⁸⁸ Recently, a clinical presentation indistinguishable from that of influenza has also been reported in healthy adults.²⁸⁹

RV alone or in combination with bacteria has been recovered from aspirates obtained by direct puncture of the maxillary sinuses of patients with acute sinusitis.²⁹⁰ Mucosal thickening and/or sinus exudates have been observed in up to 77% of subjects with acute colds.²⁹¹ These abnormalities are transient, and in uncomplicated cases they resolve within 21 days. However, clinically manifest acute bacterial sinusitis is seen in a small (0.5% to 5%) proportion of individuals with naturally occurring colds. It is presumed that the RV infection impairs mucociliary clearance and other local defenses in the sinus cavity, allowing secondary bacterial invasion.

There is increasing evidence for an important role of rhinoviruses in lower respiratory tract disease in adults and children.²⁹² RV is the second most frequently recognized agent associated with pneumonia and bronchiolitis in infants and young children and commonly causes exacerbations of preexisting airways disease in those with COPD or cystic fibrosis.²⁹³ Colds are generally more severe in atopic individuals and rhinoviruses are major causes of asthma exacerbation.²⁹⁴ Children with a history of wheezing/asthma had significantly more RV-associated hospitalizations than those without a history.²⁹⁵

RV infections may also be associated with severe lower respiratory tract disease in transplant patients²⁹⁶ and in some cases can be associated with prolonged shedding.²⁹⁷ These viruses can also be detected in lower respiratory tract disease in individuals with hematologic malignancy, often in conjunction with other pathogens.²⁹⁸

Diagnosis

Rapid tests for detecting RV nucleic acid are available in respiratory virus panels (see Chapter 17); they generally do not distinguish rhinoviruses from other enteroviruses. RVs can be isolated in cell culture, usually within 2 to 7 days after inoculation. Virus is present in nasopharyngeal secretions in highest concentrations during the first and second days of illness but may be shed for as long as 3 weeks. When indicated, identification of the specific serotype of a rhinovirus isolate is made by neutralization test.

Treatment and Prevention

The only effective therapy for RV colds currently available is symptomatic treatment of individual complaints. Remedies recommended for such treatment are described in the section on common cold in this chapter. Although hand washing is undoubtedly important in preventing transmission, a recent study could show no benefit to routine hand disinfection in the prevention of RV colds.²⁹⁹ As mentioned earlier, the plethora of rhinovirus serotypes suggests that an effective vaccine will not be forthcoming in the foreseeable future. Advances in understanding of the structural and molecular biology of the rhinoviruses has led to development of a number of strategies for antiviral intervention, including receptor blockade and capsid-binding agents. However, none of these agents has reached approval for clinical use.

VARICELLA-ZOSTER VIRUS

Varicella-zoster virus (VZV) is an enveloped double-stranded DNA virus with a large genome ($\approx 125,000$ bp). Varicella is

a highly contagious, childhood disease that typically causes community outbreaks in late winter and early spring months in temperate regions. Varicella spreads rapidly to household contacts, with an attack rate of nearly 90% within 2 weeks. Consequently, most adults in temperate areas have experienced infection during childhood, but a high proportion of adults in semitropical and tropical areas remain susceptible to primary infection.³⁰⁰ Herpes zoster is nonseasonal and is seen in persons of all ages, although its incidence increases almost linearly after 30 years of age. About 10% to 20% of adults experience zoster, typically as a single episode after the fifth decade of life. Clinically apparent reinfections can be seen with VZV.

Although the virus has been infrequently recovered from respiratory secretions of varicella patients, epidemiologic evidence indicates that the virus is spread from person to person through airborne transmission. Cutaneous lesions may also be the source of infectious virus. Susceptible persons have been infected after contact with patients with varicella, or, less often, with herpes zoster. Before the implementation of vaccination, VZV was an important cause of nosocomial outbreaks on pediatric wards, with spread by small-particle aerosols.

Pathogenesis

The incubation period of varicella averages 2 weeks, and almost all cases of varicella develop within 11 to 20 days after exposure. The initial portal of infection is the respiratory tract, with viremic dissemination leading to the extensive cutaneous and mucous membrane lesions. Following infection, VZV establishes latency in the posterior dorsal root ganglia. Reactivation of virus replication and centrifugal spread along sensory nerves lead to the unique dermatomal distribution of shingles (zoster). In immunocompromised hosts with zoster, virus may disseminate to other sites.

Clinical Illness

Varicella. In children with normal immunity, varicella is usually not associated with significant systemic or respiratory manifestations. The exanthem typically begins around the scalp and head, with subsequent involvement of the trunk and extremities. Lesions progress through various stages (erythematous macules, vesicles, pustules, crusts), so an area will have lesions in different stages of evolution. In contrast, in smallpox, a disease with which varicella was often confused, lesions begin on the face and spread outwardly to the extremities, and adjacent lesions are at the same stage of development.

In children and susceptible adults who are immunocompromised, particularly those with defects in cell mediated immunity, including HIV infection,³⁰¹ varicella follows a more severe course. Continued lesion development, particularly involving the extremities; high fever; and visceral involvement with pneumonia, meningoencephalitis, and hepatitis are common. During pregnancy, severe pneumonia can develop in approximately 10% of varicella cases.

Viral pneumonia is the major complication of varicella in normal adults, in whom the frequency is estimated to be 25-fold higher than in children.³⁰² Smoking is a significant risk factor. Pneumonia associated with varicella is usually apparent 1 to 6 days after the onset of rash. Symptoms

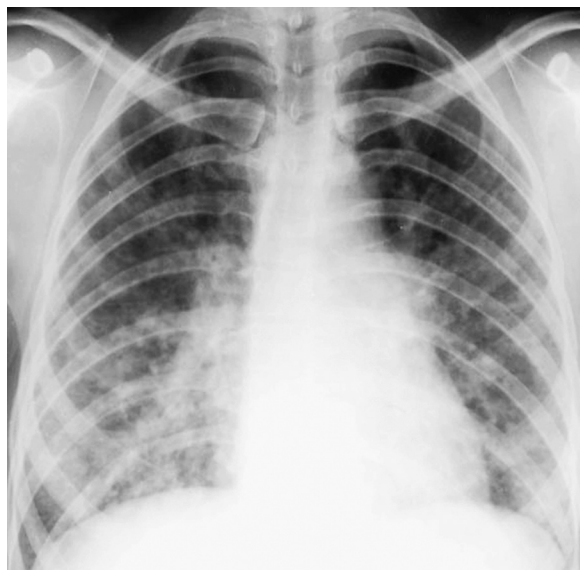


Figure 32-11 Acute varicella pneumonia. Frontal chest radiograph shows multifocal, bilateral, poorly defined nodular opacities in a predominantly perihilar and lower lobe distribution. No pleural effusion is present. (Courtesy Michael Gotway, MD.)

include cough, dyspnea, pleuritic chest pain, and hemoptysis. Physical findings other than fever and tachypnea are often modest. The intensity of the rash does not necessarily correlate with the severity of pneumonia. The characteristic chest radiographic pattern is that of diffuse nodular (1 to 10 mm) opacities (Fig. 32-11, eFig. 32-14), which may resolve with miliary calcified nodules (eFig. 32-15).³⁰³ Hilar lymphadenopathy, pleural effusions, and peribronchial opacities are frequently present. Pulmonary infarction may complicate the clinical picture. Chest CT in patients with varicella pneumonia typically shows multifocal or diffuse, variably sized nodules (1 to 10 mm), which may be circumscribed or poorly defined (eFig. 32-16). Ground-glass opacity halos may be seen around some of the nodules. Pulmonary function studies have found normal expiratory flow values but decreased carbon monoxide diffusing capacity, which may persist for months. However, many individuals with radiographic changes are relatively asymptomatic.

Herpes Zoster. Zoster represents reactivation of latent virus along one to three dermatomes and, in adults, is usually associated with pain. The thoracic dermatomes are involved in about one half of cases. Prolonged severe pain, or postherpetic neuralgia, can be a serious complication, with increased frequency in those older than 50.

Zoster presents more often in those receiving immunosuppressive therapy or chemotherapy for malignancies and at anatomic sites irradiated for treatment of malignancies. Depending on the degree of immunosuppression, herpes zoster may develop in 30% or more of patients. Cutaneous dissemination (defined as more than 20 lesions outside the primary dermatome) develops in 25% to 50% of immunosuppressed patients and in up to 2% of apparently normal patients with zoster. It is associated with visceral involvement including pneumonitis, as well as hepatitis, meningoencephalitis, and uveitis in approximately one half of those

affected. Mortality depends on the degree of immunosuppression and ranges from zero to 10%.

Diagnosis

A rapid diagnosis of herpes group infection can be established by cytologic examination of lesion scrapings (Tzanck smear and others), which has a sensitivity of 70% to 85% when lesions are in the vesicular stage. Direct immunofluorescence for VZV antigen in lesions is the most sensitive rapid laboratory test. The virus is labile but can be isolated from vesicular fluid during the first 3 days of varicella in normal hosts and for up to 10 days in immunocompromised hosts or patients with disseminated zoster. Direct inoculation of vesicular fluid onto monolayers of cell culture (human embryonic lung fibroblasts) at the bedside increases the likelihood of isolation.

Treatment and Prevention

Live, attenuated varicella vaccine generates neutralizing antibody in more than 95% of recipients and also generates long-lived CD8⁺ cytotoxic T-cell responses against varicella virus.³⁰⁴ Vaccination of immunosuppressed children, including those with leukemia, is safe, although a small proportion of children will experience a mild, varicella-like clinical syndrome approximately 1 month after vaccination.³⁰⁵ In both healthy and immunosuppressed children, the vaccine is highly effective at preventing varicella, with efficacy rates of 50% to 90%. Two doses of varicella vaccine administered subcutaneously are recommended for children 12 months and older, adolescents, and adults without evidence of prior immunity.³⁰⁶ Second-dose catch-up vaccination is recommended for those who previously received only a single dose of vaccine.

A higher-dose live vaccine effectively re-stimulates virus-specific cellular immunity in adults and can reduce the frequency of reactivation, as well as the clinical severity of zoster.³⁰⁷ The high-dose live vaccine is recommended as a single dose in all healthy individuals 60 and older.³⁰⁸

Although uncomplicated varicella in children usually requires no specific treatment, oral acyclovir initiated within 24 hours of rash onset reduces the number of lesions, duration of fever, and healing time compared with placebo in children, adolescents, and adults.³⁰⁹ Sequential intravenous and oral acyclovir has been used in therapy of varicella in immunocompromised children.³¹⁰ In immunocompromised patients with localized zoster, intravenous acyclovir has been found to halt dissemination. In addition, oral acyclovir, valacyclovir, and famciclovir are effective for the treatment of zoster and may reduce the duration of postherpetic neuralgia in healthy adults.³¹¹ Intravenous acyclovir (10 mg/kg every 8 hours for 5 to 7 days) appears efficacious in varicella pneumonia in previously healthy adults if started early.³¹²

Key Points

- Viral infections, important causes of disease of the respiratory tract, are associated with substantial morbidity and mortality in all age groups.
- Clinical syndromes such as the common cold, pharyngitis, acute bronchitis, influenza-like illness, croup,

bronchiolitis, and pneumonia—may be caused by several different viruses, and most of the major respiratory viruses may cause more than one clinical syndrome.

- There is increasing recognition of the role of respiratory viruses in lower respiratory tract disease in immunocompromised individuals; the growing availability of molecular diagnostic tests will lead to many more viral diagnoses.
- Effective vaccines are available for the prevention of disease due to some viral pathogens, including influenza, measles, mumps, rubella, and varicella virus, and antiviral agents are available for some, including influenza, herpes viruses, cytomegalovirus, and varicella-zoster virus. For most respiratory viral pathogens, neither vaccines nor antivirals are currently available.
- New respiratory viruses are continually emerging at the interface between human and animal species. Recent examples include avian and swine influenza viruses, severe acute respiratory syndrome, Middle East respiratory syndrome, and hantavirus pulmonary syndrome. Continued surveillance for new agents is critical in controlling pandemics.

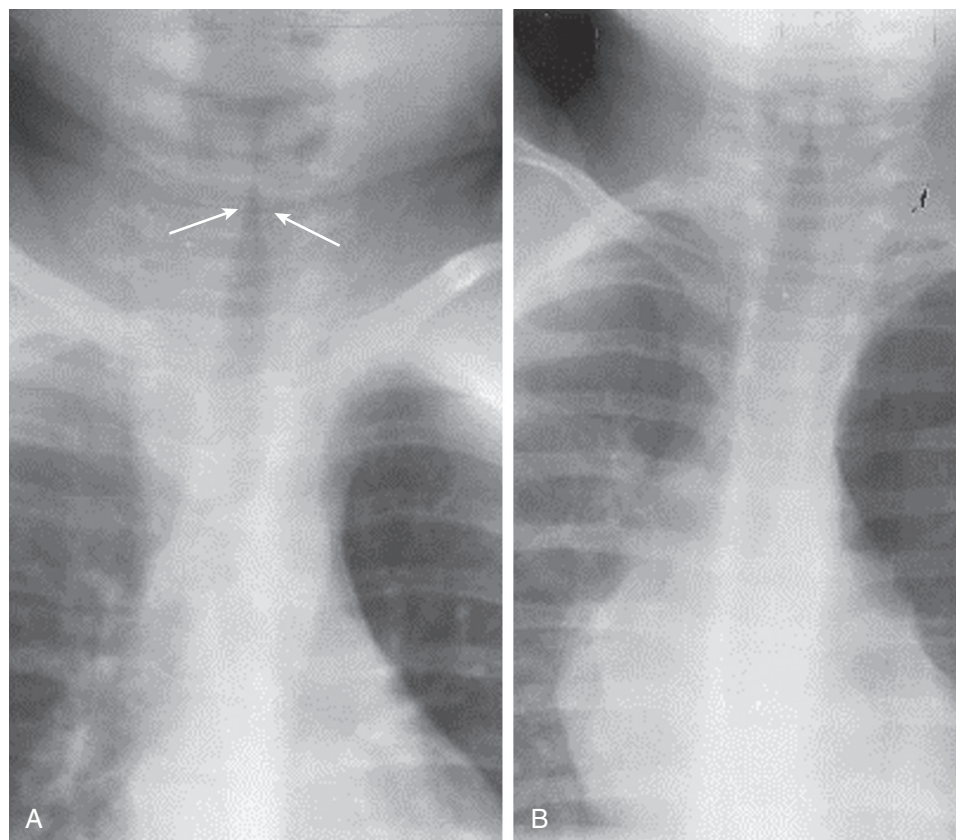
Complete reference list available at *ExpertConsult*.

Key Readings

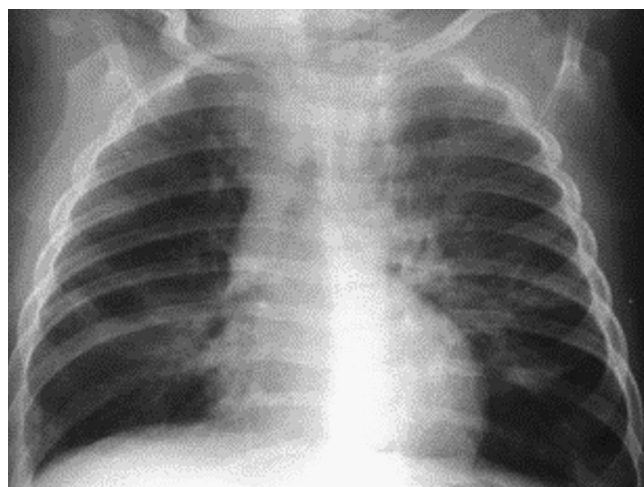
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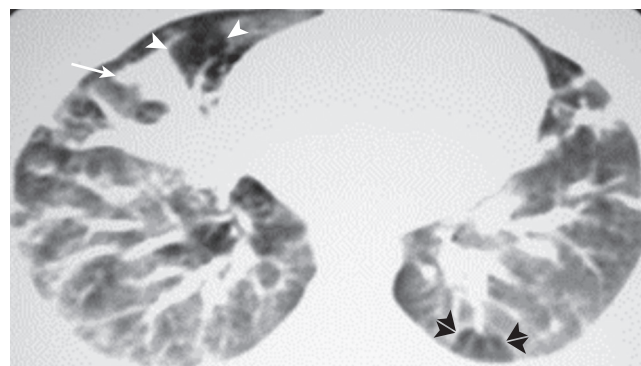
eFIGURE IMAGE GALLERY



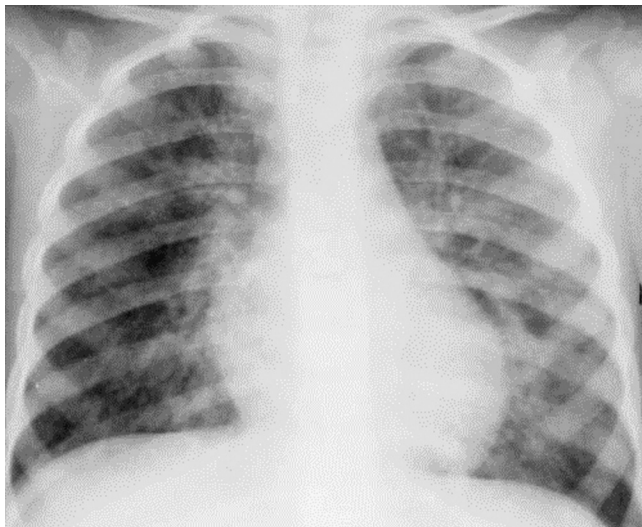
eFigure 32-1 Radiographic appearance of croup: the “steeple” sign. **A**, Detail frontal chest radiograph in a child with croup shows smooth, superiorly tapered narrowing of the subglottic tissues (*arrows*) due to edema. **B**, Normal appearance of the subglottic trachea—note the less tapered appearance. (Courtesy Michael Gotway, MD.)



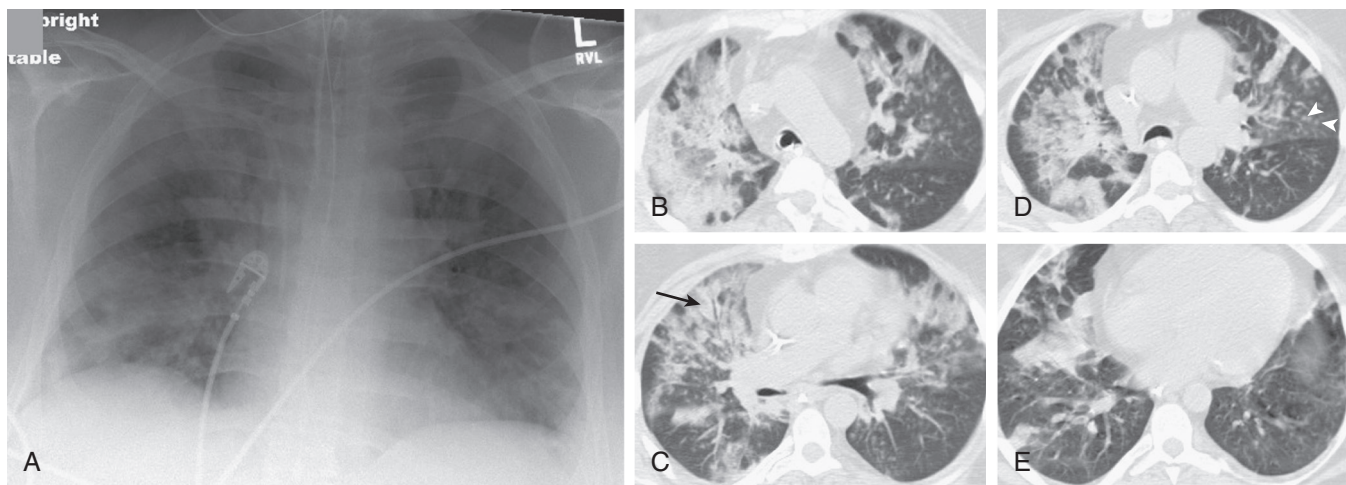
eFigure 32-2 Chest radiography: infectious bronchiolitis. Frontal chest radiograph in a pediatric patient with bronchiolitis shows patchy, bilateral perihilar linear opacities with slight depression of the left diaphragm due to left lower lobe air trapping. (Courtesy Michael Gotway, MD.)



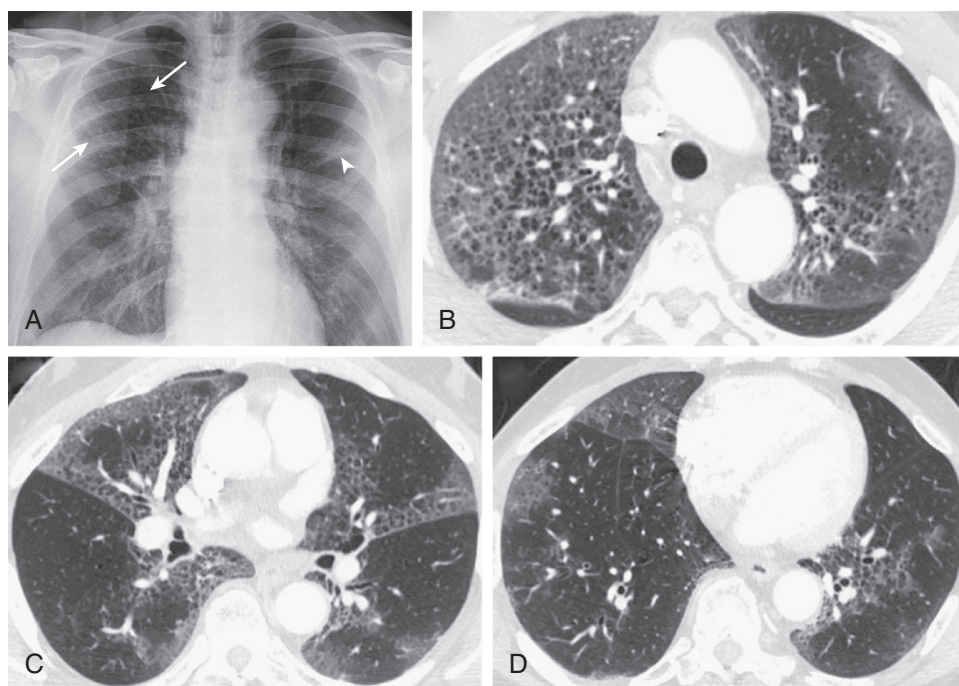
eFigure 32-3 Chest CT: infectious bronchiolitis. Axial chest CT displayed in lung windows shows patchy areas of increased attenuation due to atelectasis (*arrow*) associated with areas of decreased attenuation caused by “air trapping” (*single arrowheads*), in some areas with a clearly lobular configuration (*double arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 32-4 Chest radiography: measles pneumonia. Frontal chest radiograph in a child with a typical measles rash shows patchy, bilateral faintly nodular bronchovascular thickening with a predominantly perihilar distribution. The imaging features are consistent with viral infection but nonspecific as regards potential etiologic agents. (Courtesy Michael Gotway, MD.)



eFigure 32-5 Adenovirus pneumonia: imaging findings. **A**, Frontal chest radiograph shows bilateral areas of ground-glass opacity and consolidation without pleural effusion. **B–E**, Axial chest CT displayed in lung windows shows multifocal ground-glass opacity with areas of consolidation with air bronchograms formation (*arrow*). Small nodules (*arrowheads*) are also present. The imaging features are suggestive of pulmonary infection but nonspecific as regards etiology. (Courtesy Michael Gotway, MD.)



eFigure 32-6 Seasonal influenza A infection: imaging findings. **A**, Frontal chest radiograph shows patchy, bilateral linear interstitial thickening in a perihilar distribution, some of which represents bronchial thickening. Abnormalities are slightly more nodular appearing in the right upper lobe (*arrows*), and consolidation is developing in the left upper lobe (*arrowhead*). **B–D**, Axial chest CT displayed in lung windows shows multifocal, bilateral, upper lobe predominant ground-glass opacity associated with linear abnormalities consistent with mild, smooth interlobular septal thickening and intralobular interstitial thickening. The cystic appearance is due to centrilobular emphysema outlined and contrasted with the surrounding infiltrative lung abnormalities. (Courtesy Michael Gotway, MD.)



eFigure 32-7 Seasonal influenza A infection: variable chest radiographic findings. Frontal chest radiograph shows predominantly left perihilar peribronchovascular thickening and nodularity. The imaging findings are nonspecific and could be the result of a number of causes of bronchopneumonia. (Courtesy Michael Gotway, MD.)

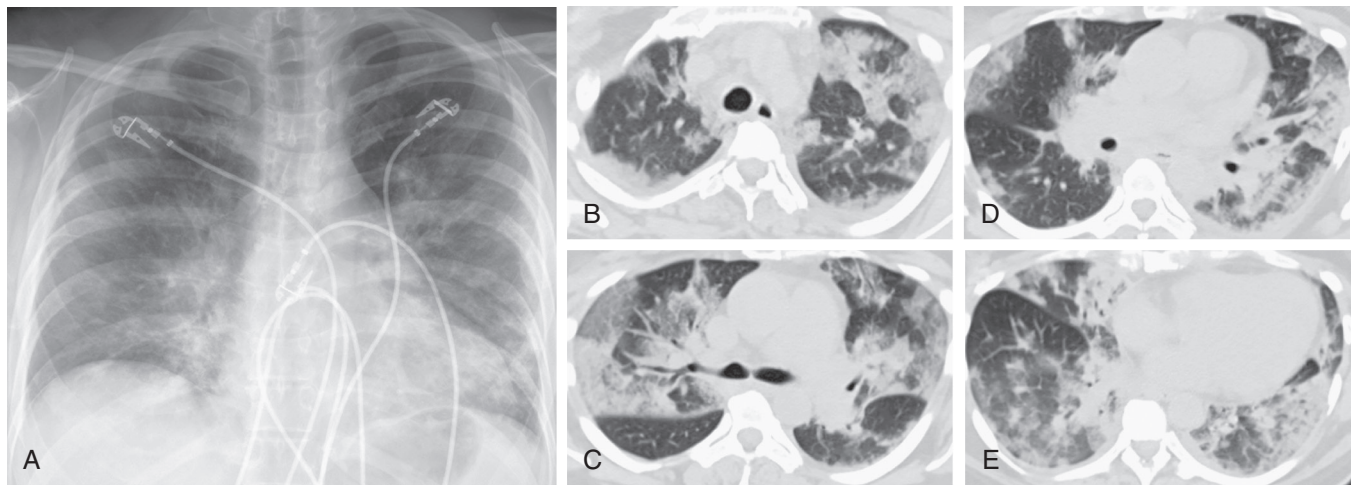


Figure 32-8 Seasonal influenza A infection progressing to respiratory failure with diffuse alveolar damage. **A**, Frontal chest radiograph in a previously healthy 51-year-old woman with no significant previous medical history presenting to the emergency department with fever, cough, and nasal congestion shows multifocal, perihilar predominantly linear opacity and bronchovascular thickening and hazy opacities. The patient had been seen as an outpatient and treated with several broad-spectrum antibiotics with no improvement. At the time the chest radiograph was performed, the patient was mildly leukopenic with an oxygen saturation of 82% on room air. **B–E**, Axial chest CT displayed in lung windows shows multifocal, bilateral, nonsegmental areas of ground-glass opacity, in some areas peripherally and peribronchially distributed, associated with intralobular interstitial thickening, mild interlobular septal thickening, and a few areas of consolidation. The imaging findings are nonspecific and can be seen with numerous causes of noninfectious acute lung injury and other pulmonary infections including severe acute respiratory syndrome (SARS). Surgical lung biopsy showed diffuse alveolar damage with some intrabronchiolar and alveolar inflammatory cells suggesting the possibility of an infectious insult, and bronchoscopy before the surgical biopsy recovered influenza A. The patient suffered hypoxic respiratory failure requiring mechanical ventilation but subsequently recovered. (Courtesy Michael Gotway, MD.)

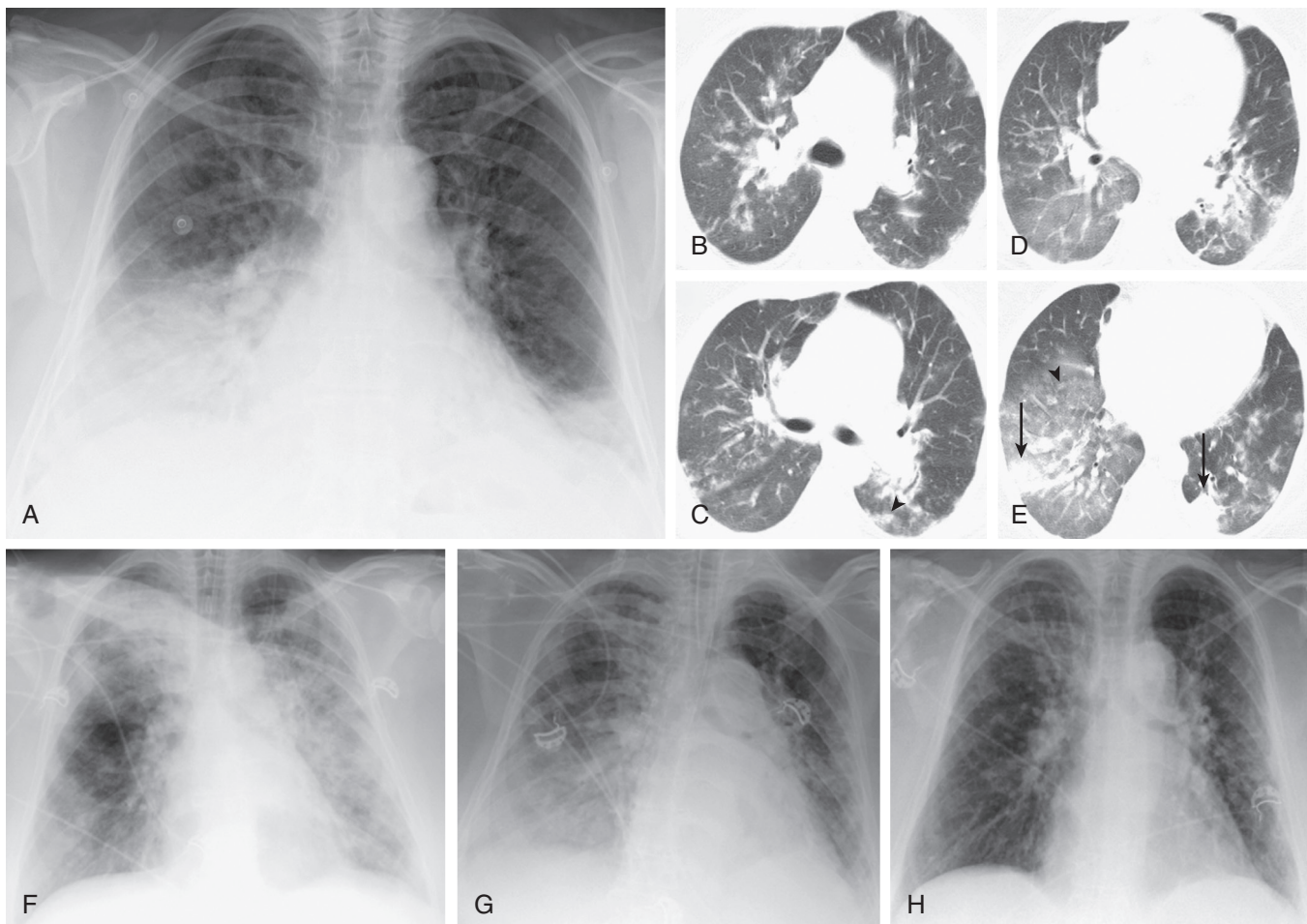
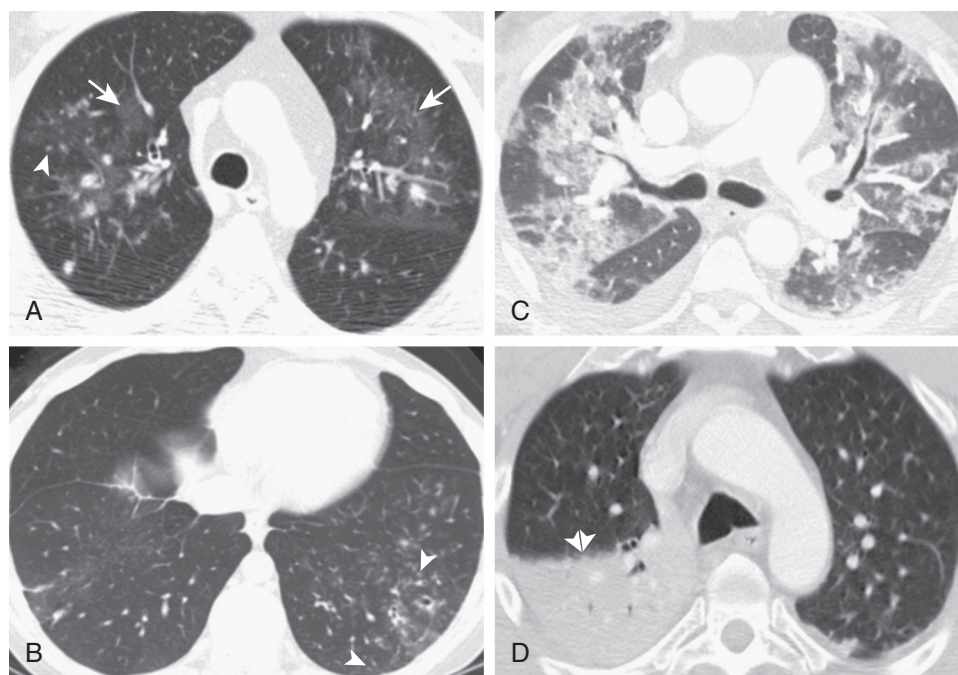
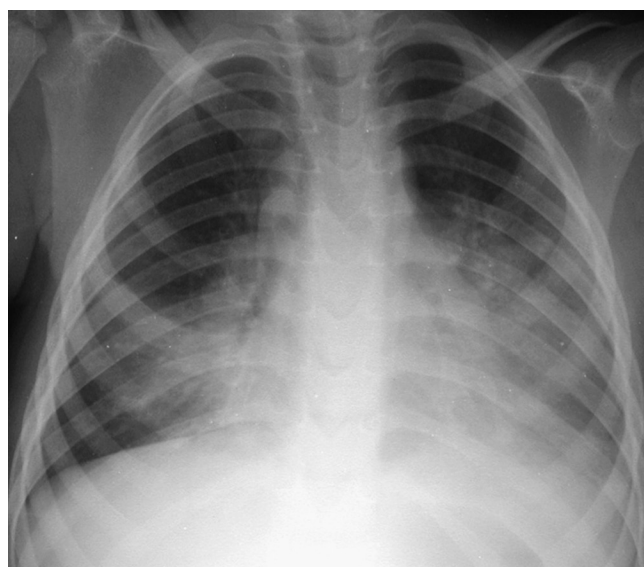


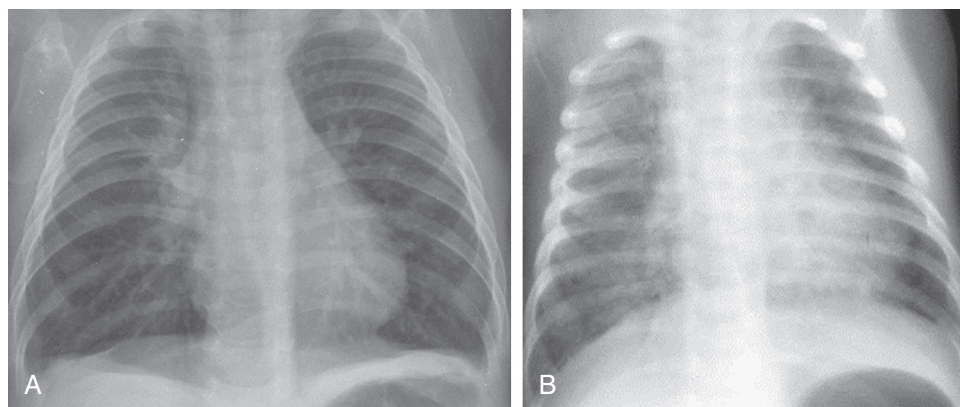
Figure 32-9 H1N1 ("swine-origin") influenza A infection: imaging findings. **A**, Frontal chest radiograph in a patient subsequently diagnosed with H1N1 influenza during the 2009 pandemic shows multifocal basal predominant consolidation, consistent with bronchopneumonia, but nonspecific. **B–E**, Axial chest CT displayed in lung windows shows nonspecific bilateral areas of ground-glass opacity, nodular subpleural consolidation (arrows) and other foci of patchy, peripheral, increased lung attenuation, and small nodules (arrowheads), some of which appear centrilobular. **F–H**, Serial frontal chest radiograph obtained during the course of the disease shows worsening of bilateral opacities associated with hypoxemic respiratory failure (**F** and **G**) but subsequent clearing of bilateral lung opacity following recovery (**H**). (Courtesy Michael Gotway, MD.)



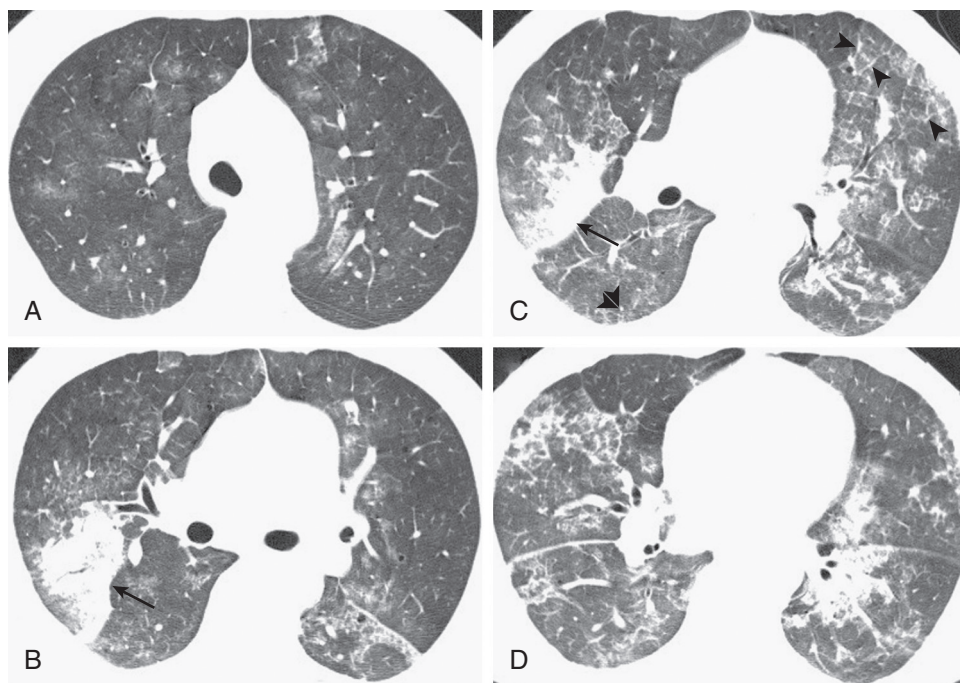
eFigure 32-10 H1N1 (“swine-origin”) influenza A infection: variable imaging findings at chest CT. **A** and **B**, Axial chest CT displayed in lung windows shows patchy areas of upper lobe predominant ground-glass opacity (*arrows*) and small, solid, centrilobular nodules (*arrowheads*). The opacity in the left lower lobe (**B**) appears somewhat segmental, suggestive of bronchopneumonia. **C**, Axial chest CT shows multifocal, bilateral areas of ground-glass opacity associated with interlobular septal thickening and intralobular interstitial thickening, but no clear zonal distribution; these findings are nonspecific and can be observed with numerous infections and noninfectious inflammatory pulmonary insults. **D**, Axial chest CT shows right lower lobe superior segmental dense consolidation (*double arrowheads*), suggestive of a lobar pneumonia pattern. (Courtesy Michael Gotway, MD.)



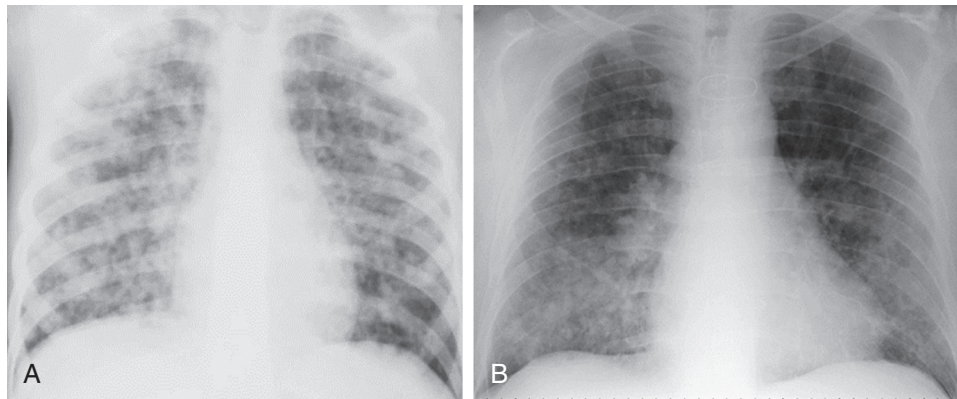
eFigure 32-11 Seasonal influenza A infection complicated by bacterial pneumonia. Frontal chest radiograph in a pediatric patient shows multifocal bilateral consolidation. The patient had been diagnosed with seasonal influenza A infection 2 weeks earlier and was recovering but then developed a high fever and new productive cough. (Courtesy Michael Gotway, MD.)



eFigure 32-12 Respiratory syncytial virus (RSV) bronchiolitis and pneumonia: chest radiographic findings. **A**, Frontal chest radiograph in a young child with RSV bronchiolitis shows bilateral basal streaky opacities associated with significant diaphragmatic flattening bilaterally, consistent with “air trapping” due to small airway inflammation and obstruction. **B**, Frontal chest radiograph in an infant with RSV pneumonia shows patchy, somewhat perihilar-predominant bronchovascular thickening. The right diaphragm is somewhat flattened, suggesting basal air trapping. (Courtesy Michael Gotway, MD.)



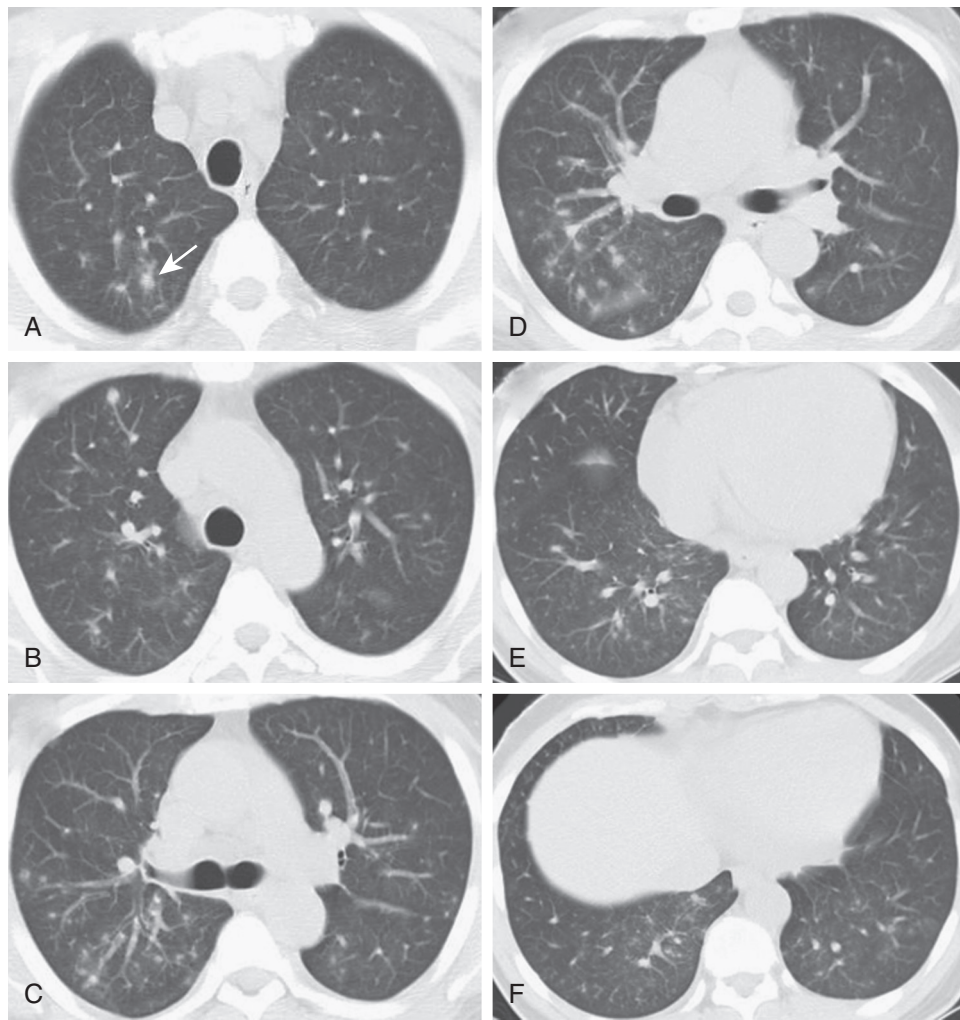
eFigure 32-13 Respiratory syncytial virus pneumonia: chest CT findings. **A–D**, Axial chest CT displayed in lung windows shows multifocal, bilateral patchy areas of ground-glass opacity associated with more focal right upper lobe posterior segmental consolidation (*arrows*). In some areas the ground-glass opacity is associated with intralobular interstitial thickening and interlobular septal thickening (*arrowheads*). Small solid nodules (**C**, *double arrowheads*) are also present. (Courtesy Michael Gotway, MD.)



eFigure 32-14 Varicella-zoster virus (VZV) pneumonia: chest radiographic findings of acute infection. **A**, Frontal chest radiograph in a young patient with VZV pneumonia shows bilateral poorly defined nodular opacities, ultimately nonspecific but typical of VZV pulmonary infection. **B**, Frontal chest radiograph in a heart transplant patient with acute VZV infection shows multifocal, bilateral, poorly defined nodules without pleural effusion. (Courtesy Michael Gotway, MD.)



eFigure 32-15 Varicella-zoster virus pneumonia: chest radiographic findings of remote infection. Frontal chest radiograph shows numerous, small, circumscribed bilateral calcified nodules. (Courtesy Michael Gotway, MD.)



eFigure 32-16 Varicella-zoster virus pneumonia: chest CT findings of acute infection. A–F, Axial chest CT displayed in lung windows shows multiple, bilateral small nodules, most of which are poorly defined. A faint ground-glass opacity halo is present around one of the nodules (*arrow*). The imaging findings are consistent with pulmonary infection but nonspecific as regards the etiologic agent. (Courtesy Michael Gotway, MD.)

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BACTERIAL PNEUMONIA AND LUNG ABSCESS

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An expanded version of this chapter is available online at ExpertConsult.

INTRODUCTION

Community-acquired pneumonia (CAP) is a frequent infectious respiratory disease.¹ Although many patients with CAP can be treated as outpatients, the mortality of CAP in those who do require hospitalization ranges from 5% to 15% and increases to 20% to 50% in patients who require intensive care unit (ICU) care. Hospital-acquired pneumonia (HAP) is the second most common and most frequently fatal nosocomial infection.

A clinical diagnosis of pneumonia can usually be established on the basis of signs, symptoms, and chest radiographs, although distinguishing CAP or HAP from conditions such as congestive heart failure, pulmonary embolism, and chemical aspiration pneumonia is sometimes difficult. Defining an etiologic agent is also challenging. Although early empirical therapy is necessary, it is important to identify the causative pathogen in patients who require hospitalization, both to confirm the appropriateness of therapy and to reduce unnecessary antimicrobial use.

Diagnosis and management of pneumonia has become more complex due to the growing number of aged and comorbid, debilitated, institutionalized, and immunocompromised individuals, to the diverse array of microorganisms that cause pneumonia, and to increasing antimicrobial resistance.

PATHOPHYSIOLOGY AND PATHOGENESIS

Aspiration of oropharyngeal or nasopharyngeal secretions is the main mechanism of contamination of lower airways by bacteria. While a person is awake, glottal reflexes prevent aspiration; during sleep, 50% of normal persons aspirate small volumes of pharyngeal secretions. Because oropharyngeal secretions may contain 10^7 to 10^{11} microorganisms per milliliter, aspiration of as little as 0.001 mL may carry more than 100,000 bacteria.

The oropharynx of healthy individuals is colonized by diverse microorganisms that vary in their potential virulence. The ability of microorganisms to colonize the oropharynx and to cause lower respiratory tract infections is determined in part by the interaction of specific microbial adhesins with cellular receptors. For example, *Streptococcus pneumoniae*, which contains multiple adhesions,² binds to the receptor for platelet-activating factor on epithelial cells, and this interaction is enhanced by cigarette smoke, infection with respiratory viruses, and particulate air pollutants,³⁻⁵ all of which are linked to increased risk for pneumococcal pneumonia. Likewise, *Staphylococcus aureus* expresses multiple adhesins that bind host extracellular matrix proteins.^{6,7} Gram-negative bacterial pathogens also possess specific adhesins, many of which form macromolecular structures, termed *pili*. *Klebsiella pneumoniae* exploits two distinct pili to adhere to epithelial cells: type 1 pili bind to diverse host target molecules with exposed mannose residues, and type 3 pili interact with extracellular matrix proteins.⁸

Several mechanisms in the airways prevent adherence and colonization by potential bacterial pathogens.

LESS COMMON CAUSES OF PNEUMONIA

Actinomycosis

Chlamydophila psittaci (Formerly *Chlamydia psittaci*)—Psittacosis

Coxiella burnetii—Q Fever

Nocardiosis

Melioidosis (*Burkholderia pseudomallei*)

Rhodococcus equi

Pulmonary Anthrax (*Bacillus anthracis*)

Tularemia (*Francisella tularensis*)

Plague (*Yersinia pestis*)

Moraxella catarrhalis

Neisseria meningitidis

Pasteurella multocida

Table 33-1 Common Causes of Community-Acquired Pneumonia in Patients Who Do Not Require Hospitalization*

Mycoplasma pneumoniae
Streptococcus pneumoniae
Chlamydophila pneumoniae
Haemophilus influenzae
Respiratory viruses

*Organisms are listed in the general order of frequency.

Respiratory epithelial cells synthesize and secrete peptides, termed *defensins* and *cathelicidins*, that possess broad-spectrum antimicrobial activity.⁹ In the distal airways and alveoli, pulmonary surfactant proteins A and C can inhibit bacterial binding to host cells and also promote phagocytosis of selected bacteria.^{10,11} The presence of complement and immunoglobulins (particularly *immunoglobulin A* [IgA]), also prevents colonization of the oropharynx. In addition to protection provided by host factors, the upper airway microbiota may modulate susceptibility to pathogens, as indicated by the evidence that broad-spectrum antimicrobial therapy predisposes to colonization and infection. The effects of the microbiota operate through competition for binding sites or nutritional resources, or by modulating expression of specific host defense molecules.¹²⁻¹⁵ Interactions between the virulence and quantity of aspirated or inhaled microorganisms and the individual's innate and adaptive immune responses determine whether pneumonia develops.¹⁶

As an alternative to aspiration of bacteria of the upper airways, *Mycoplasma pneumoniae*, *Chlamydophila* species, *Coxiella burnetii*, *Legionella*, and *Mycobacterium tuberculosis* enter the lower respiratory tract by inhalation. Inhalation pneumonia is most often due to microorganisms that survive suspended in the air for prolonged periods, are present in droplet nuclei smaller than 5 μm , and are able to evade innate immune responses.

EPIDEMIOLOGY

COMMUNITY-ACQUIRED PNEUMONIA

The true incidence of CAP is uncertain because the illness is not reportable and only 20% to 50% of patients require hospitalization. Estimates of the incidence of CAP range from 2 to 15 cases per 1000 persons per year, with substantially higher rates in older adults.¹⁷

Although the severity of disease is influenced by the patient's age and by the presence and type of coexisting conditions,¹⁸⁻²¹ the severity of disease is also related to the pathogen. *M. pneumoniae*, *S. pneumoniae*, *Chlamydophila pneumoniae*, *Haemophilus influenzae*, and viruses are causes of mild CAP (Table 33-1), whereas *S. pneumoniae*, *M. pneumoniae*, and *H. influenzae* can cause CAP severe enough to warrant hospitalization (Table 33-2).²¹⁻²³ The most frequently identified pathogens causing severe CAP (i.e., CAP requiring ICU care) include *S. pneumoniae*, enteric gram-negative bacilli, *S. aureus*, *Legionella pneumophila*, *M. pneumoniae*, *H. influenzae*, and respiratory viruses (Table 33-3).²¹⁻²⁵ Up to 20% of severe CAP episodes are caused by polymicrobial infection. Even if extensive diagnostic proce-

Table 33-2 Common Causes of Community-Acquired Pneumonia in Patients Who Require Hospitalization*

Streptococcus pneumoniae
Mycoplasma pneumoniae
Chlamydophila pneumoniae
Haemophilus influenzae
Staphylococcus aureus
Mixed infections
Enteric gram-negative bacilli
Aspiration (anaerobes)
Respiratory viruses
Legionella species

*Organisms are listed in the general order of frequency.

Table 33-3 Common Causes of Severe Community-Acquired Pneumonia*†

Streptococcus pneumoniae
Enteric gram-negative bacilli
Staphylococcus aureus
Legionella species
Mycoplasma pneumoniae
Respiratory viruses
Pseudomonas aeruginosa (relative frequency determined by the presence or absence of specific risk factors)

*Severity of disease warranting treatment in an intensive care unit.

†Organisms are listed in the general order of frequency.

dures are performed, the responsible pathogen is not isolated in up to 50% to 60% of patients with severe CAP.

Gram-negative enteric bacilli, *S. aureus*, *Legionella* species, and respiratory viruses are uncommon causes of CAP, although local outbreaks can markedly increase the incidence of *Legionella*.^{26,27} Methicillin-resistant *Staphylococcus aureus* (MRSA), originally a nosocomial pathogen, has appeared in the community where it is referred to as *community-acquired MRSA*. Community-acquired MRSA can lead to severe pulmonary infections, including necrotizing and hemorrhagic pneumonia.²⁸ *Pseudomonas aeruginosa* infection is uncommon in the absence of specific risk factors (recent antibiotic treatment, *acquired immunodeficiency syndrome* [AIDS], and severe pulmonary comorbidity, especially bronchiectasis, cystic fibrosis, and severe *chronic obstructive pulmonary disease* [COPD]).^{21,22,24}

The likely etiology of severe CAP varies in differing patient populations, depending on age and comorbidities, including HIV infection.^{22,29-31a}

Age-Related Factors

Pneumonia remains one of the major causes of morbidity in children. In Europe, there are more than 2.5 million cases of childhood pneumonia yearly, which account for about 50% of hospital admissions for children. Radiographically defined pneumonia is present in 7.5% of febrile illnesses in infants up to 3 months old and in 13% of infectious illnesses during the first 2 years of life. In children younger than 2 years, *S. pneumoniae* and respiratory syncytial virus are the most frequent microorganisms, whereas *M. pneumoniae* is a leading cause of pneumonia in older children and young adults.

In adults, increased age is associated with a change in the distribution of microbial causes and an increase in the

frequency and severity of pneumonia.³² The annual incidence of CAP in noninstitutionalized older adults is estimated between 18 and 44 per 1000 compared with 4.7 to 11.6 per 1000 in the general population.^{17,32,33} Although older adults are particularly at risk for pneumococcal pneumonia, they also have increased rates of pneumonia due to group B streptococci, *Moraxella catarrhalis*, *H. influenzae*, *L. pneumophila*, gram-negative bacilli, *C. pneumoniae*, and polymicrobial infections.^{17,24,34} Although the absolute rate of infection by *M. pneumoniae* does not decrease with age, this pathogen accounts for a smaller proportion of pneumonia in older adults than in younger populations. In patients older than 80 years, there is a higher incidence of aspiration pneumonia and lower incidence of infection with *Legionella* species than in younger patients.³⁵

Personal Habits

Alcohol consumption is an important risk factor for CAP because of its potential to impair level of consciousness, thus increasing the risk for aspiration of oropharyngeal contents. In addition, diverse effects of alcoholism on innate and adaptive immunity have been reported, which may contribute to increased risk. Alcoholism has been shown to be an independent risk factor for increased rate and severity of pneumonia, especially that due to *S. pneumoniae*.^{36,37} This predisposition persists several months after cessation of alcohol consumption.³⁷

Smoking is one of the most important risk factors for CAP and is associated with an increased frequency of CAP due to *S. pneumoniae*, *L. pneumophila*, and influenza.³⁸ Smoking alters mucociliary transport and humoral and cellular defenses, affects epithelial cells, and increases adhesion of *S. pneumoniae* and *H. influenzae* to the oropharyngeal epithelium.⁴

Comorbidities

The most frequent comorbidity associated with CAP is COPD. Patients with COPD have an increased risk for CAP, due to alterations in mechanical and cellular defenses that allow bacterial colonization of the lower airways. Patients with severe COPD (forced expiratory volume in 1 second < 30% of predicted) and bronchiectasis have an increased risk for pneumonia caused by *H. influenzae* and *P. aeruginosa*.³⁸ In patients with COPD treated with oral corticosteroids for long periods, the risk for infection with *Aspergillus* species is increased.³⁹

Pneumonia remains the major cause of morbidity and mortality in patients with cystic fibrosis. During the first decade of life, *S. aureus* and nontypeable *H. influenzae* are the most common pathogens, although *P. aeruginosa* is occasionally isolated in infants. By 18 years of age, 80% of patients with cystic fibrosis harbor *P. aeruginosa* and 3.5% harbor *Burkholderia cepacia*.⁴⁰ *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and nontuberculous mycobacteria are emerging pathogens in this population.⁴¹

Other comorbidities associated with increased rates of CAP and consequent mortality include congestive heart failure, chronic kidney or liver disease, cancer, diabetes, dementia, cerebrovascular diseases, and immunodeficiencies (e.g., neutropenia, lymphoproliferative diseases, immunoglobulin deficiencies, and human immunodeficiency virus [HIV] infection).⁴²⁻⁴⁴

Geographic and Occupational Considerations

Geographic factors, seasonal timing, travel history, and occupational or unusual exposures modify the risk of various microbial etiologies of CAP. For example, an increased frequency of *S. pneumoniae* is found in soldiers, painters, and South African gold miners. *Burkholderia pseudomallei* (melioidosis) is endemic in the rural tropics.⁴⁵ Exposure to pet birds or work on a poultry (especially turkey) farm or processing plant increases the risk of psittacosis (*Chlamydophila psittaci*), while contact with horses or other large mammals including cattle, swine, sheep, goats, or deer increases exposure to *Rhodococcus*. Rodent contact suggests the possibility of infection with *Yersinia pestis* (plague) in the rural southwestern United States⁴⁶ and *Francisella tularensis* (tularemia) in rural Arkansas or Nantucket, Massachusetts.⁴⁷ Exposure to sheep, dogs, and cats should prompt evaluation for *Coxiella burnetii* (Q fever).⁴⁸ The role of seasonal timing is illustrated by the increased incidence of lower respiratory tract infections due to *S. pneumoniae* and *H. influenzae* in winter months. Pneumonia causing the severe acute respiratory syndrome (SARS) due to a coronavirus emerged in epidemic form in Southeast Asia,^{49,50} and another coronavirus causes the emerging Middle East respiratory syndrome (MERS). Finally, the infectious agents that cause anthrax, tularemia, and plague may be used for bioterrorism or biowarfare purposes and cause lower respiratory tract infections.^{51,52}

HOSPITAL-ACQUIRED (NOSOCOMIAL) PNEUMONIA

Early-onset HAP (<5 days of hospitalization) is most often due to microorganisms that are also associated with CAP, such as *S. pneumoniae*, *H. influenzae*, and anaerobes. Late-onset HAP (>5 days of hospitalization) is mainly caused by MRSA, enteric gram-negative bacilli, *P. aeruginosa*, nonfermenters such as *Acinetobacter baumannii* and *S. maltophilia*, and polymicrobial infections.⁵³ Factors that increase the risk for HAP include antibiotic exposure, old age, severe comorbidities, underlying immunosuppression, colonization of the oropharynx by virulent microorganisms, conditions that promote pulmonary aspiration or inhibit coughing (e.g., thoracoabdominal surgery, endotracheal intubation, insertion of nasogastric tube, supine position), and exposure to contaminated respiratory equipment. A recent study suggests that multidrug-resistant microorganisms are more frequent in early-onset HAP than was initially thought⁵⁴ and that risk factors for early-onset pneumonia should be reappraised.

HEALTH CARE-ASSOCIATED PNEUMONIA

Health care now reflects a continuum with many traditional inpatient services provided in outpatient settings. Physicians often categorize new infections in such subjects as “community-acquired.” However, these health care-associated infections have a unique epidemiology more like that of hospital-acquired infections, and this has resulted in health care-acquired pneumonia (HCAP) being recognized as a separate entity by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA).⁵³ *S. aureus*

(both methicillin-sensitive and methicillin-resistant) and *P. aeruginosa* are the most frequent associated microorganisms. Compared with CAP, HCAP patients have more severe disease, higher mortality, greater length of hospital stay, and greater cost of care.⁵⁵

CLINICAL PRESENTATION

Pneumonia is characterized by the presence of fever, altered general well-being, and respiratory symptoms, such as cough (90%), sputum production (66%), dyspnea (66%), pleuritic pain (50%), and hemoptysis (15%). In older and immunocompromised patients, the signs and symptoms of pulmonary infection may be muted and overshadowed by nonspecific complaints. Temperature greater than 38.5° C or accompanied by chills should never be attributed to bronchitis without examining a chest radiograph.

Occasionally, there is a “classic” history, such as that of the patient with pneumococcal infection who presents with sudden onset of rigor followed by pleuritic chest pain, dyspnea, and cough with rusty sputum. Similarly, a patient with *Legionella* pneumonia may complain predominantly of diarrhea, fever, headache, confusion, and myalgia. For *M. pneumoniae* infection, extrapulmonary manifestations such as myringitis, encephalitis, uveitis, iritis, and myocarditis may be present. However, only rarely does the clinical history clearly suggest a specific etiologic diagnosis.

Information obtained from the clinical history and physical examination is not sufficient to confirm the diagnosis of pneumonia. A definitive diagnosis requires the finding of a new opacity on the chest radiograph.

In older patients, especially those with multiple comorbidities, pneumonia may present with general weakness, decreased appetite, altered mental status, incontinence, or decompensation due to underlying disease. The presence of tachypnea may precede other signs of pneumonia by 1 to 2 days. Tachycardia is another common initial sign but is less frequent and specific than tachypnea. Fever is absent in 30% to 40% of older patients. Owing to the lack of specific symptoms, the diagnosis of CAP is frequently delayed in older adults.^{17,34} Older patients with pneumonia who present with altered mental status without fever can have a delay in receiving antibiotics by more than 4 hours after arrival; this delay increases mortality.⁵⁶

TYPICAL VERSUS ATYPICAL PNEUMONIA

The division of CAP into typical and atypical syndromes has been used to predict the likely pathogens and select appropriate empirical therapy.¹⁸⁻²¹ The clinical picture of “typical” CAP is that of disease characteristically caused by bacteria such as *S. pneumoniae*, *H. influenzae*, and *K. pneumoniae*. The initial presentation is frequently acute, with an intense chill. Productive cough is present, and the sputum is purulent or bloody. Pleuritic pain may suggest *S. pneumoniae*. Physical examination reveals typical findings of pulmonary consolidation (see Chapter 16). Blood tests show leukocytosis with neutrophilia and the presence of band forms in most cases. Chest radiography shows lobar consolidation with air bronchograms (Fig. 33-1).

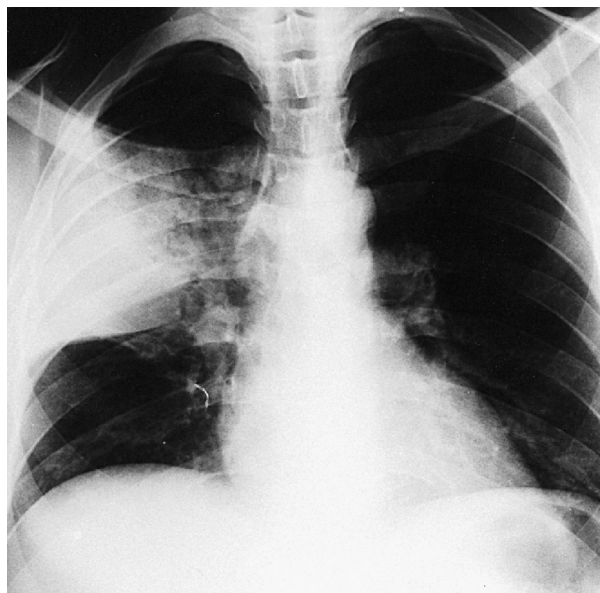


Figure 33-1 Pneumococcal pneumonia with lobar consolidation.

In contrast, the syndrome of gradual onset of fever, non-productive cough, and a relatively normal white blood cell count in a patient without a readily demonstrable bacterial pathogen has been called “atypical pneumonia.” Frequently, systemic complaints are more prominent than the respiratory ones. The atypical syndrome is characteristic of infections by pathogens such as *M. pneumoniae*, *Chlamydia* species, *C. burnetii*, and viruses. However, several studies, including one that included patients with mild CAP treated on an outpatient basis,⁵⁷ have found that neither the clinical symptoms nor the radiographic manifestations are sufficiently sensitive or specific to guide pathogen-directed antibiotic treatment against “typical” versus “atypical” microorganisms.⁵⁷ Therefore, current guidelines do not emphasize the use of the typical versus atypical classification to determine initial empirical antibiotic treatment for CAP.^{18-21,58}

PATIENT EVALUATION

CLINICAL EVALUATION

The clinical findings that best differentiate CAP from other acute respiratory tract infections are cough, fever, tachypnea, tachycardia, and pulmonary crackles; CAP is present in 20% to 50% of persons who have all five factors.⁵⁹ Specific signs of pulmonary consolidation are present in only one third of the cases that warrant hospitalization and are frequently absent in patients that are less ill. Early in the evolution of disease, pain and cough may be absent and the physical examination may be normal other than for fever. In debilitated older patients, vague clinical manifestations of pneumonia are common and the presence of fever with no apparent source, especially when accompanied by confusion or tachypnea, justifies obtaining a chest radiograph.

Clues to the etiologic diagnosis may lie outside the respiratory tract. Bradycardia in relation to the amount of fever (pulse should increase by 10 beats/min/ $^{\circ}\text{C}$ of temperature elevation) has been associated with pneumonia due to *Legionella*, *C. psittaci*, *Mycoplasma*, or *E. tularensis*. *M. pneumoniae* infection may present with extrapulmonary manifestations including arthralgia, cervical lymphadenopathy, bullous myringitis, diarrhea, myalgia, myocarditis, hepatitis, nausea, pericarditis, and vomiting.⁶⁰ Skin lesions of erythema multiforme or erythema nodosum suggest *Mycoplasma* infection (as well as tuberculosis and endemic fungal infection), whereas lesions of ecthyma gangrenosum are most often seen with *P. aeruginosa* infection. Finally, the examiner must look for the presence of complications such as pleural effusion, pericarditis, endocarditis, arthritis, and central nervous system involvement, which may necessitate further diagnostic procedures and, potentially, a change in therapy.⁶¹

LABORATORY EVALUATION

Once the patient is suspected to have pneumonia, laboratory studies should include blood cell counts, serum glucose and electrolyte measurements, and pulse oximetry or arterial blood gas assays.¹⁸⁻²¹ These data provide a basis for making decisions regarding the need for hospitalization. The increased incidence of CAP in HIV-infected individuals provides an additional rationale for HIV testing, particularly in patients with no other risk factors for CAP.

Marked leukocytosis with a leftward shift is more often encountered with infections caused by *S. pneumoniae*, *H. influenzae*, and gram-negative bacilli than with *M. pneumoniae*, *Chlamydia* species, *Coxiella*, or nonbacterial causes of pneumonia. Leukopenia may be seen with overwhelming pneumococcal or gram-negative bacillary pneumonia. The serum level of C-reactive protein and the erythrocyte sedimentation rate are increased to higher values with bacterial than with viral pneumonias. Thrombocytopenia and thrombocytosis are associated with a greater severity of pneumonia and higher mortality.

Procalcitonin (PCT), a precursor of calcitonin, is present at increased concentrations in the blood of persons with bacterial infections, and PCT assays have been used to evaluate the severity, prognosis, and evolution of pneumonia.⁶² Importantly, procalcitonin is used to deescalate antibiotics or to stop antibiotics when the levels decrease to a certain cutoff point.⁶³ A randomized trial of a PCT-guided strategy compared with a guideline-based algorithm, revealed equivalent primary outcomes of treatment of lower respiratory tract infections, but the PCT-guided strategy resulted in reduced antibiotic exposure and duration, fewer adverse effects of antibiotic treatment, and shorter length of stay.⁶⁴

RADIOGRAPHIC EVALUATION

Radiographic evaluation is necessary to establish the presence of pneumonia, because there is no combination of historical data, physical findings, or laboratory results that reliably confirms the diagnosis.^{18,21,59,65} Limitations of chest radiography include interobserver variability and suboptimal specificity, particularly in patients with the *acute respiratory distress syndrome* (ARDS).²¹ Conversely, the sensitivity

of the chest radiograph is decreased in (1) patients with emphysema, bullae, or structural abnormalities of the lung, who may present with delayed or subtle radiographic changes; (2) obese patients, in whom it may be difficult to discern the existence of pneumonia; and (3) patients with very early infection, severe dehydration, or profound granulocytopenia. *Computed tomography* (CT) of the chest provides a more sensitive means of detecting minor radiographic abnormalities.⁵⁹ However, a chest CT is not recommended for patients with suspected pneumonia who have an apparently normal chest radiograph.²¹

Although several radiographic patterns have been associated with pneumonia caused by specific microorganisms, the presence of a certain pattern is not a reliable method for diagnosing a specific pathogen.^{66,67} Nonetheless, the presence of air bronchograms and a lobar (eFig. 33-1) or segmental pattern is more characteristic of typical than atypical causes of pneumonia. In contrast, a mixed pattern (alveolar and interstitial disease (eFig. 33-2) is more frequently observed with atypical pneumonias. Pneumonia complicating aspiration (frequently from anaerobes) (eFig. 33-3) most often involves the superior segment of the right lower lobe or posterior segment of the right upper lobe, or both, as well as the corresponding segments on the left. Infections developing from hematogenous seeding often appear as multiple rounded, small opacities, sometimes with cavities, with a basal predominance, where the distribution of blood flow is greatest. Demonstration of a lung abscess (eFig. 33-4), cavitation, or necrotizing pneumonia suggests infection by anaerobes, *S. aureus*, *Streptococcus pyogenes*, or gram-negative bacilli. Pleural effusion frequently accompanies pneumonia; the size of the pleural effusion on the chest radiograph helps determine whether thoracentesis should be performed.

MICROBIOLOGIC EVALUATION

Identification of the infecting microorganism facilitates the use of specific therapy instead of unnecessarily broad-spectrum antimicrobial agents. Although the utility of sputum examination is debated (see later), pleural fluid (if present) and two sets of blood cultures should be obtained in patients hospitalized for CAP. Optimal culture results require that specimens be obtained before initiation of antimicrobial therapy. Sputum samples must be carefully collected, transported, and processed in order to optimize the recovery of common bacterial pathogens. These recommendations are summarized in Tables 33-4 and 33-5.

Sputum Examination

Microscopic examination of expectorated sputum is the easiest and most rapidly available method of evaluating the microbiology of lower respiratory tract infections. A valid expectorated sputum specimen can be obtained in about 40% of patients hospitalized with CAP. When interpreting sputum cultures, it is crucial to ensure that oropharyngeal contents do not unduly contaminate the specimens. The presence of more than 10 squamous epithelial cells per low-power field ($\times 100$ magnification) indicates excessive oropharyngeal contamination and the specimen should be discarded because it is not representative of the pulmonary milieu.¹⁸ A specimen with few or no squamous cells and

Table 33-4 Recommended Microbiologic Evaluation in Patients with Community-Acquired Pneumonia

PATIENTS WHO DO NOT REQUIRE HOSPITALIZATION

None*

PATIENTS WHO REQUIRE HOSPITALIZATION

Two sets of blood cultures (obtained prior to antibiotics)
Gram stain and culture of a valid sputum sample
Urinary antigen test for detection of *Legionella pneumophila* (in endemic areas or during outbreaks)
Stain for acid-fast bacilli and culture of sputum (if tuberculosis is suggested by clinical history or radiologic findings)
Fungal stain and culture of sputum, and fungal serologies (if infection by an endemic mycosis is suggested by the clinical history or radiologic findings)
Sputum examination for *Pneumocystis jirovecii* (if suggested by clinical history or radiologic findings)
Nucleic acid amplification tests for *Mycoplasma pneumoniae*, *Chlamydomphila pneumoniae*, *Chlamydomphila psittaci*, *Coxiella burnetii*, *Legionella* species, and respiratory viruses (in endemic areas or during outbreaks)
Culture and microscopic evaluation of pleural fluid (if significant fluid is present)

ADDITIONAL TESTS FOR PATIENTS WHO REQUIRE TREATMENT IN AN ICU

Gram stain and culture of endotracheal aspirate or bronchoscopically obtained specimens using a protected specimen brush or BAL
Other procedures as for other hospitalized patients

*Gram stain and culture should be strongly considered in patients with risk factors for infection by an antimicrobial-resistant organism or unusual pathogen.

BAL, bronchoalveolar lavage; ICU, intensive care unit.

Table 33-5 Recommended Microbiologic Evaluation in Patients with Hospital-Acquired Pneumonia

Two sets of blood cultures
Gram stain and culture of a valid sputum sample*
Urinary antigen test for detection of *Legionella pneumophila* (in endemic areas or during outbreaks)

*Gram stain and culture of valid sputum sample, endotracheal aspirate, or bronchoscopically obtained specimens using a protected specimen brush or bronchoalveolar lavage (if patient is intubated).

many polymorphonuclear white blood cells (>25 cells/low-power field in a sample from a patient who is not granulocytopenic⁶⁸) is ideal (see Fig. 33-3). Gram-stained expectorated sputum specimens of acceptable quality should be carefully examined using ×1000 magnification (oil immersion objective). Specific fluorescent antibodies are used to evaluate sputum or other respiratory tract specimens for the presence of *Legionella* and selected other pathogens (see Chapter 17).

When acceptable sputum is obtained, the specificity of the Gram stain for pneumococcal pneumonia is estimated to be greater than 80%.⁶⁹ Because the fastidious nature of *S. pneumoniae* and *H. influenzae* leads to the death of these organisms, the sensitivity of sputum culture may be lower than that of sputum Gram stain examination for *S. pneumoniae* or *H. influenzae*. In contrast, *S. aureus* and gram-negative bacilli may dominate even if they are not the cause of the patient's illness, because these bacteria are hardier and may proliferate during sample transport and processing. True pneumonia due to *S. aureus* or gram-negative bacilli is doubtful if the Gram stain of a valid sputum speci-

Table 33-6 Clinical Indications for More Extensive Testing in Community-Acquired Pneumonia

Intensive care unit admission
Failure of outpatient antibiotic therapy
Radiographic cavities
Leukopenia
Active alcohol abuse
Chronic severe liver disease
Severe obstructive/structural lung disease
Asplenia
Recent travel (within past 2 weeks)
Positive *Legionella* UAT result
Positive pneumococcal UAT result
Pleural effusion

UAT, urinary antigen test.

From Mandell LA, Wunderink RG, Anzueto A: Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia. *Clin Infect Dis* 44(Suppl 2):S27–S72, 2007.

men does not corroborate the presence of these bacteria. In good quality Gram-stained sputum, the presence of a single or a preponderant morphotype of bacteria (≥90%) is considered diagnostic. In the absence of an informative Gram stain, the predictive value of sputum culture is very low.

The latest IDSA/ATS guidelines⁵⁸ recommend obtaining a sputum sample for Gram stain and culture in hospitalized patients with the clinical indications listed in Table 33-6 but are optional for patients without these conditions.

For patients with HAP or ventilator-associated pneumonia (VAP), the range of potential pathogens is so broad and antimicrobial susceptibility patterns so diverse that vigorous diagnostic measures are justified. In ventilated patients, the equivalent of sputum is the endotracheal aspirate for which the criteria for validity are the same as those for sputum. Although the Gram stain and qualitative cultures of endotracheal aspirates have excellent sensitivity, they have poor specificity.⁷⁰ Quantitative cultures of endotracheal aspirate samples may help distinguish colonization from infection. However, there has been difficulty in choosing a quantitative threshold for VAP; some have chosen to consider a range of quantitative cultures, from 10³ to 10⁶ CFU/mL, rather than a single cutoff.⁷¹

Some bacterial agents of pneumonia cannot be cultivated on conventional laboratory media. For example, *Legionella* requires buffered charcoal yeast extract agar for isolation, whereas recovery of *Chlamydomphila* species and *C. burnetii* requires culture in mammalian cell lines. When necessary, specimens can be sent to specialized or reference laboratories for appropriate procedures. Culture of certain agents of bacterial pneumonia poses major health risks to laboratory workers (e.g., *E. tularensis*, *Bacillus anthracis*, *C. burnetii*). Specimens suspected to harbor one of these agents should be dealt with carefully in a biologic safety hood, and isolation of the pathogens should be reserved for specialized laboratories.

Blood and Pleural Fluid Cultures

Although the overall yield of blood cultures is less than 20% in patients hospitalized for CAP, a positive culture of blood or pleural fluid establishes the etiologic diagnosis of pneumonia.^{72,73} Not surprisingly, the detected rate of bacteremia is lower in patients with mild CAP and higher in patients

with severe CAP, especially those warranting ICU care. Prior antibiotic treatment decreases the yield of blood cultures.⁷⁴ The latest IDSA/ATS guidelines⁵⁸ recommend obtaining blood samples for culture in hospitalized patients with the clinical indications listed in Table 33-6 but are optional for patients without these conditions.

In up to 40% of CAP cases, a pleural effusion may be present. Although the specificity of pleural exudate cultures is very high, the sensitivity is low because of the low incidence of invasion of the pleura. Diagnostic thoracentesis should be performed when a significant pleural effusion is present. Gram stain of pleural fluid may produce an indication of the infecting organisms within 1 hour, while culture identification may require 24 to 48 hours.

Antigen Detection

Commercial assays can be used to detect capsular polysaccharide antigens of *S. pneumoniae* or *L. pneumophila* serogroup 1 in urine, and can require less than 1 hour.^{69,74,75} The sensitivity of these tests is little affected by prior antibiotic treatment; indeed, results may remain positive several weeks after successful treatment. For *L. pneumophila* serogroup 1, the sensitivity is 60% to 80%, and the specificity is greater than 95%.⁷⁶ Urinary antigen testing is currently the most helpful rapid test for the diagnosis of *Legionella* infections. The major limitation of urinary antigen tests is that currently available tests are intended to detect *L. pneumophila* serogroup 1 antigen only, although this is the most common cause of *Legionella* infection.

The sensitivity of *S. pneumoniae* urinary antigen detection is 50% to 80% and the specificity is 90%.⁷⁷ The degree of positivity for the *S. pneumoniae* urinary antigen test correlates with the *Pneumonia Severity Index* (PSI).⁷⁸ The *S. pneumoniae* antigen test may also be applied on pleural fluid with a sensitivity and specificity of almost 100%. Urine specimens of children, frequent carriers of *S. pneumoniae* in the nasopharynx, may test positive in the absence of evidence of pneumonia, and the test should therefore be interpreted with caution in children.⁷⁹ The most recent IDSA/ATS guidelines⁵⁸ recommend *S. pneumoniae* and *L. pneumophila* urinary antigen detection in hospitalized patients with the clinical indications listed in Table 33-6, but are optional for patients without these conditions.

Antigens for the many common respiratory viruses, influenza virus, respiratory syncytial virus, adenovirus, and parainfluenza viruses can be detected by direct immunofluorescence or by enzyme-linked immunoassay. A rapid antigen detection test for influenza can provide an etiologic diagnosis within 15 to 30 minutes. Test performance varies according to the test used, viral strain, sample type, duration of illness, and patient age. Most show a sensitivity ranging from 50% to 70% and a specificity approaching 100% in adults (see Chapter 17).

Nucleic Acid Amplification Tests

Culture procedures for viruses and fastidious bacteria, *M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*, and *Bordetella pertussis*, which normally do not colonize in the human respiratory tract, are too insensitive and too slow to be helpful in guiding therapy. These pathogens should be detected by nucleic acid amplification tests; their sensitivity is generally superior to that of the traditional procedures

and some are considered as the “gold standard.”⁸⁰ Real-time multiplex polymerase chain reaction assays detect respiratory viruses in both immunocompetent and immunosuppressed hosts.⁸¹ (See Chapter 17 for detailed information on nucleic acid amplification tests for respiratory pathogens.)

Serologic Evaluation

Before the development of nucleic acid amplification tests, serologic techniques were used to establish a microbiologic diagnosis for pneumonia caused by pathogens that cannot be readily cultured. Examples include common pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*, and less common causes of pneumonia such as those caused by the agents of tularemia, brucellosis, and psittacosis, and certain viruses. Diagnosis usually requires that a convalescent specimen demonstrate a fourfold increase in immunoglobulin (Ig) G titer above that present in an acute specimen. These tests are not helpful in initial patient management but are of utility in defining the epidemiology of the pertinent infectious agents. Because IgM antibodies appear earlier than IgG antibodies, the detection of pathogen-specific IgM in serum has been used for the early serologic diagnosis of certain acute infections.

INVASIVE DIAGNOSTIC TECHNIQUES

Because of problems encountered with the use of expectorated sputum, it may be necessary to perform an invasive procedure to obtain suitable material for microscopy and cultures. This may be important in the management of patients with life-threatening CAP in whom diagnostic materials cannot otherwise be obtained, patients with progressive pneumonia despite seemingly appropriate antimicrobial therapy, immunocompromised patients, and patients with HAP, especially in the setting of endotracheal intubation.^{61,82} Although qualitative culture of materials obtained by endotracheal suction has excellent sensitivity, the specificity of such cultures is poor; thus, overreliance on these cultures can lead to antibiotic overtreatment.⁷¹

Bronchoscopic Samples

The reliability of bronchoscopic procedures to determine the microbial etiology of pneumonia depends on the technique used and the organism sought. When compared with sputum cultures, optimally processed bronchoscopic specimens demonstrate improved sensitivity and equal specificity for the culture of pathogenic fungi and mycobacteria. However, such materials have unacceptably poor specificity for routine bacterial cultures owing to oropharyngeal contamination. Semiquantitative or quantitative cultures of materials obtained bronchoscopically with a protected sheath brush or through *bronchoalveolar lavage* (BAL) and by direct lung aspiration have been successfully used for aerobic and anaerobic bacterial cultures⁸³⁻⁸⁵ (see Chapters 17 and 22). For protected sheath brush cultures, a threshold of 10^3 colony-forming units (CFU)/mL has been recommended to distinguish colonization from infection. However, 14% to 40% of duplicate samples yield disparate quantitative results.

BAL fluid can be quantitatively cultured for bacteria and qualitatively cultured for fungi, mycobacteria, and viruses. A concentrate can be stained for cytochemical and

fluorescence evaluation.⁸⁵ In one study, the threshold of 10^3 CFU/mL for diagnosing bacterial pneumonia correlated well with diagnoses based on protected sheath brush results and histologic examination of the lung.⁸⁶ BAL permits identification of contaminated specimens (i.e., those with greater than 1% squamous epithelial cells), the immediate diagnosis of infection (i.e., intracellular bacteria in more than 2% to 5% of examined polymorphonuclear leukocytes), and the exclusion of infection (i.e., the absence of bacterial pathogens in culture of BAL fluid, although the sensitivity is reduced by prior antibiotic administration).^{87,88}

In one study, the use of quantitative cultures obtained by protected sheath brush and BAL, compared with qualitative cultures of endotracheal aspirates and clinical evaluation, was associated with lower 14-day mortality rates, earlier reversal of organ dysfunction, and less antibiotic use.⁸⁹ However, other randomized trials on the use of quantitative cultures of protected sheath brush and BAL specimens, rather than quantitative cultures of endotracheal aspirates, in patients with VAP have not replicated these findings.^{90,91} The use of a sophisticated algorithm (i.e., Clinical Pulmonary Infection Score) increases the diagnostic accuracy of clinical judgment.⁹²

Transthoracic Lung Aspiration

Transthoracic lung aspiration obtains specimens suitable for microbiologic and cytologic examination directly from lung parenchyma (eFig. 33-5). It is more widely used for diagnosing malignant pulmonary lesions than infectious diseases, for which, in immunocompetent hosts, the diagnostic yield by transthoracic lung aspiration is approximately 50%. Serious complications of transthoracic lung aspiration include pneumothorax and hemoptysis, even when small-gauge needles are used.

DIFFERENTIAL DIAGNOSIS

Several diseases may present with fever and chest radiographic opacities and mimic CAP (eTable 33-1)⁵⁹; such diseases should be suspected when the radiographic resolution is unusually quick or when there is a lack of response to initial or subsequent antibiotic treatments. In patients with HAP, and particularly in those with VAP, the classic signs and symptoms of pneumonia (including new radiographic changes, fever, leukocytosis or leukopenia, and purulent pulmonary secretions) are neither sufficiently sensitive nor specific to confirm the presence of a pulmonary infection. Atelectasis, pulmonary hemorrhage, ARDS, and pulmonary embolism, among others, are conditions that may mimic pneumonia. In patients with suspected HAP or VAP, the microbiologic confirmation of pneumonia is important in order to avoid unnecessary treatments and increased antibiotic resistance.

THERAPEUTIC APPROACH TO PNEUMONIA

Once the diagnosis of pneumonia is made, the clinician must decide the appropriate treatment setting: outpatient, general hospital bed, or ICU. Applying prediction rules can

facilitate this decision. The second key initial decision is the selection of initial antimicrobial therapy.

ASSESSMENT OF SEVERITY

The PSI (eTable 33-2) is a scoring system derived from a retrospective analysis of a cohort of 14,199 patients with CAP and prospectively validated in a separate cohort of 38,039 patients with CAP.⁹³ The PSI is heavily weighted by age, which means it is less useful at extremes of age and is not valid in children. Outpatient treatment is recommended for patients with a PSI score of 70 or less (class I or II). Patients with a PSI score of 71 to 90 (class III) may benefit from brief hospitalization, while inpatient care is appropriate for patients with a score greater than 90 (class IV and V). Prospective studies in both community and teaching hospitals demonstrate that the hospital admission decisions based on PSI may be safely and effectively applied in clinical practice.⁹⁴⁻⁹⁶ The PSI is complex and often needs decision support tools for efficient use in a busy emergency department.

The British Thoracic Society validated the simpler CURB-65 score for admission triage decisions.^{25,97} Their algorithm assigns 1 point for each of the following findings at presentation: (1) confusion; (2) urea higher than 7 mmol/L (equal to BUN more than 20 mg/dL); (3) respiratory rate of 30/min or more; (4) low systolic (<90 mm Hg) or diastolic (≤ 60 mm Hg) blood pressure; and (5) age 65 years or older. Outpatient treatment is recommended for 0-1 points, brief inpatient or supervised outpatient care is recommended for 2 points, and hospitalization is recommended for 3 or greater, with consideration of ICU care for patients with scores of 4 or 5.

Risk stratification for both PSI and CURB-65 was based on associated mortality. They are therefore not sensitive to logistic and social issues such as reliability of oral intake, including antibiotics, and home support.

Patients initially admitted to a general floor with subsequent transfer to the ICU have higher mortality than patients with equivalent severity of illness admitted directly to the ICU.⁹⁸ Neither PSI nor CURB-65 are accurate for determining need for ICU care in patients without an obvious indication such as the need for mechanical ventilation or vasopressor support while still in the emergency department. Several scores have been developed for this critical decision.^{58,99-101} These scores share many common risk factors (Table 33-7) and appear to be equally effective,¹⁰² and management of severe CAP per these guidelines has been associated with decreased mortality.¹⁰³⁻¹⁰⁵ The optimal use of these scores is to identify at-risk patients who need additional evaluation or monitoring even if not initially admitted to the ICU.

SELECTION OF ANTIMICROBIAL AGENTS

Whenever possible, treatment for pneumonia should use the antibiotic with the narrowest spectrum possible, selected on the basis of the underlying pathogen. However, pathogens are rarely identified at the time of presentation, especially when pneumonia is managed in the outpatient setting. Because optimal outcomes are associated with a rapid initiation of antibiotics, initial treatment for patients

eTable 33-1 Noninfectious Causes of Fever and Radiographic Changes That May Mimic Community-Acquired Pneumonia

Pulmonary edema
Pulmonary infarction
Acute respiratory distress syndrome
Pulmonary hemorrhage
Lung cancer or metastatic cancer
Atelectasis
Radiation pneumonitis
Drug reactions involving the lung
Extrinsic allergic alveolitis
Pulmonary vasculitis
Pulmonary eosinophilia
Organizing pneumonia

eTable 33-2 Scoring System for Determining Risk of Complications in Patients with Community-Acquired Pneumonia*

Patient Characteristic	Points Assigned
DEMOGRAPHIC FACTORS	
Males	Age (yr)
Females	Age (yr) – 10
Nursing home residents	Age (yr) + 10
COMORBID ILLNESSES	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
PHYSICAL EXAMINATION FINDINGS	
Altered mental status	+20
Respiratory rate 30/min or greater	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35° C or ≥40° C	+15
Pulse 125/min or greater	+10
LABORATORY FINDINGS	
pH <7.35	+30
BUN >10.7 mmol/L	+20
Sodium <130 mEq/L	+20
Glucose >13.9 mmol/L	+10
Hematocrit <30%	+10
PO ₂ <60 mm Hg or O ₂ saturation <90%	+10
Pleural effusion	+10

*A risk score is obtained by summing the patient's age in years (age – 10 for females) and the points for each applicable patient characteristic. Patients with a score <50 are candidates for outpatient treatment, whereas those with scores >90 warrant hospitalization. Proper management of patients with scores of 70 to 90 requires careful application of clinical judgment. BUN, blood urea nitrogen; PO₂, oxygen pressure.

Adapted from Fine MJ, Auble TE, Yealy DM, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 336:243–250, 1997.

Table 33-7 Criteria to Consider Admission to an Intensive Care Unit for Patients with Community-Acquired Pneumonia without Shock or Respiratory Failure

Respiratory rate > 30 breaths/min ^{*†‡§}
PaO ₂ /FIO ₂ ratio < 250 or arterial saturation ≤90% on room air ^{*†‡§}
Multilobar or bilateral radiographic involvement or pleural effusion ^{*†‡§}
Confusion or disorientation ^{*†‡}
Uremia (BUN level > 20 mg/dL) ^{*†‡}
Leukopenia (WBC count < 4000 cells/dL) or extreme leukocytosis (>20,000 cells/dL) [§]
Thrombocytopenia (platelet count < 100,000 cells/dL) [*]
Hypothermia (core temperature < 36° C) [*]
Hypotension requiring aggressive fluid resuscitation [*]
Acidosis (pH < 7.30) ^{†‡§}
Hypoalbuminemia (albumin < 3.5 g/dL) [†]
Hyponatremia (sodium < 130 mEq/L) [§]
Tachycardia (>125/min) ^{†§}

BUN, blood urea nitrogen; FIO₂, fractional concentration of oxygen in inspired gas; PaO₂, arterial oxygen pressure; WBC, white blood cell.

^{*}IDSA/ATS⁵⁸

[†]SMART-COP⁹⁹

[‡]CURXO¹⁰⁰

[§]REA-ICU¹⁰¹

with pneumonia must be empirical. In selecting initial empirical antimicrobial therapy, physicians should consider the setting in which the pneumonia arose (e.g., community, hospital, nursing home), the severity of illness, age of the patient, presence of comorbidities and immunosuppression, recent antimicrobial therapy, and specific clinical manifestations of the illness. Geographic and facility-specific factors, such as the local prevalence of specific microorganisms (e.g., *C. burnetii*, *L. pneumophila*, endemic mycoses, and multidrug-resistant [MDR] pathogens), may also affect the initial treatment choice.

In hospitalized patients, specimens for cultures of blood, sputum, and pleural fluid (if present) should be obtained before treatment. A brief delay in starting therapy while performing diagnostic procedures is reasonable in patients who are not hypotensive. However, delays of more than 4 to 8 hours may increase the length of hospitalization and have been associated with increased mortality.^{106,107}

Community-Acquired Pneumonia

The standard therapy for inpatient empirical antibiotic coverage of CAP is one of two regimens: the combination of a second- or third-generation cephalosporin combined with a macrolide or one of the fluoroquinolones with efficacy against respiratory pathogens (levofloxacin, moxifloxacin, gatifloxacin).⁵⁸ Either therapy should be effective against penicillin-resistant *S. pneumoniae*.¹⁰⁸ The North American guidelines^{20,21,58} recommend that any empirical regimen for CAP should be active against “atypical” pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. Retrospective analyses of patients hospitalized with CAP indicate that regimens that cover “atypical” pathogens and those that follow recommendations made by the ATS and the IDSA are associated with improved clinical outcomes.^{18,20,96,109,110} In contrast, some Northern European guidelines suggest atypical coverage is not needed unless

patients have clinical features more common to atypical pathogens.⁹⁷ It is important to recognize that all CAP treatment guidelines are based on broad epidemiologic considerations that may vary by location. Variation from these regimens should be based on specific epidemiologic or clinical characteristics that strongly suggest one of the less common CAP pathogens such as mixed aerobic-anaerobic flora due to aspiration or presence of gram-negative Enterobacteriaceae or *P. aeruginosa* in patients with specified risk factors.^{24,111}

When tuberculosis is a possibility, fluoroquinolones should be used cautiously in CAP, because as little as 10 days of fluoroquinolone administration is sufficient to select for fluoroquinolone-resistant *M. tuberculosis*.¹¹²

The greatest factor to consider in the choice of regimens is a history of recent use of any of the agents.¹¹³ Widespread fluoroquinolone use, especially in subtherapeutic doses, and use of ciprofloxacin has been associated with fluoroquinolone resistance in up to 13% of *S. pneumoniae* isolates in Hong Kong.¹¹⁴ Fluoroquinolone resistance and subsequent treatment failures are reported in pneumococcal CAP,¹¹⁴⁻¹¹⁶ but this is less common with use of the fluoroquinolones that have improved activity against respiratory pathogens. In contrast, the frequency of macrolide resistance in *S. pneumoniae* is increasing, and a macrolide should not be used for monotherapy of *S. pneumoniae* infection unless in vitro testing confirms that the patient's strain is susceptible to macrolides.

Empirical antibiotic treatment of severe CAP (SCAP) remains controversial, predominantly due to a lack of treatment studies specifically focused on SCAP. The spectrum of etiologies is clearly greater in SCAP. Even so, penicillin-sensitive pneumococci are still the most likely etiology. Whether SCAP justifies more aggressive diagnostic testing or broader spectrum empirical treatment in all cases has not been established. Retrospective studies suggest combination therapy specifically for severe pneumococcal pneumonia and for SCAP in general are associated with lower mortality. In a large cohort of older patients with CAP needing hospitalization, antibiotic treatment including azithromycin was associated with a lower 90-day risk mortality compared with other antibiotics.^{116a}

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

Empirical therapy for VAP is necessarily broad because the range of potential pathogens is large and mortality is increased when the responsible pathogen is resistant to the initial empirical antibiotic regimen (Table 33-8). Recommended empirical regimens include expanded-spectrum β-lactam agents, usually in combination with aminoglycosides and with MRSA coverage.⁵³ The empirical β-lactam should be based on antibiotic sensitivity patterns for common gram-negative pathogens in the relevant institution or specific unit.

Empirical antibiotics for HAP are less well studied. HAP in nonintubated patients is a mixture of CAP pathogens and the pathogens found in VAP, although the frequency of the latter is likely lower, especially in cases that present early after admission. The greatest risk for MDR pathogens in nonintubated patients with HAP is recent antibiotic therapy, and monotherapy is probably adequate for most patients

Summaries of the recent IDSA/ATS guideline CAP antibiotic recommendations are presented in eTable 33-3 and eTable 33-4, respectively.⁵⁸

eTable 33-3 Guidelines for Empirical Oral Outpatient Treatment of Immunocompetent Adults with Community-Acquired Pneumonia

BRITISH THORACIC SOCIETY

Primary: amoxicillin

Alternatives: erythromycin or clarithromycin

AMERICAN THORACIC SOCIETY

No modifying factors^{*}: Advanced macrolide[†] or doxycycline[‡]

Comorbidities^{*}: β -lactam[§] macrolide[†] or doxycycline[‡] or fluoroquinolone[¶] alone

INFECTIOUS DISEASES SOCIETY OF AMERICA

No modifying factors^{*}: advanced macrolide[†] or doxycycline

Comorbidities^{*}: fluoroquinolone[¶] or advanced macrolide[†]

Antibiotics within 3 months: fluoroquinolone[¶] alone or advanced macrolide[†] β -lactam[§]

Suspected aspiration: clindamycin or amoxicillin-clavulanate

Influenza with bacterial superinfection: β -lactam[§] or fluoroquinolone[¶]

Nursing home patient: fluoroquinolone[¶] alone, or amoxicillin-clavulanate advanced macrolide

DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE* THERAPEUTIC WORKING GROUP

Primary: macrolide, doxycycline, cefuroxime, amoxicillin, amoxicillin-clavulanate

Alternative: fluoroquinolone[¶]

CANADIAN INFECTIOUS DISEASES SOCIETY AND CANADIAN THORACIC SOCIETY

No modifying factors: macrolide or doxycycline[‡]

COPD: advanced macrolide[†] or doxycycline[‡]

COPD plus recent antibiotics or steroids: fluoroquinolone[¶] alone, amoxicillin-clavulanate macrolide[†],[‡] or second-generation cephalosporin^{**} macrolide[†]

Suspected aspiration: amoxicillin-clavulanate macrolide, or fluoroquinolone[¶] clindamycin, or metronidazole

Nursing home patient: fluoroquinolone[¶] alone or macrolide[†] plus amoxicillin-clavulanate or second-generation cephalosporin

^{*}American Thoracic Society comorbidities (modifying factors) include cardiopulmonary disease and age older than 65 years, receipt of a β -lactam antimicrobial within the prior 3 months, alcoholism, prior immunosuppressive therapy, multiple medical comorbidities, exposure to a child in a daycare center, residence in a nursing home, underlying cardiopulmonary disease, multiple comorbidities or recent antimicrobial therapy. Infectious Diseases Society of America comorbidities include only COPD, diabetes, renal or congestive heart failure, and malignancy.

[†]Advanced macrolides are azithromycin and clarithromycin. Telithromycin has similar antimicrobial activity, but is associated with a higher risk of toxicity and its indications are limited.

[‡]Second-choice agent.

[§]High-dose amoxicillin (3 to 4 g/day), high-dose amoxicillin-clavulanate (2 g amoxicillin plus 125 mg clavulanic acid every 12 hr), cefpodoxime, cefprozil, or cefuroxime.

[¶]Because of increasing macrolide resistance, erythromycin cannot be relied upon to ensure coverage of β -lactamase-producing *Haemophilus influenzae*. A combination of a β -lactam/ β -lactamase inhibitor is preferred.

[¶]Antipneumococcal fluoroquinolones include levofloxacin, and moxifloxacin.

[#]Levofloxacin or moxifloxacin.

^{**}Available oral second-generation cephalosporins include cefaclor, cefuroxime axetil, cefprozil, cefonocid, and loracarbef.

COPD, chronic obstructive pulmonary disease.

eTable 33-4 Guidelines for Empirical Parenteral Inpatient Treatment of Immunocompetent Adults with Community-Acquired Pneumonia**MILD TO MODERATE DISEASE****British Thoracic Society**

Primary: ampicillin or penicillin plus a macrolide

Alternative: fluoroquinolone*

American Thoracic SocietyNo modifying factors[‡]: azithromycin alone, doxycycline, β -lactam, or fluoroquinolone* aloneWith modifying factors[‡]: cefotaxime or ceftriaxone or ampicillin-sulbactam or high-dose ampicillin; macrolide or doxycycline; or fluoroquinolone* alone**Infectious Diseases Society of America**Primary[§]: cefotaxime, ceftriaxone, ertapenem, or ampicillin/sulbactam plus advanced macrolide[†]; or fluoroquinolone* aloneSuspected aspiration: fluoroquinolone* \pm antianaerobic agent^{||}**Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group**

Primary: cefuroxime, cefotaxime, ceftriaxone, or ampicillin-sulbactam; macrolide

Alternative: fluoroquinolone*

Canadian Infectious Diseases Society and Canadian Thoracic SocietyFluoroquinolone* or cephalosporin,[¶] macrolide****SEVERE DISEASE****British Thoracic Society**

Primary: cefuroxime, cefotaxime, or ceftriaxone; macrolide, rifampin

Alternative: fluoroquinolone* \pm penicillin IV**American Thoracic Society**

Standard: cefotaxime or ceftriaxone; azithromycin or fluoroquinolone*

At risk for *Pseudomonas aeruginosa*^{††}: antipseudomonal β -lactam^{††} ciprofloxacin or antipseudomonal β -lactam aminoglycoside plus azithromycin or fluoroquinolone***Infectious Diseases Society of America**Primary: cefotaxime, ceftriaxone, ertapenem, or ampicillin/sulbactam; advanced macrolide[†] or fluoroquinolone* β -Lactam allergy: fluoroquinolone* \pm clindamycin*Pseudomonas* risks^{††}: antipseudomonal β -lactam^{††} ciprofloxacin or antipseudomonal β -lactam^{††} aminoglycoside; fluoroquinolone* or a macrolide*Pseudomonas* risks^{††} and β -lactam allergy: aztreonam levofloxacin or aztreonam; moxifloxacin or gatifloxacin \pm an aminoglycoside**Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group**

Primary: ceftriaxone or cefotaxime, macrolide; or ceftriaxone or cefotaxime, fluoroquinolone*

Alternative (with caution): fluoroquinolone*

Canadian Infectious Diseases Society and Canadian Thoracic SocietyStandard: cefotaxime, ceftriaxone or β -lactam/ β -lactamase inhibitor; fluoroquinolone* or macrolide***Pseudomonas* risks^{††}: ciprofloxacin, antipseudomonal β -lactam^{††} or aminoglycoside or antipseudomonal β -lactam^{††} aminoglycoside macrolide**

*Antipneumococcal fluoroquinolones include levofloxacin, gatifloxacin, and moxifloxacin.

[†]Advanced macrolides are azithromycin and clarithromycin.[‡]Modifying factors include those considered to increase the risk of infection by a penicillin-resistant pneumococcus (age older than 65 years, exposure to a β -lactam antimicrobial within the prior 3 months, alcoholism, prior immunosuppressive therapy, multiple medical comorbidities, exposure to a child in a daycare center or to infection by an enteric gram-negative bacillus (residence in a nursing home, underlying cardiopulmonary disease, multiple comorbidities, or recent antimicrobial therapy).[§]Preferred regimen may be determined by whether the patient has received antibiotics within the prior 3 months.^{||}Antianaerobic agents include clindamycin, metronidazole, and β -lactam/ β -lactamase inhibitor combinations.[¶]Acceptable cephalosporins include second-generation agents (e.g., cefuroxime, cefamandole), third-generation agents (cefotaxime or ceftriaxone), or fourth-generation agents (cefepime or ceftazidime, neither of which is available in the United States).

**Second-choice agent.

^{††}American Thoracic Society risk factors for *Pseudomonas aeruginosa* are structural lung disease (i.e., bronchiectasis, cystic fibrosis), corticosteroid use (>10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, or malnutrition. The Infectious Diseases Society of American risk factors for *P. aeruginosa* include only structural lung disease or recent completion of a course of antibiotics or steroids. The Canadian risk factors include only structural lung disease, recent antibiotic therapy, or recent hospitalization in an intensive care unit.^{††}Antipseudomonal β -lactams include ceftazidime, cefepime, imipenem, meropenem, mezlocillin, piperacillin, and piperacillin-tazobactam.

Table 33-8 Guidelines for Empirical Antibiotic Treatment of Nosocomial Pneumonia*

Setting	Core Pathogens	Antimicrobial Choices
2 TO 5 DAYS IN HOSPITAL Mild to moderate pneumonia [†] Severe pneumonia “low-risk” [†]	Enterobacteriaceae <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> Methicillin-sensitive <i>Staphylococcus aureus</i>	β-Lactam/β-lactamase inhibitor [‡] or ceftriaxone or fluoroquinolone [§] All ± an aminoglycoside
≥5 DAYS IN HOSPITAL Mild to moderate pneumonia	As above	As above
≥5 DAYS IN HOSPITAL Severe HAP “low risk”	<i>Pseudomonas aeruginosa</i> <i>Enterobacter</i> spp. <i>Acinetobacter</i> spp.	Carbapenem or β-lactam/β-lactamase inhibitor [‡] or cefepime All plus amikacin or fluoroquinolone [§]
≥2 DAYS IN HOSPITAL Severe HAP “high risk”	As above	As above
SPECIAL CIRCUMSTANCES ^{19,58}		
Recent abdominal surgery or witnessed aspiration	Anaerobes	As per Table 33-9
Other sites of infection with MRSA or prior use of antistaphylococcal antibiotics	MRSA	As per Table 33-9
Prolonged ICU stay or prior use of broad-spectrum antibiotics or structural lung disease (cystic fibrosis, bronchiectasis)	<i>P. aeruginosa</i>	As per Table 33-9
Endemicity within facility and either impaired cell-mediated immunity or failure to respond to antibiotics	<i>Legionella</i>	As per Table 33-9

*High-risk criteria include age older than 65 years, pancreatitis, chronic obstructive pulmonary disease, central nervous system dysfunction (stroke, drug overdose, coma, status epilepticus), congestive heart failure, malnutrition, diabetes mellitus, endotracheal intubation, renal failure, complicated thoracoabdominal surgery, and alcoholism. All other patients are considered to be at low risk.

This protocol does not address the treatment of neutropenic or HIV-infected persons.

Severe pneumonia requiring care in an ICU is characterized by rapid radiographic progression, multilobar disease, or cavitation. All other cases of nosocomial pneumonia are considered *mild to moderate*.

[†]Antimicrobial treatment should also be sufficient to cover core pathogens.

[‡]Ticarcillin-clavulanate and piperacillin-tazobactam are the preferred β-lactam/β-lactamase inhibitors for the treatment of nosocomial pneumonia. Ampicillin-sulbactam lacks adequate activity against many nosocomial enteric gram-negative bacilli.

[§]Levofloxacin (IV or PO), gatifloxacin (IV or PO), moxifloxacin (IV or PO), or gemifloxacin (PO only) are preferred for *Streptococcus pneumoniae*. When used for severe HAP, levofloxacin should be dosed at 750 mg IV daily. Ciprofloxacin has the best in vitro activity against *Pseudomonas aeruginosa*.

HAP, hospital-acquired pneumonia; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

Modified from American Thoracic Society: Hospital-acquired pneumonia in adults: Diagnosis assessment of severity, initial antimicrobial therapy, and preventative strategies. *Am J Respir Crit Care Med* 153:1711–1725, 1995.

without recent antibiotic exposure. Anaerobes appear to play a slightly greater role in HAP than VAP because of the risk of macroaspiration, but specific anaerobic coverage is not necessary if an appropriate β-lactam is used. Unless *Legionella* is known to be endemic in the institution, targeted therapy for this pathogen is seldom necessary in the empirical treatment of HAP. Efforts to identify the cause of infection are especially crucial in patients with HAP or VAP, to allow selection of optimal antimicrobial therapy and minimize the duration of empirical broad-spectrum coverage.

Health Care–Associated Pneumonia

The optimal approach to empirical coverage for HCAP remains controversial, due to variations in health care systems and definitions.^{55,117–119} Pneumonia in nursing home and chronic care facility residents is seen in a bimodal pattern. Ambulatory patients who are able to take care of most of their activities of daily living have disease that resembles CAP,²⁹ while in contrast, severely debilitated patients with tracheostomies, feeding tubes, frequent and recent acute care hospital admissions, and frequent

exposure to antibiotics are at high risk for MDR pathogens and should be treated with VAP regimens. Culture-negative HCAP patients have equivalent or better outcomes when treated with CAP antibiotics as with broader spectrum treatment,¹¹⁹ but are difficult to identify at admission. If started on broader therapy, deescalation to CAP therapy after culture results return negative appears safe.¹²⁰

Other Pneumonia Syndromes

On initial presentation, a variety of other infectious pulmonary syndromes may not be readily differentiated from acute bacterial pneumonia. Examples include influenza A, severe acute respiratory syndrome,^{49,50} hantavirus pulmonary syndrome, and other viral pneumonias. Milder cases of viral pneumonia may be distinguished by a low PCT level and antibiotics can be safely withheld or withdrawn in these patients.¹²¹

Concerns about potential bioterrorism or biowarfare require attention to the epidemiologic, clinical, and microbiologic significance of pneumonia due to *B. anthracis* (anthrax),⁵¹ *E. tularensis* (tularemia),⁵² and *Y. pestis* (plague). These infectious agents are individually discussed later in

this chapter. Further information may be obtained from organizations such as the Centers for Disease Control and Prevention (www.cdc.gov), IDSA (www.idsociety.org), and the World Health Organization (www.who.org) (see Chapter 40).

ADJUSTMENTS IN ANTIMICROBIAL THERAPY

If the etiologic agent of a patient's pneumonia has been identified, the initial antimicrobial regimen should be adjusted based on the results of in vitro susceptibility testing. The ideal drug for a known pathogen has the narrowest spectrum of activity and is the most efficacious, least toxic, and least costly. Pathogen-based modification of therapy is particularly important in HAP because prolonged use of broad-spectrum empirical agents promotes the emergence of MDR pathogens. Recommendations for specific drug choices for specific microorganisms are discussed under the sections devoted to individual microorganisms and are summarized in Table 33-9. If a pathogen is not identified, reevaluation of the initial therapeutic regimen must take into account the patient's response to therapy. Change from parenteral to oral antimicrobial therapy can safely be made in hospitalized CAP patients when clinically stable and able to absorb effective oral antimicrobials^{122,123}; this is often achieved within 3 days. In-hospital observation after switching from intravenous to oral antibiotics for CAP patients is not needed. Because HAP pathogens are frequently resistant to available oral antimicrobials, enteral absorption is less predictable, and the severity of illness is greater, initial oral antimicrobial therapy is much less frequently appropriate.

COMMON CAUSES OF PYOGENIC PNEUMONIA

Individual pneumonia pathogens may have unique epidemiology, diagnostic tests, and/or treatment. The sections that follow emphasize these unique aspects for selected pathogens (or groups).

STREPTOCOCCUS PNEUMONIAE (PNEUMOCOCCAL PNEUMONIA)

Epidemiology

S. pneumoniae is the most frequent cause of CAP among patients who require hospitalization.^{21,22} The overall incidence of pneumococcal pneumonia is approximately 200 cases per 100,000 persons per year, with 9 to 14 cases per 100,000 cases of bacteremia. This infection accounts for 40,000 deaths annually in the United States with most deaths in the very young and the elderly. Risk factors, particularly in adults, include cigarette smoking, HIV infection (even with preserved CD4 counts), heavy alcohol use, chronic liver disease, genetic defects in host immunity, and malnutrition.^{124,125} Pneumococcal infections present predominantly in the winter and early spring and are often associated with prior infection by influenza or respiratory syncytial virus.¹²⁶

Use of the conjugate pneumococcal vaccine has markedly decreased invasive pneumococcal infections in children, with a secondary reduction in adults.^{127,127a} This latter effect probably represents interruption of transmission by aerosolized droplets and direct physical contact, in that the conjugate vaccine is effective in blocking colonization.¹²⁸ However, widespread use of the conjugate vaccine in the United States has resulted in an increase in the number and proportion of cases of invasive pneumococcal disease due to isolates with polysaccharide capsule types that are not included in the seven-valent vaccine.¹²⁹ Consequently, a conjugate vaccine containing 13 capsular polysaccharide antigens was developed; this was approved by the U.S. Food and Drug Administration in 2012.

Clinical Manifestations

The classic presentation of pneumococcal pneumonia consists of a single rigor followed by sustained fever, cough, dyspnea, and production of rusty or mucoid sputum; gross hemoptysis is unusual. Severe pleuritic chest pain is common. The radiographic appearance of pneumococcal pneumonia is often either lobar consolidation (see Fig. 33-1 and eFig. 33-1) or patchy bronchopneumonia (eFig. 33-6). Although pneumococci can cause necrotizing pneumonia, cavitation rarely develops.¹²⁵ Small, parapneumonic effusions are frequently found and can progress to frank empyema. Neutropenia may develop in patients with overwhelming infection.

Microbiologic Diagnosis

Although Gram stain of purulent sputum that reveals numerous, characteristic "lancet-shaped" diplococci with blunted ends (commonly seen in pairs and short chains) in the absence of other predominant flora is strongly suggestive of pneumococcal pneumonia (Fig. 33-2), a good quality sputum specimen cannot always be obtained.¹³⁰ The organism is recovered from sputum culture in fewer than half of cases, and even a single dose of antibiotics can affect the yield of sputum cultures, which contributes to the discrepancy between sputum Gram stain and culture results. The frequency of positive blood cultures has fallen from 30% of hospitalized patients²⁰ to less than 10% in many contemporary series. This decrease may reflect a greater percentage of blood cultures drawn after antibiotics because of the emphasis on timely antibiotic doses in the emergency department, deemphasis on blood cultures in CAP in general, and/or a benefit of vaccination on invasive pneumococcal disease.

The rapid urinary antigen *S. pneumoniae* test offers an alternative approach to the diagnosis of pneumococcal CAP and is becoming more widely used in diagnosis and in narrowing antibiotic therapy.^{74,75,77,131} Despite satisfactory sensitivity and specificity, the urinary antigen test is complementary to culture methods, since it cannot provide information on antimicrobial susceptibility of the infecting organism.

Clinical Course

With an appropriate antibiotic, a clinical response is usually expected within 24 to 48 hours. The onset of suppurative complications, such as purulent pericarditis, meningitis, endocarditis, arthritis, and cellulitis after initiation of

Table 33-9 Agents for Specific Therapy of Selected Respiratory Pathogens

Type of Infection	Preferred Agent(s)	Alternative Agent(s)
COMMUNITY-ACQUIRED PNEUMONIA		
<i>Streptococcus pneumoniae</i>		
PCN-susceptible	Penicillin G, amoxicillin, clindamycin, doxycycline	Cephalosporin, macrolide,* (MIC < 2 g/mL) fluoroquinolone [†]
PCN-resistant	Agents identified using in vitro susceptibility tests, including cefotaxime, ceftriaxone, vancomycin, and fluoroquinolone [†]	Macrolide, if susceptible
<i>Mycoplasma</i>	Doxycycline, macrolide	Fluoroquinolone [†]
<i>Chlamydia pneumoniae</i>	Doxycycline, macrolide	Fluoroquinolone [†]
<i>Legionella</i>	Azithromycin, fluoroquinolone (including ciprofloxacin), [‡] erythromycin (± rifampin)	Doxycycline ± rifampin
<i>Haemophilus influenzae</i>	Second- or third-generation cephalosporin, clarithromycin, doxycycline, β-lactam/β-lactamase inhibitor, trimethoprim-sulfamethoxazole, azithromycin	Fluoroquinolone [†]
<i>Moraxella catarrhalis</i>	Second- or third-generation cephalosporin, trimethoprim-sulfamethoxazole, macrolide	Fluoroquinolone [†]
<i>Neisseria meningitidis</i>	Penicillin	Ceftriaxone, cefotaxime, cefuroxime, chloramphenicol, fluoroquinolone [†]
Streptococci (other than <i>S. pneumoniae</i>)	Penicillin, first-generation cephalosporin	Clindamycin (susceptibility should be confirmed), vancomycin
Anaerobes	Clindamycin, β-lactam/β-lactamase inhibitor, β-lactam plus metronidazole	Carbapenem
<i>Staphylococcus aureus</i>		
Methicillin-susceptible [‡]	Oxacillin, nafcillin, cefazolin; all ± rifampin or gentamicin [‡]	Cefuroxime, cefotaxime, ceftriaxone, fluoroquinolones, [†] clindamycin, vancomycin
Methicillin-resistant [‡]	Vancomycin [‡] ± rifampin or gentamicin	Linezolid, quinupristin-dalfopristin; trimethoprim-sulfamethoxazole, fluoroquinolones, [†] and tetracyclines may also show activity (in vitro testing required)
<i>Klebsiella pneumoniae</i> and other Enterobacteriaceae (excluding <i>Enterobacter</i> spp.)	Third-generation cephalosporin or cefepime (all ± aminoglycoside) carbapenem	Aztreonam, β-lactam/β-lactamase inhibitor, [§] fluoroquinolone [†]
HOSPITAL-ACQUIRED INFECTIONS		
<i>Enterobacter</i> spp.	Carbapenem, β-lactam/β-lactamase inhibitor, cefepime, fluoroquinolone; all + aminoglycoside in seriously ill patients	Third-generation cephalosporin + aminoglycoside
<i>Pseudomonas aeruginosa</i>	Antipseudomonal β-lactam [§] + aminoglycoside, carbapenem + aminoglycoside	Ciprofloxacin + aminoglycoside, ciprofloxacin + antipseudomonal β-lactam
<i>Acinetobacter</i>	Aminoglycoside + piperacillin or a carbapenem	Doxycycline, ampicillin-sulbactam, colistin
LESS COMMON PATHOGENS		
<i>Nocardia</i>	Trimethoprim-sulfamethoxazole	Imipenem ± amikacin, doxycycline or minocycline, sulfonamide ± minocycline or amikacin
<i>Coxiella burnetii</i> (Q fever)	Doxycycline	Fluoroquinolone
<i>Chlamydia psittaci</i> (psittacosis)	Doxycycline	Erythromycin, chloramphenicol
<i>Eikenella corrodens</i>	Penicillin	Tetracyclines, β-lactam/β-lactamase inhibitor, second- and third-generation cephalosporins, fluoroquinolones

*Azithromycin (IV or PO) is the preferred macrolide; clarithromycin (PO) or erythromycin (IV or PO) may also be used.

[†]Levofloxacin (IV or PO), gatifloxacin (IV or PO), moxifloxacin (IV or PO), or gemifloxacin (PO only) are preferred for *Streptococcus pneumoniae*. Ciprofloxacin has the best in vitro activity against *Pseudomonas aeruginosa*.

[‡]Rifampin and gentamicin should be reserved for cases of bacteremic *Staphylococcus aureus* pneumonia, empyema formation, or lung abscesses. Activity of rifampin and gentamicin requires laboratory confirmation for methicillin-resistant *S. aureus*.

[§]Ticarcillin-clavulanate and piperacillin-tazobactam are the preferred β-lactam/β-lactamase inhibitors for the treatment of nosocomial pneumonia due to Enterobacteriaceae. Ampicillin-sulbactam lacks adequate activity against many nosocomial enteric gram-negative bacilli.

^{||}Antipseudomonal β-lactams ceftazidime, cefepime, imipenem, meropenem, mezlocillin, piperacillin, or piperacillin-tazobactam.

MIC, minimum inhibitory concentration.

Modified from Bartlett JG, Dowell SF, Mandell LA, et al: Practice guidelines for the management of community-acquired pneumonia in adults: Infectious Diseases Society of America. *Clin Infect Dis* 31:347–382, 2000.

therapy is uncommon in the modern era. The exception is empyema, which appears to be increased due to serotype replacement in the vaccinated populations by serotypes more often associated with empyema.¹³² Pneumococcal pneumonia remains a cause of septic shock and ARDS.¹³³

Treatment

Antimicrobial resistance complicates treatment for *S. pneumoniae* in much of the world, including in the United States.¹³⁴ For nonmeningeal isolates of *S. pneumoniae*, the redefinition of full susceptibility as a *minimum inhibitory*

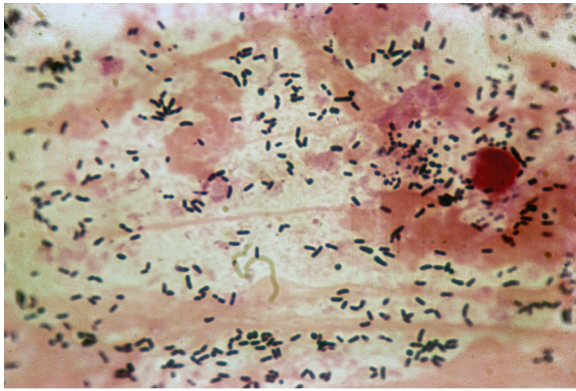


Figure 33-2 Gram stain of sputum from a patient with pneumococcal pneumonia. The predominant organisms are gram-positive lancet-shaped diplococci.

concentration (MIC) of penicillin less than or equal to 2 µg/mL and high-level resistance as MIC greater than or equal to 8 µg/mL markedly changed the incidence of penicillin resistance.¹³⁵ This redefinition was driven by discordance between the previous lower MIC breakpoints and clinical success rates. The rate of increase in the frequency of penicillin resistance may have stabilized, possibly as a consequence of the pneumococcal conjugate vaccine and a shift in the outpatient antibiotic prescription patterns away from β-lactams.¹³⁶

Penicillin resistance in *S. pneumoniae* is due to alterations in penicillin-binding proteins rather than to β-lactamase production. Unlike other β-lactams, cefotaxime, ceftriaxone, and cefepime retain activity against 75% to 95% of nonmeningeal isolates of *S. pneumoniae*.¹³⁷ *S. pneumoniae* resistance rates to other antimicrobials can be as high as 30% for trimethoprim-sulfamethoxazole (TMP-SMX), 16% for tetracyclines, 26% for macrolides, and 9% for clindamycin; these rates are higher among penicillin-resistant pneumococci.^{134,136} High-level macrolide resistance (MIC > 64 µg/mL) associated with the MLSB (macrolide, lincosamide, streptogramin B) phenotype is more common in Europe¹³⁸ and has been associated with in vitro resistance to clindamycin.¹³⁹ *S. pneumoniae* resistance to fluoroquinolones has also emerged with associated clinical treatment failures.^{113,136}

Recent exposure to an antibiotic increases the likelihood of the patient having a pneumococcal isolate resistant to that antibiotic (or class of antibiotics). Thus, it is important to avoid antibiotics that have been used in the prior 90 days when selecting a regimen for empirical treatment of a pneumococcal infection.¹¹³ Retrospective and prospective observational studies have suggested a benefit to treating severely ill patients with proven pneumococcal infections with both a β-lactam and a macrolide.^{76,140,141} Explanations that have been proposed to explain those results include nonbactericidal effects, such as inhibiting biofilm production, or an anti-inflammatory effect of the macrolide.

OTHER STREPTOCOCCI

Epidemiology

S. pyogenes (group A β-hemolytic streptococcus) can be found in the oropharynx of more than 20% of children and

a smaller percentage of adults. Carriage rates increase greatly during epidemics and in crowded conditions.^{128,142} In the United States, the incidence of pneumonia due to *S. pyogenes* was 0.15 to 0.35 per 100,000 persons per year, but may be as high as 3.6 per 100,000 in children.^{143,144} The organism is easily transferred between contacts, leading to epidemics of group A streptococcal pneumonia in military recruits, nursing homes, and other crowded settings.¹⁴² Pneumonia due to *S. pyogenes* most often manifests during the late winter and spring months, may follow an episode of influenza, measles, or varicella, and has been associated with increased age, alcohol abuse, diabetes mellitus, cancer, and HIV infection.^{143,144} *S. pyogenes* can cause necrotizing pneumonia¹⁴⁵ and is associated with pleural empyema.¹⁴⁶

Group B (i.e., *Streptococcus agalactiae*) streptococci are a major cause of neonatal sepsis and pneumonia. In adults, pneumonia accounts for approximately 15% of adult infections by group B streptococci.¹⁴⁷ Most adults with group B streptococcal pneumonia are debilitated and develop pneumonia as a consequence of aspiration.¹⁴⁷ Diabetes, cirrhosis, stroke, decubitus ulcer, and neurogenic bladder are also risk factors.¹⁴⁷

The *Streptococcus milleri* group C streptococci (which include *S. intermedius*, *S. anginosus*, and *S. constellatus*) have emerged as significant respiratory pathogens, predominantly causing empyema (eFig. 33-7 and Video 33-1) and lung abscesses as well as superinfection pneumonia in severe viral pneumonia.^{148,149} Infections with bacteria in this group share many of the features of anaerobic infections, including increased risk with periodontal disease and alcoholism. Other viridans and microaerophilic streptococci (α-hemolytic, nonpneumococcal) are rarely the sole pathogens in patients with pneumonia; they are more commonly found mixed with other facultative and anaerobic organisms in aspiration pneumonia.

Clinical Manifestations

CAP from these pathogens is clinically indistinguishable from pneumococcal pneumonia. Exudative pharyngitis may be evident and unilobar involvement is common with group A streptococcal pneumonia. Pleural effusions in group A streptococcal pneumonia are frequent, may be large, accumulate rapidly, and appear early in the course of the disease, particularly in children.¹⁴⁸ Pneumonia caused by other β-hemolytic streptococci is usually less abrupt and milder; pleural effusions are uncommon, and lung tissue necrosis is rare despite frequent bacteremia.¹⁴⁷ *S. milleri* infection is predominantly associated with empyema, with or without concomitant pneumonia.¹⁴⁸ Pneumothorax at the time of initial presentation appears to be more common with *S. milleri* than with other streptococcal empyemas.

Microbiologic Diagnosis

Because streptococci are common in the oropharynx, documentation of infection from these organisms requires isolation from a culture of blood, pleural fluid, or respiratory specimen obtained by means of an invasive procedure (Fig. 33-3). Pleural fluid cultures of children with *S. pyogenes* pneumonia are frequently positive. Polymerase chain reaction technology holds promise for aiding diagnosis, especially of group A streptococcal infections¹⁵⁰ and *S. milleri* empyema.¹⁴⁹

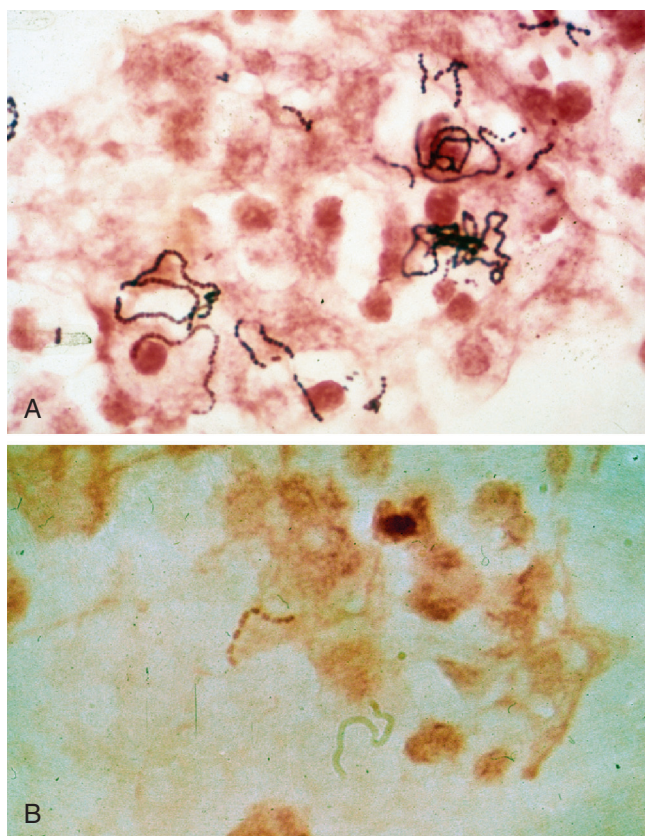


Figure 33-3 Streptococcus. **A**, Group A streptococcus (*Streptococcus pyogenes*, β -hemolytic streptococcus). **B**, Group B streptococcus (*Streptococcus agalactiae*) are indistinguishable from *Streptococcus pneumoniae* on Gram stain. Both form long chains containing multiple bacteria.

Clinical Course

Empyema and/or pericarditis are seen in 5% to 30% of patients with group A streptococcal pneumonia¹⁴³; other complications include pneumothorax, mediastinitis, and bronchopleural fistula formation. The only classic nonsuppurative complication that follows *S. pyogenes* pneumonia is glomerulonephritis.

Treatment

Most of these streptococci are susceptible to penicillin G, ampicillin, and many cephalosporins, although α -hemolytic streptococci may require high dosage, due to the phenomenon of tolerance (growth inhibition without killing, at low and intermediate drug concentrations). Because resistance to clindamycin and erythromycin is found in up to 15% to 20% of isolates, susceptibility testing is advisable before monotherapy with a macrolide or clindamycin.¹⁵¹ As for empyemas caused by other pathogens, drainage of empyema fluid is an important component of therapy.

HAEMOPHILUS INFLUENZAE

Epidemiology

Invasive infection, especially pneumonia, due to *H. influenzae* is estimated to account for approximately 1.2 cases per 100,000 adults per year in the United States, and is one of the more common causes of pneumonia in adults requiring

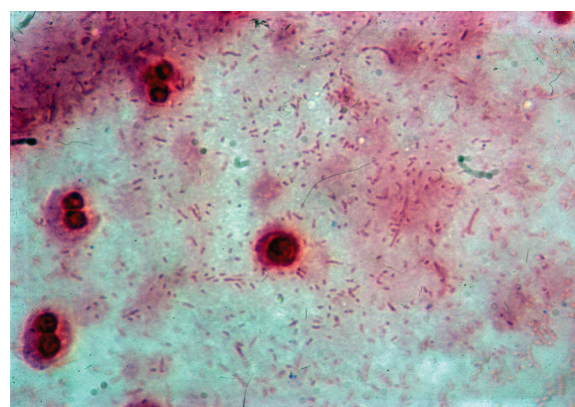


Figure 33-4 Haemophilus influenzae. Gram stain shows small pleomorphic coccobacilli diffusely across the field that, because of their size, can be missed on sputum examination.

hospitalization. Chronic lung disease, malignancy, HIV infection, and alcoholism are among the most common predisposing conditions to *Haemophilus* pneumonia. Active smoking appears to particularly increase the risk of *H. influenzae* pneumonia.

As with *S. pneumoniae*, vaccination against *H. influenzae* type b significantly changed the epidemiology of childhood pneumonia.¹⁵² Vaccinated children are still susceptible to unencapsulated (or nontypeable) strains but the incidence of *H. influenzae* pneumonia has fallen dramatically. Nonbacteremic infection by unencapsulated or non-type b strains is the most common form of *H. influenzae* pneumonia in adults.¹⁵²

Clinical Manifestations

Haemophilus pneumonia is clinically indistinguishable from other bacterial pneumonias (eFig. 33-8). On radiographs, *Haemophilus* pneumonia may be multilobar, patchy bronchopneumonia or have areas of frank consolidation. Spherical radiographic opacities (so-called round pneumonia) have been described, but cavitation is uncommon. Small parapneumonic effusions may occasionally progress to empyema. Bacteremia is more common in children than in adults.

Microbiologic Diagnosis

Diagnosing *H. influenzae* pneumonia by a Gram stain of sputum is difficult, because the small, pleomorphic coccobacilli are often overlooked. Culture of expectorated sputum reveals *H. influenzae* in only half of well-documented cases of pneumonia. Asymptomatic colonization with nontypeable strains in patients with COPD complicates analysis of Gram stain and sputum cultures (Fig. 33-4).

Clinical Course

The overall mortality rate of *H. influenzae* pneumonia is 5% to 7% but is higher in patients with bacteremia or extrapulmonary disease.¹⁵² Associated foci of infection, such as empyema, meningitis, arthritis, pericarditis, and epiglottitis are more common with encapsulated (type b) *H. influenzae*.

Treatment

H. influenzae isolates produce β -lactamase in 20% to 50% of cases and are therefore resistant to ampicillin. Increasing

macrolide resistance also compromises empirical therapy with these agents. Consequently, serious *H. influenzae* respiratory tract infections should be treated with a second- or third-generation cephalosporin, β -lactam/ β -lactamase inhibitor, or fluoroquinolone while awaiting results of susceptibility testing.

MYCOPLASMA PNEUMONIAE

Epidemiology

M. pneumoniae accounts for up to 37% of CAP in persons treated as outpatients and 10% of pneumonias requiring hospitalization.^{20,22} In the United States, there is an estimated 2 cases per year per 1000 individuals. *Mycoplasma* infections are seen throughout the year, but outbreaks are most common in the fall. Because *Mycoplasma* is readily transmitted from person to person via aerosolized respiratory droplets, outbreaks are common in families or closed populations.¹⁵³

Clinical Manifestations

The clinical picture of *M. pneumoniae* pneumonia is the paradigm of atypical CAP,^{18,21} as described previously. Pharyngitis, cervical adenopathy, and bullous myringitis may be encountered, although the latter is not more common with *Mycoplasma* pneumonia than with pneumococcal pneumonia/otitis. A wide variety of exanthems, including maculopapular eruptions, urticaria, erythema multiforme, and erythema nodosum, develop in 10% to 25% of patients. The chest radiograph usually shows an interstitial or a mixed pattern that may be more striking than expected based on chest physical findings (Fig. 33-5 and eFig. 33-9). Other chest radiographic patterns are occasionally encountered as well (eFig. 33-10).

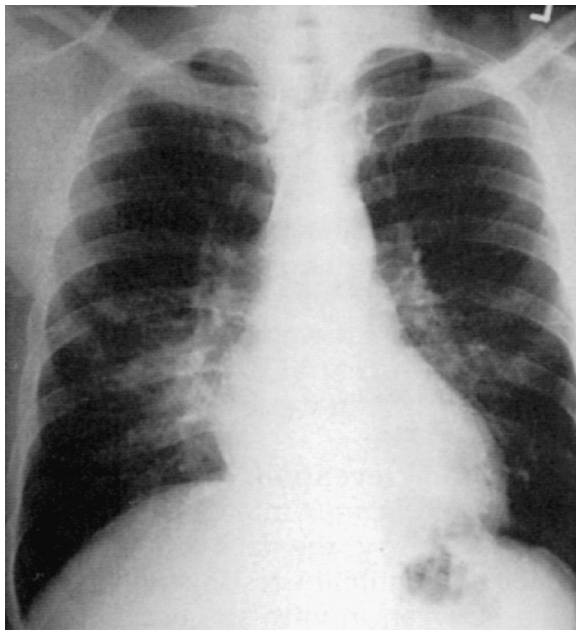


Figure 33-5 Radiographic findings in *Mycoplasma pneumoniae* pneumonia are nonspecific. Bilateral bronchopneumonia is seen in this patient.

Microbiologic Diagnosis

When obtained, sputum generally displays moderate numbers of polymorphonuclear leukocytes without a predominant organism. Recovery of *M. pneumoniae* from culture of clinical specimens requires special media and takes approximately 10 days. Although acute *Mycoplasma* pneumonia may stimulate cold agglutinin production in a titer of 32 or greater, this nonspecific result is also found in various other infectious and noninfectious conditions including pneumonia due to *Legionella*, adenovirus, and influenza.¹⁸ The shortcomings of staining, culture, and serology for detection of *Mycoplasma pneumoniae* make this pathogen especially suitable for diagnosis by nucleic acid testing. Several nucleic acid tests for *M. pneumoniae* are currently available, and their role in management of CAP is being defined (see Chapter 17).

Clinical Course

Mycoplasma pneumonia is usually a benign, often self-limited infection with an excellent prognosis for complete recovery. ARDS and death have been reported but are rare. A unique aspect of *M. pneumoniae* infection is the frequency of associated autoimmune disorders including fulminant autoimmune hemolytic anemia, Stevens-Johnson syndrome, aseptic meningitis, meningoencephalitis, pericarditis, and myocarditis.¹⁵⁴

Treatment

Antimicrobial therapy with a tetracycline, macrolide, or fluoroquinolone shortens the course of clinical symptoms and hastens resolution of radiographic abnormalities. To prevent clinical relapse, 2 weeks is the minimum recommended duration for treatment.¹⁸ Respiratory isolation can limit transmission, and azithromycin prophylaxis can prevent infection in close contacts of patients.¹⁵⁵

CHLAMYDOPHILA PNEUMONIAE

Epidemiology

C. pneumoniae (formerly *Chlamydia pneumoniae*) accounts for 5% to 15% of cases of CAP.²² Seroepidemiologic studies suggest that *C. pneumoniae* eventually causes infection in 40% to 50% of the general population.

Clinical Manifestations

Primary infection by *C. pneumoniae* is usually asymptomatic; an acute, mild respiratory tract infection is observed in only 10% of infected adolescents and young adults.¹⁵⁶ There may be bronchitis, sinusitis, laryngitis, tonsillitis, or exacerbations of asthma, with or without associated pneumonia. Sore throat with hoarseness is often severe and may precede pneumonia by up to a week and resolve before pneumonia onset, resulting in a biphasic illness. The erythrocyte sedimentation rate is elevated, but leukocytosis or elevated PCT may be absent.

Microbiologic Diagnosis

C. pneumoniae cannot be visualized by Gram stain, and tissue culture is required to grow the pathogen. Although direct fluorescent antibody detection of *C. pneumoniae* is

available, nucleic acid testing is emerging as a rapid, sensitive mode of detection that yields results in a time frame useful for clinical management (see Chapter 17).

Clinical Course and Treatment

Complete recovery following *C. pneumoniae* infection is the rule; fatalities are principally seen in patients with mixed infection and preexisting illness.^{156,157} When associated with an exacerbation of asthma, *C. pneumoniae* can require a prolonged time for recovery. Two-week treatment with a macrolide, tetracycline, doxycycline, or fluoroquinolone is recommended.^{18,157} Older adults can be reinfectd, often with severe symptoms.

STAPHYLOCOCCUS AUREUS

Epidemiology

S. aureus accounts for less than 10% of cases of CAP,²¹ but is the second or third most common etiology in patients with CAP requiring ICU admission. *S. aureus*, especially MRSA, accounts for up to 30% of nosocomial pneumonias.²⁹ Nasal colonization is the major source for pneumonia and other invasive *S. aureus* infections: 30% to 50% of healthy adults carry the organism transiently in the anterior nares. Health care workers may have even higher carriage rates. Although the organism is easily transferred from person to person by direct hand contact, 67% of patients in whom MRSA pneumonia develops have nasal colonization on admission, indicating that most cases of *S. aureus* HAP are not due to *S. aureus* transmission in the hospital.¹⁵⁸

A community-acquired strain of MRSA (CA-MRSA) has become an important CAP pathogen.¹⁵⁹⁻¹⁶² In addition to antibiotic resistance, the DNA cassette containing the *mecA* gene that confers methicillin resistance to this strain includes other virulence factors. The combination of antibiotic resistance and multiple virulence factors is associated with significantly higher mortality.¹⁶³ Typical hospital-acquired strains of MRSA also cause CAP but usually in patients with risk factors for HCAP.¹⁶⁴ The ability to differentiate clinically between hospital- and community-acquired cases is increasingly difficult because risk factors, such as prior antibiotic therapy, often overlap.

Factors that predispose patients to acquire staphylococcal pneumonia include underlying pulmonary disease (e.g., COPD, carcinoma, cystic fibrosis), chronic illness (e.g., diabetes mellitus, renal failure), or viral infection (e.g., influenza, measles).¹⁶⁵ *S. aureus*, including CA-MRSA, is second in frequency to *S. pneumoniae* as a cause of postinfluenza bacterial pneumonia. Postinfluenza CAP due to CA-MRSA is associated with a high frequency of complications and mortality. Pneumonia due to hematogenous spread of *S. aureus* is a unique type of pneumonia, usually a consequence of intravenous drug use or septic embolization from endocarditis or an infected vascular site.

Clinical Manifestations

CA-MRSA pneumonia can be seen in young patients without underlying illnesses. The clinical presentation in severe cases includes high fever, hypotension, and

hemoptysis with rapidly progressive deterioration and septic shock. Leukopenia, rather than leukocytosis, is observed in a substantial fraction of cases and is associated with poor outcomes.^{159,161,165} The radiographic features of CA-MRSA pneumonia include multilobar opacities and/or cavitory lesions (eFig. 33-11).

In cases acquired hematogenously such as in endocarditis or other endovascular infection, signs and symptoms related to the underlying endovascular infection predominate; if pulmonary infarction results from a septic embolism, pleuritic chest pain and hemoptysis are often noted. Otherwise, respiratory tract symptoms are mild or absent. The chest radiograph in patients with hematogenous staphylococcal pneumonia often reveals multiple, discrete, and often cavitory shadows with a predilection for the lower lobes (Fig. 33-6).¹⁶⁶

Microbiologic Diagnosis

Purulent sputum with multiple clusters of large gram-positive cocci, particularly if intracellular, is strongly suggestive of *S. aureus* pneumonia (Fig. 33-7). The organism is easily recovered from sputum cultures. Absence of MRSA on culture, even after several doses of antibiotics, is strong evidence that MRSA is not the causative pathogen. Fewer than 15% of pneumonias due to aspiration are associated with positive blood cultures. In contrast, hematogenous staphylococcal pneumonia usually yields multiple positive blood cultures. CA-MRSA pleural effusions are often exudative rather than grossly purulent but are still high yield on culture. An important clue to CA-MRSA is the presence of skin lesions,¹⁶⁷ which are often positive on Gram stain as well.

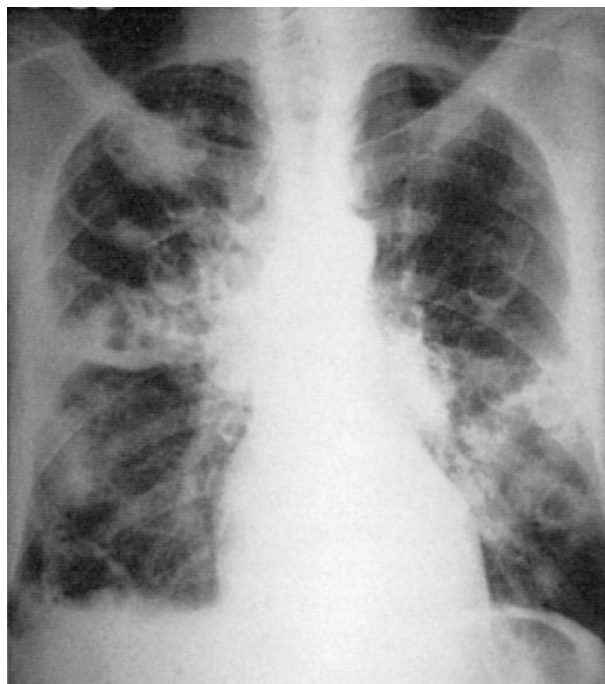


Figure 33-6 Chest radiograph shows hematogenous staphylococcal pneumonia associated with bacterial endocarditis. The pneumonia is characterized by many cavities.

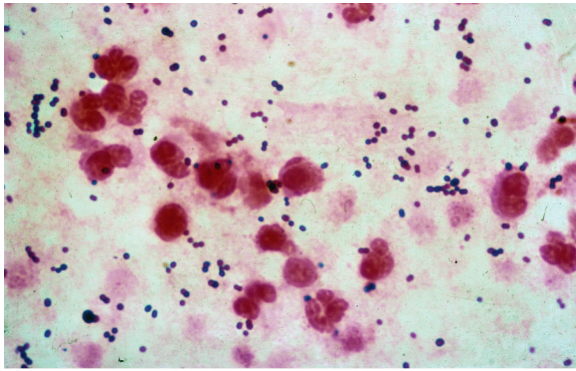


Figure 33-7 Staphylococcus. Gram stain of sputum from a patient with staphylococcal pneumonia shows abundant large, round gram-positive cocci in clusters.

Clinical Course

Even with appropriate antibiotics, the duration of fever and need for ICU care is often prolonged for *S. aureus* pneumonia, particularly CA-MRSA. Local complications of staphylococcal pneumonia include empyema and abscess formation. Infection can spread hematogenously to the central nervous system, bones, joints, skin, and kidneys. Cavities and necrotic tissue may prevent adequate local antibiotic penetration, whereas unrecognized or incompletely drained empyema may prolong fever. Most of these manifestations are due to strains secreting Panton-Valentine leukocidin or one of the other exotoxins produced by *S. aureus*. Pleuroscopy or decortication is required in a large percentage of cases with empyema.

The mortality of *S. aureus* CAP is generally higher than most etiologies, with the mortality in methicillin-sensitive strains about 30%. *S. aureus* CAP following influenza has a reported mortality of greater than 60%, even if not methicillin-resistant.¹⁶

Treatment

The treatment of choice for methicillin-susceptible *S. aureus* pneumonia is a penicillinase-resistant penicillin (e.g., oxacillin 8 to 12 g/day) or a first-generation cephalosporin. Therapy for 7 to 10 days is adequate in uncomplicated cases, but 4 to 6 weeks of treatment is recommended for patients with bacteremia or cavitation. In the penicillin-allergic patient, clindamycin or linezolid can be used.

Treatment of MRSA pneumonia is more challenging, and the incidence of CAP caused by both health care-associated MRSA and CA-MRSA strains is increasing. Although resistance to vancomycin is still rare, the MIC has been shifting upward and MICs greater than 1 µg/mL have been associated with clinical failure. In higher-risk patients, such as those with VAP or with underlying renal insufficiency, linezolid has been found to have better clinical response rates than vancomycin, although differences in patient survival have been variable.¹⁶⁸⁻¹⁷⁰ For CA-MRSA, vancomycin therapy alone has been associated with a significant failure rate.^{160,163} Addition of clindamycin or use of linezolid has been associated with improved outcomes in small case series. Unlike in MRSA skin infections, clindamycin, fluoroquinolones, and TMP-SMX are unreliable in severe CA-MRSA cases. Daptomycin is ineffective for

treatment of pneumonia, because it binds to and is inactivated by pulmonary surfactant.¹⁷¹

GRAM-NEGATIVE BACILLARY PNEUMONIA

The term *gram-negative bacillary pneumonia* refers to infections caused by members of two groups, the Enterobacteriaceae and Pseudomonadaceae and other aerobic gram-negative bacilli. Infections caused by *Haemophilus*, *Legionella*, and anaerobes are usually excluded from this categorization.

Enterobacteriaceae

Epidemiology. While they are more common as causes of HAP, gram-negative bacilli may cause up to 5% to 10% of CAP.^{21,24,111} CAP due to gram-negative bacilli is often severe and frequently requires ICU care. Patients in an ICU, especially those undergoing mechanical ventilation, have the highest risk for development of gram-negative bacillary pneumonia.

The Enterobacteriaceae normally colonize the digestive tract, and pneumonia usually results from aspiration of oropharyngeal flora. Although uncommon in healthy, non-hospitalized individuals, oropharyngeal colonization by gram-negative bacilli is greatly increased by hospitalization and antimicrobial use; the risk for aspiration is increased by comorbidities, such as cerebrovascular accidents, seizures, or anesthesia.²⁴ Occasionally, contaminated home respiratory therapy equipment directly introduces gram-negative rods into the respiratory tract. Finally, Enterobacteriaceae pneumonia may result from hematogenous seeding from infection at other anatomic sites.

Among the Enterobacteriaceae, *Escherichia coli* is the single most frequent cause of CAP.²⁴ The classic cause of community-acquired gram-negative bacillary pneumonia, *K. pneumoniae* (Friedlander pneumonia), causes fewer than 10% of CAPs, but more than 20% of nosocomial pneumonias. Alcohol abuse is the most common underlying condition for community-acquired *K. pneumoniae* pneumonia. Other underlying conditions that predispose to *Klebsiella* infections are diabetes mellitus and COPD.

Clinical Manifestations. In *Klebsiella* CAP, a syndrome of pleuritic chest pain, hemoptysis, and bloody sputum (occasionally with a “currant jelly” appearance) is classic but rarely seen. The clinical manifestations of Enterobacteriaceae pneumonias are not sufficiently unique to distinguish these infections from pneumonias due to other causes.²⁴

Most laboratory abnormalities are nonspecific, but neutropenia is associated with a poor prognosis. Chest radiographs often demonstrate lower lobe bronchopneumonia (eFig. 33-12), which is often bilateral. A classic radiographic appearance of *Klebsiella* pneumonia is upper lobe consolidation (especially on the right) (Fig. 33-8) with a bulging or bowed fissure. This manifestation is now uncommon. *Klebsiella* can also cause lung abscess (eFig. 33-13) in patients with HCAP.

Microbiologic Diagnosis. Enterobacteriaceae pneumonia should be suspected when sputum Gram stain reveals large numbers of uniform-appearing gram-negative rods

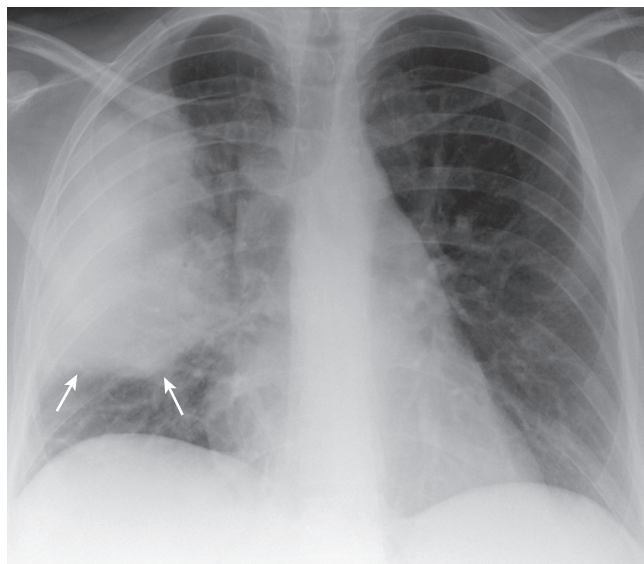


Figure 33-8 *Klebsiella pneumoniae* lobar pneumonia with “bulging” fissure. Frontal chest radiograph shows dense right upper lobe air-space opacity, which bows the right minor fissure inferiorly (arrows). The bulging fissure sign at chest radiography is traditionally associated with *Klebsiella pneumoniae* infection, but is actually nonspecific, and can be seen with other pulmonary infectious and noninfectious pulmonary processes as well. (Courtesy Michael Gotway, MD.)

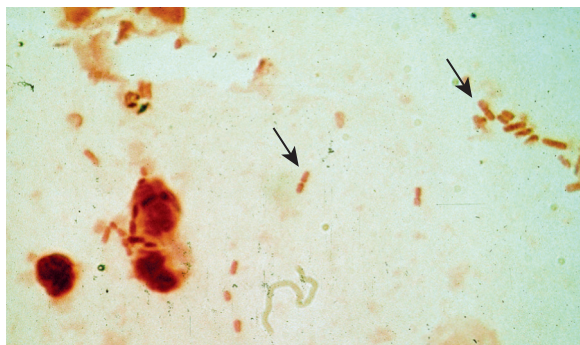


Figure 33-9 *Klebsiella pneumoniae*. Large gram-negative rods in the sputum of a patient with *Klebsiella pneumoniae* pneumonia (arrows).

(Fig. 33-9). Sputum culture alone is nonspecific for Enterobacteriaceae in either nonintubated or intubated patients because of oropharyngeal colonization and is one of the major reasons for interest in quantitative cultures as an approach to distinguishing colonization from infection.

Clinical Course. Enterobacteriaceae pneumonia fatality rates are 25% to 50%.²⁴ Bacteremia, neutropenia, and advanced age contribute to a poor prognosis. Destruction of pulmonary alveolar septae may lead to cavitation.

Treatment. Treatment of serious infections due to Enterobacteriaceae is complicated by widespread antimicrobial resistance. Extended-spectrum β -lactamase, carbapenemase, fluoroquinolone, and aminoglycoside resistance are all common in patients infected with Enterobacteriaceae.^{172,173} Due to regional and institutional variations in the frequency of resistance to specific drugs and classes of

drugs, initial therapy of possible Enterobacteriaceae pneumonia must be selected using knowledge of local antibiotic resistance patterns. In patients with serious infection, a two-drug regimen of an aminoglycoside with a broad-spectrum β -lactam or carbapenem is recommended for treatment until susceptibility results are known. Monotherapy may be reasonable for immunocompetent patients with mild to moderate disease who are infected with susceptible strains of *Proteus*, *Morganella*, *K. pneumoniae*, or *E. coli*. Recommendations for empirical therapy for HAP are listed in Table 33-8, although local resistance patterns must be taken into account.

***Pseudomonas aeruginosa* and Related Organisms**

Epidemiology. *P. aeruginosa* is an uncommon cause of CAP except in specific risk groups. Although one large study in Spain found that 7% of CAP was due to *P. aeruginosa*, most studies have found substantially lower rates.^{24,111} One major risk factor for *Pseudomonas* CAP is structural lung disease, such as cystic fibrosis, bronchiectasis, and severe COPD (forced expiratory volume in 1 second <30%). Another risk factor is HIV infection, especially with a marked deficiency of CD4⁺ T cells.¹⁷⁴⁻¹⁷⁶ *Pseudomonas* pneumonia in AIDS patients can be severe, with mortality rates as high as 50%, and be associated with cavitation, even when the patient has a profound CD4⁺ T-cell deficiency. The incidence of *Pseudomonas* pneumonia has decreased with widespread availability of combination antiretroviral therapy. *Pseudomonas* pneumonia is rare in normal hosts, but it can develop after exposure to aerosols of contaminated water such as in hot tubs.^{21,24,40,68,177,178}

P. aeruginosa is a leading cause of nosocomial pneumonia and a particularly frequent cause of VAP.¹⁷⁹ Prolonged endotracheal intubation and prior antibiotic therapy, especially with broad-spectrum antibiotics, are major risk factors for *Pseudomonas* VAP. Other nonfermenters, such as *S. maltophilia* and *B. cepacia*, cause pneumonia in patients after prolonged broad-spectrum antibiotic therapy, and are associated with a high mortality rate. *B. cepacia* is also found in outpatients with cystic fibrosis.

Clinical Manifestations. The clinical picture of pneumonia due to *P. aeruginosa* (eFig. 33-14) is indistinguishable from that of the Enterobacteriaceae. Bacteremia is slightly more common than for other gram-negative pathogens; physical examination may reveal ecthyma gangrenosum, and leukopenia is common. Its propensity to invade vascular tissue makes *Pseudomonas* the most common cause of cavitary pneumonia (eFigs. 33-15 and 33-16) in hospitalized or immunocompromised patients, and empyema can develop.

Microbiologic Diagnosis. Gram-stained sputum from patients with *Pseudomonas* pneumonia typically shows many slender, gram-negative bacilli (Fig. 33-10); neutrophils are commonly abundant in the sputum except in neutropenic patients. Since *Pseudomonas* and other gram-negative bacilli colonize the oropharynx in hospitalized or debilitated patients, Gram stain results in these patients can be misleading. In endotracheally intubated patients, the absence of *Pseudomonas* on culture is strong evidence against *Pseudomonas* as the cause of the patient's pneumonia, because the organism is typically easy to recover.

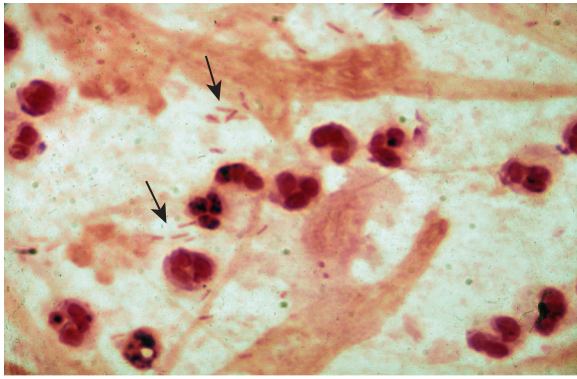


Figure 33-10 *Pseudomonas*. Gram stain of sputum showing slender gram-negative bacilli (arrows).

Clinical Course. Mortality from community-acquired *P. aeruginosa* pneumonia can exceed 25%,²⁴ and in persons with VAP due to *P. aeruginosa*, mortality rates are 40% to 70%. The prognosis in neutropenic patients with *P. aeruginosa* pneumonia is particularly poor.¹⁸⁰ *P. aeruginosa* VAP can recur in 25% to 50% of cases, approximately half due to a new strain.

Treatment. *P. aeruginosa* pneumonia should initially be treated with two antimicrobial agents expected to be active against isolates in the region, such as an aminoglycoside and an antipseudomonal β -lactam antibiotic; this is especially true for bacteremic or neutropenic patients.¹⁸⁰ Amikacin is the most reliably active aminoglycoside in most regions. The β -lactam antibiotics, in descending order of probable activity against *P. aeruginosa*, are the carbapenems (imipenem and meropenem), the acylureidopenicillins (e.g., piperacillin), cefepime, and ceftazidime.¹⁸¹ Although fluoroquinolones (particularly ciprofloxacin) initially possessed good intrinsic activity against *P. aeruginosa*, resistance is now common, making empirical fluoroquinolone monotherapy hazardous. Resistance can emerge in *Pseudomonas* during the course of fluoroquinolone monotherapy.

S. maltophilia is inherently resistant to most standard antibiotics.¹⁸² TMP-SMX is the most reliable agent, while fluoroquinolones or ticarcillin-clavulanate have activity against some strains.¹⁸⁰ Isolates of *S. maltophilia* may become resistant in the face of seemingly effective therapy. *B. cepacia* may be susceptible to acylureidopenicillins, ceftazidime, TMP-SMX, fluoroquinolones, minocycline, and chloramphenicol. Resistance rates are higher in isolates from patients with cystic fibrosis.

Acinetobacter baumannii

Epidemiology. *A. baumannii* may cause either CAP or HAP/VAP. *Acinetobacter* causes CAP in hot climates, both dry¹⁸³ and humid,^{45,184} and has become one of the most common causes of CAP in southeast Asia. In the United States, *Acinetobacter* CAP is most commonly seen in male alcoholics. The risk of *Acinetobacter* VAP varies widely by region and by health care facility. Nosocomial infections caused by *Acinetobacter* show seasonal variation, peaking in late summer, similar to patterns in CAP.

Clinical Manifestations. Patients with *Acinetobacter* CAP often present acutely ill and may have leukopenia, pleural

effusions, and empyema.¹⁸⁵ Nosocomial *Acinetobacter* pneumonia has a less dramatic presentation, similar to those of other hospital-acquired gram-negative pneumonias.⁴⁵

Microbiologic Diagnosis. Examination of expectorated sputum, which is usually purulent, may reveal a predominance of paired gram-negative coccobacilli that resemble *Neisseria*, *Haemophilus*, and *Moraxella* species. Bacteremia complicates community-acquired more often than nosocomial *Acinetobacter* pneumonia.

Clinical Course. The mortality rate of community-acquired *Acinetobacter* pneumonia approaches 50%.⁴⁵ Patients at greatest risk of death are those with leukopenia or empyema. The fatality rate for nosocomial *Acinetobacter* pneumonia is determined by the severity of underlying disease.

Treatment. Community isolates of *A. baumannii* can be susceptible to amikacin, tobramycin, ceftazidime, carbapenems, and doxycycline.¹⁸⁶ Nosocomial *Acinetobacter* species are resistant to most β -lactams and aminoglycosides and therefore are most reliably treated with carbapenems, but poor outcomes are common.¹⁸⁷ Some investigators have reported successful treatment of highly resistant isolates with ampicillin-sulbactam or colistin.^{188,189} Resistance to β -lactam antimicrobials, carbapenems, aminoglycosides, fluoroquinolones, and even polymyxin B and colistin¹⁸⁹ is increasingly common among nosocomial isolates.

LEGIONELLA

Epidemiology

L. pneumophila causes both epidemic and sporadic infections; both patterns may be seen either in the community or in hospitals. Outbreaks have been linked to contaminated potable water systems, ultrasonic mist devices, whirlpool baths, air-conditioning condensates, and water-evaporative systems.¹⁹⁰

Legionella is acquired through inhalation of contaminated aerosols or aspiration. Sporadic cases of *L. pneumophila* pneumonia (50% to 80% of which are due to serogroup 1) account for 2% to 6% of CAPs in immunocompetent hosts.²¹ *L. pneumophila* is one of the most common causes of severe CAP in certain communities. Risk factors include exposure to contaminated water, immunosuppression, cigarette use, diabetes, cancer, end-stage renal disease, and alcohol use. Infection with *L. pneumophila* is more common in specific geographic regions, such as the Mediterranean or the northeastern United States.

In addition to *L. pneumophila*, 40 other *Legionella* species have been identified. Many, such as *Legionella micdadei* and *Legionella longbeachae*, produce a pneumonic illness indistinguishable from that of *L. pneumophila*. Much less is known about the epidemiology of non-pneumophila *Legionella* infections, but they also appear to be from water or soil-related sources. Immunosuppression appears to be the major host risk for these species.

Clinical Manifestations

The incubation period for *Legionella* pneumonia is 2 to 10 days. Lethargy, headache, fever, recurring rigors, anorexia,

and myalgias are frequent early symptoms. After several days, cough becomes more pronounced; occasionally, watery or purulent sputum develops. Dyspnea is prominent in half of cases, and one third of patients complain of pleuritic chest pain. Extrapulmonary manifestations may overshadow respiratory complaints; gastrointestinal (watery diarrhea, nausea, vomiting, abdominal pain) and neurologic symptoms and signs (headache, confusion, obtundation, seizures, hallucinations) are particularly noteworthy. Patients may appear acutely ill. Temperatures reach 40.5° C in one third of patients, are typically sustained, and may be accompanied by relative bradycardia. Physical findings are usually limited to the chest, including pleural friction rubs, but generalized abdominal tenderness, hepatomegaly, splenomegaly, cutaneous rash, nuchal rigidity, and focal neurologic deficits have all been described.

Hyponatremia and hypophosphatemia are present in more than half of severe cases. Mild elevations of serum creatinine, creatine phosphokinase, and liver enzymes are also common, as are hematuria and proteinuria and occasionally frank rhabdomyolysis. There may be leukopenia and thrombocytopenia especially in severely ill patients. Cold agglutinins may be present, as in infection due to *M. pneumoniae*.

Chest radiographic findings typically lag behind the early clinical illness (Fig. 33-11). Small pleural effusions develop in 50% and may precede the parenchymal process. Multilobar opacities are commonly seen (eFig. 33-17), particularly on chest CT. Frank cavitation rarely is seen.⁶⁶

Microbiologic Diagnosis

Legionella are obligatory aerobic, fastidious, gram-negative bacilli that stain poorly with Gram stain (see Chapter 17,

Figure 17-4) and grow poorly on conventional media. *L. micdadei* and some other *Legionella* species may stain weakly acid-fast. Early in the infection, sputum Gram stain from patients with *Legionella* pneumonia contains few or no polymorphonuclear leukocytes. The sensitivity of cultures of respiratory specimens is as low as 10%, despite use of appropriate media. Culture diagnosis of *L. pneumophila* infection often requires invasive procedures because at least 25% of patients with *Legionella* infection do not produce sputum.⁷⁶ Rarely, *Legionella* has been recovered from blood, pleural fluid, and other extrapulmonary sites.

The *Legionella* urinary antigen test is currently the most commonly used method of diagnosis. It has a sensitivity of 60% to 80% and specificity greater than 95% for *L. pneumophila* serogroup 1, but the test is limited to this single species and serogroup.⁷⁶ The sensitivity of direct fluorescent antibody assay for sputum ranges from 33% to 68%, with specificity greater than 95%,⁷⁶ but its use is hindered by difficulty of obtaining sputum in some patients, the expertise required for interpretation, and the requirement for specific antibodies to the multiplicity of *Legionella* species and serogroups. Polymerase chain reaction–based assays for sputum have greater than 80% sensitivity and greater than 90% specificity, and their availability is likely to become more widespread.⁷⁶

Clinical Course

A clinical response to appropriate antibiotic therapy is usually observed within the first 48 hours. In contrast, radiographic findings may temporarily continue to progress despite observed clinical improvement and ultimately take months to resolve.⁶⁶ Acute renal failure and oliguria, often independent of shock and myoglobinuria, may develop in

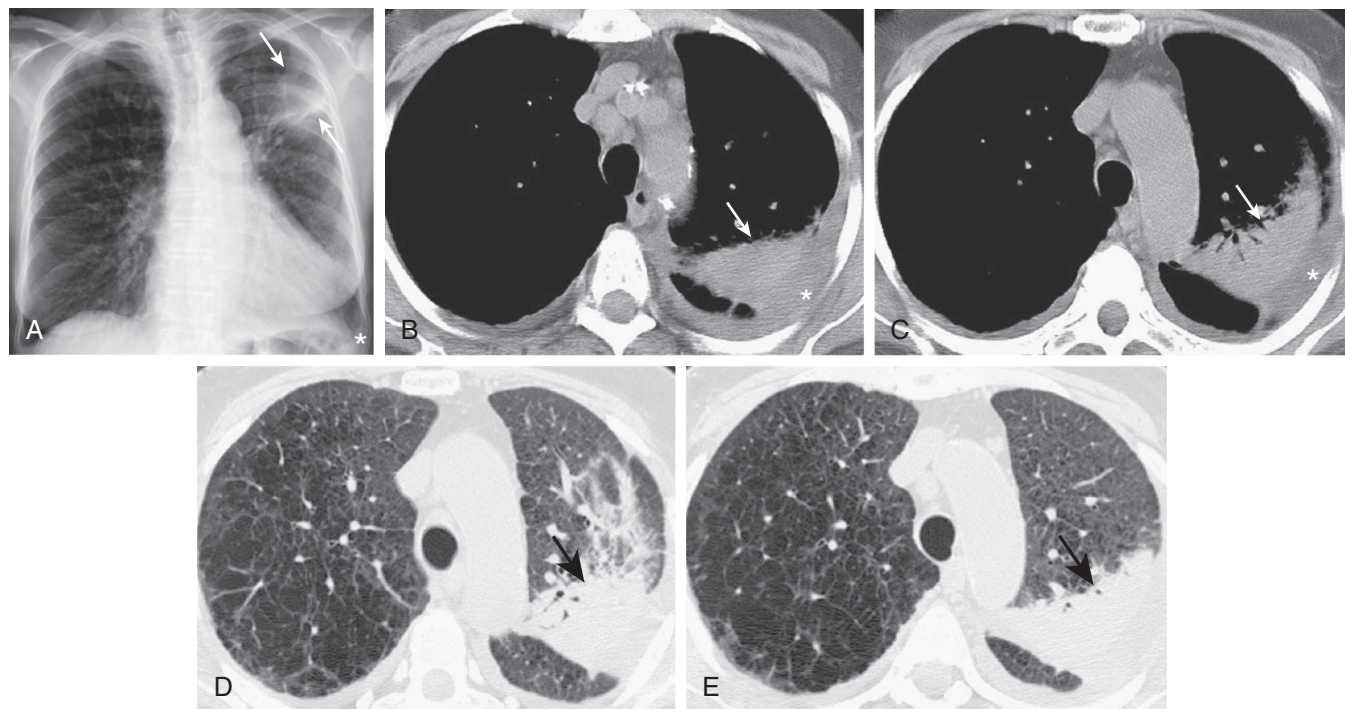


Figure 33-11 *Legionella pneumophila* pneumonia: unilateral disease. A, Frontal chest radiograph shows subpleural left upper lobe consolidation (arrows). B–E, Axial chest CT displayed in soft tissue (B and C) and lung (D and E) windows confirms left upper lobe consolidation (arrows). A small left pleural effusion (*) is present. (Courtesy Michael Gotway, MD.)

approximately 10% of patients and dialysis may be required. Many patients note lingering fatigue and weakness for months following *Legionella* pneumonia.

The mortality of community-acquired *Legionella* pneumonia is approximately 15%. Poor clinical outcomes are associated with immunodeficiencies, comorbidities, delayed initiation of appropriate therapy, and the need for ventilatory support or dialysis.

Treatment

Azithromycin and fluoroquinolones are superior to erythromycin or clarithromycin for treatment of *Legionella* infections. Although never used alone, the addition of rifampin is advised for patients who are severely ill or immunocompromised.¹⁸ Antibiotics should be continued for 10 to 21 days in immunocompetent patients to decrease the rate of relapse.¹⁸

ANAEROBIC BACTERIA

Epidemiology

Mixed aerobic and anaerobic infection is usually a complication of macroaspiration of oropharyngeal contents. Rare causes include rupture of the esophagus and extension of intra-abdominal abscesses. Underlying pulmonary conditions such as malignancy and pulmonary infarction are present in 20% of patients who have an anaerobic lung infection. Although acute complications of macroaspiration are largely due to a chemical injury pneumonitis (Mendelson syndrome) and/or infection by pathogenic aerobes in the oral flora, many of these episodes later result in the emergence of mixed aerobic and anaerobic pneumonia.

Clinical Manifestations

Anaerobic infections present as four different syndromes: chemical pneumonitis, aspiration pneumonia, anaerobic pleuropneumonia, or primary anaerobic empyema.

Chemical pneumonitis can precede anaerobic pneumonia, and is characterized by the acute onset of hypoxemia, fever, cough (often dry), dyspnea, and pleuritic pain. The foul sputum and hemoptysis characteristic of anaerobic lung abscess are absent at this stage. The risk of infection is dependent on the nature of the inoculum; many cases of aspiration pneumonitis are inflammatory alone and not infectious. Imaging may demonstrate bronchopneumonic opacities, but usually not lobar consolidation, in the aspiration-prone segments of the lung (e.g., posterior segment of the right upper lobe and superior segment of the right lower lobe; see eFig. 33-3). ARDS is a common complication of aspiration of low pH gastric fluid.

Aspiration pneumonia is indistinguishable from either CAP or HAP (eFig. 33-18), with the exception that it is seen in patients with risk factors for macroaspiration. Rapid development of pulmonary opacities over a short period of time may suggest the diagnosis of aspiration pneumonia (Fig. 33-12 and eFig. 33-19). High concentrations of amylase or pepsinogen in BAL fluid are very suggestive of this entity.¹⁹¹ Localization of an opacity in a dependent lung segment has less discriminating value.

Anaerobic pleuropneumonia is characterized by necrosis and suppuration of lung parenchyma. Early in the course,

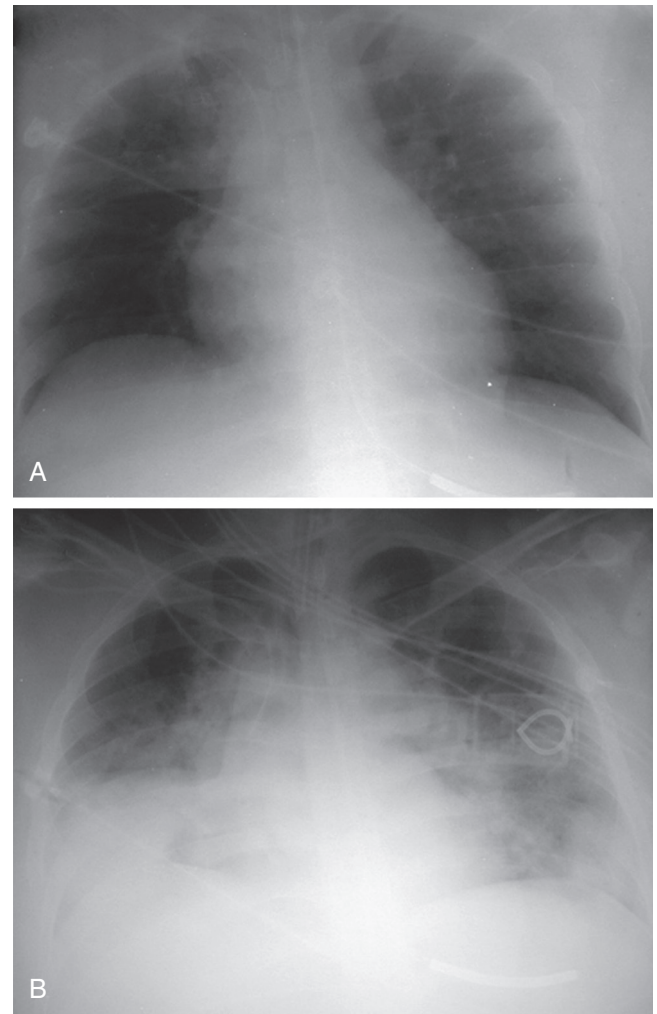


Figure 33-12 Aspiration pneumonitis: rapid interval development of pulmonary opacities. **A**, Frontal chest radiograph performed for central venous catheter placement shows a right subclavian central venous catheter without pneumothorax; the lungs are clear. **B**, Repeat frontal chest radiograph obtained following an episode of altered level of consciousness and vomiting only a few hours after **A** shows interval development of extensive mid and lower lung consolidation. Such rapid development of extensive pulmonary opacities in the context of mental status changes accompanied by vomiting is characteristic of aspiration. The differential diagnosis of rapid interval appearance of extensive pulmonary opacities also includes increased pressure edema, noncardiac edema injury, and hemorrhage. (Courtesy Michael Gotway, MD.)

imaging may demonstrate dense segmental opacification with multiple small lucent areas of lung necrosis (<2 cm in diameter), usually without air-fluid levels (eFig. 33-20). In the absence of appropriate treatment, these lesions may evolve into a primary lung abscess (eFig. 33-21) and empyema. Patients commonly present with fatigue, low-grade fever, weight loss, and productive cough for several weeks after an episode of loss of consciousness. Approximately half describe putrid sputum, and some may have hemoptysis. Patients appear chronically ill and toxic, with temperatures up to 39° C. In some patients, a single lung abscess greater than 2 cm in diameter is detected in a dependent lung segment on radiography (Fig. 33-13). The abscess may be multilocular; occasionally, multiple abscesses are located in different lung segments.

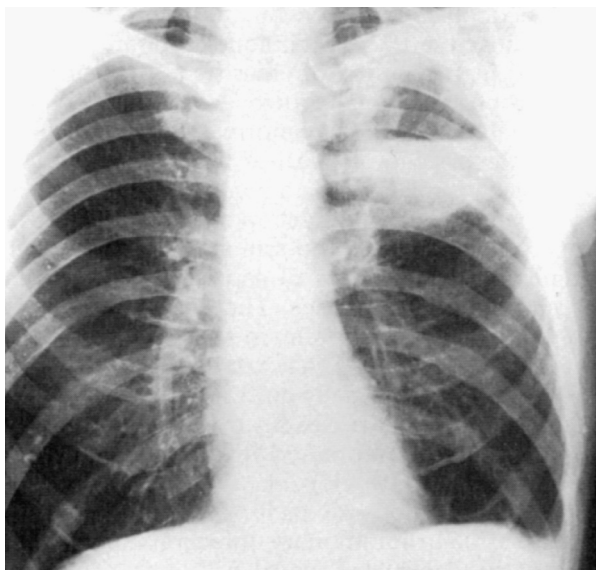


Figure 33-13 A single parenchymal cavity with an air-fluid level typifies an anaerobic lung abscess. Most often, these lesions are located in the dependent, aspiration-prone lung segments (superior segment of the right lower lobe and left lower lobe and posterior segments of the upper lobes). This patient also has a small left empyema.

Primary anaerobic empyemas are usually due to *S. milleri/intermedius* (see eFig. 33-7) rather than anaerobes.¹⁴⁹ However, anaerobes still play a significant role. In these cases, the pleural manifestations may dominate, with less evidence of pneumonia. Anaerobic empyema can also be seen in the absence of parenchymal lung infection when empyema develops in association with esophageal rupture or from subphrenic or other intra-abdominal abscesses. More information on pleural empyema is in Chapter 80.

Microbiologic Diagnosis

Gram stain of sputum or examination of a bronchoscopically obtained specimen from a patient with anaerobic pneumonia reveals numerous polymorphonuclear leukocytes with an abundance of intracellular and extracellular bacteria. Typically, a mixture of Gram stain reactions and morphologies are seen, including pale-staining gram-negative rods with tapered ends (suggestive of *Fusobacterium nucleatum*), small, pale-staining gram-negative coccobacilli, and chains of tiny gram-positive cocci.

Because the endogenous flora of the upper respiratory tract predominantly consists of anaerobic bacteria, cultures of expectorated sputum are not appropriate for diagnosis of anaerobic infections. With careful technique, recovery on average of 3.2 bacterial isolates, of which 80% are anaerobes, is possible in a case of mixed aerobic/anaerobic pneumonia or empyema. The most common anaerobes in pleuropulmonary infections include *E. nucleatum*, *Prevotella*, *Porphyromonas*, *Peptostreptococcus*, and microaerophilic *Streptococcus*. The major aerobic and facultative organisms recovered in conjunction with anaerobes are *Streptococcus* species. Although *S. aureus*, various enteric gram-negative bacilli, and *Pseudomonas* may also be isolated, their significance is often questionable. Molecular techniques can often identify anaerobes in culture negative cases.¹⁴⁹

Clinical Course

Uncomplicated aspiration pneumonia generally responds promptly to appropriate antibiotics. Fever resolves within a few days, and the chest radiograph normalizes within 3 weeks. Fever resolves more slowly in anaerobic pleuropulmonary infection. Closure of abscess cavities (see eFig. 33-21) and resorption of empyema collections may require months. Fatality rates are low in adequately treated patients, except those with necrotizing pneumonia, in which mortality approaches 20%.¹⁴⁹ Chronic lung abscess has been complicated by brain abscess, other metastatic abscess, secondary amyloidosis, life-threatening hemoptysis, bronchopleural fistula or *empyema necessitans* (rupture through the chest wall), but these complications are currently rare.

Treatment

Emergence of β -lactamase-mediated resistance mandates that penicillin G and ampicillin are no longer the drugs of choice for treatment of patients with serious anaerobic pleuropulmonary infection. There is resistance not only among *Bacteroides* species but also among *Prevotella* and some *E. nucleatum* strains. Empirical treatment for serious anaerobic pleuropulmonary infection requires the use of a β -lactam/ β -lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, or piperacillin-tazobactam) or clindamycin. Because of the frequent simultaneous presence of aerobes, metronidazole monotherapy is not adequate for suspected anaerobic pneumonia. Occasional pulmonary isolates are resistant to one or more of these agents. For example, *Eikenella corrodens* is resistant to clindamycin. Carbapenem monotherapy is also effective but generally provides unnecessarily broad coverage.

Ten days of total treatment is usually adequate for uncomplicated pneumonitis. Necrotizing pneumonia, abscess, and empyema require prolonged parenteral therapy to achieve clinical improvement, and extended courses of oral therapy, often requiring several months, may be required for cure.

Drainage of empyema fluid is required. Surgical resection of anaerobic lung abscess is almost never indicated. Bronchoscopy is useful for excluding an underlying malignancy in patients without other risk factors (i.e., edentulous patients).

NONRESPONDING PNEUMONIA/TREATMENT FAILURE

Two different clinical patterns of treatment failure in pneumonia have been described²¹²: progressive pneumonia with clinical deterioration including respiratory failure or septic shock; and nonresponding pneumonia, in which clinical improvement is not achieved (fever and clinical symptoms persist). In those treated as outpatients or inpatients, evaluation for response should be undertaken after 72 hours of antibiotic treatment, as this represents the median time required to achieve clinical improvement.²¹² In addition to clinical evaluation, reduction of procalcitonin (PCT) levels after 3 to 4 days of treatment correlates with clinical responses.²¹³ Levels of certain biomarkers, mainly PCT and

LESS COMMON CAUSES OF PNEUMONIA

A variety of pathogens are less common causes of pneumonia. These agents may be suspected in the presence of unique risk factors or presentations, or may be diagnosed by results of cultures.

ACTINOMYCOSIS

A variety of species within the two genera of the Actinomycetaceae family (*Actinomyces* and *Propionibacterium*), which are normally harmless commensals in the oropharynx, can cause subacute to chronic pulmonary infections that are virtually indistinguishable. Pulmonary actinomycosis follows aspiration of oropharyngeal material. Periodontitis and other dental disease increase the risk of cervicofacial invasion and of pneumonia. Most patients are 30 to 60 years old; men outnumber women by a ratio of 4:1.

Patients with actinomycosis appear chronically ill but not toxic. Constitutional symptoms, including fatigue, weight loss, and low-grade fever, may be present for weeks to months before diagnosis and often mimic the presentation of chronic fungal infection, tuberculosis, or malignancy. Fever may be absent. Most patients gradually develop productive cough and pleuritic chest pain, but hemoptysis and putrid sputum are unusual. Cervicofacial involvement is rarely observed in patients with thoracic involvement.

The imaging finding classic for actinomycosis is direct extension of a cavity or mass through an interlobar fissure. More commonly, changes are confined to a single lobe with one or more small cavitory lesions (eFig. 33-22). In advanced cases, the findings may be more distinctive, with penetration through the chest wall and/or destruction of adjacent bone tissue (eFig. 33-23).

Members of the *Actinomyces* and *Propionibacterium* genera are gram-positive, diphtheroidal or filamentous, branching bacilli. Most strains grow best in anaerobic conditions, although some also grow aerobically. In patients with a cutaneous chest wall sinus, the best means of establishing a diagnosis of actinomycosis is by detection of “sulfur granules” that, when crushed and stained, form a characteristic pattern of gram-positive, branching filaments (eFig. 33-24). The organism usually can be recovered from culture of this material, provided anaerobic conditions are maintained for the specimen. Diagnosis of an actinomycotic parenchymal lesion is more difficult. Sulfur granules are rarely present in sputum, and recovery of the organism in sputum cultures is unreliable because the organism may colonize without invading any mucosal surface. Definitive diagnosis depends on demonstrating the characteristic histopathology and culture from a sterile body fluid or tissue biopsy. Other organisms are commonly identified, including *Haemophilus* (*Actinobacillus*) *actinomycetemcomitans* and *Prevotella*, in addition to the *Actinomyces* or *Propionibacterium*.

Complications of pulmonary actinomycosis relate to its ability to invade across anatomic barriers. Pleural empyema, cutaneous thoracic sinuses, mediastinitis, pericarditis, and vertebral osteomyelitis are not infrequent. Metastatic infection, including brain, skin, and bone, is more commonly

seen with pulmonary actinomycosis than with other variants (e.g., cervicofacial disease) but is still unusual. With adequate therapy, death from actinomycosis is rare.

Prolonged antibiotic treatment is the key to curing actinomycosis. *Actinomyces* are universally susceptible to penicillin G, which should be given in intravenous doses of 12 to 20 million units daily for 4 to 6 weeks, followed by at least 6 months of oral penicillin V or ampicillin. Multiple other drugs have also been successfully used; prolonged therapy is essential. With polymicrobial infection, the presence of the other organisms may require modification of therapy. If β -lactamase-producing anaerobes are present, treatment choices as described for anaerobic pneumonia are recommended. On occasion, clindamycin fails because of concomitant infection by *H. actinomycetemcomitans*. Rarely, surgical resection is required for cure.

CHLAMYDOPHILA PSITTACI (FORMERLY CHLAMYDIA PSITTACI)—PSITTACOSIS

Exposure to birds is the classic risk factor for psittacosis. Multiple species harbor the organism, but most cases have been acquired from canaries, parakeets, cockatiels, parrots, and pigeons. Although infected birds are typically ill, there can be asymptomatic fecal carriage. *C. psittaci* can be detected in blood, tissues, feathers, and feces of infected birds. Human acquisition is typically via inhalation of contaminated bird excreta. Although approximately 50% of cases are reported in owners of infected pet birds, there may be sporadic cases and occasional outbreaks without a history of known bird exposure. History of exposure is more likely with more severe disease.¹⁹²

The symptoms of psittacosis may develop abruptly, with high fever and chills, or they may evolve slowly. Headache, arthralgia, and painful myalgia (especially in the head and neck) are prominent features. A severe cough develops that may be either dry and hacking or productive of mucoid sputum. Chest pain and dyspnea are present with extensive pulmonary involvement. Temperatures are 38° C to 40° C and are frequently accompanied by relative bradycardia. Splenomegaly or occasionally a pale macular rash (Horder spots) can be seen. Hematologic and blood chemistry findings are nonspecific, except occasionally for findings consistent with granulomatous hepatitis.

C. psittaci is an obligate intracellular parasite that does not stain by the Gram method but can be seen as large intracytoplasmic inclusions in infected cells when stained with Giemsa stain. Cultivation of the organism, which requires tissue culture, poses a threat to laboratory personnel and should be performed only in specialized facilities. Nucleic acid testing offers a rapid alternative method for diagnosis, with higher sensitivity than cultures.¹⁹³ In the absence of available nucleic acid testing, diagnosis of psittacosis can be made by demonstrating a fourfold rise in complement-fixing antibodies in paired acute and convalescent serum. A single titer of 16 or greater can be considered presumptive evidence of infection in a patient with a compatible illness. The antibody can cross-react with *C. burnetii* or *Brucella*.

Treatment with doxycycline is recommended, but the clinical response may be slow. Because of the risk of relapse, therapy should be given for a minimum of 2 weeks after

fever has resolved. Chloramphenicol, erythromycin, azithromycin, and moxifloxacin also have in vitro activity, but clinical experience with use of these drugs to treat *C. psittaci* is limited. The case-fatality rate is about 1% with antimicrobial therapy. Unusual complications include respiratory failure, encephalitis, hepatitis, disseminated intravascular coagulation, renal failure, and endocarditis.

COXIELLA BURNETII—Q FEVER

Worldwide, Q fever is a particular problem in farming communities in Europe, North America, and Australia. *C. burnetii* asymptomatically infects a wide variety of domestic and wild animals, as well as ticks. Transmission to humans is primarily via exposure to the urine, feces, placenta, or unpasteurized milk of an infected animal: cows, sheep, and goats are most common. Outbreaks have happened in tanneries, dairies, and wool-rendering plants, among laboratory personnel, and in household members exposed to an infected cat or dog during parturition.^{194,195}

Following an incubation period of 2 to 4 weeks, an atypical pneumonia syndrome develops in 10% to 20% of infected persons.¹⁹⁴ High temperature (>40°C), relative bradycardia, conjunctivitis, hepatosplenomegaly, and chest crackles may be detected; a rash is typically absent.¹⁹⁵

C. burnetii is a small, obligate intracellular bacterium that cannot be cultured on standard media or visualized with the Gram stain. Because of the high infectivity of the organism, cultures should be attempted only by experienced personnel in Biosafety Level-3 laboratories. At present, the diagnosis usually relies on a fourfold rise in antibody titer from acute to convalescent serum samples. Nucleic acid testing is likely to provide a more rapid diagnosis, which would be useful in guiding treatment decisions.

Although patients may be acutely ill on presentation, the disease is rarely fatal and generally runs its course in 1 to 2 weeks.¹⁹⁴ Some patients, particularly older adults, have a very prolonged illness. The most concerning aspect of Q fever is the potential for chronic vascular complications including endocarditis, vascular graft infections, and infected aortic aneurysms. Acute Q fever pneumonia during pregnancy is often associated with fetal loss.

Tetracyclines, especially doxycycline, are first-line therapy for Q fever. Quinolones have excellent in vitro activity and may be advantageous in the treatment of meningoencephalitis.¹⁹⁵

NOCARDIOSIS

Nocardia asteroides is the etiologic agent in more than 80% of pulmonary or disseminated cases of nocardiosis, although several other species (e.g., *Nocardia brasiliensis*) have also been associated with human infection. The organisms are widespread in nature, primarily in soil. The respiratory tract, skin, and gastrointestinal tract are portals of infection. Dysfunction of cell-mediated immunity and, to a much lesser extent, immunoglobulin defects predispose to infection. Thus, the infection rate is increased in patients who have lymphoma or leukemia, Cushing disease, or AIDS, or who are receiving immunosuppressive medications. The most recent cases have been reported in lung, heart, or stem-cell transplant recipients. Persons with pulmonary

alveolar proteinosis are also at increased risk. Nonetheless, approximately half of the patients in whom nocardiosis develops have no known underlying medical disorder.

Although nocardiosis and actinomycosis are clinically similar infections of the lower respiratory tract, nocardiosis can be distinguished by less proclivity for sinus tract formation and a greater tendency for hematogenous dissemination in both healthy and impaired hosts. Dissemination may involve almost every organ system, but the central nervous system and skin are most common.¹⁹⁶ Many patients with pulmonary nocardiosis have low-grade fever, fatigue, weight loss, productive cough, and pleuritic chest pain for weeks before seeking medical attention. However, some immunosuppressed patients present with acute, fulminant pneumonia. Physical examination is nonspecific unless sites of dissemination are obvious. Neurologic signs of a mass lesion may be present. Cutaneous dissemination appears as multiple subcutaneous abscesses with or without sinus tracts. Imaging commonly demonstrates localized bronchopneumonia or lobar consolidation (eFig. 33-25), but there may also be solitary, multiple (eFig. 33-26), or miliary nodules, and abscesses (eFig. 33-27). Pleural effusion develops in up to one third of cases.

Nocardia species are gram-positive bacilli that appear as beaded, branching filaments. Unlike the anaerobic Actinomycetaceae, *Nocardia* requires aerobic growth conditions and is usually weakly acid-fast when stained by the modified Ziehl-Neelsen method (eFig. 33-28). *Nocardia* can be cultivated on conventional blood agar or Sabouraud medium but growth may not be apparent for 3 to 21 days. Although an occasional colonizer of the upper respiratory tract, recovery of *Nocardia* from a culture of sputum or invasively obtained material is highly suggestive of the diagnosis.

Mortality approaches 50% in those with central nervous system lesions but is less than 10% in those with only pulmonary disease.¹⁹⁶ Because of in vitro synergy, TMP-SMX has become the standard treatment.¹⁹⁶ In case of a sulfa allergy or a resistant organism, minocycline, amikacin, cefotaxime, imipenem, or linezolid may be useful, but choices should always be guided by the results of susceptibility testing.¹⁹⁶ Prolonged therapy is needed to prevent relapse. Adequate drainage or excision of abscesses and empyema is a crucial adjunct to antimicrobial therapy.

MELIOIDOSIS (*BURKHOLDERIA PSEUDOMALLEI*)

In endemic areas such as Southeast Asia and northern Australia, melioidosis may be the most common cause of severe CAP.¹⁹⁷ *B. pseudomallei* is found in soil, vegetation, and water throughout tropical regions between latitudes 20 degrees N and 20 degrees S.^{48,198} Acquisition of the organism is through cutaneous inoculation or inhalation in patients with regular contact with water and soil.⁴⁸ Risk factors for disease include diabetes, alcoholism, and renal disease. Typhoons or episodic heavy rain may increase the risk of acute fulminant pneumonia; more than 75% of cases happen during the rainy season.¹⁹⁸

Melioidosis can produce either acute fulminant pneumonia or indolent, cavitary disease. Clinical manifestations of acute melioidosis include high fever, prostration, dyspnea, pleuritic chest pain, purulent sputum, and

hemoptysis. Concomitant bacteremia is common.¹⁹⁷ The chest radiograph typically shows diffuse miliary nodules, which may expand and cavitate. Subacute or chronic *B. pseudomallei* pneumonia is milder and often manifests after a period of latency. Patients may be entirely asymptomatic (i.e., abnormal radiograph only), or present with an illness clinically and radiographically indistinguishable from tuberculosis.

B. pseudomallei is an aerobic gram-negative bacillus that grows readily on routine culture media. Despite improvements in recognition and treatment, melioidosis is still associated with high morbidity and mortality.¹⁹⁷ *B. pseudomallei* is not sensitive to the usual CAP antibiotics but is usually susceptible to carbapenems, ceftazidime, and TMP-SMX. Optimal treatment for disseminated or life-threatening melioidosis requires initial intensive therapy with a carbapenem or ceftazidime followed by 3 months of TMP-SMX.^{48,197,199}

RHODOCOCCLUS EQUI

Rhodococcus equi may cause lung abscess and pneumonia. Most cases are seen in the setting of impaired cell-mediated immunity (e.g., high doses of corticosteroids, HIV infection, solid organ transplantation)²⁰⁰ and in persons with a history of animal exposure. Illness develops subacutely, mimicking mycobacterial or fungal infection. Chest radiographs often show upper lobe nodules that gradually cavitate.

The organism is an intracellular gram-positive bacillus. It may stain weakly acid-fast but is much smaller than mycobacteria. The most effective regimens appear to be prolonged courses of vancomycin or erythromycin. Addition of rifampin may be useful.

PULMONARY ANTHRAX (*BACILLUS ANTHRACIS*)

(see Chapter 40)

Although *B. anthracis* is detected in many agricultural regions, anthrax is a rare infection in the developed world. Spores, the transmissible agent of infection, reside in soil, water, and vegetation and primarily infect large herbivorous animals (e.g., cows, sheep, and horses). Humans are infected by spores via contact with contaminated animals or animal products (e.g., animal hides and wools).³³ *B. anthracis* is a proven agent of bioterrorism.²⁰¹⁻²⁰³

The manifestations of anthrax are cutaneous, gastrointestinal, and inhalational (wool sorter's disease); inhalational anthrax is the most severe. Disease results from germination of *B. anthracis* spores in the lungs or draining lymph nodes, followed by growth of the vegetative forms of the bacteria and production of edema toxin and lethal toxin. Clinical illness begins insidiously with fever, malaise, nonproductive cough, and precordial pain. This stage is followed by rapid pulmonary deterioration with dyspnea, stridor, chest pain, tachypnea, cyanosis, nausea, vomiting, and drenching night sweats. Diffuse edema of the neck and anterior chest may be evident, due to the action of edema toxin. Meningitis is a common complication.

Radiographically, the lung parenchyma is initially clear. A widened mediastinum and bilateral pleural effusions are clues to inhalational anthrax. Mediastinal widening is seen in 100% of inhalational anthrax cases,²⁰⁴ although a chest

CT scan may be required to define these characteristics.⁵¹ Later findings include vascular engorgement and lung parenchymal opacities.

B. anthracis is a large, facultative, gram-positive rod that forms spores. The organism grows readily on routine culture media and can be rapidly recovered from cultures of blood, sputum, and pleural fluid. In advanced disease, the organism may be demonstrated by Gram stain of peripheral blood.⁵¹ *B. anthracis* can be detected in nasal swabs of persons exposed to anthrax spores; the predictive value of this test for diagnosing clinical disease is ill-defined.⁵¹

Treatment recommendations for inhalational anthrax may be affected by resistance and the potential need to treat mass casualties. Current recommendations for inhalational anthrax call for initial treatment with ciprofloxacin plus one or two additional antibiotics with in vitro activity, such as clindamycin, vancomycin, imipenem, meropenem, chloramphenicol, penicillin, ampicillin, rifampin, and clarithromycin.²⁰⁵ If the isolate is susceptible, therapy can be changed from the fluoroquinolone to high-dose penicillin G or doxycycline. Intravenous therapy may be converted to oral therapy once the patient's condition stabilizes. Since pulmonary and systemic anthrax are associated with high mortality rates, therapy with an FDA-approved humanized monoclonal antibody (Raxibacumab) to anthrax lethal toxin is recommended as an adjunct to antimicrobial therapy.^{51a} Treatment for 60 days is recommended, to eliminate spores that could be the source of relapse. Although the reported mortality rate has been as high as 90%, 6 of 11 patients with inhalational anthrax survived during the 2001 anthrax attacks in the United States.⁵¹

TULAREMIA (*FRANCISELLA TULARENSIS*)

(see Chapter 40)

Although *F. tularensis* has been recovered from numerous insects and species of wild or domestic mammals throughout the temperate zones of the Northern Hemisphere, fewer than 200 cases of tularemia per year are reported in the United States.⁵² Humans acquire infection following direct contact with tissues of an infected animal (as when skinning or eating an infected animal), through the bite of an infected tick or deerfly, or by inhalation of contaminated aerosols.^{47,52,206} Persons engaged in landscaping or agricultural activities that generate aerosols in endemic areas are at particular risk for development of pneumonic tularemia.⁴⁷ Because of the efficiency of aerosol transmission, *F. tularensis* is regarded as a potential agent of bioterrorism.⁵²

Pneumonia develops from inhalation of contaminated aerosols or as a complication of bacteremia. Clinical manifestations typically begin abruptly with fever, chills, malaise, and headache. Shortly thereafter, dyspnea, cough, and chest pain may develop.⁵² Chest radiographs are usually normal at the onset (3 to 5 days following aerosol exposure) but ultimately show diffuse bronchopneumonia, often with hilar adenopathy.⁵² Pleural effusion is common and may be seen without parenchymal involvement.⁵²

F. tularensis is a fastidious, pleomorphic, gram-negative bacillus rarely visualized on Gram stain of sputum and requires specially enriched media for optimal recovery by culture. Because of the hazardous nature of the organism,

culture is best undertaken by reference laboratories. The organism can also be rapidly identified in tissues, secretions, and exudates by use of immunohistochemical techniques.⁵² Retrospective diagnosis can be accomplished by demonstrating a fourfold rise in agglutinating titers. A single titer of 160 or greater is compatible with either past or current infection.

Mortality can be as high as 60% if pneumonic tularemia is not suspected and treated appropriately. Although gentamicin has been used successfully, streptomycin remains the preferred therapy.⁵² Ciprofloxacin is an acceptable alternative agent; doxycycline and chloramphenicol are associated with higher relapse rates and require a longer duration of therapy.⁵² Ceftriaxone is unsatisfactory despite in vitro activity. After a known aerosol exposure to *F. tularensis*, prophylaxis with doxycycline or ciprofloxacin for 14 days is recommended.⁵²

PLAGUE (*YERSINIA PESTIS*) (see Chapter 40)

Plague is typically associated with ground squirrels, rabbits, prairie dogs, rats, and other small ground animals. Rodent fleas are responsible for transmission of the organism between animal hosts. Humans become infected when bitten by an infected rodent flea, by handling an infected animal carcass, or by inhaling an aerosol from a human or animal with pulmonary involvement. In the United States, most cases of plague are in rural New Mexico, Arizona, and California.⁴⁶ Because of the disease severity and potential for aerosol transmission, *Y. pestis* is also regarded as a potential bioterrorism weapon.²⁰⁷

Three clinical forms of infection exist: pneumonic, bubonic, and septicemic. Although the pneumonic form presents as a primary pneumonia, the lung may also be involved in bubonic and septicemic infections. Plague pneumonia may develop 2 to 7 days after the initial exposure. Early in the course of the illness, patients experience fever and toxicity, followed by chest pain, productive cough, dyspnea, and hemoptysis. The presence of hemoptysis can cause confusion with the hantavirus pulmonary syndrome, whose geographic distribution overlaps with plague in the United States. If pulmonary disease complicates bubonic plague, painful adenopathy is also noted. In the septicemic form, the patient may show only signs of septic shock. Chest radiographs in cases of pneumonic plague commonly reveal bilateral lower lobe alveolar opacities, but there may also be nodules, adenopathy, and pleural effusions.

Y. pestis is a short, nonmotile, gram-negative rod. Most patients with pneumonic plague have positive blood cultures. In addition, the organism can be recovered from sputum and lymph node aspirates by routine bacteriologic techniques. Fluorescent antibody staining of sputum and tissues facilitates the rapid diagnosis of plague but is available only in specialized laboratories.

Because of the potential for person-to-person transmission, all patients with plague pneumonia should be isolated. Recommended treatment consists of gentamicin or doxycycline.^{207,208} Alternative treatments include fluoroquinolones, streptomycin, or chloramphenicol. For all regimens, the duration of treatment is a minimum of 10 days.

MORAXELLA CATARRHALIS

M. catarrhalis causes pneumonia, acute exacerbations of COPD, otitis media, and maxillary sinusitis.²⁰⁹ Pneumonia typically is seen in patients with underlying COPD, although alcoholism, malnutrition, increased age, congestive heart failure, and malignancy are also risks.²⁰⁹

Because *M. catarrhalis* is part of the normal upper respiratory tract flora, only adequately screened sputum samples provide useful diagnostic information. A purulent specimen that contains many intracellular gram-negative diplococci and yields heavy growth of *M. catarrhalis* is highly suggestive of true pneumonia. Blood cultures are rarely positive.²⁰⁹

The mortality of *M. catarrhalis* is approximately 10%, primarily due to exacerbations of severe underlying pulmonary disease.²⁰⁹ Effective agents include TMP-SMX, cephalosporin, macrolide, tetracycline, quinolone, or β -lactam/ β -lactamase inhibitor combination. Virtually all isolates are resistant to penicillin and ampicillin because of β -lactamase production.

NEISSERIA MENINGITIDIS

N. meningitidis pneumonia is often a surprising culture diagnosis because clinical manifestations of meningococcal pneumonia resemble those of pneumococcal pneumonia. The estimated incidence of sporadic primary meningococcal pneumonia is 0.4 cases per 100,000 adults per year; pneumonia also complicates 5% to 15% of invasive meningococcal infections.²¹⁰ Asymptomatic carriage rates vary according to the season and are increased under conditions of crowding.²¹⁰ The organism is transmitted from person-to-person largely through droplet aerosols. Nosocomial clusters of meningococcal pneumonia are well described.

N. meningitidis is a gram-negative diplococcus; its appearance in sputum is similar to that of *Moraxella* and *Acinetobacter*. Rates of isolation of the organism from blood, cerebrospinal fluid, and pleural fluid from patients with meningococcal pneumonia are highly variable.

Aqueous penicillin G for 10 days, in daily doses of 4 to 6 million units, is adequate therapy for isolated pneumonia. Coexistence of septicemia or meningitis warrants increasing the dose to 18 to 24 million units per day. Isolates with decreased susceptibility to penicillin are not yet a significant problem in the United States, but have been reported in Europe and Africa.²¹¹

Because meningococci can be transmitted from patients with pneumonia to susceptible contacts, respiratory droplet isolation should be implemented during the initial days of treatment. Prophylaxis with ceftriaxone, ciprofloxacin, or rifampin is advised for household and other intimate contacts of the patient, including health care providers who have been exposed to respiratory secretions.

PASTEURELLA MULTOCIDA

Pasteurella multocida is part of the normal oral flora of many domestic and wild mammals. Although skin and soft tissue infections following a cat or dog bite are the more common

manifestations of human infection, sporadic cases of pneumonia, lung abscess, and empyema are seen in patients with chronic respiratory diseases, including COPD, carcinoma, and bronchiectasis. Most patients recall prior exposure to animals.

Pasteurella pneumonia is indistinguishable from other etiologies of CAP, although empyema may be more frequent. The organism is a small, gram-negative coccobacillus indistinguishable from other gram-negative rods by Gram stain.

Identification of the organism by culture of sputum, blood, and pleural fluid is easily accomplished.

The treatment of choice for *P. multocida* pneumonia is penicillin G, 4 to 12 million units daily for 10 to 14 days. Tetracycline, amoxicillin-clavulanate, second- and third-generation cephalosporins, TMP-SMX, fluoroquinolones, and chloramphenicol are also active. *P. multocida* is resistant to clindamycin and macrolides.

C-reactive protein, have also been found useful for predicting inadequate response. Initial higher levels of PCT or C-reactive protein represent a risk factor for inadequate response (odds ratio, 2.6),²¹³ whereas low levels are associated with responses to therapy. A recently described biomarker, MR-proadrenomedullin, has shown a greater association with severity assessment, and levels greater than 1.8 were associated with subsequent deterioration and ICU admission.²¹⁴

The causes of nonresponding pneumonia are classified as infectious, noninfectious, and of unknown origin.²¹² eTable 33-5 lists common infectious and noninfectious causes.

INFECTIOUS CAUSES

In patients hospitalized for CAP, specific infections are responsible for 40% of nonresponding cases. The most frequent microorganisms found are *S. pneumoniae*, *Legionella*, *P. aeruginosa*, and *S. aureus*.

Patients with CAP, HAP, or VAP may fail to respond because of resistance to the empirical antibiotic regimen selected. *P. aeruginosa*, which is not covered by empirical therapy for CAP, causes about 10% of cases of nonresponding CAP.²¹² Up to 50% of episodes of nonresponding VAP are caused by multiresistant microorganisms; the most frequent causes are MRSA, *P. aeruginosa*, carbapenemase-producing *Klebsiella*, and *Acinetobacter* species.²¹⁵

More unusual microorganisms in nonresponding CAP²¹² include *Mycobacteria*, *Nocardia* species, anaerobes, fungi, *Pneumocystis jirovecii*, and other organisms requiring antibiotics other than those recommended for CAP or HAP (eFig. 33-29). Investigation of the etiology of some of these microorganisms requires intensified microbiologic diagnostic testing as well as exhaustive review to search for risk factors, including epidemiology (travel, professional, leisure, or animal exposures), personal habits, and environmental factors.

Local or metastatic infectious complications also contribute to treatment failure. Empyema (see eFig. 33-7) is one of the most frequent complications in pneumonia and is thus a cause of nonresponse that must be evaluated with thoracentesis when a pleural effusion is present. Other causes of treatment failure are abscess formation (see eFig. 33-4) and necrotizing pneumonia (see eFigs. 33-20 and 33-21). Metastatic infections such as endocarditis, arthritis, pericarditis, meningitis, or peritonitis can contribute to treatment failure and are more common in bacteremic pneumonia. In approximately 30% of the cases, no specific cause for lack of response can be identified despite adequate antibiotic treatment. This may be due to the presence of comorbidities or to an exaggerated or diminished inflammatory response.^{215a}

NONINFECTIOUS CAUSES

Noninfectious diseases with acute involvement of the pulmonary parenchyma may simulate pneumonia. These include pulmonary infarction, pulmonary hemorrhage, organizing pneumonia, eosinophilic pneumonia, hypersensitivity pneumonitis, drug-induced lung disease, and neoplasms. Alveolar cell lung cancer (eFig. 33-30 and Video

33-2) may be particularly difficult to distinguish radiographically from pyogenic pneumonia. The frequency of noninfectious etiologies has been reported to be 22% in CAP²¹² and 19% in nosocomial pneumonia.²¹⁵ eTable 33-5 summarizes infectious and noninfectious causes of nonresponding pneumonia.

DIAGNOSTIC EVALUATION

The diagnostic approach to treatment failure requires a complete reevaluation of the history, physical examination, and laboratory studies including factors that may be related to delayed response.^{212,216} Reconsideration of the initial diagnosis is also an important component of the diagnostic approach. Important epidemiologic clues may suggest unusual microorganisms along with unexpected resistance to antimicrobials, or underlying immunodeficiency such as HIV infection.

MICROBIOLOGIC STUDIES

The microbiologic investigation of treatment failures requires comprehensive reexamination of initial microbiologic results, together with obtaining new samples for culture and other assays (eTable 33-6). Invasive techniques (i.e., bronchoscopy) for microbiologic samples and local evaluation of airways are recommended if they are not contraindicated. Both protected sheath brush and BAL sampling should be done during the same procedure for bacterial cultures, direct fluorescent antibody staining, and nucleic acid testing. Although culture results may be altered by the prior administration of antibiotics, the sensitivity of brush or BAL cultures approaches 40% in nonresponding CAP. In patients undergoing mechanical ventilation, the tracheal aspirate can provide diagnostic information. Gram stain of cytocentrifuged BAL fluid can rapidly identify intracellular microorganisms⁸⁸ and may guide decisions regarding changes in antimicrobial therapy. Comprehensive microbiologic studies should also be performed on samples from nonrespiratory sites (eTable 33-7). When present, pleural fluid should be obtained for culture, direct fluorescent antibody, and nucleic acid testing for likely pathogens. The role of transbronchial biopsy is not established, and its indication depends on the possible alternative diagnosis suspected.

Imaging Studies

Chest radiographs may demonstrate complications such as pleural effusion, cavitation, or new opacities. Chest CT scans provide a more detailed study of the parenchyma, interstitium, pleura, and mediastinum, potentially suggesting specific microorganisms (see eFig. 33-29) or alternative diagnoses. In a patient with applicable risk factors, the appearance of nodular images with the halo sign (i.e., a nodule surrounded by a halo of ground-glass attenuation, especially near the pleura) on CT scan is suggestive of pulmonary aspergillosis (see Chapter 91 and eFigs. 91-8A and 91-10) or mucormycosis (see Chapters 38, 91, and 95 and eFig. 91-9).^{217,218} Nodules of similar appearance have also been described in cytomegalovirus infection (see Chapter 91 and eFig. 91-2), granulomatosis with polyangiitis (formerly Wegener granulomatosis), Kaposi sarcoma, and

eTable 33-5 Causes of Nonresponding Pneumonia**INFECTIOUS**

Resistant microorganisms
 Community-acquired pneumonia (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*)
 Nosocomial pneumonia (e.g., *Acinetobacter*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*)
 Uncommon microorganisms (e.g., *Mycobacterium tuberculosis*, *Nocardia* spp., fungi, *Pneumocystis jirovecii*)
 Complications of pneumonia
 Empyema
 Abscess or necrotizing pneumonia
 Metastatic infection

NONINFECTIOUS

Neoplasms
 Pulmonary hemorrhage
 Pulmonary embolism
 Sarcoidosis
 Eosinophilic pneumonia
 Pulmonary edema
 Acute respiratory distress syndrome
 Organizing pneumonia
 Drug-induced pulmonary disease
 Pulmonary vasculitis

eTable 33-7 Possible Diseases Depending on Differential Cell Count in Bronchoalveolar Lavage Fluid**PREDOMINANCE OF POLYMORPHONUCLEAR LEUKOCYTES**

Bacterial infection
 Organizing pneumonia

PREDOMINANCE OF LYMPHOCYTES

Tuberculosis
 Hypersensitivity pneumonitis
 Sarcoidosis
 Fibrosis

HEMOSIDERIN-LADEN MACROPHAGES

Alveolar hemorrhage

EOSINOPHILS

Pulmonary eosinophilia
 Fungal infection
Pneumocystis jirovecii
 Systemic diseases
 Drug-induced disease

eTable 33-6 Recommended Microbiologic Evaluation in Patients with Nonresolving Pneumonia**BLOOD CULTURES (TWO SETS)****URINE**

Antigen test for detection of *Legionella pneumophila*

SPUTUM

Gram stain, Giemsa stain, immunofluorescence stains for *Legionella*; normal and modified Ziehl-Neelsen stain for *Mycobacterium* spp. and *Nocardia* spp.
 Cultures for conventional bacteria, *Legionella*, mycobacteria, and fungi

BRONCHOSCOPY SPECIMENS (USING PSB OR BAL)*

Gram stain, Giemsa stain, immunofluorescence stains for *Legionella* and *Pneumocystis jirovecii*; normal and modified Ziehl-Neelsen stain for *Mycobacteria* spp. and *Nocardia* spp.
 Cultures for aerobic and anaerobic bacteria, *Legionella*, mycobacteria, and fungi

PLEURAL FLUID

Gram stain, Giemsa stain, immunofluorescence stains for *Legionella*; normal and modified Ziehl-Neelsen stain for *Mycobacteria* spp. and *Nocardia* spp.
 Cultures for aerobic and anaerobic bacteria, *Legionella*, mycobacteria, and fungi

*Quantitative criteria for the interpretation of PSB and BAL specimens are described in the text.

BAL, bronchoalveolar lavage; PSB, protected specimen brush.

metastases with necrosis and/or hemorrhage. Ground-glass opacities consistent with interstitial pneumonia suggest *P. jirovecii* pneumonia. Nodules or multiple masses with or without cavitation are compatible with *Nocardia* species, *M. tuberculosis*, or Q fever. Diffuse or mixed interstitial and alveolar opacities may be due to viral infections or *M. pneumoniae*. Other imaging studies, such as chest CT pulmonary angiography should be considered to evaluate the possibility of pulmonary emboli.

THERAPEUTIC MANAGEMENT

Correction of Host Abnormalities

Defects related to the host's immune system may impede recovery from pneumonia. Immunodeficiency may arise as a complication of cancer chemotherapy, immunosuppressive agents, or corticosteroid use; or it may result from a congenital (e.g., agammaglobulinemia) or acquired (e.g., HIV infection) immune defect. Many of these immune deficiencies are not remediable; however, drug-related immunosuppression may be improved by discontinuing the offending agent or reducing the dose. Although reduction of immunosuppression may promote recovery from the active infection, it can also be complicated by enhanced inflammation due to immune reconstitution.^{219,220}

Granulocytopenia (absolute granulocyte count less than 500 cells/mm³) has been associated with fulminant, antibiotic-unresponsive pneumonia, and administration of *granulocyte colony-stimulating factor* (G-CSF) or *granulocyte-macrophage colony-stimulating factor* (GM-CSF) is effective in increasing the number of circulating neutrophils. Despite this effect on neutrophils, routine administration of G-CSF or GM-CSF has not been found to improve survival from infections.²²¹ Because pneumonia is the infection most frequently associated with a poor clinical outcome in profoundly neutropenic patients, the use of G-CSF or GM-CSF in these patients may be justified, even though a benefit has not been demonstrated.²²² Corticosteroid treatment has been investigated because of its suppressant effect on inflammatory responses; studies have yielded discordant findings. A recent meta-analysis found evidence for a positive effect on survival in severe cases of CAP.²²³ In contrast, a recent randomized trial showed no benefit, although the number of patients with severe CAP may have been insufficient to reveal a difference in this select group.²²⁴

Antimicrobial Adjustment

The optimum therapeutic approach to nonresolving pneumonia requires close monitoring, transfer to a higher level of care, and optimization of the antibiotic regimen, including dosing.²¹² The optimal time to make these changes is not defined, although it has been suggested that one should wait until 72 hours after the initiation of treatment except in the presence of severe clinical deterioration or dramatic progression as determined by chest radiograph. Before initiating a change in antibiotics, new samples should be obtained for microbiologic studies.

In nonresponding CAP, strong consideration should be given to extending the antibacterial spectrum to ensure coverage of resistant *S. pneumoniae*, *P. aeruginosa*, *S. aureus*, and anaerobes. Such broad-spectrum therapy should be

undertaken after all abscesses or empyemas have been drained, the results of all previous cultures are reviewed and, whenever possible, vigorous new efforts have been made to identify the responsible microorganisms. The specific antimicrobial regimen chosen depends on patient risk factors, disease severity, and the local epidemiology of antimicrobial resistance. In community-acquired MRSA, antimicrobial treatments may include linezolid or clindamycin plus vancomycin, depending on results of susceptibility testing.^{21,163}

In nonresponding nosocomial pneumonia, combinations of up to three antibiotics may be necessary to cover *P. aeruginosa*, MRSA, and the endemic flora of each hospital, such as *Acinetobacter* species or other microorganisms.²¹⁵ The increasing spread of virulent carbapenemase-producing *K. pneumoniae* also necessitates vigilance for these organisms and consideration of combinations of polymyxin B or E, tigecycline, and/or ampicillin-sulbactam.²²⁵ Occasionally, empirical coverage against *Aspergillus* species should be considered (i.e., severe COPD, significant immunosuppressive therapy, corticosteroid treatments), especially if supported by clinical, radiologic,²¹⁷ or laboratory data. The recommended approach is to cover empirically all likely causal microorganisms while awaiting the results of repeated respiratory samples and then adjust and deescalate antibiotics accordingly.

LUNG ABSCESS

Lung abscesses are pus-containing necrotic lesions of the lung parenchyma that result from aspiration of bacteria-laden secretions and show an air-fluid level (see Fig. 33-13). Lung abscesses are distinct from, and may follow, necrotizing pneumonia, in which multiple small cavities develop in contiguous areas of the lung.^{226,227} Lung abscesses must be distinguished from septic pulmonary emboli, which are often multiple and bilateral, involve the lower lobes (see Fig. 33-6), and are secondary to an endovascular infection.

Unlike most other respiratory infections that are caused by single pathogens, lung abscesses are caused by mixed populations of bacteria. The most common components of the mixed bacterial populations in lung abscesses are anaerobic bacteria (principally *Peptostreptococcus* species (now termed *Finegoldia magna*), *E. nucleatum*, and *Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*)). Microaerophilic streptococci and viridans streptococci are also frequently isolated and can contribute to treatment failure if appropriate antibiotics are not included.²²⁸ Lung abscess may also be associated with pyogenic bacteria, mycobacteria, fungi, and parasites such as *Paragonimus*, *Entamoeba*, and *Echinococcus* (see Chapter 39). Secondary lung abscesses develop from congenital lung abnormalities, obstructing neoplasms, foreign bodies, and bronchiectasis. Lung abscess may also complicate pulmonary infarction, primary lung cancer (central carcinoma with necrosis), metastatic malignancies, and the necrotic conglomerate lesions of silicosis and coal miners' pneumoconiosis. Lesions in diseases such as granulomatosis with polyangiitis (formerly termed Wegener granulomatosis) and rheumatoid arthritis with rheumatoid nodules may also mimic lung abscess.

The clinical manifestations of lung abscesses are distinct from those of CAP, because they are usually prolonged in time (2 weeks to 3 months or more) and include fever, night sweats, cough with foul-smelling sputum, fatigue, weight loss, and sometimes hemoptysis.

The typical appearance of a lung abscess on a chest radiograph is a thick-walled cavity with an air-fluid level (see Fig. 33-13 and eFigs. 33-4A, 33-13A, and 33-15). A contrast-enhanced CT is occasionally necessary to differentiate lung abscess from other conditions, and bronchoscopy may be needed to distinguish lung abscess from endobronchial carcinoma.

Antibiotics with activity against anaerobic and aerobic bacteria and that are unaffected by the β -lactamases produced by anaerobes are the mainstay of treatment for lung abscesses.²²⁸ Clindamycin has been widely used and is superior to penicillin alone, undoubtedly because of the increasing prevalence of β -lactamase production by the anaerobes that cause lung abscesses. More recently, β -lactam/ β -lactamase inhibitor combinations (amoxicillin-clavulanate or ampicillin-sulbactam) have been found to provide cure rates indistinguishable from those with clindamycin; moxifloxacin and carbapenems have also been used successfully.²²⁸ Metronidazole alone is not recommended, because it lacks sufficient activity against microaerophilic streptococci and viridans streptococci that are often part of the mixed microbial flora in lung abscesses. If metronidazole is used, penicillin should be added to cover streptococci. The optimal duration of antibiotic treatment has not been determined, although treatment for 6 to 8 weeks is commonly employed.

Failure to respond to antibiotics within 7 to 10 days warrants investigation for alternative diagnoses or complications. Antibiotic treatment may fail if the patient has immunodeficiency, if the cavity is large (>8 cm), or if the abscess is due to pyogenic bacteria such as *P. aeruginosa* or *S. aureus*. CT-guided percutaneous transthoracic tube drainage²²⁹ or endoscopic drainage²³⁰ are alternatives to surgical resection; the reported success rates with both of these procedures are high, although no prospective controlled trials have been reported. Complications of CT-guided tube drainage include pneumothorax, pyopneumothorax, and bronchopleural fistula. After drainage, patients show clinical improvement usually in 48 hours. Persistent fever can also be seen if there is a secondary pleural empyema that requires drainage.

PREVENTION OF PNEUMONIA

VACCINES

Prevention of pneumonia may be achieved by administering the influenza and pneumococcal vaccines. Recommendations for administration of influenza²³¹ and pneumococcal²³² vaccines are presented in eTable 33-8 and eTable 33-9, respectively.

Inactivated influenza vaccination is recommended annually for all persons aged 6 months and older, including pregnant women. For those averse to injections, a live attenuated influenza vaccine can be given by intranasal administration to healthy persons 5 to 49 years old. The live attenuated

vaccine must be avoided in pregnancy, in high-risk persons with chronic underlying diseases or immunodeficiencies, and in health care staff taking care of immunosuppressed patients; it is not approved for use in those older than 49 years. While annual influenza vaccination is widely recommended, the immunogenicity and efficacy of the currently available vaccine is lower in individuals older than 65 years of age, and breakthrough infections are frequent.²³²

Two pneumococcal vaccines are currently available. The purified polysaccharide vaccine (PPSV23) contains capsular antigens isolated from 23 of the most prevalent capsule types and is immunogenic in adults, although antibody levels decrease to prevaccination levels after 4 to 7 years. The pneumococcal conjugate vaccine (PCV13) contains the polysaccharide antigens from 13 of the most prevalent capsule types, conjugated to a nontoxic mutant of diphtheria toxin protein, which generates T-cell help and long lived memory B cells specific for the pneumococcal antigens. PPSV23 should be administered to all individuals 65 years of age and older, as well as those 19 to 64 years of age with chronic conditions that increase the risk of invasive pneumococcal infection (e.g., diabetes mellitus, chronic lung, heart, or liver disease; cigarette smoking or alcoholism). Patients aged 19 years and older with immunodeficiencies or other conditions that impose an especially high risk of invasive pneumococcal infection (asplenia, HIV or other congenital or acquired immunodeficiencies, myeloma, lymphoma, leukemia, chronic renal failure) should receive an initial dose of PCV13 followed 8 weeks or longer later by PPSV23. eTable 33-9 lists the conditions and indications for which administration of each of the pneumococcal vaccines is currently recommended.²³³ In 2014, the updated ACIP recommendations are that both PCV13 and PPSV23 should be administered in series to all adults 65 years of age and older. A dose of PCV13 should be received first followed by a dose of PPSV23 6 to 12 months later. Individuals previously vaccinated with PPSV23 should be given a dose of PCV13 after approximately 1 year.^{234,235}

SMOKING CESSATION

Not only is smoking a risk factor for pneumococcal disease, quitting smoking reduces the risk.²³⁶ The IDSA/ATS recommend smoking cessation counseling as well as pneumococcal vaccination for smokers who are hospitalized with pneumonia.¹⁸

Key Points

- All patients with suspected pneumonia should have a chest radiograph. Gram stains of sputum and cultures of blood, sputum, and other sites should be obtained in hospitalized patients before treatment. *S. pneumoniae* and *L. pneumophila* urinary antigens can make an etiologic diagnosis with reasonable sensitivity and specificity.
- Aspiration is the cause of infection with *S. pneumoniae*, *H. influenzae*, gram-negative bacilli, and other organisms, whereas aerosolization is the route of infection with intracellular bacteria such as *M. pneumoniae*, *Chlamydophila* species, and *C. burnetii*. Aside from

eTable 33-8 Recommendations for Administration of Influenza Vaccine*

Inactivated vaccine: All persons aged 6 months and older including pregnant women

Live attenuated vaccine†: Healthy, nonpregnant women aged 2 to 49 years without high-risk medical conditions

*Avoid giving vaccine to patients with anaphylactic allergy to eggs or to other influenza vaccine components. The optimal period for vaccination is October to November. However, it is acceptable to provide vaccine from September to early March.

†Health care personnel who care for severe immunocompromised persons should receive inactivated rather than live vaccine.

Modified from Recommended Immunization schedule for adults aged 19 years and older. *MMWR* 62:Suppl, 2013.

eTable 33-9 Recommendations for PPSV23 and PCV13 by Risk Group for Adults 19 Years and Older*

Risk Group	PCV13 Recommended	PPSV23 Recommended	PPSV23 Revaccination 5 Years after First Dose
Immunocompetent	Cerebrospinal fluid leak Cochlear implant	Chronic heart diseases† Chronic lung diseases‡ Diabetes mellitus Chronic liver diseases Cerebrospinal fluid leak Cochlear implant Alcohol Smoking	
Asplenia	Sickle cell disease/ hemoglobinopathy Congenital or acquired asplenia	Sickle cell disease/ hemoglobinopathy Congenital or acquired asplenia	Sickle cell disease/ hemoglobinopathy Congenital or acquired asplenia
Immunocompromised	HIV Congenital or acquired immunodeficiency Chronic renal failure Leukemia/lymphoma Generalized malignancy Solid organ transplant Multiple myeloma Iatrogenic immunosuppression§	HIV Congenital or acquired immunodeficiency Chronic renal failure Leukemia/lymphoma Generalized malignancy Solid organ transplant Multiple myeloma Iatrogenic immunosuppression	HIV Congenital or acquired immunodeficiency Chronic renal failure Leukemia/lymphoma Generalized malignancy Solid organ transplant Multiple myeloma Iatrogenic immunosuppression

*All adults aged 65 years and older should receive PCV13 and PPSV23, with the sequence and interval depending on previous history of vaccination with pneumococcal vaccine.

†Including congestive heart failure and cardiomyopathies.

‡COPD, emphysema, and asthma.

§Including long-term systemic corticosteroids and radiation therapy.

Modified from Centers for Disease Control and Prevention: Tomczyk S, Bennett NM, Stoecker C, et al: Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 63(37):822–825, 2014.

inhalational pneumonia due to *Legionella* or contaminated medical aerosols, aspiration is the cause of hospital-acquired pneumonia, especially in intubated patients.

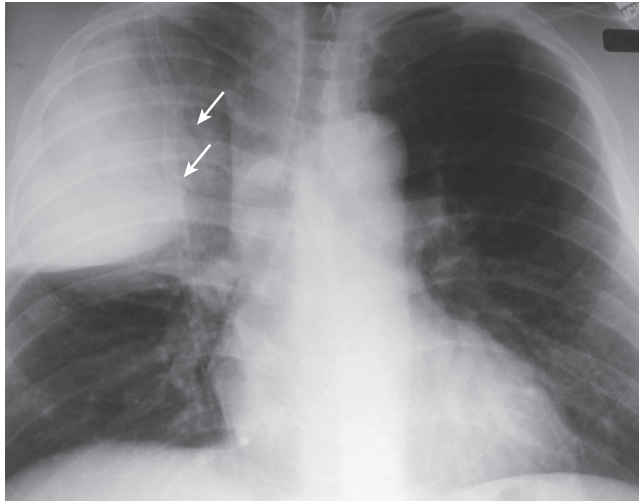
- Nucleic acid amplification tests should be used increasingly to diagnose viruses and fastidious bacteria, *M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*, and *B. pertussis* because culture procedures are too insensitive and too slow to be relevant therapeutically.
- In older and immunocompromised patients, the signs and symptoms of pneumonia may be muted and overshadowed by nonspecific complaints. Temperature greater than 38.5° C or accompanied by chills should never be attributed to bronchitis without examining a chest radiograph. Older patients with pneumonia who present with altered mental status without fever often have a delay in receiving antibiotics; this delay can increase mortality.
- The treatment for pneumonia should be pathogen-directed, but definitive identification of the patient's causal pathogen may be difficult. Therefore, the setting in which the patient resides (e.g., community, hospital, nursing home), the severity of the disease, the age of the patient, the presence of comorbidities and immunosuppression, previous antimicrobial therapy, and specific clinical and radiologic manifestations of the illness are used to select initial empirical antimicrobial therapy.
- If the etiologic agent has been identified, the antimicrobial regimen should be adjusted based on the results of in vitro susceptibility testing. The ideal drug for a known pathogen has the narrowest spectrum of activity and is the most efficacious, least toxic, and least costly.

Complete reference list available at *ExpertConsult*.

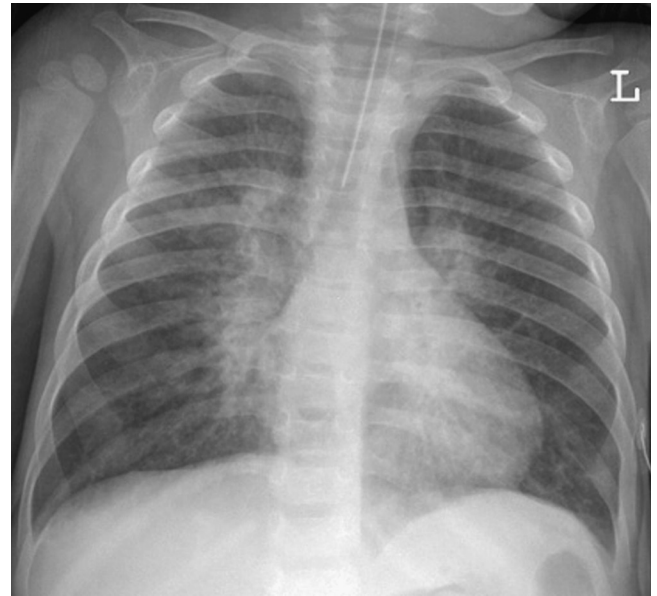
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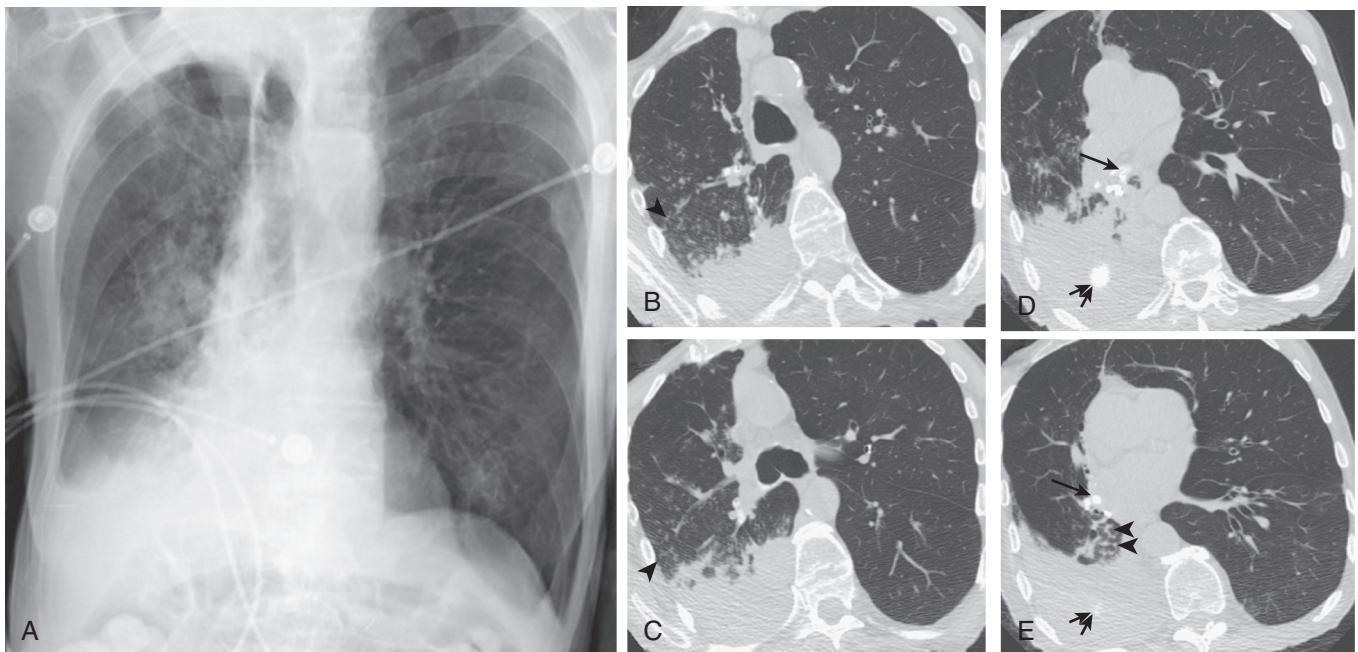
eFIGURE IMAGE GALLERY



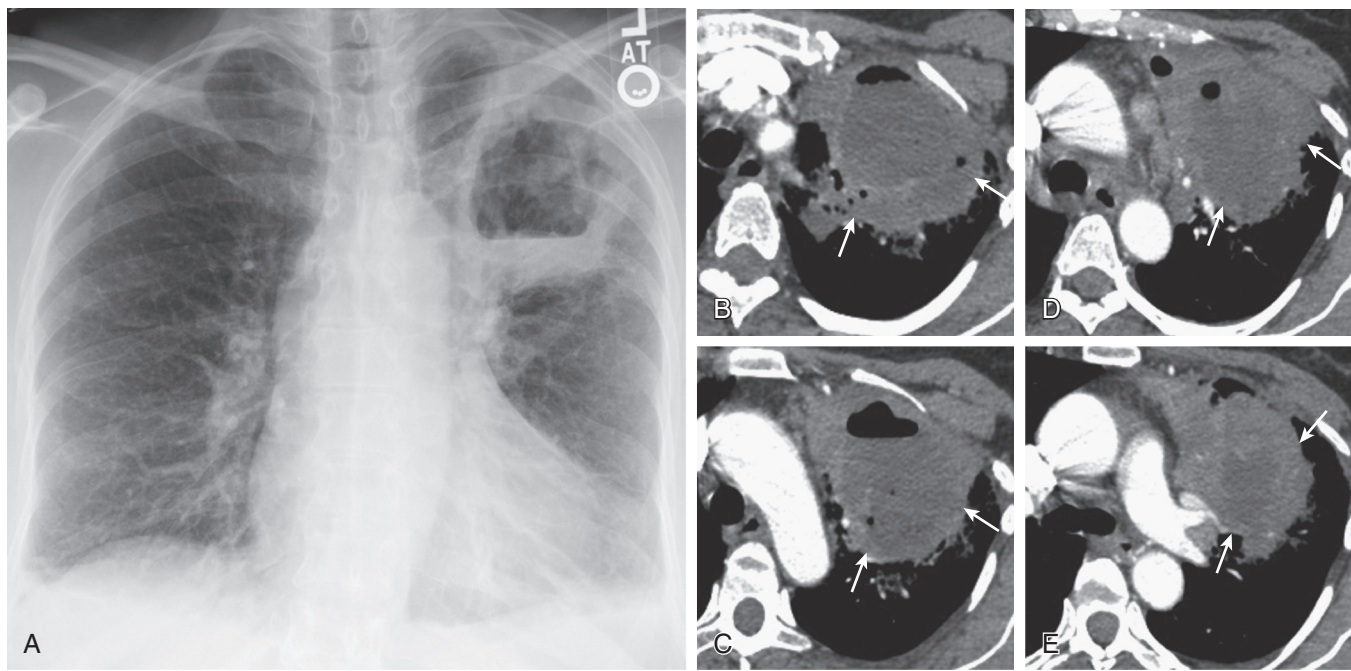
eFigure 33-1 Lobar pneumonia due to pneumococcus. Frontal chest radiograph shows homogeneous increased opacity conforming to the shape of the right upper lobe, extending to the pleural surfaces, associated with air bronchograms (arrows). These findings are typical of air space consolidation, and the pattern is consistent with lobar pneumonia, commonly seen with pneumococcal or *Klebsiella* pulmonary infections. (Courtesy Michael Gotway, MD.)



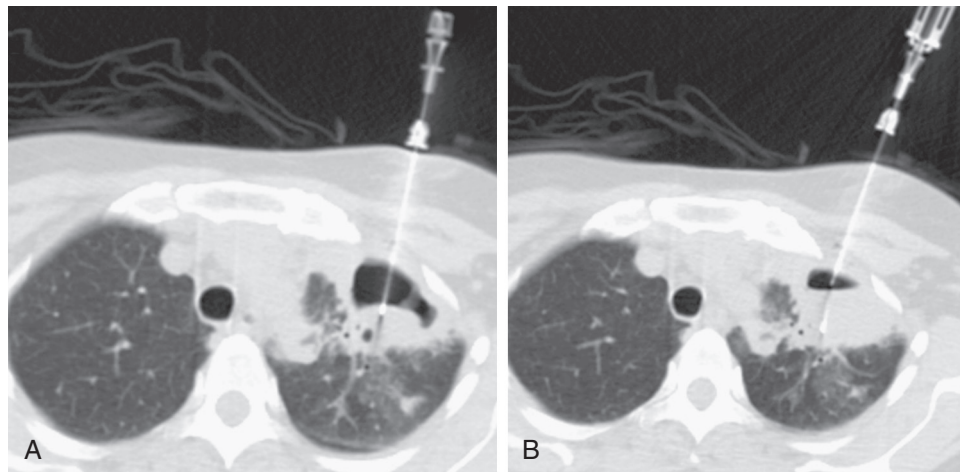
eFigure 33-2 Atypical pneumonia due to adenovirus. Frontal chest radiograph in a pediatric patient shows multifocal, bilateral central peribronchial thickening, typical of an infiltrative process involving the pulmonary interstitium, such as viral infection. (Courtesy Michael Gotway, MD.)



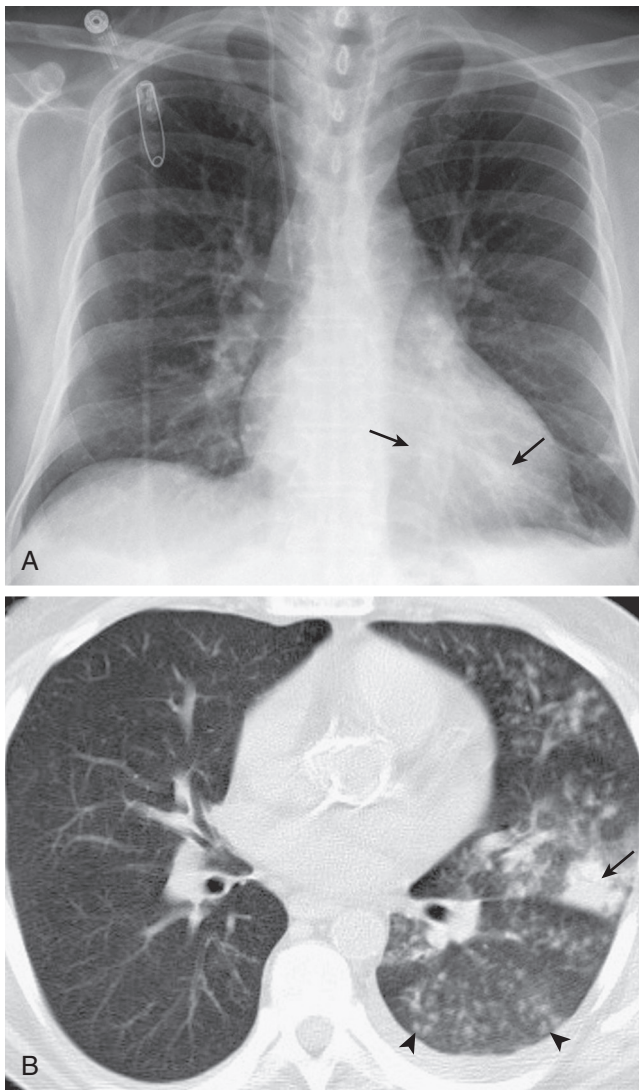
eFigure 33-3 Aspiration pneumonia. **A**, Frontal chest radiograph shows right lower lobe consolidation and volume loss; note shift of trachea and cardio-mediastinal structures toward the right. Trace right pleural effusion is present. **B–E**, Axial chest CT displayed in lung windows shows right lower lobe consolidation associated with small centrilobular nodules (arrowheads) consistent with bronchopneumonia and bronchiolitis. This pattern is consistent with aspiration pneumonia, particularly when seen in dependent lung regions, but is not completely specific for aspiration; community-acquired or health care-acquired bronchopneumonia may appear similar. However, what is specific for aspiration in this circumstance is the frank aspiration of orally administered contrast (**E**, single arrow, oral contrast in right lower lobe bronchus; **D** and **E**, double arrows, oral contrast extending into right lower lobe pulmonary parenchyma), which flows directly into the affected regions of lung. (Courtesy Michael Gotway, MD.)



eFigure 33-4 Lung abscess. **A**, Frontal chest radiograph in a patient with cough and purulent sputum shows a thick-walled cavity with an irregular internal lining and air-fluid level in the left apex. **B–E**, Axial chest CT displayed in soft tissue windows shows a rounded area of low attenuation (*arrows*) in the left upper lobe, surrounded by consolidation consistent with a pulmonary abscess. The internal low attenuation is fluid density, and an air-fluid level is present, typical of pulmonary abscess. Reactive prevascular lymph node enlargement is also evident. (Courtesy Michael Gotway, MD.)



eFigure 33-5 Percutaneous transthoracic sampling of a pulmonary abscess. **A** and **B**, Axial chest CT shows placement of a needle into a left apical cavity (same patient as in [eFig. 33-4](#)). Purulent fluid was recovered, with microbiologic analysis disclosing polymicrobial infection. The lesion resolved with antibiotic therapy. (Courtesy Michael Gotway, MD.)



eFigure 33-6 Pneumococcal bronchopneumonia. **A**, Frontal chest radiograph shows patchy bronchovascular thickening (*arrows*) in the left lower lobe; trace blunting of the left costophrenic angle is present. **B**, Axial chest CT 2 days following **A** shows nodular lingular consolidation (*arrow*) and numerous small centrilobular nodules (*arrowheads*) consistent with bronchopneumonia. This bronchopneumonia pattern contrasts with the lobar pneumonia pattern (see [Fig. 33-1](#) and [eFig. 33-1](#)). Both imaging patterns may be seen with pneumococcal pneumonia. (Courtesy Michael Gotway, MD.)

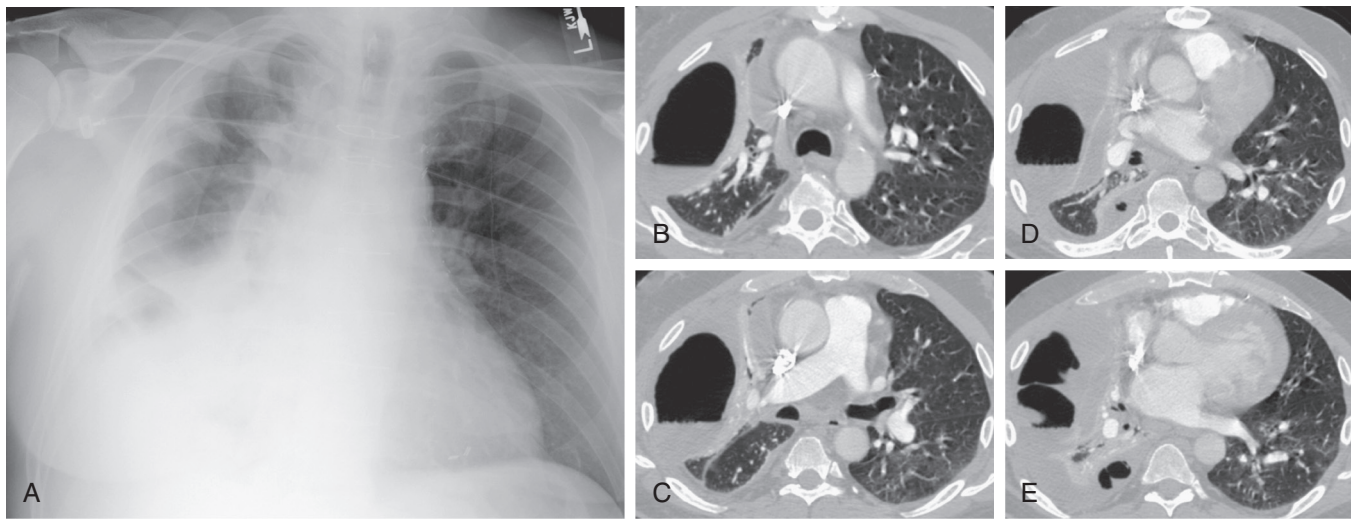
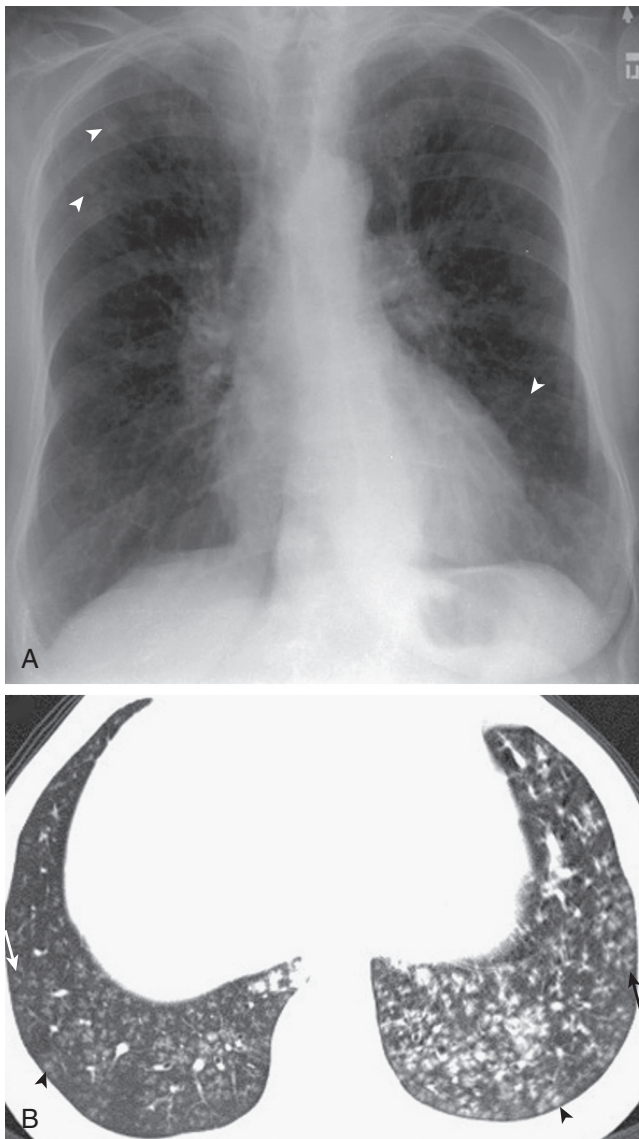
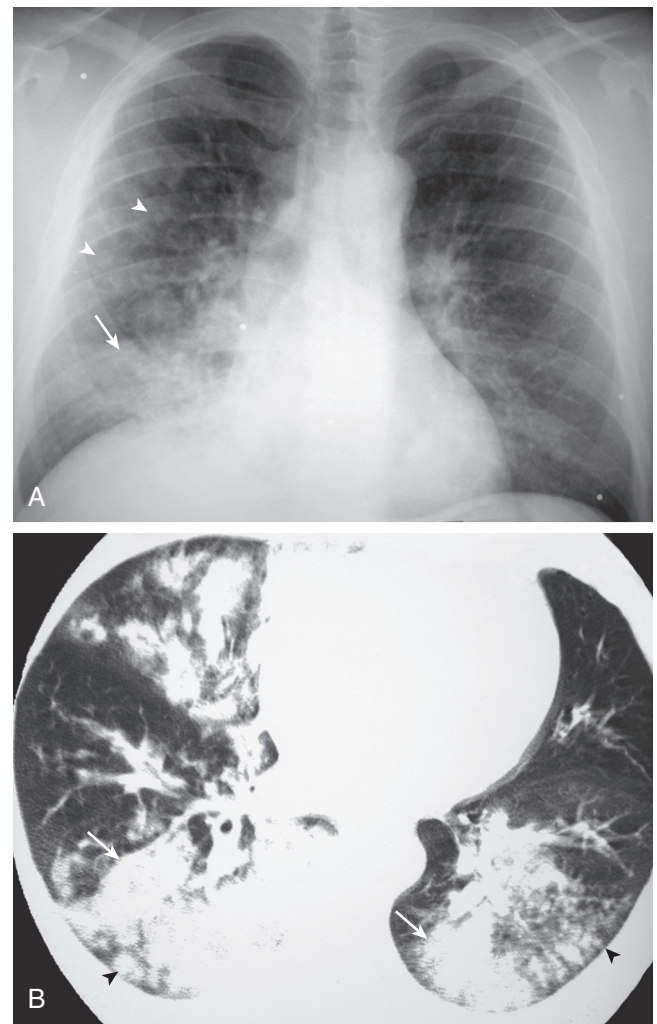


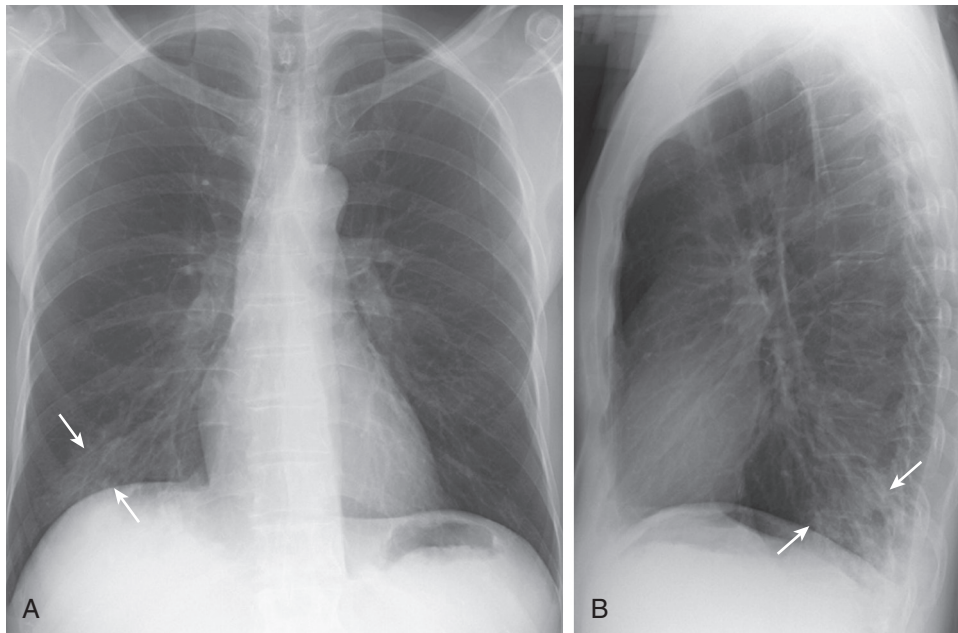
Figure 33-7 *Streptococcus intermedius* pneumonia and empyema. **A**, Frontal chest radiograph shows right lung consolidation and volume loss. Some increased opacity adjacent to the chest wall suggests pleural disease but the findings are nonspecific. **B–E**, Axial chest CT displayed in an intermediate window to highlight the lung parenchyma and soft tissue features simultaneously, obtained shortly after **A**, shows a rounded gas collection containing fluid along the right chest wall consistent with empyema and bronchopleural fistula. *S. intermedius* was recovered following right thoracostomy tube placement. (Courtesy Michael Gotway, MD.)



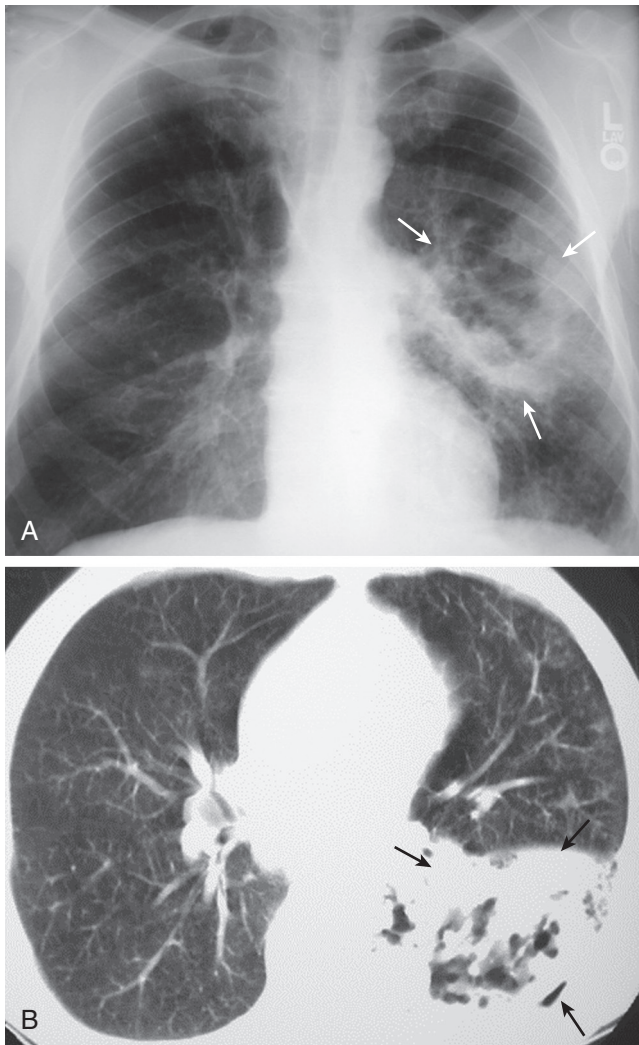
eFigure 33-8 *Haemophilus influenzae* pneumonia: bronchiolitis. **A**, Frontal chest radiograph shows several nonspecific small nodular opacities bilaterally (*arrowheads*). **B**, Axial chest CT through the lung bases shows numerous small centrilobular nodules (*arrowheads*), some with branching configurations (*arrows*), the latter consistent with "tree-in-bud" opacity, representing infectious bronchiolitis. The appearance of small centrilobular nodules with branching configurations is not specific for *Haemophilus influenzae* pneumonia and can be seen with other bacteria and occasionally with fungi or even viruses. (Courtesy Michael Gotway, MD.)



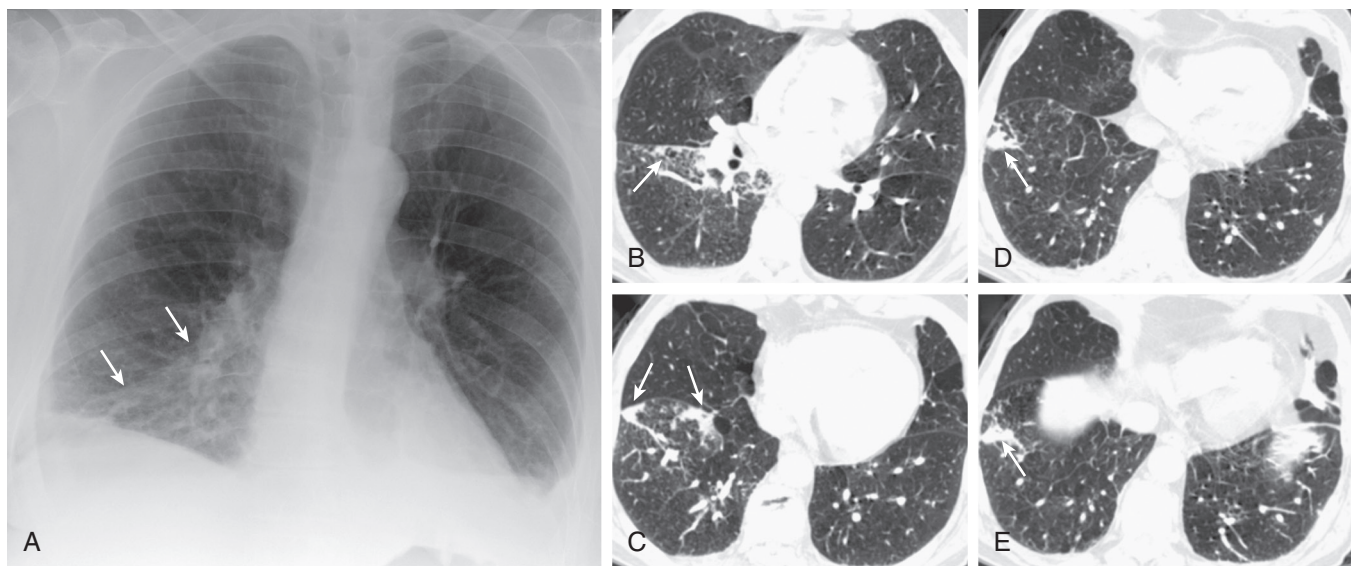
eFigure 33-9 *Mycoplasma pneumoniae* pneumonia: multilobar pneumonia. **A**, Frontal chest radiograph shows right lower lobe consolidation (*arrow*) associated with several small nodular opacities (*arrowheads*), the latter consistent with "acinar" or "air space" nodules. **B**, Axial chest CT through the lower lungs displayed in lung windows shows extensive bilateral consolidation (*arrows*) associated with small nodules (*arrowheads*), varying from 3 to 4 mm to 1 cm in size. (Courtesy Michael Gotway, MD.)



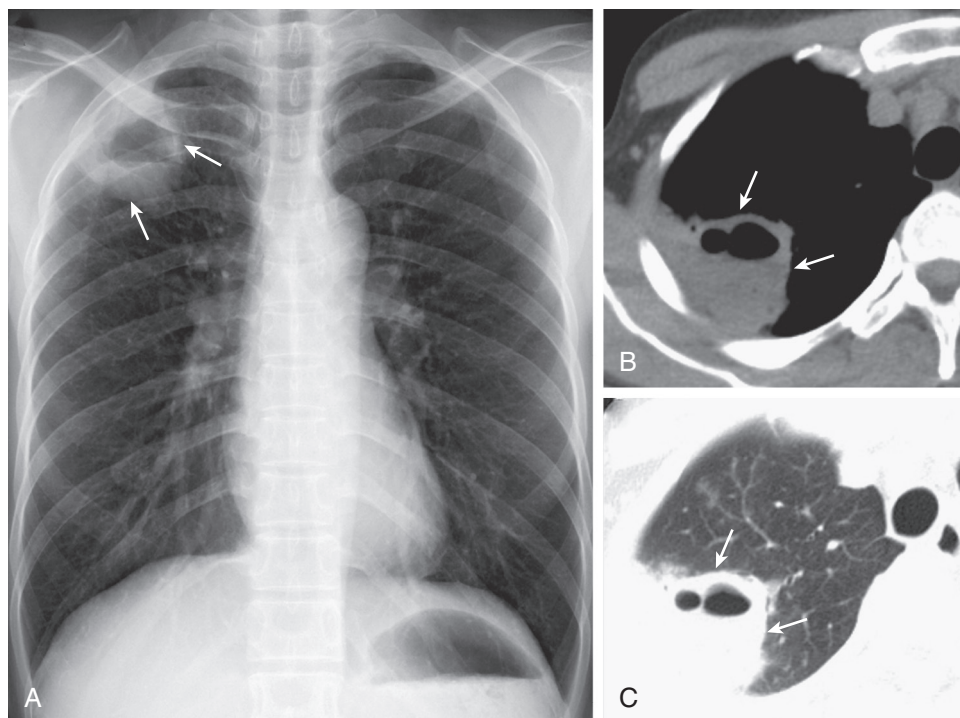
eFigure 33-10 *Mycoplasma pneumoniae* pneumonia: unilateral bronchopneumonia. Frontal (A) and lateral (B) chest radiographs in a patient with *Mycoplasma pneumoniae* pneumonia show patchy right lower lobe consolidation (arrows) consistent with bronchopneumonia, but nonspecific with regard to the specific microbiologic etiology. (Courtesy Michael Gotway, MD.)



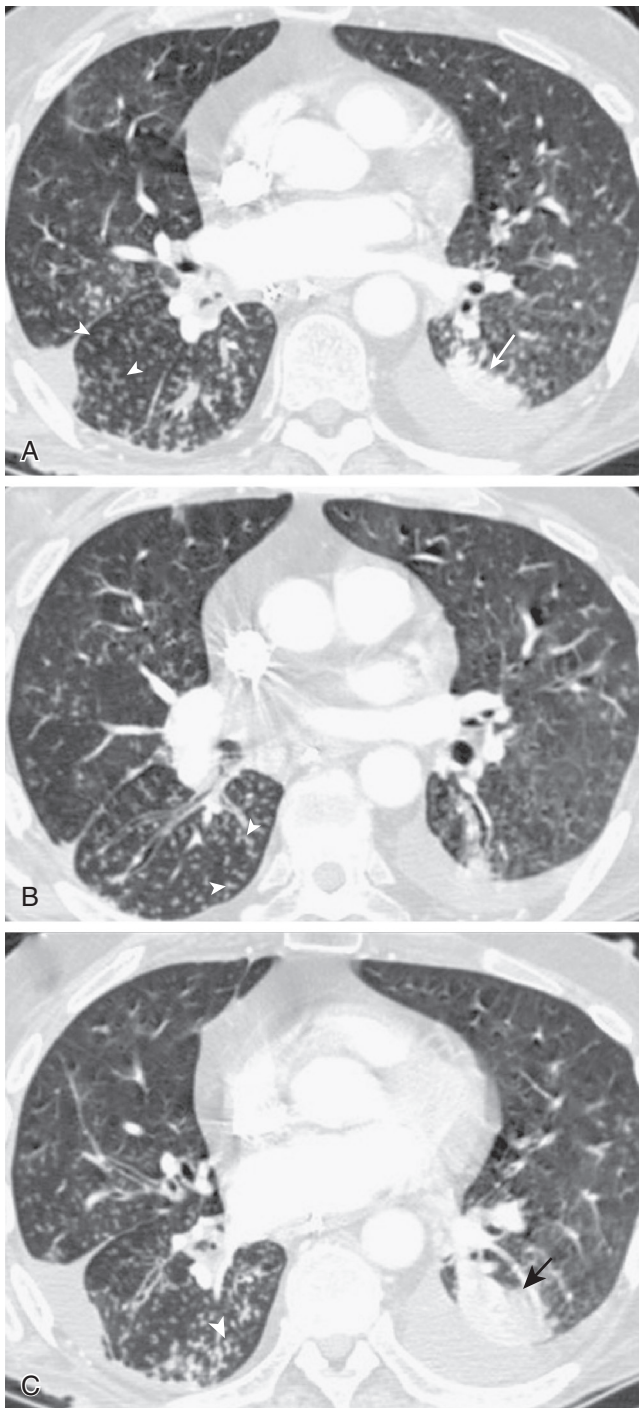
eFigure 33-11 Methicillin-resistant *Staphylococcus aureus* pneumonia. **A,** Frontal chest radiograph in a patient subsequently proven to have methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia shows left lung consolidation (*arrows*) with internal lucency consistent with necrosis and cavitation. **B,** Axial chest CT displayed in lung windows shows left lower lobe consolidation with internal lucency (*arrows*) consistent with a necrotic pneumonia. The patient recovered following antibiotic therapy. (Courtesy Michael Gotway, MD.)



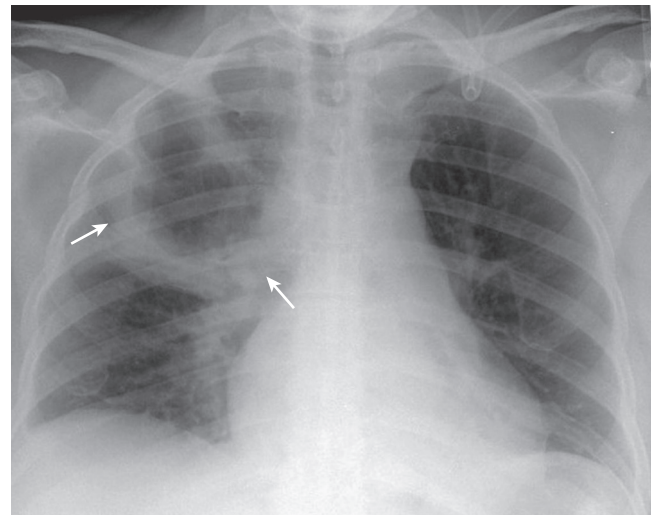
eFigure 33-12 *Klebsiella pneumoniae* bronchopneumonia. **A**, Frontal chest radiograph shows patchy right lower lobe opacity (arrows). **B–E**, Axial chest CT through the lower lobes displayed in lung windows shows patchy nodular opacities (arrows) consistent with bronchopneumonia but not specific for a microbial etiology. (Courtesy Michael Gotway, MD.)



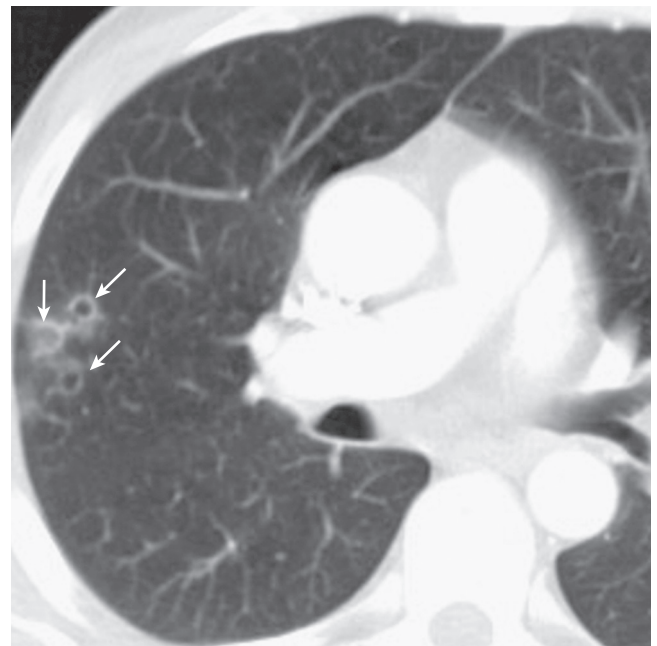
eFigure 33-13 *Klebsiella pneumoniae* lung abscess. **A**, Frontal chest radiograph shows a subpleural right apical cavity (arrows) with an air-fluid level consistent with a pulmonary abscess. Axial chest CT displayed in soft tissue (**B**) and lung (**C**) windows shows a nonspecific cavity (arrows) consistent with a pulmonary abscess but not specific for a specific microbiologic etiology. (Courtesy Michael Gotway, MD.)



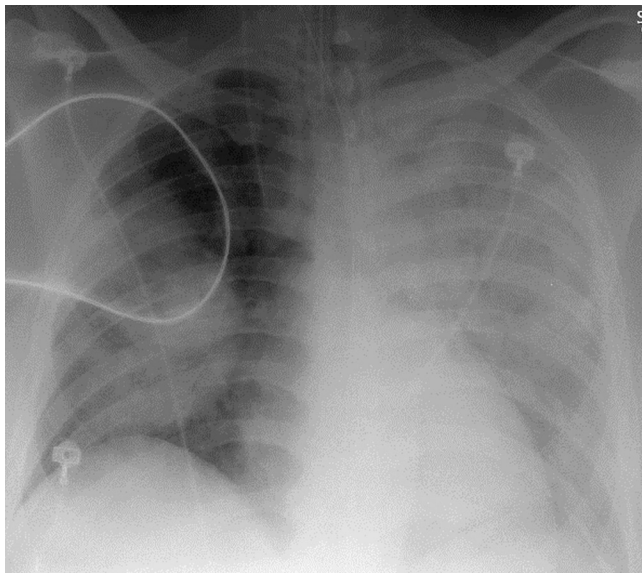
eFigure 33-14 *Pseudomonas aeruginosa* bronchopneumonia. A–C, Axial chest CT through the lower lobes displayed in lung windows shows nodular consolidation (A and C, arrows) and numerous small centrilobular nodules with branching morphologies consistent with “tree-in-bud” opacities (arrowheads). (Courtesy Michael Gotway, MD.)



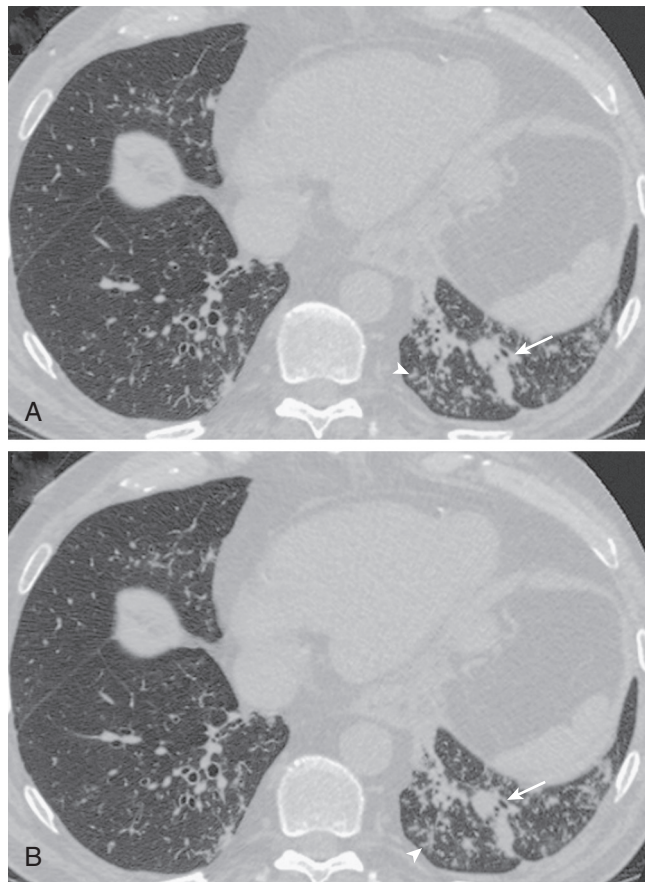
eFigure 33-15 *Pseudomonas aeruginosa* cavitary pneumonia. Frontal chest radiograph in a patient with *P. aeruginosa* pneumonia shows a large right upper lobe thick-walled cavity (arrows). (Courtesy Michael Gotway, MD.)



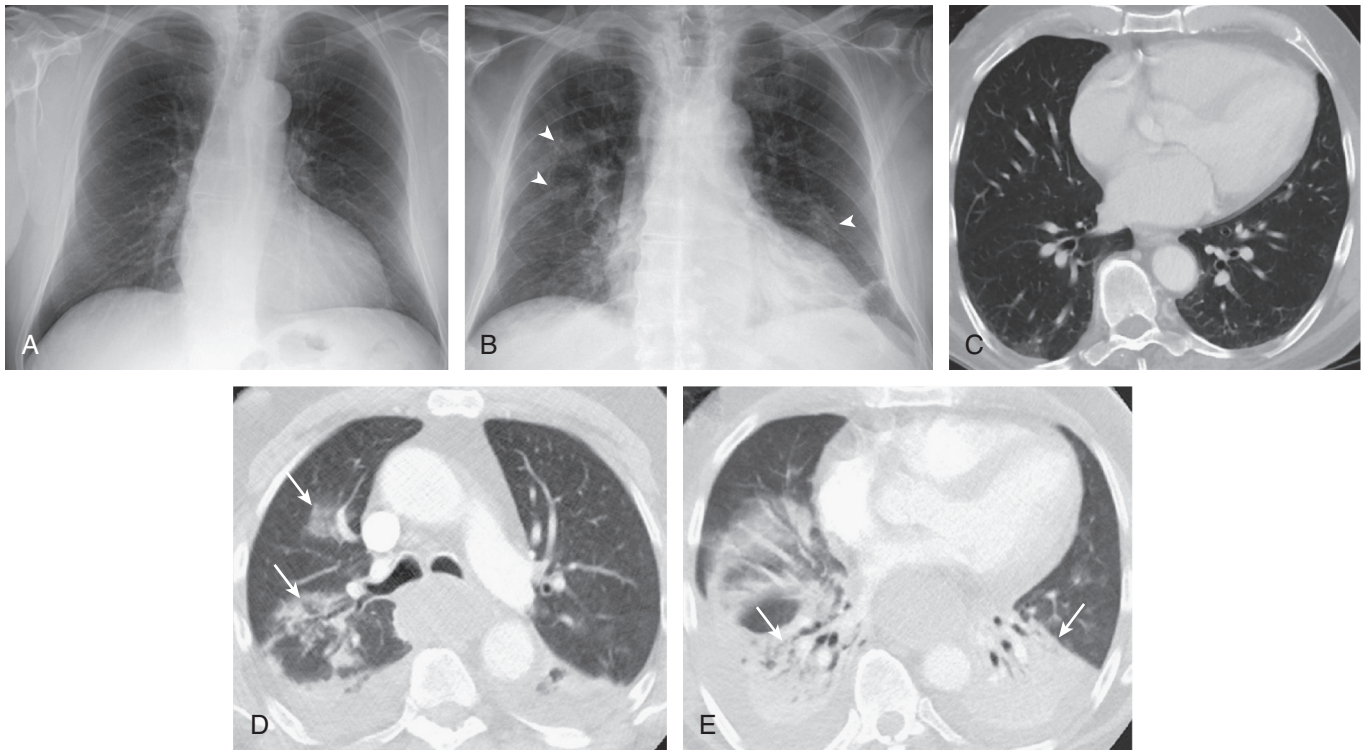
eFigure 33-16 *Pseudomonas aeruginosa* cavitary pneumonia. Axial chest CT displayed in lung windows of a patient with *P. aeruginosa* pneumonia shows several small, relatively thin-walled peripheral right upper lobe cavities (arrows). (Courtesy Michael Gotway, MD.)



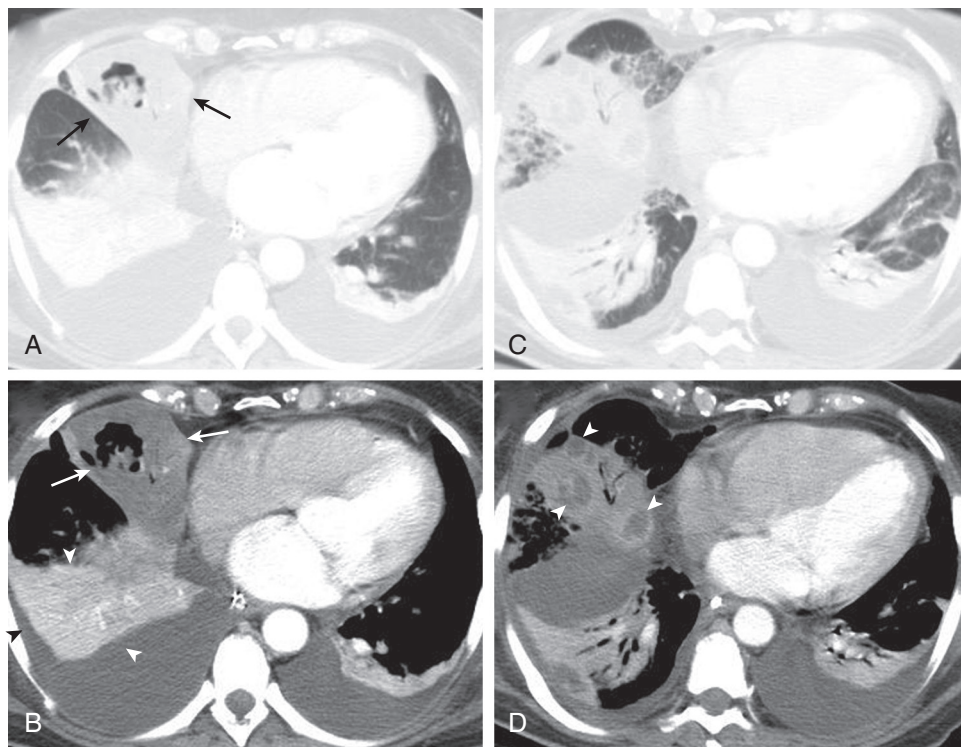
eFigure 33-17 *Legionella pneumophila* pneumonia: multilobar pneumonia. Frontal chest radiograph in a patient with *Legionella* pneumonia and respiratory failure shows left-greater-than-right multilobar consolidation. (Courtesy Michael Gotway, MD.)



eFigure 33-18 Aspiration pneumonia: bronchopneumonia/bronchiolitis appearance at chest CT. A and B, Axial chest CT through the lower lobes displayed in lung windows in a patient with swallowing dysfunction shows numerous small centrilobular nodules, some with branching morphologies (arrowheads), and peribronchial consolidation (arrows). The imaging appearance is consistent with bronchopneumonia, but not specific for aspiration. Note resemblance of this CT appearance with *P. aeruginosa* pneumonia (see eFig. 33-14), *Haemophilus influenzae* pneumonia (see eFig. 33-8B), and pneumococcal bronchopneumonia (see eFig. 33-6). (Courtesy Michael Gotway, MD.)



eFigure 33-19 Aspiration bronchopneumonia: rapid appearance of new lung opacity at imaging and dependent lung involvement. Frontal chest radiograph performed at admission (**A**) shows clear lungs; several days later, following a witnessed aspiration event, the radiograph (**B**) shows development of multifocal peribronchial nodular foci (*arrowheads*). **C**, Lower thoracic images from an abdominal CT scan several weeks before **A** and **B** shows only minimal basal atelectasis. **D** and **E**, Axial chest CT through the lower lobes performed immediately following **B** shows peribronchial consolidation (**D**, *arrows*) and extensive lower lobe, dependent consolidation (**E**, *arrows*). Note volume loss, evidenced by posterior displacement of the major fissures. (Courtesy Michael Gotway, MD.)



eFigure 33-20 Anaerobic pneumonia. **A–D**, Axial chest CT in a patient with polymicrobial anaerobic pneumonia shows multifocal consolidation in the right middle lobe (**A** and **B**, *arrows*) and bilateral lower lobes. The soft tissue window images show the right middle lobe consolidation to be hypovascular; compare attenuation characteristics of the right middle lobe opacity (*arrows*, **B**) with the appearance of the lower lobe consolidation (*arrowheads*, **B**). After several days, the poorly defined hypovascular right middle lobe consolidation (**B**, *arrows*) evolved into discrete abscesses (**D**, *arrowheads*). (Courtesy Michael Gotway, MD.)

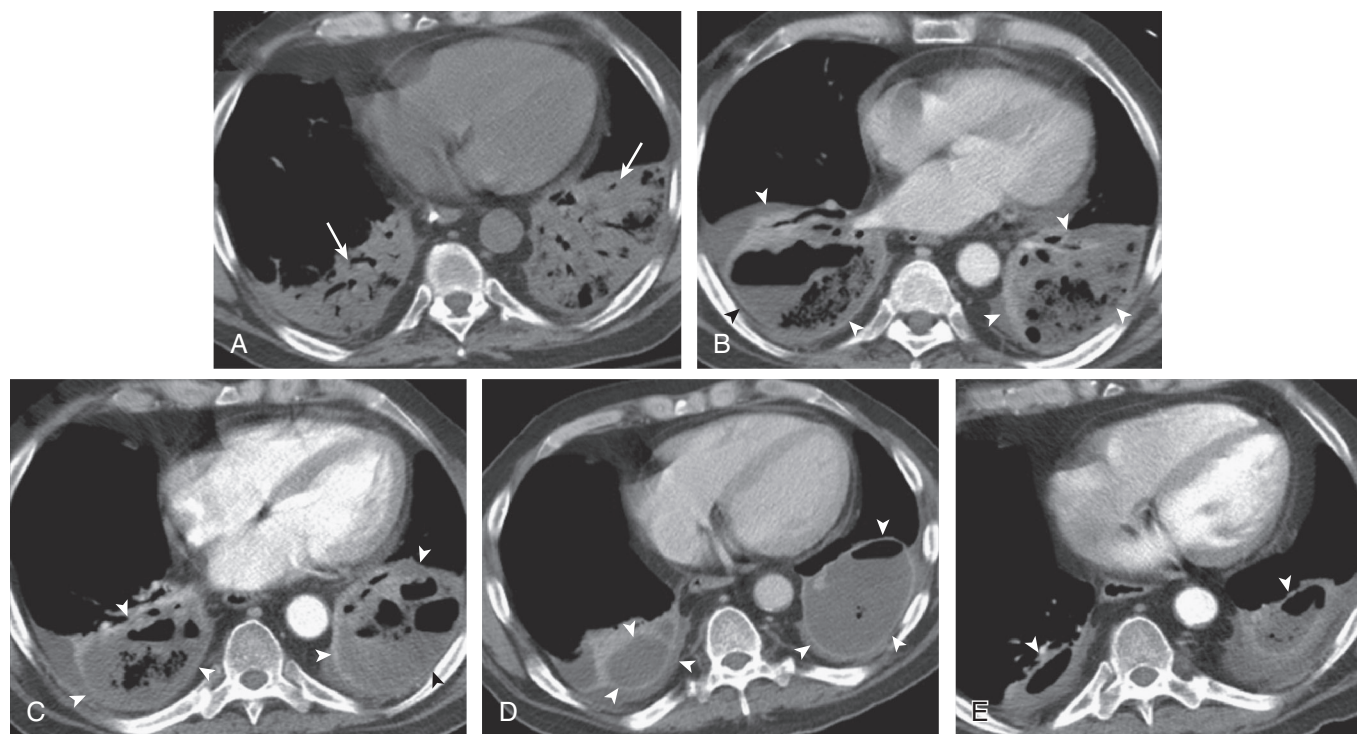


Figure 33-21 Evolution of pulmonary aspiration into lung abscess. **A**, Axial chest CT displayed in soft tissue windows performed shortly following a witnessed aspiration event shows extensive bilateral lower lobe consolidation (arrows). **B**, Contrast-enhanced chest CT performed several days following **A** shows developing necrosis and cavitation (arrowheads) within the lower lobe consolidation. **C** and **D**, Repeat contrast-enhanced chest CT performed over the ensuing week following **A** and **B** shows maturation of frank bilateral lower lobe pulmonary abscesses (arrowheads); note well-defined, enhancing walls surrounding these gas and fluid collections. **E**, Axial enhanced chest CT following 3 weeks of antibiotic therapy shows partial resolution of the bilateral lower lobe pulmonary abscesses (arrowheads). (Courtesy Michael Gotway, MD.)

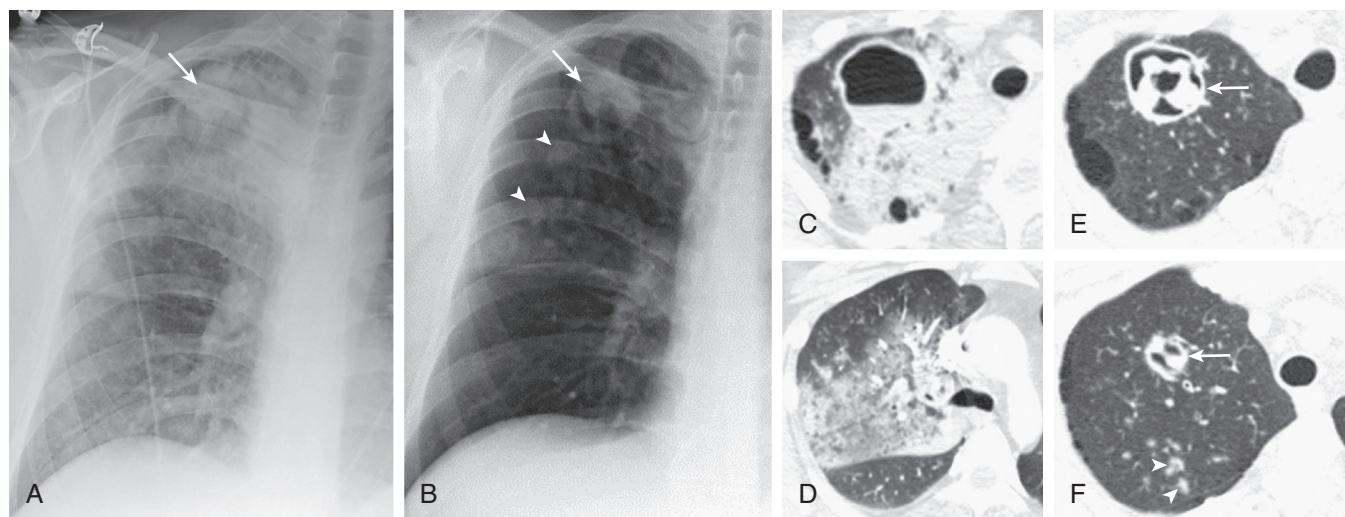
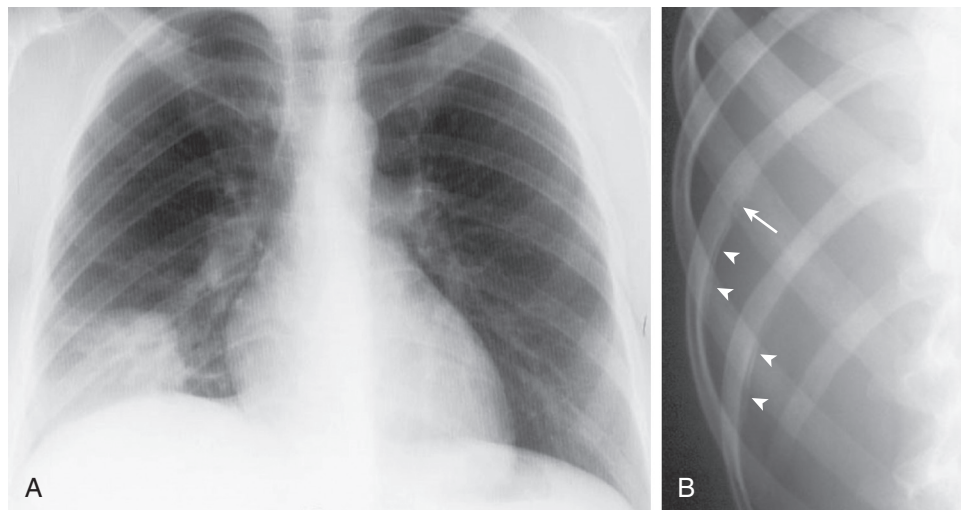
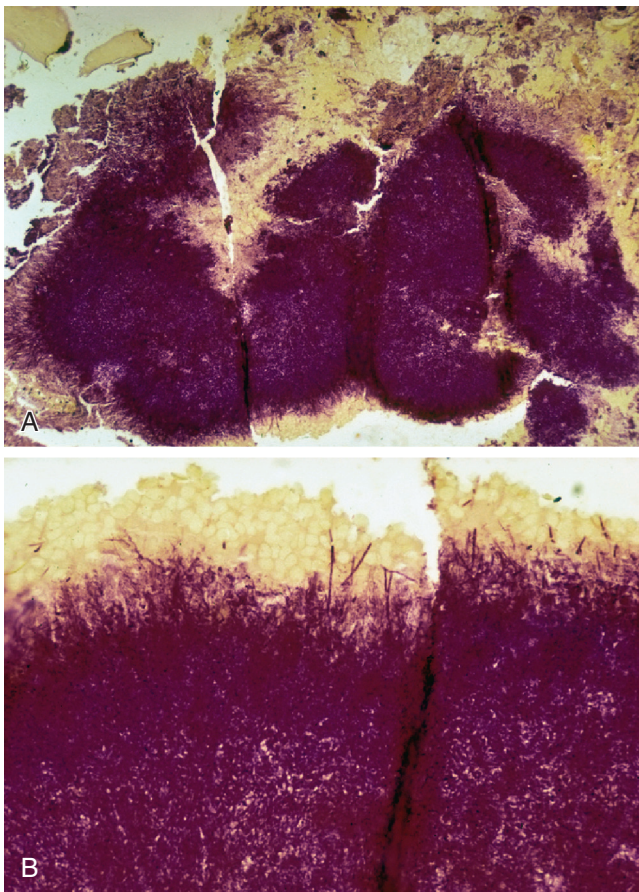


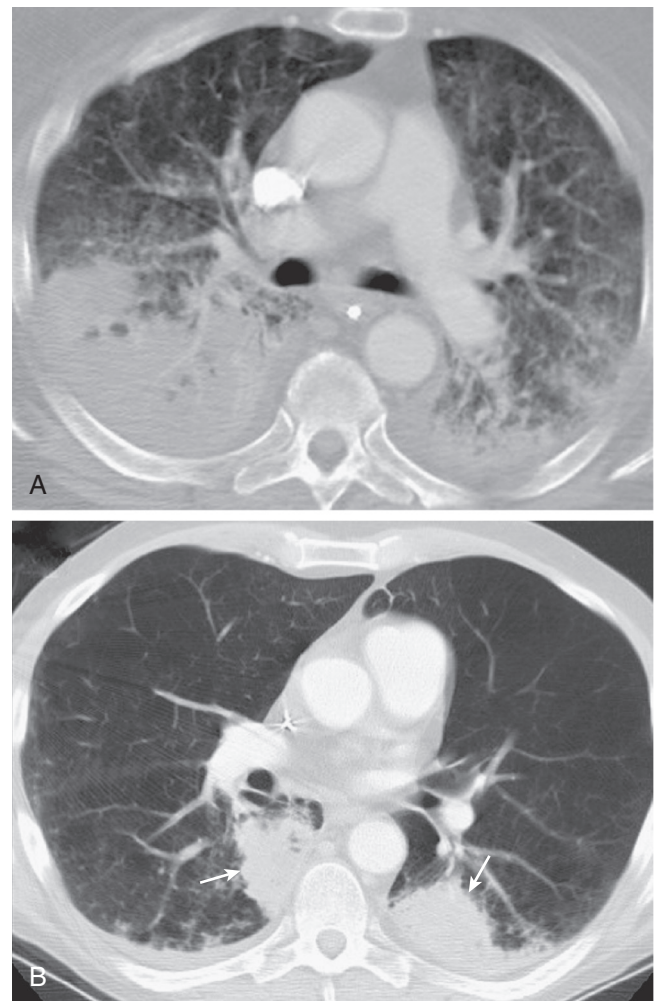
Figure 33-22 Actinomycosis: cavitory nodule. **A**, Frontal chest radiograph shows right upper lobe consolidation and a poorly defined nodular opacity (arrow). **B**, Frontal chest radiograph 2 weeks following **A** shows resolution of the right upper lobe consolidation, now exposing a dominant cavitory right apical nodule with internal opacity (arrow), and small surrounding nodules (arrowheads). **C** and **D**, Axial chest CT displayed in lung windows performed within 1 day of the presenting chest radiograph (**A**) shows the right apical opacity as a cavitory nodule with an internal air-fluid level; surrounding ground-glass opacity and consolidation are present, as seen on the chest radiograph (**A**). **E** and **F**, Chest CT displayed in lung windows performed the same day as **B** shows the dominant right apical opacity with complex internal architecture (arrows) and confirms small surrounding nodules. Biopsy of this lesion recovered *Actinomyces israelii*. (Courtesy Michael Gotway, MD.)



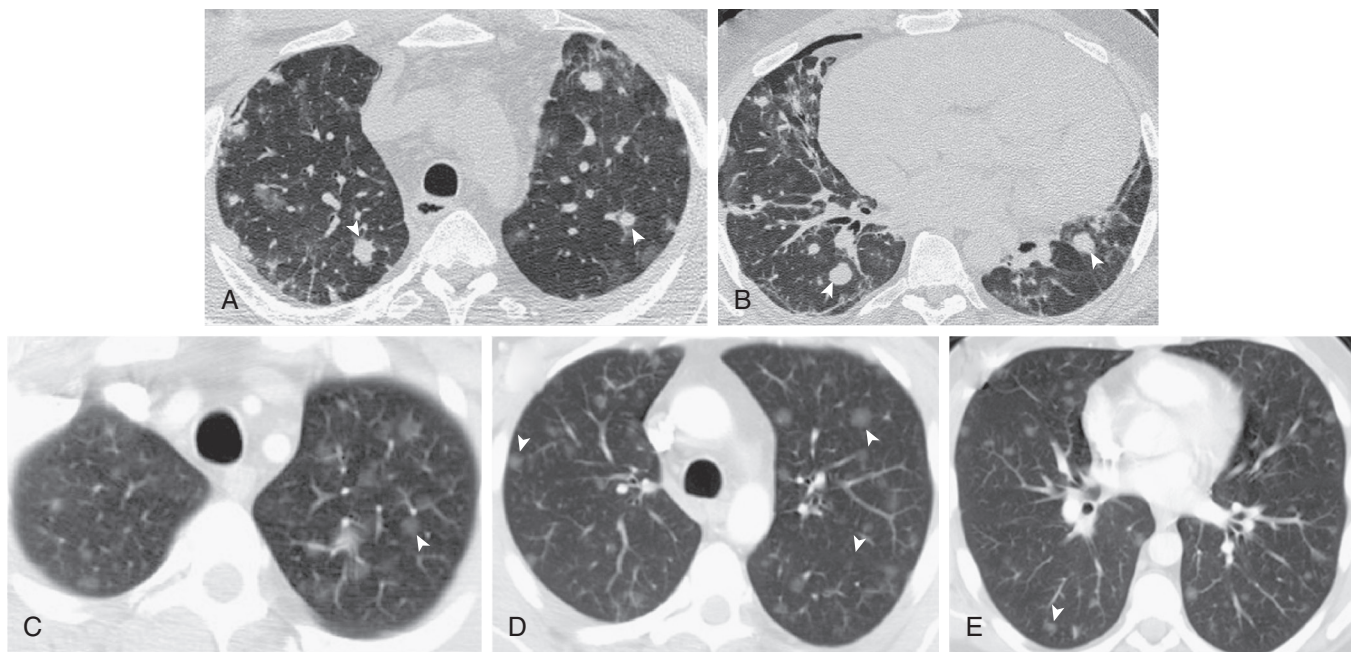
eFigure 33-23 Actinomycosis: chest wall involvement. **A**, Frontal chest radiograph shows a right lower lung mass. This finding is nonspecific. **B**, Rib detail radiograph shows subtle periosteal reaction (arrowheads) with erosion of the inferior rib cortex (arrow) consistent with chest wall invasion. Biopsy of the right lung mass recovered *Actinomyces israelii*. (Courtesy Michael Gotway, MD.)



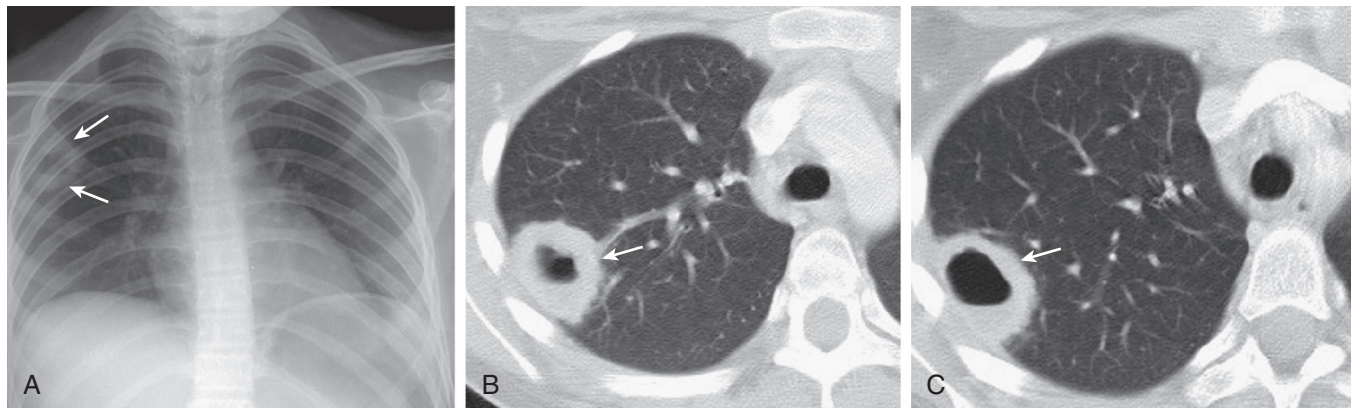
eFigure 33-24 Gram stain of an actinomycotic sulfur granule. **A**, Original magnification $\times 100$; **B**, original magnification $\times 400$. (Courtesy Michael Gotway, MD.)



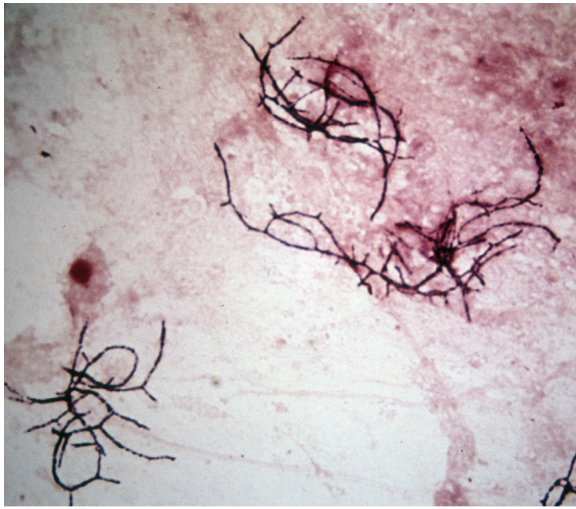
eFigure 33-25 *Nocardia asteroides* pulmonary infection: consolidation. **A**, Axial chest CT shows extensive bilateral lower lobe consolidation and more anteriorly located interstitial thickening and ground-glass opacity. The right lower lobe consolidation was cavitary at a more inferior level. **B**, Axial chest CT in a different patient shows bilateral lower lobe masslike opacities (arrows); biopsy of the left lower lobe lesion recovered *Nocardia asteroides*. (Courtesy Michael Gotway, MD.)



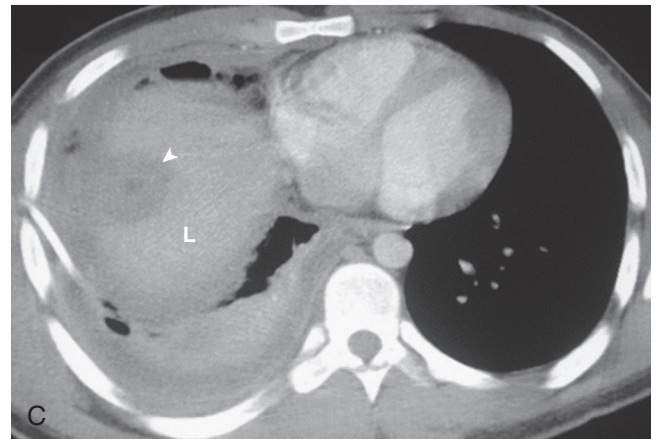
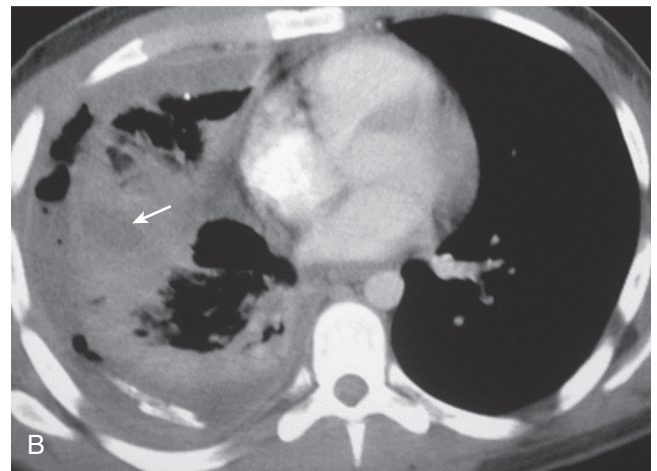
eFigure 33-26 *Nocardia asteroides* pulmonary infection: multiple nodules. **A and B,** Axial chest CT in an immunosuppressed renal transplant recipient shows multiple bilateral nodules, many of which are solid-appearing (arrowheads), due to *N. asteroides*. **C–E,** Axial chest CT in another immunosuppressed renal transplant recipient shows ground-glass opacity nodules (arrowheads), also shown to be due to *N. asteroides*. (Courtesy Michael Gotway, MD.)



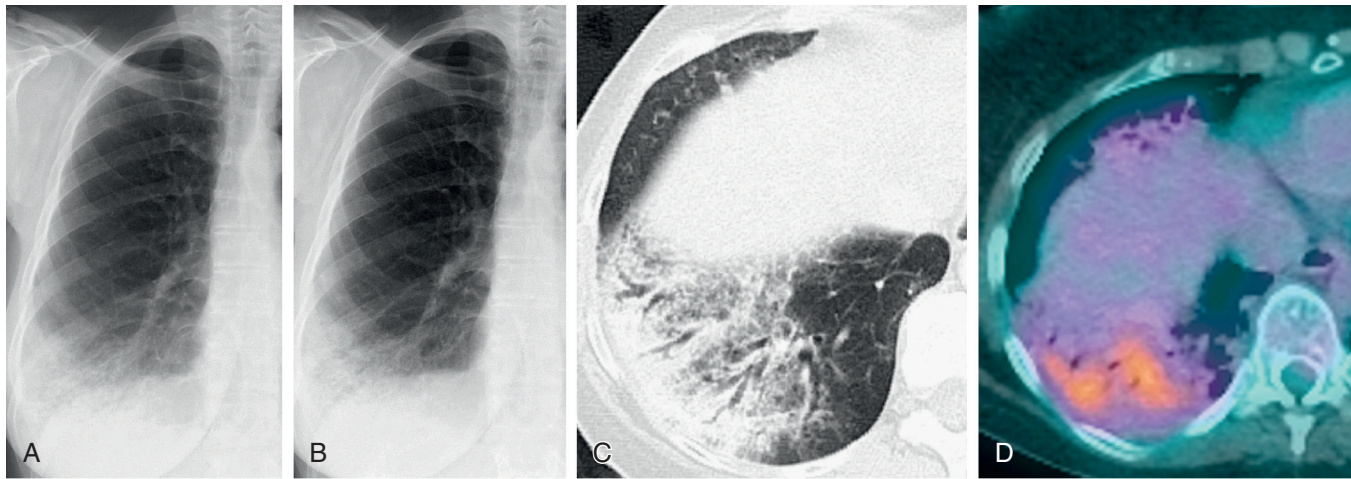
eFigure 33-27 *Nocardia asteroides* pulmonary infection: abscess. **A,** Frontal chest radiograph shows a poorly defined opacity (arrows) in the subpleural right upper lobe. **B and C,** Axial chest CT displayed in lung windows shows a subpleural right upper lobe cavity (arrows) containing an air-fluid level. This lesion is nonspecific in appearance and could be the result of a number of infections, but *N. asteroides* was recovered at biopsy. (Courtesy Michael Gotway, MD.)



eFigure 33-28 Modified acid-fast stain of sputum containing *Nocardia asteroides* shows filamentous branching organisms. (Courtesy Michael Gotway, MD.)



eFigure 33-29 An infectious cause of “nonresponding” pneumonia: amebic pleuropulmonary infection. **A**, Frontal chest radiograph in a 23-year-old man with fever and chest pain shows right lower lobe consolidation and a small-to-moderate right pleural effusion, presumed to represent pneumonia and parapneumonic effusion. **B** and **C**, Axial chest CT after the patient failed to respond to therapy for community-acquired pneumonia was performed to assess right pleural fluid drainage following thoracostomy tube placement (the thoracostomy tube is visible posteriorly in **B**). Chest CT performed through the right lower lung (**B**) shows consolidation with central low-attenuation (arrow), the latter consistent with a pulmonary abscess or area of necrosis. Chest CT through the extreme lung base and upper abdomen (**C**) shows a low attenuation focus (arrowhead) in the cranial liver (L), also consistent with an abscess. The liver and lung lesions are in close proximity to one another, suggesting that the liver lesion may have extended through the diaphragm to produce the lung findings; such behavior is typical of an amebic abscess. Further evaluation revealed that the patient recently immigrated to the United States from Mexico, and stool analysis recovered *Entamoeba histolytica* trophozoites. (Courtesy Michael Gotway, MD.)



eFigure 33-30 Noninfectious “nonresponding” pneumonia: invasive mucinous adenocarcinoma (formerly referred to as mucinous bronchioloalveolar carcinoma). **A**, Frontal chest radiograph in a patient with persistent shortness of breath shows right lower lobe consolidation. The patient was treated with broad-spectrum antibiotics for presumed community-acquired pneumonia. **B**, Repeat frontal chest radiograph 3 months following **A** shows no change in the appearance of the right lower lobe opacity. **C**, Axial chest CT through the right lung base shown in lung windows reveals relatively nonspecific subpleural consolidation with air bronchograms and reticulation associated with ground-glass opacity. **D**, Fused FDG-PET image shows the right lower lobe opacity to be hypermetabolic. Bronchoscopic evaluation did not disclose a specific diagnosis for the persistent right lower lobe opacity. Resection of the right lower lobe proved invasive mucinous adenocarcinoma. (Courtesy Michael Gotway, MD.)

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VENTILATOR-ASSOCIATED PNEUMONIA

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequent intensive care unit (ICU)-acquired infection among patients who are treated with mechanical ventilation.^{1,2} In contrast to infections of other organs (e.g., urinary tract and skin), for which mortality ranges from 1% to 4%, the mortality rate for VAP, defined as pneumonia occurring more than 48 hours after the onset of mechanical ventilation, ranges from 20% to 50%, and can even be higher when lung infection is caused by high-risk pathogens.¹⁻³ Although the attributable mortality rate for VAP is still debated, good evidence indicates that VAP prolongs the duration of mechanical ventilation and of the ICU stay.^{1,2} Approximately 50% of all antibiotics prescribed in an ICU are administered for respiratory tract infections.⁴ Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, rapid identification of infected patients and accurate selection of antimicrobial agents are important clinical goals.¹ Agreement is lacking, however, about the appropriate diagnostic, therapeutic, and preventive strategies for VAP.

PATHOGENESIS

Multiple defense mechanisms protect the normal human respiratory tract from infection. Examples include anatomic barriers, such as the glottis and larynx; cough reflexes; constituents of tracheobronchial secretions; mucociliary clearance; epithelial lining fluid and surfactant components; cell-mediated and humoral immunity; a phagocytic system that involves alveolar macrophages and recruited neutrophils; and both humoral and cell-mediated adaptive immunity.^{5,6} When these coordinated components function properly, invading microbes are eliminated and clinical disease is avoided. When these defenses are impaired, or if they are overcome by a high inoculum of organisms or organisms of unusual virulence, pneumonitis results.

As suggested by the infrequent association of VAP with bacteremia, most of these infections appear to result from aspiration of potential pathogens that have colonized the

mucosal surfaces of the oropharyngeal airways, the dental plaque, and/or the paranasal sinuses.⁶ Endotracheal intubation not only compromises the natural barrier between the oropharynx and trachea, but also facilitates the entry of bacteria into the lungs by pooling and leakage of contaminated secretions around the endotracheal tube cuff from the subglottic area to below the true vocal cords.⁷ Contaminated secretions leak into the lungs of most intubated patients and may be facilitated by the supine position.⁸ Moreover, biofilm formation on the inner and outer surfaces of the endotracheal tube provides a protected environment for pathogens. Bacterial aggregates in biofilm dislodged during suctioning are dangerous for the lung, because they are difficult to clear by host immune defenses and difficult to eradicate with antibiotics.

Tracheobronchial colonization with *gram-negative bacilli* (GNB) usually precedes the onset of VAP. Risk factors for tracheobronchial colonization appear to be the same as those that favor pneumonia and include advanced age, more severe illness, longer hospitalization, prior or concomitant use of antibiotics, malnutrition, endotracheal intubation, depressed level of consciousness, immune suppression from disease or medication, azotemia, underlying pulmonary disease, and longer duration of mechanical ventilation.^{1,9,10} Experimental studies have linked some of these risk factors with changes in adherence of GNB to respiratory epithelial cells. Although formerly attributed to loss of cell surface fibronectin, these changes in adherence also reflect alterations of cell surface carbohydrates. Bacterial adhesins and prior antimicrobial therapy appear to facilitate the process. Interestingly, Enterobacteriaceae usually appear first in the oropharynx, whereas *Pseudomonas aeruginosa* more often appear first in the trachea.¹¹

Although the stomach can be a reservoir for potential pneumonia pathogens, the gastropulmonary route of infection is not the primary route of infection in most critically ill patients.¹² Progression of colonization from the stomach to the upper respiratory tract with subsequent episodes of VAP could not be demonstrated in several studies, and efforts to eliminate the gastric reservoir with antimicrobial therapy without decontaminating the oropharyngeal cavity have generally failed to prevent VAP.¹³ In fact, there is more

than one potential pathway for colonization of the oropharynx and trachea in such a setting, including cross infection from the hands of health care personnel and contaminated respiratory therapy equipment. Patient care activities, such as bathing, oral care, tracheal suctioning, enteral feeding, and tube manipulations, provide many opportunities for transmission of pathogens when meticulous infection control practices are not followed.

EPIDEMIOLOGY

INCIDENCE

The exact incidence of VAP varies widely depending on the case definition of pneumonia and the population being evaluated. For example, the incidence of VAP may be up to two times greater in patients when diagnosis is made by qualitative or semiquantitative sputum cultures rather than quantitative cultures of lower respiratory tract secretions. However, studies have confirmed that nosocomial pneumonia is considerably more frequent in ventilated patients than in other ICU patients, with the incidence being as much as 6-fold to 20-fold higher in ventilated patients than in nonventilated patients.^{14,15} VAP manifests in 9% to 27% of all intubated patients, and its incidence increases with duration of intubation.¹⁰ The risk of VAP is highest early in the course of the hospital stay—estimated to be 3% per day during the first 5 days of intubation, 2% per day during days 5 to 10 of intubation, and 1% per day after day 10.¹⁰ Because most mechanical ventilation is short term, approximately half of all episodes of VAP develop within the first 4 days of mechanical ventilation. In a large epidemiologic study, independent predictors of VAP determined by multivariate analysis were as follows: primary admitting diagnosis of burns, trauma, central nervous system disease, respiratory disease, or cardiac disease; mechanical ventilation during the preceding 24 hours; witnessed aspiration; and use of paralytic agents. Exposure to antibiotics conferred protection, but this effect was attenuated over time.¹⁰ According to four studies, the VAP rate was higher in patients with *acute respiratory distress syndrome* (ARDS) than in other ventilated patients, affecting between 34% and more than 70% of patients with ARDS and often leading to the development of sepsis, multiple organ failure, and death.¹⁶⁻¹⁹

Attributable Mortality, Morbidity, and Costs

In mechanically ventilated patients in the ICU, those with VAP appear to have a 2-fold to 10-fold higher risk of death than those without pneumonia. Although these statistics indicate that VAP can be lethal, previous studies have not clearly demonstrated that pneumonia is responsible for the higher mortality rate of these patients. It is often difficult to determine whether ICU patients with severe underlying illness would have survived if they had not developed VAP. VAP, however, has been recognized in several case-control studies or studies using multivariate analysis as an important prognostic factor for different groups of critically ill patients.²⁰⁻²⁶ Based on a multistate progressive disability model that appropriately handled VAP as a time-dependent event in a high-quality database of 2873 mechanically

ventilated patients, VAP-attributable mortality was found to be 8.1% overall.²⁷ These results are consistent with those obtained in other observational studies using also multistate model and causal analysis, detecting a relatively limited VAP-attributable mortality.^{28,29}

Other factors beyond the simple development of VAP, such as the severity of the disease, the adequacy of antimicrobial therapy, or the responsible pathogens, may be more important determinants of outcome for patients in whom pneumonia develops. Indeed, it may be that VAP increases mortality only in the subset of patients with intermediate severity of illness,²⁴ when initial treatment is inappropriate,³⁰⁻³⁴ and/or in patients with VAP caused by high-risk pathogens, such as *P. aeruginosa*.³⁵ Patients with very low severity and early-onset pneumonia caused by organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae* have excellent prognoses with or without VAP, whereas very ill patients with late-onset VAP would be unlikely to survive.

Studies have shown clearly that patients with VAP have prolonged duration of mechanical ventilation and lengthened ICU and hospital stay than do patients who do not have VAP.^{1,2} Summarizing available data, VAP appears to extend the ICU stay by at least 4 days, with the attributable ICU length of stay being longer for medical than surgical patients and for patients infected with “high-risk” rather than “low-risk” organisms.³⁶ The prolonged hospitalization of patients with VAP underscores the considerable financial burden imposed on the health care system by the development of VAP.^{37,38}

Etiologic Agents

Microorganisms responsible for VAP differ according to the population of ICU patients, the duration of hospital and ICU stays, and the specific diagnostic methods used to establish the responsible pathogens. A number of studies have shown that GNB cause many of the respiratory infections in this setting.^{1,2} The data from 24 studies conducted on ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens, confirmed these results: GNB represented 58% of recovered organisms (Fig. 34-1). The predominant GNB were *P. aeruginosa* and *Acinetobacter* spp, followed by *Proteus* spp, *Escherichia coli*, *Klebsiella* spp, and *H. influenzae*. A relatively high rate of gram-positive pneumonias was also reported in those studies, with *Staphylococcus aureus* involved in 20% of the cases. Many episodes of VAP are caused by multiple pathogens.³⁹

Underlying diseases may predispose patients to infection with specific organisms. Patients with chronic obstructive pulmonary disease are at increased risk for *H. influenzae*, *Moraxella catarrhalis*, or *S. pneumoniae* infections; cystic fibrosis increases the risk for *P. aeruginosa* and/or *S. aureus* infections, while trauma and neurologic disease increase the risk for *S. aureus* infection. The causative agent for pneumonia also differs among ICU surgical populations, with 18% of the nosocomial pneumonias caused by *Haemophilus* spp or pneumococci, particularly in patients with trauma. *Haemophilus* spp and pneumococci are much less frequent causes of pneumonia in other surgical ICU patients, such as those with malignancy, organ transplants, or abdominal or cardiovascular surgery.^{1,2}

Despite somewhat different definitions of early-onset pneumonia, varying from onset of less than 3 to less than

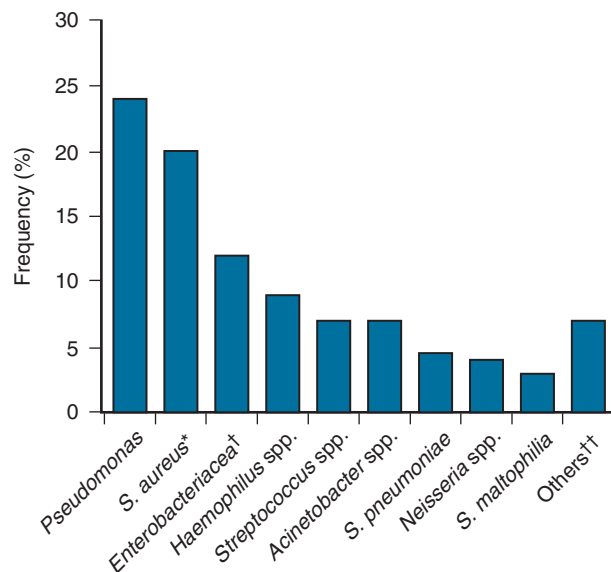


Figure 34-1 Etiology of ventilator-associated pneumonia (VAP) as documented by bronchoscopic techniques in 24 studies for a total of 1689 episodes and 2490 pathogens. *Haemophilus influenzae*, *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), and susceptible Enterobacteriaceae are found in early-onset VAP, whereas *Pseudomonas aeruginosa*, *Acinetobacter* spp, methicillin-resistant *S. aureus* (MRSA), and multiresistant gram-negative bacilli are more frequent in late-onset VAP. *MRSA, 56%; MSSA, 44%. †*Klebsiella* spp, 16%; *Escherichia coli*, 24%; *Proteus* spp, 22%; *Enterobacter* spp, 19%; *Serratia* spp, 12%; *Citrobacter* spp, 5%. ††Including *Corynebacterium* spp, *Moraxella* spp, and *Enterococcus* spp. (Adapted from Chastre J, Fagon JY: Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 165:867–903, 2002.)

7 days, high rates of infection with *H. influenzae*, *S. pneumoniae*, methicillin-sensitive *S. aureus*, or susceptible Enterobacteriaceae were consistently found in early-onset VAP, whereas *P. aeruginosa*, *Acinetobacter* spp, methicillin-resistant *S. aureus* (MRSA), and multiresistant GNB were significantly more frequent in late-onset VAP.¹ The different pattern of distribution of etiologic agents between early- and late-onset VAP is linked to prior antimicrobial therapy in many patients with late-onset VAP. When multivariate analysis was used to identify risk factors for VAP caused by drug-resistant bacteria such as MRSA, *P. aeruginosa*, *Acinetobacter baumannii*, and/or *Stenotrophomonas maltophilia* in 135 consecutive episodes of VAP, only three variables remained significant: duration of mechanical ventilation of longer than 7 days before onset of VAP, prior antibiotic use, and prior use of broad-spectrum drugs (third-generation cephalosporins, fluoroquinolones, and/or imipenem).⁴⁰ Not all studies have confirmed this distribution pattern, and in some studies the most common pathogens associated with early-onset VAP were *P. aeruginosa*, MRSA, and *Enterobacter* spp, with similar pathogens associated with late-onset VAP.^{41,42} These findings might be explained in part by prior hospitalization and the use of antibiotics before transfer to the ICU.

Legionella spp, anaerobes, fungi, viruses, and even *Pneumocystis jirovecii* are also potential causative agents, but these microbes are not commonly found when pneumonia is acquired during mechanical ventilation. Several of these causative agents, including viruses, might be more common than reported, because they are difficult to identify.^{43,44} Iso-

lation of fungi, most frequently *Candida* species, at significant concentrations poses interpretative problems. Invasive disease has been reported in VAP, but yeasts are isolated more frequently from respiratory tract specimens in the absence of apparent disease. The use of the commonly available respiratory sampling methods (bronchoscopic or nonbronchoscopic) in ventilated patients is not sufficient to make the diagnosis of *Candida* pneumonia, and evidence of lung tissue invasion is also needed.⁴⁵

DIAGNOSIS

Two diagnostic strategies can be used when VAP is suspected, typically when a patient has new or progressive radiographic infiltrates and clinical findings suggesting infection, such as the new onset of fever, purulent sputum, leukocytosis, and a decline in arterial oxygenation. The first strategy is to treat every patient clinically suspected of having a pulmonary infection with new antibiotics, even when the likelihood of infection is low, arguing that several studies showed that immediate initiation of appropriate antibiotics was associated with reduced mortality.⁴⁶ The second strategy is to use an invasive diagnostic approach based on quantitative cultures of distal respiratory specimens obtained using bronchoscopic or nonbronchoscopic techniques, such as *bronchoalveolar lavage* (BAL) or a *protected specimen brush* (PSB), in order to improve the identification of patients with true VAP and facilitate decisions about whether or not to treat with antibiotics.^{2,47,48} Although no consensus exists on the best diagnostic strategy for patients clinically suspected of having VAP, the goal of each strategy is to institute early appropriate antibiotic therapy in patients with true VAP and to withhold it in others.^{1,2}

THE CLINICAL DIAGNOSTIC STRATEGY

With the clinical strategy, all patients suspected of having VAP are treated with new antibiotics. The selection of appropriate empirical therapy is based on risk factors and local microbiologic and resistance patterns, and involves qualitative testing to identify possible pathogens. The initial antimicrobial therapy is adjusted according to culture results or clinical response (Fig. 34-2). Antimicrobial treatment is discontinued only if the following three criteria are fulfilled on day 3: (1) clinical diagnosis of VAP is unlikely (there are no definite infiltrates found on chest radiography at follow-up and no more than one of the three following findings is present: temperature greater than 38.3° C, leukocytosis or leukopenia, and purulent tracheobronchial secretions) or an alternative noninfectious diagnosis is confirmed; (2) tracheobronchial aspirate culture results are nonsignificant; and (3) severe sepsis or shock is not present.⁴⁹

This clinical approach has two undisputable advantages: first, no specialized microbiologic techniques are required, and, second, the risk of missing a patient who needs antimicrobial treatment is minimal when all suspected patients are treated with new antibiotics.

While the simple qualitative culture of *endotracheal aspirates* (EAs) is a technique with a high percentage of

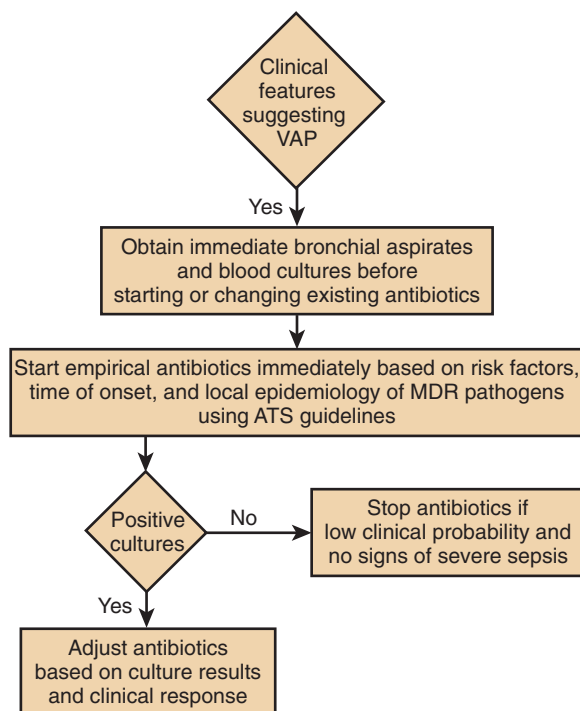


Figure 34-2 Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of ventilator-associated pneumonia (VAP) managed with the “clinical” strategy. ATS, American Thoracic Society; MDR, multi-drug resistant.

false-positive results due to bacterial colonization of the proximal airways in many ICU patients, studies using quantitative culture techniques suggest that the diagnostic accuracy of EA cultures is similar to the accuracy of more invasive techniques.⁵⁰ The inherent advantages of these techniques are that they are less invasive, they are available to nonbronchoscopists, they are less expensive than bronchoscopy, they are less likely to compromise gas exchange, and they can be performed in patients with small endotracheal tubes. The disadvantages include the potential sampling errors inherent in a blind technique and lower specificity for distinguishing airway colonization from true pneumonia.

Another option when using the clinical approach is to follow the strategy described by Singh and colleagues,⁵¹ in which decisions regarding initial antibiotic therapy are based on a clinical score constructed from seven variables, the *Clinical Pulmonary Infection Score* (CPIS). Patients with a CPIS greater than 6 are considered to have VAP and are treated with antibiotics for 10 to 21 days; if the CPIS score is 6 or less, antibiotics are discontinued after 3 days (Fig. 34-3). Such an approach avoids prolonged treatment of patients who have a low likelihood of infection, while allowing immediate treatment of patients who are more likely to have VAP. Two conditions must be fulfilled when using this strategy. First, the selection of initial antimicrobial therapy should be based on the most common microbes responsible for VAP at each institution. For example, ciprofloxacin would not be the right choice in hospitals with a high prevalence of MRSA infections. Second, physicians should reevaluate antimicrobial treatment on day 3, when susceptibility patterns of the microorganisms recovered from

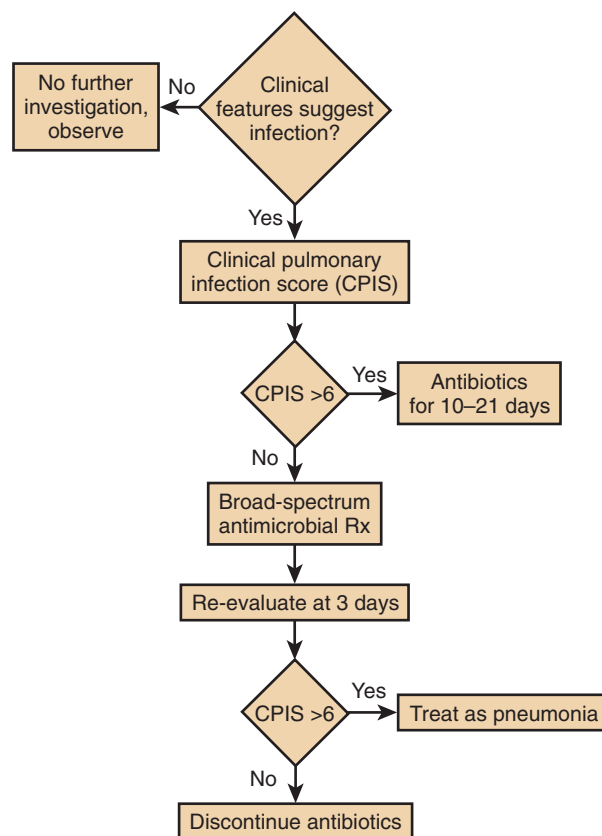


Figure 34-3 Diagnostic and therapeutic strategy applied to patients managed with a “clinical” strategy guided by a clinical pulmonary infection score (CPIS).⁵¹

pulmonary secretions are available, in order to select treatment with a narrower spectrum antibiotic.

THE INVASIVE DIAGNOSTIC STRATEGY

With the invasive strategy, quantitative cultures of lower respiratory secretions (BAL or PSB collected with or without a bronchoscope) are used to define both the presence of pneumonia and the etiologic pathogen. Growth above a threshold concentration is required to make a diagnosis of VAP and determine the causative microorganisms.⁵² Growth below the threshold is assumed to be due to colonization or contamination. Using this strategy, therapeutic decisions are made according to a strict protocol, using the results of direct examination of distal pulmonary samples and results of quantitative cultures in deciding whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy (Fig. 34-4).

Quantitative cultures of BAL and/or PSB specimens consistently yield fewer microorganisms above the diagnostic threshold than are present in qualitative cultures of tracheal aspirates.^{2,53} Thus, when therapeutic decisions are based on these data, fewer patients are treated with antibiotics and a potentially narrower spectrum of therapy is used than when using the clinical approach, thereby limiting the emergence and dissemination of drug-resistant strains and minimizing antibiotic-related toxicity.^{48,54,55}

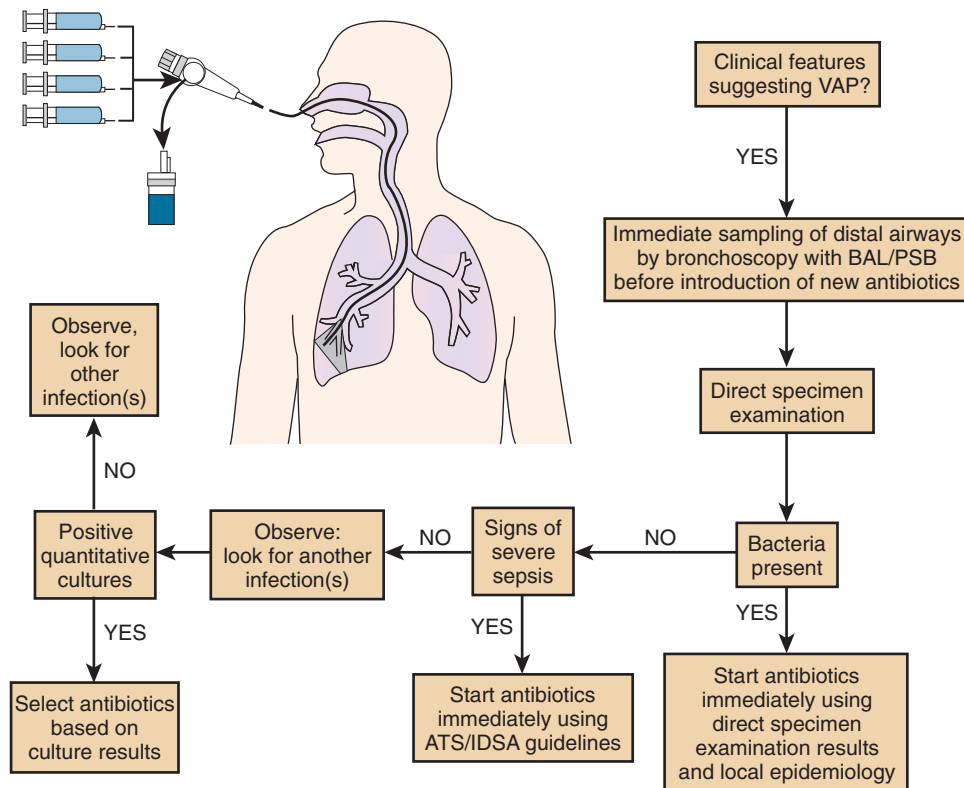


Figure 34-4 Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of ventilator-associated pneumonia managed according to the “invasive” strategy. ATS, American Thoracic Society; BAL, bronchoalveolar lavage; IDSA, Infectious Diseases Society of America; PSB, protected specimen brush.

Another compelling argument in favor of the invasive strategy is that this approach directs attention away from the lungs as the source of fever when BAL/PSB quantitative culture results are negative. Many ICU patients with negative bronchoscopic cultures have other potential sites of infection, such as the wounds, the urinary tract, or intravascular catheters, that need to be identified in order to avoid delays in initiating appropriate treatment.⁵⁶

The accuracy of bronchoscopic techniques is questionable in patients who have received prior antibiotics, particularly when new antibiotics are introduced after the onset of the symptoms suggestive of nosocomial pneumonia and before pulmonary secretions are collected. When pneumonia develops in patients who have been receiving systemic antibiotics for several days, cultures of respiratory secretions are not modified in a major way as long as the samples for culture are obtained before initiating the new antibiotics, because the bacteria responsible for the new infection are likely to be resistant to the antibiotics that were used previously.^{57,58} However, if samples for microbiologic cultures of pulmonary secretions are obtained after initiation of new antibiotics in patients suspected of having VAP, the newly initiated antibiotics can increase the number of false-negative results, regardless of the way in which the secretions are obtained.⁵⁸⁻⁶⁰

One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. The sampling area is usually selected based on the location of the radiographic infiltrate or on the bronchoscopic identification of a pulmonary segment that has purulent secretions.⁶¹ In patients with diffuse pulmo-

nary infiltrates or minimal new changes in a previously abnormal chest radiograph, determining the correct segment to sample can be difficult. In such cases, sampling should be directed to the area where endobronchial abnormalities are maximal. Because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be given priority for sampling.⁶²

SUMMARY OF THE EVIDENCE

Aside from decision-analysis studies and a single retrospective study,⁶³⁻⁶⁵ five trials to date have used a randomized scheme to assess the effect of a diagnostic strategy on antibiotic use and outcome in patients suspected of having VAP.^{31,32,48,66,67} In three randomized studies conducted in Spain, no differences were found in mortality and morbidity when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP.^{31,32,66} These studies were relatively small, ranging from 51 to 88 patients. Antibiotics were continued in all patients despite negative cultures, thereby offsetting the potential advantage of the specific diagnostic test in patients with suspected VAP. Several prospective studies have concluded that antibiotics can be stopped in patients with negative quantitative cultures, without adversely affecting the recurrence of pneumonia and mortality.^{47,55,68,69}

In a randomized French study of 413 patients, those managed with an invasive strategy using BAL and/or PSB had a lower mortality rate on day 14, lower sepsis-related

organ failure assessment scores on day 3 and 7, and less antibiotic use.⁴⁸ Of note, in the invasive strategy group, 22 nonpulmonary infections were diagnosed, whereas in the clinical strategy group, only five were diagnosed, suggesting that physicians using the clinical strategy overdiagnosed VAP and thereby failed to identify nonpulmonary infections. A randomized trial conducted by the Canadian Critical Care Trials Group investigated the effect of different diagnostic approaches on outcomes of 740 patients suspected of having VAP.⁶⁷ There was no difference in the 28-day mortality rate in patients in whom BAL was used compared with those in whom endotracheal aspiration was used as the diagnostic strategy. The BAL group and the endotracheal aspiration group also had similar rates of targeted antibiotic therapy on day 6, days alive without antibiotics, and maximum organ dysfunction scores. Unfortunately, information about how the decision algorithms were followed in the two diagnostic arms once cultures were available was not provided, raising uncertainties about how de-escalation of antibiotic therapy was pursued in patients with negative BAL cultures. The potential benefit of using a diagnostic tool such as BAL for safely restricting unnecessary antimicrobial therapy in such a setting can be obtained only when decisions regarding antibiotics are closely linked to bacteriologic results, including both direct examination and cultures of respiratory specimens.

TREATMENT

Antimicrobial therapy of patients with VAP is a two-stage process. The first stage involves administering broad-spectrum antibiotics to avoid inadequate treatment of patients with true bacterial pneumonia.¹ The second stage focuses on trying to achieve this objective without overus-

ing or abusing antibiotics. In general, the first goal can be accomplished by identifying patients with pneumonia in a rapid fashion and starting therapy with an empirical regimen that is likely to treat the most common etiologic agents in a particular institution. This requires that the initial antibiotic choice be driven by knowledge of the likely etiologic pathogens, and the local patterns of antimicrobial resistance. The second goal involves stopping therapy in patients with a low probability of VAP, focusing and narrowing treatment once the etiologic agent is known, switching to monotherapy after day 3 whenever possible, and shortening the duration of therapy to 7 to 8 days in most patients, as determined by the patient's clinical response and information about the bacteriology (Table 34-1).

INITIAL TREATMENT

Failure to initiate prompt appropriate therapy (i.e., using an agent to which the etiologic organism is sensitive, with the optimal dose and route of administration) has been consistently linked with increased mortality in patients with VAP.^{33,46,70} Due to the emergence of multiresistant GNB, such as *P. aeruginosa*, extended-spectrum β -lactamase-producing Enterobacteriaceae, and carbapenemase-producing *Klebsiella pneumoniae*, and the increasing role of gram-positive bacteria, such as MRSA, empirical treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of VAP.^{2,3} The choice of agents should be based on local patterns of antimicrobial susceptibility and anticipated side effects, and should take into account the antibiotics that the patients have received within the prior 2 weeks, striving not to use the same antimicrobial classes, if possible.^{71,72} Having current knowledge about local bacteriologic patterns can increase the

Table 34-1 Proposed Strategy for Managing Antimicrobial Therapy in Patients with Ventilator-Associated Pneumonia	
Proposed Strategy	Rationale
Step 1: Start therapy using broad-spectrum antibiotics	Due to the emergence of multiresistant GNB, such as <i>P. aeruginosa</i> and ESBL-producing GNB in many institutions, and the increasing role of MRSA, empirical treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of VAP.
Step 2: Stop therapy if the diagnosis of infection becomes unlikely	The goal is to ensure that ICU patients with true bacterial infection receive immediate appropriate treatment. However, this can result in more patients receiving antimicrobial therapy than necessary, because clinical signs of infection are nonspecific.
Step 3: Use narrower spectrum antibiotics once the etiologic agent is identified	For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures are available, either because an anticipated organism (e.g., <i>P. aeruginosa</i> and <i>Acinetobacter</i> spp. or MRSA) was not recovered, or because the organism isolated is sensitive to a more narrow-spectrum antibiotic than used in the initial regimen.*
Step 4: Use pharmacokinetic-pharmacodynamic data to optimize treatment	Clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic and pharmacodynamic properties of the agents selected for treatment.
Step 5: Switch to monotherapy on days 3 to 5	There are no clinical benefits to using a regimen combining two antibiotics for more than days 3 to 5, provided that initial therapy was appropriate, the clinical course appears favorable, and microbiologic data do not point to a very difficult-to-treat microorganism.
Step 6: Shorten the duration of therapy	Reducing duration of therapy in patients with VAP has led to good outcomes with less antibiotic use. Prolonged therapy leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP.

*Chastre J, Fagon JY: Pneumonia in the ventilator-dependent patient. In Tobin MJ, editor: *Principles and practice of mechanical ventilation*, New York, 1994, McGraw-Hill, pp 857–890; and Rello J, Vidaur L, Sandiumenge A, et al: De-escalation therapy in ventilator-associated pneumonia. *Crit Care Med* 32:2183–2190, 2004.

ESBL, extended-spectrum β -lactamase; GNB, gram-negative bacteria; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

likelihood that appropriate initial antibiotic treatment will be prescribed.^{73,73a} Only patients with early-onset infection and no specific risk factors, such as prolonged duration of hospitalization, admission from a health care–related facility, and recent prolonged antibiotic therapy, can be treated with a relatively narrow-spectrum drug, such as a nonpseudomonal third-generation cephalosporin.¹

Several published reports have demonstrated the need to adjust the target dose of antimicrobial agents used in treating severe VAP to the individual patient's pharmacokinetics and the putative bacterial pathogens' susceptibilities.^{74–83c} Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (e.g., aminoglycosides and fluoroquinolones) from those that kill by a time-dependent mechanism (e.g., β -lactams and vancomycin). Altered pharmacokinetics secondary to an increase in the volume of distribution in critically ill patients can result in insufficient serum β -lactam concentrations when standard doses are administered, emphasizing the need to monitor peak and trough levels of antibiotics carefully when treating resistant pathogens.^{83,84} Higher dosing regimens than those usually recommended and/or prolonged duration of infusion are frequently needed in such circumstances. Development of a priori dosing algorithms based on minimal inhibitory concentrations, patient creatinine clearance and weight, and the clinician-specified area under the inhibitory curve target might be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for use of antimicrobial agents.

AVOIDING THE OVERUSE OF ANTIBIOTICS

The need to ensure that ICU patients with true bacterial infections promptly receive an appropriate antibiotic regimen can lead to many more patients receiving antimicrobial therapy than is actually necessary, because clinical signs of infection are relatively nonspecific. Thus, when a clinical approach to VAP is used, it is important to perform serial clinical and microbiologic evaluations, and to reevaluate therapy after 48 to 72 hours so that it can be stopped if infection is unlikely. To accomplish this, all diagnostic strategies that are designed for managing patients with a clinical suspicion of VAP should make explicit the decision tree that is used to identify patients with a low probability of infection, in whom therapy can be stopped when infection appears improbable.

For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures are available, if no resistant organism (e.g., *P. aeruginosa*, *Acinetobacter* spp or MRSA) is recovered or if the isolated organism is sensitive to a narrower spectrum antibiotic. For example, vancomycin and linezolid should be stopped if MRSA is not identified, unless the patient is allergic to β -lactams or has developed an infection caused by a gram-positive microorganism. Very-broad-spectrum agents, such as carbapenems, piperacillin-tazobactam, and/or cefepime, should also be restricted to patients with infection caused by pathogens that are only susceptible to these agents. Clinicians must be aware that the emergence of resistant variants may lead to treatment failure when third-generation cephalosporins

are chosen to treat infections caused by *Enterobacter*, *Citrobacter*, *Morganella morganii*, indole-positive *Proteus*, and *Serratia* spp, due to the presence of inducible β -lactamases, even if the isolate is initially characterized as susceptible.

The most common reason to use combination therapy in initial management of patients with VAP is to achieve synergy in treating *P. aeruginosa* or other difficult-to-treat GNB. However, antibiotic synergy has been shown to be valuable only in vitro and in patients with neutropenia⁸⁵ or bacteremic infection,⁸⁶ which is uncommon in VAP. A recent meta-analysis evaluated all prospective randomized trials of β -lactam monotherapy compared with β -lactam/aminoglycoside combination regimens in 7586 patients with sepsis, of whom at least 1200 patients had VAP.⁸⁷ The clinical success rates were similar with monotherapy versus combination therapy, and combination therapy had no advantage in the treatment of *P. aeruginosa* infections. Importantly, combination therapy did not prevent the emergence of antimicrobial resistance during treatment, but it was associated with a significantly higher rate of nephrotoxicity. Based on these data, therapy can be switched to monotherapy in most patients after 3 or 5 days, as long as initial therapy is appropriate, the clinical course is favorable, and microbiologic data do not identify a difficult-to-treat microorganism with a high in vitro minimal inhibitory concentration, as is found with some lactose-nonfermenting GNB.

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Most patients with VAP who receive appropriate antimicrobial therapy have a good clinical response within the first 6 days.^{88–90} Prolonged therapy promotes colonization with antibiotic-resistant bacteria, which may lead to a recurrent episode of VAP. A multicenter randomized controlled trial of 401 patients with microbiologically proven VAP showed that the clinical outcomes of patients who received appropriate empirical therapy for 8 days were similar to those of patients who received therapy for 15 days.⁹¹ A trend to greater rates of relapse for short-duration therapy was seen when the etiologic agent was *P. aeruginosa* or *Acinetobacter* spp, but the clinical outcomes were indistinguishable. These results were confirmed in two later studies, including a prospective randomized trial of 290 patients evaluating an antibiotic discontinuation policy.^{92,93} Possible exceptions to this recommendation include immunosuppressed patients, those whose initial antimicrobial treatment was not appropriate for the causative microorganisms, and patients whose infection was caused by nonfermenting GNB and had no improvement in clinical signs of infection.

Many clinicians remain hesitant about prescribing antibiotics for fewer days for patients with VAP, and they prefer to customize antibiotic duration based on the clinical course of the disease and/or using serial determinations of a biomarker such as procalcitonin. The rationale for using a biomarker to tailor antibiotic treatment duration relies on evidence that the inflammatory response is often proportional to infection severity. When that response is absent or low, it might be logical to discontinue antibiotics earlier. Thus, adapting antimicrobial treatment duration to procalcitonin kinetics seems reasonable and has been demonstrated as useful in several randomized trials targeting

patients with acute respiratory infection, including five trials conducted in the ICU.⁹⁴⁻¹⁰⁰

AEROSOLIZED THERAPY

Because insufficient delivery of antibiotics to the site of infection in patients with VAP may lead to clinical and microbiologic failures, efforts to increase pulmonary delivery of antimicrobial agents have been investigated. Delivering drugs via aerosolization is one approach, assuming that this technique actually promotes higher drug concentrations at the infected site. By achieving high pulmonary antibiotic concentrations, this mode of administration could increase the antibacterial activity of concentration-dependent antibiotics, such as aminoglycosides, or provide bactericidal activity of antibiotics in infections caused by pathogens of impaired sensitivity. By limiting systemic exposure, it could also allow the administration of antibiotics with high systemic toxicity, such as aminoglycosides and polymyxins.

Several studies, based on nebulizers with improved technology, have renewed the interest in aerosolized antibiotic therapy for VAP.¹⁰¹⁻¹⁰⁴ In anesthetized piglets on mechanical ventilation for severe *E. coli* bronchopneumonia, amikacin lung tissue concentrations were markedly higher following aerosolization as compared to intravenous administration.¹⁰⁵ In a study using a device with a vibrating plate and multiple apertures to produce an aerosol of amikacin, the nebulized drug was well-distributed in the lung parenchyma, with high tracheal and alveolar levels and serum concentrations below the renal toxicity threshold.¹⁰⁶ Aerosolized amikacin was well-tolerated, without any severe adverse event, and patients who received amikacin twice daily required significantly fewer other antibiotics than patients given placebo.¹⁰⁷

Aerosolized polymyxin is also being used to treat infections caused by multidrug-resistant GNB, mainly *Acinetobacter baumannii*, *P. aeruginosa*, and carbapenemase-producing *K. pneumoniae*, with mixed results.^{103,104,108,109} In a randomized trial of 100 patients with VAP due to GNB (predominantly multi-drug resistant *A. baumannii* and/or *P. aeruginosa*), patients treated with a combination of systemic antibiotics and nebulized colistin had a higher rate of favorable microbiologic outcome compared with patients treated with systemic antibiotics alone (microbiologic eradication or presumed eradication 61% vs. 38%), but there were no differences in the rate of favorable clinical outcomes (51% vs. 53%).¹⁰⁴ In a retrospective case-control study of 86 patients with VAP due to multidrug-resistant GNB (predominantly *A. baumannii*) treated with a combination of intravenous and aerosolized colistin compared with intravenous colistin alone, there was only a trend toward improved rates of clinical cure, pathogen eradication, and mortality in the patients who received aerosolized and intravenous colistin.¹⁰³

Thus, although recent investigations emphasize the potential contribution of aerosolized antibiotics to treat VAP as an adjunctive therapy to intravenous antibiotics, the clinical impact of such a strategy has not been established. At present, aerosolized antibiotics can only be recommended to treat patients with multidrug-resistant VAP for which no effective intravenous antibiotics are available.

Large prospective trials are needed to evaluate the potential usefulness of this therapeutic modality.

PREVENTION

Because VAP is associated with increased morbidity, longer hospital stay, increased health care costs, and higher mortality rates, prevention is an important goal.^{1,110,111}

CONVENTIONAL INFECTION CONTROL APPROACHES

The design of the ICU has a direct effect on the potential for nosocomial infections. Adequate space and lighting, properly functioning ventilation systems, and appropriate handwashing facilities all lead to lower infection rates.¹¹² It is important to note, however, that upgrading the physical environment does not reduce the infection rate unless the attitudes and practices of health care personnel are also improved. In any ICU, one of the most important factors is the health care staff, including the number, quality, and motivation of medical, nursing, and ancillary members. The team should include a sufficient number of nurses to minimize their movement from one patient to another and to avoid having them work under constant pressure.¹¹³⁻¹¹⁶ The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every opportunity. It is clear that careful monitoring, decontamination, and compliance with guidelines for the use of respiratory equipment all reduce the incidence of nosocomial pneumonia.¹¹⁷ Handwashing and hand rubbing with alcohol-based solutions remain the most important components of effective infection control practices in the ICU.^{118,119}

Environmental and patient-oriented microbiologic monitoring facilitates the early recognition of colonization and infection, and has been associated with significant reductions in nosocomial infection rates.¹²⁰ The focal point for infection control activities in the ICU is a surveillance system designed to establish and maintain a database that identifies endemic rates of nosocomial infections. This information facilitates the recognition of epidemics, when infection rates rise above the endemic threshold for a specific type of nosocomial infection.

An antibiotic policy that restricts the prescription of broad-spectrum agents and inappropriate antibiotics is of major importance. Better use of antibiotics in the ICU can be achieved by implementing strict guidelines, avoiding the treatment of patients who do not have bacterial infections, using narrow-spectrum antibiotics whenever possible, and reducing the duration of treatment.^{121,122} Similarly, transfusion of red blood cells and other allogenic blood products should follow a strict policy, because several studies have identified exposure to allogenic blood products as a risk factor for postoperative infection and pneumonia.^{123,124}

SPECIFIC PROPHYLAXIS AGAINST VENTILATOR-ASSOCIATED PNEUMONIA

Specific strategies aimed at reducing the duration of mechanical ventilation (a major risk factor for VAP), such as improved methods of sedation,¹²⁵ use of protocols to

facilitate and accelerate weaning,¹²⁵⁻¹²⁷ using adequate levels of positive end-expiratory pressure,¹²⁸ and using intensive insulin therapy to control blood glucose¹²⁹ are integral parts of any infection control program. All are based on the application of strict protocols. Similarly, non-invasive positive-pressure ventilation using a face mask should be employed whenever possible.¹³⁰

Some very simple, safe, inexpensive, and logical measures may have major effects on the frequency of VAP in mechanically ventilated patients.^{1,119} These include avoiding nasal insertion of endotracheal and gastric tubes,¹³¹ maintaining the endotracheal tube cuff pressure above 20 cm H₂O to prevent leakage of bacteria around the cuff into the lower respiratory tract,^{132,133} promptly reintubating patients who are likely to fail extubation,¹³⁴ keeping patients in the semirecumbent position, especially when enteral nutrition is used,¹³⁵ removing tubing condensate,¹³⁶ and providing adequate oral hygiene with an antiseptic such as chlorhexidine.¹³⁷⁻¹³⁹

Continuous or intermittent suctioning of oropharyngeal secretions has been proposed as a means to avoid chronic aspiration of secretions through the tracheal cuff of intubated patients. Aspiration of subglottic secretions requires the use of a specially designed endotracheal tube with a separate lumen that opens into the subglottic region. Thirteen randomized controlled trials with a total of 2442 randomized patients have studied aspiration of subglottic secretions for the prevention of VAP.¹⁴⁰⁻¹⁴⁸ Of the 13 studies, 12 reported a reduction in VAP rates in the subglottic secretion drainage arm. When the results were combined in a meta-analysis, the overall risk ratio for VAP was 0.55 (95% CI, 0.46-0.66; $P < 0.00001$) with no heterogeneity, and the use of subglottic secretion drainage was associated with reduced ICU length of stay, decreased duration of mechanical ventilation, and increased time to first episode of VAP.¹⁴⁸ However, there was no effect on hospital or ICU mortality.¹⁴⁸ Preliminary data in animal models and from small randomized human studies support the hypothesis that an endotracheal tube coated externally and internally with a potent antiseptic product such as silver could have a sustained antimicrobial effect within the proximal airways and block biofilm formation at its surface.¹⁴⁹⁻¹⁵⁴ Such a device was evaluated in a large, randomized, multicenter, single-blind trial.¹⁵⁵ The authors conclude that the new device was able to lower the VAP frequency from 7.5% for the control group to 4.8% for the group receiving the silver-coated endotracheal tube. The silver-coated tube, however, did not reduce mortality rates, the duration of intubation, hospital length of stay, or the frequency or severity of adverse effects.

Gastric colonization by potentially pathogenic organisms increases with decreasing gastric acidity.¹⁵⁶ Thus, medications that decrease gastric acidity (antacids, *histamine*₂ [H₂] blockers) can increase the gastric bacterial burden and increase the risk of VAP; medications that do not affect gastric acidity (e.g., sucralfate) do not appear to increase this risk. Several meta-analyses of more than 20 randomized trials have evaluated the risk for VAP associated with methods used to prevent gastrointestinal bleeding in critically ill patients.¹⁵⁷ The largest randomized trial comparing ranitidine to sucralfate showed that ranitidine was superior in preventing gastrointestinal bleeding and did not increase the risk of VAP.¹⁵⁸ Therefore, despite the potential advantage

of sucralfate (potentially less VAP with more gastrointestinal bleeding) over H₂ blockers (potentially more VAP with less gastrointestinal bleeding) in preventing VAP, stress ulcer prophylaxis with H₂ blockers appears to be safe in patients who are at high risk for bleeding as well as VAP. Although proton-pump inhibitors are now widely used for gastric bleeding prophylaxis in the ICU, based on their potentially higher efficacy, their use is associated with similar rates of nosocomial pneumonia as H₂ blockers.¹⁵⁹⁻¹⁶⁴

Selective decontamination of the digestive tract (SDD) includes a short course of systemic antibiotic therapy, such as cefotaxime, trimethoprim or a fluoroquinolone, and topical administration of nonabsorbable antibiotics (usually an aminoglycoside, polymyxin B, and amphotericin) to the mouth and stomach, in order to eradicate potentially pathogenic bacteria and yeast that may cause infections.¹⁶⁵ Since the original study published by Stoutenbeek and coworkers in 1984,¹⁶⁶ which demonstrated a decrease of the overall infection rate in patients receiving the SDD regimen, more than 40 randomized controlled trials and eight meta-analyses have been published. All eight meta-analyses reported a significant reduction in the risk of VAP, and four reported a significant reduction in mortality.¹⁶⁷⁻¹⁷¹ Recently, three prospective, randomized, controlled trials, all performed in ICUs with low rates of antibiotic resistance, have been published that were large enough to show a significant survival benefit in SDD-treated patients.¹⁷²⁻¹⁷⁴ All three were in favor of treatment with SDD, the largest and most recent one demonstrating a relative decrease in 28-day mortality rate (OR 0.83, 95% CI, 0.72 to 0.97) and an absolute survival benefit of 3.5%.¹⁷⁴ Even so, widespread use of SDD in ICU patients remains controversial. The major concern with use of SDD is that it can promote the emergence of resistant bacteria, particularly gram-positive bacteria such as MRSA.¹⁷⁵⁻¹⁷⁹ This is likely to be even a greater problem in ICUs with a high baseline rate of resistance.^{110,111,180} In contrast to what was expected, however, most studies that have evaluated this issue showed a lower incidence of colonization with resistant bacteria in SDD-treated patients than in control patients.^{173,181-184} Putative explanations why colonization with resistant microorganisms is lower after treatment with SDD include the susceptibility of gram-negative aerobic bacteria to the commonly used combination of polymyxin E and tobramycin, the fact that treatment with polymyxin E rarely induces resistance, the very high local concentrations in the bowel of the used antibiotics, and the lower rate of use of systemic antibiotics in SDD-treated patients.¹⁸⁵

IMPLEMENTING A STRUCTURED PREVENTION POLICY

The application of consistent evidence-based interventions to prevent VAP has been highly variable from one ICU to another and is often suboptimal. Furthermore, no single preventive measure can succeed alone, emphasizing the need to use multifaceted and multidisciplinary programs to prevent VAP. Such programs are frequently referred to as "care bundles." A care bundle is a set of readily implementable interventions that are required to be undertaken for each patient on a regular basis.¹⁸⁶ The key goal is for every intervention to be implemented for every patient on

every day of his or her stay in the ICU. Compliance is assessed for the bundle as a whole, so failure to complete even a single intervention means failure of the whole bundle at a particular assessment. The interventions need to be packaged in such a way that compliance is readily assessed, which usually means that no more than five interventions are included in each care bundle. The performance goal is to routinely achieve over 95% compliance. Care bundles make it possible to introduce evidence-based preventive measures, including appropriate nurse staffing levels, hand hygiene with alcohol-based formulations, standardized weaning protocols and daily interruption of sedation, oral care with chlorhexidine, and keeping patients who receive enteral nutrition in a semirecumbent position.¹⁸⁷ Several studies using quasiexperimental design have confirmed the usefulness of this strategy for preventing VAP in the ICU.¹⁸⁸⁻²⁰²

The lack of methodologic rigor of the reported studies, however, precludes any conclusive statements about “bundle care” effectiveness or cost-effectiveness. The exact set of key interventions that should be part of the “VAP-prevention bundle” is also not currently known, nor are factors contributing to its success.^{199,203-205b} Successful VAP prevention requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation, and feedback to health care workers. As shown in a recent study, simply having a checklist available for reference without consideration of a robust implementation and adherence strategy is unlikely to maximize patient outcomes.²⁰²

In the United States, the Centers for Medicare and Medicaid Services has proposed stopping hospital reimbursements for care made necessary by preventable complications, including nosocomial infections, aiming for a zero-VAP rate.²⁰⁶ Although this plan may have the desirable consequences of improving the quality of care, it also may penalize hospitals that admit high-risk patients and inadvertently encourage institutions to underreport VAP or to overuse antibiotics, thereby favoring dissemination of multidrug-resistant microorganisms. This possibility further underscores the need to evaluate all new strategies potentially aimed at preventing VAP against current best clinical practices.

Key Points

- Ventilator-associated pneumonia (VAP) is associated with mortality in excess of that caused by the underlying disease alone, particularly in the case of infection due to high-risk pathogens, such as *P. aeruginosa* and methicillin-resistant *S. aureus*, and/or when the initial therapy is inappropriate.
- The predominant organisms responsible for infection are *P. aeruginosa*, *S. aureus*, and Enterobacteriaceae, but etiologic agents widely differ according to the population of hospital patients, the duration of hospital stay, and prior antimicrobial therapy.
- Because even a few doses of a new antimicrobial agent can negate results of microbiologic cultures, pulmonary

secretions in patients suspected of having developed VAP should always be obtained before new antibiotics are administered.

- The initial approach to antimicrobial therapy involves administering broad-spectrum antibiotics to avoid inadequate treatment in patients with true bacterial pneumonia.
- The management of antibiotic therapy for VAP should optimize care without overusing and abusing antibiotics by stopping therapy in patients with a low probability of VAP, streamlining treatment once the etiologic agent is known, switching to monotherapy after days 3 to 5, and shortening duration of therapy to 7 to 8 days, as dictated by the patient’s clinical response to therapy and information about the bacteriology of the infection.
- Very simple, no-cost measures can have an important effect on decreasing the frequency of VAP: maintaining the endotracheal tube cuff pressure above 20 cm H₂O to prevent leakage of bacteria around the cuff into the lower respiratory tract; promptly reintubating patients who are failing extubation; providing oral care with chlorhexidine; keeping patients in the semirecumbent position, especially patients receiving enteral nutrition; removing ventilator tubing condensates with minimal exposure to patients; and reducing the duration of ventilation.

Complete reference list available at **ExpertConsult**.

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INTRODUCTION**CHARACTERISTICS OF THE
MYCOBACTERIUM TUBERCULOSIS
COMPLEX ORGANISMS****DESCRIPTIVE EPIDEMIOLOGY OF
TUBERCULOSIS****TRANSMISSION OF MYCOBACTERIUM
TUBERCULOSIS**

Source Case

Environmental Factors

Circumstances of Exposure

Host Factors

PATHOGENESISIntracellular Trafficking of *Mycobacterium tuberculosis*

ESX-1 Protein Secretion System

Induction of Type I Interferons

Biologically Active Mycobacterial Lipids

Granulomas

Modulation of Apoptosis

Phylogenetic Lineage- and Strain-
Dependent Variation in Pathogenesis

Latency/Dormancy and Reactivation

IMMUNITYInnate Immunity to *Mycobacterium tuberculosis*Adaptive Immunity to *Mycobacterium tuberculosis*Contributions of Immune Responses to
Tuberculosis Pathology

Exogenous Versus Endogenous Infection

RISK FACTORS FOR DISEASE**DIAGNOSIS OF LATENT
TUBERCULOSIS INFECTION**

Tuberculin Skin Test

Interferon- γ Release Assays**DIAGNOSIS OF PULMONARY
TUBERCULOSIS**

Diagnostic Evaluation

Patient History

Physical Examination

Radiographic Features

Bacteriologic Evaluation

PLEURAL TUBERCULOSIS**DISSEMINATED TUBERCULOSIS
TREATMENT**

Current Standard Regimens

EXTRAPULMONARY TUBERCULOSIS

Lymphatic Tuberculosis

**TREATMENT OF LATENT
TUBERCULOUS INFECTION**

Indications for Treatment

Current Treatment Regimens

Management of Exposure to Drug-
Resistant Organisms**IMMUNIZATION WITH BACILLE
CALMETTE-GUÉRIN****TACKLING CURRENT PROBLEMS****INTRODUCTION**

Mycobacteria have played an extremely important role in influencing society throughout history. Tuberculosis and Hansen disease (leprosy), the two most prominent mycobacterial diseases, have been recognized as scourges of humanity since antiquity. Whereas leprosy was most apparent as a metaphor for the destitute, disabled, and disfigured, tuberculosis was the “captain of all these men of death,” according to John Bunyan—a plague that carried away the young and talented members of society. Currently, although the resurgence of tuberculosis in industrialized countries that began in the mid-1980s has subsided, the disease continues to ravage much of the developing world and to kill or disable many young, productive members of society.^{1,2}

Because pulmonary and extrapulmonary tuberculosis commonly appear together, and because the general manifestations and microbiologic features are the same with all sites of disease, this chapter addresses both pulmonary and extrapulmonary tuberculosis.

Some forms of extrapulmonary tuberculosis, such as genitourinary, bone and joint, central nervous system, abdominal, and pericardial tuberculosis are covered in the online version of this chapter, which can be found at ExpertConsult.

Because tuberculous infection is so prevalent throughout much of the developing world, the conflicts and upheavals that result in immigration from low-income to developed countries will have a continuing influence on the incidence of tuberculosis everywhere. For this reason, tuberculosis

must be viewed as a global problem, one that is not contained by national boundaries and whose effects are felt in all countries regardless of their state of development.³ In addition to *human immunodeficiency virus* (HIV) infection, drug resistance is providing increasing challenges to tuberculosis control efforts.⁴ Both *multidrug-resistant* (MDR) tuberculosis (caused by organisms resistant to at least isoniazid and rifampin) and *extensively drug-resistant* (XDR) tuberculosis (caused by MDR organisms that are also resistant to one of the fluoroquinolones and to at least one injectable second-line agent) pose significant difficulties for tuberculosis control programs in most of the world.

**CHARACTERISTICS OF THE
MYCOBACTERIUM TUBERCULOSIS
COMPLEX ORGANISMS**

The main phenotypic characteristic that defines the genus *Mycobacterium* is the property of “acid-fastness,” the ability to withstand decolorization with an acid-alcohol mixture after coloration with such stains as carbol fuchsin or auramine O (Fig. 35-1).⁵ In addition to being acid fast, the mycobacteria are primarily intracellular pathogens, are obligate aerobes, and, in the presence of a normal immune response, induce a granulomatous response in tissue. Most members of the genus that cause disease in immunocompetent humans are phylogenetically close and possess genes that encode the virulence factors ESAT-6 and CFP-10 (see “ESX-1 Protein Secretion System” later).⁶



Genitourinary Tuberculosis

Bone and Joint Tuberculosis

Central Nervous System Tuberculosis

Abdominal Tuberculosis

Pericardial Tuberculosis

APPENDIX: ESSENTIALS OF CHEMOTHERAPY

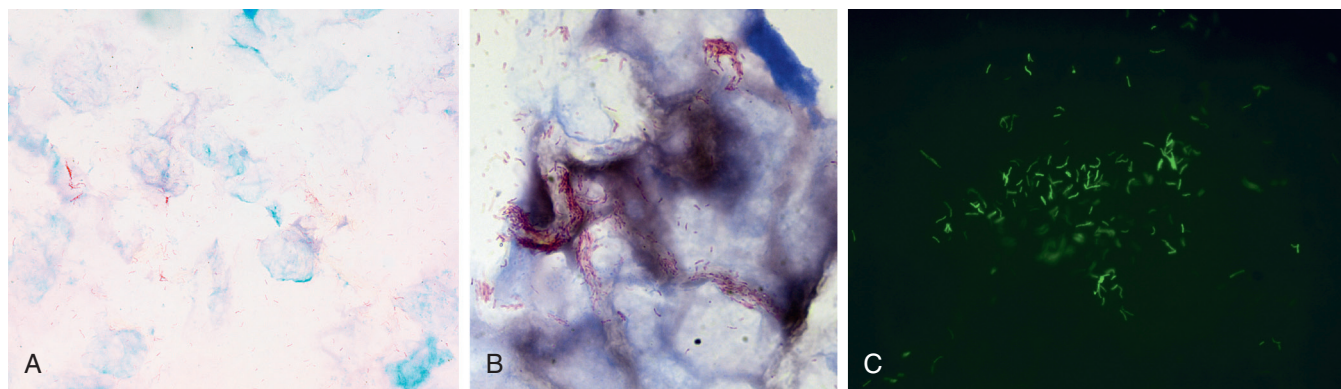


Figure 35-1 Diagnostic imaging of *M. tuberculosis*. **A** and **B**, Kinyoun-stained smears of sputum showing acid-fast bacilli (*Mycobacterium tuberculosis* confirmed by culture). (Original magnification **A**: $\times 400$; **B**: $\times 960$.) **C**, Auramine fluorochrome stain of sputum smear (*M. tuberculosis* confirmed by culture) (Original magnification, $\times 400$.) (Samples and photomicrographs courtesy Dr. Maria Agüero-Rosenfeld and Dr. Ludovic Desvignes, Bellevue Hospital and New York University Medical Center (**A** and **B**), and Dr. Niaz Banaei, Stanford University Medical Center (**C**).

Tuberculosis is caused by any one of three mycobacterial pathogens that are part of the *M. tuberculosis* complex: *M. tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium africanum*. The other members of the *M. tuberculosis* complex are: *Mycobacterium microti*, *Mycobacterium pinnipedii*, and *Mycobacterium caprae*, which only rarely cause disease in humans. *Mycobacterium magerit*⁷ and *Mycobacterium oryzi*⁸ have not been reported to cause disease in humans. *M. africanum* causes disease that is clinically indistinguishable from that of *M. tuberculosis*, but it is restricted to specific regions of Africa or people from those regions. *Mycobacterium canettii* is not part of the *M. tuberculosis* complex, but it has been identified as a cause of tuberculosis in a small number of patients from or with connection to East Africa.⁹ This strain diverged from the common ancestor of all tubercle bacilli much earlier than the *M. tuberculosis* complex.

Since the publication of the first complete genome of *M. tuberculosis* H37Rv laboratory strain,¹⁰ multiple clinical isolates have been sequenced and are publicly available in GenBank¹¹ and the Tuberculosis Database (TBDB; www.tbdb.org). The sequence of H37Rv genome is annotated and frequently revised and updated (<http://tuberculist.epfl.ch/>). The most recent version of the H37Rv annotation (R27-March 2013) included 4018 protein coding genes, of which 88% have a defined or possible function and the rest are annotated as conserved hypothetical proteins without known function.¹² The genome of *M. tuberculosis* differs from other bacterial genomes in that 6% of the genes are predicted or known to be involved in lipid biosynthesis and degradation.¹¹ Nearly 400 of its putative proteins share no homology with known proteins and, thus, could be unique to *M. tuberculosis*.¹³ The genetic makeup of the organism indicates that it has the potential to survive in a variety of environments, including those with low oxygen tension.

The potential for developing new drugs, vaccines, and diagnostic tests on the basis of the knowledge of the complete array of genes in *M. tuberculosis* is enormous and is only beginning to be realized. For example, the analysis of the whole genome sequence of 21 *M. tuberculosis* clinical isolates representative of the global bacterial population showed that human T-cell epitopes (peptide fragments in *M. tuberculosis* used by T-cell lymphocytes to recognize the

pathogen) were surprisingly highly conserved, in contrast to the situation with other pathogens in which antigens undergo a high frequency of variation.¹⁴ These results indicate that *M. tuberculosis* does not use antigenic variation as a major mechanism of immune evasion, and the results may help guide vaccine development.

In addition to providing information about the biology of *M. tuberculosis*, the analysis and comparison of whole genome sequences have provided phylogenetically robust markers that enable assessment of the evolution and classification of clinical isolates of *M. tuberculosis*, as well as provide tools to examine the impact of genetic diversity on the epidemiology and clinical features of tuberculosis.¹⁵

The *M. tuberculosis* phylogenetic tree has a geographic structure from which the initial *M. tuberculosis* major lineage names were derived: Indo-Oceanic (lineage 1), East-Asian (lineage 2), Indian and East-African (lineage 3), Euro-American (lineage 4), West-African 1 (lineage 5), and West-African 2 (lineage 6). These last two lineages are also known as *M. africanum*.¹⁵ This classification has been confirmed using large-sequence polymorphisms (insertions and deletions), multilocus sequence analysis, and genome sequencing, which is now the gold standard for phylogeny studies.¹⁶ Several studies have suggested that different lineages of *M. tuberculosis* may be associated with different degrees of pathogenicity.¹⁷⁻²¹ In The Gambia, the rate of transmission (measured by skin test conversion) of *M. tuberculosis* to household contacts was similar among different lineages. However, the proportion of contacts developing active tuberculosis within the 2-year follow-up period varied: 1% for those exposed to strains of *M. africanum*, 6% for those exposed to strains from lineage 2, and 1% to 4% for strains from lineage 4.²⁰ In San Francisco, strains from sublineage 207, a sublineage of lineage 2, were more likely to be associated with genotypic clustering (a measurement of the ability of a strain to cause secondary cases) and were more virulent in guinea pigs when compared with the other lineage 2 sublineages.^{22,23} Similarly, strains from sublineage 183, within lineage 4, caused more secondary cases compared with other lineage 4 sublineages.²⁴ In California, MDR *M. tuberculosis* caused by lineage 2 organisms was associated with genotypic clustering, whereas lineage 1 strains produced no secondary (clustered) cases.²⁵

DESCRIPTIVE EPIDEMIOLOGY OF TUBERCULOSIS

For most of recorded history, tuberculosis has been a problem of enormous dimensions worldwide—and it still is. The *World Health Organization* (WHO) estimates that nearly one third (1.9 billion people) of all the people in the world are infected with *M. tuberculosis*. According to the latest (2013) WHO Global report, in 2012 there were an estimated 8.6 million new cases, of which only 6.1 million were reported to national tuberculosis programs, leaving an estimated 2.5 million unaccounted for.² This gap is likely related to limitations in the global surveillance and reporting systems and because a large amount of care is delivered by the private sector with no reporting. The total number of prevalent cases (new and existing) in the world was estimated to be 12 million, from which there were an estimated 1.26 million deaths, making tuberculosis the eighth most common cause of death in low-income countries.²⁶ Most of the persons with tuberculosis (>95%) and nearly all of those who die from it (98%) reside in low- and middle-income countries.

Since 1990, there has been a progressive decrease in the incidence of tuberculosis in all nine WHO regions of the world, although the rates of decline in Eastern Europe and Africa lag behind other regions.² Globally the rate of decline in incidence is about 2% per year, although this rate varies from region to region. Also, in 2012, it was estimated that there were 1.1 million new cases and 300,000 deaths from tuberculosis in persons with HIV infection. The distribution of persons with coexisting HIV and tuberculosis varies considerably around the world, but most (79%) live in sub-Saharan Africa.

In spite of the staggering impact of tuberculosis in developing countries, it was believed that the disease was well on its way to being eliminated in most of the high-income, low-incidence countries, including the United States. In these high-income countries, from at least the beginning of the 20th century, tuberculosis death rates were steadily decreasing, a decline that was accelerated by the introduction of antituberculosis chemotherapy in the late 1940s. In the United States following the introduction of effective chemotherapy, rates of new cases of tuberculosis decreased steadily at an average annual rate of approximately 5%. However, between 1984 to 1992, the number of tuberculosis cases increased by 20%. With renewed effort and considerably increased funding, case rates once again began to decline in 1993, as shown in [Figure 35-2](#).

In 2012 in the United States, 9945 cases of tuberculosis (3.2 cases per 100,000 population) were reported, the lowest number since systematic national reporting began in 1953, and a 5.4% decline from 2011.²⁷ The reasons for the resurgence of tuberculosis in the late 1980s and early 1990s in the United States, as well as in Western Europe, are complex but revolve largely around two major factors: the epidemic of infection with HIV and the deterioration of public health systems.^{28,29} Interacting with and amplifying these two major factors were two additional circumstances: (1) socioeconomic conditions, particularly homelessness that led to crowding; and (2) immigration of persons from

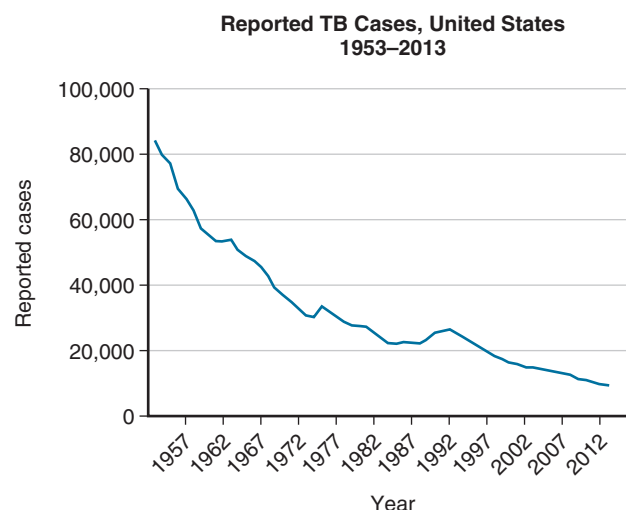


Figure 35-2 Cases of tuberculosis reported per year in the United States, 1953–2013. (From Centers for Disease Control and Prevention: Reported tuberculosis in the United States, 2013. Atlanta, 2014.)

countries in the world where the prevalence of tuberculous infection was high.

Whereas the incidence of tuberculosis decreased overall by 81% from 1993 to 2012, the incidence decreased disproportionately among the U.S.-born population.²⁷ There was a 53% reduction in incidence among the foreign born during the same time period; however, the rate remains relatively high at 15.9/100,000. Among foreign-born persons, rates of tuberculosis are the highest during the first 2 years after entry into the country, regardless of age, with annual rates especially high (>250/100,000 persons) among immigrants from sub-Saharan Africa and Southeast Asia.³ By contrast, in the United States and other low-incidence countries, tuberculosis case rates in persons born in these countries tend to be higher in older individuals, because the older a person is, the more likely he or she is to have acquired tuberculous infection, having lived during a time when the disease was more prevalent than it is today.

TRANSMISSION OF MYCOBACTERIUM TUBERCULOSIS

Knowledge of the factors that govern transmission of *M. tuberculosis* from a source case and of the sequence by which the disease develops in a potential new host is vital for devising strategies for tuberculosis control and for evaluating the risk of a person becoming infected after exposure to a patient with tuberculosis.³⁰

Transmission of *M. tuberculosis* is influenced by features of the source case, particularly the bacillary load, by the closeness of the potential recipient of the organism to the source, and by the condition of the environmental air they share. A possible additional factor is the infectivity of the organism—the degree to which *M. tuberculosis* has the ability to establish itself within the lung or other sites in the new host. However, even taking these factors into account,

there is substantial unexplained variability in the degree to which persons with untreated tuberculosis transmit the infection to persons to whom they are exposed.

SOURCE CASE

Transmission of *M. tuberculosis* is a classic example of an airborne infection.³¹ In nearly all instances, tuberculous infection is acquired by inhalation of one or more tubercle bacilli contained in an airborne particle small enough (1 to 5 μm) to reach an alveolus. For a person with tuberculosis to be infectious, the organisms must have access to environmental air and be aerosolized. By and large, this means that only patients with pulmonary tuberculosis can be regarded as infectious. However, respirable particles containing *M. tuberculosis* may rarely be generated from other sources (e.g., irrigation of a tuberculous abscess).³² After aerosolized respiratory secretions are expelled from the nose or mouth, their water content evaporates rapidly, leaving only a small residue of solid matter—the *droplet nucleus*—which may include tubercle bacilli and which may remain suspended in the air for several hours.³³ A single bacillus in a tiny droplet nucleus is more hazardous than several bacilli in larger airborne particles, which when inhaled deposit in airways rather than alveoli and which then are quickly removed by mucociliary clearance or killed.

Coughing is the most effective mechanism for generating aerosols that create droplet nuclei, but it is not the only mechanism. Forced expiratory maneuvers other than coughing—such as sneezing, yelling, singing, and loud talking—all involve, to a greater or lesser extent, the sudden acceleration of air required to disrupt a liquid surface or mucous strands, thereby aerosolizing particles. Thin, watery secretions are more easily fragmented into small respirable droplets than is more viscous mucus. In general, the greater the volume of respiratory secretions, the greater the number of potentially infectious droplets. Riley and coworkers³⁴ demonstrated marked variability in the infectious potential of tuberculosis patients that, in part, could be related to the severity of coughing. One patient with exceptionally infectious tuberculosis not only had severe pulmonary tuberculosis but tuberculous laryngitis as well. It was calculated that this patient was as contagious as a child with measles is to other susceptible children. Similar studies by Escombe and coworkers,³⁵ which described the infectiousness of HIV-infected patients with tuberculosis, reported that infectiousness was very heterogeneous. Of 97 patients (118 admissions) hospitalized in an HIV-tuberculosis ward, 10 caused 90% of the infections in guinea pigs exposed to air exhausted from the ward. Of the 10 infectious patients, 6 had MDR tuberculosis that was inadequately treated; in addition to having MDR tuberculosis, being sputum smear positive and being on suboptimal treatment both contributed to the degree of infectiousness. Likewise, in a study of household contacts of tuberculosis patients, the likelihood of transmission was lower if the source case was HIV infected and had a CD4 T-cell count lower than 250/ μL .³⁶ In that study, the effect of HIV and immunodeficiency was larger than could be explained by differences in smear status, delayed treatment, or the presence of cavitory lesions. Even when the bacillary load is taken into account, there is substantial unexplained

variability in infectiousness. Jones-Lopez and colleagues³⁷ used an air-sampling device to capture *M. tuberculosis* in exhaled (coughed) air and showed that infectiousness was associated with the presence of cultivable organisms in the sampled air. The finding of organisms in the exhaled air was quite variable from patient to patient and did not correlate with sputum smear results.

Simple maneuvers, such as covering the mouth while coughing, can reduce formation of droplet nuclei by deflecting droplets from the air stream. Similarly, a mask worn by the patient is effective because particles are trapped while they are still large, before the water content has evaporated. Masks (disposable particulate respirators) worn by persons exposed to an infectious source are less effective than are masks worn by patients, because most airborne droplet nuclei are much smaller than their parent droplets. However, properly constructed, well-fitting masks are very efficient in removing respirable particles of 1 to 5 μm ³⁸ (see also Chapter 11).

A second factor of the source case to be considered in determining infectiousness is the number of organisms contained in the lungs. This can be inferred from the extent and morphology of the disease, as determined by the chest radiograph and more directly estimated by microscopic examination of sputum. Canetti demonstrated that the bacillary population of tuberculous lesions varies greatly, depending on the morphology of the lesion.³⁹ The number of bacilli in solid nodular lesions ranges from 10^2 to 10^4 organisms, whereas in cavitory lesions, populations are on the order of 10^7 to 10^9 bacilli. Loudon and Spohn,⁴⁰ among others, demonstrated that the prevalence of tuberculin reactors among young contacts of patients with newly discovered tuberculosis increased as the radiographic extent of involvement increased. Thus, in tuberculosis control, the contacts of persons with more extensive tuberculosis should be accorded a higher priority for evaluation than the contacts of persons with less severe disease.

The most direct means of estimating bacillary population is microscopic examination of properly stained sputum smears. An average viable bacillary population of 5000 to 10,000 organisms per milliliter of sputum is required for the organisms to be seen in an acid-fast-stained sputum smear.⁴¹ The contacts of patients who have organisms present in sputum smears have a much higher prevalence of infection than do contacts of patients with negative smears and either positive or negative cultures.⁴² However, the contacts of sputum smear-negative patients may still acquire tuberculous infection and develop tuberculosis. Transmission from smear-negative patients was estimated to be the cause of approximately 17% of newly diagnosed cases in San Francisco.⁴³

A third important factor in determining the infectiousness of a source case is the use of chemotherapy. In studies designed to identify and quantify factors influencing transmissibility of *M. tuberculosis*, Sultan and associates⁴⁴ and Riley and coworkers³⁴ noted that patients who had positive sputum smears but who were receiving antituberculosis drugs were much less infectious for guinea pigs than were untreated patients. By their calculations, the relative infectiousness of untreated patients in comparison with treated patients was 50:1. Escombe and coworkers,³⁵ as already noted, came to a similar conclusion. Consistent with these

experimental observations, a substantial body of clinical data has accumulated that indicates that, once treatment to which the organisms are susceptible is begun, transmission of *M. tuberculosis* decreases quickly. The quantification of the infectiousness of cough-generated aerosols has shown the same result—that the major factor associated with persistent culture-positive aerosols was lack of effective treatment during the previous week.³⁷ The most important mechanism by which chemotherapy reduces infectiousness is the direct effect of the drug on the bacillary population in the lungs. Hobby and associates⁴¹ found that, after an average of 15.6 days of multidrug chemotherapy, there was a reduction in the number of tubercle bacilli per milliliter of sputum of at least 2 logs, from approximately 10^6 to approximately 10^4 , or a 99% decrease. These data are similar to those reported by Jindani and coworkers, who demonstrated a reduction in colony counts of nearly 2 logs per milliliter of sputum in the first 2 days of treatment and a further reduction of 1 log during the next 12 days.⁴⁵ Thus, in the initial 2 weeks of treatment, there was a decrease from approximately 10^7 to 10^4 organisms per milliliter of sputum, or a reduction of 99.9%. However, even with this profound reduction in the bacillary population, the remaining number of organisms (10,000 per milliliter of sputum) would still be sufficient to produce a positive acid-fast sputum smear. In addition to reducing the number of viable bacilli, chemotherapy also promptly decreases coughing. Loudon and Spohn⁴⁰ noted that coughing was reduced by 40% after 1 week of treatment and by 65% after 2 weeks. The sum of these effects is that, once a patient with tuberculosis is placed on effective therapy, transmission of tubercle bacilli ceases to be a concern. The decline in infectiousness is caused mainly by the rapid reduction in bacillary population in the lungs as a result of antituberculosis chemotherapy, particularly isoniazid. Drug regimens that do not include isoniazid probably should not be expected to render the patient noninfectious as rapidly as do those containing isoniazid. Likewise, the prompt reduction in infectiousness cannot be assumed in patients harboring organisms that are resistant to isoniazid.

Different strains have different infectiousness. For example, strains of *M. tuberculosis* resistant to isoniazid may be less pathogenic than fully susceptible organisms.^{46,47} Molecular epidemiologic studies suggest that the mutation conferring resistance may have a role in the pathogenicity of *M. tuberculosis*, especially mutations associated with isoniazid resistance.⁴⁸ Isolates harboring the most common mutation, *katG* S315T and the *inhA* promoter 15c-t, were able to cause secondary cases of tuberculosis (defined as genotypic clustering of strains in a population). In contrast, mutations in *katG* other than the common S315T mutation did not cause secondary cases. Although more information is necessary to confirm this association, this finding may explain the different results regarding the pathogenicity of some drug-resistant strains. It is also clear that the lesser pathogenicity can easily be offset by a prolonged period of infectiousness, as might be expected with ineffective treatment, as suggested by Escombe and associates,³⁵ or with exposure of an immunocompromised host. Outbreaks of tuberculosis caused by MDR and XDR strains of tubercle bacilli have taken place in hospitals or correctional facilities and disproportionately involve HIV-infected

persons,⁴⁹ although immunocompetent persons have also been involved.

The operational implications of these assumptions concerning infectiousness should be modified in accordance with the patient's living and working circumstances. The general principles of infection control entail an assessment of the vulnerability to tuberculous infection of persons who will potentially be exposed and the consequences should those who are exposed become infected.

ENVIRONMENTAL FACTORS

The physical laws that apply to aerosolized particles, described in detail in Chapter 11 dictate that droplet nuclei essentially become part of the environmental air; thus, environmental factors are of extreme importance in influencing transmission of tubercle bacilli. Studies by Loudon and associates⁵⁰ showed that, under standard conditions of temperature and humidity indoors, 60% to 71% of aerosolized *M. tuberculosis* organisms survived for 3 hours, 48% to 56% for 6 hours, and 28% to 32% for 9 hours. Apart from the natural death rate, the only factors influencing the infectiousness of organisms in a droplet nucleus under ordinary circumstances are its removal by venting or filtering and the death of the organisms from exposure to ultraviolet light. Environmental factors may be manipulated to decrease the concentration of tubercle bacilli, mainly removing them by effective filtration, killing them with ultraviolet light, or both.⁵¹ The influence of the concentration of organisms in environmental air in transmission of *M. tuberculosis* has been well illustrated in several microepidemics in which recirculation of air played an important role. The most dramatic example happened on board a U.S. Navy vessel that had a closed, recirculating ventilation system.⁵² The index case had a positive sputum smear and a brisk cough. As a result of this one case, 53 of 60 persons (88%) in his berth compartment acquired tuberculous infections and 6 developed tuberculosis. In a second compartment connected to the same ventilation system, 43 of 81 persons (53%) became infected and 1 developed tuberculosis. Smaller epidemics, one caused by a patient who underwent bronchoscopy in an intensive care unit, have been described.⁵³

Since early in the 20th century, it has been known that exposure to ultraviolet radiation kills tubercle bacilli. Riley and coworkers,³⁴ in their classic studies of infectiousness in a series of patients, demonstrated that ultraviolet irradiation of air passing through an air-conditioning duct completely eliminated transmission of *M. tuberculosis* to guinea pigs housed beyond the ultraviolet lights. The major usefulness of ultraviolet lights is for providing UV irradiation of room air, using appropriately shielded lamps on the upper walls in hospital areas or clinics where patients with untreated tuberculosis are likely to be encountered. This is especially important in open areas such as waiting rooms, where ventilation may not be adequate to remove infectious particles, and within ventilation systems.⁵¹

CIRCUMSTANCES OF EXPOSURE

The conditions of exposure have a major influence on the number of infectious particles inhaled. If the exposure is of long duration and takes place under conditions that would

be associated with a high concentration of droplet nuclei in the air inhaled by the contact, there is obviously a greater likelihood of transmission. This is simply a restatement of what has been known for many years: Crowding and intimacy of contact are important determinants of transmission of *M. tuberculosis*.⁵⁴ This is reflected in data from the United States showing that rates of both clinical tuberculosis and tuberculin reactivity are much higher among close (generally household) than among nonclose (generally out-of-household) contacts. In general, the rate of tuberculosis is in the range of 15 per 1000 close contacts and 3 per 1000 nonclose contacts. Of close contacts, approximately 50% are infected, in comparison with approximately 15% of nonclose contacts.⁵⁵ Because the risk of tuberculosis is higher among close contacts, they should also be considered high-priority candidates for isoniazid preventive therapy. However, a number of studies using molecular epidemiology to track transmission dynamics have shown that substantial transmission may take place outside the household, particularly in social gathering places such as bars or informal places where alcohol is consumed.⁵⁶

HOST FACTORS

There is substantial evidence that susceptibility to acquisition of infection with *M. tuberculosis* is highly variable. Most descriptions of contact investigations report that 40% to 60% of close contacts of an index case become infected, as reflected by conversion of the *tuberculin skin test* (TST) or *interferon* (IFN)- γ *release assay* from negative to positive. Although variations in the intensity of exposure contribute to the likelihood of becoming infected, variations in host susceptibility are also likely to contribute. Strong evidence for variable susceptibility to acquisition of infection with *M. tuberculosis* was provided by a prospective study of student nurses in a tuberculosis hospital in Philadelphia in the prechemotherapy era.⁵⁷ In that study, in which student nurses were assigned to rotations on the same tuberculosis wards, 30% remained uninfected (TST unreactive) after 2 years of nursing school, indicating that despite repeated exposure, some of the student nurses were less susceptible to acquisition of infection than others. However, by the end of the third year of nursing school, 100% of the students had become infected, indicating that resistance to infection is

quantitative, not absolute, and can be overcome by sufficient exposure to especially virulent strains of bacteria.

There have been few efforts to identify the determinants of resistance to acquisition of infection, although a recent study in a high-prevalence community in South Africa presented evidence for at least one host genetic determinant that influences the likelihood of acquisition of infection in children. Genomewide linkage analysis of TST-unreactive (zero-mm induration) and TST-reactive (greater than zero; median, 11.2-mm induration) children revealed evidence of a major locus that maps to chromosome region 11p14.⁵⁸ The identity of the gene(s) at that locus, together with analysis of the cellular distribution and regulation of expression and the functions of the gene products, may reveal important mechanistic information on human resistance to acquisition of infection with *M. tuberculosis*.

It is currently unclear whether HIV infection, which has a major effect on progression to active tuberculosis, also affects susceptibility to acquisition of infection.⁵⁹

PATHOGENESIS

The genesis of the pathologic reactions in tuberculosis is inextricably linked with the response of the host to the invading tubercle bacillus. In most individuals infected with *M. tuberculosis*, the host response—innate and adaptive—restricts the growth of the pathogen, thereby containing the infection.⁶⁰ Paradoxically, however, the immunologic response to *M. tuberculosis* is likely responsible for the characteristic presentation of tuberculosis.⁶¹ In contrast, the near absence of cell-mediated adaptive immunity in patients with advanced HIV infection is assumed to be responsible for the atypical presentations of tuberculosis in HIV-infected patients. Such patients tend to have multisystem involvement and tend not to have cavitary lung lesions.⁶² Although the lack of immune response minimizes tissue damage, the organism is not met with an effective protective response, thus facilitating proliferation and dissemination of the bacilli.

Figure 35-3 describes schematically the events and outcomes that result from human exposure to *M. tuberculosis*. There are two phases: the acquisition of infection and the subsequent development of tuberculosis. Tuberculosis may

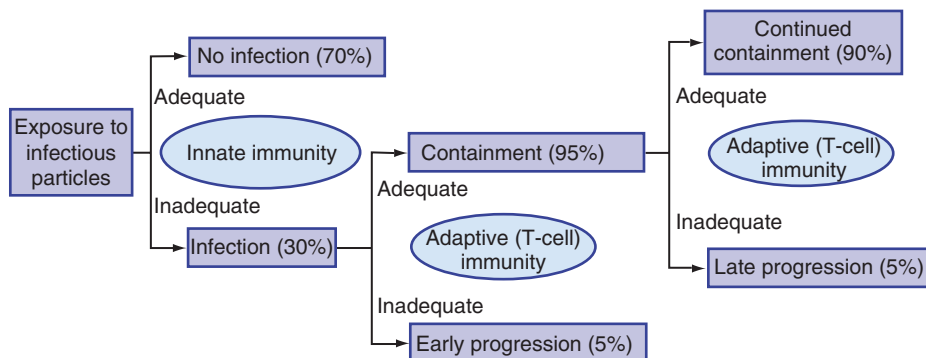


Figure 35-3 Consequences of exposure to an infectious source of tuberculosis depending on the status of immunity. Exposure to a patient with infectious tuberculosis causes tuberculous infection in approximately 30% of those exposed. Of those who are infected, 3% to 10% develop tuberculosis within 1 year of their becoming infected. Beyond 1 year, an additional 3% to 5% develop tuberculosis during the remainder of their lifetimes.

develop as direct progression from infection to disease (3% to 10% probability within 1 year of infection) or from late progression many years after infection (up to 5% probability for the lifetime of an infected person after the first year of infection).⁶³ In HIV-infected populations, the rate of developing disease is considerably higher.⁶²

Although *M. tuberculosis* possesses many features in common with other bacteria, unique characteristics that are restricted to *M. tuberculosis* and its close phylogenetic relatives are responsible for the distinct pathogenesis of tuberculosis. These unique features, principally consisting of specific secreted proteins and biologically active complex lipids, have been characterized by a combination of in vitro studies, studies in experimental animals, and studies in humans. Together, these unique features account for much of the cellular, subcellular, and molecular pathogenesis of tuberculosis.

INTRACELLULAR TRAFFICKING OF MYCOBACTERIUM TUBERCULOSIS

Seminal studies by Armstrong and D'Arcy-Hart and colleagues^{64,65} revealed that pathogenic mycobacteria survive and replicate in host phagocytes, including macrophages, by perturbing the normal pathway of phagosome maturation that eventuates in fusion with lysosomes and killing and digestion of other pathogens. Subsequent studies in basic cell biology have revealed that phagolysosome formation follows an ordered series of interactions between phagosome membrane proteins and phospholipids, relying on proteins that regulate intracellular traffic. One of these regulatory proteins, a low-molecular-weight GTPase termed Rab7, is essential for the late step of phagosome acquisition of lysosomal constituents; *M. tuberculosis* disrupts recruitment of Rab7 to the phagosome membrane.⁶⁶ Normal trafficking also requires conversion of phagosome membrane phosphatidylinositol to phosphatidylinositol-3-phosphate; virulent mycobacteria also interfere with this essential step by mechanisms that remain incompletely defined. Together, these mechanisms allow *M. tuberculosis* to survive and replicate intracellularly. Recent studies have revealed an additional requirement for the ESCRT (Endosomal Sorting Complex Required for Transport) pathway of intracellular vesicle trafficking in phagosome maturation,⁶⁷ and there is strong evidence that EsxH, a protein secreted by *M. tuberculosis*, disrupts the ESCRT pathway.⁶⁸ In addition, the autophagy system, originally characterized for its role in degradation of endogenous cellular proteins and organelles, has received considerable attention for its role in restricting growth of intracellular mycobacteria,⁶⁹ especially after stimulation of cells by the cytokine, IFN- γ . However, *M. tuberculosis* employs mechanisms to evade autophagy, including disruption of the phagosome membrane, giving the bacteria access to the host cell cytoplasm.⁷⁰⁻⁷² Thus, *M. tuberculosis* can occupy several distinct intracellular niches: immature phagosomes, autophagosomes, and the cytoplasm.

ESX-1 PROTEIN SECRETION SYSTEM

The *early secreted antigen 6 kilodaltons (ESAT-6) secretion system 1 (ESX-1)* was the first bacterial type VII secretion

system to be discovered and is essential for virulence of *M. tuberculosis*. This was first indicated by the discovery that all strains of BCG, the attenuated strain of *M. bovis* used as a vaccine for tuberculosis, lack a functional ESX-1 system.⁷³⁻⁷⁵ Of the proteins secreted by the *M. tuberculosis* ESX-1 system, ESAT-6 and *culture filtrate protein of 10 kD (CFP-10)* are the best characterized. These proteins are not present in BCG and, thus, confer specificity to IFN- γ release assays in the diagnosis of latent tuberculous infection.

Although multiple properties have been attributed to ESX-1-secreted proteins, the best characterized are their effects on host membrane integrity. ESX-1-deficient bacteria do not escape the phagosome⁷² and do not stimulate host signaling pathways whose sensing mechanisms are in the cytoplasm,⁷⁰ indicating that one target of the ESX-1 proteins is the phagosome membrane. ESX-1-deficient mycobacteria are also defective in cell-to-cell spread, most likely because they are less able to cause host cell necrosis; with cell necrosis, bacteria are released to the extracellular space, where they can access adjacent cells that support subsequent rounds of bacterial replication.^{73,74,76,77} Studies of the purified protein have directly implicated ESAT-6 in membrane perturbation. ESAT-6 has also been implicated in stimulating epithelial cells to express matrix metalloproteinase-9, which promotes migration of uninfected macrophages to the region adjacent to dying infected macrophages when they release viable bacteria, thus sustaining the infection cycle.⁷⁸

M. tuberculosis possesses five type VII secretion systems, of which ESX-1 is the best characterized. Of the remainder, ESX-3 is essential for survival of *M. tuberculosis*⁷⁹ and contributes to pathogenesis; it is responsible for secretion of the protein, EsxH (also known as Tb10.4), which interferes with the host ESCRT pathway⁶⁸ and is also a frequent target for recognition by T cells of people infected with *M. tuberculosis*.

INDUCTION OF TYPE I INTERFERONS

An important aspect of tuberculosis pathogenesis is the induction of type I IFN (IFN- α and/or IFN- β) secretion. Whole blood transcriptome analysis to discover human genes that are differentially expressed in tuberculosis revealed a transcriptional signature dominated by IFN-responsive genes,⁸⁰ and this finding has been replicated in additional patient cohorts.⁸¹⁻⁸³ The strength of the IFN transcriptional signature correlates with the extent of disease, and the transcriptional signature is rapidly reversed with effective chemotherapy.⁸⁴ Whether type I IFN plays a pathogenic role or is a secondary effect of active tuberculosis in humans remains to be defined. However, in mice, there is evidence that type I IFNs play a pathogenic role in *M. tuberculosis* infection,⁸⁵ at least partially by enhancing recruitment of mononuclear cells that support intracellular bacterial replication.^{86,87} In addition, type I IFNs limit expression of *interleukin (IL)-1- β* , a cytokine that is essential for control of *M. tuberculosis*.^{88,89} A link between virulence and induction of a host-detrimental type I IFN response has been established by the observation that intact ESX-1 secretion and phagosome permeabilization are required for *M. tuberculosis* induction of type I IFN expression.^{70,71} Despite the growing evidence for a detrimental role

of type I IFNs in tuberculosis, therapeutic administration of type I IFN for multiple sclerosis or hepatitis C has not been accompanied by a striking increase in the frequency of active tuberculosis.

BIOLOGICALLY ACTIVE MYCOBACTERIAL LIPIDS

M. tuberculosis has long been known to be rich in lipids, including mycolic acids that possess acyl chains containing up to 90 carbons. However, rather than being a mere “waxy coat” that acts as a barrier to drugs and other polar molecules, mycobacterial lipids interact directly with the host to contribute to pathogenesis.

Trehalose dimycolate (TDM), an abundant cell wall lipid traditionally known as mycobacterial “cord factor,” modulates innate immune and inflammatory responses to *M. tuberculosis* and is sufficient to induce transient granuloma formation when injected into experimental animals. Deficiency of TDM decreases pathogenicity of a mutant strain of *M. tuberculosis* experimental animals,⁹⁰ indicating that the responses induced by TDM favor the bacteria. TDM is recognized by two related C-type lectin receptors, termed Mincle (also termed Clec4e)⁹¹ and MCL (also termed Clec4d),⁹² expressed on macrophages and dendritic cells, which transduce signals that result in proinflammatory cytokine production.

Other complex mycobacterial lipids contribute to pathogenesis by mechanisms that remain under investigation. *Phthiocerol dimycocerosate* (PDIM) is present in all clinical isolates examined, despite its frequent loss during serial passage of *M. tuberculosis* in liquid culture; the persistence of PDIM in clinical isolates implies that it is essential for pathogenesis but dispensable in culture.⁹³ PDIM-deficient mutants are less pathogenic than PDIM-replete bacteria in mice^{94,95}; PDIM masks the molecules recognized by Toll-like receptors and dampens initial inflammatory responses.⁹⁶ The structurally related lipoglycans, *phosphatidylinositol mannans* (PIMs) and *lipoarabinomannan* (LAM), are implicated in specific interactions with the host. PIMs can stimulate innate immune and inflammatory responses by serving as agonists for *Toll-like receptor-2* (TLR2),⁹⁷ and studies with LAM-coated beads have indicated a potential role for LAM in altering phagosome maturation.⁹⁸

GRANULOMAS

Granulomas, consisting of aggregates of macrophages, often including multinucleated giant cells and “epithelioid” macrophages together with variable numbers of lymphocytes, are a pathologic hallmark of tuberculosis. Granulomas can also contain variable numbers of necrotic cells and microscopic and macroscopic necrotic centers; some also exhibit *caseating* necrosis (characterized by complete loss of tissue structure and a texture resembling soft cheese) and may become calcified. Granulomas have been traditionally considered to be host-protective structures, thought to “wall off” bacteria and keep them from disseminating. Whereas this view may apply in later stages of fibrotic and calcified granulomas, early granuloma formation actually promotes infection by facilitating cell-to-cell spread within the macrophage aggregates, thus optimizing expansion of

the bacterial population.⁷⁶ In addition, intravital microscopy has revealed that macrophages and lymphocytes in granulomas are dynamic, with lymphocytes freely migrating between the apparently closely apposed macrophages.⁹⁹ Together, these studies and others indicate that granulomas are dynamic structures that may benefit either the pathogen or the host, depending on the stage of infection.

MODULATION OF APOPTOSIS

As a facultative intracellular pathogen, *M. tuberculosis* shapes its environment to optimize its survival and growth. One mechanism is to inhibit apoptosis (programmed cell death) and prolong the life of infected cells, allowing the bacteria to grow to a larger population size in each infected cell before spreading to adjacent cells.¹⁰⁰ There are other benefits to *M. tuberculosis* from inhibiting apoptosis. Because uptake of apoptotic cell fragments by naive macrophages results in killing of the bacteria formerly residing in an apoptotic cell, inhibition of apoptosis allows *M. tuberculosis* to evade this mode of death.¹⁰¹ Because bacterial antigens associated with apoptotic cell fragments are subject to uptake and “cross-presentation” to CD8 T cells, inhibition of apoptosis of the infected cells minimizes the frequency of CD8 T-cell activation.¹⁰² Evidence that inhibition of apoptosis is a virulence mechanism in animal models of tuberculosis is provided by the findings that proapoptotic mutants of *M. tuberculosis* are less pathogenic in vivo.¹⁰³

PHYLOGENETIC LINEAGE- AND STRAIN-DEPENDENT VARIATION IN PATHOGENESIS

As noted earlier, use of high-resolution genotyping methods has recently revealed genetic diversity in the *M. tuberculosis* complex. This has provided a basis for comparative studies to understand the phenotypic consequences of genetic diversity. For example, *M. africanum*, which represents a distinct genetic lineage of the *M. tuberculosis* complex and is endemic in West Africa, compared with strains of other lineages, is less pathogenic at specific steps in the infection cycle. It is transmitted as readily as members of other lineages, but the progression to disease is less frequent than other lineages.²⁰ Yet once active tuberculosis develops with *M. africanum*, it is clinically indistinguishable from tuberculosis due to other lineages. Evidence that these findings are not strictly attributable to host population differences is provided by finding that *M. africanum* is also less pathogenic in inbred mice.¹⁰⁴ As another example, a subfamily of the Beijing family has been found to be more readily transmitted than other strains in the same community and causes more severe disease in experimentally infected guinea pigs.^{22,23} These examples provide evidence for intrinsic differences in strains of *M. tuberculosis* and indicate that studies linking epidemiology and pathogenesis (using animal models) can provide complementary information.

LATENCY/DORMANCY AND REACTIVATION

One of the most important characteristics of tuberculosis is the state of latent infection, which develops in the

majority of infected humans, with the ability to reactivate and cause active, transmissible disease. Although host factors (described later) contribute to establishing and maintaining the latent state, the bacteria also possess highly evolved mechanisms that are involved in latency and reactivation. A considerable amount of recent work has focused on certain *M. tuberculosis* genes in which expression is induced by hypoxia, and which are believed to be involved in latency (modeled as bacterial dormancy, wherein most of the bacterial population is not actively dividing). One group of genes whose expression is controlled by the transcription factor, *dosR*, is induced transiently by hypoxia, while other genes, collectively termed the *Enduring Hypoxic Response*, are under alternative regulation.^{105,106} Together with evidence that reoxygenation reverses the changes in gene expression, these findings provide a paradigm for understanding how *M. tuberculosis* can reversibly adapt to its environment and alter its metabolic and growth state. Evidence that such mechanisms operate during latent tuberculosis infection in humans is provided by the finding that T-cell responses to proteins encoded by these “dormancy” genes are more common in individuals with latent infection than in those with active tuberculosis.^{107,108}

The contributions of bacterial determinants to reactivation of latent infection are less well understood than are those associated with latency. However, the *M. tuberculosis* genome encodes 5 proteins with homology to a family of “resuscitation promoting factors” (RPFs) characterized in other bacteria for their ability to stimulate growth of bacteria from stagnant cultures. Although RPFs in other bacteria may act in interbacterial communication, the *M. tuberculosis* RPFs characterized to date are peptidoglycan glycosidases and appear to be involved in remodeling of the cell wall. Mutant strains of *M. tuberculosis* in which the genes encoding RPFs have been deleted are defective for reactivation in animal models,^{109–111} suggesting that RPFs may contribute to progression from latent to active tuberculosis in humans.

IMMUNITY

Countering the highly evolved pathogenetic mechanisms of *M. tuberculosis* are the host responses that limit progression from infection to disease. Although the mechanisms that determine whether an exposed individual will become infected or not (see Fig. 35-3) have not yet been identified, the mechanisms that determine the outcome after infection are increasingly well understood.

INNATE IMMUNITY TO MYCOBACTERIUM TUBERCULOSIS

Innate immunity includes cellular and humoral defenses that do not depend on clonal rearrangement of antigen receptor genes, the defining feature of acquired immunity as carried out by B and T lymphocytes. Although innate immune responses play an important role in tuberculosis, evidence from studies in individuals with HIV and in animal models have established that innate immunity is insufficient for control of *M. tuberculosis* infection.

Innate Immune Cells in Tuberculosis

M. tuberculosis interacts with diverse cell types. Macrophages have been the longstanding target of attention, ever since the studies of Florence Sabin and colleagues^{112,113} in the 1920s revealed that tubercle bacilli dwell in mononuclear cells. Although alveolar macrophages are widely believed to be the initial cells to encounter *M. tuberculosis* after inhalation of small droplet nuclei, the inflammatory macrophages recruited to the site of infection from the blood are likely to be the major reservoirs of the bacteria. In addition, neutrophils^{114–116} are increasingly recognized as having important roles as cellular sites of infection and contributors to innate immune responses in tuberculosis. In close contacts of pulmonary tuberculosis cases, a lower neutrophil count was associated with a higher likelihood of acquiring infection, and neutrophils contributed to killing of *M. tuberculosis* in an in vitro whole blood assay.¹¹⁶ Dendritic cells have also been shown to contain *M. tuberculosis* both in humans and experimentally infected mice^{117,118}; these cells serve as the dominant source of the cytokine IL-12, and they transport tubercle bacilli from the lungs to the local draining lymph nodes, where antigen-specific T-cell responses are initiated.¹¹⁹ Mononuclear phagocytes, especially dendritic cells and cytokine-activated macrophages, are also specialized to present mycobacterial antigens for recognition by CD4⁺ T cells.

M. tuberculosis enters macrophages, dendritic cells, and neutrophils by undergoing phagocytosis, using any of multiple distinct receptors that recognize ligands expressed on the bacteria.¹²⁰ In addition to phagocytic receptors, specific components of the bacteria are recognized by pattern-recognition receptors including TLR 2, 4, and 9; NOD2; DC-SIGN; Dectin-1; Mincle; and MCL.¹²¹ These receptors do not mediate phagocytosis but initiate signaling that results in secretion of specific proinflammatory and anti-inflammatory cytokines, as well as cell activation and differentiation.

In addition to mononuclear and polymorphonuclear phagocytes, certain innate lymphocytes, including *natural killer T* (NKT) cells and at least two subsets of innate T lymphocytes, respond to *M. tuberculosis* infection¹²² and are believed to be a source of cytokines early after infection, before adaptive immune responses are activated. NKT cells recognize host molecules expressed on stressed cells while invariant NKT cells recognize complex host and foreign lipids bound to the HLA class I-related molecule, CD1d. In vitro studies indicate that invariant NKT cells can be activated to secrete IFN- γ and granulysin and restrict growth of intracellular *M. tuberculosis*.¹²³ Invariant NKT cells are depleted from the blood in patients with active tuberculosis, indicating that they are involved in the response to *M. tuberculosis* in vivo.^{124,125} *Mucosal-Associated Invariant T cells* (MAITs) recognize bacterial metabolites of B vitamins, bound to an HLA class I-like molecule termed MR1, and are activated by cells infected with *M. tuberculosis* or certain other bacteria.^{126,127} Their abundance and location suggest that MAITs may be involved in clearance of *M. tuberculosis* inhaled in droplet nuclei that are too large to reach the alveoli. MAITs are depleted from blood in people infected with HIV, most likely

through an indirect effect, and are not fully reconstituted with antiretroviral therapy.^{128,129}

Molecular Mediators of Innate Immunity in Tuberculosis

Macrophages and dendritic cells respond to *M. tuberculosis* by secreting cytokines with distinct activities that contribute to control of infection and regulate specific aspects of immunity. Of the cytokines induced by *M. tuberculosis*, tumor necrosis factor (TNF) is especially well characterized as essential for immunity to tuberculosis in humans. Patients with rheumatoid arthritis and other conditions that are treated with agents that block TNF activity have up to a 25-fold higher risk of tuberculosis than in control populations¹³⁰ and are more likely to have disseminated infection.¹³¹ The risk of tuberculosis is higher in patients treated with neutralizing antibodies to TNF than with soluble receptor analogues.¹³⁰ TNF contributes to immunity to tuberculosis by activating microbicidal activities of macrophages¹³² and by modulating death of infected cells.¹³²⁻¹³⁴ In addition, one of the antibodies to TNF, infliximab, when administered to patients with rheumatoid arthritis, depletes a specific subset of CD8⁺ T cells that contain membrane-bound TNF and contribute to killing intracellular *M. tuberculosis* in an in vitro assay.¹³⁵

IFN- γ plays an essential role in immune control of tuberculosis. IFN- γ -deficient^{136,137} or IFN- γ receptor-deficient⁸⁷ mice succumb to rapidly progressive *M. tuberculosis* infection and, in patients with IFN- γ receptor mutations, tuberculosis is especially clinically severe (disseminated and/or recurrent).¹³⁸ IFN- γ is believed to contribute to immune control of tuberculosis through activating the microbicidal activities of macrophages, including through autophagy,^{139,140} and by modulating inflammation at the site of infection.^{87,141} Although multiple cell types can be sources of IFN- γ , the principal cellular sources are lymphocytes, including innate T cells, as well as adaptive CD4⁺ and CD8⁺ T cells.

Interleukin-12 (IL-12) is another essential innate cytokine for immunity to tuberculosis. The best-characterized role of IL-12 is in directing differentiation of CD4 T cells into type 1 T helper (Th1) cells that secrete IFN- γ and contribute to control of tuberculosis (see later). Evidence that IL-12 is essential for control of tuberculosis is provided by experiments in IL-12-deficient mice^{142,143} and by observations that children with mutations in the IL-12 receptor beta-1 chain are susceptible to tuberculosis and other mycobacterial infections.¹⁴⁴

Finally, vitamin D has been shown by increasingly strong evidence to contribute to human immunity to tuberculosis. Vitamin D and tuberculosis share a long history; indeed, some believe that if there was a benefit of sanatoria, it may be attributable in part to “heliotherapy,” exposure to sunlight, causing activation of vitamin D. More pertinent is that multiple studies have found low serum vitamin D levels in patients with tuberculosis (reviewed in Martineau¹⁴⁵). Moreover, a prospective study found that household contacts of persons with infectious tuberculosis were more likely to progress to active disease if they were vitamin D deficient at baseline.¹⁴⁶ In vitro studies have demonstrated that vitamin D treatment of *M. tuberculosis*-infected human macrophages leads to restriction of intracellular bacterial

replication through induction of the antibacterial peptide, cathelicidin.^{147,148} Additional studies have revealed that vitamin D is essential for the antimycobacterial action of IFN- γ on human macrophages, acting through induction of cathelicidin and activation of autophagy.¹³⁹ So far, attempts to augment the effects of chemotherapy for tuberculosis by the addition of vitamin D have had limited effects on microbiological end points¹⁴⁵ but clearly accelerate the resolution of inflammation.¹⁴⁹

ADAPTIVE IMMUNITY TO MYCOBACTERIUM TUBERCULOSIS

Early studies of the mechanisms of immunity to mycobacteria found that adoptive transfer of cells, but not serum, conferred cutaneous hypersensitivity to tuberculin on the recipients.¹⁵⁰ This initial observation was followed by studies that revealed that cell transfer also improved the ability to control mycobacteria¹⁵¹⁻¹⁵³ and that the responsible cells were T lymphocytes.¹⁵⁴ Thus, the focus of immunology studies in tuberculosis has been on T cells rather than antibodies.

CD4⁺ T Cells

CD4⁺ T cells are essential for immunity to tuberculosis. In mice, depleting CD4⁺ cells or impairing their development (by deleting MHC class II molecules, which bind antigenic peptides and are essential for development of CD4⁺ T cells) markedly accelerates the lethal course of infection.¹⁵⁵ In humans coinfecting with HIV, the progressive depletion of CD4⁺ cells increases the risk of tuberculosis and reconstitution of CD4⁺ T cells by antiretroviral therapy reduces the risk of tuberculosis.⁶² In addition to increased risk of tuberculosis per se, profound depletion of CD4⁺ T cells by HIV alters the clinical manifestations, with a higher frequency of extrapulmonary disease and a lower frequency of cavitary lung lesions.⁶²

Although the principal function of CD4⁺ T cells is to secrete cytokines such as IFN- γ , TNF, IL-2, IL-4, IL-17, or IL-22, some CD4⁺ T cells also possess cytolytic activity and can kill *M. tuberculosis*-infected cells.¹⁵⁶ Several studies have revealed that multifunctional CD4⁺ T cells (which produce multiple distinct cytokines per cell) are more common in subjects with latent TB infection, while monofunctional CD4⁺ T cells (which produce only one cytokine, usually TNF) are more common in those with active tuberculosis.^{157,158} Together, these findings indicate that multifunctional T cells may be especially important in preventing progression from latent to active tuberculosis.

CD8⁺ T Cells

Patients also develop antigen-specific CD8⁺ T-cell responses in tuberculosis. Although the functional contribution of CD8⁺ T cells in human tuberculosis is not well defined, CD8⁺ T cells contribute to control of *M. tuberculosis* in experimentally infected cattle and mice.¹⁵⁹ Evidence for a functional role of human CD8⁺ T cells in tuberculosis is provided by the discovery that treatment of patients with rheumatoid arthritis with the anti-TNF antibody, infliximab, increases the risk of tuberculosis and depletes a specific subset of CD8⁺ T cells that contribute to killing of *M. tuberculosis* in vitro.¹³⁵ *M. tuberculosis* antigen-specific CD8⁺ T cells are

detected more frequently in active tuberculosis than during latent infection,¹⁶⁰ suggesting that CD8⁺ T cells principally respond when the bacterial burden is especially high.¹⁶¹

***Mycobacterium Tuberculosis* Antigens Recognized by Human T Cells**

Classical T cells recognize peptide fragments of proteins (including from bacteria), bound to MHC (HLA in humans) class II (CD4⁺ T cells) or class I (CD8⁺ T cells) molecules on dendritic cells and macrophages. Although most studies have focused on a restricted number of secreted *M. tuberculosis* antigens, emerging evidence indicates that a broad range of mycobacterial proteins can provide peptide fragments (epitopes) that bind HLA class II molecules and are recognized by CD4⁺ T cells of people infected with *M. tuberculosis*.¹⁶²

In addition to providing protection against active disease, T-cell responses to *M. tuberculosis* antigens are the basis for TST and for *IFN-γ* release assays (IGRA, such as Quantiferon-TB and T-SPOT.TB). As noted in a separate section, the enhanced specificity of IGRAs over TSTs for *M. tuberculosis* infection is due to the use of two antigens (ESAT-6 and CFP-10) that are present in all strains of *M. tuberculosis* and uniformly absent from BCG vaccines. Insight into another potential basis for discordant results between TSTs and IGRAs is provided by the identification of antigens present in the *purified protein derivative* (PPD) used for TSTs. PPD is dominated by the presence of *M. tuberculosis* chaperone proteins (termed GroES, GroEL2, HspX, and DnaK), and contains little ESAT-6 or CFP-10.¹⁶³ Therefore, these diagnostic tests, in addition to depending on different procedures, measure responses to different bacterial antigens.

CONTRIBUTIONS OF IMMUNE RESPONSES TO TUBERCULOSIS PATHOLOGY

Tuberculosis is a prime example of an infection in which immune responses clearly contribute to the pathology of the disease, suggesting that the balance between protection and pathology requires tight regulation. For example, treatment with immunosuppressive corticosteroids predisposes to tuberculosis,¹⁶⁴ can mask the symptoms and reduce the radiographic manifestations of pulmonary tuberculosis,¹⁶⁵ and prevents mortality in some patients with tuberculous meningitis.^{166,167}

Analogous to autoimmune diseases such as type 1 diabetes mellitus and multiple sclerosis, T-cell responses can contribute to tissue destruction in tuberculosis. In mice selectively lacking PD-1, a molecule that transmits inhibitory signals in T cells, *M. tuberculosis* infection is rapidly lethal, due to excessive CD4⁺ T-cell activation and very high levels of proinflammatory cytokines.¹⁶⁸ In humans coinfecting with HIV, the frequency of cavitory lesions on chest radiographs is directly correlated with the CD4⁺ T-cell count at the time of diagnosis of tuberculosis.⁶² Since cavitory tuberculosis causes more secondary cases than noncavitory tuberculosis,^{169,170} mycobacterial induction of detrimental T-cell responses may benefit the bacteria by promoting transmission. Examination of the human T-cell epitopes in diverse strains of *M. tuberculosis* revealed a high level of sequence conservation (rather than variation, as in

the antigenic targets in other pathogens), implying an evolutionary benefit to the bacteria from T-cell recognition.¹⁴ These results suggest that T-cell responses to *M. tuberculosis*, which provide a benefit to infected people, can also benefit the bacteria by promoting pathology in a fraction of infected people, resulting in enhanced transmission. This finding may guide tuberculosis vaccine antigen selection and emphasizes the need to evaluate the potential adverse effects of new tuberculosis vaccines.

EXOGENOUS VERSUS ENDOGENOUS INFECTION

One of the historical controversies in tuberculosis has been the extent to which tuberculosis can be attributed to new infection by recently inhaled exogenous organisms (i.e., from the environment) as opposed to a reactivation of viable bacilli that have been maintained for many years in a dormant or growth-restricted state within the body.¹⁷¹ This concept is important in that current tuberculosis control efforts are based largely on the idea that most tuberculosis in low-incidence areas is the result of endogenous reactivation. Thus, prevention entails identification of infected persons and giving them preventive therapy with isoniazid.

Since the early 1990s, genotyping of *M. tuberculosis* has been successfully used to determine if tuberculosis is due to exogenous or endogenous infection. *M. tuberculosis* DNA fingerprinting derived from different genotyping markers and methods has been used to track specific isolates of *M. tuberculosis* in a community.¹⁷² For example, isolates of tubercle bacilli from HIV-positive individuals, in health care facilities or correctional institutions, frequently show identical genotypes (Fig. 35-4), indicating that these individuals

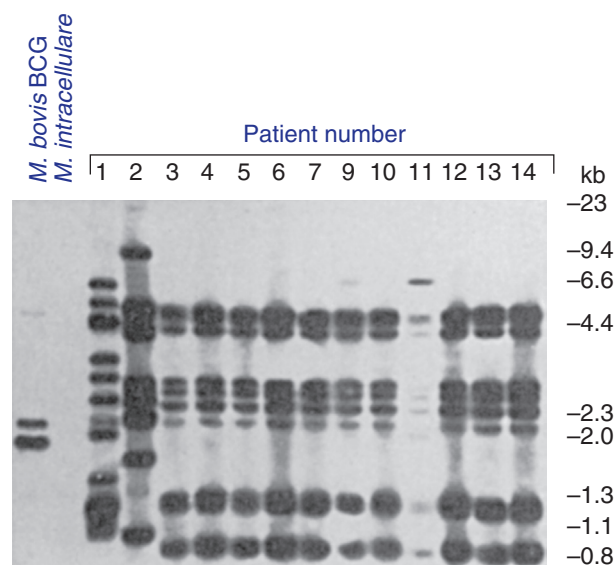


Figure 35-4 Gel electrophoresis of DNA extracted from organisms isolated from patients in an outbreak of tuberculosis in San Francisco. Cases 3 through 14 were linked epidemiologically, whereas cases 1 and 2 were not. This is an example of the use of restriction fragment length polymorphism analysis to track strains of *Mycobacterium tuberculosis*. (From Daley CL, Small PM, Schechter GF, et al: An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus: an analysis using restriction fragment length polymorphisms. *N Engl J Med* 326:231–235, 1992.)

were probably infected by the same source within the facility.^{59,173} In such situations, tuberculosis can be assumed to be due to a recent exogenous infection with rapid progression to active tuberculosis. In contrast, patients with a unique DNA fingerprint are considered to have tuberculosis due to reactivation of latent infection acquired previously. Genotyping methods can similarly be used to differentiate relapse from reinfection in a patient with recurrent tuberculosis: a patient with relapse will have a similar *M. tuberculosis* DNA fingerprint in both episodes while a patient with reinfection will have different strains.¹⁷⁴⁻¹⁷⁷ Since the early 1990s, these markers have also enabled tuberculosis control programs, mainly in high-income settings, to track specific isolates of *M. tuberculosis* in a community¹⁷² to determine population-level risk factors for transmission, establish tailored public health strategies, and gauge the success of control measures.¹⁷⁸

The genetic markers used to track strains in the community are sufficiently polymorphic to distinguish among unrelated isolates yet stable enough to recognize isolates that are part of the chain of transmission. These markers include (1) the insertion element (IS) 6110,¹⁷⁹ (2) the *polymorphic GC-rich repetitive sequences* (PGRS), (3) polymorphisms in the *clustered regularly interspaced short palindromic repeats* (CRISPRs),¹⁸⁰ and (4) the *mycobacterial interspersed repetitive unit* (MIRU)–*variable number tandem repeats* (VNTRs).¹⁸¹ The genotypes using CRISPR (also known as spoligotypes) and MIRU-VNTR (MIRU-type) are currently widely used to track a strain in the community. For both methods, there are online databases in which researchers can compare (and submit) their genotypes.^{182,183} Most recently, the availability of high-throughput technology and the dramatic decrease in costs have allowed for the use of whole genome sequencing to identify mutations as markers to study transmission of *M. tuberculosis* in a community.¹⁸⁴⁻¹⁸⁹ Compared with the other genetic markers, whole genome sequencing allows the identification of microevolutionary events (i.e., single nucleotide polymorphisms) within a chain of transmission, identifies epidemiologic links, and determines the directionality of the transmission events.

RISK FACTORS FOR DISEASE

After acquiring an infection, not all persons are at equal risk of developing disease. Many conditions increase the likelihood of tuberculosis and serve as markers of increased risk. As noted previously, in healthy populations, the risk of developing tuberculosis is highest during the first year after infection; between 3% and 10% of newly infected persons develop tuberculosis during this period. The three factors presumably involved are the pathogenicity of the bacterial strain, the dose of bacilli implanted in the lungs, and the adequacy of the host response in countering the invasion. The “inoculum effect” (in which the likelihood of infection is directly related to the dose of bacteria) has not been clearly demonstrated in humans but is strongly suggested by results of animal experiments.³⁴ It is currently assumed that beyond the first year after infection has taken place, the immune response has fully developed, the number of organisms present has been substantially reduced, and the

remaining bacterial population has shifted to a state of persistence and slow replication. Understanding how this latent infection can shift to disease is critical in controlling tuberculosis.

Age is one risk factor. Among persons with tuberculous infection, case rates vary markedly with age. Rates are considerably increased in infants and relatively increased in adolescents and young adults.¹⁹⁰ The reasons for the variations are not fully understood but are likely to relate to age-dependent influences on the effectiveness of the immune response.¹⁹¹

HIV infection is by far the most potent risk factor worldwide. In the era before effective antiviral therapy, Selwyn and coworkers¹⁹² found that 8 of 212 HIV-infected intravenous drug users developed tuberculosis in a 2-year period of observation, a case rate of 8 per 100 person-years of observation. Of these, 7 cases developed within a subset of 49 persons who were known to be TST positive. Thus, the case rate for persons who were dually infected with both HIV and *M. tuberculosis* was 7.9 per 100 person-years, which exceeds the rate in a population with tuberculous infection without HIV infection. It also appears that the risk of rapid progression of tuberculosis among persons who are infected with HIV and who then become infected with *M. tuberculosis* is tremendously increased, as has been demonstrated in descriptions of two such outbreaks.^{59,193} The reported rates of tuberculosis in cohorts of persons with HIV infection vary widely and depend on the prevalence of tuberculosis in the environment, particularly the presence of infectious cases; the frequency with which treatment for latent tuberculous infection is used; the severity of immune compromise within the HIV-infected group; and whether dually infected persons are receiving antiretroviral therapy, which substantially reduces the risk.^{194,195}

The only study conducted to address the incidence of tuberculosis prospectively in a broad-based group of persons with HIV infection in the United States—before the widespread use of combined antiretroviral therapy—was the Pulmonary Complications of HIV Infection study.¹⁹⁶ In this cohort, drawn from six centers across the country, the rate of tuberculosis was 0.71 per 100 person-years of observation. In multivariate analyses, the factors that were associated with increased rates were residence in New York City or Newark (the two East Coast centers), being TST-positive (reaction > 5 mm), and having a CD4⁺ cell count below 200 cells/μL.

Antiretroviral treatment of HIV markedly reduces the incidence of tuberculosis, although the effect is not complete. A meta-analysis that included 11 published studies revealed that antiretroviral treatment and reconstitution of CD4⁺ T-cell counts reduces the incidence of tuberculosis as much as sixfold.¹⁹⁷ However, despite immune reconstitution to CD4 T-cell counts greater than 700 cells/μL, the incidence of tuberculosis in antiretroviral-treated HIV-infected people remains 4.4-fold higher than in HIV-uninfected people in the same community.¹⁹⁸

In persons with both HIV and tuberculous infections, antiretroviral therapy and preventive treatment with isoniazid substantially decrease the incidence of tuberculosis. In a retrospective analysis of the incidence of tuberculosis among persons with HIV infection in Rio de Janeiro, Brazil, among patients who received neither antiretroviral

treatment nor isoniazid preventive therapy, the incidence of tuberculosis was 4/100 person-years.¹⁹⁹ Among patients who received antiretroviral therapy, the incidence was 1.9/100 person-years (95% confidence interval [CI], 1.7 to 2.2), and those treated with isoniazid had a rate of 1.3/100 person-years (95% CI, 0.4 to 3.0). However, the incidence among patients who received both antiretroviral therapy and isoniazid was only 0.8/100 person-years (95% CI, 0.3 to 1.5). Thus, there was a 76% reduction in tuberculosis risk among patients receiving both antiretroviral treatment and isoniazid. (Isoniazid preventive therapy is discussed in a later section.)

Inhibition of TNF is the other well-characterized risk factor for tuberculosis. TNF can be antagonized by treatment with a biologic agent, either with a monoclonal antibody to TNF itself or soluble receptor analogues that block the interaction of TNF with its receptor. As mentioned, TNF contributes to immunity to tuberculosis by activating microbicidal activities of macrophages¹³² and by modulating apoptosis.^{132,133} Patients treated with TNF antagonists have up to a 25-fold higher risk of tuberculosis than in control populations.¹³⁰ Neutralizing antibodies to TNF increase the risk several fold more and induce tuberculosis sooner than the soluble receptor analogues.²⁰⁰ This may be in part because antibodies to TNF also deplete a subset of CD8⁺ memory T cells that contribute to killing intracellular *M. tuberculosis* in an in vitro assay.¹³⁵ Screening patients by TST, followed by treatment of latent tuberculosis infection before initiation of TNF antagonists, reduces the risk of active tuberculosis in these patient populations.²⁰¹

Other conditions or therapies that interfere with cell-mediated immunity also increase the risk of tuberculosis. These relationships, although well described and generally accepted, are poorly quantified. Examples of these disorders include hematologic malignancies and cancer chemotherapy. In addition, conditions such as diabetes mellitus²⁰² and uremia are thought to fit into this general category of risk-enhancing diseases, although the basis for this effect is not established. The risk of tuberculosis is also increased considerably in persons with silicosis,²⁰³ presumably owing to the effect of silica on the function of pulmonary macrophages.

Genetic risk factors have been suggested by twin studies in which there was a greater concordance of disease in monozygotic than in dizygotic twins.²⁰⁴ However, it is difficult to separate them from linked environmental factors. Case rates among persons infected with *M. tuberculosis* living in Denmark in the 1950s were only 28 per 100,000 per year.²⁰⁵ This contrasts strikingly with annual rates of 1500 to 1800 per 100,000 in Eskimo populations in Alaska and Greenland.²⁰⁶ Genetic differences are also suggested by the pattern of tuberculosis noted among Filipinos in the U.S. Navy, whose rate of disease increased with duration of enlistment, in contrast to the decrease observed in blacks and whites.²⁰⁷

Undernutrition is known to interfere with cell-mediated responses and thus is thought to account for the increased frequency of tuberculosis in malnourished persons.²⁰⁸ In addition to overt malnutrition, other factors related to specific but poorly defined nutritional deficiencies may also be associated with an increased risk of tuberculosis. For example, observations suggest that risk is increased in

persons who have had a gastrectomy or an intestinal bypass procedure for weight control.²⁰⁹ Body build has also been related to the risk of disease among infected persons. In U.S. Navy personnel, rates of tuberculosis were nearly three times greater among men who were thin for their height; the increased incidence of tuberculosis did not appear to be related to nutritional status in that group.²⁰⁷

Vitamin D deficiency has also been linked to tuberculosis. Studies on several continents have documented a higher frequency of vitamin D deficiency in patients with active tuberculosis than in control subjects. Moreover, a study in South Africa revealed reciprocal seasonal variations in serum vitamin D levels and tuberculosis notification rates: during the winter, vitamin D levels were lowest and tuberculosis notifications were greatest, whereas the converse was true in the summer.²¹⁰ Because in vitro studies have revealed a role for vitamin D in regulating macrophage expression of antimicrobial peptides that restrict intracellular growth of *M. tuberculosis*, it is likely that vitamin D deficiency increases the risk of tuberculosis, rather than for vitamin D deficiency to be a consequence of tuberculosis.

Despite the number of risk factors for tuberculosis that have been identified, the majority of cases have no identified immunological or physiological abnormality.

DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION

As indicated previously, infection does not necessarily follow exposure to *M. tuberculosis*, but when infection develops, it causes a cell-mediated immune response that can be identified by a positive response to an intradermal test (TST) with purified protein derivative or a whole blood *IFN-γ* release assay (IGRA). Until recently the TST was the only test available to identify tuberculous infection. Although the TST continues to be used, IGRAs are widely used in high-resource settings.²¹¹⁻²¹³

TUBERCULIN SKIN TEST

Tuberculin was first prepared by Robert Koch in 1890 and was touted by him as being therapeutic for tuberculosis. Shortly thereafter, the diagnostic capabilities of the material were recognized through its use in animals. In 1934, Seibert and Glenn²¹⁴ prepared the first batch of a much more purified preparation, which they termed *purified protein derivative* (PPD). The most prevalent antigenic proteins in PPD are now known to be the bacterial heat shock proteins (or chaperonins) GroES, GroEL2, HspX, and DnaK.¹⁶³ The antigen is prepared in liquid form containing the detergent Tween 80 to decrease adsorption of protein to the glass of the vial. The standard intermediate tuberculin test consists of the intracutaneous injection (Mantoux method) of 0.1 mL of material, which contains 5 *tuberculin units* (TU). The site usually chosen is the volar surface of the forearm, but any accessible area can be used. A short-beveled 26- or 27-gauge needle should be used with a 1-mL graduated syringe. A properly placed intracutaneous injection should cause a well-demarcated wheal 6 to 10 mm in

diameter in which the hair follicles form dimples. Conventionally, the reading is done 48 to 72 hours after the injection, but it may be delayed for up to 1 week.²¹⁵

In persons such as hospital employees, who are likely to be tested repeatedly—if tuberculin negative at the outset—a two-step testing procedure is recommended to avoid confusing a boosted reaction with a true conversion.²¹⁶ The phenomenon of boosting can happen in a person who is infected but loses skin test reactivity after several years. In this situation, a single tuberculin test can be falsely negative, but the test itself can recall (i.e., boost) the waned reactivity. A subsequent test can then elicit a positive reaction. A positive reaction following a negative one may cause the person tested to be classified as a tuberculin converter. To elicit any potential boosted response and to categorize the person more accurately as infected or not infected, a second 5-TU tuberculin test is applied within 1 to 2 weeks of the first test. If the second test shows a positive reaction, it is interpreted as a boosted response indicative of prior infection; if the reaction remains negative, it is assumed to be truly negative.

The reaction to the test should be read by inspecting and palpating the area where the tuberculin was injected. The reaction size is determined by measuring the diameter of any induration with a ruler. The amount of erythema should not be taken into account; only the extent of induration is important. Readings must be recorded accurately in millimeters.

The interpretation of tuberculin tests requires clinical judgment, as well as an understanding of the test. In a population in which the only mycobacterial species causing infection is *M. tuberculosis*, the curve describing the distribution of reaction sizes in otherwise healthy infected persons given 5-TU PPD would be bell shaped, having a mode of 17 to 18 mm, with very few reactions less than 10 mm. Thus, defining the minimum reaction size indicative of tuberculous infection would be simple.²¹⁷ However, in many parts of the world, a portion of the population is infected with nontuberculous mycobacteria, which induce some degree of sensitization to tuberculin; inoculation with BCG, for many years the world's most commonly used vaccination, has the same enhancing effect on tuberculin reactivity. Although these reactions are on the whole smaller than those caused by *M. tuberculosis*, they blur the distinction between reactions in persons infected with *M. tuberculosis* and those not infected. On the basis of a large amount of epidemiologic data and skin testing with antigens prepared from nontuberculous mycobacteria, the best compromise between false-positive and false-negative readings to 5-TU PPD tuberculin tests is 10 mm. Thus, under most circumstances, a reading of 10 mm or more is considered indicative of infection with *M. tuberculosis*. However, in some situations, smaller reactions should be taken to indicate tuberculous infection. For example, a reaction of 5 mm in a child who is a contact of a person with smear-positive tuberculosis probably indicates tuberculous infection and is considered positive. Likewise, a 5-mm reaction in a person with known HIV infection should be considered positive. In the United States, the history of BCG administration is generally ignored in interpreting the results of the TST.²¹⁸

There are several reasons why the tuberculin reaction may be interpreted as negative in the presence of tuberculous infection. These include errors in application or reading of the test result, usually related to the inexperience of the tester/reader, and should be easily correctable with proper training. Problems with the antigen are infrequent unless it has been improperly handled. Many disease states, especially HIV infection, interfere with cell-mediated immune responses. Lymphoreticular malignancies such as Hodgkin disease are potent suppressors of cell-mediated immunity. Corticosteroids and immunosuppressive drugs decrease tuberculin reactivity if the patient is on a sufficient dose for a sufficient period of time; for corticosteroids, the minimum dose is 15 to 20 mg of prednisone or the equivalent of another preparation, given daily for 2 to 3 weeks.²¹⁹ As stated previously, advancing age is associated with loss of tuberculin reactivity, although it may be recalled.²¹⁵ Malnutrition also may cause defects in cell-mediated immunity with consequent diminished tuberculin reactivity. Finally, pleural tuberculosis and overwhelming tuberculosis itself may cause diminished or absent tuberculin responsiveness.

Even when the test is applied and the result is read with particular care in patients with proven tuberculosis and no apparent immunosuppression at the time they are admitted to a hospital, only 80% to 85% have reactions of 10 mm or more to 5-TU PPD.²²⁰ Thus, a negative tuberculin test result cannot be used to exclude tuberculosis as a diagnostic possibility.

The interpretation of the TST in persons with HIV infection is a particular problem because of the progressive immunosuppression in HIV disease. Individuals infected with HIV are less likely to have a positive tuberculin reaction. In a cross-sectional study of persons with HIV infection and a wide range of CD4⁺ lymphocyte counts, anergy—defined as lack of any reaction to tuberculin (5 TU) plus mumps and *Candida* antigens—was more common when the CD4⁺ count was less than 400 cells/ μ L.²²¹

INTERFERON- γ RELEASE ASSAYS

IFN- γ release assays (IGRAs) are used for the diagnosis of *latent tuberculous infection* (LTBI); these assays cannot distinguish LTBI from active tuberculosis. Two IGRAs are currently approved in the United States, the QuantiFERON-TB test and the T-SPOT.TB test. The QuantiFERON-TB (Qiagen, Alameda, CA) tests, specifically QuantiFERON-TB Gold and *QuantiFERON-TB Gold In-tube* (QFT-GIT), measure the amount of IFN- γ released from sensitized lymphocytes in whole blood incubated overnight with mixtures of *M. tuberculosis* antigens, ESAT-6 and CFP-10.²²² A newer-generation test includes an additional antigen, Tb7.7. The other approved test, the T-SPOT.TB, utilizes an ELISPOT format to quantify the number of cells in peripheral blood that secrete IFN- γ when stimulated with ESAT-6 and CFP-10 (Oxford Immunotec, Abingdon, United Kingdom).²²³

Neither the TST nor IGRAs have value for the diagnosis of active tuberculosis in adults. A systematic review and meta-analysis showed that the sensitivity to diagnose tuberculosis in low- and middle-income countries was 76% for T-SPOT.TB and 60% for QFT-GIT. The specificity was 61% and 52%, respectively.²²⁴

Compared with the TST, the IGRAs have several advantages: The tests can be performed in one patient visit, they are more specific in the presence of BCG vaccination or infection with nontuberculous mycobacteria, they are not subject to reader variability, and they do not stimulate waned immunity (the booster reaction, described earlier).²²³ A systematic review showed that IGRAs have excellent specificity and are not affected by BCG vaccination (due to the absence of ESAT-6 and CFP-10 from all strains of BCG).²²⁵ The sensitivity to diagnose infection (using culture-positive *M. tuberculosis* cases as the reference) was variable in the different studies, but T-SPOT.TB appeared to be more sensitive than QuantiFERON-TB Gold and QFT-GIT and the TST.^{225,226} In patients with HIV infection, the responses to TST and QFT-GIT correlate with the degree of immunodeficiency, whereas results of the T-SPOT.TB are independent of the level of CD4 T-cell depletion,²²⁷ which may explain the variable results of the different IFN- γ -release assays and TST among patients with HIV infection.²²⁸

IGRAs have a few disadvantages: The tests require drawing blood and processing it within a specific time, and they are less well known than the TST and, therefore, have much less evidence to characterize their performance for diagnosing latent tuberculous infection and for epidemiologic studies. For example, risk factors for conversion (from negative to positive) and reversion (from positive to negative) were different for T-SPOT.TB compared with the TST.²²⁹ The authors attributed these findings to a lack of understanding of the dynamics of the IFN- γ response to ESAT-6 and CFP-10. Also, because there is no knowledge about the time required for the IFN- γ release assays to become positive after the onset of infection, the interpretation of a negative IFN- γ release assay requires caution.

Other authors, who also found a substantial proportion of reversions, attributed their findings to the decrease of the bacterial load due to treatment and to the natural resolution of the infection.²³⁰ In a study in the United Kingdom, Wilkinson and colleagues,²³¹ using T-SPOT.TB, showed an early rise in spot-forming counts in patients given isoniazid and rifampin, then a reduction at month 3. No changes were observed in those without treatment. In India, Pai and colleagues²³² followed 216 nursing and medical students and observed that 9 (24%) of the 38 individuals with an initial positive QFT-GIT test had reversion, which was associated with a negative TST result. Interestingly, those with skin test conversion also had an increase in levels of IFN- γ . Taken together, these data underscore the uncertainty regarding the interpretation of the IFN- γ release assays in providing information about the outcome of infection with *M. tuberculosis*, both treated and untreated.

Currently, the U.S. Centers for Disease Control and Prevention (CDC) recommends using the QuantiFERON-TB Gold test for the same indications as the TST: for evaluating persons suspected of having tuberculosis and for screening, including contacts of an infectious case of tuberculosis, children younger than 17 years of age, pregnant women, and persons at increased risk of tuberculosis, particularly those with HIV infection, recent immigrants who have had BCG vaccination, and health care workers. The QuantiFERON-TB Gold test usually can be used in place of—and not in addition to—the TST.²³³

DIAGNOSIS OF PULMONARY TUBERCULOSIS

Currently, in the United States, 69% of new cases of tuberculosis involve the lungs only, 21% involve extrapulmonary sites only, and 10% involve both locations.²⁷ Although both miliary (disseminated) tuberculosis and pleural tuberculosis involve the lungs and/or pleural space, they are considered extrapulmonary forms of the disease.

DIAGNOSTIC EVALUATION

Clinicians must recognize that, in evaluating persons who may have tuberculosis, they are assuming an essential public health function and providing care to an individual patient. Early and accurate diagnosis is critical to tuberculosis care and control.²³⁴ Despite dramatically improved access to high-quality tuberculosis services worldwide during the past 2 decades, there is substantial evidence that failure to identify cases early is a major weakness in efforts to ensure optimal outcomes for the patient and to control the disease. Diagnostic delays result in ongoing transmission in the community and more severe, progressive disease in the affected person.

Globally there are three main reasons for delays in diagnosing tuberculosis: the affected person not seeking or not having access to care; the provider not suspecting the disease; and the lack of sensitivity of the most commonly available diagnostic test, sputum (or other specimen) smear microscopy.^{235,236} Approaches to reducing these delays are, obviously, quite different. Reducing delays on the part of the affected person entails providing accessible health care facilities, enhancing community and individual awareness, and active case finding in high-risk populations. Reducing provider delay is best approached by increasing provider awareness of the risks for and symptoms of tuberculosis and of the appropriate and available diagnostic tests. Rapid molecular tests that increase both the speed and the sensitivity for identifying *Mycobacterium tuberculosis* are increasingly available and, in some situations, are recommended by the WHO as the initial diagnostic test.

PATIENT HISTORY

There must be a clinical suspicion of tuberculosis before proper diagnostic tests are ordered. Clinical suspicion is prompted largely by the presence of symptoms and by awareness of comorbidities and epidemiologic circumstances that increase the risk of tuberculosis in an individual patient. These risks are summarized in the WHO guidelines for screening for tuberculosis.²³⁷ The most commonly reported symptom of pulmonary tuberculosis is persistent cough that generally, but not always, is productive of mucus and sometimes blood. In persons with tuberculosis, the cough is often accompanied by systemic symptoms, such as fever, night sweats, and weight loss. In addition, findings such as lymphadenopathy, consistent with concurrent extrapulmonary tuberculosis, may be noted, especially in patients with HIV infection. However, chronic cough with sputum production is not always present, even among

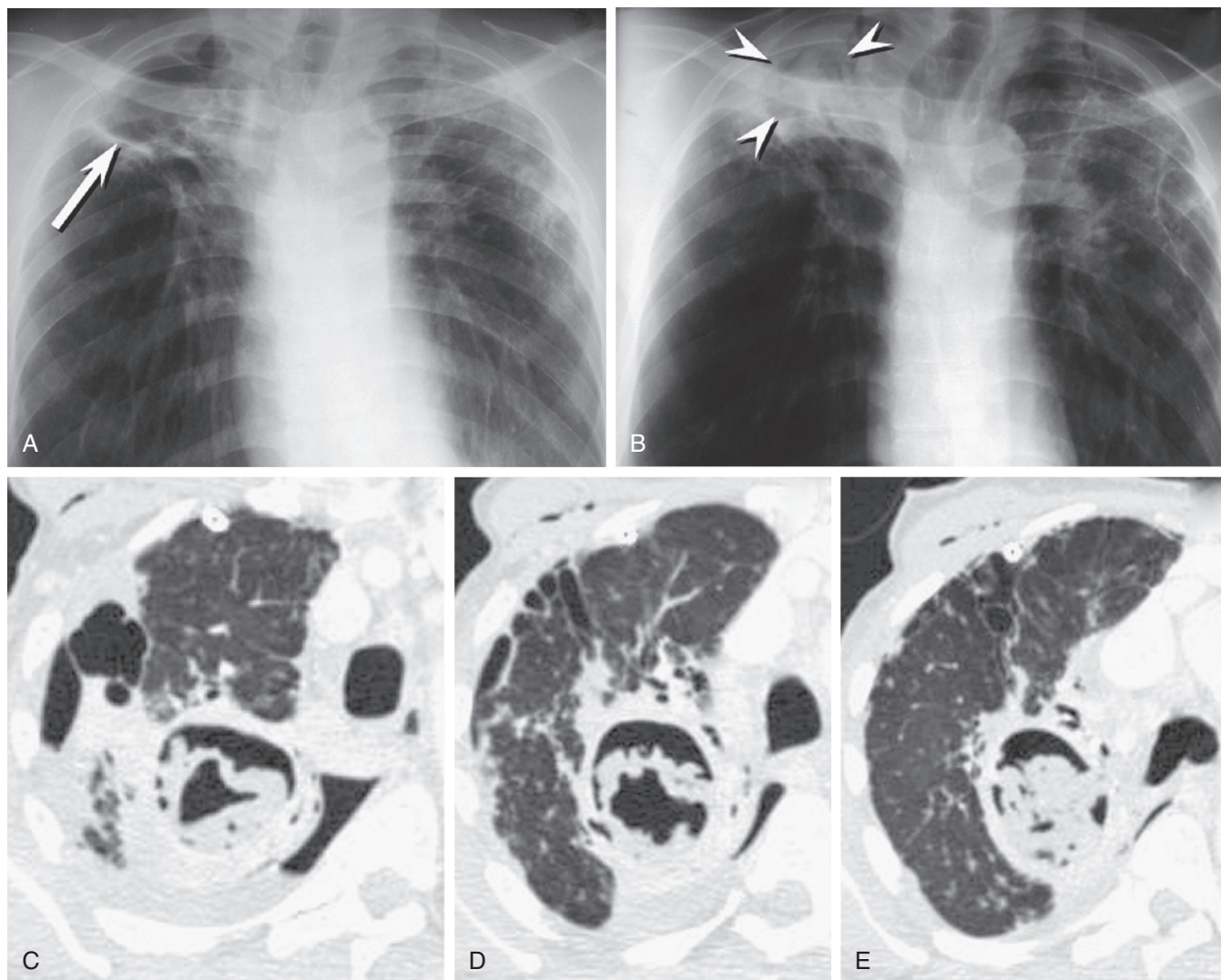


Figure 35-5 Aspergilloma developing in an old tuberculosis cavity. **A**, Front chest radiograph in a patient with tuberculosis shows bilateral upper lobe fibronodular changes with a right apical cavity (arrow). **B**, Frontal chest radiograph several years after (A) when the patient complained of hemoptysis shows development of an opacity within the right apical cavity (arrowheads) representing aspergilloma. **C-E**, Focused axial chest CT confirms the presence of aspergilloma. (Courtesy Michael Gotway, MD.)

persons with sputum smears showing acid-fast bacilli. Data from several tuberculosis prevalence surveys in countries with a high incidence of the disease show that an important proportion of persons with active tuberculosis do not have cough of 2 or more weeks, a criterion that, conventionally, has been used to define suspected tuberculosis.^{238,239} In these studies, 10% to 25% of patients with bacteriologically confirmed tuberculosis do not report cough. These data suggest that evaluation for tuberculosis, using a symptom review that includes cough of any duration, fever, night sweats or weight loss, may be indicated in selected risk groups, especially in areas where there is a high prevalence of the disease and in high-risk populations and individuals with increased susceptibility, such as persons with HIV infection. Use of this broadened set of questions in a population of persons with HIV infection was found to have a negative predictive value of 97.7% for tuberculosis.²⁴⁰ The presence of any one of the symptoms should be viewed as an indication for an evaluation for tuberculosis in high-risk groups or in high-incidence areas.

Hemoptysis is usually seen with more extensive involvement but does not necessarily indicate an active tuberculous process. Hemoptysis may also result from bronchiectasis left as a residual of healed tuberculosis; from rupture of a dilated vessel in the wall of an old cavity (*Rasmussen aneurysm*); from bacterial or fungal infection (especially in the form of a fungus ball [*aspergilloma* or *mycetoma*]) in an old residual cavity (Fig. 35-5); or from erosion of calcified lesions into the lumen of an airway (*broncholithiasis*).

The systemic features of tuberculosis include fever in approximately 35% to 80%, malaise, and weight loss; there may be a variety of hematologic abnormalities, especially leukocytosis and anemia.²⁴¹⁻²⁴³

PHYSICAL EXAMINATION

In most cases, physical findings are not particularly helpful. Crackles may be heard in the area of involvement, along with bronchial breath sounds, when lung consolidation is close to the chest wall. Amphoric breath sounds (like the

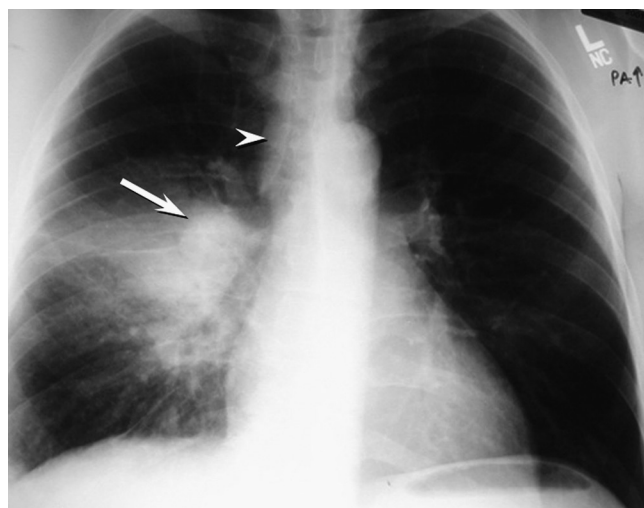


Figure 35-6 Primary tuberculosis. Frontal chest radiograph in a young adult shows superior segment right lower lobe consolidation associated with right hilar lymphadenopathy (arrow) due to primary *Mycobacterium tuberculosis* infection. Mild right paratracheal lymph node enlargement (arrowhead) is also visible. (Courtesy Michael Gotway, MD.)

low sound of blowing across the top of an open bottle) may be indicative of a cavity. Findings such as lymph node enlargement, suggestive of extrapulmonary tuberculosis, may also indicate concurrent pulmonary involvement.

RADIOGRAPHIC FEATURES

Radiographic examination of the chest is commonly the first diagnostic study undertaken, after the history and physical examination.^{244,245} However, in resource-limited settings, a chest radiograph is not necessarily included as part of the routine evaluation because of cost, complexity, and nonspecificity of the findings.

Pulmonary tuberculosis nearly always causes detectable abnormalities on the chest radiograph, although in patients with HIV infection, a chest radiograph may be normal in up to 11% of patients with positive sputum cultures.¹⁹⁶ In primary tuberculosis, resulting from recent infection, the process is generally seen as a middle or lower lung zone opacity, often associated with ipsilateral hilar adenopathy (Fig. 35-6). Atelectasis may result from compression of airways by enlarged lymph nodes. If the primary process persists beyond the time when specific cell-mediated immunity develops, cavities may form (so-called progressive primary tuberculosis).

Tuberculosis that develops at a time remote from the original infection (endogenous reactivation) usually involves the upper lobes of one or both lungs. Cavitation is common in this form of tuberculosis. The most frequent sites are the apical and posterior segments of the right upper lobe (Fig. 35-7) and the apical-posterior segment of the left upper lobe. Healing of the tuberculous lesions usually results in development of a fibrotic scar with shrinkage of the lung parenchyma and, often, calcification. Involvement of the anterior segments alone is unusual. In the immunocompetent adult with tuberculosis, intrathoracic adenopathy is uncommon. When the disease progresses, infected material may be spread via the airways

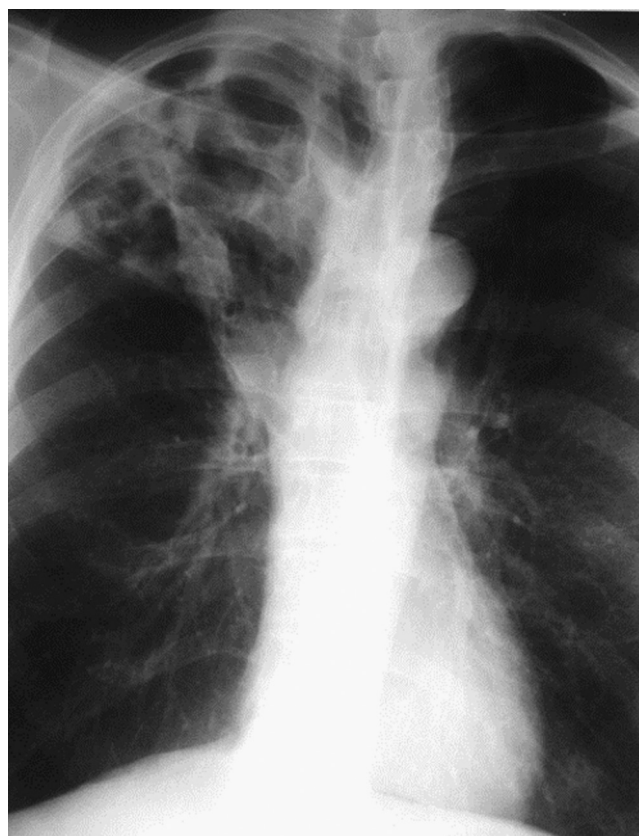


Figure 35-7 Cavitary tuberculosis. Frontal chest radiograph in a patient with tuberculosis shows extensive right upper lobe cavitation. (Courtesy Michael Gotway, MD.)



Figure 35-8 Disseminated tuberculosis. Frontal chest radiograph in a patient with disseminated tuberculosis shows numerous small, randomly distributed nodules bilaterally, representing the miliary pattern. (Courtesy Michael Gotway, MD.)

(i.e., "bronchogenic" spread) into the lower portions of the involved lung or to the other lung. Erosion of a parenchymal focus of tuberculosis into a blood or lymph vessel may result in dissemination of the organism and a miliary pattern on the chest imaging (Fig. 35-8, see Fig. 18-25). Radiographic findings in HIV-infected patients are affected

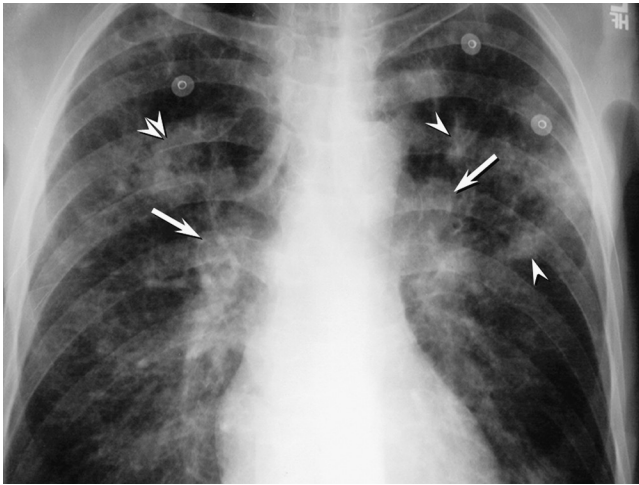


Figure 35-9 Tuberculosis in an HIV patient. Frontal chest radiograph in a patient with tuberculosis shows bilateral hilar lymph node enlargement (arrows) associated with poorly defined parenchymal nodular opacities (arrowheads) and nodular areas of consolidation (double arrowheads). (Courtesy Michael Gotway, MD.)

by the degree of immunosuppression. As further explained and illustrated in Chapter 90, tuberculosis relatively early in the course of HIV infection tends to produce typical radiographic findings with predominantly upper lobe infiltration and cavitation.²⁴⁶ With more advanced HIV disease, the radiographic findings become more “atypical”: cavitation is uncommon, and lower lung zone or diffuse opacities and intrathoracic adenopathy are frequent (Fig. 35-9). Surprisingly, a substantial number of HIV-infected patients with pulmonary tuberculosis had normal radiographs at the end of their course of treatment.²⁴⁷

The activity of a presumed tuberculous process cannot be determined simply from a single radiographic examination of the chest. A cavity might be a sterile residual of an old infection, whereas a fibrotic-appearing lesion may be active. Conversely, not all radiographic worsening of the residua of prior tuberculous lesions can be ascribed to reactivation of the disease, although such worsening should always be of concern. Superimposed infections with other organisms or bleeding from bronchiectasis or from residual cavities may cause new infiltrations to appear. In addition, carcinomas may arise from within the area of scarring (so-called scar carcinomas) and be the cause of radiographic changes.

From this discussion, it should be obvious that the chest radiograph, although extremely valuable, cannot provide a definitive diagnosis of tuberculosis. Because of the radiographic similarities among the other disorders in the differential diagnosis, and because of the uncertainties in assessing disease activity and in determining the reasons for progressive radiographic changes, careful microbiologic evaluation is always indicated. A nondiagnostic microbiologic evaluation should prompt a careful assessment for other causes of the radiographic abnormality.

BACTERIOLOGIC EVALUATION

As noted previously, a definitive diagnosis of tuberculosis can be established only by isolation of tubercle bacilli in

culture or by identification of specific nucleic acid sequences. When the lung is involved, sputum is the initial specimen of choice. Two sputum specimens should be collected, which can be obtained the same day because the sensitivity of tests using same-day specimens is similar to tests using specimens collected on different days.²⁴⁸ The collection of the sputum in 1 day allows results to be available the same day, thereby increasing the efficiency of sputum smear microscopy.²⁴⁸ The strategies for same-day microscopy include the preparation of 2 or 3 slides from sputum samples obtained the first day the patient is assessed. Collecting more than two sputum specimens increases the yield only slightly.²⁴⁹

There are several options for obtaining specimens from patients who are not producing sputum. The first and most useful in terms of yield and avoidance of patient discomfort is inducing sputum production by the inhalation of a hypertonic (3% to 5%) saline mist generated by an ultrasonic nebulizer. Sputum induced by this technique is clear and resembles saliva; thus, it must be properly labeled or it may be discarded by the laboratory. This is a benign and well-tolerated procedure, although bronchospasm may be precipitated in asthmatic patients.

Sampling of gastric contents via a nasogastric tube has a lower yield than sputum induction and is more complicated and uncomfortable for the patient. However, in children and some adults, gastric contents may be the only specimen that can be obtained. Gastric lavage should be performed early in the morning before the patient has gotten out of bed, eaten, or performed dental hygiene. Once the specimen is obtained, the specimen should be sent to the laboratory and processed the same day. To prolong the viability of the bacteria, neutralization of gastric acid with an equal volume of sterile 1% sodium bicarbonate is recommended when the specimen is not processed immediately.^{250,251}

Depending on the clinical circumstances, if the sputum is negative or cannot be obtained, the next diagnostic step is usually fiberoptic bronchoscopy with bronchoalveolar lavage, and in some instances transbronchial lung biopsy. The yield of bronchoscopy is high in miliary tuberculosis and in focal disease as well. Bronchoscopic procedures have been especially helpful in the diagnostic evaluations of patients with HIV infection with negative sputum smear microscopy.²⁵² Needle aspiration biopsy may also provide specimens from which mycobacteria are isolated, but the technique is especially suited to the evaluation of peripheral nodular lesions for which there is a suspicion of malignancy.

In some situations, a therapeutic trial of antituberculosis chemotherapy may be indicated before more invasive studies are undertaken. For example, a radiographic abnormality consistent with tuberculosis in a person who is younger than 40, is a nonsmoker, and comes from a country where there is a high prevalence of tuberculosis, either current or past tuberculosis is much more likely than a neoplasm, even in the presence of negative smears and cultures of sputum. In such a patient, improvement in the chest radiograph concomitant with antituberculosis treatment would be sufficient reason for making a diagnosis of tuberculosis and continuing with a full course of therapy. A response should be seen within 2 months of starting treatment. If no improvement is noted, the abnormality

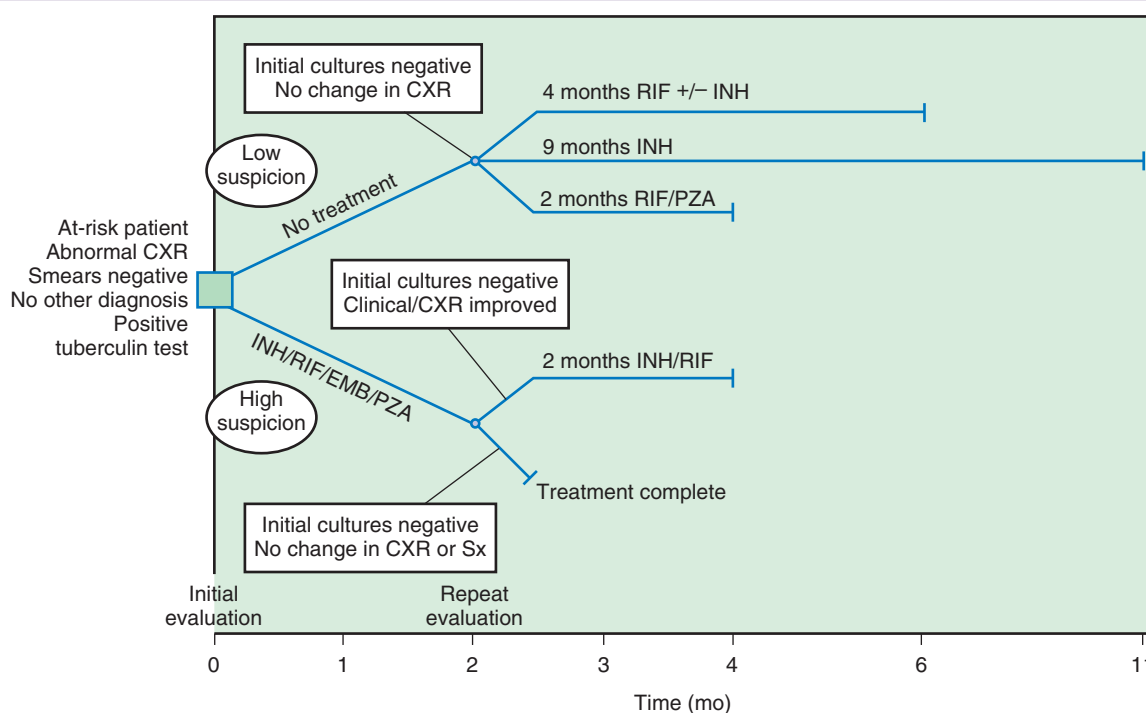


Figure 35-10 Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis. The decision to begin treatment for a patient with sputum smears that are negative depends on the degree of suspicion that the patient has tuberculosis. If the clinical suspicion is high (lower portion of figure), then multidrug therapy should be initiated before acid-fast smear/culture results are known. If the diagnosis is confirmed by a positive culture (see Fig. 35-11), treatment can be continued to complete a standard course of therapy. If initial cultures remain negative and treatment has been with multiple drugs for 2 months, then there are two options depending on repeat evaluation at 2 months (lower portion of figure). In option 1, if the patient demonstrates symptomatic or radiographic improvement without another apparent diagnosis, then a diagnosis of culture-negative tuberculosis can be inferred. Treatment should be continued with isoniazid and rifampin for an additional 2 months. In option 2, if the patient demonstrates neither symptomatic nor radiographic improvement, then tuberculosis is unlikely and treatment can be stopped. In low-suspicion patients not initially on treatment (upper portion of figure), if cultures remain negative, the patient has no symptoms, and the chest radiograph is unchanged at 2 to 3 months, there are three treatment options: (1) isoniazid for 9 months; (2) rifampin with or without isoniazid for 4 months; or (3) rifampin and pyrazinamide for 2 months. (See later discussion of latent tuberculous infection.) CXR, chest radiograph; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; Sx, symptoms. (From Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. *Am J Respir Crit Care Med* 167:603–662, 2003.)

must be the result of either old tuberculosis or another process. An algorithm illustrating this approach is shown in Figure 35-10.

Because of the potentially disastrous consequences of delays in diagnosis of tuberculosis, it is essential that tests for *M. tuberculosis* be performed rapidly and the results be reported promptly. Waiting days for the results of microscopic examinations, weeks for culture results, and months for speciation and susceptibility studies is not acceptable.

Acid-Fast Staining

The first step in the diagnostic sequence is nearly always staining and examining readily available specimens for AFB. (See below for recommendations for use of rapid molecular tests in the initial evaluation). Finding AFB is generally specific for mycobacteria but provides no information about species. However, the sensitivity of microscopic examination is relatively low; the level of detection is approximately 10,000 bacilli per milliliter of secretions if 100 oil immersion microscopic fields are examined. The sensitivity of sputum smear microscopy can be increased by concentrating the sample either by centrifugation or sedimentation preceded by chemical processing.²⁵³ Sensitivity

can also be increased by about 10% using a fluorochrome staining procedure with auramine O, a fluorescent stain²⁵⁴ (see Fig. 35-1). This procedure requires use of a fluorescent microscope, which requires an excitation light source. There are two types of light sources. The first one is the short-arc *mercury vapor lamp* (MVP) which has a limited lifespan (200 to 300 hours), is costly, requires high maintenance, and is potentially toxic due to its mercury content. The second is the *light-emitting diode* (LED) that has a life span of more than 50,000 hours, is less expensive, and has a performance similar to the MVP-based microscopy.²⁵⁵ Fluorochrome-based procedures are faster than acid-fast staining because the intensity and contrast of the fluorescent signal on a dark background enables slides to be scanned at lower magnification (see Fig. 35-1).

Smears are generally interpreted as negative or, if positive, are reported as rare (3 to 9 organisms per slide), few (10 or more per slide), or numerous (1 or more per high-power oil immersion field). In most situations in which acid-fast organisms are detected by microscopy, they should be assumed to be *M. tuberculosis* until proven otherwise. Assuming the patient has tuberculosis will trigger the appropriate prompt responses from the physicians

responsible for treatment and from public health agencies. In practice, the sensitivity of sputum smears varies widely: 20% to 80% of patients with *M. tuberculosis* isolated in culture have positive smears.²⁵³

Mycobacterial Culture

Culture in liquid media is considered the current diagnostic gold standard and can detect as few as 10 to 1000 viable mycobacteria/mL. Culture is an essential step for diagnosis and is necessary for phenotypic drug susceptibility testing. Culturing mycobacteria from clinical specimens requires a higher level of technical capability than that needed for microscopy. The need for biosafety conditions, constant-temperature incubators, and a constant power supply restricts the use of culture in many low-resource settings. Culture of sputum usually involves digestion, decontamination, and concentration of the specimen before inoculation of media. This process decreases bacterial overgrowth and, when solid media are used, enables more uniform plating of the specimen. For specimens other than sputum, digestion and decontamination are not required. At a minimum, laboratories performing culture should be able to identify *M. tuberculosis*. Isolates that are not *M. tuberculosis* or are of questionable identity should then be sent to a more specialized laboratory for definitive speciation.

Culture can be performed in solid or liquid media. Solid media are usually less expensive and allow the morphologic examination of the colonies to be used for presumptive species identification. However, results on solid media are delayed due to the slow growth of mycobacteria and, in some settings, the delayed culture results may have limited or no impact on patient management.²⁵⁶ The solid media can be based on egg such as *Lowenstein-Jensen* (LJ) media or on agar such as Middlebrook 7H10 or 7H11 media. *M. tuberculosis* colonies appear in 2 to 8 weeks, and cultures without growth at 8 weeks are reported as negative, although they are generally kept for another 2 to 4 weeks before being discarded, as some strains grow more slowly than the average.

Liquid media are more sensitive and increase the yield by 10%. They enable *M. tuberculosis* growth to be detected in 10 to 14 days. However, liquid media also have a higher rate of contamination with other bacteria or with nonmycobacteria.²⁵⁷ The growth of *M. tuberculosis* in liquid media produces fluorimetric or colorimetric reactions, which are detected using manual or automated systems. The automated systems permit a higher throughput and should be used in settings with high workloads, especially for drug susceptibility testing. The manual systems are less expensive and are used in areas with limited resources.

***M. tuberculosis* Identification.** The methods to identify *M. tuberculosis* can be classified as (1) phenotype methods that include biochemical tests and specific cell and colony characteristics and (2) molecular-based methods that target *M. tuberculosis* complex-specific nucleic acids or proteins.

PHENOTYPE-BASED IDENTIFICATION METHODS. The classical phenotype-based methods to identify *M. tuberculosis* complex require a positive culture for mycobacteria. These tests include niacin production, nitrate reduction, and inactivation of catalase at 68° C. The tests also use the time to growth, which is usually 12 to 42 days in solid media; the

presence of rough, cauliflower-like, and colorless colonies; and the presence of organisms that are tangled and form corded masses when observed using a microscope.

The *microscopic observation of drug susceptibility* (MODS) assay is a culture-based method that discriminates between *M. tuberculosis* complex and nontuberculous mycobacteria and determines the drug susceptibility to rifampin and isoniazid at the same time. MODS incorporates the antituberculosis drugs in the culture media at the beginning of the assay. The method uses a sealed 24-well tissue-culture plate with liquid culture media containing different antibiotics and controls that are examined periodically under an inverted light microscope. *M. tuberculosis* can be identified by the observation of a tangled or a corded mass of organisms and by a time to detection (including susceptibility test), typically less than 2 weeks. When compared with traditional solid or liquid culture, the overall pooled sensitivity of MODS to detect *M. tuberculosis* growth was 92% and the specificity was 96% compared with conventional culture. The mean time from receipt of specimen to results was 9.2 days, and contamination was present in 7%.²⁵⁸ There is currently a MODS kit commercially available.

MOLECULAR-BASED IDENTIFICATION METHODS. Several molecular methods are available to identify *M. tuberculosis* directly on the specimen or in mycobacterial culture. They are based on *nucleic acid amplification technologies* (NAATs) in which as few as 1 to 10 copies of DNA or ribonucleic acid specific to *M. tuberculosis* complex are amplified to detectable levels. Other targets include proteins specific to *M. tuberculosis*. All these tests identify the presence of *M. tuberculosis* complex and can rule out the presence of nontuberculous mycobacteria. Importantly, some of these methods identify drug resistance-associated mutations in the same test. There are several commercial technologies, although only one, the GenProbe *Amplified M. tuberculosis Direct* test (AMTD), is available in the United States. The current recommendation by the CDC is to use an NAAT on at least one specimen, preferably the first diagnostic specimen from each patient in whom a TB diagnosis is being considered.²⁵⁹ The recommended interpretation algorithm includes the use of clinical judgment when the nucleic acid amplification test is negative. This limitation has been applied because it has been found that the sensitivity of the tests is not sufficiently high to exclude *M. tuberculosis*.^{259,260}

A major breakthrough in NAAT has been the development of an automated, self-contained, real-time *polymerase chain reaction* (PCR) assay to detect *M. tuberculosis* complex and rifampin resistance-associated mutations directly in clinical specimens (Xpert MTB/RIF).²⁶¹ This system is based on the amplification of a sequence of the *rpoB* gene specific to members of the *M. tuberculosis* complex and the rifampin resistance-determining region. It can be used directly on clinical specimens or specimens that have been digested and decontaminated.²⁶² It requires minimal biosafety measures²⁶³ and minimal hands-on technical time.²⁶⁴ It consists of two main components: (1) a disposable cartridge that contains sample processing and the *M. tuberculosis*-specific real-time PCR reagents and (2) an instrument that controls the fluidics in the cartridge and performs the PCR analysis.²⁶¹ The operational challenges are related to the specific needs of the components: Cartridges require a temperature below 28° C and have a 12-month shelf-life, and the

instrument requires a stable electrical power supply and an ambient temperature below 30°C.²⁶⁴ A meta-analysis showed that, as an initial test replacing smear microscopy, Xpert MTB/RIF pooled sensitivity was 89% and pooled specificity 99%.²⁶⁵ As an add-on test following a negative smear microscopy result, Xpert MTB/RIF pooled sensitivity was 67% and specificity 99%. For smear-positive, culture-positive TB, Xpert MTB/RIF pooled sensitivity was 98%. For people with HIV infection, Xpert MTB/RIF pooled sensitivity was 79% and, for people without HIV infection, it was 86%. The pooled sensitivity to detect rifampin resistance was 95%, and the pooled specificity was 98%.²⁶⁵ This assay has a median time to detection of *M. tuberculosis* of hours compared with 1 day for microscopy, 16 days for culture in liquid media, and 30 days for culture on solid media. The median time to detection of rifampin resistance with the automated and self-contained real-time PCR assay was 1 day compared with 106 days for phenotypic tests.²⁶⁶ More importantly, Xpert MTB/RIF reduced the median time to treatment of patients with sputum smear-negative tuberculosis from 56 days to 5 days.²⁶⁶ On the basis of its diagnostic accuracy, WHO endorsed the Xpert MTB/RIF for the diagnosis of tuberculosis in 2010.^{267,268} WHO is recommending that, for all patients (including children) who are suspected of having pulmonary tuberculosis and are capable of producing sputum, a single specimen submitted for Xpert MTB/RIF testing can be used as the initial test in place of two specimens submitted for smear microscopy. In addition, WHO recommends that Xpert MTB/RIF should be used as the preferred initial test for patients who are at risk for drug resistance, who have HIV risks, or who are seriously ill; because of the speed of diagnosis, the test is also preferred for use with cerebrospinal fluid in patients suspected of having tuberculous meningitis.

Other commercially available molecular methods can be used directly on clinical samples or mycobacterial cultures for identification of the *M. tuberculosis* complex and drug resistance-associated mutations on the same day the specimen is received.²⁶⁹ However, these technologies require more technical expertise and a more complex laboratory infrastructure. The line probe assay uses a DNA strip test that allows the simultaneous identification of *M. tuberculosis* and common genetic mutations causing resistance to isoniazid and rifampin from smear-positive sputum samples or from positive cultures. Currently, three line probe assays exist: the INNO-LiPARif.TB assay (Fujirubio, Europe, N.V.),²⁷⁰ which is available for research use only for the detection of *M. tuberculosis* and rifampin resistance, and two versions of the GenoTypeMTBDR assay (Hain Life-Science GmbH, Nehren, Germany). The GenoTypeMTBDR plus detects *M. tuberculosis* and rifampin and isoniazid resistance,²⁷¹ and the GenoTypeMTBDRsl detects the most common mutations in the *gyrA* gene for fluoroquinolone resistance; in the *rrs* gene for amikacin, capreomycin, and kanamycin resistance; and in the *embB* gene for ethambutol resistance.²⁷² The sensitivity of the INNO-LiPARif.TB for detecting rifampin resistance in culture isolates was greater than 95%, and the specificity was 100%.²⁷⁰ A meta-analysis for the performance of the GenoTypeMTBDR showed a pooled sensitivity of 98.1% and specificity of 98.7% for rifampicin resistance and a lower sensitivity of 84.3% and specificity of 99.5% for isoniazid.²⁷¹ Meta-analysis

for the performance of the MTBDRsl was as follows: for fluoroquinolone sensitivity—87.4%, specificity—97.1%; amikacin sensitivity—82.6%, specificity—99.5%; capreomycin sensitivity—82%, specificity—97.3%; kanamycin sensitivity—44.4%, specificity—99.3%; and ethambutol sensitivity—67.9%, specificity—79.9%.²⁷² In 2008, WHO endorsed the line-probe assays for the rapid detection of first-line drug resistance in low- and middle-income settings.²⁷³

Serologic Tests

Several antigens, including highly purified and recombinant antigens specific for *M. tuberculosis* complex, have been used in serologic antibody tests with variable results. A systematic review found that the results of serologic tests are highly variable and not better than sputum smear microscopy.²⁷⁴ On the basis of these results, WHO has strongly recommended against the use of serologic tests for the diagnosis of pulmonary and extrapulmonary tuberculosis.²⁷⁵

Drug Susceptibility Testing

Determination of susceptibility to antimicrobial agents is of considerable clinical importance. Because of concerns regarding tuberculosis caused by drug-resistant organisms, drug susceptibility testing is recommended for all initial *M. tuberculosis* isolates. Unfortunately, due to lack of resources, drug susceptibility testing is not done in most high-burden areas or is limited to *M. tuberculosis* strains isolated from patients at high risk of having drug-resistant tuberculosis (see Table 35-3). There are two general methods for determining resistance: phenotypic and genotypic.²⁷⁶ Some of the methods are designed to identify *M. tuberculosis* and determine the drug susceptibility in the same test, such as MODS, Xpert MTB/RIF and line probe assays, all of which were reviewed in the previous section on *M. tuberculosis* identification.

The *phenotypic methods* are based on culture of *M. tuberculosis*. There are two methods: absolute and proportional. These can be done in liquid or solid media. The reference standard is the proportion method, and it is recommended in liquid media. The proportional methods involve inoculating one or more dilutions of cultured mycobacteria on drug-free media and on media containing appropriate concentrations of antituberculosis drugs. Resistance is generally considered to be present when the growth on the drug-containing medium is 1% or more of the control growth on the drug-free media.

There are several approaches to detect mycobacterial growth.²⁷⁷ The colorimetric method is based on the reduction of an oxidation-reduction indicator (i.e., Alamar Blue, resazurin, or tetrazolium) added to the culture media after the cells of *M. tuberculosis* are exposed to the antibiotic. Resistance to antibiotics is identified by the presence of a change in color in the media due to the oxidation/reduction process by viable mycobacteria. This method is highly sensitive and specific for the detection of rifampin and isoniazid resistance (98% and 97% sensitive, respectively; 99% and 98% specific, respectively) when compared with conventional culture-based drug susceptibility methods.^{276,278} The nitrate reductase assay is based on the ability of *M. tuberculosis* to reduce nitrate to nitrite, which is also detected by a

color reaction. The sensitivity of the test was 97%, and the specificity was 100% for the detection of rifampin resistance and 97% and 99%, respectively, for detection of isoniazid resistance.^{276,278}

Testing for susceptibility to isoniazid and rifampin is accurate,²⁷⁸ and resistance to rifampin has been used as an indicator for multidrug-resistant tuberculosis.²⁷⁹ Testing for susceptibility to streptomycin, ethambutol, and pyrazinamide is less reliable and reproducible.²⁷⁸ Testing for second-line drugs is generally performed in reference laboratories and is recommended mainly for MDR strains. Testing for resistance to aminoglycosides, capreomycin, and fluoroquinolones is relatively accurate and reproducible, and the recommendation is to use the automated liquid culture systems.^{278,280} Testing for resistance to the other second-line drugs (ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid, clofazimine, amoxicillin-clavulanate, clarithromycin, linezolid) is not standardized and not currently recommended.²⁷⁹

The *genotypic methods* to identify drug resistance are integrated with the *M. tuberculosis* identification methods; therefore, these methods are faster than culture-based tests. The genotypic methods are based on the detection of drug resistance–associated mutations: mutations in the *rpoB* rifampin resistance–determining region are present in 96% of rifampin-resistant strains,²⁸¹ mutations in *katG* or *inhA* in 65% to 75% of isoniazid-resistant strains,²⁸¹ and mutations in *gyrA* and *gyrB* in 42% to 85% of quinolone-resistant strains.^{281,282}

A common limitation of all genotypic methods is the inability to detect drug-resistant strains that do not harbor the common mutations. Therefore, it is essential to use conventional phenotypic methods to exclude drug-resistant tuberculosis.

There are several noncommercial genotypic methods. *Melting temperature (T_m)*-based assays utilize fully complementary strands of DNA that have higher melting temperatures than DNA with one or more nucleotide mismatches. This assay has been used together with “sloppy” molecular beacons to detect mutations in the rifampin resistance–determining region in a closed system minimizing cross-contamination.²⁸³ Other genotypic methods are based on sequencing genes or fragments of genes known to harbor drug resistance–associated mutations. Pyrosequencing, a rapid real-time method for sequencing small segments of genomic DNA, was successfully used to detect mutations in strains resistant to first- and second-line drugs.²⁸⁴

Another category of noncommercial methods is the bacteriophage-based assays, in which recombinant mycobacteriophage causes emission of light in the presence of live, but not dead (i.e., drug-killed), mycobacteria. These are promising, but several technical issues limit their use.²⁸⁵ The *phage-amplified biologic assay* (PhaB) can be used in sputum or mycobacterial culture to identify *M. tuberculosis* and drug-resistance mutations.²⁸⁶ The assays are relatively simple to use, they do not require extensive materials, and the results are available within 48 hours of processing. A meta-analysis demonstrated that, although these assays had good sensitivity, specificity was low and contamination was also a concern.^{285,287}

In spite of recent advances, none of the diagnostic methods is yet a point-of-care test, meaning that none of

the tests can now be used in clinics in resource-poor areas. Currently, the pipeline for such extremely rapid and simple tuberculosis diagnostics includes genotypic-based methods that could potentially be used at the patient's bedside. One group of assays is based on isothermal amplification technology that requires uniform incubation temperature (unlike PCR, which depends on a cyclical incubation temperature and requires complex equipment) utilizing simple technology that potentially could be used in peripheral laboratories where smear microscopy is performed. Loop-mediated isothermal amplification, where amplification products can be seen via fluorescence under ultraviolet light, is an example of this technology.²⁸⁸ Preliminary data showed that the loop-mediated isothermal amplification TB assay had comparable performance with other commercially available PCR-based assays used to identify *M. tuberculosis*²⁸⁸ and could potentially also identify drug-resistance mutations in the same reactions. Other point-of-care tests are based on the identification of *M. tuberculosis*–specific antigens such as *lipoarabinomannan* (LAM) using lateral flow immunochromatographic assays or strip tests to assay unprocessed urine. Unfortunately, its performance is low and its use is not recommended except for patients with advanced immunodeficiency due to HIV.²⁸⁹

PLEURAL TUBERCULOSIS

(see Chapter 80)

Although the pleural space is within the thorax, for reporting purposes it is considered an extrapulmonary site of tuberculosis. Tuberculous pleuritis accounts for 17% of the extrapulmonary cases in the United States.²⁷ The epidemiology of pleural tuberculosis parallels that of the overall pattern for tuberculosis, being more common among men and increasing in incidence with increasing age between 5 and 45 years. As noted previously, this epidemiologic pattern is modified by the presence of HIV infection, although pleural involvement seems less frequent among HIV-infected persons.

There are two mechanisms by which the pleural space becomes involved in tuberculosis. The difference in pathogenesis results in different clinical presentations, approaches to diagnosis, treatment, and sequelae. The first mechanism manifests early in the course of a tuberculous infection—a few tubercle bacilli may gain access to the pleural space and, in the presence of cell-mediated immunity, can cause a hypersensitivity response.^{290,291} This form of tuberculous pleuritis commonly goes unnoticed, and the process resolves spontaneously; those with resolved tuberculous pleuritis have a high likelihood of developing active tuberculosis in the next 2 years,²⁹² so tuberculous pleuritis should be considered and treated if found. However, in some patients, the tuberculous involvement of the pleura is manifested as an acute illness with fever and pleuritic pain.²⁹³ If the effusion is large enough, it may cause dyspnea, although the effusions are generally rather small and rarely bilateral.

The diagnosis of pleural tuberculosis is generally established by analysis of pleural fluid and by a pleural biopsy. In a patient with a pleural effusion that might be tuberculous, a diagnostic thoracentesis should be performed. Sufficient

fluid should be obtained for cell count, cytologic examination, biochemical analysis, and microbiologic evaluation (all described in detail in Chapter 79 and 80), but enough fluid should be left to allow a needle biopsy to be performed if the original specimen proves to be exudative and no diagnosis is evident. The fluid is nearly always straw colored, although it may be slightly bloody. Leukocyte counts are usually in the range of 100 to 5000 cells/ μ L.²⁹⁴ Early in the course of the process, polymorphonuclear leukocytes may predominate, but mononuclear cells soon become the majority. The fluid is exudative, with a protein concentration greater than 50% of the serum protein concentration, and the glucose level may be normal to low.

Adenosine deaminase has been shown to have high sensitivity, except in HIV-infected patients, but variable specificity, for diagnosing tuberculous pleural effusion.²⁹⁵ IFN- γ has been reported to have both high sensitivity (0.99) and high specificity (0.98) and to be equally reliable in HIV-infected and HIV-uninfected patients.^{296,297} Further studies are necessary to define the diagnostic role of this potentially useful test. Because few organisms are present in the pleural space, acid-fast smears of pleural fluid are rarely positive, and *M. tuberculosis* is isolated by culture in only 20% to 40% of patients with proven tuberculous pleuritis.^{293,298} A single closed-needle biopsy of the pleura with a Cope or an Abrams needle, with collection of three or four specimens for histologic examination, acid-fast staining, and culture of the tissue, confirms the diagnosis in approximately 65% to 75% of patients in whom tuberculous pleuritis is ultimately diagnosed. A second set of specimens in patients whose initial biopsy is negative increases the yield to 80% to 90%.²⁹⁸ The results of thoracoscopy are nearly always diagnostic, but the procedure is invasive, costly, and not always available. In a patient with an exudative mononuclear pleural effusion that remains undiagnosed after a full evaluation, including pleural biopsy, and who has a positive tuberculin reaction or IGRA result, antituberculosis treatment should be initiated.

Treatment of the hypersensitivity variety of tuberculous pleural effusion consists of standard antituberculosis drug regimens.²⁹⁹ Drainage via tube thoracostomy is rarely necessary, although repeat thoracenteses may be required to relieve symptoms. The use of corticosteroids may increase the rate of resolution and decrease the residual fluid, but such treatment is rarely indicated.³⁰⁰

The second variety of tuberculous involvement of the pleura, which is much less common than tuberculous pleurisy with effusion, is a true empyema that follows the spilling into the pleural space of a large number of organisms, usually from rupture of a cavity or an adjacent parenchymal focus via a bronchopleural fistula.³⁰¹ Tuberculous empyema is usually associated with evident pulmonary parenchymal disease on chest films. In this situation the fluid generally is thick and cloudy and may contain cholesterol, which causes the fluid to look like chyle (pseudochylous effusion). The fluid is exudative and usually has a relatively high white blood cell count, nearly all of which are lymphocytes. Acid-fast smears and mycobacterial cultures are usually positive, making pleural biopsy unnecessary.

In addition to standard antituberculosis chemotherapy, surgical drainage with an ordinary thoracostomy tube is

often necessary and may be required for a prolonged period of time. In selected patients who need ongoing drainage, creation of an Eloesser flap, in which a small portion of rib overlying the empyema space is resected and the skin is sutured to the pleura, is the procedure of choice.³⁰²

DISSEMINATED TUBERCULOSIS

Miliary tuberculosis, although it nearly always involves the lungs, is considered among the extrapulmonary forms of the disease because of the multiplicity of organs affected. The term *miliary* is derived from the similarity of the lesions to millet seeds. Grossly, these lesions are 1- to 2-mm yellowish nodules that on histologic examination are granulomas. In the past, miliary tuberculosis was mainly seen in young children, as an early consequence of initial infection and bacilleemia; currently, however, except among HIV-infected persons, it is more common among older persons, as a result of endogenous reactivation and bloodstream invasion. The shift in age-specific incidence presumably has been caused at least in part by the paucity of new infections in relation to the number of endogenous reactivations in the United States. The incidences in both sexes are nearly equal except in the HIV-infected population, in which the disease predominates among men.

Because of the multisystem involvement in disseminated tuberculosis, the clinical manifestations are protean. Initial screening laboratory studies are not particularly helpful. The chest radiograph, however, is abnormal in most but not all patients with disseminated tuberculosis: the frequency of a classic miliary pattern has ranged from 50% to 90%. Overall, it appears that, at the time of diagnosis, approximately 85% of patients have the diffuse tiny nodules characteristic of miliary tuberculosis. Other abnormalities may be present as well. These include upper lobe opacities with or without cavitation, pleural effusion, and pericardial effusion. As noted previously, HIV-infected patients may not be able to form granulomas; thus, instead of discrete individual lesions, a diffuse uniform pattern of infiltration may be seen.

Autopsy series have shown the liver, lungs, bone marrow, kidneys, adrenal glands, and spleen to be the organs most frequently involved in miliary tuberculosis, but any organ can be the site of disease.³⁰³ Because of the multiplicity of sites involved, there are many potential sources of material to provide a diagnosis. Acid-fast smears of sputum are positive in 20% to 25% of patients (even when the patient is not spontaneously coughing), and cultures of sputum are positive in 30% to 65%.³⁰⁴⁻³⁰⁶ In a patient with an abnormal chest radiograph and negative sputum examinations, bronchoscopy should be the next step. Combinations of bronchoalveolar lavage and transbronchial biopsy would be expected to have a high yield.³⁰⁷ Other potential sites for biopsy include liver and bone marrow, each of which has a high likelihood of showing granulomas (70% to 80%), but only a 25% to 40% chance of providing bacteriologic confirmation; urine cultures may be positive in up to 25% of patients.^{305,306} Selection of other potential sources of diagnostic material should be guided by specific findings.

The role of rapid nucleic acid amplification tests for identification of *M. tuberculosis* in patients with miliary

tuberculosis has not been defined, and neither of the two tests licensed by the U.S. Food and Drug Administration is approved for nonrespiratory specimens, although Xpert MTB/RIF is recommended for use with specimens from extrapulmonary sites by WHO.³⁰⁸ The reported data are difficult to interpret because, often, the results of specimens from different sites are combined, patients are selected by a variety of criteria, and test performance varies.³⁰⁹⁻³¹¹ In contrast, several studies have shown that Xpert MTB/RIF can provide rapid molecular diagnostic assessment when extrapulmonary tuberculosis is suspected. The growing body of literature, including two large studies, demonstrated a sensitivity of 81% and specificity of 99%.³¹²⁻³¹⁴

Before the era of chemotherapy, disseminated tuberculosis was uniformly fatal. With treatment, however, the reported case-fatality rates range from 29% to 64%.³⁰⁶ Meningeal involvement increases mortality and, when it is present, the duration of standard chemotherapy should be extended from 6 to 9 or 12 months, and corticosteroids may be useful to reduce mortality.³¹⁵

TREATMENT



Further information about the introduction and development of chemotherapy for pulmonary tuberculosis is provided in the [Appendix](#) for this chapter, which can be found online.

The Appendix also provides details about the mechanisms of action, genetic basis of resistance, and chief adverse effects of each of the main first- and second-line antituberculosis agents that are currently in use; also included is [Table 35A-1](#), which lists the available preparations and their recommended doses.

CURRENT STANDARD REGIMENS

The treatment regimens that are currently recommended by the American Thoracic Society, the CDC, and the Infectious Diseases Society of America and also by the WHO are shown in [Table 35-1](#).^{299,316} The recommended basic treatment regimen for previously untreated patients with pulmonary tuberculosis consists of an *initial* (or *intensive*) phase of isoniazid, rifampin, pyrazinamide, and ethambutol given for 2 months, followed by a 4-month *continuation* phase of isoniazid and rifampin. The initial phase rapidly reduces the bacterial burden, by killing the actively growing bacteria, while the continuation phase is protracted and intended to eliminate the subpopulation of bacteria that are replicating more slowly. The latter population is sometimes termed *drug tolerant*, meaning that the bacteria are not efficiently killed by drugs but have not acquired resistance mutations. As shown in [Table 35-1](#), there are several variations in the frequency of drug administration that are largely designed to enable health care personnel (or their surrogates) to provide closer supervision of treatment and produce acceptable results.^{299,316} Intermittent administration of antituberculosis drugs enables supervision to be provided more efficiently and economically with no reduction in efficacy, although daily administration provides a greater margin of safety. The evidence on effectiveness

of intermittent regimens has been reviewed.^{317,318} These reviews suggest that antituberculosis treatment may be given intermittently three times a week throughout the full course of therapy or twice weekly in the continuation phase without apparent loss of effectiveness except among individuals with advanced HIV infection.^{317,319-321} However, the WHO does not recommend the use of twice-weekly intermittent regimens because of the potentially greater consequences of missing one of the two doses.

Several caveats apply to these recommendations for treatment to be successful. First, the organisms must be susceptible to the drugs used. Because of concerns with drug resistance, initial isolates from patients with tuberculosis should have drug susceptibility tests performed and the results should be used to guide treatment. Second, patients must take all or nearly all of the prescribed treatment. Third, success should be documented by bacteriologic evaluation; that is, sputum cultures should be negative by the end of 3 months of treatment. If the sputum still contains *M. tuberculosis* after 3 months of therapy, the patient should be reassessed carefully to determine whether a change in treatment is necessary. The assessment should include a review of adherence, and evaluation for any comorbidities that might interfere with response. After 3 months of chemotherapy, more than 90% of patients taking regimens containing isoniazid and rifampin should have negative sputum cultures. Failure of the sputum to become negative generally means that either the organisms are resistant to the agents being used or the patient is not taking the drugs. Patients who continue to have *M. tuberculosis* in their sputum after 3 months of treatment should be started on directly observed therapy, if not already being supervised, and should have drug susceptibility testing performed by phenotypic methods or a rapid molecular test. If resistance is found, the regimen should be modified accordingly. If sputum samples are still positive after 4 months of therapy, the regimen should be considered a failure and a new regimen should be begun, ideally based on recent drug susceptibility test results. A list of possible regimens for non-MDR drug resistant tuberculosis (strains resistant to one or more drugs, excluding those with combined isoniazid and rifampin resistance) is shown in [Table 35-2](#).

The recommendation of a four-drug intensive phase is based, in part, on findings of the British Medical Research Council that revealed the need for a regimen that would be effective in the presence of isoniazid resistance; the inclusion of ethambutol during the intensive phase lessens the likelihood of selecting for rifampin resistance in strains with primary isoniazid resistance.³²²⁻³²⁴ Several factors have been found to be predictive of a poor therapeutic outcome, including extensive tuberculosis and a large population of bacilli, the rapidity or slowness with which sputum becomes negative after treatment is begun, and several factors associated with adherence.^{299,320,325,326} In U.S. Public Health Service Study 22, the presence of cavitation on the initial chest film and sputum culture positivity at the end of the 2-month intensive phase of treatment were highly predictive of an adverse outcome—either treatment failure or relapse.³²⁰ For this reason, in patients with cavitation on the initial chest film and who have positive sputum cultures at the end of the initial phase of treatment, prolongation of

Further information about the introduction and development of chemotherapy for pulmonary tuberculosis is provided in the [Appendix](#) for this chapter.

Table 35-1 Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

INITIAL PHASE			CONTINUATION PHASE			
Regimen	Drugs	Interval and Doses* (Minimum Duration)	Regimen	Drugs	Interval and Doses*† (Minimum Duration)	Range to Total Doses (Minimum Duration)
1	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)‡	1a	INH/RIF	7 days/wk for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)§¶	182-130 (26 wk)
			1b§	INH/RIF	Twice weekly for 36 doses (18 wk)	92-76 (26 wk)
			1c¶	INH/RPT	Once weekly for 18 doses (18 wk)	74 or 58 (26 wk)
2	INH RIF PZA EMB	7 days/wk for 14 doses (2 wk) then twice weekly for 12 doses (6 wk) or 5 days/wk for 10 doses (2 wk)‡ then twice weekly for 12 doses (6 wk)	2a§	INH/RIF	Twice weekly for 36 doses (18 wk)	62-58 (26 wk)
			2b¶	INH/RPT	Once weekly for 18 doses (18 wk)	44 or 40 (26 wk)
3	INH RIF PZA EMB	Thrice weekly for 24 doses (8 wk)	3a	INH/RIF	Thrice weekly for 54 doses (18 wk)	78 (26 wk)
4	INH RIF EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)‡	4a	INH/RIF	7 days/wk for 217 doses (31 wk) or 5 days/wk for 155 doses (28 wk)‡	273-195 (39 wk)
			4b§	INH/RIF	Twice weekly for 62 doses (31 wk)	118-102 (39 wk)

*When *directly observed therapy* (DOT) is used, drugs may be given 5 days/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice.

†Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 mo of therapy should receive a 7-mo (28-week; either 196 doses [daily] or 56 doses [twice-weekly]) continuation phase.

‡Five-day-a-week administration is always given by DOT.

§Options 1b, 2a, 4b are not recommended for HIV-infected patients with CD4⁺ cell counts less than 100 cells/μL.

¶Options 1c and 2b should only be used in HIV-negative patients who have negative sputum smears at the time of completion of 2 mo of therapy and who do not have cavitation on the initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture at 2 mo, treatment should be extended an extra 3 mo.

EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

Modified from Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. *Am J Respir Crit Care Med* 167:604–662, 2003.

the continuation phase to 7 months, making a total of 9 months of treatment, is recommended. Factors that have been associated with poor clinic attendance and, therefore, with less chance of favorable response, include use of alcohol, younger age (but older than 18), and unmarried status. Patients with any of these characteristics should be monitored especially carefully. Although directly observed therapy (DOT) is labor intensive, the improved outcomes shown in retrospective analyses justify its use in preventing treatment failure and relapse, both of which have striking cost and public health consequences.

The algorithm shown in Figure 35-11 presents the approach to treatment of pulmonary tuberculosis in patients with *M. tuberculosis* isolated from sputum, and Figure 35-10 shows a treatment algorithm for patients with radiographic evidence of tuberculosis but negative bacteriologic examinations. In the absence of bacteriologic confirmation, treatment depends first on the degree of suspicion of active disease, and second on whether or not initial treatment causes clinical or radiographic improvement.

HIV Infection

The recommended treatment regimen for HIV-infected patients with tuberculosis consists of the same 6-month regimen as described for non-HIV-infected persons, but there are several important areas in which therapy may differ. Although, in general, rates of relapse are not increased among HIV-infected patients who take a standard 6-month regimen in the United States, there is an association with acquiring rifampin resistance.³²⁷⁻³²⁹ In sub-Saharan Africa, however, the likelihood of death, especially during the first 2 months of therapy, and of relapse following apparently successful treatment is higher in HIV-infected than in non-HIV-infected patients.³³⁰

The cause of rifampin monoresistance is not clear but has been associated with the use of once- or twice-weekly drug administration in the continuation phase and prior use of rifabutin as prophylaxis for *Mycobacterium avium* complex infections.^{321,327} For this reason, the rifapentine once-weekly regimen is contraindicated for all patients with HIV infection, and a twice-weekly regimen is not

Table 35-2 Selected Treatment Regimens for Non–Multidrug-Resistant Tuberculosis*

Resistance to	Treatment Regimen	Duration of Therapy	Comments
Isoniazid (± streptomycin)	Rifampin Ethambutol Pyrazinamide	6-9 mo	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
Isoniazid and pyrazinamide	Rifampin Ethambutol Fluoroquinolone [†]	9-12 mo	A longer duration of treatment should be used for patients with extensive disease.
Isoniazid and ethambutol	Rifampin Pyrazinamide Fluoroquinolone	9-12 mo	A longer duration of treatment should be used for patients with extensive disease.
Rifampin	Isoniazid Ethambutol Fluoroquinolone plus at least 2 mo of pyrazinamide	12-18 mo	An injectable drug may strengthen the regimen for patients with extensive disease.
Rifampin and ethambutol (± streptomycin)	Isoniazid, pyrazinamide Fluoroquinolone plus injectable drug [‡] for at least the first 2-3 mo	18 mo	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.
Rifampin and pyrazinamide (± streptomycin)	Isoniazid Ethambutol Fluoroquinolone plus injectable drug for at least the first 2-3 mo	18 mo	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.
Isoniazid, ethambutol, pyrazinamide (± streptomycin)	Rifampin Fluoroquinolone plus an oral second-line agent, [§] plus injectable drug for at least the first 2-3 mo	18 mo	A longer course (6 mo) of the injectable may strengthen the regimen for patients with extensive disease.
Pyrazinamide	Isoniazid, rifampin plus at least 2 mo of ethambutol	9 mo	Most commonly seen in <i>M. bovis</i> infection.

*Strains resistant to one or more drugs, excluding combined isoniazid and rifampin resistance.

[†]Fluoroquinolones: levofloxacin or moxifloxacin.

[‡]Injectable drugs: streptomycin, amikacin, kanamycin, or capreomycin.

[§]Oral second-line drugs: ethionamide, cycloserine, or *p*-aminosalicylic acid.

From the Curry National Tuberculosis Center and California Department of Public Health, Drug-Resistant Tuberculosis: *A survival guide for clinicians*, ed 2. Sacramento, CA, 2008, California Department of Public Health, pp 34–35.

recommended for HIV-infected patients with CD4⁺ counts less than 100 cells/μL.²⁹⁹ An important concern in treating tuberculosis in patients with HIV infection is the potential for interactions with other drugs, especially antiretroviral agents, as discussed in detail in Chapter 90. Detailed, regularly updated recommendations for managing drug interactions during treatment of tuberculosis and HIV are available online (http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm). The most practical means of minimizing the effects of interactions is to use a regimen consisting of two nucleoside reverse transcriptase inhibitors plus efavirenz or, in pregnant women, nevirapine in the HIV treatment regimen, and rifabutin in place of rifampin in the antituberculosis regimen. Monitoring of serum drug concentrations may be useful in avoiding the adverse consequences of the interactions. Current recommendations are that in persons with HIV infection and tuberculosis who have profound immunosuppression (CD4 counts < 50 cells/mm³), ART should be initiated within 2 weeks of beginning treatment for tuberculosis unless tuberculous meningitis is present. For all other patients with HIV and tuberculosis, regardless of CD4 counts, antiretroviral therapy should be initiated within 8 weeks of beginning treatment for tuberculosis. In part, the recommendation for antiretroviral treatment regardless of CD4 cell counts is because of the effect in reducing transmission of HIV.³³² The exception to this recommendation is in patients with tuberculous meningitis in whom immune reconstitution may have serious

consequences.³³³ The greatest benefit for reducing mortality in patients with tuberculosis and HIV infection is realized in those having CD4⁺ counts less than 200 cells/μL. For patients with higher CD4⁺ counts, the mortality benefit is less clear.³³⁴⁻³³⁶

Another feature of the treatment of tuberculosis, as well as of other opportunistic infections, is the paradoxical worsening that may be seen in HIV-infected persons who are also receiving antiretroviral therapy, a clinical phenomenon known as the *immune reconstitution inflammatory syndrome* (IRIS). The frequency of tuberculosis-related IRIS varies, depending on the case definitions used.^{333,337} Two main syndromes or forms of IRIS are associated with tuberculosis in persons with HIV infection.³³⁸ The more common syndrome is the paradoxical tuberculosis-associated IRIS that arises within the first weeks or months after the start of antiretroviral therapy in patients already being treated for tuberculosis. The second IRIS syndrome, known as *antiretroviral therapy-associated tuberculosis*, arises when tuberculosis (or some other lurking undiagnosed HIV-linked complication) is “unmasked” and flares up not long after beginning antiretroviral therapy. Characteristic features of both forms include new or exacerbated symptoms or signs of tuberculosis including worsening of pulmonary opacities, increasing pleural effusions, or increasing lymphadenopathy (Fig. 35-12). Usually, the syndrome is self-limiting, with a median duration of 2 months. Risk factors for the development of this form of IRIS include advanced HIV

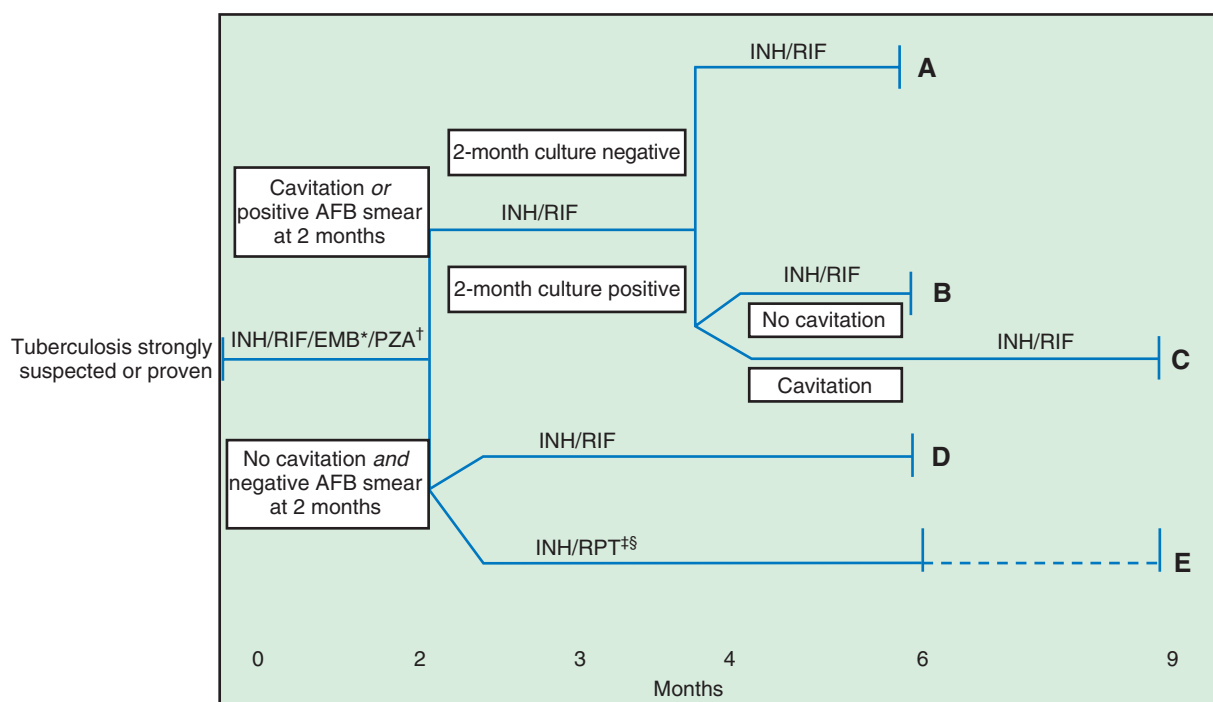


Figure 35-11 Treatment algorithm for patients with confirmed or strongly suspected tuberculosis. For patients in whom tuberculosis is confirmed or strongly suspected, the *intensive phase* of treatment should consist of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months. The choice of regimen for the *continuation phase* depends on 3 factors: 1) the presence or absence of cavitation on the initial chest radiograph, 2) the culture status at the completion of the intensive phase of treatment (month 2), and 3) the presence or absence of advanced HIV infection. In patients without advanced HIV infection, if there is cavitation on the initial chest radiograph and the 2-month culture is positive, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 7 months to complete a total of 9 months of treatment. (**Arm C**) Otherwise the continuation phase should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. (**Arms A, B, & D**) An additional option for patients without advanced HIV infection, who do not have cavitation on the initial radiograph and who have negative sputum smears at month 2, is a regimen consisting of isoniazid and rifapentine given once weekly. (**Arm E**) In this arm, if the 2-month culture becomes positive, the treatment is extended by an additional 3 months for a total of 9 months (*dashed line*). In patients with advanced HIV infection (CD4 counts of less than 100 cells/ μ l), the continuation phase should follow the same recommendations as above except that drug administration should be daily or three times weekly. Due to lack of efficacy, patients with advanced HIV should not have either twice weekly drug administration or the once weekly isoniazid-rifapentine regimen. *EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance. †PZA may be discontinued after it has been taken for 2 months (56 doses). ‡RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis. §Therapy should be extended to 9 months if 2-month culture is positive. CXR, chest radiograph; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine. (Modified from Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. *Am J Respir Crit Care Med* 167:603–662, 2003.)



Figure 35-12 Tuberculous lymphadenitis in a patient with immune reconstitution inflammatory syndrome (IRIS) after initiation of antiretroviral therapy. With development of IRIS, there was swelling of an anterior cervical node and onset of purulent drainage from the node. (Courtesy Dr. Henry M. Blumberg, Emory University.)

disease, disseminated and extrapulmonary tuberculosis, a short interval between starting antituberculosis and antiretroviral treatments, and a response to antiretroviral therapy as reflected by a decreased viral load.

Drug Resistance

The fourth Global Drug Resistance Surveillance Project conducted between 2002 and 2007 by the WHO and the International Union Against Tuberculosis and Lung Disease included more than 90,000 patients from 81 countries, representing 35% of the global notified new smear-positive cases.³³⁹ Drug resistance was found in all countries surveyed, with the exception of Iceland, with a weighted mean of 17% of new cases having resistance to at least one anti-tuberculosis drug and 2.9% having MDR (resistance to at least isoniazid and rifampin). According to the most recent WHO estimates, in 2012, approximately 450,000 new cases of MDR tuberculosis were identified worldwide. This estimate includes 3.6% of all new, never-treated patients and 20.2% of all previously treated patients.² The drug-resistance surveillance report found areas of the world in

which rates of MDR are truly alarming, such as Baku, Azerbaijan, where 56.3% of new cases were resistant to any drug and 22.3% were MDR, a considerable worsening since the previous report.³³⁹

In 2006, XDR tuberculosis—defined as tuberculosis caused by *M. tuberculosis* that is not only MDR but also resistant to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin)—was identified and rapidly recognized as a serious emerging threat to global public health.^{49,340} Subsequent reports have identified XDR tuberculosis in all regions of the world, with countries from the former Soviet Union reporting as high as 24% XDR tuberculosis among the MDR cases.² The two strongest risk factors for XDR tuberculosis are failure of a tuberculosis treatment regimen that contains second-line drugs, including an injectable agent and a fluoroquinolone, and close contact with an individual with documented XDR tuberculosis or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

Drug resistance is largely man-made; a consequence of suboptimal regimens and treatment interruptions.³⁴¹ Clinical errors that commonly lead to the emergence of drug resistance include failure to provide effective treatment support and assurance of adherence; inadequate drug regimens; adding a single new drug to a failing regimen; and failure to recognize existing drug resistance. In addition, comorbid conditions associated with reduced serum levels of antituberculosis drugs (e.g., malabsorption, rapid transit diarrhea, use of antifungal agents) and interruptions caused by adverse drug reactions may also lead to the acquisition of drug resistance.³⁴² An additional potential source of drug resistance is substandard drugs, which may exist due to poor manufacturing or deterioration due to improper storage.³⁴³

Transmission of drug-resistant strains of *M. tuberculosis* has been well described in health care facilities, in congregate settings, and in susceptible populations, notably HIV-infected persons.^{173,344-347} However, MDR *M. tuberculosis* may spread in the population at large, as was shown in data from a number of countries, including China, the Baltic States, and countries of the former Soviet Union.^{339,348-350}

The strongest factor associated with drug resistance is previous antituberculosis treatment.³³⁹ In previously treated patients, the odds of any resistance are at least 4-fold higher, and that of MDR at least 10-fold higher, than in new (untreated) patients.³⁵¹ Patients with chronic tuberculosis (sputum-positive after retreatment) and those who fail treatment are at highest risk of having MDR tuberculosis, especially if rifampin was used throughout the course of treatment. Persons who are in close contact with confirmed MDR tuberculosis patients, especially children and HIV-infected individuals, also are at high risk of being infected with MDR strains. In some closed settings, prisoners, persons staying in homeless shelters, and certain categories of immigrants and migrants are at increased risk of MDR tuberculosis. These factors are summarized and presented in descending order of level of risk in Table 35-3.

Given the importance of drug resistance, both for the individual and for the community, all patients for whom treatment is being initiated should be assessed for their risk of having tuberculosis caused by drug-resistant organisms. The assessment should be based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known). Whenever possible, the assessment should also include history of fluoroquinolone use in the period preceding diagnosis of tuberculosis because monotherapy with fluoroquinolones for as little as 10 days increases the incidence of fluoroquinolone-resistant *M. tuberculosis*.³⁵²⁻³⁵⁴ Although drug susceptibility testing

Table 35-3 Assessing Risk for Drug Resistance

Risk Factors for Resistance	Comments
Failure of retreatment regimen (a second course of treatment after failure, relapse, or default)	Patients who are still sputum smear positive at the end of a retreatment regimen have perhaps the highest drug-resistance rates of any group, often exceeding 80%.
Close contact with a known drug-resistant case	Tuberculosis in close contacts of drug-resistant TB patients is likely to be drug-resistant TB.
Failure of the initial treatment regimen	Patients who fail to become sputum smear negative while on treatment are likely to have drug-resistant organisms. However, the likelihood depends on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout treatment. Thus, a detailed history of drugs used is essential. This is especially true for patients treated by private providers, often with nonstandard regimens.
Relapse after apparently successful treatment	Most patients who relapse have fully susceptible organisms. However, under program conditions, an apparent relapse, especially an early relapse, may, in fact, be an unrecognized treatment failure and thus have a higher likelihood of drug resistance.
Return after default without recent treatment failure	The likelihood of drug resistant TB varies substantially in this group, depending in part on the duration of treatment and the degree of adherence before default.
Exposure in institutions that have drug-resistant TB outbreaks or a high drug-resistant TB prevalence	Patients who frequently stay in homeless shelters, prisoners in many countries, and health care workers in clinics, laboratories, and hospitals can have high rates of drug-resistant TB.
Residence in areas with high prevalence of drug-resistant TB	Drug-resistant TB rates in many areas of the world can be high enough to justify routine drug sensitivity testing in all new cases.

Modified from World Health Organization: Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402. www.who.int/tb/publications/2008/en/. Accessed July 8, 2014.

should be performed at the start of therapy for all patients, those who are at increased risk of drug resistance should be prioritized and a rapid molecular test (if available) should be performed. In addition, patients who remain sputum culture positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow-up, or relapsed following one or more courses of treatment, should always be assessed for drug resistance.

Because of difficulties in the design of randomized controlled treatment trials for MDR/XDR tuberculosis using multidrug regimens, none has been conducted to evaluate currently available approaches to treatment. In the absence of clinical trial data, current recommendations for treating MDR/XDR tuberculosis are based on observational studies, general microbiologic and therapeutic principles, extrapolation from available evidence from pilot MDR tuberculosis treatment projects, and expert opinion.³⁵¹⁻³⁶²

More systematic guidance has been obtained from a carefully conducted individual patient meta-analysis that examined the outcomes of treatment for MDR tuberculosis and concluded that treatment success, compared with failure/relapse or death, was associated with use of later-generation fluoroquinolones, as well as ofloxacin, ethionamide or prothionamide, use of four or more likely effective drugs in the initial intensive phase, and three or more likely effective drugs in the continuation phase.³⁶³ In addition, not surprisingly, outcomes in patients with XDR tuberculosis are worse when there was resistance to additional drugs beyond those that comprise the definition of XDR.³⁶⁴

On the basis of available information, there are three treatment options for MDR/XDR tuberculosis: standardized, empiric, and individualized regimens. The approach is dependent on having an accurate history of prior treatment, reliable drug susceptibility testing results for individual patients, and/or population data on the prevalent resistance patterns. In general, in areas where drug susceptibility is widely available, individualized treatment regimens are used.

Current global recommendations are that patients with confirmed MDR tuberculosis should be treated with a regimen consisting of an intensive phase of 6 to 8 months containing at least five drugs: pyrazinamide and four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent. The continuation phase should contain at least three drugs to which the organisms are known or presumed to be susceptible. The total treatment duration should be at least 18 to 24 months beyond culture conversion.³⁵¹ Patient-centered measures, including observation of treatment, are required to ensure adherence. Consultation with a specialist experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

On the basis of their activity, efficacy, route of administration, tolerance, availability, and costs, antituberculosis drugs can be classified in five groups.³⁵⁷ Group 1 consists of first-line drugs: isoniazid, rifampin, ethambutol, pyrazinamide, and rifabutin. Any of these drugs should be used if it is thought that susceptibility remains. Only one drug should be selected from Group 2 (injectable agents—kanamycin, amikacin, capreomycin, streptomycin) and Group 3 (fluoroquinolones) because of documented total

or partial cross-resistance and similar toxicities within the groups. Group 4 consists of less potent oral agents: ethionamide, prothionamide, cycloserine, terizidone, and *p*-aminosalicylic acid. Group 5 is composed of drugs for which antituberculosis action has not been documented in clinical trials (except for thioacetazone): clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid, and clarithromycin. A drug that has been used within a failing regimen should never be counted in the total of four drugs for retreatment, even if susceptibility is shown in the laboratory. The doses and adverse effects of second-line drugs are described in detail in the ATS/CDC/IDSA recommendations for treatment of tuberculosis.²⁹⁹

Two new second-line drugs, delamanid and bedaquiline, have been introduced, although as of this writing only bedaquiline has been approved by the U.S. Food and Drug Administration.³⁶⁵⁻³⁶⁸ Given the paucity of data describing outcomes and adverse events, the WHO recommends that bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary tuberculosis caused by MDR organisms. The recommendations also specify fairly rigid conditions under which the drug should be used. Thus, informed consent should be obtained from the patient and there should be careful monitoring for adverse drug effects.

Empiric treatment regimens are commonly used while the drug susceptibility results are pending. Empiric regimens are strongly recommended to avoid clinical deterioration and to prevent transmission of MDR strains of *M. tuberculosis* to contacts while awaiting the drug susceptibility results. Once the results of drug susceptibilities are known, an individualized regimen can be started. Individualized treatment regimens (based on susceptibility profiles and drug history of individual patients, or on local patterns of drug utilization) have the advantage of avoiding toxic and expensive drugs to which the MDR strain is resistant. However, an individualized approach requires access to substantial human, financial, and technical (laboratory) capacity. Drug susceptibility tests for second-line drugs are notoriously difficult to perform, largely because of drug instability and the fact that critical concentrations for defining drug resistance are close to the *minimal inhibitory concentration* (MIC) of individual drugs.³⁶⁹

A shorter-course standardized regimen used in Bangladesh has been described with good results reported in a small observational study.³⁷⁰ Although promising, at this point there is insufficient evidence to recommend the use of this regimen for treating MDR tuberculosis. A clinical trial is under way that should provide substantial new information on which to base recommendations. Current advice from WHO is that a short regimen for MDR tuberculosis should be used only under research conditions.³⁷¹

The outcomes of treatment for patients with MDR or XDR tuberculosis have been assessed in two systematic reviews. In the review by Johnson and colleagues³⁷² an estimated 62% of patients had successful outcomes, 13% defaulted, and 11% died. Factors associated with worse outcome included male gender, alcohol abuse, smear positivity at diagnosis, fluoroquinolone resistance, and an XDR resistance pattern. Factors associated with successful outcome were surgical intervention, no previous treatment,

and inclusion of a fluoroquinolone in the regimen (when the isolate is susceptible).

Orenstein and associates³⁷³ noted that studies combining both at least an 18-month treatment duration and directly observed treatment had significantly higher estimated success—69%, compared with other studies of treatment outcomes wherein the estimated success was 58%. Moreover, individualized regimens had an estimated success of 64%, compared with standardized regimens in which the estimated success was 54%, although the difference was not statistically significant.

More limited experience with treatment of XDR tuberculosis suggests a substantially worse outcome. In a meta-analysis of outcomes in 560 patients, Jacobson and colleagues³⁷⁴ reported a successful outcome in an estimated 44%. Their analysis also suggested that the use of a later-generation fluoroquinolone was associated with a better outcome. Substantial treatment support is commonly necessary to enable patients to complete a second-line regimen. MDR/XDR tuberculosis treatment is a complex health intervention: consultation with a specialist experienced in the management of these patients is strongly advised. Often second-line drugs are the last best hope for patients with drug-resistant tuberculosis, and it is crucial that such treatment be designed for maximal effectiveness with the active participation of the patient to overcome the challenges faced by both provider and patient with MDR/XDR tuberculosis.³⁷⁵

Of great concern, tuberculosis caused by organisms resistant to all drugs tested has been described in India but likely exists elsewhere as well.^{376,377} However, because of uncertainties about the connection between second-line drug susceptibility test results and patient outcomes, it is not clear that there are no treatment options. Nevertheless, at least at this time, there are no specific recommended treatment options for such patients and symptomatic or palliative care may be required. Although the number of such cases is likely to be small, providers should be attuned to the possibility of such situations and be prepared to provide appropriate palliative management to relieve suffering caused by the disease.

Treatment in Other Patient Groups

Children. The basic principles that apply in the management of adults with pulmonary tuberculosis are equally applicable in children. Although children have been excluded from nearly all clinical trials of short durations of chemotherapy, there are several reports documenting the usefulness of 6- and 9-month regimens in children.^{378,379} The most frequent difference between treating children and adults is the more limited use of ethambutol. Because children tend to have forms of tuberculosis that are associated with lower bacillary populations, the likelihood of drug resistance is less. Moreover, young children generally cannot have visual acuity testing performed accurately and thus cannot be monitored for toxicity. However, if ethambutol is used, the dose should be increased to 20 mg/kg because of differences in pharmacokinetics between adults and children.³⁸⁰ At least in younger children, sputum specimens for bacteriologic evaluations cannot usually be obtained.³⁸¹ Consequently, the response to treatment is assessed by clinical and radiographic criteria. For this same

reason, drug susceptibility or resistance often must be inferred from the pattern of the presumed source case or community data rather than being determined in the laboratory.

The management of children with drug-resistant tuberculosis is especially difficult because of the lack of culture and susceptibility testing to guide treatment. Consequently there is limited evidence to guide optimal treatment and follow-up in children. However, the basic principles and approaches described for drug-resistant tuberculosis, including MDR and XDR tuberculosis, apply in both children and adults.³⁸²

Pregnancy and Breast-feeding. Active untreated tuberculosis poses a far greater hazard to a pregnant woman and her fetus than does treatment for the disease.³⁸³ Pregnant women or mothers of young infants, therefore, should be started on treatment with isoniazid, rifampin, and ethambutol. Pyrazinamide is included in recommendations for treating tuberculosis in pregnant women by the WHO, but it has not been included in recommendations in the United States because of insufficient information about possible harm to the fetus. Streptomycin, which interferes with development of the ear and may cause congenital deafness, is the only antituberculosis drug documented to have harmful effects on the fetus.³⁸⁴ This potential is presumably shared by amikacin, kanamycin, and capreomycin; however, there is little or no information about the effects of these drugs on the fetus, or about the potential hazards of cycloserine, ethionamide, and pyrazinamide. Although several antituberculosis drugs are present in breast milk, their concentrations and the total amounts that could possibly be ingested by a nursing infant are such that adverse effects would be unlikely. Thus, no modifications of treatment regimens are recommended for nursing mothers.²⁹⁹

Associated Conditions. Tuberculosis commonly develops in association with other conditions, either because an underlying disease or its treatment alters immune responsiveness, thereby predisposing to tuberculosis (e.g., HIV infection, hematologic or reticuloendothelial malignancies, chronic renal disease or diabetes mellitus, use of tumor necrosis factor inhibitors), or because the accompanying condition is common in the same social and cultural milieu as tuberculosis, particularly alcoholism and all its complications and other forms of substance abuse.³⁸⁵⁻³⁸⁷ Because all of these conditions may affect the response to and outcome of treatment, therapeutic decisions must be made on an individualized basis and, when possible, steps must be taken to correct the immunosuppression.

In patients with impaired renal function, streptomycin, kanamycin, amikacin, and capreomycin should be avoided if at all possible or given two to three times per week in the usual dose. If there is severe impairment of renal function, reduction in frequency of administration of ethambutol and pyrazinamide to two to three times per week may be necessary.²⁹⁹ Liver disease, particularly alcoholic hepatitis and cirrhosis, is commonly associated with tuberculosis. In general, the complications of potentially hepatotoxic antituberculosis drugs have not been greater in patients with liver disease.³⁸⁸ However, detecting any such adverse effects may be difficult because of the preexisting disorder of

hepatic function. Moreover, a drug that would cause minor hepatotoxicity in a person with normal liver function could have major consequences in a patient with severe liver disease. Options in treating patients with severe liver disease include treatment without isoniazid by using rifampin, ethambutol, and pyrazinamide for 6 months; treatment without pyrazinamide for a total duration of 9 months; treatment with only one potentially hepatotoxic drug, usually retaining rifampin and adding ethambutol and a fluoroquinolone for a total of 12 to 18 months; or treatment with a regimen that contains no hepatotoxic drugs, such as streptomycin, ethambutol, a fluoroquinolone, and perhaps another second-line drug for 18 to 24 months.²⁹⁹ In patients with severe liver disease, routine testing of liver function should be performed at baseline and frequently during treatment. Finally, in patients with psychiatric disorders, close supervision of treatment with directly observed therapy of all medications is essential.

Adjunctive Therapy

Currently, the adjunctive therapies for pulmonary tuberculosis include surgery and corticosteroid treatment. Although surgery was once a mainstay of treatment for pulmonary tuberculosis, since the advent of chemotherapy, it has rarely been indicated. Artificial pneumothorax, pneumoperitoneum, phrenic nerve interruption, plombage, and thoracoplasty—procedures designed to collapse portions of the lung and close cavities—were common interventions until the 1960s but then rendered obsolete by the effectiveness of chemotherapy.³⁸⁹ Rarely, even now, patients with MDR pulmonary tuberculosis are treated with either pneumoperitoneum or thoracoplasty.

Currently, surgical resection is the most commonly performed surgical procedure and may be indicated in several situations. In patients with tuberculosis caused by MDR or XDR organisms anatomically limited within the lung and who are otherwise deemed to be surgical candidates, resection may be an effective therapeutic option. A systematic review and meta-analysis suggested that the outcomes were improved in patients who underwent surgery in addition to medical therapy.³⁹⁰ The outcome assessed at 12 months postprocedure was estimated as successful in 87% of patients who underwent surgery for MDR tuberculosis. All-cause mortality was 6%. The results for patients with XDR tuberculosis were estimated to be 69% successful with an all-cause mortality of 4%. However, the literature is difficult to interpret because of differences in case selection for surgical procedures, differences in the procedures performed (which often are not stated in meta-analyses), variations in extent of the tuberculous process, differing drug regimens, and finally the fact that controlled clinical trials have not been done (and would be difficult to design).

Ideally, before surgery the bacillary population should be reduced as much as possible with drugs to which the organism is susceptible. However, the timing of surgery can be difficult, in that the effectiveness of a limited second-line drug regimen cannot always be predicted. Resection may also be necessary because of massive hemoptysis associated with current or old tuberculosis, because of residual lung damage (e.g., bronchiectasis) exacerbated by recurrent bacterial infections, or because of a bronchopleural fistula usually with a tuberculous empyema. In addition to these

therapeutic indications for surgery, tuberculosis is sometimes diagnosed by examination of a pulmonary mass or nodule that was resected owing to suspicion of malignancy.

In any situation involving possible lung surgery in patients with or suspected of having tuberculosis, including the resection of a solitary nodule in a patient with a positive tuberculin reaction, it is desirable for the patient to have been receiving adequate antituberculosis chemotherapy before the operation. This will minimize the possibility of spread of tuberculosis within the lung and of bronchial stump infection and empyema. The optimum amount of time before operation that treatment should be given is not clear, but in emergencies, such as massive hemoptysis, at least single doses of the drugs should be given, whereas with elective procedures, it is desirable to wait at least until the sputum smear is negative. If the sputum smear is negative to begin with, 2 weeks of treatment is reasonable.

Corticosteroids. The use of corticosteroids in pulmonary tuberculosis has been and remains controversial. In view of the well-known effects of corticosteroids in decreasing cell-mediated immune responses, it seems counterintuitive that these same agents could be beneficial. Nevertheless, corticosteroids, by interfering with the tissue-damaging immune response, may minimize the adverse effects of the inflammatory reaction. For this reason, corticosteroids may under certain conditions be of benefit in patients with pulmonary tuberculosis who are receiving adequate chemotherapy. These conditions were defined by a controlled trial reported by Johnson and colleagues³⁹¹ in which all patients were treated with effective antituberculosis chemotherapy (although rifampin was not yet available) and were assigned at random to receive either methylprednisolone or placebo. This study demonstrated that corticosteroid treatment most benefited the seriously ill patient (defined by low serum albumin concentration, low body weight, and severe weight loss) who had extensive tuberculosis. This benefit was evidenced mainly by an increase in the rate of radiographic clearing; there was no adverse effect on the bacteriologic response. In less severely ill patients, methylprednisolone was either of no benefit or actually decreased the speed of sputum conversion. These data suggest that the major role of corticosteroid treatment is in patients with severe tuberculosis and severe systemic effects. Although not considered in the study by Johnson and colleagues, steroids may also be of benefit in patients with marked abnormalities of gas exchange and respiratory failure.³⁹² A more recent systematic review examined the results of clinical trials of corticosteroids as adjunctive therapy for pulmonary tuberculosis and came to essentially the same conclusions.³⁹³ Dexamethasone is also recommended in tuberculous meningitis¹⁶⁶ and, although the evidence is less persuasive, corticosteroids are often given in tuberculous pericarditis.

EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary tuberculosis presents more of a diagnostic and therapeutic problem than does pulmonary tuberculosis. In part this relates to its being less common and therefore

less familiar to most clinicians.^{394,395} In addition, extrapulmonary tuberculosis involves relatively inaccessible sites, and often, because of the vulnerability of the areas involved, much greater damage can be caused by fewer bacilli. The combination of small numbers of bacilli in inaccessible sites makes bacteriologic confirmation of a diagnosis more difficult, and invasive procedures are frequently necessary to establish a diagnosis. In addition to the need for invasive diagnostic procedures, surgery may be an important component of management.

In 2012 in the United States, 21% of newly reported cases of tuberculosis involved extrapulmonary sites only and an additional 10% involved both pulmonary and extrapulmonary sites.²⁷ The proportion of patients with extrapulmonary involvement is greater among patients with HIV infection. In one large retrospective study of tuberculosis in patients with HIV infection, approximately one third of the patients had only extrapulmonary sites of involvement, one third had both pulmonary and extrapulmonary disease, and one third had only pulmonary involvement.³⁹⁶ Because of the frequency of extrapulmonary tuberculosis among HIV-infected patients, diagnostic specimens from any suspected site of disease should be cultured for mycobacteria, including blood and bone marrow from any febrile patient who does not have an obvious localized site of disease.

LYMPHATIC TUBERCULOSIS

Lymphatic tuberculosis accounts for approximately 42% of the cases of extrapulmonary tuberculosis in the United States.²⁷ Although the basic descriptive epidemiology of tuberculosis applies to lymphatic tuberculosis, there are a few differences. This form of tuberculosis is more common among children than among adults. In addition, lymphatic tuberculosis differs from the overall pattern in that it happens more frequently in women. It also appears to be more common among Asians and Pacific Islanders than among blacks and whites. Among HIV-infected persons, the incidence of tuberculous lymphadenitis increases as the level of CD4⁺ T cells decreases.³⁹⁷

Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes. The nodes most commonly involved are those of the posterior or anterior cervical chain or those in the supraclavicular fossa. Frequently the process is bilateral, and other noncontiguous groups of nodes can be involved. At least initially, the nodes are discrete and the overlying skin is normal. With ongoing disease, the nodes may become matted and the overlying skin inflamed. Rupture of the node can result in formation of a sinus tract, which may persist for years. Intrathoracic adenopathy may compress bronchi, causing atelectasis, thereby leading to lung infection and perhaps bronchiectasis. Although rare, upper airway obstruction may result from cervical node enlargement. Both chylous pleural effusion and ascites have resulted from intrathoracic or abdominal node involvement with obstruction of retroperitoneal lymphatics or the thoracic duct. Tuberculous lymphadenitis may also appear or worsen as a manifestation of IRIS (see Fig. 35-12).

The diagnosis of tuberculous lymphadenopathy is established by lymph node biopsy or aspiration with histologic examination, including stains for acid-fast organisms and

culture of the material. Smears show acid-fast organisms in approximately 25% to 50% of biopsy specimens, and *M. tuberculosis* is isolated in approximately 70% of instances in which the final diagnosis is considered to be tuberculosis.³⁹⁸ Caseating granulomas are seen in nearly all biopsy specimens from immunocompetent patients. In immunodeficiency states, granulomas may be poorly formed or absent.³⁹⁹

The rate of response of tuberculous lymphadenitis to the standard 6-month regimen is much slower than that of pulmonary tuberculosis. Nodes may enlarge, new nodes may appear, and fistulas may develop during treatment that ultimately proves effective, but true bacteriologic relapse after completion of therapy is unusual.⁴⁰⁰

Corticosteroid treatment has been used to shrink intrathoracic nodes and relieve bronchial obstruction, primarily in children. In a controlled study, Nemir and coworkers⁴⁰¹ demonstrated that corticosteroids increase the rate of resolution of radiographic changes thought to be due to bronchial narrowing by lymph nodes or endobronchial lesions in children with primary tuberculosis. Apart from this indication, there is no clear role for corticosteroids in lymphatic tuberculosis.

Surgical intervention may be necessary to make a diagnosis of tuberculous lymphadenitis and, on occasion, surgical incision and drainage are needed to prevent spontaneous drainage and fistula formation. Surgical excision of involved nodes, strictly as an adjunct to chemotherapy, is associated with perhaps a slightly worse outcome than medical treatment with aspiration of the node or medical treatment alone.⁴⁰²

Various other forms of extrapulmonary tuberculosis, including genitourinary, bone and joint, central nervous system, abdominal, and pericardial tuberculosis are discussed in the online version of this chapter.



TREATMENT OF LATENT TUBERCULOUS INFECTION

The observations on which treatment of LTBI are based were made in the 1950s. In these experimental studies, it was found that animals given isoniazid before being challenged by *M. tuberculosis* had a much lower frequency of tuberculosis.⁴³¹ Subsequently, it was found that isoniazid given to children with primary tuberculosis nearly eliminated extrapulmonary spread of the disease.⁴³² These results provided the rationale for several large U.S. Public Health Service studies of the effectiveness of isoniazid in preventing tuberculosis. These studies were double-blind, placebo-controlled clinical trials that involved approximately 70,000 participants who were in a number of different settings and who had a variety of different risk factors for tuberculosis. The design and results of these studies are described in detail by Ferebee.⁴³³ The findings were remarkably similar in all groups studied; participants given isoniazid had a reduction of approximately 80% in the incidence of tuberculosis during the year the medication was given, in comparison with those given placebo. The protective effect decreased during subsequent years, but the treated groups still showed approximately 50% less

tuberculosis than did the control groups each year after the medication year through 10 to 12 years of observation. Overall, isoniazid reduced the incidence of tuberculosis by approximately 60%.

The effectiveness of antituberculosis drugs in preventing tuberculosis is presumably a result of the reduction of the viable population of sequestered bacilli in inactive or radiographically invisible lesions in the lungs and elsewhere. However, on occasion, treatment may be given to persons who have been exposed to tuberculosis but do not have a positive TST or IGRA. In this situation, treatment is assumed to prevent the establishment of a tuberculous infection, an example of “primary prophylaxis.” However, the effectiveness of antituberculous drugs in preventing tuberculosis is limited in high-prevalence populations: a recent large trial in South African gold miners found only a temporary benefit of isoniazid preventive treatment, most likely because of frequent re-exposure to tuberculosis after the end of the treatment.^{433a}

INDICATIONS FOR TREATMENT

The recommendations for testing for and treatment of LTBI reflect the concept that only persons who are at increased risk of tuberculosis should be tested for latent infection; thus, any person who is tested and is found to have a positive test should be considered for treatment.^{434,435} The two broad categories of persons in whom the risk of tuberculosis is substantially higher than that of the general population of the United States are persons who are either known or presumed to have been recently infected with *M. tuberculosis* and persons who have clinical conditions that increase the risk of progressing from latent infection to active tuberculosis. The specific groups in which treatment is indicated are as follows (in order of decreasing degree of risk for developing tuberculosis).

Persons with HIV Infection

A number of studies have shown that the rates of tuberculosis among persons who are infected with both *M. tuberculosis* and HIV are extremely high, ranging from 3% to 10% per year.^{436,437} The effectiveness of preventive therapy among persons with HIV infection has been examined in a Cochrane review that included data through April 2008.⁴³⁸ Preventive therapy (with any anti-TB drug) versus placebo was associated with a lower incidence of active tuberculosis with a *relative risk* (RR) of 0.68. The benefit was greater in individuals with a positive TST (RR 0.38) than in those who had a negative test (RR 0.89). The efficacy was similar for all regimens, regardless of drug type, frequency, or duration of treatment. However, compared with isoniazid monotherapy, short-course multidrug regimens were much more likely to require discontinuation of treatment due to adverse effects. Although there was reduction in mortality with isoniazid monotherapy, there was no evidence that preventive therapy reduced all-cause mortality.

Currently WHO recommends isoniazid given for at least 6 months to persons with HIV infection at risk of tuberculosis regardless of the TST result. Some data suggest that a 36-month treatment duration further reduces the risk of tuberculosis in persons with HIV infection in a high tuber-

culosis incidence country, perhaps by reducing reinfection with *M. tuberculosis*.⁴³⁹ However, this regimen is not recommended by WHO at this time.

Likewise, although there are data showing efficacy of the 12-dose isoniazid-rifapentine regimen in adults with HIV infection, it is not yet recommended by WHO.⁴⁴⁰ Although antiretroviral therapy has a substantial effect in reducing the risk of tuberculosis, there is additive benefit from isoniazid preventive treatment.^{197,199,441}

Close Contacts of New Cases

Two percent to 4% of persons in close contact with a person with infectious tuberculosis develop tuberculosis in the year after exposure.⁴⁴²⁻⁴⁴⁴ In young children and adolescents, the risk is perhaps twice that in adults. Because the TST or IGRA result may be negative if infection is recent, all close contacts should be treated. Those with a TST of 5 mm or more should be considered to be infected and should receive a full course of preventive therapy. Close contacts who have negative TST should be retested 2 to 3 months after the index case has ceased being infectious or after contact has been broken. If the TST at that time is less than 5 mm or if the IGRA has not converted, isoniazid can be discontinued; if the reaction is 5 mm or more or an IGRA has converted from negative or indeterminate to positive, the drug should be continued for a full course. Contacts known to be HIV-infected should be treated even if the TST result is negative.⁴³⁴

Persons with Recent Infection

As discussed in the section describing the pathogenesis of tuberculosis, the risk of developing tuberculosis is greatest during the initial 1 to 2 years after acquisition of the infection. Any person who is documented to have had a conversion of the TST or an IGRA from negative to positive should be considered newly infected and receive treatment. A skin test conversion is defined as an increase in reaction size of 10 mm or more within a 2-year period for persons younger than 35 and a 15-mm or more increase for persons older than 35. TST reactors younger than 5 years of age should be accorded a high priority for preventive therapy, both because they obviously have been infected relatively recently and because of the potential for severe disease in this age group. There is no consensus on the change in the IGRA result to define a conversion.

Persons with Stable Radiographic Findings Consistent with Previous Tuberculosis

This group includes persons with a history of tuberculosis who never received chemotherapy or were not treated adequately and persons with no known history of the disease. The rate at which new episodes of tuberculosis develop in these groups ranges from approximately 0.4% to 3.5% per year.⁴⁴⁵⁻⁴⁴⁷ The risk is lowest in persons with small lesions that have been stable for a long period. In persons with radiographic abnormalities, it is essential that current tuberculosis be excluded by a careful clinical and bacteriologic evaluation. Because exclusion of active tuberculosis might not be feasible or possible at the initiation of therapy, an alternative approach is to begin therapy with multiple drugs: isoniazid, rifampin, and pyrazinamide, sometimes with ethambutol. If disease is determined to be active by a

GENITOURINARY TUBERCULOSIS

The epidemiologic pattern of genitourinary tuberculosis parallels that of tuberculosis in general, with the exception of HIV-infected patients. The pathogenesis is thought to be due to seeding of the kidney at the time of the initial infection and bacilleemia. This mechanism is supported by the finding that, with careful study, tuberculous lesions can be found in both kidneys in 90% of patients with renal tuberculosis, even though the disease is clinically evident in only one kidney.⁴⁰³ Lower genitourinary tract involvement is thought to represent spread from the kidneys, but it may also represent spread by hematogenous seeding. Genital lesions were reported by Medlar and coworkers⁴⁰⁴ in 13% of men with disseminated renal lesions, 52% of those with caseating lesions, and 100% of those with cavitary lesions in the kidney. Genital involvement without renal involvement was reported in 11%.

In patients with genitourinary tuberculosis, local symptoms predominate and systemic symptoms are less common.^{405,406} Dysuria, hematuria, and frequent urination are common, and flank pain may also be noted. However, in general the symptoms are subtle, and often there is advanced destruction of the kidneys by the time a diagnosis is established.⁴⁰⁷ In women, genital involvement is more common without renal tuberculosis than in men and may cause pelvic pain, menstrual irregularities, and infertility as presenting complaints.⁴⁰⁶ In men, a painless or only slightly painful scrotal mass is probably the most common presenting symptom of genital involvement, but symptoms of prostatitis, orchitis, or epididymitis may also exist.⁴⁰⁵ A substantial number of patients with any form of genitourinary tuberculosis are asymptomatic, and the disease is detected because of an evaluation for an abnormal urinalysis. In patients with renal or genital tuberculosis, urinalyses are abnormal in more than 90%; the main findings are pyuria, hematuria, or mixed pyuria and hematuria. Pyuria in an acidic urine with no organisms isolated from a routine urine culture should prompt an evaluation for tuberculosis. Occasionally, when there is an isolated genital focus of disease or when a tuberculous kidney is blocked by a ureteral stricture, the urinalysis may be normal and cultures may be sterile.

The suspicion of genitourinary tuberculosis should be heightened by the presence of abnormalities on the chest film. In most series, 50% to 75% of patients have chest radiographic abnormalities, although many of these may be the result of previous, not current, tuberculosis.^{405,406}

When genitourinary tuberculosis is suspected, at least three first-voided early morning urine specimens should be collected and stained for AFB and cultured for mycobacteria. In men, saprophytic *Mycobacterium smegmatis* may cause a positive smear. However, in the presence of abnormalities suggesting tuberculosis, the finding of a positive smear should be interpreted as confirming the diagnosis of genitourinary tuberculosis until the results of cultures are known. *M. tuberculosis* is isolated from the urine in 80% to 95% of cases of genitourinary tuberculosis.^{405,406} Diagnosis of isolated genital lesions usually requires biopsy because the differential diagnosis often includes neoplasia, as well as other infectious processes.

Positive urine cultures may manifest in the absence of any clinical, laboratory, or radiographic findings, which suggests concomitant genitourinary tuberculosis in patients with other forms of tuberculosis. Bentz and coworkers⁴⁰⁸ found unanticipated positive urine cultures in 21% of patients with other extrapulmonary forms of tuberculosis and in 5% of those with pulmonary tuberculosis alone.

Renal tuberculosis, at least as indicated by a positive urine culture, may develop in patients with HIV infection. In one series, positive urine cultures were found in 12 (71%) of 17 cultures submitted in patients with tuberculosis and advanced HIV infection, although this was not a systematic sampling.³⁹⁶

There are several treatment considerations for genitourinary tuberculosis apart from standard chemotherapy. Nephrectomy, formerly a mainstay of therapy for renal tuberculosis, now is seldom indicated; however, in patients who have tuberculosis caused by MDR organisms and who can tolerate removal of a kidney, nephrectomy may be indicated. Nephrectomy may also be indicated for patients who have recurrent pyogenic bacterial infections in a kidney destroyed by tuberculosis, for patients with persistent pain, and for those with massive hematuria. Surgical or endoscopic procedures may also be necessary to correct ureteral strictures and to augment the capacity of a contracted bladder.

BONE AND JOINT TUBERCULOSIS

The incidence of tuberculosis involving the joints and bones increases with increasing age and is equally frequent among men and women. In comparison with blacks and whites, other racial groups are less likely to have skeletal involvement. Skeletal tuberculosis does not appear to be more frequent in persons with HIV infection.

It is presumed that most osteoarticular tuberculosis results from endogenous reactivation of foci of infection seeded during the initial bacilleemia, although spread from paravertebral lymph nodes has been postulated to account for the common localization of spinal tuberculosis to the lower thoracic and upper lumbar vertebrae. It is also postulated that the predilection for tuberculosis to localize in the metaphyses of long bones is due to the relatively rich blood supply and scarcity of phagocytic cells in this portion of the bone.⁴⁰⁹ After beginning in the subchondral region of the bone, the infection spreads to involve the cartilage, synovium, and joint space. This produces the typical findings of metaphyseal erosion and cysts and loss of cartilage with narrowing of the joint space. Typically, in the spine these changes involve two adjacent vertebrae and the intervertebral disc (eFig. 35-1). An "atypical" form of spondylitis without evidence of disc involvement may be seen and may account for more than half of the patients.⁴¹⁰⁻⁴¹² Paravertebral or other para-articular abscesses may develop with occasional formation of sinus tracts. Although weight-bearing joints are the most common sites for skeletal tuberculosis, any bone or joint may be involved.⁴⁰⁹ In most series of osteoarticular tuberculosis, tuberculosis of the spine (Pott disease) makes up 50% to 70% of the cases reported. In adults the lower thoracic and upper lumbar vertebrae are most commonly involved, whereas in children the upper

thoracic spine is the most frequent site. The hip or knee is involved in 15% to 20% of cases, and shoulders, elbows, ankles, wrists, and other bones or joints also make up 15% to 20%. Usually only one bone or joint is involved, but occasionally the process may be multifocal. Evidence of either previous or current pulmonary tuberculosis is found in approximately half the reported patients, and other extrapulmonary sites may be involved as well.

The first diagnostic test undertaken is usually a radiograph of the involved area. Early in the process, the only abnormality noted may be soft-tissue swelling. *Computed tomography* (CT) scans and magnetic resonance imaging of the spine are considerably more sensitive than routine films and should be obtained when there is a high index of suspicion of an infectious process. Radionuclide bone scanning with technetium-99m can demonstrate occult skeletal involvement in patients with normal radiographs. Likewise, gallium-67 scanning may define unsuspected sites, especially soft-tissue involvement not seen on the bone scan.

Confirmation of the diagnosis is obtained by aspiration of joint fluid or periarticular abscesses or by biopsy of bone or synovium with histologic and microbiologic evaluation of the material obtained. Acid-fast stains are positive in 20% to 25% of samples of joint fluid, and *M. tuberculosis* is isolated in approximately 60% to 80% of them.⁴⁰⁹ Biopsy specimens of synovium or bone have a higher yield and enable histologic examination as well. Evidence of granulomatous inflammation even in the absence of bacteriologic proof of the diagnosis is sufficient evidence of tuberculosis to begin therapy unless another cause is found.

Standard chemotherapy of 6 to 9 months' duration is highly successful in skeletal tuberculosis, but surgery is occasionally a necessary adjunct.⁴¹⁰ The longer duration of treatment has been suggested because of the difficulties in assessing response. Several controlled studies have documented that chemotherapy conducted largely on an ambulatory basis is effective in curing spinal tuberculosis without the need for immobilization.⁴¹¹ The role of emergency spinal cord decompression in patients with Pott disease and early neurologic findings is not clear, and, if paraplegia is already present, the benefit of surgical intervention is even less clear. Moreover, there is no well-defined surgical procedure of choice. An "all-or-none" approach has been advocated by several surgeons,⁴¹²⁻⁴¹⁴ which means that surgery is not performed except in patients with progressive neurologic deterioration unresponsive to chemotherapy—in whom all affected bone is removed and an anterior spinal fusion is performed; there is no role for simple debridement other than for diagnosis. Surgery may be indicated in other forms of articular tuberculosis when there is extensive destruction of the joint or surrounding soft tissues, in which case synovectomy and joint fusions may be necessary.

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

Meningitis is the most frequent form of central nervous system tuberculosis; solitary or multiple tuberculomas ensue less commonly. The epidemiologic pattern of central nervous system tuberculosis is quite different from that of either pulmonary or other forms of extrapulmonary tuberculosis, in that the peak incidence is in infants and children up to age 4. Although an appreciable number of cases exist

in adults, meningitis accounts for only approximately 6% of all cases of extrapulmonary tuberculosis, which are equally divided between males and females.²⁷

Central nervous system tuberculosis, especially tuberculomas, seems to develop with greater frequency among HIV-infected persons. Central nervous system tuberculomas have been reported even in patients who are receiving what should be adequate chemotherapy.⁴¹⁵ Because tuberculomas may be indistinguishable on CT scan from the lesions of toxoplasmosis, specific diagnosis is necessary.

Meningitis presumably can result from direct meningeal seeding and proliferation during a tuberculous bacilleemia either at the time of initial infection or reactivation of an old pulmonary focus, or it can also result from reactivation of an old parameningeal focus with rupture into the subarachnoid space.⁴¹⁶ The consequences of the subarachnoid space contamination include diffuse meningitis, a localized arteritis, encephalitis, and myelitis. The symptoms depend primarily on which of these processes predominates. With meningitis, the process is primarily located at the base of the brain.⁴¹⁷ Symptoms therefore include those related to cranial nerve involvement in addition to headache, decreased level of consciousness, and neck stiffness. The duration of illness before diagnosis is variable and related partly to the presence or absence of other sites of involvement. In a large series of patients, the average duration of illness was 12 days.⁴¹⁸ In most series, more than 50% of patients with meningitis have abnormalities on chest film that are consistent with an old or current tuberculous process, often miliary tuberculosis. At autopsy, disseminated disease is found in a high percentage of patients with meningitis. In patients with tuberculous meningitis, sputum cultures have been positive in 40% to 50%; thus, a substantial number of patients have pulmonary and systemic symptoms in addition to those referable to the central nervous system. Patients in whom arteritis is the predominant manifestation of meningitis can present with a variety of focal central nervous system ischemic syndromes in addition to the symptoms already described.

In tuberculous meningitis, the lumbar puncture usually shows increased opening pressure, and the *cerebrospinal fluid* (CSF) usually contains between 100 and 1000 cells/ μ L.^{394,418} In approximately 65% to 75% of patients, lymphocytes predominate, whereas polymorphonuclear leukocytes predominate in the remainder, generally early in the course of the illness. The CSF protein concentration is elevated in nearly all patients. Very high (>3300 mg/dL) protein concentrations have been associated with a poor prognosis; the glucose concentration in CSF is usually low, but not as low as that often found in pyogenic bacterial meningitis.⁴¹⁸ Acid-fast organisms are seen on smears of CSF in only 10% to 20% of patients, and the rate of culture positivity varies from 25% to 80% but is generally in the lower end of the range.⁴¹⁸ In a substantial number of patients, *M. tuberculosis* is isolated from other sources, which, in the presence of compatible CSF findings, is sufficient to diagnose tuberculous meningitis. In view of the severity of tuberculous meningitis, a presumptive diagnosis justifies empirical treatment if no other diagnosis can be established promptly. Because of the difficulty with establishing a diagnosis of tuberculous meningitis by bacteriologic methods, Thwaites and associates⁴¹⁸ developed and

validated a clinical scoring system by which tuberculous meningitis could be separated from pyogenic bacterial meningitis. Younger age (<36 years), lower peripheral white blood cell count (<15,000/mm³), longer duration of illness (>6 days), lower CSF white blood cell count (<900/μL), and lower percentage (<75%) of neutrophils in the CSF were associated with a greater likelihood of a tuberculous etiology.

A meta-analysis of 14 studies of nucleic acid amplification tests for the diagnosis of tuberculous meningitis found a combined sensitivity of 56% and a specificity of 98%.³⁰⁹ Thus, when a nucleic acid amplification test is positive, one can assume that the etiology is tuberculous, but a negative result does not exclude the diagnosis.

If there are no epidemiologic indicators of possible resistance, a treatment regimen of isoniazid, rifampin, pyrazinamide, and ethambutol should be effective. The recommended length of the continuation phase is at least 7 months, for a total treatment duration of 9 to 12 months, although there are no clinical trials that serve to define the optimum treatment duration.

Corticosteroid treatment has a beneficial effect in patients with tuberculous meningitis and cerebral edema,³¹⁵ and it decreases the frequency of adverse sequelae in children with less advanced disease.⁴¹⁹ Given the poor prognosis of tuberculous meningitis, the reasonably good data supporting corticosteroid use in more severe forms of the disease, and the paucity of information in patients with less advanced disease, corticosteroid treatment, specifically with dexamethasone, is recommended for all patients³¹⁵ at a dosage of 12–16 mg/day for 3 weeks, then decreased gradually during the next 3 weeks. Even with effective chemotherapy and corticosteroids, however, both the mortality rate and rate of residual neurologic abnormalities from tuberculous meningitis remain high.

The other major central nervous system form of tuberculosis, the tuberculoma, presents a more subtle clinical picture than does tuberculous meningitis.⁴²⁰ The usual presentation is that of a slowly growing focal lesion, although a few patients have increased intracranial pressure and no focal findings. The CSF is usually normal, and the diagnosis is established by CT scanning or magnetic resonance imaging and subsequent resection, biopsy, or aspiration of any ring-enhancing lesion. The response to antituberculous chemotherapy is good, and corticosteroids are indicated only if there is an increase in intracranial pressure.

ABDOMINAL TUBERCULOSIS

Tuberculosis can involve any intra-abdominal organ and peritoneum. The age distribution of abdominal tuberculosis shows a higher incidence in young adults and a second peak in older persons. Men and women have similar incidences. The abdomen is a common site of disease in HIV-infected persons.

Abdominal tuberculosis presumably results from seeding at the time of initial infection and then either direct or late progression to clinical disease. Peritonitis can also be caused by rupture of tuberculous lymph nodes within the abdomen, and intestinal tuberculosis may result from direct implantation in the gut of ingested tubercle bacilli. Before the advent of chemotherapy, tuberculous enteritis was common in

patients with advanced pulmonary tuberculosis, presumably being caused by swallowed bacilli from the lungs. In a prospective study conducted between 1924 and 1949, intestinal abnormalities compatible with tuberculous enteritis were found by contrast radiography in 1%, 4.5%, and 24.7% of patients with minimal, moderately advanced, and far advanced pulmonary tuberculosis, respectively.⁴²¹

The clinical manifestations of abdominal tuberculosis depend on the areas of involvement. In the gut itself, tuberculosis may be in any location from the mouth to the anus, although lesions proximal to the terminal ileum are unusual. The most common sites of involvement are the terminal ileum and cecum; other portions of the colon and the rectum are involved less frequently.⁴²² In the terminal ileum or cecum, the most common manifestations are pain (which may lead to a misdiagnosis of appendicitis) and intestinal obstruction. A palpable mass may be noted that, together with its radiographic appearance, can easily be mistaken as a carcinoma. Rectal lesions usually present as anal fissures or fistulas or perirectal abscesses. In addition to carcinoma, the differential diagnosis of these findings includes inflammatory bowel disease. Because of the concern regarding carcinoma, the diagnosis often is made through surgery.⁴²³

Tuberculous peritonitis commonly causes pain as its presenting manifestation, often accompanied by abdominal swelling. Fever, weight loss, and anorexia are also common. Active pulmonary tuberculosis is uncommon in patients with tuberculous peritonitis. Because the process frequently coexists with other disorders, especially cirrhosis with ascites, the symptoms of tuberculosis may be obscured. The combination of fever and abdominal tenderness in a person with ascites should always prompt an evaluation for intra-abdominal infection, and paracentesis should be performed. Ascitic fluid in tuberculous peritonitis is exudative and contains between 50 and 10,000 leukocytes per microliter, the majority of which are lymphocytes, although polymorphonuclear leukocytes occasionally predominate.⁴²⁴ Acid-fast organisms are rarely seen on smears of the fluid, and cultures are positive in only approximately 50%, although the yield increases if a large volume of fluid is submitted for culture. Because of the generally low yield from culture of the fluid, laparoscopic biopsy is often necessary to confirm the diagnosis.

Standard chemotherapy is effective in abdominal tuberculosis. Corticosteroids have been advocated in tuberculous peritonitis to reduce the risk of adhesions causing intestinal obstructions, but this recommendation is controversial because of the low frequency of obstruction. As discussed previously, surgery is often necessary to establish a diagnosis and, in addition, may be necessary to relieve intestinal obstruction.

PERICARDIAL TUBERCULOSIS

The descriptive epidemiology of pericardial tuberculosis is not well defined, but in general it tends to afflict older persons, particularly nonwhites and men. The pericardium may become involved during the initial bacillema, with early progression to clinically evident disease or recrudescence after a quiescent period. Hematogenous seeding may also be present during the course of endogenous

reactivation. Alternatively, there may be direct extension of an adjacent focus of disease from the lung parenchyma, pleura, or tracheobronchial lymph nodes into the pericardium. Like the pleura, the pericardium is a serosal surface capable of exuding large amounts of fluid in response to inflammation. As presumably happens in tuberculous pleuritis with effusion, it is likely that hypersensitivity plays a role in producing the intense inflammatory response and abundant effusion in the pericardium. This would account for the relative infrequency of isolation of tubercle bacilli from pericardial fluid, the nonpurulent nature of the fluid, and the generally prompt response to antituberculosis chemotherapy in most instances. Conversely, rupture of a caseous lymph node into the pericardium may cause contamination with a much greater number of organisms; a greater inflammatory response with thicker, more purulent fluid; and a greater likelihood of either early or late hemodynamic effects.

The most common form or stage of tuberculous pericarditis is characterized by pericardial effusion with little pericardial thickening or epicardial involvement. Because in most instances the fluid accumulates slowly, the pericardium can expand to accommodate large volumes (2 to 4 L) with little apparent hemodynamic compromise. Symptoms of cardiopulmonary origin tend to manifest later and include cough, dyspnea, orthopnea, ankle swelling, and chest pain. The chest pain may occasionally mimic angina but usually is described as being dull, aching, and often affected by position and inspiration.

The fluid itself is usually serosanguineous or occasionally grossly bloody, is exudative, and has a white blood cell count ranging from 500 to 50,000 cells/ μ L, with an average of 5000 to 7000 cells/ μ L.⁴²⁵ The cells are predominantly mononuclear, although polymorphonuclear leukocytes occasionally predominate. Tubercle bacilli have been identified in pericardial fluid in approximately 25% to 30% of cases (smear and culture combined).⁴²⁵ Biopsy of the pericardium with both histologic and bacteriologic evaluation is much more likely to provide a diagnosis, although a non-specific histologic pattern and failure to recover the organisms do not exclude a tuberculous cause.

Although not well documented, it appears that, if the patient survives the subacute phase without treatment, chronic fibrotic pericarditis nearly always follows. Before the advent of antituberculosis therapy, 88% of one series of patients who had tuberculous pericarditis developed evidence of chronic constriction.⁴²⁶ Constriction has also been observed to develop during the course of antituberculosis chemotherapy, although this appears to be uncommon in patients who have had symptoms for less than 3 months; it is frequent in patients who have had symptoms for more than 6 months.

The fibrotic reaction progresses to complete fusion of visceral and parietal pericardium and encasement of the heart in a rigid scar that often becomes calcified. Impairment of coronary circulation is common. At this point the histologic pattern is usually nonspecific; thus, confirmation of a tuberculous etiology is infrequent.

The definitive diagnosis of tuberculous pericarditis requires identification of tubercle bacilli in pericardial fluid or tissue. Although not conclusive, demonstration of caseating granulomata in the pericardium and consistent clinical circumstances provide convincing evidence of a tuberculous etiology. Less conclusive but still persuasive evidence is the finding of another form of tuberculosis in a patient with pericarditis of undetermined cause. Approximately 25% to 50% of patients with tuberculous pericarditis have evidence of other organ involvement, particularly pleuritis, at the time pericarditis is diagnosed.⁴²⁷ Still less direct and more circumstantial evidence of a tuberculous etiology is the combination of a positive intermediate-strength TST or IGRA reaction and pericarditis of unproved cause.

Because of the potentially life-threatening nature of pericardial tuberculosis, treatment with antituberculosis agents should be instituted promptly once the diagnosis is made or strongly suspected. It appears that the likelihood of constriction is greater in patients who have had symptoms longer; thus, early therapy may reduce the incidence of this complication. Several studies have suggested that corticosteroids have a beneficial effect in treating both tuberculous pericarditis with effusion and constrictive pericarditis.⁴²⁸⁻⁴³⁰ However, a meta-analysis of studies examining the effects of corticosteroids in tuberculous pericarditis concluded that, although steroids could have an important effect, the studies were too small to be conclusive.⁴²⁸ Nevertheless, patients with proven tuberculous pericarditis who are receiving adequate antituberculosis therapy and who have no major contraindications should receive corticosteroids. The optimum regimen is not known, but daily prednisone, 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and 5 mg/day for 1 week, is the recommended regimen.²⁹⁹ Corticosteroid therapy should not be used if there is a strong suspicion that the infection is caused by a drug-resistant organism unless adequate antituberculosis chemotherapy can be ensured.

In the setting of hemodynamic compromise, pericardiectomy is necessary. Although pericardiocentesis generally improves the circulatory status, the improvement is usually temporary. Pericardial windows with drainage into the left pleural space also generally provide only temporary relief. The criteria for selecting patients for pericardiectomy are not clear, apart from those patients who have refractory hemodynamic compromise.

positive culture or by radiographic improvement, therapy should be continued for 6 months. If there is no suggestion of active disease, therapy can be stopped after 4 months and the course of treatment will be sufficient for preventive purposes.⁴³⁴

Persons with Other Conditions That Increase the Risk of Tuberculosis

Although the risk of tuberculosis is not always quantifiable, there is sufficient evidence to warrant preventive therapy in certain situations: prolonged therapy with corticosteroids (usually 15 to 20 mg or more of prednisone daily, or its equivalent, for more than 2 to 3 weeks); immunosuppressive therapy; hematologic or reticuloendothelial malignancies, and perhaps certain solid tumors; end-stage renal disease; clinical conditions associated with rapid weight loss (including intestinal bypass for obesity and inadequate nutritional intake); after gastrectomy; and before treatment with anti-TNF agents; silicosis or coal workers' pneumoconiosis.^{434,448} In addition, even in the absence of any of these risk factors, persons in the following circumstances who have TST readings of 10 mm or more should be considered for preventive therapy: foreign-born persons from areas of high tuberculosis prevalence; medically underserved, low-income populations, including high-risk racial and ethnic groups; residents of long-term care facilities (e.g., correctional institutions and nursing homes); and other groups that, on the basis of local epidemiologic patterns, have been shown to have a high incidence of tuberculosis (e.g., migrant workers, homeless persons).⁴³⁴

CURRENT TREATMENT REGIMENS

For many years, the only regimen available for treating latent infection was isoniazid given for 6, 9, or 12 months. Subsequently, rifampin alone given for 4 months was shown to be effective.⁴³⁴ More recently a once-weekly combination of isoniazid and rifapentine given under direct observation for 12 doses was demonstrated to be noninferior to isoniazid alone given for 9 months.⁴⁴⁹ The CDC subsequently has published recommendations for the use of the 12-dose regimen, indicating that it should be used under direct observation in adults without HIV infection.⁴⁵⁰ The regimen that is supported most strongly is isoniazid given daily for 9 months. A 6-month regimen has also been shown to produce considerable protection and may provide the best balance between cost and benefit. Both the 6-month and the 9-month isoniazid regimens may be given twice weekly under direct observation. The second option is rifampin given daily for 4 months, although the supporting data are less strong.

Isoniazid is given in a single daily dose of 300 mg for adults and 5 to 10 mg/kg body weight (up to 300 mg/day) for children. The drug may also be given in doses of 15 mg/kg twice a week, which may facilitate direct observation of treatment. The minimum duration of treatment is 6 months; 9 months of treatment is considered optimum. Rifampin is given in a single dose of approximately 10 mg/kg body weight for both adults and children, up to a total daily dose of 600 mg. The same dose is used when the drug is given twice weekly. If rifabutin is substituted for rifampin, the dose is 5 mg/kg/day or 300 mg/day.

Treatment of LTBI with isoniazid or rifampin should not be undertaken in persons who have active, unstable liver disease. Stable chronic liver disease is not a contraindication, but such patients deserve careful consideration regarding the indications and need close attention during the course of treatment. Other persons who should be monitored especially closely during the administration of preventive therapy include persons older than 35; those taking other medications with which there may be interactions (such as phenytoin, disulfiram, or antiretroviral drugs); and persons with other disorders such as alcoholism, diabetes mellitus, or renal insufficiency that may increase the risk of adverse reactions, mainly hepatitis and peripheral neuropathy.

Pregnancy is not a contraindication to isoniazid; however, in view of the concern with elective administration of any drug during the course of pregnancy, it is generally prudent to wait until after delivery to give isoniazid. The exceptions to this general approach are women who have a documented TST conversion during pregnancy or who are HIV infected and have a positive TST.

MANAGEMENT OF EXPOSURE TO DRUG-RESISTANT ORGANISMS

Contacts of persons with drug resistant tuberculosis have a substantial risk of being infected and having active tuberculosis.⁴⁵¹ Providing preventive therapy for persons exposed to MDR or XDR organisms is especially problematic because there are no regimens with proven efficacy. The options that are available include observation only or administration of two drugs to which the source case isolate was shown to be susceptible (e.g., a 6-month regimen of ethambutol and pyrazinamide or of pyrazinamide and a fluoroquinolone). It should be noted that there are no data to guide the choice of an option. In such situations expert consultation should be obtained. Regardless of the approach that is chosen, if evidence suggesting tuberculosis arises, the patient should be treated promptly with a multidrug regimen to which the organism would be predicted to be susceptible on the basis of the susceptibility testing of the index case isolate.

IMMUNIZATION WITH BACILLE CALMETTE-GUÉRIN

Administration of BCG vaccine has been the major preventive technique used for many years throughout much of the world, yet no vaccine has been the subject of greater controversy.⁴⁵² BCG is an attenuated tubercle bacillus (*Mycobacterium bovis*) that was created beginning in 1908 by Calmette and Guérin in France and that was found to protect a variety of animal species against tuberculosis. It was first used in humans in 1921 and has since become the most widely used vaccine in the world: up to 80% of infants in developing countries receive BCG immunizations. In children, BCG has been demonstrated to prevent disseminated and miliary tuberculosis and tuberculosis meningitis.⁴⁵³ In adults, the results of BCG vaccination are less clear; of eight controlled clinical trials of BCG against pulmonary tuberculosis in adults, protection has ranged from 0 to 70%.⁴⁵²

Interestingly, when two different vaccines were used in a Medical Research Council Trial in the United Kingdom, one of which produced only poor TST reactivity, equal degrees of protection were seen. Conversely, no protection was seen in the South Indian Trial of more than 200,000 people monitored for 15 years, although all patients who developed tuberculosis had been converted to TST positivity by the vaccine.⁴⁵⁴ It is unclear why BCG appears to be effective in some parts of the world and not in others (a finding that is also evident in protection against leprosy). Clearly, there is a great deal yet to learn about the nature of protective host immune responses, host genetic factors, variations in pathogenicity of tubercle bacilli, and the role of exposure to environmental nontuberculous mycobacteria that may provide resistance or enhance susceptibility.

There are many variables that potentially could account for the discordant results. These include variations in potency of the strains of BCG used, technique of administration, handling of the vaccine, and prevalence of infection with nontuberculous mycobacteria, which may in themselves confer some degree of protection.⁴⁵⁵ Partly because of these factors, it is now generally accepted that BCG is not a tool that can be used to decrease the overall incidence of tuberculosis in a population. However, it appears that BCG reduces the likelihood of the more severe forms of the disease in children, and it is with this goal in mind that it continues to be a component of WHO immunization recommendations for developing countries. Due to the widespread acceptance and use of BCG and its benefits to young children, it is not likely that new vaccines for tuberculosis will immediately replace BCG. Instead, they will likely be used initially to boost responses after an initial dose of BCG, in an effort to induce responses that reliably protect adults against pulmonary tuberculosis.

In the United States, BCG has limited applicability. It is recommended only for TST-negative persons who are repeatedly exposed to potentially infectious patients who are being ineffectively treated. In general, the recommendation is limited to children. As a live vaccine, BCG should not be given to immunocompromised persons, including those with symptomatic HIV infection, or to pregnant women.

TACKLING CURRENT PROBLEMS

Tuberculosis is becoming a more complicated disease globally because of the appearance of MDR and XDR organisms and the increasing frequency of comorbidities, particularly HIV infection but also other risk-enhancing factors such as diabetes, renal insufficiency, immunosuppressive drugs, and tobacco and other substance addiction. Clearly, new diagnostic tools and therapeutic options are urgently needed. Currently, the most extensively used diagnostic methods around the world, both for active tuberculosis (sputum smear microscopy) and for latent tuberculosis (TST), were invented at the end of the 19th century. Similarly, BCG vaccine, despite its wide use, does not provide the needed protection. Today's standard treatment with four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) has remained unchanged for more than 30 years, must be taken for a minimum of 6 months, and is insufficient to treat patients with MDR or XDR tuberculosis. Although

there are new diagnostic methods, all of them are either an improvement of the old techniques or based on the detection of nucleic acids; none fulfill the urgent need for point-of-care diagnostic tests.

New drugs and mechanisms to reduce resistance to new drugs are a vital need, as underscored by the increase of drug-resistant tuberculosis and the detection of XDR cases.⁴⁵⁶ Also high on the list of needs is a test for the rapid detection of drug resistance suitable for point-of-care use. The current technology has identified drug targets and enabled testing of new compounds with high-throughput screening methods. Several drugs for active tuberculosis are now being tested in clinical trials.^{456,457} Some of them are candidates for first-line drugs that can reduce the treatment time, while other drugs have fewer drug interactions, with the potential benefit of being used with antiretroviral drugs. Other drugs have novel targets. However, we are still far from having a truly short treatment (currently the term *short course* is used for the 6-month regimen).

Effective vaccines will require a better understanding of the protective immune response to *M. tuberculosis* and of the pathogenesis of the disease. The availability of whole genomic sequences of thousands of clinical isolates of *M. tuberculosis*, and the recent evidence of the importance of the coevolution of the host and organism⁴⁵⁸ should assist the design of different vaccination approaches.⁴⁵⁹ A recent clinical trial demonstrated that a novel tuberculosis vaccine termed MVA85A induced the expected immune responses but failed to protect against tuberculosis when used to boost BCG vaccine in infants^{458a}; such results again demonstrate that improved understanding of tuberculosis pathogenesis and protective immunity are needed to inform development of efficacious vaccines. We are still far from understanding why the natural immune system (which prevents 90% of persons infected from developing active tuberculosis) fails in 10% of those infected and why the adaptive immune response in tuberculosis does not protect us from repeated infections. In spite of these gaps in knowledge, several additional vaccine candidates are now being tested (<http://www.aeras.org/candidates/> and <http://www.tbvi.eu/>).

Although important scientific advances have been made recently, major gaps in understanding the basic biology of the organism and the human response to infection with *M. tuberculosis* remain. The rapidly emerging new challenges to the care and control of tuberculosis, such as HIV, MDR tuberculosis, and more recently XDR tuberculosis, may outstrip the advances and threaten our ability to control the disease.

Key Points

- Although tuberculosis cases and case rates are consistently declining in high- and most middle-income countries, the disease continues to be highly prevalent in low- and some middle-income countries.
- The epidemic of HIV infection, especially in sub-Saharan Africa, is leading to extremely high tuberculosis case rates.
- Both HIV infection and resistance to antituberculosis drugs, especially multidrug resistance and extensive

drug resistance, present major problems in worldwide tuberculosis control.

- Adequate treatment for tuberculosis, both drug susceptible and drug resistant, is the major intervention for decreasing transmission of *Mycobacterium tuberculosis*. Treatment consists of an initial *intensive* phase to eliminate actively replicating bacteria quickly followed by a *continuation* phase to eliminate drug-tolerant organisms.
- Assuming an adequate regimen is prescribed, patient adherence is the critical factor that determines the success of treatment.
- The treatment of extrapulmonary tuberculosis is largely the same as the treatment of pulmonary tuberculosis. The exceptions are central nervous system tuberculosis and tuberculosis involving bones and joints, in which treatment of longer duration is recommended.
- Treating latent tuberculous infection in persons at increased risk of progressing to active tuberculosis significantly reduces the risk of disease. Such increased risks include recent conversion of tuberculin skin tests, concurrent HIV infection, chronic renal disease and use of anti-tumor necrosis factor therapy.

Complete reference list available at *ExpertConsult*.

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eFIGURE IMAGE GALLERY

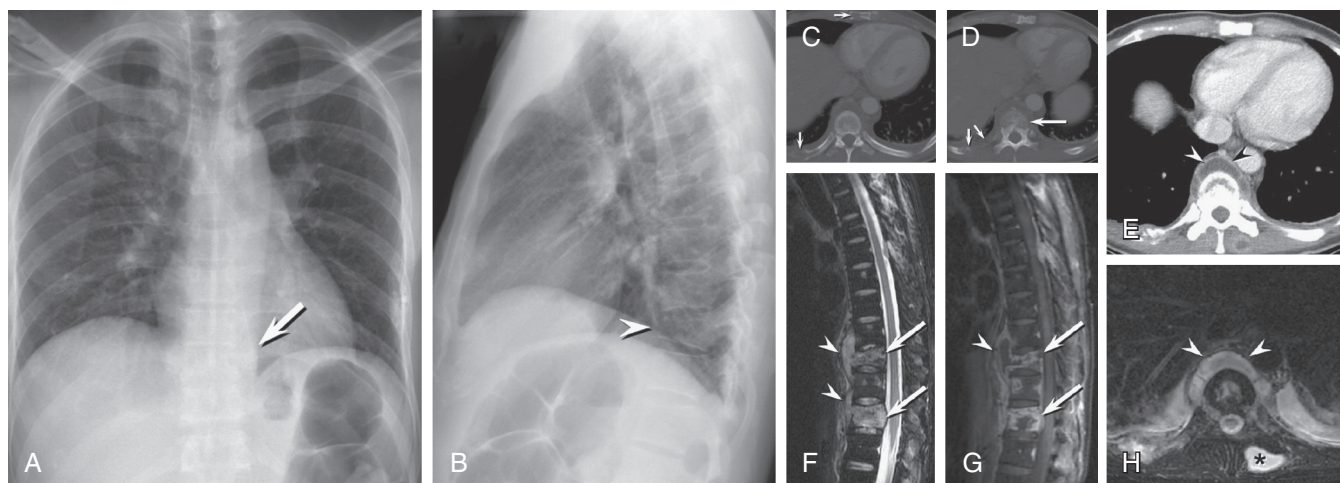


Figure 35-1 Tuberculosis involving the spine. **A**, Frontal and **B**, lateral chest radiographs show left inferior paraspinal line displacement (*arrow*, **A**) consistent with a posterior mediastinal mass. The lateral chest radiograph shows loss of height of a thoracic vertebral body (*arrowhead*) at this level, but the adjacent intervertebral disc spaces are maintained. Contrast-enhanced axial chest CT displayed in bone (**C** and **D**) and soft tissue (**E**) windows shows lytic vertebral body destruction (*long arrow*, **D**) at the level of vertebral body loss of height seen on the lateral chest radiograph (**B**). Osseous lytic foci are also present in the sternum (*short arrow*, **C**) and posterior ribs (*short arrows*, **C** and **D**). A paraspinal fluid collection with peripheral enhancement, consistent with an abscess (*arrowheads*, **E**) is seen anterior to the involved thoracic vertebral body. Sagittal T2-weighted (**F**) and contrast-enhanced T1-weighted (**G**) and axial T2-weighted (**H**) MR images show the anterior paraspinal abscesses (*arrowheads*), typical of subligamentous spread. Note the extensive high signal within the vertebral bodies (*arrows*, **F**) representing bone marrow edema. The clear vertebral body enhancement (*arrows*, **G**) indicates the presence of osteomyelitis. Note the relative sparing of the intervertebral disc spaces, typical of granulomatous infections and distinct from the common appearance of other causes of bacterial osteomyelitis. Extensive fluid collections are seen in the left erector spinae muscle (*) and involve the adjacent right posterior rib as well. These findings were all the result of tuberculosis. (Courtesy Michael Gotway, MD.)

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APPENDIX: ESSENTIALS OF CHEMOTHERAPY

INTRODUCTION

The development of successful chemotherapy for tuberculosis must rank as one of the greatest achievements of medical science. Beginning in the late 1940s, chemotherapy began to slow down—little by little—the centuries' long and ever-growing toll from the incurable “captain of all these men of death,” John Bunyan's name for the plague that has killed an estimated 2 billion human beings; more, by far, than any other disease. Notable victims included kings and princes, cardinals, famous poets, writers, musicians, and artists, and, of course, countless anonymous poor people. Finding a cure for this scourge did not happen easily, quickly, or by serendipity. It was the cumulative work over decades by many men and women dedicated to that single purpose, and—keep this in mind—these efforts are ongoing. The history of the initial taming of tuberculosis and why the task remains unfinished makes fascinating reading, especially in the accounts of Dubos and Dubos,¹ Ryan,² and Daniel.³

Even though effective treatment has been available for more than 50 years, tuberculosis continues to plague vulnerable regions of the world. More and more strains of disease-producing *Mycobacterium tuberculosis* are resistant to standard antituberculosis regimens: some strains are resistant to nearly all available agents. The most recent statistics report an estimated 8.6 million new cases and 1.26 million deaths.⁴ Globally, 4% of new cases and 20% of previously treated cases are estimated to have multidrug-resistant tuberculosis (MDR, resistant at least to isoniazid and rifampin).⁵ It is estimated that 9.6% of MDR cases are XDR (MDR to at least one fluoroquinolone and one second-line-injectable drug [amikacin, kanamycin, or capreomycin]) with 96 countries having reported at least one case of XDR.⁵ The overall frequency of pre-XDR (MDR to either fluoroquinolone or second-line-injectable drug) is not known, but studies in convenience samples report between 15%⁶ and 42%^{7,8} of MDR isolates are pre-XDR.

BEGINNINGS

To understand where we currently stand and to appreciate the enormity of the task ahead, this appendix provides a brief chronology of the use of chemotherapy for treating tuberculosis, starting with streptomycin, the original breakthrough agent, which was first injected into a desperately ill young woman in November 1944. To everyone's astonishment and relief, she did not die but slowly began to recover. Then, seemingly miraculously, so did others.⁹

But within a few years, after many more patients with tuberculosis had been treated with streptomycin, it became apparent that the striking clinical and radiographic improvement observed initially did not always last; after several months of treatment, patients began to worsen and the reason was immediately obvious: their tubercle bacilli had become resistant to streptomycin.¹⁰ The findings of clinical failure and emergence of drug resistance served to

define the major bacteriologic principle on which successful chemotherapy for tuberculosis depends: bacillary populations are not uniform in their susceptibility to antituberculosis agents; hence, it is always necessary to treat active disease with more than one drug to which the organisms are susceptible.

The concept of multiple-drug chemotherapy was first validated in 1950 by a British Medical Research Council study in which streptomycin was partnered with *para*-aminosalicylic acid, better known as PAS. Long-lasting success was achieved because PAS prevented organisms from becoming resistant to streptomycin and vice versa, and two drugs have more bacteriologic and clinical effect than only one.¹¹ Since that time, treatment with more than one drug has been standard in the management of patients with tuberculosis. Although the combination of streptomycin and PAS was effective, neither agent was well tolerated and clinical improvement was slow and hampered by side effects. The long-sought solution to antituberculosis chemotherapy arrived in 1952 with the introduction of isoniazid, a powerful drug that was not only highly effective, but well tolerated and inexpensive.¹² However, once again it was learned that single-drug treatment with isoniazid was inadequate because resistance to the agent developed quickly. The solution was clear: combine isoniazid with both streptomycin and PAS. This triple therapy became the standard treatment for tuberculosis until 1967, when a new antituberculosis agent, ethambutol, an easily tolerated and minimally toxic drug, was welcomed as a substitute for PAS.¹³

Subsequent experiments have shown that, in any wild type strain of *M. tuberculosis*, there are subpopulations with spontaneous mutations in genes that confer drug resistance. The frequency of drug-resistant mutants is 1 in 3.5×10^6 for isoniazid, 1 in 3.8×10^6 for streptomycin, 1 in 3.1×10^8 for rifampin, and 1 in 0.5×10^4 for ethambutol.¹⁴ Thus, a bacillary population of more than 10^{12} organisms would be required before one would expect to find (statistically) a single bacillus resistant to both isoniazid and streptomycin.

Once optimum doses of each component were established, wide use of triple therapy revolutionized the care of patients with tuberculosis. Springett¹⁵ reviewed death rates from tuberculosis for cohorts of patients in Birmingham, England, for the years 1947, 1950, 1953, 1956, and 1959. With increasing use of antituberculosis chemotherapy, deaths decreased dramatically during the 10 years after diagnosis, and nearly all of the reduction was accounted for by improvements in survival during the first year after diagnosis. In addition, not only were survivors more numerous, but among survivors, far fewer than in the prechemotherapy era continued to be potential sources of new infections. In the Springett study,¹⁵ both the decrease in mortality rate and the reduction in the prevalence of chronically infectious patients reached their maximum in 1956, with no further improvement in 1959.

The next major advance in chemotherapy for pulmonary tuberculosis resulted from the discovery of rifampin (or

rifampicin, as it is known in many parts of the world) and the demonstration that the combination of isoniazid and rifampin, generally with ethambutol or streptomycin, could dramatically shorten the necessary duration of treatment.¹⁶ In a series of important studies from East Africa during the 1970s, the British Medical Research Council established that a 6-month regimen consisting of isoniazid, streptomycin, and rifampin was as effective as the standard regimen used at the time in developing countries (18 months of isoniazid and thiacetazone, plus streptomycin given during the first 2 months).¹⁷

A critical factor influencing the effectiveness of chemotherapy was, and continues to be, the adherence (or lack thereof) of patients to the prescribed regimen, a fact well documented both in the United States and in developing countries.¹⁸⁻²⁰ In spite of initial high rates of success elsewhere, the results of a U.S. Public Health Service multicenter cooperative trial indicated that a 6-month regimen of isoniazid and rifampin did not have an acceptable rate of favorable outcome.²¹ Positive cultures were found in 6.1% of the patients between 3 and 6 months after treatment began. Of greater importance was that 9.2% experienced relapse after completion of treatment. Strikingly, 16.8% of the patients were withdrawn from the study because they had been delinquent about clinic visits during the 6 months of treatment. This outcome was a setback for efforts to shorten the duration of treatment to 6 months, which—assuming equal effectiveness and tolerance—would have considerable clinical and logistical advantages over 18- to 24-month regimens.

Studies of chemotherapy then began to focus on the possible benefits of pyrazinamide.²² Dickinson and coworkers²³ demonstrated that streptomycin, rifampin, and isoniazid are quickly bactericidal for rapidly growing *M. tuberculosis* in vitro. The in vitro conditions could be likened to the conditions under which the extracellular organisms in tuberculous lesions are living. Although both rifampin and isoniazid are rapidly bactericidal, Mitchison and Dickinson²⁴ demonstrated that rifampin is more effective in killing organisms that grow in spurts rather than continuously. Although both isoniazid and rifampin are effective in killing intracellular organisms, pyrazinamide is especially effective for this purpose, suggesting that the addition of pyrazinamide would strengthen the isoniazid-rifampin combination. Subsequently, two studies substantiated the fact that the addition of pyrazinamide for 2 months to a regimen of isoniazid and rifampin does indeed improve the effectiveness of a 6-month regimen.^{25,26} Thus, a 6-month regimen of isoniazid and rifampin supplemented by pyrazinamide and ethambutol for the initial 2 months is now recommended as standard treatment for most patients with newly diagnosed pulmonary tuberculosis.^{27,28}

DRUGS IN CURRENT USE

As shown in Table 35A-1, 11 drugs currently are approved by the FDA for treating tuberculosis, and 6 other drugs are effective but not approved for this indication. The table lists both first- and second-line drugs, the available preparations, and the doses currently used to treat tuberculosis.

FIRST-LINE DRUGS

Isoniazid is very effective, specific for certain mycobacteria, relatively nontoxic, easily administered, and inexpensive. It is highly active against *M. tuberculosis*: most strains are inhibited by concentrations of 0.05 to 0.20 µg/mL, and it has profound early bactericidal activity. The drug is readily absorbed from the gastrointestinal tract; blood concentrations of approximately 5 µg/mL peak 1 to 2 hours after administration of 3 to 5 mg/kg of body weight. The serum half-life varies depending on whether a person is a rapid or slow acetylator: half-lives are 2 to 4 hours in slow acetylators and 0.5 to 1.5 hours in rapid acetylators.²⁹ The drug penetrates well into all body fluids and cavities, producing concentrations similar to those found in serum.

Isoniazid is a pro-drug and is activated by bacterial KatG, a catalase/peroxidase enzyme.³⁰ Once it is activated, isoniazid inhibits NADH-dependent enoyl-ACP reductase encoded by *inhA*. This process ultimately results in the inhibition of synthesis of essential mycolic acids.³¹ The most common cause of resistance to isoniazid is deletion of or mutations in KatG that result in loss of catalase/peroxidase activity. A mutation in *katG* that results in substitution of threonine for serine in codon 315 (S315T) is the most common mutation found in isoniazid-resistant clinical isolates.^{32,33}

Mutations in the promoter of *inhA* cause resistance to isoniazid and the second-line drug ethionamide.³² These mutations are less frequent than those in *katG*. In a study of clinical isolates collected by the CDC, 82% of the *M. tuberculosis* isolates resistant to isoniazid had a mutation in *katG* only, 6% had mutations in *inhA* only, and 11% had mutations in both.³⁴ Other mutations reported to be associated with isoniazid resistance are mutations in the *furA-katG* intergenic region, as well as in the *oxyR-ahpC* region.³³

When isoniazid is used alone, a population of organisms resistant to the drug emerges rapidly. This was demonstrated in an early clinical trial in which 11%, 52%, and 71% of patients to whom isoniazid alone was given developed resistant strains after 1, 2, and 3 months of treatment, respectively.³⁵

Hepatitis is the major toxic effect of isoniazid.^{28,36,37} Asymptomatic elevations of aminotransferase—up to five times the upper limit of normal—are seen in 10% to 20% of persons receiving isoniazid alone for the treatment of latent tuberculous infection.³⁸ The enzyme levels usually return to normal even with continued administration of the drug. In 11,141 patients managed in an urban tuberculosis control program who were receiving isoniazid alone as treatment for latent tuberculous infection, hepatitis developed in 0.1% to 0.15%.³⁹ A meta-analysis of six studies estimated the rate of clinical hepatitis in patients given isoniazid to be 0.6%.⁴⁰ The rate of clinical hepatitis was 1.6% when isoniazid was given with other agents, *not* including rifampin.⁴⁰ When isoniazid was given in combination with rifampin, the rate of clinical hepatitis averaged 2.7% in 19 reports. For isoniazid alone, the risk increases with increasing age; it is uncommon in persons younger than 20 years old but is nearly 2% in persons ages 50 to 64 years.⁴¹ The risk may also be increased in persons with underlying liver disease, in those with a history of heavy alcohol consumption, and in the postpartum period, particularly among Hispanic women.^{41,42} A large survey estimated the rate of fatal

Table 35A-1 Doses* of Antituberculosis Drugs for Adults and Children†

Drug	Preparation	Adults/ Children	Daily	WEEKLY		
				1×	2×	3×
FIRST-LINE DRUGS						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for IV or IM injection	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children (max.)	10-15 mg/kg (300 mg)	—	20-30 mg/kg (900 mg)	—
Rifampin	Capsule (150 mg, 300 mg). Powder may be suspended for oral administration. Aqueous solution for IV injection	Adults [‡] (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10-20 mg/kg (600 mg)	—	10-20 mg/kg (600 mg)	—
Rifabutin	Capsule (150 mg)	Adults [‡] (max.)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
Rifapentine	Tablet (150 mg film coated)	Children	Appropriate dosing for children is unknown			
		Adults	—	10 mg/kg (continuation phase) (600 mg)	—	—
Pyrazinamide	Tablet (500 mg scored)	Children	The drug is not approved for use in children			
		Adults	20-30 mg/kg (2 g)	—	40-50 mg/kg (4 g)	30-45 mg/kg (3 g)
Ethambutol	Tablet (100 mg, 400 mg)	Children (max.)	15-30 mg/kg (2 g)	—	50 mg/kg (4 g)	—
		Adults	15-20 mg/kg (1.6 g)	—	40-50 mg/kg (2.4 g)	25-35 mg/kg (2.4 g)
		Children (max.)	20 mg/kg daily (1 g)	—	50 mg/kg (4 g)	—
SECOND-LINE DRUGS						
Cycloserine	Capsule (250 mg)	Adults (max.)	10-15 mg/kg/day (1 g in two doses), usually 500-750 mg/day in 2 doses [§]	There are no data to support intermittent administration		
		Children (max.)	10-15 mg/kg/day (1 g/day)			
Ethionamide	Tablet (250 mg)	Adults (max.)	15-20 mg/kg/day (1 g/day), usually 500-750 mg/day in a single daily dose or two divided doses	There are no data to support intermittent administration		
		Children (max.)	15-20 mg/kg/day (1 g/day)			
Streptomycin	Aqueous solution (1-g vials) for IM or IV administration	Adults (max.)	15 mg/kg/day (1 g) and 10 mg/kg in persons > 59 years (750 mg). Usual dose 750 mg-1 g IM or IV typically given as a single dose 5-7 days a wk and reduced to 2-3 times a wk after first 2-4 mo or after culture conversion, depending on the efficacy of the other drugs in the regimen			
		Children (max.)	20-40 mg/kg/day (1 g)	—	20 mg/kg	—
Amikacin/ Kanamycin	Aqueous solution (500-mg and 1-g vials) for IM or IV administration	Adults (max.)	15 mg/kg/day (1 g), and 10 mg/kg in persons > 59 (750 mg). Usual dose 750 mg-1 g IM or IV typically given as a single dose 5-7 days a week and reduced to 2-3 times a week after first 2-4 mo or after culture conversion, depending on the efficacy of the other drugs in the regimen			
		Children (max.)	15-30 mg/kg/day (1 g) IM or IV as a single daily dose	—	15-30 mg/kg	—
Capreomycin	Aqueous solution (1-g vials) for IM or IV administration	Adults (max.)	15 mg/kg/day (1 g), and 10 mg/kg in persons > 59 (750 mg). Usual dose 750 mg-1 g IM or IV typically given as a single dose 5-7 days a week and reduced to 2-3 times a week after first 2-4 mo or after culture conversion, depending on the efficacy of the other drugs in the regimen			
		Children (max.)	15-30 mg/kg/day (1 g) as a single daily dose	—	15-30 mg/kg	—

Table 35A-1 Doses* of Antituberculosis Drugs for Adults and Children (Continued)

Drug	Preparation	Adults/ Children	Daily	WEEKLY		
				1×	2×	3×
para-Aminosalicylic Acid (PAS)	Granules (4-g packets) can be mixed with food. Tablets (500 mg) are still available in some countries but not in the United States. A solution for IV administration is available in Europe	Adults Children	8-12 g/day in 2 or 3 doses 200-300 mg/kg/day in 2-4 divided doses (10 g)	There are no data to support intermittent administration		
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500-mg vials) for IV injection	Adults Children	500-1000 mg daily	There are no data to support intermittent administration. The long-term (>several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.		
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for IV injection.	Adults Children	400 mg daily	There are no data to support intermittent administration. The long-term (>several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.		
Gatifloxacin	Tablets (400 mg); aqueous solution (200 mg/20 mL; 400 mg/40 mL) for IV injection	Adults Children	400 mg daily	There are no data to support intermittent administration. The long-term (>several wk) use of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.		
Bedaquiline fumarate [†]	100-mg tablets	Adults	400 mg administered orally once daily for 2 wk, followed by 200 mg administered orally 3 times weekly, for an entire treatment duration of 24 wk			

Drugs in **bold** are approved by the U.S. Food and Drug Administration for treatment of tuberculosis.

*Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

[†]For purposes of this document, adult dosing begins at age 15.

[‡]Dose may need to be adjusted when there is concomitant use of protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

[§]It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimum dose for a given patient.

^{||}The single daily dose can be given at bedtime or with the main meal.

^{††}From Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR Recomm Rep* 62(RR-09):1–12, 2013.

Modified from Blumberg HM, Burman WJ, Chaisson RE, et al: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med* 167:604–662, 2003; and Francis J, for the Curry National Tuberculosis Center and California Department of Public Health, Drug-Resistant Tuberculosis: A survival guide for clinicians, ed 2. Sacramento, CA, 2008, California Department of Public Health.

hepatitis to be 0.023%,⁴³ but more recent studies suggest the rate is substantially lower.³⁹ The risk may be higher in women. Death has been associated with continued administration of isoniazid well after the onset of symptoms of hepatitis.

Peripheral neuropathy, the second most frequent adverse reaction associated with isoniazid administration, arises especially in persons with other disorders that may cause neuropathy (HIV infection, diabetes mellitus, uremia, and alcoholism). The neuropathy can be prevented or reversed by administration of pyridoxine 25 mg/day.

Rifampin is also rapidly bactericidal for *M. tuberculosis*. The drug is easily administered and is relatively nontoxic. It is quickly absorbed from the gastrointestinal tract; serum concentrations of 6 to 7 µg/mL are reached 1.5 to 2 hours after ingestion. The half-time in blood is 3 to 3.5 hours, although this may be decreased in persons who have been

taking the drug for several weeks.⁴⁴ The half-time increases with increasing doses of the drug. For sensitive strains of *M. tuberculosis*, the minimum inhibitory concentration of rifampin is approximately 0.5 µg/mL, although there is variation among strains.⁴⁵ Approximately 75% of the drug is protein bound, but it penetrates well into tissues and cells. Penetration through noninflamed meninges is poor; however, therapeutic concentrations are achieved in cerebrospinal fluid when the meninges are inflamed.⁴⁶

Among susceptible strains of *M. tuberculosis*, the rate of mutation seems to be less for rifampin than for isoniazid. David¹⁴ reported the rate of mutation to rifampin resistance to be approximately 10×10^{10} per generation. In spite of this rather low rate of in vitro mutation, resistance rapidly develops when rifampin is used alone in vivo.⁴⁷ Resistance to rifampin unaccompanied by resistance to other antituberculosis drugs has been reported to be much more

common among patients with HIV infection, particularly among patients being treated with once- or twice-weekly intermittent regimens containing rifamycins.⁴⁸⁻⁵⁰

Rifampin exerts its effect by binding to the β -subunit of RNA polymerase.³² For this reason, it has activity against many bacteria other than *M. tuberculosis*. Resistance to rifampin results from mutations in the *rpoB* gene, the product of which is the β -subunit of RNA polymerase. Although many different mutations may be involved, alterations in *rpoB*, specifically in a “hot spot” of 81 base pairs (the rifamycin resistance-determining region; RRDR), account for approximately 96% of the rifampin-resistant strains isolated from patients in many different parts of the world.^{27,33,34} The mechanism for resistance in the remaining 4% is not known.

Adverse reactions to daily rifampin include rashes, hepatitis, gastrointestinal upset, and, rarely, thrombocytopenia. The rates of these reactions have been variable, but in general are quite low.²⁸ Hepatitis was a complication in 3.1% of the patients in the U.S. Public Health Service study of 6-month isoniazid-rifampin treatment.²¹ Intermittent (twice-weekly) administration of higher doses of rifampin is associated with several immunologically mediated reactions, including thrombocytopenia, an influenza-like syndrome, hemolytic anemia, and acute renal failure.⁵¹

Drug-drug interactions due to rifampin induction of cytochrome P450 (CYP) enzymes, especially CYPs 1A2, 2C9, 2C19, and 3A4, are common and apply to a broad range of drugs. In the case of tuberculosis, these interactions are especially relevant in patients with HIV infection. The rifamycins—rifampin, rifabutin, and rifapentine—have marked effects on the protease inhibitor and non-nucleoside reverse transcriptase inhibitor classes of antiretroviral agents.²⁸ The interaction of these classes of drugs is bidirectional: protease inhibitors decrease clearance of rifamycins, and rifamycins accelerate metabolism of protease inhibitors by inducing CYP3A4.⁵² Of the rifamycins, rifabutin has the least effect on the concentration of antiretroviral agents. The practical implications of these interactions on treatment regimens are discussed in Chapter 90. Rifampin induces the metabolism of a number of other drugs, including methadone, warfarin, oral contraceptives, digoxin, macrolide antibiotics, and others.²⁸ Doses of these drugs need to be adjusted when rifampin is given. Fluconazole interferes with absorption of rifampin, thereby decreasing its serum concentration.

Rifabutin, although not approved by the U.S. Food and Drug Administration for the treatment of tuberculosis, may be used as a substitute for rifampin in most treatment regimens.²⁸ Because of its lesser propensity to induce cytochrome P-450 enzymes, rifabutin is generally reserved for patients who are taking any medication for which there are unacceptable interactions with rifampin. It may also be used for patients who are intolerant of rifampin. There is extensive cross-resistance among the rifamycins for *M. tuberculosis*. The toxicity profile of rifabutin is similar to that of rifampin except that, in some studies with HIV-infected patients, neutropenia has been reported and uveitis has been described when the drug is given with a macrolide antibiotic that reduces rifabutin clearance.²⁸

Rifapentine, which has the longest serum half-life of the rifamycins, is effective in combination with isoniazid given

once weekly in the continuation phase of treatment for pulmonary tuberculosis.⁵³ However, it should be emphasized that this regimen is *not* to be used for patients with HIV infection, patients who have cavitory lesions on chest film, or patients who have positive sputum smears at the end of the 2-month initial phase of treatment. The toxicity profile is similar to that of rifampin. Rifapentine, given weekly with high-dose isoniazid for a total of 12 doses, is also effective treatment of latent tuberculosis infection.⁵⁴

Ethambutol in usual doses of 15 mg/kg of body weight is generally considered to have a static effect on *M. tuberculosis*. The drug is easily administered and has a low frequency of adverse reactions. Its main effect is to reduce the risk of rifampin resistance in patients with tuberculosis caused by strains that have primary resistance to isoniazid. Peak plasma concentrations are recorded 2 to 4 hours after ingestion. With doses of 15 mg/kg, the peak concentration is approximately 4 μ g/mL.⁵⁵ The concentration increases proportionally with increasing doses. In persons with normal renal function, the half-time in blood is approximately 4 hours. Minimum inhibitory concentrations of the drug for *M. tuberculosis* range from 1 to 5 μ g/mL. Protein binding is minimal, but penetration into cells is thought to be poor. Cerebrospinal fluid concentrations of ethambutol, even in the presence of meningeal inflammation, are low, averaging 1 to 2 μ g/mL after a dose of 25 mg/kg.⁴⁹ Ethambutol appears to exert its effect by interfering with cell wall arabinogalactan biosynthesis. Mutations in the *embB* gene that codes for arabinosyltransferases are found in approximately 70% of ethambutol-resistant strains.³²⁻³⁴

Retrobulbar neuritis is the main adverse effect of ethambutol. Symptoms include blurred vision, central scotomata, and red-green color blindness. This complication is dose related, being in 15% of patients given 50 mg/kg, 1% to 5% of those given 25 mg/kg, and less than 1% in those given 15 mg/kg.²⁸ The frequency of ocular effects is increased in patients with renal failure, presumably owing to increased serum concentrations of the drug.

Streptomycin is rapidly bactericidal, although its effectiveness is inhibited by an acid pH.²⁸ Because the drug is not absorbed from the gut, it must be given parenterally. Peak serum concentrations take place approximately 1 hour after an intramuscular dose. With a dose of 15 mg/kg, the peak concentration is in the range of 40 μ g/mL. The half-time in blood is approximately 5 hours. Sensitive strains of *M. tuberculosis* are inhibited by streptomycin in a concentration of 8 μ g/mL. The drug has good tissue penetration; however, it enters the cerebrospinal fluid only in the presence of meningeal inflammation. Streptomycin and ethambutol have been found to be of approximately equal effectiveness in combination regimens; however, because of a high prevalence of resistance to streptomycin, particularly in patients from developing countries, its usefulness is limited. For this reason and because it requires parenteral administration, streptomycin is no longer considered a first-line agent in treating tuberculosis.²⁸

Streptomycin exerts its effect by interfering with ribosomal protein synthesis. This effect is mediated by binding of the drug to 16S ribosomal RNA (rRNA), thereby inhibiting initiation of translation. Mutations in the genes that code for 16S rRNA (*rrs* and *rpsL*) have been found in 65% to 77% of resistant strains. Mutations in *rpsL* have been

associated with high-level streptomycin resistance, whereas low-level resistance has been associated with *rrs* mutations.³² More recently, mutations in the gene *gidB* were found to be associated with low-level streptomycin resistance.³³ This gene encodes a methyltransferase specific for the 16S rRNA. The available data indicate that *gidB* mutations emerge spontaneously at a high frequency of 10^{-6} .³³

The most serious adverse effect of streptomycin is ototoxicity.²⁸ This usually results in vertigo, but hearing loss is also possible. The risk of ototoxicity is related to cumulative dosage and to peak serum concentrations. In general, peak concentrations of greater than 40 to 50 µg/mL should be avoided, and the total dose should not exceed 100 to 120 g.²⁸ Because of its effect on fetal auditory system development, streptomycin is contraindicated in pregnancy. Streptomycin should be used with caution in patients with renal insufficiency, in whom dosing frequency should be reduced to two to three times a week because of increased risk of nephrotoxicity and ototoxicity.²⁸

Pyrazinamide is active against *M. tuberculosis* at an acid pH, which suggests that the drug is activated under these conditions.⁵⁶ The drug is particularly active against dormant or semidormant *M. tuberculosis* in macrophages or in the acidic environment within areas of caseation and is rapidly bacteriostatic but only slowly bactericidal. Absorption from the gastrointestinal tract is nearly complete; peak serum concentrations take place approximately 2 hours after ingestion. Concentrations generally range from 30 to 50 µg/mL with doses of 20 to 25 mg/kg. The serum half-life is 9 to 10 hours. At a pH of 5.5, the minimal inhibitory concentration of pyrazinamide for *M. tuberculosis* is 20 µg/mL. Penetration of the drug into cells and tissues seems to be fairly good, although data with regard to tissue concentrations are limited.

Recent results indicate that pyrazinamide, after activation by pyrazinamidase to pyrazinoic acid, binds to ribosomal protein S1 (encoded by *rpsA*) and inhibits trans-translation, a mechanism for rescuing protein synthesis on stalled ribosomes.⁵⁷ The genetic mechanism of mycobacterial resistance to pyrazinamide is predominantly due to any of a large number of mutations in the *pncA* gene, which encodes the enzyme pyrazinamidase. This enzyme is necessary for the intracellular conversion of pyrazinamide to its active form, pyrazinoic acid. Mutations in the *pncA* gene are found in approximately 70% to 85% of pyrazinamide-resistant strains.^{32,34,58}

The most important adverse reaction to pyrazinamide is liver injury. This appears to be dose related. In a large U.S. Public Health Service study in which pyrazinamide was given in a dose of 25 mg/kg daily for 6 months, hepatotoxicity developed in 2% to 3% of patients.⁵⁹ At a dose of 40 mg/kg per day, also given for 6 months, 6% of patients developed hepatitis. All patients were also receiving isoniazid and PAS in addition to pyrazinamide. An increased frequency of hepatotoxicity has been reported in studies of pyrazinamide combined with rifampin in a 2-month treatment regimen for latent tuberculous infection in persons without HIV infection; accordingly, the indications for this regimen are limited.

Because pyrazinamide impairs renal urate clearance, hyperuricemia is reported in nearly all patients taking the drug. Clinical gout is not common, but diffuse arthralgias, apparently unrelated to the hyperuricemia, are common.

The drug may also cause nausea and vomiting and skin rashes, especially photosensitive dermatitis.

SECOND-LINE DRUGS

Five additional agents approved for treating tuberculosis are available in the United States: PAS, ethionamide, cycloserine, capreomycin, and bedaquiline. In addition, the fluoroquinolones, amikacin, kanamycin, and linezolid have antituberculosis effects and have been used to a greater or lesser extent, generally in treating patients with tuberculosis caused by drug-resistant organisms. All these second-line drugs have important limitations—effectiveness, toxicity, and cost—that interfere with their general applicability in treating tuberculosis.²⁸

Of the second-line drugs, the fluoroquinolones, levofloxacin and moxifloxacin, are the most widely used because both agents possess good in vitro bactericidal activity and moxifloxacin has good in vivo bactericidal activity against *M. tuberculosis*.^{60,61} The fluoroquinolones are currently not considered as first-line agents but should be reserved either for patients with drug-resistant organisms or those who cannot tolerate first-line drugs.²⁸ Fluoroquinolones are the most important second-line drugs available to treat MDR TB.⁶² Although earlier studies indicated that moxifloxacin substitution for isoniazid or ethambutol resulted in earlier conversion to negative sputum cultures, a recent large phase 3 trial, in which moxifloxacin was substituted for isoniazid or ethambutol in a 4 month regimen for drug-susceptible tuberculosis, revealed a higher relapse rate in patients receiving the moxifloxacin-containing 4 month regimens than in those receiving the standard 6 month regimen.^{62a}

The target of the fluoroquinolones is DNA gyrase, an enzyme that operates to increase coiling of DNA. Resistance to these agents is mediated by mutations in the *gyrA* and *gyrB* genes that encode for DNA gyrase.^{32,33} In a review of 42 studies, 64% of 1220 fluoroquinolone-resistant *M. tuberculosis* isolates had mutations in *gyrA* and 3% had *gyrB* mutations.⁶³

The quinolones are generally well tolerated. The most frequent adverse effects include nausea, vomiting, dizziness, anxiety, and other central nervous system effects. With certain agents, hypoglycemia and hyperglycemia have been observed and some are associated with prolonged QT interval, which can be associated with cardiac arrhythmias. Photosensitivity and arthropathy may also manifest. Although there are multiple small clinical studies of the usefulness of quinolones in multiple-drug regimens, and their oral administration and moderate cost make them attractive agents, their roles in regimens for MDR tuberculosis remain to be established.

Kanamycin, amikacin, and capreomycin are known as the *second-line-injectable* (SLI) drugs. According to current WHO MDR-TB treatment guidelines,⁶⁴ at least one SLI is essential in the 6-month intensive phase of treatment. These drugs are not absorbed from the gastrointestinal tract and thus must be administered parenterally. All three drugs may cause hearing loss related to both peak concentrations and cumulative doses and, in addition, may impair renal function.

Bedaquiline was approved by the FDA in 2012 as part of combination therapy (minimum four drugs) administered

by direct observation to adults 18 years old or older with MDR tuberculosis, when an effective treatment regimen cannot otherwise be provided (i.e., no other drug to which *M. tuberculosis* is susceptible, or drug intolerance).⁶⁵ Bedaquiline is a diarylquinoline and uses *adenosine 5'-triphosphate* (ATP) synthase inhibition as its mechanism of action.⁶⁶ It has in vitro activity against both replicating and nonreplicating bacilli and has bactericidal and sterilizing activity in the murine model of tuberculosis infection. No cross-resistance was found between bedaquiline and isoniazid, rifampin, ethambutol, pyrazinamide, streptomycin, amikacin, or moxifloxacin. Resistance has been observed during clinical studies; bedaquiline has a bacteriostatic effect at low serum levels (0.3 µg/mL) that might predispose to acquired resistance.⁶⁵ Drug-drug interactions exist with CYP3A4 inducers (e.g., rifampin), but their clinical significance is uncertain.⁶⁵

All of the other oral agents are difficult to administer because of adverse effects. It is strongly recommended that consultation with an expert be obtained before treatment with these drugs is undertaken.²⁸ Administration of PAS causes a high frequency of gastrointestinal upset plus hypersensitivity reactions in 5% to 10% of patients. In addition, the usual dose of 10 to 12 g/day requires ingestion of 20 to 24 tablets, although administration has been made somewhat easier by the availability of a granular formulation. Ethionamide likewise causes a high frequency of gastrointestinal side effects, often necessitating discontinuation of the drug. Cycloserine causes behavioral disturbances, ranging from irritability and depression to frank psychosis, in a large percentage of patients taking the drug; seizures and peripheral neuropathy are possible, especially with high doses and when cycloserine and isoniazid are given together. In addition to the adverse effects of PAS, ethionamide, and cycloserine, none of these drugs is particularly potent against *M. tuberculosis*. Other unapproved but possibly useful antituberculosis agents include the β-lactam imipenem, the β-lactam/β-lactamase combination amoxicillin-clavulanate, clofazimine, and linezolid.⁶⁷⁻⁶⁹ These agents have been used in small numbers of patients with tuberculosis caused by MDR organisms. However, their role in the treatment of tuberculosis has not been precisely determined. The currently available compounds of the macrolide class of agents, which are useful against *Mycobacterium avium* complex, do not have antituberculosis effects.

PROGRAMMATIC CONSIDERATIONS

The availability of powerful antituberculosis medications made it possible to cure around 95% of patients with disease caused by susceptible organisms, but it soon became apparent that drugs alone are insufficient; they are but one key element in a comprehensive tuberculosis control program. As far back as 1959, at the landmark Arden House Conference, the basic components of a national public health program were defined with, as a long-range goal, the eradication of tuberculosis in the United States.⁷⁰ Twenty years later, another conference reviewed and refined the objectives and proposed new control strategies.⁷¹ At practically

the same time, effective national tuberculosis control programs were introduced into resource-poor countries by the International Union Against Tuberculosis and Lung Disease⁷²; much later, the concepts that made these programs so efficacious were adopted, updated, and promoted by the WHO under the rubric Directly Observed Treatment Short-course, more familiarly known as DOTS.

Not surprisingly, the lessons from all these activities were similar. Among them, the most important programmatic principle is the obligation of the health care system or treating physician to provide effective supervision of therapy from beginning to end. Because of inadequacies both in the provision of tuberculosis control services and in private physician supervision of treatment, completion of therapy is often problematic.⁷³ As an extreme, at Harlem Hospital in New York during the late 1980s, 89% of patients with tuberculosis who had been started on appropriate treatment were lost to follow-up after discharge, in large part owing to cutbacks in funding of outpatient services.⁷⁴ Obviously, failure to continue medications precludes successful therapy and promotes the emergence of drug-resistant organisms as it did in New York City.

Even in well-organized tuberculosis control programs, ensuring patient adherence to therapy often presents a difficult problem. The reasons for poor adherence are complex and numerous. Prediction of who will be compliant and who will not is difficult and generally unreliable. To improve adherence, a number of modifications in the organization of treatment have been tried, with varying degrees of success.⁷⁵ These include setting clinic hours to suit the patient's schedule; directly observing treatment in the clinic, the patient's home, or another location; and offering incentives and enablers, such as meals and transportation reimbursements.²⁸ Although all of these approaches, as well as others, have had their successes, it is obvious that compliance will remain a major problem as long as treatment regimens continue to be lengthy and cumbersome. It has come to be generally accepted that the best means of ensuring completion of therapy is giving the drugs under *directly observed therapy* (DOT),^{27,28} which is one of the essential elements of the WHO's DOTS global tuberculosis control strategy, mentioned earlier.⁷⁶ The use of the DOTS strategy has been associated with improved treatment outcomes in several cohort analyses.^{20,77,78} However, a Cochrane review of 11 trials with 5609 patients did not show a significant difference in the cure of patients who were treated with observed therapy compared with self-administration.¹⁹ These results highlight the fact that simply observing medication ingestion does not ensure successful completion of treatment and that the full range of measures for supporting patients in completion of treatment must be employed.

Because of heightened public health concerns regarding transmission of *M. tuberculosis* by noncompliant patients and, in particular, concern about MDR organisms, public health statutes that could require DOT or, in some instances, confinement until treatment is completed were strengthened in the early 1990s. A review of the use and usefulness of these laws in New York City has shown that they were not abused and added significantly to the ability of health authorities to improve treatment outcome and minimize spread of tuberculous infection.

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NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

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INTRODUCTION

Soon after the discovery of *Mycobacterium tuberculosis* in 1882 by Robert Koch, several other species of mycobacteria were described. It was not until half a century later, however, that these mycobacteria were recognized to cause disease in humans, and by the 1980s they were known to cause a broad spectrum of disease.¹ Over the years, these organisms have gone by many names, including “mycobacteria other than tuberculosis,” “environmental mycobacteria,” “anonymous or atypical mycobacteria,” and “*nontuberculous mycobacteria*” (NTM), the preferred term in the United States. The epidemic of the *human immunodeficiency virus* (HIV) heralded a new awareness of NTM infections because of the high rates of disseminated infections due to *Mycobacterium avium* complex² (or, as commonly abbreviated, MAC) and other species.³ Disseminated NTM infections have declined significantly in HIV-infected populations following the advent of antiretroviral drugs whereas rates of NTM disease in HIV-uninfected populations appear to be increasing.

NTM represent a broad array of organisms that are ubiquitous in our environment. They have been isolated from natural and drinking waters as well as soil, and exposure to these reservoirs is thought to be the source of human infection. At least 160 species of NTM have been identified, and many of these have been reported to cause disease in both immunocompetent and immunocompromised patients. Unlike *Mycobacterium tuberculosis*, NTM do not appear to be transmitted from human to human in the absence of extraordinary circumstances, they vary greatly in their ability to cause disease, and evidence for latency is lacking. Unfortunately, NTM are difficult to treat because of high levels of *in vitro* resistance to antimicrobial drugs, which requires long courses of therapy with relatively poor outcomes when compared with tuberculosis. Not surprisingly, these factors result in a treatment cost comparable to other chronic infectious diseases such as HIV infection and *acquired immunodeficiency syndrome* (AIDS).⁴ To date, our lack of understanding of the transmission and pathogenesis of these increasingly important infections has limited our ability to develop public health measures aimed at preventing infection.

MICROBIOLOGY AND TAXONOMY

The genus *Mycobacterium* consists of organisms within the *M. tuberculosis* complex, *Mycobacterium leprae*, and NTM. The latter were classified in 1959 by Runyon into additional groups based on pigmentation in the presence or absence of light (photochromogens, scotochromogens, nonchromogenic) and growth characteristics (slow versus rapid).⁵ All mycobacteria are characterized by their slow rate of growth when compared with other bacterial species, and NTM are further characterized into *rapidly growing* and *slowly growing* organisms: rapid growers can be distinguished by growth in subculture in less than 7 days and slow growers by growth within 2 to 3 weeks. NTM, like all mycobacteria, are also characterized by a thin peptidoglycan layer surrounded by a thick lipid-rich outer membrane.⁶ The lipid-rich outer membrane results in a number of properties that allow the organisms to survive in diverse environments. For example, the hydrophobic cell surface allows surface attachment, resistance to disinfectants and antibiotics, slow growth, and tolerance to heat.⁷ Additional important properties that allow survival in the environment are the ability to grow in low carbon concentrations (oligotroph) and oxygen concentrations.

The availability of molecular methods has rendered the Runyon classification obsolete for clinical purposes and resulted in a marked increase in the identification of new species. In 1997, approximately 50 species of NTM had been identified, with only 13 described as respiratory pathogens.⁸ Currently, there are more than 160 identified NTM species with at least 50 that can be associated with lung infection⁹ (Table 36-1). Thus, it is reasonable to ask why there appears to be such a profusion of NTM species in general and those associated with lung disease in particular.

The primary explanation can be found in the mycobacteriology laboratory. Before the era of high-resolution methods for organism identification, NTM were identified based on their morphologic and biochemical characteristics as well as their *in vitro* susceptibility patterns. The inadequacy or insensitivity of these techniques was reflected in the number of organisms that were grouped as “complexes,” such as the “*Mycobacterium fortuitum* complex,”

Table 36-1 Slowly Growing and Rapidly Growing Nontuberculous Mycobacteria Reported to Cause Lung Disease

Slowly Growing Mycobacteria		Rapidly Growing Mycobacteria	
<i>M. arupense</i>	<i>M. nebraskense</i>	<i>M. abscessus</i>	<i>M. holsaticum</i>
<i>M. avium</i>	<i>M. nonchromogenicum</i>	<i>M. alvei</i>	<i>M. houstonense</i>
<i>M. asiaticum</i>	<i>M. palustre</i>	<i>M. boenickei</i>	<i>M. mageritense</i>
<i>M. branderi</i>	<i>M. parascrofulaceum</i>	<i>M. bolletii*</i>	<i>M. massiliense*</i>
<i>M. chimaera</i>	<i>M. phlei</i>	<i>M. brumae</i>	<i>M. mucogenicum</i>
<i>M. celatum</i>	<i>M. riyadhense</i>	<i>M. chelonae</i>	<i>M. peregrinum</i>
<i>M. florentinum</i>	<i>M. saskatchewanse</i>	<i>M. confluents</i>	<i>M. phocaicum</i>
<i>M. heckeshornense</i>	<i>M. scrofulaceum</i>	<i>M. elephantis</i>	<i>M. septicum</i>
<i>M. intermedium</i>	<i>M. sensuense</i>	<i>M. fortuitum</i>	<i>M. thermoresistible</i>
<i>M. interjectum</i>	<i>M. shimodei</i>	<i>M. goodii</i>	
<i>M. intracellulare</i>	<i>M. simiae</i>		
<i>M. iranica</i>	<i>M. szulgai</i>		
<i>M. kansasii</i>	<i>M. triviale</i>		
<i>M. kubicae</i>	<i>M. triplex</i>		
<i>M. lentiflavum</i>	<i>M. xenopi</i>		
<i>M. malmoense</i>			

*Taxonomy is in transition: consider these subspecies of *M. abscessus*.
Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 175:367–416, 2007.

which included multiple rapidly growing species such as *M. fortuitum*, *Mycobacterium chelonae*, and *Mycobacterium abscessus*. Although it was apparent that multiple species were present with similar growth and morphologic properties, standard laboratory techniques were not adequate to separate them reliably to the species level.

Currently, there are multiple methods for NTM species identification, including *high-performance liquid chromatography* (HPLC) and DNA probes for the most commonly isolated NTM species.⁹ HPLC has been especially useful in the identification of new NTM species but lacks the sensitivity of molecular techniques. The revolutionary change in NTM identification was the advent of readily available DNA sequencing, especially the sequencing of the 16S ribosomal RNA gene, which is highly conserved so that 1% or greater differences in this gene sequence can define an NTM species. Publicly available databases of 16S ribosomal RNA gene sequences allow rapid comparison of mycobacterial isolates to determine whether a new NTM species is present. Alternatively, sequences of the heat shock protein 65, *rpoB*, *secA* genes or the entire genomic DNA sequence of an NTM species can be compared to other publicly available gene sequence databases.

The expansion of new NTM species in the past 15 years is, therefore, primarily a consequence of higher resolution identification techniques capable of separating closely related NTM species, rather than a proliferation of new NTM species. Predictably, many of these newly identified species have microbiologic properties very similar to those of other closely related NTM, so that identification of the new NTM species may not be associated with any new or surprising clinical properties. It remains to be seen if this revolution in NTM species identification will have an equally profound impact on the understanding of clinical NTM disease. What is certain, however, is that clinicians will need

to become familiar with many more names as new NTM species are identified.

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE

The epidemiology of NTM disease has been difficult to determine because reporting is not mandatory in most countries and differentiation between infection and disease is often difficult. The incidence and prevalence of NTM infections have varied significantly across studies, partially because the studies have used different methodologies and studied different populations.¹⁰ Existing data suggest that the incidence and prevalence of NTM infections are increasing.

Epidemiologic studies of NTM infection and disease use one of three approaches: (1) studying the reactivity to delayed-typed hypersensitivity to mycobacterial antigens; (2) analyzing the reported isolation rate of NTM from laboratories; or (3) using both clinical and laboratory data to define disease more accurately.¹⁰ Studies using delayed-type hypersensitivity reaction to subcutaneously injected mycobacterial antigens have estimated that 11% to 33.5% of the population in the United States have skin test reactivity to NTM.¹⁰⁻¹² A study used data from the National Health and Nutritional Examination Survey cohort to describe skin reactivity to purified protein derivative B during two time periods. For the years 1971–1972 and 1999–2000, rates of a positive skin test were 11.2% and 16.6%, respectively.¹³ Skin test reactivity was noted to increase between the two time periods in foreign-born but not in U.S.-born individuals, suggesting a higher rate of exposure and infection in the foreign-born individuals.

Early laboratory-based studies used consecutive isolates from a well-defined catchment area to estimate the frequency of infection. Survey data from state laboratories in the United States in the early 1980s estimated a prevalence of NTM infection of 1 to 2 cases per 100,000 population.¹⁴ A similar follow-up survey from 1993 to 1996 reported an annual case rate in HIV-uninfected people of 7 to 8 per 100,000, documenting an increase in NTM isolation when compared to the previous survey.¹⁵ These laboratory-based surveys suffer from the fact that they provided isolate-based information but did not take into account the number of patients and whether or not the patients had disease. These early studies have largely been supplanted by better studies based on more rigorous methodologies.

Studies that combine culture and clinical data may be more useful for estimating disease incidence and prevalence. Studies since the 1950s from Czechoslovakia,¹⁶ Wales,¹⁷ Ireland,¹⁸ Australia,¹⁹ and the United States¹⁴ have reported increases in incidence or prevalence. In some reports, the increase in the rate of NTM infection was associated with a decline in the rate of tuberculosis. For example, in Japan from 1971 to 1984, the incidence of pulmonary tuberculosis decreased from 133.1 to 46.3 per 100,000 while the incidence of NTM pulmonary disease increased from 0.89 to 2.15.²⁰ Similarly, in Switzerland, the incidence of pulmonary tuberculosis decreased from 16.2 to 13.2 per 100,000 over 6 years while the incidence of pulmonary NTM increased from 0.4 to 0.9 per 100,000.²¹ In Queensland, Australia, where NTM are reportable, the incidence of clinically significant pulmonary disease rose from 2.2 per 100,000 in 1999 to 3.2 per 100,000 in 2005.²²

The most significant increases in NTM prevalence have been reported from North America. Marras and coworkers²³ reported an increase in the number of pulmonary NTM isolates in Ontario between 1997 and 2003; during this same time period, the rate of isolation of *M. tuberculosis* declined in that province. In a subsequent study, the 5-year prevalence of pulmonary NTM disease in Ontario was reported to increase from 29.3 cases per 100,000 in 1998–2002 to 41.3 cases per 100,000 persons in 2006–2010.²⁴ A recent study reported a significant increase in the annual prevalence of NTM pulmonary disease in patients hospitalized in 11 states between 1998 and 2005²⁵; annual prevalence increased among men and women in Florida (by 3.2 per year and 6.5% per year, respectively) and among women in New York (by 4.6% per year) but there was no significant increase in California. The annual prevalence of NTM pulmonary disease in U.S. Medicare beneficiaries (all 65 years of age and older) increased from 20 per 100,000 in 1997 to 47 per 100,000 in 2007.²⁶ The annual percent change for women was 9.1%, which was significantly higher than that for men (6.4%) (Fig. 36-1). In one particularly rigorous study from Oregon, clinical and radiographic studies from patients with NTM respiratory isolates were evaluated. This study found an overall prevalence of 8.6 cases per 100,000 persons and 20.4 per 100,000 in those at least 50 years of age.²⁷ While not all studies have documented an increase in NTM prevalence,²⁸ the preponderance of evidence suggests that pulmonary disease due to NTM is increasing.

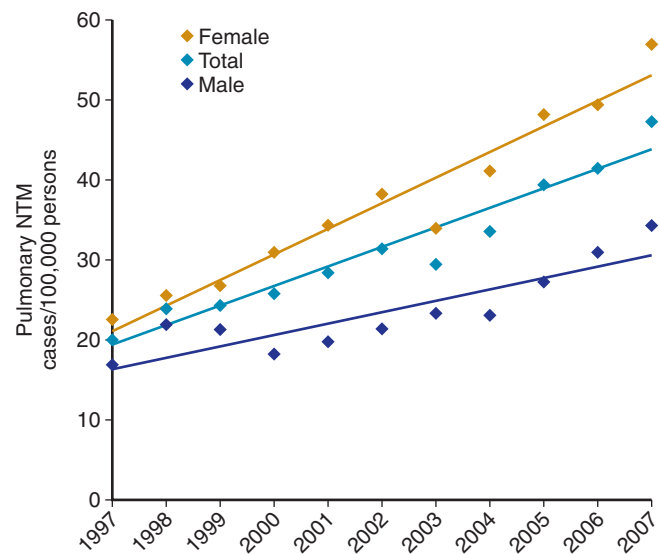


Figure 36-1 Annual prevalence of pulmonary nontuberculous mycobacteria cases among a sample of U.S. Medicare Part B enrollees by gender from 1997 to 2007. NTM, nontuberculous mycobacteria. (Adjemian J, Olivier KN, Seitz AE, et al: Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries: *Am J Respir Crit Care Med* 185:881–886, 2012.)

The reasons for the increase in incidence and prevalence have not been explained, although increased awareness of the disease and improved diagnostic techniques, especially the widespread application of high-resolution chest *computed tomography* (CT) scanning, could be a factor. A true increase in incidence could be related to changes in the host, such as an aging population, to an increased prevalence of chronic lung disease, or to an increase in the number of immunocompromised individuals. The observation of a decreased incidence of pulmonary tuberculosis and an increased incidence of pulmonary NTM, as noted previously, could be explained by cross-immunity between mycobacterial species. Finally, an increase in the prevalence or virulence of environmental organisms or changes in human behavior that would lead to increased exposure to organisms could be contributing factors.

GEOGRAPHIC DISTRIBUTION AND VARIATION

NTM have been reported to cause pulmonary disease around the globe, although there is marked variation in the prevalence of disease and the predominant species.²⁹ In the United States, the southeastern region has long been considered to have the highest rates of infection.^{14,30,31} NTM have been recovered with higher frequency from water samples in the southeastern versus northern United States, so exposure is likely higher in these regions.³² However, a recent study reported that among Medicare patients, the states with the highest prevalences of pulmonary NTM were Hawaii (396/1000,000) followed by California (191/100,000).²⁶ Florida, Louisiana, and Mississippi also had high prevalences ranging between 151/100,000 and 200/100,000.

The reasons for such geographic variation are not well understood. Pulmonary NTM cases were identified from a nationally representative sample of Medicare Part B

beneficiaries and their counties of residence were divided into low- and high-risk counties in order to identify potential sociodemographic and environmental risk factors.³³ The investigators identified seven clusters of pulmonary NTM cases within high-risk areas constituting 55 counties. The high-risk counties were then compared with 746 low-risk counties. High-risk counties were larger, had greater population densities, and higher education and income levels than the low-risk counties. In addition, high-risk counties had higher mean daily potential for evapotranspiration (the sum of evaporation and plant transpiration of water into the atmosphere) and areas covered by surface water. They were also more likely to have higher copper and sodium and lower manganese levels in the soil. Thus, specific environmental factors correlate with the rates of pulmonary NTM infection.

The predominant species in North America have been MAC, followed by *Mycobacterium kansasii*, *M. abscessus*, *M. fortuitum*, *M. chelonae*, and *M. scrofulaceum*.^{14,30} MAC has also been reported as the predominant species in Central and South America, Europe, and Asia. The predominant species of MAC also varies from region to region. In Europe and South America, *M. avium* is the predominant species whereas *M. intracellulare* is the predominant species in Australia and South Africa.²⁹ *Mycobacterium xenopi* is common in Europe and Canada, whereas *Mycobacterium malmoense* is more common in Northern than Southern Europe. Populations of miners in Czechoslovakia¹⁶ and South Africa^{34,35} have been reported to have high rates of *M. kansasii* infection.

TRANSMISSION AND PATHOGENESIS

TRANSMISSION

NTM are ubiquitous in the environment and have been found in natural and drinking waters, biofilms, soil, and aerosols.³⁶ The presumed source of infection is exposure to these environmental reservoirs because human-to-human transmission has been documented only under extraordinary circumstances.^{37,38} Studies using genotyping techniques, such as pulsed-field gel electrophoresis, *variable number tandem repeat* (VNTR) analysis, and whole genome sequencing have been able to isolate the same strains of NTM from patients and their environments.³⁹⁻⁴¹ Although the mechanism by which an environmental exposure eventually leads to pulmonary infection is poorly understood,⁴² it has been hypothesized that exposure to infected aerosols can lead to infection and possibly disease. In a study to determine whether household plumbing could serve as a source for a patient's NTM isolate, water samples were obtained from the households of 37 patients across the United States.⁴³ Seventeen (46%) of the households yielded at least one mycobacterial isolate of the same species found in the patient and in seven patients, the isolate had the same genotype. In a recent report from Australia, 35% of patients with NTM lung disease had the same species isolated from their home water supply.⁴⁴ In other reports, there are at least two cases that had the same strain of MAC isolated

from the patients' respiratory specimens and water from their shower head.^{39,40} In another report, the patient's strain of MAC was isolated from potting soil in the home.⁴¹ There have also been reports of outbreaks in which patients' isolates matched environmental isolates of NTM.⁴⁵ In a recent study using interviews of HIV-negative adults with MAC, aerosol-generating activities and home and garden water supply features were not found to be risk factors but prior lung disease and immune-suppressing drugs were.⁴⁶

Until recently, person-to-person transmission was considered an unlikely mode of transmission.⁴⁷ However, two recent studies have described possible transmission in *cystic fibrosis* (CF) clinics.^{37,38} The first report described a potential outbreak of *M. abscessus* subsp *massiliense* in a CF clinic in Seattle.³⁷ A smear-positive patient may have transmitted infection to four other patients with CF at the same clinic; the infecting strain was indistinguishable by pulsed-field electrophoresis and polymerase chain reaction analysis. An additional report from the United Kingdom also described transmission of *M. abscessus* subsp *massiliense* at a CF center.³⁸ The authors noted that direct person-to-person transmission was unlikely but that cross infection in the hospital setting was likely.

Extrapulmonary NTM infections in immunocompetent patients are usually the result of a puncture wound or surgery. A recent outbreak of skin and soft tissue infections due *M. abscessus* subspecies *massiliense* involved more than 2000 patients who had undergone invasive procedures such as laparoscopic, arthroscopic, plastic, or cosmetic surgery.⁴⁸

FACTORS ASSOCIATED WITH INFECTION

A prospective study using skin testing data from Palm Beach, Florida, reported that 32.9% of 447 participants in a population-based random household survey had a positive reaction to *M. avium* antigens.⁴⁹ Independent predictors of a positive reaction included black race, birth outside the United States, and more than 6 years' cumulative exposure to soil. Exposure to water, food, and pets was not associated with skin test reactivity. Using National Health and Nutritional Examination Survey data, investigators reported similar findings with regard to sensitization to *Mycobacterium intracellulare*¹³; male gender, non-Hispanic black race, and birth outside the United States were each independently associated with sensitization. The highest rate of skin test reactivity was found in persons who were 20 to 39 years of age; among individuals 20 years of age and older, working in agriculture or construction was strongly associated with sensitization. These two studies are interesting in that skin test reactivity to either *M. avium* or *M. intracellulare* antigens was associated with factors likely associated with soil exposure and were more common in men and foreign-born individuals. However, disease seems to be more common in older women and, at least in the United States, in U.S.-born. Additionally, the source for *M. avium* infection, frequently associated with nodular/bronchiectatic MAC lung disease, appears to be primarily municipal (tap) water in the United States, whereas *M. intracellulare* infection is acquired through some other source, likely soil.⁵⁰ Thus, it is likely that the risk factors for infection are different from those associated with disease.

FACTORS ASSOCIATED WITH DISEASE

Most NTM are significantly less pathogenic than *M. tuberculosis* and likely require some degree of host impairment to establish disease. A number of risk factors for disease have been described, and these can be subdivided broadly into three groups: (1) factors impairing host immunity, (2) factors leading to impaired local (lung) immunity, and (3) factors relating to the species. These factors can be reduced further into the “unusual dose” model and “susceptible person” model.⁴⁶ In the “unusual dose” model, it is postulated that individuals who become infected do so because of an unusually large exposure to NTM, whereas in the latter model, it is assumed that some susceptibility is necessary for infection to manifest. It is likely that, in most patients, both models of pathogenesis are at play to varying degrees.⁵¹

Increasing age has been consistently described as a risk factor for pulmonary NTM, in patients both with and without underlying lung disease.^{12,14,52,53} The most consistently reported risk factor is male gender, though there is also a population of elderly females who are at risk for nodular bronchiectatic lung disease. Perhaps the most important risk factor for the development of pulmonary NTM disease is underlying chronic lung disease. NTM disease has been described in association with CF, chronic obstructive pulmonary disease (including α_1 -antitrypsin deficiency), cavitory lung disease, pneumoconiosis, bronchiectasis, prior tuberculosis, and pulmonary alveolar proteinosis.⁵⁴ Studies have documented a high prevalence of NTM in sputum cultures from patients with CF, with estimates ranging from 3% to 19.5% prevalence of NTM, the majority of which were MAC.^{55,56}

Patients with NTM lung disease often have associated *gastroesophageal reflux disease* (GERD) or other esophageal disorders. Historically, it has been reported that patients with *rapidly growing mycobacteria* (RGM) often have associated esophageal disorders⁵⁷⁻⁵⁹; recent reports have reported that patients with lung disease due to MAC, a slow grower, also have a high frequency of GERD.^{60,61} In a report from South Korea that used pH probes to diagnose GERD, the authors reported that the prevalence of GERD was 26%, although only one fourth of these patients had typical GERD symptoms.⁶⁰ Patients with *M. abscessus* infection were more likely to have GERD than those with MAC, although the difference did not reach statistical significance.

An interesting patient population with NTM pulmonary disease consists of postmenopausal women who often have certain associated morphologic features. This constellation was first described by Prince and colleagues⁵² in 1989 and later referred to as the “Lady Windermere syndrome,” after the lead in Oscar Wilde’s play *Lady Windermere’s Fan*, who was characterized by her fastidious behavior in actively suppressing a chronic cough.⁶² The morphologic features such as pectus excavatum, scoliosis, thin body habitus, and mitral valve prolapse were described subsequently by Iseman and others.⁶³ Recently, investigators reported that women with pulmonary NTM disease were taller and thinner and weighed less than matched control subjects⁶⁴ (Fig. 36-2): 51% had scoliosis, 11% pectus excavatum, and 9% mitral valve prolapse, all significantly more common than in reference populations. Another feature of this syn-

drome is the predilection for right middle lobe and lingular bronchiectasis. To date, extensive evaluation of the immune system of these patients has shown mixed results, but mutations in the *CF transmembrane conductance regulator* (CFTR) gene are common.⁶⁴⁻⁶⁶ Among 103 women with pulmonary NTM, some intriguing cytokine relationships were found to be abnormal: compared with the findings in uninfected control subjects,⁶⁶ in those with NTM, the normal relationship between the adipokines, leptin and adiponectin, and body fat was lost and *interferon- γ* (IFN- γ) and *interleukin* (IL)-10 levels were significantly suppressed in stimulated whole blood. These intriguing in vivo and in vitro findings suggest a predisposing immunophenotype for NTM.

NTM in AIDS most commonly causes disseminated disease that presents with nonspecific symptoms such as fever, night sweats, diarrhea, abdominal pain, and lymphadenopathy, with MAC being the most frequent isolate⁶⁷ (also see Chapter 90). Despite isolation of MAC from the sputum in up to 10% of AIDS patients with CD4 T-cell counts less than 50 cells/ μ L, pulmonary disease due to MAC is uncommon.⁶⁸ Pulmonary disease has been reported in 2.5% to 8% of patients with disseminated MAC⁶⁹ and has rarely been reported in the absence of dissemination.^{69,70} Patients with pulmonary disease tend to have higher CD4 counts and focal alveolar opacities, which rarely cavitate. *Mycobacterium kansasii* can also cause disease in patients with HIV and AIDS. In one study, the risk for infection with *M. kansasii* was increased 150-fold in HIV-infected patients and 900-fold in those with AIDS.⁷¹ In contrast to MAC, *M. kansasii* should always be treated as a potential pathogen.⁷²

Pulmonary disease due to NTM has been described in several other immunocompromised populations, including transplant recipients. Rates may be as high as 6.5% following heart or lung transplantation,⁷³ and 2.9% following bone marrow transplantation,⁷⁴ but are probably much lower in patients following liver or kidney transplantation.^{75,76} *M. abscessus* infection in patients with CF who have undergone lung transplantation has been associated with severe and sometimes fatal disease.⁷⁷⁻⁷⁹

Multiple cytokines are necessary for containment of mycobacterial infections. The most important among these are IFN- γ , IL-12, and tumor necrosis factor. Patients with defects in any of these cytokines are susceptible to infection with NTM. Mutations in the genes that code for *IFN- γ receptor 1* (IFN- γ R1), IFN- γ receptor 2, IL-12 p40, and the IL-12 receptor have all been shown to lead to human disease.⁸⁰ The dominant and recessive IFN- γ R1 deficiencies have distinct clinical presentations.⁸⁰ The adult onset immunodeficiency that can result from the development of autoantibodies against IFN- γ is associated with severe disseminated opportunistic infections including NTM.⁸¹ Mutations in *GATA2* are associated with autosomal dominant and sporadic monocytopenia and disseminated mycobacterial infections called the MonoMAC syndrome.⁸² Large numbers of patients with inflammatory bowel disease, rheumatoid arthritis, or psoriatic arthritis are treated with tumor necrosis factor inhibitors. Although initially shown to predispose to tuberculosis,⁸³ recent reports have linked these therapies to NTM infections as well.⁸⁴ Patients with suspected or known mycobacterial infections should not receive these

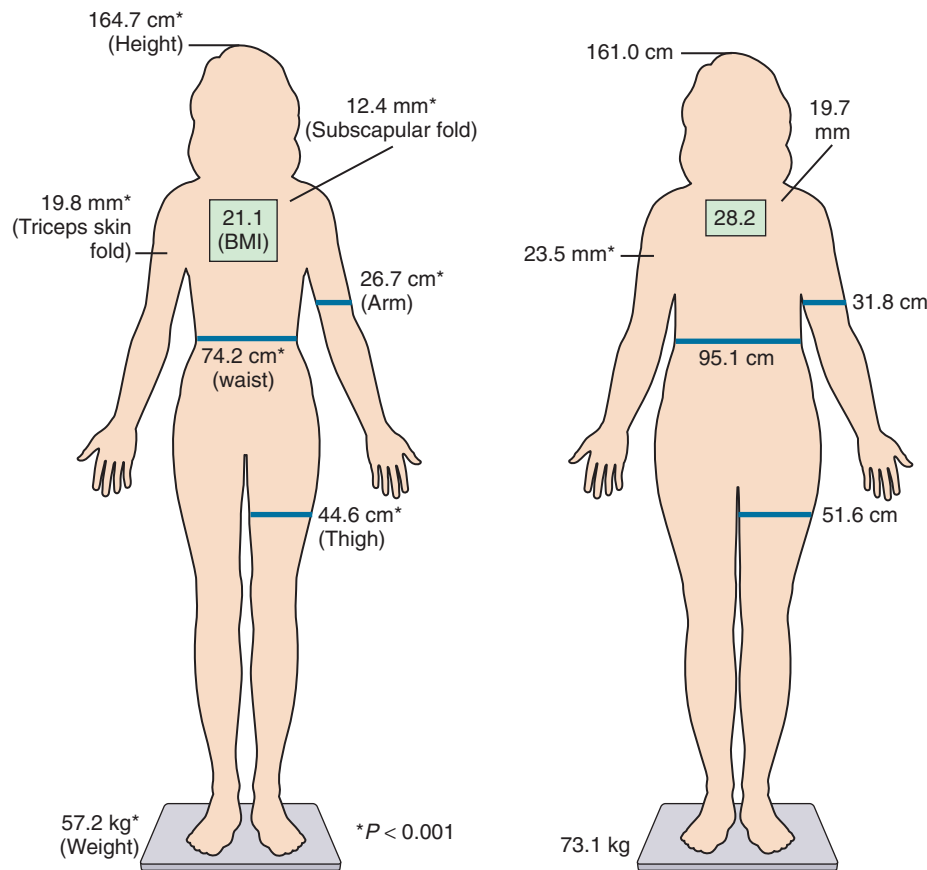


Figure 36-2 Schematic depiction of the anthropometrics of women with pulmonary nontuberculous mycobacterial disease (n = 60) (left) compared with National Health and Nutrition Examination Survey age-, gender-, and race-matched control subjects (right). (Reproduced with permission from Kim RD, Greenberg DE, Ehrmantraut ME, et al: Pulmonary nontuberculous mycobacterial disease: Prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med* 178:1006–1074, 2008.)

medications without proper antimycobacterial therapy. A potential risk factor for NTM lung infection in CF patients is the prolonged use of azithromycin, which inhibits autophagy, an intracellular mechanism that constrains mycobacterial infection.⁸⁵ Prolonged exposure to azithromycin in this context can also select for macrolide resistance in MAC.

Although most studies have focused on evaluating possible host abnormalities that could lead to NTM disease, microbial factors are likely to be important as well. Recent studies have identified isolates and phenotypes associated with increased virulence in *in vitro* models.^{86–88} *M. abscessus* is known to exist in a smooth and rough phenotype. Limited clinical data as well as data from mouse models suggest that the rough may be more virulent than the smooth phenotype. It has been reported that the presence of glycopeptidolipids on the smooth strains mask agonists of Toll-like receptor 2 and prevent induction of the proinflammatory cytokine, tumor necrosis factor, allowing the organisms to colonize and form biofilms in the lung airways.⁸⁵ If the organism then switches to a rough phenotype, the glycopeptidolipids are lost, allowing the strain to elicit an inflammatory response that paradoxically promotes invasive infection. Moreover, a recent population-based assessment of the clinical significance of NTM in a region of The Netherlands demonstrated a wide range of pathogenicity among different NTM species.⁸⁷

Table 36-2 Diversity of Nontuberculous Mycobacteria Pulmonary Disease

- Tuberculosis-like (cavitary) disease
- Disease associated with nodules/bronchiectasis
- Disease associated with genetic airway abnormalities and abnormal airway clearance (cystic fibrosis, primary ciliary dyskinesia, alpha₁-antitrypsin deficiency)
- Hypersensitivity-like lung disease
- Disease associated with esophageal motility disorders
- Disease associated with disseminated disease and immune suppression
- HIV/AIDS
- Defects in interferon- γ and interleukin-12 pathways
- Disease associated with treatment with tumor necrosis factor- α antagonists

DIAGNOSIS AND MANAGEMENT OF SPECIFIC PATHOGENS

NTM lung infection presents with diverse manifestations (Table 36-2). This chapter focuses on the most common clinical presentations in the immunocompetent hosts: chiefly, tuberculosis-like (cavitary) disease and disease associated with nodules and bronchiectasis (nodular/bronchiectatic disease). The diagnostic evaluation usually

consists of (1) assessment for the presence of one or more compatible symptoms, which are usually insidious in onset (cough, sputum production, fatigue, weight loss, fever, hemoptysis); (2) radiographic evaluation, which frequently includes *high-resolution computed tomography* (HRCT) scans of the chest; and (3) microbiologic evaluation, which usually consists of three or more sputum specimens for microscopy and mycobacterial culture and/or collection of specimens bronchoscopically. The most important diagnosis to exclude is tuberculosis. Additional laboratory evaluation aimed at identifying potential reasons for the underlying infection may include testing for CF, α_1 -antitrypsin deficiency, primary ciliary dyskinesia, or esophageal disorders in patients with pulmonary disease and, in the case of disseminated disease, the presence of cell-mediated immunodeficiency or anti-IFN- γ autoantibodies.

The diagnosis of NTM lung disease can be challenging. Unlike pulmonary tuberculosis, in which, barring laboratory contamination, a single positive culture of sputum or of a bronchoscopic specimen establishes the diagnosis, confirmation of the diagnosis of NTM lung disease usually requires repeated isolation of a particular NTM species. Diagnostic criteria have been developed to aid the clinician in the evaluation of persons suspected of having pulmonary NTM disease.⁹ The NTM diagnostic criteria outlined in Table 36-3 are based on experience with common and well-described respiratory pathogens such as MAC, *M. kansasii*, and *M. abscessus*. However, it is important to note that, because of the varying pathogenicity among the many NTM species, no single diagnostic approach will work for all cases.⁸⁷ Diagnostic criteria that are too sensitive promote overdiagnosis and the unnecessary exposure of patients to potentially toxic antimicrobial medications. By contrast, overly rigid diagnostic criteria put patients at risk for undertreatment and progressive NTM disease. Fortunately, NTM lung disease is usually sufficiently indolent that there is usually time for a careful assessment to determine with confidence the presence or absence of significant disease.

The difficulty in determining the clinical significance of an NTM respiratory isolate results from several factors. NTM isolates can contaminate clinical specimens, usually

from environmental sources. Many NTM species, such as *Mycobacterium gordonae*, are generally nonpathogenic and almost invariably represent specimen contamination rather than true infection. NTM can be found in potable (municipal or tap) water (*M. kansasii*, MAC, *Mycobacterium simiae*, *M. abscessus*, *M. xenopi*), so that their presence in a clinical specimen can be due to waterborne contamination of the specimen, even if the isolated species is one that is capable of causing clinical disease. The recovery of even potentially virulent and pathogenic NTM may be associated with the absence of active or progressive disease, for reasons that are not understood. Unfortunately, no easily applied algorithm addresses all NTM species in all clinical circumstances. The clinician must have some knowledge of the disease-producing potential of NTM species and also an awareness of the circumstances associated with the isolation of the NTM species.

A single positive sputum culture for NTM is usually regarded as indeterminate for the diagnosis of NTM lung disease. In contrast, when two or more sputum cultures are positive, the diagnosis of disease is more likely. For example, 98% of patients with two or more positive sputum cultures for MAC had evidence of progressive disease during follow-up.⁸⁹ A single positive NTM culture from bronchoscopy can be diagnostic for disease (see Table 36-3), so repeated bronchoscopy is not appropriate if its only purpose would be to obtain multiple positive cultures. However, the clinician must keep in mind those NTM species that are usually respiratory contaminants (especially *M. gordonae*) and those NTM species that can be found in tap water (discussed earlier) since “pseudo-outbreaks” of NTM disease can be the consequence of bronchoscopic equipment that has been inappropriately rinsed with tap water.⁹⁰ Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed clinically until the diagnosis is either firmly established or excluded, a process that can take months to years.

Diagnosis of NTM lung disease does not necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients. Factors that might influence the decision to treat NTM lung disease include the virulence of the NTM pathogen and the potential for disease progression, the severity (or lack of severity) of symptoms and radiographic findings, the presence of known indolent disease, and the presence of advanced age and/or severe comorbid conditions (with limited life expectancy); another factor is the inability to tolerate the prolonged and sometimes toxic antimicrobial regimens for NTM disease. Again, for optimal management of NTM lung disease, there is no substitute for physician familiarity with NTM pathogens and with the individual patient.

Other clinical manifestations of NTM infection include lymphadenitis, disseminated disease, and skin, soft tissue, and bone disease. Lymphadenitis is the most common NTM disease manifestation in children and is usually due to MAC or, less commonly, *Mycobacterium haemophilum* or *M. scrofulaceum*.⁹¹ The most important differential diagnosis is tuberculosis lymphadenitis, although NTM account for approximately 90% of mycobacterial lymphadenitis in American children (but only 10% in adults).⁹² Symptoms are usually minimal, with frequent unilateral involvement of submandibular, submaxillary, preauricular, or cervical

Table 36-3 Microbiologic Criteria for Diagnosis of NTM Lung Disease

Specimen	Results
At least three sputum results available with: or	Two positive cultures regardless of the results of AFB smear
Single available bronchial wash or lavage with: or	One positive culture regardless of the results of AFB smear
Tissue biopsy with:	Compatible histopathology (granulomatous inflammation) and a positive biopsy culture for NTM Compatible histopathology (granulomatous inflammation) and a positive sputum or bronchial wash culture for NTM

AFB, acid-fast bacilli; NTM, nontuberculous mycobacteria.

Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 175:367–416, 2007.

lymph nodes. Skin and soft tissue infections are usually due to the “rapidly growing mycobacteria,” *M. abscessus*, *M. fortuitum*, *M. chelonae*, or *M. marinum*, and are the result of direct inoculation after either trauma or surgery.^{1,93} Dissemination of NTM pathogens is most often associated with the severe immunosuppression of advanced AIDS and is caused by MAC.^{67,94-96} Disseminated NTM infections can be seen in other immune-compromised states, such as organ transplantation, autoantibodies to IFN- γ , or in association with indwelling foreign bodies such as venous catheters, dialysis catheters, or other prosthetic devices.⁹⁷⁻¹⁰⁰

LABORATORY DIAGNOSIS

The diagnosis of NTM disease is based on isolation of these organisms from clinical specimens. Cultures should include both solid and broth media for sensitive detection of mycobacteria and, ideally, a semiquantitative reporting of colony counts.⁹ The optimal temperature for growth of most NTM species is between 28°C and 37°C, although some species require either higher or lower temperatures for optimal growth and some species require special supplementation for recovery from culture.⁹ Most NTM grow within 2 to 3 weeks of subculture but the group of rapidly growing NTM appear within 7 days of subculture.

Identification of specific species can be based on phenotypic, chemotaxonomic, and molecular methods.⁹ NTM can be categorized by their growth rate and pigmentation, although these characteristics are not specific enough for final speciation. In addition, biochemical testing can be used to help speciate the NTM. However, none of these procedures is sufficient to differentiate all NTM, particularly some of the newly identified species.

Additional techniques for speciation include HPLC, nucleic acid probes, polymerase chain reaction and other amplification methods, and nucleic acid sequencing.¹⁰¹⁻¹⁰⁶ HPLC, which analyzes the chromatographic profile of the mycolic acids extracted from the bacterial cell wall, can be used to speciate a large number of NTM.¹⁰⁷ Identification of mycobacteria by 16S ribosomal DNA sequencing^{101,102} provides more accurate determination of the species, although neither HPLC nor 16S ribosomal DNA sequencing can differentiate all species of NTM. The commercially available AccuProbe technology (Gen-Probe, San Diego, CA) is currently recommended for identification of *M. tuberculosis* complex, *M. avium* complex (as well as *M. avium* and *M. intracellulare* separately), *M. kansasii*, and *M. goodii*.

The clinical usefulness of drug susceptibility testing in the management of patients with NTM disease remains controversial because in vitro results do not correlate well with clinical outcomes for some mycobacterial species. For slowly growing mycobacteria, no single susceptibility method is recommended for all species. For MAC, a broth-based culture method—with both microdilution and macrodilution methods—is considered acceptable.⁹ Initial isolates should be tested for response to clarithromycin, as should isolates from treatment failures and relapses, from patients who have taken macrolides previously, and from AIDS patients who develop bacteremia on macrolide prophylaxis. For *M. kansasii*, isolates should be tested for response to rifampin (rifampicin) because resistance to rifampin is associated with treatment failure or relapse. If

rifampin resistance is documented, additional drugs should be tested.⁹ For RGM, broth microdilution minimal inhibitory concentration determination for susceptibility testing is recommended.

SLOWLY GROWING MYCOBACTERIA

Although there are fewer species of slowly growing NTM than rapidly growing species, the slow growers are more common causes of lung disease (see Table 36-1). The slow growers include more than 70 species with a wide range of pathogenicity, from organisms such as *M. kansasii* that are probably second only to *M. tuberculosis* in terms of disease-producing capability to *M. goodii*, which rarely causes lung disease.

Mycobacterium avium Complex

Mycobacterium avium complex includes the NTM species *M. avium*, of which there are several subspecies, *M. intracellulare*, *M. chimaera*, *M. colombiense*, and *M. vulneris*, as well as some less well-described species. As noted previously, *M. avium* and *M. intracellulare* are likely acquired from different environmental sources. Differentiation of the separate MAC species is not possible with routine laboratory techniques, although DNA probes are available for *M. avium* and *M. intracellulare*. Currently, in most circumstances, the differentiation of *M. avium* and *M. intracellulare* does not make a significant difference clinically or therapeutically (although *M. avium* is more often seen with disseminated disease and, in the United States, *M. intracellulare* is more often isolated as a respiratory pathogen). However, recent data from South Korea suggest that *M. intracellulare* may be more virulent than *M. avium*: compared to those with *M. avium*, patients with *M. intracellulare* presented with more severe disease and had a worse prognosis.¹⁰⁸

MAC lung disease typically presents as apical fibrocavitary lung disease similar to tuberculosis, sometimes with large cavities, usually in males but also in females in their fifth and sixth decades who have a history of cigarette smoking and alcohol abuse (Fig. 36-3). If left untreated, this form of disease is generally progressive, can result in extensive cavitary lung destruction, and is associated with increased mortality compared with noncavitary MAC lung disease.¹⁰⁹⁻¹¹¹ The necessity for starting therapy with cavitary MAC lung disease is clearly much more pressing than with noncavitary MAC disease.

MAC lung disease also presents with nodular and interstitial nodular opacities, which frequently involve the right middle lobe or lingula, predominantly in postmenopausal nonsmoking white females (Fig. 36-4; eFig. 36-1). This form of disease, termed *nodular/bronchiectatic disease*, tends to have a much slower progression than cavitary disease, so that long-term follow-up may be necessary to demonstrate clinical or radiographic changes. Even with this more indolent form of disease, however, death may result from progressive disease.⁵² Nodular/bronchiectatic MAC lung disease is radiographically characterized by HRCT findings that include multiple small peripheral bronchiolocentric pulmonary nodules with branching configurations, and cylindrical bronchiectasis (see Fig. 36-4; see eFig. 36-1). The HRCT pattern of these predominantly peripheral small nodular branching opacities has been described as

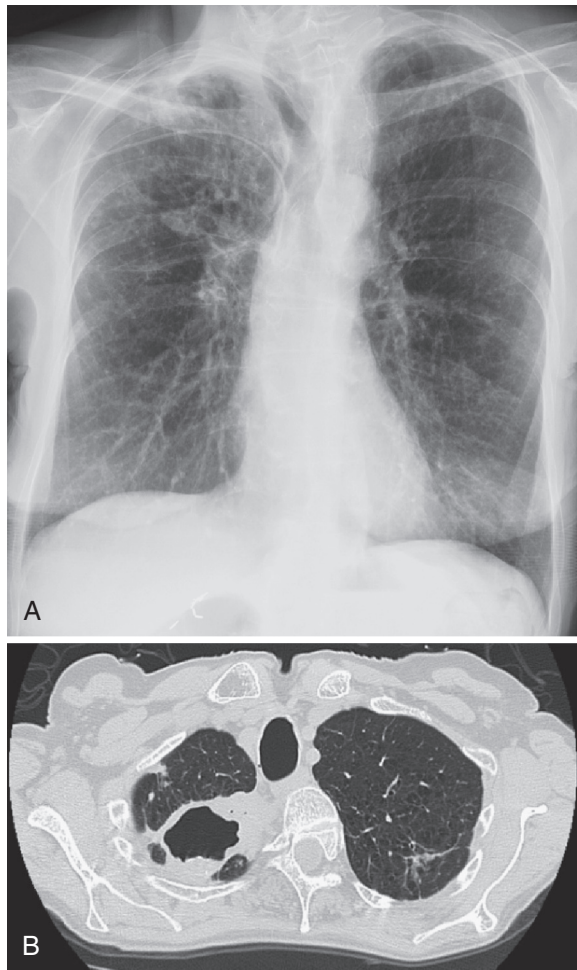


Figure 36-3 A 63-year-old female smoker with cavitary *Mycobacterium avium* complex (MAC) lung disease. The patient, who presented with cough, fatigue, weight loss, and intermittent hemoptysis, was diagnosed with MAC in 2004. She failed two courses of multidrug therapy and, at the time of this imaging, her sputum was still culture positive for MAC. **A**, Chest radiograph showing cavitary consolidation in the right apex and scattered nodular and reticulonodular opacities in both lungs. **B**, Axial chest CT shows a large right apical cavity.

“tree-in-bud,” and reflects inflammatory changes including bronchiolitis.

Patients with nodular/bronchiectatic MAC lung disease often have additional microbiologic findings associated with bronchiectasis, including respiratory cultures positive for *Pseudomonas aeruginosa*, *Nocardia* species, and occasionally other NTM such as *M. abscessus*. Because nonmycobacterial exacerbations of bronchiectasis often complicate the assessment and management of MAC disease, strategies aimed at treatment of the bronchiectasis may improve patients’ symptoms.

For many patients, perhaps the majority of patients with nodular/bronchiectatic disease, it is unknown if bronchiectasis is the result of the mycobacterial infection or if bronchiectasis due to some other process then predisposes to subsequent mycobacterial infection. In some patients with NTM lung disease, bronchiectasis is clearly the result of diseases such as CF, primary ciliary dyskinesia, or α_1 -antitrypsin deficiency and thus antedates the MAC disease.^{65,112,113} The routine evaluation of underlying causes

of bronchiectasis, such as CF and α_1 -antitrypsin deficiency, in patients with nodular/bronchiectatic MAC disease is currently controversial and no consensus exists.

Therapy of MAC Lung Disease. Several aspects of treatment for MAC lung disease are difficult to explain, and even counterintuitive. The greatest misunderstanding about treatment regimens for NTM pathogens results from the expectation that all NTM infections should respond in a predictable manner to antimicrobial therapy, similar to infections due to *M. tuberculosis*. However, even when treatment regimens are based on in vitro susceptibility testing, the NTM pathogen very often does not respond to antimicrobial agents as predicted from the susceptibility results. The most difficult and frustrating aspect of NTM therapy for many clinicians is the lack of a clear association between the in vitro susceptibility results and the in vivo, clinical response. For many NTM, including MAC, laboratory cutoffs for “susceptible” and “resistant” do not have a demonstrable clinical correlate and have not been confirmed to be clinically meaningful. Response to treatment of disease caused by MAC correlates primarily with in vitro susceptibility to macrolides (clarithromycin and azithromycin), and not to most other agents.¹¹⁴⁻¹¹⁹ However, evidence is emerging that in vitro susceptibility or resistance to amikacin does impact the outcomes of treatment regimens that include amikacin.¹²⁰ Several other NTM species (e.g., *M. abscessus*, *M. simiae*, *M. malmoense*, *M. xenopi*) lack established correlation between in vitro susceptibilities and in vivo responsiveness to any antimicrobial agent. The reason for the discordance between laboratory susceptibility testing results and clinical benefit for many NTM is not known. Accordingly, clinicians must use in vitro susceptibility data for many NTM with the awareness that the results are an imperfect guide to treatment outcome. Two recent reviews summarize the multiple and complicated factors that likely impact this troubling aspect of NTM disease therapy.^{121,122}

Because the macrolides—clarithromycin and azithromycin—are the principal and most important antimicrobial agents for which there is a demonstrated correlation between in vitro susceptibility and in vivo response for MAC lung disease, these agents, partnered with ethambutol, serve as the cornerstones of MAC therapy (Table 36-4). As also shown, this regimen must be reinforced with a rifamycin and, possibly, an injectable aminoglycoside (amikacin or streptomycin), because companion drugs are necessary to prevent the emergence of macrolide-resistant MAC isolates. Macrolides should never be used as monotherapy for treatment of MAC disease, either pulmonary or disseminated.¹²³

An additional phenomenon associated with MAC drug therapy is that patients who have failed prior MAC therapy, with or without a macrolide, have lower sputum conversion rates with macrolide-containing treatment regimens, even with macrolide-susceptible MAC isolates, than do patients with no prior therapy.^{115,118,124,125} Although the explanation for this is not clear, it is evident that the best chance for treatment success in MAC lung disease is the first treatment effort. Finally, patients who are successfully treated for nodular/bronchiectatic MAC disease can be reinfectd by new MAC isolates, sometimes with renewal of progressive disease.¹²⁶

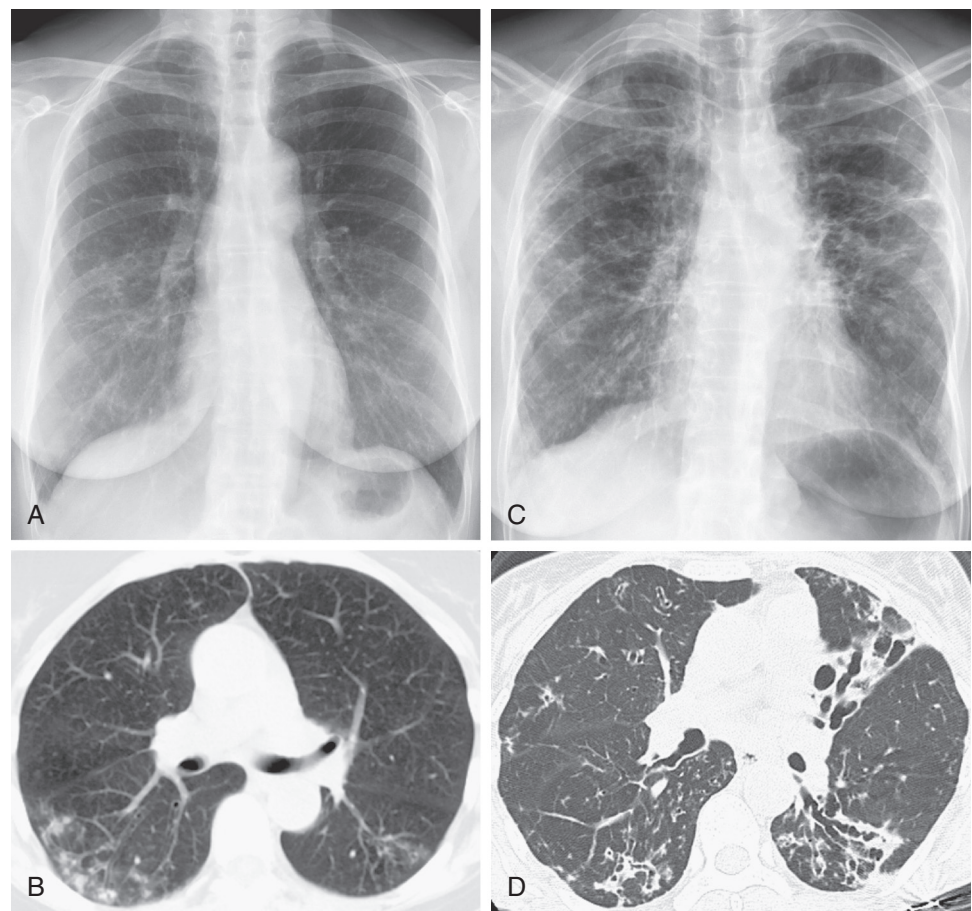


Figure 36-4 Chest radiographs and CT scans of two women with MAC lung disease. **A and B,** A 60-year-old female nonsmoker with several years of chronic cough and “recurrent pneumonia.” Sputum was acid-fast bacilli (AFB) smear positive and culture positive for MAC at the time of the radiograph and on multiple subsequent collections. **A,** Frontal chest radiograph shows primarily mid and lower lung nodular and reticulonodular abnormalities. **B,** High-resolution chest CT from this patient shows bilateral bronchiectasis with variably sized centrilobular nodules, some showing a branching configuration, consistent with nodular “tree-in-bud” pattern. **C and D,** A 74-year-old woman with more than 20 years of cough with sputum production, “recurrent pneumonia,” severe fatigue, and weight loss. Sputum is strongly AFB smear positive and culture positive for MAC on multiple collections. **C,** Frontal chest radiograph shows multifocal bilateral bronchial wall thickening and dilation and nodular opacities. **D,** High-resolution chest CT from this patient shows extensive severe multilobar bronchiectasis.

Table 36-4 Treatment of Pulmonary Disease due to <i>Mycobacterium avium</i> Complex Infections	
Type of Disease	Regimen
Nodular/bronchiectatic disease	1. Clarithromycin 1000 mg tiw or azithromycin 500 to 600 mg tiw and 2. Ethambutol 25 mg/kg tiw and 3. Rifampin 600 mg tiw
Cavitary disease	1. Clarithromycin 500 to 1000 mg/day or azithromycin 250 to 300 mg/day and 2. Ethambutol 15 mg/kg daily and 3. Rifampin 450 to 600 mg daily and 4. Consider streptomycin or amikacin 15 mg/kg tiw for first 2 to 3 months
Advanced or previously treated disease	1. Clarithromycin 500 to 1000 mg/day or azithromycin 250 to 300 mg/day and 2. Ethambutol 15 mg/kg daily and 3. Rifabutin 150 to 300 mg daily or rifampin 450 to 600 mg daily and 4. Include streptomycin or amikacin 15 mg/kg tiw for first 2 to 3 months

tiw, three times per week.
Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 175:367–416, 2007.

The recommended duration of treatment for MAC pulmonary disease is to continue therapy until 12 months of sputum culture negativity,⁹ a goal that requires patients to have sputum collected for mycobacterial culture on a regular basis throughout the course of treatment.

For some patients who are taking clarithromycin, the doses may need to be split (e.g., 500 mg twice daily) because of gastrointestinal intolerance. For patients of low body weight (<50 kg) or older age, the clarithromycin dose for daily regimens may need to be reduced to 500 mg/day or 250 mg twice daily because of gastrointestinal intolerance. However, it should be noted that, in a small (*N* = 34) three-arm retrospective study from Japan, 400 mg daily was associated with a lower sputum conversion rate at 18 months than 800 mg daily.¹²⁷ Patients receiving clarithromycin and rifabutin should be carefully monitored for rifabutin-related toxicity, especially hematologic (leukopenia) and ocular (uveitis) toxicity. For some patients, especially those with nodular/bronchiectatic MAC disease, intermittent or three times weekly therapy may facilitate tolerance of the multi-drug MAC treatment regimen and is associated with a high treatment success rate.^{127a}

Macrolide-resistant MAC lung disease is associated with a poor prognosis.¹²³ The two major risk factors for macrolide-resistant MAC disease are macrolide monotherapy or macrolide treatment with inadequate companion medications. The treatment strategy associated with the highest rates of success for macrolide-resistant MAC lung disease includes the use of a multidrug regimen, including a parenteral aminoglycoside (streptomycin or amikacin), and surgical resection (“debulking”) of diseased lung.¹²³ The optimal drug regimen for treating macrolide-resistant strains is unknown but some experts recommend ethambutol, rifabutin, an injectable agent, and possibly another oral drug such as an 8-methoxyfluoroquinolone or clofazimine. One recent study suggests a modest favorable impact of moxifloxacin in this context.¹²⁸

Patients whose disease is predominantly localized to one lung and who can tolerate resectional surgery should be considered for surgery under the following conditions: (1) poor response to drug therapy, (2) development of macrolide-resistant MAC disease, or (3) presence of significant disease-related complications, such as hemoptysis. Outcomes of surgery have generally been favorable, with more than 80% culture conversion documented postoperatively.¹²⁹ Operative mortality has been low in most series except those that reported results on patients undergoing pneumonectomy. In a recent study reporting the outcomes of 134 patients undergoing video-assisted thoracoscopic surgery, there were no deaths, the complication rate was 7%, and cultures converted in 84% of the patients.¹³⁰ When possible, surgery should be performed by thoracic surgeons who have had extensive experience with resectional lung surgery for mycobacterial disease.¹³¹

Therapy of Disseminated MAC Disease. Successful treatment of disseminated MAC disease in persons with AIDS is based on treatment of both the mycobacterial and HIV infections. Clinicians must therefore be aware of the interactions between the antimycobacterial and antiretroviral medications. Current guidelines for the use of antimycobacterial drugs with HIV therapies can be found at www.cdc.gov/tb/default.htm.

Patients with disseminated MAC disease should be treated with clarithromycin at a dose of 1000 mg/day or 500 mg twice daily (or, as an alternative, azithromycin at a dose of 500 mg daily) and ethambutol at a dose of 15 mg/kg daily.¹³²⁻¹³⁴ Rifabutin, if added, should be used at a dose of 300 mg daily, with adjustments for interactions with antiretroviral drugs. As with macrolide-resistant MAC lung disease, patients with disseminated disease from macrolide-resistant strains are far less likely to be treated successfully.¹¹⁴ In the era preceding use of combination antiretroviral therapy for HIV, clofazimine was associated with excess mortality in HIV-infected patients with MAC bacteremia.¹³⁵ Whether those results apply to HIV-uninfected people or to the current setting in which combination antiretroviral therapy is used is unknown. In the absence of immune reconstitution, treatment of MAC in patients with AIDS should be considered lifelong, although MAC treatment may be stopped for patients who are asymptomatic, have completed 12 months or more of therapy, and have maintained a CD4⁺ T-cell count more than 100 cells/ μ L for at least 12 months.¹³⁶

Preventive therapy for disseminated MAC is recommended for all HIV-infected patients with fewer than 50 CD4⁺ T-cells/ μ L.¹³⁷ Based on efficacy and ease of use, azithromycin—given as 1200 mg once weekly—is the preferred agent.¹³⁸ Clarithromycin is also effective; however, it is considered an alternative agent because it must be given twice daily and the risk of breakthrough with macrolide-resistant strains is higher with daily clarithromycin than with weekly azithromycin. Rifabutin is also effective but should only be used when a macrolide cannot be tolerated. Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4⁺ T-lymphocyte counts to more than 100 cells/ μ L for more than 3 months. Primary prophylaxis should be reintroduced if the CD4⁺ T-lymphocyte count drops below 50 to 100 cells/ μ L.

Therapy of MAC Lymphadenopathy. The treatment of choice for MAC lymphadenopathy, as well as for localized lymphadenopathy due to most NTM pathogens, is complete surgical resection of the involved lymph nodes.^{91,92,139,140}

When complete surgical resection is not possible due to nerve impingement or encasement by infected nodes, then chemotherapy with MAC treatment regimens similar to those for lung and disseminated disease are effective.¹⁴¹ Some studies have also suggested that a conservative, “wait and see” approach is also as effective as either surgery or antibiotic therapy for the majority of children with this process.¹⁴²⁻¹⁴⁴ Expert evaluation is advisable for optimal management of these children.

***Mycobacterium kansasii* Pulmonary Disease**

Mycobacterium kansasii is the second most common cause of NTM lung disease in the United States, but has also been reported in Europe, Asia, and Africa. Tap water is the major reservoir for *M. kansasii*.¹⁴⁵⁻¹⁴⁷ *Mycobacterium kansasii* lung disease most closely parallels the clinical course of *M. tuberculosis*, including radiographic abnormalities (Fig. 36-5; eFig. 36-2). While most patients with *M. kansasii* lung disease have upper lobe fibrocavitary findings, some patients have been reported with nodular/bronchiectatic radiographic abnormalities. In HIV-infected patients, *M. kansasii* can present with a wide spectrum of radiographic abnormalities (see eFig. 90-10).¹⁴⁸

Therapy of *Mycobacterium kansasii* Pulmonary Disease. The recommended regimen for treating pulmonary *M. kansasii* disease includes daily rifampin (600 mg/day), isoniazid (300 mg/day), and ethambutol (15 mg/kg/day) for a duration that includes 12 months of negative sputum cultures.⁹ Limited data suggest that therapy with rifampin, ethambutol, and clarithromycin for *M. kansasii* disease can also be successful,¹⁴⁹ including intermittent therapy.¹⁵⁰ The recommended treatment duration, as with MAC lung disease, is a duration that includes 12 months of sputum mycobacterial culture negativity.

Patients whose *M. kansasii* isolates are resistant to rifampin have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg), high-dose ethambutol (25 mg/kg/day), and sulfamethoxazole (1 g three times per day) combined with several months of streptomycin or amikacin.¹⁵¹ The excellent in vitro activity

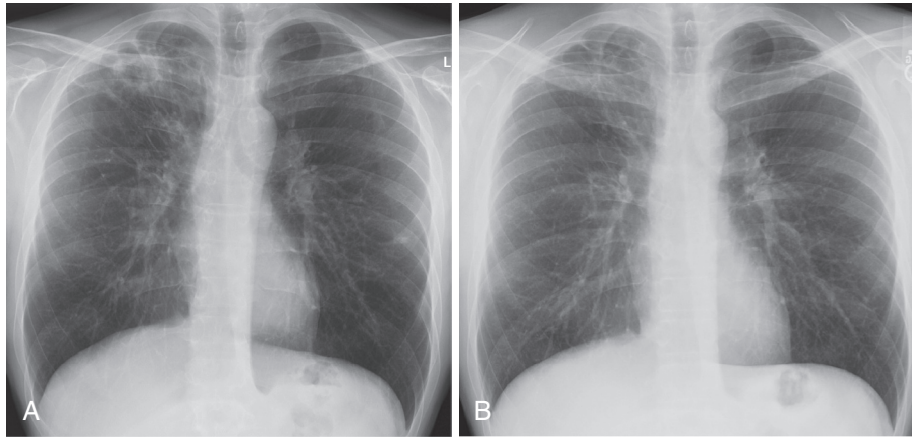


Figure 36-5 A 46-year-old male smoker with *Mycobacterium kansasii* lung disease. The patient presented with cough and weight loss. He was treated as a tuberculosis suspect initially but his sputum specimen was found to be culture positive for *M. kansasii*. **A**, Frontal chest radiograph shows a right upper lobe cavity. **B**, Frontal chest radiograph shows improvement in right upper lobe abnormalities after completing therapy.

of clarithromycin and moxifloxacin against *M. kansasii* suggests that multidrug regimens containing these agents and at least one other agent based on in vitro susceptibilities, such as ethambutol or sulfamethoxazole, are likely to be effective for treatment of a patient with rifampin-resistant *M. kansasii* disease.

Therapy of Disseminated *Mycobacterium kansasii* Disease.

The treatment regimen for disseminated disease, as usually observed in patients with AIDS, should be the same as for pulmonary disease.⁹ Because of the critically important role of rifamycins in the treatment of *M. kansasii* disease, it is important to construct *M. kansasii* and anti-retroviral treatment regimens that are compatible (see www.cdc.gov/tb/default.htm). An option for treating HIV-infected patients who receive an antiretroviral regimen not compatible with rifamycins is to substitute a macrolide or moxifloxacin for the rifamycin. There is no recommended prophylaxis regimen for disseminated *M. kansasii* disease.

Mycobacterium xenopi

Mycobacterium xenopi is a thermophile that survives in hot water systems and natural hot water reservoirs. Its survival in flowing water systems and resistance to common disinfectants enable *M. xenopi* to contaminate laboratory samples and medical devices such as bronchoscopes, thus causing health care–acquired disease, pseudoinfections, and laboratory contamination of specimens. Clusters of hospital isolates have been reported in the United States and Europe.¹⁵² Because of its environmental presence, the differentiation of true clinical infection from pseudoinfection may be difficult but is of paramount importance.

M. xenopi is rarely isolated in the United States; however, it is the second most common cause of NTM lung disease in Canada, the United Kingdom, and some parts of Europe.¹⁵³ Pulmonary infections are most common, but extrapulmonary and disseminated infections have been reported. Impaired immunity, either local (preexisting pulmonary disease) or systemic (HIV, immunosuppressive medications), appear to predispose to *M. xenopi* infections. Radiographic findings with *M. xenopi* pulmonary disease are variable but most often include upper lobe cavitory abnormalities similar to tuberculosis.

In a report of therapy for *M. xenopi* infections, overall mortality was high—and mostly unrelated to *M. xenopi* disease—and the response to chemotherapy was not correlated with in vitro susceptibility results.¹⁵⁴ In another report from Europe, *M. xenopi* isolates demonstrated favorable in vitro minimal inhibitory concentrations to isoniazid, rifampin, and ethambutol.¹⁵³ Even with variable treatment regimens, antimicrobial treatment cured 58% of patients who met American Thoracic Society criteria for *M. xenopi* lung disease.¹⁵³ In that study, there was no correlation between failure or treatment relapse and in vitro susceptibility results. In recent published treatment results, a regimen of clarithromycin, rifampin, and ethambutol was compared to ciprofloxacin, rifampin, and ethambutol; treatment success, failure, or relapse did not differ between the two groups.¹⁵⁵ All-cause mortality was again relatively high, and somewhat higher in the ciprofloxacin, rifampin, ethambutol arm. A combination of ethambutol and rifampin with either clarithromycin or moxifloxacin was bactericidal in vitro and ex vivo.¹⁵⁶ Amikacin containing regimens were the most effective in a nude mouse model. Overall, the optimal pharmacologic management has yet to be determined; however, a regimen consisting of clarithromycin (or moxifloxacin), rifampin, and ethambutol, administered for a duration of therapy that includes 12 months of sputum culture negativity, is commonly used. Addition of amikacin may be advisable in patients with more extensive disease. The unusually high overall mortality with this infection is difficult to explain, but may be a reflection of the comorbidities of the patients with *M. xenopi* disease.

Mycobacterium malmoense

Mycobacterium malmoense is considered the second most serious pathogen after MAC in Northern Europe. In patients in Europe, 70% to 80% of *M. malmoense* isolates have been considered clinically relevant, while clinical isolates in the United States are deemed clinically significant less frequently.¹⁵⁷ Patients with *M. malmoense* lung disease frequently have preexisting obstructive lung disease, and *M. malmoense* lung disease often presents in a manner similar to other cavitory NTM lung disease pathogens. Overall, the in vivo response to antimicrobials does not correlate with in vitro susceptibility to antimicrobial agents. In a recent

report, clarithromycin, rifampin, and ethambutol were compared with a regimen consisting of ciprofloxacin, rifampin, and ethambutol.¹⁵⁵ Although a more favorable response to therapy was obtained with the macrolide-containing regimen, overall mortality did not differ between the two regimens, and the optimal pharmacologic management of *M. malmoense* has yet to be determined.^{155,158} Currently, a suggested regimen for *M. malmoense* consists of rifampin, ethambutol, and clarithromycin with or without isoniazid for a duration to include 12 months of sputum culture negativity.¹⁵⁷

Mycobacterium simiae

Recovery of *M. simiae* from clinical specimens has been reported in three geographic regions, Israel, Cuba, and the Southwestern United States, including Texas, Arizona, and New Mexico. The organism is most often isolated as a single positive specimen that is smear negative and not associated with clinical disease. For several clusters of isolates, organisms were also recovered from the local tap water, suggesting it as the likely source.^{159,160} A large pseudo-outbreak of *M. simiae* isolates from an urban hospital in Texas has been reported.¹⁶¹ The source for most of the recovered organisms was a hot water holding area. In most published series, the majority of *M. simiae* isolates have been judged to be not clinically significant.^{161,162} In a recent publication, the authors noted, "The available diagnostic criteria are inadequate for the selection of patients for whom drug treatment for true *M. simiae* infection would be beneficial."¹⁶² When *M. simiae* is a significant pathogen, it is most often associated with pulmonary disease or, in immunocompromised hosts, disseminated disease.

As with other NTM, there is no established correlation between in vitro susceptibility of the organism and in vivo clinical response to antimicrobial agents, nor is there an established, predictably reliable treatment regimen for *M. simiae* disease. In a study from Israel,¹⁶³ there were no recurrences reported in 102 patients with pulmonary *M. simiae* disease after treatment with rifampin, ethambutol, and clarithromycin given daily for at least 12 months of negative sputum cultures. These results are in sharp contrast to the experience of many experts in the United States who find *M. simiae* to be among the most difficult to treat pulmonary NTM pathogens. Some experts suggest using macrolide-based regimens similar to those used for MAC; in addition, other agents such as fluoroquinolones, sulfamethoxazole, and linezolid may have some activity against this organism.

Mycobacterium szulgai

Mycobacterium szulgai is characterized primarily by cavitary lung disease in patients with underlying chronic lung disease. As with other NTM pathogens, it can also be associated with nodular/bronchiectatic disease. Most respiratory isolates of *M. szulgai* are associated with significant lung disease: 11 of 15 patients (73%) in The Netherlands who grew *M. szulgai* from their sputum met current American Thoracic Society criteria for disease.¹⁶⁴ In vitro susceptibilities demonstrate susceptibility to rifampin, isoniazid, ethambutol, and clarithromycin. A recent study suggested that regimens containing a rifamycin, ethambutol, and clarithromycin with or without a fluoroquinolone for approxi-

mately 12 months have almost 100% treatment success.¹⁶⁴ Unlike many other NTM pathogens, the in vitro susceptibilities for *M. szulgai* appear to predict favorable treatment response.

RAPIDLY GROWING MYCOBACTERIA

RGM are distinguished by growth in subculture in less than 7 days and comprise more than 80 distinct species, at least 18 of which have been associated with lung disease (see Table 36-1). Because many RGM are not pathogenic in humans, it is important to subclassify organisms within this group to the species level since this affects both treatment and prognosis. Although RGM can produce pulmonary disease, they have a propensity to produce skin and soft tissue infections.

Mycobacterium abscessus

Mycobacterium abscessus is the third most common NTM infection in the United States and causes at least 80% of pulmonary infections due to RGM.⁵⁷ By genome sequencing, *M. abscessus* can be divided into additional subspecies, *Mycobacterium bolletii* and *Mycobacterium massiliense*.¹⁶⁵ Most patients with pulmonary disease due to *M. abscessus* are nonsmoking white women older than 60 years who have no predisposing conditions. The usual clinical presentation is similar to that of other NTM pulmonary infections and includes cough and easy fatigability. For most patients without predisposing conditions, the disease is slowly progressive; however, more fulminant, rapidly progressive disease has been seen in patients with gastroesophageal disorders and CF. The chest radiograph usually shows multilobar, patchy, reticulonodular or mixed reticulonodular alveolar opacities⁵⁷ (Fig. 36-6). HRCT findings include the presence of cylindrical bronchiectasis with multiple small nodules, similar to the findings in MAC lung disease.^{57,112,166} Cavitation has been reported in 10% to 40% of patients. In one report, 20% of patients died as a consequence of *M. abscessus*.⁵⁷

Therapy of *Mycobacterium abscessus* Pulmonary Disease.

M. abscessus is typically resistant in vitro to most of the medications used to treat tuberculosis, and has demonstrated in vitro activity to only a few antimicrobial agents. Cure can be elusive for many patients with *M. abscessus* lung disease with medical therapy. Among 65 patients from South Korea with pulmonary *M. abscessus* disease who were treated with a standardized regimen including 4 weeks of intravenous amikacin and cefoxitin along with oral ciprofloxacin, clarithromycin, and doxycycline for a total duration of 24 months, sputum was converted and negative cultures were maintained for more than 12 months in only 58% of patients.^{166a} In a U.S. study of 107 patients treated with individualized therapy that included intravenous imipenem (or cefoxitin) and amikacin along with various oral and inhaled combinations of therapy,¹⁶⁷ only 48% of cases converted and maintained negative cultures for at least 12 months. Current guidelines recommend that therapy usually consists of 2 to 4 months of intravenous agents such as imipenem or cefoxitin plus amikacin given daily or three times weekly.⁹ Any oral agents that have demonstrated in vitro activity should be included in the treatment

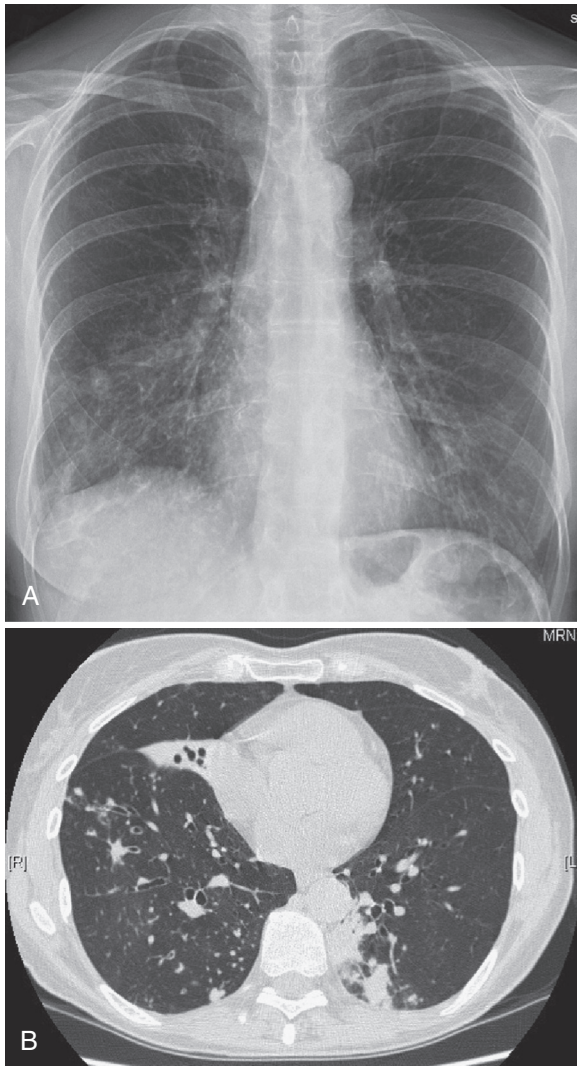


Figure 36-6 A 68-year-old nonsmoking woman with several-year history of cough, fatigue, and weight loss. Her sputum cultures were consistently positive for *M. abscessus*. **A**, Frontal chest radiograph shows middle and lower lung zone nodular opacities and bronchiectasis. **B**, Axial chest CT shows right middle lobe atelectasis and bronchiectasis with bilateral lower lobe bronchiectasis and nodular opacities. Note the left lower lobe air space opacity in this patient with severe reflux and probable chronic aspiration.

regimen. While macrolides have traditionally been used in this role, recent studies have questioned the importance of macrolides in the treatment of *M. abscessus* subspecies *abscessus* because the organism contains the *erythromycin ribosomal methylase (erm[41])* gene.¹⁶⁸ When the organism is incubated in the presence of clarithromycin, the gene is induced and the organism rapidly acquires macrolide resistance. In contrast, *M. massiliense* has a nonfunctional copy of the gene so macrolide resistance is not induced in the presence of clarithromycin. In a study from South Korea, patients infected with *M. massiliense* were more likely to improve clinically, radiographically, and bacteriologically than those with *M. abscessus*: in 88% of those with *M. massiliense*, sputum cultures converted to negative versus 25% with *M. abscessus*.¹⁶⁹ Limited data suggest that azithromycin may be more effective than clarithromycin against *M. abscessus*.^{170,171}

Species identification discriminating between *M. abscessus* and *M. massiliense* informs clinicians about the presence of an active *erm* gene and presumptive antibiotic choices but is frequently not available from reference laboratories. However, the presence of an active *erm* gene can be ascertained in most mycobacteriology laboratories in a relatively short time and is the critical information needed by the clinician to guide antibiotic therapy for isolates initially identified as *M. abscessus*.

Linezolid, an oxazolidinone, is active against some strains of *M. abscessus*, but is frequently associated with significant hematologic toxicity and peripheral neuropathy.^{171,172} Tigecycline has in vitro activity against *M. abscessus*, but is available only as an intravenous preparation and is associated with significant nausea and vomiting.^{172a} Clofazimine has in vitro activity against *M. abscessus* and synergistic activity with amikacin¹⁷³; however, its role in the management of these patients remains to be defined.

Once a patient has demonstrated a clinical response to therapy, there are several possible choices for continued treatment: (1) stop therapy after 2 to 4 months and follow the patient for signs of progression of disease and, if present, periodically reinstitute treatment; (2) stop the aminoglycoside and continue the cefoxitin or imipenem for a longer period along with an oral agent; and (3) continue an oral agent and institute inhaled amikacin. Unfortunately, none of these choices is based on evidence, so treatment decisions need to be individualized and often some form of therapy will be required periodically on a lifelong basis.

A combination of surgical resection and chemotherapy may increase the chance of cure in patients who have focal lung disease and who can tolerate resection. Patients should be treated with an initial period of antimicrobial drug therapy prior to surgery to lessen the bacillary load.⁹ In three studies, patients who underwent surgical resection in addition to antimicrobial chemotherapy had improved microbiologic outcomes compared with those who received chemotherapy alone.^{57,167,174} As with MAC lung disease, surgery should be performed by thoracic surgeons experienced in performing this type of surgery.¹³¹

Mycobacterium abscessus lung infection has been considered a contraindication for lung transplantation in patients with CF; however, recent reports suggest that lung transplantation for patients with CF can be accomplished with success rates comparable to those of noninfected patients.^{175,176}

Therapy of *Mycobacterium abscessus* Skin, Soft Tissue, and Bone Infections. Serious infections should be treated with a regimen similar to that used for pulmonary disease. Skin and soft tissue infections should be treated for a minimum of 4 months and bone infections for 6 months. Surgery is generally indicated for extensive disease, for abscesses, or when drug therapy is difficult.⁹ Foreign bodies such as prosthetic joints, percutaneous catheters, and breast implants should be removed, and the patient treated with a prolonged antimicrobial treatment regimen.

Mycobacterium chelonae

M. chelonae is more likely to produce skin, soft tissue, and bone infections than pulmonary disease. Keratitis due to *M.*

chelonae has been associated with contact lenses and with ocular surgery such as laser-assisted in situ keratomileusis (LASIK).^{177,178} Disseminated disease has been reported in immunocompromised patients and usually presents with characteristic cutaneous lesions.¹⁷⁹ The clinical and radiographic presentation of *M. chelonae* pulmonary disease is similar to that of other RGM.

Isolates of *M. chelonae* are usually susceptible to tobramycin, the macrolides, linezolid, and imipenem.^{99,180,181} The *M. chelonae* genome does not include an active *erm* gene, indicating that in vitro susceptibility to macrolides has value in predicting in vivo responses to therapy.¹⁶⁸ Other active drugs may include amikacin, clofazimine, doxycycline, and the fluoroquinolones. *M. chelonae* isolates are uniformly resistant to ceftioxin. Treatment of *M. chelonae* infections should be based on in vitro susceptibility results. Administration of clarithromycin 500 mg twice daily for 6 months was reported to have a high cure rate in patients with cutaneous lesions associated with disseminated disease.¹⁸² The one patient who relapsed did so with a macrolide-resistant strain. Patients have also responded to linezolid with or without clarithromycin.^{183,184} Patients with serious skin, soft tissue, and bone infections should be treated similarly to those with *M. abscessus* disease. For corneal infections, both topical and oral agents are often used, and many patients may require corneal transplants for recovery of vision or for cure.

Mycobacterium fortuitum

M. fortuitum is responsible for up to 15% of RGM cases in the United States but is a relatively uncommon cause of lung disease except in patients with disorders associated with chronic aspiration.⁵⁷ Among 26 patients in the Republic of Korea with two or more positive cultures for *M. fortuitum*, only one was treated and none of the 25 untreated patients showed progression during a median follow up of 12.5 months.¹⁸⁵ The clinical and radiographic presentation of patients with pulmonary disease is similar to that of other RGM. Application of contemporary diagnostic guidelines must be used with caution and even with some skepticism when evaluating patients with *M. fortuitum* respiratory isolates. Skin, soft tissue, and bone infections are more common than pulmonary disease. Both sporadic and clustered outbreaks of furunculosis due to *M. fortuitum* (and other RGM) have been reported after exposure to contaminated water during pedicures.¹⁸⁶⁻¹⁸⁸

In contrast to *M. abscessus*, *M. fortuitum* demonstrates broader in vitro susceptibility to both oral and intravenous antimicrobial drugs, including the newer macrolides, the fluoroquinolones, doxycycline, minocycline, the sulfonamides, and two intravenous drugs, imipenem and ceftioxin.⁹ Although most isolates of *M. fortuitum* are susceptible in vitro to the macrolides, these drugs should be used with caution because of the presence of an inducible *erm* gene.¹⁸⁹

Mycobacterium fortuitum lung disease should be treated with at least two drugs to which in vitro susceptibility has been demonstrated.⁹ As with other NTM lung infections, treatment should be continued for at least 12 months of negative sputum cultures. Skin, soft tissue, and bone infections should be treated similarly to *M. abscessus* infections, although oral agents are more often effective.

THERAPEUTIC DRUG MONITORING

The role of therapeutic drug monitoring in management of NTM lung disease remains controversial. Low serum concentrations of clarithromycin have been reported when the drug is given in combination with rifampin.¹⁹⁰⁻¹⁹² A recent study examined the pharmacokinetic and pharmacodynamic relationships in 481 patients with MAC lung disease.¹⁹¹ This study reported that peak serum concentrations were below the target range for ethambutol in 48% of patients, clarithromycin in 56%, and azithromycin in 35%. Concurrent administration of rifampin reduced the mean serum concentration of clarithromycin by 68% and that of azithromycin by 23%. Pharmacodynamic indices (the desired ratio of serum concentrations to the minimal inhibitory concentration of the drug) were seldom met for rifampicin, clarithromycin, amikacin, and moxifloxacin. This study did not examine a possible correlation between clinical outcome and the poor pharmacodynamics indices. A study from South Korea reported that peak plasma concentrations of clarithromycin were lower in MAC patients who received daily or intermittent therapy when combined with rifampicin compared with *M. abscessus* patients who received clarithromycin without rifampicin.¹⁹² In this study, treatment outcomes were not associated with plasma drug concentrations; however, no attempt was made to increase the dosage in patients with low concentrations to determine whether outcomes would have improved. Thus, while the role of therapeutic drug monitoring remains to be defined in uncomplicated cases of NTM infection, it should be considered in patients who are failing therapy, have end-stage renal disease, or who are taking medications that are known to involve interactions with other drugs.

HYPERSENSITIVITY PNEUMONITIS-LIKE NONTUBERCULOUS MYCOBACTERIA PULMONARY DISEASE

Most reports describing the development of a typical pattern of hypersensitivity pneumonitis-like lung disease have been in patients with hot tub exposure, although similar clinical presentations have been associated with other indoor standing water sources and exposures.^{40,193,194} In one case report, hypersensitivity-like lung disease was observed in association with an indoor shower.⁴⁰ Some investigators have used the phrase "hot tub lung" to describe the presentation associated with standing water sources. In the cases of exposure to hot tubs, MAC has been the mycobacterial organism isolated from sputum, bronchoalveolar lavage, tissue, and hot tub water. Furthermore, when assessed by genotyping methods, MAC isolates from both the hot tub water and the lung specimens have demonstrated identical patterns. Controversy still exists, however, as to whether hot tub lung is an infectious process, inflammatory process, or a combination of the two.

Patients with hypersensitivity pneumonitis-like lung disease tend to be young and without preexisting lung disease. The clinical presentation can vary from mild respiratory symptoms to respiratory failure requiring mechanical ventilatory support.¹⁹⁵ Key elements to the diagnosis of MAC hypersensitivity-like lung disease include a compatible clinical history (subacute onset of respiratory symptoms,

hot tub exposure), characteristic radiographic findings, and MAC isolates in sputum, bronchoalveolar lavage, tissue, and hot tub water (with compatible histopathology when available).

The prognosis is generally excellent and independent of severity on presentation.¹⁹³ The greatest benefit is gained by simply removing the patient from further antigen exposure. In the case of hot tub lung, removal from antigen exposure generally involves drainage of hot tub water and complete avoidance of hot tub use. Whether continued exposure to ambient environmental MAC organisms can propagate the hypersensitivity pulmonary reaction is uncertain. For selected patients with hypersensitivity pneumonitis-like lung disease, use of systemic corticosteroids may be beneficial and promote recovery of pulmonary symptoms, gas exchange abnormalities, and radiographic abnormalities. Likewise, antimycobacterial therapy, with the same medications as for standard pulmonary MAC lung disease, may be required in some patients but for shorter durations of therapy, usually 3 to 6 months. Most patients can be expected to have nearly complete resolution of respiratory symptoms as well as of pulmonary function and radiographic abnormalities.

HEALTH CARE–ASSOCIATED NONTUBERCULOUS MYCOBACTERIA DISEASE AND PREVENTION OF NTM INFECTIONS

NTM are ubiquitous in the environment, so complete avoidance is difficult if not impossible. Compared with *M. tuberculosis*, NTM have low virulence for humans, so NTM disease may be more a problem with host susceptibility than with organism contact. With some notable exceptions discussed previously, the specific susceptibility of an individual patient to NTM infection may be impossible to determine with current knowledge of immunity and pathogenesis; accordingly, disease prevention remains problematic. It also remains unclear whether patients with known heightened susceptibility to NTM infection should be advised to avoid known environmental sources of NTM. For example, it is unclear whether susceptible patients should be advised not to take showers, which are known to be associated with aerosolized NTM.³⁹

Progress has been made in prevention of nosocomial NTM infections. Transmission of NTM in health care settings has most frequently been linked to tap (municipal) water exposure.⁹⁰ While various NTM species (including MAC, *M. kansasii*, *M. xenopi*, and *M. simiae*) have been isolated from municipal water supplies, *M. fortuitum* and *M. abscessus* have most often been implicated in health care–associated NTM disease. Even with use of potent disinfectants, including organomercurials, chlorine, bromine, 2% formaldehyde, and glutaraldehyde, NTM may persist on equipment or devices after tap water exposure. A large outbreak of *M. massiliense* in Brazil involved a single clone that was tolerant to 2% glutaraldehyde.¹⁹⁶ The inability to eliminate these organisms underscores the importance of avoidance of tap water for preventing health care–associated

NTM diseases, such as those following median sternotomy, plastic surgery procedures, liposuction, LASIK, dialysis, and the implantation of long-term central intravenous catheters, tympanostomy tubes, and prosthetic devices such as heart valves, knee and hip joints, lens implants, and metal rod bone stabilizers.⁹ Pseudo-outbreaks have involved bronchoscopes contaminated with *M. abscessus* and *Mycobacterium immunogenum*. Documented outbreaks of hygiene-associated *M. fortuitum* and *Mycobacterium magritense* furunculosis in association with use of contaminated whirlpool footbaths have been described in nail salons.^{188,197}

As a result of the increased understanding of environmental NTM reservoirs and reports linking the use of tap water to health care–associated NTM infections, it is recommended that tap water not be used in preparation of surgical procedures, prosthetics, and intravascular catheters; not be used in cleaning of fiberoptic endoscopes; and not be used to rinse the mouth out before collecting expectorated sputum samples. Moreover, recognition that alternative medicines or unapproved substances for injection may also be at risk of contamination by NTM warrants caution against use of these products as well.

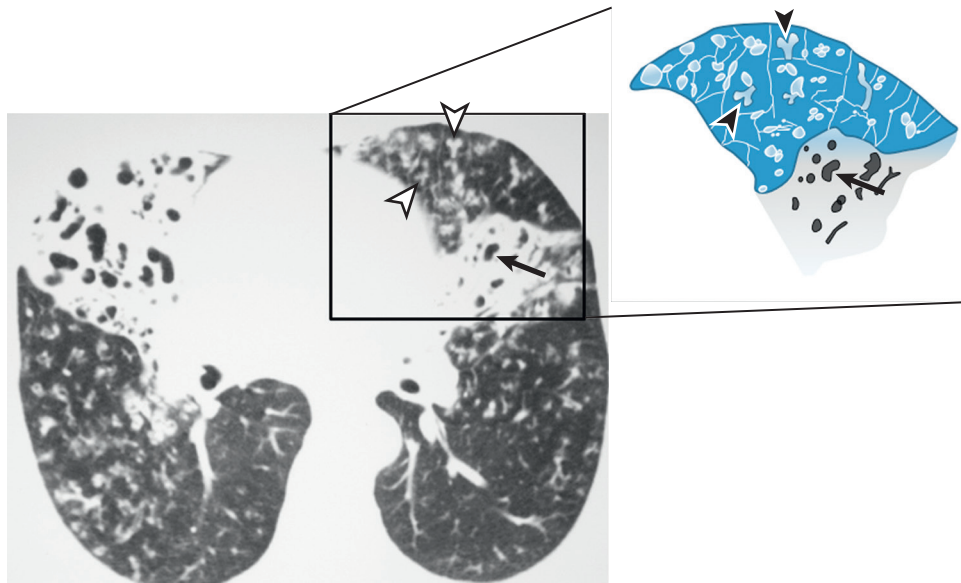
Key Points

- Nontuberculous mycobacteria (NTM) comprise more than 160 different species that are ubiquitous in the environment. Members of the *Mycobacterium avium* complex (MAC) are the most common causes of NTM lung disease.
- Infection develops after exposure to NTM in the environment; person-to-person transmission is exceptionally uncommon.
- Although there are fewer species of slowly growing NTM than rapidly growing species, the slow growers are more common causes of lung disease.
- Epidemiologic studies suggest that the prevalence of NTM infections is increasing in some areas of the world, including the United States.
- Risk factors for pulmonary NTM disease include underlying chronic lung diseases such as bronchiectasis, chronic obstructive pulmonary diseases, cystic fibrosis, alpha₁-antitrypsin deficiency, and prior tuberculosis.
- Diagnosis of pulmonary NTM infection requires that the patient meet certain clinical, radiographic, and microbiologic criteria.
- The recommended treatment for MAC pulmonary disease is a macrolide, plus ethambutol and a rifamycin, with or without an aminoglycoside, administered for at least 12 months of negative sputum cultures.
- Because of the critical importance of macrolides for the successful treatment of MAC, macrolide use should be avoided in patients who may require treatment for MAC in the future.
- The recommended treatment for *Mycobacterium kansasii* pulmonary disease is isoniazid (or macrolide), rifamycin, and ethambutol administered for at least 12 months of negative sputum cultures.
- Treatment of rapidly growing mycobacterial infections should be based on the results of in vitro drug susceptibility testing, but the clinical outcome varies significantly depending on the causative species.

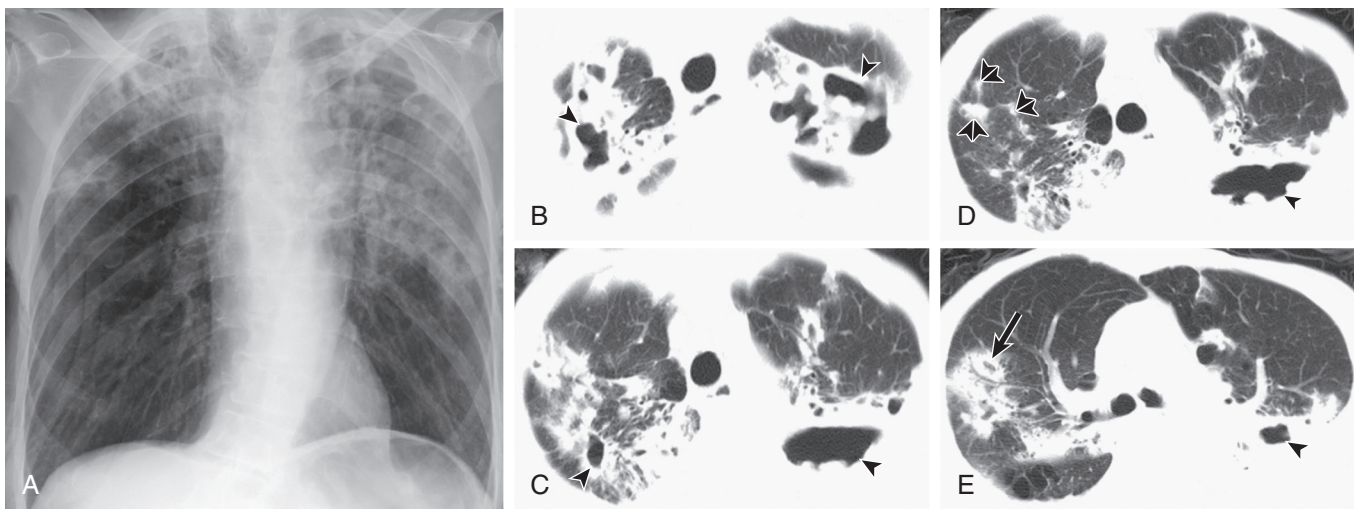
Complete reference list available at *ExpertConsult*.**Key Readings**

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eFIGURE IMAGE GALLERY



eFigure 36-1 Nodular/bronchiectatic *Mycobacterium avium* complex: high-resolution chest CT appearance. Axial high-resolution CT shows extensive bronchiectasis in the right middle lobe and lingula (arrow). Numerous small centrilobular nodules with branching configurations, representing “tree-in-bud” opacity (arrowheads), are present. *Inset:* Lingular CT findings. (Images modified from Gotway MB, Reddy GP, Webb WR, et al: High-resolution CT of the lung: patterns of disease and differential diagnoses. *Radiol Clin North Am* 43:513–542, 2005.)



eFigure 36-2 *Mycobacterium kansasii* pulmonary infection. **A**, Frontal chest radiograph shows multifocal areas of nodular consolidation and cavitation bilaterally. **B–E**, Axial chest CT displayed in lung windows shows extensive complex cavitation (arrowheads), variably sized nodules (double arrowheads), and areas of consolidation (arrow). (Courtesy Michael Gotway, MD.)

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INTRODUCTION

HISTOPLASMA

History and Epidemiology

Pathogenesis

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COCCIDIOIDOMYCOSIS

History and Epidemiology

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SPOROTRICHOSIS

PENICILLIOSIS

Detailed information on antifungal drugs and their clinical use is available in Chapter 38, *Opportunistic Mycoses*.

more than a year of treatment, and lifelong therapy may be required in the setting of irreversible immunodeficiency.

INTRODUCTION

Geographically restricted (or endemic) mycoses include histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis, and penicilliosis. Of these, histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis have the most defined geographic distributions in the Americas (Fig. 37-1). These are considered *dimorphic* pathogens because they grow as mycelium in nature and undergo morphogenesis into yeasts or spherules upon acquisition by humans. These phases can be reproduced in the laboratory by cultivation at low (approximately 25°C) or high (37°C) temperatures, respectively. Hence, these fungi are termed “thermally dimorphic.” Acquisition is typically via inhalation of spores or mycelial fragments, although sporotrichosis is most commonly initiated by skin puncture. The mycelia produce spores that are situated external to the fungus and are easily aerosolized when disturbed; these spores (e.g., conidia, macroconidia, microconidia or arthroconidia) are thought to be the infectious agents and inhalation of these spores lead to pulmonary disease. The severity of clinical illness is linked to the quantity of the inoculum as well as the susceptibility of the individual. Defects in cellular immunity are associated with more severe disease. Latent infections can reactivate in individuals whose immune responses have been compromised, such as by steroids, inhibition of tumor necrosis factor, chemotherapy, or *human immunodeficiency virus* (HIV). The geographically restricted mycoses are often overlooked as etiologies of infectious diseases such as community-acquired pneumonia; for example, it is not uncommon for these patients to receive several antibacterial antibiotics for suspected anaerobic infections before histoplasmosis is diagnosed.¹ This is due to clinical disease manifesting in geographic regions where the fungi are uncommon or absent, leading to delays in recognition and treatment. Treatment of these diseases requires several months to

HISTOPLASMA

HISTORY AND EPIDEMIOLOGY

Histoplasma capsulatum is a dimorphic fungus primarily acquired via respiratory exposure that is responsible for approximately 500,000 infections annually in the United States, which makes it the most prevalent cause of fungal pulmonary disease.² Similarly, these calculations also indicate that nearly 50 million North American residents are latently infected with the fungus. The fungus is endemic worldwide, although there are areas with a high incidence of disease. The Ohio and Mississippi River Valleys in the United States are a highly endemic region and skin testing has shown that up to 90% of adults in these regions have been exposed to the fungus.^{3,4} High endemicity areas are also present in Latin America, particularly within Brazil, Venezuela, Ecuador, Paraguay, Uruguay, and Argentina. For example, the prevalence in Midwestern and Southeastern portions of Brazil has been reported as approximately 63% and 93%, respectively.⁵

The most recent data on rates of clinically significant disease in the United States are from an extraction of data from the Nationwide Inpatient Sample, a database of diagnostic codes of diseases, for the year 2002.⁶ This methodology likely underestimates the incidence of hospitalizations for histoplasmosis or other endemic mycoses due to diagnostic difficulties and incomplete coding. Nevertheless, in 2002, there were 3259 adults (60% male, 40% female) and 111 children (42% male, 58% female) hospitalized with histoplasmosis. The majority of patients were not known to have an underlying immunodeficiency, with only 14% of adults having an immune defect while 32% of children were considered immunocompromised. In-hospital mortality rates were 8% and 5% for adults and children, respectively. Hence, there are approximately 270 deaths due to *H. capsulatum* annually in the United States. For comparison,

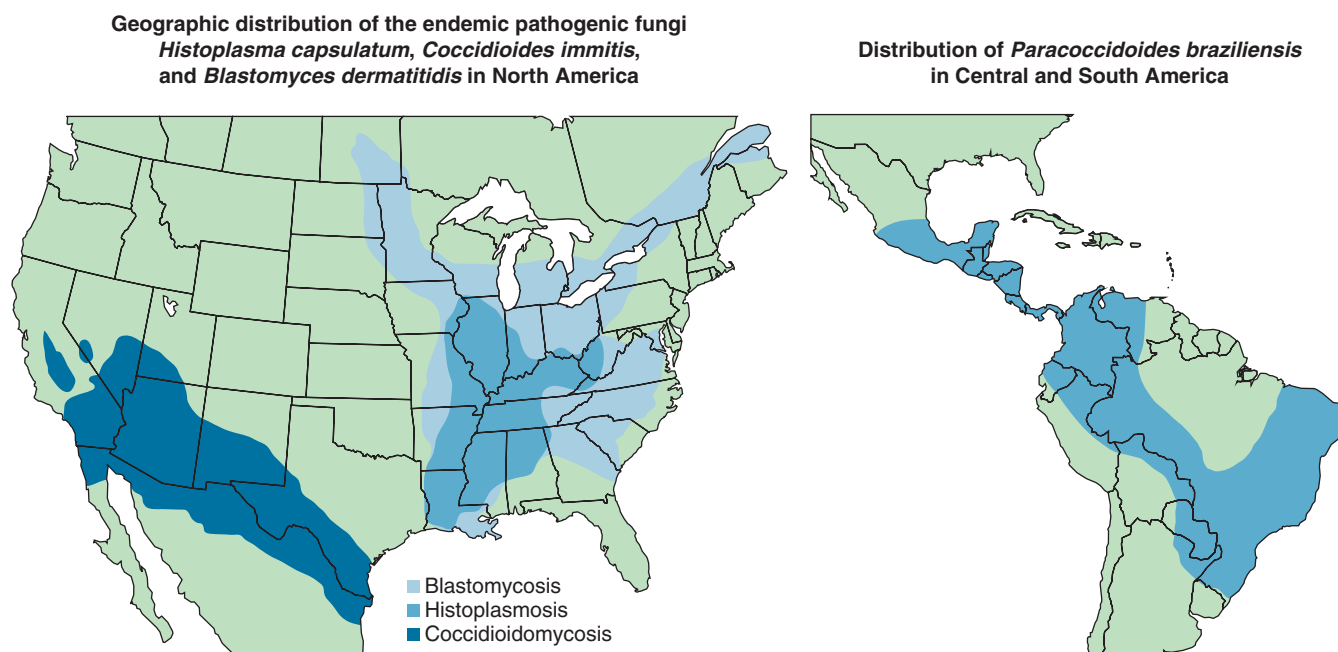


Figure 37-1 Geographic distribution of the endemic fungi in the Americas. In North America, the regions where histoplasmosis, coccidioidomycosis, and blastomycosis are endemic are shown. In South America, the region where paracoccidioidomycosis is found is shown. Note that histoplasmosis and coccidioidomycosis can also be found in Central and South America; however, blastomycosis and paracoccidioidomycosis appear to be limited to either North or South America, respectively.

in 2009 (the most current complete U.S. death statistics), 529 deaths were due to tuberculosis (405 due to respiratory tuberculosis), 99 due to meningococcal infection, 26 due to salmonellosis, and 3 due to malaria.⁷

The genus *Histoplasma* was designated in 1906 by Samuel Darling who described the fungus in the lungs, liver, spleen, and lymph nodes of a carpenter from Martinique working on the Panama canal.⁸ Darling incorrectly characterized the 1- to 4- μ m intracellular ovoid yeast as protozoa, similar to *Leishmania* sp. Subsequent to the identification of *H. capsulatum* by Darling, several varieties of *Histoplasma* were identified, with distinct geographic or host niches. More recently, analysis of sequence diversity of four protein-coding genes of *H. capsulatum* revealed that the different varieties of *Histoplasma* are not phylogenetically distinct and that *H. capsulatum* comprises seven phylogenetic species, which radiated rapidly from a single ancestor between 3 million and 13 million years ago.⁹

PATHOGENESIS

H. capsulatum exists in either a filamentous or yeast form, depending mainly on temperature and nutritional conditions.¹⁰ In the environment and at ambient temperatures, *H. capsulatum* is mycelial. This saprophytic mold grows particularly well in soils enriched with organic nitrogen sources, such as areas contaminated with bird or bat droppings. Hyphal elements are 1.25 to 2 μ m in diameter and produce two types of spores called conidia: thick walled macroconidia (8- to 15- μ m diameter) and microconidia (2- to 5- μ m diameter). Both conidial forms are produced singly at the tips of narrow, short conidiophores that branch at right angles to vegetative hyphae. The microconidia are the purported infectious particle, in that their size is

most effective for aerosolization and subsequent inhalation and deposition into distal lung structures. Environmental disturbances, especially construction or tree removal, are highly associated with aerosolization of *H. capsulatum*. At 37°C or in human tissues, the yeast form is the predominant morphology. Yeast cells have thin walls and are oval with diameters from 2 to 5 μ m. The cells reproduce by polar budding with a narrow bridge between the mother and daughter cells. Rarely, it is possible to find both yeast and mycelial forms in lung tissues¹¹ as well as on endovascular devices.¹²

Histoplasmosis is initiated by inhalation and deposition of microconidia within alveoli. This event is followed by conversion of microconidia to the yeast form,¹³ which begins within several hours to a few days.¹⁴ Morphogenesis is initiated by the shift in temperature and availability of nutrients. Notably, despite the species name, the cells lack a capsule. During primary infection, the yeast cells are phagocytosed into the endosomal compartment of phagocytes and these infected host cells then migrate to hilar and mediastinal lymph nodes and subsequently disseminate hematogenously, distributing the fungus into diverse tissues. In fact, autopsy studies have found that approximately 70% of individuals with history of histoplasmosis have splenic granulomas.¹⁵ The incubation period for disease manifestations is typically 8 to 17 days, although heavy exposure may result in disease in as little as 3 days.¹⁶

It is understood that effective control of histoplasmosis requires activation of cellular immunity in concert with innate responses, because the absence of intact immunity leads to disseminated, progressive disease.¹⁷ Additionally, impairment of cellular immunity in latently infected individuals can result in the reactivation of previously controlled foci of infection. Although significantly less common

in the current era of effective antiretroviral medications, individuals with *acquired immunodeficiency syndrome* (AIDS) are at high risk for reactivation disease (see Chapter 90). Histoplasmosis also reactivates in patients receiving anti-cytokine therapies.¹⁸ Reactivation disease has also been documented in liver transplant recipients with disease originating from latent infections in the transplanted organs,¹⁹ and disease is associated with a high incidence of graft loss and mortality.

Neutrophils are considered primary responders to *H. capsulatum* in the lung²⁰; however, the majority of yeast are found within immature dendritic cells on the first day after experimental pulmonary infection of mice. In the same murine model, neutrophils predominate for several days thereafter. Human neutrophils effectively inhibit the fungus, and azurophilic granules are responsible for this fungistatic effect.²¹ Resident and inflammatory macrophages contain significant numbers of yeast cells by 3 days after experimental infection and yeast cells are primarily in inflammatory macrophages by the end of the first week. Although experimental systems have shown that murine dendritic cells and macrophages fail to control replication and facilitate dissemination, human dendritic cells and macrophages, especially activated macrophages, can efficiently kill *H. capsulatum* yeast cells.²² Moreover, human dendritic cells can inhibit conidial germination,²³ which can modify subsequent disease progression by presenting fungal antigen to CD8⁺ T cells. Several experimental studies have suggested that CD8⁺ T cells are instrumental in initial clearance of *H. capsulatum* yeast cells, whereas CD 4⁺ T cells are required for survival.¹⁷ The role of antibody in histoplasmosis is controversial, although monoclonal antibodies have been shown to modify the pathogenesis of disease.^{24,25} Consistent with a key role for B cells in histoplasmosis is the finding that depletion of B cells significantly enhances the severity of disease.²⁶

Among the many innate elements engaged in augmentation of protective immunity to *H. capsulatum* are several cytokines, including interleukin-12, *tumor necrosis factor* (TNF)- α , granulocyte macrophage colony-stimulating factor,²⁷ and interferon- γ .¹⁷ The ability of lymphocytes and phagocytes to produce these cytokines constitutes a major effector mechanism of host resistance. The critical role of TNF is underscored, as described earlier, by the association of inhibition of this cytokine and the development of severe histoplasmosis. The lack of TNF is thought to diminish control of intracellular growth of the fungi and leads to dysregulation of granulomas containing *H. capsulatum* yeast cells and/or an inability to form new granulomas. In the setting of intact immunity, granuloma formation can be caseating and indistinguishable from that caused by *Mycobacterium tuberculosis*. As in tuberculosis, healing of granulomas can also result in calcification of lesions, especially in lymph nodes and in the liver and spleen.¹⁵

CLINICAL MANIFESTATIONS

The severity of histoplasmosis is closely linked to the number of spores inhaled, the virulence of the infecting strain, and the immunologic status of the exposed individual.²⁸ The most common presentation is pneumonia, although the disease may involve virtually any tissue and can manifest as a fulminant life-threatening disseminated sepsis. Low

inoculum infection results in development of self-limiting disease in 1% of individuals, while 99% have subclinical infection.²⁹ In contrast, high inoculum infection leads to symptomatic disease in 50% to 100% of exposures.³⁰ Therefore, infection usually results in a mild, often asymptomatic respiratory illness, but may progress to life-threatening systemic disease, particularly in immunocompromised individuals. In the setting of HIV infection, disseminated histoplasmosis has been considered an AIDS-defining illness, although the prevalence of histoplasmosis in individuals with HIV has diminished with currently available antiretroviral regimens.

Acute Histoplasmosis

As noted, the most common outcome after exposure to *H. capsulatum* is an asymptomatic infection. However, 1 to 3 weeks after acquisition, acute disease can manifest.³¹ Symptomatic histoplasmosis typically presents as a flulike illness with the rapid onset of fever, chills, headache, myalgia, nonproductive cough, and chest pain. Chest radiographs are generally unrevealing, although mediastinal lymphadenopathy with (Fig. 37-2A) or without opacities may be present. However, approximately 1 in 2,000 adults will develop acute progressive pneumonia,³² associated with a heavy exposure to *H. capsulatum*.³³ In acute disease, approximately 10% of patients have rheumatologic symptoms, such as arthritis or severe arthralgia accompanied by erythema nodosum.³⁴ Additionally, pericarditis can develop in approximately 10% of patients with acute disease,³⁵ although pericarditis is typically a late manifestation after the resolution of pulmonary symptoms. Uncommonly, lymph node enlargement may cause compression of mediastinal structures.³⁶ Although resolution is typical, surgical decompression may be required to alleviate esophageal compression or endovascular stenting may be needed to prevent superior vena caval occlusion. Mediastinal fibrosis (eFig. 37-1) is a rare postinfectious complication that is perceived to be due to an abnormal inflammatory response to residual *H. capsulatum* antigens; this disease is more common in individuals with an HLA-A2 allele.³⁷ Steroids or antifungal agents are not useful in mediastinal fibrosis and surgery has not proven to be particularly effective, although endovascular stenting has been reported to alleviate vascular complications.³⁸ The majority of patients with acute pulmonary histoplasmosis recover over several weeks without sequelae, although occasional patients complain of fatigue persisting for months. Subsequent radiographs may appear normal or demonstrate a single calcified (eFig. 37-2) or noncalcified nodule or “coin” lesion, or a miliary pattern of calcified granulomas indistinguishable from that found in certain tuberculosis patients¹⁶ (Fig. 37-3). The miliary appearance is more common in disease associated with a high inoculum exposure. Although it is well recognized that pulmonary coin lesions can be sequelae of histoplasmosis, surgical resections continue due to suspicion of neoplasm.³⁹ Positron emission tomography may be of limited value, because they can display enhanced uptake in histoplasmosis nodules.⁴⁰

Disseminated Histoplasmosis

H. capsulatum can rapidly spread throughout an infected host because the fungus is transported intracellularly by

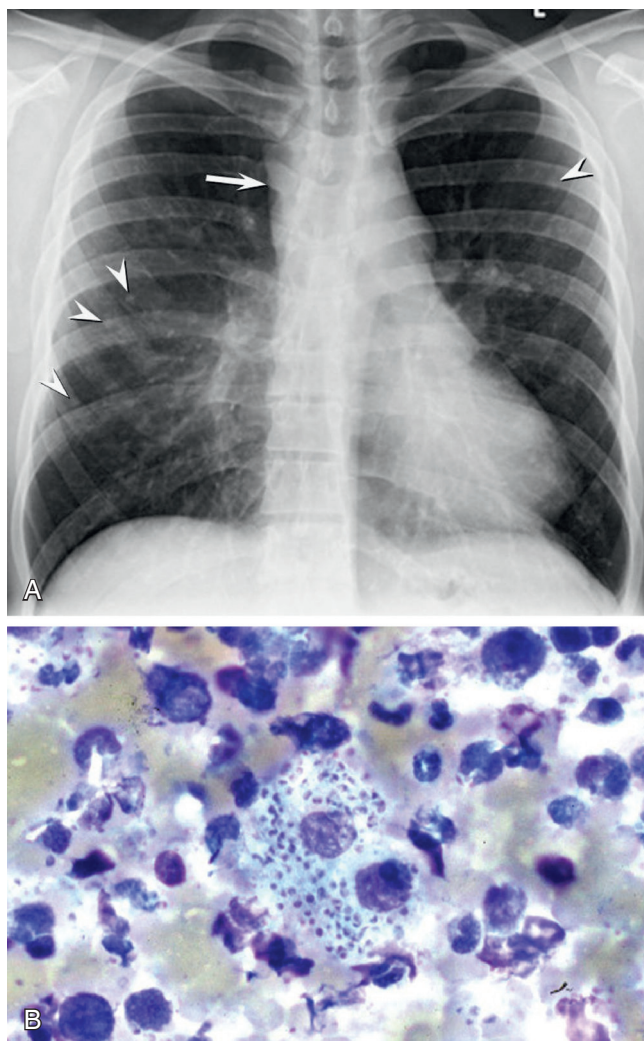


Figure 37-2 Acute histoplasmosis. **A**, Frontal chest radiograph in a patient with acute histoplasmosis shows numerous bilateral small nodules (arrowheads) and right paratracheal lymphadenopathy (arrow). **B**, Photomicrograph of bone marrow biopsy specimen shows abundant small yeast in macrophages. There were no well-formed granulomas. (Wright stain; original magnification $\times 450$.) (**A**, Courtesy Michael Gotway, MD.)

phagocytes from the lungs via the hilar lymphatics into the systemic circulation.²⁰ Although this process is controlled in most infected patients, histoplasmosis becomes systemic in approximately 0.05% of individuals after exposure.³² Histoplasmosis (eFig. 37-3) most commonly disseminates in individuals with preexisting immunosuppression largely due to malignancy, corticosteroid use, or AIDS. Clinical manifestations of disseminated histoplasmosis can vary from indolent to fulminant. Patients typically present with fever, weight loss, and respiratory symptoms. Patients often have hepatomegaly and/or splenomegaly. Cutaneous and mucous membrane lesions are not uncommon, and patients should be considered to have disseminated disease if *H. capsulatum* is isolated from these sites. Patients with acute disease often have anemia, thrombocytopenia, leukopenia, and abnormal liver function tests as well as coagulopathies.⁴¹ The majority of patients have diffuse pulmonary opacities, but chest radiographs can be unrevealing in approximately 30% of patients.⁴² The central nervous system is involved in 10% to 20% of cases.⁴³ Endovascular

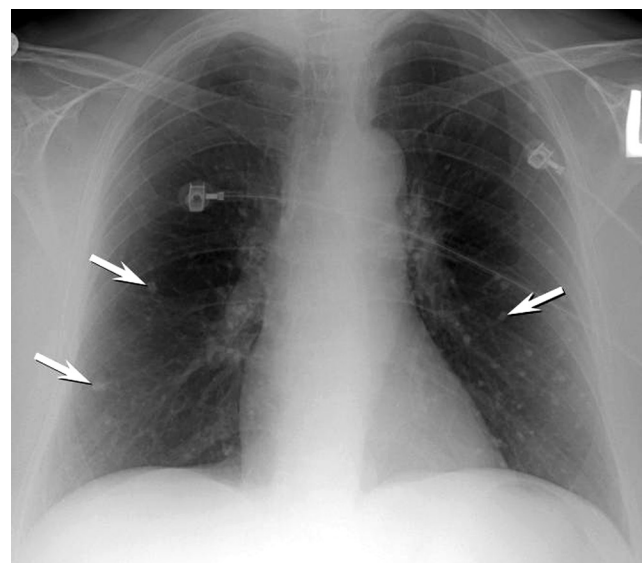


Figure 37-3 Multiple calcified pulmonary granulomas due to histoplasmosis. Frontal chest radiograph shows numerous small calcified nodules (arrows) bilaterally due to previous disseminated histoplasmosis. (Courtesy Michael Gotway, MD.)

disease is not common but, interestingly, mycelial as well as yeast forms can be present in the vegetation.¹² Adrenal dysfunction may develop in approximately 50% of patients with disseminated histoplasmosis and is variably reversible with antifungal drug treatment.⁴⁴ Mucocutaneous involvement is uncommon in immunocompetent individuals, but may present as an ulcerated lesion, especially of the skin, oral mucosa, and/or gastrointestinal tract. Acute progressive disease is lethal without treatment.

Chronic Pulmonary Histoplasmosis

Chronic respiratory illness can develop in individuals with long-standing lung diseases, particularly emphysema or chronic obstructive lung disease, who acquire *H. capsulatum*. The disease can manifest after acute infection or due to reactivation of previously latent infection. Chronic histoplasmosis is characterized by indolent, progressive lung opacities, fibrosis, and cavitation⁴⁵ (Fig. 37-4). The majority of patients present with complaints of fever, weight loss, increasingly severe cough, and dyspnea, a presentation clinically and radiographically similar to that of cavitary tuberculosis.⁴⁶ Without therapy, the disease progresses in approximately 50% of affected individuals.⁴⁵

Transmissibility

In general, *H. capsulatum* is not contagious via the person-to-person route.⁴⁷ However, *H. capsulatum* has been transmitted to transplant recipients in the transplanted organ.⁴⁸ Reactivation disease can develop during immunosuppression in transplant recipients with latent infection with *H. capsulatum*. However, the risk for reactivation during immunosuppression is low ($<0.5\%$), even in high-risk groups such as renal or bone marrow transplant patients.⁴⁹ It is also worth noting that the mycelial growth of *H. capsulatum* is extremely hazardous to laboratory workers. The ability of the spores to disseminate widely and cause disease has recently been highlighted by a report of epidemic disease due to poor air filtration in buildings within a medical

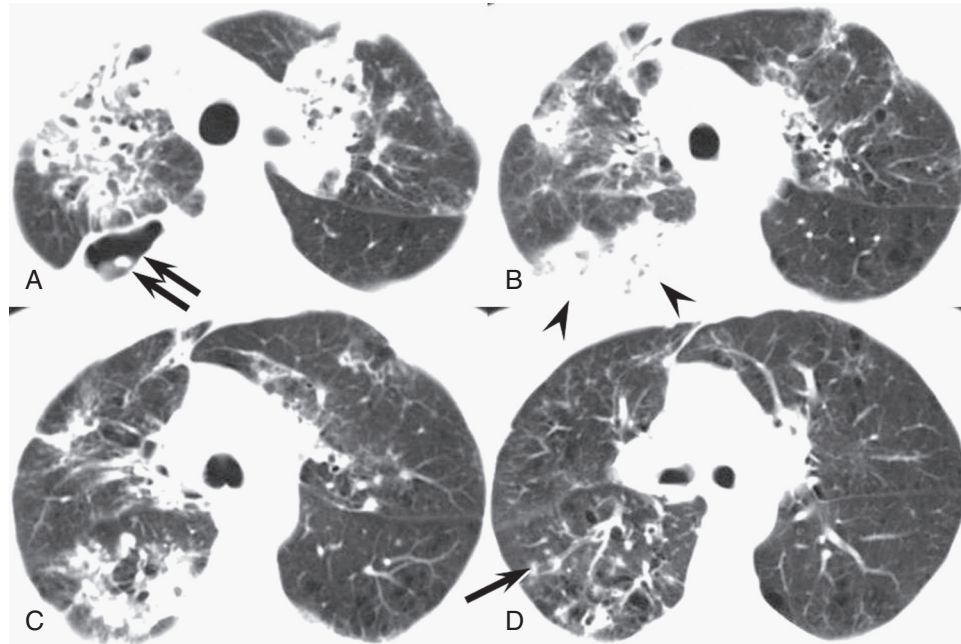


Figure 37-4 Chronic histoplasmosis. Axial chest CT (A–D) shows upper lobe bronchovascular thickening with architectural distortion and areas of consolidation (arrowheads, B). Small nodules (single arrow, D) are also present. A cavity (double arrows, A) is present within the right upper lobe. The appearance closely resembles postprimary tuberculosis. (Courtesy Michael Gotway, MD.)

school in Texas.⁵⁰ Biosafety level 3 precautions are indicated when processing *H. capsulatum* mold cultures, soil, or other material potentially contaminated with conidia. In the diagnostic laboratory, biosafety 2 precautions are appropriate for the yeastlike form.

DIAGNOSIS

The “gold standard” for diagnosis is culture of *H. capsulatum*; however, this process takes a minimum of 1 week and growth may not be detected for approximately 1 month. Moreover, *H. capsulatum* is cultured from respiratory samples in fewer than 50% of patients with acute pulmonary histoplasmosis.⁵¹ In contrast, cultures are positive in 65% to 85% of patients with chronic pulmonary histoplasmosis. These data are complicated by the fact that studies have not critically examined the relative worth of different respiratory samples, although bronchoscopy with biopsy may provide the most effective testing mechanism because it can allow rapid visualization of the fungus in the tissue (see Fig. 37-2B). Direct observation of the fungus in respiratory secretions has high specificity but low sensitivity, and may be difficult because the fungus is located within macrophages. In disseminated disease, the fungus is usually detectable in bone marrow aspirates⁵² and can even be identified in peripheral blood, especially in buffy coats.⁵³

In the absence of positive cultures, serologic techniques such as immunodiffusion,⁵⁴ complement fixation,⁵⁵ enzyme immunoassay,⁵⁶ and radioimmunoassay⁵⁷ have been used to provide immunologic evidence of *H. capsulatum* infection. These serologic tests for the detection of either antibodies and/or antigen in clinical specimens (e.g., serum or urine) offer a rapid alternative method for the diagnosis of histoplasmosis (see Chapter 17). Although promising, polymerase chain reaction or mass spectroscopy methodologies

for detecting *H. capsulatum* are not yet developed for routine use. Skin testing with *H. capsulatum* antigens is not recommended for purposes other than epidemiologic studies.

In the United States, histoplasmosis is commonly diagnosed by antigen detection. *H. capsulatum* polysaccharide antigen can be detected by enzyme-linked immunosorbent assay (ELISA) in the urine of 92% of patients with disseminated histoplasmosis, 83% with acute disease, and 88% with chronic pulmonary histoplasmosis.⁵¹ Additionally, antigen can frequently be detected in the serum of patients with disseminated disease, suggesting that testing of both urine and blood will increase the sensitivity of testing. Testing of bronchoalveolar lavage fluid or cerebrospinal fluid can lead to the diagnosis of pulmonary or meningeal histoplasmosis, respectively. The assay is useful for following response to therapy and evaluating for disease relapse. The current *Infectious Diseases Society of America* (IDSA) guidelines recommend following antigen levels during and after treatment of histoplasmosis.⁵⁸ However, existing antigen assays may also detect related antigens from other endemic fungi, indicating that their interpretation must be undertaken in the context of other diagnostic information.⁵⁹

At present, the aforementioned tests are costly and impractical for use in less economically developed countries. A mainstay of diagnosis in many regions is an immunodiffusion test for detection of H and M precipitin bands utilizing *histoplasmin* (HMIN) as the antigen; HMIN is a well characterized antigen secreted by *H. capsulatum* mycelia and yeast.⁶⁰ The H antigen is a β -glucosidase⁶¹ and the M antigen is a catalase.⁶² Antibodies to these antigens can be detected by approximately 1 month after infection. The M band is detectable in approximately 75% of patients and can persist for years, whereas antibodies to the H antigen can be identified in less than 25% of patients and are undetectable after 6 months.⁶³ Complement fixation tests use

both HMIN and intact yeast cells, and this reaction becomes positive by approximately 3 weeks of disease and can persist for months to years.⁶⁴ A titer of 32 or greater is strongly suggestive of acute disease, although a titer of 8 in a patient with a high suspicion of histoplasmosis is consistent with disease. Titers are nondiagnostic in approximately 30% of patients with acute histoplasmosis and in 50% with disseminated disease. Most laboratories perform both the immunodiffusion and complement fixation tests concurrently to increase sensitivity. In immunocompromised patients with histoplasmosis, specific antibodies to the disease cannot be routinely detected, making these tests less sensitive in this population.⁶⁵

ELISA assays for the detection of antibodies in sera using HMIN have been established. ELISAs using HMIN compared to deglycosylated HMIN have sensitivities and specificities of 57% and 93% versus 92% and 96%, respectively.^{5,56} Treatment of purified HMIN with metaperiodate may further improve the utility of ELISA.⁶⁶

TREATMENT

Detailed information on antifungal drugs and their characteristics and uses is available in Chapter 38.

Comprehensive treatment recommendations for histoplasmosis have been made by the American Thoracic Society in 2011⁶⁷ and the IDSA in 2007.⁵⁸ The majority of individuals who acquire *H. capsulatum* are either asymptomatic or have a mild, self-limited flulike illness. Unless the patient is immunocompromised, there is no need for urgent administration of antimycotics under these circumstances.⁶⁸

Mild to Moderate Acute Pulmonary Histoplasmosis

If a patient has been symptomatic for more than 3 weeks or if a patient has moderate disease, itraconazole is appropriate. Itraconazole should be given as a loading dose of 200 mg thrice daily for 3 days followed by 200 mg twice daily for 6 to 12 weeks. Voriconazole and posaconazole can be considered for use in patients not responding to itraconazole.⁶⁹⁻⁷¹ Ketoconazole and fluconazole are less effective than itraconazole. Echinocandins should not be used to treat *H. capsulatum*.⁷²

Moderately Severe to Severe Acute Pulmonary Histoplasmosis

Compared to itraconazole, liposomal amphotericin is more effective in clearance of *H. capsulatum* in experimental histoplasmosis.⁷³ Liposomal amphotericin is favored over the conventional, deoxycholate formulations because the encapsulated liposomal amphotericin has less toxicity and a survival benefit has been shown with liposomal amphotericin compared to the conventional formulation in HIV/AIDS patients with histoplasmosis.⁷⁴ Liposomal amphotericin should be administered at 3 to 5 mg/kg daily for 1 to 2 weeks followed by itraconazole 200 mg thrice daily for 3 days and then 200 mg twice daily for 12 weeks. If liposomal amphotericin is not available, 0.7 to 1 mg/kg conventional amphotericin should be used. In patients with hypoxemia or significant respiratory distress, corticosteroids should be considered, particularly in HIV-infected individuals receiving antiretroviral therapy who are at risk for immune

reconstitution syndromes.⁷⁵ Methylprednisolone 0.5 to 1 mg/kg can be administered intravenously for the first 1 to 2 weeks together with antifungals. Alternatively, prednisone 40 to 60 mg/day can be given orally.

Chronic Cavitary Histoplasmosis

Itraconazole should be given as a loading dose of 200 mg thrice daily for 3 days followed by 200 mg twice daily for a minimum of 1 year. Extending treatment to 18 to 24 months may reduce the likelihood of disease recurrence due to relapse, which otherwise happens in approximately 15% of patients. Critically ill patients may benefit from initial treatment with amphotericin.⁷⁶

Disseminated Histoplasmosis

Treatment should be initiated with liposomal amphotericin, if available, for 1 to 2 weeks followed by itraconazole. Treatment should be continued for a minimum of 1 year. Occasionally, disseminated disease can be diagnosed in patients who have only mild to moderate symptoms. In immunocompetent individuals, itraconazole can be considered for initial therapy.

Immunocompromised Patients

Therapy with itraconazole 200 mg once or twice daily should be continued in immunocompromised patients whose immunosuppression cannot be reversed. In patients with HIV, therapy should be continued lifelong unless CD4 counts can be restored to levels greater than 200/ μ L.^{76a} Patients on maintenance itraconazole should have *Histoplasma* antigen testing performed periodically.

Drug Monitoring

Due to variable bioavailability, serum levels of itraconazole should be measured at 2 weeks of therapy and then every 3 to 6 months while on therapy.⁷⁷ Similarly, if voriconazole is being used as salvage, voriconazole levels should be monitored.⁷⁸

Management of Complications

Symptomatic pericarditis during acute histoplasmosis is generally managed with administration of nonsteroidal medications. Pericardiocentesis should be performed if hemodynamic compromise is present. In patients with hemodynamic compromise or persistent symptoms despite nonsteroidal therapy, prednisone should be administered and tapered over approximately 2 weeks. Patients treated with steroids should receive antifungal treatment, such as itraconazole for 6 to 12 weeks. Broncholithiasis (eFig. 37-4) is an uncommon condition in which a calcified lymph node erodes into the airway causing wheezing, dyspnea, or hemoptysis. If the patient fails to expectorate the broncholith, bronchoscopic removal may be required⁷⁹ and, rarely, if severe obstruction, fistulization, or massive hemoptysis develops, surgery is necessary.⁸⁰ No antifungal treatment should be administered for patients with broncholithiasis in the absence of other findings. Mediastinal lymphadenitis usually does not require treatment but, if there is severe disease with complications due to compression, patients should receive steroids and itraconazole. While there is no effective medical treatment for fibrosing mediastinitis, if it is unclear whether a patient has fibrosing mediastinitis or

mediastinal granulomatous disease due to *H. capsulatum*, then itraconazole should be administered at 200 mg orally once or twice a day for 12 weeks. Rheumatologic syndromes such as erythema nodosum are also generally managed with nonsteroidal therapy. However, if symptoms do not remit, prednisone and itraconazole should be given. No antimicrobial therapy is necessary when biopsy of a nodule incidentally shows *H. capsulatum* in an asymptomatic individual, especially when the fungus is not able to be cultured.

COCCIDIOIDOMYCOSIS

HISTORY AND EPIDEMIOLOGY

Coccidioidomycosis is a primary pulmonary infection caused by two species of *Coccidioides*, *C. posadasii* and *C. immitis*, which are endemic to the Central Valley of California, southwestern United States, and Central and South America where there are arid to semiarid life zones. The association of *Coccidioides* with human disease was first made by observing symptoms traditionally associated with “Valley fever” in a medical student exposed to a culture of the fungus in a laboratory. In the United States, it is estimated that approximately 150,000 persons are infected annually and that approximately 50,000 of these develop symptomatic disease.⁸¹ California and Arizona actively track cases of coccidioidomycosis and both states have reported significant increases in disease rates over the past decade,⁸¹ with Arizona having the most cases. In 2009, there were 10,233 laboratory-confirmed cases of coccidioidomycosis (155/100,000 population) reported in Arizona. Data from 2011 in California indicates that *Coccidioides* caused 5 hospitalizations/100,000 population.^{81a} It is also estimated that these fungi are responsible for approximately 2200 hospital admissions in the United States with an in-hospital mortality rate of 6% to 8%.⁶

Acquisition of the fungus is associated with disturbances of the soil. Purportedly, hyphae grow in moist soil and viable arthroconidia exist for protracted periods during dry periods. The fungus is thought to grow to a depth of approximately 8 inches. Arthroconidia are frequently aerosolized due to agriculture, excavation, or construction; individuals participating in these activities are at high risk for coccidioidomycosis in endemic regions. Additionally, soldiers marching behind tanks or other vehicles are at significant risk for inhalation of arthroconidia. Especially valuable insight into the epidemiology of coccidioidomycosis was obtained following an earthquake that caused landslides in a mountain range and dispersal of large dust clouds to a nearby community in Southern California in 1994.⁸² As an isolated exposure, limited in space and time, the transient dispersal of dust containing *Coccidioides* arthrospores revealed a clear dose dependence between exposure and disease rate (disease was highest in those closest to the source of dust clouds and that spent the longest time in dust clouds). In addition, when adjusted for exposure dose, symptomatic disease was more frequent in those older than 40 years of age. Individuals with advanced HIV infection or patients on corticosteroids or other immunosuppressants are at increased risk for severe disease. Disseminated disease

is also more likely in women in their third trimester of pregnancy and may be more likely in individuals of Filipino or African descent.⁸³

Disease is indistinguishable between the two species of *Coccidioides*. The two species were separated due to careful phylogenetic studies demonstrating divergence between the historically well described species *C. immitis* and the newer named species, *C. posadasii*.⁸⁴ There are certain phenotypic differences, such as differential growth rates under stress conditions, but they are morphologically indistinguishable and routine laboratory testing does not separate the species. Initially, *C. immitis* was defined as limited to the San Joaquin Valley in California whereas *C. posadasii* was present diffusely throughout the endemic regions detailed for the fungus; more recent data suggest that there is significant overlap in the distribution of the two species.

Coccidioidomycosis was first described in 1892 by Alejandro Posadas in an Argentinian soldier.⁸⁵ The organism was initially thought to be a protozoan of the order Coccidia, leading to its name. *Coccidioides* was not confirmed as a fungus until 1900.⁸⁶

PATHOGENESIS

The specialized spores, arthroconidia, arise from hypha and form chains of cells. The arthroconidia are 2 to 4 $\mu\text{m} \times 5$ to 6 μm ovoid cells, and the chain usually consists of an intact multinucleate arthroconidia alternating with a degenerated cell. The thinner wall of the degenerated cell is readily disrupted when the chain is disturbed, such as during a wind storm, landslide, or construction, and individual or small collections of arthroconidia can then be aerosolized and subsequently inhaled.⁸⁷ The arthroconidia undergo morphogenesis in humans or under specialized laboratory conditions at 37°C into a unique structure, a spherule. An arthroconidia converts to a spherule over approximately 2 to 4 days with the arthroconidia first developing into a round cell. Then, the spherule forms by successive growth and segmentation into an oval structure of 20 to 150 μm in diameter that contains dozens to hundreds of 2- to 4- μm endospores (Fig. 37-5F). Rupture of mature spherules leads to the release of endospores that, in the absence of effective host immunity, can develop locally into spherules or disseminate through hematogenous or lymphatic routes to cause disease in other tissues. Notably, arthroconidia and septate hyphae can be identified in some patients with chronic disease, especially those with diabetes, in whom there is low oxygen tension and tissue necrosis.

Coccidioides cause disease in immunocompetent or immunocompromised individuals, with disease severity typically being worse in immunodeficient patients.⁸⁸ Initial host responses to arthroconidia include influxes of both macrophages and neutrophils. Neutrophils may stimulate arthroconidia to convert into spherules,⁸⁹ yet they can impede morphogenesis after the development of antibody responses.⁹⁰ The oxidative burst is effective against arthroconidia and immature, but not mature, spherules. Additionally, after conversion to a spherule, the sheer size of this form precludes its phagocytosis by neutrophils or macrophages. In tissues, organized necrotizing granulomatous inflammation predominates, with T and B lymphocytes present at the margins of the lesions.

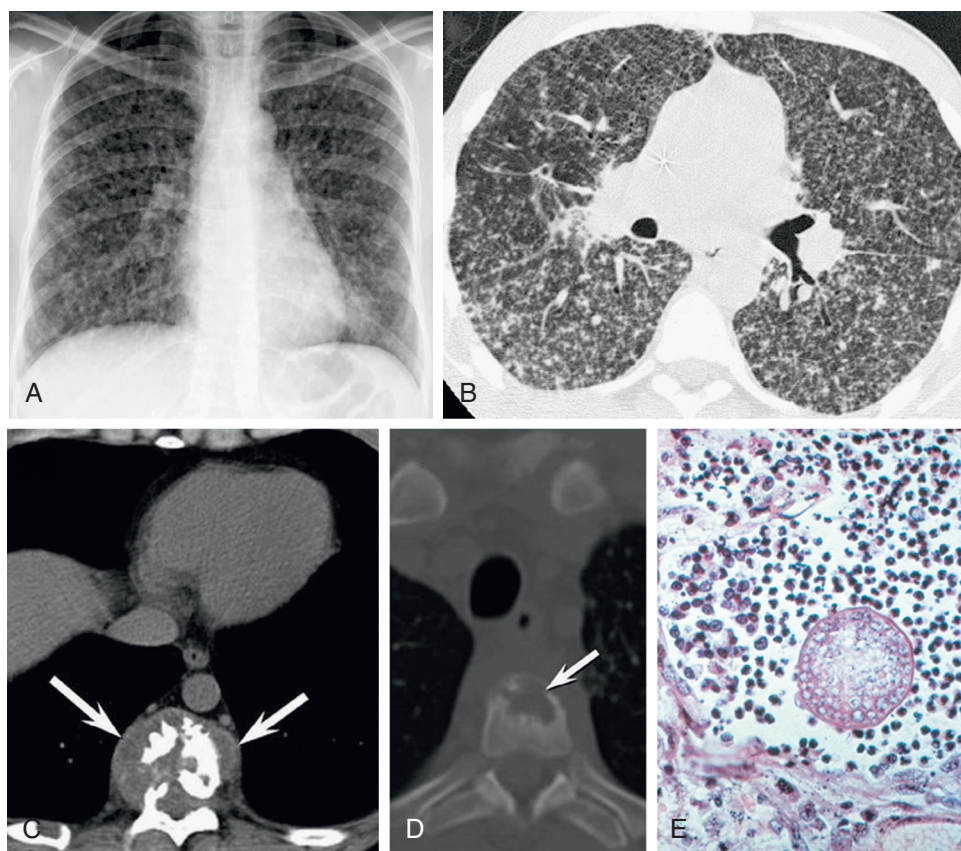


Figure 37-5 Disseminated coccidioidomycosis in an immunosuppressed patient. **A**, Frontal chest radiograph shows numerous, randomly disseminated nodules bilaterally consistent with a miliary pattern. **B**, Chest CT shown in lung windows confirms the miliary pattern. Axial chest CT shown in soft tissue (**C**) and bone (**D**) windows demonstrates bilateral paraspinal masses (arrows) associated with vertebral body destruction. The CT image shown in bone windows (**D**) reveals the vertebral body destruction (arrow) to advantage. **E**, Photomicrograph shows characteristic giant spherule of coccidioidomycosis in a lung biopsy. (Hematoxylin and eosin stain; original magnification $\times 450$.) (Courtesy Michael Gotway, MD.)

T lymphocyte responses are critical for protection against *Coccidioides*: Th1 responses are protective, whereas Th2 responses are less effective and may drive adverse outcomes. Consistent with this, lymphocyte secretion of interferon- γ is associated with resistance, whereas interleukin-4 is associated with susceptibility.⁹¹ The roles of other T-helper lymphocyte subsets in human immunity to *Coccidioides* is not yet known. Consistent with the importance of CD4⁺ T lymphocytes, severe disease is more common in patients with advanced HIV infection.

Individuals with prior symptomatic infection are generally protected against reinfection with either species of *Coccidioides*. However, waning immunity, such as in advanced HIV infection, or treatment with immunosuppressants can lead to reactivation of latent lesions or abolish protection against reinfection.

CLINICAL MANIFESTATIONS

Disease manifestations can range from asymptomatic acquisition to pneumonia, cavitary pulmonary disease, or disseminated infection that can involve skin, bone, central nervous system, and visceral organs.⁹² Of individuals infected with *Coccidioides*, 60% to 80% are either asymptomatic or have mild respiratory symptoms.⁹³ However, 15% to 35% of individuals develop respiratory symptoms,

1 to 4 weeks after inhalation of the arthroconidia. Although the majority of these cases resolve without sequelae, approximately 5% develop persistent or progressive pulmonary disease (eFig. 37-5). Furthermore, approximately 1% to 5% will have disseminated disease, which is more common in pregnant women, people of African descent, and immunocompromised individuals⁸⁸ (see Fig. 37-5).

Pulmonary Coccidioidomycosis (Valley Fever or Primary Coccidioidal Infection)

Primary symptomatic infection is typically a subacute pulmonary disease. The initial symptoms resemble influenza, with fever, cough, dyspnea, fatigue, headaches, myalgias, and arthralgias. Patients whose disease progresses to pneumonia typically have segmental or lobar disease, and mediastinal and/or hilar lymphadenopathy is characteristic (eFig. 37-6). In areas with high endemicity, approximately 15% to 30% of cases of community-acquired pneumonia may be due to *Coccidioides*.⁹⁴ Dermatologic immunologic manifestations such as erythema nodosum or erythema multiforme are associated with a favorable host response to the fungus. Pleural effusions complicate approximately 5% to 15% of cases, although the presence of an effusion does not correspond to increased severity of disease. The pleural fluid can be either transudative or exudative, and lymphocytes and eosinophils predominate. Coccidioidal

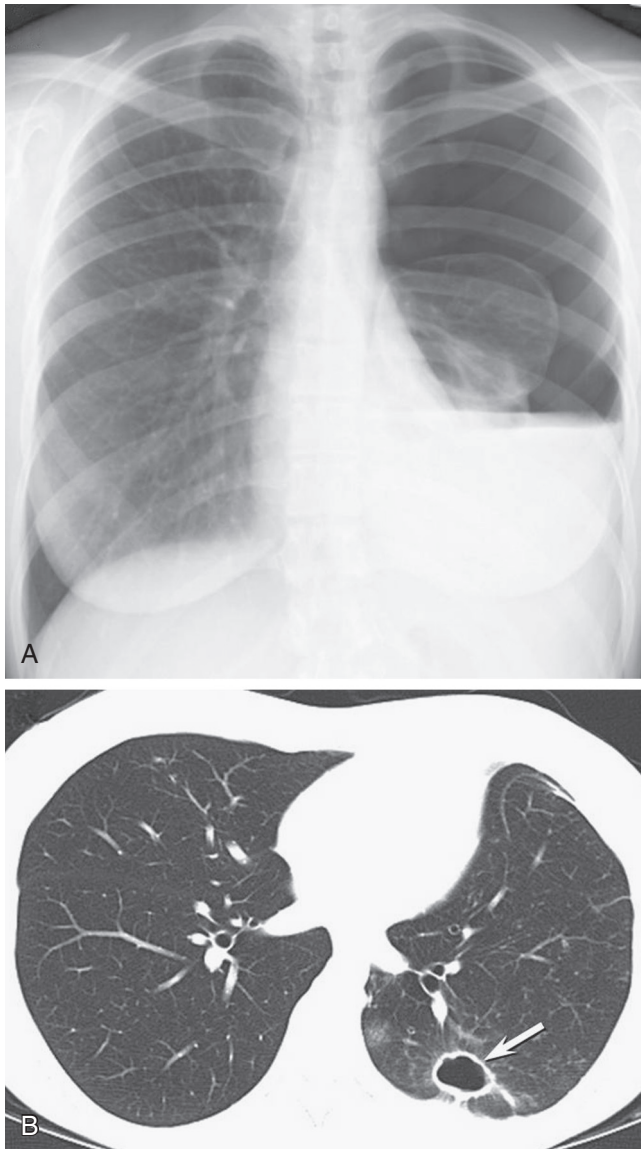


Figure 37-6 Coccidioidomycosis peripheral cavity with rupture into pleural space and empyema and bronchopleural fistula. **A**, Frontal chest radiograph shows a large left hydropneumothorax; note air-fluid level. The patient was treated with extended tube thoracostomy, antifungal therapy, and eventually video-assisted thoracoscopic pleural space débridement. *Coccidioides* spherules were recovered from the left pleural space. **B**, One year later, the chest CT shows a uniformly thin-walled, peripheral cavity (arrow) characteristic of *Coccidioides immitis* pulmonary infection. (Courtesy Michael Gotway, MD.)

empyema may develop, requiring aggressive interventions (Fig. 37-6A).

Acute Respiratory Failure and Acute Respiratory Distress Syndrome

Acute respiratory failure or *acute respiratory distress syndrome* (ARDS) due to coccidioidomycosis is atypical and is generally seen in the setting of advanced immunodeficiency. However, massive exposures to arthroconidia during construction or archeological excavation can lead to rapidly progressive respiratory failure. ARDS is even more uncommon (eFig. 37-7), but mortality rates for this form approach 100%.

Disseminated Coccidioidomycosis

Disseminated disease may be acute or chronic. Disease may be multifocal or restricted to a single extrapulmonary site. Prognosis of infection at a single extrapulmonary site is typically better than for multifocal disease, except in the case of meningitis (eFig. 37-8). Multifocal disease has a mortality rate of up to 50%. Meningitis is frequently progressive and shunts are often required to manage increased intracranial pressures.

An unusual presentation is miliary coccidioidomycosis in which numerous small granulomas develop throughout the lungs and other organs. Radiographs depict 3- to 4-mm nodules (eFig. 37-9) throughout the lung fields, indistinguishable in appearance from miliary tuberculosis. This presentation is a risk factor for the development of ARDS.

Pulmonary Nodule (Coccidioidoma)

A coccidioidoma is usually found as a single nodule (eFig. 37-10) in the peripheral lung tissue, and can be difficult to distinguish from a malignant lesion. To minimize unnecessary invasive procedures, physicians should consider the diagnosis of coccidioidomycosis in patients with a history of residence in an endemic area. In this setting, review of prior chest radiographs can be especially worthwhile in determining the likelihood of malignancy or healed fungal infection.

Cavitary Coccidioidomycosis

Although uncommon, thick or thin-walled (see Fig. 37-6B, eFig. 37-11B-D) cavities may develop during resolution of coccidioidomycosis. Cavities likely form because of infarction or liquefactive necrosis. If the cavities are peripheral, there are risks for fistula formation and/or pneumothorax (see Fig. 37-6). Larger cavities may be resected to prevent cavity rupture. Smaller cavities can be monitored radiographically (see eFig. 37-11B-D). A second cavitary disease process seen with coccidioidomycosis is a chronic fibrocavitary pneumonia (eFig. 37-12) characterized by multilobar opacities and cavities. This form is more common in patients with diabetes, and fever, chills, night sweats, and weight loss are typical.

Transmissibility

Person-to-person transmission is rare and restricted to a few instances of accidental exposure to arthroconidia from a patient with coccidioidal osteomyelitis, or organ transplantation from an infected donor.^{95,96} The infectivity of *Coccidioides* is noteworthy, and occupational infection is a risk to laboratory workers.⁹⁷ The association of Valley fever with *Coccidioides* was made in 1929 when a medical student opened a petri dish with mycelial *Coccidioides* and subsequently developed coccidioidomycosis. Thus, cultures of *Coccidioides* should only be handled under BSL3 conditions.

DIAGNOSIS

The gold standard for diagnosis remains isolation of *Coccidioides* from infected tissues; however, patients frequently do not produce sputum and the cultures take a minimum of a week to detect growth and more frequently take several

weeks. Direct examination of sputum is not sensitive. Cultures are most often used in hospitalized patients.

The most commonly used diagnostic tests depend on serologic assays for the presence of antibodies to *Coccidioides* antigens. However, antibody responses may lag behind clinical symptoms, especially in immunocompromised individuals. Hence, negative antibody testing in such patients does not exclude infection with *Coccidioides*. The immunodiffusion assays for IgM and IgG antibodies are commonly used, because they provide the greatest specificity. A commercial enzyme-linked immunoassay can detect IgM and IgG antibodies to *Coccidioides* and is more sensitive but less specific than the immunodiffusion assay. A complement fixation method that detects IgG antibodies to *Coccidioides* chitinase is also used in many laboratories. Either immunodiffusion or complement fixation assays can be used to monitor responses to treatment. Molecular methodologies have not yet been validated for *Coccidioides*. Additional information on serologic and other diagnostic testing for coccidioidomycosis is available in Chapter 17.

TREATMENT

Comprehensive treatment recommendations for coccidioidomycosis have been made by the American Thoracic Society in 2011⁶⁷ and the IDSA in 2005.⁸¹ An update in recommendations is currently in progress by the IDSA and is projected to be available by Spring 2015.

Uncomplicated Acute Pneumonia

Mild to moderate pulmonary disease in an individual with a normal immune system is not an indication for treatment, because there is no evidence that antifungal treatment hastens resolution of symptoms.⁹⁸ However, patients with HIV, pregnant women, or patients who are otherwise immunosuppressed should be treated. In immunocompetent individuals, treatment is recommended if symptoms persist for more than 8 weeks or if the patient has lost more than 10% total body weight, has night sweats for more than 3 weeks, or if disease is present in more than half of a single lung, is multilobar, or if hilar lymphadenopathy persists. Additionally, complement fixation titers greater than 16 often prompt treatment. If antifungal therapy is initiated for mild to moderate disease, it is generally administered for 3 to 6 months. If untreated disease progresses to chronic fibrocavitary pneumonia, a minimum of 1 year of antifungal therapy is recommended. Long-term azole therapy should be considered for immunocompromised individuals.

Treatment is usually with either oral fluconazole (400 to 800 mg/day) or itraconazole (200 mg two or three times daily); the higher doses are usually reserved for more complicated cases. Drug levels for itraconazole should be obtained after 2 weeks of therapy, due to its variable bioavailability.⁷⁷ In more severe disease, lipid formulations of amphotericin B (2 to 5 mg/kg daily) or conventional amphotericin B (0.5 to 1.5 mg/kg daily) may be preferred, but data from randomized comparative trials are lacking. There are insufficient data to evaluate the efficacy of voriconazole and posaconazole for coccidioidomycosis, although there are reports of responses in otherwise refractory cases. Echinocandins are not recommended, due to intrinsic resistance of *Coccidioides* to this class of drugs. Even in the

absence of treatment, patients should be monitored every 3 to 6 months for 2 years to document resolution of radiologic evidence of disease and confirm the absence of pulmonary or other complications.

Complicated Pneumonia with or Without Dissemination

Diffuse disease, particularly reticulonodular pneumonia or miliary opacities, is treated initially with an amphotericin formulation or high-dose fluconazole; the latter is also used after an initial response is achieved in patients initiated on amphotericin. If dissemination is present, especially if the patient has meningitis, treatment with fluconazole is the preferred approach. Corticosteroid therapy may be useful in patients with severe pulmonary coccidioides with ARDS using approaches validated for *Pneumocystis jirovecii*: prednisone 40 mg two times daily for 5 days, then 40 mg daily, and then 20 mg a day for 11 days. For complicated pneumonia, recovery is frequently slow, with symptoms resolving over weeks. Treatment is for a minimum of 1 year.

Pulmonary Nodule

If a solitary nodule is identified as due to *Coccidioides* after a biopsy, there is no need to administer antifungal therapy or resect the lesion. If the nodule was excised, no additional treatment is necessary. Treatment with an azole should be considered in a patient with a nodule if the patient subsequently becomes immunocompromised.

Pulmonary Cavity

Asymptomatic cavitary lesions should be followed clinically and radiographically (see eFig. 37-11). If a patient is symptomatic or has an elevated antibody titer, treatment with an azole for 3 to 6 months should be considered although 12 to 18 months may be necessary for immunocompromised individuals. Larger cavities are often resected after 2 or more years if they have not resolved. Bacterial superinfection is a complication that requires aggressive antimicrobial treatment, and subsequent resection of the cavity is prudent. Cavity rupture is rare, but can lead to pyopneumothorax (see Fig. 37-6A and B) requiring antifungal therapy and decortication.

BLASTOMYCOSIS

HISTORY AND EPIDEMIOLOGY

Blastomyces dermatitidis, the causative agent of blastomycosis, is a dimorphic fungus endemic to North America along the Mississippi, Ohio, and St. Lawrence rivers as well as in regions adjacent to the Great Lakes. The fungus also rarely causes sporadic disease in parts of Africa, although the African isolates studied vary in antigen expression relative to North American isolates.⁹⁹ *B. dermatitidis* is a soil-based fungus associated with riverbanks.¹⁰⁰ Hence, risk factors for acquisition of the fungus include exposures to waterways, soils, or woods: approximately 30% of forestry workers in endemic areas of Minnesota and Wisconsin have serologic evidence of prior infection. Infection with *B. dermatitidis* is thought to follow inhalation of aerosolized conidia, and the common clinical manifestations include pneumonia, skin

and bone lesions, and involvement of the genitourinary tract.

The rates of disease vary significantly with regions, even within the same state. For example, a 1992 study of 11 years of laboratory-confirmed blastomycosis showed that the rate of disease in Wisconsin is approximately 1.4 cases per 100,000, but there are regions where there are approximately 40 cases per 100,000.¹⁰¹ Most cases are sporadic, but outbreaks have been reported. In 2003, there were 771 patients hospitalized with a diagnosis of blastomycosis, with a 6% mortality rate in hospitalized adults.⁶

Thomas Gilchrist described blastomycosis in 1894,¹⁰² and blastomycosis is also referred to as Gilchrist disease. Interestingly, Gilchrist misidentified the fungus as a protozoan, but later corrected this error. Early descriptions emphasized the cutaneous manifestations, so blastomycosis was initially considered primarily a localized dermatologic condition rather than a systemic infection.

PATHOGENESIS

B. dermatitidis exists in a mold form in the environment or under laboratory conditions at approximately 25°C. Inhalation of conidia or cultivation at 37°C results in transformation into yeast cells (8 to 12 µm in diameter), which bud with a broad-based connection between the mother and daughter cells (see Figs. 37-7B and 17-6). In tissue, yeast forms that are 25 to 40 µm in diameter can also be seen. After inhalation, conidia are engaged by neutrophils and macrophages, which can kill the cells and/or inhibit conidial morphogenesis.¹⁰³ The yeast form is more resistant to killing, especially by neutrophils¹⁰⁴ and the yeast directly inhibit the enzymatic activity of macrophage inducible nitric oxide synthase.¹⁰⁵ The yeast cells can disseminate from the lungs via the bloodstream or lymphatics to any tissue. In tissues, neutrophilic infiltrates are seen early in disease followed by a granulomatous response characterized by multinucleated giant cells and noncaseating granulomas. Activation of effective T-cell-mediated responses is required to halt disease.¹⁰⁶ BAD-1, an essential virulence factor and adhesin of *B. dermatitidis*, promotes disease by suppressing the host inflammatory response through inhibition of TNF-α.¹⁰⁷ Hence, the outcome of this dynamic between host and pathogen responses dictates disease manifestations. There are two distinct genetic groups of *B. dermatitidis*; Group 1 isolates usually cause disease restricted to the lungs whereas Group 2 isolates have an increased propensity to cause disseminated disease.¹⁰⁸

CLINICAL MANIFESTATIONS

Pulmonary infection with *B. dermatitidis* leads to asymptomatic infection, acute or chronic pneumonia, or disseminated disease. Infection is asymptomatic in approximately 50% of individuals^{109,110}; symptomatic disease generally develops after an incubation period of 4 to 8 weeks or more. Some studies suggest a seasonality to blastomycosis, which corresponds to outdoor activities in the endemic regions, resulting in infections at the end of summer into early fall, with these individuals subsequently presenting with extrapulmonary disease in the next year.¹¹¹ The initial mild presentations manifest with influenza-

like symptoms, including fever, cough, myalgias, and arthralgias.¹¹²

Acute Pulmonary Blastomycosis

The diagnosis of pulmonary blastomycosis is often delayed because the manifestations are not sufficiently different from those of community-acquired bacterial pneumonia to raise suspicion of the diagnosis. In addition to fever and cough, mild hemoptysis may be present.¹¹³ The disease can resolve, but the incidence of resolution without subsequent dissemination is unknown. Radiologic findings can vary greatly in acute disease and these manifestations can also be present in chronic disease. The most common presentation is focal (Fig. 37-7A) or diffuse airspace consolidation.^{42,114} However, even asymptomatic patients can have mass lesions, cavities (eFig. 37-13), or single or multiple (eFig. 37-14) nodules. Acute progressive blastomycosis is infrequent, but pulmonary disease can progress to ARDS, which is associated with mortality rates of approximately 78%,¹¹⁵ and with mortality typically seen within 1 week of presentation to medical attention. Progressive disease can manifest as diffuse multilobar opacities, endobronchial

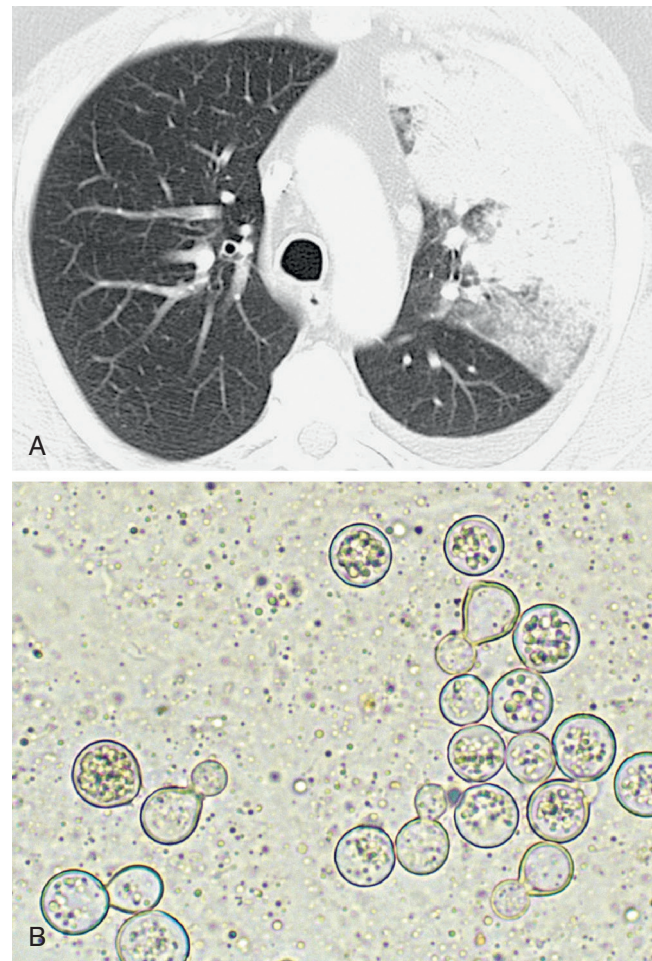


Figure 37-7 Focal pulmonary blastomycosis. **A**, Axial chest CT shows a lobar left upper lobe consolidation pattern. **B**, Micrograph shows *Blastomyces dermatitidis* in fresh sputum after 10% potassium hydroxide digestion. Note the broad neck of attachment, the double refractile cell wall, and the multiple nuclei. (Original magnification ×1000.) (A, Courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)

infection, or miliary blastomycosis. Approximately half of the patients with severe disease are immunosuppressed,¹¹⁶ including cancer patients, transplant recipients (eFig. 37-15), patients on TNF antagonists, or individuals with advanced HIV infection.

Chronic Pulmonary Blastomycosis

Similar to histoplasmosis and coccidioidomycosis, blastomycosis can present as a chronic pneumonia that is indistinguishable from tuberculosis or from pulmonary malignancies. Patients with chronic blastomycosis frequently report being ill for more than 2 months with fever, weight loss, night sweats, cough and chest pains.^{110,117} The most frequent radiographic findings include consolidations, mass lesions and interstitial fibronodular opacities.¹¹⁴ Cavitation is uncommon, although small pleural effusions may be present.

Extrapulmonary Disease

The reported incidence of extrapulmonary disease has been between approximately 20% and 75% of cases, with the upper range in patients with chronic untreated blastomycosis.^{101,110} Due to more rapid diagnosis, overall rates of disseminated disease are presently closer to 20% to 25%. The most frequent site of dissemination is the skin, seen in 40% to 80% of cases of extrapulmonary disease. The typical presentation is a crusting verrucous lesion with a central draining microabscess (Fig. 37-8); there may also be nodular, pustular, or ulcerative lesions.¹¹⁸ Multiple lesions are typically present and mucous membranes can also be involved. Cutaneous lesions can overlie bone lesions that produce sinus tracts to skin. *B. dermatitidis* infects bone in approximately 5% to 50% of patients with extrapulmonary disease; approximately 75% of patients with osseous disease have concomitant active pulmonary involvement.¹¹⁹ Bone radiographs typically reveal focal osteolytic lesions without periosteal reactivity, but some lesions can be highly destructive. The third most frequent site of extrapulmonary disease is the genitourinary tract, seen in 10% to 30% of cases. The incidence is higher in males where disease frequently mani-

festes as blastomycosis of the prostate, testicle, or epididymis. *B. dermatitidis* can affect any tissue, but the most formidable disease is that of the central nervous system, seen in up to 10% of extrapulmonary blastomycosis and generally in immunosuppressed patients. Before the availability of combination antiretroviral therapy, 40% of individuals with AIDS and blastomycosis developed central nervous system disease with approximately 40% mortality.¹²⁰ Frequency of severe or pulmonary disease is greater and mortality is increased in Aboriginal Canadians and in those with cellular immunodeficiencies and/or advanced age.¹¹⁷

Transmissibility

B. dermatitidis is generally not transmissible person-to-person. However, there have been rare cases of presumed conjugal transmission as well as acquisition in utero. Dogs are at high risk for blastomycosis in endemic areas; a vaccine utilizing the BAD-1 protein has been shown to be protective in dogs¹²¹; this is a candidate platform for a human vaccine. Bites from infected dogs have led to cutaneous blastomycosis in humans.

DIAGNOSIS

The gold standard for diagnosing blastomycosis is culture.¹¹⁹ Growth can be detected after several days to weeks on mycologic medium. However, cultures are problematic because, even with specimens obtained by bronchoscopy, the rate of positive culture is no higher than 67%. Direct observation is the most rapid method for diagnosis. Microscopic examination of *potassium hydroxide* (KOH)-treated respiratory specimens can reveal *B. dermatitidis* yeast forms (see Figs. 37-7B and 17-6) in up to 46% of patients. Cytologic evaluation with Papanicolaou or other stains can detect *B. dermatitidis* in up to 71% of patients with pulmonary disease. Histologic examination can also be helpful.

A commercial ELISA to detect *Blastomyces* antigen, similar to the *Histoplasma* urinary assay, has recently been developed that has a reported sensitivity of approximately 93%, although clinical information on the subjects was not provided.¹²² Antigenuria can be detected in patients with pulmonary or extrapulmonary disease, and testing can also be performed on serum, plasma, cerebrospinal fluid, bronchoalveolar lavage fluid, or other sterile fluids. The test is also reportedly useful to follow response to treatment or assess for relapse. However, there is significant cross-reactivity with *H. capsulatum* and other dimorphic fungi. A new promising ELISA based on the immunodominant BAD-1 protein specific for this fungus has recently been reported.^{122a} Although commercial antibody tests are available, they lack clinical utility.

TREATMENT

Comprehensive treatment recommendations for blastomycosis have been made by the American Thoracic Society in 2011⁶⁷ and the IDSA in 2008.¹²³ In an immunologically normal individual, acute disease is often mild and resolves without antifungal therapy. Nevertheless, clinical guidelines suggest that treatment should be considered for any patient, because it is not currently possible to determine the likelihood of extrapulmonary dissemination.



Figure 37-8 Cutaneous lesion of blastomycosis. (Photo courtesy Bruce Klein, MD, University of Wisconsin Departments of Pediatrics and Medical Microbiology and Immunology.)

Mild to Moderate Blastomycosis

Current consensus is that mild to moderately ill patients with pulmonary blastomycosis should receive itraconazole (200 mg twice daily) for 6 months. Levels of itraconazole should be verified after 2 weeks of administration and periodically during treatment, due to variations in blood levels achieved.⁷⁷ Therapy for mild to moderate pulmonary blastomycosis is not altered if there is nonmeningeal dissemination, except in the setting of bone disease, when therapy is extended to 1 year.

Moderately Severe to Severe Blastomycosis

Patients with moderately severe to life-threatening pulmonary blastomycosis, including ARDS, should initially be treated with liposomal amphotericin B (5 mg/kg/day) or conventional amphotericin (0.7 to 1 mg/kg/day) until clinical improvement is evident (usually 1 to 2 weeks) and then switched to itraconazole (200 mg twice daily for 6 to 12 months). Liposomal formulations are generally preferred. Although there are limited data to support the use of corticosteroids, administration of steroids in the setting of extensive disease with hypoxemia may be beneficial. If patients have meningitis, amphotericin with or without fluconazole (800 mg daily) or itraconazole (200 mg twice daily) is used initially (typically for 4 to 6 weeks) followed by 6 to 12 months of treatment with an azole, with many experts favoring a minimum of 12 months. Voriconazole may be considered for use in refractory disease. Echinocandins should not be used, due to intrinsic resistance of *Blastomyces* to this class of drugs. Immunocompromised patients should be treated for a minimum of 12 months or continued indefinitely if the immunodeficiency is irreversible.

PARACOCOCCIDIOIDOMYCOSIS

EPIDEMIOLOGY

Paracoccidioides brasiliensis, the causative agent of paracoccidioidomycosis, is a dimorphic fungus that is endemic in

southern Mexico, Central America, and South America. *P. brasiliensis* is the major causative agent of systemic mycosis in Latin America,¹²⁴ and it is a leading cause of disability and death among young adult rural workers.¹²⁵ A 2001 analysis estimated that approximately 10 million people were infected with *Paracoccidioides* spp.¹²⁶ However, symptomatic disease would be expected to develop in only approximately 1% to 2%, with pulmonary disease as the most common form. Nine-banded armadillos that burrow in the soil of endemic regions are also infected with high frequency, which provides evidence for a soil reservoir of the fungus.

Phylogenetic analyses have recently led to the separation of *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii* (formerly *P. brasiliensis* isolate 01).¹²⁷ The manifestations of infection by these two species are indistinguishable.

PATHOGENESIS

In the environment or under laboratory conditions at less than 28°C, *P. brasiliensis* grows as a mycelium that produces chlamydoconidium, terminal conidia, and arthroconidia, with arthroconidia believed to be the infectious agent. In tissues or at greater than 37°C, yeast forms predominate, which typically are a 5- to 30-μm diameter ovoid mother cell displaying several blastoconidia (forming a “pilot’s wheel”) (Fig. 37-9).

Interestingly, the ratios of clinical disease in males to females average approximately 13:1, but can be as high as 150:1. *P. brasiliensis* expresses β-estradiol receptors on the conidial cell membrane; binding to these receptors inhibits morphogenesis to the yeast form, blocking disease progression.¹²⁸ Women are not protected against infection, but clinical disease is less likely. Smoking may also exacerbate disease, although the mechanism is not clear.

The initial host response to *P. brasiliensis* consists predominantly of neutrophils followed by recruitment of macrophages and granuloma formation. This process is highly regulated by cellular responses; Th1-based responses are protective whereas Th2 type responses are common in patients unable to control their disease. The impact of cellular immunity is further underscored by the increased

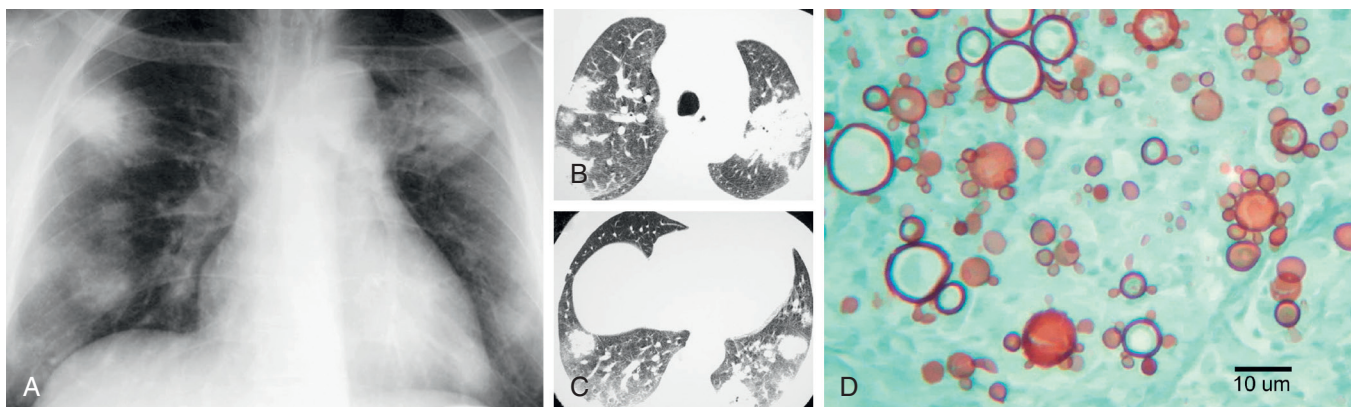


Figure 37-9 Pulmonary paracoccidioidomycosis infection. **A**, Frontal chest radiograph shows bilateral poorly defined masses. **B** and **C**, Axial chest CT images confirm the presence of bilateral nodules, masses, and masslike areas of consolidation. Percutaneous transthoracic needle biopsy subsequently proved paracoccidioidomycosis infection. **D**, *Paracoccidioides brasiliensis* yeast forms. Several large mother cells with associated blastoconidia (forming a “pilot’s wheel”) are present. (Gomori methenamine silver stain.) (**A–C**, Courtesy Michael Gotway, MD; **D**, photomicrograph courtesy Dr. Carlos Taborda, PhD, University of São Paulo, Brazil.)

incidence of disseminated disease in patients with AIDS. A review of deaths in 3583 AIDS patients due to systemic mycoses in Brazil from 1996 to 2006 revealed that paracoccidioidomycosis was responsible for approximately 50% of deaths.¹²⁹ Individuals on steroids, patients receiving chemotherapy, or patients who have received organ transplants are also at increased risk for severe disease.

CLINICAL MANIFESTATIONS

As noted, the vast majority of infections are asymptomatic, and the initial acquisition is largely believed to happen in childhood. There are two patterns of disease manifestation: the acute or subacute form (also called juvenile type) and the chronic form (or adult type). The juvenile type is seen in less than 10% of cases and most frequently develops in the age range from prepubescent teenagers to adults younger than 30 years old. Patients are acutely ill, often presenting with fever, weight loss, and lymphadenopathy. Additionally, patients can have hepatosplenomegaly, intestinal lesions, and bone disease with or without bone marrow dysfunction. In contrast, the chronic form involves the lungs in approximately 90% of patients, likely due to reactivation of latent disease. However, new acquisition of the fungus is possible. Disease is confined to the lung in approximately 25% of patients, with the remainder presenting with multifocal disease, including dissemination to mucous membranes, lymph nodes, skin, adrenals, and other organs. Disease manifestations can mimic tuberculosis, which can also coinfect approximately 10% of these patients.¹³⁰

Radiologic findings are nonspecific and range from diffuse opacities to masses (see Fig. 37-9) and cavities (eFig. 37-16). Lymphadenopathy is often a prominent feature. Long-term complications develop in more than 50% of patients with significant chronic pulmonary disease, most often owing to impaired respiratory function due to fibrosis or cavities (eFig. 37-17); cor pulmonale is common in these patients. Additionally, compression of structures, such as the trachea, can develop. Single residual nodules without calcification are common.

DIAGNOSIS

The diagnosis can be confirmed through detection of antibodies. The major diagnostic antigen is a 43-kD glycoprotein of *P. brasiliensis* (gp43, a laminin-binding protein); antibodies can be identified in serum of approximately 90% of patients.^{131,132} However, culture and microscopy are generally used for diagnosis in endemic areas. As noted, the yeast form has distinct shapes that can be identified in up to 90% of sputum, exudate, or pus samples from patients with chronic paracoccidioidomycosis (see Fig. 37-9D). Culture remains a problem because the fungus routinely takes 20 to 30 days to grow on mycologic agar; culture is thus less useful in making clinical decisions.

TREATMENT

Optimal treatment regimens for *P. brasiliensis* have not been formally validated.^{67,130} However, in seriously ill patients with dissemination, amphotericin therapy is used as initial

therapy. Amphotericin is either continued until a total dose of 2 g is achieved or until the patient improves and can be switched to an oral drug. Treatment with amphotericin B alone, even when a cumulative dose of 2 g is achieved, is associated with relapse in 25% to 30% of cases of paracoccidioidomycosis. Ketoconazole (200 to 400 mg daily) or itraconazole (200 to 400 mg daily) are the most commonly used azoles for paracoccidioidomycosis. Itraconazole is currently preferred, because its use is associated with lower relapse rates than is ketoconazole (3% to 5% vs. 10%) and is better tolerated by most patients. Voriconazole and posaconazole may also have utility, although in one published study, voriconazole was neither better tolerated nor more efficacious than itraconazole.¹³³ Azole regimens range from 6 months to 18 to 24 months, depending on the rate of clinical response and evidence of fungal clearance as reflected by serologic testing. *P. brasiliensis* is also susceptible to sulfonamides, although use of these drugs for treatment requires very prolonged courses (3 to 5 years) and is associated with relapse rates of 20% to 25%.

SPOROTRICHOSIS

Sporotrichosis is principally due to the dimorphic fungus *Sporothrix schenckii*, which is globally ubiquitous and grows in decaying vegetation, sphagnum moss, soil, and other environmental niches. The vast majority of infections arise after cutaneous inoculation of the fungus. There are several additional species of *Sporothrix* associated with human disease, particularly *S. brasiliensis*, *S. globosa*, and *S. mexicana*.¹³⁴ *S. brasiliensis* is responsible for infections associated with cat scratches in the state of Rio de Janeiro, Brazil. Pulmonary disease is rare, but can develop after inhalation of conidia. Such cases of pulmonary disease primarily present in middle aged men; risk factors include chronic obstructive lung disease and alcoholism. Radiographically, pulmonary sporotrichosis appears as cavitory and fibronodular disease.¹³⁵ Disseminated disease is rare and is primarily seen in severely immunocompromised individuals, especially in individuals with advanced HIV infection.

The standard for diagnosis of invasive sporotrichosis is culture, although *Sporothrix* typically requires 1 to 4 weeks for detectable growth from a clinical sample. Microscopic examination of biopsy material often fails to reveal the organism, likely due to the small number of organisms that are needed to cause disease. The ovoid yeast cells are 3 to 5 µm in diameter, and eosinophilic projections from the yeast may be present, resulting in a characteristic “asteroid body.” Severe to life-threatening pulmonary sporotrichosis should be initially treated with amphotericin B (3 to 5 mg/kg/day of lipid amphotericin or 0.7 to 1 mg/kg of conventional amphotericin).¹³⁶ Once the patient's condition has stabilized, typically within 2 weeks, itraconazole (200 mg twice daily) can be administered for at least 1 year of total antifungal therapy. Adjunctive surgery may be useful in the management of severe focal disease. If the disease is less severe, itraconazole can be used as initial therapy.¹³⁵ Serum levels of itraconazole should be verified after 2 weeks of administration and periodically thereafter. Treatment is generally from 3 to 6 months. Antifungals used for other manifestations of sporotrichosis, such as terbinafine,

saturated solution of potassium iodide, or fluconazole, are not effective for pulmonary disease.

PENICILLIOSIS

Penicillium marneffei, is a dimorphic fungus responsible for a systemic mycosis geographically restricted to southeast Asia, India and southern China, especially in individuals with HIV¹³⁷ (Chapter 90). In the environment, *P. marneffei* exists as a mold, whereas in tissues it is in a yeastlike form (arthroconidium), which is notable for replicating by fission. Penicilliosis is the third most common opportunistic infection in individuals with HIV in parts of tropical Asia, after tuberculosis and cryptococcosis. Although the majority of cases are seen in the setting of advanced HIV infection, disease also develops in patients with immunosuppression due to malignancy or medical therapies as well as in patients with underlying lung disease. Patients typically present with disseminated disease characterized by fever, weight loss, generalized lymphadenopathy, skin lesions (frequently papules with central necrosis), and hepatomegaly. The pathobiology of *P. marneffei* is comparable to that of histoplasmosis, in that *P. marneffei* survives within macrophages and manifests a similar spectrum of disease. Diagnosis is typically achieved by culture and microscopy. The simplest diagnostic approach is via biopsy of skin lesions or lymph nodes and histologic assessment for fission arthroconidium. *P. marneffei* can also be visualized in peripheral blood smears in patients with fulminant disease. Initial therapy is with amphotericin B followed by itraconazole.¹³⁸

Key Points

- Pulmonary infections due to endemic dimorphic fungi are more common than are typically considered in routine differential diagnoses.
- Any time that *Mycobacterium tuberculosis* is in a differential diagnosis, endemic dimorphic fungi should also be considered; indeed, dimorphic fungi cause similar numbers of deaths in the United States annually as tuberculosis.
- The common endemic dimorphic fungi in North America are *Histoplasma*, *Coccidioides*, and *Blastomyces*; in South America, the common endemic dimorphic fungus is *Paracoccidioides*.
- Disease may develop acutely after acquisition of the dimorphic fungi or remain latent for protracted periods with subsequent activation in the setting of immunologic suppression.

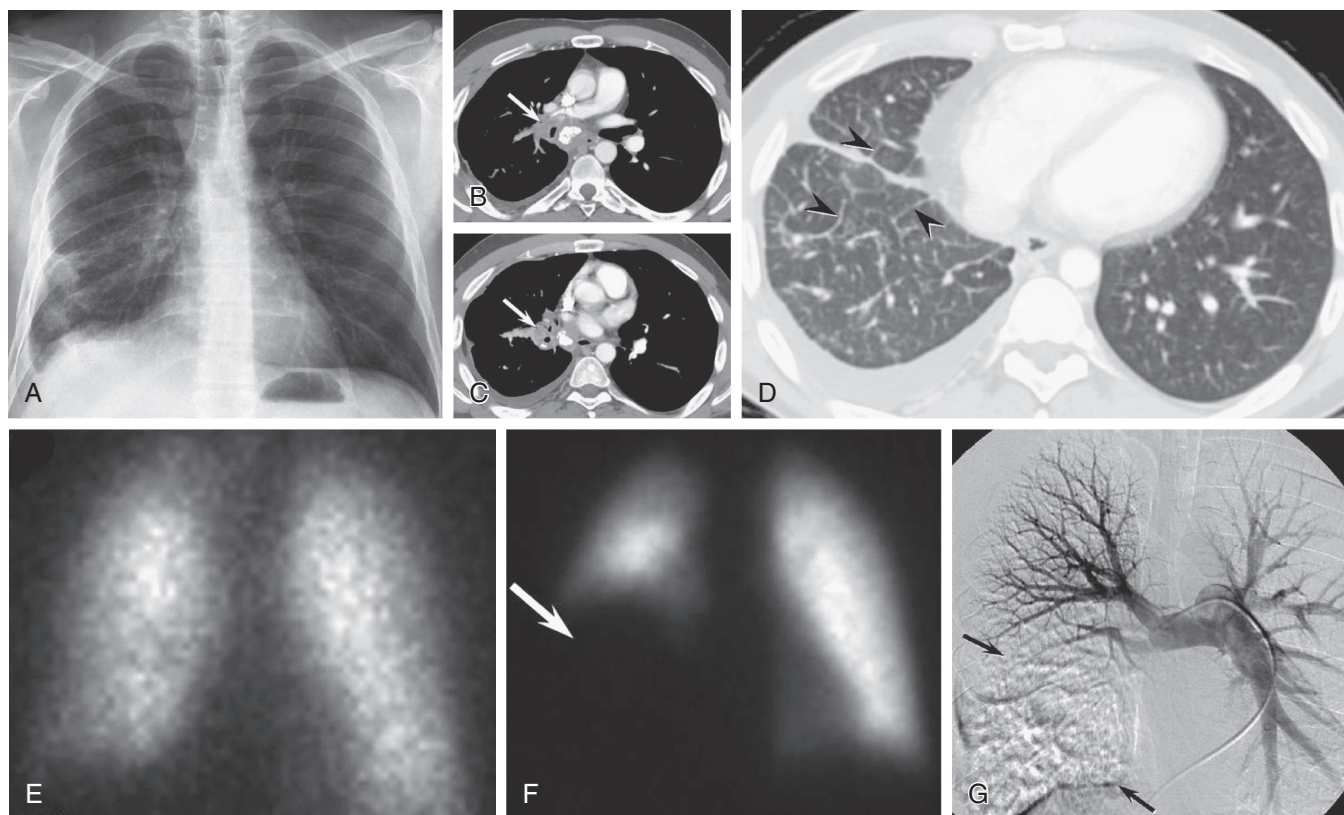
- Disease manifestations of dimorphic fungi range from mild, flulike illnesses to life-threatening systemic processes. The endemic fungi can cause disease in any tissue, although histoplasmosis frequently involves the reticuloendothelial system; coccidioides involves skin, bone, and central nervous system; and blastomycosis involves skin and bones.
- Disease severity is highly associated with the size of the inoculum as well as host immunity. Patients with defects in cellular immunity, especially of CD4⁺ T cells (i.e., advanced HIV infection), or with tumor necrosis factor alpha blockade, are at risk for more severe disease.
- Diagnosis may be challenging, because direct identification has a poor sensitivity and cultures may require up to 4 weeks before growth is detected. Diagnosis frequently utilizes serologic testing to detect antigen or antibody. Identification based on fungal morphology in tissue samples can also aid in diagnosis.
- Treatment regimens are prolonged (a minimum of several months, up to lifelong), and monitoring of serologic and radiologic responses as well as antifungal drug levels are necessary.

Complete reference list available at [ExpertConsult](#).

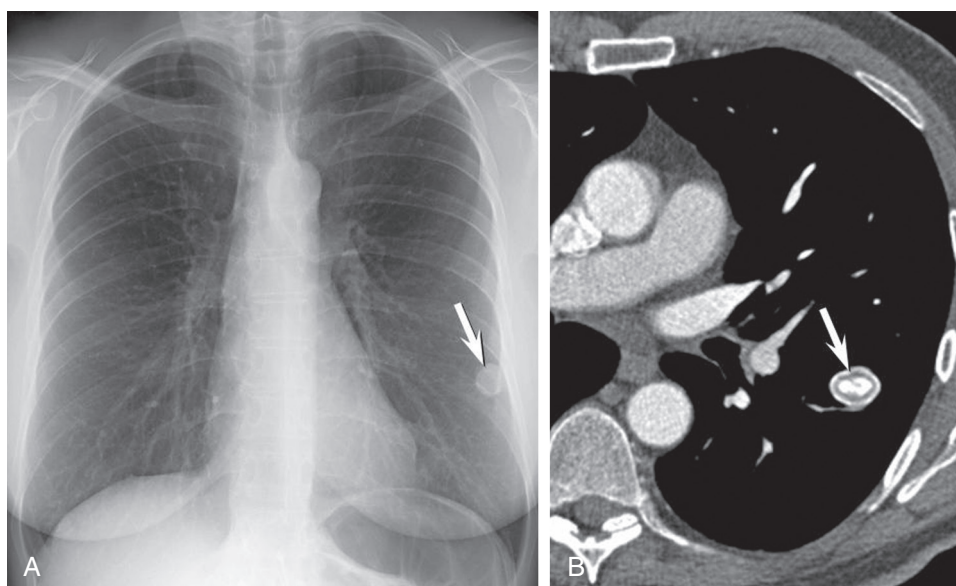
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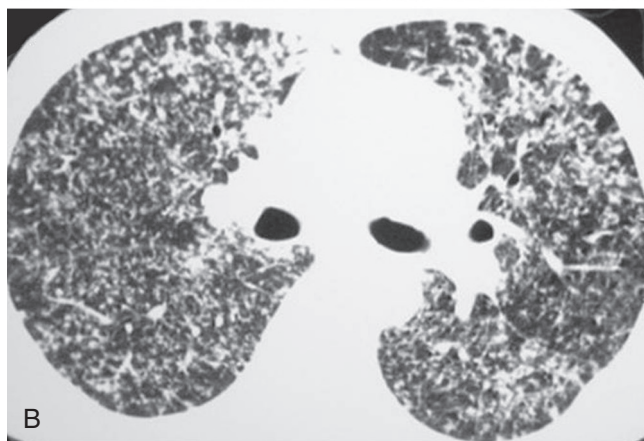
eFIGURE IMAGE GALLERY



eFigure 37-1 Fibrosing mediastinitis due to histoplasmosis. Frontal chest radiograph (A) in a patient with fibrosing mediastinitis shows linear and reticular abnormalities in the right perihilar region and right lower lobe and a small right pleural effusion. Chest CT shown in soft tissue windows (B and C) demonstrates calcified mediastinal lymphadenopathy and noncalcified right peribronchial tissue (arrows). Note that the peribronchial tissue compresses and narrows adjacent vascular structures. A small right pleural effusion is present. Chest CT shown in lung tissue windows (D) reveals right lung smooth interlobular septal thickening (arrowheads), which accounts for much of the linear abnormality apparent on chest radiography. Ventilation (E) and perfusion (F) scintigraphy in the anterior projection shows mildly decreased ventilation in the right lower lung (E), but absent perfusion in the same region on the perfusion images (F). Left lung perfusion is normal. Catheter pulmonary angiography (G) confirms absent perfusion in the right lower lung (area between arrows is right lower lobe lung parenchyma without demonstrable pulmonary blood flow) due to arterial compression, confirming the findings seen on CT (B and C). (Images courtesy Stacy M. Rissing, MD, Assistant Professor of Clinical Radiology and Imaging Sciences, Indiana University.)



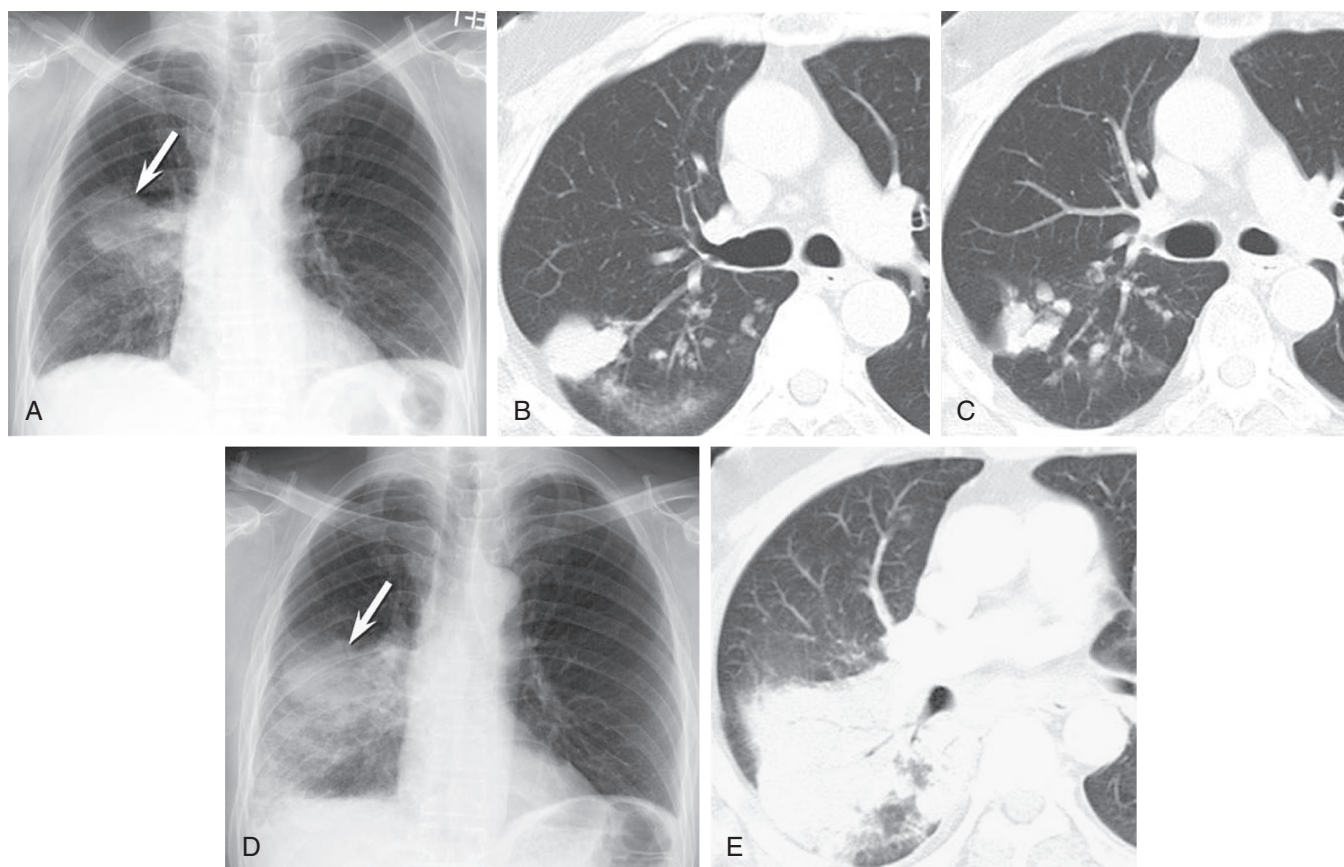
eFigure 37-2 Single calcified pulmonary granuloma due to histoplasmosis. A, Frontal chest radiograph shows a left lower lobe circumscribed nodule (arrow) with peripheral increased attenuation consistent with calcification. B, Axial chest CT confirms both peripheral and central calcification within the nodule (arrow). (Courtesy Michael Gotway, MD.)



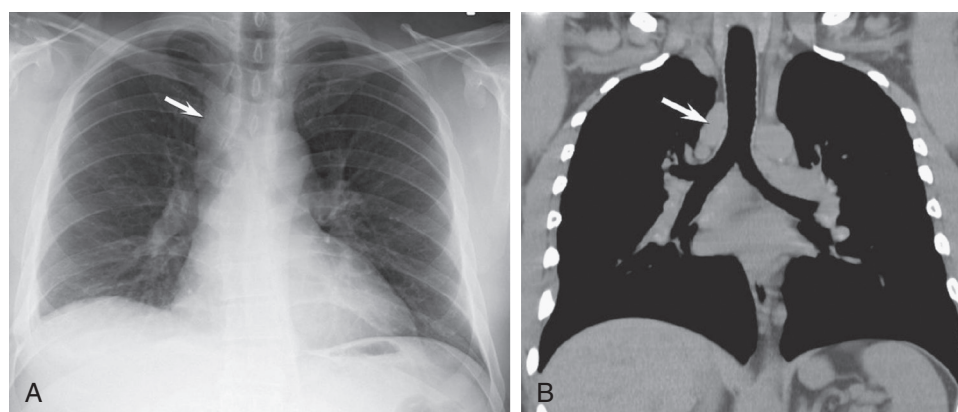
eFigure 37-3 Disseminated histoplasmosis in a patient with AIDS. **A**, Frontal chest radiograph shows numerous, randomly distributed nodules bilaterally associated with thickening of the right paratracheal region, consistent with mediastinal lymph node enlargement. **B**, Chest CT confirms numerous, randomly disseminated small nodules consistent with a miliary pattern, due to histoplasmosis. The organism was recovered from mucocutaneous lesions. (Courtesy Michael Gotway, MD.)



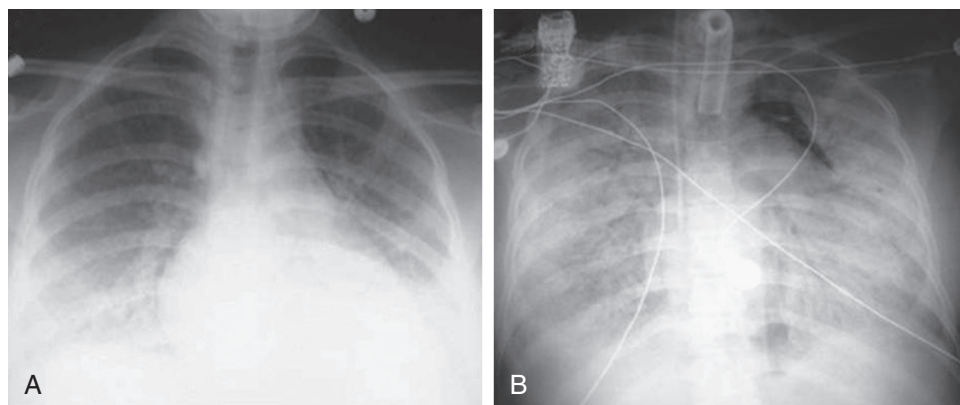
eFigure 37-4 Broncholithiasis due to histoplasmosis. Axial chest CT focused on the right lower lobe shows a high attenuation broncholith (*arrow*) within the right lower lobe bronchus. (Image courtesy Stacy M. Rissing, MD, Assistant Professor of Clinical Radiology and Imaging Sciences, Indiana University.)



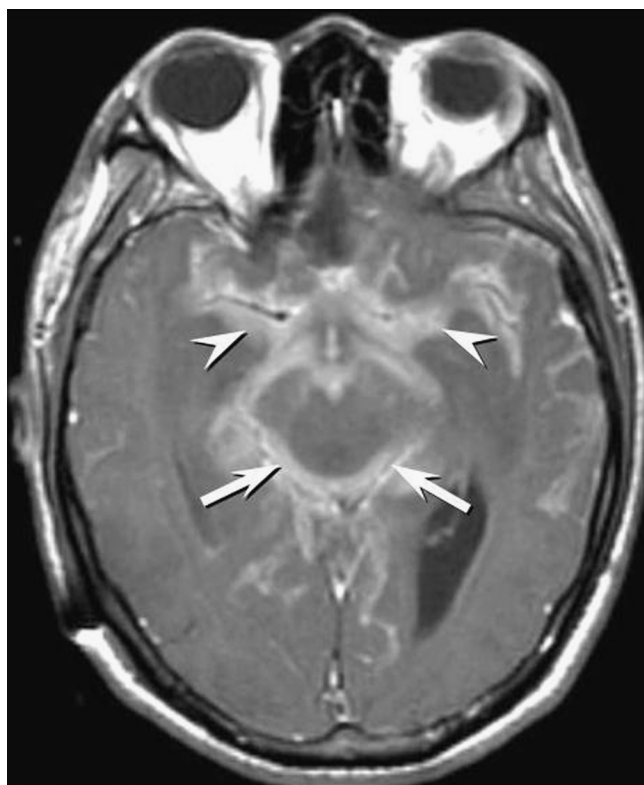
eFigure 37-5 Progressive coccidioidomycosis pulmonary infection. **A**, Frontal chest radiograph shows a right perihilar mass (*arrow*) with surrounding reticulation. Chest CT shown in lung windows (**B** and **C**) reveals a right upper lobe mass adjacent to the right major fissure as well as numerous surrounding centrilobular nodules. Biopsy of the mass proved coccidioidomycosis infection. Antifungal therapy was begun. Follow-up chest radiograph (**D**) shows increased size of the right perihilar masslike area of consolidation (*arrow*), and chest CT (**E**) confirms increasing consolidation in the area affected on the previous CT. (Courtesy Michael Gotway, MD.)



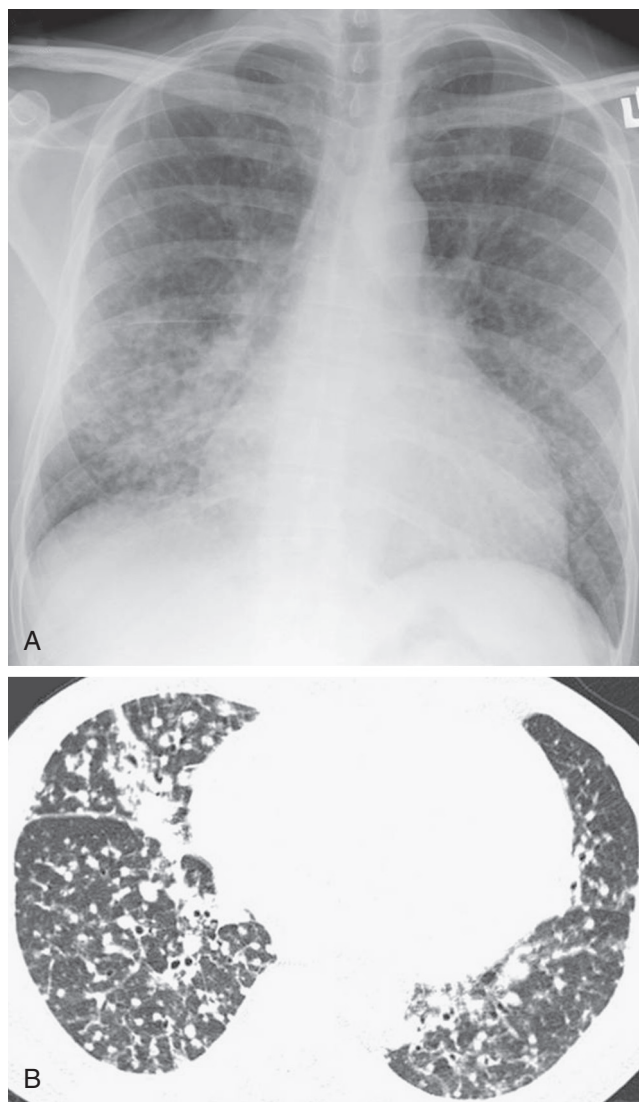
eFigure 37-6 Lymphadenopathy due to coccidioidomycosis. **A**, Frontal chest radiograph shows right paratracheal lymphadenopathy (*arrow*) due to acute coccidioidomycosis. **B**, Unenhanced coronal chest CT shown in soft tissue windows confirms right paratracheal lymphadenopathy (*arrow*). (Courtesy Michael Gotway, MD.)



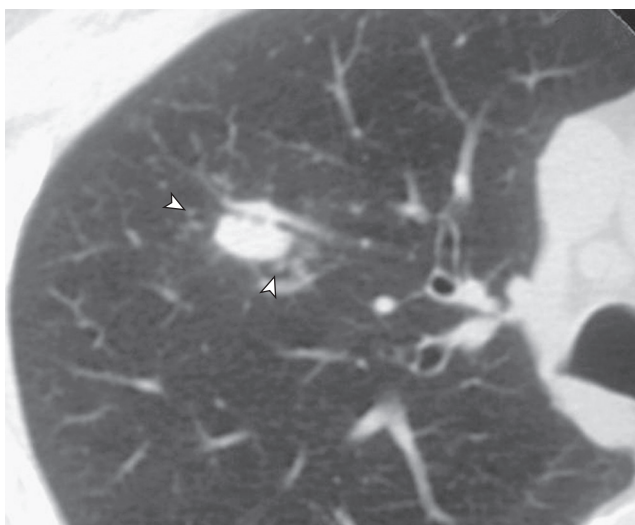
eFigure 37-7 Coccidioidomycosis causing acute respiratory distress syndrome. **A**, Frontal chest radiograph in a pregnant woman shows diffuse, fine, bilateral small nodules consistent with a miliary pattern of infection. **B**, Frontal chest radiograph obtained 2 weeks later when respiratory failure developed shows bilateral consolidation with air bronchograms consistent with acute respiratory distress syndrome. A tracheostomy has been placed in the interim and pneumomediastinum (the lucent area occupying the upper left mediastinal border) developed while the patient was on mechanical ventilation. The patient died 2 weeks after admission. (Courtesy Michael Gotway, MD.)



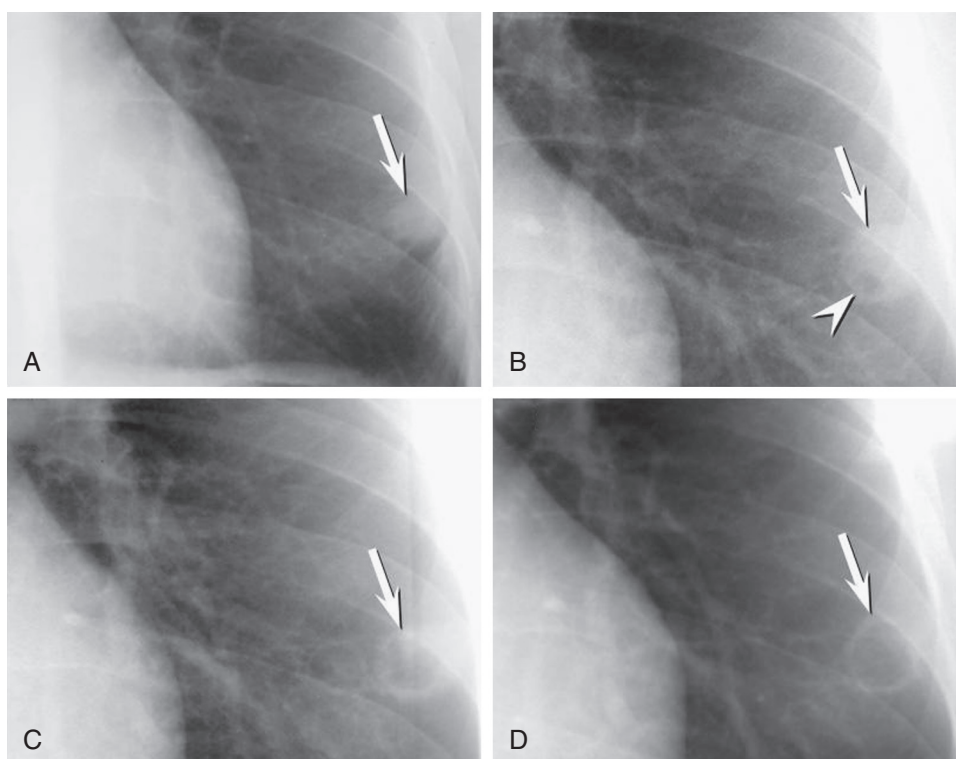
eFigure 37-8 Coccidioidomycosis meningitis. Axial contrast-enhanced magnetic resonance image of the brain shows extensive basal meningeal enhancement, particularly involving the middle cerebral artery cisterns (arrowheads) and quadrigeminal plate cistern (arrows). (Courtesy Michael Gotway, MD.)



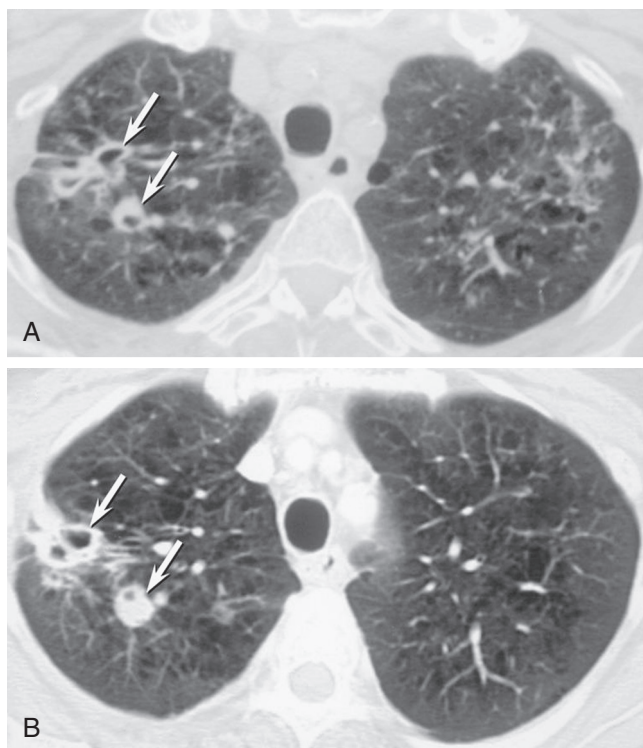
eFigure 37-9 Miliary coccidioidomycosis pulmonary infection. **A**, Frontal chest radiograph shows multiple bilateral, small, randomly disseminated nodules consistent with a miliary pattern. **B**, Chest CT shown in lung windows confirms these findings. (Courtesy Michael Gotway, MD.)



eFigure 37-10 Solitary pulmonary nodule due to *Coccidioides immitis*. Focused axial chest CT image shown in lung windows demonstrates a right upper lobe nodule with an air bronchogram. While the appearance closely resembles bronchogenic malignancy, the very small nodules surrounding the dominant opacity, often referred to as “satellite nodules” (arrowheads), are common with granulomatous infection, particularly coccidioidomycosis. Percutaneous transthoracic needle biopsy confirmed *Coccidioides immitis* infection, and the nodule resolved following treatment. (Courtesy Michael Gotway, MD.)



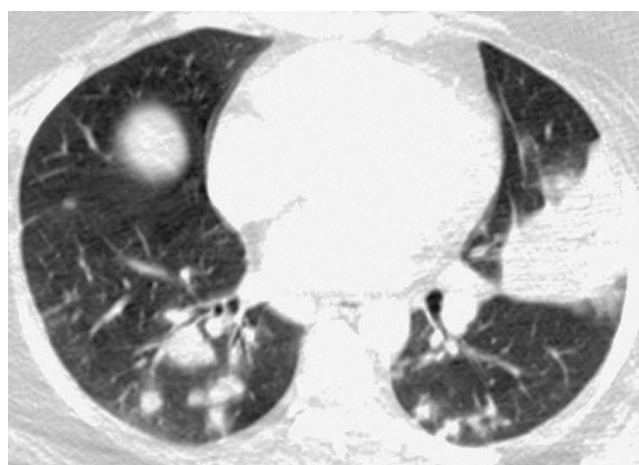
eFigure 37-11 Cavitary coccidioidomycosis. Focused frontal chest radiograph shows a nonspecific left lower lobe nodule (arrow, **A**); percutaneous transthoracic needle biopsy confirmed *Coccidioides immitis* infection. Focused serial chest radiographs obtained over the subsequent year (**B–D**) show progressive cavitation (arrowhead, **B**) within the nodule (arrow, **A–D**). Note that the nodule subsequently evolved into a thin-walled, “grape-skin” cyst (arrow, **D**). This evolution happened without treatment and the patient was asymptomatic throughout this time. The lesion subsequently resolved completely. (Courtesy Michael Gotway, MD.)



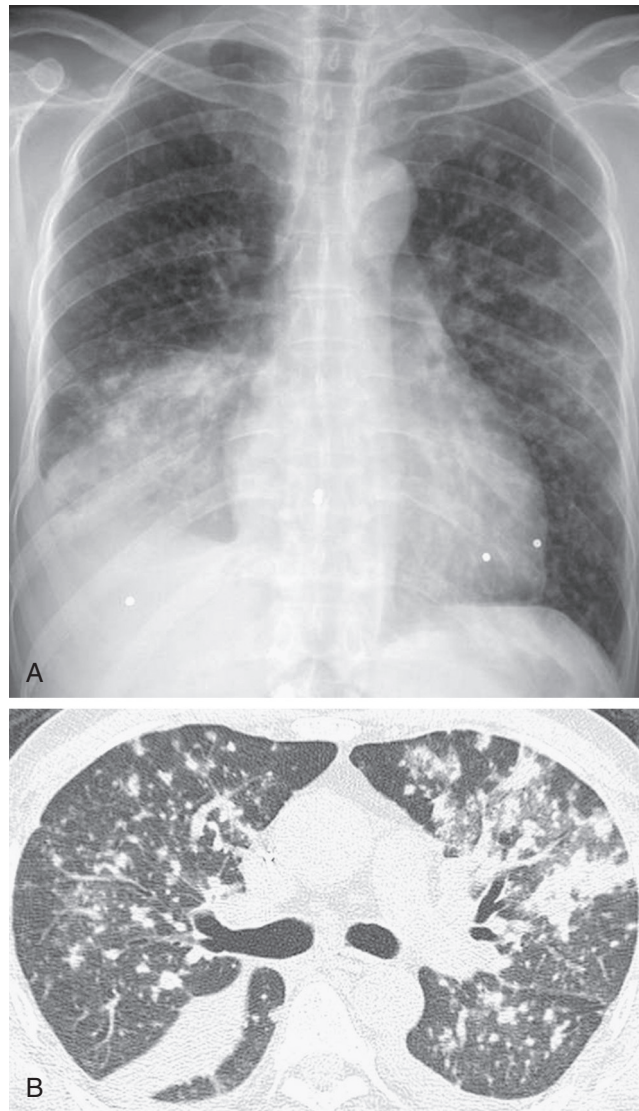
eFigure 37-12 Chronic fibrocavitary coccidioidomycosis. Axial chest CT (**A** and **B**) through the upper lobes shows cavitary nodules (*arrows*) associated with architectural distortion and peribronchovascular thickening and nodularity superimposed on emphysema. (Courtesy Michael Gotway, MD.)



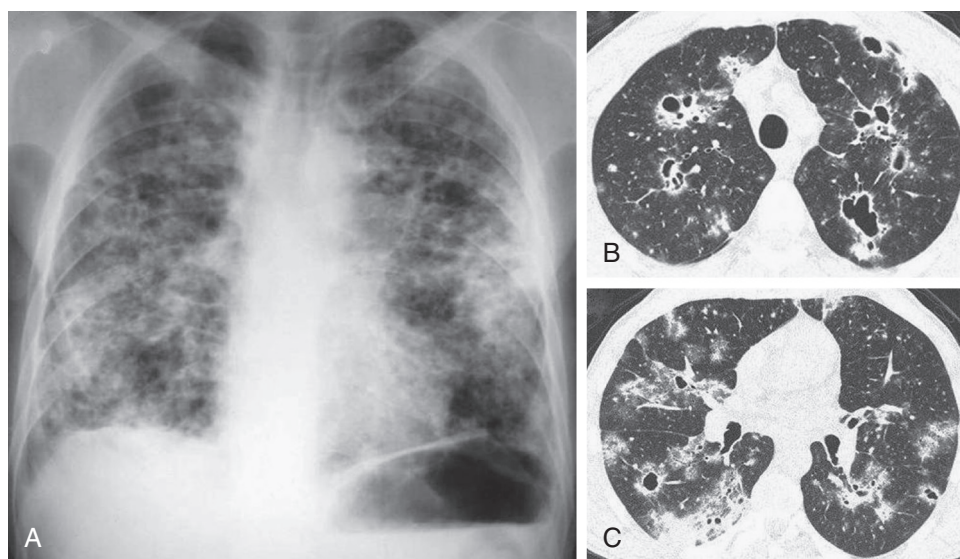
eFigure 37-13 Cavitary pulmonary blastomycosis. Axial chest CT shows cavitary (*arrow*) right upper lobe consolidation. (Image courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)



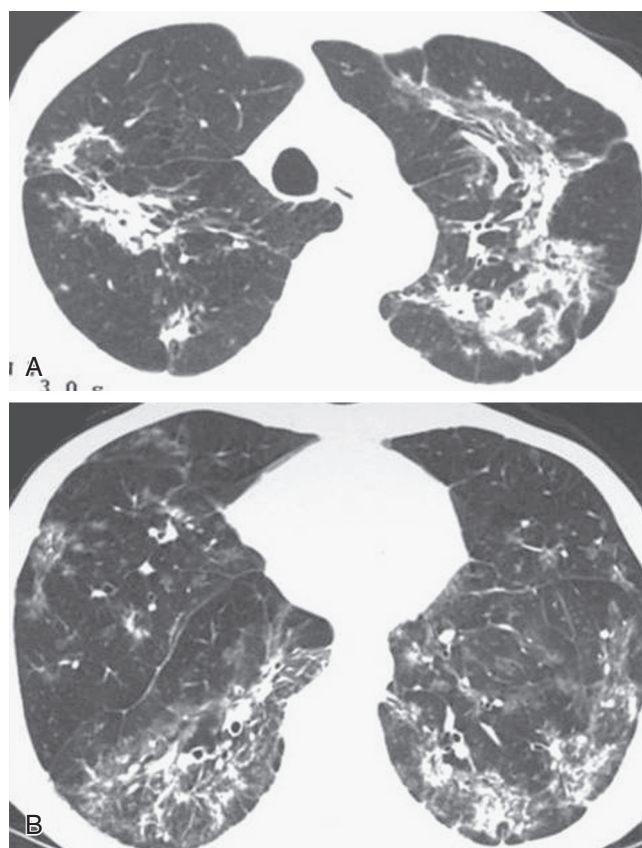
eFigure 37-14 Pulmonary blastomycosis presenting with multiple nodules. Axial chest CT shows masslike left upper lobe opacity with multiple, bilateral pulmonary nodules. (Image courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)



eFigure 37-15 Pulmonary blastomycosis in an immunosuppressed patient. **A**, Frontal chest radiograph in an immunosuppressed renal transplant patient shows extensive right lower lobe consolidation and multiple, bilateral, poorly defined nodules. **B**, Axial chest CT shows numerous, bilateral, poorly defined nodules and peribronchial consolidation in the left upper lobe. (Image courtesy Jeff Kanne, MD, Associate Professor, Thoracic Imaging, Department of Radiology University of Wisconsin School of Medicine and Public Health.)



eFigure 37-16 Pulmonary paracoccidioidomycosis infection. **A**, Frontal chest radiograph shows bilateral poorly defined masses. **B** and **C**, Axial chest CT images confirm the presence of bilateral nodules, masses, and masslike areas of consolidation. Percutaneous transthoracic needle biopsy subsequently proved paracoccidioidomycosis infection. (Courtesy Michael Gotway, MD.)



eFigure 37-17 Fibrosis in chronic pulmonary paracoccidioidomycosis infection. Axial chest CT performed through the upper (**A**) and lower (**B**) lungs shows peribronchial consolidation associated with bronchial dilation and architectural distortion. (Images courtesy Edson Marchiori, MD, Associate Professor, Radiology, Federal University of Rio de Janeiro.)

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DEMATIACEOUS (MELANIZED) FUNGI**INTRODUCTION**

The epidemiology of opportunistic mycoses is evolving. In certain populations, the frequency of opportunistic mycoses is increasing due to use of immune-modulating therapies, a higher frequency of invasive procedures and devices, and changes in climate and regional environments. In other populations, the frequency of opportunistic mycoses is decreasing, due to antifungal prophylaxis in high-risk patients and reconstitution of immunity with antiretroviral therapy for *human immunodeficiency virus* (HIV) infection. Heightened clinical awareness of fungal infections and the availability of improved diagnostics contribute to their increased recognition, and the availability of newer antifungal drugs provides broader therapeutic options.

Fungi are eukaryotic microorganisms that grow as yeasts or molds. Endemic fungi such as *Blastomyces dermatitidis* and *Histoplasma capsulatum*, reviewed in the preceding chapter, are considered dimorphic fungi, growing as molds at room temperature and yeast or yeastlike forms at body temperature. Yeasts are unicellular fungi and exist as single rounded or elongated cells and reproduce primarily by budding. The primary opportunistic yeasts reviewed here are *Candida* and *Cryptococcus*. In contrast, molds are multicellular filamentous fungi composed of hyphae that grow by branching with extension at the hyphal apices. Clinically relevant opportunistic molds are often categorized on the basis of their hyphae. Septate hyphae contain cross walls that divide the hyphae into compartments, whereas aseptate or sparsely septate hyphae either lack or infrequently demonstrate these cross walls, respectively. This distinction can be used in identifying molds in respiratory samples and tissue histopathology. Aseptate (or sparsely septate) hyphae are seen in mucormycosis, caused by molds such as *Mucor* and *Rhizopus* (historically referred to as *Zygomycetes*). Opportunistic molds producing septate hyphae are further subdivided as hyaline or dematiaceous molds. Hyaline molds produce colorless or lightly pigmented hyphae in tissue and infections are referred to *hyalohyphomycosis*.

Dematiaceous or black molds are septate molds that contain melanin in their cell walls, resulting in brown pigmentation, which can be seen in histopathology specimens and under direct microscopic examination. Infections with the dematiaceous molds are referred to as *phaeohyphomycoses*.

This chapter discusses the most common opportunistic mycoses of the respiratory tract and their epidemiology, clinical characteristics, diagnosis, and treatment. The chapter begins with discussion of the currently available antifungal agents.

ANTIFUNGAL THERAPY

Rapid initiation of antifungal therapy is essential in the management of *invasive fungal infections* (IFIs). The primary classes of antifungal agents target either the plasma membrane or the cell wall. *Amphotericin B* (AmB) was previously the primary antifungal agent for IFIs; however, newer antifungals, including the extended spectrum azoles and echinocandins, have broadened the therapeutic options, and lipid formulations of AmB have less toxicity. In addition, combination therapy should be considered in certain IFIs. The following section is a broad overview of the major antifungal agents. [Tables 38-1](#) and [38-2](#) summarize details of the available agents including their spectrum of activity, primary toxicities, interactions, recommendations for therapeutic drug monitoring, and the U.S. *Food and Drug Administration* (FDA) approved indications.

POLYENES

The polyenes were the first antifungals in clinical use and include nystatin and AmB. AmB binds to ergosterol, an essential component of the fungal cell membrane. AmB binding increases membrane permeability and causes fungal cell death.¹ AmB also induces proinflammatory cytokines by activating Toll-like receptor 2, which contributes

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Table 38-1 Comparison of Antifungal Agents

Antifungal Therapy	Fungal Spectrum of Activity ^{1,5,13,294-308}	Therapeutic Drug Monitoring ^{5,11,309-312}	*Major Adverse Effects ^{1,5,295-308}	*Major Drug Interactions ^{1,5,295-308}
POLYENES				
Amphotericin B deoxycholate (AmB-d, Fungizone)	<i>Aspergillus</i> (resistance in <i>A. terreus</i> , reduced susceptibility in others including <i>A. nidulans</i> , <i>A. ustus</i>)	TDM not recommended	Normocytic, normochromic anemia, hypokalemia, hypomagnesemia	Close monitoring when used with other nephrotoxic therapies
Lipid formulations of AmB:	<i>Candida</i> (resistance in <i>C. lusitanae</i>)		Infusion-related reactions (e.g., chills/rigors, fever, nausea, vomiting; can be reduced with preinfusion acetaminophen and diphenhydramine; meperidine may be used for rigors)	
Liposomal AmB (LAmB, AmBisome)	<i>Cryptococcus</i>		Nephrotoxicity (can be reduced with hydration, often 500 mL normal saline given before and after infusion)	
AmB Lipid Complex (ABLC, Abelcet)	Dematiaceous molds (e.g., <i>Alternaria</i> , <i>Bipolaris</i> , <i>Cladophialophora</i> , <i>Exserohilum</i> , <i>Rhinocladiella</i>)		Nephrotoxicity may be reduced with the lipid formulations of AmB	
AmB Colloidal Dispersion (ABCD, Amphotec)	Endemic fungi (e.g., blastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, <i>Penicillium marneffeii</i> , Sporotrichosis)			
	Mucormycosis (e.g., <i>Rhizopus</i> , <i>Rhizomucor</i> , <i>Mucor</i>)			
	Non- <i>Aspergillus</i> hyaline molds (resistance in some species including <i>Fusarium</i> and <i>Scedosporium</i> , also <i>Purpureocillium lilacinum</i>)			
AZOLES				
Fluconazole (FLU, Diflucan)	<i>Candida</i> (intrinsic resistance with <i>C. krusei</i> , variable susceptibility to <i>C. glabrata</i>) <i>Cryptococcus</i> Some activity against endemic mycoses (e.g., coccidioidomycosis)	TDM not recommended Renal dose adjustment is required	Alopecia (with prolonged therapy) GI effects (diarrhea, nausea, vomiting) Cardiac effects (has been associated with QT prolongation and torsades de pointes in patients with other risks) Hepatotoxicity	Fluconazole is a potent CYP2C9 inhibitor and moderate CYP3A4 inhibitor May interact with drugs metabolized through these enzyme systems Drugs that reduce FLU concentration: rifampin, rifabutin FLU increases concentration of carbamazepine, phenytoin, midazolam, rifabutin, sirolimus, some NSAIDs, tacrolimus, vinca alkaloids, zidovudine Other considerations: –QT prolongation with astemizole, haloperidol, macrolides –Potentiation of warfarin –CNS side effects with all-trans retinoic acid –Increased risk of rhabdomyolysis with atorvastatin, fluvastatin, simvastatin

Table 38-1 Comparison of Antifungal Agents (Continued)

Antifungal Therapy	Fungal Spectrum of Activity ^{1, 5, 13, 294-308}	Therapeutic Drug Monitoring ^{5, 11, 309-312}	*Major Adverse Effects ^{1, 5, 295-308}	*Major Drug Interactions ^{1, 5, 295-308}
Itraconazole (ITRA, Sporanox)	<i>Aspergillus</i> (resistance in some isolates) <i>Candida</i> (including <i>C. krusei</i> , <i>C. glabrata</i> , and <i>C. tropicalis</i>) <i>Cryptococcus</i> Dematiaceous molds Endemic mycoses (including paracoccidioidomycosis) <i>Penicillium marneffei</i> <i>Sporothrix schenckii</i> Trichophyton ITRA is not usually active against mucormycosis or many <i>Fusarium</i> and <i>Scedosporium</i> spp	TDM is recommended Random concentration measured after ≥ 2 weeks of therapy with goal $\geq 1 \mu\text{g/mL}$ For HPLC, the goal concentration is sum of ITRA and active metabolite, hydroxy-ITRA Capsules: take with food and acidic beverage (e.g., cola); avoid proton pump-inhibitors and H ₂ blockers, which decrease absorption Solution: take on empty stomach Blood concentrations $\sim 30\%$ higher with ITRA solution vs. ITRA capsule formulation	Adrenal insufficiency (long-term use, rare) CHF (avoid in patients with ventricular dysfunction or history of CHF) GI effects (diarrhea, nausea, vomiting) Headache Hearing loss Hepatotoxicity Neuropathy Peripheral edema QT prolongation and torsades de pointes in patients with multiple risks Rash	ITRA is a potent CYP3A4 inhibitor and substrate of CYP3A4; may interact with drugs metabolized through this enzyme system Drugs that decrease ITRA concentration: carbamazepine, nevirapine, phenytoin, rifabutin, rifampin Drugs that increase ITRA concentration: macrolide antibiotics, protease inhibitors ITRA increases concentration of busulfan, cyclosporine, carbamazepine, digoxin, dihydropyridines, midazolam, rifabutin, ritonavir, sirolimus, tacrolimus, vinca alkaloids Other considerations: –QT prolongation with dofetilide, pimozone, quinidine –Increased risk of rhabdomyolysis with atorvastatin, fluvastatin, simvastatin
Posaconazole (POSA, Noxafil)	<i>Aspergillus</i> <i>Candida</i> <i>Cryptococcus</i> Endemic fungi, limited data (blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis) Non- <i>Aspergillus</i> hyaline molds (species-dependent, limited data) Mucormycosis Dematiaceous molds	TDM is recommended when POSA used for prophylaxis and treatment of systemic infections. Recommendations apply to POSA suspension. See text regarding extended-release tablet and intravenous formulation. Trough concentrations measured \geq day 8 of therapy with goal concentration $\geq 0.7 \mu\text{g/mL}$ In patients not responding to treatment, consider troughs > 1 to $1.25 \mu\text{g/mL}$ Administer with high-fat meal, acidic beverage (e.g., cola, ginger ale) and avoid proton pump inhibitors Note that dose escalation beyond 800 mg/day is unlikely to result in higher concentration as absorption is saturable; increased concentration is best achieved with more frequent dosing intervals (e.g., 400 mg twice daily should be changed to 200 mg by mouth four times daily) Does not require renal dose adjustment	GI effects (diarrhea, nausea, vomiting) Headache Hepatotoxicity QT prolongation (less common than with ITRA or VORI)	POSA is an inhibitor of CYP3A4 and substrate of P-glycoprotein; may interact with drugs metabolized via these systems Drugs that decrease POSA concentration: cimetidine, efavirenz, esomeprazole, phenytoin, rifabutin POSA increases concentration of atazanavir, cyclosporine, digoxin, dihydropyridines, midazolam, rifabutin, ritonavir, sirolimus, tacrolimus, vinca alkaloids Other considerations: –QT prolongation with pimozone, quinidine –Increased risk of rhabdomyolysis with atorvastatin, lovastatin, simvastatin –Avoid use with ergot alkaloids

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Table 38-1 Comparison of Antifungal Agents (Continued)

Antifungal Therapy	Fungal Spectrum of Activity ^{1, 5, 13, 294-308}	Therapeutic Drug Monitoring ^{5, 11, 309-312}	*Major Adverse Effects ^{1, 5, 295-308}	*Major Drug Interactions ^{1, 5, 295-308}
Voriconazole (VORI, VFEND)	<p><i>Aspergillus</i> <i>Candida</i> spp <i>Cryptococcus</i> Dematiaceous molds Endemic fungi, limited data (blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis) Non-<i>Aspergillus</i> hyaline molds including <i>Acremonium</i>, <i>Fusarium</i>, <i>Paecilomyces</i>, <i>Scedosporium</i>, and <i>Trichoderma</i> VORI is not active against mucormycosis</p>	<p>TDM for prophylaxis and treatment of systemic infections is recommended Trough concentration measured \geq day 5 of therapy with goal trough $\geq 1.0 \mu\text{g/mL}$ to $5.5 \mu\text{g/mL}$; some argue for target of $\geq 2 \mu\text{g/mL}$ for treatment Administer 1 hour before or after a meal Dose adjustment of the IV formulation is required in patients with CrCl $< 50 \text{ mL/min}$ due to potential accumulation of sulfobutyl ether beta-cyclodextrin sodium (solubilizing vehicle)</p>	<p>Fluorosis and periostitis GI effects (diarrhea, nausea, vomiting) Headache Hepatotoxicity QT prolongation Skin rash, photosensitivity Visual disturbances (e.g., photopsia, color-vision change, photophobia, other visual hallucinations), rare optic neuritis and papilledema Long-term use and association with skin cancer (see text)</p>	<p>VORI is substrate of CYP2C19, CYP2C9, and CYP3A4 and is an inhibitor of CYP3A4 May interact with drugs metabolized via these systems Drugs that decrease VORI concentration: carbamazepine, efavirenz, phenobarbital, phenytoin, rifabutin, rifampin, ritonavir, St. Johns wart Drugs that increase VORI concentration: fluconazole, certain oral contraceptives VORI increases concentration of cyclosporine, efavirenz, fentanyl, methadone, some NSAIDs, phenytoin, rifabutin, sirolimus, tacrolimus Other considerations: –QT prolongation with astemizole, pimozone or quinidine –Potentiation of warfarin –Avoid use with ergot alkaloids</p>
ECHINOCANDINS				
<p>Caspofungin (CAS, Cancidas) Micafungin (MICA, Mycamine) Anidulafungin (ANI, Eraxis)</p>	<p><i>Aspergillus</i> (fungistatic) <i>Candida</i> spp (fungicidal, elevated MICs reported with <i>C. parapsilosis</i> and <i>C. guilliermondii</i>) Echinocandins have moderate activity against the mycelial phase of dimorphic fungi but lack activity against the yeast phase and are not used in treatment of endemic mycoses Echinocandins lack significant activity against mucormycosis, dematiaceous molds, non-<i>Aspergillus</i> hyaline molds (although some use in combination therapy, see text)</p>	<p>TDM not recommended No dosage adjustment required for renal dysfunction</p>	<p>GI effects (diarrhea, nausea, vomiting) Hepatotoxicity (uncommon) Infusion reactions (histamine-induced, greatest with CAS) Injection site thrombophlebitis</p>	<p>Minimal drug interactions compared with other antifungal drugs In general, poor CYP substrates (CAS/MICA) and/or weak CYP inhibitors of 3A4 (MICA) and not affected by P-glycoprotein ANI undergoes no hepatic metabolism, only chemical degradation CAS concentration decreased with rifampin, efavirenz, nevirapine, phenytoin, carbamazepine MIC increases sirolimus and nifedipine concentration</p>

Table 38-1 Comparison of Antifungal Agents (Continued)

Antifungal Therapy	Fungal Spectrum of Activity ^{1, 5, 13, 294-308}	Therapeutic Drug Monitoring ^{5, 11, 309-312}	*Major Adverse Effects ^{1, 5, 295-308}	*Major Drug Interactions ^{1, 5, 295-308}
OTHER				
Flucytosine (5-FC, Ancobon)	<i>Aspergillus</i> <i>Candida</i> <i>Cryptococcus</i> Dematiaceous fungi (some, including <i>Phialophora</i> and <i>Cladosporium</i> spp) <i>Sporothrix schenckii</i> (variable MICs) 5-FC is used in combination therapy, typically with AmB	Cryptococcal infection: concentration measured on day 3 to 5 of therapy, 2 hours after dose, target: 30 to 80 µg/mL When TDM not available both renal function and cell counts must be closely monitored Renal dose adjustment is required	Bone marrow suppression GI effects (abdominal pain, diarrhea, nausea, vomiting) Hepatotoxicity Nephrotoxicity	Aluminum hydroxide or magnesium hydroxide suspension (delays 5-FC absorption) Cytarabine (cytosine arabinoside, competitive inhibitor of 5-FC) Close monitoring when used with other nephrotoxic and myelosuppressive therapies
Terbinafine (TBF, Lamisil)	<i>Aspergillus</i> Sporotrichosis Some activity (usually in combination therapy) against non- <i>Aspergillus</i> hyaline molds (species dependent), dematiaceous molds (species dependent)	TDM not recommended Clearance is decreased by 50% when CrCl ≤ 50 mL/min	Depressive symptoms Hepatotoxicity Neutropenia Rash Smell and taste disturbances	TBF is an inhibitor of CYP2D6 May interact with drugs metabolized via this system, including tricyclic antidepressants, selective serotonin reuptake inhibitors, beta blockers, antiarrhythmic class 1C (e.g., flecainide, propafenone) Drugs that decrease TBF: rifampin Drugs that increase TBF: fluconazole TBF may decrease cyclosporine concentration

*This is not an all-inclusive list of adverse effects and/or drug interactions. Some of the listed drug interactions are considered contraindications to concomitant therapy.

ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmB-d, amphotericin B deoxycholate; ANI, anidulafungin; CAS, caspofungin; CHF, congestive heart failure; CNS, central nervous system; CrCl, creatinine clearance; CYP, cytochrome P-450 enzyme system; FLU, fluconazole; GI, gastrointestinal; H2, histamine-2 receptor; ITRA, itraconazole; IV, intravenous; MIC, minimal inhibitory concentration; MICA, micafungin; LAmB, liposomal amphotericin B; NSAIDs, nonsteroidal antiinflammatory drugs; POSA, posaconazole; spp, species; TBF, terbinafine; TDM, therapeutic drug monitoring; VORI, voriconazole; 5-FC, flucytosine.

Table 38-2 FDA Approved Fungal Indications for Specific Antifungal Agents

Antifungal Agent	FDA Approved Indications ^{266, 296-308}
POLYENES	
Amphotericin B deoxycholate (Fungizone), Apothecon Generic available (U.S.): yes	Treatment of potentially life-threatening fungal infections: Aspergillosis Blastomycosis Candidiasis, systemic Coccidioidomycosis Cryptococcosis Histoplasmosis Mucormycosis (including susceptible species of the genera <i>Abidia</i> , <i>Mucor</i> , and <i>Rhizopus</i> and infections due to related susceptible species of <i>Conidiobolus</i> and <i>Basidiobolus</i>) Sporotrichosis
Amphotericin B lipid complex, ABLC (Abelcet), Sigma-Tau Pharmaceuticals Generic available (U.S.): no	Treatment of invasive fungal infections in patients who are refractory or intolerant of conventional amphotericin B therapy
AmB Colloidal Dispersion, ABCD (Amphotec), Alkopharma Generic available (U.S.): no	Treatment of invasive aspergillosis in patients with renal impairment or who are refractory or intolerant of conventional amphotericin B therapy
Liposomal amphotericin B (AmBisome), Astellas Pharma US Generic available (U.S.): no	Treatment of: Aspergillosis and candidiasis (in patients with renal impairment or who are refractory or intolerant of conventional amphotericin B therapy) Cryptococcosis (in HIV patients with cryptococcal meningitis and for cryptococcal infections in patients with renal impairment or who are refractory or intolerant of conventional amphotericin B therapy) Empirical therapy for presumed fungal infection in febrile neutropenic patients

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Table 38-2 FDA Approved Fungal Indications for Specific Antifungal Agents (Continued)

Antifungal Agent	FDA Approved Indications ^{266,296-308}
AZOLES	
Fluconazole (Diflucan), Pfizer Generic available (U.S.): yes	Treatment of: Candidiasis (including chronic mucocutaneous candidiasis, esophageal and oropharyngeal candidiasis, <i>Candida</i> urinary tract infection and peritonitis, other systemic <i>Candida</i> infections including candidemia, disseminated candidiasis and pneumonia, vaginal candidiasis) Cryptococcal meningitis Prophylaxis for patients undergoing HSCT who receive cytotoxic chemotherapy and/or radiation therapy
Itraconazole (Sporanox), Janssen Pharmaceuticals Generic available (U.S.): yes	Treatment of: Aspergillosis (pulmonary and extrapulmonary in patients who are intolerant or refractory to amphotericin B) Blastomycosis (pulmonary and extrapulmonary infection) Histoplasmosis (chronic pulmonary disease and disseminated nonmeningeal infection) Onychomycosis of the fingernails and toenails due to dermatophytes (non-immunocompromised only)
Posaconazole (Noxafil), Merck & Co., Inc. Generic available (U.S.): no	Treatment of oropharyngeal candidiasis including that which is refractory to itraconazole and/or fluconazole Prophylaxis of invasive aspergillosis and invasive candidiasis (in severely immunocompromised patients such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy)
Voriconazole (VFEND), Pfizer Generic available (U.S.): yes	Treatment of: Aspergillosis (invasive) Candidiasis (esophageal candidiasis, candidemia in nonneutropenic patients and the following <i>Candida</i> infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds) Serious infections caused by <i>Scedosporium apiospermum</i> and <i>Fusarium</i> species, including <i>Fusarium solani</i> , in patients intolerant of, or refractory to, other therapy
ECHINOCANDINS	
Caspofungin (Cancidas), Merck & Co., Inc Generic available (U.S.): no (approval pending)	Treatment of: Aspergillosis (invasive disease in patients who are refractory to or intolerant of other therapies such as amphotericin B, lipid formulations of amphotericin B or itraconazole). Candidiasis (esophageal candidiasis, candidemia, and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis, and pleural space infections) Empirical therapy for presumed fungal infections in febrile neutropenic patients
Micafungin (Mycamine), Astellas Pharma US Generic available (U.S.): no	Treatment of candidiasis (esophageal candidiasis, candidemia, acute disseminated candidiasis, peritonitis, and abscesses) Prophylaxis of <i>Candida</i> infections in patients undergoing HSCT
Anidulafungin (Eraxis), Pfizer Generic available (U.S.): no	Treatment of candidiasis (esophageal candidiasis, candidemia, and other forms of <i>Candida</i> infections including intra-abdominal abscess and peritonitis)
OTHER	
Flucytosine (Ancobon), Valeant Pharmaceuticals Generic available (U.S.): yes	Treatment of: Candidiasis (susceptible strains causing septicemia, endocarditis, urinary tract infections, and pneumonia) Cryptococcosis (susceptible strains causing meningitis, pulmonary infections, septicemia, and urinary tract infections) Note that flucytosine should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine monotherapy
Terbinafine (Lamisil), Novartis Generic available (U.S.): yes, product dependent	Treatment of onychomycosis of the toenail or fingernail due to dermatophytes

GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; U.S., United States.

to the acute side effects of fever and myalgias, and may augment host responses to fungal infection.² AmB has activity against multiple fungal pathogens including *Aspergillus*, *Candida*, the endemic mycoses (e.g., blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis) and mucormycosis.³ However, certain fungi, including *Aspergillus terreus*, *Candida lusitanae*, *Scedosporium prolificans*, and *Trichosporon beigelii*, may be intrinsically resistant to AmB, and other pathogens such as *Fusarium* species and the dematiaceous molds may have high *minimal inhibitory concentrations* (MICs) to AmB.⁴

The lipid formulations of AmB were introduced to reduce nephrotoxicity seen with conventional amphotericin, termed *amphotericin B desoxycholate* (AmB-d). The lipid formulations of AmB are now often used first-line, particularly in patients with renal dysfunction or on concurrent nephrotoxic medications. Lipid formulations include *liposomal AmB* (LAmB) and *AmB lipid complex* (ABLC). Due to its ten- to sixty-fold lower cost compared with the lipid formulations, conventional AmB-d continues to have an important role in treatment of patients at low risk of toxicity, such as outpatients without comorbidities.

AZOLES

Certain drugs containing an imidazole ring have antimicrobial activity. N-substituted azoles, termed triazoles, have antifungal activity and acceptable host toxicity, and have emerged as a primary class of antifungals for treatment and prevention of IFIs. For the purpose of brevity, the antifungal triazoles are commonly termed *azoles*, as they are in this chapter. The most widely used azoles are fluconazole, itraconazole, posaconazole, and voriconazole. These agents act on the fungal cell membrane by inhibiting the cytochrome P-450–dependent 14- α -demethylase, a critical enzyme in the conversion of lanosterol to ergosterol. The azoles are fungistatic or fungicidal, depending on the specific azole and fungal species.⁵ Immunomodulating effects have been described with azoles and may contribute to their efficacy.² While earlier azoles, such as fluconazole, are active against yeasts, the expanded spectrum azoles, including voriconazole and posaconazole, are active against yeasts and molds. Fluconazole is active against *Cryptococcus* and *Candida*, and has variable activity against endemic fungi, including *Coccidioides*. *Candida krusei* is intrinsically resistant to fluconazole and high-level resistance is emerging among some non-*albicans* *Candida* species, including *C. glabrata*. Itraconazole has little role in treatment of opportunistic fungal infections; its principal indications are treatment of indolent, non-central nervous system (CNS) blastomycosis or histoplasmosis, and as an alternative to fluconazole for treatment of indolent non-CNS coccidioidomycosis. Itraconazole is also indicated in treatment of *allergic bronchopulmonary aspergillosis* (ABPA). Itraconazole exhibits highly variable absorption and pharmacokinetics; therapeutic drug monitoring is essential to guide optimal dosing for an individual patient.

The extended-spectrum azoles have activity against many molds, including *Aspergillus*, non-*Aspergillus* hyaline hyphomycetes such as *Fusarium*, *Scedosporium*, and *Paecilomyces*, and some dematiaceous molds. Voriconazole is the drug of choice for the treatment of invasive *Aspergillus* infections. Among the azoles, only posaconazole has activity against the agents of mucormycosis.

ECHINOCANDINS

The echinocandins, including caspofungin, micafungin, and anidulafungin, are increasingly used given their efficacy, tolerability, lack of drug interactions, and the prevalence of azole-resistant *Candida* species. Unlike AmB and the azoles, the echinocandins act on the fungal cell wall via inhibition of (1 \rightarrow 3)- β -D-glucan synthase, thereby inhibiting production of (1 \rightarrow 3)- β -D-glucan (β -D-glucan), an essential component of the fungal cell wall. Echinocandins are fungicidal against multiple *Candida* species, including *C. albicans*, *C. dubliniensis*, *C. glabrata*, and *C. krusei*; however, certain *Candida* species, such as *C. guilliermondii* and *C. parapsilosis*, typically have higher MICs. The echinocandins are fungistatic rather than fungicidal against filamentous fungi such as *Aspergillus* species because their activity is restricted to sites where the fungal cell wall is actively growing (i.e., hyphal tips and branching junctional cells), and are not active on subapical hyphal cells.⁶ Echinocandins lack significant activity against other fungal pathogens

such as *Cryptococcus*, *Mucorales*, and *Trichosporon* species and the endemic fungi.⁷ The immunostimulatory effects of echinocandins on monocytes and monocyte-derived macrophages may be of particular importance against *Aspergillus*.^{8,9}

FLUCYTOSINE

Flucytosine is an antimetabolite that inhibits fungal DNA and protein synthesis. It is used in combination with other antifungal agents given the high frequency of emergence of resistance with monotherapy.¹⁰ It is fungistatic or fungicidal, depending upon the organism, and is most often used in combination with AmB against *Cryptococcus*¹¹ and in severe *Candida* infections such as endocarditis and CNS infections.¹²

TERBINAFINE

Terbinafine is a synthetic allylamine that exerts its antifungal effects via inhibition of fungal squalene epoxidase, an enzyme involved in ergosterol formation. Terbinafine is fungicidal and is used most commonly for dermatophyte infections and the treatment of chromoblastomycosis.¹³ In vitro synergy data have led to its use in combination, most often with extended-spectrum azoles and AmB, for the management of severe or refractory mold infections such as *Scedosporium*,¹⁴ *Fusarium*,¹⁵ and other hyaline and dematiaceous molds.¹³

CRYPTOCOCCOSIS

EPIDEMIOLOGY

Cryptococcus neoformans has a global distribution and can be isolated from the soil and excreta of birds such as pigeons. *C. neoformans* var. *grubii* (serotype A) is the predominant pathogen worldwide; however, infections with *C. neoformans* var. *neoformans* (serotype D) are prevalent in Northern Europe. *C. gattii* can cause disease in immunocompetent patients. Until recently, *C. gattii* was found in Australia, Southeast Asia, and Central Africa, often associated with eucalyptus and fir trees. Recently, serious infections with *C. gattii* have been recognized in Vancouver, British Columbia, and in the Pacific Northwest United States.^{16,17} Most cryptococcal infections are seen in immunocompromised hosts, including patients with advanced HIV infection,¹⁸ malignancies,¹⁹ *solid organ transplants* (SOT),²⁰ and other conditions.²¹

Cryptococcosis is one of the most common life-threatening fungal infections in HIV-infected patients,²² and is the third most common invasive fungal pathogen (behind *Candida* and *Aspergillus*) in SOT recipients in whom it causes 8% of IFIs.²³ *Cryptococcus* affects *hematopoietic stem cell transplant* (HSCT) patients less often, in whom it causes 0.6% of IFIs.²⁴

PATHOGENESIS

Infections with *Cryptococcus* are initiated by inhalation of small yeast or spores (produced through mating). Once in the alveoli, the outcome is determined by the virulence of

the infecting strain, by host genetic polymorphisms, by innate and adaptive immune responses, and by the presence of comorbidities. The virulence of *Cryptococcus* is related to its polysaccharide capsule as well as the presence of specific enzymes including laccase (required for production of fungal melanin), phospholipase B, and inositol phosphosphingolipid-phospholipase.²⁵ In the lungs, cryptococci replicate and synthesize a large polysaccharide capsule, which protects against phagocytosis. The cryptococci that are successfully phagocytosed reside and replicate in mature phagolysosomes and subsequently spread to other cells using multiple mechanisms.²⁶

Cryptococci encounter diverse elements of the innate immune response, including polymorphonuclear cells, macrophages, and dendritic cells, which produce the cytokines that drive a type 1 helper CD4⁺ T cell response.²⁷ CD4⁺ cells are necessary to prevent dissemination from the lungs; both CD4⁺ and CD8⁺ cells are required for clearance of infection in mice.²⁸ Defects in humoral immunity are less commonly associated with cryptococcal infections than are defects in cellular immunity,²⁹ although antibody-mediated immunity contributes to control of cryptococci in mice.^{27,30} The presence of autoantibodies to granulocyte macrophage colony stimulating factors may predispose seemingly immunocompetent individuals to infection with *C. gattii*.

CLINICAL MANIFESTATIONS

The clinical presentation of cryptococcal infections is determined by the immune status of the host, the *Cryptococcus* species, and the site of infection. The lungs are the most commonly involved primary site; the CNS is the most common site of dissemination. Pulmonary involvement ranges from asymptomatic colonization to multifocal consolidation and acute respiratory distress syndrome. Most pulmonary infections are asymptomatic or mildly symptomatic in immunocompetent hosts, and may be discovered incidentally on radiographic imaging. *Cryptococcus* is also believed to cause latent infection in the lung and reactivate in the setting of depressed immunity. In fact, most infections may represent reactivation, and transfer of infection

with donor organs may contribute to risk in SOT patients.³¹ Dissemination may develop during primary infection or reactivation. Acute infection in the immunocompetent host may manifest with fever, fatigue, cough, and sputum production. In immunocompromised patients, severe symptoms, including fever, cough, and shortness of breath, can rapidly progress to respiratory failure and acute respiratory distress syndrome. In a prospective multicenter international study of 111 SOT recipients, cryptococcal infections typically were seen a median of 21 months after transplant, and pulmonary (60%) and CNS (58%) involvement were most common.³² In patients with advanced HIV infection, meningoencephalitis is the predominant presentation.³³

The radiographic findings in cryptococcal pulmonary infections commonly include focal or diffuse pulmonary nodules or patchy air-space consolidation (eFig. 38-1). However, other findings include cavitation (see eFig. 90-24), mass lesions (i.e., cryptococcomas, (see eFigs. 90-23 and 90-24), reticulonodular patterns, ground-glass attenuation (see eFig. 90-21), and associated effusions or lymphadenopathy (see eFig. 90-24A and B).^{34,35} In a study of computed tomography (CT) radiographic findings of cryptococcosis, immunocompromised patients had more extensive pulmonary involvement with cavitation and parenchymal consolidation than did immunocompetent hosts—a finding that contrasts with that in tuberculosis.³⁴ Cryptococcomas in both the CNS and in the lungs are seen more commonly with *C. gattii* than with *C. neoformans* infection, and are more common in immunocompetent hosts.³⁶

DIAGNOSIS

The diagnosis of pulmonary cryptococcosis is based on symptoms, chest radiography, culture, and/or histopathologic findings (Fig. 38-1) and cryptococcal antigen testing. *Cryptococcus* can be cultured from respiratory specimens including sputum and bronchoalveolar lavage (BAL); blood cultures are only positive in disseminated infections. *Cryptococcus* is easily identified under the microscope as 5 to 10 μ m spherical to oval yeast cells with a surrounding

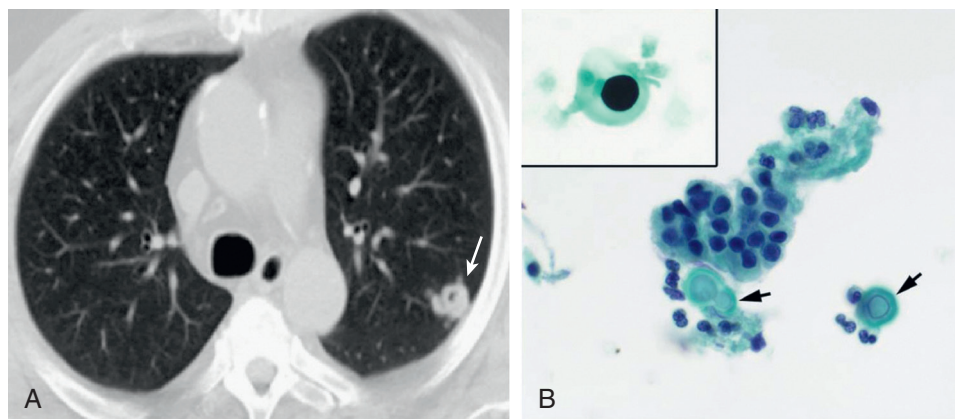


Figure 38-1 Cryptococcus. Pulmonary infection with *Cryptococcus* in an asymptomatic cardiac transplant patient on chronic immunosuppression with new, bilateral pulmonary nodules. **A**, Axial chest CT demonstrates a cavitary nodule (arrow) with small surrounding satellite nodules. **B**, CT-guided fine-needle aspiration of the pulmonary nodule shows encapsulated yeast (arrows), with the typical morphology of *Cryptococcus neoformans* (Papanicolaou stain; original magnification $\times 400$). Inset: Yeast showing mucin capsule with organism staining positive. (Methenamine silver stain; original magnification $\times 400$). (B, Courtesy Dr. Thomas Sporn, Duke University Medical Center, NC.)

capsule. Biochemical testing is used to confirm the identification; canavanine-glycine-bromothymol blue agar can be used for differentiating *C. gattii* from *C. neoformans*.³⁷ New methods are under development for rapid identification and speciation of cryptococci, including *polymerase chain reaction* (PCR)³⁸ and matrix-assisted laser desorption/ionization time of flight spectrometry.³⁹

In tissue samples, specialized stains such as Mayer's mucicarmine, which stains fungal melanin, are also helpful in establishing a diagnosis.³⁷ While the serum cryptococcal antigen assay has a high sensitivity and specificity in disseminated infection and cryptococcal meningoencephalitis, it can be negative in patients with isolated pulmonary infection. In a study of patients with SOT, serum cryptococcal antigen was detectable in 73% of patients (22 of 30) with isolated pulmonary involvement and was more likely to be negative with solitary pulmonary nodules than with multiple nodules and more extensive pulmonary disease. Titers of serum cryptococcal antigen were higher in those patients with concurrent extrapulmonary infection.⁴⁰

Determining the presence of disseminated infection and extent of organ involvement is crucial to the selection of appropriate therapy. Thus, cerebrospinal fluid evaluation (e.g., cell count, culture, and cryptococcal antigen) should be performed in all immunosuppressed patients with pulmonary cryptococcosis. Whether cerebrospinal fluid analysis is essential in immunocompetent patients with pulmonary cryptococcosis is less clear. Factors associated with higher likelihood of disseminated disease and the need for cerebrospinal fluid analysis include neurologic findings, signs of systemic infection, such as fever and weight loss, and serum cryptococcal Ag titer of at least 64.⁴¹

TREATMENT

The choice of therapy depends on the immune status of the host and the presence of extrapulmonary infection; current treatment recommendations are available from both the American Thoracic Society⁴² and *Infectious Diseases Society of America* (IDSA).¹¹ For pulmonary cryptococcosis in patients with evidence of disseminated infection, CNS involvement, or severe pneumonia, the treatment is separated into induction, consolidation, and maintenance regimens. The antimicrobials, doses, and duration are dependent on the patient's underlying risk group (e.g., HIV-infected, organ transplant recipient, and non-HIV infected, non-transplant recipient). Induction therapy is typically with AmB-d 0.7 to 1 mg/kg/day plus flucytosine 100 mg/kg/day. In transplant patients and patients with reduced renal function, lipid formulations of AmB (e.g., LAmB 3 to 4 mg/kg/day or ABLC 5 mg/kg/day) are substituted for AmB-d to minimize nephrotoxicity. Fluconazole is utilized for consolidation and maintenance therapy with doses ranging from 400 to 800 mg/day and 200 to 400 mg/day, respectively.¹¹

Mild-to-moderate infection isolated to the lungs is treated with fluconazole 400 mg/day for a minimum of 6 to 12 months. Some experts maintain that asymptomatic patients with resected solitary nodules, undetectable serum cryptococcal antigen, and no evidence of extrapulmonary infection may be observed closely without specific antifungal therapy.¹¹ Infections with *C. gattii* have been associated

with delayed clinical responses to antifungal therapy; potential explanations include high in vitro fluconazole MICs and a higher incidence of pulmonary and cerebral cryptococcomas with decreased drug penetration to these lesions.^{11,43,44}

Immune reconstitution inflammatory syndrome (IRIS) may complicate treatment of any opportunistic mycosis, but is most common in cryptococcosis. IRIS is usually characterized by worsening of clinical signs and symptoms of the original infection, which can be misinterpreted as progressive infection.^{11,45} IRIS arises most commonly with initiation of potent antiretroviral therapy in HIV infection and with abrupt improvement in immune competence in SOT recipients. Although less common, IRIS can also happen in patients with hematologic malignancies during neutrophil and monocyte recovery following myeloablative chemotherapy⁴⁶ and with lymphocyte recovery after receipt of monoclonal antibodies such as alemtuzumab.⁴⁷ The manifestations of IRIS in pulmonary disease may be severe and include acute respiratory distress syndrome. Transplant recipients developing IRIS associated with cryptococcal infection also have increased potential for allograft loss.⁴⁸ Treatment of IRIS in transplant recipients includes adjustment of immunosuppressive drugs to moderate the symptoms without promoting progression of the infection.¹¹ Nonsteroidal antiinflammatory drugs are often sufficient to ameliorate the symptoms of IRIS, but high-dose corticosteroids may be required to manage the complications of severe IRIS.

CANDIDIASIS

The epidemiology of invasive *Candida* infections has evolved substantially in the past 2 decades.^{49,50} While *Candida albicans* remains the most common species associated with invasive disease overall, more than 17 *Candida* species have been associated with human disease⁵¹ and non-*albicans* species account for an increasing proportion of infections.^{12,49,52}

Candida infections of the thorax include empyema, tracheobronchial and mediastinal infection, and pneumonia. *Candida* pneumonia is rare and is most often found in the setting of candidemia with dissemination to the lung in immunocompromised patients.^{53,54} Rarely, primary pneumonia develops due to aspiration of oropharyngeal contents.^{53,55,56} Mediastinitis may complicate thoracic surgical procedures, and tracheobronchial disease can follow lung transplantation.^{57,58} *Candida* species have multiple virulence determinants; virulent strains consistently exhibit adherence to devices and tissues and form biofilms.⁵¹ Multiple human genetic polymorphisms have been identified that contribute heightened susceptibility to mucosal and invasive *Candida* infections. These include common and rare sequence variants in Toll-like receptors 1, 2, and 4, cytokine signaling (*interleukin* [IL]-10, and the shared subunit of IL-12 and IL-23 receptors), and multiple genes whose products contribute to generating or responding to IL-17.⁵⁹

Manifestations of *Candida* pneumonia include cough, dyspnea, and fever. Radiographic findings are variable and can include lobar (eFig. 38-2) and multilobar consolidation as well as cavitation.⁵⁴ The diagnosis of *Candida* pneumonia

is complicated by the generally low specificity and low positive predictive value of isolating *Candida* in respiratory specimens, which is often interpreted as colonization.^{53,54,60,61} Consequently, histopathologic evidence of tissue invasion is required to prove *Candida* pneumonia. Detection of the fungal cell wall component β -D-glucan in serum may assist in distinguishing colonization from invasive *Candida* infection. In patients with hematologic malignancy and in critically ill patients, detection of β -D-glucan has been shown to result in earlier diagnosis of candidemia and invasive candidiasis,^{62,63} although the specificity of this test is limited by multiple sources for false-positive tests and cross-reactivity due to synthesis of β -D-glucan by other fungi, and low positive predictive value. Molecular methods such as real-time PCR testing of blood for invasive candidiasis are under development but are not yet available for clinical use.^{64,65}

Given the increasing number of infections with non-*albicans* *Candida* species and the potential for infection with azole-resistant strains, echinocandins or lipid AmB preparations are preferred for initial therapy while awaiting species identification and susceptibility testing. Whereas the extended spectrum azoles such as voriconazole may be more active against *C. glabrata* than is fluconazole,⁶⁶ there is frequent cross-resistance among the azoles.⁶⁷⁻⁶⁹ In addition, *C. glabrata* isolates have demonstrated resistance to echinocandins, often with poor outcomes.^{70,71,73,74} *C. lusitanae* is intrinsically resistant to AmB, and *C. tropicalis* has shown increasing acquired resistance to azoles and to echinocandins.^{70-72,75} *C. parapsilosis* and *C. guilliermondii* tend to have higher MICs for the echinocandins than do other species, but the clinical significance is unclear.⁷⁶⁻⁷⁸ These observations emphasize the importance of knowing the local epidemiology and resistance patterns for *Candida* within an institution, identifying the infecting pathogen to the species level and, in non-*albicans* *Candida* infections, testing susceptibility to guide therapeutic decision making. Drainage of infected fluid collections, including those in the mediastinum or pleural space, is critical for cure.

ASPERGILLOSIS

INTRODUCTION AND EPIDEMIOLOGY

Aspergillosis, caused by multiple species of the genus *Aspergillus*, is the most common mold infection worldwide. *Aspergillus* is a ubiquitous saprophytic fungus found indoors and outdoors in association with soil, organic debris, food, and water. The *Aspergillus* conidial head produces large numbers of 2 to 3 μ m conidia (asexual spores), which easily enter the lungs via inhalation. Outbreaks often follow renovation and construction, activities that place a large number of *Aspergillus* conidia in the air. While the lung is the most common site of entry, *Aspergillus* may gain access to the host via other routes, including direct cutaneous inoculation. Among *Aspergillus* species, *A. fumigatus* is the most common pathogen, in part due to specific virulence factors,⁷⁹ but non-*fumigatus* species including *A. flavus*, *A. niger*, and *A. terreus*, also cause human disease.^{23,24,80} *A. terreus* is notable for exhibiting in vitro resistance to AmB.^{81,82} *A. nidulans*, an otherwise rare pathogen, is second to *A. fumigatus* as the

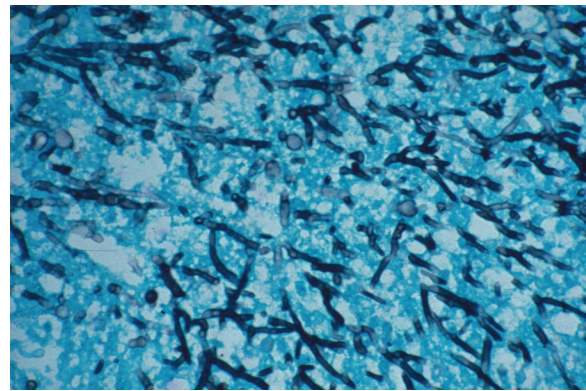


Figure 38-2 Invasive aspergillus. Micrograph shows findings of invasive *Aspergillus* infection represented by septate hyphae with finger-like branching at acute angles. (Methenamine silver stain; original magnification $\times 450$.)

most common mold causing infection in patients with chronic granulomatous disease.⁸³

Aspergillus is a hyaline hyphomycete characterized by septate, narrow (3 to 6 μ m) hyphae with acute angle (45 degrees) branching (Fig. 38-2) in respiratory secretions and tissue specimens. The non-*Aspergillus* hyaline hyphomycetes, discussed later, have a similar appearance in clinical specimens and are differentiated from *Aspergillus* in culture based on the morphologic characteristics of their reproductive structures.

Aspergillosis may present as a skin/soft tissue, ocular, gastrointestinal, cardiac, sinus, CNS, or disseminated infection, but most commonly presents as infection limited to the lung.⁸⁵ The five clinical entities addressed in the following sections include the two noninvasive forms, the saprophytic (aspergilloma) and allergic (ABPA) entities, as well as the three invasive forms, including *invasive pulmonary aspergillosis* (IPA), *tracheobronchial aspergillosis* (TBA), and chronic necrotizing pulmonary aspergillosis.

PATHOGENESIS

Although *Aspergillus* species are not obligate pathogens, their evolution to survive in decomposing organic matter has provided them with mechanisms that contribute to virulence in humans and other mammals. Through genome sequence analysis, studies of deletion mutants, and studies of infection in animal models, several determinants and mechanisms of *Aspergillus* pathogenesis have been identified. *Aspergillus* possesses multiple defenses against reactive oxygen intermediates; some of these anti-reactive oxygen intermediates defenses include melanin, catalases, superoxide dismutases, and glutathione transferases. At the same time, *Aspergillus* is able to survive in hypoxic environments, which may allow the fungus to survive in tissues that it renders hypoxic by invading blood vessel walls. Other mechanisms that may contribute to pathogenesis include production of diverse toxins, including gliotoxin and fumagillin, and secretion of elastase, which may promote tissue invasion.⁸⁸

Work in humans and in murine models has provided considerable insight into the elements and mechanisms of innate and adaptive immune responses that provide protection against invasive *Aspergillus* infections (see Chapters 12

and 13).^{89,90-93} *Aspergillus* spores possess a hydrophobic protein coat made up of rod-shaped structures (rodlets), which mask the cell wall and prevent recognition by innate immune receptors. This allows individuals to inhale millions of fungal spores every day without induction of an inflammatory response. Spores that swell and germinate before being killed expose the fungal cell wall that contains multiple pathogen-associated molecular patterns recognized by innate immune cells. In particular, β -D-glucan is recognized by host dectin-1, which initiates production of proinflammatory cytokines and chemokines, and modulates differentiation of CD4⁺ T cells. The importance of specific pathways of innate immune recognition has been demonstrated by finding that hematopoietic stem cell transplant patients who receive donor cells that possess sequence variants of Toll-like receptor 4 or dectin-1 are at increased risk for invasive *Aspergillus* infections.⁹⁴⁻⁹⁶ The chemokines produced early in infection recruit neutrophils and monocytes, both of which play important roles in ingesting and killing germinating spores and hyphae. Other important elements of innate immunity have been identified by finding that polymorphisms of mannose-binding lectin,^{97,98} chemokine (C-X-C motif) ligand 10 (CXCL-10),⁹⁴ and plasminogen⁹⁵ are associated with increased susceptibility to allergic or invasive aspergillosis in certain populations.

In humans and mice, CD4⁺ T cells also contribute to defense against invasive aspergillosis; both T-helper 1 and 17 cells contribute to optimal immunity. In contrast, excessive T-helper 2 responses contribute to the pathogenesis of ABPA.

INFECTION TYPES

Aspergilloma

Epidemiology and Definitions. An aspergilloma (or fungus ball) develops within a preexisting pulmonary cavity; it is a tangled mass of fungal hyphae, cellular debris, mucus, and fibrin that may or may not adhere to the cavity wall. Aspergillomas were previously most commonly found in cavities caused by tuberculosis,⁹⁹ but aspergillomas develop in other cavities such as those caused by bullous emphysema, fibrocavitary sarcoidosis, lung cancer, *cystic fibrosis* (CF),¹⁰⁰ or other fungal^{101,102} or nonfungal infections.⁸⁶ Aspergillomas are most commonly caused by *A. fumigatus* but can also be seen with non-*fumigatus* *Aspergil-*

lus and other molds.^{87,103-105} Chronic cavitary aspergilloma, also known as chronic cavitary pulmonary aspergillosis, is characterized by multiple cavities with or without intracavitary aspergillomas and with pulmonary and systemic symptoms.⁸⁵ Chronic cavitary pulmonary aspergillosis does not invade the surrounding pulmonary parenchyma.¹⁰⁶

The natural history of aspergillomas is variable. Aspergillomas can remain stable over long periods, regress, spontaneously resolve, or progressively enlarge.¹⁰⁷ Patients with aspergillomas are often asymptomatic, and the lesion may be discovered incidentally on chest radiography. The most common symptoms are cough and hemoptysis. Hemoptysis may develop in up to of 85% of cases and ranges from mild to life-threatening.^{107,108} Proposed mechanisms for the development of hemoptysis include vascular damage by mechanical effects of the fungus ball as well as by fungal toxins.¹⁰⁷

Imaging is key to the diagnosis of aspergillomas, which are typically found in the upper lung fields and classically appear as a solid rounded mass within a cavity (Fig. 38-3). The mass may be mobile (eFig. 38-3) or adherent to the cavity wall; peripheral lesions may be associated with pleural thickening. Nonradiographic diagnostic support includes positive serum precipitating antibodies to *Aspergillus* species, which are detectable in approximately 95% of patients.¹⁰⁵ Respiratory cultures may grow *Aspergillus* species although the sensitivity and specificity are low.^{104,107}

Optimal treatment of aspergillomas depends on the patient's symptoms, the location of the aspergilloma, and the host status. In patients with hemoptysis, the primary curative intervention is surgical resection. However, surgical resection remains a high-risk intervention in those with lung disease and poor pulmonary reserve. Potential complications from surgical resection include persistent hemorrhage, bronchopleural fistula development with further spread of the infection, and death.⁸⁵ Therefore, resection to prevent future complications and disease progression must be approached cautiously.¹⁰⁹ Bronchial artery embolization may be used in the setting of acute bleeding as a temporizing measure in nonsurgical candidates.

Systemic and/or topical (nebulized, or instilled into a cavity) antifungal therapy has been attempted in the management of aspergillomas. Systemic azole therapy is rarely curative and may be used for symptom improvement or stabilization and, in immunocompromised hosts, to prevent dissemination and invasive infection.¹¹⁰ The preponderance

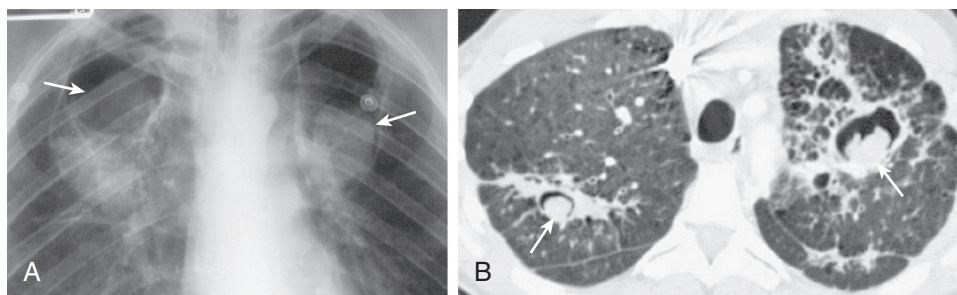


Figure 38-3 Aspergillomas in sarcoidosis cavities. **A**, Frontal chest radiograph in a patient with sarcoidosis demonstrates biapical thin-walled cavities containing rounded intracavitary opacities (arrows) that represent aspergillomas. **B**, Axial chest CT displayed in lung windows performed in another patient with sarcoidosis demonstrates biapical aspergillomas (arrows). The background bronchovascular thickening and subpleural nodularity reflects sarcoidosis. (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr* 26:159-173, 2002.)

of data supports use of oral itraconazole. An international open-label study of 42 patients with aspergillomas treated with itraconazole at a dose of 100 to 400 mg per day for 18 to 780 days found symptomatic improvement in 62% of evaluable patients ($n = 34$) and radiographic improvement in 12 (30%).¹¹¹ Although fewer data are available, voriconazole is increasingly used instead of itraconazole.^{110,112,113} Major concerns with long-term azole administration are the emergence of resistance and toxicities,^{114,115} especially with voriconazole, which has been associated with development of skin cancers including squamous cell carcinoma.¹¹⁶ Direct intracavitary instillation of antifungal agents such as AmB, nystatin, natamycin, fluconazole, and itraconazole has been used via endobronchial and percutaneous CT-guided approaches and may further reduce fungal burden and the risk of recurrent bleeding, but it is not curative.¹¹⁷⁻¹¹⁹ The optimal management of aspergillomas remains to be defined, and randomized-controlled trials are lacking.

Allergic Bronchopulmonary Aspergillosis

Epidemiology and Pathogenesis. ABPA (see also Chapter 48), first described in the early 1950s, is an allergic pulmonary disorder caused by hypersensitivity to *Aspergillus* antigens.¹²⁰ It is most often encountered in steroid-dependent asthmatics and in upwards of 15% of patients with CF.¹²¹ ABPA is most commonly associated with *A. fumigatus*; however, non-*fumigatus* *Aspergillus* species as well as non-*Aspergillus* molds can cause a similar clinical presentation (the latter termed *allergic bronchopulmonary mycosis* or ABPM). In ABPA, *Aspergillus* conidia enter the airways, germination ensues, and the hyphae colonize but do not invade. *Aspergillus* contributes to pathogenesis by producing enzymes such as elastase, collagenase, and trypsin, with airway damage and release of inflammatory cytokines.¹⁰⁰ A marked inflammatory response ensues, resulting in mucoid impaction and granulomatous inflammation, including bronchocentric granulomas. The immune mechanisms associated with ABPA include an exaggerated T-helper 2 CD4⁺ T-cell response to *Aspergillus* antigens, increased *Aspergillus*-specific and total IgE, and eosinophilia.^{100,122} The primary determinant of dysregulated immune responses in ABPA has not been identified. ABPA is common in patients with CF, and has been linked to polymorphisms in the *CF transmembrane conductance regulator* (CFTR) and pulmonary surfactant protein-A2 genes.¹⁰⁰

Clinical Presentation and Diagnosis

Symptoms of ABPA include acute attacks of wheezing, sputum expectoration containing brown plugs, pleuritic chest pain, and fever. Radiographic findings include transient pulmonary opacities, particularly in the upper lobes, bronchial wall thickening (ring sign), bronchiectasis (tram tracks), bronchial impaction, creating the so-called finger-in-glove appearance (eFig. 38-4) and, in more advanced stages, fibrosis.¹²³ The clinical criteria proposed for diagnosing ABPA differ based on the patient's underlying disease. The minimal essential clinical criteria proposed by Greenberger et al¹²⁴ for asthmatics include (1) asthma, (2) central bronchiectasis, (3) immediate cutaneous reactivity to *Aspergillus* species, (4) a total serum IgE greater than

1000 IU/mL, and (5) elevated *Aspergillus*-specific serum IgE or IgG. Asthmatics are designated as ABPA-central bronchiectasis or ABPA-seropositive, the latter lacking central bronchiectasis. Five stages of disease have been characterized, including (1) acute ABPA, (2) remission, (3) recurrent exacerbation, (4) steroid-dependent asthma, and (5) fibrosis. In patients with CF, the diagnosis is less straightforward, because frequent infections and CF exacerbations may present with symptoms similar to those of ABPA. However, clinical criteria have been proposed by the Consensus Conference of the Cystic Fibrosis Foundation to aid in the diagnosis: (1) acute or subacute pulmonary deterioration not attributable to another etiology; (2) total serum IgE greater than 500 IU/mL; (3) immediate cutaneous reactivity to *Aspergillus* or specific IgE antibodies to *Aspergillus*; and (4) one of the following: *Aspergillus* serum precipitins, elevated anti-*Aspergillus* IgG, or new or recent chest radiographic or chest CT abnormalities that have not cleared with antibiotics and chest physiotherapy.¹²²

The goal of therapy for ABPA is to manage acute disease and prevent relapse and progression to fibrosis. Corticosteroids remain the basis for therapy although there is a lack of guidance from randomized controlled trials assessing the optimal dose and duration. For acute management, oral prednisone at 0.5 mg/kg/day for 1 to 2 weeks, followed by alternate-day dosing for an additional 6 to 8 weeks with further taper is often used.¹²¹ Serum IgE concentrations, radiographic imaging, pulmonary function testing, and clinical symptoms are used to monitor response to therapy and to identify exacerbations.

Antifungal therapy aimed at reducing overall fungal burden, thereby blunting downstream immunologic response and airway inflammation is often used as an adjunctive intervention. The agent most studied for this indication is itraconazole. A meta-analysis¹²⁵ identified three randomized controlled trials evaluating azoles in ABPA, including two trials with itraconazole.^{126,127} Although the studies used different end points, the collective results demonstrated reductions in systemic and airway inflammatory parameters, reductions in steroid dose, improvements in pulmonary function, and an increase in the length of time between exacerbations. Itraconazole was studied at a dose of 400 mg/day for 16 weeks; in clinical practice, some advocate continuing treatment for a minimum of 6 months.¹²⁸ Efficacy has been demonstrated in patients with CF as well.¹²⁹ Based on existing data, the IDSA recommends combination therapy with corticosteroids and antifungals.⁸⁵ Given concerns for itraconazole tolerability, voriconazole and posaconazole have been substituted with good results.¹³⁰ Additional therapeutic considerations include omalizumab, a humanized monoclonal antibody targeting IgE and approved for the treatment of severe allergic asthma. This agent has been used in asthmatic and CF ABPA patients with mixed results.^{131,132}

Invasive Pulmonary Aspergillosis

Epidemiology and Pathogenesis. IPA is the most severe form of pulmonary aspergillosis and is a major cause of fungal morbidity and mortality, seen most commonly in immunodeficient patients, including HSCT and SOT recipients and those with advanced HIV infection, chronic granulomatous disease, and hematologic malignancies. In

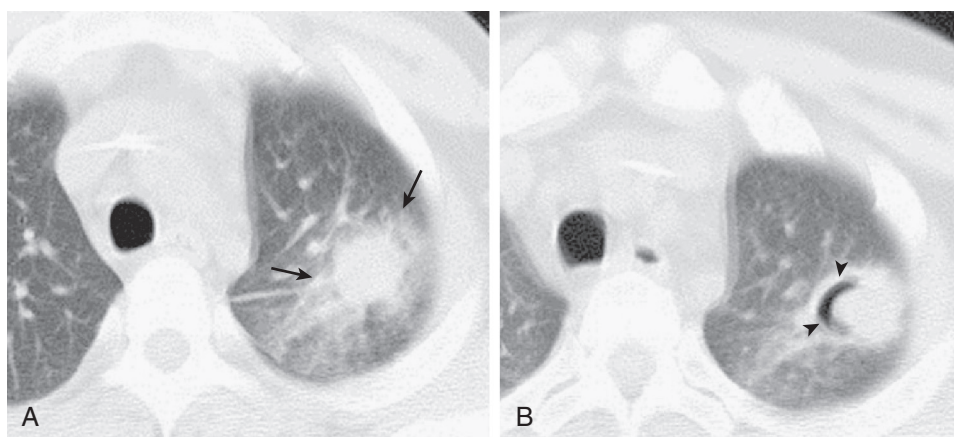


Figure 38-4 Invasive pulmonary aspergillosis. **A**, Axial chest CT displayed in lung windows performed in a hematopoietic stem cell transplant recipient during profound neutropenia demonstrates a poorly defined nodule with surrounding ground-glass opacity (arrows) representing the “halo sign.” **B**, Following engraftment, the nodule has become cavitary (arrowheads), representing the “air-crescent” sign.

a retrospective Italian cohort of nearly 12,000 patients with hematologic malignancies, more than half of the 538 proven or probable IFIs were due to molds, primarily *Aspergillus*, and patients with acute myelogenous leukemia were most commonly affected.¹³³ The elevated risk in this population is primarily driven by prolonged neutropenia induced by cytotoxic chemotherapy.¹³⁴ Multicenter, prospectively obtained epidemiologic data also confirm *Aspergillus* as the most common cause of invasive mold infection in both HSCT and SOT recipients.^{23,24} In HSCT recipients, *Aspergillus* is the most common IFI, predominantly seen during two periods: (1) early after transplantation, during neutropenia, and (2) after engraftment, in the setting of graft-versus-host disease. Of the SOT patients, lung transplant recipients are at highest risk for IPA. IPA is also increasingly reported in patients previously thought to be at low risk for invasive disease, including those with COPD on long-term corticosteroids and critically ill patients in the intensive care unit.¹³⁵

IPA is characterized by tissue invasion, frequently involving blood vessels. Hyphae within the alveoli penetrate the respiratory mucosa and alveolar capillaries into endothelial cells and pulmonary arterioles. Cell injury and inflammation contribute to intravascular thrombosis, local hypoxia, and necrosis. Angioinvasive disease is accompanied by tissue infarction and coagulative necrosis, whereas nonangioinvasive disease is more commonly associated with pyogranulomatous inflammation and inflammatory necrosis.¹⁰⁶

Clinical Presentation and Diagnosis. The clinical presentation of IPA typically involves fever, cough, hemoptysis, and pleuritic chest pain. Angioinvasive IPA is seen predominantly in the setting of neutropenia and the course in neutropenic patients can be rapid, with clinical deterioration over hours to days. Patients with disseminated disease may have additional symptoms related to other sites of infection. *Aspergillus* can extend directly to surrounding areas, including the chest wall (see Fig. 90-27),¹³⁶ mediastinum, and great vessels.¹³⁷

Early diagnosis of IPA is essential for prompt initiation of therapy, which has been associated with improved sur-

vival.¹³⁸ However, multiple factors make the diagnosis difficult, including the lack of symptoms early in the course of illness, challenges in obtaining appropriate tissue for histopathology and culture in critically ill or cytopenic hosts, and the variable sensitivity and specificity of many of the available diagnostic tests. Imaging findings associated with IPA are often nonspecific, including nodules (see eFigs. 90-27, 90-28, and 91-10), consolidation (see eFig. 91-8), cavitation (see eFigs. 90-27 and 90-28), and effusions (see eFig. 91-10). The halo sign, demonstrated by ground-glass opacities surrounding a pulmonary nodule, is the result of alveolar hemorrhage around an infarcted area of the lung (Fig. 38-4A; see eFig. 91-10) and is typically seen early in the course of infection.¹³⁹ The halo sign has a high specificity for IPA in neutropenic patients.¹⁴⁰ The air-crescent sign tends to be seen later in the course of infection (typically with recovery of neutrophils in the neutropenic host) and represents air that has filled the space between necrotic and healthy lung tissue (see Fig. 38-4B).¹⁴¹

Direct microscopy of sputum or BAL lacks both sensitivity (reported ranges from 0% to 90%) and specificity.¹⁴² Histopathologic evaluation of tissue specimens using standard hematoxylin and eosin, periodic acid-Schiff, and/or Gomori's methenamine silver staining with demonstration of characteristic hyphae supports the diagnosis of IPA, but culture or sequence data are required to confirm the identity of the pathogen (see Fig. 38-2). Furthermore, 48% to 70% of tissues with evidence of invasive septate hyphae fail to grow in culture.¹⁴³ When positive, cultures for most *Aspergillus* species typically grow within 48 to 72 hours on standard mycologic media.¹⁴⁴

Noninvasive tests are increasingly used for patients at risk for IPA. These include assays for fungal *galactomannan* (GM) and β -D-glucan. GM is a heteropolysaccharide component of the cell wall of *Aspergillus* and other fungi that is released during hyphal growth. Platelia *Aspergillus* EIA (Bio-Rad Laboratories) is an FDA-approved, commercially available diagnostic for detecting GM in neutropenic and HSCT patients with invasive *Aspergillus*, including IPA. The positive cutoff value is an optical density (OD) index of 0.5. A meta-analysis of 27 studies from 1966 to 2005 using surveillance GM in immunocompromised hosts with invasive

Aspergillus reported an overall sensitivity and specificity of 71% and 89%, respectively.¹⁴⁵ Subgroup analysis showed that test performance was higher in patients with hematologic malignancy (sensitivity, 70%; specificity, 92%) and HSCT recipients (sensitivity, 82%; specificity, 86%) compared to SOT recipients (sensitivity, 22%; specificity, 84%). One potential explanation for the improved performance in patients with hematologic malignancies or HSCT recipients was gained from an in vitro model of the human alveolus showing that detection of GM correlated with its release into the circulation following angioinvasion,¹⁴⁶ which is more common in neutropenic patients.

Assaying BAL specimens for GM by the same enzyme immunoassay may complement assays of serum. A meta-analysis of 30 studies evaluating BAL GM using a cutoff OD index of 0.5 for proven and probable invasive aspergillosis found a sensitivity of 87% and specificity of 89%. Compared to serum GM, BAL GM had a higher sensitivity but a lower specificity. By increasing the positive cutoff value to an OD index of 1, specificity was increased without decreasing sensitivity.¹⁴⁷ This is particularly important in lung transplant patients in whom high rates of colonization with molds such as *Aspergillus* and *Penicillium* can result in false-positive tests for GM. In one study, lung transplant recipients (16 of 81) accounted for more than 40% of false-positive BAL test results for GM.¹⁴⁸ Other factors that compromise the utility of the GM assay include cross-reactivity with other fungi (e.g., *Alternaria*, *Fusarium*, *Geotrichum*, *Histoplasma*, *Paecilomyces*, and *Penicillium*) and false-positive results secondary to the presence of GM in antimicrobials, such as piperacillin-tazobactam, in nutritional supplements, and in Plasmalyte. However, the magnitude of serum GM was shown to have prognostic utility in a single-center study of invasive aspergillosis in allogeneic HSCT recipients, with higher values correlated with higher all-cause mortality.¹⁴⁹ Use of the GM assay to monitor response to treatment and to detect relapse is under investigation.

β -D-glucan, another fungal cell wall component, is used in the diagnosis of invasive aspergillosis as well as other IFIs, including *Candida* and *Pneumocystis*. The FDA approved and commercially licensed assay in the United States is the Fungitell assay, which has a positive cutoff value of 80 pg/mL or greater (sensitivity, 64%; specificity, 92%) for patients with proven or probable invasive aspergillosis.¹⁵⁰ β -D-glucan may be detectable earlier in the course of invasive aspergillosis than is GM.¹⁵¹ False-positive β -D-glucan results may be associated with hemodialysis using cellulose membranes, intravenous immunoglobulin, and bacterial bloodstream infections.¹⁴² In a study to assess the utility of serially monitoring lung transplant recipients with the β -D-glucan assay, 90% of subjects without an IFI had at least one positive β -D-glucan result (≥ 80 pg/mL), leading to a low positive predictive value (9%).¹⁵² Similar issues were encountered in a study using β -D-glucan to monitor for invasive candidiasis in an intensive care unit; 45% of subjects had false-positive results, which were ultimately attributed to receipt of intravenous immunoglobulin and hemodialysis.⁶³

Nucleic acid-based tests including PCR have been explored in the diagnosis of invasive aspergillosis, although none of these have been incorporated into formal diagnostic criteria. A meta-analysis of PCR testing of blood, plasma,

or serum reported a sensitivity and specificity of 75% and 87%, respectively.¹⁵³ Avni and associates¹⁵⁴ found comparable performance of BAL-PCR versus BAL GM testing (using an OD index of 0.5) as well as improved sensitivity with stable specificity when used together, suggesting a possible advantage to combination testing. To date there is no FDA-approved nucleic acid assay for *Aspergillus* in the United States. Attempts at standardization¹⁵⁵ and the availability of a commercial PCR platform¹⁵⁶ are necessary steps toward validation and routine clinical use. Newer diagnostics, including a lateral flow device incorporating a monoclonal antibody, JF5, to detect an *Aspergillus* extracellular glycoprotein antigen may provide rapid and inexpensive point-of-care testing.¹⁵⁷

Diagnostic criteria for IPA have been proposed by the Mycoses Study Group/European Organization for Research and Treatment of Cancer and include proven, probable, and possible invasive aspergillosis.¹⁵⁸ A diagnosis of *proven* IFI requires microscopic evidence of *Aspergillus* tissue invasion or a positive culture from a normally sterile site. A diagnosis of *probable* IPA requires an at-risk host, corroborating radiographic findings, and direct (e.g., culture) or indirect mycologic evidence (e.g., positive serum, plasma, or BAL GM, or positive serum β -D-glucan). Other clinical algorithms continue to be introduced to assist in differentiating *Aspergillus* colonization from true invasive aspergillosis in critically ill intensive care unit patients without clear predisposing host factors but with positive respiratory specimens and/or clinical concern for invasive aspergillosis.¹⁵⁹

Treatment. As with other IFIs, management of IPA may involve a combination of surgical, pharmacologic, and other adjunctive interventions. Attempts to restore host immunity should be made wherever feasible, being mindful of the risk for IRIS.¹⁶⁰ Indications for surgical intervention include life-threatening hemoptysis, lesions contiguous to the great vessels and/or pericardium, and invasion of the chest wall, as well as isolated lesions in patients about to undergo intensive chemotherapy or HSCT.⁸⁵ The drug of choice for IPA is voriconazole, based on recommendations from both the IDSA⁸⁵ and American Thoracic Society⁴² and data from a large prospective randomized trial of invasive aspergillosis that demonstrated significantly better response and overall survival in those treated with voriconazole than those treated with AmB-d.¹⁶¹ The dose of voriconazole for IPA is 6 mg/kg intravenously every 12 hours on day 1, followed by 4 mg/kg every 12 hours thereafter. Therapy can be transitioned to the oral route once the patient is stable and tolerating oral medications. While most patients are treated for a minimum of 6 to 12 weeks, the total duration of pharmacologic therapy for IPA is not clearly defined and is dependent upon the immune status of the host and clinical response to treatment (eFig. 38-5).

Posaconazole may be an effective alternative to voriconazole, although it is most often used as salvage therapy because it has not been studied as primary treatment. In patients with invasive aspergillosis refractory or intolerant to other antifungal therapies, response to posaconazole was superior (45/107, 42%) compared with the external control group (22/86, 26%), primarily treated with AmB or itraconazole.¹⁶² Other researchers have also shown success with posaconazole as salvage therapy.¹⁶³

Azole resistance in *Aspergillus* was first reported with *A. fumigatus* in 1997 and appears to be increasing in frequency.^{164,165} The known mechanism of resistance is due to sequence variation in the fungal *cyp51A* gene, which encodes the drug target, 14- α -demethylase.¹⁶⁵ Many of these sequence variants result in cross-resistance between the azole compounds, namely itraconazole, voriconazole, and posaconazole. Although interpretive breakpoints defining clinical resistance have yet to be established for molds, standard methods for testing filamentous fungi have been validated,¹⁶⁶ and epidemiologic cutoff values (which define susceptibility using the MIC distribution of wild-type *Aspergillus* strains lacking known azole resistance mechanisms) have been proposed.¹⁶⁷ While epidemiologic cutoff values do not predict outcomes, they may aid in detecting isolates with potential resistance mutations, including those in *cyp51A*. Some experts advocate MIC testing as a screen for the presence of resistance mutations in patients with invasive aspergillosis that fail to respond to azole therapy.

Polyenes are used for the treatment of IPA in the setting where mucormycosis remains in the differential diagnosis or in patients intolerant or refractory to azoles. The lipid formulations of AmB are currently preferred because of their reduced nephrotoxicity compared with that of AmB-d. Currently, the IDSA recommends ABLC 5 mg/kg/day or LAmB 3 to 5 mg/kg/day for the treatment of IPA. LAmB 3 mg/kg/day was compared with LAmB 10 mg/kg/day in a double-blind trial of patients with proven or probable invasive aspergillosis to assess whether higher doses would improve response; there was no clinical advantage with the higher dose but there was significantly more hypokalemia and nephrotoxicity.¹⁶⁸

Echinocandins may be used in patients who are refractory or intolerant to other therapies, although randomized controlled trials evaluating echinocandins as primary therapy for invasive aspergillosis have not been performed. In one study, 83 adults with probable/proven invasive aspergillosis, including 64 with IPA were treated with caspofungin; 45% (50% of those with IPA) obtained a complete or partial response.^{169,170} Based on these data, caspofungin was cleared by the FDA as salvage therapy for invasive aspergillosis. For micafungin, a large report from Japan indicated a 71% (90 of 130) clinical response rate in patients with invasive aspergillosis treated with micafungin monotherapy (doses ranged from 50 to 300 mg/day) as first-line therapy.¹⁷¹

Given the high mortality associated with IPA, combination therapy is often considered. While in vitro and in vivo^{172,173} data support a role for combination therapy, the IDSA does not recommend using combination therapy as first-line therapy for invasive aspergillosis, due to the lack of data from a randomized controlled trial. When combination therapy is used, echinocandins are most often paired with polyenes or azoles based on their activity at a different site (fungal cell wall) compared with the azoles and polyenes (fungal membrane).^{174,175} A randomized controlled trial comparing voriconazole monotherapy with voriconazole plus anidulafungin in patients with invasive aspergillosis is underway.¹⁷⁶ Other adjunctive measures used to optimize outcomes of IPA include granulocyte or granulocyte-macrophage colony stimulating factor, interferon-gamma, and granulocyte infusions.⁸⁵

Tracheobronchial Aspergillosis

Epidemiology and Pathogenesis. *Tracheobronchial aspergillosis* (TBA) should be considered as a spectrum, including mild tracheobronchitis and obstructive, ulcerative, and pseudomembranous TBA, often with more than one form present concurrently.¹⁷⁷ Mild tracheobronchitis demonstrates only superficial mucosal inflammation; obstructive, ulcerative, and pseudomembranous forms may be superficial or progress to involve the entire bronchial wall with necrotizing tracheobronchitis and invasion of the surrounding tissue.¹⁷⁸ A rare form of IPA, TBA is most commonly encountered in lung and heart-lung transplant recipients,^{179,180} although it has been reported in patients with advanced HIV¹⁸¹ and hematologic malignancies, including patients undergoing HSCT.^{182,183}

Clinical Manifestations, Diagnosis and Treatment. In lung and heart-lung transplant recipients, TBA is often discovered early in the posttransplant period when patients may have ulceration and/or pseudomembrane formation at the bronchial anastomotic site visible by bronchoscopy (Fig. 38-5), even without symptoms.¹⁸⁴ In contrast, patients with hematologic malignancies are typically symptomatic at the time of discovery of TBA with productive cough, dyspnea, fever, wheezing, stridor, hemoptysis, and respiratory failure.^{177,185} Early diagnosis is crucial given the potential for progressive symptoms and disseminated infection and complications including bronchial obstruction, anastomotic rupture, and bronchopleural or bronchoarterial fistulas.^{179,186} While chest imaging may demonstrate bronchial wall thickening, luminal narrowing, and/or endobronchial lesions (eFig. 38-6),^{185,187} it cannot make the diagnosis. Serum GM is of limited value for tracheobronchial aspergillosis.¹⁸⁸ Diagnosis is made via bronchoscopy with visualization of plaques, ulceration, pseudomembranes, and obstructive mucous plugs and/or masses (Fig. 38-6) together with pathologic and microbiologic findings.

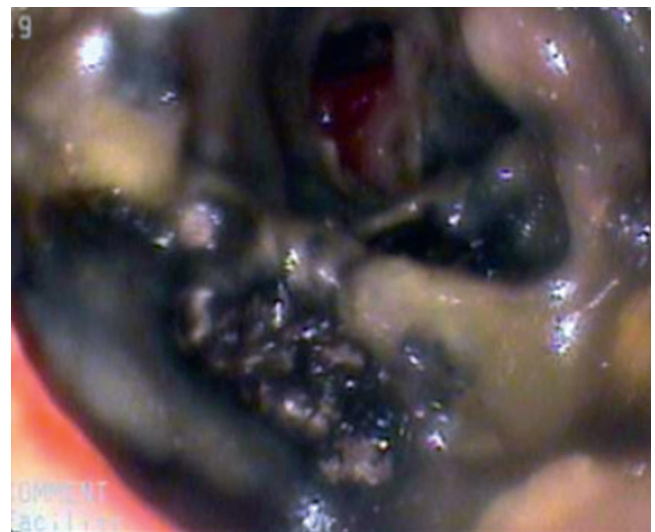


Figure 38-5 Tracheobronchial aspergillosis. Bronchoscopic visualization of the right mainstem bronchus in a lung transplant recipient demonstrates tracheobronchial aspergillosis with *Aspergillus fumigatus*. Stenosis and extensive necrotic pseudomembranes and debris are seen at the anastomotic site. (Courtesy Dr. Scott Shofer, Duke University Medical Center, NC.)

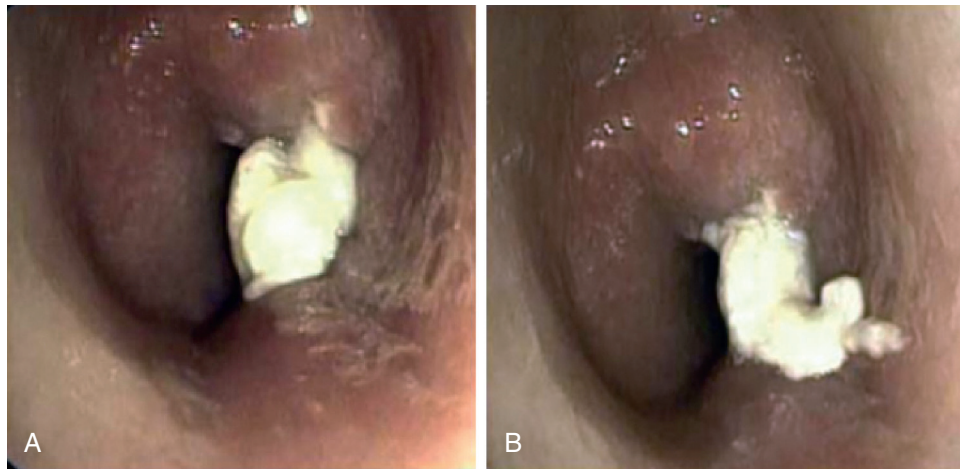


Figure 38-6 Tracheobronchial aspergillosis. Subglottic mass in a patient with a hematologic malignancy and prolonged neutropenia with histopathologic and culture data consistent with *Aspergillus fumigatus* tracheobronchial aspergillosis. **A**, Bronchoscopic visualization beyond the vocal cords revealing a friable subglottic tracheal mass with surrounding mucosal edema resulting in approximately 50% obstruction. **B**, Movement of the mass with breathing creating a ball-valve, extrathoracic obstruction. **A**, closing partially with inspiration, **B** opening partially with expiration. (Courtesy Kamran Mahmood, MD, MPH, Duke University Medical Center.)

Treatment of TBA is similar to that for other forms of IPA.⁸⁵ Voriconazole is the preferred first-line therapy; other antifungals including itraconazole, posaconazole, AmB, and echinocandins may be used. Systemic therapy has also been combined with aerosolized and topical endobronchial application of AmB-d (the latter in doses ranging from 2 to 50 mg) in severe TBA in lung transplant recipients.¹⁸⁹

Chronic Pulmonary Aspergillosis

Epidemiology and Definitions. Chronic pulmonary aspergillosis includes three entities, according to a recent nomenclature based on radiographic and clinical findings.¹⁹⁰ The first entity, termed *chronic cavitary pulmonary aspergillosis*, represents chronic cavitary disease that may be accompanied by new cavity formation, but does not demonstrate hyphal invasion into the surrounding parenchyma. The second entity, *subacute IPA*, is more invasive. In contrast to IPA, subacute IPA is characterized by slower progression and typically arises within a thin walled cavity. In contrast to aspergilloma, subacute IPA includes destruction of the pulmonary parenchyma and hyphal invasion into surrounding tissue, including the chest wall and vertebrae. The third entity, *chronic fibrosing pulmonary aspergillosis*, is defined by marked fibrosis around the cavity. These chronic forms of aspergillosis are found in individuals with structural lung disease including prior mycobacterial disease, sarcoidosis, lung cancer, emphysema, and asthma.¹⁰⁶ However, subacute IPA is also seen in patients with variable degrees of immunosuppression or comorbidities including diabetes, alcoholism, and advanced HIV.^{191,192} Progression from chronic cavitary pulmonary aspergillosis to subacute IPA during therapy with steroids demonstrates the overlap of these entities.¹⁹⁰ Sequence polymorphisms in the genes encoding mannose-binding lectin and surfactant are associated with chronic forms of pulmonary aspergillosis in some patients.^{97,193}

Clinical Presentation, Diagnosis, and Treatment. Patients with subacute IPA typically exhibit systemic symp-

toms. The course is usually indolent, with cough, dyspnea, hemoptysis, fatigue, and weight loss.¹⁹⁰ Imaging findings include cavities of variable wall thickness (eFig. 38-7), consolidation, and paracavitary opacities.^{105,190} Precipitating antibodies to *Aspergillus* are detectable in serum of nearly all patients. Respiratory cultures may be positive for *Aspergillus*, and other diagnostics such as a positive serum and/or BAL GM as well as elevated erythrocyte sedimentation rate or C-reactive protein may further support the diagnosis. Histopathologic findings of resected lesions demonstrate inflammation with hyphae both within the cavity and invading the surrounding tissue, with or without granulomas.

Treatment of all forms of chronic pulmonary aspergillosis is with systemic antifungal therapies such as voriconazole.⁸⁵ Given the long-term therapy required, oral treatment is preferred. However, in patients with severe disease, initial treatment with intravenous voriconazole or AmB may be warranted.⁴²

MUCORMYCOSIS

EPIDEMIOLOGY

Mucormycosis is caused by molds in the order Mucorales in the subphylum Mucormycotina.¹⁹⁴ *Rhizopus* and *Mucor* are the genera most commonly associated with infections although *Apophysomyces*, *Cunninghamella*, *Rhizomucor*, *Syncephalastrum*, and others also cause disease.¹⁹⁵⁻¹⁹⁸ These are ubiquitous molds found in soil and decaying plant material which gain access to the host via inhalation, skin penetration or, less commonly, ingestion. Infection sites include skin and soft tissue, rhino-orbital-cerebral, gastrointestinal, and lower respiratory tract, as well as disseminated infection with multiorgan involvement.^{197,199,200} In a retrospective series of 929 cases of mucormycosis, the most commonly affected patients were those with poorly controlled diabetes, among whom sinus involvement, including

rhino-orbital-cerebral infections, was the most frequent presentation. Patients with hematologic malignancies or undergoing HSCT were the second most commonly affected group in whom pulmonary infections predominated.¹⁹⁹ Mucormycosis is the third most common IFI in the HSCT population, representing 8% of IFIs,²⁴ compared with 2% of IFIs in SOT recipients.²³ Surveillance data suggest an increasing incidence of mucormycosis,^{24,201} and multiple reports of “breakthrough” mucormycosis in patients receiving voriconazole²⁰²⁻²⁰⁶ raise the question of whether voriconazole exposure is a risk. However, this association is likely multifactorial, including changes in immunosuppression and patient survival, and not solely attributable to the drug.

PATHOGENESIS

After the fungal spores gain access to the host, mononuclear and polymorphonuclear phagocytes normally serve as a primary host defense against invasion.²⁰⁷ However, hyperglycemia and acidosis in people with poorly controlled diabetes impair phagocyte function.²⁰⁸ Moreover, growth of pathogenic Mucorales is enhanced by free iron; thus iron overload and treatment with deferoxamine, which behaves as a siderophore that increases iron availability to the fungus, are associated with mucormycosis. Likewise, systemic acidosis increases free iron by decreasing iron binding to transferrin.²⁰⁰ Similar to *Aspergillus* and certain other pathogenic molds, mucormycosis is angioinvasive, resulting in thrombosis, infarction, and tissue necrosis, with risk for dissemination to other sites. Strong experimental evidence indicates that one mechanism that promotes angioinvasion by *Rhizopus oryzae* (the most common species in patients with mucormycosis) is glucose- and iron-induced expression of glucose-regulated protein 78 by vascular endothelial cells, which promotes binding of *Rhizopus* to endothelial cells in vitro and in vivo.²⁰⁹ The *Rhizopus* ligands for endothelial cell glucose-regulated protein 78 are two closely related surface proteins, CoH2 and CoH3, which mediate invasion of endothelial cells in vitro and are essential for virulence in vivo.²¹⁰

CLINICAL MANIFESTATIONS

Pulmonary mucormycosis is often acute and severe, particularly in neutropenic patients, with fever, cough, dyspnea, pleuritic chest pain, and hemoptysis.^{211,212} In patients with diabetes, the course may be more subacute.²¹³ Pulmonary involvement may also be associated with life-threatening hemoptysis due to vascular invasion by the fungus and the infection may disseminate or expand locally to involve contiguous structures, including the mediastinum and chest wall.²¹¹ Although uncommon, broncho-pleural, bronchocutaneous, and bronchoarterial fistulas have been reported.^{211,214} Tracheobronchial infection has been reported in patients with diabetes and in lung transplant recipients.²¹⁵ Endoscopic findings include luminal narrowing or obstruction with pseudomembranes and necrosis.

Imaging findings are similar to those described with IPA and include nodular (eFig. 38-8) and mass (eFigs. 38-9 and 38-10) lesions, ground-glass opacities, and consolidative

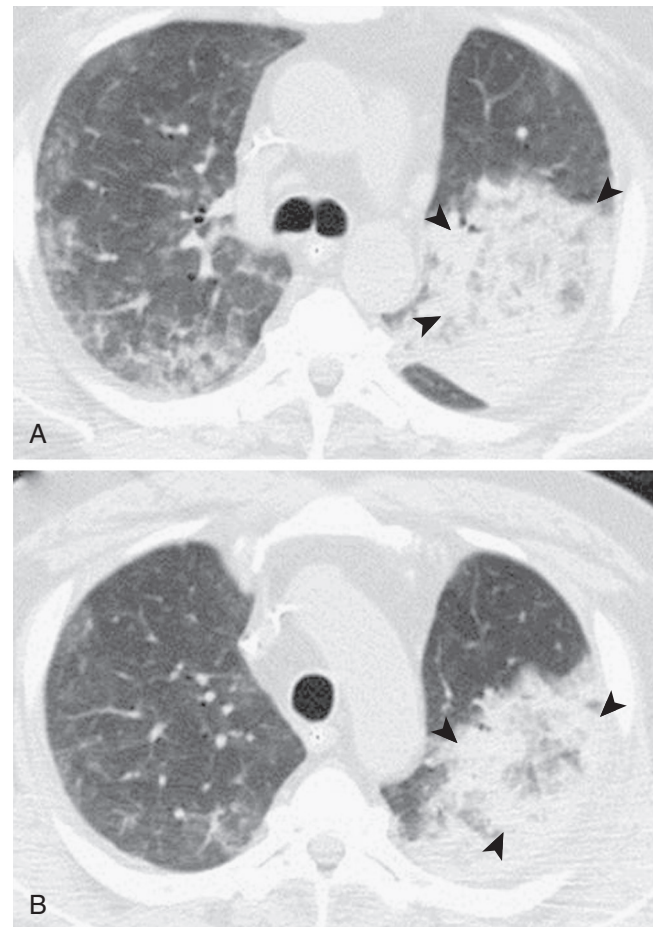


Figure 38-7 Mucormycosis. Axial chest CT displayed in lung windows performed in a hematopoietic stem cell transplant patient demonstrates left upper lobe consolidation (arrowheads) with surrounding ground-glass opacity consistent with the “reversed halo” sign.

and cavitory (see eFig. 91-9) lesions. The presence of multiple 10 or more pulmonary nodules and pleural effusions favors the diagnosis of invasive pulmonary mucormycosis over IPA, although this is not absolute.²¹² Both the halo sign and the reversed halo sign (ground-glass opacity surrounded by a ring or crescent of consolidation; Fig. 38-7) may be seen,¹⁴⁰ but in at least one series, the reversed halo was more common in mucormycosis.²¹⁶

DIAGNOSIS

The diagnosis is typically made based on a combination of clinical, imaging, culture, and histopathologic findings. Currently available noninvasive tests, such as assays of serum β -D-glucan, do not contribute to the diagnosis, because the molds that cause mucormycosis do not produce β -D-glucan. Direct examination of sputum and BAL specimens may show the characteristic broad 10- to 20- μ m, ribbon-like, irregularly branching hyphae.²¹⁷ Potassium hydroxide wet mounts enhanced with calcofluor (which stains chitin) may assist in detecting the fungus in fresh specimens; periodic acid-Schiff and/or Gomori’s methenamine silver staining are used to visualize the fungi in tissue samples.²¹⁸ Prior receipt of mold-active therapy may alter the characteristic morphology in fresh specimens. Although

organisms may be visualized in tissue or respiratory specimens, cultures may be negative in up to one third of cases.²¹⁹ The use of diagnostic techniques including direct PCR of tissue samples is under investigation.^{218,220} Because of the difficulties in obtaining diagnostic specimens in many of these critically ill hosts, noninvasive diagnostics, including quantitative PCR of serum, are also under investigation.²²¹

TREATMENT

Early treatment for mucormycosis is essential for optimal outcomes²²² and includes pharmacologic, medical (reducing immunosuppression, correcting metabolic acidosis, and optimizing control of diabetes), and often surgical intervention (eFigs. 38-11 and 38-12). Surgery, when feasible, is useful for debulking infection and preventing spread to contiguous structures, and is associated with decreased mortality compared to medical treatment alone.^{223,224}

Controlled trials to guide antifungal selection for mucormycosis are lacking, so recommendations are based on information gained through in vitro testing, animal models, and clinical observations. Polyenes remain the agents of choice in the management of mucormycosis. AmB-d has largely been replaced by lipid formulations. LAmB is considered by many to be the preferred agent, due to reduced nephrotoxicity, superior activity in murine models of infection,²²⁵ retrospective clinical data,²²⁶ and rabbit models showing improved CNS penetration compared to both AMB-d and ABLC.²²⁷ LAmB is typically initiated at a dosage of 5 mg/kg/day but has been increased to 10 to 15 mg/kg/day in severe infections that fail to respond.²²⁸ Among the azoles active against molds, itraconazole and posaconazole have in vitro activity against mucormycosis; there is more clinical experience with posaconazole, especially in cases refractory to or intolerant of polyenes or for step-down therapy following induction with a polyene. Among 91 cases of mucormycosis in which posaconazole was used for salvage therapy (either alone or in combination), 60% showed complete or partial response at 12 weeks.²²⁹ Similar responses were reported in a retrospective review of 96 cases of mucormycosis.²³⁰ The treatment dosage of posaconazole suspension is 200 mg 4 times a day and is typically administered until there are clinical and radiographic evidence of resolution, accompanied by restoration of immune functions. Therapeutic drug monitoring with the suspension formulation to ensure adequate levels of posaconazole is especially important in management of mucormycosis given concerns for reduced bioavailability.²³¹ However, posaconazole extended release tablets were approved by the FDA in late 2013 and available data suggests improved overall bioavailability compared with posaconazole suspension^{231a,231b,302} and in 2014 the FDA approved an intravenous formulation.³⁰² Furthermore, the activity of posaconazole against the agents of mucormycosis is variable depending on the genus and species.²³²⁻²³⁴ Thus identification of the infecting pathogen is critical when choosing posaconazole as a therapeutic option.

Echinocandins do not have significant in vitro activity against agents of mucormycosis and should not be used as monotherapy in the treatment of these infections. However, there may be a role for polyene-echinocandin combination

therapy. The gene encoding β -D-glucan synthase, the target enzyme of the echinocandins, has been identified in *Rhizopus oryzae*. Furthermore, studies have shown improved survival with caspofungin compared with no treatment in mice²³⁵ and with polyene-echinocandin combination therapy.^{236,237} Clinical data for combination therapy are limited and mixed. A small retrospective study from 2 centers evaluated 41 patients, most of whom had diabetes (83%) with rhino-orbital and rhino-orbital-cerebral mucormycosis, and found polyene-echinocandin combination therapy improved outcomes compared to polyene monotherapy.²³⁸

The use of adjunctive therapy with the iron chelator deferasirox showed promise in both murine models and a small clinical trial.^{239,240} However, a multicenter clinical trial comparing LAmB/deferasirox to LAmB/placebo found a significantly higher 90-day mortality in those receiving deferasirox.²⁴¹ The increased mortality may have been related to imbalanced enrollment, because more patients in the deferasirox treatment group had hematologic malignancies and neutropenia, which are associated with poorer outcomes. The role of deferasirox in the management of mucormycosis remains unclear, but its use is not currently recommended. Other adjunctive agents that have been used include hyperbaric oxygen, granulocyte colony stimulating factors and interferon gamma.²⁴²

NON-ASPERGILLUS HYALINE HYPHOMYCETES

EPIDEMIOLOGY AND PATHOGENESIS

Hyalohyphomycosis refers to infections caused by septate molds with colorless or lightly pigmented hyphae. *Aspergillus* is the most common of the hyaline molds; however, non-*Aspergillus* hyphomycetes, including *Acremonium*,^{243,244} *Fusarium*,²⁴⁵ *Geosmithia*,^{246,247} *Paecilomyces*,²⁴⁸ *Scedosporium*,²⁴⁹ and *Trichoderma*,²⁵⁰ among others, are increasingly reported.^{80,201,251} These pathogens can cause infection in immunocompetent or immunocompromised hosts. *Fusarium* and *Scedosporium* are the most common causes of infection from this group in SOT and HSCT recipients.²⁰¹

More than 50 species of *Fusarium* have been identified; some are common pathogens of plants, including vegetables. *F. solani* is the species most often associated with human infection, although *F. oxysporum* and *F. moniliforme* have also been reported.^{201,245} *Scedosporium apiospermum* (the asexual form of *Pseudallescheria boydii*) and *S. prolificans* are the most common pathogenic *Scedosporium* species.²⁵² Clinically relevant species of *Acremonium* are difficult to identify based on morphology alone and may be misidentified as other molds such as *Fusarium*.²⁴⁴ The species associated with clinical disease include *A. falciforme*, *A. kiliense*, *A. roseogriseum*, and *A. strictum*.²⁴³ *Paecilomyces* is another emerging pathogen that historically was represented by infections with *P. variotii* and *P. lilacinus*. More recently, *P. variotii* has been divided into multiple species,^{253,254} and *P. lilacinus* has been reclassified as *Purpureocillium lilacinum*.²⁵⁵ *Geosmithia argillacea*, often misidentified as *P. variotii*,^{247,254} has also been associated with severe pulmonary

infections, particularly in patients with CF²⁴⁶ and chronic granulomatous disease.²⁴⁷ Finally, infections with *Trichoderma*, particularly *T. longibrachiatum*, are increasingly reported.²⁵⁰

Because the majority of these molds are ubiquitous in nature, they are often considered environmental saprophytes when recovered from clinical specimens. Infections are commonly associated with traumatic or nontraumatic inoculation with localized nail, eye, skin, and soft tissue infections. Inhalation of airborne conidia (spores) can lead to sinopulmonary infections ranging from mild allergic sinusitis and ABPM to severe and invasive sinopulmonary infections. Many of these pathogens are uniquely capable of adventitious sporulation, the ability to sporulate in infected tissue, which when coupled with endovascular invasion, results in fungemia. Although fungemia is uncommon in *Aspergillus* infections, it is reported in more than 50% of patients with disseminated *Fusarium* infections.²⁵⁶ Adventitious sporulation has also been described with *Acremonium* and *Paecilomyces*,²⁵⁷ *Scedosporium*,²⁵⁸ and *Trichoderma*.²⁵⁰ Mycotoxin production and adherence factors that promote colonization and infection may contribute to the pathogenicity of these molds.²⁵⁹

Localized skin, soft tissue, ocular, and sinopulmonary infections are seen in immunocompetent hosts, and chronic colonization can be present in patients with lung disease (e.g., bronchiectasis, pulmonary fibrosis). Fungemia and invasive infections develop predominantly in patients with impaired cellular and/or humoral immunity. In these patients, dissemination of infection from the lungs or local spread from the sinuses can result in CNS extension and brain abscess formation. Invasive infection is limited to immunodeficient patients with one notable exception: In immunocompetent near-drowning victims, severe CNS and sinopulmonary infections with *S. apiospermum* have been described, presumably because the forceful submersion in water resulted in alveolar damage with fungal penetration and severe fungal pneumonia.^{260,261}

CLINICAL PRESENTATION AND DIAGNOSIS

The respiratory presentation of non-*Aspergillus* hyalohyphomycosis resembles that of invasive aspergillosis and includes sinusitis, ABPM, tracheobronchial disease, pneumonia, and pleuropulmonary infections. Patients may present with fever, sinus congestion and pain, cough, purulent sputum, and hemoptysis (eFig. 38-13). In patients with disseminated infection, skin manifestations may be an early clue. Skin lesions are typically painful, erythematous, nodular eruptions that rapidly develop central pallor and necrosis (Fig. 38-8).

The diagnosis of infection with one of these pathogens is challenging, due to difficulties in differentiating between fungal colonization and true infection and in obtaining appropriate tissue specimens for evaluation. Furthermore, while histopathologic, cytopathologic, or direct microscopic examination from affected tissue is critical in making the diagnosis,¹⁵⁸ these findings do not discriminate amongst the hyaline molds; culture data are required for definitive identification and diagnosis. Radiographic findings (e.g., pulmonary nodules, cavitation, and halo, reversed halo, and air-crescent signs) provide further support for infection but



Figure 38-8 Disseminated *Fusarium*. Skin lesions in a patient with disseminated *Fusarium* infection demonstrating central necrosis with surrounding erythema.

are not specific. Noninvasive diagnostic testing such as serum or BAL GM, used primarily for the diagnosis of invasive aspergillosis, may cross-react with the non-*Aspergillus* hyaline molds including *Fusarium*,²⁶² *Paecilomyces*, and *Penicillium*,²⁶³ but lack both sensitivity and specificity in diagnosing these infections. The role of other molecular diagnostics such as nucleic acid assays or matrix-assisted laser desorption/ionization time of flight mass spectrometry continues to be defined.

TREATMENT

Treatment of these infections is multimodal. Immunosuppression should be reduced whenever feasible, and augmentation of host responses with growth factors and granulocyte transfusions should be considered. Removal of foreign devices and surgical intervention/débridement, particularly in localized disease, are also critical in management. Many of these pathogens are intrinsically resistant to conventional antifungal therapies and/or have species-dependent variability in MICs to antifungal drugs; identification to the species level is imperative. In some cases (e.g., *Fusarium* for which AmB activity is variable), susceptibility testing may provide additional guidance in drug selection.

Exemplifying the complexity of managing infections with non-*Aspergillus* mold infections, *Fusarium* and *Scedosporium* species exhibit variable levels of resistance to most antifungals.²⁶⁴ *F. solani*, the most common of the clinical isolates, is also the most resistant, with high MICs to voriconazole and posaconazole.^{245,256} ABLC treatment of invasive *Fusarium* infections in patients with hematologic malignancy or undergoing HSCT, resulted in improvement or cure of infection in 46% of patients evaluated.²⁶⁵ Pooled analysis of 21 patients with invasive *Fusarium* infections treated with voriconazole showed similar success in 43%, resulting in FDA approval of voriconazole for refractory infections or intolerance to other therapies.²⁶⁶ While it is not FDA approved for this indication, posaconazole has been used as salvage therapy in patients with hematologic malignancies and invasive Fusariosis.²⁶⁷ *Fusarium* species are intrinsically resistant to echinocandins; however, in combination

therapy with AmB,²⁶⁸ synergy has been demonstrated in vitro and in vivo.^{269,270} Other combinations including lipid formulations of AmB and voriconazole²⁷¹ have been used with clinical success, as have combinations that include terbinafine.²⁷²

Among *Scedosporium* species, *S. prolificans* often demonstrates high-level resistance to all antifungals and has been associated with poor clinical outcomes.²⁵² In contrast, *S. apiospermum* tends to be more susceptible to antifungals, particularly extended-spectrum azoles such as voriconazole.²⁷³ Successful responses to voriconazole were demonstrated in 63% (15 of 24) of patients with *S. apiospermum* infections resulting in FDA approval for this specific *Scedosporium* species. A more recent compilation of the data discussed herein plus additional cases of invasive *Scedosporiosis* obtained via the voriconazole global clinical trials database (Pfizer) reported a successful therapeutic response in 57% (61 of 107) of patients with notably higher success in *S. apiospermum* (45 of 70, 64%) compared with *S. prolificans* (16 of 36, 44%) infections.²⁷³ Combination therapies of voriconazole with terbinafine²⁷⁴ or with an echinocandin with or without AmB,²⁷⁵ particularly in multidrug-resistant infections, may be effective. AmB has poor activity against *P. lilacinum* but is highly active against *P. variotti*.²⁷⁶ In addition, while voriconazole demonstrates low MICs with *P. lilacinum*, MIC ranges are notably higher for the *P. variotti* species complex such that posaconazole is the preferred extended azole for this group.^{254,277}

DEMATIACEOUS (MELANIZED) FUNGI

The dematiaceous fungi represent an assorted group of molds with more than 50 genera and 100 species.²⁷⁸ While their presence in culture is often dismissed as contamination, they are increasingly associated with infection and can be seen in immunodeficient and immunocompetent hosts. Dematiaceous fungi contain melanin in their cell walls, which contributes to their pathogenicity and accounts for the dark brown color seen in culture and/or histopathology.²⁷⁹ These fungi are found in soil and vegetation worldwide and can gain entry into the host via inhalation or the cutaneous route. They are responsible for phaeohyphomycoses, an array of infections including skin and soft tissue infections, allergic and invasive sinus disease, or pneumonia, and ocular, CNS, and disseminated infections. Isolated skin and soft tissue infections are more common in immunocompetent hosts, whereas pulmonary and disseminated infections are predominantly seen in immunosuppressed patients. *Alternaria*, *Bipolaris*, *Cladophialophora*, *Curvularia*, *Exophiala*, *Exserohilum*, *Ochroconis* (previously *Dactylaria*), and *Phialophora* are some of the more common black molds associated with infection. Intrathecal injection of *Exserohilum*-contaminated corticosteroids recently led to a large outbreak of fungal meningitis in immunocompetent patients in the United States.^{280,281} *Bipolaris* and *Curvularia* are often associated with allergic and chronic inflammatory diseases including allergic fungal sinusitis and ABPM.²⁸² *Cladophialophora bantiana*,^{283,284} *Rhinocladiella*

mackenziei,^{285,286} *Exophiala* (*Wangiella*) *dermatitidis*²⁸⁷ and *Ochroconis gallopava*²⁸⁸ have a predilection for dissemination to the brain and can cause severe disease in immunocompetent and immunosuppressed patients.²⁸⁹ Disseminated infections with dematiaceous molds have been associated with mortality rates of up to 80%.²⁹⁰

Sinopulmonary manifestations with the dematiaceous molds include asymptomatic nodules, ABPM, and allergic fungal sinusitis, as well as invasive sinus and pulmonary infections. The latter two entities more commonly infect immunocompromised hosts and those with preexisting lung disease. CT findings are often nonspecific (eFig. 38-14) and consistent with that described with the other invasive pulmonary mycoses. Fungal elements seen on direct microscopy from clinical specimens can be associated with either colonization or contamination; documentation of tissue invasion is essential for diagnosis. Pigmented hyphae can be seen on standard hematoxylin and eosin stains. However, the Fontana Masson stain is often preferred to ensure that those with decreased amounts of pigmentation are not misidentified as hyaline molds.²⁹¹

As with other invasive molds, treatment includes reduction of immunosuppression and surgical debulking (when feasible) to augment antifungal therapies. Susceptibility breakpoints for antifungals have not been defined for the dematiaceous molds. Although resistance to AmB has been seen, AmB demonstrates good in vitro activity against most of the dematiaceous molds. However, the newer extended-spectrum azoles have the best in vitro activity against the majority of dematiaceous molds^{292,293} and are used more frequently given their improved toxicity profile. Combination therapies including azoles, terbinafine, and echinocandins have been employed for severe disease; however, an optimal regimen has not been defined.²⁹¹

Key Points

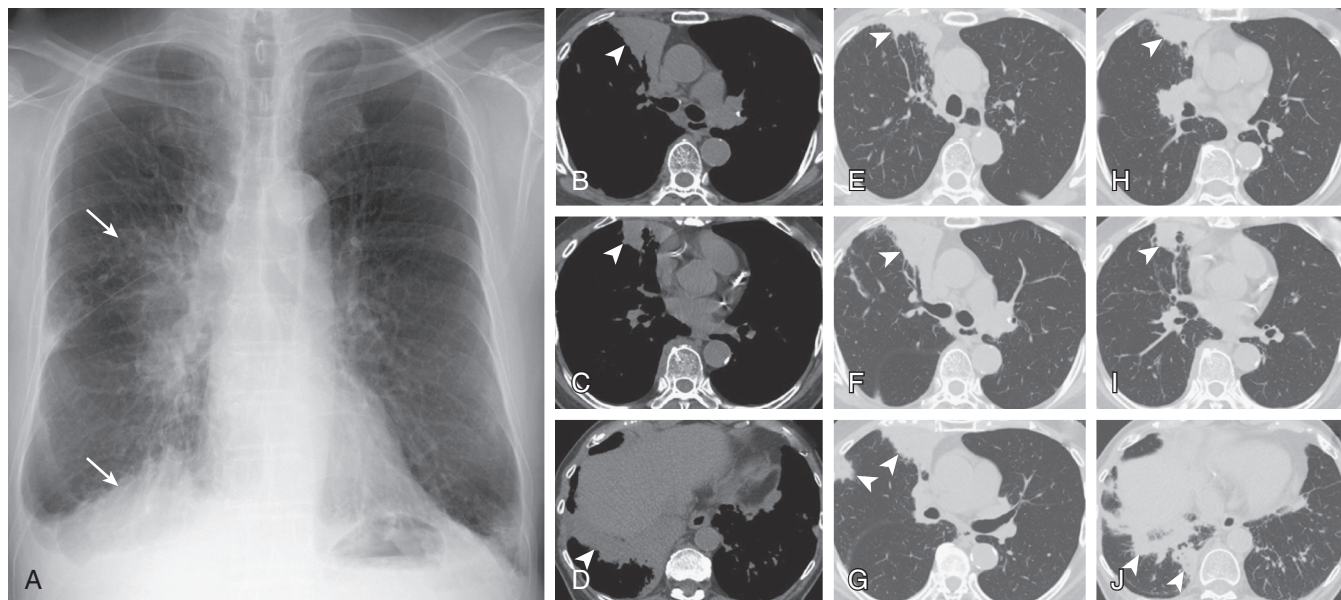
- Invasive pulmonary aspergillosis may have a clinical presentation similar to that of other angioinvasive molds such as mucormycosis and the non-*Aspergillus* hyphomycetes such as *Fusarium* and *Scedosporium*.
- β -D-glucan is a component of the cell wall of some but not all fungi and can be a useful noninvasive diagnostic aid in serum or bronchoalveolar lavage.
- Voriconazole is the treatment of choice for invasive pulmonary aspergillosis. The total duration of therapy depends on the immune status of the host and clinical and radiographic response to infection. However, patients are treated for a minimum of 6 to 12 weeks.
- Although mucormycosis can be associated with a multitude of clinical manifestations with multiorgan involvement, the most common presentations include rhino-orbital-cerebral and pulmonary infections, particularly in those with poorly controlled diabetes and in immunodeficient patients, especially those with hematologic malignancies.
- *Candida* pneumonia is rare and develops most often following candidemia and dissemination to the lung in immunocompromised populations.
- Combination antifungal therapy may offer benefit in infections due to drug-resistant fungi.

Complete reference list available at *ExpertConsult*.

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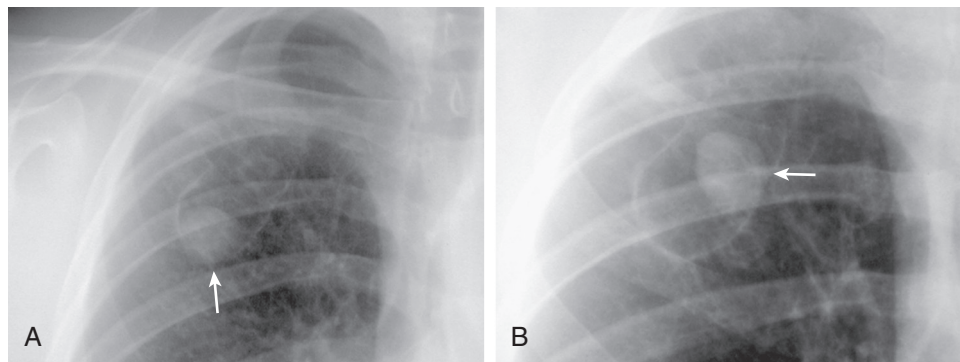
eFIGURE IMAGE GALLERY



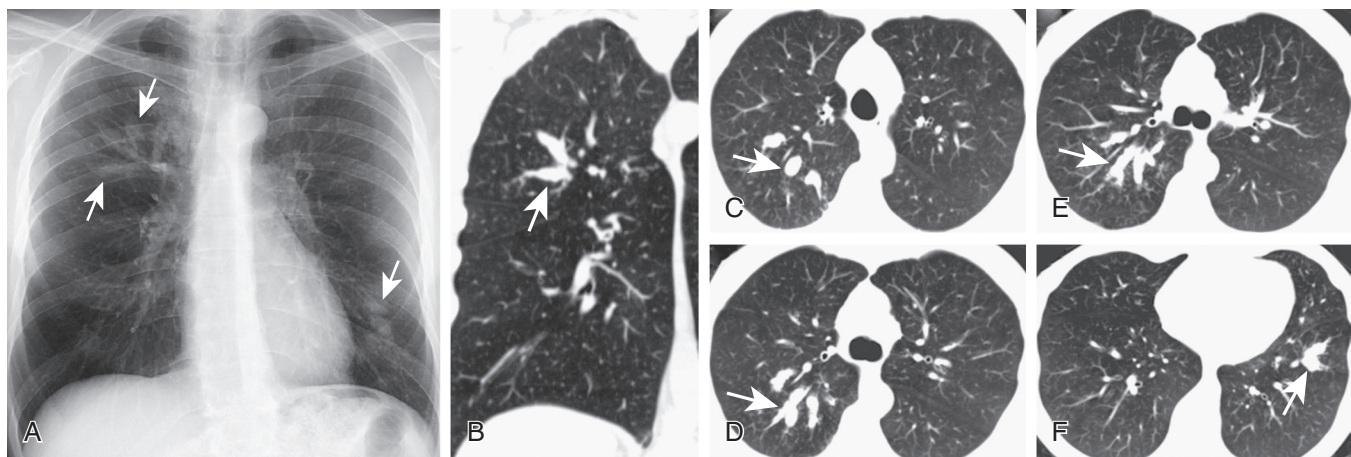
eFigure 38-1 Cryptococcal pneumonia. **A**, Frontal chest radiograph in an 80-year-old man with idiopathic CD4 lymphocytopenia shows patchy consolidation and bronchovascular thickening projected over the right hilum and in the right lower lobe (*arrows*). **B–D**, Axial unenhanced chest CT displayed in soft tissue windows shows consolidation (*arrowheads*). **E–J**, Lung windows show consolidation (*arrowheads*) with air bronchograms in the anterior segment of the right upper lobe with more nodular and lobular consolidation in the right middle and right lower lobes (*arrowheads* in **J**). *Cryptococcus neoformans* was diagnosed at bronchoscopy. (Courtesy Michael Gotway, MD.)



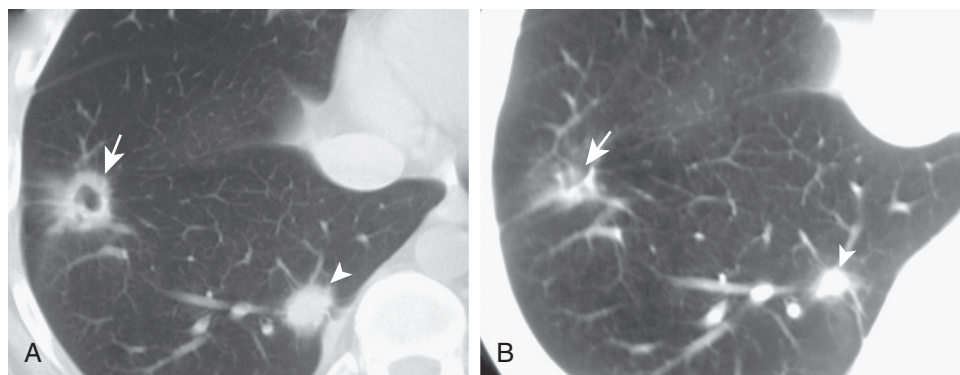
eFigure 38-2 Candida albicans pneumonia. Frontal chest radiograph in a severe immunosuppressed patient following treatment for hematologic malignancy shows a subpleural masslike opacity proven on tissue sampling to reflect candidiasis. (Courtesy Michael Gotway, MD.)



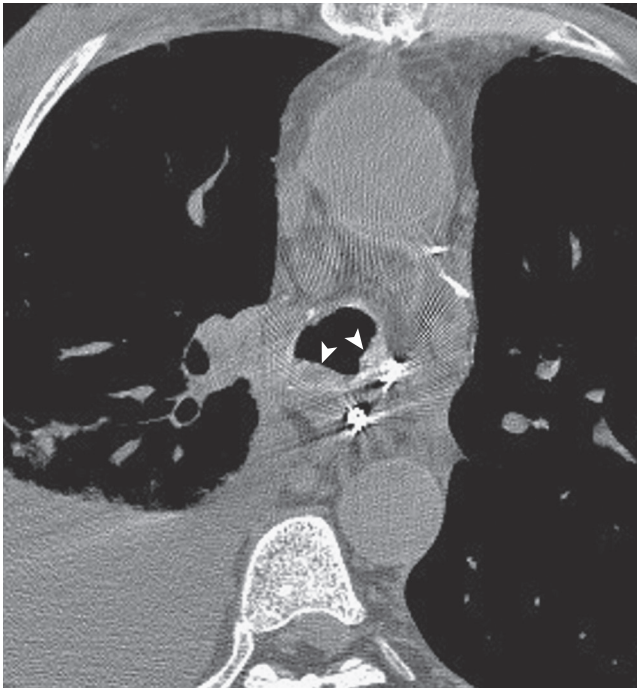
eFigure 38-3 Mycetoma: mobility demonstrated at imaging. Upright (A) and left lateral decubitus (B) focused chest radiographs show a mobile intracavitary mass (arrow) characteristic of mycetoma. (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr* 26:159–173, 2002.)



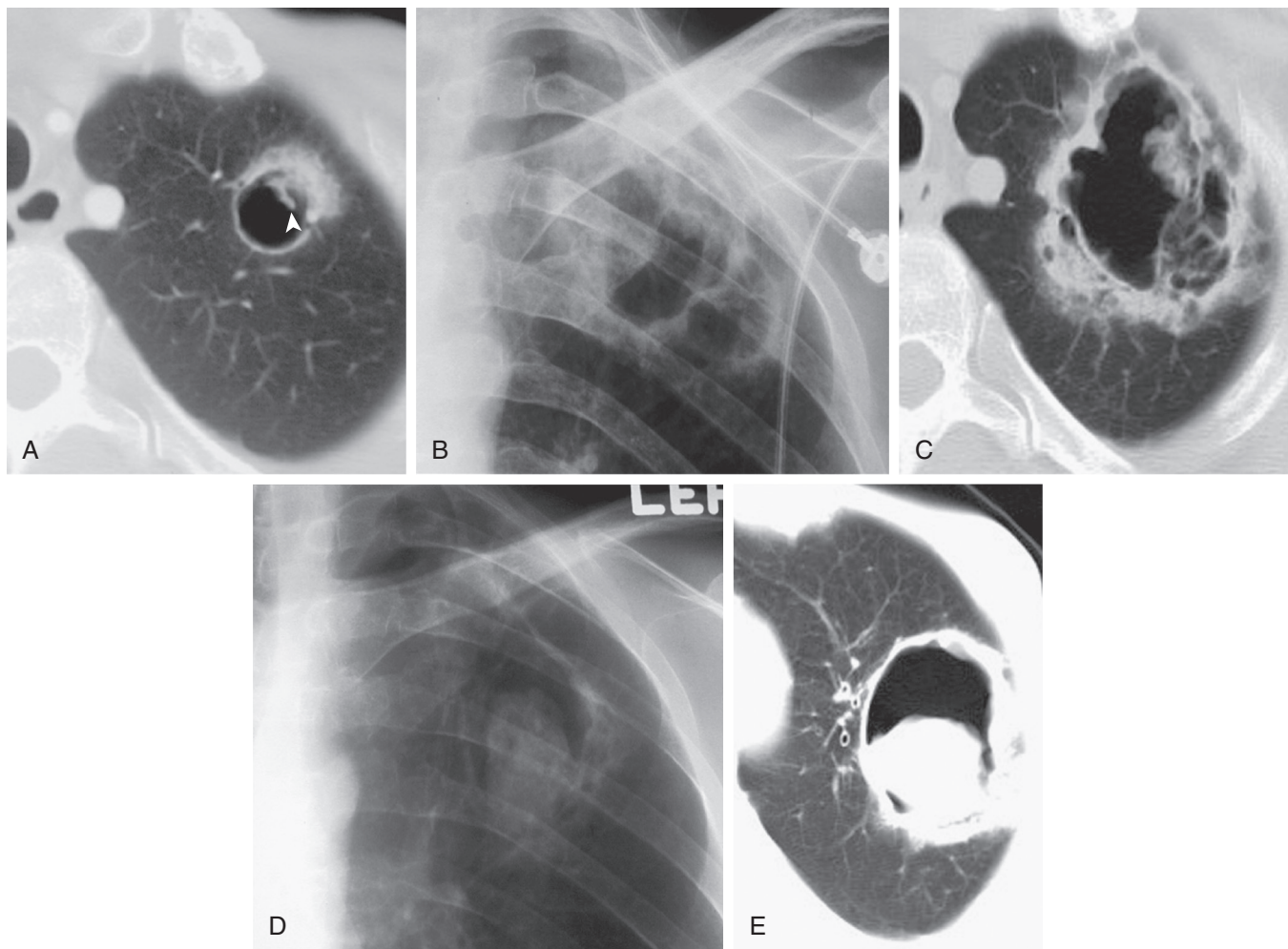
eFigure 38-4 Allergic bronchopulmonary aspergillosis. A, Frontal chest radiograph in a patient with asthma shows the characteristic “finger-in-glove” appearance of bronchial impaction (arrows) in a patient with allergic bronchopulmonary aspergillosis. Coronal (B) and axial (C–F) chest CT displayed in lung windows shows multifocal, bilateral, central bronchiectasis with bronchial impaction (arrows). (Courtesy Michael Gotway, MD.)



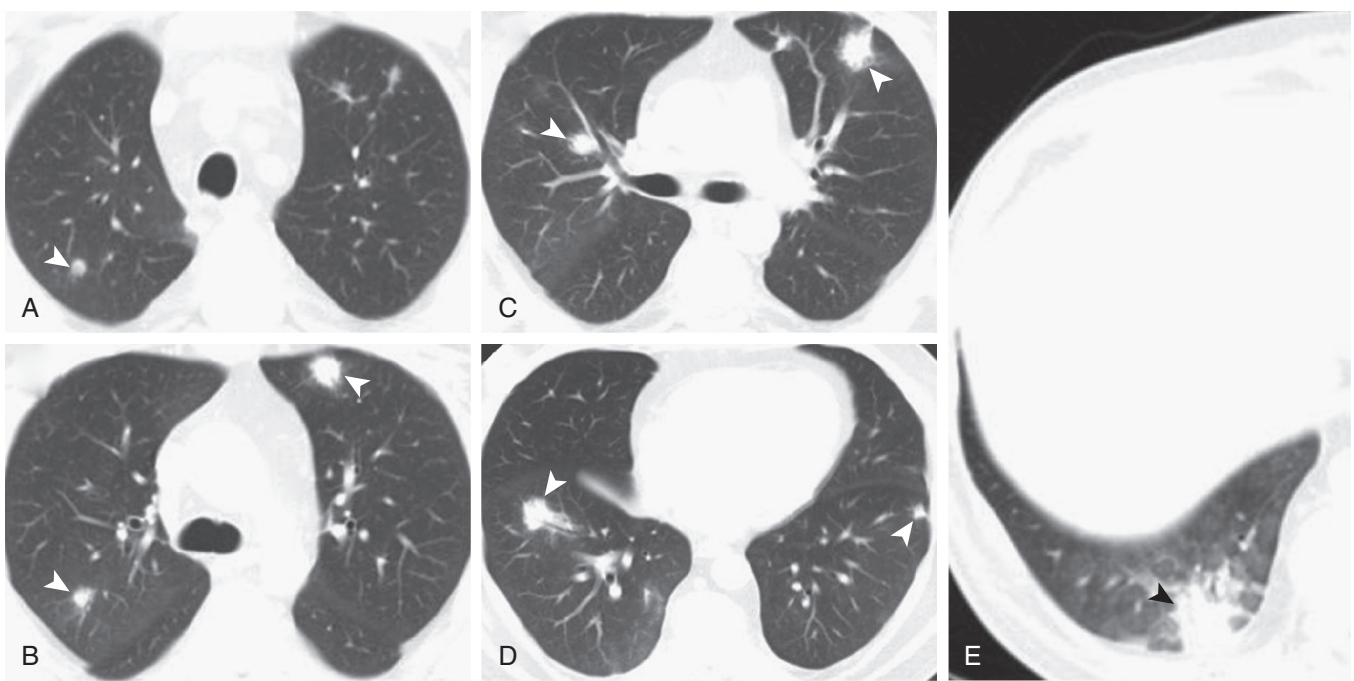
eFigure 38-5 Invasive *Aspergillus* infection: treatment response. A, Axial chest CT performed for a severely immunosuppressed patient following stem cell transplantation shows a right lower lobe cavity (arrow) and poorly defined nodule (arrowhead), consistent with invasive pulmonary aspergillosis. B, Axial chest CT performed following 6 weeks of antifungal therapy shows involution of the right lower lobe cavity (arrow) with reduction in size of the right lower lobe nodule (arrowhead). (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr* 26:159–173, 2002.)



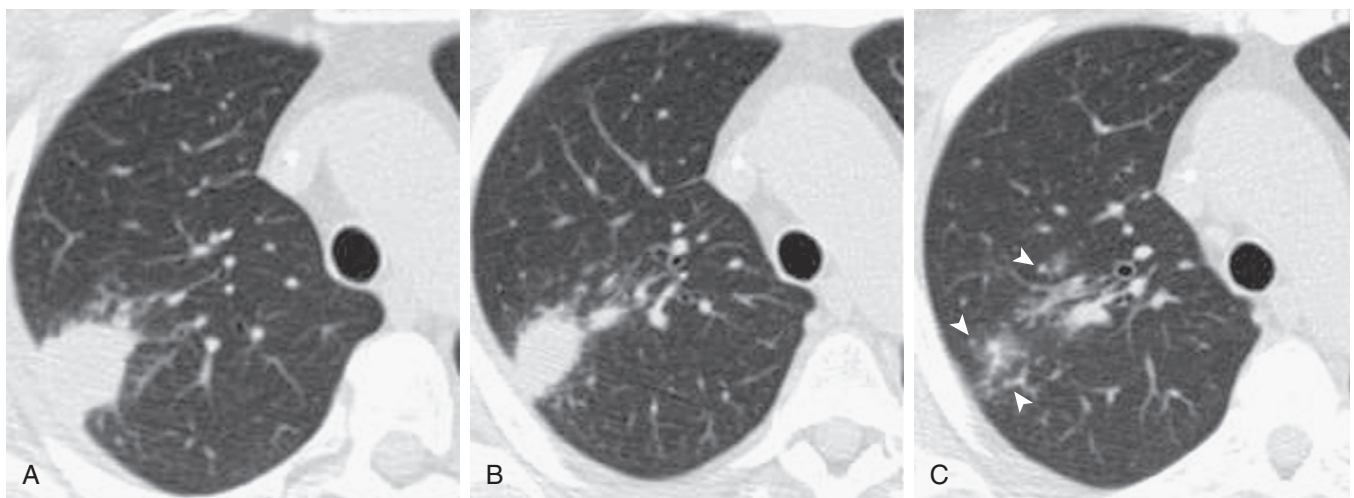
eFigure 38-6 *Aspergillus tracheitis*. Axial chest CT performed in a 62-year-old woman immunosuppressed following heart-lung transplantation shows high attenuation plaques (*arrowheads*) within the trachea, confirmed on bronchoscopy to represent *Aspergillus* infection. (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr* 26:159–173, 2002.)



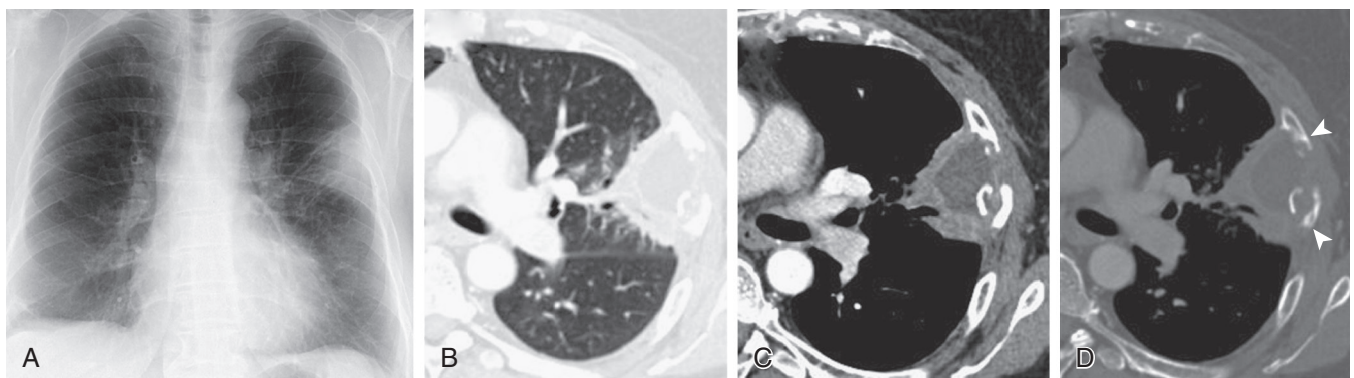
eFigure 38-7 Subacute invasive pulmonary aspergillosis (chronic necrotizing aspergillosis): slowly progressive cavitation. **A**, Axial chest CT in a patient with AIDS and diabetes mellitus shows a small cavity with an eccentrically thickened wall and early internal opacity (*arrowhead*). **B**, Focused frontal chest radiograph (**B**) and axial chest CT (**C**) performed 9 months after **A** shows increased size of the cavity with increasing wall thickness and irregularity as well as progression of the intracavitary opacity. Focused frontal chest radiograph (**D**) and axial chest CT (**E**) performed 15 months after **A** now shows an eccentrically thickened left upper lobe cavity with an internal fungus ball. (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr* 26:159–173, 2002.)



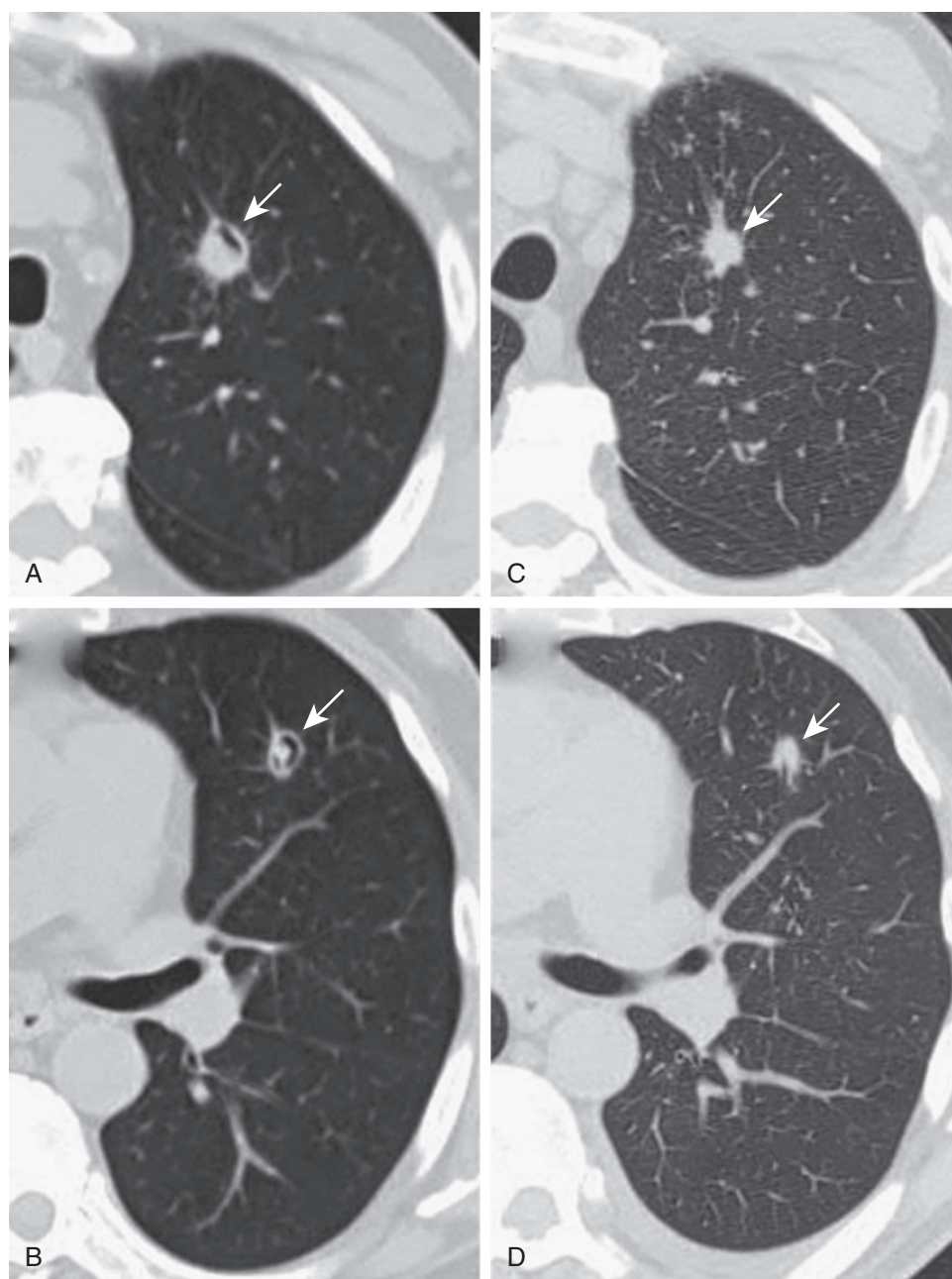
eFigure 38-8 Mucormycosis: multiple nodules. A–E, Axial chest CT displayed in lung windows performed in a severely immunosuppressed patient shows multiple, bilateral nodules (*arrowheads*), some associated with bronchi (right lower lobe in **D**, and left upper lobe in **B**), and some with ground-glass opacity halos (left upper lobe in **C**). (Courtesy Michael Gotway, MD.)



eFigure 38-9 Mucormycosis: large nodule/mass. Axial chest CT displayed in lung windows performed in a severely immunosuppressed patient shows an irregular opacity just exceeding 3 cm in size in the subpleural right chest lobe (**A**, **B**), proven to reflect *Mucor* on biopsy. Small satellite nodules (*arrowheads*) are seen along the inferior margin of the lesion in **C**. (Courtesy Michael Gotway, MD.)



eFigure 38-10 Mucormycosis: mass with chest wall invasion. **A**, Frontal chest radiograph performed in a severely immunosuppressed patient shows a masslike subpleural opacity in the left upper lobe. Focused axial chest CT displayed in lung (**B**), soft tissue (**C**), and bone (**D**) windows shows the subpleural mass is necrotic (note low attenuation centrally in **C**) associated with chest wall invasion, evidenced by rib destruction (**D**, *arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 38-11 Mucormycosis: treatment response. **A** and **B**, Axial chest CT displayed in lung windows performed in a severely immunosuppressed patient shows cavitary left upper lobe nodules with internal opacity (*arrows*), proven to reflect *Mucor*. **C** and **D**, Following antifungal therapy and restoration of immune function, the left upper lobe nodules are no longer cavitary and have decreased in size. Follow-up chest CT (not shown) showed complete resolution of the nodules. (Courtesy Michael Gotway, MD; case by Robert Viggiano, MD, Pulmonary and Critical Care Medicine, Mayo Clinic, Scottsdale, AZ.)

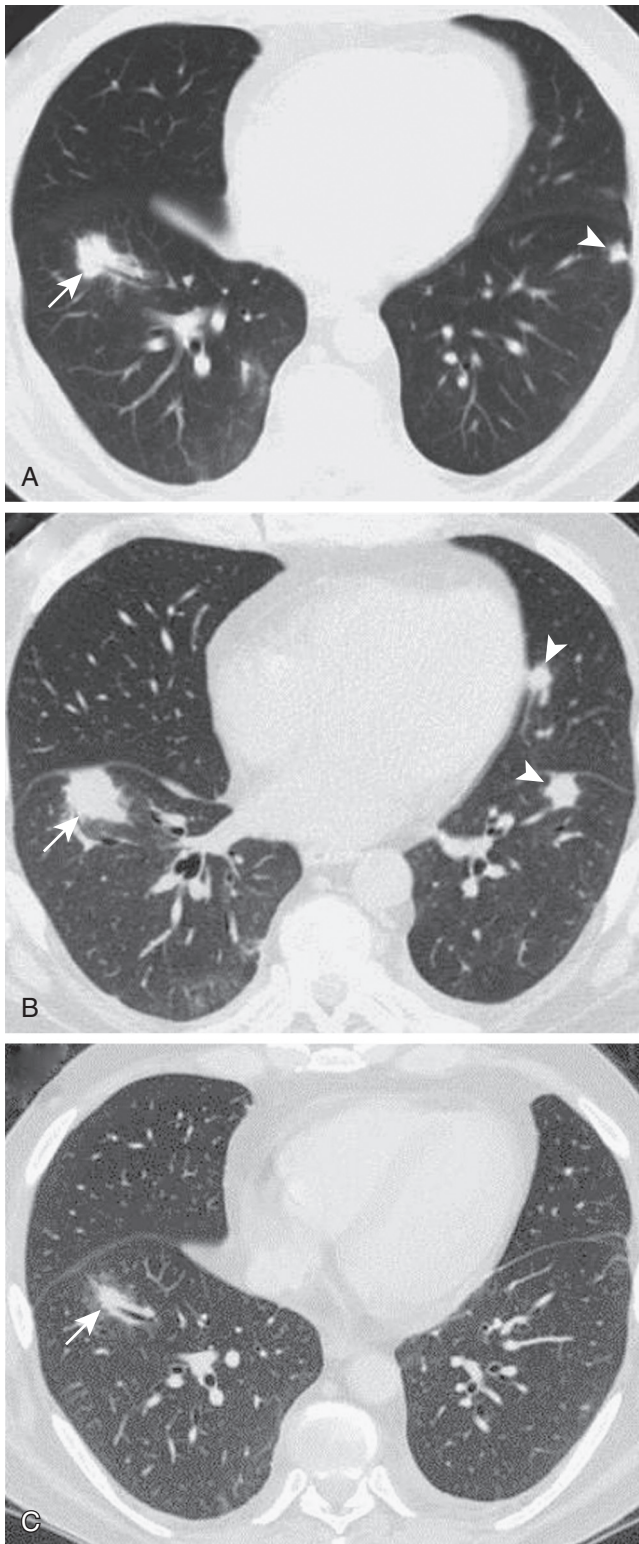
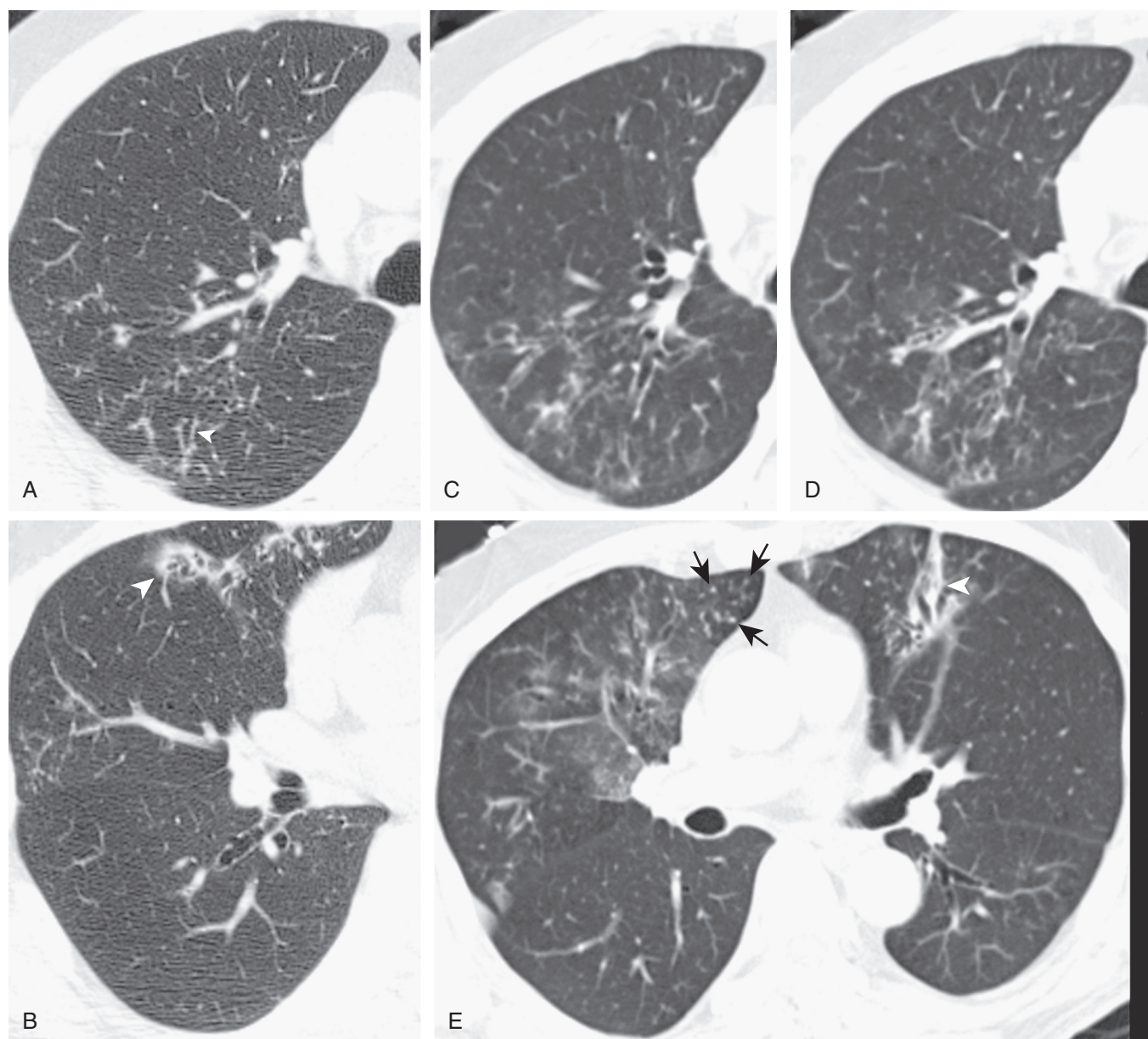


Figure 38-12 Mucormycosis: treatment response. **A**, Axial chest CT displayed in lung windows performed in a severely immunosuppressed patient shows a dominant right lower lobe nodule associated with an air bronchogram (*arrow*) and small subpleural left lower lobe nodule (*arrowhead*) due to *Mucor*. **B**, Follow-up chest CT shows enlargement of the right lower lobe nodule (*arrow*) and new left base nodules (*arrowheads*). **C**, Following antifungal treatment and resolution of immunosuppression, the dominant right lower lobe nodule (*arrow*) has decreased significantly in size. Other smaller nodules (*arrowheads*, **A** and **B**) also resolved. (Courtesy Michael Gotway, MD.)



eFigure 38-13 *Scedosporium apiospermum* infection. A–E, Axial chest CT displayed in lung windows in an 80-year-old man with cough and hemoptysis shows right upper lobe and anterior segment left upper lobe bronchiectasis and bronchovascular thickening (*arrowheads*), associated with small nodules (*arrows*, **E**). Bronchoscopy with bronchoalveolar lavage found old blood and recovered *Scedosporium apiospermum* organisms. (Courtesy Michael Gotway, MD.)

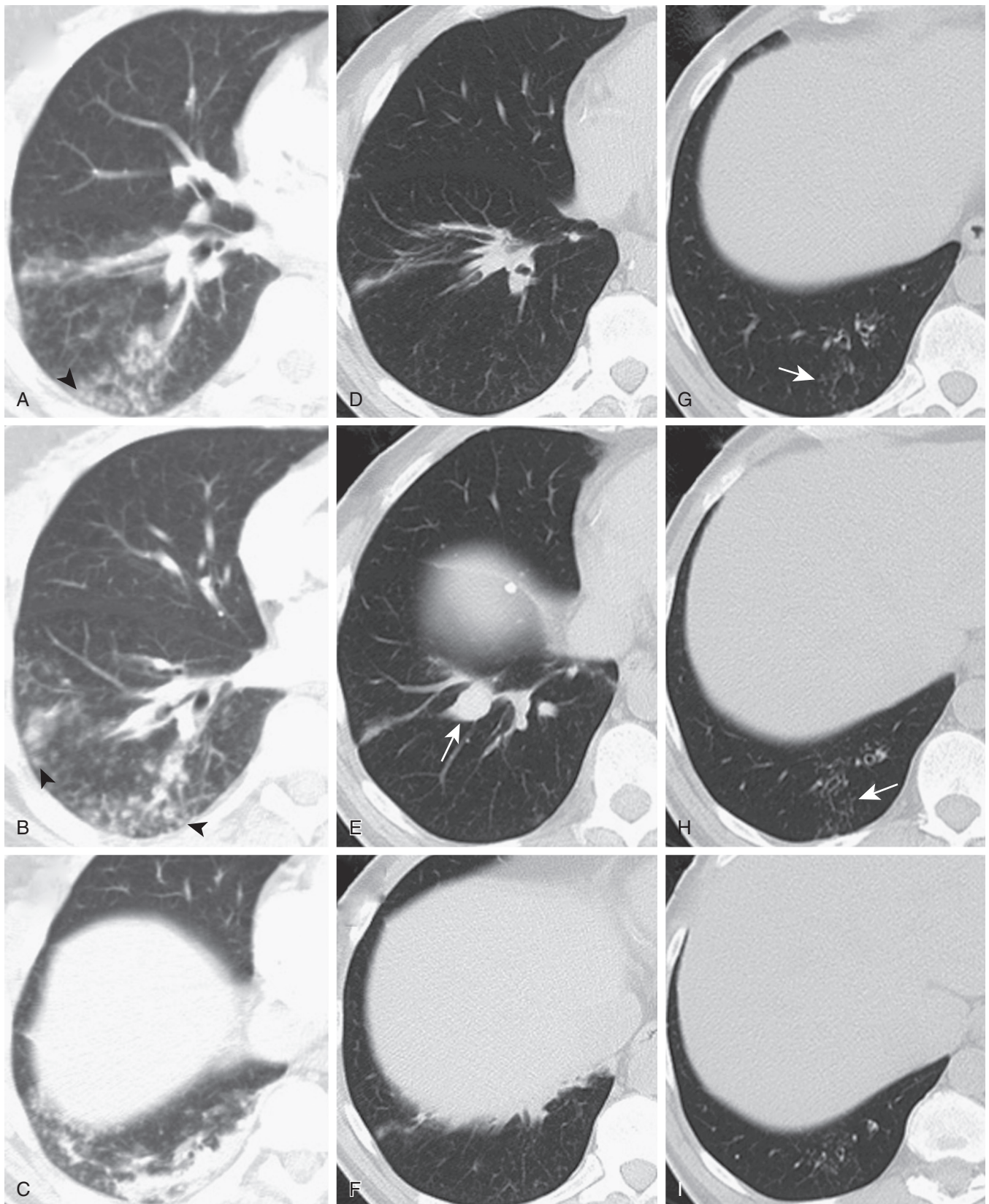


Figure 38-14 *Bipolaris* infection. **A–C**, Axial chest CT displayed in lung windows shows right lower lobe peripheral consolidation and numerous small centrilobular nodules (arrowheads, **A** and **B**). Bronchoscopy recovered *Bipolaris* organisms. **D–F**, Axial chest CT displayed in lung windows 2 months after **A–C** and following antifungal therapy shows improvement in basal consolidation and nodules, but appearance of large airway impaction (arrow, **E**). **G–I**, Axial chest CT displayed in lung windows 6 months after **A–C** shows near complete clearing of the right lower lobe process, with mild residual bronchiolitis (arrows). (Courtesy Michael Gotway, MD; case by Paul J. Conomos, MD, Arizona Pulmonary Specialists, Phoenix, AZ.)

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INTRODUCTION

Evaluation of a Patient with Possible
Parasitic Infection of the Lung

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Trematodes

Cestodes

PROTOZOA

Amebiasis

Malaria

Toxoplasmosis

Other Protozoa

INTRODUCTION

Pathogenic parasites that involve the lungs include multicellular helminths as well as unicellular protozoa. Although parasitic infections have classically been associated with tropical and subtropical regions, some are prevalent worldwide. Moreover, travel and immigration have resulted in globalization of formerly geographically restricted infectious diseases, and some of these affect the lungs.

Certain parasitic infections commonly present with pulmonary manifestations, while for others, pulmonary involvement is an unusual complication. With the exception of *Paragonimus*, the lung fluke, few parasites specifically target the lungs, although many helminths migrate through the lungs en route to the gastrointestinal tract. Some parasites that infect the lungs more commonly infect other sites such as the gastrointestinal tract (*Entamoeba*, *Echinococcus*); while others involve the lungs as part of a generalized systemic infection (*Toxoplasma*, *Plasmodium*) (Table 39-1).

Increasing use of immunosuppressive therapy, organ transplantation, and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), have led to expansion of populations vulnerable to selected parasitic diseases. Moreover, climate change and ecologic perturbations have affected the transmission and geographic range of human parasites. These factors necessitate greater familiarity of all physicians with infections that were previously seen only by specialists in tropical medicine. Clinical presentations of parasitic infections may be nonspecific and pulmonary specialists must be aware of potential pulmonary presentations.

This chapter reviews the pulmonary complications of parasitic infections that exhibit four major patterns: (1) parasites that primarily involve the lungs; (2) parasites that involve the lungs as a transient event in their life cycles; (3) parasites that involve the lungs less often than they involve other organs such as those of the gastrointestinal tract; (4) those that involve the lungs during widespread, systemic infections.

Some topics in this chapter also are discussed in the chapters on pulmonary complications of HIV (Chapter 90) and on eosinophilic lung diseases (Chapter 68).

EVALUATION OF A PATIENT WITH POSSIBLE PARASITIC INFECTION OF THE LUNG

Because specific parasitic infections differ in their geographic distribution, clinicians must consider the diseases that are prevalent in the areas where a patient has traveled or resided. A detailed travel history with information on food and liquids consumed, swimming or wading, insect bites, and medications taken are especially useful in formulating a differential diagnosis. The interval between the time of travel or emigration and the onset of symptoms may provide clues: enteric protozoa or helminthic infections typically present more than 2 weeks after exposure and some parasites such as *Strongyloides*, *Plasmodium vivax* or *ovale*, and *Entamoeba histolytica* can present years after exposure.

Some parasites have complex life cycles with numerous hosts and many are vector borne, while others are acquired by exposures to contaminated soil or water. Many emerging parasitic infections are zoonoses, in which the disease is spread from nonhuman animals to humans. In developing a differential diagnosis for respiratory complaints that may have a parasitic etiology, knowledge of the geographic distribution of various parasites, of potential vectors, and of potential sources of environmental contamination is essential.

Laboratory tests that may be helpful in initial evaluations include a complete blood count with differential, liver function tests, and a basic metabolic panel; in some contexts, examination of the sputum and/or stool samples is essential. Peripheral eosinophilia suggests a potential parasitic cause of pulmonary disease but most protozoan infections are not associated with eosinophilia, and a lack of eosinophilia does not exclude parasitic infection. Diagnosis of intestinal parasites is most often dependent upon microscopic examinations that require adequate specimens and experienced laboratory personnel. Depending on the parasite suspected, stool antigen tests (*E. histolytica*), microscopic examination of blood smears (malaria and *Babesia*), or collection of respiratory samples including sputum or bronchoalveolar lavage (BAL), or serologic tests (*Strongyloides* enzyme-linked immunosorbent assay [ELISA]) may be warranted.¹ Specialized laboratories are able to perform

Table 39-1 Characteristics of the Most Common Parasites Causing Pulmonary Pathology

Parasite	Distribution	Pulmonary Manifestation	Diagnosis	Treatment
HELMINTHS				
Nematodes				
Ascariasis: <i>Ascaris lumbricoides</i>	Worldwide, but widely in tropics	Loeffler syndrome, usually 9 to 12 days after exposure to eggs Cough Substernal discomfort Crackles and wheezing Transient opacities	Examination of sputum Eosinophilia during larval migration Stool ova and parasites: usually positive after pulmonary symptoms resolved Serology	Albendazole Mebendazole
Dirofilariasis (dog heartworm): <i>Dirofilaria immitis</i> and <i>D. repens</i>	Worldwide (associated with dogs)	Pulmonary nodule	Usually requires biopsy to rule out other causes	None (benign, so no treatment necessary)
Hookworm: <i>Ancylostoma duodenale</i> and <i>A. caninum</i> ; <i>Necator americanus</i> , <i>N. brasiliense</i>	Worldwide especially tropics	Loeffler syndrome Transient opacities	Eosinophilia during larval migration	Albendazole Mebendazole
Strongyloidiasis (also a hookworm, but unique due to autoinfection cycles): <i>Strongyloides stercoralis</i> (and sometimes other <i>Strongyloides</i> species)	Worldwide but particularly in tropic or subtropical regions	Loeffler syndrome Chronic cough Pneumonia or sepsis in hyperinfection	Sputum examination Eosinophilia during larval migration Stool ova and parasites Serology (cannot discriminate acute vs. past)	Ivermectin (may need longer doses for immunocompromised hosts); due to risk of hyperinfection, consider treating all seropositives
Trichinosis (also a hookworm but encysts): <i>Trichinella spiralis</i>	Worldwide zoonosis	Respiratory distress Radiographic appearance variable	Serology	Albendazole
Tropical pulmonary eosinophilia (lymphatic filariasis): <i>Wucheria bancrofti</i> and <i>Brugia malayi</i>	Tropics, particularly South Asia	Tropical eosinophilic pneumonia with interstitial opacities Chronic cough	Serology, Bronchoalveolar lavage Eosinophilia	DEC Doxycycline (treats symbiont)
Visceral larval migrans (nonhuman ascarid): <i>Toxocara canis</i> and <i>T. cati</i>	Worldwide	Interstitial opacities with eosinophilic pneumonia	Serology Eosinophils in blood and sputum	May not be needed Albendazole (or ivermectin) in severe cases
Cestodes				
Hydatid cyst: <i>Echinococcus granulosus</i> and <i>E. multilocularis</i>	Worldwide (especially in sheep-rearing locales)	Pulmonary cyst; second most common site after liver; hemoptysis	Serology, Eosinophilia rare	Surgical, albendazole
Trematodes				
Paragonimiasis (Lung flukes): <i>Paragonimus westermani</i> , <i>P. africanus</i> , <i>P. caliensis</i> , <i>P. kellicotti</i> (US)	Southeast Asia, Central and South America, Africa; US	Pulmonary parenchymal invasion (larvae mature in lung) with cavitary lesions Hemoptysis	Eosinophilia Eggs in sputum or stool Serology	Praziquantel
Schistosomiasis: <i>Schistosoma mansoni</i> , <i>S. haematobium</i> , <i>S. japonicum</i> , <i>S. intercalatum</i>	Asia, South America, Africa	Hematogenous seeding with heavy infection Pulmonary hypertension	Eosinophilia Serology Stool ova and parasites	Praziquantel
PROTOZOA				
Amebiasis: <i>Entamoeba histolytica</i>	Worldwide; mostly tropical	Abscess Lungs 2nd most common extraintestinal site after liver Hemoptysis	Percutaneous aspiration Serology Antigen PCR	Metronidazole Tinidazole
Malaria: <i>Plasmodium</i> species (<i>falciparum</i> , <i>vivax</i> , <i>ovale</i> , <i>malariae</i> , <i>knowlesi</i>)	Africa, Asia, Central and South America	Interstitial opacities Acute respiratory distress syndrome	Blood smear Rapid diagnostic test	Antimalarial treatment; specifics depend on species and geographic distribution of drug resistance
Toxoplasmosis: <i>Toxoplasma gondii</i>	Worldwide; most common in immunocompromised, especially HIV-infected with CD4 < 100	Interstitial pneumonia usually associated with disseminated disease	Smear of bronchoalveolar lavage PCR Serology (cannot discriminate acute from past)	Pyrimethamine/sulfadiazine Pyrimethamine/clindamycin

Continued on following page

Table 39-1 Characteristics of the Most Common Parasites Causing Pulmonary Pathology (Continued)

Parasite	Distribution	Pulmonary Manifestation	Diagnosis	Treatment
Rarer Protozoan Pulmonary Parasite Syndromes				
Free-living ameba: <i>Acanthamoeba castellanii</i> or <i>A. polyphaga</i> , <i>Balamuthia mandrillaris</i> , <i>Naegleria fowleri</i>	Worldwide	Rare, usually immunocompromised; more frequently seen as central nervous system disease	Smear/tissue section	No highly effective treatment. Treatment varies according to species involved in the infection.
Babesiosis: <i>Babesia microti</i> , <i>Babesia divergens</i>	US, Europe	Interstitial opacities: acute respiratory disease syndrome	Blood smear, PCR, serology	Quinine/clindamycin Atovaquone/azithromycin
Cryptosporidiosis: <i>Cryptosporidium parvum</i> and <i>C. hominus</i>	Worldwide	Primarily gastrointestinal; respiratory syndrome and transmission proposed	Smear of bronchoalveolar lavage or sputum Stool ova and parasites	No highly effective treatment (nitazoxanide approved for children with diarrhea)
Leishmaniasis: <i>Leishmania donovani</i>	Africa, Central and South America	Interstitial pneumonia usually associated with disseminated disease	Smear or histopathology of tissue PCR, serology	Pentavalent antimonials Amphotericin B Pentamidine Miltefosine
Microsporidiosis (related to fungi): Many species	Worldwide; especially in immunocompromised	Interstitial pneumonia Tracheobronchitis	Chromotrope 2A stains of sputum, smears, or tissue	Albendazole Fumagillin
American trypanosomiasis: <i>Trypanosoma cruzi</i>	Central and South America	Interstitial pneumonia usually associated with disseminated disease	Serology, Blood smear, PCR	Nifurtimox Benznidazole

Serologic testing can be performed by enzyme-linked immunosorbent assay (ELISA), immunofluorescence, or Western blot. In general ELISA is most common in that there are standardized cut-off points and less operator variability.

Antigen tests can be performed by Western blot or ELISA designed to detect the antigen of choice.

PCR, polymerase chain reaction.

polymerase chain reaction (PCR) tests or other nucleic acid-based tests for specific parasites but these are often not routinely available. Rapid antigen tests for the diagnosis of malaria are approved and are becoming increasingly available. In some cases, specialized testing is available at the Centers for Disease Control and Prevention (CDC); the CDC website provides useful resources for diagnostic testing (<http://www.cdc.gov/dpdx/>), and the CDC provides access for certain medications that are not routinely available in the United States.

HELMINTHS

Helminths, or worms, cause the most common parasitic infections worldwide. They are classified into two major phyla: (1) nematodes, or round worms, include the major intestinal worms, and the filarial worms that cause lymphatic filariasis and onchocerciasis; (2) platyhelminths or flat worms include flukes (or trematodes), such as *Schistosoma*, and tapeworms (or cestodes). Helminths mainly infect rural and impoverished people, and chronic infection in children may be associated with growth stunting and long-term effects on health and cognitive function.² With the exception of *Strongyloides*, helminths do not have internal autoinfection cycles in the host, and disease is generally proportional to worm burden, as assessed by the number of eggs per gram of feces.

Helminths are a common cause of eosinophilic pneumonia, although the differential diagnosis of eosinophilic pneumonia includes other infectious and noninfectious

syndromes.³ (See also Chapter 68.) Helminth infections classically present with Loeffler syndrome, characterized by transient interstitial pulmonary opacities and eosinophilia that result when larval forms of helminths migrate through the lungs. These helminth infections are often accompanied by peripheral eosinophilia, bronchospasm, and elevated *immunoglobulin* (Ig) E levels. Larvae migrate through the lungs, up the respiratory tree and then are swallowed, thereby reaching the gastrointestinal tract. Because the larvae have not yet matured into egg-bearing adults, stool ova and parasite examinations may not be helpful during acute infection. Depending on the burden of infection, helminth infestation and the accompanying eosinophilic pneumonia may result in an asthma-like syndrome, or in pulmonary damage due to release of cytotoxic cationic proteins from eosinophil granules.⁴

NEMATODES

The parasitic nematodes (round worms) of humans that cause ascariasis, hookworm disease, trichinosis, and strongyloidiasis have a lower respiratory phase as part of their life cycles. In each, larvae migrate through the lungs in transit to the gastrointestinal tract. In most cases, this migratory phase is asymptomatic, but cough, substernal discomfort and wheezing may be accompanied by transient radiographic opacities and eosinophilia (Loeffler syndrome).

Ascariasis

Ascariasis caused by the nematode *Ascaris lumbricoides* is the most common human helminth infection and is

estimated to infect almost 1 billion people.² Although it has a worldwide distribution, ascariasis is most common in tropical and semitropical regions. Although highly prevalent, ascariasis is associated with chronic disability rather than death. An estimated 4 million people in the United States are infected,⁵ primarily children in rural areas of the southern United States. Humans are the only known host of *A. lumbricoides*, although the pig species *A. suum* is similar biochemically and morphologically. Females produce eggs that are shed in stool. The eggs mature in moist environments; humans are infected by swallowing ova that contaminate water, food, or soil. In regions where there are high worm burdens, infection can also be acquired by inhalation of ova. The eggs bear rhabditiform larvae that hatch in the intestine. The resulting larvae are released, burrow through the intestinal wall, and enter the hepatic circulation via capillaries and lymphatics. They then migrate via the right side of the heart into the lungs. The worms migrate up the bronchial tree, are swallowed, and make their way to the duodenum, where they mature into adults after several months. Once the worms reach the intestines, children may have nausea, vomiting, abdominal pain, and anorexia, reflecting high worm burdens that can lead to obstruction or chronic malnutrition.⁵ Adult worms can live in the human intestine for several years.

Clinical Features. Infected individuals, usually children, are typically asymptomatic. The most common symptoms are nonspecific abdominal complaints. However, some may experience malaise and fever with or without respiratory symptoms such as cough, chest pain, dyspnea, bronchospasm, and hemoptysis. Pulmonary symptoms develop 9 to 12 days after ingestion of eggs and can persist 2 to 3 weeks. This stage of the infection may be associated with leukocytosis and eosinophilia. Acute eosinophilic pneumonia resulting in respiratory distress and requiring intubation has been reported but is rare.^{6,7} In some regions of the world, pneumonitis is seasonal, due to climate conditions that favor transmission of ascariasis.⁸

Diagnosis. Chest imaging during the initial stage of infection may reveal transient unilateral or bilateral opacities (eFig. 39-1). The diagnosis is difficult to confirm during the acute stage, because ova do not appear in the stool until 2 to 3 months after infection. Peripheral eosinophilia may be detected, and larvae, eosinophils, or Charcot-Leyden crystals may be found in sputum or gastric contents.

Treatment. The treatment of choice for ascariasis is albendazole, although mebendazole and ivermectin are also efficacious against adult worms. Although the pulmonary phase is self-limiting, the persistent gastrointestinal phase warrants treatment to relieve symptoms and reduce transmission.

Hookworm Disease

Hookworm disease is caused by *Ancylostoma duodenale*, *Ancylostoma ceylanicum*, or *Necator americanus*. These helminths infect at least a half billion people worldwide,² primarily in tropical and subtropical regions. They reside in the small intestine where they attach to the mucosa and feed on blood and host tissue, causing iron deficiency

anemia as the major cause of morbidity. Unlike other helminths, hookworm prevalence increases with age, and there is no protective immunity.

Clinical Features. Hookworm ova are passed in the stools of an infected person, which then hatch into rhabditiform larvae that molt and become filariform larvae. Filariform larvae in the soil penetrate the skin of a human host; this can be associated with a pruritic rash. The larvae enter the lymphatics or venules and ultimately reach the pulmonary circulation. Some persons experience cough, bronchospasm, and transient pulmonary opacities with or without fever.^{9,10} Bronchitis and/or pneumonia may develop when the larvae break through capillaries and enter the alveolar spaces. Peripheral and pulmonary eosinophilia are common during this stage of infection.

Once the worms reach the intestine, an individual may have nonspecific gastrointestinal symptoms including nausea and abdominal pain. Iron deficiency anemia is the most important consequence of hookworm infection and can lead to cognitive problems. Malnutrition and hypoproteinemia can also complicate hookworm infection.

Diagnosis and Treatment. Stool examination reveals hookworm ova 2 to 3 months after pulmonary symptoms, but in cases of light infection, concentration of stool may be necessary to detect the ova. Diagnosis during the pulmonary phase is difficult and relies upon isolation of larvae from respiratory secretions, BAL fluid, or gastric secretions. The treatment of choice is albendazole (single dose) or mebendazole (twice daily for 3 days). These drugs kill the adult worms but are not effective against the pulmonary larval stages. Patients should be screened for ova in stools 1 month after treatment and, if ova are still present, retreatment is indicated to eliminate adults that developed after the initial treatment.

Strongyloidiasis

Although there are more than 50 species of *Strongyloides*, *Strongyloides stercoralis* is the most common in humans. This helminth has a worldwide distribution and is endemic in Latin America, south Asia, sub-Saharan Africa, the United States (especially the southern states and Appalachia), Europe, and Australia.¹¹ Up to 100 million people are estimated to be infected,¹² although some experts believe that the worldwide prevalence of *Strongyloides* infection may be much higher.¹³ Due to lack of awareness amongst clinicians and its prevalence in people in resource poor settings, *Strongyloides* infection is often undiagnosed or diagnosed late.

Strongyloides has a complex life cycle consisting of free-living and parasitic forms. Humans are the primary reservoir and acquire infection from soil or vegetation contaminated with human feces. Similar to hookworm infection, strongyloidiasis is initiated by penetration of the skin by infective filariform larvae, frequently through the soles of the feet. After penetration of the infective larvae through the skin or gut mucosa, they are carried via the circulation to the lungs and penetrate into alveoli and then ascend the tracheobronchial tree. The larvae are swallowed and reside in the small intestine where they ultimately develop into adult worms. Ova are released and hatch into rhabditiform

larvae, which are passed in feces. These larvae transform into filariform larvae. The larvae can also molt and transform into free-living adults in soil, where they may transform into infective filariform larvae. Some rhabditiform larvae may molt into filariform larvae while still in the small bowel and then invade the mucosa of the bowel or the perianal area. Filariform larvae that form internally can cause autoinfection in which they migrate through the circulation to the lungs, thereby recapitulating the early migratory phase.¹⁴ Infection can also take place through the mucosa of the lower gastrointestinal tract or the perianal area¹⁵ from larva that have transformed into infective filariform larvae in the gut.

Infection with *Strongyloides* results in a variety of clinical syndromes ranging from a mild disease to the hyperinfection syndrome seen in immunocompromised hosts.¹⁶ Cell-mediated immunity that develops after primary infection limits the extent of autoinfection, so larvae and adult worms largely remain confined to the intestine, where they can survive for decades in immunocompetent individuals. With immune suppression, especially caused by steroids, and other immunodeficient states, especially infection with human T-lymphotropic virus-1 (HTLV-1),^{16a} autoinfection can become pronounced and lead to hyperinfection.

Clinical Features. The clinical manifestations of strongyloidiasis depend on the intensity of infection and immunologic status of the individual. Acute infection is rarely symptomatic but pneumonitis can develop during the larval migration phase. More than 50% of patients with chronic infections are asymptomatic. Up to 75% of symptomatic patients have peripheral eosinophilia and elevated serum IgE levels; strongyloidiasis should be in the differential diagnosis of any person who presents with persistent eosinophilia.

Patients can present with abdominal pain, diarrhea, and weight loss.¹² Dermatologic symptoms include pruritus, urticaria, and skin eruptions including larva currens, which is manifest as linear streaks that can be seen on the trunk, thighs, and buttocks due to migrating larvae (Fig. 39-1). The common pulmonary manifestations in immunocompetent individuals are transient pulmonary opacities with productive cough, dyspnea, and bronchospasm. Chest radiographs range from normal to bilateral nonspecific opacities. Strongyloidiasis may cause asthma, and improve-

ment may follow eradication of the infection. Reactive arthritis, nephrotic syndrome, chronic malabsorption, duodenal obstruction, and hepatic lesions have also been associated with chronic strongyloidiasis. Patients from highly endemic areas who have asthma or chronic obstructive pulmonary disease with eosinophilia should always be screened for *Strongyloides* infection before instituting steroid therapy to avoid hyperinfection.

The *Strongyloides* hyperinfection syndrome develops due to accelerated autoinfection. Hyperinfection is usually observed in the setting of immunosuppression, especially when caused by high-dose corticosteroids¹⁶⁻¹⁹ although other immunosuppressive drugs and radiation therapy have also been implicated. Infection with human T-lymphotropic virus-1 markedly predisposes to hyperinfection; this is thought to be secondary to deficiency of T-helper 2 cells that normally contribute to control of helminths.^{16,20} In addition, immunosuppression associated with lymphoma, leukemia, malnutrition, organ transplantation, and HIV/AIDS predispose to *Strongyloides* hyperinfection (see eFig. 90-30), although some studies indicate the risk is not increased by HIV.^{16,21}

Strongyloides hyperinfection is characterized by prominent gastrointestinal symptoms, including abdominal pain, nausea, vomiting, diarrhea, and ileus. The lung is also an important target in patients with *Strongyloides* hyperinfection. As filariform larvae migrate through the lungs, they cause pneumonitis with cough, hemoptysis, and respiratory failure. As the larvae leave the lumen of the gastrointestinal tract and invade the intestinal mucosa, they may carry bacteria from the gastrointestinal tract, resulting in polymicrobial bacteremia, bacterial pneumonia, acute respiratory distress syndrome, and gram-negative bacillary meningitis.²² *Strongyloides* hyperinfection has also been reported to mimic accelerated idiopathic pulmonary fibrosis.²³ Mortality of disseminated strongyloidiasis can be as high as 90%.

Diagnosis. In *Strongyloides* hyperinfection, larvae, ova, and adult worms may be observed in sputum, urine, BAL fluid, and other body fluids (see Fig. 39-1, see eFig. 90-30C). Diagnosis of *Strongyloides* infection may be difficult if the parasite load is low, because the most common diagnostic test is based on detection of *Strongyloides* ova in stool samples (see Fig. 39-1). Recently developed serology assays

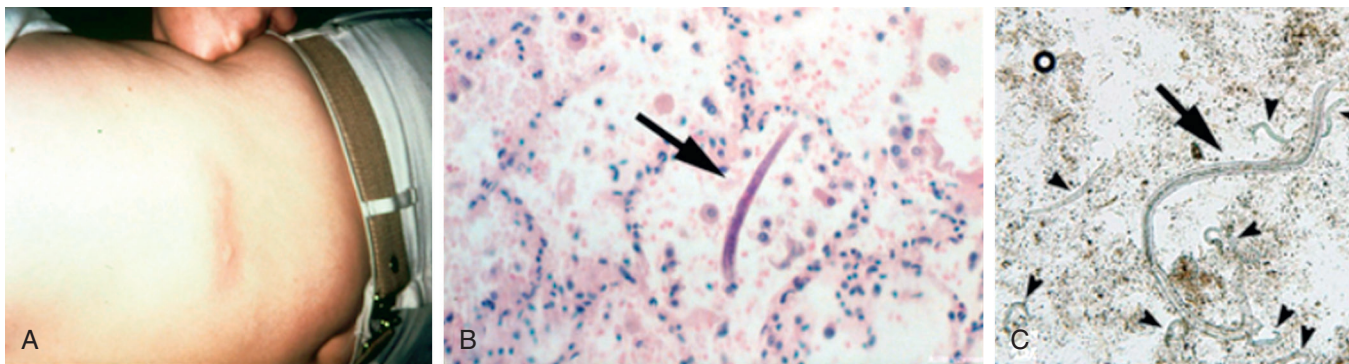


Figure 39-1 Strongyloidiasis. **A**, Larva currens in a patient with chronic strongyloidiasis. **B**, Filariform larva in a pulmonary biopsy specimen (arrow). **C**, Filariform (arrow) and rhabditiform (arrowheads) larval stages of *Strongyloides stercoralis* in the stool from a patient with hyperinfection syndrome. These were also found in the sputum. (**A** and **B**, from Herman Zaiman's "A Pictorial Presentation of Parasites" with permission of the American Society of Tropical Medicine and Hygiene.)

use ELISA or immunofluorescence to detect serum antibodies to *Strongyloides*. While ELISA is more sensitive than detecting ova in stool, the specificity of this test is suboptimal in regions where other nematodes such as filariae are endemic, because cross-reactive antibodies are common.²⁴ Eosinophilia is common during hyperinfection; lack of eosinophilia is often associated with a poor prognosis.^{16,25}

Treatment. Ivermectin is the treatment of choice and eliminates the worm in more than 90% of subjects;¹³ ivermectin is significantly more effective than albendazole.²⁶ Although ivermectin is usually prescribed as a 2-day course, treatment is usually extended and individualized for the hyperinfection syndrome, to ensure eradication.¹⁶ Human T-lymphotropic virus-1 coinfection is associated with a higher rate of treatment failure,²⁷ and some patients may require additional therapy to prevent recurrence. Combination treatment with ivermectin and albendazole has also been proposed in severe cases or in chronic infections with human T-lymphotropic virus-1 coinfection when ivermectin alone has failed. In hyperinfection cases where oral treatment cannot be absorbed or tolerated, the veterinary preparation of ivermectin has been administered subcutaneously.^{28,29} There is no reliable test to monitor for cure but many individuals have reversion or decline of IgG serologies with successful treatment.²⁴ All patients with *S. stercoralis* infection should be treated, because of the risk of autoinfection and dissemination.

Some experts recommend that patients from highly endemic areas have a screening serology for strongyloidiasis before (or at the time of) starting steroids or organ transplantation and, if seropositive, treatment is indicated to prevent the hyperinfection syndrome.

Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia (TPE) is a distinct clinical syndrome in patients from tropical areas endemic for lymphatic filariasis such as *Wuchereria bancrofti* or *Brugia malayi*.³⁰ Most cases have been described in India, Pakistan, Sri Lanka, Southeast Asia, parts of the African continent, and South America, especially Brazil and Guyana. TPE is now recognized in nonendemic areas, predominantly in immigrants; TPE is thought not to be a significant risk during a brief visit to an endemic area.

Filariae have five morphologic stages; humans are infected with third stage larvae transmitted by mosquitoes. Infective larvae molt twice and develop into adults that survive in a human host for up to 20 years. The first stage larvae, or microfilariae, are released into the circulation by female adult worms. *Wuchereria* and *Brugia* microfilariae circulate in the blood in a temporal pattern that coincides with the feeding habits of their mosquito vectors.

Clinical Features. TPE is seen predominantly (80%) in males, usually in middle age. The major clinical features of TPE include nocturnal paroxysmal cough and bronchospasm, low-grade fever, weight loss, and lymphadenopathy; some patients also have hepatosplenomegaly. Leukocytosis, marked peripheral eosinophilia, and elevated serum IgE levels are common, and sputum or BAL specimens often contain eosinophils. Pulmonary function tests reveal both restrictive and obstructive defects. Although TPE is caused by filaria, patients with TPE do not have detectable microfilaremia. The pathogenesis of TPE is poorly understood but is believed to represent a response to microfilariae that are trapped in the lungs.^{31,32}

Diagnosis. The diagnosis of TPE is based on the combination of clinical, radiologic, epidemiologic, and laboratory data, without the need for lung biopsy. Patients have nocturnal dyspnea with eosinophilia, elevated serum IgE, and a positive serologic test (ELISA) for antibodies to filarial antigens. Because the specificity of filarial serology tests is compromised by cross-reactivity with other helminths, other data are important for an accurate diagnosis.^{1,33} Chest radiographs usually reveal increased bilateral bronchovascular markings and reticulonodular opacities or diffuse miliary lesions, or opacities in the middle and lower lung fields (Fig. 39-2, eFig. 39-2). Cavitation, bronchiectasis, and pleural effusion have been reported but are uncommon; chest radiographs may also be normal. When pathological specimens have been obtained, eosinophilic infiltration of the interstitial and perivascular areas, eosinophilic abscess formation and eosinophilic granulomas can be observed, and worm fragments are occasionally found.³⁴ Electron microscopic examination of the lung has demonstrated degranulation of the eosinophils, implying that tissue destruction may be mediated by cytotoxic granule

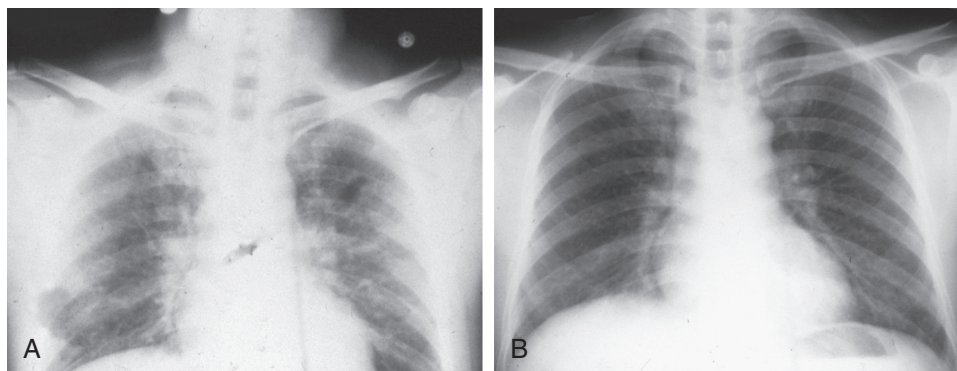


Figure 39-2 Tropical pulmonary eosinophilia. **A**, Chest radiograph of a patient from Sri Lanka with confirmed tropical pulmonary eosinophilia shows subpleural right lung consolidation, subpleural left midlung opacity, and bilateral perihilar interstitial thickening. **B**, Chest radiograph of the same patient after treatment with diethylcarbamazine. Note the improved parenchyma.

proteins released by these cells. Fibrosis may be present if the course of the disease is prolonged.

Treatment. All patients should be treated because TPE can progress to chronic restrictive lung disease. Administration of diethylcarbamazine, an antihelminthic drug, results in improvement in the signs and symptoms of TPE, with reduced eosinophilia and serum IgE levels. Some experts have suggested ivermectin therapy either alone or in combination with diethylcarbamazine, although ivermectin has little effect on adult filariae and some patients require retreatment, regardless of the regimen. Recent studies have shown that doxycycline, which eliminates the bacterial (*Wolbachia*) endosymbiont of *W. bancrofti*, is efficacious in treatment of both adults and microfilaria of filariasis.³⁵ An endosymbiont is an organism that lives within another with mutual benefit; *Wolbachia* is thought to play an important role in the disease caused by *Wuchereria* and to its survival. It is proving a valuable target for many of the filarial diseases, especially because it can be targeted with doxycycline, which is better tolerated than diethylcarbamazine. Steroid therapy should be administered with caution because TPE and pulmonary strongyloidiasis have similar presentations and steroids may enhance the morbidity and mortality of strongyloidiasis.

Visceral Larva Migrants

Visceral larva migrans (VLM) is a clinical syndrome caused by infection of humans by the dog ascarid *Toxocara canis* or the cat ascarid *Toxocara cati* in temperate and tropical climates. Children acquire infection by ingesting embryonated eggs in contaminated soil or sandbox contents; a history of pica is common in infected children.³⁶ Although VLM usually afflicts children, adults have also been described with VLM. A VLM-like syndrome has also been reported as a result of infection with *A. suum*, the parasite of pigs,³⁷ and *Baylisascaris procyonis*, the raccoon ascarid.³⁸

Because the hatched larvae cannot mature into adults in humans (which are dead-end hosts), the larvae migrate throughout the visceral organs of humans causing an acute eosinophilic syndrome.

Clinical Features. *Toxocara* infection affects diverse organ systems.³⁹ Pulmonary manifestations are present in 80% of cases and include cough, shortness of breath, and wheezing, resembling asthma.⁴⁰ Although symptoms are usually mild, severe respiratory symptoms have been reported.^{41,42} These manifestations are a result of damage to the lung by the larvae and by immune responses to them.⁴³ Other manifestations may include urticaria, lymphadenopathy, hepatosplenomegaly, and seizures. Involvement of the central nervous system,⁴⁴⁻⁴⁶ eye, and myocardium^{47,48} have been reported but are not common.

Diagnosis and Treatment. The radiographic appearance in VLM is variable and includes bilateral or segmental and patchy opacities, which can be migratory; subpleural opacities may be detected by *computed tomography* (CT). Laboratory evaluation may reveal leukocytosis, marked eosinophilia, elevated anti-A or anti-B isohemagglutinin titers, and abnormal liver function tests; IgE levels are frequently elevated. The diagnosis is made by ELISA and

immunoblot testing. Because larvae do not mature to adults in humans, there are no ova in the stool.

Because VLM is a self-limited syndrome, antiparasitic drugs may not be required. However, if the symptoms are moderate or severe, albendazole is the drug of choice; diethylcarbamazine is an alternative therapy. In severe cases, adjunctive steroids may accelerate symptom resolution. Preventive measures include control of soil contamination, curbing pica, and regular deworming of dogs and cats.

Other Ascarids

Infection with *Baylisascaris procyonis*, an ascarid of raccoons, results in a systemic disease characterized by eosinophilia. Pulmonary involvement has been reported in this infection,³⁸ although the major clinical manifestations are neurologic and ocular. There is no proven therapy, although albendazole may be beneficial.

Dirofilariasis

Dirofilaria immitis, the dog heart worm, is an important cause of morbidity and mortality in dogs.⁴⁹ It is transmitted by mosquitoes, but humans are dead-end hosts. In the United States, most cases have been described in the Southeast. The worms migrate via the venous circulation and right heart where they reach the pulmonary arteries. In humans, the filariae are vascular parasites in the pulmonary artery, inducing vasculitis and formation of a pulmonary nodule upon death of the parasite (Fig. 39-3).⁵⁰ Chest radiographs usually reveal a well-defined homogeneous spherical or oval coin lesion with smooth edges. The majority of cases are asymptomatic, although some individuals may have cough and pneumonitis.⁵⁰ Eosinophilia is absent. Because there is no reliable noninvasive test for *Dirofilaria*

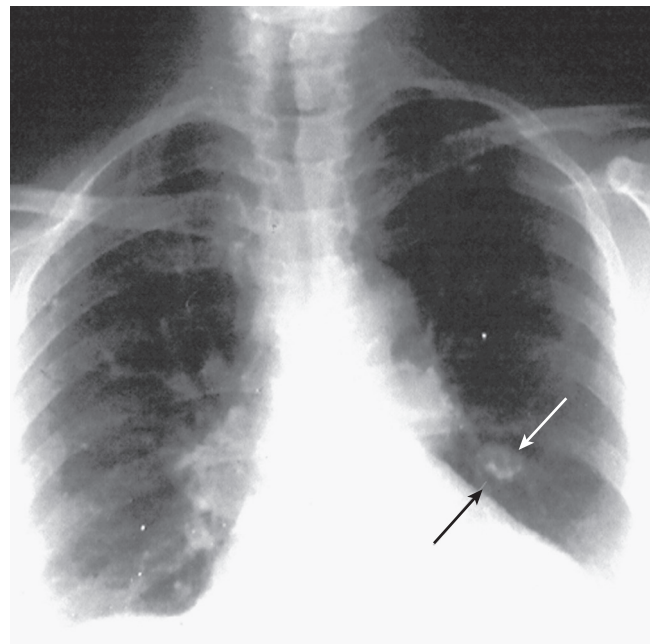


Figure 39-3 Dirofilarial infection in the lung. Chest radiograph showing a solitary nodule (arrows) in the lung from a patient with confirmed *Dirofilaria immitis*. (From McCall GW, Genchi C, Kramer LH, et al: Heartworm disease in animals and humans. *Adv Parasitol* 66:193-285, 2008.)

infection, nearly all cases require biopsy to establish the diagnosis. Surgery is both diagnostic and curative.

Trichinosis

Trichinosis is caused by the parasites of the genus *Trichinella*, especially *T. spiralis*; these are the only nematodes that occupy an intracellular location and that are acquired by ingestion of contaminated meat. Humans usually acquire the infection by ingesting cysts containing the coiled larvae in raw or partially cooked pork, pork products, or game. The larvae that emerge from the ingested cysts invade the small intestine.

Clinical Features. The enteral stage may be either asymptomatic or may be accompanied by signs and symptoms of gastroenteritis. During the ensuing parenteral stage, newborn larvae enter the bloodstream and circulate to various organs. However, they only encyst in peripheral skeletal muscle, forming the “nurse cell,” consisting of an infected myocyte fed by vessels formed by neoangiogenesis. Most symptoms are due to inflammation associated with the invasion of larvae through the intestine and with influx of eosinophils and mast cells in the region of nurse cells. During the acute stage of infection, common symptoms include malaise, abdominal pain, fever, nausea, vomiting, myalgias, and muscle weakness with facial and generalized edema. Respiratory tract involvement is uncommon but, in severe cases, there may be dyspnea and transient pulmonary opacities. Dyspnea may result from larval invasion of the diaphragm and the accessory muscles of respiration⁵¹; however, lung inflammation may also play a role.⁵²

Diagnosis and Treatment. Trichinosis is usually diagnosed based on clinical presentation, epidemiology, eosinophilia, and a positive ELISA.¹ Muscle biopsy is definitive but is not recommended because of low sensitivity. Treatment is with albendazole; corticosteroids may be added in severe cases, especially those with pneumonitis, myocarditis, or meningoencephalitis. It is unclear whether treatment alters the course of infection, particularly because it does not appear to affect worms after they have already encysted. Trichinosis is prevented by consuming meats that are fully cooked to a temperature of 140°F.

Gnathostomiasis

Gnathostomiasis is caused by helminths of the genus *Gnathostoma* and is endemic in South Asia and Southeast Asia, China, and Latin America, especially in cultures in which uncooked fish is consumed.^{53,54} *Gnathostoma spinigerum* is the most common agent of human gnathostomiasis. Humans are accidental hosts; cats and dogs are the definitive hosts. *G. spinigerum* has a complex life cycle involving two intermediate hosts.⁵⁵ Humans usually become infected with third-stage larvae by ingesting raw or inadequately cooked freshwater fish or other intermediate hosts such as snakes, frogs, and chickens. However, alternative routes of infection have also been suggested such as ingestion of water containing infected copepods and penetration of the skin of food handlers by third-stage larvae from infected meat.⁵⁴ The infective larvae released in the gut migrate to the liver and abdominal cavity and return to the stomach, where they are embedded in the wall, resembling a tumor

with an aperture communicating with the lumen to release eggs.⁵⁶ The mechanical damage of migrating larvae has been cited as the primary cause of symptoms. Migration of larvae through tissues results in characteristic hemorrhagic tracts, surrounded by eosinophilic infiltration. When the lungs are involved, patients present with cough, pleuritic chest pain, hemoptysis, lobar consolidation, lobar collapse, pleural effusion, pneumothorax, or hydrothorax. Subcutaneous swellings, unexplained eosinophilic pleural effusion, and peripheral eosinophilia are considered a clinical triad and should prompt consideration of gnathostomiasis.

Diagnosis and Treatment. Diagnosis of gnathostomiasis is based on the presence of eosinophilia, migratory inflammation, and history of exposure risk. The diagnosis can be confirmed by identification of the worm in tissue or by serology. The treatment of choice is albendazole or ivermectin.

TREMATODES

Paragonimiasis

The lung flukes of the genus *Paragonimus* encompass several species important in human disease. *Paragonimus westermani* is found in humans and animals in Asia, Africa, and South America. However, greater than 90% of the cases are seen in Asia; *P. westermani* is rarely contracted in the United States.⁵⁷ Most cases of paragonimiasis acquired in the United States are due to *Paragonimus kellicotti*^{55,58} after ingestion of crayfish. The parasite has a complex life cycle involving freshwater snails, crustaceans, and mammals.

Humans become infected by ingesting raw, partially cooked, or pickled crab or crayfish containing metacercariae, which excyst in the duodenum and penetrate the intestinal wall to enter the peritoneal cavity. Larval forms penetrate the diaphragm and enter the pleural cavity and lung parenchyma where they mature to adult worms. Pairs of adult worms live in cystic cavities near bronchial passages (Fig. 39-4) and produce eggs. Cystic cavities eventually rupture into a bronchiole, allowing eggs to be expectorated or swallowed and passed in feces.

Clinical Features. A minority of infected individuals have a symptomatic stage of acute infection approximately 2 weeks after exposure, marked by abdominal pain, diarrhea, fever, chest pain, cough, urticaria, peripheral eosinophilia, and elevated levels of IgE.⁵⁹ In contrast, most infections have an insidious onset with clinical manifestations 5 to 10 years following exposure. Symptoms of later stage infections include cough productive of thick, rusty-colored or bloody sputum with Charcot–Leyden crystals, with or without pleuritic chest pain.⁶⁰ There may be frank hemoptysis resembling that in tuberculosis.⁶¹ Fever and eosinophilia can be absent in chronic infections; a common finding is an abnormal chest radiograph in an asymptomatic patient (see Fig. 39-4).

Diagnosis. Chest radiographs may reveal a variety of lesions including focal involvement or consolidation. Cavitary lesions appear as the flukes mature and may measure up to 4 cm in diameter; small cysts and calcified or noncalcified nodules (eFig. 39-3) may be present. Pleural effusion,

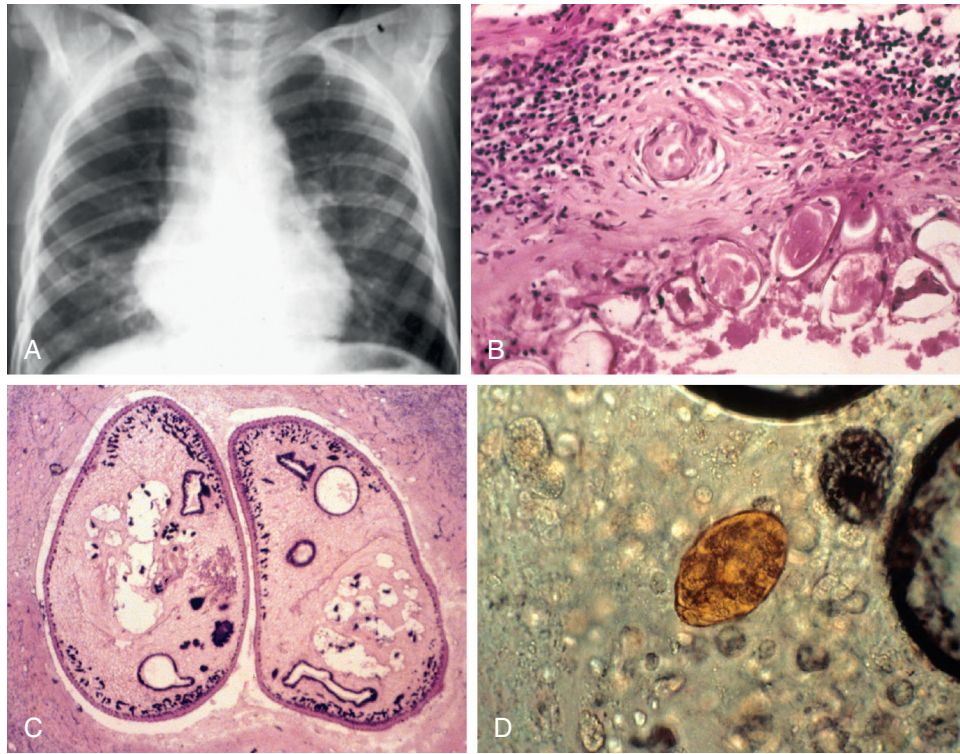


Figure 39-4 *Paragonimus westermani*. **A**, Chest radiograph of a patient who presented with hemoptysis shows minimal perihilar linear and reticular opacities. **B**, Granuloma surrounding ova. **C**, Cross section of a pair of adults in the lung. **D**, Ovum in the sputum. (From Herman Zaiman's "A Pictorial Presentation of Parasites" with permission of the American Society of Tropical Medicine and Hygiene.)

pneumothorax, and pleural thickening may develop in a minority of patients.^{60,62} The pleural fluid characteristically contains leukocytes, many eosinophils, elevated concentrations of protein and lactate dehydrogenase, and low concentrations of glucose. Histopathologic examination of the lung reveals adult worms within fibrous cysts communicating with bronchi or bronchioles; granulomas may contain eggs at the center (see Fig. 39-4). Pneumonia, bronchiectasis, and vasculitis may be present. Acute and chronic pathologic changes may coexist within the same pulmonary lesions.

When the diagnosis of paragonimiasis is suspected, it can be confirmed by finding morphologically characteristic eggs in sputum, stool, gastric aspirates, or tissue (see Fig. 39-4). Bloody sputum is the most likely to yield positive results. ELISA and immunoblot assays that detect antibodies to *Paragonimus* antigens are offered by the CDC in Atlanta, Georgia.

Treatment. Praziquantel is the drug of choice. Untreated pulmonary paragonimiasis may resolve within 5 to 10 years (the life span of the adult worms) but chronic infection may be accompanied by extensive fibrosis. Paragonimiasis can be prevented by cooking crabs and crayfish fully before ingesting.

Schistosomiasis

Schistosomiasis is one of the most important parasitic infections of humankind. It is found in tropical and subtropical areas of the world including South America, Africa, the Middle East, and East Asia, including the Philippines.⁶³ The

World Health Organization estimates that more than 200 million people are infected worldwide.⁶⁴ Five species of schistosomes cause human disease: *Schistosoma hematobium*, *S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*. Infection is acquired when cercariae penetrate the skin during interaction with fresh water while bathing, wading, or doing laundry. After penetrating the skin, the cercariae lose their tails and quickly transform into juvenile forms (schistosomula) that migrate to the lung and liver. These transform into adults that mate and then travel to their tissue destination. *S. hematobium* are found in the venous plexus of the urinary bladder while *S. mansoni* and *S. japonicum* reside in mesenteric veins. Female worms lay eggs that are excreted either in the urine (*S. hematobium*) or feces (*S. mansoni*, *S. japonicum*). Adult schistosomes may live and produce eggs for as long as 30 years.

Clinical Features. A skin reaction (erythematous raised 1- to 3-cm lesions) may develop within hours (and as late as 1 week) after cercarial penetration in those infected for the first time. In some previously unexposed persons, acute schistosomiasis, known as Katayama fever, develops after heavy exposure to *S. japonicum* or *S. mansoni*.^{65,66} Symptoms usually develop between 4 and 8 weeks after exposure, which coincides with maturation of adults and the beginning of egg laying. Acute schistosomiasis is characterized by urticaria, fever, chills, cough, wheezing, headaches, lymphadenopathy, hepatosplenomegaly, peripheral eosinophilia, and elevated serum IgE levels. This acute phase usually resolves within several weeks but can lead to death in rare instances.

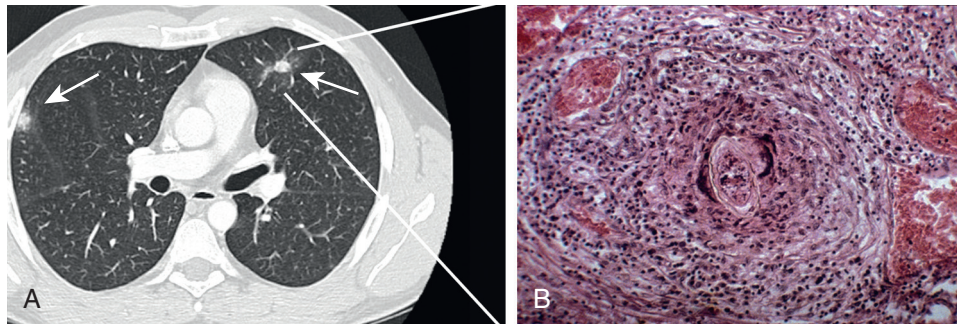


Figure 39-5 Schistosomiasis of the lung. **A**, Chest CT showing macronodules with ground-glass halo (arrows). **B**, Granuloma in the lung surrounding a *Schistosoma* ovum. (**A**, From Weber-Donat G, Donat N, Margery J: Acute pulmonary schistosomiasis: computed tomography (CT) findings. *Am J Trop Med Hyg* 82:364, 2010; **B**, from Herman Zaiman's "A Pictorial Presentation of Parasites" with permission of the American Society of Tropical Medicine and Hygiene.)

The major pathologic findings in schistosomiasis in any organ are granulomas surrounding eggs⁶⁷ (Fig. 39-5). Chronic pulmonary schistosomiasis may be the result of deposition of eggs in pulmonary vessels followed by granuloma formation and obstruction of blood flow.⁶⁸ However, vasospasm and inflammation also contribute to the pulmonary findings.⁶⁹ Chronic pulmonary hypertension develops in approximately 5% of patients with hepatosplenic schistosomiasis, usually after many years of untreated infection.^{70,71}

Diagnosis and Treatment. Chest radiographs of patients with acute symptoms may show diffuse pulmonary opacities or nodules with indistinct borders, which on CT may have a ground-glass "halo" appearance (see Fig. 39-5A).⁷² Pleural effusions and thoracic lymphadenopathy may also be present in acute schistosomiasis. Imaging in chronic pulmonary schistosomiasis reveals nodules, miliary lesions, and cavitory lesions.

Diagnosis of schistosomiasis is made by stool or urine examination or rectal biopsy, although shedding of eggs usually does not commence until 6 weeks after exposure.⁷³ Nearly all patients with symptomatic acute schistosomiasis have eosinophilia and elevated serum IgE levels. ELISA and immunoblot assays that detect antibodies to schistosome antigens are available, but these tests may be negative in acute infection and may remain positive years after treatment. Lung biopsies may reveal granulomas surrounding eggs (see Fig. 39-5B).

The treatment of choice for schistosomiasis is praziquantel. Praziquantel kills adult worms but may not kill immature parasites. In some cases, symptoms can transiently worsen after treatment; this is presumed to be due to release of proinflammatory components of dead parasites. Pulmonary hypertension due to schistosomiasis can also worsen with antiparasitic treatment.

CESTODES

Echinococcosis

The cestode *Echinococcus granulosus*, the dog tapeworm, has a scattered worldwide distribution. It remains an important public health problem in the Mediterranean basin where it is especially common in Italy, Spain, Albania, and the countries of the former Yugoslavia. *E. granulosus* is also found

throughout Central America and South America and in scattered areas of sub-Saharan Africa, China, Russia, and the countries of the former Soviet Union. *Echinococcus multilocularis*, the fox tapeworm, is endemic in Canada, parts of the United States, central Europe, the countries of the former Soviet Union, China, and northern parts of Japan.⁷⁴⁻⁷⁶

The adult tapeworm (Fig. 39-6) usually infects canines and sheds millions of eggs. The ova are excreted in feces, and intermediate hosts, including humans, become infected when they ingest the ova in contaminated food or water. In most areas, dogs are the definitive hosts, and sheep are the main intermediate hosts. Larvae are released from ova after ingestion and migrate via the bloodstream or lymphatics to various organs, usually the liver and lung, but kidney, bone, and brain may also be involved. The larvae mature into cysts and, in the case of *E. granulosus*, the cyst is fluid-filled and unilocular, consisting of an inner germinal layer and an outer acellular laminated layer. Daughter cysts may arise from the inner layer and there is an outer layer composed of fibrous tissue, which is host-derived and is also called a pericyst. While *E. granulosus* is more common in humans, *E. multilocularis* is usually more pathogenic.

Clinical Features. The lungs are involved in 20% to 40% of cases of cystic echinococcosis; the liver is involved in 50% to 70%.⁷⁷ Cystic echinococcosis usually presents as a solitary cyst involving one organ, usually the liver or lung; 10% to 15% of individuals have more than one organ involved. In children, the lungs are involved more often than the liver.⁷⁸

Pulmonary echinococcosis is commonly discovered as an incidental finding on chest imaging (eFig. 39-4). In symptomatic patients, the clinical manifestations of pulmonary echinococcosis are most often the consequence of cyst rupture; less frequently, symptoms are due to compression by an enlarging cyst. Rupture of an echinococcal (hydatid) cyst into a bronchus results in fever and cough, which can have an abrupt onset. In some patients, the sputum can contain macroscopic fragments of the parasite. Ruptured cysts that communicate with an airway can become secondarily infected by bacteria and/or fungi. Rupture of a hydatid cyst into the pleural space can be associated with hypersensitivity responses, including fever, urticaria, and wheezing; frank anaphylaxis can also develop, but is rarely fatal. Rupture into the pleural space can also cause

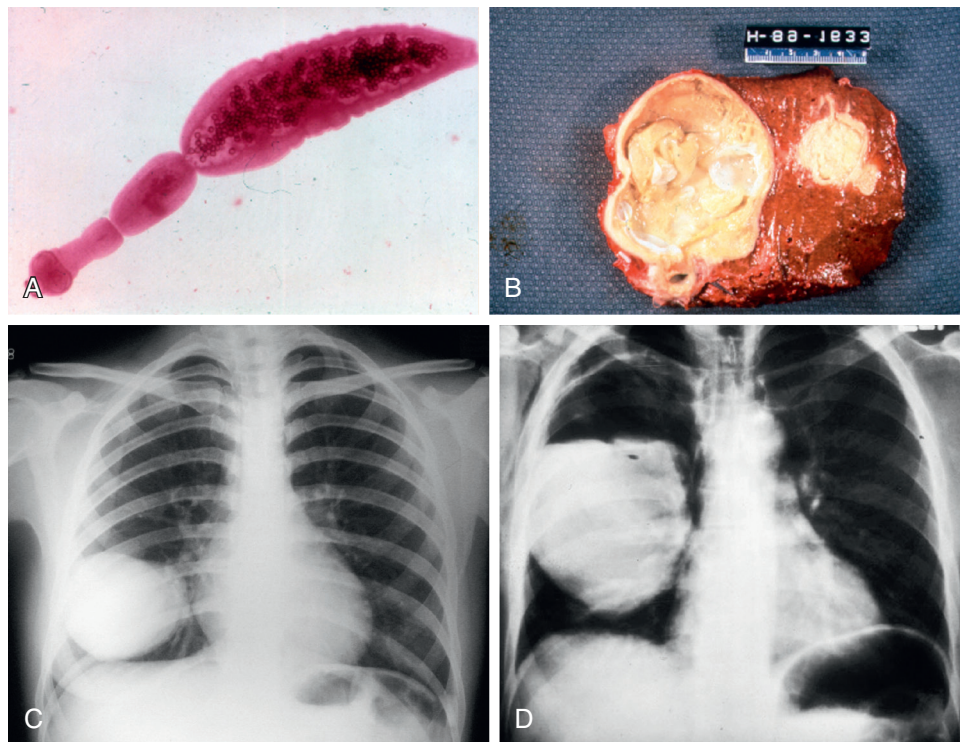


Figure 39-6 Echinococcal cysts. **A**, Adult *Echinococcus granulosus*. **B**, *Echinococcus* cyst of the liver near the diaphragm. **C**, *Echinococcus* cyst of the lung. **D**, Ruptured *Echinococcus* cyst of the lung with the “water lily” sign. (**A** and **D**, From Herman Zaiman’s “A Pictorial Presentation of Parasites” with permission of the American Society of Tropical Medicine and Hygiene; **C**, courtesy Dr. Saul Santivanez, Lima, Peru.)

empyema, with or without bacterial superinfection. Cysts that enlarge without rupturing may erode into adjacent structures and cause bone pain, hemorrhage, or airway compression.⁷⁹

Diagnosis and Treatment. Diagnosis of pulmonary echinococcosis depends on the combination of imaging, serology, and microscopy. On chest radiographs, uncomplicated (unruptured) hydatid cysts appear as homogeneous oval or round masses 1 to 20 cm in diameter with smooth borders and normal adjacent lung tissue (see Fig. 39-6C; see eFig. 39-4). If a cyst ruptures into a large airway, partial discharge of the cyst contents results in an air-fluid level. A hydatid cyst that is completely emptied of liquid contents and collapsed can exhibit a “water lily” sign (see Fig. 39-6D), which is pathognomonic of a collapsed cyst but is rare. The water lily sign is created when air enters the cyst, allowing detachment of the inner endocyst from the outer pericyst, so that the endocyst collapses to float on the fluid in the partially filled pericyst, creating the appearance of a water lily floating on a pond. CT scans may allow distinction of hydatid cysts from other pulmonary cysts by revealing the presence of daughter cysts within a larger cyst. Cardiac echinococcosis and pulmonary embolization of organisms are rare (eFig. 39-5).

Serology testing for echinococcosis currently consists of an ELISA that detects antibodies to a cyst antigen. Although the assay is quite sensitive in patients with hepatic involvement, the sensitivity in patients with pulmonary echinococcosis is approximately 50%. An additional limitation of the current assay is that there may be cross-reactivity if a

patient has another tissue helminth infection, especially cysticercosis. As a consequence of the suboptimal sensitivity and specificity, the results of echinococcus serology testing must be interpreted in the context of other clinical and radiographic evidence.

If the cyst ruptures, cyst fragments, especially the rigid mouthparts (scolices) of the parasite, may be detected by microscopic examination of sputum or pleural fluid.

Treatment. Surgical removal is the principal therapeutic approach in patients who can tolerate the procedure. The surgical approach must be planned to minimize the likelihood of intraoperative cyst rupture, in that release of the contents can result in anaphylaxis and in dissemination of the parasites, with subsequent relapse. Preoperative administration of albendazole is recommended, to reduce the consequences of dissemination.⁷⁹ Praziquantel is often added if a cyst ruptures because it has a scolicidal effect. Intraoperative administration of a helminthicide agent such as hypertonic saline or 1% formaldehyde, left in place in the cyst lumen for 15 minutes or more before further manipulation, is also thought to minimize the consequences of spillage of cyst contents.⁷⁹⁻⁸¹

In patients with symptomatic or complicated echinococcal cysts who cannot tolerate a thoracic surgical procedure, prolonged treatment with an antihelminthic may improve symptoms but is likely to be curative in only a minority of cases. Albendazole is currently the drug of choice; praziquantel also has activity, and the combination of albendazole and praziquantel may have greater efficacy than either drug alone. Monitoring responses to drug treatment must

be based on clinical findings and imaging procedures; serial serologic assays have been found to be without value.

Echinococcus multilocularis

Alveolar echinococcosis caused by *E. multilocularis* is a rare but potentially fatal disease. Wild canines are the definitive hosts and small animals are the intermediate hosts. The liver is the initial target of this parasite and the incubation period can be exceedingly long. It can spread to the lung as a result of metastatic dissemination or by direct extension through the diaphragm of a liver cyst with rupture into the thorax. *E. multilocularis* can involve the bronchial tree, pleural cavity, and mediastinal structures. The diagnosis is made by serology and biopsy. The only cure is radical resection followed by long-term therapy with albendazole. If not amenable to surgery, life-long treatment with albendazole may be beneficial.

PROTOZOA

Protozoa are unicellular eukaryotic organisms and are acquired by ingestion or by the bite of a vector. Gastrointestinal or systemic symptoms generally predominate in protozoal infections, although pulmonary symptoms can also be prominent.

AMEBIASIS

Amebiasis, caused by *E. histolytica*, is one of the most common parasitic diseases of humans. Although it predominantly affects individuals who live in Mexico, Central and South America, Africa, and the Indian subcontinent, travel and immigration have globalized this infection. *E. histolytica* is estimated to cause 40,000 to 100,000 deaths yearly,⁸² and it is estimated that 500 million people worldwide are infected with *Entamoeba*,⁸² although many are infected with nonpathogenic *Entamoeba dispar* rather than pathogenic *E. histolytica*.

E. histolytica does not involve intermediate hosts and has a simple life cycle, alternating between environmentally hardy cysts and invasive trophozoites. Although trophozoites are passed in bloody diarrhea, these forms cannot survive in the environment and are not transmitted to new hosts. Trophozoites can also survive in the intestine of asymptomatic carriers; some trophozoites differentiate into cysts in the intestine, which are then passed and serve as the source of transmission to new hosts. Cysts have a chitinous cell wall that enables them to persist in the environment for weeks to months and to infect subsequent hosts that ingest contaminated food or water. In 4% to 10% of individuals infected with *E. histolytica*, trophozoites invade the intestinal mucosa to cause intestinal disease. In others, the trophozoites enter the bloodstream and can establish infection in the liver, brain, or lungs.^{83,84}

Clinical Features. Intestinal amebiasis is associated with abdominal pain, tenesmus (constant urge to defecate), and diarrhea, which may be bloody, mucoid, or watery. Fever may be present but is not typical, and the onset of symptoms may be gradual with patients presenting with several weeks of symptoms. The course of intestinal

amebiasis can be fulminant, with ileus and intestinal perforation.

The most common site for extraintestinal amebiasis is the liver (eFig. 39-6); a smaller proportion of cases affect the lungs. Amebic brain abscesses are seen rarely. The typical patient with an amebic liver abscess is an adult male who has acquired the infection in an endemic area and presents with fever and right upper quadrant pain without intestinal symptoms. Although amebic colitis affects children and adults of both sexes, amebic liver abscesses are approximately 10-fold more common in men than women; the reason for this sex difference is unknown but is not due to differences in rates of infection.⁸⁵ Mouse models of amebiasis also demonstrate differences in host immune response between females and males.⁸⁶ Many patients presenting with extraintestinal amebiasis do not have cysts or trophozoites in the stool. A prior amebic abscess or amebiasis does not confer immunity to recurrence.

The extraintestinal manifestations of amebiasis can present years after leaving an endemic area.⁸² The lung is the second most common extraintestinal site of *E. histolytica* infection and usually results from the extension of a right lobe hepatic abscess, so patients may have right upper quadrant abdominal pain as well as pulmonary symptoms. Pleuropulmonary amebiasis complicates amebic liver abscess in 7% to 20% of cases,² although the chest radiograph is abnormal in nearly 50% of cases. Although any lobe of the lungs can be affected, the right lower lobe is most commonly involved,⁸⁷ and pulmonary amebiasis can be confused with bacterial pneumonia (see eFig. 33-27).⁸² Findings can include an elevated right hemidiaphragm, right pleural effusion, right lobe atelectasis, pulmonary consolidation with abscess formation, and hepatic-bronchial fistulas. Additionally, an empyema may develop from rupture of a liver abscess into the pleural space.⁸⁸ An occasional patient may present with shortness of breath⁸⁹ or rarely with respiratory failure⁹⁰ or the expectoration of “anchovy-paste” like sputum, which represents contents of an amebic abscess.⁹¹ Rarely, pulmonary amebiasis results from hematogenous spread without liver abscess. Hepatic abscesses can also rupture into the pericardium and cause cardiac tamponade.^{88,92,93}

Diagnosis. Molecular studies have shown that human *Entamoeba* consists of the virulent species *E. histolytica* and a nonpathogenic commensal species, *Entamoeba dispar*. Both *E. histolytica* and *E. dispar* species are frequently present in stool samples; the trophozoites are indistinguishable, although antigen and PCR assays discriminate between the species.⁹⁴ Serology tests are highly sensitive for diagnosis of extraintestinal amebiasis, but they may remain positive for years after an infection. Therefore, serology may not distinguish between current and past infection. In cases of known or suspected pulmonary involvement in amebiasis, CT scanning of the lung and adjacent liver should be used to define the extent of involvement and presence of fistulae (see eFig. 33-27).⁹⁵

Treatment. Patients with liver abscesses can usually be managed medically without percutaneous aspiration, but pleural or pericardial effusions⁸⁸ should be drained and larger lesions (>300 mL) may improve more quickly if drained.⁹⁶

The current medical treatment of choice is systemic metronidazole 750 mg three times daily for at least 10 days, monitoring clinical findings carefully. Monitoring responses with repeated imaging procedures is not generally necessary, and it is not unusual for the radiographic appearance to worsen before improvement.⁹⁵ Another nitroimidazole, tinidazole, is an alternative and has efficacy and toxicity similar to that of metronidazole. Agents such as paromomycin and diloxanide furoate that kill cysts in the intestine are not effective against extraintestinal amebiasis. After tissue invasive amebiasis has been treated with metronidazole or tinidazole, most experts recommend a course of diloxanide or paromomycin to eradicate cysts that may serve as sources of transmission or relapse.⁸² Because of the potential for asymptomatic infection to develop into dysentery or extraintestinal disease, or to be transmitted, all *E. histolytica* infections should be treated.

MALARIA

Human malaria is an acute systemic infection caused by *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, or *P. knowlesi*. *P. falciparum*, the most lethal human malaria, was estimated by the World Health Organization to cause 550 million cases per year in 2010. *P. vivax*, the second most common human malaria, is thought to cause 80 to 300 million cases. Recently, *P. knowlesi*, a simian malaria seen in Southeast Asia, has been associated with zoonotic malaria infections in humans.⁹⁷ Because this species resembles *P. malariae* morphologically, the parasite was mistaken for *P. malariae*, but *P. knowlesi* malaria has a more virulent course than *P. malariae* malaria and is more often fatal.

The World Health Organization estimated that in 2010 there were 660,000 deaths due to malaria, primarily in children infected with *P. falciparum* in sub-Saharan Africa. Although many cases of malaria are mild, severe malaria, including cerebral malaria, is still seen in many areas of the tropical and subtropical world and among travelers and immigrants in nonendemic areas. Most fatalities in the developed world are due to delayed diagnosis because either patients or clinicians are unaware of the risk of severe malaria.

Plasmodium species are transmitted by the bite of the female *Anopheles* mosquito. Sporozoites injected into the bloodstream traffic to the liver and initiate the clinically silent hepatic phase, which results in the release of thousands of merozoites that infect erythrocytes. The erythrocytic stages are responsible for clinical disease, and severe malaria includes anemia, coma, and respiratory failure; these are most frequent with *P. falciparum* infection.

The pathogenesis of severe malaria is not completely understood, but is thought to be caused by inflammatory mediators such as cytokines and chemokines and by vascular leukocyte adhesion molecules. *P. falciparum* elaborates a family of variant antigens that enables infected erythrocytes to adhere to microvascular endothelium.⁹⁸ Sequestration of infected erythrocytes in tissue microvessels is thought to be critical for pathogenesis of the most severe manifestations of malaria including cerebral malaria.⁹⁹ There is no sterile immunity to malaria, and malaria has exerted a profound selective pressure upon human evolution. Nearly all genetic erythrocyte defects, including sickle

cell anemia, thalassemia, pyruvate kinase deficiency, are most prevalent in regions of the world with high malaria prevalence and some, including heterozygous HbS, protect from severe malaria.¹⁰⁰

Clinical Features. Severe malaria is associated with fever, chills, anemia, thrombocytopenia, jaundice, and renal failure. The severity of symptoms is proportional to the parasite burden, and without treatment, *P. falciparum* malaria can progress within days to cause multiorgan failure, especially in nonimmune patients. The fevers of malaria are associated with the lysis of infected erythrocytes, and fevers are classically periodic (every 2 days for *P. falciparum*, *P. vivax*, and *P. ovale*; every 3 days for *P. malariae*) and nocturnal. However, this is not a reliable clinical sign, particularly for *P. falciparum*. *P. knowlesi* has a 24-hour cycle in erythrocytes and can be associated with rapid clinical deterioration and death.

Both *P. falciparum* and *P. vivax* are associated with systemic symptoms including pulmonary symptoms. Patients with malaria may present with cough and minimal involvement of the lung or with severe symptoms and signs of acute lung injury and acute respiratory distress syndrome.¹⁰¹ Chest radiographs may reveal bilateral opacities and lobar consolidation and pleural effusions, and alveolar macrophages may contain hemozoin, a brown degradation product of hemoglobin produced by the parasite. Bronchiolitis and pneumonia have been reported in the setting of *P. vivax* infection.¹⁰² Patients in coma as a result of cerebral malaria may be susceptible to aspiration pneumonia, and may require antibiotic therapy. Noncardiogenic pulmonary edema may develop in patients with severe malaria with any species of *Plasmodium*, even after several days of anti-malarial therapy.

Children, pregnant women, and nonimmune travelers to endemic areas are most susceptible to pulmonary complications (Fig. 39-7). The pathogenesis of the noncardiogenic pulmonary edema is unclear. Increased permeability of the alveolar capillaries appears to be an important mechanism by which the liquid fills the alveolar space, and pulmonary edema may be aggravated by fluid overload. The mortality rate of severe falciparum malaria is high.

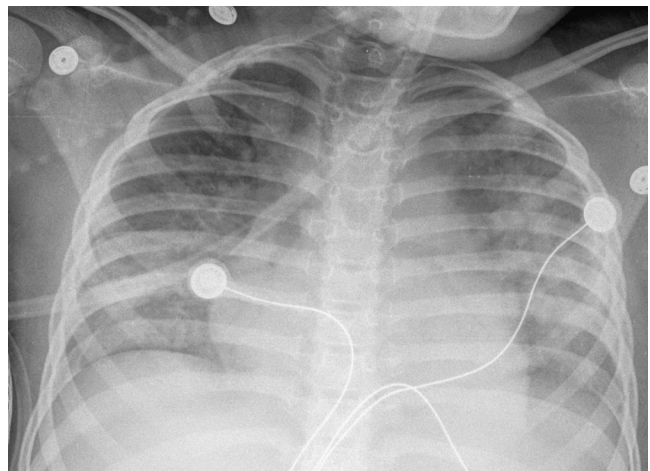


Figure 39-7 Malaria. Diffuse bilateral symmetric lung opacities resembling pulmonary edema in a child with malaria.

Diagnosis. The diagnosis of malaria is most often made by examination of a blood smear. Thick blood smears are used to determine whether parasites are present, while thin blood smears are used by experienced technicians to identify the *Plasmodium* species by morphology. For *P. falciparum*, the most lethal human malaria, only the immature ring forms are detectable in the peripheral blood, so initial malaria smears may be negative. Mature intraerythrocytic forms of *P. falciparum* cause infected cells to adhere to the microvasculature and are thus rarely evident in peripheral blood. The presence of mature *P. falciparum* forms in the blood and high parasitemia (>10% of erythrocytes containing parasites) are signs of severe disease. *P. vivax* infects only reticulocytes, so parasitemias are lower than with *P. falciparum*. Because initial malaria smears may be negative, a smear should be repeated after 8 hours, and empirical treatment begun if the patient is seriously ill.

Rapid diagnostic tests that detect *P. falciparum* and *P. vivax* malaria antigens are available as point-of-care diagnostic tests. Because antigen can persist, these tests do not reliably discriminate current from very recent infection.

Treatment. Supportive care in addition to specific antimalarial therapy is extremely important, especially in the case of noncardiogenic pulmonary edema. The treatment of malaria is dependent on the species and the geographic area of the world where it was contracted. While *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* can be treated with chloroquine, *P. falciparum* is nearly universally resistant to chloroquine. Intravenous artesunate, available from the CDC, is the treatment of choice for patients with pulmonary manifestations of malaria, which usually signifies severe malaria.¹⁰³ Artesunate has been reported to clear parasitemia more rapidly than intravenous quinine but, if artesunate is not available, intravenous quinidine or quinine should be used. Artesunate resistance has been detected in *P. falciparum* with increasing frequency, especially in Southeast Asia, and is manifest by slower clearance of parasitemia, thus requiring a longer duration of treatment to achieve cure.^{103a} Careful attention to fluid balance is required to maintain adequate end organ perfusion and prevent respiratory insufficiency due to fluid overload. Correction of hypoglycemia and attention to oxygenation is critical and, with high parasitemias, exchange transfusion may be attempted, although the clinical benefit of exchange transfusion has not been established. Severe malaria may also be complicated by concurrent pneumonia or bacterial sepsis that must be managed with appropriate antibiotics.

Once the patient improves, there are a variety of choices for oral treatment. *P. vivax* and *P. ovale* treatment regimens should include primaquine to eliminate hypnozoite forms within the liver, after determining the patient's G6PD status.

All travelers to malaria endemic regions are advised to take antimalarial prophylaxis and use insecticide-treated bed nets to prevent malaria, but a history of malarial prophylaxis does not rule out malaria and some travelers who have taken prophylaxis either have subtherapeutic levels of drug or have acquired resistant organisms. Although there are ongoing trials investigating malaria vaccines, thus far there is no clinically approved malaria vaccine. Clinicians seeking help for diagnosis or treatment of malaria should

call the CDC Malaria Hotline 770-488-7788 or 855-856-4713 toll free, with further information available at www.cdc.gov/malaria/.

TOXOPLASMOSIS

Toxoplasma gondii is a ubiquitous Apicomplexa protozoan parasite of mammals and birds. *T. gondii* does not require passage through its definitive host and thus can propagate clonally through its intermediate hosts. Intermediate hosts pass *T. gondii* latent bradyzoites within cysts that can initiate infection in new hosts that ingest the cysts in raw or undercooked meat. Cats are the definitive hosts and oocysts shed in cat feces are highly infectious, providing a source for contamination of food and water. In humans, new infection in a previously naive mother can lead to congenital toxoplasmosis, but vertical transmission from a previously exposed mother to her child is very rare, with only a few isolated reports of women who were infected before pregnancy.¹⁰⁴ The prevalence of infection, as assayed by seropositivity, varies with geography, and ranges from 10% to 90%.

T. gondii causes congenital infections in immune competent hosts and opportunistic infections in immunocompromised hosts, including individuals with AIDS (see Chapter 90).¹⁰⁵ *T. gondii* has a predilection for the central nervous system, where it causes necrotizing encephalitis, and for the eye, where it causes chorioretinitis. Although it disseminates throughout the body, CNS or ocular disease is most common. The development of clinically apparent toxoplasmosis is usually a consequence of reactivation of bradyzoites found within tissue cysts into actively replicating tachyzoites.¹⁰⁶⁻¹⁰⁸

Clinical Features. In most cases of pulmonary toxoplasmosis, pulmonary disease is part of multisystem disease in an immunocompromised host such as in persons with HIV/AIDS (CD4 T cells < 50/μL^{109-111a}), in patients with hematologic malignancies, and in organ transplant recipients.¹¹²⁻¹¹⁵ Pulmonary toxoplasmosis may rarely develop in immunocompetent persons where it may resemble atypical pneumonia.¹¹⁶ Clinical symptoms include fever, cough, and shortness of breath.¹⁰⁹⁻¹¹¹ A more fulminant pneumonia associated with acute toxoplasmosis has been seen in South America where highly virulent strains of *T. gondii* have caused "Amazonian toxoplasmosis," presenting as severe disseminated systemic disease.¹¹⁷

Diagnosis. Chest radiographs reveal bilateral diffuse opacities and/or nodular bilateral opacities that may be confused with *Pneumocystis* pneumonia.¹⁰⁹⁻¹¹¹ Examination of the sputum or fluid from BAL may reveal organisms that stain with Giemsa.¹¹⁸ Pleural fluid, if present, may contain tachyzoites.¹¹⁹ PCR-based molecular techniques are also available if the parasite is suspected but cannot be found by staining. At autopsy, the lungs are congested and hemorrhagic with areas of consolidation. Histopathologic examination reveals an interstitial pneumonitis and alveolar damage. A frank necrotizing pneumonia may also be observed, with many extracellular and intracellular tachyzoites. Nearly all patients with toxoplasmosis are seropositive, and a negative serologic test suggests another

diagnosis. Rarely, primary infection can present as disseminated disease, and serologies may be negative.

Treatment. The treatment of choice for toxoplasmosis is pyrimethamine and sulfadiazine with leucovorin (to prevent bone marrow toxicity), but there are several alternatives, including pyrimethamine and clindamycin with leucovorin. Although pyrimethamine and sulfadiazine are considered the treatment of choice, trimethoprim/sulfamethoxazole is active against *T. gondii* and has been suggested as primary therapy in resource poor areas due to its low cost.¹²⁰

OTHER PROTOZOA

Several other protozoa have been reported to be associated with pulmonary manifestations. Some of the more common parasites that can occasionally present with pulmonary disease are discussed here. Many of these have been increasingly reported, presenting as disseminated disease involving multiple organs, including the lungs, in association with HIV infection or other immunocompromised states.¹²¹ In addition, *Cyclospora cayetanensis*, *Trichomonas vaginalis*, *Trichomonas tenax*, *Trichomonas hominis*, and *Balantidium coli* have been reported to present with pulmonary disease.¹²¹

Babesiosis

Babesia are intraerythrocytic protozoan parasites.^{122,123} *Babesia microti* is carried and transmitted by the tick *Ixodes scapularis*. *B. microti* is found in Massachusetts, New York, Rhode Island, Connecticut, New Jersey, and the upper Midwest. In Europe, babesiosis is rarer but more frequently lethal, and is associated with *Babesia divergens*. Blood transfusion is another mode of transmission. The onset is usually gradual with malaise, fever, chills, sweats, and myalgias. Nausea, vomiting, headache, and psychiatric problems are also reported. There may be splenomegaly, anemia, thrombocytopenia, a normal or low white blood cell count, mild elevation of hepatic enzymes, and evidence of hemolysis. The major pulmonary complication is noncardiogenic pulmonary edema.^{124,125} As in malaria, the etiology of noncardiogenic pulmonary edema is not well understood. Parasitemia may range from less than 1% to more than 20% in persons with an intact spleen. Asplenic and immunocompromised patients often have more severe disease, including jaundice, renal failure, pancytopenia, high level parasitemia, shock, and disseminated intravascular coagulation.

Diagnosis. Diagnosis of babesiosis is made by the identification of the parasitized red blood cells on blood smears revealing a “Maltese cross” appearance. IFA-based serologic tests for *Babesia* have also been developed, but the high rate of seroprevalence in endemic regions limits the usefulness of these tests. Blood can be injected into a hamster for verification of active infection, and there are PCR-based diagnostic tests available that may be deployed for blood screening.¹²⁶

Treatment. Treatment of babesiosis is with quinine and clindamycin or azithromycin and atovaquone.¹²⁷ There have been reports of immunocompromised persons devel-

oping possible resistance to azithromycin and atovaquone after multiple treatments.¹²⁸

Cryptosporidiosis

The genus *Cryptosporidium* comprises several species widely distributed in animals including birds, cattle, and sheep. *C. parvum*, *C. hominis*, and *C. meleagridis* most commonly infect humans and are acquired by the ingestion of oocysts via water or food.

The most common clinical manifestation of cryptosporidiosis is watery diarrhea, which is self-limiting in immunocompetent hosts but chronic in immunocompromised hosts. In those with HIV/AIDS, diarrhea may be persistent, and may be massive and fatal.¹²⁹ Extraintestinal manifestations of cryptosporidiosis are observed most frequently in immunocompromised individuals. *Cryptosporidium* involvement of the lower respiratory tract is most common in patients with HIV/AIDS but can also develop in patients with other conditions.¹³⁰⁻¹³² Common symptoms include cough, fever, and shortness of breath; there may also be respiratory insufficiency.

Although the mechanism by which *Cryptosporidium* colonizes the respiratory tract is not clear, aspiration and hematogenous spread from the intestinal tract have both been suggested.¹³³ Chest radiographs are consistent with interstitial pneumonitis. Alveolar damage and interstitial fibrosis and hyperplasia of type II pneumocytes have been found at autopsy of patients with pulmonary cryptosporidia.¹³³

A recent study of HIV-negative Ugandan children with *Cryptosporidium* diarrhea and cough or other respiratory symptoms revealed that 17 of 48 (35.4%) had *Cryptosporidium* in their sputum,¹³⁴ suggesting that *Cryptosporidium* may cause more pulmonary disease than previously suspected, and that respiratory transmission is possible.

Diagnosis. Cryptosporidia can be detected in stool or respiratory samples by a modified acid-fast stain or by immunofluorescence.

Treatment. Nitazoxanide is efficacious and is approved for treatment of cryptosporidiosis in immunocompetent children and adults.¹³⁵⁻¹³⁷ Nitazoxanide is not efficacious in immunodeficient individuals with cryptosporidiosis; azithromycin and paromomycin have been associated with improvement in some patients, but clinical trials have not confirmed their efficacy in immunodeficient adults.

Free-Living Ameba

Four genera of free-living ameba infect humans: *Naegleria*, *Acanthamoeba*, *Balamuthia*, and *Sappinia*.¹³⁸ Infections with these species are rare but worldwide. *Naegleria* and *Acanthamoeba* are commonly found in lakes, swimming pools, tap water, and air conditioning units. *Acanthamoeba* sp are usually associated with granulomatous skin lesions and corneal ulcers. In immunocompromised patients, *Acanthamoeba* sp and *Balamuthia mandrillaris* may cause subacute or chronic granulomatous encephalitis accompanied by respiratory symptoms, nodular opacities, consolidation, and respiratory failure. In those patients, parasites have been recovered from BAL; organisms can also be detected in lung tissue (Fig. 39-8). *Naegleria fowleri* is associated with primary amebic meningoencephalitis that is acute and

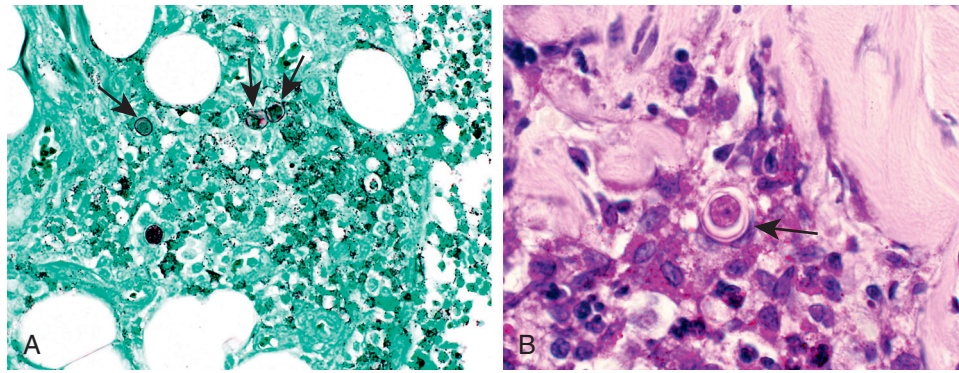


Figure 39-8 Acanthamoeba of the lung. **A**, Silver stain showing *Acanthamoeba* (arrows). **B**, PAS stain showing the organism (arrow). (**A**, From Herman Zaiman's "A Pictorial Presentation of Parasites" with permission of the American Society of Tropical Medicine and Hygiene; **B**, courtesy Dr. Govinda S. Visvesvara.)

usually lethal. A PCR-based assay to identify ameba species in clinical samples is available from the CDC.¹³⁹ The mortality of these infections is high, and there are no antimicrobial agents with proven efficacy.

Leishmaniasis

Leishmania spp are found in Asia, Africa, Central and South America, and regions of Europe that border the Mediterranean.¹⁴⁰ Transmission of *Leishmania* spp is through the bites of sand flies, and three clinical syndromes are recognized: cutaneous, mucocutaneous, and visceral. Cutaneous and mucocutaneous forms may also be observed in the viscera in immunocompromised individuals. Visceral leishmaniasis caused by *Leishmania donovani*, *L. infantum*, and *L. i. chagasi* is characterized by fever, abdominal pain, and hepatosplenomegaly, often accompanied by anemia, thrombocytopenia, leukopenia, and generalized bone marrow suppression.

In immunocompromised patients such as those with HIV/AIDS,¹⁴¹ intracellular forms (amastigotes) may be observed in macrophages of many organs. In the respiratory tract, amastigotes have been observed in the mucosa of the larynx, and in the lung and pleura.¹⁴²⁻¹⁴⁷ Interstitial pneumonitis, granulomatous inflammation of the bronchial mucosa, and mediastinal lymphadenopathy have all been described in patients with visceral leishmaniasis.¹⁴⁸

Diagnosis and Treatment. Identification of the parasite by microscopy is the most commonly used method of diagnosis. Culture and molecular techniques such as PCR with *Leishmania* species-specific primers are also available. *Leishmania* amastigotes can be found in samples obtained by BAL, thoracentesis, or transbronchial biopsy.¹⁴⁹ Therapy of leishmaniasis includes pentavalent antimony compounds and amphotericin B formulations.¹⁴¹ More recently, miltefosine, an oral agent, has been approved for the treatment of *Leishmaniasis*.^{149a}

Microsporidiosis

Microsporidia are ubiquitous intracellular parasites found in invertebrate and vertebrate hosts and are believed to be related to fungi. The phylum contains more than 1200 species distributed into more than 192 genera; some have been associated with disease in humans. Microsporidia infect nearly all animal phyla, including other protists,

and they are important agricultural parasites in insects, fish, laboratory rodents, rabbits, fur-bearing animals, and primates. Microsporidia predominantly infect the digestive tract, but infections of almost all organ systems are documented.

Microsporidia that cause human disease are zoonotic and/or water-borne. *Enterocytozoon bienersi* and *E. intestinalis* are the most common human pathogens, followed by *E. cuniculi* and *E. hellem*. The emergence of the HIV/AIDS epidemic led to reports of these organisms associated with a diarrheal and chronic wasting syndrome. Risk factors include treatment with anti-TNF- α antibodies, chemotherapy, other immune-modulating drugs, and organ transplantation. Immune restoration by antiretroviral therapy has markedly reduced the incidence of microsporidiosis in HIV-infected people.¹²⁰

Clinical Features. Involvement of the respiratory tract and the sinuses by microsporidia may cause rhinitis, sinusitis, and nasal polyposis.^{150-155a} Involvement of the lower respiratory tract has been observed in the setting of disseminated disease and presents as an interstitial pneumonitis. *Enterocytozoon hellem* infection has been reported to involve the entire length of the respiratory tract, with manifestations including erosive tracheitis and bronchiolitis. There are case reports of *E. cuniculi*, *E. hellem*, and *E. intestinalis* causing bronchiolitis with and without pneumonia. Respiratory tract infection due to *E. bienersi* has also been reported.¹⁵⁶ *Tubulonosema acridophagus* infection with respiratory failure and pulmonary opacities has been described in which spores of the organism were recovered by BAL.¹⁵⁷

Diagnosis and Treatment. Diagnosis of microsporidia infection is made by finding parasite spores in clinical samples by microscopy; PCR-based molecular techniques are also available. Treatment depends on the species identified. In general, albendazole combined with immune reconstitution is the treatment of choice, although albendazole is not recommended for *E. bienersi* or *Vittaforma corneae* infection due to intrinsic resistance.¹²⁰

Trypanosomiasis

Trypanosoma cruzi is the cause of Chagas disease, which is found in areas of Mexico and in Central and South

America.¹⁵⁸ It is transmitted by Triatominae bugs or by blood transfusion, organ transplantation, ingestion of contaminated food and fluids, or vertical transmission (mother to child). Babies born with congenital Chagas disease have a variety of manifestations including pneumonia, and amastigotes have been reported in the lung in these cases.¹⁵⁹ Pneumonitis and acute pulmonary edema may be seen in acute Chagas disease. Congenital and acute disease are treated with either nifurtimox or benznidazole.¹⁶⁰

Patients with chronic Chagasic cardiomyopathy may have congestive heart failure and thromboembolic events. Chronic Chagasic patients with megaesophagus may have a variety of pulmonary complications including aspiration pneumonia, bronchiectasis, and lung abscess.

Key Points

- Helminthic parasites often migrate through the lungs en route to another organ, particularly the gastrointestinal tract. Migration is often associated with eosinophilia or eosinophilic pneumonia.
- Tropical pulmonary eosinophilia is in the differential diagnosis of eosinophilic pneumonias, and should be considered in any patient from an endemic area of filarial infections and who presents with eosinophilia and pulmonary opacities.
- Paragonimiasis, echinococcosis, and dirofilariasis can be symptomatic or asymptomatic, and present as pulmonary nodules or mass lesions.
- Pulmonary paragonimiasis is commonly associated with hemoptysis. Because tuberculosis and paragoni-

miasis often coexist in the same geographic areas of the world, it is important to examine the sputum and stools for ova and to perform a serologic test for this parasite in those suspected of tuberculosis.

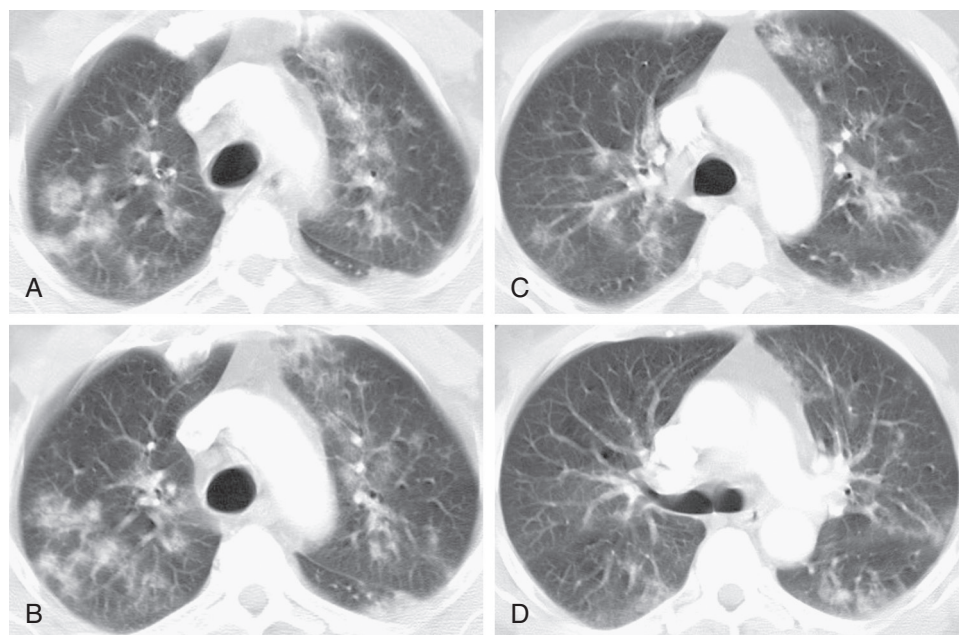
- Schistosomiasis can cause pulmonary hypertension, usually after many years of untreated infection, which is thought to be due to deposition of eggs in pulmonary vessels, granuloma formation, and obstruction to blood flow.
- Strongyloidiasis is unique in that there is chronic infection with autoinfection that can result in a potentially lethal hyperinfection syndrome, particularly in patients given glucocorticoids.
- Protozoan parasites usually do not infect the lungs preferentially but, because many are highly prevalent in human populations, pulmonary disease may be seen, particularly as part of a disseminated infection.

Complete reference list available at *ExpertConsult*.

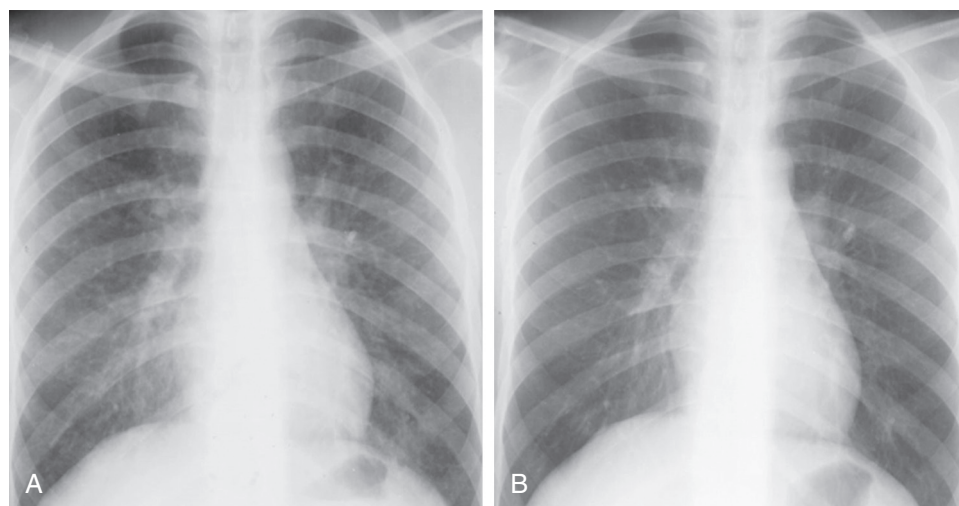
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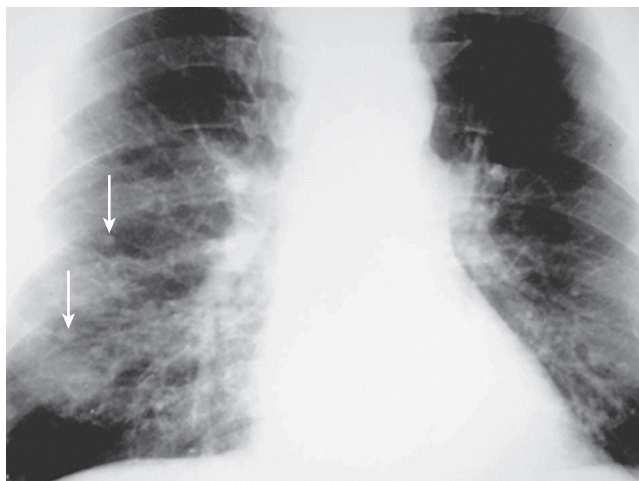
eFIGURE IMAGE GALLERY



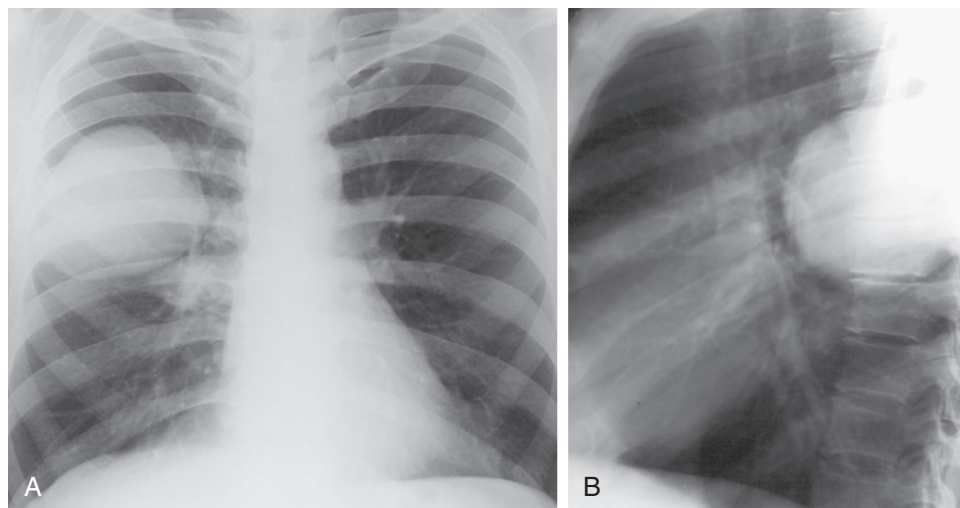
eFigure 39-1 Loeffler syndrome caused by ascariasis. A-D, Axial chest CT displayed in lung windows shows patchy bilateral nodular areas of ground-glass opacity. The patient complained of cough, hemoptysis, and chest pain, and was found to have peripheral eosinophilia. *Ascaris lumbricoides* infection was later diagnosed. (Courtesy Michael Gotway, MD.)



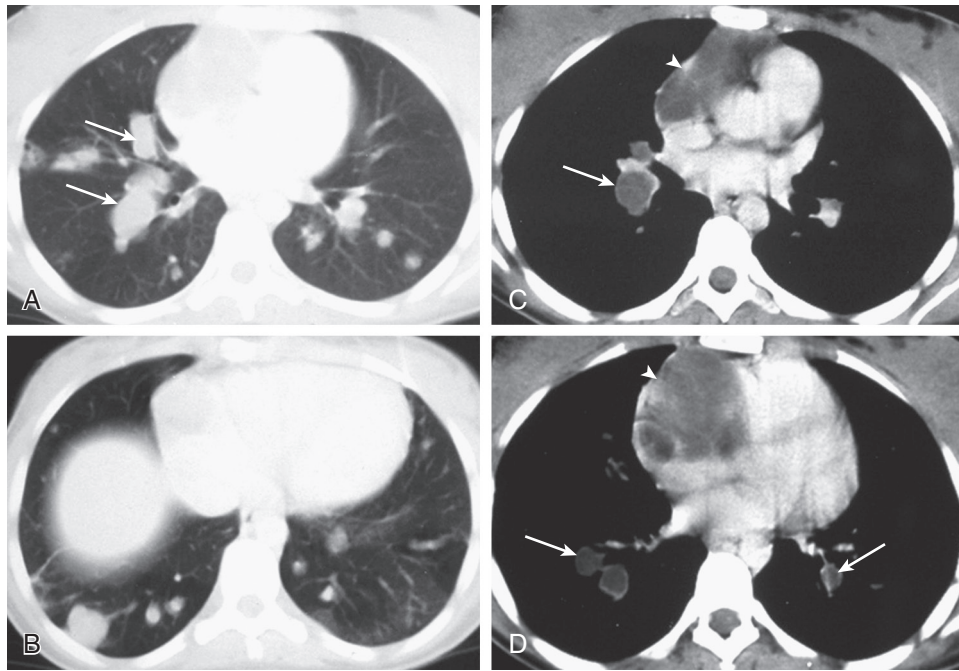
eFigure 39-2 Tropical eosinophilia. A, Frontal chest radiograph shows bilateral perihilar small nodules. The appearance is nonspecific and could be seen in a number of infections. *Wuchereria bancrofti* infection was confirmed. B, The patient was subsequently treated with diethylcarbamazine and doxycycline, leading to resolution of the small nodules. (Courtesy Michael Gotway, MD.)



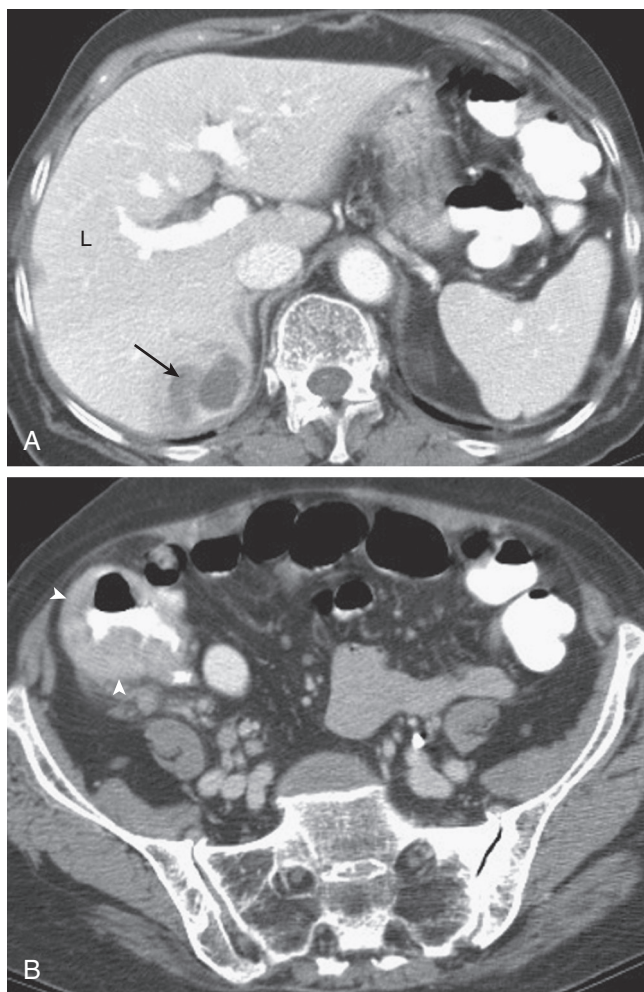
eFigure 39-3 Paragonimiasis. Frontal chest radiograph in a patient with paragonimiasis shows patchy bilateral linear opacities and interstitial thickening associated with small nodules (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 39-4 Hydatid disease: *Echinococcus granulosus* infection. Frontal (**A**) and lateral (**B**) chest radiographs show a large homogeneous mass in the posterior right upper lobe. (Courtesy Michael Gotway, MD.)



eFigure 39-5 Hydatid disease: cystic *Echinococcal* embolization. A-D, Axial enhanced chest CT performed in a 23-year-old Arab woman shows multiple bilateral circumscribed nodules, some with a somewhat tubular shape (arrows, A). The soft tissue window images (C and D) show low attenuation embolic material, representing *Echinococcus* organisms, filling and expanding the pulmonary arteries (arrows, C and D). The source of the embolic material is the right atrium (arrows, C and D); note the faint internal septation within this mass. (Courtesy Michael Gotway, MD; case by Elaine M. Caoili, MD, University of Michigan, Ann Arbor, MI.)



eFigure 39-6 Amebiasis: colitis and liver abscess. **A**, Axial contrast-enhanced image through the liver (L) shows a low attenuation posterior right lobe liver abscess (*arrow*). **B**, Axial image through the pelvis shows thickening of the cecum (*arrowheads*), consistent with colitis. (Courtesy Michael Gotway, MD.)

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INTRODUCTION**BIOTERRORISM: A HISTORICAL PERSPECTIVE****BASICS OF BIOTERRORISM****CDC CATEGORY A AGENTS**

Anthrax
Smallpox
Plague

Tularemia

Botulism

Viral Hemorrhagic Fevers

SELECT CDC CATEGORY B AGENTS

Direct Pulmonary Agents

Nonpulmonary Agents (Gastrointestinal and Toxin)

IMPACT OF H1N1 INFLUENZA PANDEMIC OF 2009 ON BIOTERRORISM RESPONSE**RECOGNITION AND RESPONSE TO A BIOTERRORISM EVENT****INFECTION CONTROL****PUBLIC HEALTH AND CRITICAL CARE RESPONSE****INTRODUCTION**

Bioterrorism, once limited to military-directed biowarfare, has developed considerable prominence due to increasing world threats and the anthrax outbreak in the United States in 2001. Clinicians and public health officials have become more aware of these rare diseases as local, state, and national programs increase detection, therapeutic options, and responses to the causative agents.

Early recognition of bioterrorism agents can be difficult since the early prodromal phase of most agents is similar and often indistinguishable from other causes of febrile respiratory illnesses. Febrile respiratory illnesses and respiratory failure can signify a natural outbreak (e.g., severe acute respiratory syndrome, plague, tularemia, or a novel strain of influenza) or a bioterrorism event.^{1,2} Most cases of febrile respiratory illnesses admitted to *intensive care units* (ICUs) are caused by community-acquired pneumonia, and respiratory failure and *acute respiratory distress syndrome* (ARDS) subsequently develop in up to 11% of these community-acquired pneumonia cases.^{3,4} Although most cases of community-acquired pneumonia are recognizable, the rare and contagious causes (e.g., plague) can have a large impact on the health care and public health systems.^{2,5} Thus, early recognition of these infections becomes important for two reasons. First, early infection control and public health preparedness strategies must be implemented to reduce spread to health care workers and the public, particularly in the acute stages of disease when patients are most contagious and most likely to undergo aerosol-generating diagnostic procedures. Second, intentional release of these agents is a bioterrorism event, and public health and law enforcement authorities are now trained to provide immediate investigation and support. Therefore, early suspicion of a bioterrorism or outbreak event, along with early protective measures and public health contact, will reduce the likelihood of transmission to health care workers, visitors, patients, and the community.

Bioterrorism involves the deliberate release of viruses, bacteria, or their products (e.g., toxins) to cause morbidity and mortality in humans, animals, or plants.^{6,7} All bioterrorism agents are naturally occurring organisms or toxins that can cause sporadic disease under ordinary circumstances, but on occasion, an agent has been manipulated

to increase resistance to antibiotics or increase organism virulence.⁷ This chapter provides an overview of the major agents of bioterrorism and highly lethal disease outbreaks along with clues for detection, steps for public health response, and infection control interventions.

BIOTERRORISM: A HISTORICAL PERSPECTIVE

Bioterrorism has existed for centuries, from ancient Mesopotamia to current times.^{7,8} The initial goal was to incapacitate the enemy through death or stir panic in the population, leading to surrender. For example, in the 14th century, the Tartars catapulted plague-infected corpses into Kaffa, leading to disease spread and defeat of the city (also starting the second wave of the Black Death in Europe).⁹ In the New World, smallpox-contaminated blankets may have been distributed by early settlers to natives in an effort to overcome the siege of Fort Pitt. However, bioterrorism took form in the last 100 years with extensive biowarfare units in World War I and II.^{7,8} Notably, Unit 731 of the Japanese army in World War II used anthrax, plague, cholera, and typhoid on Chinese prisoners with high mortality, but the transition to the battlefield was less successful.⁷⁻⁹ The Cold War saw both the United States and the former Soviet Union develop bioweapon stockpiles that have since been dismantled. However, over the past 25 years, there has been an increase in individual-initiated bioterrorism, culminating in the anthrax outbreak in 2001 that used the postal service for distribution, causing 22 cases.^{7,8,10}

BASICS OF BIOTERRORISM

The route of transmission of bioterrorism agents can be by air (e.g., aerosol generation), food (e.g., botulism), or water (e.g., gastroenteritis agents). Delivery can mimic naturally occurring disease, especially if the food or water supply to the public has been targeted. However, with aerosol generation, rapid increases in new cases are seen in low-risk populations, as seen with the anthrax cases in 2001.¹¹

Because most bioterrorism agents are infectious diseases, presentation of disease is usually covert, with health care workers seeing the initial cases. Particularly with contagious diseases such as plague pneumonia, smallpox, and viral hemorrhagic fevers, secondary infections may propagate the event, allowing it to last weeks to months, stressing the capacity of the health care system.^{2,7} Chemical and explosive forms of terrorism, however, are often overt and immediately known, with first responders in the field evaluating the initial cases and subsequent cases rarely following the initial event. Therefore, epidemiologic evidence (e.g., an increase in pneumonia or a specific rash) may be the initial clue that there has been a bioterrorism event.¹²

The Centers for Disease Control and Prevention (CDC) has separated bioterrorism agents into three broad categories (A, B, and C) based on ease of spread and severity of illness.^{7,8,13,14} *Category A agents* are considered the highest risk to the public and national security for the following reasons: (1) easy person-to-person spread; (2) high mortality; (3) major public health impact causing panic and social disruption; (4) requirement for specific and specialized public health emergency response (e.g., public prophylaxis or protective equipment)^{7,8,13,14} (Table 40-1). *Category B agents* are moderately easy to spread and result in moderate morbidity but low mortality in those affected. Fewer specific public health responses are required (Table 40-2).⁷ *Category C agents* are considered future or potential threats because they are easily available and can have a high mortality, but they have not been documented or engineered successfully

Table 40-1 Centers for Disease Control and Prevention Category A Agents of Bioterrorism

Definition: Category A agents have the potential to be easily disseminated, have higher contagiousness, have high morbidity and mortality, and require increased public health preparedness

Anthrax (*Bacillus anthracis*)

Smallpox (variola major)

Plague (*Yersinia pestis*)

Tularemia (*Francisella tularensis*)

Botulism (*Clostridium botulinum* toxin)

Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

Table 40-2 Centers for Disease Control and Prevention Category B Agents of Bioterrorism

Definition: Category B agents are moderately easy to disseminate, carry a high morbidity but low mortality, and require public health laboratory and surveillance enhancements

PULMONARY AGENTS

Glanders (*Burkholderia mallei*)

Melioidosis (*Burkholderia pseudomallei*)

Psittacosis (*Chlamydia psittaci*)

Q fever (*Coxiella burnetii*)

Ricin toxin from *Ricinus communis* (castor beans)

NONPULMONARY AGENTS

Brucellosis (*Brucella* species)

Epsilon toxin of *Clostridium perfringens*

Food safety threats (e.g., *Salmonella* species, *Escherichia coli* O157: H7, *Shigella*)

Staphylococcal enterotoxin B

(Table 40-3).¹⁴ Although all of these agents can potentially cause serious disease, the category A agents, along with select category B agents, would be seen by clinicians and have the greatest impact on the public and health care system. These agents present initially with a nonspecific prodromal phase but with epidemiologic clues that may separate them from other less threatening causes of a febrile respiratory illness. Tables 40-4 to 40-8 list the unique features associated with category A agents: clinical syndromes, preferred diagnostic methods, radiologic features, treatment, and infection control and respiratory protection.

Table 40-3 Centers for Disease Control and Prevention Category C Agents of Bioterrorism

Definition: Category C agents have the future potential for engineering for easy dissemination or high mortality

Influenza (novel strain)

Nipah virus

Typhus disease (*Rickettsia prowazekii*)

Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])

Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)

Table 40-4 Unique Clinical Syndromes Associated with the CDC Category A Agents of Bioterrorism

Agent	Unique Clinical Finding/Syndrome
Anthrax	Hemorrhagic mediastinitis
Smallpox	Poxlike rash with systemic inflammatory response syndrome leading to septic shock
Plague	Sudden acute respiratory failure and sepsis
Tularemia	Patchy alveolar pneumonia with sepsis
Botulism	Descending flaccid paralysis
Viral hemorrhagic fevers (e.g., Ebola)	Sepsis with bleeding diathesis, massive fluid loss from diarrhea and vomiting

Table 40-5 Preferred Diagnostic Methods for CDC Category A Agents

Agent	Laboratory Diagnostic Method
Anthrax	Culture of organism from blood or body fluid. Serology for uncultured cases. BSL 3 required at state and regional public health laboratory.
Smallpox*	PCR of pox lesion. EM confirmation, viral isolation from skin/fluid in BSL 4 laboratory (CDC only).
Plague	Culture of organism from blood or sputum. Serology for uncultured cases. BSL 3+ at state or regional public health laboratory.
Tularemia	PCR. Difficult to culture. Performed at local, state, and regional public health laboratories.
Botulism	Detection of toxin in blood or stool. Toxin identification (A-E) performed at state or regional public health laboratories.
Viral hemorrhagic fevers (e.g., Ebola)*	Nucleic acid detection by RT-PCR. Viral culture from blood/body fluid only performed under BSL 4 containment.

*Culture and/or species identification is performed at the CDC only.

BSL, biosafety level; CDC, Centers for Disease Control and Prevention;

EM, electron microscopy; RT-PCR, reverse transcription-polymerase chain reaction.

Table 40-6 Radiologic Features of CDC Category A Agents of Bioterrorism

Agent	Radiologic Pulmonary Findings
Anthrax	Widening of mediastinum (rapid enlargement on serial imaging), unilateral or bilateral hilar node enlargement. Peribronchovascular thickening and pleural effusion. May also have patchy alveolar opacities, but extensive consolidation uncommon. CT may show hyperattenuating lymphadenopathy
Smallpox	Patchy alveolar opacities
Plague	Patchy, potentially nodular bilateral opacities that may coalesce to more diffuse alveolar disease resembling ARDS. Cavitation uncommon. Lymph node enlargement possible, but inconsistent
Tularemia	Multifocal bronchopneumonia that may cavitate, or lobar pneumonia. Pleural effusion and lymphadenopathy not uncommon
Botulism	Normal to lower lung volumes
Viral hemorrhagic fevers (e.g., Ebola)	Few available data. Chest radiography may be normal. Diffuse alveolar opacities with areas of dense consolidation; widened mediastinum, pleural effusions also reported. American hantavirus-pulmonary edema pattern with interlobular septal thickening despite hypovolemia; may progress to bilateral air space opacities

Table 40-7 Treatment of Select CDC Category A Agents

Agent	Primary Treatment	Secondary Treatment
Anthrax	Ciprofloxacin 15 mg/kg IV twice daily Raxibacumab 40 mg/kg IV, one dose	Clindamycin 900 mg IV three times daily
Plague	Gentamicin 5 mg/kg IV/IM daily Streptomycin 1 g IM daily	Ciprofloxacin 15 mg/kg IV twice daily Chloramphenicol 15 mg/kg IV four times daily
Smallpox	Supportive care Vaccinia Immune Globulin (unproven in smallpox; approved for use in vaccine recipients with progressive vaccinia infection)	Cidofovir*
Tularemia	Gentamicin 5 mg/kg IV/IM daily Streptomycin 1 g IM daily	Doxycycline 100 mg IV twice daily Ciprofloxacin 15 mg/kg IV twice daily Chloramphenicol 15 mg/kg IV four times daily
Viral hemorrhagic fevers	Supportive care Ribavirin for Lassa fever	Investigational agents: Monoclonal antibodies, convalescent serum, antiviral agents
Botulism	Trivalent antitoxin (A, B, E) Supportive care	None

*Obtained through the CDC only (see <http://www.bt.cdc.gov/agent/smallpox/vaccination/vig.asp>).
CDC, Centers for Disease Control and Prevention; IM, intramuscularly; IV, intravenously.

Table 40-8 Infection Control and Respiratory Protection for CDC Category A Agents

Agent	Isolation	Baseline Protection	Protection in Higher Risk Procedures
Viral hemorrhagic fever	Contact	N95 mask with full face shield or PAPR; full skin coverage with fluid-resistant or impermeable gown or coveralls	Current CDC guidelines available at http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html
Smallpox	Airborne and contact	N95 mask	N95 mask or PAPR
Botulism	None	None	Surgical
Plague*	Droplet and contact	N95 mask	N95 mask or PAPR
Tularemia	None	None	Surgical
Anthrax	None	None	Surgical

*Isolation can be stopped after 48 hours of appropriate antibacterial therapy.
PAPR, powered air-purifying respirator.

CDC CATEGORY A AGENTS

ANTHRAX

General

Anthrax is caused by *Bacillus anthracis*, a spore-forming gram-positive rod. *B. anthracis* is a normal soil inhabitant; the organism can multiply if soil conditions are favorable. Otherwise, *B. anthracis* persists for long periods in a spore form, resistant to decontamination and environmental

extremes. From the soil, *B. anthracis* spreads to herbivores, such as cattle, as they come into contact with spore-containing soil through grazing.^{15,16}

Human anthrax largely arises through contact with animal products, such as animal skins, where *B. anthracis* persists as spores. In 2001 in the United States, 22 cases of anthrax were due to an act of bioterrorism through the postal system, placing anthrax on the forefront of bioterrorism.¹⁰ Apart from this outbreak in 2001, anthrax remains rare in the United States, with most endemic and epizootic



Figure 40-1 Anthrax. The anthrax lesion on the skin of the forearm is caused by the bacterium *Bacillus anthracis*. The cutaneous ulceration has begun to turn black, hence the origin of the name “anthrax,” after the Greek word for coal. (Courtesy Centers for Disease Control and Prevention/#2033; James H. Steele.)

cases seen in the Middle East. Most cases in the United States arise through the handling of animal products, such as the 2006 cases associated with animal hide drum skins imported from Africa.¹⁶

Disease begins when *B. anthracis* spores are introduced subcutaneously or via ingestion or inhalation. After introduction to oxygen and a protein-rich environment, the spores convert to the vegetative (bacillus) form and initiate replication.^{15,16} Exotoxin secretion leads to local spread, edema, hemorrhage, and tissue necrosis. The anthrax capsule, edema factor toxin, and lethal factor toxin act in concert to drive disease.^{15,16}

Clinical Presentation

Three clinical disease syndromes are seen with anthrax: cutaneous, gastrointestinal, and inhalational.¹⁵⁻¹⁷ *Cutaneous anthrax* is the most common form worldwide and has an incubation period of 7 to 14 days after inoculation of spores into the subcutaneous space. This is followed by a small, painless papule that can be pruritic. The papule enlarges and develops a central vesicle, followed by erosion into a painless black eschar (Fig. 40-1). Marked edema (mediated by anthrax edema toxin) characteristically surrounds the lesions, and there may be regional lymphadenopathy, with systemic symptoms of fever and malaise. The hands, arms, face, and neck are the areas most commonly affected.

With *inhalational anthrax*, spores that reach the distal airways are transported by inflammatory monocytes or dendritic cells to the mediastinal lymph nodes, with replication followed by onset of disease.¹⁵ The incubation period averages 1 to 7 days, followed by clinical symptoms of a nonspecific febrile illness, often mimicking influenza. However, within 24 hours, disease rapidly progresses with the development of respiratory failure, hemorrhagic mediastinitis, necrotizing pneumonia, shock, multiorgan failure, and death (see Table 40-4).¹⁷ Shock and multiorgan failure can develop rapidly, and along with hemorrhagic mediastinitis (Fig. 40-2), are the clinical hallmark of anthrax.

Gastrointestinal anthrax is rare and is usually seen in family clusters following the consumption of undercooked meats of infected animals. The disease begins with development of bowel edema, followed by mesenteric lymphadeni-

tis and necrosis, and then rapid progression to shock and death.¹⁷

Mortality for cutaneous anthrax is low (<1% in treated patients; approximately 20% in untreated), while inhalational anthrax can carry a mortality of 89%.¹⁵⁻¹⁷ The inhalational cases from 2001 in the United States had a lower mortality of 45%.¹⁰

Diagnosis

Although the initial symptoms of inhalational anthrax are nonspecific, some early findings distinguish inhalational anthrax from influenza-like illness or community-acquired pneumonia. Compared with patients who presented with community-acquired pneumonia in a retrospective study, patients with inhalational anthrax were more likely to have nausea or vomiting, tachycardia, elevated transaminases, hyponatremia, and normal white blood cell counts.¹⁸ From these observations, a scoring system was devised that had approximately 80% sensitivity and 80% specificity for distinguishing inhalation anthrax cases.¹⁸

Diagnosis of anthrax is best performed by isolation of *B. anthracis* from cultures of blood, sputum, pleural fluid, cerebrospinal fluid, or skin^{16,19} (see Table 40-5). Clinicians should notify the laboratory of suspected anthrax, because spores can form during culture, leading to spread to laboratory workers if not properly handled. Additionally, any suspect case of anthrax should involve the public health laboratories for confirmation and strain typing. *Polymerase chain reaction* (PCR) and rapid *enzyme-linked immunosorbent assays* (ELISAs) are available and have good sensitivity and specificity.^{16,19}

The radiographic imaging findings associated with anthrax include a widened mediastinum consistent with hemorrhagic mediastinitis, the hallmark of inhalation anthrax^{15,16} (see Fig. 40-2) (see Table 40-6). However, during the 2001 outbreak, other findings, including patchy alveolar opacities, lobar consolidation, and pleural effusions, were also reported.¹⁶ In each of these cases, a widened mediastinum was present on chest radiograph, with follow-up confirmation performed by computed tomography scan.

Treatment, Prophylaxis, and Prognosis

Treatment includes supportive therapy and antibiotics^{17,19} (see Table 40-7). Intensive care management with early and appropriate volume resuscitation and lung-protective low tidal volume ventilation should be used if indicated.² Antibacterial treatment includes ciprofloxacin, doxycycline, or if the isolate is susceptible, penicillin.^{17,19,20} In 2001, rifampin, clindamycin, or vancomycin in combination with ciprofloxacin was used, because the isolate was resistant to penicillin.^{17,19,20} Pleural drainage or a central nervous ventriculoperitoneal shunt may also be used in individual cases. Corticosteroids are widely used to reduce edema and hemorrhage, especially when cutaneous anthrax affects the head and neck, threatening airway integrity, but there are very limited data on their efficacy.¹⁷

Raxibacumab, a human IgG1 monoclonal antibody directed against *B. anthracis* protective antigen (whose role is to bind host cells and deliver anthrax edema factor and lethal factor to the host cell cytoplasm), has been effective for the treatment of anthrax in animal models, with

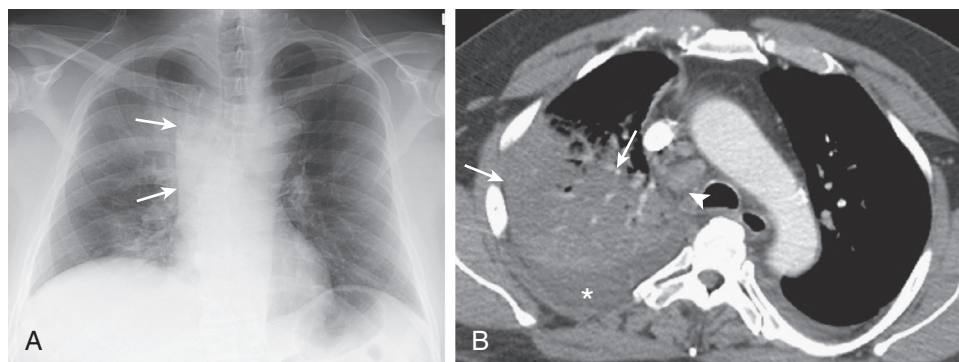


Figure 40-2 Imaging findings in inhalation anthrax: chest radiography. **A**, Frontal chest radiograph in a 61-year-old man with a 3-day history of productive cough, fever, and exertional dyspnea shows poorly defined medial right upper lobe ground-glass opacity associated with a markedly widened right mediastinum (arrows). During recent travel through parks in the western United States, he had been exposed to animal antlers and hides, wild bison, and donkeys. **B**, Axial enhanced chest CT displayed in soft tissue windows shows right upper lobe consolidation (arrows) and a small right pleural effusion (*) and trace left pleural liquid associated with right paratracheal lymphadenopathy (arrowhead). *Bacillus anthracis* was isolated from blood culture. (Images courtesy Mark D. Sprenkle, MD, Pulmonary and Critical Care Medicine, Hennepin County Medical Center, Minneapolis, MN. Reprinted with permission from Sprenkle MD, Griffith J, Marinelli W, et. al: Lethal factor and anti-protective antigen IgG levels associated with inhalation anthrax, Minnesota, USA. *Emerg Infect Dis* 20:310–314, 2014.)

improved survival at 14 and 28 days.^{21,22} In 2012, raxibacumab was approved by the U.S. *Food and Drug Administration* (FDA) for the treatment of inhalation anthrax and, as such, should be used in combination with antibiotics and initiated when the diagnosis of inhalation anthrax is suspected or confirmed. An anthrax vaccine, prepared from the culture filtrate of an attenuated strain of *B. anthracis*, is approved for humans by the FDA, but its use has been limited, due to the need for multiple doses, local side effects, and efficacy concerns, and it is currently reserved for military personnel.²³ Exposure to aerosolized spores requires prophylaxis with either ciprofloxacin or doxycycline in adults; amoxicillin is a second-line agent in children and pregnant women.^{16,19} The recommended duration of post-exposure prophylaxis is 60 days, because none of the antibiotics eradicate spores, which may germinate weeks after exposure.

Infection Control

Anthrax is not transmitted from an infected person, because *B. anthracis* is in the vegetative form during clinical infection, and only spores are transmissible^{7,16} (see [Table 40-8](#)). Contact with infected animal carcasses and animal products (especially hides) can result in infection; wearing appropriate *personal protective equipment* (PPE) is indicated when handling these materials or when exposed to other suspected contaminated objects.

SMALLPOX

General

Variola virus is the causative agent of smallpox and is a member of the Poxviridae family.²⁴ Smallpox was eradicated worldwide in 1977, but now has regained interest because of its potential as a bioterrorism agent.^{24,25} Smallpox was widely endemic and at one point accounted for more than 10% of all deaths worldwide. Smallpox is very contagious; approximately half of all unvaccinated household contacts contract disease.^{24,25} After global eradication of smallpox was declared in 1977, routine vaccination for smallpox

ceased worldwide.²⁶ Due to an increasing unvaccinated population, along with its contagiousness and ability to be transmitted by aerosol, smallpox is a CDC category A bioterrorism agent. Only two stockpiles of the virus are known to remain (at the CDC and the Russian State Research Center).^{27,28}

Smallpox exists in two forms, variola major and variola minor.^{24,25} Variola major is the most common form of smallpox, has more severe disease with an extensive rash and fever, and carries a higher mortality (around 20% in the unvaccinated). Variola minor is less common and less severe, with mortality estimated at less than 1%. Variola minor has a genetic sequence very similar to that of variola major; quantitative differences in gene expression are thought to account for the variable mortality between the major and minor forms.

Clinical Presentation

Smallpox infection begins when the virus enters the respiratory tract, replicates locally, and is transported to regional lymph nodes.^{24,25} Viremia follows with spread to lymphoid organs, followed by further viral replication and progressive symptoms. Variola major presents in five major clinical categories: ordinary, modified, flat, hemorrhagic, and variola sine eruptione.^{24,25}

Ordinary type infection accounted for more than 70% of cases when smallpox was endemic. After an incubation period of 10 to 14 days, disease (pre-eruptive phase) manifests with high temperature, severe headache, and malaise. The pre-eruptive phase can last 2 to 4 days and is followed by the eruptive phase, which is characterized by rash. The lesions first appear as small erythematous macules on the mucous membranes, tongue, and face (herald spots).^{24,25,29} The lesions spread in a centrifugal fashion, with macules evolving into papules, then vesicles, and finally the classic pustules (pox) ([Fig. 40-3](#)) by day 5 to 7 of the rash (see [Table 40-4](#)). Fever usually resolves during the eruptive phase but may persist after the pustules develop. Crusting and healing begin by day 14 of the rash.

The *modified type* of variola major is similar to the ordinary type except that the rash is more rapid but less severe;



Figure 40-3 Smallpox. The maculopapular lesions on this patient's arm were caused by the smallpox virus, *variola major*. These lesions were in their pustular phase of development. (Courtesy Centers for Disease Control and Prevention/#10495; Dr. John Noble, Jr.)

this type was common in vaccinated individuals.^{24,25,29} The *flat type* had pustules that remained flat and confluent and often was seen in children.

The *hemorrhagic type* was rare but severe, with the lesions and mucous membranes becoming hemorrhagic.^{24,25,29} This type was more common in pregnant women and led to multiorgan failure within a few days.

The *variola sine eruptione type* is associated with fever but no rash; this type was often seen in previously vaccinated individuals.

Diagnosis

Diagnosis is largely clinical, with the acute onset of fever followed by the characteristic rash of deep-seated vesicles or pustules^{24,30} (see Table 40-5). For laboratory diagnosis, variola- and orthopox-specific PCR assays are performed at the CDC or World Health Organization–sponsored laboratories.^{24,30} If a case of smallpox is suspected, information on diagnosis, infection control, and public health measures are available at <http://emergency.cdc.gov/agent/smallpox/response-plan/index.asp>.

Radiographic imaging findings in smallpox are limited largely to diffuse alveolar opacities from an inflammatory response associated with the primary infection^{24,31} (see Table 40-6). Lobar opacities may be seen and are most often associated with secondary bacterial pneumonia.

Treatment, Prophylaxis, and Prognosis

Treatment is largely supportive, with some evidence that cidofovir, an antiviral with activity against cytomegalovirus, has activity in animal models^{24,31,32} (see Table 40-7). Aggressive ICU support, including volume resuscitation, vasopressor support, and low tidal volume ventilation should be used for severe cases.¹ Vaccination as soon as possible after exposure may reduce the severity of illness and is the mainstay for reducing spread and controlling disease in the community.²⁶ Vaccination administered within 4 days of exposure can still provide protection. Passive immunization with vaccinia immune globulin is FDA approved for patients suffering progressive vaccinia infection after vaccination; whether it has efficacy in treating smallpox has not been determined.

Mortality varies with the clinical category. The ordinary type carries a mortality from multiorgan failure and hypotension of around 20%, with the flat and hemorrhagic types carrying a higher mortality and the modified and sine eruptione types carrying a much lower mortality. Complications include secondary bacterial skin infections and pneumonia, along with encephalitis, orchitis, and extensive scarring of the skin and corneas.^{24,25}

Infection Control

Spread is through contact with infected lesions or respiratory secretions and thus full PPE, including respiratory protection, gown, gloves, and face shield, is required.³² CDC guidelines recommend airborne isolation with use of an N95 particulate respirator or a powered air-purifying respirator for respiratory protection, and all health care workers involved in care of a smallpox patient must be vaccinated against smallpox³² (see Table 40-8). If smallpox is suspected, public health officials must be contacted immediately.

PLAGUE

General

Yersinia pestis is the etiologic agent of plague and has caused multiple pandemics, despite being a recently evolved pathogen.⁹ Plague is a zoonosis, primarily affecting rodents; humans and other animals (especially domestic cats) are accidental hosts.^{33,34} The natural ecosystem of *Y. pestis* depends largely on the flea-rodent interaction, with seasonal variation based on environmental conditions that favor large rodent populations. Infected fleas bite their rodent hosts, inoculating the rodent. Mortality in these animals is lower than in nonrodent mammals, and disease is passed from infected rodent to flea and the life cycle continues. *Y. pestis* is transmitted to humans by bites from rodent-infected fleas, scratches or bites from infected animals, exposure to infected humans, or bioterrorism.^{33,34} Bites by infected fleas are the most common mode of transmission; squirrels, rabbits, domestic and wild cats, and prairie dogs are the most common sources of infected fleas. Large rodent or other animal die-offs, particularly in more susceptible species, may herald a large epidemic in nature.^{33,34} Plague is found worldwide; in the United States endemic disease is concentrated in the western states; most likely because of introduction of *Y. pestis*-infected rats through the ports of San Francisco, Los Angeles, and Seattle in the late 19th century.³⁵

Clinical Presentation

Three clinical syndromes are associated with plague: bubonic plague (80% to 90% of cases), septicemic plague (10% of cases), and pneumonic plague (very rare).^{33,34} After an incubation period of 2 to 7 days, symptoms usually arise, which differ depending on the clinical syndrome. The incubation period is prolonged and asymptomatic, due to multiple mechanisms used by *Y. pestis* to minimize early innate immune responses and inflammation, including specific inhibition of inflammasome activation.³⁶

In *bubonic plague*, a sudden onset of fevers, chills, and headache is followed by pain and swelling in the regional lymph nodes proximal to the site of the bite or scratch.^{33,34}



Figure 40-4 Plague. An axillary bubo and edema exhibited by a patient with plague. (Courtesy Centers for Disease Control and Prevention/#2061; Margaret Parsons, Dr. Karl F. Meyer.)

This lymph node (bubo) is characterized by intense tenderness with erythema and edema but without fluctuation (Fig. 40-4). Without treatment, disease disseminates, leading to pneumonia, meningitis, sepsis, and multiorgan failure. The development of secondary plague pneumonia is important to detect, because such patients are highly contagious.

In *septicemic plague*, acute fever is followed by sepsis without a bubo.^{33,34} Additional symptoms such as nausea, vomiting, and diarrhea also complicate septicemic plague. Sepsis, disseminated intravascular coagulation, and multiorgan failure develop quickly.

In *pneumonic plague*, most cases are secondary (hematogenous) from bubonic or septicemic plague, but primary pneumonic plague can also develop after exposure to infected humans, animals, or aerosols in an intentional bioterror attack.^{33,34} Initial cases in outbreaks of primary pneumonic plague have a very short incubation period of hours to a few days, followed by sudden onset of fever and cough, rapid onset of respiratory failure with ARDS, and death (see Table 40-4).

Diagnosis

The clinical diagnosis of plague can be difficult, but exposure to animals in an endemic area is an important clue to seek.^{33,34,37} (see Table 40-5). During intentional dissemination, multiple cases of severe, rapidly progressive pneumonia may be the first sign of an attack. Laboratory diagnosis is primarily by culture of the sputum or blood because *Y. pestis* grows well on routine laboratory media. Serology and rapid diagnostic testing by ELISA or PCR is also available but is used primarily in field testing.^{33,34,37}

On chest radiographs, a sudden and diffuse alveolar filling process is seen consistent with acute lung injury^{33,34} (see Table 40-6). Additional mediastinal lymphadenopathy may be present, as may pleural effusion in later stages. Lobar opacities are less common.

Treatment, Prophylaxis, and Prognosis

The primary agent for antibacterial therapy of plague has long been considered streptomycin but, based on its limited availability, gentamicin or doxycycline is preferred^{33,34} (see Table 40-7). Most isolates are susceptible to gentamicin and

doxycycline; most are also susceptible to ciprofloxacin, although there is less clinical experience with this drug in plague.³⁸ Chloramphenicol is preferred for cases of meningitis due to its ability to cross the blood-brain barrier. Because most cases of primary pneumonia lead to multiorgan failure and acute lung injury, volume resuscitation, vasopressor support, and low tidal volume ventilation are indicated.² There is no evidence of benefit from corticosteroids. Postexposure prophylaxis includes ciprofloxacin and doxycycline orally, with trimethoprim-sulfamethoxazole (if the isolate from the index case is susceptible) or gentamicin for children and pregnant individuals.³⁸

Infection Control

Due to the high rate of transmission of plague via aerosols, all patients should be on strict airborne isolation until at least 48 hours of antibiotics have been given³⁴ (see Table 40-8). Infection control measures include airborne isolation, including negative-pressure ventilation. Appropriate PPE, including an N95 mask or powered air-purifying respirator, should be worn by all personnel in contact with a patient with suspected or confirmed pneumonic plague.

TULAREMIA

General

Tularemia is caused by the gram-negative bacterium *Francisella tularensis* and is a zoonotic disease; humans are accidental hosts.³⁹ *F. tularensis* is found throughout the Northern Hemisphere in a wide variety of wild and domesticated species and the organism persists in nature. Humans become infected by the bites from infected vectors (ticks and flies), the handling of infected animals, ingestion of improperly prepared animal meat, animal scratches and bites, the drinking of contaminated water, or inhalation of an aerosol of the organism from the environment or in a bioterrorism event.³⁹⁻⁴¹ Human-to-human transmission has not been described.

Clinical Presentation

Six distinct clinical syndromes have been observed with tularemia: ulceroglandular, glandular, typhoidal, pneumonic, oropharyngeal, and oculoglandular.^{42,43} *Ulceroglandular disease* accounts for approximately 60% to 70% of cases.^{42,43} After an incubation period of 2 to 10 days, there is an abrupt onset of fevers, chills, headache, and malaise. Most patients have a single papuloulcerative lesion with a central eschar and associated tender lymphadenopathy (Fig. 40-5). In *glandular disease*, lymph nodes enlarge without the characteristic lesion (about 15% of cases).^{42,43}

Pneumonic tularemia results from primary inhalation or hematogenous spread from typhoidal tularemia, and this is expected to be the main clinical presentation in a bioterrorism event with tularemia.⁴⁰ The incubation period tends to be shorter in these cases, with the rapid onset of pneumonia. Respiratory failure and ARDS develop rapidly (see Table 40-4).

Typhoidal tularemia is rare and is seen with or without pneumonia; patients present with a febrile illness followed by sepsis without the glandular disease.⁴³ *Oropharyngeal tularemia* results when undercooked infected meat or water



Figure 40-5 Tularemia. A tularemia lesion is shown on the dorsal skin of the right hand caused by the bacterium *Francisella tularensis*. (Courtesy Centers for Disease Control and Prevention/#2032; Dr. Brachman.)

is ingested and is associated with fever, pharyngitis, and cervical lymphadenopathy.⁴³

Oculoglandular tularemia results from direct inoculation from contaminated fingers or accidental exposure. Conjunctival swelling and erythema, and regional lymphadenopathy may be present.

Diagnosis

Culturing *F. tularensis* is suboptimal in a few respects: specific culture media (with cysteine) is required, growth is slow, and cultures are hazardous to laboratory personnel^{44,45} (see Table 40-5 and Chapter 17, Table 17-5). PCR detection of *F. tularensis* is rapid, is not hazardous, and has a reported sensitivity of approximately 75% and high specificity (see Table 17-5). PCR-positive fresh samples should be submitted to a reference or public health laboratory for confirmation.

Radiographic imaging studies show patchy opacities bilaterally, lobar disease, and hilar adenopathy⁴⁶ (see Table 40-6). There can also be pleural effusions and a miliary pattern, and hilar and mediastinal adenopathy.

Treatment, Prophylaxis, and Prognosis

Similar to the treatment for plague, gentamicin is the treatment of choice for tularemia^{45,47} (see Table 40-7); doxycycline or ciprofloxacin may be used as second-line therapy. For meningitis, chloramphenicol is preferred. Postexposure prophylaxis with doxycycline or ciprofloxacin may be efficacious, with trimethoprim-sulfamethoxazole or amoxicillin for children and pregnant patients.^{45,47} ICU management of tularemia includes supportive care and low tidal volume ventilation for ARDS. The overall mortality for tularemia is around 4%, but is thought to be higher in aerosolized disease that causes pneumonia or typhoidal tularemia.^{42,43}

Infection Control

Tularemia is not spread by human-to-human contact, so once the diagnosis is confirmed, respiratory isolation can be discontinued^{43,47} (see Table 40-8). Rules about reporting tularemia to public health officials varies across North America but pneumonic or typhoidal cases, particularly if thought to be secondary to a bioterrorism event, must be reported.

BOTULISM

General

Clostridium botulinum, a gram-positive, spore-forming, obligate anaerobe, is the bacterium that produces and excretes botulinum toxin.^{48,49} This neurotoxin is responsible for the clinical disease known as botulism and is the only category A agent that is a toxin. Seven serotypes of botulinum toxin exist, A through G, and are produced by different strains of *C. botulinum*. All botulinum neurotoxins act as proteases that cleave proteins on synaptic vesicles or the presynaptic plasma membrane of the neuromuscular junction and cholinergic autonomic synapses. The resulting inability to release neurotransmitters and disruption of neurotransmission account for the clinical findings. Serotypes A, B, and E predominate in human disease, although any serotype can cause disease.^{48,49} Serotypes C and D are predominantly found in animal populations. Botulinum toxin is extremely potent, with the median lethal oral dose estimated to be 1 ng/kg, although the lethal dose may be two to three times higher if exposure is by inhalation.^{48,49}

Disease presents from four potential sources: food-borne, wound, infant, and intentional.^{48,49} Food-borne disease presents in outbreaks and is often associated with home-canned foods, such as fruits, vegetables, and fermented fish. Wound botulism has been associated with intravenous and subcutaneous injection of black tar heroin, mostly of Mexican origin. Infant botulism is seen sporadically in some western states, likely from spore acquisition from soil or raw honey, with toxin production in the gastrointestinal tract. Finally, intentional release during a bioterrorism event may lead to oral ingestion or inhalation of the toxin.

Clinical Presentation

Botulism begins with the acute onset of bilateral cranial neuropathies with rapidly descending weakness (see Table 40-4). No fever is present and mental status is not affected.^{48,49} The cranial neuropathies are usually symmetrical and often begin with oculomotor dysfunction. However, asymmetrical cranial nerve dysfunction has been reported.⁵⁰ Diplopia, dysphagia, ptosis, and facial weakness are the most common early complaints.^{48,49} In food-borne exposure, there may also be gastrointestinal symptoms, including nausea and vomiting. In infant botulism, poor feeding and lethargy may be the only symptoms. Food-borne botulism usually has an onset of symptoms 12 to 36 hours after exposure; symptoms rapidly progress over the next 12 hours. If botulism is not suspected and treatment is not started rapidly, weakness and paralysis of respiratory muscles ensues, requiring mechanical ventilatory support.⁵⁰ Once the muscles of respiration are involved, mechanical support may be required from 1 to 3 months.⁵⁰ Since the toxin-mediated blockade of neuromuscular transmission is reversible, full recovery can be expected although recovery may be prolonged.

Diagnosis

Early and prompt diagnosis is essential because respiratory support is often required and early treatment may alter the extent of progression of weakness. Thus the clinical findings of cranial nerve palsies, particularly in the appropriate clinical setting (e.g., heroin use, or ingestion of the same

food as another person with botulism) should prompt consideration of botulism (see Table 40-5). Laboratory diagnosis is by toxin detection or organism isolation.⁴⁵ Detection of toxin in blood or stool is most reliable.⁵¹ The growth of *C. botulinum* from a stool or wound sample with the corresponding clinical findings can also confirm the diagnosis. Electromyography will also support the diagnosis if toxin and organism isolation is unsuccessful. There are no specific radiologic changes seen with botulism. Low lung volumes on chest radiographs may be seen but are not specific (see Table 40-6).

Treatment, Prophylaxis, and Prognosis

Supportive care is the cornerstone of management of botulism. Monitoring for impending respiratory failure and providing mechanical ventilation when needed are the highest priorities. An equine trivalent antitoxin (against serotypes A, B, and E) is available from state public health departments and the CDC, and is directed at neutralization of toxin that has not yet entered cells. Botulinum antitoxin cannot reverse botulinum intoxication^{48,49,52} (see Table 40-7). While the antitoxin is widely used in cases of botulism, its efficacy has only been inferred and, since the available antitoxin is derived from immunized horses, anaphylaxis and/or serum sickness can develop in 9% to 20% of recipients. A human-derived antitoxin is available but only for infant botulism. Human monoclonal antibodies have been prepared that neutralize multiple types of botulinum toxins, and these provide the potential for use in adults with a lower risk of adverse effects than the equine antiserum.⁵³ In wound botulism, after wound drainage, antibiotic administration is useful; penicillin or clindamycin are the drugs of choice.^{48,49} In food-borne and inhalation botulism, because the disease results from exposure to the toxin and not from infection, antibiotics are not efficacious. In all cases of botulism, routine monitoring of forced vital capacity is recommended, with early intubation if the vital capacity falls below 10 mL/kg (approximately 30% predicted). There is no direct prophylaxis for exposure, but in the setting of high-risk threats, a vaccine directed against serotypes A and E is available and has been largely used in the military.⁵² Patients die of botulism due to respiratory failure without ventilatory support or from complications during critical care.

Infection Control

Because botulism is a toxin-based disease, no specific infection control measures are required⁴⁸ (see Table 40-8). An exposure to spores or toxin should be followed by decontamination, although secondary infections or intoxication in medical personnel have not been reported.

VIRAL HEMORRHAGIC FEVERS

General

The hemorrhagic fever viruses include multiple geographically distributed viruses, including Ebola and Marburg viruses, and the viruses causing Rift Valley fever, Bolivian, Argentine, and Crimean-Congo hemorrhagic fevers, Lassa fever, yellow fever, and dengue fever.⁵⁴⁻⁵⁶ Ebola and Marburg viruses are in the family Filoviridae; Lassa virus and the

viruses causing Bolivian (Machupo virus) and Argentine (Junin virus) hemorrhagic fever are in the family Arenaviridae. The Crimean-Congo and Rift Valley fever viruses belong to the Bunyaviridae family. Only the Filoviridae (Ebola and Marburg viruses) and Arenaviridae are listed as category A agents. The Filoviridae family serves as a classic template for viral hemorrhagic fevers and is largely discussed here.⁵⁴ Marburg virus has a single species, while Ebola virus has five different species that vary in virulence in humans.^{55,56} Transmission appears to be through contact with blood or secretions of nonhuman primates and infected individuals. People have become infected after handling primate products, after consuming nonhuman primate meat, or after exposure to symptomatic patients, including in hospitals. Several cases have presented due to exposure in laboratories. The use of hemorrhagic fever viruses as bioterrorism agents has also been postulated, largely based on their high contagiousness in aerosolized primate models.^{55,56} The animal reservoir for these viruses was initially thought to be wild primates, but has recently been tentatively identified to be bats, which transmit the infection to nonhuman primates in the wild.

Clinical Presentation

The clinical manifestations of both Marburg and Ebola viruses are similar in presentation and pathophysiology.^{56,57} The incubation period after exposure to either virus is usually 5 to 10 days, but may be as long as 19 days. Clinical disease begins with the abrupt onset of fever, chills, malaise, severe headache, nausea, vomiting, diarrhea, and abdominal pain.^{56,57} Over the next few days, symptoms worsen to include prostration, stupor, and hypotension. In some patients, coagulation becomes impaired with the appearance of increased conjunctival and soft tissue bleeding. In some of the reported outbreaks, hemorrhage can be massive in the gastrointestinal and urinary tracts and, in rare instances, the lung.^{56,57} In the outbreak of Ebola virus disease centered in Guinea, Liberia, and Sierra Leone in 2014, hemorrhage was not prominent; instead, the clinical picture was dominated by voluminous diarrhea.^{57a,57b} The onset of maculopapular rash on the arms and trunk may be a very distinctive sign (Fig. 40-6). Along with volume depletion and hypotension, multiorgan failure can develop and often leads to death (see Table 40-4). Outbreaks and cases have largely been described in developing countries where critical care resources are limited, thus experience with mechanical ventilation and the development of ARDS is not well documented. Case-fatality rates have ranged from 40% to 90%.^{54,56,57,57b,58}

Diagnosis

It is important to suspect the diagnosis of a viral hemorrhagic fever in order to initiate supportive care before the onset of shock, to involve the public health department, and to implement infection control measures. Viral hemorrhagic fevers should be suspected in cases of an exposed laboratory worker or an acutely ill traveler from an endemic area (i.e., central or west Africa), or in the presence of characteristic clinical findings in the context of other cases in the community, suggesting a bioterrorism attack.⁵⁶ The presence of high temperature, malaise and joint pain, conjunctival bleeding and bruising, vomiting and diarrhea,



Figure 40-6 Marburg virus. This posterior-oblique view of the back of a patient shows the measles-like maculopapular rash, which can appear on patients with the Marburg virus infection around the fifth day after the onset of symptoms, and usually may be found on the patient's chest, back, and stomach. This patient's skin blanched under pressure, which is a common characteristic of a Marburg virus rash. (Courtesy Centers for Disease Control and Prevention/#6571; Dr. J. Lyle Conrad.)

confusion, and progression to shock and multiorgan failure should raise suspicion of a viral hemorrhagic fever. Laboratory diagnosis consists of viral nucleic acid detection by PCR⁵⁶ (see Table 40-5).

Radiologic changes include a diffuse alveolar process consistent with acute lung injury^{56,57} (see Table 40-6). As the disease progresses, the alveolar process can become dense as alveolar hemorrhage develops. Pleural effusions may also be present.

Treatment, Prophylaxis, and Prognosis

Current patient management includes supportive care, including aggressive volume resuscitation, and a lung-protective strategy with low tidal volume ventilation if ARDS is part of the disease course⁵⁵⁻⁵⁷ (see Table 40-7). Recent experiments in nonhuman primates have established therapeutic efficacy of a combination of three monoclonal antibodies to the Ebola glycoprotein.⁵⁹ This provides proof of principle that specific treatment of Ebola infection is possible, and the humanized monoclonal antibodies may progress to availability for human use. With the arenavirus group (Lassa, Junin, and Machupo viruses) and the Bunyaviridae (Crimean-Congo hemorrhagic fever and Rift Valley fever viruses), ribavirin is recommended.⁵⁵⁻⁵⁷ The recent finding that Ebola replication requires the *Abelson tyrosine kinase* (C-abl), and that C-abl kinase inhibitors (currently used for treatment of chronic myelogenous leukemia and certain other malignancies) block Ebola replication in vitro suggests an additional potential treatment approach.⁶⁰

If a health care worker is exposed, there is no approved postexposure prophylaxis; infection control and occupational health personnel should be involved immediately. Two distinct vaccines protect nonhuman primates against Ebola challenge and are entering initial trials in humans.^{61,62}

Infection Control

Transmission is by the droplet route, and the very high viral loads found in blood, diarrhea, and secretions in Ebola

patients mandate stringent precautions to protect personnel. Placement of the patient in an isolation room with strict procedures for handling waste is essential to protect healthcare and other personnel⁵⁵⁻⁵⁷ (see Table 40-8). Equipment should be dedicated to that individual, and all higher risk procedures must be done with full PPE. Any suspected case of viral hemorrhagic fever should immediately involve the public health officials and infection control department, because public health interventions and outbreak investigation are essential to reduce spread of disease within the community and to investigate any potential bioterrorism attack.

SELECT CDC CATEGORY B AGENTS

DIRECT PULMONARY AGENTS

Glanders (*Burkholderia mallei*)

Glanders is caused by the gram-negative bacterium *Burkholderia mallei*.⁶³ It is primarily a disease of horses; humans become infected through broken skin or droplet inhalation. Naturally occurring human infection is rare, but occupational cases (principally in horse veterinarians) are seen sporadically. In bioterrorism, aerosolization is the anticipated method of exposure. Glanders can present as an acute or chronic skin infection, but with aerosolization, rapid pneumonia and/or sepsis can result.⁶³ Diagnosis is by culture, but *B. mallei* can be misclassified by some automated systems as a *Pseudomonas* species. Treatment includes supportive care as well as systemic antibiotics such as a third-generation cephalosporin, imipenem, or ciprofloxacin.⁶³ Human-to-human transmission has not been detected, but universal precautions with droplet isolation for respiratory cases are recommended. Any suspect case should prompt immediate notification of the public health department.

Melioidosis (*Burkholderia pseudomallei*)

Melioidosis is caused by the gram-negative bacterium *Burkholderia pseudomallei*.^{63,64} Unlike *B. mallei*, this bacterium has a natural reservoir in the soil and contaminated water and is spread through direct contact or inhalation. Thus disease predominates during the rainy season. In bioterrorism, aerosolization would lead to a clinical picture of pneumonia or melioidosis sepsis.^{63,64} With melioidosis, the incubation period can be highly variable, with some cases presenting acutely, some having extended incubation periods, and others remaining asymptomatic.⁶³⁻⁶⁵ Sepsis with multiple metastatic foci develops in most symptomatic cases, eventually progressing to multiorgan failure. Diagnosis is by culture using routine methods. Treatment involves imipenem or a third-generation cephalosporin, followed by a 20-week treatment with doxycycline and trimethoprim-sulfamethoxazole for eradication of metastatic foci.^{63,64}

Psittacosis (*Chlamydia psittaci*)

Psittacosis is caused by *Chlamydia psittaci*, an intracellular bacterium routinely associated with birds such as parrots, cockatiels, and canaries. Psittacosis presents

nonspecifically, and most cases go undiagnosed.^{66,67} As a category B bioterrorism agent, *C. psittaci* can cause morbidity with low mortality. Intentional aerosolization would lead to multiple cases of nonspecific “atypical pneumonia” with cough, fever, and headache.^{66,67} Diagnosis has historically been difficult, but sensitive PCR techniques offer the potential for rapid, specific diagnosis (see Chapter 17; Table 17-1). Treatment is with doxycycline, a macrolide, or ciprofloxacin. Mortality is low at 1% in treated cases.^{66,67} Universal precautions are required for patient care, although an N95 mask and coveralls are recommended for environmental decontamination.

Q Fever (*Coxiella burnetii*)

Q fever is a zoonotic disease caused by *Coxiella burnetii*. Cattle, sheep, and goats are the primary reservoirs of *C. burnetii*; this disease is found worldwide.⁶⁸ *Coxiella burnetii* usually does not cause clinical disease in animals, but organisms are found in milk, urine, feces, amniotic fluids, and placenta. The organisms are resistant to heat and drying, and can cause infection by inhalation of environmental dust contaminated with dried placental material, birth fluids, and excrement. The incubation time is 1 to 2 weeks, after which clinical illness develops in approximately 50% of infected persons.⁶⁸ Q fever is characterized by high temperatures (often greater than 40°C/104°F), severe headache, myalgia, sore throat, nonproductive cough, nausea, vomiting, diarrhea, abdominal pain, and chest pain.^{68,69} Pneumonia develops in 30% to 50% of patients with symptomatic infection.

One percent to 2% of people with acute Q fever die of the disease.^{68,69} In a small percentage of those infected, chronic Q fever (infection that persists for more than 6 months), including endocarditis, develops; up to 65% of persons with chronic Q fever die of the disease. Diagnosis of Q fever depends on serologic testing, most commonly using the indirect immunofluorescence assay (see Chapter 17; Table 17-5).^{68,69} The antibiotic treatment of choice for acute Q fever is doxycycline 100 mg twice daily for 15 to 21 days.^{68,69} Fluoroquinolones may be effective alternatives.

Ricin Toxin

Ricin is a potent biologic toxin (toxic protein) derived from castor beans (*Ricinus communis*) during manufacture of castor oil.⁷⁰ Ricin acts as a toxin by the inhibition of protein synthesis; 0.2 mg (1/5000th of a gram) is thought to be the lethal dose. Symptoms begin within 4 to 12 hours after exposure. Systemic effects of ricin poisoning depend on route of exposure and exposure dosage. Signs and symptoms from oral ingestions include vomiting and profuse diarrhea; in addition, there may be fever, myalgia and arthralgia, hallucinations, and seizures.⁷⁰ Hypovolemic shock and multiorgan failure may intervene, and represent the likely cause of death.⁷⁰ Based on animal experiments, after an inhalational exposure, symptoms in humans are expected to include cough, respiratory distress, and bronchoconstriction. Influenza-like symptoms (fever, myalgia, and arthralgia) may be seen, as can hypotension, respiratory failure, and multiorgan failure.⁷⁰ Few symptoms and signs exist to separate ricin intoxication from other causes of respiratory failure, although excessive diaphoresis has been reported and would be unusual in other causes. No

specific treatment or antitoxin exists. Treatment consists of decontamination and supportive therapy.⁷⁰

NONPULMONARY AGENTS (GASTROINTESTINAL AND TOXIN)

Brucellosis (*Brucella* Species)

Brucellosis is caused by a number of species within the genus *Brucella*. Disease is common in livestock workers, particularly in areas of poor sanitation, where *Brucella* is found in domesticated animals.⁷¹ *Brucella* is a category B agent due to its low mortality and prolonged incubation period.⁷² After exposure through ingestion of contaminated food or intentional aerosolization, symptoms develop after a few weeks to months. Initially fevers persist irregularly over weeks to months, followed by arthralgias, gastrointestinal symptoms, and possibly endocarditis.⁷¹ Diagnosis is suspected with a plausible history of exposure, with isolation of the organism by blood culture. However, growth is slow, so all cultures should be kept for 4 weeks if the diagnosis is suspected. Treatment is with doxycycline for up to 6 weeks, for children, treatment is with trimethoprim-sulfamethoxazole for children.⁷¹

Epsilon Toxin of *Clostridium perfringens*

The *Clostridium* species produce multiple toxins; epsilon toxin is produced by *Clostridium perfringens* types B and D.⁷³ The toxin acts on host cell membranes, producing pores that cause nonselective permeability. *Clostridium perfringens* uses the toxin to gain access into the bloodstream from the gut. However, in bioterrorism, intentional release via ingestion or inhalation of the toxin alone is most likely.⁷⁴ Based on data from animals, rapid ingestion or inhalation would cause diffuse tissue edema and be manifested as central nervous system dysfunction (weakness, ataxia, confusion), pulmonary edema (shortness of breath, cough, bronchospasm, respiratory failure), nausea, vomiting, tachycardia, and hypotension.⁷³ Diagnosis requires clinical suspicion consistent with a bioterrorism attack; the toxin can be detected by ELISA. Treatment is supportive, with penicillin if *C. perfringens* is present in addition to the toxin.⁷³

Food Safety Threats (e.g., *Salmonella* Species, *Escherichia coli* O157:H7, *Shigella*)

Enteropathogenic gram-negative bacteria, such as *Escherichia coli*, *Salmonella*, and *Shigella*, constitute a large group of agents that make up food supply threats.⁷⁵ Public health officials are familiar with these bacteria from numerous episodes of food contamination that lead to localized outbreaks and large product recalls. In an intentional release, these agents would produce widespread gastrointestinal symptoms leading to significant morbidity but with low mortality. After an incubation period of 3 to 7 days, there would be abdominal cramping, nausea, vomiting, and diarrhea. The diarrhea may be voluminous and bloody.⁷⁵ Diagnosis is by stool culture of the agents. An aggressive public health investigation usually yields the initial agent, because bioterrorism resembles a point-source outbreak.⁷⁶ Treatment is intravenous hydration as needed and, with some agents (*Salmonella*, *Shigella*), antibacterial therapy with ciprofloxacin.⁷⁶

Staphylococcal Enterotoxin B

Staphylococcal enterotoxin B is a toxin produced by *Staphylococcus aureus* commonly associated with food poisoning. Symptoms of food poisoning include vomiting and diarrhea several hours after ingesting food.⁷⁷ Naturally occurring, it is rarely lethal. The clinical presentation would depend on the route of administration. Oral administration (poisoning of food or water supplies) would present as vomiting and diarrhea.⁷⁷ If inhaled, respiratory failure with neurotoxic effects may be seen.⁷⁷

IMPACT OF H1N1 INFLUENZA PANDEMIC OF 2009 ON BIOTERRORISM RESPONSE

In 2009–2010, a new variant of H1N1 influenza A virus emerged and caused a global influenza pandemic.⁷⁸ Treatment strategies and interventions used in this H1N1 pandemic have impacted the planning for responses to highly infectious agents, including agents of potential bioterrorism. The administration of antivirals, particularly oseltamivir, reduced hospitalizations and death when administered within 48 hours of symptom onset.^{79–82} In critically ill patients with pandemic H1N1 influenza, oseltamivir was associated with increased survival compared with no treatment (75% versus 58%) with a median time of treatment initiation 4 days from symptom onset.⁷⁹ However, treatment initiated within 5 days after symptom onset was still associated with increased survival compared with no therapy.^{80,81} Similar findings were seen in children and other at-risk individuals, including immunocompromised and pregnant women.⁸² Therefore the importance of early distribution and administration of therapy, including the rapid dissemination of therapy guidelines for practitioners, must be a cornerstone of any bioterrorism response.

Additional adjunctive therapies during the H1N1 pandemic also became a cornerstone of response, including the use of extracorporeal membrane oxygenation, which was used in some patients with ARDS (predominately single organ failure) resulting from pandemic H1N1 influenza. Small observational studies suggested a mortality benefit in patients who received extracorporeal membrane oxygenation.^{83,84} However, extracorporeal membrane oxygenation is only performed at specialized centers and is resource intensive, thus requiring regional and statewide coordination in order to ensure success. Additional therapies, such as corticosteroids, inhaled nitric oxide, N-acetyl cysteine, and proning were also administered without established benefit.⁸⁵

RECOGNITION AND RESPONSE TO A BIOTERRORISM EVENT

The recognition of a case of a disease related to a bioterrorism event relies on a high index of suspicion by the clinician. However, recognition may be difficult in the early stages of disease, in that many of the category A agents

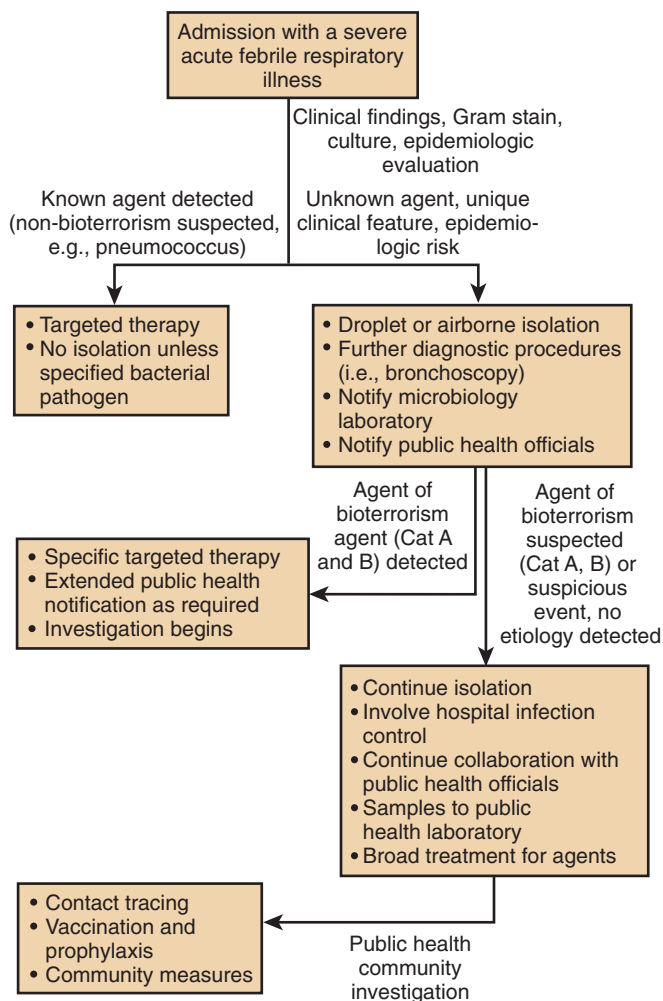


Figure 40-7 Schema of response to acute febrile illness with respiratory failure. A coordinated response to an acute febrile illness with respiratory failure is outlined involving diagnosis and treatment, respiratory precautions for hospital staff, and involvement of hospital infection control and public health officials.

present with nonspecific symptoms.⁸⁶ Figure 40-7 outlines an approach to early isolation, testing, and involvement of institutional infection control and public health officials in cases of acute febrile illness. Upon admission, cases of acute febrile illness and respiratory failure should undergo initial diagnostic testing, including pretreatment Gram stain, respiratory culture, and urine antigen testing for *Legionella*. If an etiologic agent is identified on initial screening and clinical findings (i.e., gram-positive diplococci with a lobar pneumonia on radiograph), targeted treatment should be initiated, with appropriate isolation precautions based on the pathogen. However, if an agent is not easily identified, patients should be placed in isolation and further diagnostic testing should be performed. If multiple cases with similar symptoms or a case with an uncommon epidemiologic link is determined, patients should be isolated and public health officials should be contacted. If specific clinical features subsequently arise, then directed diagnostic testing should be performed. If no clear etiology is detected, further evaluation is warranted with invasive and expanded testing.

Although bronchoscopy generates aerosols that increase the risk of transmission, bronchoscopy should be performed with appropriate protection of personnel in these cases, because identification of the etiology of illness is an essential component of an appropriate public health response. The public health authorities and the institutional infection control should be contacted as early as possible when clinical suspicion of bioterrorism arises or when diagnostic tests do not yield results.

Once a bioterrorism agent is suspected, the diagnosis is confirmed by specialized public health laboratories. Initial cases must meet a case definition for the suspected agent (see <http://emergency.cdc.gov/bioterrorism/casedef.asp>) before there is further evaluation. In order to meet the case definition, at least one critical distinguishing feature must be met along with other clinical and laboratory features.

INFECTION CONTROL

Involvement of institutional infection control, microbiology, and public health experts must be initiated as early as possible. They should be notified when there is one of four conditions: (1) a clinical or epidemiologic feature suggestive of bioterrorism (see Table 40-4), (2) an unexpected clinical link or increase in number of cases (e.g., pneumonia with respiratory failure), (3) an extensive workup of a febrile respiratory illness fails to reveal an organism and an infectious disease is suspected, or (4) transmission of disease to health care workers. Hospital infection control will assist in isolation and health care worker protection, and the hospital microbiology laboratory should be notified of suspected pathogens, allowing for worker protection and targeted testing of samples.^{1,87} Finally, public health involvement allows a broader diagnostic testing, including subtyping and resistance testing. If the agent is a novel or emerging pathogen, as seen with severe acute respiratory syndrome or avian influenza, early public health involvement allows for rapid laboratory testing, epidemiologic investigation, case definition, and community prevention.

The basic infection control requirements are outlined in Table 40-8. Anthrax and botulism are the only category A agents that are not contagious and do not require respiratory protection for caregivers. If the number of cases exceeds the health care capacity for isolation, patient cohorting and accessory isolation measures can be used. Finally, higher risk procedures should be limited in these cases (Table 40-9). Aerosol-generating procedures are most common in ICU patients, and reducing unnecessary risky procedures reduces patient and health care worker risk. However, these procedures should be performed if needed. Appropriate PPE should be worn by health care workers at all times and, if worn properly, reduces the risk of disease transmission.⁸⁸

PUBLIC HEALTH AND CRITICAL CARE RESPONSE

Acts of conventional terrorism, such as with explosive devices or chemical attacks, result in a single point of mass

Table 40-9 Respiratory Care Procedures That Carry a Higher Risk for Disease Transmission in Patients with a CDC Category A Agent

Nebulization of medication
Endotracheal intubation
Nasotracheal suctioning
Noninvasive positive-pressure ventilation
Bag-valve-mask ventilation
Bronchoscopy
Humidified oxygen delivery
Non-rebreather mask without expiratory filter

casualties with an immediate critical area response. In contrast, because some of the category A agents are spread by contact and respiratory transmission, new cases will be seen after the initial outbreak. As these cases progress, the cumulative number of cases with severe respiratory illness will increase, potentially stressing the critical care system and leading to a sustained need for *emergency mass critical care* (EMCC) for weeks to months. Sustained EMCC can lead to depletion of critical care resources, such as mechanical ventilators, specially trained staff, antibiotics and antivirals, and ICU beds.⁵ Thus, the unique issues associated with sustained EMCC have led to improved planning for a response to a bioterrorism or emerging infectious diseases outbreak.^{89,90}

Recent consensus statements have recommended special critical care preparedness to include ICU capacity expansion, critical care resource storage, and the coordination of critical care across communities to a regional and statewide level.^{89,90} Capacity for critical care should be approximately three times normal ICU capacity, with all critically ill patients to be located in acute care hospitals (less severely ill patients will be diverted to alternative sites within the community). Each hospital should have enough supplies for 10 days for each critically ill patient along with plans to have expanded care by noncritical care specialists in the case of a shortage.⁹¹ ICU admission should be limited to the most severely ill. Most importantly, establishment of a triage mechanism is required for the allocation of scarce resources in sustained EMCC, with the most identified critical resource being mechanical ventilation and medical oxygen.⁹² This triage mechanism shifts the focus of critical care from optimal care of the individual to optimal care for the population and would identify critically ill patients who may not get specific scarce resources during a period of limited supply in an outbreak. It would include inclusion and exclusion criteria for ICU admission along with a triage scoring mechanism for patient assessment. The Sequential Organ Failure Assessment score is valuable, due to its value in sequential assessments and its ease of use given its lower reliance on laboratory data. Additional triage scoring systems may be warranted in future outbreaks as disease and outbreak conditions change.

Key Points

- Bioterrorism and emerging infectious diseases present unique and different diagnostic and treatment challenges.
- Category A agents are considered the highest risk to the public and national security for the following reasons: (1) easy person-to-person spread; (2) high mortality; (3) major public health impact causing panic and social disruption; and (4) requirement for specific and specialized public health emergency response (e.g., public prophylaxis or protective equipment). Diseases caused by these agents initially present with a nonspecific prodrome that develops into severe disease with specific epidemiologic hallmarks.
- Category A agents are anthrax, smallpox, plague, tularemia, botulism, and viral hemorrhagic fevers (e.g. Ebola, Lassa).
- Category B agents are diverse but carry lower morbidity and mortality, with some having few to no pulmonary manifestations.
- Category C agents have the potential for future use as bioterrorism agents.
- Early recognition relies on the astute clinician, with early involvement of public health and institutional infection control personnel to reduce spread to health care workers and the community.
- Aggressive supportive care is the mainstay for all critically ill patients infected with a bioterrorism agent. Targeted therapy is under development.
- For inhalational anthrax, raxibacumab, a human IgG1 monoclonal antibody directed against *B. anthracis* protective antigen, has been approved for use and should be used in combination with antibiotics when

the diagnosis of inhalation anthrax is suspected or confirmed.

- During an outbreak of a category A agent, emergency mass critical care for a sustained period may be required, leading to depletion of critical patient care resources. With emergency mass critical care, the focus of critical care shifts from optimal care of the individual to optimal care for the population. Predictive mortality scores are recommended for appropriate triage of the critically ill.

Complete reference list available at *ExpertConsult*.

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OBSTRUCTIVE DISEASES

41

ASTHMA: PATHOGENESIS AND PHENOTYPES

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INTRODUCTION

Asthma is a common disease whose prevalence has increased throughout the world for several decades. For many years the major focus of asthma investigations and treatment was on allergic mechanisms. More recently, studies of the epidemiology, natural history, and pathogenesis have clearly demonstrated that asthma is a heterogeneous disease, with multiple etiologies and contributing cofactors, complex pathobiologic mechanisms, and different molecular phenotypes. Understanding these differences is critical for developing therapeutic strategies that will be effective for the various phenotypes of asthma.

EPIDEMIOLOGY

Asthma is common and its prevalence has been steadily increasing over time. In the United States, the prevalence and severity of asthma are highest in certain vulnerable populations including children, people living below the

poverty level, and specific minority groups (Puerto Ricans and black, non-Hispanic Americans). Although a family history of allergy is the strongest risk factor for asthma, early life infections are important cofactors in at least two ways. On one hand, the increasing prevalence of asthma may relate to the success of domestic hygiene in reducing the rate of exposure to bacterial products or changing the commensal microbiome in early childhood, which would otherwise consolidate antibacterial rather than allergic immune responses. On the other hand, viral respiratory infections in early childhood are thought to increase the risk for wheezing illnesses and asthma over time. A range of other exposures have been identified as risk factors for asthma, including intrauterine exposures, prematurity, breastfeeding, diet (especially vitamin intake), stress, exposure to other children, obesity, air pollution, antibiotic use, acetaminophen use, and occupational exposures. Ultimately, the natural history of asthma is heterogeneous; however, certain general patterns are common and the type of asthma that predominates in those who have their onset in childhood, teen years, and adult years may differ.

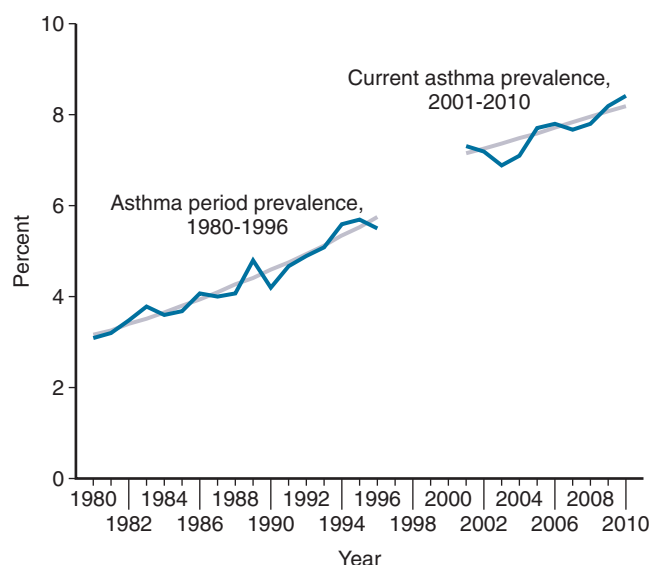


Figure 41-1 Prevalence of current asthma in the United States. Data are based on the National Health Interview Survey over two periods that used different case definitions (1980-1996 and 2001-2010). Percentages are age adjusted to the 2000 population. Blue lines connect actual data estimates, and gray lines show a modeled trend estimate. The prevalence of asthma in the United States has increased over both time periods. (From Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001–2010. *Vital Health Stat* 3 Nov(35), 1–67, 2012.)

METHODS

For studies of the epidemiology of asthma, definition of asthma remains a critical issue. Options for case definition by questionnaire include assessment of asthma symptoms, use of asthma medications, self-report of asthma, and report of physician-diagnosed asthma. These questionnaire data may be complemented by lung function testing or measurement of bronchial hyperresponsiveness.¹ In general, self-report of asthma symptoms yields higher prevalence estimates than report of asthma diagnosis.

PREVALENCE

In the United States, the overall prevalence of asthma has risen inexorably between 1980 and 2011, even after accounting for changes in the definition of current asthma in *National Health Interview Survey* (NHIS) questionnaires (Fig. 41-1). Since 2001 the estimate of asthma prevalence has been based on the following questions, “Have you ever been told by a doctor or other health professional that you had asthma?” to estimate lifetime prevalence and then “Do you still have asthma?” to estimate current prevalence. In 2012, overall lifetime prevalence of asthma was 13.0% and current prevalence of asthma was 8.3%.^{1a}

In addition to being a common diagnosis across the entire U.S. population, there are marked and persistent differences in asthma prevalence across specific subgroups of the U.S. population, making asthma extremely common in certain vulnerable populations (Fig. 41-2). In 2012, current asthma prevalence was very high in black non-Hispanics (11.9%), those of Puerto Rican heritage (18.8%), and among those living below the poverty threshold (12.4%).

Current Asthma Prevalence in 2012 NHIS Data (Percent of US population)

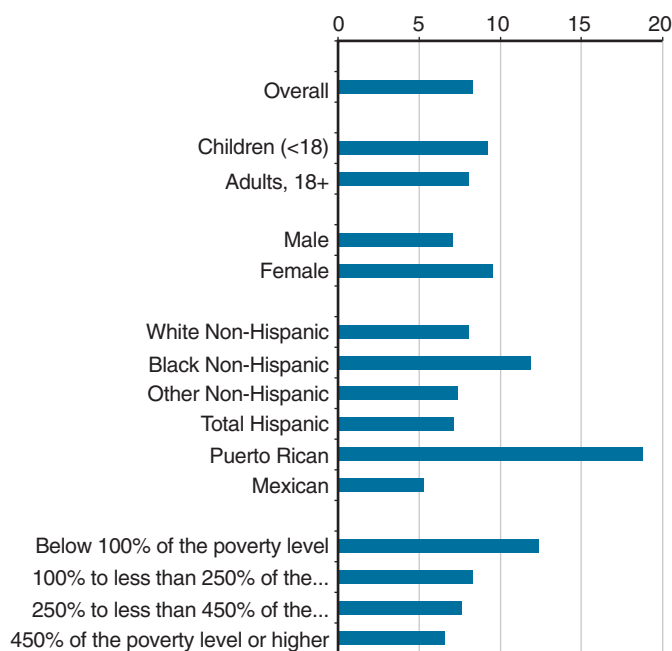


Figure 41-2 Current asthma prevalence in the United States by age, gender, ethnic group, and income. Asthma prevalence is shown as a percentage of the U.S. population for different groups. Asthma prevalence is highest in certain vulnerable populations including children, Puerto Ricans, non-Hispanic blacks, and those living below the poverty level. (Data from the 2012 National Health Interview Survey as compiled by the Centers for Disease Control and Prevention on 3/5/2014 and posted at <http://www.cdc.gov/asthma/nhis/2012/table4-1.htm>.)

Current asthma prevalence also was higher among children (9.3%) than adults (8.0%) and among females (9.5%) than males (7.0%) overall, although the female-to-male balance changes over development with asthma less common in females than males during childhood (age younger than 18, 8.6% vs. 10%, respectively) but more common in females than males during adulthood (age 18 or older, 9.8% vs. 6%, respectively). These imbalances in prevalence among males and females, adults and children, ethnic groups, and poverty levels have not changed since 2001.

Internationally, the prevalence of asthma varies dramatically, with particularly high rates in specific, developed countries including the United Kingdom, New Zealand, Australia, the United States, and Canada (Fig. 41-3). Furthermore, as in the United States, the international prevalence is increasing over time.² Two large multinational studies have systematically assessed the worldwide prevalence of asthma in adults³ and children.⁴ The *International Study of Asthma and Allergies in Childhood* (ISAAC) study used a physician diagnosis and the presence of asthma-like symptoms in a validated questionnaire. In its first iteration, ISAAC Phase I studied 156 centers in 56 countries cross-sectionally during the period 1992-1996.^{5,6} This study confirmed the great variability in asthma prevalence that was inferred from the smaller studies that preceded it, with more than a 20-fold difference in prevalence between centers. However, it also found that some low- and middle-income

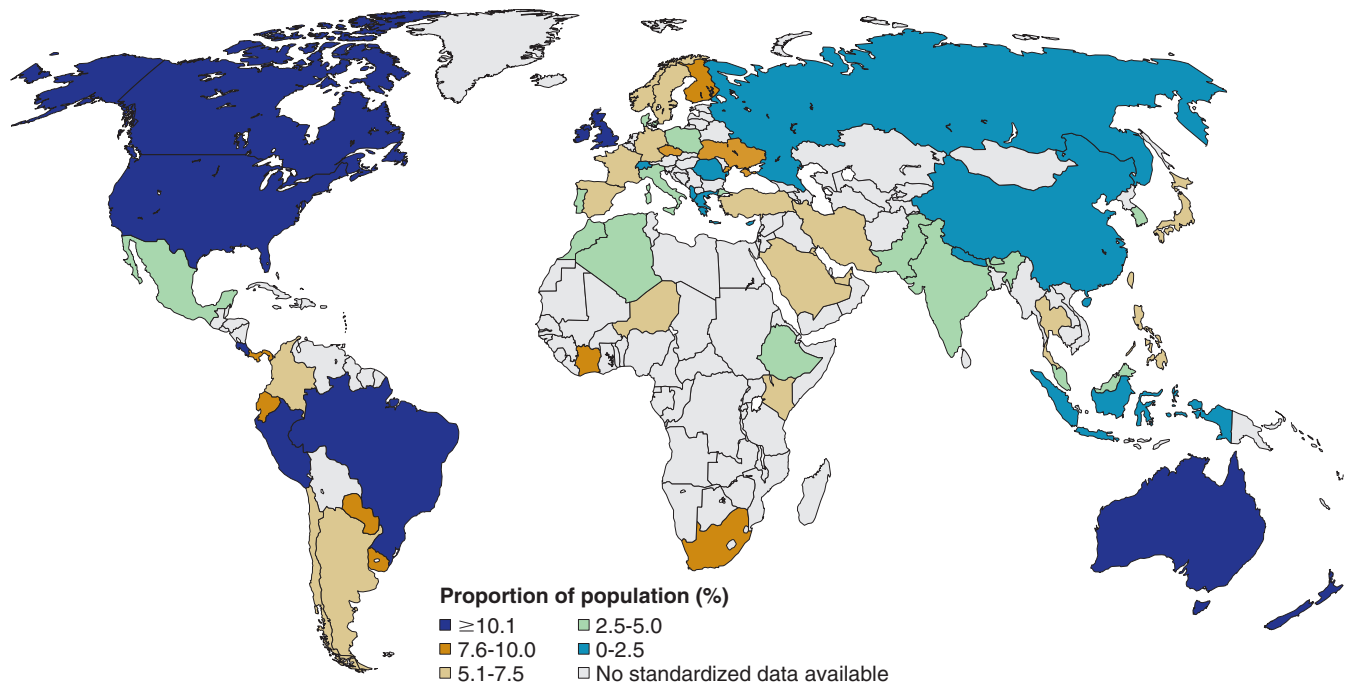


Figure 41-3 Estimated worldwide prevalence of clinical asthma. Prevalence data are estimates reflecting 50% of the prevalence of wheezing symptoms over a 12-month period in children from a range of studies, based on data on the relationship between wheezing symptoms and clinical asthma from other studies. (From Masoli M, Fabian D, Holt S, Beasley R: The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 59(5):469–478, 2004.)

countries had a prevalence of asthma symptoms that was similar to those in Western, developed countries. Thus the geographic trends are not absolute. ISAAC confirmed the overall increase in asthma prevalence on repeated evaluation from its Phase I period (1992-1996) to its Phase III period (2000-2003). However, these time trends in asthma symptom prevalence showed different regional patterns.⁷ With the exception of India, all of the countries with very low symptom prevalence rates at first evaluation reported increases in prevalence. However, in English-language developed countries, in which asthma prevalence was already high, there was little further increase. The *European Community Respiratory Health Survey* (ECRHS) used a questionnaire with seven questions relating to the 12-month prevalence of symptoms of asthma and studied representative samples of 20- to 44-year-old men and women in 48 centers, predominantly in Western Europe.⁸ Although the ECRHS included data from fewer countries than ISAAC and did not distill the broader set of questions into simple overall prevalence data, there was relatively good agreement between ISAAC and the ECRHS with respect to the prevalence of asthma symptoms across the 17 countries that both studies sampled.⁹

MORTALITY

Death from asthma was once thought to be so uncommon as to prompt Osler's adage that "the asthmatic pants into old age"¹⁰; nonetheless, data from the World Health Organization suggest there are 250,000 asthma-related deaths each year worldwide.¹¹ Although asthma mortality has historically increased in parallel with asthma prevalence in

many countries, the countries with the highest rates of death in the WHO report were not necessarily those with the highest prevalences, suggesting that poor access to care and essential medications are additional contributing factors to mortality. In specific instances, certain medications have also been suspected of contributing to asthma mortality. The event that initially attracted attention to asthma mortality was a dramatic, abrupt increase in asthma deaths in the 1960s, especially in the British Isles, Australia, New Zealand, and Norway.¹² In these countries, asthma mortality increased twofold to tenfold in less than 5 years. This increase was attributed to use of a high-dose preparation of a highly potent, nonselective inhaled β -agonist, isoproterenol, and mortality fell following the preparation's withdrawal. A second, even more dramatic increase in asthma mortality in New Zealand in the 1970s was again attributed to sales of a unique β -agonist, fenoterol.¹³

In the United States, asthma mortality has been assessed over time using the Mortality Component of the National Vital Statistics System. These data indicate an increase in asthma mortality from 14.4 per 1 million population in 1980 to 21.9 per 1 million in 1995.¹⁴ Since 1995, asthma mortality in the United States appears to have decreased to 17.2 per 1 million persons in 1999,¹⁴ and decreased further to 15 per 1 million persons in 2009.^{15a} However, as is true for asthma prevalence, asthma mortality disproportionately affects black Americans (38.7 per 1 million persons in 1999)¹⁴ and those of Puerto Rican heritage (40.1 per 1 million).¹⁵ It is not known whether high mortality among black and Puerto Rican Americans relates solely to societal factors, such as access to health care, insurance coverage, and access to medication or asthma education, or whether

specific environmental or genetic influences differentially affect these ethnic groups.

RISK FACTORS

Allergy

The strongest risk factor for asthma is a family history of atopy.^{16,17} This increases the risk of developing allergic rhinitis by fivefold and the risk of asthma by threefold to fourfold.¹⁸ In children 3 to 14 years old, both positive skin tests and increases in total serum IgE are strongly associated with asthma.^{19,20} Serum IgE also correlates strongly with bronchial hyperresponsiveness.²¹ In adults, the odds of having asthma increase with the number of positive skin tests to common allergens.²²

Because much allergic asthma is associated with sensitivity to allergens of the indoor environment and because Western styles of housing favor greater exposure to indoor allergens, initial attention focused on increased exposure to these allergens in infancy and early childhood as a primary cause of the rise in asthma. Specific allergens of interest have included house dust mite,^{23,24} dog and cat dander,²⁵ and cockroach allergen,²⁶ especially in the inner city. These and other observations strongly support the conclusion that allergen controls should be valuable in the treatment or prevention of asthma.^{27,28} However, even after more than 50 individual studies of allergen control, the conclusions drawn from those studies via meta-analyses and expert review have been at odds and hotly debated.^{29,30}

“Hygiene Hypothesis.” One compelling hypothesis for the cause of the increase in asthma and allergies in Westernized countries is the “hygiene hypothesis.” This holds that the rise in allergies in children is an unintended consequence of the success of domestic hygiene in reducing the rate of infections or exposure to bacterial products in early childhood. This hypothesis was put forward to explain the inverse relationship between hay fever and family size.³¹ The hypothesis was cited later when children raised in West Germany were found to have significantly higher rates of asthma and hay fever than did those raised in communist East Germany³² despite its more severe pollution from heavy industrialization and coal burning.³³ In these studies, children who lived on farms had a lower prevalence of hay fever and asthma than their peers who did not live in an agricultural environment. The reduction in risk was stronger for children whose families were running the farm on a full-time basis, and stronger yet if the farm included livestock.^{34,35} Factors related to environmental influences, such as increased exposure to bacterial compounds in stables, may prevent the development of allergic disorders in children. Continual long-term exposure to stables until age 5 was associated with very low rates of asthma (0.8%), hay fever (0.8%), and atopic sensitization (8.2%).³⁶ Follow-up studies of the protective effects of farm life have yielded fascinating findings. One study showed that endotoxin levels in samples of dust from the children’s homes, regarded as a marker of environmental exposure to microbial products, were inversely related to the presence of hay fever, atopic asthma, and atopic sensitization.³⁷ Another study employing two cohorts found that children who lived on

farms had lower prevalences of asthma and atopy and were exposed to a greater variety of environmental microorganisms than the children in the reference groups and that the diversity of microbial exposure was inversely related to the risk of asthma.³⁸

Human Microbiome

One potential link between changes in hygiene and allergic disease is the effect that “improved” hygiene may have on our indigenous microbiota and the role this microbiota may play in shaping our immune system.^{39–43} The biologic model most commonly cited to explain this association is that early-life exposure to factors that promote Th1 immunity are necessary to blunt exuberant *type 2 T helper* (Th2) immunity. Animal studies provide some support for this model.^{44–52} However, the results of human trials designed to treat or prevent asthma and allergy through “probiotic” live bacteria administration have thus far been mixed.^{53–55} Thus additional studies will be required to determine whether clinically relevant interventions that leverage the proposed role of the human microbiome in shaping allergic responses can be fashioned.

Respiratory Viral Infections

In parallel with, and distinct from, the emergence of the “Hygiene Hypothesis,” there has been significant progress in documenting and understanding the role that viral respiratory tract infections play in the development of asthma. A population-based study reported that a history of bronchiolitis or croup in early childhood was a predictor of increased bronchial responsiveness and of atopy in later years.⁵⁶ In a prospective, longitudinal study of children born to allergic parents, *upper respiratory infections* (URIs) were noted 1 to 2 months before the onset of allergic sensitization.⁵⁷ Children who have *lower respiratory tract infections* (LRI) caused by *respiratory syncytial virus* (RSV) are at a threefold to fourfold risk of subsequent wheezing during the early school years.^{58–61} Surprisingly, the presence of rhinovirus during wheezing episodes is an even stronger predictor of subsequent asthma.^{62,63} In some studies, the association between viral LRIs and subsequent asthma depends on concurrent atopic disease, suggesting that an interaction between atopic predisposition and LRI at an early developmental stage may be critically important.⁶²

One factor that complicates the relationship between early wheezing with LRIs and the risk of subsequent asthma is that longitudinal studies of the natural history of wheezing illnesses have identified inconsistent relationships between early wheezing phenotypes and the ultimate development of asthma. The natural history of asthma is discussed in more detail in the next section of this chapter, but, briefly, some children who have wheezing illnesses before age 3 continue to wheeze at age 6. However, not all children fit this “persistent-wheezing” pattern. Similarly, there are children who wheeze at age 6 who never had wheezing illnesses before age 3. Thus a propensity for wheezing can be transient and the causes may be different at different ages. For example, factors associated with wheezing before age 3 include small airway caliber and maternal smoking, whereas factors associated with wheezing after age 3 include elevated serum IgE and a maternal history of asthma.⁶⁴ Furthermore, it is possible that viral LRIs do not

induce asthma but rather unmask a predisposition to predominant Th2-like responses already present at the time of the infection⁶⁵ and which manifest later as asthma. The recent availability of specific therapies for the treatment and prevention of RSV infection in early childhood may provide the tools for future studies to test whether viral LRIs actually cause persistent wheezing and asthma.⁶⁶

Atypical Bacterial Infections

Although typical bacterial infections are not thought to cause asthma, at least two bacterial causes of “atypical” pneumonia have been implicated in the development of chronic wheezing illnesses, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Both commonly infect the airway epithelium, can become chronic, and stimulate local inflammatory reactions. There is some *polymerase chain reaction* (PCR) evidence that *M. pneumoniae* or *C. pneumoniae* is more common in the airway of patients with chronic stable asthma compared with healthy controls and that their presence is associated with an increase in tissue mast cells.⁶⁷ Other studies have found that these atypical infections are associated with asthma exacerbations.⁶⁸ Both organisms are sensitive to macrolide antibiotics, and several studies have evaluated the utility of macrolides in patients with chronic asthma with variable results. A randomized trial of clarithromycin for the treatment of suboptimally controlled asthma showed no improvement in asthma control, whether or not *M. pneumoniae* or *C. pneumoniae* was detected by PCR in endobronchial biopsies.⁶⁹ Another study showed that azithromycin did not reduce exacerbations overall in severe asthma, but a prespecified subgroup analysis showed improvement in the group with noneosinophilic asthma by sputum analysis.⁷⁰ This result leaves open the question as to whether any beneficial effect of macrolides is mediated by antibacterial or anti-inflammatory activity of these drugs.

Air Pollution

Although it is widely accepted that air pollution can exacerbate preexisting asthma,^{71,72} it has been more difficult to demonstrate that air pollution can contribute to the development of asthma. In principle, exposure of the lung to air pollution could increase local oxidative stress, induce or modify local inflammation, enhance sensitization to allergens, impair lung development, or injure small airways. However, epidemiologic evidence for an association between ambient levels of air pollutants and prevalent or incident asthma has yielded mixed results.⁷³ Nonetheless, several recent studies focused specifically on asthma incidence and prevalence by proximity to heavy automobile traffic and suggested that exposure to respirable particulate matter and NO₂ in this setting are both associated with the future development of asthma.^{72,74-79}

Other Early-Life Factors

Other early-life factors that influence the risk of asthma are exposures in utero, perinatally and in early childhood. Intrauterine risk factors include growth rates (both high and low),^{80,81} dietary vitamins D and E deficiency,^{82,83} exposure to microbial products,⁸⁴ parental smoking,⁸⁵ and parental stress.⁸⁶ Perinatal risk factors associated with asthma include prematurity⁸⁷ and chorioamnionitis.⁸⁸

Finally, early childhood risk factors associated with asthma include a shorter period of breastfeeding,^{89,90} obesity,⁸⁰ absence of older siblings or daycare attendance,⁹¹ bacterial colonization of the airways in early childhood,⁹² antibiotic use,⁹³ and acetaminophen use.⁹⁴

Occupational Exposures

Finally, occupational exposures constitute an important risk factor for a specific subset of patients. Asthma induced by occupational exposures accounts for up to 17% of all adult-onset asthma.⁹⁵ A full description of the occupational exposures that can cause asthma is beyond the scope of this chapter because the known exposures number in the hundreds. However, in general, occupational asthma can either result from immunologically mediated sensitization to occupational agents (i.e., sensitizer-induced occupational asthma) or from exposure to high concentrations of irritant compounds (i.e., irritant-induced occupational asthma) (see Chapter 72).

NATURAL HISTORY

The natural history of asthma is heterogeneous with different patients following different disease courses. In general, symptoms can begin at any age, although the type of asthma that predominates in those who have their onset in childhood, teen years, and adult years may differ. Over time, the symptoms of asthma can remit in any given patient, especially in childhood. Alternatively, the symptoms and the finding of airflow obstruction can persist or even worsen progressively in some patients. Other patients can be apparently well at most times but suffer from periodic worsening or exacerbations. From a population-based perspective, a relatively small but important subgroup of patients with asthma can suffer significant morbidity and some are at risk for dying from asthma.

Neonatal Period

A predisposition to asthma may begin as early as the neonatal period. The immunologic milieu at the fetal-maternal interface is skewed toward a Th2 phenotype, and this immune bias is carried into neonatal life.⁹⁶ Unless the pattern of immune response in the airways is “re-programmed” toward a Th1 pattern, the infant may have a prolonged high-risk window for allergic sensitization to aeroallergens.⁹⁷

Childhood

Patterns of wheezing in early childhood have been intensively studied in longitudinal cohorts.^{64,98} The Tucson Children’s Respiratory Health Study⁶⁴ found that 48% of children had at least one wheezing illness at some point in the first 6 years of life, 34% had at least one wheezing illness before age 3 (defined as early wheezing), and approximately half of these children continued to have at least one wheezing illness at age 6. In the remainder of children with wheezing episodes before age 3, these episodes were transient and resolved before age 6. Finally, approximately 15% of children presented with late-onset wheezing, defined as wheezing illnesses with onset at age 6. As described earlier, most of the early wheezing illnesses (before age 3) can be ascribed to viral respiratory infections such as RSV

or rhinovirus and do not necessarily reflect atopy.⁹⁹ In addition, transient early wheeze was associated with maternal smoking. However, wheezing at age 6, whether “persistent” or “late-onset,” was associated with atopy. Furthermore, children who had either “persistent” or “late-onset” wheezing at age 6 were more likely to go on to wheeze later in life and be diagnosed with asthma. The risk for persistence rather than remission after age 6 appears to be associated with severity of airflow obstruction and the degree of allergen sensitization.¹⁰⁰ The British Avon Longitudinal Study of Parents and Children provided some additional detail to the categories of childhood wheezing illnesses by defining “intermediate-onset wheeze” (defined as onset of symptoms after 18 months) and “early prolonged wheeze” (defined as onset in the first year of life but remission at 69 months).⁹⁸

Atopic or Allergic March

The terms “atopic march” and “allergic march” are synonyms that refer to a characteristic pattern of atopic disease development during infancy and childhood.^{101,102} The most common pattern begins with atopic dermatitis or eczema in the first year of life, sometimes associated with food intolerance or food allergy, followed by rhinoconjunctivitis, and/or wheezing illnesses that are ultimately diagnosed as asthma. Thus the natural history of atopic disease, more generally, may follow a specific pattern of organ-specific development, which suggests a stereotyped set of underlying cellular and molecular mechanisms.¹⁰³

Teenage Years

After puberty, the demographics of patients with prevalent asthma switches from a male predominance to a female predominance, which suggests a change in the nature of incident cases of asthma. One straightforward inference would be that some incident cases of asthma in girls during teenage years relate specifically to hormonal factors. This is a compelling hypothesis and there are some data that provide clues to potential mechanisms,¹⁰⁴⁻¹⁰⁶ but specific hypotheses are difficult to test and establish in clinical studies. Nonetheless, these observations invite speculation that the onset of asthma in specific phases of life may reflect different underlying biologic underpinning or different endotypes of asthma.

Remission

Long-term follow-up of a population-based birth cohort of more than 1000 children born in Dunedin, New Zealand over a 12-month period in 1972-1973 who were evaluated annually to age 26 has provided a clear picture of the natural history of the disease.¹⁰⁷ Just over half the children (51%) reported wheezing at more than one assessment, confirming the high prevalence of asthma in New Zealand. Wheezing persisted until adulthood in 15%, whereas wheezing appeared and remitted in 27%. This remission was often unsustained, however, for wheezing recurred by age 26 in nearly half of those in whom it had remitted. This finding echoes the findings of 15 earlier studies of the natural history of asthma, showing that about 50% of adults who recall having childhood asthma continue to have symptoms.¹⁰⁸ Risk factors associated with greater likelihood of persistence of asthma into adulthood include sensitization to house dust mites, lower FEV₁, airway hyper-

responsiveness, female gender, and smoking at the age of 21 years.¹⁰⁷ Whether “spontaneous remission” truly reflects disappearance of the eosinophilic, lymphocytic bronchial inflammation of asthma has been questioned. Even in patients with complete absence of symptoms while taking no asthma medications for at least 12 months, the fraction of nitric oxide in exhaled gas is elevated, airway responsiveness is increased, and bronchial biopsies show increases in eosinophils, T cells, mast cells, and increased subepithelial fibrosis.^{109,110}

Progressive Airflow Obstruction

Longitudinal studies have shown that people with asthma have greater rates of decline in pulmonary function than healthy nonsmokers, and asthmatic smokers have greater rates of decline than healthy smokers.^{111,112} Furthermore, many nonsmoking asthmatics have severe, irreversible airflow obstruction.^{113,114} The progressive narrowing of the airways in chronic asthma is hypothesized to result from the deposition of collagen and growth of vessels, smooth muscle, secretory cells, and glands, presumably mediated by the products of inflammatory cells activated in the airways.^{115,116} Nonetheless, it is not possible to prove that this “airway remodeling” is the cause of progressive airflow obstruction in asthma.

Adulthood

Because many adults with chronic asthma had the onset of symptoms during childhood,¹¹⁷⁻¹¹⁹ understanding the biologic events underlying the development and the prevention of asthma during childhood will likely make a significant impact on the prevalence of asthma in adults as well. However, even though many adults with asthma had asthma during childhood, adult asthma is particularly heterogeneous. The female predominance in asthma prevalence that first appears in teenage years continues in adult asthma, suggesting that a significant proportion of adults with asthma share the common underlying factors of teenage-onset asthma. Finally, asthma symptoms can begin *de novo* in an adult. Some of these patients have clear-cut atopy, but others have more predominantly nonatopic features. In some instances, the onset of wheezing is attributed to a specific acute respiratory illness that became persistent. In others, it is possible that atopy and wheezing illnesses as a child were modest and subclinical.

Asthma in the Elderly

If asthma is present in an adult, it will often remain as that adult ages. Surprisingly, new-onset asthma can also arise in the elderly. One retrospective cohort study of residents of Rochester, Minnesota reported that the incidence of new-onset asthma after age 65 was 95/100,000.¹²⁰ In this age group, misdiagnosis of asthma (often as COPD) and undertreatment appear to be common.^{121,122} Furthermore, elderly patients with asthma are more likely than younger patients to have fixed airflow obstruction.¹²³ Mortality rates from asthma appear to be higher in the elderly because NHIS data from 2001-2003 indicate that the age-adjusted rate of mortality was 10.5 per 100,000 among people older than 65. All other adult age groups had asthma-specific mortality rates less than 2.2 per 100,000.¹²⁴ However, these NHIS data appear to contrast with those of the

Rochester, Minnesota retrospective cohort study described earlier, which found no difference in mortality between elderly patients with asthma and similarly aged historical control subjects.¹²⁰ The term “intrinsic asthma,” often used to describe nonatopic reversible bronchoconstriction, has traditionally been associated with asthma in the elderly,¹²⁵ and more than 60% of elderly patients in one study reported the first onset of asthma symptoms following a URI.¹²⁰ However, at least one study has shown positive skin reactivity to one or more common allergens in almost two thirds of elderly asthmatic patients.¹²⁶

MOLECULAR AND CELLULAR BASIS OF ASTHMA

Type 2 immune responses in the lower airway are the central immunologic abnormality in asthma. Type 1 and type 2 immune responses differ in how they are induced and by the types of effector cells and molecules they employ.¹²⁷ For example, type 1 immune responses are mounted against intracellular bacteria, viruses, and protozoa and are mediated by Th1 CD4⁺ cells, cytotoxic CD8⁺ T cells, and IgG antibodies. Type 1 responses can also be inappropriately mounted against self-antigens, and this is one mechanism of autoimmune disease. In contrast, type 2 immune responses usually arise in response to helminth and parasite infections and are mediated by Th2 CD4⁺ cells and IgE. Type 2 responses can also be inappropriately mounted against innocuous environmental antigens resulting in allergy. Th2 CD4⁺ cells are characterized by high expression of the transacting T-cell-specific transcription factor GATA-3 and by secretion of type 2 cytokines (*interleukin* [IL]-4, IL-5, IL-9, and IL-13).¹²⁸ An excess of type 2 cytokines in the lower airway will promote IgE-mediated hypersensitivity, activate epithelial cells, mediate inflammatory cell influx to the airway, and cause remodeling responses in the epithelium and subepithelial matrix.^{129,130} This cascade of inflammatory events downstream of type 2 cytokines explains much of the pathology underlying the key clinical features of asthma (airway hyperresponsiveness, airflow obstruction, and mucus secretion).

INITIATION OF ALLERGIC LOWER AIRWAY RESPONSES AND ASTHMA

An accepted view now is that environmental stimuli in early childhood activate airway epithelial cells to initiate allergic airway responses and asthma in children who are susceptible because they have preexisting atopy, specific genetic risk factors, and other less well-understood vulnerabilities. How atopy and viral airway infections interact to initiate type 2 immune responses is incompletely understood. It has been postulated that communication between cells in the airway epithelium and cells in the underlying mesenchyme/submucosa is a fundamental mechanism of asthma.^{131,132} (Fig. 41-4). Environmental stimuli that can activate epithelial cells include oxidants (cigarette smoke, car exhaust pollutants), aeroallergens, and microbial infections, especially viruses. Airway epithelial cells express multiple pattern recognition receptors to detect and respond

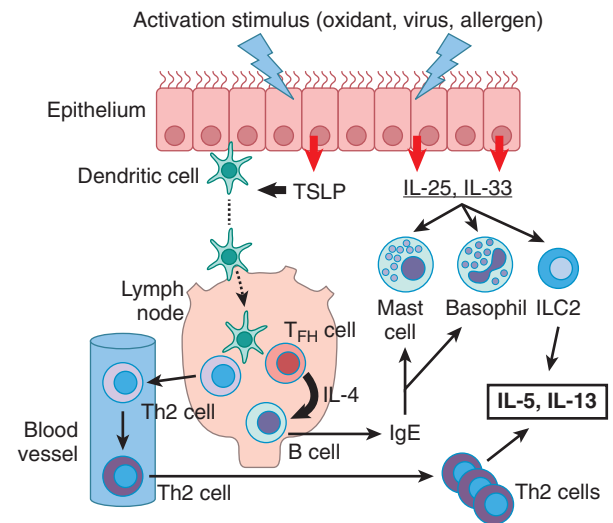


Figure 41-4 Generation of Type 2 immune responses in the lower airway. The airway epithelium is activated to release thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. TSLP mediates maturation and migration of dendritic cells to local lymph nodes, where they have the following effects: (1) generation of Th2 cells from Th0 cells; (2) generation of IL-4-secreting T_H cells; and (3) B cell isotype-switching to IgE, which arms mast cells and basophils for allergen-specific activation. IL-33 promotes IL-4 release from basophils, and IL-25 and IL-33 promote IL-5 and IL-13 release from innate lymphoid type 2 (ILC2) cells and Th2 cells (see text for details). T_H, T follicular helper cells. (From Locksley RM: Asthma and allergic inflammation. *Cell* 140(6):777–783, 2010.)

to danger signals, such as *pathogen-associated molecular patterns* (“PAMPs”) on microbes or *damage-associated molecular patterns* (“DAMPs”) released by endogenous cells during periods of inflammation or cellular stress. Other pattern recognition receptors on airway epithelial cells include *Toll-like receptors* (TLRs) and receptors for *alarmins*, such as uric acid and adenosine triphosphate, which are endogenous molecules that signal damage. Activation of pattern recognition receptors on airway epithelial cells can trigger release of a variety of cytokines, chemokines, antimicrobial peptides, lipid mediators, nitric oxide, and reactive oxygen species. These inflammatory mediators have multiple consequences, including recruitment of circulating leukocytes to the airway, regulation of airway tone, regulation of airway secretions, and promotion of antimicrobial and antiviral activity. The release of epithelial cytokines, particularly IL-25, IL-33, and *thymic stromal lymphopoietin* (TSLP), appears to be the key upstream event that initiates type 2 immune responses and the allergic inflammatory environment in asthma.^{128,133} Specifically, IL-25, IL-33, and TSLP released from epithelial cells by allergenic stimuli target resident hematopoietic cells to induce the influx of inflammatory cells and the activation and mobilization of dendritic cells. Dendritic cells are specialized immune cells that use the class 2 *major histocompatibility complex* (MHC) system to mediate T helper cell responses to foreign proteins such as aeroallergens.¹³⁴ Dendritic cells are required for the differentiation of naive T cells into T helper subsets including Th2 cells. Immature dendritic cells from the bone marrow home to the airway under the influence of epithelial cell signals. Once in the airway mucosa, dendritic cell projections interdigitate between epithelial cells and form tight junctions with them,

maintaining the integrity of the epithelial barrier. In this location, dendritic cells sample inhaled antigens, process them to linear peptides, and present them on their cell surface as part of the class II MHC heterodimer complex. Epithelial cytokines, especially TSLP, promote mobilization of dendritic cells to local draining lymph nodes, where they activate naive CD4⁺ T cells to an IL-4-competent state. These IL-4-competent T cells in lymph nodes migrate to B-cell zones, where they differentiate into *T follicular helper* (T_{FH}) cells. In addition, they move to the circulation to complete maturation as Th2 cells (see Fig. 41-4).¹²⁸ Whereas IL-4-secreting developing T_{FH} cells in parafollicular B-cell areas and germinal centers mediate IgE switching in B cells, Th2 cells that migrate to the airway epithelium and the subepithelial mucosa secrete IL-5 and IL-13 to mediate the characteristic pathologic features of asthma, including eosinophilic inflammation and remodeling changes in the epithelium and submucosa.¹³⁰

The aeroallergens of relevance to asthma such as pollens, house dust mite proteins, and proteins from furred animals are considered innocuous and should induce immune tolerance when inhaled. The breach in tolerance that takes place in asthmatic airways is incompletely understood. Some aeroallergens have physical properties that allow them to be aerosolized and reach conducting airways. Some also have protease activity that equips them to penetrate airway mucus barriers. Still others have molecular mimicry properties that trigger innate pattern recognition receptors on airway epithelial cells and other antigen-presenting cells. For example, house dust mite allergens have a papain-like cysteine protease and a lipid-binding MD-2 molecular mimetic capable of augmenting TLR4 signaling,¹³⁵ while many other allergens contain chitin, which induces a leukotriene-mediated infiltrate of eosinophils and basophils and drives alternative activation of macrophages.¹³⁶

Breach in tolerance may also involve cooperative pathologic behavior between epithelial cells and dendritic cells. In mouse models, dendritic cells do not always recognize inhaled allergens. Rather, activated epithelial cells use a pattern recognition molecule such as TLR4 to sample allergens such as house dust mite protein and then orchestrate dendritic cell responses (recruitment, activation, lymph node migration) that lead to sensitization.¹³³ These findings provide a framework for how an environmental stimulus might direct epithelial and dendritic cell responses in the airway toward allergic responses. Normal tolerance in the airway may also be breached because *T regulatory cell* (Treg) function is compromised. Tregs may induce peripheral tolerance to allergens through direct interactions with dendritic cells or competition with naive T cells for growth and differentiation factors.¹³⁷ Another possible mechanism is that Tregs characteristically secrete IL-10 and *transforming growth factor* (TGF)- β , cytokines that have multiple activities relevant to tolerance, including synthesis of noninflammatory IgG4 and IgA isotypes and regulatory effects on T cells and dendritic cells. Although specific evidence for Treg cell dysfunction in asthma is lacking, the central role of Treg cells in controlling immune responses is well recognized in human disease.¹³⁸

Viral infections are among the most important of the environmental stimuli that are implicated in asthma initiation. Airway epithelial cells are considered active sentinels

and master coordinators of antiviral responses in the lung. Airway epithelial cells are primed to produce *interferon* (IFN) and express hundreds of *IFN-stimulated genes* (ISGs) in response to viral infection. STAT1 is a key regulator of ISG expression, and ISGs encode proteins that inhibit viral production directly or indirectly by activating immune cells and killing infected host cells.¹³⁹ Because the functional level of antiviral responses correlates with the degree of host protection, it is possible that a deficiency of IFN makes some people susceptible to virus-initiated or virus-exacerbated asthma. Data from mouse models suggest that a deficiency of IFN signaling in airway epithelial cells compromises host defense against respiratory viruses,^{139,140} and data from these models and epidemiologic studies show that more severe viral infections are more likely to lead to asthma.¹⁴¹ Although some studies have shown a deficiency in IFN- β and IFN- λ production in response to rhinovirus infection in asthmatic airway epithelial cells,^{142,143} it is not yet established that a defect in IFN-dependent control of viral replication is a mechanism of asthma initiation or exacerbation.^{139,144}

ATOPY, ASTHMA, AND OTHER ALLERGIC DISEASES

Studies of the childhood origins of asthma reveal a sequence in which atopy arises first, followed by viral airway infections and then the onset of asthma.¹⁴⁵ Atopic illnesses in childhood include allergic rhinitis, atopic dermatitis, eosinophilic esophagitis, and asthma. Many children only develop one of these atopic diseases, which raises the possibility that atopy represents one hit along a multihit continuum with different hits resulting in different atopic diseases. For example, atopy combined with filaggrin mutations may be required to cause atopic eczema. In this instance, filaggrin dysfunction may alter the skin epithelial barrier in ways that promote eczema.¹⁴⁶ Atopy combined with mutations in TSLP may cause eosinophilic esophagitis. In this instance, TSLP dysfunction in esophageal epithelial cells may interact with T cells, basophils, or innate lymphoid cells to initiate eosinophilic esophageal disease.¹⁴⁷ Whereas genetic studies clearly point to mutations in the filaggrin and TSLP genes as susceptibility factors for eczema and eosinophilic esophagitis, respectively, the genetic pointers in asthma are toward IL-33 and its receptor (ST2, suppression of tumorigenicity 2).¹⁴⁸⁻¹⁵⁰ Thus atopy may be the core pathologic abnormality in a variety of allergic diseases, but each of these atopic diseases may require an additional and specific genetic susceptibility to confer organ-specific risk of disease.

IL-33/ST2 AXIS IN ASTHMA

IL-33 is an epithelial cell cytokine that is considered a key mediator of type 2 immune responses in asthma.¹⁵¹⁻¹⁵³ IL-33 is classified as a member of the IL-1 family of cytokines because it has an IL-1–type cytokine-signaling domain in its C terminal region.^{154,155} Unlike other members of the IL-1 cytokine family, IL-33 is active in its full-length form, although protease digestion of specific N terminal regions can increase its activity.¹⁵⁵ IL-33 triggers biologic responses in effector cells by assembling a heterotrimeric signaling complex with two receptor chains that comprise a

high-affinity primary receptor called IL1RL1 (better known as ST2) and a low-affinity coreceptor called IL-1RAcP.¹⁵⁶ In the airway, IL-33 localizes mainly to the nuclei of epithelial basal cells,¹⁵⁷ and this unusual cellular location reflects its dual roles. One role that depends on its nuclear localization is as a repressor of gene transcription; a second (better understood) role depends on its extracellular secretion and activity as a cytokine. The principal cytokine activity of IL-33 is to promote Th2 inflammation through release of Th2 cytokines by ST2-bearing cells. ST2 is expressed on a wide range of innate and adaptive immune cells, including CD4⁺ T cells, mast cells, basophils, and *innate lymphoid type 2* (ILC2) cells. ILC2 cells are recently characterized lineage negative IL-25R⁺ lymphoid cells.¹⁵⁸ Although CD4⁺ T cells are the dominant source of Th2 cytokines in the airway, the ILC2 cell is increasingly recognized as a rare but potentially important cellular source.

The emphasis on IL-33 as a key epithelial cell mediator of type 2 immune responses in asthma stems from multiple *genome-wide association studies* (GWASs) that have consistently found associations between asthma and genetic polymorphisms at the IL-33 locus and the ST2 locus.^{148,149,159,160} The ST2 gene locus encodes the *full-length ST2 receptor* (ST2L) and the *short soluble form of ST2* (sST2) that acts as a potent negative regulator of extracellular IL-33 activity. Interestingly, genetic polymorphisms in ST2 are associated with low levels of circulating sST2 and high numbers of peripheral blood eosinophils,¹⁶¹ so a relative deficiency in sST2 may be a mechanism of Th2-type inflammation. Thus the IL-33/ST2 axis in asthma is a complex signaling system in which regulation of IL-33, ST2L, and sST2 all contribute to net effects on type 2 immune responses in the airway. The genetic defects in IL-33 and ST2 identified in GWAS studies are presumed to result in net positive IL-33 activity. To date, the specific functional consequences of genetic mutations in IL-33 and ST2 are poorly understood, but additional mechanistic studies should clarify how these genetic abnormalities promote airway Th2 inflammation to cause asthma.

MECHANISMS OF PERSISTENCE OF ASTHMA

As described earlier, the initiation of asthma involves the development of type 2 immune responses to inhaled allergen in young children who have a family and personal history of atopy and who frequently have a history of respiratory tract infection. The mechanisms of persistent type 2 immune responses in asthma are not well understood. One possibility is that aberrant immune programs become fixed because they are established during critical time windows in early life when the immune system is plastic. In this window, it may be that epithelial cells are particularly susceptible to epigenetic changes that lead to persistent changes in cell behavior. Epigenetic changes include DNA methylation or post-translational modification of the amino acid tails of histones by acetylation, phosphorylation, methylation, sumoylation, or ubiquitylation.^{162,163} Because epigenetic changes persist in dividing cells, they provide a mechanism by which environmental factors can cause stable alterations in phenotype without changes in genotype. Most epigenetic changes take place prenatally and shortly after birth, which would coincide with the specific

time periods when individuals are most susceptible to environmental exposures that induce asthma. Although the epigenetic hypothesis is attractive, there is little direct evidence for it yet in asthma.

INFLAMMATORY MECHANISMS IN CHRONIC ASTHMA

Current concepts hold that upstream events in the airway epithelium involving master regulators such as IL-33 result in increased activity of type 2 cytokines in the airway, secreted mainly by CD4⁺ T cells, and driving a cascade of downstream events, including IgE-mediated hypersensitivity, activation of airway epithelial cells, chemoattraction of effector cells (mast cells, eosinophils, and basophils), and remodeling of the epithelium and subepithelial matrix (Fig. 41-5).

CD4⁺ T Cells

CD4⁺ T lymphocyte subsets are categorized on the basis of their cellular functions and capacity to secrete specific cytokines. CD4⁺ Th2 lymphocytes evolved to mediate type 2 immune responses to helminths and parasites, but they are also central to mechanisms of atopy and asthma. IL-4 is the most potent Th2 polarizing factor,¹⁶⁴ and Th2 cells secrete IL-4, IL-5, IL-9, and IL-13.¹²⁷⁻¹²⁹ There is evidence in human asthma for an excess of CD4⁺ Th2 lymphocytes in the airway. Lavage fluid from asthmatic subjects has increased numbers of T cells expressing mRNA for IL-4 and IL-5 (but not IFN- γ).¹⁶⁵ Subsequent studies have confirmed either an excess of Th2 lymphocytes or increases in Th2 cytokine transcripts, protein, or activity in the airway.^{166,167} CD4⁺ Th2 cells are not the sole source of Th2 cytokines because mast cells, basophils, and ILC2 cells also secrete these cytokines, but they do appear to be the dominant source in chronic established disease. CD4⁺ Th2 cells are CCR4⁺ and are responsive to CCL17 (also called thymus and activation-regulated chemokine, TARC), which is an epithelial cell-derived chemokine important for Th2 cell accumulation in the airway (see Fig. 41-5). CD4⁺ Th2 cells also display multiple other receptors, including CRTH2, ST2, TSLPR, and IL17BR, which means that they can also respond to PGD2, IL-33, TSLP, and IL-25, respectively.¹⁶⁸ IL-5 from Th2 cells promotes tissue eosinophilia, whereas IL-9 promotes mast cell hyperplasia, and IL-13 causes epithelial cell activation, as described earlier.

IgE-Mediated Hypersensitivity

As described previously, the production of allergen-specific IgE requires that allergens are taken up by dendritic cells or other antigen-presenting cells, which, in the presence of IL-4, present the processed antigens to naive T cells to direct them toward a Th2 cell phenotype. IL-4 also induces isotype switching in B cells, resulting in IgE production.¹⁶⁹ Notably, the IL-4-producing cells that interact with B cells in secondary lymphoid organs are T_{FH} cells, and not Th2 cells.¹⁷⁰ IgE has two IgE receptors—Fc ϵ RI and Fc ϵ R2. Fc ϵ RI is a high-affinity receptor found on mast cells and basophils.¹⁷¹ Fc ϵ R2 (CD23) is a low-affinity receptor found on epithelial cells, B cells, and myeloid cells.¹⁷² Antigen-induced aggregation of IgE bound to Fc ϵ RI stimulates mast cells to release diverse biologically active products. Preformed products in

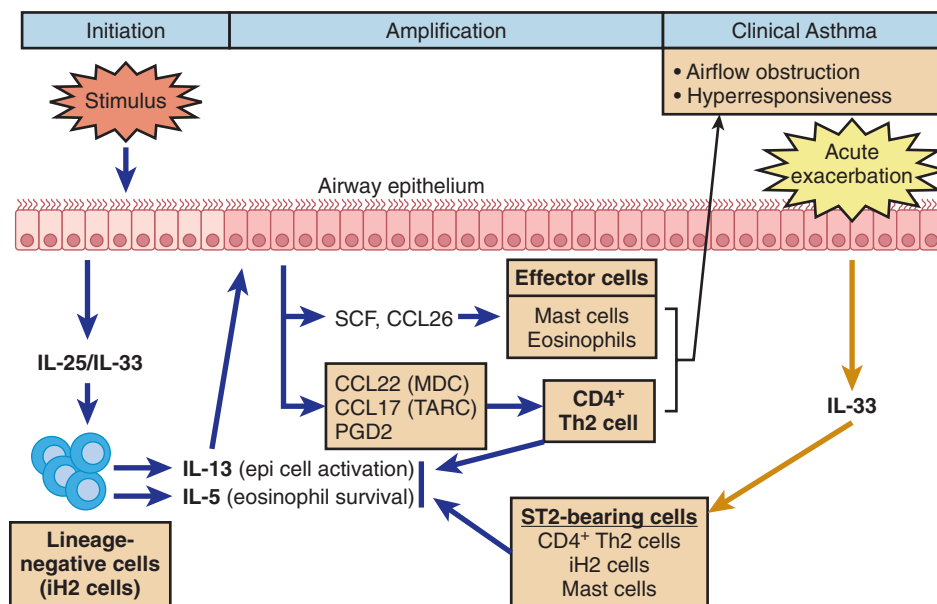


Figure 41-5 Schematic depicting roles for the airway epithelium in the initiation and amplification of airway Th2 responses. IL-25 and IL-33 released by epithelial cells during initiating stimuli interact with lineage-negative IL-25R⁺ lymphoid cells, which also bear the ST2 receptor. Activation of these cells causes secretion of IL-5 and IL-13, which in turn activate the airway epithelium to release CC chemokines and other mediators, which recruit CD4⁺ T cells, eosinophils, and mast cells to promote and sustain Th2 inflammation and the asthma phenotype. SCF, stem cell factor; iH2, innate helper type 2 cells; ST2, suppression of tumorigenicity 2. (From Fahy JV, Locksley RM: The airway epithelium as a regulator of Th2 responses in asthma. *Am J Respir Crit Care Med* 184(4):390–392, 2011.)

cytoplasmic granules include histamine, serotonin, tryptase, chymase, carboxypeptidase A3, and proteoglycans (heparin and/or chondroitin sulfates). Other products are synthesized *de novo* and include lipid-derived mediators (PGD2, LTB4, LTC4, LTD4, and LTE4) and Th2 cytokines. Mediators are released within minutes of antigen exposure, and the aggregate response to mediators released shortly after antigen- and IgE-induced mast cell degranulation is called an immediate-hypersensitivity (“early-phase”) reaction.¹⁷³ This reaction includes airway smooth muscle contraction, heightened bronchovascular permeability, and increases in mucin secretion. The physiologic consequence is a decrease in airflow but can include hypotension and anaphylaxis if the immediate hypersensitivity response is systemic. Although the inflammation and functional changes associated with early-phase responses resolve within 1 to 3 hours, a second (“late-phase”) reaction can develop in some asthmatics, typically beginning 2 to 6 hours after exposure and lasting for 24 to 48 hours.¹⁷⁴ Late-phase responders are often studied in proof-of-concept studies of novel controller medications for asthma because a drug’s ability to inhibit late-phase responses to inhaled allergen is a good predictor of its efficacy in improving asthma control outcomes. For example, omalizumab is a recombinant humanized monoclonal antibody directed against IgE. In early proof of concept studies, omalizumab was shown to inhibit both early and late phase responses.¹⁷⁵ In subsequent clinical trials it was shown to decrease exacerbation rates in asthmatics.^{176,177}

Activation of Airway Epithelial Cells

Unbiased studies of gene expression in airway epithelial cells show a gene profile consistent with IL-13 activation.¹⁷⁸ Gene transcripts for IL-13 in the airway epithelium itself

are sparse but are more easily detectable in submucosal tissue or in sputum cells.¹⁶⁶ Thus the cellular source of the IL-13 is the cells in the submucosa or in the supramucosal mucus layer. These IL-13–producing cells comprise mainly CD4⁺ T cells, but ILC2 cells and mast cells likely contribute as well. IL-13 has many effects on airway epithelial cells.¹³⁰ Genes upregulated include eotaxins (especially eotaxin-3, also called CCL26), CCL17 (TARC), and stem cell factor, which provide chemotactic or survival signals for eosinophils, CD4⁺ Th2 cells, and mast cells, respectively. Also upregulated are *inducible nitric oxide synthase* (iNOS), periostin, and some mucin genes. iNOS catalyzes the production of NO from L-arginine, and exhaled NO can therefore be used as a biomarker of IL-13 activation of the airway epithelium.¹⁷⁹ Because iNOS is a steroid-sensitive gene, exhaled NO levels are typically low in asthmatic patients taking corticosteroid medications.¹⁸⁰ Periostin is a secreted protein of the fascilin family that interacts with integrins, TGF- β , and matrix proteins to initiate a variety of biologic effects including cell proliferation and migration, Treg cell regulation, and modulation of the biomechanical properties of collagen.¹⁸¹ Although periostin gene expression is high in airway epithelial cells, periostin protein does not immunolocalize to airway epithelial cells, because it is rapidly secreted in a basal direction.¹⁸¹ This rapid secretion from epithelial cells explains why periostin immunolocalizes to the subepithelial matrix, where it is proposed to bind and stiffen collagen.¹⁸¹ In this location, periostin is also accessible to the systemic circulation via the subepithelial bronchial venous plexus. Periostin is therefore a useful blood-based biomarker of airway epithelial cell activation by IL-13.¹⁸² The biologic consequence of periostin upregulation in asthma is uncertain. Although *in vitro* studies show that periostin potently upregulates TGF- β in epithelial

cells to induce *epithelial mesenchymal transition* (EMT),¹⁸¹ there is little evidence that EMT takes place in vivo in asthma. Mice deficient in periostin have exaggerated responses to inhaled allergen, suggesting that periostin has protective functions in the airway, perhaps through its regulation of TGF- β and Treg cell function.¹⁸³ Multiple other proteins in the airway epithelium are dysregulated by IL-13, including mucin genes.^{166,184} An overarching principle, though, is that, although epithelial-derived cytokines such as IL-33 are important for initiating and perhaps perpetuating asthma, activation of epithelial cells by IL-13 is an important amplification mechanism in the pathophysiology of asthma (see Fig. 41-5).

Eosinophils

An increase in the number of eosinophils in the airway is a pathologic hallmark of asthma.¹⁸⁵ Peripheral blood eosinophilia is frequent as well.¹⁸⁶ Airway eosinophilia is associated with worse measures of lung function, including airway hyperresponsiveness.¹⁸⁷ Drugs that suppress airway eosinophilia, including corticosteroids, anti-IgE, and anti-IL-5, are all consistently effective in reducing asthma exacerbation rates.¹⁸⁸⁻¹⁹¹ Eosinophils are thought to alter lung function in asthma via the activity of potent cytoplasmic granule proteins and through their capacity to secrete cytokines. Eosinophil granule proteins include *major basic protein* (MBP), *eosinophil cationic protein* (ECP), *eosinophil peroxidase* (EPX), and *eosinophil-derived neurotoxin* (EDN).¹⁸⁵ MBP is cytotoxic against helminths and can disrupt the integrity of lipid bilayers in mammalian cells.¹⁹² It is also an antagonist of the airway M2 muscarinic receptors that normally provide negative feedback to limit neurotransmission and bronchoconstriction.¹⁹³ ECP and EDN have ribonuclease activities that mediate neurotoxic effects, and both proteins have antiviral activity¹⁹²; EPX is a peroxidase that generates reactive oxidants and radical species.¹⁹² The overall effects of eosinophil granule proteins could be to promote nerve-mediated bronchoconstriction and activate epithelial cells. The role of eosinophil cytokines, which include TGF- α and TGF- β , may be to mediate mechanisms of airway mucin secretion and fibrosis, respectively.¹⁹⁴

Mast Cells

Mast cells have long been known to be central effector cells in asthma with multiple studies showing increases in mast cells in the airway mucosa and in airway secretions.¹⁹⁵⁻¹⁹⁷ The importance of the mast cell has been emphasized again recently by data from microarray studies in asthma and better understanding of IL-33/ST2 biology. Specifically, microarray studies in airway epithelial brushings show that mast cell genes are among the most highly upregulated genes in asthma.¹⁷⁸ Immunolocalization studies confirm increased numbers of epithelial mast cells in asthma, characterized by high expression of tryptase and carboxypeptidase A3 and low expression of chymase.¹⁹⁷ Other studies have emphasized the immunolocalization of mast cells to the submucosal airway smooth muscle, where they may contribute to airway smooth muscle hyperplasia and hyperresponsiveness.¹⁹⁸ Mast cells constitutively express multiple cell surface receptors, including Fc ϵ RI and ST2. Cross-linking of Fc ϵ RI by IgE-antigen complexes leads to mast cell degranulation and release of multiple preformed and newly

generated mediators. These IgE-mediated degranulation events are well known. ST2-mediated mast cell activation is less well appreciated but probably also important in the pathogenesis of asthma. Specifically, IL-33 binds ST2 on mast cells to enhance mast cell survival and provide a stimulus for secretion of IL-6, IL-8, and IL-13.¹⁹⁹ IL-33-mediated activation of mast cells may be of particular importance in the pathophysiology of asthma exacerbations when IL-33 is released from epithelial cells as an alarmin. Indeed, mast cells may be a cellular source of the high levels of IL-6 and IL-8 detectable in airway secretions in acute severe asthma.^{200,201}

Basophils

Basophils are circulating granulocytes that respond to allergic stimuli by migrating and accumulating at sites of allergic inflammation.^{202,203} They contain cytoplasmic granules with similar histamine levels per cell as mast cells. In contrast, the amount of tryptase in basophils is less than 1% of that in mast cells.²⁰³ Cross-linking of the Fc ϵ RI by IgE-antigen complexes causes basophil degranulation and mediator release, particularly of histamine. In addition, epithelial cell cytokines, including IL-33 and TSLP, bind to ST2 or TSLPR on basophils to cause cytokine secretion, particularly of IL-4.²⁰⁴ Recently, a role for basophils in type 2 immune responses is being explored.²⁰⁵ For example, in a mouse model of eosinophilic esophagitis, basophils are required for eosinophilic and Th2 cytokine responses.²⁰⁶ Similar information about a central role for basophils in asthma is currently lacking.

Macrophages

Macrophages are abundant in the lung and they adopt different phenotypes on the basis of signals they encounter. Exposure to IFN- γ , TNF- α , or lipopolysaccharide drives differentiation of macrophages to a classically activated (M1) phenotype.²⁰⁷ This phenotype has important roles in host defense against intracellular pathogens. Although M1 macrophages have been implicated in nonatopic asthma and in some subtypes of severe asthma, alternatively activated (M2) macrophages are more usually associated with asthma. Type 2 immune responses drive lung macrophages toward an M2 phenotype that is characterized by upregulated expression of mannose receptors and transglutaminase 2 in man and mice and by upregulated expression of arginase-1, chitinase-3-like protein-3 (also known as Ym1), and resistin-like molecule- α (also known as FIZZ1) in mice only.²⁰⁸ Markers expressed by M2 macrophages have been found in asthma in some studies²⁰⁹ but not in others.²¹⁰ Overall, airway macrophages have capacity to secrete a wide array of inflammatory mediators, but their role in asthma pathogenesis remains uncertain.

PRODUCTS OF ARACHIDONIC ACID METABOLISM—LEUKOTRIENES, PROSTAGLANDINS, AND LIPOXINS

The *cysteinyl leukotrienes* (cys-LTs) are peptide-conjugated arachidonic acid-derived inflammatory mediators that are generated by eosinophils, basophils, mast cells, macrophages, and myeloid dendritic cells.²¹¹ Cys-LTs are generated in the lipid bilayer of the cell membrane when

arachidonic acid is oxidized by 5-lipoxygenase in successive enzymatic conversions to generate *leukotriene C₄* (LTC₄), LTD₄, and LTE₄.²¹¹ Cys-LTs activate at least two receptors on smooth muscle cells to induce muscle contraction and on endothelial cells to increase vascular permeability. Medications targeting this pathway include zileuton (a 5-lipoxygenase inhibitor) and montelukast and zafirlukast (selective antagonists of cys-LT₁ receptor) and are effective in asthma, especially in patients with aspirin sensitivity and Samter triad (aspirin sensitivity, nasal polyps, and asthma).²¹² When these patients ingest cyclooxygenase-1 inhibitors, such as aspirin or other *nonsteroidal anti-inflammatory drugs* (NSAIDs), arachidonic acid metabolism is diverted away from prostanoid metabolites of arachidonate and toward excessive generation of cys-LTs. Consequently, urinary LTE₄ levels are especially high in aspirin-sensitive patients.²¹³

Prostaglandins are generated by metabolism of arachidonic acid by prostaglandin synthase enzymes and cyclooxygenase. *Prostaglandin D₂* (PGD₂) is the prostanoid most relevant to asthma pathogenesis. Mast cells are the most important cellular source of PGD₂, but Th2 cells, dendritic cells, and airway epithelial cells also produce PGD₂ at relatively low levels.^{214,215} There is good evidence that PGD₂ participates in airway responses to inhaled allergen in asthmatics. Allergen challenge in asthmatic patients leads to rapid and large increases in PGD₂ in bronchoalveolar lavage fluid,²¹⁶ and PGD₂ inhalation challenge causes bronchoconstriction and airway eosinophilia.²¹⁷ PGD₂ exerts its biologic effects via three receptors—DP1/DP, TP, and CRTH2/DP2—that are expressed collectively on hematopoietic cells, dendritic cells, epithelial cells, goblet cells, endothelial cells, and platelets.²¹⁵ Small molecule inhibitors of CRTH2 are currently in clinical trials as treatments for asthma, atopic dermatitis, and allergic rhinitis.

Lipoxins (LXs) are enzyme-derived products of arachidonic acid and ω-3 fatty acids, with putative but less well-established roles in asthma. They are counter-regulatory lipid mediators that inhibit inflammation and are rapidly inactivated. Anti-inflammatory actions include inhibition of granulocyte activation and locomotion, promotion of monocyte-derived macrophage phagocytosis of apoptotic granulocytes, blockade of T lymphocyte cytokine release, and epithelial proinflammatory cytokine and chemokine release. LXA₄ also prevents prostaglandin D₂-stimulated release of IL-13 from ILC2s.

NERVES AND NERVE RECEPTORS IN ASTHMA

The lungs are highly innervated and peptidergic, cholinergic, adrenergic, and other neurogenic mediators and their receptors may modulate airway tone and airway inflammation.²¹⁸ *Adrenergic* receptor agonists and *cholinergic* receptor antagonists are mainstays of current bronchodilator therapy for asthma. The term “neurogenic inflammation” refers to the inflammatory responses caused by tachykinins that activate specific receptors as part of the *nonadrenergic noncholinergic* (NANC) system.²¹⁹ Excitatory NANC effects are mediated by release of tachykinins such as neurokinin A and substance P acting on NK₁ and NK₂ receptors. In general, NK₁ receptors mediate gland secretion, plasma extravasation, vasodilation, and leukocyte adhesion,

whereas NK₂ receptors mediate contractions of airway smooth muscle. Inhibitory NANC effects are thought to be mediated principally by vasoactive intestinal peptide and nitric oxide. Evidence for the NANC system in asthma comes from studies showing that asthmatic subjects develop bronchoconstriction after inhaling neurokinin A or substance P.²²⁰ Although an NK₁/NK₂ receptor antagonist protected against bradykinin-induced bronchoconstriction in asthmatic subjects, a selective NK₁ receptor antagonist did not protect against hypertonic saline-induced cough or bronchoconstriction.²²¹

Parasympathetic nerves innervate airway smooth muscle, and hyperresponsiveness of airway smooth muscle is a central pathophysiologic feature of asthma. However, this hyperresponsiveness is not due to increased responsiveness to muscarinic signaling in smooth muscle cells because airway smooth muscle isolated from asthmatics does not show increased sensitivity to muscarinic agonists.²²² Parasympathetic nerves also innervate submucosal glands and regulate mucin secretion from submucosal gland cells.²²³ Notably, inflammatory cells in the airway all express muscarinic receptors, so these cells may be under parasympathetic nerve control. Relevant here is the fact that nerves produce and release inflammatory mediators and can contribute to the recruitment and activation of leukocytes.²²² These leukocytes can then alter production and release of neurotransmitters from nerves. In this way, cross talk between airway nerves and leukocytes may help maintain chronic inflammation in asthma. All of this suggests that anticholinergic treatment should benefit patients with asthma and not just because of bronchodilator effects. Indeed, it is known that vagotomy decreases inflammation in the lungs of asthmatic patients and that treating patients with uncontrolled asthma with a long-acting anticholinergic drug (tiotropium bromide) improves asthma control.²²⁴

NON-TYPE 2 IMMUNE RESPONSES IN ASTHMA

So far this chapter has emphasized type 2 immune responses in asthma, and type 2 responses are indeed the immune responses typical of many patients with asthma. However, appreciation of the heterogeneous nature of asthma at both clinical and molecular levels is driving new research to uncover the disease mechanisms that operate in “Th2-low” subsets of asthma.^{225,226} For now, relatively little is known about the mechanisms of disease in these subsets of patients, but there has been interest in exploring whether some asthma subsets are driven by type 1 immune responses or by IL-17-mediated inflammatory mechanisms. The possibility that there is a subtype of asthma that is mediated by IL-17 inflammation (characterized by neutrophilia) has been of particular interest.²²⁷

IL-17 in Asthma

The IL-17 cytokine family has members designated as IL-17A through IL-17F. CD4⁺ T cells that produce IL-17 are a distinct lineage (Th17 cells), but multiple other immune cell types also produce IL-17, including invariant natural killer T cells, CD8⁺ T cells, *lymphoid tissue inducer* (LTI)-like cells, and *gamma delta T* (γδT) cells.²²⁸ Possible pathogenic roles for IL-17 cytokines in the asthmatic airway include mediation of airway hyperresponsiveness and airway

neutrophilia. Although data from mouse models show that IL-17A produced by Th17 cells contributes to allergen-induced airway hyperresponsiveness through direct effects on airway smooth muscle,²²⁹ there is only limited evidence of this mechanism in human asthma. Similarly, the evidence linking IL-17 to airway neutrophilia in asthma is limited. Ongoing clinical trials of IL-17 inhibitors in asthma should soon clarify the importance of IL-17 family members as cytokine mediators of asthma.

Neutrophils in Asthma

Neutrophils are abundant in airway secretions in both healthy and asthmatic subjects.^{187,200} Airway neutrophils are not elevated in mild or moderate asthma but are characteristically elevated in more severe asthma²³⁰ and asthma exacerbations.²⁰⁰ In addition, neutrophil numbers correlate inversely with measures of airflow in asthma.^{231,232} Whether this neutrophil association with low airflow is causal is not known, because specific neutrophil-directed treatments have not been used in asthma. Possible mechanisms by which neutrophils could lower lung function in asthma include neutrophil-mediated oxidative stress, neutrophil protease-mediated activation of airway epithelial cells, or neutrophil protease-mediated goblet cell degranulation. The proteases secreted by neutrophils include neutrophil elastase, cathepsin G, and matrix metalloproteinase, especially MMP9. Neutrophils may not always have a pathogenic role in asthma. For example, neutrophil numbers may increase markedly in the airways in acute severe asthma, where they may have a beneficial role. Specifically, it is postulated that neutrophil elastase may digest mucin polymers to promote mucus turnover, an important recovery step in acute asthma.²³³

AIRWAY AND GUT MICROBIOME IN ASTHMA

Multiple factors have increased interest in the airway and gut microbiome as drivers of altered immune responses in asthma. First, there are data in mouse models indicating that the intestinal microbiome is a key regulator of immune cell function in early life²³⁴ and data from children show that *Bacteroides fragilis* colonization at age 3 weeks is associated with increased risk of asthma.²³⁵ Second, there are epidemiologic data that children raised on farms have lower prevalence of asthma, an association thought likely to relate to farm-related microbial exposures that influence the host microbiome.²³⁶ And, third, analysis of the microbiome of airway secretions from asthmatics and controls shows that upper airway colonization in infants by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* predicts later development of asthma.²³⁷ In addition, sequencing- and microarray-based analyses of lower airway biospecimens from asthmatics show abnormalities in the composition of bacterial microbiota, especially Proteobacteria (which include *H. influenzae*, *Pseudomonas*, *Neisseria*, *Burkholderia* species, and *Enterobacteriaceae* species.²³⁷ Notably, Proteobacterial species promote neutrophilic inflammation, and there is now great interest in whether specific microbial pathogens drive specific subtypes of asthma (such as neutrophilic asthma). Studies of the airway and gut microbiome in asthma are currently in their infancy, however, and ongoing research should reveal

whether treatment with microbes can prevent asthma in some cases or if suppression of specific microbial species can improve asthma in established disease.

MECHANISMS OF ASTHMA EXACERBATION

Asthma exacerbations represent acute-on-chronic worsening of airflow obstruction that is a consequence of worsening airway smooth muscle contraction, airway wall edema, and luminal obstruction with mucus.²³⁸ The mucus pathology is especially problematic in fatal and near fatal asthma (see later). Common upper respiratory tract viruses, especially rhinoviruses, are the most common and important cause of exacerbations in both children and adults.^{239,240} Susceptibility to acute reductions in airflow in asthmatics relates to airway mucosal remodeling. Changes in the epithelium to increase mucin stores, in airway smooth muscle to render it more hyperreactive, and in blood vessels to make them leakier render many asthmatics vulnerable to exaggerated airway responses to inhaled environmental insults, such as viruses, allergens, or pollutants.²³⁸ Asthmatic airways are hyperreactive in more ways than one—concentric smooth muscle contraction from hyperresponsiveness is one element, but mucosal edema from vascular permeability and excess mucus from mucin hypersecretion are others. The efficacy of corticosteroids in preventing exacerbations likely relates to their effects in not only reducing inflammatory cell numbers (especially eosinophils) but also improving pathologic changes in goblet cells, smooth muscle cells, and blood vessels.

PATHOLOGIC CHANGES IN THE AIRWAY IN ASTHMA

Asthma is characterized by structural changes in both the epithelium and the submucosa. These changes include abnormal deposition of collagen in the subepithelium (subepithelial fibrosis) and changes in structural cells such as goblet cells, submucosal gland cells, smooth muscle cells, and blood vessel cells (Fig. 41-6).

Pathologic Changes in Epithelial Cells in Asthma

Epithelial desquamation in asthma is a feature of acute severe asthma exacerbations, but not of chronic stable asthma. Squamous metaplasia is also not usually a feature of asthma (it is more a feature of smoking-related lung disease). The main changes in epithelial cells seen in asthma are goblet cell metaplasia and hyperplasia, which has the effect of increasing the amount of gel-forming mucins that are stored in the airway epithelium.²⁴¹

Pathologic Changes in Airway Mucus in Asthma

Airway mucus is qualitatively abnormal in asthma, reflecting changes in its cellular and biochemical constituents.²⁴² For example, eosinophil numbers are increased in asthmatic sputum²⁴³ and account for the occasional presence of bipyramidal crystals (Charcot-Leyden crystals), which are composed of eosinophil lysophospholipase.²⁴⁴ Mucin glycoproteins (“mucins”) are the predominant protein in sputum, and mucin concentrations are higher than normal in asthma.²⁴⁵ Mucins in airway mucus are the protein products of two mucin genes—MUC5AC and MUC5B. The gene

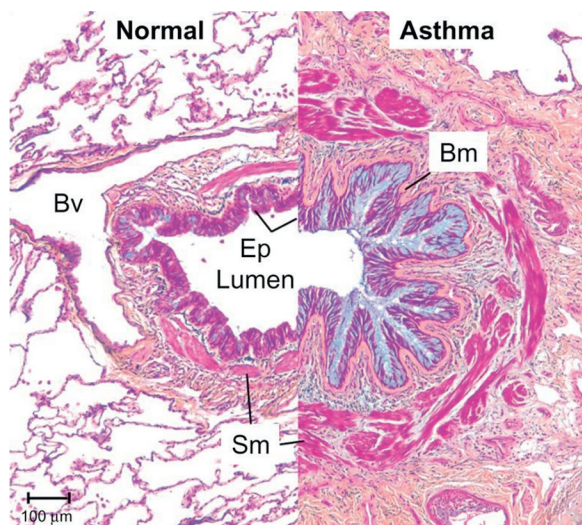


Figure 41-6 Airway pathology in asthma. Photomicrograph illustrating pathologic differences in a medium-sized airway from a nonasthmatic patient (left) and a patient with asthma (right). The stain is a Movat pentachrome stain. The airways in asthma show significant structural remodeling. The epithelium in asthma shows goblet cell hyperplasia, subepithelial fibrosis, and increased smooth muscle (Sm) volume. Scale bar 100 μ m. Bm, basement membrane; Bv, blood vessel; Ep, epithelium. (From Wadsworth S, Sin D, Dorscheid D: Clinical update on the use of biomarkers of airway inflammation in the management of asthma. *J Asthma Allergy* 4:77–86, 2011.)

expression of MUC5AC is increased in airway epithelial cells in asthma, whereas the gene expression of MUC5B is decreased.^{166,246} The functional consequence of the change in relative amounts of gene transcripts for MUC5AC and MUC5B is unknown. Albumin is another prominent protein component of airway mucus in asthma,^{200,233} and its presence in mucus reflects the heightened bronchovascular permeability in asthma, especially in acute exacerbations. Increases in the concentration of plasma proteins and mucins can alter the viscoelastic properties of airway mucus in asthma, but such changes are usually much more marked in acute asthma than in chronic asthma.²³³

Subepithelial Fibrosis

Increased amounts of types I, III, and V collagen, as well as fibronectin and tenascin, are deposited immediately beneath the epithelium in asthma.^{247,248} These structural proteins differ from typical basement membrane proteins such as collagen IV and laminin, so the subepithelial fibrosis of asthma is not a thickening of the true basement membrane but rather a deposition of a layer of interstitial collagens immediately beneath it. Although the cellular source of these proteins may be the overlying epithelial cells, myofibroblasts are increased in number in asthma and are likely a more important source.²⁴⁹ Subepithelial fibrosis is most prominent in patients with eosinophilia and airway Th2 inflammation.^{166,250} Increased amounts of collagen and other matrix proteins and abnormal cross-linking of these proteins will increase the stiffness of the subepithelial matrix. A stiff matrix can influence cell growth, survival, migration, and tissue-specific differentiation,²⁵¹ so subepithelial fibrosis may cause persistent activation of overlying epithelial cells and of embedded fibroblasts and smooth

muscle cells. Clinical studies show associations with airflow obstruction and decreased airway distensibility,²⁵² but the consequences of subepithelial fibrosis for immune dysfunction in asthma are unclear. Some have speculated that fibrosis represents a secondary barrier that impedes the passage of aeroallergens into the subepithelial space.²⁵³ Still others have hypothesized that the presence of subepithelial fibrosis promotes aeroallergen sensitization.¹³³

Airway Smooth Muscle Cells

In mild to moderate asthma there is hyperplasia of *airway smooth muscle* (ASM) that is thought to be an important mechanism for bronchial hyperresponsiveness.²⁵⁴ ASM undergoes hypertrophy together with hyperplasia in more severe subtypes of asthma.²⁵⁵ These morphometric changes in ASM have been easily demonstrated. Less straightforward have been studies of inherent smooth muscle function. Although it has long been speculated that ASM cells in asthma may be inherently hypercontractile, and such a cell phenotype can be generated in vitro,²⁵⁶ it is not proven that ASM in asthma is hypercontractile. Indeed, gene expression profiling has not identified gene signatures of such a phenotype.²⁵⁴ In addition, measurements of isometric tension in ASM from asthmatic subjects have not shown consistent evidence for enhanced force generation but have shown increased shortening.²⁵⁷ Such increases in isotonic shortening could result from alterations in contractile apparatus,²⁵⁸ tissue elastance, or extracellular matrix.²⁵⁹

Blood Vessels

The number and size of bronchial blood vessels is increased in asthma, and these vessels may have an important role in regulating airway caliber because an increase in vascular volume may swell the mucosa and narrow the airway lumen.^{260,261} Many inflammatory mediators cause vasodilation, a response that may be accompanied by increased permeability at the postcapillary venule, plasma extravasation, and airway mucosal edema.

Airway Pathology in Fatal Cases of Asthma

Exacerbations of asthma can be fatal as a result of severe airflow obstruction that is characterized by severe concentric smooth muscle contractions and extensive mucus plugging of airways. These changes were described in multiple studies in the mid-20th century, which emphasized the extensive mucus plugging of airways as a key pathologic feature.²⁶² Near-fatal asthma is also frequently associated with segmental or subsegmental lung collapse because of mucus plugs. In addition, autopsy studies showed that the degrees of airway wall thickening, smooth muscle hypertrophy, and submucosal gland hypertrophy are greater in patients who die from an asthmatic attack than in patients with asthma who die from other causes.²⁶³ Eosinophils are prominent in the airways in fatal asthma, but neutrophils may also be prominent, especially in the airways of asthmatic patients who die quickly after the onset of the fatal attack.²⁶⁴ More recent studies that have used silicone to make casts of airways from fatal cases of asthma confirm and extend the earlier gross pathology studies. The silicone cast studies show dramatic loss of airways due to mucous plugs and bronchoconstriction.²⁶⁵ Both fatal asthma and nonfatal asthma cases also show severe airway surface

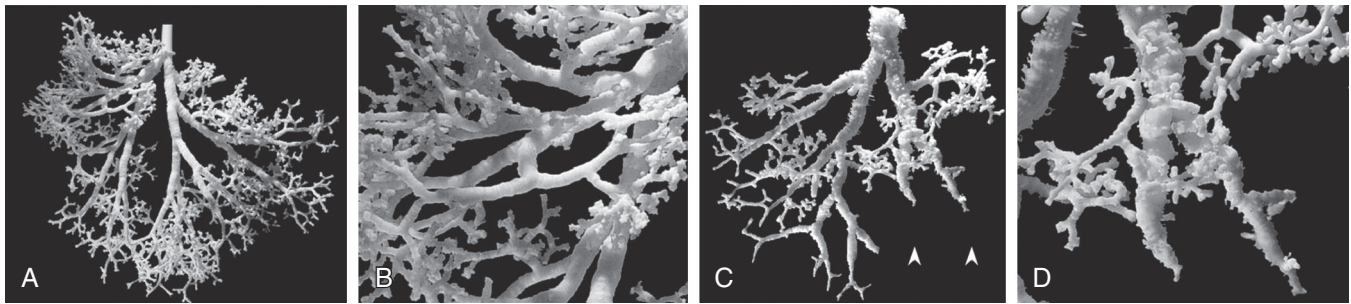


Figure 41-7 Silicone rubber casts of lungs from a control and a case of fatal asthma. **A**, Low-power photograph of a control cast of the superior segment of the left lower lobe from a person without asthma. The cast shows characteristic dichotomous branching pattern with smooth parallel-sided segments and complete filling to the level of respiratory bronchioles (shown in greater detail in **B**). **C**, Cast of 18-year-old female who died of asthma. The cast shows irregular segments with tapering, constrictions, and surface protrusions. The latter corresponded to ectatic mucous gland ducts on histology. Many of the segments are truncated due to airway constriction. Close-up of two truncated airways (arrowheads) seen in **C** are shown at greater detail in **D**. (From Boser SR, Park H, Perry SF, et al: Fractal geometry of airway remodeling in human asthma. *Am J Respir Crit Care Med* 172(7):817–823, 2005.)

abnormalities that correspond to smooth muscle hypertrophy, longitudinal elastic bundles, and ectatic mucous gland ducts (Fig. 41-7).

PHENOTYPING

ASTHMA HETEROGENEITY

All asthmatics manifest airflow limitation on spirometry, airway hyperresponsiveness to specific or nonspecific challenge, and symptoms that include shortness of breath, chest tightness, wheeze, and cough. Nonetheless, patients with asthma can have a great deal of heterogeneity with respect to severity of airflow limitation, symptoms, degree of reversibility, and therapeutic response. Up to 30% to 45% of asthmatics do not respond to high doses of *inhaled corticosteroids* (ICSs) with improvements in lung function.^{266,267} Furthermore, there is significant heterogeneity in asthma triggers, the frequency and severity of exacerbations, and long-term outcomes such as irreversible loss of lung function due to airway remodeling.

Several approaches have been taken to assign asthmatics to distinct subphenotypes. Degree of airway obstruction or frequency of symptoms and rescue medication use have been used for asthma classification and care,²⁶⁸ but these categories do not provide insight into molecular or cellular mechanisms. These guidelines have been instrumental in public health efforts to improve asthma education and care through the promotion of inhaled corticosteroid use, but a better appreciation of disease heterogeneity at a molecular and cellular level will be important in treating severe asthma and in the clinical application of emerging asthma therapies.

CELLULAR PHENOTYPES

Analyses of sputum, bronchoalveolar lavage, and endo-bronchial biopsy specimens from living asthmatics and postmortem samples from fatal asthma have found that the majority of asthmatics have elevated eosinophils.²⁶⁹ However, not all asthmatics have eosinophils in their sputum; noneosinophilia may be seen in up to 25% of asthmatics not on treatment and in up to 50% of those on

treatment.²⁷⁰ Noneosinophilic asthma responds poorly to ICSs.^{271,272} Furthermore, noneosinophilic asthma is seen across a range of asthma severity and, in severe asthma, has been associated with a lower FEV₁, fewer mast cells, and less subepithelial fibrosis (i.e., airway remodeling).²⁷³ These observations and others have led to a cellular classification of asthma based on induced sputum cytologic analysis, which has four categories: (1) eosinophilic, (2) neutrophilic, (3) mixed eosinophilic and neutrophilic, and (4) paucigranulocytic asthma, where there is no observable presence of inflammatory cells.^{270,274,275} Eosinophilia is most commonly seen in classic atopic asthma with allergen-mediated inflammation and, except for severe cases, generally responds to ICSs with reduced eosinophils, improved airway obstruction, and decreased symptoms.^{250,270,276,277} Neutrophilia has been noted in asthmatics with acute and chronic infection, obesity, smoking, and exposure to irritants such as pollutants²⁷⁰; in subsets of patients with severe asthma²⁷³; and during acute asthma exacerbations.²⁰⁰ Neutrophilia is also associated with reduced FEV₁, independent of eosinophils.^{232,278} Mixed neutrophilia and eosinophilia have been reported in refractory asthma. One study found that subjects with mixed neutrophilia and eosinophilia had the poorest lung function, highest frequency of daily wheeze, and highest health care utilization.²⁷⁴

CLINICAL PHENOTYPES

Asthma heterogeneity has been analyzed at the clinical level using cluster-based multivariate approaches, designed to overcome the limitations of using only one variable, such as severity of airflow obstruction or type of cellular inflammation. Halder and colleagues²⁷⁹ used a principal components analysis and clinical experience to select variables that were measured in clinical practice—age of asthma onset, gender, atopic status, body mass index, peak flow variability, induced sputum eosinophil counts, and symptom scores. They identified three distinct clusters in mild to moderate asthmatics: one with early-onset atopic asthma and eosinophilia; another with a preponderance of obesity, females, and lack of eosinophilia; and a third with mild disease and lack of airway eosinophilia. When applied to asthmatics with more severe, refractory disease (as defined by American Thoracic Society criteria²⁸⁰), the same

analysis revealed four clusters, two similar to the early-onset atopic and obese noneosinophilic clusters identified in milder asthmatics; the other two clusters had a dissociation between eosinophilia and asthma, one with early onset and symptoms in the absence of eosinophilia and the other with late onset, minimal symptoms, and marked sputum eosinophilia. These clusters were validated by their presence in an independent prospective cohort of severe asthmatics.

Moore and associates²⁸¹ studied asthma heterogeneity through multivariate clustering of subjects from the Severe Asthma Research Program in the United States, by using only spirometric measurements and clinical characteristics. This study identified five distinct clusters. Three (one of which had severe disease) had features consistent with allergic disease—early age of onset and atopy. One additional cluster was composed of an obese, female-predominant, late-onset, nonatopic group, similar to the obese, noneosinophilic cluster in the Haldar analysis. The final cluster was a second severe asthma group, predominantly women with later-onset asthma, less atopy, and poorer response to bronchodilator. Longer disease duration correlated with asthma severity and low lung function across all study subjects.

MOLECULAR PHENOTYPES (ENDOTYPES)

An alternative approach to clustering subjects with asthma is to group them on the basis of molecular pathways found to be active in individual patients. Creating subgroups based on the activity of specific cytokine pathways has the added advantage that it points to specific pharmacologic targets and biomarkers for clinical trials. Subgroups of patients who share an underlying disease biology have been named “endotypes.”

One such study analyzed the expression levels of three epithelial genes that can serve as surrogate markers of inflammation associated with Th2-cytokines, especially IL-13.¹⁶⁶ These three genes, *POSTN* (the gene coding for periostin), *CLCA1*, and *SERPINB2*, were previously identi-

fied using genome-wide profiling of airway epithelial brushing obtained at bronchoscopy.¹⁷⁸ In this study, which examined the expression of these three genes in epithelial brushings, half the subjects had elevated levels but nearly half of subjects with mild-to-moderate asthma were indistinguishable from healthy controls. Such differential expression of Th2 genes suggested that this population of asthmatics was heterogeneous; some had Th2-high inflammation and others had Th2-low inflammation. Increased expression of IL-13 and IL-5 in Th2-high subjects, as assessed by qPCR in bronchial biopsy specimens, provided further confirmation for these endotypes. In subsequent analyses, Th2-high asthma was found to have exaggerated airway hyperresponsiveness (PC₂₀ methacholine), higher serum IgE levels, and both blood and especially bronchoalveolar lavage eosinophilia.¹⁶⁶ Th2-high subjects also had increased thickness of fibrosis below the airway epithelial basement membrane, differences in the mucin genes expressed by goblet cells (increased *MUC5AC/MUC5B* ratio), and increased numbers of intra-epithelial mast cells.¹⁹⁷ Although these analyses suggest a clinically useful dichotomous classification of distinct endotypes of asthma based on degree of Th2-inflammation, the degree of Th2-inflammation present in subjects with asthma can alternatively be seen as a continuum (Fig. 41-8).

CELLULAR BIOMARKERS

Three randomized controlled trials have found that induced sputum eosinophil counts in moderate-to-severe asthmatics can be used to tailor the dose of ICSs. All three trials found a reduction in the frequency and severity of asthma exacerbations when the ICS dose was adjusted on the basis of induced sputum eosinophil counts compared with adjustment by symptoms, lung function, or rescue medication use.²⁸²⁻²⁸⁴ There was no significant difference in lung function assessed by peak expiratory flow or spirometry. Sputum eosinophilia has also guided the use of a novel, targeted asthma treatment, mepolizumab, a humanized

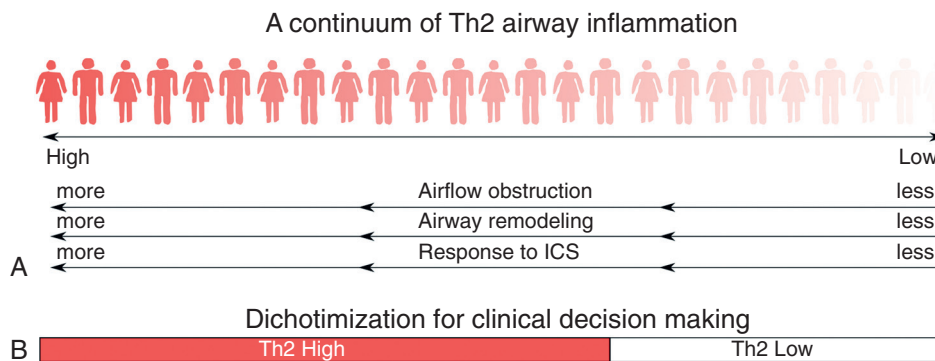


Figure 41-8 Molecular phenotypes (endotypes) in asthma. **A**, Type 2 (Th2)-driven inflammation is a dominant signal inflammatory signal in asthma. Nonetheless, among individuals, there is a continuum of Th2 inflammation, ranging from high levels of Th2 inflammation to low levels, approaching the baseline activity found in healthy controls. Higher Th2 inflammation is associated with greater airflow obstruction and airway remodeling, as well as a greater improvement in lung function with inhaled corticosteroids. The long-term temporal stability of these phenotypes is not yet known. **B**, The level of Th2 inflammation can guide the use of targeted therapies by dichotomizing individuals to either “Th2 High” or “Th2 Low” groups. A number of non-Th2 pathways in the airways have been under investigation. These additional mechanisms may explain “Th2 Low asthma” and may also coexist with Th2 inflammation across the continuum, contributing further to interindividual variation in disease. Pathways and mechanisms under investigation include Th1 inflammation, Th17 inflammation, arachidonic acid metabolism, neutrophils, obesity, intrinsic airway smooth muscle abnormalities, and abnormalities in nerves and nerve receptors.

monoclonal blocking antibody against IL-5, a key mediator in the differentiation, recruitment, and activation of eosinophils.²⁸⁵ Although early clinical trials with mepolizumab were unfavorable,^{286,287} the results of clinical studies improved when patient selection was based on the presence of eosinophils in induced sputum.^{288,289} One of these studies found a reduction in asthma exacerbations when the drug was given to subjects with refractory eosinophilic asthma, defined by sputum eosinophils greater than 3% on at least one occasion in the previous 2 years, despite high-dose ICS treatment.²⁸⁸ In another study, mepolizumab reduced the number of blood and sputum eosinophils and allowed reduction of prednisone dose.²⁸⁹ More recently, a randomized clinical trial of dupilumab, a monoclonal antibody to the α -subunit of the IL-4 receptor, showed efficacy with respect to asthma exacerbation rates in patients selected on the basis of elevated blood or sputum eosinophils.²⁹⁰

EXHALED NITRIC OXIDE AS A BIOMARKER

Measurement of the *fraction exhaled nitric oxide* (FeNO) is an alternative noninvasive biomarker of airway inflammation. FeNO levels are increased in asthma^{291,292} and are highly reproducible.²⁹³ In the setting of Th2 cytokine-driven airway inflammation, cells such as eosinophils and epithelial cells can increase NO production in part through increased transcription of inducible iNOS. Although there is a strong rationale for the use of FeNO as an asthma biomarker, the results of clinical trials that apply FeNO to guide treatment have been mixed. A randomized trial of 118 subjects with asthma did not show a difference in exacerbation frequency or total ICS used over a 1-year period when asthma treatment was based on FeNO as compared with standard guidelines.²⁹⁴ Two other studies also showed no change in exacerbation frequency, although in one, ICS dose was reduced significantly²⁹⁵ and, in the other, bronchial hyperresponsiveness improved in children.²⁹⁶ Possible reasons for the mixed performance of FeNO in these clinical studies include high sensitivity but poor specificity for eosinophilic inflammation based on the cutoff selected in specific studies,²⁹⁴ the existence of noneosinophilic asthma, and confounding by comorbidities that influence FeNO, such as nasal polyps.²⁹⁷

TH2 INFLAMMATION AS A BIOMARKER

As described earlier, the expression level of IL-13–induced genes in epithelial brushing samples allowed categorization of asthma patients into Th2-high and Th2-low endotypes.¹⁶⁶ A randomized placebo-controlled trial of ICSs in this same study showed that the Th2-low endotype did not respond to inhaled corticosteroids with an improvement in lung function, whereas the Th2-high group responded as expected. Periostin, one of the Th2 markers used in that study, is secreted basolaterally by epithelial cells,¹⁸¹ can be measured in the blood and has been used to quantify the degree of Th2 inflammation in clinical studies. Serum periostin protein levels correlated with persistent eosinophilic airway inflammation despite ICS treatment.¹⁸² This serum periostin assay was used to assess activity of the Th2 pathway and prespecify Th2 high and low subgroups in a randomized controlled trial of the anti-IL-13 monoclonal

antibody lebrikizumab in severe asthmatics.¹⁷⁹ With high serum periostin marking the Th2 high endotype, the primary outcome of improvement in FEV₁ at 12 weeks was significant only in the Th2-high group, supporting the important clinical potential of asthma endotypes in guiding the application of cytokine-based therapies for severe asthma. However, in a second randomized trial, this time performed in mild-to-moderate asthmatics who were not concurrently using ICS, treatment with lebrikizumab was not associated with clinical benefit and serum periostin levels did not identify a responsive subgroup.²⁹⁸ Whether this result represents a failure of these biomarkers to endotype patients adequately, or decreased efficacy of lebrikizumab in the absence of concomitant ICS is unclear. Finally, in a subgroup analysis within a third randomized controlled trial, elevated blood levels of periostin as well as FeNO and blood eosinophils predicted response to omalizumab, an anti-IgE monoclonal antibody.²⁹⁹ Given this mixed experience to date, additional studies will be required to define the value of blood periostin levels as a companion diagnostic in the application of Th2-targeted therapies.

NON-TH2 ASTHMA PHENOTYPES

Whether Th2-low endotypes of asthma reflect inflammatory mechanisms that are distinct from Th2 skewed inflammation or reflect non-inflammatory mechanisms is uncertain (see Fig. 41-8). Despite the focus on Th2 inflammation in mouse models of asthma and in the development of new therapies for human asthma, there is experimental evidence that both Th1- and Th17-driven inflammation can lead to airflow obstruction and exacerbate an asthma phenotype. Adoptive transfer of antigen-specific Th1 cells into ovalbumin-challenged mice led to airway hyperresponsiveness and airway inflammation that was independent of IL-13 and IL-4 in one study³⁰⁰ and dependent on IL-13 and IL-18 in another.³⁰¹ Interestingly, adoptive transfer of antigen-specific Th1 cells into antigen-challenged mice led to the development of IFN γ -dependent airway hyperresponsiveness that failed to improve with dexamethasone treatment,³⁰² suggesting a role for Th1-dependent inflammation in corticosteroid resistance. Th17 cells, on the other hand, are characterized by the secretion of IL-17A, IL-17F, IL-21, and IL-22, but not IFN- γ or IL-4.^{303,304} Most parenchymal cells, including airway epithelial cells, express receptors for Th17 cytokines including IL-17A and IL-17F, and signaling through these receptors leads to the production of pro-inflammatory factors such as IL-6, IL-1, TNF- α , and IL-8 (CXCL8, a neutrophil chemoattractant). IL-17 could contribute to the asthma phenotype by causing airway hyperresponsiveness,²²⁹ by recruiting neutrophils, and by increasing epithelial production of secreted mucins.^{305,306} In human studies, bronchoalveolar lavage samples from patients with asthma have shown increased numbers of IL-17A–producing cells,³⁰⁷ and similar findings in induced sputum also point to a positive correlation with the severity of airway hyperresponsiveness.³⁰⁸⁻³¹⁰ Furthermore, evidence of Th17 activity through identification of specific Th17 cells and IL-17A/F has also been found in human airway tissue³¹¹⁻³¹³ and peripheral blood with a positive correlation with asthma severity.^{314,315} It is also possible that Th17 inflammation contributes to corticosteroid resistance

in severe asthma, as was found in a mouse model of Th17-mediated allergic airway inflammation and hyperresponsiveness.³¹⁶ Th17-mediated inflammation may coexist with the Th2-high phenotype and augment Th2 responses.^{317,318} If there is evidence that Th1- or Th17-mediated inflammation is present in a subgroup of asthmatics, biomarkers and targeted therapeutics may be indicated. Finally, it is possible that airway inflammation does not play a dominant role in the clinical manifestations of a subset of patients with Th2-low asthma. Airway hyperresponsiveness may be the result of an abnormal airway smooth muscle response to mediators of contraction such as histamine and acetylcholine. Although a proinflammatory cytokine milieu and infiltration of smooth muscle with inflammatory cells are likely major influences on abnormal airway smooth muscle contraction, intrinsic abnormalities in the signal transduction or contractile functions of smooth muscle cells in human asthma are relatively less well studied. Because a role of airway smooth muscle hyperplasia or hypertrophy has been demonstrated in patients with asthma,^{254,319} abnormal accumulation of smooth muscle and increased airway narrowing on that basis represents another possible noninflammatory mechanism for increased airway hyperresponsiveness in asthma.

Key Points

- Asthma is common and its prevalence has been steadily increasing. In the United States, the prevalence and severity of asthma are highest in certain vulnerable populations, including children, people living below the poverty level, and specific minority groups (Puerto Ricans, black, and non-Hispanic Americans).
- Internationally, the prevalence of asthma varies dramatically, with particularly high rates in certain developed countries, including the United Kingdom, New Zealand, Australia, the United States, and Canada.
- The most common immunopathology in asthma is type 2 inflammation initiated by upstream events in the airway epithelium involving epithelial cytokines such as IL-33. The epithelial cytokines increase activity of type 2 cytokines in the airway, secreted mainly by CD4⁺ T cells, and possibly by innate lymphoid cells.

- Local type 2 cytokine secretion drives a cascade of downstream events, including IgE-mediated hypersensitivity, activation of airway epithelial cells, chemotaxis of effector cells (mast cells, eosinophils, and basophils), and remodeling of the epithelium and subepithelial matrix.
- Although asthma is defined by shared clinical characteristics such as episodic airflow limitation, chest symptoms, and airway hyperresponsiveness, asthma shows heterogeneity in other clinical characteristics including severity and response to treatment.
- The clinical heterogeneity of asthma may be explained by different underlying mechanisms. For example, type 2 inflammation is associated with greater airflow obstruction and airway remodeling. However, the degree of type 2 inflammation varies across individuals, ranging from high levels (termed “Th2-high asthma”) to low or absent levels (termed “Th2-low asthma”).
- The recognition that asthma is heterogeneous and comprises molecular phenotypes, or endotypes, is leading to the development of targeted therapies and of biomarkers that can identify those who will respond to these treatments.

Complete reference list available at [ExpertConsult](#).

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ASTHMA: CLINICAL DIAGNOSIS AND MANAGEMENT

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INTRODUCTION

Asthma is one of the oldest known diseases, but it has only been recognized as a major public health problem since the mid-1970s. The prevalence of asthma has increased dramatically, and asthma is now recognized as a major cause of disability, medical expense, and preventable death. Asthma has attracted the full spectrum of biomedical investigation, from studies of the prevalence of asthmatic symptoms in different populations to studies of the effects of substitution of single base pairs in genes in animal models of allergic sensitization of the airways. These studies continue to refine the scientific understanding of asthma and suggest new approaches to diagnosis and treatment. The scope and depth of these studies present significant challenges in reviewing the topic of asthma. This chapter combines the perspectives of the authors with a “snapshot” of the body of knowledge, which is expanding at an explosive pace.

DEFINITION

Although asthma is a clearly recognized clinical entity, agreement on a precise definition has proved elusive. Asthma has been more often described than defined. The earliest feature described was the labored, rapid breathing typical of asthmatic attacks; the word “asthma” is derived from the ancient Greek word for “panting.” As knowledge about asthma has grown, the features described as characteristic of asthma have expanded. Measurement of maximal expiratory flow led to recognition of reversible airflow obstruction as a characteristic feature; measurement of changes in airflow after inhalation of chemical or physical irritants led to the definition of bronchial hyperresponsiveness. In addition, studies of bronchial biopsies added a description of characteristic pathologic features. This evolution in the understanding of asthma is summarized in the definition offered in the *National Heart, Lung, and Blood Institute’s* (NHLBI’s) 2007 Update on Asthma Pathophysiology and Treatment Guidelines¹:

“Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in bronchial hyperresponsiveness to a variety of stimuli.”

A feature found even more consistently than eosinophilia in bronchial biopsies from patients with asthma is thickening of the *lamina reticularis* immediately underneath the subepithelial basement membrane. This thickening is considered a hallmark of airway “remodeling”; however, this feature has not yet been incorporated into consensus definitions of asthma.

The consensus conference “definition” of asthma serves well as a description of the major features of asthma but does not hold up as a precise definition. No feature is unique to asthma, and no feature is universal in patients with the condition. For example, all tests of airway caliber may be normal between attacks, even in patients whose attacks are sudden and severe. Bronchial responsiveness may be normal over most of the year in patients with seasonal asthma, and bronchial hyperresponsiveness is often found in people with allergic rhinitis but without asthma. Even the association between eosinophilic bronchial inflammation and asthma is inconstant. Some patients with recurrent episodes of wheezing and dyspnea associated with reversible airflow obstruction and bronchial hyperresponsiveness have no evidence of eosinophilic inflammation on bronchial biopsies. Other patients have eosinophilic inflammation of the bronchial mucosa and chronic cough responsive to

treatment with an inhaled corticosteroid but have neither airflow obstruction nor bronchial hyperresponsiveness. Finally, some patients with severe asthma have a predominance of neutrophils, rather than eosinophils, in their bronchial mucosa.

The lack of firm, universally agreed-upon criteria for defining asthma complicates epidemiologic studies of the prevalence of asthma in different populations and of changes in prevalence in the same population over time, but agreement on “working definitions” of asthma has led to many informative studies.

The recognition of asthma as a complex, multifactorial disorder has led to a greater focus on the individual and the varied disturbances in function that contribute to a more or less common clinical expression. Recent advances in science have not necessarily led to a more precise definition of asthma; rather, these advances have made the need for agreement on a definition seem less urgent.

CLINICAL DIAGNOSIS

The diagnosis of asthma is often made in the ambulatory care setting and is based on a careful personal history, physical examination, and lung function testing (Fig. 42-1). A number of different diseases can mimic asthma and cause some or all of the symptoms of asthma. These include vocal cord dysfunction, *chronic obstructive pulmonary disease* (COPD), cystic fibrosis, bronchiectasis, congestive heart failure, sleep apnea, pneumonia, sarcoidosis, and psychosomatic diseases and need to be considered when making the diagnosis of asthma.

PERSONAL HISTORY

Asthma can arise at any age but usually presents for the first time in childhood.² Risk factors for asthma include a family history of asthma and a personal or family history of atopy (e.g., atopic dermatitis, seasonal allergic rhinitis,

conjunctivitis).³ In addition, asthma can develop in individuals sensitive to aspirin or exposed to chemical toxins or environmental allergens.⁴

A comprehensive history is therefore critical in the assessment of the asthmatic patient. Most patients with asthma complain of intermittent symptoms of cough, shortness of breath, and/or wheezing, often described as a high-pitched musical whistling. They often experience periods of symptom-free normal breathing interrupted by periods of difficulty breathing. Asthma symptoms can last for a few minutes or days. Cough is a frequent complaint in asthma; the cough may or may not be accompanied by sputum production, may worsen at night or with activity, and/or may develop after exposure to allergens.^{5,6} Shortness of breath and wheezing, usually on exhalation, often manifest during an exacerbation and can be triggered by infection, cold air, exercise, exposure to chemical fumes or other airborne irritants, pet dander, molds, house dust mites, or other allergens.⁷ In addition, some patients describe bandlike chest tightness, or chest heaviness, during an exacerbation. Complaints of sharp stabbing or knifelike pain would be unusual in asthma and should direct the clinician to alternative diagnoses.

WORK HISTORY

Symptoms that improve on weekends and vacations and worsen at work should raise the suspicion of occupational and/or work-exacerbated asthma. Occupational asthma is new-onset asthma due to causes and conditions attributable to a particular occupational environment, whereas work-exacerbated asthma is defined as exacerbation of known asthma by the work environment.⁸ Indeed, up to 15% of all adult asthma can be attributed to occupation.^{9,10} The work exposure history should focus on identifying agents that were present at the time of asthma diagnosis or when asthma symptoms worsened. There are two major types of occupational asthma: sensitizer-induced asthma and irritant-induced asthma. Sensitizers are often further

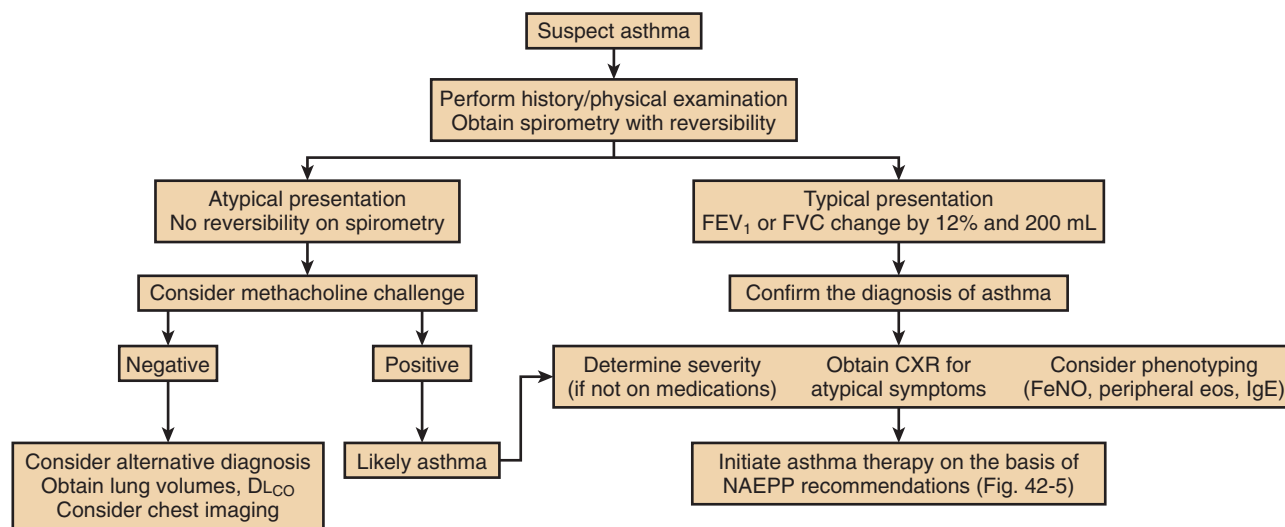


Figure 42-1 Algorithm for diagnosing asthma in adults. CXR, chest radiograph; DL_{CO}, diffusing capacity for carbon monoxide; eos, eosinophils; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; NAEPP, National Asthma Education and Prevention Program.

classified into low-molecular-weight (small chemicals) and high-molecular-weight (usually proteins) agents.⁴ *Reactive airway dysfunction syndrome* (RADS), the best-defined form of irritant-induced asthma, results from a single high-dose exposure to irritants. (For a more detailed discussion of RADS and occupational asthma, see Chapter 72.)

PHYSICAL EXAMINATION

The physical examination should focus on the head and neck, chest, and skin. The physical examination is often normal; however, findings such as wheezing during normal breathing and/or a prolonged expiratory phase may suggest asthma. A maneuver to enhance wheezing, forced exhalation, is not specific for asthma, but suggests airway obstruction or collapse.¹¹ In addition to breathing abnormalities, subjects with asthma often have concomitant signs of associated allergic conditions and evidence of upper respiratory tract inflammation and obstruction with inflamed nasal passages and/or nasal polyps or large tonsils. The findings of eczema, hives, or atopic dermatitis on skin examination are supportive of an asthma diagnosis.^{12,12a}

PHYSIOLOGY OF AIRFLOW LIMITATION

As understanding of the pathogenesis of asthma improves and strategies for treatment evolve, it is important to recognize that the link between the pathophysiology and the treatment of asthma is functional, involving variable limitation of air flow. These two cardinal manifestations of asthma, variability of symptoms in response to environmental factors and limitation of air flow, are crucial to making the diagnosis of asthma and distinguishing asthma from other obstructive lung diseases.

During asthma exacerbations, diffuse narrowing of the airways results in profound physiologic consequences. This narrowing has been thought to take place disproportionately in the small bronchi,¹³ although more recent studies suggest a prominent role for large and medium airways.¹⁴ As a result, lung function tests are abnormal, with an increase in airway resistance and a decline in maximal expiratory flow. Airway narrowing also prevents the lungs from completely emptying (“air trapping”) due to resistance to expiratory flow and bronchial closure at higher than normal lung volumes. The breath-to-breath variability of asthmatic obstruction and air trapping led to the concept of dynamic hyperinflation.¹⁵ As a result of dynamic hyperinflation, asthmatic patients breathe at higher total lung volumes, detectable as increased residual volume.^{16,17} Despite elevated total lung volumes, asthmatics typically have reduced tidal ventilation. Decreasing *forced vital capacity* (FVC) suggests worsening air trapping, whereas worsening of the *forced expiratory volume in 1 second* (FEV₁)/FVC ratio indicates increasing airway narrowing.¹⁶

At high lung volumes, flow limitation due to bronchial narrowing is offset by increased circumferential traction on the bronchial airways due to “tethering” of airways to inflated alveoli.¹⁸ This tethering effect may be less effective in asthma because the altered mechanical properties of the extracellular matrix in asthmatic airways stiffen the airways and reduce the mechanical forces opposing *airway smooth muscle* (ASM) contraction.¹⁹ The net effect is that the work

of breathing increases significantly, due in part to decreased lung and chest wall compliance at higher thoracic volumes and in part to the greater effort required to overcome the resistance of narrowed airways. The diaphragm and intercostal muscles are overloaded due to thoracic hyperinflation and mechanically disadvantaged due to suboptimal positioning on their length-tension curves.²⁰ As a result, accessory muscles of respiration, including the abdominal muscles and the sternocleidomastoids, are required.²¹ A large proportion of the subjective dyspnea associated with asthma exacerbations has been attributed to respiratory muscle fatigue.²²

The airway obstruction and closure in asthma is nonuniform, with significant regional variability that may not be completely reflected by decreases in peak flow.^{23,24} Although pulmonary blood flow is reduced in areas of alveolar hypoventilation, the magnitude of this response is insufficient to offset more than moderate or severe airflow obstruction. Ventilation-perfusion mismatching leads to a widened alveolar-arterial oxygen difference that tracks with increasing asthma severity; the arterial oxygen tension in acute severe asthma typically falls below 70 mm Hg.^{25,26} Arterial carbon dioxide tension initially falls as alveolar ventilation increases because carbon dioxide elimination is less impaired by ventilation-perfusion mismatching than is oxygen uptake.²⁷ As respiratory muscles fatigue, carbon dioxide tension increases, so a normal or elevated PCO₂ during an asthma exacerbation suggests impending respiratory failure.²⁸ Worsening of airflow obstruction or any factor that decreases respiratory drive (such as sedation) can drop alveolar ventilation precipitously; the resultant rise in PCO₂ further inhibits respiratory drive and muscle performance and hastens respiratory failure.²⁹

PULMONARY FUNCTION TESTING

(see Chapter 25)

Even between asthma exacerbations, pulmonary function testing shows characteristic changes reflecting the reduced flow and air trapping of dynamic hyperinflation. Decreased expiratory flow can be easily and reproducibly detected with a peak flowmeter in ambulatory patients, and *peak expiratory flow* (PEF) measurement is an accepted method to correlate physiologic function with the clinical severity of asthma. However, peak flow measurements are not standardized and cannot be correlated with other measures of lung function.³⁰ PEF as a percentage of the predicted value is 10% higher than FEV₁ on average, with a great deal of variability between measurements.³¹ PEF measurements tend to underestimate less severe obstruction and overestimate more severe obstruction.³² Currently, the recommended use of PEF measurement is for the daily monitoring of ambulatory patients with difficult-to-manage asthma. In this situation, the values should be compared with an individual patient's baseline measurement obtained when asymptomatic and well controlled.^{33,34}

Spirometry

The best and most standardized test of airflow obstruction is the FEV₁. The FEV₁ has the advantage of being an objective, non-patient-reported measurement of lung function. Improvement in FEV₁ of more than 12% and 200 mL after

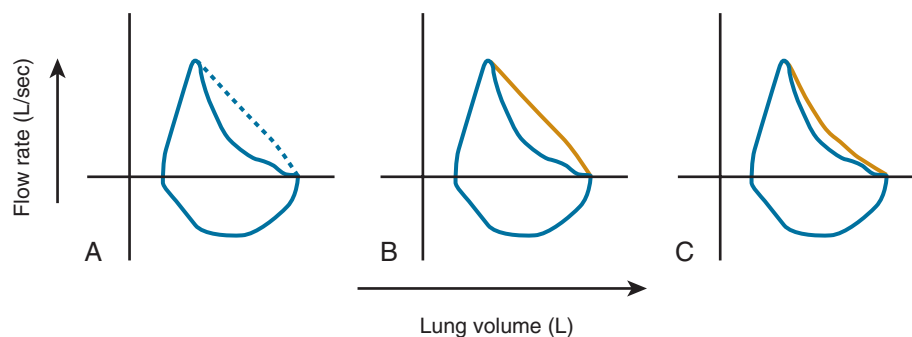


Figure 42-2 Flow-volume loops in asthma. **A**, The typical scooped appearance of the flow-volume loop in asthma is shown as the *solid blue line*. The predicted normal flow-volume loop is shown by the *dashed line*. **B**, The scooped appearance of the initial flow-volume loop (*blue line*) may show complete reversal following use of a bronchodilator (*brown line*). **C**, In some cases, the reversal of the scooped appearance following use of a bronchodilator is incomplete (*brown line*). (Adapted from Sameer KM: Asthma: diagnosis and management. *Med Clin North Am* 90:39–60, 2006.)

bronchodilator treatment indicates reversible airflow obstruction and is suggestive, but not diagnostic, of asthma.³⁷ Accurate measurement requires stopping *long-acting* β_2 -agonists (LABAs) for at least 12 hours and short-acting bronchodilators for at least 6 hours. Because the FEV₁ may be normal or near-normal between asthma flares, it is a poor marker of response to bronchodilators in mild asthma. The absolute value of the FEV₁ is dependent on the FVC and also reflects the small airways. Interpretation of FEV₁ therefore requires simultaneous FVC measurement. In asthma, the relative reduction in FEV₁ is typically greater than the reduction in the FVC. As a result, the FEV₁/FVC ratio in asthma is usually less than 70%. A characteristic flow-volume loop is created with scooping of the expiratory loop consistent with airflow limitation (Fig. 42-2). However, in severe asthma, this ratio may actually increase as air trapping increases residual volume and reduces the FVC. This apparent reversible restriction due to air trapping has been reported in asthma,^{16,40} but lung volumes measured by body plethysmography are usually normal or elevated.

The performance of the forced expiratory maneuver requires inhalation to total lung capacity before exhalation. In normal patients, the resultant stretch of intrapulmonary airways causes reflex bronchodilation and a shift in the pressure-volume curve. This alteration in lung mechanics is generally attributed to a transient decrease in ASM tone.⁴¹ However, some asthmatics have the opposite response, developing bronchoconstriction during deep inspiration. The mechanism of this “spirometry-induced bronchoconstriction” is unknown, but some evidence suggests that it may be partly due to increased inflammation and remodeling of asthmatic airways.⁴²

An alternative measure of airflow obstruction is the midexpiratory flow, measured between 25% and 75% of the FVC (*forced expiratory flow* [FEF]_{25%-75%}). Measured at lower lung volumes than FEV₁, reductions in the FEF_{25%-75%} may be more sensitive for identifying obstruction in small airways.⁴³ Studies in patients at high risk for asthma based on atopic symptoms have shown that this index is valuable in predicting airway hyperresponsiveness.⁴⁴ Similarly, in childhood asthmatics who have become asymptomatic, the FEF_{25%-75%} is a sensitive marker of residual physiologic abnormalities.⁴⁵ The clinical utility of the FEF_{25%-75%} is limited by the lack of acceptable standardized values.

High numbers of false-positive and false-negative results are seen when 80% of predicted FEF_{25%-75%} is used for classification.⁴⁶

The limitations of the FEF_{25%-75%} are due in part to large variation in the duration of FVC maneuvers. To address this issue, measurement of the *forced expiratory volume over the first 6 seconds* (FEV₆) has been proposed as an alternative to the FVC. The advantages of this maneuver over the FVC include ease of measurement, a more explicit end-of-test definition, and reduced risk of syncope.⁴⁷ Data are available suggesting parameters that may be used for disease classification, although the sensitivity and specificity of the FEV₁/FEV₆ in comparison with the FEV₁/FVC ratio remain controversial.^{48,49}

Lung Volumes and Diffusing Capacity

As a result of dynamic hyperinflation and consequent air trapping, residual volume, functional residual capacity, and total lung capacity may be elevated in asthma. Gas dilution techniques measure only the communicating volume of gas that equilibrates with the tracer gas during the single or multiple breath maneuvers and may underestimate these volumes due to regional heterogeneity in the distribution of ventilation.⁵⁰ For this reason, body plethysmography is often considered the method of choice for lung volume evaluation in severe asthma. However, because plethysmography measures the total volume of compressible gas within the thorax and abdomen, the inclusion of intra-abdominal gas may lead to overestimation of total lung capacity, particularly in severely obstructed asthmatics.⁵¹

Single-breath diffusing capacity is a marker of carbon monoxide gas transfer in the lungs and is reduced in most chronic lung diseases because of altered alveolar capillary volume and/or maldistribution of inspired gas due to airflow obstruction. In asthma the diffusing capacity is normal or elevated if airflow obstruction is not severe, and this finding can be useful in distinguishing asthma from other obstructive lung diseases.⁵² Elevated diffusing capacity in asthma has been attributed to increased perfusion of well-ventilated upper lung zones and is associated with large lung volumes. The unexpected finding of an increase in diffusing capacity should raise the possibility of undiagnosed asthma, whereas decreased diffusing capacity in a suspected asthmatic is suggestive of an alternate diagnosis or coexisting condition.⁵³

PROVOCATIVE CHALLENGES AND AIRWAY HYPERRESPONSIVENESS

Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) is a characteristic feature of asthma. Hyperresponsiveness can develop in response to a number of nonspecific environmental irritants, pharmacologic agonists, and inflammatory mediators. In the past, the predominant view was that airway inflammation was the mechanism causing AHR. This concept has been criticized because a number of studies have shown dissociation between AHR and inflammation,^{54,55} highlighting the fact that inflammation alone is insufficient as a mechanism of disease. Evidence suggests that a number of inflammatory *type 2 T helper* (Th2) cytokines, CD4 cells, and biochemical mediators contribute to the development of AHR in asthma. Exposure to Th2 cytokines in asthmatic airways can increase the isometric constrictor response of ASM by increasing calcium release from intracellular stores.^{56,57} In addition to the airway inflammation, factors contributing to mechanical airway obstruction have also been implicated in the pathogenesis of AHR, including epithelial permeability, smooth muscle hypertrophy, mucus hypersecretion, and airway remodeling.

AHR to environmental stimuli is a hallmark of asthma. Patients suspected of having asthma despite normal lung function testing usually develop bronchoconstriction in response to a provocative stimulus. Direct stimulation, during which a substance known to induce bronchoconstriction via direct action on smooth muscle is inhaled into the airways, is the most widely used method of assessing bronchial hyperresponsiveness. Nebulized methacholine, delivered in doubling concentrations until FEV₁ falls by more than 20%, is the agent most commonly used for bronchoprovocation. The concentration that causes a 20% fall is labeled the PC₂₀ (provocative concentration resulting in 20% fall in the FEV₁) and can be used to quantify the degree of AHR. A PC₂₀ less than 16 mg/mL is consistent with mild AHR, less than 4 mg/mL is consistent with moderate AHR, and less than 1 mg/mL with severe AHR,⁵⁸ with lower PC₂₀ levels generally corresponding to more severe asthma.⁵⁹ Bronchial hyperresponsiveness also has been associated with increased risk of developing persistent asthma and airway remodeling.⁶⁰

Indirect stimuli, such as cold air, exercise, inhalation of hypertonic saline, mannitol, and adenosine monophosphate, may also induce bronchoconstriction. Rather than working directly on smooth muscle, indirect stimuli cause the release of inflammatory mediators from airway cells that then interact with ASM to induce bronchoconstriction. Although the dose response is more difficult to assess with indirect stimuli, the results have direct applicability to daily asthma symptoms. For example, direct challenge of athletes suspected of having exercise-induced bronchoconstriction is less likely to uncover bronchoconstriction than indirect challenge using a surrogate for physical activity.⁶¹ There also may be differences between direct and indirect stimuli in the evaluation of response to treatment, with indirect challenge providing a better idea about response to therapy.⁶²

Impulse Oscillometry

Impulse oscillometry (IOS) is a form of forced oscillometry testing, a noninvasive technique to characterize the airway through the superimposition of pressure fluctuations into the airway during normal tidal breathing.⁶³ IOS delivers pressure oscillations via fixed square waves of 5- to 20-Hz frequency to measure airway resistance, the energy required to propagate a pressure wave through the airway, and reactance, the energy generated by the lungs' recoil against that pressure wave. These measurements allow calculation of the force necessary to propagate this pressure wave through the respiratory system, known as impedance. The location of airway diseases can also be localized because lower-frequency oscillations tend to travel to the lung periphery and higher-frequency ones reach only the most proximal airways.

Measurements are recorded during normal passive tidal breathing and require little training. Not surprisingly, IOS is most well studied in younger children. Significant correlations between FEV₁ and FVC by spirometry and impedance and resistance by IOS have been described.^{64,65} Most impressively, IOS has outperformed spirometry in sensitivity and specificity for the diagnosis of asthma in young children when compared to a methacholine challenge and validated clinical questionnaire.^{66,67} Despite increasing acceptance in the pediatric population, experience in adult patients remains limited.⁶⁸

IMAGING

Although traditionally, thoracic imaging has been used to rule out alternative pathologies, recent advances in imaging offer additional noninvasive techniques to support the diagnosis of asthma. The chest radiograph is most commonly normal in stable asthmatics, although nonspecific findings such as hyperinflation and bronchial wall thickening can be appreciated.⁶⁹ The primary role of the plain chest radiograph remains to rule out asthma mimics in those with atypical symptoms and to evaluate difficult-to-control symptoms.

Most commonly, chest *computed tomography* (CT) is used to evaluate chest radiographic abnormalities or identify those mimics less apparent on traditional chest radiography, such as bronchiolitis, bronchiectasis, tracheobronchomalacia, endobronchial lesions, and vascular anomalies.^{69,70} Increasingly, high-resolution chest CT techniques offer a useful tool to assess large and small airway pathology directly and indirectly. Nonspecific findings such as bronchial wall thickening, bronchial wall dilation, airway dilation, bronchiectasis, mucoid impaction, and mosaic lung attenuation consistent with air trapping are described in studies of asthmatic subjects. In a recent qualitative analysis of high-resolution CT scans of 185 severe asthma patients, abnormalities were present in 80% of the subjects with 62% demonstrating bronchial wall thickening and 40% bronchiectasis.⁷¹ Quantitative assessments of the airway tree and lung parenchyma are now possible with advances in CT technology and a number of associated proposed algorithms.⁷² Several studies have demonstrated increased large airway wall thickness in asthmatic patients

versus healthy controls regardless of disease severity.⁷³ Others support a further relationship between asthma severity and measured airway thickness.⁷⁴⁻⁷⁶ Clinical application of these techniques, however, remains limited by mostly single-center experiences and a lack of proof-of-concept studies. Despite the limited data, this is an emerging area in the diagnosis and phenotypic characterization of asthma.

Fraction of Exhaled Nitric Oxide

Nitric oxide (NO) and related compounds are generated by various resident and inflammatory airway cells and have a broad variety of functions as inflammatory mediators, vasodilators, bronchodilators, and neurotransmitters.⁷⁷ In the asthmatic airway, NO exhibits a paradoxical response by enhancing airway dilation at low concentrations but propagating inflammatory responses at higher concentrations. Eosinophilic airway inflammation, as measured by tissue-based eosinophilia, bronchoalveolar lavage eosinophilia and bronchial epithelial major basic protein density, correlates with *fraction of exhaled NO* (FeNO) in some asthma patients.

Noninvasive measurements of FeNO have been standardized for clinical use and may serve as a complementary tool in asthma diagnosis. However, the FeNO in stable, mild asthma after use of inhaled corticosteroids is often in the same range as that in normal, nonasthmatic patients.^{78,79} FeNO falls in a dose-dependent manner with steroid use, making FeNO less useful as an ongoing biomarker in patients using steroid therapy.^{80,81} A recent trial showed that an FeNO greater than 45 parts/billion excludes well-controlled asthma with a negative predictive value of nearly 90%. High FeNO suggests a severe, steroid-responsive phenotype. A decline in FeNO greater than 40% between visits is a sign of improved control, and low levels of FeNO predict lower risk of acute exacerbation.⁸² Measuring the FeNO during a period of good control can provide a baseline for comparing trends over time when following symptoms and response to treatment. The *American Thoracic Society* (ATS) has published guidelines on the use of FeNO for the diagnosis and management of asthma; however, widespread use of this technology is still lagging.⁶⁵ More recently, International ATS/*European Respiratory Society* (ERS) guidelines warned against the use of FeNO to guide treatment in severe asthma, citing low-quality evidence.⁸³

MANAGEMENT OF ASTHMA

INTRODUCTION

The inherent complexities in evaluating and treating asthma are evident from studies in the 1970s and 1980s documenting a significant number of asthma deaths that were attributable to failure of clinicians to recognize the clinical severity of asthma, thus leading to inadequate management. For example, a study of asthma deaths in the West Midland and Mersey regions of England in 1979 led to the conclusion that failure to recognize the severity of asthma delayed treatment, that routine asthma management was unsatisfactory, and that 86% of the deaths might have been preventable.⁸⁴ A similar study in 1988 included the observation that a large number of asthmatics admitted

to the hospital for observation were discharged with no escalation in the management of their asthma.⁸⁵ This ultimately led the NHLBI to convene the first expert panel to develop guidelines for the diagnosis and treatment of asthma, and the resulting recommendations were published in 1991.⁸⁶ Other guidelines soon followed, extending the NHLBI's initial recommendations. Subsequent revisions have provided clinicians with a reliable framework for evidence-based management of patients with asthma. These guidelines emphasize maintaining long-term control of symptoms through attention to environmental and social components of asthma and using treatment regimens tailored to the severity of each patient's symptoms. Crucial components of management include initial evaluation of severity (Table 42-1) and ongoing assessment of control; appropriate pharmacologic therapy to reverse bronchoconstriction and ameliorate inflammation; identification and control of environmental factors that worsen symptoms or trigger exacerbations; and creation of a partnership between the patient and the health care professional to ensure that therapy is tailored to symptoms.

ASSESSMENT

Asthma Control

The assessment of patients with asthma involves five essential steps: determining the current degree of control based on symptoms, reliever medication use, recent exacerbations, and lung function; and evaluating the risk of future adverse outcomes. With this in mind, the NHLBI updated guidelines and the *Global Initiative for Asthma* (GINA) proposed a parallel scheme for asthma control based on expert opinion³⁴ (Table 42-2). The NHLBI and GINA categorizations represent categorical interval variables with threshold values. For example, GINA guidelines accept some daytime symptoms (<2 times/week) in the definition of "controlled" asthma, whereas nocturnal symptoms move a patient to the "partially controlled" category. The importance of control indices is underscored by the relationship between poor asthma control and substantial degrees of physical impairment and diminished quality of life, even after taking the baseline severity of asthma into account.⁸⁷

Several different validated instruments exist for assessing asthma, including the Asthma Control Questionnaire (Table 42-3), Asthma Control Test (Fig. 42-3), Asthma Therapy Assessment Questionnaire (Table 42-4), and Asthma Control Scoring System (Fig. 42-4).⁸⁸⁻⁹¹ All are useful because they direct history taking, provide goals for the management of symptoms, and guide adjustments in treatment.⁹²

Lung Function

Lung function testing is an important part of assessing asthma, both for making the initial diagnosis and as a means of evaluating the response to therapy. A study from the Genetics in Asthma Network⁹³ suggested that FEV₁ and FVC are useful components of a standardized scheme for identifying the contribution of genes and environments to disease expression. Further proof of the importance of lung function testing was provided by a report that asthmatic patients with lower FEV₁ values were at significantly higher risk of needing acute care.⁹⁴ Although the FEV₁, FEV₁/FVC

Table 42-1 Classification of Severity of Asthma in Adults and Children Older Than 12 not Currently Taking Long-Term Controllers

CLASSIFICATION OF ASTHMA SEVERITY (YOUTHS ≥ 12 YR AND ADULTS)				
Components of Severity	Intermittent	PERSISTENT		
		Mild	Moderate	Severe
IMPAIRMENT				
Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings	<2×/mo	3–4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β ₂ -agonist use for symptom control	≤2 days/wk	>2 days/wk but not daily	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal FEV ₁ between exacerbations <ul style="list-style-type: none">■ FEV₁ > 80% predicted■ FEV₁/FVC normal	<ul style="list-style-type: none">■ FEV₁ > 80% predicted■ FEV₁/FVC normal	<ul style="list-style-type: none">■ FEV₁ > 60% but < 80% predicted■ FEV₁/FVC reduced 5%	<ul style="list-style-type: none">■ FEV₁ < 60% predicted■ FEV₁/FVC reduced > 5%
RISK				
Exacerbations (consider frequency and severity)	0–2/yr Frequency and severity may fluctuate over time Relative annual risk of exacerbations may be related to FEV ₁	>2/yr	>2/yr	>2/yr

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the diagnosis and management of asthma (EPR-3) DRAFT, page 74, section 3, component 1: Measures of Asthma Assessment and Monitoring.

Table 42-2 Classification of Asthma Control in Adults and Children Older Than 12

Components of Control	CLASSIFICATION OF ASTHMA CONTROL (YOUTHS ≥ 12 YR AND ADULTS)		
	Well Controlled	Not Well Controlled	Very Poorly Controlled
IMPAIRMENT			
Symptoms	≤2 days/wk	>2 days/wk	Throughout the day
Nighttime awakening	≤2 times/mo	1–3 times/wk	≥4 times/wk
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting β-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times/day
FEV ₁ or peak flow	>80% predicted/personal best	60%–80% predicted/personal best	<60% predicted/personal best
Validated questionnaires			
ATAQ	0	1–2	3–4
ACQ	≤0.75*	≥1.5	N/A
ACT	≥20	16–19	≤15
RISK			
Exacerbations	0–1/yr Consider severity and interval since last exacerbation	≥2/yr [†]	
Progressive loss of lung function	Evaluation requires long-term follow-up care		
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

[†](1) The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 wk and by spirometry or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit. (2) At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had two or more exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire; EIB, exercise-induced bronchospasm; FEV₁, forced expiratory volume in 1 second; N/A, not applicable.

Adapted from National Heart, Lung, and Blood Institute as a part of the National Institutes of Health and the U.S. Department of Health and Human Services, 2007.

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an **X** in the one box that best describes your answer.

1. In the **past 4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. During the **past 4 weeks**, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

3. During the **past 4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

4. During the **past 4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, or Maxair®)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

5. How would you rate your **asthma** control during the **past 4 weeks**?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Asthma Control Test™ copyright, QualityMetric Incorporated 2002, 2004. All Rights Reserved.
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Figure 42-3 The Asthma Control Test is a validated questionnaire that assesses the presence of asthma symptoms and use of asthma medications over the prior 4-week period. (Copyright 2002, 2004 by QualityMetric Incorporated. All rights reserved. Asthma Control Test™ [ACT] is copyrighted by QualityMetric Incorporated. No part of the Asthma Control Test™ may be reproduced or transmitted in any form or by any means electronic, mechanical, including photocopy, recording, or any information storage or retrieval system—without permission of the copyright holder. It should be used only as text. Licensing & Registration. For permission to reproduce the survey and/or any associated intellectual property [e.g., trademarks, scoring algorithms, interpretation guidelines, and normative data] for any purpose, registration must be made and license obtained at www.qualitymetric.com.)

Table 42-3 Sample Question from The Asthma Control Questionnaire*

Please answer questions 1–6.	
1. On average, during the past week, how often were you woken by your asthma during the night?	<div>0 Never</div> <div>1 Hardly ever</div> <div>2 A few minutes</div> <div>3 Several times</div> <div>4 Many times</div> <div>5 A great many times</div> <div>6 Unable to sleep because of asthma</div>

*This is a validated questionnaire that assesses asthma control during the prior week by determining the presence of symptoms of asthma and use of rescue medication.

Note: The complete user package for the ACQ may be obtained from: <http://www.qoltech.co.uk/acq.html>. This is provided to all clinicians and academics free of charge but for commercial organizations and commercially funded research, there is a one-time user fee.

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ratio, and PEF are useful in the diagnosis and monitoring of asthma, the utility of these measurements in improving the outcome of asthma remains incompletely defined. However, a low prebronchodilator FEV₁ is a strong predictor of decline in asthma control and a low postbronchodilator FEV₁ is a marker of future risk.^{38,39} In mild asthma, however, FEV₁ is often normal or near-normal and thus may be poorly responsive to bronchodilators.

Table 42-4 Asthma Therapy Assessment Questionnaire on Asthma Control

1. In the past 4 weeks, did you miss any work, school, or normal daily activities because of your asthma? (1 point for YES)
2. In the past 4 weeks, did you wake up at night because of your asthma? (1 point for YES)
3. Do you believe your asthma was well controlled in the past 4 weeks? (1 point for NO)
4. Do you use an inhaler for quick relief from asthma symptoms? If yes, what is the highest number of puffs in 1 day you took of this inhaler? (1 point for more than 12)
Total points—0–4, with more points indicating more control problems

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PEF measurement is a standard method to correlate physiologic function with asthma severity and has been used as a marker of asthma control in many clinical trials. However, individual peak flow measurements are highly variable and the *variability* in peak flow has a greater predictive value for future exacerbations than individual PEF measurements themselves.^{35,36} The clinical usefulness of peak flow measurements is also limited by patient resistance to home monitoring and difficulty with consistently maintaining peak flow records.

Asthma Control Scoring System**Clinical assessment**

Symptoms score	25%	20%	15%	10%	5%	Total score
Diurnal symptoms	None	<4 times/w	4–7 times/w	>once/day	Severe	15
Nocturnal symptoms	None	<1 night/w	1–3 nights/w	4–7 nights/w	Severe	20
β ₂ -agonist on demand*	None	<4 doses/w	4–7 times/w	>1 dose/day	>4 doses/day	15
Physical activity	None	Very little limitation	Some limitation	Moderate limitation	Severe limitation	15
Total score						65%

Physiologic assessment

Score (%) [†]	100	80	60	40	20	Total score
FEV ₁ or PEF (% of predicted or optimal value)	>90%	80%–89%	70%–79%	60%–69%	<60%	60%
PEF variation	<10% >5 days/w	<10% >5 days/w	10%–15% >5 days/w	16%–25% >5 days/w	>25% >5 days/w	Not done

Inflammatory assessment

Score (%)	100	80	60	40	20	Total score
Airway eosinophilia (%)	0	2 or less	>2–5	5.1–8	>8	60%

* Excluding 1 dose/ day before exercise.

† Score divided by 2 if the two criteria are used.

Figure 42-4 The Asthma Control Scoring System is a means of determining the percent asthma control for a specific patient on the basis of symptoms, expiratory flows, and airway inflammation (induced-sputum eosinophilia). For each section, a percentage score is obtained. It can be added and divided by 3 to obtain a global asthma control score. The present example is about a patient who has diurnal symptoms five times a week (w), has nocturnal asthma about twice a month, uses his rescue bronchodilator almost daily, has some limitations of his activities, and has a baseline FEV₁ of 74% and 5% eosinophils in induced sputum. The global score for this patient is $65 + 60 + 60\%/3 \cong 62\%$. (From Boulet L-P, Boulet V, Milot J: How should we quantify asthma control?: a proposal. *Chest* 122(6):2217–2223, 2002.)

Biomarkers

The emergence of an increased body of literature to support the presence of asthma endotypes has made it imperative that we develop and identify biomarkers associated with each asthma type.⁹⁵⁻⁹⁷ These biomarkers will become increasingly important in determining the specific therapies that are administered to a particular patient. Currently, there are two accepted types of inflammation in asthma based on the presence or absence of Th2 inflammation: a “Th2 high” phenotype that is characterized by the presence

of peripheral eosinophilia, sputum eosinophils, elevated FeNO and/or increased markers associated with Th2 inflammation (e.g., serum periostin)⁹⁸ and a “Th2 low” phenotype characterized by the absence of any of these markers of Th2 high status. In fact, the Th2 low phenotype has no known biomarkers and this phenotype clearly requires additional study.

Before the introduction of specific biomarkers, elevated blood eosinophils were proposed as a means to identify patients with predominant Th2 inflammation. Alterations

in blood eosinophil levels are associated with response to various therapies,^{99,100} and increased eosinophils are correlated with more severe disease.^{101,102} A blood eosinophil level of greater than or equal to $0.3 \times 10^9/L$ (300 cells/ μL) has become increasingly accepted as a peripheral marker of eosinophilic inflammation. An elevated level of blood eosinophils is predictive of response to anti-IL-5 therapy.⁹⁹

High sputum eosinophil counts predict response to inhaled corticosteroids and an increased risk of future exacerbations,^{103,104} and an increase in sputum eosinophil counts following corticosteroid dose reduction predicts future deterioration of asthma control.¹⁰⁵⁻¹⁰⁷ A change of 50% in sputum eosinophil counts is considered to be a clinically significant marker of response to therapy.^{108,109} However, sputum eosinophils may be difficult to quantify in clinical practice and their current value is primarily in clinical research.

FeNO has some advantages compared with counting the number of sputum eosinophils. Measurement of FeNO can be performed rapidly in a primary care setting, requires less technical expertise, and provides real-time objective physiologic data. In particular, when accompanied by more traditional diagnostic tools, it may be used to identify eosinophilic asthma. ATS guidelines support the use of FeNO for the diagnoses of eosinophilic airway inflammation and asthma when objective evidence is necessary.⁶⁵ FeNO concentrations less than 25 ppb (<20 ppb in children) suggest that eosinophilic airway inflammation and responsiveness to corticosteroids are unlikely; elevated levels suggest eosinophilic airway inflammation and responsiveness to corticosteroids.¹¹⁰ Major limitations of using FeNO to confirm the diagnosis of asthma include the relatively high prevalence of noneosinophilic phenotypes that are characterized by a lack of increased FeNO and difficulty with clinical interpretation of values obtained in the setting of concomitant steroid use that may lead to false-negative results.^{65,77} Of note, the ATS guidelines predominantly apply to patients with mild to moderate asthma. A recent ERS/ATS task force recommended against the routine use of FeNO to diagnose asthma and to evaluate response to therapy in patients with severe disease.⁸³ However, there is still a role for FeNO in phenotyping patients by identifying those with a Th2 high/eosinophilic phenotype, regardless of asthma severity.

Serum total *immunoglobulin E* (IgE) has been used to identify patients with asthma who are likely to respond to

therapy with omalizumab, a drug that targets IgE. Omalizumab prevents IgE from binding to its receptor on the cell surface and reduces the amount of free IgE present in the blood. There are currently no commercially available assays to measure free IgE. Baseline IgE is only a modest predictor of response to omalizumab therapy.¹¹¹

Periostin is secreted by bronchial epithelial cells and fibroblasts in response to IL-4 and IL-13.^{112,113} Periostin is expressed in asthma patients and can be measured in the serum. Periostin is an emerging biomarker that offers some advantages over peripheral eosinophilia and FeNO because serum levels of periostin tend to be less variable, correlate well with tissue eosinophilia, and are not altered by treatment with steroids.⁹⁸ More importantly, serum periostin is predictive of response to therapy with biologic agents that target IL-13, making its future use as a biomarker much more promising.^{114,115} Periostin is the first biomarker in asthma to be directly correlated with the underlying pathophysiology and makes the possibility of personalizing asthma therapy more likely to be realized.¹¹⁶

The increased interest in identifying biomarkers for use in clinical practice and standardizing of biomarkers obtained in asthma clinical trials led to the convening of a task force to identify biomarkers that should be included in asthma outcomes. The task force recommended FeNO, sputum eosinophils, blood eosinophils, total IgE, allergen-specific IgE, urinary leukotriene E₄, and several new emerging markers. The emerging markers include airway imaging, exhaled breath condensate, and proteomic and genomic techniques to identify signatures in tissue obtained from patients with asthma. Although these rapid throughput methods are promising, they may be years away from clinical application.^{117,117a} The current biomarkers are summarized in Table 42-5.

ASTHMA TREATMENT APPROACHES

Overview

Current guidelines recommend adjusting therapy in a stepwise fashion to reduce daily symptoms and risk of exacerbations while minimizing the use of medications (Fig. 42-5).^{12,118} The hierarchy of treatment recommendations is based on the available literature about efficacy and safety and provides a prominent role for controller medications at all levels of asthma treatment. In general, the strategy and

Table 42-5 Asthma Biomarkers and Associated Phenotypes as Predictors of Response to Specific Therapies

Biomarker	Asthma Phenotype	Predicts
Periostin	Th2 high	Response to anti-IL-13 and IL-4 therapy ¹¹²⁻¹¹⁶
Elevated exhaled nitric oxide (>50 ppb in adults, >35 ppb in children)	Th2 high	Response to inhaled steroids ^{65,110}
Sputum eosinophils >3%	Th2 high	Response to inhaled steroids ^{103-107,109,207}
Peripheral eosinophils ($>0.3 \times 10^9/L$ or 300/ μL)	Th2 high	Response to anti-IL-5 therapy ^{99,100,292}
Elevated total IgE > 30 IU	Allergic	Response to omalizumab ^{111,202}
Allergy skin tests and elevated specific IgE	Allergic asthma with atopy	Response to immunotherapy, omalizumab
Lack of elevated peripheral and sputum eosinophils and low FeNO	Th2 low	Response to tiotropium and macrolides (likely to be poor responders to steroids) ^{215,216}

Stepwise Approach for Managing Asthma in Patients ≥ 12

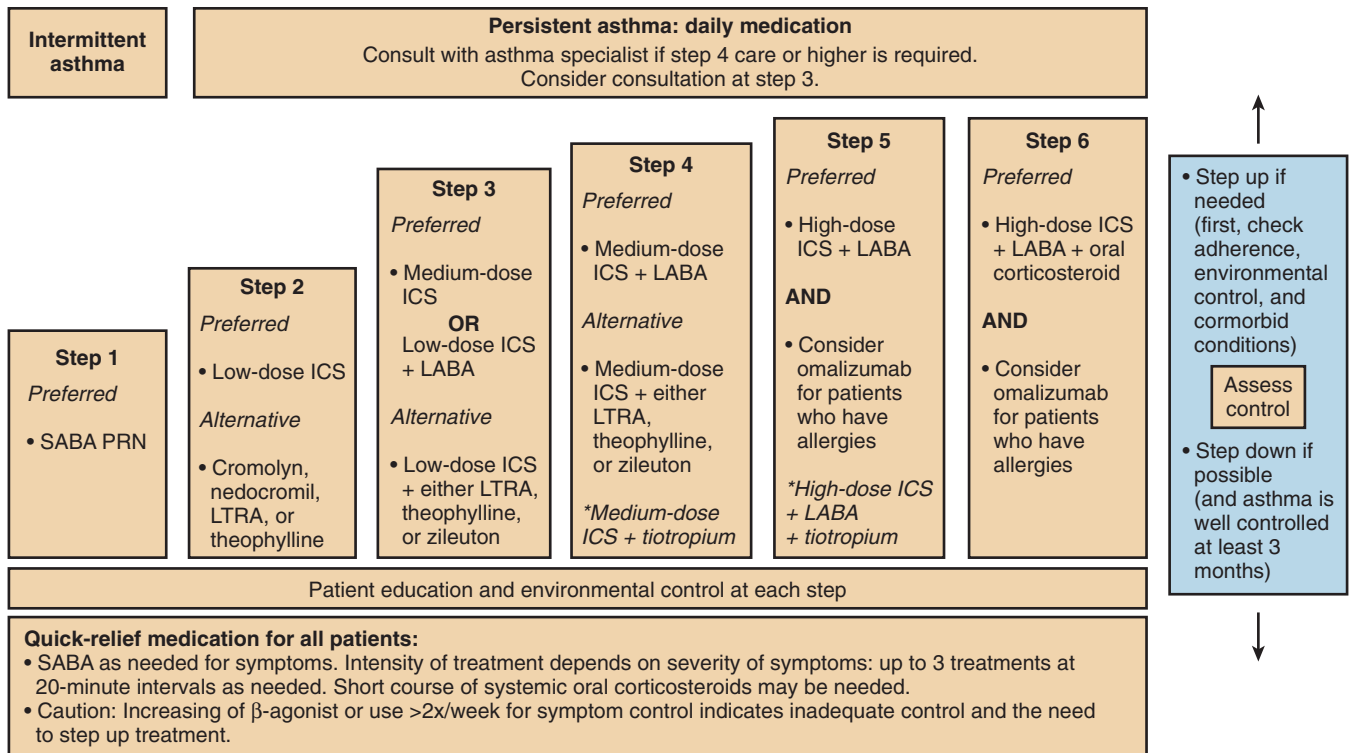


Figure 42-5 Medication recommendations for control of asthma in adults and children older than 12. SABA, short-acting β_2 -agonist; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long-acting β_2 -agonist. (Adapted from National Asthma Education and Prevention Program EPR-3 guidelines from the National Heart, Lung, and Blood Institute 2007.)

recommendations in adults and children are similar. However, the increased risk of adverse effects and/or the lack of safety data in pediatric patients for theophylline, omalizumab, and the 5-lipoxygenase inhibitor zileuton led to their exclusion from current pediatric treatment guidelines (eFigs. 42-1 and 42-2).¹¹⁸

Specific Pharmacologic Agents

β_2 -agonists. β_2 -agonists have been used for thousands of years in the form of the ephedrine-containing herbal preparation, ma huang.¹¹⁹ However, it was not until the 1940s, when the nonselective β -agonist isoproterenol was introduced, that β -agonists became the standard of care for treating airway disease. The subsequent development of the β_2 -selective agents, albuterol and terbutaline, with improved side effect profiles, led to their current role as the cornerstone of asthma therapy.¹²⁰

β_2 -agonist activity is primarily mediated by binding to a specific G-coupled transmembrane receptor found in high abundance on ASM. Receptor binding leads to increased intracellular cyclic adenosine monophosphate and relaxation of ASM.¹²¹ Notably, β_2 -receptors are also found on other resident airway cells, including airway epithelial cells and circulating immune cells, and binding to these sites may reduce vascular permeability and inflammatory mediator release.¹²² One concern raised about the chronic use of β_2 -agonists is that of receptor desensitization.¹²³ As with most signaling receptors, repeated exposure to β_2 -agonists can lead to decreased responsiveness of membrane receptors through receptor down-regulation via receptor endo-

cytosis and uncoupling of receptors from downstream transduction pathways. This response appears to be self-limited and minor in ASM.

β_2 -selective agonists are usually administered by aerosol, which maximizes delivery to target tissue (ASM), while minimizing the exposure of nontarget tissues. Both *short-acting β_2 -agonists* (SABAs) and LABAs are available, and the onset and duration of action are primarily related to lipophilicity.¹²⁴ Short-acting agents are used for rescue or emergent treatment, whereas LABAs are used in combination with inhaled corticosteroids for chronic management.

A number of highly selective SABAs are now available, and all have a rapid onset of action with peak action between 60 and 90 minutes. Because they are inhaled directly into the airways, systemic side effects are minimal, even at high doses. A β_2 -agonist preparation containing only the active enantiomer of albuterol was developed in an attempt to minimize side effects. However, clinical trials have not shown significant differences in outcome or tolerability compared with racemic albuterol.¹²⁵ On the basis of current guidelines, these medications should be used to treat symptoms not adequately controlled on a regimen of long-acting controller agents. Increased frequency of SABA use is a sign of inadequate control of symptoms or overreliance on rescue medication. Patients using more than one canister a month or requiring excessive doses of rescue inhalers (defined as > 2 doses/week) should be considered for a step-up in therapy.^{12,118}

LABAs have minimal utility for treating acute asthmatic symptoms because of their delayed onset of action. However,

in patients with inadequately controlled asthma, they can be added to an *inhaled corticosteroid* (ICS) to improve symptoms and efficacy of the ICS. Formoterol and salmeterol are the two LABAs available. Formoterol has a shorter onset of action than salmeterol, whereas salmeterol has a longer duration of action. Each has been shown to improve lung function, reduce symptoms, and reduce the frequency of exacerbations.¹²⁶

Adverse events associated with the use of β_2 -agonists are primarily due to unwanted activation of β_2 -receptors in nonpulmonary tissue. Cardiac stimulation causes tachycardia and arrhythmias, whereas skeletal muscle stimulation causes tremors and hypokalemia. Since the introduction of β -agonists, there has been concern about the clinical implications of receptor desensitization. Two unique SABAs, isoproterenol forte and fenoterol, were implicated in two “epidemics” of increased asthma deaths in the 1960s and 1970s, respectively^{127,128}; later analysis suggested that this might have been due to excessive use, rebound bronchoconstriction due to short duration of action, tachyphylaxis, or lipophilicity. After these agents were withdrawn from the market, mortality declined¹²⁹ and the safety profile of subsequent SABAs has been good. Clinical data suggest that “as-needed” versus scheduled SABA treatment is associated with improved physiology^{130,131} and fewer, less severe exacerbations.¹³²

Adverse events with LABAs have also been of concern, particularly because of their long duration of action. In the *Salmeterol Multicenter Asthma Research Trial* (SMART),¹³³ patients were randomized to salmeterol or placebo plus usual care, with approximately 13,000 patients in each arm. There was no significant difference in risk of death in either group, but subgroup analysis identified a small but increased risk of death that was more prominent in African American subjects in the salmeterol arm of the trial. However, the African American patients also had poorer control of symptoms at baseline (with more exacerbations and hospitalizations) and a lower rate of inhaled corticosteroid use than the white patients.¹³³ Importantly, the use of LABAs with inhaled corticosteroids in the same metered-dose inhaler has been shown to be safe and effective.¹³⁴

Several studies have explored the relationship between polymorphisms in the β_2 -receptor and responses to β -agonist therapy. Specifically, in patients treated with scheduled albuterol, the presence of the Arg/Arg polymorphism at the codon 16 locus (B16) was associated with lower PEF and FEV₁, and increased symptoms, more rescue inhaler use, and a higher rate of exacerbations as compared with patients who were Arg/Gly or homozygous Gly/Gly. All of these symptoms improved when regular albuterol was withdrawn.^{130,135,136} Use of LABAs (with and without inhaled corticosteroids) has been shown to worsen physiologic markers of respiratory function in Arg/Arg patients in some studies, although these findings are not consistent.^{137,138} The LARGE study demonstrated beneficial effects of LABAs in combination with ICS irrespective of B16 genotype, and the authors recommended against alterations in the current use of LABA.¹³⁹ Further research is required; however, thus far there are no indications that use of LABA in the Arg/Arg genotype is associated with undue risk. Additional genetic studies are examining potential mechanisms by which β -adrenergic receptor polymorphisms may

contribute to the risk of LABA therapy in some patients with asthma.¹⁴⁰

LABAs have modest effects on improving asthma control and reducing severe exacerbations, with an uncertain safety profile.^{141,142,142a} Despite the conflicting data on the safety of LABA therapy in certain populations, the U.S. *Food and Drug Administration* (FDA) felt that there was enough concern to warrant the addition of a black box warning on all drugs containing LABAs. The use of LABAs should be judicious, and clinicians should strive to discontinue these medications if patients no longer require them. Additionally, it is critical to prescribe LABAs only with concomitant ICSs and to warn patients about the potential dangers of LABA monotherapy. In fact, the FDA recommends the use of combination inhalers rather than two separate inhalers in order to avoid the possibility of patients using monotherapy. In 2010 the FDA mandated that manufacturers of drugs containing LABAs conduct large studies to demonstrate safety, and these studies are ongoing.¹⁴³

Other Bronchodilators. Anticholinergic agents act as bronchodilators via competition with acetylcholine at neuromuscular junctions, thereby blocking transmission of bronchoconstrictor reflexes.¹⁴⁴ The short-acting anticholinergic ipratropium bromide is effective in patients with COPD but is considered a second-line agent for treating asthma, most likely because cholinergic tone contributes less to bronchoconstriction in asthma. Although no trials have compared short-acting anticholinergics with SABAs, randomized trials studying the addition of anticholinergics to β -agonists do not show any additional benefit in patients with chronic asthma.¹⁴⁵ However, specific asthma phenotypes might be more likely to respond to anticholinergic treatment, including patients with fixed airflow obstruction, advanced age,¹⁴⁶ or longer duration of disease.¹⁴⁷ Furthermore, anticholinergics may be an acceptable alternative for certain subgroups of patients who do not tolerate β -agonist treatment or for patients with the Arg/Arg B16 genotype, although this has not been studied directly.

Tiotropium, a long-acting anticholinergic agent, has been shown to be beneficial for treating the symptoms of COPD. Spirometric improvement has been demonstrated in case series of asthmatics who do not have sputum eosinophilia¹⁴⁸ and asthmatics with concomitant COPD.¹⁴⁹ Three recent randomized controlled trials have indicated a role for tiotropium as add-on therapy to both inhaled corticosteroids and ICS/LABA combination therapy in patients with moderate to severe asthma with improved markers of airway function.¹⁵⁰⁻¹⁵² Bronchodilator responsiveness to albuterol, higher resting cholinergic tone (defined by a lower resting heart rate), and increased airway obstruction (defined by a lower FEV₁/FVC ratio) are predictors of response to tiotropium.¹⁵³ Although not yet approved for asthma, it is expected that it will be approved within the next 3 to 5 years.

Inhaled Corticosteroids. With recognition of the central role of inflammation in the pathophysiology of asthma, contemporary treatment strategies now emphasize inhaled corticosteroids for long-term control of symptoms. Corticosteroids suppress inflammatory responses through a broad influence on signal transduction and gene expression

pathways. Corticosteroids bind to a specific cytoplasmic receptor that translocates to the nucleus, where it modulates expression of inflammatory genes through inhibition of histone acetyltransferases and recruitment of histone deacetylases, two classes of histone modifiers that control DNA unwinding and gene expression epigenetically.^{154,155} Airway inflammatory cell influx and markers of airway inflammation in asthma are reduced by corticosteroid administration.^{156,157}

Systemic corticosteroids have been used in the treatment of asthma since the 1940s and continue to be a cornerstone of the management of acute exacerbations. However, systemically administered corticosteroids are associated with a variety of undesirable side effects. The introduction of ICSs in the 1970s ushered in a new era in the treatment of asthma. As with bronchodilators, delivery of drug directly into the lungs through the use of inhaled preparations minimizes systemic toxicity and improves therapeutic benefit.

The use of ICSs improves all aspects of asthma control. ICSs reduce asthmatic symptoms, improve lung function, decrease airway inflammation, and control AHR.^{158,159} A large meta-analysis showed that ICSs reduce asthma exacerbations by 55% when compared with placebo¹⁶⁰ and reduce the risk of hospitalization by 50% when compared with use of as-needed β -agonists alone.¹⁶¹ Furthermore,

risk of death from asthma is reduced in a dose-response manner with the use of ICS.¹⁶² As a result, ICSs are considered to be first-line therapy for all patients requiring more than twice-weekly β -agonist use.¹² Predictors of response to inhaled corticosteroids include FeNO level greater than 47 ppb,¹¹⁰ reversibility to albuterol and a decreased FEV1,¹⁶³ and the presence of increased sputum eosinophils (>2% to 3%).¹⁰⁰ Interestingly, a large proportion of asthma patients are persistently noneosinophilic and unlikely to respond to therapy with ICS, supporting the need for standard phenotyping of asthma with subsequent personalized therapy.^{100,164,165}

The initial recommendations regarding the use of ICS in patients with mild to moderate persistent asthma emphasized their use on a daily to twice-daily basis. Recently, there has been increased evidence that ICSs can be efficacious at reducing asthma symptoms and achieving asthma control when used intermittently in both children and adults.¹⁶⁶⁻¹⁶⁹ Despite these studies, there is still debate about the intermittent use of ICS; certainly ICS should not be used intermittently in patients with severe disease.

There are multiple different inhaled corticosteroid preparations and delivery devices on the market (Table 42-6). The inhalers differ in particle size ranging from a median mass aerodynamic diameter of about 1 micron to those with large particles that are 2 to 5 microns in size. The delivery

Table 42-6 Inhaled Steroid Preparations and Dosages

ICS Generic/Trade Names	Dosage Forms	Age	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone ■ QVAR	HFA MDI: 40 or 80 μ g/puff	5–11 ≥12	80–160 80–240	>160–320 >240–480	>320 >480
Budesonide ■ Pulmicort ■ Symbicort (with formoterol)	Respules for nebulization: 0.25, 0.5, 1.0 mg/neb Flexhaler DPI: 90 or 180 μ g/inh Symbicort HFA MDI: 80/4.5 or 160/4.5 μ g/puff	0–4 5–11 5–11 ≥12 ≥12	0.25–0.5 0.5 180–400 180–600 320 (80/4.5 2 puffs bid)	>0.5–1.0 1.0 >400–800 >600–1200 640 (160/4.5 2 puffs bid)	>1.0 2.0 >800 >1200
Ciclesonide ■ Alvesco	HFA MDI: 80 or 160 μ g/puff	5–11* ≥12	80–160 160–320	>160–320 >320–640	>320 >640 (Mfr highest recommended dose 640 μ g/day)
Fluticasone ■ Flovent ■ Advair (with salmeterol)	HFA MDI: 44, 110, or 220 μ g/puff Flovent Diskus DPI: 50, 100, or 250 μ g/inh Advair HFA MDI: 45/21, 115/21, or 230/21 μ g/puff Advair Diskus DPI: 100/50, 250/50, or 500/50 μ g/inh	0–11 ≥12 5–11 ≥12 4–11 ≥12 4–11 ≥12	88–176 88–264 100–200 100–300 180 (45/21 2 puffs bid) 180 (45/21 2 puffs bid) 200 (100/50 1 inh bid) 200 (100/50 1 inh bid)	>176–352 >264–440 >200–400 >300–500 460 (115/21 2 puff bid) 500 (250/50 1 inh bid)	>352 >440 >400 >500 460–920 (115–230/21 2 puffs bid) 920 (230/21 2 puffs bid) 500–1000 (250–500/50 1 inh bid) 1000 (500/50 1 inh bid)
Mometasone ■ Asmanex ■ Dulera (with formoterol)	Asmanex Twisthaler DPI: 110 or 220 μ g/inh Dulera HFA MDI: 100/5 or 200/5 μ g/puff	4–11 ≥12 ≥12	110 (Mfr highest recommended dose 110 μ g/day) 220	220–440 440 400 (100/5 2 puffs bid)	>440 >440 (Mfr highest recommended dose 800 μ g/day) 800 (200/5 2 puffs bid)

*Not FDA approved for children < 12 years.

DPI, dry powder inhaler; HFA, hydrofluoroalkane, a safe propellant; MDI, metered-dose inhaler; Mfr, manufacturer.

Adapted from National Asthma Education and Prevention Program EPR-3 guidelines from the NHLBI 2007. Obtained from ainotes.wikispaces.com/Asthma+controller+medications. Accessed March 8, 2014.

devices include dry powder inhalers and metered dose inhalers. The choice of inhaled corticosteroids is based on the physician's discretion about the patient's needs and often rests on cost, convenience of dosing, and reduction of side effects.

One key factor that warrants consideration is the role of small airway inflammation and associated obstruction as a key component of asthma pathophysiology. The presence of preserved FEV₁ with decreased mid expiratory flow and increased distal resistance is indicative of a small airway phenotype.¹⁷² Targeted therapies to help modulate small airway inflammation are important, and there are several small-particle-size inhalers that have improved deposition into the distal lung.¹⁷³ Small-particle-size inhalers include ciclesonide and beclomethasone, which has been shown to have improved deposition into the lungs.^{170,171} Utilization of these inhalers results in improvements in lung function measurements and asthma control.^{173,174} In spite of the increased evidence that small-particle-size inhalers are efficacious, superiority comparisons with large-particle-size inhalers are lacking and therefore specific recommendations to help guide clinicians on choice of ICS for any particular patient cannot be made at this time.¹⁷⁵

The risk of systemic toxicity is diminished with the use of ICS, particularly at doses less than 400 µg budesonide daily or the equivalent, but the risk is not absent. Data are conflicting about the risk of bone demineralization from ICS; although a small observational study suggested increased risk,^{176,177} a meta-analysis of several randomized controlled trials did not corroborate this finding.^{177,178} The risks of cataract formation¹⁷⁸ and glaucoma¹⁷⁹ are slightly increased, whereas hypothalamic-pituitary axis suppression, gastrointestinal bleeding, and other complications of systemic steroids are not associated with inhaled preparations. The *Towards a Revolution in COPD Health* (TORCH) trial of the use of ICS for COPD showed an increased risk of pneumonia, but this has not been demonstrated in patients with asthma.¹⁸⁰ The use of ICS in the pediatric population has raised concerns about growth suppression. However, available data show only a small and transient decrease in growth trajectory that does not translate into a reduction in adult height.^{159,164,181}

Leukotriene Modifiers. *Leukotrienes* (LTs) are derived from cell membrane arachidonic acid metabolism. LT receptors on ASM and macrophages mediate bronchoconstriction, mucus hypersecretion, and mucosal edema.¹⁸² As a result, the LT pathway is a primary target for the development of novel asthma controller medications. Commercially available *leukotriene modifiers* (LTMs) work in one of two places in the LT pathway. Zileuton inhibits the activity of 5-lipoxygenase, the enzyme that converts arachidonic acid to leukotriene A₄, which is the first step in LT synthesis. Montelukast, zafirlukast, and pranlukast are all *cysteinyl leukotriene 1* (CysLT1) *receptor antagonists* (LTRA), blocking the final step in the LT pathway. All are taken orally as either once-daily or twice-daily doses.

LTMs have a modest bronchodilator effect and may improve asthma symptoms and exacerbation rates.¹⁸³ Physiologic benefits have also been seen, with improvements in spirometry and measures of airway inflammation.¹⁸⁴ Whereas the subpopulation of patients with aspirin-

sensitive asthma may derive great benefit from LTMs,¹⁸⁵ data also suggest that LTMs are adequate as single agents in mild persistent asthma.^{186,187} Although LTMs treat multiple asthma symptoms, they are less effective than low-dose ICSs. LTMs can be used as monotherapy in exercise-induced asthma and in patients with relatively mild asthma symptoms that do not require therapy with ICS.¹⁸⁶ However, patients who require ICS for asthma control are often not candidates for LTM monotherapy. Therefore, the primary role of LTMs is as an adjunct to ICS, and the addition of LTMs typically leads to a reduction in the corticosteroid dose or an improvement in asthma control.^{188,189} Recent data suggest that the substitution of LTMs for ICS in smokers with asthma leads to similar symptomatic benefits, possibly due to impaired therapeutic responses to ICS in this population. However, it is not clear whether this benefit would persist with the addition of LTMs to ICS in patients who smoke cigarettes.¹⁹⁰ In general, LTMs are less effective than LABAs as adjunctive therapy and do not seem to confer added benefits when added to a regimen that includes an ICS and an LABA.^{191,192}

Overall, LTMs are well tolerated. Initial reports suggested a link between LTMs and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), but this is now thought more likely to be due to an unmasking of the syndrome by a reduction in corticosteroid dose with the introduction of an LTM.¹⁹³ Zileuton is metabolized by the cytochrome P-450 system and has been associated with reports of hepatotoxicity. As a result, liver function should be monitored during its use. The availability of a sustained-release preparation of zileuton has made it a better option as adjunctive therapy. At present, zileuton is reserved for patients with refractory asthma or who have an asthmatic phenotype suggesting benefit from the use of a leukotriene modifier.¹⁹⁴

Phosphodiesterase Inhibitors (Theophylline). Theophylline is a well-established phosphodiesterase inhibitor that has mild anti-inflammatory properties. Because of its narrow therapeutic index, theophylline is not widely used in treating asthma. However, the discovery of additional anti-inflammatory properties, likely mediated by histone deacetylation, has led to a resurgence of interest.¹⁹⁵ Although no longer a first-line therapy, theophylline is currently used in low doses as adjunctive treatment for asthma that is difficult to control with steroids alone.¹⁹⁶ The addition of theophylline to an existing drug regimen for poorly controlled asthma improves markers of control (less rescue inhaler use, better lung function) to a greater extent than LTMs.¹⁹⁰ Dose-related side effects, such as anorexia, palpitations, dysrhythmias, and seizures, require careful clinical and laboratory monitoring. Newer specific phosphodiesterase type 4 inhibitor drugs have been developed, and their safety profile is better than that of theophylline. Roflumilast has demonstrated efficacy in improving FEV₁ in asthma.^{197,198} Roflumilast is not approved for asthma but certainly has bronchodilating and anti-inflammatory properties that can be beneficial in asthma.

Targeted Biologic Agents. The introduction of omalizumab, a monoclonal antibody that binds IgE, represents a new era of therapy targeted to specific asthma phenotypes.

Omalizumab targets the receptor-binding portion of IgE, preventing it from interacting with immune cells to cause degranulation.¹⁹⁹ It must be administered subcutaneously, and the dose is based on IgE levels and body surface area. The addition of omalizumab to ICS in poorly controlled allergic asthmatics is associated with improved asthma control and fewer exacerbations.²⁰⁰ Omalizumab is generally well tolerated, but rare reports of anaphylaxis have led to recommendations that patients be observed for 2 hours after each of the first three injections to ensure safety.²⁰¹ High cost, the requirement for monitoring during treatment, and the need for careful selection of patients likely to benefit have limited the use of omalizumab. The importance of utilizing biomarkers to identify responders to omalizumab was highlighted by the EXTRA study that demonstrated significantly decreased numbers of exacerbations in subjects with high FeNO, high serum eosinophils, and elevated serum periostin in comparison with subjects with low biomarker levels.²⁰² It is critical to develop clinically applicable parameters that can guide clinician decision making about which patients should receive omalizumab for severe asthma. There is an increased degree of urgency given the cost and complexity of administering therapy with omalizumab. However, cost analysis suggests that anti-IgE therapy in patients with severe allergic asthma results in a cost-per-quality-adjusted life year that compares favorably with other uses of expensive health care resources.²⁰³ There are an increasing number of targeted biologic therapies that are currently in phase II and III trials. The early-phase studies with anti-IL-5 therapy did not demonstrate efficacy; however, this may have been due to the primary outcomes chosen and the population of patients enrolled in the these studies, underscoring the importance of identifying the correct target population for given therapies.^{204,205} Mepolizumab, a humanized monoclonal antibody to IL-5, has since demonstrated efficacy in reducing exacerbations in patients with severe asthma.^{99,206} The anti-IL-5 antibody significantly decreases eosinophil differentiation, maturation, and migration.²⁰⁷ Other biologic agents show promise for patients with severe asthma and persistent eosinophilic inflammation, including anti-IL-13 and anti-IL-4 receptor alpha antibodies.^{208,209} The emergence of new therapies for asthma holds promise for alleviating the suffering of patients with severe asthma that are failing all available therapies and experiencing untoward side effects of oral and high doses of inhaled corticosteroids.

Macrolides and Asthma. Macrolides were shown to be effective in a subset of asthma patients who had evidence of mycoplasma in their airways by polymerase chain reaction.^{210,211} These positive results generated interest in a broader use of macrolides for poorly controlled asthma. Additional randomized controlled trials demonstrated variable effects on improving asthma symptoms^{212,213} and AHR with no effect on reducing asthma control or exacerbations.²¹⁴ Recently, macrolides are reemerging as a potential therapy for patients with severe noneosinophilic or neutrophilic asthma. Two randomized controlled trials demonstrated improvements in exacerbations in patients with noneosinophilic asthma treated with macrolides; however, these outcomes were seen only in subgroup analyses.^{215,216} Therefore, the role of macrolides remains controversial,

and a recent ATS/ERS statement on severe asthma recommended against their use.⁸³ Further studies are clearly required before the controversy can be resolved.

Nonpharmacologic Treatment

Hypercontractility of ASM is believed to be a key determinant of the development of AHR in asthma. It is still unclear whether contractile force is enhanced in the asthmatic airway in which inflammatory mediators accumulate, or whether smooth muscle is abnormal in asthma. Numerous reports have identified increased ASM mass in fatal and nonfatal asthma. The cellular mechanism of increased ASM mass in asthma represents a balance between smooth muscle hypertrophy and proliferation.²¹⁷ Benayoun and associates²¹⁸ found that patients with mild asthma had larger smooth muscle cell diameter in their airways than control subjects. The increase in ASM mass correlated with asthma severity, suggesting a causal role for smooth muscle hypertrophy in the development of AHR. Conversely, Woodruff and colleagues²¹⁹ found that hyperplasia of smooth muscle is seen in mild to moderate asthma without changes in cell size or gene expression.

Current alternative nonpharmacologic treatment approaches in asthma focus on the mechanical reduction of airway smooth muscle mass in order to improve physiologic function. The application of controlled thermal energy via a radiofrequency catheter to reduce smooth muscle mass has been shown to reduce methacholine responsiveness in dogs.²²⁰ Bronchial thermoplasty is a novel intervention for asthma that is directed at the increased ASM mass. During thermoplasty, controlled thermal energy is delivered to the airway wall, thereby reducing ASM mass. In studies of thermoplasty or sham thermoplasty in patients with moderately severe asthma, thermoplasty has been shown to reduce airway responsiveness to an inhaled constrictor and to improve lung function.²²¹ Treatment leads to improvements in symptoms and quality of life and reduction in the use of rescue medication in patients with moderate or severe asthma.²²² Improvements in asthma outcomes in those receiving the sham procedure and the use of asthma quality of life as a primary outcome makes it difficult to provide strong recommendations in support of bronchial thermoplasty at this time. In addition, treatment requires a series of three bronchoscopies, exposing patients to the concomitant procedural risk. Long-term 5-year data demonstrate sustained improvements in asthma control, reduced exacerbations and decreased medication use, and a lack of evidence of long-term adverse effects.²²³ Despite this, in 2014 the ERS/ATS severe asthma guidelines recommended against the wide use of bronchial thermoplasty and suggested that this procedure should be recommended in the context of a clinical trial or in a large academic center coupled with a registry aimed at identifying predictors of response.⁸³ This recommendation was based on the perception that long-term safety data are lacking and that the procedure does not offer universal benefits to all severe asthma patients.^{223a} As for other expensive asthma therapies, it is imperative to identify responders and target this therapy to those that are most likely to benefit from the procedure.

With an increased understanding of the molecular mechanisms of asthma pathophysiology and airway

remodeling, more focused therapeutic strategies can be explored.²²⁴ In vitro studies of compounds targeting putative mediators involved in remodeling suggest a role for novel agents in the treatment of asthma.²²⁵⁻²²⁷ Recent studies highlighting novel genes associated with airway remodeling and asthmatic symptoms suggest new therapeutic avenues targeting the underlying pathogenesis of airway remodeling in asthma.²²⁸

ADDITIONAL MANAGEMENT STRATEGIES

Control of Triggers

Factors including tobacco smoke, comorbid conditions, allergen exposures, occupational exposures, pollutants, and respiratory infections have been shown to contribute to the pathogenesis and manifestations of asthma (Table 42-7). Cigarette smoking decreases asthma control and reduces the efficacy of corticosteroids. All patients with asthma who smoke cigarettes should be strongly encouraged to quit.²²⁹ Comorbid conditions, including *gastroesophageal reflux disease* (GERD) and rhinosinusitis, may worsen asthma symptoms and severity. Because treatment of GERD and sinusitis often improves the control of asthma, all difficult-to-treat patients with asthma should be evaluated for these underlying conditions.²³⁰⁻²³⁴ Reduction of allergen exposure and provision of allergen *immunotherapy* (IT) are common strategies for treating asthma. Allergic asthmatics improve when removed from their domestic environment, but environmental control is often difficult to achieve.²³⁵ The most common allergens include dust mites and cat dander. Whereas avoiding environmental allergens is ideal, most patients do not like the idea of avoiding or giving away their pets. Although overall data are mixed, several studies

have shown clinical benefits from dust mite control measures (e.g., impermeable mattress covers, frequent vacuuming, cockroach control).^{236,237} For patients with an allergic asthma phenotype, allergen-specific IT may reduce asthma symptoms and improve bronchial hyperreactivity.^{238,239} However, IT must take place under careful conditions owing to the risk of anaphylaxis, and the optimal duration of treatment is not completely clear.

Medication Adjustment Based on Asthma Control

The definition of asthma severity is based on the severity of symptoms at the time of diagnosis. More recent definitions take into account the degree of treatment necessary to maintain control and the frequency of exacerbations. Asthma control, defined as the degree of symptoms present while on appropriate therapy, is more fluid. Depending on the extent of control, a more or less aggressive approach to symptom management may be necessary. Recent studies support the importance of focusing on asthma control as a means of reducing exacerbations and morbidity.²⁴⁰ Published guidelines provide an up-to-date framework for medication choices when “stepping up” therapy to improve asthma control and “stepping down” therapy when control has been achieved (see Fig. 42-5). For patients with mild, intermittent asthma, with symptoms that return to baseline between episodes, as-needed use of a short-acting bronchodilator is usually sufficient to maintain control of symptoms. For patients with chronic asthma (symptoms > 2 times/week, nocturnal symptoms, or symptoms that affect activity), the addition of a controller medication is necessary and an ICS is the initial agent of choice.^{159,241,242} As mentioned previously, when used properly, ICSs ameliorate all asthma symptoms, improve airway physiology, and reduce hospitalizations and asthma mortality. Failure to

Table 42-7 Factors That Contribute to Worsening Asthma Control and Coexisting Conditions

Contributing Factor	Proposed Intervention
Tobacco use	<ul style="list-style-type: none"> Encourage tobacco cessation and assist with both nonpharmacologic and pharmacologic methods to help patients quit smoking
GERD	<ul style="list-style-type: none"> Consider empiric therapy for symptomatic GERD Barium swallow or pH probe study to diagnose GERD Impedance study if nonacid reflux is suspected Referral to gastroenterology for evaluation and treatment Consider surgical management for refractory cases
Atopy and allergic rhinitis	<ul style="list-style-type: none"> Consider empiric therapy with nasal steroids, nasal and oral antihistamines, leukotriene antagonists Consider skin prick testing or specific IgE testing Referral to allergist or ENT physician for evaluation Consider allergy immunotherapy for cases of severe disease or refractory symptoms
Nasal polyps and chronic sinusitis	<ul style="list-style-type: none"> Refer to ENT for evaluation and treatment Possible surgical intervention for refractory cases Consider aspirin desensitization and treatment for patients with nasal polyps and aspirin sensitivity
Vocal cord dysfunction*	<ul style="list-style-type: none"> Laryngoscopy to diagnose vocal cord dysfunction Referral to speech pathologist for evaluation and treatment
Obesity*	<ul style="list-style-type: none"> Encourage weight loss Consider bariatric surgery
Obstructive sleep apnea*	<ul style="list-style-type: none"> Referral for sleep study and initiate therapy for sleep apnea Referral to sleep specialist for complex cases
Psychological factors*	<ul style="list-style-type: none"> Evaluate for anxiety and depression

*May coexist with asthma with overlapping symptoms.

ENT, ear, nose, and throat specialist; GERD, gastroesophageal reflux disease.

respond to ICSs suggests nonadherence to medications, uncontrolled trigger exposures and/or comorbidities, or a steroid-nonresponsive phenotype. Approximately 30% of asthmatics fall into the latter category and demonstrate noneosinophilic inflammation and associated decreased response to conventional asthma therapy with ICS,¹⁰⁰ unlike patients with eosinophilic inflammation who demonstrate maximal response to a low dose of ICS.^{243,244} LTMs are an alternative for patients who do not tolerate or respond to ICS and are the preferred agent for patients with concomitant allergic rhinitis.^{183,184,245}

For patients with persistent asthmatic symptoms despite the appropriate use of a controller medication, clinicians have several different options for “stepping up” therapy. Some guidelines recommend the addition of a LABA to low-dose ICS (often in a combination inhaler) based on a large amount of efficacy data.²⁴⁵⁻²⁴⁸ However, because of concerns over the potential side effects of LABAs, the National Asthma Education and Prevention Program guidelines give the options of increasing the dose of ICS or adding an LABA. This is also the preferred approach for pediatric patients. Recommendations regarding up-titration of inhaled steroids have typically focused on doubling the dose of inhaled corticosteroids in patients that are not well controlled on low-dose ICS. However, there is increased recognition that doubling the dose is not efficacious at improving asthma control or lung function measurements. Furthermore, glucocorticoid resistance has been described in asthmatics that are obese.²⁴⁹⁻²⁵¹ In fact, recent studies have supported the assertion that quadrupling the dose of ICS yields improvements in asthma control and may be as effective as adding LABA therapy.²⁵² These findings will likely result in changes in future revisions of the guidelines. A third option is the addition of LTMs to low-dose ICSs.¹⁸⁹

If symptoms are still not controlled on one of the regimens just discussed, the next medication added depends on previous medication choices. For patients on increased doses of ICSs, the recommended next step is the combination of a moderate- to high-dose ICS with a LABA. However, increasing the ICS dose for a patient already on an ICS/LABA combination is less likely to be effective.^{253,254} Other options include the addition of an LTM or sustained-release theophylline to an ICS.²⁵⁵ If symptoms are not controlled on a full complement of standard medications, options include the addition of systemic corticosteroids or specific anti-IgE therapy for patients with allergic asthma.²⁰⁰

Once symptoms are controlled for a protracted period of time, therapy can be stepped down. Strategies for deescalation of therapy are determined by a patient's controller regimen. Patients on an ICS alone can be considered for a decrease in dose or dosing interval. Some data suggest that conversion to as-needed combined SABA/ICS may be effective with a lower total steroid dose.^{166,256} However, an as-needed regimen is not yet part of NHLBI guidelines. Similarly, for patients on a combined ICS/LABA or ICS/LTM regimen, clinicians should focus first on reducing the ICS component.

Assessment and Management of Concomitant Diagnoses

Vocal Cord Dysfunction. *Vocal cord dysfunction* (VCD), also referred to as paroxysmal vocal fold motion, was first

described as a separate clinical entity in 1983 and is one of the great mimics of asthma. VCD presents more often in women than in men and is common in persons 20 to 40 years old.^{257,258} It is characterized by intermittent abnormal paradoxical adduction of the true vocal cords during respiration. Patients with VCD often experience shortness of breath, neck/chest tightness, stridor, wheezing, hoarseness, frequent throat clearing, and cough. VCD patients can have normal head and neck and lung examinations or abnormal examinations with upper airway noise or stridor. Although many causes of VCD have been identified, most patients experience one of three subtypes: psychogenic VCD, irritant-associated VCD, or exercise-induced VCD.

The majority of patients with psychogenic VCD have previously been diagnosed with a psychiatric illness such as depression, anxiety, or factitious or somatoform disorder.²⁵⁹ For these patients, the vocal cords are their “stress organ” and learning how to manage stress is critical in treating their disease.

Exercise-induced VCD is often described as episodic dyspnea or shortness of breath that manifests within the first 5 minutes of exercise and resolves abruptly. These patients are frequently misdiagnosed with exercise-induced bronchospasm but fail to respond to bronchodilator therapy or steroids.²⁶⁰

Irritant-associated VCD is linked to chronic irritation of the throat resulting in vocal cord hypersensitivity. The irritants are categorized as either intrinsic (gastroesophageal reflux, laryngopharyngeal reflux, allergic rhinitis) or extrinsic (chemical or sensory irritants).

The diagnosis of VCD can be challenging because symptoms are frequently intermittent, and patients need to be symptomatic during testing. Difficulty in making the diagnosis is further complicated by the fact that up to 75% of asthmatics have coexistent VCD.^{257,261} Pulmonary function studies can reveal normal spirometry (without bronchodilator responsiveness) or an abnormal truncated inspiratory flow volume loop. Methacholine challenge has been used as a provocative measure to recreate symptoms and induce paradoxical closure of the vocal cords. Flow volume loops before and after methacholine challenge in patients with VCD often demonstrate flattening of the inspiratory curve after methacholine challenge, resulting in reversal of the MIF 50:MEF 50 (maximal inspiratory flow at 50% vital capacity-to-maximal expiratory flow at 50%) ratio from greater than 1 to less than 1.²⁶² However, specificity of these findings for VCD is limited.²⁶³ Flexible laryngoscopy and videolaryngostroboscopy are the gold standards for diagnosing VCD. Direct visualization of the cords classically demonstrates abnormal adduction of the anterior two thirds of the true vocal cords with inspiration and “chinking” of the posterior cords; the chink describes the small triangular opening that remains patent at the posterior segment of the vocal cords.²⁶⁴ The vocal cords can be seen in adduction during inspiration or during both inspiration and expiration.

Beyond treating the underlying disorder (GERD, rhinitis, and depression), there is no specific medication that treats VCD. Acute VCD can be managed with heliox to reduce airway resistance rapidly.²⁶⁵ Long term, patients are often referred to speech therapy for initiation of relaxed throat breathing exercises and diaphragmatic breathing exercises.

Although these exercises have been reported to be effective in case reports, randomized clinical trials to validate effectiveness are necessary (see Chapter 49).

Allergic Bronchopulmonary Aspergillosis. *Allergic bronchopulmonary aspergillosis* (ABPA) is a complex hypersensitivity reaction to *Aspergillus fumigatus* colonization in the airways of atopic patients.²⁶⁶ It is present in 2% to 32% of patients with asthma.²⁶⁷ Although this reaction is most commonly attributed to *A. fumigatus*, clinically identical reactions have been described for a wide variety of fungi. A more detailed description of ABPA can be found in Chapter 38. The immunopathogenesis remains incompletely understood, but current evidence suggests that persistent *A. fumigatus* colonization results in an exaggerated IgE- and IgG-mediated response driven by aspergillus-sensitive Th2 helper cells in the airway.²⁶⁶ This persistent and/or recurrent airway inflammation may be silent but generally presents clinically as severe or difficult to control asthma with dyspnea, cough and wheezing, bronchiectasis with abundant viscous mucus production, and even hemoptysis or recurrent pneumonias with migratory pulmonary opacities.

Diagnostic criteria for ABPA include a history of asthma, radiographic chest opacities positive skin test to *A. fumigatus* antigen, peripheral eosinophilia, precipitating antibodies against *A. fumigatus* antigen, elevated serum IgE, central bronchiectasis, and elevated IgE and/or IgG *A. fumigatus*-specific antibodies.²⁶⁶ The diagnosis often remains elusive because many patients do not fulfill all eight major diagnostic criteria, especially early in the disease course or when receiving corticosteroids. Treatment of ABPA targets acute airway inflammation and the prevention of the long-term complications of persistent airway inflammation. Glucocorticoids are the mainstay of therapy with the antifungal itraconazole or voriconazole reserved for patients with glucocorticoid-resistant disease.

MANAGEMENT OF ACUTE ASTHMA

Asthma is a common cause of emergency department visits and hospital admissions. Hospitalizations for asthma in adults remained relatively stable from 2000 to 2010 at approximately 119 per 100,000. Interestingly, pediatric admissions from asthma declined during the same period from 165 per 100,000 to 130 per 100,000.²⁶⁸ The treatment of acute asthma is based on the cornerstones of chronic asthma therapy but typically requires greater attention to patient monitoring and an escalation in the aggressiveness of asthma care.

Asthma exacerbations are characterized by increased shortness of breath, coughing, and/or chest tightness, and airflow limitation (as measured by decreased peak flow or FEV₁). Increased symptoms typically precede a detectable decrease in air flow,^{269,270} although a subset of patients are at high risk of exacerbations due to poor perception of airflow limitation. In the outpatient setting, an increased requirement for rescue inhalers, especially in a patient previously on a stable regimen, suggests an asthma flare. There is increased recognition that the pathophysiological mechanisms underlying asthma exacerbations are as heterogeneous as the underlying disease itself. Although we currently

treat all exacerbations similarly, some data suggest that targeted therapies for asthma exacerbations and the management of triggers may be warranted and have the potential to reduce the morbidity associated with our current therapies.²⁷¹ Exacerbations have a significant impact on asthma morbidity and mortality, and therefore it is imperative to decrease the rate of asthma exacerbations whenever possible.²⁷² Research studies focused on asthma exacerbations have used a variety of definitions, which makes it particularly challenging to compare studies. Given the recognition that standardization was needed, the National Institutes of Health convened a task force that defined an exacerbation as “a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome.”²⁷³ Exacerbations are caused by a variety of triggers including infection, environmental exposures, and allergens, as well as nonadherence with prescribed asthma medications.

Patients with asthma exacerbations require prompt evaluation and treatment in order to limit morbidity and mortality. Goals include relief of airflow obstruction and amelioration of respiratory symptoms. Patients with milder symptoms (with peak flow decrease < 20%) may be evaluated in an outpatient setting but should be referred to an acute care facility if they fail to respond promptly to aggressive treatment with bronchodilators and systemic glucocorticoids.¹¹⁸ Conversely, certain patients are at high risk of asthma-related death and should be evaluated in the emergency department as soon as possible when their symptoms worsen. This includes patients with a history of recent exacerbation or previous near-fatal asthma, overutilization of SABAs or underutilization of ICSs, recent oral glucocorticoid use, poor compliance with asthma action plans, or concomitant psychiatric disease.²⁷⁰

In the acute care setting, the severity of an asthma exacerbation should be assessed by physical examination, including oximetry and measurement of peak expiratory flow. Use of accessory muscles, ability to complete sentences, and arterial oxygen tension should all be evaluated. Patients require close monitoring during the early stages of treatment because it may take several hours for symptoms to resolve. Chest radiography is useful if pneumothorax is suspected but does not usually provide clues as to the etiology of an exacerbation. Arterial blood gas measurement typically reflects mild hypoxemia and respiratory alkalosis; the normalization of arterial PCO₂ in the absence of significant symptomatic improvement suggests impending respiratory failure. Venous blood gases should not be relied on to follow PCO₂; whereas venous pH values generally agree with arterial values, venous PCO₂ poorly reflects arterial PCO₂.²⁷⁴ Anion gap metabolic acidosis may also be present, which is usually due to elevated lactate levels. Patients who fail to respond to albuterol administration within 30 to 60 minutes, with persistent dyspnea and peak flow less than 70% of baseline, require hospital admission.¹¹⁸

Key pharmacologic components of treatment include repeated or continuous short-acting bronchodilator administration (via nebulizer or metered-dose inhaler with a spacer) and systemic glucocorticoids.^{275,276} The combination of SABAs and ipratropium at the initiation of treatment is associated with physiologic improvements and

reduced rate of hospitalization, but the benefits do not persist after hospitalization.²⁷⁷ Systemic corticosteroids are unequivocally associated with more rapid return to baseline function and are considered the first-line therapy for acute asthma exacerbations. More importantly, the early administration of steroids is important in reducing the need for hospitalization and improving asthma symptoms.^{278,279} The initial dosing range for adult hospitalized patients is from 1.5 to 2 mg/kg of intravenous methylprednisolone or the equivalent.²⁸⁰ Oral steroids have been shown to have similar efficacy to intravenous preparations in the treatment of acute asthma exacerbations and therefore are an acceptable alternative in patients without life-threatening asthma.²⁸¹ ICSs are typically not used acutely, although data suggest that the addition of inhaled budesonide to systemic corticosteroids following an emergency department visit leads to improved symptoms and a decreased relapse rate.²⁸²⁻²⁸⁴ Intravenous magnesium sulfate, usually given as a 2-g bolus, may act as a smooth muscle relaxant and has been shown to reduce hospital admission rates.²⁸⁵ Supplemental oxygen to keep saturations above 90% helps maintain oxygen delivery to peripheral tissues and minimizes hypoxic pulmonary vasoconstriction.

Severe exacerbations of asthma are characterized by persistent reductions in PEF of less than 40% predicted with poor response to initial treatment. These patients may demonstrate progressive hypercapnia, fatigue, altered sensorium, and dysrhythmias and are at high risk for respiratory arrest. Low-level noninvasive positive-pressure ventilation without positive end-expiratory pressure has been shown to reduce the rate of hospitalization and may be considered in alert, cooperative patients who are not in immediate need of intubation.²⁸⁶ Heliox increases flow at the same pressure and may be a useful adjunct in patients with severe exacerbations that do not respond to initial emergency treatment.^{287,288}

Oral intubation and mechanical ventilation are mandatory for patients in respiratory arrest or impending respiratory arrest. Mechanical ventilation in patients with severe asthma exacerbations may be complicated by immediate postintubation worsening of gas exchange and hemodynamic instability due to increased airway and intrathoracic pressures from dynamic lung hyperinflation. Provided that the patient is adequately oxygenated, briefly decreasing the mandatory respiratory rate to allow an extended expiratory phase is often successful. Initial ventilator settings should be focused on minimizing dynamic hyperinflation by using a relatively low minute ventilation (with respiratory rate between 12 and 14/min and tidal volumes in the 6 to 8 mL/kg range), a high inspiratory flow rate, and minimal to no positive end-expiratory pressure.²⁸⁹ Aggressive sedation should be given to improve comfort and patient-ventilator synchrony. Short-term paralysis may be necessary in patients for whom ventilator synchrony cannot be achieved with sedation alone. Bronchodilator administration should be continued until airway resistance decreases (see Chapters 99 and 101).

CLINICIAN-PATIENT PARTNERSHIP

For chronic asthma, treatment should balance the best symptom control with the lowest possible dosage of medica-

tion.¹¹⁸ Effective management requires that patients form a partnership with health care providers in order to ensure an appropriate flow of information, with the patients assuming a major role in the assessment and treatment of their disease. Through collaborative effort, a guided self-management plan can be developed, allowing patients to titrate their own treatment on the basis of changes in symptoms and peak expiratory flow with some degree of independence. The use of such guided self-management reduces asthma morbidity in different patient populations and patient care settings.²⁹⁰ Interestingly, patient-guided use of asthma medications based on symptoms was superior to physician and biomarker-based adjustments to asthma therapies as reported by the Asthma Clinical Research Network,¹³¹ further highlighting the importance of actively involving patients in decisions regarding management of their asthma.

Crucial components of self-management plans include education, self-monitoring with symptoms and/or peak flow, regular review, and patient-directed self-management using a written action plan. Effective patient education is central to this approach. Better communication by health care providers translates into measurably better outcomes with no additional physician time commitment. Even for patients unable to engage in guided self-management, regular follow-up and medication review is beneficial because approximately 50% of patients on long-term therapy fail to take medications as directed at least some of the time.²⁹¹

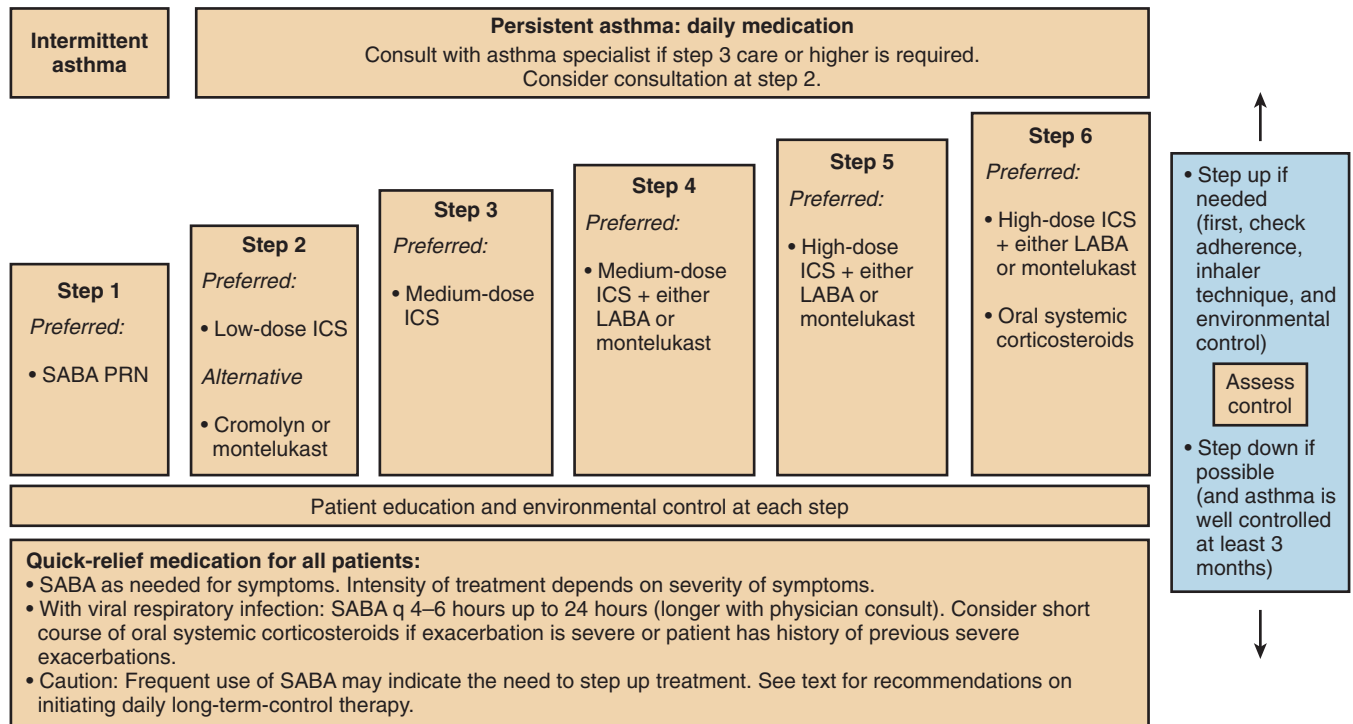
Key Points

- The approach to the diagnosis, assessment, and treatment of asthma has changed in response to the recognition that asthma is a heterogeneous disease that encompasses many phenotypes with variable responses to therapy.
- Currently, the two main phenotypes appear to be eosinophilic (Th2 high) and noneosinophilic (Th2 low) asthma. Future approaches to managing asthma will require more detailed procedures to phenotype patients in order to determine what targeted therapies will be most efficacious.
- Inhaled corticosteroids are the mainstay of asthma therapy; however, only 30% of patients have eosinophilic inflammation that is predictive of response to inhaled corticosteroids. Future studies should focus on therapies that may benefit asthmatics with noneosinophilic inflammation.
- Exhaled nitric oxide levels may be used to diagnose asthma in mild-moderate patients but should not be used to guide therapy, particularly in patients with severe asthma.
- Bronchial thermoplasty is approved for asthma treatment; however, more studies are required to determine which patients with severe persistent asthma are likely to benefit.
- Asthma education and collaboration between physicians and patients are essential in improving asthma-related outcomes.

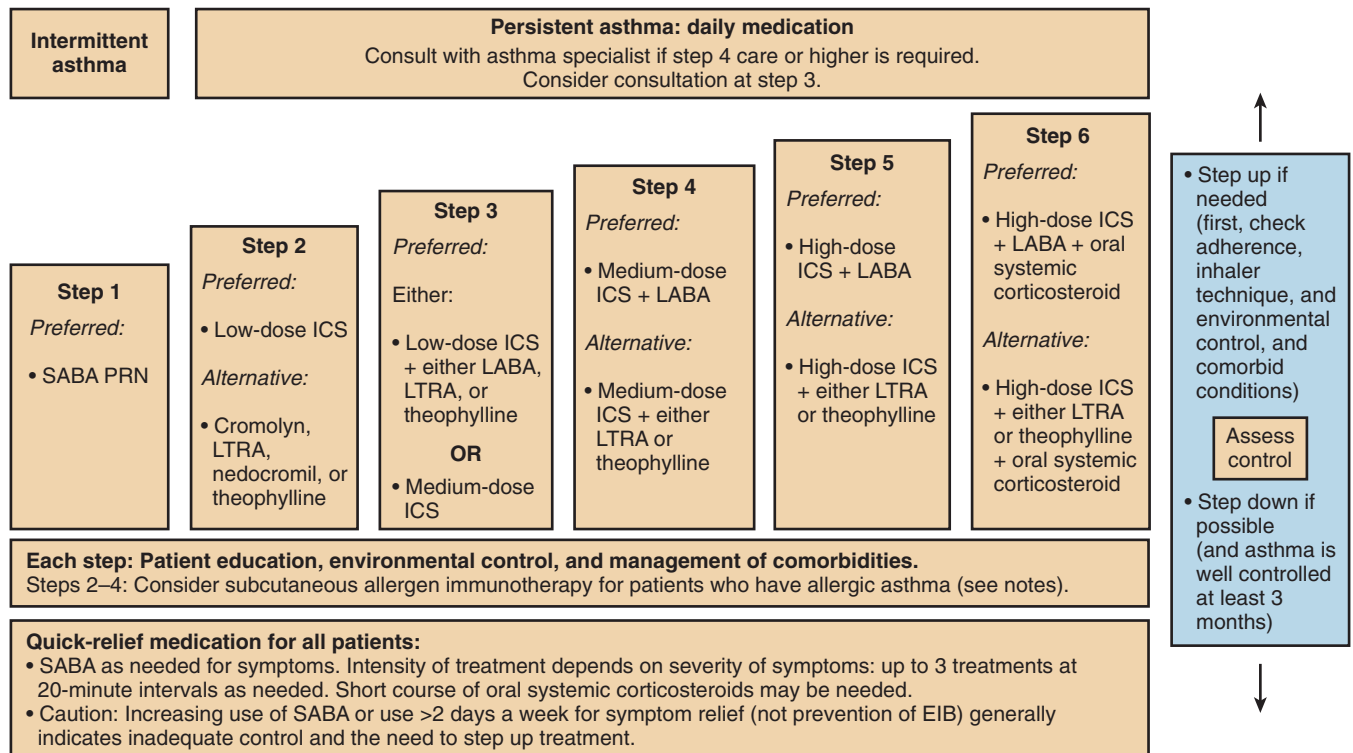
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eFIGURE IMAGE GALLERY



eFigure 42-1 Medication recommendations for control of asthma in children 0 to 4 years old. (Adapted from National Asthma Education and Prevention Program EPR-3 guidelines from the National Heart, Lung, and Blood Institute 2007.)



eFigure 42-2 Medication recommendations for control of asthma in children 5 to 11 years old. (Adapted from National Asthma Education and Prevention Program EPR-3 guidelines from the National Heart, Lung, and Blood Institute 2007.)

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COPD: PATHOGENESIS AND NATURAL HISTORY

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INTRODUCTION

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APOPTOSIS AND EMPHYSEMA

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition characterized by persistent airflow limitation that is usually progressive and is associated with a chronic enhanced inflammatory response in the airways and lungs to noxious particles and gases.¹ In developed countries, cigarette smoking is the main etiologic factor, outweighing any of the other risk factors. However, in developing countries, the major cause is exposure to biomass fuels. The pathogenesis of COPD is strongly linked to the effects of cigarette smoke on the lungs. There is a general relationship between the extent of the smoking history and the severity of the airflow limitation; however, there is a huge individual variation.² Fletcher and colleagues,³ in an 8-year prospective study of working men in west London, showed that the average decline in FEV₁ in smokers is faster (60 mL/year) than in nonsmokers (30 mL/year). However, smokers who develop COPD have an average decline in FEV₁ of greater than 60 mL/year, although only a proportion of smokers develop clinically significant COPD. It is from these studies that the concept of the “susceptible smoker” developed.

The pathogenesis of COPD is generally thought to involve an abnormal inflammatory response in the lungs to the inhalation of toxic particles and gases, derived from tobacco smoke, air pollution, or occupational exposures. All smokers develop lung inflammation,⁴ but this is enhanced and fails to resolve after smoking cessation in those who develop COPD.⁵ This suggests that, in smokers who develop COPD, there is abnormal regulation of the inflammatory response in the lungs. The susceptibility factors are still poorly understood and likely involve genetic and epigenetic factors, infections, altered immune regulation, or impaired resolution of inflammation and abnormal repair mechanisms.⁶ However, the relationship between the inflammatory responses in the lungs and the accelerated decline in FEV₁, which characterizes this condition, is far from clear. More-

over, it is now well recognized that COPD is a heterogeneous condition with pathologic changes in the large and small airways (chronic bronchitis and bronchiolitis) and lung parenchyma (emphysema) that vary greatly in their expression among patients.⁷ Thus, the mechanisms resulting in these pathogenic changes are also likely to be different.

PATHOLOGIC CHANGES IN COPD

CHRONIC BRONCHITIS

Chronic bronchitis is defined in clinical terms as the presence of cough and sputum production for most days over 3 months for 2 consecutive years. This clinical definition does not include the presence of airflow limitation. It is thought to result from an innate immune response to inhaled toxic particles and gases, particularly in tobacco smoke. Inflammation is present in the epithelium of the central airways and in the mucus-producing glands in chronic bronchitis.^{4,7} This airway inflammation is associated with increased mucus production, reduced mucociliary clearance, and increased permeability of the airspace epithelial barrier.

The contribution that mucus hypersecretion makes to the airflow limitation in COPD is still uncertain. In the early stages of COPD, its contribution is small because mucus production in smokers with normal lung function does not appear to predict later development of COPD.⁸ However, in the later stages of the disease, chronic mucus hypersecretion may accelerate the loss of FEV₁ due to an increased risk of exacerbations.⁹ Chronic mucus hypersecretion may result from an inflammatory response in the submucosal glands. Inflammatory cells release serine proteases that are potent secretagogues for mucus.¹⁰ Oxidants derived from cigarette smoke and released from inflammatory leukocytes may also stimulate the overproduction of mucin by induction of the *MUC5AC* gene.¹¹

EMPHYSEMA

Emphysema is defined as enlargement of the airspaces distal to the terminal bronchioles, due to destruction of the alveolar walls (Fig. 43-1).¹² Distal airspace enlargement with alveolar destruction reduces maximal expiratory airflow by decreasing the lung elastic recoil. The centrilobular or centriacinar form of emphysema results from dilatation or destruction of the respiratory bronchioles, is the type most closely associated with tobacco smoking, and is thought to be more associated with severe small-airway obstruction.¹³ The panlobular or panacinar form of emphysema, which is associated with α_1 -antitrypsin (α_1 -AT) deficiency, results in a more even dilatation and destruction of the entire acinus. Although one or the other of these types may predominate, there is great heterogeneity. The distribution of these types of emphysema is different with an upper lobe predominance common in centrilobular emphysema

and lower lobe predominance in panlobular emphysema. The reason for this is not clear and whether different pathogenic mechanisms are involved is also unknown.

There is a relationship between the degree of emphysema and pack-years of smoking, but the relationship is not strong.⁴ Around 40% of smokers develop substantial lung destruction from emphysema, and emphysema can be found in some individuals who have normal lung function.⁴

SMALL-AIRWAY DISEASE

A major site of airflow limitation in COPD is the small conducting airways (<2 mm in diameter).¹⁴ Niewoehner and coworkers¹⁵ were the first to show that inflammation involving clusters of monocytes and macrophages could be found in the bronchioles of asymptomatic smokers who died of non-smoking-related causes out of hospital. More recent studies have shown that there are abnormalities in small

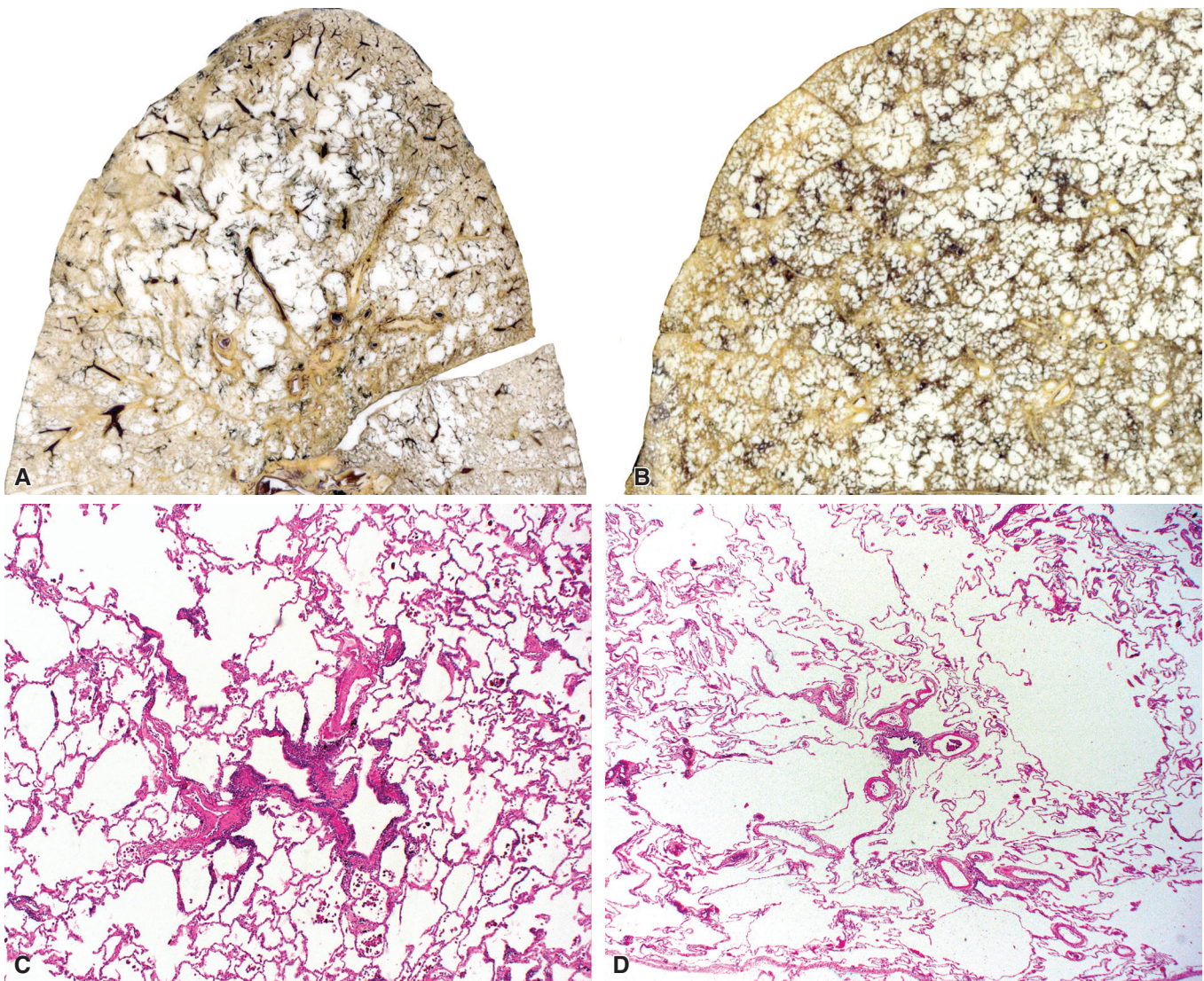


Figure 43-1 Emphysema. Paper-thin Gough-Wentworth sections prepared from whole lungs. **A**, Centriacinar emphysema in a smoker. **B**, Panacinar emphysema in α_1 -antitrypsin deficiency. The type and severity of emphysema may be difficult or impossible to determine on histopathologic grounds. **C**, Here, centriacinar emphysema is seen with dilatation of the air spaces surrounding the bronchiole. **D**, By contrast, panacinar emphysema features a more diffuse air space dilatation. (A and B, from Leslie KO, Wick MR: Practical pulmonary pathology: a diagnostic approach, ed 2. Philadelphia, 2011, Saunders; original Gough sections (C and D) prepared by T.V. Colby and the Charles B. Carrington Memorial Lung Pathology Library.)

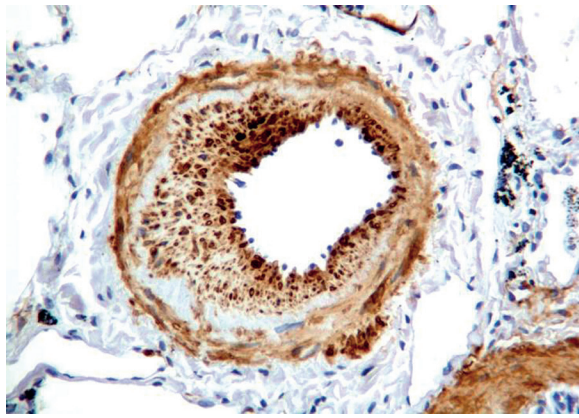


Figure 43-2 Photomicrograph of a pulmonary artery from a patient with COPD showing prominent intimal hyperplasia and luminal narrowing. Immunostaining with antibody against α -smooth muscle actin reveals marked proliferation of smooth muscle cells in the intima. (From Rodríguez-Roisin R, Barberà JA: Pulmonary vessels. In Barnes PJ, Drazen JM, Rennard SI, Thomson NC, editors: *Asthma and COPD*, ed 2. Waltham, MA, 2008, Academic Press, Fig. 20-1.)

airways in smokers with and without COPD.¹⁶ There is also a relationship between the severity of COPD and the extent of occlusion of the airway lumen by inflammatory mucus exudates.¹⁷ Inflammation and peribronchial fibrosis contribute to the fixed airway obstruction in the small airways in COPD, and chronic inflammation, resulting in the destruction of the alveolar attachments on the outer walls of the small airways, may also contribute.

PATHOGENESIS OF COPD

PULMONARY CIRCULATION

Sustained pulmonary hypertension develops late in the course of COPD, although pathologic changes in the pulmonary vasculature with intimal hyperplasia and muscularization of small pulmonary arteries can develop in mild COPD in heavy smokers with normal lung function (Fig. 43-2). Factors that contribute to pulmonary hypertension include the following:

- Pulmonary arterial constriction as a result of hypoxia
- Endothelial dysfunction
- Remodeling (smooth muscle hypertrophy and hyperplasia) of the pulmonary arteries
- Destruction of the pulmonary capillary bed

The development of structural changes in the pulmonary arterioles leads to persistent pulmonary hypertension and right ventricular hypertrophy/enlargement and dysfunction (cor pulmonale) (see Chapter 59).

A summary of the pathologic changes in the lungs in COPD is given in Table 43-1.

An overview of the pathogenic mechanisms in COPD is given in Figure 43-3.

INFLAMMATION IN THE LUNGS OF SMOKERS WITHOUT COPD

Tobacco smoke causes airway inflammatory responses within minutes or hours of exposure.¹⁸ One of the earliest

Table 43-1 Pathologic Changes Found in COPD

PROXIMAL AIRWAYS (CARTILAGINOUS, >2-MM DIAMETER)

- ↑ Macrophages and CD8 T lymphocytes
- Few neutrophils and eosinophils (neutrophils increase with progressive disease)
- Submucosal bronchial gland enlargement and goblet cell metaplasia (results in excessive mucous production or chronic bronchitis)
- Cellular infiltrates (neutrophils and lymphocytes) of bronchial glands
- Airway epithelial squamous metaplasia, ciliary dysfunction, ↑ smooth muscle and connective tissue

PERIPHERAL AIRWAYS (NONCARTILAGINOUS, <2-MM DIAMETER)

- ↑ Macrophages and T lymphocytes (CD8 > CD4)
- ↑ B lymphocytes, lymphoid follicles and fibroblasts
- Few neutrophils or eosinophils
- Bronchiolitis at an early stage
- Luminal and inflammatory exudates
- Pathologic extension of goblet cells and squamous metaplasia into peripheral airways
- Peribronchial fibrosis and airway narrowing with progressive disease

LUNG PARENCHYMA (RESPIRATORY BRONCHIOLES AND ALVEOLI)

- ↑ Macrophages and CD8 T lymphocytes
- Alveolar wall destruction due to loss of epithelial and endothelial cells
- Development of emphysema (abnormal enlargement of airspaces distal to terminal bronchioles)
- Microscopic emphysematous changes:
 - Centrilobular (dilatation and destruction of respiratory bronchioles, commonly found in smokers and predominantly in upper zones)
 - Panacinar (destruction of the whole acinus—commonly found in α 1-antitrypsin deficiency and more common in lower zones)
- Macroscopic emphysematous changes:
 - Microscopic changes progress to bullae formation (defined as an emphysematous airspace > 1 cm in diameter)

PULMONARY VASCULATURE

- ↑ Macrophages and T lymphocytes
- Early changes:
 - Intimal thickening
 - Endothelial dysfunction
- Late changes:
 - ↑ Vascular smooth muscle
 - Collagen deposition
 - Destruction of capillary bed
 - Development of pulmonary hypertension and cor pulmonale

manifestations is a breach in the vascular and airway barrier function,¹⁹ with rapid recruitment of circulating inflammatory cells to the lung. Inflammation is found in the peripheral airways of all smokers even before COPD is established and consists of mononuclear cell infiltrates and clusters of macrophages in the walls of the respiratory bronchioles.¹⁵ These lesions develop initially in the absence of any significant tissue destruction or fibrosis and may be reversible. An inflammatory process involving T lymphocytes and macrophages has also been described in the large airways of smokers with chronic bronchitis.²⁰ Acute cigarette smoke exposure can result in tissue damage with degradation of extracellular matrix proteins and lipid peroxidation products.²¹

These early inflammatory changes in the airways likely represent the nonspecific innate immune response to airway injury from tobacco smoke. It is unclear why some smokers

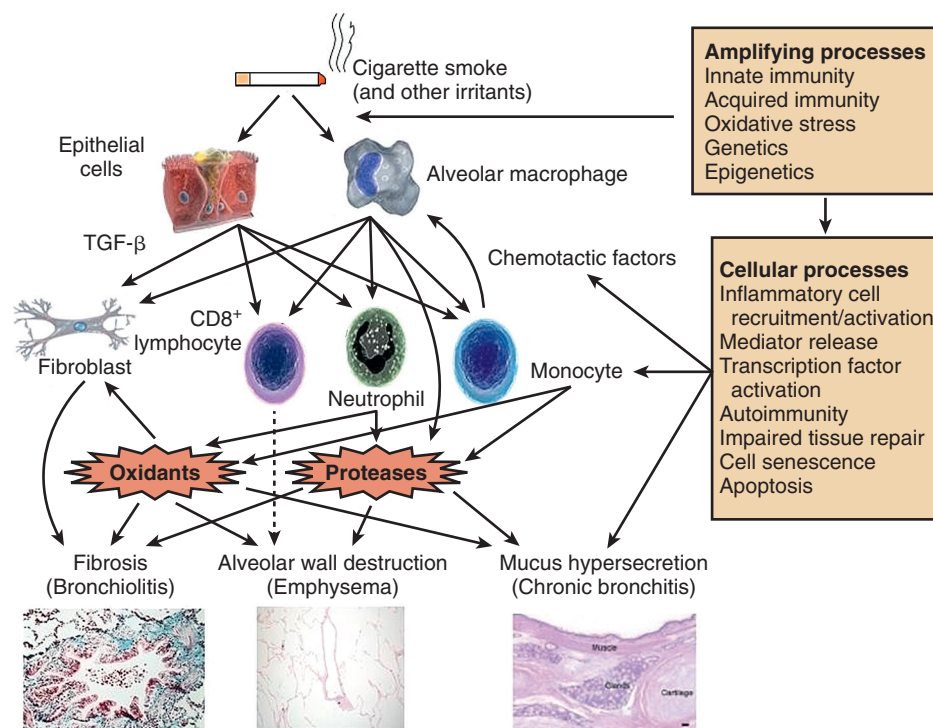


Figure 43-3 Overview of the pathogenesis of COPD. Cigarette smoke activates macrophages and epithelial cells to produce chemotactic factors that recruit neutrophils and CD8 cells from the circulation. These cells release factors that activate fibroblasts, resulting in abnormal repair processes and bronchiolar fibrosis. Imbalance between proteases released from neutrophils and macrophages and antiproteases leads to alveolar wall destruction (emphysema). Proteases also cause the release of mucus. An increased oxidant burden resulting from smoke inhalation or release of oxidants from inflammatory leucocytes causes epithelial and other cells to release chemotactic factors, inactivates antiproteases, directly injures alveolar walls, and causes mucus hypersecretion. Several processes are involved in amplifying the inflammatory responses in COPD.

develop structural abnormalities that eventually lead to clinically detectable COPD, whereas others continue to show an inflammatory infiltrate but maintain otherwise normal airways and lung parenchyma and only mild functional changes that do not become clinically relevant.

Smoking cessation alters the inflammatory response in the lungs in asymptomatic smokers and in patients with COPD.⁵ Cross-sectional studies of the effects of smoking cessation^{22,23} show that ex-smokers have less goblet cell hyperplasia and less squamous cell metaplasia in the small, but not the large, airways. Smooth muscle mass in the peripheral and central airways, fibrosis, deposition in the airway wall, fibrosis of the peripheral airways, and the degree of alveolar destruction is not different in asymptomatic ex-smokers and current smokers, nor is the inflammatory response different. There are limited longitudinal studies of the effects of smoking cessation on the inflammatory response in the lungs.^{5,24} Large airway inflammation indicating chronic bronchitis decreased by 3 months and disappeared after 6 months of smoking cessation. Inflammation as assessed in sputum and from bronchial biopsies decreased 1 year after smoking cessation in asymptomatic smokers.²⁴

INFLAMMATION IN THE LUNGS IN COPD

Studies of lung or bronchial biopsies and induced sputum have shown that lung inflammation is present in all cigarette smokers. However, an enhanced or abnormal inflammatory response to inhaled particles or gases, beyond the

normal protective inflammatory response, is a characteristic feature of COPD and has the potential to produce lung injury. Both the innate and adaptive inflammatory and immune responses are involved in the lung inflammation in COPD patients. Recent studies have characterized the inflammation in the lung in COPD in terms of its type, site, degree, and relationship to severity of disease.

CELLULAR INFLAMMATORY RESPONSES

Bronchial biopsies from smokers with symptoms of chronic bronchitis who have not developed airflow limitation demonstrate that the airway epithelium remains intact; however, the epithelium shows squamous metaplasia and there is an increase in goblet cells.²⁵ In contrast to asthma, the epithelial reticular basement membrane is not thickened.²⁶ In patients with mild to moderate COPD, there is an increase in inflammatory cell infiltration in the central airways, compared with nonsmokers or smokers who have not developed the disease.²⁷ In the bronchial epithelium and submucosa in COPD patients,²⁵ monocytes are the major cell with scanty neutrophils.²⁷ Of the monocyte component, T lymphocytes predominate, mainly CD8⁺ cells (T-cytotoxic lymphocytes) and macrophages (CD68⁺ cells)²⁸ (eTable 43-1), in contrast to asthma, in which CD4⁺T-helper (T helper 2) lymphocytes predominate.²⁹ Thus, the ratio of CD8⁺/CD4⁺ increases in COPD.^{20,28} Morphometric analyses of bronchial biopsies show that the ratios of CD8⁺/CD4⁺ T cells are 1.3, 11.8, and 4.3 (mean/mm³) in healthy smokers,

eTable 43-1 Variation of Inflammatory Cells and Markers of Inflammation in the Bronchial Submucosa

	CD45	CD3	PMN	EOS	Mast	CD68	CD8	CD4
Severe COPD	—	↓ ⁵³	↑ ⁴⁵	→ ⁴⁵	→ ⁴⁵	↑ ⁶	↓ ⁵³	→ ⁵³
Mild/moderate COPD	↑ ^{20,26}	↑ ^{26,29,53} → ⁵³	→ ^{20,26} ↑ ⁴⁵	→ ^{20,26,45}	→ ^{20,26,45}	↑ ^{20,26} → ⁴⁵	↑ ^{26,53} → ^{20,53}	→ ^{20,26,53}
Control Smokers	→ ²⁶	→ ^{26,30} ↑ ⁵³	→ ^{26,45}	→ ^{26,45}	→ ^{26,45}	→ ^{26,45}	↑ ⁵³ → ^{26,53}	→ ^{26,53}
Control Nonsmokers	→ ^{20,26}	→ ^{20,26,29,53}	→ ^{20,26}	→ ^{20,26}	→ ^{20,26}	→ ^{20,26}	→ ^{20,26,53}	→ ^{20,26,53}

↑, Significantly increased values in comparison with that indicated by →; →, basal values or values insignificantly changed; ↓, significantly decreased values in comparison with that indicated by →; —, no data available.

Numbers indicate references.

EOS, eosinophils; PMN, polymorphonuclear leukocytes.

Adapted from Willemse BW, ten Hacken NH, Rutgers B, et al: Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *Eur Respir J* 26:835–845, 2005.

stable chronic bronchitis, and exacerbated chronic bronchitis, respectively.²⁵ CD8⁺ T cells are also observed in the sputum,^{30,31} bronchial glands,³² bronchial smooth muscle,³³ and around lymphoid follicles.¹⁶ It has been suggested that the presence of increased CD8⁺ T lymphocytes differentiates between smokers with and without COPD and that there is a correlation between T-cell numbers, the smoking history, the amount of alveolar destruction, and the severity of airflow limitation.^{25,28} However, smokers with normal lung function also show an increased number of CD8⁺ cells compared with control nonsmokers.²⁰

The mechanism by which CD8⁺ T lymphocytes accumulate in the airways in COPD is not fully understood. There is increased expression of CXCR3 on T cells in the peripheral airways in COPD patients. CXCR3 is a receptor activated by *interferon-inducible protein* (IP)-10, and the expression of IP-10 itself is increased in bronchiolar epithelial cells. This could contribute to the accumulation of CD8⁺ cells, which preferentially express CXCR3. Circulating CD8⁺ cells are also increased in number in COPD patients.³⁴ These changes suggest chronic immune stimulation. CD8⁺ cells have a well-recognized role in respiratory viral infections, contributing to viral clearance. It may be that chronic colonization of the lower respiratory tract of COPD patients by bacterial and viral pathogens is responsible for this enhanced inflammatory response.⁷ An increase in B lymphocytes and in bronchial-associated lymphoid tissue in small airways also is present as the disease progresses,¹⁶ suggesting an adaptive immune response. It is possible that cigarette smoke damages airway cells, creating new autoantigens that drive the immuno-inflammatory response.³⁵

The role of T cells in the pathogenesis of COPD is not fully understood. CD8⁺ cells have the potential to release *tumor necrosis factor* (TNF)- α , perforins, and granzymes. CD8⁺ T lymphocytes isolated from the sputum of smokers are activated and release perforin.³⁰ In addition, CD8⁺ cells activate the Fas/Fas ligand apoptotic pathway and there is an association between CD8⁺ cells and alveolar epithelial cell apoptosis in subjects with emphysema.

Increased numbers of activated neutrophils are found in both *bronchoalveolar lavage* (BAL) fluid and sputum from patients with COPD.^{27,37} The mechanism of neutrophil passage into the airway lumen in COPD is not entirely clear. Cigarette smoking is known to increase circulating neutrophil counts and to cause sequestration of neutrophils in the lung capillaries¹⁸ by decreasing their deformability. Cigarette smoke also has a direct stimulatory effect on granulocyte production in the bone marrow, possibly mediated by *granulocyte macrophage colony-stimulating factor* (GM-CSF) and G-CSF released from macrophages.³⁸ Once sequestered in the pulmonary microcirculation, it is possible that an imbalance between proinflammatory and anti-inflammatory cytokines may result in neutrophil migration into the airspaces. Expression of anti-inflammatory mediators, such as *secretory component* (SC), club cell (Clara) protein (CC16), and *interleukin* (IL)-10, are decreased in the airway lumen of smokers with COPD,^{39,40} whereas cytokines, such as IL-8 and *monocyte chemoattractant protein* (MCP)-1, which promote the chemotaxis of neutrophils and monocytes, respectively, and TNF- α , which activates adhesion molecules, are increased.⁴¹⁻⁴³ Up-regulation of E-selectin and *intercellular adhesion molecule* (ICAM)-1 on submucosal vessels and on

bronchial epithelium of subjects with COPD⁴² suggests that these adhesion molecules may be involved in the recruitment of neutrophils from the circulation and their migration from bronchial subepithelial capillaries into and through the epithelium to enter the airway lumen. The airway epithelium is a rich source of the cytokines/chemokines that recruit both neutrophils and macrophages into the airspaces. Many of these cytokines/chemokines are overexpressed in COPD.⁴³ IL-6, IL-1 β , TNF- α , *growth-related gene*- α (GRO- α)/*keratinocyte-derived chemokine* (KC, CXCL1), MCP-1, and IL-8 are increased in the sputum in COPD patients and the bronchiolar epithelium overexpresses MCP-1, its receptor CCR2, MIP1 α , and IL-8.

The role of neutrophils in the pathogenesis of COPD is not entirely clear. Neutrophils can secrete serum proteinases, including neutrophil elastase, cathepsin G, and proteinase 3, as well as *matrix metalloproteinase* (MMP)-8 and MMP-9. These proteases may contribute to alveolar destruction and are also potent stimuli of mucus secretion. Relationships have been shown between circulating neutrophils and the decline in FEV₁.⁴⁴ Similarly, neutrophil numbers in bronchial biopsy specimens and induced sputum are related to disease severity⁴⁵ and the rate of decline in lung function.⁴⁶

There is a 5- to 10-fold increase in the numbers of macrophages in the airways, lung parenchyma, and BAL in patients with COPD. Macrophage numbers in the airways correlate with the severity of the airflow limitation in COPD.⁴⁷ Cigarette smoke activates macrophages to release inflammatory mediators, including TNF- α , IL-8, and other CXC chemokines, MCP-1, leukotriene B₄, and *reactive oxygen species* (ROS). Macrophages also secrete proteases, including MMP-2, MMP-9, MMP-12, cathepsins K, L, and S, and neutrophil elastase taken up from neutrophils. Macrophages from COPD patients are more activated, secrete more inflammatory proteins, and have greater elastolytic activity when compared with macrophages from normal smokers; macrophage activation is further enhanced by exposure to cigarette smoke.^{47,48} Increased numbers of macrophages in the lungs of COPD patients and smokers may result from increased recruitment of monocytes from the circulation in response to monocyte chemotactic chemokines such as MCP-1, which is increased in sputum and BAL in patients with COPD.⁴⁹ CXC chemokines also act as chemoattractants to monocytes. The concentration of CXCL1 is markedly increased in sputum and BAL from patients with COPD. Furthermore, monocytes from patients with COPD show a greater chemotactic response to CXCL1 than the monocytes from normal smokers and nonsmokers.⁵⁰

Dendritic cells are present in increased numbers in the airways and alveolar walls of smokers.⁵¹ The role of dendritic cells in COPD is not yet defined, but the cells are likely to have an important role in the innate and adaptive immune responses in COPD.

Cigarette smoke activates airway epithelial cells to produce inflammatory mediators, including TNF- α , IL-1 β , GM-CSF, and IL-8. The epithelium in the small airways may be an important source of *transforming growth factor* (TGF)- β , which may induce local fibrosis.⁵² Epithelial cells can also secrete antioxidants and antiproteases and transport immunoglobulin- α and thus may be involved in adaptive

immunity. Cigarette smoke may impair these innate and adaptive immune responses of the airway epithelium and increase the likelihood of infection.

The expression of many of the inflammatory mediators implicated in the inflammatory response in the lungs in COPD is controlled by the transcription factor *nuclear factor* (NF)- κ B. NF- κ B is up-regulated in alveolar macrophages in patients with COPD and in airway cells in patients with mild/moderate COPD in comparison with control nonsmokers.^{53,54} Up-regulation of NF- κ B in lung cells in COPD may be a key molecular mechanism in the ongoing inflammation in the airways. Epigenetic modifications may also contribute to the enhanced inflammation in the lungs in COPD. *Histone deacetylase* (HDAC) 2 has been shown to be reduced in lung cells of subjects with COPD; a reduction of HDAC would allow increased acetylation of histone residues on DNA, a greater unwinding of DNA, and a greater access of transcription factors such as NF- κ B that up-regulate proinflammatory genes.

In general, with increasing severity of COPD there is a further increase in the inflammatory response. There is an increase in the number of neutrophils and macrophages in severe disease and a decrease in T lymphocytes (CD3⁺ cells) (see eTable 43-1). There appears to be a shift in the cellular type in severe disease toward cells with a phagocytic and proteolytic role in the bronchial tissues (see eTables 43-1 to 43-3).

CYTOKINES AND CHEMOKINES⁵⁵

In patients with severe emphysema, lymphocytes in the lungs strongly express TH1 cytokines and secrete high levels of *interferon* (IFN)- γ , CCR5, and CXCR3. In addition, they show increased expression of CXCR3 ligands, *monokine induced by interferon gamma* (MIG), and IP-10.⁵⁶ This polarization of alveolar lymphocytes toward the TH1 phenotype predominates in severe emphysema.

TNF- α has also been implicated in cigarette smoke-induced emphysema. Increased levels of TNF- α are present in the airways in cigarette smokers.³⁶ Animals that overexpress TNF- α show evidence of emphysema and an exaggerated alveolar inflammatory response,⁵⁷ while TNF receptor knockout mice demonstrate significant protection against cigarette smoke-induced emphysema.⁵⁸ With respect to emphysema, TNF- α stimulates MMP synthesis by alveolar macrophages.⁴⁷ Cultured macrophages exposed to cigarette smoke extract release TNF- α ⁴⁷ and, in addition, circulating TNF- α soluble receptors p55 and p75 are significantly increased in COPD patients compared with healthy controls.⁵⁹ In animal studies, absence of TNF- α receptor type 2 was associated with reduced inflammatory responses in terms of neutrophil, macrophage, CD4 and CD8 cell influx, and protection against cigarette smoke-induced emphysema.⁶⁰

IL-1 β may also play a role in the development of emphysema. In animal models, lung-specific induction of human IL-1 β resulted in emphysema,⁶¹ whereas inhibition with IL-1 β antibody reduced alveolar macrophage influx into the airspaces following cigarette smoke exposure.⁶² Furthermore, double IL-1 receptor and TNF- α receptor knockout mice are protected against elastase-induced emphysema.⁶³

Inflammation, Airway Remodeling, and Airflow Limitation

The peripheral airways (bronchioles < 2 mm in diameter) are the major site of increased resistance to airflow in COPD.^{14,64} The main pathologic lesions in the peripheral airways include increased number of inflammatory cells (see Table 43-1 and eTable 43-2) and structural changes, such as epithelial goblet cell metaplasia, airway wall fibrosis, and smooth muscle hypertrophy.^{25,65,66} The increase in the thickness of the airway wall, inflammation, fibrosis, and smooth muscle hypertrophy will encroach on the lumen and reduce airway diameter; increased wall thickness may also uncouple the airways and the surrounding lung parenchyma, thereby reducing the elastic force that opposes bronchiolar smooth muscle contraction and promoting airway closure. Airway wall inflammation can also contribute to the destruction of alveolar-bronchiolar attachments, producing deformation and narrowing of the airway lumen. This is supported by the observation that, in smokers, the destruction of alveolar attachments correlates with the degree of inflammation in peripheral airways.⁶⁷

Increased goblet cell metaplasia and subsequent hyperplasia in the small airways of smokers may also limit airflow.⁶⁵ The goblet cell may contribute to the increased peripheral airway resistance by producing mucus at a site where it is not normally produced, leading to a marked increase in the surface tension of the airway lining fluid. This would lead to instability of the peripheral airways, facilitating their early closure during expiration. The increase in goblet cells in the peripheral airway epithelium of smokers is associated with an increased number of neutrophils.⁶⁵ Because neutrophil elastase is a potent secretagogue,¹⁰ the colocalization of neutrophils and goblet cells within the epithelium in COPD may result in increased secretion of mucus by goblet cells.

In smokers with COPD, CD8⁺ T lymphocytes are increased not only in central airways but also in peripheral airways and in the lung parenchyma⁶⁸ (see eTable 43-2). CD8⁺ cytotoxic T cells are thought to play a role in the rapid resolution of acute viral infections that are frequent in patients with COPD. The observation that people with frequent childhood respiratory infections are more prone to develop COPD⁶⁹ supports the role of current and latent viral infections in this disease.^{70,71} In response to repeated or persistent viral infection, it is possible that an excessive number of CD8⁺ T lymphocytes may be recruited and damage the lung in susceptible smokers, possibly through the release of TNF- α and perforins.^{72,73} Conversely, it is also possible that CD8⁺ T lymphocytes can damage the lung directly, even in the absence of viral infection. It has been hypothesized that the CD8⁺ cytotoxic T cell and other inflammatory cells accumulate in response to an autoantigen.^{35,74}

Inflammatory changes appear to target the peripheral airways and alveoli. A comparison of the central and peripheral airways shows that the total number of inflammatory cells is increased in the peripheral airways (<3 mm diameter) in patients with chronic bronchitis with normal lung function, compared with control smokers (see eTable 43-2). Some studies have shown an increase in total leukocytes and in CD8⁺ cells in the peripheral airways of patients with mild/moderate COPD in comparison with control

eTable 43-2 Variation of Inflammatory Cells and Markers of Inflammation in the Central and Peripheral Airways

	CENTRAL AIRWAYS						PERIPHERAL AIRWAYS (<3 MM DIAMETER)				
	PMN	CD68	CD4	CD8	IL-4	IL-5	PMN	CD68	CD4	CD8	Total Inflammation
Mild/moderate COPD	→ ³²	→ ³²	→ ³²	→ ³²	↓ ³⁰⁷	→ ³⁰⁷	→ ^{66,308,309,311}	↑ ^{308,310} → ^{66,309,311}	→ ^{66,308,309,310,311}	↑ ⁶⁶ → ^{308,309,310,311}	↑ ⁶⁶ → ^{308,309,310,311}
Chronic bronchitis with normal FEV ₁	—	—	—	—	↑ ³⁰⁷	→ ³⁰⁷	—	—	—	—	↑ ²³
Control smokers	→ ³²	→ ³²	→ ³²	→ ³²	→ ³⁰⁷	→ ³⁰⁷	→ ^{66,308,309,311}	→ ^{66,308,309,310,311}	→ ^{66,308,309,310,311}	→ ^{66,308,309,310,311}	→ ^{23,66,308,309,310,311}

↑, Significantly increased values in comparison with that indicated by →; →, basal values or values insignificantly changed; ↓, significantly decreased values in comparison with that indicated by →; —, no data available. Numbers indicate references.

FEV₁, forced expiratory volume in 1 second.

Adapted from Willemse BW, ten Hacken NH, Rutgers B, et al: Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *Eur Respir J* 26:835–845, 2005.

eTable 43-3 Variation of Inflammatory Cells in the Lung Parenchyma

	PMN	CD68	CD3	CD4	CD8	EOS
Mild/moderate COPD	→ ^{36,161}	→ ³¹³	↑ ¹⁶¹	→ ^{36,161}	↑ ^{36,161}	→ ³⁶
Smokers with normal FEV ₁	→ ^{36,161,164}	↑ ⁶⁴ → ³⁶	↑ ⁶⁴ → ¹⁶¹	→ ^{36,161}	→ ^{36,161}	→ ³⁶
Control Nonsmokers	↑ ⁶⁴ → ^{161,213}	→ ^{36,76}	→ ^{64,161}	→ ^{36,161}	→ ^{36,161}	→ ³⁶

↑, Significantly increased values in comparison with that indicated by →; →, basal values or values insignificantly changed; ↓, significantly decreased values in comparison with that indicated by →.

Numbers indicate references.

EOS, eosinophils; FEV₁, forced expiratory volume in 1 second; PMN, polymorphonuclear leukocytes.

Adapted from Willemse BW, ten Hacken NH, Rutgers B, et al: Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *Eur Respir J* 26:835–845, 2005.

smokers.⁷⁵ Studies of tissue obtained from lung volume reduction surgery in patients with severe COPD have shown an increase in total leukocytes and in CD4⁺ and CD8⁺ lymphocytes in both the peripheral airways and the lung parenchyma.¹⁶ In contrast, smokers with normal lung function show an increased number of macrophages and T lymphocytes in lung parenchyma compared with control nonsmokers, with no changes in CD4⁺ and CD8⁺ cells. In patients with mild to moderate COPD, there is an increase in CD8⁺ cells in the alveolar septa compared with control nonsmokers, with no change in the numbers of neutrophils, macrophages, or CD4⁺ cells.⁷⁵

The inflammatory response in the peripheral airways may play a role in the fibrosis that characterizes the small airways in patients with moderate/severe COPD.⁷⁶⁻⁷⁸ As the disease progresses, small airways develop increased thickness and enhanced inflammatory infiltrate by neutrophils, macrophages, and T lymphocytes (CD4⁺ and CD8⁺ T cells), and B lymphocytes. Lymphoid follicles also accumulate within the walls of the bronchioles, and the lumen of these airways are often obliterated by mucus.^{16,17,78} A number of mechanisms have been proposed to link inflammation and small airway remodeling. *Fibroblast growth factor* (FGF) and *FGF receptor* (FGFR) signaling appear to be associated with airway vascular remodeling in chronic bronchitis. In studies of lung tissue from COPD, FGF1 and its receptor FGFR1 are detected by immunohistochemistry in vascular and airway smooth muscle and in airway epithelial cells.⁷⁹ FGF1 and/or FGF2 increase the mRNA levels of FGFR1 and induce cellular proliferation of cultured human airway smooth muscle cells.⁸⁰ Smokers with COPD show increased expression of FGF in central airways, predominantly due to enhanced expression in the bronchial glands, suggesting that FGF may also have a role in promoting mucus hypersecretion in smokers.⁸¹

The pattern of cytokine profile and chemokine receptor expression has been investigated in the peripheral airways in COPD. CD8⁺ T cells in the peripheral airways in COPD are associated with IFN- γ and express CXCR3,⁸² a chemokine receptor that is thought to be preferentially expressed on TH1 cells. Moreover, CXCR3 expression is associated with the expression in the epithelium of its ligand CXCL10. This suggests that the CXCR3/CXCL10 axis may be involved in the recruitment of TH1 cells into the peripheral airways of smokers with COPD. These studies also showed that the interaction of CXCL10 with CXCR3 drives the release of macrophage MMP12 by macrophages. MMP12 is a potent elastolytic enzyme, which can cause lung tissue destruction. These data suggest a possible mechanism by which TH1 lymphocytes can drive the progression of small airway and emphysematous destruction, thus relating the inflammation in peripheral airways to surrounding alveoli. Studies also indicate that differences in gene expression in the small airways and surrounding lung parenchyma may result preferentially in fibrosis of small airways but in loss of alveolar cells in the lung parenchyma, resulting in emphysematous destruction.⁸³

MUCUS HYPERSECRETION

Mucus forms a film that coats the airway epithelium and is propelled from the periphery of the lung to the upper

airways by the coordinated movement of cilia. The main constituents of the mucus layer are mucus glycoproteins (mucins), water, and peptides. Mucus plays a key role in the clearance of foreign material and infectious agents and has important antioxidant properties. In chronic bronchitis, there is an increase in mucus in the airways, resulting from increased production of mucins and increased secretion from goblet cells.

Mucus production and secretion in COPD is regulated by multiple cellular and molecular mechanisms. Goblet cells express MUC5AC and MUC2 while glandular mucosal cells express MUC5B, MUC8, and MUC9.⁸⁴ Enhanced expression of MUC5B has been shown in the bronchiolar epithelium of COPD patients.⁸⁵ A number of stimuli such as neutrophil elastase, *lipopolysaccharides* (LPSs), IL-1 β , TNF- α , cigarette smoke, and oxidative stress cause goblet cell metaplasia and mucus hypersecretion.⁸⁶ Neutrophil elastase increases MUC5AC mRNA levels by enhancing mRNA stability.⁸⁷ LPS also induces MUC5AC expression in animal models, associated with neutrophil infiltration⁸⁸ and increased expression of MMP9.⁸⁹

Signaling pathways initiated by *epidermal growth factor* (EGF) receptor phosphorylation, which can be induced by cigarette smoke-derived oxidative stress, EGF, or TGF- α , also play an important role in mucin production in airway epithelial cells.⁸⁶ ROS can activate the serine protease tissue kallikrein, which can then cleave the transmembrane precursor of EGF.⁹⁰ Cigarette smoke produces ROS, also resulting in *vascular endothelial growth factor receptor* (VEGFR) activation and mucus production by activation of the *TNF α converting enzyme* (TACE), resulting in loss of TGF- α in airway epithelial cells.⁹¹ Acrolein, a component of cigarette smoke, can also induce MUC5AC expression created by ligand/dependent activation of EGFR and mediated by TACE and MMP9.⁹² In addition, ROS derived from cigarette smoke can activate an Src-dependent signaling cascade and trigger transcriptional regulation of MUC5AC mediated by binding of the activator protein-1 response element by JunD and Fra-2.⁹³ Moreover, cigarette smoke extract has been shown to synergize with LPS or TNF- α in the induction of MUC5AC expression, suggesting a potential amplification by cigarette smoke and inflammatory stimuli relevant to the pathogenesis of COPD.⁹⁴ A number of transgenic mice experiments have begun to unravel the complex interplay between inflammation, oxidative stress, and growth factors in the development of mucus hyperplasia. These studies suggest that CD4⁺ Th2 cells and the cytokine network including IL-4, IL-10, and IL-13 play a crucial role in the development of goblet cell hyperplasia/metaplasia.⁹⁴⁻⁹⁷

PROTEASES/ANTIPROTEASES

A protease/antiprotease imbalance, leading to the breakdown of connective tissue components, particularly elastin, has been considered to be the critical mechanism in the pathogenesis of emphysema in smokers. This concept developed from studies showing the development of early-onset emphysema in patients deficient in the major *anti-elastase* α_1 -antitrypsin (A1AT)⁹⁸ and from animal studies showing the development of emphysema in response to the instillation of proteolytic enzymes.⁹⁹ Pallid mice, which have

decreased A1AT levels, develop emphysema earlier on exposure to cigarette smoke than mice with normal A1AT levels.^{100,101} Furthermore, mice lacking neutrophil elastase are protected from chronic cigarette smoke-induced emphysema.¹⁰²

Elastin is the principal component of elastic fibers and is secreted from several cell types as a precursor, tropoelastin. These tropoelastin molecules become aligned in the extracellular space on microfibrils. Under the action of lysyl oxidase, the lysine residues in tropoelastin are modified, causing the tropoelastin monomers to cross-link and form larger, insoluble elastin polymers. Because the cross-links, known as *desmosines*, are unique to elastin, they have been used as a marker of elastin degradation. Elastin turnover is minimal in normal subjects; thus, breakdown products should not be detectable. However, desmosine and elastin peptides are elevated in smokers and patients with COPD.¹⁰³ In addition, studies have shown that the annual rate of decline in FEV₁ in a group of smokers correlated positively with urine levels of desmosine.¹⁰⁴

Elastin is an important target for proteolytic enzymes, and its destruction results in loss of elasticity in the lung parenchyma. Together with the destruction of elastin, inactivation of antiproteases is central to the protease/antiprotease imbalance hypothesis. Early studies showed that the function of A1AT was reduced by about 40% in smokers, compared with nonsmokers.¹⁰⁵ This “functional A1AT deficiency” was thought to result from inactivation of A1AT by oxidants in cigarette smoke. However, most of the A1AT in cigarette smokers remains active and is therefore still capable of protecting against the increased protease burden. Studies assessing the function of A1AT in either chronic or acute cigarette smoking have not been definitive. Only a transient and nonsignificant fall in A1AT activity has been measured in BAL 1 hour after smoking.¹⁰⁶ Thus, the hypothesis that the major event is an imbalance between an increased elastase burden in the lungs and a “functional deficiency” of A1AT, due to its inactivation, is an oversimplification.

There are increased numbers of neutrophils and macrophages in the airspaces in chronic smokers, which may increase the elastase burden by the release of elastase from activated neutrophils. In support of this, neutrophils isolated from patients with emphysema show greater elastase-induced fibronectin degradation in vitro than cells from control subjects matched for age and smoking history.¹⁰⁷ Other studies have invoked a contributory role for other antiproteases, such as antileukoprotease, or more subtle changes (e.g., a decrease in the association rate constant of A1AT for neutrophil elastase, which may contribute to elastin degradation).

There is also evidence that an abnormality in elastin synthesis and repair may be involved in the pathogenesis of emphysema. In an animal model of elastase-induced emphysema, treatment with retinoic acid restored normal alveolar architecture.¹⁰⁸ These studies in adult rats (which have continued lung growth throughout their adult life, in contrast with humans) provide some evidence that the destructive process in emphysema, which was always considered irreversible, may be capable of repair. However, human studies of retinoic acid have not shown any evidence of repair of emphysema.¹⁰⁹

In addition to serine proteases, cysteine proteases (cathepsins) may have a role in the pathogenesis of COPD. Cathepsin-L has been detected in BAL from patients with emphysema,¹¹⁰ and alveolar macrophages in patients with COPD secrete more cysteine proteases than macrophages from normal smokers or nonsmokers.¹¹¹

Matrix metalloproteases (MMPs) are a group of at least 20 proteolytic enzymes that have a role in tissue remodeling and repair associated with normal development and inflammation, by degrading collagen, laminin, and elastin. They are characterized in distinct subclasses depending on their substrate specificity, amino acid similarity, and identifiable sequence molecules. The subclasses are collagenases (MMP1, 8, 13), gelatinases (MMP2, 9), stromelysin S (MMP3, 10, 11), membrane-type MMP14–MMP25), matrilysin (MMP7), and macrophage metalloelastase (MMP12).¹¹² The major inhibitors of MMPs are alpha-2 macroglobulin and the *tissue inhibitor of metalloproteases* (TIMP) family.

There is substantial evidence for a role of MMPs in the pathogenesis of COPD.¹¹³ Several studies have shown increased expression of several MMPs in the lungs of COPD patients. MMP12 protein has been observed in sputum, BAL, bronchial biopsies,^{113,114} and peripheral lung tissue in patients with severe emphysema.¹¹⁵ Increased concentrations of MMP1 (collagenase) and MMP9 (gelatinase B) are present in BAL from patients with COPD,^{116,117} and there is increased activity of MMP9 in the lung parenchyma of patients with emphysema.¹¹⁸ MMP12 mRNA can be induced by exposure of human bronchial epithelial cells to cigarette smoke extract or cytokine mix (TNF- α and IFN- γ).^{119,120} Alveolar macrophages from smokers express more MMP9 than those from normal subjects, and there is an even greater increase in patients with COPD.⁴⁷

There is considerable evidence from experimental models to link MMP12 and the development of emphysema. Increased MMP12 expression was present in alveolar macrophages after smoke exposure in C57BL/6 mice,¹²¹ and animal models have shown that cigarette smoke does not induce emphysema in mice lacking MMP12.¹²² MMPs are also known to activate the latent form of TGF- β . In mice lacking the integrin α V β 6, there is a failure to activate TGF- β , and these animals do not develop age-related emphysema, which can be overcome by overexpression of TGF- β 1.¹²³ These data suggest that TGF- β may down-regulate MMP12 under normal conditions and that the absence of TGF- β results in excessive MMP12 production and emphysema. Although MMP9 and MMP2 both degrade elastin and are both expressed in COPD lungs, the role of these MMPs in the pathogenesis of COPD remains unclear.

OXIDANTS/ANTIOXIDANTS IN COPD

Cigarette smoke is a complex mixture of more than 4700 chemical compounds, including high concentrations of free radicals and other oxidants.¹²⁴ The oxidant burden in lungs may be further enhanced in smokers by the increased numbers of neutrophils and macrophages in the alveolar space that release increased amounts of oxidants, such as oxygen and H₂O₂.¹²⁵ Other sources of ROS are those generated through normal cellular processes in the lungs, such as those produced by normal cellular respiration, or by inhalation of air pollutants, such as particulate pollution.

A delicate balance exists between the toxicity of oxidants and the protective effects of intracellular and extracellular antioxidant defense systems, which are critically important for the maintenance of normal pulmonary cellular functions. A shift of the oxidant/antioxidant balance in favor of oxidants is known as oxidative stress. There is now considerable evidence of increased oxidative stress in smokers and patients with COPD.¹²⁶

All tissues are vulnerable to oxidant damage but, by virtue of its direct contact with the environment, the airspace epithelial surface of the lung is particularly vulnerable. Injury to the epithelium, manifested as an increase in airspace epithelial permeability, may be an important early event following exposure to cigarette smoke.¹²⁷ Extracellular and intracellular glutathione, an antioxidant, appears to be critical to the maintenance of epithelial integrity following exposure to cigarette smoke. This was shown in studies in which the increased permeability of epithelial cell monolayers in vitro, and in rat lungs in vivo, following exposure to cigarette smoke condensate, was associated with profound changes in the homeostasis of glutathione.^{128,129} These in vitro and animal studies are paralleled by human studies demonstrating increased epithelial permeability in chronic smokers compared with nonsmokers, with a further increase in epithelial permeability following acute smoking.¹²⁷ Thus, cigarette smoke has a detrimental effect on alveolar epithelial cell function that is, in part, oxidant mediated.

A major site of free radical attack is on polyunsaturated fatty acids in cell membranes producing lipid peroxidation, a process that may continue as a chain reaction to generate hydroperoxides and long-lived aldehydes. Levels of products of lipid peroxidation in plasma and BAL are significantly increased in healthy smokers and in patients with acute exacerbations of COPD, compared with healthy nonsmokers.^{126,130}

Several studies demonstrate increased levels of oxidants in exhaled air or breath condensates in COPD patients.¹³¹⁻¹³⁴ Furthermore, there is evidence that oxidative stress can cause increased lipid peroxidation in lung tissue in COPD patients compared with smokers who have a similar smoking history but have not developed the disease, with the level of lipid peroxidation correlating with the degree of airflow limitation.¹³⁵

Free iron is a critical element in many oxidative processes. Macrophages from smokers have been shown to contain more iron than those from nonsmokers, and they release more iron, thus potentially increasing the oxidant burden in smokers.^{136,137}

The major antioxidants in respiratory tract lining fluid include mucin, reduced glutathione, uric acid, protein (largely albumin), and ascorbic acid.¹³⁸ There is limited information on respiratory epithelial antioxidant defenses in smokers, and even less on those in COPD patients. Studies have shown that glutathione is elevated in the BAL from chronic smokers.¹²⁶ Even so, glutathione may not be present in sufficient quantities to deal with the excessive oxidant burden during acute smoking because cigarette smoke exposure depletes glutathione in a dose- and time-dependent manner.¹³⁹

Other antioxidants such as vitamin C and E have shown variable changes in COPD patients. Reduced levels of

vitamin E are present in the BAL of smokers compared with nonsmokers.¹⁴⁰ By contrast, other studies found a marginal increase in vitamin C in the BAL of smokers, compared with nonsmokers.¹⁴¹ The apparent discrepancy may be due to different smoking histories in chronic smokers, particularly the time of the last cigarette in relation to the sampling of BAL.

There is an imbalance between oxidants and antioxidants in COPD resulting in oxidative stress, which underlies many of the pathogenic mechanisms in COPD.¹⁴² Numerous studies documented increased expression of markers of oxidative stress in the lungs of COPD patients, compared with smokers who have not developed COPD. *4-hydroxy-2-nonenal* (4HNE), a highly reactive lipid peroxidation end product, reacts quickly with extracellular proteins to form adducts.¹⁴³ 4HNE adducts are present in greater quantities in airway epithelial and endothelial cells in the lungs of COPD patients, compared with smokers with a similar smoking history who have not developed the disease.¹³⁵ 4HNE can act as a chemoattractant for neutrophils¹⁴² and is also involved in numerous cellular functions such as cell proliferation, growth inhibition,¹⁴⁴ T-cell apoptosis,¹⁴⁵ and activation of various signaling pathways.¹⁴⁶ 4HNE has also been shown to activate the synthesis of the antioxidant glutathione, by induction of the glutamate cysteine ligase gene as an antioxidant response to increased oxidative stress, and also of a variety of proinflammatory genes coding for IL-8, MCP-1, EGF, and MUC5AC.¹⁴⁵ The presence of increased oxidative stress in COPD lungs is confirmed by the finding of increased expression of 8-hydroxy-2 deoxyguanosine, formed by the reaction of hydroperoxides with the DNA base guanosine.¹⁴⁷

Many actions of oxidative stress can potentially play a role in the pathogenesis of COPD. These include the inactivation of anti-proteases (such as A1AT or secretory leuko-protease inhibitor)¹⁴⁸ or activation of metalloproteases by oxidants, resulting in a protease/antiprotease imbalance in the lungs.¹⁴⁹ Oxidants can directly damage components of the lung matrix (e.g., elastin and collagen) and also interfere with elastin synthesis and repair.¹⁴²

Oxidative stress also influences the molecular mechanisms involved in proinflammatory gene expression. Gene activation by transcription factors is dependent on a number of factors, among which is the remodeling of DNA dependent on the nuclear histone acetylation/deacetylation balance,¹⁵⁰ controlled by the activities of *histone acetyltransferases* (HATs) and *histone deacetylases* (HDACs). DNA in the resting cell is coiled around a nucleosome core of histone residues. This configuration suppresses the accessibility of transcription factors such as NF- κ B to their cognate DNA sequences. Acetylation of the lysine residues in the core histones results in uncoiling of the DNA, increasing the accessibility of transcription factors and RNA polymerase 2 and hence increased gene transcription. Deacetylation, under the influence of HDACs, results in rewinding of the DNA around the histone proteins, decreasing gene transcription. Macrophages from cigarette smokers show a decrease in histone deacetylase activity,¹⁵¹ as has also been shown in the lungs of smoke-exposed animals associated with nitrotyrosine, 4HNE, and aldehyde-modified HDAC proteins, resulting in their enhanced degradation in the proteasome system and thus decreased HDAC activity.¹⁵²

Studies of resected lung indicate that HDAC2 activity is reduced in lung tissue in COPD, associated with lower HDAC2 RNA levels and expression of HDAC2 protein as a result of modification of HDACs by oxidants.^{153,154} This decrease in HDAC increased with disease severity and was associated with an increase in histone-4 acetylation at the IL-8 promoter and increased in IL-8 mRNA expression. Thus, molecular mechanisms such as transcription factor activation and chromatin remodeling, as a result of increased oxidative stress, may be responsible for perpetuating inflammation in COPD.

The most compelling data in support of the causal role of oxidative stress in the pathogenesis of emphysema have been provided by studies outlining the role of the master antioxidant transcription factor *nuclear erythroid-related factor 2* (NRF2) in the disease. NRF2 controls the expression of more than 100 gene products, including several of the most important antioxidant enzymes. Human lungs and alveolar macrophages from COPD patients have decreased expression of NRF2 transcriptional activity.^{155,156} The protective role of NRF2 in emphysema is underscored by the increased susceptibility of NRF2 null mice to cigarette smoke.^{157,158} Furthermore, enhancement of NRF2 expression using a small molecule activator protected wild type mice against cigarette smoke-induced emphysema.¹⁵⁹

Oxidative stress is linked to cell death, including alveolar cell apoptosis in the setting of human and experimental emphysema.¹⁶⁰⁻¹⁶² Moreover, oxidative stress underlies several of the mechanisms thought to participate in aging, which may lower the threshold for lung injury to cigarette smoke.¹⁶³

APOPTOSIS AND EMPHYSEMA

ALVEOLAR CELL DEATH IN EMPHYSEMA

Studies have documented that lung cells undergo apoptosis in emphysematous lungs, predominantly involving endothelial cells in the alveolar walls, compared with normal smokers' lungs.^{36,160,161,164} Experimental emphysema in animals can be produced by decreased VEGF or VEGF signaling, and studies in human lungs demonstrated decreased expression of VEGF and VEGF-receptor 2 expression in association with emphysema.¹⁶⁰ The aggregate of these data led to the concept of an alveolar maintenance program that was required for structural preservation of the lungs. Cigarette smoke is thought to cause destruction of this maintenance program, thus causing emphysema.

Lung tissue is destroyed due to the mutual interaction of alveolar cell apoptosis, oxidative stress, and protease/antiprotease imbalance.¹⁶⁴ This concept is supported by observations that antioxidant treatment prevented both apoptosis and emphysema induced by down-regulation of VEGF.¹⁶⁵

Inflammation can be triggered and amplified by alveolar injury, including either enhanced alveolar cell apoptosis or defective apoptotic cell clearance.¹⁶⁶ Targeted alveolar cell apoptosis using a chimeric peptide containing a lung homing sequence linked to a proapoptotic peptide led to emphysematous enlargement of murine lungs, associated with alveolar cell apoptosis, oxidative stress, macrophage

influx, and increases in ceramide levels.¹⁶⁷ Moreover, viral infections (such as influenza virus) can synergize with cigarette smoke to cause experimental emphysematous tissue destruction involving alveolar cell death and secondary lung inflammation.¹⁶⁸

ROLE OF AGING IN THE PATHOGENESIS OF EMPHYSEMA

The evidence of shared features between pulmonary emphysema and lung aging has led to the hypothesis that both conditions share underlying mechanisms, including oxidative stress, inflammation, and apoptosis.^{169,170}

The cellular equivalent of aging is senescence, which is characterized by a nonproliferative state in which cells are metabolically active and apoptosis resistant. A number of molecular and cellular mechanisms are associated with cellular senescence, including accumulation of DNA damage,¹⁷¹ impairment of DNA repair,¹⁷² epigenetic modifications in nuclear DNA,¹⁷³ protein damage¹⁷⁴ from oxidative stress, and telomere attrition.¹⁷⁵ Central to "end replication senescence" is the erosion of telomeres, with the ensuing activation of DNA repair enzymes, and the cell cycle control kinase inhibitors p53, p21, and p16. These signaling processes converge on de-phosphorylated retinoblastoma protein, which potently inhibits cell cycle progression. Cellular senescence also takes place in vivo, particularly in conditions associated with aging. Several markers of cellular senescence are present in vivo, particularly *senescence-associated β -galactosidase* (SA- β -gal), and the increased expression of cyclin-kinase inhibitors p16 and p21.¹⁷⁶

Cigarette smoke extract leads to increased SA- β -gal expression in cultured type II cells¹⁷⁷ or lung fibroblasts,¹⁷⁸ which have also been shown in lung fibroblasts from emphysematous lungs.¹⁷⁹ Oxidative stress enhances telomere shortening.¹⁸⁰ Furthermore, alveolar epithelial and endothelial cells in emphysematous lungs also have increased expression of p21 associated with decreased telomere length.¹⁸¹ The decreased telomere length parallels similar findings in circulating peripheral blood leukocytes. An association has been shown between blood leukocyte telomere length and pack-years of smoking,¹⁸² and telomeres are shorter in blood leukocytes from COPD patients compared with control subjects.¹⁸³

Sirtuins are type III histone deacetylases that have a role in a number of processes including stress resistance, apoptosis, cell senescence, differentiation, and aging.¹⁸⁴ *Sirtuin-1* (SIRT1) is essential for maintaining silent chromatin via the deacetylation of chromatin.¹⁸⁵ Environmental stress, such as cigarette smoke exposure, decreases SIRT1 levels in both macrophages in vitro and in rat lungs in vivo, associated with increased expression of inflammatory cytokines.¹⁸⁶ SIRT1 has been shown to be decreased in lung cells from COPD patients, compared with smokers who have not developed the disease, as a result of post-translational oxidative modification.¹⁸⁷ This would accelerate the process of aging and also enhance inflammation.

No single mechanism can account for the complex pathology in COPD. It is likely that interactions transpire between different mechanisms. For example, there are probably interrelationships between protease/antiprotease, oxidative stress, and apoptosis as destructive processes in

emphysema. Better understanding of the relative importance of these different pathogenic mechanisms will come from proof-of-concept therapeutic intervention studies.

EPIDEMIOLOGY

SIZE OF THE PROBLEM

COPD is a global health problem and a leading cause of mortality throughout the world. COPD will increase as a result of increased aging, as well as more widespread smoking in developing countries.

COPD is also associated with significant economic burden. In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget.¹⁹⁰ In the United States, the direct costs of COPD almost 10 years ago were estimated to be \$29.5 billion and the indirect costs \$20.4 billion.¹⁹¹ COPD exacerbations account for the greatest proportion of the total COPD burden on the health care system, especially hospitalization costs, which increase rapidly as COPD severity increases. Indirect costs are difficult to assess in COPD. However, particularly in developing countries, the impact of COPD on workplace and home productivity outweighs direct costs for disease management.

PREVALENCE AND INCIDENCE

COPD prevalence data vary significantly because of geographic variation, differences in survey methods, and diagnostic criteria.¹⁹² The widespread under-recognition and under-diagnosis of COPD¹⁹³ means that self-report surveys will underestimate the true prevalence of COPD. In studies using spirometry, prevalence depends on the diagnostic criterion. Using the diagnostic criteria for a clinical diagnosis suggested by the *Global Initiative for Obstructive Lung Diseases* (GOLD)¹⁹⁴ will lead to higher figures than using *lower limit of normal* (LLN) for the FEV₁/FVC ratio.¹⁹⁵ The *Burden of Obstructive Lung Diseases* (BOLD) program has generally combined the fixed FEV₁/FVC ratio of 0.70 in combination with an FEV₁ less than 80% of the percentage predicted as the diagnostic criteria for COPD. BOLD has carried out surveys in several parts of the world and has documented more severe disease than previously found, with COPD prevalence using this criterion varying from 6% in Hannover, Germany, to 19% in Cape Town, South Africa¹⁹⁶ (Fig. 43-4). In these studies, a substantial prevalence (3% to 11%) of COPD among never-smokers was also found.

A random-digit dialed telephone survey in the United States (Behavioral Risk Factor Surveillance System, United States, 2011) found that 6.3% of adults had been told by a physician that they had COPD. Of these, approximately three quarters had pulmonary function testing and half of them received at least one daily medication.¹⁹⁷ In a BOLD survey in Kentucky, the prevalence of COPD defined as FEV₁/FVC less than 0.70 was 19.6%.¹⁹⁸

Incidence data are even fewer. The notion that 10% to 15% of smokers develop COPD is not justified.¹⁹⁹ However, the number may have value regarding clinically relevant COPD. Newer long-term follow-up studies indicate that the life-time prevalence of COPD in continuing smokers is close

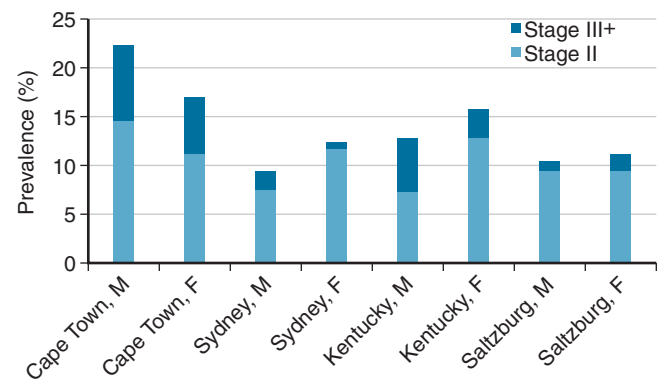


Figure 43-4 Prevalence of moderate (stage II) and severe/very severe (stage III+) COPD in selected geographic regions. F, female; M, male. (Adapted from Buist AS, McBurnie MA, Vollmer WM, et al: International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 370:741–750, 2007.)

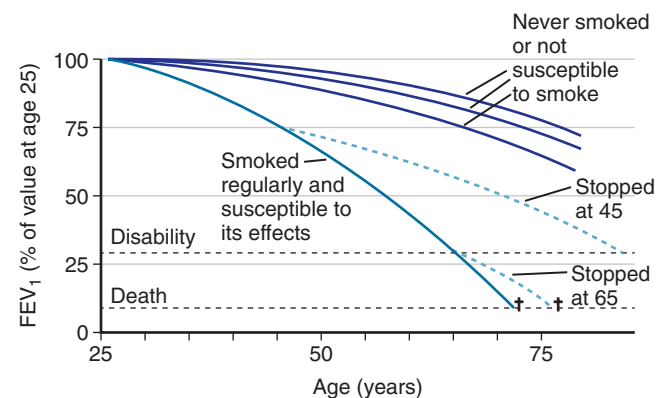


Figure 43-5 The natural history of COPD as depicted by Fletcher and colleagues. (Modified from Fletcher C, Peto R: The natural history of chronic airflow obstruction. *Br Med J* 1:1645–1648, 1977.)

to 50%.^{200,201} The incidence of COPD in populations more heavily exposed to biomass fuel or other non-tobacco-related exposures is not known.

NATURAL HISTORY

Our conception of the natural history of COPD was formed by Fletcher and coworkers³ in their seminal studies in the 1970s and is most often illustrated as shown in Figure 43-5.

This concept emphasizes an excess FEV₁ decline as the hallmark of COPD and numerous epidemiologic studies have subsequently examined FEV₁ and defined risk factors according to their effect on change in FEV₁.²⁰²⁻²⁰⁸ Although the concept of an excess decline is undoubtedly correct,²⁰⁹ the view of COPD being caused by an excess decline alone is too simple, as Fletcher and coworkers acknowledged. Prenatal factors and perinatal events affect both lung growth and subsequent risk of COPD, and more recent studies have underlined the effect of early life events on subsequent COPD risk.^{210,211} The natural history of COPD thus starts prenatally and stretches over the entire lifetime; important factors include those responsible for lung and airway development at birth, for lung growth and maximally attained

lung function, for the plateau of lung function in early adulthood, and for subsequent decline in lung function.

Most studies have used simple spirometry to evaluate the natural history of COPD. It is today unclear if different phenotypes of COPD show different patterns of natural history, and we may in fact be dealing with several natural histories rather than just one.²¹² In established COPD, the subsequent course is highly variable; it seems clear that, in a substantial proportion of patients, disease progression, as evaluated by FEV1 decline, stops.^{213,214}

MORTALITY AND MORBIDITY

COPD is one of the most important causes of death in most countries. The Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020¹⁸⁸; a newer projection estimated COPD will be the fourth leading cause of death in 2030.¹⁸⁹ These data likely underestimate the true COPD mortality because under-recognition and underdiagnosis of COPD affect the accuracy of mortality data, with COPD being listed only as contributory cause of death or not listed at all on the death certificate.²¹⁵ At the same time, mortality in COPD is strongly influenced by the presence of comorbidities.

Morbidity measures traditionally include hospitalizations, physician visits, and use of medications. Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, the limited data available indicate that morbidity due to COPD increases with age. Morbidity from COPD may be affected by other comorbid chronic conditions (e.g., cardiovascular disease, musculoskeletal impairment, diabetes mellitus) that are related to COPD and may have an impact on the patient's health status, as well as interfering with COPD management.

RISK FACTORS

Risk factors can be considered as “exposures” and “endogenous factors” as shown in Figure 43-6 and discussed as follows.

GENETICS

A significant familial risk of airflow limitation has been observed in smoking siblings of patients with severe

COPD,²¹⁶ suggesting that genetic, together with environmental factors, could influence this susceptibility. Deficiency of A1AT, a major circulating inhibitor of serine proteases, is the best documented genetic risk factor for developing emphysema.^{217,218} Although A1AT deficiency is relevant to only a small part of the world's population, its potentiating effect on the harmful effects of smoking illustrates the interaction between genes and environmental exposures leading to COPD. Other single genes have some effect on the risk of developing COPD, including the alpha-nicotinic acetylcholine receptor, as well as the hedgehog-interacting protein gene, the *FAM13* gene, and the gene encoding MMP12. A few other genes have been implicated, but there remains a discrepancy between findings from analyses of COPD and lung function, as well as between *genome-wide association study* (GWAS) analyses and candidate gene analyses.²¹⁹⁻²²¹ In addition, none of the genes yet identified by GWAS in patients with COPD overlap with genes found to have an effect on the level of lung function.^{222,223}

SMOKING

Globally, cigarette smoking is the most commonly encountered risk factor for COPD. Smoking during pregnancy poses a risk for the fetus, by affecting lung growth and development in utero.^{224,225} Smoking in childhood and adolescence leads to stunting of lung growth and earlier decline in lung function than in nonsmokers.²²⁶ Adult cigarette smokers have a higher prevalence of respiratory symptoms, lower lung function, a greater annual rate of decline in FEV₁, a greater loss of lung density, and a greater COPD mortality rate than nonsmokers.^{202,227} The crucial factor seems to be the amount smoked and the extent of inhalation.²⁰⁴ Filtered cigarettes do not differ significantly from cigarettes without filters, and other types of tobacco and marijuana are also risk factors for COPD.^{228,229} Smoking cessation has, in several surveys, been shown to be associated with both a lower prevalence of respiratory symptoms and a slower decline in FEV₁, in both population studies and patient cohorts.^{204,213,230,231}

OTHER ENVIRONMENTAL FACTORS

Exposures other than smoking are risk factors for the development of COPD; however, less is known about the impact of single risk factors, their dose-response relationship, and the pathophysiologic, as well as clinical, features of nonsmoking-related COPD. Occupational exposures are a recognized risk factor for COPD.^{205,208,232} Data from the NHANES III survey found that the fraction of COPD attributable to occupational exposures was 19% overall and 31% among never-smokers.²³³ These figures are consistent with an American Thoracic Society statement that concluded that occupational exposures account for 10% to 20% of either symptoms or functional impairment consistent with COPD.²³⁴

Biomass fuel exposure is the term covering exposure to smoke from wood, animal dung, crop residues, and coal, typically burned in open fires or primitive stoves. Biomass fuel exposure is an important source of indoor air pollution in undeveloped countries, where almost 3 billion people are



Figure 43-6 COPD risk factors showing environmental exposures that interact with individual propensities.

exposed, and there is increasing evidence that this exposure is an important risk factor for COPD.²³⁵⁻²³⁹

INFECTIONS AND EXACERBATIONS

A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood.^{240,241} In established COPD, more focus has recently been on infections and exacerbations and the progression of disease. Susceptibility to infections plays a role in exacerbations of COPD, and exacerbations increase the excess decline in FEV₁,²⁴²⁻²⁴⁴ although the actual impact may be modest.²¹³

Tuberculosis has been shown to be a risk factor for COPD,^{245,246} but whether this is mainly due to airflow limitation from scarring or to true COPD is not clear.

ASTHMA AND BRONCHIAL HYPERREACTIVITY

Asthma and COPD are generally viewed as two different diseases with a variable overlap.²⁴⁷⁻²⁴⁹ However, asthma may also be viewed as a risk factor for the development of COPD. In the Tucson study, adults with asthma were found to have a 12-fold higher risk of acquiring COPD over time than those without asthma, after adjusting for smoking.²⁵⁰ A Dutch study of people with asthma found that 20% of subjects developed irreversible airflow limitation²⁵¹ and, in a Danish longitudinal population study, self-reported asthma was associated with an excess loss of FEV₁.²⁵²

In the European Community Respiratory Health Survey, bronchial hyperresponsiveness was second only to cigarette smoking as the leading risk factor for COPD, responsible for 15% of the population attributable risk.²⁵³ This is in accordance with previous studies showing a strong impact of bronchial hyperresponsiveness on FEV₁ decline, also in the absence of asthma.²⁵⁴⁻²⁵⁶

OTHERS

In the seminal study by Fletcher and coworkers,³ chronic bronchitis was not associated with decline in lung function. However, a more recent population study found an association between mucus hypersecretion and FEV₁ decline⁹ and, in younger adults who smoke, the presence of chronic bronchitis is associated with an increased likelihood of developing COPD.^{257,258} Most likely, chronic bronchitis affects FEV₁ decline by increasing lower respiratory tract infections.

COPD IN THE FUTURE

COPD used to be a disease of the smoking man in the industrialized world. Today, women have as much COPD as men, and although the prevalence seems to be stable or even increasing in many developed countries, this is more likely to be the result of ageing rather than increased risk.²⁵⁹ However, in developing countries, the exposure to biomass fuel with the added exposure to tobacco is bound to result in an increase in COPD morbidity and mortality and this will drive the real increase in COPD in the future.^{188,189} Thus, the typical COPD patient in 2030 is likely to live outside Europe and the United States and to have COPD based on mixed risk and with poorer access to treatment.

CLINICAL CHARACTERIZATION OF COPD

The clinical presentation of COPD is highly heterogeneous.²⁶⁰ The most common respiratory symptoms (breathlessness, cough, and expectoration), pathologic changes (chronic bronchitis, emphysema), and lung function abnormalities (mostly airflow limitation) vary greatly between patients and are poorly related (Fig. 43-7). Likewise, the relationship between many of the extrapulmonary manifestations and comorbid diseases frequently present in COPD are, by and large, independent of the severity of airflow limitation and also highly variable between patients.²⁶¹ Therefore, the clinical characterization of COPD should be multidimensional and should consider carefully several aspects and concepts, as discussed later.

SEVERITY, ACTIVITY, AND IMPACT OF COPD

The *severity* of a given disease (including COPD) relates to the “*extent of functional impairment of the target organ(s)*.”²⁶² Traditionally, the severity of COPD has been assessed by the severity of airflow limitation (FEV₁).¹ However, other domains of the disease (such as symptoms and frequency of exacerbations) are also clinically relevant and have been recently proposed by the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) to be considered in the clinical assessment of these patients.¹⁹⁴ To this end, several prognostic composite indices have also been proposed, including the BODE²⁶³ (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) and the ADO (Age, Dyspnea, and airflow Obstruction)²⁶⁴ indices.

The *activity* of a disease relates to the “*level of activation of the biological processes that drive disease progression*.”²⁶² At variance with other chronic diseases, such as rheumatoid arthritis, this has been a largely forgotten concept in COPD. Traditionally, disease progression in COPD has been assessed by the decline in lung function with time^{203,204}. Recent research, however, challenged the paradigm that COPD was inevitably associated with an accelerated decline of FEV₁ with time by showing that lung function can be stable, or even improve over time in a proportion of treated COPD patients.^{213,214,265} Furthermore, because COPD is a highly heterogeneous disease,²⁶⁰ it is likely that different components of the disease (1) progress at different rates, (2) require different monitoring approaches to determine “progression” of clinical, functional, structural, and biologic variables, and (3) differ between patients depending on their specific clinical phenotype and/or the result of therapy.

How to determine COPD disease *activity* in the clinic has not yet been resolved, but several potential candidate markers of disease *progression* can be envisaged, including the following: (1) *clinical markers*, such as the presence/increase in symptoms,²⁶⁶ rate of FEV₁ decline,²¹³ frequency of exacerbations,²⁶⁷ unintended weight loss,²⁶⁸ poor exercise capacity, and/or appearance/worsening of comorbidities²⁶¹; (2) *imaging markers*, such as the presence/progression of emphysema,²⁶⁹⁻²⁷¹ airway disease including the presence of bronchiectasis²⁷² and/or a number of molecular imaging markers of inflammation²⁷³; and, finally, (3) *biomarkers of*

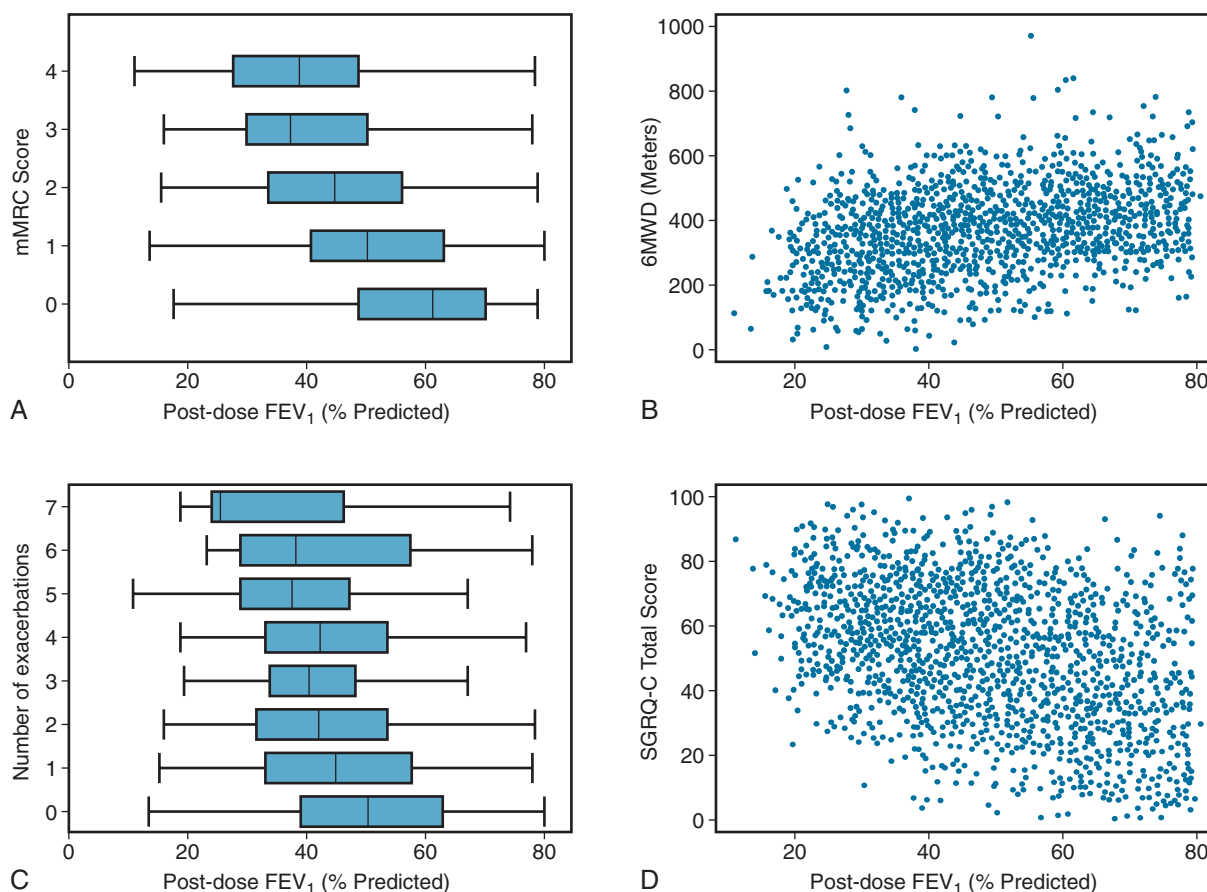


Figure 43-7 The severity of airflow limitation (FEV_1) is poorly related to **A**, level of breathlessness, as assessed by the mMRC questionnaire; **B**, exercise capacity as assessed by the six minute walk distance (6MWD); **C**, previous history of exacerbations; and **D**, health status as assessed by the Saint George Respiratory Questionnaire (SGRQ-C). For further explanations see text. (From Agustí A, Calverley P, Celli B, et al: Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 11:122–136, 2010.)

inflammation/repair in circulating blood,^{274–276} exhaled air,²⁷⁷ and/or urine.²⁷⁸

The interaction between disease activity and severity is likely to be a key determinant of the *impact* of the disease on the patient, which is how this is perceived by the patient and how the disease interferes with his or her activities of daily living.²⁶² This has potentially relevant clinical implications because it is likely that disease severity and disease activity require different therapeutic approaches in order to minimize disease impact. Hence, although the treatment of disease severity should aim at improving the functional capacity of the patient (bronchodilators, oxygen therapy, rehabilitation, among others),¹⁹⁴ that of disease activity should aim at stopping or reducing the intensity of the biologic processes that drive disease progression (e.g., inflammation) using anti-inflammatory or proresolution therapeutic alternatives.²⁷⁹

EARLY VERSUS LATE DISEASE

Since the seminal paper of Fletcher and Peto,³ COPD has been considered as a progressive disease in which so-called “susceptible smokers” develop an accelerated decline in lung function (FEV_1) with age. However, because almost all studies published so far included patients with a mean age of 60 to 65 years, there is a paucity of information on

“earlier” stages of the disease. The term *early disease* refers then to an “early” time point in the natural history of the disease, at which the patient is diagnosed or studied (i.e., the age of the patient at that time point).²⁶² Yet often the concept of “early” disease is confused with that of “mild” disease, something that has to do with the severity of the disease (FEV_1) and not with its timing (age); clearly, an “old” patient with “mild” disease does not have “early” disease.²⁸⁰ Although the relationship between disease activity and disease severity is unclear, different possibilities can be conceived. For instance, in “early” disease (i.e., at young age), “disease activity” is likely to be high and severity low, whereas, depending on the natural history of the disease and/or the effectiveness of available therapies, in severe disease (at any given age) “disease activity” may be high, low, or intermediate.

COPD PHENOTYPES

Given the heterogeneous clinical presentation of COPD (see Fig. 43-7) there is considerable interest in identifying groups of patients with similar prognosis or therapeutic requirements.²⁸¹ Strictly speaking, a phenotype is defined by the observable properties (or *phenotypic traits*) of an organism, as determined by its genotype and modulated by its environment.²⁸² In order to provide some clinical perspective, a

recent consensus definition has proposed the concept of a *clinical phenotype*, which is defined as: “a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death).”²⁸¹

Many disease characteristics (i.e., phenotypic traits) have been proposed as potential COPD *phenotypes*, but only a few have been validated prospectively according to this definition²⁸¹: (1) *alpha₁-antitrypsin deficiency*, where the specific gene/protein has been identified and specific therapy has been developed,²⁸³ (2) *upper lobe emphysema, with poor exercise tolerance after rehabilitation*, in patients with severe airflow limitation, whose survival improves with lung volume reduction surgery,²⁸⁴ and (3) *frequent exacerbations* (two or more per year²⁶⁷) that can benefit from anti-inflammatory therapy.^{244,285}

The identification and validation of novel clinical phenotypes can advance the clinical management of COPD by identifying novel therapeutic targets and determining the efficacy of a pharmacologic treatment/procedure in subgroups with specific attributes.²⁸⁶ To this end, well-designed, long-term longitudinal studies are necessary. The ECLIPSE, COPDgene, and SPIROMICS studies are beginning to address this need. Important caveats to consider include (1) certain disease attributes, such as dyspnea, depression, or exacerbations, could be viewed as phenotypic traits or outcomes, depending on the clinical context in which they are used²⁸¹; (2) the clinical presentation of some clinical phenotypes may change (for better or worse) over time due to either the effect of therapy and/or the natural course of the disease; (3) two prevalent diseases can coexist (for instance, COPD and asthma²⁴⁹ or COPD and obstructive sleep apnea²⁸⁷); (4) any given patient can belong to more than one clinical phenotype; (5) chronic respiratory failure, whose prognosis is improved by long-term home oxygen therapy in COPD^{288,289}, should not be considered a COPD phenotype because it is a final functional state common to many other diseases. It is, however, a marker of “severity” of the disease; and (6) it is plausible that the severity/activity of the disease should be assessed differently in different clinical phenotypes, and that the relationship between disease activity and disease severity might differ across phenotypes.

Potential clinical COPD phenotypes that require validation include (1) disproportionate dyspnea (it predicts excessive mortality,^{290,291} but the role of concomitant comorbidities is unclear.²⁹² Likewise, whether comorbidities constitute a specific phenotype or simply represent the coincidence of prevalent aging-associated diseases in the same patient is unclear^{261,292}); (2) persistent systemic inflammation, which is associated with increased mortality and exacerbation rate²⁷⁴; (3) chronic bronchitis, although available scientific evidence is controversial^{9,293}; (4) presence of chronic airway bacterial colonization^{294,295}; (5) emphysema²⁷¹ and its relation with pulmonary hyperinflation²⁹⁶ and lung cancer²⁹⁷; (6) the mixed phenotype asthma/COPD²⁴⁹; and (7) “out-of-proportion” pulmonary hypertension.²⁹⁸

GOLD COMBINED ASSESSMENT PROPOSAL

GOLD has recently proposed a new multidimensional system for the assessment and management of COPD

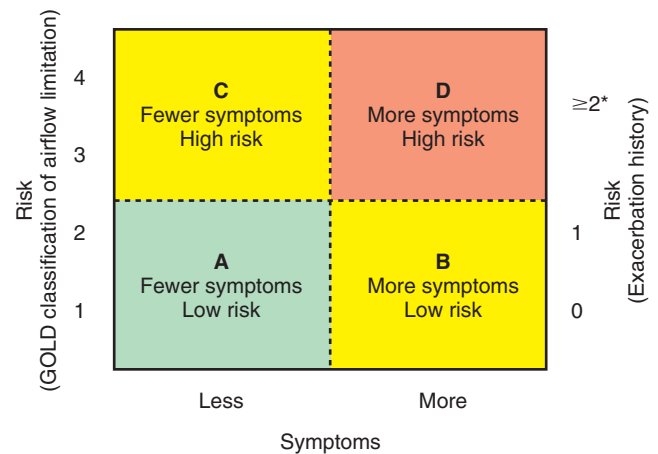


Figure 43-8 GOLD classification system. COPD patient groups according to the 2011 GOLD assessment proposal. * or 1 hospitalization. (Modified from Agusti A, Hurd S, Jones P, et al: Frequently asked questions (FAQs) about the GOLD 2011 assessment proposal of COPD. *Eur Respir J* 42:1391–1401, 2013).

patients that combines (1) the symptoms perceived by the patient, (2) the severity of the airflow limitation, and (3) the previous history of exacerbations.¹⁹⁴ In this proposed assessment, COPD patients are classified into four categories or groups (A, B, C, and D) (Fig. 43-8) that, together with the assessment of potential comorbidities, can assist clinicians in guiding therapy. There are still many unresolved questions about this new proposal, but there is no doubt that it is an important step toward a more personalized assessment and treatment of patients with COPD.²⁹⁹ It is possible that, in the future, the characterization and assessment of COPD will require the consideration of other domains not currently included in this proposal. Recently a “COPD control panel” that combines a “severity” module, an “activity,” module, and an “impact” module (Fig. 43-9) has been proposed as a potential way forward.³⁰⁰

The emerging fields of *systems biology* and *network medicine*³⁰¹ can help in understanding the complexity of the inter-related biologic mechanisms (so-called “intermediate phenotypes”^{302,303} or “endotypes”³⁰⁴) underlying different clinical phenotypes in COPD, as well as in the identification of clinically useful biomarkers³⁰⁵ and novel therapeutic targets.²⁹⁹ A more global, unbiased approach to “airway diseases” may eventually generate a new taxonomy with specific therapeutic implications.³⁰⁶

Key Points

- Pathology of COPD is heterogeneous with pathologic changes in the large airways (chronic bronchitis), small airways (bronchiolitis), and lung parenchyma (emphysema) that vary in their expression among patients.
- The pathogenesis of COPD is generally thought to result from an abnormal inflammatory response in the lungs to toxic particles and gases.
- No single mechanism can account for the complex pathology in COPD. It is likely that interactions among different mechanisms are involved, including inflammatory immune responses, protease/antiprotease and

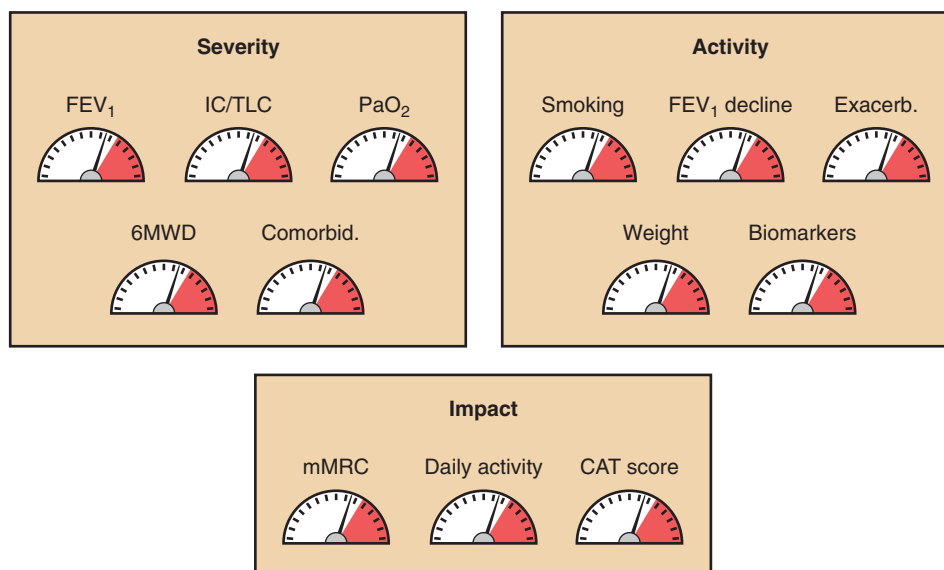


Figure 43-9 A COPD control panel. Collecting information in the three domains of severity, activity, and impact may provide guidance for optimal management of individual patients with COPD. 6MWD, 6-minute walk distance; CAT, COPD assessment test; FEV₁, forced expiratory volume in 1 second; IC/TLC, inspiratory-to-total lung capacity ratio; mMRC, modified Medical Research Council dyspnea scale; PaO₂, arterial oxygen pressure. (From Agusti A, MacNee W: The COPD control panel: towards personalized medicine in COPD. *Thorax* 68:687–690, 2013.)

oxidant/antioxidant imbalance, apoptosis, cell senescence, and aging.

- COPD often results from a combination of genetic susceptibility, poor lung growth, and an excess loss of lung function in adulthood.
- The clinical presentation of COPD is highly heterogeneous, and therefore the clinical characterization of COPD should be multidimensional and should consider factors related to disease severity, activity, and impact. Several disease phenotypes of COPD that benefit from specific treatment have been identified.

Complete reference list available at ExpertConsult.

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COPD: CLINICAL DIAGNOSIS AND MANAGEMENT

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INTRODUCTION AND HISTORY

Chronic obstructive pulmonary disease (COPD), as it is currently defined, is a spectrum of lung abnormalities characterized physiologically by persistent airflow obstruction. The histologic abnormalities seen most commonly are lung tissue destruction, or emphysema, and airway disease, recognized clinically as chronic bronchitis. From a historical perspective, emphysema was recognized first. Dating back to the 17th and 18th centuries, clinicians recognized what were termed abnormally “voluminous” lungs.¹ In 1789, Baillie published a series of illustrations demonstrating the classic pathologic features of emphysema. A bit later, chronic bronchitis was described, best documented by the clinician, pathologist, and inventor of the stethoscope, Laennec. In his 1821 “A Treatise on the Diseases of the Chest,” Laennec describes lungs that are hyperinflated and do not empty well.² But, upon pathologic inspection, he also noted the “bronchus of the trachea are often...filled with mucous fluid.” At that time, smoking was not common and Laennec attributed the principal causes of this disease to environmental and genetic factors. However, it is important to note that Laennec identified both of the characteristic features of COPD: emphysema and chronic bronchitis.

By the 1940s, master clinicians were becoming familiar with an entity characterized by dyspnea on exertion in patients with physical signs of emphysema along with chronic bronchitis and asthma.³ However, the ability to diagnose this entity reliably was not possible until the invention of spirometry. In 1846, John Hutchinson invented the spirometer, which was capable of measuring vital capacity, but 100 years later, it was Tiffeneau who introduced the concept of a timed vital capacity as a measure of airflow that allowed the spirometer to become a diagnostic instrument for airflow obstruction.⁴ By the 1950s, clinicians recognized that specific spirometric and flow volume patterns indicated the presence of emphysema.⁵ In fact, the first edition of Hinshaw and Garland in 1956 depicted spiograms indicating airflow obstruction in emphysema.⁶

Groundwork for the modern definition of COPD was established at two major scientific conferences, the CIBA Guest Symposium⁷ in 1959 and the *American Thoracic Society* (ATS) Committee on Diagnostic Standards⁸ in 1962. The ATS committee defined chronic bronchitis clinically as chronic cough lasting at least 3 months for at least 2 years; emphysema was defined histologically as enlarged alveolar spaces; asthma was defined as airway hyperresponsiveness.⁹ It was then that Dr. William Briscoe at the ninth Aspen Emphysema Conference in 1965 first introduced the term “COPD.” Several years later, Drs. Charles Fletcher and Richard Peto provided support for the link between smoking and the development of COPD in their 1976 landmark book documenting that continued smoking accelerates the disease, whereas smoking cessation attenuates lung function loss.¹⁰

The modern definition of COPD, as put forth by the ATS and *European Respiratory Society* (ERS), describes it as “a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.”⁹ While this definition describes a physiologic abnormality associated with exposure to noxious stimuli, the challenge that remains for both clinician and researcher is understanding the significant heterogeneity in disease presentation and progression that still exists within this umbrella definition.

CLINICAL FEATURES

SYMPTOMS

Individuals with early COPD are often asymptomatic. However, as the disease progresses, dyspnea, wheezing, cough and sputum production typically become more

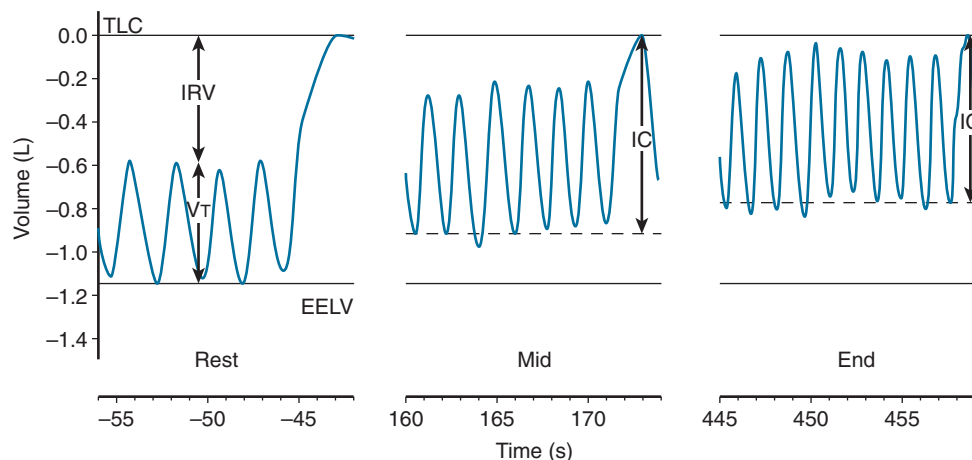


Figure 44-1 Dynamic hyperinflation. Volume tracing from a patient with severe COPD who demonstrated ventilatory dependent dynamic hyperinflation. Inspiratory capacity (IC) decreases and end-expiratory lung volume (EELV) increases as ventilation increases during exercise. IRV, inspiratory reserve volume; TLC, total lung capacity; VT, tidal volume. (From Dolmage TE, Evans RA, Goldstein RS: Defining hyperinflation as ‘dynamic’: moving toward the slope. *Respir Med*. Mar 7, 2013. Figure 1.)

prominent. Any of these features should trigger an evaluation including spirometry both for diagnosis, if not already established, and for disease staging. Early in the disease course, dyspnea may be experienced only with exertion and patients may attribute these symptoms to other factors and not seek treatment. Patients may also modify their activities to avoid dyspnea so that the progression of pulmonary limitation may be rather insidious. In fact, patients’ activity may be severely limited even when they believe their disease process is still mild.¹¹ Eventually, however, as the disease progresses, dyspnea may ultimately be present with activities of daily living. Whereas the mechanism for dyspnea in COPD is likely multifactorial, exercise-induced air trapping otherwise known as “dynamic hyperinflation” likely plays a significant role (Fig. 44-1).

As with dyspnea, patients may attribute cough to other factors such as smoking and therefore may not complain about this symptom unless prompted. In general, current smokers have more sputum production, which paradoxically may increase transiently after smoking cessation.¹² While the presence of cough and sputum production in COPD is often more variable than the presence of dyspnea, it can significantly impact quality of life.¹¹ Sputum, when present, tends to be mucoid, clear to white in appearance, and more purulent with exacerbations. Chronic bronchitis is also clinically significant because it is associated with more frequent exacerbations¹³ and has specific therapeutic implications (see [Treatment](#)).^{14,15} Excessive sputum production (more than 2 to 3 tablespoons daily) may indicate the presence of bronchiectasis, which has been reported to range in prevalence between 29% and 52% in moderate-to-severe COPD and has been associated with increased mortality.¹⁶ Hemoptysis may be seen with both chronic bronchitis and bronchiectasis, particularly during COPD exacerbations. However, the presence of hemoptysis in a patient with COPD should raise concern for other possible causes, including lung cancer, given the increased risk for lung cancer in this patient population.¹⁷

Several instruments have been developed to assess health status in COPD, most notably the *St. George’s Respiratory Questionnaire*¹⁸ (SGRQ) and the *COPD Assessment Test*¹⁹

(CAT) (Fig. 44-2). Both are multidimensional instruments encompassing symptoms such as cough and sputum production as well as breathlessness and activity limitation. Both the SGRQ and CAT demonstrate rough but imperfect correlations with *forced expiratory volume in 1 second* (FEV_1) but, more importantly, demonstrate changes after interventions^{20,21} and with exacerbations.^{22,23} While the SGRQ is longer and used primarily in the research setting, the CAT consists of only eight questions and is practical for use within the clinical setting. The Modified Medical Research Council scale is a 5-point dyspnea scale²⁴ that, while not developed specifically for COPD, is relevant because it relates to mortality in COPD alone²⁵ or when used to calculate the BODE (BMI, obstruction, dyspnea, exercise capacity) index, a mortality predictor in COPD²⁶ (Table 44-1).

PHYSICAL EXAMINATION

Early in the course of the disease, no specific abnormalities may be noted on physical examination. Wheezing may or may not be present and does not necessarily relate to the severity of airflow obstruction. Prolonged expiratory time is a more consistent finding in COPD, particularly as the disease progresses. A forced expiratory time of more than 6 seconds corresponds to an FEV_1 /forced vital capacity (FVC) ratio of less than 50% to 60%.^{27,28} In very severe disease, patients develop physical signs indicative of hyperinflation, including a barrel-shaped chest, decreased breath sounds, distant heart sounds, and increased resonance to percussion. Patients may breathe in a “tripod” position in which the individual leans forward and supports his or her upper body with extended arms. This maneuver takes advantage of the accessory muscles of the neck and upper chest to increase air movement. Patients with severe disease may also use pursed-lip breathing, which involves exhaling through tightly pressed, pursed lips. This technique creates back-pressure and is thought to reduce dynamic hyperinflation although it may also work by reducing bronchoconstriction via neutrally mediated mechanisms.²⁹

In patients with severe disease, other systemic manifestations may include signs of cor pulmonale, or right-sided

How is your COPD?

For each item below, place a mark (✓) in the box that best describes your experience.

Example: I am very happy

0	✓	1	2	3	4	5
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 I am very sad

		SCORE							
I never cough	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	I cough all the time	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				
I have no phlegm (mucus) in my chest at all	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	My chest is completely full of phlegm (mucus)	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				
My chest does not feel tight at all	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	My chest feels very tight	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				
When I walk up a hill or one flight of stairs I am not breathless	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				
I am not limited doing any activities at home	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	I am very limited doing activities at home	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				
I am confident leaving my home despite my lung condition	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				
I sleep soundly	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	I don't sleep soundly because of my lung condition	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				
I have lots of energy	<table border="1" style="display: inline-table;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr></table>	0	1	2	3	4	5	I have no energy at all	<input style="width: 30px; height: 30px;" type="text"/>
0	1	2	3	4	5				

SCORE

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Reproduced with permission from GlaxoSmithKline. GlaxoSmithKline is the copyright owner of the COPD Assessment Test (CAT). However, third parties will be allowed to use the CAT free of charge. The CAT must always be used in its entirety. Except for limited reformatting the CAT may not be modified or combined with other instruments without prior written approval. The eight questions of the CAT must appear verbatim, in order, and together as they are presented and not divided on separate pages. All trademark and copyright information must be maintained as they appear on the bottom of the CAT and on all copies. The final layout of the final authorised CAT questionnaire may differ slightly but the item wording will not change. The CAT score is calculated as the sum of the responses present. If more than two responses are missing, a score cannot be calculated; when one or two items are missing their scores can be set to the average of the non-missing item scores.

Figure 44-2 COPD assessment test. (Reproduced with permission from GlaxoSmithKline.)

heart failure, leading to lower extremity edema. An accentuated P2 or pulmonic component of the second heart sound may also be appreciated. Tar stains on the fingers from cigarette smoking may be present. Clubbing is not a typical feature of COPD, even when hypoxemia is present,

and should suggest evaluation for other comorbidities including lung cancer.

Two commonly recognized COPD subtypes are the “pink puffers” and “blue bloaters.” Pink puffers, typically associated with significant emphysema, compensate by

Table 44-1 The BODE Index

Variable	Points on the BODE index			
	0	1	2	3
B—Body mass index (kg/m ²)*	>21	≤21	—	—
O—FEV ₁ (% of predicted) [†]	≥65	50–64	36–49	≤35
D—Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
E—MMRC dyspnea scale (score)	0–1	2	3	4

Four variables identified as being predictive of survival in patients with COPD, and the values (0–3) assigned to each variable by category. FEV₁, forced expiratory volume in 1 s; MMRC, modified Medical Research Council.

*Values for body mass index are 0 or 1 owing to the inflection point in the inverse relationship between survival and body mass index at a value of 21 kg/m².

[†]FEV₁ categories are based upon stages identified by the American Thoracic Society.

(From Celli B, Goldstein R, Jardim J, Knobil K: Future perspectives in COPD. *Respir Med* 99:S41–S48, 2005, Table 1.)

hyperventilation and often manifest muscle wasting and weight loss. Compared with blue bloaters, pink puffers are less hypoxemic and therefore appear “pink.” Blue bloaters typically have chronic bronchitis and tend to have decreased ventilation and greater *ventilation-perfusion* (V/Q) mismatch than pink puffers, leading to hypoxemia and hence cyanosis and to cor pulmonale with edema or “bloating.”

PULMONARY FUNCTION TESTING AND DIAGNOSIS

Spirometry

Pulmonary function testing (see Chapter 25) and, in particular, spirometry is essential to establish a diagnosis of COPD. While symptoms suggest a diagnosis, unfortunately their predictive value for a diagnosis of COPD is poor.³⁰ Several screening tools have been developed, including questionnaires³¹ and questionnaires used in conjunction with peak expiratory flow.³² Several studies suggest that among the various risk factors, older age and smoking history are the two most important risk factors for development of COPD.^{30,31,33} Spirometry can be performed in the physician’s office and should be done in any patient with symptoms (e.g., cough, sputum, dyspnea) and risk factors. When performing spirometry, a subject exhales forcefully and the FEV₁ is compared against the total air exhaled, which is the FVC. COPD is defined by a reduction in the FEV₁/FVC ratio. The degree of FEV₁ reduction defines the severity of airflow obstruction. The flow volume loop in COPD typically has a concave appearance and the volume-time curve demonstrates a prolonged expiratory time (Fig. 44-3).

The ATS and the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) recommend that post-bronchodilator values be used to help distinguish COPD from asthma. GOLD recommends an FEV₁/FVC less than 0.70 as the threshold for presence of airflow obstruction.³⁴ Rather than using the fixed ratio, the ATS/ERS recommends using the fifth percentile for the lower limit of normal.⁹ In general, the fixed ratio approach leads to overdiagnosis in older subjects

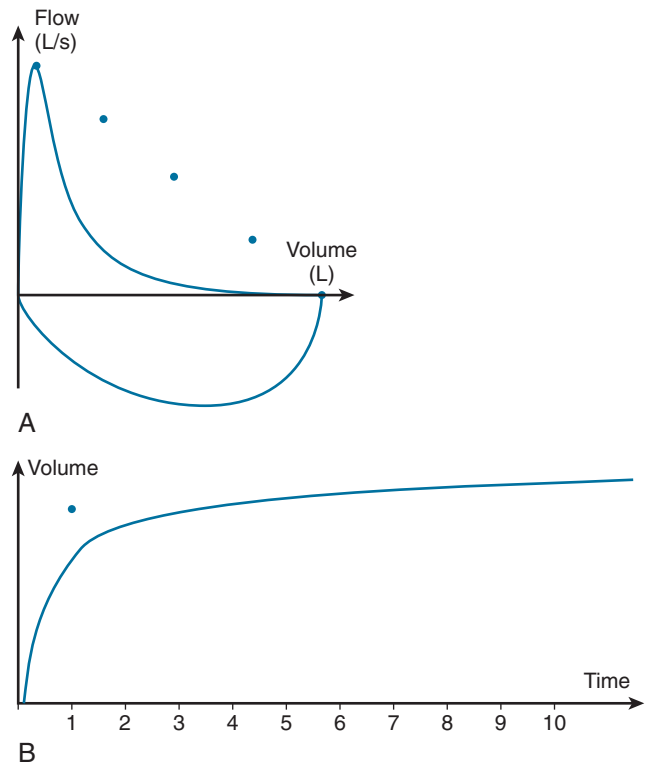


Figure 44-3 Flow volume loop in COPD. **A**, The tracing shows a concave flow volume loop with reduction of flow at all lung volumes. The dots indicate the expected flow at various lung volumes. **B**, The volume-time curve shows a prolonged expiratory time. The dot demonstrates the predicted FEV₁.

Table 44-2 GOLD Classification of Severity of Airflow Limitation in COPD, Based on Post-Bronchodilator FEV₁

In Patients with FEV ₁ /FVC < 0.70	
GOLD 1: mild	FEV ₁ ≥ 80% predicted
GOLD 2: moderate	50% ≤ FEV ₁ < 80% predicted
GOLD 3: severe	30% ≤ FEV ₁ < 50% predicted
GOLD 4: very severe	FEV ₁ < 30% predicted

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second.

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: <http://www.goldcopd.org/>.

because the FEV₁/FVC ratio declines with age, even in healthy individuals.³⁵ However, the fixed ratio approach carries the advantage of simplicity.

While COPD severity has typically been graded based on FEV₁% predicted, which is part of the GOLD (Table 44-2) and ATS/ERS recommendations, recent updates to the GOLD recommendations now incorporate symptoms and exacerbation risk as part of disease staging.

Lung Volumes

Other lung volumes including *total lung capacity* (TLC) and *residual volume* (RV) must be measured via plethysmography, which is typically performed in a pulmonary function laboratory. TLC is increased in COPD, particularly in the

presence of emphysema where there is significant loss of elastic recoil, resulting in lung hyperinflation. Increases in RV and functional residual capacity may also be seen. RV tends to increase to a greater extent than TLC, leading to an increase in the RV/TLC ratio. Vital capacity in COPD is also typically decreased because of hyperinflation.

Diffusing Capacity

Diffusing capacity for carbon monoxide (DL_{CO}) reflects the alveolar capillary blood volume and consequently is decreased in the presence of emphysema, but may also be reduced in the presence of other abnormalities that affect the alveolar capillary bed including pulmonary fibrosis. Near-normal spirometry and lung volumes in the setting of severely reduced diffusing capacity and radiographic evidence of emphysema should suggest a possible diagnosis of combined pulmonary fibrosis emphysema syndrome.³⁶

Exercise Testing

The *6-minute walk test* (6MWT) is probably the most frequently employed exercise test in COPD. The distance that a patient can walk in 6 minutes is termed the *6-minute walk distance* (6MWD).³⁷ Measuring distance walked during a defined time period was first described in the early 1960s.³⁸ An advantage of the 6MWT is that it requires little training to administer and no specialized equipment. While a 6MWT is not required to make a diagnosis of COPD, it allows the clinician to assess oxygenation during ambulation and the potential need for supplemental oxygen. 6MWD is also frequently employed during lung transplant evaluation to gauge functional status and prognosis. 6MWD has been demonstrated to relate to mortality in COPD and is a component of the BODE mortality index.²⁶ The 6MWT however does not provide diagnostic information regarding specific causes for dyspnea or exercise limitation, which can only be obtained through more formal *cardiopulmonary exercise testing* (CPET). CPET can be performed with either a treadmill or cycle ergometer.³⁹ A large number of parameters can be measured or derived during a CPET, including *maximal oxygen uptake* ($\dot{V}O_2$), *carbon dioxide output* ($\dot{V}CO_2$), maximal work rate, and anaerobic threshold. While there is good correlation between 6MWD and peak oxygen uptake in end-stage lung disease,^{40,41} the 6MWT should be considered complementary to the CPET. Most patients do not achieve maximal exercise capacity during the 6MWT and consequently the 6MWD may better reflect functional exercise capacity.⁴² The 6MWD also correlates better with quality of life measures; therapeutic interventions resulting in changes in 6MWD also correlate with improvements in dyspnea.⁴³⁻⁴⁵ Some form of exercise testing is typically employed before and after pulmonary rehabilitation to assess improvement. CPET is also a necessary part of evaluation for *lung volume reduction surgery* (LVRS), because LVRS may provide a survival benefit for those with a low work rate after pulmonary rehabilitation.⁴⁶

IMAGING

Chest radiography and *computed tomography* (CT) are the two imaging modalities most commonly used in COPD. While not required to diagnose COPD, imaging can be helpful to rule out concomitant processes. Chest radio-

graphs are frequently obtained to investigate dyspnea or hemoptysis or to look for pneumonia, heart failure, lung cancer, or pneumothorax. Chest radiography is not particularly sensitive or specific for the diagnosis of COPD. There are certain features, however, that are often seen in COPD. Radiolucency, diaphragmatic flattening, and increased retrosternal airspace on the lateral radiograph may be seen when hyperinflation is present (Fig. 44-4, Video 44-1). Occasionally large bullae may manifest as radiolucent areas.

Chest CT allows better detection and quantification of emphysema than does traditional chest radiography. Areas of low attenuation are a marker of emphysema; thickened airways indicative of bronchial thickening may also be seen (Fig. 44-5). If expiratory views are obtained, areas of air trapping indicative of small airway obstruction and emphysema may also be seen. CT is not indicated in the routine diagnosis or evaluation of COPD, but can be helpful when evaluating individuals with very severe COPD. CT imaging is required to quantify emphysema extent and distribution for the purposes of LVRS.⁴⁶ Individuals with very severe COPD undergoing transplant evaluation typically require a chest CT to rule out the presence of lung cancer and aid with surgical planning. CT imaging is also helpful when the clinician is concerned about a concomitant process such as interstitial lung disease which may be suggested on pulmonary function testing (see section on PFT's) or when hemoptysis or other unexplained changes in symptoms develop. Bronchiectasis, which may be reflected by copious sputum production and cough and has been associated with increased mortality,¹⁶ is also best assessed on CT.

Although CT is not required for routine practice, the potential clinical importance of CT imaging is becoming better appreciated. Several studies demonstrate a strong relationship between emphysema and both lung function decline^{47,48} and mortality.^{49,50} Bronchial thickening as assessed by CT also appears to have a strong relationship with symptoms as measured by the SGRQ.

The COPD patient population is at increased risk for lung cancer and the mortality benefit of screening CTs in smokers has now been established.⁵¹ Therefore a low-dose screening CT for lung cancer in individuals aged 55 to 74 years with at least a 30 pack-year smoking history, including those who quit in the preceding 15 years, may be appropriate (see Chapters 18 and 53).

LABORATORY TESTING

Arterial Blood Gases

Arterial blood gases (ABGs) are not indicated as part of the routine evaluation for patients with mild to moderate COPD. For many patients, pulse oximetry will suffice to provide an estimate of oxygen saturation. However, ABGs can be helpful to assess hypoxemia and to provide information regarding hypercapnia, particularly in individuals with more severe disease or during an acute exacerbation. ABG abnormalities also tend to worsen during exercise⁵² and sleep.⁵³ Early in the disease course, mild to moderate hypoxemia without hypercapnia is typically seen. Later in the disease course, hypercapnia may develop, particularly in individuals with FEV_1 less than 1 L.

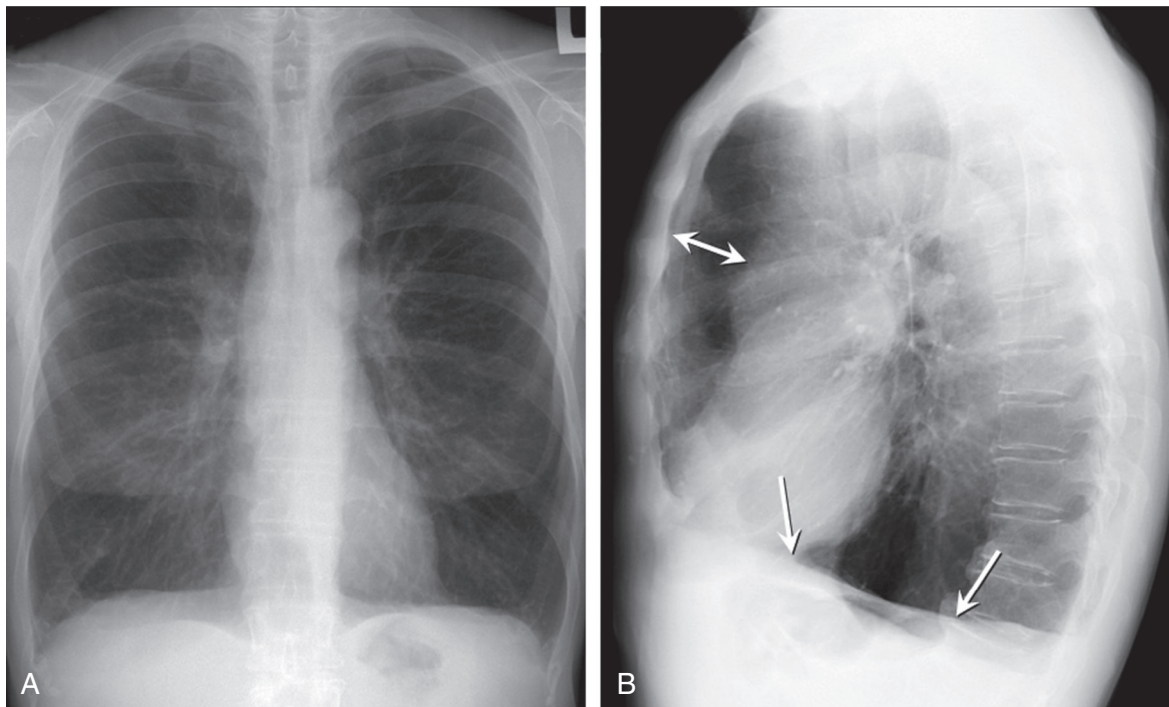




Figure 44-4 Centriacinar emphysema. Frontal (A) and lateral (B) chest radiograph in a 54-year-old female smoker with centriacinar emphysema. Note the very large lung volumes, with hyperlucency primarily seen in the upper lobes, consistent with a centriacinar emphysema pattern. Flattening of the diaphragms (arrows), a prominent retrosternal clear space on the lateral radiograph (double arrow), and a small-appearing heart on the frontal radiograph are findings consistent with abnormally increased lung volumes and are typical of advanced emphysema. The upper lobe lucency typical of centriacinar emphysema contrasts with the lower lobe predominant lucency seen in patients with panacinar emphysema. See [Video 44-1](#) for CT video of this patient. 

Erythrocytosis. Elevated hemoglobin may be seen in COPD, particularly in the presence of chronic hypoxemia. A hemoglobin value is also helpful in the evaluation of dyspnea because anemia is a common cause of dyspnea that should be ruled out. In addition, DL_{CO} is most accurate when adjusted for hemoglobin.

Serum Bicarbonate. An elevated serum bicarbonate can suggest chronic hypercapnia; in the setting of hypercapnia, serum bicarbonate is increased due to compensatory metabolic alkalosis.

Alpha₁-Antitrypsin Deficiency

The ATS guidelines recommend testing for A1AT deficiency for all individuals with persistent airflow obstruction.⁵⁴ A1AT is a protease that inactivates neutrophil elastase. Clinical features suggestive of A1AT deficiency include emphysema at a young age, emphysema in an individual with minimal or no smoking history, lower lobe predominant emphysema, and a family history of emphysema. However, A1AT deficiency can also be present in patients with more typical COPD presentations. In individuals with established COPD, diagnostic testing is recommended. Concern for the diagnosis is raised based on A1AT serum levels below 11 micromol/L (approximately 50 mg/dL using nephelometry (i.e., immunoturbidimetry) and 80 mg/dL by radial immunodiffusion) but should be confirmed with genotyping (high-risk genotypes include S, Z, and null alleles as the most deficient). Occasionally the serum level and genotyping are discordant; in this situation, protein phenotype analysis via electrophoresis can identify alleles with abnormal protein migration patterns. The chest radiograph and CT show the predominantly

lower lobe distribution of emphysema, consistent with a panacinar pattern (Fig. 44-6, [Video 44-2](#)) and different from the more common centriacinar pattern (see Fig. 44-4 and [Video 44-1](#)). 

Sputum. Sputum evaluation is not indicated in the routine diagnosis and care of the COPD patient. In patients with stable disease, sputum examination typically reveals a predominance of macrophages and few bacteria. During exacerbations, the number of organisms on Gram stain typically increases. The most common pathogens identified on sputum culture include *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*.⁵⁵ Less frequently identified organisms include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative rods. However, the relationship between identification of organisms in sputum and pathogenic contribution to acute exacerbations has been questioned because longitudinal studies have suggested that the incidence of bacterial isolation from sputum during an acute exacerbation of COPD was no different from that of the stable state,^{56,57} although bacteria identified in sputum during stable COPD have been associated with a greater exacerbation frequency⁵⁸ and lung function decline.⁵⁹ In general, exacerbations typically respond to empirical treatment.

COMPLICATIONS

PNEUMOTHORAX

Pneumothoraces may develop spontaneously in patients with COPD. Depending on the degree of respiratory

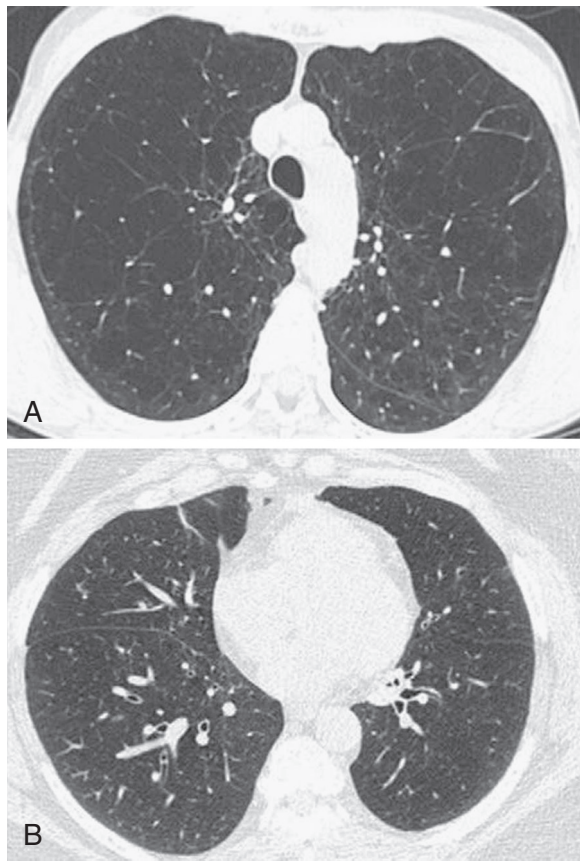


Figure 44-5 Two radiologic phenotypes of COPD. CT of two patients with COPD demonstrating the significant difference in the type of disease that may be present. Two patients with moderately severe disease are shown. **A**, The patient demonstrates predominantly emphysema whereas the patient shown in **B** demonstrates predominantly airway thickening. (From Han MK, Kazerooni EA, Lynch DA, et al: Chronic obstructive pulmonary disease exacerbations in the COPDGen study: associated radiologic phenotypes. *Radiology* 261:274–282, 2011.)

impairment, a pneumothorax may result in significant dyspnea and even acute respiratory failure. Pneumothoraces are treated similarly in COPD as in other conditions, although patients with severe emphysema are at increased risk for persistent air leaks, which may be difficult to treat.

GIANT BULLAE

Emphysema may present with large bullae that can occupy a good portion of the hemithorax. Surgical treatment can be considered if compression of adjacent lung tissue is significant and surgical intervention is expected to improve pulmonary mechanics.⁶⁰ Bullae may also become infected. An increased frequency of lung cancer has been reported in association with large bullae, seen either as a mass within the bulla or a thickening of the wall.^{61,62}

PNEUMONIA

Pneumonia is not uncommon in patients with COPD and should be in the differential diagnosis for any patient with COPD presenting with increased dyspnea, cough, sputum production, and/or fever, which can make it difficult to distinguish from an acute exacerbation of COPD without a chest radiograph. While COPD is believed to increase the

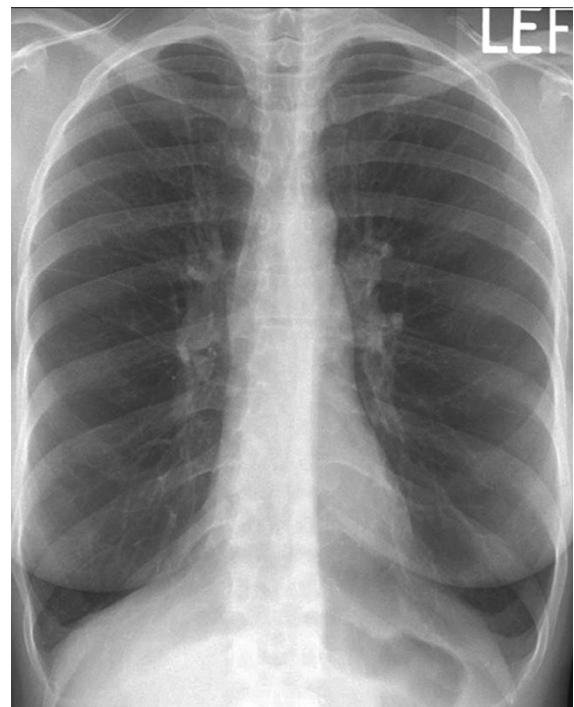


Figure 44-6 Panacinar emphysema. Frontal chest radiograph in a 51-year-old woman with α_1 -protease inhibitor deficiency presenting for lung transplant evaluation. Note the very large lung volumes with hyperlucency primarily seen in the bases, consistent with panacinar emphysema, as well as flattening of the diaphragms. Contrast the lower lobe lucency in this radiograph with [Figure 44-4](#), which shows upper lobe hyperlucency in a patient with centriacinar emphysema. See [CT Video 44-2](#) of this patient.

risk for pneumonia, epidemiologic data are limited.^{63,64} *Inhaled corticosteroids* (ICS), which are frequently employed in the treatment of COPD because they reduce the frequency of COPD exacerbations, have been associated with an increased risk for pneumonia, particularly in older patients with COPD⁶⁵. All patients with COPD should be immunized against pneumococcus.

COR PULMONALE

Cor pulmonale refers to altered structure or function of the right ventricle resulting from *pulmonary hypertension* (PH) associated with chronic lung disease (see Chapter 59). The prevalence of cor pulmonale in COPD is not known with certainty but reported prevalence ranges from 1% to more than 70% depending on the patient population examined and the methodology employed for defining PH.⁶⁶ When PH develops in the setting of COPD, the severity tends to be modest; severe resting PH due to COPD is relatively uncommon (see Fig. 59-3). Signs and symptoms of cor pulmonale include an increase in dyspnea, chest pain, and syncope. Severe cor pulmonale often presents with an increase in lower extremity edema, which should prompt further investigation. Other physical examination findings include right ventricular heave, prominent pulmonic component to the second heart sound, tricuspid regurgitation murmur, and a right-sided S4. Electrocardiographic findings may include right axis deviation, evidence of right ventricular hypertrophy, and right bundle-branch block (see Fig. 59-6), but overall these findings are rather insensitive for diagnosis of PH. Echocardiography can be diagnostically helpful (see

Fig. 59-7 and Videos 59-1AB and 59-2AB), although not infrequently images are limited in patients with parenchymal lung disease and hyperinflation. In addition, the correlation between echocardiogram and right heart catheterization is imperfect; sensitivity tends to be better than specificity, suggesting that normal results on echocardiogram can help exclude significant cor pulmonale. Right heart catheterization remains the “gold standard” for diagnosis (see Fig. 59-9). PH in COPD is associated with worse outcomes, including increased risk for hospitalization⁶⁷ and worse survival.^{68,69} There are few data to support the use of vasodilators for treatment of PH in COPD. Oxygen is the only therapy for PH in COPD and also improves mortality in appropriately selected patients.⁶⁶

SLEEP DISORDERS

As many as 40% of COPD patients report sleep difficulties such as poor sleep quality or difficulties initiating or maintaining sleep.⁷⁰ The combination of COPD and *obstructive sleep apnea* (OSA) is commonly referred to as “overlap syndrome.” The frequency of OSA in the COPD patient population has been estimated to be approximately 16%,⁷¹ which is roughly similar to that of the general population, although the consequences of OSA in patients with COPD are more significant. Compared to patients with OSA alone or with COPD alone, patients with COPD with OSA tend to have more severe nocturnal hypercapnia and hypoxemia as well as increased risk for PH.⁷² OSA in COPD is also associated with poorer quality of life, frequent exacerbations, and increased mortality.^{73,74} Diagnosis of OSA in COPD is important because continuous positive airway pressure therapy for patients with overlap syndrome has been associated with both decreased risk of death and decreased incidence of severe exacerbations.⁷⁴

SYSTEMIC MANIFESTATIONS AND COMORBIDITIES

Cardiovascular Disease

Ischemic cardiovascular disease is a leading cause of death in COPD.⁷⁵ Tobacco use is a shared risk factor that contributes to this association, but epidemiologic data suggest impaired lung function is an independent risk factor for increased cardiovascular mortality even when adjusted for smoking status.⁷⁶ Among those with COPD, FEV₁ also predicts the presence of atherosclerosis⁷⁷ and cardiovascular mortality.^{78,79} Patients with COPD are also at increased risk for hospitalization due to cardiovascular events.⁸⁰ Atherosclerosis is a disease of systemic inflammation,⁸¹ which may help explain the link to COPD. Elevated C-reactive protein levels correlate not only with the presence of COPD but also with the presence of exacerbations, severity of lung function, and risk for hospitalization and death.⁶⁶ Although clinicians need to be aware of the increased risk for the presence of both disorders, no therapeutic strategies have yet been demonstrated to benefit this subgroup of patients specifically. Cardioselective β -blocker medications that are frequently used in patients with cardiovascular disease have traditionally raised safety concerns in patients with COPD. However, while clinicians should be aware that β -blockers

can theoretically worsen bronchospasm, accumulating data from several studies now suggest that β -blocker medication in COPD actually reduces all-cause mortality, suggesting an overall benefit to the use of β -blockers in COPD.⁸²⁻⁸⁴

Osteoporosis

A clear association between osteoporosis and COPD has been established, with studies suggesting a twofold to fivefold increase in prevalence of osteoporosis in patients with COPD compared with age-matched controls.^{85,86} Multiple shared risk factors between COPD and osteoporosis likely influence this association, including oral and inhaled steroid use, smoking, and low body mass index. However these factors do not completely explain the association because lower bone mineral density in patients with COPD has been documented even in the absence of systemic steroids.⁸⁷ Clinicians must be mindful of this association in both their male and female patients with COPD. Pulmonary rehabilitation improves the functional status of patients with COPD and may diminish fracture risk by decreasing the risk of falls.⁸⁸

Diabetes

As with osteoporosis, diabetes is another comorbidity with increased prevalence in COPD. Decreased lung function has been associated with the coexistence of metabolic syndrome as well as the development of insulin resistance and diabetes.⁸⁹⁻⁹¹ The cause for this association is not known with certainty. ICS may be a contributing factor. Some data suggest a dose-dependent association between ICS use and diabetes control or new-onset diabetes,⁹² while a retrospective analysis of 8 COPD trials and 26 asthma trials found no association between ICS use and new onset diabetes or hyperglycemia.⁹³

Gastroesophageal Reflux Disease

The prevalence of gastroesophageal reflux disease in COPD also appears to be increased.^{94,95} More importantly, gastroesophageal reflux disease in the setting of COPD has specific clinical implications. Reflux in COPD is associated with poorer quality of life,⁹⁶ as well as more frequent exacerbations.^{95,97} Reflux may also be more common in COPD patients with chronic bronchitis⁹⁸. A clear cause for the association between gastroesophageal reflux disease and COPD has not been identified. Unfortunately, only limited data suggest that treatment for gastroesophageal reflux disease may reduce the risk of exacerbations.⁹⁹

Depression and Anxiety

Coexistent depression and anxiety are prevalent in COPD,^{100,101} with conservative estimates suggesting anxiety and depression may be present in at least 10% of the general COPD population. Significantly higher estimates have been reported for patients with severe COPD.¹⁰² Risk factors for depression in COPD also include limited mobility, need for supplemental oxygen therapy, comorbid conditions, and female gender.^{103,104} Patients with COPD and comorbid depression and anxiety experience poorer clinical outcomes. Patients with anxiety are at increased risk for COPD exacerbations and higher mortality.¹⁰⁵ Depressive symptoms are also associated with increased risk of

death.^{106,107} Specific therapies for anxiety and depression have not been demonstrated to improve COPD outcomes, although pulmonary rehabilitation has been shown to improve not only anxiety and depression but also other outcomes in patients with COPD, including quality of life and functional capacity.¹⁰⁸

DIFFERENTIAL DIAGNOSIS

Several disorders may mimic aspects of COPD, and certainly many conditions may be associated with dyspnea. However, there are a handful of disorders that are particularly challenging because they may be associated with cough, sputum production, airflow obstruction, or emphysema-like radiographic changes. Careful clinical assessment can help differentiate these disorders from COPD although, in some instances, these disorders may be present in addition to COPD.

CHRONIC OBSTRUCTIVE ASTHMA

Chronic asthma may be associated with the development of persistent airflow obstruction that is not completely reversible (i.e., due to “remodeling”). Hence, a clear distinction from COPD may not be possible; chronic asthma may also coexist with COPD. However, several clinical features tend to be more likely associated with each of the two disorders. In general, the age of onset for asthma tends to be earlier. Asthmatic patients may have a history of atopy and a family history of asthma. Airflow obstruction abnormalities are usually less severe with asthma, with greater prevalence of reversibility. Sputum production is less common in asthma. These patients also tend to have less of a smoking history and greater steroid responsiveness than patients with COPD. Chronic asthma is also not associated with emphysema; the DL_{CO} is normal or increased in chronic asthma, whereas it is decreased in emphysema.

CHRONIC BRONCHITIS WITHOUT AIRFLOW OBSTRUCTION

Chronic cough and sputum production may be present in the absence of airflow obstruction. The accepted definition for chronic bronchitis is a productive cough for 3 months for 2 successive years.¹⁰⁹ Diagnostically, this is often mistaken for COPD because chronic bronchitis even in the absence of airflow obstruction is often associated with smoking. Chronic exposure to poor air quality or industrial dusts/fumes also increase risk for this disorder. While no specific therapies have been developed for chronic bronchitis without airflow obstruction, the morbidity and mortality associated with this disorder should not be ignored. Such patients still experience poorer quality of life and increased risk of death as opposed to healthy controls.¹¹⁰⁻¹¹²

BRONCHIECTASIS

Bronchiectasis is characterized by dyspnea and in particular copious mucopurulent sputum that tends to be greater than in typical COPD. Diagnosis can be established with the aid of high-resolution CT wherein bronchial wall thicken-

ing and luminal dilation is seen. It is not uncommon to see concurrent mild bronchiectasis in both COPD and asthma. Bronchiectasis in COPD is associated with increased mortality.¹⁶ Moderate to severe bronchiectasis should raise a clinician's concern for immunodeficiency, cystic fibrosis, rheumatic disorders, ciliary motility disorders, α_1 -antitrypsin deficiency, allergic bronchopulmonary aspergillosis, and mycobacterial infection.

BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans (BO) is also known as constrictive bronchiolitis. This disorder is characterized by submucosal fibrosis resulting in narrowing of the bronchiolar lumen. BO is a known complication of lung, heart, and bone marrow transplants but also may be seen in association with connective tissue diseases and inflammatory bowel disease. Inhalation of dusts or toxins, infection, and drug reactions are less frequent causes of BO. In some cases, no clear etiology is identified. As opposed to those with COPD, patients with BO may have no significant smoking history and typically do not have significant emphysema on CT, which may show only hyperinflation and air trapping. Mosaic attenuation indicative of localized air trapping is common. Bronchial wall thickening may also be present. Pulmonary function testing demonstrates severe, progressive, and irreversible airflow obstruction but is not typically associated with severe DL_{CO} impairment. Unfortunately, BO responds poorly to therapy (see Chapter 50).

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis is a rare form of bronchiolitis involving the upper and lower respiratory tracts that is seen primarily in Japan and only rarely outside the Far East. Genetic factors, specific human leukocyte antigen (HLA) haplotypes, are thought to contribute to the pathogenesis and geographic distribution of this disease. Such patients typically present with chronic sinusitis, cough productive of copious sputum, dyspnea, wheezing, and weight loss. Airflow obstruction is a common feature, and HRCT may show diffusely thickened and dilated bronchi or tree-in-bud opacities corresponding to bronchiolitis. Confirming this diagnosis is important, because diffuse panbronchiolitis often improves with macrolide antibiotics.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis is a rare disorder affecting women almost exclusively.¹¹³ It is caused by a mutation in the tuberous sclerosis-1 or -2 gene, either sporadically or in the setting of tuberous sclerosis, resulting in the proliferation of interstitial smooth muscle cells and pulmonary cyst formation. Other clinical characteristics include renal angiomyolipomas and chylous effusions. Lymphangioleiomyomatosis is also characterized by airflow obstruction and spontaneous pneumothoraces. Therefore it is not infrequently mistaken for emphysema. However, an expert radiologist should be able to distinguish pulmonary cystic changes from emphysematous holes. The presence of other characteristic clinical features can be helpful in the diagnosis.

EPIDEMIOLOGY

COPD is currently the third leading cause of death in the United States¹¹⁴ and is projected to be the third leading cause of death worldwide by 2020.¹¹⁵ To give some sense of its impact, in 2006, COPD killed more American women than breast cancer and diabetes combined.¹¹⁶ COPD is also associated with significant morbidity. In the United States in 2006, COPD was responsible for an estimated 672,000 hospitalizations. The cost for caring for patients with COPD continues to increase, with an estimated \$49.9 billion spent in 2010.¹¹⁷ A significant proportion of these costs are attributable to acute exacerbations.¹¹⁸ COPD patients also have significant comorbidities that likely contribute to their increased cost of care. (For a more detailed discussion of COPD epidemiology, see Chapter 43.)

ENVIRONMENTAL INFLUENCES

The primary risk factor for the development of COPD is tobacco smoke exposure. Data suggest the prevalence of COPD in smokers is approximately 20% compared with 4% in nonsmokers.¹¹⁹ While not all smokers develop COPD, smokers still lose lung function in a dose-dependent manner.¹²⁰ Furthermore, smoking is associated with reduced life expectancy. The life expectancy for nonsmokers with COPD is modestly reduced; for current and former smokers with COPD, life expectancy is significantly reduced.¹²¹ Data from smoking cessation studies provide additional support for the association between smoking and COPD. The rate of FEV₁ decline is greatest in patients who smoke the most and is lowest in those who quit smoking.¹²² “Second hand smoke” or “environmental tobacco smoke” exposure has also been associated with increased risk for COPD.¹²³

Data from the Third National Health and Nutrition Epidemiological Survey put the prevalence of COPD in nonsmokers in the United States at approximately 6.6%,¹²⁴ although worldwide estimates for non-tobacco-related COPD range from 20% to 50% of all COPD cases depending on locale.¹²⁵ Factors such as traffic, outdoor pollution, and biomass smoke contribute to these findings.^{126,127} Smoke generated from biomass fuels is an important etiology of COPD, particularly in women in developing countries where biomass fuels are used for cooking.¹²⁸ In total it has been estimated that the attributable fraction of COPD due to cigarette smoking is approximately 80% to 90%,¹²⁹ while occupational exposures including gas, dust, and fumes contribute to the population burden of COPD by approximately 15%.¹²⁹

HOST FACTORS

Genetics

COPD results from an interaction between environmental exposures, most notably tobacco smoke, and increased genetic susceptibility. Family history of COPD also appears to be a risk factor for COPD development, independent of family smoking history, personal smoking history, or childhood environmental tobacco exposure.¹³⁰ The strongest genetic risk factor that has been identified is mutation in the

A1AT protease, resulting in a deficiency in the resultant protein (discussed previously). Unfortunately, the combination of A1AT deficiency and smoking leads to a marked acceleration in loss of lung function compared with the presence of either alone.¹³¹ The discovery of A1AT deficiency more than 40 years ago raised hopes that other COPD susceptibility genes would be identified rapidly. However, it is only recently that data from genome-wide association studies have led to consistent associations between new genetic loci and COPD susceptibility. Data from genome-wide association studies provide good evidence that the cholinergic nicotinic acetylcholine receptor *CHRNA3/5*, *HHIP*, and *FAM13A* loci all appear to be associated with disease susceptibility.¹³² In particular, the *CHRNA3/5* locus appears to be associated with increased smoking intensity and emphysema in individuals with COPD. The *HHIP* locus has been associated with the systemic components of COPD, frequency of COPD exacerbations, and FEV₁/FVC ratio.^{133,134} The *FAM13A* locus has also been associated with FEV₁/FVC.¹³³ Efforts to identify other genetic loci are ongoing in multiple cohorts. (For more discussion of the genetics of COPD, see Chapter 45.)

Other Modifying Factors

Gender is an important clinical feature that also may influence multiple aspects of COPD, including susceptibility. Conflicting data have been published regarding whether women are more susceptible to developing COPD adjusted for smoking exposure.¹²⁸ However, the most recent epidemiologic data suggest the prevalence of COPD worldwide by gender is becoming increasingly similar and likely reflective of cigarette and other environmental exposures.¹³⁵ Gender may modify other aspects of the disease, however. In general, women report more dyspnea, similar severity of cough, but less sputum than men.¹³⁶ Recent data also suggest that COPD exacerbations are more frequent in women, but whether this represents a difference in disease biology or reporting patterns is unknown.^{137,138} Maternal smoking and female gender have also been associated with severe, early-onset COPD.¹³⁹

Several other factors have been identified that modify COPD prevalence and presentation. Lower socioeconomic status significantly increases morbidity and mortality of COPD.¹⁴⁰ The reasons for this are not understood with certainty but may be connected to differences in access to care. Less data are available on the influences of race although, within the United States, there appears to be increasing prevalence of COPD among African Americans as well as a significant increase in mortality.¹⁴¹ African Americans may also be more susceptible to the harm from tobacco smoke than whites.¹⁴² Exacerbations during hospitalization may also be more frequent in African Americans.¹⁴³ Cultural, socioeconomic, and biologic influences could all contribute to these findings.

TREATMENT

Until recently, treatment of COPD was focused entirely on relief of symptoms, because treatment options were few and were believed to be largely ineffective. In fact, the literature reported that the only interventions that changed the

natural history of COPD were smoking cessation,^{122,144} and oxygen in patients with hypoxemia.^{145,146} More recently, however, clinical trials have demonstrated that pharmacologic treatments can prevent or attenuate acute exacerbations of COPD, and the data suggest that some can slow the inexorable loss of lung function over time that is the hallmark of COPD.¹⁴⁷⁻¹⁴⁹ These observations have appropriately shifted the focus to a more proactive approach, aiming to identify patients earlier in the course of their disease and to implement treatment regimens that would not only relieve symptoms but also prevent exacerbations, prevent disease progression, improve exercise tolerance, and improve quality of life.

GENERAL PRINCIPLES OF TREATMENT

Goals of treatment of COPD are to *reduce symptoms*, which includes relief of dyspnea, improved exercise tolerance, and improved health status, to *reduce risk* by preventing and treating exacerbations, preventing disease progression, and reducing mortality, and, at the same time, to *minimize the adverse effects* of medications.

Reduction of Risk Factors

In the case of COPD, risk reduction refers to interventions that may decrease the likelihood of developing the disease, slow disease progression, decrease exacerbations, and reduce mortality. Although our knowledge of the factors that contribute to each of these is limited, there are substantial data on some factors that contribute to each of these.

Smoking Cessation. Throughout the developed world, cigarette smoking is the most important risk factor for the development of COPD. Public health and educational programs aimed at discouraging people from smoking (“primary prevention”) and efforts to help active smokers stop are probably the most important intervention for COPD. In their landmark publication in 1977,¹⁴⁴ Fletcher and Peto showed that, in patients with COPD who stopped smoking, the accelerated loss of lung function slowed until it more closely paralleled the annual decrement seen in nonsmokers (Fig 44-7) (see Chapter 43). Nearly 2 decades later, the National Institutes of Health–sponsored Lung Health Study demonstrated that in smokers with COPD, smoking cessation reduced the rate of decline in lung function, whereas inhaled bronchodilator did not.¹²² In a 14.5-year follow-up to the Lung Health Study, Anthonisen and colleagues reported that the lung-function benefit continued for persistent quitters; there was also a mortality (all cause) benefit for those who maintained abstinence. Perhaps more important, even those whose smoking cessation was intermittent experienced a benefit compared with continued smokers.^{150,151} Smoking cessation education and support should be offered to every patient with COPD, at every visit. (For more detail on smoking cessation, see Chapter 46.)

Biomass Fuel. In the developing world, cigarette smoke is less of an issue than is exposure to biomass fuel, used for cooking and heating. The exposure is particularly great for women and their young children, who may spend the

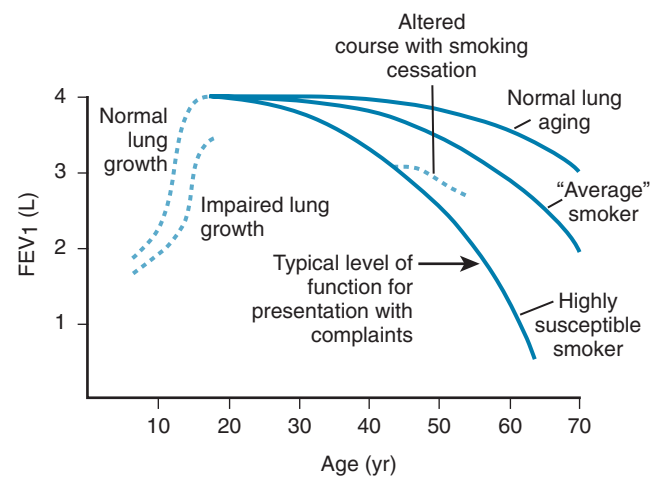


Figure 44-7 Fletcher Peto curve of the natural history of COPD. Lung function increases with growth in childhood and adolescence. Fetal and childhood events can affect lung growth and development, resulting in reduced maximally attained lung function, for convenience shown here as an FEV₁ of 4 L. Actual predicted values depend on height and gender. After growth is completed, lung function remains constant for some time, the “plateau phase,” after which lung function declines at an accelerating rate with age. Smoking reduces the duration of the plateau phase and accelerates the rate of lung function loss. Smoking cessation early in the course of the disease can reduce the rate of lung function loss to that of a non-smoker. Patients typically present with symptoms when lung function declines below 50% of that in young adulthood but may have limitation much earlier. (See text for details.)

greater part of each day indoors with an unvented fire, fueled by wood, dung, or kerosene. Such exposure has been associated with chronic bronchitis and COPD.¹⁵²⁻¹⁵⁵ Guarnieri and colleagues showed that something as simple as a vented stove can decrease gene expression for markers of inflammation in sputum.¹⁵⁶ (For more information, see Chapter 74.)

Environmental Controls. In addition to active and secondary smoke exposure, allergens and air pollutants may have an impact on COPD. Catastrophic air pollution events in the Meuse Valley, Donora, and London speak to the potential for air quality to impact people with lung disease. In addition, a growing body of evidence suggests that long-term exposure to even low levels of air pollution increase the risk for COPD.¹⁵⁷ Also, people with COPD who also have allergic disease have higher levels of respiratory symptoms and are at higher risk for COPD exacerbations.¹⁵⁸ As a consequence, people with COPD should avoid noxious exposures, heed air quality warnings, and be cautious of ongoing occupational exposures.

Prevention of Respiratory Infections. A significant proportion of COPD exacerbations are triggered by respiratory infections. Although there are some data to suggest that patients with COPD are more susceptible to respiratory infections because of impaired mucociliary clearance, a more important issue is that those with COPD are more susceptible to the *consequences* of respiratory tract infections. As a general rule, every patient with COPD should be immunized annually against influenza, which is effective at reducing the incidence of influenza regardless of the severity of COPD,¹⁵⁹ and has been demonstrated to reduce mortality in older adults.^{160,161} In addition all should be

vaccinated against *S. pneumoniae*. Despite a belief that older patients with COPD might not respond well to immunization, pneumococcal vaccines have been shown to work in this population.^{162,163} Chronic antibiotics for prophylaxis are not a part of standard care for COPD because early trials showed they were not useful.¹⁶⁴⁻¹⁶⁷ However, more recent trials with erythromycin and moxifloxacin have demonstrated a reduction in exacerbations.^{168,169} There has been a particular interest in macrolide antibiotics, because of their demonstrated value in diffuse panbronchiolitis and in cystic fibrosis, and because they may have anti-inflammatory as well as antimicrobial properties. In a prospective, randomized, double-blind trial of 1142 patients with exacerbation-prone COPD, the National Heart, Lung, and Blood Institute's COPD Clinical Research Network found that daily azithromycin for 1 year decreased the frequency of exacerbations by 27% and improved quality of life.¹⁷⁰ Enthusiasm for this approach has been tempered by the small risk of ototoxicity and by the potential for QTc prolongation by macrolides. Data suggest that screening subjects for history of cardiac disease and obtaining ECGs prior to starting macrolides reduces the risk of cardiac rhythm disturbance.¹⁷¹ Thus, in selected patients who neither have cardiac disease nor take concomitant medications that affect the QTc interval and who experience frequent exacerbations with the attendant morbidity and mortality, the small risk of azithromycin is probably warranted.

Prevention of Exacerbations. Exacerbations of COPD are sentinel events and are closely associated with disease progression. Increasing severity of COPD is associated with increased exacerbations and need for hospitalization, but for every stage of severity, severe exacerbations are associated with increases in short-term and long-term all-cause mortality.¹⁷² Exacerbations have an independent negative effect on prognosis, and mortality increases with the frequency of hospitalizations. In one study of 305 men with COPD, only 20% to 30% of patients who were readmitted for exacerbations survived 5 years.¹⁷³ Although supporting data are lacking, the hope is that, by preventing exacerbations, lung function may be preserved and deterioration prevented. ICS, long-acting β -agonists, long-acting muscarinic antagonists, and macrolide antibiotics have all been shown to reduce exacerbations. Unfortunately, even patients taking these medications may still experience as many as 1.4 exacerbations per year.¹⁷⁴

PHARMACOTHERAPY

The goal of treatment was once primarily symptom relief. Now that goal includes an attempt to improve lung function or slow the loss of lung function, and to prevent exacerbations. Most medications for COPD are administered by inhalation. Standard therapy consists of inhaled bronchodilators, either β -agonists or antimuscarinics (anticholinergics), and ICS. Oral agents, used less commonly, include methylxanthines (e.g., theophylline), phosphodiesterase-4 inhibitors (e.g., roflumilast), and corticosteroids (prednisone or prednisolone).

The choice of medications should be based on an assessment of the severity of airflow obstruction, symptoms, fre-

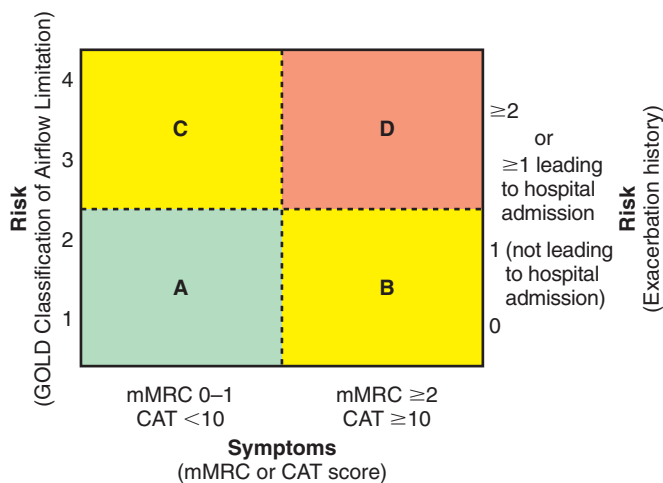


Figure 44-8 GOLD classification system.³⁴ When assessing risk, choose the highest risk according to airflow limitation or exacerbation history. (One or more hospitalizations for COPD exacerbations should be considered high risk.) (Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: <http://www.goldcopd.org/>.)

quency and severity of exacerbations, and patient's functional limitation, as well as on the availability and local cost of medications. Formerly, medication decisions were based primarily on severity of airflow obstruction; guidelines now, as exemplified by GOLD,¹⁷⁵ emphasize a metric that includes obstruction (GOLD grade), based on FEV₁ percent predicted (see Table 44-2), symptoms (based on either the Medical Research Council dyspnea scale¹⁷⁶ or the COPD Assessment Test¹⁹), and risk of exacerbations. Using this tool, patients can be categorized into class A, B, C, or D (Fig. 44-8), and GOLD provides specific treatment recommendations for each category (Table 44-3).

Bronchodilators

Bronchodilators are recommended for all patients with COPD. Pharmaceutical classes of bronchodilators include β -agonists, antimuscarinics (anticholinergics), and methylxanthines. Unlike asthma, where bronchodilator reversibility is part of the definition, airflow obstruction in COPD is often thought of as "irreversible." This is not, however, completely true. Although the diagnosis of COPD requires airflow obstruction that persists after bronchodilators, most patients with COPD demonstrate some improvement in spirometry. This response can vary from day to day.¹⁷⁷ In one study of 1552 patients with COPD who were tested with albuterol, ipratropium, or the combination on four occasions over 3 months, only 37% to 56% had 15% or better improvement in FEV₁ on all four test dates, but 90% or more had greater than or equal to 15% reversal on at least one occasion.¹⁷⁸ Therefore, even patients who do not respond to bronchodilator testing in the pulmonary function laboratory should be given a clinical trial of bronchodilators. Although the increase in FEV₁ may be modest, it may be sufficient to improve lung emptying and, by this mechanism, reduce dynamic hyperinflation.¹⁷⁹⁻¹⁸¹ In multiple studies, bronchodilators have been shown to reduce dyspnea and increase exercise tolerance in patients with chronic stable COPD.^{182,183}

Table 44-3 Pharmacologic Management of COPD*

Patient Group	Recommended First choice	Alternative Choice	Other Possible Treatments†
A	SAMA prn or SABA prn	LAMA or LABA or SABA and SAMA	Theophylline
B	LAMA or LABA	LAMA and LABA	SABA and/or SAMA Theophylline
C	ICS + LABA or LABA	LAMA and LABA or LABA and PDE4-inh. or LABA and PDE4-inh.	SABA and/or SAMA Theophylline
D	ICS + LABA and/or LABA	ICS and LABA and LABA or ICS and LABA and PDE4-inh. or LABA and LABA or LABA and PDE4-inh.	Carbocysteine SABA and/or SAMA Theophylline

*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.

†Medications in this column can be used alone or in combination with other options in the Recommended First Choice and Alternative Choice columns.

Abbreviations are defined in the text.

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: <http://www.goldcopd.org/>.

β-Adrenergic Agonists

These medications bind directly to β-receptors located on airway smooth muscle and dilate the airway. Less prominent effects include increased ciliary beat frequency that promotes mucus transport along the mucociliary escalator¹⁸⁴ and improved respiratory muscle endurance.¹⁸⁵ β-agonists are available in both short-acting and long-acting preparations, and can be administered by inhalation, orally, subcutaneously, or intravenously. For treatment of COPD, β-agonists should only be given as inhaled aerosols, because the other routes are associated with an unacceptably high risk of systemic adverse effects.

Short-acting beta agonists (SABAs) include albuterol (salbutamol), levalbuterol, terbutaline, and fenoterol. Albuterol is a racemic mixture of both (R)- and (S)-enantiomers of albuterol; levalbuterol is the (R)-enantiomer alone. The (R)-enantiomer is thought to be responsible for bronchodilation while the (S)-enantiomer is believed to cause tremor, tachycardia, and perhaps airway inflammation. Thus, levalbuterol would be expected to be better tolerated than albuterol. In fact, for most patients with stable COPD who use their short-acting β-agonist for symptom management, the added advantage of levalbuterol over albuterol¹⁸⁶ is probably not significant.¹⁸⁷ Albuterol is also available in combination with ipratropium (a muscarinic antagonist). Terbutaline inhalers are no longer sold in the United States; fenoterol is available in many parts of the world, but not in the United States.

Short-acting β-agonists for inhalation are available in solution for administration by nebulizer, as well as by metered-dose inhaler and *dry powder inhaler* (DPI). The

combination of albuterol and ipratropium is available in a soft mist inhaler. Many studies have shown that metered-dose inhalers, DPIs, and soft mist inhalers are as effective as nebulizers in patients who are able to use the devices properly. Unfortunately, the proper technique for using different devices is not the same, and patients need detailed instruction and periodic assessment of their technique. In addition, DPIs require a much higher inspiratory flow than do metered-dose inhalers and some patients with moderate-to-severe COPD may not be able to generate adequate flows. For these individuals and for those whose medical or mental status makes coordinated breathing efforts difficult, nebulized β-agonists may be preferable.¹⁸⁸

The major advantage of short-acting β-agonists is their rapid onset of action, within 5 to 15 minutes after inhalation. Their effects last for 2 to 6 hours. As noted earlier, most patients with COPD demonstrate a modest improvement in FEV₁, and many studies and meta-analyses support their use for COPD.¹⁸⁹ The combination of albuterol and ipratropium results in greater and more sustained improvement in lung function than either drug alone.¹⁹⁰⁻¹⁹² When used at the recommended doses, inhaled short-acting β-agonists are thought to be safe. The major adverse effects include tremor, anxiety, tachycardia, and hypokalemia. A recent retrospective case-control cohort study of more than 70,000 patients with COPD from Quebec suggested that the new use of short- or long-acting beta agonists was associated with increased risk for arrhythmias,¹⁹³ but the study did not account for multiple potential confounders. Adverse effects are dose-dependent and are less common with inhaled compared with systemic dosing, and when inhaler technique is optimized. Fortunately, tachyphylaxis to the systemic side effects of β-agonists is greater than tachyphylaxis to the bronchodilator effect.

Long-acting β-agonists (LABAs) typically produce bronchodilation that lasts for 12 hours or more. Salmeterol was the first LABA to be studied extensively. Its onset of action is much slower than that of albuterol, on the order of 20 to 30 minutes. Formoterol has a similar duration of action, but an onset of action that is nearly identical to albuterol. Both salmeterol and formoterol must be taken twice daily. Arformoterol is the (R)-enantiomer of formoterol. Indacaterol has a rapid onset and a duration of action of nearly 24 hours, and thus requires only once daily dosing. The bronchodilator effect of indacaterol is greater than that of salmeterol or formoterol. Vilanterol is another LABA with a rapid onset of action and a duration of action of approximately 24 hours. It is not used as monotherapy, but has recently been approved in the United States and in Europe for use in combination with the ICS fluticasone.

Many studies have demonstrated a benefit of LABAs in patients with stable COPD.^{65,194-201} Salmeterol and formoterol significantly improve lung function, dyspnea, quality of life, and the rate of exacerbations.^{65,202-206} Salmeterol has been shown to reduce hospitalizations.⁶⁵ Indacaterol improves dyspnea and health status, and reduces exacerbations.²⁰⁷⁻²¹⁰ The adverse effects reported with LABAs are similar to those described for short-acting β-agonists. Of note, the association of LABA use with deaths that raised concern in the asthma community (see Chapter 42) has not been seen for COPD, and monotherapy with an LABA appears to be both safe and efficacious.

LABAs are frequently combined with an ICS in the same inhaler, and currently available preparations include salmeterol/fluticasone, formoterol/budesonide, formoterol/mometasone, and vilanterol/fluticasone. Many studies have shown that combination therapy is often more effective than either agent alone, and various guidelines provide recommendations for how and when to escalate treatment beyond short-acting bronchodilators.

Antimuscarinics

Antimuscarinics, also known as anticholinergics or muscarinic antagonists, block the effects of acetylcholine on M3 muscarinic receptors on airway smooth muscle. Anticholinergics were used historically, long before β -agonists, in the form of stramonium and belladonna alkaloids,^{211,212} then atropine. The newer quaternary amines such as ipratropium and glycopyrrolate, as well as tiotropium and aclidinium, are better tolerated because they do not cross the blood-brain barrier. In addition, both tiotropium and aclidinium have pharmacokinetic selectivity for the M3 receptor and dissociate more rapidly from M2 receptors, which are found on cholinergic nerve terminals and inhibit acetylcholine release.²¹³ Thus, the relative lack of M2 binding by these muscarinic antagonists may allow acetylcholine to bind to M2 receptors, thereby inhibiting further acetylcholine release and reducing bronchoconstriction.²¹⁴

Short-acting muscarinic antagonists (SAMAs) include ipratropium and oxitropium. They increase FEV₁ with an onset of action of 10 to 15 minutes and a duration of action of 4 to 6 hours. Ipratropium improves lung function, increases exercise capacity, decreases dyspnea, and decreases cough.²¹⁵ The magnitude of bronchodilation with ipratropium is comparable to that seen with albuterol but, when used in combination, their effects are additive and the duration is longer.¹⁹⁰⁻¹⁹²

Long-acting muscarinic antagonists (LAMAs) include tiotropium and aclidinium, which are slower in onset than ipratropium, but last longer, with bronchodilation lasting at least 12 hours after aclidinium²¹⁶ and more than 24 hours after tiotropium.²¹⁷⁻²¹⁹ In the United States, tiotropium is available as the HandiHaler DPI; in Europe, it is available as a soft-mist inhaler (RespiMat). Aclidinium is provided in a DPI that registers when a dose is inhaled. Tiotropium decreases symptoms, improves health status, and reduces exacerbations by 20% to 25%^{220,221} and hospitalizations.²¹⁸ It appears to improve the effectiveness of pulmonary rehabilitation, perhaps by decreasing dynamic hyperinflation.²²² When compared head-to-head with salmeterol, tiotropium increased time to first exacerbation and reduced the annual rate of exacerbations more than did salmeterol.²²³ Although less data are available for aclidinium, its effects on lung function and on dyspnea appears to be similar to those of tiotropium.²¹⁶

In general, both short- and long-acting muscarinic antagonists have good safety profiles. The most common side effects are dry mouth and urinary retention. Medication that contacts the eye, either by hand contact or by aerosolization, can cause blurred vision and can precipitate glaucoma. A retrospective database review²²⁴ and a meta-analysis of ipratropium and tiotropium in COPD²²⁵ suggested that anticholinergic therapy was associated with an

increased risk of cardiovascular death, myocardial infarction, and stroke. However, a prospective study of almost 6000 patients with COPD who were treated with tiotropium or placebo found no increased risk of cardiovascular events or mortality,^{226,227} and a long-term study of more than 17,000 patients with COPD, designed specifically to examine safety, concluded that tiotropium administered by the new soft-mist Respimat device had a safety profile similar to tiotropium delivered by the current DPI HandiHaler device in patients with COPD and was not associated with an increased risk of death.²²⁸

Methylxanthines

Methylxanthines are nonselective inhibitors of phosphodiesterase, and by this mechanism have a modest bronchodilator effect.^{205,229,230} Theophylline is the most commonly used methylxanthine and, in stable COPD, its effect is greater than that of placebo but less than that of LABAs or LAMAs. In addition to its bronchodilator effect, theophylline is reported to improve inspiratory muscle function²³¹⁻²³³ and to have anti-inflammatory effects.²³⁴ Its effect on reducing symptoms is greater than its effect on airway function, suggesting that these alternative mechanisms may be important. Because theophylline is a nonselective phosphodiesterase inhibitor, its actions are not all beneficial. The major adverse effects are insomnia, nausea, vomiting, cardiac arrhythmias, and seizures. These toxicities are dose-dependent, but the onset of severe adverse events (e.g., ventricular arrhythmias, seizures) may not be preceded by nausea or insomnia. In addition, blood levels are affected by age, by liver disease, by congestive heart failure, and by many drug interactions. To minimize toxicity, current guidelines recommend target blood levels of 5 to 10 $\mu\text{g/mL}$ rather than 15 to 20 $\mu\text{g/mL}$ as was done previously. Because of its narrow therapeutic index and modest benefits, theophylline is not recommended as a first line drug, but can serve as an alternative for patients intolerant of LABAs and LAMAs or in settings where these drugs are too expensive.

Phosphodiesterase-4 Inhibitors

Phosphodiesterase-4 (PDE-4) inhibitors act by blocking the breakdown of cyclic adenosine monophosphate. By this mechanism, they decrease airway inflammation; they have no direct bronchodilator activity. Roflumilast is an oral PDE-4 inhibitor that has been approved for patients with chronic bronchitis and a history of exacerbations.¹⁴ In a meta-analysis of 23 randomized trials of two different PDE-4 inhibitors (roflumilast and cilomilast), the PDE-4 inhibitors reduced exacerbations (OR 0.78, 95% CI 0.72 to 0.85) and produced a modest increase in FEV₁ (50 mL, 95% CI 39 to 52).²³⁵ When roflumilast was added to salmeterol or tiotropium, the prebronchodilator FEV₁ increased.^{14,15} Because its effect on exacerbations is much greater than its effect on airway function, guidelines recommend that roflumilast be used in combination with a long-acting bronchodilator.¹⁷⁵ Use of PDE-4 inhibitors has been limited by side effects. The most common are nausea, anorexia, abdominal pain, diarrhea, weight loss, sleep disturbances, and headache.^{14,15,236} Monitoring weight during treatment is warranted.¹⁷⁵

Corticosteroids

Inhaled Corticosteroids. Airway as well as systemic inflammation are critical components of the pathogenesis of COPD.²³⁷⁻²³⁹ Therefore, corticosteroids, with their anti-inflammatory effects, are an appealing intervention. ICS offer the additional advantage of minimizing systemic exposure. Early studies of ICS sought unsuccessfully to alter the natural history of COPD. However, ICS have been shown to improve symptoms, lung function, and quality of life, and to reduce the frequency of COPD exacerbations, especially in patients with an FEV₁ less than or equal to 60% of predicted. The improvement in FEV₁ achieved with ICS (50 to 100 mL) is typically less than that observed with bronchodilators.^{147,148} The reduction of exacerbations by ICS is more significant and is comparable to that observed with LABAs or LAMAs (approximately 20% to 25%).²⁴⁰⁻²⁴² Guidelines recommend that ICS be used in combination with a long-acting bronchodilator in subjects who are prone to exacerbations, but that they not be used as monotherapy.¹⁷⁵ Four large trials in which patients with COPD were treated with ICS for 3 to 5 years failed to reduce the loss of lung function over time.^{147,148,243,244} However, in a post hoc analysis of the TORCH trial in which 6112 subjects with moderate-to-severe COPD were randomly treated for 3 years with placebo, fluticasone, salmeterol, or the fluticasone/salmeterol combination, Celli and colleagues²⁴⁵ reported that each active treatment arm reduced the rate of decline in FEV₁. Whether this benefit reflects the reduction in exacerbations or a more direct effect on the airway, perhaps by decreasing inflammation, is not known.

ICS are relatively safe, especially in comparison to systemic corticosteroids. The most common adverse effects are oral candidiasis (thrush) and dysphonia, both of which can be minimized by careful inhalation technique followed by rinsing the mouth and gargling.^{147,148} Increased skin bruising is probably a manifestation of capillary fragility. Reduced bone density has been reported after long-term treatment with triamcinolone,²⁴⁶ but studies with budesonide and fluticasone have not found similar results, perhaps because these patients with COPD had a high prevalence of osteoporosis at baseline.^{247,248} Finally, although ICS clearly reduce the frequency of exacerbations in COPD, they have been associated with an increased incidence of pneumonia.⁶⁵

Systemic Corticosteroids. With rare exceptions, the use of systemic corticosteroids should be reserved for the treatment of exacerbations. In patients with stable disease, even when severe, the risk of adverse effects is probably greater than the likelihood of benefit. Chronic use of systemic corticosteroids is associated with increased mortality,^{249,250} which may reflect corticosteroid effects or the underlying severity of the COPD. Occasionally, in exacerbation-prone patients who require frequent courses of high dose systemic corticosteroids, a very low daily dose of corticosteroids may protect against exacerbations and thereby reduce the total annual steroid exposure. If this unusual approach is followed, the lowest possible dose of corticosteroids should be used. Spirometric stability may be useful in encouraging patients who are experiencing nonpulmonary benefit that dose reduction is safe.

Combination Therapy

Patients who remain symptomatic after a period of treatment with a single long-acting bronchodilator (either LABA or LAMA) may benefit from addition of a second drug. Choices include either an ICS or a second long-acting bronchodilator from the other pharmacologic class; literature to inform this decision is not clear. ICS should probably be considered as the first addition in patients with evidence of airway inflammation and those with frequent exacerbations. In two large trials, combination therapy improved outcomes significantly compared to each of the other treatment arms alone (placebo LABA, ICS, LAMA). In the TORCH trial of 6112 patients with moderate-to-severe COPD, the combination of salmeterol/fluticasone improved lung function, health status, and exacerbations more than either agent alone⁶⁵ and was cost effective.²⁵¹ In the INSPIRE trial, 1323 patients with severe COPD were randomly treated with salmeterol/fluticasone or tiotropium for 2 years.²⁵² There was no difference in exacerbations, but mortality was less in the salmeterol/fluticasone group and health status was better. Pneumonia was more frequent in the salmeterol/fluticasone group. Combinations of formoterol/budesonide, formoterol/mometasone, and vilanterol/fluticasone have also been shown to improve some clinical outcomes.

While many studies have compared the ICS/LABA combination to its individual components, fewer studies have compared ICS/LABA to LABA/LAMA. Rabe and colleagues²⁵³ randomized 592 patients with moderate-to-severe COPD to tiotropium/formoterol or fluticasone/salmeterol. After 6 weeks, FEV₁ was larger in the tiotropium/formoterol group and the use of rescue medications did not differ.²⁵³

Finally, guidelines suggest “triple inhaler therapy” for subjects whose symptoms are not controlled by any of the combinations already described.¹⁷⁵ This recommendation is in part empirical, because each of the drugs or combinations have been shown to be effective. However, several retrospective cohort studies have described decreased mortality, and fewer exacerbations and hospitalizations with triple therapy.^{254,255} The only prospective data comes from the UPLIFT trial, in which patients were randomized to receive “usual care” with or without tiotropium. In those patients who were already taking an ICS and a LABA (two thirds of the group), the addition of tiotropium significantly improved lung function, reduced exacerbations, and improved health-related quality of life.²²⁶ Further studies are needed to define the role of triple-therapy.

Stepwise Pharmacologic Management

We have made enormous progress from the time, not long ago, when we had few drugs for COPD in our therapeutic armamentarium. Now there are many pharmaceutical categories that have been shown to improve outcomes in COPD. Often there are many choices within each drug class, and a variety of ways to progress through a therapeutic algorithm. The GOLD guidelines provide a framework for making these decisions.

In the past, recommendations for pharmacologic treatment were based primarily on spirometry, and Table 44-2 shows the GOLD classification scheme based on lung

function. Recognizing that FEV₁ alone is a poor descriptor of disease status, the GOLD committee revised the approach to include symptoms and future risk of exacerbations, in addition to lung function (see Fig. 44-8). Based on these three variables, patients are assigned to groups A, B, C, or D, and recommendations for initial management are provided for each group (see Table 44-3).

Antioxidants and Mucolytics

Increased mucus production by hypertrophied and hyperplastic airway submucosal glands and goblet cells, together with impaired mucociliary clearance and cough are frequent in patients with COPD. Although mucolytics have been evaluated in a number of long-term studies in COPD, the results are mixed and, in those studies demonstrating benefit, the effect is modest.²⁵⁶⁻²⁵⁸ *N-acetylcysteine* (NAC) is a mucolytic and antioxidant that has been tested for its ability to slow the decline in lung function and prevent exacerbations. In the BRONCUS study, 523 patients at 50 centers were randomly assigned to 600 mg NAC or placebo daily. Patients were followed for 3 years. Neither the yearly rate of decline in FEV₁ nor the number of exacerbations per year differed between the NAC and the placebo group. However, subgroup analysis of those subjects who were not treated with an ICS suggested that NAC reduced exacerbations and hyperinflation.²⁵⁹ A Cochrane review of 30 trials that included more than 7000 patients treated with NAC or other mucolytics concluded that there was a small effect on exacerbations, but no effect on quality of life.²⁶⁰ In its 2014 revision, the GOLD panel advised against the widespread use of these agents.¹⁷⁵

LEUKOTRIENE MODIFIERS

Although the 5-lipoxygenase inhibitor zileuton and the cysteinyl leukotriene antagonists montelukast and zafirlukast are sometimes used for COPD, there are no data to support their use and guidelines do not recommend their use.¹⁷⁵

NONPHARMACOLOGIC TREATMENT

Mucus Clearance

In patients with mucus hypersecretion and airflow obstruction, it may be very difficult to mobilize secretions. Maneuvers such as controlled cough²⁶¹ and the huff cough²⁶² can be helpful. In the former, patients take a deep breath, hold their breath for a few seconds, then cough two or three times with their mouth open and without taking another breath. The sequence is then repeated several times. Huff coughing involves one or two forced expirations starting at mid-lung volume and performed with the glottis open. Mucus clearance can also be facilitated by having patients breathe or cough through a device that generates high amplitude oscillations,²⁶³ or with an external percussive device. These maneuvers are considered safe, but data supporting their use is limited.²⁶⁴⁻²⁶⁷

Oxygen

Two landmark studies conducted more than 30 years ago demonstrated the value of long-term oxygen therapy in

patients with COPD and hypoxemia. The National Institute of Health's *Nocturnal Oxygen Therapy Trial* (NOTT) randomized 203 patients with COPD and hypoxemia to receive oxygen either for 12 hours overnight or for 24 hours/day for at least 12 months.¹⁴⁵ Overall mortality in the nocturnal oxygen group was 1.94 times that in the continuous oxygen group ($P = 0.01$). Almost simultaneously, the British Medical Research Council compared the effect of oxygen administered for 15 hours/day with no oxygen (control) in 87 patients with COPD, hypoxemia, carbon dioxide retention, and heart failure. Forty-five percent of the oxygen-treated patients died during the 5-year follow-up period compared with 67% of the control group.¹⁴⁶ In addition to this survival benefit, administration of oxygen for at least 15 hours per day improves quality of life and neuropsychiatric metrics, reduces erythrocytosis, and improves pulmonary hemodynamics in patients with COPD and hypoxemia.^{145,268,269}

Indications for Oxygen. Based on these data, guidelines recommend long-term administration of oxygen (>15 hours/day) to patients with COPD with resting hypoxemia. Criteria include arterial PO₂ less than 55 mm Hg, or arterial SO₂ less than 88% while breathing room air at rest. For those whose resting arterial PO₂ is between 56 and 59 mm Hg, long-term oxygen treatment is indicated if they demonstrate erythrocytosis (hematocrit $\geq 55\%$) or cor pulmonale. Following an exacerbation or another acute respiratory event, patients often have hypoxemia that resolves slowly over 1 to 2 months. For this reason, patients given oxygen as they are recovering should be reevaluated after approximately 1 month to determine if they continue to meet criteria for long-term oxygen treatment.

Oxygen During Exercise. Patients whose arterial PO₂ or SpO₂ are borderline at rest may develop worsening hypoxemia with exercise. This is especially true for patients with emphysema and a low diffusing capacity. Supplementary oxygen improves exercise endurance,^{270,271} and even patients without hypoxemia may improve their exercise capacity with supplementary oxygen.²⁷² However, long-term benefits of oxygen in this patient group are unknown. The National Heart, Lung, and Blood Institute is sponsoring the *Long-term Oxygen Treatment Trial* (LOTT) that will examine mortality, hospitalizations, quality of life, and a variety of other outcomes in 737 patients with COPD and SpO₂ between 89% and 93% at rest, or greater than 94% at rest with a desaturation to less than 90% with exercise.²⁷³

One of the goals of oxygen therapy is to permit patients to remain active. Ambulatory oxygen systems are intended to provide a lightweight, portable source of oxygen that can be carried as the patient pursues activities of daily living. Unfortunately, patients are often provided with "portable" systems that are not really conducive to ambulation. The standard E-cylinder, for example, weighs 22 pounds and must be pulled along on a bulky wheeled cart. Various lightweight oxygen reservoirs do exist, weighing as little as 4 pounds; portable oxygen concentrators are another lightweight option. Health care providers must specify to oxygen vendors which ambulatory system they want for their patients.

Oxygen During Sleep. Just as they do with exercise, patients with COPD may experience a significant drop in arterial oxygen tension during sleep, due to a combination of increases in ventilation-perfusion mismatch and a change in ventilatory pattern.²⁷⁴ In patients who are not hypoxemic at rest, the long-term consequences of these episodes of nocturnal hypoxemia are unknown, as are the benefits of long-term oxygen for these patients. Although many clinicians prescribe nocturnal oxygen for these patients, there is no evidence to support this approach. The LOTT trial will provide information on this clinical subgroup.

Oxygen for Air Travel. When flying at altitudes greater than 12,000 feet, aircraft are pressurized to protect passengers and crew from hypoxemia and other manifestations of altitude sickness (see Chapter 77). The *Federal Aviation Administration* (FAA) mandates that the cabin altitude must not exceed 8000 ft. Although this pressurization is sufficient to prevent most barotrauma and altitude sickness, it does not eliminate the possibility of hypoxemia. Arterial PO_2 will drop and in patients who are hypoxemic at rest at sea level or those who are borderline, the arterial PO_2 may fall to dangerous levels at altitude. Patients whose resting arterial PO_2 at sea level is greater than 70 mm Hg are likely to be safe to fly without supplementary oxygen.^{275,276} When there is uncertainty about a patient's potential oxygen requirement at altitude, an altitude simulation test can be performed, using 16% oxygen to simulate the partial pressure of oxygen at 8000 feet.²⁷⁷

For patients who require in-flight oxygen, arrangements must be made with the airline in advance. In general, patients may not bring their own oxygen supply, and airlines usually charge for the oxygen they provide. Lightweight portable oxygen concentrators have become available in recent years, and these are approved by the FAA for commercial air travel. Some airlines allow passengers to travel with their own concentrators.

Technical Issues for Oxygen Use

Most patients receive oxygen via a nasal cannula. Flow rates should be adjusted to achieve an SpO_2 greater than 90% (arterial $\text{PO}_2 > 60$ mm Hg). In general, patients who use oxygen 24 hours/day should increase the oxygen flow by 1 L/min during sleep and exercise, to prevent falls in arterial PO_2 during these periods. Oxygen conserving devices that improve the efficiency of oxygen delivery increase the time that a given volume of portable oxygen will last, allowing patients greater mobility. These include nasal cannulae with reservoirs that store oxygen during exhalation for delivery during inhalation, as well as breath-activated regulators that deliver an oxygen pulse only during inspiration. For use in the home, electric-powered oxygen concentrators are the most convenient, for they do not require refilling or replacement as is the case with gas cylinders or liquid oxygen. It is important that patients who depend on a concentrator have back up cylinders on hand, in case of a power failure. Ambulatory systems include E-cylinders on wheeled carts, lightweight aluminum cylinders, liquid oxygen reservoirs, and portable concentrators. Many of these ambulatory systems weigh less than 10 pounds and provide oxygen for 4 to 6 hours at a flow of 2 L/min.

PULMONARY REHABILITATION

Pulmonary rehabilitation is a comprehensive program that combines exercise training, smoking cessation, nutrition counseling, and education, in an attempt to improve the functional capacity and quality of life of patients with COPD. Formal rehabilitation programs have been shown to improve exercise capacity and quality of life, and to decrease dyspnea and health care utilization.²⁷⁸⁻²⁸¹ In addition, a recent Cochrane review suggests that pulmonary rehabilitation decreases mortality.²⁸² Pulmonary rehabilitation should be offered to all patients with COPD who are symptomatic (see Chapter 105).

SURGICAL TREATMENT OF EMPHYSEMA

More than 50 years ago, anecdotal reports of symptomatic improvement in patients with emphysema who underwent resection of concomitant lung cancers or bullae led physiologists to consider *lung volume reduction surgery* (LVRS) to improve the mechanical efficiency of respiratory muscles. Because of hyperinflation, respiratory muscles are forced to operate on the disadvantageous part of the length-tension curve; reducing hyperinflation was predicted to improve force generation by respiratory muscles, to improve lung elastic recoil, and to improve expiratory flow rates. Unfortunately, early procedures were associated with an unacceptably high mortality rate. In 1995, Cooper and colleagues²⁸³ reported on their experience with 20 patients who underwent bilateral LVRS. By using a linear stapling device and strips of bovine pericardium to minimize air leak through the staple holes, they were able to eliminate this major cause of early mortality, and reported very impressive improvements in FEV_1 , arterial PO_2 , 6MWD, dyspnea, and quality of life. This was followed by the *National Emphysema Treatment Trial* (NETT), a precedent-setting collaborative effort of the Centers for Medicare and Medicaid Services, the National Heart, Lung, and Blood Institute, and the Agency for Healthcare Research and Quality. NETT enrolled 1218 patients with severe emphysema and compared LVRS to maximal medical treatment.⁴⁶ In patients with upper lobe predominant emphysema and a low post-rehabilitation exercise capacity, LVRS improved survival and quality of life.²⁸⁴ In those patients with FEV_1 less than or equal to 20% predicted and either homogeneous distribution of emphysema or DL_{CO} less than or equal to 20% predicted, mortality was greater with LVRS compared to medical management.²⁸⁵ These criteria are currently used to select patients for LVRS.

In an attempt to minimize risk, several groups have developed techniques for bronchoscopic lung volume reduction. Using a flexible bronchoscope, one-way endobronchial valves are placed in airways that lead to emphysematous areas of the lung. In the presence of intact interlobular fissures (and thus little collateral ventilation), air leaves and cannot reenter these areas, causing them to collapse. As a result, hyperinflation is less, and more ventilation goes to more normal lung.²⁸⁶ The largest prospective trial to date described modest improvements in lung function, 6MWD, and symptoms, but this was associated with more frequent exacerbations of COPD, more pneumonia, and hemoptysis after implantation.²⁸⁶ The role of endobronchial valves for

emphysema remains to be determined, and studies are ongoing to define the best valve design, the best technique, and the most appropriate patient population.

ACUTE EXACERBATIONS

Definition

Perhaps surprisingly, it has not been easy to define an acute exacerbation of COPD. GOLD¹⁷⁵ states, “An exacerbation of COPD is an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.”²⁸⁷⁻²⁸⁹ This works sufficiently well that it allows for classification of events in various studies and for comparisons across trials.

Triggers

Exacerbations of COPD are precipitated most often by respiratory tract infections. These may be viral or bacterial. Recent data suggest that a key event, even in individuals whose airways are chronically colonized by bacteria, is the acquisition of bacterial strains that are new to that patient.²⁹⁰ Many patients are sensitive to air pollutants and suffer an exacerbation when ambient levels increase.²⁹¹⁻²⁹³ In perhaps 30% of patients with COPD, no cause for exacerbations can be identified. Interestingly, some patients have an exacerbation whenever one of these events takes place; others rarely do. Those who experience two or more exacerbations per year are often defined as “frequent exacerbators”¹³⁷ and pose a unique challenge for management.

Treatment

The goal of treatment is to minimize the impact of the current exacerbation, to minimize loss of lung function, and to prevent the development of subsequent exacerbations. The vast majority of exacerbations can be managed without hospitalization. Indications for hospitalization include severe dyspnea or respiratory insufficiency, severe underlying COPD, serious comorbidities, frequent exacerbator phenotype, older age, and insufficient support at home. Supplemental oxygen should be administered if necessary, to achieve an SpO₂ greater than 88%. After 30 to 60 minutes, arterial blood gases should be assessed for evidence of carbon dioxide retention.

Bronchodilators. During an acute exacerbation, short-acting β -agonists should be used aggressively, alone or in combination with muscarinic antagonists. Although metered dose inhalers, when used correctly, can be as effective as nebulizers,²⁹⁴ it can be difficult for severely dyspneic patients to coordinate their efforts to use a metered-dose inhaler, or to generate sufficient inspiratory flow required for some devices.

Corticosteroids. Substantial data support the use of systemic corticosteroids for treatment of exacerbations of COPD. Their use is associated with a more rapid recovery, improvement in lung function and hypoxemia, and a reduced risk of relapse.²⁹⁵⁻²⁹⁸ Guidelines recommend 40 to 60 mg prednisone per day for 2 weeks, but a recent prospec-

tive trial of more than 300 patients found that 5 days of prednisone was not inferior to 14 days of prednisone for preventing reexacerbation within 6 months and was associated with a significantly lower total corticosteroid exposure.²⁹⁹

Antibiotics. The use of antibiotics for exacerbations of COPD is somewhat controversial, largely because of the paucity of data documenting bacterial colonization or infection. Studies have suggested that nearly 50% of acute exacerbations are associated with *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.³⁰⁰ Even when patients are chronically colonized, changes in strain may be associated with exacerbations.²⁹⁰ Sputum cultures are of limited utility because they do not distinguish between colonization and infection, and because of the time required for results. Most guidelines recommend empirical treatment when infection seems likely, based on what are sometimes called the “Anthonisen criteria”: increased dyspnea, sputum volume, and sputum purulence,³⁰¹ with greater weight given to meeting all three criteria. The recommended length of antibiotic treatment is 5 to 10 days.

DEVELOPMENT OF NEW TREATMENTS

Despite advances in recent years, treatment options for COPD are woefully inadequate. Other than smoking cessation and supplementary oxygen in patients who are hypoxemic, there are no treatments that reduce mortality. Several factors have contributed to the lack of progress. COPD is highly heterogeneous: in some patients, emphysema predominates; in others, bronchitis predominates. Still others may have both. COPD is a systemic disease and, as a consequence, comorbid extrapulmonary conditions are common. Because treatment effects are small, very large studies are required to test potential new interventions. For all of these reasons, investigators are beginning to explore individual patient subtypes, looking for subpopulations that might benefit from unique therapeutic regimens, and for intermediate outcomes measures that might increase the efficiency of clinical trials. To this end, the National Heart, Lung, and Blood Institute has funded the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS),³⁰² a prospective observational study of COPD subjects and controls. Complementary studies such as Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)³⁰³ and COPDGene³⁰⁴ will hopefully add to the explosion of knowledge in the next few years, aimed at improving treatment for patients with COPD.

Key Points

- Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease and a leading cause of mortality. COPD is significantly underdiagnosed.
- COPD is characterized by airflow obstruction that is not fully reversible. Spirometry is required for diagnosis.
- Older age and a history of smoking are the two most important risk factors for COPD.

- Emphysema at a young age or in an individual with minimal or no smoking history should suggest α_1 -antitrypsin deficiency.
- Smoking cessation is the only intervention demonstrated to alter the course of lung function decline. Smoking cessation also conveys a long-term mortality benefit.
- Pharmacotherapy is no longer for symptom relief only. Short- and long-acting muscarinic antagonists, long-acting β -agonists, and inhaled corticosteroids have been shown to improve exercise capacity, improve quality of life, and reduce exacerbations.
- Choice of medications is based in part on the availability of medication and the patient's response. The Global Initiative for COPD has proposed a stepwise treatment algorithm, based on a combination of airflow obstruction (spirometry), symptoms, and risk of future exacerbations.
- In patients with hypoxemia, continuous oxygen treatment for at least 15 hours/day improves survival, quality of life, and a number of other measures.
- Patients with arterial PO_2 less than 55 mm Hg or SpO_2 less than 88% while breathing room air at rest, or patients with arterial PO_2 56–59 mm Hg and erythrocytosis or cor pulmonale, should be offered continuous oxygen treatment.
- Pulmonary rehabilitation improves exercise capacity and quality of life, and decreases dyspnea and health care utilization, as well as hospitalizations and mortality. Pulmonary rehabilitation should be offered to any patient in whom shortness of breath develops while walking.
- Lung volume reduction surgery may be beneficial for the small subgroup of patients with upper lobe-predominant emphysema and a low post-rehabilitation exercise capacity.

Complete reference list available at *ExpertConsult*.

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Epigenetics in Asthma and COPD

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GENETICS OF ASTHMA AND COPD: LESSONS LEARNED AFTER 20 YEARS OF EXPERIENCE**INTRODUCTION**

Asthma and *chronic obstructive pulmonary disease* (COPD) are chronic inflammatory airway diseases that result from an interaction between genetic or host susceptibility and different environmental exposures. Both airway diseases are common with an estimated 300 million individuals with asthma and 64 million individuals with COPD worldwide.^{1,2} Genetic variation has major effects on asthma and COPD susceptibility; however, these are not isolated to a single gene, but represent the effects of many different genes that are polymorphic (contain gene variants or polymorphisms) or undergo epigenetic regulation (changes in gene expression without changes in the genetic code, i.e., gene methylation), causing disease risk or severity (Fig. 45-1). Thus, in contrast to *single gene disorders* such as cystic fibrosis, asthma and COPD are caused by the effects of multiple genes with smaller effects and genetically are referred to as *complex genetic disorders*. Recent genetic studies suggest that there may be common genetic variants that influence the susceptibility and severity of both of these “complex”

obstructive airway diseases. Multiple potential environmental exposures interact with risk or severity genes for the development or progression of asthma, while cigarette smoke exposure is the primary environmental factor for the development of COPD.

Information from genetic studies has advanced remarkably since the sequencing of the first genome in 2001 and the completion of the International HapMap project in 2005. Based on initial studies in families, it is clear that susceptibility to asthma and COPD is determined by multiple genetic loci in different genes.³ Since then, high-throughput genotyping techniques using chip technologies for *genome-wide association studies* (GWAS) have facilitated comprehensive assessment of gene variation in a larger number of subjects and, more recently, sequencing of the whole genome or of all of the exomes. In contrast to asthma, which may be recognized as early as infancy, COPD presents at a later age; therefore, family-based studies are not practical or feasible. Thus, candidate gene association and GWAS have been used to investigate the genetic basis of COPD. The exponential growth of the field of asthma and COPD

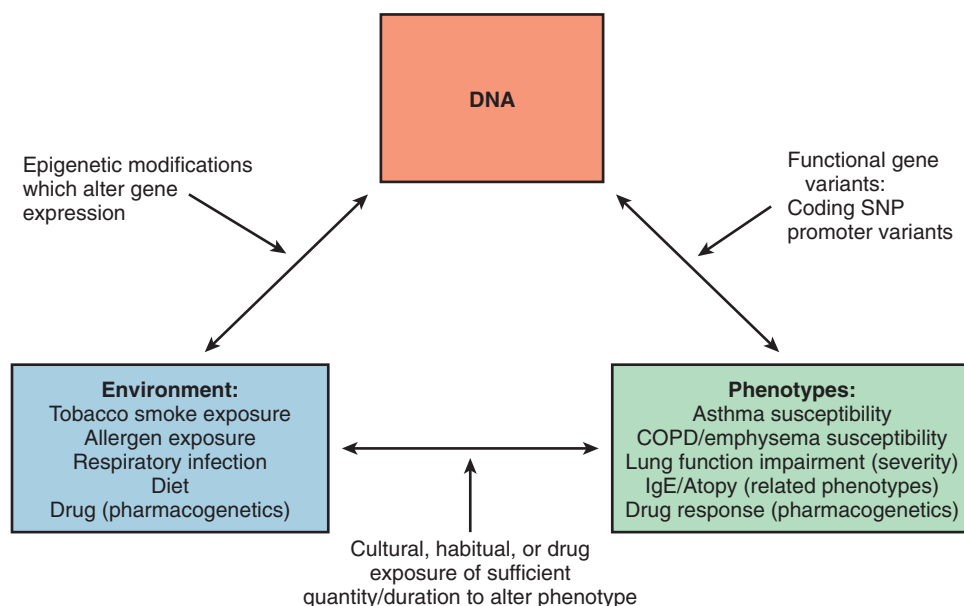


Figure 45-1 Premise of genetic research in complex diseases. Genetic research studies the role of genetic variability in determining risk for complex airway diseases, related phenotypes, and disease severity. Genetic risk can be altered by gene variants that directly impact biologic function or act through gene-by-environment interactions that alter gene function or expression through epigenetic mechanisms. Pharmacogenetics research studies a similar gene-by-environment interaction by analyzing the effect of genotype and exposure to a medication in determining interindividual responses to pharmacologic therapies. IgE, immunoglobulin E; SNP, single nucleotide polymorphism.

genetics in the past decade has dramatically shortened the time from identification of phenotype to discovery of the gene variant in these complex airway diseases.

Different genetic studies have focused on disease susceptibility, disease severity, and therapeutic responses (i.e., pharmacogenetics). These genetic approaches require large, well-characterized populations. Unfortunately, because of the large population samples required for GWAS, the emphasis on comprehensive phenotyping has not been given priority and the results of these resource-intensive genetic studies have not always provided adequate information on subpopulations and disease heterogeneity. Overall, genomic approaches will provide a basis for the development of personalized medical strategies where molecular profiles based on variation in multiple genes or gene pathways will be used to develop a predictive genetic disease or severity score.⁴⁻⁶ Such a score could be used to predict which individuals are at risk for asthma or COPD and would facilitate the development of strategies to prevent disease development or progression.⁷ In those who already have these diseases, genetic profiles would provide a molecular rationale for disease heterogeneity, progression, and the basis for variable responses to therapeutic agents.^{8,9} These genetic profiles should facilitate precise, personalized, and patient-focused therapeutic approaches with the potential to target disease progression, maximize therapeutic efficacy, and minimize unwanted side effects or negative responses.^{7,10,11}

This chapter outlines how human genetic studies in asthma and COPD have identified gene targets, which has substantially improved understanding of the molecular basis of the development, progression, and pharmacogenetics in asthma and COPD. These genetic approaches have the potential to contribute to the development of precision or personalized medicine in obstructive airway disease.⁴ These same genetic approaches have been used in other

complex diseases (e.g., cardiovascular, metabolic, cancer) to identify genetic determinants of disease susceptibility and progression.¹²

EARLY GENETIC STUDIES OF ASTHMA SUSCEPTIBILITY: FAMILY-BASED GENETIC STUDIES

EVIDENCE THAT ASTHMA IS HERITABLE

A genetic basis for asthma was recognized as early as 1860 when Henry Salter reported that asthma was a heritable disease with “distinct traces of inheritance” among related individuals.¹³ Salter’s observation was confirmed in studies demonstrating that asthma prevalence was between 20% and 25% among first-degree relatives of asthma subjects, significantly higher than the approximately 5% prevalence in the general population.^{14,15} The clustering of asthma in families is estimated by comparing the risk for developing asthma in those related to an asthmatic proband with the risk for asthma in the general population as a *lambda ratio* (λ_R). A higher λ_R indicates that the disease has greater heritability and, therefore, a stronger genetic component. For instance, asthma has a λ_R of 2 to 4 while an autosomal recessive disease such as cystic fibrosis has a much higher λ_R . The lower λ_R of a common, complex disease such as asthma is likely caused by multiple gene variants each with small effects interacting with factors not detected in heritability studies, including a diverse group of environmental exposures and disease triggers. The observed heritability for asthma demonstrated in these early studies provided the rationale for the comprehensive genetic studies discussed in this chapter.

THE FIRST GENOME-WIDE SCREENS FOR SUSCEPTIBILITY LOCI: FAMILY-BASED STUDIES

The first genetic studies for asthma susceptibility, which were performed before the first genomes were sequenced, used family-based approaches.^{3,16-26} They used genetic variants that are equally spaced throughout the genome to identify chromosomal susceptibility regions for asthma or associated phenotypes (e.g., bronchial hyperresponsiveness, serum IgE levels, skin test atopy). In family-based genetic studies, linkage analysis is used to identify genetic loci that cosegregate or are coinherited with a trait such as asthma in families. The degree of linkage is measured as an LOD score, the “likelihood of the odds” that a genomic region and trait cosegregate (Table 45-1). An LOD score of 3 or more is considered significant and is equal to a 1000:1 odds that a genomic region is in linkage or coinherited with a specific trait or phenotype. Family-based studies have been successful in identifying genetic diseases with an autosomal dominant or recessive mode of inheritance, but are less powerful for complex or multifactorial diseases wherein

multiple genes interact to determine disease susceptibility or severity. Transmission disequilibrium testing is another family-based association test that compares the transmission of a genetic marker from both parents to their affected offspring with a disease or trait of interest (see Table 45-1 and Fig. 45-2).²⁷

Early family-based genome-wide studies demonstrated that multiple genes are associated with development of asthma and of related phenotypes such as atopy and elevated serum *immunoglobulin E* (IgE). These studies, including those performed by the *National Heart, Lung, and Blood Institute (NHLBI) Collaborative Study on the Genetics of Asthma* (CSGA), provided evidence for linkage with asthma and related phenotypes in multiple different chromosomal regions: chromosome 5q, 6p, 7q, 11q, 12q, 14q, and 16q.^{3,24,26,28-40} The genetic markers identified by these family-based studies represent chromosomal regions that have subsequently been studied to identify specific risk genes responsible for these linkages (eTable 45-1).

These early linkage studies demonstrated gene-gene interactions in asthma susceptibility between chromosomes

Table 45-1 Different Methodologies* for Genetic Studies			
Methodologies	Population	Genome Coverage	Test Measurement
Family, twin, or segregation study	Families	None	Clustering in families to estimate heritability
Linkage study	Families (pedigrees)	Genome-wide	Cosegregation of a marker and phenotype with the likelihood of the odds score
Family-based association test	Small families (trios)	Gene to genome-wide	Transmission of a marker from parents to cases-controls with transmission disequilibrium testing
Candidate gene association study	Cases and controls	Gene	Odds ratio or genetic risk and <i>P</i> -value
Genome-wide association study	Cases and controls	Genome-wide	Odds ratio or genetic risk and <i>P</i> -value
Admixture mapping	Cases and controls	Gene to Genome-wide	Admixture mapping association peak and <i>P</i> -value

*Methodologies are described by the target population analyzed, coverage ranging from the individual gene-level to genome-wide level resolution, and the analytical test measured.

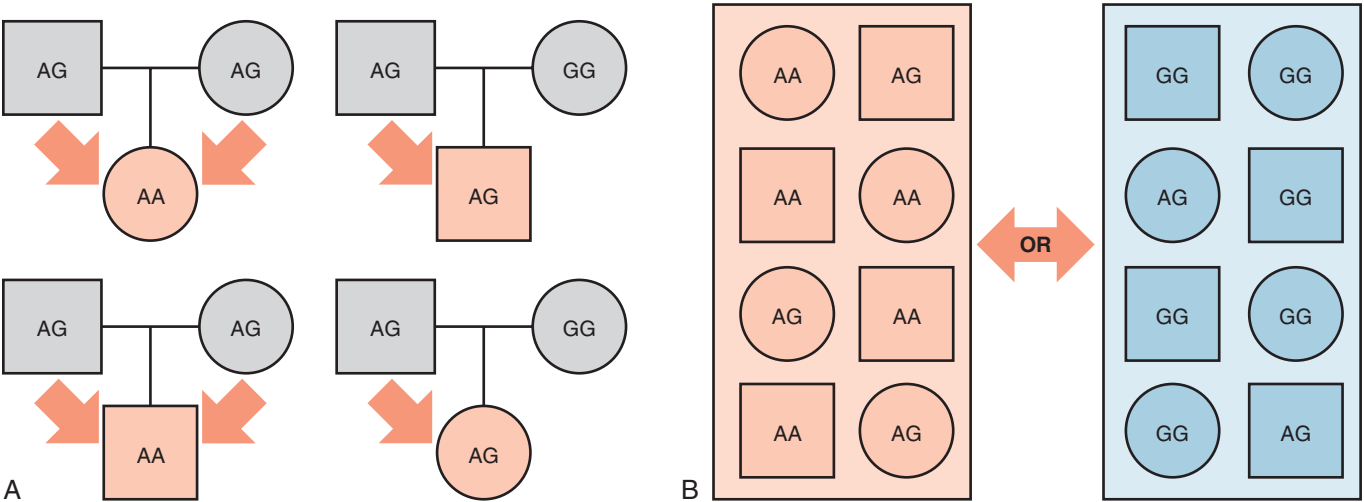


Figure 45-2 Two commonly used association testing methods: family-based and case-control. **A**, Family-based association testing. The basic fundamental unit of family-based association testing are the trios of affected (cases in red) probands. Trios consist of cases or affected probands and their parents, whose affected status is not necessarily known (in gray). In family-based studies, the over transmission of an allele of a polymorphism to affected probands is measured (red arrows). This demonstrates how a single nucleotide polymorphism (SNP) with alleles “A” or “G” shows overtransmission of the “A” allele to affected probands. The strength of the overtransmission or association at this locus is estimated using the *P*-value. **B**, Case-control association testing. Case-control association testing compares the frequency of the different alleles for this SNP in unrelated cases (in red) and controls (in blue) to determine an odds ratio (OR, red double-arrow) or genetic effect. The basic illustration demonstrates that the “A” allele is more frequent among cases compared to controls. The strength of the association at this locus is estimated using the *P*-value.

eTable 45-1 Candidate Genes for Susceptibility to Asthma and Related Phenotypes in Chromosomal Regions Identified through Linkage Studies*

Gene Names	Chr Pos	Gene ID	Associated Phenotypes	References
A Disintegrin And Metalloprotease-33	20p13	<i>ADAM33</i>	Asthma, bronchial responsiveness, lung function, lung function rate decline	21, 50–52
β-chain of the high-affinity receptor for IgE	11q13	<i>FCER1B</i>	Asthma, IgE, skin test atopy	3, 35–37, 71, 75
Dipeptidyl Peptidase-10	2q14	<i>DPP10</i>	Asthma, IgE, skin test atopy	3, 58, 59, 114, 115
Interleukin-4	5q31	<i>IL4</i>	Asthma, IgE, skin test atopy, lung function	25, 31, 33, 83–89, 98
α-chain of the Interleukin-4 Receptor	5q31	<i>IL4R</i>	Asthma, IgE, skin test atopy, lung function	25, 31, 33, 95, 96, 98–100
Interleukin-13	5q31	<i>IL13</i>	Asthma, bronchial responsiveness, IgE, skin test atopy	25, 31, 33, 72, 79–82, 98
CD14	5q31	<i>CD14</i>	Asthma	25, 31, 33, 76, 77
Protocadherin-1	5q31	<i>PCDH1</i>	Bronchial responsiveness	25, 31, 33
Tumor Necrosis Factor-α	6p21	<i>TNF</i>	Asthma, bronchial responsiveness, IgE, skin test atopy	3, 24, 40, 64, 66–70, 114
Human Leukocyte Antigen Complex DPB1	6p21	<i>HLA-DPB1</i>	Asthma	3, 24, 40, 74, 114
Human Leukocyte Antigen Complex DQB1	6p21	<i>HLA-DQB1</i>	Asthma	3, 24, 40, 72, 73, 114
Human Leukocyte Antigen Complex DRB1	6p21	<i>HLA-DRB1</i>	Asthma, skin test atopy	3, 20, 24, 40, 114, 145
Human Leukocyte Antigen Complex G	6p22	<i>HLA-G</i>	Asthma, bronchial responsiveness	3, 24, 40, 63, 114
Neuropeptide S Receptor-1 (NPSR1)	7p14	<i>GPRA</i>	Asthma, IgE	38, 63a
PHD Finger Protein-11	13q14	<i>PHF11</i>	Asthma, IgE	3, 61

*Candidate genes listed are within linkage regions from family-based studies or replicated in case-control association studies. Genes are summarized by full gene name, chromosomal position (Chr Pos), gene identification (ID) acronym, associated asthma or related phenotype, and references cited.

5q31, 8p23, and 12q22, and 15q13.²² In addition, these studies provided evidence for gene-by-environment interactions between passive cigarette smoking and asthma susceptibility at chromosomes 1p, 5q, and 9q, and 17q21.^{17,41-43} These gene-by-environment interactions provided the earliest examples of important epigenetic effects in asthma in which environmentally induced DNA modifications alter transcription without a change in gene sequence.

Early family-based linkage studies also provided evidence for genetic determinants of altered pulmonary function in asthma. In these studies, a quantitative trait locus on chromosome 5q33 and 2q32 was linked with important lung function measures.^{18,44-46} The quantitative trait locus in chromosome 2q32 was adjacent to the region linked to *forced expiratory volume in 1 second/forced vital capacity* (FEV₁/FVC) in families with early-onset COPD suggesting that there may be similar genes that affect the development of both asthma and COPD.⁴⁷

LINKAGE STUDIES PROVIDE IMPORTANT INSIGHT INTO THE COMPLEXITY OF ASTHMA PATHOGENESIS

The limitations of family-based linkage studies include the challenge of recruiting and characterizing related subjects and the use of genetic markers that cover genomic regions that contain hundreds of genes, requiring more detailed analysis with fine mapping or positional cloning to identify individual susceptibility genes. Another important limitation of family-based linkage studies is that they were designed to identify loci containing gene variants with a strong effect on disease susceptibility and are underpowered to detect common gene variation with a weak or modest effect. Despite these limitations, novel asthma genes have been identified (see eTable 45-1) which provide insight into the polygenic pathogenesis and the importance of gene-environment interactions in asthma.

LINKAGE ANALYSIS AND POSITIONAL CLONING REVEAL NOVEL ASTHMA SUSCEPTIBILITY LOCI

A *disintegrin and metalloprotease-33 gene* (*ADAM33*) was the first gene identified for asthma susceptibility using a family-based linkage study followed by fine mapping and association studies with cases and controls (i.e., positional cloning). It was identified by positional cloning on chromosome 20p13.²¹ *ADAM33* encodes for a membrane-anchored glycoprotein that controls cell-matrix interactions and is involved in regulation of lung growth and morphogenesis.^{48,49} The *ADAM33* protein is expressed in airway smooth muscle cells and lung fibroblasts, contains a catalytic domain with proteolytic activity and affects airway remodeling. *ADAM33* is among the most replicated genes for asthma susceptibility in different racial and ethnic groups.⁵⁰⁻⁵³ *ADAM33* gene variants have been associated with accelerated decline in lung function in asthma and in COPD, suggesting a role of this gene in the pathogenesis of progressive airflow obstruction.⁵⁴⁻⁵⁶ This is further supported by the observation that bronchoalveolar lavage concentrations of soluble *ADAM33* correlate with asthma severity and inversely correlate with lung function.⁵⁷

Other family-based whole-genome studies used positional cloning to identify the *dipeptidyl peptidase-10* (*DPP10*) gene on chromosome 2q14 as a locus for asthma susceptibility.⁵⁸ A *single nucleotide polymorphism* (SNP) in *DPP10* was recently identified in a GWAS of African Americans and African Caribbeans, providing additional evidence that *DPP10* is an asthma susceptibility locus.⁵⁹ Dipeptidyl peptidases cleave the terminal peptides of cytokines and chemokines and enhance airway inflammation. Several other asthma susceptibility genes have been identified using fine mapping or positional cloning techniques and include the *protocadherin-1* gene (*PCDH1*) on chromosome 5q31, *human leukocyte antigen complex G* (HLA-G) on chromosome 6p22, the *neuropeptide S receptor-1* gene (*GPRA*) on chromosome 7p14, and *PHD finger protein-11* (*PHF11*) on chromosome 13q14 (see eTable 45-1).^{3,38,60-63,63a} The identification of asthma susceptibility loci is an example of the use of *unbiased* genetic techniques, that is, without preconceived notions of mechanism, to delineate novel biologic mechanisms that are important in the pathogenesis of asthma.

CANDIDATE GENE ASSOCIATION STUDIES IN ASTHMA

As high-throughput genotyping technologies emerged that facilitated genotyping in larger populations, a greater number of biologic candidate genes were investigated in unrelated asthma case and control populations. In contrast to family-based approaches, case-control association studies compare the frequency of the alleles of a gene variant between unrelated cases and controls (see Fig. 45-2). Association analysis is a very useful approach for common diseases wherein alleles confer a small disease risk. SNPs (i.e., point mutations) represent the substitution of a single nucleotide for another, resulting in variable frequencies of the variant allele in a sample population. SNPs are denoted as a *reference sequence* (rs) number or by the coding change at a specific codon position number for nonsynonymous SNPs (e.g., rs1042713 or Gly¹⁶Arg) and represent the primary gene variants used in association studies. (*Nonsynonymous* refers to a change in sequence that alters the amino acid sequence of a protein; *synonymous*, on the other hand, is a change in sequence that does not alter the protein.)

More than 100 genes have been studied as biologic candidate genes based on plausible biologic mechanisms in asthma or locations in chromosomal regions linked to asthma (see eTable 45-1).^{21,58} For each replicated candidate gene for asthma susceptibility that has been discovered, there are studies that may not show an association, perhaps because of differences in phenotypes or differences in race between populations (see later). The most replicated candidate genes appear to be related to broad categories of lung development (e.g., *ADAM33*), the *type 2 T helper cell* (Th2) inflammatory pathway (*IL4*, *IL13*, *IL4R*), innate immunity (*HLA-DRB1*, *HLA-DQB1*, *CD14*), and cellular inflammation (*TNF*, *FCER1B*, *DPP10*) (see eTable 45-1).^{3,21,58,59,63-75} In addition, candidate genes within the glucocorticoid receptor complex pathway, the leukotriene pathway (*LTC4S*), the

β_2 -adrenergic receptor gene (*ADRB2*), and the Th2 inflammatory pathway signaling (*IL4R*) have also been evaluated as potential pharmacogenetic loci that modify responses to pharmacologic therapy.⁷⁶⁻⁹⁴

HIGHLY REPLICATED CANDIDATE GENES ON CHROMOSOME 5q31 AND EVIDENCE FOR GENE-GENE INTERACTIONS

Linkage analyses of chromosome 5q31-35 have consistently provided evidence that this region is linked to asthma or closely related phenotypes.^{25,31,33,62} This inflammatory gene-rich region contains multiple candidate genes related to allergic inflammation, including *IL3*, *IL4*, *IL5*, *IL13*, *CD14*, *serine peptidase inhibitor Kazal type 5* (*SPINK5*), the β_2 -adrenergic receptor (*ADRB2*), and *leukotriene C4 synthase* (*LTC4S*). The gene encoding for *IL-13* and *IL-4* contains promoter SNPs and variants consistently associated with asthma and related phenotypes in multiple populations.^{79,80,84,86-88} *IL-13* and *IL-4* bind to the α chain of the *IL-4* receptor encoded by *IL4R* on chromosome 16p12, which also contains variants associated with asthma and related phenotypes.^{95,96} The interaction of two variants in *IL4R* has been associated with risk for life-threatening asthma exacerbations in persistent asthmatics suggesting a role of this pathway in determining disease severity.⁹⁷ In addition, interactions between genetic variants in *IL4*, *IL13*, and *IL4R* and other pathway-related genes such as *STAT6* on chromosome 12q13 cumulatively determine asthma risk and serum IgE at a greater level than does each individual locus, supporting the role of multiple genes interacting in asthma susceptibility and pathogenesis.⁹⁸⁻¹⁰⁰ Finally, one of the first GWAS in a population of severe or difficult-to-treat asthmatics demonstrated SNPs in *IL13* and a neighboring gene encoding for a DNA repair protein (*RAD50*) as a locus for asthma susceptibility.⁷² The interaction of variants in different Th2 inflammatory pathway signaling genes has been critical to understanding the nature of gene-gene interactions in determining asthma susceptibility and severity. Furthermore, these positive associations for the *IL-4*–*IL-13* pathways have supported the current development of biologic therapies targeting these cytokines.^{93,101,102}

LIMITATIONS OF CANDIDATE GENE ASSOCIATION STUDIES: LESSONS LEARNED AND THE ROAD TO GWAS

All association studies, including candidate gene studies, are limited by the need to ascertain well-characterized case-control populations.^{103,104} An issue with early association studies was the small sample sizes (<200 cases) resulting in studies underpowered to identify gene variants with small effects and prone to false-positive results. Unrelated cases and controls have variable ancestral backgrounds, which may lead to false-positive results. SNP allele frequencies vary in different populations based on ancestry (population stratification), which may cause spurious differences in allele frequencies between cases and controls if different ethnic groups are analyzed (i.e., false positives).

The need to account for potential population stratification in genetic association studies is true for all types of

association studies but was well recognized and implemented in candidate gene studies. Another limitation of all association studies is the underlying correlation of alleles in genetic loci located in a chromosomal region (i.e., *linkage disequilibrium* or LD). For example, if two genetic loci are physically close together, they will be inherited as one unit through multiple generations. In this case, an association study would result in positive results for both genes, making it difficult to isolate the gene or variant of interest. This is especially true for SNPs within a gene. However, in older populations of more generations or admixed population, there have been more opportunities to break the correlation, thus allowing the true risk allele or loci to be identified.

GENOME-WIDE ASSOCIATION STUDIES FOR ASTHMA SUSCEPTIBILITY

In GWAS, large numbers of SNPs are genotyped using chip technologies that cover the genome, usually with 500,000 to more than 1 million SNP genotypes (SNP variants) assessed in large case and control populations. Earlier chips contained fewer SNPs and did not provide good coverage of the genome in all races that show differences in allele frequencies based on ancestry. The overall limitation is the degree of phenotyping that can be performed in these large samples (see Fig. 45-2). In GWAS, the frequencies of the alleles of each SNP are compared between unrelated cases and controls on a genome-wide scale (see Fig. 45-2).

SNPs are the most common form of gene variation and are seen in 1 of every 100 nucleotides in the human genome; therefore, SNPs used for GWAS provide comprehensive coverage of each gene and the entire genome. The ability to genotype a larger number of SNPs rapidly and simultaneously has enabled GWAS approaches to identify a number of novel loci associated with asthma susceptibility, related phenotypes, and disease severity. In addition, whole-genome genotyping provides information about population substructure, an index of ancestral admixture. All GWAS studies discussed later have adjusted associations by population substructure to minimize confounding by population stratification (eTable 45-2). A small number of studies have used genome-wide family-based association studies (i.e., transmission disequilibrium test) to minimize this source of confounding by population stratification (see Fig. 45-2).²⁷ GWAS requires a more stringent *P*-value due to multiple testing of a large number of SNPs, and subsequent replication testing of significant SNP associations in independent samples is important.

GWAS IDENTIFIES *ORMDL3* AS A SUSCEPTIBILITY LOCUS

In 2007, a GWAS for asthma susceptibility was performed in a European cohort (GABRIEL). SNPs in the *ORM1-like 3 gene* (*ORMDL3*) region on chromosome 17q12 were significantly associated with the diagnosis of childhood asthma and this finding was replicated in two independent cohorts.¹⁶ A second larger GWAS by the European GABRIEL

eTable 45-2 Major Susceptibility Loci for Asthma Identified through GWAS*

Gene Names	Chr Pos	Gene ID	Racial or Ethnic Populations	Initial Reported Locus	References
ORM1-Like 3	17q12	<i>ORMDL3</i>	European, European American, African American, African Caribbean, Hispanic, Chinese	rs7216389	16, 73, 105–110
Gasderminlike B	17q12	<i>GSDMB</i>	European, European American, Chinese	rs2305480	73, 108, 130
Interleukin-1 Receptor	2q12	<i>IL1RL1</i>	European, European American, African American, African Caribbean, Hispanic	rs1420101	73
Interleukin-18 Receptor	2q12	<i>IL18R1</i>	European	rs3771166	73
Human Leukocyte Antigen Complex DQB1	6p21	<i>HLA-DQB1</i>	European and Japanese	rs9273349	72, 73
Interleukin-33	9p24	<i>IL33</i>	European, European American, African American, African Caribbean, Hispanic	rs1342326	73, 109
Interleukin-2 Receptor, β Subunit	22q12	<i>IL2RB</i>	European	rs2284033	73
SMAD Family Member 3	15q22	<i>SMAD3</i>	European	rs744910	73
RAR-Related Orphan Receptor A	15q22	<i>RORA</i>	European	rs11071559	73
Thymic Stromal Lymphopoietin	5q22	<i>TSLP</i>	European American, African American, African Caribbean, Hispanic, Japanese	rs1837253	73, 109, 145
WD Repeat Domain 36	5q22	<i>WDR36</i>	European, East Asian	rs2416257	150
RAD50 Homolog	5q31	<i>RAD50</i>	European American	rs2244012	72
Interleukin-13	5q31	<i>IL13</i>	European American	rs1295686	72, 130
cAMP-Specific Phosphodiesterase 4D	5q11	<i>PDE4D</i>	European, European American, Hispanic	rs1588265	110
Pyrin and HIN Domain Family Member 1	1q23	<i>PYHIN1</i>	African American and African Caribbean	rs1102000	109
Interleukin-6 Receptor	1q21	<i>IL6R</i>	European	rs4129267	106
GRB2-Associated Binding Protein 1	4q31	<i>GAB1</i>	Japanese	rs1397527	145
Ubiquitin Specific Peptidase 38	4q31	<i>USP38</i>	Japanese	rs7686660	145
GATA Binding Protein 3	10p14	<i>GATA3</i>	Japanese	rs10508372	145
Ikaros Family Zinc Finger 4	12q13	<i>IKZF4</i>	Japanese	rs1701704	145
Human Leukocyte Antigen Complex DPA1	6p21	<i>HLA-DPA1</i>	Japanese	rs987870	74
α -1B-Adrenergic Receptor	5q33	<i>ADRA1B</i>	African American	rs10515807	59
Prion-Related Protein	20p12	<i>PRNP</i>	African American	rs6052761	59
Dipeptidyl Peptidase-10	2q14	<i>DPP10</i>	African American	rs1435879	59
TNFAIP3 Interacting Protein 1	5q33	<i>TNIP1</i>	European American	rs1422673	130
Human Leukocyte Antigen Complex DRA	6p21	<i>HLA-DRA</i>	European American	rs2395185	130

*Susceptibility loci for asthma identified through genome-wide association studies summarized by full gene name, chromosomal position (Chr Pos), gene identification (ID) acronym, racial or ethnic groups where associations were observed, initial locus (by single nucleotide polymorphism rs number) reported to be associated with asthma through GWAS, and references cited.

consortium validated *ORMDL3* as a locus for asthma risk while identifying additional susceptibility loci in the neighboring gasdermin-like genes (*GSDMB* and *GSDMA*) as well as other loci in the genome, including *IL1RL1/IL18RL1* (between the *IL1* and *IL18* receptor genes, rs3771166) on chromosome 2q12, *HLA-DQB1* (rs9273349), *IL33* on chromosome 9p24 (rs1342326), *SMAD3* on chromosome 15q22 (rs744910), and *IL2RB* on chromosome 22q12 (rs2284033).⁷³

Gene variants in the *ORMDL3* locus have been associated with asthma in multiple subsequent GWAS, making *ORMDL3* the most replicated locus using genome-wide screening methods in case-control populations.¹⁰⁵⁻¹¹⁰ The challenge of interpreting genetic associations in chromosome 17q12 is the strong *linkage disequilibrium* (LD) that exists between the variants in multiple genes that span this region. It remains unclear whether the causative gene is *ORMDL3* or an adjacent gene, such as *GSDMB* or *GSDMA*.^{111,112}

This novel asthma susceptibility gene (*ORMDL3*) is a member of a class of genes that encodes transmembrane proteins anchored in the endoplasmic reticulum; however, its specific biologic role in asthma pathogenesis remains unknown. GWAS in asthma have demonstrated a predilection for genes that regulate relevant molecular pathways and are related to epithelial damage and adaptive immune response. It is likely that altered production of cytokines such as *thymic stromal lymphopoietin* (TSLP) and IL-33 from damaged or disrupted epithelial cells promotes Th2-mediated inflammatory responses by activating IL1RL1 receptors on mast cells, Th2 lymphocytes, and regulatory T cells.

GWAS IN AFRICAN AMERICANS AND OTHER ASTHMA POPULATIONS

Subsequent GWAS were performed in multiethnic populations including non-Hispanic white and African American subjects to understand the genetic diversity of populations from different ancestral backgrounds (i.e., ethnic groups) as well as to address the genetic causes of differences in the frequency and severity of asthma in different ethnicities. This is particularly important for ethnic groups such as African Americans and Puerto Ricans who have a greater asthma incidence associated with higher asthma-related morbidity and mortality. These groups may have unique genetic loci due to a higher frequency of risk alleles that determine disease susceptibility or severity.¹¹³ For example, African Americans are at low risk for cystic fibrosis because of the low frequency of *CFTR* mutations in this ancestral population while at higher risk for sickle cell disease due to increased frequency of mutations in that gene.

The EVE consortium combined 5416 asthma cases in a large, multiethnic population representing Americans of European descent, African Americans, African Caribbean, and Hispanics (Mexican Americans and Puerto Ricans) with replication in 12,649 subjects. This large-scale multiethnic GWAS for asthma susceptibility identified genome-wide significant associations with SNPs on chromosome 17q12 (spanning *IKZF3/ZPBP2/GSDMB/ORMDL3*), *IL1RL1*, and *TSLP* on chromosome 5q22. Associations at these loci and a SNP in *IL33* were replicated in indepen-

dent cohorts.¹⁰⁹ This GWAS validated the susceptibility loci identified on the chromosome 17q12 locus and *IL1RL1* confirming their importance in asthma risk (see eTable 45-2).^{16,73}

The EVE consortium also identified SNPs in the pyrin and HIN domain family member 1 (*IFIX*, interferon inducible nuclear protein X gene, *PYHIN1*) associated with asthma in African American and African Caribbean cohorts.¹⁰⁹ The first GWAS of a population from a primarily African ancestry also identified novel susceptibility loci in the α_{1B} -adrenergic receptor on chromosome 5q33 (*ADRA1B*) and prion-related protein on chromosome 20p12 (*PRNP*). In addition, the *DPP10* locus was associated with asthma, confirming earlier positional cloning studies.^{3,58,59,114,115}

GWAS in Asian populations confirm the importance of previously described asthma susceptibility loci in *HLA-DQ*, *HLA-DPA1*, *HLA-DPB1*, and *TSLP* in Japanese and Korean populations.^{74,109,116,117} In addition, five polymorphisms in chromosome 17q12 encompassing *ORMDL3*, *GSDMB*, *ZPBP2*, and *IKZF3* were associated with asthma in a Han Chinese population (see eTable 45-2).¹⁰⁸

ADMIXTURE MAPPING AS AN ALTERNATIVE APPROACH IN ADMIXED POPULATIONS

The colonization of the Americas by the Europeans and the subsequent African slave trade has resulted in the mixing of genetic ancestries and the complex population structures encountered in the genomes of African Americans, African Caribbean, Mexican Americans, and Puerto Ricans. There is marked variability in the demographic histories of these admixed populations of African origin, resulting in a complex population structure and reduced LD that is not fully captured with GWAS that use genotyping platforms designed for non-Hispanic white populations. The recent mixing of these ancestries provides the rationale for genome-wide ancestry-based approaches. African Americans, on average, have an estimated 20% European ancestry (80% African) while Hispanic ethnic groups such as Puerto Ricans and Mexican Americans have a combination of three different ancestries.¹¹⁸⁻¹²⁰

Mapping by admixture linkage (admixture mapping, Fig. 45-3) is a genome-wide approach that is based on the principle that many SNPs show marked variable allele frequencies between different ancestral populations. In admixture mapping, estimates of ancestry at each SNP are tested for association with a phenotype, in contrast to GWAS which compares allele frequencies. Admixture mapping requires a substantially smaller number of genetic markers compared to GWAS and can evaluate regions with rare variants (Fig. 45-4) and other variants such as polynucleotide insertion-deletions. The optimal setting for the use of admixture mapping is in admixed populations where there are marked racial disparities in disease phenotype not attributed completely to environmental factors.^{113,121-123}

Studies of African ancestry in African Americans from the general population have suggested a role for gene variation related to African ancestry on lung function and asthma severity. Estimates of African ancestry are inversely associated with baseline lung function measures in three independent African American populations and Puerto Ricans.^{120,123a} In African Americans, each percentage of

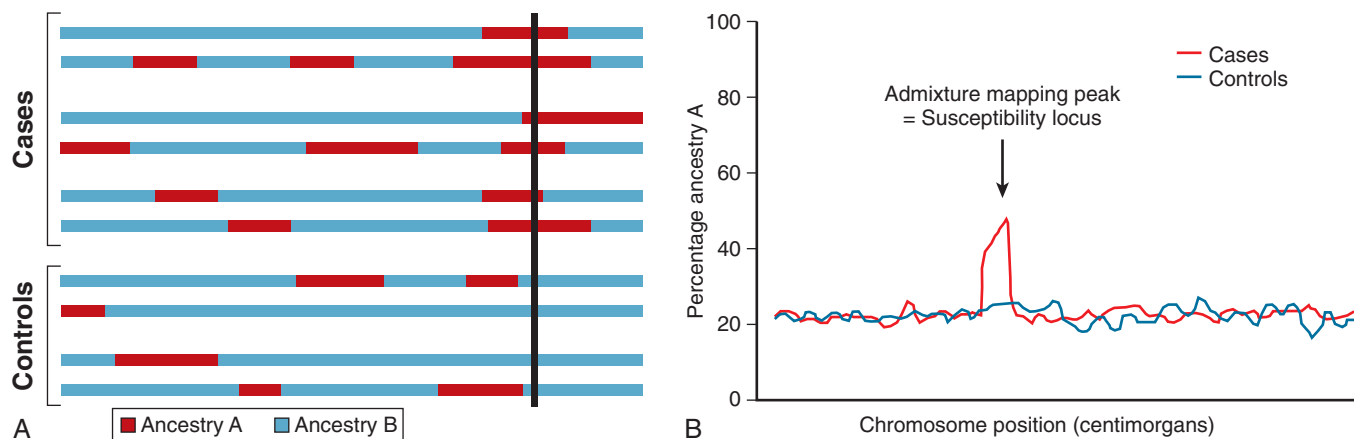


Figure 45-3 Illustration of admixture mapping. **A**, The hypothesis behind mapping by admixture linkage disequilibrium or admixture mapping is that chromosomes from an admixed population (shown with red and blue genetic regions from different ancestries) contain a susceptibility allele that is more frequent in the red ancestral region versus the blue. Admixture mapping identifies increased ancestry at a susceptibility locus in cases compared to controls (region intersected by thick black line). **B**, Loci with significant associations between ancestry and disease risk are represented by admixture mapping peaks or chromosomal regions with an overrepresentation of ancestry from the ancestral population with the highest proportion of risk alleles at the locus containing the risk-invoking variant. (**A**, Adapted from Montana G, Pritchard JK: Statistical tests for admixture mapping with case-control and cases-only data. *Am J Hum Genet* 75:771–789, 2004. **B**, From Patterson N, Hattangadi N, Lane B, et al: Methods for high-density admixture mapping of disease genes. *Am J Hum Genet* 74:979–1000, 2004, Fig. 1.)

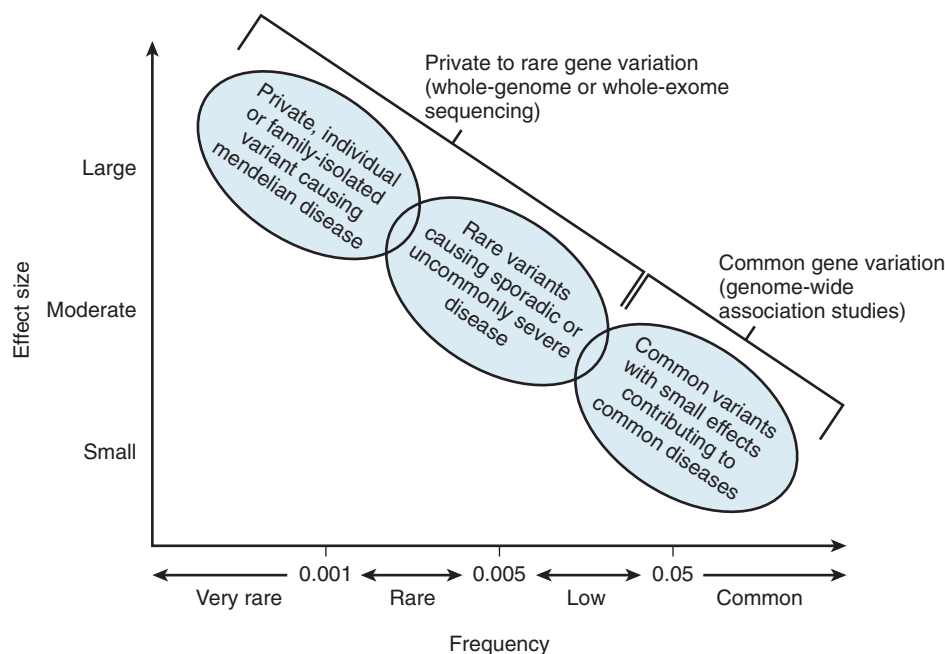


Figure 45-4 Impact of genetic variants in human disease. The “common disease–common allele” hypothesis states that multiple common genetic variants with small to modest effect sizes contribute to common disease susceptibility in an additive fashion. Genome-wide association studies (GWAS) have identified multiple common variants associated with risk for different common diseases. In contrast, the “common disease–rare allele” hypothesis states that rare genetic variants with a large effect size contribute to susceptibility for common diseases. Rare variants can only be evaluated with family-based genetic studies, DNA sequencing, and admixture mapping, and are not easily evaluated with GWAS. (Adapted from Tsuji S: Genetics of neurodegenerative diseases: insights from high-throughput resequencing. *Hum Mol Genet* 19:R65–70, 2010.)

African ancestry was associated with a 3 to 5 mL lower FEV₁. This finding has implications for calculating predicted normal lung function in admixed ethnic groups. For example, an African American with 50% African Ancestry is likely to have an FEV₁ up to 200 mL higher compared to an African American of the same age, sex, and height with 90% African ancestry. Estimates of African ancestry have also been associated with risk for self-reported asthma and

asthma exacerbations in African Americans from the United States.^{124,125}

Genome-wide admixture mapping studies have the potential to identify the genetic loci that account for the increased asthma incidence in those with significant African ancestry. Admixture mapping for susceptibility loci has been performed in Puerto Ricans and Mexican Americans from the *Genetics of Asthma in Latino Americans* (GALA)

cohort, and SNPs in nearly 62 loci associated with asthma (i.e., admixture mapping peaks, see Fig. 45-3) have been identified.^{126,127} Admixture mapping in African American and Puerto Rican asthma subjects from the NHLBI-sponsored *Severe Asthma Research Program* (SARP), CSGA, and GALA cohorts has also identified a novel asthma susceptibility locus on chromosome 6q14.1.¹²⁸

GWAS AND ASSOCIATION STUDIES OF SEVERE ASTHMA

Initially, GWAS in asthma were designed to detect susceptibility loci, because detailed phenotyping is time intensive and costly, resulting in small case-control cohorts. Larger populations of comprehensively characterized cohorts were recruited for the NHLBI-sponsored SARP and the TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) Study. A GWAS of severe asthmatics from TENOR identified multiple loci associated with asthma: rs2244012 in *RAD50* adjacent to *IL13*, rs1063355 in *HLA-DQB1*, and rs3998159 between *HLA-DQB1* and *HLA-DQA2*. These findings confirm the importance of Th2 cytokine and antigen presentation genes in asthma pathogenesis and potentially in asthma severity.^{3,24,40,72,79,80,114,129} Associations at these loci have also provided evidence for a common immunogenic pathway between asthma and autoimmune disease. For example, the *IL13* asthma locus is also associated with psoriasis.¹³⁰ A recent GWAS of children between 2 and 6 years of age from the Copenhagen Prospective Studies on Asthma in Childhood Exacerbation cohort with recurrent, severe exacerbations identified four previously identified susceptibility loci in *GSDMB*, *IL33*, *RAD50*, and *IL1RL1* as associated with risk for this severe asthma phenotype.^{16,73,109,131} In addition, this GWAS identified a novel locus for severe childhood asthma on the gene encoding *cadherin-related family member-3* (*CDRH3*): a genotype-phenotype relationship that is important in determining severity risk in childhood asthma.¹³¹

GWAS have also identified asthma susceptibility loci associated with lung function, a fundamental determinant of asthma severity.^{132,133} A SNP in the *IL-6 receptor* gene (rs4129267, *IL6R*) has been associated with asthma in a large GWAS and was among the top SNPs associated with baseline lung function in a GWAS of the Framingham Heart Study cohort.^{106,134} This *IL6R* SNP is in LD with a coding variant (Asp³⁵⁸Ala) where the minor allele (Ala³⁵⁸) is associated with lower baseline lung function and increased methacholine bronchial responsiveness.¹³⁵ IL-6 is a proinflammatory cytokine expressed in inflammatory diseases such as asthma and COPD, and represents a potential therapeutic target because IL-6 receptor antagonists are available for the treatment of rheumatoid arthritis.¹³⁶⁻¹³⁸

Li and coworkers performed a meta-analysis of 14 SNPs previously associated with lung function in GWAS of controls from the *Cohorts for Heart and Aging Research in Genomic Epidemiology* (CHARGE) and SpiroMeta consortia. This analysis demonstrated that SNPs in the gene encoding for *hedgehog-interacting protein* (*HHIP*) were significantly associated with lung function in African American and non-Hispanic White asthma subjects. In addition, an increase in

the number of risk alleles for SNPs in *HHIP*, *PTCH1*, and *FAM13A* resulted in a significant stepwise decrease in lung function.¹³⁹ More recent studies have shown that Th1 immunity pathway genes (*IL12A*, *IL12RB1*, *STAT4*, *IRF2*) also appear to influence lung function and severity in asthma.¹⁴⁰

Elevated serum IgE is a primary associated phenotype for allergy in asthma. Two large GWAS of general population cohorts from the GABRIEL and EVE consortia have identified SNPs in *FCER1A* on chromosome 1q23, *RAD50*, *STAT6*, *IL13*, and the HLA complex associated with serum IgE concentrations, confirming prior linkage and association studies.^{33,34,39,72,73,98-100,141-145}

In non-Hispanic whites, four SNPs in the chromosome 11 open reading frame and the leucine rich repeat containing 32 gene (*C11orf30-LRRC32*) were associated with serum IgE.¹⁴⁶ The *C11orf30-LRRC32* genomic region contained SNPs associated with other inflammatory diseases such as atopic dermatitis, childhood eczema, and Crohn disease.¹⁴⁷⁻¹⁴⁹

Blood eosinophil levels and eosinophilic inflammation are related to asthma pathogenesis and severity and have been evaluated by GWAS. In a general population sample from Iceland and replication cohorts from Europe and East Asia SNPs in *IL1RL1* (rs1420101), chromosome 2q13 (rs12619285), chromosome 3q21 (rs4857855), chromosome 5q31 (rs4143832), and *SH2B3* on chromosome 12q24 (rs3184504) were associated with peripheral blood eosinophilia. The *IL1RL1* locus has been associated with asthma and loci in *WDR36* and *IL33* showed suggestive associations with eosinophil counts and atopic asthma.¹⁵⁰ Loci adjacent to *WDR36* (*TSLP*), *IL1RL1*, and *IL33* have also been associated with asthma in prior GWAS.^{73,109} Fraction of exhaled nitric oxide, a biomarker of eosinophilic airway inflammation, was evaluated in a GWAS in 14 pediatric cohorts that included asthmatics and control subjects. This GWAS identified loci associated with childhood exhaled nitric oxide levels in two genes on chromosome 17q11.2-q12, *LYRM9* and inducible nitric oxide synthase-2 (rs944722, *NOS2*), and adjacent to a previously replicated asthma susceptibility locus, *GSDMB* (rs8069176).¹⁵¹

Chitinases are a family of conserved hydrolases that cleave chitin and mediate Th2-driven airway inflammation in murine models.¹⁵² YKL-40 is a chitinase-like protein that has been evaluated as a biomarker for airway inflammation and remodeling in asthma. Serum YKL-40 levels are elevated in asthmatics and have been associated with disease severity.¹⁵³ A GWAS identified a SNP in the promoter of the chitinase 3-like 1 gene, which was associated with serum YKL-40 levels, asthma diagnosis, bronchial responsiveness, and lung function in an isolated population (Hutterites).¹⁵⁴

GWAS of lung function and inflammatory biomarkers have identified genes that impact disease severity. The impact of “lung function genes” on asthma severity provides an excellent example of how genetic markers from different genes can contribute to disease severity in an additive manner.¹³⁹ Gene variants important in asthma susceptibility likely differ from genes that cause asthma progression and severity. This concept is outlined in Figure 45-5, which proposes mechanisms by which susceptibility and severity genes interact in the development and progression of asthma.¹⁴⁰ Thus, susceptibility to asthma is genetically

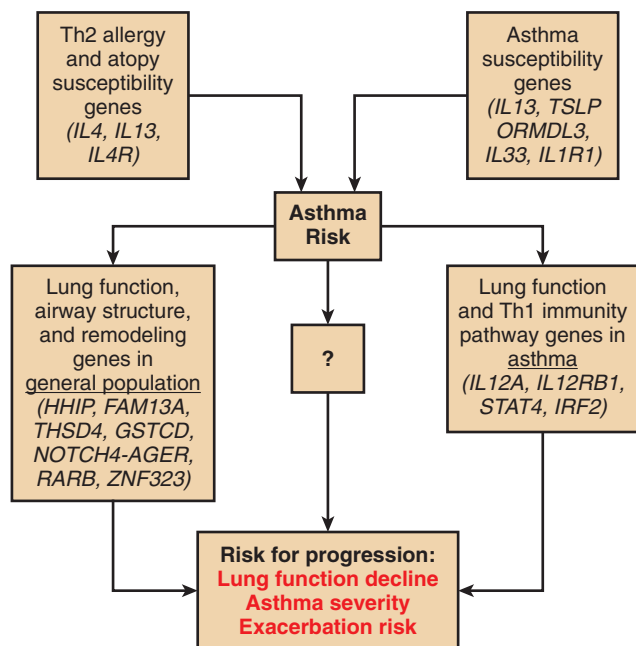


Figure 45-5 Genetic factors determine susceptibility and severity of asthma through independent pathogenic pathways. This flow diagram demonstrates how susceptibility loci for asthma and related phenotypes (including allergic or atopic characteristics) contribute to risk for asthma. In turn, different genetic determinants for lung function such as loci that accelerate airway remodeling or alter early lung development in combination with altered T type 1 helper (Th1) innate immunity in response to infection result in asthma progression. Many of the genes for risk of asthma susceptibility, progression, and severity are from different gene pathways. (Adapted from Li X, Hawkins GA, Ampleford EJ, et al: Genome-wide association study identifies Th1 pathway genes associated with lung function in asthmatic patients. *J Allergy Clin Immunol* 132:313–320 e15, 2013. Figure 3.)

determined by the gene variants identified in GWAS of asthma susceptibility. Disease progression is modulated by additional genes that determine asthma severity. For example, if the genome of an individual has gene variants conferring asthma susceptibility and also contains gene variants that encode for reduced lung function, this additive combination will result in the expression of a more severe asthma phenotype.¹³⁹ Furthermore, genetic markers of asthma severity could be used to generate genetic profiles that predict risk for disease progression.^{6,155}

GENE-ENVIRONMENT INTERACTIONS: GENETIC AND EPIGENETIC STUDIES FOR ASTHMA SUSCEPTIBILITY AND SEVERITY

Environmental factors have an important role in the pathogenesis of asthma and gene-environment interactions have been identified for asthma susceptibility and severity. Gene-environment interactions have the potential to identify factors that contribute to the missing heritability not accounted for by the effects of gene variants alone. Environmental cigarette smoke exposure is the most replicated environmental factor impacting genetic studies for

asthma susceptibility. Linkage studies in families from the CSGA cohort in the United States and The Netherlands both identified a linkage signal for asthma susceptibility and bronchial responsiveness on chromosome 5q31 that was dependent on passive cigarette smoke exposure.^{17,41} Another linkage study in French families from the EGEA (*Epidemiological Study on the Genetics and Environment of Asthma*) cohort also detected linkage for markers on chromosome 17q12 that was dependent on a gene-environment interaction with smoke exposure.^{42,43} In a family-based association study of 36 SNPs from the chromosome 17q12 in the *ORMDL3* region in the EGEA cohort, Bouzigon and coworkers¹⁵⁶ demonstrated 11 SNPs associated with an increased risk for asthma; however, the risk for early-onset asthma for the SNP with the strongest association (rs8069176) was 2.9 times greater in the subgroup exposed to cigarette smoke compared with the unexposed subgroup. These effects may be mediated by epigenetic regulation and demonstrate the complexity and interaction of genetic and environmental interactions in the pathogenesis of asthma.

Dietary factors such as vitamin D deficiency are associated with asthma development and severity.^{157,158} A genome-wide family-based association study identified genetic risk factors that interact with serum vitamin D levels affecting asthma severity. Three SNPs in the class I MHC-restricted T cell-associated molecule gene (*CRTAM*) were associated with an increased frequency of asthma exacerbations with low vitamin D levels. *CRTAM* is expressed in lung and by natural killer T and CD8⁺ cells; therefore, it is plausible that these gene variants interact with vitamin D, altering the immune response to viral infections.¹⁵⁹

The list of genes associated with asthma or related phenotypes is large and demonstrates that there are a number of biologic pathways important in asthma pathogenesis (see eTables 45-1 and 45-2). However, with the use of systems biologic approaches, there is potential for the development of genetic risk and severity profiles that can be used for early disease diagnosis and prediction of asthma progression.⁴

PHARMACOGENETICS OF ASTHMA

RATIONALE FOR PHARMACOGENETIC RESEARCH IN ASTHMA

Pharmacogenetics examines the role of gene variation in therapeutic responses to pharmacologic therapies. Pharmacogenetics is a gene-environment interaction wherein the therapeutic agent is the environmental exposure. There is evidence that genetic factors play an important role in the observed variability in therapeutic responses to different drugs. Approximately, 70% to 80% of asthmatics show varying responses to common antiasthma therapies, resulting in a marked variance in therapeutic drug responses.¹⁶⁰ Genetic variation might contribute to a large percentage of the variability in drug response, whether beneficial or adverse.^{160,161} The rationale for pharmacogenetic studies in asthma is that genetic markers could be used to identify subgroups of nonresponders, responders, or a subgroup at risk for adverse responses.

Pharmacogenetic research in asthma is driven by two major challenges related to asthma management. First, a small subgroup of approximately 5% to 10% of asthmatics experiences uncontrolled symptoms and recurrent exacerbations despite treatment with multiple antiasthma therapies, including high doses of inhaled or oral corticosteroids.^{8,9} This population with refractory asthma experiences substantial morbidity and generates a major financial burden compared to those with controlled mild or intermittent asthma.¹⁶² Second, adverse effects have been associated with some asthma therapies, particularly rare, life-threatening events associated with the use β_2 -adrenergic receptor agonists (i.e., β -agonists).^{10,11,163} Pharmacogenetic studies have the potential to identify genetic markers that would personalize therapeutic approaches in individual asthmatics to optimize therapeutic response and prevent adverse side effects.⁴

Pharmacogenetic studies of asthma therapies have been based on the primary clinical end points used in asthma clinical trials. In most pharmacogenetic studies, these predetermined clinical end points are analyzed for genetic associations with candidate gene studies or GWAS after the clinical trial is completed. These pharmacogenetic studies are important for the identification of genes or gene variants that influence drug responses. A minority of pharmacogenetic studies employs a prospective, genotype-stratified study design in which DNA is collected and genotyped for a risk variant of interest and subjects are randomized based on their genotype to treatment or placebo groups.¹⁶⁴ The advantage of a prospective, genotype-stratified approach is that it can ensure sufficient statistical power to analyze less common genetic variants because the population is recruited based on a predefined risk gene variant. However, a genotype-stratified pharmacogenetic trial is feasible if only a limited number (one or two) genotypes are being considered.

GLUCOCORTICOID PHARMACOGENETICS

Inhaled corticosteroids (ICS) have consistently been shown to be the most effective therapy to control persistent asthma.^{165,166} However, some asthmatics respond poorly to ICS.¹⁶⁷ The pharmacogenetics of the glucocorticoid pathway is based on genes that code for a complex pathway consisting of the glucocorticoid biosynthetic pathway, chaperone proteins, and the cytosolic receptor heterocomplex (eTable 45-3).¹⁶⁸

A candidate gene analysis of the *corticotropin-releasing hormone* (*CRHR1*) gene in more than 1000 asthma subjects from the National Institutes of Health and industry clinical trial cohorts identified two SNPs (rs242941 and rs1876828) that were associated with a change in lung function during ICS treatment.¹⁶⁷ In another study, the gene coding for a glucocorticoid receptor complex chaperone protein, the heat shock organizing protein (*STIP1*), identified three SNPs (rs2236647, rs6591838, and rs1011219) that were also associated with a significant change in lung function during ICS treatment.¹⁶⁹ The corticosteroid pathway interacts with other gene pathways that have been evaluated using a candidate gene approach in different clinical trial cohorts.^{170,171} The “T-box expressed in T-cells transcription factor” is encoded by *TBX21* and is an important regulator of the naive T-lymphocyte develop-

ment pathway. *TBX21* contains a coding SNP (rs2240017, His³³Gln) that was associated with “bronchoprotection,” that is, a reduction in bronchial hyperresponsiveness, during ICS treatment in the NHLBI *Childhood Asthma Management Program* (CAMP) and a Korean cohort.^{172,173} Adenyl cyclase type 9 is a key enzyme in the β_2 -adrenergic receptor pathway and is encoded by *ADCY9*, which contains a coding SNP (rs2230739, Met⁷⁷²Ile) that has been associated with an albuterol bronchodilator response in the CAMP cohort during ICS treatment.¹⁷⁴

Use of GWAS approaches has the potential to identify novel pharmacogenetic loci for ICS response. The first GWAS evaluating ICS treatment response was performed using family-based testing in CAMP followed by association studies for replication in more than 900 asthma subjects from four independent clinical trial cohorts. A promoter SNP in the glucocorticoid-induced transcript-1 gene (rs37972 in *GLCC11*) was associated with changes in lung function in response to ICS treatment. An in vitro study was also performed in which cells were transfected with another promoter variant in LD with rs37972 (rs37973) resulting in decreased gene expression.¹⁷⁵ These studies were primarily performed in children with fewer years of exposure to corticosteroids compared to adult asthmatics. Interestingly, more recent studies using large clinical trial cohorts of adult asthmatics were not able to replicate this association.¹⁷⁶ Functionally, *GLCC11* is an important regulator of apoptosis in response to glucocorticoids; therefore, this promoter variant may delay apoptosis of eosinophils during ICS therapy, thereby modulating therapeutic responses in asthma.¹⁷⁵

Another GWAS for ICS response was performed in asthma subjects from the NHLBI CAMP, *Asthma Clinical Research Network* (ACRN), and *Childhood Asthma Research and Education Network*. This GWAS identified SNPs in the *T* gene (rs3127412 and rs6456042) that were associated with changes in FEV₁ during ICS treatment. Subsequent detailed genotyping identified SNPs (rs3099266, rs2305089, rs1134481) within functional regions of the *T* gene.¹⁷⁷ Pharmacogenetic loci in the glucocorticoid pathway, *GLCC11*, and the *T* gene account for a small proportion of the interindividual variability for ICS therapeutic responses in asthma. It has yet to be determined whether these loci have additive effects with other pathway-related gene variants or are independent determinants of ICS response. Future pharmacogenetic studies in independent, large clinical trial cohorts or genotype-stratified trials are necessary to confirm and characterize these genes associated with ICS therapeutic responses and develop a genetic profile that may be used to predict therapeutic responsiveness to corticosteroids.

CYSTEINYL LEUKOTRIENE PHARMACOGENETICS

The cysteinyl leukotriene pathway is an inflammatory pathway containing potential pharmacogenetic loci for two classes of antiasthma therapies: 5-lipoxygenase (5-LO) inhibitors (e.g., zileuton) and cysteinyl leukotriene antagonists (e.g., montelukast and zafirlukast). The cysteinyl leukotriene biosynthetic pathway is initiated by 5-LO (encoded by *ALOX5*) followed by *leukotriene A₄ hydrolase* (*LTA4H*), and *leukotriene C₄ synthase* (*LTC4S*). Synthesized leukotrienes

eTable 45-3 Pharmacogenetic Candidate Genes in Asthma*

Drug Classes	Gene	Associated Loci	Study Designs	Response Phenotype	Sample Size	References
Inhaled glucocorticoids: (Fluticasone, budesonide, flunisolide, triamcinolone)	<i>CRHR1</i>	rs242941, rs1876828	Candidate gene study	FEV ₁ response	1117	167
	<i>STIP1</i>	rs2236647, rs6591838, rs1011219	Candidate gene study	FEV ₁ response	382	169
	<i>TBX21</i>	rs2240017 (His33Gln)	Candidate gene study	Bronchoprotection	53, 701	172, 173
	<i>GLCCI1</i>	rs37972=rs37973	GWAS	FEV ₁ response	1053	175
	<i>T</i> Gene	rs3127412, rs6456042, rs3099266, rs2305089	GWAS	FEV ₁ response	815	177
	<i>ADCY9</i>	rs2230739 (Met ⁷⁷² Ile)	Candidate gene study	Long-term FEV ₁ response	86	174
Leukotriene receptor modifiers:	<i>ALOX5</i>	Promoter repeat, rs892690, rs2029253, rs2115819	Candidate gene study	FEV ₁ response	114, 577	178, 179
5-lipoxygenase inhibitors (ABT-761 and zileuton)	<i>LTC4S</i>	rs272431	Candidate gene study	FEV ₁ response	577	180
	<i>MRP1</i>	rs215066, rs119774	Candidate gene study	FEV ₁ response	577	180
Cysteinyl leukotriene antagonists (montelukast)	<i>ALOX5</i>	Promoter repeat, rs2115819	Candidate gene study	FEV ₁ response	61, 174	181, 182
	<i>LTC4S</i>	rs730012	Candidate gene study	Exacerbation risk	61	182
	<i>LTA4H</i>	rs266845	Candidate gene study	Exacerbation risk	61	182
	<i>MRP1</i>	rs119774	Candidate gene study	FEV ₁ response	61	182
Inhaled β₂-adrenergic receptor agonists:	<i>CRHR2</i>	rs7793837	Candidate gene study	Acute FEV ₁ bronchodilation	1186 2145	214, 218
Short-acting β-agonists (Albuterol)	<i>ADCY9</i>	rs2230739 (Met ⁷⁷² Ile)	Candidate gene study	Acute FEV ₁ bronchodilation	436 2145	174, 218
	<i>ADRB2</i>	rs1042713 (Gly ¹⁶ Arg)	Retrospective and prospective, genotype stratified	Acute FEV ₁ bronchodilation	16–707	199, 200, 202
				Long-term PEFR response	78	164
			Candidate gene study	Long-term PEFR response	108	201
	<i>ARG1</i>	rs2781659, rs2781667	Candidate gene study	Acute FEV ₁ bronchodilation	200–2145	215, 216, 218
	<i>ARG2</i>	rs7140310, rs10483801	Candidate gene study	Acute FEV ₁ bronchodilation	200	216
	<i>NOS3</i>	rs1799983 (Asp ²⁹⁸ Glu)	Candidate gene study	Acute FEV ₁ bronchodilation	81	375
	<i>SPATS2L</i>	rs295137	GWAS	Acute FEV ₁ bronchodilation	2145	218
	<i>ADCY9</i>	rs2230739 (Met ⁷⁷² Ile)	Candidate gene study	Long-term FEV ₁ response	86	213
	<i>ADRB2</i>	rs1042713 (Gly ¹⁶ Arg)	Candidate gene study	Long-term PEFR response	48–108	201, 203
Long-acting β-agonists (salmeterol and formoterol)			Retrospective and prospective, genotype-stratified	No effect on PEFR response	87–2655	201, 204–207
			prospective, genotype-stratified	Bronchoprotection	87, 152	207, 376
			prospective, genotype-stratified	Preference for montelukast or LABA as add-on to ICS	62	208

*Biologic candidate genes are summarized by drug class, associated polymorphisms (rs number and coding change, if relevant), study design, number of cohorts studied, population size, and response phenotype for which a pharmacogenetic effect has been detected.

ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 second; GWAS, genome-wide association study; LABA, long-acting β-agonists; PEFR, peak flow rate.

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are transported to the extracellular space by *multidrug resistance protein 1* (MRP1) and activate *cysteinyl leukotriene receptors* (CYSLTR1 and CYSLTR2).

ALOX5 has a tandem repeat polymorphism in its promoter that has been associated with changes in lung function during treatment with leukotriene antagonists.^{178,179} An analysis of the cysteinyl leukotriene pathway in asthmatics treated with zileuton also identified SNPs in ALOX5 (rs892690, rs2029253, and rs2115819), LTC4S (rs272431), and MRP1 (rs215066 and rs119774) that were associated with changes in lung function during 5-LO inhibition.¹⁸⁰ Variation in leukotriene pathway genes has been reported in additional, smaller studies. These results support the finding that some of the variation in therapeutic responses to leukotriene modifiers is regulated by pharmacogenetic mechanisms (see eTable 45-3).^{90,180,182}

β₂-ADRENERGIC RECEPTOR PHARMACOGENETICS

Inhaled β-agonist treatment for asthma includes *short-acting β-agonists* (SABA) and *long-acting β-agonists* (LABA).¹⁸³ β-Agonists activate a G protein–coupled receptor pathway via adenylyl cyclase type 9 that regulates airway smooth muscle relaxation.¹⁷⁴ Inhaled β-agonists are the most commonly used treatment for asthma despite having been associated with very rare life-threatening adverse responses since the 1960s.¹⁸⁴⁻¹⁸⁸

While various analyses have attempted to explain these “mini-epidemics” of asthma mortality,^{10,11,184-191} the U.S. Food and Drug Administration issued a boxed warning for all LABA-containing inhalers regarding the risk for life-threatening exacerbations.¹⁹² This LABA safety controversy is being evaluated in 46,800 asthma subjects who are currently being recruited for the U.S. Food and Drug Administration–mandated international LABA safety study.^{192,193} Pharmacogenetic studies have attempted to identify genetic markers for β-agonist response to identify a subgroup that is susceptible to these serious adverse effects. These studies have primarily focused on genes related to the β₂-adrenergic receptor and nitric oxide synthetic pathways (see eTable 45-3).

The gene encoding the β₂-adrenergic receptor (ADRB2) has a single exon and is located on chromosome 5q31 with more than 49 polymorphisms identified.^{194,195} The most studied of these ADRB2 polymorphisms is the common coding variant, Gly¹⁶Arg.^{194,196} In vitro, receptors expressing the Gly¹⁶ variant show increased receptor down-regulation in response to β-agonist stimulation compared to Arg¹⁶.^{197,198}

Two early pharmacogenetic studies of ADRB2 in asthmatic children demonstrated that Arg¹⁶ homozygotes experienced a greater bronchodilator response to a single dose of albuterol compared to Gly¹⁶ homozygotes.^{91,92} This effect of Gly¹⁶Arg genotypes on acute SABA bronchodilator response was confirmed in small asthma populations.^{199,200} In contrast, pharmacogenetic studies of long-term, regular SABA treatment in two independent clinical trial cohorts demonstrated effects on therapeutic responses: Arg¹⁶ homozygotes experienced a decline in *peak flow rate* (PEFR) during chronic SABA treatment while Gly¹⁶ homozygotes did not experience changes in PEFR.^{201,202}

In a genotype-stratified, crossover trial, the ACRN, Gly¹⁶ and Arg¹⁶ homozygotes were randomized to treatment with regular albuterol or placebo. Gly¹⁶ homozygotes showed an increase in PEFR during regular albuterol treatment while Arg¹⁶ homozygotes showed no changes in PEFR with regular albuterol but had an increase in PEFR during as-needed albuterol treatment (Fig. 45-6). In addition, regular albuterol treatment resulted in decreased rescue inhaler use and asthma symptom scores in Gly¹⁶ homozygotes, while Arg¹⁶ homozygotes experienced a deterioration of these secondary outcomes.¹⁶⁴ Although the adverse effects of regular SABA treatment in Arg¹⁶ homozygotes are important to understand, asthma guidelines do not recommend regular scheduled SABA in asthma. However, regular scheduled LABA is used to control asthmatics who are symptomatic on ICS alone. Thus, pharmacogenetic effects related to LABA exposure would have major therapeutic implications.

The genotypic effects of Gly¹⁶Arg during long-term LABA therapy were evaluated in two small trial arms from larger NHLBI ACRN clinical trials. Results from these trials showed a potential for reduced effectiveness of LABA in Arg¹⁶

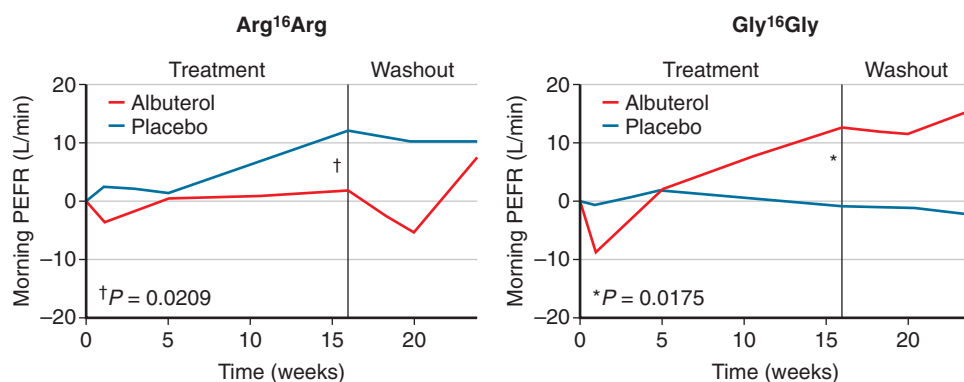


Figure 45-6 The Asthma Clinical Research Network Beta Agonist Response by Genotype (BARGE) Trial. The BARGE trial evaluated the effect of genotypes in response to regular short-acting β-agonist (albuterol) therapy or placebo given four times daily for 16-week treatment periods. For patients with the Gly/Gly genotype, the PEFR improved significantly more when they were treated with albuterol (red line) compared with placebo. In contrast, patients with the Arg/Arg genotype improved more when treated with placebo (blue line) compared with albuterol. PEFR, peak flow rate. (Adapted from Israel E, Chinchilli VM, Ford JG, et al: Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 364:1505–1512, 2004. Figure 3.)

homozygotes.²⁰³ Subsequent prospective clinical trials and pharmacogenetic analyses with larger cohorts including two genotype-stratified trials did not show evidence for reduced therapeutic effectiveness of LABA therapy in Arg¹⁶ homozygotes compared to Gly¹⁶ homozygotes.^{201,204-207} Interestingly, in one of these prospective genotype-stratified trials, Gly¹⁶ homozygotes experienced a more prolonged protection from methacholine-induced bronchoconstriction than was observed in Arg¹⁶ homozygotes.²⁰⁷ Another genotype-stratified study randomized 62 Arg¹⁶ homozygotes to either montelukast or LABA in addition to ICS therapy and demonstrated greater symptom control with the addition of montelukast. This study suggested that the Gly¹⁶Arg locus could interact with other therapies in asthma.²⁰⁸

In contrast to a common variant such as Gly¹⁶Arg that likely exhibits smaller effects, it is possible that rare genetic variants with strong effects might be responsible for some of the uncommon and severe adverse responses associated with LABA treatment in asthma (see Fig. 45-4). A rare variant within the fourth transmembrane domain of ADRB2, Thr¹⁶⁴Ile, results in a protein with decreased β_2 -adrenergic receptor ligand binding, coupling to G_s protein, and sequestration in response to SABAs and LABAs in vitro.^{209,210} This rare variant also significantly impairs the binding of salmeterol to its “exosite,” or secondary binding site, on the β_2 -adrenergic receptor.²¹⁰ The Ile¹⁶⁴ allele was associated with an increased risk of airflow obstruction and reduced lung function in a cross-sectional population-based study of nearly 60,000 subjects.²¹¹ Thr¹⁶⁴Ile and a 25 base pair insertion variant found only in African Americans, have also been associated with severe exacerbations requiring hospitalization in asthma patients treated with a LABA. Thr¹⁶⁴Ile has also been associated with poor symptom control during LABA treatment in two independent cohorts. This finding of a rare genetic variant and adverse LABA effects has the potential to identify a very important at-risk asthma subpopulation. Thus, rare variants such as those in ADRB2 are potential biomarkers for more personalized, precise guideline-based treatment strategies in the small subset of asthmatics that have altered responsiveness to the combination therapy of a LABA with ICS.²¹² In addition, a recent study combining admixture mapping and GWAS in Puerto Ricans and Mexican asthmatic children from GALA has identified rare variants in solute carrier genes associated with bronchodilator response to SABAs, providing further evidence for the role of rare genetic variation as pharmacogenetic loci.^{212a}

Association studies of candidate genes related to the β_2 -adrenergic receptor pathway have identified additional common polymorphisms that have been associated with the acute bronchodilator response to SABA. ADCY9 is a canonical β_2 -adrenergic receptor pathway gene with a common coding variant, Ile⁷⁷²Met, associated with increased acute FEV₁ bronchodilator response to albuterol during ICS therapy in children from the CAMP cohort.¹⁷⁴ The effect of Met⁷⁷²Ile genotypes on the bronchodilator response to β -agonists during ICS therapy was also reported in a Korean population treated with a LABA (formoterol).²¹³ CRHR2 is another pathway-related gene with SNPs that have been associated with the SABA response. CRHR2 encodes the corticotropin-releasing hormone receptor-2, a

G-coupled protein receptor that regulates relaxation of airway smooth muscle through a signaling pathway similar to that of the β_2 -adrenergic receptor (via activation of adenylyl cyclase and protein kinase A). Five SNPs in CRHR2 were associated with acute bronchodilator responses to SABA in asthma subjects from three independent clinical trial cohorts.²¹⁴

Association studies of genes indirectly related to the β_2 -adrenergic receptor pathway have identified variants within the nitric oxide biosynthetic pathway associated with acute SABA bronchodilator response. An association study of 111 genes from the β_2 -adrenergic receptor and glucocorticoid pathways in subjects from the CAMP cohort and three independent trial cohorts identified a SNP in *arginase 1* (ARG1), rs2781659, which was associated with an acute bronchodilator response.²¹⁵ SNPs in ARG2 have also been associated with a SABA bronchodilator response.²¹⁶ Arginase 1 and 2 metabolize L-arginine, which is a natural substrate for nitric oxide synthase, resulting in the production of nitric oxide. Nitric oxide is an endogenous bronchodilator; therefore, ARG1 and ARG2 polymorphisms may alter airway smooth muscle relaxation during β -agonist treatment.²¹⁷

Finally, a GWAS reported by Himes and colleagues²¹⁸ identified a novel genetic locus for acute SABA bronchodilator responses. The primary GWAS analyzed 1644 asthmatics from six clinical trial cohorts with replication assessed in 1051 subjects from SARP and a Dutch asthma cohort. A SNP within the promoter region of the *spermatogenesis associated, serine-rich 2-like* gene (rs295137 in SPATS2L) was associated with the acute bronchodilator response to albuterol. In human airway smooth muscle cells, the functional importance of SPATS2L in the β_2 -adrenergic receptor pathway was confirmed after a knockdown of this gene resulted in increased β_2 -adrenergic receptor expression.²¹⁸ The investigators also confirmed previous associations for three candidate genes for albuterol bronchodilator response: ADCY9, CRHR2, and ARG1.^{174,214,215,218}

LIMITATION OF CURRENT PHARMACOGENETIC ASSOCIATIONS AND FUTURE DIRECTIONS

Most of the pharmacogenetic associations for therapeutic response do not account for a significant amount of the variability in drug responses. In part, this is because multiple genes influence these responses. In addition, pharmacogenetic analysis was not the primary outcome of most of these studies and sample sizes were too small to assess single or multiple gene interactions. Furthermore, when the combination of a LABA and ICS are used, polymorphisms in the β_2 -adrenergic receptor pathway might result in a negative treatment response that interacts with polymorphisms in the same pathway or an alternative (i.e., glucocorticoid) pathway to obscure associations.

Pharmacogenetic studies have the potential to identify the subgroup of asthmatics who are more or less responsive to biologic therapies currently under development. Biologic therapies are more expensive and have the potential to cause unwanted adverse responses. Thus, pharmacogenetic therapeutic “biomarkers” that identify susceptible asthmatics should facilitate development and registration of biologic therapies. Pitracinra is a molecular inhibitor of the

IL4 α receptor subunit that inhibits both IL-4 and IL-13, which are important in the regulation of Th2 allergic inflammation. In a phase 2b clinical trial, specific variants in the gene coding for the *IL4 α receptor subunit* (*IL4RA*) have been associated with changes in antigen-induced bronchial hyperresponsiveness in atopic asthmatics treated with pirarctinra, and improvements in asthma exacerbation frequency.^{93,102} These results are an excellent example of the use of a pharmacogenetic “biomarker” to identify the subset (approximately 35 percent) of responders to this IL4 α receptor antagonist.

Pharmacogenetic studies in asthma had initially been limited to candidate gene studies in smaller clinical trial cohorts; however, investigators have more recently performed GWAS which have identified novel pharmacogenetic loci (see eTable 45-3). *In vitro* studies have been used to validate the function of these SNPs. Future pharmacogenetic studies in independent, large clinical trial cohorts or genotype-stratified trials will be necessary to evaluate the importance of these gene variants, to confirm previous associations, and to determine whether these polymorphisms act independently or have additive effects on therapeutic responses to ICS, inhaled β -agonists, leukotriene modifiers, and other, newer asthma therapies. Understanding the pharmacologic and genetic basis of therapeutic responsiveness in asthma may lead to the development of more effective therapeutic agents. These approaches, when performed in adequately powered pharmacogenetic trials using unbiased methodology (GWAS), have delineated genetic determinants of pharmacologic treatment, with both beneficial and adverse responses, in other complex diseases such as those currently under investigation in the National Institutes of Health Pharmacogenomics Research Network.^{219,220} Thus, future precise therapeutic approaches in asthma will include the use of genetic pharmacogenetic profiles.

GENETIC STUDIES OF COPD SUSCEPTIBILITY

EVIDENCE THAT LUNG FUNCTION IMPAIRMENT AND COPD ARE HERITABLE

COPD results from the interaction of different genetic factors and environmental exposures. COPD is a common, complex, and heterogeneous airway disease characterized by chronic bronchitis, mucus hypersecretion, emphysema with the loss of elastic recoil, and destruction of small airways.²²¹ Tobacco smoke is the most common environmental exposure known to cause COPD while biomass smoke is an established exposure in developing countries.²²²⁻²²⁴ The diagnosis of COPD is based on spirometric measurements, and the severity of COPD, in part, is based on the level of FEV₁ as the percentage predicted.² Thus, the major phenotype for genetic studies evaluating COPD susceptibility and severity is the presence and degree of airflow obstruction. This definition raises an important question: how to interpret genetic associations with reduced lung function in a disease defined by airflow obstruction? The question becomes whether disease susceptibility genes are related

directly to reduced pulmonary function or whether lung function modifier genes accelerate loss of pulmonary function over time.

There is evidence of overlap between gene variants associated with disease severity in asthma and COPD cohorts. Similar genetic associations have been reported for lung function in both obstructive airway diseases. In addition, exposure to tobacco smoke (passive and active) alters asthma phenotypes.^{139,225} Genetic studies related to COPD susceptibility usually adjust for environment interactions with tobacco smoke exposure due to its strong association with risk for COPD. Despite this strong association, lung function decline is highly variable among unrelated cigarette smokers, suggesting genetic factors as well as environmental exposures are important in the pathogenesis of COPD.²²⁶

Family and twin-based studies demonstrate that lung function has an estimated heritability up to 100% and that 20% to 60% of the variance in lung function could be influenced by familial factors.^{45,46,227-232} Epidemiologic studies have demonstrated that COPD is more prevalent among the relatives of individuals with COPD than in a population of unrelated individuals, strongly suggesting heritable factors.²³³ However, these factors do not follow a simple mendelian pattern of inheritance because of interactions between multiple genetic and environmental factors.^{228,234,235} Heritability in COPD was demonstrated in a study in which first-degree relatives of probands with COPD had a lower FEV₁ and FEV₁/FVC ratio than unrelated controls. In addition, reduced lung function was only identified in first-degree relatives who had currently or previously smoked cigarettes, suggesting interactions between hereditary and environmental influences.²³⁶ The evidence of heritable factors for COPD susceptibility provides a rationale for genetic studies to identify genes that confer susceptibility and risk for disease progression and severity.

FAMILY-BASED LINKAGE STUDIES FOR LUNG FUNCTION IMPAIRMENT AND COPD

In contrast to asthma, COPD is an adult-onset disease and therefore has been studied less often by family-based linkage studies and mostly by case-control population-based studies including GWAS. The only single gene variants (mendelian) known to be directly associated with COPD are in genes coding for *serpin peptidase inhibitor, clade A (α_1 -antitrypsin), member 1* (*SERPINA1*) on chromosome 14q31 for which more than 100 rare variants have been identified as genetic determinants for emphysema and COPD.²³⁷ The relationship between α_1 -antitrypsin (A1AT) deficiency and emphysema was initially described in 1964; however, it was not until 1976 that gene variants in *SERPINA1* were identified as the cause of A1AT deficiency.²³⁸⁻²⁴⁰ A1AT deficiency is inherited through an autosomal codominant pattern of inheritance resulting in a rare, early-onset obstructive lung disease accounting for only 1% to 2% of all cases of COPD.²⁴¹ Thus, variants in other genes contribute to the pathogenesis of COPD in the vast majority.

Most linkage studies for COPD susceptibility have evaluated lung function in related subjects from the general population or susceptibility in families ascertained through

probands diagnosed with early-onset COPD.^{45-47,242} A linkage study in a Hutterite general population identified a locus linked to FEV₁/FVC ratio on chromosome 5q33, which was confirmed in a Utah reference population.^{45,46} The first linkage studies for susceptibility to COPD and lung function were performed in a cohort of families with severe, early-onset COPD by the *Boston Early-Onset COPD* (BEOCOPD) study group, which identified linkage at loci on chromosome 12p12 and 19q for both moderate airflow obstruction (FEV₁ < 60% of predicted) and mild airflow obstruction (FEV₁ < 80% of predicted).^{47,242}

Detailed mapping of the chromosome 12p region in COPD cases and controls from the *National Emphysema Treatment Trial* (NETT) and the *Normative Aging Study* (NAS) subsequently identified a SNP associated with COPD in the *SRY* (*sex determining region Y*)-box 5 gene (*SOX5*). Detailed mapping of the chromosome 19q region identified SNPs in the *transforming growth factor-β1* gene (*TGFB1*) as associated with COPD.²⁴³ Interestingly, both regions on chromosome 12p and 19q have also been identified as susceptibility loci for asthma.^{24,26} *SOX5* functions in lung development while *TGFB1* codes for a proinflammatory cytokine that has been intensively studied as a candidate gene for COPD.^{244,245} The *TGFB1* locus on chromosome 19q was identified as a COPD susceptibility locus and was associated with COPD in the BEOCOPD cohort.^{243,251-254} A *TGFB1* promoter SNP has also been associated with asthma susceptibility and severity.²⁴⁶⁻²⁴⁹ *TGFβ1* is a multifunctional cytokine secreted by airway epithelial cells, macrophages, fibroblasts, and Th2 lymphocytes to regulate cellular growth and development, tissue repair and fibrosis, and inflammatory immune responses.²⁴⁴

Other studies from the BEOCOPD cohort identified evidence of linkage for loci on chromosome 2q with baseline FEV₁ and FEV₁/FVC. This locus on chromosome 2q was also linked with a very high likelihood (LOD score of approximately 5) to FEV₁/FVC in Dutch families with asthma.^{18,47} These early genetic approaches in COPD identified relevant biologic COPD susceptibility genes and also showed evidence that some of these genetic loci overlap with asthma loci, thus providing evidence for pathogenic similarities in asthma and COPD.^{18,24,26,47,242}

CANDIDATE GENE ASSOCIATION STUDIES FOR LUNG FUNCTION AND COPD

Initial candidate gene association studies for COPD susceptibility focused on genes from inflammatory, protease-antiprotease, and oxidant-antioxidant pathways (eTable 45-4). These early studies were limited by small cohorts, absence of a standardized COPD diagnosis, and analyses that did not adjust for population stratification. Two meta-analyses of 12 candidate genes demonstrated that most gene variants previously associated with COPD were not true associations.^{250,251} The loci that have been consistently associated with susceptibility to COPD include *TGFB1*, *GSTM1*, *GSTP1*, *ADAM33*, and *MMP12* (see eTable 45-4).^{54,56,243,252-255}

ANTIOXIDANT PATHWAY GENES AND COPD SUSCEPTIBILITY

Genes within the antioxidant pathway regulate the metabolism of reactive oxygen and nitrogen species delivered from tobacco smoking and, thus, are appropriate biologic candidate genes for COPD (see eTable 45-4). The most extensively studied antioxidant pathway-related genes include those that code for microsomal *epoxide hydrolase* (*EPHX1*) and *glutathione S-transferase* (*GST*) subunits *Pi-1*, *Mu-1*, and *Theta-1* (*GSTP1*, *GSTM1*, *GSTT1*). Small association studies of polymorphisms in *EPHX1*, *GSTP1*, and *GSTM1* have shown significant associations with COPD.^{250,251,256-264} Subsequent meta-analyses have combined these studies to confirm variant associations for COPD susceptibility with antioxidant pathway genes in different population-based cohorts.^{251,265} In addition, polynucleotide deletions at *GSTM1* and *GSTT1* have been associated with lung function decline in subjects from the Swiss Cohort Study on Air Pollutants and Lung and Heart Diseases in Adults cohorts demonstrating the importance of gene-gene interactions in COPD.²⁶⁶

ADAM33 IS A LOCUS FOR ACCELERATED LUNG FUNCTION DECLINE AND COPD

ADAM33 is among the most replicated genes for asthma susceptibility and associations with lung function decline in asthma subjects.^{21,50-52,55} *ADAM33* polymorphisms have been associated with lung function decline and baseline airflow obstruction in general population cohorts, suggesting a role for *ADAM33* in the pathogenesis of COPD (eTable 45-5).⁵⁶ An association study of *ADAM33* in long-term smokers identified five SNPs significantly associated with COPD defined by lung function, suggesting that *ADAM33* is a susceptibility locus for COPD and pulmonary function abnormalities in cigarette smokers.⁵⁴

MMP12 AND COPD SUSCEPTIBILITY

The gene coding for *matrix metalloproteinase 12* (*MMP12*) has a promoter SNP (rs2276109) associated with lung function and COPD in a large association study of seven independent cohorts totaling 8300 subjects. *Reference sequence* (rs)2276109 was associated with COPD and lung function in prior cigarette smokers but not among never-smokers.²⁵⁵ *MMP12* is highly expressed in alveolar macrophages from cigarette smokers compared to non-smokers and appears to have important functions in the development of emphysema during cigarette smoke exposure.^{267,268}

GENOME-WIDE ASSOCIATION STUDIES OF LUNG FUNCTION IN THE GENERAL POPULATION

Decreased pulmonary function is important in the diagnosis of COPD, for the characterization of disease severity, and as a predictor of overall survival.^{44,269} GWAS for lung

eTable 45-4 Major Susceptibility Loci for Chronic Obstructive Pulmonary Disease or Emphysema by Biologic Pathway*

COPD/Emphysema Candidate Genes by Pathway	Gene ID	Discovery Method	Initially Reported Loci	Associated Phenotypes	References
INFLAMMATORY PATHWAY					
Interleukin-6 Receptor	<i>IL6R</i>	GWAS	rs4129267	COPD, asthma, lung function, bronchial responsiveness	106, 134, 135
Interleukin-6	<i>IL6</i>	Candidate gene	rs1800795	COPD, lung function decline, serum IL-6	279–281
Transforming Growth Factor- β 1	<i>TGFB1</i>	Linkage, mapping	rs2241712, rs1982073, rs6957	COPD, lung function	47, 243
PROTEOLYTIC PATHWAY					
Serpin Peptidase Inhibitor, Clade A	<i>SERPINA1</i>	Protein electrophoresis	rs28929474 (Glu ³⁴⁷ Lys)	α_1 -Antitrypsin deficiency, COPD, emphysema	237–240
Matrix Metalloproteinase-12	<i>MMP12</i>	Candidate gene	rs2276109	COPD, lung function	255
A Disintegrin And Metalloprotease-33	<i>ADAM33</i>	Candidate gene	rs3918396 (Ile ⁷¹⁰ Val), rs543749	COPD, asthma, lung function, lung function decline, bronchial responsiveness	21, 50–52, 54–56
OXIDATIVE STRESS AND ANTIOXIDANT PATHWAY					
Microsomal Epoxide Hydrolase	<i>EPHX1</i>	Candidate gene	rs2234922 (His ¹³⁹ Arg)	COPD, SABA bronchodilation	250, 251, 256–261, 343
Glutathione S-Transferase Pi-1 Subunit	<i>GSTP1</i>	Candidate gene	rs1695 (Ile ¹⁰⁵ Val)	COPD	250, 263, 264
Glutathione S-Transferase Mu-1 Subunit	<i>GSTM1</i>	Candidate gene	Gene deletion (null genotype)	COPD, lung function decline	259, 261, 262, 266
Family with Sequence Similarity 13, Member A	<i>FAM13A</i>	GWAS	rs2869967	COPD, lung function, lung cancer	139, 272, 317, 321
Iron Responsive Element Binding Protein-2	<i>IREB2</i>	GWAS	rs8034191	COPD, lung cancer	288, 302–304, 306–310
LUNG DEVELOPMENT PATHWAY					
SRY (Sex Determining Region Y)-Box 5	<i>SOX5</i>	Linkage, mapping	rs11046966	COPD	47, 243
Hedgehog-Interacting Protein	<i>HHIP</i>	GWAS	rs13147758	COPD, lung function	139, 270–272, 285–288
<i>Drosophila</i> Gene Bicaudal D Homolog 1	<i>BICD1</i>	GWAS	rs10844154	Emphysema, telomere length	335, 339
RAB Protein, Member RAS Oncogene Family	<i>RAB4B</i>	GWAS	rs7937, rs2604894	COPD	313
NICOTINE DEPENDENCE PATHWAY					
α 3-Nicotinic Acetylcholine Receptor	<i>CHRNA3</i>	GWAS	rs1051730	COPD, smoking behavior, lung cancer	288, 302–304, 306–310
α 5-Nicotinic Acetylcholine Receptor	<i>CHRNA5</i>	GWAS	rs8034191	COPD, smoking behavior, lung cancer	288, 302–304, 306–310
Cytochrome P-450 2A6	<i>CYP2A6</i>	GWAS	rs7937, rs2604894	COPD, smoking behavior, lung cancer	307, 312, 313, 331

*Susceptibility genes for COPD and emphysema are categorized by molecular pathway. These loci have been identified through linkage studies, genome-wide association studies (GWAS), or candidate gene association studies. Genes are summarized by full gene name, gene identification (ID) acronym, initial locus (by single nucleotide polymorphism rs number), and associated phenotypes.

eTable 45-5 Major Lung Function Candidate Genes from General Population Studies by Biologic Pathway*

Lung Function Candidate Genes by Pathway	Gene ID	Discovery Method	Initially Reported Loci	Associated Phenotypes	References
INFLAMMATORY PATHWAY					
Interleukin-6 Receptor	<i>IL6R</i>	GWAS	rs4129267	COPD, asthma, lung function, bronchial responsiveness	106, 134, 135
Transforming Growth Factor-β1	<i>TGFB1</i>	Linkage, mapping	rs2241712, rs1982073, rs6957	COPD, lung function	47, 243
Transforming Growth Factor-β2	<i>TGFB2</i>	GWAS	rs993925	Lung function	289
Histone Deacetylase-4	<i>HDAC4</i>	GWAS	rs12477314	Lung function	289
Thrombospondin Type 1 Domain Containing-4	<i>THSD4</i>	GWAS	rs12899618	Lung function	271, 272
Tensin-1	<i>TNS1</i>	GWAS	rs2571445	Lung function	271, 272
5-Hydroxytryptamine Receptor-4	<i>HTR4</i>	GWAS	rs11168048, rs6889822	Lung function	271, 272
PROTEOLYTIC PATHWAY					
Matrix Metalloproteinase-12	<i>MMP12</i>	Candidate gene	rs2276109	COPD, lung function	255
A Disintegrin And Metalloprotease-33	<i>ADAM33</i>	Candidate gene	rs3918396 (Ile ⁷¹⁰ Val), rs543749	COPD, asthma, lung function, lung function decline, bronchial responsiveness	21, 50–52, 54–56
A Disintegrin And Metalloprotease-19	<i>ADAM19</i>	GWAS	rs2277027	Lung function	272
Matrix Metalloproteinase-15	<i>MMP15</i>	GWAS	rs12447804	Lung function	289
Advanced Glycosylation End Product Receptor	<i>AGER</i>	GWAS	rs2070600 (Gly ⁸²⁵ Ser)	Lung function	271, 272
OXIDATIVE STRESS AND ANTIOXIDANT PATHWAY					
Glutathione S-Transferase Omega-1 Subunit	<i>GSTO2</i>	GWAS	rs156697 (Asn ¹⁴² Asp)	Lung function	134
Family with Sequence Similarity 13, Member A	<i>FAM13A</i>	GWAS	rs2869967	COPD, lung function, lung cancer	139, 272, 317, 321
C-terminal Domain-Containing Glutathione S-Transferase	<i>GSTCD</i>	GWAS	rs17331332	Lung function	272
Cell Division Cycle 123 Homolog	<i>CDC123</i>	GWAS	rs7068966	Lung function	289
LUNG DEVELOPMENT PATHWAY					
Hedgehog-Interacting Protein	<i>HHIP</i>	GWAS	rs13147758	COPD, lung function	271, 272, 285–288
Patched 1, a Receptor for Hedgehog Proteins	<i>PTCH1</i>	GWAS	rs16909898	Lung function	139, 272
G Protein–Coupled Receptor 126	<i>GPR126</i>	GWAS	rs3817928	Lung function	272
Retinoic Acid Receptor β	<i>RARB</i>	GWAS	rs1529672	Lung function	289
Craniofacial Development Protein 1	<i>CFDP1</i>	GWAS	rs2865531	Lung function	289

*Candidate genes for lung function are categorized by molecular pathway. These loci have been identified through linkage studies, genome-wide association studies (GWAS), or candidate gene association studies in the general population and further characterized in COPD study cohorts. Genes are summarized by full gene name, gene identification (ID) acronym, initially reported locus (by single nucleotide polymorphism rs number), and associated phenotypes.

function, performed in general population cohorts, have provided insight into mechanisms that contribute to an accelerated loss of lung function and impairment in baseline pulmonary function in both COPD and asthma (see eTable 45-5). GWAS in two general populations derived from large cardiovascular epidemiology cohorts have identified candidate genes from different biologic pathways that have a potential biologic role in the susceptibility and progression of COPD and emphysema.^{134,270-272} It is important to note that these general populations may have included subjects with unrecognized asthma, COPD, or emphysema; however, these GWAS are very large and represent genetic loci for lung function genes that primarily reflect these general population samples. In both asthma and COPD, it has been useful to study candidate genes for lung function identified in these general population studies to identify genetic loci that may contribute to reduced lung function and, thus, in COPD to susceptibility and severity. These candidate genes are discussed in the context of their initial identification in general populations as well as biologic plausibility and studies in cohorts with established COPD.

GSTO2 AND IL6R AS LOCI FOR LUNG FUNCTION

The first GWAS for lung function was performed in the Framingham Heart Study cohort and identified a coding SNP in *glutathione-S-transferase omega-2* (*GSTO2*) on chromosome 10q25 (Asn¹⁴²Asp, rs156697) that was associated with FEV₁ and FVC, and a SNP in *IL6R* (rs4129267) that was associated with forced expiratory flow rates.¹³⁴ The soluble IL-6 receptor forms a complex with IL-6, which is involved in the inflammatory responses initiated by cigarette smoke exposure. IL-6 levels are elevated in the airways of subjects with COPD compared to healthy nonsmokers.²⁷³⁻²⁷⁵ Sputum and serum IL-6 concentrations increase during COPD exacerbations and have been associated with reduced lung function and accelerated lung function decline in subjects with COPD, asthma, and the general population.^{136,276-278} *IL6* variants have been associated with serum IL-6 concentrations in control subjects from the Cardiovascular Health Study as well as COPD and accelerated lung function decline in other cohorts.²⁷⁹⁻²⁸¹ The *IL6R* locus has also been associated with asthma susceptibility in a GWAS of European white subjects and is in LD with a coding SNP in *IL6R*, Asp³⁵⁸Ala, associated with lung function in more severe asthma, demonstrating the overlapping biologic mechanisms in these obstructive airway diseases.^{106,135}

HEDGEHOG-INTERACTING PROTEIN GENE AS A LOCUS FOR LUNG FUNCTION

Large GWAS for lung function, the CHARGE and the SpiroMeta consortia (general population samples), identified SNPs on chromosome 4q31 in *HHIP* as associated with FEV₁/FVC ratio.²⁷⁰⁻²⁷² *HHIP* regulates the hedgehog signaling important in lung branching morphogenesis and airway smooth muscle differentiation in murine models.²⁸²⁻²⁸⁴ Altered lung development might result in impaired respiratory reserve and increase the risk for COPD, particularly during exposure to tobacco smoke. Subsequent association studies have confirmed the role of gene variants in *HHIP* as

an important gene in COPD susceptibility.²⁸⁵⁻²⁸⁸ In addition, gene variants in *HHIP* have also been associated with reduced lung function in asthma, demonstrating evidence for overlapping genetic regulation of lung function in these two diseases.¹³⁹

TWO LARGE GENERAL POPULATION CONSORTIA IDENTIFY SEVEN LOCI FOR LUNG FUNCTION

Two large meta-analyses by the CHARGE and SpiroMeta consortia identified seven novel loci for lung function (see eTable 45-5).^{271,272} These loci regulate processes related to lung development (*ADAM19*, *GPR126*), inflammation (*HTR4*, *THSD4*), tissue remodeling (*ADAM19*, *AGER*, *HTR4*, *THSD4*, *TNS1*), and the antioxidant pathway (*GSTCD*). These gene targets have been evaluated in subsequent association studies. For COPD, SNPs in *TNS1*, *GSTCD*, *HTR4*, *AGER*, and *THSD4* were associated with COPD susceptibility and severity (lung function) in 12 population-based cohorts. In addition, a six-SNP (0 to 12 alleles) risk score incorporating risk variants from *TNS1*, *GSTCD*, *HTR4*, *AGER*, *THSD4*, and *HHIP* resulted in a stepwise decrease in pulmonary function and increase in COPD risk in subjects with a greater number of risk variants.²⁸⁷ This additive, detrimental effect of risk variants on lung function has also been reported in asthma subjects.¹³⁹ A large-scale meta-analysis of the combined CHARGE and SpiroMeta consortia (a joint analysis of 94,612 non-Hispanic whites) identified loci on or near 16 additional genes associated with lung function in the discovery and replication cohorts, further demonstrating the complex genetic factors that influence lung function in the general population.²⁸⁹ While these loci have been associated with lung function in the general population, some of these loci represent plausible biologic candidate genes for the susceptibility or severity of obstructive airway diseases.

AGER codes for the *advanced glycosylation end product receptor* (*AGER*), which regulates the production of IL-6, TNF- α , and matrix metalloproteinases. A coding SNP in *AGER* (Gly⁸²Ser), associated with FEV₁/FVC, results in enhanced ligand binding affinity and increased cytokine/MMP production upon receptor activation.²⁹⁰ *AGER* is expressed in the human lung and has been implicated in idiopathic pulmonary fibrosis.^{291,292} *HTR4* codes for *5-hydroxytryptamine* (5-HT or serotonin) receptor-4. Activation of the 5-HT₄ receptor in airway epithelial cells promotes the production of proinflammatory cytokines, including IL-6, an inflammatory biomarker for lung function and COPD.²⁹³ *THSD4* (encodes thrombospondin, type 1, domain containing-4 gene) and *TNS1* (encodes tensin-1) potentially contribute to airway remodeling through altered signal transduction in pathways that regulate cell migration, proliferation, and adhesion in the setting of inflammation.²⁹⁴⁻²⁹⁶

ADAM19 has not been implicated in lung disease but is expressed in alveolar epithelial cells and airway smooth muscle cells.²⁹⁷ Like other ADAM proteins, including *ADAM33*, *ADAM19* has the potential to regulate proteolytic activity, cell-matrix interactions, and lung morphogenesis.^{48,49} *GPR126* codes for an adhesion G-coupled protein receptor essential for cell-cell and cell-matrix interactions

during organ development and has been consistently associated with adult height.²⁹⁸⁻³⁰¹ These gene variants in *ADAM19*, *HHIP*, and *GPR126* may affect lung development, resulting in impaired respiratory function.²⁸⁴

GENOME-WIDE ASSOCIATION STUDIES FOR COPD SUSCEPTIBILITY

α -NICOTINIC ACETYLCHOLINE RECEPTOR 3/5 GENES AS LOCI FOR COPD SUSCEPTIBILITY

The first GWAS for COPD susceptibility identified SNPs in the gene coding for the α -nicotinic acetylcholine receptor [*CHRNA3* and *CHRNA5* (*CHRNA3/5*)] on chromosome 15q25. In the BEOCPD cohort, *CHRNA3/5* was associated with baseline FEV₁.²⁸⁸ The genomic region on chromosome 15q25 tagged by these SNPs spans other genes, including *IREB2*, which have been associated with COPD in subsequent studies.³⁰² These findings suggest a gene-environment interaction on chromosome 15q25 that may modulate COPD susceptibility. Variants in *CHRNA3/5* alter nicotine dependence pathways resulting in enhanced nicotine addiction and a reduced likelihood for cigarette smoking cessation leading to the development of COPD. Interestingly, this gene has also been associated with lung cancer in cigarette smokers, suggesting overlapping mechanisms perhaps related to tobacco dependence or effects on lung inflammation^{303,304} (see Chapter 51). Alternatively, variants in a neighboring gene, *IREB2*, directly alter the antioxidant pathway, an important biologic factor for COPD susceptibility.^{302,305,306}

Two GWAS and multiple candidate gene studies have confirmed the role of *CHRNA3/5* as a locus for nicotine addiction.³⁰³⁻³¹⁰ Altered nicotine addiction and COPD risk is supported by the identification of *CYP2A6* (key enzyme for the conversion of nicotine to cotinine) as another locus that has been associated with both nicotine addiction and COPD risk.^{307,311-313} However, the *CHRNA3/5* locus contains variants in LD with SNPs in an adjacent gene *IREB2*, which codes for the iron-responsive element binding protein-2. Iron regulatory proteins regulate iron uptake, distribution, and metabolism and are activated at lower oxygen tensions.³¹⁴ Iron and iron-binding proteins show regional variability in the lungs of smokers, which may result in differences in the production of proinflammatory mediators in response to iron accumulation.^{315,316} Thus, gene variants in *IREB2* may alter the burden of oxidative injury to the lung in response to cigarette smoking and promote the development of COPD. An integrative approach identified altered gene expression of *IREB2* in lung tissue from patients with COPD, and subsequently three SNPs in *IREB2* were associated with COPD and lung function in subjects from the NETT, BEOCPD, and the International COPD Genetics Network cohorts.³⁰²

FAM13A AS A COMMON LOCUS FOR COPD AND LUNG CANCER SUSCEPTIBILITY

A second larger GWAS for COPD susceptibility performed in current or former smokers from a large international

consortium on COPD genetics [Norway, NETT, NAS, and the multicenter *Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points* (ECLIPSE) Studies] identified two SNPs in *FAM13A* on chromosome 4q22 significantly associated with COPD and replicated in the COPD Gene Study cohort and in families from BEOCPD and International COPD Genetics Network.³¹⁷ These findings are consistent with GWAS results from earlier studies for determinants of lung function impairment in general populations (CHARGE consortium).²⁷² *FAM13A* codes for the family with sequence similarity 13, member A protein and is differentially expressed in epithelial and endothelial cells in response to hypoxia.³¹⁸ It is also expressed in human alveolar type II cells during epithelial cell differentiation and is differentially expressed in cystic fibrosis.^{319,320} *FAM13A* variants have been associated with lung cancer, suggesting that this locus is a common genetic factor for these pulmonary diseases.^{321,322} *FAM13A* SNPs have not been associated with pack-years of cigarette smoking nor does adjustment for pack-years impact these associations.^{317,321,322} This factor may relate to a *Rho-GTPase-activating protein* (Rho-GAP) domain within the second to fifth exons of *FAM13A*, which may have tumor suppressor activity or impair clearance of apoptotic alveolar macrophages in response to oxidative stress from cigarette smoke exposure.³²³⁻³²⁷

CYP2A6 AS A LOCUS FOR COPD SUSCEPTIBILITY

Recent GWAS for COPD susceptibility (ECLIPSE, NETT, Norway COPD, COPD Gene, and NAS cohorts) identified a novel susceptibility locus on chromosome 19q13, which has been replicated. This COPD susceptibility locus contains genes encoding a *RAB protein* (*RAB4B*), a *melanoma inhibitory variant* (*MIA*), *EGL nine homolog 2* (*EGLN2*), and *cytochrome P-450 2A6* (*CYP2A6*) (see eTable 45-4).³¹³ *RAB4B*, *MIA*, and *EGLN2* are expressed in the developing lungs of animals and humans and thus may regulate lung development and baseline respiratory reserve.³²⁸⁻³³⁰ The *CYP2A6* locus codes for a key enzyme responsible for the metabolism of nicotine to cotinine and has been consistently associated with smoking behavior in multiple independent cohorts.^{307,311,312} The *CYP2A6* locus has also been associated with both smoking behavior and lung cancer in independent cohorts.^{312,331} The association of the same gene variants for COPD and lung cancer supports the overall importance of overlapping biologic mechanisms that may be present for both of these diseases.

GWAS FOR EMPHYSEMA, A COPD-RELATED PHENOTYPE

While initial GWAS for COPD susceptibility were based on lung function analyses, there have been more recent studies evaluating genetic determinants of emphysema. Emphysema can be diagnosed using lung density with computed tomography. Early candidate gene studies for emphysema analyzed genes in the protease-antiprotease and antioxidant pathways in small cohorts and reported associations between emphysema-specific phenotypes and *MMP9* and *EPHX1* (see eTable 45-4).^{256,332-334}

The first GWAS for emphysema was performed using phenotypes characterized by both quantitative (presence versus

absence of emphysema) and qualitative methods (measure of lung density < -950 Hounsfield units) in COPD subjects in the ECLIPSE, NETT, and Norway cohorts. In a combined meta-analysis, a SNP in the gene encoding a homolog for the *Drosophila* gene *bicaudal D homolog 1* (*BICD1*) on chromosome 12p11 was associated with emphysema based on the qualitative method.³³⁵ The associated *BICD1* locus covers a genomic region that contains a coiled-coil domain important for dynein-mediated intracellular processes including mitosis, mRNA transport, and vesicular transport.³³⁶⁻³³⁸ Another regulatory *BICD1* SNP was associated with leukocyte telomere length in an independent genome-wide linkage analysis.³³⁹ Telomeres maintain the integrity of chromosomes and shorten during the aging process, resulting in different age-related diseases; therefore, *BICD1* is a locus that potentially links aging with emphysema or COPD through altered epithelial integrity.^{340,341} Mechanistic evidence for this link is based on studies in telomerase-null mice that develop emphysematous air space enlargement during chronic exposure to cigarette smoke.³⁴⁰

While this list of gene targets related to COPD susceptibility and severity seem diverse and complex, a composite of regulatory genes and pathways is developing. These risk genotypes can be combined with clinical risk factors and COPD phenotypes (including pulmonary function, comorbidities, and imaging assessment of emphysema) to develop “clinical genetic profiles” for risk prediction for COPD susceptibility and severity. Furthermore, these genes can be evaluated as potential disease-modifying therapeutic targets in COPD.

PHARMACOGENETICS OF COPD

RATIONALE FOR PHARMACOGENETICS IN COPD

The most commonly used medical therapies for COPD include LABA, *long-acting antimuscarinics* (LAMA) and ICS therapy for long-term management with SABA and short-acting antimuscarinics used for as-needed rescue therapy. Most pharmacogenetic studies in COPD have been limited to candidate gene studies based on predetermined clinical trial end points. These usually include changes in FEV₁ or exacerbation frequency in response to therapies, mostly β -agonists. Pharmacogenetic studies have the potential to develop biomarkers that would identify the most appropriate current or future therapies for individuals with COPD.

β_2 -ADRENERGIC RECEPTOR PHARMACOGENETICS

The majority of pharmacogenetic studies focus on the bronchodilator response to SABA for two reasons: First, SABA therapy is the most prescribed treatment for the management of COPD, and second, acute bronchodilator response to SABA is a simple measurement.² One of the earliest pharmacogenetic studies for SABA was a linkage analysis of the BEOCOPD cohort, which estimated a heritability of 10% and 26% for acute bronchodilator responsiveness.³⁴²

The most intensively studied locus for β_2 -adrenergic receptor agonist bronchodilator response has focused on

variation in *ADRB2*. Multiple candidate gene studies have evaluated the role of Gly¹⁶Arg and other variants (including Gln²⁷Glu) at the *ADRB2* locus in determining lung function responses to SABA. These studies have reported conflicting results that favor the absence of a genotypic effect for any single variant. For example, two noncoding *ADRB2* SNPs were associated with albuterol bronchodilator response in the NETT cohort but not replicated in the BEOCOPD cohort (which consisted of probands with early-onset COPD and, for the most part, unaffected family members). In addition, haplotypes of two coding SNPs in *ADRB2* (Gly¹⁶Arg and Gln²⁷Glu) were associated with bronchodilator responsiveness in the NETT cohort but not in BEOCOPD subjects.³⁴³ Gly¹⁶Arg and Arg¹⁶Gln²⁷ genotypes were also associated with acute bronchodilator response to albuterol in Japanese subjects with COPD; this association was not observed in other studies of *ADRB2* in Japanese subjects with COPD.^{344,345} In the latter Japanese study, Gly¹⁶Arg was associated with preferential response to either the short-acting muscarinic receptor antagonist oxytropium or the SABA albuterol.³⁴⁴

Additional genes outside of *ADRB2* and the β_2 -adrenergic receptor pathway have been evaluated as potential loci for lung function responses to acute SABA therapy through candidate gene studies. A study of different biologic COPD candidate genes in the NETT cohort identified three SNPs in *EPHX1* and three SNPs in *SERPINE2* associated with the bronchodilator response to albuterol. Of these, one SNP in *EPHX1* was replicated in the BEOCOPD cohort.³⁴³

Long-acting bronchodilators such as LABA and LAMA are among the most effective and commonly used long-term therapies for COPD and have been evaluated by different pharmacogenetic association studies, most of which have focused on variation in *ADRB2*. Among the first pharmacogenetic studies for LABA in COPD was an analysis of the Korean Obstructive Lung Disease cohort treated with a LABA, salmeterol, and an ICS, fluticasone, for 12 weeks. LABA and ICS treatment resulted in improvements in lung function, independent of *ADRB2* genotype.³⁴⁶ Gene variation at the Gly¹⁶Arg locus was also not associated with changes in lung function or exacerbation frequency in response to LABA in two large independent COPD studies in the United States, which randomized subjects to treatment with the LABA, formoterol, with or without an ICS, budesonide.³⁴⁷ Similar to pharmacogenetic studies in asthma, variation at the *ADRB2* locus does not appear to impact therapeutic responses to LABA therapy in COPD.

The muscarinic acetylcholine receptor is a G protein-coupled receptor that activates phospholipase C and protein kinase A, leading to increased airway smooth muscle contractility.³⁴⁸ The muscarinic receptor subtype M₃ is implicated in airway smooth muscle contractility in COPD and is the target for inhaled LAMA therapy.^{349,350} In addition, the M₃ receptor has been shown to phosphorylate the β_2 -adrenergic receptor and the G_s subunit, resulting in the β_2 -adrenergic receptor desensitization.³⁵¹ The intracellular signaling cross-talk between the two G protein-coupled receptor signal transduction pathways regulated by the muscarinic receptor and the β_2 -adrenergic receptor provides the rationale for the study of *ADRB2* polymorphisms in COPD cohorts treated with LAMA therapy.

Some pharmacogenetic studies have evaluated variants at the *ADRB2* locus in COPD clinical trial cohorts where subjects were randomized to LABA or LAMA therapy. A candidate gene study of COPD subjects randomized to tiotropium for 8 weeks demonstrated that Arg¹⁶ homozygotes experienced greater improvements in FEV₁ and symptom control during tiotropium treatment than did Gly¹⁶Arg heterozygotes and Gly¹⁶ homozygotes.³⁵² A larger study of COPD subjects randomized to salmeterol or tiotropium for 1 year demonstrated that salmeterol was more effective in preventing COPD exacerbations in Arg¹⁶ homozygotes than in those with the remaining Gly¹⁶Arg genotypes, perhaps implying effects of different variants in LD with this locus.^{353,354}

Pharmacogenetic studies in COPD remain limited to candidate gene studies in clinical trial cohorts. Future pharmacogenetic studies should be performed using GWAS, independent large clinical trial cohorts, or genotype-stratified trials to replicate known pharmacogenetic loci and identify novel gene pathways that either act independently or through additive effects on therapeutic responses to inhaled β -agonists, LAMA, and ICS therapies. Just as for asthma, pharmacogenetic studies in COPD have the potential to identify genetic markers that could be used to characterize subgroups of nonresponders, responders, or a subgroup at risk for adverse responses, which will facilitate the development of precise combination therapies.

EPIGENETICS AND RARE GENE VARIATION IN ASTHMA AND COPD

Epigenetic regulation is mediated by gene modifications that alter transcription without a change in the DNA sequence. Environmental exposures may trigger epigenetic modifications and, therefore, contribute to asthma or COPD pathogenesis in ways that are not detectable using traditional genetic approaches. *Rare genetic variants*, which have allele frequencies of less than 1% to 5%, are not genotyped in GWAS, which were designed to tag genomic regions with common SNPs. Rare variants have the potential to exhibit strong effects on phenotype similar to what happens in single gene diseases such as cystic fibrosis.

EPIGENETICS IN ASTHMA AND COPD

Epigenetic regulation can be mediated through DNA methylation, histone acetylation, or chromatin condensation at gene promoters, which alter gene transcription without changes in the DNA code. DNA methylation is mediated by enzymes (DNA methyltransferases) that transfer a methyl group to cytosine at position 5. Methylation of DNA at regulatory regions such as gene promoters results in enhanced binding of methyl-cytosine binding proteins and *histone deacetylases* (HDACs) to repress gene transcription. HDACs are nuclear enzymes that deacetylate core histones, resulting in chromatin condensation that blocks the binding of transcription factors and RNA polymerase to gene promoters, thus repressing gene transcription. Histone acetyltransferases are nuclear enzymes that acetylate core

histone, resulting in chromatin relaxation, which enhances gene transcription.³⁵⁵

In COPD, HDACs have been shown to be critical to the epigenetic regulation of different proinflammatory cytokines in alveolar macrophages. In alveolar macrophages, treatment with the glucocorticoid dexamethasone resulted in recruitment of HDAC2 to the *granulocyte-macrophage colony stimulating factor* (GM-CSF) promoter region and inhibition of histone acetyltransferases. These epigenetic modifications blocked histone H4 acetylation at the GM-CSF promoter, resulting in repression of IL-1 β -stimulated GM-CSF transcription, an anti-inflammatory effect in response to glucocorticoid treatment.³⁵⁶ The epigenetic regulation of airway inflammation through histone acetylation and its impact on COPD severity was evaluated in surgically resected lung tissue specimens from subjects with COPD of varying severity and nonsmoker controls without COPD. Expression of *HDAC2*, *HDAC5*, and *HDAC8* was lower in lung tissue from COPD subjects than in nonsmoking controls, while total HDAC activity was significantly lower in those with COPD. In addition, HDAC activity directly correlated with FEV₁ and FEV₁/FVC, and inversely correlated with histone H4 acetylation and IL-8 mRNA expression in all subjects and those with COPD.³⁵⁷ The role of HDACs as an important epigenetic factor for COPD pathogenesis was subsequently demonstrated in a large-scale meta-analysis GWAS of more than 48,000 non-Hispanic white subjects from the SpiroMeta and CHARGE consortia and an independent replication cohort of more than 46,000, which identified *HDAC4* on chromosome 2q37 as a locus for lung function in the general population.²⁸⁹

The *ADAM33* promoter has variable methylation at CpG-rich regions (cytosine next to a guanine) or CpG islands resulting in gene hypermethylation or silencing in epithelial cells and hypomethylation or increased expression in fibroblasts.³⁵⁸ In addition, transforming growth factor- β stimulation reduces *ADAM33* mRNA expression in fibroblasts through histone methylation and deacetylation, which results in chromatin condensation at the *ADAM33* promoter and reduced gene transcription.³⁵⁹ Epigenetic mechanisms appear to regulate *ADAM33* expression; however, case-control studies have failed to show differences in *ADAM33* methylation between asthmatic and control subjects.³⁶⁰ Whole-genome epigenetic studies have been performed in small asthma cohorts; larger studies are needed in well-characterized cohorts to identify novel epigenetic mechanisms through which specific environmental exposures contribute to the heritability of asthma and COPD.^{361,362}

RARE VARIANTS IN ASTHMA AND COPD

The analysis of common variants in asthma and COPD was initially based on the common variant–common disease hypothesis that multiple common variants with weak to modest effect determine disease susceptibility and severity. Nearly all genetic studies in asthma and COPD analyzed common SNPs from the individual gene to the whole-genome level. Common SNPs were critical for the creation of cost-effective genome-wide genotyping panels for GWAS in large human populations and have been able to scan entire genomes based on LD with other variants and, thus,

the tagging of haplotype blocks. GWAS have only investigated discoveries based on common variant associations; however, rare variants have become increasingly recognized as potential loci for disease susceptibility.

Next-generation, whole-genome sequencing has the potential to identify rare variants, including SNPs and polynucleotide insertions and deletions, which are not evaluated in a GWAS. The 1000 Genomes Project Consortium used whole-genome sequencing technology to map human variation by sequencing 1097 individual genomes from 14 different populations drawn from Europe, East Asia, sub-Saharan Africa, and the Americas. The 1000 Genomes Project investigators reported an enrichment of rare variants with an allele frequency less than 0.005 in subjects from all populations, likely due to a recent explosion in population size.^{363,364} Populations from an African ancestry had three times as many rare variants with an allele frequency less than 0.05 than did those of European and Asian origin, reflecting ancestral bottlenecks in the latter, non-African populations.^{364,365} The investigators also reported that each individual had at least 240 rare coding variants (allele frequency less than 0.05) and hundreds of noncoding variants at conserved motifs such as transcription factor binding sites.³⁶⁴

Based on the high frequency of potentially functional rare variants, it became evident that rare functional variants might play a role in disease pathogenesis. The analysis of rare variants in human disease is based on the rare variant–common disease hypothesis that rare variants with strong effects on phenotype have major effects on disease risk. Rare variants were initially analyzed by collapsing variants within an individual gene to overcome the statistical challenge of small sample sizes; however, newer methods have been developed that account for the directionality of individual rare variants.^{142,366–374}

The number of studies analyzing rare variants in asthma and COPD is small but informative and provides preliminary evidence that justifies further study. Torgerson and coworkers³⁶⁹ analyzed rare variants in 53 asthma candidate genes from 450 asthma subjects and 515 controls from Childhood Asthma Research and Education Network, SARP, CSGA, and the Genomic Research on Asthma in the African Diaspora cohorts. C-alpha testing for gene-level rare variant associations identified significant rare variant associations with asthma susceptibility for rare coding variants in *DPP10* for African Americans and *IL12RB1* for non-Hispanic whites.³⁶⁹ This study provided the first evidence for the role of rare variants in asthma susceptibility; to date, there has not been a whole-genome association study of rare variants for asthma susceptibility loci.

ADRB2 has a rare coding variant, Thr¹⁶⁴Ile, which has been associated with reduced baseline lung function and baseline airflow obstruction ($FEV_1/FVC < 0.7$) in a cross-sectional analysis of more than 62,000 subjects from the Copenhagen General Population Study and the Copenhagen City Heart Study including a subset of 1300 patients with self-reported asthma.²¹¹ Thr¹⁶⁴Ile is located within the fourth transmembrane domain of the β_2 -adrenergic receptor and is associated with impaired receptor ligand binding affinity and coupling to G_s protein in response to different SABAs and LABAs, as well as decreased binding of salmeterol to the “salmeterol exosite.”^{209,210} Thr¹⁶⁴Ile has been

implicated as a locus for baseline lung function and potentially COPD in this population-based cohort; this rare variant also has the potential to contribute to uncommon, life-threatening adverse responses to inhaled β -agonists as discussed previously.²¹²

Our understanding of the role of rare variants in asthma and COPD susceptibility and severity will be further studied as more genomes from different racial groups are sequenced and as statistical methodologies are developed to analyze this ever expanding volume of genetic data.

GENETICS OF ASTHMA AND COPD: LESSONS LEARNED AFTER 20 YEARS OF EXPERIENCE

Research on the genetics of asthma and COPD over the past 20 years has demonstrated that variation in multiple genes from interacting pathways contributes to disease susceptibility, disease severity, and the response to different therapeutic agents. Earlier family-based studies provided the first clues about the polygenic nature of these obstructive airway diseases. Subsequent, biologic candidate gene studies and larger GWAS resulted in discoveries demonstrating important susceptibility or disease-modifying loci, which have added to our understanding of the complex genetics underlying asthma and COPD. Within each disease, there are common biologic gene pathways. In asthma, these genes primarily regulate proinflammatory pathways, the response to epithelial injury, and lung development. In COPD, these genes regulate nicotine addiction, lung development, proinflammatory pathways, and the antioxidant pathways. Some genes are common to both asthma and COPD as loci for susceptibility or disease severity and include genes that regulate lung development and the IL-6 inflammatory pathway.

The past 20 years have witnessed the mapping of the human genome, the development of high-throughput genotyping for GWAS, and, more recently, the completion of the 1000 Genomes Project through next-generation sequencing. Despite these accomplishments, many of the scientific discoveries stemming from these advances have not completely explained the heritability for asthma and COPD. In GWAS, some of this stems from the need to evaluate very large population cohorts in which comprehensive phenotyping is not practical. Thus, disease heterogeneity and subphenotypes are not adequately investigated, thereby reducing the ability of genetic approaches to characterize pathogenetic disease mechanisms. In addition, unlike single-gene mendelian diseases, such as cystic fibrosis, multiple genetic loci need to be interrogated to determine genetic profiles that predict disease susceptibility and progression. These same issues are true for most diseases, including cardiovascular, metabolic, and neoplastic disorders. Future genomic approaches will continue to focus on larger populations using unbiased, genome-wide approaches to identify novel genetic loci of disease susceptibility, disease severity, and therapeutic responses. Continued evaluation of new discoveries in the context of previously known loci will facilitate the identification of gene-gene interactions and the critical additive effects

of multiple genes that will serve to predict disease susceptibility, risk for progression of severity, and have the potential of leading to the development of novel therapies.

Next-generation DNA sequencing is based on massively parallel sequencing technologies that will allow for high-throughput whole-genome and whole-exome sequencing with the potential to identify rare variants, polynucleotide insertion-deletions, duplications, and epigenetic modifications, which are not captured by current SNP-based panels, thus further capturing hereditary factors in asthma and COPD. The challenge for these whole-genome sequencing approaches will be the extensive bioinformatics resources required. Larger-scale genotyping platforms covering 2 million or more SNPs can now be developed based on whole-genome sequence mapping data from different racial groups, thus allowing for cost-effective, comprehensive genotyping in admixed populations. As the costs associated with comprehensive genotyping and DNA sequencing decline and our understanding of the genetics of asthma and COPD improves, it will then be possible to create biomarker panels designed for precise approaches in medicine.⁴ Before genomics research can be applied to precise, personalized medicine, it will be necessary to continue adapting to the analysis of the exponentially increasing volumes of genetic data to identify and replicate associations in larger, comprehensively characterized human cohorts with a combination of analytic methods and in vitro functional studies.

Key Points

- Genetic variation has major effects on asthma and COPD susceptibility due to the action of many different genes that are polymorphic (contain gene variants or polymorphisms) or undergo epigenetic regulation (changes in gene expression without changes in the genetic code, e.g., gene methylation).
- Multiple potential environmental exposures interact with risk or severity genes for the *development* or *progression* of asthma and COPD, whereas cigarette smoke exposure is the primary environmental factor for the development of COPD and emphysema.
- Family-based studies provided the first clues about the polygenic nature of asthma and COPD; subsequent, biologic candidate gene studies and larger *genome-wide association studies* (GWAS) have resulted in discoveries of important susceptibility and disease-modifying loci.
- These genetic studies have identified common biologic gene pathways that regulate proinflammatory pathways, responses to epithelial injury, and lung development important in determining asthma susceptibility and severity; gene pathways that regulate nicotine addiction, lung development, proinflammatory pathways, and the antioxidant pathways are important in COPD.
- Variation in genes within these pathways have been identified as genetic factors for disease susceptibility, progression, and severity in both asthma and COPD, thus demonstrating overlapping biologic mechanisms in these obstructive airway diseases.
- Pharmacogenetics examines the role of gene variation in therapeutic responses to pharmacologic therapies.

In asthma and COPD, most pharmacogenetic studies have evaluated biologic candidate genes with few GWAS performed for inhaled glucocorticoid and short-acting β -agonist bronchodilator response in asthma.

- The discoveries that have stemmed from linkage studies, biologic candidate gene studies, and GWAS have not completely explained the heritability for asthma and COPD, likely because of the need to evaluate larger well-characterized populations, the role of gene-by-environment interactions (epigenetic regulation), and the potential strong effects of rare genetic variants on phenotype, which have not been evaluated by GWAS.
- Unlike single-gene mendelian diseases, such as cystic fibrosis, multiple genetic loci need to be interrogated to determine genetic profiles that predict disease susceptibility and progression in asthma and COPD. Precise medicine is becoming a realistic goal because of the large volume of genetic and phenotype data now being collected with next-generation DNA sequencing, increasingly comprehensive whole-genome genotyping chips, and larger, well-characterized study cohorts with these obstructive airway diseases.

Complete reference list available at *ExpertConsult*.

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SMOKING HAZARDS AND CESSATION

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INTRODUCTION

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INTRODUCTION

Cigarette smoking remains the leading cause of preventable premature morbidity and mortality in the United States and in many countries around the world. An average of 443,000 people in the United States die prematurely from tobacco-related disease in a year, which includes one of every three cancers and one in five overall deaths.¹ A lifelong smoker has about a one in three chance of dying prematurely from a complication of smoking.² Life expectancy is shortened by more than 10 years among current smokers.³ The increased risk for death from smoking is now equal between men and women in the United States,⁴ and the World Health Organization has estimated that more than a billion deaths in the 21st century will be attributed to tobacco consumption.

Smoking is particularly relevant to respiratory medicine, because it is by far the major cause of lung cancer and *chronic obstructive pulmonary disease* (COPD) in developed countries. Smoking is also a substantial causative factor in respiratory infections, including pneumococcal pneumonia, influenza, and tuberculosis.

EPIDEMIOLOGY OF CIGARETTE SMOKING

Currently about 42.1 million individuals (18.1% of the adult population) in the United States are cigarette smokers, including 20.5% of men and 15.8% of women.¹ The percentage who smoked 30 or more cigarettes per day declined significantly, from 12.6% in 2005 to 9.1% in 2011, and the proportion of those who smoked 1 to 9 cigarettes per day increased from 16.4% to 22.0%. In the United States an increasing number of smokers (as many as 25% in some areas) are nondaily smokers. People who are less well educated and/or have unskilled occupations are more likely to smoke. For example, 33.8% of people with 9 to 11 grades of education are smokers, compared to 9.9% of those with a college degree. High rates are seen in those living below

the federal poverty level (27.7%), those 18 to 24 years of age (23.8%), and those in construction and extraction industries (30%).⁵

There are more than 1 billion smokers worldwide, the majority of whom live in low- and middle-income countries.⁶ Cigarette smoking and exposure to secondhand smoke together are responsible for about 6.3 million annual deaths worldwide and 6.3% of the global burden of disease. The World Health Organization Framework Convention on Tobacco Control aims to reduce both the demand and the supply of tobacco around the world through educational, political, and legislative means.⁷

TOXICOLOGY OF CIGARETTE SMOKE

Tobacco smoke is an aerosol of droplets (particulates) containing water, nicotine and other alkaloids, and tar. Tobacco smoke contains several thousand different chemicals, many of which may contribute to human disease.⁸ Major toxic chemicals in the particulate phase of tobacco include nicotine, benzo(a)pyrene and other polycyclic hydrocarbons, *N*'-nitrosonornicotine, β -naphthylamine, polonium-210, nickel, cadmium, arsenic, and lead. The gaseous phase contains carbon monoxide, acetaldehyde, acetone, methanol, nitrogen oxides, hydrogen cyanide, acrolein, ammonia, benzene, formaldehyde, nitrosamines, and vinyl chloride. Tobacco smoke may produce illness by way of systemic absorption of toxins and/or cause local pulmonary injury by oxidant chemicals.

SMOKING-RELATED DISEASES

Tobacco use is a major cause of death from cancer, cardiovascular disease, and pulmonary disease (Table 46-1). Smoking is also a major risk factor for osteoporosis, reproductive disorders, and fire-related and trauma-related injuries.

Table 46-1 Health Hazards of Tobacco Use (Risks Increased by Smoking)

CANCER (See Table 46-2)

CARDIOVASCULAR DISEASE

Sudden death
Acute myocardial infarction
Unstable angina
Stroke
Peripheral arterial occlusive disease (including thromboangiitis obliterans)
Aortic aneurysm

PULMONARY DISEASE

Lung cancer
Chronic bronchitis
Emphysema
Asthma
Increased susceptibility to pneumonia and to pulmonary tuberculosis
Increased susceptibility to desquamative interstitial pneumonitis
Increased morbidity from viral respiratory infection

GASTROINTESTINAL DISEASE

Peptic ulcer
Esophageal reflux

REPRODUCTIVE DISTURBANCES

Reduced fertility
Premature birth
Lower birth weight
Spontaneous abortion
Abruptio placentae
Premature rupture of membranes
Increased perinatal mortality

ORAL DISEASE (SMOKELESS TOBACCO)

Oral cancer
Leukoplakia
Gingivitis
Gingival recession
Tooth staining

OTHER

Non-insulin-dependent diabetes mellitus
Earlier menopause
Osteoporosis
Cataract
Tobacco amblyopia (loss of vision)
Age-related macular degeneration
Premature skin wrinkling
Aggravation of hypothyroidism
Altered drug metabolism or effects

CANCER

Smoking, the largest preventable cause of cancer (Table 46-2), is responsible for about 30% of cancer deaths.⁹ Many chemicals in tobacco smoke may contribute to carcinogenesis as tumor initiators, co-carcinogens, tumor promoters, or complete carcinogens.^{8,10} Complexes of tobacco smoke carcinogens and DNA are thought to be a crucial step in cancer induction.¹¹ Cigarette smoking induces specific patterns of p53 gene mutations that are associated with squamous cell carcinomas of the lung, head, and neck.¹² Lung cancer is the leading cause of cancer deaths in the United States and is predominantly attributable to cigarette smoking.⁴ The risk for lung and other cancers is proportional to the number of cigarettes smoked per day and even more strongly to the duration of smoking. In current smokers the levels of DNA adducts (covalently bound car-

Table 46-2 Cigarette Smoking and Cancer Risk

Cancer Site	Average Relative Risk
Lung	15.0–30.0
Larynx	10.0*
Oral cavity	4.0–5.0
Oropharynx and hypopharynx	4.0–5.0*
Esophagus	1.5–5.0*
Pancreas	2.0–4.0
Urinary tract	3.0
Nasal cavity, sinuses, nasopharynx	1.5–2.5
Stomach	1.5–2.0
Liver	1.5–2.5
Kidney	1.5–2.0
Uterine cervix	1.5–2.5
Myeloid leukemia	1.5–2.0

*Synergistic interaction with alcohol use.
Adapted from Vineis P, Alavanja M, Buffler P, et al: Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst* 96:99–106, 2004; and International Council for Research on Cancer: *Tobacco smoking and involuntary smoking*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC Scientific Publication 83. Lyon, France, 2004, IARC.

cinogens) in nontumor lung tissue or blood mononuclear cells are related to cigarette consumption.¹³ Of note, however, in former smokers DNA adduct levels were inversely associated with age of initiation of smoking.¹⁴ This finding suggests that young smokers are more susceptible to DNA damage and persistence of genetic alterations than are those who begin smoking at an older age, which has substantial implications for the need to prevent adolescent smoking. A recent genome-wide association study analysis of a cohort of smokers compared to a cohort of never smokers has confirmed that the expression of thousands of genes is altered by cigarette exposure.¹⁵ Additional information from deep sequencing of a lung cancer tumor provides a picture of widespread genetic mutational change with hundreds of point somatic variants and multiple large structural genetic changes such as chromosomal segment deletion.¹⁶

Workplace exposure to asbestos or α -radiation (the latter in uranium miners) synergistically increases the risk for lung cancer in cigarette smokers.¹⁷ Alcohol use interacts synergistically with tobacco in causing oral, laryngeal, and esophageal cancer.¹⁸ The mechanism of interaction may involve alcohol solubilizing tobacco carcinogens and/or alcohol-related induction of liver or gastrointestinal enzymes that metabolize and activate tobacco carcinogens. Smoking is associated with 15% of leukemia cases in adults and 20% of colorectal cancers.^{19,20} Based on large cohort studies and a meta-analysis, cigarette smoking in women before having their first child is associated with increased breast cancer risk.²¹

A detailed description of the epidemiology and the pathogenesis of smoking-induced lung cancer is presented elsewhere in this textbook (see Chapters 51 and 52).

CHRONIC PULMONARY DISEASE

More than 80% of chronic obstructive lung disease in the United States is attributable to cigarette smoking. Cigarette

smoking also increases the risk for respiratory infection, including pneumonia, and results in greater disability from viral respiratory tract infections.^{22,23} Pulmonary disease from smoking includes the overlapping syndromes of chronic bronchitis (cough and mucus secretion), emphysema, and airway obstruction. The lung pathologic conditions produced by cigarette smoking include loss of cilia, mucous gland hyperplasia, increased number of goblet cells in the central airways, inflammation, goblet cell metaplasia, squamous metaplasia, mucus plugging of small airways, destruction of alveoli, and a reduced number of small arteries. The mechanism of injury is complex and seems to include inflammation as well as direct injury by oxidant chemicals, increased elastase activity (a protein that breaks down elastin and other connective tissue), and decreased antiprotease activity.²⁴ A genetic deficiency of α_1 -antiprotease activity produces a similar imbalance between pulmonary protease and antiprotease activity and is a risk factor for early and severe smoking-induced pulmonary disease.²⁵

In addition to the effects of cigarette smoke-induced injury, the delivery of carbon monoxide from cigarette smoke serves to worsen the level of functioning in smokers who have significant COPD. Carbon monoxide avidly binds to hemoglobin, reduces the capacity of hemoglobin to carry oxygen, and impairs oxygen release at the tissues. Thus carbon monoxide exposure produces a functional anemia. Carboxyhemoglobin levels are typically 5% to 10% in smokers, compared to 1% or less in nonsmokers. In a normal person, carbon monoxide from cigarette smoke causes few symptoms, but, in patients with pulmonary disease, carbon monoxide has the potential to cause significant impairment. Exposure to carbon monoxide at levels even less than that derived from cigarette smoking have been shown to reduce exercise tolerance in patients with COPD.

Cigarette smoking may contribute to the development of asthma, although this potential link could be confounded by the increased rate of pulmonary infections observed in smokers. A longitudinal study of 5800 individuals taking part in a British national study suggested that regular smoking was associated with asthma in people between the ages of 17 and 33 (*odds ratio* [OR] = 4.4).²⁶ The relationship between asthma and smoking was further studied in more than 14,000 Finnish adults, and the prevalence of asthma was higher among male smokers than among male nonsmokers (relative risk = 1.7), although no smoking effect was observed for women.²⁷ Current smokers, compared to never and ex-smokers, demonstrate higher asthma severity scores, more frequent asthma symptoms, and more frequent asthma attacks (OR = 2.4).²⁸ Silverman and coworkers²⁹ evaluated 1847 emergency department patients presenting with acute asthma and found that 35% of patients were current smokers. Half of these smoking asthmatics reported that cigarette use worsened their asthma symptoms.

The link between secondhand smoke and asthma would support the hypothesis that tobacco exposure worsens bronchial hyperresponsiveness. A study evaluating infants in their first year of life exposed to smoking mothers demonstrated they were 2.1 times more likely to develop asthma than children of nonsmoking mothers.³⁰ Likewise, the Swiss Study on Air Pollution and Lung Disease in Adults

suggested that secondhand smoke was associated with an increased risk for asthma (OR = 1.4) or reactive airway disease in nonsmoking adults.³¹

There are other links between smoking and inflammatory lung conditions such as asthma. In a small cohort of healthy nonasthmatic smokers, bronchoalveolar lavage fluid documented altered macrophage cytokine release, increased cellularity, and depressed levels of interleukin-6.³² These abnormalities would further suggest a plausible link between smoking and an increased incidence and severity of chronic lung inflammatory conditions.

Cigarette smoking has been associated with multiple non-neoplastic pulmonary disorders other than emphysema and chronic bronchitis. These include respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonitis, Langerhans cell histiocytosis, cryptogenic interstitial fibrosing alveolitis, and eosinophilic pneumonia.³³ Ninety percent of patients with pulmonary Langerhans cell histiocytosis are smokers. Respiratory bronchiolitis and desquamative interstitial pneumonitis have similar histopathologic features and are characterized by the accumulation of pigmented macrophages within the alveoli. Respiratory bronchiolitis ("smoker's bronchiolitis") is most often an asymptomatic finding that can persist after smoking cessation.³⁴ Desquamative interstitial pneumonitis often affects smokers in their fourth or fifth decade of life, and the symptoms are more frequent in smokers.³³ Smoking may also have an association with idiopathic pulmonary fibrosis.³⁵ Smoking is over-represented in patients with idiopathic pulmonary fibrosis compared to the general population, and the overall OR for smoking as a risk factor for idiopathic pulmonary fibrosis was 1.6.³⁶

INFECTION

Cigarette smoking is a major risk factor for respiratory tract and other systemic infections. Both active and passive cigarette smoke exposure increase the risk for infection.^{37,38} The mechanisms by which smoking increases risk are multifactorial and include structural and immunologic alterations. As mentioned previously, cigarette smoking causes structural changes in the respiratory tract. These changes include peribronchiolar inflammation and fibrosis, increased mucosal permeability, impairment of mucociliary clearance, changes in pathogen adherence, and disruption of the respiratory epithelium. A number of components of cigarette smoke, including acrolein, acetaldehyde, formaldehyde, free radicals produced from chemical reactions within the cigarette smoke, and nitric oxide, may contribute to the observed structural alterations in airway epithelial cells.

Immunologic mechanisms include alterations in cellular and humoral immune system function. These include a decreased level of circulating immunoglobulins, a depression of antibody response to certain antigens, a decrease in CD4⁺ lymphocyte counts, an increase in CD8⁺ lymphocyte counts, depressed phagocyte activity, and decreased release of proinflammatory cytokines. Many of the immunologic disturbances in smokers resolve within 6 weeks after smoking cessation, supporting the idea that smoking cessation is highly effective in a relatively short period of time in the prevention of infection.³⁷

Table 46-3 Cigarette Smoking and Infection

	Odds Ratio (95% CI)
Tuberculosis	4.5 (4.0–5.0)
Legionnaires' disease	3.5 (2.1–5.8)
HIV infection	3.4 (1.6–7.5)
Periodontal disease	2.8 (1.9–4.1)
Pneumococcal pneumonia	2.6 (1.9–3.5)
Meningococcal disease	2.4 (0.9–6.6)
Influenza	2.4 (1.5–3.8)
<i>Helicobacter pylori</i>	2.2 (1.2–4.0)
Common cold	1.5 (1.1–1.8)

CI, confidence interval; HIV, human immunodeficiency virus.

Cigarette smoking is associated with an increased risk for bacterial and viral infections (Table 46-3). Cigarette smoking is a substantial risk factor for pneumococcal pneumonia, especially in patients with COPD. Smoking is strongly associated with invasive pneumococcal disease in otherwise healthy adults.²³ A population-based case control study showed smoking was the strongest independent risk factor for invasive pneumococcal disease among immunocompetent adults. The OR was 4.1 (95% confidence interval [CI], 2.4 to 7.3) for active smoking and 2.5 (95% CI, 1.2 to 5.1) for passive smoke exposure in nonsmokers compared to nonexposed nonsmokers. The attributable risk in this population was 51% for cigarette smoking and 17% for passive smoking, and this effect showed a strong dose response. The risk for pneumococcal disease declined to nonsmoker levels 10 years after cessation. Cigarette smoking has also been shown to be associated with a nearly twofold increased risk for community-acquired pneumonia, with 32% of the risk attributable to cigarette smoking.³⁹

Cigarette smoking increases the risk for developing and the severity of viral infections, including the common cold, influenza, and varicella. Influenza infections are more severe, with more cough, acute and chronic phlegm production, breathlessness, and wheezing in smokers.²² Influenza infections produce more lost workdays in smokers compared to nonsmokers. Influenza vaccination is effective in preventing the disease in smokers, and smoking should be considered to be a high-priority indication for influenza vaccination. The role of development of varicella pneumonitis in adults is reported to be substantially greater in smokers compared to nonsmokers.⁴⁰

Tuberculosis is perhaps the most important smoking-associated infection. Cigarette smoking is a risk factor for tuberculin skin test reactivity, for skin test conversion, and for the development of active tuberculosis. A large case-control study from India examined smoking and tuberculosis in men between 35 and 69 years of age. The tuberculosis prevalence relative risk was 2.9 (95% CI, 2.6 to 3.3) for ever smokers compared to never smokers, and the prevalence was higher with a higher level of cigarette consumption.⁴¹ The mortality from tuberculosis among men 25 to 69 years old showed a relative risk of 4.5 (95% CI, 4.0 to 5.0) and 4.2 (95% CI, 3.7 to 4.8) for urban and rural residents, respectively. The authors found that the proportion of deaths from tuberculosis attributable to smoking was 61% greater than the proportion of deaths from vas-

cular disease or cancer attributable to smoking. Thus it is likely that smoking contributes substantially to the worldwide disease burden of tuberculosis.⁴²

Of historical interest is the relationship between tuberculosis and the risk for cigarette smoking in the early 20th century. Before that time, chewing tobacco was the preferred type of tobacco. Public fear that users of chewing tobacco who spit in public places might be spreading tuberculosis is one of the factors that led to the increase in cigarette sales in the United States. This is nicely described by Kluger as follows: "Chewing tobacco was no longer merely messy but socially disagreeable in more crowded urban America, and in its inevitable byproduct, spitting, was now identified as a spreader of tuberculosis and other contagions and, thus, an official health menace. The leisurely pipe all at once seemed a remnant of a slower-tempo age, and cigar fumes were newly offensive amid thronged city life. The cigarette by contrast, could be quickly consumed and easily snuffed out on the job as well as to and from work."⁴³

CARDIOVASCULAR DISEASE

Although not the focus of this textbook, cardiovascular disease is common in patients with respiratory disease. This relates to the facts that both diseases are common and both increase with age and that smoking is a major risk factor for both respiratory disease and cardiovascular disease.

Cigarette smoking accounts for about 20% of cardiovascular deaths in the United States. Risks are increased for coronary artery disease, sudden death, cerebrovascular disease, and peripheral vascular disease, including aortic aneurysm.^{8,44} Cigarette smoking accelerates atherosclerosis and promotes acute ischemic events. The mechanisms of the effects of cigarette smoking are not fully elucidated but are believed to include (1) hemodynamic stress (nicotine increases the heart rate and transiently increases blood pressure); (2) endothelial injury and dysfunction (nitric oxide release and resultant vasodilation are impaired); (3) development of an atherogenic lipid profile (smokers have on average higher low-density lipoprotein levels, more oxidized low-density lipoprotein, and lower high-density lipoprotein cholesterol than nonsmokers do); (4) enhanced coagulability; (5) arrhythmogenesis; and (6) relative hypoxemia because of the effects of carbon monoxide.⁴⁵ As mentioned, carbon monoxide reduces the capacity of hemoglobin to carry oxygen and impairs the release of oxygen from hemoglobin to body tissues, both of which combine to result in a state of relative "anemia." As a compensation for the reduced oxygen-carrying capacity, polycythemia develops in smokers, with hematocrits often 50% or more. The polycythemia and the increased fibrinogen levels that are found in cigarette smokers also increase blood viscosity, which adds to the risk for thrombotic events. Cigarette smoking also induces a chronic inflammatory state, as evidenced by increased neutrophil count and increased levels of fibrinogen and C-reactive protein in the blood of smokers. Chronic inflammation is thought to contribute to atherogenesis.

Cigarette smoking acts synergistically with other cardiac risk factors to increase the risk for atherogenesis, plaque rupture, and acute ischemic events. Although the risk for cardiovascular disease is roughly proportional to cigarette consumption, the risk persists even at low levels of smoking,

that is, at one to two cigarettes per day.⁴⁶ Cigarette smoking reduces exercise tolerance in patients with angina pectoris and with intermittent claudication; in smokers, vasospastic angina is more common and the response to vasodilator medication is impaired. Smoking substantially increases the number and total duration of ischemic episodes as assessed by ambulatory electrocardiographic monitoring in patients with coronary heart disease.⁴⁷ The increase in relative risk for coronary heart disease because of cigarette smoking is greatest in young adults, who, in the absence of cigarette smoking, would have a relatively low risk.⁴⁴ Women who use oral contraceptives and smoke cigarettes have a synergistically increased risk for both myocardial infarction and stroke. Data suggest that implementing smoking bans at the community level has an appreciable impact on lowering hospital admission rates for coronary artery disease.^{48,49}

After acute myocardial infarction, persistent smokers have an increased risk for recurrent myocardial infarction and half the expected survival over the next 12 years compared to quitters.⁵⁰ Smoking also interferes with revascularization therapy for acute myocardial infarction. After thrombolysis, persistent smokers suffer a fourfold increased reocclusion rate than those who quit.⁵¹ Smokers also have an increased risk for reocclusion of a coronary artery after angioplasty or of occlusion of a bypass graft.⁵² Cigarette smoking is not a risk factor for hypertension per se but does increase the risk for complications, including the development of nephrosclerosis and progression to malignant hypertension.⁵³ Cigarette smoking has been shown to be a substantial contributor to morbidity and mortality in patients with left ventricular dysfunction. The mortality benefit of stopping smoking in such patients is equal to or greater than the benefit of therapy with angiotensin-converting enzyme inhibitors, β -blockers, or spironolactone.⁵⁴

WOUND HEALING/POSTOPERATIVE COMPLICATIONS

Cigarette smoking is associated with adverse postoperative events and delayed wound healing.⁵⁵ Postoperative complications can be tied to impaired clearance of secretions, altered immune function, and altered collagen synthesis, as well as the influence of underlying tobacco-related diseases (e.g., COPD and altered cardiovascular function). The mechanisms that can delay wound healing include cutaneous vasoconstriction (reducing skin blood flow), local thrombosis, and reduced oxygen-carrying capacity.

Smoking cessation substantially reduces postoperative complications. Moller and colleagues⁵⁶ published the results of a randomized, controlled trial of smokers awaiting elective hip or knee surgery at three hospitals in Copenhagen. They compared 56 patients in a smoking cessation intervention arm (83% stopped or reduced smoking) to 62 patients in a usual care arm targeting cessation 6 to 8 weeks before surgery. The overall complication rate was 18% in the smoking cessation arm and 52% in the controls, a highly significant difference. The greatest differences were seen in wound complication rates (5% versus 31%) and cardiovascular complications (0% versus 2%), without a significant difference in length of hospital stay.

A study of 489 adult patients undergoing ambulatory surgery demonstrated a significantly higher rate of respiratory complications in smokers compared to nonsmokers (32.8% in smokers versus 25.9% in nonsmokers) and wound infections (3.6% in smokers versus 0.6% in nonsmokers).⁵⁷ Causes of major pulmonary events after pneumonectomy for lung surgery were sought in a retrospective analysis of 261 patients.⁵⁸ Patients who continued to smoke within 1 month of operation were determined to be at an increased risk for pulmonary events, which was associated with increased postoperative mortality. Cigarette smoking is associated with an increased risk for hepatic artery thrombosis after liver transplantation, and cessation 2 years before transplantation was associated with a decreased risk.⁵⁹ Similar data exist regarding renal transplantation and allograft survival in smokers compared to nonsmokers.⁶⁰

The optimal window for smoking cessation intervention may be at 8 weeks before elective surgery, as suggested by data demonstrating that patients who had stopped smoking at least 2 months preoperatively had nearly maximal reduction in postoperative respiratory complications.⁶¹ A meta-analysis found that smoking cessation reduced postoperative complications by 41% and that each week of cessation increased the magnitude of benefit by 19%.⁶² An important issue related to elective surgery is that patients are often highly motivated to quit smoking just before elective surgery and can benefit from cessation counseling before surgery as well as in-hospital cessation counseling and medication in the postoperative setting. Specific issues related to smoking cessation are discussed later in this chapter.

OTHER COMPLICATIONS OF CIGARETTE SMOKING

Cigarette smoking increases the risk for duodenal and gastric ulcers, delays the rate of ulcer healing, and increases the risk for relapse after ulcer treatment.⁶³ Smoking is also associated with esophageal reflux symptoms. Smoking produces ulcer disease by increasing acid secretion, reducing pancreatic bicarbonate secretion, impairing the gastric mucosal barrier (related to decreased gastric mucosal blood flow and/or inhibition of prostaglandin synthesis), reducing pyloric sphincter tone, and increasing the risk for *Helicobacter pylori* infection.^{64,64a} Cigarette smoking is an independent risk factor for the development of non-insulin-dependent diabetes mellitus, which is a consequence of development of resistance to the effects of insulin.⁶⁵ The effects of nicotine seem to contribute at least in part to insulin resistance, and insulin resistance has been described in users of smokeless tobacco, who are not exposed to tobacco combustion products.

Cigarette smoking increases the risk for osteoporosis by reducing the peak bone mass attained in early adulthood and increasing the rate of bone loss in later adulthood. Smoking antagonizes the protective effect of estrogen replacement therapy on the risk for osteoporosis in postmenopausal women.⁶⁶ Cigarette smoking is a major cause of reproductive problems and results in approximately 4600 U.S. infant deaths annually. Growth retardation from cigarette smoking has been termed "fetal tobacco syndrome." Cigarette smoking causes reproductive

Table 46-4 Interaction Between Cigarette Smoking and Drugs

Drugs	Interaction (Effects Compared with Nonsmokers)	Significance
Antipyrine Caffeine Chlorpromazine Clozapine Desmethyldiazepam Estradiol Estrone Flecainide Fluvoxamine Haloperidol Imipramine Lidocaine Olanzapine Oxazepam Pentazocine Phenacetin Phenylbutazone Propranolol Tacrine Theophylline	Accelerated metabolism	May require higher doses in smokers, reduced doses after quitting
Oral contraceptives	Enhanced thrombosis, increased risk for stroke and myocardial infarction	Do not prescribe to smokers, especially if >35 years old
Cimetidine and other H ₂ -blockers	Lower rate of ulcer healing, higher ulcer recurrence rates	Consider using mucosal protective agents
Propranolol	Less antihypertensive effect, less antianginal efficacy; more effective in reducing mortality after myocardial infarction	Consider the use of cardioselective β-blockers
Nifedipine (and probably other calcium blockers)	Less antianginal effect	May require higher doses and/or multiple-drug antianginal therapy
Diazepam, chlordiazepoxide (and possibly other sedative-hypnotics)	Less sedation	Smokers may need higher doses
Chlorpromazine (and possibly other neuroleptics)	Less sedation, possibly reduced efficacy	Smokers may need higher doses
Propoxyphene	Reduced analgesia	Smokers may need higher doses

H₂, histamine₂.

complications by causing placental ischemia mediated by the hypoxic effects of chronic carbon monoxide exposure, endothelial dysfunction, and the general increase in coagulability produced by oxidant chemicals in cigarette smoke.⁶⁷

Other adverse effects of cigarette smoking include premature facial wrinkling, an increased risk for cataracts, age-related macular degeneration, olfactory dysfunction, and fire-related injuries. The last mentioned contributes significantly to the economic costs of tobacco use. Smoking reduces the secretion of thyroid hormone in women with subclinical hypothyroidism and increases the severity of clinical symptoms of hypothyroidism in women with subclinical or overt hypothyroidism, the latter effect reflecting antagonism of thyroid hormone action.⁶⁸ Cigarette smoking also potentially interacts with a variety of drugs by accelerating drug metabolism or by the antagonistic pharmacologic actions that nicotine and/or other constituents of tobacco have with other drugs (Table 46-4).

HEALTH HAZARDS OF SECONDHAND SMOKE

Considerable evidence indicates that exposure to secondhand smoke is harmful to the health of nonsmokers (Table

Table 46-5 Health Hazards of Secondhand Smoke in Nonsmokers

Children	Adults
Hospitalization for respiratory tract infection in first year of life	Lung cancer
Wheezing	Myocardial infarction
Middle ear effusion	Reduced pulmonary function
Asthma	Irritation of eyes, nasal congestion, headache
Sudden infant death syndrome	Cough

46-5). The U.S. Environmental Protection Agency classifies secondhand smoke as a class A carcinogen, which means that it has been shown to cause cancer in humans.⁶⁹

Secondhand smoke, also known as environmental tobacco smoke, consists of sidestream smoke that is generated while the cigarette is smoldering and mainstream smoke that has been exhaled by the smoker. Of the total combustion product from a cigarette, 75% or more enters the air. The constituents of secondhand smoke are qualitatively similar to those of mainstream smoke. However, some toxins, such as ammonia, formaldehyde, and nitrosamines, are present in much higher concentrations in secondhand smoke than in mainstream smoke. The Environmental Protection Agency has estimated that secondhand smoke is responsible for approximately 3000 lung cancer deaths

annually in nonsmokers in the United States, is causally associated with 150,000 to 300,000 cases of lower respiratory tract infection in infants and young children up to 18 months of age, and is causally associated with the aggravation of asthma in 200,000 to 1 million children.⁶⁹ Secondhand smoke exposure is also responsible for 40,000 cardiovascular deaths.⁷⁰ An appreciation of the hazards of secondhand smoke is important to the physician because it provides a basis for advising parents not to smoke when children are in the home, for insisting that child care facilities be smoke-free, and for recommending smoking restrictions in work sites and other public places.

NICOTINE ADDICTION

Tobacco use is motivated primarily by the desire for nicotine. Drug addiction is defined as compulsive use of a psychoactive substance, the consequences of which are detrimental to the individual or society. Understanding addiction is useful in providing effective smoking cessation therapy.⁷¹ Nicotine is absorbed rapidly from tobacco smoke into the pulmonary circulation; it then moves quickly to the brain, where it acts on nicotinic cholinergic receptors to produce its gratifying effects within 10 to 15 seconds after a puff. Smokeless tobacco is absorbed more slowly and results in less intense acute pharmacologic effects. With long-term use of tobacco, physical dependence develops, associated with an increased number of nicotinic cholinergic receptors in the brain. When tobacco is unavailable, even for only a few hours, withdrawal symptoms often develop, including anxiety, irritability, difficulty concentrating, restlessness, hunger, craving for tobacco, disturbed sleep, and, in some people, depression.

Addiction to tobacco is multifactorial, including a desire for the direct pharmacologic actions of nicotine, relief of withdrawal symptoms, and learned associations. Smokers report a variety of reasons for smoking, including pleasure, arousal, enhanced vigilance, improved performance, relief of anxiety or depression, reduced hunger, and control of body weight. Environmental cues—such as having a meal or a cup of coffee, talking on the phone, drinking an alcoholic beverage, or being with friends who smoke—often trigger an urge to smoke. Smoking and depression are strongly linked. Smokers are more likely to have a history of major depression than are nonsmokers. Smokers with a history of depression are also likely to be more highly dependent on nicotine and have a lower likelihood of quitting. When they do quit, depression is more apt to be a prominent withdrawal symptom.

Most tobacco use begins in childhood or adolescence.⁷² Risk factors for youth smoking include peer and parental influences; behavioral problems (e.g., poor school performance); personality characteristics such as rebelliousness or risk taking, depression, and anxiety; and genetic influences. The adolescent's desire to appear older and more sophisticated, such as emulating more mature role models, is another strong motivator. Environmental influences such as advertising and smoking in movies also contribute. Although smoking rates among adults have been declining since the 1970s, initiation rates for youth have remained constant since the mid-1980s. Approaches to preventing

tobacco addiction in youth include educational activities in schools, aggressive antitobacco media campaigns, taxation of tobacco products, changing the social and environmental norms (restricting indoor smoking, educating parents not to smoke around children), and deglamorizing smoking.

NEUROBIOLOGIC MECHANISMS OF ADDICTION

Nicotine binds stereoselectively to nicotinic cholinergic receptors in the brain, autonomic ganglia, the adrenal medulla, and neuromuscular junctions. Most relevant to nicotine addiction are the neuronal nicotinic cholinergic receptors. These are found throughout the brain, with the greatest number of binding sites in the cortex, thalamus, and interpeduncular nucleus, and substantial binding in the amygdala, septum, brain-stem motor nuclei, and locus coeruleus. The nicotinic cholinergic receptor is a ligand-gated ion channel, composed of five subunits. Most brain nicotinic cholinergic receptors are composed of α - and β -subunits. Usually there are two α - and three β -subunits, with the α -subunits responsible for ligand binding and the β -subunits mediating other aspects of receptor function.⁷³ There is much diversity of nicotinic cholinergic receptors with nine α -subunit isoforms (α_2 through α_{10}) and three β -subunit isoforms (β_2 through β_4) identified in brain tissues. Different nicotinic receptors are found in different parts of the brain and have different chemical conductances for sodium and calcium and different sensitivity to different nicotinic agonists. The different nicotinic receptors are believed to mediate different pharmacologic actions of nicotine, perhaps corresponding to the multiple effects of nicotine experienced by human smokers.⁷⁴

Nicotine receptors appear to be located both on cell bodies and at nerve terminals. All nicotine receptors are permeable to calcium ions. Nicotinic receptor activation works, at least in part and possibly in the main, by facilitating the release of neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, β -endorphin, gamma aminobutyric acid, and others.⁷⁵ Nicotine enhances fast excitatory synaptic transmission, which may contribute to learning and memory.^{76,77} Nicotine also releases growth hormone, prolactin, vasopressin, and adrenocorticotrophic hormone. The behavioral rewards from nicotine and perhaps nicotine addiction as well appear to be linked to dopamine release.⁷⁸

The two main dopamine systems in the brain are the mesocorticolimbic and the nigrostriatal systems. The mesocorticolimbic system includes the ventral tegmental area projecting to the nucleus accumbens, the cortex, and limbic regions. The nigrostriatal system includes the substantia nigra, pars compacta projecting to the dorsal striatum. Nicotine causes an increase in burst firing of ventral tegmental area neurons, resulting in release of dopamine in the nucleus accumbens.⁷⁸ Dopamine release is potentiated and sustained by nicotine-mediated release of glutamate.⁷⁹ Dopamine release in the outer shell of the nucleus accumbens is characteristic of the effects of many addicting drugs (e.g., heroin, cocaine, alcohol) and is thought to be an important site for drug-mediated reinforcement.⁸⁰

Whereas acute exposure to nicotine produces stimulation of dopaminergic neurons in mesolimbic pathways, chronic exposure to nicotine and other drugs of abuse produces other changes in mesolimbic function. Chronic

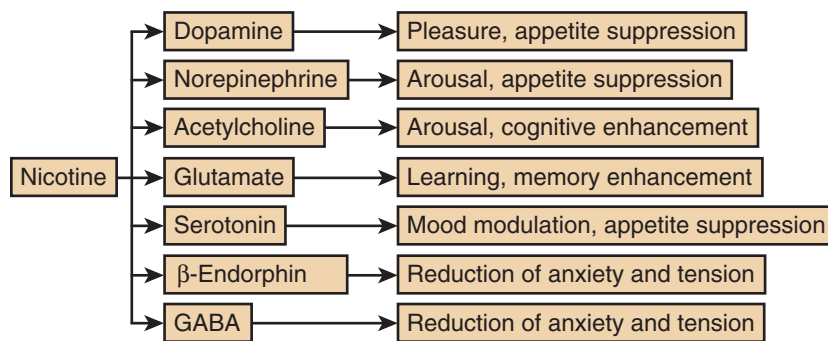


Figure 46-1 Neurochemical effects of nicotine. Nicotine leads to the release of many neurotransmitters, each of which may mediate specific aspects of nicotine addiction and reward. Dopamine release is believed to be the major link to behavioral rewards from nicotine. GABA, gamma aminobutyric acid.

nicotine exposure results in neuroadaptation or the development of tolerance, and the absence of nicotine results in subnormal release of dopamine and other neurotransmitters. Thus nicotine withdrawal may result in a state of deficient dopamine responses to novel stimuli in general and to a state of malaise and inability to experience pleasure. This has been termed “hedonic dysregulation” by Koob and LeMoal.⁸¹ Hedonic dysregulation may explain craving. The sensitivity to drug effects may explain why even a single slip might easily result in a return to compulsive drug use.

The release of various neurotransmitters discussed previously results in behavioral arousal, sympathetic neural activation, and a number of other effects that are believed to be rewarding. The release of specific neurotransmitters has been speculatively linked to the reported reinforcing effects of nicotine (Fig. 46-1). For example, enhanced release of dopamine and norepinephrine may be associated with pleasure as well as appetite suppression, the latter of which may contribute to lower body weight.⁸² Release of acetylcholine may be associated with improved performance on behavioral tasks and improvement of memory. Release of β -endorphin may be associated with reduction of anxiety and tension.

Although smokers give different explanations for their smoking, most agree that smoking produces arousal, particularly with the first cigarettes of the day, and relaxation, particularly in stressful situations. Consistent with reports of arousal, electroencephalographic desynchronization with an upward shift in the dominant alpha frequency and decreased total alpha and theta power follows cigarette smoking or the administration of nicotine.⁸³

LOW-YIELD CIGARETTES

It has been well demonstrated that smokers regulate their intake of nicotine. Smokers change the way they puff a cigarette depending on the nicotine yield as measured by the cigarette smoking machine.^{84,85} They puff lower-yield cigarettes more frequently or more intensely than higher-yield cigarettes, presumably to obtain more nicotine. Smokers who switch from higher-yield to lower-yield cigarettes consume more nicotine from the lower-yield cigarettes than is predicted by smoking machine tests. Conversely, smokers consume less nicotine than predicted from higher-yield cigarettes. The intake of nicotine, as measured using blood cotinine or nicotine concentrations or urine metabolites as markers of nicotine intake, has been studied in large groups of people smoking their own chosen

brand of cigarettes.⁸⁴ In such studies, nicotine intake correlates only weakly with the machine-determined yield. Despite smoking cigarettes with widely differing nicotine yields, smokers demonstrate only small differences in nicotine intake. Correspondingly, there is little or no health benefit of switching to lower- rather than higher-yield cigarettes.^{86,87}

The shift over the years from higher- to lower-yield cigarettes may explain the change in the pathologic characteristics of lung cancer.⁸⁸ That is, the percentage of lung cancers that are adenocarcinomas has increased, whereas the percentage of squamous cell cancers has decreased. The change in tumor type is believed to reflect the higher nitrosamine delivery of lower-yield cigarettes and the greater volume of inhalation of low-yield cigarettes that smokers adopt to compensate for lower level concentrations of nicotine in the smoke.

SMOKING CESSATION

Of cigarette smokers, 70% state they would like to quit and approximately 50% try to quit each year. Spontaneous quit rates are about 1% per year. Simple physician advice to quit increases the quit rate to 3%. Minimal intervention programs increase quit rates to 5% to 10%, whereas more intensive treatments, including smoking cessation clinics, can yield quit rates of 25% to 30%.⁸⁹

The main strategies for cessation are behavioral counseling, pharmacologic intervention, or a combination of the two. Many patients try over-the-counter smoking cessation medications before discussing smoking with their health care providers. The efficacy of over-the-counter medications may be limited by improper use of medications and concomitant untreated issues such as depression, alcoholism, or other factors. Assessing stress, exposure to family members or roommates who smoke, or other factors shown to predict relapse are an important part of history taking before a therapeutic intervention is undertaken.

GUIDELINES

Evidence-based guidelines for the treatment of tobacco addiction emphasize identifying all tobacco users in a physician's practice and ascertaining each patient's intent with respect to quitting smoking (Fig. 46-2).⁹⁰ Identification of tobacco use is facilitated by the implementation of an office-based system so that patients are queried about tobacco use

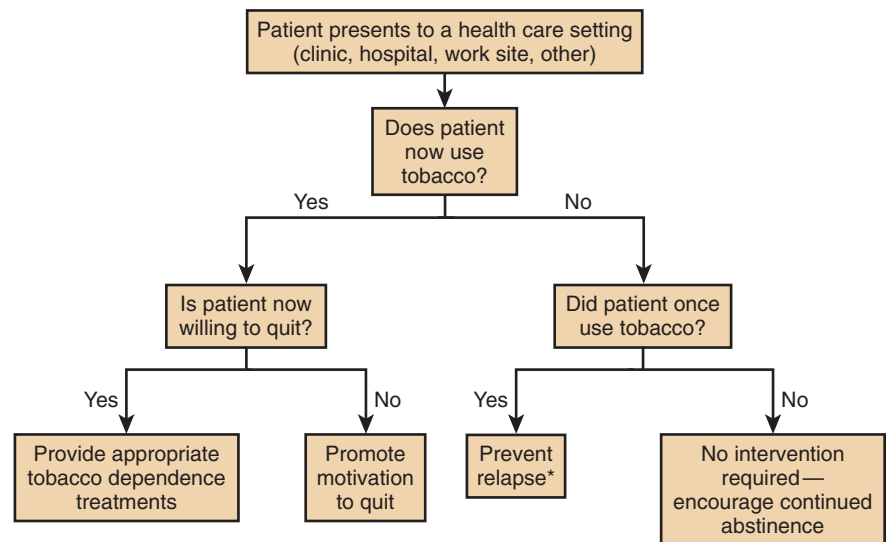


Figure 46-2 An algorithm for treating tobacco use. One of the main interventions is the first step, namely asking about and recording tobacco use at each office visit.

*Relapse prevention interventions are not necessary in the case of the adult who has not used tobacco for many years.

Table 46-6 Brief Strategies to Help the Patient Willing to Quit Tobacco Use—The “5 A’s”

Strategies for Implementation	Action
Ask—Systematically identify all tobacco users at every visit.	Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented.
Advise—Strongly urge all tobacco users to quit.	In a clear, strong, and personalized manner, urge every tobacco user to quit.
Assess—Determine willingness to make a quit attempt.	Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).
Assist—Aid the patient in quitting.	Help the patient with a quit plan. Provide practical counseling (problem solving/skills training). Provide intra-treatment social support. Help patient obtain extra-treatment social support. Recommend the use of approved pharmacotherapy except in special circumstances.
Arrange—Schedule follow-up contact.	Schedule follow-up contact, either in person or via telephone.

Adapted from A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med* 35:158–176, 2008.

at every visit. Tobacco use should be treated as a vital sign by using tobacco status stickers on patients’ charts, electronic medical records, or computer reminder systems. The practice of routinely recording a patient’s tobacco use status increases the OR for quitting by twofold.

Brief strategies to help a patient quit (the “5 A’s”) (Table 46-6), which can be implemented in as little as 3 minutes, increase cessation rates significantly. In a meta-analysis of 31 trials, brief physician advice increased quit rates by 70%.⁸⁹ Intensive behavioral treatment of tobacco dependence produces higher success rates than brief advice does and is cost-effective. However, these intensive programs are less widely available and may be less acceptable to patients than brief interventions. Nevertheless, clinicians with training in intensive smoking cessation therapy should be identified as a referral source for smokers who are interested.

Multiple smoking cessation smart phone applications are now available to patients, but unfortunately they rarely adhere to guidelines. Although text messaging has not been demonstrated to enhance cessation rates, it may lead to lower consumption.⁹¹ This field of research in preventive

medicine is expanding rapidly, particularly in diabetes and hypertension care, and recent federal policy changes are becoming more supportive of preventive counseling. As services expand, there is a concomitant increased attention to the health-related costs of smokers and an increasing trend of businesses not to hire smokers.⁹²

Public Health Service guidelines recommend that all smokers trying to quit should be offered pharmacotherapy (Table 46-7).⁹⁰ In brief, three types of medications have been approved by the U.S. Food and Drug Administration (FDA) for smoking cessation—nicotine, bupropion, which was originally marketed as an antidepressant drug, and varenicline (Table 46-8). Other drugs such as nortriptyline and clonidine have been shown in clinical trials to be effective in aiding smoking cessation but have not been approved by the FDA for this purpose.

SMOKING CESSATION COUNSELING

Counseling smokers about the dangerous effects of tobacco should be routine medical practice and has been shown to be an effective method of improving cessation rates. Based

Table 46-7 General Clinical Guidelines for Prescribing Pharmacotherapy for Smoking Cessation

- In general, all smokers trying to quit smoking should be offered pharmacotherapy.
- There are seven first-line smoking cessation medications—five types of nicotine replacement therapy, sustained-release bupropion, and varenicline. Varenicline or the combination of nicotine patch plus ad libitum short-acting nicotine products appears to be most effective. However, the choice of first-line therapy should be governed by patient preference, familiarity of the clinician with the medication, contraindications for specific patients, and prior experience of the patient with specific pharmacotherapies.
- Second-line therapies include clonidine and nortriptyline. These should be reserved for individuals with contraindications to/or failure of response to first-line medications.
- Bupropion and nicotine replacement therapies may delay but not prevent weight gain after smoking cessation. It is recommended that patients start or increase physical activity, but strict dieting is discouraged because this appears to increase the likelihood of relapse to smoking. Patients should be reassured that weight gain after quitting is self-limited and poses much less of a risk to health than smoking.
- Transdermal nicotine (patches), nicotine gum, and bupropion appear to be safe for patients with chronic cardiovascular disease. Other medications are likely to be much safer than smoking in the presence of medical disease but need further evaluation.
- In smokers with prolonged withdrawal symptoms or in those who cannot resist smoking without medication, long-term therapy with nicotine replacement medication, bupropion, or varenicline appears to be safe and effective therapy.
- Recent research suggests that combining bupropion with nicotine patches or combining nicotine patches with ad libitum use of nicotine gum or nicotine nasal spray increases abstinence rates compared to the rates produced by a single form of therapy.

Adapted from A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med* 35:158–176, 2008.

on a review of 188 randomized trials, personal advice and encouragement to stop smoking provided by a physician during a routine office visit resulted in an estimated 2% of all smokers stopping and not relapsing over 1 year.⁹³ Although this percentage seems low, it is both cost-effective and important when considering the large population and the risk for disease. Specific patient populations may have better results—8% of pregnant smokers, 21% of healthy men at risk for cardiovascular disease, and 36% of survivors of myocardial infarction will stop smoking when receiving advice and encouragement. This high success rate reflects the patient's inherent motivation once challenged by a condition that has been caused or may be aggravated by cigarette smoking.

Group counseling is less cost-effective than brief advice but may be necessary for smokers who are having a hard time quitting with less intensive therapy. A review of 16 studies comparing group counseling found increased rates of cessation compared to self-help programs (16 studies; OR = 2.0) or no intervention (6 studies; OR = 2.2).⁸⁹ There is no evidence that group counseling is more effective than a similar intensity of individual counseling.

Telephone counseling is effective in promoting cessation. In a large randomized, controlled trial of 1973 intensively counseled callers versus 1309 controls, telephone counseling through the California Quitline nearly doubled abstinence rates.⁹⁴ The 12 months' self-reported cessation rates

for those who made one or more cessation attempts was 23.3% in the treatment group and 18.4% in the control group. A recent meta-analysis of quit line trials confirmed the benefit of this intervention and suggested that multiple calls provided more benefit than a single call.⁹⁵ Telephone hotlines for smoking cessation are available at no cost in many states across the United States. Thus the busiest physician can easily refer patients to a hotline for cessation if personal counseling time is not readily available.

In-hospital counseling is found to be effective for patients admitted with cardiovascular disease but is not well studied in other populations. Counseling may also be enhanced with concurrent pharmacotherapy. In a randomized, controlled trial of 274 patients, Molyneux and associates⁹⁶ found that nicotine replacement therapy given with brief counseling is more effective than counseling alone or usual care. Counseling alone was not more effective than usual care, and differences between all groups disappeared at 12 months. These findings underscore the value of cessation medications when given with even brief advice. Longer physician counseling time and more office visits translate into higher cessation rates, independent of pharmacotherapy. Inpatient counseling from nurses and respiratory therapists can significantly improve cessation rates and should be routine clinical practice to maximize the “teachable moment” available during a hospitalization.⁹⁷

PHARMACOTHERAPY OF SMOKING CESSATION

Nicotine Replacement Therapy

Currently three medications have been approved for smoking cessation: nicotine, bupropion, and varenicline. All types of smoking cessation medications, if used properly, double smoking cessation rates compared with placebo treatments.^{90,98}

Nicotine replacement medications include nicotine polacrilex gum, transdermal nicotine patches, nicotine nasal spray, the nicotine inhaler, and nicotine lozenges. All seem to have comparable efficacy, but, in a randomized study, compliance was greatest for the patch, lower for gum, and very low for the spray and the inhaler.⁹⁹ A smoker should be instructed to quit smoking entirely before beginning nicotine replacement therapies.

Nicotine gum should be used with instructions to chew slowly, to chew 8 to 10 pieces per day for 20 to 30 minutes each, and to continue for an adequate period for the smoker to learn a lifestyle without cigarettes, usually 3 months or longer. Side effects of nicotine gum are primarily local and can include jaw fatigue, sore mouth and throat, upset stomach, and hiccups.

Transdermal nicotine patches are marketed in several preparations—some deliver 21 mg over a 24-hour period, and one delivers 15 mg over a period of 16 hours. Most brands have lower-dose patches for tapering. Patches are applied in the morning and removed either the next morning or at bedtime, depending on the patch. Patches intended for 24-hour use can also be removed at bedtime if the patient is experiencing insomnia or disturbing dreams. Full-dose patches are recommended for most smokers for the first 1 to 3 months, followed by one to two tapering doses for 2 to 4 weeks each.

Table 46-8 Suggestions for the Clinical Use of Pharmacotherapies for Smoking Cessation

Pharmacotherapy	Precautions/ Contraindications	Adverse Effects	Dosage	Duration	Availability
FIRST-LINE					
Bupropion hydrochloride, sustained release	History of seizure History of eating disorders	Insomnia Dry mouth	150 mg every morning for 3 days then 150 mg twice daily (begin treatment 1–2 wk prequit)	7–12 wk maintenance up to 6 mo	Prescription only
Nicotine gum	Temporomandibular joint disorder	Mouth soreness Dyspepsia	If 1–24 cigarettes/day, 2 mg gum (≤ 24 pieces/day) If ≥ 25 cigarettes/day, 4 mg gum (≤ 24 pieces/day)	Up to 12 wk	OTC only
Nicotine inhaler		Local irritation of mouth and throat	6–16 cartridges/day	Up to 6 mo	Prescription only
Nicotine nasal spray	Chronic nasal disorders, including rhinitis, polyps, and sinusitis	Nasal irritation Throat burning	8–40 doses/day	3–6 mo	Prescription only
Nicotine patch	Skin diseases, such as atopic or eczematous dermatitis	Local skin reaction Insomnia	21 mg/24 hr 14 mg/24 hr 7 mg/24 hr 15 mg/16 hr	4 wk then 2 wk then 2 wk 8 wk	Prescription and OTC
Nicotine lozenge	None	Nausea, hiccups, heartburn	If time to first cigarette >30 min, 2 mg; if time to first cigarette <30 min, 4 mg, up to 20 per day	12 weeks	OTC only
Varenicline	Significant kidney disease Patients on dialysis	Nausea Abnormal or vivid strange dreams Depressed mood and other psychiatric symptoms Trouble sleeping	0.5 mg/day for 3 days, 0.5 mg twice /day for 4 days, then 1 mg twice/day (begin treatment 1 wk prequit)	3–6 mo	Prescription only
SECOND-LINE					
Clonidine	Rebound hypertension	Dry mouth Drowsiness Dizziness Sedation	Initial 0.10 mg twice daily, titrate to 0.15–0.75 mg/day	3–10 wk	Prescription only (oral formulation) Prescription only (patch)
Nortriptyline	Risk for arrhythmias	Sedation Dry mouth	Initial 25 mg/day, titrate to 75–100 mg/day	3–6 mo	Prescription only

OTC, over-the-counter.

Adapted from A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med* 35:158–176, 2008.

Nicotine nasal spray, one spray into each nostril, delivers about 0.5 mg nicotine systemically and can be used every 30 to 60 minutes. Local irritation of the nose commonly produces burning, sneezing, and watery eyes during initial treatment, but tolerance develops to these effects in 1 to 2 days.

Nicotine inhalers actually deliver nicotine to the throat and upper airway, where it is absorbed similarly to the nicotine from gum. It is marketed as a cigarette-like plastic device and can be used ad libitum.

Nicotine lozenges are available over the counter in 2-mg and 4-mg strengths and are to be placed in the buccal cavity, where they are slowly absorbed over 30 minutes.¹⁰⁰ Smokers are instructed to choose their dose according to how long after awakening in the morning they smoked their first cigarette (a measure of the level of dependence). Those who smoke within 30 minutes are advised to use the 4-mg lozenge, whereas those who smoke their first cigarette at 30 or more minutes are advised to use the 2-mg lozenges. Use is recommended every 1 to 2 hours.

Nicotine medications seem to be safe in patients with cardiovascular disease and should be offered to cardiovascular patients.^{101–103} Although smoking cessation medications are recommended by the manufacturer for relatively short-term use (generally 3 to 6 months), the use of these medications for 6 months or longer is safe and may be helpful in smokers who fear relapse without medications. There is also evidence that treatment of smokers with nicotine patches before smoking cessation results in decreased cigarette consumption and subsequently higher quit rates.¹⁰⁴

Bupropion

Bupropion sustained release (Zyban) is a dopamine-norepinephrine reuptake inhibitor originally marketed and still widely used as an antidepressant. Bupropion was found to aid smoking cessation whether or not a smoker was depressed.¹⁰⁵ Hurt and colleagues demonstrated that, with a 300-mg sustained-release dose, 44% of patients quit at 7 weeks versus 19% of controls. This difference was sustained at 12 months (23% versus 12%). This study also indicated

that when smokers quit they gain less weight while taking bupropion compared to placebo. An additional randomized, placebo-controlled trial demonstrated that the combination of bupropion with nicotine patch was safe, and that bupropion alone or in combination was as effective or more effective than patch alone.¹⁰⁶ Bupropion used for 1 year for relapse prevention was demonstrated to be safe and effective and significantly better at promoting cessation (55%) than placebo (42%).¹⁰⁷ Given its antidepressant properties, bupropion is a logical choice for depressed smokers but, as mentioned previously, has clear efficacy in smokers without depression as well.

Bupropion is dosed at 150 mg sustained release per day for 3 days, then 150 mg twice daily. Bupropion should be initiated 1 to 2 weeks prior to the quit date, then continued at 300 mg/day for the next 6 to 12 weeks. Bupropion in excessive doses can cause seizures and should not be used in an individual with a history of seizures or with eating disorders (bulimia or anorexia).

Varenicline

Varenicline, available by prescription only, is a nicotinic receptor partial agonist that selectively binds to $\alpha 4\beta 2$ nicotinic cholinergic receptors in the brain.¹⁰⁸ This receptor mediates dopamine release and is thought to be the major receptor involved in nicotine addiction. A partial agonist means that the drug both activates the receptor and blocks the effects of other agonists on the receptor. Varenicline activates the $\alpha 4\beta 2$ nicotinic cholinergic receptor with a maximal effect about 50% that of nicotine and, at the same time, blocks effects of nicotine from tobacco use on the receptor. As a consequence of the receptor stimulation, nicotine withdrawal symptoms are relieved, and, as a consequence of receptor blockade, the rewarding effects of cigarettes are diminished. The latter effect reduces the desire to smoke and, in the case of a lapse, may prevent continued smoking.

In clinical trials, varenicline treatment for 12 weeks has been shown to be more effective than bupropion sustained release 300 mg and placebo.¹⁰⁹ With varenicline, bupropion, and placebo, continuous abstinence rates from 9 to 52 weeks were 23%, 15%, and 10%, respectively. Varenicline has also been shown to be effective in preventing relapse over 6 months.¹¹⁰

A recent meta-analysis suggests that varenicline is also more effective than nicotine replacement therapy alone. The major side effects of varenicline are nausea, vomiting, and insomnia.⁹⁸ A variety of neuropsychiatric side effects, including depression, psychosis, and suicide, have been reported anecdotally but were not observed in clinical trials.¹¹¹ The causal relationship between varenicline and these neuropsychiatric events has not been established because smoking cessation itself can be associated with mood disturbances, including suicidality. In any case, smokers treated with varenicline should be advised about possible neuropsychiatric effects and monitored for such events during treatment. Varenicline has been shown to be effective in promoting smoking cessation in patients with cardiovascular and with pulmonary disease.^{112,113} Cardiovascular safety concerns with varenicline have been raised with one meta-analysis showing a small but significant

increased risk but another meta-analysis showed no significant increase.^{114,115}

Varenicline is initiated in a dose of 0.5 mg per day for 3 days, then 0.5 mg twice daily for 4 days, followed by a maintenance dose of 1 mg twice daily. Begin treatment 1 week prior to quit date. Lower doses may be used if nausea is a problem at higher doses. Because varenicline is eliminated by the kidneys, dose reductions are required in the presence of severe renal disease. The approved duration of treatment is 3 months, with another 3 months optional for prevention of relapse.

Combination Therapy

Combined medications for smoking cessation are more effective than individual therapies, particularly when combining long-acting medications such as nicotine patch or bupropion with short-acting nicotine replacement therapy used at times of intense urges or cravings to smoke.⁹⁸ Only bupropion and transdermal nicotine in combination have been approved by the FDA. However, a number of studies have looked at various combinations of medications, and there have been no significant safety issues.^{107,116-118} Studies comparing different therapies have found that combinations are two to three times more effective than single medications used alone. A stepwise process that incorporates combination therapies after patients have failed single therapies would be logical and would balance the increased costs of additional medications with increased benefit.

MOTIVATING SMOKERS TO QUIT

The well-known association between cigarette use and lethal diseases such as lung cancer, myocardial infarction, stroke, and COPD is insufficient to motivate many cigarette smokers to quit. This is due to the effects of the addiction to nicotine, which include denial and rationalization, a part of all drug addictions. As described previously, many smokers depend on nicotine to cope with stressors encountered in daily life. The perceived stress-reducing effect of nicotine is rapid and readily available. In contrast, quitting for many smokers results in a period of intense dysphoria and dysfunction, which can easily be avoided by smoking one or more cigarettes. A telephone-based survey conducted in 1999 found that only 29% of smokers felt that they were at greater risk for myocardial infarction, and only 40% felt they were at greater risk for development of cancer compared to nonsmokers.¹¹⁹ This clearly indicates denial of risk and may explain why many smokers become motivated to quit only when they develop a medical condition later in life. Becoming a nonsmoker requires a profound change of self-image and a discovery of personal coping skills that may have not been used previously.

The physician's role in the motivation process can be substantial. The message to the smoker must be consistent and inspirational. Patients clearly respond to physician advice, and hopelessness can be allayed by describing the many options available for cessation medication and counseling. Smoking cessation is the most important health initiative many patients will ever undertake and is highly cost-effective for the health care system. It is difficult to address

smoking in patients when three or four medical issues are being managed in addition to smoking cessation. For this reason, a separate return appointment focused solely on smoking cessation is recommended.

Motivating patients to quit needs to be more than steering them away from disease, but also steering them toward greater self-control, self-expression, independence, and positive role modeling. Exercise during trials of smoking cessation may reduce anxiety, tension, and stress but was not found to be an independent predictor of success in a randomized, controlled trial.¹²⁰ Walking on a regular basis is a reasonable initial step and in many cases improves self-esteem and investment in health.

BENEFITS OF QUITTING

The benefits of quitting smoking are substantial for smokers of any age. A person who quits smoking before age 50 has half the risk for dying in the next 15 years compared with a continuing smoker.¹²¹ Life expectancy was shortened by more than 10 years among a large cohort of current smokers compared to never smokers; quitting at an earlier age (e.g., 25 to 34) extended life expectancy by 10 years compared to quitting later (e.g., 45 to 54), when the added life expectancy was 6 years.³ These results confirm the known dangers of smoking and must be translated into a heightened effort to help younger smokers quit.

Smoking cessation reduces the risk for developing lung cancer, with the risk falling to half that of a continuing smoker by 10 years and one-sixth that of a smoker after 15 years' cessation. Quitting smoking in middle age substantially reduces lung cancer risk, with a 50% reduction in risk if a lifelong smoker quits at age 55 compared with age 75.¹²² The risk for acute myocardial infarction falls rapidly after quitting smoking and approaches nonsmoking levels within 1 year of abstinence. Cigarette smoking produces a progressive loss of airway function over time that is characterized by an accelerated loss of *forced expiratory volume in 1 second* (FEV₁) with increasing age. Loss of FEV₁ due to cigarette smoking cannot be regained by cessation, but the rate of decline slows after smoking cessation and returns to that of nonsmokers (see Fig. 43-5).¹²³ Women who stop smoking during the first 3 to 4 months of pregnancy reduce the risk for having a low-birth-weight infant to that of a woman who has never smoked.

After quitting, smokers gain an average of 5 to 7 pounds, which is perceived by some smokers as undesirable and as a reason not to quit.¹²⁴ Smokers tend to be thinner because nicotine increases energy expenditure and suppresses a compensatory increase in food consumption.⁸² After they quit smoking, ex-smokers tend to reach the weight expected had they never smoked. On balance, the benefits of quitting far outweigh the risks associated with weight gain, and patients should be counseled accordingly.

RESOURCES FOR PHYSICIANS

Most hospitals have smoking cessation services available that will enable referral of smokers if deemed necessary. Most states have toll-free quit lines that can be accessed

through a national network at 1-800-QUIT-NOW (1-800-784-8669) and that provide smoking cessation information and counseling and have been shown to be effective.⁹⁴ Internet-based programs such as QuitNet (www.quitnet.com) can provide online chat rooms and can give smokers with access to a computer a sense of community with other smokers in a similar position. If patients do not have their own computer, the public library is a smoke-free environment where they can access computers. The American Lung Association has significant information and an online program called "Freedom From Smoking" to which patients can be referred (<http://www.ffsonline.org/>). The Centers for Disease Control and Prevention has information that can be downloaded for adults, youth, and Spanish-speaking patients (www.cdc.gov/tobacco/). Patients suspected of having underlying depression, anxiety, or other substance abuse disorders may benefit from psychiatric referral to evaluate these conditions known to reduce the likelihood of smoking cessation.

FEDERAL REGULATION OF TOBACCO





In 2009 the U.S. Congress, through the Family Smoking Prevention and Tobacco Control Act, gave the FDA the authority to regulate the manufacture, distribution, and marketing of tobacco products to protect public health.¹²⁵ The Act (1) restricts cigarette and smokeless tobacco sales, advertising, and marketing to youth; (2) prohibits "reduced harm" claims such as "light" or "mild"; (3) requires bigger and more prominent warning labels; and (4) gives the FDA authority to regulate product standards, including banning characterizing flavors (except menthol), and allows the FDA to reduce potentially toxic constituents, including nicotine (although nicotine levels cannot be reduced to zero). FDA regulation of the addictiveness of tobacco has the potential to substantially reduce the prevalence of cigarette smoking and resultant disability and death in the future.¹²⁶

ELECTRONIC CIGARETTES

Electronic cigarettes (also known as e-cigarettes or electronic nicotine delivery devices) heat a nicotine solution to generate an aerosol (called a *vapor*) that is inhaled, without the combustion of tobacco and its toxic constituents. The devices consist of a cartridge containing a liquid (propylene glycol, sometimes with vegetable glycerin, nicotine, and flavorings), a heating element, a battery, and a microchip (Table 46-9). E-cigarettes are marketed with claims of health benefit compared with smoking cigarettes; they are marketed for use in reducing and quitting smoking, for use when a person is forbidden to smoke cigarettes, and for use in avoiding generating smelly and irritating secondhand smoke. The prevalence of the use of e-cigarettes has exploded since they were first marketed in 2006, with an 11.4% prevalence of ever use and 4.1% prevalence of use in the past 30 days in the United States in 2011.¹²⁷ In the European Union in 2012, 20.3% of current smokers, 4.7%

Table 46-9 E-Cigarette Designs, Descriptions, and Brand Names

E-cigarettes come in various sizes and designs. All contain a cartridge, a heating element, and a battery and provide an aerosol containing nicotine.

Product	Description	Some Brands
Disposable e-cigarette 	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing vapor.	NJoy, Blu, Green Smoke
Rechargeable e-cigarette 	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and/or how many puffs may be taken consecutively.	V2 Cigs, Halo G6, Mark Ten
Pen-style, medium-sized rechargeable e-cigarette 	Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing the smoker to regulate length and frequency of puffs.	eGo, Kanger EVOD, Halo Triton
Tank-style, large-sized rechargeable e-cigarette 	Much larger than a cigarette with a higher-capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.	Kanger Aerotank, Innokin iClear, Aspire Nautilus

From Grana R, Benowitz N, Glantz SA: Background paper on e-cigarettes (electronic nicotine delivery systems): prepared for the 7th meeting of the WHO Study Group on Tobacco Product Regulation. San Francisco, 2013, UCSF.

of ex-smokers, and 1.2% of never smokers reported having used an e-cigarette.^{127a} As of 2013, there are more than 400 brands on the U.S. market, and they vary in the size of the device, the size of the cartridge, and the strength of the battery. Some look like cigarettes and are disposable; others look like pens or cigars and have refillable tanks. E-cigarette liquids are sold over the Internet or in “vape” shops, in which the user can select the liquid, including the vehicle, nicotine concentration, and flavor.

There is currently considerable debate in the public health community about the safety and benefit of e-cigarettes. All agree that e-cigarettes could be a health benefit if people would use e-cigarettes and stop smoking cigarettes entirely. There are many anecdotal reports of people quitting smoking using e-cigarettes, and one controlled clinical trial showing noninferiority of e-cigarettes compared to nicotine patches for cessation with minimal counseling via quit lines.¹²⁸ However, the quit rates in this trial were low, and population survey data do not show that people who have used e-cigarettes are more likely to quit than those who have not.¹²⁹ Many e-cigarette users report smoking fewer cigarettes per day while using e-cigarettes, but the health benefits of such reduction are not clear, and there is concern that the availability of e-cigarettes when one cannot smoke conventional cigarettes may impede quitting, resulting in more smokers and more population harm.

There are also concerns about the potential toxicity of e-cigarettes. The products that were marketed initially were contaminated with tobacco-specific nitrosamines and alkaloids other than nicotine, which were extracted along with nicotine from tobacco. Some more recently marketed products do not have such contamination. Propylene glycol in aerosol form can be a pulmonary irritant and reduces

dynamic airway resistance.¹³⁰ E-cigarette use could be detrimental to people with asthma and COPD. Nicotine itself has some potentially deleterious effects on cardiovascular hemodynamics (increased heart rate and blood pressure) and may impair endothelial function and promote insulin resistance; however, its effects are certainly much less than those of the combustion products in cigarette smoke. In addition, some e-cigarettes deliver nanoparticles containing tin, nickel, and/or chromium, the toxicity of which is unknown.

The most important potential population harm may be the renormalization of cigarette smoking behavior, resulting in more youth initiation and fewer adults quitting smoking. Currently e-cigarette advertising is unregulated and includes the use of young models and celebrities to convey images of the product as glamorous and modern. Recent data indicate a substantial increase in e-cigarette use among youth, including a number of youth who have used e-cigarettes without ever having smoked conventional cigarettes.¹³¹ Whether such users become addicted to nicotine and become cigarette smokers later is unknown at this time.

At present e-cigarettes are not regulated in the United States, although the FDA has signaled its intention to do so.¹³² FDA regulation would be particularly useful in ensuring the safety of these products, in limiting marketing and access to youth, and in restricting use in situations where smoking is banned so as to both minimize environmental pollution with e-cigarette vapor and to mitigate the renormalization of smoking behavior. Some clinicians will likely recommend e-cigarette use to patients who have been unable to quit smoking using traditional counseling and medications, although the use of e-cigarettes in such a role has not been proven.

Key Points

- For most smokers, quitting smoking is the single most important intervention to improve long-term health and is highly cost-effective for the health care system.
- In addition to causing cancer and COPD, smoking increases the risk for other pulmonary diseases, including respiratory infection (including pneumococcal pneumonia and tuberculosis), desquamative interstitial pneumonitis, and idiopathic pulmonary fibrosis, and increases the incidence of cardiopulmonary complications after surgery and in critically ill patients.
- Compulsive tobacco use is sustained by the addictive effects of nicotine, which include pleasure, modulation of mood and arousal, and avoidance of withdrawal symptoms.
- Optimal smoking cessation interventions in a physician's office should include systematically asking about tobacco use at every visit, advising smokers to quit and assessing their willingness to do so, providing or referring for counseling, provision of pharmacotherapy, and follow-up to encourage continued abstinence or to manage relapses.
- Quitting smoking even in middle age substantially reduces the risk for lung cancer and cardiovascular disease.
- Electronic cigarettes that deliver a nicotine aerosol without tobacco combustion products are being mar-

keted with claims to reduce smoking, to aid quitting, and to use where conventional smoking is banned. The potential benefit of e-cigarettes at present is unknown. The greatest potential harm of e-cigarettes would be in the renormalization of cigarette smoking behavior, resulting in more youth initiation and fewer adults quitting smoking.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION

Cystic fibrosis (CF) is a multisystem genetic disease that affects children and young adults. CF is the most common monogenetic disease in Caucasian populations. The disease is caused by mutations in the *CF transmembrane conductance regulator* (CFTR) protein, an anion channel expressed on the epithelial surface. CF is typified by the presence of chronic upper and lower respiratory tract infection leading to bronchiectasis and end-stage lung disease. Manifestations in the pancreas, gastrointestinal tract, skin, and male reproductive tract are also prominent.

Understanding the biology and treatment strategies in CF is important for several reasons. First, it is the most common cause of chronic respiratory failure in children and young adults. Second, CF is the most common reason for pancreatic exocrine dysfunction in children and young adults. Third, it is a major cause of bronchiectasis and pansinusitis, among other sinopulmonary conditions in this age group, and therefore figures prominently in the differential diagnosis of various syndromes. Finally, advances in CF research have provided a roadmap for the understanding of pathophysiology and treatment for other severe airway diseases including chronic obstructive pulmonary disease, asthma, and non-CF bronchiectasis.

Through an increased understanding of CF pathobiology, the partnership of academic and pharmaceutical research enterprises with a multinational team of care centers and the Cystic Fibrosis Foundation, CF care represents a model for the treatment of chronic, life-threatening disease. It also provides a seminal example of the potential for translational medicine to deliver scientific advances that have transformed a universally fatal condition by the advent of comprehensive care centers and targeted therapeutics. Future advances will capitalize on personalized therapies directed at the underlying cause of the disease.

This chapter highlights the current understanding of CF pathobiology, with particular emphasis on the role of CFTR in disease pathogenesis. Insights into diagnosis, prognosis, and natural history are explored. CF therapeutics, including a special emphasis on the development of new therapies that target the basic defect, are also described in detail.

HISTORICAL PERSPECTIVE

Descriptions of abnormally high sweat salinity in children associated with premature death date back to 1650, but the first comprehensive description of CF as a distinct clinical entity was published in 1938 by Anderson who named the disease “*cystic fibrosis of the exocrine pancreas*.”¹ In 1945, Farber described the condition as a generalized *mucoviscidosis* resulting from obstruction of exocrine glands, a theme that has engendered recent interest as further research has described innate abnormalities of CF mucus.² Also in the 1940s, clinical descriptions first linked mucoviscidosis to severe and recurrent lung infections. With the advent of effective antibiotics, antimicrobial therapy began to be used for treatment of severe pulmonary infections for the first time.

The onset of an extreme heat wave in the northeastern United States in the summer of 1948 led di Sant’Agnese to describe high salt concentrations in the sweat of infants with CF and introduce the concept linking abnormal ion transport with the clinical features of the disease.³ Hence the end organ dysfunction in the sweat gland caused by functional decrements in CFTR were among the first characteristics recognized with the disorder. In this seminal work, di Sant’Agnese demonstrated elevated levels of sodium and chloride in sweat in greater than 98% of subjects with CF, a finding that remains a cornerstone

underlying the diagnosis today and explains an old Irish folk saying that “if your baby tastes of salt, he is not long for this world.”

Before the discovery of the *CFTR* gene and description of the *CFTR* protein in 1989,⁴⁻⁶ early observations based on di Sant’ Agnese’s work led to postulation of a derangement of a chloride anion channel as central to disease pathogenesis. To measure this phenomenon, Gibson and Cooke developed the pilocarpine method of sweat chloride testing, which remains a key diagnostic test for CF.^{6a} Additional observations by Quinton demonstrated that the sweat gland in CF patients is impervious to chloride.^{7,8} At the same time, a number of contributions regarding abnormalities of ion transport within the nasal epithelium by Knowles and colleagues^{9,10} and subsequent membrane patch-clamp analysis of epithelial cells from the airways of patients with CF by Welsh and Liedtke¹¹ provided conclusive evidence of a defect in chloride permeability of plasma membranes in the lung, in addition to an associated abnormality in measures of sodium transport.^{9,10} Soon thereafter Frizzell¹² identified the role of *CFTR* as an ion channel tightly regulated by phosphorylation. Restriction fragment-length polymorphism mapping by Collins, Riordan, and Tsui^{5,13,14} located the *CFTR* gene, among the first human genes to be identified, to the long arm of chromosome 7. This finding helped set the stage for isolation and cloning of the *CFTR* gene and the most common mutation, F508del *CFTR*, ultimately leading to an improved understanding of CF pathogenesis and new molecular therapeutics directed toward the basic defect.¹⁵

EPIDEMIOLOGY

CF is the most common genetic disease in Caucasians, found in 1 in 2500 to 3500 live births in the United States with lesser frequencies among African Americans (1:17,000). There is a varied incidence in particular ethnic groups, ranging from 1:569 in an isolated Ohio Amish population to 1:90,000 in Asian populations.¹⁶

CFTR mutations are most prevalent in persons from or descended from central and Northern European populations. Non-European-descendent white populations demonstrate intermediate rates of *CFTR* mutations, and Native Americans, Asian populations, and black Africans demonstrate the lowest rates. Proposed reasons for the selectivity of *CFTR* mutations in these populations include a heterozygote advantage in epidemic illnesses such as cholera, tuberculosis, or plague; the former is of particular interest because the absence of *CFTR*-dependent chloride transport could confer an advantage on cyclic 3',5'-adenosine monophosphate (cAMP) activation by cholera toxin. Conversely, selectively lower rates of *CFTR* mutations in populations living in tropical or semitropical environs could be due to propensity for dehydration and salt wasting. In white populations, 1 in 25 Caucasians are carriers for gene mutations,¹⁷ resulting in a carrier rate of 2% to 5%. CF carriers do not exhibit manifestations of CF illness, although carrier status has been proposed to increase the propensity and/or severity of respiratory disorders such as asthma and rhinosinusitis.^{18,19}

GENETIC BASIS

CF is an autosomal recessive disease caused by single gene mutations of the *CFTR* gene on the long arm of chromosome 7.^{5,13,14} This gene encodes a full-length protein in the *adenosine triphosphate (ATP) binding cassette (ABC)* transporter family, sharing primary and secondary structural elements with other membrane pump proteins from this family. The approximately 250 kB *CFTR* gene encodes for 27 exons for a full-length protein consisting of two membrane-spanning domains, two *nucleotide binding domains* (NBDs), and a single *regulatory domain* (R domain). A schematic proposed structure of the *CFTR* protein is shown in Figure 47-1.

There are many causative *CFTR* mutations, with more than 1900 recently described.¹⁶ Despite this, relatively few mutations account for the majority of *CFTR* alleles and are particularly common in the northern European descent population (Table 47-1). For example, the most frequent 159 mutations account for 96% of CF-causing alleles. The most prevalent mutation is F508del (c.1521_1523delCTT), which causes a 3-base pair deletion that results in omission of phenylalanine at position 508. This mutation accounts for about 75% of all *CFTR* alleles, though the distribution of this mutation is heterogeneous among particular ethnic populations and as high as 86% in Northern European Caucasians.¹⁶

F508del *CFTR* causes protein misfolding, resulting in endoplasmic reticulum-associated degradation. F508del is the prototypical class II mutation (mutations that result in premature degradation or incomplete maturation). Other mutations fall into several classes on the basis of molecular mechanism (Fig. 47-2). This includes incomplete synthesis due to *premature termination codons* (PTCs, class I); disordered regulation and gating, causing diminished ATP binding and hydrolysis (class III), which includes the G551D mutation; defective chloride conductance (class IV); and a reduced number of *CFTR* transcripts due to a promoter or splicing abnormality (class V). Mutations in class I, II, and III tend to cause severe *CFTR* functional abnormalities, whereas class IV and V mutants often exhibit preserved function (i.e., mild/variable mutations). Understanding the molecular abnormality in each mutational class is important for addressing the defect via pharmacologic agents such as *CFTR* modulators, discussed later in this chapter.

Despite robust knowledge of the various mutations in *CFTR*, still only 90% of CF patients have identified disease-causing mutations, although this is increasing with more frequent use of protein sequencing. In addition, the pathogenetic role of many mutations remains unknown but is being determined in a centralized fashion through the “CFTR2” project (www.CFTR2.org).²⁰ Some common variants such as M470V have been determined to be common polymorphisms rather than disease-causing alleles, although they may have a role in expression of the F508del defect.¹⁶ Others, such as the poly T sequence located within intron 10, can modify *CFTR* expression, thus acting as an important covariate to disease expression.²¹

The functional basis of various *CFTR* mutations allows correlation of genotype to phenotype, although *CFTR* genetics alone explain only some of the outcome of CF patients. For example, when two severe (class I, II, or III)

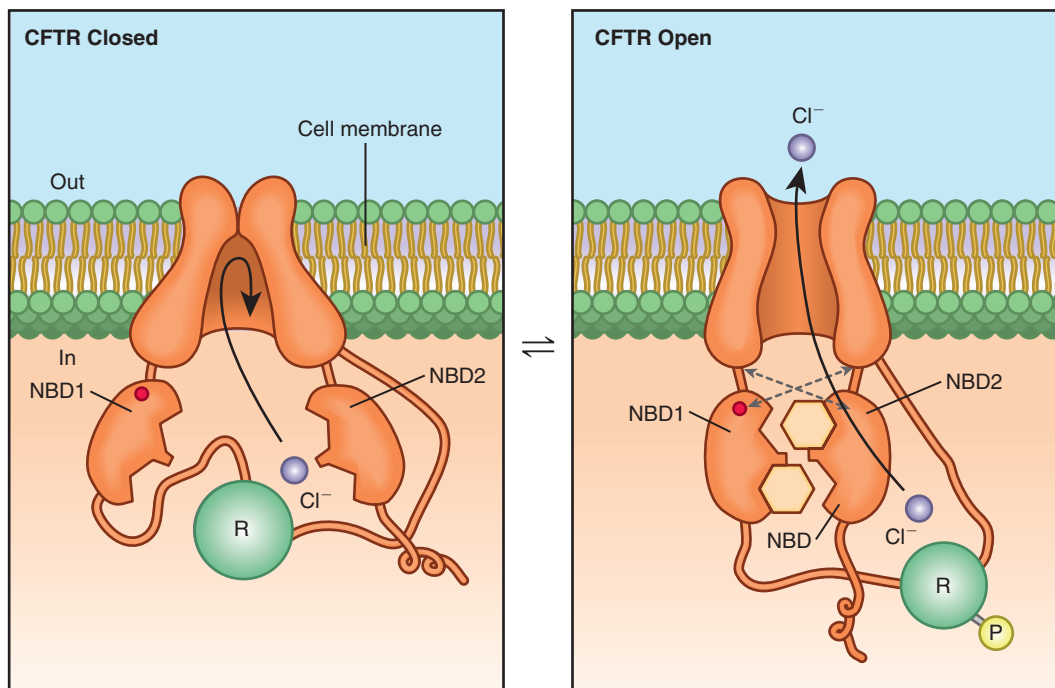


Figure 47-1 CFTR structure and domain assembly. Schematic representing the proposed structure of the cystic fibrosis transmembrane conductance regulator (CFTR) in its closed (*left*) and open (*right*) configurations. The two transmembrane spanning domains consist of six alpha helices each and together form the channel pore. Gating of the channel is controlled by the two intracytoplasmic nucleotide binding domains (NBD1 and NBD2) as they bind and hydrolyze ATP (hexagons), in addition to a regulatory domain (R), which contains numerous sites of phosphorylation. Normal activation of the protein requires phosphorylation of the regulatory domain. The NBDs bind and hydrolyze ATP, inducing channel gating by conferring opening of the pore through interfaces with the transmembrane domains via their extracellular loops (symbolized by dotted lines), which also function to stabilize the overall protein structure. The location of the F508del mutation (red dot) is on the surface of NBD1, compromising its stability and interrupting interactions with the transmembrane domains.

mutations are present, pancreatic insufficiency usually results (especially in those patients homozygous for F508del). The presence of two severe mutations also confers risk for severe phenotypic manifestations including meconium ileus and hepatobiliary disease. Alternatively, the presence of one or more mild/variable mutations may confer enough residual CFTR function to alter expression or severity. CF patients with mild mutations have intermediate sweat chloride, which correlates with the presence of pancreatic sufficiency.^{16,22} When two mild/variable mutations are present, atypical forms of CF arise, such as congenital absence of the vas deferens, idiopathic pancreatitis, or late-onset respiratory disease without other characteristic features of the CF syndrome.^{21,23-25}

Disease severity and expression can also be affected by non-CFTR genetic modifiers, which have received significant attention in the last decade. *Transforming growth factor* (TGF)- β has repeatedly been shown to modify disease severity, even among subjects homozygous for F508del CFTR.^{26,27} Other genetic modifier loci on chromosome regions 4q35, 8p23, 11q25, and 19q13 confer increased risk of meconium ileus,^{28,29} and various modifiers are associated with acquisition of *Pseudomonas aeruginosa* infection.^{30,31}

PATHOPHYSIOLOGY

CFTR AS AN ABC GENE

CFTR is categorized as a member of the ABC or traffic ATPase family of genes.^{15,32,33} These ancient genes code for

hundreds of polypeptides from both prokaryotes and eukaryotes, which transport nutrients, metabolites, toxins, and other small molecules across cellular membranes. All ABC proteins are characterized by two NBDs encoding canonical Walker A and B motifs (capable of binding and hydrolyzing ATP). ABC proteins also contain two *membrane-spanning domains* (MSDs) with multiple alpha helices that form highly selective passageways across lipid bilayers. Among ABC proteins, CFTR is atypical by virtue of a *regulatory domain* (R domain) with numerous sites for protein kinase A/cAMP-dependent protein kinase (cAMP/PKA) phosphorylation, as well as a *regulatory insertion* (RI) in *nucleotide binding domain 1* (NBD1) believed to participate in channel gating^{15,34,35} (see Fig. 47-1).

STRUCTURE/ACTIVITY AND CFTR GATING MECHANISM

The CFTR gene product is composed of approximately 1500 amino acids and functions as a transporter of Cl^- and HCO_3^- in numerous epithelial tissues. Although a high-resolution, three-dimensional structure of full-length CFTR is not yet available, site-directed mutagenesis indicates that gating is enabled by cAMP/PKA dependent phosphorylation of the R domain. The phosphorylation step has been shown to elicit a conformational change in the regulatory insertion, leading to NBD1/NBD2 heterodimerization and structural realignment in MSD1 and MSD2 that open the ion conductive pore.³⁶ Key interactions between the intracellular loops of the transmembrane domains and the nucleotide binding domains are integral to protein stability and interdomain

Table 47-1 Prevalence of the Most Common *CFTR* Mutations in U.S. Caucasians of Northern-European Descent

Mutation	Number of Patients*	Percent of Patients*
F508del	23,053	86.7
G542X	1,217	4.6
G551D	1,149	4.3
R117H	729	2.7
N1303K	659	2.5
W1282X	616	2.3
R553X	495	1.9
621+1G->T	453	1.7
1717-1G->A	431	1.6
3849+10kbC->T	412	1.5
2789+5G->A	344	1.3
3120+1G->A	281	1.1
I507del	218	0.8
R1162X	206	0.8
1898+1G->A	190	0.7
3659delC	183	0.7
G85E	167	0.6
D1152H	167	0.6
R560T	164	0.6
R347P	154	0.6
2184insA	142	0.5
A455E	140	0.5
R334W	134	0.5
Q493X	124	0.5
2184delA	122	0.5

*Includes patients with one or two copies of the mutation. Courtesy CFF Registry Report 2013.

assembly, as well as to transmission of the forces required for channel opening (see Fig. 47-1).³⁷⁻³⁹ NBD dimerization is greatly augmented when two ATP binding sites (at the NBD1/2 interface) are occupied; closing of CFTR is attributable to ATP hydrolysis.^{40,41} It should be noted that ATP binding is not absolutely required for channel gating (so-called ATP-independent channels can also open, presumably on the basis of the tendency of NBDs to bind each other spontaneously).⁴¹ Transepithelial transport through CFTR is governed by the electrochemical driving force, and a CFTR bioelectric signature (by membrane patch clamp analysis or planar lipid bilayer reconstitution) describes an approximately 8 picosiemens channel with linear current/voltage relationship and characteristic opening bursts. CFTR therefore employs ATP binding to enable passive ion transport, rather than subserving the function typical of the ABC gene family (i.e., pumping of larger metabolites with a stoichiometric dependence on ATP hydrolysis).

BIOGENESIS AND PROCESSING OF NATIVE CFTR

Wild-type CFTR matures by a conventional pathway that includes cotranslational insertion in the *endoplasmic reticulum* (ER) membrane and post-translational modifications

such as N-linked glycosylation and ubiquitination (Fig. 47-3). Subdomain folding (e.g., within NBDs) and achievement of final tertiary structure requires complex domain binding interactions and represents a topic of intense interest due to the importance of misfolding as a mediator of clinical disease.^{37,38,42,43} As even wild-type CFTR processing is not completely efficient, a subset of CFTR molecules is targeted for proteosomal hydrolysis by *ER-associated degradation* (ERAD). For CFTR that advances from ER to Golgi, complex glycosylation takes place at two asparagine residues. CFTR reaching the Golgi is transported to the cell surface by vesicular traffic with subsequent recycling through sorting and recycling endosomes and reinsertion in the plasma membrane or routing to the lysosome. The cell surface apparatus that governs CFTR peripheral stability (i.e., plasma membrane) has been well characterized and includes ubiquitin conjugation to regulate internalization in response to environmental stress.⁴⁴

CELLULAR DEFECTS ATTRIBUTABLE TO F508DEL CFTR

The vast majority of F508del CFTR is retained in the ER, heavily ubiquitinated, and routed to the proteasome by ERAD.⁴⁵ As a consequence, F508del CFTR visualized by SDS PAGE is predominantly an ER localized, approximately 150KDa core glycosylated ("band B") glycoform, whereas a substantial portion of post ER, wild-type protein migrates more slowly due to complex glycosylation (\approx 180 KDa "band C"). The F508del trafficking defect is temperature sensitive, and growth of epithelium at lower temperatures (e.g., 27°C) leads to measurable levels of band C with partial restoration of cell surface function.

The maturational processing defect mediated by F508del involves at least two distinct abnormalities.^{37,38,46} Omission of F508 (which is located on an externally exposed peptide loop of the first nucleotide binding domain) leads to pronounced loss of NBD1 stability as judged by thermal and isothermal calorimetry, protein aggregation, and protein yield measurements following recombinant overexpression. In addition, F508 facilitates binding of a cytosolic loop from MSD2, and disruption of the NBD1/MSD2 interface (independent of NBD1 stability) leads to further impairment of F508del maturation.

F508del CFTR molecules that have been rescued to the cell surface by low temperature display intrinsic channel gating abnormalities, diminished plasma membrane stability, and pronounced thermal unfolding with loss of function following incubation at 37°C.^{47,48} In addition, F508del CFTR mRNA may be misfolded and poorly utilized (leading to lower levels of CFTR translation) due to omission of the F508 codon.^{49,50} The observation of multiple distinct CFTR defects attributable to F508del points to the challenge of identifying a single agent capable of restoring mutant CFTR to therapeutically relevant levels. Intramolecular suppressor mutations that specifically ameliorate F508del NBD1 instability or the defective NBD1/MSD1 interface have been identified.^{37,38} CFTR constructs encoding these suppressors provide a means to characterize F508del corrective strategies and will enable compound library screening tailored to specific CFTR folding defects in the future.

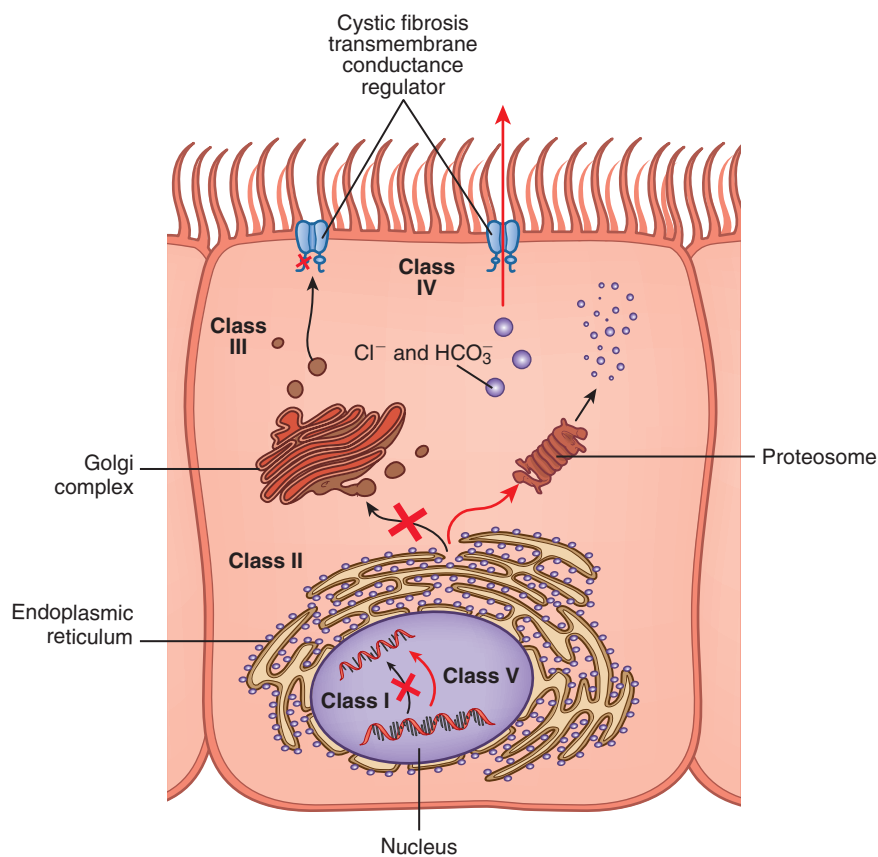


Figure 47-2 CFTR mutations and molecular consequences. Classes of defects in the *CFTR* gene product include the absence of synthesis (*class I*); defective protein maturation and premature degradation (*class II*); disordered regulation, such as diminished ATP binding and hydrolysis (*class III*); defective chloride conductance or channel gating (*class IV*); and a reduced number of CFTR transcripts due to a promoter or splicing abnormality (*class V*).

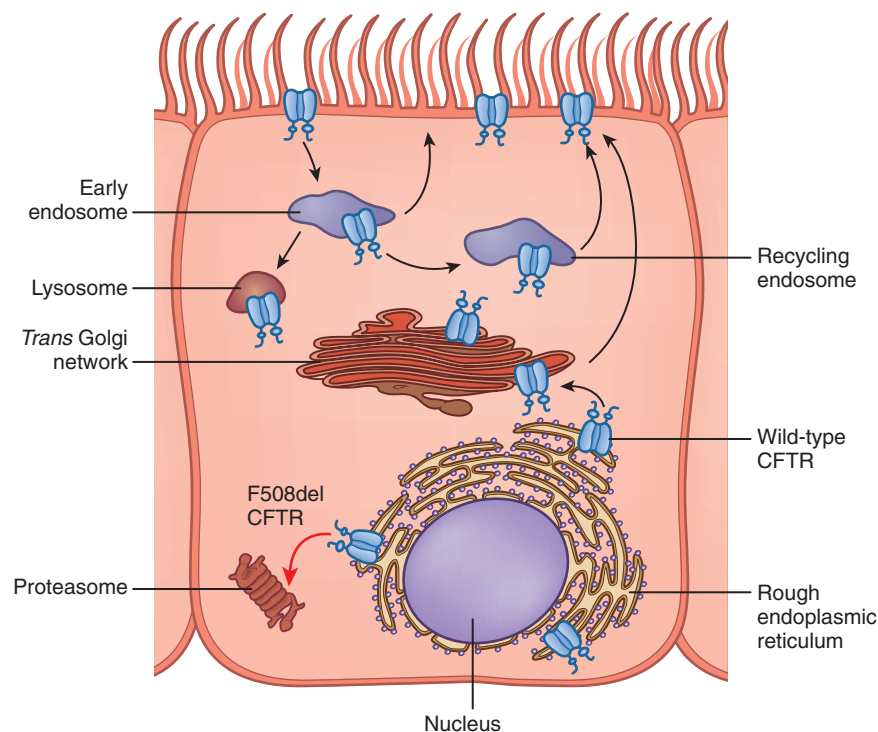


Figure 47-3 Scheme of CFTR biogenesis. Biogenesis of CFTR in normal epithelial cell (right side of cell) and F508del cystic fibrosis (CF)-affected epithelial cell (left side). In the normal epithelial cell, CFTR is synthesized in the rough endoplasmic reticulum, glycosylated and folded in the Golgi apparatus, and chaperoned to the cell surface. In the F508del-affected epithelial cells, the CFTR polypeptide is misfolded and tagged for premature degradation via endoplasmic reticulum-associated degradation (red arrow) before reaching the cell surface (*class II* mutation). (Adapted from Ameen N, Silvis M, Bradbury NA: Endocytic trafficking of CFTR in health and disease. *J Cystic Fibrosis* 6:1–14, Fig. 1, 2007.)

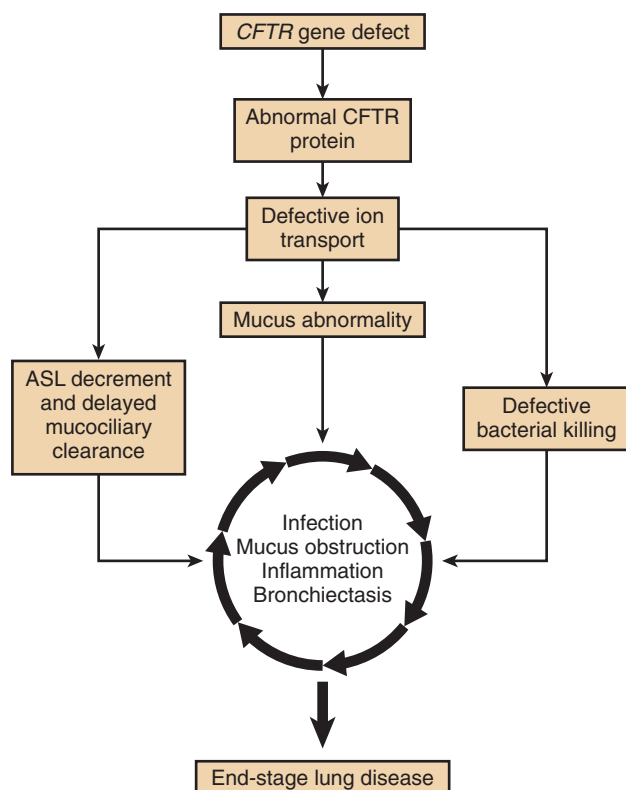


Figure 47-4 CF pathophysiology. CF lung disease results from consequences of genetic mutations in *CFTR*. Major operative pathways include reduced mucociliary clearance due to depleted airway surface liquid (ASL) hydration, abnormal mucus adhesion and viscosity, and defective bacterial killing that each contribute to the cycle of destruction.

OVERVIEW OF LUNG PATHOPHYSIOLOGY

An improved understanding of CF pathogenesis has led to better diagnostic strategies, an improved understanding of the onset and progression of lung disease, and therapeutic approaches to target the underlying disease. An overview is provided in [Figure 47-4](#) and described in further detail later. As with other monogenetic diseases, absent or dysfunctional *CFTR* results in diminished functional protein, which is necessary to transport chloride and bicarbonate across the airway epithelium. Several key manifestations include delayed mucociliary clearance because of depletion of *airway surface liquid* (ASL), abnormalities of the physical properties of CF mucus, and a predisposition to early infection because of abnormal mucosal defense; there may also be dysregulated inflammation. These processes initiate and perpetuate a cycle of destruction that ultimately results in irreversible lung injury, bronchiectasis, and respiratory failure.^{15,51}

In the lungs, CF manifests as infected mucus secretions that compromise the airway lumen and contribute to obstructive pulmonary disease and reduced FEV₁ ([Fig. 47-5](#)). Airway disease is thought to begin in the small airways, resulting in airflow obstruction detected by spirometry midflows (i.e., FEF_{25%-75%}). Submucosal gland hyperplasia and inspissated mucus secretions emanating from the glands are also prominent. Radiographic changes consistent with small airway obstruction (e.g., tree-in-bud

opacities) followed by bronchiectasis become apparent over time. Development of bronchiectasis leads to irreversible changes that encourage continued infection and accelerate disease pathogenesis.

CELLULAR FUNCTIONS OF THE *CFTR* GENE PRODUCT

The *CFTR* gene is hundreds of millions of years old and utilized by diverse species including fish, amphibian, fowl, and mammalian. Although best described as a chloride and bicarbonate transporter, the protein appears to regulate numerous processes in addition to anion secretion. *CFTR* is situated within membrane complexes by virtue of a PDZ-type binding motif and configured in close proximity to a number of integral membrane proteins including other ion channels. In experimental systems, *CFTR* exerts a regulatory influence on the *epithelial sodium channel* (ENaC).⁵² Proteomic and transcriptome analyses demonstrate hundreds of cellular gene products that directly bind or are regulated by the gene product.⁵³

REGULATION OF AIRWAY SURFACE LIQUID HOMEOSTASIS

In a conventional model of CF respiratory pathogenesis, absence of apical *CFTR* leads to failure of chloride and bicarbonate secretion.^{15,52} Because release of water into the periciliary region is driven in large measure by a *CFTR*-dependent osmotic gradient, *CFTR* deficiency leads to failure of ASL hydration ([Fig. 47-6](#)). In addition, a considerable body of evidence suggests that ENaC present on the airway surface may be down-regulated by wild-type *CFTR*, and that loss of the *CF* gene confers elevated ENaC-dependent sodium and water uptake, further exacerbating ASL desiccation. According to this prevailing model, depleted ASL leads to inadequate ciliary extension and impairment of mucociliary clearance.^{54,55}

Recent findings indicate significant new levels of complexity with regard to the mechanisms that govern ASL depth and mucociliary clearance. For example, although the periciliary fluid layer has traditionally been viewed as primarily aqueous in composition, recent data indicate that a fluid layer containing tethered mucins is characterized by intrinsic viscosity that is sensitive to the osmolar forces of the overlying mucus, which are expected to strongly influence mucociliary clearance when the periciliary layer collapses due to mucus dehydration.⁵⁶ Moreover, ENaC hyperactivity across the CF airway surface—thought to be a hallmark of CF pathophysiology in the past—has recently been questioned on the basis of (1) absence of sodium hyperabsorption from airway mucosa in newborn CF pigs (together with evidence of normal ASL depth) and (2) studies of primary human airway epithelium indicating that elevated sodium reabsorption in CF can be explained by an increased gradient for sodium uptake (rather than a direct biochemical influence on ENaC, per se).^{15,57-59}

Findings such as these pose a challenge to interpretation of experimental therapies intended to augment ASL depth by blocking respiratory ENaC or activating non-*CFTR* chloride secretory pathways. Such interventions represent an important approach for improving mucociliary clearance,

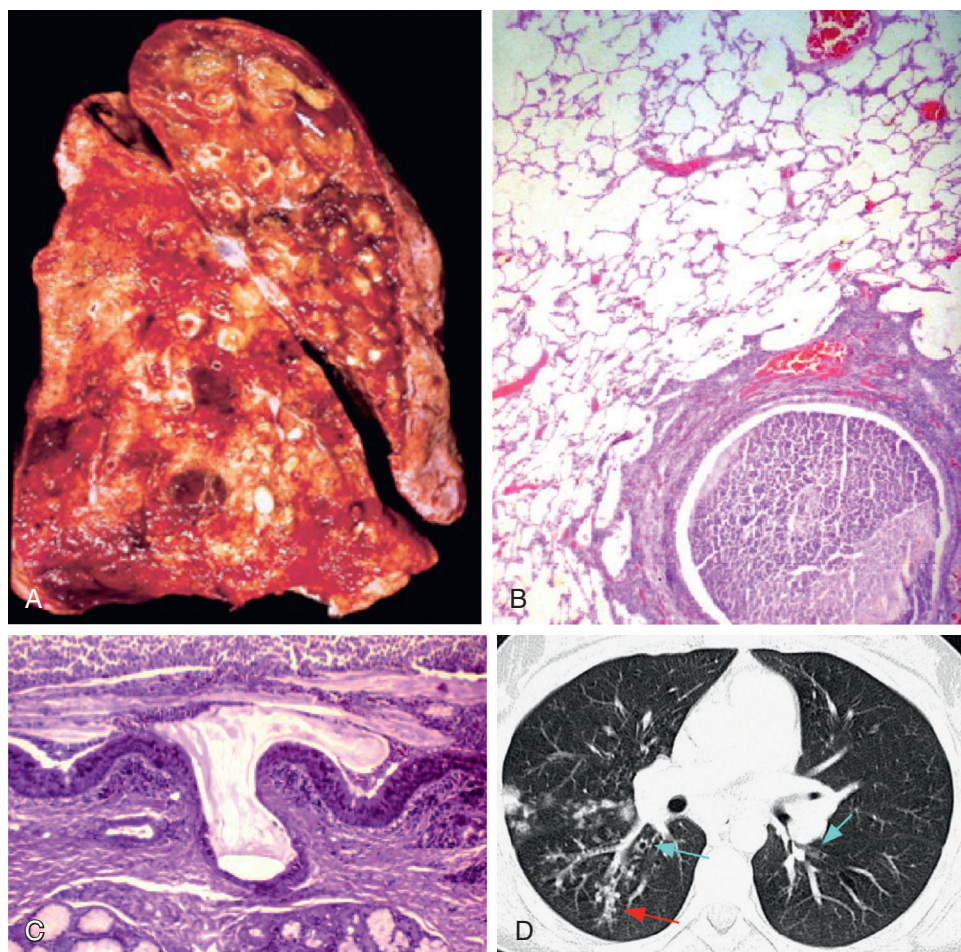


Figure 47-5 CF pathologic and radiologic correlation. **A**, Gross pathologic specimen of explanted CF lung from a patient with end-stage CF lung disease. This specimen demonstrates heavy lungs characterized by bronchiectasis and numerous mucopurulent plugs. **B**, Large airway pathology of CF. A large mucus plug filled with inflammatory infiltrate is clearly seen, in addition to remodeling of the medium-sized airway (hematoxylin-eosin stain). **C**, Representative photomicrographs from a CF patient with end-stage lung disease is depicted. Note the thickening of the lamina propria (higher Reid index), the prominent arborized mucus plug extruding from the submucosal gland onto the airway lumen, and the hypertrophic surface epithelium (periodic acid-Schiff stain). **D**, Sagittal high-resolution CT image from a 16-year-old male with CF demonstrating mild to moderate multilobar bronchiectasis (cyan arrows) and tree-in-bud opacities representing small airways mucus plugs (red arrow). (A–C, Images courtesy Dr. David Kelly, University of Alabama, Birmingham.)

and such strategies could improve mucus clearance regardless of their relationship to the fundamental CF defect. The significance of ASL expansion is underscored by therapeutic improvement among patients treated with hypertonic saline aerosols and dry powder mannitol to improve mucociliary clearance in CF lung disease by providing airway hydration.

REGULATION OF SWEAT CHLORIDE BY CFTR

The concentration of chloride in human sweat is determined by the balance of secretion and reabsorption of sodium and chloride in the sweat gland and duct. Chloride is secreted by two parallel pathways. One involves CFTR; the other utilizes a CFTR-independent, calcium-activated chloride channel. Because CFTR is not the only pathway by which chloride exits the apical membrane, chloride is secreted into sweat even in the absence of functional CFTR. Normally, sodium is reabsorbed in the duct of the sweat gland because of ENaC in the apical membrane of the duct cells. Chloride follows sodium into the cell, through the

CFTR chloride channel. In CF, with absent or defective CFTR, chloride reabsorption is significantly reduced and the chloride content of sweat is abnormally high.

CYSTIC FIBROSIS EXOCRINE GLANDULAR EPITHELIUM

Submucosal glandular ducts filled with inspissated mucus are observed early in the course of CF pulmonary involvement. CFTR is heavily expressed within epithelial cells of submucosal glands, where it functions to activate fluid and electrolyte secretion and promote release of mucus onto the airway surface.⁶⁰ The relative contributions of submucosal glands to overall CF respiratory pathophysiology are not known. Although absence of a lung phenotype in CF murine models has been attributed to non-CFTR Cl^- secretory pathways that are highly active in mouse lungs,⁶¹ the paucity of murine airway glands has also been implicated (see Chapter 1 for differences in mouse and human lungs). The relative lack of murine airway glands is a likely explanation for the lack of a murine lung phenotype, particularly

because other CF null animals with extensive submucosal gland formation (i.e., pig, ferret) exhibit a pulmonary phenotype similar to humans. The recent development of confocal imaging modalities that allow direct visualization of glandular activity in full-thickness airways and the ability to analyze biophysical properties of mucus extruded from CF pig, ferret, or rat submucosal glands⁶² will contribute new and important knowledge in this area.

MUCUS BIOGENESIS, ADHESION, AND TRANSPORT

Hyperviscous respiratory secretions obstruct small- and medium-sized airways in CF, leading to profound failure of mucociliary clearance that can be verified macroscopically by radioligand imaging.⁶³ A primary biochemical defect in mucus composition has been extensively sought but not well established as a fundamental cause of the disease. Studies of CF pulmonary secretion are complicated

by difficulty retrieving standardized mucus samples, the diversity of respiratory pathogens, pronounced lung inflammation, and other variables. Specific mucins expressed in CF respiratory secretions include the gel-forming mucins MUC5B and MUC5AC, in addition to a complex array of extracellular proteins.⁶⁴ DNA strands released from dying bacteria, epithelial cells, and inflammatory cells represent an important contributor to excess mucus viscosity and provide rationale for use of recombinant DNase as an aerosolized mucolytic.

In extrapulmonary CF organs characterized by hyperviscous secretion (e.g., pancreas, liver), profound ductular obstruction is observed in the absence of polymicrobial infection, allowing more direct studies of the relationship between CFTR and mucus formation. An emerging notion implicates defective bicarbonate transport as a mediator of hyperviscosity and mucosal adhesion in CF secretions. In this model, exocrine mucus (highly negative in charge) is produced by acinar and other epithelial cells in compacted

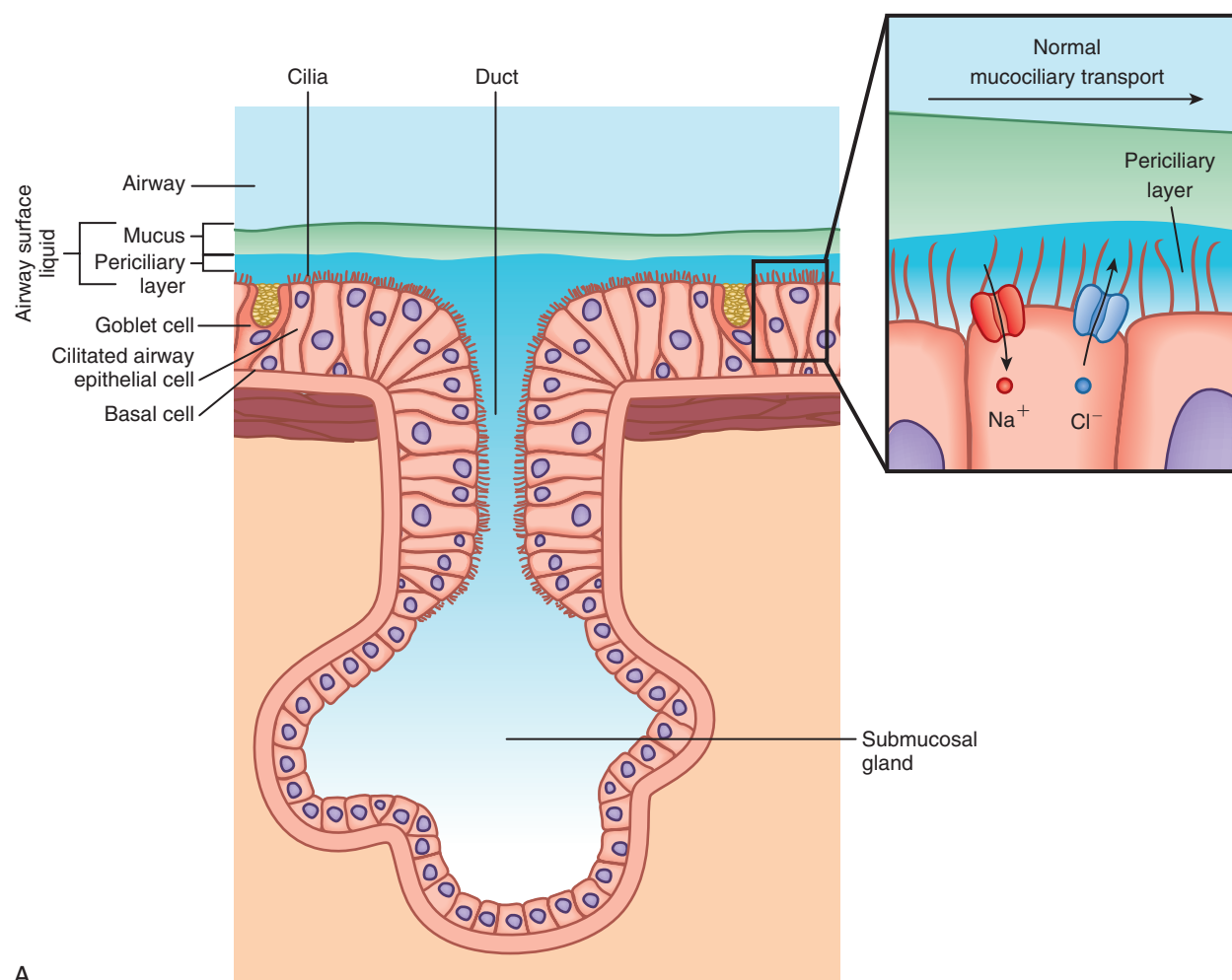


Figure 47-6 CF airway surface and mucus transport defect. Schematic of the mucociliary transport defect in CF. In the healthy state (**A**), adequate airway surface homeostasis ensures effective transport of mucus extruding from airway surface goblet cells and the submucosal glands. The airway surface liquid (ASL) is maintained by fluid secretion via the CFTR and fluid absorption via the epithelial sodium channel, ENaC (inset box on right) (CFTR, surface receptor in blue; ENaC, surface receptor in red). In CF (**B**), the ASL is depleted through the absence of CFTR-mediated fluid secretion accompanied by tonic fluid absorption via the ENaC. CFTR-dependent liquid dessication decreases the depth of the ASL including the periciliary layer causing abnormal clearance of mucus from the epithelial cell surface in the airways.

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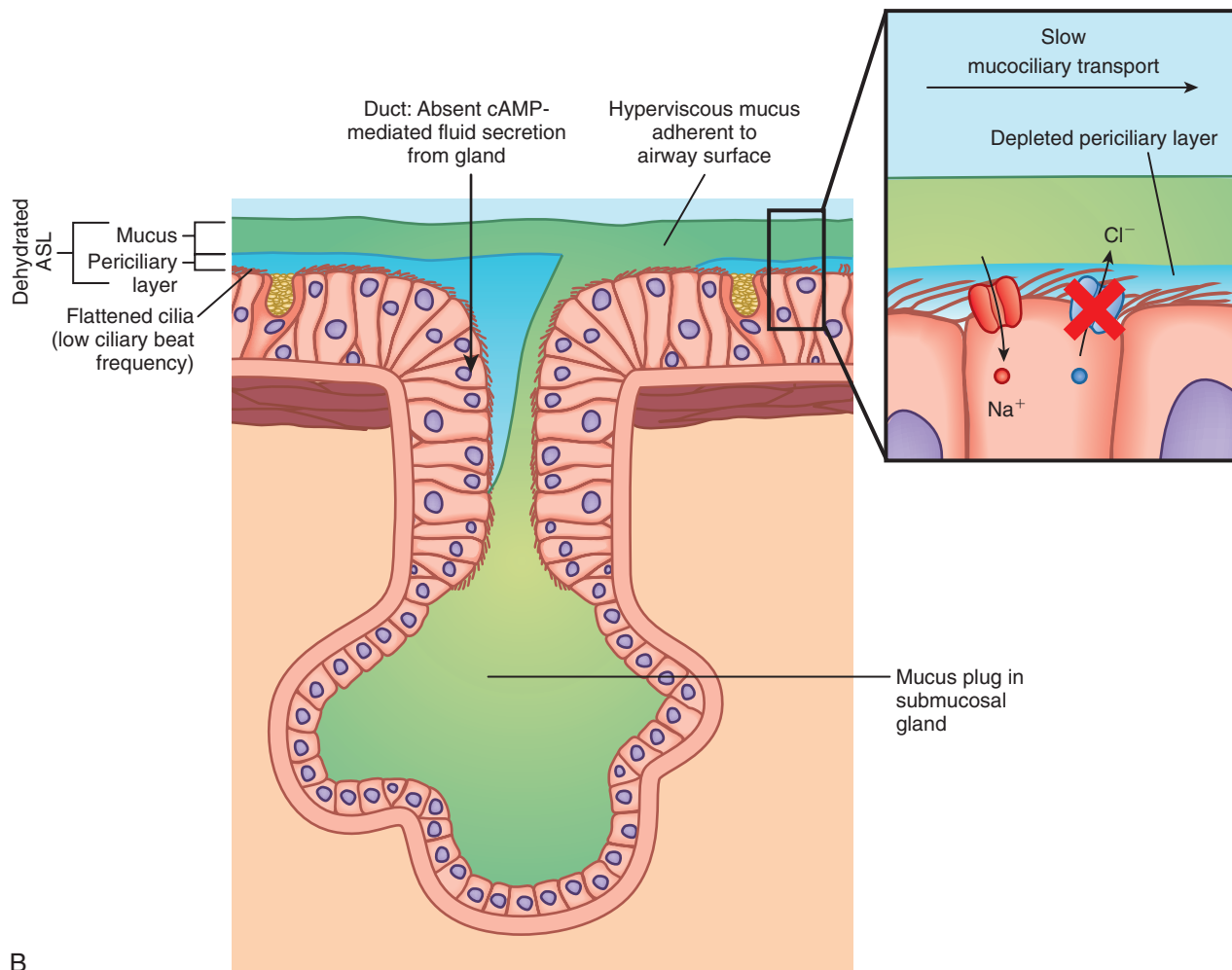


Figure 47-6, cont'd

form due to bound calcium, which shields the negative repulsive force between sulfates and other anionic groups on constituent mucins.² Bicarbonate secretion via CFTR chelates the calcium and permits mucinous expansion and a viscoelastic state compatible with physiologic clearance. Failure of bicarbonate release is hypothesized to result in a defective mucin expansion, leading to hyperviscous secretion with abnormally adherent properties (i.e., mucus that is tightly bound to the respiratory surface and difficult to mobilize). Evidence of excessive mucus adhesion that can be reversed by bicarbonate has been observed in the intestine of CF mice.^{65,66}

HOST DEFENSE AND INFECTION

CF lungs are characterized by intense neutrophilic inflammation with polymorphonuclear cells densely infiltrating airway secretions. Whether robust lung inflammation is mediated directly by CFTR (as opposed to a consequence of polymicrobial infection) is a topic of considerable debate.^{67,68} Neutrophil chemoattractants such as interleukin-8, tumor necrosis factor (TNF)- α , and a collagen fragment, proline-glycine-proline, are present at high levels in airway secretions, and abnormalities of CFTR-dependent macrophage function have also been implicated. Although

anti-inflammatory therapies can improve lung function and slow the rate of CF respiratory decline, immune blockade also can predispose individuals to worsening lung infection, and the proper clinical balance has been difficult to achieve.⁶⁹

Bacteria typically colonize the CF respiratory tract during infancy or early childhood. Longitudinal analysis of *P. aeruginosa* indicates sentinel infection due to a single genotype of the organism that often persists throughout the life of an individual patient.⁷⁰ The explanation for early colonization is not well understood. Previous studies have suggested increased binding of CF pathogens to CFTR $-/-$ airway epithelial cells or that antimicrobial peptides present in pulmonary secretions are inactivated by high salt concentrations bathing the respiratory surface.^{71,72} A recent study implicated acidic pH within CF ASL (attributable to absent CFTR bicarbonate release) as a likely cause of the increased susceptibility to bacteria.⁷³ Findings such as these are most relevant to initial colonization events because airway pH may not be affected later in life.

Virulent respiratory pathogens such as *P. aeruginosa* evolve in a stereotypic fashion during the lifespan of individuals with CF and are characterized by rapid phenotype change and hypermutability.⁷⁴ After several years of pulmonary infection, *P. aeruginosa* typically develops a

mucoïd phenotype in which considerable metabolic reserves are expended to synthesize and release the polyanionic protein, alginate. Appearance of mucoïd *P. aeruginosa* in CF is a negative prognostic indicator. Selective advantage of alginate release has been attributed to the immunomodulating role of this exoproduct.^{75,76} Recent studies have demonstrated the complexity of the CF microbiome, which can be altered during exacerbation by the presence of a dominant pathogen.⁷⁷

Porcine and ferret models of CF pulmonary disease, as well as identification of very young CF patients by newborn screening, provide an important means to clarify relationships that exist among initial bacterial colonization, chronic infection, and inflammation in CF lungs. Longitudinal monitoring of CF respiratory infection in humans and transgenic animals will also facilitate a more sophisticated understanding of the complex CF microbiome and could provide new therapeutic opportunities in the future.

CFTR AND PULMONARY REMODELING

Measurements in the CF porcine model indicate a change in tracheal diameter and density of submucosal glands before the advent of hyperviscous mucus obstruction. Similar findings have been reported in human CF lungs and in *Cftr* $-/-$ rats (despite the absence of mucus plugging in the rodent model).⁷⁸ In tissues such as porcine and human pancreas, fibrotic damage and fatty replacement can be profound, with extensive parenchymal scarring.⁷⁹ Myofibroblast proliferation appears to mediate this effect, and TGF- β signal transduction (which engenders myofibroblast transformation) is markedly increased throughout the CF lung.⁸⁰ TGF- β is also a well-established genetic modifier of F508del homozygous CF lung disease,^{26,81} and these findings suggest that changes in TGF- β -dependent profibrotic pathways govern lung tissue remodeling (in addition to inflammatory responsiveness elicited by the cytokine).

DIAGNOSIS

OVERVIEW

The diagnosis of CF is predicated on clinical suspicion for the disease, as indicated by clinical manifestations or family history, or alternatively through newborn screening programs. Early detection through newborn screening is leading to earlier recognition of illness before the clinical characteristics become apparent. The first organized CF newborn screening programs were developed in the 1980s and implemented in Colorado in 1987 and in the 1980s in Australia and Europe⁸² after retrospective trials demonstrated improved mortality and clinical outcomes.⁸³ The number of programs in the United States and abroad increased in the past decade, and now all U.S. states have implemented newborn screening programs after a CDC/Cystic Fibrosis Foundation Consensus Statement in 2004 recommended this practice.⁸⁴ The report invoked emerging prospective data that screening and early interventions in CF newborns diagnosed by newborn screening improved nutritional, gastrointestinal, respiratory, and cognitive functioning.⁸⁵⁻⁸⁸

Several different screening algorithms are used and vary by state program, but serum detection of *immunoreactive trypsinogen* (IRT) is typically the primary screening method. IRT is quantified from blood spots taken in the perinatal period. IRT is a highly sensitive serum marker of obstructive pancreatic injury, although it is not specific for CF and thus additional testing is required to confirm the diagnosis. Elevated IRT in the perinatal period is typically followed by repeat IRT testing and/or a DNA panel for common CFTR mutations. If positive, refer to a diagnostic clinic for assessment of CFTR through mutation analysis and functional assays, such as sweat chloride, to confirm the diagnosis; this is frequently accomplished before the onset of clinical manifestations.

Diagnostic Algorithms

The diagnosis of CF is based on a positive newborn screening test or suspicious clinical characteristics in patients in infancy through adulthood (Table 47-2). In 2008, the Cystic Fibrosis Foundation published comprehensive diagnostic guidelines for infants and adults with suspected CF⁸⁹ (Fig. 47-7A and B); a similar approach was adopted in the European CF Society's 2006 guidelines. The guidelines primarily differed only in the timing of CFTR mutation analysis and sweat chloride normative values.⁹⁰ In addition, as compared with the European diagnostic guideline, the U.S. guideline deemphasizes measurement of *nasal potential difference* (NPD), a bioelectric measure of CFTR activity, mainly due to lack of standardization, although NPD is recommended as an alternative diagnostic modality. There is good concordance when comparing these methodologies for diagnostic accuracy.⁹¹

Table 47-2 Diagnostic Criteria for CF by Clinical Phenotypic and CFTR Functional Abnormalities

The diagnosis of CF is confirmed by the presence of:

Appropriate phenotypic clinical features (any of):

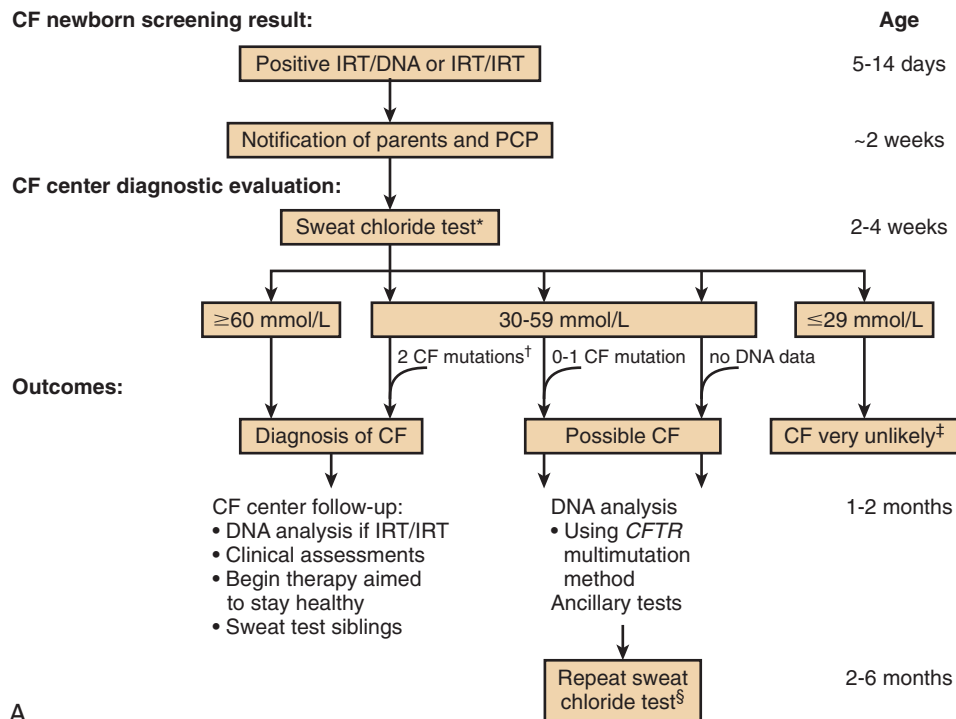
- Chronic sinopulmonary disease
- Chronic cough and sputum production
- Persistent infection with characteristic pathogens (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, other gram-negative organisms)
- Airflow obstruction
- Chronic chest radiographic abnormalities
- Sinus disease; nasal polyposis
- Gastrointestinal and nutritional abnormalities
- Exocrine pancreatic insufficiency
- Recurrent pancreatitis
- Fat-soluble vitamin deficiency
- Meconium ileus; DIOS
- Obstructive azoospermia in males

Plus,

Laboratory evidence of CFTR dysfunction (one or more of following):

- Elevated sweat chloride
- Disease-causing mutation in CFTR gene in both alleles
- Characteristic bioelectric abnormalities (potential difference) in nasal epithelium
- Abnormal ex vivo intestinal short-circuit current measurement

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DIOS, distal intestinal obstruction syndrome.



A

* If the baby is at least 2 kg and more than 36 weeks' gestation at birth, perform bilateral sweat sampling/analysis with either Gibson-Cooke or Macroduct method; repeat as soon as possible if sweat quantity is less than 75 mg or 15 μ L, respectively.

† CF mutation refers to a *CFTR* mutant allele known to cause CF disease.

‡ The disease is very unlikely; however, if there are two CF mutations in trans, CF may be diagnosed.

§ After a repeat sweat test, further evaluation depends on the results as implied above.

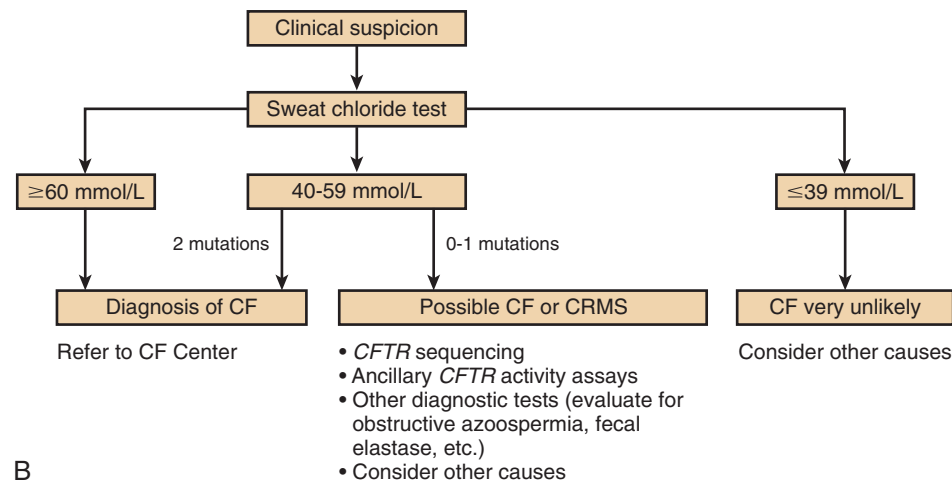


Figure 47-7 Diagnostic algorithm for CF. **A**, Schematic depiction of the diagnostic algorithm for the diagnosis of CF in infants emphasizing newborn screening programs. **B**, Schematic depiction of a diagnostic algorithm for children and adults emphasizing sweat chloride as the cornerstone of the diagnosis. Note the differences in the lower limit of normal of sweat chloride for infants versus children and adults. Genetic testing for intermediate probability cases should trigger *CFTR* sequencing since analysis for only limited number of mutations can result in false negative evaluations in this disease category. CRMS, *CFTR*-related metabolic syndrome; IRT, immunoreactive trypsinogen; IRT/DNA, means confirmation with a DNA assay (see text); IRT/IRT, confirmation with a second IRT test; PCP, primary care physician. (**B**, Adapted from Farrell PM, Rosenstein BJ, White TB, et al: Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 153(2):S4–S14, 2008.)

In the North American (CFF) algorithm (see Fig. 47-7A), newborns are screened for CF using IRT, a byproduct of prenatal pancreatic inflammation. In most states this test is paired with a DNA probe panel for common *CFTR* mutations. IRT is not a highly specific measurement due to

elevated levels observed in prematurity, traumatic delivery, and other neonatal gastrointestinal disorders.⁹² Because of declining IRT levels in the first few months after birth in CF and non-CF infants,⁹³ this test is only useful for screening in the first few weeks after birth. Thereby, family history or

clinical suspicion based on symptoms is the main impetus for diagnostic evaluation after the neonatal period has passed (see Fig. 47-7B).

If the IRT is elevated or in situations where CF is suspected, the diagnosis should be confirmed by sweat chloride testing. Sweat chloride testing is available in many clinical laboratories and has been standardized to ensure accuracy. Because of its high sensitivity, sweat chloride testing has a central role in establishing the diagnosis in both the Cystic Fibrosis Foundation and European algorithms in the presence of a positive newborn screening or compatible clinical characteristics.

For infants screened at birth, a low sweat chloride value (<29 mmol/L) effectively rules out CF, whereas a high sweat chloride concentration (≥ 60 mmol/L) definitively establishes the diagnosis. In the case of clinical suspicion with an intermediate sweat chloride concentration (30 to 59 mmol/L), guidelines recommend performing *CFTR* sequencing or high-sensitivity DNA probe testing to establish the presence of *CFTR* mutations. If two *CFTR* mutations are found, the diagnosis of CF is established. If one or zero mutations are present, then repeat sweat chloride testing is recommended. It should be noted that standard genetic panels (i.e., panels that test fewer than 40 mutations) are not sufficient in patients with elevated sweat chloride and atypical manifestations because rare, partially functional mutations are common in these cases and may not be detected in limited panels. Some patients exhibit CF-like disease even in the absence of *CFTR* mutations, a finding probably caused by mutations in genes coding for other related proteins that can mimic mutations in *CFTR* (i.e., mutations in the ENaC channel).⁹⁴

If clinical suspicion remains elevated and sweat chloride is in the intermediate range, there are several alternatives to confirm *CFTR* functional deficits. NPD testing, available at select CF specialty centers, is viewed as an acceptable alternative in cases of inconclusive sweat chlorides values or inadequate genetic analysis. Testing of intestinal current measurements, another alternative, is only available at a few centers in the world and requires a biopsy of the rectal mucosa.^{95,96} Additionally, other measures of pancreatic function such as fecal elastase may help to support the diagnosis in this setting.

In analogous fashion, children and adults with clinical syndromes suspicious for CF are also first screened for *CFTR* dysfunction using sweat chloride testing (see Fig. 47-7B). If the sweat chloride is low (≤ 39 mmol/L) CF is ruled out and other causes of the clinical syndrome should be sought. The lower limit of normal for sweat chloride values is higher in adults due to a relative, normal increase in sweat chloride with aging. In the presence of an elevated sweat chloride (>60 mmol/L), the diagnosis of CF is established in the patient and referral to a CF specialty center is recommended. In the case of an intermediate sweat chloride value (40 to 59 mmol/L), further *CFTR* genetic testing (i.e., sequencing) or alternative diagnostic testing as described earlier are appropriate. Additionally, in adult males, the diagnosis may be strongly suggested by the presence of a positive urologic evaluation for obstructive azoospermia.

It is increasingly recognized that *CFTR*-related disorders represent a spectrum of disease, with pancreatic-insufficient CF as the most severe form (Fig. 47-8). It is notable that

functional assessments of *CFTR* reflect this diversity, although the relationship between genotype and *CFTR* functional decrements can vary. *CFTR* biomarkers are generally able to distinguish between mild and severe phenotypes by demonstrating a continuum of *CFTR* decrement that correlates to clinical phenotype and is not apparent by genotype alone.²²

CLINICAL MANIFESTATIONS

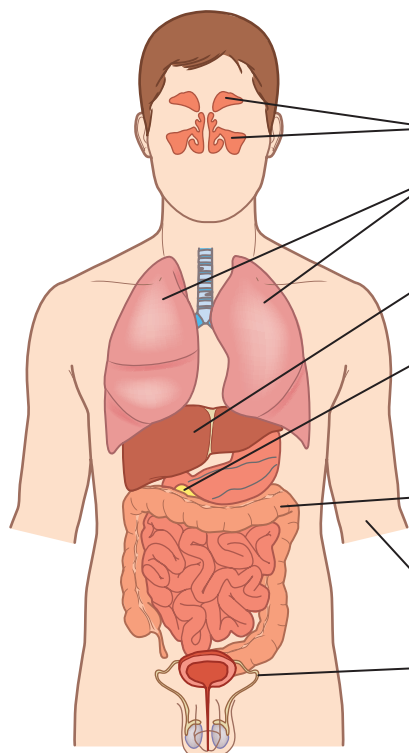
CF has historically presented with protean manifestations with symptoms that may mimic or resemble other disease processes. Usual presentations include early onset of respiratory tract symptoms, particularly persistent cough and recurrent or refractory chest radiographic changes. Gastrointestinal presentations are also prominent and include meconium ileus in approximately 15% of patients and failure to thrive with steatorrhea due to pancreatic insufficiency. A list of unusual presentations is compiled in Table 47-3, and presentations that are common during adolescence or early adulthood due to residual levels of *CFTR* activity are highlighted. Clinical severity can vary widely; less severe disease states can be initially misdiagnosed as other more common respiratory conditions.

With the widespread acceptance of newborn screening programs in the United States, it is now typical to diagnose CF before the onset of respiratory disease. Although this has tremendous clinical benefit, a high index of suspicion must be maintained to ensure diagnosis in the event of a screening failure or in individuals born before the initiation of screening programs. Consequently, a significant number of CF patients may present in adulthood because symptoms are unusual, subtle, or even absent early in life, resulting in a delayed presentation. Oftentimes these nonclassic presentations are due to partially active *CFTR* alleles or other ameliorating mutations.⁹⁷ Recognition of the variable manifestations of CF is required to detect CF, either in childhood or later in life.

LOWER RESPIRATORY TRACT DISEASE

Progressive obstructive lung disease leading to bronchiectasis and respiratory failure causes the vast majority of mortality in individuals with CF. Even seemingly healthy infants with CF have significant subclinical lung disease; inflammation is often disproportionate to the degree of infection.⁹⁸ The most common manifestation of lung disease is cough in association with bronchitis. Early in life, symptoms are often intermittent and exacerbated by episodes of acute respiratory tract infection that tend to exhibit a protracted course. With time, cough becomes a daily event. It is often worse at night and on arising in the morning. With progression or during exacerbations of lung disease, cough can become productive of tenacious, mucopurulent sputum secondary to chronic bacterial infection and resultant neutrophilic inflammation.

Hyperinflation of the lungs is common and often observed early in the progression of lung disease.⁹⁹ Asthmatic or bronchiolitic-type wheezing is common during the first 2 years of life but may be encountered at any age. Wheezing is noted in up to one third of infants and may be present



Organ System	CF-Pancreatic Insufficient	CF-Pancreatic Sufficient	CFTR-Related Disorder*
Typical genotype	Two severe mutations	At least one mild/variable mutation	Two mild mutations or heterozygous
Sinus	Chronic sinusitis	Chronic sinusitis	Chronic sinusitis
Airways	Severe chronic bacterial infection	Chronic bacterial infection, later onset, variable	Chronic bacterial infection, mild, later onset, variable
Liver	Severe hepatobiliary disease (5%-10%)	Usually absent	Absent
Pancreas	Exocrine insufficiency	Adequate exocrine function until late in life, pancreatitis (pancreatitis in minority)	Adequate exocrine function, pancreatitis (can be presenting symptom)
Bowel	Risk of meconium ileus, DIOS	Nonspecific bowel complaints, low risk of DIOS	Nonspecific bowel complaints
Sweat chloride	90-110 mmol/L	60-90 mmol/L	40-60 mmol/L
Vas deferens	Obstructive azoospermia	Obstructive azoospermia	Normal, CUAVD, or CBAVD
Endocrine Pancreas	High risk of CF-related diabetes mellitus	Low risk of CF-related diabetes mellitus	Minimal risk of CF-related diabetes mellitus

Figure 47-8 Spectrum of CF disorders. This figure compares the findings in severe CF with the milder forms of the disease. Although manifestations are variable, severity in each organ system is generally consistent with degree of CFTR dysfunction conferred by genotype. CBAVD, congenital bilateral absence of the vas deferens; CUAVD, congenital unilateral absence of the vas deferens; DIOS, distal intestinal obstruction syndrome. *Refers to CFTR-related metabolic syndrome or CFTR-related disorders which are being defined currently.

Table 47-3 Atypical Presentations of Cystic Fibrosis*

Respiratory	Bronchiolitis/asthma <i>Pseudomonas aeruginosa</i> or <i>Staphylococcus aureus</i> colonization of the respiratory tract Staphylococcal pneumonia Nasal polyposis Nontuberculous mycobacterial infection
Gastrointestinal	Meconium plug syndrome Rectal prolapse Recurrent abdominal pain and/or right lower quadrant mass Hypoproteinemic edema Prolonged neonatal jaundice Biliary cirrhosis with portal hypertension Vitamin deficiency states (A, D, E, K) Acrodermatitis enteropathica–like eruption with fatty acid and zinc deficiency Recurrent pancreatitis
Genitourinary	Male infertility Female infertility
Other	Hypochloremic, hyponatremic alkalosis Mother of a child with cystic fibrosis

*Presentations noted in **boldface** are those that may present in adolescents or adults with cystic fibrosis.

with or without evidence of atopy.¹⁰⁰ Early in life, CF may often mimic the clinical manifestations of asthma and/or coexist with asthma syndrome, leading to delayed recognition.

Lung sounds are often unremarkable early in the disease process; the first detectable abnormalities may be a diminished intensity of breath sounds or subtle prolongation of the expiratory phase. Once CF lung disease becomes clinically apparent, adventitious lung sounds are usually first noted in the upper lobes. CF patients may have only mild bronchitic symptoms for long periods of time as lung homeostasis is maintained but typically manifest exacerbations of symptoms of increased cough intensity and sputum production. These exacerbations often present as tachypnea, shortness of breath, malaise, anorexia, and weight loss. Viral respiratory tract infection is a frequent trigger, as are other infectious agents, cigarette smoke,¹⁰¹ pollutants,¹⁰² allergens, and respiratory irritants that have been implicated in disturbing lower airway homeostasis. Initiation of broad-spectrum antibiotic therapy and aggressive maneuvers to facilitate clearance of mucus are usually required to improve symptoms and restore lung function. These pulmonary exacerbations are now recognized as a major driver of disease progression, and greater attempts to recognize and treat them before irreversible injury have

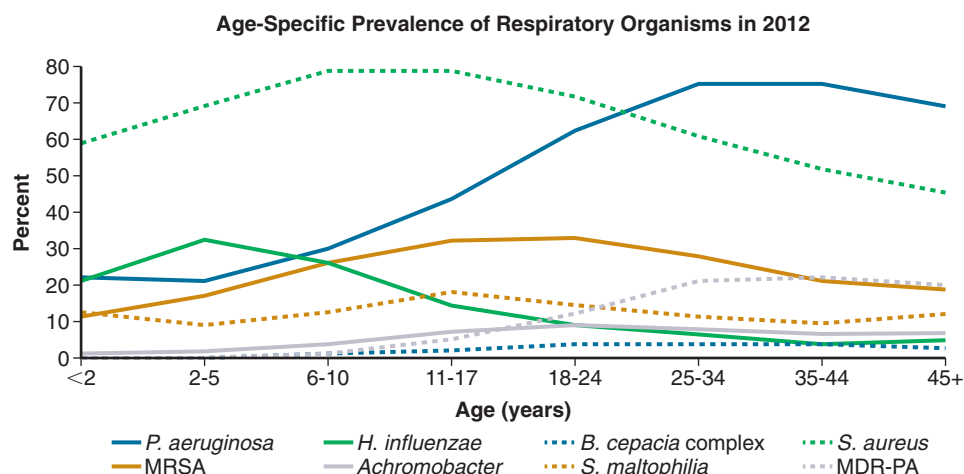


Figure 47-9 Alterations in sputum microbiology with age. This figure depicts increasing chronic infection with *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) with advancing age based on data from CF centers in the National CF Patient Registry. This is contrasted with the higher prevalence of *Haemophilus influenzae* and methicillin-sensitive *S. aureus* in childhood and adolescence. MDR-PA, multidrug-resistant *P. aeruginosa*. (Data from the Cystic Fibrosis Foundation Patient Registry; Bethesda, MD; 2012).

become a priority.¹⁰³ As lung disease progresses, exacerbations characteristically become more frequent and severe, often requiring extended courses of *intravenous* (IV) antibiotics and hospitalization. End-stage lung disease associated with impairment of daily activities heralds a sequence of terminal events in the absence of lung transplantation, including hypoxemia, pulmonary hypertension, cor pulmonale, respiratory failure, and death.

MICROBIOLOGY

Patients with CF demonstrate colonization of the airways early in life with bacteria characteristic for the disease. Chronic infection of the lower airways, once established, is difficult to eradicate. *Staphylococcus aureus* and *Haemophilus influenzae* are usually the first organisms detected and often present with a benign clinical picture (Fig. 47-9).¹⁰⁴ Historically, acquisition of *P. aeruginosa* or *Burkholderia cepacia* was regarded as a particularly ominous clinical finding because these infections are associated with accelerated decline in lung function and increased mortality.¹⁰⁵ With the increased prevalence of microbiologic screening and more aggressive antimicrobial treatment regimens, a more broad and diversified group of respiratory pathogens has emerged.¹⁰⁶ These pathogens include *methicillin-resistant S. aureus* (MRSA), multidrug-resistant gram-negative rods, atypical mycobacteria, and fungal organisms.¹⁰⁷ Often the clinical significance and factors contributing to the presence of these organisms in sputum culture are complex and multifactorial and thus require careful clinical consideration to determine the appropriate timing and intensity for treatment because some organisms may represent benign colonization.

The prevalence of *P. aeruginosa* increases with age, infecting greater than two thirds of patients by the third decade of life. The frequency of detection earlier in life has increased in the era of newborn screening and may be as high as 20% in children younger than 2; detection in infants at the time of diagnosis is not uncommon. Acquisition of *P. aeruginosa* increases longitudinally (see Fig. 47-9) and has been associ-

ated with genotype severity—individuals homozygous for F508del demonstrate a higher prevalence of chronic infection.¹⁰⁸

Considerable concern has emerged surrounding the nosocomial acquisition of new infections and transmission of multidrug-resistant organisms.¹⁰⁹ As the concept of eradication of initial infection has become standard practice, identification and earlier treatment of initial infection with *P. aeruginosa* using frequent respiratory sputum sampling to detect these inciting events is recommended in those not previously colonized.¹¹⁰⁻¹¹² Sputum bacteriology correlates reasonably well with specimens obtained directly from the lower respiratory tract, although microbial sequencing is lending new insights into the validity of this conclusion. Oropharyngeal swab cultures that yield *S. aureus* or *P. aeruginosa* are modestly predictive of results from bronchoscopic specimens, but negative pharyngeal cultures do not rule out the presence of these organisms in lower airways.¹¹³ Nevertheless, recent studies supporting sputum or oropharyngeal swab culture surveillance and subsequent treatment with intent to eradicate infection have demonstrated similar efficacy to more invasive detection regimens.¹¹⁴ Other more sensitive means to detect *P. aeruginosa*, such as PCR, may further improve sensitivity of noninvasive techniques. Quantitative bacteriology may be particularly useful for determining the relative contributions of isolated organisms.

As lung disease progresses, *P. aeruginosa* often becomes the predominant organism recovered from sputum and may be present in multiple strains with different antibiotic sensitivity patterns. The emergence of a mucoid phenotype due to elaboration of large amounts of alginate is associated with worsened clinical outcome.¹¹⁵ Mucoid organisms are found as microcolonies of pseudomonads embedded and growing in biofilms of alginate.¹¹⁶ Biofilms inhibit phagocytosis and enhance bacterial adherence while limiting exposure to antibiotics and reactive intermediates produced by leukocytes.¹¹⁷⁻¹²⁰ Although the presence of a mucoid phenotype is clearly associated with colonization, new mucoid *Pseudomonas* infection or conversion to mucoid phenotype

may also be amenable to aggressive eradication strategies.^{121,122} Isolation of *P. aeruginosa* from the lower respiratory tract of a child or young adult with chronic lung symptoms is highly suggestive of CF but has been reported in patients with primary ciliary dyskinesia or other severe obstructive lung diseases.¹²³

Although *P. aeruginosa* has remained the dominant pathogen in adult CF lung disease, MRSA has emerged as a significant contributor to disease progression and mortality. In contrast, methicillin-susceptible strains are associated with improved outcomes.¹²⁴ As MRSA has continued to emerge as a significant public health issue, its prevalence and severity in CF lung disease has become more evident.¹²⁵ Two studies using the U.S. CF registry have demonstrated an association between MRSA and worsened lung function, whereas another has shown MRSA infection to be an independent risk factor for mortality.^{126,127} Considerable interest has emerged in the epidemiology and biologic significance of the *staphylococcal chromosomal cassette* (SCC) containing the methicillin-resistance gene (*mecA*) and the *Panton-Valentine leukocidin* (PVL) expressing strains, both of which have an effect on their virulence and impact on disease severity.¹⁰⁷ Small-colony staphylococcus variants may also represent a distinct entity highly resistant to traditional therapy.¹²⁸

Many different gram-negative pathogens in addition to *P. aeruginosa* have demonstrated significant clinical impact on respiratory health, lending support to the consideration that CF lung infection represents a more complex microbiome than previously realized.¹²⁹ Of these, *B. cepacia* has remained the most ominous due to its inherent multidrug antibiotic resistance and association with rapid decline in respiratory health.¹³⁰ Infection can spread from patient to patient, leading to stringent infection control measures within CF care settings.^{131,132} Infection has been linked to the rapid demise of a small percentage of patients with what is referred to as “*cepacia* syndrome.”¹³³ Molecular analyses have shown that *B. cepacia* complex is composed of at least nine phenotypically indistinguishable but genetically distinct species known as genomovars.^{111,134,135} Genomovars II (*Burkholderia multivorans*) and III (*B. cenocepacia*) have been associated with the *cepacia* syndrome, and genomovar III includes the highly transmissible strain that may be linked to expression of the cable pilus.¹³⁵⁻¹³⁷ Other gram-negative rods present in sputum include mucoid *Escherichia coli*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Klebsiella*, and *Proteus*. Of these, *S. maltophilia* and *A. xylosoxidans* appear to have the strongest association with poor respiratory outcomes, but their clinical significance warrants further evaluation. Other gram-negative organisms such as *Pandoraea* and *Ralstonia* spp. have been isolated from CF sputum samples, but further clinical investigations are necessary to determine significant clinical associations. Obligate anaerobes have been identified from CF lung tissue; they are typically undetected by traditional clinical microbiologic samples but may be found in large abscess cavities on rare occasions.^{138,139}

Infection with nontuberculous mycobacteria is increasing in the CF population presumably due to concomitant antibacterial therapy resulting in a favorable ecologic niche, host susceptibility, improved detection, and environmental prevalence.¹⁴⁰⁻¹⁴⁵ Up to 20% of adult patients in some clinics

are colonized by nontuberculous mycobacteria. Although infection is often transient, the clinical impact of infection with these organisms appears to be increasing. *Mycobacterium avium* complex infection is of variable clinical significance, yet rapidly growing mycobacteria such as *Mycobacterium abscessus* can exhibit a more virulent course, prompting aggressive and long treatment regimens.¹⁴³ In contrast, *Mycobacterium tuberculosis* infection has only been seen in sporadic cases. Studies to standardize treatment for these emerging pathogens have been proposed.

Nearly 40% of individuals with CF will grow *Aspergillus fumigatus* in the sputum during their lifetime; patients who have severe lung disease appear to have an even higher incidence of sputum positivity.¹⁴⁶ The pathogenic potential of *Aspergillus* in an otherwise immunocompetent host is not well established. However, *Aspergillus* is clearly associated with allergic bronchopulmonary aspergillosis (ABPA). ABPA is present in approximately 2% of CF patients and adds a considerable burden of care.^{147,148} See ABPA in Chapters 38 and 48.

IMAGING

The earliest radiographic change in CF lung disease is usually hyperinflation of the lungs, reflecting obstruction of small airways. Central airway thickening and linear opacities, often producing a “tram-track” appearance, representing bronchiectasis, are eventually seen (eFig. 47-1) and often progress with age (eFig. 47-2). Frequently these findings are most easily appreciated in the right upper lobe (eFig. 47-3), and this lobe is often involved before other regions of lung are affected. The appearance of bronchiectasis at chest CT is characteristic (eFigs. 47-1B-E and 47-2B-E; see Chapter 48). Although chest radiography is appealing due to accessibility and relatively low doses of radiation exposure, its sensitivity for detecting acute or subtle chronic changes during a period of acute exacerbation remains limited.¹⁴⁹ Despite its limitations, chest radiographs remain the standard first-line imaging in surveillance and during acute exacerbations, episodes of hemoptysis (eFig. 47-4), or to identify complications such as pneumothorax¹⁵⁰ (eFig. 47-5); its use is recommended biannually in stable CF patients.¹⁵¹

High-resolution cross-sectional imaging using computed tomography (CT) is clearly superior for detecting mild disease and quantifying the extent and pattern of bronchiectasis (eFigs. 47-1B-E and 47-2B-E).^{152,153} Mosaic perfusion, manifesting as areas of inhomogeneous lung opacity and resulting from air trapping producing disordered pulmonary parenchymal perfusion resulting in maldistribution of pulmonary blood flow, is common at chest CT in patients with CF (eFig. 47-6). Small nodules resulting from bronchial and bronchiolar impaction are commonly seen at chest CT (eFig. 47-7). CT studies have demonstrated significant early changes in young children, before obvious clinical disease, supporting the notion that CF lung disease begins early in life and its detection is limited by the sensitivity of routine clinical procedures including spirometry.¹⁵² Regardless of the imaging modality used, the degree of hyperinflation generally increases over time. As endobronchial infection and reactive inflammation emerge, peribronchial cuffing becomes increasingly evident. Evidence of bronchiectasis,

such as enlarged ring shadows or airway dilation and cysts, is common even early in life (see eFig. 47-1); upwards of 50% of patients demonstrate bronchiectasis by 3 to 5 years of age.¹⁵³

During acute pulmonary exacerbations, a variety of radiographic findings may be noted such as peripheral round densities and mucoid impaction seen radiographically as branching opacities. These may resolve during treatment, replaced by the emergence of bronchiectasis or cystic changes. Additional findings including subpleural blebs often become evident during the second decade of life and are most prominent along the mediastinal border.¹⁵⁴

The indications for CT scanning in place of routine chest radiography are not established. One clear indication may be the evaluation of a patient with focal disease who may be considered for lobectomy, or patients that suffer acute deteriorations to help detect complications or evidence of new pathogens. *Magnetic resonance* (MR) imaging, which avoids radiation associated with CT scans, can also define lung morphology, particularly as techniques have improved, but the relative sensitivity and specificity of MR techniques have not yet been established.¹⁵⁵ MR-based ventilation scans are also possible using hyperpolarized gas; although they sensitively demonstrate airway obstruction, the method is generally restricted to research use due to poor availability and stability of the noble gases required.

LUNG FUNCTION

Lung function is believed to be normal at birth in infants with CF, though recent studies have demonstrated the cycle of inflammation and infection is present within weeks to months, and reduced cartilage size may impact early airway obstruction.¹⁵⁶ Infants with CF can exhibit increased airway resistance, gas trapping, and diminished flow rates.¹⁵⁷⁻¹⁵⁹ Many centers use infant pulmonary function testing to detect early evidence of airway obstruction and guide institution of therapeutic strategies before permanent lung injury. Lung clearance index, a test performed by measuring the time for clearance of an inert gas through multiple breath washout technique, is also emerging as a research tool to detect early evidence of ventilation abnormality and is not confounded by patient effort.¹⁶⁰⁻¹⁶² Reliable and consistent spirometry can be obtained routinely at 5 to 6 years of age when children are able to cooperate.^{163,164}

The earliest evidence of airway obstruction is typically limited to the small airways and thus is often first detectable by reduced forced midexpiratory flow rates, reduced flows at low lung volumes, and gas trapping (i.e., elevated *residual volume to total lung capacity* ratio [RV/TLC]). Although infrequently used in clinical applications, abnormalities such as increased alveolar-arterial oxygen gradient, frequency dependence of dynamic compliance, reduced response of flows to a helium-oxygen mixture, elevated slope of phase III of the single-breath nitrogen washout, and an elevated physiologic dead space are often present.¹⁶⁵ Spirometry is the most clinically useful test to follow the course of respiratory disease progression and is typically measured at each clinic visit. Equally important is assessment of the flow volume loop, which may demonstrate obstruction via concavity toward the volume axis before either the FEV₁ or FEF_{25%-75%} is affected.

Over time patients with active lung disease can experience a progressive deterioration of lung function; the annualized rate of decline in FEV₁ is approximately 2% to 3% of the predicted FEV₁ annually.¹⁶⁶ Despite recent advances, this progressive loss of lung function often accelerates in young adulthood.¹⁶⁷ As lung disease progresses, peripheral airway obstruction yields to more generalized obstruction and progressive air trapping late in the disease as airways cease to contribute to gas exchange, mimicking a restrictive pattern on spirometric measurements of lung function.¹⁶⁸

As the chronic cycle of inflammation and infection contributes to lung disease, many patients with CF begin to show mild decrements of arterial PO₂. Oxygenation declines slowly throughout life and this decline is often not clinically significant until late in the disease course. Patients who are able to sustain adequate oxygenation usually function well despite the presence of obstructive impairment. When arterial PO₂ values are sustained below 55 mm Hg, patients are at high risk for symptomatic pulmonary hypertension.^{169,170} Clinically significant hypoxemia most commonly presents during sleep, particularly during REM-associated hypoventilation, and is a significant factor leading to pulmonary hypertension.¹⁷¹ Desaturation at rest or with exertion as measured during a 6-minute walk are strong predictors of mortality.¹⁷² Elevation of arterial PCO₂ and FEV₁ less than 30% define end-stage disease. Patients with FEV₁ less than 30% of predicted, arterial PCO₂ greater than 50 mm Hg, or arterial PO₂ less than 55 mm have a predicted 2-year mortality of 50% and should be considered for lung transplantation.¹⁷³ Other prediction tools can also facilitate appropriate patient selection for referral and outperform reliance on any single criterion.¹⁷⁴

Bronchial hyperresponsiveness is a consistent finding in asthma, but its presence and clinical significance in CF remain controversial.^{175,176} Bronchial hyperresponsiveness in CF has been demonstrated during exercise testing, bronchoprovocation testing, or response to bronchodilators, with two thirds of CF patients demonstrating decreased forced expiratory flows after a bronchoconstrictive challenge. In contrast to cross-sectional studies, repeated tests every 1 to 3 months for a year have demonstrated bronchodilator responsiveness at least once in 95% of subjects.¹⁷⁷ Despite its frequency, the pathogenesis of bronchial hyperresponsiveness in CF is unclear. Hyperresponsiveness is unrelated to the severity of pulmonary disease or indices of atopy but seems to be more prevalent during winter months. Hyperresponsiveness diminishes with exacerbations of lung disease but returns as lung function improves after 2 weeks of intensive antibiotic therapy. Patients with CF may also have a lack of response to bronchodilators that may be related to loss of tone in bronchiectatic airways.

Exercise tolerance in CF is related to the severity of airway obstruction.¹⁷⁸ Nearly 50% of patients with moderate to severe airway obstruction may experience oxygen desaturation to below 90% during peak exercise.¹⁷⁹ Persons with CF have higher than expected ventilatory muscle endurance, and this endurance can be further improved with inspiratory muscle training. However, improved inspiratory muscle strength and endurance do not augment exercise performance.

Exercise therapy has many physiologic and biologic benefits but has not been convincingly demonstrated to improve

standard spirometry. Nevertheless, standardized aerobic and resistive exercise does improve cardiorespiratory fitness and *quality of life* (QOL) and has been associated with a reduced risk of hospitalization.¹⁸⁰ Maximum oxygen consumption during exercise may be a better predictor of survival than routine pulmonary function testing, but the test is time consuming and not available in all clinical settings.¹⁸¹ Several more clinically efficient measures of physical fitness show strong correlation with peak oxygen consumption and disease prognosis, further reinforcing that improvement of physical health through exercise may positively affect overall health in CF.¹⁸²

UPPER RESPIRATORY TRACT DISEASE

Chronic rhinosinusitis is present in virtually all patients with CF. CF sinus disease manifests as chronic, relapsing symptoms of increased upper airway secretions, moderate airflow obstruction, and widening of the nasal bridge.¹⁸³ This is seen at imaging (eFig. 47-8) as opacification of the paranasal sinuses in more than 90% of patients in the first year of life. Nasal polyps are seen in an additional 15% to 20% of patients.¹⁸⁴ Nasal polyps usually present toward the end of the first or during the second decade of life and may be the clinical finding that triggers diagnostic evaluation.¹⁸⁵ The presence of acute and chronic nasal obstruction can diminish olfactory function and may contribute to diminished dietary intake and subsequent nutritional decline.¹⁸⁶ Despite the presence of radiographic abnormalities, symptoms can be surprisingly well tolerated. Acute or chronic symptoms of sinusitis manifest in less than 10% of children and in approximately 24% of adults.^{187,188} Nevertheless, colonization of the upper airway may contribute to lower airway disease, necessitating attention to its presence and severity.

COMPLICATIONS OF RESPIRATORY TRACT DISEASE

Atelectasis is present in approximately 5% of CF patients during the first 5 years of life with diminishing frequency with advanced age.¹⁸⁹ Atelectasis may be lobar or subsegmental, with the right lung being the most commonly affected. Furthermore, it may develop concurrently with pulmonary exacerbations or in the absence of clinical symptoms. Occasionally, atelectasis may result from endobronchial aspergillosis presenting as mucoid impaction with volume loss.¹⁹⁰ However, in most instances, a discrete mucus plug is not evident on bronchoscopy.

Pneumothorax (see eFig. 47-5) is a well-recognized CF complication due to air trapping and subsequent rupture of subpleural blebs. Although the overall incidence is equal among sexes and fairly low (about 1% per year), this increases sharply with age and disease severity, with 20% of CF adults experiencing at least one pneumothorax during their lifetime.¹⁹¹ Typical presentations include acute onset of chest pain, dyspnea, respiratory distress, or hemoptysis.¹⁹² Tension pneumothorax, which is more common in CF than in other obstructive lung diseases, represents an emergent situation because the rapid accumulation of pleural air may become life-threatening. Similarly, simultaneous bilateral pneumothoraces have been described and consti-

tute an emergency. Small asymptomatic pneumothoraces may also be discovered in patients following routine surveillance chest radiography. Recurrent pneumothoraces are common.

Hemoptysis is a relatively common event in CF (see eFig. 47-4) and is believed to result from mucosal erosions and bronchial artery hypertrophy, which are a consequence of chronic inflammation.¹⁹³ The presence of hemoptysis correlates with disease severity and is more common in the setting of chronic MRSA infection.¹⁹² Blood streaking in the sputum is a frequent finding and may be chronic. Massive hemoptysis (>240 mL blood in 24 hours) presents in approximately 5% of patients during their lifetime.¹⁹⁴ Due to the strong correlation between hemoptysis and exacerbations of lung infection, initial treatment should include antibiotic therapy and rest from chest physiotherapy. Typically, aerosol therapies are temporarily held and measures to promote clot stabilization are considered. There are anecdotal reports of the use of the antifibrinolytic, tranexamic acid.¹⁹⁵ Beta blockade has also been reported to be helpful in acute and chronic hemoptysis presumably by reducing blood pressure and blunting the sympathetic response to coughing spells.¹⁹⁶ Although bronchoscopy can help to localize the site of bleeding, emergent bronchoscopy or radiographic imaging are of limited clinical utility. Often, emergent bronchial artery embolization (see eFig. 47-4F and G) should be attempted without waiting for these measures. Advances in invasive vascular interventions and improved clinical management strategies have resulted in significantly reduced mortality, which was historically as high as 10% after massive hemoptysis.¹⁹⁷

ABPA has a lifetime incidence of 2% to 8% in CF patients, although a few small cohorts report an incidence rate as high as 20%, suggesting an environmental association.^{198,199} *Aspergillus* is a common environmental mold and is frequently recovered in sputum culture. Although up to 50% of patients with CF may demonstrate precipitating antibodies to *A. fumigatus* in their serum, an IgE-mediated allergic hypersensitization must develop to manifest ABPA clinically.²⁰⁰ Clinical features include increased cough, dyspnea, wheezing, and the expectoration of rusty brown plugs containing many eosinophils. Radiographic findings can be present, including characteristic finger-in-glove pattern. Atelectasis and volume loss may also result from hyphae-laden mucoid impaction in segmental bronchi. A diagnosis of ABPA is made by fulfilling major and minor criteria that include characteristic clinical findings plus skin test hypersensitivity, elevated total IgE, and elevated levels of IgG and IgE antibodies against *A. fumigatus* or other fungi.¹⁴⁷ (See Chapters 38 and 48.)

Staphylococcal and pseudomonal empyemas have been described in patients with CF, but respiratory tract infections usually spare the pleural space, making complications such as *pleural effusions* and *empyema* uncommon. Nonetheless, pulmonary exacerbations may often be accompanied by pleuritic-type pain.²⁰¹

Digital *clubbing*, which is caused by hyperplasia and hypertrophy of connective tissue and increased vascularity of the distal phalanges, appears in virtually all patients with advanced CF and is often present early in individuals with active lung disease. The cause of clubbing is unknown, but it is known to resolve following lung transplantation.²⁰² Its

severity generally correlates with the severity of lung disease.²⁰³ *Hypertrophic pulmonary osteoarthropathy* is a common clinical entity presenting with advanced CF lung disease in up to 15% of older adolescents and adults.¹⁷⁰ Radiographic evidence for periostitis may be present in up to 8% of subjects. The distal aspects of the tibia, fibula, radius, and ulna are the most commonly affected sites. Signs and symptoms include pain, bone tenderness, swelling, and warmth over the involved areas; however, some patients may not manifest clinical symptoms. Effusions are uncommon but may arise in adjacent joints. Pain with ambulation or following strenuous physical exercise is common.²⁰⁴ Hypertrophic pulmonary osteoarthropathy is exacerbated during periods of poor respiratory health and tends to subside with the resolution of pulmonary exacerbations. Its presence with end-stage lung disease may yield persistent clinical symptoms requiring chronic analgesic therapy. There are also rare instances of cutaneous vasculitis causing self-limited, painless, palpable purpura, typically involving the lower extremities.²⁰⁵⁻²⁰⁷

Respiratory failure is the greatest contributor to mortality and is the cause of death in 90% of CF patients. *Hypoxemia* is first seen during exertion or sleep and progresses with lung disease.^{171,208} *Hypercapnia* is a late finding reflecting advanced lung disease, which typically progresses with disease severity and worsens during pulmonary exacerbations. Pulmonary hypertension and cor pulmonale may develop late in the disease process, resulting in hepatic congestion and peripheral edema.²⁰⁹ The role of pulmonary hypertension in CF is currently being studied to prioritize treatment regimens.²¹⁰ Hypoxemia, if not recognized or adequately treated, will contribute to worsening pulmonary hypertension and cardiac failure. Pneumothorax, hemoptysis, and infections such as respiratory syncytial virus or influenza can cause acute respiratory failure that is reversible with aggressive treatment.^{211,212}

GASTROINTESTINAL MANIFESTATIONS

Meconium ileus is seen in about 15% of newborns and is pathognomonic for CF. Failure to pass thick inspissated meconium in the first 48 hours of life is associated with abdominal distention and rapidly advances to bilious emesis. Affected infants are at risk for intestinal perforation and peritonitis accompanied by shock. Radiographic features are typical of high-grade bowel obstruction revealing multiple dilated loops of intestine and air-fluid levels (eFig. 47-9). A granular appearance of the lower abdomen may be noted due to accumulated meconium containing small air bubbles. The colon is characteristically small when visualized with contrast imaging (eFig. 47-10). Scrotal and peritoneal calcification can be seen following ileal perforation in utero. Meconium obstruction in the colon may only delay passage of stool. This has been termed the *meconium plug syndrome* and is much less specific for CF.²¹³

Beyond the newborn period, 20% of patients may develop the *distal intestinal obstruction syndrome* (DIOS). This is characterized by obstruction in the cecum, proximal colon, or terminal ileum associated with voluminous, viscous, and incompletely digested intestinal contents and is similar to meconium ileus (eFig. 47-11). Partial obstruction may manifest as a chronic or recurrent entity with intermittent

crampy abdominal pain as the only symptom. Fulminant complete obstruction is associated with failure to pass stool, resulting in abdominal distention and vomiting that may be bilious or fecal if allowed to progress. A mobile right lower quadrant mass may be palpable. Risk factors for DIOS include previous episodes, dehydration, dietary change, immobilization, bacterial overgrowth, treatment with antibiotics, and constipating medications. Other causes of acute abdominal pain with obstruction should also be considered, including intussusception, intestinal adhesions from previous abdominal surgery, and appendicitis, which may be partially suppressed due to concurrent antibiotic therapy. Appendicitis is thought to be uncommon in CF, with a 2% lifetime risk compared with a 7% to 8% risk in the general population.²¹⁴ Nonfilling of the appendix with contrast enema is seen in patients with CF; radiographic and histologic findings of a dilated, mucus-filled appendix are typical features,^{215,216} although the uninflamed appendix is frequently enlarged at CT in CF patients (eFig. 47-12). The loss of pancreatic and bowel secretion of bicarbonate to buffer gastric acid may result in duodenal irritation and recurrent epigastric pain.²¹⁷

Gastroesophageal reflux is common in CF; increased abdominal pressure associated with obstructive lung disease contributes to its high prevalence.²¹⁸ Consideration of gastroesophageal reflux is important because it can impair nutritional status and may contribute to microaspiration, accelerating lung disease. The presence of gastroesophageal reflux has been associated with worsened outcome after lung transplantation, and therefore patients with CF considered for lung transplantation should be evaluated thoroughly; some centers advocate surgical therapy for ongoing reflux during the peritransplant period.²¹⁹

Rectal prolapse develops in nearly 20% of children with CF but is an infrequent event for adults.²²⁰ Rectal prolapse in a child should raise consideration of CF even if it is the only obvious clinical symptom. Rectal prolapse is precipitated by the presence of bulky, sticky stools that adhere to rectal mucosa, poor nutritional status with loss of the perirectal fat that normally supports the rectum, and the presence of high intra-abdominal pressure due to frequent paroxysmal coughing.

PANCREATIC DISEASE

Exocrine pancreatic insufficiency (PI), due to intraluminal obstruction with thickened, dehydrated secretions, is present from birth in 85% of patients with CF.^{221,222} Adequate exocrine pancreatic secretion is present in 10% to 15% of patients and has defined genotypic associations. Insufficient release of pancreatic enzymes into the gut results in impaired fat and protein digestion and impaired absorption in the small bowel. Pancreatic insufficiency results in frequent bulky, greasy, foul-smelling stools and protuberance of the abdomen due to increased intraluminal bacterial gas production. Assessment of pancreatic function by ELISA measurement of stool fecal elastase-1 may enhance clinical assessment of PI.²²³

Untreated malabsorption results in nutritional failure and ultimately failure of linear growth, which has been linked to worsened outcomes.²²⁴ Patients with CF also grow slowly because of factors beyond nutritional intake and

intestinal absorption. For example, increased expenditure of energy to accomplish the work of breathing may be an important contributor; systemic inflammation may also play a role.²²² Fat-soluble vitamin deficiency was historically a common association at diagnosis in young children presenting with nutritional failure but is much less common in the era of newborn screening.

Symptomatic pancreatitis develops in less than 1% of adolescent or adult CF patients, usually in patients who have at least some residual exocrine pancreatic function.²²⁵ However, recurrent pancreatitis has been reported in association with CFTR dysfunction and can be the presenting feature of the disorder.^{24,226} Complete fatty replacement of the pancreas is common at CT (eFig. 47-13), and pancreatic lipomatosis and fibrosis are characteristic of pediatric CF. Pancreatic ductal dilation and calcifications may also be seen in CF patients. Rarely, there may be cystic replacement of the pancreas, referred to as *pancreatic cystosis*.

HEPATOBIILIARY DISEASE

Although relatively common, there is not yet consensus on the definition of CF-associated liver disease. Histologically, liver disease manifests as focal biliary cirrhosis and produces clinically significant liver disease in a greater proportion of CF patients as longevity increases. One description of clinically significant disease includes the constellation of an abnormal physical exam, abnormal liver function testing, and imaging findings.²²⁷ Liver disease may present as hepatosplenomegaly or as persistent elevation of hepatic enzymes (AST, ALT, bilirubin, GGT). Current guidelines recommend evaluation for liver disease when enzymes are elevated more than 3 times normal or remain 1.5 to 3 times normal for 3 months. Patients with CF-associated liver disease rarely develop acute fulminant hepatic failure but with advanced cirrhosis can develop portal hypertension and clinically significant esophageal varices.²²⁸ Steatosis is a common clinical finding and has been associated with malnutrition, essential fatty acid deficiency, and/or oxidative stress.²²⁷ Ultrasound is generally used to monitor severity and is currently being studied in longitudinal studies.

Biliary tract disease is common in CF. Cholelithiasis develops in approximately 10% of patients but causes significant clinical symptoms in less than 4% of cases.²²⁹ Formation of stones is encouraged by the abnormal ion transport environment resident in the gallbladder. A small or microgallbladder is seen in 20% to 30% of patients and is of unknown clinical significance.²³⁰

GENITOURINARY TRACT ABNORMALITIES

The vas deferens is congenitally absent in almost all males with CF.²³¹ Semen analysis is typically required to identify the 1% of male CF patients who are fertile. The volume of ejaculate is usually one third to one half of normal; complete absence of spermatozoa in addition to a number of chemical abnormalities that reflect absence of secretions from the seminal vesicles is usually apparent.²³² An increased incidence of inguinal hernia and hydrocele has also been reported.

Although significantly less common, female infertility in CF may be as high as 20%.²³³ Many women with CF and

advanced lung disease and/or malnutrition are anovulatory. Another obstacle to conception is the presence of thick tenacious cervical mucus and an increased presence of endocervicitis. This dehydrated mucus also has abnormal electrolyte concentrations, preventing the usual ferning at midcycle. As a result, this mucosal abnormality is thought to impede normal sperm migration.²³³ Urinary incontinence can be seen beginning in adolescence and does not clearly correlate with disease severity; rather, incontinence probably reflects chronic cough and increased abdominal pressure due to airflow obstruction.²³⁴

Pregnancy in females with CF appears to be increasing as clinical outcomes have improved. A longitudinal study of 325 pregnant women with CF demonstrated 258 live births (79%) and 67% therapeutic abortions.²³⁵ Compared with 1142 age- and severity-matched controls, pregnancy in a woman with CF did not have an independent negative effect on pulmonary status or mortality over 2 years.²³⁶ Successful pregnancy and delivery is possible and may be carried out safely, but it is essential that women with CF consider implications to their health as they consider family planning. Successful breast feeding has been reported in women with CF.²³⁷

SWEAT GLAND DYSFUNCTION

Sweat chloride is elevated in most CF patients due to abnormal chloride reabsorption in the sweat duct due to the absence of CFTR. This may predispose individuals with CF to excessive salt loss in certain settings. Young children are especially susceptible to depletion, especially when exposed to warm arid climates, or when there is additional salt loss due to vomiting or diarrhea. Typically children in this circumstance present with lethargy, anorexia, and hypochloremic alkalosis and/or hyponatremia.²³⁸

TREATMENT

OVERVIEW

Considerable progress in the understanding of CF lung disease and a concerted effort to address disease manifestations in a comprehensive fashion have led to a number of new therapeutic approaches to the disease.¹⁵ Therapies including mucolytics,²³⁹ hydrators of the airway surface,^{240,241} inhaled antimicrobials,²⁴²⁻²⁴⁴ systemic anti-inflammatory treatments,²⁴⁵⁻²⁴⁷ and nutritional support are the mainstays of current CF treatment (Table 47-4). These sorts of supportive therapies, in addition to comprehensive care undertaken at organized CF clinical centers, are responsible for the steadily improving life expectancy observed over the past decade (Fig. 47-10), resulting in a median life expectancy of 41 years in 2012, based on the latest analysis of the U.S. registry.²⁴⁸ Similar improvements have been observed in other developed countries. More recently, the first treatment that addresses the basic defect in CF by restoring CFTR function in patients with the G551D CFTR gating mutation has been approved, resulting in marked improvements among individuals with this mutation.²⁴⁹ Other therapies that address more common CFTR alleles or aim to replace CFTR with gene therapy are in

various stages of clinical development and promise to open a new therapeutic era in the disease (Fig. 47-11).

MONITORING AND AGGRESSIVE APPROACH

Aggressive monitoring and treatment of pulmonary infections and other common CF complications has been a key advance that is believed to have contributed significantly to improved clinical outcomes in the past decade.^{167,250,251} As

discussed earlier, the predominant lower airway pathogen changes through the lifetime of CF patients, with *S. aureus* and *H. influenza* being the most common organisms isolated during infancy and early childhood, while *P. aeruginosa* typically becomes the dominant pathogen later in the disease.²⁵² (See Fig. 47-9.) New attention has focused on the efforts to delay or prevent chronic colonization with *P. aeruginosa*, with a number of studies evaluating various regimens to best achieve sustained clearance. Coincident with this approach is increased attention to infection control to prevent acquisition of virulent organisms, particularly in health care settings where risk of acquisition is significant. Segregation of clinics by *Pseudomonas* status can reduce acquisition of epidemic organisms; standard infection control procedures alone may not be sufficient,^{253,254} leading to even more rigorous guidelines for patient isolation and prevention against comingling.²⁵⁵ Once established, *P. aeruginosa* is challenging to eradicate with antimicrobial therapy alone,^{74,256-259} although it can be accomplished in selected patients.¹²² Chronic colonization with *Pseudomonas* is associated with a more rapid decline in respiratory status,^{105,115,260} although not as severely as more virulent organisms such as *B. cepacia*^{261,262} or *B. dolosa*,²⁶³ which can also be associated with outbreaks due to nosocomial spread. As with chronic infection, early and aggressive nutritional therapy, particularly among young children with CF, has been crucial to achieving improved outcomes. Despite advances in lung function and delays in *Pseudomonas* growth, delaying the progression of CF in the adolescent years remains a challenge.

Sponsored in part by the CF Foundation, U.S. centers have embarked on a rigorous quality improvement program to facilitate best practices in CF care. Outcomes are compared between centers and made publically available to

Table 47-4 Cystic Fibrosis Therapeutics by Category	
Agent	Predominant Mechanism of Action
Restoration of Airway Surface Hydration	
Hypertonic saline*	Osmotic increase of airway hydration; expectorant
Mannitol†	Osmotic increase of airway hydration; expectorant
Mucolytics	
Dornase alfa	Cleaves DNA polymers
Anti-Inflammatory	
Ibuprofen	Reduce airway inflammation
Anti-Infectives	
Inhaled tobramycin	Chronic treatment of <i>Pseudomonas aeruginosa</i>
Inhaled aztreonam	Chronic treatment of <i>P. aeruginosa</i>
Dry powder tobramycin	Chronic treatment of <i>P. aeruginosa</i>
Azithromycin	Anti-inflammatory/anti-infective for chronic <i>P. aeruginosa</i> infection
Nutritional Therapies	
AquADEKs	Restore fat-soluble vitamin levels
Pancrelipase	Restore pancreatic enzyme levels

*Therapy commonly used but not FDA approved.

†Therapy only approved in Europe, Australia, and New Zealand.

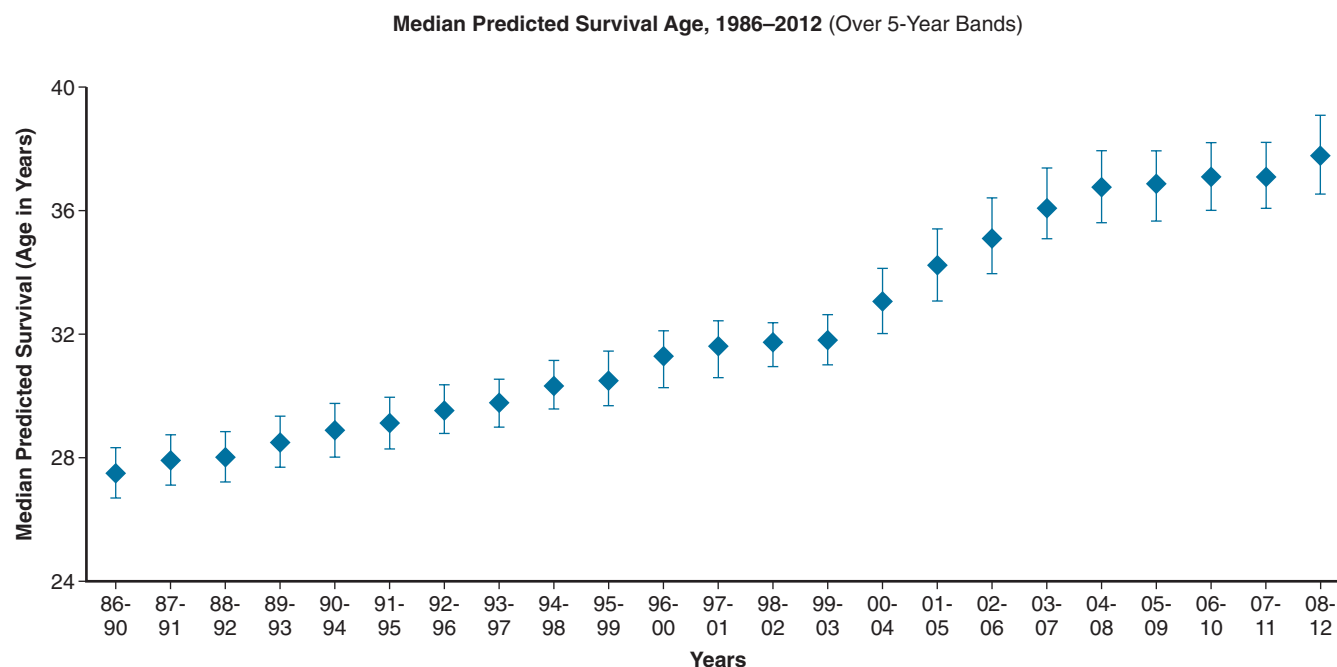


Figure 47-10 Median predicted survival in CF. Median predicted survival for CF patients in U.S. Cystic Fibrosis centers in the CF registry from 2012. Data are depicted as medians for 5-year time spans from 1986–2012. Since the mid-1980s, predicted survival has increased from about 27 years of age to older than 36 years of age for the most recent 5-year time span. (Data from the Cystic Fibrosis Foundation Patient Registry, Bethesda, MD; 2012.)

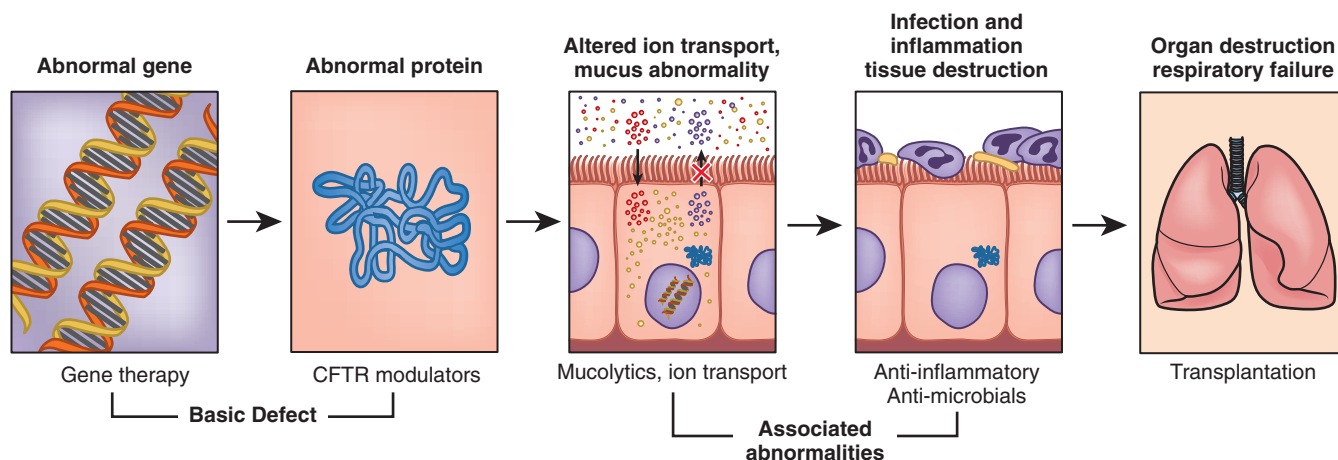


Figure 47-11 CF therapeutics by category. This figure depicts the mechanisms of CF airway pathology. CF therapeutics attempt to address defective CFTR function by gene therapy or modulation of CFTR expression or function; to address the diminished airway surface liquid, abnormally viscous mucus, and disrupted mucociliary clearance; and finally, to address chronic airways infection and inflammation. When respiratory failure develops, lung transplantation is the remaining option.

encourage continuous improvement.²⁶⁴ A culture of cooperation among centers, patients, families, and the Cystic Fibrosis Foundation has led to evidence-based guidelines, protocol-driven therapies, and rapid dissemination of results to facilitate advances in health care delivery.²⁶⁵

CFTR Potentiators, Correctors, and Other Treatments for the Basic Defect

On the basis of functional consequences of various *CFTR* mutations, specific therapeutic strategies to restore deficient or defective protein function are being developed by altering *CFTR* expression or function (Fig. 47-12 and Table 47-5). Because of ambitious high-throughput screening efforts,^{58,266-269} the benefits of these new *CFTR* modulators have begun to come to fruition for CF patients. Results in the clinic demonstrate that the rescue of the *CFTR* protein by the archetype *CFTR* modulator ivacaftor is associated with marked improvements in the clinical outcome that compare favorably with previous therapies widely used by CF patients.^{249,270,271} The *CFTR* potentiator ivacaftor (formerly VX-770) was the first to advance as an approved CF treatment among patients with the G551D gating mutation, an allele represented in approximately 4% of CF patients. ***CFTR* potentiators** function to activate *CFTR* channels located at the cell surface. They potentiate cAMP-mediated channel gating via decoupling with ATP hydrolysis^{58,272,273} and may be more broadly useful against a greater variety of *CFTR* missense alleles, including other class III gating mutations and other *CFTR* forms that exhibit residual activity at the cell surface (i.e., conductance and mild processing mutants).^{274,275} The highly efficacious treatment benefit observed with ivacaftor therapy has engendered considerable interest toward recapitulating its effects among other more common *CFTR* alleles.²⁷⁶ This includes correctors of F508del *CFTR* misfolding, termed *CFTR* correctors. ***CFTR* correctors** attempt to restore normal *CFTR* processing to the most common *CFTR* mutation. Other agents that induce readthrough (or suppression) of PTCs to induce expression of full-length *CFTR* are also under development and have shown promise in proof-of-concept clinical

trials.²⁷⁷⁻²⁸⁰ Other approaches beyond these small molecule *CFTR* modulators are also being explored. For example, gene replacement by viral and nonviral gene therapy remains an approach under active investigation,²⁸¹ as well as newer strategies that attempt to express *CFTR* through transduction of mRNA alone.^{282,283} In total, this class of agents that target the basic CF defect serves as both a prime example of the potential for new genetic-based approaches in CF and a seminal example for other genetic diseases. Because many patients (~40%) are complex heterozygotes for more than one *CFTR* mutation,²⁸⁴ combination therapeutics addressing more than one *CFTR* allele or use of multidrug therapy seem likely in the future and will dictate a need for individualized therapeutics optimized for particular patients on the basis of their underlying disease and other genetic covariates.²⁷⁶

***CFTR* Potentiators.** *CFTR* potentiators activate mutant *CFTR* localized to the cell surface by potentiating channel gating stimulated by physiologic activation of cyclic AMP.^{58,269,285-287} The impetus for development included the anticipated need to activate F508del *CFTR* once localized to the cell surface, in addition to the need to activate other mutant channels that reside at the plasma membrane but are dysfunctional due to aberrant gating, impaired conductance, or a reduced number of channels due to mild processing mutations or splice variants. Early attempts included use of genistein, a natural flavonoid molecule that demonstrates strong activation of *CFTR* but is poorly absorbed and exhibits other undesirable physiologic properties.^{286,288,289} Subsequently ivacaftor and other investigational *CFTR* potentiators were discovered via high-throughput screening approaches that identified small molecule potentiators optimized for druglike qualities through traditional medicinal chemistry approaches.^{58,269,285-287} Ivacaftor induced about 50% *CFTR* activity in G551D/F508del *CFTR*-expressing primary epithelial cells, an emerging benchmark for preclinical development of *CFTR* modulators.⁵⁸

In a long-term Phase III placebo-controlled trial conducted in older children and adults (age 12 and older) with

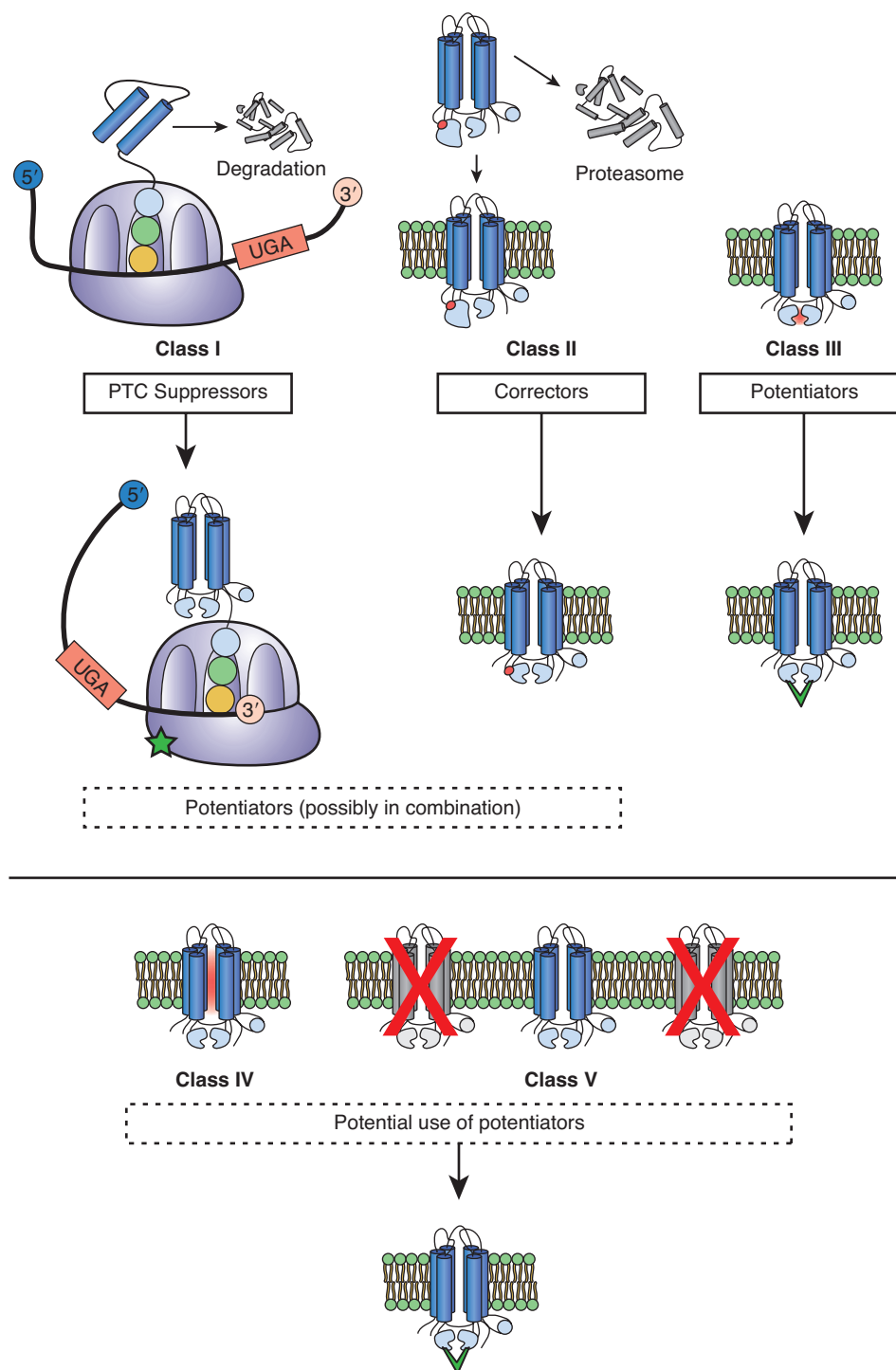


Figure 47-12 CFTR modulators by mutation class. Classes of defects in the *CFTR* gene include premature termination codons (PTCs) causing truncated protein translation (class I); misfolded CFTR, including deletion of phenylalanine at position 508 (class II, location shown with a red dot); full-length CFTR that reaches the cell surface but exhibits abnormal channel gating (class III; ATP hydrolysis is disrupted, at site identified in red) or reduced pore conductivity (class IV); and full-length CFTR with splicing errors (class V); premature termination codon suppressors (e.g., aminoglycosides, ataluren) bind to ribosomal subunits (green star) to allow suppression of PTCs and expression of full-length protein. Class II mutations like F508del can respond to small-molecule corrector compounds to restore folding defects and/or enhance expression of the channel at the cell membrane (e.g., lumacaftor, VX-661). Without correction, almost all class II CFTR is sent to the proteasome, leaving detectable surface protein in only rare individuals. CFTR potentiators include ivacaftor (green chevron) for patients with *CFTR* gating mutations. Future directions include exploring the use of CFTR potentiators for other mutant CFTR known to reside at the cell surface, such as noncanonical splicing mutations. Combination therapy with potentiators has also been proposed for classes I and II *CFTR* mutations. (Adapted from Rowe SM, Borowitz DS, Burns JL, et al: Progress in cystic fibrosis and the CF Therapeutics Development Network. *Thorax* 67(10):882–890, Fig. 1, 2012.)

Table 47-5 Approved and/or Investigational Therapeutics Targeting Each *CFTR* Mutational Class

CFTR Modulator Class	Representative Molecules	CFTR Mutations Affected	CFTR Mutation Class
Potentiator	Ivacaftor (VX-770)	G551D, non-G551D gating mutations*, other surface localized <i>CFTR</i> alleles*, F508del <i>CFTR</i> [†]	Class III Possibly classes IV, II, and I
Corrector	Lumacaftor (VX-809), VX-661, N6022 (N30 Pharma)	F508del*	Class II
Premature termination codon suppressor	Ataluren (PTC124), aminoglycosides	Nonsense mutations	Class I
Splicing repair	Antisense oligonucleotides	Splicing mutations*	Class V

*Investigational.

[†]In combination with a *CFTR* corrector.*CFTR*, cystic fibrosis transmembrane conductance regulator.

CF and with at least one copy of the G551D-*CFTR* mutation, ivacaftor caused a roughly 10% absolute improvement in FEV₁ at 24 weeks, an effect durable through 48 weeks of testing, providing confirmation of prior Phase II testing.²⁴⁹ In addition, all secondary clinical end points showed meaningful and statistically significant improvements, including a 55% reduction in the probability of experiencing a pulmonary exacerbation, improved weight gain, and an improvement in respiratory symptoms. Sweat chloride testing also exhibited marked improvements (mean of sweat chloride was about 55 mEq/L, a value below the traditional diagnostic threshold). Of note the improvement in spirometry was rapid; within 2 weeks, 90% of the maximal improvement was observed, suggesting that the mechanism was clearance of mucus, rather than the reversal of longstanding structural lung disease. In a smaller study that enrolled pediatric G551D CF patients 6 to 12 years old,²⁷¹ benefit was also documented by lung clearance index measurements in CF patients with minimal detectable lung function abnormality by spirometry, likely reflecting activity in the small airways.²⁹⁰ The degree of improvement in spirometry among participants of the Phase III trial of ivacaftor compares favorably with that of commonly used therapies for chronic CF care, including inhaled recombinant human DNase,²³⁹ inhaled tobramycin,²⁴² azithromycin,²⁴⁶ and hypertonic saline.²⁴⁰ In all clinical studies to date, ivacaftor appeared safe and well tolerated, although monitoring of liver function tests is recommended.²⁹¹

In contrast to the large effect in G551D patients, ivacaftor monotherapy had no meaningful effect in CF patients homozygous for F508del *CFTR*, establishing that *CFTR* potentiation alone is unlikely to be effective without concomitant administration of a corrector molecule to bring F508del *CFTR* to the cell surface.²⁹²

These findings have formed the basis of clinical approval for ivacaftor in CF patients with G551D mutations, and this treatment has rapidly been deployed to children and adults with the appropriate mutation. Establishing the proof of concept that *CFTR* modulation could have pronounced clinical effects among CF patients has also engendered considerable interest in extending these findings toward other *CFTR* mutations in which ivacaftor might be effective and developing *CFTR* modulators for other common *CFTR* alleles.^{274,275} The long-term benefit of effective modulation of *CFTR* will also be evaluated in ongoing

long-term observational studies, which will examine the effects of ivacaftor in G551D CF patients on clinical outcome, sputum microbiology, and systemic inflammation, among other parameters.

Because ivacaftor also increased *CFTR* activity in other gating mutations in vitro,²⁷⁵ these non-G551D gating mutations were also tested; the beneficial effects of ivacaftor were also observed in patients with other non-G551D class III gating mutations. Patients observed a large increase in FEV₁ and similar decrease in sweat chloride compared with that seen in patients with G551D, suggesting a class effect. Other *CFTR* mutations, such as conductance mutations, mild processing mutations, or *CFTR* splice variants allow low levels of partially active *CFTR* channels to reach the cell surface, conferring partial *CFTR* function²⁷⁴ and typically a milder CF phenotype. The effect of ivacaftor on partially active missense mutations from these *CFTR* classes is generally proportionate to basal *CFTR* function, reflecting the ability of increased gating to compensate in part for reduced surface expression or conductance, even when gating is normal in these *CFTR* forms.²⁷⁴ With this information in mind, ivacaftor is being tested in the archetype conductance mutation R117H in addition to individuals who exhibit residual *CFTR* function and a relevant *CFTR* allele. These results may justify use of *CFTR* potentiators in a broader group of individuals with CF. Combined with individuals with gating mutations, this represents approximately 10% to 15% of the CF population who ultimately might benefit from monotherapy with a *CFTR* potentiator.

CFTR Correctors. Significant effort has been directed toward the goal of correcting the folding of F508del *CFTR*, thus restoring ion channel activity to the misfolded protein. Early attempts include the evaluation of agents such as 4-phenyl butyrate to down-regulate HSC70 (or other protein processing chaperones), a pathway central to the protein folding process that has been shown to augment F508del *CFTR* expression in vitro and represent an early example of compounds tested in the clinic.^{293,294} Curcumin and 8-cyclopentyl-1,3-dipropylxanthine are examples of F508del *CFTR* processing correctors that did not successfully translate from in vitro studies to clinical results.²⁹⁵⁻²⁹⁷ More recent efforts have resulted from high-throughput library screens for chloride channel function following incubation of test compounds with F508del expressing cells.^{267,269,298} A number of these strategies have identified

F508del correctors that may address cell biogenesis through chaperone pathways. Pharmacologic activity of such agents has also been reported to augment F508del CFTR half-life in the plasma membrane through altered surface recycling attributed to features of the cellular processing machinery²⁹⁹ or reduced endocytic trafficking.³⁰⁰ This class of agents may be potential drug development candidates if their safety in vivo is confirmed. Other compounds have been shown to directly interact with CFTR^{301,302} and may offer greater specificity than agents that alter general aspects of cell folding or cellular quality control.

Success toward effective correction of F508del CFTR was seen during initial Phase II testing of lumacaftor (formerly VX-809), a putative F508del CFTR corrector. Results demonstrated modest decreases in sweat chloride compared with placebo but were not accompanied by improvements in spirometry or other clinical measures.³⁰³ Although this established that rescue of F508del CFTR in human subjects is achievable by a systemically delivered small molecule, the degree of CFTR rescue was insufficient to confer clinical improvement. Because F508del CFTR also exhibits abnormal channel gating, in addition to aberrant cellular processing, an approach to address insufficient activity is to coadminister a CFTR potentiator with a CFTR corrector.³⁰⁴ This approach is substantiated by in vitro results demonstrating that combination therapy increased CFTR function in F508del CFTR homozygous HBE cells.³⁰⁴ Recently a Phase II trial demonstrated that coadministration of lumacaftor and ivacaftor resulted in significant improvements in FEV₁ (≈6% treatment effect), although changes in sweat chloride did not correlate with additional benefit seen following addition of the potentiator.^{304a} Lesser effects were observed in CF patients heterozygous for F508del CFTR, providing evidence of a gene dose effect. The potential benefit of ivacaftor and lumacaftor in combination among F508del homozygous CF patients is presently being pursued in two large international Phase III trials. If positive, results could justify use of corrector-potentiator combination therapy for the most common CFTR mutation. An alternative corrector, VX-661, which has a similar mechanism as lumacaftor but more advantageous pharmacologic properties, also demonstrated additive benefit when used in combination with ivacaftor in individuals homozygous for F508del CFTR alleles in Phase II testing, providing additional confidence that the combination of corrector and potentiator agents could be effective among individuals expressing F508del CFTR. The results also suggest that ivacaftor may be useful to augment the rescue of other mutant forms of CFTR, such as premature termination codons or other processing mutants (e.g., class II mutations) sensitive to the effects of CFTR correctors.

Other strategies to identify agents that augment F508del CFTR folding are also being developed, and interest has accelerated with recent successes in clinical studies. Using a trafficking assay based on epitope-tagged CFTR, phosphodiesterase inhibitors including sildenafil and other active analogues have been shown to improve surface localization of the mutant protein. The same agents augment short-circuit current in F508del CFTR-expressing cell lines³⁰⁵ and enhance NPD in CF mice,^{306,307} as did the related compound vardenafil.³⁰⁸ Because misfolded F508del CFTR exhibits two fundamentally distinct properties that alter its processing

(namely nucleotide binding domain 1 stability and interdomain assembly), it has subsequently been recognized that compounds that address these mechanisms independently can exhibit additive or synergistic effects of correction of F508del CFTR misfolding. Moreover, the global cellular response to misfolded protein may also represent a target. For example, treatment of CF cells with *histone deacetylase* (HDAC) inhibitors can modulate ER stress, and HDACs such as *suberoylanilide hydroxamic acid* (SAHA), as well as siRNA-silencing, increase levels of F508del CFTR in the cell membrane.³⁰⁹ Additive or synergistic rescue of F508del CFTR using more than one such strategy may offer hope of achieving ion transport activity sufficient to confer a normal phenotype in CF respiratory epithelia.^{298,310}

Translational Readthrough. Readthrough of *premature termination codons* (PTC) represents a potential approach to address CF caused by this mechanism, which could also be applicable to many other genetic disease caused by nonsense mutations. The approach was identified when certain aminoglycoside antibiotics were found to interact with the eukaryotic rRNA within the ribosomal subunits.³¹¹ Through this interaction, the fidelity of eukaryotic translation can be altered by interrupting the normal proofreading function of the ribosome.³¹²⁻³¹⁸ Insertion of a near cognate *amino acid* (AA) at a PTC allows protein translation to continue normally.³¹⁴ Specificity is conferred by greater termination codon fidelity at the authentic (3') end of mRNA and has been established in vitro by demonstrating that there is no detectable elongation beyond native termination codons.³¹⁹⁻³²² This has been bolstered by a good safety profile in both preclinical and clinical studies and has subsequently been adopted in a number of relatively common genetic diseases aside from CF in which premature termination codons are relatively prevalent, including Duchenne muscular dystrophy,³²³⁻³²⁵ Hurler syndrome,^{67,81,82} ceroid lipofuscinosis,³²⁶ nephropathic cystinosis,³²⁷ and expression of mutated p53.³²⁸

Proof of concept experiments with aminoglycosides established that PTCs within CFTR in human subjects can be suppressed, resulting in the synthesis of full-length, functional CFTR protein.^{319-322,329} The approach has also demonstrated success in mouse models of CF.^{330,331} Following two small pilot trials indicating restoration of chloride secretion in CF subjects harboring PTCs,^{320,322} a double-blind, placebo-controlled trial conducted in Israel showed correction of nasal ion transport specifically in subjects with nonsense mutations following topical administration of gentamicin, and as expected, not in CF controls homozygous for F508del.³²¹ A trial examining systemic gentamicin in seven French subjects with Y122X CFTR, a mutation highly susceptible to readthrough, also indicated rescue of CFTR activity in the airway and sweat duct.³¹⁹ Not all aminoglycoside trials in CF have demonstrated success, suggesting low levels of protein correction. Regardless, due to the known toxicity and poor bioavailability of aminoglycosides, more efficacious agents that avoid undesirable properties of aminoglycosides will be needed for the long-term genetic treatment of CF. One promising approach uses medicinal chemistry optimization to identify the antimicrobial, toxic, and readthrough effects of aminoglycoside scaffolds, a strategy demonstrating initial success using in vitro

reporters of efficacy and toxicity,³³² and cell- and animal-based models of CFTR rescue.³³³

Others have attempted to identify novel compounds that address the disadvantages of aminoglycosides. One such molecule is ataluren (formerly PTC124), an investigational agent resulting from high-throughput screening efforts to identify molecules that induce translational readthrough.³³⁴ Ataluren is an orally bioavailable agent^{330,335} that has demonstrated efficacy in vivo in a transgenic mouse model of nonsense-mediated CF.³³⁶ The drug is well tolerated in normal and CF subjects,^{335,337} leading to a series of clinical trials examining ataluren in CF individuals harboring nonsense alleles. Results thus far have been mixed. Two studies, conducted in Israel among adults²⁷⁸ and France/Belgium³²⁹ in pediatric subjects, detected rescue of CFTR activity (as detected by the NPD) in open-label, two-dose crossover Phase II trials in CF subjects possessing at least one premature termination codon. The former study included follow-up testing that examined the effect of ataluren for 3 months in 19 subjects previously studied for 2 weeks; significant and time-dependent improvement in CFTR activity following the treatment period were observed.³³⁸ In contrast, a nearly identical trial conducted in the United States did not demonstrate improvement in CFTR function,³³⁹ raising questions about efficacy. Subsequent Phase III testing conducted over 1 year was negative, although a trend toward improved FEV₁ and exacerbation frequency was observed, which was statistically significant in a subgroup of individuals not exposed to inhaled tobramycin, a concomitant medication later shown to attenuate the beneficial effect of ataluren in vitro.³⁴⁰ Future studies will evaluate the effect of ataluren in CF subjects with nonsense mutations that are not exposed to tobramycin. The effects of ataluren are likely also modulated by genetic founder effects including the degree of *CFTR* mRNA expression at baseline as modulated by nonsense mediated decay.^{278,341} Poor selection and optimization of ataluren efficacy has also been suggested to have affected successful development of this agent, due in part to its stabilization of firefly luciferase,³⁴² which induces a paradoxical and off-target increase in the reporter assay used to select the agent.³⁰⁹ More recent studies have highlighted its relatively poor activity.³⁴³ Given new knowledge regarding the best models to identify and optimize CFTR drug candidates that has emerged since the identification of ataluren, it is possible that identification of new chemicals using alternate readthrough assays might yield more efficacious compounds.

Gene Therapy

Nasal administration of *CFTR* gene transfer agents rescued CFTR-dependent Cl⁻ transport in proof-of-concept trials, but variable efficiency of vectors coupled with heterogeneous transgene expression and adverse effects from inflammation have dampened enthusiasm. With NPD as an outcome, viral vectors have demonstrated transgene delivery using adenovirus^{344,345} and *adeno-associated adenovirus* (AAV),³⁴⁶ but positive results have not been universal.³⁴⁷ Failure of a pulmonary AAV technology diminished enthusiasm in the United States. Improvements in Cl⁻ transport using lipid-based gene transfer vectors were initially limited to small and questionable changes³⁴⁸⁻³⁵⁰ or improvements in specific subgroups.³⁵¹⁻³⁵³ More recent preparations have

demonstrated somewhat improved transfer³⁵⁴⁻³⁵⁶ but have been hampered by concerns regarding safety and consistent expression. Several technologies including compacted DNA nanoparticles^{357,358} or depletion of immunogenic CpG motifs have shown promise toward improving delivery. The latter is the basis of the lead vector employed by the U.K. gene therapy consortium, which is currently being evaluated in a large and long-term clinical trial.³⁵⁸ Newer viral transfer technologies that promise sustained gene expression are also under development.³⁵⁹

Splicing and Other RNA Repair

Splicing mutation represents a relatively common minority of *CFTR* alleles. For example, the 10th most common CF mutation is 3849+10kb C-to-T, which leads to inclusion of an 84-base pair cryptic exon in the mature mRNA.³⁶⁰ This cryptic exon contains an in-frame nonsense codon, which leads to production of truncated nonfunctional proteins. Splicing machinery is heterogeneous both among patients and also among tissues within an individual, resulting in relatively heterogeneous expression of the disease. This forms the basis of examining the potential of a CFTR potentiator in individuals with relatively preserved CFTR expression due to reasonable levels of CFTR expression. The variation in splicing efficiency can also be exploited using antisense oligonucleotides to induce normal splicing by masking mutant splice sites. Although this would require specific antisense oligonucleotides to be developed for each *CFTR* splice mutation, recently use of such technology has shown therapeutic efficacy in Duchenne muscular dystrophy.³⁶¹ Thus, a similar approach in CF has been proposed, which could be combined with other CFTR therapeutics on an individual basis. Full-length RNA transduction has also been suggested for the treatment of genetic diseases and could be exploited in CF.

Insights on Disease Mechanism Revealed by CFTR Modulators

Effective modulation of CFTR function has provided a new opportunity to determine the disease pathogenesis, including heretofore unanticipated effects of CFTR. Although CFTR clearly functions as a chloride transporter on the epithelial surface, there is emerging interest in CFTR-mediated regulation of mucociliary clearance, and whether CFTR has important effects on the physical properties of mucus itself due to its role as a bicarbonate transporter and regulator of airway pH. This is supported by data that ivacaftor improves airway obstruction due to resolution of mucus plugging in susceptible airways as observed by He³ magnetic resonance imaging before and after ivacaftor administration in G551D CF subjects^{362,363} and also augments mucociliary clearance as observed by clearance of inhaled Tc99 radiolabeled particles. Colonization of *P. aeruginosa* also improves within 6 months, suggesting the possibility that innate defense is augmented simply by enhancement of CFTR function, before any improvement of structural lung disease. The relatively large magnitude of weight gain observed with ivacaftor in CF patients with G551D-*CFTR* has recently been attributed to its beneficial effect on intestinal pH via bicarbonate secretion, raising the possibility that mucosal integrity might also be improved throughout the gut. Other potential avenues for exploration include the

effect of CFTR modulation on other manifestations of CF, such as glucose metabolism, innate immunity and leukocyte function, osteopenia, pancreatic insufficiency, and gastrointestinal absorption, some of which may be directly tied to CFTR activity.

RESPIRATORY THERAPIES

Physical Airway Clearance

The combination of cough augmented with chest vibration or percussion to loosen mucus represents a cornerstone of the daily care of CF to reduce airway obstruction and prevent CF exacerbations.³⁶⁴ Daily clearance maneuvers including chest physiotherapy by vibropercussion, hand-administered therapy, or the chest physiotherapy vest clearance system, are considered standard of care, although the long-term benefit has not been systematically examined in randomized controlled trials.^{365,366} Rather, the benefits were established in a small trial of older children demonstrating improvements in FEV₁ and sputum production, which has been further supported by a series of nonrandomized trials.^{367,368} Alternative airway clearance techniques include *positive expiratory pressure* (PEP), “huff coughing,” and the use of vibratory flutter valves.³⁶⁸

Exercise therapy may have additive benefit to the physical maneuvers described earlier. Standardized, aerobic exercise programs targeting 70% to 85% of maximal heart rate have demonstrated benefits on exercise tolerance but do not improve lung function. Similar results are observed in isometric exercise programs.³⁶⁹ The role of supervised pulmonary rehabilitation programs in severe CF lung disease is currently being explored.³⁷⁰

Airway Rehydration Therapy

Efforts to rehydrate the ASL to augment mucociliary clearance have led to studies examining nebulized *hypertonic saline* (HTS). HTS improves airway hydration in CF models and causes a durable increase in mucociliary clearance in CF subjects.²⁴¹ A multicenter, randomized, placebo-controlled trial showed a modest improvement in pulmonary function and a 56% reduction in frequency of CF pulmonary exacerbation despite relatively poor compliance ($\approx 63\%$ at the end of the trial).²⁴⁰ Evidence suggests that the effects of HTS are additive to rhDNase.^{240,371,372}

The ISIS (*Infant Study of Inhaled Saline* in CF) trial examined the effect of HTS administration to young children with CF (ages 4 months to 5 years, before spirometry can be reliably conducted). Although this study did not demonstrate a benefit on the primary end point of rate of pulmonary exacerbations, the rate of these events was extremely low, limiting sensitivity.³⁷³ Nevertheless, a substudy of patients who underwent infant PFTs demonstrated significant improvements in FEV_{0.5}, a finding that will be tested using the Lung Clearance Index, an effort-independent measure of pulmonary obstruction. Until results are confirmed, HTS therapy is not recommended in this age group.¹⁵¹

Because a minority of subjects develops bronchospasm on administration of HTS, inhaled β_2 -agonist is generally recommended before HTS dosing; moreover, HTS should be used cautiously in those with severe pulmonary

obstruction. Many will exhibit excessive cough, limiting use, although this will often decrease with repeated administration.²⁴⁰

The use of nonabsorbable sugars, such as mannitol, to hydrate the airways by generating an osmotic gradient of fluid to the airway surface is an alternative to HTS. After success in early-phase trials,³⁷⁴ two large-scale clinical trials were recently conducted. Although the North American trial demonstrated a trend toward improved FEV₁ at 26 weeks of therapy, a parallel trial in Europe and Oceania demonstrated reduced exacerbations in the treatment arm.^{375,376} On the basis of this success, inhaled mannitol therapy is approved for CF patients older than 18 in Europe, Australia, and New Zealand, although intermediate results combined with a potential risk of hemoptysis have been a barrier to approval in the United States.

Dornase Alfa

Use of inhaled recombinant human DNase (dornase alfa), a pharmacologic treatment to improve the physical properties of mucus, has been shown to be beneficial in randomized, placebo-controlled trials in CF subjects and was among the first CF-specific medicines to be approved for respiratory disease. Dornase alfa causes dissolution of excess DNA debris that accumulates due to bacterial infection, mucus stasis, and the large influx of neutrophils into the airway lumen. Dornase alfa has improved pulmonary function, frequency of pulmonary exacerbation, and QOL.²³⁹ Trials examining dornase alfa therapy in individuals with severe pulmonary disease (FVC < 40% predicted) also show continued benefit.³⁷⁷ It also appears beneficial in mild disease; dornase alfa stabilized an increase in inflammatory markers in bronchoalveolar lavage fluid of young children³⁷⁸ and improved radiographic measures of gas trapping.³⁷⁹ Dornase alfa also improved ventilation inhomogeneity as determined by lung clearance index in pediatric patients with minimal decrement in spirometry.³⁸⁰ Thus, dornase alfa therapy is recommended for CF patients in all ranges of disease severity.³⁸¹

Inhaled Antibiotics

Chronic infection is a sine qua non of bronchiectasis, and aggressive antimicrobial therapy to curb or control chronic infection is a mainstay of chronic CF care. Because the inhaled route provides higher doses of antibiotics to the mucopurulent-filled airways, several antimicrobials are frequently used in chronic CF care and have been shown to improve lung function and reduce pulmonary exacerbations. Alternating use of chronic inhalational antibiotics is intended to target the airways while avoiding systemic toxicities and limiting emergence of bacterial resistance through continuous selection pressure. The first agent to be approved for this purpose was inhaled tobramycin, which has been shown to be associated with improved pulmonary function, reduced exacerbation rate, and increased weight compared with placebo when administered twice daily on alternate 4-week periods.^{151,382} Concerns about daily burden of therapy leading to patient nonadherence have led to the development of a dry powder formulation, which was shown to be noninferior to conventional nebulized tobramycin²⁴² and improved patient satisfaction when tolerated.

More recently, the inhaled monobactam aztreonam has been developed for chronic use in CF. Initial studies demonstrated improved QOL and prolonged gap between exacerbations.^{383,384} A large 6-month trial involving CF patients older than 6 who previously used inhaled tobramycin demonstrated improved FEV₁ and reduced exacerbations with aztreonam every other month³⁸⁵ compared with those assigned to continue every-other-month inhaled tobramycin. A similar study in subjects with milder lung function abnormalities demonstrated more modest improvements in FEV₁ and QOL.³⁸⁶ Thus, inhaled aztreonam is currently recommended for CF patients older than 6 with chronic *Pseudomonas* infection of all lung function ranges.³⁸⁷ Inhaled colistin is often used as an alternative antipseudomonal agent in subjects with resistant strains, although it is not FDA approved for this purpose and is associated with side effects such as bronchospasm.^{151,388,389}

It is not yet clear which antimicrobial is best for individual patients, but the choice of agent is generally driven by the dominant pathogen, antimicrobial resistance patterns, and patient preference because antimicrobial resistance does not always predict clinical response. Some clinicians, particularly in Europe, currently endorse a continuous alternating therapy approach using two or more inhalational antibiotics on the basis of the empiric finding that certain patients frequently exhibit exacerbations when off antibiotics. Formal investigation of this approach using continuous alternating 28-day cycles of inhaled tobramycin and aztreonam is presently under way. A number of other antibiotic regimens, generally derived from effective systemic antibiotics, are also under investigation and could provide additional options for long-term control of chronic respiratory infections. These include inhaled fluoroquinolones³⁹⁰ and vancomycin.³⁹¹ Whether suppression or eradication of *Staphylococcus* species, including MRSA, offer benefit is an open question. Of note, oral prophylaxis for *S. aureus* led to increased *Pseudomonas* infection in treated patients, warranting caution.³⁹²

Bacterial Eradication

The primary morbidity and mortality in CF is attributable to obstructive respiratory disease produced by chronic endobronchial infection with opportunistic bacteria. *P. aeruginosa* infection is clearly associated with decline in respiratory function, and early acquisition of *Pseudomonas* is associated with increased morbidity and mortality.^{105,393-398} Consequently, identification of infection and eradication via treatment with anti-pseudomonal antibiotics is believed to result in sustained lung function and delayed mortality.^{115,399} Furthermore, early isolates are present at lower density, are generally nonmucoid, and display favorable microbial resistance profiles, reflecting a “window of opportunity” for treatment and eradication.^{400,401} *Pseudomonas* infection becomes more prevalent with increasing age, with positive respiratory tract cultures reported in up to 30% of infants, 30% to 40% of children (2 to 10 years), and 60% to 80% of adolescents and adults.⁴⁰² Newborn screening for CF may allow earlier identification of *P. aeruginosa* infection in children before the onset of significant lung disease and the development of antimicrobial resistance that may limit the efficacy of therapy. Following detection of *P. aeruginosa* in asymp-

tomatic children, current opinion supports clinical intervention to eradicate the organism. Antimicrobial regimens differ from minimally invasive inhaled antibiotics to aggressive intravenous dosing.¹¹⁰ Although several studies have validated the efficacy of various treatment regimens, no treatment regimen has demonstrated clear superiority. Obstructive lung disease may limit efficacy of inhaled antibiotics. Successful eradication of other CF pathogens such as *B. cepacia* and MRSA has also been reported, but no conclusive standard eradication practice exists.

Macrolide Therapy

Although macrolide antibiotics do not exhibit significant antipseudomonal properties, the utility of these agents in diffuse panbronchiolitis, a rare disease that resembles CF (including chronic infection with *P. aeruginosa*), led to therapeutic trials in CF patients.⁴⁰³⁻⁴⁰⁶ In a multicenter, randomized, placebo-controlled trial, alternating-day oral azithromycin demonstrated improved pulmonary function that was accompanied by a large reduction in pulmonary exacerbations.⁴⁰⁷ Similar results were seen in a Canadian study using clarithromycin.⁴⁰⁸ Beneficial effects of azithromycin can also be observed in CF patients who are not chronically infected with *Pseudomonas* (through less well-described anti-inflammatory effects), further suggesting that the mechanism is independent of antimicrobial properties; a large clinical trial demonstrated improved rates of exacerbation,⁴⁰⁹ although improved FEV₁ was not observed. On the basis of current evidence, the present guidelines assign a lower priority for chronic azithromycin in noninfected patients.²⁴⁵ The rising incidence of nontuberculous mycobacterial infections raises concern about the long-term use of azithromycin due to the potential for inducible macrolide resistance. Some in vitro data suggest increased risk of inducing atypical mycobacteria,¹⁵¹ although this has not been observed in epidemiologic studies.⁴¹⁰ Nevertheless, annual screening for atypical mycobacteria is recommended and is particularly important in azithromycin-treated patients. Safety and efficacy of azithromycin in young infants with CF at high risk for bronchiectasis as detected by elevated neutrophil elastase is currently under way.

Anti-inflammatory Therapy

Intense neutrophilic inflammation is characteristic of CF and remains a therapeutic target that has not been fully realized.^{140,411-413} Early trials utilizing chronic, alternate-day systemic corticosteroids showed a beneficial effect of prednisone (1 mg/kg) on lung function, but its use remains limited by steroid toxicities and is not recommended for routine use.⁴¹⁴⁻⁴¹⁶ Inhaled steroids have frequently been studied in small trials. In some studies, improved airway reactivity has been observed, but they have not demonstrated sustained effects on lung function and withdrawal can be tolerated without clinical deterioration.^{417,418} Use is generally limited to individuals with an asthmatic phenotype given the potential concern for bone demineralization, adrenal suppression, and growth retardation in pediatric patients.

A number of other anti-inflammatory molecules have been studied in CF, although the appropriate window where blockade of inflammation, which has both destructive and

beneficial anti-infective effects, is not yet clear. High-dose ibuprofen, a *nonsteroidal anti-inflammatory drug* (NSAID), has been shown to improve the rate of pulmonary function decline, but its beneficial effects were greatest in young children.⁴¹⁹ Confirmatory studies also demonstrated beneficial effects.^{247,420} Despite this evidence, NSAID therapy is not widely utilized in the United States due to concerns of chronic toxicities, particularly in older individuals, and the need for pharmacokinetic monitoring to achieve adequate serum levels.⁴²¹ For example, inadequate levels are associated with a paradoxical proinflammatory effect producing increased neutrophil migration.^{247,422}

Attempts to extend the observed benefits of anti-inflammatory therapy to other eicosanoid-active agents (e.g., leukotriene inhibitors) have been variable and include an increase in pulmonary complications with a nonselective LTB₄ antagonist.^{69,423} Along similar lines, aerosolized administration of interferon gamma-1 β was not effective in a randomized, placebo-controlled trial,⁴²⁴ nor were initial attempts to block proteases with inhaled antitrypsin.⁴²⁵ Other agents such as HMG Co-A reductase inhibitors, hydroxychloroquine, and methotrexate have not demonstrated convincing benefit, illustrating the challenge of successfully targeting this mechanism. Nevertheless, more therapies are under development and could circumvent problems if appropriate patient selection is considered.

OTHER SUPPORTIVE CARE

Pulmonary Exacerbations

Exacerbations of CF pulmonary disease are characterized by increased cough and sputum production, respiratory distress, diminished physiologic tolerance, weight loss, decreased spirometry, increased hypoxemia, or development of a major pulmonary complication such as hemoptysis.⁴²⁶⁻⁴²⁹ Treatment includes intensifying airway clearance and systemic antimicrobial therapy generally directed against the most recent pathogens. Both inpatient and outpatient treatment are used; factors important in this distinction include severity of disease, baseline lung function, microbial organisms and resistance pattern, the presence of additional complications, and the ability to adhere to an outpatient regimen. Acute pulmonary exacerbation is the most common indication for hospitalization in CF and is indicated when episodes are severe, refractory to outpatient management, or not suited to home therapy for psychosocial reasons. Hospitalization facilitates controlled administration of intravenous antibiotics to treat exacerbating infections and provides a setting conducive to sustained intensification of chest physiotherapy. Although the historical standard for pulmonary exacerbations is hospital-based therapy, with adequate resources and adherence, home therapy that includes the use of parenteral antimicrobials and mucus clearance procedures may achieve equivalent outcomes in appropriately selected patients.^{430,431}

In general, the primary goal of therapy is to improve clinical symptoms and return pulmonary function to baseline. However, in some patients, lung function does not return to previous levels despite clinical improvement and can decline further days to weeks following treatment.⁴³³⁻⁴³⁵ A severe decrement in spirometry from baseline is a major risk factor

for sustained loss of lung function, suggesting the need for early and aggressive treatment at the onset of exacerbation.⁴³⁴⁻⁴³⁶

Antibiotic therapy should be broad based due to the polymicrobial nature of CF lung disease and is primarily selected on the basis of respiratory tract culture and susceptibility results. Of note, despite this recommendation, in vitro sensitivities do not predict clinical response, suggesting significant limitations to this general strategy.⁴³⁶ Treatment of *Pseudomonas* is the first consideration, and two mechanistically distinct antibiotics should be used to maximize efficacy, unless oral therapy is used, in which fluoroquinolones are the mainstay, but could potentially lead to increased acquisition of bacterial resistance.⁴³⁷ Aminoglycosides continue to have optimal antimicrobial activity for anti-*Pseudomonas* therapy requiring intravenous antibiotics and have been the mainstay for many years but require monitoring to optimize therapy. Traditional dosing of aminoglycosides two to three times a day has shifted in favor of once-daily dosing.^{438,439} Once-daily dosing, in the range of 8 to 12 mg/kg/day, achieves higher peak concentrations (20 to 30 μ g/mL) that potentiate bactericidal effect and limits toxicity by extending troughs, which are typically undetectable in the setting of normal renal function.^{168,440} Patients should be monitored carefully during aminoglycoside therapy for emergence of nephrotoxicity and ototoxicity. Aminoglycosides are usually paired with a β -lactam to maximize efficacy. A third antibiotic may also be useful to control MRSA or other atypical organism. Although there is no consensus on duration of therapy, a clinical response with respect to symptoms or pulmonary function is usually apparent 4 to 7 days after initiation of therapy. A duration of 10 to 14 days appears to be adequate to achieve maximal improvement in lung function and sustained health in most cases.^{441,442} With refractory infection, treatment for 3 weeks or more is not unusual but may not be successful. Recent studies have demonstrated that FEV₁ plateaus following 10 days of inpatient treatment, raising a question of the benefit and risk of longer hospital and parenteral antibiotic courses.^{431,443} Because there is no clear guideline for duration of therapy, each treatment course requires careful assessment by the clinician. Shorter treatments may improve QOL and compliance, limit drug-associated morbidities, and be less costly. However, this may not be sufficient to clear a chest infection and may result in less sustained benefit and an early recurrence of exacerbation. Prolonged courses of antibiotic therapy should include respiratory tract cultures for bacterial and fungal organisms because antibiotic sensitivities can shift.⁴⁴⁴ For patients requiring frequent courses or long-term home antibiotic therapy, subcutaneous central intravenous catheters can provide stable intravenous access to facilitate treatment. This carries a risk of catheter-associated infections and thrombosis.⁴⁴⁵ For this reason, exogenous estrogen should be avoided in female patients with central venous catheters if possible.

TREATMENT OF LUNG COMPLICATIONS

Treatments directed to control airway infection, limit inflammation, and optimize airway clearance are the cornerstone of therapy in both early and advanced CF lung

disease. Hypoxemic respiratory insufficiency should be recognized and treated with supplemental oxygen. Low-flow oxygen is effective at relieving nocturnal, exertional, and resting hypoxemia and does not usually cause significant hypercapnia.⁴⁴⁶ The development of nocturnal or resting hypoxemia is strongly associated with the onset of pulmonary hypertension and is associated with increased mortality.⁴⁴⁷ Diuretics, inotropic agents, and theophylline provide little to no benefit in CF and are rarely used. Cor pulmonale is an end-stage finding in advanced disease with few viable treatment options beyond those to stabilize lung disease and symptomatically treat pulmonary hypertension.⁴⁴⁸

Acute respiratory failure due to reversible insults can be stabilized by either non invasive or invasive ventilatory support.^{211,449,450} Although the associated mortality with mechanical ventilation is high, it is not absolute. It has been reported that one third of CF patients with advanced lung disease survive events requiring mechanical ventilation.²¹² Mechanical ventilation can also be used as a bridge to lung transplant at appropriate centers.^{212,450,451} Extracorporeal membrane oxygenation has also been used for this purpose.⁴⁵²

Atelectasis is managed by escalating the intensity and frequency of airway clearance and usual therapy directed at pulmonary exacerbations. Systemic or inhaled corticosteroids may be helpful in the presence of asthma, ABPA, or significant airway inflammation refractory to antimicrobial therapy. There is little evidence that bronchoscopy and lavage are effective in treating atelectasis. However, bronchoscopic evaluation of atelectasis and treatment of mucoid impaction in association with endobronchial aspergillosis and ABPA have been described.^{453,454} ABPA typically responds to standard doses of systemic corticosteroids.¹⁹⁰ Inhaled corticosteroids,⁴⁵⁵ suppressive oral antifungal therapy,⁴⁵⁶ and omalizumab⁴⁵⁷ may be useful in limiting the systemic steroid burden.

When small and minimally symptomatic, a pneumothorax can be observed with expectation of spontaneous resolution. Pneumothoraces of greater volume (e.g. >20%) or that compromise ventilation or physiologic stability require chest tube decompression.⁴⁵⁸ Recurrent pneumothoraces are common in advanced lung disease and are associated with higher mortality. Patients with chronic pneumothorax who are clinically unstable or experience significant morbidity may benefit from chemical and/or mechanical pleurodesis.⁴⁵⁹ Prior pleurodesis is not considered a contraindication to lung transplantation.⁴⁵⁹

Major *hemoptysis* is treated with antibiotics and chest rest, although reinstitution of therapy has become more aggressive over time. Supplemental vitamin K should be given if the prothrombin time is prolonged due to malabsorption. Clot stabilization with tranexamic acid and systemic blood pressure reduction with beta-blockade may have some clinical utility.^{195,460} Massive hemoptysis may resolve with conservative therapy, but bronchial artery embolization provides more definitive clinical control and can also be considered in recurrent cases of submassive bleeding.¹⁹⁶

Treatment of Gastrointestinal Complications

Meconium ileus can often be relieved with enemas refluxing water-soluble radiographic contrast into the terminal

ileum under fluoroscopy.¹⁹⁷ If this is not successful, or there is concern for intestinal perforation due to severity of involvement, surgical consultation should be sought. DIOS is typically treated with large volume-balanced electrolyte solutions containing osmotic laxatives (polyethylene glycol) and mucolytics (N-acetylcysteine).⁴⁶¹ Contrast enemas that reach the terminal ileum can complement therapy. In the setting of significant abdominal distension or intractable emesis, concern of bowel obstruction or bilious/fecal emesis necessitates surgical consultation.⁴⁶² *Rectal prolapse* can be voluntarily reduced in patients experienced with techniques involving the abdominal, perineal, and gluteal muscles. Young children often require manual reduction by gentle pressure in the knee-chest position.⁴⁶² Appropriate pancreatic enzyme replacement therapy, improved nutritional status, and control of lung disease usually prevent recurrence. Surgical stabilization of the rectum is required if prolapse is chronic and refractory to medical intervention.

CFTR dysfunction resulting in abnormal bile secretion is believed to be the cause of CF liver disease. *Ursodeoxycholic acid* (URSO) is used to treat primary biliary cirrhosis.²²⁰ Although its impact on the liver disease is unclear, several studies have demonstrated that URSO improves liver function tests; however, the long-term effect on liver function is unknown.⁴⁶³ The thresholds for initiating therapy and clinical outcomes are under investigation; in the absence of empirical data, guidelines presently recommend consideration of URSO treatment.⁴⁶⁴ Aggressive nutritional support should be instituted in the absence of specific therapy. Bleeding esophageal varices that complicate cirrhosis often can be managed with banding or sclerotherapy. Portal hypertension and severe, refractory variceal bleeding have been treated successfully with portosystemic shunting.⁴⁶⁵ Hepatic failure and ascites are treated in standard fashion. Liver transplantation is successful in CF with survival rates at 1 and 5 years reported at greater than 80%.⁴⁶⁶ Pancreatitis is treated with standard measures such as bowel rest and supportive medical care.

Hyperglycemia can complicate CF at any age, but it is generally first encountered in the second and third decades of life.^{467,468} Ketoacidosis is not typically a feature of CF-related diabetes mellitus. Treatment of elevated blood glucose in CF has become more aggressive because advancing survival has provided evidence of the complications of diabetes and increased recognition of its impact on pulmonary disease progression.⁴⁶⁹ Vascular disease affecting the retina and kidneys has been documented in CF patients who have had prolonged hyperglycemia.^{469,470} Thus, long-term control of blood sugar levels is indicated. Intensive screening and management regimens have been recommended.^{468,471-473} Insulin therapy is the mainstay of treatment as its anabolic effects may also be beneficial^{468,472-474}; dietary management is also important.

Surgical Therapy

Endoscopic sinus surgery and nasal polypectomy to relieve obstruction are the most common surgical procedures in CF.⁴⁷⁴⁻⁴⁷⁶ Although most patients experience improvement postoperatively, recurrence is common and often requires repetitive procedures.⁴⁷⁷ The incidence of polyposis tends to wane in adulthood.⁴⁷⁵ More aggressive sinus surgery to

marsupialize the sinus cavity may also be beneficial.⁴⁷⁸ Symptomatic gallstones may require elective cholecystectomy.⁴⁷⁷ Pulmonary resection has historically been considered when severe focal lung disease is thought to lead to clinical instability and accelerated decline in lung function. Although surgical therapy has been reported to stabilize the clinical course and reduce exacerbation frequency, surgical treatment is rare at present likely due to improved treatment strategies and overall health of individuals with CF.^{229,479-482} Patients must be carefully selected because short-term loss of lung function postoperatively is expected.⁴⁸³ Massive hemoptysis refractory to standard therapy may require lobectomy.

Nutrition

Improved nutritional status in patients with CF is associated with better long-term clinical outcomes.⁴⁸¹ Patients with CF have increased caloric requirements that have been attributed to residual malabsorption, increased work of breathing, and factors related to infection and inflammation. Dietary recommendations include a high calorie (20% to 50% greater than standard recommended intake), high-protein diet including a moderate amount of dietary fat (35% to 45% of caloric intake), and limited processed carbohydrates.⁴⁸⁴ Patients with a body mass index below the 25th percentile are typically considered to be in nutritional failure and warrant aggressive nutritional counseling and dietary supplementation. If nutritional counseling is unsuccessful, consideration of appetite stimulants, or alternatively gastrostomy tube feedings, is warranted because supplementation with elemental dietary preparations by mouth is unlikely to be sustained over an extended period of time.

Due to pancreatic insufficiency, 90% of patients with CF require pancreatic enzyme replacement therapy. The enzymes are supplied as capsules containing acid-resistant enteric coated granules, containing doses of lipase from 3,000 to 40,000 units. Dosing is typically based on weight and is adjusted on the basis of the presence of symptoms of malabsorption such as abdominal cramping, excessive flatulence, and fatty stools. Dosage ranges should be limited to current guidelines (2500 lipase units/kg/meal; 10,000 lipase units/kg/day). Dosages exceeding these limitations have been associated with fibrosing colonopathy.⁴⁸⁵⁻⁴⁸⁸

A daily multivitamin is standard to CF care with additional supplementation depending on serum levels or clinical factors. Vitamins A and E are often adequately supplied by a standard daily multiple-vitamin preparation. Vitamin A deficiency is easily corrected by dietary supplementation. Symptomatic deficiency is rare and typically is found in patients who do not take supplementary vitamins or pancreatic enzymes but may result in increased intracranial pressure, xerophthalmia, and night blindness. Vitamin D deficiency presenting as rickets is rarely seen. Patients with CF often have inadequate levels (<30 to 60 ng/mL) that can be refractory to high-dose supplementation. Bone demineralization is common, and the considerable interest regarding the association of inadequate vitamin D levels with poor health-related outcomes has led to recommendations of aggressive supplementation. Vitamin E is deficient only in unsupplemented patients and rarely causes increased red

blood cell destruction and neuroaxonal dystrophy.⁴⁸⁹ Vitamin K deficiency may result in bleeding diathesis. Although clinically significant hemorrhagic problems manifest mostly in children, vitamin K deficiency in the setting of hemoptysis may present significant complications in older patients. Other vitamins and trace minerals, specifically zinc, may be deficient and require supplementation on a selective basis.⁴⁹⁰

Psychosocial Factors

Outcomes are improving and new therapies hold even greater promise, but CF remains a fatal chronic disease. With the advent of newborn screening and patients surviving into adulthood, the psychosocial aspects of CF have broadened and continue to affect the patient, family, and community. Medical therapies continue to offer significant benefit but can be limited by the patient's psychosocial well-being, attitude, and ultimately adherence to therapy. Approaches to delivery of clinical care that promote a positive self-concept and support the patient and/or family to manage their medical therapy and maximize health-related QOL are likely to have a positive impact on outcomes and ultimately on longevity. Providers with expertise in psychosocial support are invaluable to the CF care team.⁴⁸⁵ Major depression is a common comorbidity as patients grow older and can be a negative influence on clinical outcome; aggressive monitoring and treatment are warranted.⁴⁹¹

Lung Transplantation

Sequential double-lung transplantation is an accepted therapy for respiratory failure secondary to CF.⁴⁹² Living lobar transplantation is an effective alternative to conventional cadaveric lung transplants but is only performed in selected centers.⁴⁹³ More than 2300 lung transplants have been performed for CF around the world, and the rate is increasing. The 5-year survival is just above 50%, which compares favorably to the survival of lung transplant performed in other lung diseases.⁴⁹⁴ Given the limited survival and complex treatment required, consideration of lung transplantation requires a careful psychological and social evaluation. Should lung transplantation be chosen, patients should be thoroughly evaluated and referred when they have a survival benefit or predicted mortality in the range of 2 to 3 years; prediction formulas can assist with this process.¹⁷⁴ Following successful transplantation, the patient can experience a dramatically improved respiratory status and QOL, but significant medical treatment burden can remain.

Key Points

- Cystic fibrosis (CF) is the most common monogenetic disease in Caucasians and results from mutations in the *CF transmembrane conductance regulator* (CFTR) gene.
- Absent CFTR causes delayed mucociliary clearance, abnormalities in mucus, and a host defense defect, initiating chronic, progressive sinopulmonary infections and a cycle of lung destruction, leading to bronchiectasis and end-organ failure.

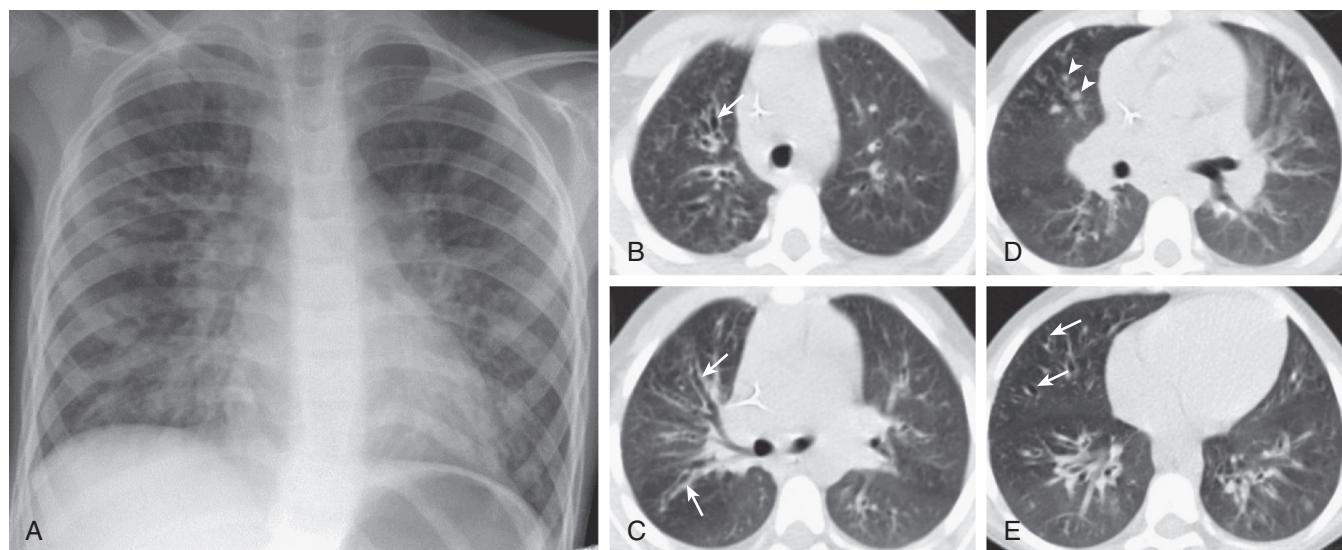
- Extrapulmonary manifestations are observed where CFTR is highly expressed normally, such as in the endocrine and exocrine pancreas, gastrointestinal tract, skin, bone, and male reproductive tract.
- The diagnostic paradigms emphasize early detection by newborn screening and a high index of suspicion to recognize atypical cases later in life, which are generally caused by *CFTR* alleles that code for partially functional CFTR.
- Effective treatment and monitoring through a network of specialized CF care and research centers have improved morbidity and mortality.
- Aggressive treatment of CF pulmonary exacerbations is required to delay progression and reduce complications of end-stage lung disease.
- Treatment strategies for chronic lung disease generally address downstream manifestations of CF pathophysiology; such treatments include rehydrators of diminished airway surface liquid, mucolytics to enhance mucus clearance, antimicrobial therapies, and chronic anti-inflammatory agents.
- Recently, the successful development and approval of ivacaftor for CF patients with the G551D *CFTR* mutation has provided a roadmap that has invigorated investigators working to develop novel modulators of CFTR function to correct the underlying defect caused by the most common *CFTR* alleles.

Complete reference list available at *ExpertConsult*.

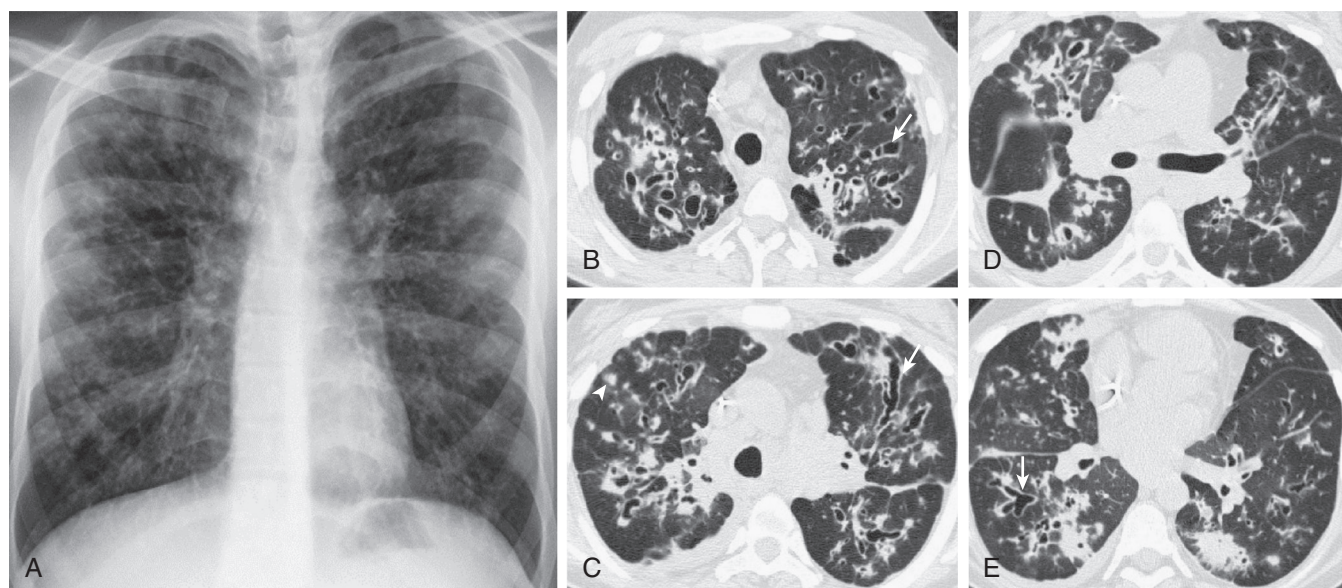
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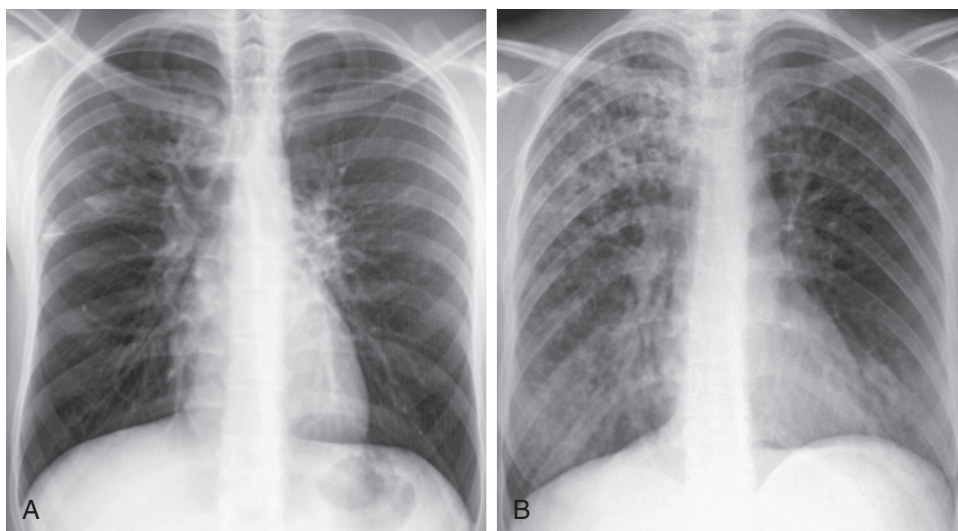
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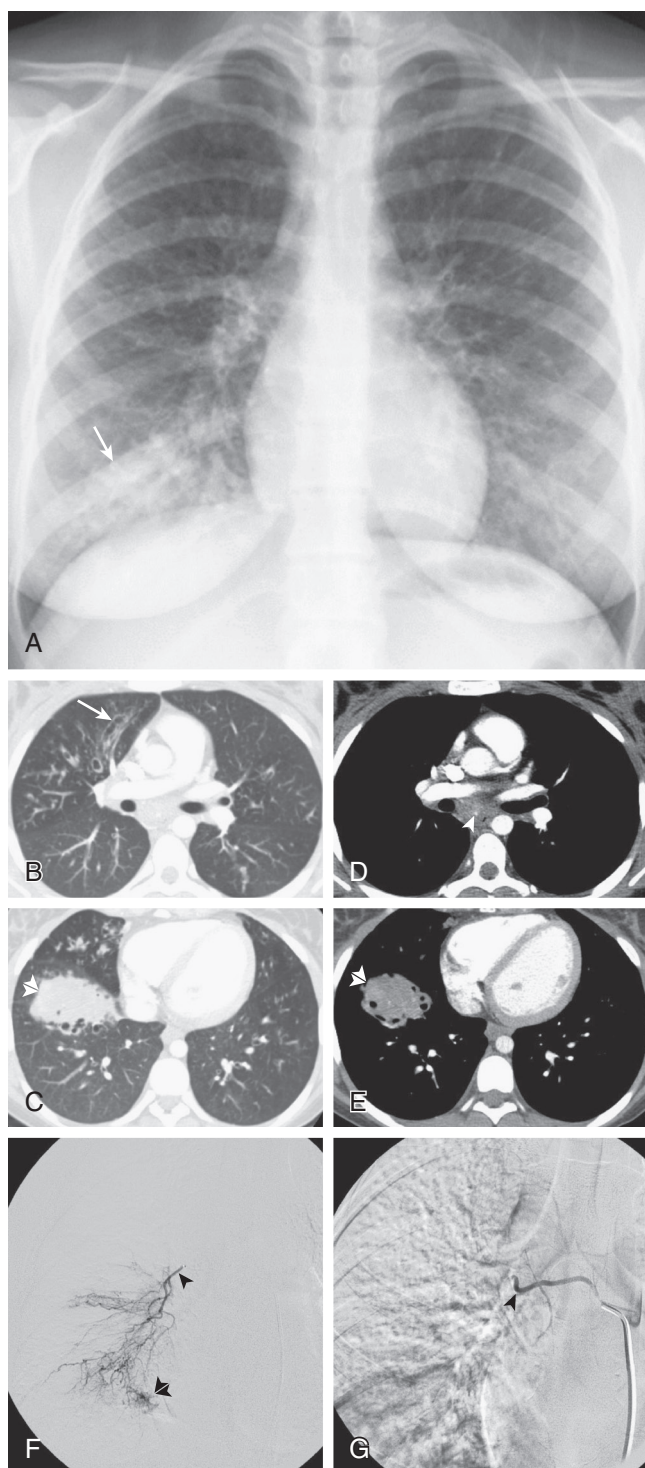
eFigure 47-1 Cystic fibrosis (CF): chest radiographic and chest CT findings. **A**, Frontal chest radiograph in a 4-year-old patient with CF shows mildly increased lung volumes associated with central airway thickening and extensive linear opacity representing bronchiectasis and bronchial wall thickening. **B–E**, Axial chest CT displayed in lung windows shows extensive cylindrical bronchiectasis (*arrows*), as well as extensive bronchial wall thickening and small nodules (*arrowheads*), the latter reflecting distal bronchial and small airway impaction. (Courtesy Michael Gotway, MD.)



eFigure 47-2 CF: chest radiographic and chest CT findings. **A**, Frontal chest radiography in a young adult with CF shows large lung volumes associated with central airway thickening and extensive linear opacity representing bronchiectasis and bronchial wall thickening. **B–E**, Axial chest CT displayed in lung windows shows extensive cylindrical bronchiectasis (*arrows*), as well as extensive bronchial wall thickening and small nodules (*arrowhead*), the latter reflecting distal bronchial and small airway impaction. (Courtesy Michael Gotway, MD.)



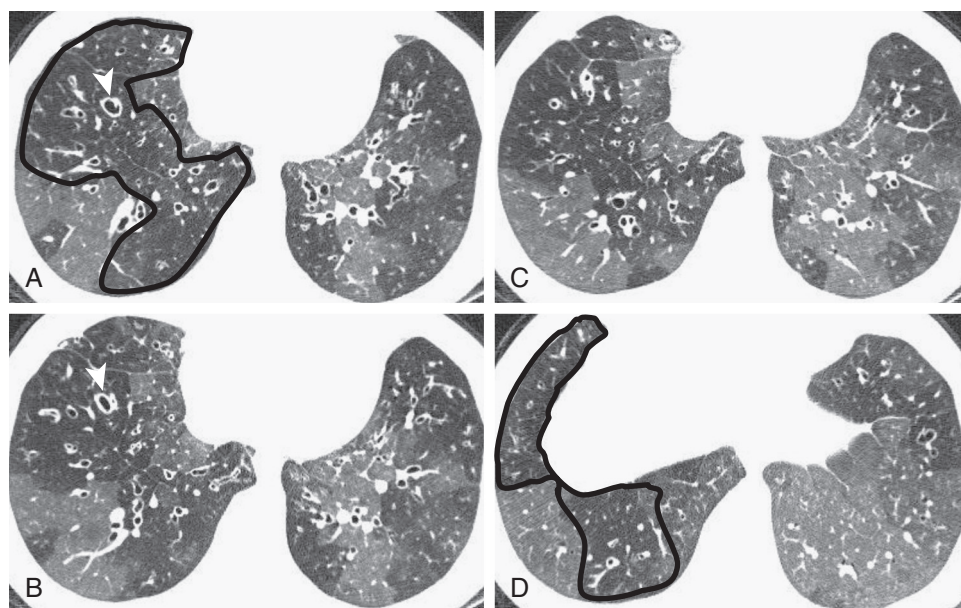
eFigure 47-3 CF: predominant right upper lobe involvement. A and B, Frontal chest radiograph in two separate patients with CF shows multifocal bronchial wall thickening and dilation, most pronounced in the right upper lobe. (Courtesy Michael Gotway, MD.)



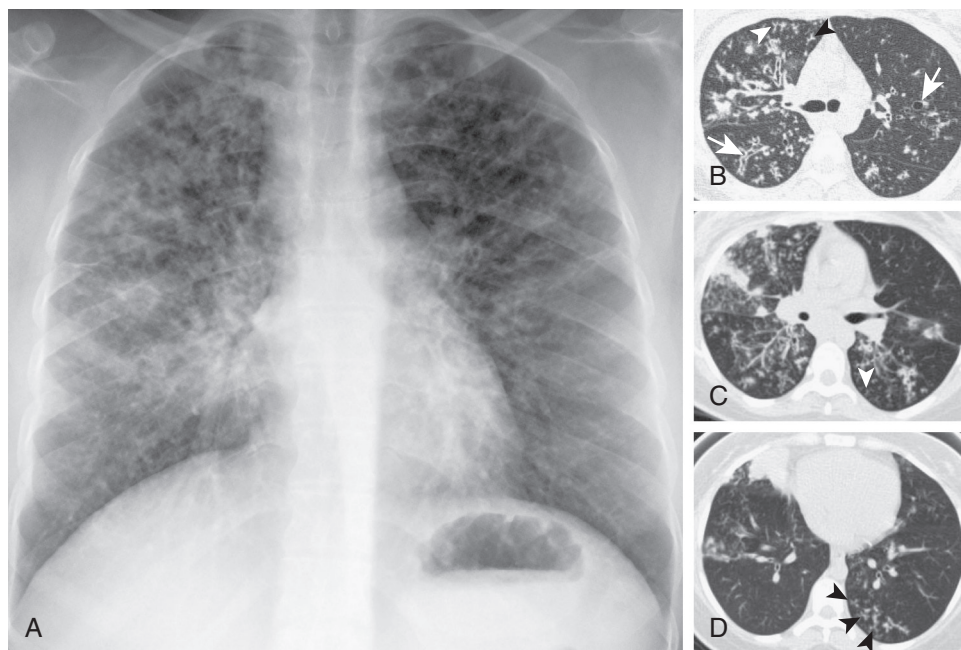
eFigure 47-4 CF with hemoptysis treated with bronchial arterial embolization. **A**, Frontal chest radiograph shows central perihilar predominant bronchial wall thickening and bronchiectasis. Focal consolidation (arrow) in the right lower lobe was new compared with prior studies. **B–E**, Axial enhanced chest CT displayed in lung (**B** and **C**) and soft tissue (**D** and **E**) windows shows multifocal bronchiectasis (arrow), typical of CF. Bronchial artery hypertrophy (arrowhead, **D**) is present, commonly observed in patients with chronic inflammatory airway diseases. **E**, A mildly hyperattenuating mass (double arrowheads) is present in the anterior right lower lobe, correlating with the new finding at chest radiography and presumed to reflect hematoma in the setting of a patient with CF and new hemoptysis. **F** and **G**, Pre (**F**) and post (**G**) catheter bronchial artery embolization images show an enlarged bronchial artery (arrowhead) associated with a prominent “vascular blush” (double arrowhead) in the region of the anterior right lower lobe mass at chest CT. The postembolization image (**G**) shows lack of opacification of the region of the vascular blush, and essentially no flow is now seen in the hypertrophied bronchial artery (arrowhead). (Courtesy Michael Gotway, MD.)



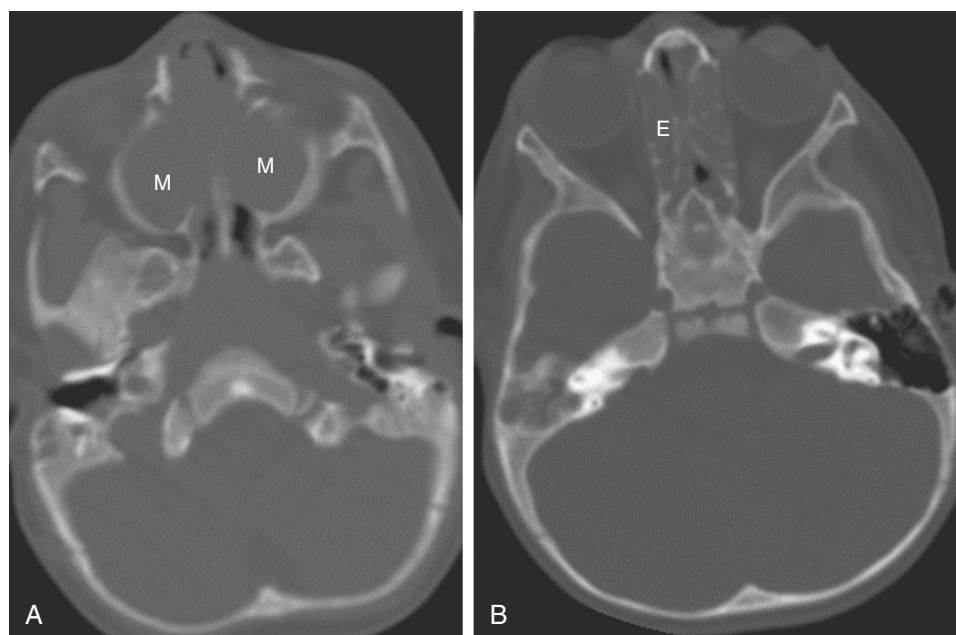
eFigure 47-5 CF with spontaneous pneumothorax. Frontal chest radiography shows typical changes of CF, included extensive bronchiectasis, and peribronchial consolidation with large lung volumes. A small, spontaneous right apical pneumothorax (arrowheads) is present. (Courtesy Michael Gotway, MD.)



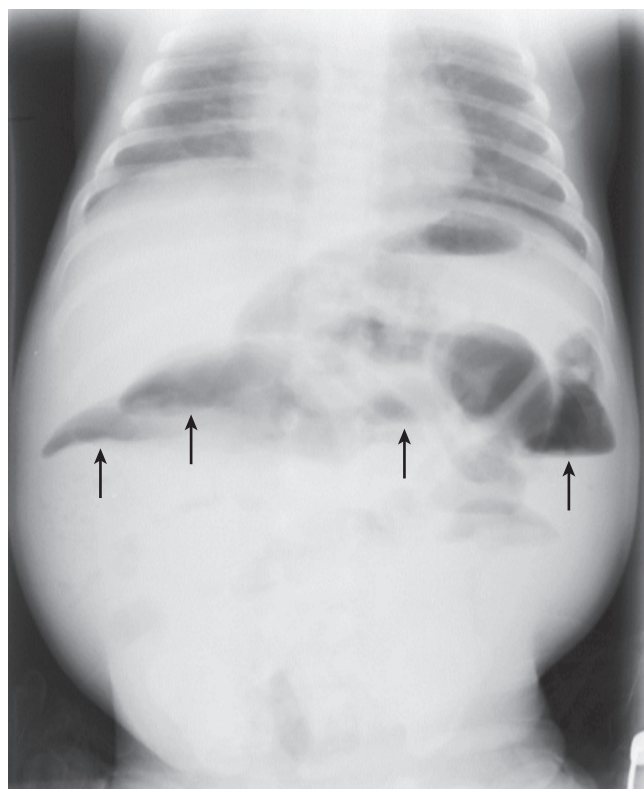
eFigure 47-6 CF: mosaic perfusion. A–D, Axial chest CT through the lung bases displayed in lung windows shows cylindrical bronchiectasis (*arrowheads*) and extensive bronchial wall thickening, typical of CF. Extensive, bilateral inhomogeneous lung opacity is present, manifesting as geographic areas of increased and decreased pulmonary parenchymal attenuation. The areas of decreased attenuation (see *black outlines* in **A** and **D**) show small pulmonary vessels, reflecting vasoconstriction and decreased pulmonary parenchymal perfusion due to air trapping, and are referred to as “mosaic perfusion.” Although the areas of increased attenuation resemble ground-glass opacity, they actually represent relatively normal but hyperperfused pulmonary parenchyma. Such findings may happen with large or small airway obstructive disorders. (Courtesy Michael Gotway, MD.)



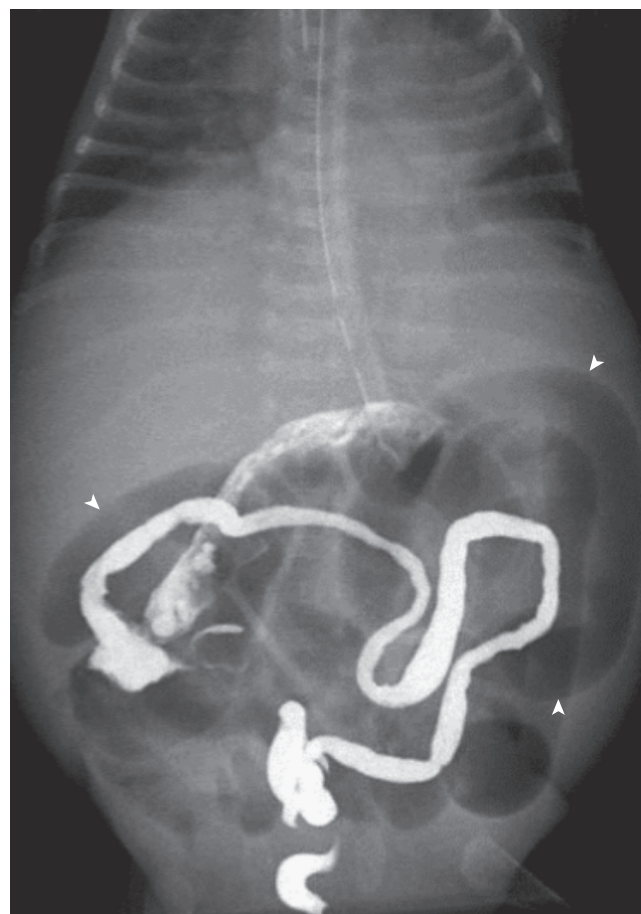
eFigure 47-7 CF: chest radiographic and chest CT findings of small airway impaction/obstruction. A, Frontal chest radiography in a patient with CF shows large lung volumes associated with central airway thickening and extensive linear opacity, representing bronchiectasis and bronchial wall thickening. A number of small, poorly defined upper lobe opacities, particularly on the right, are evident. **B–D,** Axial chest CT displayed in lung windows shows extensive cylindrical bronchiectasis (*arrows*) and extensive bronchial wall thickening. Numerous small, solid, centrilobular nodules showing branching configurations, consistent with “tree-in-bud” opacity (*arrowheads*), are evident. (Courtesy Michael Gotway, MD.)



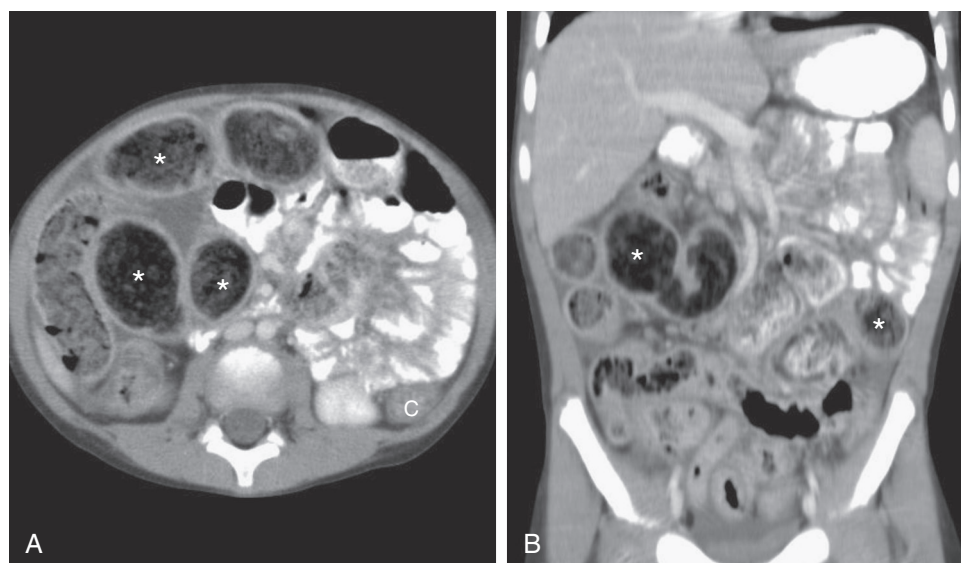
eFigure 47-8 Upper respiratory tract manifestations of CF: sinusitis. A and B, Axial sinus CT shows complete opacification of the maxillary sinuses (M) and ethmoid (E) air cells. (Courtesy Michael Gotway, MD.)



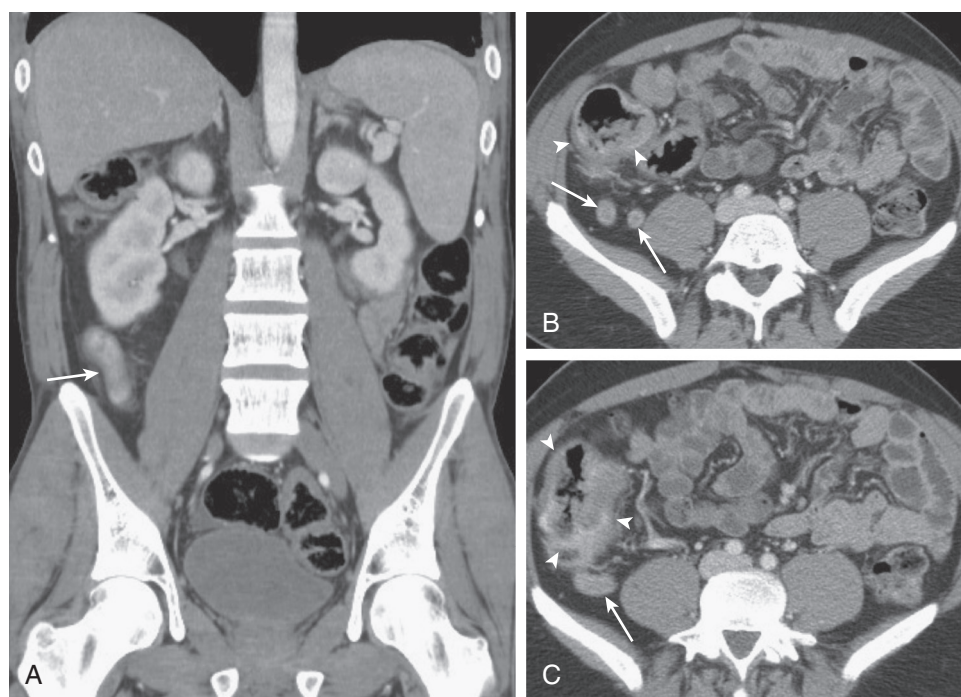
eFigure 47-9 Gastrointestinal complications of CF: meconium ileus with small bowel obstruction. Frontal view of the abdomen shows dilated small bowel with numerous gas-fluid levels (arrows) representing small bowel obstruction. The appearance is not specific for meconium ileus, but that diagnosis was proved subsequently. (Courtesy Michael Gotway, MD.)



eFigure 47-10 Gastrointestinal complications of CF: meconium ileus. Postevacuation image following contrast enema shows a small, opacified colon, consistent with a “microcolon.” Distended small bowel (arrowheads), consistent with small bowel obstruction, is present. (Courtesy Michael Gotway, MD.)



eFigure 47-11 Gastrointestinal complications of CF: distal intestinal obstruction syndrome. A, Axial and B, coronal contrast-enhanced abdominal-pelvic CT in a child with CF shows opacified normal caliber proximal small bowel but dilated, debris-filled distal small bowel (*), consistent with the distal intestinal obstruction syndrome. C, left colon. (Courtesy Michael Gotway, MD.)



eFigure 47-12 Gastrointestinal manifestations of CF: enlarged appendix. A, Coronal and B and C, axial enhanced abdominal CT shows a dilated appendix (arrows); this finding was unchanged from a study several years earlier. The colon (arrowheads) is somewhat redundant and thick-walled, with mild infiltration of the pericolonic fat; these findings may be occasionally encountered in CF patients as well. (Courtesy Michael Gotway, MD.)

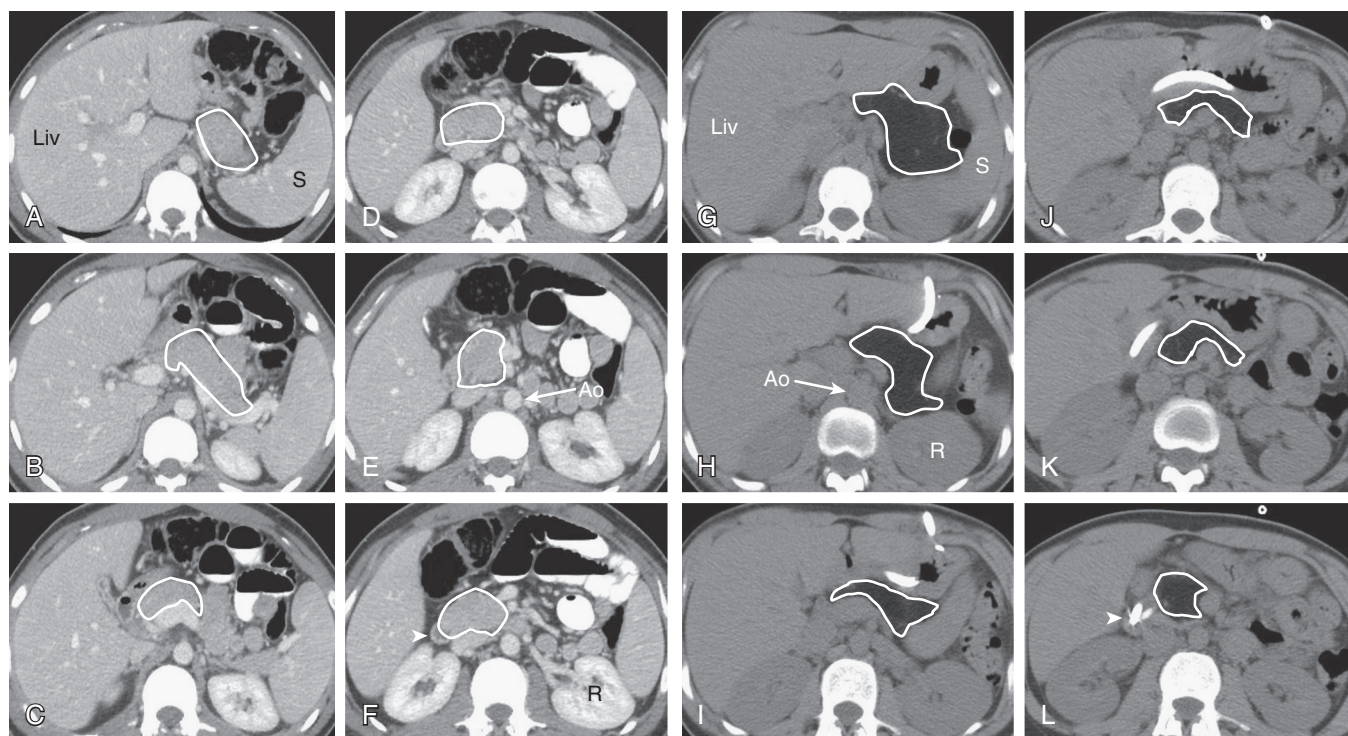


Figure 47-13 Gastrointestinal manifestations of CF: fatty replacement of the pancreas. **A–F,** Axial enhanced abdominal CT in a patient without CF shows a normal pancreas (*white outline shape*); note close relationship of the tail of the pancreas to the spleen (S). The normal pancreas is obliquely oriented with the tail superiorly and left laterally positioned compared with the more medial and inferiorly located pancreas head (*outline shape* in panels **E** and **F**); the head of the pancreas is closely related to the junction of the second and third portions of the duodenum (*arrowheads* in **F** and **L**. The enteric tube in **L** also marks the position of the duodenum). **G–L,** Axial unenhanced abdominal CT in a patient with CF shows complete fatty replacement of the pancreas—note the homogeneous low attenuation, consistent with fat and equivalent in attenuation to subcutaneous fat, occupying the position of the pancreas (*white outline shape* in **G–L**). Ao and arrow, abdominal aorta; Liv, liver; R, renal/kidney. (Courtesy Michael Gotway, MD.)

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INTRODUCTION**CLASSIFICATION****EPIDEMIOLOGY****PATHOGENESIS****“VICIOUS CIRCLE” AND
MICROBIOLOGY****BIOFILMS****ASSOCIATED DISORDERS AND
PREDISPOSITIONS**

Lung Injury due to Acute Infection

Cystic Fibrosis

Disorders of Immunity

Alpha₁-Antitrypsin Anomalies

COPD

Ciliated Epithelium Abnormalities

Bronchial Cartilage or Elastic Fiber
Defects

Connective Tissue Abnormalities

Congenital and Developmental
Anomalies

Idiopathic Inflammatory Disorders

Aspiration/Inhalation Accidents

Postobstructive Disorders

Allergic Bronchopulmonary Aspergillosis

Idiopathic Bronchiectasis

Miscellaneous

DIAGNOSIS**MANAGEMENT**Airway Hygiene and Hyperosmotic
Agents

Antimicrobial Therapy

Anti-inflammatory Therapy

Surgery

Miscellaneous

INTRODUCTION

Bronchiectasis is defined by dilation, or ectasia, of the airways or bronchus. The primary clinical manifestations of bronchiectasis are recurrent, chronic, or refractory infections. Other significant sequelae include hemoptysis, chronic airflow obstruction, and progressive impairment of breathing. In the preantibiotic era, secondary amyloidosis and embolic brain abscesses were reported as consequences of chronic suppuration in the lungs; such complications are extremely rare now in industrialized nations.

There are many and varied pathways that lead to the development of bronchiectasis (Table 48-1). Broadly, bronchiectasis may develop because of an incidental event or episode that does not reflect the patient's intrinsic host defenses. Examples might include a necrotizing pneumonia following aspiration or chronic infection distal to an obstructing bronchial adenoma. Often, however, bronchiectasis evolves due to conditions that are inherent in the patient's basic genetic constitution. The most common and dramatic example of this is *cystic fibrosis* (CF). The distinction between these two models is an important element of prognosis and management.

A central issue in understanding the pathogenesis of bronchiectasis is whether infection is truly the proximate cause of bronchiectasis or whether infections develop because of an underlying predisposing condition. For example, it has been a commonly held adage that many cases of bronchiectasis in adults are due to childhood bouts of pertussis or measles.¹ Pasteur and coworkers investigated the causative factors in 150 adults with bronchiectasis.¹ In 70 (47%) of the patients, they were able to identify one or more “causes” for the bronchiectasis. Although they found that “childhood pneumonia, pertussis, or measles” was a cause or contributed to the cause of bronchiectasis in 44 of the 70 patients, it is important to emphasize that this finding was based on recall of remote past medical history and provides at most only an associative link and not a causal link.¹ Although these childhood infections can

undoubtedly cause bronchiectasis, one might be skeptical of this simple construct, asking why formerly common childhood illnesses resulted in bronchiectasis in only a small proportion of the patients. The question that should be addressed more thoroughly is whether the individuals were particularly vulnerable to complications; for example, did the pertussis or measles result in excessive damage due to innate susceptibility of the hosts?

CLASSIFICATION

Although there is considerable overlap and coexistence among the various forms of bronchiectasis, the radiographic patterns and distribution may provide clues to diagnosis, management, and prognosis.² Thus, characterizing the morphologic features and distribution of bronchiectasis is a useful exercise. In this era, bronchiectasis is primarily identified and described by chest *computed tomography* (CT), especially *high-resolution CT* (HRCT; see later).

Cylindrical bronchiectasis is described as failure of the involved airways to taper progressively in their distal course. Usually, in this condition the bronchial walls are smooth or regular (Fig. 48-1A). *Varicoid* bronchiectasis is an allusion to varicose veins and is marked by irregular dilation, narrowing, and outpouching of the airways (see Fig. 48-1B). *Saccular* bronchiectasis, also known as cystic bronchiectasis, includes focal or cystic distortion of the distal airways; it may be isolated (see Fig. 48-1C) or may be more confluent, producing the appearance of bronchiectatic consolidation and volume loss (Fig. 48-2).

A traditional clinical distinction within bronchiectasis has been “wet” versus “dry.” Historically it was observed that some patients with bronchiectasis had continuous or frequent productive cough that typically yielded copious, often purulent secretions—hence “wet.” Others who carried the diagnosis of bronchiectasis rarely experienced cough, and if they did so, rarely was their cough productive—hence “dry.” Independent of cause, “wet” and “dry”

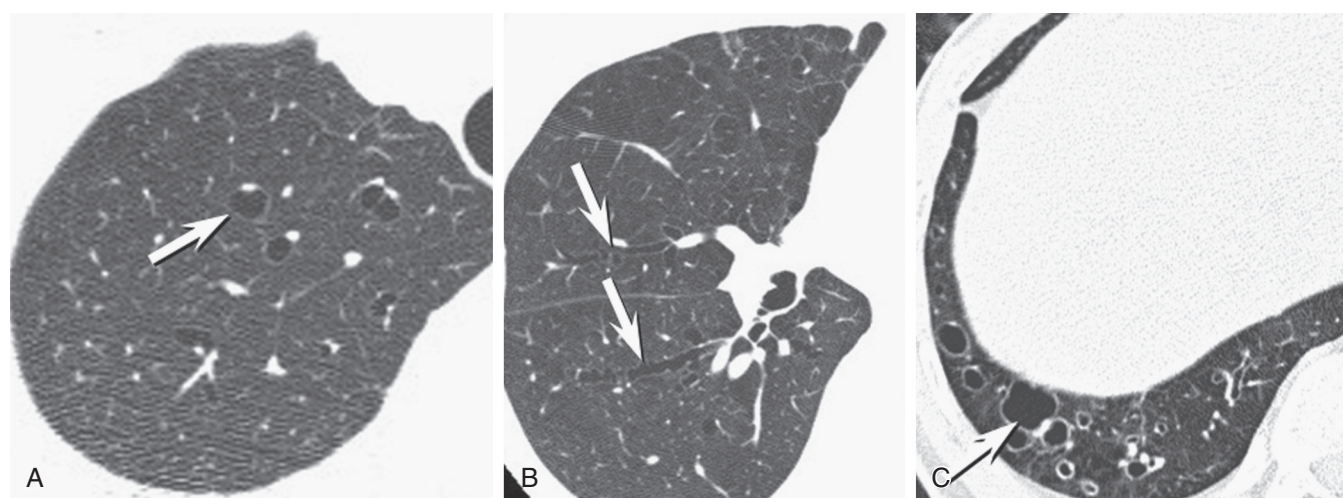


Figure 48-1 Bronchiectasis classification. **A**, Cylindrical bronchiectasis with the characteristic signet ring appearance (arrow), **B**, Varicoid bronchiectasis (arrows; diagnosed only in longitudinal plane), **C**, Cystic bronchiectasis (arrow). (Courtesy Michael Gotway, MD.)

Table 48-1 Conditions Associated with Bronchiectasis

POSTINFECTIOUS CONDITIONS

Childhood lower respiratory tract infections
Granulomatous infections
Necrotizing pneumonias in adults
Other respiratory infections

PRIMARY IMMUNE DISORDERS

Humoral defects
Cellular and/or mixed disorders
Neutrophil dysfunction
Other

CYSTIC FIBROSIS (CF)

Classic CF
Variants of CF
Young syndrome

ALPHA₁-ANTITRYPSIN SYSTEM

Deficiencies
Anomalies

HERITABLE STRUCTURAL ABNORMALITIES

Primary ciliary dyskinesia
Williams-Campbell syndrome
Mounier-Kuhn syndrome
Marfan syndrome
Sequestration, agenesis, hypoplasia, dwarfism

IDIOPATHIC INFLAMMATORY DISORDERS

Sarcoidosis
Rheumatoid arthritis
Ankylosing spondylitis
Systemic lupus erythematosus
Sjögren syndrome
Inflammatory bowel disease
Relapsing polychondritis

INHALATION AND OBSTRUCTION

Gastroesophageal reflux/aspiration
Pneumonia
Toxic inhalation/thermal injury
Postobstruction accident
Foreign body
Tumors, benign and malignant
Extrinsic airway compression
Allergic bronchopulmonary aspergillosis/mycosis

MISCELLANEOUS

HIV infection/AIDS
Yellow nail syndrome
Radiation injury
Lung fibrosis



Figure 48-2 Bronchiectatic consolidation. The inferomedial aspect of the right middle lobe is involved with a coarse cystic process, with essentially no normal remaining lung. Similar changes are often seen in the inferior segment of the lingula. In many cases such findings are associated with nontuberculous mycobacterial infection; however, in this case the patient was infected only with gram-negative bacilli, including *Pseudomonas aeruginosa* and *Alcaligenes xylosoxidans*.

bronchiectasis tend to have distinct localization patterns. Bronchiectasis involving dependent zones (lower lobes, the right middle lobe, or the lingular segment of the left upper lobe) tends to entail frequent or chronic infections and to be “wet” in nature. By contrast, chronic bronchiectasis isolated to the upper lobes is less commonly involved with infection and is often “dry.” Presumably, this is related in large measure to gravity-driven drainage of the upper zones in contrast to pooling of secretions in the dependent regions.

EPIDEMIOLOGY

There are no systematic data on the incidence or prevalence of bronchiectasis. Historically it has been thought that, as

antibiotics and vaccines were introduced in the 20th century, there has been a declining rate of bronchiectasis.^{3,4} The presumed mechanism was that these modalities lessened the frequency, severity, and duration of lower respiratory tract infections that might result in bronchiectasis. In this regard it is suggested that bronchiectasis remains relatively more common in regions where prompt and effective medical care is not available.⁵ In the United States it is estimated that the prevalence of bronchiectasis is approximately 4 per 100,000 for young adults and 272 per 100,000 among those 75 years old or older.⁶ In a retrospective analysis of hospital discharges from 12 states with bronchiectasis as a discharge diagnosis recorded in the state inpatient databases, the average annual bronchiectasis-associated hospitalization rate from 1993 to 2006 was 16.5 per 100,000.⁷ Furthermore, during this time period the age-adjusted rate increased significantly with an average annual percentage increase of 2.4% for men and 3.0% for women.⁷ Whether these rising rates reflect a true rise in incidence or enhanced detection of “incidental bronchiectasis” due to more frequent use of CT scans is not known. The observation that bronchiectasis was the *primary* diagnosis in a minority (<20%) of all the bronchiectasis-associated hospitalizations supports the concept that greater incidental diagnosis is being made from more frequent use of CT scans.⁷

In the United States there appear to be increasing numbers of bronchiectasis cases associated with environmental or *nontuberculous mycobacteria* (NTM).^{8,9} Recent studies estimate the incidence of NTM lung disease in the United States to be 5 to 6 cases per 100,000 and as high as 15.5 cases per 100,000 in persons over 50 years old.¹⁰⁻¹³ Furthermore, due to high rates of treatment failure or relapses, the prevalence of NTM lung disease is estimated to be 10 to 40 cases per 100,000.¹⁴ Based on serial observations in a cohort now numbering approximately 2000, our group believes that, in the majority of cases, the mycobacterial infections both initiate and “drive” the evolution of bronchiectasis. Of interest, this disorder seems disproportionately to involve females, predominantly slender white women.^{15,16} Although it is not possible to determine whether the incidence of NTM-associated bronchiectasis is truly increasing, or is an artifact of increased awareness and improved diagnostic techniques, or both, there is reason to suspect that the exposure and infection from NTM is increasing. For example, there has been an increase in the positive skin test reaction to Battey antigen (purified protein derivative-B of *Mycobacterium intracellulare*) from 11% in the 1971–1972 period to 17% positivity in the 1999–2000 period.¹⁷

PATHOGENESIS

Various mechanisms operate to produce permanent, pathologic dilation and damage of the airways. In simplest terms, they may be thought of in terms of traction, pulsion, and weakened tensile strength of the airways. In most cases the pathogenesis becomes inextricably linked with and propelled by the destructive effects of chronic infection.

In normal lungs, airways are held patent by a combination of negative intrapleural pressure (which maintains the

lungs in an inflated state) and the cartilaginous rings of the trachea and the large and medium airways. The distending forces of the negative intrapleural pressure are transmitted to the airways by a diffuse system of interstitial tethering. As the lung undergoes fibrotic changes consequent to disorders such as sarcoidosis, interstitial lung disorders, or infections such as tuberculosis, local retractile forces result in fixed dilation of the airways, or “traction” bronchiectasis.

The prototypic “pulsion” bronchiectasis (i.e., permanent airway dilatation as a result of intense inflammation originating in the lumen) is seen with *allergic bronchopulmonary aspergillosis* (ABPA). In ABPA there are intense, immunologically mediated reactions to inhaled *Aspergillus* that has lodged in the airways. The proliferating fungi form large mucoid conglomerates that fill the central airways; a sequela of this airway inflammatory process and mucoid impaction is bronchiectasis (Fig. 48-3).

Weakness of the airways contributing to the development of bronchiectasis may take many forms. Classic postinfectious bronchiectasis presumably is mediated in part by chronic damage to the walls of the airways, resulting in secondary loss of structural integrity.^{18,19} This is coupled with scarring and loss of volume of the local lung units, leading to regional increases in retractile forces. Examples of primary weakness of the airways contributing to bronchiectasis include Mounier-Kuhn syndrome (congenital tracheobronchomegaly due to atrophy of airway elastic fibers), Williams-Campbell syndrome (absence of cartilaginous rings in the segmental and subsegmental generations of bronchi), Marfan syndrome, and relapsing polychondritis. A case is made later that the apparent propensity of slender women for bronchiectasis may be based in part on mechanisms analogous to Marfan syndrome.

One particular component of the posited role of “weakened airways” in the pathogenesis of bronchiectasis that has not received adequate attention is the potential impact of airway collapsibility on the effectiveness of the cough mechanism. Coughing is an essential, primary element of lung defense. An effective cough sends columns of air rushing upward through the bronchial tree at peak speeds measured in the range of 600 mph.²⁰ To generate these high flow rates, the cartilaginous rings must have the structural integrity to remain patent while the posterior membranous element invaginates into the lumen of the airway, thereby decreasing the cross-sectional diameter of the airway and accelerating airflow. While performing bronchoscopy on patients with bronchiectasis, it is common to observe extraordinary collapsibility of the airways, virtually obstructing the bronchi. It seems likely that such amplified airway compressibility impedes the air-driven propulsion of secretions out of the bronchial tree and helps propagate the chronic or recurring infections that mark most cases of bronchiectasis.

“VICIOUS CIRCLE” AND MICROBIOLOGY

Because the lung is constantly exposed to the environment, resident or recruited lung phagocytes such as macrophages,

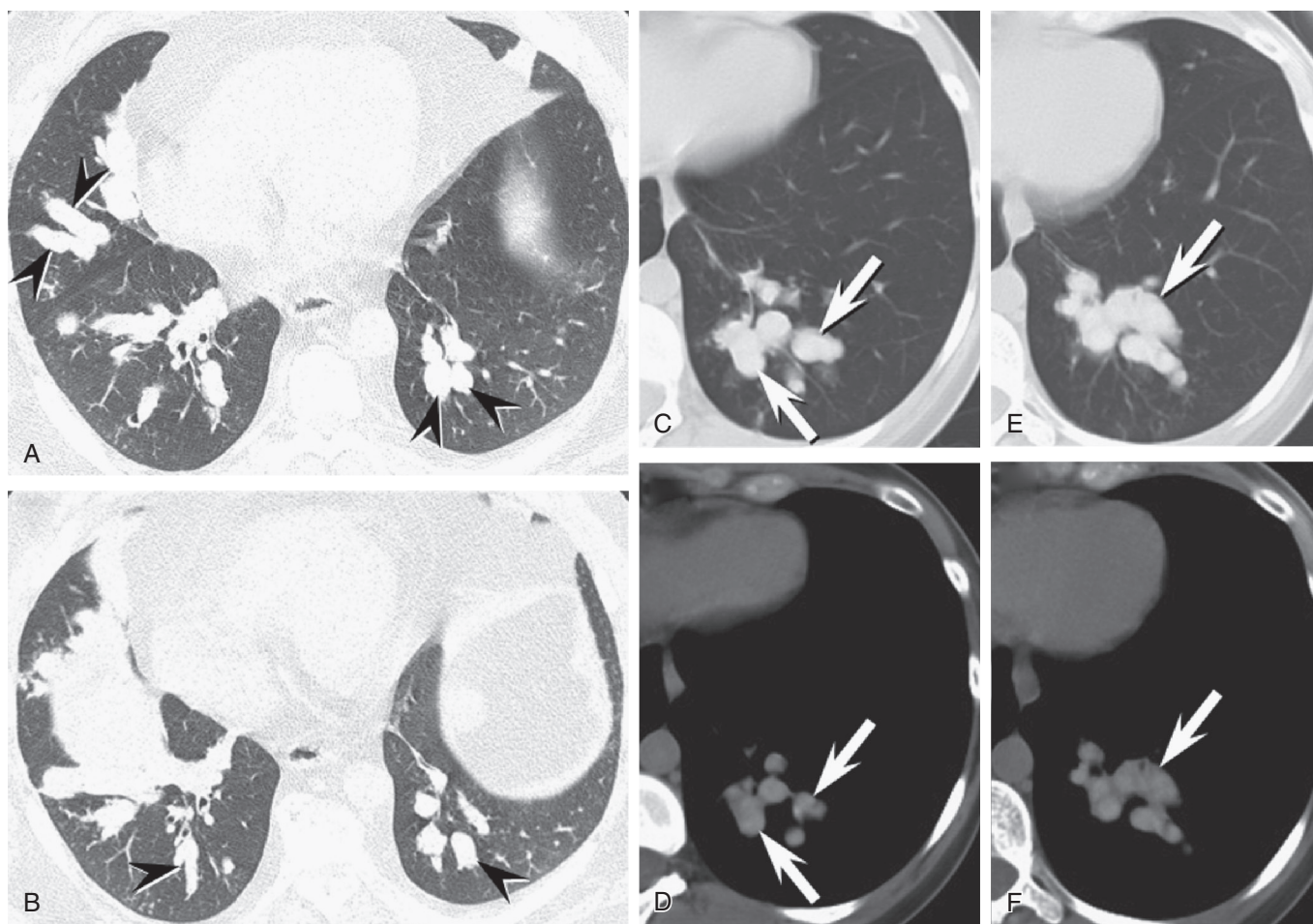


Figure 48-3 Allergic bronchopulmonary aspergillosis with bronchiectasis and bronchial mucus impaction. **A and B,** Axial chest CT displayed in lung windows shows multifocal, bilateral tubular opacities (arrowheads) consistent with mucus impaction. **C–F,** Axial chest CT from another patient displayed in lung (**C and E**) and soft tissue (**D and F**) windows shows tubular branching opacities (arrows) in the left lower lobe consistent with mucus impaction. Note that the opacities show faintly increased attenuation on the soft tissue windows (arrows in **D and F**), representing mucus impaction containing calcium salts and/or metallic ions. (Courtesy Michael Gotway, MD.)

dendritic cells, and neutrophils play an important host-defense role against inhaled or aspirated microbes. In addition, the host employs an array of other mechanisms to defend against microbial organisms that invade the respiratory tract, including the cough reflex, mucociliary escalator, antimicrobial peptides (lysozymes, secretory leukocyte protease inhibitor, defensins, and cathelicidin), secretory immunoglobulin (Ig) A, and with more sustained infection, the recruitment of T effector lymphocytes. Airway epithelial cells are also able to contribute to the lines of defense by secreting antimicrobial peptides and phagocytosing microbes.^{21,21a} Thus, in addition to the three aforementioned mechanisms by which physical forces or primary weakness of the airway walls may result in bronchiectasis, the other major element in the pathogenesis of bronchiectasis is the vicious circle of recurrent or sustained infection and inflammation, as described by Cole.^{22,23} Transmural inflammation causes damage to the bronchi and bronchioles, which then become susceptible to chronic colonization by certain microorganisms such as *Pseudomonas aeruginosa*, NTM, and *Aspergillus*, resulting in further injury and lessened capacity to resist infection. Analysis of cellular and noncellular constituents in the bronchiectatic airways typi-

cally demonstrates intense infiltration by neutrophils as well as mononuclear cells and lymphocytes.²⁴ Indeed, bacterial load in the airways correlates directly with markers of airway inflammation in the sputum (e.g., myeloperoxidase activity, neutrophil elastase activity, interleukin-8 [IL-8], tumor necrosis factor- α [TNF- α], and IL-1- β) and with markers of systemic inflammation in the serum (e.g., intercellular adhesion molecule-1, E-selectin, and vascular cell adhesion molecule-1).²⁵

Another important component in the development of bronchiectasis is impaired mucociliary clearance, a key factor in the pathophysiology of CF and *primary ciliary dyskinesia* (PCD)—discussed in more detail later—diseases almost always characterized by bronchiectasis. In CF and PCD, production of abnormal mucus and dysfunctional cilia, respectively, prevent sufficient clearance of microbes, thus increasing the risk for colonization.²⁶ When these initial defenses are unable to contain the infection, a robust immune response ensues, orchestrated by airway epithelial cells and phagocytes through the release of inflammatory cytokines and chemokines that include macrophage inflammatory protein-2, IL-8, and TNF- α . Consequently, airway infiltration by predominantly neutrophils, macrophages,

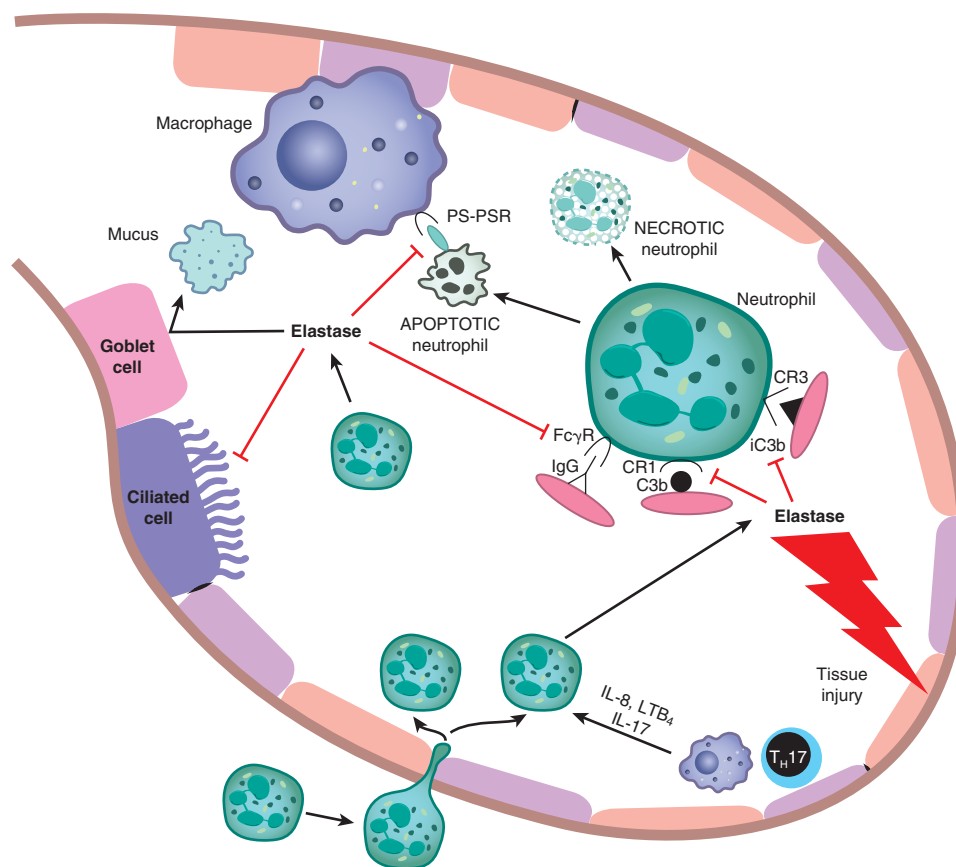


Figure 48-4 The prominent role of neutrophils and neutrophil elastase in the pathogenesis of bronchiectasis. Diagram shows a dilated cystic bronchus lined by epithelial cells. Regardless of the primary underlying cause of bronchiectasis, the “vicious circle” phase of bronchiectasis is dominated by the influx of neutrophils (polymorphonuclear leukocytes [PMNs], green cells). PMNs are attracted by the release of chemokines such as interleukin-8 (IL-8) and leukotriene B_4 (LTB_4) from macrophages, and IL-17 from T_H17 cells; their migration from the bloodstream into the airways is facilitated by increased expression of the E-selectin and intercellular adhesion molecule-1 on endothelial cells, which bind to L-selectin and CD11 on PMNs, respectively. PMNs, which then enter the airway lumina through gaps between epithelial cells, have a relatively short life span, undergoing both apoptotic and necrotic cell death. PMN proteases such as elastase but also cathepsins, matrix metalloproteinases, and proteinase-3 can cause epithelial cell damage and induce further inflammation. In addition to the tissue damage, elastase can induce mucous hypersecretion, inhibit ciliary function, and impair efferocytosis (i.e., phagocytosis of apoptotic neutrophils) by cleavage of phosphatidylserine (PS) on the surface of apoptotic cells, preventing binding to PS receptors (PSRs) on macrophage surfaces. Elastase also inhibits killing of bacteria by inhibiting the opsonization of bacteria through degradation of opsonins immunoglobulin G (IgG) and complement component $iC3b$ as well as cleavage of $Fc\gamma$ receptors ($Fc\gamma R$ s) and complement receptor (CR) 1. Black arrows, activation or “leading to”; red “T-bars,” inhibition or degradation.

and lymphocytes causes damage to the airway epithelium through the release of various proteolytic enzymes such as neutrophil elastase and metalloproteinases, which results in erosion of mucosal barriers, creating microabscesses that can harbor bacteria. Neutrophil elastase has also been shown to cause ciliary dysfunction, mucous gland hyperplasia, and increased mucus secretion, thus further impairing clearance (Fig. 48-4).²⁷⁻²⁹ Moreover, elastase and other proteases released by neutrophils can cleave $Fc\gamma$ receptors and complement receptor 1 from neutrophil surfaces as well as digest immunoglobulins and complement components from bacterial surfaces. These activities impair opsonization of bacteria and reduce recognition of bacteria by neutrophils, leading to decreased phagocytosis and bacterial killing (see Fig. 48-4).^{30,31} Neutrophils undergo both necrotic and apoptotic forms of cell death. Necrotic neutrophils can incite more inflammation as well as the release of highly viscous DNA, which contributes to the volume and inspissated quality of bronchiectatic mucus. Although phagocytosis of apoptotic neutrophils—a process known

as efferocytosis and requiring engagement of phosphatidylserine on apoptotic cells and phosphatidylserine receptor on macrophages—can limit inflammation, elastase can inhibit efferocytosis by cleavage of phosphatidylserine.³² In summary, damaged airways are vulnerable to infection, leading to more damage.

Simple colonization and infection of the airways is not sufficient to produce true bronchiectasis. Sputum from patients with smoking-related chronic bronchitis typically yields organisms such as *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, a microbial spectrum similar to that seen with bronchiectasis.³³⁻³⁶ In addition, in this setting there is heavy cellular traffic and the presence of a variety of inflammatory mediators. However, significant bronchiectasis is uncommon among patients with typical chronic bronchitis. Hence it is probable that systemic conditions or focal disturbances as described earlier are required for the development of classic bronchiectasis. Notably, however, the appearance in respiratory secretions of *P. aeruginosa* on a

chronic or recurring basis does pose the risk for deleterious effects on ciliary function and other host defenses.³⁷ Pseudomonal infections may be of particular importance due to their role in the formation of biofilms (see later). Three reports note worsened lung function^{37,38} and quality of life³⁹ among bronchiectasis patients who become infected with *P. aeruginosa*. In a longitudinal study of the microbiologic characteristics of 89 patients with bronchiectasis over a 5-year period, 47% were colonized with *H. influenzae*, 12% with *P. aeruginosa*, and 21% had no identifiable pathogen. After 5 years there was a slight increase in the number of those colonized with *P. aeruginosa*. As expected, those with the mildest disease had no identifiable pathogens, whereas those with the worst disease were colonized with *P. aeruginosa*.⁴⁰

As previously noted, NTM can colonize bronchiectatic airways as well as cause bronchiectasis. Based on two recent studies from the United Kingdom, the prevalence of NTM isolated from a heterogeneous group of bronchiectatic patients was approximately 2% to 10%.⁴¹ Furthermore, bronchiectatic patients with NTM infections also have a greater likelihood of having concomitant *Aspergillus* lung disease.⁴²

Genetic techniques have been used to identify the bacterial flora in patients with bronchiectasis. Using 16S ribosomal RNA gene pyrosequencing of paired induced sputum and bronchoalveolar lavage samples, the bacterial flora of lower airway samples was analyzed in 41 adult patients with non-CF bronchiectasis.⁴³ A group of core bacterial species, defined as those frequently detected, was found to consist of commonly recognized pathogens (e.g., *P. aeruginosa*, *H. influenzae*, and *S. pneumoniae*) but also organisms not typically detected by routine cultures (e.g., *Veillonella*, *Prevotella*).⁴³ This burgeoning field of genetically categorizing lung microbiota in patients with bronchiectasis and determining the significance of the microbiota signature with relevant clinical end points such as exacerbations is still in its infancy. Although a study showed that there was no significant difference in the overall microbial community diversity between patients with stable bronchiectasis and those with exacerbations, it was clear that *Acinetobacter* and *Stenotrophomonas* were seen primarily during exacerbations.⁴⁴ In an editorial that accompanied this report, the authors raised the critical question of whether analyzing the mountain of 16S-derived microbiota data in the context of the microbial community (“the forest”) masks the importance of individual microbes detected (“the trees”).⁴⁵

BIOFILMS

Costerton⁴⁶ in 1984 hypothesized that *P. aeruginosa* in human infections “attaches to solid or tissue surfaces and grows predominantly in biofilms that release mobile swarmer cells into the surrounding fluid phase.” These natural and pathogenic biofilms are covered by an exopolysaccharide matrix (glycocalyx) that serves as a barrier against hostile environmental factors such as host defense mechanisms and antibiotics.⁴⁶ Since this discovery, there has been clear evidence for the clinical significance of biofilms in promoting chronic infection in the airways of CF patients⁴⁷ as well as a variety of other infections.⁴⁸ *P.*

aeruginosa, among its various attributes, enjoys cilia-driven motility, which appears critical in the aggregation phase of early biofilm formation.⁴⁹ Once biofilm formation commences, features of growth and gene activation that release virulence factors are influenced by a type of cell-cell communication called “quorum sensing.” Owing to a combination of physicochemical factors that protect the microbes from host defense cells and/or antibiotics, infection may persist despite aggressive treatment. In vitro testing indicates that bacteria embedded in biofilms can survive despite exposure to concentrations of antimicrobials that exceed the minimal inhibitory concentration by 1000-fold.⁵⁰ We may anticipate that future understanding and optimal management of patients with chronic bronchiectasis will entail interventions to modify or interfere with biofilms.⁴⁹

ASSOCIATED DISORDERS AND PREDISPOSITIONS

LUNG INJURY DUE TO ACUTE INFECTION

In the traditional model of lung injury due to acute infection, patients are deemed to have normal airways and lungs until they experience a specific lower respiratory tract infection resulting in irreversible damage to their airways. In the modern era in industrialized nations, most episodes of lower respiratory tract infection—adequately treated—resolve without residual damage. However, among the older generations who were not protected by readily available antibiotics and vaccines, there are individuals who offer a convincing story of recurring, localized infections following a discrete episode of “pneumonia” in their childhood or early adult years that presumably produced irreversible damage leading to bronchiectasis.¹

Specific traditional pathogens to which bronchiectasis has been ascribed include *Bordetella pertussis*, mucoid strains of *S. pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, adenoviruses, rubeola (measles), and influenza. Chronic granulomatous pathogens commonly related to bronchiectasis include *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, and NTM such as *Mycobacterium avium* complex (MAC). In addition, mixed infection, including anaerobic mouth flora related to aspiration, may result in extensive damage to the parenchyma (“lung abscesses”) with subsequent bronchiectasis.

CYSTIC FIBROSIS

CF and CF variants are arguably the most common causes of bronchiectasis in the United States and other industrialized nations of the Western Hemisphere today. Being the most common autosomal recessive disorder among whites (1 in 2000 to 2500 live births),⁵¹ CF is increasingly prevalent as improved therapies allow those who are afflicted to live longer. At present, there are approximately 30,000 CF patients in the United States with approximately 45% of them estimated to be over 18 years old, or roughly 12,000 to 14,000 adults with CF. In the next decade it is predicted that about 50% of all CF patients

will be adults.⁵² The specific manifestations, severity, and rapidity of progression of CF vary highly according to the genotype and other modifying factors. However, the majority of those with childhood-onset CF who survive into their adolescence or early adult years have bronchiectasis (eFig. 48-1). (See Chapter 47 for details.)

In addition to these “typical” cases in which CF is recognized early in life, variants may be present in the population that predispose to bronchiectasis in adults. Among a large series of adult patients seen at *National Jewish Health* (NJH) in Denver with bronchiectasis associated with NTM, 117 of 865 (13.5%) were found to have one or more abnormal alleles of the cystic fibrosis transmembrane regulator gene, *CFTR*,⁵³ well in excess of the anticipated carrier rate of 6% in the general population. In 19 of these patients (2.2% overall), there were two abnormal alleles and, in the remaining 98 (11.3%), there was only one mutation. Of note, the mean age of these patients was 61 years. The clinical importance of these heterozygous mutations may be disputed; however, patients in this cohort had a high frequency of chronic airflow obstruction, sinusitis, difficulties with conception, and coinfection with pathogens typical of CF, including mucoid strains of *P. aeruginosa*—all features compatible with clinical CF. Among another series of patients with bronchiectasis and/or NTM lung disease, 24 of 50 (48%) had one or more *CFTR* mutations.⁵⁴ Similarly, among a cohort of 63 patients with NTM lung disease studied at the National Institutes of Health, 36% had mutations in the *CFTR* gene.⁵⁵ Consistent with the assertion that these heterozygous mutations are clinically relevant is a series of 30 patients with clinical features of CF who were reported to have normal *CFTR* alleles on comprehensive gene sequencing.⁵⁶ The authors concluded that factors other than mutations in *CFTR* could result in a clinical condition consistent with CF. It is our contention that heterozygous anomalies in the CF gene act as a predisposing factor for bronchiectasis.

Based on contemporary understanding of the complex and diverse features of CF, there appear to be two groups in whom bronchiectasis develops. The first and obvious group includes those with classic infancy/childhood-onset disease in whom clinical and laboratory data readily confirm the diagnosis of CF. The other group involves those with less severe disease that manifests later in life and for whom diagnostic testing is ambiguous.⁵⁷ Sweat chloride test results may or may not be abnormal, and genotyping may demonstrate heterozygous or even normal *CFTR* alleles. We might include under this rubric males with congenital bilateral absence of the vas deferens,⁵⁸ who have not been consistently regarded as having variant CF. In addition, there are a wide variety of genetic factors other than *CFTR* that influence the clinical phenotypes of the patients.⁵⁹ (See Chapter 47 for additional discussion.)

Bronchiectasis has been described in a condition identified in the 1970s called Young syndrome. Although Young syndrome is not CF, it has a number of similar clinical features such as bronchiectasis, sinusitis, and infertility.⁶⁰ However, unlike CF, the genetic basis for Young syndrome is not known, and, because the definition includes azoospermia, it is seen only in males. Furthermore, whereas the azoospermia related to CF is due to congenital absence of the vas deferens, in Young syndrome it is due to obstruction

in the distal epididymis (i.e., obstructive azoospermia).^{58,61} In a comprehensive study of 15 patients with a clinical diagnosis of Young syndrome, the mean nasal mucociliary clearance, as measured by the saccharin test, was prolonged nearly threefold compared to nonsmoking controls, but the ciliary beat frequency and ultrastructural anatomy of the cilia were considered to be within normal limits.⁶¹ Interestingly, in one subject in whom a sample of epididymis was available, microtubular disarrangement—mostly missing or “displaced” microtubules—was seen in approximately 13% of the cilia examined.⁶¹ Because the incidence of Young syndrome appears to be decreasing dramatically since it was originally reported in the 1970s, it has been hypothesized that Young syndrome may be due to poisoning from mercurous chloride (calomel), a compound contained in teething powder and antihelmintics that has since been banned.^{62,63} Furthermore, we posit that, with more comprehensive testing for the *CFTR* mutation, it is quite plausible that some cases diagnosed as Young syndrome were in fact CF.

DISORDERS OF IMMUNITY

Immunologic deficiencies are also associated with the development of bronchiectasis. Primary diseases that result in immunodeficiency may devolve from mutations that impair B or T lymphocytes and cause abnormal humoral immunity, cellular immunity, or both. Less frequent anomalies may involve *natural killer* (NK) lymphocytes, neutrophils, or complement proteins. Some specific immune disorders are noted later.

Common variable immunodeficiency, or acquired hypogammaglobulinemia, is the most frequent syndrome recognized in this group of diseases. Clinically, it is seen equally among males and females, distinguishing it from X-linked agammaglobulinemia (Bruton disease), which exclusively involves young males. It may be seen throughout all age-groups, although it is most commonly recognized in early childhood. Although there are normal numbers of circulating B lymphocytes, they fail to differentiate into antibody-producing cells. This results in particular vulnerability to infections with encapsulated bacteria such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *P. aeruginosa*. Recurring infections of the airways with these and other organisms frequently result in bronchiectasis (eFig. 48-2).⁶⁴ The diagnosis is established by demonstrating low levels of IgG, absent or markedly reduced IgA levels, and normal or reduced levels of IgM, and the failure to produce appropriate antibody responses following vaccination (normal response is a four-fold or greater increase in specific IgG level 4 weeks after immunization or at least the presence of protective titers if less than threefold increase from baseline). A variant of the hypogammaglobulinemic disorders is selective deficiency of subclasses of IgG, notably IgG2 and IgG4.⁶⁵ Because repletion with gamma globulin is so useful in controlling the recurrent infections, pursuit of the diagnosis of deficient antibody production (common variable immunodeficiency or Bruton disease) is strongly indicated. By contrast, selective deficiency of secretory IgA, another cause of recurrent respiratory infections, cannot be controlled by repletion.⁶⁶

Other, less common primary immune disorders that may result in recurrent or refractory respiratory infections

leading to bronchiectasis include hyper-IgM or hyper-IgE (Job syndrome) and thymic hypoplasia resulting in abnormal cellular immunity (DiGeorge syndrome). There are two forms of the hyper-IgE syndrome: an autosomal dominant form caused by mutations in the *signal transducer and activator of transcription 3* (*STAT3*) gene, resulting in *STAT3* deficiency, and an autosomal recessive form for which the precise genetic cause is not known.⁶⁷ The susceptibility of individuals with dominant hyper-IgE syndrome to pyogenic bacteria and NTM organisms may be due to impaired production of cytokines secreted by type 1 helper T cells such as *interferon-γ* (IFN-γ) and TNF-α, cytokines known to be important in controlling such infections.⁶⁸ Genetic anomalies that may result in combined humoral and cellular impairment include severe combined immunodeficiency syndrome, “bare lymphocyte” syndrome, Wiskott-Aldrich syndrome (an X-linked recessive illness associated with small platelets and eczema), cartilage-hair hypoplasia (associated with short-limbed dwarfism), ataxia-telangiectasia syndrome, and a variety of other rare disorders.

ALPHA₁-ANTITRYPSIN ANOMALIES

Deficiency or anomalies in *alpha₁-antitrypsin* (AAT) may predispose to bronchiectasis. Various phenotypic abnormalities of AAT were described prominently in a recent series of patients seen at the NJH with bronchiectasis associated with NTM.⁶⁹ Previously there had been reports of the relationship between AAT deficiency and bronchiectasis.^{70,71} However, in the great majority of cases in the NJH series, the patients were not deficient in AAT but had heterozygous phenotypes, mainly MS, to a lesser extent MZ, with normal AAT levels. The prevalence of AAT anomalies in the overall cohort of NJH patients with various NTM infections was 17%⁶⁹; even more striking was the 27% prevalence of AAT anomalies in the patients with NTM lung disease due to rapidly growing mycobacteria.⁷² Based on various surveys, AAT anomalies would be anticipated in roughly 8% to 9% of the U.S. population.⁷³ However, the role of heterozygous anomalies of the AAT system in the pathogenesis of lung disease is controversial.⁷⁴ The majority of the NJH patients did not have clinically significant *chronic obstructive pulmonary disease* (COPD) or grossly visible emphysema on CT scanning. Hence we postulate that the AAT anomalies render the patients more vulnerable to respiratory tract infections. Inferential evidence in support of this hypothesis includes an informal survey done among emphysema patients being repleted with alpha₁-proteinase inhibitor (Prolastin)⁷⁵; 74 of the 89 responding patients described a perceptible benefit, and 56 of the 74 identified a reduction in the frequency of infectious exacerbations of their COPD. Possibly relevant to the development of bronchiectasis is the observation that AAT is produced in airway epithelium (as well as the liver) and “Z” AAT may polymerize in the lung and act as a chemoattractant for neutrophils.⁷⁶ Evidence in support of the effect of a direct effect of AAT on infection includes the finding that aerosolized AAT suppresses *P. aeruginosa* lung infection in an animal model^{77,78} and the observation by Shapiro and colleagues⁷⁹ that AAT inhibits replication of the *human immunodeficiency virus* (HIV) in whole blood. Further

support for a direct role of AAT in resistance to infection is the observation in an African population that two polymorphic variants of the AAT haplotype were associated with significantly greater risks for HIV infection when compared with the other nine haplotypes common in sub-Saharan African populations.⁸⁰ Chan and coworkers⁷² showed that AAT inhibits phagocytosis of *Mycobacterium abscessus* by human macrophages, partially denying the mycobacteria their preferred intracellular milieu. It should be noted that a group from France studied AAT alleles in a large cohort of bronchiectasis patients and reached a different conclusion.⁸¹ They found the following phenotypes in their patients: MS, 11.9%; MZ, 3.5%; SS, 1.5%; SZ, 0.5%; and ZZ, 0.5%. In this study the distribution of these phenotypes was not significantly different in their controls, and they inferred that AAT anomalies did not contribute to the risk for bronchiectasis. In a study of 74 patients with severe AAT deficiency (PiZ phenotype), however, remarkably 70 (95%) had bronchiectatic changes on CT scan (eFig. 48-3) and 20 (27%) had clinically significant bronchiectasis, defined as bronchiectasis in four or more bronchopulmonary segments and chronic sputum production.⁸² Thus it appears that if one examines a group of unselected bronchiectasis patients, the prevalence of AAT anomalies is low; however, if one starts with a group with known AAT deficiency, bronchiectasis is commonly found. This observation may be related to the notion that COPD itself may be associated with bronchiectasis as discussed in the next section.

COPD

Over the past decade, likely due to increasing use of HRCT scans, a relatively high prevalence of bronchiectasis has been reported in patients with moderate-to-severe COPD.⁸³⁻⁸⁷ Given the 30% to 60% prevalence of bronchiectasis found in COPD patients in these studies, it would be important to evaluate AAT phenotypes to determine whether the bronchiectasis is associated more closely with severe COPD per se or with associated AAT anomalies. In one study, COPD patients with bronchiectasis had higher levels of the neutrophil chemoattractant IL-8 in the sputa and increased bacterial colonization of the lower airways, and they experienced more severe exacerbations than those without bronchiectasis.⁸⁶ Whether bronchiectasis is a coincident sequela in COPD patients with frequent exacerbations, identifies a subgroup of COPD patients with different pathogenic mechanism, or both, remains to be determined.⁸⁸ Martínez-García and associates⁸⁵ found that, although COPD patients with bronchiectasis had lower FEV₁ and FEV₁/FVC ratio, the presence of bronchiectasis was independently and significantly associated with increased all-cause mortality in multivariate analysis.

CILIATED EPITHELIUM ABNORMALITIES

Congenital structural and functional disturbances of the ciliated epithelial cells are seen in association with bronchiectasis, as well as with frequent and severe upper respiratory tract problems.^{89,90} These disorders appear to be an autosomal recessive process, with an estimated frequency between 1 in 12,500 to 1 in 40,000.⁹¹ PCD embraces a

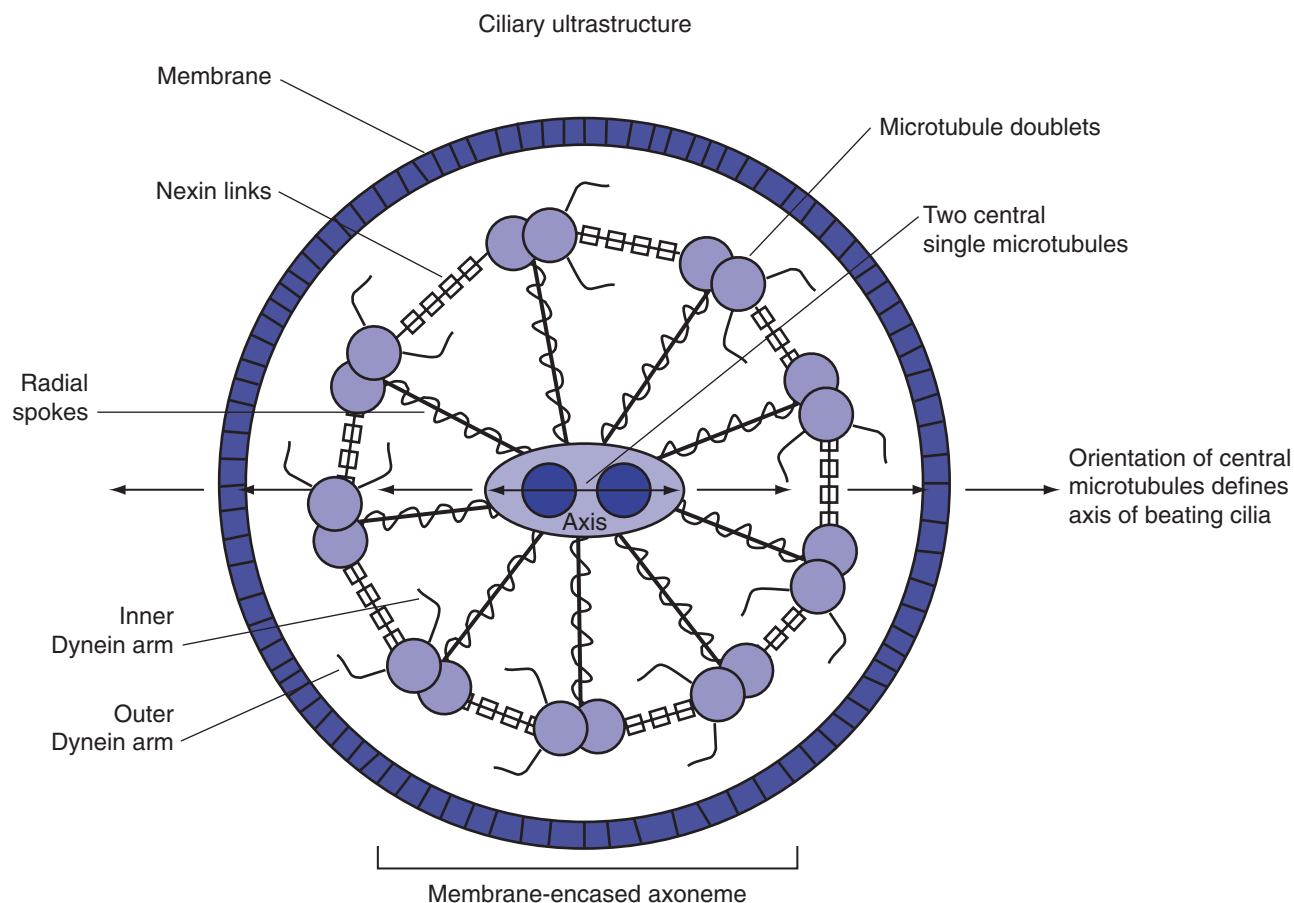


Figure 48-5 Ultrastructure of the cilia. The structure and function of cilia are elegant and complex. Each ciliated epithelial cell possesses approximately 200 cilia. The direction of ciliary beating is determined by the orientation of the central pair of microtubules. Dysfunction of the ciliary apparatus may involve a variety of structural abnormalities in the cilia or disorganization of the ciliary axes. The cilia beat in a relatively fluidic periciliary medium; above that, adherent by a thin physicochemical junction, is a gelatinous layer of mucus (not shown).

heterogeneous group of ultrastructural deficits involving the axoneme or central functional element of the cilia.⁹² The normal axoneme is composed of nine paired or doublet microtubules arrayed peripherally around two central, single microtubules; attached to the peripheral doublet microtubules are outer and inner dynein arms as well as radial spokes (Fig. 48-5). The direction in which the cilia beat is determined by the orientation of the two central microtubules. In a local sheet of bronchial ciliated epithelium, the axes of the central microtubules are arrayed within a fairly narrow range, typically deviating 25 degrees or less from each other along the long axis of the airway. A variety of abnormalities have been described, including the complete or partial absence of outer or inner dynein arms, a lack of radial spokes, disordered microtubule arrangements, ciliary disorientation, and other rare disturbances. Functionally these disturbances result in reduced or disorganized beating of the ciliated epithelial cells or, in some cases, gross immotility. There may also be inversion of the normal anatomic locations for the organs of the thorax and abdomen, situs inversus universalis or partialis. PCD with situs inversus universalis is known as Kartagener syndrome (Fig. 48-6). In the absence of normal ciliary activity, organ orientation appears random during embryogenesis, resulting in situs inversus in roughly half of the cases. Evi-

dence in support of this theory includes discordant organ orientation in monozygotic twins with disordered ciliary motility.⁹³

The ineffectual beating of the ciliated cells results in stagnation and accumulation of mucus, which classically is associated with early-onset refractory or recurrent infections of the upper and lower respiratory tract, including otitis media, mastoiditis, sinusitis, and bronchitis. Bronchiectasis is a common sequela of PCD, typically involving the dependent zones, including the lower lobes, right middle lobe, and/or the lingular segment of the left upper lobe (Fig. 48-7). Patients with PCD, sinusitis, and bronchiectasis also have a marked tendency toward colonization and infection with *H. influenzae*.⁹⁴ The mechanism(s) for this predilection is unknown, but defective adaptive immunity is a plausible candidate. The ciliary defect also involves the flagella of the spermatozoa, resulting usually, although not universally, in male infertility. Patients may have a history of neonatal respiratory distress, a characteristic early-life complication of PCD.

Diagnosing PCD is often problematic.⁹⁴ Consideration of this diagnosis should be given in the setting of early-onset upper and lower respiratory infections (see earlier). Male infertility, although suggestive, may be due to Young syndrome in a North American population. A suggestive

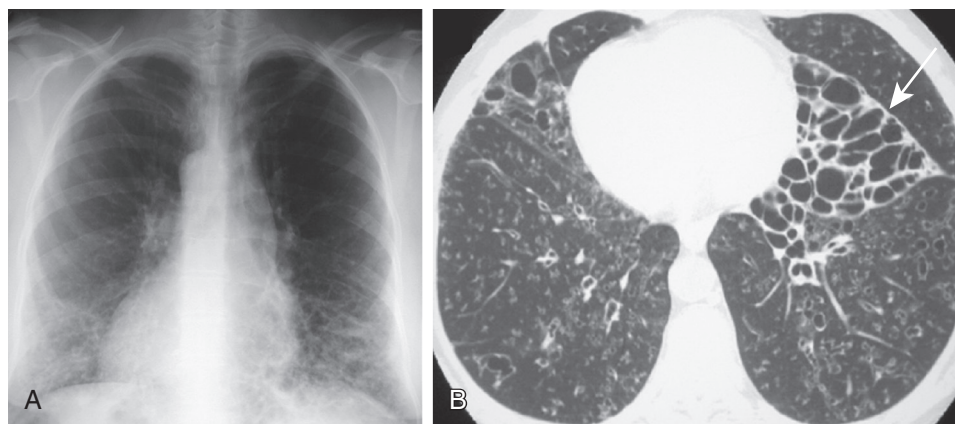


Figure 48-6 Bronchiectasis: Kartagener syndrome. **A**, Frontal chest radiograph shows dextrocardia with basal predominant linear opacities, the latter consistent with bronchial wall thickening and bronchiectasis. **B**, Axial chest CT shows dextrocardia and severe, cystic bronchiectasis, particularly on the left (arrow). Note the left lung shows a morphologic configuration resembling a right middle lobe (same arrow). Numerous small nodules are consistent with small airway impaction. (Courtesy Michael Gotway, MD.)



Figure 48-7 Dependent-zone bronchiectasis in primary ciliary dyskinesia (PCD). This 35-year-old white woman has classic PCD. She has atelectasis and saccular bronchiectasis involving the right middle lobe, the medial basilar segment of the right lower lobe, and the anteromedial aspects of her left lower lobe. She has previously been treated for *Mycobacterium avium* complex and now has refractory infections with *P. aeruginosa*.

feature on HRCT is predominant bronchiectasis in the lower lobes, with or without right middle lobe or lingular involvement and sparing of the upper lobes (unpublished data). Diffuse, poorly defined flocculent centrilobular opacities in the lower lobes is typical of PCD, reflecting chronic bronchiolitis. Either electron microscopic analysis of the ultrastructure of the cilia or clearly documented ciliary dysfunction via high-speed video microscopy is the gold standard for diagnosis. However, such testing is complicated by the following factors: (1) chronic infection may denude the airways of ciliated epithelium, and (2) chronic infection may damage cilia, resulting in nondiagnostic findings. In one report, computer-assisted analysis was shown to increase the diagnostic yield significantly over conventional transmission electron microscopy for inner dynein arm disturbances.⁹⁵ Direct measurements of ciliary beat frequency or coordination is available only in selected research centers.

Using a ciliary beat frequency of less than 11 beats/sec to determine who should have ultrastructural analysis may result in an unacceptable number of missed cases.⁹⁶ Instead, measurement of the ciliary dyskinesia score—a reflection of the ciliary beat pattern—is a significantly more sensitive and specific screening test for PCD using ultrastructural analysis as the gold standard.⁹⁶ Among males, dysmotile or immotile spermatozoa may be demonstrated, and ultrastructural analysis of the sperm flagella may confirm the diagnosis. The saccharin test has also been employed as an inferential test of ciliary dysfunction. In this minimally invasive test, a particle of sodium saccharin (≈ 1 mm in diameter) is placed on the inferior turbinate, roughly 1 cm from the anterior end of the turbinate to avoid the area covered with squamous epithelium.⁹⁷ The patient remains in the sitting position with the head slightly tipped forward and breathing normally. The time for the subject to taste sweetness—an indication of nasal mucociliary clearance and thus of ciliary function in other parts of the body—is then recorded. In negative (normal) test results, the elapsed time is less than 30 minutes. The primary utility of the saccharin test is to exclude PCD. Abnormal saccharin test results are consistent with, but not diagnostic of, PCD, because individuals with other disorders that result in chronic rhinosinusitis may have denuded their ciliated epithelium or have inflammatory factors that impair ciliary beating. Thus the test should not be done within a month of an upper respiratory infection.

A relatively accurate test for PCD is measurement of nasal *nitric oxide* (NO) levels.⁹⁴ In a large cohort with proven PCD, nasal NO levels were significantly lower than in normal persons or subjects with CF. Of interest, parents of PCD patients had lower-than-normal nasal NO levels, intermediate between controls and patients, despite the absence of clinical disease. Several mutations are known to be associated with PCD in genes, including *DNAI1*, *DNAH5*, and *DNAH11*,⁹⁸⁻¹⁰² that encode axonemal motor proteins, structural and regulatory elements, and cytoplasmic proteins involved in assembly of cilia.^{102a,102b} While genetic testing for PCD is not widely available, it is likely to be the diagnostic test of choice in the not too distant future.

BRONCHIAL CARTILAGE OR ELASTIC FIBER DEFECTS

Cartilaginous “C-rings” are present throughout the entire trachea as well as in the large and medium-sized airways, typically down to the fourth through sixth generations of the ramifying bronchi. The primary functional role of these structures is to maintain airway patency during expiration, including during cough.

Mounier-Kuhn syndrome, or congenital tracheobronchomegaly, is a rare disorder associated with gross enlargement or dilation of the trachea and segmental bronchi¹⁰³ (Fig. 48-8 and eFig. 48-4). The underlying defect is atrophy and even absence of elastic fibers and smooth muscle tissues of the large airways.¹⁰⁴ In addition, primary or secondary atrophy of the connective tissue between the rings may result in outpouchings or diverticula, potentially serving as reservoirs for recurrent infections. Distal to the involved airways, bronchial structures generally appear normal. Clinically, Mounier-Kuhn patients may present in their early years or as late as the fourth decade with recurring lower respiratory infections. In advanced stages, airway collapsibility may result in severe airflow obstruction. The diagnosis is readily made by finding extraordinary dilation of the trachea and central bronchi on CT scans (see eFig. 48-4B-D), with airway dimensions 3 standard deviations greater than normal; for men, transverse and sagittal tracheal diameter greater than 25 mm and greater than 27 mm, respectively, is considered abnormally enlarged,

whereas in women, the respective values are greater than 21 mm and greater than 23 mm. Special considerations in management include positive end-expiratory pressure support and silicone or metallic stenting. Lung transplantation is an option, although unique issues associated with Mounier-Kuhn syndrome include recurrent infections when tracheal diverticula are present and difficulty with bronchial anastomosis due to discrepancy in the airway diameters between the donor and the recipient lungs.

Williams-Campbell syndrome, or congenital bronchial cartilage deficiency syndrome, is another rare disorder that tends to present early in life with recurring infection and bronchiectasis.¹⁰⁵ Familial cases have been reported in this condition, although the precise genetic defect is not known. The absence of cartilage from the segmental to the first few generations of the subsegmental airways is the typical finding in Williams-Campbell syndrome, although more proximal bronchi (lobar and main stem) may be rarely affected as well. There is no evidence that cartilage is deficient in tissues other than the lungs. Characteristic findings on CT scan include more extensive peripheral bronchiectasis than would be anticipated by the clinical history and a more proximal extension of bronchiectasis than usual (Fig. 48-9 and eFig. 48-5). Inspiratory ballooning and expiratory collapse of the airways on chest CT scan is characteristic of Williams-Campbell syndrome.¹⁰⁶ The degree of peripheral airway distortion suggests that this disorder entails more than simply the absence of proximal cartilage. Patients with Williams-Campbell syndrome are particularly

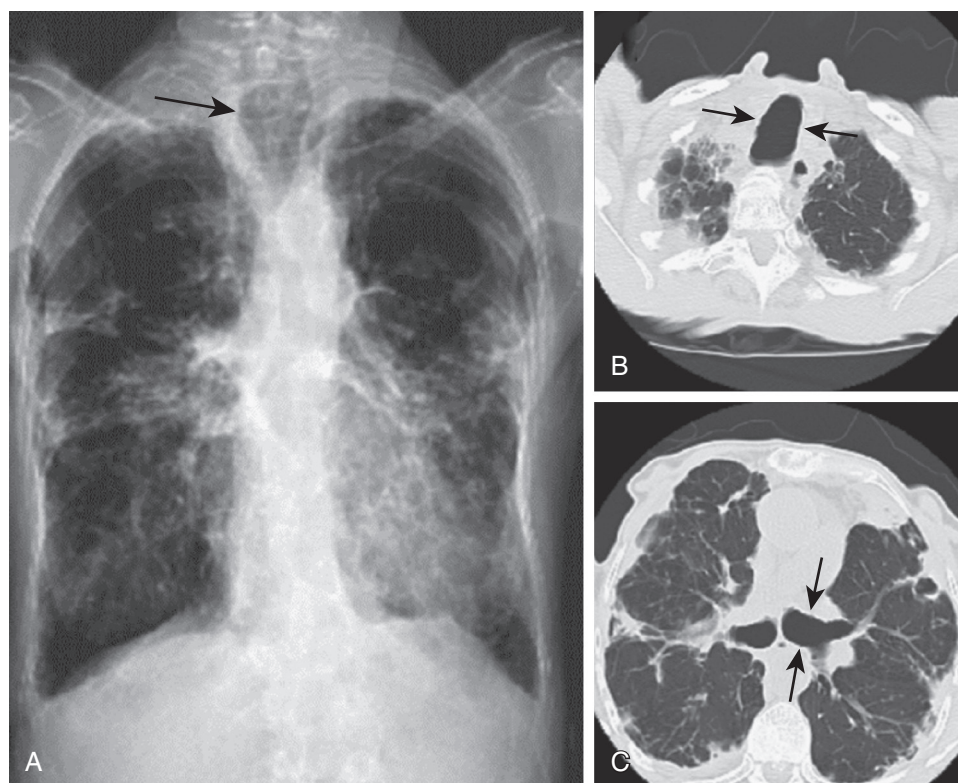


Figure 48-8 Congenital tracheobronchomegaly (Mounier-Kuhn syndrome) with bronchiectasis. This 73-year-old woman has had recurring respiratory infections throughout her adult life, most recently associated with *Mycobacterium avium* complex. **A**, On the posteroanterior view, a massively dilated trachea (arrow) is seen. **B**, The dilated trachea with prominent cartilaginous rings is confirmed on a CT scan (between arrows). **C**, Not only is the trachea enlarged, but the main-stem bronchi are dilated (between arrows). (Courtesy Michael Gotway, MD.)

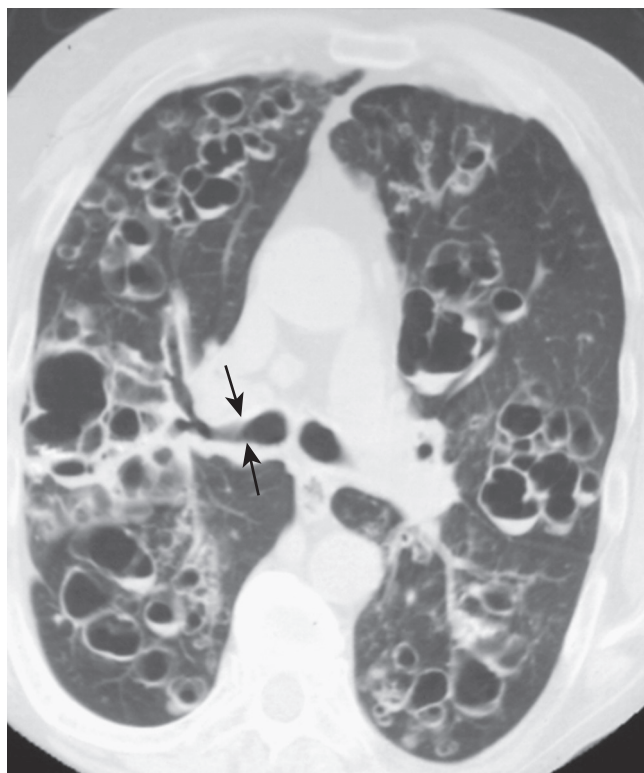


Figure 48-9 Williams-Campbell syndrome. This 50-year-old man had a lifelong history of recurring respiratory infections and productive cough. The airways are massively dilated with collections of respiratory secretions pooling in some of the cystic spaces. Notable are the normal dimensions of the main-stem bronchi (between arrows).

predisposed to proximal bronchomalacia after transplantation due to the combined effects of cartilage deficiency in the main-stem bronchi plus decreased blood supply to the proximal airways due to loss of collateral circulation of the transplanted lung.¹⁰⁷

CONNECTIVE TISSUE ABNORMALITIES

Among the various formally described heritable disorders of the connective tissues, Marfan syndrome has been reported to be associated with bronchiectasis.¹⁰⁸⁻¹¹⁰ Other lung disorders associated with Marfan syndrome include distal acinar emphysema, cystic degeneration, spontaneous pneumothorax, bullae, apical fibrosis, and a congenital pulmonary malformation known as middle lobe hypoplasia.¹¹⁰ In addition to the airway and parenchymal abnormalities, persons with Marfan syndrome may have various other anomalies, including pectus excavatum, pectus carinatum, scoliosis, straight back syndrome, mitral valve prolapse, and aortic insufficiency with dilation of the aortic root. Two of these conditions, scoliosis and pectus excavatum, are also found often in patients with other heritable connective tissue disorders, including Loeys-Dietz syndrome, Shprintzen-Goldberg syndrome, Ehlers-Danlos syndrome, and cutis laxa.¹¹¹⁻¹¹³

This constellation of findings is reminiscent of the prototypic female patients we and others see with bronchiectasis, most commonly in association with chronic NTM lung disease. Based on analogy to these heritable disorders, we

believe that there may be subtle anomalies or polymorphic variants of connective tissue that predispose to bronchiectasis and/or to NTM infection eventually leading to formation of bronchiectasis. Phenotypic findings that are common among these patients include various combinations of scoliosis, straight back syndrome, pectus excavatum or unusually narrowed anteroposterior chest diameter, pectus carinatum, and/or mitral valve prolapse. In 67 consecutive pulmonary NTM patients seen at the NJH between 1985 and 1987, of whom 43 (64%) were women, pectus excavatum and scoliosis were found to be significantly more prevalent in NTM patients compared to contemporary pulmonary tuberculosis patients (27% versus 9% for pectus excavatum and 52% versus 13% for scoliosis).¹¹⁴ Among a series of 63 patients reported from the National Institutes of Health with NTM lung disease, predominantly manifested by bronchiectasis, careful morphometric studies were performed.⁵⁵ Compared with the women in the National Health and Nutrition Examination Survey database, patients with NTM lung disease were found to be significantly taller and more slender. In addition, pectus excavatum, scoliosis, and mitral valve prolapse were found in excess of expected rates. However, the patients did not have dolichostenomelia (a long, narrow frame), hyperdistensible joints, arachnodactyly, or overt aortic root involvement to suggest classic Marfan syndrome.⁵⁵ Neither do they have the cutaneous or joint abnormalities typical of Ehlers-Danlos syndrome.

A large, prospective study of 103 pulmonary NTM patients (all of whom had bronchiectasis) and 101 uninfected controls well matched for age, sex, and race found that NTM patients were significantly taller, had significantly lower mean body mass index and percent body fat, and had significantly higher prevalence of scoliosis and pectus excavatum than controls.¹¹⁵ In addition, following stimulation of whole blood with various agonists, including live *M. intracellulare*, pulmonary NTM patients had significantly lower mean IFN- γ level than controls but similar levels of other proinflammatory cytokines and chemokines, including TNF- α , IL-1 β , IL-6, IL-8, IL-12, IL-18, and *regulated on activation, normal T-cell expressed and secreted* (RANTES).¹¹⁵ In a follow-up study, unstimulated and *M. intracellulare*-stimulated blood from 20 pulmonary NTM patients and 20 controls were randomly selected from the same two original cohorts and measured for *transforming growth factor- β* (TGF- β).¹¹⁶ In contrast to that seen with IFN- γ , the mean *M. intracellulare*-stimulated TGF- β level was significantly greater in pulmonary NTM patients than controls.¹¹⁶ Whether this reduced production of the host-protective cytokine IFN- γ and/or increased production of the immunosuppressive cytokine TGF- β plays a role in causing NTM lung disease remains to be determined.

Because the thoracic abnormalities such as pectus excavatum, scoliosis, straight back syndrome, and mitral valve prolapse that have been described in a substantial number of patients with NTM lung disease are some of the classic features of Marfan syndrome, we reasoned that perhaps some NTM patients, although not meeting clinical criteria for classic Marfan syndrome, possess a subclinical variant of Marfan syndrome.^{55,114,117,118} Marfan syndrome is caused by mutations of the fibrillin 1 (*FBN1*) gene, with more than 600 different mutations of *FBN1* identified. Because some

mutations may result in a milder Marfan syndrome phenotype,¹¹⁸ we posit that some who possess a lesser variant of *FBN1* gene mutation do not have overt Marfan syndrome but remain at increased risk for NTM lung disease.

Our hypothesis does not identify the “prime factor” in the pathogenesis of the bronchiectasis: do the airways dilate because of an intrinsic structural defect, is there an immune defect that increases the risks for infections that set in motion the coughing and inflammation that lead to bronchiectasis, or are both factors present? The first supposition is that there is a propensity for bronchiectasis due to “weakness” of the connective tissue of the bronchial tree. The observation that fibrillin-1 is part of the extracellular matrix and that bronchiectasis and cystic changes seen in Marfan syndrome may develop without overt NTM lung infection suggests the plausibility of intrinsic vulnerability of the bronchial wall to bronchiectasis. Furthermore, it is also of great interest that Marfan syndrome has been linked to middle lobe hypoplasia¹¹⁰ because the right middle lobe is arguably the most commonly affected lobe in NTM-associated bronchiectasis. The second supposition is supported by the fact that the morphologic anomalies seen with Marfan syndrome have been traced to increased localized production of TGF- β , a cytokine that increases susceptibility to mycobacteria.¹¹⁹⁻¹²² Interestingly, some of the other heritable conditions with overlapping physical features to Marfan syndrome, despite having mutations in entirely different genes—*FBN1* in Marfan syndrome, *TGFBR1* and *TGFBR2* genes in Loey-Dietz syndrome, and *SKI* gene in Shprintzen-Goldberg syndrome—all have in common an increase in TGF- β signaling.¹²³

Could slenderness itself—independent of malnutrition or any underlying illness—predispose individuals to mycobacterial infections? One intriguing hypothesis for the increased susceptibility to mycobacterial infections in thin individuals is that the susceptibility is due to a relative deficiency of leptin, which is normally produced by fat cells. A study of over 100 pulmonary NTM patients and a similar number of uninfected controls demonstrated that the normal direct relationship between body fat and leptin—and the expected inverse relationship between body fat and adiponectin—were preserved in the control subjects, but both relationships were lost in pulmonary NTM patients.¹¹⁵ Experimental corroboration for the leptin hypothesis comes from studies showing that leptin-deficient (Ob/Ob) mice are more susceptible to *Mycobacterium tuberculosis*¹²⁴ and *M. abscessus* lung infections.¹²⁵

In view of the preponderance of females in recent series with bronchiectasis associated with MAC, two theories have been proposed. “Lady Windermere’s syndrome,” named after a character in a novel by Oscar Wilde, posits that women—in the effort to be demure or elegant—voluntarily suppress their cough, leading to accumulation of secretions and chronic infections.¹²⁶ However, it has been our observation that these patients cough frequently.^{127,128} Rather than voluntary suppression, it seems more plausible that their coughing may be ineffectual due to airway collapsibility, which interrupts movement of secretions out of the bronchial tree.

An alternative proposition came from Japan, where they, too, have noted a particular female vulnerability to

bronchiectasis with MAC, largely among elderly, postmenopausal women.¹²⁹ Tsuyuguchi and associates¹²⁹ demonstrated that among female mice, oophorectomy led to higher mycobacterial loads in the lungs and spleen following intravenous challenge with MAC. Furthermore, estrogen repletion normalized the bacillary burden, and ex vivo macrophages supplemented by estrogens were more competent at limiting mycobacterial growth.

However, neither the putative relationship to connective tissue disorders nor the alleged role of estrogen deficiency can explain the high prevalence of females in recent reports of MAC-related bronchiectasis. In these series, 80% to 95% of patients described have been women.^{8,9,15} Certainly, this might reflect referral or reporting bias. Furthermore, we cannot exclude the possibility of sex-associated effects on connective tissue strength/integrity or cellular immunity.

An additional remarkable element of the reported cases of MAC-associated bronchiectasis is the strong preponderance of whites. White females constitute 80% to 95% in recent series, including those compiled in communities/areas with large African American, Hispanic, or other minority populations.^{8,9,15} Again, given the potential for referral, reporting, or ascertainment biases, we cannot be sure of the validity of these observations. However, among the specialists with whom we correspond, this is a strongly held perception. The relatively higher prevalences of CF and AAT anomalies in European-derived populations may partially, but not wholly, explain this apparent imbalance in the white population but would not explain the preponderance of white women in some series.

Fowler and coworkers¹³⁰ compared ciliary beat frequency in epithelial cells obtained from the nasal turbinates of patients with pulmonary NTM disease, PCD, CF, and in healthy normal subjects. Interestingly, they found reduced basal ciliary beat frequency (≈ 2 beats/sec less than normal subjects) and less-than-expected increases in ciliary beat frequency upon stimulation of the epithelial cells with various Toll-like receptor agonists. In contrast, a normal increase in ciliary beat frequency was seen with Toll-like receptor 4 agonist (lipopolysaccharide) stimulation, suggesting that the ciliary defect may be more functional than anatomic. Nasal NO level was also decreased in the pulmonary NTM patients compared to normal subjects; significantly, addition of either a chemical NO donor or a cyclic 3',5'-guanosine monophosphate-specific phosphodiesterase type 5 inhibitor (sildenafil) to the respiratory epithelial cell of pulmonary NTM patients restored their ciliary beat frequency.

CONGENITAL AND DEVELOPMENTAL ANOMALIES

Conditions such as sequestration, agenesis, hypoplasia, and atresia may primarily cause bronchiectasis or may predispose to infections that secondarily cause bronchiectasis. Sequestrations presumably develop because of accessory primordial lung buds, which may be invested within normal lung tissue (intralobar) or external to the normal lungs (extralobar). Sequestrations may or may not connect with the bronchial tree and often derive their blood supply directly from the aorta. Clinically, they most commonly

present with recurrent and/or chronic lower respiratory tract infections beginning in the second or third decade of life. Radiographically, they usually appear as irregular, peculiar densities abutting the diaphragm in the posterior basal regions. Unilateral hyperlucent lung (Swyer-James-MacLeod syndrome) is characterized by unilateral bronchiolitis leading to hyperinflation. In some cases, bronchiectasis is present. The etiology and pathogenesis of this rare disorder are uncertain but may involve developmental or acquired disturbances of the bronchial tree.

IDIOPATHIC INFLAMMATORY DISORDERS

There are a wide array of conditions associated with bronchiectasis that might be included under the rubric of idiopathic inflammatory disorders. They are all systemic illnesses that variably involve the lungs and, in such cases, may or may not result in bronchiectasis.

Sarcoidosis is by far the most common of these disorders. (See Chapter 66 for a comprehensive review.) Broadly, sarcoidosis may involve the airways by several fundamental mechanisms: diffuse parenchymal scarring resulting in traction (eFig. 48-6) and airway distortion, endobronchial granulomatous inflammation including stricture with post-stenotic infection, or compression secondary to hypertrophic peribronchial lymphadenopathy.¹³¹

Rheumatoid arthritis (RA) may entail a variety of pulmonary manifestations. In two early series, bronchiectasis was seen in 3.2%¹³² and 5.2%¹³³ of referral populations of RA patients. More recently, bronchiectasis has been described in considerably higher percentages of RA patients undergoing HRCT scanning: 20% to 35%¹³⁴; surely these studies were skewed by selecting patients with respiratory problems to undergo CT scanning. However, bronchiectasis was seen in 8% of RA patients without respiratory symptoms.¹³⁵ Notably, the majority of the patients in the previously discussed series did not have RA-associated interstitial fibrosis as a presumed cause of the bronchiectasis. Potential causal mechanisms include increased propensity for infections, either intrinsic to RA or secondary to steroid or cytotoxic therapy. Sjögren syndrome in association with RA has also been proposed as a risk factor, but the evidence is inconsistent.¹³⁴ Clinically, it should be noted that the presence of bronchiectasis in RA patients was associated with an unfavorable prognosis in one series.¹³⁶

Ankylosing spondylitis has been classically associated with upper lung zone fibrocystic degeneration (see Fig. 98-16) and ankylosed fusion of the junctions of the ribs and vertebrae, resulting in restricted ventilation. However, in a large series from the Mayo Clinic, pulmonary involvement was described in only 1.2% of the patients (eFig. 48-7).¹³⁷ Bronchiectasis independent of apical fibrocystic disease has been seen in a small series from the United Kingdom.¹³⁸ Ankylosing spondylitis was reported in association with MAC in an early series from the NJH.¹³⁹

Systemic lupus erythematosus may involve an assortment of pulmonary complications, including those intrinsic to systemic lupus erythematosus and others related iatrogenically (see Chapter 65). Bronchiectasis, as such, was described in 21% of systemic lupus erythematosus patients studied with HRCT in one series¹⁴⁰; factors related to bronchiectasis were not well studied. As with RA,

the presence of Sjögren syndrome may be a comorbid element.

Sjögren syndrome, keratoconjunctivitis sicca, and xerostomia (dry eyes and mouth), may exist in the primary form or in association with other collagen vascular diseases such as RA or systemic lupus erythematosus. Pulmonary complications of Sjögren's syndrome include lymphocytic interstitial pneumonia, lymphoma or pseudolymphoma, and/or pulmonary hypertension (see Chapter 65). Bronchiectasis has also been noted.¹⁴¹⁻¹⁴³ It is reasoned that lymphocytic inflammation results in impaired function of mucous glands, in turn resulting in decreased volumes and increased viscosity of mucus. This leads to airway obstruction, poor clearance, and chronic infection. There have not been large surveys employing the CT lung scan in Sjögren syndrome patients to quantify the risk for bronchiectasis. However, we have recently seen several elderly female patients with primary Sjögren syndrome in whom bronchiectasis was prominent.

Inflammatory bowel disease has been related directly to bronchiectasis.¹⁴⁴ Inflammatory bowel disease-associated bronchiectasis appears to be more common with ulcerative colitis than Crohn disease.¹⁴⁵ In the majority of cases, the inflammatory bowel disease antedates the lung manifestations, but in some cases the pulmonary symptoms may herald the inflammatory bowel disease. One unique observation of ulcerative colitis-associated bronchiectasis is that it may develop after therapeutic colectomy.¹⁴⁶ Proposed pathogenic relationships include a cryptogenic infection that incites both airway and intestinal inflammation, common epithelial targets of autoimmunity, or sensitizing agents that are inhaled and/or ingested.

Relapsing polychondritis is identified essentially as progressive inflammation, weakness, and deformity of cartilaginous structures, including the ears, nose, larynx, and tracheobronchial tree, typically associated with nonerosive polyarthritis. In addition, there may be inflammatory and/or functional disturbances of the eyes, auditory/vestibular components of the ears, and aorta (vasculitis with aneurysm). Respiratory involvement is a common clinical element of relapsing polychondritis (tracheal and bronchial cartilage inflammation, resulting airway collapse and airflow limitation) (eFig. 48-8) and a major cause of mortality. Bronchiectasis in such patients may be due to primary bronchial damage and/or recurrent infection.¹⁴⁷

ASPIRATION/INHALATION ACCIDENTS

Spillage of foreign matter into the airways may result in bronchiectasis. There are two fairly distinct scenarios in which such matter might be aspirated into the lungs and cause sufficient damage to result in chronic deformity of the airways. One is the direct spillage of secretions from the oropharynx, infamous for containing a plethora of microorganisms, including microaerophilic and anaerobic bacteria, which can produce necrotizing pneumonia. The other is introduction of materials refluxed from the esophagus and/or stomach, which, in addition to the microorganisms noted earlier, contain food particles, hydrochloric acid, biliary or pancreatic secretions, and microbes indigenous to the gut, including *Helicobacter pylori*.¹⁴⁸

Laryngeal protective functions are imperfect, and “micro-aspiration” is common. Thus we might presume that aspiration leading to lower respiratory tract infections involves greater-than-usual volumes and/or more noxious contents. Also, it is reasonable to posit that once the airways have been damaged, a lesser inoculum can have more substantial clinical effects, a variant of the “vicious circle” theory.

Many factors influence the likelihood/frequency of aspiration. They include (1) depressed sensorium (trauma, alcohol or drug abuse, postictal confusion state, general anesthesia); (2) altered brain-stem function (following cerebrovascular accident, after polio, primary neurologic diseases such as multiple sclerosis, amyotrophic lateral sclerosis, or syringomyelia); (3) altered laryngeal structure/function (after surgery following irradiation); (4) esophageal disorders (dysmotility, obstruction by tumors or strictures, muscular dystrophy, achalasia, tracheoesophageal fistulas, or lower esophageal sphincter incompetence); and (5) gastric dysfunction (dysmotility or outlet obstruction).

Although all of these elements may contribute to the risk for infection (and bronchiectasis), it seems likely that gastroesophageal reflux is the most common factor. Among a cohort of bronchiectasis patients noted previously from the NJH, approximately three fourths of them had demonstrated abnormalities of esophageal morphologic features (dilation and thickening), function (dysmotility), anatomy (hiatal herniation), or competence (overt reflux).¹⁴⁹ Indeed, the frequency of esophageal disturbances was so high that one might question whether the esophageal findings were the cause of recurring infections/bronchiectasis or, in some cases, an effect. In the latter regard, it is important to note that among series of patients with chronic asthma and idiopathic pulmonary fibrosis, the incidence of demonstrated esophageal dysfunction ranged from 80% to 95%.^{150,151} It is plausible that labored breathing with wide disparities between intra-abdominal and intrathoracic pressure and/or chronic coughing, which stresses and dilates the diaphragmatic ring, might disrupt the lower esophageal sphincter and subject the esophagus to distending forces.¹⁵² An additional factor that could contribute to gastroesophageal reflux disease is the medications employed for these pulmonary disorders, including anticholinergics, β_2 -agonists, theophylline, and corticosteroids, all of which impair lower esophageal sphincter function,¹⁵³ and broad-spectrum antibiotics, which alter gastroesophageal flora.

In any case, clinicians should be alert to the potential of gastroesophageal reflux disease/aspiration as having a primary or contributing role in the development of bronchiectasis. For those suspected of disordered deglutition, tailored hypopharyngography employing contrast materials of varying consistency may identify unsuspected aspiration. It is important to note that some patients spill contrast material into their trachea without any awareness or coughing. Such studies may be performed with a speech therapist, who can also aid patients with safer techniques for eating, drinking, and swallowing.

Impaired esophageal motility may be suggested on CT scans of the lungs in which the esophagus is grossly dilated, there is excessive air present along the course of the esophagus, or the walls of the esophagus are thickened. Impaired motility may often be demonstrated on a simple barium swallow. The extent of impaired contractility may be

measured by esophageal manometry; this is critical if reconstitution of the lower esophageal sphincter is contemplated. Demonstrating actual reflux may be problematic. If gross reflux is demonstrated on a routine study, it is sufficient for a presumptive diagnosis. However, if symptoms or other clinical features suggest gastroesophageal reflux disease and the upper gastrointestinal series has negative results, an 18- to 24-hour pH probe with or without measurement of impedance may both identify and quantify reflux episodes.¹⁵⁰ Nonacid reflux may result in chronic cough and even lung injury.¹⁵⁴ Among the implications of these findings is that acid-inhibition measures may not be sufficient to protect the airways. For individuals with evidence of recurrent aspiration, elevation of the head of the bed should be done routinely.

Toxic inhalation or thermal injury may also be associated with bronchiectasis. Acute and chronic inflammation of the tracheobronchial tree, bronchiolitis, bronchiolitis obliterans, and diffuse alveolar damage may be a consequence of exposure to toxic metal fumes (e.g., aluminum, cadmium, chromium, nickel) or toxic gases (e.g., ammonia, chlorine, phosgene, sulfur dioxide) (see Chapter 75). In severe cases, bronchiectasis may ensue because of either infectious complications of the exposure, denuding of the ciliated epithelium, or progressive fibrosis. Similarly, chronic airway damage and bronchiectasis may evolve following thermal or smoke injury.

POSTOBSTRUCTIVE DISORDERS

Foreign bodies may be aspirated into the airways in association with infants and children putting foreign objects in their mouths, choking events while eating, trauma, or loss of consciousness, including seizures. In some cases the obstructing object may be radiopaque (teeth, bone, or metal objects), but in most instances the obstructing material (e.g., peanuts, vegetables) is not discernible by radiographic study. Tumors, benign or malignant, may also result in airway obstruction, poor drainage, recurrent/chronic infection, and bronchiectasis. The more common tumor types include bronchogenic carcinomas (particularly the squamous cell variety), carcinoid tumors (eFig. 48-9), and papillomas. Extrinsic airway compression due most often to hypertrophic lymphadenitis from granulomatous diseases such as sarcoidosis or infections, including tuberculosis or histoplasmosis, may severely narrow or even occlude large airways. In patients with “focal” bronchiectasis (particularly those with disease limited to only one region, one segment, one lobe [see eFig. 48-9], or even one lung), bronchoscopic examination to exclude an obstructing lesion should be performed early if other causes are not evident.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

In acute or subacute *allergic bronchopulmonary aspergillosis* (or other mycoses) (ABPA/M), patients develop mucoid plugs in the medium-sized bronchi. The inflammation and distention typically results in thin-walled bronchiectasis of the central airways (Fig. 48-10; see Fig. 48-3). Central bronchiectasis, often with mucoid impaction, is characteristic of ABPA, and occasionally the mucoid impaction may

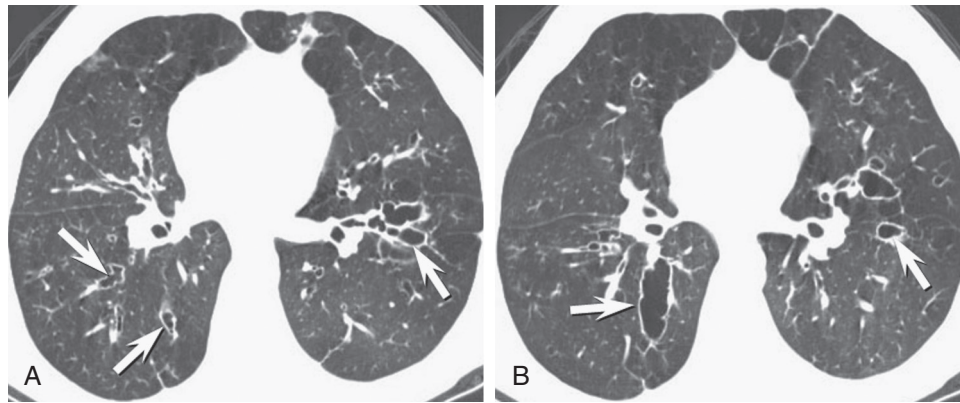


Figure 48-10 Bronchiectasis: allergic bronchopulmonary aspergillosis. **A** and **B**, Axial chest CT shows central bronchiectasis (arrows), typical of allergic bronchopulmonary aspergillosis. (Courtesy Michael Gotway, MD.)

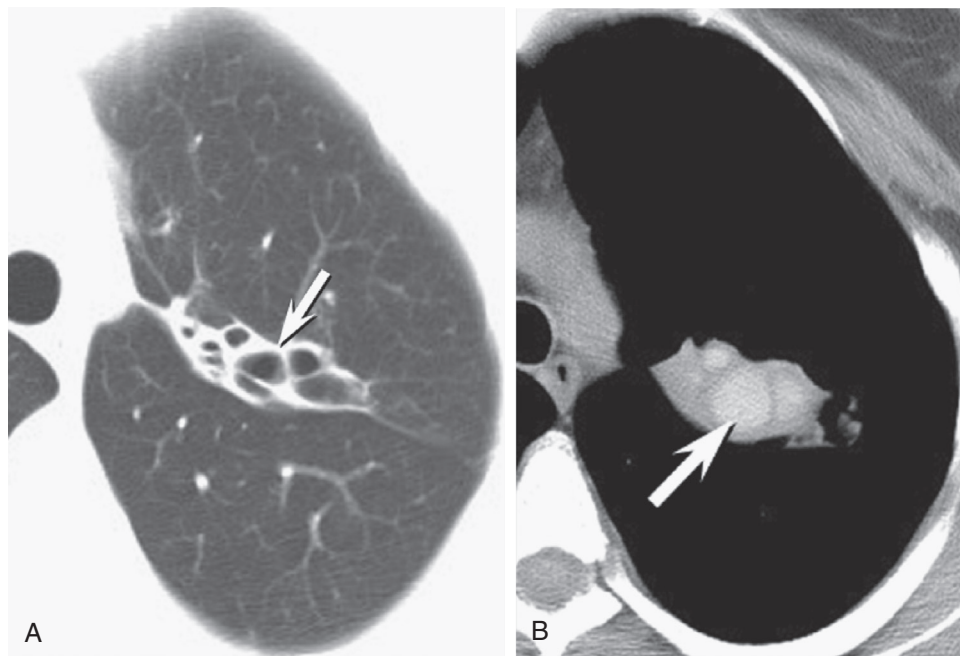


Figure 48-11 Allergic bronchopulmonary aspergillosis with bronchiectasis and high-attenuation mucous impaction. **A**, Axial chest CT displayed in lung windows shows focal left upper lobe bronchiectasis (arrow). **B**, Axial chest CT several years following **A**, displayed in soft tissue windows, shows new consolidation surrounding high-attenuation mucous impaction (arrow) in the region of preexisting bronchiectasis. High-attenuation mucus impaction is characteristic of allergic bronchopulmonary aspergillosis owing to the organism's ability to fix metallic ions. (Courtesy Michael Gotway, MD.)

show high attenuation, reflecting the organism's ability to fix calcium salts, iron, and manganese (Fig. 48-11). Although ABPA/M typically is seen in the setting of recurrent/refractory (steroid-dependent) asthma, clinicians should be aware that these episodes may also include fever, malaise, pleuritic chest pain, and cough productive of purulent secretions. Such episodes may be confused with pneumonia, acute bronchitis, and/or exacerbations of simple bronchiectasis, especially if the asthmatic component is absent or minimal. The picture may be particularly obscure if the ABPA/M is present in individuals with CF, a disorder in which ABPA/M is relatively more common. Features mindful of ABPA/M include characteristic findings on CT scanning, eosinophilia, elevated IgE levels, and dramatic responses to corticosteroids.

The other pathway to bronchiectasis is in the setting of long-standing, inadequately controlled ABPA/M. In such cases, extensive fibrosis and airway distortion may evolve because of uncontrolled inflammation. In these cases the patients may acquire secondary airway pathogens including *P. aeruginosa* or other gram-negative bacilli as well as NTM. In these “burned-out” cases, the patients may not demonstrate asthma, eosinophilia, or elevated levels of IgE.

IDIOPATHIC BRONCHIECTASIS

Depending on the extent of evaluation and perhaps referral bias, “idiopathic” bronchiectasis, for which no known predisposition is identified, is estimated to account for 25% to 50% of cases.^{1,155,156} Although the diagnosis of idiopathic

bronchiectasis can be made after known causes of bronchiectasis are effectively excluded, it often has a characteristic phenotype of bilateral lower lobe bronchiectasis and chronic rhinosinusitis.¹ Genotyping studies of class I and class II major histocompatibility complex molecules indicated that allelic polymorphism for *human leukocyte antigen* (HLA)-B (HLA-B5 and HLA-B52), HLA-C (HLA-Cw*03 and especially HLA-C group 1 homozygosity), and HLA-DR/DQ (HLA-DR1/DQ5) are statistically associated with idiopathic bronchiectasis.¹⁵⁷⁻¹⁶⁰ Because NK cells use their “killer cell immunoglobulin-like receptors” to recognize abnormal HLA-C molecules on the surfaces of infected cells, genotypic analysis of HLA-C–killer cell immunoglobulin-like receptor combinations predicted the possibility of increased NK cell activation in the pathogenesis of idiopathic bronchiectasis.¹⁵⁷ However, to the best of our knowledge, functional studies to confirm excessive NK cell activity in patients with idiopathic bronchiectasis have not been done. Nevertheless, this hypothesis is supported by the presence of bronchiectasis in patients with the transporter-for-antigen-presentation deficiency syndrome, a genetic disorder with impaired HLA class I expression and dysregulated NK, $\gamma\delta$ cytotoxic T cell, and CD8⁺ T-cell function. In this disorder the defective HLA class I expression results in increased NK and $\gamma\delta$ T-cell activities because HLA class I normally serves as an inhibitory ligand for these cell types; on the other hand, abnormal HLA class I expression reduced CD8⁺ T-cell function.¹⁶¹

MISCELLANEOUS

There are numerous other causes of bronchiectasis, including such diverse entities as HIV infection/*acquired immunodeficiency syndrome* (AIDS), yellow nail syndrome, or radiation therapy injury.

Among persons with AIDS, bronchiectasis has been identified in a significant proportion of those undergoing CT scans, including children.^{162,163} Obviously this is skewed by the selection of those with respiratory problems for imaging. Presumably the pathogenesis of the bronchiectasis involves severe, chronic, and recurrent infections with a variety of opportunistic pathogens. An additional element that has not been fully addressed is the potential impact of oxidative damage associated with infection or other stressors on the AAT system.^{164,165} Impairment of AAT function may contribute to the accelerated lung damage, including bronchiectasis, in persons with AIDS.^{166,167}

Yellow nail syndrome is an uncommon disorder marked by the triad of yellow, thick, dystrophic nails; chronic lymphedema of the face, hands, and lower extremities; and pleural effusions.¹⁶⁸ Females are more often involved than males; the median age of onset is 40 years, with cases ranging from infancy to the seventh decade. The most prominent pulmonary finding is bilateral exudative pleural effusions.¹⁶⁹ Recurrent sinusitis and lower respiratory tract infections are common.¹⁷⁰ Bronchiectasis presumably evolves because of chronic infection. Contributing factors may entail abnormal lymphatic structure, increased vascular permeability, deficient immunoglobulin production, and/or ciliary dysfunction.

Radiation therapy, typically delivered for carcinoma of the breast or mediastinal tumors including lymphomas,

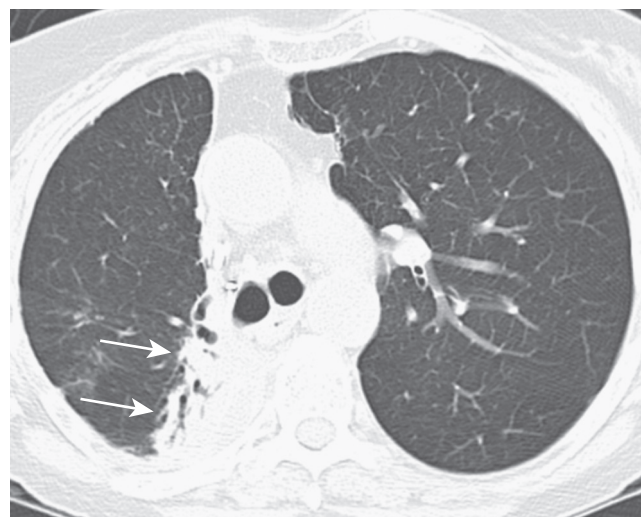


Figure 48-12 Bronchiectasis in a field of therapeutic x-irradiation. This 68-year-old woman had been diagnosed with a non-small cell carcinoma of the lung. She received radiation therapy to the right hilar region approximately 18 months previously. Her CT scan shows dense fibrosis and bronchiectasis in the radiation field (arrows). Inferior to this process she had a necrotic cavitary process associated with *Mycobacterium avium* complex infection.

may result in profound damage to the central airways. This reaction is not part of the postirradiation bronchiolitis obliterans syndrome but a distinctive condition marked by focal damage to the cartilage and mucosa of the airways leading to patulous distention and irregularities of the major bronchi in the field of irradiation. In our experience, bronchiectasis secondary to radiation therapy for neoplasms has become less common in the recent era when the control of dosage and field has become more refined. In some cases this condition may be recognized by lung parenchymal scarring in the field of irradiation (Fig. 48-12).

DIAGNOSIS

In the great majority of cases, bronchiectasis is recognized in the context of chronic or recurring lower respiratory tract infections (deemed to be “bronchitis” or “pneumonia”) over many months or years. Some bronchiectasis patients in whom wheezing is a prominent element may have been identified and treated as “asthmatic patients” for many years. Occasionally patients come to attention following an episode of hemoptysis. Less frequently, bronchiectasis is identified on CT scans done for other considerations.

Although chest radiography can suggest bronchiectasis with “tram tracks” (Fig. 48-13) or multiple ring shadows (Fig. 48-14), CT scanning is the current diagnostic study of choice. The finding on imaging of atelectasis of the right middle lobe and/or lingula (Fig. 48-15) is highly suggestive of coexisting bronchiectasis and should be investigated by CT scanning in patients with persistent abnormalities and chronic symptoms. Classic HRCT scan findings of bronchiectasis include lack of bronchial tapering, bronchi visible in the peripheral 1 cm of the lungs, and increased bronchoarterial ratio, producing the signet ring sign (see Fig. 48-1A).¹⁷¹

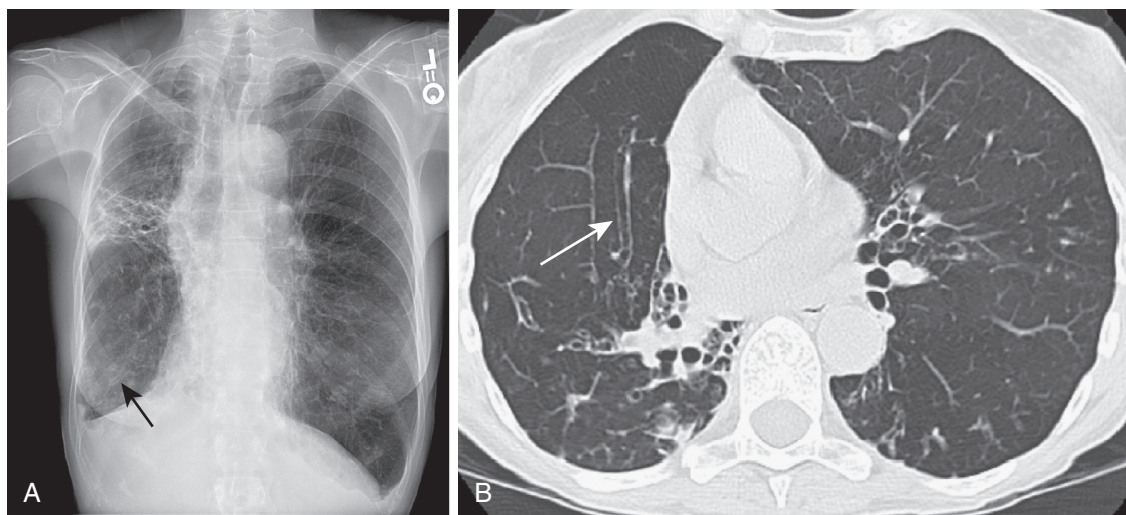


Figure 48-13 “Tram tracks” on the routine chest radiograph in bronchiectasis. **A**, In the right lower lobe are parallel, nontapering shadows, “tram tracks” (arrow), representing bronchiectasis. **B**, The airway is seen as cylindrical bronchiectasis (arrow).

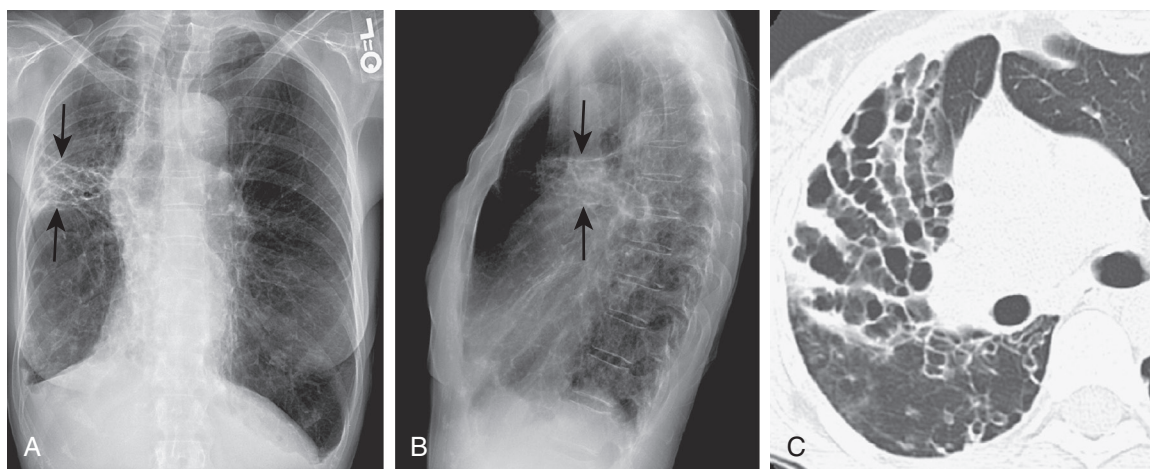


Figure 48-14 Multiple ring shadows on chest radiography in bronchiectasis. **A**, On the posteroanterior view, thin-walled cystic shadowing is seen in the right mid-lung field (between arrows). The trachea and mediastinum are shifted to the right, indicating extensive volume loss. **B**, The lateral view confirms the presence of multiple ring shadows in the mid-zone (between arrows). **C**, CT scan of this 65-year-old white woman indicates severe varicoid bronchiectasis involving her entire right middle lobe and the anterior segment of the right upper lobe.

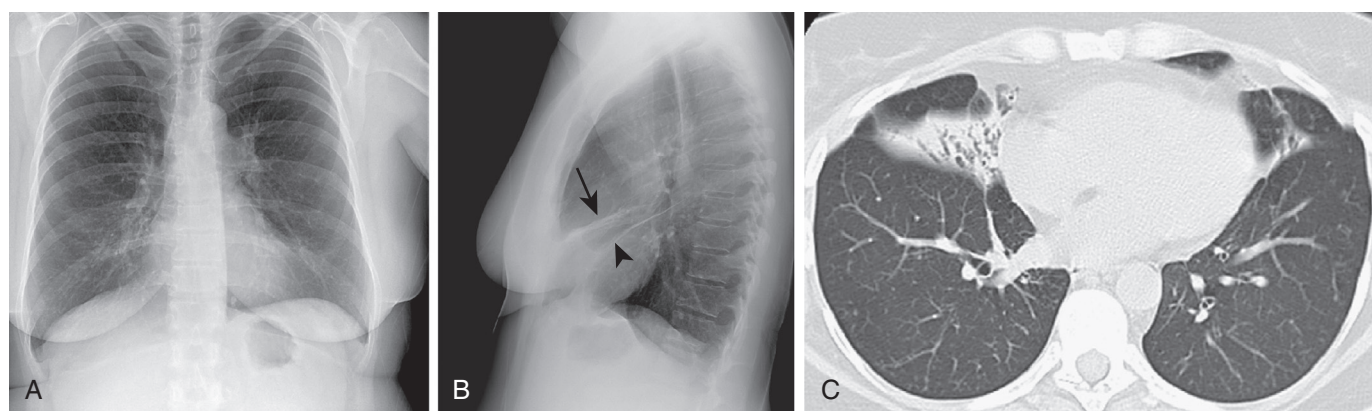


Figure 48-15 Atelectasis and bronchiectasis involving the right middle lobe and lingula on chest radiographs and a CT scan. This 60-year-old woman has had recurring “pneumonia” throughout life. **A**, Posteroanterior view shows subtle effacement of the right heart border and cardiophrenic sulcus as well as a hazy opacity at the left heart border. **B**, On the lateral view, there are two oblique densities representing the atelectatic right middle lobe (arrow) and lingula (arrowhead). **C**, CT scan demonstrates bronchiectasis and atelectasis of the right middle lobe and inferior segment of the lingula.

Once bronchiectasis has been identified on CT scan, what studies should be performed to help direct management and classify the disease? Certainly, a careful family history may be useful in identifying genetic risk factors; however, the family pattern is rarely specific for a particular disorder unless there is a clear story for CF.

Past medical history and review of systems should focus on the various disorders noted in [Table 48-1](#) and delineated earlier in the discussion of associated disorders and predispositions.

Laboratory testing may variously include the studies noted in [Table 48-2](#). These tests need not all be performed on initial assessment but may be done sequentially, with the more probable disorders being checked initially.

MANAGEMENT

The care of patients with bronchiectasis typically involves many layers, which may be partitioned into five broad components: airway hygiene, antimicrobial treatment, anti-inflammatory therapy, surgery, and miscellaneous. These modalities are delineated in [Table 48-3](#). Although most patients with bronchiectasis require various elements of each of these components to enjoy optimal health, there is not a standard formula for treating this disorder. The great majority of recurrently or chronically symptomatic patients benefit from a regular mucus-clearing regimen and periodic antibiotic therapy. For most patients a pragmatic or “trial-and-error” approach is required to determine individual needs, preferences, and tolerances.

It is important to note that most elements described in this section have not been proved to be efficacious by randomized, controlled clinical trials. Thus meta-analyses (such as the Cochrane Database of Systematic Reviews) generally cannot confirm the benefits or disutility of such approaches.¹⁷²⁻¹⁷⁹ Perhaps because bronchiectasis is such a complex mix of varying conditions and/or has been an underappreciated “orphan” disease, a paucity of systematic research has been directed at this very troublesome disorder.

AIRWAY HYGIENE AND HYPEROSMOTIC AGENTS

Airway hygiene consists of nonantibiotic therapies directed toward mobilizing and eliminating inflammatory secretions from the tracheobronchial tree and from the paranasal sinuses. Modern devices to facilitate airway clearance of secretions include the Flutter valve, Acapella valve, and high-frequency chest compression vests (see [Table 48-3](#)). Also included under this rubric are steps to prevent/limit aspiration of oropharyngeal or gastroesophageal contents into the airways.

Hypertonic saline, 7% twice or four times daily, has been shown to accelerate mucus clearance, decrease exacerbations, and improve lung function in CF patients.¹⁸⁰ However, its role in non-CF bronchiectasis remains to be seen. Inhaled dry powder mannitol appears promising in airway clearance in bronchiectatic patients,^{181,182} although more definitive studies are needed.

ANTIMICROBIAL THERAPY

Antimicrobial therapy historically has been the centerpiece of bronchiectasis care. However, there is no clear consensus on the major questions in this area, including whether treatment should be given on a routine, periodic schedule (“rotating”) or an as-needed basis for clinical exacerbations. In a meta-analysis that studied the use of prolonged oral antibiotics for purulent bronchiectasis, sputum volume/purulence was shown to decrease, but there were no significant beneficial effects in regard to rates of exacerbations, lung function, or death.¹⁸³ There are also limited data on the preferability of empirical selection of an antimicrobial agent or treatment guided by species identification and in vitro susceptibility testing. For patients unresponsive to empiric antibiotics or who experience frequent exacerbations, it appears prudent to obtain comprehensive microbiologic cultures (including for NTM and fungal organisms) and to tailor antibiotics based on the type of organism identified and drug susceptibility profile.

Aerosolized antibiotics also appear promising in treating or preventing exacerbations. Addition of inhaled tobramycin to oral ciprofloxacin for *Pseudomonas*-associated exacerbation of non-CF bronchiectasis showed improved microbiologic outcome; however, there was no additional clinical benefit over ciprofloxacin alone perhaps due to approximately threefold greater incidence of bronchospasm in the tobramycin arm.¹⁸⁴ In patients with CF, inhaled tobramycin twice daily given in alternating months decreased the frequency of exacerbations due to *P. aeruginosa*.¹⁸⁵ Even in patients without CF, inhaled tobramycin was found to be efficacious.¹⁸⁶ In a randomized study of nebulized saline versus gentamicin (twice daily for 12 months) of 65 patients with non-CF bronchiectasis, the gentamicin-treated subjects had reduced microbial burden, airway neutrophils, and sputum purulence.¹⁸⁷ Improved exercise capacity, decreased exacerbation frequency, and better health-related quality-of-life measure were also seen in the gentamicin arm with the caveat that patients were not blinded, suggesting an element of bias may have been introduced.¹⁸⁸ Compared to nebulized saline as a control, nebulized gentamicin given prophylactically for 12 months also showed significant reduction in markers of inflammation in both the airways (IL-8, TNF- α , IL-1 β) and the circulation (intercellular adhesion molecule-1 and E-selectin).²⁵

ANTI-INFLAMMATORY THERAPY

The obvious rationale for using the anti-inflammatory agents in bronchiectasis is that they may reduce the inflammatory cascade, with the goals of reducing symptoms and limiting the progression of disease and decline in lung function. Anti-inflammatory agents that have been examined in bronchiectasis include the *nonsteroidal anti-inflammatory drugs* (NSAIDs), inhaled corticosteroids, and intermittent macrolides to exploit their anti-inflammatory and other nonmicrobicidal activities.¹⁸⁹

NSAIDs

Because prostaglandins may play a role in augmenting airway secretions, the NSAIDs—by blocking the cyclooxygenase pathway—have been studied in bronchiectasis.

Table 48-2 Diagnostic Studies for the Classification and Management of Patients with Bronchiectasis

Test	Comments
ROUTINE, UNIVERSAL STUDIES	
High-resolution CT (HRCT) of the lungs	If bronchiectasis is suspected, chest CT, particularly HRCT, is the definitive test to confirm suspected bronchiectasis. HRCT may help detect subtle airway dilation before bronchial walls are grossly thickened. The distribution of the bronchiectasis often helps in the differential diagnosis of the underlying cause of the bronchiectasis. HRCT may also identify esophageal abnormalities.
Pulmonary function tests (PFTs)	For patients with significant bronchiectasis, comprehensive PFTs, including spirometry, bronchodilator responsiveness, lung volumes, and diffusion capacity, are important studies that aid in management and prognosis. PFTs may also provide useful hints regarding predisposing conditions.
Complete blood count	Anemia may reflect effects of chronic infection or blood loss (consider inflammatory bowel disorders). Leukocytosis may mark severity of infection.
ESR, C-reactive protein	Eosinophilia may suggest ABPA/M. Nonspecific markers of inflammation; very high levels may suggest underlying connective tissue disease or vasculitis.
Routine sputum culture	Antibiotic therapy in bronchiectasis should generally be directed against specific pathogens and guided by in vitro susceptibility. The presence of mucoid strains of <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i> may raise suspicions for CF. <i>Stenotrophomonas maltophilia</i> , <i>Alcaligenes xylosoxidans</i> , and <i>Burkholderia cepacia</i> are gram-negative bacilli that may prove problematic pathogens in patients with long-standing bronchiectasis. Isolation of <i>B. cepacia</i> and <i>Helicobacter pylori</i> require special laboratory techniques.
Mycobacterial sputum culture	Environmental mycobacteria such as <i>Mycobacterium avium</i> complex, <i>M. chelonae</i> , and <i>M. abscessus</i> appear to be increasingly common in contemporary bronchiectasis. May be commensal but often are pathogenic.
Fungal sputum culture	Especially in patients with an asthmatic component, the presence of <i>Aspergillus</i> species (or other molds, including <i>Pseudallescheria</i> or <i>Penicillium</i>) may suggest cause.
CT scan of sinuses	Many bronchiectasis patients also suffer chronic rhinosinusitis. The presence of extensive sinus involvement suggests possible CF, immunoglobulin deficiencies, or ciliary disorders. Also, optimal management often entails aggressive sinus care.
SPECIFIC, DIRECTED STUDIES	
Sweat chloride, CF genotyping, and nasal potential differences	For bronchiectasis patients with bilateral disease, sinusitis, and no other identified risk factor, mild variants of CF appear to be relatively common (see text and Chapter 47). Sweat chloride is regarded as the primary screening test for CF, but many adults with CF have borderline or normal results. Nasal potential difference may be useful for identifying CF in equivocal cases (see Chapter 47).
Alpha ₁ -antitrypsin (AAT) levels and phenotype	AAT anomalies appear to be a substantial risk factor for bronchiectasis, especially in white females. Abnormal proteinase inhibitor phenotypes, even heterozygous patterns such as MS, appear to confer risk even with normal levels of AAT (see text). Repletion of AAT may enhance resistance to lower respiratory tract infections.
Immunoglobulin (Ig) levels	Deficiencies of IgG or IgA may promote bronchiectasis; IgG subclass deficiencies may also be a factor. Elevated levels of IgE may suggest ABPA/M or Job syndrome. Hyper-IgM may be associated, as well, with chronic infections.
Ciliary morphologic configuration or function	For individuals with suggestive stories (see text), a nasal ciliated epithelium biopsy with transmission electron microscopy may identify PCD. Other studies, including ex vivo ciliary activity, the saccharin test, or spermatozoa analysis, may aid in this diagnosis (see text).
Nasal nitric oxide (NNO) levels	Patients with documented PCD have significantly lower levels of NNO than normal subjects or patients with CF. ⁹⁴ Although not universally available, such testing may prove highly useful in identifying PCD. Paradoxically, exhaled NO levels have been elevated in bronchiectasis of diverse causes ²¹⁹ except CF.
Barium swallow	Barium swallow may detect disturbed deglutition, esophageal diverticula, obstructing lesions (tumors or strictures), hypomotility, achalasia, hiatal hernias, or lower esophageal sphincter incompetence with reflux. Note that the absence of reflux on a barium swallow does not exclude this problem (see pH probe).
pH probe	For patients suspected of gastroesophageal reflux, an 18- to 24-hour study with a transnasal pH probe may identify, quantitate, and characterize reflux. Obviously medications that inhibit acid production must be stopped before such tests.
Esophageal manometry	For patients being considered for surgical repair of the lower esophageal sphincter, manometry should be performed to determine that the esophagus generates sufficient pressure to propel food and liquids through the tightened sphincter.
Tailored hypopharyngography (TH)	TH is useful in detecting abnormalities of the initial phase of swallowing, deglutition. Persons particularly prone to problems include those with prior strokes, Parkinson disease, bulbar disorders including postpolio syndrome, and those with prior laryngeal or pharyngeal surgery. Even without such risk factors, some patients have gross aspiration without clinical manifestations (choking, coughing).
LESS COMMON, EXOTIC STUDIES	
Collagen vascular disease (CVD) serologic studies	Various CVDs may contribute to the risk for bronchiectasis, including rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus. Thus, for patients with compatible histories or physical findings, assays for rheumatoid factor, anti-CCP antibody, HLA-B27, and ANA may be useful. CVD serologic studies may also suggest the diagnosis of Sjögren syndrome, particularly SSA/Ro and/or SSB/La.
Schirmer test	For patients with histories suggestive of “sicca syndrome” (dry eyes, dry mouth, oral ulcers), positive Schirmer test results may indicate the presence of either primary or secondary (associated with a CVD) Sjögren syndrome.

ABPA/M, allergic bronchopulmonary aspergillosis (or other mycoses); ANA, antinuclear antibody; anti-CCP, anti-cyclic citrullinated peptide; CF, cystic fibrosis; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; PCD, primary ciliary dyskinesia.

Table 48-3 Elements for Management of Patients with Bronchiectasis

Procedure	Comments
AIRWAY HYGIENE	
Tracheobronchial Clearance Techniques	
Mechanical “valve” devices (Flutter, Pep, Acapella, and others)	A variety of these devices are designed to transmit agitating forces to the airways to loosen and help propel tenacious secretions out of the bronchial passages. By retarding expiratory flow, they may also stent the airways open. For optimal results, respiratory therapists should assess individual patients’ needs and abilities and train them in proper usage.
Postural drainage and chest physiotherapy	For patients with dependent-zone bronchiectasis, positioning in the prone head-down, Trendelenburg, and/or lateral decubitus postures may promote local drainage. This might be optimized by pretreatment with mucus-mobilizing methods (see later) and clapping or vibrating techniques while in these postures.
Therapeutic vest	The pneumatically powered jacket produces high-energy and high-frequency inflation and deflation forces throughout the entire thorax. Of proven utility in CF, ²²⁰ the vest may also be useful with bronchiectasis of other causes.
Mucus-Mobilizing Methods	
Inhaled β_2 -agonists and/or anticholinergic bronchodilators	Inhaled β_2 -agonists may accelerate ciliary beat frequency as well as relieve the bronchospasm present in some bronchiectasis patients. Although the anticholinergic bronchodilators pose a theoretical risk for “drying” secretions, most bronchiectasis patients tolerate them and enjoy modest benefits not provided by β_2 -agonists. ^{221,222}
Hypertonic saline or mannitol inhalation	Nebulizing hypertonic solutions, including saline or mannitol, into the airways appears to aid patients in the clearance of tenacious secretions. ²²³ Hypertonic saline is considerably less expensive than dornase alfa (see next).
Dornase alfa (Pulmozyme)	This product hydrolyzes neutrophil DNA, which contributes to the viscosity of inflammatory secretions. Of proven utility in CF patients, ^{224,225} it was not beneficial in non-CF bronchiectasis in one trial. ²²⁶ Extended administration in CF patients has been shown to reduce neutrophilic inflammation of the airways. ²²⁷ However, we have found it useful in some patients with diagnoses other than CF. It is quite expensive and should be used judiciously.
N-Acetylcysteine (Mucomyst)	Also used primarily in CF patients, it has been generally supplanted by dornase alfa. ²²⁰ Its side effects include airway irritation when used in high concentrations. Given orally in Europe, this approach has not been proved efficacious, nor is it approved in the United States.
Anti-inflammatory Airway Management	
Systemic steroids	Mucosal edema and the production of inflammatory secretions may be partially alleviated by corticosteroids. Randomized, controlled trials in young patients with CF have shown improvements in clinical and physiologic parameters with extended courses of alternate-day steroids. ^{228,229} (See Chapter 47 for details.) However, there were significant adverse effects, particularly on growth rates in males. ²³⁰ Given these and other deleterious effects of long-term systemic steroids, such treatment arguably should be reserved for refractory cases.
Inhaled corticosteroids (ICS)	To avoid some of the complications of systemic steroids, inhaled treatment is a logical approach. Modest evidence of efficacy has been shown in some but not all trials with CF. ¹⁹⁶ ICS may also improve the airway hyperreactivity common among bronchiectasis patients.
Macrolide antibiotics	In addition to their antimicrobial effects, macrolides have demonstrated host defense–modifying activities that include anti-inflammatory effects. ^{148,231} Azithromycin, an azalide, given over many months has resulted in clinical and physiologic improvement among CF patients infected with <i>Pseudomonas aeruginosa</i> . ²³²⁻²³⁴ Chronic, low-dose erythromycin appears clinically useful in patients with non-CF bronchiectasis. ²¹² These effects must be balanced against the considerable expense and potential for producing drug resistance among bacterial and mycobacterial pathogens common to bronchiectasis. (Patients should be screened for mycobacterial infections before use.)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Among young CF patients, long-term administration of ibuprofen has shown some benefits. ²³⁵ However, these results may not be generalized, and NSAID therapy should be approached cautiously given the potential side effects.
Anti-aspiration Measures	
Anti-GER management	Teaching patients to alter their dietary practices (reduced food and liquid intake in the evening), elevating the head of the bed, or most drastically, providing surgical revision of the LES or hiatal hernia may lessen the risk for recurrent airway soilage.
Improved deglutition	For patients who aspirate on swallowing, changing the consistency of foods or employing maneuvers such as the “chin tuck” may lessen the risk for airway soilage.
Reducing gastric acid	Although lowering gastric acidity with proton pump inhibitors or H_2 -blockers may diminish the symptoms of reflux, it is illogical to think that it should protect against aspiration. Theoretically, lowered acidity of the aspirated matter might result in reduced damage to the lungs; however, it should not be regarded as a lung-protective intervention.

Continued on following page

Table 48-3 Elements for Management of Patients with Bronchiectasis (Continued)

Procedure	Comments
ANTIMICROBIAL THERAPY	
Episodic, targeted antibiotics	Rather than administering “rotating” or “empirical” agents, this approach involves sampling respiratory secretions during clinical exacerbations and employing antimicrobials on the basis of species identification and in vitro susceptibility. Although logically an attractive option, it entails inevitable delays in treatment and may be confounded by the presence of multiple potential pathogens.
Rotating antibiotic therapy	A popular practice, clinicians might treat bronchiectasis patients with a 1 wk/mo cycle of arbitrarily selected antimicrobials such as, for example, amoxicillin, a fluoroquinolone, and a macrolide. There is some evidence of utility for long-term antibiotic therapy ²³⁶ ; however, the potential for selecting for drug-resistant strains is a consideration. Imperfect evidence reported in a recent analysis suggests that patients with chronic <i>P. aeruginosa</i> infection do better with targeted therapy. ²³⁷
Initial empirical followed by targeted antibiotics	This approach offers the advantage of prompt treatment for an exacerbation, followed by a more narrowly focused regimen based on the results of the initial sputum cultures. To be representative, sputum sampling should be done before initiating empirical antimicrobial therapy.
Role of inhaled antibiotics	The model of inhaled tobramycin in controlling pseudomonal infections in CF patients ^{238,239} (see Chapter 47) is an attractive model for non-CF bronchiectasis as well. ²⁴⁰ Certainly, for those patients with chronic or recurrent gram-negative bacillary infections, this approach might be considered. However, our early experience suggests less tolerance of tobramycin in elderly patients.
Therapy for exotic pathogens	Patients may either acquire secondary infections of preexisting bronchiectasis or primarily develop bronchiectasis due to exotic microbes such as environmental mycobacteria or fungi. In such cases, specific therapy may be indicated.
SURGERY	
Resectional surgery	There are no systematic studies of surgical interventions in bronchiectasis. However, anecdotal observations suggest that extirpation of severely damaged lobes may confer considerable benefit. Disease limited to the right middle lobe or lingula may be particularly amenable. ²⁴¹⁻²⁴³ Whether such resections should be done through the lateral thoracotomy or VATS approach is unresolved, although our group strongly prefers the former.
Transplantation	For younger patients with bronchiectasis-associated respiratory insufficiency, the question of transplantation may arise. Based on the model of CF, it is a plausible consideration.
MISCELLANEOUS	
Vaccination against <i>Streptococcus pneumoniae</i> and against influenza	Although not specifically proved in bronchiectasis, this vaccine seems an obvious adjunct. In addition to vaccination, bronchiectasis patients should be considered for antiviral therapy if they develop clinical influenza.
Smoking cessation	A priority for all pulmonary patients.
Alpha ₁ -antitrypsin (AAT) repletion	Among COPD patients receiving AAT repletion, there was a perception of reduced frequency of infectious exacerbations (see text). For bronchiectasis associated with AAT anomalies, repletion might confer protection against recurrent infections.
Oxygen	Patients with bronchiectasis, especially extensive lower lobe disease, may become hypoxemic with exertion or with sleep. Early detection and O ₂ supplementation may improve exercise tolerance and physical conditioning. Nocturnal O ₂ may lessen pulmonary hypertension and delay the appearance of cor pulmonale.
Methylxanthines	Oral theophylline theoretically might augment bronchodilation, enhance mucus clearance, and enhance diaphragmatic contractility. However, the side effects, variable pharmacokinetics including interactions with macrolide antibiotics, and GER-promoting effects make methylxanthines a potential problem for most bronchiectasis patients.
Cromolyn, nedocromil, or leukotriene modifiers	Although these various asthma medications may have some theoretical roles in bronchiectasis, there have been no studies demonstrating efficacy.

CF, cystic fibrosis; GER, gastroesophageal reflux; LES, lower esophageal sphincter; VATS, video-assisted thoracoscopic surgery.

In a double-blind, placebo-controlled study in patients with bronchorrhea due to chronic bronchitis, diffuse panbronchiolitis, and bronchiectasis, inhaled indomethacin significantly decreased the amount of sputum by half as well as the perceived dyspnea.¹⁹⁰ Another mechanism by which indomethacin may help in bronchiectasis is via inhibition of neutrophil chemotaxis and neutrophil degradation of fibronectin, thereby decreasing airway inflammation and purulence.¹⁹¹

In a comprehensive Cochrane Database review of randomized trials of NSAIDs in CF patients, high-dose ibuprofen has been shown to slow the progression of lung disease, especially in children.¹⁹² In contrast, there have been no randomized, controlled trials on the use of NSAIDs in bronchiectatic patients without CF.¹⁹³

Inhaled Corticosteroids

Although some studies show improved symptoms and lung function in CF patients treated with *inhaled corticosteroids* (ICS),^{194,195} others—including a review of clinical trials—have not found ICS to be beneficial.^{196,197} In non-CF bronchiectasis, relatively small studies indicate that ICS provides symptomatic relief (e.g., reduction in dyspnea, cough, and sputum production).¹⁹⁸⁻²⁰¹ High doses of ICS are typically tried in bronchiectasis because of the notion that neutrophils, dominant in bronchiectatic airways, are relatively resistant to the (apoptotic) effects of corticosteroids.²⁰² Although bronchiectatic patients are often treated with β_2 -agonists and ICS based on extrapolation by clinicians of treatment for COPD and asthma, there is limited evidence of their efficacy with bronchiectasis. Martinez-Garcia and

associates²⁰² performed a pilot study comparing high-dose budesonide 800 µg every 12 hours to budesonide 640 µg plus formoterol once daily and found that the combined treatment with the lower dose of ICS resulted in a greater improvement of dyspnea score, health-related quality of life assessment, and reduced ICS-associated side effects such as pharyngeal irritation and dysphonia. Because of the potential risk for pneumonia with ICS use, as has been documented with COPD,²⁰³ it seems prudent to limit the duration of ICS whenever possible, while monitoring closely for worsening respiratory symptoms and function. It is clear that larger studies are needed to determine the benefits and risks of ICS, long-acting β_2 -agonists, or in combination as maintenance treatment or rescue therapy for exacerbations.²⁰⁴

Intermittent Macrolide Therapy

Independent of their antimicrobial properties, macrolide antibiotics hold great promise in inhibiting disease activity in bronchiectasis because of their non-antimicrobial immunomodulatory effects.²⁰⁵ Intermittent macrolide therapy may help in bronchiectasis via different mechanisms, including decreasing chloride diffusion potential gradient across the airway mucosa (resulting in decreased sputum volume), reducing airway levels of the neutrophil chemotactic factor IL-8, inhibiting both neutrophil and *Pseudomonas* migration, suppressing *Pseudomonas* quorum sensing, disrupting the established biofilm layer, and enhancing alveolar macrophage phagocytic ability.^{206,207} Clarithromycin but not amoxicillin or cefaclor was shown to significantly reduce sputum production in patients with chronic bronchitis or bronchiectasis.²⁰⁸ In a study of a small number of patients with bronchiectasis randomized to standard care for 6 months followed by the addition of azithromycin given at a dose of 500 mg twice weekly for 6 months or vice versa, azithromycin significantly decreased the incidence of exacerbations and sputum volume compared with standard care.²⁰⁹ Similar beneficial effects plus improvement in lung function have been shown in various trials using intermittent azithromycin therapy in CF patients chronically infected with *P. aeruginosa* but also in younger CF patients before they have been colonized with *P. aeruginosa*.²¹⁰ In a double-blind study of about 200 CF patients randomized to azithromycin either 250 mg daily or 1200 mg weekly, there were no differences in improvements in lung function, C-reactive protein level, or days hospitalized, although gastrointestinal side effects were more common with weekly therapy.²¹¹ In a double-blind, placebo-controlled trial of approximately 120 patients with non-CF bronchiectasis and a history of frequent pulmonary exacerbations, low-dose erythromycin (400 mg twice daily) for 12 months significantly reduced (1) the number of pulmonary exacerbations overall by roughly one third as well as in those with baseline *P. aeruginosa* airway infection, (2) sputum production, and (3) lung function decline as measured by FEV₁.²¹² However, erythromycin prophylaxis was associated with increased frequency of macrolide-resistant oropharyngeal streptococci.²¹² Two double-blind, placebo-controlled trials of azithromycin 250 mg daily for 12 months or 500 mg thrice weekly

for 6 months resulted in significantly lower rates of exacerbations compared to placebo.^{213,214} In one study, however, there was a nearly threefold increase in macrolide resistance of bacteria in the azithromycin group, as well as significantly higher incidence of abdominal pain and diarrhea, although these gastrointestinal symptoms did not prevent continuation of azithromycin.²¹⁵ In addition to the potential increase in antibiotic resistance in pyogenic bacteria, long-term azithromycin may predispose to drug-resistant NTM infections in patients with bronchiectasis.²¹⁵ In addition, azithromycin has been shown to inhibit autophagy, a normal homeostatic cell process whereby cells recycle nonessential molecules and organelles in times of nutrient deprivation but an increasingly recognized mechanism in the killing of intracellular mycobacteria.²¹⁵ Other potential serious adverse effects of azithromycin include dysrhythmias and cardiac-related deaths, especially in those with underlying risk factors for cardiovascular disease.^{216,216a}

SURGERY

The role of surgery in the management of bronchiectasis is uncertain. No formal systematic studies of the indications and efficacy of resectional surgery have been conducted among patients with bronchiectasis. Traditional indications for resectional surgery have included chronic disabling infection, recurrent infections of intolerable frequency, or irreversible lung damage distal to a foreign body or benign tumor. Life-threatening hemoptysis may also provoke consideration of surgery, although therapeutic bronchial artery embolization may be the initial treatment of choice. A historical adage has been that surgery does not cure bronchiectasis. If true, it is likely due to our evolving understanding that most cases of bronchiectasis are due to innate risk factors that predispose to recurrence. However, surgery may be an appropriate palliative measure in selected cases.

MISCELLANEOUS

Additional measures, such as smoking cessation and vaccination against pneumococcal disease and influenza are appropriate for all patients. Intuitively, these measures seem particularly important for those with bronchiectasis; however, no systematic information is available to confirm their usefulness in this setting. On the other hand, early recognition of exercise and sleep-related hypoxia has demonstrated substantial benefits in regard to morbidity and mortality. As with all individuals, it seems sensible to ensure that patients with bronchiectasis have repleted vitamin D levels because vitamin D has been shown to induce cathelicidin, an antimicrobial peptide.²¹⁷ Recently it was reported that bronchiectasis patients with vitamin D deficiency have more frequent bacterial colonization (especially *P. aeruginosa*), worse airflow, more frequent exacerbations, higher levels of inflammatory markers in sputa, and more rapid decline in lung function over a 3-year follow-up.²¹⁸

Key Points

- Bronchiectasis is defined by the presence of permanent dilation of the medium-to-large bronchi. The main clinical significance of bronchiectasis is recurrent airway infections by bacterial and fungal organisms resulting in chronic cough, sputum, weight loss, and respiratory compromise.
- Most bronchiectasis is due to a combination of host susceptibility factors—which may be overt or covert—and the recurrent infections and the largely neutrophilic inflammatory response that perpetuate the airway injury.
- Whereas localized bronchiectasis is most often due to suboptimally treated bacterial infections, bronchiectasis due to nontuberculous mycobacteria appears increasingly prevalent; bronchiectasis due to nontuberculous mycobacteria is typically seen in postmenopausal women with lingular and right middle lobe involvement but can also be seen in men.
- Bronchiectasis that is more diffuse is generally due to an underlying host disorder such as cystic fibrosis, primary ciliary dyskinesia, Mounier-Kuhn and Williams-Campbell syndromes, common variable immune deficiency, and allergic bronchopulmonary aspergillosis.
- Bronchiectasis has also been associated with extrapulmonary disorders such as ulcerative colitis and collagen vascular diseases. Severe fibrotic lung diseases from any cause may also result in a form of bronchiectasis known as traction bronchiectasis.
- The linchpins in the management of bronchiectasis are the timely institution of empirical antimicrobials to treat the most likely pathogens and diligent airway clearance measures to improve symptoms. For patients unresponsive to empirical antibiotics or those with frequent exacerbations, sputum cultures should be obtained, drug susceptibility determined, and treatment tailored to more objective data. Surgical lung resection should also be considered for patients with severe localized disease that is recalcitrant to medical treatment.

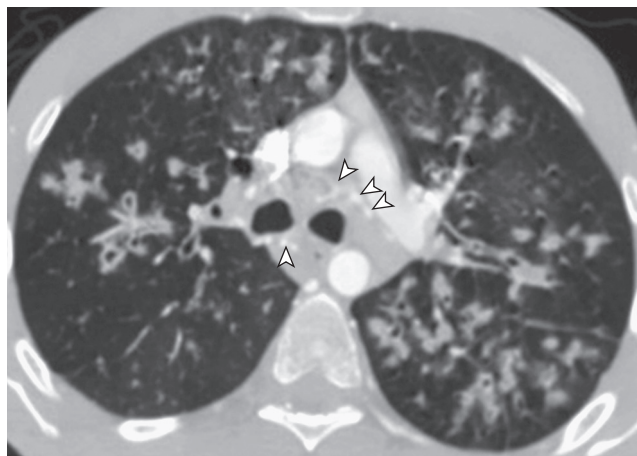
- Anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs, inhaled corticosteroids, and low-dose intermittent macrolides show promise in alleviating symptoms and reducing the rate of disease progression, but definitive recommendations for their use remain to be defined.

Complete reference list available at *ExpertConsult*.

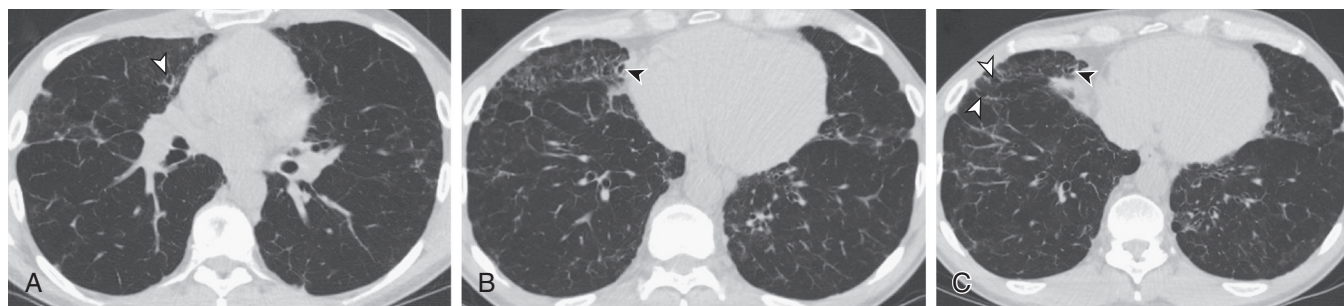
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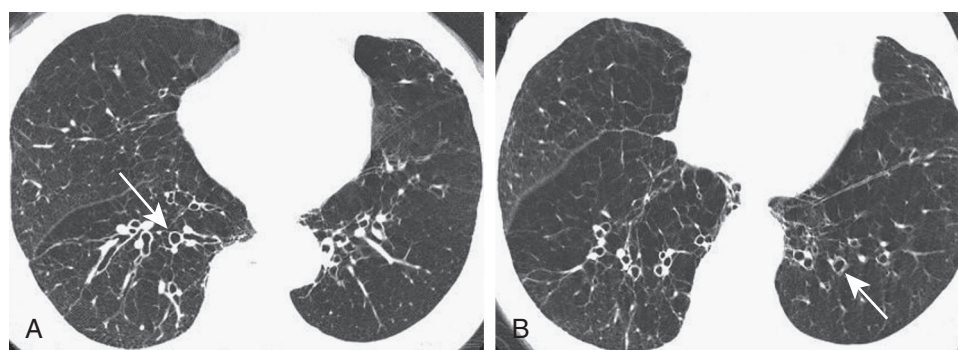
eFIGURE IMAGE GALLERY



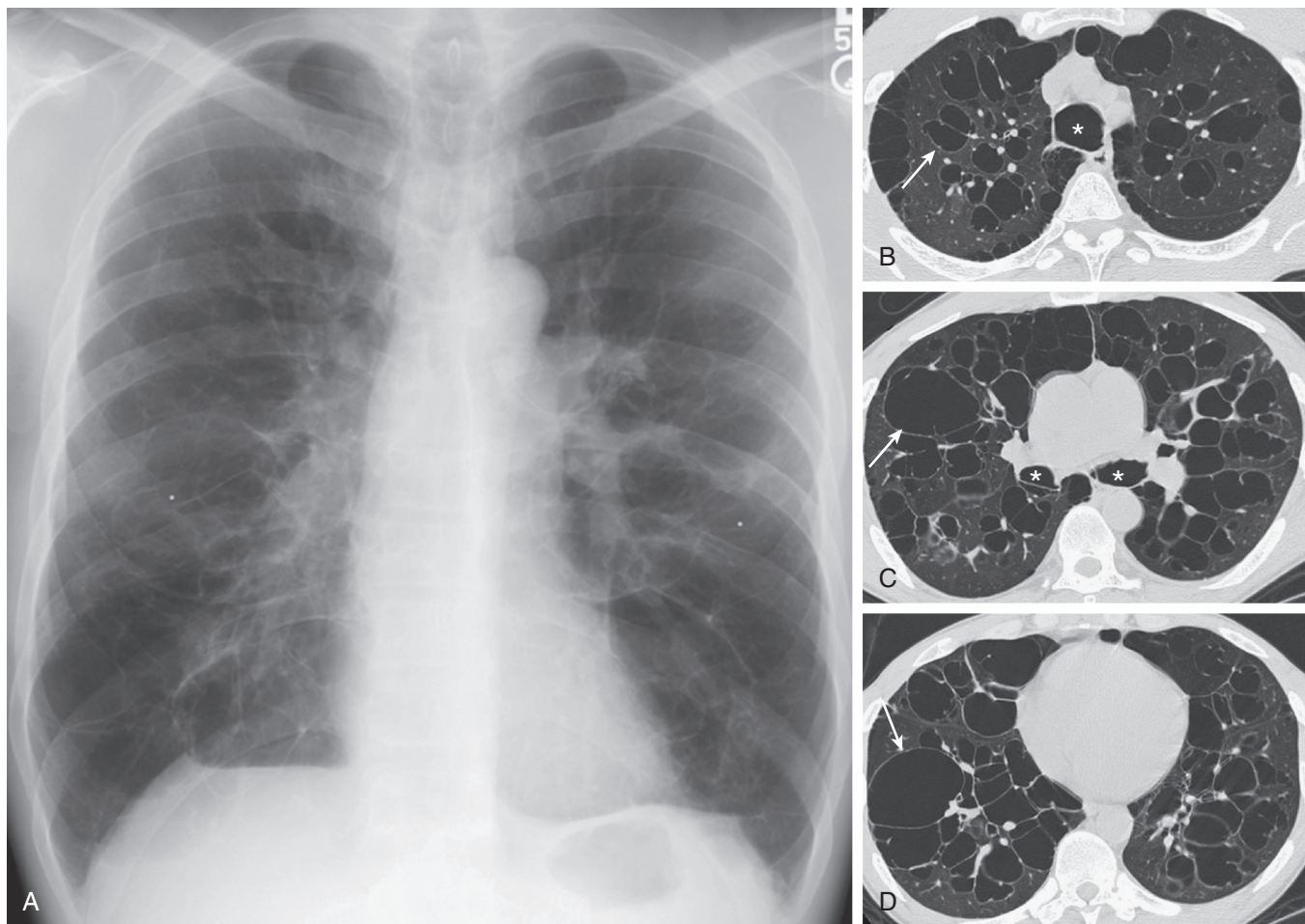
eFigure 48-1 Bronchiectasis: cystic fibrosis. Axial chest CT shows bilateral bronchial dilation and bronchial wall thickening with peribronchovascular opacity. Bronchovascular hypertrophy (*arrowheads*) is present and commonly associated with chronic pulmonary inflammatory conditions such as bronchiectasis. (Courtesy Michael Gotway, MD.)



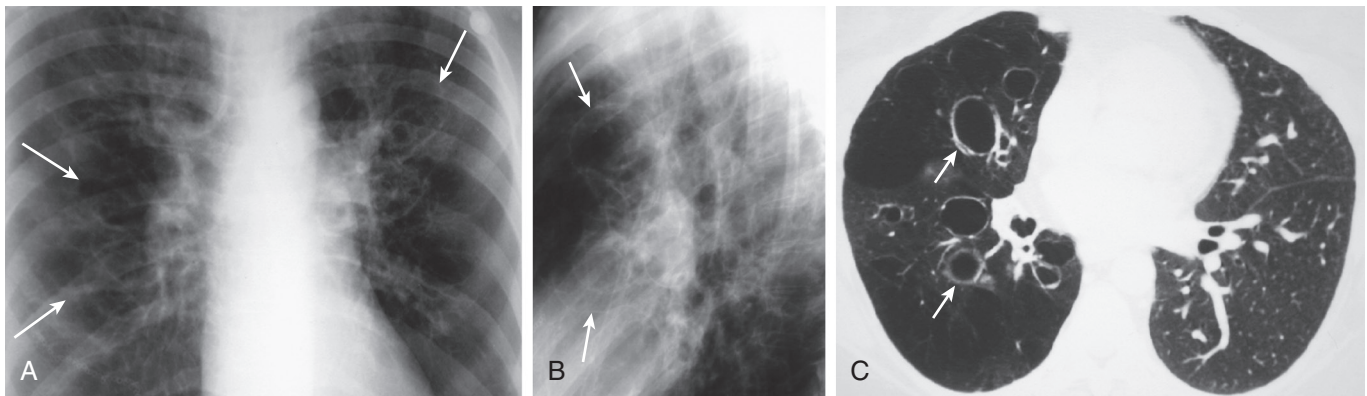
eFigure 48-2 Bronchiectasis: common variable immunodeficiency. A–C, Axial chest CT displayed in lung windows shows multifocal areas of reticulation reflecting scarring from recurrent inflammatory episodes. Bronchiectasis (*arrowheads*) is best visualized in the right middle lobe. (Courtesy Michael Gotway, MD.)



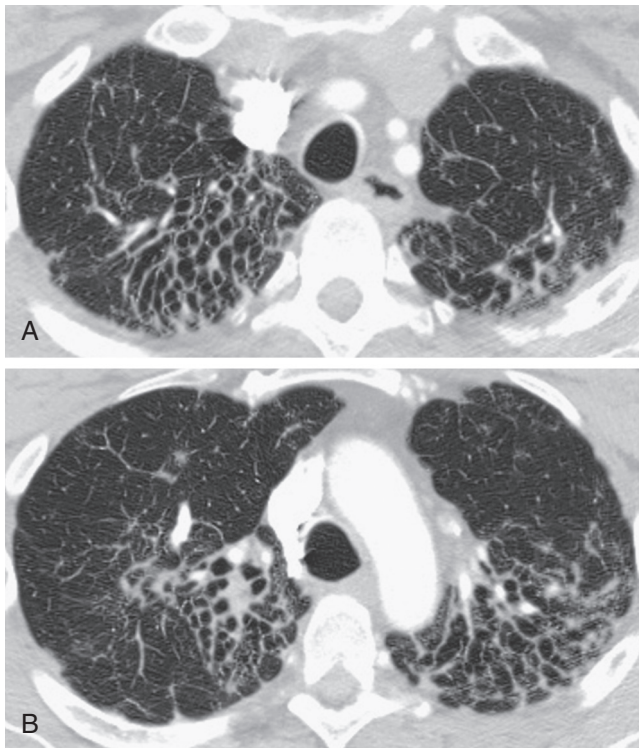
eFigure 48-3 Bronchiectasis: alpha₁-antitrypsin deficiency. A and B, Axial chest CT in a patient with panlobular emphysema due to alpha₁-antitrypsin deficiency shows mild bilateral lower lobe bronchiectasis (*arrows*). (Courtesy Michael Gotway, MD.)



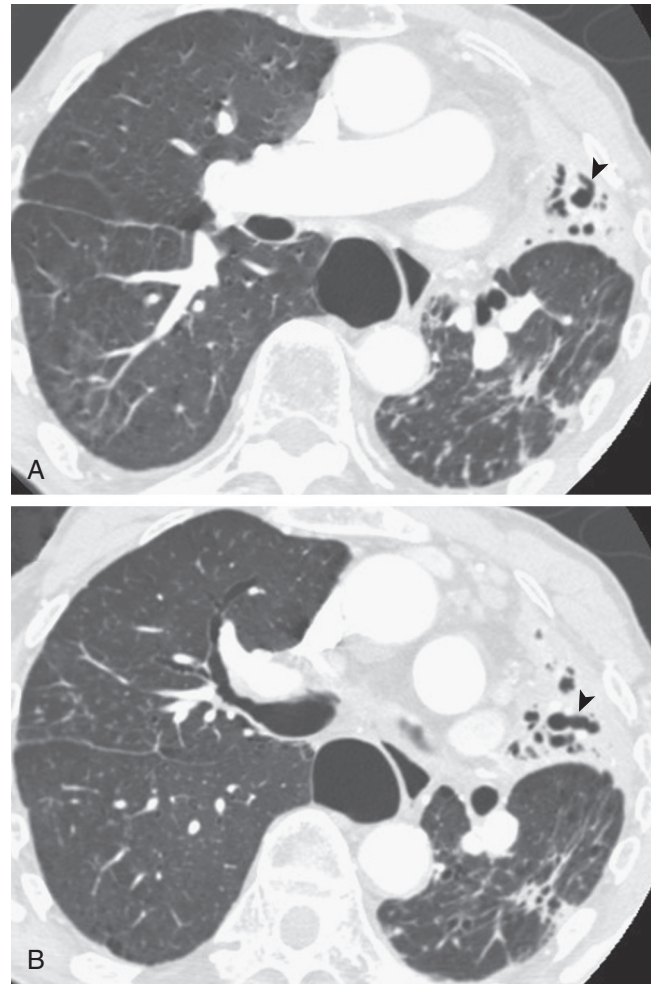
eFigure 48-4 Bronchiectasis: Mounier-Kuhn syndrome. **A**, Frontal chest radiograph shows large lung volumes, consistent with obstructive pulmonary disease. Bilateral linear and reticular opacities represent the walls of severely dilated bronchi. **B–D**, Axial chest CT images show multifocal, thin-walled cystic bronchiectasis (*arrows*), associated with dilated trachea and central bronchi (*). The tubular nature of the cystic bronchiectasis can be appreciated best in the right upper lobe (*arrow*, **B**). In the left upper lobe, note that the cysts are closely related to pulmonary arteries, which allows the cysts to be identified as bronchial in origin rather than to cystic lung disease of other causes. (Courtesy Michael Gotway, MD.)



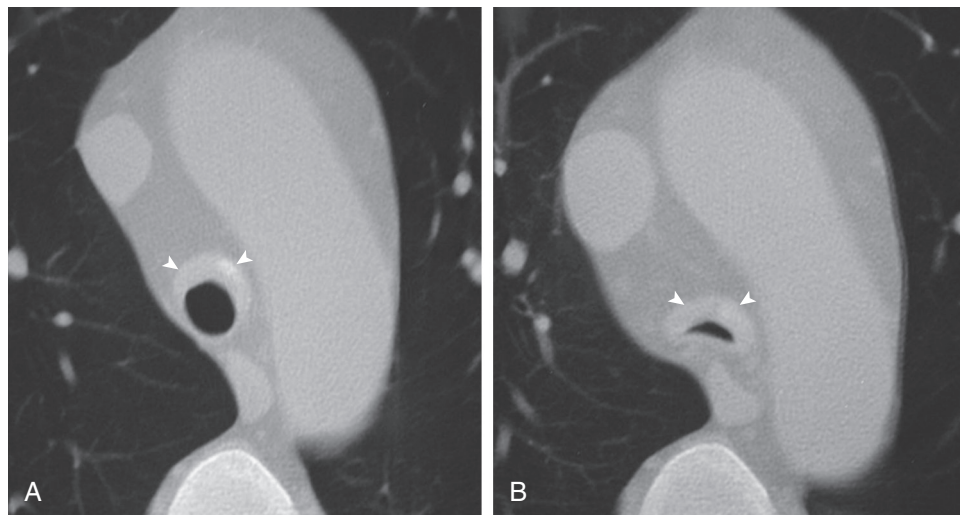
eFigure 48-5 Bronchiectasis: Williams-Campbell syndrome. Frontal (**A**) and lateral (**B**) chest radiographs show bilateral linear and reticular opacities (*arrows*) representing the walls of severely dilated bronchi. **C**, Axial chest CT following left lung transplantation shows severe cystic bronchiectasis (*arrows*) in the native right lung. (Courtesy Michael Gotway, MD.)



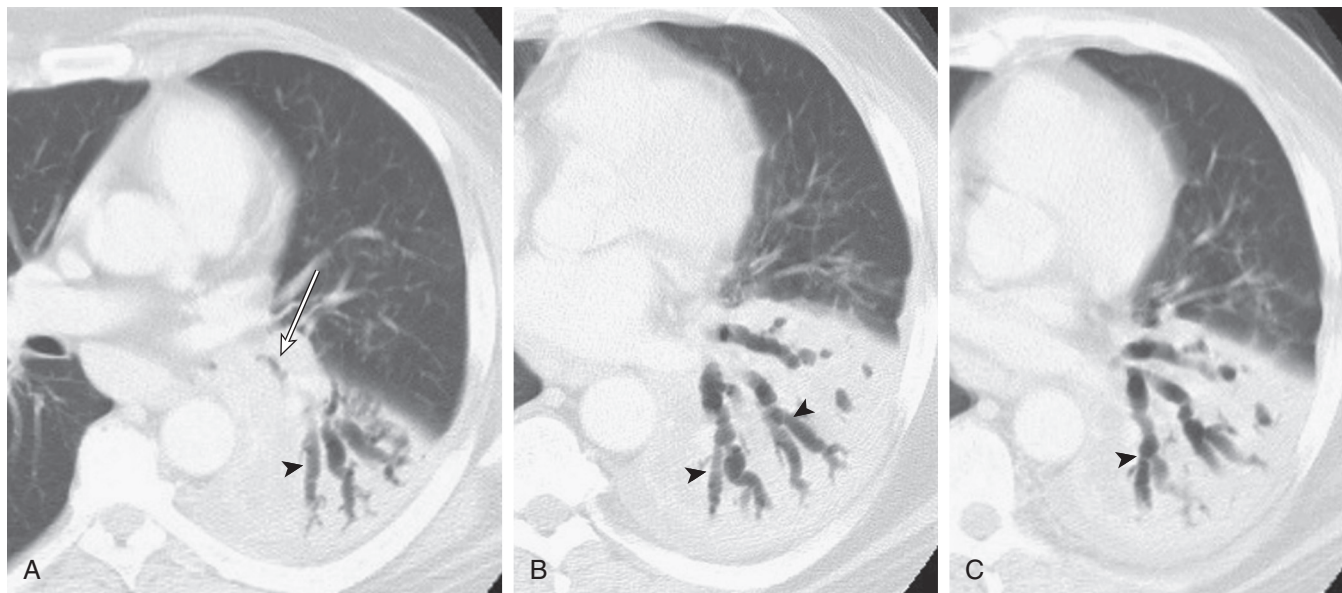
eFigure 48-6 Bronchiectasis: sarcoidosis. A and B, Axial chest CT through the upper lobes in a patient with sarcoidosis shows biapical bronchiectasis with architectural distortion, the latter consistent with fibrosis. (Courtesy Michael Gotway, MD.)



eFigure 48-7 Bronchiectasis: ankylosing spondylitis. A and B, Axial chest CT shows lingular bronchiectasis (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 48-8 Relapsing polychondritis. **A**, Axial inspiratory chest CT shows thickening of the anterior two thirds of the trachea (*arrowheads*). A tiny focus of calcification is present within the thickened trachea at the 1 o'clock position. **B**, Axial chest CT performed following a forced vital capacity maneuver shows excessive trachea collapse (*arrowheads*), consistent with airway malacia. The constellation of findings is typical of relapsing polychondritis. (Courtesy Michael Gotway, MD.)



eFigure 48-9 Postobstructive bronchiectasis. **A–C**, Axial chest CT shows severe narrowing of the left lower lobe bronchus (*arrow*), due to carcinoid tumor. Multifocal bronchiectatic consolidation (*arrowheads*) is present throughout the left lower lobe. (Courtesy Michael Gotway, MD.)

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INTRODUCTION

The upper airway ranges from the nares to the subglottis and includes diverse anatomic structures with a wide variety of functions. Along with assisting in respiration, the structures of the upper airway contain the nerves for the sensory functions of taste and smell, create a functionally safe swallow by separating deglutition from respiration, and allow for communication through the generation of voice and speech. The nasal cavity has a defined role in filtering and humidifying air for presentation to the lower airway.¹⁻³ The glottis performs the functions of protecting the airway to prevent aspiration, regulating airflow and vocalization. The pharynx and oral cavity assist in these functions by controlling and shaping substances to be swallowed and modulating voiced sounds from the glottis into words and speech. The upper airway is controlled by both voluntary and involuntary mechanisms. Therefore respiratory function can be affected through uncoordinated or inefficient muscular activity, centrally mediated neurologic reflex activity, and/or humoral or immunologic responses. The exact function of some areas within the upper airway, such as the paranasal sinuses, is unclear.

Pathologic changes in the upper airway are often associated with lower airway disease. Swallowing disorders may result in aspiration with inflammatory and infectious complications in the lungs. Chronic inflammation of the paranasal sinuses is frequently associated with asthma.⁴⁻⁷ Long-standing infection in the sinuses has been implicated as a possible reservoir for recurrent pulmonary infection.⁸⁻¹⁰ Laryngeal dysfunction may create symptoms similar to reactive airway disease. Finally, stenosis of the subglottis or cervical trachea is often misdiagnosed as asthma. In this chapter we discuss the anatomy and clinical conditions of the upper airway and their influence on lower airway function.

THE NOSE**ANATOMY, HISTOLOGY, AND PHYSIOLOGY**

The nose represents the initial site of air entry for the majority of respiration. The external nose has important structural components that, when compromised, may inhibit nasal airflow. The nasal dorsum is made up of three structurally distinct subunits (Fig. 49-1). The upper third of the nasal dorsum is supported by the nasal bones. At their distal end, the nasal bones articulate with the upper lateral cartilages in a region known as the keystone area. The upper lateral cartilages define the middle third of the nose. The structure of the lower third, or nasal tip, is defined primarily by the lower lateral cartilages. The nasal septum divides the right and left sides of the nose and provides additional structural support to the lower two thirds of the nose. The quadrangular cartilage forms the anterior septum. The bone of the vomer, perpendicular plate of the ethmoid, and maxillary crest form the posterior and inferior aspects of the septum.

Airflow through the nose may be limited by the cross-sectional area of the external and internal nasal valves (Fig. 49-2). The relationship between the lower lateral cartilage, the septum, and the inferior turbinate largely determines the external valve area. The angle between the upper lateral cartilage and septum impacts airflow through the internal nasal valve. Facial musculature that attaches to the upper and lower cartilages of the nose can widen these principal areas of resistance, enhancing nasal respiration.¹¹⁻¹² Patients with narrowing or structural weakness in these regions may suffer from nasal obstruction. The external and internal nasal valves are frequently the target of nasoseptal reconstructive surgery.

Another common area implicated in narrowing of the nasal cavity and subsequent nasal obstruction is the nasal septum. Deviation of the septum diminishes the cross-sectional area of the affected nasal passage and can

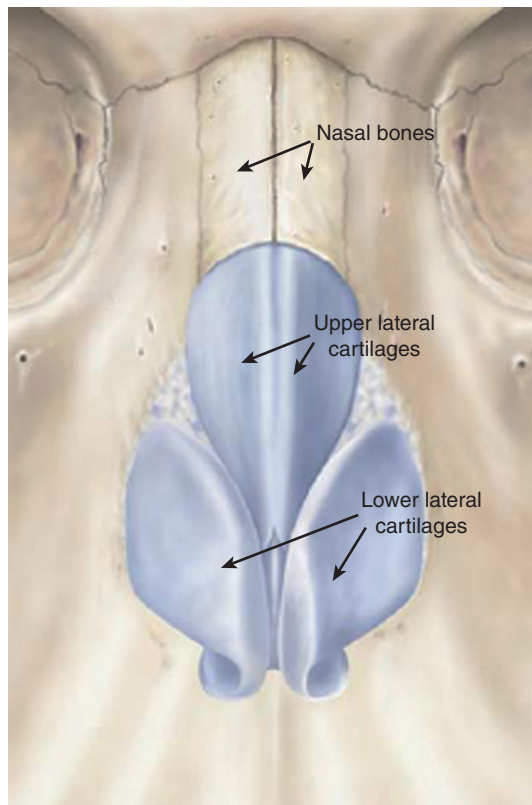


Figure 49-1 Vertical thirds of the nose. The upper, middle, and lower third of the nose are structurally supported by the nasal bones, the upper lateral cartilages, and the lower lateral cartilages, respectively. (From Hafezi F, Naghibzadeh B, Nouhi AH: Applied anatomy of the nasal lower lateral cartilage: a new finding. *Aesthetic Plast Surg* 342:244–248, 2010.)

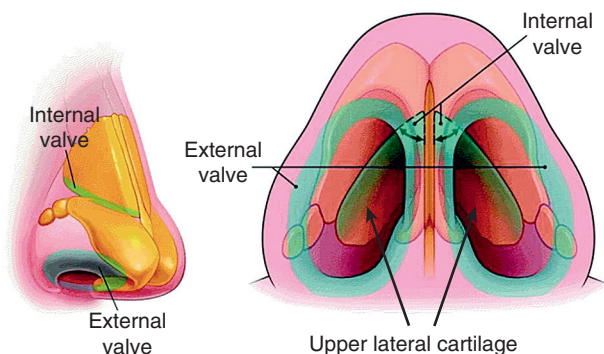


Figure 49-2 The internal and external nasal valves. The external nasal valve exists at the level of the inner nostril and is formed by the caudal edge of the lateral crus of the lower lateral cartilage, the soft-tissue alae, the membranous septum, and the sill of the nostril. The internal nasal valve accounts for approximately half of the total airway resistance and is bordered medially by the septum, inferiorly by the nasal floor, laterally by the inferior turbinate, and superiorly by the caudal border of the upper lateral cartilage. The junction between the septum and upper lateral cartilage is normally 10 to 15 degrees. (From Howard BK, Rohrich RJ: Understanding the nasal airway: principles and practice. *Plast Reconstr Surg* 109:1128–1146, 2002.)

significantly impact nasal airflow. Most patients have some degree of septal deviation, so anatomic changes in this area must be correlated with clinical findings when determining if a septal deviation would benefit from treatment. Nasal trauma may lead to septal deviations and spurs; many

patients will relate a history of trauma to the nose. Developmental variations are perhaps a more common cause of deviation and spurs of the nasal septum than is trauma. Overgrowth of the quadrangular cartilage may result in bowing of the cartilage or spurs at the junction of the cartilage and bones that make up the nasal septum. Nasal obstruction related to septal deviation may respond either to surgical or to medical treatment. In patients with concomitant turbinate hypertrophy or chronic rhinitis, treatment with intranasal corticosteroids may diminish mucosal swelling and provide an adequate airway despite the septal deviation. Surgery to straighten the septum has few risks and complications and is an effective method for improving the nasal airway in patients with narrowing secondary to septal deviation. Septal deviations have been implicated as a cause for acute or chronic rhinosinusitis. This is a rare cause for inflammatory sinus disease, and caution is advised in diagnosing or treating rhinosinusitis based upon septal findings alone.

Air that enters the nasal sill (or floor of the nose) and passes through the internal nasal valve accelerates as it passes through this area of narrowing. There is also a change in direction of airflow because inspired air shifts from a vertical to a horizontal trajectory at this site. This combination of acceleration and change in flow vector causes the majority of airborne particles to be deposited in the anterior nasal cavity.^{13,14} Airflow through the nose slows as the nasal passages widen beyond the internal nasal valve.

Upon entry into the nasal cavity, the stratified squamous epithelium of the nasal sill quickly transitions to a respiratory epithelium. Located along the lateral nasal wall, the turbinates (or conchae) serve to warm and humidify air passing through the nasal cavity. Rich vasculature, including venous sinusoids, allows the turbinates to enlarge and shrink in response to various stimuli.¹⁵⁻¹⁷ Fenestrated subepithelial capillaries facilitate heat and gas exchange, enhancing humidification during nasal inhalation.¹⁷ Engorgement of the turbinates increases the surface area and mucosal contact with inspired air. The slowing of airflow beyond the internal nasal valve provides prolonged mucosal contact during nasal inspiration and allows efficient humidification and filtration of inspired air so that even at extremes of ambient temperature and humidity, air that reaches the trachea is very close to body temperature and 98% humidity.

The respiratory mucosa of the turbinates contains both goblet cells and seromucous glands. These structures combine to produce a mucus blanket that is mobilized by coordinated beating of this ciliated epithelium. Nasal irritants, microbes, and other particles are swept through the nasal cavity by this mucociliary clearance mechanism to be swallowed, preventing exposure of the lower airways. The lower airways are further protected by immune function within the nasal mucosa. Both the innate and humoral immune arms of the immune system function within the nasal mucosa, resulting in the secretion of immunoglobulins (primarily immunoglobulin [Ig] A)^{18,19} and microbial toxins such as lysozyme and lactoferrin.^{20,21} Emerging evidence suggests that commensal microbes inhabiting the mucosal surface or mucus layer of the nasal cavity contribute to host defense mechanisms within the nasal cavity

through competitive colonization and perhaps immune regulation.²²

The turbinates are dynamic structures that swell and shrink in response to multiple stimuli. Gravity, nasal irritants, allergic response, and autonomic neural input all regulate the blood supply and venous drainage of the submucosal tissue of the inferior turbinate, resulting in marked fluctuations in turbinate size.^{17,23} The size of the inferior turbinate fluctuates alternately on the right and left side as part of the normal nasal cycle.²³ Pathologic enlargement of the inferior turbinate is one of the most common causes of nasal congestion and nasal obstruction.^{24,25}

The tubular structure of the turbinates contributes to a laminar air flow pattern through the nasal cavity.^{26,27} Aggressive resection of the turbinates enlarges the cross-sectional area of the nasal cavity but risks a paradoxical worsening of nasal obstruction. The humidification function of the turbinates can also be lost with resection, resulting in possible dryness and crusting. This constellation of symptoms following turbinate resection has been referred to as “empty nose syndrome.”²⁸ A conservative surgical approach to nasal obstruction due to turbinate hypertrophy is therefore recommended in patients who do not receive adequate relief from medical therapy.

The superior aspects of the nasal septum, middle turbinate, and superior turbinate are lined with olfactory epithelium. Successful olfaction requires that airborne or mucus-soluble particles reach this epithelium. Odorant-specific receptors of the olfactory epithelium send projections intracranially, through the bone of the cribriform plate. Axons from the olfactory epithelium synapse within the olfactory bulb, and these signals are then routed for central processing. Smell disorders may arise from mucosal inflammation and edema that prevent odorant exposure to the olfactory epithelium. This is frequently a reversible condition. Direct viral injury of the olfactory epithelium has also been postulated as a cause for smell loss, which may result in long-term dysfunction.^{29,30}

Sneezing is a nonspecific, involuntary response to nasal irritation. Allergens, microbes, and other nasal irritants may precipitate this reaction when they contact the nasal mucosa and trigger histamine release. The trigeminal nucleus coordinates the sneeze reflex, which involves muscles of the pharynx, larynx, oral cavity, and chest wall. The pressure generated from a sneeze may expel irritants and can contribute to spread of infections conditions. In susceptible individuals, sudden exposure to bright light may trigger the sneeze reflex. This is an autosomal dominant trait impacting approximately one fourth of the human population.³¹

PATHOLOGIC CONDITIONS OF THE NASAL CAVITY

Rhinitis

Rhinitis, or inflammation of the nasal cavity, may result from multiple causes. Rhinitis may be classified by duration (acute versus chronic) and further segregated as allergic versus nonallergic. Acute rhinitis is a self-limited inflammation, most commonly secondary to viral infection. Many of the clinical features of acute rhinitis may result from the

immune response to viral pathogens. Release of inflammatory cytokines and chemokines including *interleukin* (IL)-6, tumor necrosis factor- α , and interferon- γ results in tissue edema, increased mucus production, and vascular dilation.³² The clinical manifestations of these changes are well known as symptoms of the “common cold”: nasal congestion and obstruction, increased nasal drainage, and diminished sense of smell. Nasal irritants, including perfumes, smoke, and cleaning products, can cause a similar constellation of symptoms although typically of shorter duration.

Allergic Rhinitis

Epidemiology. *Allergic rhinitis* (AR) is a common disorder that is estimated to be the sixth most common chronic illness in the United States.³³ The prevalence of AR is 10% to 20% in the United States and Europe.³⁴ There are an estimated 18 million adults in the United States who suffer from AR, resulting in significant health care expenditures.³⁵ A diagnosis of allergic rhinitis adds approximately \$1500 per patient per year in direct health care costs.³⁵ A similar prevalence of AR is evident in children, and AR in this population is associated with a significant decrease in both physical and emotional health, as well as sleep disturbance.³⁶ As many as 13 million Americans in the workforce suffer from AR, and it is estimated that 3.5 million workdays and 2 million school days are lost each year because of this condition.^{37,38} Overall annual direct and indirect costs of AR in the United States have been estimated at \$5 to \$8 billion and \$11 billion, respectively.³⁹

The incidence of allergic rhinitis has been rising over the past 3 decades. One explanation for this is the “hygiene hypothesis”: early exposure to antigens allows for proper immune system development and a reduced risk for allergic rhinitis and other atopic disease.⁴⁰ Recent data suggest that early microbial exposure may be particularly important in the prevention of not only atopic, but also autoimmune disease.⁴¹⁻⁴³

Diagnosis. Allergic rhinitis symptoms may be seasonal or perennial, depending upon the specific allergen. Pollens from trees and grasses are the most common triggers for seasonal symptoms, whereas dust mites and pet dander represent common triggers for perennial disease. Identification of offending allergens may be accomplished through a variety of approaches. Skin reaction to allergens may be measured through either prick testing or intradermal injection using serial end-point dilution techniques. Both of these approaches carry a rare but important risk for anaphylaxis.⁴⁴ Testing centers must have personnel and equipment to deal with such emergencies. Immunoassays for allergen-specific IgE such as ImmunoCAP have largely replaced radioallergosorbent test as an alternative to intradermal skin testing. This approach demonstrates a similar sensitivity as skin testing. Efficacy of both dermal testing and immunoassays is dependent upon proper antigen selection. Knowledge of local flora is particularly important in patients with seasonal allergic rhinitis. This knowledge is also critical in identifying clinically significant allergens. Identification of offending allergens allows counseling of allergen avoidance and may be used to initiate immunomodulatory therapy.

Pathophysiology. Following an initial allergen exposure, inhaled antigens provoke both early- and late-phase reactions in the nasal cavity. The early phase is initiated by the recognition of a specific allergen by IgE subunits on the surface of mast cells and basophils. IgE activation results in antibody cross-linking, which, through a series of downstream mediators, causes degranulation of mast cells and basophils with release of preformed mediators. Histamine is the primary inflammatory mediator released during degranulation. Tryptase release and de novo formation of leukotrienes may also contribute to nasal inflammation and symptoms. Exposure to inflammatory mediators results in marked tissue edema and mucus secretion, which manifests clinically as rhinorrhea and nasal congestion and obstruction, frequently in association with sneezing. These symptoms develop within minutes of allergen exposure.

The late phase of allergic rhinitis typically arises 4 to 8 hours after allergen exposure. Nasal congestion is typically the dominant symptom. Chemoattractants and adhesion molecules released in response to the initial inflammatory mediators promote infiltration of leukocytes, eosinophils, basophils, CD4⁺ lymphocytes, and monocytes. Activation of these cells results in the release of a second wave of inflammatory mediators.⁴⁵ The early- and late-phase reactions in allergic rhinitis mimic those of allergic asthma.

Another important concept in the pathophysiology of allergic rhinitis is that of priming of the immune response. Repeated allergen exposure results in amplification of mucosal hyperresponsiveness. In patients with seasonal allergic rhinitis, the severity of allergic response depends not only on the current pollen count and allergen exposure, but also upon the cumulative exposure for a given allergy season. Because of this phenomenon, severe symptoms of allergic rhinitis may persist late in the allergy season despite a waning pollen count. This increased allergen sensitivity may be secondary to both a neural hyperresponsiveness and amplification of the immune response through recruitment of mast cells and basophils. Immune system priming is not an allergen-specific phenomenon; patients report increased sensitivity to nonspecific nasal irritants, including smoke and perfume.^{46,47}

Association with Asthma. Allergic rhinitis and asthma are linked through both pathophysiology and epidemiology.^{45,47,48} Eighty percent of patients with allergic asthma also suffer from allergic rhinitis. The presence of allergic rhinitis is a risk factor for the future development of asthma. Guidelines suggest screening patients with persistent allergic rhinitis for asthma and evaluating asthmatic patients for rhinitis.^{47,48}

The unified airway theory suggests that inflammatory cell migration from an inflamed area within the airway may impact distant airway locations. In patients with allergic rhinitis and asthma, segmental bronchial allergen challenge results in an inflammatory response not only in bronchi, but also in the nasal cavity.⁴⁹ When treated with intranasal corticosteroids, these same patients demonstrate a decrease in both nasal and bronchial hyperreactivity.^{50,51}

Treatment. There are three modalities of treatment for allergic rhinitis: allergen avoidance, pharmacotherapy, and

immunomodulatory treatments. Recent consensus panels suggest evaluating the severity and frequency of AR symptoms to guide treatment. Severity of symptoms is categorized as mild or moderate/severe as determined by the level of impact on daily activities and sleep disturbance. Symptoms are classified as intermittent if the duration is less than 4 days per week or for fewer than 4 weeks and as persistent if the duration satisfies both of these criteria.⁴⁸ Figure 49-3 depicts a consensus management strategy for allergic rhinitis.⁵² The vast majority of patients are effectively treated with pharmacotherapy and allergen avoidance. Saline irrigation results in modest symptomatic improvement and may reduce the need for medications with more significant side effect profiles. Evidence-based AR treatment recommendations for allergen avoidance, individual medications, and immunotherapy were revised in 2010.⁵³ Allergen avoidance strategies for patients with allergic rhinitis are similar to those for patients with allergic asthma and require identification of offending allergens. Following identification of clinically significant allergens, environmental precautions may be instituted.

Immunotherapy. Although pharmacologic treatment of allergic rhinitis may be quite effective in managing symptoms, immunotherapy offers the only approach known to impact the natural history of the disease. *Subcutaneous immunotherapy* (SCIT) regimens involve once or twice weekly subcutaneous antigen injections with gradual escalation of the antigen dose. This is the most well-studied and commonly used approach in the United States. More recently, *sublingual immunotherapy* (SLIT) has emerged as an option that avoids injection appointments. This approach has been primarily studied and is frequently used in Europe but has not yet been approved for use in the United States. The overall treatment course for SCIT or SLIT is 2 to 3 years.

With repeated allergen exposure, a shift in allergen-specific T cells to a regulatory phenotype results in suppression of type 2 T helper inflammatory cytokines and enhanced production of IL-10 and antigen-specific IgG4. This results in suppression of allergen-specific IgE and mast cells and appears to inhibit antigen capture and presentation to T cells.⁵⁴ This immune modulation may diminish the onset of additional atopic disorders such as asthma in patients with allergic rhinitis.

Systemic responses to immunotherapy are rare and typically mild. Nevertheless, deaths have been reported from anaphylactic response during immunotherapy, and vigilance is required. SCIT has a higher (although still very low) incidence of systemic response than SLIT; SLIT has a high rate of mild local (mucosal) side effects, which rarely impact the treatment regimen.⁵⁵ Practitioners who administer allergy shots require appropriate training and access to emergency equipment to address the rare systemic response. With sublingual administration, patients often self-administer the allergen, and proper patient selection and education is critical. Multiple trials demonstrate efficacy of both SLIT and SCIT; they appear to have similar efficacy, but head-to-head trials are lacking.⁵⁶⁻⁵⁸ Use of SLIT in the United States is limited by a lack of approval of the U.S. Food and Drug Administration and limited insurance coverage.⁵⁹

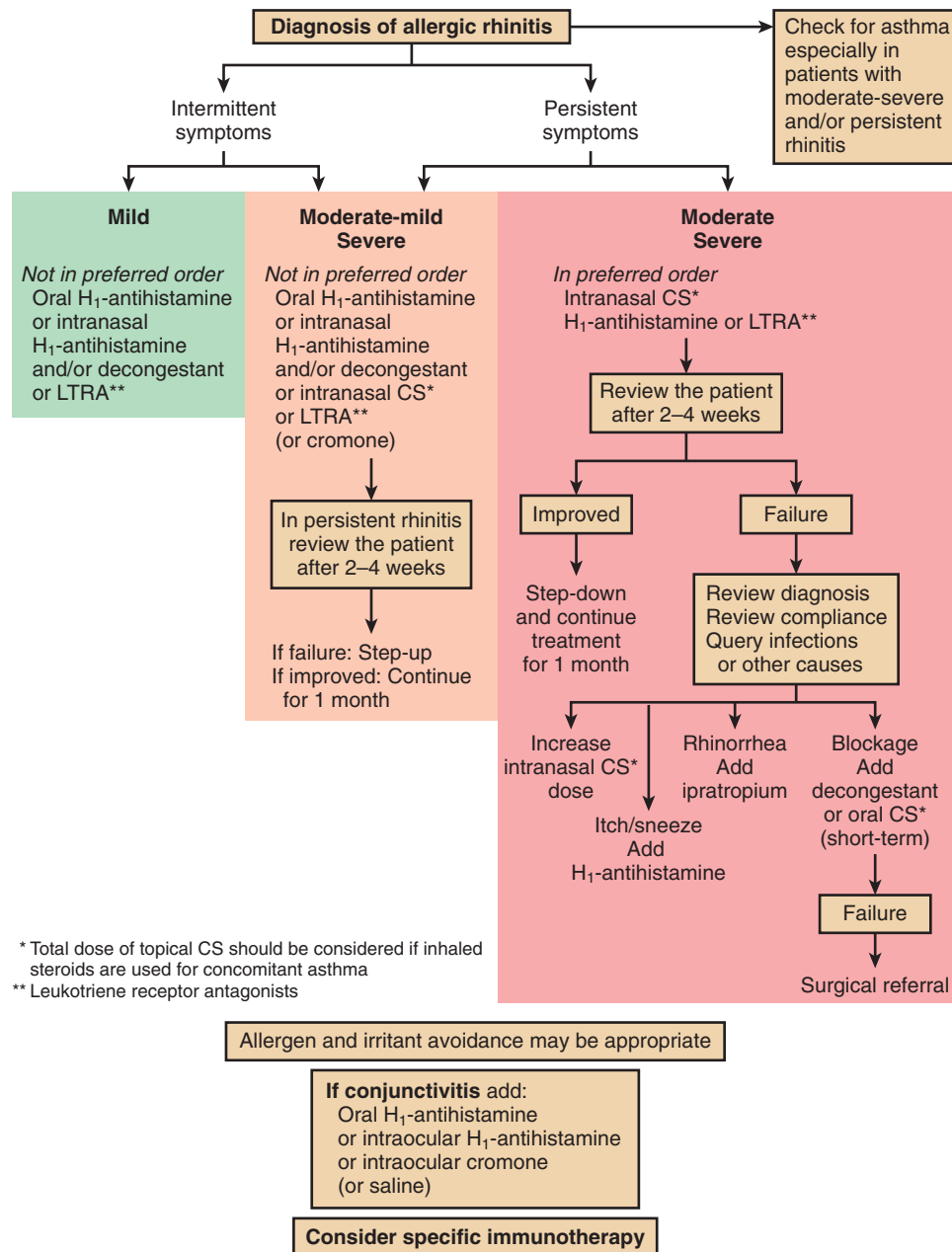


Figure 49-3 Algorithm for the management of allergic rhinitis. CS, corticosteroid; H₁, histamine₁. (From Bousquet J, et al: Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* 130:1049–1062, 2012.)

Nonallergic Chronic Rhinitis

Overall, nonallergic rhinitis is poorly characterized. *Vasomotor rhinitis* is a subgroup of nonallergic patients thought to suffer from aberrant parasympathetic innervation in the nose. Patients frequently note rhinorrhea in association with eating or a change in the weather. This disorder is more common in elderly patients and may respond well to ipratropium nasal spray. Additional non-inflammatory disorders of the nasal cavity, including nonallergic rhinitis with eosinophilia, may improve with nasal steroid treatment. Symptomatic treatment with saline irrigation is another popular treatment for nonallergic rhinitis.

THE PARANASAL SINUSES

ANATOMY, HISTOLOGY, AND PHYSIOLOGY

The paranasal sinuses are aerated cavities within the skull that connect to the nasal cavity. There are four sets of paired sinuses: the maxillary, ethmoid, frontal, and sphenoid sinuses. The sinuses are lined with a pseudostratified, ciliated epithelium. Goblet cells within the epithelium produce mucus, and the coordinated action of the cilia moves this mucus through the sinus cavities and into the nose. Once thought to be sterile, it is now known that bacterial communities inhabit the mucosal surfaces of the paranasal sinuses in both health and disease.²²

The function of the sinuses has not been clearly established. They may serve a protective role in force dissipation with blunt trauma to the head or face. The paranasal sinuses can impact vocal resonance, which may have aided their evolution. The sinuses may allow for enhanced facial aesthetics. They may play a role in mucus production and immune surveillance in the nasal cavity.

The four paired sinuses are named after the bones that they aerate. The maxillary and ethmoid sinuses are the first to develop and are present at birth. The frontal and sphenoid sinuses develop more slowly. A visible frontal sinus is often not present until age 4 or 5, and continued aeration and development persist throughout the teenage years.⁶⁰ Asymmetric aeration of the sinuses is common, particularly in the later-developing frontal and sphenoid sinuses. The frontal sinus may be absent in up to 10% of normal patients.^{61,62} An increased incidence of frontal sinus aplasia and diminished overall paranasal sinus aeration is seen in patients with congenital disorders that impact the sinuses such as cystic fibrosis.⁶³

Mucus produced in the sinuses is propelled into the nasal cavity by coordinated ciliary motion. The maxillary (Fig. 49-4) and sphenoid sinuses are connected to the nasal cavity by discrete ostia, which often have a diameter of no more than 4 mm. The ethmoid sinuses are made up of a labyrinth of small cavities called air cells that sit between the orbit and the nasal septum. The ethmoid sinus typically drains through clefts between air cells rather than discrete ostia. The anterior ethmoid air cells drain through the middle meatus, between the middle turbinate and the lateral nasal wall. The posterior ethmoid cells drain through the superior meatus, between the superior turbinate and lateral nasal wall. The frontal sinus drainage tract is determined by the variable anatomy of the underlying anterior ethmoid air cells and eventually leads to the middle meatus.

Blood supply to the paranasal sinuses is provided through both the internal and external carotid systems. The *sphenopalatine artery* (SPA) is the terminal branch of the internal maxillary artery, which originates from the external carotid

artery. The SPA enters the nasal cavity through the sphenopalatine foramen just behind the posterior wall of the maxillary sinus. The majority of the blood supply to the nasal cavity is provided by the SPA. The blood supply to the superior nasal cavity, and much of the ethmoid system, arises from the anterior and posterior ethmoid arteries. These vessels are branches from the ophthalmic artery of the internal carotid system and typically run within the skull base along the roof of the ethmoid sinuses. All of these vessels may contribute to refractory or “posterior” nosebleeds. Epistaxis originating from the SPA is amenable to embolization or surgical ligation of the SPA. The anterior and posterior ethmoid arteries are not amenable to embolization due to their origin from the ophthalmic artery and the associated risk for blindness. These vessels are amenable to surgical ligation in cases of refractory epistaxis.⁶⁴

PARANASAL SINUS DISEASE

Overall, inflammatory disease of the paranasal sinuses is poorly understood. Sinusitis likely represents a wide variety of pathologic conditions that may cause either acute or chronic inflammation. Paranasal sinus inflammation is almost inevitably accompanied by inflammation of the nasal cavity, or rhinitis. Thus the term *rhinosinusitis* is typically used to describe this condition.

Diagnosis of rhinosinusitis is based upon the presence of both clinical symptoms and objective evidence of sinus inflammation.^{65,66} Table 49-1 demonstrates the diagnostic criteria for acute, chronic, and recurrent acute rhinosinusitis. The duration of symptoms is the primary factor used to differentiate between acute and chronic rhinosinusitis. Acute sinusitis lasts up to 4 weeks. Patients with signs and symptoms for 12 weeks or longer are diagnosed with chronic sinusitis. Whereas the duration of symptoms is used to distinguish between acute and chronic disease, the pathophysiologic features, symptoms, and treatment of these entities are different. Acute rhinosinusitis is most commonly an acute infectious disorder, and patients

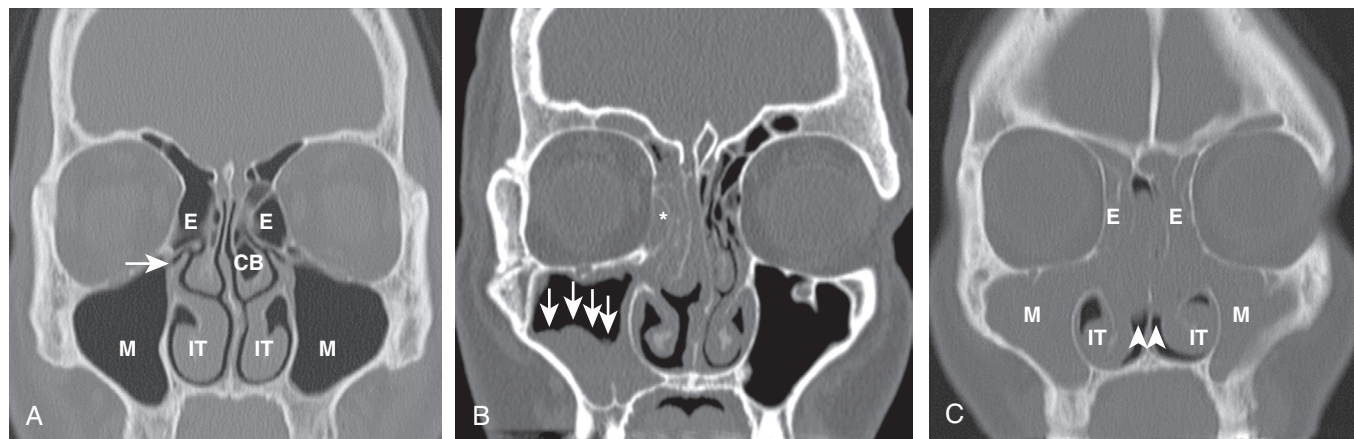


Figure 49-4 Coronal CT imaging of the paranasal sinuses. **A**, Normal anatomy including well-aerated maxillary (M) and ethmoid (E) sinuses bilaterally, patency of the osteomeatal complex (arrow), and normal appearance of the inferior turbinates (IT). Incidentally noted is a left concha bullosa (CB), a normal variant involving aeration of the middle turbinate, which occurs in approximately 30% of patients. **B**, CT findings consistent with acute sinusitis. There is unilateral opacification of the ethmoid sinuses (*) as well as a fluid level within the right maxillary sinus (arrows). Acute sinusitis may present with unilateral or bilateral disease and routine CT imaging is not recommended. **C**, Bilateral chronic sinusitis with nasal polyposis. There is complete opacification of the maxillary (M) and ethmoid (E) sinuses bilaterally. Arrowheads demonstrate bilateral nasal polyps; soft-tissue density within the nasal cavity and adjacent to the inferior turbinates (IT).

Table 49-1 Diagnostic Criteria for Rhinosinusitis

Term	Definition
ACUTE	
Acute rhinosinusitis	Up to four (4) weeks of <i>purulent nasal drainage</i> (anterior, posterior, or both) accompanied by <i>nasal obstruction</i> , <i>facial pain-pressure-fullness</i> , or both: <ul style="list-style-type: none"> ■ <i>Purulent nasal discharge</i> is cloudy or colored, in contrast to the clear secretions that typically accompany viral upper respiratory infection, and may be reported by the patient or observed on physical examination ■ <i>Nasal obstruction</i> may be reported by the patient as nasal obstruction, congestion, blockage, or stuffiness, or may be diagnosed by physical examination ■ <i>Facial pain-pressure-fullness</i> may involve the anterior face, periorbital region, or manifest with headache that is localized or diffuse
Viral rhinosinusitis (VRS)	Acute rhinosinusitis that is caused by, or is presumed to be caused by, viral infection. A clinician should diagnose VRS when: <ol style="list-style-type: none"> Symptoms or signs of acute rhinosinusitis are present less than 10 days and the symptoms are not worsening
Acute bacterial rhinosinusitis (ABRS)	Acute rhinosinusitis that is caused by, or is presumed to be caused by, bacterial infection. A clinician should diagnose ABRS when: <ol style="list-style-type: none"> Symptoms or signs of acute rhinosinusitis are present 10 days or more beyond the onset of upper respiratory symptoms, or Symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement (double worsening)
CHRONIC AND RECURRENT	
Chronic rhinosinusitis (CRS)	Twelve (12) weeks or longer of two or more of the following signs and symptoms: <ul style="list-style-type: none"> ■ Mucopurulent drainage (anterior, posterior, or both) ■ Nasal obstruction (congestion) ■ Facial pain-pressure-fullness, or ■ Decreased sense of smell ■ AND inflammation is documented by one or more of the following findings: <ul style="list-style-type: none"> ■ Purulent (not clear) mucus or edema in the middle meatus or ethmoid region ■ Polyps in nasal cavity or the middle meatus, and/or ■ Radiographic imaging showing inflammation of the paranasal sinuses
Recurrent acute rhinosinusitis	Four (4) or more episodes per year of ABRS without signs or symptoms of rhinosinusitis between episodes: <ol style="list-style-type: none"> Each episode of ABRS should meet diagnostic criteria above

From Rosenfeld RM, et al: Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg* 137(3 Suppl):S1–31, 2007.

present with fever and facial pain as characteristic symptoms. *Chronic rhinosinusitis* (CRS) is primarily an inflammatory disorder in which the role of microbes is not well established. Patients with CRS typically note nasal congestion, thick nasal drainage, and facial pressure, but fever⁶⁷ and pain are uncommon in the absence of acute exacerbations.

Objective findings of rhinosinusitis may be present on routine physical examination during evaluation of the anterior nasal cavity or anterior rhinoscopy. Acute rhinosinusitis may be diagnosed by history and anterior rhinoscopy alone; imaging studies are not recommended for uncomplicated acute sinusitis.^{65,66} Objective evidence of inflammation in patients with chronic sinusitis is often difficult to establish on anterior rhinoscopy, so nasal endoscopy or imaging of the sinuses is often required to establish the diagnosis. *Computed tomography* (CT) (see Fig. 49-4) is the preferred method of imaging for the paranasal sinuses; radiographs of the paranasal sinuses lack sufficient specificity and sensitivity and have little clinical utility.

ACUTE RHINOSINUSITIS

Epidemiology

Acute rhinosinusitis is extremely common and typically of viral etiology. It is estimated that adults suffer two to five episodes of viral rhinosinusitis (common cold) annually. School-age children may suffer 7 to 10 colds per year.⁶⁵ In the United States, upper respiratory tract infection is the

Table 49-2 Microbiology of Acute Rhinosinusitis in Adults

Organism	Range of Prevalence (%)
<i>Streptococcus pneumoniae</i>	20–43
<i>Haemophilus influenzae</i>	22–35
<i>Streptococcus</i> spp.	3–9
Anaerobes	0–9
<i>Moraxella catarrhalis</i>	2–10
<i>Staphylococcus aureus</i>	0–8
Other	4

third most common reason for a primary care provider consultation, with approximately a third of these attributed to acute rhinosinusitis.⁶⁸ Gwaltney and colleagues⁶⁹ demonstrated that 60% of viral upper respiratory infections demonstrate radiologic evidence of inflammation within the ethmoid and maxillary sinuses on CT imaging. This study also highlights the futility of CT imaging for distinguishing between acute viral and acute bacterial rhinosinusitis.

Between 0.5% and 2% of viral rhinosinusitis episodes will progress to *acute bacterial rhinosinusitis* (ABRS).⁶⁵ The proposed pathophysiology is that virally mediated mucosal inflammation and edema result in ciliary dysfunction and obstruction of the sinus ostia. This disruption of mucociliary clearance results in mucus stasis and a vulnerability to bacterial superinfection. The most common organisms seen in ABRS are noted in Table 49-2.

Treatment

Distinguishing the self-limited, viral-induced inflammation of the common cold from ABRs is a challenge often faced by primary care physicians. Clinical guidelines suggest that a detailed history is somewhat effective in making this distinction.^{65,66} Patients who fail to demonstrate significant clinical improvement after 10 days or experience a worsening of symptoms after 5 days of the onset of symptoms, also referred to as “double sickening,” are more likely to suffer from ABRs.⁶⁶ Additionally, facial pain beyond what is expected from a viral upper respiratory infection or evidence of extrasinus extension of infection such as periorbital edema may be used to diagnose ABRs. Although patients who meet these clinical criteria demonstrate decreased duration and severity of symptoms when treated with antibiotics, the magnitude of improvement is relatively small.⁶⁶ For patients with severe symptoms, antibiotic treatment is recommended. In patients with moderate symptoms beyond 10 days or who worsen after 5 days, antibiotic treatment is an option.⁶⁵ Amoxicillin has been recommended as a first-line treatment for uncomplicated ABRs with trimethoprim-sulfamethoxazole encouraged for penicillin-allergic patients.⁶⁶ However, with the emergence of resistant pathogens, the Infectious Diseases Society of America now recommends amoxicillin-clavulanate as first choice in adults, followed by doxycycline or a respiratory fluoroquinolone.⁷⁰ Diagnostic imaging, including both radiographs and CT images of the sinuses, do not adequately distinguish between ABRs and acute viral rhinosinusitis and are not recommended unless extrasinus spread of infection is suspected.^{65,66}

Recurrent acute rhinosinusitis, defined as four or more episodes of ABRs per year, may arise in the context of predisposing anatomic variations, exacerbations of CRS, immune compromise, or without identifiable predisposing factors.⁶⁶ Surgical intervention with widening of sinus ostia and removal of ethmoid septations may decrease the frequency and severity of symptoms.^{71,72} Although uncommon, complications arising from rhinosinusitis are seen more frequently in acute than chronic rhinosinusitis. Infection may spread to the orbit or intracranial cavity, a complication more common in children.^{73,74} Group B streptococcus is the most likely pathogen. Urgent evaluation and treatment, often including surgical drainage of affected sinuses and associated abscesses, is required to minimize the risk for visual loss, seizures, meningitis, and even death.

Invasive fungal sinusitis is a life-threatening condition that develops in patients with significant immune compromise. Diabetics with poorly controlled blood glucose levels and patients undergoing bone marrow transplantation are at highest risk. The diagnosis is suspected in this patient population with the development of facial pain, swelling, cranial neuropathies, or unexplained fevers. Imaging studies (CT and magnetic resonance imaging) are sensitive, but not specific, for invasive fungal sinusitis. The diagnosis is established by biopsy results demonstrating fungal invasion into the sinus tissues. Frozen section of diseased tissue may expedite this analysis. Cultures may be helpful to guide antifungal treatment; the morphologic features of fungal elements seen on pathologic evaluation may also assist in identifying the offending fungi. Extrasinus invasion is most common with mucormycosis. Treatment involves surgical

débridement, systemic antifungal medications, and, when possible, reversal of underlying immune dysfunction. Even with appropriate medical care, mortality for this condition approaches 50%.⁷⁵ Aggressive surgical débridement must therefore be considered in the context of the patient's goals of care.

A slowly progressive, indolent form of invasive fungal sinusitis is seen in patients with less severe immune compromise. Solid organ transplant recipients and patients with chronic corticosteroid use are at risk for this disorder. *Aspergillus* is the most common pathogen. The treatment principles are the same as for patients with acute invasive fungal sinusitis.

CHRONIC RHINOSINUSITIS

Epidemiology

Chronic rhinosinusitis (CRS) has an uncertain incidence because the diagnosis often requires both subjective symptoms and nasal endoscopy or CT evaluation. Surveys, which rely only on patient symptom reports, suggest that more than 15% of the U.S. population suffers from CRS,^{76,77} likely a significant overestimation of the true incidence.⁶⁵ The prevalence of physician-diagnosed CRS using diagnostic coding reporting in a limited geographic area was closer to 2%.⁷⁸ The impact of CRS on overall quality of life is estimated to be similar to that of *chronic obstructive pulmonary disease* (COPD) and congestive heart failure.⁷⁹ In the United States the overall cost burden for chronic sinusitis is estimated at \$8.6 billion/year.⁸⁰

Pathophysiology

CRS is characterized by persistent mucosal inflammation of the paranasal sinuses. The cause of this inflammation is variable and often poorly understood. Numerous theories have been proposed, including systemic immune dysfunction,⁸¹⁻⁸³ staphylococcal superantigens,⁸⁴ pathologic bacterial biofilms,⁸⁵⁻⁸⁷ aberrant immune response to fungus,⁸⁸ and dysbiosis (e.g., imbalance of the resident microbial population).²² Several subtypes of CRS have been well established.

The bacteriology of CRS differs from that of acute sinusitis. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and anaerobic bacteria are more commonly cultured from patients with chronic disease than with acute disease. Recent studies using culture-independent bacterial identification demonstrate that healthy sinuses contain diverse bacterial communities, which may serve a protective role in the sinuses. Chronically inflamed sinuses are characterized by a loss of bacterial diversity with overgrowth of a pathologic species. *Corynebacterium tuberculostrictum* may represent a previously unrecognized bacterial pathogen. Furthermore, in a mouse model of sinusitis, the pathogenic potential of bacteria is enhanced with depletion of native bacterial communities through antibiotic treatment. Coinstallation of presumed probiotic microbes appears to protect against the inflammatory changes induced by exposure to pathologic bacteria.²²

Association with Allergy and Asthma

The role of allergy and atopy in CRS is unclear. Studies suggest a higher rate of positive skin tests in patients with

CRS⁸⁹ but may be confounded by selection bias. Although a causal role for allergy in patients with CRS has not been demonstrated, treatment of allergy in atopic patients with CRS improves patient outcomes.⁹⁰

CRS with nasal polyps (CRSwNP) demonstrates a more clear association with asthma. Nearly 30% to 40% of patients with polyps describe wheezing and respiratory discomfort. In addition, 26% of patients with polyps report a diagnosis of asthma, compared to 6% of control patients.⁹¹ Patients with asthma also demonstrate a high incidence of sinus mucosal thickening on CT imaging.^{92,93} Although asthmatic patients demonstrate a high incidence of nasal polyps, nonatopic asthma is more strongly associated (13%) with nasal polyps than atopic asthma (5%).⁹⁴ Asthmatic patients who undergo endoscopic sinus surgery for CRSwNP demonstrate clinical improvement in both upper and lower airway disease.⁹⁵⁻⁹⁷

CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

CRSwNP is frequently seen in combination with asthma, and the pathologic findings in these two disorders are similar. Nasal polyp tissue classically demonstrates an eosinophilic infiltrate with a predominance of type 2 T helper inflammatory mediators. CT findings include extensive opacification of the paranasal sinuses and nasal cavities (see Fig. 49-4). Although nasal polyps may be visible on anterior rhinoscopy and may even extend to or beyond the nasal vestibule, more frequently nasal endoscopy is required to visualize nasal polyps. Patients typically present with nasal congestion, obstruction, thick nasal drainage, and anosmia. Facial pressure is common. Severe pain, headache, and fever are unusual in the absence of acute exacerbations of chronic disease. Fatigue and difficulty sleeping are also common symptoms.

Patients with asthma and nasal polyps should be queried regarding sensitivity to aspirin and *nonsteroidal anti-inflammatory drugs* (NSAIDs). Aspirin-exacerbated respiratory disease is found in a subset of CRSwNP patients and is characterized by nasal polyps, asthma, and NSAID sensitivity. Patients with aspirin-exacerbated respiratory disease demonstrate abnormalities in arachidonic acid metabolism, characterized by increased production of proinflammatory

products of the 5-lipoxygenase pathway, and exposure to cyclooxygenase-1 inhibitors, such as aspirin and NSAIDs, results in shunting through the lipoxygenase pathway and in upper and lower airway inflammation. Patients often develop persistent rhinitis in their late teenage years with asthma and sinusitis developing over the next several years. Aspirin and NSAID sensitivity may develop at any point along the course of the disease.⁹⁸ Aspirin-exacerbated respiratory disease represents a significant proportion of patients with asthma (9%)⁹⁹ and CRSwNP (13%).⁹⁴ These patients demonstrate a more refractory clinical course in the treatment of their sinus disease. Aspirin desensitization improves both asthma and sinus disease in this patient population.¹⁰⁰⁻¹⁰³

Patients with unilateral nasal polyps should be evaluated for sinonasal neoplasms with imaging and consideration of biopsy. Before performing a biopsy of a sinonasal mass, the clinician should evaluate the relationship of the mass to the skull base to rule out an encephalocele. Assessment of surrounding vasculature is also critical because both aneurysms of the carotid artery and juvenile nasal angiofibromas may present as a nasal mass. Biopsy of these entities may lead to severe hemorrhagic complications.

Allergic fungal rhinosinusitis (AFRS) is a distinct category of chronic sinusitis. Unlike the majority of chronic inflammatory sinus disease, AFRS is often unilateral. This diagnosis is established by the presence of nasal polyps, eosinophilic mucus with Charcot-Leyden crystals, and skin or blood testing demonstrating allergy to fungus.¹⁰⁴ The incidence of AFRS is higher in African American patients, and the disorder is more common in humid regions, including the southern United States.^{105,106} Bone expansion and erosion may result in initial difficulty distinguishing AFRS from sinonasal neoplasms. In such cases, magnetic resonance imaging findings are also helpful in the diagnosis of AFRS (Fig. 49-5).

Congenital disorders that result in impairment of mucociliary clearance have a high incidence of CRS. Because nasal polyps are unusual in pediatric patients, their presence should trigger evaluation for cystic fibrosis and ciliary dyskinesia. Pathologic evaluation of polyps in these patients is more likely to demonstrate a neutrophilic infiltrate and a predominately type 1 T helper cell-mediated inflammatory process.^{107,108}

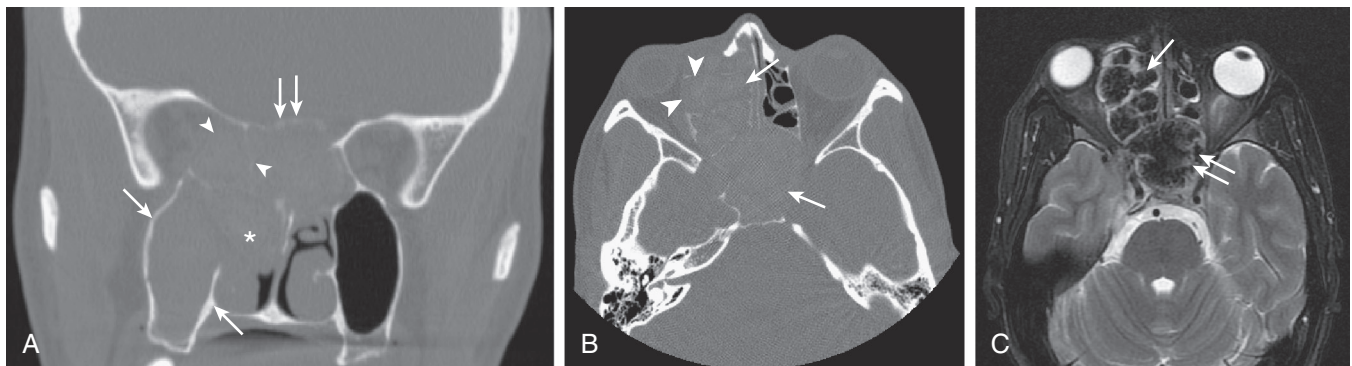


Figure 49-5 CT and MRI of allergic fungal rhinosinusitis. Coronal (A) and axial (B) CT images demonstrating allergic fungal rhinosinusitis. Note the extensive expansion of the right maxillary sinus (arrows, A), sphenoid and ethmoid sinuses (arrowheads, B), and right nasopharynx (*, A), with extension of abnormal soft tissue into the medial right orbit (arrowheads, A and B), with destruction of the medial right orbital wall. Note erosion of the skull base (double arrows). Axial T2-weighted MRI (C) demonstrates a loss of signal within the affected sinuses (arrow, right ethmoid sinuses, double arrows, sphenoid sinuses), which is characteristic of allergic fungal rhinosinusitis. (Courtesy Michael Gotway, MD.)

Treatment

Treatment of CRSwNP is challenging. Most patients receive temporary, if any, benefit from antibiotic therapy.^{109,110,110a} Topical steroid sprays often provide improvement^{110,111} but rarely provide adequate symptomatic relief for patients with a significant polyp burden. Systemic steroid therapy frequently provides significant symptomatic improvement.¹¹² Unfortunately, systemic side effects limit long-term use of this medication, and symptoms often recur quickly following cessation of exogenous glucocorticoids. Initial enthusiasm for antifungal irrigations has waned with the publication of trials that demonstrate not only a lack of efficacy, but worsened symptoms when compared to placebo saline irrigations.^{109,110a,113} Endoscopic sinus surgery with removal of polyps and cleaning of mucus and debris from within the sinuses results in significant symptomatic improvement.^{114,114a} Systemic corticosteroids are frequently initiated before surgery for CRSwNP to decrease mucosal inflammation, which improves hemostasis and endoscopic visualization during surgery. Corticosteroids also enhance control of asthma during endotracheal anesthesia and the postoperative period. Even in the setting of appropriately performed endoscopic sinus surgery, recurrence of polyps is common. Combining medical and surgical interventions is critical in this patient population. Surgery enhances postoperative access to the sinuses, allowing enhanced penetration of topical steroid irrigations. Steroid-impregnated implantable materials have also been used to extend the duration of symptomatic improvement following surgery.¹¹⁵⁻¹¹⁷

New biologic treatments hold promise for the treatment of CRS. Omalizumab (anti-IgE) has been used to treat refractory asthma and, although clinical data are limited, early trials suggest that omalizumab may reduce polyp burden and symptoms in CRSwNP patients.^{110,118} Interleukin-5 is an important driver of eosinophil differentiation and survival, and an anti-IL-5 (mepolizumab) has shown promise in early trials as a treatment for CRSwNP.¹¹⁹ A recently completed randomized, controlled trial evaluating anti-IL-4 (dupilumab) as a treatment for refractory asthma demonstrated improvement in CRS symptoms as assessed by a validated, disease-specific CRS outcome score.¹²⁰ Availability and cost currently limit both clinical use and investigational studies into the efficacy of these biologic agents as treatments for CRS.

THE ORAL CAVITY, OROPHARYNX, HYPOPHARYNX, AND LARYNX

ANATOMY, HISTOLOGY, AND PHYSIOLOGY

Oral Cavity

The *oral cavity* is defined as the space from the lips to the end of the hard palate. It contains the teeth, the buccal and gingival mucosa, the mandible and hard palate, the floor of the mouth and the tongue anterior to the circumvallate papilla (Fig. 49-6). The oral cavity structures are mostly under voluntary control. The oral cavity functions to control the ingestion of substances. The structures control

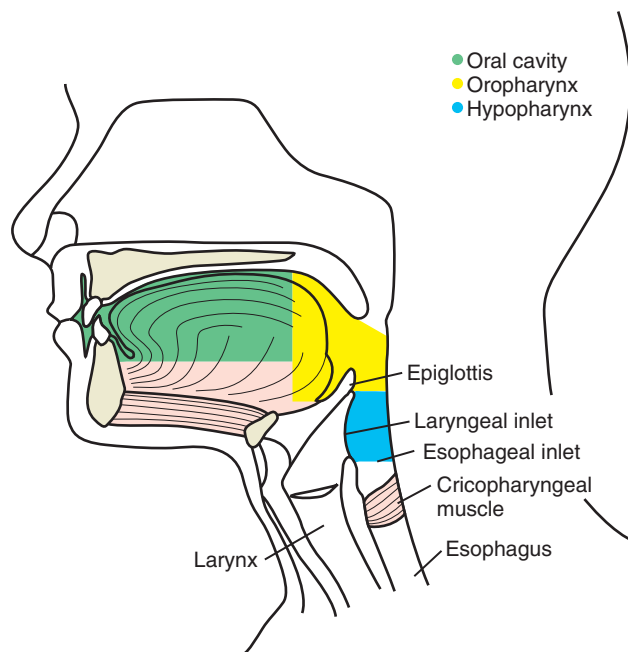


Figure 49-6 Schematic of the oral cavity (green), oropharynx (yellow), and hypopharynx (blue) along with the esophageal inlet, cricopharyngeal muscle, and upper esophageal sphincter.

the substance during mastication and preparation of a bolus suitable for presentation to the oropharynx for reflexive swallowing. This involves the muscles of mastication for opening and closing of the jaws as well as the muscles in the lips and cheeks to control the size of the cavity and the muscles of the tongue to move the food particles around the mouth and shape them into the required bolus. In addition to controlling the intake of substances, the structures in the oral cavity are responsible for voluntary modulation of air exhaled from the lungs. This voluntary control is used to control the rate of the air exhaled, as well as to shape the noises created by air flow into speech and song.

Oropharynx

The *oropharynx* is defined as the space from the end of the hard palate to a plane parallel to the top of the epiglottis (see Fig. 49-6). This space includes the structures of the lateral pharyngeal walls made up by the middle constrictors, the palatoglossus and the palatopharyngeus, the palatine tonsils, the soft palate and uvula, the vallecula, and the base of the tongue. Although these muscles and structures are under voluntary control for assistance in the rate of exhaled air from the lungs and shaping sounds released from the vocal tract, they are under reflexive control for swallowing. Once the sensory nerves are triggered by the exposure to a bolus of solids or liquids, the central nervous system sends a reflexive response to swallow. This reflex results in orderly contraction of the tongue base, soft palate, and lateral pharyngeal walls to propel the bolus posteriorly, seal off the nasopharynx, and propel the bolus to the hypopharynx, respectively. Again, the skeletal muscles of these structures are under both voluntary and reflexive central nervous system control.

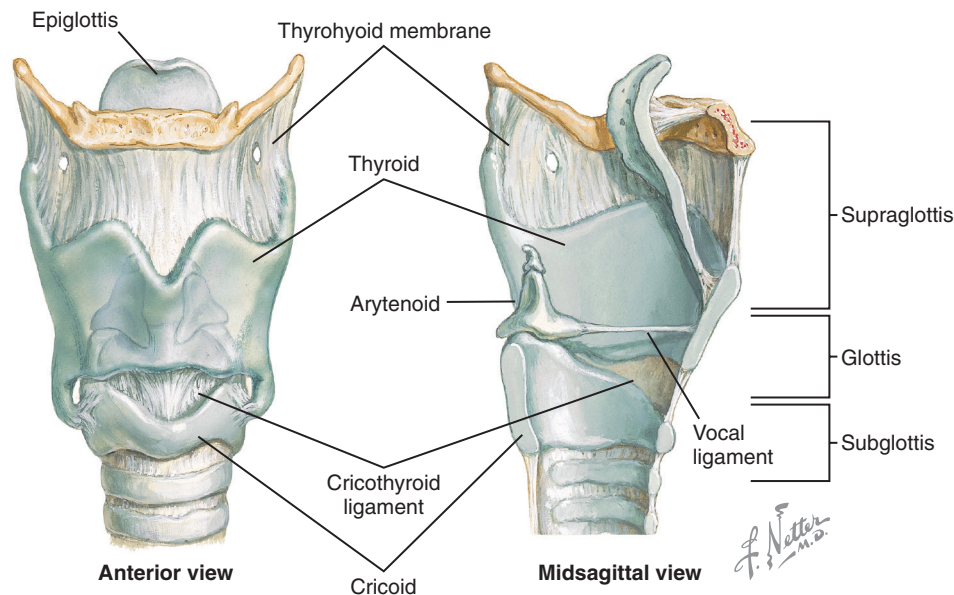


Figure 49-7 Schematic view of the larynx with the cartilage and ligamentous structures. The supraglottis, glottis, and subglottic subdivisions are marked. (Modified from Netter FH: *Atlas of human anatomy*, ed 5, Philadelphia, 2010, Saunders. Netter illustration from www.netterimages.com, ID: 1495. © Elsevier Inc. All rights reserved.)

Hypopharynx

The *hypopharynx* is defined as the space from a plane perpendicular to the tip of the epiglottis to the superior and lateral aspect of the larynx down to the esophageal inlet (see Fig. 49-6). This includes the structure of the lateral pharyngeal walls, including the inferior constrictors and mucosal membranes, as well as the bilateral pyriform sinuses. As for the oropharynx, the skeletal muscles that make up these structures are under voluntary control for assisting in regulation of airflow out of the lungs and shaping the airflow into speech as well as reflexive central nervous system control for swallowing. The distal end of the hypopharynx culminates in the upper esophageal sphincter. This is a region of the pharynx that controls opening of the proximal esophagus to allow passage of food into the alimentary track and to prevent the inadvertent regurgitation of food or secretions back into the pharynx and upper airway. Although the upper esophageal sphincter is several centimeters in length, the primary portion is made up of the cricopharyngeus muscle (see Fig. 49-6). This circumferential, slinglike skeletal muscle is maintained in a tonic contracted and closed state. The act of swallowing initiates reflexive inhibition of the neural input, resulting in muscular relaxation. As the larynx and pharynx are pulled upward and forward by the actions of other muscles, the relaxed upper esophageal sphincter is stretched open. This allows the passage of the food bolus. The bolus can fail to pass either because of failure of relaxation of the cricopharyngeus muscle segment or failure to stretch the area open through pull of coordinated muscles on the relaxed upper esophageal sphincter segment. Either will result in the retention of foods and secretions, which can then spill into the upper airway.

Larynx

The *larynx* is made of the bone, cartilage, muscular, and mucosal structures from the epiglottis to the bottom of the

cricoid ring. It is divided into three regions based on the lymphatic drainage patterns. These regions include (1) the supraglottis from the tip of the epiglottis to the top of the vocal folds (also known as the “vocal cords”), including the upper part of the arytenoid; (2) the glottis, which includes the tissue from the top of the vocal fold to 1 cm below the top of the vocal folds; and (3) the subglottis, which is below the vocal fold to the first ring of trachea (Fig. 49-7).

Bone and Cartilage. The structural bone and cartilages of the larynx include the hyoid bone, paired thyroid lamina, and cricoid ring. These structures have ligamentous and cartilaginous attachments to each other to allow them to function as one organ. Specifically, the hyoid is attached to the thyroid cartilage by the thyrohyoid ligament. The thyroid laminae are attached to the cricoid laterally by the fibrous cricothyroid joint and anteriorly by the cricothyroid ligament and membrane. The hyoid bone is attached to the skull base by the styloglossus muscle, the mandible by the geniohyoid muscle, and the tongue base by the hyoglossus muscle. The laryngeal cartilage is attached to the pharyngeal wall through the inferior pharyngeal constrictor muscle and to the cricoid ring by the cricothyroid joint, membrane, ligament, and muscle. The cricoid is attached to the trachea through fibrous attachments. These connections support the airway. Other cartilaginous structures within the larynx include the arytenoid complex cartilages known as cuneiform, corniculate, and arytenoid cartilages and the epiglottic cartilage. The mucosal and muscular structures of the larynx include the aryepiglottic folds connecting the arytenoid complex to the epiglottis, the false vocal folds running from the body of the arytenoid to the base of the epiglottis, and the true vocal folds running from the arytenoid to the thyroid cartilage (Fig. 49-8). The laryngeal ventricle is a cleft between the true and false vocal folds. It contains mucus-producing cells and minor salivary

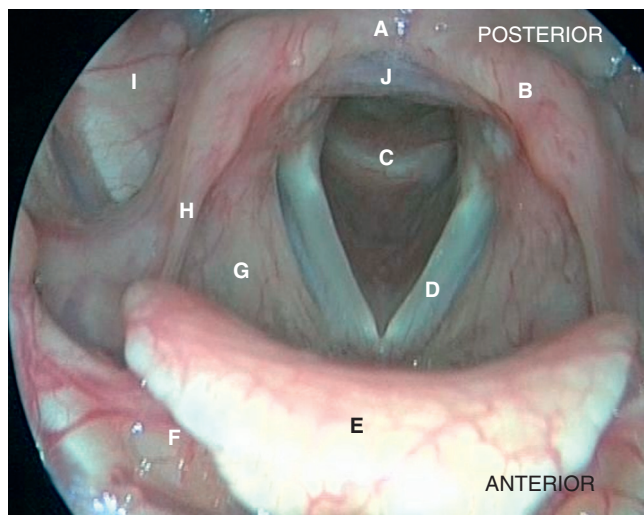


Figure 49-8 Upper airway anatomy: endoscopic view. A, esophageal inlet; B, arytenoid; C, trachea; D, true vocal folds; E, epiglottis; F, vallecula; G, false vocal folds; H, aryepiglottic folds; I, pyriform sinus; J, interarytenoid region.

glands that lubricate the tissue of the larynx during respiration and voice production. In addition, the shape of the ventricle probably creates turbulence in airflow that is significant for vocal fold vibration during voice production¹²¹ but of relatively little significance for airflow during respiration.

Arytenoid Complex. The arytenoid cartilage is attached to the cricoid ring through a series of anterior and posterior ligaments that form the capsule of the synovial cricoarytenoid joint. The corniculate and cuneiform cartilages have fibrous attachments to the arytenoids and are located on top of and anterior to the arytenoid cartilage, respectively. The true function of these structures is unknown, but they increase and stiffen the aryepiglottic fold and may therefore aid in prevention of aspiration during swallowing. The cricoarytenoid joint allows movement of the arytenoid on the cricoid ring for vocal fold abduction and adduction, which is controlled by the action of the intrinsic laryngeal musculature on the arytenoid. Specifically, the lateral cricoarytenoid muscle attaches from the lateral aspect of the cricoid to the muscular process on the posterolateral aspect of the arytenoid. Contraction of the lateral cricoarytenoid muscle creates inward rotation of the arytenoid on the cricoid and closes the laryngeal airway during swallowing, voicing, and respiration (exhalation). This activity is supplemented by the action of the interarytenoid muscle, which runs between the upper bodies of the arytenoids and pulls the arytenoids together. The interarytenoid muscle is probably more important during voice production than during respiration. The posterior cricoarytenoid muscle attaches from the posterior aspect of the cricoid ring also to the muscular process on the posterolateral aspect of the arytenoid. Contraction of the posterior cricoarytenoid muscle creates outward rotation of the arytenoid on the cricoid and opens the airway during respiration (inspiration).

Epiglottis. The epiglottis has ligamentous attachments to the hyoid bone (hyoepiglottic ligament) and thyroid

cartilage (thyroepiglottic ligament) and fibromuscular attachments to the arytenoid complex (aryepiglottic fold). As the names of these attachments imply (origin to insertion), the epiglottis moves in relation to these supportive structures during respiration and swallowing. This movement is passive. As the tongue base and pharyngeal walls contract and the hyoid and attaching laryngeal supporting framework are pulled upward, the epiglottis tilts posteriorly (passive inversion) to cover the top of the airway and divert the bolus to be swallowed to the outside of the larynx. The epiglottis does not completely cover the airway, but rather steers the bolus through the pyriform sinus and outside of the laryngeal airway. Patients who lose their epiglottis secondary to cancer treatment can be taught to swallow again by strongly contracting the tongue base to pull the larynx forward and partially cover the laryngeal airway. Usually this results in a small amount of residue deposited on the top portion of the larynx and/or vocal folds that then must be cleared out of the larynx into the hypopharynx with a throat clear or cough and swallowed a second time. This is known as a “supraglottic swallowing technique” and is useful in preventing aspiration in cases of epiglottic loss or malfunction.

Mucosal and Fibromuscular Structures. The mucosal and fibromuscular structures include the aryepiglottic folds, false vocal folds, and true folds. As stated previously, the aryepiglottic folds run from the arytenoid complex to the epiglottis. They separate the pyriform sinus of the hypopharynx from the supraglottic larynx and form a sling of tissue around the vocal folds to prevent aspiration during swallowing. They consist of fibrofatty tissue and contain minor salivary glands and mucus-producing cells. If a significant portion of the aryepiglottic fold is removed during surgery, then the liquid or food bolus can fall into the larynx and increase the risk for aspiration. At the inferior portion of the aryepiglottic fold is the false vocal fold. This is a fibrofatty collection of tissue also covered with epithelium and contains minor salivary glands and mucus-producing cells. The true function of the false vocal folds is unknown, but they most likely affect the resonance characteristics of the voice rather than have any effect on respiration or deglutition. The aryepiglottic folds and false vocal folds are part of the supraglottis and can be covered with either respiratory epithelium or squamous epithelium.¹²²

The true vocal folds are composed of the *thyroarytenoid* (TA) muscle covered with mucosa. The mucosa is a stratified squamous epithelium supported by a specialized submucosa or lamina propria that differentiates into three layers. This differentiation is likely secondary to use of the vocal folds for phonation, which causes the supporting fibroblasts to produce and secrete proteins and carbohydrates.¹²³ These extracellular particles are then layered in a particular order with dense collagen as the deepest layer, an elastin-rich middle layer, and glycosaminoglycans and glycoproteins forming a spongy superficial layer. The middle and deep layer form a transition zone known as the vocal ligament, which runs from the anterior aspect of the thyroid cartilage to the vocal process of the arytenoid. This ligament allows the superficial layers to separate from the deeper layers as the vocal folds vibrate to produce voice and is probably responsible for the relatively wide vocal pitch

range that humans are able to produce. The TA muscle runs from the anterior aspect of the thyroid cartilage and attaches along the body of the arytenoid cartilage. As the TA contracts, it adducts, tenses, shortens, and thickens the vocal fold. This is important because, as the TA muscle changes tension and shape, it has an indirect effect on the vocal fold mucosa, which is involved in vocal fold vibration. The vibration frequency of an object is related to the driving force for vibration as well as the tension and mass of the object. Therefore, as we adjust the tension in the vocal fold, through voluntary contraction of the intrinsic skeletal muscle of the larynx, we affect the frequency of vocal fold vibration, which is perceived as the pitch of the voice. In the case of vocal fold tension and mass, the two most important muscles are the TA along with the cricothyroid muscle. As the cricothyroid muscle, which originates on the cricoid ring anteriorly and inserts on the thyroid cartilage, contracts, the thyroid cartilage is subluxed on the cricoid ring. This results in stretching the vocal fold and increasing the tension, which drives up the frequency of vibration and the pitch of the voice.

Pathophysiology. As can be inferred from the previous section, the pharynx and larynx have prominent and complex functions in the upper airway to separate the alimentary tract from the respiratory tract for human survival. For swallowing and respiration the pharynx and larynx must work in a coordinated manner. If these systems fail to function properly, then the airway can be obstructed or pharyngeal contents can be aspirated and potentially lead to lung disease.

DISORDERS OF SWALLOWING

Epidemiology

Disorders of swallowing caused by either neurologic or muscular diseases interrupting the normal sequences of upper airway and pharyngeal activity can lead to the aspiration of pharyngeal contents either directly, during the swallowing act, or indirectly from refluxed gastric contents. Aspiration of large quantities of liquid material or of large solid substances can lead to airway obstruction with asphyxiation and death. Acute aspiration of small amounts of substances has been shown to produce acute pulmonary inflammation.¹²⁴ Aspiration of acidic materials appears to be more inflammatory than aspiration of less acidic materials.¹²⁵ If the aspiration is an isolated single event, then the inflammation resolves with little consequence.¹²⁴ However, repeated aspiration can damage the alveolar lining of cells and capillaries and lead to bacterial invasion, mucosal desquamation, and mononuclear cell inflammation.¹²⁵ In lung transplant patients, chronic aspiration of refluxed gastric contents has been associated with increased failure rates of grafts through the development of bronchiolitis obliterans syndrome.¹²⁶ Although the exact mechanism is unknown, it appears to be related to fibrosis that develops as a response to chronic repeated inflammation. This response may be reduced through the use of agents that reduce inflammation.¹²⁷

Disorders of swallowing, commonly called dysphagia, affect between 2% and 11% of the general population.¹²⁸

The etiology is varied. Dysphagia may arise in response to normal aging due to weakening of the pharyngeal musculature. Neurologic disease, such as stroke, motor neuron disease, or Parkinson disease may cause dysphagia due to mistiming of the swallow with poor coordination, as well as secondary to weakness or spasticity of the pharyngeal musculature. Finally, dysphagia often results from medical intervention for the treatment of head and neck disease or following intubation for respiratory failure.

Dysphagia is reported to develop in 40% to 50% of patients intubated for more than 48 hours.¹²⁹⁻¹³¹ Furthermore, the incidence of postextubation dysphagia rises by 14% for each additional day of intubation and is significantly more common in older patients.^{130,132} The cause of dysphagia due to prolonged intubation is not completely understood. However, because the incidence is remarkably high, all patients intubated for prolonged periods should be evaluated with at least a bedside swallow examination before the initiation of oral feeding after extubation.¹²⁹ Clinical studies have also revealed that aspiration after extubation from prolonged intubation may be silent due to changes in laryngeal and pharyngeal sensation; therefore some authors recommend more aggressive intervention with flexible endoscopic examinations.¹³² Although dysphagia with aspiration does not always lead to pneumonia,¹³² dysphagia alone is correlated with prolonged hospital stays.¹³¹ The incidence of postintubation dysphagia can be reduced by using smaller endotracheal tubes and with careful monitoring of the endotracheal tube cuff pressure.^{133,134}

Symptoms of Disorders of Swallowing

The most common symptoms in patients with disordered swallowing are chronic coughing, weight loss, and repeated episodes of pneumonia. On questioning, patients report that they cough during meals. In general, a greater difficulty with swallowing liquids is indicative of neurologic dysfunction or muscular weakness, and a greater difficulty with solids is more indicative of obstruction. The examiner should inquire about what substances cause the most difficulty, the timing of the cough in relation to eating, the length of time required to finish a moderate-sized meal, and where food appears to create the greatest difficulty during the swallow.

Coughing early during the act of swallowing indicates poor oral motor control of the bolus. Patients with neurologic disorders may notice that they cannot control the food within the oral cavity and the food prematurely spills into the oropharynx or hypopharynx before the patient is ready to swallow. Patients find that substances that break apart easily or consist of both liquids and solids are most difficult because portions of the bolus can escape. Coughing during or after the swallow is most indicative of pharyngeal dysfunction due to either disordered reflex timing of the pharyngeal contraction or muscular weakness that prevents the bolus from moving through the pharynx as required.

Prolongation of mealtimes often leads to malnutrition and weight loss. Patients with an intact swallow mechanism can usually finish a complete meal in 15 minutes. Longer mealtimes are suggestive of dysphagia. When patients go beyond 30 minutes for a meal, they typically begin to lose interest in eating. In most cases, this prolongation is socially

unacceptable, and dining companions begin to leave the table, forcing the patient to stop eating.

Dysphagia can be roughly divided into pharyngeal phase dysphagia and esophageal phase dysphagia. Patients with pharyngeal phase problems will complain of substances sticking in the back of their “throat” and coughing, because of aspiration of retained substances, whereas patients with esophageal phase disorders will complain of food lodging in the chest that needs to be regurgitated or “washed down” with liquids. Cough may also be stimulated at the distal esophagus, but this is after the swallow, nonproductive, and not associated with the development of pneumonia.

Evaluation of Dysphagia

Evaluation is best done by a team of physicians and speech-language pathologists interested in disorders of swallowing. After a careful history the patient can be given a sip of water during palpation of the laryngeal complex. As the patient swallows, the larynx should elevate briskly about 2 cm. In addition, the patient should not cough and should then be able to speak without a wet-sounding voice. If the patient passes this initial screening, then he or she should be asked to take multiple sips to see if the swallowing reflex breaks down. Next, complete head and neck evaluation, and indirect endoscopy of the hypopharynx and larynx is undertaken to assess for lip and tongue mobility and strength and for patterns of retained secretions or food particles. Patients with normal tongue function should be able to protrude the tongue and move it side to side without associated movement of the mandible. Retention of food particles within the oral cavity or inability to move the tongue freely is indicative of weakness or restricted motion. Indirect endoscopy identifying pooling at the base of the tongue within the vallecula is suggestive of weakness of the tongue base, pooling of secretions within the pyriform sinuses is indicative of pharyngeal weakness, and pooling of secretions in the esophageal inlet is indicative of failure of cricopharyngeal opening or obstruction of the esophagus.

To confirm these patterns of weakness, flexible endoscopic evaluation of swallowing¹³⁵ or modified barium swallowing examination can be performed. These tests are usually performed by a qualified speech-language pathologist. Rather than just being a screening test for aspiration, these examinations should be used to identify which deficits within the swallowing act are responsible for the dysphagia. This information will direct treatment strategies.

Treatment

Treatment for disorders of swallowing involves precise identification of the region and type of the swallowing deficit. If muscular weakness is identified, patients can be given a series of exercises that target specific areas of either the tongue base^{136,137} or lateral pharyngeal walls.¹³⁸ If neurologic deficits are identified that result in reflex timing issues or if the muscular deficits are insurmountable, then patients can be taught compensatory strategies to improve the safety of the swallow. These strategies include repositioning of the patient during the swallow so that the bolus is less likely to fall into the airway, chin tuck to keep the bolus in the mouth during mastication, or head turning to close off the weakened side of the pharynx during the swallow act. Finally, if

none of these techniques are beneficial, and the patient and the family are interested, a feeding tube can be inserted to prevent weight loss and lessen the burden of needing to ingest a sufficient amount of calories orally to maintain weight. If repeated aspiration persists, then laryngotracheal separation should be considered.

GASTROESOPHAGEAL AND LARYNGOPHARYNGEAL REFLUX DISEASE

Association with Asthma and COPD

The relationship between reflux disease and asthma and COPD is complex. Although the association between reflux and severe asthma is well accepted, the empirical evidence for causation of one by the other is lacking. Lung disease may be related to reflux disease by different mechanisms. First, direct microaspiration of contents refluxed into the pharynx on a chronic basis may lead to pulmonary remodeling. The extent of injury is related to the amount and characteristics of the aspirate, the frequency of aspiration, and the effectiveness of protective lung-clearance mechanisms. This is the proposed mechanism for the development of bronchiolitis obliterans syndrome in transplant patients. Second, reflux or reduced clearance of food from esophageal dysmotility may cause vagally induced bronchospasm. Vagally induced bronchospasm is associated with increased acidification of the lower esophagus and may be ameliorated by deacidification of the gastric contents in patients with difficult-to-control asthma.¹³⁹ Treatment with a *proton pump inhibitor* (PPI) improves asthma control in individuals with symptomatic *gastroesophageal reflux disease* (GERD), but not in those without symptoms.^{140,141}

However, as previously stated, the association between reflux disease and lung disease does not prove causation. It is possible that the medications for the treatment of asthma increase reflux or that changes from chronic lung disease increase reflux as well. Albuterol is known to lower the resting pressure of the lower esophageal sphincter and decrease esophageal contraction amplitude. These changes may increase the incidence of reflux.¹⁴² Prednisone, which is often prescribed in patients with difficult-to-control asthma, has been shown to increase esophageal acid exposure times.¹⁴³ Chronic lung disease can lead to hyperinflation with flattening of the diaphragm. The diaphragm, specifically the crura around the esophageal hiatus, forms a critical part of the lower esophageal sphincter. Therefore flattening of the diaphragm decreases the protective reflux barrier of the diaphragm. An increased transdiaphragmatic pressure gradient, as seen in patients with COPD, predisposes to the movement of gastric contents into the esophagus.

Evaluation of GERD and Laryngopharyngeal Reflux Disease

There are no universally accepted physical findings in the oral cavity and oropharynx that are pathognomonic for extraesophageal reflux disease.¹⁴⁴ In addition, although attempts have been undertaken to develop a “reflux finding score” for physical changes in the larynx in patients with presumed extraesophageal reflux,¹⁴⁵ attempts at validation of these findings through correlation with pH manometry

have been unsuccessful. It is widely believed that any source of irritation, reflux or otherwise, can lead to the same changes. Therefore the findings previously ascribed to laryngeal reflux disease are nonspecific.

Therefore, after a careful history for symptoms of both classic GERD and extraesophageal reflux disease has been completed, most patients will be placed on a trial of antireflux medications. If the trial results in amelioration of the symptoms, then the symptoms are commonly believed to be secondary to reflux disease. This method of evaluation for reflux with an empirical trial of medications is problematic because there may be a considerable placebo effect. Meta-analysis of randomized controlled clinical trials has shown that the effect of medications in alleviating symptoms is not significantly different from the effect of placebo.¹⁴⁶ Some clinicians proceed to 24-hour pH monitoring and/or impedance testing. Although 24-hour pH analysis is considered the gold standard for esophageal reflux, there are no universally accepted tests for the diagnosis of extraesophageal reflux. Even if attempts are made to measure pH within the hypopharynx to assess for extraesophageal spillage of gastric contents, widely accepted normative data do not exist, and there is significant debate as to what constitutes an abnormal finding.¹⁴⁷

Treatment of GERD

Treatment of GERD or extraesophageal reflux disease causing pulmonary problems is best started with dietary modifications and twice-daily PPI medications. The rationale for these aggressive management strategies is that the pharynx, larynx, and trachea have few if any natural protective mechanisms for the neutralization of aspirated gastric contents.^{148,149}

If there is strong suspicion of GERD or extraesophageal reflux causing pulmonary disease, then consideration can be given to surgical therapies such as Nissen fundoplication. Studies evaluating the true response of symptoms from extraesophageal reflux disease to surgical intervention show conflicting results. This is due in part to the significant difficulty in diagnosing extraesophageal reflux accurately as well as in understanding the role extraesophageal reflux may play in the pulmonary disease process.¹⁵⁰ The best results are obtained when classic GERD is identified and surgery, Nissen fundoplication, is performed for significant reflux within the lower esophagus.¹⁵¹⁻¹⁵³

PARADOXICAL VOCAL FOLD MOTION DISORDER AND LARYNGOSPASM

Definition and Diagnosis

Also known as vocal cord dysfunction, *paradoxical vocal fold motion disorder* (PVFMD) is a descriptive term for inappropriate adduction of the vocal folds during inspiration. The mistimed vocal fold closure creates difficulty breathing and is often misdiagnosed as asthma. The diagnosis of PVFMD is made on the basis of history followed by spirometry and laryngeal examination. Patients present with a constellation of symptoms, including difficulty breathing, a sensation of a foreign body or lump in their throat, a dry, nonproductive cough, and possibly chest tightness. These symptoms can manifest at rest, after talking, or

after physical exertion. Often the symptoms are exacerbated as the patient increases the intensity of the precipitating behavior. The disease is commonly misdiagnosed as asthma; however, the symptoms are refractory to standard management protocols. In patients with PVFMD, spirometry performed during an episode may reveal flattening of the inspiratory limb of the flow-volume curve, indicative of a variable extrathoracic obstruction¹⁵⁴⁻¹⁵⁶ (see Fig. 25-8, right panel). Laryngoscopy, considered by some to be the gold standard for diagnosis,^{154,157,158} may reveal paradoxical closure of the vocal folds during inspiration. Typically, paradoxical closure is observed during active or forced inhalation through either the mouth or the nose but is considered pathognomic by some when seen at the end of a speech utterance.¹⁵⁵ Provocation testing through increased exercise challenge, odor exposure, or even methacholine challenge may increase the sensitivity of laryngoscopy in the identification of paradoxical closure. However, even with these challenges, the sensitivity of endoscopy is still only 60% in patients with symptoms.¹⁵⁹ Therefore a presumptive diagnosis and empirical treatment may be warranted in all patients with symptoms who do not respond well to medical management for asthma.

Laryngospasm, closing of the vocal folds preventing inhalation, is a physiologic protective reflex to prevent aspiration when foreign particles stimulate the vocal folds or supraglottic structures. Laryngospasm is most commonly encountered during extubation from general anesthesia. It is managed with positive-pressure ventilation and small doses of paralytic agents to weaken vocal fold closure. Severe episodes are complicated by postobstructive pulmonary edema, which can require relatively prolonged management in the intensive care unit. In the absence of a known stimulus, recurrent episodes of laryngospasm can develop in patients with progressive neurologic disease^{160,161} or can be associated with severe forms of PVFMD. These often lead to recurrent trips to the emergency department and can be misdiagnosed as bilateral vocal fold paralysis.

In patients with recurrent episodic laryngospasm, complete neurologic examination should be undertaken to rule out a neurologic disorder. In the absence of neurologic disease, laryngospasm will often respond to the same management strategies that can be used for patients with PVFMD.

Etiology

The etiology of PVFMD is unclear. Considered by some to be a psychologic disturbance of young women, PVFMD is associated with asthma and GERD.¹⁶² High levels of stress, chronic postnasal drip, and environmental exposure to inhaled or aspirated irritants, allergies, or GERD may lead to laryngeal hyperresponsiveness, which in turn triggers paradoxical laryngeal closure. In one study,¹⁶² when patients with PVFMD were compared with normative data on the Minnesota Multiphasic Personality Inventory, 40% of the patients with PVFMD demonstrated elevation on the hypochondriasis and hysteria scales and minor elevation on the depression scale in a pattern consistent with conversion disorder. An additional 29% of these patients had significant differences in these scales but did not fit the classic conversion disorder pattern, whereas only 24% of patients

had scores suggestive of no psychopathologic conditions. Interestingly, patients with a history of asthma or GERD also scored significantly higher on the hypochondriasis scale than patients without those disorders.

The association of PVFMD with asthma, GERD, and environmental exposure to irritants raises the possibility of an organic cause in a percentage of patients with the disease. Some authors have suggested that when an organic cause is suspected, then the term *irritable larynx* should be used to describe the disorder.¹⁵⁶ In one study of patients with asthma, 19% had coexistent PVFMD, whereas only 5% of asymptomatic control subjects had any evidence of paradoxical vocal fold closure.¹⁶³

Treatment

The first step in the treatment of PVFMD is recognition of the disease. The clinical presentation is often confusing because patients may have coexistent asthma or GERD and are often resistant to the idea that behavioral change could result in any significant reduction in their symptom severity. One study estimated that the association with asthma and GERD is as high as 65% and 51%, respectively.¹⁵⁷ This association along with patients' desires to use medication to treat their problems usually leads to attempted medical trials for asthma management and therapy for GERD. With these strategies the symptoms may be reduced modestly, but the acute attacks of intermittent dyspnea, cough, and chest tightness can still be difficult to control. Therefore referral to a specialist able to perform nonsedated pharyngeal and laryngeal endoscopy is required. If the true coexistence of asthma is questionable because there is little if any response to bronchodilator therapy, then repeat pulmonary function testing before and after bronchodilator therapy and possibly with methacholine challenge is indicated. If the test results are positive, then the management of the reactive airway disease should be maximized. If the test results are negative, then all medical therapy should be stopped because the asthma medications may be exacerbating the disease by irritating the laryngeal mucosa, increasing patient anxiety, or increasing the risk for gastroesophageal reflux. If symptoms lead to a suspicion that GERD or laryngopharyngeal reflux disease is a contributing factor, then it is reasonable to treat the patient with dietary modifications and PPI therapy. Dietary modifications include avoidance of foods known to cause reflux, small meals, and avoiding reclining after eating. Therapy with PPIs should be initiated on a twice-daily basis 1 hour before the first and last meal of the day. Reflux that reaches the hypopharynx most frequently happens after meals. Therefore PPIs should be given before the meal so that a serum level can be achieved before the stimulation of acid production by the ingested food. If symptoms have not improved by 2 to 3 months after the initiation of therapy, then it is reasonable to assume that acid reflux is not playing a significant role in the pathogenesis of the patient's disease, and PPI therapy can be terminated.

Following careful history and endoscopy to rule out other causes of airway obstruction, the treatment of acute episodes of PVFMD includes reassurance, breathing instruction, and possibly the use of helium and oxygen mixture ("heliox").^{164,165} Often acute exacerbations will precipitate visits to an emergency department. The patient presents

with dyspnea, a rapid respiratory rate, and stridor. Rather than immobile vocal folds or an obstructing mass lesion, endoscopy usually reveals that the vocal folds are held in a paramedian position through inspiration and expiration. If patients are asked to cough or clear their throat, the vocal folds will usually abduct. Vocal fold abduction can be further stimulated by reassuring the patient and attempting to provide a calm, relaxed environment. Inhaling through the nose and exhaling through the nose or pursed lips (metered breathing) may also be beneficial. Alternatively the patient can be asked to breathe through a straw. Placing a restriction in the airway before the laryngeal inlet, both with the nose and lips or a straw, facilitates the patient's ability to control his or her breath and promotes laryngeal relaxation with appropriate laryngeal activity. Respiratory control or metered breathing reduces the laryngeal hypersensitivity by reducing either the respiratory rate or breath volume or both. This type of respiratory retraining is the key to chronic management of patients with PVFMD.^{166,167}

Difficulties in establishing diagnostic criteria for PVFMD are even greater than for asthma. With asthma, objective pulmonary function measures can document reversible airflow obstruction, or methacholine bronchoprovocation can demonstrate bronchial hyperreactivity. Patients with PVFMD may show flattening of the inspiratory limb of the flow-volume curve as is seen in patients with variable extra-thoracic airway obstruction, but these changes can be mimicked by submaximal inspiratory effort. Therefore there are truly no objective measures of the disease, and establishing objective diagnostic criteria is not possible. Treatment then may involve placebo effects from medications for other disorders such as GERD or asthma or active respiratory retraining to engage the patient in regaining control of his or her breathing. This respiratory training uses techniques to reduce the rate and or volume of the breath and to engage the patient in a conscious effort to control his or her breathing. Due to the difficulty in establishing diagnostic criteria, there have been few randomized controlled trials of respiratory retraining in patients with PVFMD. Limited evidence from case series has shown a reduction in the severity of patient symptoms and improvements in quality of life, which can be maintained through periodic long-term follow-up.¹⁶⁸

VOCAL FOLD PARALYSIS

Unilateral

Unilateral vocal fold paralysis rarely produces symptoms of airway obstruction. Although changes in pulmonary function can be measured during both quiet and active breathing, these are rarely clinically significant.¹⁶⁹ The proposed mechanism for potential airway obstruction when it is present is either (1) the action of inspiratory airflow producing a Bernoulli effect on the flaccid vocal fold or (2) inappropriate reinnervation of the paralyzed vocal fold with active signals for adduction during inspiration (e.g., synkinesis).¹⁷⁰ The findings can be corrected through surgery to stabilize the flaccid vocal fold complex, botulinum toxin injections to reduce the effects of the inappropriate reinnervation, or surgery to reduce the nerve supply to the synkinetic vocal fold.¹⁷¹

Bilateral

Bilateral vocal fold paralysis most commonly develops secondary to surgery in the anterior compartment of the neck for thyroid disease.¹⁷² The recurrent laryngeal nerves are either crushed or cut during the intervention, and vocal fold abduction for inspiration and adduction for phonation are lost. Immediately after the onset of the injury, patients are often able to tolerate the loss of vocal fold abduction, because the vocal folds are flaccid and immobile in a lateral position. The voice is weak and breathy. However, the recurrent laryngeal nerve contains all axons for abduction and adduction in a single fascicle. As axons regrow, the vocal fold muscles regain tone without active adduction or abduction. Because of the increased mass of the adductor muscles compared to the abductor muscle, the vocal folds adopt a more medial position. Vocal fold tone recovers in the majority of patients who suffer an injury to the recurrent laryngeal nerve.¹⁷³ This process of neural regeneration takes 3 to 9 months and leads to slowly progressive improvement in voice but progressive airway compromise. Patients adapt to this progressive airway compromise by decreasing their level of activity. The majority of patients can be managed without a tracheotomy.

A small percentage of patients develop bilateral vocal fold paralysis secondary to a Chiari malformation with increased intracranial pressure and compression of cranial nerve X in the foramen magnum by the base of the brain as it herniates through the foramen. This condition can be extremely difficult to diagnosis. Finally, a small percentage of patients will have an idiopathic etiology. In these instances the paralysis can develop bilaterally simultaneously or unilaterally separated by years.¹⁷⁴

Patient with bilateral vocal fold paralysis typically complain of minimal voice changes and note marked dyspnea on exertion. Careful history usually reveals the cause as prior surgical intervention,¹⁷² and general examination reveals prolongation of inspiration with mild to moderate inspiratory stridor. Endoscopic examination reveals bilateral vocal fold immobility with possible elongation of the vocal folds on inhalation.¹⁷² Pulmonary function testing demonstrates a classic pattern of variable extrathoracic obstruction with flattening of the inspiratory limb of the flow-volume curve and little change in the expiratory limb (see Fig. 25-8, right panel). When maximal inspiratory flow falls below 1.5 L/sec, most patients are markedly symptomatic, and intervention is warranted. If inspiratory flow is maintained around 2 L/sec, most patients can perform modest activity such as climbing one flight of stairs or walking on level surfaces.

The treatment of bilateral vocal fold paralysis is directed at static enlargement of the airway. This can be accomplished through tracheotomy. If patients choose this option, then consideration should be given to the creation of a skin-lined tracheostomy tract. This will reduce the risk for granulation tissue growth at the stoma, provide a safe stable stoma for patients to manage by themselves on a chronic basis, and allow patients to use an appliance that will hold a one-way valve so that digital occlusion is not required for phonation.¹⁷⁵ Bilateral vocal fold paralysis can also be treated by injecting botulinum toxin into the muscles of adduction. This reduces the adductor force and allows

improved function of the abductor muscles. Voice is fairly well preserved because the patient can usually override some of the effects of the botulinum toxin. The disadvantage of this treatment option is that the patient will require repeat injections.¹⁷⁶ Cordotomy or partial arytenoidectomy are also surgical options for treatment designed to remove the posterior portion of the vocal fold or a portion of the arytenoid cartilage, respectively. This enlarges the cartilaginous portion of the laryngeal airway by 1 to 2 mm without interfering too greatly with the anterior vibratory function of the vocal folds. However, because the posterior portion of the airway is enlarged on a static basis, air will leak out during phonation, and the voice will be reduced in volume as well as breathy in quality. This is referred to as “the great compromise” because the larger the airway for breathing and activity tolerance, then the worse the voice. The patient and surgeon must decide on a balance.¹⁷⁷ Additionally, one or both of the vocal folds can be sutured in a lateral position through a myriad of different techniques referred to as “suture lateralization.” Some of these techniques are potentially reversible and can be used in patients in whom recovery of function is possible, to improve their airway during this period.¹⁷⁸ Finally, experimental surgical strategies for management with electrical stimulation of the abductor muscles to open the glottis are being conducted. Initial results indicate that abduction for respiration can be achieved without compromise of vocal fold closure for voice production.

GLOTTIC STENOSIS

Scarring of the larynx, usually in the posterior portion, referred to as *posterior glottis stenosis* (PGS), most commonly develops secondary to prolonged intubation for mechanical ventilation. In fact, when patients present with bilateral vocal fold immobility after prolonged intubation, then 95% of the time the immobility is secondary to scar formation in and around the cricoarytenoid joints.¹⁷² This is a decidedly different process from bilateral vocal fold paralysis, but clinically and endoscopically it can be difficult to distinguish because visual inspection reveals the vocal folds to be immobile in the paramedian position in most patients. Helpful clinical clues to diagnosis are the events and timing around the onset of symptoms. The most common event associated with onset is prolonged intubation. As the endotracheal tube rubs against the mucosa of the posterior larynx, the mucosa is eroded and inflammation develops. Reflux may play a role in adding to inflammation or mucosal erosion.¹⁷⁹ Secondary infection of the mucosal ulceration may also play a role in adding to inflammation. After the endotracheal tube is removed, the mucosa heals by secondary intention over a 6-week period. Thus the patient notices deterioration of respiration more rapidly after a mucosal injury than after a neurologic injury; following a neurologic injury, the difficulty with respiration develops over a 3- to 6-month period as the nerve recovers partial tone.

Examination also reveals subtle differences in patients with PGS from those with bilateral vocal fold paralysis. First, patients with PGS usually have a normal voice because vocal fold adduction is maintained. On endoscopic examination there are subtle differences in the appearance of the vocal fold motion. Because the reduction in vocal fold

abduction and adduction is mechanical, the physical activity that remains is usually appropriate with abduction and adduction being well timed with inspiration and voicing. There is no evidence of spastic or synkinetic activity in patients with PGS as there may be in patients with bilateral vocal fold paralysis. Careful endoscopic evaluation usually reveals scar tissue over and around the cricoarytenoid joint. This can be subtle, with a relatively normal appearance and only slight reduction in the normal size and shape of the posterior portion of the larynx, or obvious, with overt scar tissue built up in the posterior portion of the glottis.¹⁸⁰ Finally, pulmonary function testing usually reveals a fixed extrathoracic pattern with flattening of both the inspiratory and expiratory limbs of the flow-volume loop.

Distinguishing between PGS and bilateral vocal fold paralysis is clinically significant because treatment options and outcomes are different. Whereas both bilateral paralysis and PGS will respond to tracheotomy, PGS does not respond favorably to botulinum toxin injections because of the mechanical fixation of the joint, which does not allow the entire vocal fold to move laterally when the adductors are relaxed. Rather, the relaxed vocal fold muscle tissue is held near the midline by the fixed joint. This can then collapse into the airway during inspiration secondary to Bernoulli forces and exacerbate airway obstruction. In PGS the initial surgical treatment should be aimed at release of the scar tissue that holds the joint in the fixed position. If this is not possible due to loss or remodeling of the cartilaginous joint structure, then portions of the cartilage or vocal fold can be removed. If possible, mucosal advancement flaps should be designed to cover the site of surgical excision. Because the tissue of the posterior glottis is scarred, simple incision through prior scar tissue is less likely to provide sustained significant release and more likely to heal with recurrent scar. Injudicious surgery can make the problem worse.

UPPER AERODIGESTIVE TRACT MALIGNANCIES

Malignancies of the upper aerodigestive tract are a significant cause of morbidity and mortality. Cancers of the upper aerodigestive tract constitute approximately 4% of all malignancies.¹⁸¹ *Squamous cell carcinoma* (SCC) is the predominant cancer in this region, and smoking and alcohol use have been the traditional risk factors. Surgery, radiation, and chemotherapy all play an important role in the treatment of this disease; a thorough discussion of this topic is beyond the scope of this chapter.

In the oropharynx, recent evidence has identified *human papillomavirus* (HPV) as an emerging, and now dominant, cause of malignancies. In all, 80% to 90% of newly diagnosed SCC of the tonsils or base of the tongue are HPV induced. HPV-associated oropharyngeal SCC represents a distinct clinical entity with a significantly better prognosis than non-HPV-associated oropharyngeal SCC. National Cancer Center Network guidelines now recommend HPV testing for all oropharyngeal malignancies. HPV-16 is identified as the most common HPV subtype associated with oropharyngeal malignancy.¹⁸² In SCC of the oral cavity, oral

tongue, and larynx, HPV is less commonly found; in this region, tobacco and alcohol use remain the primary risk factors. Whereas the incidence of these nonoropharyngeal SCCs is declining likely secondary to a decrease in tobacco use, the incidence of oropharyngeal carcinoma is rising, likely due to HPV.

Laryngeal cancers usually present early with voice changes. However, if the cancer arises in the supraglottic area, the subglottis, or pyriform sinus, or if the patient ignores the changes in voice and the diagnosis is otherwise delayed, then airway obstruction can be one of the presenting symptoms. In these instances the diagnosis is made through endoscopic evaluation, and the airway should be managed with endoscopic debulking of the tumor before definitive therapy is undertaken.¹⁸³

SUBGLOTTIS AND CERVICAL TRACHEA

ANATOMY, HISTOLOGY, AND PHYSIOLOGY

The subglottis is the area within the cricoid ring from the bottom of the vocal folds to the top of the first tracheal ring. The latter is the only complete ring in the airway and structurally functions to support the larynx and suspend the trachea. The subglottis is lined with a respiratory mucosa with goblet cells for mucus production and minor salivary glands as well. Mucus and saliva travel upward because of the actions of the ciliated epithelium and airflow and help humidify the airway as well as lubricate the vocal fold mucosa. In the adult human the subglottis is the narrowest portion of the airway and ranges from 15 to 18 mm in diameter. It is roughly a round or slightly oval tubular space that is narrowest just below the vocal folds and widens out at the bottom at the transition into the cervical trachea. The space extends for 1 to 2 cm in vertical dimension from the bottom of the vocal folds to the first tracheal ring. The shape of the subglottis is probably important for establishing laminar flow through the glottis. This is important for both the clearance of secretions and generating flow that will efficiently drive vocal fold vibration. Irregularities in the subglottic mucosa often lead to turbulent airflow with crust formation, which can further compromise the airway. The cervical trachea is the first four or five tracheal rings.

SUBGLOTTIC AND CERVICAL TRACHEAL STENOSIS

Pathophysiology

Because the subglottis is surrounded by a firm cartilaginous structure and the mucosa lies over the surface with only a normal submucosa for support of the epithelium, the area is particularly prone to injury from surgical manipulation or intubation, reflux disease, and autoimmune disease. Injury to the mucosa by any one of the prior processes can lead to exposure of the perichondrium, which then responds with inflammation and scar tissue formation. The scar tissue impedes airflow and mucus clearance, which can create a fixed extrathoracic airway obstruction.

The cervical trachea is most commonly injured through intervention from prolonged intubation (eFig. 49-1) or tracheotomy. Again, sloughing of mucosa from traumatic manipulation due to a movement of an endotracheal tube or repetitive deep suctioning can lead to exposure of the cartilage with inflammation and secondary collapse. Neoplasia of the minor salivary glands or squamous mucosa can also lead to obstruction.

Diagnosis

The diagnosis of subglottic or tracheal stenosis is made on the basis of patient's medical history, surgical history, and symptoms. The symptoms are primarily dyspnea on exertion and biphasic stridor. If the patient has had a prior intubation or tracheotomy, then the possibility of physical obstruction due to scarring should be considered. If a patient has known granulomatosis with polyangiitis (Wegener granulomatosis), then consideration should be given to involvement of the subglottic mucosa with inflammation, vasculitis, and granuloma formation (eFig. 49-2). In the case of idiopathic subglottic stenosis, patients are often treated for reactive airways disease without success.¹⁸⁴ These patients will benefit from early endoscopy/visualization of the subglottic region rather than weeks to months of ineffective treatment. As the name implies, there is no known cause for idiopathic subglottic stenosis. It has been presumed to be autoimmune, and the relationship with extraesophageal reflux disease is established, but the causal nature is unknown.^{179,185} Because idiopathic subglottic stenosis is found almost exclusively in women, some authors have proposed a hormonal cause.

High-resolution CT imaging (see eFigs. 49-1 and 49-2) and/or three-dimensional reconstruction of the CT images may help in diagnosis and characterization of the stenotic airway segment. But these imaging modalities are not always available, and, even if available, they may miss a short area of obstruction. Pulmonary function tests will demonstrate a characteristic plateau on the flow-volume curve (see Fig. 25-8, right panel), and the measured maximal flow can provide an estimate of the functional diameter of the flow-limiting segment (see eFig. 25-1).

The diagnosis of stenosis is confirmed with endoscopic visualization of the area. Endoscopy of the subglottis and cervical trachea for confirmation of stenosis is easily accomplished with a transnasal scope in the office setting. Lidocaine (4%) can be applied topically to the nose and can also be sprayed onto the vocal fold from above with a curved cannula or from below by injecting it percutaneously into the subglottis and asking the patient to cough. Then the flexible scope can be passed through the vocal folds and the area evaluated.

Treatment

Surgery is the primary mode of treatment of subglottic and cervical tracheal stenosis. The type of surgery, either endoscopic or open, and the use of adjuvant agents such as steroid injections or fibroblast activity inhibitors such as mitomycin C depend in part on the cause and characteristics of the stenosis. Usually treatment begins with an endoscopic approach. Rigid endoscopy allows palpation of the area to determine the nature of the scar tissue and the length of the segment of the airway that is involved. If

the segment is relatively short (less than 1.5 cm in length), occludes less than 50% of the airway diameter, and is primarily soft tissue in nature, then it will likely respond to endoscopic incision and dilation performed in a nontraumatic manner.¹⁸⁶ The incisions, which can be made with either cold steel or a laser, control the area of injury and allow the surgeon to identify the nature of the stenosis without further injury of the cartilaginous airway support. If the laser is used injudiciously, however, the surgeon can create more injury and damage to the cartilage. New-generation lasers have a very short pulse structure that results in minimal heat dissipation into the tissue beyond what is seen. Once the extent of the soft stenosis is identified, the surgeon can use that information to decide on the amount of dilation that the area will accept. The area is then dilated with a balloon to the appropriate size. Care is taken to spare islands of mucosa between the incisions to facilitate re-epithelialization before scar tissue reformation.

For very short stenotic segments or webs, any technique such as dilation alone to break up the web usually works after one or two procedures. When performed with the appropriate technique, the area of stenosis should remain dilated after the procedure during visual inspection. If the area collapses immediately after the dilation, then it is unlikely that the procedure will have lasting benefits. In addition to endoscopic incision and dilation, short and relatively discrete segments of cartilage collapse, such as may be seen at a tracheotomy site, can be resected endoscopically. Care should be exercised so that no more than 90 to 120 degrees of trachea are treated at one time. This may necessitate staging of the procedures with two or three attempts to resect the area.¹⁸⁷ The primary goal of endoscopy is to characterize the stenotic segment. If the segment is too long, involves too much cartilage, or collapses immediately after completion of the procedure, it is probably wise to proceed to open resection of the segment.

Key Points

- The upper airway contains diverse anatomic structures with a variety of functions that contribute to respiration, vocalization, smell, and taste.
- Allergic rhinitis and asthma are linked in both pathophysiologic and epidemiologic characteristics. Patients with persistent allergic rhinitis should be screened for asthma, and patients with asthma should be evaluated for allergic rhinitis.
- Although multiple medical therapies demonstrate efficacy in the treatment of allergic rhinitis, immunotherapy is the only approach known to alter the natural history of the disease.
- Chronic rhinosinusitis is an inflammatory disease of the paranasal sinuses without a single clear cause. Immune dysregulation, staphylococcal superantigens, and dysbiosis of the sinus microbiome have all been proposed as primary causes for chronic rhinosinusitis.
- Asthmatic patients demonstrate a high incidence of nasal polyps; this association is more pronounced in nonatopic asthma.

- Asthmatic patients with comorbid chronic sinusitis often experience improvement in both upper and lower airway disease after both medical and surgical treatment of chronic rhinosinusitis.
- The oral cavity structures are under voluntary control and function to regulate the intake of substances and the outflow of air for respiration and communication.
- In swallowing, the oral cavity creates a bolus of the ingested substance and presents this, in an orderly fashion, to the oropharynx and hypopharynx, where the reflexive portion of swallowing takes place. This requires structural and functional integrity and is under control of the central nervous system.
- The larynx is divided into the supraglottis, glottis, and subglottis and functions to regulate inspiratory and expiratory airflow. During swallowing, the larynx is pulled up and forward, to allow the upper esophageal sphincter to open. The bolus passes through the pyriform sinus and into the esophagus.
- During respiration the vocal folds normally open for inspiration and then close slightly during exhalation to control the rate of air egress. In *paradoxical vocal fold motion disease* (PVFMD), it is believed that these actions are reversed. The mechanism for this reversal is unknown. However, behavioral interventions designed to retrain breathing are often beneficial in patients demonstrating this finding.
- PVFMD can often be confused with asthma, but it is typically unresponsive to medical management.
- The contribution of gastroesophageal reflux disease and extraesophageal reflux disease to respiratory disorders is incompletely understood. Most of the evidence supporting an association is derived from studies

that measure patient response to empirical therapy. A few small studies using blinded randomized controls of medication and placebo do not demonstrate significant benefit of medication compared to placebo.

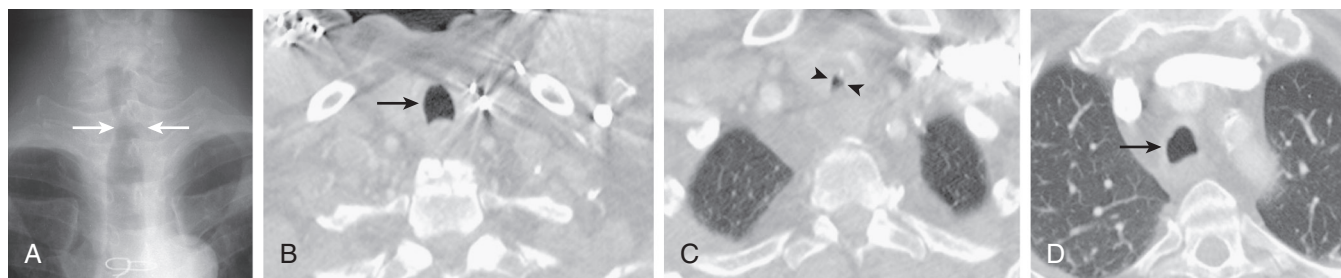
- Bilateral vocal fold paralysis, posterior glottic stenosis, and subglottic stenosis can often cause airway obstruction that may be misdiagnosed as asthma. Diagnosis requires suspicion based on events in the patient history and endoscopic evaluation. Treatment is usually surgical and is designed to enlarge the airway.

Complete reference list available at *ExpertConsult*.

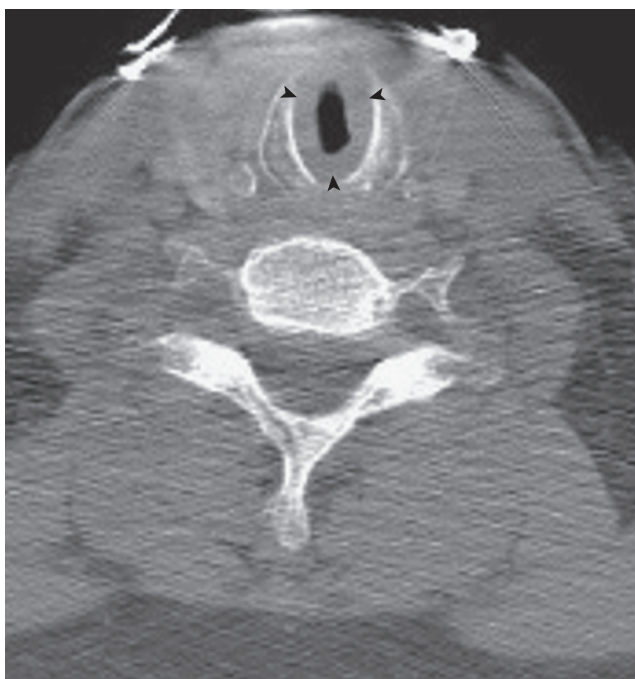
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eFIGURE IMAGE GALLERY



eFigure 49-1 Postintubation tracheal stenosis. **A**, Focused image from a frontal chest radiograph of a patient who was intubated for a prolonged interval following cardiac bypass grafting surgery shows focal narrowing of the trachea (*arrows*) at the thoracic inlet. **B–D**, Axial chest CT displayed in lung windows shows a normal caliber trachea (*arrows*) cranial and caudal to the focally stenotic region (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 49-2 Tracheal stenosis due to granulomatosis with polyangiitis (Wegener granulomatosis). Axial CT through the lower neck shows circumferential tracheal mucosal thickening (*arrowheads*). (Courtesy Michael Gotway, MD.)

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BRONCHIOLITIS AND OTHER INTRATHORACIC AIRWAY DISORDERS

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INTRODUCTION

Previous chapters focused on the major diseases affecting primarily the intrathoracic airways. These diseases include asthma, bronchitis, cystic fibrosis, and bronchiectasis. Less common entities also primarily affect airways. Unlike the diseases discussed earlier, these entities, when diffuse, demonstrate a predilection for the peripheral airways. Their early diagnosis remains difficult, however. The large cross-sectional area of peripheral airways protects patients from symptoms of dyspnea and limits detection of flow abnormalities on functional testing until late in the disease course. Diseases affecting the peripheral airways, however, may have profound effects on lung function. Because pathologic narrowing of peripheral airways is difficult to detect, these airways may be considered a “silent zone” of the lung. Despite efforts to design tests to identify peripheral airway obstruction, none have been entirely successful. More recently, heightened recognition of the entities affecting peripheral airways and diagnostic advances have increased the frequency of diagnosis. Nevertheless, the epidemiology of disorders of the peripheral airways remains largely unknown.¹ This chapter takes into account the heightened clinical recognition and evolving efforts at classification as our understanding of these entities advances. This is most evident for *bronchiolitis obliterans* (BO). In this chapter we will first review the anatomy of the peripheral airways. Next, we will present a classification for bronchiolitis and BO that reflects a contemporary hybrid understanding of bronchiolitis based on both clinical and histologic features. Lastly, we will review focal processes involving intrathoracic airways, including a review of tracheobronchial stents.

DISORDERS WITH DIFFUSE INVOLVEMENT

ANATOMIC AND PHYSIOLOGIC FEATURES

Among other roles, the intrathoracic airways serve as a conduit between the outside environment and alveolar units. Moving distally from the trachea, bronchi transition to membranous bronchioles and ultimately to the terminal respiratory units. These transitions are defined by changes in the constellation of cell types and by architectural features. *Bronchi* are characterized by incomplete cartilaginous rings, ciliated epithelium, goblet cells, submucosal glands, and smooth muscle innervated by muscarinic output via the vagus nerve. *Bronchioles* feature sparsely ciliated simple columnar epithelium and secretory club cells (Clara) but lack cartilage, goblet cells, and glands. Bronchiolar smooth muscle is not innervated by the vagus nerve; the diameter of bronchioles ranges from 0.5 mm to 1 mm.

Because of their relatively small total cross-sectional area, bronchi are responsible for most airflow resistance in the lung. In contrast, bronchioles contribute little to total airflow resistance at high and normal lung volumes. This limited contribution is attributable to dichotomous branching that arranges vast numbers of bronchioles in parallel. This translates into a much larger total cross-sectional area for bronchioles relative to bronchi. At low lung volumes, bronchioles increase their relative contribution to total airflow resistance. As residual volume is approached, the flexible, thin-walled bronchioles, supported only by connective tissue, may collapse. Despite significant disease of the bronchioles, however, *pulmonary function test* (PFT) results

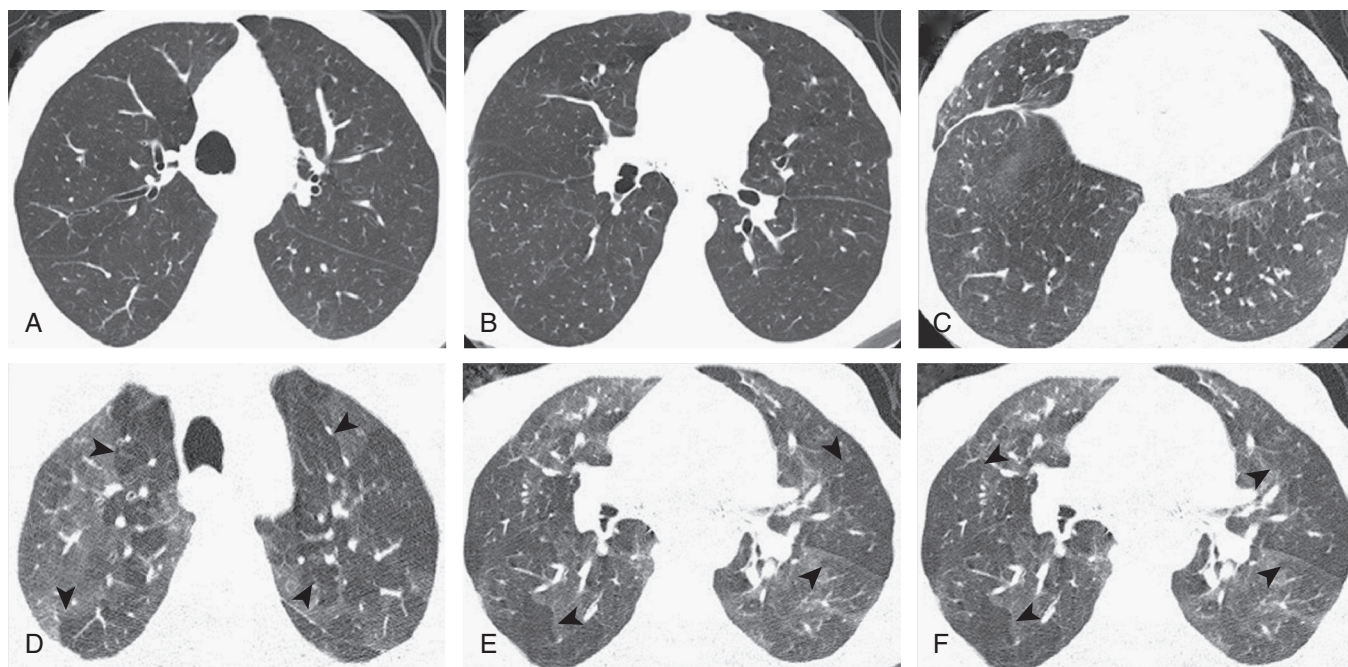


Figure 50-1 High-resolution CT scan demonstrating air trapping during expiration. A–C, Axial chest CT images performed through the upper (A), mid (B), and lower (C) lungs obtained during inspiration (see [Video 106-1](#)) in a bilateral lung transplant recipient show only minimal inhomogeneous lung opacity. Expiratory chest CT images performed through the upper (D), mid (E), and lower (F) lungs show extensive accentuation of the bilateral inhomogeneous opacity. The areas of increased attenuation represent normal collapsing lung during exhalation; the areas of relatively decreased attenuation (*arrowheads*) represent air trapping due to constrictive bronchiolitis as a result of chronic rejection.

may be normal. More commonly they may demonstrate upward concavity (“curvilinearity”) of the flow-volume curve, especially at low lung volumes, an increased slope of phase III (the alveolar plateau) of the single-breath nitrogen washout test, and air trapping. *Computed tomography* (CT) scans or magnetic resonance imaging with hyperpolarized gases, similarly, may demonstrate inhomogeneity of ventilation and air trapping ([Fig. 50-1](#) and see [Videos 106-1](#) to [106-3](#)).

DEFINING BRONCHIOLITIS

Bronchiolitis refers to a nonspecific cellular and mesenchymal reaction of the bronchioles. Developing a straightforward classification, however, is difficult. Perhaps most importantly, bronchiolitis is a catchall term subsuming several unique clinical syndromes as well as a histopathologically diverse set of lesions identifiable in many diseases. Next, there are many diseases that, in addition to causing bronchiolitis, also cause disease proximal (e.g., bronchiectasis) or distal (e.g., organizing pneumonia) to the bronchioles. As a result, some avoid defining the precise site of involvement, instead referring to peripheral airways (<2 mm diameter) as “small airways.” Lastly, clinical bronchiolitis syndromes may demonstrate more than one histologic pattern temporally and spatially. These factors conspire to preclude defining a mutually exclusive classification system. Therefore definitive diagnosis of a specific bronchiolitis entity requires clinical, diagnostic (imaging, PFTs), and frequently, histopathologic evaluation. Definitive diagnosis depends on excluding bronchial and alveolar involvement seen in alternative diagnoses. The remainder of this section will focus on diseases predominantly affecting the

bronchioles. A hybrid classification schema based on both histopathologic findings and clinical syndromes is presented in [Figure 50-2](#). The early branch points in this schema are driven by histopathologic findings, whereas later branch points are driven by clinical syndromes and exposures.

INFECTIOUS BRONCHIOLITIS

Although relatively rare in adults, infectious bronchiolitis is common in infants and young children. Community-acquired respiratory viruses are the most common cause of infectious bronchiolitis, especially respiratory syncytial virus.² Rhinovirus is the second most commonly identified virus; other viruses and bacteria may also cause disease.³⁻⁵ Infection damages bronchiolar epithelial cells. Edema, epithelial sloughing, and mucus secretion cause small airway obstruction and atelectasis. In severe cases there may be peribronchiolar lymphocytic infiltration and even mural necrosis ([Fig. 50-3A](#); see [Fig. 50-2](#), classified under the Chronic/Cellular Bronchiolitis heading). Bronchiolitis in infancy (especially non-respiratory syncytial virus) has been associated with an increased risk for subsequent wheezing and bronchial hyperreactivity.^{6,7} Although a direct link to chronic obstructive pulmonary disease has not been shown, unusual sequelae may include BO (proliferative and constrictive), bronchiolectasis, and localized emphysema.²

Typically affecting children younger than 2 years of age, bronchiolitis begins as an acute upper respiratory tract infection with rhinorrhea or nasal congestion and cough. Within days, the cough worsens and dyspnea and fever develop. Although wheezing, chest wall retractions, and cyanosis may be seen, respiratory failure is uncommon.

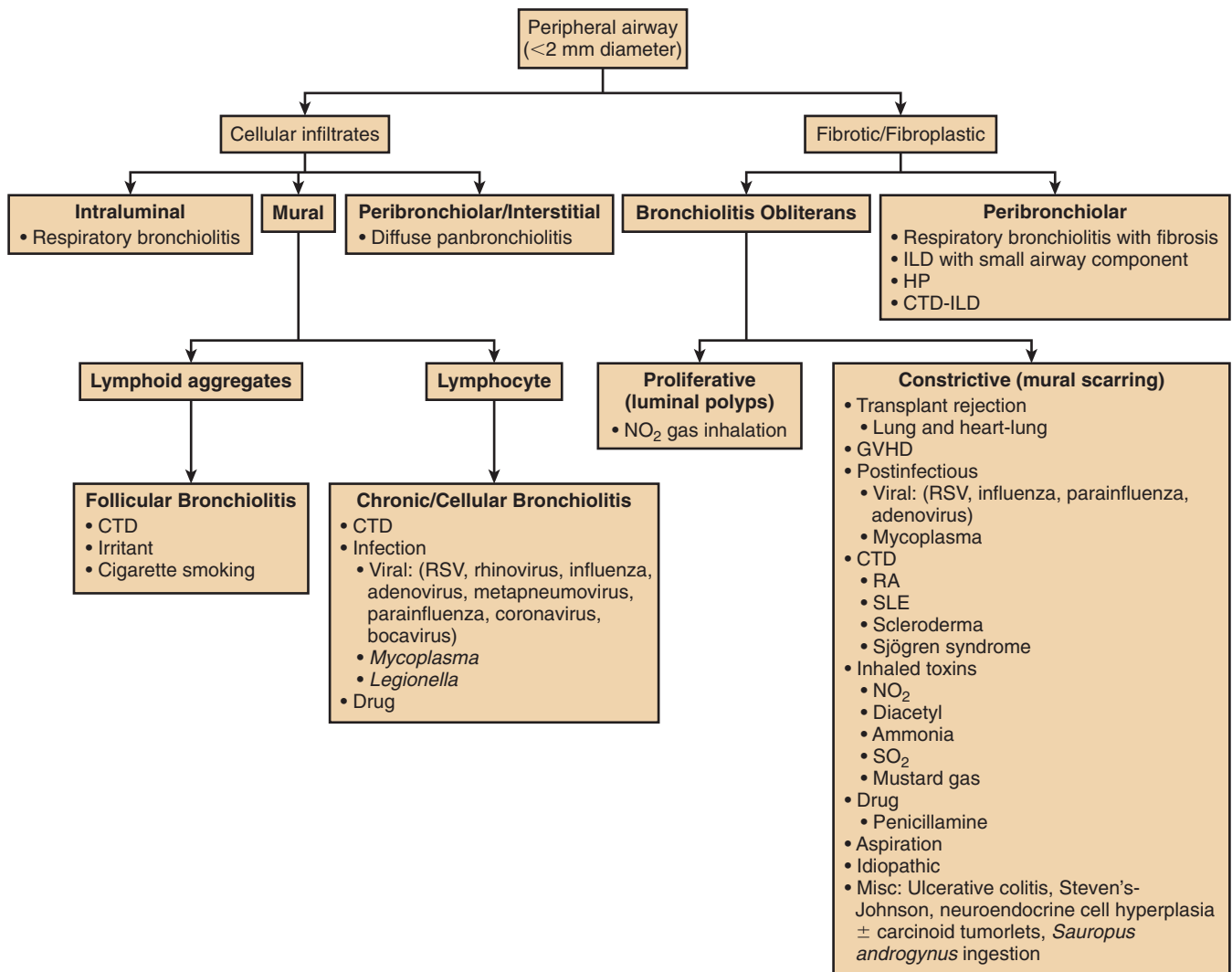


Figure 50-2 Classification schema for bronchiolitis. Traditionally bronchiolitis has been defined by clinical syndromes, as well as histopathologic lesions, making classification difficult. In this schema, early classification branch points are defined by histopathologic findings (e.g., cellular infiltrates in the small airways versus fibrosis). Later branch points are defined by specific clinical entities. CTD, connective tissue disease; GVHD, graft-versus-host disease; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; NO₂, nitrogen dioxide; RA, rheumatoid arthritis; RSV, respiratory syncytial virus; SLE, systemic lupus erythematosus; SO₂, sulfur dioxide.

Examination typically demonstrates mildly depressed oxygen saturation, tachypnea, mild chest wall retractions, expiratory wheezing, and crackles; in more severe cases, nasal flaring, grunting, pronounced chest wall retractions, prolonged expiratory phase, and cyanosis may be seen. Epithelial sloughing with bronchiolar obstruction may cause hyperinflation and gas exchange abnormalities.⁸ Generally, infectious bronchiolitis is diagnosed based on clinical signs and symptoms. When obtained, radiographs generally show hyperinflation; nodular shadows may appear in areas of focal atelectasis or pneumonia.^{5,9,10} Symptomatic treatment with nasal bulb suctioning, supplementary oxygen, and hydration is usually all that is necessary; patients usually recover within weeks. Although inhaled bronchodilators are commonly used in severe cases, their efficacy remains uncertain.¹¹⁻¹⁴ There is no proven role for corticosteroids or antibiotics, although the former are sometimes used empirically in hopes of preventing progression. Elevated cysteinyl-leukotriene levels have been reported,^{15,16}

and leukotriene modifiers have been shown to reduce respiratory symptoms and wheezing after respiratory syncytial virus bronchiolitis in some^{17,18} but not all¹⁹ studies.

BRONCHIOLITIS FROM INHALED OR INGESTED TOXINS

A generalized inflammatory response of the peripheral airways may follow inhalation of toxicants in gas, vapor, fume, or aerosol states (see Chapter 75). The location of damage is determined in part by the toxicant solubility. Highly soluble irritants such as sulfur dioxide and ammonia dissolve in the lining fluid of the upper airway, causing damage primarily there. Less soluble gases such as oxides of nitrogen are able to pass into and therefore damage the peripheral airways.^{20,21} Such exposures are a significant industrial and environmental hazard. Oxides of nitrogen, for example, may be found in silo gas (silo filler's disease), jet and missile fuel, metal pickling fumes, and certain fires.

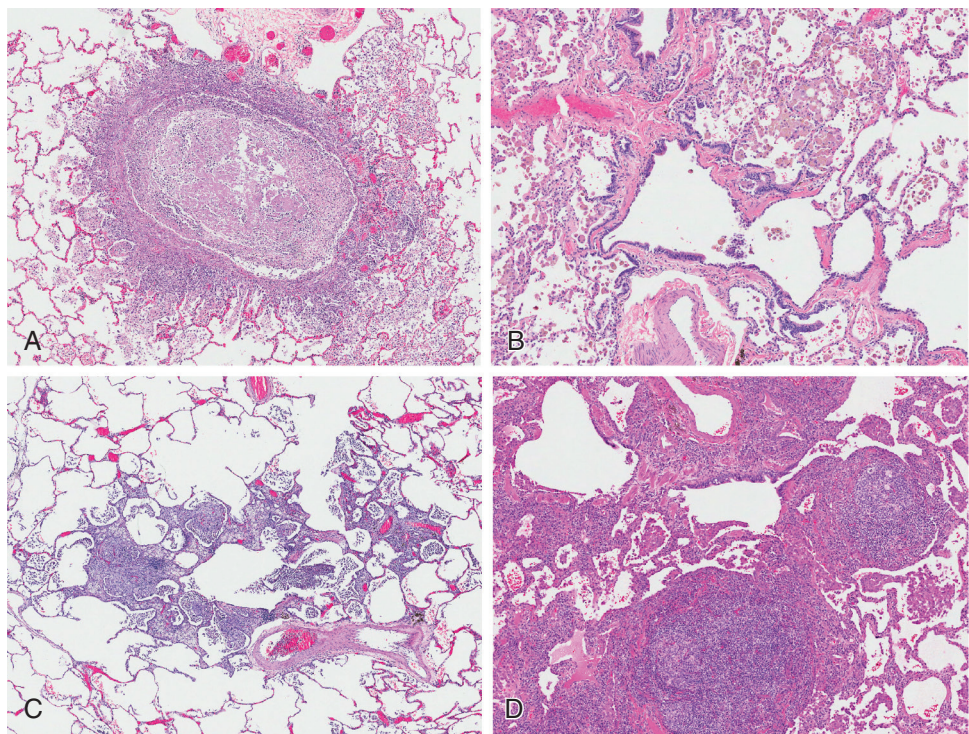


Figure 50-3 Pathologic patterns of bronchiolitis. **A**, Infectious bronchiolitis. The bronchiolar wall shows marked acute inflammation with neutrophils and apoptotic debris extending from the sloughed epithelial surface transmurally to the adjacent alveolar spaces. **B**, Respiratory bronchiolitis. The terminal bronchiole and peribronchiolar alveolar spaces show consolidation by lightly pigmented “smoker’s” alveolar macrophages. Mild peribronchiolar fibrosis is present. **C**, Diffuse panbronchiolitis. The terminal bronchiole shows mural lymphoid inflammation, luminal inflammation and organization, and peri-bronchiolar interstitial expansion by foamy macrophages. **D**, Follicular bronchiolitis. Prominent lymphoid aggregates with well-formed germinal centers are noted adjacent to bronchioles.

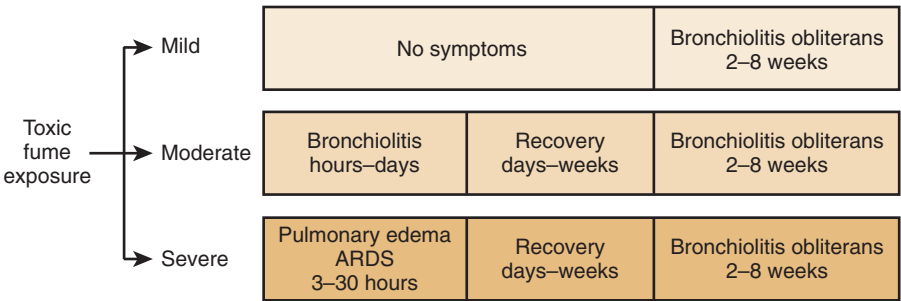


Figure 50-4 Clinical patterns of response to toxic fumes. The severity of acute bronchiolitis following inhalation of toxic fumes depends in part on the magnitude of the exposure. Most patients will recover from the acute event, although some, including some with no symptoms initially, will develop bronchiolitis obliterans (constrictive) 2 to 8 weeks after the initial insult. ARDS, acute respiratory distress syndrome.

Other fumes, such as diacetyl used in food flavoring, have been implicated in bronchiolitis as well as the development of BO (see the discussion of constrictive bronchiolitis below).^{22–24} Bronchiolitis may also result from systemic toxicant exposure as seen after administration of busulfan, gold, or penicillamine.²⁵ These causes of bronchiolitis are identified in [Figure 50-2](#) under both proliferative and constrictive BO headings.

Three clinical patterns may develop following toxicant exposure, based on several factors, including the type of toxicant, duration and intensity of exposure, and host factors ([Fig. 50-4](#)).^{20,21} Acutely, patients may develop cough, dyspnea, cyanosis, hemoptysis, hypoxemia, and loss of consciousness. These symptoms and signs may last hours to weeks before resolving. In patients exposed to higher

concentrations, pulmonary edema and acute respiratory distress syndrome may develop immediately or following a latent period of up to 30 hours. Although most patients recover, some may die from respiratory failure. Finally, some patients develop irreversible obstructive (i.e., BO) or restrictive (i.e., organizing pneumonia) abnormalities 2 to 8 weeks after exposure. This may even be seen in patients who had no initial illness; it is characterized by the gradual onset of dyspnea and nonproductive cough and may result in respiratory failure and death.^{21,26}

RESPIRATORY BRONCHIOLITIS

Respiratory bronchiolitis (RB) is a pathologic entity characterized by pigmented alveolar macrophage accumulation in

respiratory bronchioles and adjacent alveoli. Peribronchiolar inflammation or fibrosis and epithelial metaplasia extending into adjacent alveoli (lambsertosis) may be present (see Fig. 50-3B). Although nearly universally seen in cigarette smokers,²⁷ it may also be seen following mineral dust exposure.²⁸⁻³⁰ RB rarely causes symptoms or physiologic abnormalities. It is most commonly incidentally diagnosed by imaging (see Fig. 50-2, classified under the Peribronchiolar heading). In some cases, more extensive fibrosis extends into the alveolar septa. In these cases the term *RB-associated interstitial lung disease* (RB-ILD) is applied^{27,30-32} (see Chapter 63). In RB-ILD, patients present with subacute cough, dyspnea, and crackles.³³ PFTs show restriction and reduced diffusing capacity. *High-resolution CT* (HRCT) imaging shows a distinctive pattern of bronchial wall thickening, centrilobular nodules, reticulation, and diffuse or patchy ground-glass opacities.^{32,34,35} RB and RB-ILD may represent a single entity along a continuum of disease severity.^{28,33,36} Although smoking cessation leads to resolution or stabilization of disease in one third of patients,³⁷ some develop progressive ILD. Improvement with corticosteroid treatment has been described but not studied prospectively.^{27,30,31}

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis (DPB) is an obscure inflammatory disease of the respiratory bronchioles. Since its first description in 1969,³⁸ more than 1000 cases have been identified in Japan.³⁹ On histologic examination DPB is characterized by the triad of bronchiolocentric inflammation, lymphoid hyperplasia, and accumulation of interstitial foam cells (see Fig. 50-2, classified under the Peribronchiolar/Interstitial heading, and Fig. 50-3C).⁴⁰⁻⁴² Notably, similar findings are also seen in bronchiectasis, underscoring the importance of developing a diagnostic approach to bronchiolitis that considers clinical, functional, radiographic, and histopathologic findings.

Given the rarity of DPB, epidemiologic data are limited. It affects Japanese and, less commonly, other East Asian populations.⁴⁰ It is rarely diagnosed in Western countries and in persons of non-East Asian descent,^{43,44} although underrecognition may account for some of this. Clinically, DPB has a slight male predilection, and symptoms manifest in early to mid adulthood.^{39,40,45} Chronic sinusitis is exceedingly common and frequently precedes pulmonary symptoms. Before diagnosis, patients report years of nasal discharge or congestion, cough, dyspnea, and sputum production that exceeds 50 mL/day.⁴⁶ Radiographs demonstrate hyperinflation, diffuse small nodular opacities, and, in advanced disease, ring shadows and “tram track” opacities consistent with bronchiectasis. In early disease, HRCT findings may include centrilobular nodules, including “tree in bud” pattern, and air trapping on expiratory images. Mosaic perfusion is atypical. In advanced disease, bronchiolar wall thickening, dilation, and cysts are seen.^{35,47} PFTs demonstrate a progressive airflow obstruction with reduced diffusing capacity. Less commonly, a mixed obstructive-restrictive pattern may be observed.⁴⁴ Although clinical diagnostic criteria have been proposed for Japan, surgical lung biopsy is required in countries and populations in which the disease is rare.⁴⁵ If untreated, DPB leads to bronchiectasis, pulmonary hypertension, respiratory failure,

and ultimately death. Although the etiology of DPB remains obscure, both genetic and environmental factors are believed to be important.⁴⁸⁻⁵⁰ *Human leukocyte antigen* (HLA)-Bw54 is associated with a 13.3-fold increase in risk for diffuse panbronchiolitis.⁴⁹ Polymorphisms of the genes for *interleukin* (IL)-8⁵⁰ and MUC5B⁵¹ have been associated with diffuse panbronchiolitis.

Macrolides are the cornerstone of treatment.⁵²⁻⁵⁴ Although the exact mechanism of action remains undefined, anti-inflammatory and immunoregulatory properties of macrolides are likely important because their antimicrobial properties alone do not explain their benefit.⁵² Airway neutrophilia is common in DPB. Macrolides inhibit proinflammatory cytokine production, including neutrophil chemoattractants IL-8 and leukotriene B₄^{55,56}; bronchoalveolar lavage fluid levels of IL-8 and leukotriene B₄ are reduced after erythromycin treatment.⁵⁷⁻⁵⁹ Other potential mechanisms include blockage of adhesion molecules required for neutrophil trafficking,^{57,60-63} inhibition of mucin,^{64,65} and water⁶⁶ secretion into the bronchiolar lumen. Notably, 14- and 15-membered lactone ring macrolides (e.g., erythromycin, clarithromycin, azithromycin) are effective in treating DPB, whereas 16-membered lactone ring macrolides (e.g., tylosin, spiramycin) are not. For severe cases, lung transplantation has been performed, although the disease may recur in the allograft.⁶⁷

Originally DPB was a highly mortal disease. In the 1980s, 5- and 10-year survivals were approximately 62% and 33%, respectively. With macrolide therapy, increased disease diagnosis, and early, aggressive treatment of bacterial infections, 10-year survival now exceeds 90%.⁵⁴ Recurrent respiratory infections are common, and *Pseudomonas* infection, often arising late in the disease, is associated with markedly increased mortality.

FOLLICULAR BRONCHIOLITIS

Follicular bronchiolitis (lymphoid hyperplasia) is characterized by peribronchiolar hyperplastic lymphoid follicles with germinal centers (see Fig. 50-3D).^{68,69} It has been described with primary pulmonary lymphoid hyperplasia⁷⁰ or as a secondary event in collagen vascular diseases (especially rheumatoid arthritis and Sjögren syndrome), underlying congenital or acquired immunodeficiencies, bronchiectasis, or other infections^{68,71,72} (see Fig. 50-2, classified under the Lymphoid Aggregates heading). Most patients report slowly progressive exertional dyspnea, fever, recurrent pneumonia, and cough.^{68,73} PFT findings may show restrictive, obstructive, or mixed patterns. HRCT findings include small (<3 mm) centrilobular or peribronchial nodules and ground-glass opacities.⁷⁰ The natural history of this condition is unknown. Treatment is directed at the underlying disease.

DEFINING BRONCHIOLITIS OBLITERANS

BO can be stratified into “constrictive” and “proliferative” bronchiolitis. Although not absolute, this stratification is largely supported by histopathologic and clinical evidence. Unique entities featuring BO are listed in Figure 50-2; more common entities are discussed in greater detail below. Histologically, *constrictive bronchiolitis* defines a submucosal

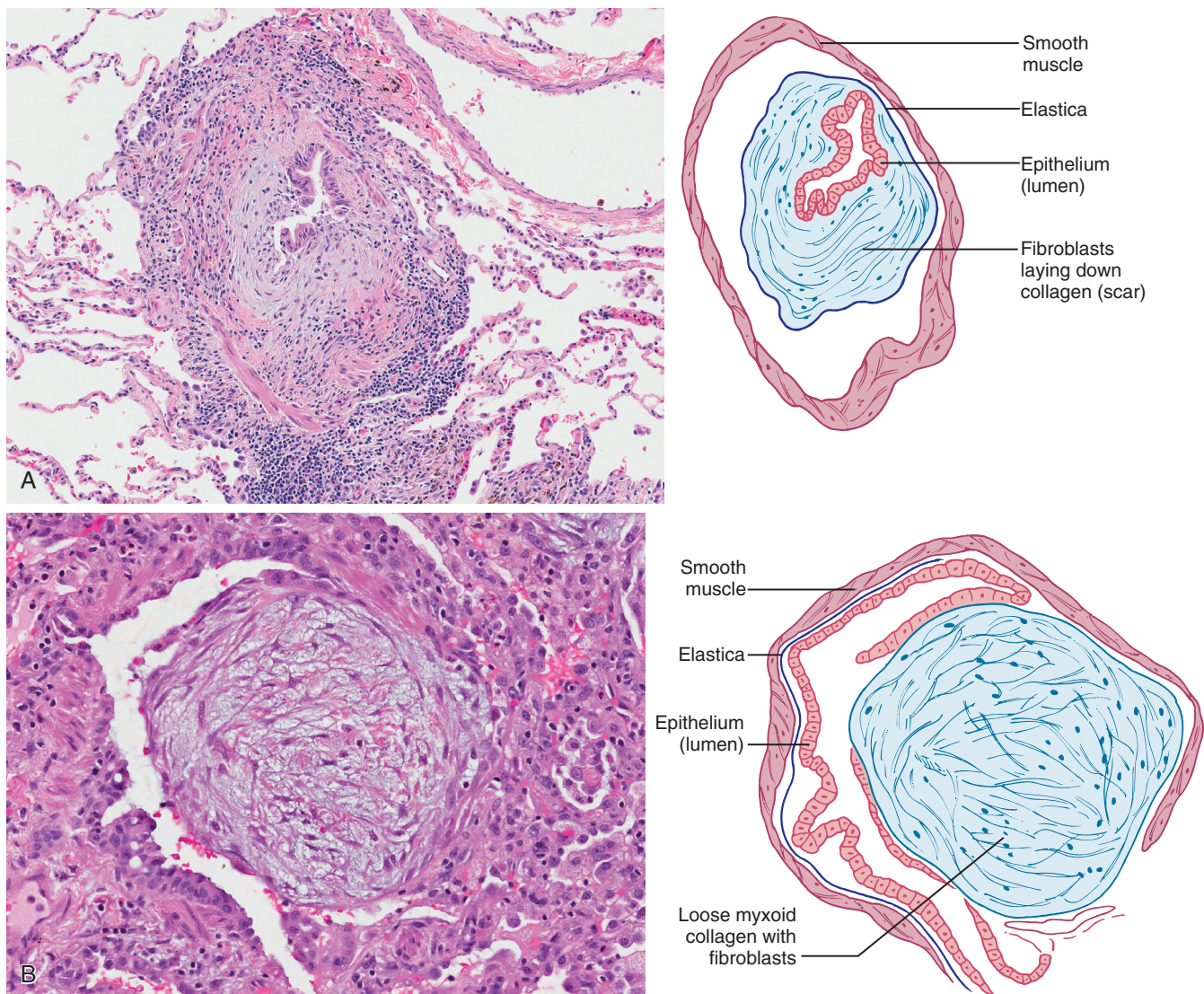


Figure 50-5 Pathologic patterns of bronchiolitis obliterans. A, Constrictive bronchiolitis. Circumferential subepithelial intramural fibrosis is present. This fibrosis separates the normally approximated epithelium and elastica. This scarring results in luminal constriction and narrowing, often with irreversible complete obstruction. **B,** Proliferative bronchiolitis. Although the diameter of the airway remains unchanged, the functional area of the lumen is reduced by a rounded intraluminal polypoid plug of granulation tissue, extending from the subepithelium and filling the airway lumen.

and peribronchiolar fibrotic process that circumferentially and externally compresses the bronchiolar lumen (Fig. 50-5A).⁷⁴ Patchy and focal in distribution, progressive fibrosis observed in constrictive bronchiolitis ultimately results in slitlike or completely obliterated bronchiolar lumens. Clinically, patients describe progressive dyspnea and nonproductive cough. Auscultation demonstrates early inspiratory crackles and occasional squeaks. PFTs demonstrate obstruction and air trapping. Radiographs may have normal findings or show hyperinflation. HRCT can demonstrate ground-glass nodules, air trapping, and, in advanced disease, bronchiectasis. Today the most common cause of constrictive bronchiolitis is chronic allograft rejection in recipients of lung transplantation.⁷⁵

Histologically, *proliferative bronchiolitis* is defined by the proliferation of intraluminal polypoid organizing fibroblastic tissue (see Fig. 50-5B).⁷⁴ Isolated proliferative bronchiolitis is rare, observed only in specific inhalational (e.g.,

nitrogen gas) exposures or localized injuries. Much more commonly, fibroblastic tissue extends from the bronchioles into adjacent alveoli. The term *organizing pneumonia* defines this organizing fibroblastic tissue in alveoli. Given the relatively common coexistence of proliferative bronchiolitis and organizing pneumonia, the term *bronchiolitis obliterans with organizing pneumonia* (BOOP) had been employed. There is little overlap, however, between the clinical entities featuring constrictive bronchiolitis and those featuring BOOP. Further, BOOP presents as a restrictive pattern on PFTs compared with the obstructive pattern seen in constrictive bronchiolitis. For these reasons, this nomenclature caused confusion. In response to this confusion, in 2002 the American Thoracic Society and European Respiratory Society jointly recommended abandoning the term BOOP in favor of *organizing pneumonia* with appropriate qualifiers. When idiopathic, for example, the term *cryptogenic organizing pneumonia* is used.⁷⁶ In rare situations, acute injury causing

proliferative bronchiolitis may progress into constrictive bronchiolitis.

Despite this evolution in nomenclature, “bronchiolitis obliterans” continues to be used imprecisely in clinical practice and in biomedical literature. The terms *BOOP*, *bronchiolitis obliterans with intraluminal polyps*, and *bronchiolitis obliterans* applied to both BO and organizing pneumonia persist. Importantly, organizing pneumonia tends to be responsive to corticosteroid treatment, whereas constrictive bronchiolitis is typically resistant. This absence of a precise nomenclature makes studies of the epidemiology, clinical features, and treatment responsiveness of “bronchiolitis obliterans” difficult to interpret. Given the substantial differences in both etiology and prognosis, we favor using the term *proliferative* or *constrictive* to more clearly define bronchiolitis obliterans.

BRONCHIOLITIS OBLITERANS AFTER LUNG TRANSPLANTATION

Over the last 3 decades, surgical and medical advancements have improved survival after transplant, resulting in increased demand for this procedure.⁷⁵ Despite these advancements, chronic lung allograft dysfunction (also known as chronic rejection) remains the major cause of morbidity and mortality in lung transplant recipients surviving beyond the first postoperative year.⁷⁵ Although new phenotypes of chronic lung allograft dysfunction have been identified,^{77,78,78a} BO is the most common form, observed in 50% of recipients by 5 years after transplant.⁷⁵ Importantly, given the patchy nature of BO, diagnosis by transbronchial biopsies is unreliable.^{79,80} In response, the International Society for Heart and Lung Transplantation devised clinical criteria for BO based on spirometric airflow obstruction “for which there is no other cause” (Table 50-1).⁸¹ Termed *bronchiolitis obliterans syndrome* (BOS), this syndrome does not require histopathologic confirmation. Most literature in human lung transplantation employs BOS as a surrogate marker for BO.

The onset of BOS is variable based on donor, recipient, and environmental factors discussed below. It presents at a median of 16 to 20 months after transplant. Patients have a median survival of 3 to 4 years after diagnosis. They report progressive dyspnea and, occasionally, dry cough. In advanced disease with bronchiectasis, the cough is productive. Spirometry demonstrates irreversible airflow obstruction with reduced diffusing capacity. CT findings in early BOS demonstrate air trapping (see Fig. 50-1 and see Videos

106-1 to 106-3). As BOS progresses, findings consistent with bronchiectasis may be seen.

BO represents the final histologic lesion likely resulting from injury to the airway epithelium and subcellular matrix via both alloimmune and nonalloimmune mechanisms.⁸² Alloimmune T-cell reactivity plays a central role in the development of BO (Fig. 50-6).⁸² Acute rejection is considered the most significant single risk factor for subsequent BOS. Although high-grade (\geq A3) rejection is a major risk factor for BOS,⁸³ even minimal (grade A1) rejection may increase the risk.⁸⁴ Additionally, frequent rejection,⁸⁵ lymphocytic bronchiolitis,^{86,87} and lymphocytic bronchitis⁸⁸ are associated with increased risk for BOS. Enhanced expression of donor *major histocompatibility complex* (MHC) antigens has been found in bronchiolar and alveolar epithelium of lung transplant recipients with BOS.⁸⁹⁻⁹¹ Recipient-derived T cells may recognize these antigens as foreign, resulting in a cascade of lymphocyte activation, proliferation, and differentiation.⁹² This concept is supported by the demonstration of activated T-cell infiltrates in allograft rejection.⁹³ A predominant CD4⁺ cell population is associated with *acute* rejection; a predominant CD8⁺ cell population is associated with BOS.⁹⁴ Animal models demonstrate that BO results from a type 1 T helper alloimmune response.⁹⁵⁻⁹⁷ The high incidence of BOS despite T-cell targeted immunosuppression, however, underscores the importance of alternate pathways to BOS.

Humoral immunity resulting in antibody-mediated rejection is increasingly recognized as a second important driver of BOS (Fig. 50-7). Donor and recipient HLA locus mismatch is associated with increased risk for BO.^{98,99} Further, donor-specific alloantibodies developing *de novo* after transplant can damage airway epithelium and endothelium and up-regulate cytokines associated with BOS.^{86,100-103} Although the link between the emergence of donor-specific antibodies and subsequent BOS is strong,^{104,104a} the diagnosis of antibody-mediated rejection remains a challenge. Defining the specific histologic features of antibody-mediated rejection is a work in progress.¹⁰⁵

BO may also develop through an autoimmune pathway (Fig. 50-8).¹⁰⁶ Through a variety of insults, injury may expose lung self-antigens, which are then presented to autoreactive T cells. This presentation induces either a cellular or humoral response ultimately resulting in BO. One such antigen is *type V collagen* (col[V]), expressed on the basement membrane of small airway epithelial cells and perivascular and peribronchiolar tissues. In murine models of acute rejection, anti-col(V) antibody deposition has been observed.¹⁰⁷ Further, col(V)-induced oral tolerance prevents both acute and chronic rejection.^{108,109} Interestingly, administration of anti-MHC class I antibodies in mice induces anti-col(V) antibody generation with resultant airway lesions resembling BO in human lung transplant recipients. Autoantibodies to the airway epithelial antigen K- α 1 tubulin increase fibrotic growth factors and other transcription factors related to BO.¹¹⁰ In lung transplant recipients, circulating autoantibodies against both col(V) and K- α 1 tubulin are strongly linked with the subsequent development of BOS.^{111,112} These responses support a link between alloimmunity and autoimmunity.

Finally, innate immunity plays a role in BOS.¹¹² Toll-like receptors on lung epithelium and antigen-presenting cells

Table 50-1 Bronchiolitis Obliterans Syndrome in Lung Transplantation Classification System

BOS 0	FEV ₁ > 90% of baseline and FEF _{25%-75%} > 75% of baseline*
BOS 0 p	FEV ₁ 81%–90% of baseline and/or FEF _{25%-75%} < 75% of baseline
BOS 1	FEV ₁ 66%–80% of baseline
BOS 2	FEV ₁ 51%–65% of baseline
BOS 3	FEV ₁ < 50% of baseline

*Baseline is the best FEV₁ and FEF_{25%-75%} obtained after transplant.

BOS, bronchiolitis obliterans syndrome; p, potential.

Adapted from Estenne M, Maurer JR, Boehler A, et al: Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 21:297–310, 2002.

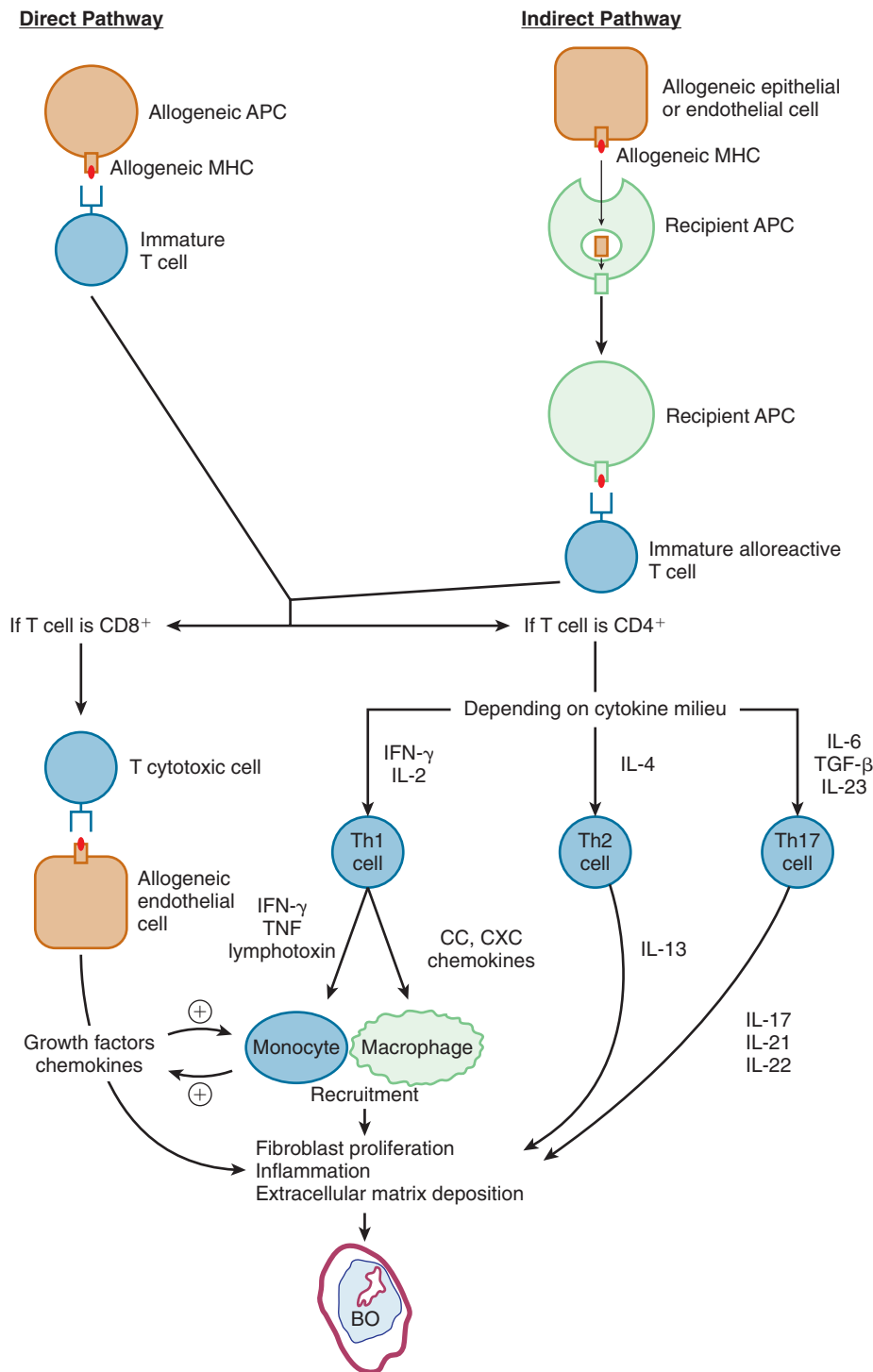


Figure 50-6 Alloimmune T-cell-mediated pathway. In the direct pathway, allogeneic peptides displayed on donor-derived antigen-presenting cells (APCs) are recognized by alloreactive recipient immature T cells. In the indirect pathway, recipient APCs engulf, process, and display allogeneic peptides to immature T cells. Immature CD8⁺ T cells differentiate into T cytotoxic cells capable of inducing growth factor and chemokine secretion. These factors (1) induce fibroblast proliferation and extracellular matrix deposition, resulting in bronchiolitis obliterans, and (2) trigger monocyte and macrophage recruitment. Macrophages trigger further growth factor/chemokine secretion as well as fibroblast proliferation. Immature CD4⁺ T cells develop into either Th1, Th2, or Th17 effector cells depending on the cytokine milieu. Each of these effector T-cell subtypes elaborates unique cytokines capable of causing bronchiolitis obliterans through different pathways. BO, bronchiolitis obliterans; CD, cluster of differentiation (e.g., CD4⁺); IFN- γ , interferon- γ ; IL, interleukin (e.g., IL-2, IL-4); MHC, major histocompatibility complex; TGF- β , transforming growth factor- β ; Th, T helper; TNF, tumor necrosis factor.

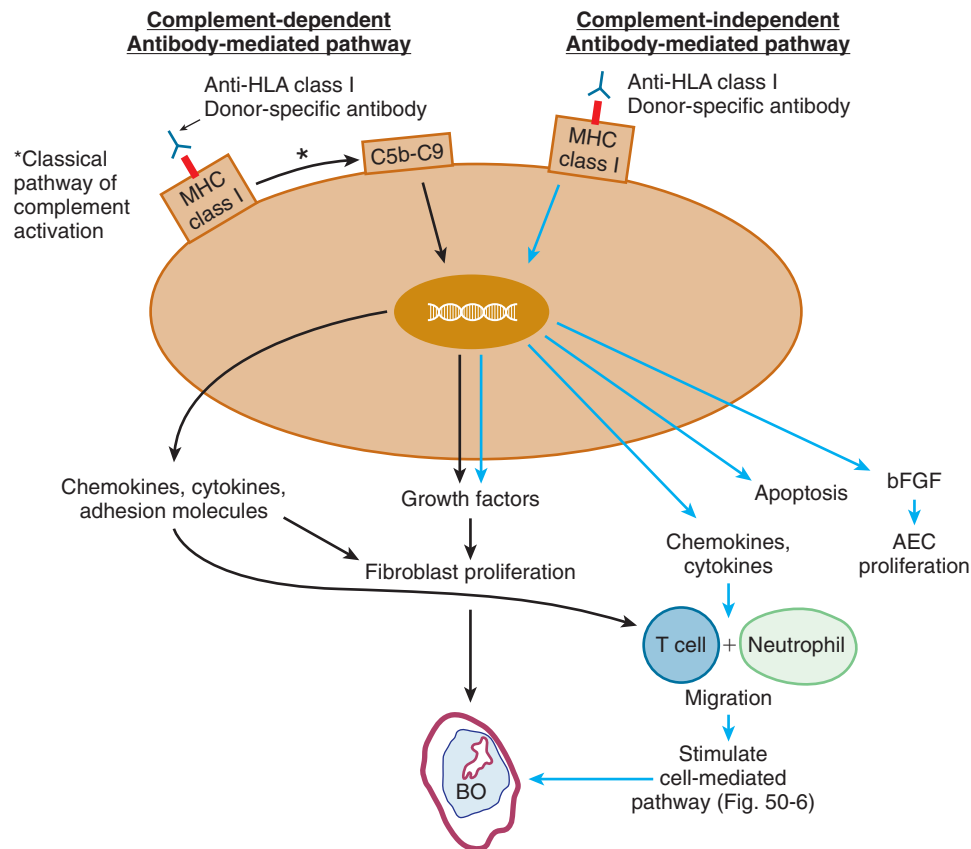


Figure 50-7 Alloimmune humoral-mediated pathway. Anti-HLA antibodies bind to donor antigens expressed on airway epithelial cells. This binding triggers a complex intracellular signaling cascade via either complement-dependent or complement-independent pathways. Complement-dependent pathways activate inflammatory genes that result in the secretion of cytokines, chemokines, costimulatory molecules (e.g., CCL2, CCL5, CXCL8, VCAM1, ICAM1), and growth factors (e.g., PDGF, HBEGF, bFGF, IGF1). These molecules can directly stimulate fibroblast proliferation, resulting in bronchiolitis obliterans (BO). In addition to growth factor secretion, complement-independent pathways stimulate chemokine and cytokine secretion (e.g., CCL2, CCL5, CXCL8), recruiting neutrophils and stimulating cell-mediated pathways (see Fig. 50-6) that also lead to BO. AEC, alveolar epithelial cell; bFGF, basic fibroblast growth factor; C5b, complement component 5b; C9, complement component 9; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; HB-EGF, heparin-binding epidermal growth factor; HLA, human leukocyte antigen; ICAM1, intercellular adhesion molecule 1; IGF1, insulin-like growth factor 1; MHC, major histocompatibility complex; PDGF, platelet-derived growth factor; VCAM1, vascular cell adhesion molecule 1.

regulate the adaptive immune response (Fig. 50-9). Loss- and gain-of-function Toll-like receptor polymorphisms are associated with differential risk for BOS.^{113,114} Although the mechanisms may be myriad, it is possible that clinical and environmental risk factors for BOS, including primary graft dysfunction,¹¹⁵⁻¹¹⁷ gastroesophageal reflux and aspiration,¹¹⁸ community-acquired viruses^{119,120} and cytomegalovirus,^{121,122} air pollution,¹²³ and fungal¹²⁴ and bacterial¹²⁵ colonization, may operate in part via the innate immune pathway. Some, for example, cytomegalovirus, may also increase the risk for BOS by increasing MHC antigen expression¹²⁶⁻¹²⁸ or through molecular mimicry.¹²⁹

BRONCHIOLITIS OBLITERANS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

BO is an uncommon complication of allogeneic stem cell transplantation, seen in 2% to 3% of patients and in 6% to 10% of those who develop chronic *graft-versus-host disease* (GVHD).¹³⁰ The histologic and clinical features of the disease are virtually identical to those seen in lung transplantation.¹³⁰ As in lung transplantation, the morbidity and mortality associated with a surgical approach to

diagnosis of BO has led investigators to avoid surgery by defining a BO *syndrome* based on clinical, radiographic, and spirometric criteria.¹³¹ This BOS is nearly always preceded or accompanied by typical findings of GVHD: mucositis, esophagitis, and/or skin rash.¹³² Four to 6 months after the onset of GVHD patients develop dyspnea and a nonproductive cough that may be severe and rapidly progressive. Physical examination may reveal scattered wheezing and frequently bibasilar crackles. Hypoxemia is common.¹³⁰ Spirometry and radiographic findings are the same as those observed in BOS in lung transplantation. Relative to lung transplantation, however, we have less understanding of the mechanisms driving BOS in stem cell transplantation. The rarity of BO following autologous stem cell transplantation and its histologic similarities to BO in lung transplantation lends support to alloimmune T-cell-mediated pathogenesis. Other mechanisms, however, have been proposed.¹³²⁻¹³⁴ The most significant risk factor for BOS is GVHD.¹³³ Other risk factors include busulfan or methotrexate¹³³ administration at the time of transplant, older age,¹³⁵ poor lung function before transplant, and respiratory viral infection within the first 100 days after transplant.¹³⁵⁻¹³⁷

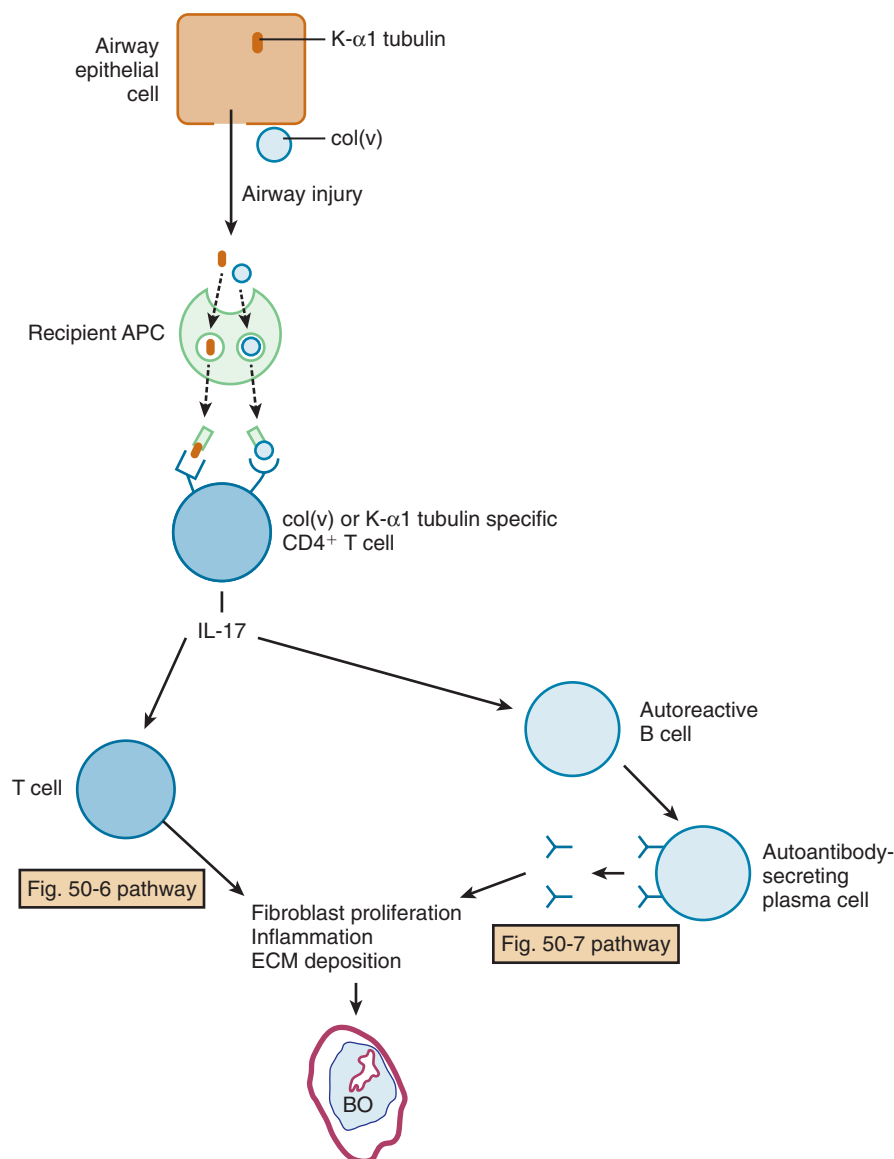


Figure 50-8 Autoimmune-mediated pathway. Lung injury caused by primary graft dysfunction, community-acquired viruses, and other causes exposes small airway epithelial cell self-antigens col(V) and K- α 1 tubulin. Antigen-presenting cells (APCs) engulf, process, and present fragments of these antigens to CD4⁺ T cells. These autoantigen-reactive CD4⁺ T cells can activate either cell-mediated or humoral-mediated pathways (see Figs. 50-6 and 50-7), ultimately resulting in bronchiolitis obliterans (BO). col(V), type V collagen; ECM, extracellular matrix; IL, interleukin. (Adapted from Weber DJ, Wilkes DS: The role of autoimmunity in obliterative bronchiolitis after lung transplantation. *Am J Physiol Lung Cell Mol Physiol* 304: L307–L311, 2013.)

BRONCHIOLITIS OBLITERANS AND CONNECTIVE TISSUE DISEASES

BO may present uncommonly with connective tissue or collagen vascular diseases. Most literature linking BO and connective tissue diseases refers to cases of “BOOP.” However, constrictive BO has been reported in association with some diseases. Constrictive BO is most well characterized in rheumatoid arthritis.^{71,138} When present, it primarily affects women with long-standing rheumatoid arthritis who are smokers.^{139,140} The onset and progression of dyspnea and nonproductive cough are rapid, as is the rate of progression of airflow obstruction. Unfortunately, no consistent response to corticosteroids has been documented, and the prognosis for these patients generally is poor,¹⁴¹ although a subset of patients may have a more insidious course.¹⁴² Penicillamine, used to treat rheumatoid arthritis, has been implicated as a potential cause of BO, but confirmation of an etiologic relationship is lacking. BO has also been reported in systemic lupus erythemato-

sus,¹⁴³ in Sjögren syndrome,^{144,145} and in scleroderma, where reflux and chronic microaspiration may play an important role.^{146,147}

TREATMENT OF BRONCHIOLITIS OBLITERANS

Unfortunately, treatment of constrictive BO is often ineffective. Although there is little evidence that smooth muscle contraction plays a significant role, β -adrenergic agonists are frequently attempted to provide symptomatic relief. Literature supporting the important role of early administration of corticosteroids frequently contains mixed populations, including cases of BOOP. This is particularly true of BO after exposure to toxic fumes.^{20,148,149} Nevertheless, in an individual patient, a trial of corticosteroid therapy should be considered; if a response is identified, the corticosteroid should be continued for at least 2 to 3 months, then reduced slowly, to minimize the likelihood of relapse.¹⁴⁸⁻¹⁵² In some cases it may be necessary to continue low-dose or alternate-day therapy for months or years.

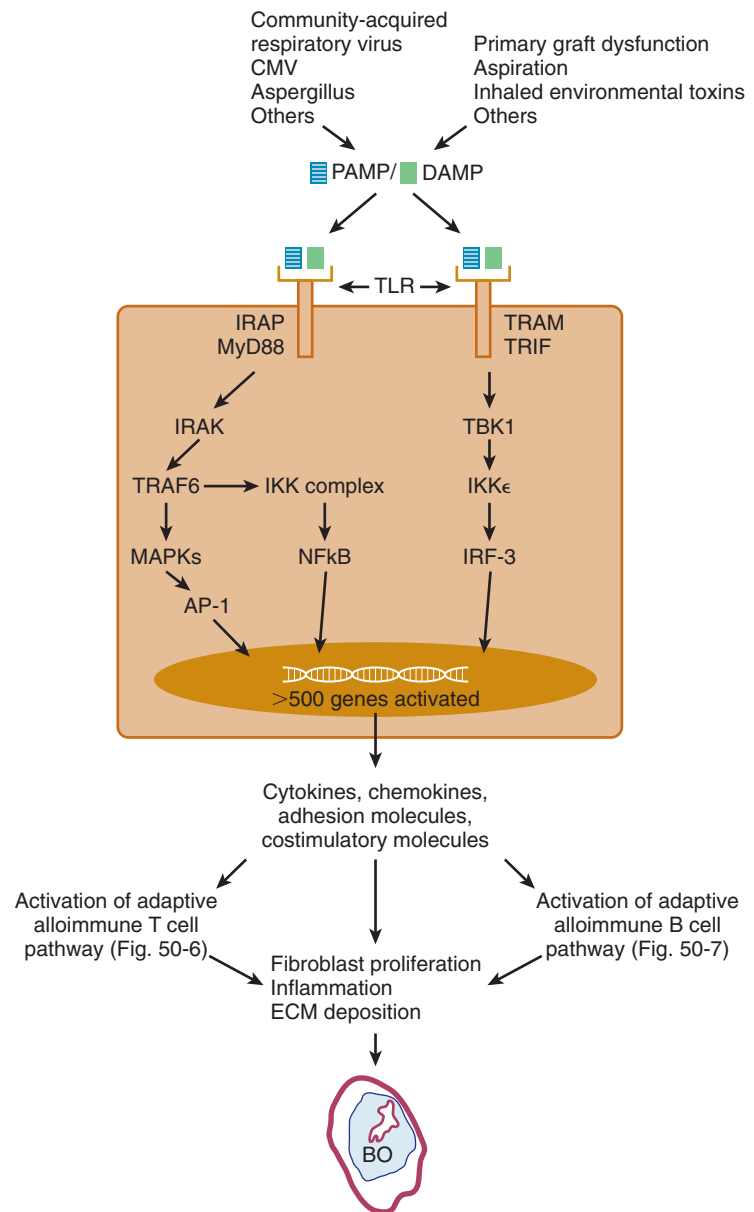


Figure 50-9 Innate immune-mediated pathway operates via Toll-like receptor (TLR)-triggered signaling pathways.

These pathways ultimately result in activation of innate immunity genes involved in inflammation and adaptive immune response activation. Numerous infectious and inflammatory events release pathogen-associated molecular patterns (PAMPs) and damage- (or danger-) associated molecular patterns (DAMPs). TLRs recognize PAMPs and DAMPs and trigger complex intracellular signal transduction via the adaptor protein MyD88 pathway or through MyD88 independent pathways. These pathways result in transcription factor activation, including NF- κ B, AP-1, and IRF-3. Transcription factors activate numerous genes involved in the innate immune response, resulting in secretion of cytokines, chemokines, and other costimulatory molecules. These molecules stimulate the adaptive immune response and directly stimulate fibroblast proliferation and extracellular matrix deposition, ultimately resulting in bronchiolitis obliterans (BO). AP1, activator protein-1; CMV, cytomegalovirus; ECM, extracellular matrix; IKK, I κ B kinase complex; IKK ϵ , inducible I κ B kinase- ϵ ; IRAP, interleukin-1 receptor antagonist protein; IRAK1, interleukin-1 receptor (IL-1R)-associated kinase; IRF-3, interferon regulatory transcription factor 3; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation factor 88; NF κ B, nuclear factor- κ light chain enhancer of activated B cells; TBK1, TANK-binding kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; TRAM, TRIF-related adaptor molecule; TRIF, TIR domain-containing adaptor protein inducing IFN- β .

Treatment of established BOS after lung transplantation remains disappointingly ineffective.^{152a} Augmentation or changing immunosuppression has been tried with variable response.⁸² Thrice-weekly azithromycin does improve lung function in patients with a subset of BOS demonstrating neutrophilia on BAL.^{153-155,155a} Statins may be associated with decreased rejection and BOS, perhaps by inhibiting expression of MHC class II molecules or by a variety of other antiinflammatory and immunomodulatory effects.¹⁵⁶ Uncommonly used, extracorporeal photophoresis may decrease the rate of decline in FEV₁ in established BOS.¹⁵⁷ Limited data and marginal efficacy in conjunction with the burden of delivering this intensive treatment have tempered enthusiasm for this potential therapy. For severe BOS, retransplant is the only definitive treatment and may be an option for some. The rates of recurrent BOS after a second transplant are similar to those of first transplant.^{158,159}

The most effective strategy for BOS therapy in lung transplant is primary prevention. Substantial attention is paid to identifying and treating patient-specific risk factors for BOS. Examples include surveillance bronchoscopy for acute rejection,¹⁶⁰ cytomegalovirus-specific antiviral prophylaxis,¹⁶¹ reducing aspiration through lifestyle modifications and gastric fundoplication,^{162,163} and treatment of certain community-acquired respiratory viral infections.¹⁶⁴⁻¹⁶⁶

As in lung transplant recipients, the response to BOS therapy in stem cell transplant patients is poor. Bronchodilators and corticosteroids do not generally improve airflow, and the use of immunosuppressive agents to treat chronic GVHD, although occasionally effective,^{167,168} has not consistently changed the course of BO.¹⁴¹ Macrolide antibiotics are sometimes used empirically, but there is little evidence to support this practice.^{169,170} Prophylaxis against GVHD and viral infection may reduce the risk for subsequent BOS.

BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia (BPD) is a respiratory complication of premature birth. Since the first description of BPD in 1967,¹⁷¹ the management of prematurity has evolved, including the use of antenatal glucocorticoids, perinatal surfactant, and modified mechanical ventilation. This evolution has resulted in different clinical and histopathologic entities termed “old” and “new” BPD. Old BPD was identified in newborn babies with infant respiratory distress syndrome following prolonged treatment with high concentrations of inspired oxygen and positive pressure ventilation.¹⁷¹ Characteristic histologic features include unusual abnormalities of the bronchioles, including marked metaplasia, obliteration, and cystic changes.¹⁷² The entity also has been described in adults after adult respiratory distress syndrome¹⁷³ and may be more frequent than is currently recognized. The pathologic process includes significant fibrosis of alveolar septa and resembles the honeycombing seen in other fibrotic interstitial lung diseases.^{174,175}

Contemporary management of premature infancy has improved survival of increasingly immature infants, who may experience “new” BPD.^{176,177} New BPD is milder clinically and probably reflects developmental arrest in an immature lung rather than barotrauma and oxygen toxicity.^{177,178} Histopathologic examination reveals enlarged air spaces with simplified alveolar and alveolar-capillary development. Unlike in the original disease, airway abnormalities are uncommon.¹⁷⁷

LOCALIZED DISORDERS

Many of the specific causes of localized abnormalities of bronchi also underlie abnormalities of the upper airway. Examples are neoplasms, extrinsic compression, granulomatous disease, malacic lesions, and trauma. However, the manifestations, diagnosis, and therapy of localized bronchial disorders are substantially different from similar disorders in the larynx or trachea.

NEOPLASMS

Because lung cancers are common, any endobronchial mass must be evaluated carefully for possible malignancy. All histopathologic types of primary lung cancer may protrude into a bronchus and narrow or occlude it. Malignant endobronchial tumors often have an irregular, rather than smooth, surface on bronchoscopic examination. Primary malignant tumors of the lung are described in detail in Chapters 53 and 54.

Of patients with extrapulmonary malignancies metastatic to the lung, approximately 5% have predominantly endobronchial metastases.¹⁷⁹ The most common primary malignancies are renal cell, colonic, rectal, cervical, and breast carcinomas and malignant melanomas.¹⁸⁰ In most instances the manifestations of the primary tumor are apparent before the endobronchial metastasis is discovered.¹⁷⁹ Metastatic malignancies of the lung are discussed in detail in Chapter 55.

In patients with lymphomas or leukemia, malignant infiltrations of the bronchial mucosa are rare. In Hodgkin

disease or non-Hodgkin lymphoma, the endobronchial malignant cells may originate in bronchus-associated lymphoid tissue, may invade the bronchial mucosa by direct extension from hilar or peribronchial lymph nodes, or may seed the bronchial mucosa via lymphatic or blood vessels.¹⁸¹ Leukemic infiltration of bronchial mucosa is a rare late manifestation of chronic lymphocytic leukemia.¹⁸²

The lung is involved in one third to one half of patients with *acquired immunodeficiency syndrome* (AIDS) and Kaposi sarcoma (see Chapter 90). Endobronchial lesions are seen frequently, but they rarely cause airway obstruction or hemoptysis. The lesions are usually multiple, bright red or violaceous, and flat when visualized through the bronchoscope. On CT scans, Kaposi sarcoma may appear as irregular and ill-defined, sometimes flame-shaped, nodules, with peribronchovascular interstitial thickening beginning in the perihilar region and extending toward the periphery. The diagnosis of endobronchial Kaposi sarcoma is established when a patient with AIDS has widespread extrapulmonary Kaposi sarcoma and characteristic-appearing endobronchial lesions. Biopsy of the endobronchial lesions is seldom necessary for diagnosis and may be hazardous because of excessive bleeding.¹⁸³

Benign lung tumors frequently originate from cells in the airways, including nerves (schwannomas, neurofibromas, neurilemmomas), smooth muscle (leiomyomas), cartilage (chondromas), blood vessels (hemangiomas), fat cells (lipomas), glands (cystadenomas, oxyphilic adenomas), and epithelium (papillomas). These tumors often narrow or obstruct bronchi. By bronchoscopic examination, the tumors often are smooth, round, and well localized. Benign tumors of the lung are described in detail in Chapter 56.

BRONCHIAL COMPRESSION

When peribronchial lymph nodes are enlarged by carcinoma, lymphoma, or granulomatous infection, they may narrow the adjacent bronchi. Although sarcoidosis frequently results in enlarged hilar and mediastinal lymph nodes, bronchial narrowing from compression by lymph nodes in sarcoidosis is rare. In infants with congenital heart defects such as tetralogy of Fallot and transposition of the great vessels with ventricular septal defect, bronchial compression by dilated pulmonary arteries is an occasional complication.

MEDIASTINAL FIBROSIS (see Chapter 54 and 84)

In patients with pulmonary histoplasmosis or tuberculosis, an interesting and rare complication is mediastinal fibrosis,¹⁸⁴⁻¹⁸⁶ also called sclerosing or fibrosing mediastinitis. In such patients, it appears that fungal or bacterial antigens from granulomatous foci in mediastinal lymph nodes stimulate fibrogenesis in surrounding tissue, perhaps because of unusual sensitivity to the antigens.¹⁸⁴ The fibrosis may result in narrowing or occlusion of vital mediastinal structures, and the structures affected depend on the specific lymph nodes involved by the original infection. Mediastinal fibrosis originating from subcarinal or hilar lymph nodes may result in occlusion of main-stem bronchi, pulmonary blood vessels, or the esophagus. Mediastinal

fibrosis originating from right paratracheal lymph nodes commonly produces obstruction of the superior vena cava and azygos veins.¹⁸⁴ CT and magnetic resonance imaging are useful for diagnosing and following this condition.¹⁸⁷ No medical intervention has been shown to be effective. Patients sometimes benefit from endovascular and/or endobronchial stenting.

BRONCHIAL ANTHRACOFIBROSIS

Bronchial stenosis or obliteration with anthracotic pigmentation in the mucosa was first described as a discrete clinical entity in 1998, in a retrospective analysis of 28 patients from Korea.¹⁸⁸ Characterized by multifocal bronchial stenosis, especially in the upper and right middle lobes, with multiple pigmented anthracotic lesions, the condition is thought to be due to prolonged exposure to biomass fuel.¹⁸⁹ There is a very strong association between bronchial anthracofibrosis and tuberculosis.¹⁹⁰ The diagnosis can be made at bronchoscopy, but bronchial anthracofibrosis is often mistakenly identified as mediastinal fibrosis or endobronchial tuberculosis.^{190a}

FOREIGN BODIES

Accidental inhalation of foreign bodies is a major cause of death in children, resulting in approximately 2000 deaths annually in the United States. The foreign bodies, which may be seeds, nuts, nails, or a variety of other objects, most frequently lodge in the right main-stem bronchus. Children with aspirated foreign bodies may present with immediate cyanosis, cough, and wheezing or with the delayed onset of pneumonia or bronchiectasis. Suspected aspiration of a foreign body is an indication for immediate bronchoscopic examination of the airways. In the presence of asphyxia, rigid bronchoscopy is appropriate. In most other situations, foreign bodies can be extracted with the flexible bronchoscope, but personnel and equipment for rigid bronchoscopy should be available (see Chapter 23).

GRANULOMATOUS INFLAMMATION

In patients with pulmonary tuberculosis, spillage of infected material into the middle and lower lobes occasionally causes localized endobronchial infection. Endobronchial tuberculosis may present with hemoptysis, bronchorrhea, or localized bronchial obstruction, causing lobar collapse and persistent postobstructive pneumonitis. These findings may develop during active pulmonary infection by tuberculosis or many years after its treatment. The diagnosis is established most readily by fiberoptic bronchoscopy.¹⁹¹ The typical finding is the presence of localized endobronchial gelatinous granulation tissue. The mucosa may be nodular, red, and ulcerated, and often the diagnosis of bronchogenic neoplasm is suggested until pathologic examination of biopsy material has been carried out.

In patients with pulmonary sarcoidosis, localized endobronchial granulomatous inflammation rarely may lead to stenosis of bronchi.¹⁹² PFT results often show airway obstruction, but the common causes of the obstruction are the structural distortion of bronchi and bronchioles that accompanies pulmonary fibrosis,¹⁹³ nonspecific bronchial

hyperreactivity,¹⁹⁴ or laryngeal sarcoidosis.¹⁹⁵ Only rarely is bronchostenosis present.

Bronchocentric granulomatosis is an uncommon inflammatory lesion defined morphologically by the presence of necrotizing granulomas surrounding bronchi.¹⁹⁶ The entity develops most commonly in asthmatic patients with allergic bronchopulmonary aspergillosis, and considerable evidence suggests that the granulomatous bronchitis is an immunologic response to endobronchial fungi. Cases have also been reported in association with other infections (mycobacterial or fungal) and with rheumatologic disease, and a significant proportion are idiopathic. The bronchi may be narrowed or obliterated because of the inflammatory reaction itself or because of associated mucoid impaction.¹⁹⁶

BRONCHOLITHIASIS

Broncholithiasis is defined as the presence of a calcified fragment of tissue within a bronchus.¹⁹⁷ Any disorder that leads to calcification of lung tissue or of lymph nodes may result in broncholithiasis. This most often happens when hilar or peribronchial lymph nodes become calcified as a result of granulomatous infections such as histoplasmosis or tuberculosis, or less commonly from actinomycosis, coccidioidomycosis, cryptococcosis, or silicosis.^{197,197a} Necrotizing pneumonias and bronchiectasis may lead to calcification of bronchial cartilage, which can fragment to produce broncholiths. Occasionally, retained foreign bodies may become calcified. Broncholithiasis manifests clinically when calcified stones erode or break loose into the airways (see later). These stones are composed of 85% to 90% calcium phosphate and 10% to 15% calcium carbonate and thus closely resemble the composition of bone.

AMYLOIDOSIS

Amyloidosis is defined on the basis of the extracellular deposition of the fibrous protein amyloid. In both the primary and secondary forms of the disease, amyloid can deposit endobronchially, producing hoarseness, wheezing, or stridor, or incidental findings at the time of bronchoscopy.¹⁹⁸ The airway mucosa demonstrates irregular thickening with waxy firm deposits that may appear white, gray, or yellow. As many as 30% of patients with primary amyloidosis are symptomatic. Pulmonary involvement is usually associated with amyloid of the light chain variety.¹⁹⁹ The definitive diagnosis of endobronchial amyloidosis requires biopsy and demonstration of amyloid deposits, as defined by their green birefringence when viewed with polarized light after staining with Congo red.¹⁹⁸ A recent report suggests that confocal endomicroscopy may identify early-stage tracheobronchial amyloid.²⁰⁰ Endobronchial amyloid has been treated successfully with *neodymium:yttrium-aluminum-garnet* (Nd:YAG) laser therapy.²⁰¹

TRACHEOMALACIA AND BRONCHOMALACIA

Softening of the tracheal or bronchial walls may contribute to narrowing and collapse of the airways during exhalation. This can develop as a result of inherited disease (e.g., congenital polychondritis) or may be acquired as a result of

trauma, infection, chronic inflammation (e.g., relapsing polychondritis), or emphysema. Less commonly, bronchomalacia may be found in infants because of inadequate development of bronchial cartilage. These infants generally present with dyspnea, atelectasis, or recurrent pneumonias. CT scans, maximal flow-volume curves, and direct visualization by bronchoscopy are all helpful in confirming the diagnosis. Pharmacologic treatment is rarely effective, and stents or surgical intervention may be necessary for patients who are very symptomatic.

TRAUMATIC INJURY (see Chapter 76)

Tears or complete ruptures of main-stem bronchi or the bronchus intermedius are occasional complications of blunt trauma to the chest. The diagnosis should be suspected in any posttraumatic patient with new onset of cough, respiratory distress, subcutaneous and mediastinal emphysema, or pneumothorax. The associated presence of hemoptysis or hemothorax indicates bronchial vascular damage. Occasionally the development of manifestations of bronchial tears may be delayed days or weeks after the traumatic injury.

CLINICAL FEATURES OF LOCALIZED DISORDERS

Patients with localized endobronchial lesions generally present with symptomatic, physical, or radiographic manifestations of the lesion itself or of underlying conditions (e.g., malignancy, infection, AIDS, or sarcoidosis). Only the manifestations of the lesions themselves will be described in this section.

The most common symptoms of localized endobronchial disease are cough, hemoptysis, wheeze, dyspnea, and fever and chills secondary to postobstructive pneumonia. If an endobronchial lesion only partially obstructs a bronchus, patients may show manifestations of chronic pulmonary infections, such as lung abscess (see Chapter 33) or bronchiectasis (see Chapter 48). A history of recurrent pneumonias in the same segment or lobe of the lung should prompt a careful evaluation for partial bronchial obstruction by an endobronchial lesion. Similarly, for any edentulous elderly patient with a history of a severe anaerobic pulmonary infection, endobronchial obstruction should be considered.

Symptoms of broncholithiasis include cough, hemoptysis, fever associated with purulent sputum, and expectoration of stones. Often the cough in broncholithiasis is productive of a mixture of gritty, sandy particles and purulent or bloody sputum.

The physical examination in patients with localized endobronchial lesions may reveal fever and tachypnea. When a bronchus is narrowed but not completely obstructed, examination of the chest may reveal a unilateral palpable rhonchus, a localized wheeze during a forced expiratory maneuver, or a prolonged sibilant sound that persists after the expiratory or inspiratory effort has ended, the “bagpipe sound.”²⁰² Once the obstruction is complete, there is a loss of breath sounds and tactile fremitus over the portion of the lung distal to the obstruction.

In patients with localized endobronchial disease, the chest radiograph may show no abnormality. Radiographi-

cally apparent lung collapse depends on the completeness of the obstruction and on the extent to which collateral ventilation from adjacent lung is present. In infants the pores of Kohn, the sites of collateral ventilation, are poorly developed. Hence the likelihood of complete collapse from localized bronchial disease is great in this age-group. Other findings on the plain chest radiograph include mediastinal adenopathy with or without calcification, lung abscess, bronchiectasis, or pneumonia. The presence of air bronchograms in a consolidated region of the lung suggests that the bronchus supplying that region is at least partially patent.

Middle lobe syndrome refers to chronic or recurrent radiographic evidence of collapse of the *right middle lobe* (RML). Originally it was postulated that the cause was tuberculous adenitis of lymph nodes in the RML causing bronchial compression.²⁰³ *Obstructive middle lobe syndrome* can result from extrinsic compression by inflammatory lymphadenopathy or from endobronchial tumors. However, in most patients, bronchoscopy and CT scans do not demonstrate obstruction. This *nonobstructive middle lobe syndrome* is thought to relate to the normal, relatively long length and narrow caliber of the RML bronchus or to the relatively ineffective collateral ventilation normally present in this lobe.²⁰⁴ The anatomy itself leads to poor mucus clearance from the RML and to mucus plugging of peripheral airways. The poor collateral ventilation of the RML limits reexpansion once there is atelectasis. Patients with middle lobe syndrome often report multiple episodes of recurrent RML pneumonia. In addition, bronchiectasis is found in approximately 50% of patients with middle lobe syndrome. The most common clinical features of middle lobe syndrome are recurrent infection, chronic productive cough, chest pain, or dyspnea.²⁰⁵

DIAGNOSIS OF LOCALIZED DISORDERS

In patients with only partial obstruction of a bronchus, comparing radiographs obtained at full inspiration with those obtained at full expiration may assist in establishing the diagnosis. Upon inspiration, the negative intrathoracic pressure distends the partially obstructed bronchus, and air enters the distal lung. Upon expiration, the obstruction becomes complete, and air is trapped behind it. The result is a mediastinal shift away from the affected side on expiration. CT scans may identify hyperinflation, compressing lymph nodes, or calcifications in patients with broncholithiasis, or subtle endobronchial abnormalities.²⁰⁶

The definitive procedure for diagnosing localized bronchial abnormalities is direct examination of the bronchi via fiberoptic bronchoscopy. In general, any visualized abnormality should be biopsied and the biopsied materials submitted for histologic examination as well as for culture. If the lesion is friable and bleeds easily during its examination and manipulation, rigid bronchoscopy may be required.

Routine PFT results in general do not distinguish between localized and widespread bronchial obstruction. In patients with bronchial compression or mediastinal fibrosis, skin tests for histoplasmosis or tuberculosis may be positive.¹⁸⁴ In bronchocentric granulomatosis, peripheral blood eosinophilia and serum precipitins for *Aspergillus* may be present.¹⁹⁶ Because bronchocentric granulomatosis is probably a

hypersensitivity reaction to *Aspergillus*, galactomannan levels are typically normal.²⁰⁷ In endobronchial amyloidosis, immunoelectrophoretic analysis of blood or urine shows evidence of monoclonal gammopathy in 90% of cases.²⁰⁸

TREATMENT

The appropriate therapy for localized lesions of the bronchi depends on the specific underlying cause. Treatment of bronchial obstruction is described in Chapter 23. In some patients with inoperable obstructive neoplasms of the trachea, main-stem bronchi, or bronchus intermedius, the use of the Nd:YAG laser, electrocautery, or argon plasma coagulation can provide immediate relief; the therapeutic effects of cryotherapy, brachytherapy, and photodynamic therapy are slower in onset. Bronchial obstruction from extrinsic compression or endobronchial granulomatous inflammation may be relieved by medical treatment of the underlying condition (e.g., lymphoma, tuberculosis), but irreversible fibrotic narrowing often requires surgical resection or stenting. There are reports that airway and vascular obstruction due to mediastinal fibrosis may improve with corticosteroids or with stenting, and that anthracofibrosis may improve with antituberculous treatment, but prospective trials are lacking. Foreign bodies usually can be removed with specialized wire claws or baskets inserted through a bronchoscope. When they are lodged in central airways, removal of foreign bodies is performed most effectively via a rigid bronchoscope. Broncholithiasis is often self-limited, requiring no further evaluation or treatment. However, if hemoptysis, persistent cough, atelectasis, or infection is present, bronchoscopic evaluation should be considered for stone removal. Antibiotics should be administered to treat postobstructive infections. Occasionally, surgical intervention is required to manage persistent or recurrent broncholithiasis.¹⁹⁷ In infants with bronchomalacia, effective treatment may require long-term ventilation of the lungs until normal cartilage is formed, which usually happens by 6 months to 2 years of age. Patients with suspected traumatic bronchial injury should undergo immediate endotracheal intubation and fiberoptic bronchoscopy followed by thoracotomy.

TRACHEOBRONCHIAL STENTS

Although prostheses have been used to relieve tracheal and bronchial obstruction for many years,²⁰⁹ recent technical advances have made the procedure easier and more effective.^{209a} More than 20 types of tracheobronchial stents are now available, in metal, mesh, or silicone rubber; insertion usually can be accomplished by fiberoptic bronchoscopy without general anesthesia. Stents have been used effectively to relieve airway obstruction caused by malignancy, postinflammatory stenosis, and tracheobronchomalacia, and to occlude tracheoesophageal fistulas. The success rate is greater than 80% to 90% in selected patients.²¹⁰⁻²¹² Fenestrated or mesh stents are more effective for benign lesions than for neoplasms, which tend to grow through the metal mesh. Careful patient selection, choice of the correct stent, and an experienced bronchoscopist are important determinants of success. Virtual bronchoscopy using CT is often useful in planning stent placement.

Key Points

- Because of the large cross-sectional area of the peripheral airways, symptoms and physiologic changes develop late in disease involving the peripheral airways and conditions affecting these airways, including bronchiolitis and mucus plugging, can be silent.
- Bronchiolitis obliterans syndrome after lung transplantation results from chronic graft rejection; it is the final result of several immune-mediated pathways, including cell-mediated, humoral, autoimmune, and innate.
- Bronchiolitis obliterans after bone marrow transplantation results from chronic graft-versus-host disease.
- Diffuse panbronchiolitis responds to treatment with macrolide antibiotics.
- Endotracheal and endobronchial stents are effective for treating obstruction caused by tumors, postinflammatory stenosis, and tracheobronchomalacia.

Complete reference list available at *ExpertConsult*.

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NEOPLASMS OF THE LUNG

51

BIOLOGY OF LUNG CANCER

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INTRODUCTION

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INTRODUCTION

Lung cancer is the number one cause of cancer-related death in the Western world. Lung cancer remains the leading cause of cancer mortality for both men and women in the United States.¹ Its incidence is highly correlated with cigarette smoking, and lung cancer is eventually diagnosed in about 10% of long-term smokers. Among the 10% to 15% of patients without a smoking history in whom lung cancer develops, environmental or inherited causes of lung cancer contribute to the risk. As large as the clinical challenges patients and physicians face in managing this disease, equally enormous are the challenges in detailing the complex molecular pathogenesis of lung cancer. Major progress has been made, however, and we are beginning to see this knowledge translated into the clinic. In this chapter, we summarize our understanding of how lung epithelial cell injury leads to signaling pathway activation that triggers the uncontrolled proliferation, resistance to apoptosis, metastasis, and escape from immune surveillance seen in lung cancer. Whereas all subtypes of lung cancer have historically been divided between *non-small cell lung cancer* (NSCLC) and *small cell lung cancer* (SCLC), the field is stepping away from purely histologic classification and moving into molecular classification of tumors based on better

understanding of driver genes² and the potential benefit of therapeutic strategies using targeted therapies that interfere with mechanisms of tumor growth and progression.³

The pathogenesis of lung cancer involves the accumulation of multiple molecular abnormalities over a long period of time.⁴ Alterations in gene expression can result from abnormal microRNA expression or methylation, DNA sequence changes, DNA segment amplification, deletion, or whole chromosome gains or losses. These lesions allow cells to escape the normal regulation of cell division, apoptosis, and invasion and/or alter its interaction with the host. The historical focus of much of this research has been to identify and study the role of specific genetic abnormalities in tumor cells related to chromosomal abnormalities, inactivation of specific tumor suppressor genes, the activation of specific oncogenes, and the expression of hormone receptors and growth factor production associated with the development of cancer. More recently, the contribution of stromal interactions, the induction of angiogenesis, the control of apoptosis, and epigenetic phenomena such as posttranslational modification of critical genes have been the subject of intense research. The completion of the first draft of the human genome sequence^{5,6} and the availability of high-throughput technologies (e.g., microarrays) have also prompted investigators to propose studies to discover

molecular alterations of individual tumors with incredible sensitivity and unprecedented scope. Common molecular abnormalities in both precancerous and invasive lung cancers are being integrated and hold the promise for potential utility in prevention, early detection, and therapy.

PREDISPOSITION TO LUNG CANCER

SMOKING

Tobacco use continues to be a major cause of cancer in the world. Worldwide, tobacco use causes more than 5 million deaths per year, and current trends show that tobacco use will cause more than 8 million deaths annually by 2030.⁷ Tobacco control efforts are leading to a decrease in cancer mortality in some areas of the world,⁸ but globally there are still more than 1 billion smokers.⁹ More than 85% of all lung cancers are attributable to cigarette smoking; however, lung cancer develops in only a fraction of long-term cigarette smokers, suggesting a role for variable inherited genetic susceptibility in lung tumorigenesis.

Lung cancer develops through a multistage process in a background of increasing genomic instability and inflammation.¹⁰ For example, cytogenetic alterations arise throughout the airways with monoclonal and trisomic clonal patches observed.¹¹ Patches of epithelial cells presenting with $2n + 1$ number of chromosomes develop diffusely in the airway following the distribution of cigarette smoke exposure and confirm the “field cancerization” hypothesis.¹² Elucidating the molecular determinants responsible for the development of lung cancer and identifying intermediate biomarkers associated with malignant progression remain a priority. Cigarette smoking clearly contributes to the accumulation of genetic alterations in lung cancer.^{13–15} Tobacco is rich in pulmonary carcinogens and causes many genetic changes by inducing DNA mutation.^{16,17} Tobacco-specific nitrosamines induce DNA methylation¹⁸; levels of DNA adducts such as methylated DNA can, in fact, be used as an index of human tobacco exposure. Tobacco causes methylation of tumor suppressor genes.^{19,20} Cigarette smoke has also been shown to induce demethylation of the proto-oncogene synuclein- γ in lung cancer.²¹ Therefore, cigarette smoke could lead to specific patterns of chromatin structure alterations that may promote cancer development. In the future, specific epigenetic alterations induced by cigarette smoking may be useful as biomarkers of lung cancer development. Chronic exposure to carcinogens initiates a process characterized by genetic abnormalities, phenotypic changes, and overgrowth of clones of genetically altered epithelial cells throughout the lungs.²² Genomic alterations may form a pattern referred to as a “genomic signature.” The signatures found in NSCLC may contain information about their induction by cigarette smoke²³ and may reflect the pathways to cancer development or represent the product of competitive selection of clones.^{24–27} In fact, the clinical profile (Table 51-1) and molecular profile of lung tumors arising from never-smokers are quite distinct from their smoker counterparts.²⁸

Table 51-1 Characteristics of Lung Cancer Found in Never-Smokers

Peripheral disease in distal airways
Adenocarcinoma
Female
Younger age
Environment tobacco smoke, human papillomavirus 16 and 18 infection
Familial and genetic risk
Frequent <i>EGFR</i> and <i>TP53</i> mutations
Rare <i>KRAS</i> mutations

GENETIC SUSCEPTIBILITY AND FAMILIAL PREDISPOSITION

In epidemiologic studies, smoking confers an approximately 14-fold increased risk for lung cancer and, after controlling for tobacco use, a family history of lung cancer accounts for an approximately 2.5-fold increased risk. Here, we address susceptibility as it relates to genetic susceptibility and familial predisposition separately.

Genetic susceptibility may be seen with rare autosomal dominant genes that explain cases of early-onset lung cancer but more common genetic variants or polymorphisms are more likely to affect lung cancer risk. Inherited differences in DNA repair capacity in response to tobacco-mediated damage have been incriminated as underlying some of this susceptibility. When lymphocytes from lung cancer patients and age-matched controls are exposed to bleomycin, the lymphocytes from lung cancer cases develop more chromatid breaks than the control lymphocytes.²⁹ A similar assay has been developed using benzo(α)pyrene diol-epoxide, a reactive substrate that is derived by in vitro processes from benzo(α)pyrene, a major carcinogen in tobacco smoke.³⁰ These results suggest that the DNA repair capacity influences risk for lung cancer. Telomere length has also been inversely associated with lung cancer risk.³¹ Nicotinic acetylcholine receptor subunit genes may contribute to the risk of smoking as well as the risk of lung cancer. In three lung cancer genome-wide association studies, polymorphic differences in chromosome 15q25 have been associated with the risk of developing lung cancer.^{32–34} Single nucleotide polymorphisms mapped to a region of strong linkage disequilibrium within 15q25.1 contain nicotinic acetylcholine receptor subunit genes. The genetic variants were associated both with nicotine dependence as well as with certain lung cancer phenotypes, including lung cancer developing in younger patients and in patients with lower amounts of smoking; the variants were not associated with lung cancer in nonsmokers or with other smoking-related cancers like renal or bladder.³⁵ Since then, subsequent analyses have identified additional variants that influence lung cancer risk,³⁶ which will require further investigation in a larger sample size. The relative impact of the nicotinic acetylcholine receptor gene variants on the propensity to smoke or on the response to the direct carcinogenic effects of smoke is undergoing validation in large numbers of smokers and nonsmokers.

Familial risks of lung cancer provide another route for uncovering susceptibility genes. In one genome-wide linkage analysis, a genomic locus on chromosome 6q23–25 has now been associated with a familial risk of lung cancer.³⁷

To date, no tumor suppressor genes inactivated by mutation have been identified in this locus, although the frequent inactivation of multiple candidate tumor suppressor genes within chromosome 6q likely contributes to development of sporadic lung cancer.³⁸ Finally, a genome-wide association analysis was conducted to investigate associations between single nucleotide polymorphisms and the risk of lung cancer in 194 patients with familial lung cancer and 219 cancer-free control subjects.³⁹ A strong association was found between common sequence variants at 15q24-25.1 and lung cancer.⁴⁰ The risk of lung cancer was more than fivefold higher among those subjects who had both a family history of lung cancer and two copies of high-risk alleles in the 15q24-25.1 locus as compared with control subjects.³⁹ Thus, studies into sporadic and familial cancer risk may identify some of the same genetic predispositions, such as 15q24-25.1 or germline *EGFR* T790M mutations,^{41,42} and have the potential to identify novel genetic predispositions.

Mathematical models integrating clinical, physiologic, imaging, and biologic variables are now proposed for evaluating risk for lung cancer in clinical practice.⁴³⁻⁴⁷ This field has made tremendous progress, and prediction models are being proposed for implementation in selecting populations for screening and/or chemoprevention trials.

EARLY EVENTS IN LUNG TUMORIGENESIS

FIELD CANCERIZATION EFFECT

Whereas lung cancer may originate from only one or a few airway epithelial cells, it is clear that exposure of the whole airway mucosa to tobacco smoke can cause the entire bronchial tree to be at increased risk for development of lung cancer, leading to the concept of field cancerization (Fig. 51-1). Field cancerization was first proposed in the 1950s,¹² and its molecular correlates were later confirmed in the airways of human smokers.⁴⁸ Field cancerization is also demonstrated by the elevated Ki-67 labeling index in the airways of smokers at more than one site.⁴⁹ In addition, evidence has been found in a single smoker with diffuse dysplasia that a single identical point mutation of *TP53* could be found diffusely in both lungs, but not in the blood or other solid organs, suggesting that a single progenitor bronchial epithelial clone populated the bronchial mucosa. Although the risk of developing lung cancer increases with the presence of such preinvasive lesions, clearly the entire at-risk epithelium does not undergo malignant transformation, and no one has identified the molecular determinants of preinvasive lesions that may predict irreversible progression to lung cancer. Thus, if one considers the total number of bronchial epithelial cells and the proliferation rate of patches of clonal abnormalities, cancer remains a rare event.⁵⁰

The concept of field cancerization has implications for approaching diagnosis, prevention, and treatment of lung cancer. For example, diagnostic information may be contained even in the normal-appearing airway epithelium; in patients with and without lung cancer, changes in the airway field have been found to correlate with the presence

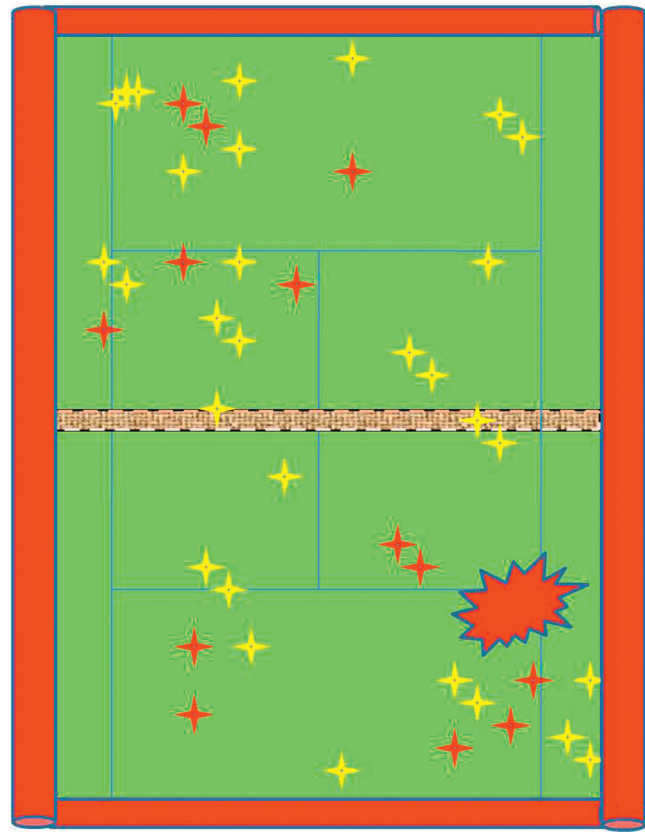


Figure 51-1 The field of injury. The field of injury could serve as means for assessing the risk of developing lung cancer, of having lung cancer, or even predicting the behavior of a tumor in the field. In this figure, the lung epithelial surface area is displayed as if it were a tennis court, known to be of roughly comparable size. The tumor (red) and associated genetic alterations (red and yellow stars) are shown as stochastic events. Investigations to understand the role of the field in disease pathogenesis can take advantage of the study of tumor samples, and adjacent bronchial biopsies, bronchial brushings, or related serum or plasma (red area surrounding the field) as well as tumor samples.

of lung cancer elsewhere in the airways or with an elevated risk for transformation.^{25,51} Similarly, prevention efforts should be directed to the entire epithelium, which can then also provide biomarkers for effective prevention. Finally, the field cancerization concept has major implications for therapy, because one should consider treating the entire field as opposed to limiting treatment efforts to preinvasive lesions that may never develop into lung cancer.^{52,53}

GENOMIC INSTABILITY

Lung cancer develops along a multistage process in a setting of increasing genomic instability. Genomic instability is universally found during accumulation of these genetic abnormalities.^{54,55} Genome instability is a fundamental characteristic of cancer initiation and progression. However, our understanding of the onset of instability, the rate of instability, and the mechanisms leading to instability is far from complete. We do know that—from initiation, to promotion, to the development of an invasive phenotype—a series of molecular changes contribute to a molecular instability that puts the airway epithelium of some smokers at greater risk for lung cancer.

Two main theories of the genomic changes underlying lung tumorigenesis have emerged: the stochastic (random) and the gene-centric (nonrandom) theories. The *stochastic theory* argues that lung cancer arises by genomic aberrations that are stochastic or random in nature.⁵⁶ Indeed, in many tumor types, there are relatively few cancer-specific mutations, whereas there can be a high degree of chromosomal aberrations.⁵⁷⁻⁵⁹ Some of these low-level aberrations have been called noise but may reflect the underlying instability. Nonclonal chromosomal alterations such as defective mitotic figures, chromosomal fragmentation, or nonrecurrent genomic alterations indicate a dynamic process leading to instability.⁵⁶ Nonclonal chromosomal alterations may provide a survival advantage, whereas clonal chromosomal alterations at a later stage of progression may confer a growth advantage.⁶⁰

In contrast, the *gene-centric theory* argues that sequential accumulation of epigenetic and genetic aberrations is important for lung cancer development.⁶¹ This gene-centric theory is particularly appealing to explain clonal alterations in genes implicated in tumor cell growth and survival that represent possible targets for the management of cancer.⁶² These alterations include single nucleotide point mutations, changes in chromosome copy number (aneuploidy),^{63,64} and specific genomic amplifications or deletions.⁶⁵⁻⁶⁷ These genetic changes are implicated in the pathogenesis of tumor development in part through the activation of oncogenes and inactivation of tumor suppressor genes and are considered one of the key hallmarks of cancer.⁶⁸ Some genomic signatures seem to persist after tumor development and throughout their progression and their histologic differentiation. The fact that smoking history leads to specific genomic alterations across different tumors also suggests a specific pathogenesis with genomic alteration resulting from a series of dysregulations in DNA repair mechanisms and chromosomal segregation.

The two theories are not necessarily mutually exclusive, and both random and nonrandom changes may be important. The progressive accumulation of mutations, loss of apoptotic control and regulation of cell proliferation, and the appearance of an abnormal number of chromosomes (aneuploidy) are associated with worsening dysplasia phenotypes and may reflect underlying dysregulation of mechanisms controlling genomic fidelity. In some lung tumors, mismatch repair deficiency leads to microsatellite instability at the nucleotide sequence level, whereas in other tumors, aneuploidy is the dominant feature.⁶⁹ Specific defects in DNA repair may also be present. Polymorphisms in DNA repair genes *XPB* (codon 312 Asp/Asp vs. Asp/Asn) are associated with impaired efficiency of DNA repair and apoptotic function in lung cancer.⁷⁰ Measures of genomic instability parallel rates of loss of heterozygosity⁷¹ and accumulation of other genomic abnormalities.⁶⁹ In the airways, progressively more severe and more frequent abnormalities are seen in preinvasive lesions. The progressive accumulation of genomic abnormalities associated with clonal growth among populations of tumor cells is well described. Recent reports use *array comparative genomic hybridization* (aCGH) to assess genomic instability; in these reports, in addition to numerical chromosome changes, smaller aberrations are found at specific chromosome loci.⁷² Clearly, genomic instability itself drives malignant progres-

sion, and this instability may itself be a target for prevention or therapy of lung cancer.

MUCOSAL RESPONSE TO INJURY, THE EMERGENCE OF CRITICAL MUTATIONS

Since the late 1970s, somatic mutations have been identified and associated with the development of cancer. These mutations, involving those of tumor suppressor genes or oncogenes, may or may not be critical events in the formation of the cancer. Epidemiologic data support the hypothesis that clones of cells accumulate several key mutations during oncogenesis. Proposed by Loeb,⁵⁵ the model of the mutator phenotype, a phenotype in which mutations develop faster than in normal cells, suggests that this propensity for rapid mutation may be required for multistage carcinogenesis and may be acquired by cells early on. This phenotype may also be hereditary.

DNA mutations may arise from a failure to repair DNA damage. In addition to damage and mutations due to environmental carcinogens, spontaneous errors of replication attributed to DNA polymerase take place at a rate of 1/10,000 to 1/100,000 base pairs. These intrinsic mutations may also be an important component underlying genomic instability and eventually tumor development. A recent analysis of 623 genes in 188 lung adenocarcinomas revealed more than 1000 somatic mutations, and those in 26 different genes were found to be mutated at significant frequencies.⁷³ Many of these mutated genes fall into a handful of common signaling pathways. We briefly comment on a few examples of these commonly acquired mutations in *KRAS*, *TP53*, *p16*, *BRAF*, *PIK3CA*, *epidermal growth factor receptor* (*EGFR*), and *anaplastic lymphoma kinase* (*ALK*).

KRAS mutations are among the most common mutations found in lung cancer. The mutations are found in 30% of adenocarcinomas of the lung,⁷⁴ but much less frequently in other subtypes. Mutations in *KRAS* lead to activation of several pathways. Ras proteins activate the RAF/MEK/ERK pathway, which mediates cell growth and cell cycle entry by phosphorylation of transcription factors (e.g., such as c-FOS, ELK1, and MYC); phosphorylation of the RSK (*ribosomal protein S6 kinase*) and MNK (*mitogen-activated protein kinase* [MAPK]-interacting serine/threonine kinase) family of kinases; and the *phosphatidylinositol-3-kinase* (PI3K)/protein kinase B (AKT) pathway, which controls cell survival, cell growth, and metabolism.⁷⁵ Mutant *KRAS* (most frequently, codon 12 G-T transversions) can transform airway epithelial cells⁷⁶ by activating the *extracellular signal-regulated kinase* (ERK)-MAPK and PI3K/AKT pathways. Because the *KRAS* mutation is found early in alveolar atypical hyperplasia, a presumed precursor lesion to adenocarcinomas, *KRAS* mutation may be an important step in the genesis of this subtype of lung cancer. The fact that mutant ras transgenic mice develop adenocarcinomas of the lung supports this hypothesis.⁷⁷

TP53 is a prototype tumor suppressor gene that is the most common genetic lesion in human cancers⁷⁸ and is thus well suited for analysis of the mutational spectrum in human cancers. The gene product p53 is a potent regulator of cell growth and DNA damage responses, and directly regulates the cell cycle via induction of p21. Mutations of

TP53 are most commonly seen in squamous carcinoma and small cell carcinoma of the lung. Mutations predominantly representing G to T transversions consistent with causation by bulky DNA adducts such as the polycyclic hydrocarbons are frequently found in the lungs of smokers.¹³ When the gene is mutated, the p53 protein can function as an oncogene. Mutated p53 exhibits a prolonged half-life, and the protein can be found to be overexpressed in about 50% of lung cancers by immunohistochemistry.⁷⁹ Although not consistently associated with prognostic significance, there is little doubt that *TP53* mutations play a key role in tumor development by dysregulation of cell cycle control and apoptosis.

p16, a cyclin-dependent kinase inhibitor, functions as a tumor suppressor and critical member of the *retinoblastoma* (Rb) cell cycle control pathway. The gene is inactivated in more than 40% of NSCLCs. Previous studies have demonstrated that point mutations, deletion or loss of heterozygosity (when one parental copy of a region is lost) on 9p21, or hypermethylation of the gene provides alternate mechanisms of inactivation in 30% to 50% of NSCLCs. In smokers, the loss of *P16* appears to be from different mechanisms than in nonsmokers. In tumors arising in smokers, *P16* was found to be lost due to point mutations or homozygous deletions, whereas in tumors from nonsmokers, *P16* was lost via promoter hypermethylation.⁸⁰ The relationship between the loss of *P16* and tobacco points to *P16* as another genetic target of cigarette smoke in the pathogenesis of lung cancer.

BRAF is a serine/threonine kinase that belongs to the RAS/RAF/MEK/ERK/MAPK pathway, and is important for transducing mitogenic signals from the cell surface. *BRAF* mutations were found in thyroid, colorectal, and lung cancer as well as in a majority of malignant melanomas.⁸¹ The percentage of *BRAF*-mutant lung cancers appears to be less than 5% and to be limited to lung adenocarcinomas.⁸² This observation has led to drug discovery programs dedicated to specific targeting of BRAF-dependent tumors. Trials investigating the efficacy of these agents are ongoing in several tumor types.⁸³ Whether *BRAF*-mutant lung cancer can be successfully treated with inhibitors targeting downstream pathway members of BRAF remains to be established.

PIK3CA, the gene encoding the catalytic subunit of the class-1a phosphoinositide-(3,4,5)-kinase, is an important component of the AKT antiapoptotic pathway. Mutations in this gene have been found in a large fraction of epithelial cancers.⁸⁴ Although the most frequently mutated oncogene in breast cancer, *PIK3CA* was found to be mutated in less than 5% of lung cancers. In several functional analyses, these mutations were found to be oncogenic by their ability to activate the AKT survival pathway.⁸⁵ Most recently, pre-clinical studies involving new generation PI3K-kinase inhibitors suggest that tumors carrying these mutations might be exquisitely sensitive to pathway inhibition.⁸⁶

The gene for the receptor tyrosine kinase EGFR is mutated in approximately 10% of white and 40% of East Asian patients with NSCLC,⁸⁷⁻⁸⁹ leading to constitutive activation of this growth factor receptor. These mutations are more common in patients who have never smoked, whose tumors are of adenocarcinoma histology, and who are of East Asian ethnicity. Exon resequencing in responders to the tyrosine

kinase inhibitors, gefitinib or erlotinib, revealed that most of them had deletion mutations in exon 19 or point mutations in exon 21 of the *EGFR* kinase domain, but patients not responding to these drugs only rarely had these mutations.⁹⁰ Inhibition of mutant EGFR is an example of successful therapeutic targeting of oncogenically activated tyrosine kinases in cancer. The presence and type of *EGFR* mutations indicate which patients will respond to therapy with EGFR inhibitors. Trials selecting patients on the basis of *EGFR* mutations have yielded response rates to EGFR inhibition therapy exceeding 70% and led to median overall survival exceeding 20 months.⁹¹⁻⁹³

Even though dramatic responses are frequently seen in patients with the common *EGFR* mutations, most patients initially responding to EGFR inhibitors eventually relapse. These relapses may be explained by additional mutations in *EGFR* or activation of other growth pathways. In certain cases, resistance has been found to be due to an activating mutation of *EGFR* at a second site. This mutation, T790M, is analogous to the T315I mutation of the murine leukemia viral oncogene homolog (ABL) that causes acquired resistance in chronic myelogenous leukemia patients who had initially responded to imatinib.^{94,95} An additional mechanism of acquired resistance is the *de novo* amplification of the MET receptor tyrosine kinase gene.^{96,97} Understanding the sources of acquired resistance may reveal strategies for prevention of resistance.

The ALK is a receptor tyrosine kinase that is aberrant in a variety of malignancies. ALK was originally discovered in anaplastic large cell lymphoma as part of a chromosomal translocation t(2,5), which fuses the C-terminal kinase domain of *ALK* encoded on chromosome 2p23 to the N-terminus of nucleophosmin on chromosome 5q35.⁹⁸ Subsequently, a variety of ALK fusion proteins have been found in multiple malignancies, including inflammatory myofibroblastic tumor and NSCLC.^{99,100} ALK fusion proteins are transforming and are highly susceptible to ALK inhibitors.¹⁰⁰ Indeed, the ALK tyrosine kinase inhibitor (TKI) crizotinib was recently approved for the treatment of ALK fusion-positive lung cancer.¹⁰¹ Because crizotinib has “off-target” activity against the ROS1 kinase, somatic activating ROS1 fusions may also be susceptible to crizotinib.¹⁰² Rearrangements involving another kinase, RET, may be targetable with RET TKIs.¹⁰³ Because of their ability to guide therapeutic decision making, *EGFR*, *KRAS*, *ALK*, *ROS1*, *RET*, *BRAF*, and *PIK3CA* mutation testing have become part of standard pathologic analysis of lung adenocarcinomas in many centers.

The efforts to characterize the genomes of major human cancer types¹⁰⁴ have revealed that, beyond known cancer-related genes, many additional genes are mutated in individual cancers. However, most of these mutations are found in only a single tumor, suggesting that each tumor contains an individual set of mutations contributing to tumorigenesis. Ding and coworkers⁷³ found between zero and 40 mutations in individual lung adenocarcinomas, with an average of 24.3 for those with a mutant *PRKDC* gene (involved in DNA repair) and 4.7 for those without this mutation. The average number of mutations for different tumors range significantly from 0.39 mutations per one million bases (mut/MB) to the highest in small cell lung cancer (7.34 mut/MB) followed closely by melanoma.¹⁰⁵⁻¹⁰⁸

Mutagens

Cigarette smoking may account for 85% of lung cancers. Approximately 1 in 10 life-smokers will develop lung cancer, suggesting individual differences in susceptibility.^{109,110} Environmental carcinogenesis resulting from tobacco smoke exposure is a complex process that can involve activation of procarcinogens that lead to DNA adduct formation and subsequent failure of DNA repair, which should normally remove these adducts. Studies comparing DNA repair capacity among newly diagnosed lung cancer patients and age-matched controls indicate significant differences between the two groups.¹¹¹

The majority of lung cancers are now diagnosed among ex-smokers.¹¹² This suggests that the accumulation of molecular damage during cigarette exposure initiates a cascade of events that lead to cancer even decades after smoking cessation. Risk factors for lung cancer include smoking, including total consumption, age of initiation, and years of smoking; occupational and environmental exposure (asbestos, uranium, radiation), diet (vitamin A, vitamin E, cholesterol), and host (familial aggregation) and genetic factors (see Chapter 52). Cigarette smoke is a complex mixture and includes substances that are responsible for DNA adduct formation such as polycyclic aromatic hydrocarbons, aromatic amines, and tobacco-specific nitrosamines. These form DNA adducts that may escape normal adduct repair mechanisms and result in heritable alterations in DNA sequence. For example, the conversion of G-C base pairs to T-A is involved in the activation of the *KRAS* oncogene and inactivation of the *TP53* tumor suppressor gene.¹⁷ The activated form of benzopyrene is the diol epoxide benzo(α)pyrene that can cause DNA adducts, leading to point mutations and single-strand chromatid breaks.¹¹³ A major concern is that people who start smoking at young ages seem to have greater amounts of permanent DNA alterations than smokers who start smoking later.¹⁴

ROLE OF INFLAMMATION IN LUNG TUMORIGENESIS

The tumor cell signaling pathways that trigger the uncontrolled proliferation, resistance to apoptosis, metastasis, and escape from immune surveillance are partially understood. In contrast, how inflammation and its control may participate in lung tumorigenesis remains more poorly understood.

The reason why some smokers develop *chronic obstructive pulmonary disease* (COPD), some develop lung cancer, and some develop both diseases remains unclear.¹¹⁴ Cigarette smoke contains high concentrations of oxidants and free radicals, together with thousands of particles. Local antioxidant and metabolizing enzymes inactivate many toxic species. Nuclear factor-κB activation and subsequent transactivation of inflammation-related genes appear to play a central role in both COPD and cancer.¹¹⁵ How some smokers remain free of disease while others develop COPD or cancer may be determined by the activation of genes in response to cigarette smoke.¹¹⁶ Following exposure to the same toxic smoke, individuals appear to progress toward disease along different paths. In those who develop lung cancer, genomic instability develops that causes further

chromosomal abnormalities resulting in clonal expansion of cells that have a growth advantage, whereas in those who develop COPD, an intense immune response and further inflammation predominate. The process by which these events diverge is unclear. More likely, heritable genetic polymorphisms that influence susceptibility to DNA or connective tissue damage, efficiency of DNA or connective tissue repair, the intensity of immune responses to constituents of tobacco smoke, intrinsic or acquired genomic instability, or the induction of factors that suppress immune surveillance likely determine the disease pathway taken.

Toll-like receptors (TLRs), which recognize a variety of pathogen-associated molecular patterns, are centrally involved in the initiation of the innate and adaptive immune responses. Recent evidence shows that functional TLRs are also expressed on a wide variety of tumors, suggesting that TLRs may play important roles in tumor biology, and are being evaluated as therapeutic targets.^{117,118} Activation of tumor cell TLRs not only promotes tumor cell proliferation and resistance to apoptosis but also enhances tumor cell invasion and metastasis by regulating metalloproteinases and integrins. Moreover, the activation of TLR signaling in tumor cells induces the synthesis of proinflammatory factors and immunosuppressive molecules, which enhances the resistance of tumor cells to attack by cytotoxic lymphocytes and leads to immune evasion. Thus, the TLR signaling pathways may be usurped by the neoplastic process to advance cancer progression, which suggests that targeting tumor TLR signaling pathways may open novel therapeutic avenues.

Inflammation and tumor-infiltrating inflammatory cells have been shown to induce and help sustain tumor angiogenesis and sustain cellular proliferation.¹¹⁹ COPD and its underlying chronic airway inflammation provide support of lung cancer growth.¹²⁰ Chemokines, a component of cancer-related inflammation, predispose to cancer by affecting multiple pathways of tumor progression, including leukocyte recruitment and function; cellular senescence; tumor cell proliferation and survival; invasion and metastasis.¹²¹ The inflammatory system is expected to provide valuable targets for the development of innovative therapeutic strategies.

ROLE OF VIRUSES IN LUNG TUMORIGENESIS

Viruses can cause lung cancer in animal models; such viruses, including SV40 large T antigen and polyomavirus large and middle T antigens, cause lung cancer in transgenic models. No common respiratory viruses have been conclusively incriminated in the development of human lung cancer, but several have been implicated. Human papillomavirus, for example, has been associated with lung cancer and, in particular, lung cancer arising in women.¹²² These results remain controversial because *The Cancer Genome Atlas*, a coordinated effort supervised by the National Cancer Institute to apply high-throughput genome analysis to the study of cancers, has not reported viral sequences in tumors. Similarly, controversy persists on the role of other viruses. Simian virus 40 has been suspected in the development of mesothelioma¹²³; Epstein-Barr virus has been suspected to be involved in the development of papillomas, mesotheliomas, and lymphomas of the lung;

the Jaagsiekte sheep retrovirus or a variant has been thought to cause adenocarcinoma in situ in humans as it does in sheep.¹²⁴ However, many polymerase chain reaction–based assays have attempted to correlate bronchogenic carcinomas with respiratory viruses without success. Recent advances in proteomics may be useful in studying the role of viral infection in airway epithelial cell transformation. The proteomic analysis of tumors may allow the identification of peptide sequences specific to pathogens otherwise unknown in tumorigenesis.

In recent reports, infectious agents associated with diseased human tissues have been discovered by high-throughput sequencing technologies.¹²⁵ However, identification of a nucleic acid sequence in a sample does not necessarily implicate an organism as causal in a disease. Viral nucleic acid may be found because of contamination of tissues, because of a subclinical infection unrelated to the disease, or because it is latent in human tissue but not actively causing illness (e.g., human herpesvirus and human papillomavirus).

NEUROENDOCRINE TUMOR DEVELOPMENT, GENOMICS OF SCLC

SCLC develops from neuroendocrine cells in the lung. The evidence for this is best established from mouse studies with deletion of *Rb* and *TP53*.^{126,127} In these studies, mouse SCLCs often arise in the lung epithelium, where neuroendocrine cells are located, and the majority of early lesions were composed of proliferating neuroendocrine cells. When *Rb* and *TP53* were deleted in nonneuroendocrine lung epithelial cells, mice did not develop SCLC.^{128,129}

Recent publications offer new molecular characterization of SCLC. Using comprehensive genomic analysis of SCLCs^{130,130a} with high-throughput sequencing techniques, Rudin and colleagues have demonstrated that SCLCs are composed of multiple known and new molecular abnormalities. They confirmed known SCLC molecular alterations to genes such as *TP53*, *RB1*, *PIK3CA*, *CDKN2A*, and *PTEN*. In addition, they identified other genes coding for proteins with a wide array of cellular functions such as the RAS family regulator, chromatin-modifying enzymes, transcription regulators, kinases, protein phosphatases of G-protein coupled receptors. Further genetic mutational clustering identified specific pathways at the epicenter of SCLC pathogenesis, which included PI3K, Hedgehog, NOTCH, mediator complex, glutamate receptor, DNA repair, and the SOX family. This study showed a high mutational frequency of several SOX genes and overexpression of SOX2 in close to 25% of the SCLCs analyzed. Lastly, they identified new mutations to genes coding for tyrosine kinases such as *FLT1*, *FLT4*, *KDR*, and *KIT* as well as several fusion proteins such as *RLF-MYCL1* which could be potentially targeted therapeutically.

In another integrative genomic analysis of 99 SCLC tumors and lines, Peifer and coworkers confirmed recurrent losses of the tumor suppressor genes *TP53* and *RB1* and novel amplifications of *FGFR1*, *MYCL1*, and *MYCN* in SCLC.¹⁰⁵ These findings were found to be similar to findings in *TP53/Rb1* conditional knockout mice that, in the absence of p53 and RB1 protein expression, developed several SCLCs expressing amplifications of *MYCL1*, *MYCN*, and *NFIB*. Exome sequencing, transcriptome sequencing, and genome sequencing confirmed that SCLCs have a high mutation rate (7.4 protein-altering mutations per MB) that

corresponds with tobacco-associated carcinogen exposure. From these studies, they identified *TP53*, *RB1*, *CREBBP*, *EP300*, *SLIT2*, *MLL*, *COBL*, and *EPHA7* as potential oncogenic drivers, which were classified into five major groups: (1) *receptor tyrosine kinases* (RTK), (2) PI3-kinase and p53 pathways, (3) cell cycle control, (4) histone modifiers, and (5) SLIT-ROBO signaling. Using reverse phase protein arrays, Byers and associates identified PARP1, a DNA repair protein and E2F1 coactivator, to be highly expressed at the mRNA and protein levels in SCLCs. PARP inhibition down-regulated key components of the DNA repair machinery and enhanced the efficacy of chemotherapy,¹³¹ justifying future clinical studies evaluating PARP and EZH2 inhibition, together with chemotherapy or other agents. These gene-centric approaches will have to be complemented by genome control studies, studies aimed at understanding gene regulatory mechanisms by investigating the whole genome structure, including chromatin structure and epigenetic alterations, and function. Understanding both the genes and their control will be necessary to resolve the molecular networks explaining the heterogeneity found in tumors and their functional implications.

Small cell lung cancer has worse clinical outcomes and no currently proven personalized therapy. SCLC and NSCLC account for 15% to 20% and 80% to 85% of annual lung cancer cases, respectively. SCLC is clinically more aggressive with an untreated median survival of 2 to 4 months.¹³² Despite initial complete responses exceeding 50%, the best combinations of chemotherapy and radiation result in less than 5% of patients surviving 5 years from initial diagnosis.¹³² Efforts to identify driver mutations, gene amplifications, or signatures with clinical utility in SCLC have thus far not translated to new therapies. In addition, prognostic or diagnostic markers for SCLC are scarce.¹³³⁻¹³⁵ Over the past decade, several molecular abnormalities have been described as indicators of chemotherapy resistance and poor prognosis in NSCLCs.¹³⁶ As described earlier, recent seminal studies have identified genomic aberrations in SCLC that will hopefully lead to successful therapeutic strategies.

Why is no targeted therapy available in SCLC? The discovery of new targets for early detection and for therapeutics has been hindered by the fact that SCLC is often detected late and tissue is rarely obtained for study because surgical resection is not standard therapy. Another major shortcoming associated with the slow progress has been the lack of sensitive and robust technology to detect the signatures of cancer cells from minute quantities of available tissues or serum. Recently, advances in genomic technology provide high-resolution, high-throughput tools to measure copy number, gene expression, DNA methylation, and nucleotide sequence in cancer have started to move the field forward.^{105,130,137} These reports predict rapid evolution in the understanding and management of SCLC.

OTHER MOLECULAR ALTERATIONS DRIVING THE TUMOR PHENOTYPE

CHROMOSOMAL CHANGES

Cancer cells are characterized not only by mutations but also by a series of other chromosomal aberrations including

deletions and amplifications.¹³⁸⁻¹⁴⁰ Although chromosomal aberrations have been linked to most tumors and are a characteristic of cancer,⁶⁸ chromosomal aberrations are recognized as increasingly complicated.^{11,141} Many of the observed alterations have been considered consequences instead of causes of lung cancer development. However, there are chromosomal regions with frequent losses found in regions coding for essential tumor suppressor genes and DNA repair genes that may be involved in the pathogenesis of several tumor types.¹⁴²

Chromosomal alterations in NSCLC have been measured by aCGH.^{66,67,143} Specific areas of amplification and deletion can distinguish squamous from adenocarcinoma of the lung and other subtypes. Among many areas of genomic abnormality, amplification of chromosomal region 3q26-3q29 was the most prevalent abnormality in squamous carcinoma of the lung. These studies confirm and refine previously documented copy number alterations in lung cancer using CGH analysis^{64,144} and show particularly common amplified regions on chromosomal arms 1q, 3q, 5p, 8q, 11q, 12p, 17q, and 20q.

Chromosomal abnormalities may have a role in classifying tumors. Attempts have been made to look comprehensively at the genome to identify tumors with common groups of genetic features that might provide biologic or clinical guidance beyond traditional classification by light microscopy. Single nucleotide polymorphism arrays have been developed that are able to analyze loss or gain of genetic material at very high resolution⁶⁷ and cancer genome sequencing efforts have uncovered common mutations.^{106,107,145,146} From genomic analyses, relatively small differences have been observed between squamous and adenocarcinoma of the lung. The most prevalent differences were found on chromosome 3q and include the p63 gene.^{143,147,148} Accumulation of specific chromosomal abnormalities has been correlated with clinical and pathologic data in NSCLC. Chromosomal abnormalities have been correlated with clinical outcome for a variety of cancers,¹⁴⁰ but often, the genes or networks responsible for the observed biology are very difficult to define and are only partly understood.^{146,149-151}

Chromosomal abnormalities may underlie the progression of cancer. Loss of chromosomal regions on chromosomes 3p and 9p have been recognized as early events and identified in preinvasive lesions and in the normal-appearing epithelium of smokers.^{152,153} In contrast, *TP53* and *KRAS* mutations have been seen primarily in later stages of preneoplasia or frank invasive lesions.¹⁵⁴ Amplification of large regions on the q arm of chromosome 3 has been characterized in invasive carcinomas^{64,66,144,155} and only recently in preinvasive lesions.¹⁴⁷ Patterns of chromosomal change may be specific to cigarette smoke. In fact, lessons have been learned from the molecular analysis of lung cancers from patients with and without a history of smoking. For example, *loss of heterozygosity* (LOH), the loss of a chromosome containing a wild-type gene when the gene on the other allele was previously mutated, at chromosome 3p14 was evaluated in smokers and ex-smokers. LOH at this site was found to be more frequent in current smokers (22/25 cases) than in former smokers (5/11 cases), and the high frequency in smokers correlated with a high metaplasia index.^{152,153} This implies that not only are these chromosomal changes frequent in normal-appearing bronchial

epithelia but also that cells with these changes may regress after smoking cessation and be replaced by cells without this damage. Patterns of lung cancer allelic loss have been investigated in detail and new regions of allelic loss have been identified using high-throughput technologies.⁷¹ Interestingly, chromosome losses such as LOH and chromosomal gains are more prevalent at all sites in cancers from smokers than from nonsmokers, indicating a greater chromosomal instability in the cancers from smokers.¹⁵ aCGH has been used to discover specific patterns of genomic alterations found in NSCLC that might be related to smoking history. Smoking-related genomic signatures were identified in NSCLCs and could be predicted with an overall 88% accuracy.²³ Lung tumors arising from current smokers had the greatest number of copy number alterations. The genomic regions most significantly associated with smoking were located within 32 regions and functionally associated with genes controlling the M phase of the cell cycle, the segregation of chromosomes, and the methylation of DNA. Understanding chromosomal abnormalities specific to cigarette smoke exposure may point to the etiology of smoking-induced lung cancer.

Specific translocation is another chromosomal abnormality found in lung cancer, but much less commonly than in hematologic or mesodermal tumors.^{156,157} Chromosomal translocations modify gene function through the deregulated expression of cellular proto-oncogenes without altering the structure of the protein product or by generating and expressing a chimeric protein with growth-promoting activities. Unbalanced translocations are also responsible for a large number of LOHs, which is a genetic event known to cause inactivation of tumor suppressor genes.¹⁵⁸ Dang and colleagues¹⁵⁹ identified a chromosome 19-15 balanced translocation associated with overexpression of *NOTCH3*, a protein that establishes an intercellular signaling pathway that plays a key role in development. The authors developed a transgenic mouse model overexpressing *NOTCH3* causing neonatal mortality with a phenotype suggestive of alveolar cell hyperplasia. These data suggest that *NOTCH3* overexpression prevents epithelial differentiation and this may play a significant role in promoting oncogenesis in a subset of lung cancers.¹⁶⁰

Similarly, recent findings are pointing towards new fusion genes such as *ALK*, *ROS1*, and *RET* (discussed earlier) with rapid translation toward novel therapeutics in lung cancer.^{100,102,161-163}

EPIGENETIC ALTERATIONS OF GENE EXPRESSION IN LUNG CANCER

DNA Adducts

DNA adducts are covalent modifications of the DNA that result from exposure to specific carcinogens and thus, the level of DNA adducts in normal cells can serve as a biomarker for a significant exposure to carcinogens. In addition to being markers of carcinogen exposure, DNA adducts may directly alter regulation of transcription of tumor suppressors or oncogenes.¹⁶⁴ Because DNA adduct levels in tumor tissue and in blood lymphocytes have been associated with lung cancer¹⁶⁵ and because these levels correlate with daily or lifetime cigarette consumption and do not

reverse after smoking cessation,¹⁶⁶ DNA adducts have been proposed as potential biomarkers of risk for lung cancer.

In an attempt to identify risk factors associated with the level of DNA adduct accumulation, Wiencke and associates studied DNA adducts in current and former smokers and found that, for current smokers, the most important variable in determining the level of DNA adducts was the number of cigarettes smoked per day.¹⁶⁴ In contrast, they found that for ex-smokers, the most important variable was age at initiation. Mechanisms responsible for the relationship between DNA adduct levels and age of initiation are unknown; the relative contribution of increased adduct formation at younger ages or perhaps decreased adduct removal by impaired DNA repair is yet to be determined. Prospective studies are needed to follow current and ex-smokers over time to determine the value of adduct levels in risk assessment.

DNA adducts have also been associated with risk of lung cancer. In a matched case-control study nested within the prospective Physicians' Health Study, there was an increased level of DNA adducts in active smokers who later developed lung cancer than in smokers who did not develop lung cancer.¹⁶⁷ The level of adducts has also been found to be more prevalent among female than male smokers. Women smokers may be at higher risk of developing lung cancer for a given tobacco exposure and women also seem to accumulate aromatic/hydrophobic DNA adducts at a faster rate than men.¹⁶⁸ (See Chapter 52.)

DNA Methylation

DNA methylation alters gene expression by increasing the density of methylation at promoter regions. In contrast to genetic mutations that require two hits to inhibit both alleles, aberrant methylation is a dynamic process over multiple division cycles and may cause increasing degrees of gene function loss over time. "CpG islands," the major targets of DNA methyltransferase, are associated with the transcription start sites in almost half of human genes.¹⁶⁹ Dense methylation of cytosines within CpG islands can cause heritable gene silencing.¹⁷⁰ Genomic DNA hypomethylation, leading to genomic instability, as well as promoter hypermethylation, leading to inactivation of tumor suppressor genes, have been shown to be common events in human cancer.¹⁷¹ Gain of methylation in normally unmethylated CpG islands surrounding gene transcription start sites is an increasingly recognized and important means by which gene expression is altered in tumors.¹⁷² The genes affected include more than half of the tumor suppressor genes that are known to cause familial cancers. Aberrant methylation can begin early in tumor progression and cause loss of cell cycle control (e.g., p16),¹⁷³ loss of mismatch repair function (e.g., MLH1), and loss of cell-cell interaction (e.g., E-cadherin). The exact mechanism by which hypermethylation may cause tumor progression is still unknown. In fact, there is still debate about whether methylation is a result of or a cause of gene function loss.¹⁷⁴

Promoter region hypermethylation has also been proposed as an excellent tumor marker. In lung cancer, methylated loci were found in both tumor and sputum DNA and have been detected in the sputum for up to 3 years before the diagnosis of cancer.¹⁷⁵ Recently, methylation of the

promoter region of four genes (*TP16*, *CDH13*, *RASSF1A*, and *APC*) in patients with stage I NSCLC was shown to be associated with early recurrence.¹⁷⁶ The recent effort in *The Cancer Genome Atlas* also reported the landscape of alterations in methylation across a large number of lung cancers.¹⁷⁷

Histone Deacetylation

Histone deacetylation is another mechanism of epigenetic control. Histones are nuclear proteins that package DNA and allow ribosomal access to the DNA. Acetylation of histone tails on the nucleosome is associated with chromatin unfolding and increased regional transcriptional activity. Histone deacetylases modulate chromatin structure by regulating acetylation of core histone proteins. Deacetylation of histones is thus associated with compacting the DNA and repressing transcription. In lung cancer cell lines, for example, deacetylation of histone 3 correlated with refractoriness to retinoic acid, a phenomenon related to RARbeta promoter methylation in a subset of cell lines.¹⁷⁸ Inhibitors of histone deacetylases have already been shown to decrease the level of a series of oncoproteins,¹⁷⁹ suggesting a potential role as antitumor therapeutic agents.

Regulation by miRNAs

Micro-RNA (miRNA) are a large family of single-stranded noncoding RNAs that direct the posttranscriptional repression of protein-coding.^{180,181} In a study analyzing 104 pairs of NSCLC and corresponding normal lung tissues, an expression profile of 43 miRNAs discriminated lung cancers from noncancerous lung tissues.¹⁸² Six miRNAs (hsa-mir-205, hsa-mir-99b, hsa-mir-203, hsa-mir-202, hsa-mir-102, and hsa-mir-204-prec) were differentially expressed in adenocarcinomas when compared with squamous cell carcinomas. Furthermore, high hsa-mir-155 and low hsa-let-7a-2 expression correlated with poor survival in lung adenocarcinomas. In another study of 143 surgically resected NSCLCs, low let-7 expression was also significantly associated with shorter survival, whereas overexpression of let-7 in the A549 lung adenocarcinoma cell line inhibited lung cancer cell growth in vitro.¹⁸³

Differentially expressed miRNA genes in NSCLC are frequently located in fragile sites of chromosomes highly prone to mutation and/or chromosomal regions with frequent copy number alterations, suggesting that differences in miRNA expression may be induced by genomic alterations. Because greater than 50% of miRNAs are present at cancer-related chromosomal regions, miRNAs are also suspected to play a role as oncogenes or tumor suppressor genes. miRNA expression profiles represent potential markers for lung cancer diagnosis, classification, and prognosis. Methodologic issues related to the reproducibility of the analytic platforms should be resolved soon.

PROTEOMIC ALTERATIONS

Changes in DNA and in RNA may not be reflected in changes in protein expression. In fact, recent advances in protein profiling have suggested a poor correlation between gene expression and protein expression. It is now well established that protein activity is often highly regulated by

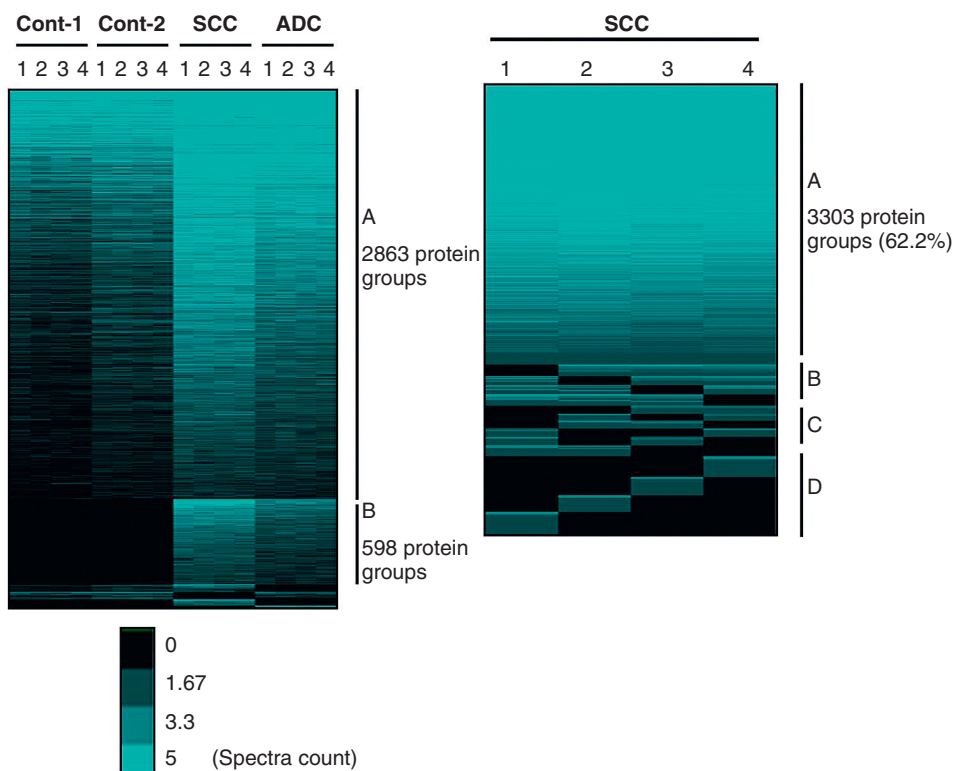


Figure 51-2 The shotgun proteomic method reproducibly identifies large numbers of proteins from clinical samples. *Left*, Heat map view of all identified proteins. Peptides were generated from three different histology pools including two control pools (Cont-1 and Cont-2), squamous cell carcinoma (SCC), and adenocarcinoma (ADC) pools. The number of protein groups (2863) found across all pools (top), are shown at the upper right side of the panel. Protein groups present only in the SCC and ADC tumor pools (598) (bottom), are shown at the lower right. Control: Noninvasive lung tissue. *Right*, We identified proteins in the SCC pool from four repeated experiments as indicated by the numbers 1 through 4 shown above each row. Out of the 5310 protein groups identified, 3303 (62.2%) protein groups were observed in every experiment (A), and 487 (9.2%) protein groups were observed in three experiments (B). The number of proteins observed in two experiments (C) and one experiment (D) was 597 (11.2%) and 923 (17.3%), respectively. The blue lines in each row represent identified protein groups. The intensity of each line is indicative of the spectra counts for each protein group with the scale shown at the bottom of the figure. (Adapted from Kikuchi T, Hassanein M, Amann JM, et al: In-depth proteomic analysis of nonsmall cell lung cancer to discover molecular targets and candidate biomarkers. *Mol Cell Proteomics* 11:916–932, 2012.)

posttranslational modifications such as proteolysis and phosphorylation. Neither protein expression levels nor posttranslational modification can be assessed by genomic or cDNA microarray technologies, prompting interest in evaluation of protein expression, commonly referred to as “proteomics.”

Lung cancer has been studied by several proteomic methods including two-dimensional gel electrophoresis, mass spectrometry, and immunohistochemistry to identify biomarkers in tumors.¹⁸⁴⁻¹⁸⁶ or in biologic fluids such as bronchoalveolar lavage¹⁸⁷ of patients with or without cancer. Matrix-assisted laser desorption ionization profiling is rapid, high throughput, but detects only the most abundant proteins of relatively low molecular weight and does not enable direct identification when applied to complex proteomes. Two-dimensional gel-based analysis suffers problems of interlaboratory reproducibility and throughput. Mass spectrometry has an even lower throughput, but yields confident identification of large numbers of proteins from every cellular compartment.

Advances in proteomic analysis of human samples are driving critical aspects of biomarker discovery and the identification of molecular pathways involved in disease etiology. Our group has used a standardized *shotgun pro-*

teomic analysis method, which consists of identifying proteins in complex mixtures using a combination of high performance liquid chromatography and mass spectrometry, for profiling the two major subtypes of NSCLC and normal lung tissues (Fig. 51-2). With this approach, 3621 proteins were identified from the analysis of pooled human samples of squamous cell carcinoma, adenocarcinoma, and control specimens. In addition to proteins previously shown to be implicated in lung cancer, multiple new proteins were found of potential interest as therapeutic targets or diagnostic biomarkers, including some that were not identified by transcriptome profiling.¹⁸⁸ Up-regulation of these proteins was confirmed by multiple reaction monitoring mass spectrometry. This proteomic technology platform allows deep mining of lung tumor proteomes, enabling the identification of novel, previously undetected biomarker candidates and potential targets for therapy, such as SLC1A5, a neutral amino acid transporter that is responsible for more than 50% of glutamine transport into lung cancer cells.¹⁸⁹ SLC1A5 is also located at the cytoplasmic membrane and its inhibition decreased cell growth and viability in lung cancer cells. Such approaches may uncover novel and hopefully useful biomarkers of lung cancer.

Reverse phase protein arrays¹⁹⁰ are a means to validate protein biomarkers in biologic specimens. The major advantage is that it allows rapid evaluation of known signaling pathways in lung cancer and it requires a minute amount of tissue.^{131,191} The limitation is that this method is a targeted one and dependent on the validation of specific antibodies.

STRATEGIES TO DEEPEN OUR UNDERSTANDING OF LUNG CANCER

HIGH-THROUGHPUT PROFILING TECHNIQUES

Expression Arrays to Next Generation Sequencing

Because DNA ultimately affects cellular behavior via proteins translated from the RNA, RNA expression patterns may be more relevant than either DNA copy number or epigenetic DNA changes. The microarray technology developed in the mid-1990s offers the hope that a fingerprint of the genetic expression of these tumors can be developed and then associated with clinical features. Beyond allowing for better classification of lung cancers, this technical advance in profiling gene expression opens a window into the world of tumor behavior (disease progression, recurrence, response to therapy) as well as to the mechanisms of tumor development. Tumor gene expression profiles are also influenced by the surrounding nonmalignant cells and so profiling both the tumor and nontumor will allow for the study of the regulatory role of both entities.¹⁹²

Expression array data have provided new ways to distinguish and classify tumors. Selected genes allow the discrimination between primary lung cancer and metastasis of extrapulmonary sites.¹⁹³ Studies of expression profiles of adenocarcinomas of the lung using commercially available gene chips¹⁹³ or custom arrays^{194,195} have identified different classes of tumors, albeit with some overlap. For example, four classes of adenocarcinomas were found to have specific prognoses and expression signatures. These were characterized respectively by their (1) expression of cell cycle or proliferation genes, (2) expression of neuroendocrine markers, (3) expression of markers of alveolar origin, and (4) expression of ornithine decarboxylase or glutathione S-transferase.¹⁹³ The neuroendocrine subclass was found to have a clinical outcome significantly worse than the others. These subclass differences may suggest possible new therapies targeted to these subsets and explain why tumors that superficially seem similar may respond quite differently to therapy. For example, when cDNA microarrays were used to study neuroendocrine tumors, a poor correlation was found between genes expressed in carcinoid and SCLC,¹⁹⁶ tumors that may be morphologically similar but that behave very different clinically.

In sum, since the late 1990s, we have learned that the somatic molecular alterations in cancers yield signatures that can be used for subclassification^{193,195} or for predicting patient survival,^{195,197} risk of recurrence,¹⁹⁸ and response to therapy.¹⁹³ However, these signatures have not always withstood independent validation.¹⁹⁹

Advanced Proteomic Strategies

Mass spectrometry-based technologies are capable of very high throughput, allowing a sample to be analyzed in seconds and with a higher tolerance for salts, buffers, and other biologic contaminants. Because of these attributes, matrix-assisted laser desorption ionization mass spectrometry has been used to study proteins/peptides in serum,²⁰⁰⁻²⁰³ urine,²⁰⁴ tissue extracts,^{205,206} whole cells,²⁰⁷ and laser-captured microdissected cells.²⁰⁸ These profiling experiments have been applied to a series of biologic specimens. In one matrix-assisted laser desorption ionization mass spectrometry study from our group,²⁰⁹ hierarchical clustering of data from lung cancers and normal tissues allowed the identification of patterns distinguishing between tumor and normal as well as between histologic subgroups. Shotgun proteomic approaches allow the survey of increasing numbers of proteins and uncovers new molecular characteristics of lung cancers, as recently demonstrated in NSCLC.¹⁸⁸ Using an integrative proteomic and transcriptomic analysis, molecular differences between SCLCs and NSCLCs have been identified, supporting the potential role for PARP1 and EZH2 in SCLC.¹³¹ In general, however, because of a lack of reproducibility between platforms and institutions, proteomic profiling, unlike genomic signature profiling, has not yet made a major impact in clinical practice.²¹⁰⁻²¹²

Proteomic profiling in biologic fluids or tissue samples has also been studied, but is not without challenges. The complexity of the sample composition and the predominance of few abundant proteins in the sample that can mask lower abundant proteins currently limit the utility of this approach. A newer serum proteomic platform has been tested in retrospective studies and shown to have the ability to predict whether or not NSCLC patients will benefit from the EGFR TKI erlotinib.²¹³⁻²¹⁵ Future efforts to analyze specific proteins or protein signatures in serum or other fluids has potential for diagnosis, prediction of therapeutic response and monitoring.

MOLECULAR NETWORKS—SYSTEM BIOLOGY

To determine the most informative molecular targets from high-throughput assays, increasingly sophisticated analytic tools are being developed. These analytic tools help define biologic processes, cellular components, or molecular pathways as well as provide gene ontology information about genes of interest; such analytic tools include WebGestalt,²¹⁶ Pathway Studio, and Ingenuity. The Kyoto Encyclopedia of Genes and Genomes is a knowledge base for systematic analysis of gene functions in terms of the networks of genes and molecules.²¹⁷ Although most pathway and network analysis tools are gene-centric, tools for combining and integrating multidimensional information at various levels are rapidly developing.²¹⁸ Network analysis helps identify central genes or proteins, called *hubs*, that link many others in the network. One can assume that mutations in regulatory (hub) genes or proteins, for example, are more likely to cause disease than mutations in those less connected and peripheral in the network.²¹⁹ These hubs may also be target sites for therapy. Therefore, quantitative systems biology applied to cancer offers a unique approach for defining the pathogenesis, and developing

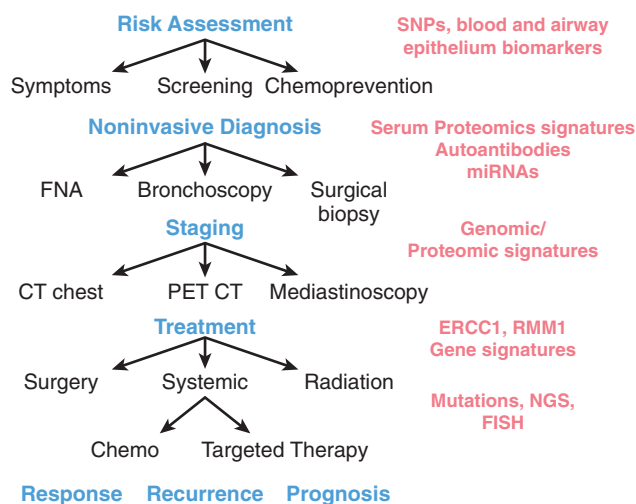


Figure 51-3 Future applications envisioned for biomarker-driven personalized management of lung cancer. At each step in the course of the management of lung cancer, important clinical decisions are made. Biomarkers of risk, diagnosis, prognosis, and response to therapy are becoming available and are already driving a personalized approach to lung cancer. Examples of such candidate biomarkers are provided in the figure at points in the decision tree where they may affect decision making in the near future. ERCC1, excision repair cross-complementation group 1; FISH, fluorescent in situ hybridization; FNA, fine needle aspiration; miRNAs, microRNAs; NGS, next generation sequencing; RMM1, ribonucleotide reductase; SNPs, single nucleotide polymorphisms.

individualized (personalized) treatment strategies that can take full advantage of modern molecular pathobiology and the comprehensive data sets that are rapidly becoming available for populations and individuals.

TRANSLATING LUNG CANCER BIOLOGY TO THE CLINIC

BIOMARKERS

Biomarkers are measurable products of tumors that can assist in the diagnosis (identification of cases), prognosis (correlation with outcome independent of interventions), or prediction (associated with outcome after a specific intervention). It is clear that lung cancer outcomes could be improved by high-quality biomarkers addressing each of these categories (Fig. 51-3). The biggest strides made to date have been in choosing treatments for patients with advanced lung cancer. However, to decrease lung cancer deaths, we need to devise biomarker-driven strategies for prevention, early detection, and treatment of early-stage lung cancers.

The discovery of biomarkers for early-stage lung cancer has been hampered by the slow onset of lung cancer and the lack of screening tests to identify early disease, although with the recent positive screening trial of low-dose *computed tomography* (CT) scans for heavy smokers, we are hopeful that the biologic samples collected from participants will be a useful resource for discovery for biomarkers.^{220,221} The assumption underlying the concept of biomarkers is that certain molecular characteristics of the lesions are highly correlated with specific, clinically-relevant biologic states.

Table 51-2 Characteristics of a Successful Diagnostic Biomarker

Measurable, noninvasive, with strong performance characteristics (with emphasis on positive and negative predictive values), robust, reproducible, and biologically relevant
Proven to add clinical value to current standards *and* to trigger a clinical decision
Adopted by the clinical community for the benefits it affords
Competitive in terms of cost and insurance reimbursement

These characteristics include changes in expression levels of genes and proteins and their posttranslational modifications. Detection of cancers at early stages maximizes survival, and identification of blood-borne markers would lead to minimally invasive tests. The best biomarkers are those that are reproducibly measured, that are related to the disease process, and that trigger a clinical decision resulting in improved clinical outcomes (Table 51-2). Despite an intense search for such biomarkers, there are none currently validated for the early diagnosis of lung cancer.²²²⁻²²⁴

Biomarkers based on the earliest known molecular abnormalities found in lung cancer could aid the early detection of lung cancer. Sputum sample analysis for DNA methylation, miRNAs, or chromosomal abnormalities by fluorescence in situ hybridization may represent approaches suitable for early detection. New detection methods such as exhaled breath condensate for tumor metabolites^{225,226} may be found to be efficient ways of assessing high-risk individuals. As alluded to earlier, early detection by low-dose CT scanning has been shown to be effective in lowering both overall and cancer-specific mortality in the National Lung Cancer Screening Trial.²²⁰ The addition of molecular studies may significantly increase the sensitivity and specificity of this new strategy for early detection.

Biomarkers may also provide prognostic and predictive information. Expression array signatures and serum proteomic assays have been discussed previously. Polymorphisms or expression of DNA repair genes (e.g., ERCC and RRM) have been associated with predicting response to chemotherapy,²²⁷ but also have been shown to have significant practical obstacles in terms of the performance reliability of antibody-based immunohistochemical tests,²²⁸ raising questions about their clinical utility.²²⁹ Cyclooxygenase-2 expression and urinary prostaglandins have been associated with benefit from COX inhibitors^{230,231} and are being further studied.

PERSONALIZED MEDICINE AND MOLECULAR THERAPEUTICS

The biggest impact of biomarkers in NSCLC clinical care has been in testing patients with advanced or metastatic disease for the presence of “driver” genotypes, which can then be matched to corresponding targeted therapies (Fig. 51-4). The term *driver* genotype refers to a crucial, necessary biologic change, usually a gain-of-function imparted by a gene mutation, amplification, or translocation. This driver is oncogenic and plays a critical role in the signaling that drives the malignant phenotype of the cancer. A wide range

of such driver genotypes have been found consistently in NSCLC, predominantly in adenocarcinoma tumors but to some extent in squamous cell cancers as well.^{232,233} Genotype screening of large patient populations has demonstrated that the driver genotypes tend to be mutually exclusive, suggesting that indeed these changes play a role in the early development of cancer and confirming the

notion that genotypic biomarkers can be used to distinguish one subtype of lung cancer from another. Clinical standards of diagnosis for NSCLC are evolving to take genotyping into account at the time of diagnosis; multiplexed platforms are being developed to accomplish testing in a time, money, and tissue-efficient manner.²³⁴ The genotype information is then used to match patients with targeted therapies, typically small molecular inhibitors that specifically block signaling of the driver pathway. A friendly tool available online at “www.mycancergenome.org” provides such support in an unprecedented way.²³⁵

There are several *EGFR* mutations (most commonly deletions in exon 19 and the L858R point mutation in exon 21) that have been found in adenocarcinomas among patients with a low smoking history.⁸⁷⁻⁸⁹ *EGFR* mutations are much more frequent in patients originally from East Asian nations, for reasons that are unknown; about 10% to 15% of North American and European lung cancer patients have *EGFR* mutations, whereas in Japan the proportion is 50% or greater.²³² These mutations lead to a constitutive activation of the EGF receptor and its downstream growth pathways and patients with *EGFR* mutations can respond in a dramatic way to the approved *EGFR* TKIs gefitinib, erlotinib, and afatinib (Fig. 51-5 and Table 51-3).^{92,211,236} For context,

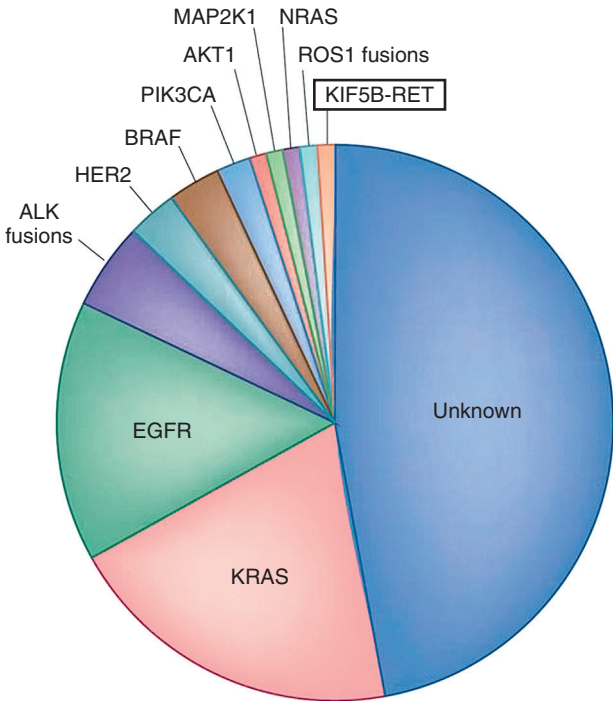


Figure 51-4 Pie chart showing the percentage distribution of genetic abnormalities in lung adenocarcinoma. Treatment decisions about lung cancer have shifted from those based only on histology to those incorporating genetic alterations. As seen in this pie chart, the genome of lung cancer is being chipped away, with discovery of driver mutations that lead to constitutively active signaling proteins and provide a target for therapy. The most recently identified *KIF5B-RET* fusion subset, which accounts for approximately 1% of this distribution, is boxed. *NRAS*, neuroblastoma *RAS* viral (v-ras) oncogene homolog; *MAP2K1*, mitogen-activated protein kinase 1; *AKT1*, v-akt murine thymoma viral oncogene homolog 1; *PIK3CA*, phosphoinositide-3-kinase, catalytic, α polypeptide; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *HER2*, human epidermal growth factor receptor 2; *EGFR*, epidermal growth factor receptor; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog. (From Pao W, Hutchinson KE: Chipping away at the lung cancer genome. *Nature Med* 18:349–351, 2012.)

Table 51-3 Molecular Targets in Lung Cancer	
Characteristics of Cancer	Possible Molecular Targets
Self-sufficient cell growth	EGFR, PIK3CA, PDGFR, MAPK, EML4ALK, ROS1, ALK, RET, HER2, BRAF, MET
Insensitivity to anti-growth	SMADs, Rb, cyclin-dependent kinases, MYC
Limitless replicative potential	p53, Rb, hTERT, EML4-ALK
Evading apoptosis	KRAS, p53, BCL-2, caspases, FAS, TNFR, DR5, IGF/PI3K/AKT, mTOR, PTEN, MET
Sustained angiogenesis	NF- κ B, VEGF, TGF- β , α v β 3, thrombospondin-1, HIF1 α

AKT, protein kinase B; EGFR, epidermal growth factor receptor; EML4-ALK, echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase; HIF1 α , hypoxia inducible factor 1 alpha; IGF, insulin-like growth factor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor- κ B; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol-3-kinase; pRb, retinoblastoma protein; PTEN, phosphatase and tensin homologue gene; TGF- β , transforming growth factor- β ; VEGF, vascular endothelial growth factor.

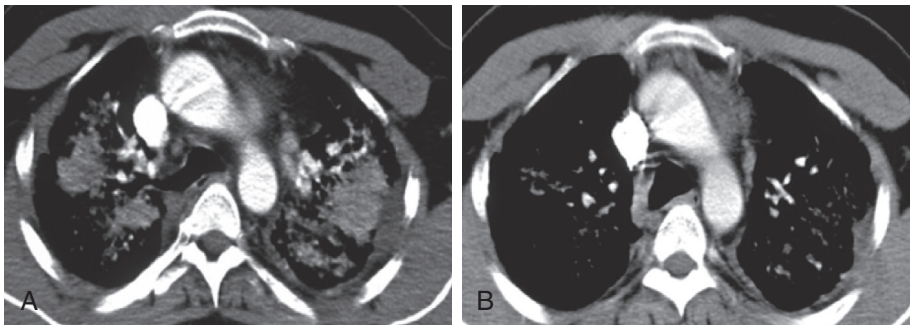


Figure 51-5 A response to anti-epidermal growth factor receptor (EGFR)-targeted therapy. Axial chest CT scan of a woman with chemotherapy-refractory adenocarcinoma shows a dramatic response to gefitinib (*EGFR* tyrosine kinase inhibitor) after 2 months of treatment (A, before treatment; B, after treatment). This woman was a never-smoker of Asian ethnicity with an activating *EGFR* mutation.

Table 51-4 Targets Identified in Lung Cancer Along with Current or Potential Therapies

Driver Genotype	Targeted Therapies
<i>EGFR</i> mutations	Approved <i>EGFR</i> TKIs: gefitinib, erlotinib and afatinib Experimental <i>EGFR</i> TKIs: dacomitinib, CO-1686, AZD9291
<i>ALK</i> translocations	Approved <i>ALK</i> TKIs: crizotinib Experimental <i>ALK</i> TKIs: LDK378, AP26113, CH5424802, X-396
<i>ROS1</i> translocations	Experimental <i>ROS1</i> TKIs: crizotinib
<i>MET</i> amplification	Experimental <i>MET</i> TKIs: crizotinib
<i>BRAF</i> mutations	Experimental <i>BRAF</i> TKIs: dabrafenib, vemurafenib
<i>HER2</i> mutations or amplification	Experimental <i>HER2</i> monoclonal antibodies: trastuzumab Experimental <i>HER2</i> TKIs: afatinib
<i>KRAS</i>	Experimental <i>MEK</i> TKIs: selumetinib, trametinib

the response to first-line chemotherapy for lung cancer patients is approximately 20% to 35% and the median *progression-free survival* (PFS; how long patients remain on treatment without progressing) is about 5 to 6 months.^{237,238} An *EGFR* mutation-positive patient typically has a 75% response rate to an *EGFR* TKI with a corresponding PFS of 10 to 13 months. In a series of prospective randomized trials, it has been shown convincingly that initial treatment of advanced lung cancer in patients with *EGFR* mutations with an *EGFR* TKI instead of with standard chemotherapy significantly improves PFS and quality of life; this has now become the standard of care.^{212,239,240}

Translocations that result in the apposition of the *ALK* receptor tyrosine kinase gene near the *EML4* or other similar promoter regions have been identified in about 5% of NSCLC cases, again most commonly found in patients with a low smoking history.^{100,241} *ALK* rearrangements confer sensitivity to the *ALK* TKI crizotinib with an approximate 70% response rate and a PFS of 10 months (Table 51-4).^{101,242} Patients with *ALK* translocations previously treated with chemotherapy have been randomized to crizotinib versus standard second-line chemotherapy; crizotinib was found to be more effective in term of response and PFS.²⁴³ In addition, a retrospective analysis suggests that patients with *ALK* translocations treated with crizotinib have an improved overall survival compared to patients that were unable to receive crizotinib or were diagnosed and treated prior to the availability of crizotinib.²⁴⁴ This is an important issue because targeted therapies proven to yield dramatic responses in a genotype-defined population pose an ethical dilemma for future randomized trials, because it is no longer feasible to randomize patients away from the effective targeted therapy without allowing crossover at the time of progression. The *ROS1* receptor tyrosine kinase can undergo an activating translocation in 1% or less of NSCLC cases. Given the homology of *ROS1* to *ALK*, the TKI crizotinib also happens to be a specific and effective inhibitor for this subset of lung cancer patients.¹⁰² Interestingly, crizotinib also inhibits the *MET* tyrosine kinase, and about 1% or less of NSCLC patients have a driver genotype characterized by high-level amplification of *MET*. Case reports have

described patients with this genotype who respond to crizotinib therapy.²⁴⁵

Even though more common in melanoma, *BRAF* mutations are also found in about 1% of NSCLC patients.^{232,246} Both *HER2* mutations and *HER2* amplification are seen in a small percentage (1% to 2%) of lung cancer patients and are associated with response to the *HER2* monoclonal antibody trastuzumab and the TKI afatinib.^{247,248} Other rare driver genotypes are emerging in rapid succession.

KRAS mutations are the most common genotype but have so far been refractory to therapeutic targeting. In colon cancer, the presence of *KRAS* mutation has been a robust negative predictor for *EGFR*-targeted therapies (mainly monoclonal antibodies),²⁴⁹ but in NSCLC it has been less clear that *KRAS* mutations should disqualify patients for *EGFR* therapy.^{250,251} Development of downstream signaling inhibitors looks like a potential promising strategy for *KRAS* mutants and a randomized phase 2 study of docetaxel chemotherapy with or without the *MEK* inhibitor selumetinib showed an interesting increase in response rate and in PFS.²⁵²

Harnessing the immune system to attack cancer has long been a dream of physicians, but progress has historically been slow. However, recently, new treatment options in the form of “checkpoint” modulators have emerged as highly promising therapeutic options. *Programmed death 1* (PD-1) protein, a T-cell coinhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumor cells to evade the host’s immune system. Blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models. In two pivotal phase I trials, antibodies against PD-1²⁵³ and PD-L1²⁵⁴ have led to remarkably high response rates with durable clinical benefit. CTLA-4 is another protein receptor that down-regulates the immune system. The anti-CTLA-4 antibody, ipilimumab, was approved for use in melanoma²⁵⁵ and is being tested in lung cancer. Combinations of anti-PD-1 and anti-CTLA-4 antibodies may be even more active, as has been shown in melanoma.²⁵⁶ Anti-PD-1 and -PD-L1 antibodies may be most effective in tumors expressing the proteins,^{254,257} but the biomarkers have not yet been established as definitive predictors of response.

MECHANISMS OF RESISTANCE

One of the most active areas of research currently in the field of targeted therapy for lung cancer is how to overcome acquired resistance. The genotypes with the most proven success in treatment with targeted agents (*EGFR* mutations and rearrangements in *ALK* and *ROS1*) have also demonstrated that resistance is acquired after 1 to 2 years for most patients. Resistance is often in the form of a point mutation at the gatekeeper location within the RTK,^{94,95,210,258,259} but may also be in the form of a bypass track, or detour using another cancer signaling pathway.^{96,97,258,260} Evolution of the cancer histology from adenocarcinoma to small cell lung cancer has been noted in some patients with *EGFR* mutations with acquired resistance to *EGFR* TKIs but the mechanism is not well understood.^{260,261} Several therapies for acquired resistance to therapy are being studied, primarily in NSCLC with *EGFR* mutations and *ALK* rearrangements.

Key Points

- Lung cancer in smokers is preceded by an accumulation of genetic, epigenetic, and posttranslational abnormalities in the entire bronchial epithelium, showing the validity of the field cancerization concept.
- Lung cancer in never-smokers is less well understood. Nonetheless, the risk for either type of cancer (among smokers or nonsmokers) appears to have a hereditary predisposition, as seen, for example, with genetic alterations in the nicotinic acetylcholine receptors.
- Sequencing of hundreds of candidate genes in adenocarcinomas has shown that there are between zero and 40 lesions in individual lung tumors, which often fall into a handful of previously defined pathways.
- The most common genes altered in lung cancer are *TP53* and *KRAS*, for which effective targeted therapies do not yet exist.
- For some genetic lesions, particularly driver mutations or translocations in *EGFR*, *ALK* and *ROS1*, targeted therapies exist and striking clinical effectiveness has been observed.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION PATTERNS

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INTRODUCTION

As the leading cause of cancer death in the world, lung cancer is currently a public health problem of enormous magnitude. In 2008 more than 1.6 million people were newly diagnosed with lung cancer, comprising 13% of all new cancer diagnoses; furthermore, 1.4 million, or 18% of all cancer deaths, were from lung cancer.¹ In contrast, at the start of the 20th century, lung cancer was considered a rare disease. However, its epidemic rise across the first decades of that century was soon identified as clinicians began to provide care for increasing numbers of patients with lung cancer and routine vital statistics documented rising mortality. Although tobacco had been widely used throughout the world for centuries, the pandemic of lung cancer followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure of the lung to inhaled carcinogens.² Epidemiologic research linked smoking to lung cancer in investigations that began in the 1930s and provided convincing and consistent evidence from the 1950s forward.³ Whereas its predominant cause—tobacco smoking—is now well known, there are other causes of lung cancer as well, some acting in concert with smoking to increase risk synergistically.

This chapter provides a summary of the epidemiologic evidence on lung cancer. It is based primarily on summaries of the evidence prepared by expert committees, and it includes findings of representative and particularly informative studies. Syntheses have been periodically carried out by expert review groups, dating back to reports such as the 1962 report of the Royal College of Physicians⁴ and the landmark 1964 Report of the U.S. Surgeon General.⁵ More recent reports include those prepared by the International Agency for Research on Cancer in 2004,⁶ the 2004 and 2006 reports of the Surgeon General on active and passive smoking, respectively,^{7,8} and the 2010 report of the Surgeon General on the mechanistic basis of smoking-caused pathogenesis.⁹ The 2014 U.S. Surgeon General's Report commemorated the 50th anniversary of the landmark 1964 report and once again updated the evidence on the adverse health effects of cigarette smoking.^{9a} The U.S. Surgeon

General's Reports have provided evidence syntheses and inferences that have guided the conclusions that active and passive cigarette smoking are causally associated with the risk of lung cancer.^{9b} In turn, the evidence on these topics have been historically important in the development of epidemiology.^{9b}

PATTERNS

TEMPORAL TRENDS

Because of the high case-fatality rate of lung cancer, incidence and mortality rates are nearly equivalent; consequently, routinely collected vital statistics provide a long record of lung cancer. We are amidst an epidemic of lung cancer that dates to the mid-20th century (Fig. 52-1).^{10,11} The epidemic among women followed that among men, with a sharp rise in rates from the 1960s to the present, making lung cancer the most frequent cause of female cancer mortality in the United States.¹² The epidemic among women not only arose later but also will not peak as high as among men because smoking prevalence crested at substantially lower levels among women than among men.¹³⁻¹⁵

Trends of age-specific lung cancer mortality rates in the United States show differing epidemic patterns in men than in women (Fig. 52-2).^{14,16-19} In the older age groups, the rates continue to increase in both sexes, but the rates of increase are decelerating more in men than in women. The rates of lung cancer are now decreasing in the younger age groups, more for men but also becoming evident in women.¹⁴

Notable shifts have taken place in the incidence rates of lung cancer by histologic type.²⁰ After steadily increasing in incidence between 1973 and 1987, adenocarcinoma supplanted squamous cell carcinoma as the most frequent form of lung cancer (Table 52-1).^{20,21}

RACE AND ETHNICITY

In the United States, whereas lung cancer incidence rates and mortality rates are similar among African American women and white women, incidence rates are 26% higher

and mortality rates are 23% higher in African American men than in white men.²² A marked reduction in cigarette smoking among African American youths²³ forecasts a possible reversal of this trend. In addition, lung cancer mortality rates among African Americans and non-Hispanic whites are significantly higher than rates among Hispanics, Native Americans, and Asian/Pacific Islanders.^{24,25} However, racial differences in historical patterns of cigarette smoking do not fully account for the racial disparities in lung cancer incidence and mortality rates.²⁶ The high rates in African Americans may be partially due to greater

susceptibility of African American smokers to smoking-induced lung carcinogenesis.²⁷ The higher mortality rates of lung cancer in African Americans than in white Americans reflect not only their higher incidence rate but also poorer survival. In 2009, the 5-year relative survival rate was 19% lower in African Americans than in white Americans.

GEOGRAPHIC PATTERNS

Lung cancer is the most commonly diagnosed cancer worldwide,^{27,28} but its geographic distribution shows marked regional variation²⁹: age-standardized incidence rates vary over a wide range, more than fourfold among men and fivefold among women (Fig. 52-3).³⁰ This marked variation in rates cannot be explained on the basis of diagnostic practices and data quality alone. Lung cancer tends to be most common in developed countries, particularly in North America and Europe, and less common in developing countries, particularly in Africa and South America.³¹ However, the lung cancer epidemic is on the rise in the developing world.³²

The epidemic of tobacco addiction in China illustrates the ongoing trend of a shift in the global lung cancer burden from high-income Western countries to low- and middle-income countries, particularly in Asia. In 2008, newly diagnosed lung cancers in developing countries exceeded the number in developed countries by 22% (884,500 and 724,300, respectively).³³ The situation in China is particularly serious. Due to a striking increase in active smoking, Chinese males are a population of particular concern. Per capita cigarette consumption in Chinese men increased from one cigarette per day in 1952, to four in 1972, and

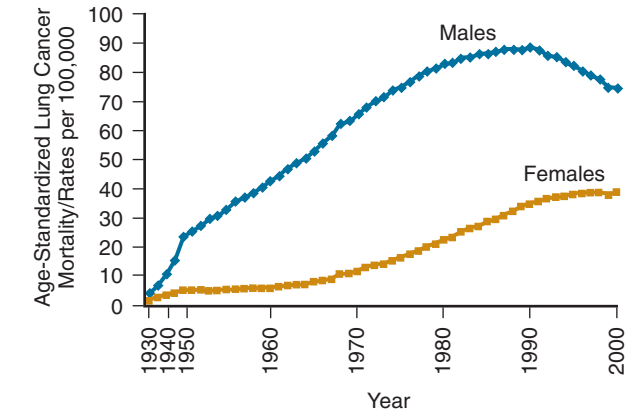


Figure 52-1 Age-standardized lung cancer mortality rates, United States: 1930–2000, age-standardized to 2000 U.S. population. (Data from Wingo PA, Cardinez CJ, Landis SH, et al: Long-term trends in cancer mortality in the United States, 1930–1998. *Cancer* 97:3133–3275, 2003; and National Cancer Institute and National Center for Health Statistics: Surveillance, Epidemiology, and End Results [SEER] Program. SEER Stat Database: Mortality 2003. <http://seer.cancer.gov/>.)

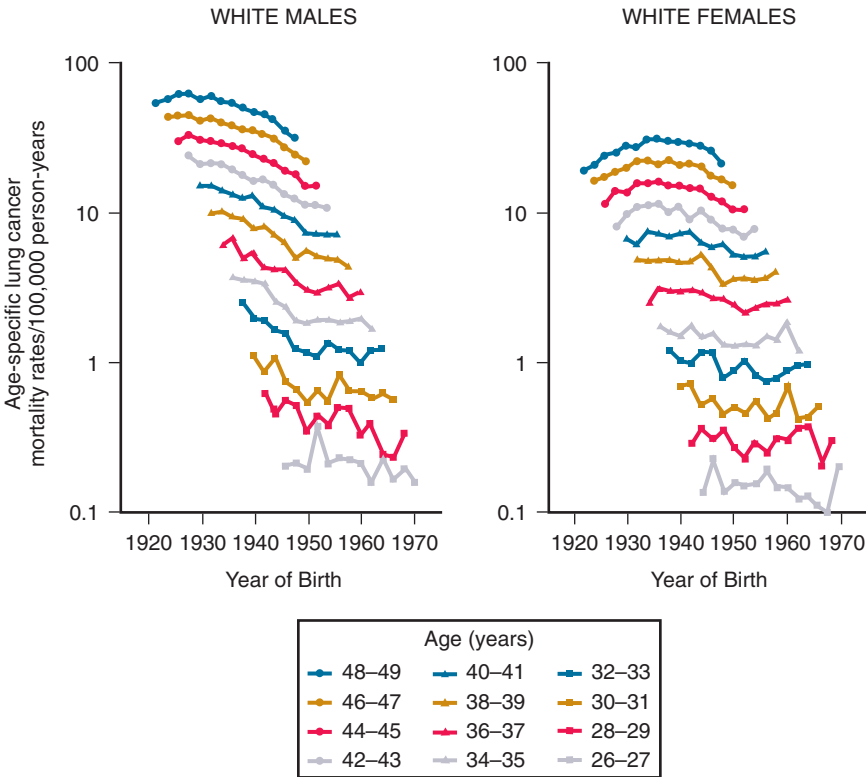


Figure 52-2 U.S. age-specific lung cancer mortality rates (white males and white females) by 2-year age intervals from 26 to 27 years of age through 48 to 49 years of age, plotted against birth cohort. (Data from Jemal A, Chu KC, Tarone RE: Recent trends in lung cancer mortality in the United States. *J Natl Cancer Inst* 93:277–283, 2001; McKay FW, Hanson MR, Miller RW: Cancer mortality in the United States: 1950–1977. *Natl Cancer Inst Monogr* 59:1–475, 1982; Ries LAG, Miller BA, Hankey BF, et al: *Cancer statistics review*. Bethesda, MD: U.S. Government Printing Office, 1995, pp 1973–1991; Horm JW, Cicero JB: SEER Program: *Cancer incidence and mortality in the United States*. Washington, DC: U.S. Government Printing Office, 1984, pp 1973–1981; and National Cancer Institute: National Cancer Institute SEER website. Surveillance, Epidemiology, and End Results [SEER] Program. 2001. <http://seer.cancer.gov/>.)

Table 52-1 Age-Adjusted Incidence Rate (per 100,000) of Lung Cancer by Histologic Subtype and Time Period, SEER 1973–1977, 1978–1982, 1983–1987, and 1990–2000

Group	Subtype	1973–1977*	1978–1982*	1983–1987*	1990–2000†
Total		39.5	46.8	51.4	66.9
	Squamous cell carcinoma	13.4	15.1	15.3	14.4
	Adenocarcinoma	10.5	14.2	16.7	22.1
	Small cell	5.9	8.2	9.4	9.8
	Large cell	0.0	3.9	4.9	NA
White males		24.3	26.8	25.5	22.3
	Squamous cell carcinoma	14.5	19.0	21.3	26.3
	Adenocarcinoma	9.5	12.5	13.1	12.2
	Small cell	0.0	5.9	7.2	NA
	Large cell				
White females		4.0	5.5	6.6	8.2
	Squamous cell carcinoma	6.9	10.2	12.9	19.1
	Adenocarcinoma	3.4	5.5	7.1	8.9
	Small cell	0.0	2.2	3.1	NA
	Large cell				
African American males		43.9	46.3	48.5	39.7
	Squamous cell carcinoma	18.1	27.4	32.5	36.2
	Adenocarcinoma	9.5	13.3	14.0	12.7
	Small cell	0.0	8.0	10.8	NA
	Large cell				
African American females		5.6	6.8	9.5	11.4
	Squamous cell carcinoma	6.8	10.8	13.3	18.9
	Adenocarcinoma	3.6	3.9	6.0	7.2
	Small cell	0.0	2.0	3.0	NA
	Large cell				

*Data from reference 20.

†Calculated from reference 21.

NA, not available; SEER, Surveillance, Epidemiology, and End Results.

to 10 in 1992.³⁴ As a consequence, the lung cancer mortality rates have already increased 27% from 1990 to 2010³⁵ and will continue to rise substantially in the absence of aggressive tobacco control measures. The increase in lung cancer among Chinese males will have a major impact on the global burden of lung cancer in the 21st century, given the size of this population of smokers, which is more than 300 million. A unique feature of the epidemiology of lung cancer in China is the high lung cancer mortality rates among Chinese women despite the low prevalence of cigarette smoking. The inordinately high rates in women seem to be attributable to exposure to risk factors such as second-hand smoke exposure and indoor air pollution from cooking fumes.¹

Substantial geographic variation in lung cancer mortality rates has also been observed within countries, providing clues about the determinants of lung cancer. In the past, rates tended to be highest in urban areas, which led to conjecture that air pollution might be a cause of the lung cancer epidemic.³⁶ High rates in coastal areas in the United States from 1950 to 1969 were linked to asbestos exposure in shipyards.³⁷ Now lung cancer mortality rates among white males are highest in the South and lower in the Northeast, likely reflecting patterns of cigarette smoking.³⁸

LUNG CANCER BY HISTOLOGIC TYPE

Lung cancer manifests itself in multiple histologic types as classified by conventional light microscopy. The four major types, as traditionally identified by histologic appearance, include squamous cell carcinoma, adenocarcinoma, large

cell carcinoma, and small cell undifferentiated carcinoma; together these four types of lung cancer account for more than 90% of lung cancer cases in the United States.³⁹ These primary bronchogenic carcinomas are composed of a family of epithelial tumors that represent a subset of a larger collection of lung and pleural tumors classified by the *World Health Organization* (WHO) in 2004.⁴⁰ However, recent advances in molecular biology, surgery, and clinical medicine have rendered these traditional histologic classifications inadequate for optimal patient care. The need for more refined classifications was necessitated by several developments: (1) adenocarcinoma with *epidermal growth factor receptor* (EGFR) mutations was found to be sensitive to tyrosine kinase inhibitors, (2) eligibility for certain novel medications was limited to those with adenocarcinoma, and (3) *computed tomography* (CT) screening studies were detecting ground-glass infiltrative lesions that posed diagnostic challenges for both radiologists and pathologists. Consequently, the classification of adenocarcinoma was refined as part of a multidisciplinary, international effort to incorporate molecular and clinical parameters, define terms uniformly, and optimize relevance to patient care.⁴¹ The evidence-based recommendations created new adenocarcinoma subtypes according to prognostic criteria and molecular patterns, and discontinued the term “bronchioloalveolar carcinoma.” Reports have subsequently corroborated the new classification and documented its improved relevance to patient care.^{42–44} This topic is covered in detail in Chapters 14 and 53, but is included here because future research into the etiology of lung cancer would be strengthened by integrating these new lung cancer classification criteria.

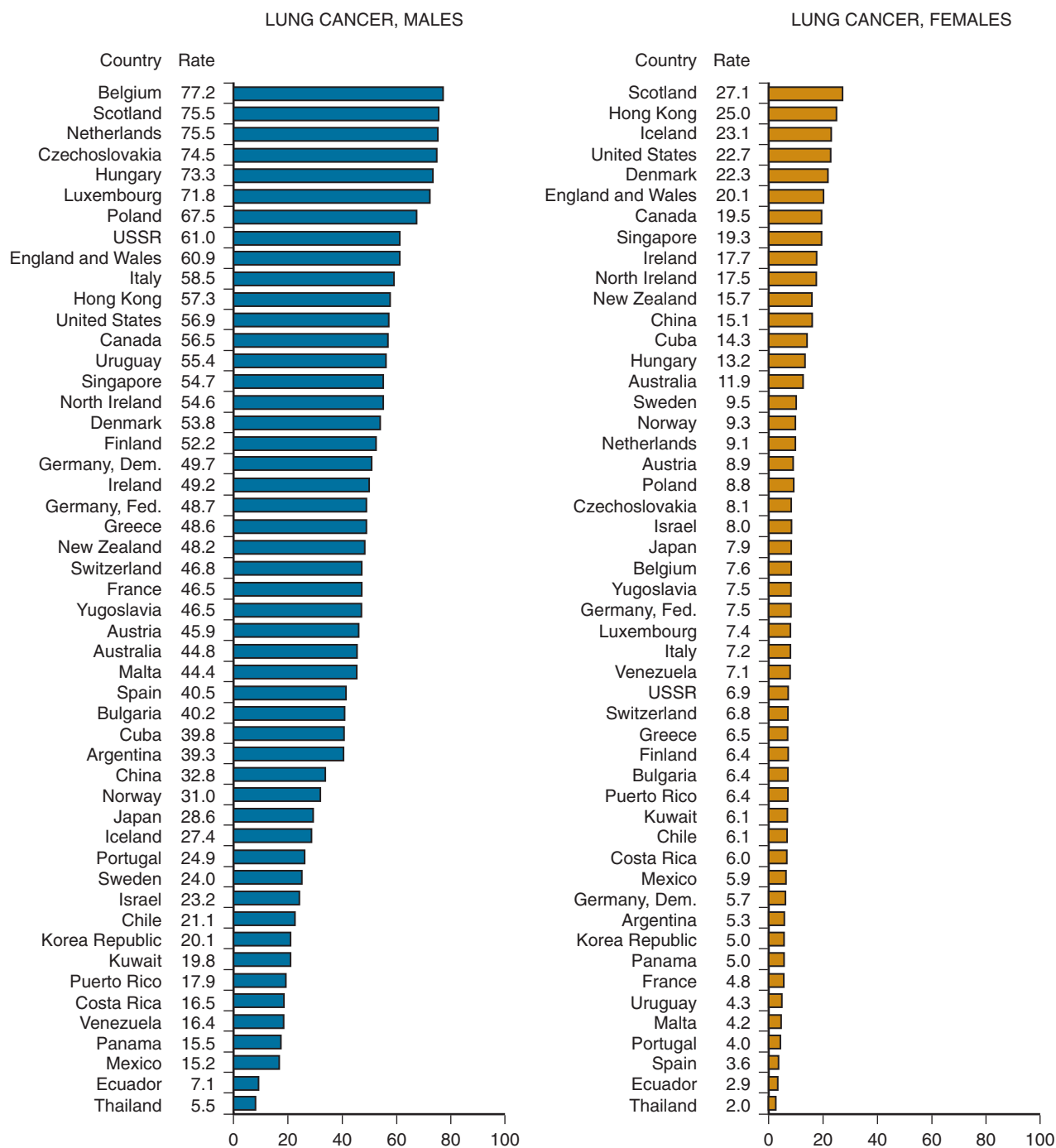


Figure 52-3 Age-adjusted death rates per 100,000 population, male and female, 1986 to 1988. (Data from National Cancer Institute [NCI], Cancer Statistics Branch, and Division of Cancer Prevention and Control: *Cancer rates and risks*. Bethesda, MD: National Institutes of Health, 1996.)

Few links have been made between particular etiologic agents and the development of a particular histologic type of lung cancer. Cigarette smoking increases risk for all major histologic types.⁴⁵⁻⁴⁷ The dose-response relationship of increased lung cancer risk according to number of cigarettes smoked varies across the types, being steepest for small cell undifferentiated carcinoma.⁴⁵⁻⁴⁷ A few occupational exposures, such as chloromethyl ethers and radon, have been linked to small cell lung cancer.^{39,48}

In the United States, during the initial decades of the smoking-caused epidemic of lung cancer, the most frequent

type of lung cancer was squamous cell carcinoma, followed by small cell carcinoma. In the 1970s, a shift toward a predominance of adenocarcinoma was noted,^{39,49,50} and with the persistence of this trend, adenocarcinoma is now the most common histologic type.^{13,20} In U.S. men, the shift to adenocarcinoma developed in part because, whereas lung cancer incidence and mortality rates began to decline during the 1990s, the decline in lung cancer rates was more rapid for squamous cell and small cell carcinomas than for adenocarcinoma, which is just beginning to show a lower incidence rate (Fig. 52-4).¹³ In U.S. women, the

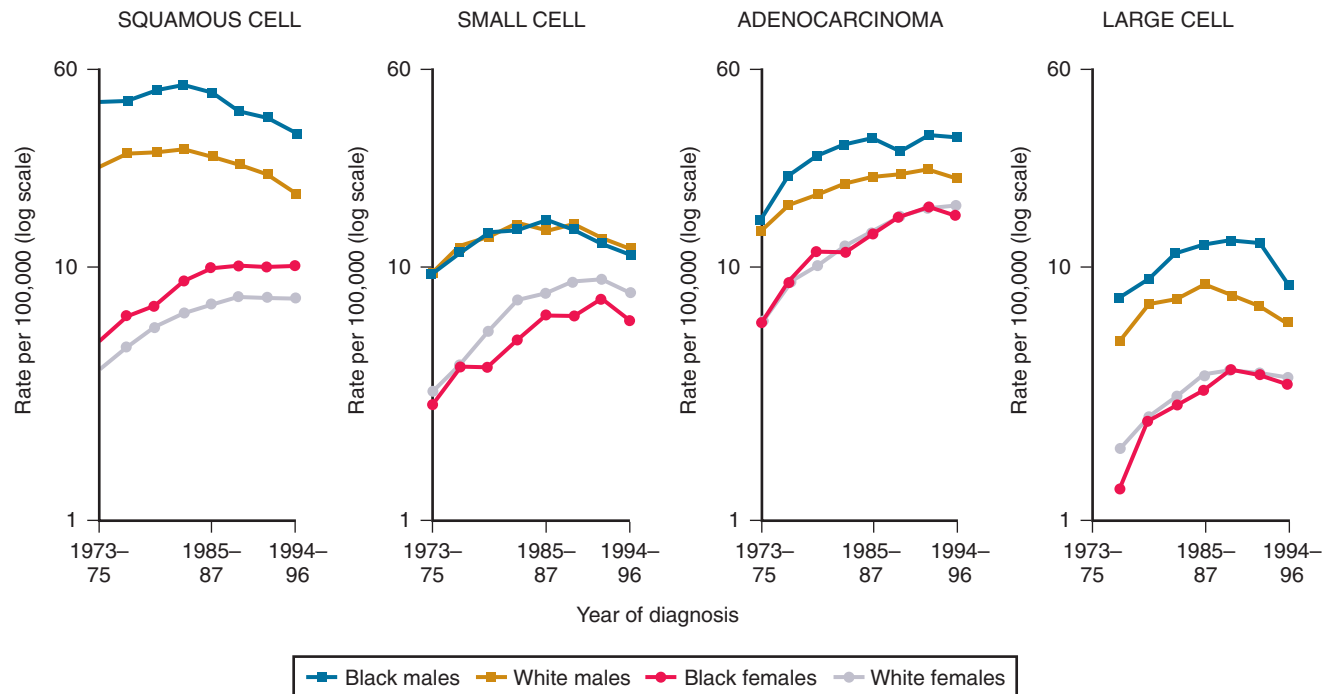


Figure 52-4 Cancer of the lung and bronchus: Surveillance, Epidemiology and End Results (SEER) incidence rates, by histologic type, sex, race, and ethnicity, all ages, 1973 to 1996. (Data from Wingo PA, Ries LA, Giovino GA, et al: Annual report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. *J Natl Cancer Inst* 91:675–690, 1999.)

increase in lung cancer incidence rates was more pronounced for adenocarcinoma than for any other cell type, perhaps because lung cancer rates increased most rapidly among U.S. women during the time period of changing histology.

Similar trends have been noted throughout the globe. Worldwide, adenocarcinoma tends to be the most common cell type seen in female lung cancer patients, accounting for approximately one-third of all lung cancer diagnoses in most regions.⁵¹ In males, squamous cell carcinoma is still the most common cell type in some geographic regions where the lung cancer epidemic has peaked, but trends indicate that the overall percentage of this cell type has fallen over time to 40% or less.

Hypotheses concerning the shift from squamous cell carcinoma to adenocarcinoma have focused on the potential role of changes in the characteristics of cigarettes and consequent changes in the doses and types of carcinogens inhaled.^{7,52,53} The resulting evidence from studies that have tested these hypotheses indicates that the trend of increasing rates of adenocarcinoma is primarily due to changes in cigarette smoking behavior and features of cigarettes (see later).^{54,55}

THE ETIOLOGY OF LUNG CANCER: OVERVIEW

Although the causes of lung cancer are almost exclusively environmental, there is likely substantial individual variation in susceptibility to respiratory carcinogens. For example, lung cancer develops in only a minority of smokers. The disease can be conceptualized as the consequence of the interrelationship between (1) exposure to

etiologic (or protective) agents and (2) individual susceptibility to these agents. Given lung cancer's multifactorial etiology, synergistic interactions among risk factors have substantial consequences for lung cancer risk. These interactions have typically been considered on an agent-by-agent basis, for example, as in studies of the synergistic effect of cigarette smoking on the lung cancer risk from asbestos exposure.⁶ Our emerging understanding of cancer genetics indicates the additional relevance of gene-environment interactions.

Given the many risk factors that have been identified for lung cancer, a practical question is: What is the relative contribution of these factors to the overall burden of lung cancer? In the United States, active smoking is estimated to be responsible for about 85% of lung cancer⁷; occupational exposures to carcinogens account for approximately 5% to 10%; radon causes 15% of lung cancer,⁴⁸ and outdoor air pollution perhaps 1% to 2%.⁵⁶ These known causes may not fully account for the development of lung cancer in never smokers, an important group for whom further epidemiologic research is needed.⁵⁷ Because these attributable risk estimates include joint contributions of risk factors, for example, smoking and occupation, the total percentage can exceed 100%.

ENVIRONMENTAL AND OCCUPATIONAL AGENTS

SMOKING (Chapter 46)

Overview

Cigarette smoking is by far the leading cause of lung cancer, accounting for approximately 80% to 90% of lung cancer

Table 52-2 Age-Specific Lung Cancer Mortality Rates (per 100,000) Among Men and Women 60 to 69 Years of Age by Smoking Levels in the American Cancer Society's Cancer Prevention Study II

Group	Never Smokers	SMOKED 20 CIGARETTES PER DAY FOR		SMOKED 40 CIGARETTES PER DAY FOR	
		30 Years	40 Years	30 Years	40 Years
Men	11.9	224.3	486.8	572.8	606.6
Women	9.8	200.8	264.4	257.7	552.8

From Thun MJ, Day-Lally CA, Myers DG, et al: Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959–1965) and II (1982–1988). In Burns DM, Garfinkel L, Samet JM, editors: *Changes in cigarette-related disease risks and their implication for prevention and control*. Bethesda, MD: U.S. Government Printing Office, 1997, pp 305–382.

cases in the United States⁷ and in other countries where cigarette smoking is common.⁴⁸ Compared with never smokers, current smokers have about a 25-fold increase in lung cancer risk, far higher than the risks for diseases associated with other environmental agents.⁵⁸ Cigar and pipe smoking are also established causes of lung cancer.⁵⁹ In general, lung cancer trends closely reflect patterns of smoking, but rates of lung cancer lag smoking rates by about 20 years. According to the Centers for Disease Control and Prevention, in the United States, 156,900 men and women die of smoking-related lung cancer each year.⁶⁰ Worldwide, 5.4 million people die of smoking-related lung cancer each year.⁶¹

Quantitative Risks

The risk of lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day (Table 52-2).⁶² In one widely cited analysis, Doll and Peto⁶³ proposed a quantitative model for lung cancer risk based on data from the cohort study of British physicians. This model predicted a stronger effect from the duration of smoking than from the amount smoked per day. Thus a tripling of the number of cigarettes smoked per day was estimated to triple the risk whereas a tripling of duration of smoking was estimated to increase the risk 100-fold.⁶⁴ These quantitative dimensions of the dose-response relationship between smoking and lung cancer have implications concerning the now widespread smoking among youths. Those starting at younger ages have a greater likelihood of becoming heavier smokers and remaining smokers.⁶⁵ The exponential effect of duration of smoking on lung cancer risk markedly increases the lifetime risk for those who become regular smokers in childhood.

Smoking Cessation

Cigarette smokers of any age can benefit from quitting smoking.^{58,66,67} Among those who quit smoking, the likelihood of developing lung cancer decreases when compared with those who continue to smoke^{7,58,67-69} (Table 52-3). As the period of abstinence from smoking cigarettes increases, the risk of lung cancer decreases.^{68,69} However, even for periods of abstinence of more than 40 years, the risk of lung cancer for former smokers remains elevated compared

Table 52-3 Risk of Lung Cancer Among Ex-Smokers Relative to Never Smokers According to Length of Time Since Smoking Cessation and Number of Cigarettes Formerly Smoked Among a Cohort of U.S. Veterans

Years Since Smoked	CIGARETTES SMOKED PER DAY				Total
	1–9	10–20	21–39	40	
<5	7.6*	12.5	20.6	26.9	16.1
5–9	3.6	5.1	11.5	13.6	7.8
10–19	2.2	4.3	6.8	7.8	5.1
20–29	1.7	3.3	3.4	5.9	3.3
30–39	0.5	2.1	2.8	4.5	2.0
≥40	1.1	1.6	1.8	2.3	1.5

*Relative risk compared with referent category of never smokers (=1). Adapted from Hrubec Z, McLaughlin JK: Former cigarette smoking and mortality among U.S. veterans: A 26-year follow-up, 1954–1980. In Burns DM, Garfinkel L, Samet JM, editors: *Changes in cigarette-related disease risks and their implication for prevention and control*. Bethesda, MD, 1997, U.S. Government Printing Office, pp 501–530.

with that for never smokers (see Table 52-3). The benefits derived from smoking cessation also depend on the prior duration of smoking: for a given period of abstinence, the risk decreases with a decrease in the duration of previous smoking.⁶⁹

The Changing Cigarette and Expanding Marketplace

The composition and design of cigarettes has changed considerably since the 1950s. The marketplace has shifted from mainly unfiltered cigarettes to predominantly filtered cigarettes and to products that are labeled “light” or “mild.” In the mid-1960s, ventilation holes were added to the filter, which draw in air and dilute the inhaled smoke. However, whereas these holes effectively decrease the tar measured by the testing machines, smokers can readily block the holes with their fingers, thereby increasing their tar inhalation and exposure to carcinogens. Reconstituted tobacco, essentially reprocessed tobacco leaf wastes, has been used increasingly since the 1960s, and there have been changes to the cigarette paper and additives.⁷⁰ These changes in design and content may also have affected carcinogenicity.

Despite product marketing that would make these changes appear to be less harmful, the evidence indicates that, if anything, the changes in cigarettes have yielded greater—not lower—risks for lung cancer. A comparison of three U.S. cohorts, each comprised of more than 500,000 participants followed from 1959 to 1965, 1982 to 1988, and 2000 to 2010, provide very strong evidence to assess temporal trends in the association between cigarette smoking and lung cancer.⁵⁸ The relative risks of current smoking in relation to lung cancer mortality increased across these three time periods, a trend that was most pronounced in women among whom the relative risk increased across these three time periods from 2.7 to 12.7 to 25.7. In men, the relative risk increased and then plateaued, from 12.2 to 23.8 to 25. With respect to lung cancer risk, these data provide strong evidence that cigarettes have become more harmful rather than less harmful over time. These

findings are consistent with the conclusions of several expert panels that reviewed prior evidence.^{6,7,71,72}

During the past decade, the marketplace for tobacco products and devices that deliver nicotine has greatly expanded even as smoking bans have increasingly limited the locations where cigarette smoking is allowed.⁷³⁻⁷⁶ This diversification exists for both tobacco products and nontobacco products that deliver nicotine. In addition to the traditional smokeless tobacco products of loose leaf chewing tobacco and moist snuff, newer or more broadly marketed products include snus (a tobacco powder product packaged in a bag that is moister than snuff and does not require spitting) and dissolvable tobacco.⁷³ Furthermore, an increase in the prevalence of smoking roll-your-own cigarettes has been observed in the United States and elsewhere.^{77,78} The prevalence of smoking tobacco through a waterpipe, also referred to as “hookah,” has increased worldwide.^{76,79} Electronic cigarettes (or “e-cigarettes”) are non-tobacco-containing nicotine delivery devices that have experienced a rapid upsurge in use and are now marketed by the major U.S. tobacco companies.^{73,74,80,81}

Drawing upon past experience with the changing cigarette, it is clear that monitoring this expansion in products and how the products are used is not only critical to tobacco control but also directly relevant to the prevention of lung cancer. A product such as the e-cigarette that ostensibly decreases delivery of carcinogens to the lung would reduce the risk for development of lung cancer if current cigarette smokers switched from smoking cigarettes to exclusive use of the e-cigarette. In contrast, the risk for lung cancer could be increased if the e-cigarette maintained nicotine addiction and its users continued to smoke cigarettes as well in the increasingly common pattern of use of multiple products that deliver nicotine. Furthermore, these alternative products may serve as a gateway for youths to initiate smoking and thus start on a path that eventually leads to tobacco addiction. Questions such as these, along with the direct adverse health effects associated with use of these alternative products, are important lines of inquiry for future research.

Passive Smoking

Passive smokers inhale a complex mixture of smoke now widely referred to as “environmental tobacco smoke” or “secondhand smoke.” Passive smoking was first considered as a possible risk factor for lung cancer in 1981 when two studies were published that described increased lung cancer risk among never-smoking women who were married to smokers.^{82,83} Additional evidence rapidly accrued so that by 1986, two reports, from the National Research Council⁸⁴ and the 1986 Surgeon General’s Report,⁸⁵ both concluded that passive smoking causally increased risk for lung cancer. Estimates indicate that passive smoking accounts for about 3400 lung cancer deaths per year in the United States.⁸⁶

Since these conclusions were reached, numerous studies have been carried out to characterize further the association of passive smoking with lung cancer, while taking into account some of the limitations of earlier studies, particularly small sample sizes, exposure misclassification, and omission of some potential confounding factors.^{87,88} Various panels since 1986 have also concluded that passive smoking

increases lung cancer risk, including the International Agency for Research on Cancer,⁶ the California Environmental Protection Agency,⁸⁶ and once again, the U.S. Surgeon General.⁸

Passive smoking is more weakly associated with lung cancer than is active smoking, as expected given the lower doses of carcinogens received by the nonsmoker compared with the smoker. Marriage to a smoker is associated with about a 20% increase in risk⁸⁹ and exposure in the workplace is associated with between a 24% increase in risk up to a twofold increase at the highest levels of exposure.⁹⁰ In general, the risk of lung cancer increases as the exposure to secondhand smoke increases.⁹⁰

DIET

The possible role of diet in modifying the risk for lung cancer has been the focus of intensive investigation, driven initially by the rationale that specific micronutrients might have anticarcinogenic activity. The most thoroughly investigated dietary factors are also those that at present appear to have the greatest implications for prevention: fruits, vegetables, and specific antioxidant micronutrients that are commonly found in fruits and vegetables.

The results of case-control and prospective cohort studies have tended to show that individuals with high dietary intake of fruits or vegetables have a lower risk for lung cancer than those with a low intake.⁹¹ To understand the basis of this protective association, researchers have grouped fruits and vegetables into classes and examined them individually in relation to lung cancer risk. For example, tomatoes⁹¹ and cruciferous vegetables^{91,92} have been associated with a reduced risk for lung cancer in a number of studies. These food-based analyses can help clarify whether protection arises from the complex mixture that composes fruits and vegetables or from specific biochemical constituents present in particular fruits and vegetables.

Fruits and vegetables are the major dietary source of antioxidant micronutrients. Much of the research on diet and lung cancer has been motivated by the hypothesis that diets high in antioxidant micronutrients may protect against oxidative DNA damage and thereby protect against cancer. For example, this was one of the hypothesized roles for β -carotene,⁹³ the focus of now controversial clinical trials. Two different strategies are used to evaluate the relationship of micronutrients to lung cancer risk in observational epidemiologic studies: (1) estimating micronutrient intake from food-frequency questionnaires and (2) measuring serum concentrations of micronutrients. Prospective studies of both dietary intake⁹⁴ and prediagnostic blood concentrations⁹⁴ suggest that carotenoids are inversely associated with lung cancer risk.

The protective association predicted between β -carotene and lung cancer on the basis of these observational epidemiologic studies was not confirmed in three randomized, double-blind, placebo-controlled chemoprevention trials.⁹⁵⁻⁹⁷ In fact, two of these studies with participants at high risk for lung cancer (heavy smokers and asbestos-exposed workers) were stopped early because significantly increased risk for lung cancer was observed in the β -carotene group compared with the placebo group.^{96,97}

The results of the randomized chemoprevention trials stand in sharp contrast to the considerable observational epidemiologic evidence favoring a protective association. Among the potential explanations for the contradictory findings are that the randomized trials used relatively high doses of β -carotene and that the observational epidemiologic studies may have been flawed by uncontrolled confounding or selection bias.⁹⁴ Because of the powerful role of smoking as a cause of lung cancer, disentangling the effects of other lifestyle-related factors, such as diet, from the effect of smoking may be particularly difficult. Further complicating the assessment of protection by dietary factors is the narrow range of likely effects, much smaller than the effect of smoking, and the unavoidable problem of measurement error, that is, the inevitable inaccuracy in estimating usual dietary consumption of particular foods or groups of foods.

Studies of fruits, vegetables, and micronutrients have been the centerpiece of studies of diet and lung cancer, but other factors have also been investigated. For example, the results of a meta-analysis showed alcohol drinking in the highest consumption categories was associated with increased risk for lung cancer.⁹⁸ In addition, anthropometric measures have been studied, indicating a tendency for persons with lower body mass index to have increased lung cancer risk relative to heavier persons.⁹¹ However, both alcohol drinking and low body mass index may be difficult to separate from the concomitant effects of smoking. At present, when considering the possible relationships between lung cancer and factors such as alcohol drinking and lower body mass index, residual confounding by cigarette smoking cannot be dismissed as a possible explanation.

ENVIRONMENTAL EXPOSURES

Occupational Exposures

Lung cancer has been found to be associated causally with many workplace exposures, including arsenic, beryllium, cadmium, chromium, and nickel in addition to those described later.^{99,100} Occupational exposure to lung carcinogens have been estimated by case-control studies to account for 9% to 15% of lung cancer cases.¹⁰¹ As lung carcinogens have been identified in the workplace and regulations established to prevent workers from being exposed, this proportion has been decreasing over time. Cigarette smoking also potentiates the effect of some of the known occupational lung carcinogens.⁶

Asbestos

Asbestos, a well-established occupational carcinogen,^{99,100} refers to several forms of fibrous, natural silicate minerals.¹⁰² The epidemiologic evidence that asbestos causes lung cancer dates to the 1950s. In a retrospective cohort study published in 1955, Doll observed that asbestos textile workers at a factory in the United Kingdom had a ten-fold elevation in lung cancer risk and that the risk was most heavily concentrated during the timeframe before regulations were implemented to limit asbestos dust in factories.¹⁰³ A sevenfold excess of lung cancer was subsequently observed among insulation workers in the United States,^{104,105} with peak incidence at 30 to 35 years after the initial exposure to asbestos.¹⁰⁶ The risk of lung cancer has been noted to increase with increased exposure to asbes-

tos¹⁰⁷ and to be associated with each of the principal commercial forms of asbestos.¹⁰⁸ Whether asbestos acts directly as a carcinogen or indirectly, for example, by causing chronic inflammation that eventually leads to cancer, remains controversial.¹⁰⁹⁻¹¹¹ For the mechanism of asbestos-induced lung cancer, two competing hypotheses have been posed: (1) lung cancer arises as a consequence of the asbestos-induced lung disease asbestosis and (2) lung cancer arises directly from asbestos exposure while the asbestosis merely serves as a marker of asbestos dose. Regardless of mechanism, asbestos is a known lung carcinogen and the number of exposed workers is increasing in South America, Asia, and the former Soviet Union.¹⁰⁰

Asbestos and cigarette smoking are both independent causes of lung cancer but, in combination, they act synergistically to increase risk. Uncertainty remains as to the precise quantitative characterization of this synergy, reflecting limitations of the available data⁶ and lack of understanding of the underlying mechanisms.¹¹² Nonetheless, the risk of the combined exposure is much higher than would be expected if one merely added the risks together, showing a strong interaction between the two. In fact, the risks are approximately multiplicative. A person who smokes and has been exposed to asbestos has a greater than 50-fold elevated risk for lung cancer than does a nonsmoker with no asbestos exposure, and a much higher risk than a person exposed to cigarette smoke alone (relative risk, 10.9) or to asbestos alone (relative risk, 5.2) (Table 52-4).¹¹³

Radiation

Epidemiologic studies of populations exposed to high doses of radiation show that lung cancer is causally associated with exposure to ionizing radiation. Two types of radiation, classified by the rate of energy transfer to the tissue, are relevant to lung cancer: high *linear energy transfer* (LET) radiation (e.g., neutrons and radon) and low-LET radiation (e.g., x-rays and γ -rays). High-LET radiation produces ionization of relatively higher density in tissues than low-LET radiation, so in equivalent doses, more biologic damage is produced by high-LET than low-LET radiation.¹¹⁴ For both types of radiation, the epidemiologic evidence initially came

Table 52-4 Relationship Between Cigarette Smoking and Asbestos Exposure on Lung Cancer Mortality Risk

SMOKING	MORTALITY RATES		DIFFERENCE IN RATES		RATIO OF RATES	
	ASBESTOS		ASBESTOS		ASBESTOS	
	No	Yes	No	Yes	No	Yes
No	11.3*	58.4	0	47.1	1.0	5.2
Yes	122.6	601.6	111.3	590.3†	10.9	53.2‡

*Mortality rate per 100,000.
†Difference in rates compared to no smoking/no asbestos exposure; if there were no interaction of asbestos and smoking, the expected rate of lung cancer in those exposed to both would be the sum of each alone (47.1 + 111.3 = 158.4). The actual value of 590.3 greatly exceeds 158.4, providing evidence of a strong interaction between smoking and asbestos.
‡Ratio of rates compared to no smoking/no asbestos exposure; the expected value if risks were multiplicative would be the multiple of the rates, 5.2 \times 10.9 = 56.7, close to the actual value of 53.2.
Adapted from Hammond EC, Selikoff IJ, Seidman H: Asbestos exposure, cigarette smoking and death rates. *Ann N Y Acad Sci* 330:473-490, 1979.

primarily from cohorts exposed at levels substantially greater than those experienced by the general population and risk assessment methods were used to estimate risks to the general population. More recently, studies have generated evidence concerning exposure levels experienced directly by the general population.

High-LET Radiation: Radon. Radon is an inert gas produced naturally from radium in the decay series of uranium. Two of the radon decay products emit alpha particles that can, consequent to high energy and mass, cause damage to the DNA of cells of the respiratory epithelium. Epidemiologic studies of underground miners of uranium and other ores have established exposure to radon daughters as a cause of lung cancer.^{48,115} In the underground miners exposed to radon in past centuries, very high lung cancer risks were observed; in the miners in more contemporary workplaces, the observed risks have been much less as exposure concentrations have been better controlled, but still show clear evidence of existing cancer risk.⁴⁸ Cigarette smoking and radon decay products synergistically influence lung cancer risk, for example, in a manner that is greater than simply adding the risks of each together.⁴⁸ For this reason, the bulk of the lung cancer burden caused by radon exposure in the general population is concentrated within cigarette smokers.¹¹⁶

Radon is of broader societal interest because it is a ubiquitous air pollutant that enters buildings from the underlying soil. On average, indoor exposures to radon for the general population are much less than for occupational groups such as uranium miners; but the results of case-control studies of indoor radon exposure have documented that residential exposure to radon in indoor air is significantly associated with increased lung cancer risk.^{117,118}

The assumptions made by the Environmental Protection Agency and the Biological Effects of Ionizing Radiation VI Committee of the National Research Council have led to estimates that approximately 15,000 to 20,000 lung cancer deaths per year in the United States are caused by radon.¹¹⁹ In the United States, the Environmental Protection Agency has called for testing of all residences and mitigation when guideline values are exceeded.

Low-LET Radiation: X-Rays and γ -Rays. Earlier epidemiologic data relating low-LET radiation to lung cancer stem from three principal populations¹²⁰: the atomic bomb survivors in Japan, patients with diseases such as ankylosing spondylitis or tuberculosis who received multiple radiation treatments, and occupational groups in professions exposed to radiation. The single, high-dose exposure of the atomic bomb survivors was associated with significant lung cancer risk.¹²¹ Regardless of age at the time of the blast, the excess of lung cancer appeared when the survivors reached the older ages at which cancer usually develops.¹²² Quantitative risk models are available that describe how risk increases with radiation dose.¹²⁰

Over the past several decades, medical radiation has replaced radon as the leading contributor to the population's radiation exposure. In general, a substantial proportion of the U.S. population is now exposed to ionizing radiation from medical diagnostics, particularly from CT scans. The exposure is of sufficient magnitude to be of

concern as a cause of increased population risk for cancer.¹²³⁻¹²⁵ The findings from the National Lung Screening Trial showed that *low-dose spiral CT* (LDCT) screening significantly reduced lung cancer mortality among those at high risk for lung cancer defined by age (55 to 74 years) and smoking history (≥ 30 pack-year smoking history).¹²⁶ Based on the findings of the National Lung Screening Trial, the U.S. Preventive Services Task Force recommends annual screening in the high-risk group as defined in the National Lung Screening Trial.¹²⁷ LDCT screening will result in increased exposure of smokers to ionizing radiation. In making their recommendation in support of LDCT screening, the U.S. Preventive Services Task Force acknowledged that there is uncertainty about the magnitude of the radiation-associated risks. Characterizing the magnitude of risks associated with LDCT screening is an important future priority, because risk models that have attempted to quantify these risks indicate that they are not trivial.^{128,129}

AIR POLLUTION

During a typical day, the average adult inhales about 10,000 L of air.¹³⁰ Consequently, even the carcinogens present in the air at low concentrations are of concern as a risk factor for lung cancer.

Atmospheric Air Pollution

Outdoor air can contain a number of hazardous agents. Many of these are generated by the combustion of fossil fuels, including carcinogens such as polycyclic aromatic hydrocarbons and metals such as arsenic, nickel, and chromium.¹⁰⁰ Depending on the pollution sources, the constituents of "air pollution" vary by locale and over time.

Particulate matter, which has multiple sources in urban air, has been studied as a potential lung cancer risk factor. In a study in six U.S. cities, a 40% increase in lung cancer risk was found in residents in the city with the highest concentration of fine particles in the atmosphere compared to the city with the lowest concentration.¹³¹ The data from the American Cancer Society's Cancer Prevention Study II showed that each 10 g/m³ increase in concentration of fine particles carried an increased lung cancer risk of 14%.¹³² A European study of more than 300,000 individuals from nine countries observed that the risk of lung cancer increased significantly as the concentration of particulate matter increased.¹³³ Further evidence indicating an association between constituents of ambient air pollution and increased lung cancer mortality continues to accrue, with reports from Japan,¹³⁴ China,¹³⁵ and New Zealand¹³⁶ documenting increased risks with measures of particulate matter, sulfur dioxide, and nitrogen dioxide. The existing evidence base indicates that atmospheric air pollution is a risk factor for lung cancer. The evidence is strongest for particulate matter, but may also extend to other constituents of polluted air. A large number of people who live in cities are exposed to outdoor air pollution, so even a small effect is of public health importance.

Indoor Air Pollution

Indoor air pollution arises from pollutants that enter from the outside as well as those that originate indoors from tobacco smoking, building materials, soil gases, household

products, and combustion from heating and cooking.¹³⁷ In the more developed countries, two of the most important indoor pollutants that influence lung cancer risk in never smokers are passive smoking⁸⁵ and radon.¹¹⁵ In the developing world, the major source of indoor air contamination results from the use of unprocessed solid fuels, notably coal (a fossil fuel) but also biomass fuels, for cooking and space heating.¹³⁸ Mumford and coworkers¹³⁹ inferred that smoky coal was a major determinant of the geographic distribution of lung cancer in Xuan Wei, China, a finding corroborated by an animal model.¹⁴⁰ Evidence supporting a causal association was subsequently strengthened by studies documenting that switching from use of unvented fire pits to stoves with chimneys¹⁴¹ or to portable stoves¹⁴² cut the lung cancer risk in half.

Indoor burning of biomass, such as wood, is associated with lung cancer risk, but the association is weaker than for fossil fuel burning. This was illustrated in a pooled analysis of seven case-control studies, in which the risk of lung cancer was strongest for indoor burning of coal in Asia (*odds ratio* [OR] 4.9; 95% *confidence interval* [CI] 3.7 to 6.5) and weaker—but still statistically significant—for indoor burning of wood in Europe and North America (OR 1.2; 95% CI 1.1 to 1.4).¹⁴³ These findings were corroborated in a meta-analysis of published studies.¹⁴⁴ Indoor burning of solid fuel is a major cause of lung cancer in China and one that is preventable.³⁵ Based on statistical models, projections indicate that reductions in the indoor burning of solid fuel would substantially reduce lung cancer deaths.¹⁴⁵

HOST FACTORS

OVERVIEW

The long-standing interest in genetic susceptibility to lung cancer has recently intensified. Environmental agents, even cigarette smoking, cause lung cancer in only a minority of exposed persons, leading to the hypothesis that susceptibility is inherently determined. Studies showing that a family history of lung cancer predicts increased risk further support a genetic basis for lung cancer susceptibility. This long-postulated hypothesis is now being actively addressed using the approach of molecular epidemiology. Aspects of genetic susceptibility have been reviewed.¹⁴⁶

A positive family history of lung cancer is a clinically useful risk indicator. In a meta-analysis, a positive family history of lung cancer was associated with a 1.7-fold increased risk of lung cancer (95% CI 1.6 to 1.9), an association that was only slightly weaker among nonsmokers (OR 1.4; 95% CI 1.2 to 1.7).¹⁴⁷ A positive family history of lung cancer in two or more relatives was associated with substantially greater risk (OR 3.60; 95% CI 1.6 to 8.3).¹⁴⁷ These findings were reinforced by the results of a pooled analysis in which a positive history of lung cancer in a first-degree relative was associated with 1.5-fold increased risk for lung cancer (95% CI 1.4 to 1.6) with a significant but slightly weaker association among never smokers (OR 1.3; 95% CI 1.03 to 1.5).¹⁴⁸ The familial risk for lung cancer is approximately equal to the associations observed for prostate, breast, and colon cancers, which have a known genetic component.¹⁴⁹

In a large study in Louisiana, segregation analysis suggested that lung cancer inheritance was consistent with a mendelian codominant autosomal gene determining early onset of disease.¹⁵⁰ Conversely, the largest study of lung cancer in twins reported to date did not provide evidence indicating a genetic basis for susceptibility.¹⁵¹

In a genetic epidemiology study of lung cancer in nonsmokers in Detroit, Schwartz, Yang, and colleagues^{152,153} explored familial risk for lung cancer. In nonsmokers, Schwartz and associates¹⁵² found an association between risk and a history of lung cancer in a first-degree relative (OR 1.4; 95% CI 0.8 to 2.5). The association was much stronger in those aged 40 to 59 years at diagnosis than in older persons, suggesting that genetic factors may be more important at younger ages. This general finding was confirmed by a subsequent complex segregation analysis of the same data.¹⁵³

RESEARCH FINDINGS ON THE GENETIC BASIS OF LUNG CANCER (Chapter 51)

Studies to investigate genotypic variation in relation to lung cancer risk have evolved rapidly since the 1980s. Initially, the research paradigm relied on identifying and studying candidate genes with functional polymorphisms hypothesized to be related to lung carcinogenesis, such as carcinogen detoxification or DNA repair genes. The sequencing of the human genome and the development of high-throughput assays that enable increasingly larger numbers of single nucleotide polymorphisms to be measured in larger studies has led to the new paradigm of *genome-wide association studies* (GWAS). In contrast to the candidate gene approach, which is based on deduction, the GWAS approach is inherently inductive. GWAS studies entail measuring as many single nucleotide polymorphisms as possible—currently more than a million—to determine which regions of the genome are associated with lung cancer risk. Because there is no need to have prior knowledge of the genetic function of the region under consideration, the GWAS approach is exploratory and studies using this approach must be specifically designed to guard against false-positive findings and overfitting. As such, sample sizes tend to be large.

Of primary interest in studies using the candidate gene approach are genes that encode for enzymes in carcinogen metabolism and DNA repair pathways and that are polymorphic in humans. Selected examples are described later. The metabolism of toxic agents, including carcinogens, generally proceeds through two phases.¹⁵⁴

In phase 1, unreactive nonpolar compounds are converted, usually by oxidative reactions, to highly reactive intermediates. Many carcinogenic compounds in tobacco smoke (e.g., polycyclic aromatic hydrocarbons) undergo metabolic activation by phase 1 enzymes of the cytochrome P-450 system to form reactive intermediates that bind to DNA and cause genetic injury. For example, for the gene that encodes one of the P-450 enzymes, *CYP1A1*, the current evidence suggests that two specific polymorphisms, in *MspI*¹⁵⁵ and in exon 7,¹⁵⁶ are associated with increased lung cancer risk.

In phase 2, these intermediates are joined with conjugating molecules to form complexes, which are usually less reactive and more easily excreted. However, the intermediate metabolite may react with other cellular components,

such as DNA, before it is conjugated. This binding to DNA may be the first step in the initiation of the carcinogenic process.¹⁵⁴ One of the phase 2 enzymes, glutathione S-transferase, detoxifies reactive metabolites of polycyclic aromatic hydrocarbons. The results of a meta-analysis indicated that those with the GSTM1-null had a slightly higher lung cancer risk than the GSTM1-present genotype, but a pooled analysis of data from 21 case-control studies did not indicate that this susceptibility was stronger among cigarette smokers than among nonsmokers.¹⁵⁷

Another pathway where genetic variation has been of hypothesized importance in determining susceptibility to lung cancer is DNA repair.^{158,159} One of the most extensively studied DNA repair genes to date is the nucleotide excision repair gene *XPB*.^{160,161} The evidence has not yet revealed a consistent pattern of associations for lung cancer and any specific polymorphism. In summary, the candidate gene approach has not yielded clear-cut associations with lung cancer risk.

GWAS are now being reported, with encouraging results. The results of four separate studies, all published in 2008, have been remarkably consistent in identifying a region on the long arm of chromosome 15 (15q24-25.1).¹⁶²⁻¹⁶⁵ For example, subjects with at least one variant allele of a specific single nucleotide polymorphism in this region (rs8034191), present in approximately one-third of the study population, were at 1.3 times greater risk for lung cancer than those with the wild-type allele.¹⁶³⁻¹⁶⁵ This region of chromosome 15 contains 3 identified coding areas for nicotine acetylcholine receptors. Nicotine acetylcholine receptors mediate an individual's sensitivity to nicotine, suggesting that those with these variant alleles may be at an increased risk for nicotine addiction and hence tobacco carcinogen exposure. A second region on the short arm of chromosome 6 (6p21) was reported to be involved in cancer risk in two European studies in 2008.^{163,166} This locus, which maps to the major histocompatibility complex, was also associated with increased lung cancer susceptibility and poor survival in an Asian population with advanced non-small cell lung cancer.¹⁶⁷ A third gene region identified another susceptibility locus on the short arm of chromosome 5 that contains two genes known to be biologically relevant in lung cancer, *TERT* (human telomerase reverse transcriptase) and *CLPTMIL* (cleft lip and palate transmembrane-1-like).¹⁶⁸ Despite the identification of these three susceptibility loci, cumulatively they represent less than 10% of the familial lung cancer risk. It is possible that rare variants may explain some of the residual familial lung cancer risk.

With application of the new and powerful tools of modern molecular biology, research findings are now characterizing the changes in cells that are caused by exposure to tobacco smoke and providing a framework for understanding the genetic and epigenetic basis of lung cancer risk. A rapidly expanding literature, termed "molecular epidemiology," is based both on laboratory and on observational data addressing dosimetry and metabolism of tobacco carcinogens at the cellular and molecular levels. This literature also analyzes the resulting patterns of genetic and epigenetic changes in the smoking-related cancers that develop as well as the "field" changes in the tissues surrounding those cancers, which also have genetic and epigenetic changes

caused by cigarette smoking. This literature has necessarily become more sophisticated in its description of the changes in cells induced by tobacco carcinogens as being genetic or epigenetic; DNA, RNA, or protein-based; and, more recently, reflective of the metabolic state of the cell.

As part of the Cancer Genome Atlas Project, the genomic and epigenomic profiles of 178 lung squamous cell carcinomas were characterized.¹⁶⁹ The data showed complex genomic alterations, with hundreds of exonic mutations, genomic rearrangements, and copy number alterations per tumor, in addition to many correlations between genomic and epigenomic aberrations. Common abnormalities in p53 and several cell cycle, oxidative stress, and apoptotic signaling pathways suggest a common mechanism for this cancer.

The understanding of the epigenetic changes that may be involved in the causal pathway to lung cancer is advancing rapidly. Methylation of cytosine in the DNA, leading to hypermethylation of promoter regions is important in regulating biochemical pathways and is a frequent alteration in most types of cancers, including lung cancer.¹⁷⁰ Promoter regions of many human genes have loci rich in CpG dinucleotides, regions referred to as CpG islands.^{170,171} Comprehensive genome-wide searches have identified numerous CpG island genes epigenetically silenced by DNA methylation that are able to distinguish neoplastic from nonneoplastic tissue. Cells with abnormal methylation of genes have been detected in sputum of subjects before their diagnosis of lung cancer, suggesting that hypermethylation could be a useful marker for early detection.^{172,173}

In a general formulation of determinants of cancer risk, the risk depends on carcinogen exposure as well as the factors that determine host susceptibility, including genetic predisposition.¹⁷⁴ Central to the molecular epidemiology approach are biomarkers, measures of indicators of exposure and dose, susceptibility, and response in biologic materials, including tissue samples, blood, urine, and saliva.¹⁷⁵ As research evolves within this paradigm, a more complete biologic understanding of the specific events underlying the multistage model, originally proposed on a conceptual basis, can be anticipated.

This framework indicates multiple points where genetically determined host characteristics might be important: carcinogen metabolism and activation, DNA repair, and cell cycle control/apoptotic response. There is a rapidly expanding literature on the molecular and cellular basis of lung cancer.¹⁴⁶ The evidence has expanded and deepened our understanding of how smoking injures cells and causes cancer, and indicates potential approaches to identifying high-risk individuals and molecular screening.

PRESENCE OF HUMAN IMMUNODEFICIENCY VIRUS

As the population of patients infected with *human immunodeficiency virus* (HIV) has aged, due to improved survival from highly active antiretroviral therapy, evidence from case reports,¹⁷⁶ patient series,¹⁷⁷ and observational studies¹⁷⁸⁻¹⁸⁰ has indicated that HIV-positive individuals have an increased risk for lung cancer. Best estimates from the cumulative data in observational cohorts and clinical registries suggest that HIV infection increases lung cancer risk at least 2.5-fold compared with risk in the

general population, independent of smoking status.¹⁸⁸ Consequently, lung cancer is now the most common and most fatal non-acquired immunodeficiency syndrome-associated malignancy in the HIV-positive population, accounting for 16% of deaths among all HIV patients.¹⁸¹

Some aspects of lung cancer in HIV-positive patients follow patterns observed in the general population. This includes the predominance of non-small cell lung cancer,^{182,183} with adenocarcinoma and squamous cell carcinoma as the two most common cell types^{180,182,184} and the presentation with advanced stage lung cancer, with only 10% to 15% of HIV-infected patients with diagnosed lung cancer amenable to curative resection.¹⁷⁸ However, other characteristics of this population are representative of the HIV-positive population. For example, the preponderance of HIV-positive patients with lung cancer are males,¹⁸² consistent with the higher prevalence of HIV infection in men than in women. Interestingly, lung cancer is diagnosed in HIV-positive individuals at younger ages than the norm, perhaps indicative of enhanced susceptibility to lung cancer or perhaps just due to the younger age of HIV-positive individuals.^{180,185} Remarkably, in the United States, approximately 80% of HIV-infected individuals with lung cancer are African Americans in some studies,¹⁷⁸ despite African Americans comprising only 12% of the general population and 46% of the HIV-infected population.¹⁸⁶

Even though HIV-positive individuals have an increased lung cancer risk above and beyond that due to cigarette smoking, the primary lung cancer risk factor in HIV-infected people, as in the general population, is cigarette smoking. In fact, in most studies, there are few HIV-positive lung cancer patients who are not also cigarette smokers. Despite the high risk for lung cancer in HIV-infected people, the cumulative duration of smoking exposure for HIV-infected lung cancer patients, for example, is less than in the general population,^{178,185} probably due to their younger age. This is consistent with the possibility that HIV infection enhances susceptibility to smoking-caused lung cancer, which is one of several hypotheses to explain why there is an excess lung cancer risk in HIV-positive individuals. The elevated lung cancer risk could also simply be due to a higher prevalence of cigarette smoking in HIV-positive individuals.^{182,187} Alternatively, HIV may itself contribute to lung carcinogenesis.¹⁸⁸ If so, potential explanations for the increased lung cancer risk could include (1) a direct carcinogenic effect of HIV, (2) a defective immune surveillance, and (3) inflammation due to recurrent opportunistic infections and parenchymal lung injury leading to inflammatory foci and scar carcinomas. Whereas recent evidence supports the notion that immunosuppression increases the risk for lung cancer development,¹⁸⁸ most HIV-infected lung cancer patients have only moderate immunosuppression¹⁷⁸ and other measures of immunocompetence such as CD4 count and HIV viral load do not seem to be strongly related to increased lung cancer risk.¹⁷⁹ Increased immunodeficiency in these patients, however, adversely affects response to treatment, because of an inability to tolerate cytotoxic therapy¹⁸⁹ as well as a reduced long-term survival after surgery.¹⁹⁰

Older age and more extensive histories of cigarette smoking are strongly associated with increased lung cancer risk, so as the population of HIV-infected individuals ages, the combined effect of age, the high prevalence of smoking,

and the excess lung cancer risk in this population will make this a very high-risk subgroup of the general population. Because of the high risk for lung cancer in HIV-infected individuals who are 55 years of age or older and have a history of cigarette smoking, it will be important to target this subgroup with smoking cessation interventions for primary prevention and with LDCT for early detection.

PRESENCE OF ACQUIRED LUNG DISEASE

In addition to hereditary factors, increased susceptibility to lung cancer may result from underlying lung disease. Such acquired lung diseases assume two major forms: (1) airway disorders that obstruct airflow, such as *chronic obstructive pulmonary disease* (COPD), and (2) fibrotic disorders that restrict lung capacity, such as pneumoconiosis.¹⁹¹

A substantial body of evidence suggests that COPD or impaired lung function is associated with the development of lung cancer.¹⁹² However, because cigarette smoking is the principal cause of both COPD¹⁹³ and lung cancer, statistical adjustment procedures that “remove” the effect of cigarette smoking may not be well founded. For example, the presence of COPD may indicate that the affected individual has received a greater dose of tobacco carcinogens than the typical unaffected individual. Alternatively, cigarette smoke may induce inflammation that can contribute both to COPD and to lung cancer.¹⁹⁴ Regardless of the mechanism, the presence of COPD is a clinically useful risk indicator.

Clarifying the possible relationship between pneumoconioses and lung cancer poses particularly vexing challenges. Even for asbestos exposure, which is clearly established as a potent cause of lung cancer,¹⁰⁸ whether lung cancer results from asbestos per se or from asbestosis remains unresolved (see earlier). For other mineral fibers, the evidence is even more uncertain.¹⁹⁵ For example, determining whether silica exposure or silicosis mediates the increased lung cancer risk in silica-exposed persons has proved difficult.^{196,197} It is recognized that the presence of silicosis is associated with an increased risk for lung cancer,¹⁹⁸ but understanding the basis of this association will entail isolating the independent effects of silica exposure and lung fibrosis while controlling for exposure to smoking and other lung carcinogens.¹⁹⁵

Such differences in the pattern of associations between pneumoconioses and lung cancer emphasize that “fibrosis” is not a homogeneous exposure but is dependent upon the properties of the specific mineral fiber or other environmental agent. Properties of the agent, such as its size, shape, and durability, and the effects of other exposures such as cigarette smoking are important considerations in assessing its potential harmfulness.¹⁹⁹

GENDER

The hypothesis has been advanced that females may have a greater lung cancer risk than males at the same level of smoking.^{200,201} However, direct tests of this hypothesis suggest it is not correct, because the results of studies that have compared the relative risk estimates for men and women for a specific degree of smoking history demonstrate very similar risks.^{58,202} In fact, as shown in the results

summarized in Table 52-2, women may even show a substantially lower risk for lung cancer than men for a specific smoking history. Some have hypothesized that women may have a lower lung cancer risk because men have higher exposures to other environmental lung carcinogens, such as occupational exposures, that synergistically interact with cigarette smoking. In another study of more than 950,000 individuals in the United States from 2000 to 2010, the relative risks of dying of lung cancer in current smokers compared with never smokers were nearly identical in women (relative risk 26) and men (relative risk 25).⁵⁸ Thus, for the same amount of smoking, women would appear to have the same or lower risk of lung cancer than men but not a higher risk.

However, interesting differences in characteristics of lung cancer between men and women have been noted.²⁰³ First, women with lung cancer have a better prognosis than men. Second, and somewhat in contrast with this notion, estrogen may enhance lung cancer risk. For example, a significantly increased risk of lung cancer (relative risk 1.4; 95% CI 1.03 to 1.8) was observed for hormonal therapy with estrogen plus progestin formulations in a meta-analysis of data from two large-scale randomized controlled trials.²⁰⁴ In addition, results of studies published after the meta-analysis reinforced the notion that hormonal therapy with estrogen plus progestin formulations may increase lung cancer risk.^{205,206} Third, some clear gender differences have become apparent in never smokers. Among never smokers, women have higher lung cancer incidence rates than men. Among never smokers in whom lung cancer develops, women have a higher percentage of adenocarcinomas than men and, in the subjects with adenocarcinomas, women have a higher prevalence of *EGFR* mutations than men. Observations such as these hint that distinct gender differences in lung carcinogenesis may exist that could potentially be clinically important.

FUTURE DIRECTIONS

In developing lung cancer prevention strategies, certain groups warrant particular attention. Steps need to be taken toward the goal of reducing the very high lung cancer incidence rates in African American men.²⁰⁷ Lung cancer is also a major women's health issue. Owing to historical cigarette smoking patterns, the epidemic of lung cancer started later in women than in men but, in contrast to the situation in men, lung cancer incidence rates in women are just now starting to decrease.²⁰⁸ Even though lung cancer remains a critical public health problem, the decrease in the overall lung cancer burden now seen in the United States, as in much of the developed world, reflects the successes of preventive strategies. A critical global priority is to prevent the uptake of cigarette smoking in developing countries where smoking prevalence is still low.

A consideration of the epidemiology of lung cancer consistently reinforces one major theme: the pandemic of lung

cancer is a consequence of the tragic and widespread addiction to cigarettes throughout the world. Curtailing the pandemic of lung cancer will require preventing youths from starting to smoke cigarettes and effectively promoting smoking cessation among addicted smokers. The rapidly expanding marketplace for tobacco products and nicotine-delivery devices and the shift toward patterns of mixed-use in younger smokers will require surveillance to characterize the prevalence of use and etiologic research to determine the net impact of the real-world use of these products.

Key Points

- In the United States, lung cancer remains the leading cause of cancer death in both men and women.
- The predominant cause of lung cancer is exposure to tobacco smoke, with active smoking causing most cases but passive smoking also contributing to the lung cancer burden.
- The reductions in smoking prevalence in men in the late 1960s through the 1980s will continue to drive lung cancer mortality rates downward during the first portion of the 21st century.
- Fortunately, exposures to major occupational respiratory carcinogens have largely been controlled, but the population is still exposed to environmental causes of lung cancer, including radon, the second leading cause of lung cancer death.
- Lung cancer is significantly more likely to develop in individuals infected with HIV than in uninfected individuals; the mechanisms underlying this association are not yet clearly established.
- Gender similarities and differences exist in lung cancer. The most important fact is that, among smokers, a similar smoking history results in similar lung cancer risk for women and men. Among never smokers, compared to men, women have a higher overall incidence of lung cancer, particularly of adenocarcinoma with epidermal growth factor receptor mutations.

Complete reference list available at [ExpertConsult](#).

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CLINICAL ASPECTS OF LUNG CANCER

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INTRODUCTION

Lung cancer is the most common cause of cancer deaths worldwide. In the United States, lung cancer accounted for more than 250,000 cases of cancer and greater than 150,000 deaths from cancer in 2013.¹ Chapter 52 is dedicated to the epidemiology of lung cancer but some of the information found therein is worth repeating. For example, the number of lung cancer deaths each year exceeds the number of cancer deaths from breast, colon, and prostate cancer combined. A common misconception among the general public is that breast cancer accounts for more cancer deaths in women. However, lung cancer is now the greatest cancer killer of women and will account for 25% of cancer-related deaths among women in the United States. Particularly alarming is the fact that young women are in the fastest rising demographic of new cigarette smokers in the United States. Many have clearly made the association between weight control and cigarette smoking. This will have effects on the prevalence of lung cancer in the decades to come.

One of the more disturbing trends in lung cancer is the explosion in rates of lung cancer in countries of the developing world. In 1985, it was estimated that there were 921,000 lung cancer deaths worldwide—an increase of 17% from 1980.² In 2011, lung cancer accounted for 13% of cases (1.6 million) and 18% of deaths (1.4 million) worldwide.¹ The International Agency for Research on Cancer in France found that the rates of lung cancer in Africa in the early 1990s were similar to those in the United States in the 1930s, at about 5 per 100,000. By 1999, the rate of lung cancer in males in developing countries was 14 in 100,000 and on the rise, compared with a rate of 71 in 100,000 in developed countries, which continues to decline. These rates may actually be underestimates of the true

rates of lung cancer, because many cases may go undiagnosed or underreported in areas where health care is not readily available.² The seriousness of this problem is exemplified in China, where it is estimated that nearly 800,000 Chinese men died of lung cancer in 1998.² It remains imperative that the medical community devotes much of its educational efforts and resources to the elimination of cigarette smoking worldwide, which would nearly eliminate the development of lung cancer (see also Chapter 46).

This chapter reviews the current strategies for the diagnosis, reviews the staging system, and describes the current treatment of lung cancer. As much as possible, evidence-based review of the best currently available literature has been included. The role of the pulmonologist is described for every aspect of lung cancer care, from diagnosis to staging to caring for the complications of the disease itself and the complications of cancer treatment.

SCREENING FOR LUNG CANCER

The U.S. Preventive Services Task Force now recommends screening for lung cancer with low dose *computed tomography* (CT) in high-risk patients (see Chapter 18). Before 2013, there was insufficient evidence to support screening for lung cancer.³ For example, the 2004 U.S. Preventive Services Task Force position was based on the results of five randomized, controlled trials that suggested that neither chest radiography nor sputum cytology satisfies the primary criterion of a beneficial screening test: a reduction in lung cancer mortality.⁴⁻⁶ One deficiency was that most of these studies did not include a “no screening” arm. Others arguably had an inadequate sample size. In 2011, the results of the lung arm of the National Cancer Institute’s Prostate, Lung, Colorectal, and Ovarian Trial demonstrated that, in

a randomized trial of chest radiography versus no screening in a low-risk population of both genders, there was no reduction in mortality from lung cancer in the chest radiography screened group compared with usual care.⁷

Chest CT has been shown to be much more sensitive for detecting pulmonary nodules than the standard chest radiograph. There have been a number of single-arm screening trials utilizing *low-dose computed tomography* (LDCT), defined as a single breath-hold scan that exposes the patient to a five to six times smaller radiation dose than a standard CT scan, with or without sputum cytology.^{4,8-13} Although these trials consistently showed that chest CT detects more lung cancers than chest radiography, they were not designed to provide information on mortality benefit. Trials without control arms can be subject to different potential sources of bias.^{10,14} *Lead-time bias* is the detection of tumors earlier in their course; *length-time bias* is the greater detection of less aggressive, slower-growing tumors than more aggressive, faster-growing tumors; and *overdiagnosis* is the detection of tumors that would otherwise never cause symptoms or death.

The *National Lung Cancer Screening Trial* (NLST) is the first large-scale randomized trial to demonstrate a convincing mortality benefit for LDCT lung cancer screening in high-risk individuals. The trial included 33 centers across the United States. Eligible participants were between ages 55 and 74 years at the time of randomization, had a history of at least 30 pack-years of cigarette smoking, and, if former smokers, had quit within the past 15 years.¹⁵ A total of 53,454 persons were enrolled; 26,722 were randomly assigned to screening with LDCT and 26,732 to screening with chest radiography. Any noncalcified nodule found on LDCT measuring at least 4 mm in any diameter and chest radiographic images with any noncalcified nodule or mass were classified as positive. The LDCT-screened group had a substantially higher rate of positive screening tests compared with the radiography group (round 1: 27.3% vs. 9.2%; round 2: 27.9% vs. 6.2%; round 3: 16.8% vs. 5%). Overall, 39.1% of participants in the LDCT group and 16% in the radiography group had at least one positive screening result. Of those with a positive screening result, the false-positive rate was 96.4% in the LDCT group and 94.5% in the radiography group.

In the LDCT group, 649 cancers were diagnosed after a positive screening test, 44 after a negative screening test, and 367 among participants who either missed the screening or received the diagnosis after the completion of the screening phase. In the radiography group, 279 cancers were diagnosed after a positive screening test, 137 after a negative screening test, and 525 among participants who either missed the screening or received the diagnosis after the completion of the screening phase. There were a total of 356 deaths from lung cancer in the LDCT group and 443 in the chest radiography group, with a relative reduction in the rate of death from lung cancer of 20% with LDCT screening. Overall mortality was reduced by 6.7%. The number needed to screen with LDCT to prevent 1 death from lung cancer was 320, which is comparable to the numbers in studies on screening mammography for breast cancer in women older than 50 years.

One of the concerns with using LDCT for lung cancer screening is the high rate of positive test results necessitat-

ing further workup. Investigators from the NELSON study demonstrated that this can be overcome by using semiautomated volumetry software to measure diameter and volume doubling time.¹⁶ Growth was defined as a change in volume between the first and the second scan of 25% or greater. Nodules meeting growth criteria were then classified into three categories based on volume doubling time (<400 days; 400–600 days; >600 days). This approach to nodule management resulted in a decrease in the rate of positive test results at baseline from 30% to 2%. The final results regarding the reduction in mortality from lung cancer in this trial are pending.

Despite the impressive results from NLST in high-risk adults, the ability to generalize the results to other populations has been questioned. Participants in the NLST were enrolled in urban tertiary care hospitals with expertise in all aspects of cancer care. LDCT studies were interpreted by dedicated chest radiologists with expertise in characterizing nodules and providing appropriate recommendations for follow-up. As a result, few patients required further invasive testing, and radiographic follow-up was sufficient for many.

In contrast, community practice gives rise to the potential for considerable variation in the management of solitary pulmonary nodules identified by screening LDCT. One study demonstrated a twofold variation among geographic regions in use of CT-guided biopsy, ranging from 14.7 to 36.2 per 100,000 adults. This substantial variation in the management of solitary pulmonary nodules may lead to an increased number of invasive procedures with risk of harm. For instance, complications from transthoracic biopsies include a 1% rate of bleeding (with one third of affected patients requiring transfusion) and a 15% rate of pneumothorax. More than 6% of CT-guided biopsies result in a pneumothorax requiring chest tube drainage, a clinically important complication that results in pain, serial imaging with radiation exposure, and hospitalization. Older patients and those with *chronic obstructive pulmonary disease* (COPD) have an increased risk of biopsy-related complications that can result in longer length of hospital stay, contributing both to increased cost and higher rates of respiratory failure that can affect long-term health.¹⁷⁻¹⁹

Another difference between the results of the NLST and community practice is that the mortality from lung cancer surgery was 1% in the NLST, whereas the national average is between 3% and 5% for a lobectomy. Whereas NLST participants were allowed to choose where they had their evaluation and management for screen-detected nodules, many were managed at an NLST site with high volume and dedicated thoracic surgery support, both of which have been shown to have better outcomes.^{20,21} Even though 70 years is the average age at lung cancer diagnosis, only 9% of the NLST study population was older than age 70. The patients enrolled in NLST were younger and healthier than persons who would participate in a broad-based lung cancer screening. Participants had to be medically fit to undergo surgery. Those screened in the NLST were also less likely to be current smokers, less ethnically diverse, and more educated than the general U.S. population.²² These differences follow the healthy volunteer effect of screening trials in which there is a self-selection of persons who are better educated and more health-conscious and who have better access to medical care.²³

The evidence of the NLST contributed to a systematic review that serves as the basis for a multisociety recommendation for screening in those people meeting the NLST entry criteria.²⁴ The caveat to the recommendations is that screening should only be done in those centers with multidisciplinary groups capable of providing comprehensive care as was present in the trial. Based largely in part on the results of the NLST, in 2013, the U.S. Preventive Services Task Force published a draft recommendation giving lung cancer screening a grade B recommendation (moderate certainty that annual screening for lung cancer with LDCT is of moderate net benefit in high-risk asymptomatic persons).²⁵ The U.S. Preventive Services Task Force found there to be adequate evidence to screen asymptomatic patients aged 55 to 79 years with significant tobacco use history. Their assessment was that the moderate net benefit of screening depends on two factors: (1) the accuracy of image interpretation would be comparable to that in the NLST and (2) most false-positive could be handled without invasive procedures.²⁵

There may be potential barriers to lung cancer screening, especially in current smokers. In one study, current smokers were less likely to believe that early cancer detection would result in a good chance of survival. Current smokers are also less likely to consider CT screening for lung cancer (71.2%) than are never smokers (87.6%). In addition, only half of the current smokers surveyed would opt for surgical resection of a screening-diagnosed cancer.²⁶ Finally, it is significant that smokers make up 31% of the population below the poverty line compared with 20% of those at or above the poverty line²⁷; as a result, smokers are likely to be a target population more difficult to reach for large-scale screening in the community.

PRESENTATION

Unfortunately, the symptoms of lung cancer can be nonspecific and variable, thereby delaying diagnosis and frequently leading to an advanced stage at the time of diagnosis. The focus of an initial patient evaluation should include signs and symptoms related to the following: local tumor effects, extension of disease into the thoracic cavity, radiologic correlation, paraneoplastic syndromes, and distant metastatic disease. Whereas only 40% of patients with lung cancer in a screened high-risk outpatient population had symptoms, 98% of patients in a hospitalized population presented with symptoms.^{28,29} In general, only approximately one fourth of patients are asymptomatic at the time lung cancer is diagnosed, and these patients are more likely to have less advanced disease.³⁰ Table 53-1 displays some of the common symptoms associated with the presentation of lung cancer. Most are nonspecific; however, some clues can be gained from the history, thus raising the clinician’s suspicion that lung cancer is present.

Although many smokers cough, lung cancer patients usually admit to a change in the character of their cough. The cough can increase in frequency or strength, or may not be relieved with local measures. Chest pain can be present in 25% to 50% of patients at the time of presentation for evaluation for lung cancer.^{28,31} The pain is generally dull in nature, tends to be persistent, remains in the same

Table 53-1 Presenting Symptoms with Bronchogenic Carcinoma

Symptoms and Signs	Frequency, %
Cough	8–75
Weight loss	0–68
Dyspnea	3–60
Chest pain	20–49
Hemoptysis	6–35
Bone pain	6–25
Clubbing	0–20
Fever	0–20
Hoarseness	2–18
Weakness	0–10
Superior vena cava obstruction	0–4
Dysphagia	0–2
Wheezing and stridor	0–2

Modified from references 31 and 290 to 295.

location, and is not relieved with local measures. Chest pain is usually related to involvement of the pleura but can be related to extension into the mediastinum or chest wall. However, chest pain in and of itself does not preclude the patient from consideration for surgery with curative intent. Dyspnea is frequently a complaint of patients who present with bronchogenic carcinoma, noted in half of all new patients at presentation.²⁸ A partial list of the reasons for dyspnea related to lung cancer includes pulmonary embolism, superior vena cava (SVC) syndrome, deconditioning, reactive airway disease, endobronchial obstruction with tumor, prior obstructive pneumonia, hemoptysis, hemorrhage, malignant pleural effusion, and extrinsic compression of the airway by tumor.

Hemoptysis in a smoker should raise suspicion of lung cancer. Hemoptysis can present as blood streaking of the sputum and can be noted over a lengthy period of time before presentation to the physician’s office because the patient attributes it to smoking-related bronchitis. The clinician should not be led astray, even if the chest radiograph is normal, because up to 5% of patients with hemoptysis and a smoking history and a normal radiograph can harbor lung cancer.³² Because of the vascular nature of lung cancer, patients can also present with massive hemoptysis.

Weight loss, a nonspecific symptom, in the right clinical setting should raise the suspicion of both lung cancer and metastatic disease. Weight loss alone has been correlated with an advanced presentation and poor outcome in lung cancer cases.

In summary, patients with lung cancer can present asymptotically or with relatively nonspecific symptoms of underlying pulmonary disease. There are often clues in the history that should alert the clinician that lung cancer is a possibility and further investigation is warranted.

LUNG CANCER STAGING

Perhaps the most critical role of the pulmonologist in the management of lung cancer is in the diagnostic and staging

evaluation of the patient. Accurately staging patients with newly diagnosed lung cancer is critical because staging dictates the patient's treatment options and predicts survival. It is intuitive that early-stage disease has a much better survival than late-stage disease. What may not be so obvious is that simple staging procedures are available to the diagnostician that can help stage patients accurately. The treatment options for lung cancer have now evolved so that treatment for patients in different stages is vastly different. In general, stage I (early-stage lung cancer) is treated with surgery alone. Stage II lung cancer (a less common stage, intermediate between early and locally advanced) is treated with surgery followed by adjuvant chemotherapy. Stage IIIA and B (locally advanced lung cancer) is treated with a combination of chemotherapy and radiotherapy, and stage IV (metastatic disease) is treated with chemotherapy alone. However, there are important exceptions to these general rules that are discussed later in this chapter.

The staging of *non-small cell lung cancer* (NSCLC) using the *tumor-node-metastasis* (TNM) classification underwent a major revision in 2007.^{33,34} The new staging system is remarkable in that it is based on more than 100,000 cases of lung cancer from 23 institutions, 12 countries, and 3 continents. The data are robust, internally validated, and externally validated against the Surveillance Epidemiology and End Results cancer registry.³³ Tables 53-2 and 53-3 show the current TNM descriptors and stage groupings.

There are several important changes adopted in the 2007 revision. The main modifications are in the T and M classification; the N status remains the same. Within the T classification, tumor size was found to be an important prognosticator and the T factor was subdivided based upon five different size criteria. Because survivorship was better than previously thought, a primary tumor with satellite nodules in the same lobe was reclassified from T4 to T3 and a tumor with additional nodules in a different lobe of the ipsilateral lung was moved from an M1 designation to T4. This change in classification and stage allows more patients to be considered for surgery. Malignant pleural effusion was reclassified from T4 (or stage IIIB) disease to M1 disease because the survival of patients in this group was found to resemble the survival of those with metastatic disease more closely than those with locally advanced disease. Another significant change is that the M status is now split into M1a (metastatic disease confined to the chest) and M1b (extrathoracic metastatic disease) because survival was found to be better in those patients with metastatic disease confined to the thorax compared with those with extrathoracic metastases.

Whereas the TNM staging system is applied to NSCLC, a more simplified version is employed for patients with *small cell lung cancer* (SCLC). In this classification, patients are classified as having limited or extensive disease. *Limited disease* (LD) is disease limited to one hemithorax, although it can include supraclavicular and mediastinal lymphadenopathy; *extensive disease* (ED) is any disease outside of the hemithorax. The implication in this classification is that LD is treated with chemotherapy and radiotherapy and ED is treated with chemotherapy alone.³⁵ Malignant pleural effusion can technically be categorized as LD in the staging classification for SCLC if the patient otherwise meets criteria. However, for all intents and purposes, patients with

Table 53-2 Tumor-Node-Metastasis (TNM) Descriptors in the Revised 7th Edition of the TNM Classification of Lung Cancer

T (PRIMARY TUMOR)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if < 5 cm) Involves main bronchus, ≥ 2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe
N (REGIONAL LYMPH NODES)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (DISTANT METASTASIS)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion†
M1b	Distant metastasis

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified at T1.

†Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

From Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project. *J Thorac Oncol* 2:709, 2007.

Table 53-3 Stage Grouping Comparisons: AJCC Staging Manual 6th versus 7th Edition Descriptors, T and M Categories, and Stage Groupings

T and M Descriptor (6th edition)	T and M Descriptor (7th edition)	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2 to 3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5 to 7 cm)	T2b	IIA	IIIB	IIIA	IIIB
T2 (>7 cm)	T3	IIIB	IIIA	IIIA	IIIB
T3 (invasion)	T3	IIIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	IIIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)	T4	IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Bold font indicates a change from the sixth edition for a particular TNM category.
From Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2:706-714, 2007.

malignant pleural effusions and SCLC have the same characteristics as those with ED, and the large cooperative group trials have treated them as such.

Some important nuances to staging are described in detail later in this chapter. However, there are certain tenets of staging that must be emphasized. Before classifying a patient within a certain stage, the clinician should make every effort to verify any noninvasive radiologic findings with tissue confirmation of malignancy. This is particularly important when surgical resection would be precluded based on noninvasive radiologic tests. Thus a patient who would otherwise be resectable except for a single abnormality suspicious for metastasis should have tissue confirmation of that abnormality before being deemed unresectable. As is pointed out later in this chapter, no noninvasive radiologic study is infallible. In studies of the mediastinum, false-positive findings range from 12% in *positron emission tomography* (PET) scans to nearly 20% in CT scans (eFigs. 53-1 and 53-2) with lower false-positive findings using integrated PET-CT, at the cost of lower sensitivity.^{36,37} Therefore reliance on the scan alone to predict malignancy is simply not appropriate.

Staging can be accomplished by a number of noninvasive and invasive studies. The choice of the most appropriate study rests with the clinician and is based on how the patient presents. Some patients—for example, those with isolated solitary pulmonary nodules—may be referred for immediate surgical resection as both a diagnostic and a therapeutic maneuver. Others, such as those with extremely poor performance status or those suspected of widely metastatic disease, may undergo no testing at all. The next sections present a discussion of the attributes of each of the staging options available, divided into noninvasive and invasive techniques.

NONINVASIVE STAGING TECHNIQUES

CHEST RADIOGRAPHY

Many lung cancers are detected initially by plain chest radiograph. In certain situations, chest radiography may be sufficient to detect spread to the mediastinum. For example, the presence of bulky lymphadenopathy in the superior or contralateral mediastinal areas may be considered adequate evidence of metastatic disease to preclude further imaging evaluation of the chest. This may be particularly true if the patient is too ill or unwilling to undergo treatment of any kind. Still, most patients should undergo a chest CT scan unless they are so debilitated that no further evaluation or treatment is planned. The chest radiograph is simply too insensitive a measure of mediastinal lymph node involvement with lung cancer and thus further noninvasive or invasive assessment is usually necessary.

CHEST COMPUTED TOMOGRAPHY

The vast majority of patients who present with lung cancer will undergo chest CT, which can confirm the suspicion of lung cancer or raise the suspicion of an alternate diagnosis. CT is helpful in defining the size, location, and characteristics of the primary mass (e.g., circumscribed, spiculated, calcified), the presence or absence of lymphadenopathy, and, if performed through the adrenal glands, the presence of abnormalities in the liver and adrenal glands. The bony structures of the thoracic cavity can also be evaluated by chest CT.

Chest CT is the most widely available and commonly used noninvasive modality for evaluation of the mediastinum in lung cancer. Numerous studies of CT have been performed comparing clinical staging by CT with the “gold standards” of mediastinoscopy or surgery. The results demonstrated that, regardless of the lymph node size used as a threshold for defining malignant adenopathy, CT findings in isolation could not be considered as conclusive evidence that lymph nodes were malignant. In other words, in all studies, there are meaningful numbers of false-positive cases detected by CT (see eFigs. 53-1 and 53-2). The vast majority of reports evaluating the accuracy of CT for mediastinal lymph node staging have employed the administration of intravenous contrast material. Although contrast is not absolutely necessary in performing chest CT for this indication, it is helpful to distinguish vascular structures from lymph nodes as well as to delineate mediastinal invasion from centrally located tumors. The most widely accepted criterion for an abnormal lymph node on CT is a lymph node with a diameter of 1 cm or greater across the short axis.

The *American College of Chest Physicians* (ACCP) compiled the studies assessing the performance characteristics of CT for staging the mediastinum in a meta-analytic format.³⁸ Thirty-five studies were identified, comprising 5111 evaluable patients. The pooled sensitivity of CT for staging the mediastinum was 51% (95% CI, 47% to 54%) and the pooled specificity was 86% (95% CI, 84% to 88%). The corresponding positive and negative likelihood ratios were 3.4 and 0.6, respectively, confirming that CT has a limited

ability to either confirm or exclude mediastinal metastasis.³⁸ However, because CT guides the selection of nodes for biopsy by mediastinoscopy or transbronchial, transthoracic, or transesophageal needle aspiration, it remains an important diagnostic tool in lung cancer. The limitation of CT-based mediastinal lymph node evaluation is evident in that 5% to 15% of patients with clinical T1N0 lesions will be found to have positive lymph node involvement by surgical lymph node sampling (eFig. 53-3).³⁹ Perhaps the most important message in evaluating the accuracy of CT is that approximately 40% of all nodes deemed malignant by CT criteria are actually benign (see eFigs. 53-1 and 53-2), depending on the patient population.⁴⁰ Specificity can be affected by clinical factors such as the presence of obstructive pneumonitis.⁴⁰ There is no node size that can reliably determine stage and operability. When CT criteria for identification of a metastatic node are met, the clinician must still prove beyond reasonable doubt by biopsy or resection that the node is indeed malignant. Given the limitations of the imperfect sensitivity and specificity of CT, it is usually inappropriate to rely solely on CT to determine mediastinal lymph node status. Nonetheless, CT continues to play an important and necessary role in the evaluation of patients with either a known or suspected lung cancer who are eligible for treatment.³⁷

CT can also be helpful in the evaluation of pleural effusion in patients with lung cancer. The CT scan can indicate the presence or absence of fluid, the contour of the pleural space, and whether or not nodules or masses are present on the pleural surface (eFig. 53-4A and B). However, the clinician should interpret these findings with caution because pleural disease can predate cancer and the presence of pleural effusion does not guarantee that the cytology will be positive. This is an important staging issue because the finding of malignant pleural effusion in NSCLC is considered evidence of metastatic disease (stage IV). If the pleural fluid has benign cytology (e.g., it represents fluid from obstructive pneumonia), then the patient may still be considered for surgical resection. To resolve this issue, recommendations have been made to perform thoracentesis with cytology on two separate occasions, followed by thoracoscopy to evaluate the pleural surface directly (eFig. 53-5). If the patient remains cytology-negative, then the patient should be considered to be at the lower, nonmetastatic stage and be treated accordingly. Thoracoscopy can be helpful in differentiating the extent of the primary tumor involvement into or through the pleura but, at times, open thoracotomy is needed to sort out this issue. (See Chapters 24 and 82.)

POSITRON EMISSION TOMOGRAPHY

Perhaps the single most notable addition to the staging armamentarium for the evaluation of lung cancer is PET (see Chapter 21). Because the image is created by the biologic activity of neoplastic cells, PET is a metabolic imaging technique based on the function of a tissue rather than on its anatomy. Lung cancer cells demonstrate increased cellular uptake of glucose and a higher rate of glycolysis when compared with normal cells.⁴¹ The radiolabeled glucose analogue ¹⁸F-fluorodeoxyglucose (FDG) undergoes the same cellular uptake as glucose but, after phosphorylation, is not further metabolized and becomes trapped in cells.⁴²

Accumulation of the isotope can then be identified using a PET detector. Specific criteria for an abnormal PET scan are either a standard uptake value of greater than 2.5 or uptake in the lesion that is greater than the background activity of the mediastinum (see eFig. 53-1B and C, eFig. 53-3B, E, and F, and Fig. 21-1F-J). It has proved useful in differentiating neoplastic from normal tissues. In two well-performed studies that evaluated the use of PET in the preoperative setting for lung cancer,^{43,44} nearly 20% of patients were staged differently after evaluation by PET (see eFigs. 53-1, 53-2, and 53-3, and Fig. 21-3). However, the technique is not infallible because certain nonneoplastic processes, including granulomatous (eFig. 53-6) and other inflammatory diseases and infections may also demonstrate positive PET imaging. Furthermore, size limitations are also an issue, with the lower limit of resolution of the study being approximately 7 to 8 mm depending on the intensity of uptake of the isotope in the abnormal cells (eFig. 53-7A-D).⁴³ One should not rely on a negative PET finding for lesions less than 1 cm on CT.

A burgeoning number of studies in the last several years have reported on the utility of PET in the assessment of the mediastinum in patients with lung cancer. Increasing availability of the technology now allows PET to be used widely as a diagnostic tool. PET is primarily a metabolic examination and has limited anatomic resolution. It is possible for PET to identify lymph node stations but not individual lymph nodes. CT provides much more anatomic detail but lacks the functional information provided by PET. The third edition of the ACCP guidelines on lung cancer reviewed the complexity surrounding PET.³⁷ While PET provides information about the primary tumor, mediastinal lymph nodes, and sites of distant metastasis, the contribution that it makes to the stage evaluation is influenced by a multitude of factors. These include the probability of cancer, likelihood of metastasis, and the extent that the investigation for metastases has been completed by other modalities.

To date, there have been five randomized controlled trials to evaluate the role of PET.⁴⁵⁻⁴⁹ The variation in results among the studies was likely due to the significant differences among the patients involved, the prior evaluations, and risk for advanced disease. While two of the studies demonstrated a reduction in the number of noncurative resections from 40% to 20%,^{46,49} another detected no difference in the number of thoracotomies performed or of sites of distant metastasis.⁴⁵ This latter study primarily involved stage I patients with extensive preenrollment imaging explaining why there was no difference detected between the PET and conventional staging arms.

Population-based studies using the U.S. National Cancer Data Base and the Surveillance, Epidemiology and End Results registry suggest that the use of PET has had a positive impact on stage migration from stage III to stage IV classification (eFig. 53-8).^{50,51} Conversely, PET adds little to the staging of patients with clinical stage I cancers.^{50,52} PET is also of limited value in those with ground-glass opacities with or without a solid component because these patients are at low risk for nodal and distant metastatic disease.⁵³

Compared with conventional staging, staging by PET is, on average, 20% more correct in identifying nodal or distant metastasis in randomized controlled trials.⁴⁴⁻⁴⁶ Confirmation of PET findings, however, is imperative because, as is

known for CT, PET can be wrong. PET also carries the possibility of incorrectly upstaging a patient. Whereas a negative mediastinal PET may obviate the need for mediastinoscopy before thoracotomy in certain situations, a positive mediastinal PET should not negate further evaluation or the possibility of resection. In the latter case, lymph node sampling should still be pursued because the possibility of a false-positive PET scan cannot be ignored.

Where PET is available, a PET scan should be obtained during the staging evaluation for lung cancer.⁵⁴ Newer technology includes CT-PET fusion, a single machine that incorporates CT and PET during the same scan. This allows the clinician to obtain anatomic (CT) and functional (PET) images simultaneously. Studies suggest an improvement in the number of patients correctly staged with this modality over CT or PET alone.^{55,56} The future of PET in lung cancer may also include its use to evaluate response to treatment. Due to potential false positive images, the optimal timing for PET following treatments will require further evaluation, especially when chest radiotherapy is used. For example, it may be more useful later in the post-*stereotactic body radiation therapy* (SBRT) period (i.e., after the first year) rather than early in the period (i.e., within the first 3 to 6 months).^{56a}

MAGNETIC RESONANCE IMAGING

There are very few circumstances in which *magnetic resonance imaging* (MRI) is a useful tool in staging lung cancer. However, MRI can be useful in evaluating superior sulcus tumors, especially for possible invasion of the brachial plexus, and for evaluating vertebral invasion.

SEARCH FOR METASTATIC DISEASE

The purpose of extrathoracic scanning in NSCLC is usually to detect metastatic disease at common metastatic sites, such as the adrenal glands, liver, brain, and skeletal system, thereby sparing the patient fruitless surgical intervention.⁵⁷ CT of the chest (eFig. 53-9A), CT (eFig. 53-9C) or MRI with contrast of the brain, and ^{99m}Tc nuclear imaging of the skeletal system are the conventional staging studies when the clinician needs to evaluate for metastatic disease. The use of whole-body PET and PET-CT (see eFig. 53-8) for extrathoracic staging has advanced the field of metastatic disease evaluation. Studies demonstrate that PET and PET-CT outperform conventional staging tests in the evaluation of metastatic disease to key specific distant sites including adrenal glands, liver, and bone (see eFig. 53-8). PET reveals unsuspected metastases in 6% to 37%⁵⁸⁻⁶¹ (see eFig. 53-8 and Fig. 21-4). This allows for more accurate TNM staging,⁶² stage shift,^{50,63} and changes in management including more appropriate consideration of surgical candidacy.^{62,64,65} Detection of brain metastases is a problem for PET because the high background brain FDG uptake can mask the small size of most brain metastases, which can be either hypermetabolic or hypometabolic.⁶⁶ There is some evidence to suggest that integrated PET-CT has an accuracy that nears diagnostic brain CT (see eFig. 53-8B).⁶⁷

The initial clinical evaluation may reveal abnormalities, such as abnormal symptoms, physical findings, and routine blood tests, that then lead to an expanded clinical evaluation

Table 53-4 Expanded Clinical Evaluation

SYMPTOMS ELICITED IN HISTORY
Constitutional—weight loss >10 lb (>4.5 kg)
Musculoskeletal—focal skeletal pain
Neurologic—headaches, syncope, seizures, extremity weakness, recent change in mental status
SIGNS FOUND ON PHYSICAL EXAMINATION
Lymphadenopathy (>1 cm)
Hoarseness, superior vena cava syndrome
Bone tenderness
Hepatomegaly (>13-cm span)
Focal neurologic signs, papilledema
Soft tissue mass
ROUTINE LABORATORY TESTS
Hematocrit < 40% in males
Hematocrit < 35% in females
Elevated alkaline phosphatase, GGT, AST, calcium

AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

(Table 53-4).⁵⁷ If a patient has abnormalities on these clinical evaluations, scans will be abnormal in around 50% of cases. The third iteration of the ACCP guidelines for NSCLC staging recommends PET to evaluate for metastasis (except for metastasis to the brain) for patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT being considered for curative-intent treatment.³⁷ Advanced thoracic lesions and mediastinal lymphadenopathy are important variables because these are associated with more scan abnormalities.^{57,68} This is particularly true for N2 disease, in which asymptomatic metastases have been documented at a higher rate than would have been expected (see eFig. 53-8).⁶⁸ Although several studies have documented a higher incidence of brain metastases in patients with adenocarcinomas than in those with squamous cell cancers,^{69,70} the largest single series of patients with stage I and II lung cancer found no difference.⁷¹

Several important caveats must be considered in the search for metastatic disease. First and foremost, there is the problem of false-positive scans. Adrenal adenomas (present in 2% to 9% of the general population), hepatic cysts, degenerative joint disease, old fractures, and a variety of nonmetastatic space-occupying brain lesions are present in the general population. When clinically indicated, additional imaging studies, biopsies, or both are performed to establish the diagnosis; however, complications and costs resulting from such subsequent investigations have received less attention.⁷² There is also the problem of false-negative scans, scans that fail to detect actual metastases. For example, in a CT study of the adrenal glands, Pagani⁷³ found metastatic NSCLC by percutaneous biopsy in 12% of radiologically normal adrenal glands. An additional problem is that the studies in this area often fail to specify exactly which elements make up the prescan clinical evaluation or that the studies use differing clinical indicators. For example, organ-specific findings such as headache and non-organ-specific complaints such as weight loss are both important.^{74,75} In addition, in many studies, abnormal findings on scans have not been pursued with biopsies to prove metastatic disease. Finally, there are few prospective randomized trials and outcome studies to guide appropriate use

and interpretation of extrathoracic scanning. It is hoped that careful studies will improve the workup of patients with lung cancer.

Adrenal and Hepatic Imaging

It is relatively common to encounter adrenal masses on routine CT, but many of these lesions are probably unrelated to the malignant process. A unilateral adrenal mass in a patient with NSCLC is more likely to be a metastasis than a benign lesion according to some studies,^{76,77} but not others.^{78,79} In the setting of clinical T1N0 NSCLC, adenomas predominate,^{80,81} whereas in the setting of large intrathoracic tumors or other extrathoracic metastases, adrenal metastases are more common.^{77,82} Many studies suggest that the size of a unilateral adrenal abnormality on CT is an important predictor of metastatic spread, but this is not a universal finding.⁸³ Lesions larger than 3 cm are more likely to signify metastases (see eFig. 53-9A), but benign disease is still possible.

For adrenal masses, CT, MRI, PET, percutaneous biopsy, and even adrenalectomy can be used to help distinguish benign from malignant disease. Well-defined, low-attenuation (fatty) lesions with a smooth rim on unenhanced CT are more likely to be benign adenomas,⁸⁴⁻⁸⁶ but the CT appearance of many lesions is insufficiently distinctive.⁸⁴ Follow-up scanning with repeat CT, serial ultrasonography, MRI (especially with chemical shift and dynamic gadolinium-enhanced techniques⁸⁷), or 6-β-iodo-¹³¹I-methyl-norcholesterol scanning⁸⁸ can sometimes help with the critical distinction between metastatic disease and adenoma. One study demonstrated the utility of PET-CT in differentiating between benign and metastatic malignant adrenal masses in patients with lung cancer.⁸⁹ In 110 adrenal masses ranging in size from 0.5 to 6.3 cm, the sensitivity, specificity, and accuracy for detecting metastatic disease were 97% (74 of 76), 94% (31 of 34), and 95% (105 of 110), respectively (eFig. 53-10). The positive predictive value was 95% (74 of 77), and the negative predictive value was 94% (31 of 33).

Percutaneous adrenal biopsy is a relatively safe and effective means of achieving a definitive diagnosis in doubtful cases and is especially important when the histology of the adrenal mass will dictate subsequent management.^{90,91} However, this procedure may be nondiagnostic or infeasible due to anatomic constraints. When insufficient material results from a biopsy, repeat aspiration or even adrenalectomy should be considered.^{83,84}

Most liver lesions are benign cysts and hemangiomas, but CT with intravenous contrast (or ultrasound) is often required to establish a likely diagnosis.³⁹ Percutaneous biopsy can be performed when diagnostic certainty is required. PET can detect liver metastases with a diagnostic accuracy ranging from 92% to 100% (eFig. 53-11) with rare false-positive results; however, the data in NSCLC are currently limited.⁹²⁻⁹⁴

Brain Imaging

In most studies, the yield of CT/MRI of the brain in NSCLC patients with negative clinical examinations is 0% to 10%,^{57,95-100} possibly rendering the test cost-ineffective.¹⁰¹ The negative predictive value of the clinical evaluation in this setting is 95% (range, 91% to 96%).

An association of positive findings between brain metastases and N2 disease in the chest and adenocarcinoma has been described.^{70,97,99} The false-negative rate, wherein patients return with brain metastases within 12 months of the original scan, is reported to be 3%.⁹⁹ False-positive scans can be a problem in up to 11% of cases due to brain abscesses, gliomas, and other lesions¹⁰²; therefore biopsy may be essential in cases in which management is critically dependent on the histology of the brain lesion.

MRI is more sensitive than CT of the brain and picks up more lesions and smaller lesions¹⁰³ but, in some studies, this has not translated into a clinically meaningful difference in terms of survival.¹⁰⁴ Although studies show that MRI can identify additional brain lesions in a particular patient, there are no studies that show that MRI is better than CT in its ability to identify additional patients with brain metastases from lung cancer. Therefore CT is an acceptable modality for evaluating patients for metastatic disease.³⁷ However, MRI remains the preferred modality at many centers.

Bone Imaging

False-positive abnormalities in radionuclide bone scintigraphy are common concerns because of the frequency of degenerative and traumatic skeletal damage and the difficulty in obtaining a definitive diagnosis via follow-up imaging or biopsy. With a negative clinical assessment, the negative predictive value for radionuclide bone imaging is 90%. PET has excellent performance characteristics for determining bone metastases (eFig. 53-12) with a specificity, sensitivity, negative predictive value, and positive predictive value all greater than 90%.^{94,105} The accuracy of PET was superior to radionuclide bone scanning in direct comparison studies.¹⁰⁶⁻¹⁰⁸

SUMMARY

The noninvasive clinical staging of lung cancer relies on the clinical evaluation and a number of readily available staging studies. The clinician must be wary of abnormal scans that may falsely suggest metastatic disease to the mediastinum and distant sites. Tissue confirmation by whatever means necessary is the rule rather than the exception before deciding on correct stage and the most appropriate treatment. If the patient has clinical findings indicative of metastatic disease, further evaluation is necessary because nearly 50% of the time the patient will have metastases. Even if the clinical evaluation is normal and imaging does not demonstrate suspicious extrathoracic abnormalities, PET imaging should be done where available in those being considered for curative-intent treatment.³⁷

INVASIVE DIAGNOSTIC AND STAGING TECHNIQUES

There are a myriad of methods that can be used to diagnose and stage patients with lung cancer. In certain circumstances, this is accomplished with a single test. For example, a positive percutaneous biopsy (or endoscopic ultrasound-guided fine-needle aspiration) of the adrenal

gland performed as a first test in a patient with a lung mass will provide both a diagnosis and a stage (stage IV) simultaneously. Every effort should be made to use the least invasive, most accurate procedure to expedite the patient's treatment, to minimize patient discomfort and inconvenience, and to ensure that the most appropriate treatment is rendered.

SPUTUM CYTOLOGY

Sputum cytology is the least invasive method for obtaining a diagnosis of lung cancer. Its accuracy depends on the expertise of the health care team in obtaining the sample (three samples are required), the preservation technique, and the size and location of the lesion. Central lesions are more likely to yield positive cytologic results than are peripheral lesions.¹⁰⁹ Sputum cytology should be obtained in all patients with central lesions who are at risk for more invasive biopsy techniques and considered in those with hemoptysis with or without a mass on chest radiography. Previously published systematic reviews have summarized the performance characteristics for sputum cytology for the diagnosis of suspected lung cancer.^{109,110} The ranges for sensitivity and specificity were 42% to 97% and 68% to 100%, respectively. The accuracy of sputum cytology is highly variable, so, in patients suspected of having lung cancer with negative sputum cytology, further testing should be performed.⁵³

TRANSTHORACIC NEEDLE ASPIRATION

Transthoracic needle aspiration (TTNA), usually under ultrasound (see Fig. 19-3), CT, or fluoroscopic guidance, is an expedient and relatively safe way to diagnose the primary tumor mass and establish a diagnosis of lung cancer (see Figs. 19-1 and 19-6). As a general rule, if a lesion is less than 3 cm in size and lateral to the mid-clavicular line (eFig. 53-13), TTNA should be considered if tissue diagnosis is necessary. One important point about TTNA or other nonsurgical biopsy techniques for peripheral pulmonary lesions is that they afford no preoperative benefit because they do not eliminate the need for surgery in most cases.¹¹¹ For a patient presenting with a solitary pulmonary nodule suspicious for malignancy (e.g., noncalcified, upper lobe, spiculated lesion in a long-term smoker), the diagnosis, stage, and therapy can be accomplished simultaneously with a thoracotomy and surgical resection. Thus TTNA may be essential only in certain situations: patients who are poor surgical candidates but who require tissue diagnosis prior to treatment, patients in whom a noncancerous lesion is strongly suspected (see Fig. 19-7), patients who request that a diagnosis of cancer be confirmed before considering surgery, and patients with high likelihood of metastatic disease (see Fig. 19-2). The sensitivity and specificity of TTNA are 90% and 97%, respectively¹⁰⁹ (see Chapter 19).

One drawback of TTNA is the risk of pneumothorax. Several investigations have reported a 15% to 45% risk of pneumothorax for CT-guided TTNA.^{17,112-114} Although pneumothorax may lead to hemodynamic compromise without therapeutic tube thoracostomy, in most cases of pneumothorax secondary to TTNA, treatment is not

required.¹¹⁵ The primary factors shown to increase the risk or incidence of pneumothorax are the presence of emphysema, a smaller lesion size, and a greater depth of needle penetration from the pleural surface to the edge of the lesion.

FIBEROPTIC BRONCHOSCOPY

More than 50% of patients with advanced-stage lung cancer will have involvement of the central airways either by bulky endobronchial disease, extension into the airways, or extrinsic compression of the airways by the tumor or by lymphadenopathy.¹¹⁶ Patients with known or suspected lung cancer may have symptoms due to endobronchial involvement that require airway inspection with bronchoscopy: shortness of breath, unilateral wheezing, hemoptysis, and cough. Endobronchial lesions can be visualized easily and biopsied through a flexible bronchoscope. The yield with three or more biopsies should approach 100% for centrally located lesions.^{117,118} Data from 4507 patients revealed that central endobronchial biopsies provide the highest sensitivity (74%), followed by brushings (61%) and washings (47%).¹⁰⁹ The combination provides a diagnosis in 88% of cases.¹⁰⁹ Endobronchial needle aspiration may be helpful especially when a rim of necrotic debris surrounds an endobronchial malignancy, because deeper tissue penetration may access viable tumor cells. The addition of endobronchial needle aspiration to forceps biopsies and brushings may improve sensitivity to 95% for the diagnosis of endobronchial cancer.^{119,120}

Submucosal and Peribronchial Lesions

When lung cancer presents with submucosal infiltration or extrinsic compression from peribronchial disease, endobronchial forceps biopsy has a lower yield (55%) than *transbronchial needle aspiration* (TBNA) (71%).¹²¹ In these situations, normal mucosal markings are often obscured and the surface is replaced with bronchial collateral vessels and firmer surface tissue, which may have to be penetrated to reach malignant cells. In addition, peribronchial tumor may be inaccessible to biopsy forceps. TBNA can be more effective if the lesion is close enough to the tracheobronchial tree to be encountered with a 1.3- to 1.5-cm-long needle. Of note, in cases like this when sampling error may be high, diagnostic yields may be improved by combining different methods or by using with *endobronchial ultrasound* (EBUS)-TBNA, which offers the advantages of real-time ultrasound and an adjustable needle length up to 4 cm.

Navigational Bronchoscopy

Navigational bronchoscopy provides a novel option for the diagnosis of peripheral lung lesions (see Chapter 22). It has a lower pneumothorax risk than TTNA and a higher diagnostic yield for peripheral lesions than traditional bronchoscopy.¹²² In general, there are three types of navigational bronchoscopy: (1) radial probe endobronchial ultrasonography, which is conventional radial EBUS using guide sheaths that allow the use of biopsy tools after successful navigation to the target; (2) virtual bronchoscopy, which creates a CT-based "road map" overlaid on endoscopic real-time images; and (3) electromagnetic navigational bronchoscopy which uses a virtual navigation system with

steerable devices.¹²³ A combination of navigational techniques has been shown to augment the diagnostic yield (88%) when compared to either radial probe endobronchial ultrasonography or electromagnetic navigational bronchoscopy alone.¹²⁴ A meta-analysis reported the accuracy and side effect profile of all available guided bronchoscopy procedures. In 39 studies, which together included more than 3000 patients, the pooled diagnostic yield was approximately 70% (with wide variation) and the pneumothorax rate was less than 2% (need for chest tube insertion less than 1%).¹²⁵ In addition, navigation may be used for placement of fiducial markers for stereotactic radiation treatments.¹²⁶

Bronchoscopy for Staging Lung Cancer

Initially, the role of bronchoscopy in staging lung cancer was limited to the determination of T (tumor) status. Now bronchoscopy has a crucial role in determining the presence of metastatic deposits of tumor in mediastinal lymph nodes, thus contributing to an accurate and a minimally invasive staging method for lung cancer.

The use of traditional TBNA in staging lung cancer has been reported to be both sensitive and specific in diagnosing spread of cancer to lymph nodes.¹²⁷⁻¹²⁹ The overall sensitivity of TBNA for NSCLC is 78% and the specificity is 99%.¹³⁰ The standard method of performing TBNA starts with a CT scan of the chest to guide needle aspirations toward the most involved group of lymph nodes. Lesions localized by CT can be accessed with bronchoscopy by measuring the number of CT slices above or below the carina (or other airway landmarks) and placing the needle the required distance above or below the landmark corresponding to that number of CT slices. When performing TBNA, the question invariably arises about the number of negative passes to perform before stopping. For various reasons, such as patient comfort and safety, need for sedation, and time spent by medical staff, it is imperative to manage the time for bronchoscopy. It has been shown that a plateau in yield for malignancy is achieved after seven passes with the needle through a lymph node.¹³¹ The importance of having a qualified and experienced cytopathologist on site cannot be overemphasized. Thorough interpretation by such individuals who are available for rapid on-site evaluation has been shown to enhance yield from TBNA.¹³² With the assistance of these individuals, the adequacy of sampling can be rigorously assessed. All samples should contain a preponderance of lymphocytes to define true nodal sampling. Specimens without lymphocytes should be deemed unsatisfactory, and the presence of respiratory epithelium should raise concerns about contamination.

TBNA allows for minimally invasive sampling of the mediastinum and hilar lymph nodes and potentially avoids more invasive procedures such as mediastinoscopy, mediastinotomy, and open thoracotomy. There is no doubt that the combined use of TBNA and CT can improve not only the diagnostic but also the staging evaluation of lung cancer. However, thus far, there has been wide variability in training and in usage of this helpful procedure. It is also operator-dependent, with certain techniques allowing for higher yields. See Chapter 22 for an in-depth discussion of bronchoscopy.

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS) is another modality that has significantly impacted lung cancer staging, primarily due to its superior ability to sample the posterior mediastinum through the esophageal wall. Currently, EUS with fine-needle aspiration is performed using real-time ultrasound. In pooled analysis of 2433 patients with lung cancer and mediastinal adenopathy, EUS had a sensitivity and specificity of 89% and 100%, respectively.^{37,130,133-156} In patients with lung cancer who have no adenopathy seen on CT, EUS has been shown to sample nodes as small as 3 mm in diameter. This is useful given the high incidence of metastasis found in normal-sized lymph nodes in lung cancer.¹⁵⁷ Based on surgical studies, it may be possible to predict the location of mediastinal lymph node metastases at certain levels based on the location of the tumor. This relationship may influence the use of EUS in certain patients without adenopathy on chest CT. Lymphatic pathways favor spread to aortopulmonary window nodes from left upper lobe tumors and to subcarinal nodes from left and right lower lobe lesions.¹⁵⁸ EUS has been studied in patients with known lung cancer without enlarged mediastinal lymph nodes on CT, and it has detected mediastinal involvement (stage III or IV disease) in up to 42% of cases.¹⁵⁹

In addition, EUS has the advantage of being able to stage lung cancer from locations outside the mediastinum. The left lobe of the liver, a substantial part of the right lobe of the liver, and the left (but not the right) adrenal gland can be identified and sampled in 97% of patients.¹⁶⁰ In addition, left pleural effusions can be visualized and sampled during an EUS procedure. EUS is increasingly being combined with EBUS for minimally invasive staging of lung cancer.¹⁶¹

ENDOBONCHIAL ULTRASOUND

Perhaps the greatest addition in the armamentarium for staging lung cancer is *endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA)*. EBUS-TBNA is indicated for the assessment of mediastinal and hilar lymph nodes and diagnosis of lung and mediastinal tumors. It can be used to sample the highest mediastinal (station 1), the upper paratracheal (station 2R, 2L), the lower paratracheal (station 4R, 4L), the subcarinal (station 7), as well as the hilar (station 10) and the interlobar (station 11) lymph nodes (Fig. 53-1A). The para-aortic (station 6), aortopulmonary window or subaortic (station 5), paraesophageal (station 8), and pulmonary ligament (station 9) lymph node stations are usually not accessible by this technique (see Fig. 53-1B). Pooled analysis of 2756 patients shows that EBUS-TBNA has a sensitivity and specificity of 89% and 100%, respectively.³⁷ If a patient presents with a lung mass and mediastinal lymphadenopathy in accessible lymph node stations, EBUS-TBNA should be considered as the test of first choice because this modality can provide a diagnosis and stage simultaneously. In addition, the role of EBUS in lung cancer has expanded to include preoperative mediastinal staging and tissue acquisition for molecular analysis in addition to immunohistochemical staining.¹⁶²⁻¹⁶⁴

The combination of EUS and EBUS has shown better yield than either technique alone. A pooled analysis from 7 studies and 811 patients showed a sensitivity and specificity

of 91% and 100%, respectively.^{37,135,139,140,165-168} These complementary procedures provide near-complete access to the mediastinum for staging,¹³⁵ even in the radiologically normal mediastinum.¹⁴⁰ Among patients with (suspected) NSCLC, a staging strategy combining endosonography and mediastinoscopy compared with mediastinoscopy alone was shown to have greater sensitivity for mediastinal nodal metastases and led to fewer unnecessary thoracotomies.¹⁶⁵

For further discussion of EBUS, see Chapter 22.

MEDIASTINOSCOPY

Mediastinoscopy is the historical gold standard for invasively staging the mediastinum in patients with known or suspected lung cancer; however, if local expertise is available, ultrasound-guided needle techniques (EBUS-TBNA, EUS, or their combination) are now recommended as the best first tests. If there is mediastinal lymph node enlargement regardless of FDG uptake on PET or if there is FDG uptake in a lymph mediastinal node regardless of its size, a surgical mediastinal procedure should be performed before

thoracotomy despite a negative needle technique. Mediastinoscopy is most often used to sample nodes of the paratracheal (station 4), and anterior subcarinal (station 7) region (see Fig. 53-1A). Because the subcarinal area is more difficult to sample, mediastinoscopy has a lower yield for lymph nodes in this area. An extended cervical mediastinoscopy can be carried out to reach aortopulmonary and para-aortic lymph nodes (stations 5 and 6) by using the same cervical incision as mediastinoscopy but dissecting into a different fascial plane. Alternatively, an anterior mediastinotomy (the so-called Chamberlain procedure) may be needed to sample lymph nodes in these aortopulmonary and para-aortic locations (stations 5 and 6) (see Fig. 53-1B). Overall, mediastinoscopy has a reported sensitivity of 78%, with a specificity of 100%.¹³⁰ Mediastinoscopy may also differentiate between stage IIIA and IIIB mediastinal involvement, which may be important for prognosis and potential therapy. As with any surgical procedure, mediastinoscopy has risks and limitations. It requires general anesthesia, with a morbidity of 2% and a mortality of 0.08%.¹³⁰

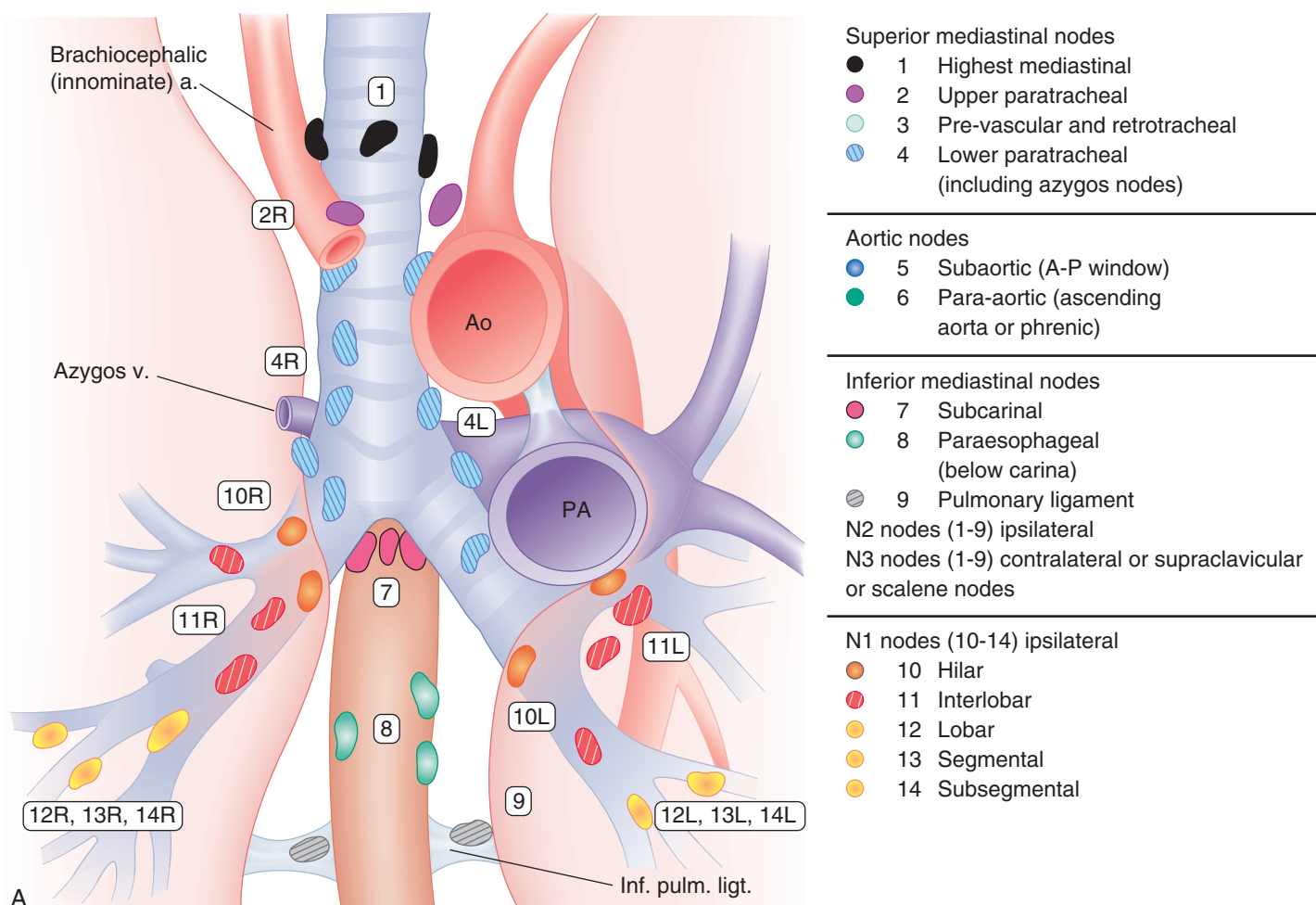


Figure 53-1 Mediastinal lymph node maps. A and B, the 14 stations for lymph nodes used in lung cancer staging are shown in association with anatomic landmarks. The N2 nodes are within the mediastinal pleural envelope (1-9) and the N1 nodes are outside the mediastinal pleural envelope, in the hilar (10) or intrapulmonary (11-14) locations. a, artery; Ao, aorta; A-P, aortic-pulmonary; PA, pulmonary artery; v, vein. (Redrawn from Mountain CF, Dresler CM: Regional lymph node classification for lung cancer staging. *Chest* 111:1719, 1997.)

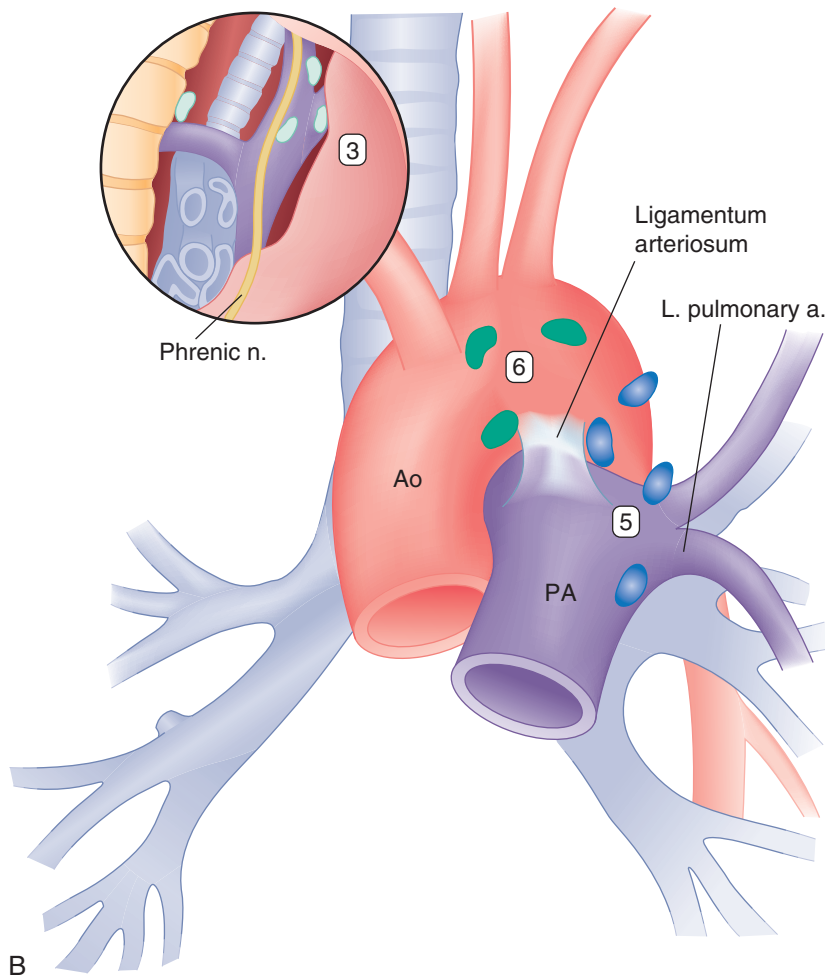


Figure 53-1, cont'd.

- Superior mediastinal nodes
- 1 Highest mediastinal
 - 2 Upper paratracheal
 - 3 Pre-vascular and retrotracheal
 - 4 Lower paratracheal (including azygos nodes)

- Aortic nodes
- 5 Subaortic (A-P window)
 - 6 Para-aortic (ascending aorta or phrenic)

- Inferior mediastinal nodes
- 7 Subcarinal
 - 8 Paraesophageal (below carina)
 - 9 Pulmonary ligament
- N2 nodes (1-9) ipsilateral
- N3 nodes (1-9) contralateral or supraclavicular or scalene nodes

- N1 nodes (10-14) ipsilateral
- 10 Hilar
 - 11 Interlobar
 - 12 Lobar
 - 13 Segmental
 - 14 Subsegmental

TREATMENT OF LUNG CANCER

The overall 5-year survival for patients diagnosed with lung cancer is a dismal 14%.¹⁶⁹ This figure has not changed substantially since the 1980s. The survival curves vary by stage, with earlier stage lung cancer patients enjoying a much better survival than patients with later stage disease. Treatment is based on the stage of the disease and the patients' performance status at the time therapy is initiated. In general, early stage disease is surgically managed, locally advanced disease is managed with chemotherapy and radiotherapy, and advanced disease is managed with chemotherapy with supportive care or supportive care alone. This paradigm has shifted toward more multimodality therapy (surgery, chemotherapy, and radiotherapy).¹⁷⁰⁻¹⁷³ This raises the issue of how best to manage patients with newly diagnosed lung cancer through their diagnosis, staging, and therapy. The ACCP guidelines on lung cancer recommend the use of a multidisciplinary lung cancer setting wherein patients can be evaluated by the major disciplines involved in the care of these patients, namely the pulmonologist, the thoracic surgeon, and the medical and radiation oncologists.¹⁷⁴ A "tumor board" that includes the aforementioned specialties, with the addition of chest radiology, pathology, nursing, and social work, should review

all new cases to ensure that patients receive optimal treatment and are considered for enrollment in clinical trials.

In addition to surgery, treatment such as chemotherapy and or radiotherapy can be applied in a neoadjuvant or adjuvant fashion. *Neoadjuvant* therapy indicates therapy given before the main treatment; it has the potential to reduce tumor volume, treat micrometastases, and improve outcomes. *Adjuvant* therapy is therapy given after the main treatment; it is aimed at treating any residual tumor or micrometastases with the aim of preventing tumor recurrence. The efficacy of treatments can be assessed by *median survival time* (MST) or by *progression-free survival* (PFS), the length of time a patient lives with lung cancer before it progresses.

PROGNOSTIC FACTORS FOR LUNG CANCER

Based on an analysis of large databases of inoperable lung cancer cases, the strongest predictors of survival are good performance score (Karnofsky scale), lower extent of disease (stage), age, and absence of weight loss.¹⁷⁵⁻¹⁷⁷ Some reports have shown female gender to be a predictor of better survival, but this varies between studies. Performance score and the presence or absence of symptoms are predictors of outcome even with resectable early-stage disease.¹⁷⁸⁻¹⁸⁰ For

Table 53-5 Summary of Current Treatment Strategies for Non–Small Cell Lung Cancer

Stage	Surgery	Chemotherapy	Radiotherapy	Chemoradiotherapy	Comments
I and II	1st line	Adjuvant—stage IIA, IIB	2nd line	No	Survival improvement with adjuvant therapy (= 5%) Radiotherapy for inoperable patients
IIB (T3N0M0) Pancoast	1st line	No	No	1st line—neoadjuvant	Neoadjuvant chemoradiotherapy improves survival in this subset of stage IIB
IIIA	1st line	Adjuvant treatment—in totally resected IIIA	Controversial	1st line	Combined chemoradiotherapy followed by surgery is feasible, but more data are needed to recommend routinely
IIIB Unresectable	No	No	No	1st line	Treatment similar to unresectable stage IIIA
IV	No	1st line*	No	No	Radiotherapy is used for palliation only All stage IV should have mutational analysis, including <i>EGFR</i> , <i>EML4-ALK</i> , and <i>KRAS</i> .

Bevacizumab is approved as an adjunct to chemotherapy in the first-line setting in patients with nonsquamous histology and no other contraindications.

*The targeted therapies are indicated as first-line treatment for those with advanced NSCLC and documented *EGFR* mutations or *EML4-ALK* fusion. Erlotinib is FDA-approved as first-line treatment of metastatic NSCLC for patients whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations.

EGFR, epidermal growth factor receptor; FDA, U.S. Food and Drug Administration; NSCLC, non–small cell lung cancer.

example, in stage I NSCLC patients undergoing curative resection, those who were symptomatic at presentation had worse survival than those who were asymptomatic.¹⁷⁹ Although individual reports have noted superior survival for patients with one cell type of NSCLC versus another, the general consensus in the literature is that histologic subtypes of NSCLC are not a major predictor of survival.^{178,179,181} Absence of smoking or smoking cessation has been associated with improved survival. The maximal standard uptake value of the primary tumor on PET has been inversely correlated with survival.¹⁸²

In more recent years, there have been numerous reports that various molecular markers are associated with outcome. Some of the best known markers include *KRAS*, *epithelial growth factor receptor (EGFR)*, *EML4-ALK* translocation, p53, p16, and BCL2. However, in many instances, the results are conflicting about the prognostic significance of these individual molecular markers,¹⁸³⁻¹⁸⁵ perhaps due to the types of cases under review and to individual laboratory variations in techniques for measuring these molecular markers. In a meta-analysis, *KRAS* mutations were associated with poorer survival, especially in adenocarcinoma in which the hazard ratio was 1.6 (95% CI, 1.3 to 2).¹⁸⁶ Testing the genetic profile of samples obtained from metastatic lymph nodes or malignant pleural effusions in those patients with stage III and IV disease has become standard practice, because this allows for the selection of targeted drug therapies specific for the mutation as first-line chemotherapy.

NON–SMALL CELL LUNG CANCER TREATMENT BY STAGE

This section presents a discussion of the treatment of NSCLC by stage and cell type, followed by a discussion of the treatment of SCLC. Table 53-5 presents an overview of treatment strategies for NSCLC based on stage.

Stage I

In the most recent staging system for NSCLC, stage I NSCLC is broken down into stage IA (tumors ≤ 2 cm [T1a] (eFig. 53-14A) and tumors between 2 and 3 cm [T1b]) (see eFig.

53-14B) and stage IB (tumors between 3 and 5 cm [T2a]) (see eFig. 53-15). All stage I tumors are completely surrounded by lung parenchyma greater than 2 cm away from the carina and do not invade the chest wall or parietal pleura (Fig. 53-2). Stage I lung cancer does not include patients who have malignant lymph node disease or patients with metastatic disease. Thus the TNM classification is either T1aN0M0, T1bN0M0 (stage IA), or T2aN0M0 (stage IB). The differences between the two are the size of the primary tumor and the survival after surgical resection. Although stage I disease offers the best chance for long-term survival, the sad fact is that only 15% of all lung cancers present with stage I disease.^{187,188}

The current treatment for stage I lung cancer is surgery alone. The surgical procedure of choice is a lobectomy or pneumonectomy with mediastinal lymph node sampling. It should be recognized that the patient must be a reasonable surgical candidate. The 5-year survival for surgically resected stage IA lung cancer is 73%, whereas the survival for stage IB lung cancer is 58%.³³ Local postoperative radiation for stage I and II lung cancer, after either complete or incomplete resection of the tumor, has not been found to be of any benefit.¹⁸⁷ Postoperative adjuvant chemotherapy has not been shown to improve survival for those with resected stage I disease.¹⁸⁹ A further discussion of postoperative adjuvant therapy is presented later (see “Stage IIIA”).

Some patients are surgically resectable but medically inoperable, usually because the patient does not have the pulmonary reserve to tolerate a lobectomy. These patients, particularly those with T1 tumors, may be able to tolerate a wedge resection or segmentectomy of their tumor as opposed to a lobectomy or pneumonectomy. In such cases, the local recurrence rate is higher than that of a complete resection, but the overall 5-year mortality is no different.¹⁹⁰ However, for patients with smaller peripheral stage I lung cancers, anatomic segmentectomy may offer local control, the opportunity for prolonged disease free survival, and overall survival that is comparable to lobectomy.^{190a} Still, whenever possible, a complete anatomic resection is preferred over a minimal resection. For discussion of

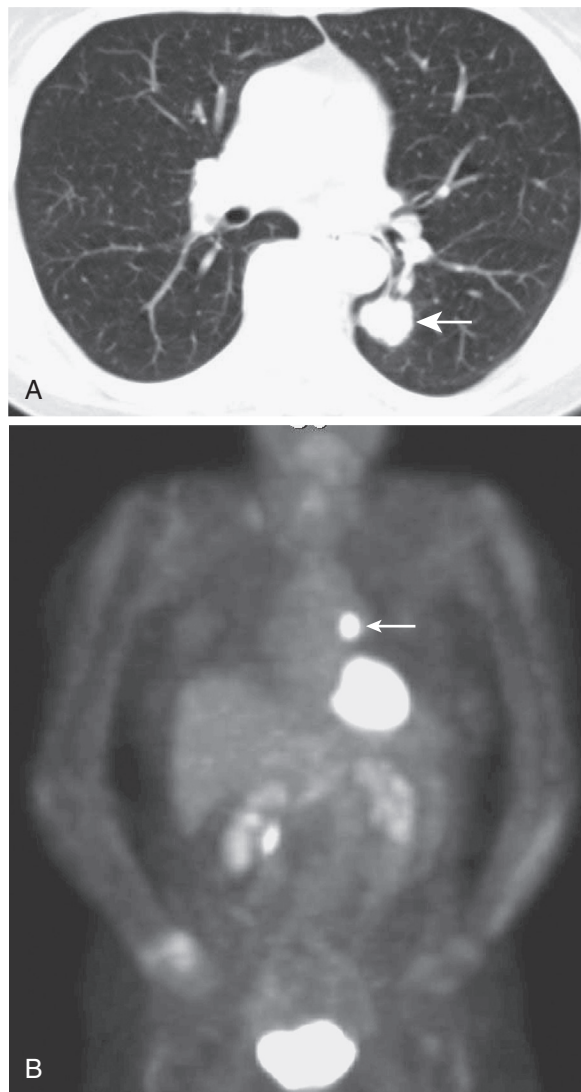


Figure 53-2 Stage I disease. CT (A) and PET (B) scans of a patient with T1N0M0 tumor (arrows).

radiofrequency ablation and other nonsurgical treatments, see Chapter 19.

Patients who are “close calls” for surgery should be thoroughly evaluated by both a pulmonologist and a thoracic surgeon before making a decision on operability. As previously stated, there is a difference between a patient who is resectable and a patient who is operable. Chapter 27 is devoted to the preoperative evaluation of patients with lung disease, but a brief review is warranted here. Patients with a postoperative percent predicted forced expiratory volume in 1 second or diffusion capacity less than 40% will have a higher morbidity and mortality following lung cancer surgery. Patients with borderline values preoperatively should be referred for a differential ventilation-perfusion scan for a better prediction of postoperative function. When there is still a question, a cardiopulmonary exercise test can be obtained. Compared with those with an oxygen consumption greater than 20 mL/kg/min, patients with an oxygen consumption between 11 and 19 mL/kg/min have a higher morbidity but no greater mortality and those with

an oxygen consumption less than 10 mL/kg/min have both a higher predicted morbidity and mortality.¹⁹¹

For patients who either refuse surgery or are deemed medically unfit for surgery, primary radiotherapy for cure can be considered. This approach was evaluated in a meta-analysis of 1 randomized and 35 nonrandomized trials.¹⁹² The studies were heterogeneous, and the 5-year cancer-specific survival ranged between 13% and 39%. The authors concluded that, even in patients with severe emphysema, radiation therapy can be tolerated if careful planning with three-dimensional conformal techniques is undertaken. *Conformal* indicates that the radiation is designed in 3 dimensions to match the shape of the tumor allowing maximal targeting to the tumor with minimal injury to adjacent normal tissue.

More recently, stereotactic body radiation therapy has been introduced as a highly precise and accurate delivery method of highly conformal and dose-intensive radiation to small-volume targets. This method is also referred to as stereotactic ablative body radiotherapy and stereotactic radiosurgery. It is a more aggressive dose intensification than could previously be achieved using conventional radiotherapy methods.¹⁹³

In the Radiation Therapy Oncology Group trial (ROTG 0236), patients with biopsy proven stage I NSCLC deemed medically inoperable received stereotactic body radiation therapy with 60 Gy in three fractions. Primary tumor control of 98%, regional control of 87%, and overall survival of 56% at 3 years were achieved.¹⁹⁴ This study and others (ROTG 0618) have demonstrated a dose-response relationship that favors more intensive regimens with biologically equivalent doses of more than 100 Gy consistently resulting in more than 90% primary tumor control for T1 tumors and overall survival greater than 50%. A meta-analysis demonstrated an overall survival improvement with stereotactic body radiation therapy compared with conventionally fractionated radiation therapy.¹⁹⁵

Stage II

Stage II NSCLC lung cancer is divided into stage IIA and stage IIB. Stage IIA is defined as a T1a-T2aN1M0 and T2bN0M0 disease and stage IIB includes T2bN1M0 and T3N0M0. The 5-year survivals for stage IIA and IIB are 46% and 36%, respectively.

Stage IIA lung cancer is quite uncommon, representing between 1% and 5% of patients treated in several surgical series.¹⁹⁶⁻²⁰¹ Stage IIB cancer may represent up to 15% of surgically resected cases.^{189,196,198,201} For stage IIA and IIB cancer, surgical therapy is the treatment of choice. There is no benefit to postoperative radiotherapy. The value of adjuvant chemotherapy after surgery is discussed later (see “Stage IIIA”) but, in short, adjuvant chemotherapy is recommended for all patients with resected stage II disease. With chest wall invasion (T3N0M0) (eFig. 53-16), an en bloc resection of the tumor and chest wall is the treatment of choice. A specific discussion of the evaluation and treatment of Pancoast tumor is discussed later in the chapter.

The outcome of lung cancer surgery is improved when the surgery is performed at hospitals with a higher volume of procedures.¹⁹⁷ It is also important that the surgery be performed by a thoracic surgeon; when lobectomy is

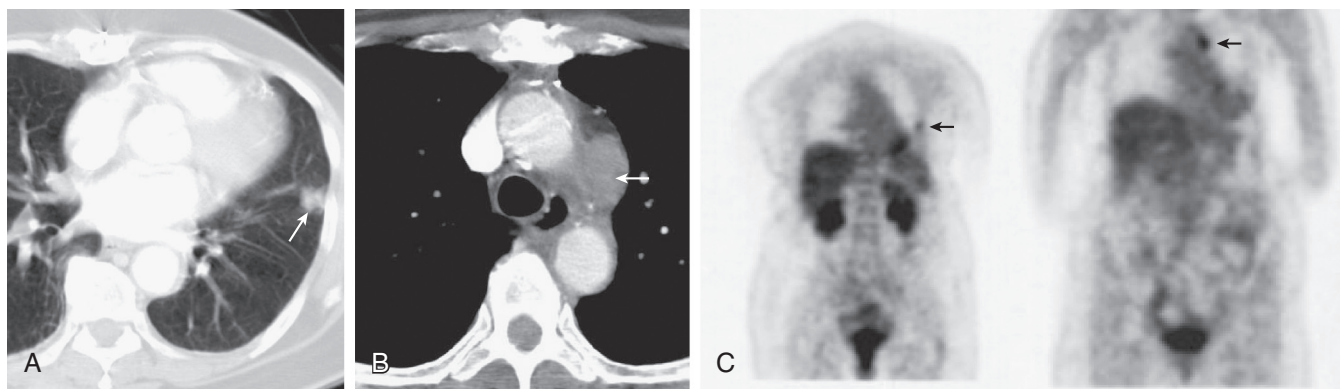


Figure 53-3 Stage IIIA disease. **A**, CT depicts a primary tumor mass invading the chest wall, resulting in stage IIIA non-small cell lung cancer (NSCLC; T3N2) (arrow). **B**, CT depicts enlarged aortopulmonary lymph node (arrow). **C**, PET with uptake in primary tumor (left image, arrow) and lymph node (right image, arrow).

performed by a thoracic surgeon compared to a general surgeon, mortality is nearly halved.²⁰²

Stage IIIA

Stage IIIA NSCLC represents a heterogeneous group of patients with N2 disease (Fig. 53-3) and includes T3N1 patients. In addition, within the new staging system, patients with T4N0-1 have been down-staged to IIIA from their previous classification.^{33,203}

For carefully selected T4N0-1M0 patients, surgery may be indicated with or without neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (superior sulcus tumors) (eFigs. 53-17 and 53-18).²⁰⁴ Individuals with T4N0-1 disease due to main carinal involvement have been treated with carinal resection with or without pulmonary resection. Carinal resection carries an operative mortality of 10% to 15% and 5-year survival of approximately 20% in carefully selected series. Patients who are T4N0 solely due to tumor nodules within the ipsilateral nonprimary lobe (eFig. 53-19) have a 5-year survival of around 20% with surgery alone.²⁰⁵

There is substantial debate over what constitutes resectable IIIA (N2) disease. However, there is no debate that T3N1 disease is best treated with surgical resection. At surgery, when a complete resection of the lymph nodes and the primary tumor is possible, some patients are found to have occult N2 metastasis. If so, these patients are best served by a resection of all known disease and then by consideration for adjuvant chemotherapy.^{33,203}

It is less certain how best to treat patients when N2 (single or multiple station) metastases are documented before thoracotomy. The new ACCP guidelines used the groupings of infiltrative stage III (N2/N3) tumors and stage III with discrete N2 involvement. In infiltrative stage III with N2/N3 involvement, the mediastinal nodes can no longer be clearly distinguished and measured (eFig. 53-20). These patients have extensive tumor infiltration in the mediastinum, which partially surrounds the major structures. In patients with infiltrative stage III (N2/N3), good performance score, and minimal weight loss ($\leq 10\%$), the recommended treatment with curative intent is with concurrent chemoradiotherapy.^{33,203}

Two multicenter trials have concluded that concurrent chemoradiotherapy is superior to sequential therapy with chemotherapy followed by thoracic radiotherapy.^{206,207}

Concurrent therapy, however, is associated with a higher rate of severe esophagitis than is sequential therapy. The recommended chemotherapy is a platinum doublet and the most common agents are etoposide and cisplatin.²⁰⁸⁻²¹⁰ Three cooperative group trials of definitive chemoradiotherapy for unresectable stage III had an MST of 19 to 22 months with 2-year survivals of 40% to 45% and a 5-year survival of approximately 20%.

For patients with discrete N2 involvement, the ACCP guidelines recommend that the treatment plan be discussed by a multidisciplinary team. Either definitive chemoradiotherapy or induction therapy followed by surgery is recommended over either surgery or radiation alone. These recommendations were largely influenced by the two cooperative group trials that evaluated the role of surgery in patients with N2 disease.^{208,211} The European trial randomized patients with histologically proven N2 disease to radiotherapy or surgery after initial induction therapy with three cycles of a cisplatin doublet chemotherapy.²¹¹ The MST was 16 months in the surgery arm and 17 months in the radiotherapy arm.²⁰⁶ The 5-year survival in both arms was 16% and 14%, respectively, and was not significantly different. The North American trial also required pathologic proof of N2 disease and randomized patients to completion radiotherapy or surgery after induction of two cycles of etoposide and cisplatin with concurrent thoracic radiotherapy of 45 Gy in 25 fractions over 5 weeks.²⁰⁸ The MST was 24 and 22 months in the surgery and radiotherapy arms, respectively, with 5-year survivals of 27% and 20% (hazard ratio 0.87, $P=0.24$). These survival differences were not statistically significant. However, the PFS favored the surgery arm. A subset analysis in those having only a lobectomy after induction therapy did better than a matched group receiving only chemoradiotherapy. This was an unplanned subset analysis that weakens the strength of this analysis. Accordingly, the role of surgery for stage III with discrete N2 disease has not been definitively answered.

In patients with stage II or IIIA totally resected NSCLC, adjuvant chemotherapy with four cycles of a cisplatin-based doublet chemotherapy is recommended.^{203,212} The *Lung Adjuvant Cisplatin Evaluation* (LACE) meta-analysis evaluated all stages of totally resected disease and observed a 5.4% overall 5-year survival benefit with adjuvant chemotherapy. The benefit was the greatest for patients with stage II and III disease and those with better performance

status. The role of postoperative radiation therapy for patients with totally resected stage III (N2) remains controversial. Local recurrence varies in reports from 20% to 60%. Some nonrandomized trials suggest possible benefit from postoperative radiation therapy.^{213,214} Accordingly, this option should be discussed with fit patients. A randomized phase III *Adjuvant Radiotherapy* (ART) trial is underway to evaluate postoperative radiation therapy in these patients.

Stage IIIB

Stage IIIB is also a heterogeneous group and includes T4N2M0 and any T N3M0 patients. There are no phase III randomized trials to date that demonstrate that neoadjuvant chemoradiotherapy followed by surgery for stage IIIB disease results in prolonged survival compared with chemoradiotherapy alone.²⁰³

Patients with unresectable stage IIIB NSCLC are treated the same as those with unresectable IIIA disease. The MST is generally 19 to 22 months, with a 5-year survival of 10% to 20%. The randomized trials of chemoradiotherapy included both stage IIIA and IIIB disease participants so it is not possible to separate out the survival of stage IIIB patients specifically.^{209,210} Concurrent chemoradiotherapy is recommended for both unresectable stage IIIA and IIIB disease.²⁰³ Trials have evaluated multiple daily fractions of thoracic radiotherapy, but there are no convincing data that hyperfractionated thoracic radiotherapy (the same total dose of radiation therapy split into two treatments in the same day) is superior to standard once-daily treatment.

Stage IV

Stage IV NSCLC is generally considered to be incurable with 5-year survivals of 1% to 3%. The goal of therapy is to try to control the disease and palliate symptoms. Major response rates with current chemotherapy regimens are 10% to 30%. Patients who respond to chemotherapy may gain an additional 3 to 9 months of life on average but eventually relapse and die of their disease. In previous trials in the 1970s and 1980s, patients were randomized to best supportive care or systemic chemotherapy. A meta-analysis evaluated eight of these randomized trials, including more than 700 patients.²¹⁵ Each of these trials used a cisplatin-based chemotherapy versus supportive care. With best supportive care, the MST was 4 months and the 1-year survival was 15%; with chemotherapy, there was an increase in the MST of 1.5 months and an increase in 1-year survival of 10%. In the 1990s, a number of new chemotherapy agents were introduced, including paclitaxel, docetaxel, irinotecan, vinorelbine, and gemcitabine. Phase III trials have incorporated these newer agents in combination with cisplatin or carboplatin.²¹⁶

Trials comparing single-agent chemotherapy to a chemotherapy doublet containing a platinum compound have shown that the chemotherapy doublet is superior. Treatment with three drugs has not been shown to be superior to that with two drugs. Large randomized trials have tried to identify the optimum chemotherapy doublet.²¹⁷⁻²¹⁹ The results were uniformly similar, with response rates of 20% to 30% and MST of 7 to 9 months. No one platinum doublet has been shown to be superior. The chemotherapy combinations did have different toxicity profiles.

Histology influences response to certain chemotherapeutic agents. A large phase III trial randomized patients to cisplatin and pemetrexed or gemcitabine and cisplatin. Whereas there was no difference in the overall survival for the 847 patients with adenocarcinoma, the survival was significantly better with the pemetrexed regimen (MST 12.6 months vs. 10.9 months). Conversely, squamous cell cancers had superior survival with the gemcitabine regimen (MST 10.8 months vs. 9.4 months).²²⁰ The ACCP guidelines recommend that chemotherapy for stage IV NSCLC should be guided by histology. Pemetrexed should be limited to patients with nonsquamous NSCLC.²²¹ In patients with a good performance score, a platinum-based doublet chemotherapy regimen is recommended.

In the Eastern Oncology Group Trial (E4500), patients with nonsquamous histology were randomized to treatment with carboplatin and paclitaxel with or without bevacizumab, a monoclonal antibody that inhibits a vascular endothelial growth factor. Bevacizumab was continued as maintenance therapy after six cycles of therapy in those responding to treatment or with stable disease.^{221a} Patients in the bevacizumab arm had a higher response rate (35% vs. 15%) and better survival (MST 12.3 months vs. 10.3 months; 2-year survival 44% vs. 15%). A meta-analysis of four randomized trials of NSCLC patients treated with bevacizumab demonstrated increased PFS and overall survival in patients treated with combination chemotherapy and bevacizumab than in patients treated with chemotherapy alone.²²² In selected patients with nonsquamous histology and good performance scores, the addition of bevacizumab is recommended. Hemoptysis, uncontrolled brain metastasis, deep venous thrombosis, and anticoagulation treatment are contraindications to using bevacizumab.²²¹

In patients with stable or responding disease whose initial therapy included bevacizumab, maintenance treatment with bevacizumab until progression is generally recommended. For patients with an initial platinum-based doublet chemotherapy and responding or stable disease, maintenance treatment with pemetrexed has been shown to prolong survival.²²¹ A randomized Eastern Oncology Group Trial is currently evaluating maintenance treatment with bevacizumab versus pemetrexed versus the two-drug combination. This is likely to be a definitive study on maintenance therapy.

Targeted Therapy

In 2004, investigators identified activating mutations in the tyrosine kinase domain of *EGFR* that predicted response to novel *tyrosine kinase inhibitors* (TKIs) in selected patients with NSCLC^{223,224} (see Chapter 51). This activating mutation was found to be a “driver” mutation because it was causal in tumor development; the mutation activated EGFR signaling thereby driving and sustaining the tumor. *Driver* mutations, as opposed to the much more common *passenger* mutations, thereby render a tumor vulnerable to blockade of that single pathway.

Multiple studies have demonstrated that the phenotype most associated with response to the EGFR-TKIs, gefitinib and erlotinib, includes adenocarcinoma, never-smoker, female, and East Asian descent. Subsequent reports have shown that these are the groups most likely to harbor the

activating *EGFR* mutations. Emerging data have demonstrated that *KRAS* and *EGFR* mutations are almost always mutually exclusive and that patients with *KRAS* mutations do not respond to *EGFR*-TKIs.²²⁵ Erlotinib has been shown in a phase III trial in previously treated patients with NSCLC to result in superior survival versus placebo (6.7 vs. 4.7 months).²²⁶ On this basis, erlotinib was approved by the U.S. Food and Drug Administration (FDA) for second-line treatment. A phase III trial of gefitinib in second-line therapy failed to show a significant improvement in survival and approval for second-line therapy was withdrawn by the FDA in North America.²²⁷ In a landmark phase III trial in East Asia, patients with untreated stage IV disease were randomized to gefitinib or platinum-based chemotherapy. Of the 437 patient samples tested, 60% were positive for an activating mutation of *EGFR*. This subgroup had a significantly better response and PFS after gefitinib than after chemotherapy. The subgroup negative for mutations responded better and had a better PFS after chemotherapy.²²⁸

Since that key study of first-line treatment with an *EGFR*-TKI or with chemotherapy, there have been multiple additional trials in patients with *EGFR* activating mutations. A meta-analysis of the use of *EGFR*-TKI in a first-line (13 trials) or in a second-line setting (7 trials) observed a PFS advantage (HR 0.43) in those patients with an activating *EGFR* mutation treated with an *EGFR*-TKI in the first-line setting.²²⁹ Results were similar when the *EGFR*-TKI was used in the second-line setting in those with an activating *EGFR* mutation (HR 0.34 for PFS). For patients whose tumor contains an activating *EGFR* mutation, the response rate to an *EGFR*-TKI is 60% to 80% with a median PFS of 9 to 12 months and an overall survival of approximately 2 years.²³⁰ As a result of these and other studies, erlotinib is FDA-approved as first-line treatment of metastatic NSCLC for patients whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations.

The *anaplastic lymphoma kinase* (*ALK*) fusion gene is the second most common driver mutation for which there is an effective TKI. The efficacy of the first generation *ALK*-TKI, crizotinib, was demonstrated in a phase I study that was expanded and resulted in a rapid FDA approval of the drug. Of 143 patients with stage IV NSCLC with an *ALK* fusion, the objective response rate was 61% and a median PFS was 9.7 months. The estimated 12-month survival was 75% and the MST had not been reached at the time of publication.²³¹

In a randomized phase III trial, advanced stage NSCLC patients with an *ALK* fusion who failed one prior platinum-based treatment were treated with crizotinib (*ALK*-TKI) or single agent pemetrexed or docetaxel.²³² The median PFS was 7.7 months in the crizotinib group compared with 3 months in the chemotherapy group (HR 0.49). The response rate favored crizotinib treatment (65% vs. 20%), even though there was no significant difference in survival between the two treatment arms. The FDA has approved ceritinib for the treatment of NSCLC patients with an *ALK* fusion who were previously treated with crizotinib, to which some cancers develop resistance.^{232a,232b}

The Lung Cancer Mutation Consortium consists of 14 cancer centers in the United States and is sponsored by the National Cancer Institute. These centers have tested more

than 1000 lung adenocarcinomas to look for driver mutations in 10 genes with a goal of determining treatment based on the molecular subtypes.²³³ A driver mutation was detected in 63% of 733 fully genotyped cases. The driver mutations identified were *KRAS* (25%), activating *EGFR* (15%), *ALK* rearrangements (8%), *BRAF* (2%), *HER2* (2%), *PIK3CA* (1%), and *MET* amplification (1%). Results were used to select targeted therapy or targeted therapy trials in 279 patients with a driver mutation (28% of 1007). This study demonstrated the potential for multiplex genomic testing in patients with advanced NSCLC and is certainly the direction for the future.

Recently, joint guidelines by the College of American Pathologists, International Association for the Study of Lung Cancer, and the Association of Molecular Pathology have recommended that all patients with advanced stage adenocarcinomas should be tested for *EGFR* and *ALK* mutations and patients should not be excluded from testing based on clinical characteristics. These results should be used to select patients for targeted therapy with *EGFR*-TKIs or *ALK*-TKIs. Ideally, this testing should be performed before initial treatment of advanced stage lung cancer.²³⁴ In addition to targeted therapy based on mutation analysis, immunotherapy is a promising future direction in therapy for NSCLC. There are several large clinical trials underway using vaccines and checkpoint inhibitors which may provide additional therapeutic options.^{234a}

SMALL CELL LUNG CANCER

SCLC accounts for approximately 15% of all lung cancers. This cell type has the strongest association with cigarette smoking and is rarely observed in a never-smoker. It is the cell type most commonly associated with paraneoplastic syndromes such as the syndrome of *inappropriate (excessive) antidiuretic hormone secretion* (SIADH), ectopic corticotropin secretion, *Lambert-Eaton myasthenic syndrome* (LEMS), and sensory neuropathy.

SCLC usually presents as a centrally located mass in the hilum on chest radiograph (eFig. 53-21) and may be associated with obstructive pneumonia. In 5% or fewer cases, SCLC may present as a solitary pulmonary nodule/mass (eFig. 53-22). SCLC is generally staged according to the Veterans Administration Staging System, and classified as *limited disease* (LD) or *extensive disease* (ED). LD is confined to one hemithorax, the mediastinum, and the ipsilateral supraclavicular lymph nodes, and the disease can be encompassed adequately in a safe radiation portal.²³⁵ ED is any disease spread beyond these limits. Malignant pleural effusion or disease extending to the contralateral supraclavicular or hilar lymph nodes is generally considered to be ED. More recently, it has been proposed that the new TNM staging system (7th edition) should also be used for small cell lung cancer. The clinical stage groupings of I to IV were predictive of overall survival and the findings were validated in a cohort from the Surveillance Epidemiology and End Results registry²³⁶ and the California Cancer Registry.²³⁷ The survival rate for patients with LD with pleural effusions was intermediate between those with ED and LD without pleural effusions. The TNM staging is most helpful in potentially resectable patients with T1-2N0 disease. Accordingly, it would be advisable to use both the TNM for

tumor registries and clinical trials to define patients with minimal disease.

After establishing the histologic diagnosis of SCLC, patients are usually staged with MRI of the brain, CT of the chest (through the adrenal glands), and bone scan or PET. In an evidence-based review of the literature, staging using PET was compared with conventional staging using non-PET imaging. Of 267 patients with LD by conventional imaging, 16% were upstaged by PET. Of 199 patients with ED, PET resulted in 11% being down-staged. In total, staging with PET improves the accuracy of initial staging and radiotherapy planning.²³⁵ If a PET scan is obtained, then a bone scan may be omitted. In the unusual case when SCLC presents as a peripheral nodule, the treatment of choice is surgical resection followed by adjuvant chemotherapy and possibly sequential thoracic radiotherapy. Careful preoperative staging should be performed in these individuals to rule out metastatic disease. Pre-resection mediastinoscopy should also be performed in all patients being considered for resection with curative intent. If there are mediastinal node metastases, then surgery should be abandoned, and the patient treated with concurrent chemoradiotherapy as outlined later. The 5-year survival for peripheral SCLC that is treated with surgery and adjuvant therapy is approximately 40% to 50%.^{238,239} Approximately one third of patients have LD at diagnosis. LD-SCLC has a response rate of 70% to 80% with standard chemotherapy and thoracic radiotherapy (eFig. 53-23), and a complete clinical response of 50% to 60%. In a meta-analysis of trials with chemotherapy alone versus combined chemotherapy and thoracic radiotherapy, survival was significantly better with combined modality therapy. A meta-analysis evaluated the timing of thoracic radiotherapy.²⁴⁰ Early thoracic radiotherapy (<9 weeks from the start of chemotherapy) resulted in a 5.2% increase in 2-year survival. The interval from start of treatment to the end of radiotherapy was also identified as an important predictor of outcome.²⁴¹ Accordingly, data suggest that thoracic radiotherapy should begin early and be completed quickly.²³⁵ Chemotherapy usually consists of a platinum-based regimen. The two most commonly used regimens are etoposide and cisplatin or etoposide and carboplatin. Chemotherapy beyond four to six cycles has not been shown to prolong survival.

The National Comprehensive Cancer Network and the ACCP guidelines recommend treatment with four to six cycles of a platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan.²³⁵ Multiple trials have evaluated a number of the novel molecularly targeted agents but to date none have shown improved outcomes when added to standard treatment of small cell lung cancer.²⁴² A number of trials evaluating insulin-like growth factor receptor inhibitors, antiangiogenesis, and immunomodulatory drugs are under evaluation.

If a patient with SCLC achieves a complete remission, then there is a 50% chance of development of cranial metastasis within the next 2 years. A meta-analysis of seven randomized trials of *prophylactic cranial irradiation* (PCI) versus no PCI for patients in complete remission reported an observed beneficial effect after PCI, with a 5.4% increase in absolute survival (20.7% vs. 15.3%) at 3 years.²⁴³ The major questions raised by the meta-analysis concern the optimal dose of PCI and the neuropsychological sequelae.

PCI is recommended in patients who achieve a complete remission with initial therapy. PCI has also been shown to result in a survival advantage in patients with ED-SCLC who achieve a complete or partial response to initial therapy.²⁴⁴ PCI at 25 Gy in 10 fractions is the standard dose fractionation used in SCLC.²⁴⁵

When patients relapse after initial therapy, the median survival is 3 to 4 months. There are no cures with second-line therapy. If a patient has been off treatment for 6 months or longer, then it is reasonable to use the same agents that he or she received initially. If initial therapy did not include a platinum agent, then second-line therapy should be with a platinum-containing doublet. Currently, the only drug approved for second-line treatment of SCLC by the FDA is single-agent topotecan.^{235,246} Other single agents such as oral etoposide, paclitaxel, docetaxel, irinotecan, gemcitabine, and amrubicin are active but are not yet approved by the FDA for second-line treatment of SCLC. Amrubicin is commercially available and approved for second-line treatment in Japan but is not available in the United States. No molecularly targeted therapy has been approved for SCLC in either the first-line or second-line setting.

PALLIATIVE CARE

Although much of this chapter is devoted to efforts to cure lung cancer, most patients will eventually succumb to their disease. Although pulmonologists are adept at providing supportive care in the intensive care unit, caring for the ambulatory dying patient with lung cancer requires special consideration (see Chapter 104). There is a vast literature on ambulatory pain management, the use of interventional pulmonary techniques such as tumor ablation and stent placement to relieve malignant airway obstruction (see Chapter 19), and the use of hospice to provide end-of-life care in the home setting. With the tools now available to physicians, patients need not suffer debilitating cough, nausea, dyspnea, or pain. Pulmonologists are encouraged to provide “aggressive palliation” with the same conviction that they provide treatments for critically ill patients in the intensive care unit.²⁴⁷

SPECIAL CONSIDERATIONS IN LUNG CANCER

SUPERIOR SULCUS TUMORS AND PANCOAST SYNDROME

Pancoast syndrome is a constellation of symptoms and signs that include shoulder and arm pain along the distribution of the eighth cranial nerve trunk and first and second thoracic nerve trunks, Horner syndrome, and weakness and atrophy of the hand.²⁴⁸⁻²⁵⁰ The underlying cause is usually local extension of an apical lung tumor located in the superior pulmonary sulcus (Pancoast tumor) (see eFig. 53-17). Pancoast syndrome is present in approximately one third of patients with superior sulcus tumors. The most common cause of this symptom complex is NSCLC; however, SCLC and a number of other types of tumors and infections may rarely present in this manner.²⁴⁸

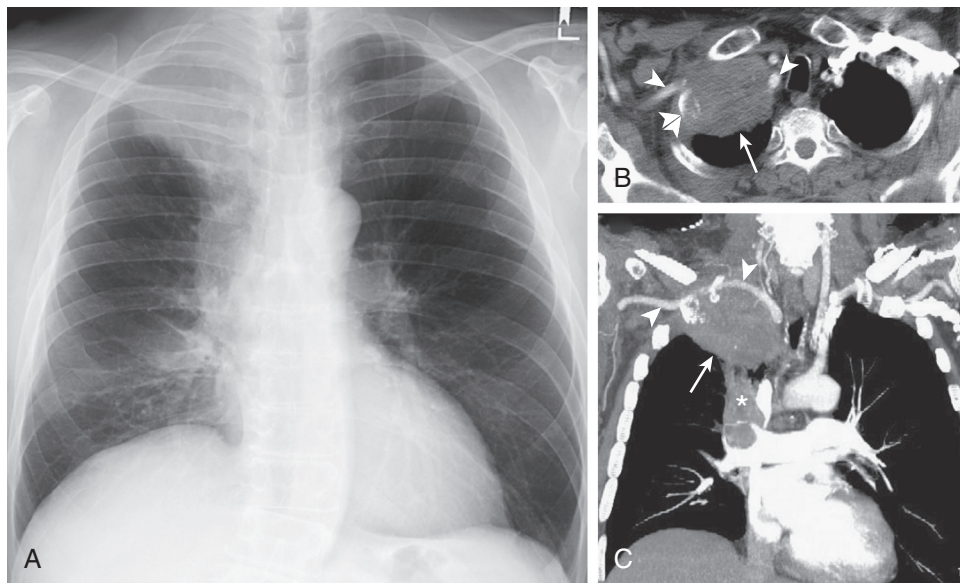


Figure 53-4 Superior sulcus (Pancoast) tumor. **A**, Frontal chest radiograph shows a mass at the extreme right pulmonary apex. Axial (**B**) and coronal (**C**) enhanced chest CT shows a mass (arrow) at the right apex, arising from the superior sulcus region, identified by the presence of the subclavian artery (arrowheads). Note first rib destruction (double arrowheads, **B**). Right paratracheal lymphadenopathy (*, **C**) is present. (Courtesy Michael Gotway, MD.)

The most common initial symptom is shoulder pain, which is produced by tumor involvement of the parietal pleura, brachial plexus, vertebral bodies, and first, second, and third ribs. The pain may radiate along the upper back or shoulder into the axilla and along the distribution of the ulnar nerve. Patients are commonly treated for arthritis or bursitis of the shoulder for months before the correct diagnosis is determined. Horner syndrome consists of ptosis, miosis, and anhidrosis and is caused by the invasion of the paravertebral sympathetic chain and the inferior cervical (stellate) ganglion.²⁴⁸ The intrinsic muscles of the hands may become weak and atrophied as the tumor progresses. With further extension through the intervertebral foramina, spinal compression and paraplegia may develop.

The chest radiograph may show an apical tumor (Fig. 53-4A), although in some cases, a tumor can be identified only on chest CT (Fig. 53-4B and C; see eFig. 53-18A). If the diagnosis is suspected but the chest radiograph is negative, then a chest CT scan should be obtained (see eFigs. 53-17 and 53-18A). CT also provides additional information about the extent of the tumor (see Fig. 53-4B) and is especially helpful in identifying other pulmonary nodules and mediastinal adenopathy (see Fig. 53-4C). MRI of the chest is considered to be superior for evaluating patients with superior sulcus tumors because of better assessment of invasion through the pleura and subpleural fat, better evaluation of plexus involvement (see eFig. 53-18B and C), and better definition of subclavian vessel involvement.²⁵¹ Magnetic resonance angiography may give the best assessment of vascular invasion of the subclavian vessels. Flexible fiberoptic bronchoscopy is frequently the first diagnostic test for apical tumors and has a diagnostic yield of approximately 50%.²⁵² TTNA has a very high diagnostic yield (>90%) even if the bronchoscopy is nondiagnostic.²⁵³ Superior sulcus tumors are usually staged as T3N0M0 (stage IIB) or higher depending on size of the tumor (T3 or T4) and extent of lymph node involvement. In a large series from M.

D. Anderson, 25% of patients were stage IIB, 22% were IIIA, and 53% were stage IIIB (T4 or N3).²⁵⁴ Some patients who were stage IV at diagnosis were excluded from that report. It is estimated that one third to one half of all superior sulcus tumors have identifiable distant metastasis at diagnosis. In addition to the stage of disease and performance score, other important poor prognostic factors include weight loss and vertebral body or supraclavicular involvement. The presence of N1 or N2 nodal involvement and incomplete resections have a worse prognosis.^{254,255} In patients treated for localized disease (stage IIB or IIIB), the brain is the most common site of relapse.²⁵⁶

In the past, the most common treatment for localized superior sulcus tumors due to NSCLC was preoperative radiotherapy of 30 to 50 Gy followed by resection. This resulted in a 5-year survival of 25% to 35%. The current standard of practice is to perform neoadjuvant chemoradiotherapy followed by resection. This is based on results of the North America Intergroup Trial in which patients with a negative mediastinoscopy were treated with two cycles of etoposide and cisplatin chemotherapy and concurrent thoracic radiotherapy (45 Gy in 5 wk). In the resected specimen, a pathologic complete response or minimal microscopic disease was identified in 66% of patients. The overall survival at 5 years was 44% and, for those with a complete resection, 54%.²⁵⁶ In a phase II trial in Japan, chemotherapy with mitomycin, vindesine, and cisplatin with concurrent thoracic radiotherapy led to a 5-year survival of 56%.²⁵⁷ Although the optimal regimen of treatment has not been proved, a reasonable choice is that used in the U.S. Intergroup Trial study described earlier.

SUPERIOR VENA CAVA SYNDROME

The blockage of blood flow in the SVC results in SVC syndrome.²⁵⁸ Bronchogenic carcinoma (see eFig. 83-1A-D and



Figure 53-5 SVC syndrome. **A**, Facial swelling in a patient with superior vena cava (SVC) syndrome. **B**, The same patient also presented with jagged, blanching, violaceous plaques on the upper chest and abdomen. **C**, Chest radiograph shows a right mediastinal mass in another patient with SVC syndrome. (A and B, From Ratnarathorn M, Craig E: Cutaneous findings leading to a diagnosis of superior vena cava syndrome: a case report and review of the literature. *Dermatol Online J* 17, 2011. Figs. 1 and 2; C, courtesy Michael Gotway, MD.)

Video 83-1) accounts for the vast majority of these cases in older adults.^{259,260} In teenagers and young adults, SVC syndrome is usually due to non-Hodgkin lymphoma (see Fig. 83-2A-D and **Video 83-2**). Patients complain of dyspnea and a sensation of fullness in the head and/or light-headedness when bending over. They may also note facial swelling. Cough, pain, and dysphagia are less frequent symptoms. Physical examination findings included dilated neck veins, a prominent venous pattern on the chest, facial edema, and a plethoric appearance (Fig. 53-5A). The chest radiograph typically shows widening of the mediastinum or a right hilar mass (see Fig. 53-5B). Occasionally, it may be normal. Dilated veins on the anterior chest wall and compression of the SVC (see eFigs. 83-1 and 83-2, and **Videos 83-1** and **83-2**) may be demonstrated with CT with intravenous contrast. SVC syndrome is not generally a medical emergency, and patients should not be treated without a tissue diagnosis. Bronchoscopy or mediastinoscopy can be safely performed in the setting of SVC syndrome.²⁶¹ Because SCLC is chemosensitive, SVC syndrome due to SCLC is best treated with chemotherapy; generally, after treatment, symptoms start to resolve in 5 to 7 days.²⁶² NSCLC is best treated with concurrent chemoradiotherapy (see earlier discussion of treatment of stage IIIA/IIIB NSCLC). If there is a need for immediate relief of SVC obstruction, vascular stenting should be strongly considered. A Cochrane meta-analysis reported that SVC stents relieved obstruction in 95% of cases.²⁶² Stenting has been associated with a complication rate of 3% to 7%.

PARANEOPLASTIC SYNDROMES

Hormonal, neurologic, hematologic, or other remote effects of cancer not related to the direct invasion, obstruction, or metastatic effects of tumor are generally termed *paraneoplastic syndromes*. Paraneoplastic syndromes related to bronchogenic carcinoma develop in 10% to 20% of patients (Table 53-6).

MUSCULOSKELETAL EFFECTS

Clubbing of the digits may be a manifestation of lung cancer or other diseases (see Fig. 16-3). Clubbing may involve the fingers and toes and consists of selective enlargement of the connective tissue in the terminal phalanges. Physical findings include loss of the angle between the base of the nail bed and the cuticle, rounded nails, and enlarged fingertips. Clubbing is an isolated finding and is usually asymptomatic. Nonmalignant causes of clubbing include pulmonary fibrosis, congenital heart disease, and bronchiectasis.

Hypertrophic pulmonary osteoarthropathy (HPO) is an uncommon process associated with lung cancer. HPO is characterized by painful arthropathy that usually involves the ankles, knees, wrists, and elbows and is most often symmetrical. The pain and arthropathy are caused by proliferative periostitis that involves the long bones but may also affect metacarpal, metatarsal, and phalangeal bones. Patients may have clubbing of fingers and toes in addition to the painful arthralgias. The pathogenesis of HPO is uncertain, but it may arise from a humoral agent. For patients who smoke and have a new onset of arthralgias, HPO must be considered. A radiograph of the long bones (i.e., tibia and fibula) usually shows characteristic periosteal new bone formation (Fig. 53-6B). A radionuclide bone scan (see Fig. 53-6C) typically demonstrates diffuse uptake by the long bones. Large cell and adenocarcinoma are the most common histologic types associated with HPO (see Fig. 53-6A). The symptoms of HPO may resolve after thoracotomy, whether the primary cancer is resected or not. For inoperable patients, treatment is with nonsteroidal anti-inflammatory agents. Recently, case reports have observed resolution or marked improvement of symptoms with bisphosphonate treatment.²⁶³

Although still a topic of debate, population-based studies from Scandinavia suggest a frequency of malignancy of 15% to 25% in patients with dermatomyositis-polymyositis.²⁶⁴ The highest risk of malignancy is in the first

Table 53-6 Paraneoplastic Syndromes Associated with Bronchogenic Carcinoma

System	Paraneoplastic Syndrome
Musculoskeletal	Clubbing Hypertrophic osteoarthropathy Polymyositis Osteomalacia Myopathy
Cutaneous	Dermatomyositis Acanthosis nigricans Pruritus Erythema multiforme Hyperpigmentation Urticaria Scleroderma
Endocrinologic	Cushing syndrome Syndrome of inappropriate secretion of antidiuretic hormone Hypercalcemia Carcinoid syndrome Hyperglycemia/hypoglycemia Gynecomastia Galactorrhea Growth hormone excess Calcitonin secretion Thyroid-stimulating hormone
Neurologic	Lambert-Eaton myasthenic syndrome Peripheral neuropathy Encephalopathy Myelopathy Cerebellar degeneration Psychosis Dementia
Vascular/hematologic	Thrombophlebitis Arterial thrombosis Nonbacterial thrombotic endocarditis Thrombocytosis Polycythemia Hemolytic anemia Red cell aplasia Dysproteinemia Leukemoid reaction Eosinophilia Thrombocytopenic purpura
Miscellaneous	Cachexia Hyperuricemia Nephrotic syndrome

2 years after the diagnosis of dermatomyositis-polymyositis. A reasonable approach to cancer surveillance in these patients is a careful history and physical examination, chest radiograph, basic laboratory tests, and age-appropriate cancer screening examinations. Other tests should be based on abnormalities detected during the basic evaluation.

HEMATOLOGIC EFFECTS

Anemia is common in patients who have lung cancer and may be caused by iron deficiency, chronic disease, or bone marrow infiltration. Eosinophilia is more often associated with Hodgkin disease but may also be seen in patients with lung cancer. Production of various cytokines by neoplastic cells may result in eosinophilia, leukocytosis, or thrombocytosis, of which thrombocytosis is by far the most common. Many of the hematologic effects of lung cancer do not lead to clinical sequelae, and specific hormones or antibodies responsible for the effects are typically not found.

The association of deep venous thrombosis and malignancy was described by Trousseau more than a century ago, and lung cancer is the most common malignancy associated with hypercoagulability. The causes of the hypercoagulable state remain poorly understood. One large study documented a clinically significant association of idiopathic thrombosis with the subsequent development of overt cancer; however, other investigators concluded that the literature does not enable firm recommendations about whether to screen for a malignant neoplasm in patients who have unexplained venous thromboembolism.²⁶⁵ Thromboembolism in the patient who has malignancy is often refractory to warfarin treatment, and treatment with *low-molecular-weight heparin* (LMWH) on a long-term basis is likely more effective. In a randomized trial, patients with cancer and deep vein thrombosis, pulmonary embolism, or both were randomized to receive LMWH (dalteparin) subcutaneously once daily or oral warfarin daily for 6 months.²⁶⁶ At 6 months, the probability of recurrent thromboembolism was 9% with dalteparin treatment and 17% with warfarin, a difference that was highly significant. The risks of major bleeding or any bleeding were not different in the two groups. The other advantage of LMWH is that it is not necessary to monitor the anticoagulant effect, except in some patients with renal insufficiency. A recent Cochrane analysis concluded that, for long-term treatment in patients with cancer, LMWH reduced venous thromboembolism events, but not death, as compared with vitamin K antagonists. There was no significant difference in the risk of bleeding²⁶⁷ (see Chapter 57).

HYPERCALCEMIA

Hypercalcemia of malignancy may arise from a bony metastasis, accelerated bone resorption, decreased bone deposition, or increased renal tubular reabsorption of calcium, but, most commonly, is due to secretion by the tumor of a *parathyroid hormone–related protein* (PTHrP) or other bone-resorbing cytokine (see Chapter 95). Lung cancer is the most common solid tumor associated with hypercalcemia, but other cancers also have an association, such as kidney, breast, and head and neck cancer, myeloma, and lymphoma. In one study of 690 consecutive lung cancers, 2.5% of cases had tumor-induced hypercalcemia.²⁶⁸ Squamous cell histology is the most common cell type associated with hypercalcemia, but hypercalcemia does not rule out other lung cancers such as adenocarcinoma or, very rarely, small cell carcinoma. Generally, lung cancer patients with hypercalcemia have advanced disease (stage III or IV) and are unresectable.

Symptoms of hypercalcemia include anorexia, nausea, vomiting, constipation, lethargy, polyuria, polydipsia, and dehydration. Confusion and coma are late manifestations, as are renal failure and nephrocalcinosis. Cardiovascular effects include shortened QT interval, broad T wave, heart block, ventricular arrhythmia, and asystole. Individual patients may manifest any combination of these signs and symptoms in various degrees.

Accelerated bone resorption is caused by activation of osteoclasts by cytokines or PTHrP in most cases. Serum parathyroid hormone levels are usually normal or low, but an elevated level of PTHrP can be detected in the serum in

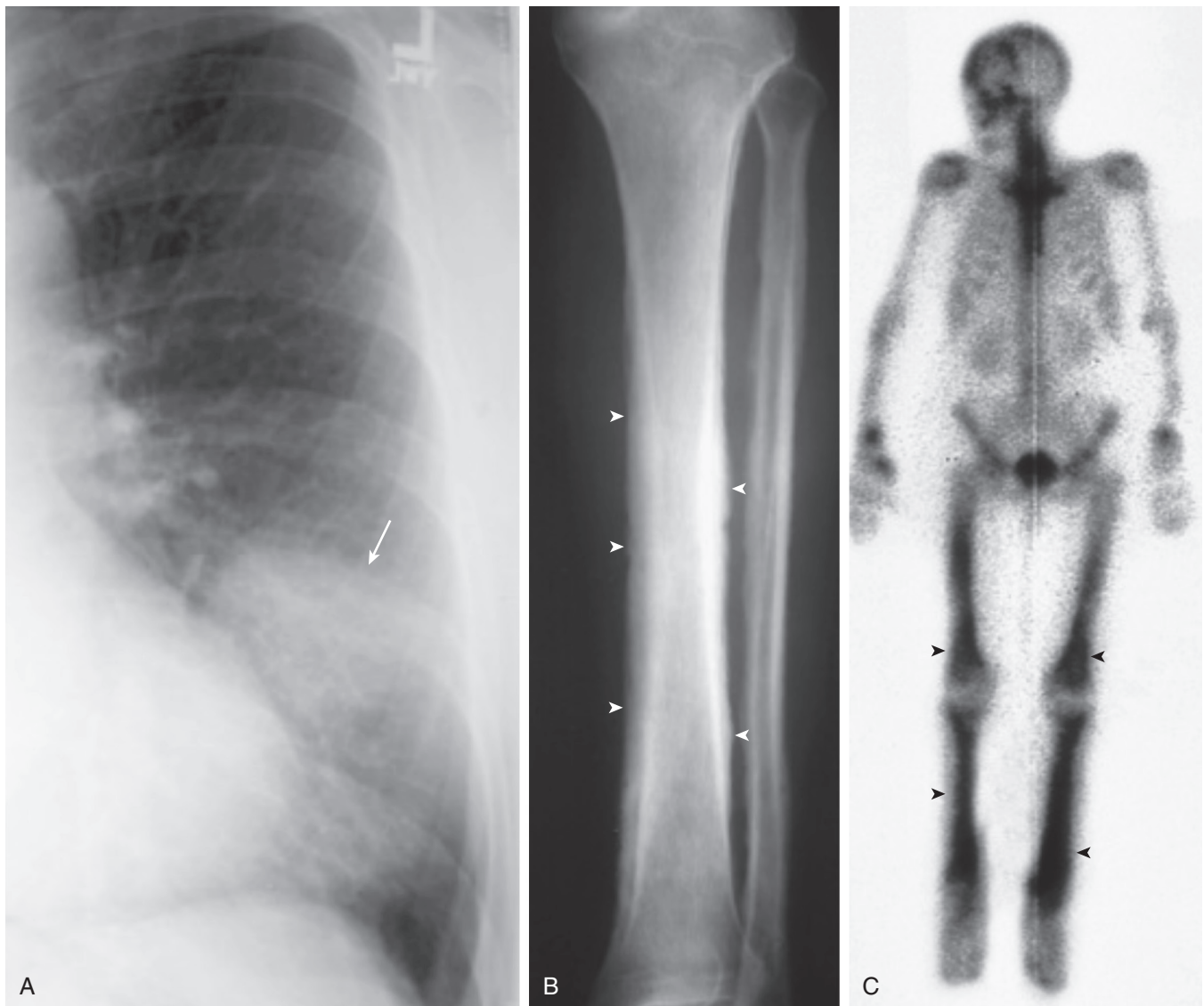


Figure 53-6 Lung carcinoma and hypertrophic osteoarthropathy. **A**, Frontal chest radiograph shows a left lung malignancy (*arrow*). **B**, Radiograph of the tibia and fibula shows diaphyseal periosteal reaction (*arrowheads*). **C**, Radionuclide bone scan shows fairly symmetric, bilateral lower extremity tracer uptake, consistent with hypertrophic osteoarthropathy. (Courtesy Michael Gotway, MD.)

approximately one half of these patients.²⁶⁸ Cytokines or PTHrP are secreted autonomously by the tumor. Not only does PTHrP cause renal calcium reabsorption, but also it interferes with renal mechanisms for reabsorption of sodium and water, with resultant polyuria. Polyuria and vomiting result in dehydration; decreases in glomerular filtration further aggravate the hypercalcemia.

While most patients who have a serum calcium of 12 to 13 mg/dL or higher are treated, mild elevation of serum calcium may not require treatment, so the decision is based on the patient's symptoms. For patients who have widely metastatic and incurable malignancy, it may be most appropriate to give supportive care only and not treat the hypercalcemia. The average life expectancy in this situation is 30 to 45 days, even with aggressive treatment.²⁶⁹

The four basic goals of treatment are to (1) correct dehydration, (2) increase renal excretion of calcium, (3) inhibit bone resorption, and (4) treat the underlying malignancy. Because of the polyuria, patients with hypercalcemia are

usually volume-depleted. Initial treatment is with intravenous normal saline, using 3 to 6 L/24 hr as tolerated, with careful attention to volume status. Previously, a loop diuretic such as furosemide or ethacrynic acid was added to maximize calcium excretion but has become less commonly used due to the efficacy of the bisphosphonates in inhibiting bone resorption. Thiazide diuretics are not used because they increase calcium reabsorption in the distal tubule. Fluids and diuretics generally result in only a mild decrease of the calcium; additional treatment is needed to inhibit the accelerated bone resorption. The bisphosphonates have a high affinity for bone and inhibit osteoclast activity. Zoledronate, a newer bisphosphonate, is the most effective; the usual dose is 4 mg given intravenously over 15 minutes.²⁷⁰ Normal calcium levels are achieved within 4 to 10 days in 85% of patients and last a median of 30 to 40 days. Adverse effects are generally mild and transient and include fever, hypophosphatemia, asymptomatic hypocalcemia and, occasionally, renal failure. Calcitonin inhibits bone

resorption, increases renal calcium excretion, and has a rapid onset of action, but the duration of action is short lived. Calcitonin is a relatively weak agent and, when used alone, does not usually normalize the serum calcium of patients who have marked hypercalcemia. Use of calcitonin is appropriate when the calcium is greater than 14 mg/dL or needs to be lowered urgently (onset of action is 4 to 6 hours) while waiting for the more effective but slower acting agents to take effect or when relief of bone pain is desired. The effects of calcitonin and bisphosphonates are additive. Tachyphylaxis to calcitonin may be seen 48 hours after administration. Other agents such as gallium nitrate or plicamycin have been used to treat hypercalcemia but have not generally been adopted as first-line therapies because of inconvenience of administration schedules or associated toxicities.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Hyponatremia is noted at the time of presentation in approximately 15% of patients with SCLC and 1% of patients with NSCLC and, in most cases, is due to ectopic production of arginine vasopressin by the cancer cells.²⁷¹ Under normal conditions, antidiuretic hormone (vasopressin) is secreted in the anterior hypothalamus and exerts its action on the renal collecting ducts by enhancing the flow of water from the lumen into the medullary interstitium, thereby concentrating the urine. The criteria for the diagnosis of SIADH include (1) hyponatremia associated with serum hypo-osmolality (<275 mOsm/kg), (2) inappropriately elevated urine osmolality (>200 mOsm/kg) relative to serum osmolality; (3) elevated urine sodium (>20 mEq/L); (4) clinical euolemia without edema; (5) normal renal, adrenal, and thyroid function. The serum uric acid is usually low, and the urine osmolality-to-serum osmolality ratio is frequently greater than 2.

The severity of symptoms is related to the degree of hyponatremia and the rapidity of the fall in serum sodium. In one large series of patients with SIADH, only 27% had signs or symptoms of hyponatremia despite a median sodium of 117 mEq/L (range, 101 to 129 mEq/L). Symptoms of hyponatremia include anorexia, nausea, and vomiting. With a rapid onset of hyponatremia, symptoms caused by cerebral edema may include irritability, restlessness, personality changes, confusion, coma, seizures, and respiratory arrest.

In minimally symptomatic or asymptomatic patients, fluid restriction of 500 to 1000 mL/24 hr is the initial treatment of choice. Conivaptan is an intravenous vasopressin receptor antagonist that has been shown to be useful in correcting hyponatremia but its use is limited to hospitalized patients. The oral vasopressin receptor antagonist tolvaptan is now available for clinically significant hypervolemic and for euolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction). It should not be used in patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurologic symptoms.²⁷²⁻²⁷⁴ If further treatment is needed, oral demeclocycline (900 to 1200 mg/day) can be considered. Demeclocycline induces a nephrogenic diabetes insipidus and blocks the action of antidiuretic

hormone on the renal tubule, thereby increasing water excretion. The onset of action varies from a few hours to a few weeks, so this drug is not recommended for acute emergency treatment. Demeclocycline has potential kidney toxicity. In patients who have more severe or life-threatening symptoms (serum sodium < 115 mEq/L), treatment consists of intravenous saline, supplemental potassium, and diuresis with loop diuretics such as furosemide or ethacrynic acid. With severe confusion, convulsions, or coma, it may be appropriate to treat with 300 mL of 3% saline given over 3 to 4 hours in combination with a loop diuretic (saline without a diuretic will not increase the sodium concentration).

Rapid correction of the sodium may have life-threatening consequences, and caution is advised.²⁷⁵ The rate of correction of the sodium is best limited to a maximum of 12 mEq/L/day, until a level of 120 to 130 mEq/L is reached. Faster correction has been associated with the development of central pontine myelinolysis, which may result in quadriplegia, cranial nerve abnormalities that manifest as pseudobulbar palsy, alteration in mental status, and subsequent death. Accordingly, in the course of treating hyponatremia, the serum sodium must be monitored frequently to ensure that correction is not too rapid. For patients with SIADH due to SCLC, treatment with chemotherapy should be initiated as soon as possible and is likely to result in improvement in the hyponatremia within a few weeks. After an initial response to chemotherapy, SIADH may recur when the tumor relapses.

ECTOPIC CORTICOTROPIN SYNDROME

Ectopic production of corticotropin or corticotropin-releasing hormone with associated Cushing syndrome has been identified in patients with SCLC, carcinoid tumor (lung, thymus, or pancreas), and neurocrest tumors such as pheochromocytoma, neuroblastoma, and medullary carcinoma of the thyroid.²⁷⁶ Of those with ectopic corticotropin secretion, SCLC accounts for 75% of cases, although Cushing syndrome develops in only 1% to 2% of patients with SCLC. Cushing syndrome is seldom caused by NSCLC.

Classic features of Cushing syndrome include truncal obesity, striae, rounded (moon) facies, dorsocervical fat pad (buffalo hump), myopathy and weakness, osteoporosis, diabetes mellitus, hypertension, and personality changes. However, the rapid growth of SCLC means that patients are more likely to present with edema, hypertension, and muscular weakness than with the classic features of Cushing syndrome. Hypokalemic alkalosis and hyperglycemia are usually present. Patients with SCLC and Cushing syndrome appear to have shortened survival compared to those without the syndrome, perhaps because of more frequent opportunistic infections.

The best screen for Cushing syndrome is the 24-hour urine free cortisol measurement. Elevation of cortisol production, lack of suppression with high-dose dexamethasone, and plasma corticotropin levels greater than 200 pg/mL (40 pmol/L) are highly suggestive of ectopic corticotropin as the cause of Cushing syndrome in the absence of a pituitary adenoma. The plasma level of corticotropin is elevated in many, but not all, patients.

Treatment of Cushing syndrome due to ectopic corticotropin has included adrenal enzyme inhibitors such as metyrapone, aminoglutethimide, and ketoconazole, given alone or in combination. Ketoconazole given orally at a dosage of 400 to 1200 mg/day or metyrapone 250 to 750 mg three times per day may control hypercortisolism within a few days to weeks, but the response is variable.²⁷⁷ Dose adjustments are based on achieving normal urinary free cortisol levels or morning plasma cortisol levels of 7 to 11 µg/mL. Symptomatic hypoadrenalism may result from treatment, and some authorities recommend a replacement dose of glucocorticoid when an enzyme inhibitor is started. When Cushing syndrome arises from SCLC, it is advisable to proceed with appropriate chemotherapy and carefully watch for superimposed infections, as for any patient who is receiving high-dose corticosteroids. Cushing syndrome related to a bronchial carcinoid or thymic carcinoid is best treated by surgical resection of the tumor.

NEUROLOGIC EFFECTS

The paraneoplastic neurologic syndromes associated with lung cancer, mostly small cell type, are variable and include LEMS, subacute sensory neuropathy, encephalomyelopathy, cerebellar degeneration, autonomic neuropathy, retinal degeneration, and opsoclonus/myoclonus.²⁷⁸ The frequency of any of these neurologic syndromes in SCLC is approximately 5%, and neurologic symptoms may precede the diagnosis by months to years.^{279,280} Most patients with SCLC who have an associated paraneoplastic syndrome have LD-SCLC that may or may not be obvious on initial evaluation. Careful radiographic evaluation of the lungs and mediastinum is indicated in a smoker who has a suspected paraneoplastic neurologic syndrome. In this setting, even subtle abnormalities of the mediastinum require a biopsy. PET may help identify an occult lesion and facilitate biopsy confirmation of the diagnosis.^{281,282} Many reports have suggested that patients with paraneoplastic neurologic syndromes have a better prognosis than those without the paraneoplastic syndromes with similar stage and histology.

These paraneoplastic neurologic syndromes are thought to be immune-mediated, based on the identification of a number of antibodies in the serum that react with both the nervous system and the underlying cancer.²⁷⁸ However, not all patients with paraneoplastic syndromes have identifiable antibodies in their serum. The literature is confusing because of different names employed by various investigators. The anti-Hu antibody is the same as *antineuronal nuclear antibody type 1* (ANNA-1), and the anti-Ri antibody is identical to ANNA-2. Both of these antibodies, but predominantly anti-Hu, have been associated with SCLC. Anti-Hu is an IgG antibody found in the sera and cerebrospinal fluid and binds to the nuclei of all neurons in the central and peripheral nervous system, including the sensory and autonomic ganglia, the myenteric plexus, and cells of the adrenal medulla. Such antibodies should not be confused with the anti-Purkinje cell antibody (anti-Yo), which is characteristically found in patients who have subacute cerebellar degeneration as a manifestation of gynecologic malignancy or breast cancer. The CRMP-5 antibody, known as anti-CV-2, has also been associated with SCLC and thymomas.²⁷⁸

In a review of 162 sequential patients who had elevated anti-Hu (ANNA-1), 142 (88%) were proved to have cancer, 132 of whom had SCLC.²⁸⁰ In 97% of these cases, the neurologic syndrome preceded the diagnosis of SCLC, usually by less than 6 months but, in 20%, by more than 6 months. Of special note is that 90% of cases had disease limited to the lung or to the lung and mediastinum (LD-SCLC). In a report from Europe, 144 patients of 200 with anti-Hu antibodies had a tumor in the chest.²⁷⁹ Of these, 111 were proved to be SCLC. In one large series, ANNA-1 antibodies were identified in 16% of all patients with SCLC. These antibodies were associated with limited-stage disease, complete response to therapy, and longer survival compared with patients who had SCLC and no ANNA-1 antibody. These neurologic syndromes seldom improve with treatment, so the goal is to prevent progression by starting treatment of the underlying tumor as soon as possible.

Less common manifestations of neurologic paraneoplastic syndromes are orthostatic hypotension and intestinal dysmotility. The gastrointestinal symptoms may present as nausea, vomiting, abdominal discomfort, or altered bowel habits suggestive of intestinal pseudo-obstruction. Many of these patients present with gastrointestinal symptoms and significant weight loss before the diagnosis of SCLC.

LEMS is characterized by proximal muscle weakness, hyporeflexia, and autonomic dysfunction.^{283,284} Cranial nerve involvement may be present and does not differentiate LEMS from myasthenia gravis. LEMS has been strongly associated with antibodies directed against P/Q-type presynaptic *voltage-gated calcium channels* (anti-VGCC antibodies) of peripheral cholinergic nerve terminals. These anti-VGCC antibodies, identified in more than 90% of patients with LEMS, block the normal release of acetylcholine at the neuromuscular junction. (In contrast, myasthenia gravis is associated with anti-acetylcholine receptor antibodies, which are present in approximately 90% of myasthenic patients.)

Of patients with LEMS, malignancy is present in approximately half and, of the cancers, SCLC is by far the most common. And yet, when SCLC patients are studied prospectively, LEMS is uncommon. In a recent study of 63 patients with SCLC examined prospectively, only 3% had clinical and electrophysiologic signs of LEMS, 8% had elevated anti-VGCC antibodies, and 26% had other neurologic symptoms unrelated to LEMS.²⁸⁵ The diagnosis of LEMS is based on characteristic electromyographic findings that show a small amplitude of the resting compound muscle action potential and facilitation with rapid, repetitive, supramaximal nerve stimulation or after brief exercise of the muscle. A single-fiber electromyogram is optimal for making the diagnosis. LEMS is the predominant paraneoplastic neurologic syndrome that may improve with successful treatment of the associated lung cancer. The use of acetylcholinesterase inhibitors is of limited benefit in LEMS.²⁸⁶ However, diaminopyridine, which enhances the release of acetylcholine, has been used with sustained improvement over months in the majority of patients with LEMS with or without cancer.²⁸⁷

Opsoclonus consists of rapid involuntary eye movements that are conjugate in vertical and horizontal directions. In patients with SCLC, NSCLC, or other solid tumors, it is frequently associated with myoclonus. While the

anti-Hu antibody has been identified in patients with SCLC and opsoclonus/myoclonus, the syndrome of opsoclonus/myoclonus is the primary presentation of paraneoplastic cerebellar degeneration associated with anti-Ri antibodies.^{288,289}

Key Points

- Lung cancer currently claims more lives than breast, colon, and prostate cancer combined and is the number-one cancer killer of both men and women in the United States and worldwide.
- Routine screening for lung cancer with low-dose CT scanning is now recommended for certain at-risk groups.
- Accurate staging of lung cancer is critical because treatment strategies and outcome vary significantly by stage. The pulmonologist is uniquely positioned to stage lung cancer appropriately.
- In general, for non-small cell lung cancer, early lung cancer (stage I) is treated with surgery alone, stage II lung cancer is treated with surgery followed by adjuvant chemotherapy, locally advanced lung cancer (stage IIIA and B) is treated with a combination of chemotherapy and radiotherapy, and metastatic disease (stage IV) is treated with chemotherapy alone.
- For small cell lung cancer, localized disease (disease within one hemithorax that can be encompassed in a radiation port) is treated by chemoradiotherapy; extensive disease is treated with chemotherapy alone.
- A certain subgroup of lung cancer patients with an activating mutation of the tyrosine kinase domain of the epidermal growth factor receptor respond to tyrosine kinase inhibitors such as erlotinib or gefitinib. Patients with an *EML4-ALK* translocation can respond to the tyrosine kinase inhibitor, crizotinib.
- Therapy targeted to block driver mutations is a major advance in the approach to lung cancer therapy and will be the focus for developing new treatments for lung cancer.

Complete reference list available at *ExpertConsult*.

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eFIGURE IMAGE GALLERY

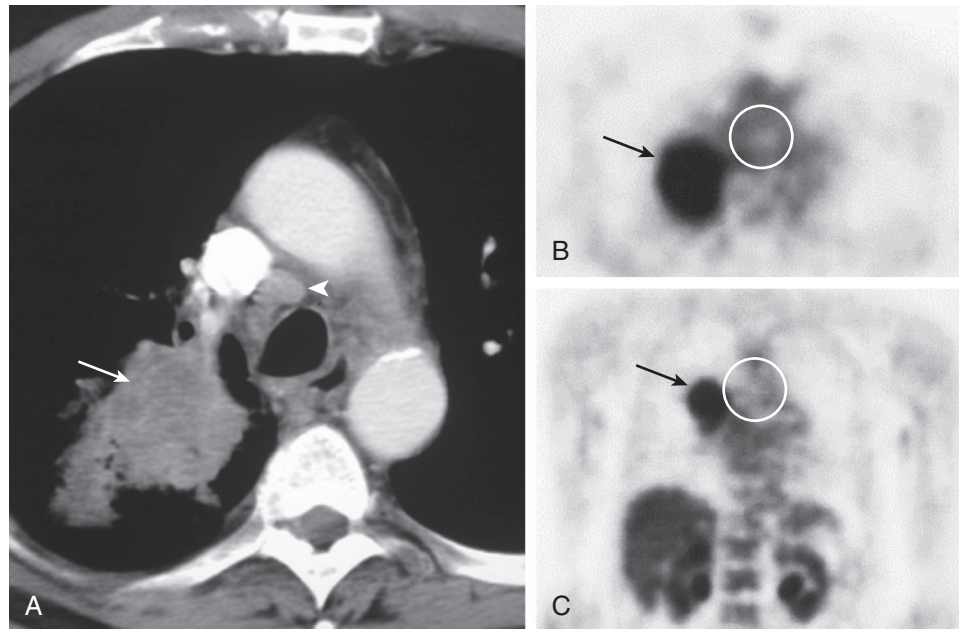


Figure 53-1 Lung carcinoma staging: false-positive CT and true-negative PET mediastinal lymph node assessment. **A**, Axial chest CT shows a right upper lobe primary lung malignancy (*arrow*) and a mildly enlarged right paratracheal lymph node (*arrowhead*). Axial (**B**) and coronal (**C**) PET images show intense metabolic activity within the right upper lobe neoplasm (*arrows*) but lack of tracer uptake in the right paratracheal node region (*circle, B and C*), suggesting no tumor involvement in the latter location. Surgical resection confirmed the right paratracheal lymph nodes were free of tumor. (Courtesy Michael Gotway, MD.)

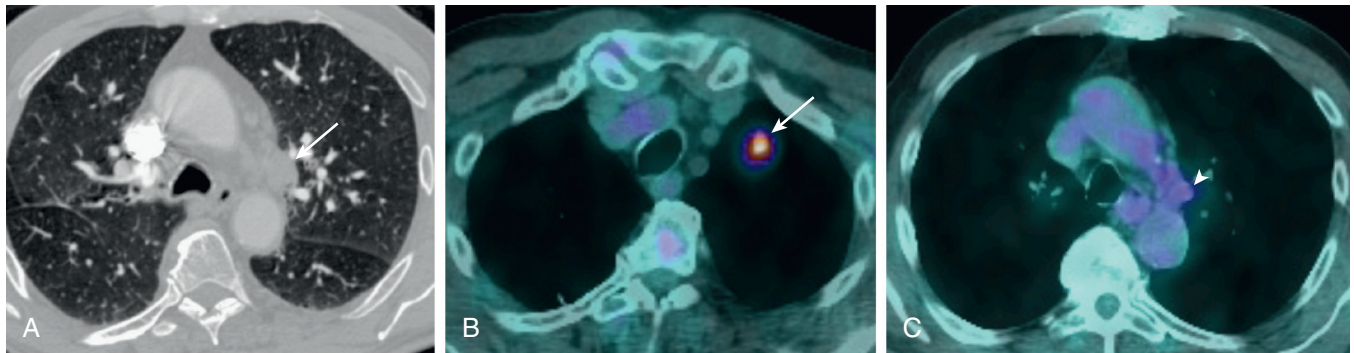


Figure 53-2 Lung carcinoma staging: false-positive CT and true-negative PET mediastinal lymph node assessment. **A**, Axial chest CT shows an enlarged aortopulmonary window lymph node (*arrow*) in a patient with a left upper lobe primary lung malignancy, raising the possibility of N2 disease. **B** and **C**, Axial fused PET images show intense metabolic activity within the left upper lobe lesion (*arrow, B*), but no significant tracer accumulation within the aortopulmonary window lymph node (*arrowhead, C*). The aortopulmonary window lymph nodes were free of malignancy at pathologic analysis following surgical resection. (Courtesy Michael Gotway, MD.)

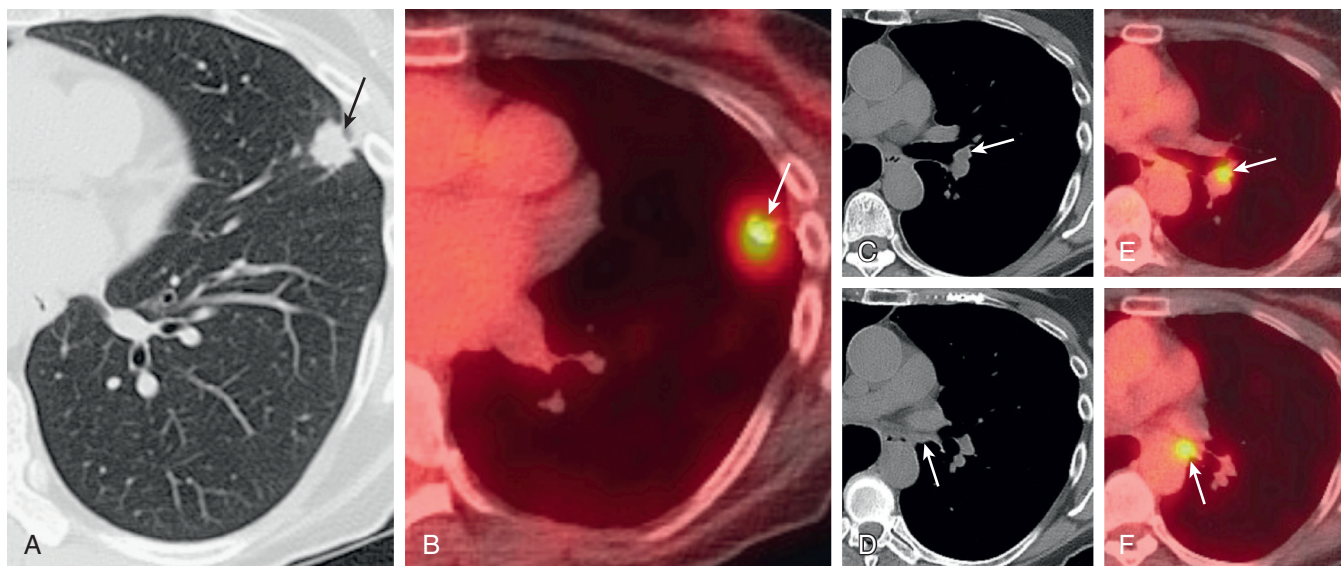
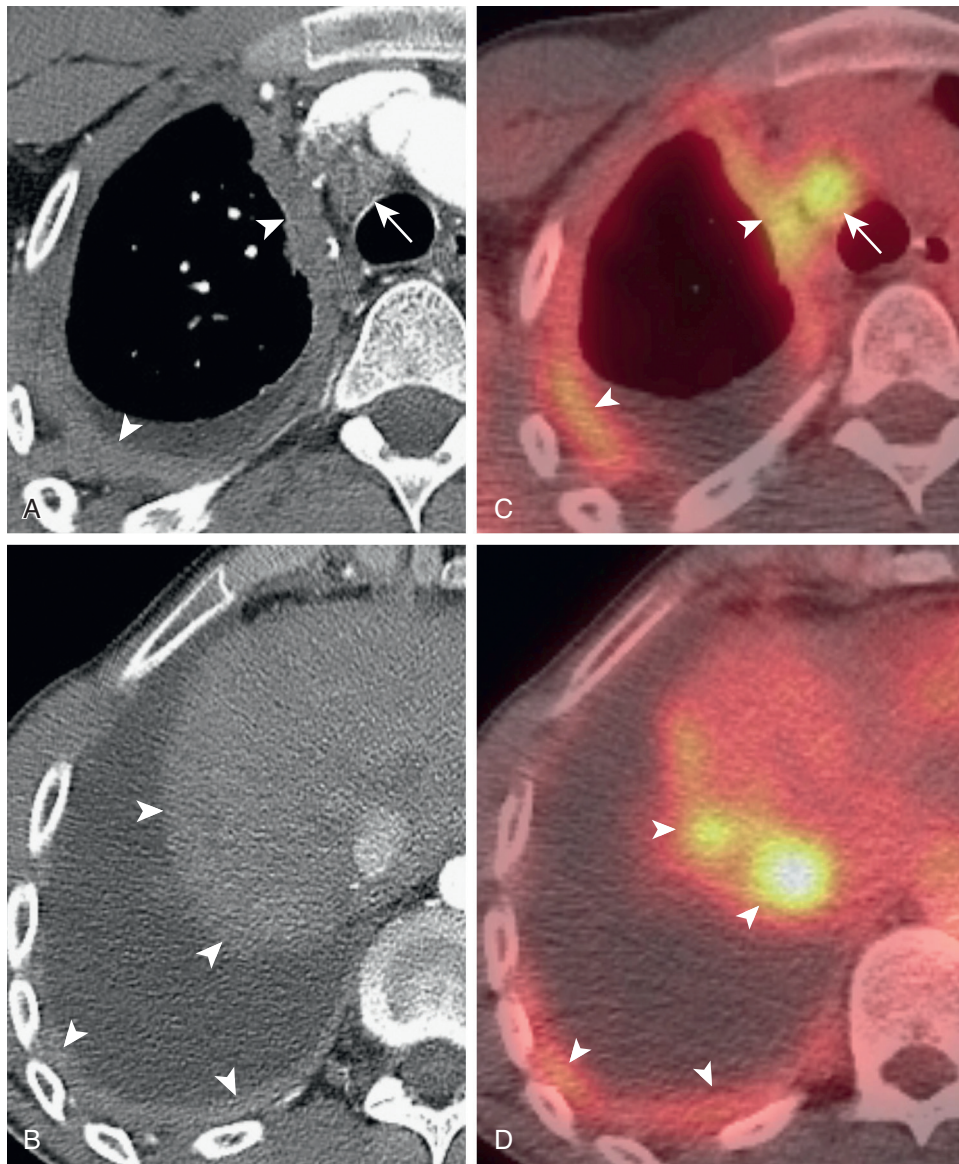
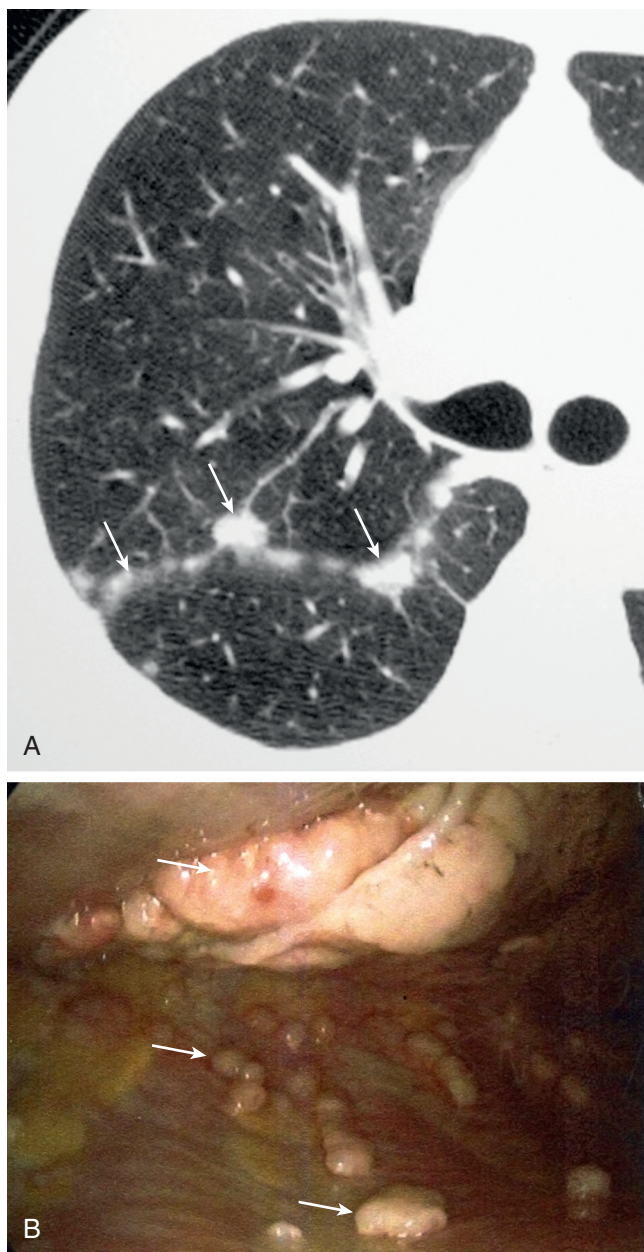


Figure 53-3 Lung carcinoma staging: false-negative CT and true positive PET mediastinal lymph node assessment. **A**, Axial chest CT shows a peripheral lingular lobulated nodule (*arrow*) representing pulmonary adenocarcinoma. **B**, Axial fused PET image shows intense metabolic activity within the lingular neoplasm (*arrow*). **C** and **D**, Axial unenhanced chest CT shows normal-sized left peribronchial (*arrow*, **C**) and mediastinal (*arrow*, **D**) lymph nodes. **E** and **F**, Axial fused PET images show intense metabolic activity within these lymph nodes (*arrows*). Malignant infiltration of the lymph nodes was shown at biopsy. (Courtesy Michael Gotway, MD.)



eFigure 53-4 Lung carcinoma staging: malignant pleural disease. **A** and **B**, Axial enhanced chest CT in a patient with primary lung malignancy shows features of malignant pleural disease: circumferential, nodular pleural thickening (*arrowheads*). Right paratracheal lymphadenopathy (*arrow*) is present. **C** and **D**, Axial fused PET images show tracer accumulation within both the pleural malignancy (*arrowheads*) and right paratracheal lymph node (*arrow*). (Courtesy Michael Gotway, MD.)



eFigure 53-5 Lung carcinoma staging: malignant pleural disease/dry pleural dissemination. A, Axial chest CT shows nodular thickening of the right major fissure (*arrows*). **B,** Image from video-assisted thoracoscopic surgery shows numerous pleural nodules (*arrows*). (Courtesy Michael Gotway, MD.)

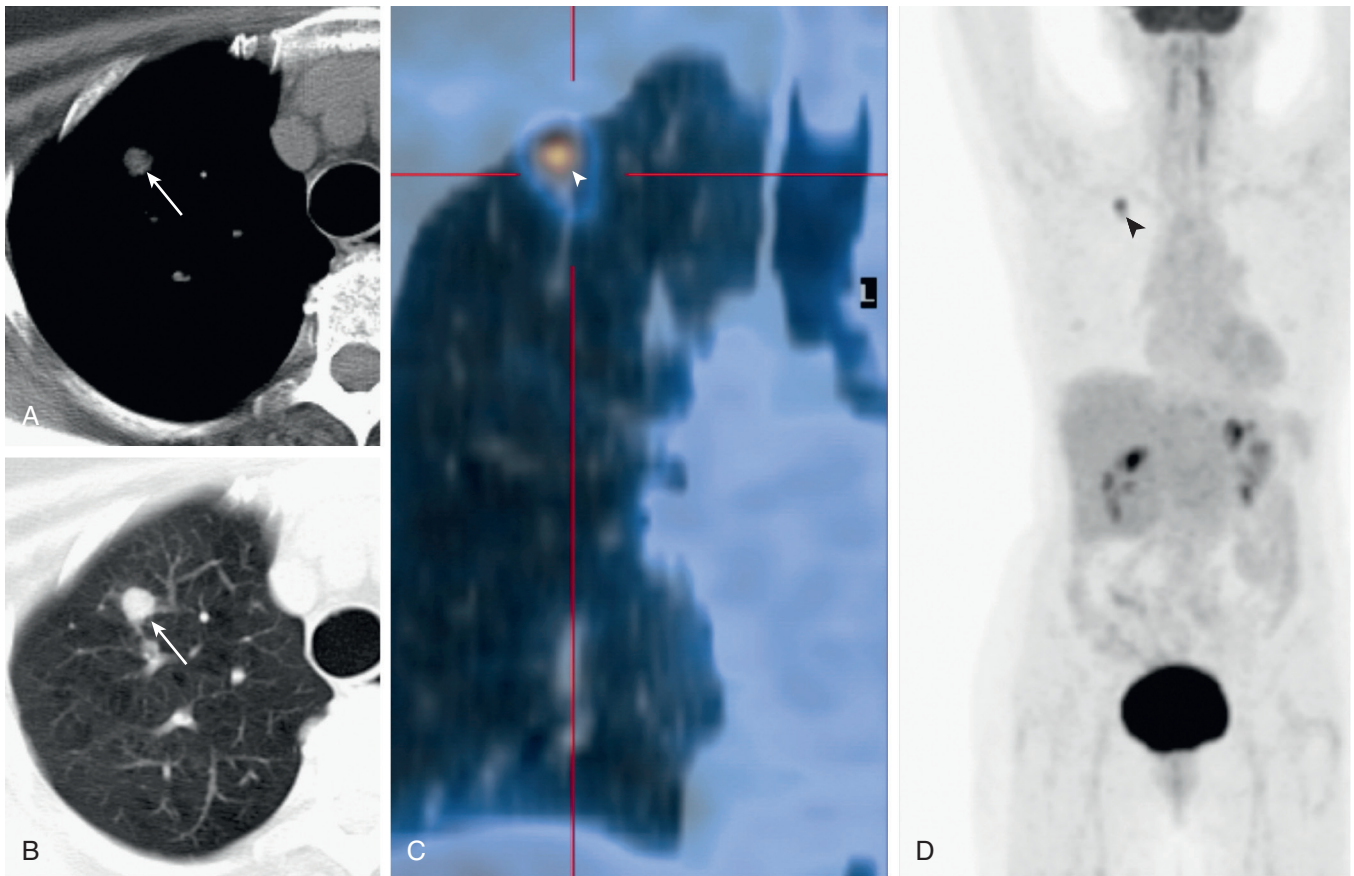


Figure 53-6 False-positive PET in the assessment of suspected lung cancer in a patient with a solitary pulmonary nodule. Axial chest CT shown in soft tissue (**A**) and lung (**B**) windows shows a lobulated, noncalcified right upper lobe nodule (*arrows*). Coronal fused (**C**) and whole-body (**D**) PET images show significant tracer accumulation within the nodule (*arrowheads*), suggesting possible neoplasm. Biopsy revealed *Mycobacterium scrofulaceum*. (Courtesy Michael Gotway, MD.)

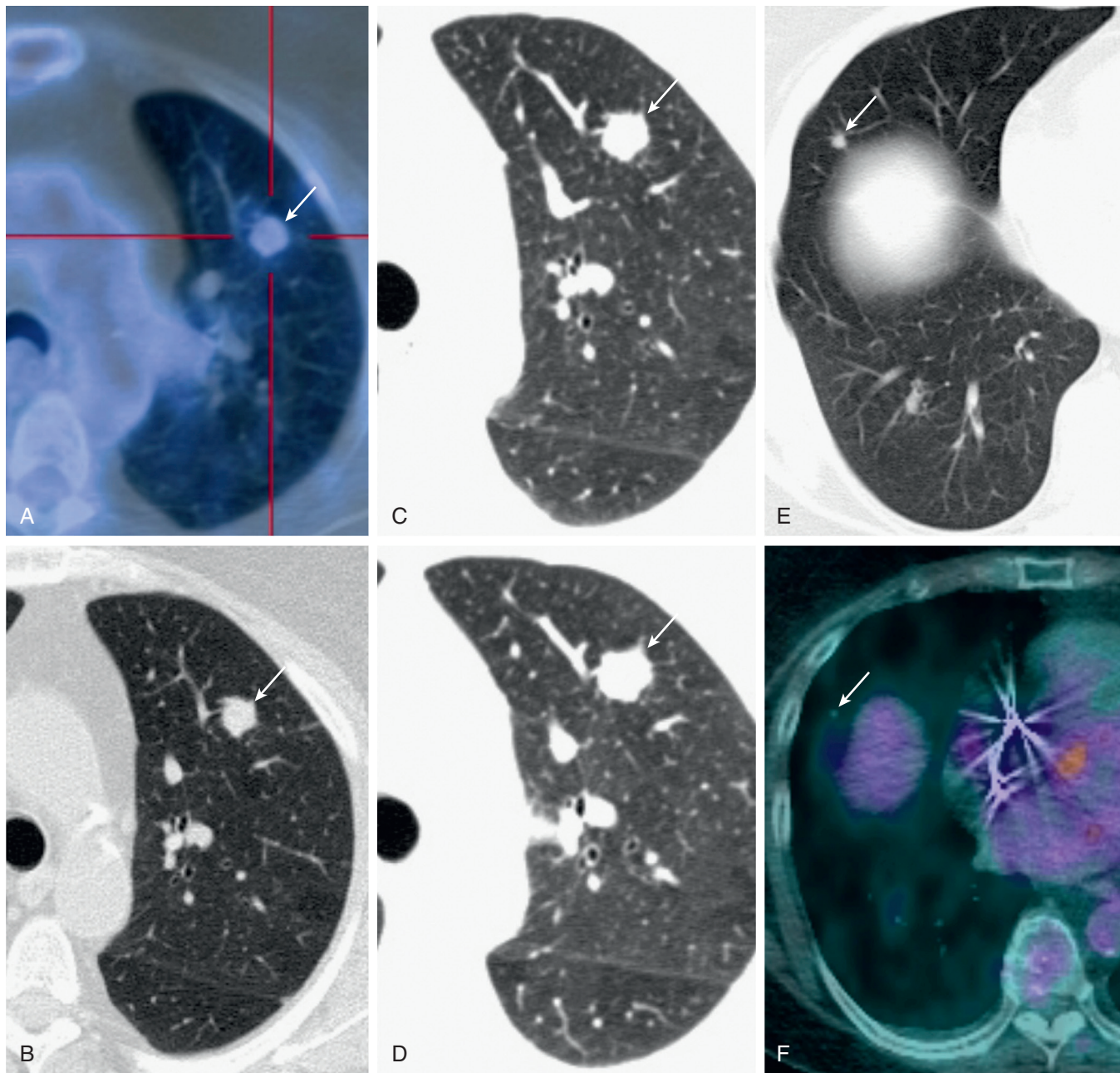
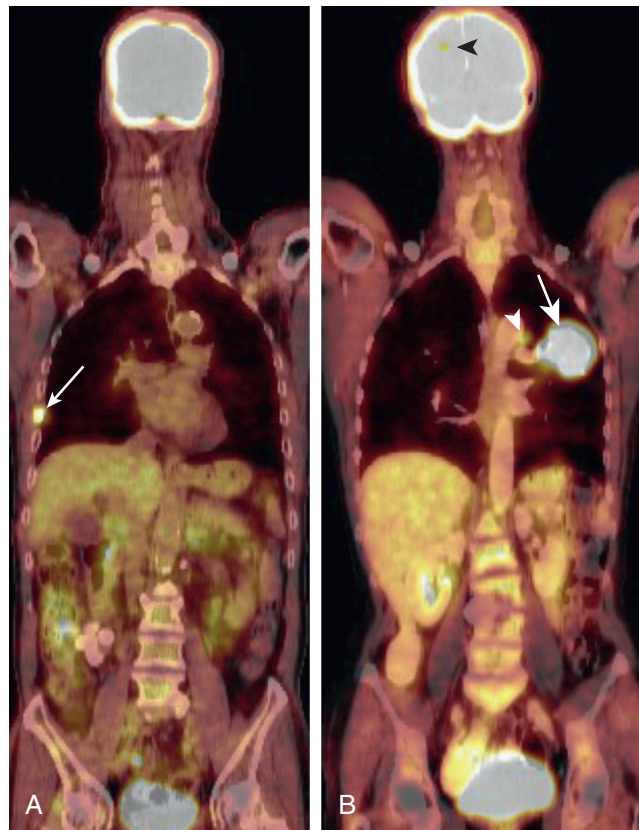
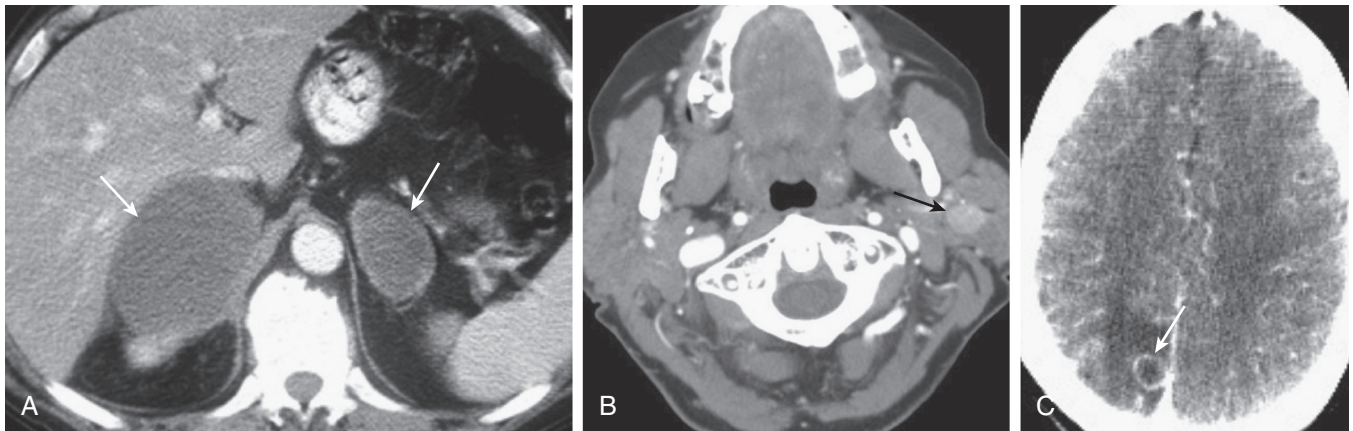


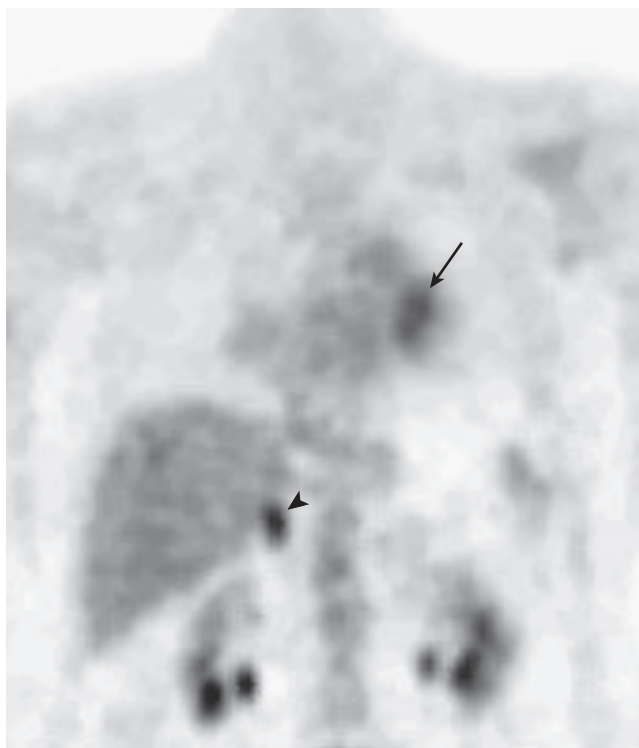
Figure 53-7 False-negative PET in the assessment of suspected lung cancer in a patient with a solitary pulmonary nodule: limitations due to low metabolic activity malignancy and spatial resolution. **A**, Fused PET image shows lack of significant tracer accumulation within a lobulated left upper lobe nodule (arrow). **B**, Axial chest CT shown in lung windows, performed near the time of the PET scan, shows an indeterminate lobulated left upper lobe nodule. **C** and **D**, Axial chest CT scans obtained 3 and 6 months, respectively, following **A** and **B** show growth in the left upper lobe nodule. Biopsy subsequently confirmed primary lung malignancy. Lack of significant accumulation of tracer at PET imaging, even though the nodule exceeded 1 cm in size, was the result of low metabolic activity within this malignant nodule. Axial chest CT (**E**) and axial fused PET images (**F**) in a patient with primary pulmonary malignancy show a small right base nodule (arrows). This small nodule shows no significant tracer accumulation at PET. The lesion was followed with serial chest CT and subsequently showed growth. Primary pulmonary malignancy was ultimately proven at biopsy. (Courtesy Michael Gotway, MD.)



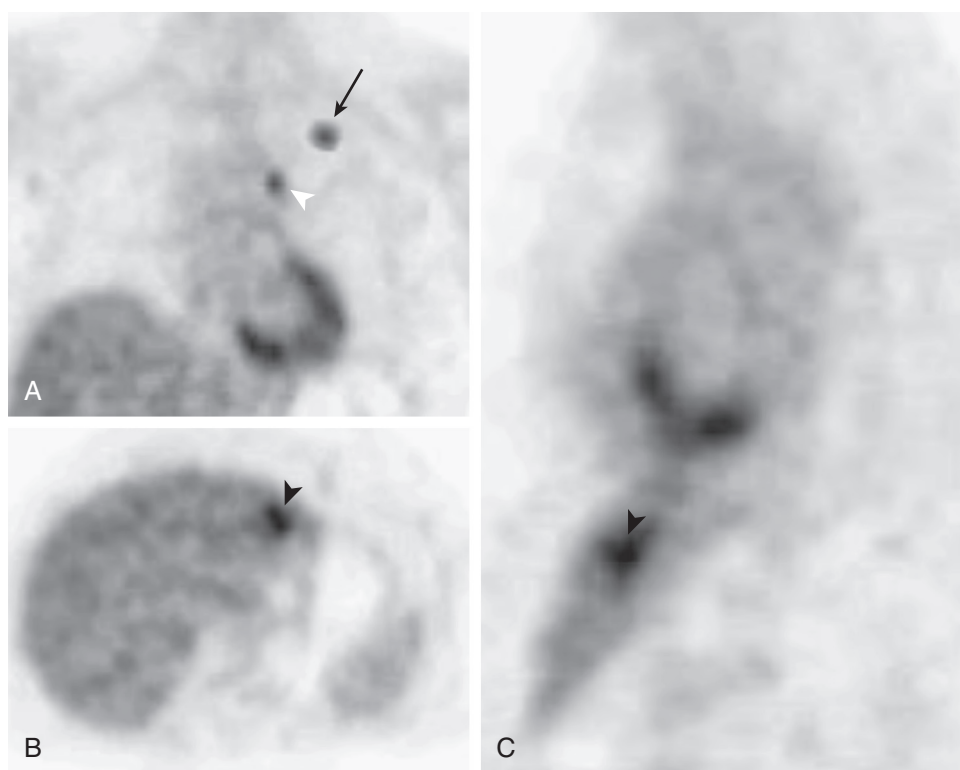
eFigure 53-8 Positive impact of PET on lung carcinoma: stage migration from stage III to stage IV classification. **A** and **B**, Coronal whole-body fused PET images in a patient with a left upper lobe pulmonary malignancy (*large arrow, B*) show ipsilateral mediastinal lymph node involvement (*white arrowhead, B*) and an unsuspected isolated contralateral rib metastasis (*small arrow, A*) and brain metastasis (*black arrowhead, B*). (Courtesy Michael Gotway, MD.)



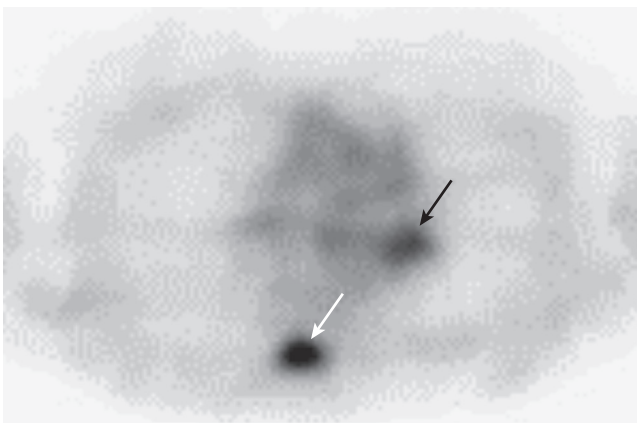
eFigure 53-9 Extrathoracic metastatic disease from lung carcinoma shown at CT. **A**, Caudal image from enhanced chest CT shows bilateral cystic adrenal metastases (*arrows*). **B**, Enhanced neck CT shows an avidly enhancing left parotid nodule, proven on biopsy to reflect metastatic lung carcinoma. **C**, Contrast-enhanced axial brain CT shows a peripherally enhancing brain metastasis (*arrow*) with surrounding vasogenic edema. (Courtesy Michael Gotway, MD.)



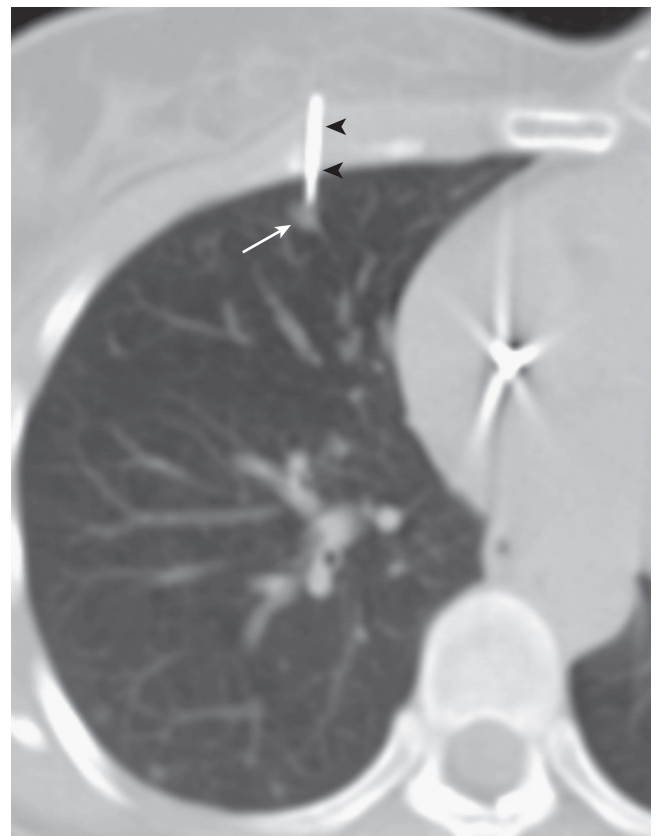
eFigure 53-10 Lung cancer staging with PET: adrenal metastasis. Coronal PET shows a medial left lung malignancy (*arrow*) with an isolated right adrenal metastatic focus (*arrowhead*). (Courtesy Michael Gotway, MD.)



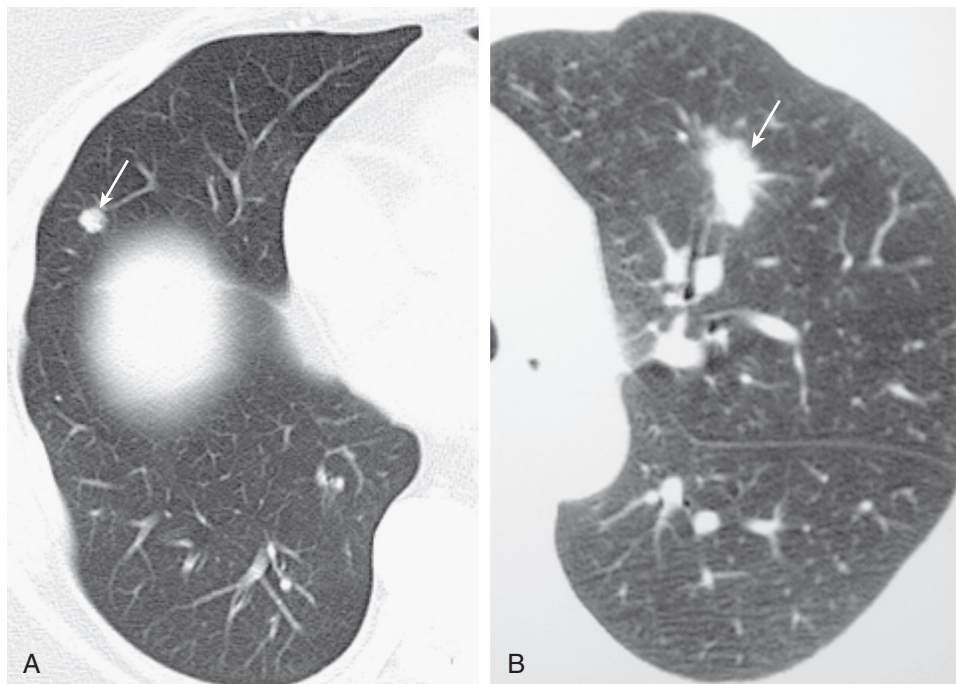
eFigure 53-11 Lung cancer staging with PET: hepatic metastasis. Coronal (**A**), axial (**B**), and sagittal (**C**) PET imaging shows a left upper lobe pulmonary malignancy (*arrow*, **A**) and ipsilateral mediastinal lymph node involvement (*arrowhead*) associated with an isolated hepatic metastatic focus (*arrowheads*, **B** and **C**). (Courtesy Michael Gotway, MD.)



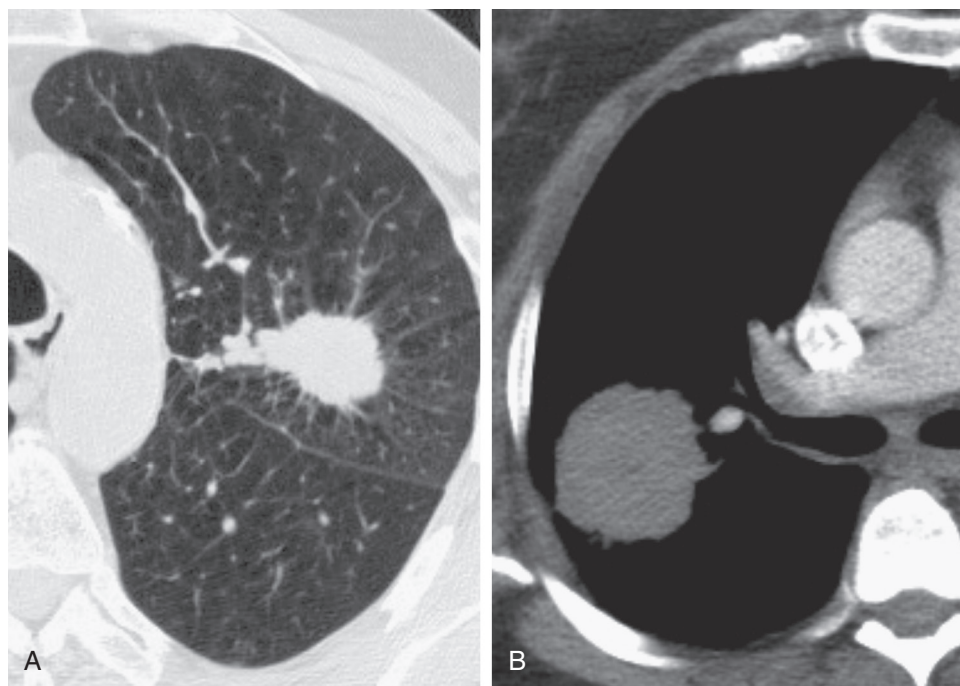
eFigure 53-12 Lung cancer staging with PET: osseous metastasis. Axial PET image shows a medial left lung malignancy (*black arrow*) associated with a vertebral body metastatic focus (*white arrow*). (Courtesy Michael Gotway, MD.)



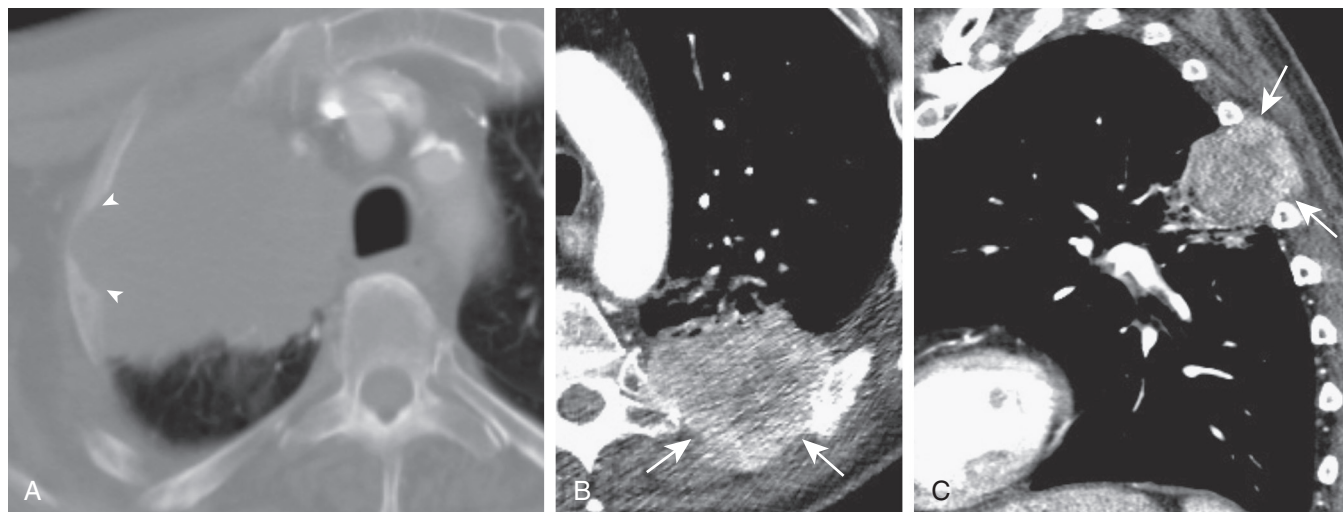
eFigure 53-13 Transthoracic percutaneous lung biopsy for the diagnosis of pulmonary malignancy. Axial chest CT image acquired during a percutaneous biopsy procedure. The biopsy needle (*arrowheads*) has been advanced to biopsy a nodule (*arrow*). (Courtesy Michael Gotway, MD.)



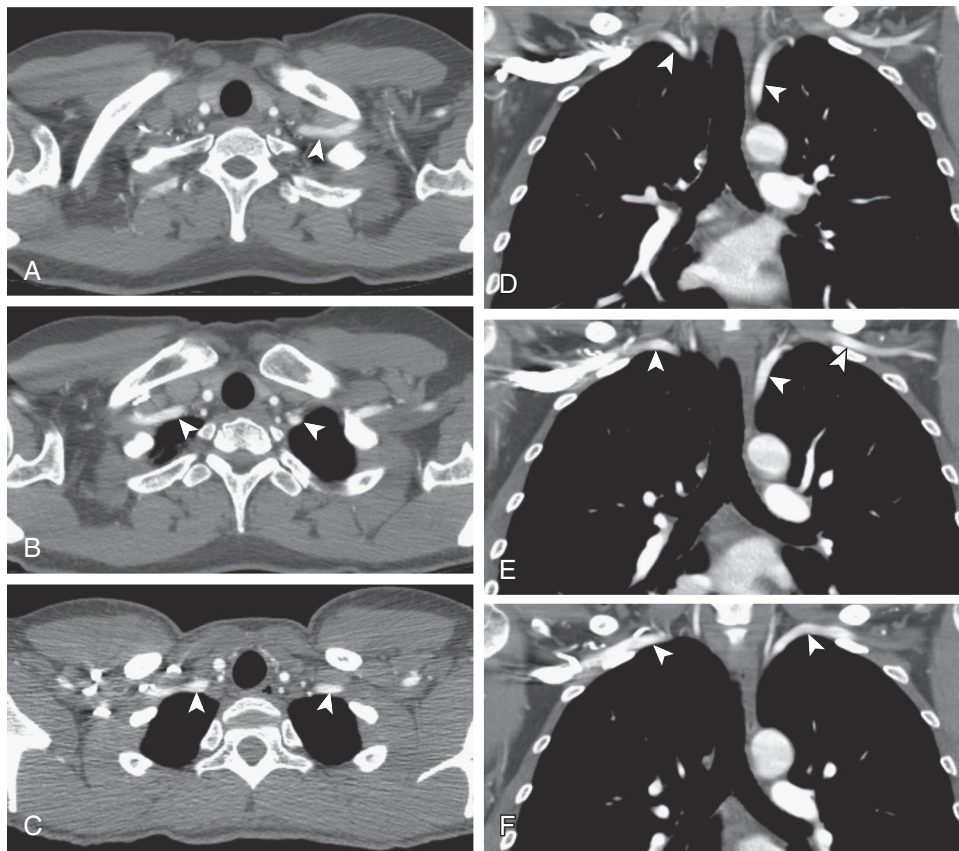
eFigure 53-14 T staging for primary pulmonary malignancy. **A**, T1a lung carcinoma: 8-mm lobulated nodule (*arrow*) in the inferior right middle lobe, completely surrounded by lung. **B**, T2a lung carcinoma: 2.8-cm spiculated left upper lobe nodule (*arrow*), completely surrounded by lung parenchyma, greater than 2 cm away from the carina, and without chest wall or parietal pleural invasion. (Courtesy Michael Gotway, MD.)



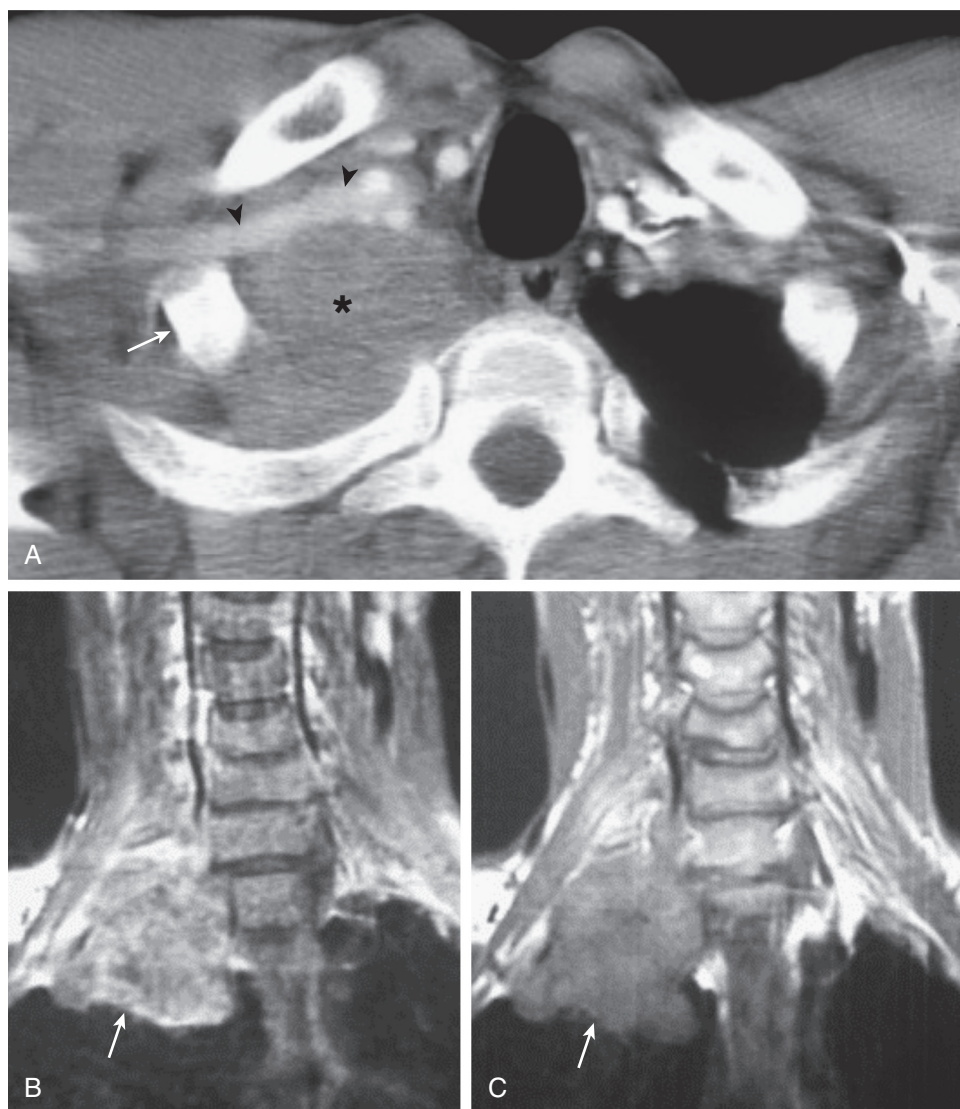
eFigure 53-15 T staging for primary pulmonary malignancy: locally restricted disease. T2a lung carcinoma: 3.8 cm left upper lobe spiculated mass, completely surrounded by lung parenchyma, greater than 2 cm away from the carina, and without chest wall or parietal pleural invasion (**A**), and 4.8 cm right upper lobe mass, completely surrounded by lung parenchyma, greater than 2 cm away from the carina, and without chest wall or parietal pleural invasion (**B**). (Courtesy Michael Gotway, MD.)



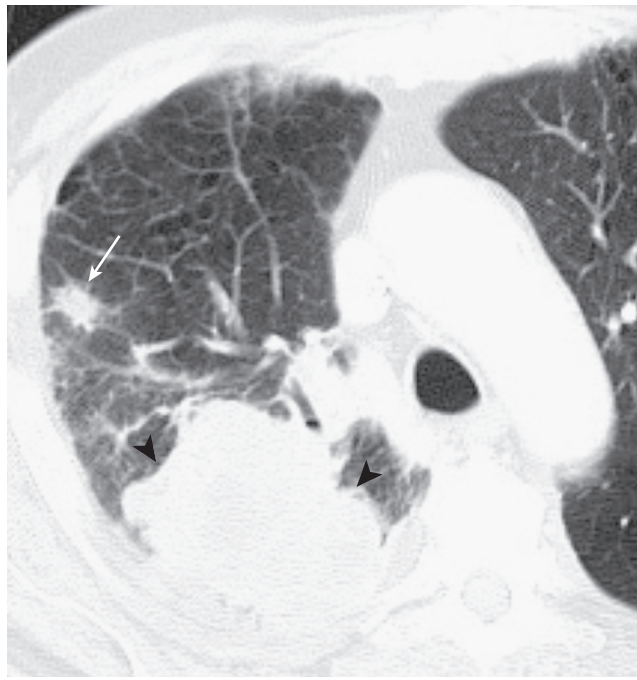
eFigure 53-16 T staging for primary pulmonary malignancy: chest wall invasion. **A**, Axial chest CT displayed in bone windows shows a large right upper lobe mass with clear erosion of the internal cortex of the rib (*arrowheads*). **B** and **C**, Axial and sagittal enhanced chest CT shows an avidly enhancing subpleural left upper lobe mass extending into the soft tissues of the chest wall (*arrows*). (Courtesy Michael Gotway, MD.)



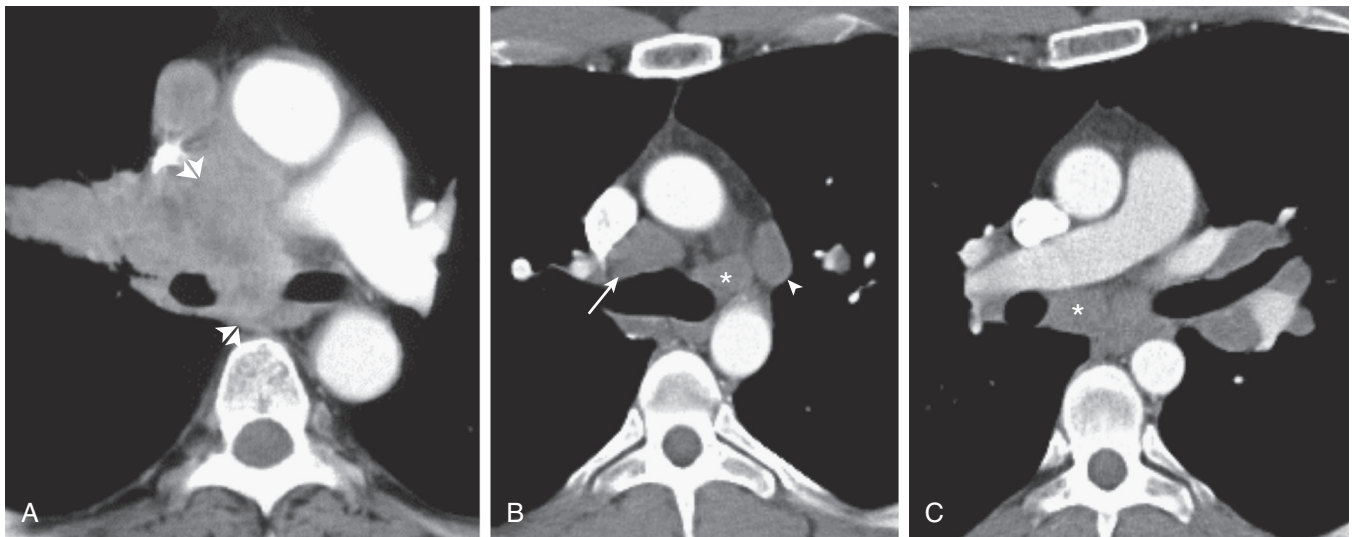
eFigure 53-17 Superior sulcus anatomy. Axial (A–C) and coronal (D–F) enhanced chest CT through the upper thorax shows the region of the superior sulcus. A–C, Axial enhanced chest CT shows the region of the superior sulcus, extending from the inferior neck superiorly and bounded by the first rib inferiorly and vertebral body medially, and containing structures such as the brachial plexus, stellate ganglion, apical pleura and Sibson fascia, subclavian vein, and subclavian artery (*arrowheads*). (Courtesy Michael Gotway, MD.)



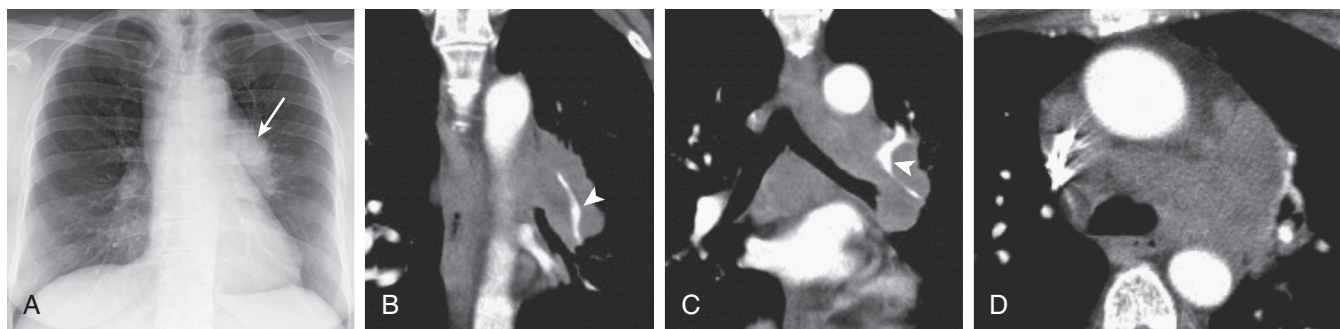
eFigure 53-18 Primary pulmonary malignancy arising in the superior sulcus. **A**, Axial enhanced chest CT shows a mass (*) in the superior sulcus. The region of the superior sulcus on axial CT can be readily and quickly identified when the subclavian artery (*arrowheads*) and first rib (*arrow*) are seen. Coronal T2-weighted (**B**) and T1-weighted (**C**) MRI shows the right upper lobe mass (*arrows*) extending cranially into the neck soft tissues, involving the brachial plexus. (Courtesy Michael Gotway, MD.)



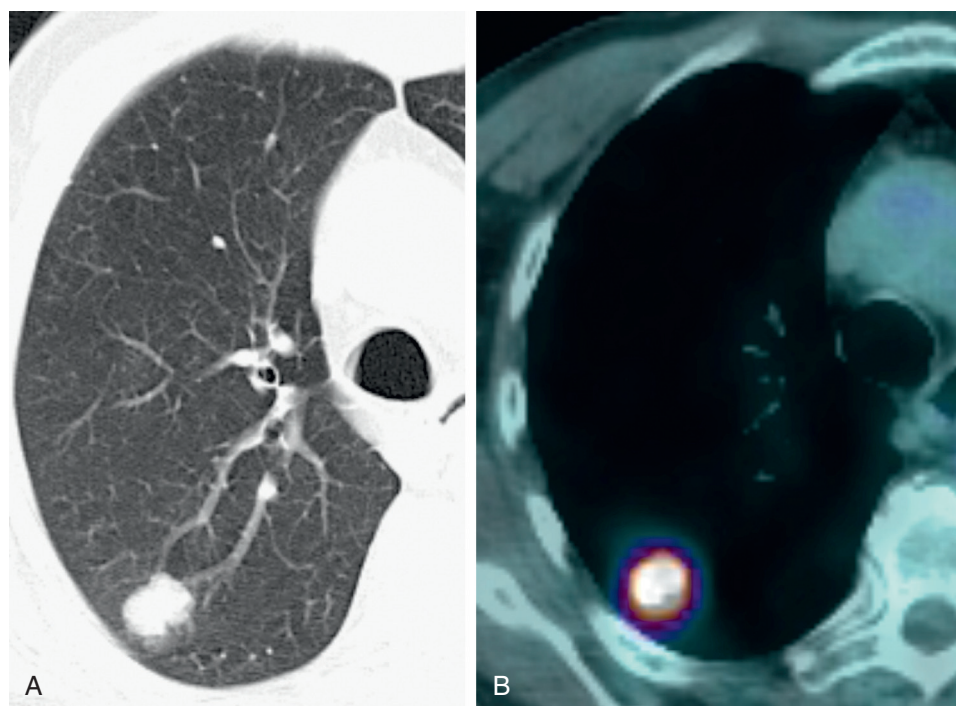
eFigure 53-19 T staging for primary pulmonary malignancy: locally advanced disease. Axial chest CT shows a large primary pulmonary malignancy (*arrowheads*) in the superior segment of the right lower lobe, with a separate tumor nodule in the right upper lobe (*arrow*) (an ipsilateral nonprimary lobe), consistent with T4 disease. (Courtesy Michael Gotway, MD.)



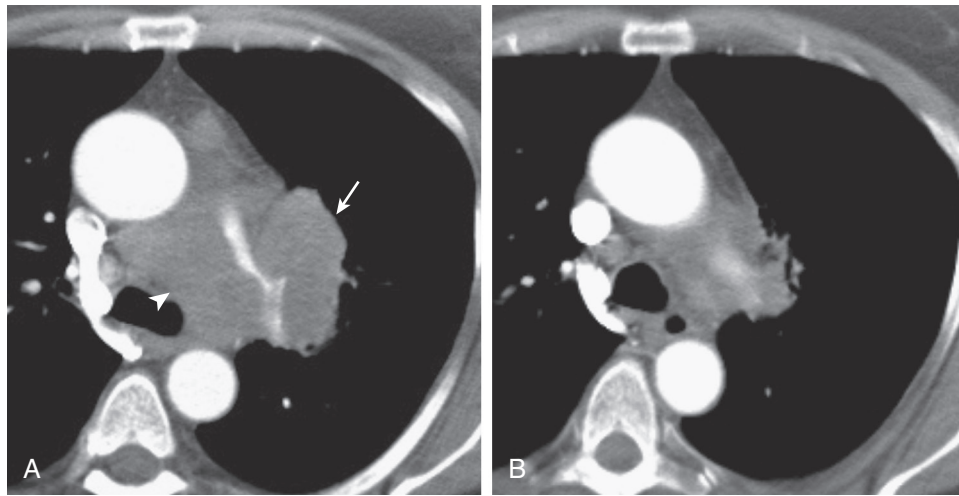
eFigure 53-20 Infiltrating lymphadenopathy versus discrete lymphadenopathy. **A**, Axial enhanced chest CT at the level of the carina shows confluent soft tissue with areas of low attenuation (*double arrowheads*) occupying the right paratracheal and subcarinal spaces, extending toward the right peribronchial region. **B** and **C**, Axial enhanced chest CT shows discretely enlarged lymph nodes in the right paratracheal space (station 4R) (*arrow*, **B**), left tracheobronchial angle (station 4L) (*, **B**), aortopulmonary window region (station 5) (*arrowhead*, **B**), and subcarinal space (station 7) (*, **C**). (Courtesy Michael Gotway, MD.)



eFigure 53-21 Small cell carcinoma: typical imaging appearance. **A**, Frontal chest radiograph shows increased density and enlargement of the left hilum (*arrow*). Coronal (**B** and **C**) and axial (**D**) enhanced chest CT shows confluent soft tissue surrounding and narrowing the left pulmonary artery (*arrowheads*, **B** and **C**) and extending into the mediastinum. (Courtesy Michael Gotway, MD.)



eFigure 53-22 Small cell carcinoma presenting as a solitary pulmonary nodule. **A**, Axial chest CT shows a lobulated peripheral right upper lobe nodule. Appearance suggests pulmonary malignancy, especially adenocarcinoma. **B**, Fused axial PET shows intense metabolic activity within the nodule. Biopsy revealed small cell lung carcinoma. (Courtesy Michael Gotway, MD.)



eFigure 53-23 Small cell carcinoma: treatment response. **A**, Axial enhanced chest CT shows confluent left hilar (*arrow*) and mediastinal (*arrowhead*) lymphadenopathy, proven to represent small cell carcinoma. **B**, Axial enhanced chest CT following therapy shows marked regression in the confluent lymphadenopathy. (Courtesy Michael Gotway, MD.)

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INTRODUCTION

Rare lung tumors are defined as lung tumors with low prevalence and unusual histology. Overall, these tumors account for less than 1% of all primary lung tumors, whereas they correspond to more than 100 different histologic, clinical, radiologic, and prognostic entities.¹⁻⁴ Some rare lung tumors are specific to the lung, whereas others represent tumors more frequently found in other organs that are only rarely detected in the lungs. It is estimated that about 60% of rare primary pulmonary tumors correspond to benign and low-grade lesions and that 40% are malignant.^{1,2} The rare tumors are characterized by their low incidence, but also by poor clinical and imaging descriptions, by the low number of experienced specialists for each tumor subtype, and by the limited amount of specific therapeutic data. Recognition of rare lung tumors relies on characteristic clinical and radiologic signs, on a modified diagnostic and imaging strategy, and on the determination of their primary or secondary nature. Interestingly, some of the rare lung tumors may have a propensity to mimic lung carcinoma as well as benign orphan lung diseases, because they may share clinical, imaging, pathologic, and even molecular features.^{4,5}

Pseudotumors have further been described in the thorax, historically referring to any pseudoneoplasm, but currently restricted to a specific heterogeneous group of diseases characterized by circumscribed fibrous tissue associated with inflammatory and myofibroblastic cells.⁵⁻⁷ Among those, borderline neoplastic/non-neoplastic disorders have been identified, such as inflammatory myofibroblastic tumor with clonal proliferation, thus emerging as a true neoplasm.⁵⁻⁷ Other rare pulmonary disorders are emerging as borderline neoplastic/non-neoplastic disorders, which require multidisciplinary expertise both in the field of

orphan pulmonary diseases and in thoracic oncology, including, for example, amyloidosis or Langerhans cell histiocytosis.

Here our objective is to provide the reader with a practical overview of these disorders. Selected lesions of special interest with relatively high incidence are discussed to illustrate specific issues regarding the overall diagnostic and therapeutic management of rare malignant primary pulmonary tumors and borderline entities. In a closely related chapter, Chapter 56, some of the same entities are discussed when they have overlap between benign and malignant behavior.

CHARACTERIZATION OF RARE LUNG TUMORS

Although accounting for less than 1% of lung malignancies, rare lung tumors correspond to a large array of histopathologic, clinical, radiologic entities.¹⁻⁴ Prevalence may also range from merely uncommon lesions, such as carcinoids, which account for 0.15% of primary lung tumors, to extremely unusual tumors, such as primary pulmonary melanoma, with fewer than 50 reported cases.^{8,9} Overall, the most frequent rare malignant primary lung tumors are, in decreasing order of frequency: carcinoid, *mucosa-associated lymphoid tissue* (MALT) lymphoma, and pneumoblastoma.^{1,10}

Most rare lung tumors develop from orthotopic tissues, constitutive of the normal lung parenchyma, and from hematopoietic tissues,^{1,2} whereas tumors derived from ectopic tissues, including melanoma and meningioma, are more uncommon.¹¹ Some rare tumor subtypes, such as *lymphomatoid granulomatosis* (LG), arise specifically

within the lung, whereas others, such as blastomas and perivascular epithelioid cell tumors, arise in many different tissues of the body including the lung and are infrequent wherever they are located. Furthermore, some primary tumors that are uncommon within the lung may be frequent in other locations, including lymph node lymphomas and soft tissue sarcomas, which present with specific histopathologic differentiation when originating in the lung, such as MALT lymphoma and angiosarcoma, respectively.¹

From a clinical point of view, the hallmarks of rare lung tumors may be, more than their actual low frequency, the absence of comprehensive clinical data, the low number of specialized groups for the care of each tumor subtype, and the lack of specific therapeutic recommendations. More than 90% of rare lung tumor observations are published as case reports or small series including fewer than five patients.^{1,7} Currently, only carcinoids and large cell neuroendocrine carcinoma, as the most frequent of the rare tumor subtypes, have been characterized regarding their clinical, therapeutic, and prognostic features in large retrospective and prospective studies.¹²⁻²⁰

Patients with rare lung tumors, like many patients with cancer, tend to go through several stages of grief, including depression, uncertainty, hope, disappointment, and in most cases, physical degradation and social isolation. The rarity of the tumor may also enhance these feelings, owing to the relative lack of information and the increased feeling of isolation, the geographic disparity in access to specific care, the longer duration of the pretherapeutic workup, the involvement of multiple specialists, a feeling of injustice especially in young and never-smoking patients, and the complex management undertaken in a state of uncertainty.²¹ As a result, patients with rare lung tumors may not receive equal care and some may feel “orphaned,” being incompletely integrated in the process of care of patients with the more frequent bronchogenic carcinoma.

PRIMARY PULMONARY LYMPHOMA AND OTHER LYMPHOPROLIFERATIVE DISEASES

Primary pulmonary lymphoma is defined as a lymphoma affecting one or both lungs, without evidence of extrapulmonary involvement or bone marrow disease at the time of diagnosis and during the subsequent 3 months.²²⁻²⁴ For clinicians, pulmonary lymphomas associated with small-size satellite mediastinal and/or systemic nodes are also regarded as originating from the lung.²³⁻²⁷ Even including these tumors, primary pulmonary lymphomas are rare, representing 0.4% of all lymphomas.²² The most frequent subtypes are MALT-type lymphoma and LG. Other subtypes are found only in immunocompromised patients (eFigs. 90-33 through 90-37, 91-16, and 91-17). Primary pulmonary lymphoproliferative disorders may present with a wide range of radiologic features, mimicking organizing pneumonia, interstitial diseases, or lung cancer.

MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA

Pulmonary MALT lymphoma is referred to as nodal marginal-zone B-cell lymphoma, with similar cytopathologic features to other MALT lymphomas, especially gastric lymphoma.²⁸ These low-grade lymphomas account for 70% to 90% of primary pulmonary lymphomas. At pathologic examination, MALT lymphoma appears as a diffuse infiltrate of small monomorphic lymphoid cells, with a typical lymphangitic growth pattern spreading along the broncho-vascular bundles and interlobular septa, and forming solid nodules that fill the alveolar spaces and obliterate the normal lung architecture (Fig. 54-1C and D). Immunohistochemistry forms the basis of the subtype classification, with the expression of the pan-B-markers CD20 and CD79 and the absence of staining for CD5 and CD10.^{28,29} The proliferation is monotypic, with surface and/or cytoplasmic expression of *immunoglobulin* (Ig) M and, less frequently, IgG and IgA (see Fig. 54-1E and F). Light chain restriction can be detected in the plasmacytic component using flow cytometry. MALT lymphomas are associated with unique chromosomal translocations, such as the t(11;18)(q21,q21) resulting in a fusion of the *API2* and *MALT1* genes, the t(1;14) (p22;q32) involving the *BCL10* and *IGH* genes—which is overall much less frequent, more specific to lung locations, and never found in high-grade lymphoma—and the t(14;18)(q32;q21) involving the *IGH* and *MALT1* genes.³⁰⁻³² The precise mechanisms leading to the development of these translocations remain unknown, but they all appear to result in an inhibition of apoptosis and a survival advantage to the cells. In cases with the t(1;14) (*BCL10/IGH*) translocation, immunohistochemistry on paraffin-embedded tissues can detect the strong nuclear overexpression of BCL10, thought to have prosurvival functions. Amplification of the *IGH* gene from paraffin-embedded or cytologic samples with *polymerase chain reaction* (PCR)-based assays was demonstrated to be a reliable method to detect monoclonality in more than 60% of MALT lymphomas.³⁰⁻³²

Contrary to extrapulmonary MALT lymphomas, for which a strong relationship has been established with chronic bacterial inflammation related to *Helicobacter pylori* in the stomach and to *Chlamydia psittaci* in the ocular adnexa, no chronic infectious condition has been associated with pulmonary MALT lymphoma, although concurrent evolution with chronic hepatitis C has been described. However, MALT is absent in the normal bronchial tree and is thought to develop only after long-term inflammation secondary to smoking or to an autoimmune condition.

MALT lymphoma has mainly been observed in patients older than 45 years, with a slight male predominance, but it may also arise in younger patients with underlying immunosuppression, especially related to *human immunodeficiency virus* (HIV) infection, or with inflammatory conditions such as Sjögren disease or rheumatoid arthritis, or in association with *Epstein-Barr virus* (EBV) infection.^{22-27,33,34} Less than 50% of patients are symptomatic, with nonspecific symptoms including cough, dyspnea, and chest pain.^{23,25,26} Unlike the situation with other lymphomas, systemic signs such as fever, swelling, and weight loss are uncommon. Association with IgM or IgG blood monoclonal

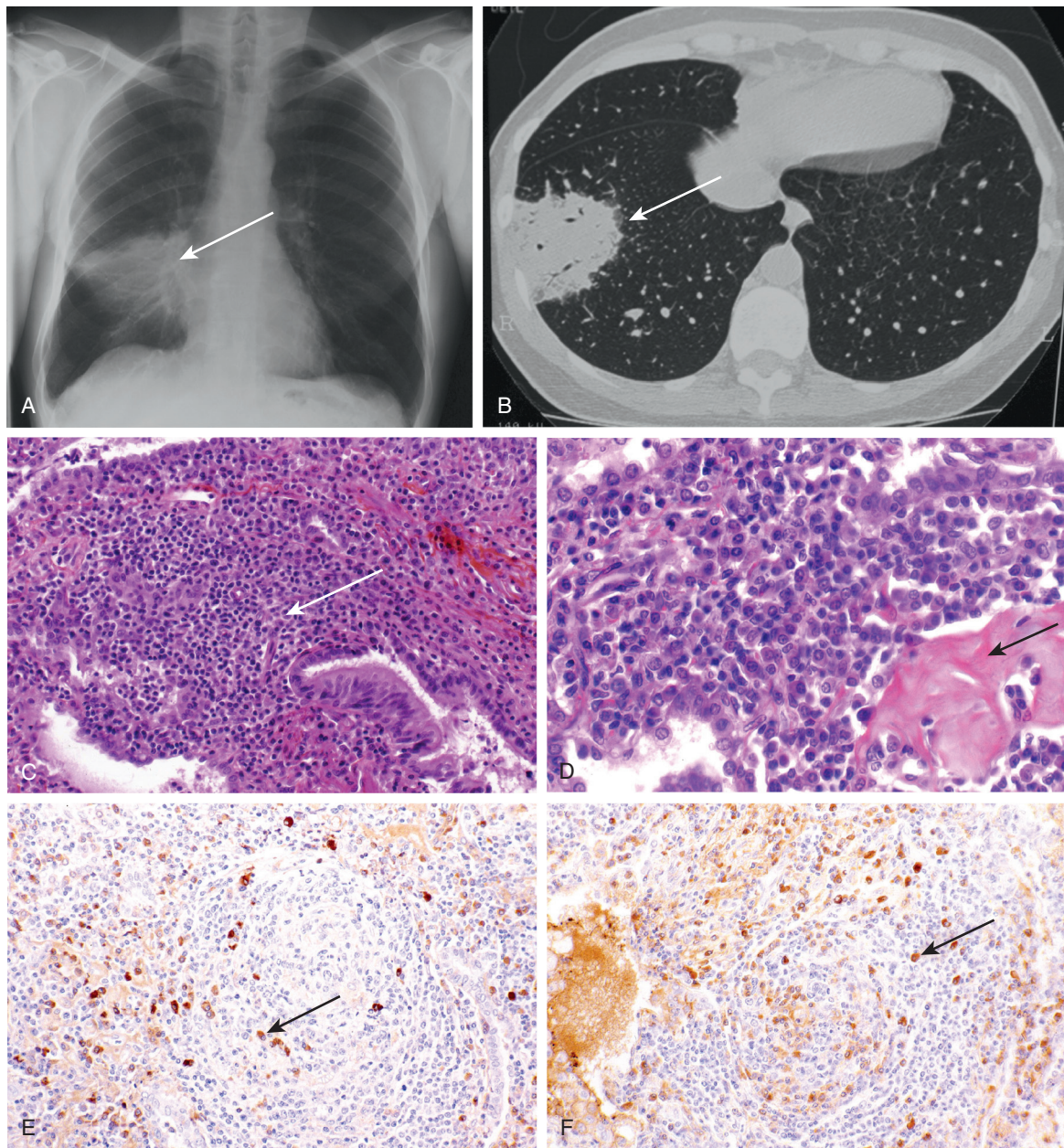


Figure 54-1 Primary pulmonary mucosa-associated lymphoid tissue lymphoma. Chest radiograph (A) and chest CT (B) show a focus of consolidation in the right lower lobe that persisted despite prolonged antibiotic therapy. C, Pathologic examination of surgical biopsy showed proliferation of small-size lymphoid cells infiltrating the bronchial wall. Note a bronchial epithelium encased by destructive lymphoid proliferation (arrow). D, At high magnification, lymphoplasmacytic-like cells of the marginal zone lymphoma are associated with an amyloid deposit (arrow). E, With immunoglobulin (Ig) lambda light chain immunostaining, there is a predominance of lambda chain plasma cells (lambda chain restriction; arrow). F, With Ig mu heavy chain immunostaining, there is a predominance of IgM type in plasmacytic and plasma cells (arrow). (C, H&E stain; original magnification $\times 40$. D, Original magnification $\times 100$. E and F, Original magnification $\times 40$.)

gammopathy is observed in 30% of cases. MALT lymphoma exhibits three imaging patterns on chest radiography and computed tomography (CT), which are challenging for differential diagnosis: (1) the most frequent and suggestive is the “pneumonia-like” alveolar consolidation with air bronchograms (see Fig. 54-1A and B) that is typically localized in the middle lobe; (2) a “tumor-like” appearance with a solitary circumscribed nodular opacity (30% of cases) (eFig. 54-1) and possible central air bronchogram; and (3) the “infiltrative” pattern with diffuse poorly defined ground-glass opacities (eFig. 54-2), assumed to represent early-

stage disease before tumor cells invade alveolar spaces.^{22-27,35} The combination of a nodular opacity with peripheral peribronchovascular ground-glass attenuation halo is frequent. Pleural effusion is unusual.

About a third of MALT lymphomas are multifocal at the time of diagnosis, a presentation that may hamper the determination of the primary site.³⁵⁻³⁶ Pulmonary MALT lymphomas are associated with tumor locations in the gastric mucosa in 10% to 20% of patients and in the bone marrow in 15% to 20% of patients. Gastroscopy and bone marrow biopsy are then frequently performed as a

pretreatment workup. ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning may not be sensitive enough in MALT lymphoma to exclude extrathoracic disease.^{23,37} The Ann Arbor staging system, although not designed for extranodal lymphoma, may be applied in pulmonary MALT lymphoma, which would be staged as IE (one site, extranodal) in case of lung unilateral or bilateral involvement, and IIE (two sites, both above the diaphragm, extranodal) in case of hilar or mediastinal lymph nodes.

The diagnosis often requires a surgical lung biopsy, because cytologic examination of bronchoalveolar lavage or fine-needle biopsy may show the CD20-positive B-cell infiltration but fail to exclude differential diagnoses, such as reactional lymphoid proliferation, follicular bronchiolitis, or lymphoid interstitial pneumonia. *MALT1* gene rearrangements may be diagnosed on bronchoalveolar lavage.^{31,32}

Therapeutic options are based on the degree of tumor extension. Surgical resection ensures both the diagnosis and the treatment of nodular lesions. In asymptomatic patients, a watch-and-wait attitude may be preferred to aggressive treatment. More advanced MALT lymphoma requires more aggressive management, and several options have been described, from resection to radiotherapy, or single-agent chemotherapy with chlorambucil, fludarabine, or rituximab; chlorambucil may produce the best results.³⁸ Rituximab, an anti-CD20 antibody, is particularly effective and well tolerated and may represent an alternative to chemotherapy, especially in the case of t(11;18) translocation.³⁹ Current data favor systemic treatments in MALT lymphomas, considering that these tumors may represent the early-stage manifestation of a systemic disorder of mucosal immunity.²⁶ Furthermore, the fact that surgical resection has not been shown to improve prognosis in some series is an additional argument against local treatments. Recently, the addition of rituximab to chlorambucil demonstrated a significant effect on survival in patients with MALT lymphoma.^{39a} Prognosis of MALT lymphomas is excellent, with an indolent and localized prolonged course. Historical series reported 5-year survival rates higher than 80%, and the more recent availability of rituximab may even improve these results.^{23-25,27} Local and systemic recurrences develop in about 50% of cases, but are usually controllable with chemotherapy. Evolution to high-grade B-cell lymphoma is seen in less than 5% of cases. Young age is the most significant favorable prognostic factor.

LYMPHOMATOID GRANULOMATOSIS

Lymphomatoid granulomatosis (LG), also called “angiocentric lymphoma,” is a malignant B-cell angiocentric and angiodestructive lymphoproliferative disorder. For a long time, LG was considered an inflammatory granulomatous disease owing to a clinical presentation similar to other granulomatoses, such as granulomatosis with polyangiitis (formerly Wegener disease) and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome). Now, LG is recognized as a true EBV-related lymphoid malignancy. Differential diagnosis also includes allergic bronchopulmonary aspergillosis. The lung is the most frequent location, but the disease may also involve the brain, the skin, and the liver.⁴⁰⁻⁴³

LG forms multiple and confluent nodules composed of an atypical, angiocentric, and polymorphous lymphoid infiltration involving the vascular walls, from the subendothelium to the adventitial zones, with focal lumen obliteration. By immunohistochemistry, these lymphoid cells are characterized mostly as CD4⁺ T-lymphocytes, with scattered atypical cells of B phenotype.⁴⁰ Large B cells are infected with EBV in 65% of cases, a fact that correlates with the grade of the lesion. Pulmonary biopsy is required in most cases to exclude other granulomatoses.

LG arises in middle-aged patients between 40 and 50 years old, with a male predominance.^{41,42} Nearly all patients present with respiratory and systemic symptoms, consisting of cough, dyspnea, hemoptysis, chest pain, fever, and weight loss. Peripheral and mediastinal lymphadenopathy is absent. Prolonged immunosuppression is a frequent underlying condition. Hypereosinophilia may be observed in the blood and/or in the bronchoalveolar lavage. The typical radiologic presentation consists of multiple smooth bilateral nodules ranging from 2 to 10 cm mainly localized in the lower lobes, exhibiting a peribronchovascular pattern and mimicking multiple metastases (eFigs. 54-3 and 54-4).^{1,5,22,41} As in other granulomatoses, convergent nodules may migrate and form cavitated pseudotumoral masses. Ground-glass opacities may be present. Peripheral and mediastinal lymphadenopathy is absent. Lung biopsy is required in most cases to make the diagnosis.

Chemotherapy based on high-dose steroids with cyclophosphamide is the most frequently reported treatment. The additional use of rituximab may increase the efficacy of these cytotoxic agents.^{44,45} The overall prognosis is grim, with a 5-year survival of 30% to 40%, owing to progression to nodal diffuse aggressive lymphoma in 20% to 50% of patients. As in lymphoma, the main prognostic factors are age, extension of the lesions, and response to first-line chemotherapy.^{43,45} LG is increasingly considered a low-grade or early-stage lymphoma, and a histopathologic grading system has been developed, based on the degree of cellular atypia and necrosis, to predict the risk of evolution to high-grade lymphoma and to select patients for early aggressive treatment.⁴⁵

OTHER LYMPHOMAS AND LYMPHOPROLIFERATIVE DISEASES

Other primary pulmonary malignant lymphoproliferative diseases are very rare and include high-grade diffuse large B-cell lymphoma, intravascular large cell lymphoma, Hodgkin lymphoma, and plasmacytoma.

Primary pulmonary diffuse large B-cell lymphoma is likely underrecognized owing to its rapid spread to mediastinal nodes and other extrathoracic sites, which may hide its pulmonary origin.^{33,34} Histologically, it shows characteristics similar to those of diffuse large B-cell lymphomas at other sites, with diffuse infiltration of large blastic lymphoid cells, expressing pan-B antigens (CD20 and CD79a). Primary pulmonary high-grade B-cell lymphomas typically develop in immunocompetent patients in their sixth to seventh decade. In younger patients, large B-cell lymphoma may be caused by latent EBV infection, which may develop following drug-induced immunosuppression, as from methotrexate or antilymphocyte antibodies in

transplant recipients,^{46,47} or following HIV-related immunosuppression. In patients with HIV infection, the availability of highly active antiretroviral therapy led to the near disappearance of primary pulmonary high-grade lymphomas, which are now less frequent than MALT lymphomas in these patients.^{22,33} Patients often present with marked respiratory and systemic symptoms. Radiologic studies usually show multiple well-defined rounded solid masses of various sizes, more frequently in the subpleural areas of the lower lobes (see eFigs. 90-33 through 90-35).^{34,47} Chemotherapy is based on the same multiagent regimens as those used in high-grade nodal lymphomas, including doxorubicin (Adriamycin), prednisone, and rituximab.^{22,33} The overall prognosis is much worse than for MALT lymphoma, with a 5-year survival lower than 20%.

Intravascular large cell lymphoma is a variant of non-Hodgkin lymphoma, in which neoplastic lymphoid cells proliferate within the lumen of small and intermediate-sized blood vessels, resulting in thrombotic and ischemic complications.⁴⁶ Clinical manifestations are multiple, but lymphadenopathy is usually absent. Pulmonary imaging features include bilateral ground-glass opacities and/or sometimes migratory atelectatic shadows (eFig. 54-5).⁴⁸ Treatment with conventional combination chemotherapy with or without rituximab leads to remission and prolonged survival.^{22,48}

Primary pulmonary Hodgkin lymphoma has been reported exclusively in old studies, and might actually correspond to nodal Hodgkin disease with secondary pulmonary involvement.⁴⁹ On chest radiography, it is described as a solitary mass (eFig. 54-6) with cystic and heterogeneous features, typically involving the upper lobes, or as a multinodular disease. Diagnosis is based on the recognition of characteristic Reed-Sternberg cells at pathologic examination. The overall outcome is poorer than in nodal Hodgkin lymphoma.

Primary pulmonary plasmacytoma is a solitary lesion exclusively composed of atypical monoclonal plasmocytes, possibly associated with amyloid deposition, without evidence of extrapulmonary myelomatous disease.^{50,51} Again, the apparent decrease of the incidence of primary pulmonary plasmacytoma may be related to the increased sensitivity of biologic and imaging studies for the detection of primary extrapulmonary disease. Moreover, about one third of patients operated on for pulmonary plasmacytoma were reported to present with multiple myeloma in following years.^{50,51} Surgical resection is, however, recommended for solitary tumors, with a 5-year survival of 60%.⁵¹

CARCINOIDS AND OTHER NEUROENDOCRINE TUMORS

Primary lung neuroendocrine tumors share common histopathologic features and correspond to four different clinical and prognostic entities: (1) low-grade typical carcinoids, (2) intermediate-grade atypical carcinoids, and (3) high-grade large and (4) small cell neuroendocrine carcinomas.⁵² The small cell lung carcinomas are common, accounting for 15% to 20% of all primary lung malignancies. On the contrary, carcinoids and large cell neuroendocrine carcino-

mas account for 0.5% to 2% of lung tumors and are thus considered the most frequent lesions among the rare lung tumors.

PATHOLOGIC CLASSIFICATION

Neuroendocrine tumors share varying degrees of neuroendocrine morphologic features, including organoid nesting, the palisading and trabecular pattern, and “rosette-like” structures. Classification is mainly based on the mitotic index and the amount of necrosis.^{16,52} Typical carcinoids exhibit neuroendocrine features, with a mitotic index less than 2 mitoses per 10 high-power fields (2 mm²), and the absence of necrosis in a tumor that is more than 5 mm in diameter. Atypical carcinoids exhibit a mitotic index ranging from 2 to 10, or areas of focal necrosis. Peripheral carcinoids often may also be associated with small (<5 mm) neuroendocrine “tumorlets” and/or with diffuse hyperplasia of pulmonary neuroendocrine cells.⁵³ These lesions may correspond to early-stage in situ carcinoid proliferation.

Large cell neuroendocrine carcinomas exhibit a mitotic index higher than 10 (ranging from 70 to 80 in most cases) and extensive necrosis. Unlike small cell carcinoma, large cell carcinomas have large tumor cells, with moderate to abundant cytoplasm and, frequently, prominent nucleoli.^{16,52} Immunohistochemically, the expression of at least one neuroendocrine marker, including chromogranin, synaptophysin, or N-CAM (CD56), confirms the diagnosis. The pathologic classification also distinguishes large cell neuroendocrine carcinoma from *non-small cell lung cancer* (NSCLC) “with neuroendocrine differentiation,” a pattern without specific prognostic or therapeutic implications.⁵⁴

CARCINOID TUMORS

Excluding small cell lung cancer, more than 80% of lung neuroendocrine tumors are carcinoids.¹⁴ Carcinoids arise mostly in never-smokers (60% to 80% of cases).⁸ Carcinoids develop in the proximal airways in 60% to 70% of cases and may produce chronic cough, hemoptysis, and signs of bronchial obstruction. Peripheral carcinoids are asymptomatic, unless they are associated with diffuse hyperplasia of pulmonary neuroendocrine cells that produces bronchiolar obstruction in 50% of cases⁵⁵ and possible airflow obstruction. Unlike carcinoids in extrathoracic locations, lung carcinoids are small size lesions only rarely associated with liver metastases and do not generally produce the carcinoid syndrome (<2% of cases).^{5,11} CT shows a peripheral or proximal circumscribed solitary nodular lesion in 90% of cases,⁵⁵ often manifesting as a hilar or perihilar mass (eFig. 54-7). Carcinoid tumors may present as “iceberg-like” lesions, with a small amount of endobronchial growth and a prominent parenchymal mass (Fig. 54-2). In some cases, carcinoid tumors may present as endobronchial lesions, with or without (eFig. 54-8) lobar or segmental atelectasis. Calcification (see eFig. 54-7C) may be observed in up to 30% of cases.⁵⁵ Their hypervascularity (see eFig. 54-7B and C) can distinguish carcinoids from mucous plugging. Regional lymph node invasion is more frequent in atypical carcinoids (40% to 50% of cases vs. 10% to 15% of typical carcinoids) (eFig. 54-9), and the tumor-node-metastasis classification, although designed for

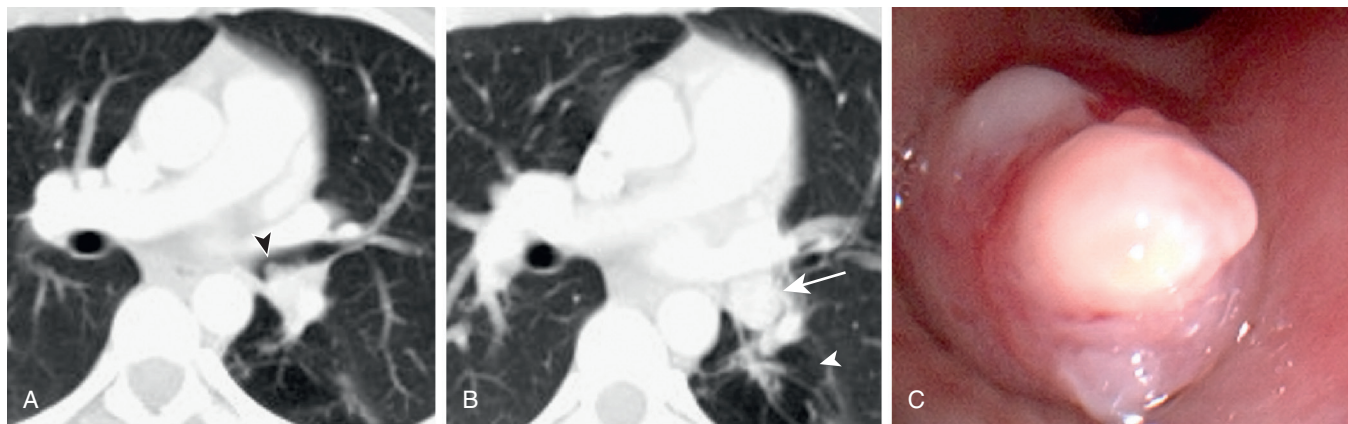


Figure 54-2 “Typical” carcinoid tumor: “iceberg-like” endobronchial mass. **A** and **B**, Axial chest CT displayed in lung windows in a 32-year-old woman with recurrent pneumonia shows complete obstruction of the left lower lobe bronchus (**B**, arrow), with a small portion of tumor protruding into the left mainstem bronchus (**A**, arrowhead), in a manner analogous to the small portion of an iceberg that protrudes above the ocean water. Left lower lobe postobstructive air trapping (**B**, arrowhead) is present, which confirms an airway origin for the lesion. **C**, Bronchoscopic image shows the left lower lobe lesion protruding into the left mainstem bronchus. (Courtesy Michael Gotway, MD.)

carcinomas, has been used to stage carcinoids.^{8,55} Although hypervascularized, carcinoids generally exhibit a low to moderate activity on PET scanning.⁵⁶ Imaging for somatostatin receptors using¹¹¹ Indium-labeled octreotide (eFig. 54-10) has shown great promise and may increase the sensitivity for diagnosis, staging, and follow-up for recurrence.⁵⁷ The risk of hemorrhage following endobronchial biopsy is less than 1%.⁵⁵

Surgery is the standard treatment for stage I-II and most stage III carcinoids, which account for 75% and 15% of cases, respectively. Typical carcinoids, with a low local recurrence rate, can be treated with limited resection with segmentectomy and regional lymph node dissection; this local approach is associated with local control and survival rates identical to that following extensive procedures.^{13,20} Endobronchial techniques, such as cryotherapy, have also been reported as an alternative approach for typical carcinoid but fail to ensure accurate counting of the mitotic index and, therefore, the confirmation of the subtype.⁵⁸ Atypical carcinoids, which have a higher local recurrence rate, require lobectomy and mediastinal lymph node dissection.^{13,20,59} Lung carcinoids metastasize in less than 10% of cases. In those cases, cisplatin-based chemotherapy is ineffective, whereas local treatment of metastases may lead to prolonged remission. Combination of everolimus plus octreotide may represent the best option.¹⁷ In sum, the most significant prognostic factor is the histopathologic subtype, because 5-year survival rates of typical and atypical carcinoids are 87% to 98% and 56% to 73%, respectively.¹²⁻¹⁶

LARGE CELL NEUROENDOCRINE CARCINOMA

The incidence of large cell neuroendocrine carcinoma has long been underestimated, probably because these tumors are often misdiagnosed as large cell undifferentiated carcinoma either on cytology or on tissue sections in the absence of immunostaining for neuroendocrine markers.^{16,60} Large cell neuroendocrine carcinomas are strongly associated with tobacco smoking (90% of cases).^{60,61} Clinical and radiologic (eFig. 54-11) features are similar to those of other bronchogenic carcinomas and, in most reported

series, treatment follows recommendations for NSCLC, including resection in stage I-II tumors.^{19,62} Epidermal growth factor receptor (EGFR) mutations may be present.⁶³ Efficacy of chemotherapy is significantly better, with up to 75% of response to the cisplatin-etoposide combination in a neoadjuvant (presurgical) setting.^{18,19,64,65} Several studies, including one prospective trial, showed a reduced metastatic recurrence rate and increased survival in patients receiving adjuvant chemotherapy even in early-stage tumors.^{60,62,64} Overall survival is better than in small cell carcinoma, with stage being the most significant prognostic factor. Five-year survival is 52% to 88%, 20% to 45%, and 0% to 15% in stages I-II, III, and IV, respectively.⁶⁰⁻⁶⁴

RARE MALIGNANT PRIMARY PULMONARY EPITHELIAL TUMORS

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma is the most frequent salivary gland-type tumor arising in the lung; other subtypes include adenoid cystic carcinoma and epithelial-myoeplithelial carcinoma. Mucoepidermoid carcinoma is a mixed malignant tumor characterized by the presence of squamous cells, goblet mucin-secreting cells, and cells of intermediate type (Fig. 54-3C and D).⁶⁵ Identification of these three cellular subtypes in cytologic examination is pathognomonic.^{65,66} Tumors are classified as low-, intermediate-, and high-grade lesions, depending on the mitotic index, the degree of cellular atypia, and the degree of necrosis. High-grade tumors contain predominantly squamous and intermediate cells and tend to infiltrate the lung parenchyma.

Mucoepidermoid carcinoma in adults mostly develops between the third and fourth decades, with an equal sex distribution.⁶⁶⁻⁶⁹ High-grade tumors (30% of cases) are usually diagnosed in older patients. Mucoepidermoid carcinoma is often associated with tobacco smoking. Symptoms, including dyspnea, cough, and hemoptysis, are related to the level of bronchial obstruction (eFig. 54-12). Metastases

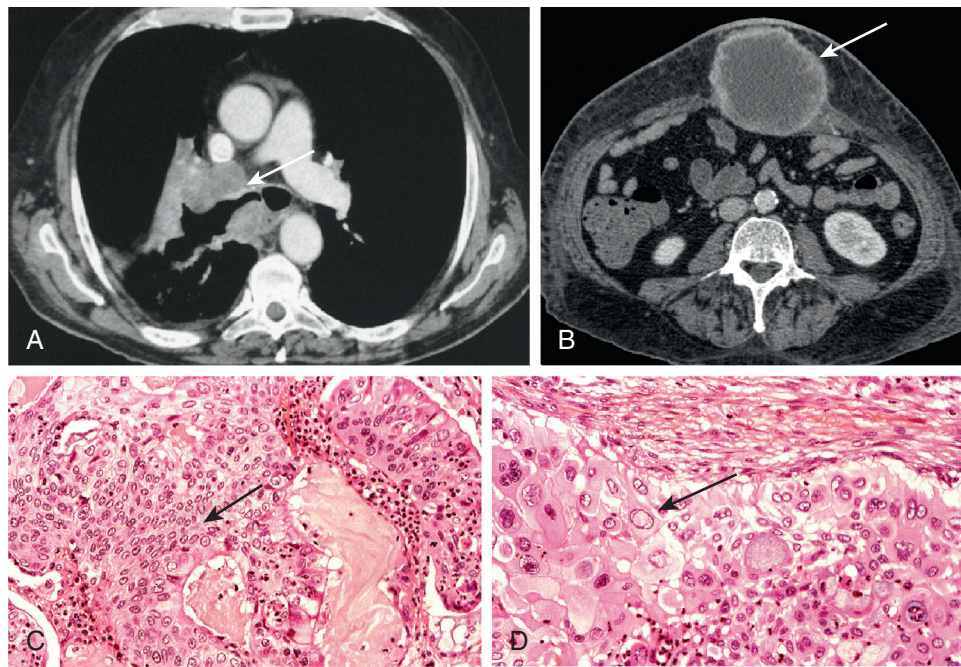


Figure 54-3 Primary pulmonary mucoepidermoid carcinoma. **A**, The tumor is located in the right upper lobe and is invading the mediastinum (arrow). Radiologic imaging features are identical to those of non-small cell lung cancer. **B**, A metastatic mass is discovered on clinical examination of the abdomen. Axial enhanced abdominal CT confirms the location in the anterior abdominal wall (arrow). Histopathologic features: a mixture of squamoid (**C**) and mucin-secreting (**D**) cells (arrows). (**C** and **D**, Original magnification $\times 40$.)

are found at time of diagnosis in 20% of cases, mainly in the liver, the bone, and the subcutaneous tissues (see Fig. 54-3B). In the lung, mucoepidermoid carcinoma often presents as a well-circumscribed homogeneous, lobulated homogenous mass, often with cystic features and/or calcification (see Fig. 54-3A).⁷⁰ The lesion is solitary in 40% to 70% of cases. Hilar involvement is found only for high-grade lesions. There is increased uptake on PET scanning.^{70,71} Proximal mucoepidermoid tumors can be diagnosed using endobronchial biopsy.⁶⁷

Treatment is the same as for NSCLC with, when feasible, extensive surgical resection including mediastinal lymph node dissection.⁶⁶⁻⁶⁹ High-grade lesions have often been reported to receive postoperative radiotherapy and chemotherapy, without clear benefit. Chemotherapy of metastatic tumors in most cases is based on cisplatin and/or 5-fluorouracil. As in NSCLC, a small number of patients with mucoepidermoid carcinoma may benefit from EGFR tyrosine kinase inhibitors.⁷² Prognosis is correlated with the grade of the lesion, the existence of nodal involvement, and the success of the initial surgical resection. Low-grade mucoepidermoid tumors mostly present in children and young adults, usually without hilar involvement, and have a 5-year survival ranging from 70% to 80%. High-grade tumors have a substantially worse prognosis, with a 5-year survival of only 30% to 45%.

PNEUMOBLASTOMA

Pulmonary blastoma is a biphasic tumor that is classified among the sarcomatoid carcinomas in the current World Health Organization classification. This tumor contains both an epithelial well-differentiated component, showing tubular architecture resembling the normal fetal lung, and

a mesenchymal undifferentiated stroma, defining the “blastema-like” configuration.⁷³ Pulmonary pneumoblastoma arises in adults and must be distinguished from “pleuropulmonary blastoma,” a tumor of early childhood related to other embryonic neoplasms, such as nephroblastoma and neuroblastoma.

Pulmonary pneumoblastoma arises in patients aged 30 to 45 years, with a marked female predominance (70% of cases) and frequent association with tobacco smoking.⁷⁴⁻⁷⁶ CT shows a solitary circumscribed homogeneous mass,⁷⁷ often with cystic and necrotic features. PET scans show increased uptake. In many cases, the tumor is initially thought to be a bronchogenic carcinoma, and complete surgical resection with mediastinal lymph node dissection ensures both the initial diagnosis and the therapy.^{74,76,78,79} Adjuvant treatment, mostly consisting of radiotherapy, has been reported in a few cases following incomplete resection or in patients with N2 mediastinal involvement.^{76,79-82} In unresectable tumors, chemotherapy is based on protocols used for sarcomas, including doxorubicin and ifosfamide. In most recent reports, survival is better than in NSCLC, especially in completely resected cases.⁷⁴

SARCOMATOID CARCINOMAS (OTHER THAN PNEUMOBLASTOMA)

Sarcomatoid carcinomas are a group of poorly differentiated non-small cell carcinomas that contain a sarcomatous component. In addition to pneumoblastoma, four subtypes are recognized:

1. Pleomorphic carcinoma, which corresponds the combination of adenocarcinoma, squamous cell carcinoma, or large cell carcinoma with spindle or giant cells.^{83,84}

2. Spindle cell carcinoma, which consists exclusively of fascicular cells.
3. Giant cell carcinoma, composed of highly pleomorphic mononucleated or multinucleated cells.⁸⁴
4. Carcinosarcoma, containing a mixture of carcinoma (frequently of epidermoid subtype) and poorly differentiated fibromatous sarcoma.⁸⁵

Sarcomatoid carcinoma has been defined in the 1999 World Health Organization classification. These tumors represent from 0.3% to 1.3% of lung tumors, and their specific clinical and radiologic features are rarely reported. Moreover, small biopsies usually do not disclose both the epithelial and the sarcomatous components of the tumor, which is then misdiagnosed as NSCLC in more than 60% of cases.¹ Clinical features are similar to other non-small cell carcinomas. Sarcomatoid carcinomas develop mostly in men, at a mean age of 65 years at diagnosis.⁸³⁻⁸⁶ Tobacco smoking is described in more than 80% of cases. Radiologic studies usually show a solitary voluminous peripheral heterogeneous mass invading the chest wall in 60% of cases.^{87,88} Vascular invasion is observed in 20% of cases. PET scans show increased uptake.

Sarcomatoid carcinomas are often treated as other non-small cell carcinomas. Alternatively, chemotherapy has been reported to follow soft tissue sarcoma regimens.⁸⁹ Response to EGFR-targeted therapies is infrequent, which may be related to frequent *KRAS* mutations in the epithelial component.^{90,91}

Contrary to pneumoblastomas, the other sarcomatoid carcinomas have been considered as highly aggressive tumors with early metastatic spread,⁹² especially in unusual sites such as the esophagus, the peritoneum, the kidney, and the subcutaneous tissues. Chemoresistance is frequent.⁹³ Median overall survival ranges from 6 to 20 months.^{83-86,88} The main favorable prognostic factors include tumor size, stage, and the absence of mediastinal involvement.^{83-86,88-90,94}

PRIMARY PULMONARY SARCOMAS

Primary pulmonary sarcomas account for 20% of all primary rare lung malignancies and comprise (1) parenchymal lung sarcomas, which usually present as a lung mass, and (2) pulmonary vascular sarcomas, which include pulmonary artery sarcomas, which may mimic chronic pulmonary embolism, and small vessel sarcomas, which may produce interstitial lung disease.^{1,2}

PARENCHYMAL SARCOMAS

Primary lung parenchymal sarcomas show identical pathologic subtypes to those of their soft tissue counterparts, with a wide spectrum of differentiation from low to high grade. Leiomyosarcoma is the most frequent primary lung sarcoma⁹⁵⁻⁹⁸ and presents with fascicles of spindle cells at right angles and/or an epithelioid growth pattern with marked hypercellularity and polymorphism. Tumor cells have irregular nuclear chromatin and prominent nucleoli.

Immunohistochemistry shows a high level of muscular actin, vimentin, and h-caldesmon, an actin-binding protein. Synovial sarcoma is the second most frequent subtype and presents with a prevalent monophasic growth pattern consisting of interweaving fascicles of densely packed spindle cells. As in their soft tissue location, the chromosomal translocation t(X;18) (p11.2;q11.2) is pathognomonic of the diagnosis⁹⁹ and results in the fusion of two genes, *SYT-SSX1* and *SYT-SSX2*. Other subtypes include pleomorphic sarcoma, made of atypical spindle cells showing a “cartwheel” or so-called storiform or radiating pattern, with elongated nuclei and giant cells with multiple and bizarre nuclei and prominent nucleoli, as well as osteosarcoma and chondrosarcoma. Because most mesenchymal malignant tumors have a benign counterpart, pathologic examination must first evaluate the grade of the lesion, according to the three-grade system of the French Federation of Cancer Centers Sarcoma Group,¹⁰⁰ and second rule out other epithelial tumors with sarcomatoid differentiation, such as pneumoblastoma or myofibroblastic tumors.^{1,5} Differential diagnosis also includes “benign” metastases from uterus (metastasizing leiomyoma) or bone (giant cell tumor).

Compared with their soft tissue counterparts, primary pulmonary sarcomas present in older patients, mainly in the sixth to eighth decade.^{96-98,101-104} Clinical symptoms are nonspecific and usually consist of cough, dyspnea, and hemoptysis, depending on the size and the location of the lesions. The incidence of radiation-induced sarcomas has decreased because cobalt-based radiotherapy has been abandoned.¹⁰⁵ Unlike metastatic sarcoma, primary pulmonary sarcoma presents as a solitary lesion (eFigs. 54-13 and 54-14), with heterogeneous cystic, necrotic, or hemorrhagic features but well-defined circumference. Size ranges from 4 to 25 cm (Fig. 54-4A). PET scanning shows increased uptake (see Fig. 54-4B and eFig. 54-14D).¹⁰⁶ Tumor progression is mainly local, and mediastinal lymph node invasion and systemic metastases are rare at the time of diagnosis (<2%).^{95,96,101}

Surgery is then the most effective initial treatment, and complete resection is obtained in 80% of cases.^{95-98,101-104} Strategies developed in soft tissue sarcoma may not be applicable to primary lung sarcomas: for example, neoadjuvant chemotherapy, based on anthracycline and ifosfamide, is commonly used in soft tissue locations but has been disappointing in primary lung tumors.^{96,98,107,108} In case of unresectable lesions, chemoradiation may be the best therapeutic strategy. As in soft tissue sarcoma, the chemotherapeutic drug trabectedin may be an option for second-line treatment. Prognosis mainly depends on the completeness of initial surgical resection, which, when combined with the grade of the lesion, is the best predictive factor of recurrence-free and overall survival. Overall 5-year survival varies from 30% to 50%^{95-98,101-104} and may be better for leiomyosarcomas.¹⁰⁹

VASCULAR SARCOMAS

Primary pulmonary vascular sarcomas include pulmonary artery sarcomas and small vessel sarcomas, corresponding to epithelioid hemangioendothelioma and its high-grade counterpart, angiosarcoma.¹¹⁰

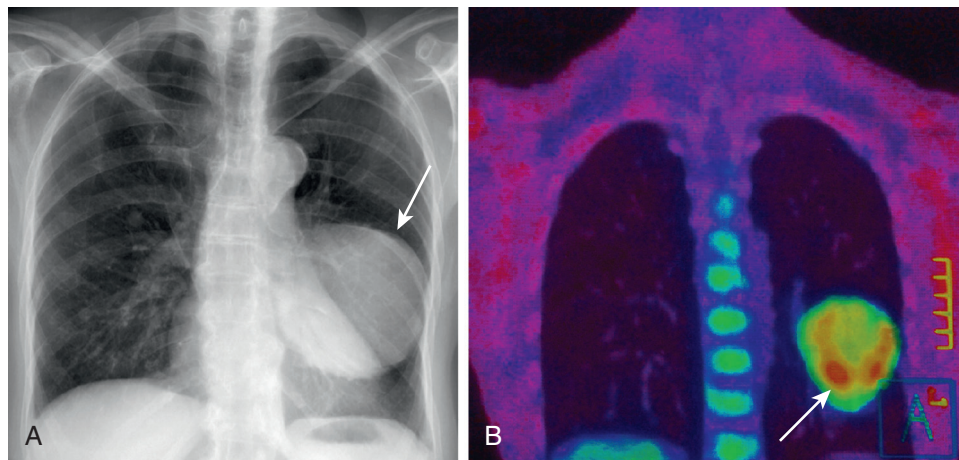


Figure 54-4 Primary pulmonary leiomyosarcoma. **A**, Chest radiograph shows a large circumscribed homogeneous mass in the left lung (arrow). **B**, Coronal PET shows marked hypermetabolism within the lesion (arrow).

Pulmonary artery sarcoma presents as an endoluminal polypoid or nodular mass, which spreads along the intima of the pulmonary artery. Histologic features consist of an undifferentiated spindle cell proliferation, with marked cellular pleomorphism and high mitotic index.¹¹⁰ Leiomyosarcoma is the most frequent subtype (60% of cases).^{110,111} Pulmonary artery sarcomas mainly develop in patients in their fifth to sixth decade.^{112,113} Symptoms may mimic pulmonary embolism, with dyspnea, chest pain, cough, and hemoptysis.¹¹²⁻¹¹⁴ Failure of anticoagulants in this setting, as well as the presence of symptoms of weight loss and fever (arising in 40% of cases), may also suggest the diagnosis. Imaging findings also help differentiate between pulmonary artery sarcoma and pulmonary embolism: CT scanning may show a polypoid filling defect in the pulmonary artery but, contrary to thromboembolic disease, sarcoma forms a contiguously soft, smooth, tapering tissue, with possible extravascular nodular spread in the parenchyma (40% of cases) (eFig. 54-15 and Video 54-1) and localized ground-glass opacities (Fig. 54-5A and B).^{113,114} Sarcoma also presents with a heterogeneous appearance including areas of necrosis and hemorrhage, and with intense hyperactivity on PET scanning (see eFig. 54-15F and G).¹¹⁵ Magnetic resonance imaging (MRI) shows intermediate to mildly increased signal on T1-weighted images, often with heterogeneous enhancement (eFig. 54-16), and T2-weighted images show intermediate to diminished signal relative to skeletal muscle; furthermore, the intravascular mass may enhance, a feature not typically encountered with uncomplicated thromboembolic disease. Surgery is the only potentially curative treatment and, even if performed in an emergency setting in case of acute right-sided heart failure, allows resectability in 60% to 75% of cases¹¹¹⁻¹¹⁶ (see Fig. 54-5C). Alternatively, heart and lung transplantation may be an alternative option for unresectable tumors. A slight improvement of overall survival has also been reported following adjuvant chemotherapy and/or radiotherapy. Contrary to soft tissue sarcoma, prognosis is mainly related to tumor location, because half of the patients die as a result of the progressive obstruction of the pulmonary trunk.¹¹⁵ Reoperation is feasible in 30% of cases. However, in recent series, overall median survival is as low as 6 to 12 months (eFig. 54-17).^{114,115}

Epithelioid hemangioendothelioma (EHE), a small vessel sarcoma, is a low- to intermediate-grade mixed epithelioid, endothelial, and vascular tumor.^{117,118} Lung is the most frequent extrahepatic location (10% of cases), because EHE can also arise from the liver (63% of cases), the bone (8% of cases), and the skin (6% of cases).^{119,120} EHE was initially considered an intravascular and intra-alveolar extension of bronchoalveolar carcinoma and thus was called “intravascular bronchoalveolar tumor.”¹¹⁷ Now, however, it is clearly identified as a mesenchymal tumor corresponding to low-grade angiosarcoma. EHE is characterized by polypoid nodules, with a central sclerotic paucicellular zone, growing into the alveolar spaces with an angiocentric distribution. Lymphangitic spread may mimic metastatic carcinoma. A recently identified translocation t(1;3) (p36.3;q25) involving the *PAX7* gene, which encodes a transcription factor involved in regulation of development, may be helpful in making the diagnosis.¹²¹ EBV RNA sequences are detected in 90% of cases. Overlapping entities with IgG4-related disease have been described (see later).

Clinically, 80% of cases of EHE are seen in white females.^{119,120,122} The tumor is asymptomatic in 50% of cases; when present, symptoms are nonspecific and include pleuritic chest pain, nonproductive cough, dyspnea, and rarely hemoptysis. Physical examination may reveal inspiratory crackles in 30% of cases. By CT imaging, EHE appears either with bilateral slow-growing perivascular multiple nodules, usually located adjacent to small vessels or bronchi, or with predominant infiltrative ground-glass opacities (eFig. 54-18) with a micronodular pattern, mimicking carcinomatous lymphangitis. EHE nodules usually range from 3 to 50 mm, and their number varies from 10 to 20 lesions.^{119,120,122} Nodules in patients with EHE may show increased uptake on PET scans.¹²³

Although there are a few reports of spontaneous remission, the complete resection of all pulmonary nodules is the only curative treatment of EHE.^{124,125} Surgery remains effective even in cases of localized recurrence. In contrast, EHE is generally insensitive to chemotherapy (cisplatin-based) or radiotherapy. Treatments with rituximab or antiangiogenic kinase inhibitors, such as sorafenib or bevacizumab, have been reported to be effective in isolated case reports.¹²⁶ In most cases, EHE is a slow-growing tumor

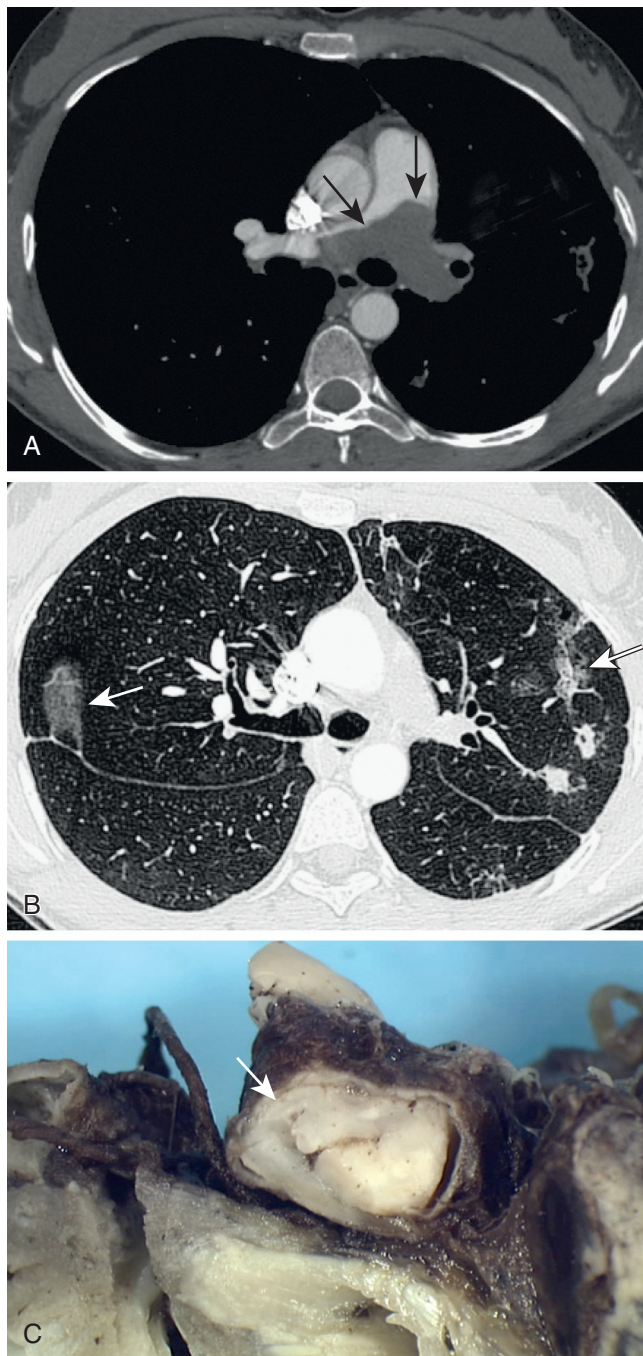


Figure 54-5 Pulmonary artery sarcoma. **A**, CT displayed in soft tissue windows shows a mass filling the pulmonary artery lumen (arrows). **B**, CT displayed in lung windows shows peripheral, irregular alveolar opacities (arrows) without pleural contact. **C**, Specimen at pneumonectomy shows the infiltration of the pulmonary artery wall by the tumor (arrow).

that rarely metastasizes and is associated with a median survival of 5 to 6 years. Endobronchial spread, pleural effusion, and extended endovascular disease have been identified as unfavorable prognostic factors.¹²⁴

Angiosarcoma is a high-grade primary pulmonary vascular sarcoma considered a counterpart of EHE. However, no direct transformation from EHE to angiosarcoma has been reported yet. Clinical features of angiosarcoma are similar to EHE, but massive hemoptysis is more frequent. Radio-

logic features of angiosarcoma include multiple nodules with a typical surrounding halo of ground-glass attenuation, with a specific “cauliflower-like” appearance on T2-weighted MRI.¹²⁷ This aspect may be shared by other disorders, including malignancies (e.g., adenocarcinoma with lepidic pattern, metastatic sarcomas, choriocarcinoma, melanoma, lymphoma), infectious diseases (e.g., mycobacteriosis, aspergillosis, cytomegalovirus infection), granulomatosis with polyangiitis, and eosinophilic conditions. Management of angiosarcoma is not established: surgical resection is rarely possible owing to local and regional invasion; radiotherapy and chemotherapy are poorly effective as seen in other locations of angiosarcoma.

INTRATHORACIC PSEUDOTUMORS

Pseudotumors represent a wide range of etiologic, pathologic, and clinical-radiologic disorders that all share some degree of reactive inflammation and may present with some cancer-related biologic hallmarks. Pseudotumors may mimic the clinical and radiologic features of various intrathoracic diseases.

INFLAMMATORY MYOFIBROBLASTIC TUMOR

Inflammatory myofibroblastic tumor (IMT) is the most representative entity of the pulmonary pseudotumors^{6,7,128} and encompasses a wide spectrum of lesions previously called “inflammatory pseudotumor,” “fibroma,” “fibroxanthoma,” “fibrous histiocytoma,” “plasma cell/mast-cell/solitary granuloma,” “plasma cell histiocytoma complex,” or “pseudosarcomatous tumor.” IMT has a prevalence of 0.04% of resected pulmonary neoplasms in the surgical series of the Mayo Clinic.⁶ IMT, which includes both benign and malignant features, represents an archetype of borderline neoplastic/non-neoplastic disorders.⁵

IMT appears as an intraparenchymatous well-circumscribed mass of variable size.¹²⁸⁻¹³⁰ Histologically, the tumor is made of irregular proliferation of fibroblasts and myofibroblasts intermixed with an infiltrate of inflammatory cells, mainly lymphocytes and plasma cells. Three distinct histologic patterns are usually recognized^{6,7,128-130}:

1. Plasma cell variant, also called the “lymphoplasma-cytic” variant, which is composed of inflammatory myxoid proliferation with fascicles of spindled fibroblasts or myofibroblasts, abundant lymphocytes and plasma cells, and minimal fibrous connective tissue.
2. Fibrohistiocytic type, which appears as a compact spindle-cell pattern simulating fibrous histiocytoma that is characterized by a myxoid proliferation of fibroblasts and myofibroblasts associated with polyclonal plasma cells, xanthoma cells, and rare giant cells.
3. Organizing pneumonia-like type, which has a hypocellular pattern characterized by dense collagen with sparse spindle cells.

The proliferating myofibroblastic cells show no cellular atypia, no necrosis, and only rare mitotic figures. The myofibroblastic cells usually stain for vimentin and smooth

muscle actin. Differential pathologic diagnosis includes all the diseases composed of fibroblasts and myofibroblasts, some of which may overlap with IMT: benign and malignant fibrous histiocytoma, myofibroblastoma, inflammatory fibrosarcoma, spindle cell carcinomas, plasmacytoma, and organizing pneumonia.

The concept of IMT as a proliferating neoplasm has been questioned.⁷ Historically, IMT, which was then called “inflammatory pseudotumor,” was thought to originate from organizing pneumonia through an exaggerated inflammatory response to injury. Older case reports emphasized that, in as many as 30% of cases, chronic or repeated infections could be a potential cause, but this concept was reconsidered with more recent reports that included chest CT studies, suggesting that recurrent pulmonary infections were rather a consequence of bronchial obstruction by the tumor.^{6,129} The concept of IMT as an immunologic disorder was raised after the detection of EBV and human herpesvirus 8 sequences in myofibroblastic cells, with associated expression of cytokines such as interleukin-6 and -8, and cyclin D1.^{6,131} The recent identification of IgG4 expression in polyclonal plasma cells extracted from intrathoracic IMTs suggested that an immunopathologic process may participate in the development of these tumors, especially the plasma cell variants. Such proliferation of IgG4-positive cells has also been associated with autoimmune disorders, including sclerosing pancreatitis and retroperitoneal and mediastinal fibrosis.¹³² IMTs may then be part of IgG4-related disease, a newly recognized fibroinflammatory condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and often, but not always, elevated serum IgG4 concentrations. Based on molecular data, myofibroblasts are considered to be pivotal in the development of IMT. Clonal gene rearrangements may be observed,¹³³ especially involving the *anaplastic lymphoma kinase* (*ALK*) gene located in region 2p23.¹³⁴ *ALK* overexpression is observed in 40% to 70% of IMTs at immunohistochemistry, but may also be at low levels in a wide variety of non-IMT soft tissue tumors. *ALK* rearrangement is identified in 40% to 50% of IMT cases, especially in younger patients, and most frequently consists of t(1;2)(q21;p23) translocation implicating the tropomyosin 3 gene.¹³⁵ Other translocations have been reported.¹³⁶ Given the oncogenic nature of *ALK* activation, these data lead some authors to consider IMT as a true neoplasm. Other elements further reinforce this concept, including the presence of vascular invasion, the local recurrence rate as high as 25%,⁶ the existence of multifocal lesions in 5% of cases, reports about malignant transformation, and genomic and expression profiling data, showing DNA aneuploidy, abnormal p53 expression, and up-regulation of other known cancer-related genes such as glutathione-S-transferase.¹³⁷ Overlap exists between IMT, IgG4-related disorders, and inflammatory fibrosarcoma that exhibits prominent cellular atypias and necrosis.

Pulmonary IMTs usually appear before the fourth decade, accounting for more than 50% of pulmonary tumors in children.^{6,129,138} Patients are asymptomatic in about 60% of cases, or may present with nonspecific symptoms, including chronic cough, dyspnea, or rarely hemoptysis. At imaging,

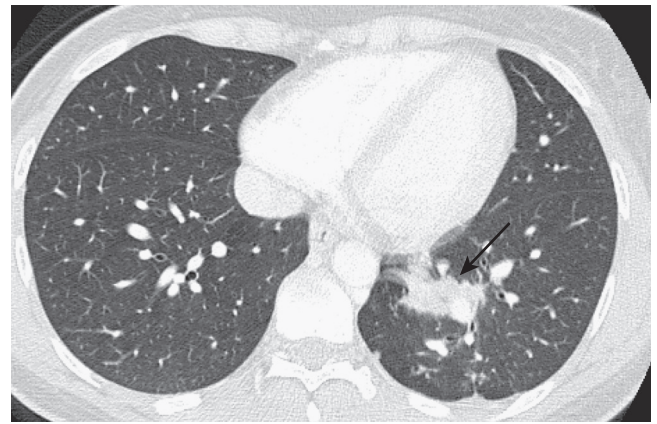


Figure 54-6 Inflammatory myofibroblastic tumor. CT performed for a 31-year-old man who presented with persistent cough and hemoptysis following infectious pneumonia. A poorly defined infiltrative-appearing opacity is present in the posterior and medial left lower lobe (arrow). Percutaneous transthoracic needle biopsy showed polymorphic inflammation without tumor cells.

IMT appears as a solitary well-circumscribed peripheral mass, ranging from 2 to 15 cm in size (Fig. 54-6; eFig. 54-19). Contrary to its presentation at extrathoracic locations, pulmonary IMT is usually solitary. Calcifications are observed in 15% of cases. The usual stability in size over time is an important imaging feature. Multifocal and bilateral IMTs are exceptional (eFig. 54-20) and are considered as overlapping forms of low-grade fibrosarcoma or malignant fibrous histiocytoma. IMTs are usually hypermetabolic on PET scanning. Extrapulmonary involvement is seen in 10% to 20% of cases and is mostly observed in the mediastinum and pleura. Conversely, extrapulmonary IMTs may metastasize to the lung, especially in younger patients. Preoperative diagnosis with endoscopic or percutaneous biopsies remains difficult due to the heterogeneous morphology of IMTs. Cytologic fine-needle aspiration accuracy was as low as 42% in a recent study.¹³⁹

Even if historically considered a benign lesion with possible spontaneous regression, IMT is usually treated by surgical resection due to its tendency to grow, to provoke local complications including hemoptysis and infection, and to relapse with local, pleural, parietal, or mediastinal invasiveness (15% to 25% of cases and 3% to 5% of cases, respectively).^{140,141} The need for adjuvant treatment in case of incomplete resection has not been evaluated. In nonoperable patients, focal conformation radiotherapy or corticosteroid challenge may represent an alternative. Corticosteroids are reported to induce objective responses in as many as 50% of cases, especially in predominantly plasma-cell tumors and IgG4-positive tumors.¹⁴¹ In recurrent or multifocal lesions, chemotherapy may use the same regimens as for soft tissue sarcomas. Crizotinib, a small pharmacological tyrosine kinase inhibitor of *ALK*, was recently reported to produce tumor responses in two patients with *ALK*-rearranged extrathoracic IMTs.¹⁴²

Patients with a resected IMT have a 5-year overall survival ranging from 75% to 100%.¹³⁹⁻¹⁴² Transformation to low- and/or high-grade fibrosarcoma has exceptionally been reported and may correspond to initially misdiagnosed

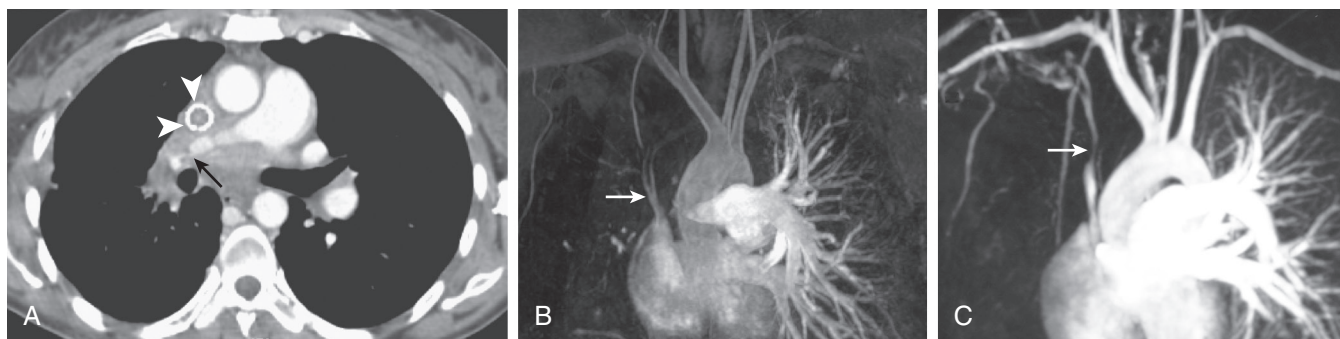


Figure 54-7 Mediastinal fibrosis. **A**, CT performed for a 32-year-old woman who presented with progressive dyspnea and superior vena cava syndrome. Poorly defined soft tissue opacities are seen throughout the mediastinum, compressing the right pulmonary artery (arrow). Surgical biopsy was performed to make the diagnosis. Coronal early arterial (**B**) and late arterial (**C**) magnetic resonance angiograms show severe stenosis of the superior vena cava (arrow), requiring intravascular stent placement (visible in **A**, arrowheads). Note the markedly impaired perfusion to the right lung compared with the left, implying the presence of severe right pulmonary arterial stenosis.

high-grade tumors.¹⁴¹ ALK-positive tumors are considered to be more aggressive but can recur locally regardless of ALK expression level.¹³⁴ The most consistent prognostic factor is the initial invasiveness of the tumor.

MEDIASTINAL FIBROSIS AND HYALINIZING GRANULOMA (see Chapter 84)

Similar to IMT, mediastinal fibrosis and hyalinizing granuloma both consist of tissue infiltration by dense collagen fibrosis forming lamellar bands, interspersed with lymphocytes and plasma cells.¹⁴³⁻¹⁴⁵ These two entities differ by the primary anatomic location: mediastinal fibrosis, also known as sclerosing mediastinitis, predominantly involves the mediastinum, with possible extension to the lung parenchyma; hyalinizing granuloma involves the lung parenchyma without contiguous involvement of the mediastinum. Overlap exists between these entities and other fibrosing disorders such as IMT, retroperitoneal fibrosis, and other IgG4-related disorders.

A hallmark of mediastinal fibrosis is the obstruction of major mediastinal veins with multifocal venous infarcts observed in the tumor leading to cellular fibrosis, hemorrhage, and necrosis. Mediastinal fibrosis has mostly been described in North America, where it is thought to result in most cases from exacerbated responses to *Histoplasma*.¹⁴⁶ Because the fungus is not typically cultured, it is thought that the fibrosis is a response to fungal antigens leaking from mediastinal nodes. Mediastinal fibrosis may be idiopathic, familial, or associated with various disorders, including infections with other fungi, such as *Aspergillus* or *Cryptococcus*, and tuberculosis or sarcoidosis. It has also been described following therapy with radiation, ergot derivatives, and beta-blockers. Autoimmune reactions may also participate, because an association with elevated serum IgG4 syndrome has been reported.¹⁴⁷ Clinically, mediastinal fibrosis is observed in the fourth decade, with a slight male predominance. Patients may be asymptomatic or develop chest pain, fever, hemoptysis, and dyspnea, as well as signs related to invasion of mediastinal structures. Pulmonary venous infarction can be the first manifestation of the disease. The severity of symptoms is related to the extension of the fibrosis. At imaging, mediastinal fibrosis

presents either as a localized mass (eFig. 54-21), possibly calcified, in the paratracheal, hilar, or subcarinal areas, or as diffuse infiltration throughout the mediastinum, without calcification (Fig. 54-7 and eFig. 54-22). The lung may be marginally affected, with consolidated areas resulting from venous infarction (see eFig. 54-22A and B), and possible pleural effusion. Surgical biopsy is often necessary to obtain a definite diagnosis. Prognosis depends on the structures involved. Treatment of mediastinal fibrosis may involve surgical resection, which often may be only palliative given the extent of the fibrosis, or the use of stents to restore patency of critical vessels. There is little evidence to support use of antifungal agents or corticosteroids, but trials of these are sometimes attempted.

Hyalinizing granuloma is seen in young to middle-aged adults with a slight predominance in men.¹⁴⁸ Patients usually have symptoms (80% of reported cases), consisting of cough, dyspnea, and pleuritic chest pain. Association with other fibrosing diseases has been reported, including mediastinal fibrosis (15% of cases) and retroperitoneal fibrosis (10% of cases). The radiologic presentation is that of solitary or multiple well-circumscribed lung nodules, usually 2-4 cm in size, which may grow over time and thus mimic cancer. The lesion may be found in the context of sarcoidosis and IgG4-related disease (Fig. 54-8).¹⁴⁹ The main differential diagnosis is nodular amyloidosis, because hyalinizing granuloma may demonstrate factitious Congo red positivity. The clinical course is benign.

OTHER PSEUDOTUMORS

The most common mechanism causing the development of a pseudotumor is thought to be an exaggerated host response to injury. Developmental pseudotumors include benign lesions such as hamartomas (eFigs. 54-23 through 54-27), leiomyomas, and choristomas.^{4,5,9} Tissue remnants or heterotopias related to embryologic variation is another etiologic group, the most frequent entity being minute meningioma-like nodules (eFig. 54-28) that correspond to glial heterotopias.¹⁵⁰ Similarly, clear cell tumors, also called “sugar tumors,” are derived from perivascular epithelioid cells of the lung epithelium; these cells are of neuroectodermal origin and are also implicated in the

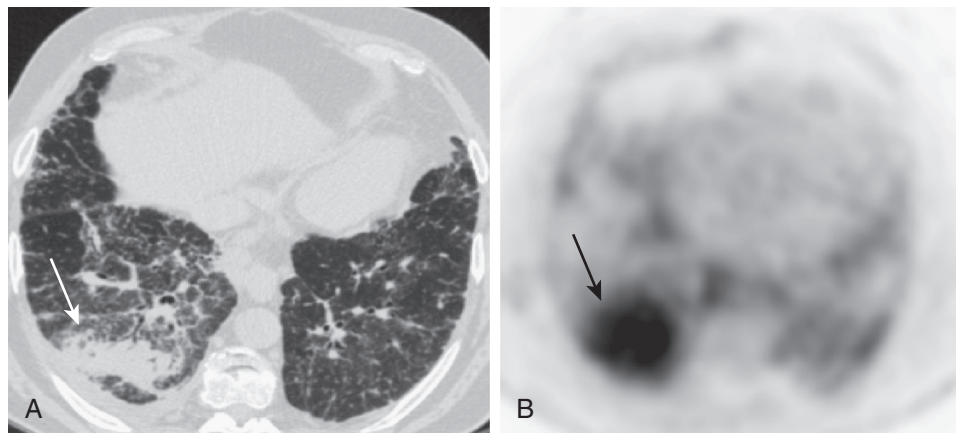


Figure 54-8 Hyalinizing granuloma. **A**, Chest CT performed for a 62-year-old man with a history of sarcoidosis, COPD emphysema, and liver transplantation for cirrhosis shows right lower lobe parenchymal consolidation with surrounding interlobular septal thickening (arrow). **B**, Axial PET scan shows tracer activity within the mass (arrow). The patient presented with recurrent spontaneous pneumothorax and underwent thoracoscopy for pleurodesis. Resection of the lesion was performed, leading to the diagnosis of hyalinizing granuloma.

development of perivascular epithelioid cell tumor and lymphangioleiomyomatosis.

Functional pseudotumors are related to dysfunctional pathophysiologic states, often of an endocrine nature, and are rare in the lung parenchyma. Iatrogenic pseudotumors are due to several medical procedures that can produce tissue reactions, most of which are reparative in nature. Infectious pseudotumors may be produced by mycobacteria (tuberculoma), fungi (aspergilloma), or even viruses (EBV, HIV, cytomegalovirus). The pathogenesis of these tumors may be complex, possibly implicating multiple mechanisms. The clinical and radiologic features of these tumors may be similar to that of IMT.

BORDERLINE ENTITIES

Benign tumors and preneoplastic conditions of the lung are considered elsewhere in Chapter 56. *Borderline* neoplastic and non-neoplastic disorders include entities that are generally considered to have benign behavior despite being associated with true neoplasm or presenting with some pathologic or molecular characteristic of neoplasia, including clonal proliferation. Borderline lesions may also have features of malignant behavior, such as invasion and recurrence following resection. These disorders may also present as pulmonary nodules or infiltrative disease, mimicking bronchogenic carcinoma or interstitial pneumonias, respectively.

MESENCHYMAL BORDERLINE DISORDERS

Some benign lesions, presenting as slow-growing intraparenchymal masses with homogeneous attenuation and regular contours, may present with clonal chromosomal aberrations. For example, hamartomas may exhibit gene rearrangements in regions 12q15 and 6p21.¹⁵¹ These regions contain the *high mobility group AT-hook* genes, respectively, encoding nonhistone nuclear proteins that

participate in the regulation of gene expression via alteration of chromatin structure. Interestingly, similar alterations have been described in other mesenchymal tumors. Similarly, multiple minute pulmonary meningothelial-like nodules (see eFig. 54-28), which are millimeter-sized nodular proliferations of oval to spindle-shaped cells resembling meningioma and arranged in a nested pattern, exhibit loss of heterozygosity in multiple genomic loci in 33% of cases.¹⁵² Relationship of minute meningothelial-like nodules with primary pulmonary meningioma is not certain, given the contrast between the relatively high prevalence of meningothelial-like nodules and the low frequency of meningioma as a primary lung tumor.

RESPIRATORY TRACT PAPILLOMATOSIS

Some lesions thought to be benign may have a borderline presentation and outcome. One relevant example is recurrent respiratory papillomatosis. Papillomas usually present in the upper respiratory tract but may rarely spread to the lung parenchyma (less than 5% of cases).^{153,154} Histologically, squamous papillomas are usually exophytic with an epithelial layer covering a central fibrovascular core that forms a frondlike architecture protruding into the lumen of the airway. Squamous papillomas are lined by stratified squamous epithelium, sometimes keratinized. Distal papillomas exhibit a more inverted growth pattern. Papillomas may exhibit imaging features similar to those of lung cancer, including heterogeneous, cavitating, or poorly defined masses.

Pulmonary papillomas may be solitary or multiple (eFigs. 54-29, 54-30, and 54-31); if multiple, these are associated with multiple papillomas of the upper respiratory and aerodigestive tract. As in other locations, the pathogenesis of squamous papillomas is linked with *human papillomavirus* (HPV) infection, often acquired at birth.¹⁵⁵ Specifically, HPV type 11 infection has been reported to bear a high-risk of transformation of papilloma to squamous cell carcinoma (eFig. 54-32).¹⁵⁶ Molecularly, loss of the tumor suppressor genes *TP53*, *RB*, and *P21* has been reported in squamous

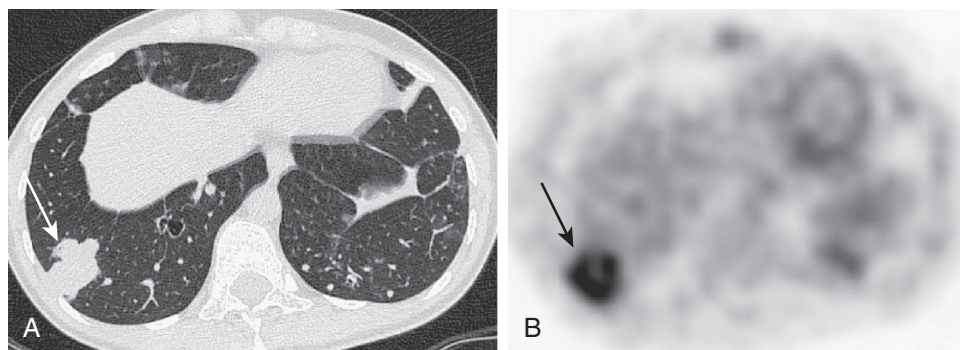


Figure 54-9 Pulmonary squamous cell carcinoma development in a patient with papillomatosis. **A**, Chest CT performed for a 32-year-old woman with a history of upper and lower respiratory tract papillomatosis, complaining of worsening cough and weight loss shows a subpleural mass in the right lower lobe (*arrow*). A thin-walled cyst is also present within the right lower lobe, and small centrilobular nodules are seen in the left lower lobe. Percutaneous transthoracic needle biopsy showed squamous cell carcinoma. **B**, PET shows increased uptake of the mass (*arrow*); moderate uptake of the mediastinal nodes was thought to be related to papillomatosis. Surgical resection was performed.

cell carcinomas originating from papillomas. Mutation of HPV-11 with duplication of promoter and oncogene regions has been described in a case responding to vorinostat.¹⁵⁷ PET scanning may not be useful given the mild hypermetabolism of high-grade papillomas. Pathologically, the distinction with invasive squamous cell carcinoma can be difficult in some exophytic cases or when there is atypical cytology. Given this uncertain malignant potential and the difficult differential diagnosis with lung cancer, complete resection of papillomas is recommended if possible; complete resection may not be possible in the setting of multiple and bilateral lesions (Fig. 54-9).

NODULAR LYMPHOID HYPERPLASIA

Pulmonary *nodular lymphoid hyperplasia* (NLH), historically called “pseudolymphoma,” is a nodular reactive polyclonal lymphoid proliferation infiltrating the lung, characterized by low-grade histology, presence of lymphoid follicles, and a benign clinical course.^{158,159} Histologically, NLH corresponds to lymphoid follicles with intercalated prominent plasma cells and usually mild interstitial fibrosis. Lymphocytes and plasma cells may distribute along lymphatics in the bronchovascular bundles and interlobular septa. Immunohistochemistry shows a mixture of polytypic B and T cells. No immunoglobulin heavy chain gene rearrangement has been identified. Differential diagnoses are MALT lymphoma, lymphocytic interstitial pneumonia, lymphomatoid granulomatosis; overlap entities, such as “atypical lymphoid proliferation,” have also been described. Sjögren syndrome may also have peribronchial lymphocytic infiltrates and may be associated with true lymphoma. In several cases of pulmonary NLH compared to other lymphoid proliferations of the lung, NLH was found to overexpress IgG4, suggesting that NLH may lie within the family of IgG4-related sclerosing diseases.¹⁵⁹

In a series of 14 well-characterized NLHs published in 2000,¹⁵⁸ most patients (81%) were asymptomatic. Radiologic presentation was that of a solitary peripheral nodule in nine patients, median size was 3 cm, and multifocal nodules were seen in five patients. Five patients (36%) also had concomitant hilar, mediastinal, or paraesophageal lymphadenopathy. In most cases, given the initial consideration of lung cancer, treatment consisted of surgical

resection. Interestingly, no recurrence or progression to more aggressive lymphoproliferative disease was documented, stressing the usually benign behavior of NLH.

AMYLOIDOSIS

Amyloidosis is characterized histopathologically by tissue infiltration with fibrillar protein with a β -sheet structural conformation, specifically stained by Congo red dye with a yellow-green birefringence under polarized light.¹⁶⁰ Amyloidosis has a highly variable presentation and may manifest in the lung as either parenchymal nodules (eFigs. 54-33 through 54-36) or masses.¹⁶⁰ Pulmonary amyloidosis may be localized to the lung or be associated with systemic amyloidosis.

Pulmonary nodules usually consist of AL (“amyloid light chain”) amyloid, which is the most common subtype of amyloidosis deposition.¹⁶⁰ AL amyloidosis is primary in more than 80% of cases and associated with inflammatory or lymphoproliferative disease in 20% of cases. AL amyloidosis develops as a result of the abnormal production of light immunoglobulin chains, often of lambda isotype. AL amyloidosis may be either systemic (e.g., in myeloma) or localized (e.g., in primary pulmonary lymphoma), with mild pulmonary interstitial (especially vascular) involvement that is usually asymptomatic.¹⁶¹ Serum and/or urinary monoclonal gammopathy is frequent.¹⁶²

Pulmonary nodular amyloidosis has been observed in patients in their seventh decade, without gender predominance. Patients are usually asymptomatic. Association with Sjögren’s syndrome has been reported.¹⁶³ Radiologically, pulmonary nodules are rounded and sharply delimited (see eFig. 54-34). Most nodules are peripheral. The nodules may range from 5 mm to more than 15 cm, may be solitary or multiple, and may be calcified. Nodules have shown increased activity on PET scans and may thus mimic bronchogenic carcinoma,¹⁶⁴ although lack of FDG avidity is also seen (see eFig. 54-35F and G). Other unusual imaging patterns may rarely be encountered (see eFigs. 54-35A-D and 54-36). Fine-needle biopsy may provide a pathologic diagnosis.¹⁶⁵ Pulmonary amyloid nodules may remain stable for years,¹⁶⁶ and surgical resection is proposed only in case of threatening symptoms. Recurrence is frequent after surgery.¹⁶⁷

NONAMYLOIDOTIC MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASE

Nonamyloidotic monoclonal immunoglobulin deposition disease is more rare than amyloidosis and presents with deposits that are not stained by Congo red dye and do not demonstrate birefringence under polarized light.¹⁶⁸ These deposits most often consist of light chains, frequently kappa, or more rarely of single heavy chains or of mixed light and heavy chains.¹⁶⁸ The lung is a very unusual location.¹⁶⁹⁻¹⁷¹ Pulmonary nonamyloidotic monoclonal immunoglobulin deposition disease most frequently presents as multiple parenchymal nodules or, less frequently, as multiple cysts; deposition is usually limited to the lung without systemic involvement. Approximately half of the cases are associated with hematologic malignancies. Treatment of any underlying hematologic disease usually leads to regression of the monoclonal peak but has little effect on existing deposits. Pulmonary nonamyloidotic monoclonal immunoglobulin deposition disease may benefit from lung transplantation in cases of severe respiratory failure and in the absence of an underlying hematologic disorder.¹⁷⁰

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) is a heterogeneous disease defined by the proliferation of Langerhans cells, corresponding to CD1a-positive histiocytes exhibiting Birbeck granules on electron microscopy.^{172,173} These cells of dendritic lineage derive from CD34-positive bone marrow stem cells. If the lung is the sole location of the disease, it is called “pulmonary LCH.” In less than 15% of cases, LCH is associated with multisystem disease, corresponding to “acute disseminated LCH” involving the lung as well as the bone, the skin, and the pituitary gland.¹⁷⁴ The pathogenic concepts about LCH mostly involve an uncontrolled immune response to a yet undetermined stimulus, leading to the recruitment of Langerhans cells in the lung parenchyma. Smoking exposure is found in the majority of patients developing pulmonary LCH and is thought to stimulate this process in the bronchiolar epithelium.¹⁷⁵ The true nature of LCH remains elusive. Strongly favoring the hypothesis of a neoplastic disorder is the observation that Langerhans cells, isolated from patients with either pulmonary or disseminated LCH, are clonal.¹⁷⁶ An activating *BRAF* mutation, similar to that observed in melanoma, may be identified in LCH pulmonary nodules.¹⁷⁷ However, the limited proliferation of Langerhans cells, the absence of cellular atypia, the low number of Langerhans cells in high-stage lesions, and the possibility of spontaneous regression argue against a cancerous nature of LCH.

Pathologically, LCH lesions are made of Langerhans cells that proliferate and aggregate to form stellate nodules in the interstitium, with a bronchiolocentric pattern and linear distal and proximal spread. High-stage lesions are characterized by disappearance of Langerhans cells, increased amounts of fibrosis, and cavitation of the nodules leading to cyst formation.¹⁷²

Clinically, pulmonary LCH develops in young smokers who present with nonspecific respiratory symptoms, including dyspnea, cough, and chest pain. Pneumothorax may herald the disease in 15% of patients; 10% to 25% of patients

are asymptomatic. The most typical imaging feature is the combination of pulmonary multiple cysts and micronodules sparing the lower zones of the lung.¹⁷²⁻¹⁷⁴ Nodules, ranging from 5 mm to 2 cm in size, are centrilobular and may be solid or cavitated (eFig. 54-37A and B) with smooth or irregular margins. LCH is an active process, with predominant nodular aspect at early stages of the disease (see eFig. 54-37A and B), evolving to cavitated nodules, cysts of variable wall thickness (see eFig. 54-37C), and confluent cystic lesions over time (see eFig. 54-37D). Lesions of different age are usually observed. Rarely, pulmonary LCH presents as a single nodule, localized consolidation, or mediastinal disease.

Whereas the typical clinical-radiologic presentation may be virtually diagnostic for pulmonary LCH, pulmonary biopsy may be required in case of a tumor-like nodular or atypical (eFig. 54-38) presentation. Open lung biopsy is usually performed in patients with pneumothorax who require surgical intervention. Increased uptake on PET may suggest lung cancer; in a recent study of 11 patients, nodular lesions exhibited hyperavidity, with maximum standardized uptake values ranging from 2 to 18.¹⁷⁸ PET might be useful in the follow-up of the activity of the disease and is the subject of current research. Smoking cessation may lead to regression in as many as 25% of patients. No other treatment has been confirmed to be useful in pulmonary LCH, which may also regress spontaneously. Patients with progressive or multiorgan disease may benefit from chemotherapy with cladribine, which produced a 75% objective response rate in a landmark study of 13 patients.¹⁷⁹⁻¹⁸⁰ Supporting the neoplastic hypothesis, pulmonary LCH can recur following lung transplantation.

LESSONS LEARNED FOR THE MANAGEMENT OF RARE PRIMARY PULMONARY TUMORS

GENERAL ISSUES

The main differential diagnosis of rare pulmonary tumors is lung cancer. The absence of a tobacco-smoking history, especially in men, is more frequently seen for rare lung tumors and pseudotumors than for bronchogenic carcinoma (60% vs. 15%, respectively). Young age at diagnosis is another feature to consider, because more than 50% of pseudotumors present before the fourth decade. Given the frequent initial suspicion of lung cancer, most patients undergo complete oncologic workup. The PET scan may frequently be positive in pseudotumors, tending to support the presumptive diagnosis of lung carcinoma. Preoperative biopsies and intraoperative frozen sections may not be sufficiently representative of the tumor to ensure accurate histopathologic diagnosis, especially in biphasic or composite tumors, for which small-size samples may identify only one cellular component. Sophisticated pathologic studies, including flow cytometry and molecular and cytogenetic analysis, may have a critical role in diagnosis (evaluation of tumor grade) as well as in therapeutics, such as for lymphoma, IMT, or sarcomas. Frozen specimen collection and storage is mandatory to preserve the tumor for additional analyses.

DISTINGUISHING PRIMARY TUMORS FROM METASTASES

In making the diagnosis of a rare primary lung tumor, one must also consider the fact that most lung tumors with unusual histology represent metastases from extrapulmonary tumors, not primary tumors. The main criteria favoring metastases include a prior history of extrathoracic tumor and the finding of multiple pulmonary lesions. PET scanning may also be helpful, assuming that the metabolic features of each rare tumor subtype are sufficiently well described. The primary pulmonary nature of some rare tumors may actually be difficult to establish, either because of early systemic spread, as for EHE, which presents with synchronous pulmonary and hepatic lesions in 20% of cases, or because of an ectopic origin, as for melanoma or Hodgkin disease, for which a primary pulmonary origin is highly controversial.

GENERAL THERAPEUTIC MANAGEMENT

In many cases, initial surgical resection provides the correct diagnosis and the first step of the therapy. However, preoperative diagnosis remains important for specific subtypes, such as lymphoma, for which extensive resection is not recommended, and for sarcoma, which usually does not spread to the mediastinal lymph nodes and thus would not require nodal resection. Surgical biopsy may be required to obtain sufficient tissue material for extensive pathologic and molecular diagnoses, especially when clinical-radiologic presentation is not typical of neoplastic or non-neoplastic disease.

Finally, three main clinical scenarios may arise in the course of evaluation of patients with rare lung tumors:

1. Surgical resection of a tumor assumed to be NSCLC was complete, and pathologic examination disclosed an unusual histopathologic subtype, such as carcinoid. In this case, no adjuvant therapy is recommended.
2. Specific clinical and radiologic signs led to recognition of a rare tumor, such as lymphoma or pulmonary artery sarcoma, followed by specific diagnostic and therapeutic management.
3. Surgery of a pulmonary mass initially thought to be NSCLC led to recognition of a rare tumor subtype, and therapeutic and prognostic implications are unknown. In those cases, decision of adjuvant treatment is based either on an NSCLC standard of care (e.g., to use radiotherapy in case of incomplete surgical resection) or on therapeutic strategies established for similar tumor subtype in other locations (as it is done for lymphoma and sarcoma).

In the absence of evidence-based recommendations, expert consensus is mandatory for selection of a specific therapeutic strategy, possibly based on strategies developed for lesions of similar histology arising in other anatomic locations. Molecularly targeted treatment may be useful. Also, these issues emphasize the need for multicenter collaboration to generate cohorts and to launch observational studies and clinical trials of rare lung tumors.

Key Points

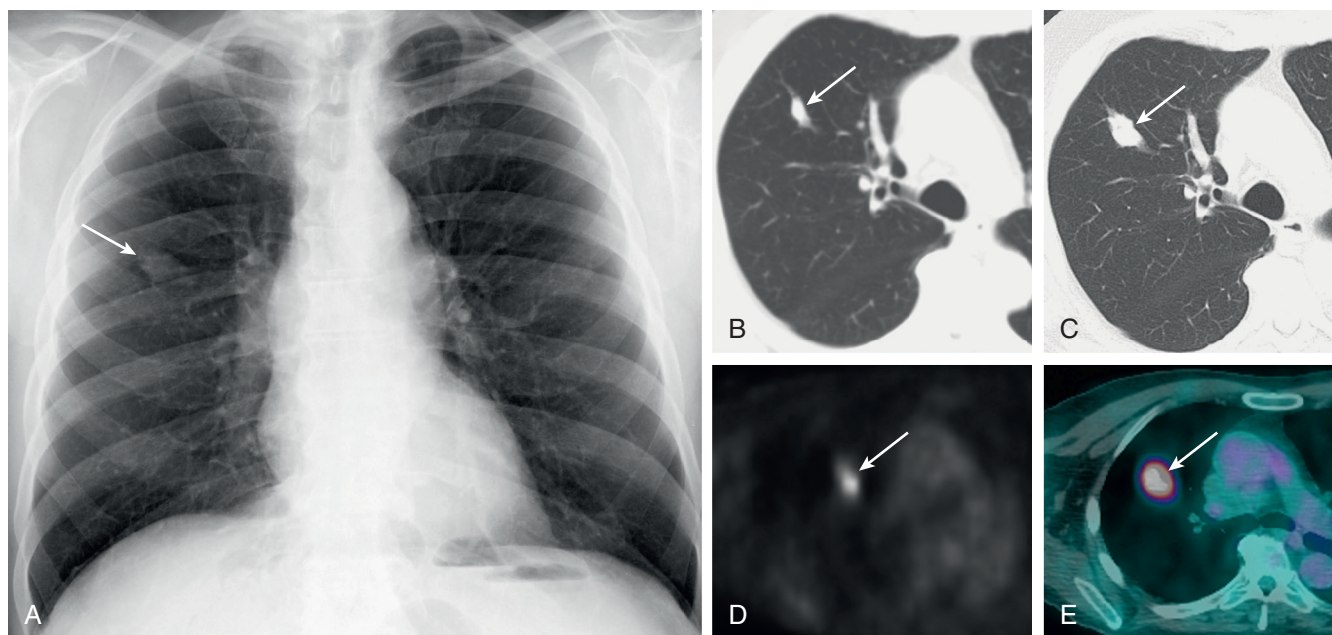
- Rare lung tumors are mainly defined as uncommon lung tumors with unusual histology. Rare tumors account for less than 1% of all primary lung tumors, whereas they correspond to more than 100 different histologic entities.
- Some rare lung tumors are specific to the lung, whereas others represent tumors more frequently found in other organs which only rarely present in the lungs. Determining whether they are primary or metastatic is a major step in the diagnostic evaluation.
- Rare lung tumors may mimic lung carcinoma or benign orphan lung diseases because they may share clinical, imaging, pathologic, and even molecular features.
- The most frequent rare primary lung tumors are carcinoids, mucosa-associated lymphoid tissue lymphoma, and pneumoblastoma. Specific therapeutic recommendations are available for carcinoids and large cell neuroendocrine carcinoma. In other cases, expert consensus is mandatory to plan specific therapeutic strategies.
- Pseudotumors are currently restricted to a specific heterogeneous group of diseases characterized by a circumscribed fibrous tissue associated with inflammatory and myofibroblastic cells; inflammatory myofibroblastic tumor is the most frequent entity.

Complete reference list available at *ExpertConsult*.

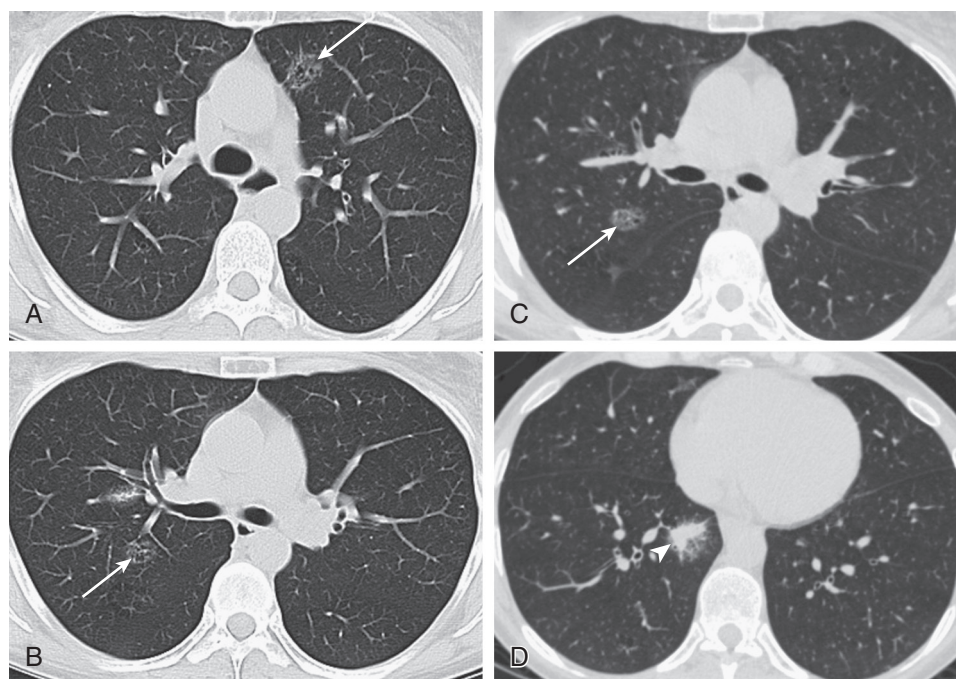
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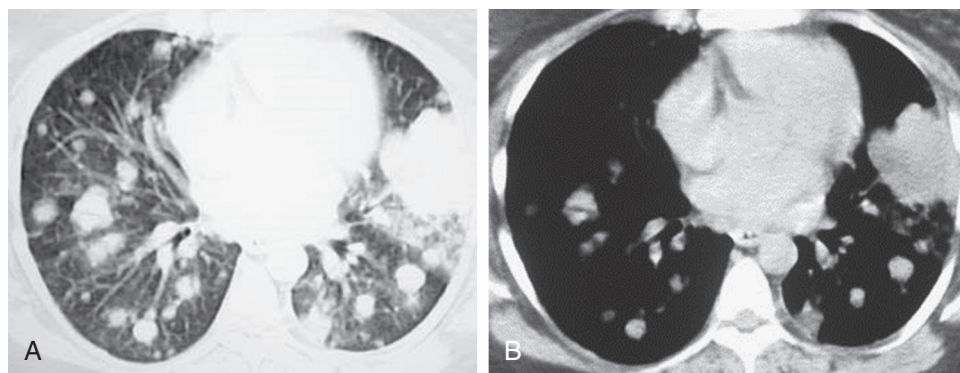
eFIGURE IMAGE GALLERY



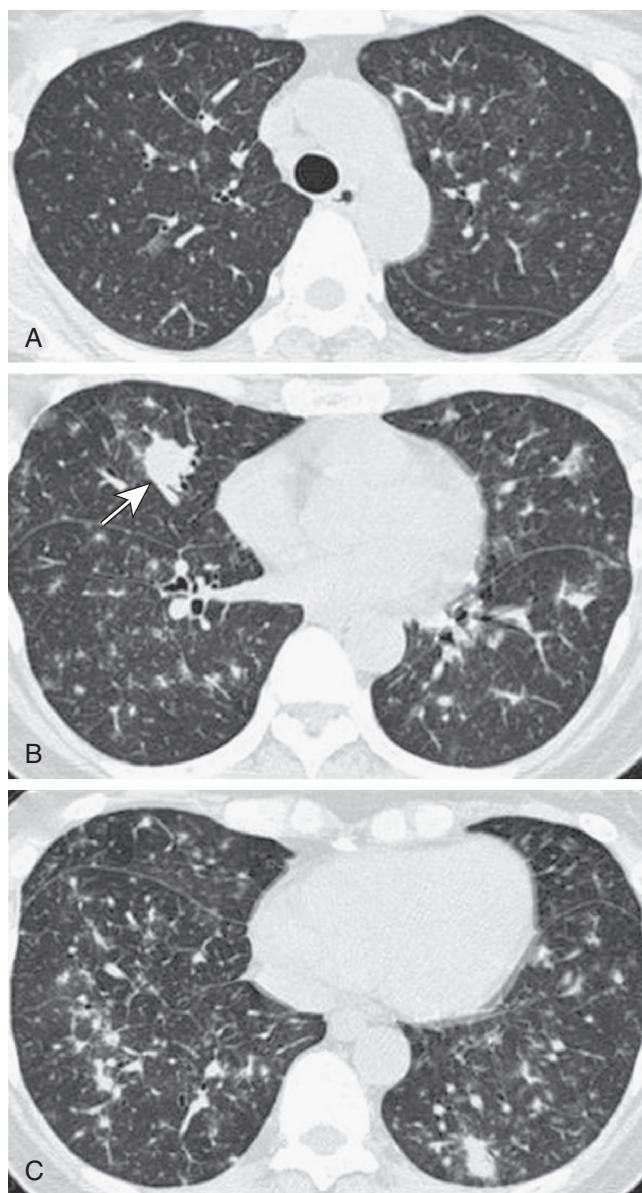
eFigure 54-1 Primary pulmonary MALT lymphoma: solitary pulmonary nodule. **A**, Frontal chest radiograph shows a nonspecific, solitary, lobulated right upper lobe pulmonary nodule (*arrow*). **B** and **C**, Axial enhanced chest CT scans displayed in lung windows show rapid growth of the nodule (*arrows*) over a 3-month period. **D** and **E**, PET and fused PET imaging obtained at nearly the same time as the CT studies (**B** and **C**) show marked metabolic activity within the nodule (*arrows*). Percutaneous transthoracic fine-needle aspiration and core biopsy showed pulmonary lymphoma. (Courtesy Michael Gotway, MD.)



eFigure 54-2 Primary pulmonary MALT lymphoma: multiple nodules. **A–D**, Axial chest CT scans displayed in lung windows show multiple ground-glass opacity nodules (*arrows*) associated with small lucent foci. One right lower lobe nodule (*arrowhead*) shows a solid component. Percutaneous transthoracic fine-needle aspiration and core biopsy showed pulmonary lymphoma. (Courtesy Michael Gotway, MD.)



eFigure 54-3 Pulmonary lymphomatoid granulomatosis. Axial chest CT scans displayed in lung (A) and soft tissue (B) windows show multiple, bilateral pulmonary nodules and a lingular mass, shown to represent pulmonary lymphomatoid granulomatosis at biopsy. (Courtesy Michael Gotway, MD.)



eFigure 54-4 Pulmonary lymphomatoid granulomatosis. A–C, Axial chest CT scans displayed in lung windows show multiple small nodules distributed along the bronchovascular bundles. A right middle lobe nodule (arrow) associated with an air bronchogram is present. Surgical lung biopsy showed pulmonary lymphomatoid granulomatosis. (Courtesy Michael Gotway, MD.)

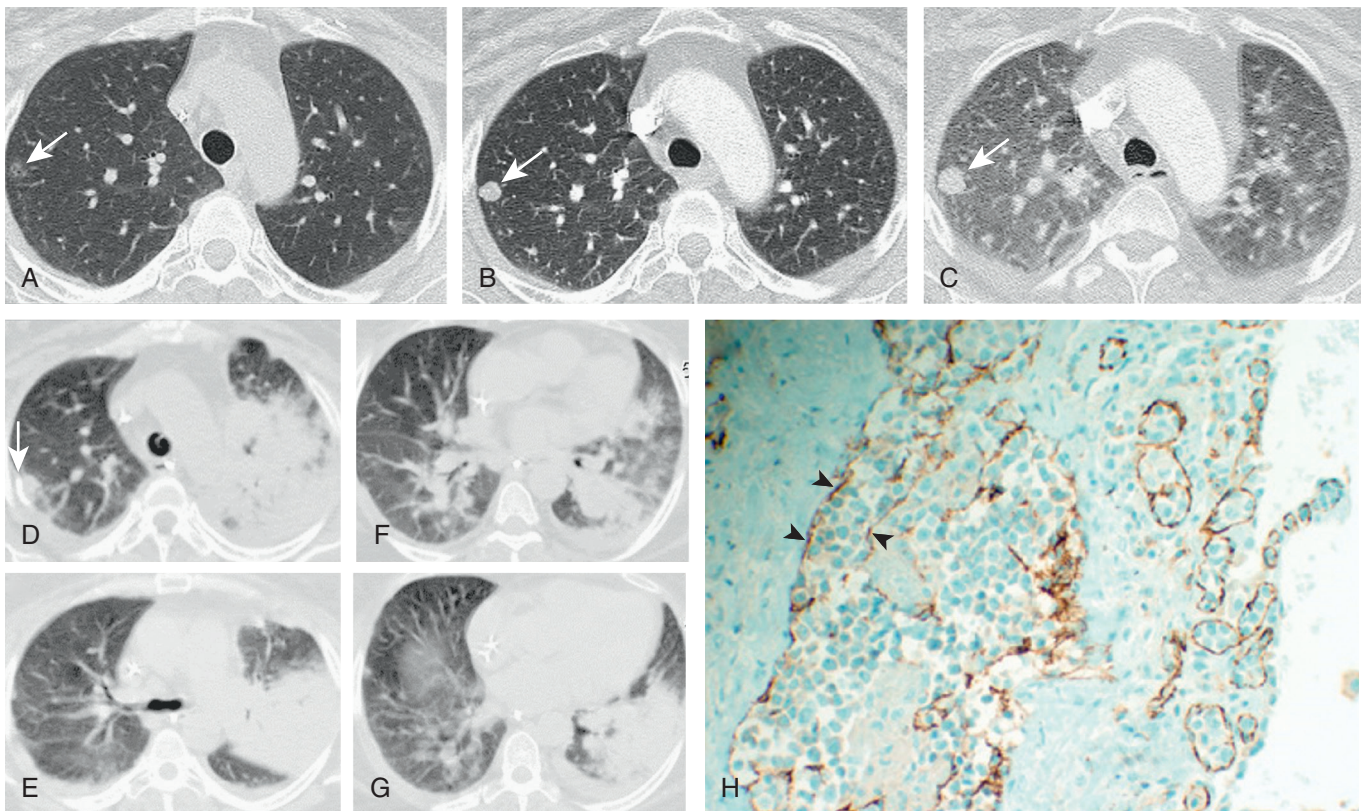


Figure 54-5 Intravascular large cell lymphoma. **A–C,** Axial chest CT scans displayed in lung windows in a 46-year-old woman with sarcoidosis and systemic lupus erythematosus who complained of daily fever and progressive shortness of breath shows a right upper lobe nodule (*arrows*), growing rapidly over a 2-month period. A corticosteroid therapy burst for 1 week was initiated in addition to the patient's baseline daily dose of 40 mg prednisone, but the patient's complaints persisted following return to the baseline therapy. **D–G,** Axial chest CT scans after return to the baseline prednisone dose of 40 mg shows interval development of multiple, bilateral areas of consolidation and nodularity. A surgical lung biopsy of the right upper lobe nodule, evidenced by right upper lobe suture (*arrow*), was performed. **H,** CD31 stain for endothelial cells outlines pulmonary vessels (brown lined areas, *arrowheads*). Note intravascular tumor cells consistent with intravascular large B-cell lymphoma. (**H,** Original magnification $\times 40$.) (Images courtesy Cristian Jivcu, MD, Cardio-Pulmonary Associates, Monterey, CA.)

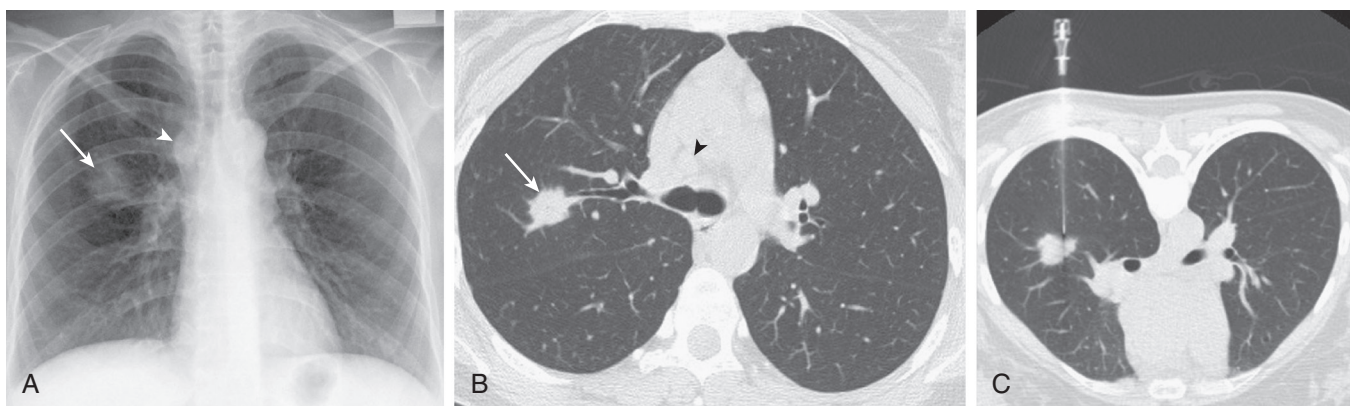
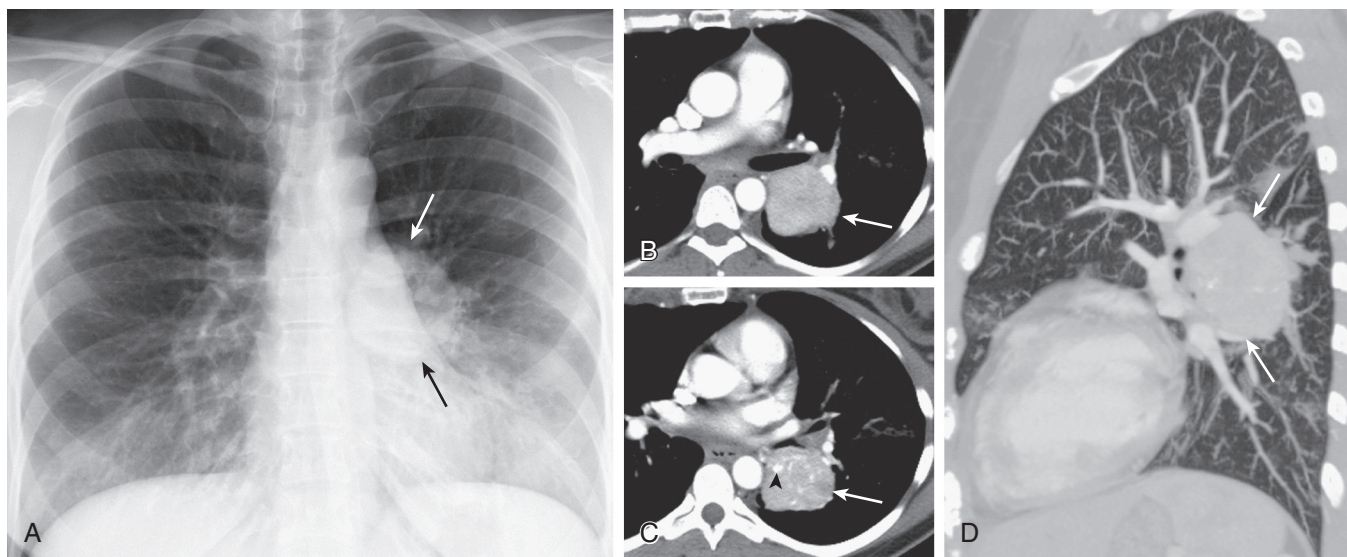
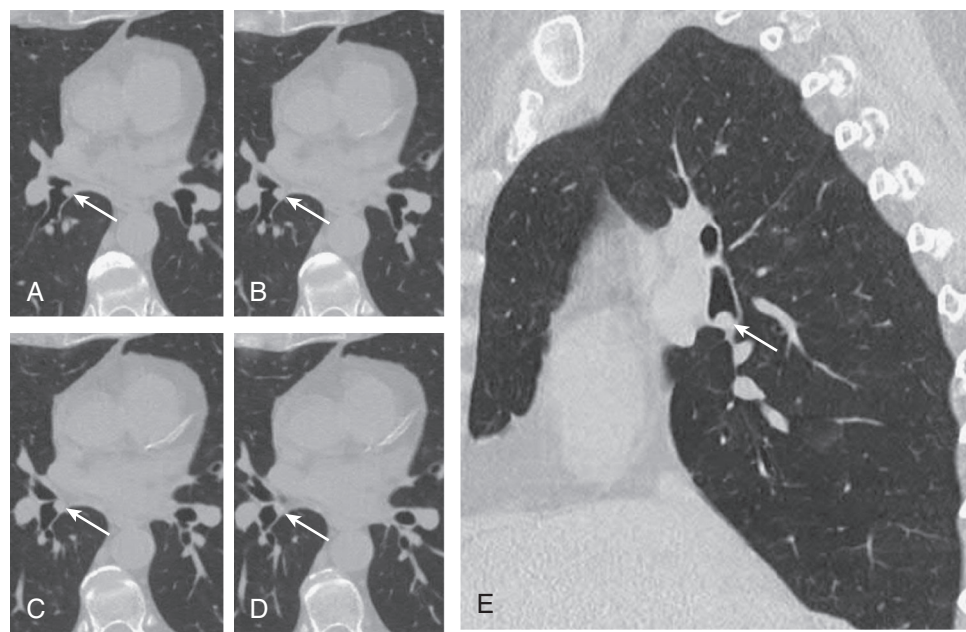


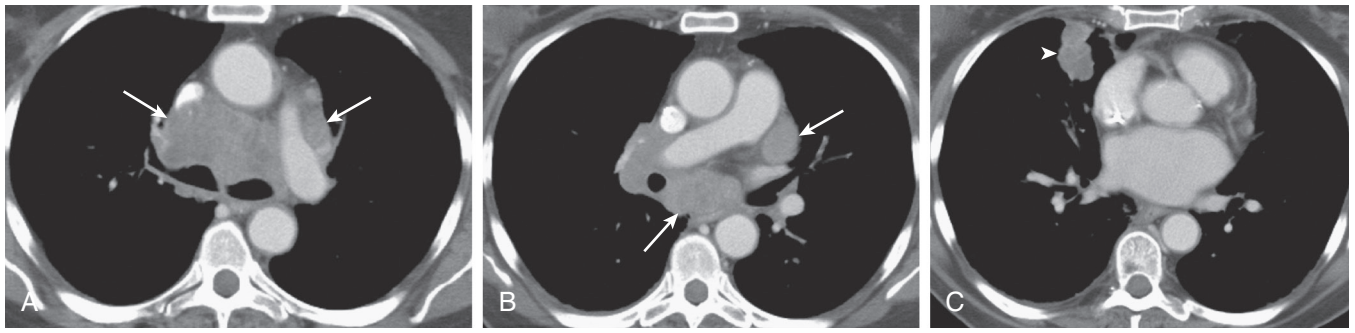
Figure 54-6 Pulmonary Hodgkin disease. **A,** Frontal chest radiograph in a 33-year-old woman shows a poorly defined right upper lobe nodule (*arrow*). Right paratracheal lymph node enlargement is also visible (*arrowhead*). **B,** Axial chest CT displayed in lung windows shows the poorly defined right upper lobe nodule (*arrow*) associated with a bronchus. The enlarged right paratracheal lymph node (*arrowhead*) is visible. **C,** Prone CT image obtained during transthoracic fine-needle aspiration and core biopsy. Material retrieved at this procedure did not allow a specific diagnosis. Subsequent surgical excision of the right upper lobe nodule revealed Hodgkin lymphoma. (Courtesy Michael Gotway, MD.)



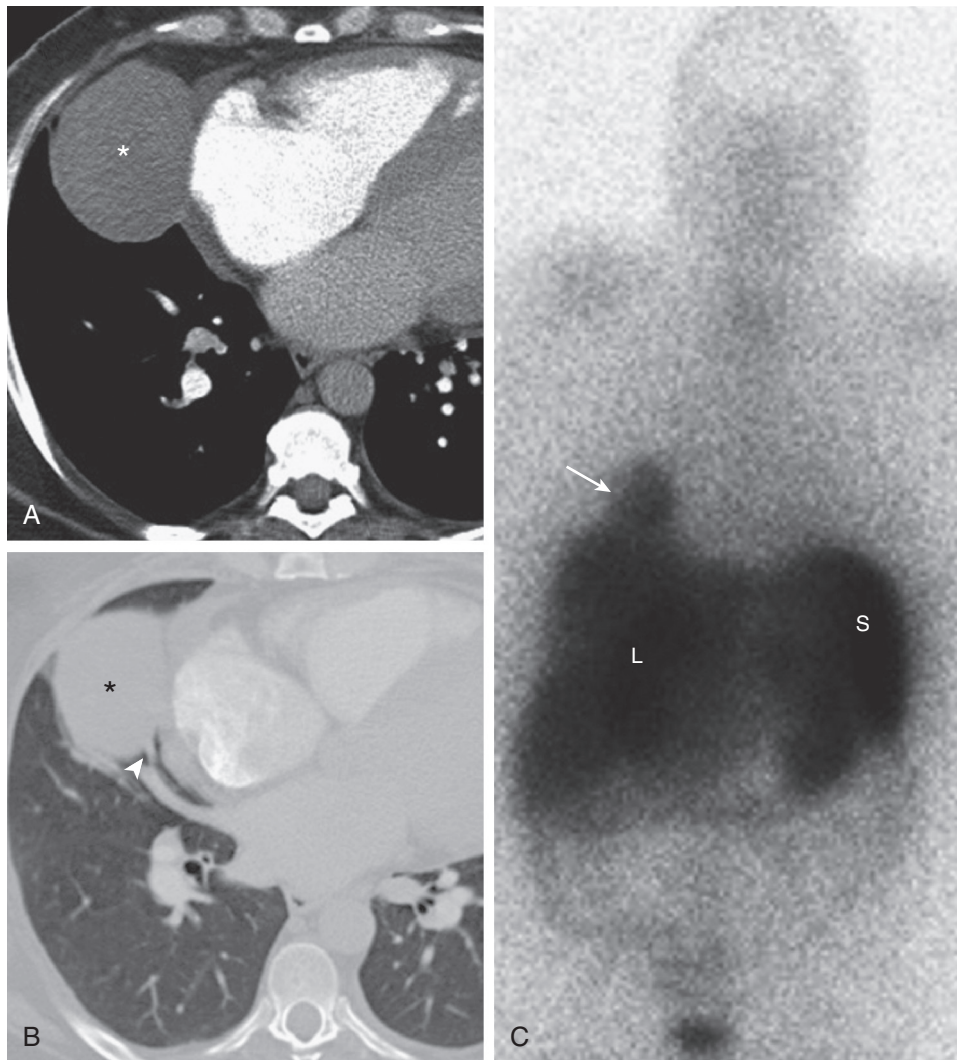
eFigure 54-7 “Typical” carcinoid tumor: hilar mass. **A**, Frontal chest radiograph shows a circumscribed left hilar mass (*arrows*). **B** and **C**, Enhanced axial chest CT scans shown in soft tissue windows. **D**, Sagittal lung window shows an enhancing mass (*arrows*) arising from and obstructing the left lower lobe bronchus. Calcification (see *arrows*) is present within the mass. (Courtesy Michael Gotway, MD.)



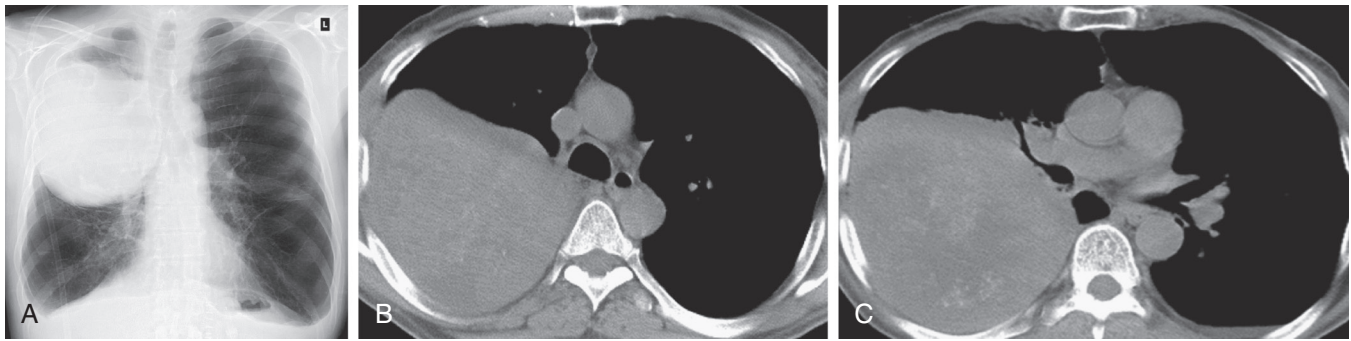
eFigure 54-8 “Typical” carcinoid tumor: endobronchial lesion without postobstructive changes. Axial (**A–D**) and sagittal (**E**) unenhanced chest CT images show a small, circumscribed opacity (*arrows*) attached to the medial aspect of the cranial right lower lobe bronchus, unassociated with postobstructive pneumonia or atelectasis. Bronchoscopy and biopsy proved carcinoid tumor. (Courtesy Michael Gotway, MD.)



eFigure 54-9 Atypical carcinoid tumor. A–C, Axial enhanced chest CT scans displayed in soft tissue windows show extensive mediastinal lymph node enlargement (A and B, arrows) associated with a right middle lobe atypical carcinoid tumor (C, arrowhead). The appearance is indistinguishable from bronchogenic malignancy. (Courtesy Michael Gotway, MD.)



eFigure 54-10 “Typical” carcinoid tumor: somatostatin (octreotide) scintigraphy. Axial enhanced chest CT scans displayed in soft tissue (A) and lung (B) windows show a circumscribed soft tissue mass (*) in the right middle lobe, closely associated with bronchi (B, arrowhead), proven to represent typical carcinoid tumor. C, Coronal planar octreotide scan shows tracer uptake within the right middle lobe lesion (arrow). Normal physiologic uptake is seen within the liver (L) and spleen (S). (Courtesy Michael Gotway, MD.)



eFigure 54-11 Large cell neuroendocrine neoplasm. **A**, Frontal chest radiograph in a patient with biopsy-proven large cell neuroendocrine neoplasm shows a large right upper lobe mass. **B** and **C**, Axial chest CT scans displayed in soft tissue windows show a heterogeneous right upper lobe mass with foci of faint internal hyperattenuation. The appearance is nonspecific and indistinguishable from bronchogenic malignancy. (Courtesy Michael Gotway, MD.)

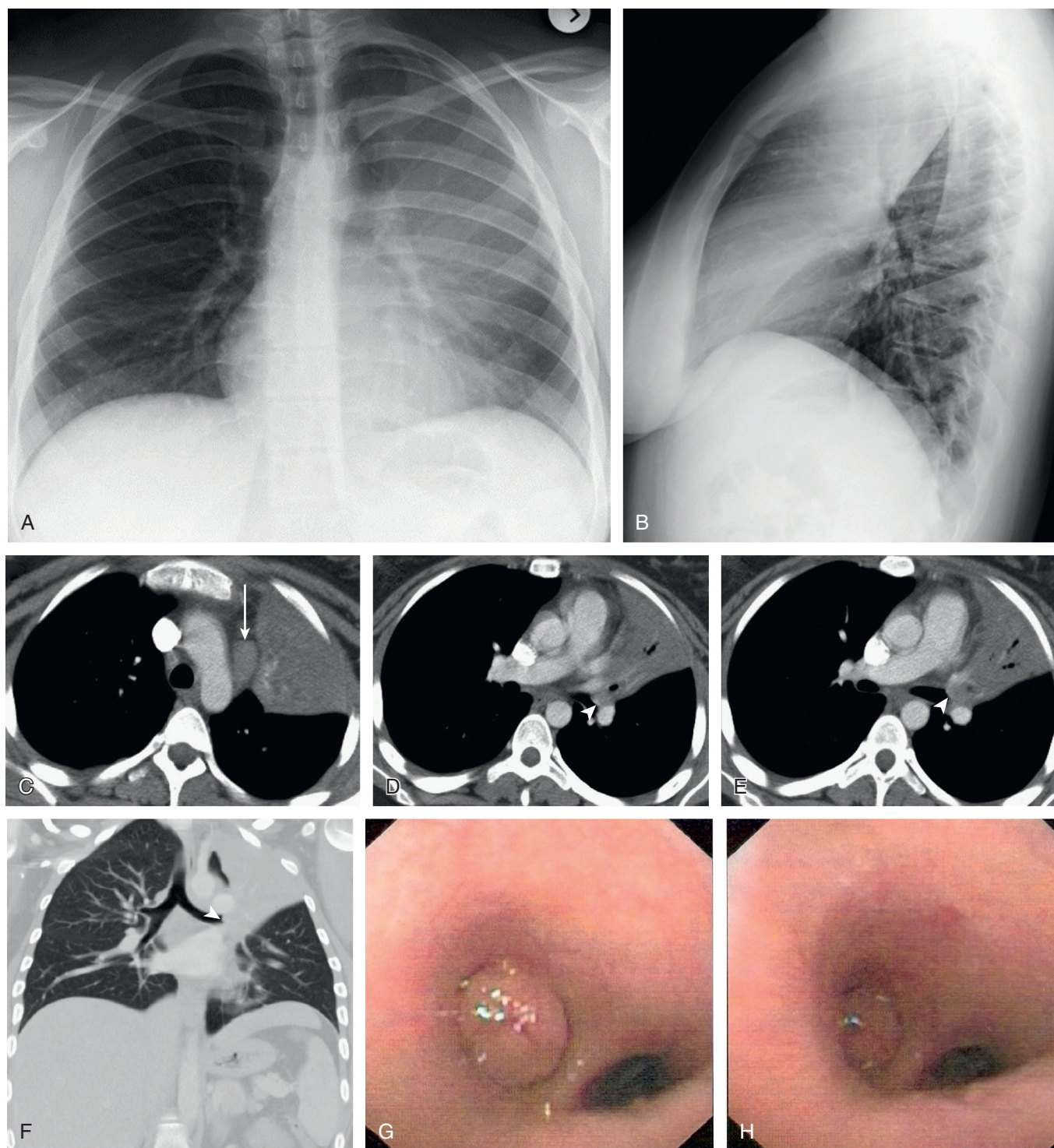
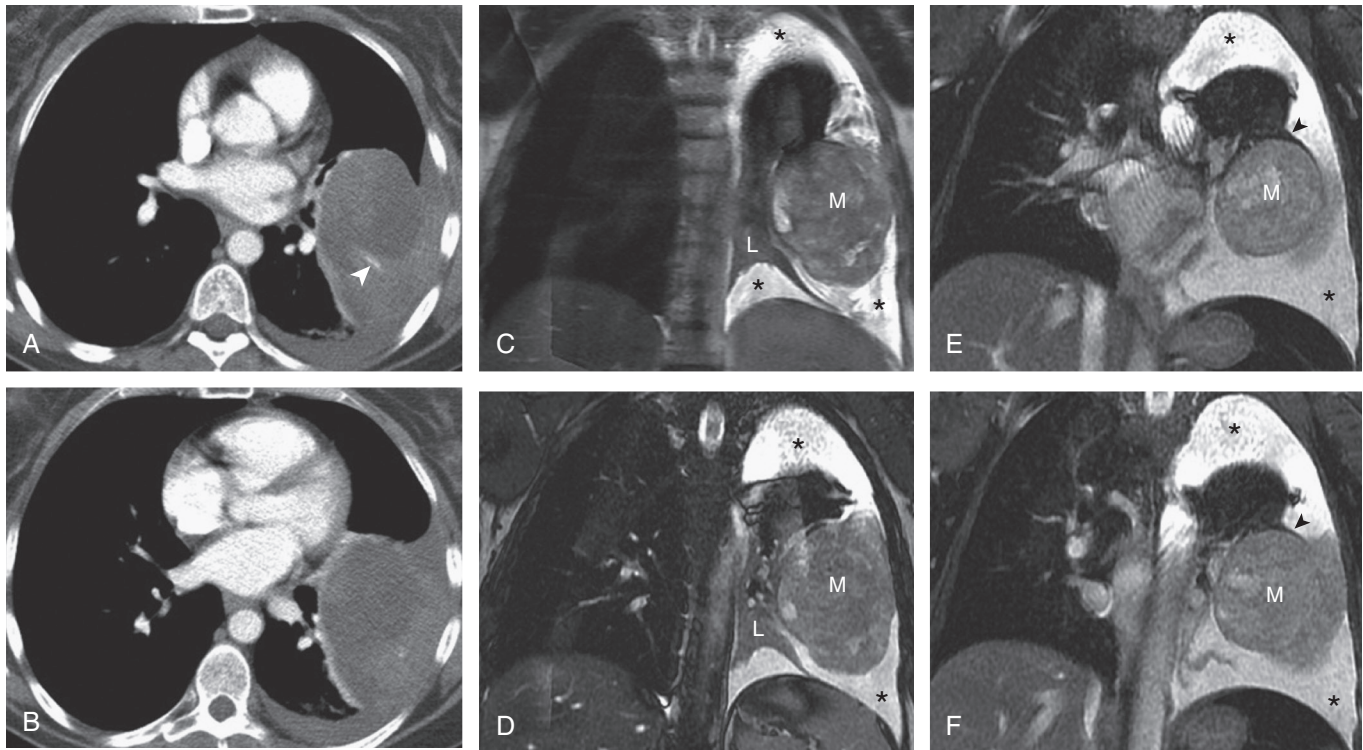
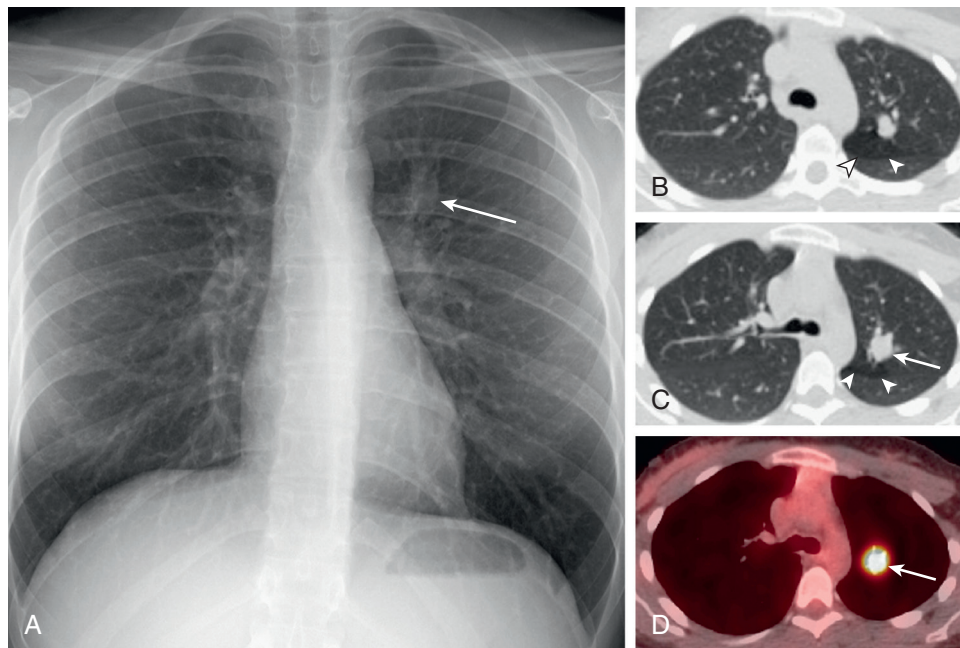


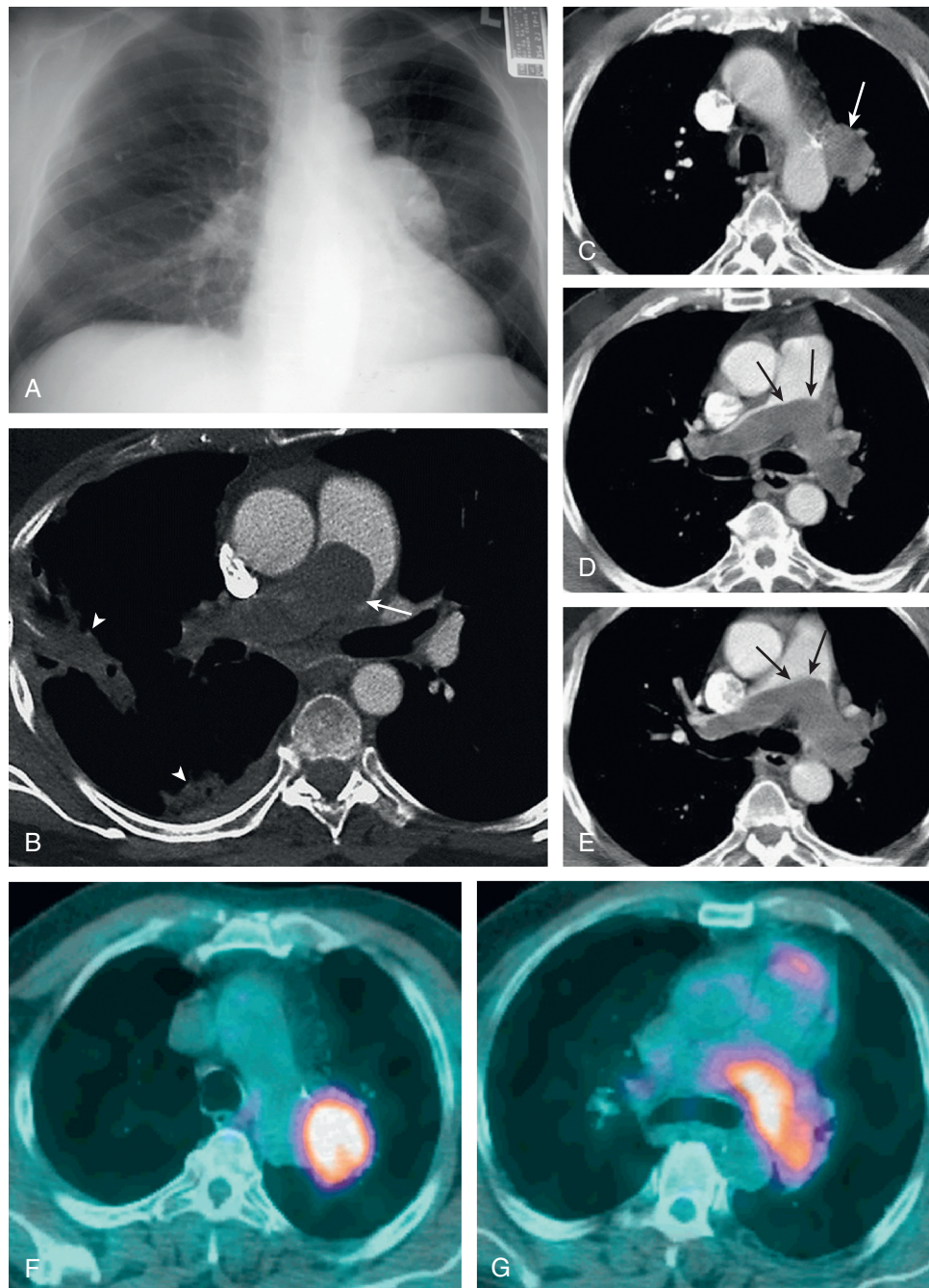
Figure 54-12 Mucoepidermoid carcinoma. Frontal (A) and lateral (B) chest radiographs in a young woman with mucoepidermoid carcinoma show the classic chest radiographic appearance of left upper lobe collapse. Left para-aortic lymphadenopathy (C, arrow) is present. C–E, Axial enhanced chest CT scans displayed in soft tissue windows show left upper lobe collapse and reveal the obstructing lesion (D and E, arrowheads). F, Coronal reformatted image displayed in an intermediate window again shows complete left upper lobe collapse as well as the obstructing lesion within the left upper lobe bronchus (arrowhead). G and H, Bronchoscopic images show the mucoepidermoid tumor completely obstructing the left upper lobe bronchial orifice. (Courtesy Michael Gotway, MD; case by Ewa Lupa-Laskus, MD, Arizona Pulmonary Specialists, Ltd, Scottsdale, AZ.)



eFigure 54-13 Primary pulmonary leiomyosarcoma. **A** and **B**, Axial enhanced chest CT scans show a large peripheral lung mass associated with a small left pleural effusion. A prominent vessel (**A**, arrowhead) is seen within the mass. **C–F**, Coronal MR images show a heterogeneous mass (**M**) with intermediate signal intensity, which reflects the relatively cellular and fibrotic nature of the lesion, arising from the peripheral left lung (**L**). Some areas of cystic change (the hyperintense foci) are present within the mass. The pulmonary origin of the mass, rather than pleural origin, is suggested by the visible “claw” of lung tissue (**E** and **F**, arrowheads) surrounding a portion of the lesion. A moderate left pleural effusion (*) is present. (Courtesy Michael Gotway, MD.)



eFigure 54-14 Primary pulmonary leiomyosarcoma: endobronchial origin. **A**, Frontal chest radiograph shows a poorly defined medial left upper lobe nodule (arrow). **B** and **C**, Axial chest CT scans displayed in lung windows show a circumscribed lesion (arrow) in the left upper lobe that could be traced to the apical-posterior segmental left upper lobe bronchus; note presence of hyperlucency distal to the lesion (arrowheads), representing postobstructive air trapping. **D**, Fused axial PET image shows intense metabolic activity within the lesion (arrow). (Courtesy Michael Gotway, MD.)



eFigure 54-15 Pulmonary artery sarcoma: imaging appearances. **A**, Frontal chest radiograph shows a smoothly enlarged left pulmonary artery associated with left lung oligemia. Whereas pulmonary embolism can result in similar findings, emboli rarely produce findings of this magnitude. **B–E**, Axial enhanced chest CT scans in two patients show a large hypoattenuating lesion completely filling the right pulmonary artery (**A**, arrow), associated with pulmonary infarction (**A**, arrowheads). The second patient (**C–E**) shows a large lesion simulating a saddle pulmonary embolism (arrows). Both patients were hemodynamically stable and presented with subacute shortness of breath; such a presentation would be exceedingly unlikely if pulmonary emboli were the cause of these large, obstructing central intravascular lesions. The full extent of the intravascular lesion and its resemblance to thromboembolic disease is demonstrated in [Video 54-1](#). **F** and **G**, Axial PET scan (same patient as in **C–E**) shows intense hypermetabolic activity within the intravascular lesion, consistent with neoplasm. (Courtesy Michael Gotway, MD.)

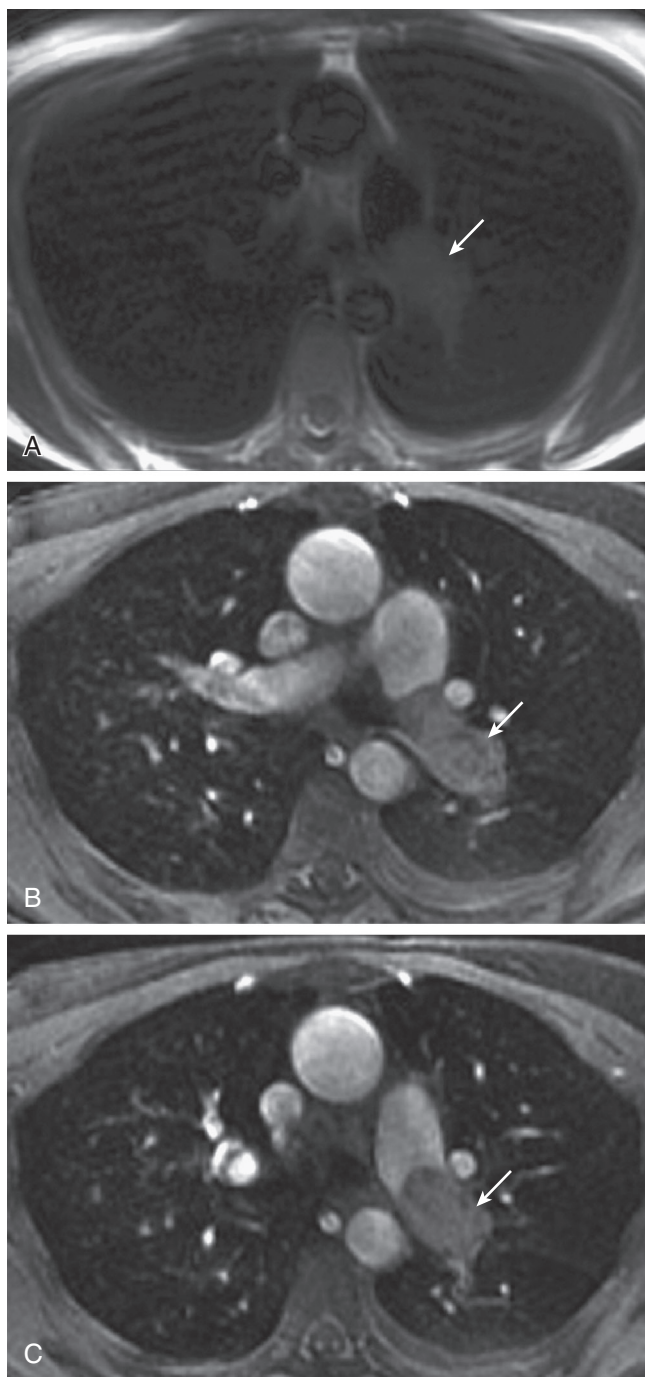
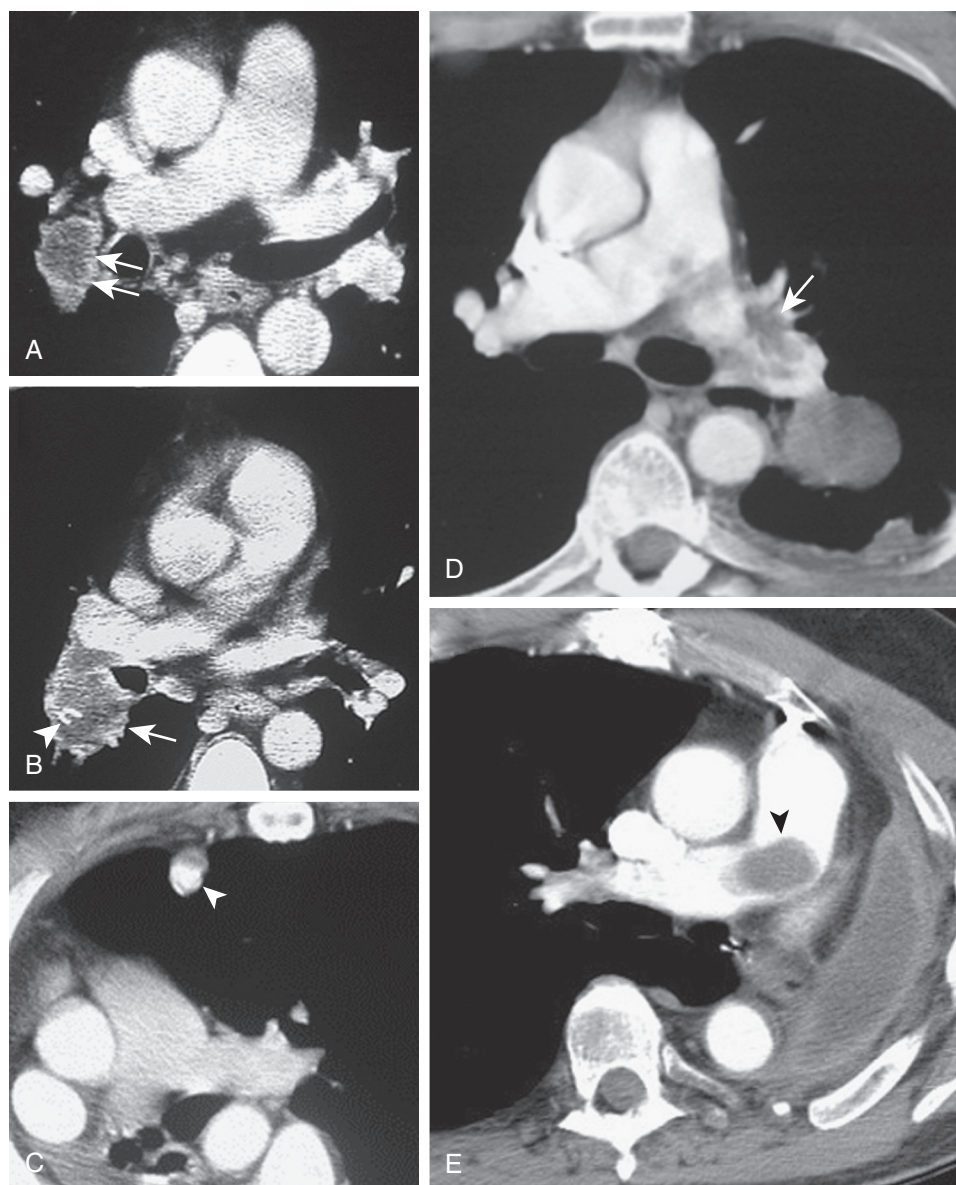
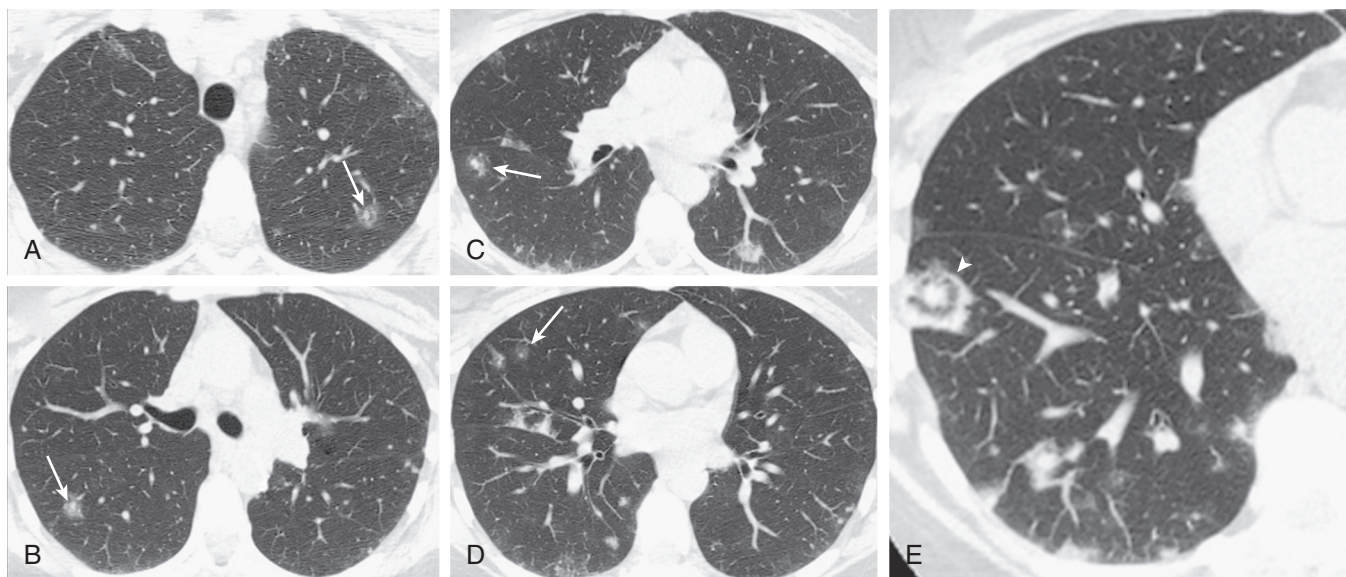


Figure 54-16 Pulmonary artery sarcoma: MR appearance. Axial double-inversion recovery T1-weighted image (**A**) and axial enhanced fast spoiled gradient echo images (**B** and **C**) show a soft tissue mass completely filling the left pulmonary artery. Note the faint internal enhancement visible within the intravascular lesion in **B**. (Courtesy Michael Gotway, MD.)



eFigure 54-17 Pulmonary artery sarcoma: tumor recurrence. **A–C**, Axial enhanced chest CT scans show right peribronchial lymph node enlargement (**A**, *double arrows*) associated with a tumor mass arising from the right lower lobe artery (**B**, *arrow*). Note the small focus of hyperattenuation present within the primary tumor (**B**, *arrowhead*). The lesion was an osteosarcoma arising with the pulmonary artery. Just over a year following right pneumonectomy, ossified metastatic nodules (**C**, *arrowhead*) appeared within the left lung. **D** and **E**, Left pulmonary artery sarcoma (**D**, *arrow*) with recurrence (**E**, *arrowhead*) 1 year after left pneumonectomy. (Courtesy Michael Gotway, MD.)



eFigure 54-18 Pulmonary hemangioendothelioma. A–E, Axial chest CT scans in a 39-year-old woman with cough and hemoptysis displayed in lung windows show multiple, bilateral, variably sized ground-glass opacity nodules with foci of solid nodular internal opacity centrally (*arrows*). One right lower lobe lesion shows peripheral consolidation surrounding ground-glass opacity with a centrally located solid nodular focus (**E**, *arrowhead*). Surgical lung biopsy proved pulmonary hemangioendothelioma. The lesions have been stable for 1 year during follow-up. (Courtesy Michael Gotway, MD.)

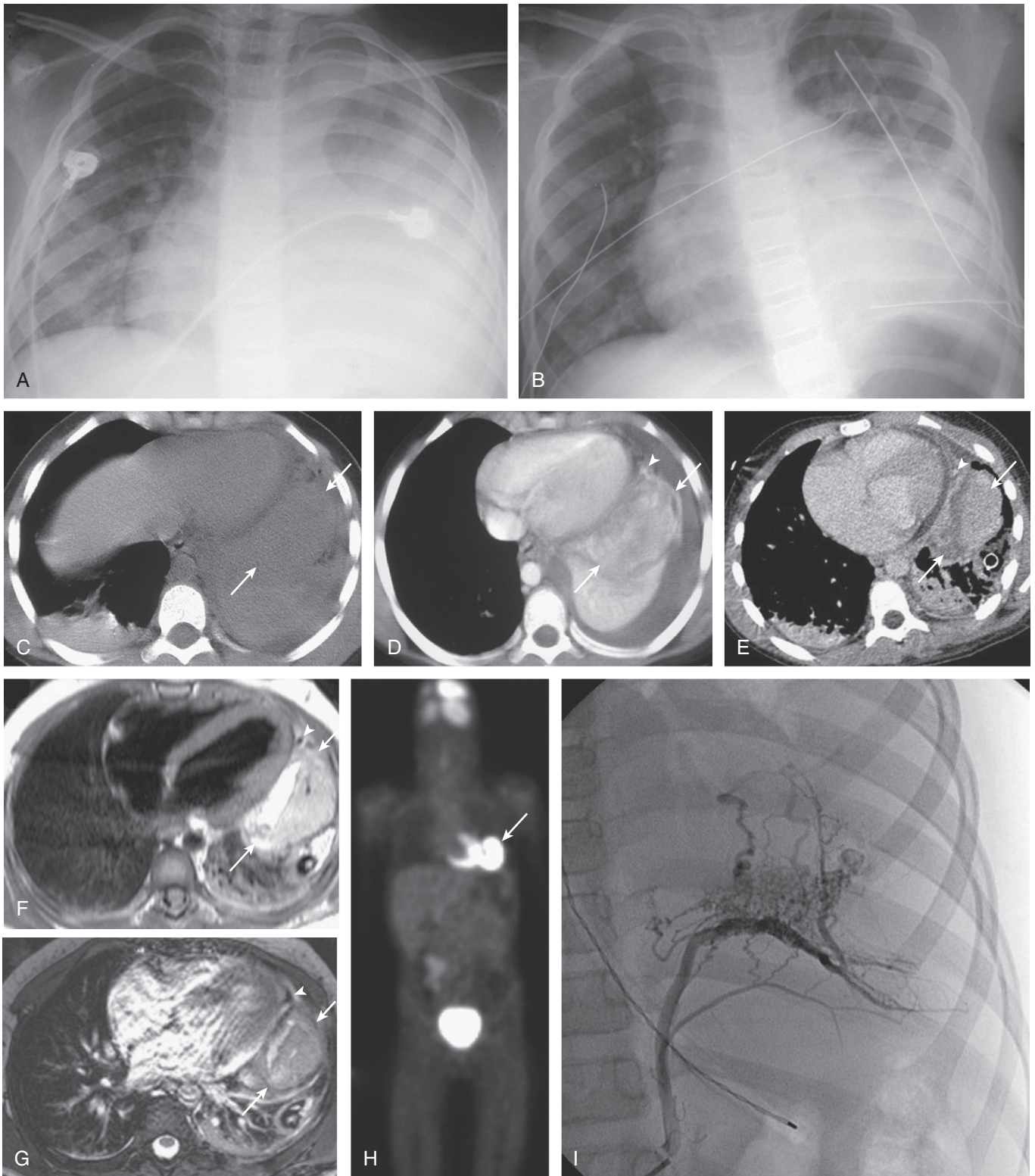
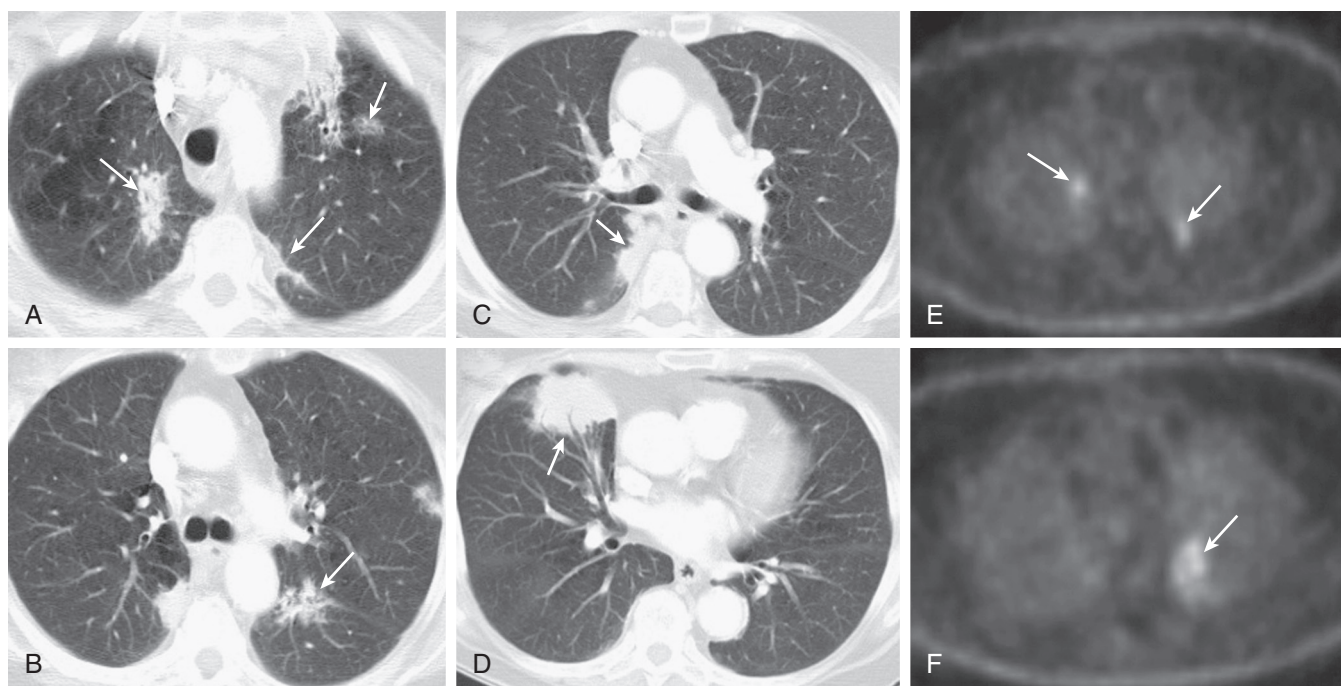
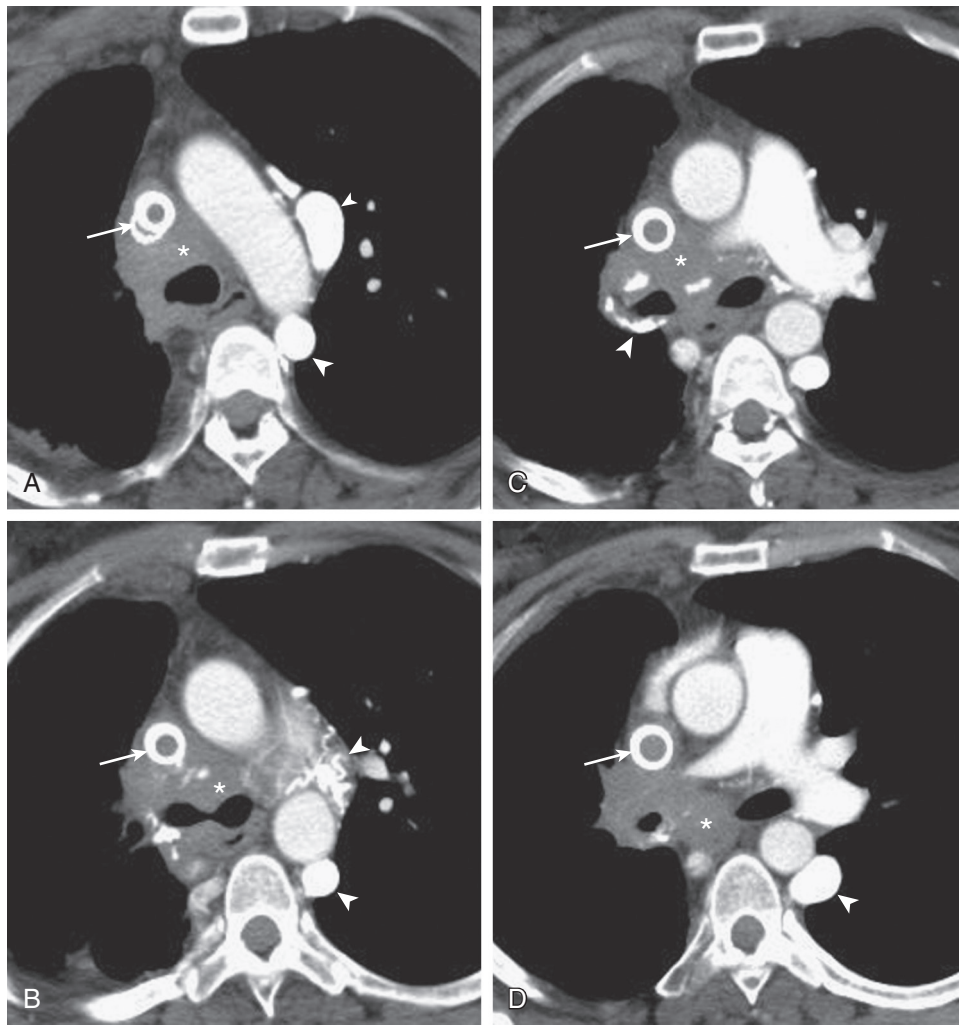


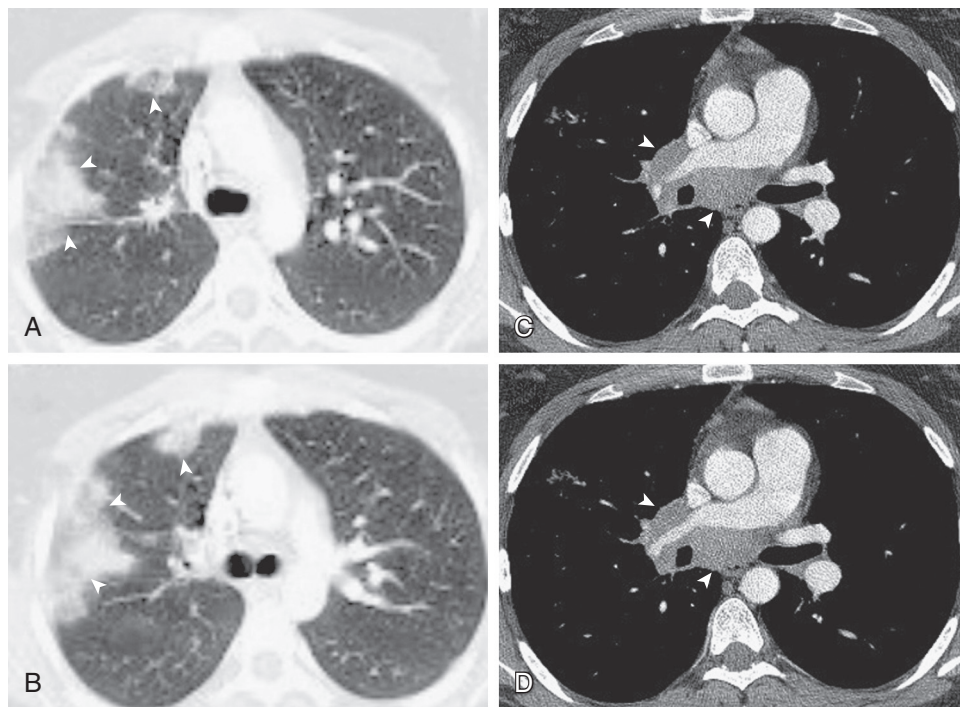
Figure 54-19 Inflammatory myofibroblastic tumor. **A**, Frontal chest radiograph obtained in an 8-year-old boy after being struck by an automobile shows a large left pleural effusion and basal predominant left lung opacity. **B**, Frontal chest radiograph obtained after insertion of a surgical thoracostomy tube shows removal of the pleural fluid. During the placement of this tube, the surgeon noted a lesion in the left chest and obtained a small biopsy specimen, but profuse bleeding prevented further assessment. Axial unenhanced (**C**) and enhanced (**D**) chest CT shows a left lower anterior chest mass (arrows); the mass shows intense enhancement following intravenous contrast administration. A large vessel (**D**, arrowhead) is present in the anterior mediastinum adjacent to the mass. **E**, Axial enhanced multislice chest CT again shows the mass (arrows) and prominent mediastinal vessel (arrowhead). This examination was obtained to search for aberrant systemic arterial supply on the assumption that the lesion might represent a sequestration. No systemic arterial supply arising from the thoracic aorta was seen, but the examination was not extended into the upper abdomen to evaluate the cranial abdominal aorta. Axial T1-weighted (**F**) and axial gradient echo (**G**) MR images show that the mass (arrows) contains high signal in T1-weighted and intermediate-to-low signal on gradient echo imaging, consistent with hemorrhage. The hypointense structure in the mediastinum adjacent to the mass (arrowheads) represents a flow void within a large vessel. **H**, Coronal PET image shows intense metabolic activity within the lesion (arrow). **I**, Coronal preoperative angiogram shows aberrant systemic arterial supply to the mass derived from the cranial abdominal aorta; this vessel was embolized to decrease intraoperative blood loss. Inflammatory myofibroblastic tumor was confirmed following surgical resection, and the lesion was noted to be highly vascular and to have invaded the mediastinum at surgery, with the venous drainage of the mass corresponding to the large anterior mediastinal vessel seen on CT (**D** and **E**) and MRI (**F** and **G**). (From Gotway MB, Dawn SK: An unusual cause of a pulmonary mass. *Clin Pulmon Med* 11:266–268, 2004.)



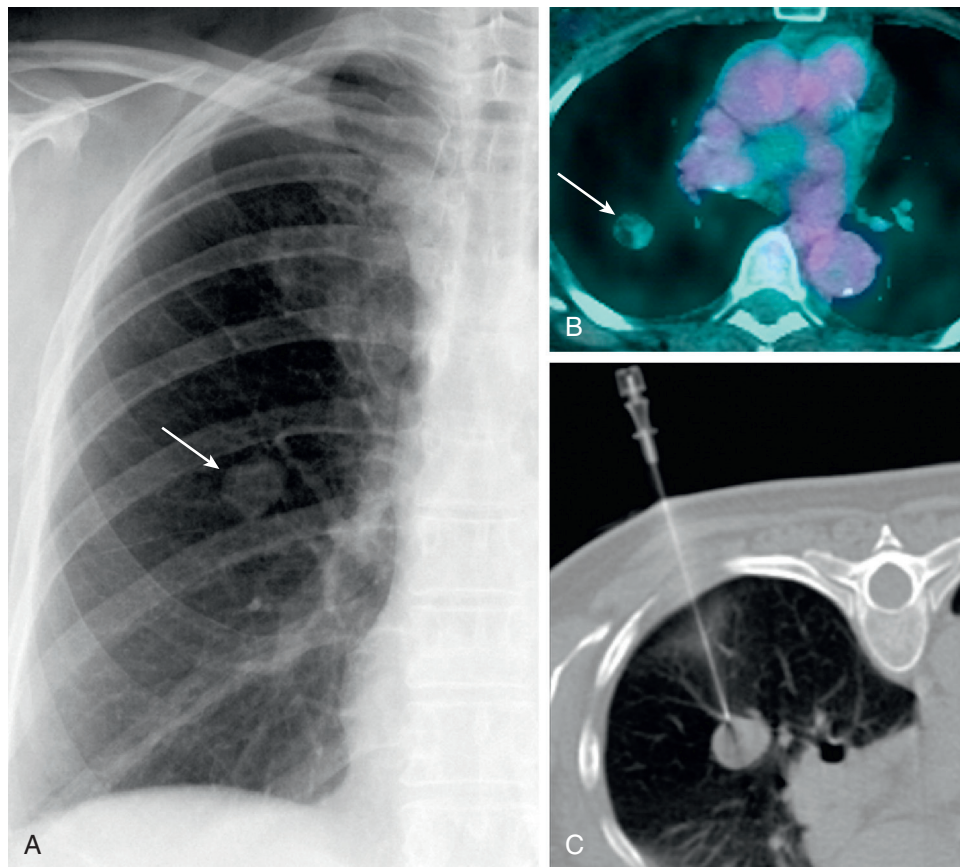
eFigure 54-20 Multicentric inflammatory myofibroblastic tumor. **A–D,** Axial chest CT scans displayed in lung windows show multiple, variably sized, poorly defined nodules (*arrows*). **E and F,** Axial PET images show mildly increased metabolic activity within several of the nodules (*arrows*). The imaging features are ultimately nonspecific, and surgical excision was required to establish the diagnosis. (Courtesy Michael Gotway, MD.)



eFigure 54-21 Mediastinal fibrosis: noncalcified mediastinal soft tissue. **A–D,** Axial enhanced chest CT scans show infiltrating soft tissue (*) throughout the mediastinum, associated with occlusion of the superior vena cava, which prompted stent placement (*arrows*). The venous compression resulted in extensive venous collateral vessel formation (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 54-22 Mediastinal fibrosis: venous infarction and noncalcified mediastinal soft tissue. Axial enhanced chest CT scans displayed in lung (A and B) windows show subpleural right upper lobe opacities (arrowheads) representing pulmonary infarction, resulting from pulmonary venous compression. Mediastinal soft tissue (C and D, arrowheads) is seen compressing the right pulmonary artery. (Courtesy Michael Gotway, MD.)



eFigure 54-23 Pulmonary hamartoma: nonspecific nodule. A, Frontal chest radiograph shows a nonspecific right perihilar pulmonary nodule (arrow). B, Fused axial PET scan shows no significant FDG uptake within the nodule (arrow). C, Prone CT obtained during transthoracic fine-needle aspiration and core biopsy shows no fat or calcium within the lesion. The biopsy established the diagnosis. (Courtesy Michael Gotway, MD.)

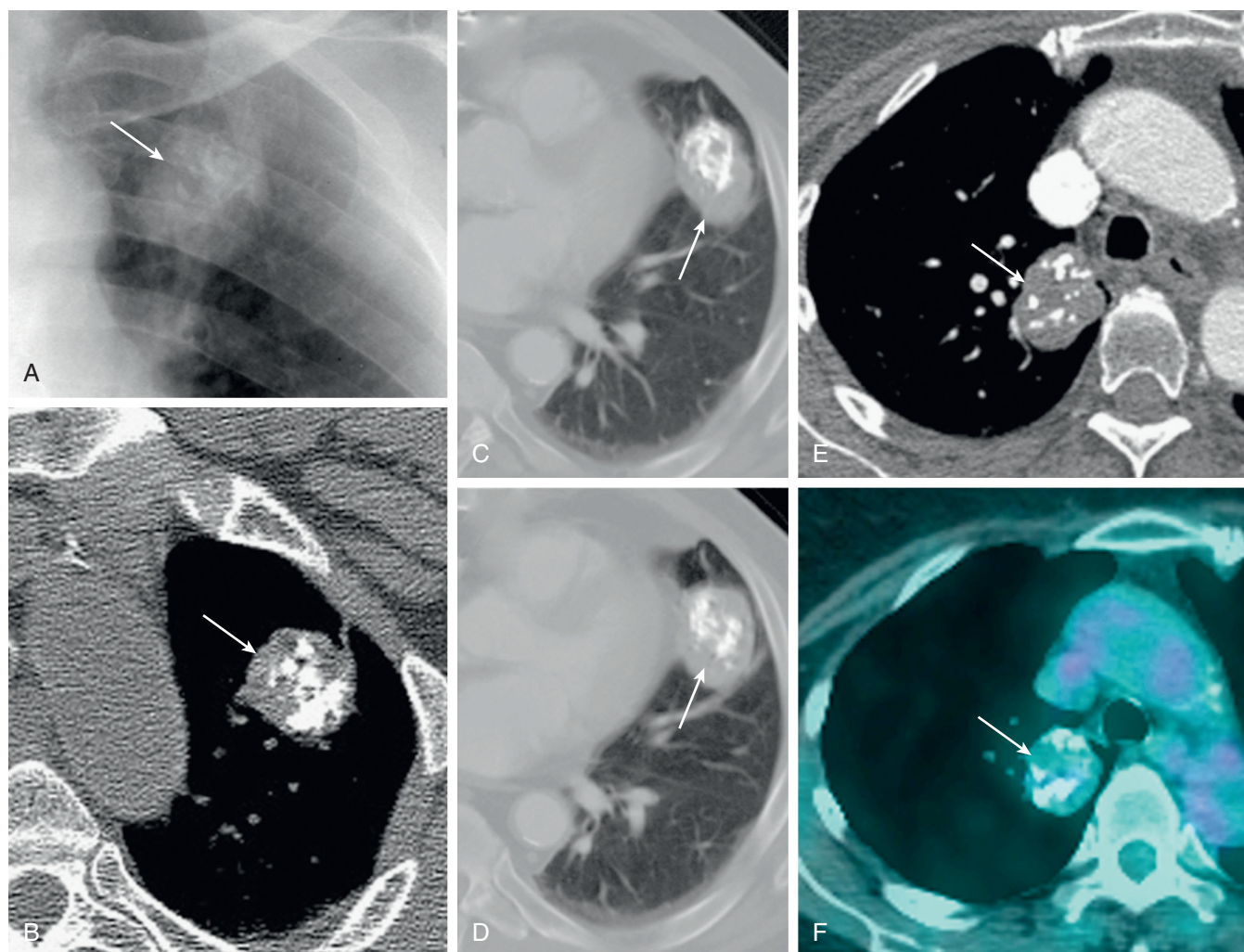
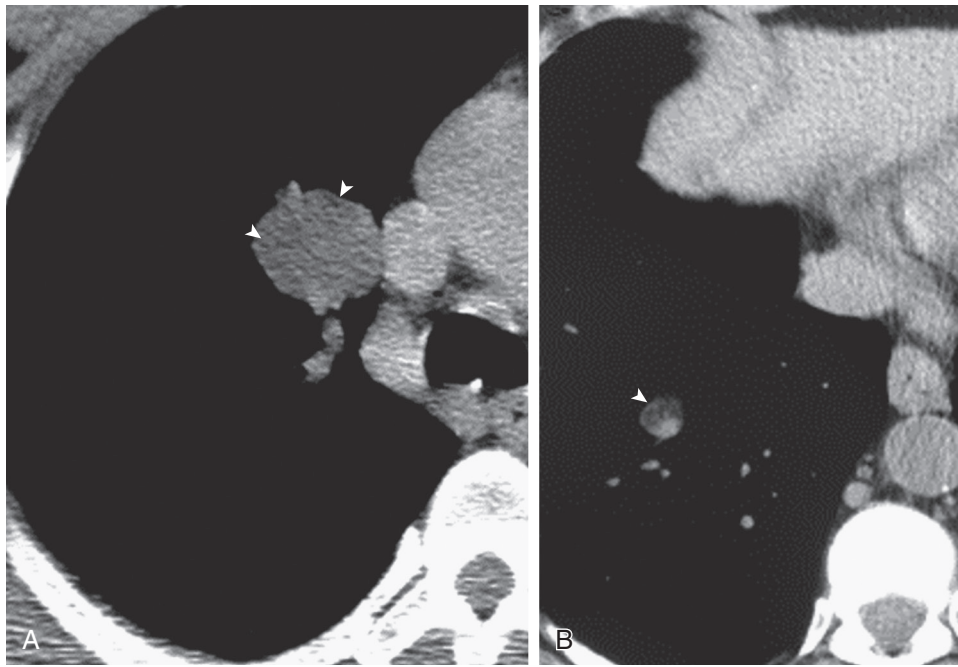


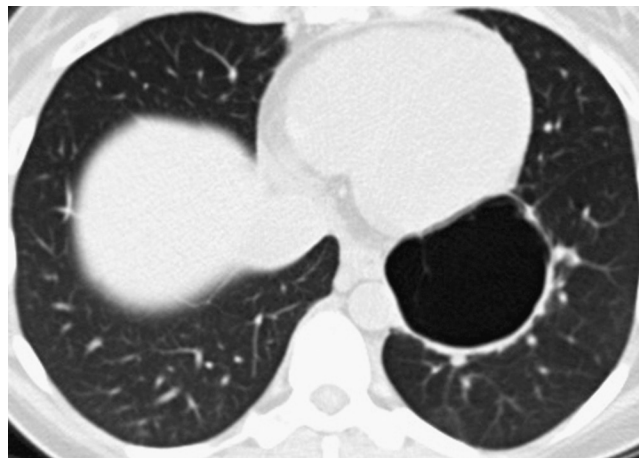
Figure 54-24 Pulmonary hamartoma: chondroid calcification. **A**, Focused frontal chest radiograph shows a left apical nodule (*arrow*) associated with internal calcification. Note that the pattern of calcification can be described as “rings and arcs,” which is consistent with calcification within cartilage. **B**, Axial unenhanced chest CT confirms the presence of calcium within the nodule (*arrow*) seen at chest radiography (**A**). This pattern of calcification is reminiscent of a popped kernel of popcorn; hence, the pattern of chondroid calcification is also often referred to as “popcorn” calcification. **C** and **D**, Axial chest CT scans show another hamartoma (*arrows*) with the characteristic chondroid calcification pattern. Axial enhanced chest CT (**E**) and axial fused PET scan (**F**) show typical chondroid calcification within a pulmonary nodule (*arrows*), consistent with hamartoma. The nodule (*arrows*) shows no significant metabolic activity. (Courtesy Michael Gotway, MD.)



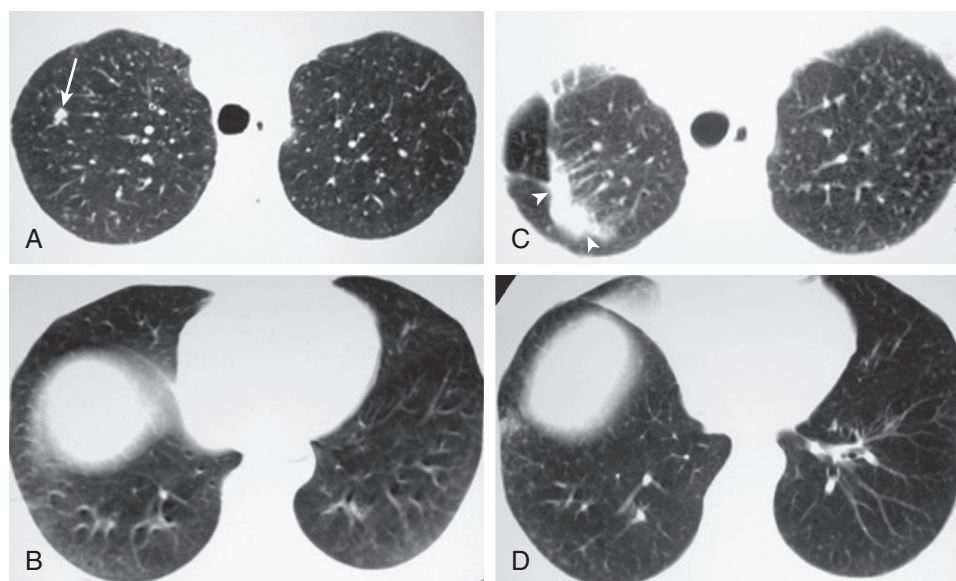
Figure 54-25 Pulmonary hamartoma: “giant” chondroid hamartoma. Axial chest CT shows a very large right lower lobe mass, but the lesion contains typical chondroid calcification. The lesion was resected due to its large size and was found to represent hamartoma. (Courtesy Michael Gotway, MD.)



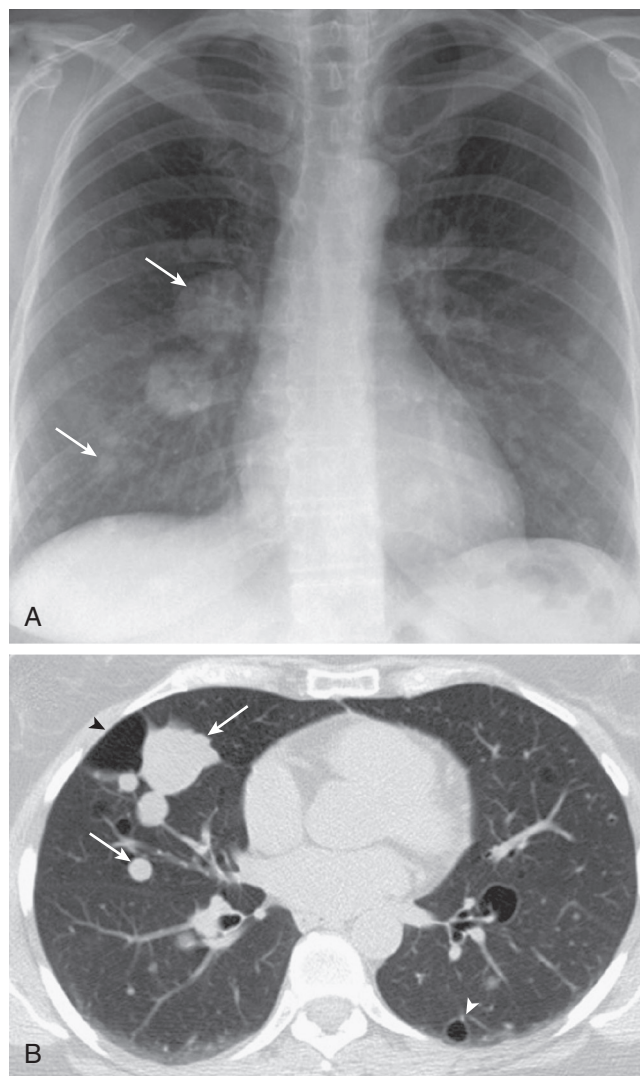
eFigure 54-26 Pulmonary hamartoma: intralesional fat. **A**, Axial chest CT, which was obtained for evaluation of a nodule that was incidentally detected on chest radiography, shows a nonspecific medial right upper lobe nodule. No calcification is present. A few hypoattenuating areas (*arrowheads*), suggesting intralesional fat, were noted, but were not sufficiently visualized to allow a confident noninvasive diagnosis of hamartoma. The lesion was resected and hamartoma containing fat was confirmed. **B**, Axial chest CT, which was obtained in another patient for evaluation of a nodule that was incidentally detected on chest radiography shows a right lower lobe nodule that clearly contains low attenuation tissue (*arrowhead*); the attenuation coefficient within the hypoattenuating area was -65 HU, indicating the presence of fat within the lesion and consistent with hamartoma. (Courtesy Michael Gotway, MD.)



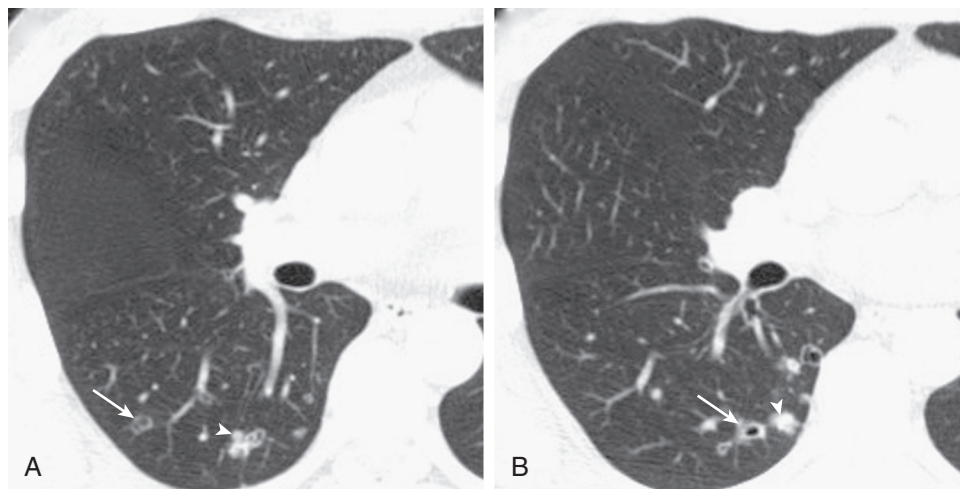
eFigure 54-27 Pulmonary hamartoma: cystic chondroid hamartoma. Axial chest CT shows a nonspecific left lower lobe thin-walled cystic lesion. This lesion had expanded slowly over a 7-year period, eventually causing symptoms and prompting resection, at which time the diagnosis of cystic chondroid hamartoma was established. (Courtesy Michael Gotway, MD.)



eFigure 54-28 Minute pulmonary meningothelial-like nodules. **A** and **B**, Axial chest CT scans displayed in lung windows obtained for evaluation of a right upper lobe nodule confirm the presence of a small right upper lobe nodule (**A**, *arrow*), as well as numerous very small pulmonary nodules in the upper lobes bilaterally. **C** and **D**, Axial chest CT scans displayed in lung windows obtained following surgical resection of the right upper lobe nodule (pathologically confirmed adenocarcinoma; *arrowheads* show site of postoperative change) again show the small bilateral pulmonary nodules. These nodules were seen in the right upper lobe wedge resection specimen and conformed to represent minute pulmonary meningothelial-like nodules. (From Sellami D, Gotway MB, Hanks DK, Webb WR: Minute pulmonary meningothelial-like nodules: thin-section CT appearance. *J Comput Assist Tomogr* 25:311–313, 2001.)



eFigure 54-29 Tracheobronchial papillomatosis: typical chest radiographic and CT findings. **A**, Frontal chest radiograph in a patient with tracheobronchial papillomatosis shows several variably sized nodules (*arrows*) bilaterally. **B**, Axial chest CT displayed in lung windows shows the typical combination of nodules (*arrows*) and cysts (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 54-30 Tracheobronchial papillomatosis: early disease. **A** and **B**, Axial chest CT scans displayed in lung windows show small centrilobular nodules (*arrowheads*) and thin-walled cavities (*arrows*) in the superior segment of the right lower lobe (a relatively dependent distribution). (Courtesy Michael Gotway, MD.)

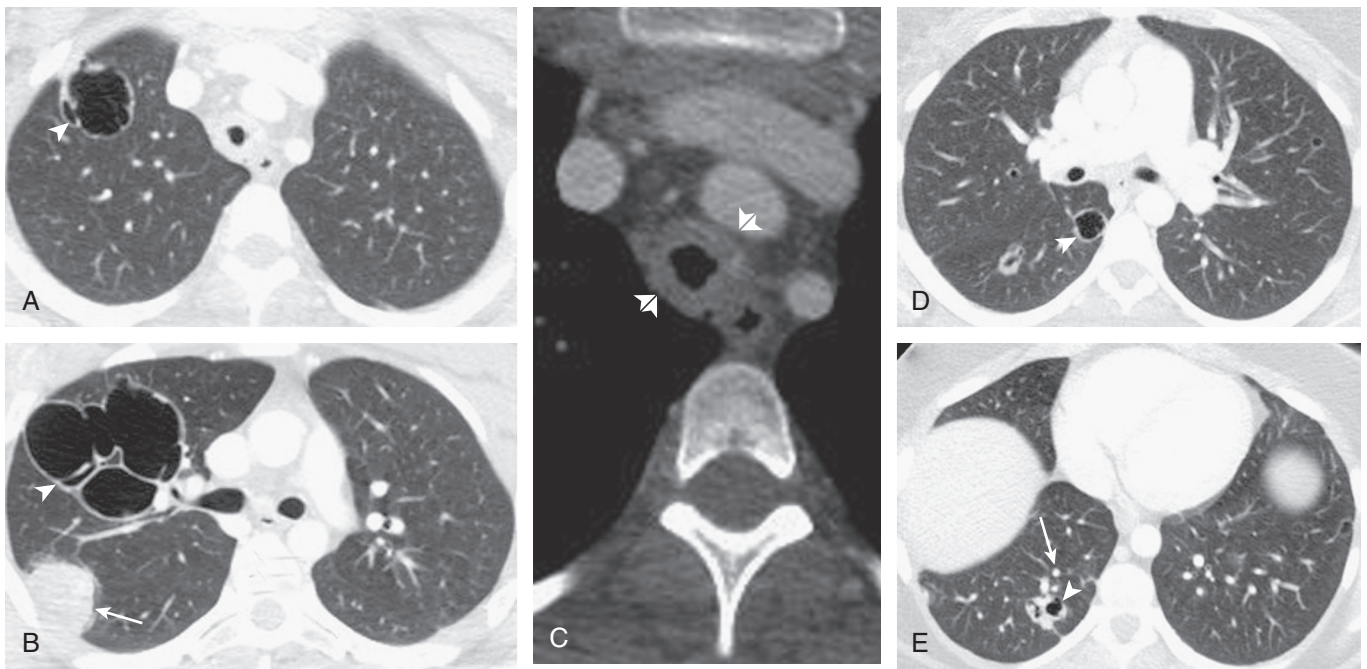


Figure 54-31 Tracheobronchial papillomatosis: **A, B, D, and E,** Axial chest CT scans displayed in lung windows show relatively thin-walled, variably sized cysts (*arrowheads*) and nodules (*arrows*). **C,** Axial enhanced chest CT displayed in soft tissue windows shows circumferential tracheal wall thickening (*double arrowheads*). (Courtesy Michael Gotway, MD.)

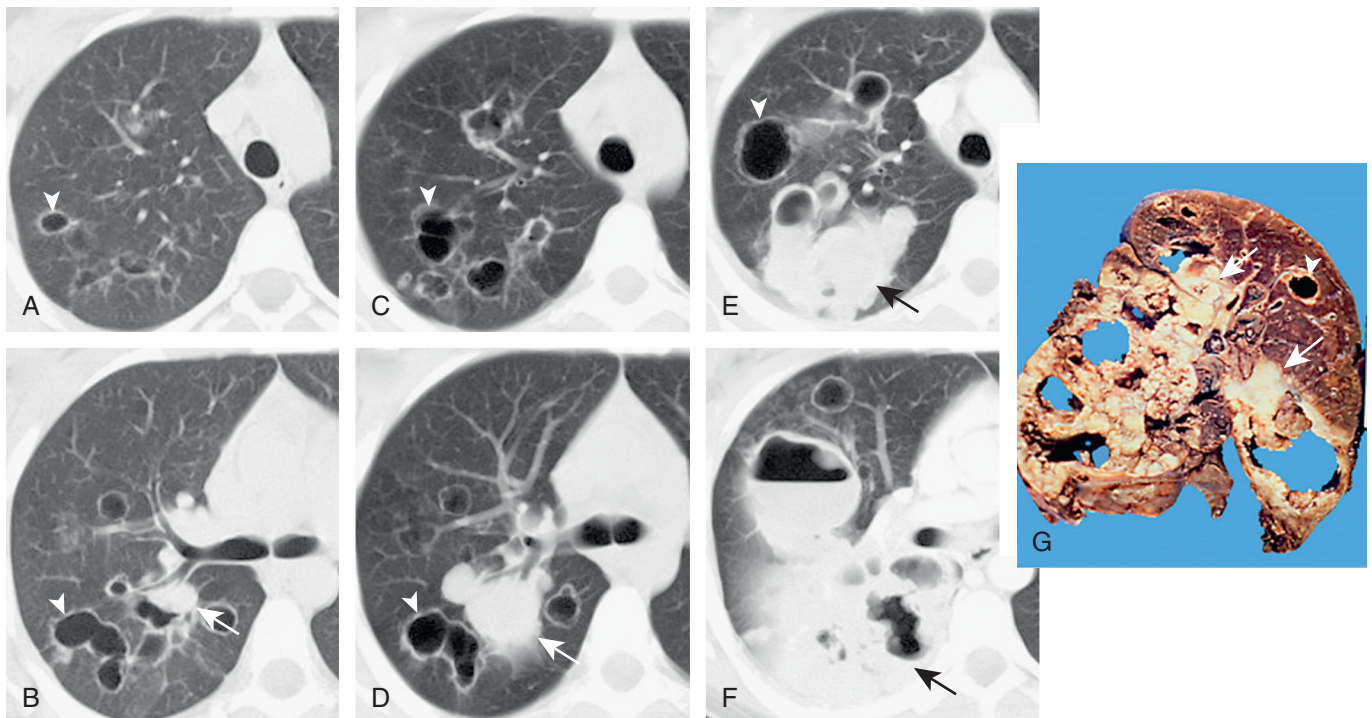
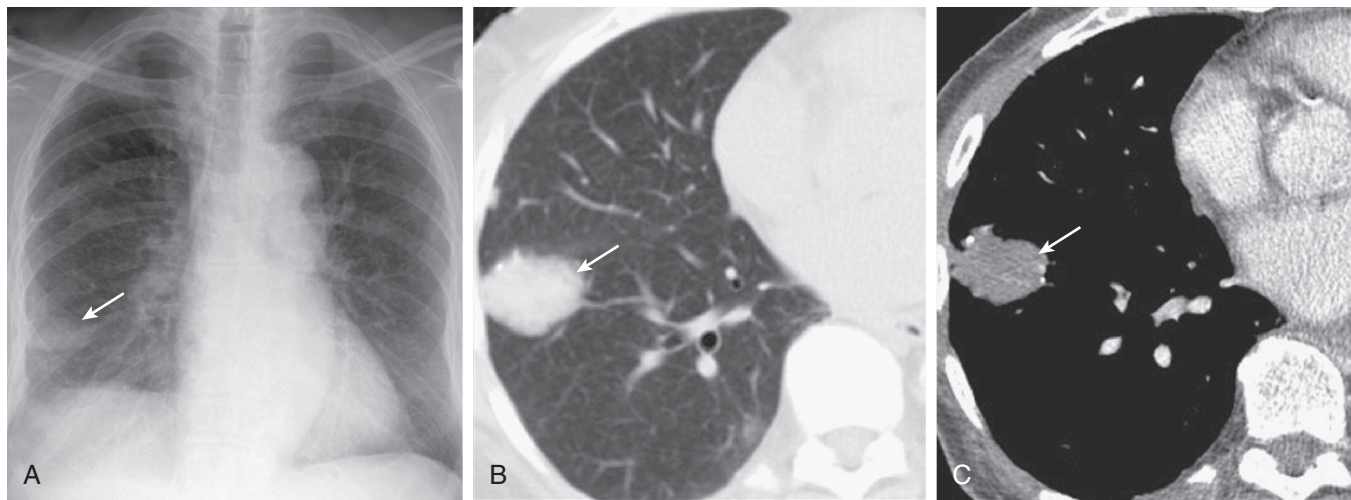
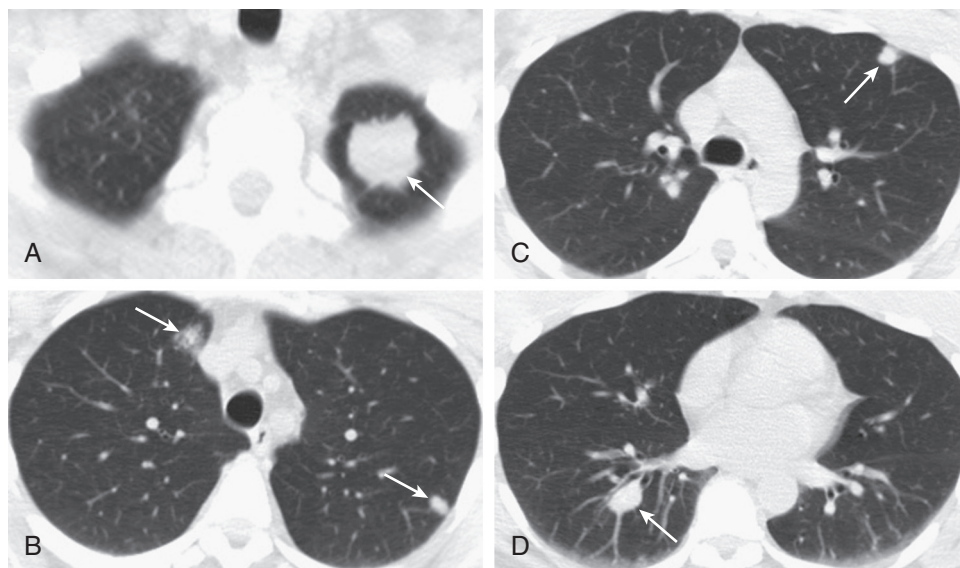


Figure 54-32 Tracheobronchial papillomatosis: progressive disease with malignant transformation. **A–F,** Axial chest CT images displayed in lung windows show progressive cyst and cavity enlargement with increasing nodularity related to the cyst walls. **A and B,** Axial chest CT scans show mostly thin-walled cyst formation (*arrowheads*) with relatively mild nodularity (**B, arrow**). Axial chest CT obtained just over 1 year after **A** and **B** shows enlarging cysts (**C and D, arrowheads**) and marked increase in nodular opacity related to the posterior segment right upper lobe bronchus (**D, arrow**). **E and F,** Axial chest CT scans performed just over 2 years following **A** and **B** show further enlargement of pulmonary cysts and cavities (*arrowheads*), with marked increase in cavitory nodular right lung opacity (*arrows*). **G,** Gross right lung specimen following pneumonectomy shows cystic change (*arrowhead*) with extensive cavitation with internal mural nodularity (*arrows*). The mural nodular opacity represents squamous cell carcinoma development. (**A to F,** Courtesy Michael Gotway, MD.)



eFigure 54-33 Pulmonary amyloidosis: solitary pulmonary nodule. **A**, Frontal chest radiograph shows an oblong, nonspecific right lower lobe nodule (*arrow*). Axial enhanced chest CT scans displayed in lung (**B**) and soft tissue (**C**) windows show a lobulated, noncalcified right lower lobe nodule (*arrows*). The imaging features are nonspecific, but transthoracic fine-needle aspiration and core biopsy revealed that the nodule was due to amyloid. (Courtesy Michael Gotway, MD.)



eFigure 54-34 Pulmonary amyloidosis: multiple pulmonary nodules. **A–D**, Axial chest CT scans displayed in lung windows show multiple variably sized bilateral pulmonary nodules (*arrows*), which were shown on biopsy to represent amyloidosis. (Courtesy Michael Gotway, MD.)

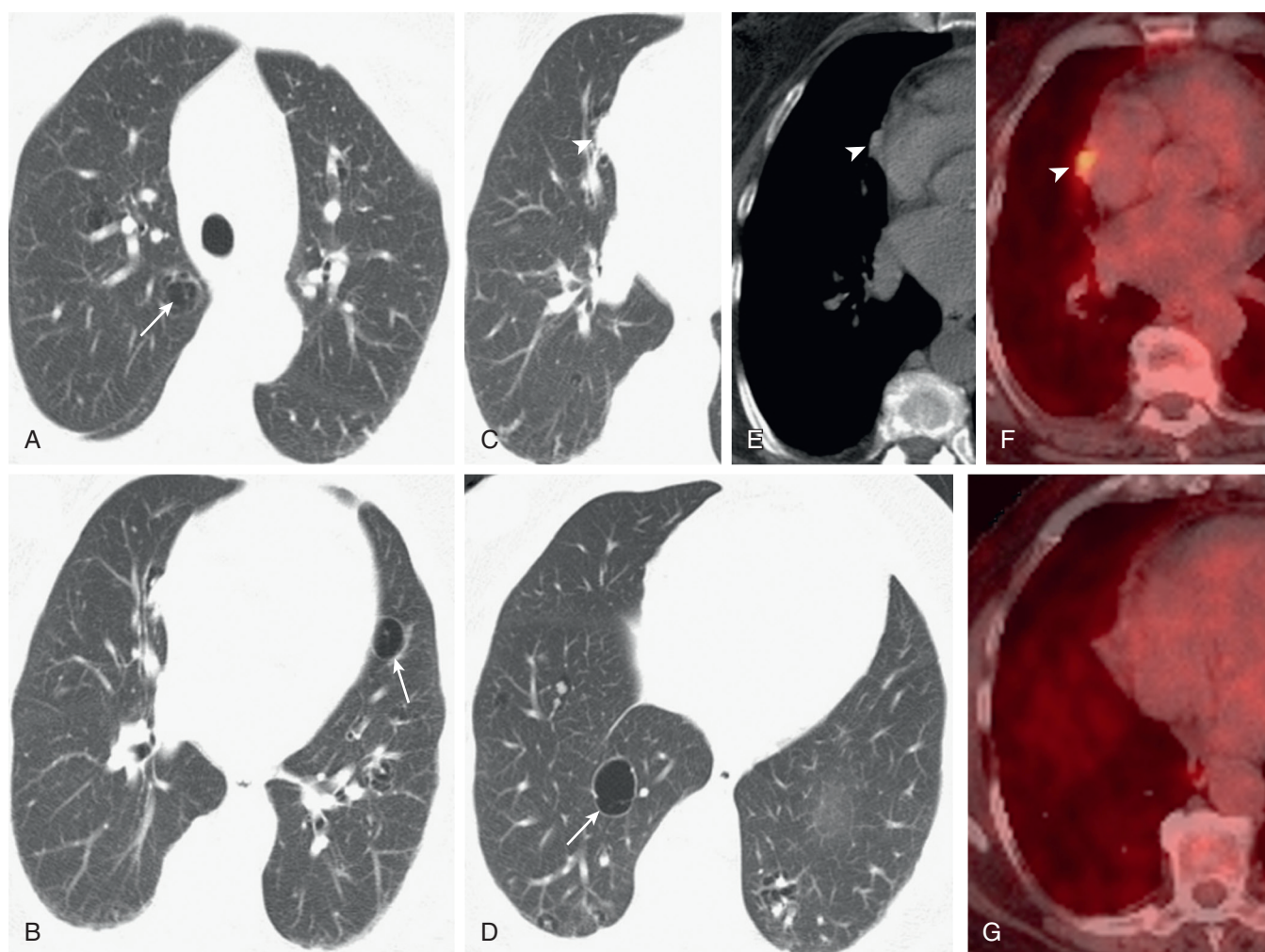
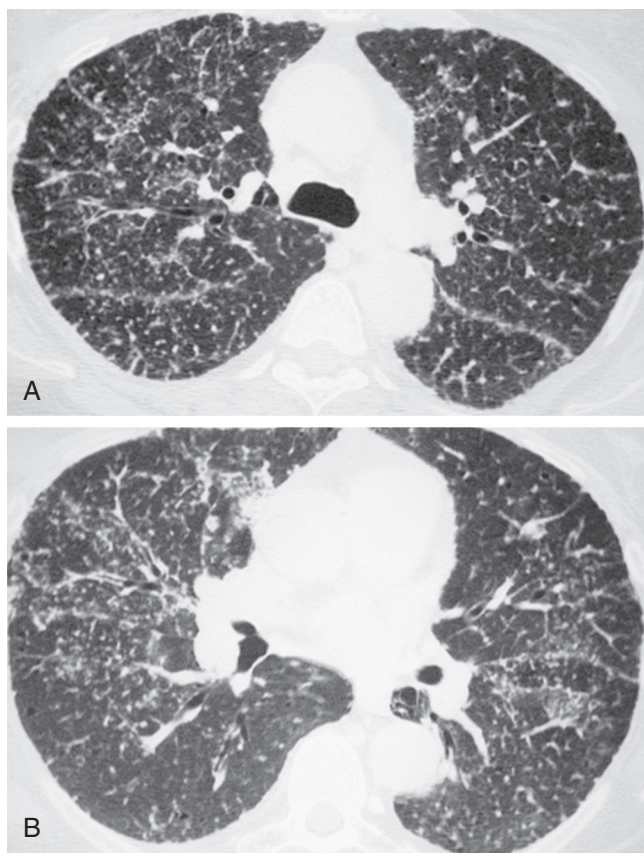
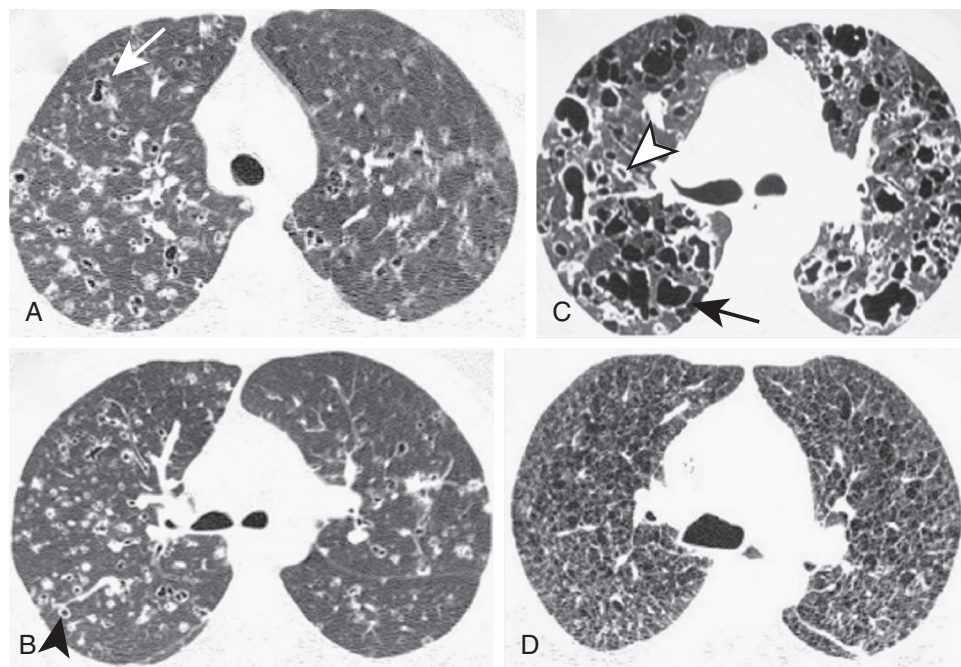


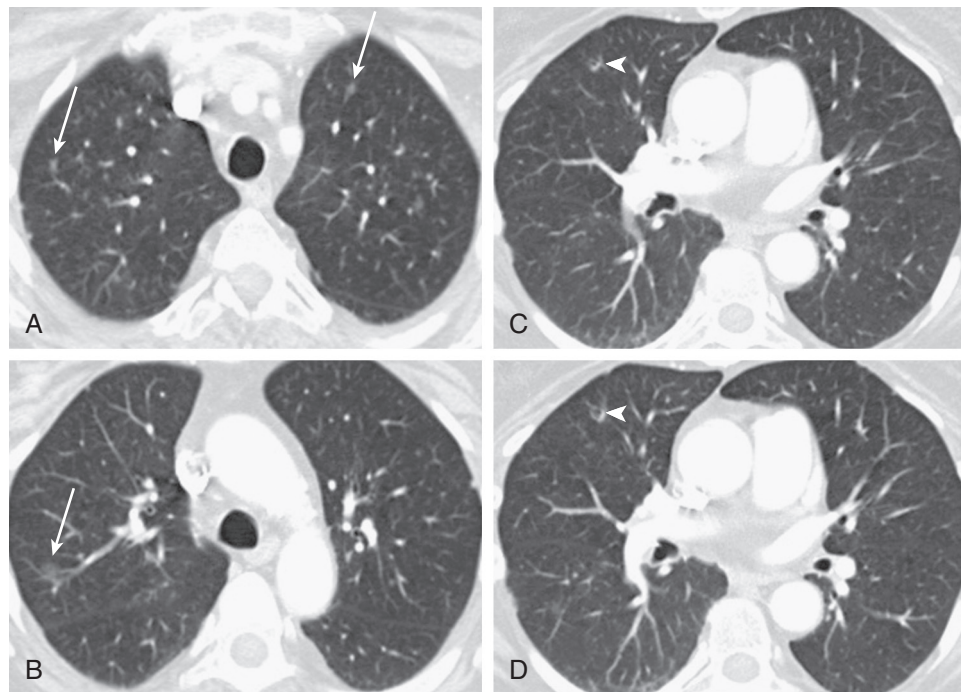
Figure 54-35 Pulmonary amyloidosis: nodules, cysts, and nodule-within-cyst morphology. **A–D,** Axial chest CT scans displayed in lung windows show multiple thin-walled cysts (*arrows*), some of which contain faint internal nodular opacity. A solid nodule (**C**, *arrowhead*) is present in the medial right middle lobe. **E,** Axial chest CT displayed in soft tissue shows no evidence of calcification within one nodule located in the medial right middle lobe nodule (*arrowhead*). **F and G,** Axial fused PET scan shows active tracer utilization within the medial right middle lobe nodule (**F**, *arrowhead*), but not within the right basal cystic lesion. No tracer utilization was present in the other cystic foci elsewhere. Surgical excision of several of the cystic and nodular foci showed amyloidosis. (Courtesy Michael Gotway, MD.)



eFigure 54-36 Light chain deposition disease. **A** and **B**, Axial chest CT scans displayed in lung windows show numerous small, circumscribed nodules distributed along interlobular septae and fissural surfaces. The nodule distribution appears perilymphatic, and sarcoidosis was the working diagnosis. Bronchoscopy with transbronchial biopsy established the diagnosis of light chain deposition disease. (Courtesy Michael Gotway, MD.)



eFigure 54-37 Langerhans cell histiocytosis. **A** and **B**, Axial chest CT scans displayed in lung windows performed in a 17-year-old patient show features consistent with relatively “early” Langerhans cell histiocytosis: numerous small nodules, some showing cavitation (**B**, arrowhead), and a few developing bizarre-shaped cysts (**A**, arrow). **C**, Axial chest CT displayed in lung windows performed in a 30-year-old smoker shows features consistent with more developed Langerhans cell histiocytosis: prominent, bizarre-shaped cysts (arrow), with a few small solid and cavitating (arrowhead) nodules. **D**, Axial chest CT displayed in lung windows performed in a 55-year-old smoker shows features consistent with relatively “late,” or “burned-out,” Langerhans cell histiocytosis: innumerable small cystic areas resembling pulmonary emphysema (which is often coexistent). (Courtesy Michael Gotway, MD.)



eFigure 54-38 Atypical imaging manifestation of Langerhans cell histiocytosis. **A–D**, Axial chest CT images displayed in lung windows show a few small nodules (**A** and **B**, arrows) with a relatively thin-walled cavitory lesion (**C** and **D**, arrowheads) in the right middle lobe. The imaging features are nonspecific and the diagnosis was established through video-assisted thoracoscopic wedge resection of several of the pulmonary opacities. (Courtesy Michael Gotway, MD.)

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METASTATIC MALIGNANT TUMORS

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INTRODUCTION

The lung is a common site for metastasis of malignant tumors from other organs. Logic would suggest that the lung is such a common destination for metastasis because it alone receives the entire cardiac output.¹ Indeed, this likely does play a role in the eventual seeding of the lungs when cancers metastasize via the hematogenous route. However, a more detailed understanding of the molecular mechanisms dictating organ-specific metastases has made it clear that specific properties of the primary tumor and the microenvironment of the tissue of origin and of the lung play a significant role in directing the process of metastasis to the lung. Paget initially proposed what became known as the “seed and soil” hypothesis in 1889 based upon his observations of the nonrandom nature of breast cancer metastasis.² While we can now begin to define mechanisms of organ-specific metastases at a molecular level, we still lack therapeutic tools specifically aimed at preventing metastases.³ This chapter reviews the epidemiology of lung metastasis, advances in our knowledge of the pathophysiology of metastasis, approaches to help distinguish metastasis from primary lung cancer, advances in diagnostic methods, and treatment options that vary from palliation to curative surgery.

EPIDEMIOLOGY

Estimates of the incidence of lung metastasis among patients with cancer vary from 20% to 40%.^{1,4} However, estimates of the incidence of lung metastasis have limitations. Most series focus on a single tumor type as the origin of lung metastases. The incidence of lung metastasis also varies depending on the means used for detection and for follow-up; a lower incidence is reported if the metastases are detected by the presence of respiratory symptoms and rises progressively when metastases are detected by routine surveillance with chest radiographs or with *computed tomography* (CT) scans, or autopsy data. Not surprisingly, the detection of metastases for any given solid tumor type

will be greater when ¹⁸F-fluorodeoxyglucose positron emission tomography (PET) scanning is used as a method of surveillance.⁵ While reports of the proportion of cancers that metastasize to the lung vary, the lung is always among the most common sites of metastasis of solid tumors.⁴

CLINICAL HISTORY

Lung nodules or effusions developing in the context of an extrapulmonary neoplasm can either be *synchronous* (discovered at the same time as the primary tumor) or *metachronous* (discovered at some period after the initial solid tumor, either incidentally in the course of follow up of a prior malignancy or in the context of new pulmonary symptoms). Because of the large degree of reserve pulmonary function in most individuals, metastases to the lungs rarely produce symptoms, and even patients with a large metastatic tumor burden can present with minimal or no pulmonary symptoms. When nonspecific symptoms of cough, dyspnea, or chest pain and discomfort can be attributed to metastatic lesions, they usually result from either a very large tumor burden (Fig. 55-1), extensive lymphatic infiltration, airway involvement, or a large pleural effusion. The first clue to the presence of lung metastasis comes most commonly from surveillance radiographs in patients with known prior cancer. The most common presentation of lung metastasis is the finding of multiple nodules in the lower lobes. The finding of an incidental solitary pulmonary nodule as the first sign of an extrapulmonary neoplasm makes the distinction of metastasis from that of a primary lung tumor challenging. The physical examination is unlikely to disclose evidence of lung metastasis but, in the context of a solitary pulmonary nodule, the examination should include a search for malignancy elsewhere in the body (e.g., breast or abdominal masses, enlarged lymph nodes). Rarely, a metastasis can affect the larger central airways, producing localized wheezing, which an astute clinician discovers on auscultation. Malignant pleural fluid accumulation produces the physical findings of reduced breath sounds, a dull percussion note, and decreased tactile fremitus.

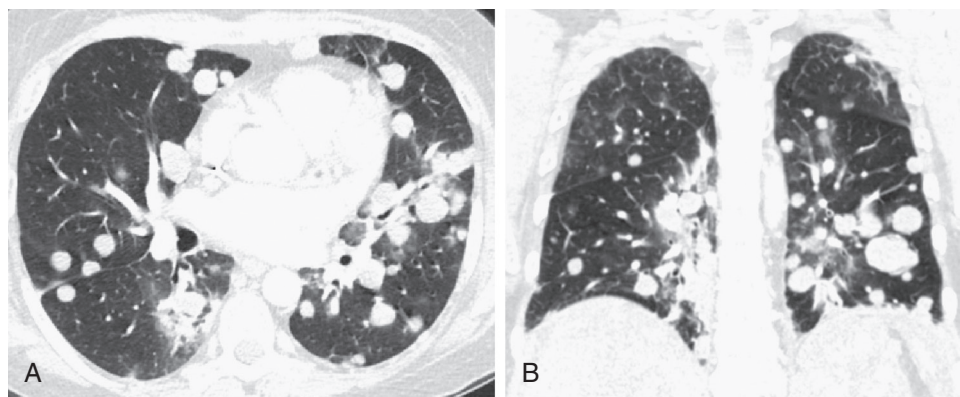


Figure 55-1 Typical appearance of metastatic disease. Axial (A) and coronal (B) chest CT displayed in lung windows of a patient with innumerable rounded lower lobe nodules and a prior history of melanoma. The pretest probability of metastases is so high in such a case that the oncologist may not require a tissue confirmation.

MECHANISM OF METASTASIS TO THE LUNG

When one considers that the lung receives the entire cardiac output, it is perhaps surprising that lung metastases are not even more common among patients with cancer. However, research has shown that the majority of cancer cells that circulate in the blood never result in a clinically overt metastatic focus,^{6,7} suggesting that mere access to the lung is not sufficient to lead to clinically evident metastasis. Additional mechanisms must therefore account for the propensity of certain tumors to seed distant organs preferentially.

One of the main processes involves expression of receptors that bind to ligands in metastatic sites. Chemokines are a group of small cytokines originally discovered as mediators of leukocyte trafficking. Chemokines mediate several important pathologic aspects of tumor biology, including angiogenesis, cell proliferation, invasion, and metastasis.⁸ The pattern of constitutive expression of chemokine receptors on cancer cells combined with expression of the corresponding chemokine ligands in various organs may be responsible for the organ-specific pattern of metastasis of a variety of solid tumor types, including breast, prostate, and lung cancer.⁹⁻¹¹ For example, the chemokine receptors CXCR4 and CCR7 are highly expressed in human breast cancer cell lines, in primary breast tumor samples, and in their metastases. The corresponding ligands for the CXCR4 and CCR7 receptors, CXCL12 and CCL21, are constitutively expressed in organs to which these tumors commonly metastasize (lung, brain, bone, and lymph nodes).¹¹ In breast cancer cell lines, signaling through the receptors CXCR4 or CCR7 promotes *in vitro* migration and invasion. Most interestingly, antibodies or small molecule antagonists directed against CXCR4 significantly impaired metastasis of breast cancer cells to regional lymph nodes and lung *in vivo*. In addition, malignant melanoma, which has a similar metastatic pattern as breast cancer but also a high incidence of skin metastases, showed high expression of the chemokine receptor CCR10 in addition to CXCR4 and CCR7. The ligand for CCR10 (cutaneous T-cell attracting chemokine, or CTACK/CCL27) is highly expressed in normal dermis.¹² In a study of metastasis of non-small cell lung

cancer, metastatic cells were found to be enriched for the expression of CXCR4 compared to cells from the primary tumors, suggesting that CXCR4-expressing cells had an advantage in reaching or surviving in the metastatic niche.¹⁰ Chemokine receptors on cancer cells, in concert with tissue-specific expression of their chemokine ligands, appear to have a critical role in determining the metastatic destination of circulating tumor cells.

Certain molecular processes may increase lung vascular permeability to metastatic cells. In an elegant study, transforming growth factor- β was shown to prime breast cancer cells for lung-specific metastasis by up-regulation of the gene *angiopoietin-like 4* (ANGPTL4).¹³ Transforming growth factor- β induction of ANGPTL4 in breast cancer cells enhanced their subsequent retention in the lungs but not in bone. Tumor cell-derived ANGPTL4 disrupted the pulmonary microvascular cell-cell junctions, increasing the permeability of lung capillaries and facilitating the passage of tumor cells into the lung parenchyma. In contrast, in the bone marrow sinusoids, which are normally more leaky microvascular beds, this mechanism does not confer an advantage.¹³

Other processes may help support the metastatic cell in its lung niche. In another elegant mouse study, tumor cells were shown to be preceded into the metastatic niche by *bone marrow derived cells* (BMDCs) that express the type 1 *vascular endothelial cell growth factor receptor* (VEGFR1+BMDC). These authors demonstrated that VEGFR1+BMDCs were hematopoietic progenitor cells that (1) arrived at the metastatic site before tumor cells, (2) accumulated in the target organ of metastasis following either injection of tumor cells or treatment with tumor cell conditioned media, and (3) established a premetastatic niche in a tumor-specific fashion (i.e., they established a permissive environment for metastasis in an organ-specific pattern that varied depending on the tumor type).

Finally, other processes may enhance lung-specific adherence. As illustrated by Brown and Ruoslahti,¹⁴ the protein, *metadherin*, was found by phage display to be present on the surface of metastatic breast cancer cells that preferentially allowed adherence to the pulmonary vascular endothelium.¹⁴ In summary, tissue-specific metastases arise in a nonrandom fashion determined by specific

molecular mechanisms that involve both tumor-derived soluble factors and microenvironment-specific ligand-receptor interactions.

A further refinement in our understanding of the mechanisms of metastasis comes from a study that examined isolated efferent blood from primary tumors in mice and found that primary tumors also shed tumor fragments consisting of both malignant cells and host stromal fibroblasts. Importantly, the viability of circulating malignant cells was nearly twofold higher in these heterotypic tumor fragments than in single tumor cells shed from the primary tumor. These chaperone stromal fibroblasts survived, proliferated, and conferred a survival advantage to lung metastatic deposits. When the investigators selectively depleted carcinoma-associated fibroblasts from mice after primary tumor removal, the growth of metastatic deposits was significantly inhibited. The study further demonstrated that human brain metastases, but not primary brain tumors, contained carcinoma-associated fibroblasts, supporting the hypothesis that the fibroblasts enhanced the metastatic malignant process. This elegantly designed and executed series of experiments, which required modern molecular techniques and lineage tracking of cells, brought the field back full circle to Paget's seed-and-soil hypothesis because, as the authors correctly point out, the tumor cells facilitate lung metastasis by "bringing their own soil."¹⁵ While these molecular insights have not yet led to specific interventions to prevent metastasis, such advances in the knowledge of molecular mechanisms that promote or facilitate organ-specific metastasis can be expected to drive the search for new treatments to prevent cancer metastasis. Metastases are nearly universally responsible for cancer mortality and, if metastases can be prevented or treated by novel strategies based on these molecular insights, survival with cancer (as opposed to a cure for cancer) is an attainable goal. A diagram illustrating potential mechanisms behind tissue specific metastasis to the lung from extrapulmonary malignancies is shown in Figure 55-2.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Given the range of diagnostic and therapeutic options in cases of known or suspected lung metastasis, patient care is optimal when delivered within the context of a multidisciplinary team. For example, when deciding whether to biopsy a lung nodule in a patient with a prior cancer, a chest physician is well served by speaking to the oncologist and/or the surgeon to learn whether a patient with metastatic cancer has therapeutic options and whether the results of a biopsy would alter those options. If a patient with a solitary nodule suspected to be an isolated lung metastasis is a surgical candidate and a complete resection is feasible, a preoperative tissue diagnosis may not change the treatment plan and, if so, should not be undertaken. Conversely, surgeons may prefer a preoperative tissue diagnosis to improve their discussion of risks, benefits, and alternatives with the patient. Surgeons may also prefer knowing whether a nodule is a metastasis or a primary lung cancer in planning the appropriate surgical procedure, either a

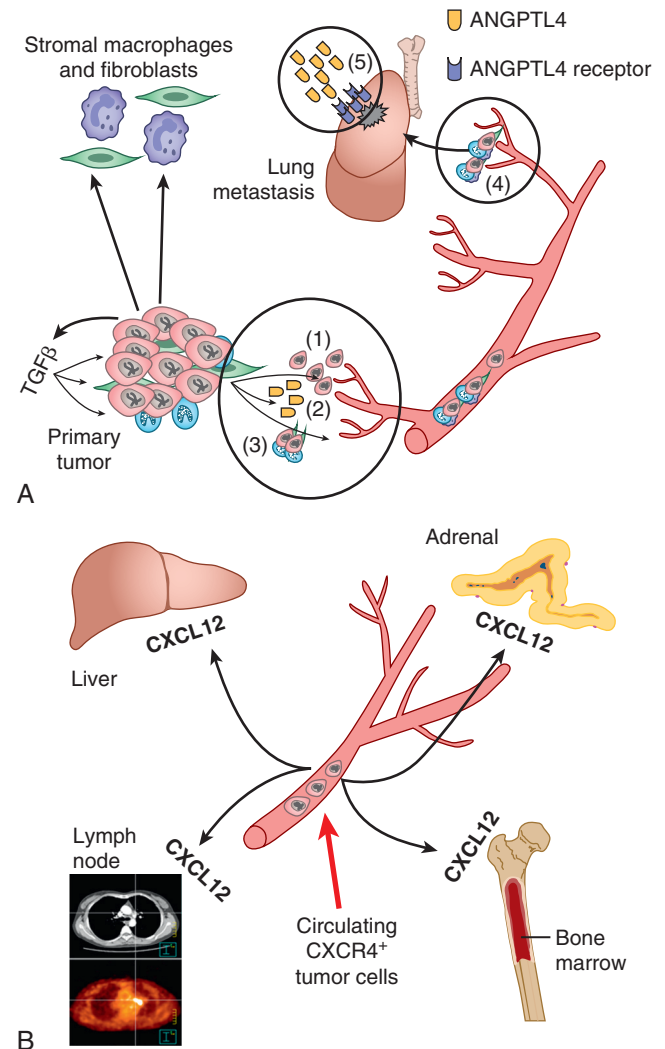


Figure 55-2 Illustration of molecular mechanisms that can drive lung specific metastasis from extrapulmonary malignancy. A, The primary tumor can release (1) single tumor cells, (2) soluble substances such as angiopoietin-like 4 (ANGPTL4), and (3) heterotypic tumor fragments, which enjoy a survival advantage that renders them more likely to reach the lung (4). In the lung, tumor-derived ANGPTL4 creates a microvascular bed that is leaky and conducive to entry of tumor cells in the lung (5). **B,** Tumor cells bearing CXCR4, the receptor for the CXC chemokine CXCL12, are preferentially attracted to organs that constitutively produce CXCL12.

lobectomy or an anatomic segmentectomy. For these and other reasons, the management of these patients is best served when clinicians are readily able to communicate patient-specific concerns to one another, such as in a multidisciplinary conference.

In general, the patient with a prior history of cancer and suspicion of a lung metastasis should be managed with knowledge of several interacting factors: the type of prior cancer, its natural history, its propensity to cause lung metastasis, its sensitivity to systemic or radiation therapy, and the number and location of lung nodules. A decision to biopsy should take into account the likelihood of an alternative diagnosis and whether the results of the biopsy will change the management options. The diagnostic possibilities for a lung nodule or multiple nodules in the patient with

Table 55-1 Differential Diagnosis of Single or Multiple Pulmonary Nodules in Patients with Prior Cancer

MALIGNANT

Metastasis
Primary lung cancer

BENIGN

Infectious

Fungal infection
Mycobacterial infection
Nocardia
Septic emboli

Noninfectious

Rheumatoid nodules
Hamartoma
Carcinoid
Sarcoidosis
Cryptogenic organizing pneumonia
Vasculitis (granulomatous angiitis)

a history of cancer vary with the type of prior cancer. For example, the implications of finding a cavitary nodule in a patient with prior leukemia after a bone marrow transplant are quite different from finding the same cavitary nodule in an individual with prior head and neck cancer. In general, the differential diagnosis of a lung nodule in a patient with prior cancer includes the same diagnoses found in the general population, with the obvious exception that metastatic disease must be considered as well. Both primary malignant and benign causes, including infectious and noninfectious etiologies, should be considered (Table 55-1).

DISTINGUISHING METASTASIS FROM PRIMARY LUNG TUMORS

When a nodule or nodules are discovered in a patient with a prior history of cancer, it is important to distinguish lung metastasis from a primary lung cancer because the treatment can be very different. Clues such as the type of prior cancer, radiologic characteristics of the nodule, and pathologic appearance of subsequent biopsy material can be used to guide treatment decisions. Multiple pulmonary nodules with smooth borders located in the lower (dependent) lobes are most likely to be metastatic based on clinical grounds alone. When a single nodule is the only evidence of metastasis, recognizing it as metastatic can be more difficult. In some instances, the type of prior cancer can provide a clue to the likelihood of a metastasis versus a primary lung cancer. In a retrospective study of patients with single pulmonary nodules and a prior history of cancer, multiple factors were examined as possible predictors for metastasis including the histologic characteristics of the original extrapulmonary neoplasm, patient age, and smoking history. Of 161 patients with solitary pulmonary nodules, 81 (50%) were determined to have a primary lung cancer; this outcome was more common in patients with a prior history of cancer of the head and neck, bladder, breast, cervix, bile ducts, esophagus, ovary, prostate, or stomach. Fifty patients (31%) were determined to have metastasis, a finding more common in patients with salivary, thyroid, and adrenal tumors, melanoma, and sarcoma. Primary

lung cancer or metastases were equally likely in patients with prior cancer of the colon, kidney, or uterus. In those with prior lymphoma or leukemia, there was a high proportion of patients with a benign diagnosis (6 of 14), perhaps reflecting the predisposition of these patients to infections.¹⁶ In total, 30 of 161 patients (19%) had nodules of a benign nature. The large percentage of benign diagnoses in this study by Quint and colleagues¹⁶ (1994–1999) contrasts with a larger but much older study by Cahan and associates¹⁷ (1940–1975) in which only 11 of 800 patients (1.3%) had benign disease. The higher incidence of benign disease in the more recent study can probably be explained by two factors: (1) because of the greater use of CT scanning and thus higher rate of detection of nodules in the later study and (2) because the earlier study was a surgical series in which patients with a high pretest probability of benign disease may have been excluded. A consistent finding in these two studies representing nearly 40 total years from two large centers was the high proportion of patients with head and neck squamous or esophageal cancers in whom a primary lung cancer subsequently developed. Aerodigestive cancers share common risk factors, and the presence of a smoking history increases the likelihood that a solitary lung nodule in someone with a prior extrapulmonary neoplasm will prove to be a lung cancer. By understanding the data in these and other studies, clinicians can more accurately estimate the likelihood that a pulmonary nodule is a metastatic malignancy, a primary lung cancer, or benign.

PATHOLOGY

When a nodule is found to be malignant, the etiology of the nodule can be assessed by comparing the pathology of the prior cancer and the lung nodule. The pathologist's approach begins with a knowledge of the prior cancer, its stage and grade (if applicable), and the pretest likelihood of lung metastasis from a tumor with such characteristics. The gross and microscopic pattern of the possible metastasis may be sufficiently similar to the original primary tumor that the diagnosis is rendered easily. In many situations, the histology is not sufficiently distinctive to permit a differentiation between metastasis and primary lung cancer,¹⁸ and immunohistochemical stains are used to help guide the diagnosis (Table 55-2). Lung adenocarcinoma can be identified by specific immunohistochemical markers including cytokeratin-7, *thyroid transcription factor 1* (TTF1, see Fig. 19-4B), and napsin.^{18,19} For example, cytokeratin-7 can be useful for distinguishing adenocarcinoma of the lung from colon cancer metastasis, with cytokeratin-7 favoring lung and cytokeratin-20 favoring a colon primary.¹⁸ TTF1, a nuclear transcription protein expressed in embryonic and adult epithelial cells of the lung and thyroid,²⁰ is detected in 75% of lung adenocarcinomas, but rarely detected in other adenocarcinomas that commonly metastasize to the lungs except for thyroid cancer.²⁰ Napsin is an aspartic proteinase that is present in lung and kidney epithelial cells, and is a newer marker for lung adenocarcinoma with similar sensitivity but slightly greater specificity for lung origin than TTF1. Markers specific for other tumors can be used to identify lesions as metastatic; for example, breast cancers can generally be identified if they maintain their original pattern of staining for estrogen receptor or Her-2/Neu, melanomas

Table 55-2 Immunohistochemical Stains Useful for Distinguishing Primary Lung Cancer from Metastatic Cancer Secondary to an Extrapulmonary Primary Cancer

Cancer	Positive Markers	Negative Markers
Lung	CK7, TTF1,* SP-A, SP-B, Napsin,* p63 [†]	CK20, PAX2, PAX8
Colon	CK20	TTF1, Napsin
Bladder (urothelium)	S100P, GATA3	TTF1, Napsin
Breast	ER, PR, HER2/neu	TTF1, Napsin
Prostate	PSA, prostatic acid phosphatase	TTF1, Napsin
Melanoma	HMB45, S100, tyrosine hydroxylase	Cytokeratin [‡]
Thyroid	TTF1, thyroglobulin	Napsin
Germ cell	Alpha-fetoprotein	TTF1, Napsin
Renal cell	PAX2, PAX8, RCCma	TTF1, Napsin

*Adenocarcinoma specific.

[†]Squamous carcinoma specific.[‡]Fewer than 10% of melanoma metastases stain positively for cytokeratin.

CK, cytokeratin; ER, estrogen receptor; PAX2, paired box gene; PR, progesterone receptor; RCCma, renal cell carcinoma marker; TTF, thyroid transcription factor; PSA prostate specific antigen.

can be identified by S100 or HMB45 immunoreactivity, and renal carcinoma can be identified by immunostaining for the product of paired box 2 or 8 genes, *PAX2* or *PAX8*. Thus, when the primary tumor stains for specific markers, these stains can be useful for identifying a lesion as a metastasis. Squamous carcinoma presents a particular challenge for distinguishing between a metastasis and a primary lung carcinoma, because there are no markers currently capable of distinguishing between squamous tumors of lung origin and those from extrapulmonary epithelial tissues.

Molecular Classification

Progress in transcriptional and proteomic characterization of tumors has provided tools to assist in determining the nature of a lung nodule. Giordano and colleagues attempted to develop a molecular classification scheme to discriminate adenocarcinomas of the lung, colon, and ovary.²¹ They identified three groups of 20 differentially expressed genes that correctly identified the origins of all but 2 of 154 tumors.²¹ Other groups of investigators have proposed classifiers for a broader representation of tumors in an effort to categorize tumors diagnosed as carcinoma of unknown primary. Tothill and colleagues developed a gene array-based classifier using a microarray platform and validated with real-time polymerase chain reaction on 229 samples of known origin (a training set).²² This gene classifier was then able to assign a “tissue of origin” in 9 of 11 cases of carcinoma with unknown primary.²² They noted that the two specimens that the gene classifier failed to classify were actually both squamous carcinomas. Subsequent review of the clinical course of the patients supported the assessment of the gene classifier.²² In another study, a gene expression-based classifier was devised to distinguish metastases of head and neck squamous carcinoma from primary lung squamous cancer, a task made difficult by both the histo-

logic similarity as well as shared risks for both diseases. Ten genes were identified whose expressions enabled discrimination between tumors of the lung and of the upper aerodigestive origin with high accuracy in both the training and validation samples.²³ Certainly, molecular techniques provide new ways of classifying tumors and, in so doing, improve the ability to identify the origin of a lung nodule. When the prior tissue is available for comparison, molecular testing may also assist identification of the new nodule as either a metastasis or a new cancer.

Finding viral antigens may help identify malignancies and reveal different roles in pathogenesis. Recent recognition of the role of certain strains of *human papillomavirus* (HPV) in squamous carcinogenesis of the cervix and oropharyngeal mucosa had caused some investigators to investigate whether this oncogenic virus was involved in the development of lung squamous carcinoma.²⁴ However, in a recent study, investigators using both in situ hybridization and polymerase chain reaction based genotyping found that, in 132 squamous lung carcinomas, only 5 (1.5%) contained the HPV genome. All five of these patients had prior diagnoses of HPV-related squamous carcinoma in a different tissue and thus the HPV-positive tumors were considered to be metastatic.²⁵ This would suggest that the finding of HPV-associated squamous cancer in the lung might serve as an indicator of metastasis, particularly in the setting of a prior HPV-positive extrapulmonary malignancy.

OPTIONS FOR OBTAINING A TISSUE DIAGNOSIS

A diagnosis may be confidently made without the need for a biopsy when a patient with a history of prior cancer known to metastasize to the lungs presents with nodules with highly typical characteristics: multiple, new, or growing lower lobe pulmonary nodules with smooth borders. A diagnosis may also be possible without the need for a biopsy when, less commonly, there are measurable diagnostic serum markers (CA19-9, CA125, carcinoembryonic antigen, alpha-fetoprotein, β human chorionic gonadotropin, CYFRA21-1). However, for most tumors other than those of germ cell origin, these epithelial markers are not sufficiently specific and a biopsy is warranted to guide therapy. In all cases, before performing a lung biopsy, it is important to search for evidence of metastasis to other sites where a less invasive biopsy may yield the diagnosis. This should begin with a thorough physical examination directed to finding any enlarged lymph nodes, skeletal tenderness, or hepatomegaly that would guide the next imaging study or tissue sampling. In older series, much of the data on tissue biopsies is derived from surgical material, and this remains the “gold standard” due to the quantity of material available to the pathologist.¹⁷ Surgery is often used for diagnosis when it is the appropriate definitive therapy for patients with lung metastases from solid tumors. However, there are nonsurgical biopsy options, each with strengths and drawbacks that can be weighed to achieve the best balance between certainty, risk, and cost. Fiberoptic bronchoscopy, percutaneous CT-guided biopsy, and surgical resection are discussed herein, with each successive option providing increased accuracy (sensitivity and negative predictive value) but also increased risk and cost.

Bronchoscopy

Fiberoptic bronchoscopy is particularly useful for accessing centrally located lesions and mediastinal lymph nodes. Transbronchial needle aspiration of enlarged mediastinal lymph nodes is safe and has excellent diagnostic accuracy for malignant involvement of mediastinal lymph nodes. Use of *endobronchial ultrasound* (EBUS) improves sensitivity and permits the biopsy of much smaller lymph nodes in both the mediastinum and hilar lymph node stations (see Chapter 22). The accuracy of standard bronchoscopy for lung parenchymal lesions declines rapidly as the distance from the main-stem bronchi increases, so that traditional transbronchial sampling techniques have less than 20% sensitivity for peripheral lung nodules.²⁶ The increasing use and availability of navigational bronchoscopy has allowed biopsy of small peripheral lung nodules with significantly greater accuracy. Experienced users of this newer approach report a 69% to 80% sensitivity for the diagnosis of small peripheral lung nodules (as small as 7 mm, ranging up to 8 cm, and average size less than 2 cm).²⁷⁻²⁹ Combining navigation-assisted bronchoscopy with real-time imaging using a radial probe ultrasound catheter to confirm the location suggested by virtual images further increased the accuracy of transbronchial biopsy to 88% in one series.³⁰ Using bronchoscopy, multiple samples can be taken from one area or from multiple different nodules in a single procedure without an appreciable increase in the risk for pneumothorax. Given the low risk of pneumothorax (1% to 5%) and of major bleeding, the chief risk of the bronchoscopic biopsy, even when combined with electromagnetic navigation and real-time radial probe ultrasound, is that of a false-negative biopsy result.²⁹

CT-Guided Biopsy

CT-guided biopsy by experienced clinicians has excellent accuracy (see Chapter 19, Figs. 19-1 to 19-2).³¹ This approach has greater sensitivity than bronchoscopy, particularly for peripheral lesions. The sensitivity of CT-guided biopsy of lung nodules varies with the size of the lesion, with a 65% to 75% accuracy for smaller lesions (<1 cm diameter) and a greater than 95% sensitivity for lesions larger than 1.5 cm in diameter.³²⁻³⁴ Larger size and a more peripheral location are associated with greater diagnostic accuracy.³⁵ Core biopsies, in addition to or instead of cytologic material, can be obtained with larger 19-gauge needles (see Fig. 19-6). The major risk of CT-guided transthoracic needle biopsy is pneumothorax, which develops in up to 35% of patients and 10% to 15% requiring tube thoracostomy or catheter drainage.³⁶ The risk of pneumothorax appears to increase with the length of the needle tract, as well as the presence of obstructive lung disease.³⁵ In one large retrospective series, severe complications of CT-guided biopsy were quite rare. Of 9783 biopsies, 74 (0.75%) patients were reported to have severe complications, including 6 patients with air embolism (see eFig. 19-2), 10 with tension pneumothorax, 6 with severe pulmonary hemorrhage, 9 with hemothorax (see eFig. 19-1), and 6 with seeding of the needle tract. Eight deaths were reported.³⁶ In general, CT-guided biopsies are safe and accurate for peripheral lesions.

Surgery

Resection of a nodule provides the greatest diagnostic sensitivity and may provide both a diagnosis and treatment in a single procedure. The selection of patients for whom nodule resection is appropriate is a matter of controversy. There are few, if any, randomized studies comparing surgical and nonsurgical treatment of lung metastasis, and the data from reported series on surgical treatment of lung metastases suffer from a lack of uniformity in selection criteria. The sensitivity of surgery for diagnosis is likely close to 100% given that it is the accepted gold standard for tissue diagnosis of lung lesions. However, very small lung lesions can be difficult for the surgeon to palpate and may be missed. The risks of surgery include those for general anesthesia in addition to the risks associated with lung resection. Thoracoscopic surgery is discussed later and is the preferred option when surgery is required for diagnosis.

TREATMENT

MULTIMODALITY THERAPY OF POTENTIALLY CURABLE DISEASE

Treatment for lung metastasis is largely dictated by the tissue of origin (Fig. 55-3). In cases of curable cancers, patients with lung metastases should be treated aggressively with appropriate multimodal therapy. Germ cell tumors, neuroblastoma, gestational trophoblastic tumors, lymphoma, and osteosarcoma are included in this category. In certain cases, residual nodules persist following chemotherapy and can then be resected. In patients with nonseminomatous germ cell tumors, resection of residual nodules or masses after systemic chemotherapy is an aggressive but appropriate approach. In cases of testicular cancer, such residual masses after chemotherapy remain in approximately 40% of patients who had advanced disease but negative serum tumor markers at the conclusion of treatment.^{37,38} When resected, approximately half of these masses contain only necrotic tissue, a further 25% show a mature teratoma, and the rest contain residual carcinoma. Long-term follow-up studies after chemotherapy suggest that 90% of patients found to have mature teratoma on resection and 50% of those with residual carcinoma are cured by “adjuvant” surgery.^{37,38} In other tumors, treatment options are mainly nonsurgical. For patients with lymphoma, for example, in whom treatment alternatives are more numerous and systemic therapy is necessary, biopsy rather than excision is more appropriate. These varied treatment options highlight the importance of undertaking the care of these patients with multidisciplinary input.

PALLIATIVE CARE

Unfortunately, most adults with pulmonary metastases from solid tumors have incurable disease and palliative therapy is warranted. For selected cancers, palliative treatment may include radiotherapy, chemotherapy, or hormonal or biologic/targeted therapies. Agents chosen for

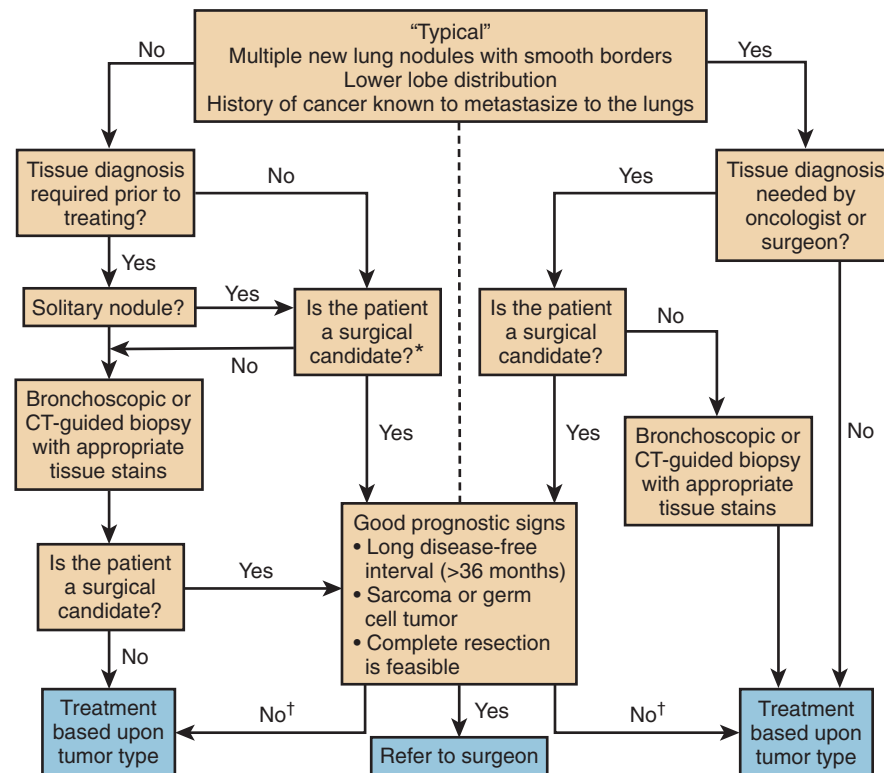


Figure 55-3 Suggested management algorithm for patients with known prior cancer and a new lung nodule. A suggested management algorithm taking into account the typical or atypical appearance of a lung nodule in a patient with prior known cancer, the utility of a tissue diagnosis to the treating physicians, the physiologic fitness of the patient for surgery, and the known prognostic indicators for a favorable outcome after metastasectomy. Each patient should be managed individually, within the context of the skills and experience of local providers with the varied diagnostic and therapeutic options. *Patients at high risk for primary lung cancer may be considered for diagnostic lobectomy, when appropriate. †These are suggested criteria for surgical resection of lung metastases, and multidisciplinary teams should make this decision. Radiofrequency ablation may be an excellent choice for these patients as well.

palliative therapy should balance acceptable levels of toxicity with the expected degree of tumor response and symptom control. Radiation therapy for patients with radiosensitive tumors can provide rapid and effective symptom relief. For patients with endobronchial obstruction, endobronchial tumor ablation using brachytherapy, laser, or cryoprobes can be very effective for palliation (see Chapter 23). Because these approaches require specialized training, it is best to seek referral to a center with experience in such techniques when they are needed. Because most centers may only specialize in one, or at most two, of these interventional methods, direct comparisons of the efficacy and safety of palliative interventions for malignant airway obstruction have not been reported. For patients with end-stage dyspnea, opiates, and oxygen therapy may relieve symptoms. In general, for end-of-life care, social, emotional, and physical rehabilitation support as well as hospice services are valuable.

RADIOFREQUENCY ABLATION OF METASTASES

Thermal ablation is a minimally invasive therapy that can be used for local cure or control of either primary or metastatic lung tumors. *Radiofrequency ablation* (RFA), which uses radiofrequency energy to generate frictional heating that leads to cell death, is the most commonly performed thermal ablation procedure used to treat lung tumors.

While the role of RFA is not as clearly defined as other options, studies supporting use of this procedure for lung metastases are mounting and the role for RFA in treating lung metastasis is gaining increased acceptance. Although RFA is more commonly performed to treat hepatic and renal tumors, it may be well suited to the lung due to its ability to concentrate thermal energy focally within tumor tissue with little or no energy spreading to the adjacent aerated normal lung parenchyma.³⁹

Smaller tumors, 3 cm or less in diameter, are more readily treated with RFA than larger tumors.^{40,41} Peripheral tumors surrounded by lung parenchyma and away from hilar structures can be safely treated with RFA (see Fig. 19-15).^{42,43} However, recent studies report that even tumors contiguous with certain vital structures, such as the thoracic aorta and pulmonary vessels, can be safely treated,⁴⁴ because the cooling effect of constant blood flow in large vessels may protect them from tissue damage. Multiple lesions in the same hemithorax can be treated at one sitting by experienced providers; however, because of the risk of pneumothorax (as high as 50% in one series⁴⁵), bilateral lesions should not be treated during the same procedure.

SURGICAL RESECTION OF METASTASES

As measured by length of survival and quality of life, surgical resection of pulmonary metastases can be the

Table 55-3 Suggested Criteria and Indications for Pulmonary Metastasectomy⁴⁸⁻⁵¹

ABSOLUTE CRITERIA
The patient must be able to tolerate the planned operative procedure
The primary tumor is controlled
No extrapulmonary metastases exist; or, if present, they must be controllable
Pulmonary metastases are completely resectable
RELATIVE INDICATIONS
Pulmonary metastases are symptomatic (e.g., pneumothorax, hemoptysis)
Surgery is necessary to differentiate metastasis from primary lung cancer

appropriate choice. As resection has become more common, factors associated with good outcome have been identified from registries of patients treated with surgery. In general, the most important factor associated with improved survival is the complete resection of all metastases. Incomplete resection is associated with dismal survival rates that do not differ from those with no treatment at all. Another important favorable prognostic factor in numerous large series is a long disease-free interval between initial diagnosis of cancer and the discovery of lung metastasis.⁴⁶⁻⁴⁸ Five-year survival was 33% when the disease-free interval was 0 to 11 months compared with 45% when the disease-free interval was more than 36 months.^{49,50} Although once considered a poor prognostic factor, a higher number of pulmonary metastases has not been consistently shown to be a negative predictive factor. More accurate prognostic factors must be identified to improve selection of patients for metastasectomy. Suggested selection criteria for pulmonary metastasectomy, taken from various large series,^{48,51} are shown in Table 55-3. In a retrospective analysis, selection of patients for pulmonary metastasectomy according to these criteria was associated with longer survival times.⁴⁸

In 1991, the International Registry of Lung Metastases (comprised of more than 5000 cases) was established to record and report upon the long-term results of pulmonary metastasectomy for various primary malignancies.⁵¹ According to the registry, long-term success of pulmonary metastasectomy varies according to the primary malignancy. Cancers that metastasize exclusively to the lungs have more favorable outcomes from pulmonary metastasectomy than cancers that metastasize more widely. Malignancies with the greatest long-term survival after pulmonary metastasectomy include osteogenic and soft tissue sarcoma, colorectal cancer, uterine/cervical tumors, head and neck cancer, breast cancer, testicular tumors, renal cell tumors, and melanoma (Table 55-4). Patients undergoing lung metastasectomy for osteosarcoma have some of the best results, but long-term survival after metastasectomy is not limited to patients with sarcoma.⁵¹ Prolonged disease-free survival has been reported for patients with colon cancer, breast cancer, prostate cancer, and other malignancies. Pulmonary metastasectomy for any cancer mandates adherence to certain surgical principles: complete resection is possible, the primary tumor is controlled, and there are no other uncontrolled extrapulmonary metastasis.

Table 55-4 Tumor-Specific 5-Year Survival Rates Following Pulmonary Metastasectomy

Primary Malignancy	5-Year Survival (%)
Soft tissue sarcoma ⁶³⁻⁶⁵	20-35
Osteosarcoma ⁶⁶	25-50
Melanoma ^{67,68}	5-33
Colorectal ^{69,70}	13-40
Testis (germ cell) ^{37,71}	50-80
Renal ^{72,73}	15-20
Breast ^{47,74,75}	25-50
Head and neck ⁷⁶	30

Surgical resection of pulmonary metastases requires careful planning and preparation. As with any lung resection, the number, location, and size of the lesion, pulmonary function, and the general condition of the patient must be considered, as must any evidence for local invasion, or the prospects for response to systemic therapy. CT has the greatest sensitivity and accuracy for localizing pulmonary nodules for resection. Small nodules can be localized using image-guided wires, dyes, and coils, as well as ultrasound and radiation probes. An emerging strategy is to mark small peripheral tumors before thoracoscopic resection using wire, dye, radioactive tracer, or coils (see Fig. 19-17).⁵² These markers can be placed either percutaneously or bronchoscopically (typically using navigational bronchoscopy) before resection. Intraoperative localization of small nonpalpable nodules can be aided with a sterile ultrasound or radioactivity probe in deflated lung.

In tumors that can be detected with PET scanning, the scanning should be performed before pulmonary metastasectomy to exclude the presence of synchronous extrapulmonary metastasis that would negate the benefit of lung resection. Uptake on PET or lymph node enlargement seen on CT can suggest less invasive biopsy techniques such as mediastinoscopy, transthoracic needle biopsy, and transbronchial needle biopsy (with or without endobronchial ultrasound). With the exception of certain germ cell tumors (which may remain curable despite metastatic disease), finding synchronous metastasis outside the lung would be a contraindication to pulmonary metastasectomy.

Thoracotomy has been the most frequently used approach for unilateral metastasectomy, primarily because it enables the surgeon to palpate the lung for lesions. Similarly, sternotomy has been used for bilateral palpation and metastasectomy. To avoid the morbidity of a thoracotomy or sternotomy, alternate surgical approaches have been sought. Subxiphoid pulmonary metastasectomy has been described.⁵³ The subxiphoid approach permits palpation of both lungs without transecting large muscles or bone. Thoracoscopy also allows minimally invasive resection of pulmonary metastases, but thoracoscopic pulmonary metastasectomy has been criticized based upon its limited ability to permit palpation of the lungs to identify unknown metastases. However, as the resolution of CT scanning improves, the likelihood of pulmonary nodules that can be palpated but not visualized on CT scan decreases dramatically, thus improving the relative utility of a thoracoscopic

approach for metastasectomy. In addition, instruments and techniques have evolved to allow enhanced visualization and even thoroscopic palpation of lung parenchyma. Compared to thoracotomy, thoroscopic metastasectomy has several advantages including smaller incisions, less pain, earlier recovery, and fewer postoperative adhesions. The latter is especially important in that repeat pulmonary metastasectomy may be indicated based on the same criteria as the initial metastasectomy.^{50,51} Indeed, recurrence develops in more than 50% of patients who undergo complete pulmonary metastasectomy. The probability of relapse is higher for sarcoma and melanoma than for epithelial or germ cell tumors. In the international registry, repeat metastasectomy yielded 44% survival at 5 years and 29% at 10 years,⁵¹ which is comparable to the results after initial metastasectomy. A retrospective nonrandomized study comparing outcomes of patients who had undergone metastasectomy with open versus thoroscopic approaches did not find differences in survival, although complications and hospital length of stay were predictably less after a thoroscopic approach in this nonrandomized comparison.⁵⁴ Thus, the approach for surgical resection should be carefully planned with respect to several criteria, including the number and location of lesions, the surgeon's experience, and the possible need for repeat metastasectomy.

Before any resection, all lung lesions should be identified in order to plan a resection that minimizes the loss of lung parenchyma. The extent of pulmonary resection is an important consideration. Of those undergoing surgical resection of metastatic disease, metastasectomy was achieved by wedge resections in 67%, segmentectomy in 9%, and lobectomy or bilobectomy in 21%.⁵¹ Lymph node dissection is not encouraged due to the low incidence of nodal involvement with pulmonary metastasis, associated morbidity, and the poor survival of patients with nodal metastasis regardless of resection. Pneumonectomy or extended resection was rarely used (3%) and should be reserved for special circumstances when there is acceptable surgical risk and a reasonable likelihood of long-term survival.⁵¹

The morbidity and mortality for pulmonary metastasectomy should be very low. Most series report less than 2% mortality and 10% morbidity.⁵¹ The most common complications are persistent air leak and infection. Preoperative chemotherapy or radiation may increase the risk of respiratory failure after metastasectomy when high fractional concentrations of oxygen are used perioperatively.³⁸ Anesthesiologists should be alerted to a history of chest irradiation or chemotherapy (particularly with bleomycin used for germ cell tumors) and use the lowest possible fractions of inspired oxygen for these patients. With appropriate patient selection, the survival following pulmonary metastasectomy can be quite good. The decision to operate should be influenced less by the type of prior cancer than on the eligibility criteria described in [Table 55-3](#).

Most reports regarding the effectiveness of pulmonary metastasectomy have been retrospective. These nonrandomized and uncontrolled series introduce selection and lead-time bias, which must be kept in mind when considering treatment options. Reported survival rates of 30% to 40% at 5 years is encouraging, but the selection criteria used for surgical resection, as well as the nonrandomized

nature of these studies, must be taken into consideration. Additional studies are needed to define candidates that will receive maximum benefit from pulmonary metastasectomy. For example, molecular predictors of prognosis have been used to assess treatment options for primary tumors, but this has been more difficult to incorporate into an algorithm for treating metastases because of the diversity of origins of primary tumors and relatively small numbers reported in any given series of metastasectomy.⁵⁵

SPECIAL CASES

AIRWAY METASTASIS

While rare, large airway involvement with endobronchial metastasis can produce very distressing symptoms of dyspnea and/or hemoptysis. Awareness of the clinical scenario along with available diagnostic and management strategies can be very helpful in palliating these patients. Reported series of patients with endobronchial metastasis are generally small but uniformly emphasize the utility of fiberoptic bronchoscopy for diagnosis, as well as interventional methods for symptom control and palliation. Other than lung cancer, many tumors metastasize to the bronchi, including colon, breast, renal cell carcinoma ([eFig. 55-1](#)), and melanoma.⁵⁶⁻⁵⁸ Breast and colon cancers predominate in reported case series of endobronchial metastases, perhaps because they are more prevalent in the general population of cancer patients. It should be noted that colon cancer can metastasize to the bronchi without involvement of the liver.⁵⁷ Radiation can be used for palliation in patients with malignant airway obstruction and radiosensitive tumors. Mechanical means, including stents and endobronchial ablative methods (laser, cryoprobe, argon plasma coagulation, or physical débridement) can be used for tumors that are relatively radioresistant (see [Chapter 23](#)).

VASCULAR EMBOLIC METASTASIS

A rare but dramatic presentation of lung metastasis is tumor embolism. When clinically evident, the symptoms are those of "subacute cor pulmonale" with dyspnea, edema, elevated jugular venous pressure, and auscultatory evidence of pulmonary hypertension and right ventricular failure. Premortem diagnosis is difficult unless clinical suspicion is high. Tumor emboli have been reported as the initial presentation of extrapulmonary cancer or as a postmortem finding in those with no premortem respiratory symptoms.⁵⁹ In a series of 214 selected autopsies, 89 patients had evidence of tumor emboli, and only 50 of these had clinical records indicating the presence of respiratory symptoms before death. However, in 29 of the 50, tumor emboli were the recorded cause of death.⁶⁰ Tumors arising from the breast, liver, and pancreas accounted for more than 50% of the cases, but many tumor types were represented among this series.⁵⁹ Pulmonary arterial tumor emboli may affect larger pulmonary arteries, so-called macroscopic tumor embolization, which may be visible on chest CT ([eFigs. 55-2](#) and [55-3](#)). Small pulmonary arteries may also be affected by tumor embolization, a situation often referred to as "microscopic tumor embolization" ([eFig.](#)

55-4). Chest CT findings of this condition (see eFig. 55-4A-C) include small centrilobular opacities, possibly with branching configurations (simulating infection), smooth or nodular interlobular septal thickening, and areas of ground-glass opacity or parenchymal consolidation, reflecting hemorrhage or infarction. When tumor embolism is suspected, cytologic examination of pulmonary capillary blood obtained via a wedged pulmonary arterial catheter is a possible diagnostic method.⁶¹

PLEURAL METASTASES (see Chapter 82)

Malignant pleural effusions are always metastatic and are a significant cause of morbidity in patients with cancer. Diagnosis is typically straightforward and can be made in pleural fluid with cytology, although this may require more than one thoracentesis if initial cytology is negative. Flexible thoracoscopic examination of the pleural space is increasingly used to diagnose pleural metastasis. A recent randomized study demonstrated the superiority of indwelling tunneled pleural catheters using outcome measures of long term symptom relief and initial hospital length of stay when compared with talc pleurodesis. However, there was no difference in validated quality of life metrics between the two groups, and blockage of the indwelling catheter was a common complication of the group treated with this approach.⁶²

Key Points

- Lung metastases are common and arise from most types of solid tumors.
- In addition to benign causes, a pulmonary nodule in a patient with prior cancer can be a metastasis or a primary lung cancer; the likelihood of metastasis will vary with the original type of cancer and lung cancer risk factors.
- When clinical and/or histologic evaluation cannot distinguish primary lung cancer from metastasis, immunohistochemistry for tumor-specific markers

can be useful. Future directions will include molecular phenotyping.

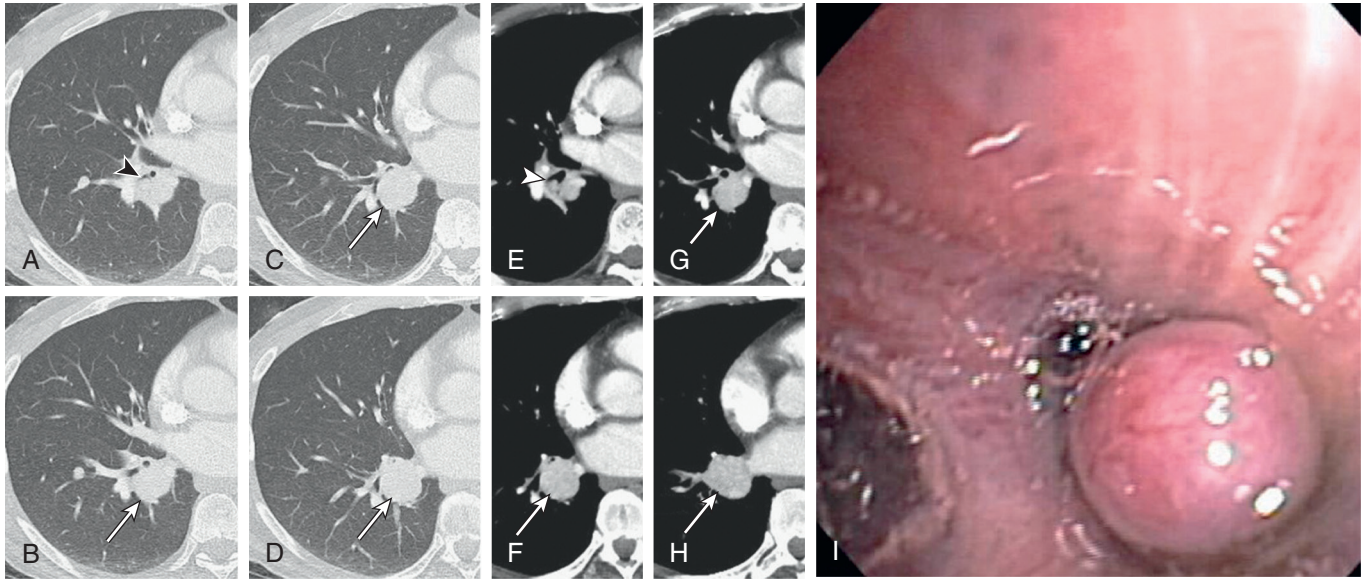
- The choice of diagnostic method will be determined by the patient's status, the natural history of the prior cancer, the availability of specialized diagnostic methods and the need, or lack thereof, for a tissue diagnosis before offering therapy.
- Radiofrequency thermal ablation is a potential therapeutic option when surgical resection, radiation, or systemic therapy is not.
- Surgery for both diagnosis and treatment is appropriate for selected patients. The most important predictor of successful treatment is the ability to achieve complete metastasectomy of all visible and palpable lung nodules.

Complete reference list available at *ExpertConsult*.

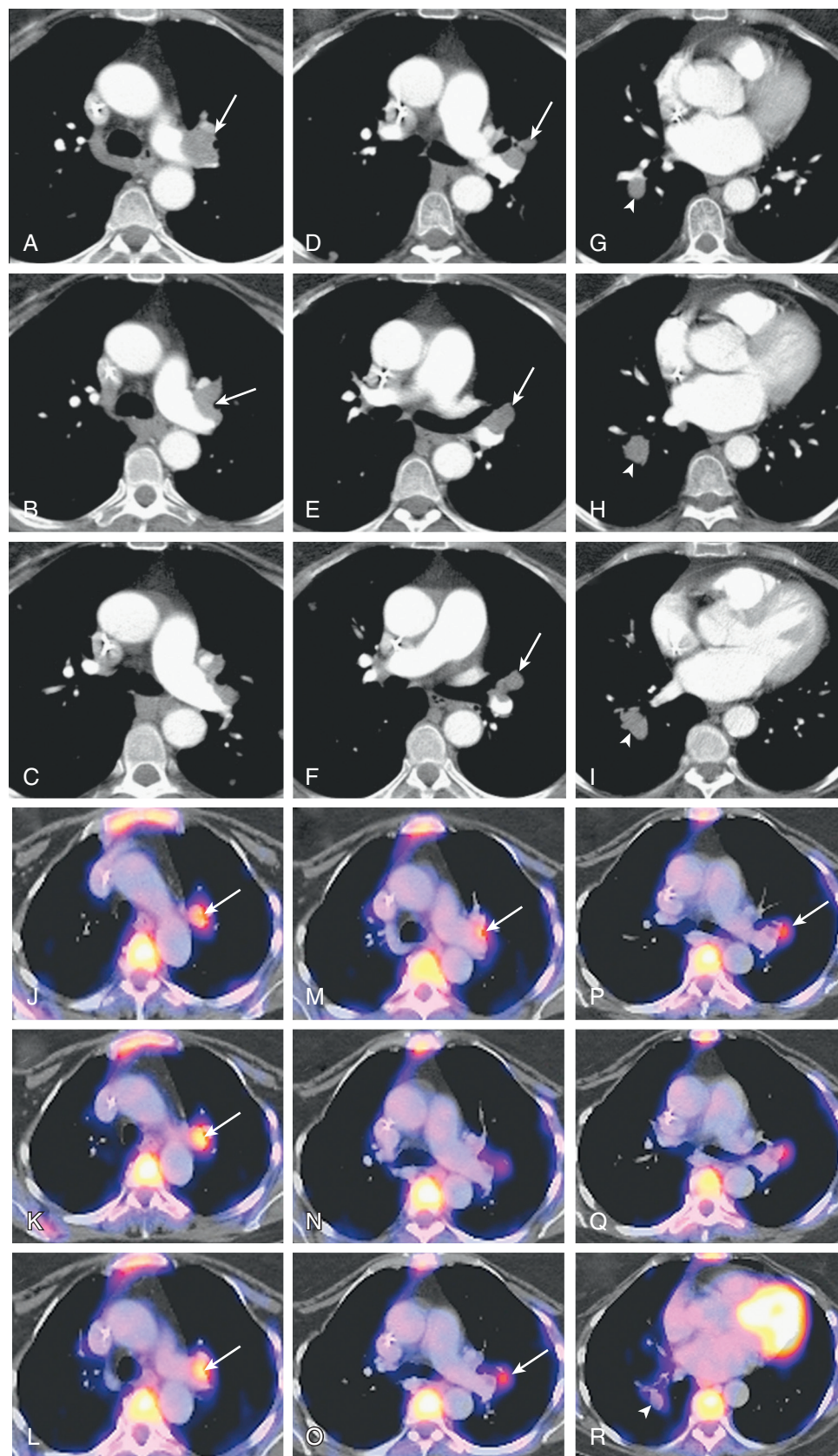
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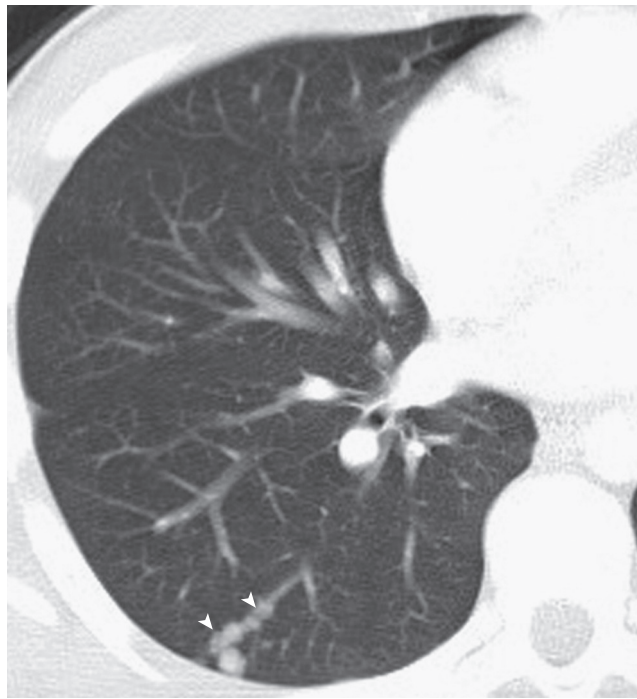
eFIGURE IMAGE GALLERY



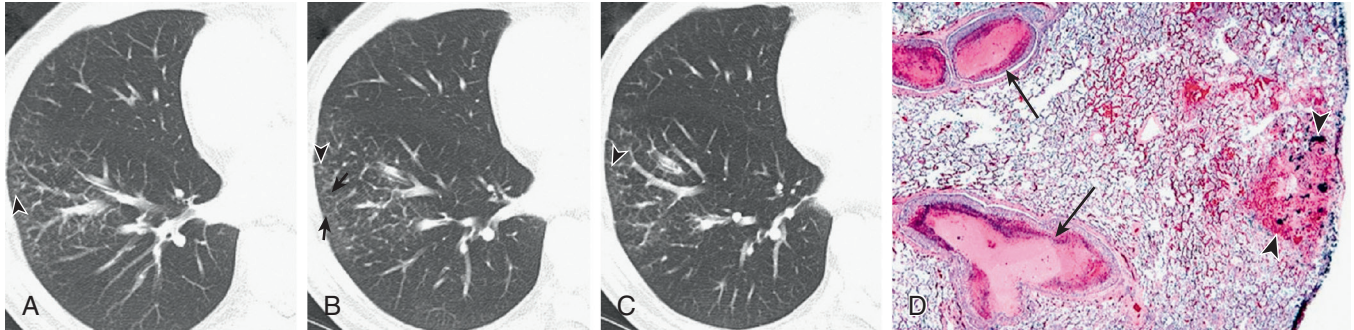
eFigure 55-1 Endobronchial metastasis from renal cell carcinoma. Axial enhanced chest CT displayed in lung windows (**A–D**) and soft tissue windows (**E–H**) shows an enhancing nodule (*arrows*, **B–D**, **F**, **G**, and **H**) related to the right lower lobe posterolateral basal bronchial trunk. Note displacement of the anterior basal segmental right lower lobe airway (*arrowheads*, **A** and **E**). **I**, Bronchoscopic image shows the endobronchial tumor protruding into the airway. (**A–H**, Courtesy Michael Gotway, MD.)



eFigure 55-2 Large vessel tumor emboli. A–I, Axial chest CT displayed in soft tissue windows shows low attenuation filling defects in the left (arrows, A, B, D–F) and right (arrowheads, G–I) pulmonary arteries, mimicking pulmonary emboli. J–R, Axial fused PET images show metabolic activity with the left (arrows, J–M, O and P) and right (arrowhead, R) intravascular filling defects, consistent with macroscopic large vessel tumor emboli. These abnormalities did not resolve with anticoagulation and progressed in a fashion similar to other metastatic foci elsewhere. (Courtesy Michael Gotway, MD.)



eFigure 55-3 Macroscopic large vessel tumor emboli from Ewing sarcoma. Axial chest CT displayed in lung windows shows a “beaded” appearance of a peripheral right lower lobe pulmonary artery (*arrowheads*), characteristic of macroscopic tumor emboli. (Courtesy Michael Gotway, MD.)



eFigure 55-4 Microscopic tumor emboli in a patient with gastrointestinal malignancy. **A–C,** Axial chest CT images displayed in lung windows shows very small centrilobular opacities (*arrowheads*, **A–C**) and interlobular septal thickening (*small arrows*, **B**) in a restricted portion of the right lower lobe. **D,** Histopathologic specimen shows small pulmonary arterial tumor emboli with necrosis (*arrows*) and subpleural infarction (*arrowheads*). (A–C, Courtesy Michael Gotway, MD; D, courtesy Martha Warnock, MD, Professor Emerita, Department of Pathology, University of California, San Francisco.)

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INTRODUCTION**CLINICAL MANIFESTATIONS****BENIGN EPITHELIAL TUMORS**

Papillomas and Adenomas

Micronodular Pneumocyte Hyperplasia

Sclerosing Hemangioma

BENIGN NONEPITHELIAL LESIONS

Hamartoma and Related Lesions

Inflammatory Myofibroblastic Tumor

Solitary Fibrous Tumor

Meningothelial-like Nodules and
Intrapulmonary Meningioma**MISCELLANEOUS****SUMMARY****INTRODUCTION**

Although in practice the terms “tumor” and “neoplasm” tend to be used interchangeably, there is an important and substantial difference between them. A “tumor” need not be a neoplasm (e.g., a granuloma forms a “tumor”), and “neoplasms” do not always form tumors (e.g., lymphangitic carcinoma or leukemia). Entities discussed in this chapter are all benign neoplasms (generally distinguished from malignant neoplasms by their lack of invasion or metastasis) that form tumors. In general, these benign entities are uncommon, accounting for fewer than 5% of resected lung neoplasms. While many are rare, some benign lung tumors are seen with sufficient frequency to pose periodic diagnostic challenges for primary care providers, pulmonologists, radiologists, surgeons, and pathologists alike. In this chapter, we briefly review the clinical and pathologic features of benign lung neoplasms. Nonneoplastic conditions that may mimic tumors on imaging studies (e.g., granulomas, organizing pneumonia) or certain low-grade but fully malignant neoplasms, such as carcinoid tumors, are not discussed.

CLINICAL MANIFESTATIONS

Most benign lung tumors present as asymptomatic solitary pulmonary nodules typically discovered on chest radiographs or *computed tomography* (CT) scans performed for other purposes. A minority cause symptoms due to airway obstruction, bleeding, or compression of other structures. A preoperative diagnosis may be possible based on a combination of imaging studies and either endoscopic or percutaneous needle biopsies, but most are recognized only after surgical resection of a lesion in which the possibility of malignancy could not be categorically excluded.^{1,2}

A decision to proceed with surgical resection in a patient with an unexplained solitary pulmonary nodule is complex and predicated on analysis of various risk factors. Currently recommended approaches include watchful waiting in selected patients.³⁻⁷ Prediction models for the likelihood of malignancy⁸⁻¹² and Fleischner guidelines for the management of indeterminate pulmonary nodules^{11,12} are very useful in suggesting watchful waiting for nodules at low risk (<10% probability of malignancy). The approach to the solitary pulmonary nodule is also discussed in Chapter 53.

It is worth noting that many benign lung tumors are discovered as solitary pulmonary nodules. As such, individuals with these entities are often evaluated by ¹⁸F-fluorodeoxyglucose positron emission tomography (PET) scans. Contrary to what one might expect, ¹⁸F-fluorodeoxyglucose (FDG) uptake is quite common among benign lung tumors, and the PET scan cannot therefore reliably discriminate benign from malignant lung tumors.

BENIGN EPITHELIAL TUMORS**PAPILLOMAS AND ADENOMAS****Solitary Papillomas**

Papilloma refers to exophytic endobronchial lesions with a papillary architecture (Fig. 56-1). Most solitary papillomas arise in central large airways (see eFig. 56-1); rarely, they arise in smaller bronchioles and present as peripheral nodules.¹³ Flieder and associates divided lung papillomas into three categories based on the lining epithelium: squamous cell, glandular, and mixed types.¹⁴ Squamous lesions account for nearly 70% of reported cases and are seen more frequently in men, and are more often associated with cigarette smoking and *human papillomavirus* (HPV) infection. Associated foci of squamous cell carcinoma in situ are rare, with only a single well-documented example of invasive carcinoma developing in a patient without respiratory papillomatosis (see later).¹⁵ Most patients with papillomas do well regardless of histologic type. Surgical resection is curative. Local recurrences are rare and limited to patients whose papilloma is not completely resected either because they undergo only biopsy or receive a subtotal bronchoscopic removal. The differential diagnosis includes rare endobronchial papillary variants of squamous cell or adenocarcinoma, a distinction that depends on recognition of cytologic atypia and stromal invasion.

Recurrent respiratory papillomatosis (RRP), also termed juvenile laryngeal or laryngotracheal papillomatosis, is a form of HPV-mediated papillomatosis that presents in early childhood.¹⁶ Presenting symptoms include hoarseness, change or loss of voice, cough, and respiratory distress or stridor. HPV types 11 and 6 have been most commonly implicated and are perinatally acquired from mothers with genital infection.¹⁶ Surgical excision or laser ablation are

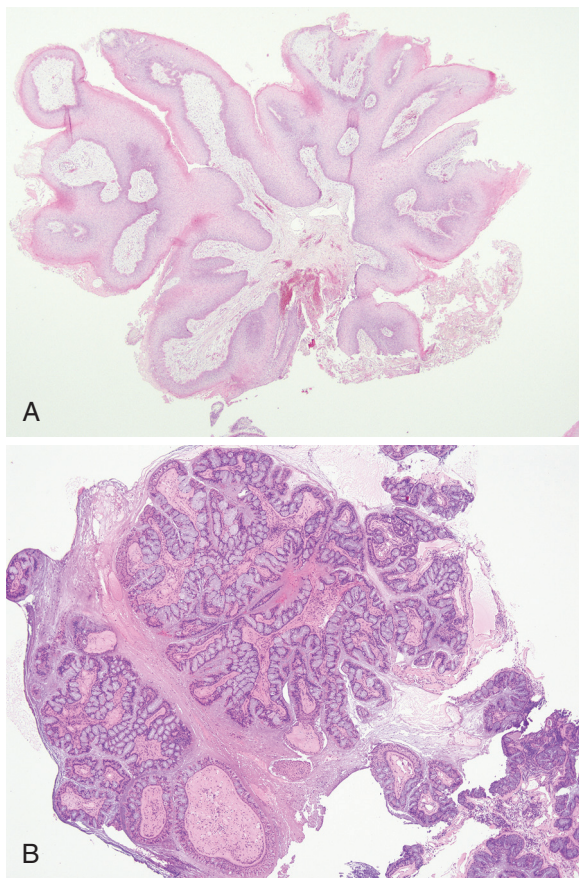


Figure 56-1 Papillomas. Low-magnification photomicrographs illustrate two different solitary endobronchial papillomas from adults. **A**, Squamous papilloma showing papillary architecture with central connective tissue stalk covered by benign squamous epithelium with associated keratinous debris. (H&E stain; original magnification $\times 20$.) **B**, Glandular papilloma lined by benign mucinous columnar cells with abundant extracellular mucus. (H&E stain; original magnification $\times 40$.)

the mainstays of therapy for patients with symptomatic disease.¹⁶ Recurrences are the rule and often necessitate multiple procedures. Squamous cell carcinoma is an infrequent complication but can affect either the upper or lower respiratory tracts.¹⁷⁻¹⁹

The lung parenchyma is involved in about 3% of patients with juvenile onset RRP.^{20,21} HPV-11 is especially prevalent in patients in whom peripheral lung disease develops, accounting for nearly 90% in whom testing was performed.²⁰ The latent period between diagnosis of RRP and recognition of lung involvement is variable, usually 8 to 10 years.²⁰ Parenchymal disease presents as multiple asymptomatic nodules that may be cystic or solid (Figs. 56-2 and 56-3; see eFigs. 54-29 through 54-31).²⁰⁻²² Symptomatic patients present with cough and various combinations of hemoptysis, dyspnea, fever, and chest pain. Case reports describing significant uptake of FDG in PET scans suggest that lesions of RRP can be very FDG-avid.¹⁹ The histopathologic findings are unique, demonstrating tufts of benign squamous papillomas emanating from distal bronchioles with polypoid extensions into adjacent alveolar spaces (Fig. 56-4). The involved bronchioles are often ectatic, thus mimicking the appearance of cavitation on imaging studies.



Figure 56-2 Recurrent respiratory papillomatosis. CT of a patient with recurrent respiratory papillomatosis involving her right lung. There are multiple nodules and opacities, the largest measuring 3 cm in greatest dimension. Some of the nodules appear cavitated. (Courtesy Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

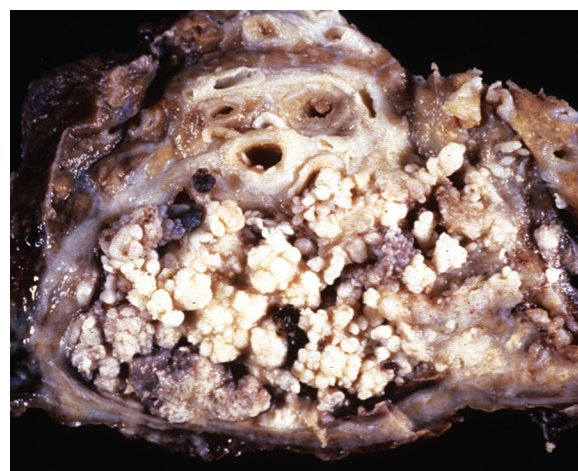


Figure 56-3 Recurrent respiratory papillomatosis. Gross photograph of excised left lower lobe from a 19-year-old with multiple recurrences of respiratory papillomatosis as described by Kerley and coworkers.²² The patient had extensive papillomatosis involving his central airways and a large cystic cavity containing innumerable papillomas replacing much of his left lower lobe.

Parenchymal lung involvement in patients with RRP is often associated with an aggressive course. There is currently no effective medical therapy. Interferon and cidofovir, an antiviral agent, show inconsistent results; in addition, cidofovir has been implicated as potentially oncogenic.²⁰ About 15% of patients with parenchymal disease develop squamous cell carcinoma of the lung, with an average age at carcinoma diagnosis of 23 years (see eFig. 54-32).²⁰ No risk factors clearly identify those patients likely to develop lung carcinoma. Nearly two thirds of reported patients have died of disease, many of squamous cell carcinoma.²¹

Adenomas

Historically the term *adenoma* was applied to a pathologically heterogeneous group of low-grade endobronchial malignancies that included carcinoid tumors and carcinomas homologous to those arising from salivary glands (i.e., adenoid cystic and mucoepidermoid carcinomas).²³⁻²⁵

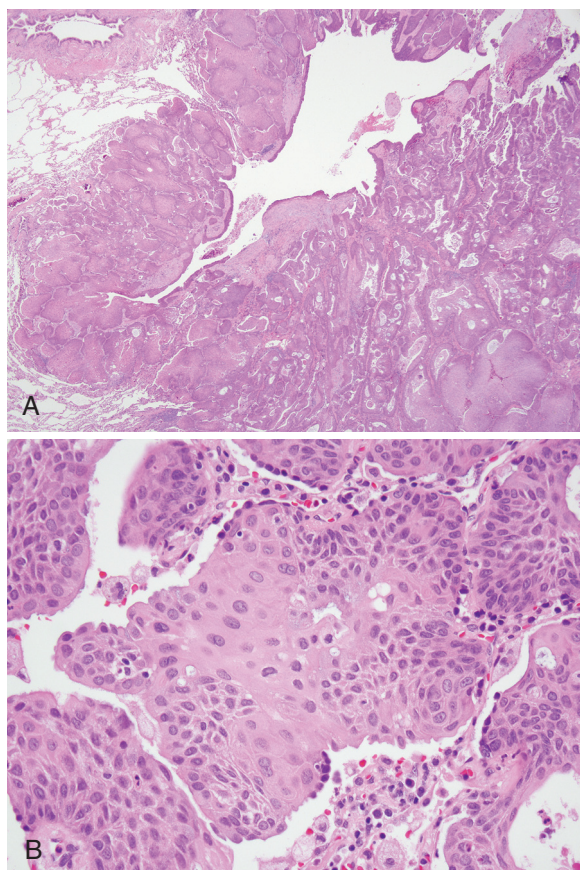


Figure 56-4 Recurrent respiratory papillomatosis. Photomicrographs illustrate lung involvement in a 40-year-old woman first diagnosed with recurrent respiratory papillomatosis at the age of 2 years. She underwent multiple resections of lung nodules starting in her second decade of life. **A**, Low-magnification photomicrograph illustrates multiple benign papillomas within an ectatic bronchiole with a centrally dilated lumen. (H&E stain; original magnification $\times 20$.) **B**, High-magnification photomicrograph illustrates cytologically bland, benign appearance of the lung papillomas. (H&E stain; original magnification $\times 400$.)

Today the term is restricted to a group of benign neoplasms with variable clinical presentations and histologic appearances.

Endobronchial adenomas include two entities analogous to salivary gland counterparts. *Mucous gland adenomas* are rare, presenting as potentially obstructing, sessile, endobronchial masses arising at the level of lobar or segmental bronchi.²⁶⁻²⁸ Average age at diagnosis is 52 to 54 years but with a broad age range that extends to childhood. Most patients are symptomatic at the time of diagnosis. The most frequent complaints are cough, shortness of breath, and wheezing, a combination of findings that can be misconstrued as asthma.²⁸ Some patients are symptomatic for years before the diagnosis is made. Chest radiographs may be normal but more commonly show a solitary pulmonary nodule and/or postobstructive atelectasis or consolidation.²⁷ CT scans show discrete nodules that may be accompanied by an air-meniscus sign attesting to an endobronchial location.²⁷ Histologically, mucous gland adenomas are variably solid and cystic, and composed of cytologically bland columnar mucinous cells (Fig. 56-5). Surgical resection, which is often required for diagnosis, is curative.

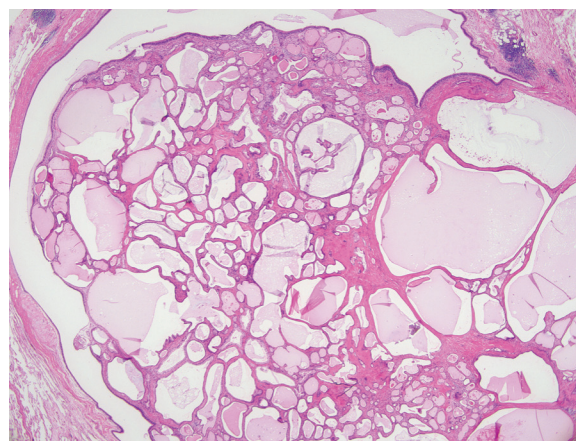


Figure 56-5 Endobronchial mucous gland adenoma. This low magnification photomicrograph shows that the smooth surface is covered by ciliated respiratory epithelium whereas the core comprises predominantly cystic spaces lined by variably attenuated columnar mucinous cells. (H&E stain; original magnification $\times 20$.)

Pleomorphic adenomas, also termed benign mixed tumors, are biphasic neoplasms composed of stromal and epithelial elements. They usually arise in major salivary glands; there are fewer than 20 well documented examples of primary lung tumors.²⁹⁻⁴⁰ Primary pulmonary pleomorphic adenomas have been reported more commonly in women than men (ratio 2:1), with an average age at diagnosis of about 51 years. Cough is the most frequent presenting complaint and is sometimes associated with postobstructive pneumonia. One third of patients are asymptomatic when a solitary pulmonary nodule is discovered. Eighty percent are found within the larger central airways as polypoid exophytic tumors. Chest radiographs and CT scans show a solitary well-circumscribed solid mass without distinctive features. PET in a single patient showed high FDG avidity.³³ Complete surgical resection with tumor-free margins is curative. As can happen with their salivary gland counterparts, benign pleomorphic adenomas can undergo transformation to malignant carcinoma (*carcinoma ex pleomorphic adenoma*).³⁴ Primary pleomorphic adenoma must be distinguished from so-called benign metastasizing pleomorphic adenoma, a term that refers to rare patients in whom histologically benign salivary gland tumors inexplicably metastasize to various sites, including lung.^{41,42}

Adenomas involving peripheral lung parenchyma are rare. *Alveolar adenoma* is the most common variant with just under 30 reported examples.⁴³⁻⁴⁷ Average age at diagnosis is between 50 and 55 years. Nearly all patients are asymptomatic at the time of diagnosis. Radiologically, alveolar adenomas present as well circumscribed peripheral nodules averaging just over 2 cm in greatest dimension. Magnetic resonance imaging may show a cystic space with central fluid and thin-rim enhancement.⁴⁴ Pathologically, alveolar adenomas are partially cystic nodules in which connective tissue septa are lined by cytologically bland epithelial cells (Fig. 56-6). The epithelial cells are derived from pneumocytes while the stromal cells are undifferentiated fibroblasts. Cytogenetic studies performed in a single case demonstrated a clonal translocation supporting the conclusion that these are indeed neoplasms, although their behavior is benign.⁴⁸

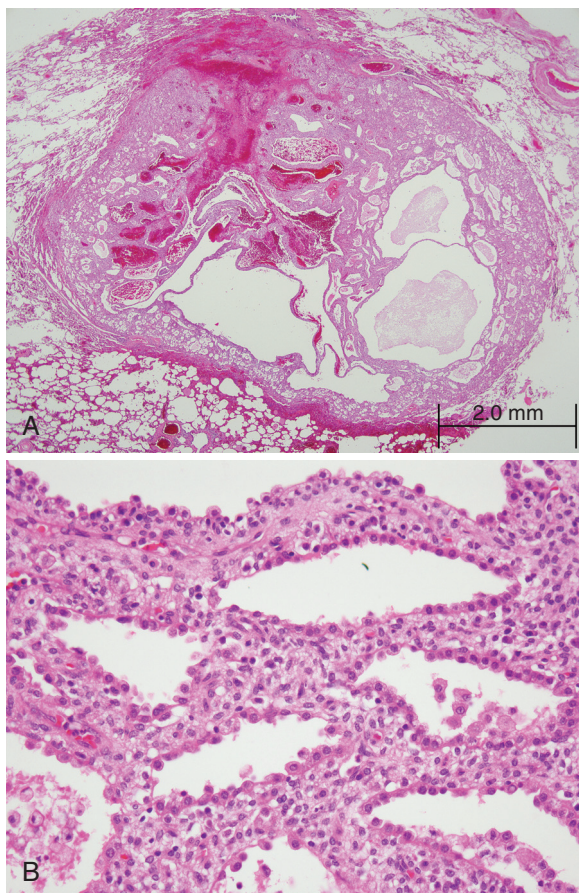


Figure 56-6 Alveolar adenoma. **A**, Low-magnification photomicrograph shows a well-demarcated partially cystic mass in a peripheral lung biopsy. (H&E stain; original magnification $\times 20$.) **B**, Higher-magnification photomicrograph illustrates connective tissue septa lined by bland pneumocytes. (H&E stain; original magnification $\times 400$.)

Papillary adenomas have been described in fewer than 10 patients.⁴⁹⁻⁵² All patients in whom the lesion was discovered during life underwent surgical resection for an asymptomatic solitary peripheral nodule and remained free of disease at follow-up. Histologically, papillary adenomas are circumscribed lesions composed of connective tissue fronds lined by bland type 2 pneumocytes (Fig. 56-7).

Mucinous cystadenoma is a rare lung neoplasm that overlaps with unequivocally malignant mucinous adenocarcinomas.⁵³⁻⁵⁸ Gao and Urbanski proposed separating them into three histologically defined categories: mucinous cystadenoma, mucinous cystic tumor with atypia, and mucinous cystadenocarcinoma.⁵⁴ Histologically, benign tumors without atypia accounted for only 13% of reported patients, further emphasizing that this is an extremely rare neoplasm. Patients typically present with slowly growing, well-demarcated, peripheral lung masses that may or may not appear cystic.⁵⁶⁻⁵⁹ All patients with histologically benign cystadenomas have remained free of disease after surgical resection.

MICRONODULAR PNEUMOCYTE HYPERPLASIA

Micronodular pneumocyte hyperplasia is an unusual proliferation of alveolar epithelium seen almost exclusively in

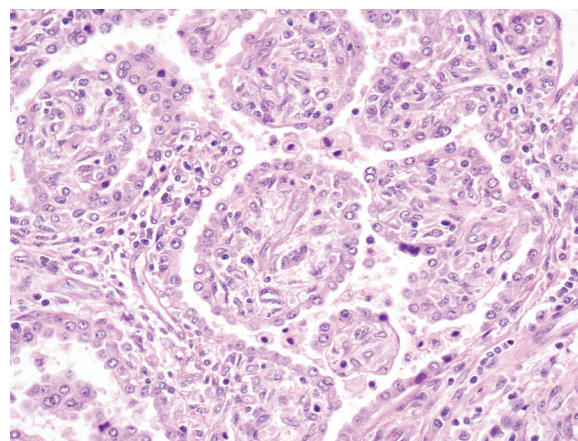


Figure 56-7 Papillary adenoma. High-magnification photomicrograph of a solitary peripheral lung nodule shows papillary connective tissue cores lined by bland cuboidal pneumocytes. (H&E stain; original magnification $\times 400$.)

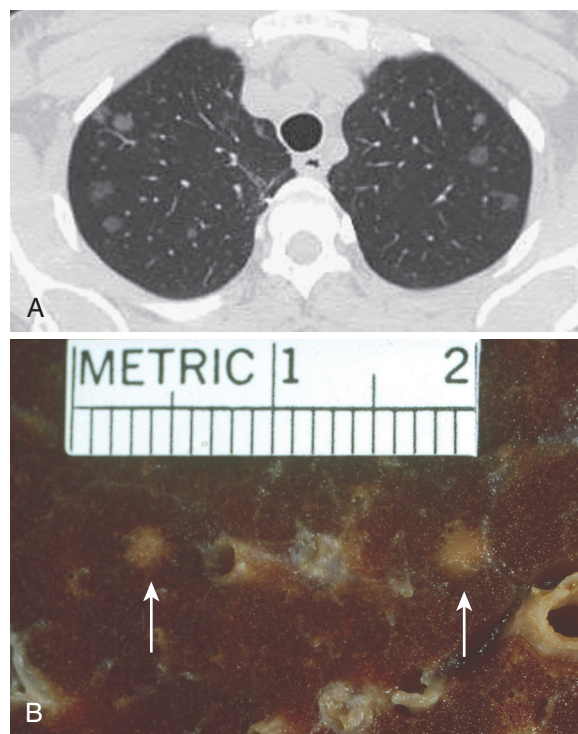


Figure 56-8 Micronodular pneumocyte hyperplasia (MNPH) in tuberous sclerosis complex (TSC) without lymphangioleiomyomatosis. **A**, CT of a 41-year-old woman with TSC and MNPH shows multiple bilateral nodules characterized by ground-glass attenuation. **B**, Photograph of autopsy lung specimen from another patient with TSC and MNPH (arrows). (**A**, courtesy Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

patients with underlying tuberous sclerosis complex and/or lymphangioleiomyomatosis.⁶⁰⁻⁶⁴ More than 85% of reported patients were women. Radiologic findings are characterized by scattered nodules that are occasionally numerous and distributed in a miliary fashion, with or without the associated cystic changes typical of lymphangioleiomyomatosis (see eFig. 56-2).^{61,63} The radiologic abnormalities correspond to ill-defined pale peripheral nodules that are seen either in isolation or in the setting of lymphangioleiomyomatosis (Figs. 56-8 and 56-9). Histologically, micronodular

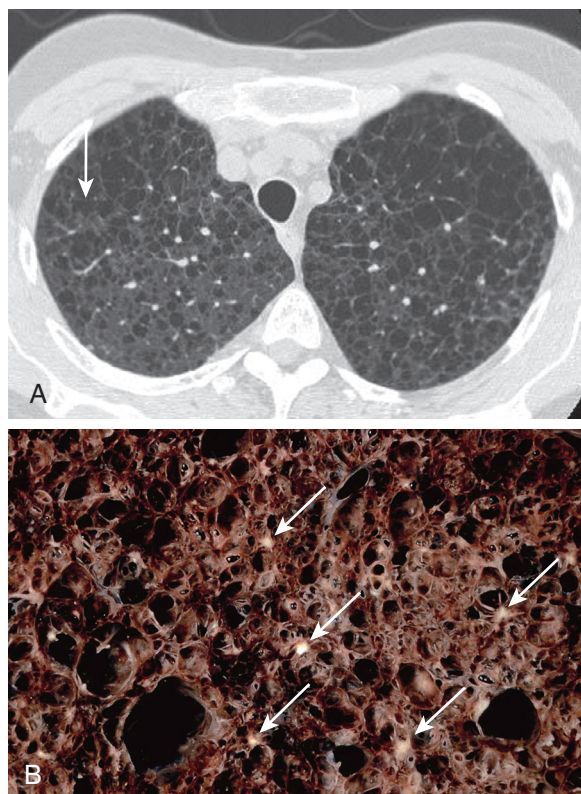


Figure 56-9 Micronodular pneumocyte hyperplasia (MNPH) associated with lymphangioleiomyomatosis (LAM). **A**, CT scan of a 55-year-old woman with tuberous sclerosis complex and LAM and a right lung nodule (arrow) attributed to MNPH. **B**, Photograph of a surgical lung specimen shows a combination of LAM and MNPH (arrows). (A, courtesy Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

pneumocyte hyperplasia demonstrates circumscribed proliferations of bland pneumocytes cytologically identical to those seen in papillary adenomas, differing in that they are distributed along intact alveolar septa rather than along papillae (Fig. 56-10).

SCLEROSING HEMANGIOMA

Sclerosing hemangiomas (SH) are benign lung neoplasms derived from incompletely differentiated respiratory epithelium. The term *hemangioma* is a misnomer based on pseudovascular blood-filled spaces seen in some cases. SH presents with a female-to-male predominance of 7:1.⁶⁵⁻⁷³ Mean age at diagnosis is the fifth decade of life, although they have been reported in a wide age range including children. More than three fourths of patients are asymptomatic at the time they are discovered to have a solitary pulmonary nodule. CT scans show a well-circumscribed round or oval subpleural nodule with smooth margins and inhomogeneous enhancement (see eFig. 56-3).^{74,75} Associated calcifications are present in about one third of patients. Dynamic contrast CT studies show strong, rapid enhancement that rivals the imaging characteristic of malignancies.⁷⁶ PET scanning has been reported in only one patient and was

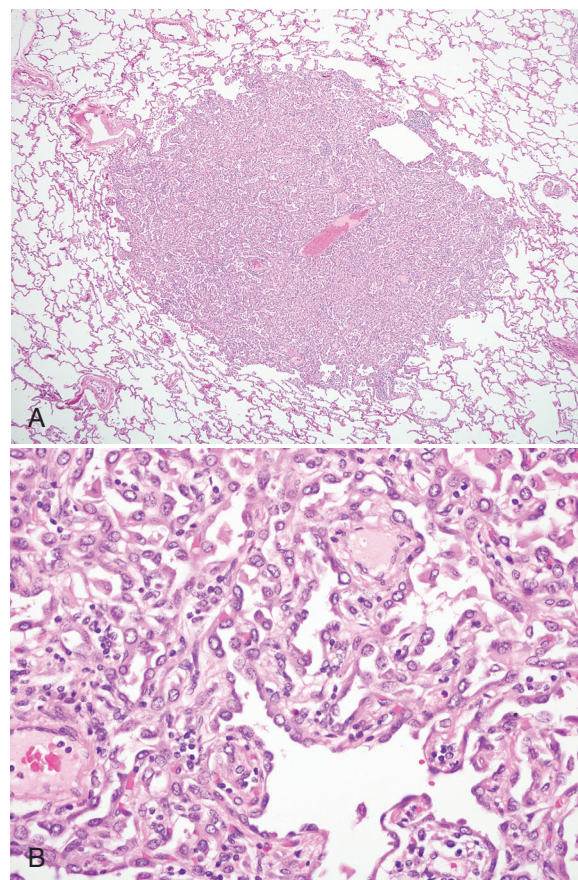


Figure 56-10 Micronodular pneumocyte hyperplasia. Histologic features are shown from the tuberous sclerosis complex patient also illustrated in Figure 56-8B. **A**, Low-magnification photomicrograph shows a well-circumscribed nodule. (H&E stain; original magnification $\times 20$.) **B**, High-magnification photomicrograph shows cytologically bland pneumocytes distributed along alveolar septa. (H&E stain; original magnification $\times 400$.)

characterized by intermediate FDG avidity.⁷⁷ Multiple lesions are seen in about 2% of patients. Deposits in regional lymph nodes are rare and have no impact on the fundamentally benign behavior of these lesions.⁷⁸⁻⁸⁰

Resected SH are well circumscribed subpleural nodules averaging 2 to 3 cm in diameter (Fig. 56-11). The histologic hallmark is a heterogeneous appearance resulting from both a mixture of cell types and highly variable growth patterns. Two populations of epithelial cells are a characteristic feature: (1) surface cuboidal cells derived from pneumocytes or club cell (Clara), and (2) pale interstitial round cells with an incompletely differentiated respiratory epithelial phenotype.^{69,81-83} Molecular studies using a variety of techniques suggest that both populations of cells are neoplastic, an observation that fits with descriptions of both components in nodal deposits.^{79,84,85} The cells are arranged in various growth patterns that include a focally conspicuous sclerotic stroma that is often calcified (Fig. 56-12).

Recent molecular studies of SH have demonstrated alterations at *P16* and *RB* that resemble those found in early stage adenocarcinomas, supporting an origin from

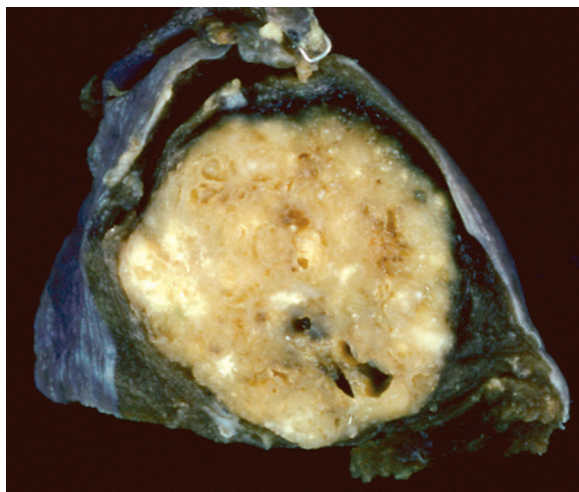


Figure 56-11 Photograph of resected sclerosing hemangioma. The lobulated nodule is well circumscribed and situated near the visceral pleura. The cut surface betrays the fundamentally heterogeneous nature of these neoplasms, showing a variegated pattern of pale brown and white with both solid and spongy areas.

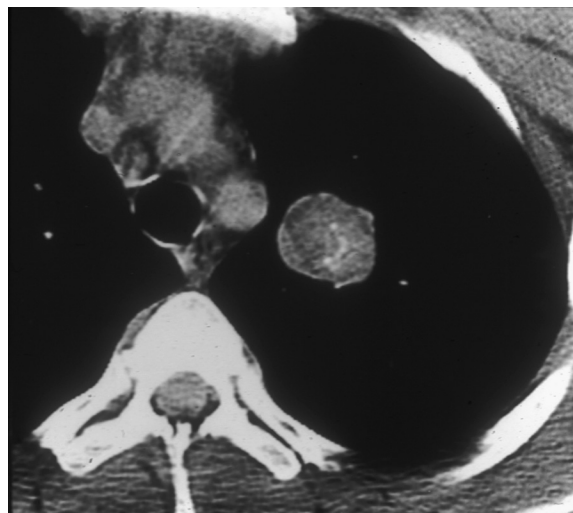


Figure 56-13 Pulmonary hamartoma. CT of a proven hamartoma shows a well-margined nodule in which there is evidence of intratumoral fat and calcification. This combination is characteristic but is seen in only about a fourth of cases.

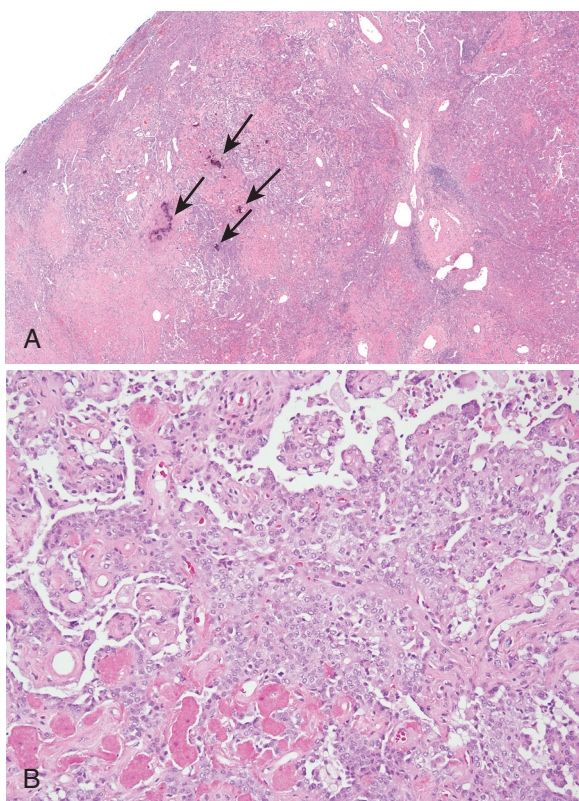


Figure 56-12 Sclerosing hemangioma. **A**, Low-magnification photomicrograph shows the classic features of sclerosing hemangioma in which sclerotic zones with dense collagen deposition and focal calcifications (arrows) alternate with variably cellular regions. (H&E stain; original magnification $\times 2$.) **B**, Higher-magnification photomicrograph shows solid and papillary growth patterns. The central area is solid and composed of the pale-staining round cells demonstrating a phenotype consistent with incompletely differentiated respiratory epithelium. (H&E stain; original magnification $\times 400$.)

respiratory epithelial cells and suggesting similarities between the molecular pathogenesis of SH and lung carcinoma.⁸⁶ However, a more recent molecular analysis of SH failed to identify alterations in some genes (*EGFR*, *HER2*, and *KRAS*) that are commonly mutated in adenocarcinoma, thereby raising doubts about a common link.⁸⁵ Genome-wide approaches will likely be necessary to resolve this controversy.

BENIGN NONEPITHELIAL LESIONS

HAMARTOMA AND RELATED LESIONS

Pulmonary hamartomas are the most common benign neoplasm in adults who undergo surgical resection. They are present in less than 0.5% of consecutively autopsied patients.^{2,87,88} Although the term *hamartoma* implies that these are tumor-like malformations rather than true neoplasms, recent studies show consistent and characteristic genetic abnormalities indicating that hamartomas are clonal neoplasms.

Pulmonary hamartomas are discovered in men more often than in women by a ratio of 2:1 with an average age at diagnosis in the sixth or seventh decade of life.^{89,90} Most patients present with asymptomatic solitary lung nodules with no lobar predilection. Multiple nodules are present in 2% or less of patients.^{89,91} Endobronchial hamartomas (see eFig. 56-4 and Video 56-1), more likely to be associated with cough, are seen in about 10% of patients. CT scans show a characteristic combination of calcifications and/or fat in two thirds of patients (Fig. 56-13; see eFigs. 54-23 through 54-27).⁹² Resection is nearly always curative with rare reports of recurrence or malignant transformation.^{93,94}

Pulmonary hamartomas usually manifest as well-circumscribed nodules, averaging 1.5 to 2 cm in diameter. A variegated cut surface reflects an admixture of stromal elements (Fig. 56-14). Mature hyaline cartilage is an almost universal component and is typically intermingled with

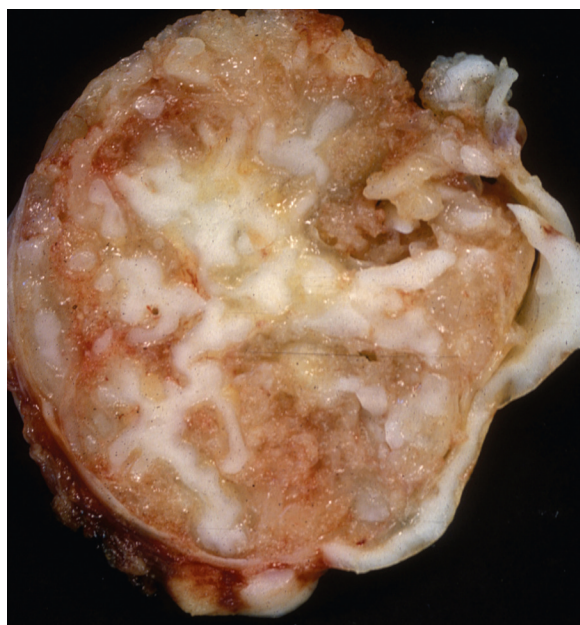


Figure 56-14 Photograph of resected hamartoma. The cut surface of this well-circumscribed nodule shows glistening irregularly shaped cartilaginous islands alternating with pale yellow adipose tissue. The tumor was 4 cm in greatest dimension.

mature fat, fibromyxoid tissue, and rare smooth muscle cells (Fig. 56-15). Any of the stromal components can predominate, however, resulting in a histologic spectrum of neoplasms that includes *leiomyomas* and *lipomas*.⁹⁵⁻⁹⁷ Entrapped nonneoplastic respiratory epithelium often results in a characteristically biphasic appearance, a phenomenon that contributes to relatively high rates of false-positive diagnoses of carcinoma in fine-needle aspiration biopsies (the most common false-positive diagnoses being carcinoid, adenocarcinoma, and small cell carcinoma).⁹⁸

Pulmonary hamartomas, like other benign mesenchymal tumors such as lipoma and leiomyomas, frequently contain chromosomal rearrangements of genes encoding nonhistone chromosomal high-mobility group family of proteins (HMG family) with AT-hook DNA-binding motifs.⁹⁹⁻¹⁰² These proteins play a broad role in growth, differentiation, proliferation, and death of mesenchymal cells through a mechanism that involves regulation of transcription via modification of DNA conformation.¹⁰³ Two main cytogenetic regions containing abnormalities have been defined in pulmonary hamartoma: 6p21 and 12q14-15. The *HMGA1* (also known as *HMG1Y*) gene maps to 6p21.3, whereas *HMGA2* (also known as *HMGIC*) maps to 12q14-15. Their dual role as regulators of mesenchymal differentiation and of gene expression is provocative, although additional work needs to be done to fully elucidate the role of *HMGA* fusion genes in pulmonary hamartoma.

Pulmonary chondroma, a related cartilaginous lung tumor, constitutes one component of the triad (i.e., pulmonary chondroma, paraganglioma, gastric stromal tumors) described by Carney in 1977.¹⁰⁴ Pulmonary chondromas develop in about three fourths of patients with Carney syndrome and are multiple in half of these.^{91,105} Chondromas are distinct in being purely cartilaginous without the other stromal and epithelial elements characteristic of hamartoma.⁹¹

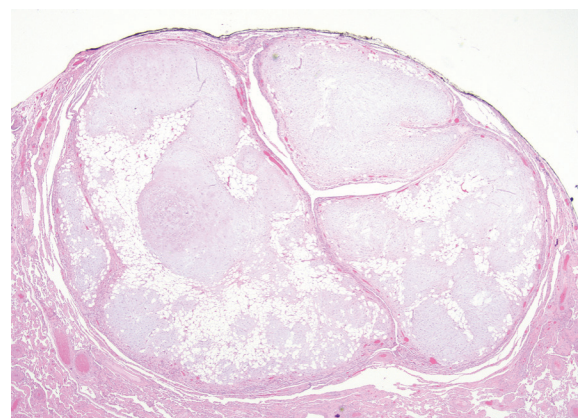


Figure 56-15 Pulmonary hamartoma. Low-magnification photograph of a typical pulmonary hamartoma in which cartilaginous islands are interspersed with adipose tissue resulting in a lobulated appearance. (H&E stain; original magnification $\times 20$.)

INFLAMMATORY MYOFIBROBLASTIC TUMOR

Inflammatory myofibroblastic tumors (IMTs) of the lung comprise a spectrum of lesions ranging from benign spindle cell tumors to frankly malignant sarcomas. Pulmonary IMTs, also termed *plasma cell granulomas* by Bahadori and Liebow,¹⁰⁶ are defined in the WHO classification of lung tumors as “a subgroup of the broad category of ‘inflammatory pseudotumours.’”¹⁰⁷ The staggering profusion of synonyms that have been applied to these unusual tumors, which also is seen in multiple extrapulmonary sites, reflects the controversy and confusion regarding their pathogenesis and histogenesis.

IMTs of the lung can arise in any age group but tend to affect children and young adults; more than half of patients are younger than 40 years of age at the time of diagnosis.¹⁰⁶⁻¹¹³ Most patients present with asymptomatic peripheral lung nodules. Endobronchial tumors (see eFig. 56-5) account for around 15% of patients and may be accompanied by symptoms of cough and/or hemoptysis. Chest imaging studies typically show a well-circumscribed mass ranging in size from 0.8 cm to more than 30 cm (Fig. 56-16, see eFigs. 54-19 and 54-20 and eFig. 56-6), with the majority measuring between 1 and 6 cm in greatest dimension.^{106,110,112,114-116} Most primary pulmonary IMTs are cured with complete surgical resection.^{108,112,115} Incomplete resection is associated with substantial risk of recurrence and rarely locally aggressive behavior and death.^{109,116} COX-2 inhibitors may have therapeutic value in large unresectable tumors, a treatment strategy for which only limited anecdotal evidence is available.¹¹⁷⁻¹¹⁹

The long list of competing terms for IMTs attests to its histologic diversity. The most consistent histologic finding is a combination of neoplastic spindle cells and a variably dense infiltrate of polyclonal plasma cells (Fig. 56-17). Immunohistochemical and ultrastructural studies show that the spindle cells have features of myofibroblasts, including expression of smooth muscle-associated proteins. ALK1, a tyrosine kinase receptor, is expressed in between a third and a half of lung tumors, is more frequent in young patients,^{109,120-122} and reflects the observation that *ALK* is fused to a variety of constitutively activated genes via balanced translocations (see later).^{123,124} Interestingly, absence

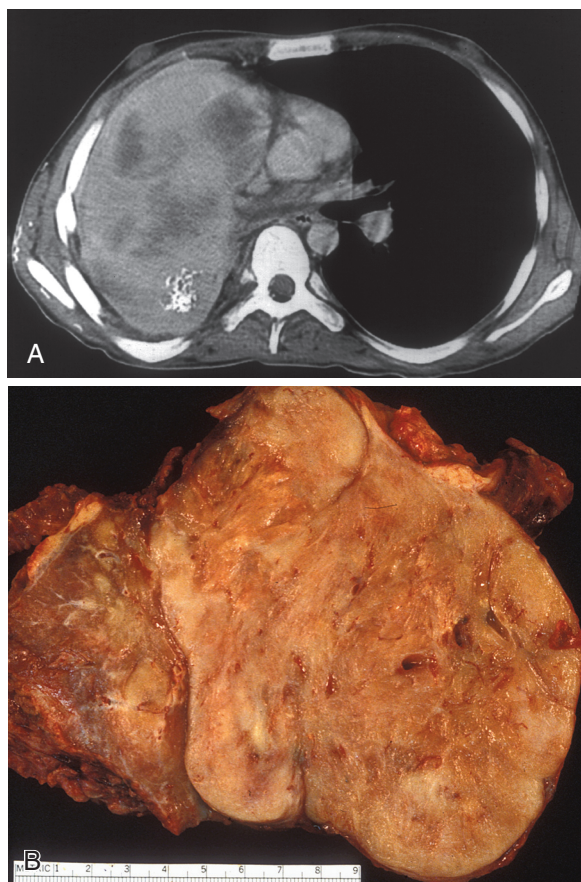


Figure 56-16 Inflammatory myofibroblastic tumor (IMT). Large IMT in a 21-year-old man in whom an intrathoracic mass was first detected at the age of 10. **A**, CT shows a large mass filling the right hemithorax with heterogeneous attenuation and calcification. **B**, Photograph of right pneumonectomy specimen shows a large mass that, despite its size, was well circumscribed without invasion beyond lung parenchyma.

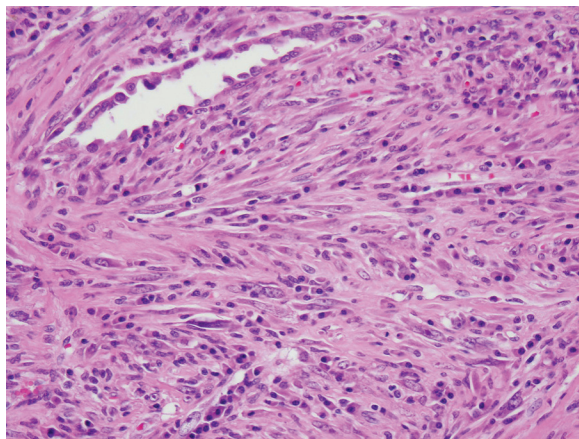


Figure 56-17 Inflammatory myofibroblastic tumor. High-magnification photomicrograph from the tumor illustrated in Figure 56-16. Neoplastic spindle cells are associated with a prominent infiltrate of plasma cells. Nonneoplastic respiratory epithelium (upper left) is surrounded by neoplastic spindle cells, resulting in a biphasic appearance, a common phenomenon in benign or low-grade nonepithelial tumors. (H&E stain; original magnification $\times 400$.)

of ALK expression may be associated with a greater risk for aggressive behavior.^{109,125}

Although the name suggests a nonneoplastic inflammatory tumor, IMTs are actually low-grade neoplasms. Various techniques have identified a range of genetic abnormalities consistent with the neoplastic nature of IMTs.^{121,123,124,126-128}

The most consistent molecular alteration is a balanced translocation of the *ALK* gene locus (2p23). Fusion of a silent gene (*ALK*) with one of several constitutively expressed genes (e.g., *TPM3*, *TPM4*, *CLTC*) results in aberrant expression of the silent gene that then typically functions as an oncogene. A similar role for *ALK* gene fusions is observed in anaplastic large cell lymphomas and lung adenocarcinoma. The *ALK* inhibitor crizotinib has been used successfully to induce at least a partial response in a patient with IMT bearing an *ALK* rearrangement.¹²⁵ The role of human herpesvirus 8 in the pathogenesis of IMT is controversial and uncertain.¹¹³

SOLITARY FIBROUS TUMOR

Solitary fibrous tumors (SFTs), formerly referred to as *localized fibrous mesotheliomas*, are mesenchymal neoplasms that frequently arise from the pleura. SFTs are not unique to the pleura, however, and have been described in the parenchyma of the lung (*intrapulmonary SFT*), in the mediastinum, and in numerous extrathoracic sites.¹²⁹⁻¹³³

Pleural and intrapulmonary SFTs affect men and women equally.¹³⁴⁻¹³⁹ Mean age at diagnosis is the sixth decade of life. Just more than half of patients are symptomatic with presenting complaints that include chest pain (25%), shortness of breath (15%), and/or cough (12%), attesting to the often large size of these tumors.^{135,136,138,140}

Clubbing is present in about 2% of patients. A paraneoplastic syndrome of hypoglycemia is rare and results from tumor production of insulin-like growth factor.^{36,141-144} Imaging studies show large intrathoracic masses with an average maximum diameter of between 8.5 and 10.5 cm.^{135,136,139,140,145} Chest imaging studies show a lobulated and sharply marginated mass with a broad base abutting the chest wall, frequently associated with compression of surrounding structures (Fig. 56-18, see eFigs. 56-7 through 56-11 and Video 56-2).^{145,146} Heterogeneous attenuation and heterogeneous enhancement are characteristic (see eFig. 56-7 and 56-9).¹⁴⁵ Calcifications are rare. Most pleural and intrapulmonary SFTs behave as benign neoplasms. Patients with histologically benign tumors are cured with complete surgical excision. A more aggressive course is seen in just over 10% of patients and is limited to those who either undergo incomplete surgical excision or have histologically malignant tumors (*malignant SFT*, see eFigs. 56-12 and 56-13).^{134-136,138-140,147}

SFTs are three times more likely to arise from visceral than parietal pleura (see eFig. 56-11). Those arising from visceral pleura are frequently pedunculated and attached to the lung surface by a connective tissue pedicle (Fig. 56-19). Occasional examples arise within the fissures, resulting in a radiologic appearance difficult to separate from an intrapulmonary tumor (see eFig. 56-11). Parietal pleural lesions are more commonly sessile with a broad base of attachment to chest wall, diaphragm, or mediastinum. Histologically, SFTs are variably cellular spindle cell neoplasms with a

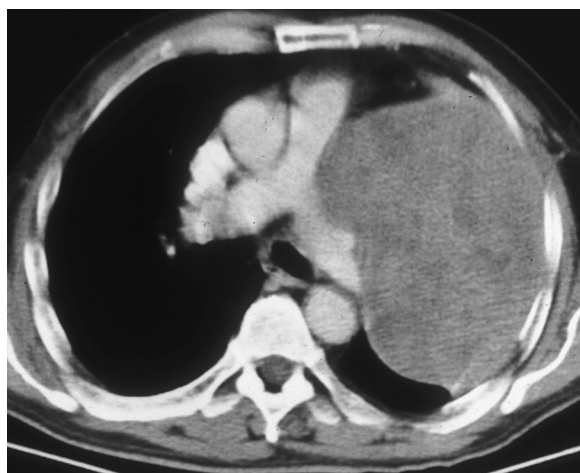


Figure 56-18 Solitary fibrous tumor (SFT). CT shows a large benign SFT arising from the visceral pleura with nearly complete atelectasis of the left lung. Together, SFT and inflammatory myofibroblastic tumor are the most likely diagnoses in patients who present with large benign intrathoracic tumors.

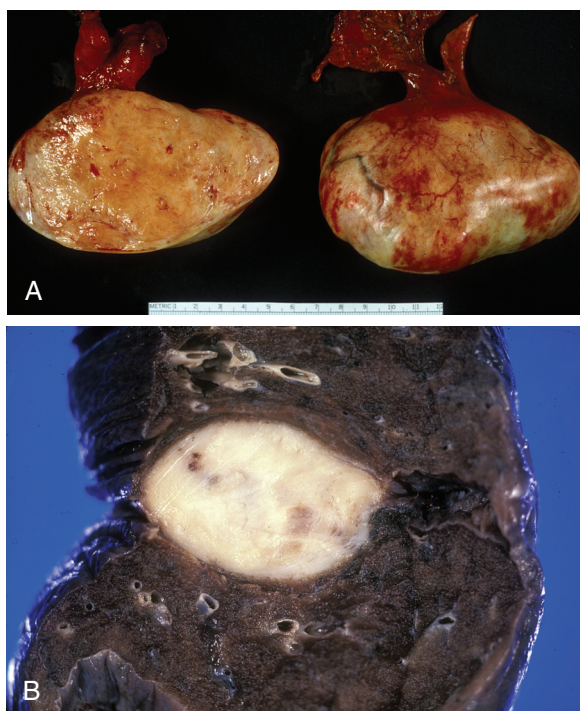


Figure 56-19 Solitary fibrous tumor (SFT). Photograph of a resected SFT arising from the visceral pleura. **A**, As demonstrated in this example, most visceral pleural SFTs are attached to the lung by a pedicle and are characterized by a smooth glistening surface (*right*) and an encapsulated homogeneous cut surface without necrosis (*left*). **B**, Less commonly, SFT arises within the fissures as illustrated in this bilobectomy specimen.

collagenous stroma. Malignant variants are larger, more likely to have an invasive growth pattern, and more cellular with associated cytologic atypia, increased mitotic rates, and necrosis.¹³⁵

Recent discovery of recurrent *NAB2-STAT6* gene fusions in solitary fibrous tumors provides a genetic signature helpful in separating SFT from other intrathoracic spindle cell neoplasms.^{147a} Commercially available antibodies for *STAT6* provide a useful diagnostic tool for routine clinical practice.^{147b}

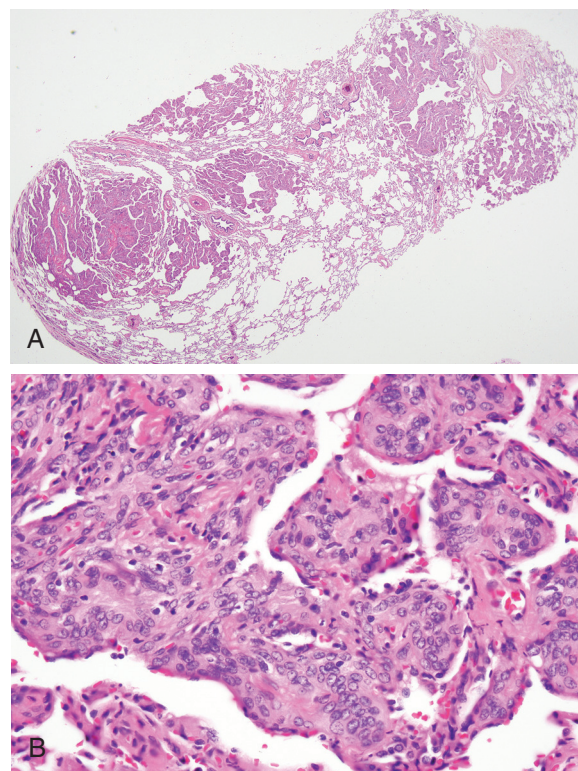


Figure 56-20 Multiple meningothelial-like nodules. Also called diffuse pulmonary meningotheliomatosis, the multiple nodules are shown in a surgical lung biopsy from a 56-year-old woman who presented with dyspnea. **A**, At low magnification, multiple nodules are seen randomly distributed throughout the biopsy. (H&E stain; original magnification $\times 20$.) **B**, At higher magnification, the nodules comprise bland meningothelial cells arranged in poorly formed nests and expanding the interstitium. (H&E stain; original magnification $\times 400$.)

MENINGOTHELIAL-LIKE NODULES AND INTRAPULMONARY MENINGIOMA

Pulmonary *meningothelial-like nodules* (MLNs), historically termed *chemodectomas*, present in less than 5% of autopsies but are frequently seen as incidental findings in surgical specimens from adults.¹⁴⁸⁻¹⁵² MLNs are more common in women and are seen with greater frequency in patients with chronic lung diseases, including chronic interstitial pneumonias and thromboembolic disease.¹⁵⁰ A rare syndrome of multiple bilateral MLNs (*diffuse pulmonary meningotheliomatosis*) has been described in women who present in the sixth to eighth decade of life with multiple nodules seen on CT (see [eFig. 54-28](#)).^{153,154} Half complain of dyspnea and/or cough at presentation. Microscopically, MLNs are composed of nests of epithelioid cells that are histologically and immunophenotypically indistinguishable from meningothelial cells of the central nervous system ([Fig. 56-20](#)). Despite this unexplained phenotypic overlap, molecular studies demonstrate significant differences between MLNs and conventional central nervous system meningiomas.¹⁵³

Primary *intrapulmonary meningiomas* are rare solitary lesions that are unrelated to MLN.¹⁵⁵⁻¹⁵⁷ Men and women are affected equally and present at an average age of 56 years with asymptomatic solitary nodules averaging 3 cm in greatest dimension. Patients with multiple lesions should be presumed to have metastatic disease from a central



Figure 56-21 Granular cell tumor. Photograph demonstrates the cut surface of pneumonectomy specimen in which a granular cell tumor (arrows) partially obstructs the lower lobe bronchus.

nervous system primary until proven otherwise.¹⁵⁸ PET scanning in one series demonstrated uptake consistent with a pulmonary neoplasm.¹⁵⁹ Complete surgical resection is curative in patients with histologically benign meningiomas.

MISCELLANEOUS

Granular cell tumors, referred to in older literature as *granular cell myoblastomas*, are uncommon primary lung neoplasms that typically present as pedunculated or sessile endobronchial tumors (Fig. 56-21, see eFig. 56-14).^{160,161} Lesions are multiple in a fourth of patients. Symptoms are reported in half and result from airway obstruction. Peripheral lung nodules are rare. Pulmonary GCTs are benign and can usually be managed with conservative excision.

Clear cell ("sugar") tumors are rare primary lung tumors that invariably present as asymptomatic solitary lung nodules.¹⁶² Histologic, ultrastructural, and immunophenotypic features are indistinguishable from PEComas and renal angiomyolipomas, a family of neoplasms derived from *perivascular epithelioid cells* (PEC) and related to muta-

tions of the tuberous sclerosis complex genes that affect regulation of the *mammalian target of rapamycin* (mTOR) pathway.^{163,164}

SUMMARY

Benign lung tumors are uncommon but frequently present challenges in diagnosis and management. They comprise a diverse group of epithelial and nonepithelial neoplasms that may present as symptomatic endobronchial lesions or asymptomatic solitary peripheral nodules. Some may become large enough to cause symptoms by compression or displacement of intrathoracic structures. Surgical resection is frequently required for diagnosis and is usually curative.

Key Points

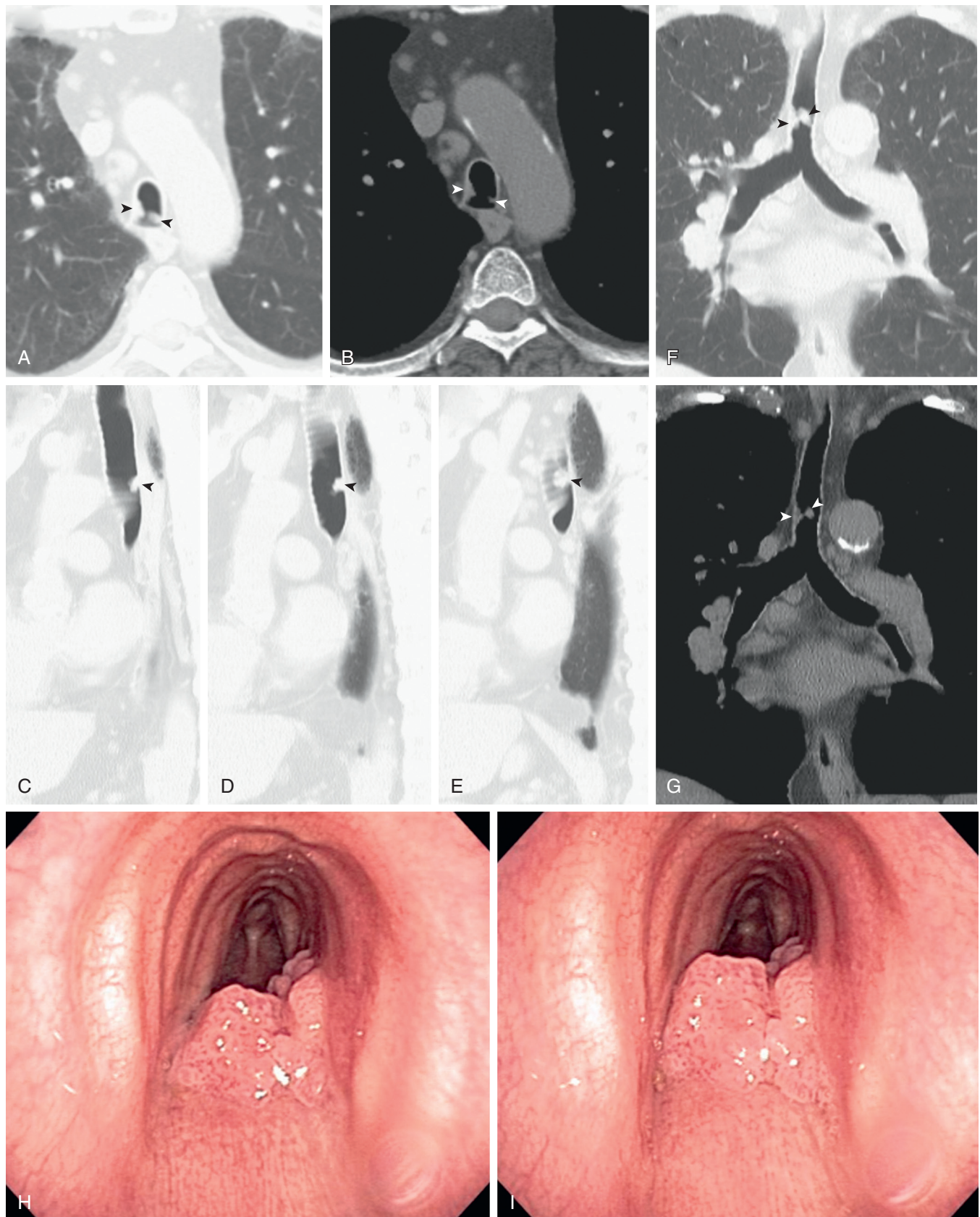
- Benign lung tumors can arise from all cell types within the lung.
- With few exceptions, clues as to the benign nature of the nodules are often lacking on radiographic images and, contrary to expectations, PET scans may also be positive.
- Fat density or specific benign patterns of calcification on imaging are the exceptions that can suggest a benign diagnosis.
- Rare inflammatory myofibroblastic tumors may be associated with *ALK* gene rearrangements that respond to crizotinib.

Complete reference list available at [ExpertConsult](#).

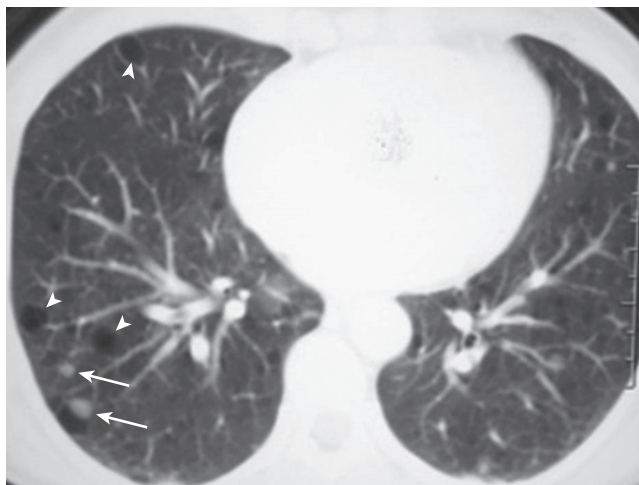
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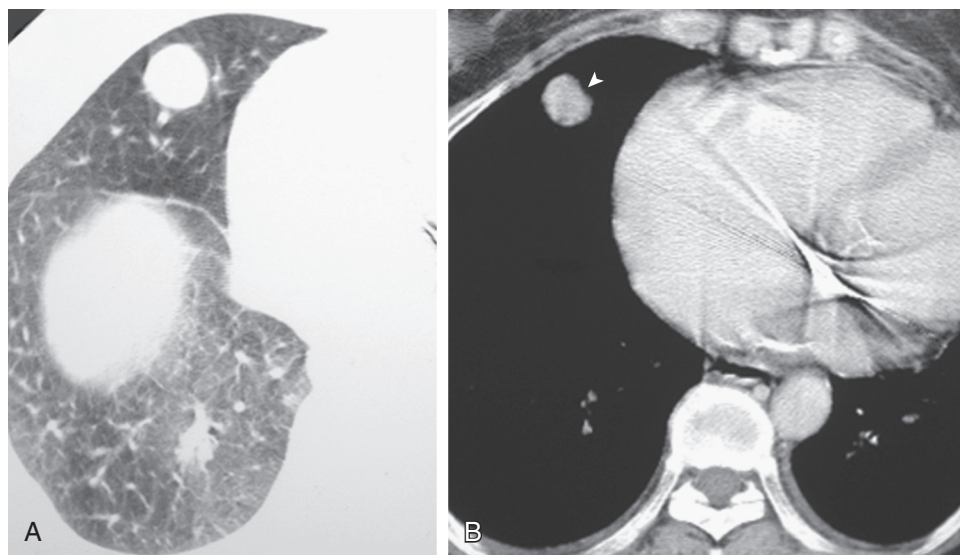
eFIGURE IMAGE GALLERY



eFigure 56-1 Squamous papilloma of the trachea. Axial chest CT displayed in lung (A) (see [Video 56-1A](#)) and soft tissue (B) windows shows a multilobulated tracheal lesion (arrowheads). C–E, Sagittal images show the lesion (arrowheads) residing along the posterior tracheal wall. Coronal CT images displayed in lung (F) and soft tissue (G) windows show the tracheal lesion (arrowheads) arising from the posterior and right lateral wall (see [Video 56-1B](#)). H and I, Bronchoscopic images show a multilobulated posterior tracheal lesion; biopsy confirmed squamous papilloma. (Courtesy Michael Gotway, MD; case by Allen Thomas, MD, Veterans Affairs Medical Center, Phoenix, AZ.)



eFigure 56-2 Micronodular pneumocyte hyperplasia in a patient with tuberous sclerosis-lymphangioleiomyomatosis complex. Axial chest CT displayed in lung windows shows several thin-walled cysts (*arrowheads*) associated with small, nonspecific lung nodules (*arrows*), the latter representing micronodular pneumocyte hyperplasia. (Courtesy Michael Gotway, MD.)



eFigure 56-3 Sclerosing hemangioma. Axial enhanced chest CT shown in lung (**A**) and soft tissue (**B**) windows shows a nonspecific, enhancing, circumscribed right middle lobe nodule (*arrowhead*) proven on resection to represent sclerosing hemangioma. (Courtesy Michael Gotway, MD.)

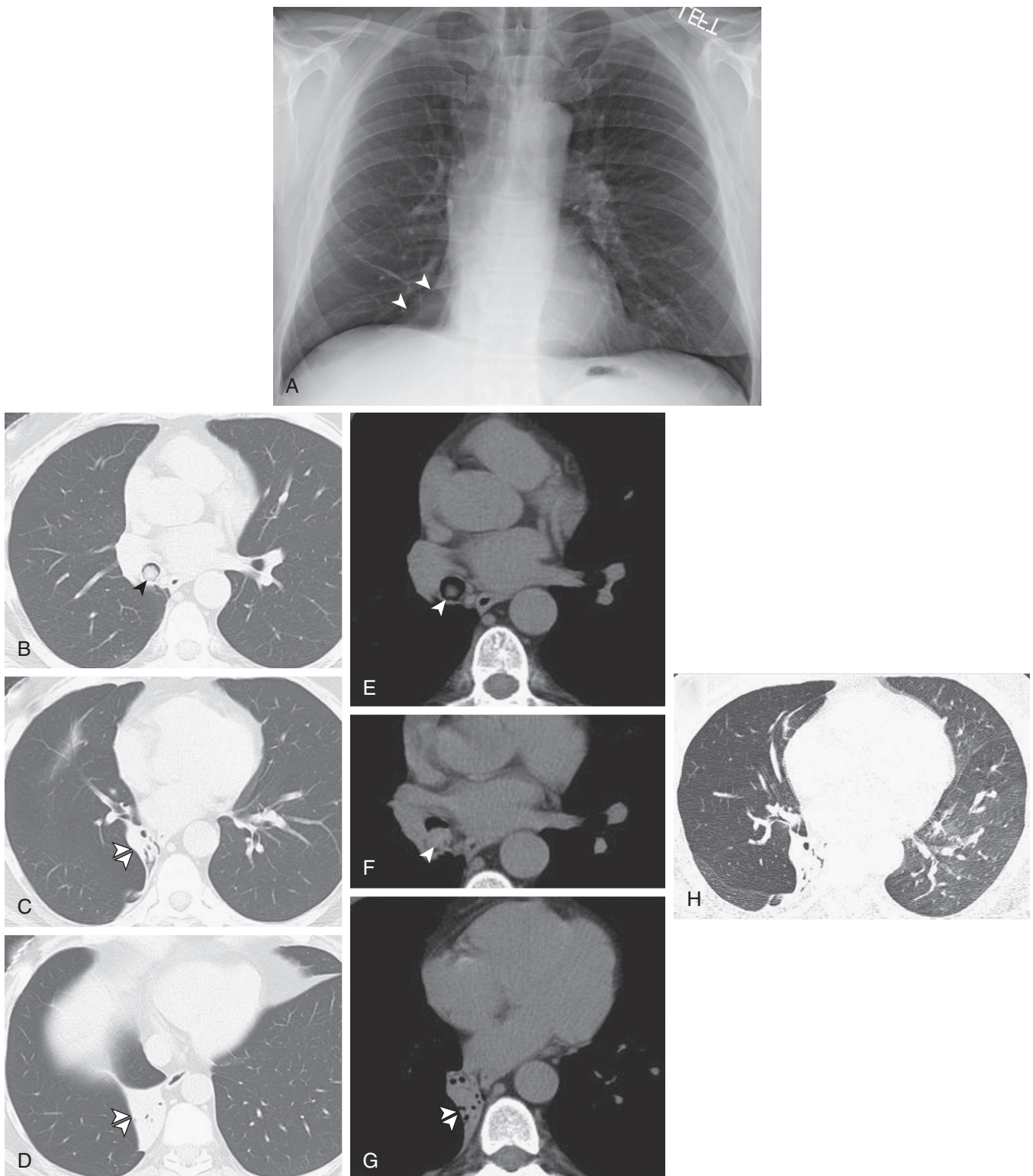
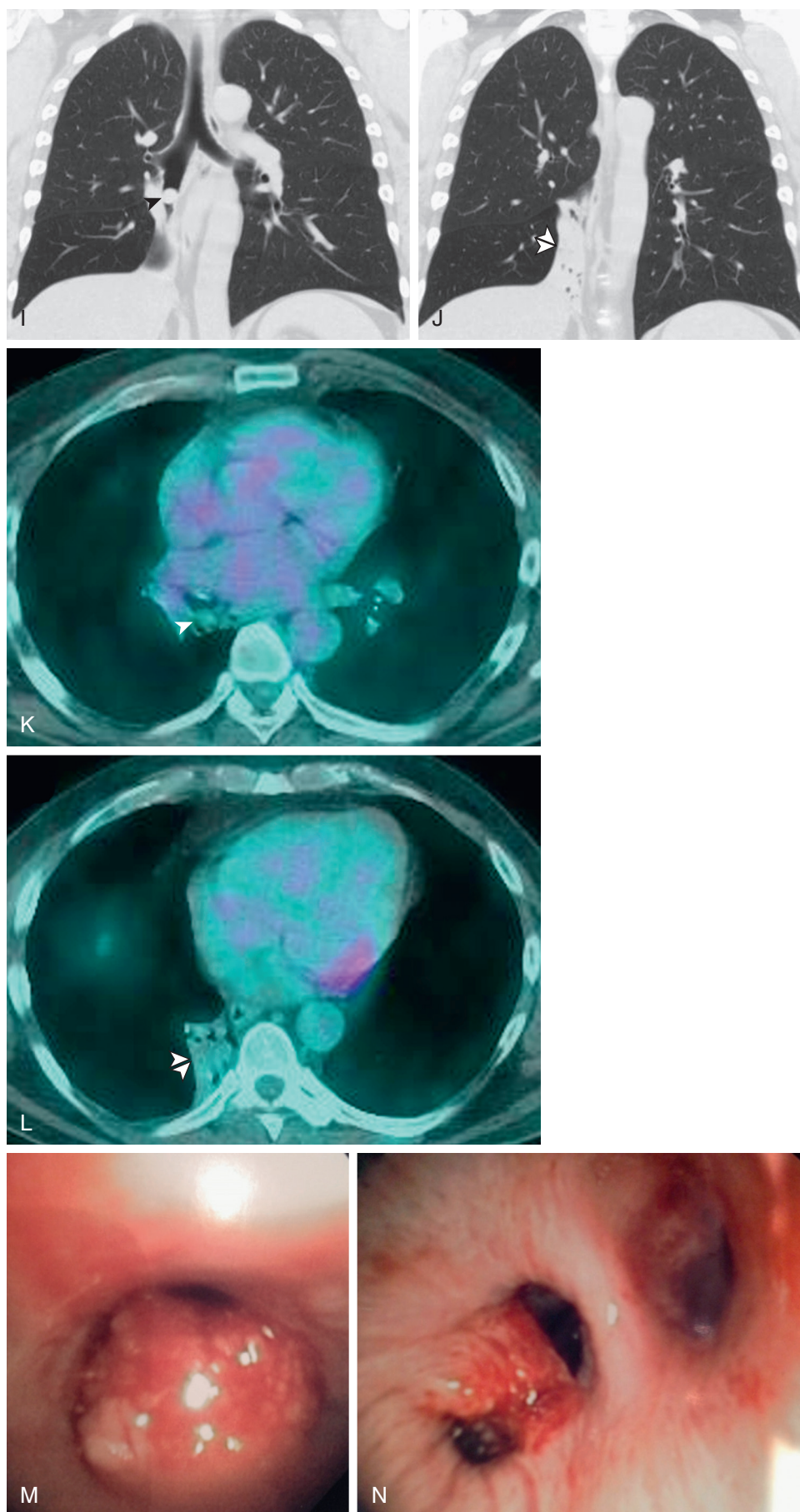
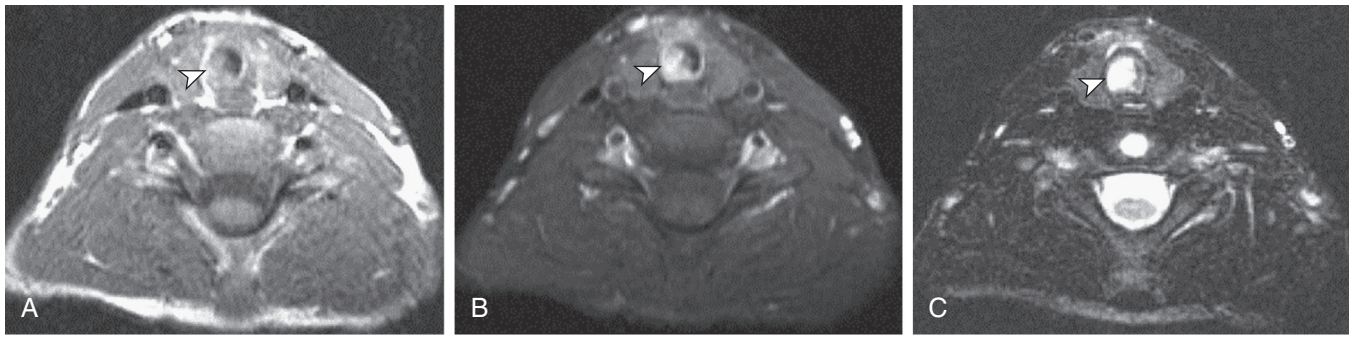


Figure 56-4 Endobronchial hamartoma. **A**, Frontal chest radiograph shows right lower lobe collapse, evidenced by medial and inferior retraction of the right major fissure (*arrowheads*). Right lung volume is diminished overall compared with the left. Axial unenhanced chest CT scans displayed in lung (**B–D**) and soft tissue (**E–G**) windows shows a solid lesion residing within the bronchus intermedius (*arrowheads*, **B**, **E**, and **F**). Right lower lobe collapse (*double arrowheads*, **C**, **D**, and **G**) is present. **H**, Axial high-resolution CT shows hyperexpansion of the right middle lobe, partially compensating for the right lower lobe collapse.

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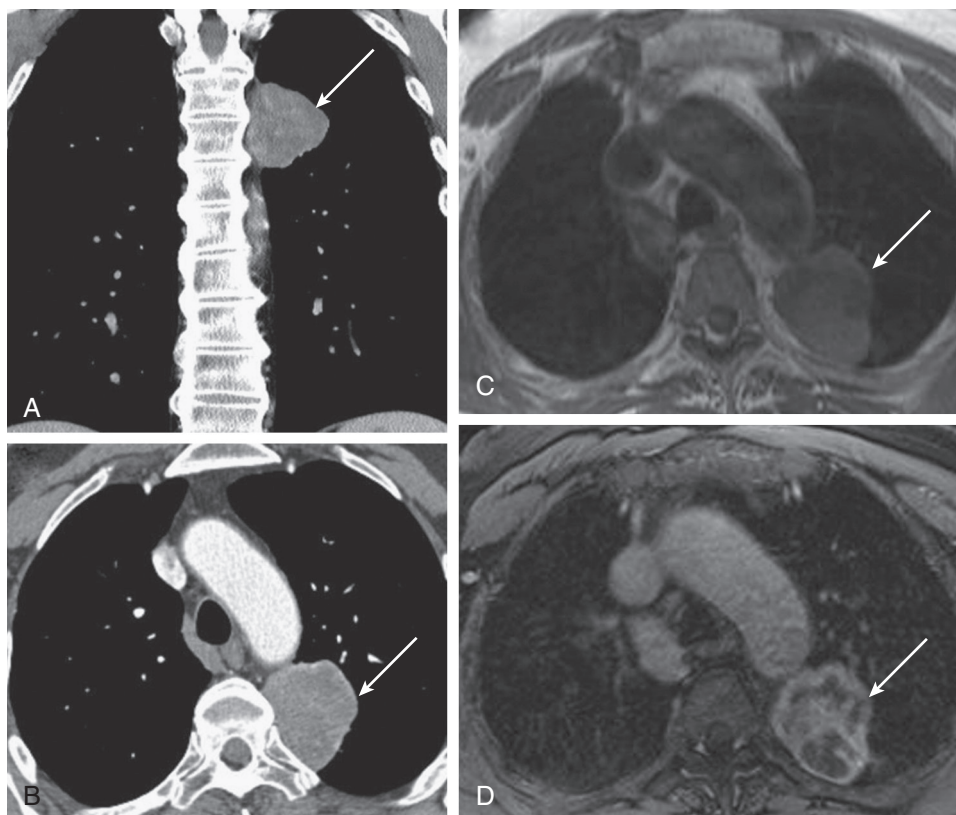
eFigure 56-4, cont'd **I** and **J**, Coronal chest CT images show the endobronchial lesion (*arrowhead*) within the bronchus intermedius and the right lower lobe collapse (*double arrowheads*) to advantage. **K** and **L**, Axial fused PET-CT images show no significant tracer accumulation within the bronchus intermedius lesion (*arrowhead*) or the collapsed right lower lobe (*double arrowheads*). **M** and **N**, Bronchoscopic images before (**M**) and after (**N**) treatment show decrease in size of the lesion, shown on biopsy to represent hamartoma. (Images courtesy Andrew H. Goldstein, MD.)



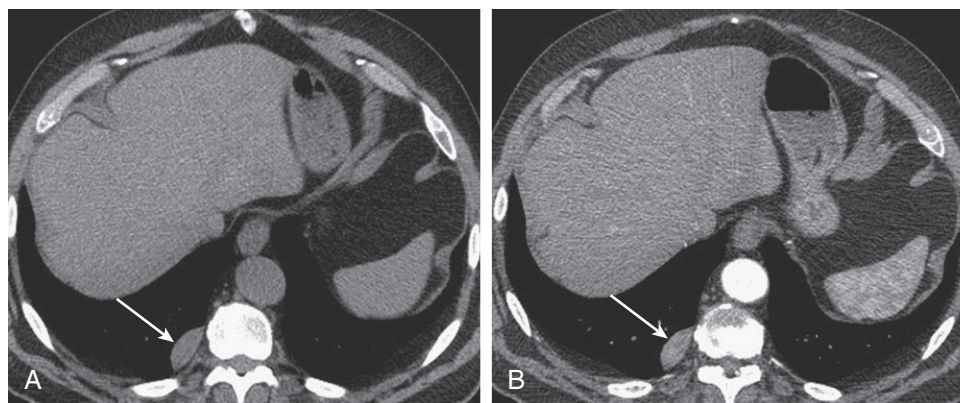
eFigure 56-5 Tracheal inflammatory myofibroblastic tumor. T1-weighted axial MR images before (A) and after (B) intravenous gadolinium administration show an irregular lesion (arrowheads) arising from the right lateral tracheal wall. C, Axial T2-weighted MR image shows high signal within the lesion (arrowhead), consistent with fluid density. Biopsy showed inflammatory myofibroblastic tumor. (Courtesy Michael Gotway, MD.)



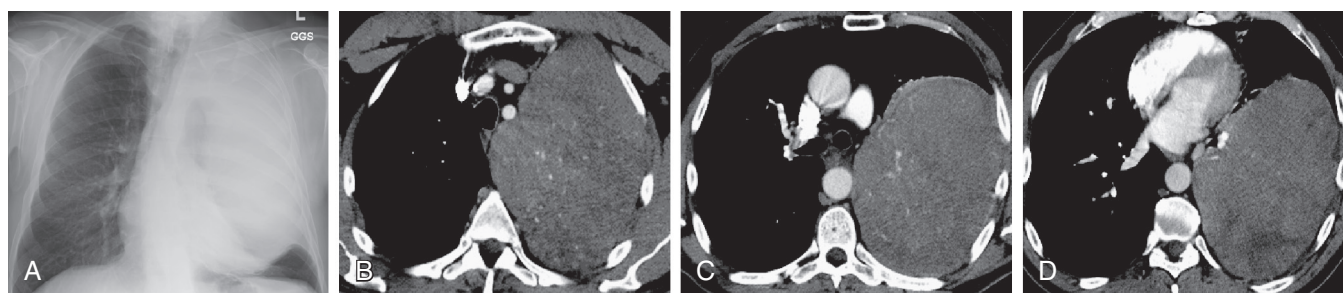
eFigure 56-6 Inflammatory myofibroblastic tumor. A, Frontal chest radiograph shows a circumscribed nodule (arrow) projected over the right hilum. Axial contrast-enhanced chest CT displayed in lung (B) and soft tissue (C) windows shows a finely lobulated superior segment right lower lobe nodule. Small satellite nodules were present more inferiorly. The appearance of the lesion is nonspecific. Biopsy showed inflammatory myofibroblastic tumor. (Courtesy Michael Gotway, MD; case by Paul J. Conomos, MD, Arizona Pulmonary Specialists, Phoenix, AZ.)



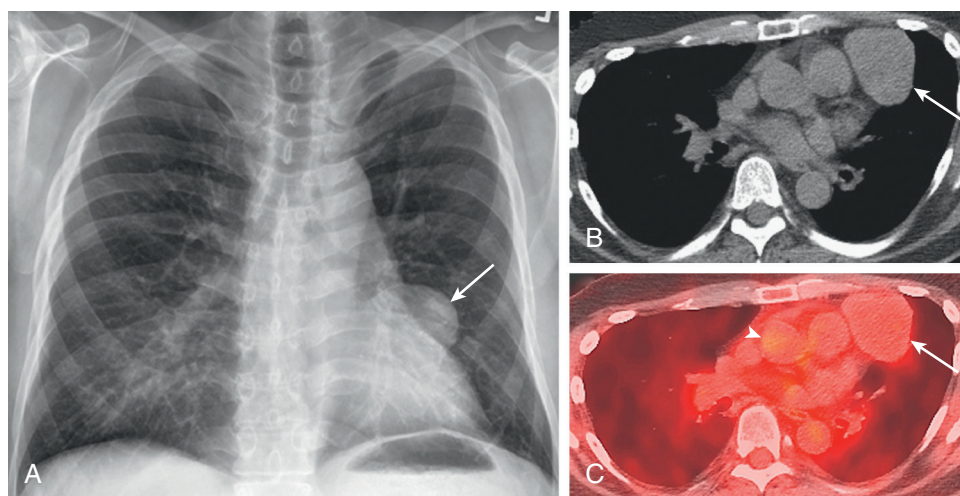
eFigure 56-7 Solitary fibrous tumor of the pleura. Coronal (A) and axial (B) contrast-enhanced chest CT shows an enhancing lesion with extensive mediastinal pleural contact (arrow), suggesting an extrapulmonary origin (see [Video 56-2](#)). C, Axial T1-weighted MR image before intravenous contrast administration. D, Axial contrast-enhanced 3D spoiled fast gradient echo image shows extensive lesion enhancement (arrow). Surgical resection proved solitary fibrous tumor of the pleura. (Courtesy Michael Gotway, MD.)



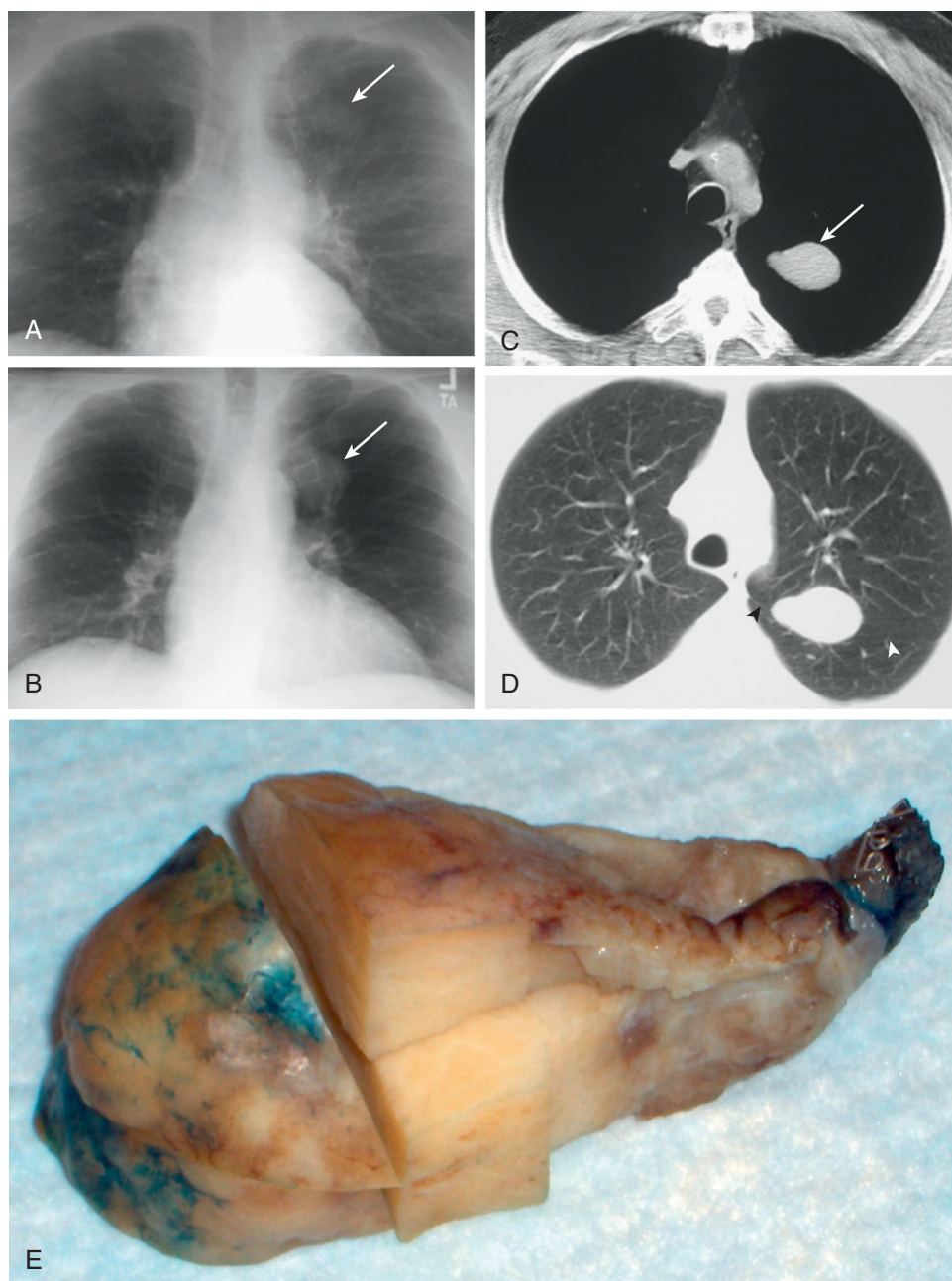
eFigure 56-8 Solitary fibrous tumor of the pleura. Unenhanced (A) and contrast-enhanced (B) chest CT shows the typical appearance of an extrapulmonary lesion (arrows): a circumscribed, lenticular- or oblong-shaped opacity creating obtuse margins with the chest wall. Surgical resection proved solitary fibrous tumor of the pleura. (Courtesy Michael Gotway, MD.)



eFigure 56-9 Solitary fibrous tumor of the pleura; large. A, Frontal chest radiograph shows near complete opacification of the left thorax with slight shift of the cardiomeastinal structures to the contralateral side. B–D, Axial contrast-enhanced chest CT shows a solid, vascularized lesion occupying much of the left thorax. The large size of the lesion makes determination of the organ of origin difficult, but solitary fibrous tumor of the pleura is a consideration, particularly when no overtly aggressive features, such as a large pleural effusion, rib destruction, or lymph node enlargement, are evident. (Courtesy Michael Gotway, MD.)



eFigure 56-10 Solitary fibrous tumor of the pleura. A, Frontal chest radiograph shows a circumscribed mass (arrow) along the left heart border. The mediastinal contact, smoothly margined character of the lesion, and obtuse angles of the lesion at its interface with the lung suggest an extrapulmonary origin. B, Unenhanced chest CT shows the lesion (arrow) has mildly inhomogeneous attenuation and significantly contacts the left mediastinum and pericardium. C, Axial fused PET-CT image shows little tracer accumulation within the lesion (arrow); note the similarity in tracer uptake between the lesion (arrow) and mediastinal blood pool in the aorta (arrowhead). Surgical resection proved solitary fibrous tumor of the pleura. (Courtesy Michael Gotway, MD.)



eFigure 56-11 Solitary fibrous tumor of the pleura: visceral pleural origin evident on imaging. **A**, Frontal chest radiograph shows a poorly defined left upper lobe opacity (*arrow*). **B**, Repeat frontal chest radiograph 5 years following **A** shows slow interval growth in the lesion (*arrow*). Axial unenhanced chest CT images displayed in soft tissue (**C**) and lung (**D**) windows shows a homogeneous, circumscribed, noncalcified lesion (*arrow*, **C**). On the lung window image (**D**), the lesion is clearly related to the left major fissure (*arrowheads*). **E**, Specimen following surgical resection was shown to be solitary fibrous tumor of the pleura. (**A–D**, Courtesy Michael Gotway, MD.)

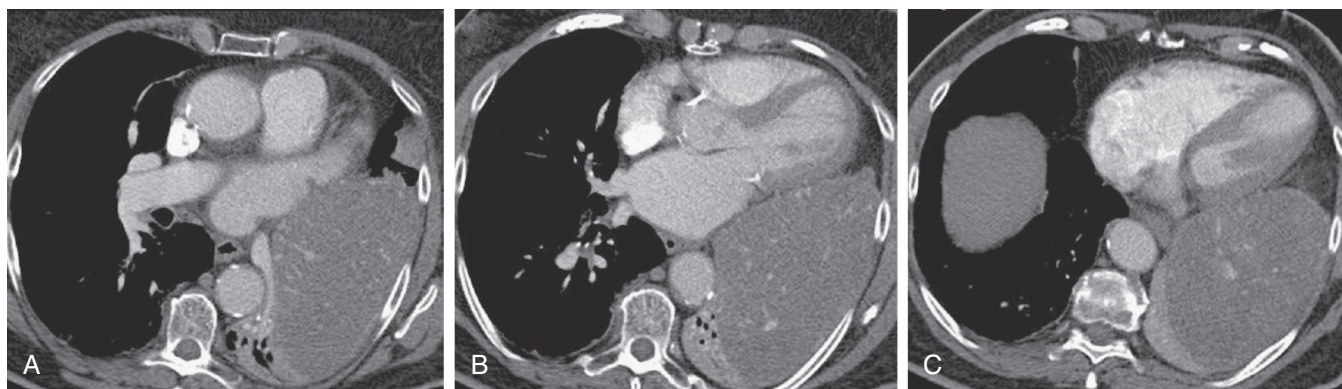


Figure 56-12 Malignant solitary fibrous tumor of the pleura. A–C, Axial contrast-enhanced chest CT shows a large, homogeneous, solid, vascularized left-sided mass with broad pleural surface contact. Biopsy showed features consistent with malignant fibrous tumor of the pleura. (Courtesy Michael Gotway, MD.)

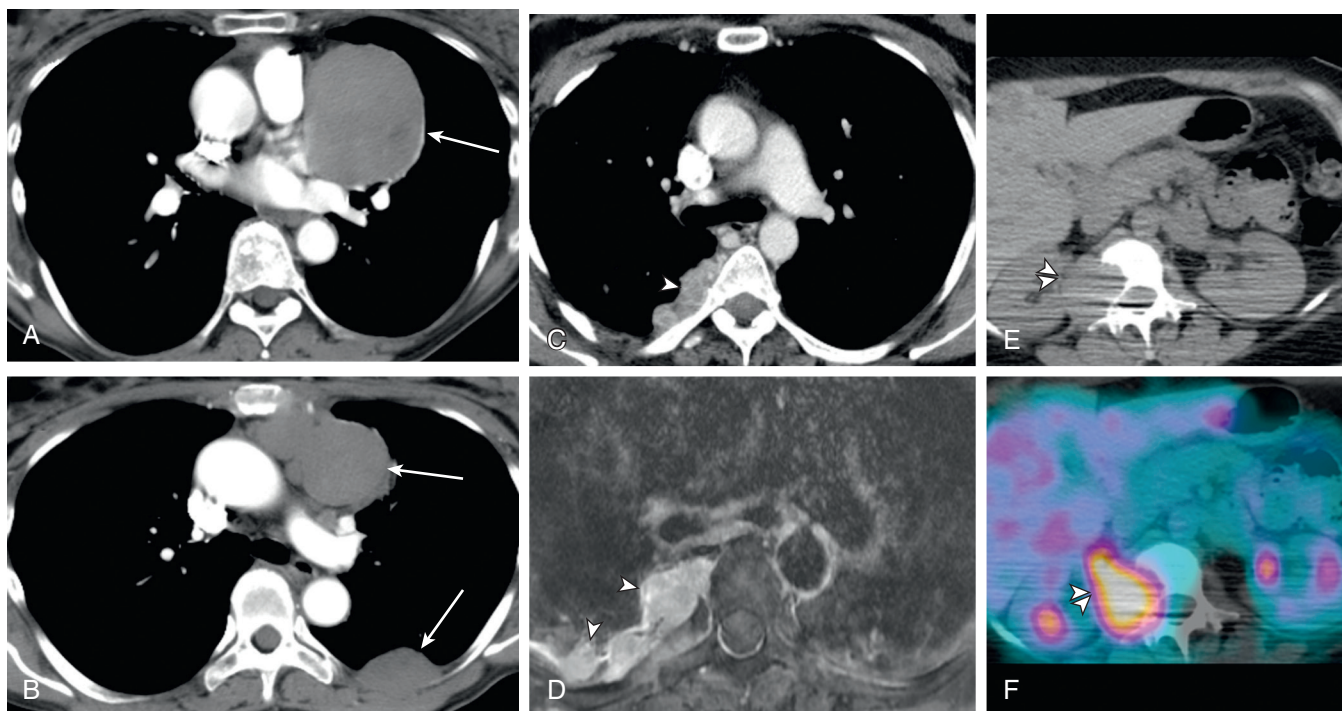


Figure 56-13 Malignant solitary fibrous tumor of the pleura. A and B, Axial contrast-enhanced chest CT displayed in soft tissue windows shows circumscribed and lobulated soft tissue masses (*arrows*) involving the mediastinal and posterior pleural surfaces, proven on biopsy to represent fibrous tumor of the pleura. Axial contrast-enhanced chest CT (C) and axial T2-weighted MRI (D) show lobulated soft tissue masses (*arrowheads*) related to the right mediastinal and posteromedial pleural surfaces, again reflecting fibrous tumor of the pleura. Axial unenhanced chest CT (E) and fused PET-CT image (F) show a metabolically active lesion involving L1, representing metastatic malignant fibrous tumor of the pleura. This patient originally had a right upper thoracic pleural fibrous tumor arising from the pleura resected in 1997. (Images courtesy Diego Ruiz, MD, Palo Alto Medical Clinic, CA.)

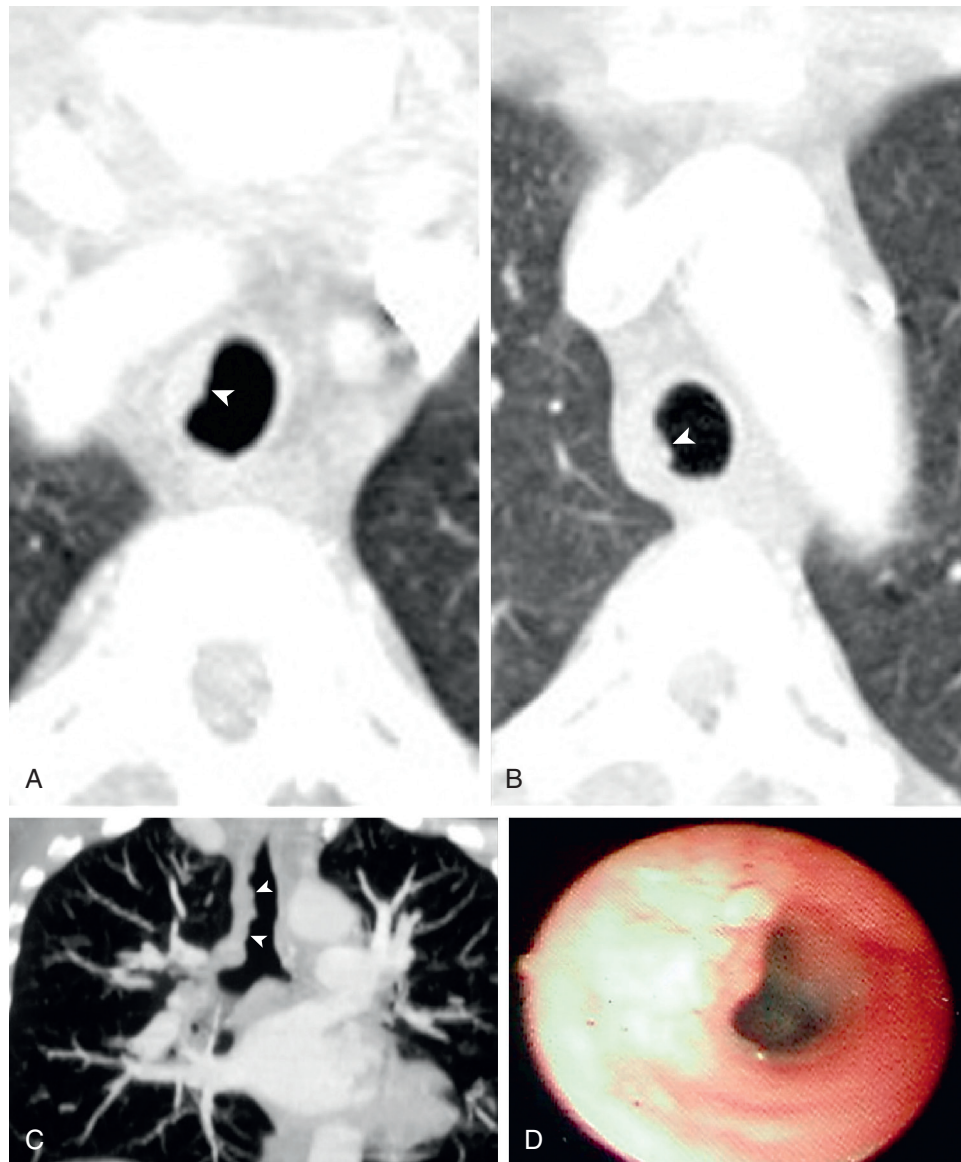


Figure 56-14 Granular cell tumor of the trachea. Axial enhanced chest CT (**A** and **B**) and coronal maximum intensity projection (**C**) performed as part of CT aortography in a patient with chest pain shows the incidental detection of a plaque-like lesion (*arrowheads*) along the right lateral tracheal wall. **D**, Bronchoscopic image shows a lobulated lesion corresponding to the CT abnormality. Biopsy proved malignant granular cell tumor. (**A–C**, Courtesy Michael Gotway, MD.)

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DISORDERS OF THE PULMONARY CIRCULATION

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PULMONARY THROMBOEMBOLISM

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INTRODUCTION

The one generalization about *venous thromboembolism* (VTE) that is free from controversy is that many aspects of this disorder remain controversial. There are multiple reasons why VTE continues to engender lively debate. Perhaps the major reason, notwithstanding the substantial advances that have been made since the late 1990s, is that a number of fundamental questions continue to exist regarding the pathogenesis, clinical presentation, diagnosis, and therapy of the disease.

VTE represents a potentially fatal disease process with a clinical presentation that is often silent or nonspecific and for which a wide range of diagnostic techniques is available, many with technical and interpretive limitations. Although estimates vary widely, the best available information suggests that there are at least 5 million episodes of venous thrombosis annually in the United States.¹ The annual incidence of acute *pulmonary embolism* (PE) is approximately 70 per 100,000,^{2,3} and PE accounts for more than 200,000 hospital admissions per year on the basis of discharge diagnosis (ICD-9) codes.⁴ These data, of course,

OTHER FORMS OF EMBOLISM

Schistosomiasis

Air Embolism

Fat Embolism

Amniotic Fluid Embolism

Septic Embolism

Other Emboli

represent only those patients in whom the diagnosis of acute PE was made correctly. Autopsy series suggest that the true number of deaths from acute PE (including those patients who died without the diagnosis ever being made) is at least threefold higher.⁵⁻⁸ For this reason, it is likely that the majority of PE-related deaths can be attributed to PE that was undiagnosed (and therefore untreated) during life.

Up to 10% of patients who suffer embolism may die from their disease.⁹ The overwhelming majority of these deaths do not appear to arise from therapeutic failure. With the exception of patients who initially present with hemodynamic impairment, in whom mortality rates approach 20% to 30%, embolic recurrence is rare and death is uncommon once the diagnosis of embolism is confirmed and appropriate therapy initiated.¹⁰ The majority of deaths related to embolism appear to arise from a failure to prevent the disease in patients at risk of it and from a failure to make the diagnosis in those afflicted.⁹ The incidence of fatal PE appears to have declined over the past several decades.^{11,12} For example, the Centers for Disease Control *Compressed Mortality File* (CMF) reported an age-adjusted death rate of 875/100,000 in 1999, which steadily decreased over the decade to 747/100,000 by 2010.¹³ It is noteworthy that these statistics do not account for fatal PE that was undiagnosed clinically, as described earlier. Balancing these facts are some data that suggest that the increasing reliance on chest *computed tomography* (CT) angiography may be leading to overdiagnosis of PE in some populations.¹⁴ Despite this controversy, mortality from acute PE remains a substantial public health care problem as a result of the demographics of an aging population.¹⁵

Contributing to the debate surrounding VTE is the involvement of a wide range of medical disciplines in its prevention, diagnosis, and management. Thrombosis is not a discrete clinical subspecialty. The problem of VTE involves pulmonologists, cardiologists, hematologists, internists, specialists in vascular disease, radiologists, a range of surgical subspecialists, obstetricians, and others. Because specific prophylactic, diagnostic, and therapeutic strategies within one discipline may not necessarily be applicable to another, a perception of coherence in the clinical approach to this disease process often appears to be lacking.

Many of the long-standing controversies surrounding the natural history, diagnosis, and therapy of VTE have been partially or completely reconciled, resulting in substantial changes in the diagnostic and therapeutic approach to the disease. The persistence of a number of unresolved issues, as well as the emergence of still others, should not be a cause for cynicism. In the approach to the patient with suspected VTE, an understanding of what is unknown can prove invaluable to the decision-making process.

PATHOGENESIS AND RISK FACTORS

The triad of venous stasis, alterations in coagulation, and vascular injury identified by Virchow in 1856 as primary factors in the pathogenesis of VTE has been supported by a considerable amount of clinical and experimental evidence. Over the past several decades, severe abnormalities of the

Table 57-1 Thromboembolic Risk Factors

HEREDITARY THROMBOPHILIAS

Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Factor V Leiden mutation
Prothrombin 20210 G → A variation
Hyperhomocysteinemia
Dysfibrinogenemia
Familial plasminogen deficiency

ACQUIRED SURGICAL PREDISPOSITIONS

Major thoracic, abdominal, or neurosurgical procedures requiring general anesthesia and lasting >30 min
Hip arthroplasty
Knee arthroplasty
Knee arthroscopy
Hip fracture
Major trauma
Open prostatectomy
Spinal cord injury

ACQUIRED MEDICAL PREDISPOSITIONS

Prior venous thromboembolism
Advanced age (>60 yr)
Malignancy
Congestive heart failure
Cerebrovascular accident
Nephrotic syndrome
Estrogen therapy
Pregnancy and the postpartum period
Obesity
Prolonged immobilization
Antiphospholipid antibody syndrome
Lupus anticoagulant
Inflammatory bowel disease
Paroxysmal nocturnal hemoglobinuria
Behçet syndrome

coagulation and fibrinolytic system, including isolated deficiencies of antithrombin III, protein C, protein S, and plasminogen, as well as the presence of a lupus anticoagulant, have been described and their association with first-time and recurrent VTE has been confirmed (Table 57-1).^{16,17} In addition, there has been increasing recognition of less severe, but more common, inherited “thrombophilic” conditions that are capable of shifting the hemostatic balance toward thrombosis and mildly increasing the risk of venous thromboembolic events. Although they also appear to increase the risk of recurrence slightly, the magnitude of the increase is unlikely to warrant changes in therapeutic strategies for patients with those thrombophilias.¹⁸

The most common of the inherited thrombophilic conditions, first described in 1993 by Dahlback and designated *factor V Leiden mutation*, is the consequence of a single point mutation in the factor V gene (adenine for guanine) resulting in activated factor V (factor Va) with diminished sensitivity to the natural anticoagulant effect of activated protein C.¹⁹ Approximately 5% of whites in Europe and North America are heterozygous for this genetic defect; lower rates of carrier frequency have been reported among Native American, African, and Asian populations.^{20,21} Although initially detected in up to 60% of selected patients with VTE, subsequent studies have detected the mutation in 10% to 20% of unselected patients.²² The heterozygous state carries a 5- to 10-fold increase in lifetime risk for VTE.^{23,24} Whereas

the relative risk among patients homozygous for this mutation has been estimated to be as high as 80-fold, the estimates are based on a small number of patients and may be somewhat imprecise.^{23,24} Factor V Leiden mutation appears to be an important risk factor for VTE during pregnancy, in the postpartum period, and during oral contraceptive use.^{25,26} Compared with women who do not use oral contraceptives and are not carriers of the factor V mutation, the risk of thrombosis among those with both risk factors is increased approximately 30-fold.²⁷ In view of the prevalence of thrombophilia and the low prevalence of VTE in nonusers of combined oral contraceptives, the absolute risk remains low. Because the absolute increase in VTE is modest, selective thrombophilia screening based on previous personal or family history of VTE is more cost-effective than universal screening.

A sequence variation in the prothrombin gene (G20210A) was described in 1996 and is estimated to exist in approximately 2% to 4% of the population.²⁸ This mutation results in an overproduction of prothrombin, which is otherwise normal. It is associated with a threefold to fourfold increased risk of lower extremity venous thrombosis.^{28,29}

Hyperhomocysteinemia has also been identified as a potential independent predisposition to VTE. Elevation of plasma homocysteine levels may be the result of genetic abnormalities; nutritional deficiencies of vitamins (B₆, B₁₂, folate); clinical disorders (renal insufficiency, hypothyroidism, inflammatory bowel disease); or a combination of the three. Although retrospective, case-control studies demonstrate an association between hyperhomocysteinemia and VTE, the results of prospective studies have not been uniform.^{30,31}

The three “common genetic thrombophilias” (factor V Leiden, prothrombin G20210A, and hyperhomocysteinemia) appear to act as independent risk factors for increasing thrombosis risk.^{32,33} Thus, the relative risk for patients with multiple thrombophilic conditions is higher than for patients with only one of them.

The identification of these risk factors, and the likelihood that others exist, raises the possibility that screening to determine relative thromboembolic risk may be feasible in the future. However, a consensus for such an approach does not exist at the present time. Despite its prevalence in the general population, screening for factor V Leiden mutation is not advised because the overwhelming majority of patients with this abnormality will never suffer a thromboembolic event. Furthermore, the absence of this abnormality should not influence the decision to provide prophylaxis to patients at clinical risk. In addition, there is no evidence that prolonged anticoagulation would be more beneficial for VTE patients with either factor V Leiden³⁴ or the prothrombin G20210A gene³⁵ than in VTE patients without these mutations.¹⁸

Patients with spontaneous (“unprovoked”) VTE who have *both* factor V Leiden and the prothrombin G20210A gene³⁵ appear to be at somewhat higher risk for recurrence than similar patients without those mutations. This observation does not establish a risk-benefit relationship for prolonged anticoagulation in patients with the combination of thrombophilic mutations, which remains unknown.

For all the reasons stated previously, the benefit of screening for the common thrombophilias is controversial. Patient

groups in whom screening is likely to yield positive results include those with a history of recurrent VTE or with a confirmed family history of thromboembolism, a first episode of thromboembolism at an early age, spontaneous venous thrombosis, thromboses in unusual anatomic sites, arterial thrombosis, and thromboembolism associated with pregnancy^{36,37} or estrogen use. Whether screening should be performed before the initiation of oral contraceptive agents remains a matter of debate.^{38,39} The relative risk of VTE is increased approximately fourfold in users of oral contraceptives, although the increase in absolute risk is modest.^{27,40} A policy of routine screening would deny effective contraception to a substantial number of women while preventing only a small number of PEs. A similar situation exists for pregnancy, in which the presence of factor V Leiden or the prothrombin G20210A mutation increases the relative risk of VTE but only slightly increases the absolute risk.³⁷

In most patients, even those with an identified thrombophilic state, clinical conditions associated with venous stasis, intimal injury, or both serve as the basis for the thromboembolic event.⁴¹ Furthermore, the risk of VTE in hospitalized patients is not limited to patients undergoing surgical procedures. Thromboembolic risk in patients admitted with a wide range of acute medical problems is comparable with that seen in surgical patients.⁴²⁻⁴⁴

Major risk factors include pelvic or lower extremity fractures, hip and knee surgery, a past history of VTE, acute paralytic stroke or spinal injury, major traumatic injury, open prostatectomy, and abdominal or pelvic surgery for malignant disease. Other factors that enhance risk include prolonged general anesthesia, advancing age, cardiac disease, pregnancy,³⁶ the postpartum state, the use of estrogen-containing hormone replacement therapy,⁴⁵ malignancy, nephrotic syndrome,⁴⁶ the presence of a lupus anticoagulant or antiphospholipid antibody, and prolonged immobilization.⁴⁷ Air travel is a relatively modest risk factor,⁴⁸ as is the presence of inflammatory bowel disease.⁴⁹ It is important to recognize that these risk factors may be multiplicative.^{37,41} Thromboembolic risk in an otherwise healthy 45-year-old individual undergoing an elective cholecystectomy is considerably less than the risk experienced by an obese 75-year-old with a history of prior VTE undergoing the same procedure. Similarly, the patient with hip fracture or hip replacement has, by virtue of that condition alone, a 60% to 70% risk of *deep venous thrombosis* (DVT) and a 2% to 4% risk of experiencing a fatal thromboembolic event in the absence of preventive measures. Add other risk factors, as well as the incidence of DVT, and the likelihood of a fatal complication will be even higher. These considerations allow the development of a reasonable “risk profile” in an individual patient, a profile that should influence the use and intensity of prophylactic intervention.⁴¹

NATURAL HISTORY: DEEP VENOUS THROMBOSIS

Venous thrombi appear to originate either in the vicinity of a venous valve cusp, where eddy currents arise, or

at the site of intimal injury.⁵⁰ Platelet aggregation and release of mediators initiate the sequence. With local accumulation of such factors, the coagulation cascade is activated and thrombus develops, composed primarily of fibrin and erythrocytes. As the thrombus extends, local fibrinolytic activity is enhanced. Thus thrombus behavior becomes a dynamic process that may result in complete dissolution, partial resolution resulting in a variable degree of intimal narrowing and valvular damage, progressive proximal extension, or embolization. In more than half of patients, the venous wall suffers some degree of permanent scarring, which is visible on ultrasound⁵¹; if the venous wall scarring causes severe obstruction, collateral veins develop.

Extensive autopsy and clinical studies have established that some 90% of PEs that elicit clinical attention arise from venous thrombosis in the deep veins of the lower extremities.⁵² In fact, a conservative estimate is that at least one third of deep venous thrombosis is complicated by symptomatic or asymptomatic PE.⁵³ Venous thrombi capable of embolization can also arise from other sites. Primary iliac or proximal femoral thrombi may develop in patients undergoing surgery involving the hip, and pelvic vein thrombosis may develop in patients undergoing pelvic or prostatic surgery. Axillosubclavian vein thrombosis may be spontaneous, resulting from congenital abnormalities of the thoracic outlet, or may be related to indwelling central venous catheters, pulmonary artery catheters, or transvenous pacing wires.^{54,55} Increasing use of central venous catheters has been implicated in a rise in the incidence of upper extremity deep venous thrombosis.⁵⁶ In patients with dilated right heart chambers or pulmonary arteries, thrombi can form at those sites and embolize distally into the branches of the pulmonary artery.

The likelihood of embolism is influenced by the location of thrombi in the veins of the lower extremity. Although the majority of thrombi originate in the veins of the calf, it has been clearly demonstrated that thrombi that remain limited to the calf veins rarely result in PE.⁵⁷ However, 15% to 25% of symptomatic, isolated calf thrombi when left untreated will extend to involve the proximal veins (popliteal, superficial femoral, and common femoral veins, or even more proximally).^{58,59} (It is worth emphasizing that the superficial femoral vein is actually not superficial and represents one of the deep veins.⁶⁰) Proximal extension poses a risk of embolization that approaches 50%.^{61,62} For that reason, about one in eight patients with distal deep vein thromboses will develop PE.⁵³

This natural history of DVT has several important diagnostic and therapeutic implications. First, because the vast majority of emboli arise from thrombi in the veins in the lower extremity, diagnostic approaches to DVT can focus on techniques that detect lower extremity DVT. Second, techniques that detect above-knee thrombi are of particular value whether or not they can detect calf-limited thrombi. Finally, although it is true that calf-limited thrombi rarely embolize, many have incorrectly concluded from this information that *symptomatic*, calf-limited DVT represents a clinically irrelevant condition. Calf-limited thrombi may extend proximally. Furthermore, symptomatic calf vein thrombosis appears to be subject to recurrence, albeit at a lower risk than proximal vein thrombosis.^{59,63}

Although most above-knee thrombi represent extensions from calf thrombi, some do arise in the larger, proximal veins *de novo*. This appears to be restricted principally to patients with hip fracture or replacement, pelvic surgery (including prostatic resection), and other high inguinal pelvic trauma.

At any time during this process, a portion or all of the thrombus can detach as an embolus. This risk is highest early in thrombus development before there is significant fibrinolysis or organization. Beyond this acute phase, the long-term outlook is influenced principally by the extent of residual venous obstruction and valvular damage. If significant obstruction or valvular damage persists, downstream stasis will be present, leading to a risk of recurrent DVT and development of the postphlebotic syndrome.^{64,65}

NATURAL HISTORY: PULMONARY EMBOLISM

PE causes a number of consequences to gas exchange and other pulmonary functions.⁶⁶ Regional obstruction to pulmonary blood flow and diversion of the flow to unobstructed portions of the lung may alter the ventilation-perfusion balance in both the obstructed and unobstructed regions.^{67,68} In the regions with pulmonary vascular obstruction, alveolar dead space is created.⁶⁹ If a region's blood flow is severely obstructed, there may be bronchoconstriction in the lung distal to the area of obstruction as a result of alveolar hypocapnia.⁷⁰ This is probably uncommon in patients because they are free to inhale carbon dioxide-rich dead-space air into the associated lung regions and because obstruction is rarely total. PE almost always leads to hyperventilation, the mechanism for which remains uncertain.

The characteristic gas exchange abnormality is hypoxemia, generally caused by the venous admixture due to areas of low ventilation/perfusion ratio or of shunt. Arterial hypoxemia may be worsened when acute increases in right ventricular afterload lower the cardiac output enough to widen the arteriovenous oxygen difference and decrease the oxygen saturation of mixed venous blood.⁷¹ This lowering of the mixed venous oxygen content magnifies the effects of the normal venous admixture, thereby further lowering the resultant arterial oxygen pressure (PO_2). Another potential mechanism for hypoxemia in patients with massive PE is right-to-left shunt, on either an intrapulmonary or intracardiac basis.⁷² With embolic occlusion sufficient to increase pulmonary artery pressure, hypoxic vasoconstrictive mechanisms can be overwhelmed and perfusion may increase in poorly ventilated or nonventilated lung regions. On occasion, embolic events massive enough to increase right atrial pressure may result in intracardiac right-to-left shunting through a patent foramen ovale. The final mechanism for hypoxemia relates to the loss of pulmonary surfactant.⁷³ Surfactant is not lost immediately; it requires approximately 24 hours of total occlusion and lack of blood flow to develop. At that time or later, surfactant becomes depleted in the obstructed alveolar zones, resulting in atelectasis and edema. If the thrombus resolves and perfusion to this atelectatic region resumes, hypoxemia may result.

One uncommon local consequence of PE is pulmonary infarction. Infarction is uncommon because the pulmonary parenchyma has three potential sources of oxygen: the pulmonary arteries, the bronchial arteries, and the conducting airways.⁷⁴ In patients with no coexisting cardiopulmonary disease, large infarctions (such as those visible by chest radiography) are rare.^{75,76} However, autopsy series suggest that infarctions of smaller pulmonary arteries are more common.^{77,78} Infarction develops in approximately 20% to 33% of patients with significant cardiac or pulmonary disease that compromises either bronchial arterial flow or airway patency. In patients with left ventricular failure, infarction may result if the increased pulmonary venous pressure compromises bronchial flow.⁷⁹

The cardiac and hemodynamic effects of embolism are related to three factors: the degree of reduction of the cross-sectional area of the pulmonary vascular bed, the preexisting status of the cardiopulmonary system, and the physiologic consequences of both hypoxic-mediated and neurohumorally mediated vasoconstriction.⁸⁰⁻⁸⁵ Mechanical obstruction of the pulmonary vascular bed by embolism accounts for most of the increase in *pulmonary vascular resistance* (PVR), although resistance is typically worsened by release of vasoconstrictive substances such as endothelin, thromboxane A₂, and serotonin.^{86,87} The combination of factors acutely increases the workload on the right ventricle, a chamber ill-equipped to deal with an acute elevation in pressure load. In patients without preexisting cardiopulmonary disease, obstruction of less than 20% of the pulmonary vascular bed results in a number of compensatory events that minimize adverse hemodynamic consequences. Pulmonary vessels are recruited and become distended, resulting in a normal or near-normal PVR and pulmonary artery pressure; cardiac output is maintained by increases in the right ventricular stroke volume and increases in the heart rate. As the degree of pulmonary vascular obstruction exceeds 30% to 40%, there are increases in pulmonary artery pressure and modest increases in right atrial pressure. The Frank-Starling mechanism maintains right ventricular stroke work and cardiac output. When the degree of pulmonary artery obstruction exceeds 50% to 60%, compensatory mechanisms are overwhelmed, cardiac output begins to fall, and right atrial pressure increases dramatically. With acute obstruction beyond this amount, the right heart dilates, right ventricular wall tension increases, right ventricular ischemia may develop, the cardiac output falls, and systemic hypotension develops. Hypotension worsens the situation by decreasing the coronary perfusion pressure to the already tense right ventricle.⁸⁸ In patients without prior cardiopulmonary disease, the maximal mean pulmonary artery pressure that can be generated by the right ventricle appears to be 40 mm Hg (representing a pulmonary artery systolic pressure of ≈ 70 mm Hg). The correlation between the extent of pulmonary vascular obstruction and PVR appears to be hyperbolic; with increasing vascular obstruction, PVR rises slowly as the remaining pulmonary vascular bed expands and recruits additional vessels and then rises rapidly when that reserve is exhausted.⁸⁹

The hemodynamic response to acute PE in patients with preexisting cardiopulmonary disease may be considerably different from that in patients without prior disease.⁸⁵ In

patients without prior cardiopulmonary disease, there is a general relationship between the rise in pulmonary artery pressure and the pulmonary vascular obstruction, whereas in patients with prior cardiopulmonary disease, pulmonary artery pressures may rise disproportionately. As a result, severe pulmonary hypertension may develop in response to a relatively small reduction in pulmonary artery cross-sectional area. In addition, evidence of right ventricular hypertrophy (rather than right ventricular dilation) associated with a mean pulmonary artery pressure in excess of 40 mm Hg (pulmonary artery systolic pressure in excess of ≈ 70 mm Hg) in a patient suspected of embolism should suggest an element of chronic pulmonary hypertension resulting from a potentially diverse group of etiologic possibilities (e.g., chronic thromboembolic pulmonary hypertension, left ventricular failure, valvular disease, right-to-left cardiac shunts).

Beyond the acute embolic event, the behavior of emboli parallels that previously described for venous thrombi; that is, they undergo resolution by fibrinolysis, by organization and recanalization, or both. Although there is a great deal of interpatient variability, resolution of PEs typically is substantial during the first week, somewhat more gradual for the next 4 to 8 weeks, and then slow thereafter.^{69,90-95} (The most rapid resolution of a large embolus that has been documented is 51 hours.⁹⁶) The term *resolution* is used here because it is uncertain, in humans, to what degree lysis (versus organization) participates in embolic resolution. Most sequential data regarding resolution in humans are based on perfusion scan, not angiographic, data. However, these data suggest that residual anatomic defects are common following embolism and, contrary to prior opinion, that complete restoration of pulmonary blood flow represents the exception rather than the rule.^{69,90-95} In terms of hemodynamic resolution, it would appear that a stable pulmonary artery pressure is reached within 6 weeks.⁹⁷ How often anatomic and mild hemodynamic residuals persist is not known. Nearly one third of patients with acute PE may have residual perfusion defects, which may be associated with a spectrum of symptoms including dyspnea, lower exercise tolerance, and higher pulmonary arterial pressures of various intensities.⁹⁸ However, residual obstruction sufficient to cause clinically significant pulmonary hypertension is rare. For this small group of patients with significant residual obstruction, the clinical course and management are dealt with later in this chapter.

CLINICAL PRESENTATION

The most common symptoms and physical findings of venous thrombosis include swelling, pain, erythema, and warmth. "Classic" findings such as *Homan sign* (calf pain with flexion of the knee and dorsiflexion of the ankle), *Moses sign* (pain with calf compression against the tibia), or a palpable cord are infrequent and nonspecific.

As established by multiple investigations, the clinical diagnosis of venous thrombosis is imprecise.^{52,99-102} In patients with clinical signs and symptoms suggestive of venous thrombosis, 60% to 80% will not have the diagnosis by objective testing. Furthermore, and even more disquieting, the majority of high-risk patients who are

monitored and who develop DVT will not have signs or symptoms suggesting the diagnosis.¹⁰³ Algorithmic clinical models incorporating risk factors, symptoms, and physical signs have been demonstrated to have the ability to stratify *symptomatic* patients into risk categories, although not to a level in which clinical diagnosis, in the absence of objective testing, can be relied on either to confirm or exclude the diagnosis.^{101,104} The differential diagnosis of DVT is extensive and includes cellulitis, arthritis, muscular injury or tear, neuropathy, arterial insufficiency, lymphedema, ruptured Baker cyst, superficial thrombophlebitis, and chronic venous insufficiency.

Similarly, the diagnosis of PE cannot be confirmed or excluded solely on clinical grounds.¹⁰⁵⁻¹⁰⁷ However, recognition of the clinical signs and symptoms associated with PE is valuable because clinical findings and clinical suspicion represent an essential first step in the diagnostic pathway. Although a somewhat arbitrary classification because presenting symptoms and signs of embolism frequently overlap, the presentation of PE can be categorized into one of three clinical syndromes: (1) isolated dyspnea; (2) pleuritic pain or hemoptysis; and (3) circulatory collapse.¹⁰⁸ Among patients without prior cardiopulmonary disease in the *Prospective Investigation of Pulmonary Embolism Diagnosis* (PIOPED) study, the syndrome of pleuritic pain or hemoptysis was the most common mode of presentation, seen in approximately 60% of patients; isolated dyspnea was noted in approximately 25%, and circulatory collapse in 10%.

The most common presenting symptom of acute embolism is the sudden onset of dyspnea.¹⁰⁷⁻¹⁰⁹ In various studies, dyspnea was a presenting symptom in the majority of patients. However, it must be emphasized that, in the PIOPED study,¹⁰⁹ dyspnea was not present in 27% of patients ultimately proven to have embolism. Pleuritic chest pain was present in 66% of patients, whereas hemoptysis (15%) was uncommon. Less than 50% of patients had cough (37%), leg swelling (28%), and leg pain (26%). A sense of impending doom also is reported, particularly with massive embolism. Angina also can result from massive embolism representing, in this circumstance, right ventricular ischemia. Syncope also may be a presenting complaint in major embolic occlusion.

The most common physical finding is tachypnea (respiratory rate >20/min). In the PIOPED study,¹⁰⁹ however, tachypnea was not present in approximately 30% of patients with embolism. Clinical findings noted less frequently include crackles (55%), tachycardia (30%), and an increased pulmonic component of the second heart sound (S2; 23%). Fever may develop some hours after the event and often reaches but rarely exceeds 38.3° C. As noted previously, hemoptysis may be observed; it usually is quite modest in extent, although it may persist for some days. Brisk hemoptysis is rare and is almost never the initial finding. With massive embolism, there may be evidence of right ventricular overload or failure, such as a right ventricular tap along the left sternal border and an accentuated pulmonary valve closure sound. If right ventricular failure develops, there may be narrowed or fixed splitting of an S2, an S3, and/or an S4, distended neck veins, and cyanosis. Careful examination of the legs may elicit evidence suggesting venous

thrombosis. In the PIOPED study,¹⁰⁹ clinically apparent venous thrombosis was found in only 15% of patients.

Obviously, these symptoms and signs are nonspecific. In the PIOPED study,^{108,109} none of the presenting symptoms was capable of discriminating between patients with positive and negative angiograms. Also, in terms of presenting signs, only the presence of crackles, an S4, and an increased pulmonic component of S2 could differentiate between those with positive and negative angiograms.^{108,109} Furthermore, in patients with underlying cardiopulmonary disease, the presenting symptoms and signs frequently may be obscured by elements of the underlying illness.¹⁰⁶ It is also important to recognize that the clinical presentation of embolism has been characterized in trials composed of *symptomatic* patients, although it is known that many PE do not produce symptoms. In prospective studies of high-risk patients with proximal DVT, PE can be documented in 40% of patients who had no symptoms of PE.^{61,105,110} It is likely that the frequency and severity of symptoms are influenced by the extent of embolic occlusion and the prior cardiopulmonary status of the patient. Small- or moderate-sized emboli may induce few or no symptoms in an otherwise normal individual. In patients with preexisting cardiopulmonary disease, symptoms are more common and severe.¹¹¹

Owing to the nonspecific presentation of PE, the differential diagnosis is varied and extensive, especially in hospitalized patients with coexisting cardiac or pulmonary disease. Common considerations include congestive heart failure, exacerbation of chronic lung disease, postoperative atelectasis, and viral pleurisy. PE presenting with fever, dyspnea, and chest radiographic abnormalities easily can be confused with a bacterial pneumonia. The presence of fever and leukocytosis (rarely >15,000 cells/μL) are uncommon but well-described accompaniments of VTE.^{112,113}

These precautionary statements regarding clinical diagnosis are not meant to suggest that the clinical presentation of venous thrombosis or PE cannot be used as a basis for clinical decision making. However, they are meant as a reminder that the clinical presentation of VTE and PE may often be atypical or subtle and should serve only to generate a suspicion of that diagnosis. A reliance on symptoms and signs that are considered “classic” before making the decision to proceed to confirmatory testing may lead to underdiagnosis and unnecessary mortality.

DIAGNOSIS OF VENOUS THROMBOSIS

The proper diagnostic approach to VTE must take into account the central fact that venous thrombosis and PE are manifestations of the same disease process: venous thrombosis representing the source of PE and PE representing a complication of venous thrombosis.

CONTRAST VENOGRAPHY

In validating any test, there must be a “gold standard.” In the case of lower extremity venous thrombosis, that

standard is contrast venography (Fig. 57-1). In investigative contexts, it is a good gold standard (as indicated later, however, that often is not the case in clinical contexts). The venogram is performed according to a specific protocol described by Rabinov and Paulin in 1972.¹¹⁴ The most reliable criterion for the diagnosis of venous thrombosis is a constant intraluminal filling defect evident in two or more

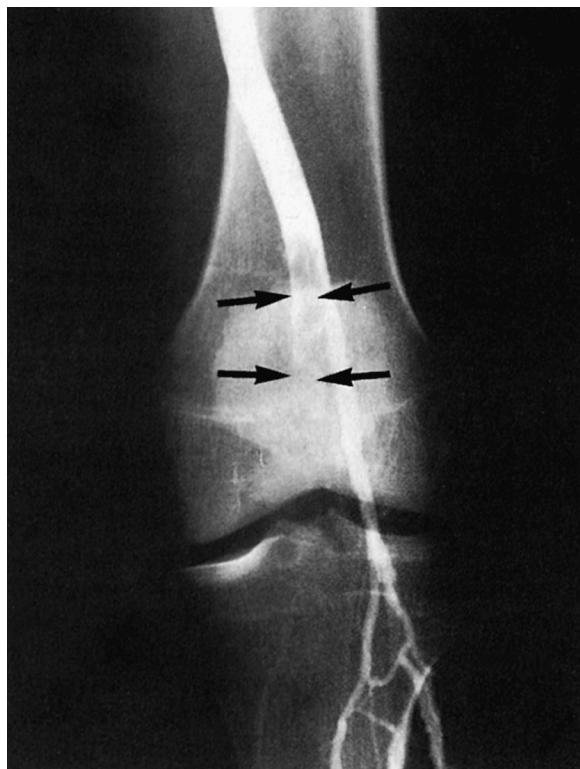


Figure 57-1 Venography for DVT. Contrast venogram shows a large filling defect (arrows) due to thrombus in the popliteal and distal superficial femoral veins. Such thrombi pose substantial embolic risk.

views. Other criteria such as nonvisualization of deep veins, presence of venous collaterals, or nonconstant filling defects are less reliable. Under circumstances in which the proper protocol and interpretative criteria are utilized, contrast venography has high sensitivity and specificity. However, the study is not without shortcomings. As those who have seen many venograms recognize, the study is not easy to interpret, especially in patients with a prior history of venous thrombosis. Venous cannulation may often be difficult, especially in the presence of edema; expert interpretation is essential for accurate diagnosis; injection of contrast material with its associated allergic and nephrotoxic risks is necessary; venous thrombosis may be induced by the procedure itself; and the cost, invasive nature, and discomfort of the study make sequential studies impractical.

Owing to these limitations, a number of noninvasive studies capable of being performed on a sequential basis were introduced into clinical practice. At present, duplex ultrasonography is the most commonly used noninvasive technique. *Magnetic resonance imaging* (MRI) and CT have proved capable of detecting thrombi, but their widespread utilization has been limited by cost, limited access, and, in the case of CT, the need for contrast administration.

DUPLEX ULTRASONOGRAPHY

Since the late 1990s, duplex ultrasonography, which refers to the combination of Doppler venous flow detection and real-time B-mode imaging, has assumed a central role in the noninvasive diagnosis of symptomatic lower extremity DVT.¹¹⁵ A number of criteria are used to diagnose venous thrombosis, the most reliable of which is the noncompressibility of a venous segment (Fig. 57-2). Secondary, less reliable criteria include the presence of echogenic material within the venous lumen (eFig. 57-1), venous distention, and loss of phasic change with respiration, lack of response at the *common femoral vein* (CFV) to Valsalva maneuver,

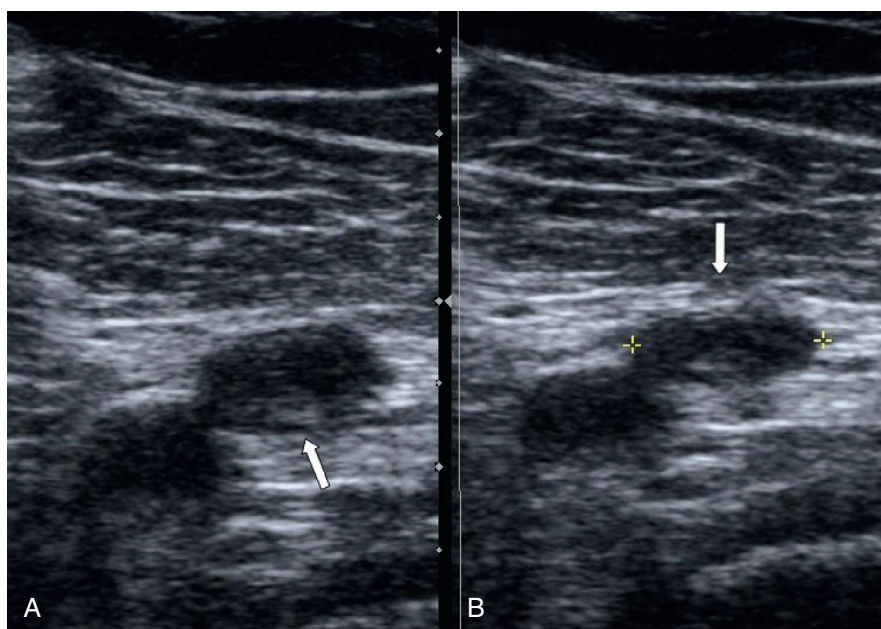


Figure 57-2 Compression ultrasonography for DVT. A, Rest and B, compression duplex ultrasonography demonstrates a noncompressible distal superficial femoral vein containing an echogenic mass (arrows), consistent with venous thrombosis.

diminished or absent color flow with color Doppler sonography (eFig. 57-2), and lack of augmentation of flow at the CFV with compression of the calf. The two signs showing a lack of increase in flow, either with Valsalva or with calf compression, can indicate obstruction of veins between the site of increased pressure and the measured vein. The absence of an echogenic luminal mass cannot be considered useful in excluding the diagnosis of venous thrombosis because acute thrombus may not demonstrate echogenicity (eFig. 57-3).

Multiple studies since the late 1990s have demonstrated sensitivities and specificities exceeding 95% in *symptomatic* patients with proximal venous thrombosis. Although simplified compression examinations limited to the symptomatic leg or to the common femoral and popliteal veins (rather than the entire lower extremity venous system) have been suggested, the time saved with such approaches is limited, and a number of isolated superficial femoral vein or calf-limited thrombi may be overlooked.¹¹⁶⁻¹¹⁸ Asymptomatic thrombi in the contralateral leg can be detected in approximately 5% to 10% of patients presenting with symptomatic acute venous thrombosis.¹¹⁹ Although the detection of asymptomatic, contralateral thrombi has little impact on the immediate management of the patient, it may have long-term consequences when recurrence is suspected. A more prudent approach appears to be a complete examination extending from the inguinal ligament to the popliteal vein and examination of the contralateral extremity if thrombus is detected in the symptomatic leg.

Duplex ultrasonography is less accurate in the detection of symptomatic calf-limited thrombi (sensitivity \approx 70%) and in asymptomatic proximal vein thrombi (sensitivity \approx 50%), thereby limiting its utility as a screening study in high-risk populations.¹²⁰ When ultrasonography is negative in patients with suspected venous thrombosis, a strategy of *serial* testing, consisting of one or two additional tests over the subsequent week, has proved to be effective in detecting proximal extension.¹²¹

MAGNETIC RESONANCE IMAGING

MRI techniques for detecting venous thrombosis include spin-echo magnetic resonance, gradient-recalled-echo magnetic resonance, and magnetic resonance venography. Preliminary reports suggest that MRI is at least as sensitive and specific as duplex ultrasonography.^{122,123} A potential advantage of MRI is that the entire length of the venous system, including the pelvic veins, can be evaluated. Disadvantages associated with MRI include cost and limited access, as well as the expertise required to perform and interpret the studies properly.

COMPUTED TOMOGRAPHY

The role of CT as a stand-alone test for venous thrombosis is limited. The sensitivity and specificity of CT venography are comparable with those of ultrasonography but mandate contrast injection with its associated risks and radiation exposure. Potential advantages of CT venography include the ability to visualize the pelvic veins (eFig. 57-4) and vena cava (eFig. 57-5). A diagnostic approach combining CT venography with *CT pulmonary angiography* (CTPA) may

have a role in patients undergoing evaluation for PE (see later).^{124,125}

HEMOSTASEOLOGIC ASSAYS

The development of a rapid and accurate blood test capable of diagnosing VTE has held special appeal and has been the subject of considerable investigative interest. A number of different serologic markers have been investigated, including D-dimer, fibrin monomer, prothrombin fragment, thrombin–antithrombin III complex, fibrinopeptide B, and fibronectin. Of these, D-dimer, alone and in combination with other noninvasive studies, has been subjected to the most rigorous clinical evaluation.^{126,127} D-dimer testing has proved to be highly sensitive but not specific; that is, elevated levels are present in nearly all patients with thromboembolism but also in a wide range of circumstances, including advancing age, pregnancy, trauma, infections, the postoperative period, inflammatory states, and malignancy. Therefore the role of D-dimer testing is limited to one of exclusion of VTE. Multiple assays have been developed with sensitivities that range from 80% to almost 100%.¹²⁶⁻¹²⁸ Highly sensitive assays, such as the enzyme-linked immunosorbent assay, are capable of excluding thromboembolism but are associated with such a high frequency of false-positive results that their clinical utility is limited.

Less sensitive assays (e.g., latex agglutination, red cell agglutination) lack the ability to exclude thromboembolism in isolation but have been used successfully in combination with either a clinical probability estimate or a noninvasive diagnostic study. Although potentially of substantial value in diagnostic pathways, the burgeoning selection of available assays, variations in sensitivity and specificity related to the type of assay, a range of discriminate values for positivity, and lack of standardization have limited generalized application of the technique due to uncertainty among clinicians regarding the predictive value of the particular test they are using. D-dimer testing has been used successfully as part of a number of different diagnostic strategies, and negative results of standardized, highly sensitive assays have proved capable of safely excluding venous thrombosis in outpatients presenting with a low or intermediate clinical likelihood of the disease.^{129,130}

CLINICAL PREDICTION RULES

A major advance in the diagnostic approach to both venous thrombosis and PE has been a transition from a technique-oriented approach to one that utilizes Bayesian analysis. In this strategy, the pretest probability of the disease, calculated independently of a particular test result either through empirical means or through a standardized prediction rule, is evaluated in combination with a test's likelihood ratio (derived from the sensitivity and specificity of that test) to create a posttest probability of the disease. This posttest probability can then be utilized as a basis for clinical judgment, either excluding the disease with a certain level of probability, confirming the disease with a certain level of probability, or supporting the need for additional diagnostic testing. This approach to diagnosis has proved especially useful in an era of noninvasive testing in which results are

often presented as probabilities rather than as discrete answers.

Several clinical prediction rules for venous thrombosis have been developed and validated.¹³¹ The Wells rule, initially described in 1995 and revised subsequently to include nine clinical features, proved capable of stratifying patients with suspected venous thrombosis into three probability categories—low, moderate, and high—in which the incidence of venous thrombosis approximates 3%, 17%, and 75%, respectively.¹³² By utilizing this prediction rule in combination with lower extremity ultrasonography, the diagnosis of venous thrombosis can be safely excluded in patients with a low clinical likelihood of venous thrombosis in combination with a negative lower extremity ultrasound and confirmed in patients with a high clinical probability and a positive lower extremity ultrasound. Such an approach dramatically reduces the need for contrast venography or serial lower extremity ultrasound studies.

The Wells prediction rule was again revised to include 10 clinical characteristics capable of stratifying outpatients into “clinically likely” and “clinically unlikely” categories (Table 57-2). For outpatients falling into the clinically unlikely category, DVT was reliably excluded when the result of a sensitive D-dimer assay was negative, thereby limiting the need for ultrasound evaluation.¹³⁰ The ability to exclude venous thrombosis in outpatients using a clinical prediction rule and negative results of a D-dimer assay has been confirmed in other studies.¹³³ It should be emphasized that clinical prediction rules constructed and validated in outpatients should be viewed critically before they are applied to an inpatient population.

Table 57-2 Wells Clinical Model for Predicting the Pretest Probability of Deep Venous Thrombosis

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep venous thrombosis	1
Alternate diagnosis at least as likely as deep venous thrombosis	-2
Score	Clinical Assessment Probability
<2 points	Unlikely
≥2 points	Likely

From Wells PS, Anderson DR, Rodger M, et al: Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. *N Engl J Med* 349:1227–1235, 2003.

DIAGNOSIS OF PULMONARY EMBOLISM

Certain parallels between the approaches to the diagnosis of DVT and PE exist. Perhaps the most important parallels are that clinical evidence in isolation, although capable of raising the suspicion of the disease, cannot be relied on to confirm or exclude the diagnosis and that the use of clinical prediction rules in combination with noninvasive testing can substantially decrease the need for invasive diagnostic testing.

STANDARD LABORATORY EVALUATION

Routine laboratory studies cannot make the diagnosis of PE. Although none have the discriminatory power to confirm the diagnosis of embolism, they do provide valuable adjunctive information and support for therapeutic interventions and may confirm the presence of an alternative diagnosis.

The majority of patients with PE have abnormal chest radiographs.¹³⁴ However, these abnormalities are usually subtle, nonspecific, and therefore nondiagnostic (Fig. 57-3). In the PIOPED study,¹⁰⁹ the most common radiographic abnormalities were atelectasis and pulmonary opacities. There is some confusion about the diagnostic configuration of radiographic abnormalities due to embolism. Although usually abutting a pleural surface, the opacities can be of any shape, not necessarily wedge-shaped (eFig. 57-6). Although pleural effusions are seen in almost half of the patients, the majority of effusions are small and involve only blunting of the costophrenic angle.¹⁰⁷ Findings once considered specific for embolism, such as the *Westermarck sign* (focal areas of avascularity, eFig. 57-7), the *Hampton hump* (pleural-based, wedge-shaped opacity, eFig. 57-8), and the *Fleischner sign* (prominence of the central pulmonary artery, eFig. 57-9), have not proved to have discriminatory value. In a patient with hypoxemia or pulmonary complaints, a normal chest radiograph may be quite useful in raising the index of suspicion of embolism and in excluding confounding diagnostic options. The major roles of chest radiography in suspected PE, therefore, are to exclude competing diagnoses and, if ventilation-perfusion (V/Q) scanning is anticipated, to evaluate the pulmonary parenchyma.

Likewise, electrocardiographic findings in PE, although common, are diverse and nonspecific.¹³⁵ The most common abnormalities include nonspecific tachycardia, T wave inversion, and abnormalities of the ST segment. With more extensive occlusion, the electrocardiogram may reveal the more “classic” findings of right heart strain, including an “S₁Q₃T₃” pattern, a pseudoinfarction pattern (Qr in V₁), a complete or incomplete right bundle-branch block, or right axis deviation.^{135,136} Rhythm disturbances other than sinus tachycardia are uncommon and usually confined to patients with underlying cardiac disease.¹³⁵

Arterial blood gas analysis is helpful, although not definitive.¹³⁷ Arterial hypoxemia may be present, and the more massive the obstruction, the more severe the hypoxemia is likely to be. However, many other conditions also cause hypoxemia, and embolism often does not cause hypoxemia

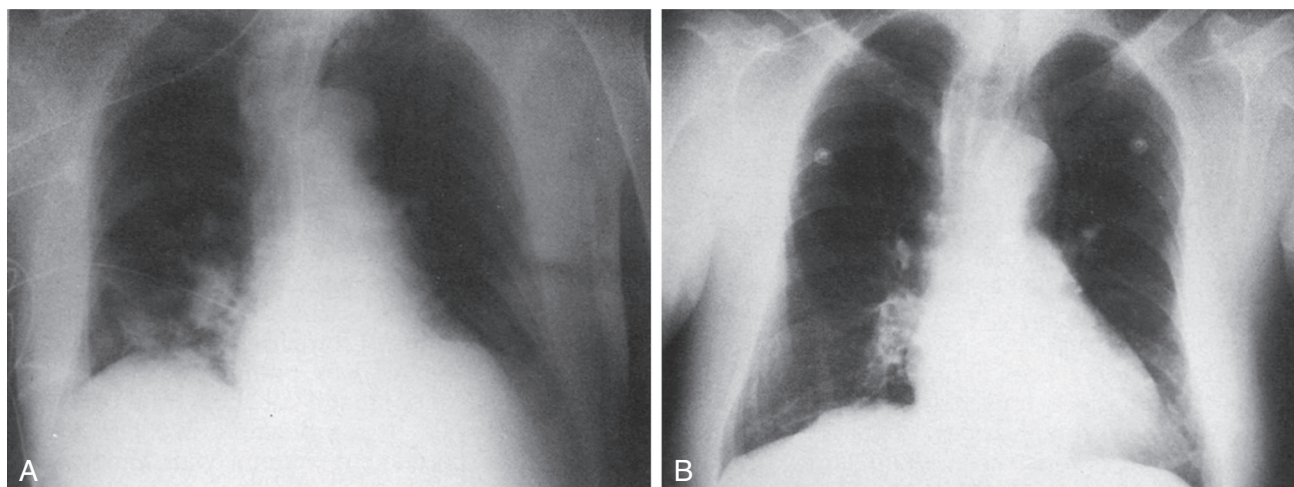


Figure 57-3 Chest radiographs in a patient with pulmonary embolism. **A**, Opacities caused by atelectasis with edema in the right lower lobe and in the retrocardiac area in a patient with angiographically confirmed pulmonary embolus. **B**, Two weeks later, the opacities have cleared. (Courtesy Michael Gotway, MD.)

or even a widening of the alveolar-arterial PO_2 difference. Hypocapnia usually is present with embolism; hypercapnia, conversely, is rare. Hypercapnia appears with embolism only in patients with marked antecedent ventilatory limitation or when such limitation has been imposed because the patient is on controlled mechanical ventilation.

ECHOCARDIOGRAPHY

Echocardiography may serve a valuable role in the diagnostic approach to PE. Under appropriate clinical circumstances, the detection of unexplained right ventricular volume (eFig. 57-10A) or pressure overload might suggest the possibility of embolism and lead to confirmatory testing (eFig. 57-10B). A distinct echocardiographic pattern involving akinesia of the mid-free right ventricular wall with apical sparing has been described, known as McConnell sign (Video 57-1)^{138,139} Direct visualization of right heart chamber emboli is uncommon but possible (Video 57-2). Properly performed *transesophageal* echocardiography has demonstrated excellent specificity for the detection of proximal emboli that involve the pulmonary trunk and the right and left main pulmonary arteries.¹⁴⁰ Transesophageal echocardiography also has proved valuable in the evaluation of competing diagnostic possibilities such as right ventricular infarction, endocarditis, pericardial tamponade, and aortic dissection in patients with unexplained shock and evidence of elevated central venous pressure. The overall sensitivity of *transthoracic* echocardiography in PE approximates 50%.¹⁴¹ Therefore it cannot be considered a primary diagnostic technique. Consideration can be given to its use in that subset of patients with suspected massive PE who are too ill for transportation or who have an absolute contraindication to the administration of a contrast agent.

VENTILATION-PERFUSION SCANNING

Despite significant limitations, V/Q lung scanning can be a valuable step in the diagnosis of PE if one of the two definitive results are found (i.e., either a *negative* or a *high-probability* scan).^{109,142}

First, a negative study excludes the diagnosis of PE with the same degree of certainty as a negative pulmonary angiogram (Fig. 57-4) and with a higher degree of certainty than is achieved by a negative CT scan.¹⁴³ This conclusion is illustrated by the results of two large prospective clinical trials comparing perfusion scanning to pulmonary angiography, the PIOPED trial¹⁰⁹ (performed in the United States) and the *Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis* (PISA-PED) trial¹⁴⁴ (performed in Europe). In both trials, normal pulmonary perfusion scanning was a highly sensitive method for excluding the presence of PE. The value of a normal perfusion scan was not diminished even in a subset of patients who had a high pretest probability for PE¹⁰⁹ or were critically ill.¹⁴⁵

The significance of a normal perfusion scan, as reported by the PIOPED and PISA-PED trials, is consistent with all published longitudinal studies.¹⁴⁶⁻¹⁴⁸ A meta-analysis of diagnostic studies for PE calculated the incidence of PE following a normal perfusion scan to be 0.3%.¹⁴⁹ A subsequent case series of consecutive patients followed clinically after objective testing for PE disclosed no PE in 188 patients who had normal perfusion scans.¹⁵⁰ These data support the clinical guidelines of the American Thoracic Society,¹⁵¹ British Thoracic Society,¹⁵² American Heart Association,¹⁵³ and European Society of Cardiology,¹⁵⁴ all of which recommend that a normal perfusion scan be accepted as reliably ruling out PE, with the same validity as a pulmonary angiogram.

Second, a “high-probability” study (one characterized by multiple, segmental-sized, mismatched defects) is associated with embolism in approximately 87% of patients, as shown in the PIOPED study¹⁰⁹; when coupled with a high clinical probability of embolism, the positive predictive value increased to 96% (Fig. 57-5).

Limitations of V/Q scanning are significant. For example, the PIOPED data provided several pieces of disquieting information: (1) the overwhelming majority of patients with suspected embolism did not have scan findings that fell into a high-probability or normal category, the only categories that can be considered definitive; (2) the majority of patients with embolism did not have a high-probability scan finding; (3) the overwhelming majority of patients without



Figure 57-4 Normal six-view lung perfusion scan. This finding is capable of excluding the diagnosis of embolism.

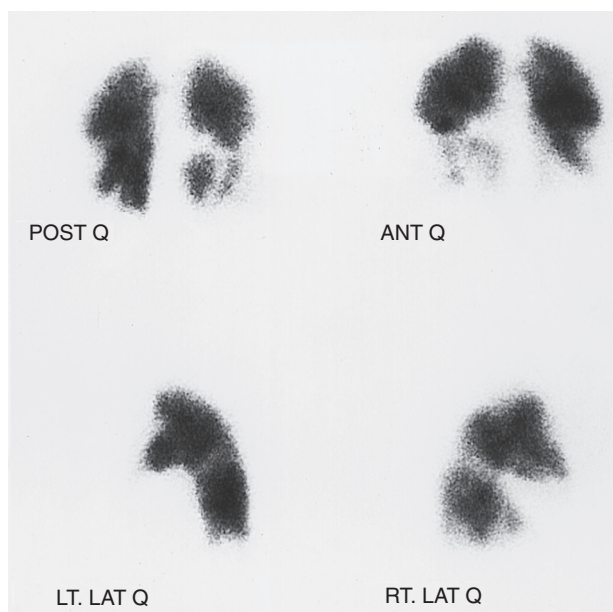


Figure 57-5 Lung perfusion (Q) scan shows major segmental and lobar defects bilaterally. The ventilation scan (not shown) and chest radiograph were normal. This pattern is strongly associated with the presence of embolism.

embolism did not have a normal scan; and (4) a substantial and clinically significant percentage of patients with scan findings interpreted as intermediate probability (33%) and low probability (16%) were subsequently demonstrated to have angiographic evidence of embolism.¹⁰⁹ It is essential that clinicians recognize that the concept of a low-probability scan (eFig. 57-11) is misleading and potentially dangerous because of the frequency of PE in patients exhibiting this scan pattern.¹⁵⁵

In order to improve perfusion scan specificity, traditional interpretive criteria, including the PIOPED criteria, rely on the number and size of the perfusion defects, as well as on the results of a concurrent ventilation image. The intended basis for doing so is to differentiate primary *vascular* obstruction (“mismatched” defects) from primary *parenchymal* disorders that result in compensatory pulmonary vasoconstriction (“matched” defects). The PISA-PED investigators¹⁵⁶ utilized a fundamentally different interpretive scheme that relied on the shape of the perfusion defects regardless of their number or size or their association with ventilation findings. The results of this study suggest that embolism can be diagnosed accurately and the need for angiography limited by perfusion results combined with an assessment of clinical likelihood in the absence of ventilation imaging. An analysis of a subset of patients from the PIOPED study came to a similar conclusion.¹⁵⁷

The diagnostic approach to PE in patients with underlying *chronic obstructive pulmonary disease* (COPD) remains especially problematic because the presentation of PE in this population may closely mimic an exacerbation of their underlying disease. Unfortunately, the value of V/Q scanning in this population is even more limited than that in the general population because an even higher proportion of scans fall into an indeterminate category.¹⁵⁸ However, among the more than half of COPD patients who had high-probability, normal, or near-normal scans, both the positive predictive value and the negative predictive value were equivalent to that in the general population.

COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY

CTPA has represented a major advance in the diagnosis of PE (see also Chapter 18). Unlike V/Q scanning, it provides

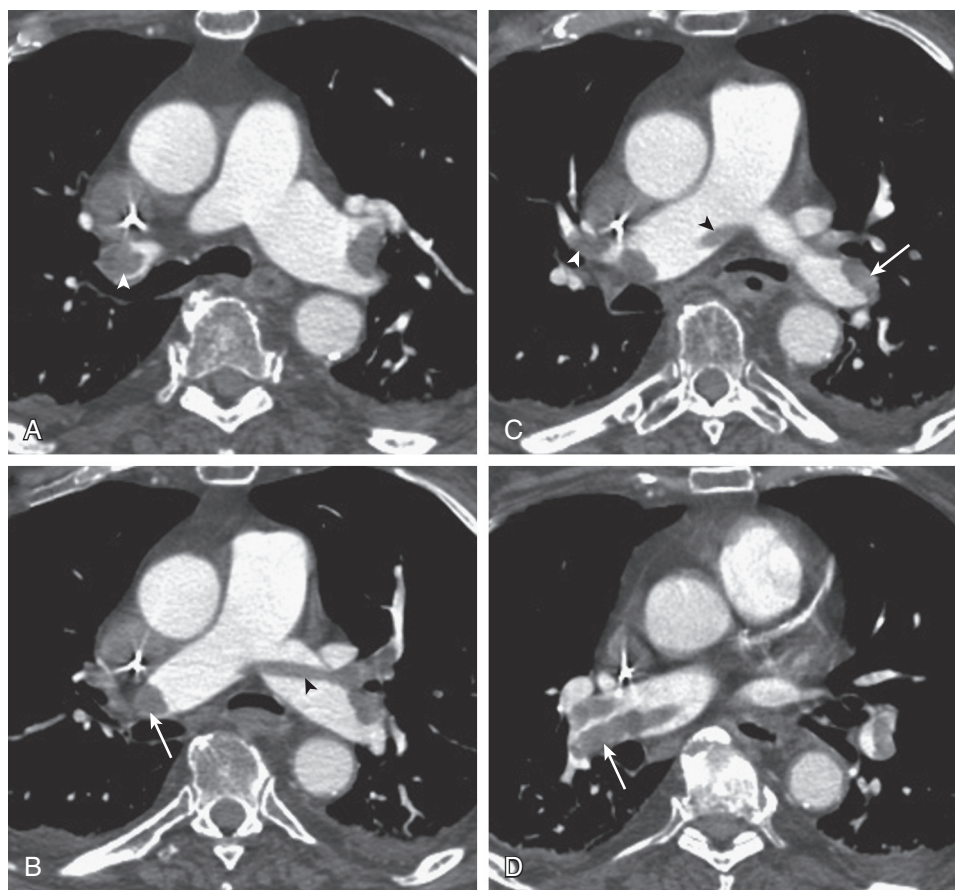


Figure 57-6 CT pulmonary angiography of pulmonary embolism. A–D, Chest CT pulmonary angiography shows bilateral pulmonary emboli, including a “saddle” embolism (black arrowheads, **B** and **C**); right upper lobe emboli (white arrowheads, **A** and **C**), and interlobar emboli (arrows, **B–D**). For a video clip of the full CT study, see [Video 57-3](#).

the ability to visualize emboli directly, as well as to detect parenchymal abnormalities that may support the diagnosis of embolism or provide an alternative basis for the patient's complaints ([Fig. 57-6](#); [Video 57-3](#)). The reported sensitivity of chest CT scanning for embolism has ranged from 57% to 100%, with a specificity ranging from 78% to 100%.¹⁵⁹ Factors responsible for this wide divergence relate to the proximal extent of vascular obstruction that can be detected and, in part, to advances in CT technology that allow higher resolution, dramatically faster scanning times, more peripheral visualization, and less motion artifact than that provided by earlier-generation scanners. Sensitivity and specificity of CT scanning for emboli involving the main and lobar pulmonary arteries exceeds 95%. Vascular involvement confined to segmental or subsegmental pulmonary vessels is associated with a decline in both sensitivity and specificity. In one series, the sensitivity of CT scanning for subsegmental arteries reported by two readers ranged between 71% and 84% even after nonevaluable scans were excluded.¹⁶⁰ Isolated involvement of the subsegmental pulmonary arteries is not unusual and, in various series, may be found in up to 30% of patients.^{161,162} These findings suggest that filling defects consistent with embolism involving the main or lobar pulmonary arteries can be considered diagnostic of embolism. By contrast, defects involving the segmental and subsegmental arteries can be considered suggestive of embolism but should be supported by additional objective data. The absence of detectable filling

defects reduces the likelihood of embolism but appears incapable of excluding the possibility with the same degree of certainty as a negative V/Q scan. The importance of treating patients with CTPA findings suggestive of *exclusively* subsegmental emboli has been questioned recently, especially in patients with good cardiopulmonary reserve and no coexisting DVT or persistent risk factors. However, no large trials have yet demonstrated the safety of withholding anticoagulants in this patient population.¹⁶³

Although CTPA scanning has increased the number of cases of acute PE that are diagnosed,¹⁶⁴ it has inherent limitations. The technique requires infusion of intravascular iodinated contrast agents, and the most common serious complications of testing arise from their use. During CT scanning, the peripherally infused dye fills the lumen of the pulmonary arteries, hopefully at the exact time that the chest is imaged. Emboli are detected as focal defects in pulmonary artery filling. When performed and interpreted expertly, CTPA scans are capable of identifying emboli in the segmental or larger pulmonary arteries (as does V/Q scanning^{165,166}). However, certain areas, such as the hila, are prone to false positives. Reading emboli in these areas should be done with special care. Perhaps more importantly, CT scans have difficulty imaging emboli in subsegmental pulmonary arteries. In selected populations, smaller emboli may account for up to 20% to 30% of PEs^{161,167} and represent the very cases in which V/Q scans are the most limited.¹⁰⁹

The National Institutes of Health-funded *Prospective Investigation of Pulmonary Embolism Diagnosis-2* (PIOPED-2) study highlighted the strengths and limitations of CTPA.¹²⁵ Before enrolling the study population of 1090 patients, the investigators excluded 1350 patients because their abnormal creatinine levels reflected some degree of renal dysfunction, which would have increased the risk involved with the administration of contrast dye. An additional 272 patients were excluded because of a history of contrast dye allergy. During the performance of the trial, 6% of the scans were excluded because the images were of poor quality. Even after the inconclusive scans were disregarded, the sensitivity of the chest CT scans was only 83%, although it is difficult to be confident of the gold standard used to compare to CTPA.

The PIOPED-2 investigators also excluded another 976 patients from the study because they had histories of long-term anticoagulation therapy. This highlights another weakness of CTPA in that luminal filling defects remain long after an acute pulmonary embolic event, so the test cannot easily differentiate between chronic and acute VTE. This is clinically relevant because the rate of recurrence is about 7% during the half-year after an acute PE and about 3% per year for the subsequent 5 years.¹⁶⁸

Finally, CTPA can expose patients to clinically significant doses of radiation.^{169,170} Current clinical protocols deliver a radiation dose to the female breast ranging from 4 to 6 cGy per scan.¹⁷⁰ This dose is especially concerning because most CTPA evaluations are negative, even when the criteria for scanning are rigorously followed.^{125,142} In addition, because PE has a relatively high rate of recurrence, patients are commonly reimaged after their first embolism. Younger women, who have a known elevated incidence of PE, are particularly at risk from radiation damage to breast and lungs.

From a clinical (outcomes-based) perspective, CT scanning and V/Q scanning have many similarities, and either can be used to exclude clinically significant PE in stable patients under many circumstances. Outcome studies have demonstrated that withholding anticoagulant therapy in patients with a negative CT scan coupled with a negative lower extremity ultrasound study appears to be a safe strategy except in those patients who present with a high clinical likelihood of embolism.^{171,172} Similarly, withholding anticoagulation from patients with “non-high-probability” findings on V/Q scan coupled with negative lower extremity studies is safe, except in those with inadequate cardiopulmonary reserve.^{173,174} A recent randomized, controlled trial comparing CT and V/Q for the management of suspected PE found the two studies to be comparable for excluding clinically significant PE.¹⁴² Specifically, the study disclosed no difference in outcome among patients in whom anticoagulation was withheld on the basis of the combination of a negative CT and negative leg studies compared with patients in whom anticoagulation was withheld based on the combination of a “non-high-probability” V/Q scan and negative leg studies or on a negative V/Q scan (without the need for leg studies). However, it should be emphasized that the outcome studies were done on relatively stable patients. Those with instability or poor cardiopulmonary reserve may require a higher degree of diagnostic certainty in order to rule out PE.¹⁷⁴

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY VENTILATION/PERFUSION SCANS

Single-photon emission computed tomography (SPECT) is a nuclear medicine technique that constructs three-dimensional images from scintigraphic data, in a similar way that CT constructs three-dimensional images from transmitted radiographs. SPECT ventilation and perfusion imaging (SPECT-V/Q) is a promising tool for diagnosing acute PE.¹⁷⁵⁻¹⁷⁷ The tomographic images can identify perfusion defects in areas of the lung that are hard to visualize with planar V/Q scans because of interposing lung tissue (e.g., the medial basilar segments of the lower lobes¹⁷⁸). As a result, SPECT-V/Q has far fewer nondiagnostic test results than planar V/Q, which removes one of the major limitations of planar V/Q testing. In fact, nondiagnostic results were reported in only 0.5% to 3% of SPECT-V/Q studies.¹⁷⁹⁻¹⁸¹ Another advantage of SPECT-V/Q is that it delivers only about one fourth of the radiation to the breast tissue than what is typical for CTPA scans.¹⁸²

Although the lack of a diagnostic gold standard limits our knowledge of its true accuracy (a phenomenon common to many tests for PE), several different analyses support the accuracy of SPECT-V/Q for PE. SPECT-V/Q had a high degree of agreement with the results of CTPA in patients suspected of having PE.¹⁸⁰ When compared with consensus diagnoses of PE (which, admittedly, included the SPECT-V/Q results themselves) SPECT-V/Q had sensitivities and specificities for PE that were typically in the 95% to 100% range.^{180,183,184} Similar to studies with CTPA scans, the clinical outcomes of patients with negative SPECT-V/Q, in whom anticoagulation was not given, were excellent.^{179,181,185} These findings suggest that SPECT-V/Q is highly sensitive for clinically important PE in the populations tested.

SPECT-V/Q is a promising technique but has not undergone extensive testing sufficient to merit replacement of CTPA as the primary diagnostic tool for PE. It may be especially useful for patients with nondiagnostic CTPA results or in those in whom the lower radiation dose to the chest would be especially advantageous. It may be useful as well for the follow-up of PE patients in order to detect and quantify residual perfusion defects.

LOWER EXTREMITY VENOUS EVALUATION

Because the majority of PEs arise from the deep veins of the lower extremities, the detection of lower extremity proximal vein thrombosis in a patient suspected of embolism, although not confirming PE, is strongly suggestive of that diagnosis and has an equivalent therapeutic implication. Positive ultrasound findings without symptoms or signs referable to the lower extremities should be interpreted judiciously, especially in patients with low pretest probability of PE, because even a highly specific test can yield false-positive results in some circumstances.¹⁸⁶ Lower extremity ultrasonography has a low yield in patients without leg symptoms or risk factors strongly suggestive of thromboembolism.^{187,188} Conversely, it is typically positive in only about 10% to 20% of patients with suspected PE and in 50% of patients with proven PE.¹⁸⁹ Therefore a negative ultrasound

finding cannot exclude the diagnosis. CT venography (see eFig. 57-4) as an adjunct to chest CTPA scanning appears to be capable of detecting femoropopliteal thrombosis with the same accuracy as duplex ultrasonography while also detecting pelvic and abdominal thrombosis.^{124,125} However, the combined CT technique is technically complicated¹²⁵ and significantly increases the amount of pelvic radiation exposure to the patient.^{169,170,190}

D-DIMER TESTING

The utility of D-dimer testing in PE diagnostic pathways is limited by the same shortfalls as those encountered in venous thrombosis pathways (i.e., a low specificity, which makes it most useful as an exclusionary technique in outpatients, and a lack of standardization). However, studies have demonstrated that a normal D-dimer result can safely exclude embolism in patients with a low clinical probability of disease.¹⁹¹⁻¹⁹³ Although preliminary data suggest that a highly sensitive assay is capable of excluding embolism at all levels of clinical probability, these results require confirmation.¹⁹³

PULMONARY ANGIOGRAPHY

The studies reviewed to date are capable of excluding or confirming the diagnosis of embolism in the majority of patients with suspected embolism. Angiography should be considered in patients in whom the diagnosis has not been confirmed or excluded using noninvasive techniques and when it is considered unsafe to withhold anticoagulation, when cardiopulmonary instability is present, and when the results of diagnostic testing are at such odds with the clinical impression as to warrant the risk of the procedure. Like contrast venography, however, pulmonary angiography has a number of limitations as a gold standard. First, the procedure is invasive and not without risk, especially in patients with acute right ventricular failure. However, experience has demonstrated that the perception of risk associated with angiography outweighs the actual risk.^{194,195} Pulmonary angiography can be performed quite safely if certain safeguards are observed and experienced personnel are involved.

Even though the risk of angiography should be nominal, the procedure has other limitations. One is accessibility: Angiography is performed in a special facility to which the patient must be transported. In some institutions, the logistical problems involved are modest; in others, they are substantial. The other limitation is interpretation. The interpretation of pulmonary angiograms is heavily influenced by three factors: location of the thromboembolic obstruction, quality of the images, and experience of the interpreters. Only two angiographic findings are diagnostic of acute embolism: the filling defect and abrupt cutoff of a vessel (Fig. 57-7). Technical adequacy of the angiogram is critical to accurate identification of both. Flow artifacts can falsely suggest a filling defect. It is essential that good vessel opacification be obtained and that the filling defects be identified as present on a sequence of images.

Although concern about risk should not deter pulmonary angiography, there are noteworthy limitations on its performance and value. Still, it is a rather odd commentary

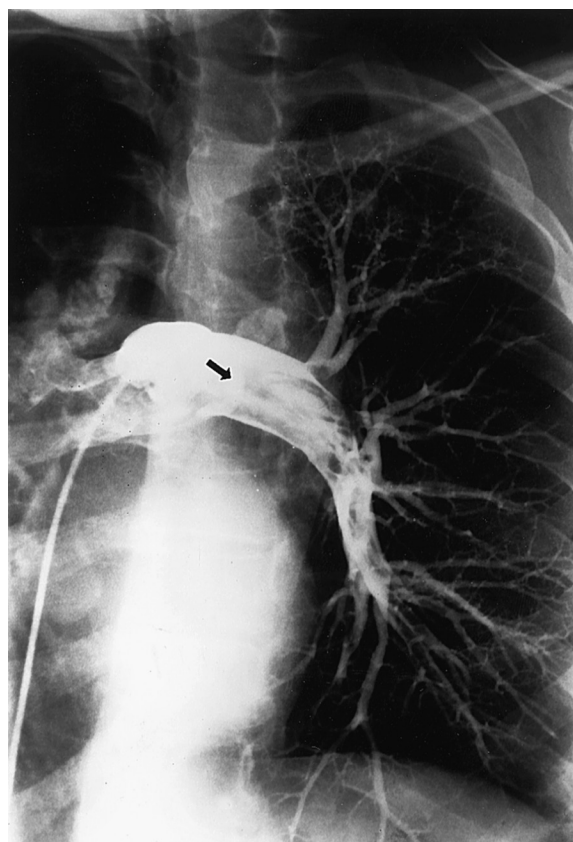


Figure 57-7 Pulmonary angiography for pulmonary embolism. Left-sided pulmonary angiogram shows extensive filling defects within the left pulmonary artery (arrow) and the upper lobe, lingula, and lower lobe arteries, consistent with the diagnosis of pulmonary embolism.

on medical thinking that few would advise against performance of a coronary angiogram in a patient with coronary thrombosis or ischemia because of risk, yet the question of risk often deters pulmonary angiography in a patient in whom embolism is suspected. Given that the case-fatality rate of undiagnosed and untreated embolism exceeds that of myocardial infarction, it is not clear why this disparity exists; it should not exist, given equal competence in the performance and interpretation of these two procedures.

CLINICAL PREDICTION RULES

The development of clinical prediction rules has aided the diagnostic approach to PE, as it has the diagnostic approach to venous thrombosis. A number of standardized prediction rules that range widely in their complexity have been evaluated and published. Simple, standardized prediction rules (Table 57-3) involve information that can be easily acquired even in an outpatient setting or the emergency department.^{191,196} Complicated prediction rules involve an increased number of clinical variables and require expert interpretation of radiographic and electrocardiographic data.^{197,198} Alternatively, the clinician may make a subjective (“gestalt”) assessment of the probability of PE. So long as it is performed deliberately and independently of subsequent testing, the “gestalt” method appears to have comparable sensitivity to clinical prediction rules.¹⁹⁹

Although probability assessments, whether empirical or standardized, are incapable of confirming or excluding the presence of PE with a clinically acceptable degree of certainty, they have proved capable of stratifying patients into categories of likelihood. By combining this derived clinical probability with the results of a noninvasive diagnostic technique, diagnostic accuracy in terms of both the confirmation and the exclusion of embolism can be increased well

Table 57-3 Wells Clinical Model for Predicting the Pretest Probability of Pulmonary Embolism

Variable	Points Assigned
Clinical signs and symptoms of deep venous thrombosis	3.0
An alternative diagnosis is less likely than pulmonary embolism	3.0
Heart rate >100 beats/min	1.5
Immobilization or surgery in the previous 4 wk	1.5
Previous deep venous thrombosis or pulmonary embolism	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the past 6 mo, or palliative)	1.0
Score	Clinical Assessment Probability
<2 points	Low probability
2–6 points	Intermediate probability
>6 points	High probability

From Kearon C: Diagnosis of pulmonary embolism. *CMAJ* 168:183–194, 2003.

beyond that achieved by the use of either clinical probability or the noninvasive diagnostic technique alone. In addition, the appropriate application of clinical prediction rules and D-dimer testing can substantially limit the number of patients who require thoracic imaging.²⁰⁰⁻²⁰²

In summary, an almost bewildering array of diagnostic techniques is available for patients with suspected VTE. What the clinician at the bedside must understand and accept is that multiple approaches are possible and that a stepwise diagnostic strategy, rather than any single diagnostic technique, may be necessary to confirm or exclude the diagnosis (Fig. 57-8). Furthermore, the clinician must understand that these steps are essential and potentially lifesaving. Withholding anticoagulation in a patient who has suffered an embolic event places that patient at risk for recurrent, potentially lethal events; instituting empirical anticoagulant therapy in a patient who has not suffered an embolic event involves unnecessary hospitalization and therapy, places the patient at risk for hemorrhagic complications, and establishes a “preexisting” condition that may adversely affect future health care costs. Finally, the clinician must understand that the use of a clinical prediction rule derived from an outpatient population might have a very different predictive value when applied to a less healthy inpatient population.

Many strategies to confirm or exclude the diagnosis of PE have been investigated. Because the initiating point for the diagnostic pathway begins with clinical suspicion, the following discussion centers about that approach. Also, given substantial variations in practice that currently exist, strategies that incorporate V/Q scanning or CTPA as the initial objective diagnostic technique are considered.

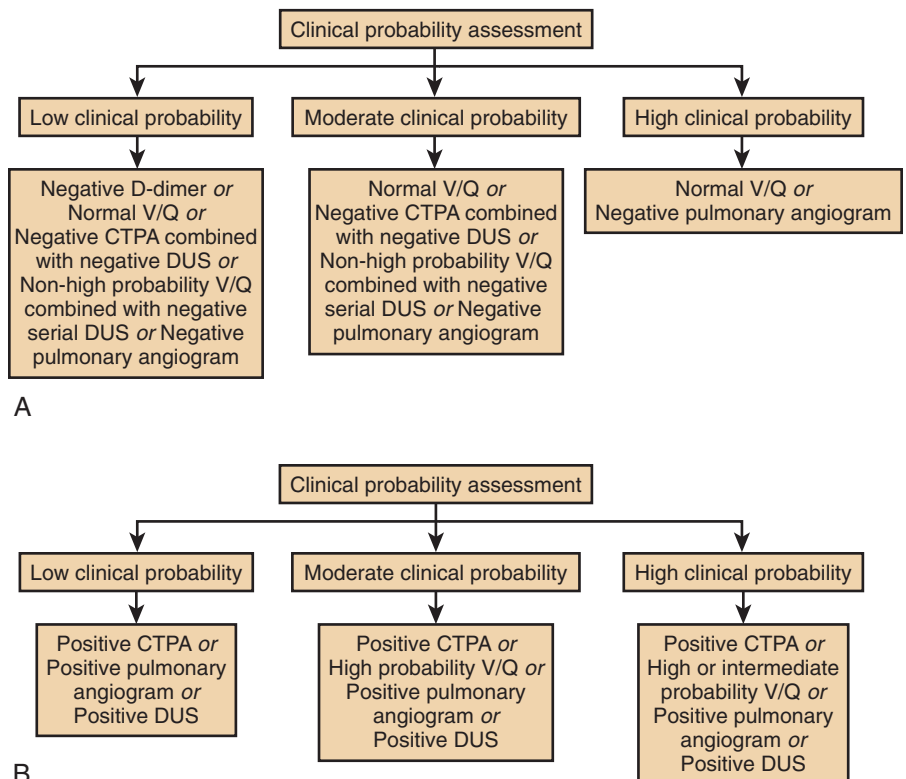


Figure 57-8 Diagnostic strategies capable of excluding (A) and confirming (B) the diagnosis of pulmonary embolism. CTPA, computed tomographic pulmonary angiography; DUS, Doppler ultrasound; serial DUS, serial Doppler ultrasound (1–2 additional tests over the subsequent week); V/Q, ventilation-perfusion scan.

In patients in whom the clinical suspicion of PE is considered high (>70% likelihood), a positive CTPA scan or a high-probability V/Q scan or SPECT-V/Q scan result would be considered diagnostic of embolism with greater than 95% certainty, whereas a negative perfusion scan (planar or SPECT) would exclude the diagnosis. In all other patients (non-high-probability planar V/Q scan or SPECT-V/Q or negative CTPA scan), lower extremity evaluation may be undertaken. A positive study would confirm the diagnosis. In the remaining patients, several strategies are possible. Serial lower extremity evaluations could be performed. Although not excluding embolism, negative results would suggest that the likelihood of recurrence is small. Alternatively, pulmonary angiography could be performed. This latter approach is especially applicable to unstable patients with preexisting cardiopulmonary disease, in whom the consequences of recurrence could be catastrophic.

When the clinical assessment is taken into account, the predictive value of CTPA varies substantially, especially when there is discordance between the clinical assessment and the CT finding. Both the positive predictive value of CTPA in patients with a low clinical probability and the negative predictive value in those with a high clinical probability are in the range of 60%. In patients with a low clinical probability of disease, a negative, highly sensitive D-dimer assay; a negative CTPA; or a normal V/Q scan are capable of excluding the disease. In those same patients, confirmation of the disease can be accomplished with a lower extremity duplex ultrasonography showing proximal DVT or by conventional pulmonary angiography. A high or intermediate probability V/Q scan or a positive CTPA, especially when the involved areas of embolism are beyond the segmental level, should raise questions about the diagnosis and lead to additional diagnostic testing.

Special circumstances that may guide the diagnostic approach do exist. In the setting of severe, preexisting pulmonary parenchymal or airway disease, planar V/Q scanning is of limited utility given the high likelihood that the scan result will be nondiagnostic. Although the positive predictive value of a high-probability scan and the negative predictive value of a normal or near-normal scan in patients with underlying lung disease are similar to that in the general population, the proportion of patients whose scans fall into a nondiagnostic category is increased substantially.¹⁵⁸ Under this circumstance, an approach utilizing chest CTPA scanning or SPECT-V/Q as the initial objective diagnostic study would be appropriate. The use of iodinated contrast required for CT scanning has been reduced over the years but nonetheless poses some risk of radiocontrast-induced nephropathy for patients with preexisting renal insufficiency, especially when it is associated with diabetes mellitus.²⁰³ In such patients, SPECT-V/Q may be the diagnostic test of choice. If it is unavailable or nondiagnostic, a strategy utilizing duplex ultrasonography and V/Q scanning would appear prudent, followed by selective conventional pulmonary angiography should the noninvasive techniques not yield a definitive diagnosis.

VTE is a leading cause of maternal mortality²⁰⁴; however, given the potential risk of radiation exposure to the fetus,¹⁹⁰ a diagnostic approach that limits that exposure is warranted. Therefore duplex ultrasonography is an appro-

priate initial diagnostic approach. If ultrasonography is negative, the diagnostic evaluation should proceed as previously described on the basis of the clinical assessment probability and using V/Q scanning or SPECT-V/Q as the next diagnostic technique. CTPA has a comparable accuracy to V/Q for pregnancy-associated PE but delivers a higher maternal radiation dose (7.3 mSv for CTPA vs. 0.9 mSv for V/Q).²⁰⁵ However, some data suggest that fetal radiation exposure with CT scanning is comparable or perhaps even lower than with V/Q scanning.^{170,206} (See also Chapter 18.)

PREVENTION OF VENOUS THROMBOEMBOLISM

One of the most striking changes in the field of VTE since the late 1980s has been an emphasis on prevention. This emphasis is totally appropriate and, indeed, should be the cornerstone of modern management. It is clear that if the goal is to prevent PE, the only effective approach is to prevent DVT. The basic information and tools required for developing a prophylactic strategy are now available.

For such a strategy, three fundamentals must be in place: (1) the population at risk must be identified; (2) the duration of the increased thromboembolic risk must be ascertained; and (3) effective, low-risk prophylactic options must be available. Populations at risk of DVT, and therefore of PE, have been identified and such risk can also be quantified as high, moderate, or low. Furthermore, a variety of effective and safe prophylactic approaches are available. It should be emphasized that the trend toward earlier hospital discharge has been accompanied by an increased incidence of post-discharge VTE. Thromboembolic risk does not necessarily end at the time of hospital discharge or of transfer to a lower level of care.²⁰⁷ In patients with an ongoing predisposition to thrombosis at the time of discharge from an acute inpatient setting (e.g., those who underwent major orthopedic, abdominal, or pelvic surgery), prophylaxis should be continued until the risk for VTE has resolved.²⁰⁸

The objective of the prophylactic strategy is to identify the degree of thromboembolic risk in the individual patient and to match the intensity of prophylaxis to that degree of risk. Although a variety of prophylactic approaches have been investigated and utilized, four approaches to the acute phase of treatment have proved effective: low-dose unfractionated heparin, *low-molecular-weight heparin* (LMWH), intermittent pneumatic compression devices, and warfarin.

LOW-DOSE UNFRACTIONATED HEPARIN

Low-dose heparin has been widely studied as a prophylactic modality. Heparin, given subcutaneously in a dose of 5000 units every 8 or 12 hours, is begun as soon as the risk of DVT is evident and is continued until that risk has abated. This regimen has been shown to be effective in reducing the incidence of DVT, PE, and fatal PE in patients at low to moderate risk, such as those undergoing surgical procedures requiring general anesthesia for 30 minutes or longer and with medical conditions requiring bed rest for several

days.²⁰⁹ However, this form of prophylaxis has not been optimally effective in patients whose thromboembolic risk is higher, such as those with hip fracture or hip replacement, those undergoing prostate surgery, and patients suffering major traumatic injuries.²¹⁰ Furthermore, although the bleeding risk of low-dose heparin is nominal in most patients, there are groups of patients in whom heparin administration is contraindicated (e.g., those with active bleeding, hemorrhagic diathesis, and hemorrhagic stroke and those undergoing neurologic or ocular surgery). Patients to be placed on prophylactic heparin should be screened with an initial platelet count, partial thromboplastin time, and prothrombin time. During therapy, however, monitoring of coagulation tests is not useful because such tests do not reflect the safety or efficacy of the regimen. Monitoring of platelet counts on at least a weekly basis would appear to be a prudent option.

LOW-MOLECULAR-WEIGHT HEPARIN

LMWH preparations represent another prophylactic option. In trials that have been performed comparing the prophylactic efficacy of LMWH with unfractionated heparin in general surgical and medical populations, LMWH has not proved superior to unfractionated heparin, although a trend toward decreased bleeding complications associated with LMWH may exist.²¹¹ However, this may simply represent a dose effect. LMWH preparations appear more effective than unfractionated heparin as prophylactic agents in several high-risk groups: patients undergoing hip or knee replacement, patients with spinal cord injury, patients with ischemic strokes, and patients with multiple trauma.^{210,211} LMWH is renally cleared, however, so it must be used with caution in patients with renal insufficiency.

PNEUMATIC COMPRESSION DEVICES

Another extensively evaluated and effective prophylactic approach in low- to moderate-risk patients is the use of mechanical leg compressive devices.^{210,212} These devices periodically (e.g., once or twice per minute) compress the leg by an air-inflatable bladder. A variety of devices are available: thigh-length systems that provide both thigh and calf compression, calf-compressive devices, single-pulse systems, and sequential compression systems. A variety of questions remain unanswered about pneumatic compression devices. For example, it is not known whether the various compressive devices differ in efficacy. It is also unknown whether efficacy depends on strict (24/7) compliance with this intervention during the period of increased thromboembolic risk.^{213,214} However, they appear to reduce the incidence of VTE by about two thirds in most studies.²¹⁵ It is unclear whether pneumatic compression devices are as effective as unfractionated heparin in general medical, surgical, gynecologic, and urologic patients, but they are a useful alternative in patients in whom pharmacologic methods of prophylaxis are contraindicated. The combined use of mechanical prophylaxis and pharmacologic methods in some high-risk patient populations appears to reduce VTE by 50% to 85% more than pharmacologic methods alone.^{212,215,216}

WARFARIN

Warfarin and other “prothrombinopenic” drugs, started like heparin at the onset of high risk (e.g., preoperatively), also have been shown to be effective and safe.²¹⁰ Unfortunately, use of “prothrombinopenic” agents has not gained wide favor as a prophylactic approach. The use of warfarin requires careful monitoring, and there is a perception among physicians that the bleeding risk associated with its use is greater than that reported in the literature. In patients undergoing hip replacement, warfarin has proved effective and has achieved general acceptance. Two regimens are widely used: small doses (1 to 2 mg) given daily for several days before surgery, with dose escalation to therapeutic range, or initiation after surgery.²¹⁷ LMWH preparations appear superior to warfarin, albeit at higher bleeding risk, in patients undergoing knee or hip replacement, with efficacy related, in part, to timing of administration.²¹⁸ It also has become evident that increased thromboembolic risk in patients undergoing hip or knee replacement can extend for 4 to 6 weeks after hospital discharge.²¹⁹ A strategy of extended prophylaxis may be appropriate.²²⁰

FONDAPARINUX

Fondaparinux, a synthetic pentasaccharide that selectively inhibits activated factor X (factor Xa), has been demonstrated in several trials to be effective in the prevention of VTE in patients undergoing lower extremity orthopedic surgery.^{210,221,222} Like unfractionated heparin and LMWH, fondaparinux works by binding to and enhancing the activity of antithrombin. Because of its small size, it enhances antithrombin-mediated inactivation of Xa exclusively. Fondaparinux has almost complete bioavailability and has a longer half-life than LMWH.

DIRECT INHIBITORS OF FACTOR Xa AND OF THROMBIN

Several synthetic oral anticoagulants have recently become available, including rivaroxaban (a specific inhibitor of activated factor X),²²³⁻²²⁶ dabigatran (a direct thrombin inhibitor active against both free and clot-bound thrombin),²²⁷⁻²²⁹ and apixaban (also a specific inhibitor of activated factor X).^{230,231} They have shown varying degrees of promise in randomized controlled trials compared against the LMWH enoxaparin in patients undergoing hip or knee surgery. They appear to be at least noninferior to enoxaparin in this specific population of orthopedic patients in terms of prevention of VTE, with a small but significant trend toward lower associated bleeding risk. However, there are two important considerations relevant to their use. First, there are no specific antidotes if clinically relevant bleeding develops. This is a major limitation to the utility of these drugs for VTE prophylaxis, especially in hospitalized medical patients whose risk of bleeding may be more unpredictable than in orthopedic patients. Second, the increased cost of these newer agents compared with unfractionated heparin and the LMWHs for minimal incremental benefit must be justified before they can be recommended for widespread use.

There is one option available to prevent PE in patients at high risk who cannot be provided pharmacologic or mechanical prophylaxis. Patients with extensive trauma often fall into this category, particularly those with pelvic or lower extremity fractures and internal or intracranial bleeding. In this group, prophylactic placement of an inferior vena cava filter in selected patients provides protection against otherwise nonpreventable emboli.²³²

In summary, given the effective options available, most patients at risk for venous thrombosis can be protected. However, despite this awareness, surveys have demonstrated that prophylaxis is underused in populations at risk.^{233,234} A number of different rationales have been proposed to account for this lack of compliance. The overstated concern for bleeding complications associated with pharmacologic methods of prophylaxis appears to be a deterrent. Furthermore, fatal PE is generally uncommon in any individual physician's experience, thereby diminishing the perception of risk. Finally, the issue of prophylaxis is often subordinated to the compelling demands of the patient's admitting diagnosis and therapy. Whatever the reason, use of prophylaxis must increase if a substantial impact is to be made on the considerable and often unnecessary morbidity and mortality associated with PE. Prophylaxis must not only be applied but also applied in a manner proportionate to the patient's risk of thromboembolism.

MANAGEMENT OF VENOUS THROMBOEMBOLISM

The basic approaches to management are defined chiefly by what is known, as already described, about the pathogenesis, pathophysiology, and natural history of venous thrombosis and PE.

UNFRACTIONATED HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN

Heparin, both unfractionated and LMWH, remains the mainstay of therapy for venous thrombosis and for PE not associated with hemodynamic compromise.²³⁵ With a strong suspicion of embolism based on clinical findings and laboratory tests, heparin therapy should be instituted immediately, without awaiting diagnostic confirmation, unless anticoagulation places the patient at significant risk.

Data suggest that physician practices in the administration of unfractionated heparin often result in levels of anticoagulation that fall below those currently recommended in the literature.²³⁶ To overcome these problems, standardized protocols for heparin administration and monitoring have been recommended. A number of different intravenous heparin dosing schemes have been published, all of which have demonstrated the potential to reach a therapeutic threshold more rapidly than a nonstandardized approach.²³⁷ The most widely utilized of these is a weight-based system that includes an 80 unit/kg intravenous bolus of heparin followed by an 18 unit/kg/hr infusion.²³⁸

Whatever regimen is used, an activated partial thromboplastin time (aPTT) is generally obtained 6 hours after the bolus dose, 6 hours after each prescribed dose adjustment,

and then on a daily basis for the duration of therapy. Because maintenance of the aPTT within a rigidly defined range does not appear to increase the efficacy or safety of the drug, frequent dosage adjustments are not necessary once the dose has been stabilized within a therapeutic range. This therapeutic range of aPTT, which corresponds to heparin levels of 0.2 to 0.4 unit/mL by protamine sulfate titration or 0.3 to 0.7 unit/mL by anti-factor Xa assay, may vary substantially depending on the sensitivity of the reagent utilized and among coagulation analyzers.²³⁹ Given the variance in aPTT values possible with different reagents and analyzers, individual institutional validation should be performed to define a therapeutic aPTT value. It also should be recognized that heparin requirements tend to decrease during the course of therapy, resulting in an increase in the level of the aPTT. For patients with heparin resistance (defined as the need for >40,000 units/day), monitoring heparin with an anti-factor Xa assay appears safe and effective and results in less escalation of the heparin dose than monitoring with the aPTT.²⁴⁰

Interestingly, *supratherapeutic* aPTT values are not associated with an increased risk of clinically important bleeding complications.²⁴¹ There is no direct evidence that the absolute dose of heparin or the level of the aPTT can predict the likelihood of bleeding. Instead, bleeding during heparin therapy appears to be related to the presence of concurrent illness such as renal disease, a history of heavy alcohol consumption, aspirin use, and prior surgical procedures or peptic ulcer disease. Thus these data encourage adequate use of heparin doses. In fact, failure to treat patients early with sufficient heparin doses appears to have long-term and short-term implications for thromboembolic recurrence. It is somewhat controversial, however, whether the aPTT level itself, independent of the heparin dose, is associated with higher recurrence rates²⁴² or whether it is strictly a matter of insufficient dosing itself.²⁴³

Subcutaneous LMWHs are widely used for the treatment of VTE because of their high bioavailability and longer half-life, which allows the strategy of dosing once or twice daily, with adjustment for weight but without the need for adjustment by aPTT monitoring.^{235,244} Indeed, the same strategy is appropriate for subcutaneous (unfractionated) heparin as well, administered in high doses. An approach utilizing a fixed dose of subcutaneous unfractionated heparin, administered as an initial dose of 333 U/kg followed by a dose of 250 U/kg every 12 hours, has been demonstrated to be as safe and effective as LMWH in patients presenting with venous thrombosis and PE.²⁴⁵ Clinicians must recognize that the administration of LMWH may not be preferable under certain clinical circumstances. Standardized dosing can be a problem in patients at the extremes of body weight; because the drug is renally cleared, dose adjustments and monitoring with anti-factor Xa levels are necessary in patients with renal insufficiency; the anticoagulant effect of the drug cannot be monitored easily; populations exist (e.g., patients at high bleeding risk) in which a longer drug half-life is not a desirable effect; the ability of protamine sulfate to reverse the anticoagulant effect remains uncertain; and drug costs are substantially higher than with unfractionated heparin.

Clinical trials have demonstrated that the safety and efficacy of LMWH preparations are comparable with those of

unfractionated heparin in patients with venous thrombosis.²⁴⁶ In selected patients, fixed-dose subcutaneous LMWH appears to be safer and more effective than intravenous adjusted-dose unfractionated heparin.²⁴⁷ However, fixed-dose subcutaneous LMWH appears to be comparable with subcutaneous unfractionated heparin, either in adjusted doses^{247,248} or fixed doses.²⁴⁹ Trials have also demonstrated that most patients with acute venous thrombosis can be treated safely on an outpatient basis with LMWH and that outpatient therapy can reduce total medical expenditure.²⁵⁰ However, not all patients with venous thrombosis can or should be treated in an outpatient setting. Approximately 50% of patients are ineligible for outpatient therapy owing to such factors as major bleeding risk, compliance problems, renal failure, significant comorbid disease, inadequate cardiopulmonary reserve, and inaccessibility for follow-up. Furthermore, embolism can happen during the early aspects of therapy in patients treated with both unfractionated and LMWH preparations. Although this circumstance would not be diminished in an inpatient setting, the potential consequences of recurrence, especially in patients with preexisting cardiopulmonary disease, might be more promptly detected and managed in this setting.

The Hestia Study demonstrated the feasibility of outpatient therapy for acute PE patients who are hemodynamically stable (without perceived need for thrombolysis or embolectomy), at low risk for bleeding, not hypoxemic, free of severe liver or kidney dysfunction, without severe pain or other reason for hospital admission and who did not develop PE while on anticoagulants or while pregnant.^{251,252} About one quarter of the patients who met these criteria were briefly admitted for evaluation and discharged in less than 24 hours. The Hestia criteria for outpatient therapy appear to be useful even in patients with CTPA evidence of enlarged right ventricular dimensions, provided they are otherwise hemodynamically stable.²⁵³ Even in patients who require initial inpatient management, the duration of hospitalization can be decreased considerably by a quick transition to outpatient therapy as their conditions stabilize.

In terms of duration of heparin/LMWH therapy, studies have shown that utilizing a 5-day course of therapy in patients with proximal venous thrombosis is associated with a recurrence rate identical to that of a 10-day course.²⁵⁴ This assumes, of course, that warfarin is started early and is in a therapeutic range for 2 consecutive days before heparin is discontinued, a target often difficult to achieve. It is likely that a short course of heparin therapy would be similarly effective in patients with uncomplicated PE. However, a longer course of therapy is advisable in patients with major PE or extensive iliofemoral venous thrombosis.

The major complications of unfractionated heparin and LMWH are bleeding and the development of thrombocytopenia.^{255,256} There are no predisposing factors to heparin-associated thrombocytopenia other than a history of a previous exposure, and it develops at the same frequency with either (unfractionated) heparin or LMWH.²⁵⁷ Two types of thrombocytopenia are associated with heparin administration: an early-onset (1-5 days), non-immune-mediated reduction in platelet count (type I) believed to be secondary to a direct agglutinating effect of heparin on platelets and a late-onset (≥ 4 days), immune-mediated thrombocytopenia (type II) that may be associated with

venous and arterial thrombosis. Immune-mediated thrombocytopenia can also arise within a day of initiating therapy in patients who have been exposed to the drug within the prior 100 days.²⁵⁸ The incidence of thrombosis with heparin-associated thrombocytopenia appears to be low, but when it happens, it is associated with considerable morbidity and mortality. Therefore heparin should be immediately withdrawn if this diagnosis is suspected. If heparin-associated thrombocytopenia type II is confirmed by either a functional assay or an immunoassay, withdrawal of heparin alone may be associated with an adverse outcome.²⁵⁹ A number of therapeutic alternatives exist, including direct thrombin inhibitors (lepirudin or argatroban), which do not react with heparin antibodies, or danaparoid, which appears to have a low rate of *in vivo* cross reactivity with heparin.^{260,261} Cross reactivity between unfractionated heparin and LMWH is relatively common, and these drugs should be avoided.²⁶²

FONDAPARINUX

Fondaparinux is effective and safe for the initial treatment of PE²⁶³ and of DVT.²⁶⁴ The dosing regimen used in these trials was straightforward: 7.5 mg subcutaneously once daily in patients who weighed from 50 to 100 kg (85% of cases). The dose was decreased to 5 mg in patients weighing less than 50 kg and increased to 10 mg in those weighing more than 100 kg. As is the case for unfractionated heparin and LMWH, the treatment was continued for at least 5 days, during which time warfarin was administered. After 5 days and once warfarin was therapeutic, treatment with fondaparinux was stopped. In a double-blinded randomized trial for the treatment of acute proximal lower extremity DVT,²⁶⁴ this regimen was as effective in preventing recurrent symptomatic VTE as enoxaparin, 1 mg/kg body weight twice per day. A randomized, open-label clinical trial compared the same fondaparinux treatment regimen with intravenous unfractionated heparin (using standard aPTT-driven dosage adjustments) for the treatment of pulmonary embolism.²⁶³ The outcomes of the two treatments appeared identical: the fondaparinux and standard therapy groups did not significantly differ with respect to the incidence of recurrent VTE, bleeding, overall mortality, or mortality due to PE. It is noteworthy that fondaparinux may accumulate to dangerous levels in patients with renal insufficiency because of its near total renal clearance.²⁶³⁻²⁶⁵

DIRECT INHIBITORS OF FACTOR Xa AND OF THROMBIN

Rivaroxaban is a synthetic inhibitor of Xa that can be used in the acute phase of VTE treatment. It differs from the parenteral agents (unfractionated, LMWH, and fondaparinux) in that it is a direct inhibitor. For this reason, it does not depend on the body's antithrombin in order to inactivate thrombosis. Another important difference is that it is well absorbed when given orally. Rivaroxaban is safe and effective for the treatment of the acute phase, as well as the 3-month follow-up phase of treatment for PE²⁶⁶ and for DVT.²⁶⁷ However, the acute phase of VTE treatment with rivaroxaban lasts for 3 weeks, as opposed to the shorter acute phase used with parenteral agents.

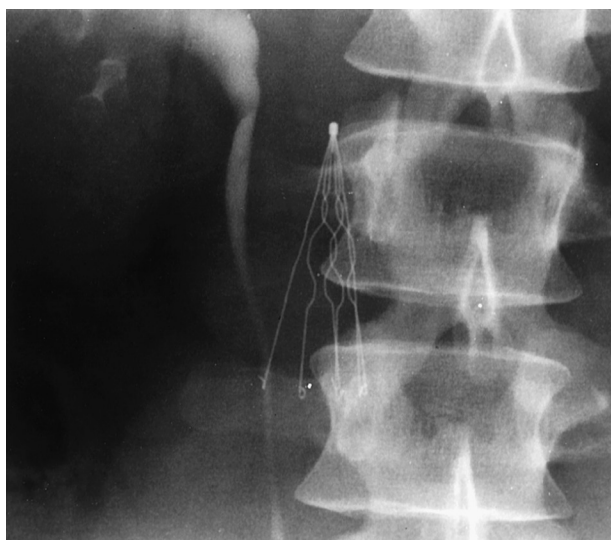


Figure 57-9 Inferior vena cava filter in place below the renal veins.

The high bioavailability and pharmacokinetic predictability of once- or twice-daily oral rivaroxaban,^{268,269} as well as the safety of using it without the need for adjustment by INR values, is advantageous. Rivaroxaban is cleared by both renal and hepatic routes, including cytochrome P₄₅₀-mediated metabolism. In the trials listed earlier, patients with severe renal or hepatic dysfunction were excluded. There are also potential drug interactions with agents that inhibit cytochrome P₄₅₀ 3A4, such as azole compounds or HIV-protease inhibitors.

INFERIOR VENA CAVA FILTERS

Scientific evidence supporting the use of inferior vena cava filters (Fig. 57-9) is limited.^{270,271} Established indications for filter placement in the therapy of VTE include (1) protection against PE in patients with acute VTE in whom conventional anticoagulation is contraindicated (recent surgery, hemorrhagic cerebrovascular accident, active bleeding, heparin-associated thrombocytopenia, etc.); (2) protection against PE in patients with acute VTE in whom conventional anticoagulation has proved ineffective; and (3) protection of an already compromised pulmonary vascular bed from further thromboembolic risk (massive PE, chronic thromboembolic pulmonary hypertension). In support of the third indication is the recent review of a national inpatient database that disclosed that unstable PE patients who received *inferior vena cava* (IVC) filters had higher survival rates than those who did not receive them.⁴

Mortality from filter placement appears to be quite low regardless of what filter is used.²⁷⁰ Nonfatal complications of IVCs include (1) complications relating to the insertion process, (2) venous thrombosis at the site of insertion, (3) filter migration, (4) filter erosion through the inferior vena cava wall, and (5) inferior vena cava obstruction. The majority of clinically important complications appear to involve venous thrombosis at the insertion site and inferior vena cava obstruction.²⁷¹

Filter placement should not be considered as the sole therapy for VTE unless an absolute contraindication to

anticoagulation exists. Although protecting the pulmonary vascular bed, filter placement does not inhibit the extension of existing venous thrombi or diminish the systemic prothrombotic state. Small thrombi can pass through patent filters or through collaterals around obstructed filters; furthermore, thrombus can extend through the filter itself. One study demonstrated that placement of a vena cava filter was capable of diminishing the incidence of early PE.²⁷¹ The benefit was somewhat offset by an increased risk of recurrent DVT within 2 years, although an 8-year follow-up did not disclose an increased risk of recurrence or postthrombotic syndrome.²⁷² The development of retrievable filters suggests that the intervention will no longer be irreversible, although extensive randomized clinical trials have not yet been performed to establish the safety and efficacy of this strategy.^{273,274} Given these considerations, long-term anticoagulation should be utilized following filter placement if no contraindications exist or as soon as any existing bleeding risk resolves.

MASSIVE PULMONARY EMBOLISM

The significant mortality associated with massive PE justifies a separate consideration of the diagnostic and therapeutic approach to this problem.²⁷⁵ The definition of massive PE should be based on hemodynamic considerations rather than purely anatomic ones. This impression is supported by mortality statistics from the urokinase trials and others.²⁷⁶⁻²⁷⁸ Although anatomically massive emboli have a greater likelihood of being associated with hemodynamic compromise, not all anatomically massive emboli lead to circulatory insufficiency. Irrespective of the degree of vascular obstruction, patients with PE who present with shock have a mortality rate, regardless of the type of intervention, that approaches 30%.

STRATIFICATION ACCORDING TO THE RISK OF MASSIVE PULMONARY EMBOLISM

The risk of mortality and significant morbidity from acute PE is substantially influenced by patient's premorbid conditions and clinical presentation.²⁷⁹ Such risk has been usefully assessed by clinical scoring systems. The *Pulmonary Embolism Severity Index* (PESI), a risk-stratification scoring system derived from patients' demographic characteristics (gender and age), analyzes coexisting illnesses (cancer, heart failure, and chronic lung disease) and physical findings related to cardiopulmonary status (heart rate, systolic blood pressure, respiratory rate, temperature, mental status, and oxygenation).^{280,281} The PESI divides PE patients into five distinct classes of risk, and the mortality associated with each class was remarkably consistent across several validation populations. Mortality was typically between 0% and 1.6% for class I, 2% and 3.5% for class II, 6.5% and 7.7% for class III, 10.4% and 12.2% for class IV, and 17.9% and 24.5% for class V. One small validation population, in which the sickest patients had been excluded, demonstrated about half the mortality for each of the five classes. A simplified version of the PESI score (including only age, cancer,

chronic cardiopulmonary disease, heart rate, systolic blood pressure, and oxyhemoglobin saturation levels) appears to perform just as well as the more complicated one.²⁸² Regardless of the scoring system used, it is important to remember that clinical judgment is paramount. A patient with a low PESI score who nonetheless appears severely ill should be monitored according to clinical judgment, rather than by the score itself.²⁸¹

Echocardiography and other techniques have been investigated as means of stratifying risk in patients with embolism.²⁸³ Short-term mortality risk in PE is strongly related to the presence of systemic hypotension at the time of diagnosis. However, systemic hypotension represents a late and potentially fatal manifestation of right ventricular dysfunction. For this reason, transthoracic echocardiography²⁸³ and biochemical markers such as serum troponin²⁸⁴ or serum brain natriuretic hormone²⁸⁵ levels have been investigated as a means of evaluating right ventricular function in patients with embolism. Clinical studies have suggested that although these techniques are reasonably capable of distinguishing patients with a good prognosis from those at risk for death and other adverse events, they lack the predictive power to warrant clinical decision making exclusively on the basis of a single test.²⁸⁶⁻²⁸⁸ Moreover, it has not been conclusively established that the potential risks of a more aggressive therapeutic approach in all “high-risk” patients, the majority of whom have a satisfactory outcome when treated with conventional therapy alone, justify the potential benefit.²⁸⁹

The therapeutic approach to the patient with hemodynamically massive PE should be designed to counteract the adverse physiologic consequence of pulmonary vascular obstruction, whether or not that obstruction is anatomically massive. Basic care of a critically ill patient should not be overlooked while specific diagnostic and therapeutic considerations are being implemented. Oxygen should be administered to alleviate the hypoxic pulmonary vasoconstriction, which might be contributing to the pulmonary hypertension. Intubation and mechanical ventilatory support might be required to improve oxygenation and decrease metabolic demands. Although volume resuscitation has been advised, excessive preload may further distend the right ventricle and increase right ventricular wall tension, resulting in decreased coronary perfusion and right ventricular ischemia. The judicious use of inotropic support can also prove useful in increasing blood pressure, preserving right coronary artery perfusion, and supporting right ventricular function.²⁹⁰ Although there is a tendency to utilize central hemodynamic monitoring in critically ill hypotensive patients, this intervention should be considered carefully in the patient with massive PE. A femoral approach poses the risk of dislodging residual iliofemoral thrombus, and balloon flotation poses the risk of dislodging embolic material that might be trapped within the right atrial or ventricular cavities (see [Video 57-2](#)).

Although the central goal of therapy in massive PE should be to relieve pulmonary vascular obstruction, the severely compromised nature of the pulmonary vascular bed makes prevention of recurrence an important secondary consideration. Therefore, assuming the requisite expertise in filter placement is available and that placement of a filter will not interfere with the primary management of the

patient, placement of a filter should be considered in all patients with hemodynamically massive embolism.

THROMBOLYTIC THERAPY

The use of thrombolytic agents in acute PE remains controversial.^{291,292} Although thrombolytic therapy with plasminogen-activating medications does appear to accelerate the rate of thrombolysis, there is no convincing evidence to suggest that it decreases mortality, increases the ultimate extent of resolution when measured at 7 days, reduces thromboembolic recurrence rates, improves symptomatic outcome, or decreases the incidence of thromboembolic pulmonary hypertension.²⁹³⁻²⁹⁵ The one issue about which there can be little controversy is that the use of thrombolytic agents is associated with a substantially increased risk of bleeding, including intracranial hemorrhage. Intracranial hemorrhage has developed in 0.5% to 2% of patients treated with thrombolytic agents in trials evaluating the use of these agents in both PE and myocardial infarction.^{294,296}

On the basis of these data, and assuming there is no contraindication to its use, the role of thrombolytic therapy in PE should be limited to those circumstances in which an accelerated rate of thrombolysis may be considered lifesaving (i.e., in patients with PE who present with hemodynamic compromise or who develop hemodynamic compromise during conventional therapy with heparin). In patients with embolism associated with intracavitary right atrial or ventricular thrombi, thrombolytics may be a reasonable consideration, although direct, surgical removal should also be considered.^{297,298} At present, the finding of right ventricular dysfunction on echocardiography in the absence of hemodynamic instability should not serve as a justification for thrombolytic therapy.^{289,291} Approximately one third of patients with PE will have echocardiographic evidence of right ventricular dysfunction²⁹⁹ and there is insufficient evidence to warrant a change in therapy on the basis of that finding alone.²⁸⁸ Unless a subset of patients with right ventricular dysfunction who are at risk for an adverse outcome and benefit from thrombolytic therapy can be identified,³⁰⁰ there is little basis for exposing all such patients to the considerable risk of hemorrhagic complications with thrombolysis. This is especially true given the recent advances in heparin administration strategies.

PULMONARY EMBOLECTOMY

The role of pulmonary embolectomy in acute hemodynamically massive PE also remains controversial.³⁰¹⁻³⁰⁴ Patients with anatomically massive or submassive emboli who are hemodynamically compromised, who have not had a cardiac arrest, and who do not have an absolute contraindication to thrombolytic therapy should be managed initially with aggressive medical therapy, including thrombolytic therapy plus heparin. Patients in whom acute embolectomy might be considered include those with hemodynamically massive PE who have an absolute contraindication to anticoagulant or thrombolytic therapy, those who have suffered a cardiopulmonary arrest (although the mortality associated with embolectomy in those who have

had one is far higher than those who have not), and those in whom aggressive medical therapy, including the use of thrombolytics, has proved ineffective.³⁰⁵

The concept of relieving the pulmonary vascular obstruction and decreasing right ventricular afterload with a percutaneous device has been appealing.³⁰⁶ Catheter-directed therapy for acute PE may be accomplished by mechanical disruption and aspiration, by infusion of plasminogen-activating medications, or both. Uncontrolled (mostly retrospective) clinical studies suggest that catheter-directed thrombolysis may entail less hemorrhagic risk than systemic administration of thrombolytic agents. However, there are no randomized controlled trials to indicate when catheter-directed thrombolysis would result in better outcomes than other forms of therapy.³⁰⁷

POSTEMBOLIC PROPHYLAXIS

After the acute phase of treatment, recurrence is substantially reduced by a follow-up course of anticoagulation for at least 3 months.³⁰⁸ Anticoagulation is typically accomplished with warfarin, adjusted to keep the *international normalized ratio* (INR) of prothrombin time between 2 and 3. In patients with cancer-associated thromboembolism, follow-up therapy with LMWH led to better outcomes than treatment with warfarin.³⁰⁹

Direct inhibitors of factor Xa and of thrombin are promising alternatives to warfarin for follow-up therapy for thromboembolism. Rivaroxaban (described earlier for the acute phase of VTE treatment) has been shown to be safe and effective for follow-up treatment of PE²⁶⁶ and DVT.²⁶⁷ It is well absorbed orally and does not require close therapeutic monitoring or INR values, which are necessary for warfarin treatment.

Dabigatran, a direct thrombin inhibitor, is another alternative to warfarin for the follow-up phases of treatment for venous thromboembolism. Like rivaroxaban, it is a direct inhibitor that does not rely on the patient's antithrombin for its activity. Another similarity is that it is well absorbed orally; it is not, however, recommended for the acute phase of treatment. Dabigatran was comparable with warfarin in a randomized controlled trial for the follow-up treatment of venous thromboembolism.³¹⁰ After acute treatment with heparin or LMWH, patients were randomized to dabigatran, 150 mg orally twice a day without dosage adjustment, or warfarin, adjusted to an INR of 2 to 3. The outcome of the two groups was similar with respect to symptomatic recurrent VTE and major bleeding. These results suggest that dabigatran is an acceptable alternative to warfarin for the 6-month treatment of VTE following acute therapy with heparin or LMWH. It has the advantage of not requiring INR-guided dosage adjustment, which can be labor intensive for clinicians and patients. Dabigatran is well absorbed orally and has a pharmacokinetic profile in most patients that allows dosing for either prophylaxis or treatment of VTE without adjustment in most patients. The simplicity of the dosing regimens suggests that dabigatran would be an attractive option for patients with normal renal and hepatic function. However, clinical trials typically excluded patients with creatinine clearances less than 30 mL/minute and those with severe hepatic enzyme elevations.

The duration of outpatient anticoagulation for patients with PE remains a subject of controversy.^{63,311-314} Much of the difficulty in making definitive recommendations regarding the duration of outpatient anticoagulation results from the diverse population that is affected by the disease process. The decision to continue or withdraw therapy should be made on an individual basis and take into account factors such as the nature of the initial thromboembolic event (spontaneous or associated with a defined clinical circumstance), the type of initial event (venous thrombosis or PE), the presence of an ongoing predisposition (either clinical or hereditary), and possibly the persistence of residual venous thrombosis as determined by ultrasonography or persistently high D-dimer levels in the blood.^{63,65,311-316}

Patients with a clearly defined initial predisposition, whose initial thromboembolic risk factors have resolved and whose V/Q scan and noninvasive lower extremity test results have normalized, can likely be managed with a 3-month course of anticoagulation.³¹⁴ This maxim is especially warranted when the thromboembolism was provoked by surgery.³¹⁷ Patients without a clearly defined initial predisposition to thromboembolism have about a 30% to 50% risk of recurrence during the subsequent 10 years.^{318,319} Those with persistent large lung perfusion defects or abnormal lower extremity test results probably may also have higher rates of recurrence.^{235,311,312} Although the topic is controversial, those patients may benefit from an indefinite period of anticoagulation, even though such a strategy is associated with an increased risk of hemorrhagic complications.³²⁰ Clinical circumstances in which indefinite periods of anticoagulation should be considered quite strongly include a history of more than one episode of idiopathic venous thrombosis or PE; the presence of certain irreversible acquired or hereditary risk factors that strongly predispose toward VTE (active cancer, immobilization, antiphospholipid antibody syndrome, and hereditary deficiencies of antithrombin III, protein C, or protein S³²¹); the presence of extensive residual venous thrombosis or the postthrombotic syndrome; and the presence of extensive residual V/Q scan or CT scan defects or pulmonary hypertension. Although the presence of the heterozygous factor V Leiden mutation or the prothrombin gene mutation individually does not appear to increase the absolute risk of recurrence substantially,¹⁸ the presence of the homozygous factor V Leiden mutation or the heterozygous factor V Leiden mutation in combination with the prothrombin gene mutation does appear to be associated with an increased recurrence risk.³³

A standard for repeating noninvasive testing of either the lungs or the deep veins of the lower extremities at the anticipated time of anticoagulant discontinuation does not exist. Although the cost implications would be substantial, such an approach would be beneficial in establishing a new baseline study that could be used for comparison in the event thromboembolic recurrence was suspected and in identifying patients with pulmonary vascular obstruction of sufficient extent to place them at risk for the development of chronic thromboembolic pulmonary hypertension.

Regarding postembolic anticoagulant "intensity," the recommended therapeutic range for the INR in the majority of patients with VTE is 2 to 3. It is controversial whether patients with the antiphospholipid syndrome should be an

exception to this rule because a retrospective analysis suggested that an INR of 3 to 4 was considered more effective in reducing recurrence rates than an INR less than 3.³²² However, subsequent randomized treatment trials of patients with the antiphospholipid syndrome showed the standard INR target of 2 to 3 to be just as effective as the higher target range.^{323,324} In patients with a lupus anticoagulant, in whom the baseline INR may be elevated, the INR may not reliably reflect the level of anticoagulation. In these patients, the use of tests that are insensitive to the lupus anticoagulant, such as the prothrombin-proconvertin time or chromogenic factor X assay, has been recommended.³²⁵

Trials evaluating the effectiveness of low-intensity anticoagulation (maintaining the INR in a range of 1.5 to 2) following a standard 3- to 6-month period of anticoagulation have demonstrated that such an approach is superior to placebo but less effective than standard therapy, without an appreciable reduction in bleeding complications.^{326,327}

Aspirin is another alternative for extended therapy of unprovoked venous thromboembolism in patients who have completed the standard (acute and several-month follow-up) course of anticoagulation. However, its effectiveness in preventing recurrence was variable in clinical trials and substantially less than what is observed with warfarin. In one trial, aspirin moderately reduced (but did not eliminate) the rate of recurrence,³²⁸ but in a similarly conducted trial, it did not significantly reduce recurrence.³²⁹ In both trials, however, aspirin did not appreciably increase bleeding risk. In addition, the benefits of aspirin on other cardiovascular causes of morbidity and mortality (stroke, myocardial infarction, etc.)³²⁹ make it an attractive option for patients with unprovoked venous thromboembolism who are not candidates for more effective forms of extended anticoagulation therapy.

RESOLUTION VERSUS PERSISTENCE OF THROMBOEMBOLISM

After a PE, the embolic material in the pulmonary arteries either resolves by fibrinolysis or is remodeled into organized scars. The extent of remodeling and the severity of the resulting vascular obstruction varies among patients; in some, lung perfusion is rapidly restored,⁹⁶ although the resolution in the first week is typically incomplete. Embolic remodeling probably continues at a slower pace for the next 1 to 2 months.^{330,331} Residual defects commonly persist beyond this period, suggesting that the emboli have been remodeled into permanent vascular scars.^{69,90-95,332-334}

Although the mechanism is not well understood, restoration of lung perfusion is frequently incomplete.³³⁵⁻³⁴⁶ Persistent perfusion defects are associated with respiratory symptoms,³³⁹ hypoxemia,^{335,340,346} gas exchange deficits,^{340,347,348} exercise intolerance,³⁴⁹ and other serious clinical consequences.^{335,339,340,346-350} Persistent perfusion defects are also associated with worsened *New York Heart Association* dyspnea classification, increased pulmonary artery pressure, and a markedly increased risk of chronic thromboembolic pulmonary hypertension.⁹⁸

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

In a small percentage of patients, estimated to represent about 0.4% to 3.8% of the 450,000 patients who survive a pulmonary embolic event each year in the United States, the emboli do not resolve and the residual obstruction is sufficient to cause persistent pulmonary hypertension.³⁵¹⁻³⁵⁸

Most patients who present with chronic thromboembolic pulmonary hypertension were previously diagnosed with acute pulmonary emboli or DVT, and their presentations (e.g., embolic burden, clinical stability) appear indistinguishable from patients who do resolve their acute emboli.³⁵¹ A prospective study of patients presenting with PE disclosed that, in addition to the size of the initial PE, factors such as recurrent PE, idiopathic PE, and PE at a young age were associated with an elevated risk for chronic thromboembolic pulmonary hypertension.³⁵⁹ Other clinical factors associated with chronic thromboembolic pulmonary hypertension are right heart strain (e.g., pulmonary artery systolic pressures >50 mm Hg) during the acute PE,^{97,359} advanced age,³⁵⁹ previous splenectomy,^{360,361} the presence of a ventriculoatrial shunt for the treatment of hydrocephalus,^{360,361} and a variety of chronic inflammatory disorders (e.g., osteomyelitis, inflammatory bowel disease).^{360,361} A number of laboratory findings have also been associated with chronic thromboembolic pulmonary hypertension, the most prominent of which is the lupus anticoagulant, which has been reported in 10% to 50% of these patients.^{362,363} Elevated plasma levels of factor VIII,³⁶⁴ lipoprotein (a),³⁶⁵ and even non-O blood groups³⁶⁶ have a statistical association with the development of chronic thromboembolic pulmonary hypertension after an acute PE. However, the prevalence of other thrombophilic tendencies, such as the factor V Leiden mutation, anti-thrombin III, protein C, and protein S deficiency, does not appear to be higher in these patients than that encountered in the normal population.

Despite the epidemiologic associations, the mechanism underlying chronic thromboembolic pulmonary hypertension development remains unclear.³⁶⁷ A subset of patients appears to have an intrinsic resistance to fibrinolysis.³⁶⁸ The resistance is associated with abnormalities in fibrinogen that alter its molecular structure.^{369,370} Such alterations in fibrinogen likely deform and disorganize the fibrin polymer networks, thereby making them more resistant to fibrinolysis and perhaps stimulating remodeling of thromboemboli into scars.

In about half of the patients, the initial acute pulmonary thromboembolism is not clinically recognized.³⁷¹ The diagnosis of thromboembolic pulmonary hypertension is usually not made until the degree of pulmonary hypertension is advanced. As a result, the exact hemodynamic evolution of the disease has not been fully established.³⁷² The extent of pulmonary vascular obstruction appears to be a major determinant of disease initiation, with involvement of greater than 40% of the pulmonary vascular bed present in the majority of patients. Hemodynamic progression in certain patients may involve thromboembolic recurrence or in situ pulmonary artery thrombosis. However, hemodynamic progression in many patients appears to involve the

development of a hypertensive pulmonary arteriopathy, similar to that encountered in other causes of secondary pulmonary hypertension.³⁷³ This supposition is supported by several lines of evidence: a poor correlation between the extent of central anatomic obstruction and the degree of pulmonary hypertension; documented hemodynamic progression in the absence of recurrent embolic events or evidence of *in situ* pulmonary artery thrombosis; and histopathology demonstrating arteriopathic changes in the resistance vessels of both the involved and uninvolved pulmonary vascular system.

Survival without intervention is poor and proportional to the degree of pulmonary hypertension at the time of diagnosis. In one study, the 5-year survival rate was 30% when the mean pulmonary artery pressure exceeded 40 mm Hg and 10% when it exceeded 50 mm Hg.³⁷⁴ In another study, a mean pulmonary artery pressure above 30 mm Hg appeared to serve as a threshold value portending a poor prognosis.³⁷⁵

DIAGNOSIS

Perhaps the most important aspect of dealing with this patient group is the proper approach to its recognition.³⁷⁶ Progressive dyspnea is a complaint common to all patients with chronic thromboembolic pulmonary hypertension. Later in the course of the disease, exertional chest pain, near-syncope or syncope, or lower extremity edema may develop.

Although a history of documented thromboembolism may not be present, many patients can provide a history consistent with an acute embolic event. They may describe an episode of “pleurisy,” lower extremity “muscle strain,” or prolonged, atypical “pneumonia,” or they may describe a hospitalization or surgical procedure from which they never fully recovered. That an episode of VTE was not diagnosed, or was misdiagnosed, is not surprising because venous thrombosis and PE are often overlooked.³⁷⁷

Diagnosis is commonly delayed, particularly in the absence of an acute history of VTE. Progressive dyspnea and exercise intolerance are often attributed to coronary artery disease, cardiomyopathy, interstitial lung disease, asthma, deconditioning, or psychogenic dyspnea. Therefore an abnormality of the pulmonary vascular bed should be considered in any patient with dyspnea in whom a definitive etiology cannot be defined. Later in the course of the disease, the patient may experience exertional chest pain, presyncope, or syncope due to the presence of severe pulmonary hypertension and the inability of a compromised right ventricle to meet cardiac output demands.

Physical examination findings may be subtle early in the course of the illness, thereby contributing to this diagnostic delay. Before the development of significant right ventricular hypertrophy or overt right ventricular failure, physical examination abnormalities may be limited to a narrowing of S2 or to a subtle accentuation of its pulmonic component. Late in the course of the disease, obvious findings such as a right ventricular heave, jugular venous distention, prominent a- and v-wave venous pulsations, fixed splitting of S2, a right ventricular S3, murmurs of tricuspid regurgitation or pulmonic insufficiency, hepatomegaly, and ascites may develop. Peripheral edema, a result of chronic

lower extremity venous outflow obstruction or right ventricular failure, may be present.

A unique physical finding in certain patients with chronic thromboembolic disease is the presence of flow murmurs over the lung fields.³⁷⁸ These subtle bruits, which appear to originate from turbulent flow through partially obstructed or recanalized thrombi, are high pitched and blowing in quality, heard over the lung fields rather than the precordium, accentuated during inspiration, and frequently heard only during periods of breath-holding. These bruits have not been described in primary pulmonary hypertension, the most common competing diagnostic possibility.

The intent of the diagnostic evaluation is to establish the presence and degree of pulmonary hypertension, define its etiology, and, if major vessel thromboembolic disease is present, determine whether it is accessible to surgical intervention. Findings on standard laboratory tests are nonspecific, depending on the point in the natural history of the disease at which they are obtained, and reflective of the hemodynamic and gas-exchange consequences of the thromboembolic obstruction and the accompanying cardiac dysfunction.

Chest radiography, although often normal, may demonstrate findings that suggest the diagnosis.³⁷⁹ Enlargement of both main pulmonary arteries or asymmetry in the size of the central pulmonary arteries may be present (Fig. 57-10). Areas of hypoperfusion or hyperperfusion may be present. There also may be evidence of old pleural disease, unilaterally or bilaterally. The cardiac silhouette may reflect obvious right atrial or right ventricular enlargement; more often, right ventricular hypertrophy and enlargement are suggested only on the lateral image by encroachment on the normally empty retrosternal space.

Early in the course of the disease, electrocardiographic findings may be normal. Later in the course, electrocardiography demonstrates evidence of right ventricular hypertrophy. Pulmonary function testing, performed to evaluate the patient's dyspnea, is often within normal limits. The majority of patients have a reduction in the single-breath diffusing capacity for carbon monoxide; however, a normal value does not exclude the diagnosis. Approximately 20% of patients demonstrate a mild to moderate restrictive defect due in part to the presence of infarct-related parenchymal scars.³⁸⁰ However, the degree of spirometric defect is almost always disproportionate to the patient's gas-exchange abnormalities, symptomatic complaints, and degree of pulmonary hypertension.

In terms of gas-exchange findings, the arterial PO₂ may be within normal limits. However, the alveolar-arterial PO₂ difference is typically widened, and the majority of patients have a decline in the arterial PO₂ with exercise. Dead-space ventilation is often increased at rest and worsens with exercise. Minute ventilation is typically elevated as a result of this increased dead-space ventilation.³⁸¹

Echocardiography commonly provides the initial objective evidence that pulmonary hypertension is present. Once the diagnosis of pulmonary hypertension has been established, determination of whether it originates from abnormalities of the small, resistance vessels or from central, chronic thromboembolic obstruction is essential.

V/Q lung scanning appears to provide an excellent, noninvasive means of distinguishing between potentially

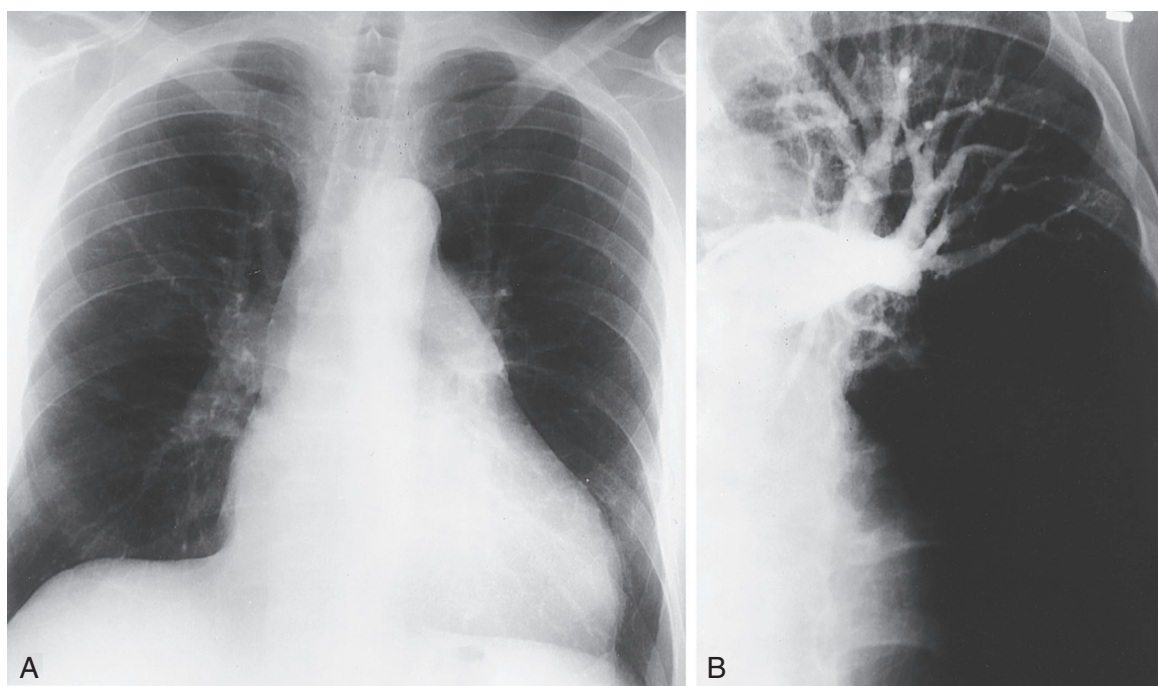


Figure 57-10 Chest radiograph in a patient with chronic thromboembolic pulmonary hypertension. A, Note asymmetry of central pulmonary arteries, absence of descending left pulmonary artery, left lower lobe oligemia, and peripheral opacity representing prior infarct. **B,** Angiogram in the same patient demonstrates complete proximal occlusion of the descending left pulmonary artery.

operable major vessel thromboembolic pulmonary hypertension and small vessel pulmonary hypertension.^{382,383} In chronic thromboembolic disease, at least one (and, more commonly, several) segmental or larger mismatched V/Q defects are present. In primary pulmonary hypertension, perfusion scans are either normal or exhibit a “mottled” appearance characterized by subsegmental defects. Other disorders leading to pulmonary hypertension may be associated with segmental defects on perfusion scan, including pulmonary veno-occlusive disease, pulmonary artery sarcoma, mediastinal fibrosis, and large vessel vasculitides.³⁸⁴ It is important to recognize that the V/Q often understates the actual extent of central pulmonary vascular obstruction (see eFig. 57-11).³⁸⁵ Channels through central obstructing lesions or partial flow around them, a result of the often complex patterns of recanalization and organization that take place following an embolic event, allow the radioisotopic agent to reach the periphery of the lung. Depending on the distribution of flow, these areas may appear normal or as relatively hypoperfused “gray zones.” Therefore V/Q scanning, although capable of suggesting the potential presence of chronic thromboembolic obstruction, is incapable of determining the magnitude, location, or proximal extent of the disease, information critical to the question of surgical accessibility.

The role of CT scanning in the evaluation of patients with chronic thromboembolic disease is evolving.^{386,387} A variety of CT abnormalities (eFig. 57-12) have been described: chronic thromboembolic material located in an eccentric position within the central pulmonary arteries, right ventricular enlargement, dilated central pulmonary arteries, bronchial artery collateral flow, parenchymal abnormalities consistent with prior infarcts, and mosaic

attenuation of the pulmonary parenchyma.³⁸⁸ However, the absence of these findings does not preclude the possibility of surgically accessible chronic thromboembolic disease. Furthermore, the presence of central thrombus has been described in primary pulmonary hypertension and other chronic pulmonary disorders.³⁸⁹ CT scanning is also incapable of providing essential hemodynamic data. CT is particularly useful in the evaluation of the main pulmonary arteries and of unilateral or predominantly unilateral pulmonary vascular obstruction as determined by V/Q scanning.³⁸⁸ Under these circumstances, the probability of other diagnostic possibilities such as pulmonary artery sarcoma (see Fig. 54-5, eFigs. 54-15, 54-16 and 54-17), vasculitis, malignancy, and mediastinal fibrosis (see eFigs. 37-1A-G and 54-7, 54-21 and 54-22) is increased. CT also has a role, along with physiologic testing, in helping to evaluate the status of the pulmonary parenchyma in patients with coexisting obstructive or restrictive lung disease.

Right-heart catheterization and pulmonary angiography are essential to designate the degree of pulmonary hypertension, exclude competing diagnoses, and define the surgical accessibility of the obstructing thrombotic lesions. If hemodynamic measurements at rest demonstrate only modest degrees of pulmonary hypertension, measurements should be obtained following a short period of exercise. In patients with chronic thromboembolic obstruction sufficient to abolish normal compensatory mechanisms, exercise-related increases in cardiac output will be accompanied by an almost linear elevation in pulmonary artery pressure. The angiographic findings in chronic thromboembolic disease bear little resemblance to the sharply defined, intraluminal defects diagnostic of acute embolism.³⁹⁰ Five distinct angiographic patterns that correlate with the

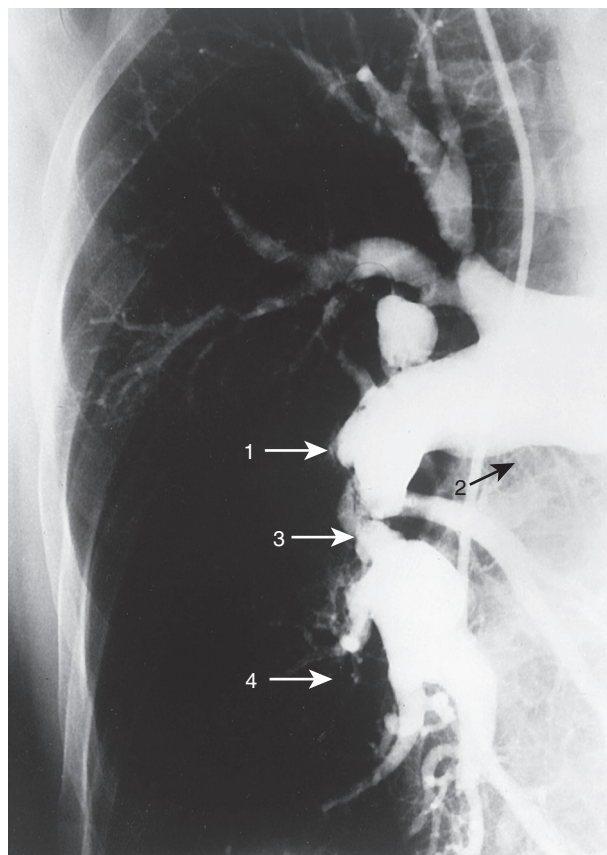


Figure 57-11 Right-sided pulmonary angiogram in a patient with chronic thromboembolic pulmonary hypertension. Many of the classic angiographic findings associated with this disease are present, including pouch defects (arrow 1), intimal irregularity (arrow 2), pulmonary artery webs (arrow 3) with poststenotic dilation, and complete obstruction (arrow 4) to flow of the right middle lobe and several lower lobe segmental arteries.

finding of organized thromboembolic material at the time of thromboendarterectomy have been described (Fig. 57-11): (1) pouch defects, (2) pulmonary artery webs or bands, (3) intimal irregularities, (4) abrupt narrowing of the major pulmonary arteries, and (5) obstruction of lobar or segmental vessels at their point of origin, with complete absence of blood flow to pulmonary segments normally perfused by those vessels.

Although pulmonary angiography usually completes the diagnostic sequence and confirms surgical accessibility, adjunctive studies may be necessary to exclude competing diagnoses. CT of the chest can be useful in determining whether a mediastinal process (e.g., mediastinal fibrosis, malignancy) is responsible for the angiographic findings and, in selected cases, in defining the extent and accessibility of the obstructing thrombi. Arch aortography can be useful if an arteritis is being considered.³⁹¹

The major conditions from which thromboembolic pulmonary hypertension must be distinguished include primary pulmonary hypertension and other forms of secondary pulmonary hypertension such as mediastinal fibrosis with pulmonary arterial or venous obstruction, pulmonary hypertension associated with congenital atrial or ventricular septal defects, congenital pulmonary artery branch stenoses, pulmonary artery agenesis, tumors arising in or obstructing the central pulmonary arteries, and

Takayasu arteritis. The standard diagnostic approaches previously discussed, preferably performed at a center experienced in the management of pulmonary hypertension, are capable of excluding the majority of these competing diagnoses.

TREATMENT

For patients suffering from chronic thromboembolic pulmonary hypertension, the decision to proceed to pulmonary thromboendarterectomy is based on both objective and subjective factors, which are carefully defined during the preoperative evaluation.³⁹²

Pulmonary thromboendarterectomy is considered in symptomatic patients with hemodynamic or ventilatory impairment at rest or with exercise. The mean pulmonary vascular resistance in patients undergoing surgery is typically 800 to 1000 dyne·sec·cm⁻⁵, with a range of 300 to 2000 dyne·sec·cm⁻⁵.³⁷² Patients in the lower range of pulmonary hemodynamic impairment include those with involvement limited to one main pulmonary artery, those with vigorous lifestyle expectations in whom high dead-space and minute ventilatory demands are disabling, and those who live at altitude. Thromboendarterectomy is also considered in patients with normal or near-normal pulmonary hemodynamics at rest who develop significant levels of pulmonary hypertension with exercise. If surgery is deferred in patients with this hemodynamic profile, careful monitoring is recommended to detect whether pulmonary hypertension progresses.

The location and extent of the proximal thromboembolic obstruction is the most critical determinant of operability. Occluding thrombi must involve the main, lobar, or proximal segmental arteries. Those that originate more distally are not amenable to thromboendarterectomy with current surgical techniques. In terms of extent, the anatomic and hemodynamic findings must be interpreted in concert. An acceptable postoperative hemodynamic outcome requires that the preoperative hemodynamic impairment be consistent with the magnitude of surgically accessible thromboembolic material determined by angiography. This determination is critical. If the major component of the preoperative hemodynamic impairment derives from surgically inaccessible disease or from the resistance conferred by a secondary, small vessel arteriopathy, residual pulmonary hypertension will be present postoperatively. Depending on the extent of the postoperative pulmonary hypertension, this outcome may be associated with adverse short-term and long-term consequences.

The only absolute contraindication to thromboendarterectomy is the presence of severe underlying lung disease, either obstructive or restrictive. Thromboendarterectomy in this population can improve the hemodynamic profile but may have little effect on the ventilatory impairment. Advanced age, severe right ventricular failure, and the presence of collateral disease influence risk assessment but do not represent absolute contraindications to the procedure if the anticipated relief of the pulmonary hypertension will improve both the quality and duration of life. Patients as young as 16 and as old as 84 years of age, as well as those with complex comorbid conditions, have successfully undergone the procedure.

Before surgery, several other essential issues must be considered. It is important that the patient be protected against embolic recurrence, both over the long term and during the high-risk perioperative period. Therefore an inferior vena cava filter should be placed before surgery unless there is an obvious source of embolism outside the lower extremities or pelvis. For those at risk of coronary artery disease, coronary angiography is routinely performed before surgery, usually at the time of the right heart catheterization and pulmonary angiography. Coronary artery bypass grafting, if necessary, can be performed safely at the time of the thromboendarterectomy.³⁹²

Sternotomy with cardiopulmonary bypass and periods of circulatory arrest represents the procedure of choice.³⁹³ This approach allows access to both pulmonary arteries and ensures more complete removal of the chronically obstructing material.³⁹⁴ A sternotomy approach also provides adequate exposure for additional procedures that need to be performed. In a review of 1190 patients undergoing thromboendarterectomy, 90 patients (7.6%) required such a combined procedure exclusive of solitary closure of a patent foramen ovale, which is performed in approximately 30% of thromboendarterectomy procedures.³⁹² The use of cardiopulmonary bypass allows periods of complete circulatory arrest, which provide a bloodless operative field essential for meticulous lobar and segmental dissections.

Thromboendarterectomy bears little resemblance to acute pulmonary embolectomy. The neointima in chronic thromboembolic disease is deceptive and is often not easily recognizable as chronic thrombus. The procedure is a true endarterectomy that requires careful dissection of chronic endothelialized material from the native intima to restore pulmonary arterial patency. Considerable experience is required by the surgical team to identify the correct operative plane and remove the segmental-level extensions of the more proximal obstruction (Fig. 57-12). Failure to do so results in an inadequate hemodynamic outcome.

During the development of and early experience with this procedure, mortality was related to many causes. At present, the major causes of death have been related to



Figure 57-12 Specimen obtained at the time of pulmonary thromboendarterectomy. In addition to central thromboembolic obstruction, note multiple segmental extensions. Failure to remove these distal extensions adequately will result in an inadequate hemodynamic outcome. (From Marshall PS, Kerr KM, Auger WR: Chronic thromboembolic pulmonary hypertension. *Clin Chest Med* 34:779–797, 2013. Fig. 5.)

reperfusion pulmonary edema and to residual postoperative pulmonary hypertension and right ventricular failure in patients in whom pulmonary thromboendarterectomy failed to achieve substantial improvement in pulmonary hemodynamics.³⁹⁴

Although pulmonary hemodynamics may improve immediately, the postoperative course can be complex. In addition to complications common to other forms of cardiac surgery (e.g., arrhythmias, atelectasis, wound infection, pericardial effusions, delirium), patients undergoing pulmonary thromboendarterectomy often experience two unique complications capable of significantly impairing gas exchange: reperfusion pulmonary edema and pulmonary artery “steal.”^{395,396}

Pulmonary artery steal (Fig. 57-13) represents a postoperative redistribution of pulmonary arterial blood flow away from previously well-perfused segments and into the newly endarterectomized segments. Long-term follow-up has demonstrated that pulmonary vascular steal resolves in the majority of patients.³⁹⁷ Reperfusion pulmonary edema appears to represent a form of high-permeability lung injury that is limited to those areas of lung from which proximal thromboembolic obstructions have been removed (Fig. 57-14). It may appear up to 72 hours after surgery and is highly variable in severity, ranging from a mild form of edema resulting in postoperative hypoxemia to an acute, hemorrhagic, and fatal complication. When associated with pulmonary artery steal, reperfusion pulmonary edema can represent a significant challenge in terms of postoperative gas exchange. Pulmonary blood flow is directed toward edematous, noncompliant areas of lung that contribute poorly to gas exchange. Management of reperfusion edema, as with other forms of acute lung injury, is supportive.

Although exact figures are not available, approximately 5000 to 6000 thromboendarterectomy procedures have been performed worldwide, with 3000 of these cases performed at University of California, San Diego. In reported series of patients undergoing thromboendarterectomy since 1999, in-hospital mortality rates have ranged between 4.4% and 21.4%.^{394,398–402} In an update of the University of California, San Diego experience, the mortality for the last 500 patients was 2.2%.⁴⁰³ The specific factors affecting perioperative mortality have not been completely defined. Several studies have suggested that New York Heart Association functional class IV status, age older than 70, the severity of preoperative pulmonary vascular resistance, the presence of right ventricular failure as manifested by high right atrial pressures, details of the postoperative management, and perhaps the duration of pulmonary hypertension may adversely influence outcome. It is also reasonable to suggest that there may exist a strong relationship between volume of procedures performed and outcome, as has been demonstrated with other high-risk surgical procedures.⁴⁰⁴ In the case of thromboendarterectomy, this may be related to consistency of patient evaluation, surgical experience, uniform delivery of postoperative care, and the presence of dedicated resources for dealing with postoperative complications. Should this prove to be the case, strong consideration could be given to performing the procedure at a limited number of referral centers.

Given what is known about the natural history of the disease and the progressive nature of the pulmonary

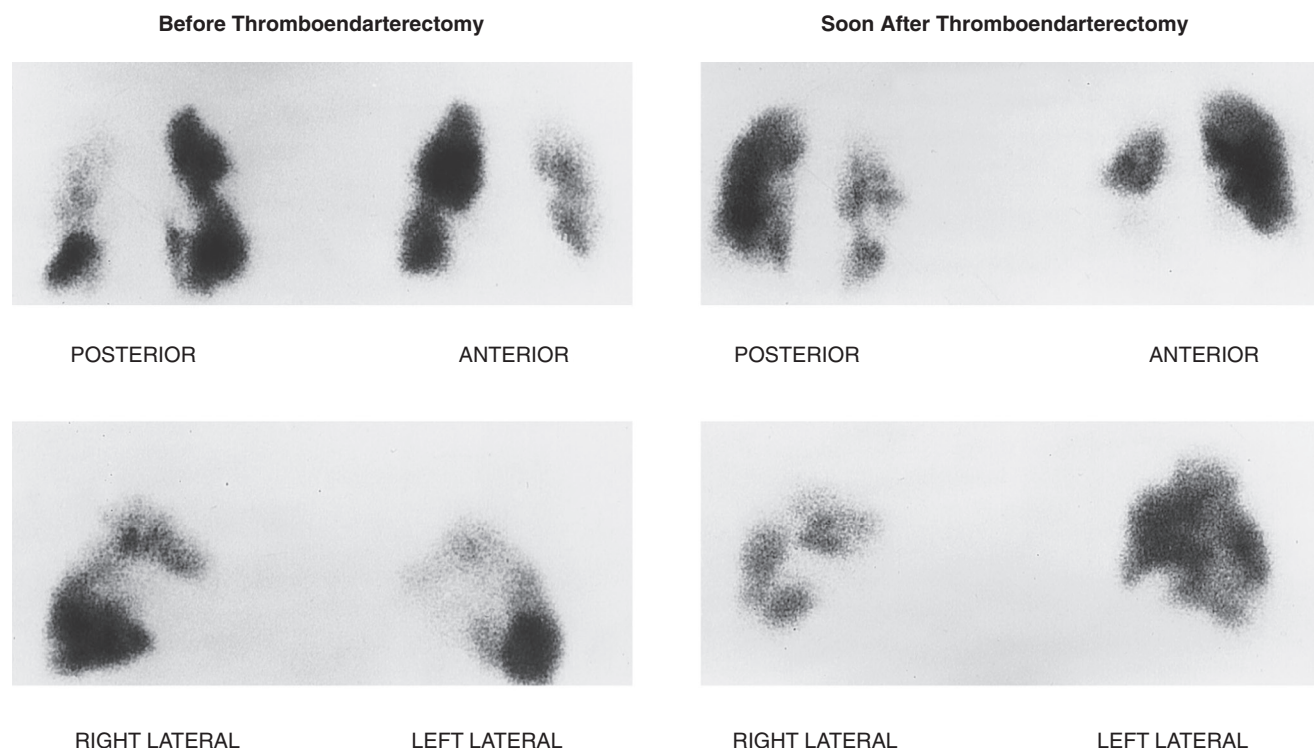


Figure 57-13 Perfusion scans show pulmonary artery steal. On the left, preoperative perfusion scan demonstrates minimal flow to the left lung. On the right, perfusion scan obtained in the early postoperative period demonstrates dramatic reversal of flow with vascular “steal” from right lung. Equilibration and normalization of flow over time is the rule.

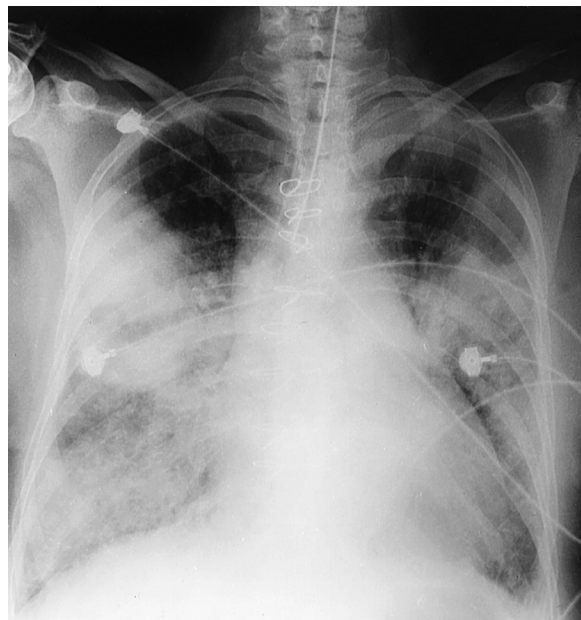


Figure 57-14 Chest radiograph shows postoperative reperfusion pulmonary edema. Only the upper lobes, from which no thromboembolic material was dissected, are spared.

hypertension associated with it, these findings suggest that early referral is preferable to late unless the possibility of a recent embolic event exists. Under this circumstance, a period of 6 to 8 weeks of conventional therapy is recommended to allow optimum thrombus resolution. Beyond

this period, further improvement in the level of pulmonary hypertension cannot be achieved with medical therapy alone.⁹⁷

Among survivors of thromboendarterectomy, restoration of pulmonary artery patency results in an immediate and dramatic hemodynamic improvement (Fig. 57-15). In published series, the mean reduction in pulmonary vascular resistance has approximated 70%, and a pulmonary vascular resistance in the range of 200 to 350 dyne·sec·cm⁻⁵ can be achieved. The long-term hemodynamic and symptomatic outcomes have been equally dramatic. Many patients are restored to normal activity, the majority return to class I functional status, and essentially all have improved at least one grade in the classification of cardiac disability.⁴⁰⁵⁻⁴⁰⁷ Anticoagulation is continued lifelong in order to prevent recurrence. Approximately 10% to 15% of patients undergoing thromboendarterectomy will have residual levels of pulmonary hypertension after the procedure that have been associated with a negative long-term outcome. One therapeutic option for patients who have undergone thromboendarterectomy with an inadequate hemodynamic outcome and for those not deemed candidates for thromboendarterectomy is lung transplantation. Preliminary results suggest that patients who are not considered candidates for thromboendarterectomy and those with residual pulmonary hypertension following the procedure may benefit from medical therapy including prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors.⁴⁰⁸⁻⁴¹¹ Epoprostenol has been used preoperatively in patients with chronic thromboembolic pulmonary hypertension associated with severe hemodynamic impairment and has been

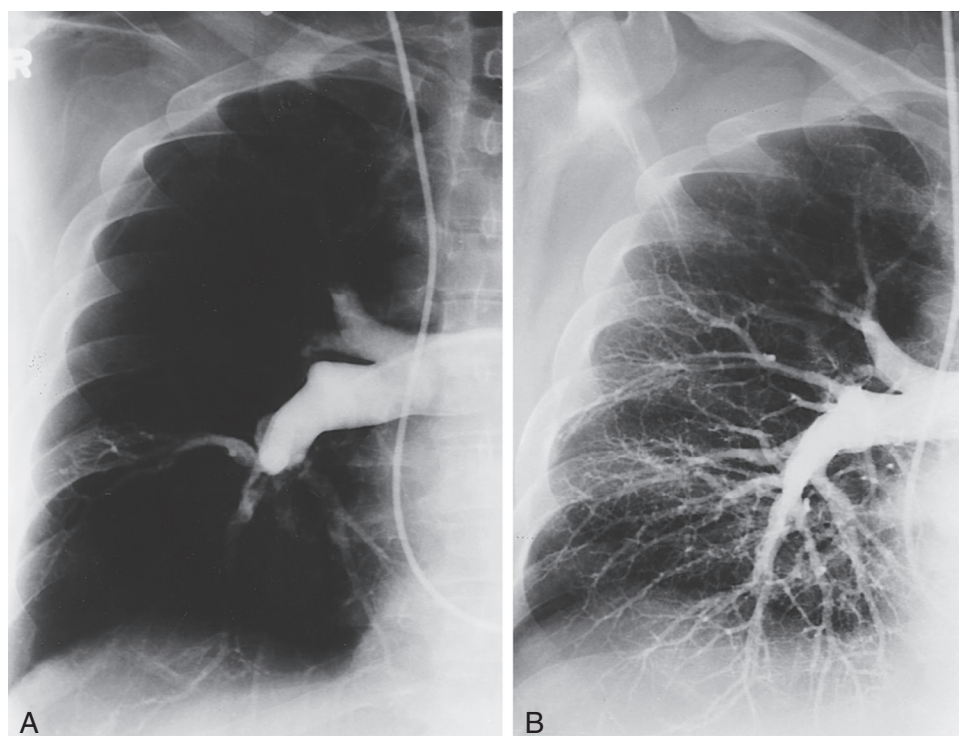


Figure 57-15 Pulmonary angiography before and after thromboendarterectomy. **A**, Preoperative pulmonary angiogram shows thromboembolic obstruction involving the right upper, middle, and lower lobe arteries. **B**, Postoperative angiogram shows near-normalization of flow. This angiographic improvement was accompanied by a corresponding hemodynamic improvement.

demonstrated to improve the hemodynamic profile.⁴¹² Whether such an approach improves outcome or decreases the incidence and severity of postoperative complications has not been determined.

Limited observational data suggest a potential role for percutaneous pulmonary balloon angioplasty in selected patients with inoperable chronic thromboembolic pulmonary hypertension.⁴¹³⁻⁴¹⁵ Percutaneous balloon angioplasty carries significant risk of reperfusion injury, cerebral and systemic embolism, and pulmonary artery perforation. Further study is necessary before it is used outside of specialized centers.



Supplemental information about other forms of embolism including schistosomiasis, air and fat embolism, amniotic fluid embolism, and septic embolism are available online at ExpertConsult.

Key Points

- Pulmonary embolism from deep venous thrombosis is an extremely important and still underrecognized cause of morbidity and mortality.
- Morbidity and mortality from pulmonary embolism will only be reduced by the widespread use of prophylactic measures in populations at risk and by a heightened clinical suspicion and awareness of the often subtle and nonspecific presentation of the disease.
- Appropriate use of anticoagulants decreases the risk of further thrombosis and recurrent embolism. Newer agents include direct inhibitors of factor Xa and of thrombin.

- Remaining uncertainties that need resolution include risk stratification in patients with confirmed embolism; the choice among treatment options for patients with unstable pulmonary embolism; selection of populations in which outpatient management is feasible; and prediction of the risk for development of chronic thromboembolic pulmonary hypertension.
- Chronic thromboembolic disease may develop in up to 4% of those with acute pulmonary embolism. Recognition is important because surgical thromboendarterectomy can improve hemodynamics and quality of life. Less invasive options such as percutaneous angioplasty may have a role in selected patients at specialized centers.

Complete reference list available at ExpertConsult.

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OTHER FORMS OF EMBOLISM

Because the lungs receive all of the blood flow returned from the venous system, the pulmonary vascular bed serves as a “sieve” for all particulates entering the venous blood and is the first vascular bed to be exposed to any toxic substance injected intravenously. As a result of its strategic position, the pulmonary vascular bed is therefore exposed to a wide variety of potentially obstructing and injurious agents.

SCHISTOSOMIASIS

Among such agents, the most common on a worldwide basis, although not within the United States, is schistosomiasis.⁴¹⁶ This parasitic disorder may cause pulmonary hypertension by three mechanisms: anatomic obstruction by the organism itself, an intense inflammatory vasculitic response to the components of the organism, and the development of portopulmonary hypertension. In endemic areas, schistosomal disease is the most common cause of cor pulmonale. Limited data suggest that cardiopulmonary schistosomiasis is seen most often in *Schistosoma mansoni* infection. This form of cor pulmonale is always seen with concomitant schistosomal liver disease because the liver is always involved, usually quite extensively, before the lung. The premortem diagnosis of cardiopulmonary schistosomiasis depends on serology and the detection of schistosomal ova in stool or urine along with evidence of hepatic fibrosis and pulmonary hypertension. Treatment with praziquantel can eradicate schistosomal infections with minimal toxicity. However, cardiopulmonary manifestations are not likely to be reversible once chronic fibrosis develops (see Chapter 39).

AIR EMBOLISM

An increasingly common form of nonthrombotic embolism in the United States is air embolism.⁴¹⁷ The increasing frequency of the problem reflects the wide variety of invasive surgical and medical procedures now available (see eFig. 19-2), the broad use of indwelling central venous catheters, the use of positive-pressure ventilation with high levels of positive end-expiratory pressure, and the frequency of thoracic and other forms of trauma.⁴¹⁸ The simple inadvertent transection or disconnection of a large-bore intravenous catheter (eFig. 57-13), particularly in the jugular or subclavian vein, can result in ingress of substantial quantities of air. Air bubbles enter the pulmonary vascular bed and, from there, are diffusely distributed throughout the body either by way of an intracardiac shunt or, more likely, through microvascular pulmonary shunts.

Physiologic consequences of pulmonary air embolism include an abrupt rise in pulmonary artery pressure. Increased permeability (noncardiogenic) pulmonary edema may develop, lung compliance falls, and hypoxemia ensues. The symptoms of air embolism are variable and nonspecific and may include alterations in sensorium, chest pain, dyspnea, or a sense of impending doom. These and other consequences appear to be due to two phenomena: actual lodgment of the bubbles in capillary beds, which interferes

with nutrient supply to the affected organs; and the formation of platelet-fibrin aggregates, creating diffuse microthrombi.⁴¹⁹ Thrombocytopenia may be seen as a consequence of this latter event. The most serious consequences result from cerebral or coronary artery air embolism, the severity of the consequences depending on the volume of air that gains access to the venous circulation.⁴¹⁷

The best approaches to air embolism are prevention and early detection. Treatment consists of measures designed to restore blood flow and to promote reabsorption of the intravascular air. Measures designed to restore flow include patient positioning (Trendelenburg position with the left side down), removal of air through central venous catheters or direct needle aspiration, and closed-chest cardiac massage. Measures designed to increase absorption include the use of 100% oxygen and the institution of hyperbaric oxygen therapy as early as possible.^{420,421} Utilizing such aggressive measures, mortality from air embolism has been dramatically reduced.

FAT EMBOLISM

Another reasonably frequent and dramatic form of nonthrombotic embolism is fat embolism.⁴²² A rather characteristic syndrome follows entry of neutral fat into the vascular system, consisting of the onset of dyspnea, petechiae, and mental confusion. There is a variable lag time of 24 to 48 hours in the onset of the syndrome following the inciting event.

By far the most common inciting event is traumatic fracture of marrow-containing long bones; the incidence of fat embolism rises with the number of fractures. However, orthopedic procedures and trauma to other fat-laden tissues (e.g., fatty liver) are occasionally followed by the same syndrome.

The reasons for the variability in incidence of the syndrome after apparently comparable injuries are not clear. Perhaps variations in incidence and severity relate to the amount of fat released. The pathophysiologic consequences appear to derive from two events: (1) actual vascular obstruction by neutral particles of fat and (2) the injurious effects of free fatty acids released by the action of lipases on the neutral fat.⁴²³ The latter effect is probably the more important, causing a diffuse vasculitis with leakage from cerebral, pulmonary, and other vascular beds.⁴²⁴

The diagnosis of fat embolism syndrome is a clinical one suggested by the onset of dyspnea, neurologic abnormalities, petechiae, and fever in the proper clinical context (see eFig. 94-2).⁴²⁵ Petechiae, typically distributed over the head, neck, anterior chest, and axillae, are present in only 20% to 50% of cases.⁴²⁶ Therefore their absence should not preclude consideration of the disease. No laboratory test is diagnostic of the syndrome.

Although a variety of treatments have been suggested (e.g., intravenous ethanol, albumin, dextran, heparin), none has proved effective. There is some evidence to suggest that corticosteroid therapy might prevent the onset of fat embolism syndrome after an inciting event, but controlled studies are sparse and the topic remains controversial.⁴²⁷ Supportive treatment, including mechanical ventilatory support, when necessary, is the primary approach and, with meticulous supportive care, survival is now the rule.

AMNIOTIC FLUID EMBOLISM (see Chapter 96)

Another special form of embolism is amniotic fluid embolism, a rare but unpredictable and catastrophic complication of pregnancy that represents the third leading cause of maternal mortality.^{428,429} This disorder may arise during or after delivery when amniotic fluid gains access to uterine venous channels and, from there, to the pulmonary and general circulations. The delivery may be either spontaneous or by Caesarean section; there are case reports of amniotic fluid embolism following therapeutic abortion. Unexpectedly and suddenly, the patient may have severe respiratory distress, cyanosis, hypotension, and often, cardiovascular collapse. Although obstruction of the pulmonary vascular bed may exist, the major hemodynamic impairment appears to be related to left ventricular dysfunction.⁴³⁰ Most cases develop during labor (see Fig. 96-6), but delayed onset of symptoms up to 48 hours after delivery has been reported.⁴³¹ Induction of labor, multiparity, advanced maternal age, ethnic minority women, Caesarian delivery, placental abnormalities, eclampsia, polyhydramnios, cervical lacerations, uterine rupture, premature placental separation, fetal death, and meconium staining of amniotic fluid are associated with increased risk of amniotic fluid embolism.^{432,433}

Amniotic fluid contains particulate materials that can cause pulmonary vascular obstruction, but the major pathogenetic mechanism of the syndrome remains uncertain. Amniotic fluid does have thromboplastic activity that leads to extensive fibrin deposition in the lung vasculature and, occasionally, in other organs. Pulmonary vascular resistance can rise, leading to right ventricular failure and shock.⁴³³

As a consequence of fibrin deposition, a severe consumptive coagulopathy develops, including marked hypofibrinogenemia and thrombocytopenia. After the acute event, an enhanced fibrinolytic state often exists.^{426,434}

The diagnosis of amniotic fluid embolism is based on a compatible clinical picture, often enhanced by finding amniotic fluid components in the pulmonary circulation. The presence of squamous cells in pulmonary arterial blood, once considered pathognomonic, has proved to be a nonspecific finding.⁴²⁸

Although various forms of therapy have been suggested (e.g., antifibrinolytic agents such as aminocaproic acid, cryoprecipitate, factor VIIA, pulmonary vasodilators), the best approach is supportive.⁴³³ Even in the setting of aggressive supportive measures, however, maternal mortality is in the range of 60% to 80%, with many survivors suffering from long-term neurologic disability.

SEPTIC EMBOLISM

Septic embolism is another special disorder that, unfortunately, is also increasing in frequency owing to widespread injection drug use and the expanding use of indwelling intravenous catheters. Previously, septic embolism was almost exclusively a complication of septic pelvic thrombophlebitis secondary to both septic abortion and postpuer-

peral uterine infection. Although these conditions still lead to septic emboli, injection drug use is now by far the more common cause.⁴³⁵ An increasingly common cause is iatrogenic: infections secondary to indwelling catheters inserted for a variety of diagnostic or therapeutic purposes.^{436,437}

Microscopically, septic phlebitis consists of purulent material admixed with fibrin thrombus. Embolization can result in obstruction of small pulmonary vessels, but the major consequence is pulmonary infection. Characteristically, imaging shows peripherally distributed pulmonary nodular opacities that undergo cavitation (eFig. 57-14A-G). An increasing number of such opacities develop over periods of hours to a few days. Symptoms and signs include a septic temperature course, dyspnea, cough, pleuritic chest pain, and hemoptysis. Initial treatment consists of appropriate antimicrobial drugs. If an indwelling catheter is suspected to be the source of the infection, it should be removed. If there is not a prompt response to this regimen, surgical isolation of the septic vein, if present, should be considered. The role of systemic anticoagulation remains uncertain. Endocarditis may complicate septic phlebitis or mimic it, particularly in drug addicts.

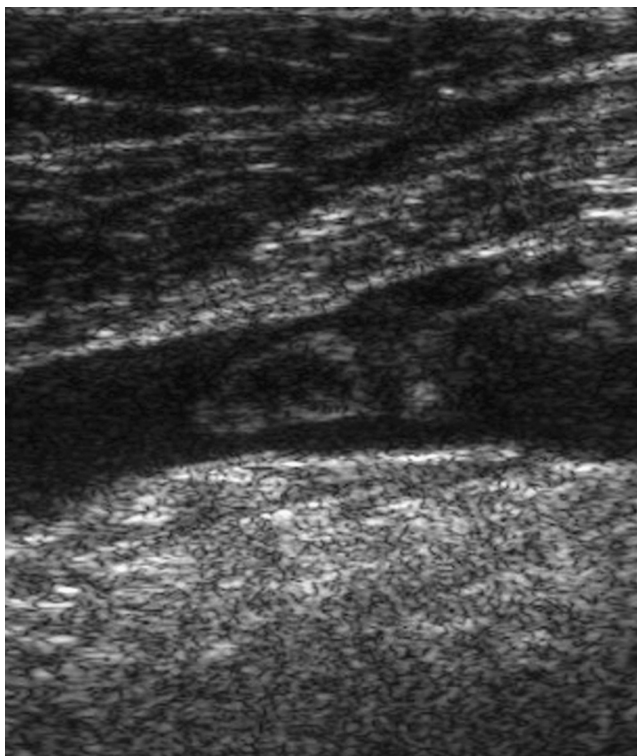
OTHER EMBOLI

Because of its sieve function, the lung may also be embolized on occasion by a wide variety of other materials.⁴³⁸ Cancer cells, of course, often find their way into and adhere to the pulmonary vessels; on occasion, tumor emboli (admixture of thrombus with cells) can form and mimic bland embolization (see eFigs. 55-2 and 55-3). Trophoblastic tissue can escape the uterus and lodge in the pulmonary circulation during evacuation of a molar pregnancy or during hysterectomy for an invasive mole. After head trauma, brain tissue has been found in the lungs; the same is true of liver cells following abdominal trauma and of bone marrow after cardiopulmonary resuscitation. In rare instances, iatrogenic emboli can arise from injection therapy (e.g., treatment of gastric varices) or even procedures such as vertebroplasty (eFigs. 57-15 and 57-16).

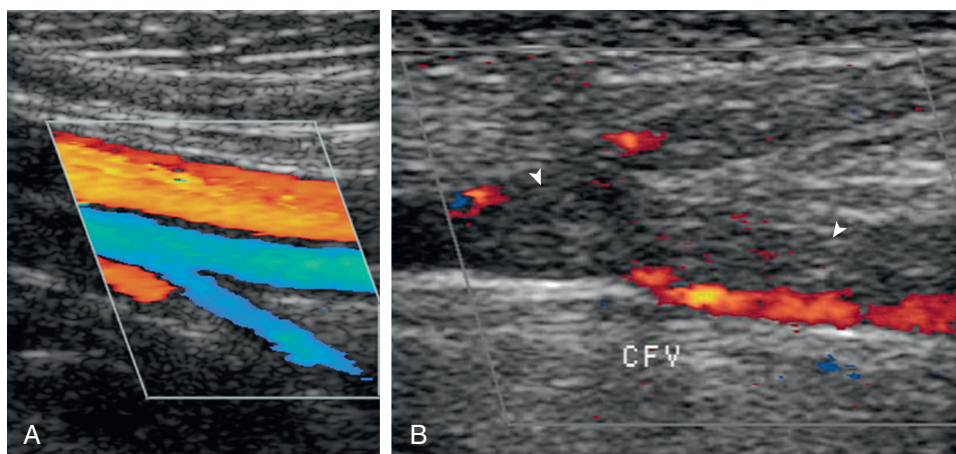
Pulmonary artery thrombi, either from thromboembolism or in situ thrombosis, are found in 10% to 20% of patients with acute chest syndrome from sickle cell crisis (see Chapter 94).⁴³⁹ During acute chest syndrome patients, pulmonary artery thrombosis may present without clinical findings suggestive of PE in other patient populations, so clinicians would be wise to have a high index of suspicion for this complication. Patients with sickle cell disease may also develop pulmonary artery hypertension.⁴⁴⁰ Unfortunately, echocardiogram has a poor specificity for identifying this subset of patients.⁴⁴⁰

Finally, in this era of injection drug use, noninfectious vasculitic-thrombotic complications are being seen with increasing frequency. Particulate and irritant drug carriers (e.g., talc [see eFig. 71-16], and cellulose [see eFig. 71-17]), and occasionally, the drugs themselves, may cause vascular inflammation and secondary thrombosis.⁴⁴¹ More commonly, uptake of the talc into the pulmonary interstitium results in fibrosis and advanced emphysema.⁴⁴²⁻⁴⁴⁴

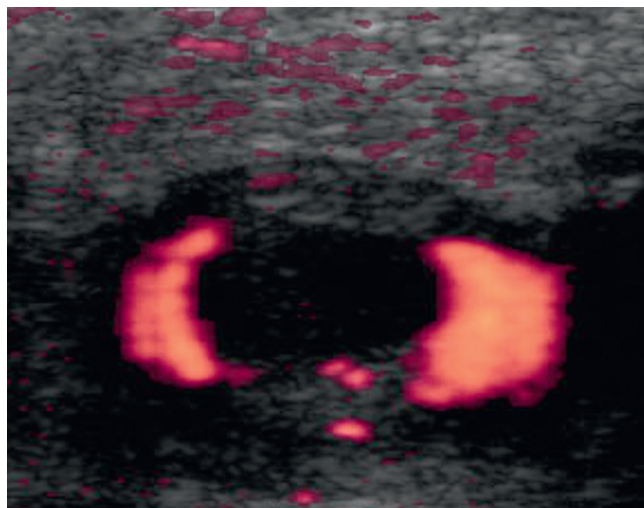
eFIGURE IMAGE GALLERY



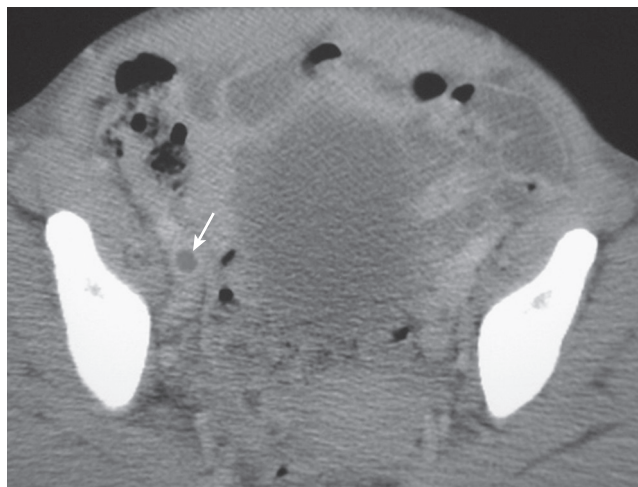
eFigure 57-1 Ultrasound image of DVT. Longitudinal ultrasound image shows mixed echogenicity material within the popliteal vein, consistent with acute deep venous thrombosis. (Courtesy Michael Gotway, MD.)



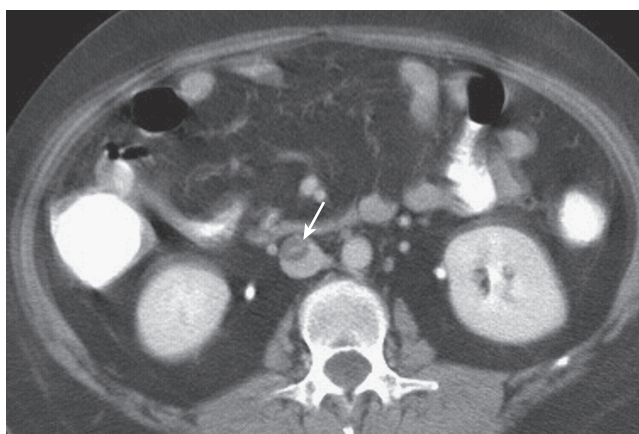
eFigure 57-2 Color Doppler ultrasound of the lower extremity. **A**, Normal color Doppler examination of the lower extremity venous and arterial systems. **B**, Echogenic material representing deep venous thrombosis (*arrowheads*) is present with the superficial femoral vein, entering the common femoral vein; thrombus can be seen filling the saphenous vein anteriorly at the junction of the superficial and common femoral veins. Note the displacement of color Doppler flow to the periphery of the thrombosed superficial femoral vein. (Courtesy Michael Gotway, MD.)



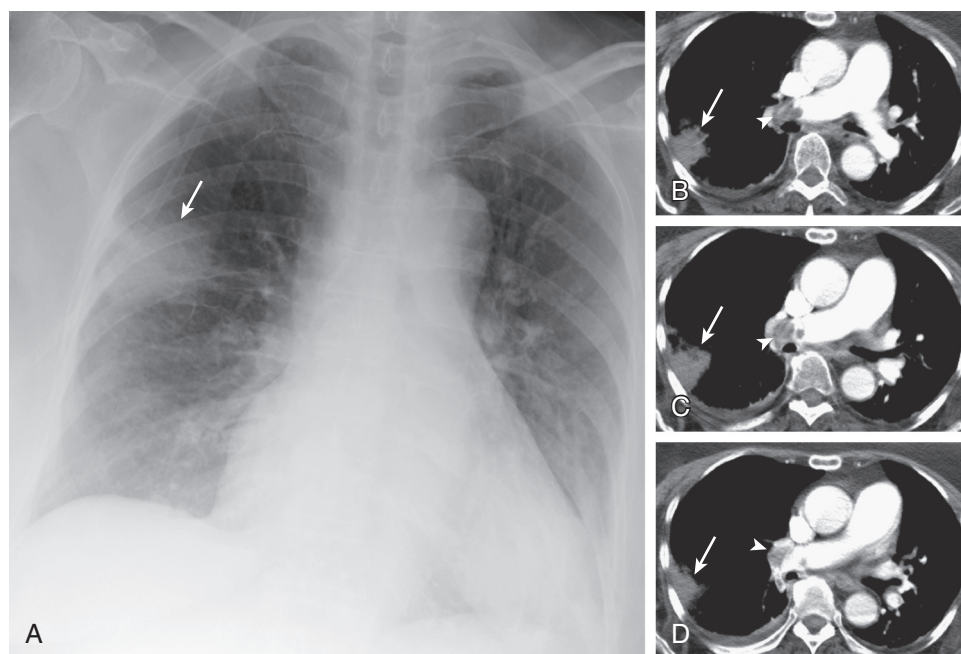
eFigure 57-3 Acute deep venous thrombosis presenting as nearly completely anechoic material filling the venous lumen. Note peripheral displacement of color Doppler signal, marking the remaining patent lateral portions of the common femoral vein. Some echogenic thrombus is seen peripherally both anteriorly and posteriorly as well. (Courtesy Michael Gotway, MD.)



eFigure 57-4 Indirect contrast venography. Axial contrast-enhanced image through the pelvis performed in the course of indirect contrast venography shows a low-attenuation filling defect within the right external iliac vein (*arrow*), consistent with deep venous thrombosis. (Courtesy Michael Gotway, MD.)



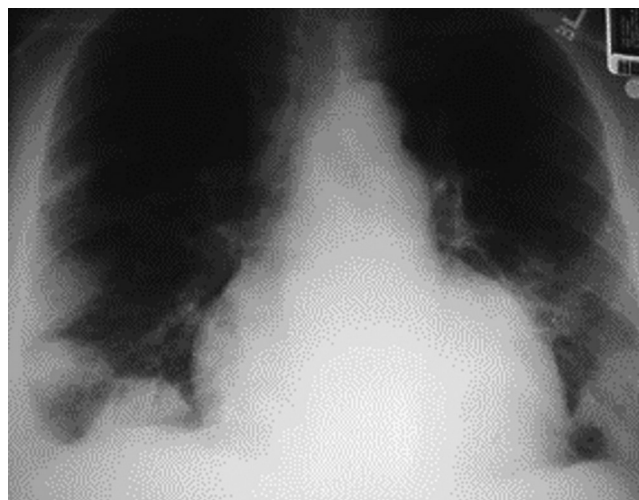
eFigure 57-5 Indirect contrast venography. Axial contrast-enhanced image through the lower abdomen performed in the course of indirect contrast venography shows a low-attenuation filling defect within the inferior vena cava (*arrow*), consistent with deep venous thrombosis. (Courtesy Michael Gotway, MD.)



eFigure 57-6 Acute pulmonary embolism. **A**, Frontal chest radiograph in a patient with acute pulmonary embolism shows a rounded opacity in the peripheral right upper lung (*arrow*) shown to represent pulmonary infarction. **B–D**, Chest CT pulmonary angiography shows pulmonary emboli in the right upper and interlobar arteries (*arrowheads*) as well as subpleural, wedge-shaped opacity representing pulmonary infarction (*arrows*). (Courtesy Michael Gotway, MD.)



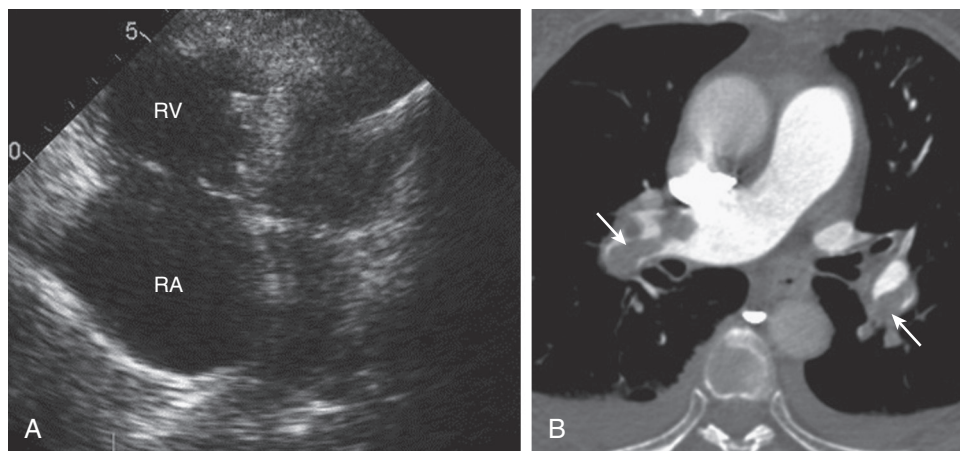
eFigure 57-7 The Westermark sign of pulmonary embolism. Frontal chest radiograph in a patient with acute pulmonary embolism shows hyperlucency of the right thorax compared with the left, consistent with oligemia, representing the Westermark sign. (Courtesy Michael Gotway, MD.)



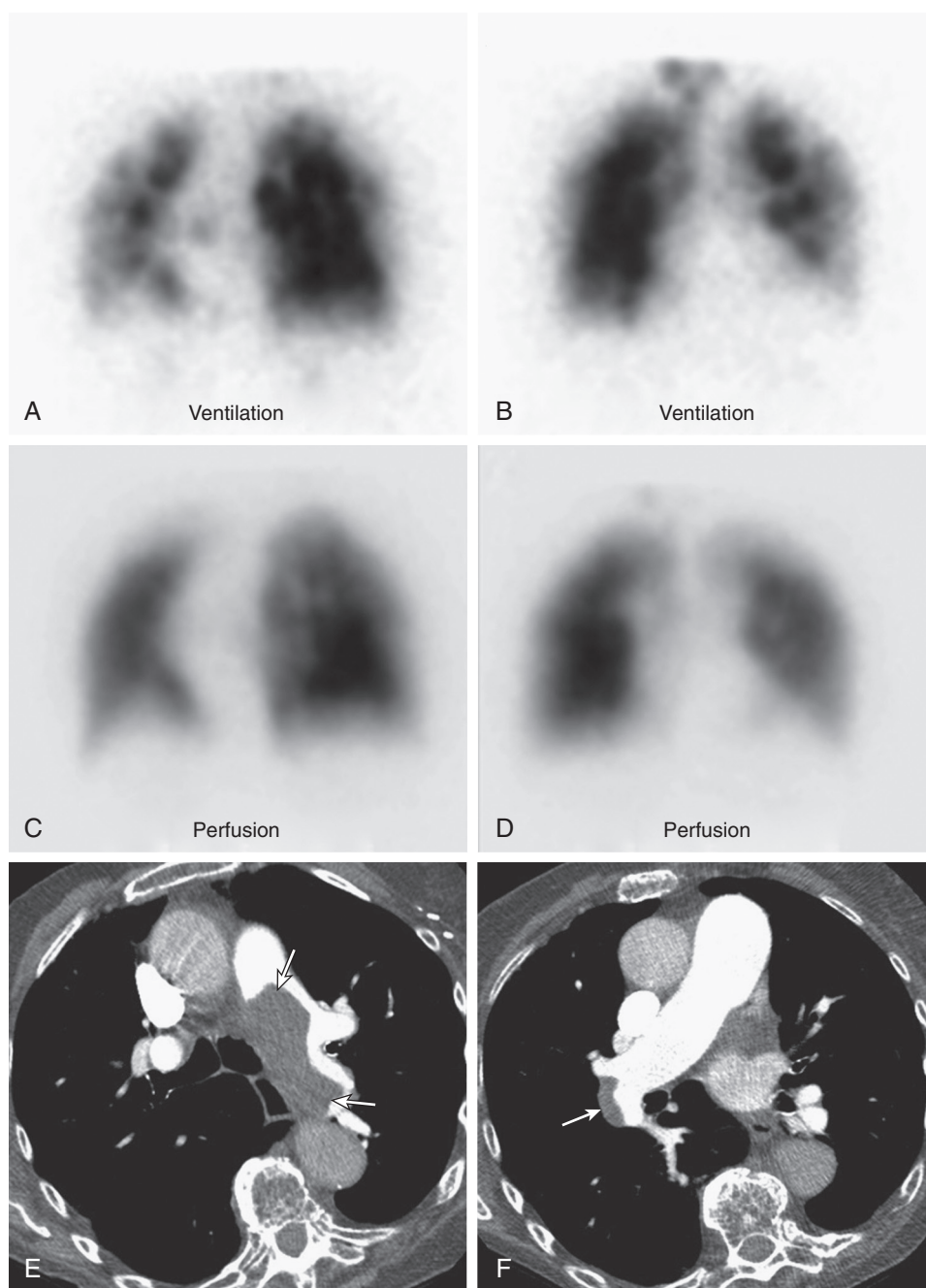
eFigure 57-8 Acute pulmonary embolism. Frontal chest radiograph in a 36-year-old bus driver with acute pulmonary embolism shows extensive, bilateral, basal subpleural wedge-shaped opacities representing pulmonary infarction. (Courtesy Michael Gotway, MD.)



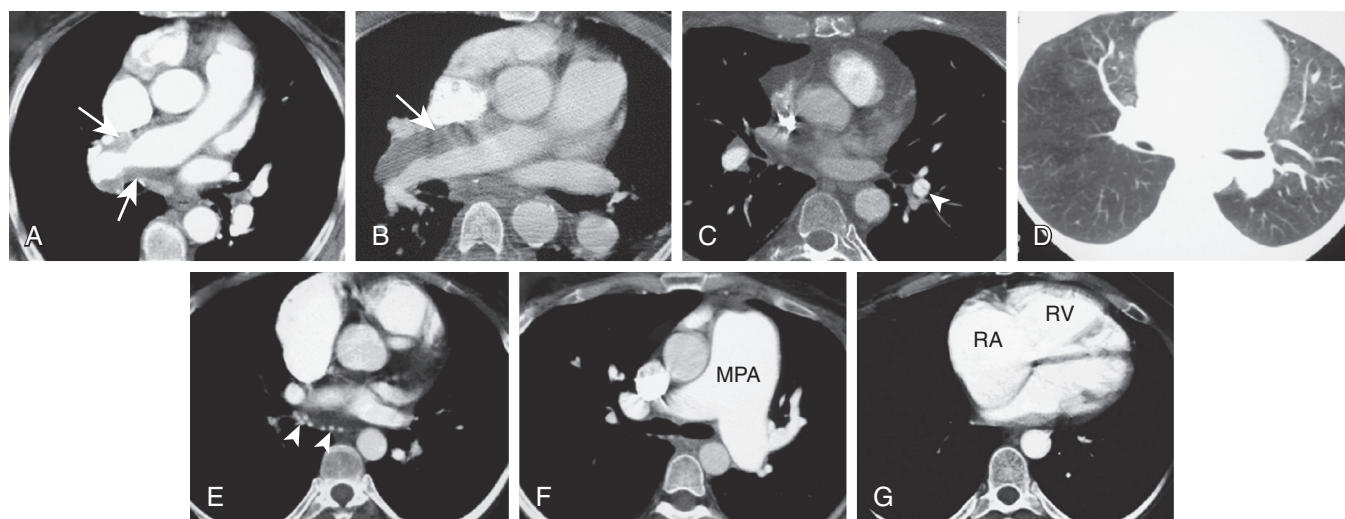
eFigure 57-9 Fleischner and Westermark signs of pulmonary embolism. Frontal chest radiograph in a patient with acute pulmonary embolism shows enlargement of the left pulmonary artery, consistent with Fleischner's sign. Also note the relative hyperlucency of the left thorax compared with the right, consistent with oligemia, representing the Westermark sign. (Courtesy Michael Gotway, MD.)



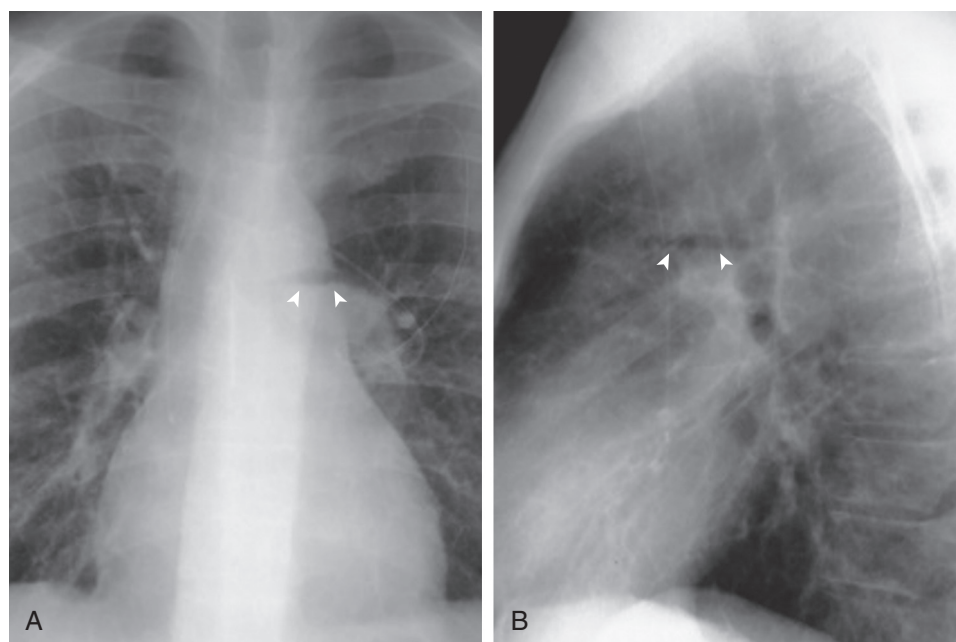
eFigure 57-10 Right ventricular enlargement with pulmonary embolism. **A**, Four-chamber echocardiographic image shows enlargement of the right atrium (RA) and right ventricle (RV). **B**, Chest CT pulmonary angiography shows bilateral pulmonary emboli (arrows), indicating the cause of the right heart chamber enlargement. (Courtesy Michael Gotway, MD.)



eFigure 57-11 Chronic thromboembolic disease. A–D, Ventilation-perfusion scintigraphy (A and B, ventilation images performed with ^{133}Xe ; C and D, perfusion images performed with ^{99}Tc -macroaggregated albumin) show inhomogeneous ventilation bilaterally, but perfusion images show relatively uniform tracer distribution. The study is consistent with a low probability for pulmonary embolism. E and F, Chest CT pulmonary angiography shows eccentric low-attenuation material (arrows) within the central pulmonary arteries consistent with chronic thromboembolic disease. (Courtesy Michael Gotway, MD.)



eFigure 57-12 Chronic thromboembolic disease. Chest CT pulmonary angiographic findings of chronic thromboembolic disease. **A**, Recanalized arterial lumen, showing peripheral hypoattenuating material (*arrows*); **B**, Eccentric low-attenuation material along the wall of the affected vessel (*arrow*); **C**, Intra-vascular web (*arrowhead*); **D**, Inhomogeneous lung opacity representing areas of oligemia (the areas of decreased attenuation); **E**, Bronchial artery collateral vessels (*arrowheads*); **F**, Main pulmonary artery (MPA) enlargement, consistent with pulmonary hypertension; and **G**, Enlargement of the right atrium (RA) and right ventricle (RV), consistent with pulmonary hypertension. Note straightening of the interventricular septum, also consistent with elevated right heart pressures. (Courtesy Michael Gotway, MD.)



eFigure 57-13 Pulmonary artery air embolism. **A**, Frontal and **B**, lateral chest radiography performed for acute-onset chest pain following manipulation of a central venous catheter shows a gas and fluid level (*arrowheads*) in the main pulmonary artery. This finding resolved without sequelae. (Courtesy Michael Gotway, MD.)

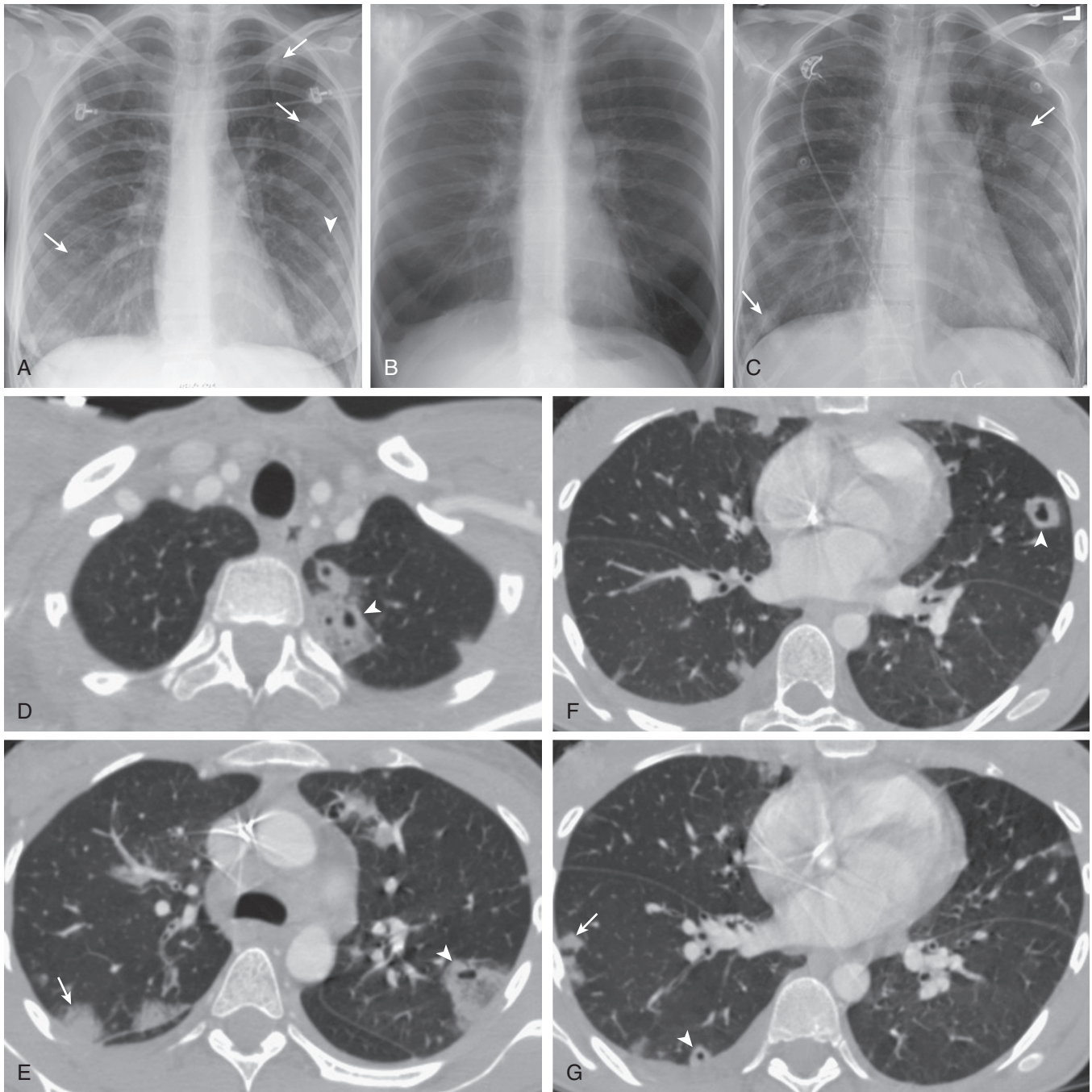
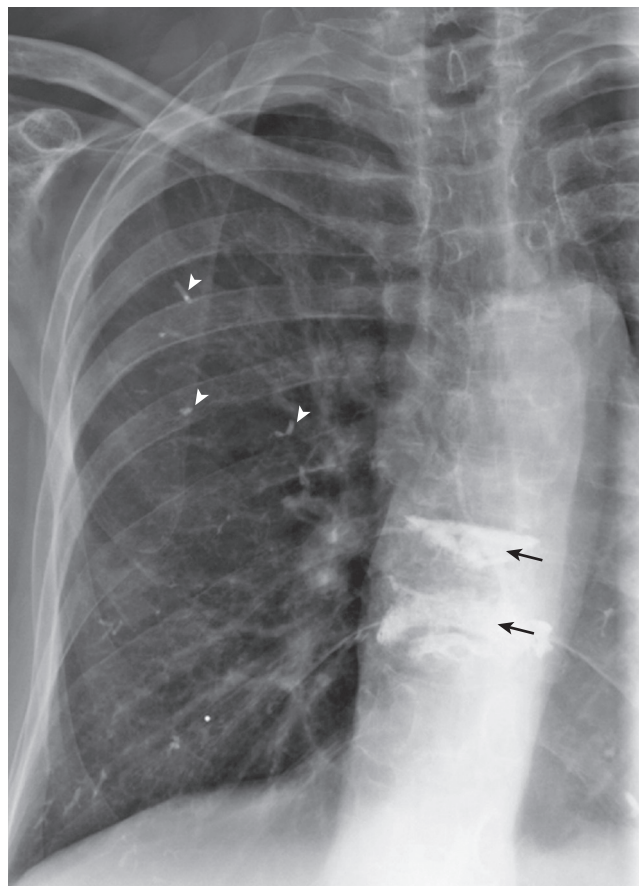
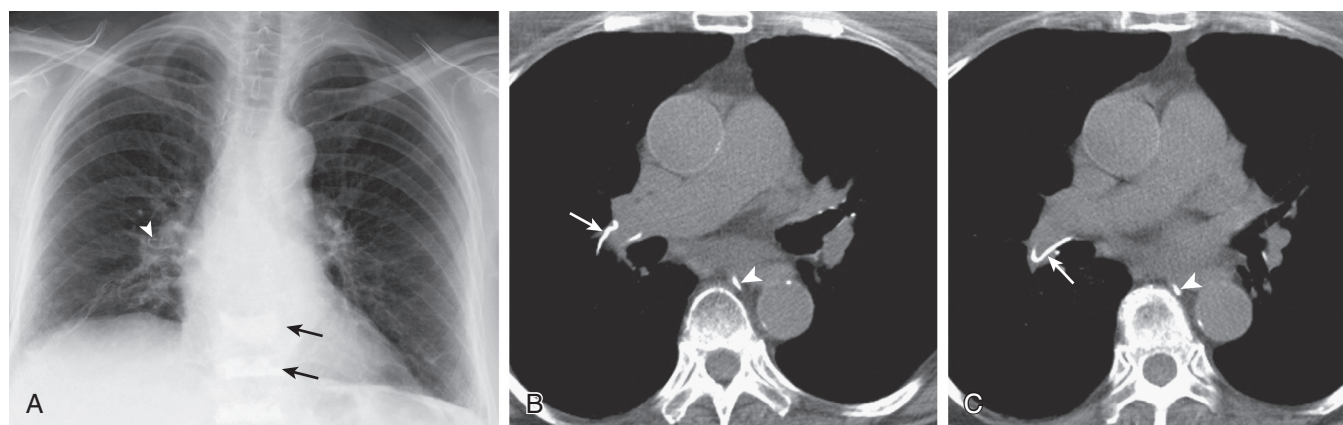


Figure 57-14 Septic embolization. **A**, Frontal chest radiography performed in an intravenous drug user with fever shows multiple, bilateral, poorly defined nodular opacities (*arrows*), one of which is cavitory (*arrowhead*). **B**, Frontal chest radiography performed 2 years earlier, for comparison, appears normal. **C**, Frontal chest radiography performed one day following (**A**) shows progression in size of the nodular opacities (*arrows*). **D-G**, Axial-enhanced chest CT confirms the presence of multiple, bilateral, peripherally distributed nodules (*arrows*), many of which are cavitory (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 57-15 Methyl methacrylate pulmonary emboli following vertebroplasty. Oblique frontal image of the chest shows thoracic spine vertebroplasty material (*arrows*) with small foci of methyl methacrylate emboli in the right upper lobe (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 57-16 Methyl methacrylate pulmonary emboli following vertebroplasty. **A**, Frontal chest radiograph shows thoracic spine vertebroplasty material (*arrows*) with a small curvilinear focus of methyl methacrylate in the right interlobar pulmonary artery (*arrowhead*). **B** and **C**, Axial unenhanced chest CT confirms high attenuation in the right interlobar pulmonary artery (*arrows*), representing a methyl methacrylate embolism. Methyl methacrylate is also present in the azygos vein (*arrowheads*). (Courtesy Michael Gotway, MD.)

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INTRODUCTION**EPIDEMIOLOGY****PATHOLOGY****PATHOGENESIS AND ETIOLOGY****OTHER GROUP 1 CONDITIONS**

Pulmonary Veno-occlusive Disease

Pulmonary Arterial Hypertension

Associated with Other Conditions

SYMPTOMS**PHYSICAL FINDINGS****DIAGNOSIS**

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Cardiac Catheterization

TREATMENT AND PROGNOSIS

Supportive Therapies

Targeted Therapies

Combination Therapy

Lung Transplantation

Overall Therapeutic Strategy

Survival

INTRODUCTION

Pulmonary hypertension manifests as an idiopathic form and as a complication of other circulatory conditions related to increases in pulmonary vascular resistance, increases in pulmonary arterial blood flow, and/or elevated left heart filling pressures. Five major pulmonary hypertension categories are recognized and organized into *World Health Organization* (WHO) groups based on similarities in clinical features and pathophysiologic and histologic findings (Table 58-1). One of these categories, pulmonary hypertension due to lung diseases and/or hypoxemia (group 3) is discussed in detail in Chapter 59 and chronic thromboembolic pulmonary hypertension (group 4) is discussed in detail in Chapter 57. This chapter focuses particularly on *pulmonary arterial hypertension* (PAH) and other conditions in group 1; it is primarily this group for which disease-specific therapies exist.

Pulmonary hypertension in general is not uncommon; it is diagnosed in more than 2% of all patients discharged from U.S. hospitals and in up to 9% of echocardiograms performed in a community setting.^{1,2} The majority of pulmonary hypertension diagnoses relate to left heart disease or lung disease, with only a small fraction accounted for by PAH (group 1) and chronic thromboembolic pulmonary hypertension (group 4). Idiopathic PAH in particular is rare, with an estimated incidence of approximately 1 case per million and a prevalence of 7 cases per million.^{3,4} Because current disease-specific pulmonary hypertension medications are approved only for idiopathic PAH and other WHO group 1 conditions, as listed in Table 58-1, it is critical for treating physicians to have a thorough understanding of the differential diagnosis and workup that is required for patients with suspected pulmonary hypertension.

EPIDEMIOLOGY

What is now called idiopathic PAH was first described at autopsy by Romberg in 1891.⁵ Patients with pulmonary hypertension of unknown cause were reported infrequently over the next 60 years,⁶ but began to be recognized more commonly after the advent of cardiac catheterization in the 1940s.^{7,8}

Idiopathic PAH was initially described as a disease of young women. The National Institutes of Health registry, conducted from 1981 to 1988, reported a mean age of 36 ± 15 years with a female-to-male ratio of 1.7:1,⁹ and other registries—including the more recent REVEAL registry—have reported even higher ratios of female to male patients.^{4,10,11} However, patients of both genders and of all ages are affected, and older patients are now recognized more frequently, with a mean age of approximately 50 years reported in registries from both the United States and Europe.^{10,11}

Patients older than 65 years with idiopathic PAH are also being recognized with greater frequency in the current era than in the past.^{12,13} Although most of these patients have pulmonary hypertension secondary to left heart disease or lung disease, idiopathic PAH does present in this age group. Patients with idiopathic PAH in the older age range have a more balanced gender ratio (female-to-male 1.2:1), greater abnormalities in baseline functional class and 6-minute walk distance (6MWD), and a worse prognosis, despite having a lower pulmonary vascular resistance at diagnosis (average 8.3 Wood units vs. 12 Wood units in younger patients).¹²

PATHOLOGY

Wood, in 1958,¹⁴ divided pulmonary hypertension into six types: (1) *passive*, as seen with increased pulmonary venous pressure due to raised left atrial or ventricular pressure; (2) *hyperkinetic*, caused by increased pulmonary blood flow; (3) *obstructive*, resulting from pulmonary embolism or thrombosis; (4) *obliterative*, manifested by a reduction of pulmonary vascular capacity; (5) *vasoconstrictive*, brought about by functional and presumably reversible vasospasm; and (6) *polygenic*, arising in two or more of the preceding ways. Vasoconstrictive pulmonary hypertension was noted most reliably in association with acute alveolar hypoxia, but was also seen as an added component in some patients with other forms of pulmonary hypertension. Wood¹⁴ also hypothesized that widespread “obliterative” pulmonary vascular disease potentially might complicate virtually all varieties of long-standing, severe pulmonary hypertension. Because multiple mechanisms are now known to be

Table 58-1 Fifth World Symposium on Diagnostic Classification of Pulmonary Hypertension (2013)**GROUP 1: PULMONARY ARTERIAL HYPERTENSION (PAH)**

Idiopathic PAH
 Heritable PAH
BMPR2
ALK1, ENG, SMAD9, CAV1, KCNK3
 Unknown genes
 Drug- and toxin-induced
 Associated with:
 Connective tissue diseases
 HIV infection
 Portal hypertension
 Congenital heart disease
 Schistosomiasis

GROUP 1': PULMONARY VENO-OCCLUSIVE DISEASE (PVOD) AND/OR PULMONARY CAPILLARY HEMANGIOMATOSIS (PCH)**GROUP 1'': PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN****GROUP 2: PULMONARY HYPERTENSION DUE TO LEFT HEART DISEASE**

Left ventricular systolic dysfunction
 Left ventricular diastolic dysfunction
 Valvular disease
 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

GROUP 3: PULMONARY HYPERTENSION DUE TO LUNG DISEASES AND/OR HYPOXIA

Chronic obstructive pulmonary disease
 Interstitial lung disease
 Other pulmonary diseases with mixed restrictive and obstructive pattern
 Sleep-disordered breathing
 Alveolar hypoventilation disorders
 Chronic exposure to high altitude
 Developmental lung diseases

GROUP 4: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)**GROUP 5: PULMONARY HYPERTENSION WITH UNCLEAR MULTIFACTORIAL MECHANISMS**

Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

ALK1, activin receptor-like kinase type 1; *BMPR2*, bone morphogenetic protein receptor type 2; *CAV1*, caveolin-1; *ENG*, endoglin; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.
 From Simonneau G, Gatzoulis MA, Adatia I, et al: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 62:D34–D41, 2013.

common in severe pulmonary hypertension, regardless of underlying etiology, the modern classification has moved toward a more disease-focused classification. Nevertheless, these six pathophysiologic mechanisms remain relevant to modern understanding of the disease.

Also in 1958, Heath and Edwards¹⁵ documented the pathology of hypertensive pulmonary vascular disease in a study of 67 patients with congenital heart disease and 2 patients with idiopathic PAH, focusing on the muscular pulmonary arteries 100 to 1000 μ m in size. These investiga-

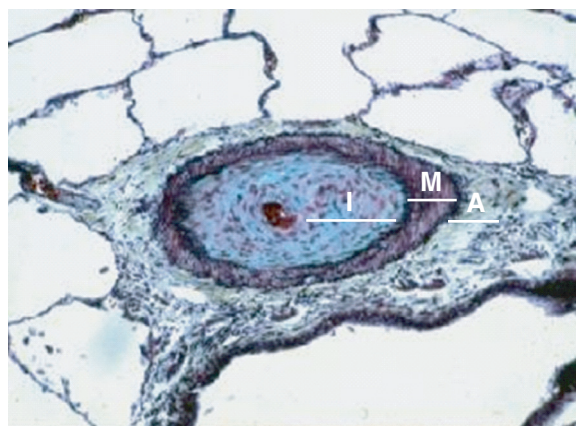


Figure 58-1 Typical advanced pulmonary arteriopathy in idiopathic pulmonary arterial hypertension. Note the proliferative changes in all three vessel layers, including intimal hyperplasia (I), medial hypertrophy (M), and adventitial fibrosis (A).

tors argued that the progression of lesions in these patients was so stereotyped as to allow division of the structural effects of pulmonary hypertension into six grades as follows: grade 1, medial hypertrophy of the pulmonary arteries and arterioles without intimal changes; grade 2, medial hypertrophy with cellular intimal proliferation; grade 3, medial hypertrophy, intimal proliferation, and intimal fibrosis; grade 4, progressive generalized vascular dilation and occlusion by intimal fibrosis and fibroelastosis; grade 5, appearance of dilation lesions, including veinlike branches of occluded pulmonary arteries, plexiform lesions, angiomatoid lesions, and cavernous lesions; and grade 6, necrotizing arteritis.

Heath and Edwards¹⁵ lumped the pathology of PAH associated with congenital heart disease and idiopathic PAH together, and large series of patients with the latter disorder were not available until 1970. In that year, Wagenvoort and Wagenvoort¹⁶ described the morphology of the pulmonary vessels of 150 persons in whom a diagnosis of unexplained PAH had been made. The largest subset ($N = 110$, 73%) had a histology consistent with what is now termed idiopathic PAH, and the pathologic abnormalities were strikingly similar to those described earlier by Heath and Edwards¹⁵ and Wood.¹⁴ The earliest abnormalities were medial hypertrophy of the muscular pulmonary arteries and muscularization of the arterioles, apparent in both children and adults with the disease. Less marked in children but apparent in all adults studied were intimal proliferation and laminar intimal fibrosis that gave an onionskin appearance to the pulmonary arteries, and plexiform lesions were found in 70%.¹⁶ A typical arteriopathic muscular artery is shown in **Figure 58-1**.

A pathologic pattern consistent with chronic pulmonary thromboembolism was also seen in some of the patients with unexplained pulmonary hypertension in this series, present in 31 patients (21%). Half were noted in retrospect to have had other evidence of chronic thromboembolism, such as deep venous thrombosis. These patients had a combination of abnormalities including evidence of recent pulmonary thrombi, thrombi in the process of reorganization, and older organized fibrosis, appearing as intimal fibrosis, and lacked onion skin lesions, plexiform and other

dilation lesions. Notably, this chronic thromboembolic pattern is rarely seen in patients diagnosed as idiopathic PAH in modern series, likely due to universal screening for chronic thromboembolic disease.¹⁷ These earlier histopathologic studies were, no doubt, limited by incomplete or erroneous phenotyping, in that the appropriate workup of pulmonary hypertension patients has only been clarified in the “recent” era, that is, when approved therapies became available.

Pulmonary veno-occlusive disease (PVOD) is a rare form of PAH that has virtually identical hemodynamic findings and in many cases similar clinical findings as in idiopathic PAH. It was seen in 3% of the pathology specimens in the series by Wagenvoort and Wagenvoort, and continues to be difficult, in many cases, to distinguish from idiopathic PAH using clinical means. The characteristic histologic feature of PVOD is obstruction of pulmonary venules and veins by loose, fibrous remodeling of the intima that may totally occlude the lumen; in addition arterial changes are usually evident.¹⁷⁻¹⁹

Despite the distinct pathologic findings in idiopathic PAH, some degree of vascular remodeling takes place with essentially all forms of pulmonary hypertension,²⁰⁻²² and even severe arteriopathic changes are, in fact, not unique to idiopathic PAH, having been reported in other forms of PAH (group 1)^{23,24} and in chronic thromboembolic pulmonary hypertension.²⁵ For this reason, in addition to the risk of lung biopsy in patients with pulmonary hypertension, one rarely obtains pathologic tissue before lung transplantation or death. Similarly, lung biopsy in pulmonary hypertension due to congenital heart disease with left-to-right shunting is also no longer common.

PATHOGENESIS AND ETIOLOGY

A dramatic change has taken place over the past several years in our thinking regarding the pathogenesis of idiopathic PAH. The “paradigm” has shifted from one of vasoconstriction to one of growth and proliferation. There are several lines of evidence suggesting that idiopathic PAH develops as a result of abnormal proliferation of vascular smooth muscle cells affecting all three layers of the vessel wall and leading to intimal hyperplasia, medial hypertrophy, and adventitial proliferation. What initiates this abnormal growth is not entirely known, but there are several clues. The concept of genetic predisposition toward growth and proliferation has more recently emerged. Mutations in the *bone morphogenic protein receptor 2 (BMPR2)* gene have been reported in patients with the familial form of idiopathic PAH.²⁶ This gene contributes to the apoptotic process through a complex series of messenger proteins, as part of the *transforming growth factor-β* family of genes.

Accordingly, the possibility emerges that pulmonary arteriopathy is a failure of normal apoptosis. Some investigators have even referred to idiopathic PAH as “cancer of the pulmonary artery.” Although this is an attractive hypothesis, the story is not that simple. For one, the presence of a *BMPR2* mutation is not always associated with the development of idiopathic PAH. It is likely that another genetic or acquired insult is required to initiate the arteriopathic process. Defects in a specific voltage-gated

potassium ion channel, the *Kv1.5* channel, have been found in the pulmonary artery smooth muscle cells from patients with idiopathic PAH.²⁶ A defect or deficiency of this channel allows excess calcium to enter the cell and thus promotes both cell contraction and growth. Overexpression of the serotonin transporter has been described in patients with idiopathic PAH.²⁷ This genetic defect might lead to increased internalization of serotonin and subsequent smooth muscle cell growth. Recent interest has focused on the role of impaired apoptosis on the development of proliferative arteriopathy in idiopathic PAH. It is clear that functional mutations seen in the *BMPR2* gene with resultant abnormal downstream signaling results in impaired apoptosis.²⁸⁻³⁰

In addition to potential genetic defects, several abnormalities in endothelial cell function have been found, many of which are likely a result of some vascular insult. The basis for currently approved therapeutics is the deficiency in prostacyclin and nitric oxide release and the excess in endothelin-1 and its receptor expression in patients with pulmonary hypertension.³¹⁻³⁴ Some of the complex cellular and molecular processes contributing to idiopathic PAH are shown in Figure 58-2.

OTHER GROUP 1 CONDITIONS

PULMONARY VENO-OCCLUSIVE DISEASE

Veno-occlusive disease has been associated with viral syndromes, toxin exposure, and chemotherapy, but may also be seen in an idiopathic form.¹⁹ Unlike idiopathic PAH, the male-to-female ratio in adults with PVOD is close to 1:1. A familial form of veno-occlusive disease also has been noted, including a subset of patients who carry the *BMPR2* mutation.¹⁹ Differentiation from idiopathic PAH can be difficult. Suggestive findings include more hypoxia, a lower *DL_{CO}* on pulmonary function testing, and prominent interlobular septal thickening (Kerley B) lines on chest radiographs in the absence of other signs of left-sided heart failure (Fig. 58-3A). *Computed tomography (CT)* scanning may reveal interlobular septal thickening (see Fig. 58-3B), pleural effusions, and enlarged pulmonary arteries. The perfusion lung scan may show defects suggestive of thromboembolism but with unremarkable pulmonary angiograms.³⁵ In addition, patients with PVOD may develop acute pulmonary edema in response to pharmacologic agents that reduce upstream *pulmonary vascular resistance (PVR)* and increase cardiac output, such as prostacyclin. This phenomenon probably is caused by an increase in pulmonary blood volume in the face of downstream vascular obstruction. A recent analysis of PVOD cases suggested that *bronchoalveolar lavage (BAL)* could be useful, because patients with PVOD almost always had increased hemosiderin-laden macrophages in BAL fluid.³⁶

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH OTHER CONDITIONS

Several systemic diseases or exposures have been shown, epidemiologically, to be associated with PAH (see Table 58-1). For example, approximately 8% of patients with the

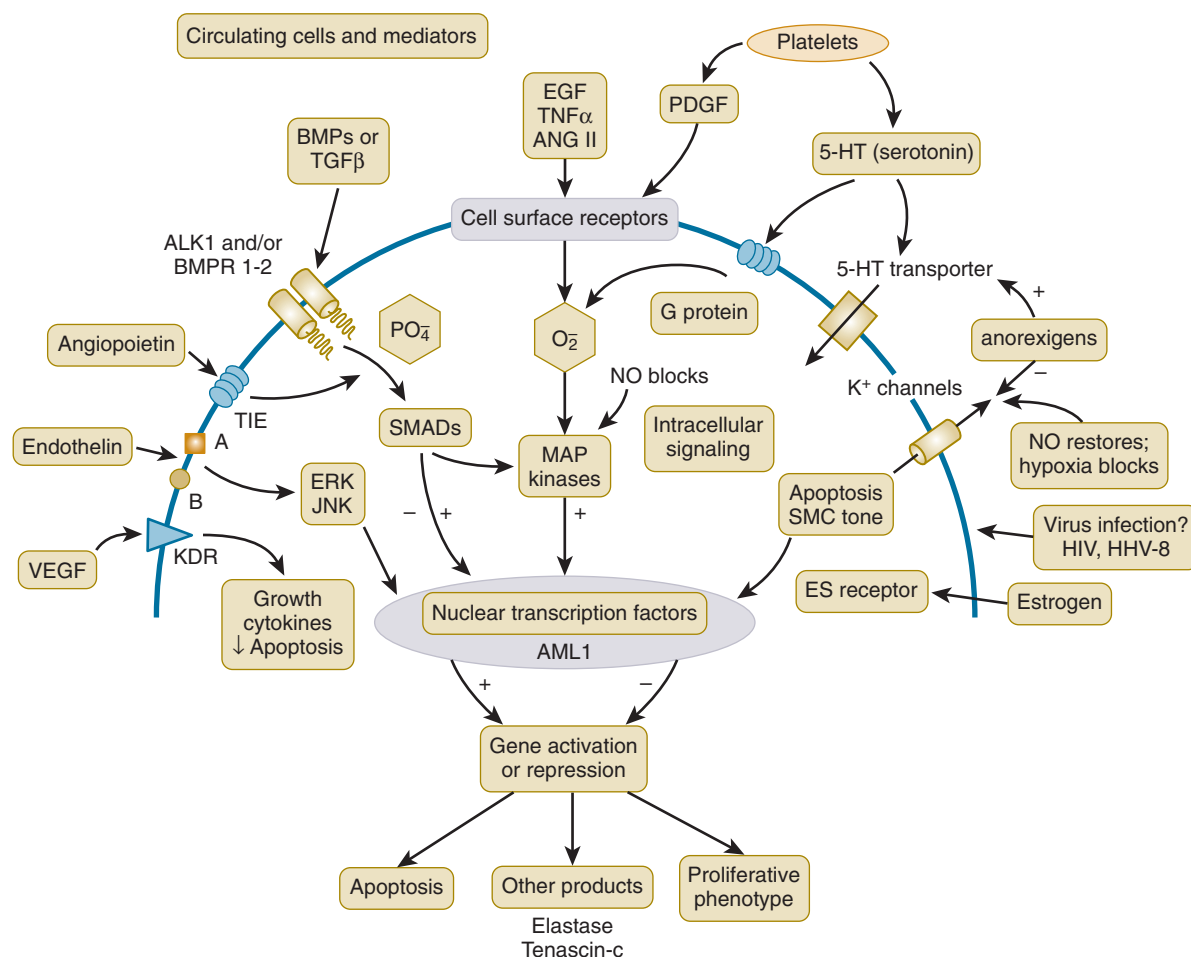


Figure 58-2 Schematic of the possible pathogenetic factors in idiopathic pulmonary arterial hypertension. A, endothelin A receptor; ALK, activin receptor kinase-like; AML1, acute myeloid leukemia 1; Ang II, angiotensin II; B, endothelin B receptor; BMP, bone morphogenetic protein; BMPR1-2, bone morphogenetic protein 1-2; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinases; 5-HT, serotonin; HHV-8, human herpes virus 8; HIV, human immunodeficiency virus; JNK, c-Jun amino-terminal kinases; KDR, kinase insert domain receptor; MAP, mitogen activated protein; NO, nitric oxide; PDGF, platelet derived growth factor; SMADs, Sma and Mad related proteins; TGF β , transforming growth factor beta; TIE, tyrosine kinase with immunoglobulin-line and EGF-like domains; TNF α , tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

scleroderma spectrum of diseases, most notably limited scleroderma (previously CREST, or calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) have been reported to have PAH (eFig. 58-1) confirmed by right heart catheterization,³⁷ and even higher rates have been seen in some echocardiography series.³⁸ Pulmonary vascular involvement is associated with worse survival in scleroderma.³⁹ Other connective tissue diseases associated with PAH, albeit less commonly, include systemic lupus erythematosus, mixed connective tissue disease, and rheumatoid arthritis.⁴⁰

Congenital heart disease is a well-recognized “risk factor” for development of PAH. In 1958, Wood¹⁴ coined the term “Eisenmenger’s complex” to describe pulmonary hypertension due to high PVR, with reversed (i.e., right-to-left) shunting through a large ventricular septal defect. Subsequently, the term has been used to describe pulmonary hypertension with cyanosis coupled with any systemic-to-pulmonary circulatory shunt. The likelihood of developing pulmonary hypertension depends on the size of the defect. However, patients with even small atrial septal defects can develop pulmonary hypertension. These patients may, in

fact, have idiopathic PAH and the atrial septal defect merely serves as a “trigger” in a susceptible patient.

In patients with ventricular septal defects, it has been shown that only 3% of patients with a defect of 1.5 cm or smaller develop Eisenmenger syndrome, whereas 50% of patients with a large defect develop significant pulmonary hypertension, which also appears earlier than in atrial septal defect (eFig. 58-2), often in infancy.⁴¹ PAH due to true Eisenmenger syndrome is associated with a longer natural history and more preserved right ventricular compensation and, hence, longer periods of clinical stability. The defect itself may also provide a protective mechanism, providing a route for blood to reach the underfilled left ventricle. However, right heart failure does eventually develop in many patients, and just as in idiopathic PAH, an elevated right atrial pressure and low cardiac output carry a poor prognosis.⁴²

The effects of drugs and toxins on the human pulmonary circulation have been graphically demonstrated in the past. Between 1967 and 1970 in Switzerland, Austria, and Germany, a 20-fold increase in pulmonary hypertension was observed after the introduction of aminorex, an

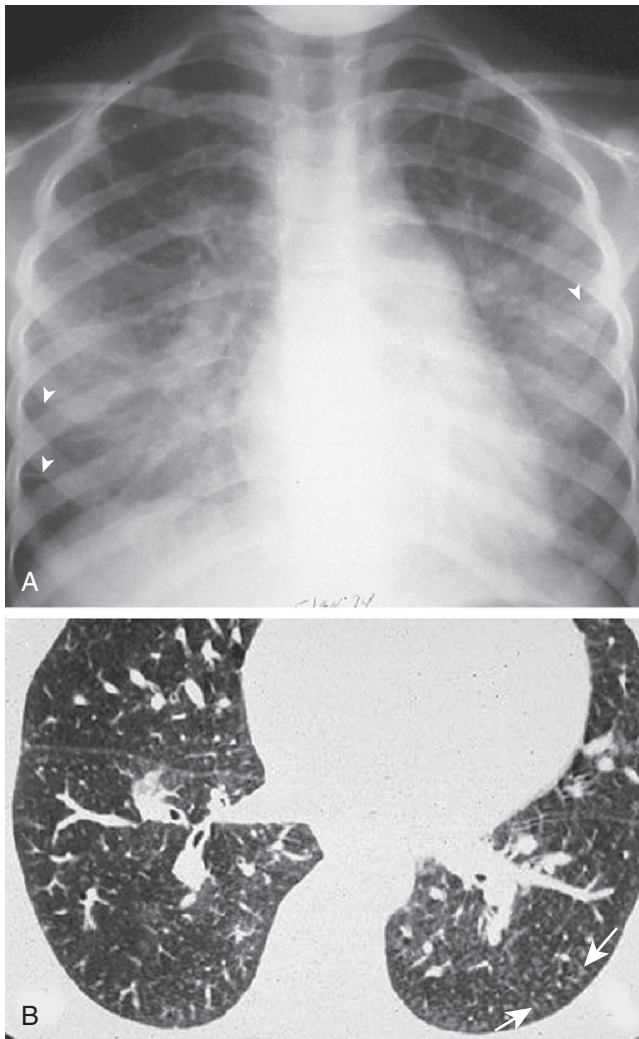


Figure 58-3 Pulmonary veno-occlusive disease. **A**, Frontal chest radiograph shows central pulmonary arterial enlargement, consistent with pulmonary hypertension. Central increased opacity is noted, with a background of linear opacities, some of which are consistent with interlobular septal thickening (also called Kerley B lines, *arrowheads*). **B**, Axial chest CT displayed in lung windows shows patchy areas of inhomogeneous lung opacity, with some areas of increased attenuation consistent with ground-glass opacity, best seen in the medial lung bases. Faint peripheral linear opacity and interlobular septal thickening (*arrows*) is present. The patient eventually was treated with bilateral lung transplantation. (Courtesy Michael Gotway, MD.)

appetite suppressant resembling epinephrine and amphetamine.⁴³ The pulmonary lesions produced by this agent resembled plexogenic pulmonary arteriopathy in every respect. Pulmonary hypertension has also been associated with the appetite suppressants fenfluramine (eFig. 58-3) and dexfenfluramine.⁴⁴ In a case-controlled prospective study performed in Europe, the risk of developing pulmonary hypertension was increased by 20-fold in individuals who used one of these drugs for periods exceeding 3 months. Stimulants have also been suspected of causing pulmonary hypertension, based on both mechanistic similarities with the anorexigens and case reports, case series, and a single-center case-control study.^{45,46} In the latter study, an especially strong association between methamphetamine use and PAH was identified, with patients with PAH and no other identifiable risk factors 10 times more likely to have

used methamphetamine than a matched control group of patients with other forms of PAH.⁴⁷ Other medications suspected of causing pulmonary hypertension include chemotherapeutic agents, mainly in association with PVOD,⁴⁸ and dasatinib, a tyrosine kinase inhibitor whose use in the treatment of chronic myelogenous leukemia has been associated with the development of PAH.⁴⁹

Portal hypertension is another disease associated with PAH (eFig. 58-4) and is discussed further in Chapter 93. Mantz and Craig⁵⁰ first described simultaneous presentation of portal and pulmonary hypertension in a patient with portal vein thrombosis, speculating, as would others in the years following,⁵¹ that multiple emboli emanating from portacaval anastomoses were responsible for the pulmonary hypertension. Subsequent hypotheses have suggested a vasoactive mediator-based mechanism related to porto-systemic shunting, whereby vasoactive substances, normally cleared in the liver, reach the pulmonary vasculature, while yet another hypothesis has focused on derangements in genes related to estrogen signaling.⁵² Portopulmonary hypertension is similar to other types of PAH histologically and is characterized hemodynamically by elevations in pulmonary arterial pressure and pulmonary vascular resistance. Incidence is estimated at 0.73% of all patients with portal hypertension, based on a large autopsy study,⁵³ and rates of up to 4% to 5% have been reported in end-stage patients undergoing workup for liver transplantation.^{54,55}

In end-stage liver disease, hemodynamic assessment is frequently complicated by the presence of a high cardiac output related to splanchnic vasodilation and by the presence of volume overload and/or diastolic heart failure.⁵⁵ As a result, portopulmonary hypertension patients tend to have higher cardiac outputs and lower PVRs compared with other WHO group 1 PAH patients.⁵⁶ Despite more favorable hemodynamics, the mortality risk following liver transplantation has been shown to be approximately 50% in patients with even mild to moderate pulmonary hypertension (defined as a PVR >3.1 Wood units in this series), particularly when undiagnosed until the time of transplantation.⁵⁷ Knowledge regarding the high mortality in patients with portopulmonary hypertension undergoing orthotopic liver transplantation has led to development of aggressive strategies for screening and treatment of these patients before transplantation; recommendations include echocardiography in all patients, right heart catheterization for patients whose estimated right ventricular systolic pressure exceeds 50 mm Hg, vasodilator treatment of patients whose pulmonary hypertension is due to PAH, and liver transplantation of these patients only when treatment is successful in lowering the mean PAH to less than approximately 35 mm Hg.^{55,58}

The association between *human immunodeficiency virus* (HIV) and PAH is well known. In several studies, the incidence of pulmonary hypertension in HIV has been reported as high as 0.5%.^{59,60} The mechanism of HIV-associated pulmonary hypertension is not known, although theories include release of cytokines and growth factors and the presence of human herpesvirus 8, a promoter of angiogenesis as seen in Kaposi sarcoma. One report noted the presence of human herpesvirus 8 in the cells from plexiform lesions in 10 of 16 patients with idiopathic PAH.⁶¹ Subsequent reports, however, failed to reveal human herpesvirus

8 in plexiform lesions.^{62,63} Pulmonary hypertension can develop in all stages of HIV, including in patients with no detectable viral load. A concomitant history of illicit intravenous drug use is noted in as many as 42% of cases,⁶⁴ and at the authors' Pulmonary Hypertension Center, the vast majority of patients with HIV-associated PAH have a methamphetamine use history, suggesting the possibility that illicit drugs contribute substantially to the risk of PAH in HIV patients. Clinical and hemodynamic features of HIV-associated pulmonary hypertension are similar to those of idiopathic PAH (eFig. 58-5), although increased mortality is associated both with measures of HIV severity (high viral load, low CD4 count) and with typical PAH prognostic markers, such as worse functional class, low cardiac index, and history of right heart failure.⁶⁵

SYMPTOMS

Dyspnea is the cardinal symptom of idiopathic PAH, described by more than 95% of patients in major clinical series,⁹ usually noted first on exertion and gradually with less and less activity. Closely related to dyspnea are sensations of fatigue and weakness, reported by a majority of patients with idiopathic PAH.⁹ These sensations usually are experienced before the general disability that is present with advanced disease, and presumably reflect impaired tissue oxygenation resulting from inadequate cardiac output.

Substernal chest pain is also commonly reported in patients with idiopathic PAH,⁶⁶ and frequently arises on exertion, radiating to the left shoulder or axilla, and relieved by rest. Similarities with angina pectoris have led to the suggestion that the pain may relate to coronary insufficiency in the presence of increased right ventricular work and hypoxemia. However, pain may be present in young patients without coronary artery disease, and alternative mechanisms that have been considered include subendocardial ischemia related to demand-perfusion mismatch,⁶⁷ ischemia related to direct compression of the left main coronary artery by the enlarged pulmonary trunk,⁶⁸ and nonischemic pain caused directly by the distention of the pulmonary artery, whose afferents enter the nervous system along the same pathways as afferents from the heart.⁶⁹ In addition to chest pain, hoarseness may result if the enlarged main pulmonary artery compresses the recurrent laryngeal nerve.

Syncope, usually with exertion, occurs in some patients with idiopathic PAH and may be its initial manifestation. Syncope is probably caused by a decrease in cerebral blood flow that follows an increase in pulmonary artery pressure and a decrease in cardiac output, and it is associated with a poor prognosis. Late findings in PAH include peripheral edema and ascites related to decompensated right ventricular failure, and hemoptysis. For the latter, bronchial artery embolization is often successful, but mortality following an initial episode of hemoptysis is high.⁷⁰

PHYSICAL FINDINGS

Patients with early idiopathic PAH may manifest no obvious physical abnormality. However, signs of pulmonary hyper-

tension and right ventricular failure should be evident with advanced disease. As Wood¹⁴ observed, the hands and feet of a patient with severe pulmonary hypertension are cold, the peripheral pulse is diminished, the blood pressure is likely to be low, and the pulse pressure is reduced. Signs of systemic venous hypertension are often present, including a prominent jugular venous *a* wave, which is exaggerated by abdominal compression (hepatojugular reflux) and transmitted to the liver in a presystolic hepatic pulse, and prominent *c-v* waves, which are indicative of tricuspid regurgitation. Palpation of the chest may reveal a right ventricular lift at the left sternal border that is sustained throughout the pressure-overloaded cardiac contraction, in contrast to the unsustained parasternal impulse felt in pure volume overload.

On auscultation of the chest, the second heart sound is closely split, and the second (pulmonic) component is accentuated. The valvular closure sound should increase in intensity on inspiration and may become palpable as pulmonary artery pressure rises. A systolic ejection click reflecting sudden distention of the right ventricular wall also may be heard. A murmur of tricuspid regurgitation heard best along the left sternal border and increasing in intensity with inspiration, is frequent. A pulmonic regurgitant murmur may become evident after dilation of the main pulmonary artery and its valvular annulus. Diastolic vibration of the aortic valve leaflet (Graham Steell murmur) may be present along with third and fourth heart sounds. In addition to these findings, patients with right-sided heart failure usually have peripheral edema and abdominal distention due to ascites. If tricuspid regurgitation is present, the liver may become pulsatile.

Cyanosis is seen with variable frequency in patients with idiopathic PAH and is likely to be a late phenomenon. It is most marked during exercise but also may be present at rest. Peripheral vasoconstriction and impaired oxygenation of arterial blood due to mixed venous hypoxemia resulting from the decreased cardiac output appear to be the most common mechanisms. Patients in whom right atrial pressure equals or exceeds left atrial pressure may develop severe hypoxemia and cyanosis because of opening of the foramen ovale with subsequent right-to-left shunting of blood. In addition to cyanosis, vascular plethora may be observed in hypoxemic patients with secondary polycythemia. Clubbing is not a usual manifestation of idiopathic PAH. The presence of clubbing warrants a careful search for other causes of pulmonary vascular disease such as congenital heart disease, liver disease, PVOD, or idiopathic pulmonary fibrosis.

DIAGNOSIS

A thorough workup is required in all patients in whom PAH (WHO group 1) is suspected. A diagnostic algorithm has been developed, including basic tests—that should be completed in all patients—and optional tests that are performed when indicated (Fig. 58-4). A similarly thorough workup will be required in many patients felt to have pulmonary hypertension related to a WHO group 2 or 3 condition, but a more limited evaluation may be appropriate in a subset of patients with advanced left heart or lung disease, borderline

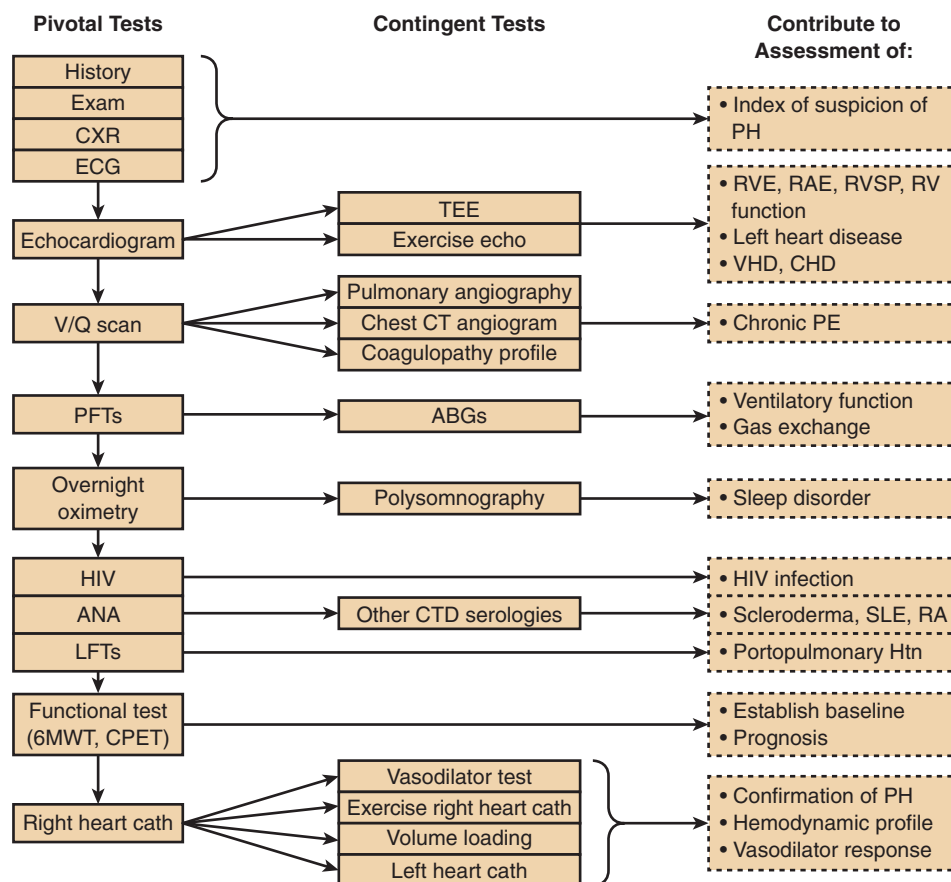


Figure 58-4 Diagnostic approach to pulmonary arterial hypertension. Pivotal tests are required for a definitive diagnosis of idiopathic pulmonary arterial hypertension, while contingent tests are performed when clinically indicated. ABGs, arterial blood gas; ANA, antinuclear antibody; CHD, congenital heart disease; CPET, cardiopulmonary exercise test; CTD, connective tissue disease; CXR, chest xray; ECG, electrocardiogram; HIV, human immunodeficiency virus; HTN, hypertension; LFTs, liver function tests; PE, pulmonary embolism; RA, rheumatoid arthritis; RAE, right atrial enlargement; RV, right ventricle; RVE, right ventricular enlargement; RVSP, right ventricular systolic pressure; 6MWT, six minute walk test; SLE, systemic lupus erythematosus; TEE, transesophageal echocardiogram; V/Q, ventilation perfusion scan; VHD, valvular heart disease. (From McLaughlin VV, Archer SL, Badesch DB, et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 119:2250–2294, 2009.)

or mild pulmonary hypertension based on echocardiogram (right ventricular systolic pressure <50 mm Hg, no right ventricular dysfunction), and plans to focus therapy on the underlying disease process (i.e., no PAH-specific therapies).

The initial history should include a thorough review of symptoms as well as any potential pulmonary hypertension risk factors, including connective tissue disease, congenital heart disease, liver disease, obstructive sleep apnea, prior pulmonary embolism, and prior diet pill or stimulant use. Family history should be reviewed, including any family members with pulmonary hypertension, pulmonary embolism, or hereditary hemorrhagic telangiectasia. On physical examination, in addition to the potential physical findings described, particular attention should also be paid to findings that would suggest a non-idiopathic PAH diagnosis, such as significant crackles or wheezing on pulmonary examination, skin changes suggestive of connective tissue disease, pulmonary flow murmurs (suggestive of chronic thromboembolic disease), or evidence of clubbing.

Chest radiography is useful for suggesting the presence of pulmonary hypertension and in providing clues of underlying conditions such as parenchymal lung disease. In patients with idiopathic PAH, the radiograph characteristi-

cally reveals enlargement of the main pulmonary artery, increased width of the descending branch of the right pulmonary artery, peripheral oligemia, and an enlarged heart (Fig. 58-5 and eFig. 58-6). The axial CT scan can confirm the increased diameter of the main pulmonary artery (see Fig. 58-5).

The electrocardiogram usually discloses right ventricular hypertrophy in patients with advanced idiopathic PAH. Electrocardiographic criteria for right ventricular hypertrophy include a QRS axis in the frontal plane that is greater than or equal to 110 degrees, an R wave in lead V1 that is greater than 5 mm, an R-to-S ratio in V1 that is greater than 1, and an R-to-S ratio in lead V6 that is less than 1. Patients also may manifest right atrial enlargement with a symmetrical and peaked P wave in lead II that is greater than 2.5 mm in amplitude. ST segment depression and T-wave inversion may be seen in the anterior chest leads. These abnormalities may not be present if pulmonary hypertension is not pronounced or if patients are young.

Systemic arterial blood gas analysis in patients with idiopathic PAH usually reveals a low arterial carbon dioxide pressure (arterial PCO_2) and a normal pH, reflecting chronic respiratory alkalosis. The systemic arterial oxygen pressure

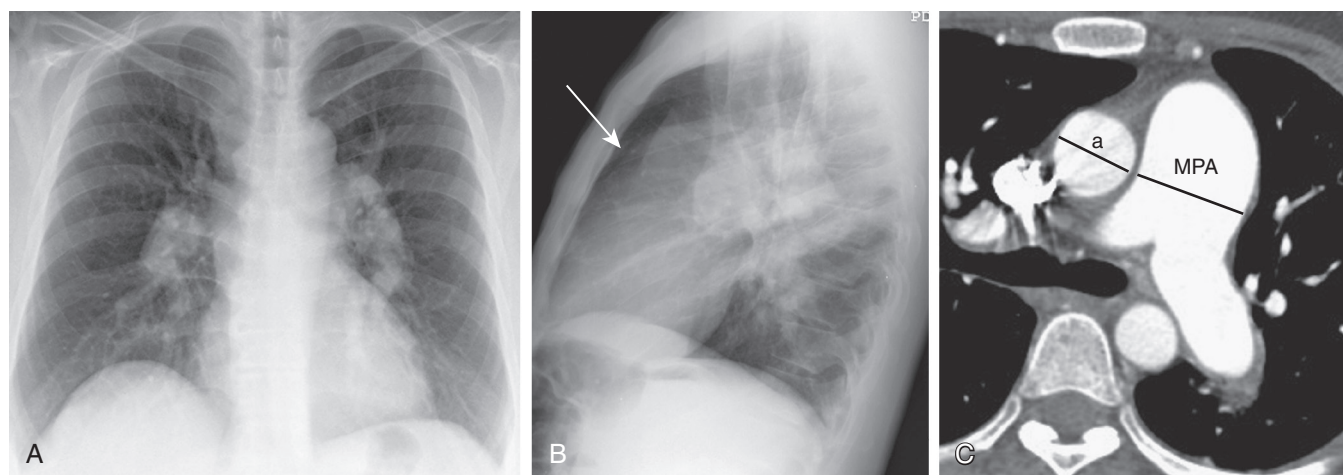


Figure 58-5 Idiopathic pulmonary arterial hypertension: chest radiographic and chest CT findings. Frontal (A) and lateral (B) chest radiographs show bilateral, symmetrical central pulmonary arterial enlargement. The lateral radiograph (B) reveals “filling” of the substernal regions (the “retrosternal clear space”), representing enlargement of the right ventricular outflow tract (arrow). C, Axial enhanced chest CT shows enlargement of the main pulmonary artery, consistent with elevated pulmonary arterial pressure. The main pulmonary artery (MPA) is measured as indicated, typically at the widest portion of the vessel at or near the level of the bifurcation: ≥ 29 mm in transverse diameter is considered abnormal. Alternatively, the size of the main pulmonary artery may be compared with the ascending aorta (a) at the same level. Assuming the aorta is not pathologically enlarged, the main pulmonary artery may be considered abnormally enlarged if its diameter, typically measured at the main pulmonary artery bifurcation, exceeds the ascending aortic diameter at the same level, as is seen in this case. (Courtesy Michael Gotway, MD.)

(arterial PO_2) may be normal or abnormal, but the alveolar-to-arterial PO_2 difference usually is increased. Several mechanisms have been proposed for the hypoxemia of patients with idiopathic PAH, including diffusion impairment caused by a reduction in the number of pulmonary vessels coupled with the shortened time spent by erythrocytes in traversing the pulmonary circulation; ventilation-perfusion mismatching due to alterations in pulmonary blood flow; and concomitant conditions such as bronchospasm, right-to-left intracardiac shunting through a patent foramen ovale, and a reduced mixed venous PO_2 resulting from a low cardiac output.⁷¹ Blood studies are another important part of the laboratory evaluation. The complete blood count is particularly helpful in documenting polycythemia, which is present in hypoxemic patients with PAH or pulmonary hypertension related to lung disease.

Ventilation-perfusion lung scanning has been used primarily to differentiate idiopathic PAH from chronic pulmonary thromboembolism. Worsley and associates studied 75 patients with pulmonary hypertension of various types and found that 24 of 25 (96%) patients with chronic thromboembolic pulmonary hypertension had high probability scans, while one patient had an intermediate probability scan.⁷² In contrast, 33 of 35 patients (94%) with idiopathic PAH had a low probability scan (eFig. 58-7), one had an intermediate probability scan, and one had a high probability scan. Based on these and other studies,⁷³ patients with otherwise unexplained PAH who have an intermediate or high probability V/Q scan should undergo further evaluation, including pulmonary angiography. CT scanning is not recommended for evaluating chronic pulmonary embolism, because the sensitivity has been lower than V/Q scanning in head-to-head studies.⁷⁴

Pulmonary function tests performed in patients with idiopathic PAH usually reveal normal expiratory flow rates with normal or mildly reduced lung volumes. The modest restrictive defect has been attributed to diminished disten-

sibility of the pulmonary vessels.⁷⁵ The DL_{CO} is often reduced to a mild or moderate degree,⁹ and a low DL_{CO} out of proportion to lung volumes has been used in screening algorithms to identify scleroderma patients who are at increased risk of having pulmonary hypertension.⁷⁶

Exercise testing may serve to unmask physiologic abnormalities in patients with idiopathic PAH if these abnormalities are not present at rest. Characteristically, patients with PAH achieve their target heart rate and anaerobic threshold at low levels of exercise, often accompanied by a reduction in the arterial PO_2 or an increase in the alveolar-to-arterial PO_2 difference. The dead space-to-tidal volume ratio either fails to decrease, as it should in healthy persons, or actually increases during graded exercise. Submaximal exercise testing measured by the 6MWD is extremely useful as a prognostic marker and in following patients on therapy; individuals whose walk distance is greater than 380 to 400 m have a better prognosis.⁷⁷ Additionally, patients with a postwalk test decline in heart rate of at least 16 beats/min have a better prognosis than those with a smaller decline, measured as heart rate at end of the test versus heart rate after 1 minute of recovery.⁷⁸ The 6MWD has served as the primary outcome end point in several pivotal pulmonary hypertension clinical trials.

ECHOCARDIOGRAM

The echocardiogram is a key diagnostic test in the evaluation of PAH, providing an assessment of right ventricular size and function, an estimate of the pulmonary arterial systolic pressure, and in ruling out other cardiac conditions such as mitral valve disease and left ventricular systolic or diastolic dysfunction. Current guidelines recommend using echocardiography to estimate the *likelihood* of pulmonary hypertension, based on the Doppler-derived peak *tricuspid jet velocity* (TR jet) and using the equation: right ventricular systolic pressure = $[(TR \text{ jet})^2 \times 4] + \text{estimated central venous}$

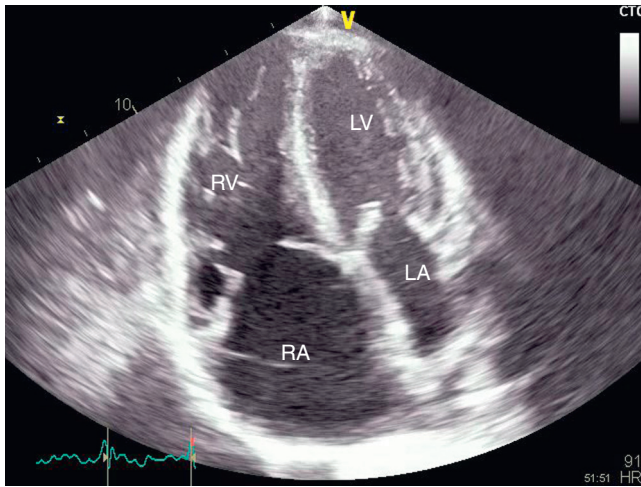


Figure 58-6 Echocardiogram in pulmonary hypertension. In addition to an elevated estimated pulmonary artery systolic pressure, the echocardiogram in pulmonary hypertension may show a variety of abnormalities including a dilated right atrium (RA) and right ventricle (RV), as seen on this image, shift of the interventricular septum, and a pericardial effusion. (See also [Video 58-1](#).) LA, left atrium; LV, left ventricle.

pressure. Specifically, a peak TR jet less than 2.8 m/sec is unlikely to represent PAH, whereas a velocity greater than 3.4 m/sec is consistent with probable pulmonary hypertension, and values between 2.8 and 3.4 m/sec, corresponding to estimated right ventricular systolic pressures of 37 to 50 mm Hg, are considered indeterminate.⁷⁹

Importantly, the accuracy and precision of this estimate compared with right heart catheterization measurement has been only moderate in many studies and, in certain circumstances, a decision to proceed with right heart catheterization may be appropriate even with a normal estimated pulmonary artery systolic pressure. It is also important to look for other echocardiographic findings suggestive of pulmonary hypertension. Suspicious findings include dilated right heart chambers, systolic flattening or diastolic bulging of the interventricular septum ([Fig. 58-6](#) and [Video 58-1](#)), and a short pulmonary arterial acceleration time, although in general these tend to be later findings.⁸⁰ Intracardiac shunting may be observed after the intravenous injection of contrast or microbubbles. Echocardiographic measurements may also be useful in estimating prognosis and tracking response to therapy. Importantly, this does not include estimated pulmonary arterial systolic pressure, which by itself does not have prognostic value in idiopathic PAH. Instead, echocardiographic measures suggesting right ventricular dysfunction should be sought, including dilated right heart chambers, reduced right ventricular systolic function, significant tricuspid regurgitation, marked septal shift with a small left ventricular chamber, and a pericardial effusion.⁸¹

CARDIAC CATHETERIZATION

In the evaluation of idiopathic PAH, right heart catheterization is mandatory to document the presence and severity of pulmonary hypertension, rule out cardiac causes, and determine whether there is acute pulmonary vasoreactivity using pharmacologic agents. Hemodynamic values, espe-

cially right atrial pressure and cardiac index, correlate closely with survival.^{82,83} Cardiac chamber and pulmonary arterial pressures are recorded, and the *pulmonary capillary wedge pressure* (PPW) is measured to rule out disease at the level of the left ventricle, left atrium, or large pulmonary veins. Cardiac output is measured, and the pulmonary and systemic vascular resistances are calculated. Blood gas samples are obtained to determine oxygen tensions and contents in the two circulations. Left-to-right intracardiac shunts may be excluded by the measurements of blood oxygen tensions and contents in the various cardiac chambers and by indicator techniques.

PAH—without left-sided heart involvement—is defined hemodynamically as a mean pulmonary arterial pressure greater than or equal to 25 mm Hg and a PPW less than 16 mm Hg. A PVR greater than or equal to 3 Wood units has been included in some but not other definitions, and the vast majority of patients with idiopathic PAH will easily meet this cutoff at diagnosis, with an average PVR at diagnosis of 12 Wood units or higher.^{10,84,85}

The measurement of PPW in pulmonary hypertension deserves extra attention, because a reading greater than 15 mm Hg suggests a diagnosis of left-sided heart disease rather than PAH. The PPW is obtained by transiently occluding blood flow in the pulmonary artery using an inflated, balloon-tipped catheter. The PPW can be inaccurate because of incomplete occlusion, resulting in a blunted pulmonary arterial pressure measurement rather than a true PPW, or because the catheter tip is not located centrally within the pulmonary artery. Inspecting the catheter location under fluoroscopy and ensuring that the resultant pressure tracings are consistent with a left atrial pressure waveform helps ensure an accurate reading. In some cases, a better waveform may be obtained by partially deflating the balloon and repositioning it. Additionally, a wedge position of the catheter can be confirmed by aspirating blood from the distal lumen and documenting high oxygen saturation indicative of pulmonary capillary blood. Because this measurement is so critical to the diagnosis, some centers routinely measure left ventricular end-diastolic pressures during all diagnostic right heart catheterizations.

Acute vasodilator testing is often performed during the initial catheterization. This study is performed using a short-acting agent, such as inhaled nitric oxide, adenosine, or prostacyclin. Oxygen and nitrates are not adequate testing agents in patients with idiopathic PAH. Criteria for defining vasoresponsiveness are discussed later, but basically, acute testing is performed to identify patients who will benefit from long-term vasodilator therapy.

TREATMENT AND PROGNOSIS

Idiopathic and other forms of PAH are now treatable diseases. Clear-cut short- and long-term benefits are seen with currently available therapies.⁸⁶ To optimize a patient's outcome, a comprehensive medical approach is essential. Once the diagnostic process in a patient with pulmonary hypertension is complete and the patient is characterized as having PAH (WHO group 1), therapy should be initiated. But many questions arise regarding PAH therapy. What are the goals and expected outcomes of treatment? Which drug

should be used first? When should another therapy be added? Should more than one therapy be used? In what order? When should transplantation be considered?

Therapy for PAH may be subdivided into “supportive” or “conventional” therapies, defined as empirical treatments or recommendations for which there is no prospective, randomized, controlled data, and “specific” or “targeted” therapies, which have been tested and approved by regulatory authorities for the treatment of PAH.

SUPPORTIVE THERAPIES

Exercise and Physical Activity

Although data are limited, consensus guidelines support the benefits of exercise in PAH patients. However, patients should avoid activities that lead to undue symptoms such as severe dyspnea, chest pain, light-headedness, or syncope. Two small studies ($N = 22$ and $N = 30$) have demonstrated that exercise and respiratory training can be safe and lead to measurable improvements in subjective and objective parameters.^{87,88} In these studies, patients undergoing 12- to 15-week courses of supervised aerobic exercise and resistance training were found to have significant improvement in 6MWD outcomes and peak oxygen consumption compared to controls. No significant safety concerns were identified, and there were no significant changes in echocardiographic measures of right heart function or in brain natriuretic peptide levels.

Avoidance of Altitude

Hypobaric hypoxia causes pulmonary vasoconstriction and, thus, can worsen pulmonary hypertension and lead to symptomatic worsening in PAH patients. It is generally recommended that patients flying on commercial airliners (pressurized to 1500 to 2400 m) or traveling to elevation above 5000 feet be evaluated for supplemental oxygen⁸⁹ (see Chapter 25). Not surprisingly, patients with severe PAH residing at high elevations may improve if they move to sea level.

Avoidance of Pregnancy

Pregnancy is extremely risky in patients with PAH, with a high peripartum mortality rate, especially after delivery.⁹⁰ Although there are case reports of patients managed with epoprostenol and undergoing successful pregnancies and deliveries,^{91,92} it is strongly recommended that women of childbearing potential use appropriate methods of birth control to avoid pregnancy. In terms of which birth control method is preferable, none of the highly effective methods are absolutely contraindicated in PAH, although surgical procedures (sterilization) may be too high risk for many patients. Additionally, some experts recommend avoiding estrogen-containing hormonal contraceptives, particularly in patients who are not anticoagulated. Efficacy can be generally thought of in three tiers: (1) sterilization, intrauterine devices, and progestin-containing implants; (2) combination and progestin-only birth control pills, the estrogen-containing transvaginal ring, and injectable progestins; and (3) barrier methods, such as the condom and diaphragm, with the latter choices considered appropriate in PAH only when used in combination with another method.⁹³

Anticoagulation

There is strong rationale for the use of anticoagulants in PAH. Many of the endothelial cell abnormalities that predispose patients to pulmonary arteriopathy also increase thrombosis. The presence of heart failure and an indwelling central venous catheter are independent risk factors for thromboembolic events, which are poorly tolerated by patients with an already marginal pulmonary vascular reserve. In addition, microscopic thrombotic lesions in the pulmonary vasculature are well documented in PAH patients.

Warfarin. Warfarin is the anticoagulant most frequently used in patients with PAH. In PAH clinical trial registries, about 50% to 85% of patients are on anticoagulants at study entry.⁹⁴ However, anticoagulation has risks (i.e., bleeding) as well as the need for frequent monitoring. To justify the use of warfarin in PAH, nine studies have examined the effects of warfarin in idiopathic PAH. All were retrospective analyses with some patients on warfarin and others untreated.^{95,96,96a} Although better survival was documented in patients on warfarin compared with those not anticoagulated in six of nine studies, including the study by Rich and coworkers,¹¹⁵ as shown in Figure 58-7, none of them were randomized and few were conducted in the modern era of effective PAH therapies. There have been two studies using warfarin conducted in the modern PAH therapy era; one resulted in better survival in idiopathic PAH, while the other was inconclusive.^{96,96a}

Despite the serious limitations in the existing data, published guidelines recommend that patients with idiopathic PAH be treated with warfarin.^{79,97} There is less guidance regarding the use of anticoagulation in other forms of PAH, such as that associated with congenital systemic-to-pulmonary shunts or associated with connective tissue diseases. Warfarin is clearly indicated for patients with Group 4 PAH (chronic thromboembolic disease). Other potential

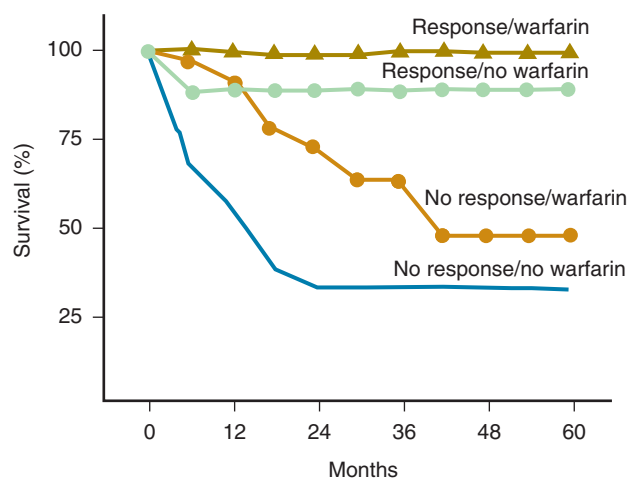


Figure 58-7 Survival in patients with idiopathic pulmonary arterial hypertension based on acute vasoreactivity and treatment with calcium channel blockers or warfarin. In patients who were not vasoreactive (lower two lines), warfarin was associated with a modest survival advantage. (Redrawn from Rich S, Kaufmann RN, Levy PS: The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 327:76–81, 1992.)

situations in which warfarin may be considered include advanced heart failure or the presence of indwelling central venous catheters. Conversely, if there is increased risk for bleeding (thrombocytopenia, history of hemoptysis, or gastrointestinal bleeding), withholding anticoagulation is advised.

Factor Xa Inhibitors. Despite its pharmacologic limitations and need for frequent coagulation monitoring, warfarin, since 1954, has had virtually no competition as the clinical agent of choice for long-term anticoagulation. Recently, however, a novel group of oral anticoagulants—known as factor Xa inhibitors—has altered the current anticoagulation picture. Most clinical studies have compared the efficacy and safety of the standard regimen of parenteral enoxaparin followed by warfarin compared with a fixed-dose of a factor Xa inhibitor for treatment of either acute venous thromboembolism or atrial fibrillation; results to date indicate that long-term warfarin has equal anticoagulant effectiveness as one of several factor Xa inhibitors.⁹⁸ Furthermore, an experimental study of a factor Xa inhibitor using a rat model of PAH also showed beneficial results.⁹⁹ No effective antidote for serious bleeding related to factor Xa inhibitors is yet available, but major hemorrhage is infrequent. More information about this promising group of compounds is eagerly awaited.

Aspirin has also been considered potentially beneficial in PAH, based on evidence of platelet activation in PAH and on evidence of improved outcomes in animal models of pulmonary hypertension.¹⁰⁰ However, its use did not lead to improved outcomes in a randomized controlled clinical trial in PAH and it is therefore not recommended unless required for other indications.¹⁰¹

Supplemental Oxygen

The benefits of supplemental oxygen in PAH patients, unlike patients with pulmonary hypertension associated with lung diseases such as chronic obstructive pulmonary disease,^{102,103} are not clear. In fact, most PAH patients are not hypoxemic at rest. Mild hypoxemia, when present, is likely on the basis of reduced mixed venous oxygen saturation levels caused by low cardiac output with mild ventilation/perfusion inequality. The presence of more profound hypoxemia in a patient with PAH should raise suspicion for underlying parenchymal lung disease, systemic to pulmonary shunting, PVOD, pulmonary capillary hemangiomatosis, or pulmonary arteriovenous malformations as seen in pulmonary hypertension due to hereditary hemorrhagic telangiectasia. Of note, a patent foramen ovale, present in more than 20% of the population, can contribute to hypoxemia in pulmonary hypertension.

Although oxygen is a pulmonary vasodilator, there are no long-term studies supporting its efficacy. However, the consensus is that, if arterial PO_2 is less than 60 mm Hg or systemic arterial O_2 saturation is less than 90% at rest, supplemental oxygen is indicated. One exception to this approach is in patients with Eisenmenger syndrome, with hypoxemia due to right-to-left shunting; in this group, the use of supplemental oxygen may have negligible benefit.^{104,105} There is also no general agreement about whether exercise-only systemic arterial O_2 desaturation warrants oxygen supplementation. In addition, the “stigma”

of nasal cannulae for a PAH patient often limits compliance outside the home.

Diuretics

Diuretics have long been mainstays of therapy for heart failure, including right ventricular failure. Both total-body and intravascular volume overload are common in PAH patients. In pivotal trials of PAH drugs, the majority of patients were on chronic diuretic therapy.^{106,107}

In addition to causing symptomatic peripheral edema and renal¹⁰⁸ and hepatic congestion, volume overload of the right ventricle can cause compression of the left ventricle and contribute to decreased cardiac output and prerenal azotemia. Thus, it is a common observation that in decompensated PAH patients, aggressive diuresis leads to clinical and physiologic improvements. Despite the benefits of diuretics in PAH patients, there are no controlled studies to guide the clinician in using these agents.

A loop diuretic is frequently used first. Although furosemide is often the loop diuretic of choice, there is some evidence that torsemide might be more efficacious without increased side effects.¹⁰⁹ In addition, in patients with marked extravascular fluid accumulation and poor intestinal absorption, intravenous diuretic therapy is frequently needed. Anti-aldosterone drugs (e.g., spironolactone) are commonly combined with loop diuretics in PAH patients. Whether data suggesting a morbidity and mortality benefit of spironolactone in left-sided heart failure can be extrapolated to right-sided heart failure is not known.¹¹⁰

In some cases, the addition of a thiazide diuretic to the regimen is appropriate. The combination of metolazone and furosemide has been found by the authors to be effective in causing a brisk diuresis. However, marked hypokalemia can be seen with this regimen. Although it is possible that in some patients with PAH, the right ventricle is preload dependent and therefore over diuresis can be detrimental, this has not been the authors' experience. More often, aggressive diuresis (1- to 3-L negative fluid balance per day) leads to improvement in renal function and blood pressure.

Calcium Channel Antagonists

In 1958, Paul Wood¹⁴ first defined the clinical entity of pulmonary hypertension with reference to the “vasoconstrictive factor.” It is not surprising, then, that a search for pulmonary vasodilators as effective therapies ensued. Agents including phentolamine,¹¹¹ tolazine,¹¹² captopril,¹¹³ and hydralazine¹¹⁴ were evaluated in uncontrolled reports. Results, although variable, were not overwhelmingly favorable. No systematic studies of these medications were carried out. Out of the myriad of oral antihypertensive agents emerged calcium channel blockers. Ostensibly, this class of agents “made sense” for treating pulmonary hypertension. Calcium channel blockers have acceptable side effect profiles and are potent pulmonary as well as systemic vasodilator agents. The role of intracellular cytosolic calcium in the vasoconstriction of pulmonary artery smooth cells was well established. Thus, blocking influx of calcium into the cells seemed desirable.

In a highly quoted paper, Rich and associates¹¹⁵ described favorable survival in a subgroup of idiopathic PAH patients treated with either diltiazem or nifedipine. In that study,

patients manifesting acute pulmonary vasoreactivity with calcium channel blockers, defined as an acute decrease in mean pulmonary arterial pressure and PVR of at least 20%, had a 5-year survival of 94% (see Fig. 58-7). In contrast, patients who did not have an acute response had a 5-year survival of only 55%. In addition, the observed survival for the “acute responders” was significantly better than the survival predicted using an equation based on hemodynamics at time of diagnosis. Although not a placebo-controlled study, these data suggested a benefit with calcium channel blockers in some idiopathic PAH patients.

The Rich and associates’ study,¹¹⁵ although seminal, likely led to overuse of calcium channel blockers, not only for idiopathic PAH but for other forms of PAH. Calcium channel blockers are not selective pulmonary vasodilators and, in the setting of a nondilatable pulmonary vascular bed, the systemic vasodilating effects of these agents may lead to severe symptomatic hypotension. In addition, calcium channel blockers have potential negative inotropic effects. Thus, in patients with minimal or no acute pulmonary vasoreactivity, the negative effects of calcium channel blockers can become predominant, with potential for catastrophic consequences.

A subsequent large retrospective study by Sitbon and colleagues⁶⁹ has further narrowed the role of calcium channel blockers in patients with idiopathic PAH. In that study, 557 patients with idiopathic PAH were tested for acute pulmonary vasoreactivity using either intravenous prostacyclin (e.g., epoprostenol) or inhaled nitric oxide. Seventy patients (about 13%) had an acute response (at least a 20% fall in mean pulmonary artery pressure and PVR) and were treated with calcium channel blockers. However, only half of those “acute responders” (about 7% of the total) did “well” long term on calcium channel blockers, defined as being alive and in functional class 1 or 2 at 5-year follow-up. The long-term survivors had less severe disease as assessed by hemodynamics at baseline and had reached a lower mean pulmonary artery pressure with acute vasodilator challenge than those who failed with the long-term calcium channel blockers (33 mm Hg vs. 46 mm Hg). In other words, rather than the percent drop in mean pulmonary artery pressure during an acute test, the absolute mean pulmonary artery pressure reached appeared to be better in defining the patients who would benefit long-term with calcium channel blockers. These data have been codified into evidence-based guidelines,^{79,116} which define potential calcium channel blocker candidates as idiopathic PAH patients in whom, during an acute pulmonary vasoreactivity test, the mean pulmonary artery pressure decreases by at least 10 mm Hg to a level below 40 mm Hg, with no decrease in cardiac output.

The method for performing acute pulmonary vasoreactivity testing varies among pulmonary hypertension centers. Most frequently, one of three short-acting pulmonary vasodilators is used in the cardiac catheterization laboratory (i.e., inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol). Using a short-acting agent prevents refractory systemic hypotension that could result when a patient with PAH with minimal pulmonary vasoreactivity is given a systemic vasodilator. A distinct advantage of inhaled nitric oxide is the absence of systemic hemodynamic effects, the very rapid “on-off” properties of the drug

(i.e., half-life 20 seconds), and the absence of side effects. With inhaled nitric oxide, an acute pulmonary vasoreactivity test with repeat hemodynamic measurements can be accomplished in less than 10 minutes.

TARGETED THERAPIES

PAH-specific therapies have been available since 1995, when intravenous epoprostenol was approved by the U.S. Food and Drug Administration (FDA), based on the first prospective randomized controlled trial done in PAH. Since then, an additional 11 therapies have been approved for PAH: subcutaneous, inhaled, intravenous, and oral treprostinil; inhaled iloprost; the oral endothelin receptor antagonists bosentan, ambrisentan, and macitentan; the phosphodiesterase-5 inhibitors sildenafil and tadalafil; and the guanylate cyclase stimulator riociguat (Table 58-2). These therapies are targeted to offset the imbalance in endothelial-derived mediators seen in PAH: excessive endothelin-1 production, abnormal nitric oxide production, and deficient prostacyclin (Fig. 58-8).

Prostacyclin Analogues

Epoprostenol (Flolan/Veletri). Continuous intravenous infusions of prostacyclin (prostaglandin I₂, epoprostenol) produce sustained improvement in hemodynamics and exercise tolerance and prolonged survival. In the first randomized prospective study of epoprostenol,¹⁰⁶ 81 patients with New York Heart Association (NYHA) class III or IV symptoms, despite treatment with conventional therapy, were randomized either to continuous intravenous epoprostenol plus conventional therapy or to conventional therapy alone for 12 weeks. At 12 weeks, 6MWD, the primary end point, had improved in the continuous intravenous epoprostenol group by 32 m and decreased by 15 m in the conventional therapy group. There were also significant improvements in the epoprostenol group in hemodynamics, quality of life, and NYHA functional class. Eight patients died during the 12-week study, all in the conventional treatment group. Notably, this is the only randomized controlled PAH trial to date ever to show a significant effect on survival. A subsequent study found significant improvements in 6MWD, functional class, and exercise capacity in patients with scleroderma-associated PAH.¹¹⁷

Long-term follow-up studies have shown sustained benefits, including improved functional class and improved survival compared with historical controls. Five-year survival of greater than 60% has been seen in treated patients in two series,^{83,118} an improvement from the median survival in the “pre-epoprostenol” era of less than 3 years. Despite its clear benefits, chronic use of epoprostenol is complex and requires an indwelling central venous catheter, continuous-infusion pump, and daily preparation of the medication. In addition, there are numerous side effects including jaw claudication, leg and foot pain, diarrhea, rash, and weight loss occasionally with ascites. The complexities of dosing prostacyclin and assessing response to the therapy obligate a dedicated team, typically present only at large pulmonary hypertension centers.

Subcutaneous and Intravenous Treprostinil Sodium (Remodulin). Treprostinil sodium is a tricyclic benzidine

Table 58-2 Randomized Clinical Trials of Approved Drugs in Pulmonary Arterial Hypertension

	N	Wk	Other PAH Rx (%)	Δ6MWD vs. Placebo (m)	FC	QOL	Cath	CW or Death	NT-BNP
PROSTACYCLINS									
1996 Epoprostenol IV (IPAH) (106)	81	12	None	60	Y♦	Y	Y	Y	
2000 Epoprostenol IV (Scleroderma PAH) (117)	111	12	None	108	Y♦	Y	Y		
2002 Treprostinil SC (119)	470	12	None	16	Y♦		Y		
2002 AIR, iloprost INH (130)	203	12	None	36	Y●	Y●	Y	N	
2010 TRIUMPH 1, treprostinil INH (131)	235	12	ERA /PDE-5 100%	20	Y♦	N	Y	N	Y
2012 FREEDOM C, treprostinil PO (125)	350	16	ERA, PDE-5, or both 100%	11	N♦	N	Y	N	
2013 FREEDOM M, treprostinil PO (123)	349	12	None	26	Y♦	N		N	
2013 FREEDOM C2, treprostinil PO (124)	310	16	ERA, PDE-5, or both 100%	10	N♦	N	N	N	N
ENDOTHELIN RECEPTOR ANTAGONISTS									
2001 Bosentan (133)	32	12	None	76	Y♦	Y		Y	
2002 BREATHE-1, bosentan (107)	213	16	None	35	Y♦	Y		Y	
2008 ARIES-1, ambrisentan (151)	202	12	None	31 (5 mg) 51 (10 mg)	Y♦	Y	N	N	Y
2008 ARIES-2, ambrisentan (151)	192	12	None	59 (5 mg)	Y♦	N	Y	Y	Y
2013 SERAPHIN, macitentan (152)	742	85-104*	PDE ₅ 61% Prostanoid 5%	22	Y	Y	Y	Y♦	
PDE₅ INHIBITORS									
2005 SUPER, sildenafil (136)	278	12	None	45	Y♦	Y		Y	N
2009 PHIRST, tadalafil (137)	405	16	ERA, 53%	33	Y♦	N	Y	Y	Y
SOLUBLE GUANYLATE CYCLASE STIMULATORS									
2013 PATENT-1 (153)	443	12	ERA, 44% Prostanoid 6%	36	Y♦	Y	N	Y	Y

Head to head studies are lacking; comparing outcomes across studies is discouraged due to heterogeneity in response depending on baseline characteristics and other factors, particularly for 6MWD.

*Seraphin had a morbidity and mortality primary end point; study had a mean treatment duration of 85 weeks, 100 weeks, and 104 weeks (placebo, 3 mg macitentan, and 10 mg macitentan, respectively.)

Y: statistically significant, $P < 0.05$; N: $P > 0.05$; ♦, 1° end point; blank, not reported. Walk distance results are for approved dose if multiple doses were tested. 6MWD, 6-minute walk distance; cath, catheterization; CW, clinical worsening; ERA, endothelin receptor antagonist; FC, World Health Organization functional class; INH, inhalational; IV, intravenous; NT-BNP, N-terminal brain natriuretic peptide; PDE-5, phosphodiesterase type-5 inhibitor; PO, by mouth; QOL, quality of life; Rx, treatment; SC, subcutaneous; Wk, weeks; ● Air 1° end point: number with 10% improvement in 6MWD + improved FC.

analogue of prostacyclin that is chemically stable at room temperature and has a half-life of approximately 4 hours. Treprostinil was initially approved for continuous subcutaneous delivery, based on a double-blind, randomized, controlled trial that included 470 patients with idiopathic PAH (58%), PAH associated with connective tissue disease, or PAH associated with congenital systemic pulmonary shunts.¹¹⁹ As with other PAH trials, the primary outcome measure was exercise capacity defined as placebo-corrected improvement in 6MWD. The placebo-corrected improvement in 6MWD was 16 m ($P = 0.006$). Borg dyspnea scores, quality of life measures, and hemodynamics were also significantly improved in the treprostinil group compared with placebo.

Dosing of treprostinil in this trial and in all other systemic prostacyclin studies was left to the treating physician, with dose increases based on clinical response and side effects. Notably, walk distance improvement among treprostinil-treated patients varied by dosing quartile, with the greatest improvement seen in patients in the highest dosing quartile (>13.8 ng/kg/min). Infusion site pain was the major adverse event, experienced by 200 (85%) patients in the treprostinil group versus 62 (27%) in the placebo arm.

Other common side effects, all of which are seen with systemic prostacyclins as a class, included jaw pain, headache, and diarrhea.

Intravenous treprostinil was subsequently approved based on bioequivalence with subcutaneous treprostinil, with an intended use in patients not tolerating subcutaneous infusion. Intravenous treprostinil was later shown to lead to improvements in 6MWD versus placebo in one small randomized controlled clinical trial,¹²⁰ and it has also been the subject of several uncontrolled reports.^{121,122} Finally, sustained-release oral treprostinil is also now approved. Oral treprostinil led to significant improvement in 6MWD when taken as monotherapy in a 12-week PAH trial (FREEDOM-M),¹²³ but failed to lead to significant improvement in studies enrolling patients on background therapies (FREEDOM-C and C2).^{124,125} Hemodynamic effects and longer term results for other outcomes have not been reported.

Prostacyclin Dosing

There have been no studies formally comparing dosing strategies of continuous epoprostenol and treprostinil, and only very limited acute dose-ranging studies.¹²⁶

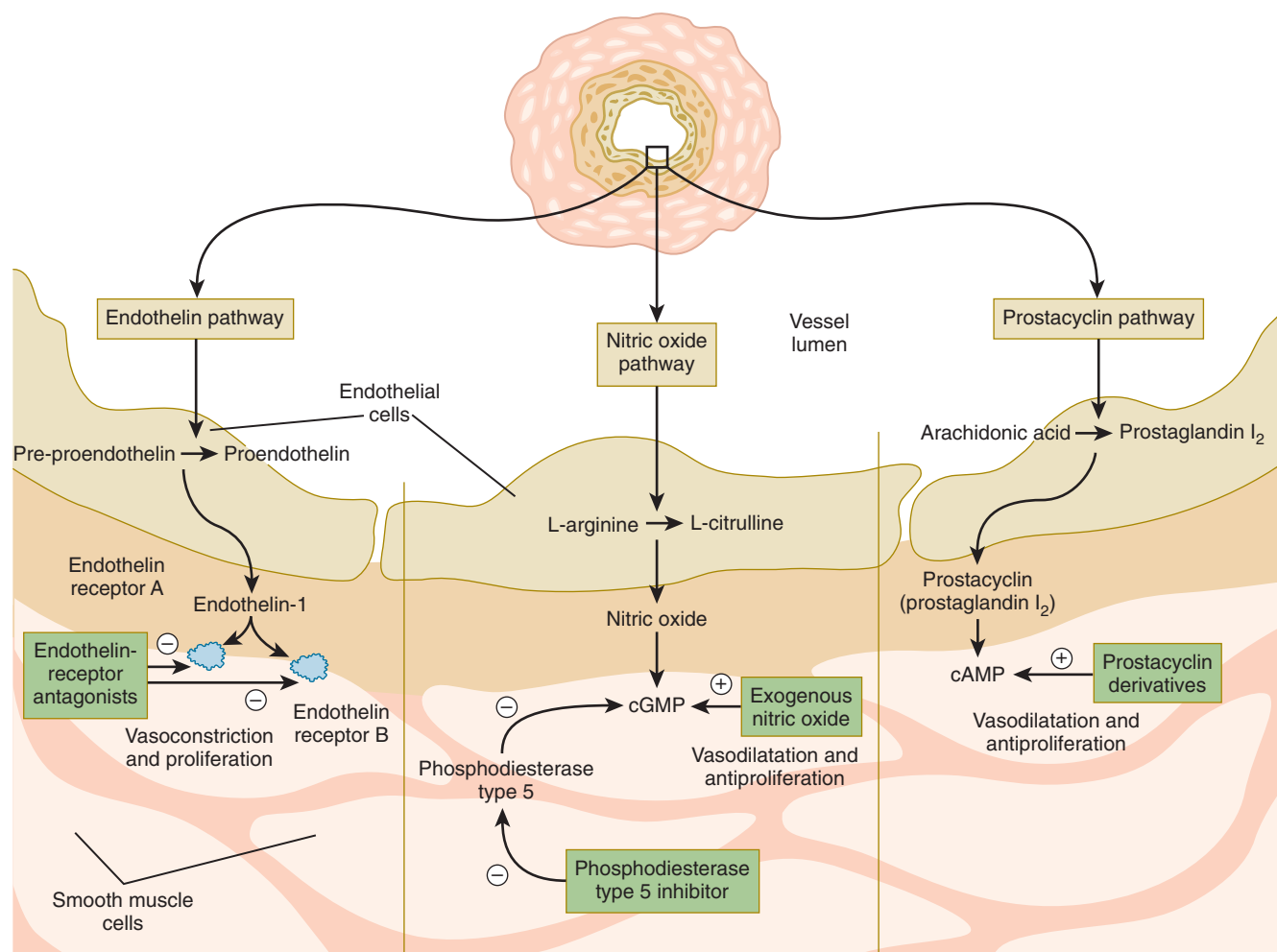


Figure 58-8 Schematic of three abnormal endothelial mediator pathways that are targeted by current therapies. cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.

Nevertheless, there are observational data, particularly for treprostinil,¹²⁷ suggesting that higher doses are associated with improved outcomes. At the same time, other studies suggest that excessive dosing of epoprostenol can lead to an abnormally high cardiac output and more severe side effects.¹²⁸ Individualized dosing and periodic hemodynamic monitoring is therefore recommended for all patients on parenteral prostacyclins.¹²⁸

Intravenous epoprostenol is typically initiated in the hospital setting at 1 to 2 ng/kg/min and titrated up slowly over a few days to approximately 4 to 6 ng/kg/min, aiming to titrate up to an effective dose as quickly as possible, while at the same time avoiding excessive side effects of headache, flushing, nausea, and diarrhea, among others. After an initial inpatient titration, patients follow an outpatient dosing chart, continuing to increase on their own at approximately 3- to 7-day intervals until a target dose is reached. In clinical trials, the average dose achieved at 2 to 3 months (end of study) was 8 to 11 ng/kg/min.^{106,117,129} Long-term, average doses of 21 ng/kg/min at 1 year⁸³ and 35 ng/kg/min at approximately 1½ years¹¹⁸ have been reported.

Subcutaneous and intravenous treprostinil are initiated in a similar manner, but an overall higher dose is typically

targeted. This is based on the finding that, in one conversion study, patients who transitioned from epoprostenol to treprostinil required an approximately twofold higher dose of treprostinil to control their symptoms.¹²² Long-term open label studies of subcutaneous treprostinil have also suggested that achieving a subcutaneous treprostinil dose greater than 40 ng/kg/min is independently associated with improved survival.¹²⁷

Inhaled Iloprost (Ventavis) and Treprostinil (Tyvaso).

Iloprost, a stable prostacyclin analogue, was approved by the FDA as an inhaled formulation in 2004, based on the Aerosolized Iloprost Randomized study.¹³⁰ The primary outcome was a combined end point: at least 10% improvement in 6MWD, improvement in at least one NYHA functional class, and survival. This composite end point was achieved by 17% of patients in the iloprost group versus 5% in the placebo arm (estimated odds ratio of 4, $P < 0.05$). Positive secondary end points included improvement when compared with placebo in functional class, quality of life, and preinhalation pulmonary vascular resistance. Hemodynamic measures were also repeated following an iloprost treatment, and additional improvement in pulmonary vascular resistance compared to baseline in cardiac output and

pulmonary arterial pressure were seen. Inhaled iloprost is delivered via ultrasonic nebulizer at a starting dose of 2.5 µg delivered six to nine times daily and increased to 5 µg six to nine times daily if well-tolerated. Adverse events noted in the iloprost group during the clinical trial included syncope, flushing, jaw pain, and increased cough. Vital signs should be monitored during drug initiation; patients with preexisting hypotension (systemic blood pressure less than 85 mm Hg) should not receive iloprost.

Inhaled treprostinil received FDA approval in 2009, based on the TRIUMPH-1 study, a randomized controlled clinical trial involving 235 patients with PAH.¹³¹ Patients in the treatment arm showed a 20-m improvement in 6MWD compared with placebo ($P < 0.05$), and also showed improvement compared to placebo in secondary end points of *N-terminal brain natriuretic peptide* (NT-BNP) and quality of life, as assessed by the Minnesota Living with Heart Failure questionnaire. No significant improvement was seen in time to clinical worsening or functional class. Unlike prior studies, TRIUMPH-1 enrolled only patients receiving background therapy, requiring all patients to be on either an endothelin-1 antagonist or a phosphodiesterase-1 inhibitor. Inhaled treprostinil is delivered via an ultrasonic nebulizer, the Tyvaso Inhalation System, at a starting dose of three breaths four times daily. Dosage is increased by three breaths per treatment every 1 to 2 weeks, as tolerated, until a dose of nine breaths four times daily is reached. Adverse events in the clinical trial included cough, headache, and flushing.

Endothelin Receptor Antagonists

In humans, two *endothelin* (ET)-1 receptor subtypes are found, ET-A and ET-B. Antagonism of one or both receptors has been shown to be an effective treatment strategy for idiopathic PAH, with two FDA-approved therapies, bosentan and ambrisentan. Bosentan (Tracleer) is a nonpeptide oral ET-A and B receptor antagonist. Bosentan received FDA approval in 2001 based on two randomized controlled clinical trials showing significant improvement in 6MWD among bosentan versus placebo-treated patients.^{107,132} Pulmonary hemodynamics were evaluated in the smaller of the two studies, and significant improvement in right atrial pressure, pulmonary arterial pressure, pulmonary vascular resistance, and cardiac index were seen.¹³³ Other positive findings in both studies included improvement both in Borg dyspnea index and in clinical features. In addition to the two “registration” trials, bosentan has also shown benefit in two other randomized controlled clinical trials: BREATHE-5, enrolling patients with uncorrected congenital heart disease and Eisenmenger syndrome, and EARLY (Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension), a randomized controlled clinical trial in functional class 2 patients with PAH; results are shown in Table 58-2.

Ambrisentan (Letairis) is a specific ET-A receptor antagonist approved for PAH at doses of 5 or 10 mg once daily. Following a phase 2 dosing study showing favorable pulmonary hemodynamic effects,¹³⁴ two randomized, controlled trials of ambrisentan (*Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies* [ARIES] 1: 5 mg, 10 mg, placebo; ARIES 2: 2.5 mg, 5 mg, placebo) enrolled

a total of 394 patients.¹³⁴ Both trials demonstrated benefits of ambrisentan on the primary end point of placebo-corrected improvement in 6MWD. In ARIES-2, there was a significant improvement in time to clinical worsening in the treatment group compared with placebo. There was a trend toward improvement in time to clinical worsening in the ARIES-1 study, but it was not statistically significant ($P = 0.3$).

Macitentan is a nonselective ET-A/ET-B antagonist with greater tissue penetration relative to bosentan that was evaluated in the SERAPHIN clinical trial. In SERAPHIN, patients were randomized 1:1:1 to placebo, macitentan 3 mg, or macitentan 10 mg, using a novel morbidity and mortality primary end point. Seven hundred and forty-two patients participated, and 64% were receiving a background PAH therapy. Overall, macitentan 3 mg and 10 mg resulted in a risk reduction for the primary end point of 30% and 45%, respectively, compared with placebo. Both doses of macitentan also led to significant reductions in time to PAH-related death or hospitalization and significant improvement compared with placebo in change in 6MWD at 6 months.¹³⁵

Sitaxsentan is an endothelin-1 antagonist that was shown to have beneficial effects in PAH, but it was removed from the market after it was linked to acute liver failure.

Endothelin-1 Antagonist Therapy

Endothelin-1 antagonists as a class are considered teratogenic, and therefore women of childbearing potential require monthly pregnancy testing and the use of two reliable forms of birth control during therapy. Increases in liver aminotransferases greater than eight times the upper limit of normal were also noted with bosentan therapy during randomized controlled clinical trials and, as a result, all patients receiving bosentan are required to undergo monthly liver function testing. The rate of liver function test abnormalities during ambrisentan administration has been found to be similar to that of the general population, and monthly testing is no longer required. Drug should be discontinued in patients taking either drug in whom liver function tests become abnormal during therapy, that is, aspartate aminotransferase or alanine transaminase elevations greater than fivefold normal or total bilirubin levels equal to or higher than twofold normal. In addition, for bosentan, aspartate aminotransferase or alanine transaminase elevations between three and five times the upper limit of normal require either a dose-reduction or drug cessation. Hemoglobin levels should also be monitored periodically, because anemia has been reported during therapy with endothelin-1 antagonists.

Endothelin-1 antagonists are well-tolerated by most patients, but significant peripheral edema was noted during the clinical trials, particularly in older patients. Close monitoring of volume status is therefore indicated during drug initiation and up-titration. Nasal congestion has also been reported, mainly with ambrisentan. Several significant drug interactions exist. For bosentan, both glyburide and cyclosporine are contraindicated, and strong cytochrome P450 inhibitors (rifampin, others) should be used with caution. For ambrisentan, the only clinically relevant interaction that has been identified is an increase in ambrisentan levels with cyclosporine; as a result, the ambrisentan dose

should be limited to 5 mg daily when taken with cyclosporine (see package inserts for additional details on pregnancy prevention, drug interactions, and laboratory monitoring).

Phosphodiesterase Type 5 Inhibitors

Sildenafil (Revatio) was evaluated in the SUPER-1 (*Sildenafil Use in Pulmonary Arterial Hypertension*) trial, a 12-week randomized, double-blind, placebo-controlled trial comparing placebo, 20 mg, 40 mg, and 80 mg three times daily.¹³⁶ There was a significant improvement in exercise capacity, functional class, and hemodynamics but not in time to clinical worsening. Walk distance improvement was similar across the three doses. However, hemodynamic improvement was greater with higher doses, as was the percentage of patients with improved functional class (7% in placebo group, 28% in the 20-mg group, 36% in the 40-mg group, and 42% in the 80-mg group). Despite these trends, the only U.S. FDA and European Medicines Association approved dosage is 20 mg three times daily.

Tadalafil. Tadalafil (Adcirca) was approved in 2009 based on the PHIRST trial, a 16-week study of 2.5 mg, 10 mg, 20 mg, and 40 mg tadalafil versus placebo.¹³⁷ Tadalafil 40 mg led to improvement in exercise capacity, quality of life, hemodynamics, and time to clinical worsening. Smaller but statistically significant improvement in walk distance was also seen for the 10-mg and 20-mg groups, but not for the 2.5-mg group; 40 mg once daily is the recommended dosage.

Phosphodiesterase-5 Inhibitor Therapy

Sildenafil and tadalafil are selective inhibitors of cyclic guanosine monophosphate-specific phosphodiesterase-5, an enzyme that promotes the breakdown of cyclic guanosine monophosphate. Both sildenafil and tadalafil appear to be well-tolerated clinically, and there were no significant laboratory abnormalities noted during the pivotal clinical trials. Many drug interactions have been described and should be considered before initiation: use with nitrates is contraindicated due to risk of excessive hypotension, and use with

potent cytochrome P-450 inhibitors should be avoided with both drugs (see package inserts for details).

Common adverse events during the clinical trials included headache, myalgias, flushing, epistaxis, and dyspepsia. Both drugs can be initiated at their approved dosage (sildenafil 20 mg three times daily or tadalafil 40 mg daily) but, at the authors' centers, tadalafil is initiated at a 20-mg dose for the first week in an attempt to lessen headaches and other side effects.

Impaired vision and hearing have been reported with the use of phosphodiesterase-5 inhibitors. Mild vision changes including particularly color vision changes are thought to relate to cross reactivity with and inhibition of retinal phosphodiesterase-6. More severe vision changes including sudden vision loss have also been reported, and hearing loss has been reported as well; both are of unclear mechanism.¹³⁸ Patients should seek immediate medical attention in the event of sudden loss of vision in one or both eyes or with sudden changes in hearing.

Soluble Guanylyl Cyclase Activators

Riociguat, a direct activator of guanylyl cyclase, increases levels of cyclic GMP by stimulating its synthesis.¹³⁹ It has been studied in two phase 3 randomized controlled clinical trials, PATENT, a study in PAH, and CHEST, a study in patients with chronic thromboembolic disease that is either inoperable or persistent following pulmonary thromboendarterectomy. In both studies, riociguat led to improvement in the primary end point, change in 6MWD versus placebo at 12 weeks (PATENT) or 16 weeks (CHEST), and to improvement in a number of secondary end points including PVR, NT-BNP level, and WHO functional class.¹⁴⁰

COMBINATION THERAPY

There is strong rationale for combining drugs to treat idiopathic PAH, and an increasing number of clinical trials show benefit with this approach (Table 58-3). In current practice, about 52% of patients receive combination therapy, based on data from the REVEAL registry.⁹⁴

Table 58-3 Combination Therapy and Select Other Clinical Trials in Pulmonary Arterial Hypertension

	N	Wk	Other PAH Rx (%)	Δ6MWD vs. Placebo (m)	FC	QOL	Cath	CW or Death	NT-BNP
PHASE IV—COMBINATIONS									
2004 BREATHE-2, bosentan + epoprostenol vs. epo alone (154)	33	16	None	−6	N		N♦		
2006 STEP, iloprost (155)	67	12	ERA, 100%	26	N♦	Y	Y	Y	
2006 COMBI, iloprost (156)	40	12	ERA, 100%	−10	N♦	N		N	
2008 PACES, sildenafil (141)	267	16	PGI ₂ , 100%	29	Y♦	Y		Y	
PHASE IV—OTHER									
2006 BREATHE-5, bosentan, congenital heart disease (157)	54	16	None	53	Y		Y♦		
2008 EARLY, bosentan (FC II) (158)	185	24	PDE-5, 16%	19	N♦^	Y	Y	Y♦^	Y
IN DEVELOPMENT									
2012-Selexipag Phase 2 (159)	43	17	ERA, PDE-5, both, 100%	24	N		Y♦		N

Y: statistically significant, $P < 0.05$; N: $P > 0.05$; ♦, 1° end point; blank, not reported. Walk distance results are for approved doses.

6MWD, 6-minute walk distance; CW, clinical worsening; ERA, endothelin receptor antagonist; FC, World Health Organization functional class; NT-BNP,

N-terminal brain natriuretic peptide; PDE-5, phosphodiesterase type-5 inhibitor; PGI₂, prostacyclin/epoprostenol; QOL, quality of life; Rx, treatment; Wk, weeks; ^, Co-primary end point.

The PACES (*Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil*) trial evaluated sildenafil versus placebo as add-on therapy in 267 patients on epoprostenol. Subjects were randomized to either additional sildenafil 80 mg three times daily or placebo for 16 weeks.¹⁴¹ The trial demonstrated a placebo-corrected 6MWD improvement in the sildenafil-epoprostenol group of 29 m. In addition, significant hemodynamic improvements and improvement in time to clinical worsening were seen in the sildenafil-epoprostenol group compared with the placebo-epoprostenol group. Although mortality was not a prespecified end point, there were seven deaths during the trial, all of which were in the placebo-epoprostenol group. Subsequently, multiple additional randomized controlled clinical studies that involved combination therapy have been conducted and are either in process or have recently been completed (see [Tables 58-2](#) and [58-3](#)).

Perhaps not surprisingly, the incremental improvements in 6MWD obtained by adding an agent in combination therapy studies have been smaller than those reported with the first agent in monotherapy studies. This observation has raised questions in some cases about whether very small improvements in 6MWD alone are sufficient evidence of benefit for novel drugs in PAH, particularly in studies where no improvement is seen in other important secondary end points such as clinical worsening, functional class and/or quality of life.¹⁴²⁻¹⁴⁴ As a result, alternative study designs, including long-term morbidity and mortality trials are being used in some current and recently completed clinical trials. Additionally, the optimal *timing* of combination therapy is unclear. Several ongoing studies are investigating the feasibility and efficacy of up-front combination therapy.

LUNG TRANSPLANTATION

In patients failing maximal medical therapy, lung transplantation is the “ultimate” option (see Chapter 106). According to the International Society of Heart and Lung Transplantation, current recommendations for consideration of transplantation in PAH include persistent NYHA class III or IV on maximal medical therapy, low or declining 6MWD, failing therapy with intravenous epoprostenol, cardiac failure with cardiac index less than 2 L/min/m², and elevated right atrial pressure (>15 mm Hg).¹⁴⁵ Additionally, all patients with PVOD should be referred for transplant evaluation at the time of diagnosis, given its poor response to therapy.

The current lung allocation scoring system was designed to improve the overall likelihood of transplant and to reduce wait list and posttransplant mortality compared with the prior system. Patients are now prioritized based on a computer-generated severity score rather than the amount of time they have been on the waiting list. As a whole, the system appears to have achieved many of its goals, because the percentage of patients transplanted within 1 year of listing has increased substantially and mortality on the waiting list has fallen.

However, this has not been the case in PAH. Patients with PAH have lower lung allocation scores and lower transplantation rates than do patients with other lung diseases and higher wait list mortality.¹⁴⁶ Modifications to the lung allocation score have been proposed, including the addition

of prognostic markers that have relevance in PAH, rather than relying on factors that are not very prognostic in PAH, such as pulmonary function test results and oxygen requirements. In the meantime, “exceptions” to the lung allocation score can be requested for patients who are deteriorating on optimal therapy with a right atrial pressure above 15 mm Hg or a cardiac index below 1.8 L/min/m².

One-year survival after lung transplantation for pulmonary hypertension is approximately 70%, which is lower than that of other groups due in part to higher rates of immediate posttransplant complications. In the long term, PAH patients do as well or better than patients transplanted for other lung diseases, with those surviving the first year having a conditional average survival of 10 years.¹⁴⁷

OVERALL THERAPEUTIC STRATEGY

With multiple effective medical therapies and lung transplantation available for treatment of PAH, how does one decide what therapy to use, when to reassess, when to add or change therapy, and what to add or change? Several consensus committees have attempted to evaluate the evidence for approved therapies.^{79,148} The most recent guidelines suggest making treatment decisions based on both symptoms and results of prognostic tests that are most predictive of outcomes in PAH.

Supportive therapies including warfarin, need for diuretics, and oxygen are considered. An acute vasoreactivity test is recommended for patients with idiopathic PAH and, if a positive response is seen, calcium channel blocker treatment is recommended. For patients with idiopathic PAH without acute vasoreactivity and for other PAH groups in general, the initial treatment decision is made based on PAH severity. Patients at highest risk for death or clinical worsening are treated with a systemic prostacyclin as the initial therapy, while lower risk patients may be offered therapy with an oral or in some cases an inhaled medication. There is no single prognostic marker that is sufficient in making this decision, but a combination of clinical impression, functional class, 6MWD, laboratory results, catheterization results, and assessment of right ventricular function by imaging can be used to assess risk ([Table 58-4](#)).

Consideration of combination therapy is also recommended for patients who have an inadequate response to a single agent, with response typically assessed at 3 to 6 months. Adding a second agent rather than switching from one class of medication to another is generally recommended, given the lack of clinical trial data investigating the latter approach.

SURVIVAL

Long-term survival data are emerging in the era of idiopathic PAH treatment. In patients treated with epoprostenol, two papers demonstrated survival estimates of approximately 60% at 3 years.^{83,118} In these retrospective studies, favorable survival was best predicted by response to therapy (improvement in 6MWD, functional class, and PVR). Observational survival data over several years is also available for other specific therapies and for PAH in general, based on the extension studies from several clinical trials and from cohort studies such as the REVEAL registry. For

Table 58-4 Variables with Established Importance for Assessing Pulmonary Arterial Hypertension Disease Severity

Determinants of Prognosis	Better Prognosis	Worse Prognosis
Clinical evidence of RV failure	No	Yes
Rate of progression of symptoms	Slow	Rapid
Syncope	No	Yes
WHO functional class	I, II	IV
6MWD	Longer (>500 m)*	Shorter (<300 m)
Cardiopulmonary exercise testing	Peak O ₂ consumption > 15 mL/min/kg	Peak O ₂ consumption < 12 mL/min/kg
BNP/NT-proBNP plasma levels	Normal or near-normal	Very elevated and rising
Echocardiographic findings†	No pericardial effusion TAPSE‡ >2.0 cm	Pericardial effusion TAPSE‡ < 1.5 cm
Hemodynamics	RAP < 8 mm Hg and CI ≥ 2.5 L/min/m ²	RAP > 15 mm Hg or CI ≤ 2 L/min/m ²

*Depending on age.

†TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients.

BNP, brain natriuretic peptide; CI, cardiac index; 6MWD, 6-minute walking distance; RAP, right atrial pressure; TAPSE, tricuspid annular plane systolic excursion. Adapted from McLaughlin VV, McGoon MD: Pulmonary arterial hypertension. *Circulation* 114:1417–1431, 2006.

example, in 169 idiopathic PAH patients enrolled in the two pivotal trials of bosentan, estimated survival at 1 and 2 years was 96% and 89%, respectively, compared with the predicted survival of 69% and 57%^{107,149} (based on a validated equation calculating predicted survival from baseline hemodynamics). Similarly, survival times for patients with idiopathic PAH in REVEAL on any PAH therapy were 91%, 74%, and 65% at 1, 3, and 5 years.¹⁵⁰

ACKNOWLEDGMENTS

The authors would like to thank Dr. Lewis Rubin for his contributions to prior editions of this chapter.

Key Points

- Pulmonary hypertension has been classified into five World Health Organization groups: (1) pulmonary arterial hypertension, (2) pulmonary hypertension with heart disease, (3) pulmonary hypertension with lung disease, (4) pulmonary hypertension with pulmonary thromboembolism, and (5) miscellaneous.
- Group 1 Pulmonary arterial hypertension has further been classified as (1) idiopathic, (2) heritable, (3) related to other conditions, (4) primary pulmonary hypertension of the newborn, and (5) pulmonary veno-occlusive disease.
- Heritable pulmonary hypertension has been associated with mutations in *BMPR2*, *ALK1* and other genes, but pulmonary hypertension does not develop in all carriers, indicating other defects or insults are required.
- The basis for treatment of idiopathic pulmonary artery hypertension stems from its known deficiencies in prostacyclin and nitric oxide release and excess endothelin-1.
- Pulmonary hypertension can be suspected based on physical examination, chest radiology, electrocardiography, and echocardiography, but establishing the diagnosis with certainty requires a right-sided cardiac catheterization to exclude left heart failure,

determine severity, and assess response to pulmonary vasodilators.

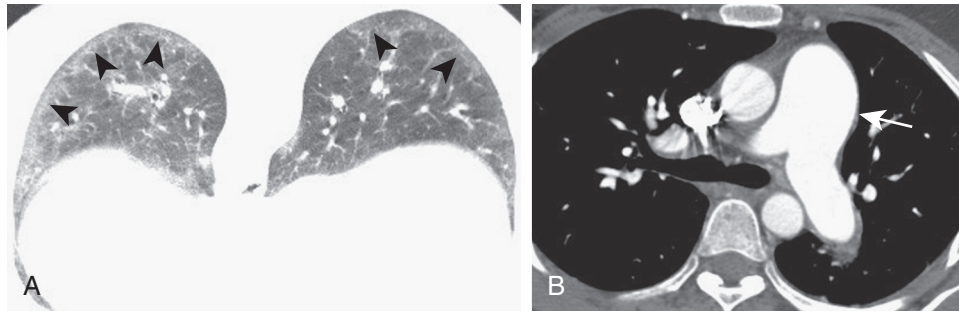
- Targeted therapy with the prostacyclins, phosphodiesterase inhibitors, and endothelin receptor antagonists has made major improvements in the life of patients with pulmonary artery hypertension and, based on meta-analysis and observational studies, has led to improvements in survival.

Complete reference list available at *ExpertConsult*.

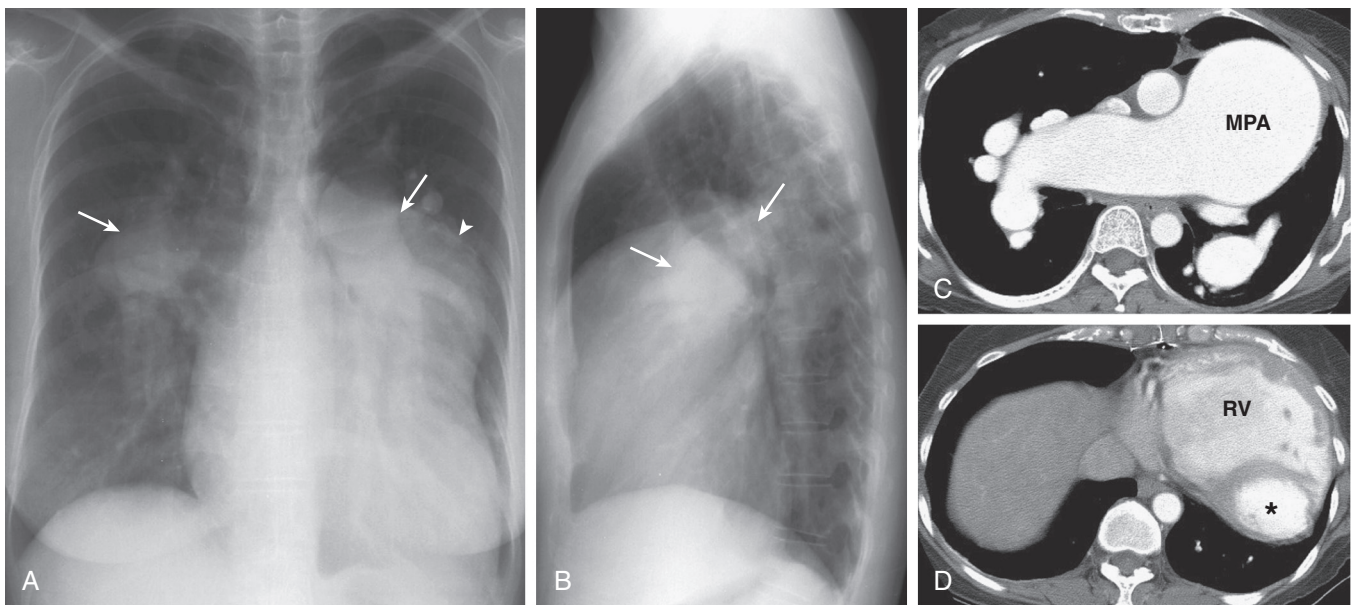
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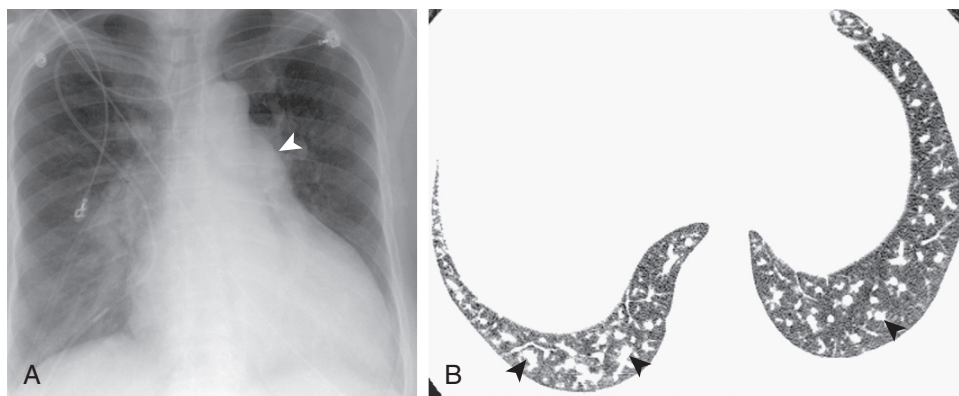
eFIGURE IMAGE GALLERY



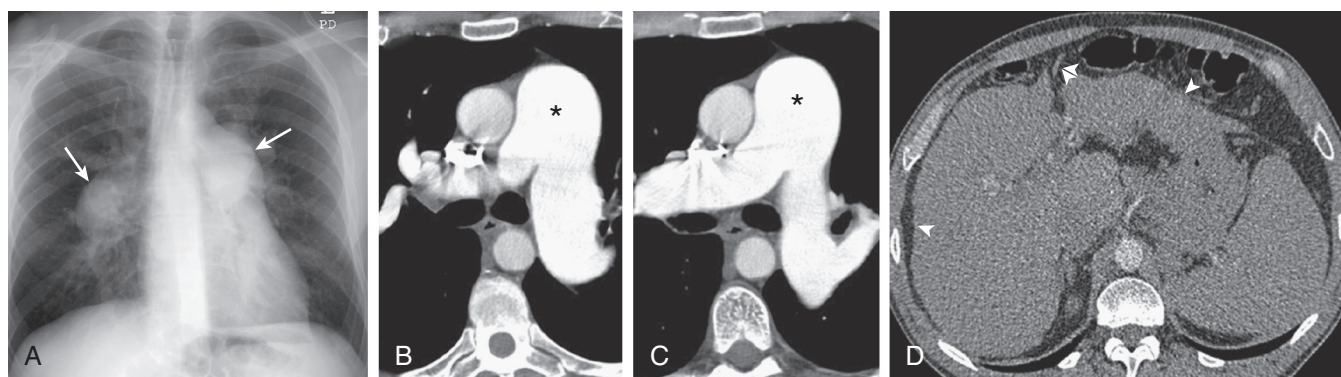
eFigure 58-1 Scleroderma lung disease associated with pulmonary hypertension. **A**, Prone axial chest high-resolution CT shows bilateral subpleural reticulation and ground-glass opacity unassociated with honeycombing (*arrowheads*). **B**, Axial chest CT displayed in soft tissue windows shows enlargement of the main pulmonary artery (*arrow*), consistent with pulmonary hypertension. (Courtesy Michael Gotway, MD.)



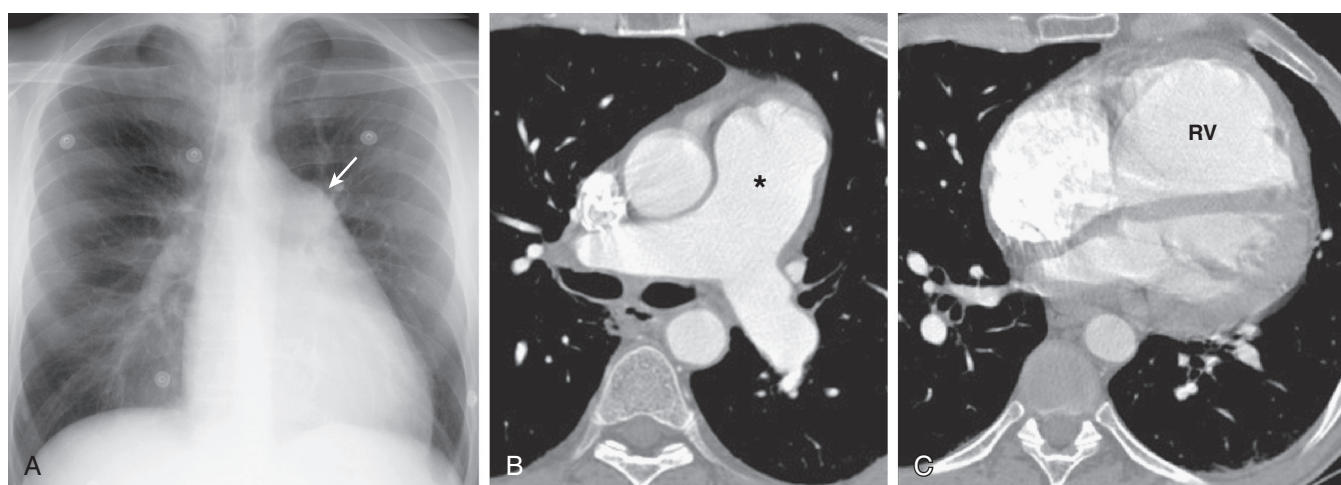
eFigure 58-2 Pulmonary hypertension with Eisenmenger syndrome due to an atrial septal defect. Frontal (**A**) and lateral (**B**) chest radiographs show massive enlargement of the right and left (*arrows*) pulmonary arteries and main (*arrowhead*) pulmonary artery. **C** and **D**, Axial contrast-enhanced chest CT shows massive enlargement of the main pulmonary artery (MPA). The right ventricle (RV) is enlarged with muscular hypertrophy (* = left ventricle). (Courtesy Michael Gotway, MD.)



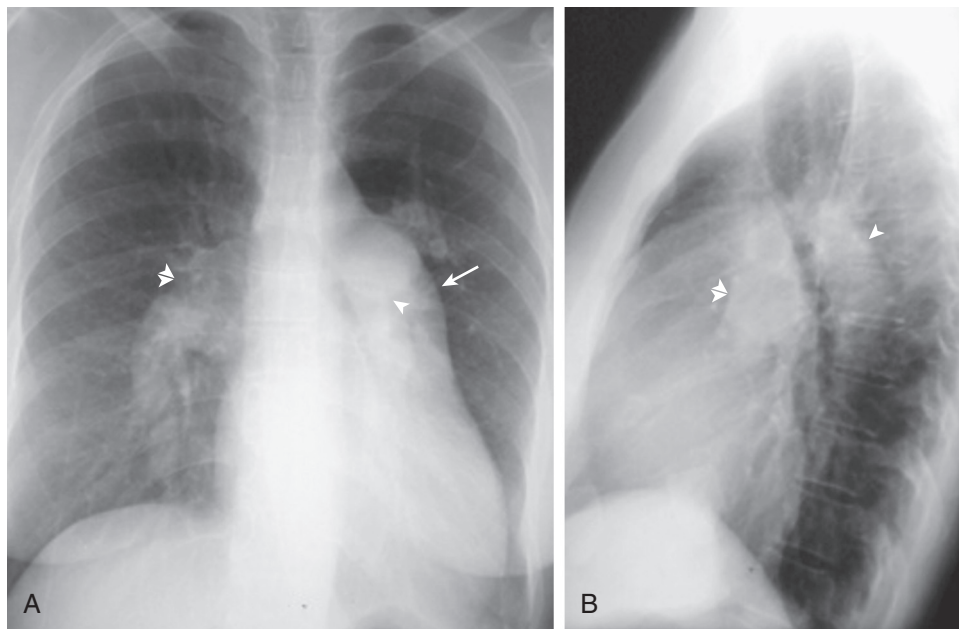
eFigure 58-3 Pulmonary hypertension associated with fenfluramine use. **A**, Frontal chest radiograph shows enlarged central pulmonary arteries (*arrowhead*, main pulmonary artery). **B**, Axial chest CT through the lung bases displayed in lung windows shows enlarged peripheral pulmonary arteries (*arrowheads*). The imaging findings are consistent with pulmonary hypertension, although the findings are not specific for a particular etiology. (Courtesy Michael Gotway, MD.)



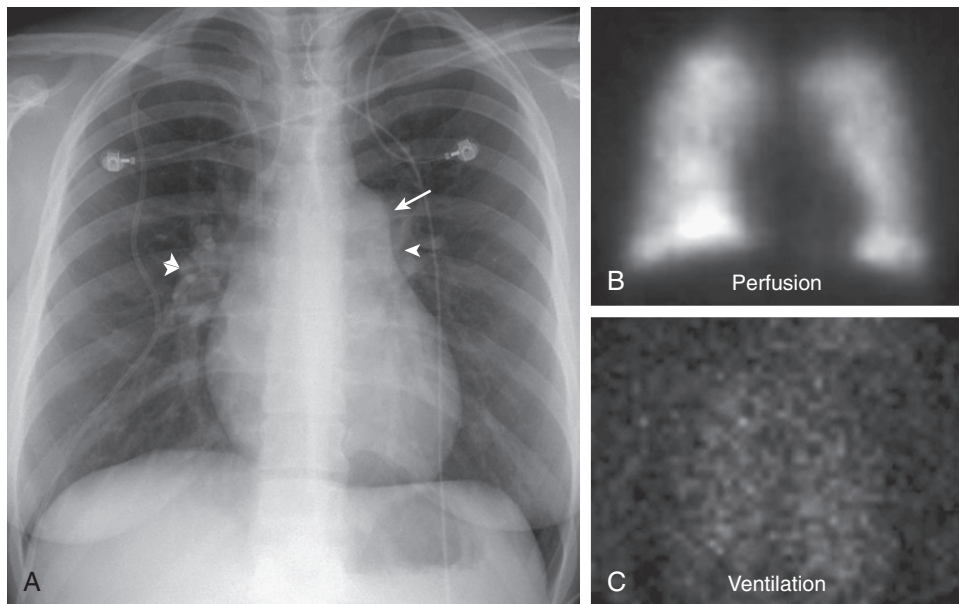
eFigure 58-4 Portopulmonary hypertension: imaging findings. **A**, Frontal chest radiograph shows enlarged central pulmonary arteries (*arrows*). **B** and **C**, Axial enhanced chest CT shows an enlarged main pulmonary artery (*); the imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. **D**, Axial enhanced CT through the abdomen shows a scalloped liver contour (*single arrowheads*), consistent with cirrhosis. An enlarged (“recanalized”) paraumbilical vein (*double arrowheads*) consistent with portal hypertension is present. (Courtesy Michael Gotway, MD.)



eFigure 58-5 Pulmonary hypertension in HIV: imaging findings. **A**, Frontal chest radiograph shows an enlarged main pulmonary artery (*arrow*). **B** and **C**, Axial enhanced chest CT shows an enlarged main pulmonary artery (*) and right ventricle (RV); the imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. (Courtesy Michael Gotway, MD.)



eFigure 58-6 Idiopathic pulmonary hypertension: chest radiographic findings. Frontal (A) and lateral (B) chest radiographs show an enlarged main pulmonary artery (*arrow*) and enlargement of the right (*double arrowheads*) and left (*single arrowheads*) pulmonary arteries. The peripheral pulmonary arteries appear rather small, particularly given the marked central pulmonary arterial enlargement. The imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. (Courtesy Michael Gotway, MD.)



eFigure 58-7 Idiopathic pulmonary hypertension: chest radiographic and ventilation-perfusion scintigraphy findings. A, Frontal chest radiograph shows an enlarged main pulmonary artery (*arrow*) and enlargement of the right (*double arrowheads*) and left (*single arrowheads*) pulmonary arteries. The peripheral pulmonary arteries appear rather small, particularly given the marked central pulmonary arterial enlargement. The imaging findings are consistent with pulmonary hypertension, although the findings are not specific for the underlying etiology. Ventilation-perfusion scintigraphy shows fairly homogeneous perfusion (B) and ventilation (C), consistent with a low probability study. The patient subsequently underwent bilateral lung transplantation. (Courtesy Michael Gotway, MD.)

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PULMONARY HYPERTENSION DUE TO LUNG DISEASE

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INTRODUCTION

This chapter will focus on the *pulmonary hypertension* (PH) that results from chronic lung diseases. This is a common and significant clinical complication of lung disease, and it is a PH that differs from the other types both in causation and in therapeutic approach. The current (2013) “Updated Clinical Classification of Pulmonary Hypertension” (Table 59-1) serves to define the terminology used in this chapter and in Chapter 58.¹ These groups are classified according to the underlying pathologic process that leads to PH. Note that the term *pulmonary arterial hypertension* (PAH) refers specifically to diseases in group 1, including idiopathic PAH. PH is used for the PH in groups 2, 3, 4, and 5. *PH due to lung disease* (PH-LD) is categorized in group 3. This is the PH that will be the topic of this chapter. Group 1 PH (PAH) is covered in Chapter 58, and group 4 PH (chronic thromboembolic PH) is covered in Chapter 57.

In previous editions the title of this chapter was “Cor Pulmonale.” Historically, there has been no consensus about the definition of the term *cor pulmonale*.^{2,3} Today the term *cor pulmonale* generally refers to abnormalities of right heart structure and function that develop in the setting of lung disease and/or hypoxemia, including parenchymal lung disease, ventilatory impairment, or high-altitude hypoxemia. *Cor pulmonale* develops secondary to pulmonary hypertension, characterized by elevations in *pulmonary vascular resistance* (PVR) and in *pulmonary artery pressure* (PPA), which causes increased right ventricular afterload and, in susceptible patients, eventually progresses to right ventricular failure.

The development of PH and subsequent *cor pulmonale* in patients with lung disease is clinically important because it is common and is associated with increased morbidity and mortality. In one large community-based series, PH-LD was the second most common cause of PH after left heart disease⁴ (Fig. 59-1). Available data show that nearly all types of advanced lung disease can be

complicated by PH and eventually progress to right heart failure. However, patients with *chronic obstructive pulmonary disease* (COPD) and *idiopathic pulmonary fibrosis* (IPF) will be the focus of this chapter. As in all patients with PH, a thorough and exhaustive diagnostic evaluation is critical to determine the primary cause of PH and to identify concomitant conditions that might worsen PH and right heart failure. The different groups of PH affect different areas of the pulmonary circulation (Fig. 59-2); nonetheless, even those that affect the pulmonary arterioles have a different underlying pathologic process and response to treatment. Distinguishing between group 3 PH-LD and group 1 PAH is especially important because these diseases are pathologically and clinically distinct and respond differently to treatment. The best treatment of patients with PH-LD and subsequent *cor pulmonale* continues to be optimal management of the underlying lung disease, correction of hypoxemia, and timely consideration for lung transplantation.

EPIDEMIOLOGY OF PULMONARY HYPERTENSION DUE TO LUNG DISEASE

PREVALENCE

The prevalence of PH among patients with known lung disease has been assessed in numerous studies. Available studies suffer from significant limitations, including inconsistent definitions of PH and frequent use of echocardiography rather than right heart catheterization to assess hemodynamics. Additionally, patient cohorts are often heterogeneous, and comprehensive assessments to exclude other important and common causes of PH (e.g., chronic thromboembolic PH, and left heart disease) generally have not been performed.

Table 59-1 Group 3 PH as Outlined in the Fifth World Symposium Clinical Classification of Pulmonary Hypertension (2013)*

GROUP 1: PULMONARY ARTERIAL HYPERTENSION (PAH)

GROUP 1': PULMONARY VENO-OCCLUSIVE DISEASE (PVOD) AND/OR PULMONARY CAPILLARY HEMANGIOMATOSIS (PCH)

GROUP 1'' PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

GROUP 2: PULMONARY HYPERTENSION DUE TO LEFT HEART DISEASE

GROUP 3: PULMONARY HYPERTENSION DUE TO LUNG DISEASES AND/OR HYPOXIA

COPD

Interstitial lung disease

Other pulmonary diseases with mixed restrictive and obstructive pattern

Sleep-disordered breathing

Alveolar hypoventilation disorders

Chronic exposure to high altitude

Developmental lung diseases

GROUP 4: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

GROUP 5: PULMONARY HYPERTENSION WITH UNCLEAR MULTIFACTORIAL MECHANISMS

*See Table 58-1 for complete classification.

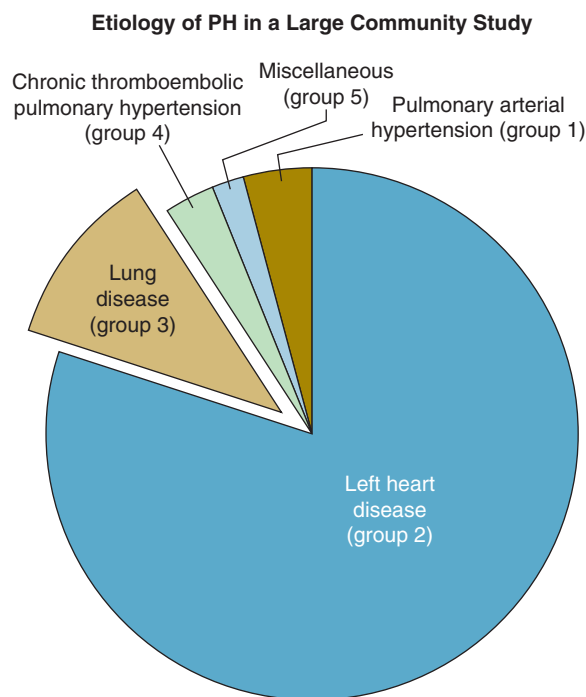


Figure 59-1 Prevalence of pulmonary hypertension by cause in a large community-based study. Note that left heart disease is by far the most common cause of pulmonary hypertension, whereas chronic lung disease is the second most frequent cause. (Data from Strange G, Playford D, Stewart S, et al: Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart* 98:1805–1811, 2012.)

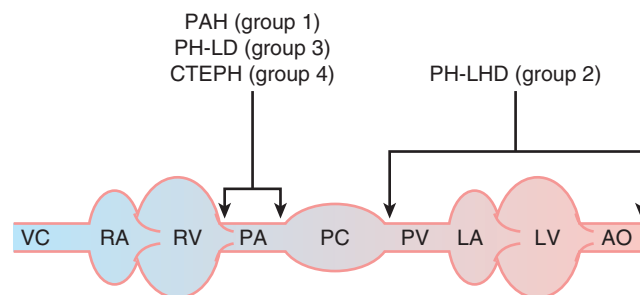


Figure 59-2 Localization of abnormalities in pulmonary hypertension. Pathologic changes that result in pulmonary hypertension from group 3 chronic lung disease (PH-LD) primarily target pulmonary arterioles, the same location as abnormalities in group 1 pulmonary arterial hypertension (PAH) and group 4 chronic thromboembolic pulmonary hypertension (CTEPH). Abnormalities that result in PH in group 2 left heart disease (PH-LHD) are found mostly on the venous side of the pulmonary circulation. AO, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PC, pulmonary capillaries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; VC, vena cavae.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The lung disease most frequently associated with PH is COPD (PH-COPD), which is by far the most common cause of cor pulmonale, accounting for more than 80% of all cases.⁵ However, the estimated prevalence of PH in patients with known COPD varies dramatically—from 2.7% to 90.8%^{6,7}—depending on the definition of PH and the study population.

The standard definition of PH in this population, as in other populations, is a *mean P_{PA}* (*P_{PA}*) greater than 25 mm Hg, although some studies have used different cutoff values (e.g., 20 mm Hg). The gold standard for this measurement is the right heart catheterization. A more convenient but less accurate measurement is by echocardiography which requires a tricuspid regurgitant jet to measure the pressure gradient across the valve and thus estimate *pulmonary artery systolic pressure* (PASP). Echocardiographic estimates of PASP are possible only in those patients with a measurable tricuspid regurgitant jet and are known to overestimate and underestimate true PASP.

An early study of right heart catheterization in 175 patients with severe COPD showed that 35.4% of patients had a *P_{PA}* greater than or equal to 20 mm Hg and 9.7% had a *P_{PA}* greater than 30 mm Hg.⁸ In another study, invasive hemodynamic values were assessed in 120 patients with severe airflow obstruction (mean FEV₁ 27% of predicted) at the time of enrollment in the National Emphysema Treatment Trial. In this cohort, 90.8% of patients had a *P_{PA}* greater than 20 mm Hg, but only 5% had a *P_{PA}* greater than 35 mm Hg. Importantly, *pulmonary capillary wedge pressure* (PPW) was greater than 12 mm Hg in 61.4% of patients and greater than 20 mm Hg in 6.4% of patients, suggesting that left-sided heart failure was an important contributor to PH in this population.⁷ To assess the prevalence of PH in an outpatient population with stable COPD, echocardiography was performed in 159 patients to estimate PASP. Tricuspid regurgitation was adequate to estimate PASP in 105 patients, and, of those, 60% had a PASP greater than or equal to 35 mm Hg and were classified as having PH.⁹ Patients with PASP greater than or equal to 35 mm Hg were older and had lower FEV₁ and DL_{CO} values.

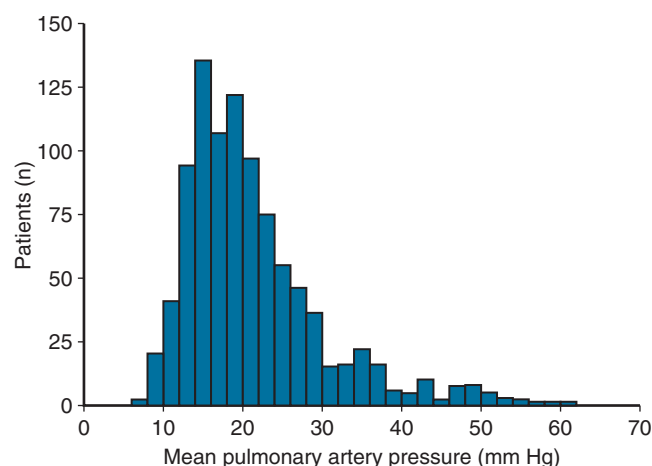


Figure 59-3 Severity of pulmonary hypertension in patients with COPD in a large French cohort. Although elevation in pulmonary artery pressure is common in patients with COPD, severe pulmonary hypertension is unusual. For many of the patients with severe pulmonary hypertension in this cohort, another medical problem such as chronic thromboembolic disease or left heart disease was judged to be the primary cause of pulmonary hypertension. (From Chaouat A, Naeije R, Weitzenblum E: Pulmonary hypertension in COPD. *Eur Respir J* 32:1371–1385, 2008. Fig. 1; based on data from Chaouat A, Bugnet AS, Kadaoui N, et al: Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 172:189–194, 2005. doi:10.1183/09031936.00015608. Reproduced with permission of the European Respiratory Society.)

In one well-designed study,⁶ 998 patients underwent right heart catheterization at a referral center in France as part of evaluation for chronic respiratory failure; severe PH, defined as $\overline{\text{PPA}}$ greater than or equal to 40 mm Hg, was diagnosed in 27 patients (2.7%) (Fig. 59-3). Another cause of PH was found in 16 patients, resulting in a final diagnosis of PH secondary to COPD in only 11 patients (1.1%). Compared to other patients in the cohort, the patients with severe PH had lower DLCO and arterial PCO_2 and PO_2 values. Patients with severe PH also had lower cardiac indices and higher right atrial pressures, suggesting reduced right ventricular function.

These studies demonstrate that mild PH is common among stable outpatients with COPD. Importantly, more severe hemodynamic abnormalities were observed only in a very small number of patients, and, among those patients, other causes of PH were common.

Examining cohorts of patients undergoing evaluation for lung transplantation is useful because they include a relatively homogenous patient population with complete hemodynamic data; however, they represent a cohort with particularly advanced lung disease in whom PH might be expected to be more frequent and more severe.

A recent retrospective study used right heart catheterization data from the Organ Procurement and Transplantation Network database to study PH in 4930 patients with COPD listed for lung transplantation.¹⁰ The prevalence of mild and moderate PH defined as a $\overline{\text{PPA}}$ greater than or equal to 25 mm Hg and less than 35 mm Hg with a PPw less than or equal to 15 mm Hg was 30.4%, and the prevalence of severe PH defined as a $\overline{\text{PPA}}$ greater than or equal to 35 mm Hg with a wedge pressure less than or equal to 15 mm Hg was 4.0%. A significant number of patients, 17.2%, had a $\overline{\text{PPA}}$ greater than or equal to 25 mm Hg but

also had a PPw greater than 15 mm Hg. Moreover, the PPw was greater than 15 mm Hg in about 50% of the patients with $\overline{\text{PPA}}$ greater than or equal to 31 mm Hg, demonstrating that elevated left heart filling pressures are common in this population and may contribute significantly to PH. Findings were similar in another study of 409 patients with COPD undergoing evaluation for lung transplantation in Denmark.¹¹ In this study 36% of patients had PH with a $\overline{\text{PPA}}$ greater than or equal to 25 mm Hg, PPw less than or equal to 15 mm Hg, and 13% had a $\overline{\text{PPA}}$ greater than or equal to 25 mm Hg but also had a PPw greater than 15 mm Hg. Only 6 (1.5%) patients had a $\overline{\text{PPA}}$ greater than or equal to 40 mm Hg. In this population, PH was associated with the presence of more severe hypoxemia and lower FEV_1 values. Similar to the previously discussed studies, patients being evaluated for transplant frequently have elevations in $\overline{\text{PPA}}$; however, there is a low prevalence of severe PH, and a significant proportion of patients have elevated PPw, which suggests a contribution from left-sided heart failure.

There are limited longitudinal data concerning PH-COPD; however, the progression of PH in these patients appears to be slow.¹² Among patients who are found to have normal $\overline{\text{PPA}}$ at rest, changes in pulmonary hemodynamics are frequently minimal over time. For example, in a group of 61 patients without initial PH, all of whom had arterial hypoxemia, a second right heart catheterization almost 8 years later revealed an average change in $\overline{\text{PPA}}$ from 15.5 ± 2.4 to 19.6 ± 7.0 mm Hg.¹³ In a second group of 32 patients who had PH on their first catheterization, there was a nonsignificant rise in $\overline{\text{PPA}}$, from 27.7 ± 6.0 to 31.0 ± 9.3 mm Hg, after 5 years.¹⁴ An increase of 5 mm Hg or more was seen in approximately one third of patients and was clearly related to worsening hypoxemia.

In patients with COPD the presence of PH is clinically important because it is associated with worse exercise tolerance and survival compared to COPD patients without PH. In the retrospective organ procurement database study, 6-minute walk distance (6MWD) was on average 28 m less in patients with PH compared to those with normal hemodynamics; in addition, $\overline{\text{PPA}}$ was an independent predictor of a low 6MWD in a multivariate model. In this study, adjusted risk for death on the transplant list was significantly increased in patients with PH (hazard ratio 1.27).¹⁰ Findings were similar in a study of 362 patients at a single center undergoing transplant evaluation. In multivariate analysis, higher $\overline{\text{PPA}}$ was associated with a shorter 6MWD, including a reduction of 11 m for every 5 mm Hg increase in $\overline{\text{PPA}}$.¹⁵ In the Danish cohort, PH did not affect 6MWD but did affect the survival rate; the survival rate at 5 years was 37% for patients with PH compared to 63% in patients without PH ($P = 0.016$). In this cohort the presence of PH did not affect outcomes following lung transplantation.¹¹ Among the 11 patients with severe PH in the French COPD cohort, exertional dyspnea was significantly worse and survival was significantly shorter compared to patients without severe PH.⁶ In another study, the effects of PH on survival were assessed in a cohort of 84 patients who underwent hemodynamic evaluation before institution of long-term oxygen therapy. Adjusted 5-year survival rate was 62% for patients with an initial $\overline{\text{PPA}}$ of 25 mm Hg or less, whereas it was only 36% in the 40 remaining patients who had an

initial $\overline{\text{PpA}}$ higher than 25 mm Hg. In this cohort, initial $\overline{\text{PpA}}$ was a better prognostic indicator than either the FEV_1 , the degree of hypoxemia, or the level of hypercapnia.¹⁶ The results of a study of 101 patients with PH and COPD at a PH referral center came to similar conclusions. Survival at 3 years was 33% in patients with $\overline{\text{PpA}}$ greater than or equal to 40 mm Hg versus 55% in patients with $\overline{\text{PpA}}$ of 25 to 39 mm Hg. In a multivariate analysis, age, DL_{CO} , mixed venous oxygen saturation, and World Health Organization functional classification were independent predictors of survival.¹⁷ These findings suggest that even mild PH may have a significant negative impact on exercise tolerance and survival and that the presence of PH may be a more important prognostic factor than the severity of lung disease.

IDIOPATHIC PULMONARY FIBROSIS

Most of the available data regarding PH associated with IPF (PH-IPF) comes from patients undergoing evaluation for lung transplantation. In a study of 79 patients with IPF referred for lung transplantation who had a right heart catheterization, 32% (25 of 79) had PH documented by a $\overline{\text{PpA}}$ greater than 25 mm Hg.¹⁸ In another cohort of 124 patients undergoing evaluation for lung transplant at the Cleveland Clinic, 44% (54 of 124) had a $\overline{\text{PpA}}$ greater than or equal to 25 mm Hg.¹⁹ A study of 101 Japanese patients with IPF who underwent right heart catheterization showed similar results with a prevalence of $\overline{\text{PpA}}$ greater than 25 mm Hg of 15% (15 of 101).²⁰ These studies show an overall high rate of PH-IPF in patients with advanced IPF.

The presence of PH-IPF is associated with worsening symptoms, functional impairment, and increased morbidity and mortality.^{18,21-23} In a retrospective study of 136 patients with IPF, the median survival of those with estimated PASP of greater than 50 mm Hg by echocardiography was less than 1 year ($P = 0.009$) compared to 4.8 years for patients without PH (PASP < 35 mm Hg), and 4.1 years for patients with mild PH (PASP 36 to 50 mm Hg).²² The 1-year survival rate in 79 patients undergoing lung transplant evaluation was lower (72%) in those patients with PH compared to IPF patients without PH (94.5%; $P = 0.002$).¹⁸ Furthermore, patients with PH who had lower DL_{CO} values were more likely to require supplemental oxygen, to have shorter 6MWD, and to exhibit a lower arterial oxygen saturation nadir. In one study of 78 patients with PH-IPF, using a cutoff based on a receiver operating curve, the 5-year survival rate was 62% for the group ($n = 37$) with $\overline{\text{PpA}}$ values less than 17 mm Hg compared to 17% for the group ($n = 24$) with $\overline{\text{PpA}}$ values greater than 17 mm Hg ($P < 0.001$). The relative risk for death was significantly higher at 2.2 for the high- $\overline{\text{PpA}}$ group.¹⁹ According to an analysis of 2972 patients with advanced IPF listed for lung transplantation between 1995 and 2004, those with PH were 1.6 times more likely to die after being listed for transplantation compared to those without PH.²³ These data suggest that, similar to patients with PH-COPD, the consequences of PH-IPF are serious and that even mild increases in $\overline{\text{PpA}}$ are associated with increased mortality.

The presence of pretransplant PH may even have a significant effect on posttransplant outcomes. In a cohort of 126 patients, those who developed primary graft dysfunction had high pretransplant $\overline{\text{PpA}}$ values, and each 10 mm Hg

increase in $\overline{\text{PpA}}$ was associated with an increase in the odds of primary graft dysfunction by 1.64.²⁴

OTHER LUNG DISEASES

Patients with the syndrome of combined emphysema and pulmonary fibrosis seem to be at particularly high risk for developing PH, with grave consequences. Prevalence of PH in these patients has been described to be between 30% and 50%; this group had markedly reduced survival.^{25,26} In one retrospective series of 40 patients with combined emphysema and pulmonary fibrosis, elevated $\overline{\text{PpA}}$ above 40 mm Hg was present in 48% of patients.^{26a} Patients had severe symptoms, 85% with New York Heart Association functional class III or IV, and an average 6MWD of 244 m. Outcomes in this population were poor. For those with a PVR above the median value, one year survival was 48% while, for those with a PVR below the median, one year survival was 100%.

In patients without parenchymal lung disease, hypoxemia from high altitude, obstructive sleep apnea (OSA), and obesity hypoventilation syndrome are important independent causes of PH by themselves, or they may contribute significantly to PH from other causes. Because of the large number of individuals who live and visit at high altitudes, environmental hypoxemia related to altitude may be one of the most common causes of PH worldwide.^{27,28} OSA appears to be an increasingly common cause of PH. In multiple studies of patients with OSA, the prevalence of PH ranges from 20% to 40% with mild elevation in $\overline{\text{PpA}}$ (23-32 mm Hg). Interestingly, this PH may be reversible; a well-designed prospective trial²⁹ showed that treatment with continuous positive airway pressure over 6 months reduced $\overline{\text{PpA}}$ in patients with OSA.²⁹ Obesity hypoventilation syndrome, which is increasingly common worldwide, also causes PH. The prevalence of $\overline{\text{PpA}}$ greater than 20 mm Hg among 29 patients with obesity hypoventilation syndrome was 59% in a cohort of untreated patients.³⁰ In another study of 21 patients with obesity hypoventilation syndrome treated with noninvasive positive pressure ventilation, the prevalence of $\overline{\text{PpA}}$ greater than 20 mm Hg was 81%, although only 3 patients (14%) had severe PH with $\overline{\text{PpA}}$ greater than 35 mm Hg. In this study, $\overline{\text{PpA}}$ correlated negatively with use of noninvasive positive pressure ventilation, and, by multivariate regression, the presence of PH was an independent predictor of poor physical functioning.³¹

Case reports and small series describing PH as a complication of a variety of other lung diseases have been published. These conditions will not be specifically discussed here but may include sarcoidosis, Langerhans cell histiocytosis, lymphangioleiomyomatosis, adult bronchopulmonary dysplasia, and cystic fibrosis. Limited published data suggest that development of PH in all of these conditions is associated with worse outcomes.^{32-32b}

PATHOLOGIC CHANGES AND PATHOGENESIS

Although the mechanisms underlying the development and progression of PH in patients with lung disease are

incompletely understood, they appear to be multifactorial and to vary with the underlying lung disease. It is likely that early vascular endothelial injury is caused by factors such as hypoxemia and inflammation leading to endothelial dysfunction and subsequently the development of structural vascular changes. These abnormalities lead to an increase in PVR and a subsequent increase in PPA.

PULMONARY VASCULAR REMODELING

Many of the individual elements of pulmonary vascular remodeling seen in PH-LD are similar to those seen in PAH. The primary differentiating pathologic feature is that patients with PH-LD generally do not have the plexiform lesions that are seen in patients with PAH.³⁴ Multiple mechanisms most likely contribute to the development of the vascular pathologic features observed in PH-LD, which, once established, contribute to elevated PPA.^{35,35a}

There are a variety of pathologic vascular changes described in PH-LD that vary with the type of lung disease and overlap significantly with the changes seen in PAH (Fig. 59-4). Knowledge about pathologic changes in PH-LD comes from autopsy series and studies of explanted lungs

at the time of transplant. A characteristic feature often seen in PH-LD that is also seen in PAH is the extension of smooth muscle into small pulmonary arterioles less than 80 μm , where it is not found in healthy lungs. This is termed “muscularization” and is characterized by circularly oriented smooth muscle cells between the two layers of elastic lamina.³⁶ Muscularization may result from hypertrophy and proliferation of existing smooth muscle and from development of new smooth muscle cells. Another common finding in lungs from patients with PH-LD that overlaps with PAH is proliferation of the intimal layers of the pulmonary arterioles. Inflammation and thrombosis in situ may also be seen.

Pathologic changes that are unique to PH-LD are those that are associated with the underlying lung disease. In patients with PH-COPD there is destruction of alveoli and concomitant destruction of the associated pulmonary vasculature, which causes a further reduction in the pulmonary vascular cross-sectional area, leading to an increase in PVR.³⁷ A unique finding in patients with PH-IPF is that vascular changes are seen both in areas of lung fibrosis and in areas of normal lung, though the vascular changes in areas of normal lung are less severe and found in a smaller

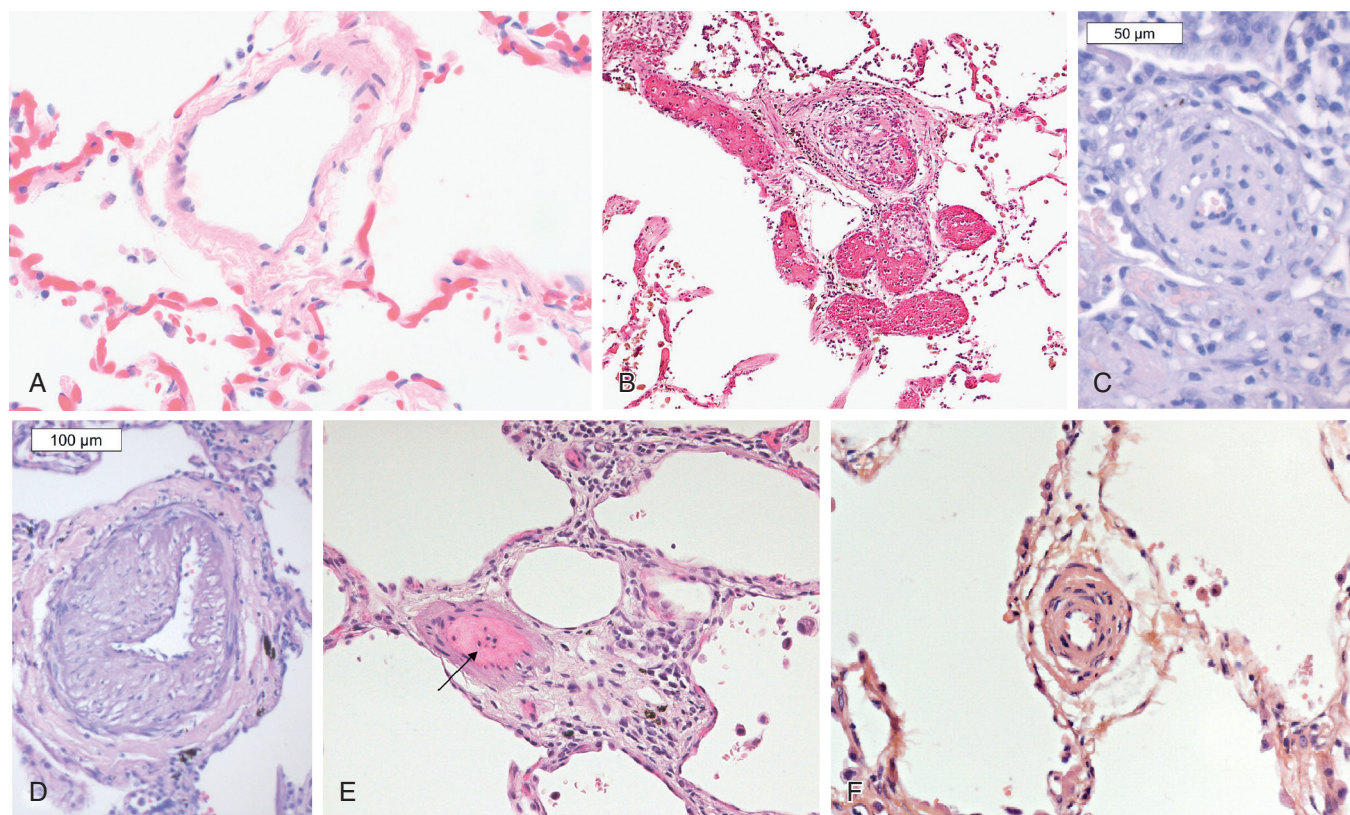


Figure 59-4 Histologic appearance of normal and abnormal pulmonary arterioles. **A**, Normal pulmonary arteriole. Characteristic features include a large lumen relative to wall thickness, a single elastic lamina and the absence of medial smooth muscle. **B**, Typical plexiform lesion from a patient with pulmonary arterial hypertension. **C**, Pulmonary arteriole from a patient with pulmonary hypertension from COPD showing cellular intimal proliferation in small muscular arteries. **D**, Pulmonary arteriole from a patient with pulmonary hypertension from COPD showing medial hypertrophy and concentric laminar intimal fibrosis. **E**, Pulmonary arteriole from a patient with pulmonary hypertension from idiopathic pulmonary fibrosis showing vascular intimal fibrosis with luminal obliteration (arrow) in a region of interstitial fibrosis and chronic inflammation. **F**, Pulmonary arteriole from a patient with pulmonary hypertension from IPF showing muscularization of a small pulmonary arteriole. (**A**, Courtesy Dr. Philip Ursell, University of California, San Francisco; **B**, from Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, Fig. 11-13A; **C** and **D**, from Carlsen J, Andersen KH, Boesgaard S, et al: Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. *J Heart Lung Transplant* 32:347–354, 2013, Fig. 2B and C; **E**, courtesy Dr. Rubin Tudor, Baltimore, MD; **F**, from Colombat M, Mal H, Groussard O, et al: Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis: histopathologic study on lung explant specimens and correlations with pulmonary hemodynamics. *Hum Pathol* 38:60–65, 2007, Fig. 1C.)

proportion of vessels. Also, occlusive pathologic changes of pulmonary veins have been observed much more frequently in PH-IPF than in PAH. Ultimately, in patients with IPF, large portions of the pulmonary vascular bed may be destroyed or obliterated from progressive parenchymal fibrosis, inflammation, perivascular fibrosis, and/or thrombotic angiopathy.³⁸⁻⁴⁰

The severity and extent of structural changes correlate variably with the degree of hemodynamic abnormalities seen in PH-LD. A recent study compared the structural changes observed in pulmonary arterioles from patients with COPD with and without PH undergoing transplant. Even without PH, patients with COPD frequently had muscularization and medial thickening of the pulmonary arterioles. Severity of pathologic changes worsened as the hemodynamic abnormalities worsened.⁴¹ In another study of tissue from COPD patients who died during the National Institutes of Health Nocturnal Oxygen Therapy Trial, there was no correlation between the histologic appearance of pulmonary arterioles and PH severity or change in PPA.

Several studies suggest that vascular remodeling in patients with mild COPD without concomitant hypoxemia is a component of early-stage disease as evidenced by increased inflammatory cell density in the adventitia and increased thickness of the intima of pulmonary arteries.^{42,43} Furthermore, endothelial lesions have been shown to be present in cigarette smokers without chronic airflow obstruction.⁴⁴ These findings suggest that, although the pathologic changes in the pulmonary vasculature predominate, other abnormalities appear to contribute to the development of clinically relevant PH.

PATHOGENESIS

The pathogenesis of PH-LD may have multiple mechanisms, including hypoxic pulmonary vasoconstriction, vasoconstrictive neurohormones, and inflammation.

Hypoxic Pulmonary Vasoconstriction

Among all the mechanisms leading to PH in lung disease, the most potent and most important is alveolar hypoxia.⁴⁵ Hypoxic pulmonary vasoconstriction is a normal physiologic response to alveolar hypoxia that was first demonstrated in isolated cat lungs⁴⁶ and subsequently confirmed in healthy human volunteers.⁴⁷ This effect is unique to the pulmonary circulation. Whereas acute hypoxia in the systemic circulation induces vasodilation, acute hypoxia in the pulmonary circulation causes constriction. The constriction of precapillary pulmonary arterioles effectively shunts blood away from poorly ventilated lung units to preserve optimal ventilation-perfusion matching.⁴⁸

Hypoxic pulmonary vasoconstriction results from hypoxia-mediated inhibition of voltage-gated potassium channels in pulmonary artery smooth muscle cells. Hypoxia inhibits the outward flow of potassium through these channels, resulting in depolarization of the membrane and entry of calcium, which causes smooth muscle cell contraction and sustained vasoconstriction.⁴⁸ When activated, this mechanism results in smooth muscle contraction within seconds of exposure to hypoxia. Smooth muscle contraction is augmented by the activity of RhoA and Rho-associated kinase. Hypoxia signals through the G protein

RhoA stimulating Rho-associated kinase to increase phosphorylation of smooth muscle cell myosin light chain and to augment smooth muscle cell contraction, regardless of the level of intracellular calcium.⁴⁸

Even brief periods of hypoxia may result in persistent hemodynamic abnormalities. In six healthy volunteers exposed to 8 hours of hypoxia, there was an increase in PVR, which did not return to normal after 2 hours of normoxia.⁴⁹

Long-term hypoxia-induced structural changes in the pulmonary arterioles were demonstrated in an invasive hemodynamic study of 11 high-altitude natives, which showed that hemodynamics did not normalize even after 2 years at low altitude.⁵⁰ Structural changes in the pulmonary vasculature similar to those observed in COPD and IPF patients are present in the lungs of animals and humans exposed to hypoxia. In an autopsy series of tissues from Andean subjects born and living at high altitude who died without cardiac or pulmonary disease, medial hypertrophy of the pulmonary arteries was seen.²⁸

The degree of increase in PPA secondary to hypoxic pulmonary vasoconstriction varies by species. Pigs, horses, and cows respond with brisk increases in PPA, whereas dogs, yaks, and llamas have a minimal response; humans and rodents have an intermediate response.^{51,52} In addition, the response in humans varies widely among individuals from absent to very intense, with a rise to a \overline{PPA} of 40 mm Hg in 1% to 2% of healthy individuals.^{52,53} One explanation for the observation that some patients with lung disease develop PH whereas others do not is that there are heritable differences in ventilatory sensitivity either to hypoxia and carbon dioxide or in pulmonary vascular reactivity, or both.⁵⁴

Although hypoxia may be a significant contributing factor in the development of PH in chronic lung disease, hypoxia is not the sole factor in generating PH.⁵⁵ This conclusion is supported by the finding that oxygen therapy in patients with lung disease has an inconsistent effect and does not normalize PPA.^{56,57} In addition, hypoxia is not necessary to produce vascular changes; pulmonary vascular structural changes have been observed in patients with mild COPD who do not have hypoxemia, and structural changes seen in the pulmonary vasculature in patients with IPF are more extensive than can be explained by hypoxia alone.⁵⁸

The development of hypercapnia may be one reason why patients with lung disease develop more PH than individuals exposed to environmental hypoxia, such as those living at high altitudes. In patients with PH-COPD, hypoxia is often accompanied by hypoventilation and hypercapnia, causing acidosis, which worsens hypoxic pulmonary vasoconstriction and PVR. This is in contrast to high-altitude dwellers such as healthy Andeans who have chronic hypoxia but generally have hyperventilation with resultant hypocapnia. Despite the presence of hypoxia, the high-altitude dwellers generally do not develop PH, suggesting that hypercapnia and acidemia are important contributing elements.

Neurohormones

Neurohormonal abnormalities and increased sympathetic nervous system activation are observed in patients with

PH-LD and cor pulmonale and contribute to development of hemodynamic abnormalities. Plasma catecholamine levels generally rise in patients with decompensated right heart disease in a manner comparable to that seen in patients with heart failure secondary to primary myocardial disorders. It is clear that increased sympathetic activity is present with decompensation from cor pulmonale, resulting in high plasma levels of circulating catecholamines and stimulation of the renin-angiotensin-aldosterone systems. In the measurements by Anand and associates,⁵⁹ vasopressin actually rose to a higher level in patients with heart failure due to PH-COPD than was seen in comparable patients with heart failure not associated with COPD. Because cardiac output is often normal or may even be increased in decompensated cor pulmonale, it is likely that the decrease in *systemic vascular resistance* (SVR) resulting from both hypercapnia and hypoxia leads to a reflex increase in circulating catecholamines and other neural hormones. Central sympathetic stimulation may also be encouraged by the direct effect of the increased PCO₂ on the central nervous system.

Angiotensin. Angiotensin II is a potent vasoconstrictor of the pulmonary vascular bed. The pulmonary vasculature appears to be even more sensitive to the vasoconstrictor effects of angiotensin II than is the systemic vascular bed. This is noteworthy because increased circulating levels of angiotensin II and aldosterone are found in patients with cor pulmonale secondary to COPD who have hypoxia and hypercapnia.⁶⁰ Activation of the renin-angiotensin-aldosterone systems, together with hypoxemia, is probably an underlying pathophysiologic mechanism responsible for the elevation in PVR that is observed in patients with decompensated cor pulmonale.

Angiotensin induces a dose-response increase in PVR in normal subjects.⁶¹ Angiotensin II inhibitors have been shown to lower PVR and to be beneficial in patients with cor pulmonale, especially in patients with IPF. Angiotensin II inhibitors have also been demonstrated to improve survival in patients with systolic heart failure caused by both coronary disease and idiopathic dilated cardiomyopathy. It is encouraging to note that the angiotensin-converting enzyme inhibitor lisinopril has been demonstrated experimentally to attenuate the pulmonary pressor response to hypoxic pulmonary vasoconstriction in healthy human volunteers.⁶² In addition, angiotensin II receptor blockade has been shown to produce a similar effect in hypoxic pulmonary vasoconstriction in humans.⁶³ However, studies performed to date have not clarified a role for angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists in the treatment of cor pulmonale.

Endothelin. *Endothelin-1* (ET1) is a 21-amino acid peptide secreted by vascular endothelial cells in response to stimuli, including pulsatile stretch, sheer stress, neurohormones, cytokines, growth factors, and thrombin. The secretion of ET1 has been shown to be increased by hypoxemia in humans. The effects of ET1 are mediated by both *endothelin A* (ET_A) and *endothelin B* (ET_B) receptors. ET_A is localized on vascular smooth muscle cells, and ET_B is expressed on vascular smooth muscle cells, endothelial cells, and fibroblasts. The effects of ET1 include vasoconstriction, hyperplasia,

hypertrophy, fibrosis, and increased vascular permeability. Activation of ET_B receptors on endothelial cells mediates release of prostacyclin (prostaglandin I₂) and *nitric oxide* (NO), which exert vasodilatory and antiproliferative effects while also inhibiting ET1 production by endothelial cells. Furthermore, the pulmonary endothelial ET_B receptors are responsible for the pulmonary clearance of up to 50% of circulating ET1.⁶⁴ Endothelin-1 is a potent vasoconstrictor and mitogen, and NO is a pulmonary vasodilator and inhibitor of fibrosis.

Increased ET1 production has been described in patients with PAH, and both increased ET1 levels and increased expression of receptors have been shown to be present in plexiform lesions of the lung in patients with PAH.^{64,65} Furthermore, the high plasma levels of ET1 correlate with disease severity and adverse prognosis.⁶⁵⁻⁶⁹ ET1 concentration is also elevated in the sputum and urine of patients with COPD compared to normal subjects; moreover, urinary levels increase further during COPD exacerbations.^{70,71} In addition, plasma ET1 levels have been shown to be increased in subjects who exhibit worsening oxygen saturation with exercise or at night.^{72,73} In another study, patients with PH-COPD were shown to have elevated transpulmonary ET1 levels.⁷⁴ Increased plasma levels and lung tissue expression of ET1 have also been identified in patients with IPF with or without PH.⁷⁵

Inflammation

Inflammation has been hypothesized to play a significant role in the development of the vascular changes seen in PH-LD because increased markers of inflammation and inflammatory mediators have been observed in patients with PH-LD. However, the exact role of inflammation in PH-LD remains controversial.⁷⁶ Increased numbers of CD8⁺ T lymphocytes have been observed in the walls of pulmonary vessels of patients with COPD. Furthermore, the presence of these cells was correlated to the enlargement of the intimal layer.⁴² Similar findings have been observed in the lungs of smokers without COPD or PH, suggesting that cigarette smoke might induce these inflammatory markers. In another study, elevated serum levels of inflammatory cytokines, including C-reactive protein and tumor necrosis factor- α , were seen in patients with PH-COPD.⁷⁷ In patients with PH-IPF, elevated levels of multiple inflammatory mediators have been seen, including thromboxane A₂, tumor necrosis factor- α , platelet-derived growth factor, transforming growth factor- β , and fibroblast growth factor.^{56,78,79} Studies of gene expression suggest that inflammatory mediators are overexpressed in patients with PH-IPF.⁸⁰ Further studies are needed to determine the causal nature of these changes and whether antagonizing inflammation could be of therapeutic value.

RIGHT VENTRICLE

The healthy *right ventricle* (RV) is a thin-walled structure with a complex shape that appears crescentic when viewed in cross section and triangular when viewed from the side (Fig. 59-5). Superficial RV muscle fibers are arranged circumferentially, and deep fibers are arranged longitudinally from apex to base so that the RV contracts by three separate mechanisms: (1) shortening along the long axis, drawing

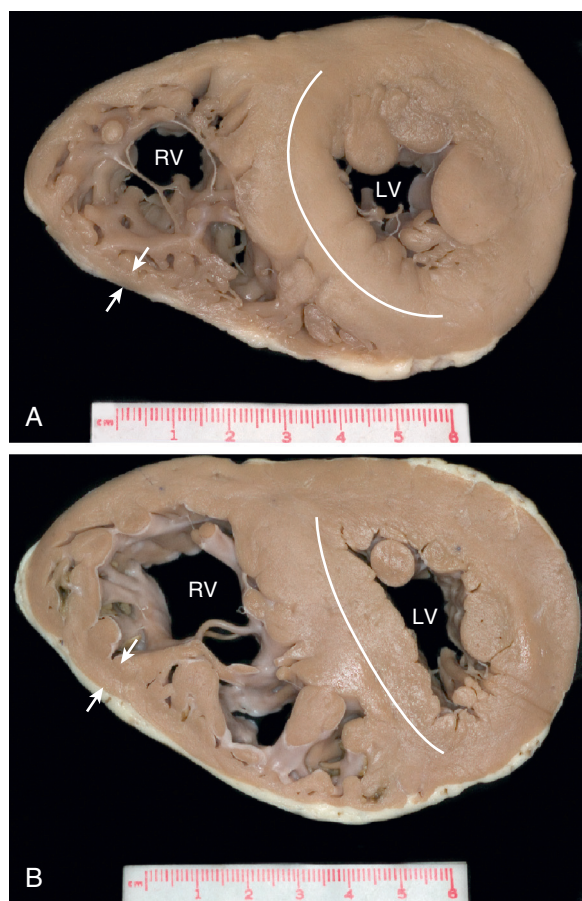


Figure 59-5 Appearance of the right ventricle in pulmonary hypertension. **A**, A transverse section through a normal heart illustrates a crescent-shaped right ventricular cavity, thin right ventricular free wall (arrows) and round left ventricular cavity (line). **B**, Transverse section of a heart from a patient who had severe pulmonary hypertension showing dilation of the right ventricular cavity, giving the heart a more spherical shape than the normal heart. Also seen is thickening of the right ventricular free wall (arrows) and flattening of the interventricular septum (line). (Scale below in centimeters). LV, left ventricle; RV, right ventricle. (Courtesy Dr. Philip Ursell, University of California, San Francisco.)

the base to the apex; (2) inward movement of the free wall, which produces a bellows effect with the RV squeezing against the thick wall of the left ventricle (LV); and (3) traction on the RV free wall at the point of attachment with the LV.⁸¹ Because the RV is in series with the LV, cardiac output from both chambers is equal. The RV, however, is coupled to the normally low-pressure and compliant pulmonary arterial tree so that RV stroke work is significantly less and the RV functions as a volume pump as opposed to a pressure pump like the LV. Under normal physiologic conditions, the RV handles increased volume easily by increasing RV stroke volume. Regulation of RV contractility in the healthy RV is similar to the LV and is dependent on factors such as heart rate, the Frank-Starling mechanism (stroke volume increases as preload increases), and autonomic neural input.⁸¹⁻⁸³

The pattern of development of RV structural and functional abnormalities is similar in patients with PH-LD and PAH and is secondary to the increased afterload on the RV that results from the increase in PVR (see Fig. 59-5). The changes in the RV from pressure overload are distinct from

changes in the RV secondary to volume overload as from conditions such as severe tricuspid regurgitation. RV afterload generally increases slowly in patients with chronic lung disease as PPA and PVR rise, leading to progressive RV hypertrophy, which minimizes wall stress. The RV eventually dilates so that the normal crescent shape of the RV is progressively transformed into a more spherical structure that is better able to generate an increased stroke work (see Fig. 59-5). RV dilation and wall thinning result in increased RV wall stress that, along with increased heart rate, leads to further increases in myocardial oxygen consumption, decreased myocardial perfusion, and RV ischemia. As the RV dilates, severe tricuspid regurgitation may develop, further compromising RV cardiac output and LV filling. RV dilation in the setting of an intact pericardium compromises LV filling by shifting the interventricular septum toward the LV and reducing LV filling and cardiac output.⁶³ Nevertheless, several studies of end-diastolic pressure-volume relationships suggested well-preserved RV contractility in patients with COPD.⁸⁴ Only the additional presence of acidemia or infection precipitates RV failure. When chronic hypercapnia with acidosis is present in patients with alveolar hypoventilation, the ability of the RV to increase its work appears to be significantly impaired, and RV end-diastolic pressure increases.

There may be subtle changes before elevations in PPA can be detected. For example, even before the development of significant elevations in PPA, RV hypertrophy and pathologic remodeling has been observed in patients with chronic lung disease. This was studied by echocardiographic and invasive hemodynamic evaluation of the RV in a group of 98 patients with stable moderate to severe COPD and no known heart disease.⁸⁵ Compared to 34 healthy controls, patients with COPD but without PH had increased RV wall thickness, RV size, and outflow tract dimension, as well as functional abnormalities assessed by myocardial performance index, RV isovolumic acceleration, and RV strain. In another study of patients with COPD, pulmonary artery compliance was reduced before PVR was significantly elevated, suggesting that decreases in compliance may be an early marker of hemodynamic compromise. In patients with lung disease, it is likely that early destruction of the pulmonary vascular bed, though not sufficient to increase PVR, significantly reduces pulmonary artery compliance and contributes to early increases in RV afterload and subsequent RV hypertrophy.⁸⁶

RV myocardial ischemia may also play a role in RV failure. RV coronary perfusion decreases with the increase in wall thickness even as the hypertrophy and dilation of the RV produces a significant increase in RV myocardial oxygen consumption. RV coronary perfusion also decreases with the increase in end-diastolic pressure as RV stiffness increases during diastole. Taken together, these factors result in an imbalance between RV myocardial oxygen demand and supply.

This impairment of myocardial contractility in the presence of hypercapnia probably plays a significant role in producing decompensated pulmonary heart disease in response to acute increases in arterial PCO₂ associated with exacerbations of COPD and accompanying decreases in alveolar ventilation. The development of RV volume overload with ventricular dilation results in a decreased ejection fraction,

because stroke volume tends to be maintained close to the normal range in decompensated cor pulmonale.⁸⁷ With exercise, patients with COPD significantly raise their RV afterload, which causes further increases in RV end-diastolic volume and decreases in ejection fraction. It is likely that this deterioration in hemodynamic performance with exercise is a major factor limiting the ability of such patients to exercise normally.

In the presence of RV failure and elevated central venous pressure, the patient can stand up without a decrease in RV end-diastolic volume or stroke volume; consequently, the heart rate does not change. This lack of postural reflex compensation is attributable to failure of any incremental gravitational pooling of blood in the venous system, because of increased plasma volume, increased tissue pressure from edema with decreasing venous dispensability, and increased venomotor tone.⁸⁸

LEFT VENTRICLE

Although LV ejection performance is unimpaired, cardiac catheterization studies have revealed abnormal LV end-diastolic pressure-volume relationships.⁸⁹ Echocardiographic studies have also shown progressive impairment of LV diastolic function that correlates with the severity of PH.⁹⁰ It is likely that this results, in large part, from bulging of the interventricular septum from the hypertrophied and dilated RV into the cavity of the LV, and ventricular interdependence exerted by pericardial constraint.^{63,91} As a result, LV diastolic geometry becomes distorted,⁹² and filling characteristics may be altered so that a higher filling pressure is required to accomplish the same end-diastolic fiber stretch needed for a given stroke work, in accordance with the Frank-Starling mechanism. With severe RV failure and marked elevation in right atrial pressure, coronary venous pressure increases significantly; this increase in coronary venous pressure can result in an increase in LV wall dimension limiting LV distensibility. This mechanism leading to reduced LV preload appears to act independently of diastolic ventricular interaction caused by RV enlargement as previously described.⁹³

LUNG MECHANICS

In healthy individuals, ordinary inspiration causes a small reduction of 3 to 5 cm H₂O in pleural pressure that is adequate to generate a normal tidal volume with only a small transmission of intrathoracic pressure affecting the heart and pulmonary vasculature. Increased stiffness of the chest wall or the lung parenchyma means that patients with obesity or obstructive or restrictive lung diseases must generate more negative pleural pressures to achieve an adequate tidal volume. Additionally, patients with COPD often have lung hyperinflation secondary to airflow obstruction, loss of elastic lung parenchyma, or dynamic hyperinflation. These abnormalities in pulmonary mechanics may contribute significantly to the pathophysiologic features of PH.

Lung hyperinflation affects RV function through changes in RV preload and afterload. Increased lung volumes in diseases such as COPD can passively compress alveolar vessels directly, increasing PVR and RV afterload,⁹⁴ and in some

cases, hyperexpanded lungs may even directly compress the heart with negative effects on cardiac performance.⁹⁵ Exaggerated swings in intrathoracic pressure such as those seen in patients with OSA can result in increased right-sided venous return, which causes acute RV enlargement and in turn impedes LV filling and cardiac output. At the same time, reductions in intrathoracic pressure increase LV afterload, which may be transmitted backwards and result in transient increases in PPA.⁹⁶ In patients with acute bronchospasm, echocardiographic studies have shown acute inspiratory RV dilation and simultaneous reduction in LV cavity size that reverse during expiration, resulting in increased PVR from hyperinflation and increased RV wall tension from exaggerated negative pleural pressure. Importantly, the clinical significance of these effects may depend largely on the cardiovascular reserve of the specific patient.⁹⁴

CLINICAL PRESENTATION

There are many causes of PH, as noted in [Table 59-1](#). At times the underlying cause may be difficult to establish, and often the cause of PH is multifactorial. In one study of 998 patients with COPD undergoing right heart catheterization, 27 were found to have PPA greater than or equal to 40 mm Hg; after complete evaluation, 16 (59%) were found to have another cause of PH, including administration of appetite suppressants, left ventricular dysfunction, chronic thromboembolic PH, collagen vascular disease, portal hypertension, and OSA.⁶ When evaluating a patient with a new diagnosis of PH, an exhaustive evaluation is required to identify all possible causes of increased PPA.⁹⁷ The prognosis and treatment of PH vary dramatically with the cause so that the significance of PH and optimal treatment require a complete and accurate understanding of the underlying cause or causes.

SYMPTOMS AND SIGNS

The first step in the evaluation is a comprehensive history and physical examination to identify any conditions that might cause PH. Specifically the patients should be questioned regarding use of appetite suppressants or other toxic substances, a history of liver disease and portal hypertension and diagnosis or symptoms of systemic lupus erythematosus, scleroderma, or other collagen vascular disease, or a history of venous thromboembolism. In patients already diagnosed with lung disease, it is important that the lung disease be well characterized and that definitive diagnostic studies have been performed and are reviewed. Studies to exclude daytime hypoxemia with exercise and nocturnal hypoxemia from OSA should be performed. Left-sided heart disease is the most common cause of PH⁴ and must be identified if it is contributing to PH. Although echocardiography is useful to detect LV systolic dysfunction and valvular abnormalities that may cause PH, heart failure with preserved ejection fraction (formerly called diastolic heart failure) can be missed and may be detected only during comprehensive invasive hemodynamic assessment.^{7,10}

Mild PH-LD reflected in small chronic elevations in RV pressure generally causes minimal, if any, clinical, radiologic, or electrocardiographic findings. When moderate or

severe PH-LD develops ($\overline{\text{PPA}} > 40$ mm Hg), symptoms are often similar to those associated with the underlying pulmonary disease. Most commonly, these are dyspnea on exertion, chronic cough productive of mucoid sputum, wheezing, and occasional cyanosis. Clubbing of the fingers may be present. In addition to exertional dyspnea and fatigue, some patients experience dizziness or exertional syncope, attributable to the inability to increase cardiac output during exercise in the face of a marked increase in PVR. Furthermore, these patients may have chest pain owing to RV ischemia or stretching of the main pulmonary artery.

When resting PPA is sufficiently elevated, patients may eventually reach a point at which the RV cannot meet the need for increased stroke work without a significant increase in right heart filling pressures. The resultant increase in central venous pressure is associated with developing symptoms of right-sided heart failure, such as peripheral edema, right upper quadrant discomfort, nocturia, and easy fatigability.

On examination, the patient is often cyanotic and sitting upright with tachypnea, with prominent use of the accessory muscles of breathing, and arms extended holding on to the edges of the mattress. In COPD, pulsus paradoxus may be present, the chest is often hyperinflated, and otherwise mild wheezing may be audible. Sinus tachycardia is often present; however, atrial and ventricular arrhythmias are also common.⁹⁸ Evidence of fluid retention may include dependent edema and ascites. The liver may be enlarged and tender to palpation and may be pulsatile, reflecting the presence of severe tricuspid regurgitation. Similarly, the neck veins may be distended and, when tricuspid regurgitation is present, show a large *c-v* wave with rapid *y* descent. Signs of volume overload secondary to RV dysfunction must be distinguished from sympathetically mediated renal salt and water retention without RV dysfunction, which can also develop in patients with lung disease.⁹⁹

On examination of the chest, there may be a left parasternal systolic lift, owing to the overactivity of the enlarged RV, and a thud felt over the pulmonary area as the pulmonary valve closes. The heart sounds are often difficult to hear if the patient has underlying COPD. The pulmonic component of the *second heart sound* (*S*₂) may be accentuated and be heard earlier than usual, so the normal splitting may be abolished and a single loud *S*₂ heard. Normally not heard at the apex, the pulmonic component of *S*₂ may be clearly heard. A high-pitched systolic ejection click may be heard in the second and third left intercostal spaces next to the sternum. It is often followed by a soft, localized systolic ejection murmur produced by ejection of the stroke volume into a dilated pulmonary artery. An *S*₃ gallop arising from the right side of the heart may be heard in the fourth and fifth interspaces immediately to the left of the sternum or even next to the xiphoid process. A presystolic *S*₄ gallop may also be heard, reflecting the increased forcible contraction of the right atrium with expulsion of blood into the hypertrophied and dilated RV. Often tricuspid regurgitation is present, and this results in a prominent blowing pansystolic murmur with respiratory variation in the same location. When prominent PH is present, a diastolic murmur of pulmonic valve regurgitation may be heard; this murmur, known as a Graham Steell murmur, is a soft, blowing decrescendo

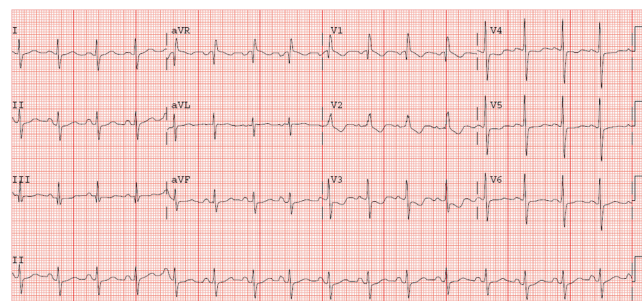


Figure 59-6 Electrocardiogram from a patient with pulmonary hypertension. Findings include a prominent “p pulmonale” and increased R wave voltage in the anterior precordial leads suggestive of right atrial and right ventricular abnormalities.

diastolic murmur, usually well localized to the second and third left intercostal spaces next to the sternum.

ELECTROCARDIOGRAPHY

Characteristically, the P wave of the electrocardiogram has a “p pulmonale” pattern with right-axis deviation resulting in an increase in its amplitude in leads II, III, and aVF to more than 2.5 mm (Fig. 59-6). The P wave may also be tall in the right precordial leads. The QRS vector in the frontal plane often shifts to the right in cor pulmonale, and a low-voltage QRS complex is common if lung hyperinflation is present. Prominent S waves are seen in leads I, II, and III. An incomplete right bundle-branch block pattern is also frequently observed. When PH is moderate or severe, the more classic findings of RV hypertrophy may dominate the electrocardiogram, including tall R waves in *V*₁ with an R/S ratio of more than 1, and a prominent S wave in *V*₅ and *V*₆ with an R/S ratio of less than 1. The presence of electrocardiographic evidence of cor pulmonale in patients with COPD is a poor prognostic sign.¹⁰⁰

CHEST RADIOGRAPHY

In addition to radiographic findings of the underlying lung disease, the chest radiograph should be evaluated for features of right heart failure and pulmonary vascular abnormalities. There may be enlargement of the main pulmonary artery as well as enlargement of the right and left descending pulmonary arteries. Abrupt tapering of the peripheral vessels may result in disproportionately large central pulmonary arteries and attenuated distal vessels. A right descending pulmonary artery with a diameter greater than 16 mm suggests PH.¹⁰¹ Enlargement of the RV may be seen on the lateral projection of the chest radiograph as a reduced retrosternal space. If hyperinflation of the lungs is present, the overall diameter of the cardiac silhouette may not be increased, although the heart may have a globular appearance.

The chest radiograph should be carefully evaluated for evidence of left heart failure. Pleural effusions are seldom seen in patients presenting with PH-LD and right heart failure unless coexisting left ventricular dysfunction and failure are also present. Radiographic findings of pulmonary edema also point to left heart failure as a likely cause of PH. Additionally, a diagnosis of pulmonary

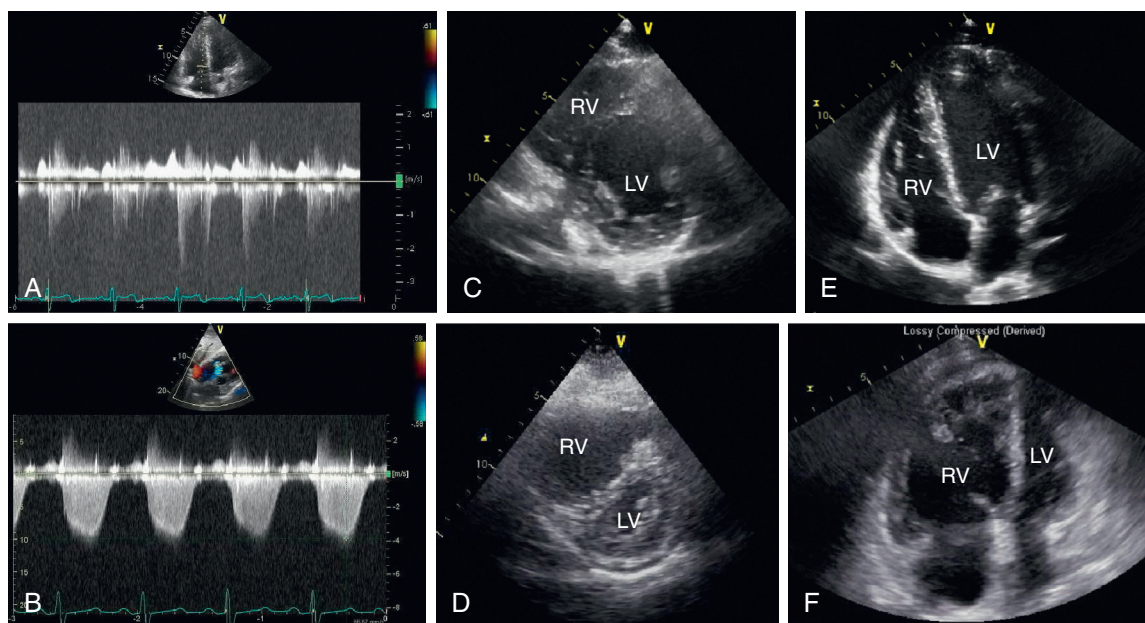


Figure 59-7 Echocardiography in the evaluation of pulmonary hypertension. **A**, Poor-quality tricuspid regurgitant jet from which the pulmonary artery systolic pressure (PASP) cannot be estimated. **B**, Good-quality tricuspid regurgitant jet that is useful for estimating the PASP. Even when a good-quality jet can be obtained, the echocardiographic assessment of PASP may be inaccurate. **C**, Short-axis echocardiographic image of a normal heart demonstrating a rounded left ventricle (LV) and normal-appearing right ventricle (RV). **D**, Short-axis echocardiographic image from a patient with pulmonary hypertension demonstrating flattening of the interventricular septum and a D-shaped LV during systole and a large RV. **E**, Apical four-chamber echocardiographic view of a normal heart demonstrating a normal-sized RV and LV. **F**, Apical four-chamber echocardiographic view from a patient with pulmonary hypertension demonstrating a markedly enlarged RV with a small, compressed LV. There is also enlargement of the right atrium. (See Videos 59-1A and B and 59-2A and B.)

veno-occlusive disease should be considered in patients with PH and pleural effusions.

ECHOCARDIOGRAPHY

Echocardiography is widely available, inexpensive, uses no radiation, and can be performed serially, making it a useful tool for estimating PPA and evaluating RV structure and function (Fig. 59-7, Videos 59-1A and B and 59-2A and B). An echocardiogram is often the earliest test that suggests a diagnosis of PH and is important in assisting the clinician in eliminating various nonpulmonary causes of PH, such as ischemic or nonischemic LV systolic dysfunction, aortic or mitral valve disease, and congenital heart disease with left-to-right shunt.

Echocardiography is often used to estimate the PASP, which can be determined in 36% to 86% of patients with PH-LD by taking advantage of the presence of tricuspid regurgitation and using continuous-wave Doppler recording to obtain the tricuspid regurgitant jet velocity.^{9,102} First, the pressure gradient across the tricuspid valve between the right atrium and ventricle is calculated using the modified Bernoulli equation ($\text{pressure gradient} = 4v^2$), where v is the tricuspid regurgitant jet velocity; this value is then added to the right atrial pressure—estimated by the size and collapsibility of the inferior vena cava—to obtain an estimate of the RV systolic pressure, which in the absence of pulmonary valve stenosis equals PASP.¹⁰³

Echocardiographic estimates of PASP are subject to important limitations, especially among patients with parenchymal lung disease and obese patients. The presence

of hyperinflation of the lungs impairs the transmission of ultrasound and can result in suboptimal image quality so that an adequate tricuspid regurgitant jet cannot be measured; in one large series of patients with advanced lung disease, a satisfactory PASP could be estimated in only 44% of patients.¹⁰⁴ The sensitivity and specificity of Doppler echocardiography to predict the presence of PH range from 0.79 to 1.0 and from 0.6 to 0.98, respectively.¹⁰² However, when compared to invasive assessment, the echocardiographic estimate of PASP shows only moderate correlation and is often inaccurate.¹⁰⁴⁻¹⁰⁶ Therefore, in patients with symptoms or clinical signs that are concerning for PH, right heart catheterization should be considered even if the echocardiographically estimated PASP is normal.

Structural and functional information about the size of the right atrium and RV is probably the most valuable information that can be obtained from the echocardiogram.¹⁰⁷ Right atrial pressure can be assessed by evaluating the size of the inferior vena cava and changes in its size with respiration. Flattening or leftward shift of the interventricular septum during systole and septal flattening during diastole both suggest RV volume overload. Assessment of RV function by echocardiography is challenging because the RV is often difficult to image and image quality may be inadequate to perform objective measurements. In a study of 32 patients with advanced lung disease, Schenk and colleagues¹⁰⁸ found that, among various echocardiographic parameters, RV end-diastolic area and fractional area change from the apical four-chamber view correlated best with the gold standard *magnetic resonance imaging* (MRI)–derived RV volume and ejection fraction, respectively.

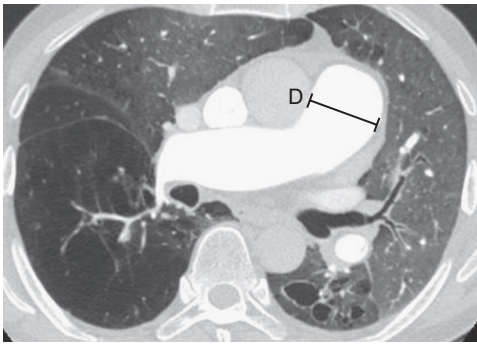


Figure 59-8 Chest CT scan in a patient with chronic lung disease demonstrating enlargement of the main pulmonary artery. Enlargement of the main pulmonary artery suggests the diagnosis of pulmonary hypertension. $D = 36.4$ mm, whereas the mean main pulmonary artery diameter in healthy controls is 25.1 ± 2.8 mm.^{110a}

Doppler-derived indices of RV function, the tricuspid annular plane excursion¹⁰⁹ and RV myocardial performance index,¹¹⁰ have both been shown to have prognostic value in patients with idiopathic PAH and are being studied in other groups of PH.

COMPUTED TOMOGRAPHY

Chest *computed tomography* (CT) is often used to visualize the pulmonary parenchyma in patients with respiratory disease. Using this imaging modality, the size of the pulmonary artery can be measured, and, in patients with moderate to severe PH, enlargement of the main pulmonary artery or an increased diameter of the pulmonary artery (>29 mm) may be documented (Fig. 59-8). This finding may have prognostic significance, and, in a study of 3464 patients with COPD, a pulmonary artery-to-aorta ratio higher than 1 was associated with future severe COPD exacerbations (odds ratio, 3.44; $P < 0.001$).¹¹¹ However, in a study of 65 patients with advanced IPF, main pulmonary artery diameter on chest CT failed to differentiate between those who did or did not have PH diagnosed by right heart catheterization.¹¹² Other findings such as dilated right-sided heart chambers on contrast-enhanced CT imaging are suggestive but not diagnostic of cor pulmonale in patients with severe parenchymal lung abnormalities.

MAGNETIC RESONANCE IMAGING

Currently MRI is the most accurate method for assessing characteristics of the RV, including its volume, mass, and systolic function. Additionally, phase-contrast MRI has the capability to calculate accurate flow characteristics, including cardiac output, valvular regurgitant fraction, and both right- and left-sided shunt fractions. MRI has significant advantages over echocardiography in that it can image in any desired imaging plane, has a large field of view, and is not limited by acoustic windows. Although high cost, relatively long image acquisition time, and lack of widespread availability limit its use compared with echocardiography, cardiac MRI is increasingly being used as the standard method for evaluating RV structure and function in patients with PH.^{113,114}

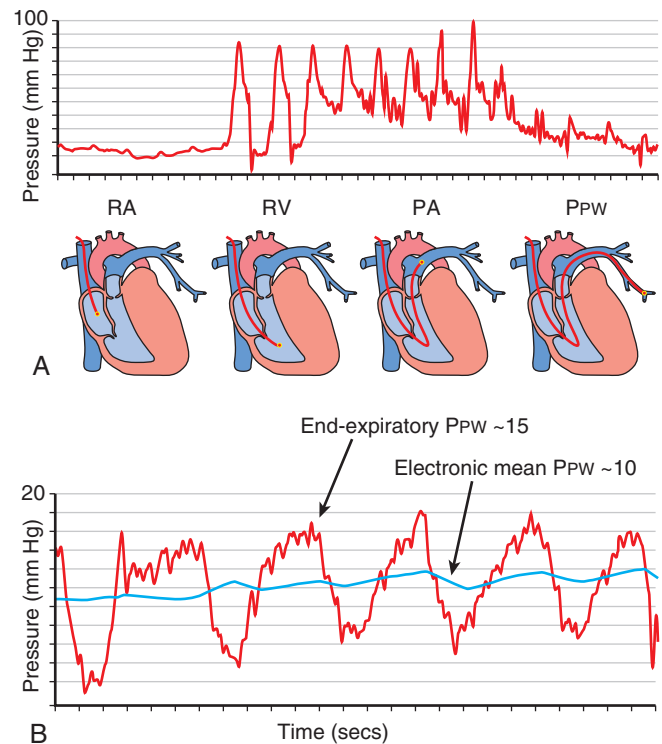


Figure 59-9 Tracings from right heart catheterization in patients with pulmonary hypertension. **A**, Waveforms that are obtained as the catheter passes from the right atrium (RA) through the right ventricle (RV), pulmonary artery (PA), and into the pulmonary capillary wedge position in a patient with pulmonary hypertension. Notable findings include the markedly elevated pulmonary artery pressure and the normal pulmonary capillary wedge pressure (PPW). **B**, PPW tracing from another patient with chronic lung disease demonstrating marked respiratory variation in the wedge pressure. Abrupt rise in pressure in some respiratory cycles at the end of expiration likely represents forceful expiration, which is sometimes seen in patients with lung disease. It is important to identify and measure the pressure at end-expiration correctly. Use of the computer-measured mean wedge pressure is misleading because the mean wedge pressure is calculated to be normal, whereas the actual end-expiratory wedge pressure is elevated, suggesting a diagnosis of pulmonary hypertension from left heart disease.

RIGHT HEART CATHETERIZATION

In patients with PH, right heart catheterization is required to confirm the diagnosis and is the gold standard test to measure PPA. Besides measuring PPA, right atrial pressure, cardiac output, and left-sided filling pressures, wedge pressure (Fig. 59-9) should be determined. Using these data, values for PVR, SVR and PVR-to-SVR ratio can be calculated. The presence of a congenital systemic-to-pulmonary shunt can be assessed during right heart catheterization by performing an oxygen saturation assessment across the right-sided heart chambers. If echocardiographic imaging is not adequate, hemodynamic assessment of right-sided heart valves can also be performed during right heart catheterization. Pulmonary angiography may be performed if there is a concern for chronic thromboembolic PH.¹¹⁵

It is important that right heart catheterization be performed in centers with experience evaluating patients with PH. Attention to technical aspects of the procedure is needed to ensure that good quality data are obtained; it is important that the transducer is properly leveled and zeroed

and that all measurements are made at end-expiration, when gas flow is minimal and transthoracic pressure is zero, to assess hemodynamics without respiratory influence.¹¹⁶ Improper performance of the hemodynamic assessment may lead to incorrect diagnosis of the underlying cause of PH.¹¹⁷ The correct timing of hemodynamic measurements may be particularly difficult in patients with parenchymal lung disease who may be breathing forcefully and increase their intrathoracic pressure at the end of expiration. Because left-sided heart abnormalities and increased filling pressures are common in patients with lung disease^{118,119} and can be treated with diuretics, it is critical that wedge pressure be properly measured so as not to miss a contribution of elevated LV filling pressures to PH. A blood sample drawn from the right heart catheter in the wedge position showing an oxygen saturation similar to the systemic arterial saturation is useful to confirm a correctly measured wedge pressure. Uncertainty about the validity of the measured wedge pressure may be resolved by direct measurement of left ventricular end-diastolic pressure. Assessments of cardiac output in patients with PH-LD should be made using both the Fick and thermodilution cardiac output methods.¹¹³ Challenge with vasodilators should not be routinely performed in the evaluation of patients with PH-LD (see “Treatment” section).

The 2013 guidelines provide recommendations for terminology and classification of patients with lung disease based on invasive hemodynamic assessment.¹²⁰ These guidelines specifically recommend against the use of the term *out of proportion PH*, which has been used frequently in the past. Patients are instead placed in one of three possible categories: (1) lung disease without PH ($\overline{PPA} < 25$ mm Hg), (2) lung disease with PH ($\overline{PPA} \geq 25$ mm Hg), and (3) lung disease with severe PH ($\overline{PPA} \geq 35$ mm Hg **or** $\overline{PPA} \geq 25$ mm Hg and cardiac index < 2.0 L/min/m²).

B-TYPE NATRIURETIC PEPTIDES

Measurement of *B-type natriuretic peptides* (BNPs) may be useful in the assessment of patients with lung disease and possible PH if there are no other reasons for elevated BNP values. In one study, plasma BNP was measured in 176 consecutive patients with a variety of pulmonary diseases¹²¹; elevated BNP levels identified PH (defined as $PASP > 35$ mm Hg) with a sensitivity of 0.85 and a specificity of 0.88 and predicted mortality. In both univariate and multivariate analysis, BNP was found to be a risk factor for death independent of pulmonary function impairment or hypoxemia.¹²¹

TREATMENT

In the vast majority of patients with PH-LD, optimal treatment of the underlying lung disease according to established guidelines is by far the best approach to managing PH. Comorbidities that worsen PH, such as left-sided heart disease, valvular disease, pulmonary emboli, and sleep-disordered breathing should also be sought and aggressively treated. Because PH portends a poor prognosis in patients with lung disease, timely referral for lung transplant evaluation is imperative. Although it may be tempt-

ing to treat patients who have PH-LD with therapies proven useful in group 1 PAH, these treatments have not been shown to be useful, and some have been harmful in patients with lung disease. Updated guidelines strongly discourage using treatments for PAH in patients with PH-LD.^{120,122} We recommend consultation at a center of excellence with experience in the evaluation and management of PH-LD disease before initiation of PAH-specific therapy; if warranted, patients should be enrolled in prospective treatment trials.

TREATMENTS USEFUL IN ALL PATIENTS WITH PH-LD

In patients with PH-LD, optimal treatment directed at the specific underlying pulmonary disorder is mandatory and is the subject of most of this textbook. The overall therapeutic strategies for PH-LD and RV failure are shown in Table 59-2.^{123,124}

Lifestyle Modifications

In the management of PH-LD, diet and lifestyle modifications are crucially important. Smoking cessation is the most important of all preventive lifestyle interventions, especially considering the possible direct harmful effect of cigarette smoke on the pulmonary vasculature.⁴³ Other safeguards consist of sodium restriction, weight loss, and exercise training to improve functional performance. Structured rehabilitation programs and breathing training have been shown to be useful.^{63,125} Patients with severe PH or RV dysfunction, especially those with a history of syncope, should avoid overexertion, pregnancy, and high altitudes (>1220 m [4000 feet]).

Table 59-2 Therapeutic Strategies for Pulmonary Hypertension Due to Lung Disease

FOR ALL PATIENTS

- Treatment of underlying lung disease
- Lifestyle modification
- Smoking cessation
- Sodium restriction
- Weight loss
- Judicious exercise training
- Structured rehabilitation and breathing training programs
- Avoidance of overexertion
- Avoidance of pregnancy
- Avoidance of high altitudes
- Supplemental oxygen
- Diuretics
- Treatment of sleep-disordered breathing and alveolar hypoventilation disorders (CPAP, BiPAP, surgery)
- Lung transplantation

FOR SELECTED PATIENTS

- Anticoagulation
- Digoxin
- Lung volume reduction surgery
- Phlebotomy
- Iron supplementation
- PAH-specific therapies (use discouraged except in highly selected circumstances and when managed by a pulmonary hypertension referral center)

BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; PAH, pulmonary arterial hypertension.

Oxygen

Alveolar hypoxia may make a major contribution to the genesis of PH-LD, and aggressive treatment with supplemental oxygen to correct hypoxia is central to optimal treatment. Controlled trials evaluating long-term oxygen administration in COPD showed improvement in survival. Oxygen administration may have beneficial effects on hemodynamics,^{126,127} RV function,¹²⁸ and exercise tolerance.

The effects of oxygen supplementation in PH-LD have been studied in two major randomized trials. First, in the British Medical Research Council evaluation of long-term home oxygen in chronic hypoxic cor pulmonale, long-term oxygen administration for at least 15 hr/day lessened mortality and appeared to prevent further increases in PPA, compared with no oxygen administration in control patients.¹²⁹ Second, in a National Institutes of Health-sponsored study in the United States, continuous oxygen therapy was better than nocturnal therapy alone; furthermore, continuous oxygen lessened mortality rate at 2 years¹³⁰ and decreased PVR in comparison with the group receiving only nocturnal therapy. These findings were confirmed in two more recent studies both showing stabilization of PPA with long-term oxygen therapy.^{131,132} There are other beneficial effects of oxygen therapy, including relief of renal vasoconstriction and improvement in oxygen delivery to critical organs such as the heart and brain.¹³³

Based on the results of these studies, it is clear that hypoxemic patients with COPD should receive supplemental oxygen therapy. Additionally, there is evidence that oxygen improves functional class and symptoms in patients with IPF so that in these patients maintenance of arterial oxygen saturation at or slightly over 90% at rest and especially with activity has been recommended.⁷⁹ It must be remembered, however, that the acute administration of inordinate concentrations of oxygen to a patient can have adverse effects on breathing and carbon dioxide removal, particularly in patients already hypoventilating with evidence of hypercapnia. Patients given oxygen need to be observed closely when they are initially being instructed on the use of this therapy to ensure that arterial oxygen saturation actually rises, but not too high: flow rates of 1 to 3 L/min generally suffice. Further information about the long-term use of oxygen in pulmonary rehabilitation is provided in Chapter 105.

Diuretics

Diuretic therapy to optimize volume status alleviates dyspnea, hepatic congestion, and peripheral edema. Decompression of the RV with diuretics may also improve RV performance by reducing preload and wall stress. Judicious diuresis may reduce intrapericardial pressure and potentially attenuate interventricular septal shift toward the LV, resulting in increased LV filling and improved systemic cardiac output.

Treatment of Sleep-Disordered Breathing

Sleep-disordered breathing is common in patients with COPD and can contribute to nocturnal hypoxemia and hypercapnia, leading to increased pulmonary vasoconstriction. As described in Chapter 88, continuous positive airway

pressure exerts its beneficial effects by maintaining patency of both upper and lower airways and improving gas exchange. Patients diagnosed with OSA should be treated with continuous positive airway pressure and supplemental oxygen as required; in patients with OSA, continuous positive airway pressure is associated with improved ventricular function and survival and reduced hematocrit level.¹³⁴⁻¹³⁶ In patients who have nocturnal hypoxemia without evidence of OSA, supplemental oxygen alone may be adequate.

Lung Transplantation

There is a clear role for lung transplantation in patients with PH-LD.¹³⁷ Because development of PH and right heart failure in patients with lung disease portends a poor prognosis and there are no effective medical therapies, timely referral for evaluation for lung transplantation is critical. Early referral to a transplantation center is preferred so that candidacy can be determined and barriers to transplantation can be identified and addressed. Recovery of RV function and good long-term prognosis have been demonstrated in patients following both single- and double-lung transplant for PH.^{138,139}

There is conflicting evidence regarding the effects of pretransplantation hemodynamics on posttransplantation mortality in patients with PH-LD. A retrospective study of 830 patients treated with lung transplant for IPF found that 90-day posttransplantation mortality increased with increasing pretransplant PPA.¹⁴⁰ Another retrospective study showed that, in COPD patients undergoing lung transplantation, a preoperative echo-estimated PASP of 45 mm Hg or higher was associated with increased intensive care unit length of stay and duration of mechanical ventilation but was not associated with reduced survival.¹⁴¹ The degree of pretransplantation RV dysfunction is potentially more important than PPA and may be considered by the transplantation team when determining risk and transplantation candidacy and the optimal surgical approach (single or double lung, on pump or off pump).¹⁴² In patients with more advanced RV dysfunction, use of mechanical support such as extracorporeal membrane oxygenation during the perioperative period has been used to provide hemodynamic support and permit transplantation in patients with right heart failure^{143,144} (see Chapter 103).

TREATMENTS THAT MAY BE CONSIDERED IN SELECTED PATIENTS

Anticoagulation

In patients with group 1 PAH, oral anticoagulation is considered the standard of care¹⁴⁵ based on one retrospective and one prospective trial that showed a mortality benefit.^{146,147} In patients with PH-LD, on the other hand, there are currently no data regarding the utility of treatment with anticoagulation. Patients with pulmonary emboli or lower extremity deep venous thrombosis should be treated according to current guidelines. Patients with PH-LD who also have evidence of chronic thromboembolic disease should be treated lifelong with warfarin to achieve a target international normalized ratio of 2 to 3. In other selected patients with PH-LD who are at low risk for

complications from anticoagulation treatment, warfarin can be considered with the recognition that there are no clear benefits. Anticoagulation with direct thrombin inhibitors and factor Xa antagonists has not been studied in the treatment of PH-LD, and these agents currently have no role in the treatment of PH-LD.

Digoxin

In a small study of patients with COPD and cor pulmonale, digoxin had a favorable effect on RV function without changes in pulmonary function, exercise capacity, or symptoms.¹⁴⁸ Current data do not support a recommendation for the routine use of digoxin in patients with cor pulmonale from PH-LD. Digoxin may be better tolerated than negative inotropic agents, such as β -blockers or calcium channel blockers for rate control in patients with PH-LD who develop arrhythmias such as atrial fibrillation. It must be emphasized that patients with COPD are particularly sensitive to digoxin, and close attention to dosage and electrolyte balance to prevent toxicity is necessary.

Lung Volume Reduction Surgery

The effects of *lung volume reduction surgery* (LVRS) on pulmonary hemodynamics remain controversial. LVRS has been shown to improve symptoms and quality of life in patients with emphysema and may improve pulmonary hemodynamics by improving oxygenation and reducing hyperinflation; by contrast, pulmonary hemodynamics may be worsened by removing or altering the pulmonary vasculature. Results of retrospective studies have shown variable effects of LVRS on hemodynamics; some have shown improvement in RV function¹⁴⁹ and reduction in wedge pressure,¹⁵⁰ whereas others have found an increase in PPA and PVR.^{151,152} The prospective cardiovascular sub-study of the National Emphysema Treatment Trial attempted to clarify the hemodynamic effects of LVRS by randomizing 110 patients to either LVRS or medical therapy.¹⁵³ Six months after treatment, hemodynamics were similar in both groups with the exception of a small reduction in wedge pressure in the LVRS group. Based on these results, LVRS is not currently recommended for routine treatment of PH-LD.

Phlebotomy for Polycythemia

If severe polycythemia is present, phlebotomy may be helpful, although clinicians are frequently reluctant to undertake this type of therapy today. An elevated hematocrit above 40% is known to increase viscosity and PVR (see Fig. 6-6). Phlebotomy in patients with polycythemia and chronic hypoxemia may also improve RV ejection fraction, exercise tolerance, and neuropsychological function.⁶³ For those with an elevated hematocrit, for example above 55%, phlebotomy should be considered and, if the patient benefits, repeated as needed to maintain a lower hematocrit.¹⁵⁴⁻¹⁵⁶

Iron Supplementation

Experiments in animals and human tissue cells have revealed that the hypoxia-inducible factor family of transcription factors are integral to regulation of the pulmonary vascular response to hypoxia.¹⁵⁷ Hypoxia-inducible factor is primarily regulated by oxygen-dependent proteosomal degradation, a process that is up-regulated or

down-regulated based on iron availability. A study in humans showed that intravenous iron infusions into healthy iron-replete volunteers blunted the pulmonary vasoconstrictor response to hypoxia, whereas a reduction in available iron through chelation to those same volunteers enhanced the pulmonary vasoconstrictor response to hypoxia.¹⁵⁸

In a follow-up study, PPA was assessed by echocardiography in 22 healthy volunteers at sea level.¹⁵⁹ Subjects were then taken to 4340 m for 3 days and treated with either intravenous iron or saline; repeat assessment showed a reduction in PASP in iron-treated patients compared to controls. Another trial evaluated the effects of standard therapy, phlebotomy, followed by iron infusion or saline infusion in 11 patients with chronic mountain sickness.¹⁵⁹ Following phlebotomy, all patients developed iron deficiency with an increase in PASP of 9 mm Hg that did not reverse acutely with intravenous iron treatment. Further randomized trials are needed; however, these studies suggest that evaluation for and correction of iron deficiency in patients with cor pulmonale may be beneficial.

PAH-Specific Therapies

Multiple therapies are now available with proven efficacy in the treatment of PAH (see Chapter 58). Acute hemodynamic benefits in PH-LD have been demonstrated with some of these agents^{160,161}; however, none of these therapies have had long-term benefits in patients with PH-LD.^{161a} Adverse effects, including worsening hypoxemia from reversal of physiologic ventilation-perfusion matching and reduction in systemic blood pressure from peripheral vasodilator effects, have also been seen.^{161,162} Additionally, studies of IPF patients treated with *endothelin receptor antagonists* (ERAs) have resulted in worse outcomes in the experimental group compared to placebo.^{163,164}

A comprehensive review of the studies of PAH-specific treatment in patients with PH-LD can be found in the online version of this chapter at *ExpertConsult*.

Current guidelines discourage the use of PAH-specific therapy in PH-LD patients because of lack of efficacy and risk for adverse effects.^{120,122} These agents might be considered in highly selected patients such as those who also have evidence of concomitant group 1 PAH or group 4 chronic thromboembolic PH and to manage right heart failure in PH-LD patients awaiting lung transplant. If treatment with PAH-specific therapies is considered, we recommend consultation at a PH center of excellence before initiating therapy and, if possible, enrollment in a clinical trial.

TREATMENT OF DECOMPENSATED RV FAILURE

Management of patients with decompensated RV failure from cor pulmonale must focus on improvement of the underlying pulmonary disorder.¹²³ The precipitating event for decompensation in patients with stabilized chronic cor pulmonale from either COPD or infiltrative lung disease is often an associated upper respiratory infection. Increased secretions and infection are likely to tip the balance toward further arterial hypoxemia, hypercapnia, and acidemia, which aggravate PH and worsen ventricular contractility, resulting in cardiac decompensation.



Of major concern in patients with PH-LD is that pharmacologic reversal of hypoxic pulmonary vasoconstriction with vasodilators may increase pulmonary blood flow to poorly ventilated or nonventilated alveoli and cause arterial PO_2 to fall despite a drop in PPA. Ventilation-perfusion mismatching also affects carbon dioxide elimination; therefore minute ventilation may increase to compensate for the retention of carbon dioxide, although arterial PO_2 may still fall.¹⁶⁵ Another practical problem limiting the use of pulmonary vasodilators is that very often they also act as systemic vasodilators and cause significant hypotension.

Calcium Channel Blockers. Calcium channel blockers are not useful in the treatment of PH-LD. In a study of 53 patients with COPD and PH, treatment with nifedipine reduced PVR at baseline by 23% at rest and 35% during exercise, but the benefits were no longer seen after an average of 13 months of treatment.¹⁶⁰ Another study randomized 20 patients with COPD and mild PH to either placebo or nifedipine. There were no acute improvements with the first dose of nifedipine, and 18 months later cardiac output was slightly higher in nifedipine-treated patients accompanied by a nonsignificant reduction in arterial PO_2 . In another study of felodipine in 13 patients, hemodynamics were improved and gas exchange remained stable at 12 weeks compared to baseline, but exercise tolerance was not improved.¹⁶⁶ Due to the lack of long-term benefits and potential side effects from calcium channel blockers (worsening hypoxemia, systemic hypotension, and peripheral edema), we recommend against attempts to treat PH-LD with calcium channel blockers.

Endothelin Receptor Antagonists. Three ERAs are approved by the Food and Drug Administration for the treatment of PAH. Bosentan and macitentan are dual ET_A and ET_B receptors, and ambrisentan is a selective ET_A receptor antagonist.¹⁶⁷ Studies of ERAs in lung disease have been designed to evaluate the effects of endothelin blockade on lung fibrosis and have not specifically included patients with PH-LD.

BUILD 3 (Bosentan Use in Interstitial Lung Disease) was a large, randomized trial of bosentan to reduce the rate of IPF worsening or death. Results of BUILD 3 showed no significant difference in the primary end point of rate of IPF worsening or death in the 407 patients treated with bosentan versus the 209 in the placebo group. Another study evaluated the effects of bosentan on exercise capacity in patients with severe or very severe COPD; at the end of 12 weeks, only 16 of 20 patients randomized to bosentan remained in the treatment group with the remainder dropping out because of adverse effects.¹⁶⁸ There was no difference in exercise capacity in the bosentan-treated group compared to the placebo group, and, in addition, there was a significant reduction in arterial oxygenation and quality of life in the bosentan-treated patients.

In Artemis-IPF, the largest study of ET_A receptor antagonists in the treatment of IPF, ambrisentan was studied in patients with IPF with minimal lung fibrosis.¹⁶³ The study was terminated early because interim analysis suggested a low likelihood of meeting the primary end point. Analysis of data from patients who were enrolled showed that those in the ambrisentan group were more likely than control

subjects to experience disease progression (27.4% vs. 17.2% in the placebo group); this end point was primarily driven by higher rates of hospitalization in the ambrisentan group.

The effect of macitentan on forced vital capacity was studied in patients with IPF in the MUSIC trial, in which 178 subjects were randomized to macitentan or placebo. Hemodynamic assessments were not reported in this study. After 12 months there was no difference in change from baseline forced vital capacity, but there was a trend toward a higher rate of worsening of IPF in the macitentan group.¹⁶⁴

In summary, in patients with lung disease no benefits to treatment with ERAs have been demonstrated, and the Artemis-IPF and MUSIC studies show ERAs may be harmful in this population. From these findings we conclude that ERAs should not be used to treat PH-LD, and further studies of ET_A receptor antagonists in patients with lung disease seem unlikely.

Prostacyclin and Its Analogues. Prostanoids such as epoprostenol are potent pulmonary vasodilators normally synthesized by the pulmonary vascular endothelium, and exogenous prostanoids have a central role in the treatment of PAH.¹⁶⁹ Studies in animals and humans have shown that hypoxemia results in relative prostanoid deficiency^{170,171}; however, studies in patients have not found treatment with prostanoids to be beneficial in PH-LD.

Intravenous epoprostenol was studied in a small number of patients with respiratory failure secondary to COPD. Those treated with epoprostenol experienced significant reductions in arterial PO_2 , most likely from nonselective pulmonary and systemic vasodilatation, resulting in a worsening ventilation-perfusion relationship.¹⁷²

Studies of inhalational prostanoids were performed because it was thought they might cause less nonselective pulmonary vasodilation, preserving ventilation-perfusion relationships and minimizing hypoxemia. Beneficial effects using inhaled prostanoids were shown in several early trials. In one small study, treatment with aerosolized iloprost resulted in preferential pulmonary vasodilation and significant reduction in $P\bar{P}A$ and PVR.¹⁷³ Another study evaluated the effects of a single dose of inhaled iloprost in 10 patients with PH-COPD and right ventricular abnormalities; patients had a statistically significant improvement of 49.8 m on the 6MWD without a significant change in arterial PO_2 and without adverse hemodynamic effects.¹⁷⁴

The same beneficial effects of inhaled prostanoids were not seen in a more recent randomized double-blind crossover trial of inhaled iloprost in COPD patients with right heart catheterization-confirmed PH.¹⁷⁵ In this study, placebo, 10 μ g and 20 μ g of iloprost were studied in 16 patients during three separate study visits. There was no difference in 6MWD after either dose of iloprost compared to placebo. A significant reduction in arterial SO_2 was seen at rest, and a nonsignificant reduction was seen with exercise. The subgroup of 3 participants with right ventricular abnormalities and more severe PPA did have an improvement in exercise tolerance. Based on these results, inhaled prostanoids should not be routinely used in these patients due to lack of benefit and risk for worsening hypoxemia; however, it is possible that inhaled prostanoids may be beneficial in some highly selected patients with PH-LD. Further

well-designed trials with appropriately selected study populations are needed to clarify the role of inhaled prostanoids in this population.

Nitric Oxide. NO is produced by the enzyme NO synthase within endothelial cells and activates guanylate cyclase, increasing smooth muscle cell cyclic guanosine monophosphate, which causes pulmonary vasodilation.^{176,177} A possible role in the treatment of PH-LD has been suggested based on data demonstrating that NO reverses hypoxic pulmonary vasoconstriction in healthy volunteers.^{178,179} Similar to inhaled prostanoids, inhaled NO would be expected to cause less nonselective dilation of the pulmonary vasculature and less ventilation-perfusion mismatch. Furthermore, inhaled NO is inactivated before it reaches the systemic circulation so that less systemic hemodynamic effects would be expected. Only limited, conflicting data are available regarding the effects of NO on hypoxemia in advanced COPD; one small study reported a decrease¹⁸⁰ and another no change¹⁸¹ in arterial PO_2 after inhaled NO. However, because treatment with NO is technically challenging, costly, and associated with a variety of potential adverse effects, clinical use remains impractical at this time.

Phosphodiesterase Type 5 Antagonists. Sildenafil and tadalafil are selective inhibitors of cyclic guanosine monophosphate-specific phosphodiesterase type 5 and cause pulmonary arteriolar smooth muscle cell relaxation and vasodilation. Additionally, sildenafil has antifibrotic activity that has been tested in patients with lung disease.

The acute effects of sildenafil on hemodynamics and oxygenation were studied at rest and with exercise in 20 patients with COPD and mild PH after a single dose of 20 mg or 40 mg of sildenafil.¹⁶¹ There was a significant 21% reduction in resting PPA 1 hour after sildenafil that was accompanied by worsening gas exchange with a reduction in arterial PO_2 of 9%. A similar reduction in PPA was seen during exercise with no significant change in oxygenation; concomitant studies showed that worsening hypoxemia was related to worsening of ventilation-perfusion matching after sildenafil.

Three studies have attempted to address the effects of sildenafil on exercise tolerance in patients with COPD. In the first, sildenafil was administered to 15 COPD patients for 3 months; compared to baseline, there was no difference in the right ventricular stroke volume measured by MRI or in exercise tolerance measured by cardiopulmonary exercise testing and the 6MWD.¹⁸² The effects of sildenafil on exercise capacity were studied in 10 patients in a randomized double-blind placebo-controlled crossover study.¹⁸³ Patients with PH were specifically excluded from this study. After 14 days of sildenafil treatment, there was no difference in exercise capacity, but there was worsening of oxygenation and quality of life with increasing symptoms and adverse events in the sildenafil group. Another study randomized 63 patients with COPD and moderate PH documented by echocardiography to treatment with sildenafil for 3 months

during pulmonary rehabilitation; in this study sildenafil had no effect on exercise capacity or oxygenation.¹⁸⁴

The acute effects of sildenafil have also been evaluated in patients with interstitial lung disease. Sixteen hospitalized patients with pulmonary fibrosis were treated with inhaled NO and then randomized to receive open-label intravenous epoprostenol (mean dose 8 ng/kg/min) or a single dose of oral sildenafil 50 mg.¹⁶² All three agents reduced the PVR index to a similar extent. However, only inhaled NO and sildenafil reduced the PVR-to-SVR ratio. Intravenous epoprostenol also decreased mean systemic arterial pressure and PO_2 values, owing to ventilation-perfusion mismatching. By contrast, during treatment with inhaled NO and sildenafil, ventilation-perfusion matching was maintained. Therefore, among patients in this study, sildenafil exerted a selective pulmonary arterial vasodilatory effect without worsening hypoxemia.

The effects of sildenafil on exercise tolerance in patients with PH-IPF were examined in two studies. In one small open-label study 14 patients with IPF and mild PH received sildenafil 20 to 50 mg three times daily for 12 weeks.¹⁸⁵ At the end of the study, of the 11 patients who completed the 6MWD, 9 demonstrated an improvement in the mean 6MWD of 49 m (90% confidence interval, 17.5 to 84 m). The largest study of sildenafil in patients with IPF to date was STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis).¹⁸⁶ In this study, patients with IPF were randomized to either sildenafil ($n = 89$) or placebo ($n = 91$) for 12 weeks of treatment without any assessment for the presence or severity of PH. The primary end point of improvement in 6MWD was not met; however, patients taking sildenafil had improved dyspnea, quality of life, and less deterioration in oxygenation.

Overall, the results of these studies are highly variable but suggest that in certain patients with lung disease sildenafil might confer some early hemodynamic and symptomatic improvement, potentially at the expense of worsening ventilation-perfusion matching and worsening oxygenation and without any clear long-term benefits. Further well-designed studies are needed to determine if there is a role for these agents in PH-LD.

Riociguat. Riociguat is a soluble guanylate cyclase agonist approved by the Food and Drug Administration in 2013 for the treatment of PAH that was studied in patients with PH-LD. In an open-label trial, riociguat was studied in 23 patients with interstitial lung disease who also had PH with a PPA above 30 mm Hg and no more than mild airflow obstruction. At 12 weeks there were small but statistically significant improvements in cardiac output, PVR, and SVR compared to baseline. The PVR-to-SVR ratio remained largely unchanged, and the PPA was increased in some patients, suggestive of an increase in blood flow that may be attributable to reduction in the SVR. There was also statistically significant worsening of oxygenation. These findings of no improvement in hemodynamics and worsening oxygenation suggest that riociguat should not be considered in patients with PH-LD.

Improvement in RV performance is best accomplished not only by correcting acidemia, but also by reducing the afterload facing the RV (i.e., reducing \overline{PPA}). Correction of arterial hypoxemia through the administration of an increased concentration of oxygen lowers PPA in patients with hypoxic pulmonary vasoconstriction. Improvement in alveolar ventilation with intubation and mechanical ventilation helps eliminate the acute hypercapnia and acidemia that depress myocardial contractility.

In the setting of severe acute RV decompensation with hypoperfusion, low-dose intravenous infusion of dopamine and dobutamine (1 to 2 mg/kg/min) may improve cardiac output, blood pressure, and renal perfusion. Oxygen and dopamine have been shown to be equipotent renal vasodilators in hypoxic COPD. Low-dose dopamine infusion (2 to 5 mg/kg/min) can increase cardiac output, reduce PVR, and improve oxygen delivery.¹⁸⁷ Higher infusions of dopamine (10 mg/kg/min) have been shown to increase diaphragmatic blood flow and contraction.¹⁸⁸ Although they are effective in acute decompensated RV failure, the value of these agents in chronic cor pulmonale is yet to be determined.

Key Points

- Pulmonary hypertension is present in approximately 25% of patients with advanced lung disease and is associated with significantly worsened symptoms and functional impairment and with increased morbidity and mortality.
- The pathogenesis of pulmonary hypertension due to lung disease involves combinations of hypoxic pulmonary vasoconstriction and pulmonary vascular remodeling, which are related to anatomic restriction and/or obliteration of the pulmonary vascular bed from alveolar destruction, fibrosis, inflammation, thrombosis, and the effects of mitogenic mediators specific to the underlying lung disease.
- The diagnostic evaluation of patients with pulmonary hypertension due to lung disease should include a comprehensive evaluation to identify any other medical conditions that can elevate pulmonary arterial pressure, including sleep-disordered breathing and chronic thromboembolic pulmonary hypertension.
- The optimal approach to management of patients with pulmonary hypertension due to lung disease and

cor pulmonale includes aggressive treatment of the underlying lung disease and administration of supplemental oxygen.

- Currently there are no U.S. Food and Drug Administration–approved therapies for the treatment of pulmonary hypertension due to lung disease, apart from the administration of oxygen; accordingly, early referral for evaluation of lung transplantation is important, and, if specific treatment for pulmonary hypertension is warranted, expert consultation before initiating therapy is recommended.

Complete reference list available at [ExpertConsult](#).

Key Readings

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INTRODUCTION AND DEFINITIONS**CLASSIFICATION****EPIDEMIOLOGY****NORMAL VASCULAR ANATOMY AND HISTOLOGY****HISTOPATHOLOGY OF VASCULITIS****PATHOGENESIS AND ETIOLOGY****INITIAL DIAGNOSIS**

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INTRODUCTION AND DEFINITIONS

Pulmonary vasculitis is a general term that encompasses a wide variety of individual disease entities, all of which share a unifying finding of inflammation and destruction of blood vessels within the lung. More specifically, these entities are characterized pathologically by the presence of a variety of types of cellular infiltration within vessel walls, resulting in vessel destruction, and ultimately tissue necrosis. The clinical features of a specific disorder are determined by the site, size, and type of vessel involved as well as the relative amounts of vessel inflammation, destruction, and tissue necrosis. While simple to define, the recognition, diagnosis, and management of the pulmonary vasculitides are among the most demanding challenges in medicine. Protean in their presentation and variable in their clinical evolution, their signs and symptoms fully overlap with infection, adverse medication reaction, connective tissue disease, and malignancy. Even in patients with a known vasculitis, separating active disease from complicating infection, drug toxicity, or some combination thereof, will challenge the most skilled physician. Amplifying the problem, these diseases are often deadly; even when appropriately treated, the long-term survival among patients with *antineutrophil cytoplasmic antibody positive* (ANCA)-associated vasculitis (AAV) is considerably less than for the general population—88% survival at 1 year and 78% survival at 5 years, or a relative mortality risk of 2.6.¹ Despite these hurdles, the astute clinician can make the diagnosis, initiate and manage therapy, and minimize complications by keeping some broad concepts in mind.

CLASSIFICATION

The major clinical benefit of classifying the vasculitides is to provide a framework that allows for an appreciation of the presenting features of disease. The most current broadly accepted system is the 2012 Revised International Chapel

Hill Consensus Conference nomenclature,² which is based on clinicopathologic presentations rather than etiology or disease mechanism (Table 60-1). It is important to recall that this classification system cannot be used to inform diagnosis or management. *The diagnosis of vasculitis relies upon the bedside clinician recognizing patterns of disease made up of specific clinical, laboratory, imaging, and pathologic features.* There are no strict classification criteria or clinical diagnostic guidelines. It is up to the clinician to determine whether or not the preponderance of the data supports the diagnosis of a pulmonary vasculitis.

Nevertheless, there are still useful paradigms by which to organize one's diagnostic approach. A commonly used scheme uses vessel size (large, medium, and small). The large vessels are made up of the aorta, its largest branches (e.g., carotid, cerebral, iliac, subclavian, and femoral vessels) and the main pulmonary artery. The medium-sized vessels are made up of the main visceral arteries (e.g., renal, hepatic, coronary, and mesenteric vessels), whereas the small vessels are made up of arterioles, capillaries, and venules. There can be overlap, because the small and large vessel vasculitides sometimes involve medium-sized arteries, but large and medium vessel vasculitides generally do not involve vessels smaller than arteries.

A second classification scheme uses ANCA. The identification of these antibodies in the 1980s revolutionized thinking regarding diagnosis and pathogenesis (see later). The vasculitides that are most commonly encountered in the practice of pulmonary medicine, the primary, idiopathic small-vessel vasculitides, are also ANCA-positive and described as AAV. These include *granulomatosis with polyangiitis* (GPA) (formerly known as Wegener granulomatosis), *eosinophilic granulomatosis with polyangiitis* (EGPA) (formerly known as Churg-Strauss syndrome), and *microscopic polyangiitis* (MPA). A third approach to classification is sometimes used, defining the vasculitides by the presence or absence of granulomatous inflammation. Two of the AAVs—GPA and EGPA—as well as the large vessel vasculitides, Takayasu arteritis and *giant cell arteritis* (GCA), are characterized by the presence of granulomatous inflammation.

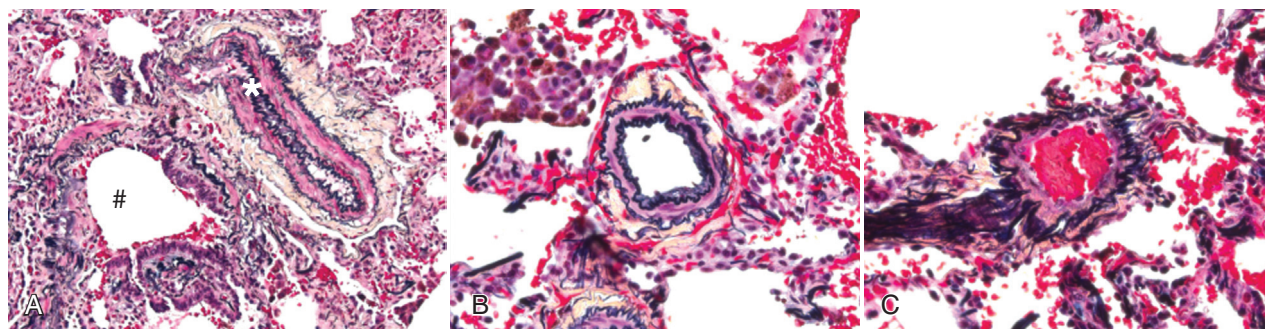


Figure 60-1 Normal appearance of pulmonary artery, small muscular pulmonary artery, and vein. **A**, Pentachrome (Movat) stain illustrating the relationship between pulmonary artery (*) and bronchiole (#). **B**, Muscular pulmonary artery in the peripheral lung showing internal and external elastic lamina in black (pentachrome/Movat stain). **C**, Small pulmonary vein in peripheral lung showing one elastic lamina in black (pentachrome/Movat stain).

Table 60-1 Classification of Vasculitis^{1,143,144}

PRIMARY IDIOPATHIC

Small Vessel

Granulomatosis with polyangiitis (Wegener granulomatosis)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis)
Microscopic polyangiitis
Idiopathic pauci-immune glomerulonephritis
Idiopathic capillaritis

Medium Vessel

Polyarteritis nodosa
Kawasaki disease

Large Vessel

Takayasu arteritis
Giant cell arteritis

PRIMARY IMMUNE COMPLEX MEDIATED

Anti-glomerular basement membrane disease (Goodpasture syndrome)
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulinemic vasculitis
Hypocomplementemic urticarial vasculitis

SECONDARY VASCULITIS

Classic autoimmune disease
 Systemic lupus erythematosus
 Rheumatoid arthritis
 Antiphospholipid antibody syndrome
Infection
Paraneoplastic
Drug-induced (e.g., propylthiouracil)
Inflammatory bowel disease

European populations. Among the individual disorders, the annual incidence of GPA ranges from 4.9 to 10.5 per million, of EGPA from 0.5 to 4.2 per million, and of MPA from 2.7 to 11.6 per million. The prevalence of GPA ranges from 24 to 157 per million, of EGPA from 7 to 38 per million, and of MPA from 0 to 66 per million. Among the secondary vasculitides, the best data are for rheumatoid arthritis-associated vasculitis (incidence of 12.5 per million), although with the advent of biologic therapy, this rate appears to have decreased dramatically. Finally, the incidence of *systemic lupus erythematosus* (SLE)-associated vasculitis is 3.6 per million.³

NORMAL VASCULAR ANATOMY AND HISTOLOGY

In a group of diseases pathologically defined by abnormalities of the vasculature, understanding the normal organization and location of the arterial and venous blood supplies in the lung is useful in appreciating their clinical features. The lung has a dual blood supply: the pulmonary and the bronchial circulations. The bronchial arteries arise from the systemic circulation (aorta and intercostal arteries) and form a plexus in the bronchial wall. The bronchial veins associate closely with the bronchial arteries, although neither is commonly affected in the pulmonary vasculitides (see Chapter 1).

During embryogenesis, the pulmonary arterial system forms in tandem with the branching bronchial buds and is recognized on histologic examination by its close proximity to the corresponding bronchi or bronchiole (Fig. 60-1A; see also Fig. 1-17). In the normal lung, arteries and adjacent airways are similar in size to bronchi and bronchioles, so marked differences can be an indication of pathology.⁴ The arterial system consists of four components: elastic arteries, muscular arteries, arterioles, and capillaries. *Elastic arteries* are larger than 0.5 to 1 mm in diameter and can be recognized macroscopically. They are composed of an endothelial cell lining layer, a smooth muscle medial layer, and have well-developed, multiple elastic laminae. *Muscular arteries* are between 100 and 500 μ m in diameter, and are composed of an endothelial cell lining, a smooth muscle media bound by two elastic laminae (inner and outer), and a collagenous adventitia. The smooth muscle layer progressively

EPIDEMIOLOGY

The true overall incidence and prevalence of vasculitis is difficult to gauge, in that all of the available epidemiologic studies contain significant flaws that limit their applicability. The available data are neither geographically nor ethnically diverse, and the case definitions and acquisition methodology vary from study to study. With these caveats in mind, GCA is the most frequently recognized systemic vasculitis with an annual incidence of 150 to 350 per million persons older than age 50 years. Persons of Nordic heritage appear at particularly high risk, especially in older age. The primary systemic vasculitides have an overall prevalence estimated at between 90 and 300 per million in

decreases in thickness until one reaches the arterioles. *Arterioles* are defined by a diameter of less than 100 μm and the absence of a muscular media; however, these can become muscularized in a variety of diseased states. The arterioles connect with capillaries. *Capillaries* are characterized by the presence of a single layer of endothelial cells and an underlying basement membrane. They form part of the alveolar septa, and are the most common vessel affected in pulmonary vasculitis. On hematoxylin and eosin stains of surgical lung biopsies, identifying the capillaries is difficult because a number of cells—endothelial cells, fibroblasts, and mononuclear inflammatory cells—all are normal occupants of the alveolar septa.

The location of the pulmonary veins in the mature lung is typically away from the bronchi and within interlobular septa, because the embryonic pulmonary veins form branches that grow into the mesenchyme surrounding the lung buds. Although pulmonary veins can be distinguished from pulmonary arteries by their single elastic lamina (see Fig. 60-1B and C), in the diseased lung, there can be reduplication of the elastic lamina, causing “arterialization” of the pulmonary veins, and anatomic location may be the only indicator of vessel type.

HISTOPATHOLOGY OF VASCULITIS

Although the diagnosis of vasculitis never relies on histopathology alone, both the diagnosis and subclassification can be suggested based on the size and location of the affected vessels (Fig. 60-2). The findings common to all the pulmonary vasculitides are inflammatory cell infiltration (inflammation) of the vessel wall with destruction of elastic laminae (in the case of arteries and veins) and often, an accompanying fibrinoid necrosis. The lining endothelial cells may show abnormalities, with subendothelial inflammation (endothelialitis), cellular disruption and even loss of endothelial cells. The type of inflammation can vary widely; neutrophilic, eosinophilic, lymphoplasmacytic, or mixed infiltrates can all be seen. Granulomatous inflammation, consisting of poorly formed granulomas or multinucleated giant cells and/or epithelioid histiocytes, is of particular

importance because one level of classification is based on its presence or absence (see earlier).

The term *capillaritis* is used to describe vasculitis of capillaries; however, it is often difficult to identify the capillary on routine hematoxylin and eosin stains, much less the endothelial disruption necessary to make the diagnosis. Therefore identifying neutrophils and nuclear debris (evidence of apoptosis) within alveolar septal walls is used as an indirect sign of capillaritis.

Not only do the size and type of vessel affected provide important information, but changes to the associated lung parenchyma provide additional clues. For example, a nodular parenchymal infiltrate is commonly seen in GPA, with microabscesses, necrosis, eosinophilic pneumonia, organizing pneumonia and/or hemorrhage. The specific pathologic findings associated with each entity are discussed in more detail later.

PATHOGENESIS AND ETIOLOGY

Most of the vasculitic syndromes are hypothesized to be mediated by immunopathogenic mechanisms that arise in response to antigenic stimuli. Why some patients develop vasculitis in response to a particular stimulus, while others do not, is unknown. The etiology is likely multifactorial, including genetic predisposition, environmental exposures, and individual immune responses. A recent large genome-wide association study found both major-histocompatibility complex and non-major histocompatibility complex associations with AAV, confirming a genetic contribution to disease development.⁵ Three broadly defined mechanisms have been proposed: pathogenic autoantibody formation with neutrophil activation and endothelial damage, immune complex deposition, and pathogenic lymphocyte responses. For each of these mechanisms, some combination of the direct immunologic attack and endothelial and vascular wall response appears responsible for the subsequent clinical and pathologic findings.⁶

A large variety of autoantibodies have been described, including the antiglomerular basement membrane (collagen type IV) antibodies seen in anti-glomerular basement membrane disease, antiendothelial cell antibodies, anti-laminin antibodies, antiphospholipid (e.g., anti-beta-2

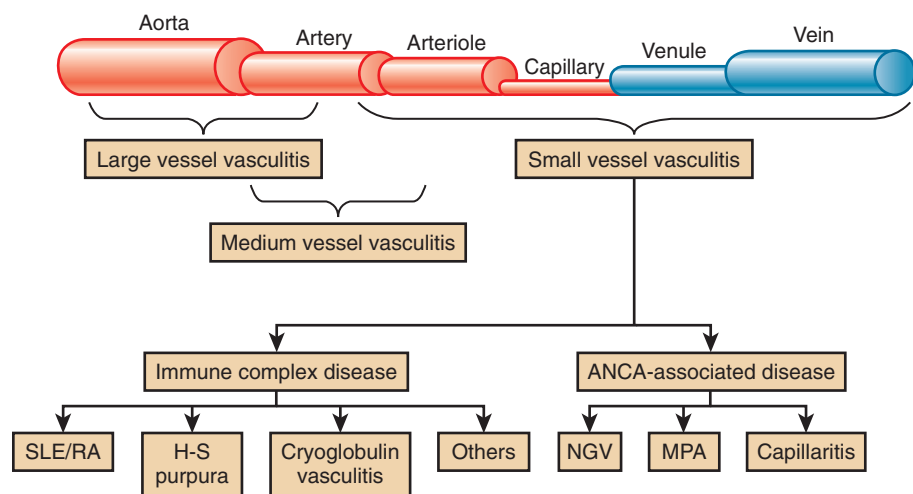


Figure 60-2 Relationship between vessel size and mechanism. The small vessel vasculitides are diagrammed as immune complex disease and ANCA-associated disease. ANCA, antineutrophil cytoplasmic antibodies; H-S, Henoch-Schönlein; MPA, microscopic polyangiitis; NGV, necrotizing granulomatous vasculitis; SLE/RA, systemic lupus erythematosus/rheumatoid arthritis.

glycoprotein I and anticardiolipin) antibodies, and ANCA, among others. Of these, the best studied mechanism is that proposed for the AAVs, especially GPA. While the clinical syndrome was described in the 1930s,^{7,8,9} it was not until 1982 that specific autoantibodies, now known as ANCA, were described.¹⁰ While the role of ANCA in the pathogenesis of disease remains to be fully elucidated, there is compelling in vitro, animal model and clinical evidence supporting a key role for the pathogenicity of ANCA. Some clinical data suggest that, while not sufficient to cause disease alone, the presence of ANCA appears to be required for the development or recurrence of systemic disease. These data include (1) the link between the presence of these autoantibodies, the development of systemic vasculitic complications, and prognosis; (2) the effectiveness of the anti-CD20 monoclonal antibody rituximab at reducing ANCA titers and controlling disease activity; and (3) the finding that patients who become ANCA negative are at low risk for clinical relapse.

Mechanistically, the majority of the clinically significant ANCAs are directed against microbicidal components used by neutrophils in host defense. These antibodies have been shown to have significant proinflammatory effects with activation of neutrophils, monocytes, and endothelial cells.¹¹ ANCA stimulate the release of chemokines from neutrophils, monocytes, and endothelial cells, enhance the expression of cell adhesion molecules on endothelium, and activate primed neutrophils to release proteolytic enzymes and oxygen radicals.^{12,13} Each of these steps can contribute to the vascular and tissue damage seen. Moreover, an animal model has demonstrated the ability of *antimyeloperoxidase antibodies* (anti-MPO) to induce necrotizing vasculitis, further strengthening the link between antibody formation and disease development.^{14,15}

The trigger for ANCA production and persistence is poorly understood. A role for active infection/inflammation in the disease pathophysiology has been proposed because there is evidence that chronic or concurrent infections can lead to disease exacerbation or relapse.¹⁶⁻¹⁸ ANCA positivity has also been directed against a variety of antigens seen with viral, fungal, bacterial, and protozoal infection, as well as subacute bacterial endocarditis and cystic fibrosis.^{19,20} It has been hypothesized that infections may give rise to ANCA through molecular mimicry and contribute to their persistence through T- and B-cell stimulation by microbial superantigens. For example, some patients with AAV have been shown to elaborate antibodies against *lysosome-associated membrane protein 2* (LAMP2) found in neutrophils. The LAMP2 protein bears close homology to the bacterial adhesin FimH protein expressed in gram-negative bacteria, and antibodies against LAMP2 and FimH are capable of producing glomerulonephritis in animal models.²¹

Other potential mechanisms for the development of vasculitis include the direct invasion of the vessel wall by pathogenic organisms (e.g., bacterial, mycobacterial, spirochetal, rickettsial, fungal, viral), leading to an acute, direct vasculitic response as well as deposition of circulating immune complexes in the blood vessel wall. This deposition of immune complexes can lead to complement activation, anaphylatoxin production, and mast cell degranulation. Mast cell degranulation leads to release of vasoactive substances and the anaphylatoxins can act as chemotactic

agents for neutrophils, eosinophils, and mononuclear inflammatory cells. The prototypical disease for this mechanism is SLE, in which complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins lead to vascular injury.^{22,23} Other immune complex-mediated vasculitides include rheumatoid vasculitis, Henoch-Schönlein purpura, and cryoglobulinemic vasculitis.

Aberrant lymphocyte responses are hypothesized to contribute to both the granulomatous inflammation seen in GPA and EGPA (T cells) as well as the production of ANCA (B cells). Activated T cells may be found in the peripheral blood of patients with GPA, even when the disease is in remission, and markers of T-cell activation appear to correlate with disease activity.²⁴ Furthermore, there appears to be an increase in Th17-positive T-cell populations (believed to promote autoimmunity) and reduced regulatory T-cell (Treg) functionality, suggesting a loss of tolerance.²⁴⁻²⁷ Finally, there is increased elaboration of Th1 cytokines in patients with GPA (tumor necrosis factor- α , *interleukin* (IL)-1 and IL-8), while there is increased interferon- γ , IL-4, IL-5, and IL-13 in patients with EGPA.^{28,29}

INITIAL DIAGNOSIS

CLINICAL SCENARIOS SUGGESTIVE OF VASCULITIS

The importance of the initial history in the evaluation of a patient with suspected vasculitis cannot be overemphasized. Symptoms that initially seem unrelated and of only minor importance may need to be explored more fully because both vasculitis and its mimics (e.g., connective tissue diseases, infection, malignancy, drug toxicity) present with and evolve through a variety of confusing clinical manifestations. Similarly, a careful physical examination may reveal otherwise asymptomatic disease that suggests the presence of a systemic disorder. To put some order to this, the identification of particular clinical scenarios can suggest the presence of a systemic vasculitis.³⁰

Destructive Upper Airway Lesions

Chronic refractory sinusitis in which primary infectious, allergic, and anatomic causes have been excluded and/or when destructive soft tissue or bone lesions or chronic ulcerative lesions are present can raise suspicion of an underlying vasculitis.

Chest Imaging Findings of Cavitory or Nodular Disease

Whereas a wide variety of nonspecific findings may be seen on chest imaging, the presence of nodular or cavitory disease should raise one's suspicion. While infection and malignancy are the most common explanations, in the correct clinical setting a vasculitis, particularly an AAV, should be considered. Illustrating this point, cavities are found in 35% to 50% and nodules in 55% to 70% of patients with GPA.^{31,32}

Diffuse Alveolar Hemorrhage (see Chapter 67)

Diffuse alveolar hemorrhage (DAH) refers to the presence of diffuse intra-alveolar bleeding generally from the alveolar

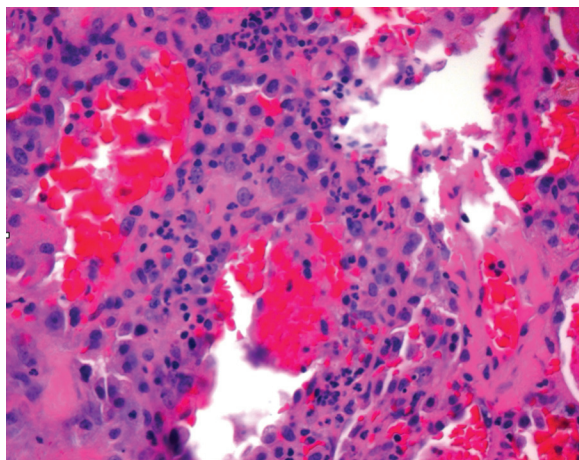


Figure 60-3 Capillaritis showing disruption of the alveolar septa by infiltrates of neutrophils and nuclear debris. The septal borders are vague, indicating wall damage.

capillaries and less frequently from the precapillary arterioles and postcapillary venules. While patients “classically” present with hemoptysis, diffuse alveolar opacities, and a drop in hematocrit, DAH must be considered in all patients with unexplained air space disease. Hemoptysis can be difficult to identify because it is often only intermittent and is not seen at all in up to one third of patients. The alveolar opacities do not have to be diffuse, and a drop in hematocrit can be difficult to document. Therefore DAH should be considered in patients with otherwise unexplained diffuse alveolar opacities, particularly when these findings complicate symptoms of a connective tissue disease or new onset renal insufficiency. While an increase in the diffusion capacity of more than 30% over baseline can be suggestive, it is rare to obtain a diffusing capacity in an acutely ill patient.

DAH is diagnosed by bronchoalveolar lavage. With the bronchoscope in wedge position, serial aliquots (30 to 60 mL in volume) of sterile saline are instilled and aspirated (for a total volume of 100 to 300 mL). If the serial aliquots of fluid reveal an increasingly hemorrhagic or, at a minimum, a persistently bloody return, then the diagnosis of DAH is made (see Fig. 67-3). The finding of DAH is not diagnostic of vasculitis. DAH can be caused by diseases associated with the histopathologic finding of capillaritis (including the primary idiopathic and secondary vasculitides) (Fig. 60-3), as well as by diseases with diffuse alveolar damage and bland hemorrhage (Table 60-2). When DAH is a complication of an AAV, capillaritis is almost always found; however, bland hemorrhage may be the only finding, particularly if treatment has been initiated. When DAH with pathologic pulmonary capillaritis is the only clinical manifestation of a vasculitis, the term *idiopathic pauci-immune pulmonary capillaritis* is used, and this syndrome is classified in the family of primary idiopathic small-vessel vasculitides regardless of ANCA status.

Acute Glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is defined by the identification of an active urinary sediment on urinalysis, including hematuria (especially with dysmorphic red cells), red cell casts, and proteinuria (>500 mg/d) in the setting of a rising blood urea nitrogen and serum creatinine. The microscopic examination of the urine needs to be

Table 60-2 Causes of Diffuse Alveolar Hemorrhage^{145,146}

WITH HISTOPATHOLOGIC CAPILLARITIS

Classic vasculitides

- Primary idiopathic small vessel vasculitis
- ANCA-associated—GPA, EGPA, MPA
- Isolated pauci-immune pulmonary capillaritis

Immune complex mediated

- Anti-glomerular basement membrane disease (Goodpasture syndrome)
- IgA vasculitis (Henoch-Schönlein purpura)
- Cryoglobulinemic vasculitis

Secondary vasculitis

- Classic autoimmune disease
- Systemic lupus erythematosus
- Other (e.g., rheumatoid arthritis, scleroderma)
- Primary anti-phospholipid antibody syndrome

Hematopoietic stem cell transplantation

- Drug-associated disease (chemotherapeutic agents, diphenylhydantoin)

Behçet disease

WITHOUT CAPILLARITIS (BLAND HEMORRHAGE)

Idiopathic pulmonary hemosiderosis

- Coagulopathy
- Mitral stenosis
- Inhalation injury
- Drug-associated disease (chemotherapeutic agents, penicillamine, trimellitic anhydride, amiodarone, nitrofurantoin)

ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

performed on a fresh urine sample because red cell casts and dysmorphic red cells degenerate within 30 to 60 minutes in a freshly voided sample. Once RPGN is identified, the differential diagnosis includes AAV, idiopathic pauci-immune glomerulonephritis (isolated small-vessel renal vasculitis), SLE, Goodpasture syndrome, post-infectious glomerulonephritis, IgA nephropathy, Henoch-Schönlein purpura, essential cryoglobulinemia, and membranoproliferative glomerulonephritis.³³⁻³⁶

Pulmonary-Renal Syndrome

Pulmonary-renal syndromes are classically defined as the presence of both DAH and RPGN. However, whenever a destructive airway lesion or chest imaging finding of nodules or cavities is seen together with renal insufficiency, vasculitis should also be considered. When this happens, the primary differential includes the AAVs, Goodpasture syndrome, and SLE.

Palpable Purpura

The presence of palpable purpura on physical examination implies a small vessel, cutaneous vasculitis.³⁷ The most common explanation is a cutaneous (hypersensitivity) vasculitis secondary to a drug reaction; however, the AAV, cryoglobulinemia, connective tissue diseases, infections, and malignancy should all be considered.

Mononeuritis Multiplex

Defined by the development of abnormalities in two or more peripheral nerve distributions, mononeuritis multiplex should raise particular suspicion.^{38,39} A variety of other central or peripheral nervous system symptoms can also be seen, including pain, numbness, paresthesias, weakness, or

loss of function (e.g., sudden onset of a foot drop or wrist drop).

Multisystem Disease

Unusual combinations of signs and symptoms that involve multiple organ systems either simultaneously or over time could raise the possibility of a vasculitis. This requires a high index of suspicion from the clinician because items such as constitutional symptoms (e.g., fever of unknown origin), unusual “rashes,” migratory polyarthritides, or “chronic sinus disease” may be relevant when the primary clinical presentation is breathlessness, renal failure, or abnormal findings on chest imaging.

SPECIFIC TESTING

Antineutrophil Cytoplasmic Antibodies

ANCA were first described by Davies and coworkers¹⁰ in the early 1980s in patients with glomerulonephritis and GPA, and were recognized by a pattern of diffuse immunofluorescent staining of ethanol-fixed neutrophils. At nearly the same time, a pattern of perinuclear immunofluorescent staining of ethanol-fixed neutrophils was described in patients with MPA and pauci-immune glomerulonephritis.¹⁰ Currently, three specific *indirect immunofluorescent* (IIF) staining patterns are described: *cytoplasmic* (c-ANCA) (Fig. 60-4A), *perinuclear* (p-ANCA) (see Fig. 60-4B), and *atypical* (a-ANCA). c-ANCA are primarily, but not exclusively, directed against *proteinase 3* (PR3, in azurophilic granules), while the p-ANCA are most commonly directed against myeloperoxidase (MPO, also in azurophilic granules), but with a much wider group of potential intracellular targets. Specific *enzyme-linked immunosorbent assay* (ELISA) testing for PR3 and MPO are commercially available and of considerable clinical utility. These antibodies are closely associated with the small-vessel vasculitides of the lung, GPA, EGPA, and MPA. These “ANCA-associated small-vessel vasculitides” all involve the small vessels and share a number of clinical features including, when present, pauci-immune, crescentic and focal necrotizing glomerulonephritis. However, while ANCA positivity is common in these disorders, it is by no means universal.

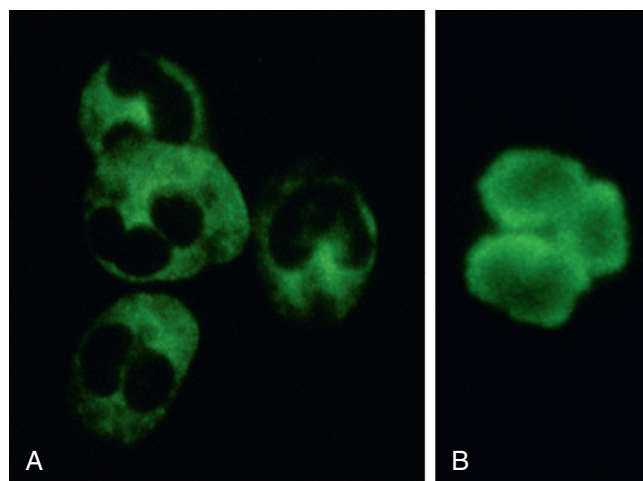


Figure 60-4 Indirect immunofluorescent staining patterns of c-ANCA (A) and p-ANCA (B).

The diagnostic utility of ANCA testing is dependent upon the sensitivity, specificity, and positive predictive value of c-ANCA (or anti-PR3) for GPA and p-ANCA (or anti-MPO) for MPA and EGPA. When applied indiscriminately, the positive predictive value of the testing declines dramatically. Mandl and associates⁴⁰ demonstrated that by using clinical guidelines to identify at-risk patients, the positive predictive value of the tests increased without reducing sensitivity. While ANCA testing alone or PR3 and MPO ELISA testing alone are used by many centers as their initial screening test, the combination of ANCA IIF testing plus ELISA testing maximizes their sensitivity.⁴⁰⁻⁴⁴

With the caveats noted earlier, c-ANCA is highly sensitive (90% to 95%) in active, systemic GPA but less so (65% to 85% sensitive) in single organ-limited disease, and even less so for GPA in remission.⁴⁵ Specificity is approximately 90%. In the proper clinical setting, with a very high pretest probability of disease, a positive c-ANCA/anti-PR3 has sufficient positive predictive value to obviate the necessity of a biopsy.⁴⁶ On the other hand, p-ANCA and anti-MPO generally lack sufficient sensitivity and may provide no more than suggestive evidence of EGPA, MPA, or pauci-immune RPGN, because it can also be found in rheumatoid arthritis, Goodpasture syndrome, autoimmune hepatitis, inflammatory bowel disease, and a wide variety of other clinical circumstances.⁴³

Considerable attention has been focused on the utility of ANCA to assess disease activity, particularly the role of rising ANCA titers in predicting relapse.⁴⁸ Unfortunately there appears to be no clear relationship between antibody titers and disease activity. In a prospective interventional study in which PR3-ANCA levels were routinely obtained, decreasing ANCA titers did not predict time to remission and increasing titers did not predict relapse. Increasing titers were associated with a relapse in only 40% of patients over a 12-month period. Therefore the decision to modify therapy in patients with ANCA-associated vasculitis must be a clinical decision based on clinical evidence of disease activity independent of ANCA titers.⁴⁵

Based on high-quality evidence, recommendations have been offered that ANCA testing by IIF should be performed in the appropriate clinical context to detect the labeling pattern and that all positive samples be tested for anti-PR3 and MPO specificity.⁴⁹ A positive test for c-ANCA targeted to PR3 or p-ANCA targeted to MPO has a high sensitivity and specificity for the diagnosis of AAV. It should also be recognized that the absence of a positive test does not rule out a diagnosis of vasculitis. Indeed, while the concept of “ANCA-associated” applies to the patient population as a whole and has implications for pathogenesis, it must be emphasized that an individual patient may well be ANCA (or PR3/MPO) negative and still have what we describe as an AAV. ANCA testing should be performed in accredited laboratories that participate in external quality control programs and undergo regular review of laboratory management and staff performing the assays.⁵⁰

OTHER LABORATORY STUDIES

Cultures of blood and other potentially affected organs (when tissue is obtained) should be performed to exclude infection. Routine laboratories (complete blood count with differential, chemistries, liver function tests, blood urea

nitrogen, and creatinine) should be obtained, although the findings are generally nonspecific. An elevated erythrocyte sedimentation rate and elevated C-reactive protein lack specificity but are common findings. Urinalysis with microscopy should be performed on a fresh sample in all patients, because proteinuria and microscopic hematuria are common early findings in GPA and MPA. Anti-GBM antibodies should be obtained in all patients with pulmonary hemorrhage or a pulmonary-renal syndrome. Antinuclear antibodies and rheumatoid factor can be positive, although high titers; especially with the presence of disease-specific antibodies (e.g., dsDNA, SS-A/SS-B, anti-RNP, anti-Scl-70, anti-centromere antibodies, anti-JO-1) favor a connective tissue disease. IgE and circulating eosinophil counts should be obtained when EGPA is being considered.

CHEST IMAGING

Chest radiography and *computed tomography* (CT) findings are often abnormal even in the absence of symptoms, because more than 80% of patients with GPA and EGPA have some radiographic abnormalities. Specific findings are best described in GPA and include nodular opacities (eFig. 60-1) and masses, particularly those that cavitate (eFig. 60-2), diffuse ground-glass opacification (eFig. 60-3) (especially when DAH is a possibility), consolidation (eFigs. 60-4 and 60-5), atelectasis, and airway complications such as stenoses (eFig. 60-6) and ulcerations (eFig. 60-7). Lymphadenopathy (eFig. 60-8) is not common and is more suggestive of infection or malignancy.⁵¹ Patients with EGPA commonly demonstrate patchy, heterogeneous ground-glass opacities or consolidation as well as evidence of airways disease.

OTHER IMAGING STUDIES

CT of the sinuses (see eFig. 60-7) similarly demonstrates abnormalities in a majority (70% to 90%) of patients with GPA and EGPA, and may help identify destructive or ulcerating disease in patients with GPA. Electrocardiograms and echocardiography are useful in identifying cardiac involvement. The heart is involved in only 5% to 15% of patients with GPA but in as many as 30% to 50% of patients with EGPA and potentially carries a high attributable mortality. Routine screening of patients with proven or suspected AAV with electrocardiogram and echocardiography is commonly performed. Additional imaging or functional studies are determined by the clinical scenario and the signs and symptoms present in the individual patient (e.g., abdominal CT, brain CT/MRI, nerve conduction studies).

BRONCHOSCOPY

Bronchoscopy is primarily used to look for malignancy, infection, stenotic or ulcerative upper airway or endobronchial lesions, pulmonary eosinophilia, and alveolar hemorrhage. Bronchoalveolar lavage should be grossly examined for evidence of alveolar hemorrhage, sent for culture (bacterial, fungal, and mycobacterial), cytology, and a differential cell count. Transbronchial biopsies may provide important information that helps exclude infection or malignancy; however, they are rarely useful in making a

positive diagnosis of vasculitis. When Hoffman and colleagues⁵² performed 59 transbronchial biopsies in 48 patients with GPA, only four provided useful diagnostic features. Schnabel and coworkers⁵³ found that transbronchial biopsies provided support for a diagnosis of GPA in only 2 of 17 patients, while otolaryngologic examination and biopsy of the clinically involved areas of the upper respiratory tract yielded useful information in 13 of 19 patients with GPA.

DIAGNOSTIC BIOPSY

While a confident diagnosis may occasionally be made without tissue, diagnostic tissue biopsy remains necessary for a definitive diagnosis. Biopsy of the skin or upper airway is generally safe and these sites are easily accessible, but they less commonly yield diagnostic tissue when compared with a needle biopsy of the kidney or a surgical biopsy of the lung. When Hoffman and colleagues⁵² examined 82 open lung biopsies in patients with small-vessel vasculitis, diagnostic features were found in 90%. Renal biopsy is often performed to determine the cause of an acute glomerulonephritis. Specific features indicative of vasculitis such as granulomatous inflammation or vascular necrosis are rarely found; however, the presence of focal, segmental necrotizing glomerulonephritis without immune deposits (pauci-immune)^{52,54-56} is strongly suggestive of a systemic vasculitis.

It is important to appreciate that the pathologic features of vasculitis often overlap with other inflammatory lesions such as necrotizing *infectious* granulomas. In addition, not all the histopathologic features of vasculitis may be present because of the timing of the biopsy and/or modification of the histology secondary to prior treatment, particularly corticosteroids. Because of this, it is critical for the surgeon, pulmonologist, and pathologist to have a coordinated plan before the biopsy. The clinical differential will dictate the appropriate specimens to collect, including fresh tissue for culture and immunofluorescence (the presence of characteristic immunofluorescence patterns, such as IgA deposition in Henoch-Schönlein purpura, linear IgG deposition in Goodpasture syndrome, and irregular immunoglobulin and complement deposition in SLE can be diagnostic) as well as for formalin-fixation.

SPECIFIC CLINICAL DISORDERS

As systemic disorders, essentially all of the vasculitides can involve the lung. This involvement ranges from diffuse alveolar hemorrhage to cavitary nodules, parenchymal inflammation, pleural disease, vascular aneurysms, and thrombotic and thromboembolic phenomena. A full accounting of each described disorder and its pulmonary manifestations is beyond the scope of this chapter. However, the primary idiopathic small-vessel vasculitides deserve special attention.

GRANULOMATOSIS WITH POLYANGIITIS

GPA is the most common of the ANCA-associated small-vessel vasculitides, arises at any age (generally 40 to 60

years), and equally affects the sexes. It is clinically recognized by its ability to involve the upper airway (e.g., chronic sinusitis and/or otitis, upper airway ulceration and/or structural deformity, subglottic or endobronchial stenosis), lower respiratory tract (e.g., chest symptoms of cough, chest pain, shortness of breath, hemoptysis and/or chest imaging abnormalities), and kidney (e.g., glomerulonephritis) (Table 60-3). However, involvement of all three sites is neither necessary nor common at presentation. For example, even though 80% to 90% of patients ultimately develop renal disease, as few as 40% have renal involvement at time of first presentation.⁵⁷⁻⁵⁹ Constitutional symptoms as well as skin, eye, musculoskeletal, peripheral, and central nervous system disease are common.^{36,57-59} Chest imaging findings are abnormal in most patients, showing alveolar, mixed, or interstitial opacities (eFigs. 60-3 through 60-5), and nodular (see eFig. 60-1) or cavitory disease (see eFig. 60-2).^{31,32} A positive c-ANCA is seen in 90% to 95% of active systemic disease but in only 60% to 65% in limited disease.^{47,60-62} The histopathology on surgical lung biopsy is

dependent on the stage of the disease and whether there has been prior immunomodulatory treatment. Involvement of a small and medium-sized vessel with necrotizing vasculitis with granulomatous inflammation and parenchymal necrosis, often with a geographic appearance, is characteristic (Fig. 60-5A).⁶³⁻⁶⁷ The pathologic manifestations can be divided into major and minor histologic features. The three major features include (1) lung parenchymal necrosis, either in the form of geographic necrosis or neutrophilic microabscesses; (2) vasculitis (generally involving small to medium-sized arteries, but which can also involve veins and capillaries) (see Fig. 60-5B and C); and (3) granulomatous inflammation (see Fig. 60-5D).

Although the inflammation in GPA is typically described as granulomatous, it is often mixed and includes granulomas, giant cells, neutrophils, lymphocytes, plasma cells, histiocytes, and eosinophils. The minor histologic criteria include organizing pneumonia (70% of cases), diffuse alveolar hemorrhage (10% of cases), eosinophilia, and bronchocentric granulomatosis (1% of cases).^{63,68} If the biopsy

Table 60-3 Clinical Findings in the ANCA-Associated Vasculitides

	GPA	EGPA	MPA
Constitutional	Common. Includes fatigue, malaise, fevers, and weight loss.	Common. Weight loss, fatigue, fevers, myalgias and arthralgias.	Very common. Generally precedes renal disease by months.
Pulmonary	70% to 95% of patients with respiratory symptoms or chest imaging abnormalities. Tracheobronchial and endobronchial disease in 10% to 50%.	Asthma essentially universal. Patchy, heterogeneous radiographic opacities in >70%.	10% to 30% with diffuse alveolar hemorrhage.
Renal	50% to 90% of patients.	20% to 50% of patients.	RPGN is almost universal.
Upper airway	70% to 95% of patients. Destructive or ulcerating lesions are suggestive.	Sinusitis, polyposis, and/or rhinitis in ≥ 70% of patients. Generally not destructive.	5% to 30% with sinus disease most common.
Musculoskeletal	Arthralgias, synovitis and myalgias in up to 80%.	Arthralgias and myalgias reported in up to 50%.	Arthralgias and myalgias in at least 50% of patients.
Eyes	25% to 60% of patients. Vision-threatening disease including uveitis, ocular ulcers.	<5%	Up to 30% of patients. May be clinically silent.
Cardiac	5% to 25% of patients. Conduction delays or other electrocardiographic abnormality, systolic or diastolic dysfunction, pericarditis, or coronary artery vasculitis.	30% to 50% of patients and a major cause of mortality. Conduction delays, or other electrocardiographic abnormality, systolic or diastolic dysfunction, pericarditis, or coronary artery vasculitis.	10% to 20%. Congestive heart failure and pericarditis have been described.
Gastrointestinal	<10%	30% to 50% of patients and a major cause of morbidity and mortality. Hemorrhage, abdominal pain, infarct, or perforated viscus.	35% to 55% of patients. Findings similar to polyarteritis nodosa. Pain, bleeding, and ischemia. Rare visceral aneurysms.
Dermatologic	Up to 60%. Palpable purpura, ulcers, nodules or vesicles.	50% to 70% purpura, nodules, papules, leukocytoclastic vasculitis with or without eosinophils.	35% to 60% of patients with purpura common.
Neurologic	Both central and peripheral nervous system involvement.	Mononeuritis multiplex in 50% to 75%. Central nervous system in 5% to 40%.	Mononeuritis multiplex in 10% to 50%.
Chest imaging	Abnormal in >80%. Alveolar, interstitial, or mixed opacities, often with nodular and/or cavitory disease.	Opacities in >70%. Airways disease common (airway wall thickening, hyperinflation).	Opacities in 10% to 30%. Pleural effusions in 5% to 20%.
ANCA	ANCA positive > 90% and c-ANCA/anti-PR3 ELISA positive in > 85% with generalized active disease.	ANCA positive in 30% to 70% with most of these being p-ANCA/anti-MPO positive.	ANCA positive in 50% to 75% with most of these being p-ANCA/anti-MPO positive.

ANCA, antineutrophil cytoplasmic antibody; anti-MPO, antimyeloperoxidase antibodies; anti-PR3, antiproteinase antibodies; EGPA, eosinophilic granulomatosis with polyangiitis; ELISA, enzyme-linked immunosorbent assay; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RPGN, rapidly progressive glomerulonephritis.

Data from references 31, 36, 52, 57, 72, 74, 76, 82, 91, 94, 141, and 147–161.

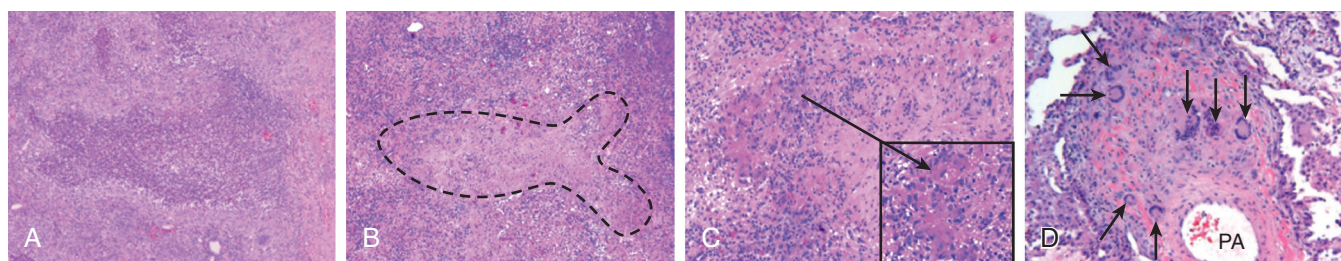


Figure 60-5 Granulomatosis with polyangiitis. **A**, Irregular outlines of geographic necrosis are typical of the parenchymal necrosis found in granulomatosis with polyangiitis. **B**, Low power view of a branching vessel (*dashed line*) demonstrating necrotizing vasculitis (hematoxylin and eosin). **C**, Higher power views of same vessel shown in **B**. Note the basophilic necrosis accompanied by chronic inflammation and vague granulomas (*inset*). **D**, Granulomatous inflammation including giant cells (*arrows*), of the adventitia of a pulmonary artery (PA). (**A**, Case courtesy Dr. Christopher Bee.)

is performed early in the course of disease, some of the classic histologic findings may be absent. With prior treatment, there may be no significant inflammatory infiltrates and the only (nonspecific) clue may be scarring of arteries and/or airways.⁶⁹ A distinctive, but uncommon, histologic appearance is isolated capillaritis (see Fig. 60-3).

Appropriately treated disease is associated with a 5-year survival rate of 75%. While it is commonly assumed that active vasculitis itself accounts for this excess mortality, the mortality can be attributed to a variety of causes, including infection, malignancy, thromboembolic disease, cardiac disease, renal failure, and drug toxicity. Indeed, the leading cause of death among patients with AAV is infection rather than uncontrolled disease activity.⁷⁰ Poor outcomes correlate with advanced age, lack of upper airway involvement, more severe renal impairment, pulmonary involvement (particularly with alveolar hemorrhage), cardiac involvement, and high-level anti-PR3 positivity.⁷¹

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (see Chapter 68)

EGPA is a specific ANCA-associated small-vessel vasculitis that is clinically distinct from GPA and MPA (see Table 60-3), affects adults of all ages, and affects both genders equally. Its presentation often overlaps with the eosinophilic lung diseases (chronic eosinophilic pneumonia, allergic bronchopulmonary mycosis, drug reactions, hypereosinophilic syndrome, parasitic infection, asthma/atopic disease) and difficult-to-control asthma/atopy. The syndrome has its own triad of (1) asthma, (2) hypereosinophilia, and (3) necrotizing vasculitis that classically has a three-phase presentation with the initial presence of atopy/rhinitis/sinusitis/asthma, followed by an eosinophilia, and finally vasculitis. However, the three phases do not need to present sequentially, and the asthma may even postdate the vasculitis. Asthma is essentially universal and, while EGPA may present with any degree of severity and duration, severe (steroid-requiring) asthma is common with patients having asthma for 7 to 10 years before the vasculitis diagnosis.⁷¹ The upper airway is commonly involved with chronic rhinitis and sinusitis (with or without nasal polyposis), although generally without any of the destructive features associated with GPA.

Chest imaging is abnormal in more than two thirds of patients.⁷² Most commonly, waxing and waning parenchymal opacities (ground-glass attenuation and consolidation) (eFig. 60-9) and less commonly nodules are seen on CT of

the chest. Effusions can be seen in 10%. In contrast to GPA and MPA, pulmonary hemorrhage and glomerulonephritis are much less common in EGPA.⁷²⁻⁷⁶ Significant cardiac (conduction abnormalities, systolic or diastolic dysfunction, intracavitary thrombus, pericarditis) or gastrointestinal disease (perforation, ischemia, bleeding) are dreaded and well recognized complications. ANCA is positive in a perinuclear IIF pattern (p-ANCA) in 30% to 70% of cases, with peripheral eosinophilia (absolute eosinophil count > 1500 cells/ μ L) almost universal at some point in the course.

Recently, it has been identified that patients with EGPA segregate into two distinct clinical phenotypes. One subset is characterized by a greater incidence of neurologic, renal, gastrointestinal, and cutaneous involvement that is more commonly ANCA or MPO-positive (i.e., shares a high degree of overlapping features with GPA and MPA). The other subset of patients shares features with the hypereosinophilic syndromes, namely cardiac manifestations, migratory lung opacities (eosinophilic pneumonia), and an ANCA-negative/MPO-negative serologic profile.⁷⁶⁻⁷⁸

Pathologically, patients with EGPA demonstrate both a necrotizing, small-vessel vasculitis and an eosinophil-rich cellular infiltrate.^{79,80} The diagnostic findings on lung biopsy include eosinophilic pneumonia, necrotizing vasculitis, and granulomatous inflammation (Fig. 60-6). The vasculitis consists of artery, vein, or capillary wall infiltration by lymphocytes and eosinophils. The granulomas often show central areas of necrosis with abundant necrotic eosinophils, surrounded by palisaded histiocytes and multinucleated giant cells. Findings highly suggestive of EGPA include eosinophilic pneumonia and necrotizing vasculitis; findings suggestive of EGPA include eosinophilic pneumonia and parenchymal necrosis.⁸⁰

Mortality is generally due to cardiac complications (which constitute up to half of EGPA-related deaths), gastrointestinal complications, or status asthmaticus and respiratory failure.^{72,73,81} While mortality rates of up to 40% were described in the 1970s, more recent data suggest that, when adequately treated, patients may have a normal life span.⁸² A recent single center study demonstrated that a comprehensive vasculitis center-based management strategy of patients with EGPA without heart failure had a survival rate no different than that of a matched general population.⁸³ Overall 5-year survival rates have been estimated at 68% to 100%.⁷¹

In the late 1990s, an association between the use of leukotriene inhibitors and EGPA had been suggested in a number of case reports and case series^{84,85}; this led to the

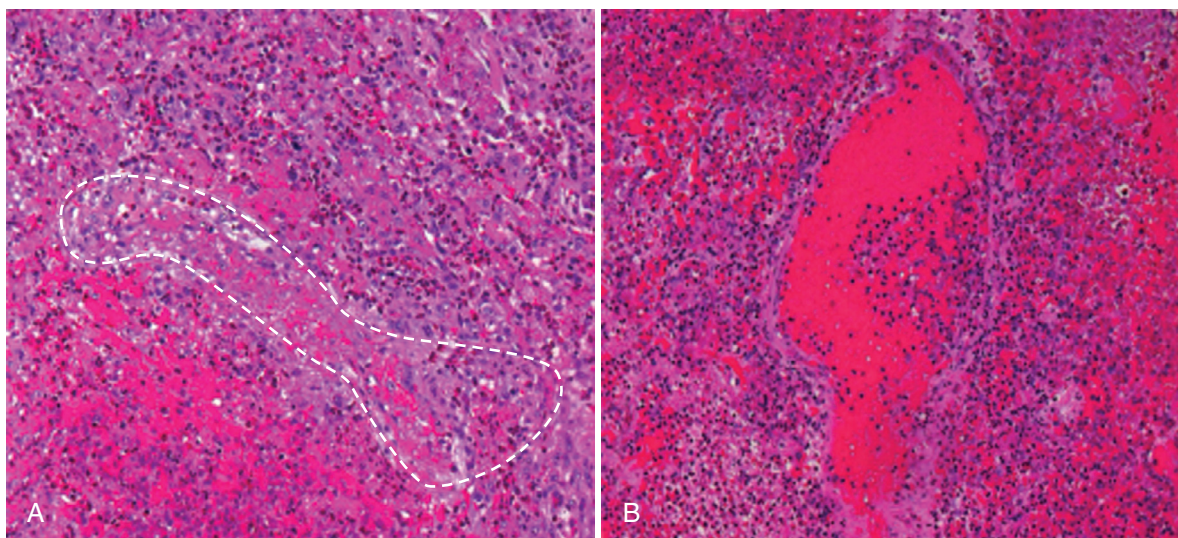


Figure 60-6 Eosinophilic granulomatosis with polyangiitis. **A**, Outline (*dashed line*) of a destroyed vessel. Note the marked eosinophilic infiltration. **B**, A small vein showing destruction of its wall by eosinophils. There is an accompanying eosinophilic pneumonia characterized by numerous clusters of eosinophils within the air spaces. Hemorrhage is also present.

concern that leukotriene inhibitors may help promote the biologic conversion of severe asthma/atopic disease to EGPA.⁸⁶ However, analyses of postmarketing surveillance data and a number of patient cohorts over the mid-2000s argued against this relationship, leading to the hypothesis that these excess cases were due either to reporting bias or to the unmasking of EGPA precipitated by the withdrawal of corticosteroids.^{82,87-89} However, in 2010, an analysis of the U.S. Food and Drug Administration Adverse Event Reporting Database found that only 36% of cases of leukotriene-associated EGPA had preexisting clinical evidence suggesting possible EGPA or had an associated tapering of the patient's corticosteroids; hence the majority of cases of EGPA associated with leukotriene antagonists could not otherwise be explained.⁹⁰ Similar findings were identified in the U.K. Committee on Safety of Medicines' "yellow card" scheme. As such, the pendulum has swung back toward favoring a very small but potentially real relationship between the use of leukotriene antagonists and the development of EGPA.

MICROSCOPIC POLYANGIITIS

Clinically, MPA is an ANCA-associated small-vessel vasculitis generally heralded by weeks to months or longer of profound constitutional symptoms (fever, asthenia, fatigue, malaise, myalgias, arthralgias) followed by the development of renal disease, generally RPGN (see [Table 60-3](#)). It is more common in males, with an average age of onset in the sixth decade. Its clinical manifestations overlap with those of polyarteritis nodosa, which accounts for the decades of confusion over their relationship. The glomerulonephritis is essentially universal, whereas the lungs are involved in a minority of patients (10% to 30%).⁹¹⁻⁹³ For patients in whom lung disease develops, diffuse alveolar hemorrhage/capillaritis is the most common manifestation ([eFig. 60-10](#)). Pulmonary fibrosis is uncommon but associated with a high mortality rate.⁷¹ The skin is involved in more than half of patients, most commonly with purpura. The peripheral

nervous system (most commonly with mononeuritis multiplex) is involved more frequently than the central nervous system, and the gastrointestinal tract becomes involved, with bleeding and ischemia, with some frequency.⁹⁴ ANCA is positive in a perinuclear pattern in 50% to 75% of cases.

Pathologically, a focal, segmental necrotizing vasculitis and a mixed inflammatory infiltrate without granulomata are seen. The vasculitis of MPA affects venules, capillaries, and arterioles. Neutrophilic capillaritis (see [Fig. 60-3](#)) is the classic histologic finding in the lung, with pulmonary alveolar hemorrhage and hemosiderin-laden macrophages ([Fig. 60-7A and B](#)). As the lesions heal, plugs of organizing pneumonia may fill air spaces, resulting in an organizing pneumonia-like pattern. Unlike the other small-vessel vasculitides, MPA lacks granulomatous inflammation. The overall 5-year survival rate has been estimated to range from 45% to 75%.⁷¹ Relapses after successful induction therapy are common (25% to 33%),⁹¹ but are usually less severe and responsive to therapy.

TREATMENT

GENERAL PRINCIPLES

Because therapy for the vasculitides involves aggressive immunosuppression with cytotoxic agents and corticosteroids, treatment-related complications are common and can be severe. Given the risks directly associated with therapy, the intensity of immunosuppression must be titrated to the severity of the disease; therefore the intensity of therapy is not driven by the diagnosis, but rather by disease severity. The goal is achieving disease control while minimizing the risk of treatment-related adverse events. As such, instruments and systems to accurately grade disease severity have been developed as documented in [Table 60-4](#) and accompanying references. Additionally, similar to cancer therapy, treatment is divided into two phases, an initial "remission-induction" phase to control

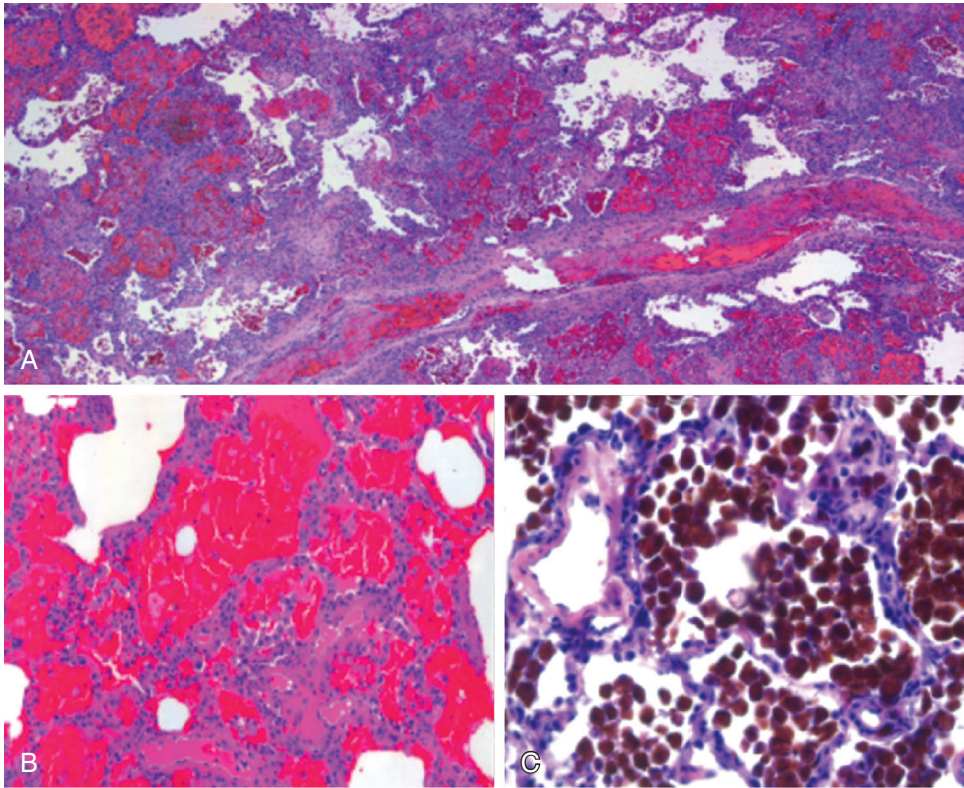


Figure 60-7 Microscopic polyangiitis. **A**, Low power view of diffuse alveolar hemorrhage. The air spaces are filled with red blood cells and the alveolar septa show concomitant inflammatory thickening. **B**, Alveolar hemorrhage demonstrating the smudged, homogeneous appearance of the disrupted red blood cells in the air spaces. Occasional hemosiderin-laden macrophages can be seen in the center. **C**, Hemosiderin-laden macrophages within the air spaces indicating chronic alveolar hemorrhage.

Table 60-4 European Vasculitis Study Group Disease Severity and First-Line Treatment Options for Induction Therapy				
Disease Classification	Constitutional Symptoms	Renal Function	Threatened Organ Function	Treatment Options for Induction
Limited	No	Serum creatinine < 120 mmol/L (1.4 mg/dL)	No	Corticosteroids OR methotrexate OR azathioprine
Early generalized	Yes	Serum creatinine < 120 mmol/L (1.4 mg/dL)	No	Cyclophosphamide + corticosteroids OR Methotrexate + corticosteroids
Active generalized	Yes	Serum creatinine < 500 mmol/L (5.7 mg/dL)	Yes	Cyclophosphamide + Corticosteroids OR Rituximab + corticosteroids
Severe	Yes	Serum creatinine > 500 mmol/L (5.7 mg/dL)	Yes	Corticosteroids + plasma exchange + cyclophosphamide (or rituximab)
Refractory	Yes	Any	Yes	Consider investigational or compassionate use agents (see text)
Maintenance of remission	No	N/A	No	If patient was induced with cyclophosphamide, then: azathioprine ± low-dose oral corticosteroids OR Methotrexate ± low-dose oral corticosteroids If patient was induced with rituximab, then: fixed schedule rituximab ± low-dose oral corticosteroids

From references 99, 106, 107, 110, 111, 122, 124, 127, 132, 149, and 162-168.

active disease and a “maintenance” phase to maintain disease remission while lowering treatment-related risk. Regardless of the phase of therapy, both disease-specific and drug-specific monitoring is required, focused on the early identification of disease activity and adverse events (e.g., infection and drug toxicity). Clinicians should be familiar with the common toxicities associated with each drug and

have a standard protocol for the monitoring of potential treatment-related adverse effects during both remission-induction and maintenance therapy. Not to be forgotten, oxygen therapy when needed, the treatment of comorbid disease, appropriate vaccinations, *Pneumocystis jirovecii* prophylaxis, physical and occupational therapy, a regular exercise regimen to maintain conditioning, proper

nutrition along with achieving and maintaining ideal body weight, proper sleep hygiene, bone health, and psychosocial support should be provided to help minimize the morbidity associated with these diseases.

As noted earlier, treatment recommendations depend on an accurate assessment of disease severity. The *European Vasculitis Study Group* (EUVAS) has devised a clinically useful grading system that categorizes active disease into one of five levels of severity: (1) limited, (2) early, generalized, (3) active, generalized, (4) severe, and (5) refractory, or as (6) in remission. Clinical criteria and first line treatment recommendations appear in Table 60-4. Alternatively, the French Vasculitis Study Group has validated an alternative, the *five-factor score* (FFS). Originally validated in EGPA and MPA, the FFS has now been validated across all AAV.⁹⁵ The FFS is calculated by adding +1 point for the presence of each of the following: (1) renal insufficiency, (2) clinically significant gastrointestinal disease, (3) cardiac symptoms, (4) the *absence* of upper airway (ear, nose, or throat) involvement, and (5) age 65 and older. Five-year mortality rates for scores of 0, 1, and 2 or more are 9%, 21%, and 40%, respectively.⁹⁵

To improve interobserver reliability and to make disease activity and vasculitic damage scoring more objective, reliable, and reproducible, specific instruments have been developed. The Birmingham Vasculitis Activity Score (version 3.0) is an inventory of signs, symptoms, and laboratory findings commonly associated with AAV that is commonly used in clinical trials to grade and quantify vasculitic disease activity.⁹⁶ The instrument quantifies the history, examination, review of systems, and routine laboratories obtained by the bedside clinician caring for the vasculitis patient. The Vasculitis Damage Index similarly quantifies vasculitic damage.⁹⁷ Both of these instruments are well validated and commonly used in the conduct of clinical trials.

REMISSION-INDUCTION

Limited Disease

Limited disease refers to localized disease of the upper airway. There are no systemic symptoms, end organ function is not threatened, and there is no renal involvement. While there are few data to inform management decisions in this subgroup, expert opinion holds that therapy can often be limited to a single agent, such as corticosteroids, azathioprine, or methotrexate. While some authors have recommended *trimethoprim/sulfamethoxazole* (T/S) alone for this group,⁹⁸ it is not clear whether T/S alone represents effective therapy and therefore remains controversial (see later). For more aggressive limited disease, therapy outlined for early generalized or active generalized disease may be necessary.

Early Generalized Disease

Early generalized disease differs from active generalized disease by the absence of an immediate threat to specific organ function. Still, patients with early generalized disease have constitutional symptoms and measurable end-organ involvement. While treatment recommendations have traditionally been similar for both early generalized and active

generalized disease (cyclophosphamide plus corticosteroids), investigators have sought alternative approaches for the early, generalized disease, hypothesizing that a less aggressive treatment regimen may be sufficient to induce disease remission while decreasing the potential for drug toxicity. To this end, the EUVAS-sponsored Methotrexate versus Cyclophosphamide for 'Early Systemic Disease' trial (NORAM) was performed. In this head-to-head comparison of methotrexate versus cyclophosphamide, the investigators found that oral methotrexate was as efficacious as oral cyclophosphamide in the induction of disease remission in early generalized disease at 6 months (84% vs. 83%), albeit with a longer time to remission (5.2 months vs. 3.2 months).⁹⁹⁻¹⁰¹ Moreover, while methotrexate had fewer side effects, its rate of relapse was also higher (74% vs. 42%). Indeed, the long-term follow-up data from this trial demonstrated that the cyclophosphamide arm was superior to methotrexate as measured by cumulative relapse-free survival, and no differences in major adverse events were observed between treatment groups.¹⁰² Thus, while both agents may be "acceptable" first-line therapy in early disease, cyclophosphamide appears to provide more effective overall disease control.

Mycophenolate mofetil and azathioprine have also been proposed as possible alternatives to cyclophosphamide in the induction of disease remission in patients with early, generalized disease; however, data are sparse. Silva and colleagues¹⁰³ published a small case series evaluating mycophenolate mofetil combined with corticosteroids for induction of remission in patients with MPA and mild-moderate renal disease with promising preliminary results (70% sustained remission at 18 months). The EUVAS study group is in the process of conducting a large prospective, randomized, controlled phase II/III trial comparing the efficacy of mycophenolate with cyclophosphamide for the induction of disease remission. Trial results are expected.

Active Generalized Disease

Fauci's early studies⁵⁸ of cyclophosphamide plus corticosteroids dramatically changed the field of vasculitis therapy, and this therapeutic combination has remained primary first-line therapy for the treatment of active generalized disease. The combination of oral cyclophosphamide plus oral corticosteroids in this initial study yielded a remission rate of greater than 90%. Before the advent of this regimen, the prognosis for patients with AAV was uniformly poor with 5-year mortality rates as high as 85%.

To reduce the side effects and toxicity associated with oral cyclophosphamide induction therapy, while preserving high rates of disease remission, a number of clinical trials have been performed looking at alternative regimens. Pulsed intravenous cyclophosphamide was compared head-to-head with oral cyclophosphamide in the EUVAS-sponsored CYCLOPS trial (Daily Oral versus Pulse Cyclophosphamide for Renal Vasculitis).¹⁰⁴⁻¹⁰⁶ While the investigators found that intravenous cyclophosphamide was as effective as oral cyclophosphamide at inducing disease remission and was associated with fewer side effects, long-term follow-up data found that the risk of relapse was significantly higher (29.5% vs. 20.8%).^{106,107} On the other hand, no significant differences were found between the two groups regarding survival, renal function, or adverse events.

Both ANCA and B cells have been implicated in the pathogenesis of AAV and, as such, the anti-CD20 monoclonal antibody rituximab was proposed as a potential therapy. After a number of promising case series, two large randomized, multicentered controlled clinical trials were performed comparing rituximab with cyclophosphamide for the induction of disease remission.^{108,109} The RAVE trial (Rituximab vs. Cyclophosphamide for ANCA-Associated Vasculitis) compared rituximab with daily oral cyclophosphamide. In this study, rituximab was shown to be noninferior to cyclophosphamide as measured by the primary end point of disease remission plus successful tapering of corticosteroids at 6 months.¹¹⁰ Subgroup analysis found that there was no difference in efficacy for the treatment of alveolar hemorrhage and that rituximab may be superior for the treatment of relapsing disease. No differences were noted in the rate of adverse events. Similar findings were found in the RITUX-VAS trial (Rituximab vs. Cyclophosphamide in ANCA-Associated Renal Vasculitis) in which rates of sustained remission, median time to remission, and adverse events were similar between the two treatment groups.¹¹¹ As such, rituximab now also represents first-line therapy for the induction of disease remission in GPA and MPA with active generalized disease.

Severe Disease

Severe disease is defined by an immediate threat of organ failure or death. Thus patients with severe renal disease (creatinine > 5.7 mg/dL), DAH, cardiomyopathy/heart failure, or other organ-threatening disease would be classified as having severe disease. Based on the results of the MEPEX trial (Randomized Trial of Plasma Exchange or High Dosage Methylprednisolone as Adjunctive therapy for Severe Renal Vasculitis) in a cohort of patients with severe renal disease, the addition of plasma exchange therapy to the standard cyclophosphamide plus corticosteroid regimen is recognized to be superior to high-dose, pulsed intravenous steroids as measured by dialysis-free survival (69% vs. 49%).¹¹²⁻¹¹⁸ Based on a 20-patient case series and a number of case reports, this strategy also appears to be effective for the treatment of DAH.¹¹⁷ Additional therapies described at the case report level for patients with unresponsive DAH include activated human factor VII to control ongoing refractory hemorrhage in patients with respiratory failure^{119,120} and extracorporeal membrane oxygenation, which has been used to treat refractory hypoxemic respiratory failure in patients with severe hemorrhage until other interventions have had a chance to work.¹²¹

Refractory Disease

Patients who have not responded to high-dose corticosteroids, cytotoxic agents, and plasma exchange are deemed to have refractory disease. There is no standard therapy that has been shown to work in this group of patients, and one must consider the use of novel or experimental agents. Fortunately, advances in the treatment of vasculitis have steadily reduced the numbers of patients with refractory disease. Treatments such as intravenous immunoglobulin, deoxyspergualin (an antitumor and immunosuppressant agent), and antithymocyte globulin¹²² have all been suggested. When feasible, patients with refractory disease

should be cared for in centers with specialized expertise in the management of vasculitis.

Maintenance

Maintenance therapy is designed to preserve disease control while reducing the risk or severity of medication-related adverse effects. During this phase of treatment, patients who undergo induction of remission with cyclophosphamide are generally converted to therapy with azathioprine or methotrexate, often combined with low-dose corticosteroids. Patients who undergo induction of remission with rituximab are generally treated with repeated dosing of rituximab plus low-dose corticosteroids. However, the optimal maintenance regimen for patients who are induced with rituximab remains an active area of investigation. As with all cytotoxic agents, these agents must be introduced with drug-specific monitoring to identify adverse effects as early as possible. Additional agents that have been used in selected patients include mycophenolate mofetil, leflunomide, and cyclosporine.^{99,100,123-126}

The timing of transition from the induction agent to the maintenance therapy had been a subject of debate, with one school of thought arguing that patients should have defined courses of therapy to “consolidate” the induction of remission, whereas another school of thought argued that clinical evidence of disease activity or lack thereof should serve as the chief determinant of the time to transition to maintenance therapy. The results of the CYCAZAREM trial (Cyclophosphamide vs. Azathioprine for Remission in Generalized Vasculitis) demonstrated that patients with active generalized vasculitis may be transitioned from oral cyclophosphamide to azathioprine once a clinical remission (using defined criteria) has been reached (generally within 3 to 6 months). Patients in the clinically determined (early) transition group demonstrated no increase in the rate of relapse, disease activity scores, or change in renal function.¹²⁷

As with induction therapy, a number of clinical trials have been conducted looking for pharmacologic agents that might offer superior results with regard to maintenance of remission and/or adverse effects relative to azathioprine. Weekly methotrexate has been compared head-to-head with daily oral azathioprine in a large, randomized, controlled trial and has been found to be equally efficacious for maintenance of disease remission; however, the methotrexate arm was found to have a significantly higher rate of adverse events (19% vs. 11%).¹²⁸ Similarly, mycophenolate mofetil was compared head-to-head with azathioprine in the IMPROVE trial (International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides). In this trial, azathioprine was found to be superior to mycophenolate for maintenance of disease remission with no differences in the adverse event rate.¹²⁹ The German Vasculitis Study Group has reported good outcomes in patients maintained on leflunomide in small clinical trials, comparable to those reported with azathioprine, but these results have yet to be more widely replicated.^{130,131} Thus azathioprine remains first-line therapy for maintenance of disease remission, with methotrexate as the most attractive alternative for patients who cannot tolerate azathioprine.

For patients who undergo induction therapy with rituximab, management decisions about maintenance therapy are less well informed by data. The early time points studied

in the RAVE and RITUXVAS trials make it difficult to extrapolate the results of those trials to longitudinal management. Options for maintenance therapy following rituximab induction have included corticosteroids alone, corticosteroids plus a cytotoxic agent (similar to therapy in patients induced with cyclophosphamide), or rituximab redosed at regular intervals. Recent data from the University of Cambridge argues for fixed interval rituximab retreatment because this strategy resulted in a markedly reduced relapse rate (26% at 2 years opposed to 86% in those patients followed with prospective management) as well as reduced corticosteroid requirements.¹³² This is a rapidly evolving area, and the reevaluation of the most current literature before making patient management decisions is recommended.

The optimal duration of maintenance therapy is also a source of uncertainty. Absent convincing data and based upon inferences drawn from a number of large clinical trials evaluating differing treatment regimens, experts have advocated for the use of at least 2 years of maintenance therapy before treatment cessation is considered.¹³³ The EUVAS-sponsored REMAIN (Randomised Trial of Prolonged Remission-Maintenance Therapy in Systemic Vasculitis) is designed to answer at least a portion of this question and will compare 24 months of maintenance therapy with 48 months of therapy. Enrollment was completed in 2010 and results are expected in 2015.

Another point of controversy has been the optimal dosage and duration of the corticosteroid component of the treatment regimen. While there is general agreement that “high-dose” corticosteroids should be introduced in patients with active disease as part of their induction therapy (e.g., 1 mg/kg/day of oral prednisone or equivalent) and that this should be “slowly tapered” (e.g., 3 months) toward a “low” maintenance dose (e.g., 5 to 10 mg/day of oral prednisone or equivalent), there is no validated, widely accepted corticosteroid protocol. Whether the corticosteroids should be tapered off or remain at a low dose for a prolonged period of time remains controversial, with experts weighing in on both sides of the argument. With that said, a meta-analysis of thirteen large clinical trials has suggested that patients maintained on some dose (i.e., “non-zero”) of corticosteroids have a lower rate of disease relapse than patients who are weaned entirely off (14% vs. 43%). Still, this has not been replicated in a well-designed, prospective clinical trial and even low-dose corticosteroids carry a risk of adverse side effects.

Finally, the use of T/S^{18,134} may have an adjunctive role in the management of AAV.^{17,135} Studies have demonstrated a reduced frequency of disease relapse in patients who are maintained on T/S compared to those without,¹³⁴ with additional work suggesting that this is related to *Staphylococcus aureus* nasal carriage.^{17,135} Regardless, T/S should be considered for *Pneumocystis jirovecii* prophylaxis in patients maintained on cyclophosphamide or other aggressive immunosuppression regimens, barring a sulfa allergy or other contraindication.

MONITORING FOR COMPLICATIONS

Monitoring for complications is mandatory to minimize the morbidity and mortality of both the disease and its

Table 60-5 Causes of Common Complications of Vasculitides and Potential Interventions

Common Complications	Potential Interventions
Infection	Pneumocystis prophylaxis Vaccination Tailor treatment intensity to disease severity
Drug toxicity	Drug-specific standardized monitoring
Disease recurrence or relapse	Disease-specific monitoring
Comorbid disease	As appropriate for specific disease
Osteoporosis	Bone mineral testing and prophylaxis as appropriate for corticosteroid dose
Venous thromboembolism	Appropriate therapy
Deconditioning	Physical therapy, occupational therapy, routine aerobic exercise, nutrition
Psychosocial distress	Patient support groups

treatment. When clinical deterioration is noted, infection, drug toxicity, disease relapse, thromboembolic disease, and disease processes unrelated to the underlying vasculitis¹³⁶ should all be considered (Table 60-5).

Infection is the leading cause of morbidity and mortality in patients with vasculitis. Infections may present with atypical clinical features or atypical organisms and are frequently difficult to separate from disease activity. Infection may also contribute to triggering or increasing disease activity, and the immune dysfunction associated with disease activity appears to place patients at increased risk for infection, so that disease flares and infections may coincide. Ultimately, infection accounts for 13% to 48% of deaths in patients with vasculitis.^{2,137,138} Combining high-dose glucocorticoids with cytotoxic therapy puts patients at especially high risk.

Historically, up to 50% of patients with an ANCA-associated vasculitis have suffered at least one relapse despite active treatment. Relapses are more common among patients with GPA (40% to 65%) and less common among patients with EGPA (15% to 25%).^{67,139} The features of clinical deterioration during a relapse may be similar to those of the patient's original presentation or there may be novel symptoms and signs that appear in previously unaffected organs. A relapse generally requires reinduction therapy. While disease relapse remains a clinical diagnosis, a recent study applying a proteomic approach to identifying remission in GPA suggests that serum markers may one day permit accurate discrimination between quiescent and active disease.¹⁴⁰

Drug toxicity is also common. In patients with GPA treated with cyclophosphamide, cystitis is described in up to 12%, myelodysplastic syndrome in 8%, and solid malignancy in 5%.¹⁴¹ Ultimately, the bedside clinician must be familiar with the adverse effects associated with the therapies deployed and have a system in place for the monitoring of cytotoxic/immunosuppressive therapies so as to identify toxicity as early as possible. Evidence-based clinical practice guidelines have been developed by the American College of Chest Physicians to assist with informing monitoring practices.¹⁴²

Thromboembolic disease is an underrecognized complication of vasculitis, particularly in the setting of GPA. Patients with GPA have the same rate of venous thromboembolic disease as patients with a known prior history of thromboembolic disease, 7 events per 100 person-years. As such, pulmonary embolism and deep venous thrombosis must also be considered in the differential diagnosis of a patient with new chest or lower extremity symptoms. The rate of thromboembolic disease in MPA and EGPA has yet to be defined.

Key Points

- Pulmonary vasculitis describes a variety of disorders characterized by their ability to cause vascular inflammation, destruction, and tissue necrosis in the lung.
- The presentation, clinical features, and evaluation overlap fully with more common diseases including infection and drug toxicity. The initial history is critical to the evaluation of a patient with suspected vasculitis.
- A confident diagnosis may occasionally be made without tissue biopsy; however, diagnostic tissue biopsy remains necessary for a definitive diagnosis.
- The ANCA-associated vasculitides—granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis—are the most commonly encountered vasculitides in the practice of pulmonary medicine.
- A number of high-quality randomized, controlled trials have enhanced the development of evidence-based treatment recommendations with the expectation of a favorable response.

- Therapy for the vasculitides involves aggressive immunosuppression; consequently treatment-related complications are common and can be severe. Common complications that arise during the course of disease include infection, disease relapse, comorbid disease, and venous thromboembolism.

Complete reference list available at *ExpertConsult*.

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eFIGURE IMAGE GALLERY

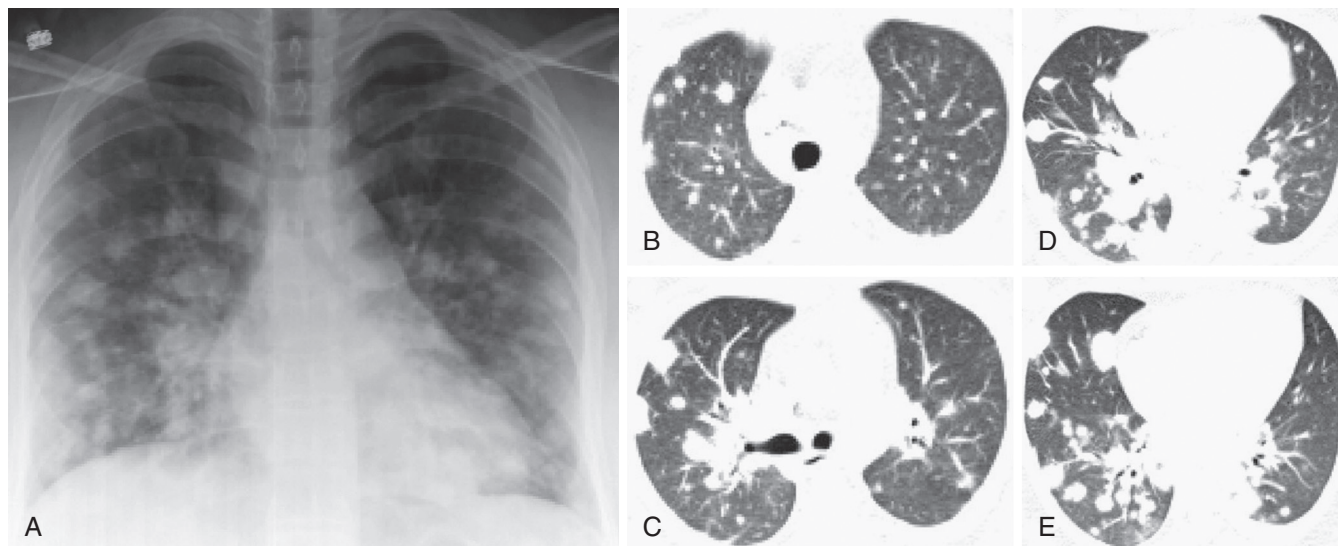


Figure 60-1 Imaging of granulomatosis with polyangiitis: nodules. **A**, Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows numerous bilateral, variably sized pulmonary nodules. **B–E**, Axial chest CT displayed in lung windows confirms the presence of numerous nodules without cavitation. (Courtesy Michael Gotway, MD.)

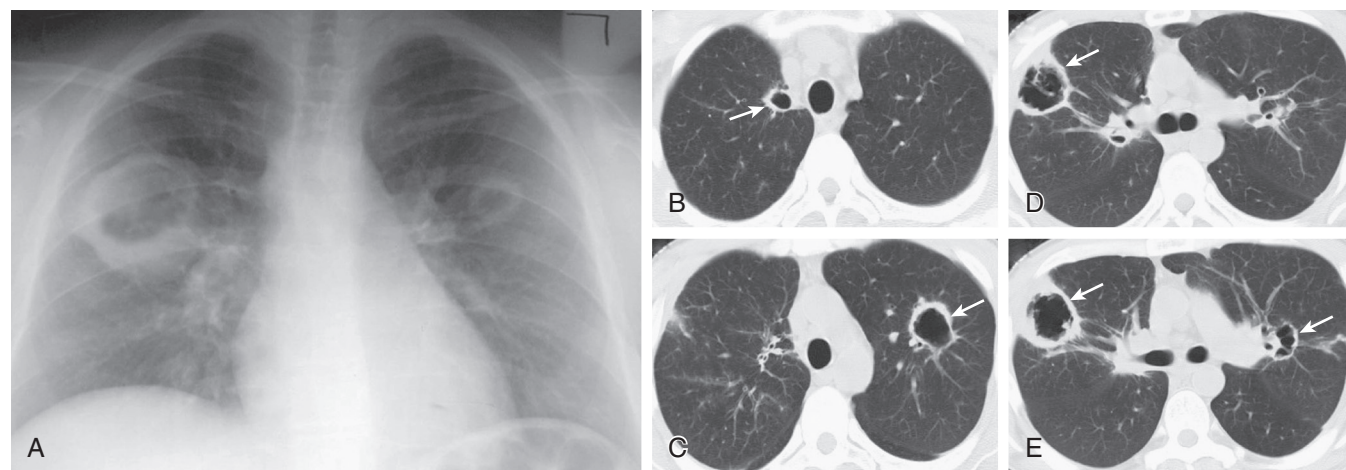


Figure 60-2 Imaging of granulomatosis with polyangiitis: cavities. **A**, Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows bilateral, variably sized pulmonary cavities. **B–E**, Axial chest CT displayed in lung windows confirms the presence of numerous (arrows) cavities with variable wall thickness; some contain internal opacity, but without air-fluid levels. (Courtesy Michael Gotway, MD.)

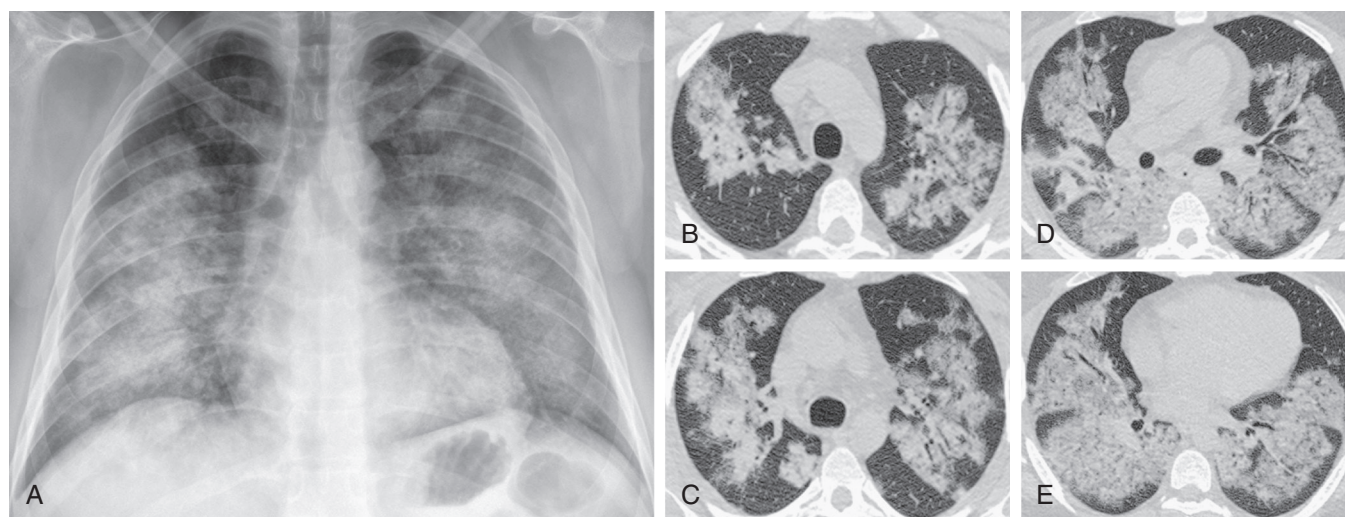


Figure 60-3 Imaging of granulomatosis with polyangiitis: diffuse pulmonary opacities due to pulmonary hemorrhage. **A**, Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows multifocal, bilateral, ground-glass opacity and consolidation. **B–E**, Axial chest CT displayed in lung windows shows multifocal ground-glass opacity associated with linear and reticular opacities; prominent peribronchial localization of these opacities is visible in the upper lobes (panel), with numerous air bronchograms as well. These findings are consistent with pulmonary hemorrhage, but are non-specific. (Courtesy Michael Gotway, MD.)

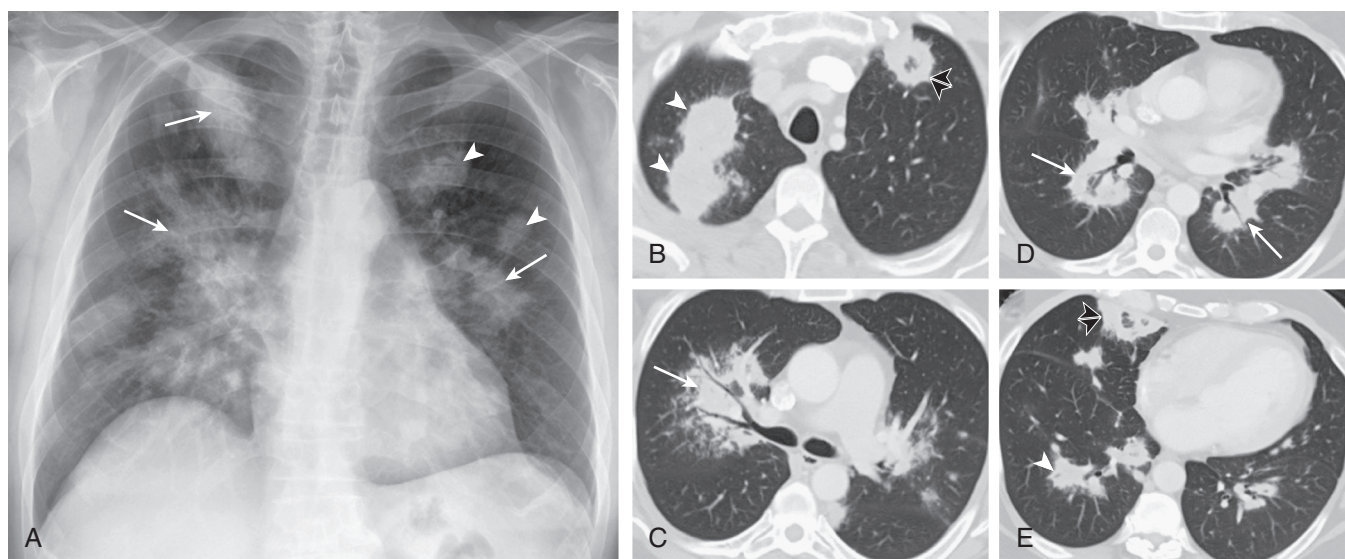
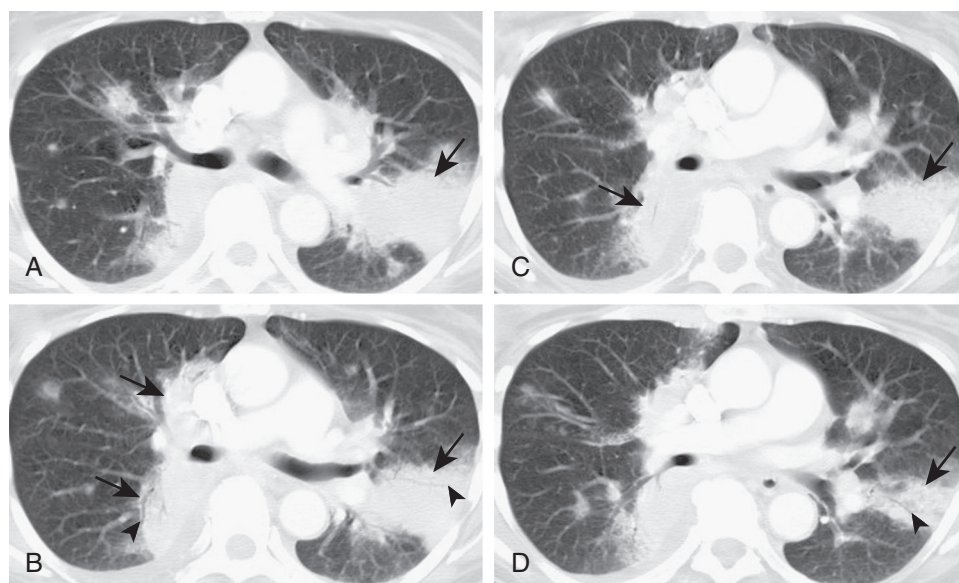
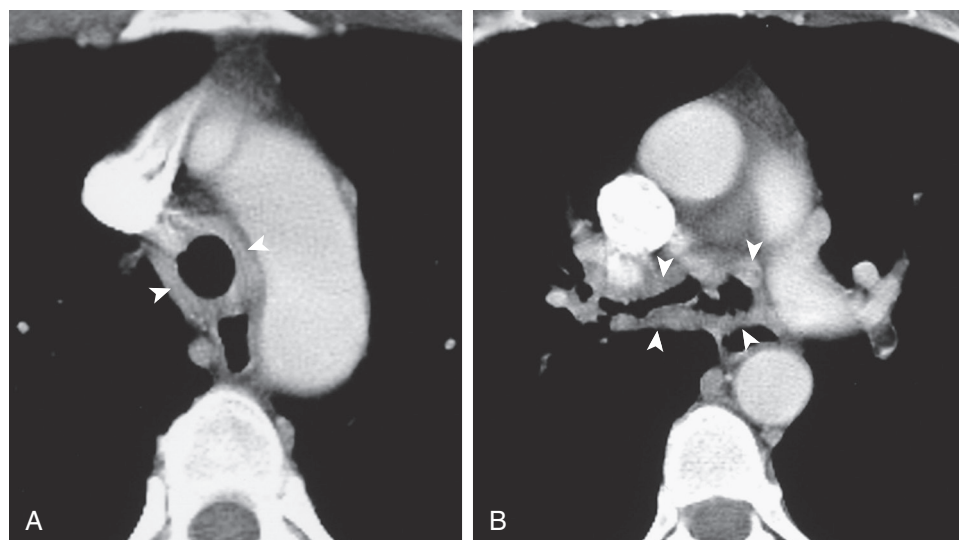


Figure 60-4 Imaging of granulomatosis with polyangiitis: consolidation. **A**, Frontal chest radiograph in a patient with granulomatosis with polyangiitis shows several nodular and masslike areas (*arrowheads*) as well as foci of consolidation (*arrows*). **B–E**, Axial chest CT displayed in lung windows shows nodules and masses (*arrowheads*), with areas of increased opacity and air bronchograms (*arrows*) consistent with consolidation. Some of the masses show internal ground-glass opacity surrounded by consolidation (*double arrowheads*), representing the “reverse ground-glass halo” (or “atoll”) sign, representing areas of pulmonary infarction in this clinical context. (Courtesy Michael Gotway, MD.)



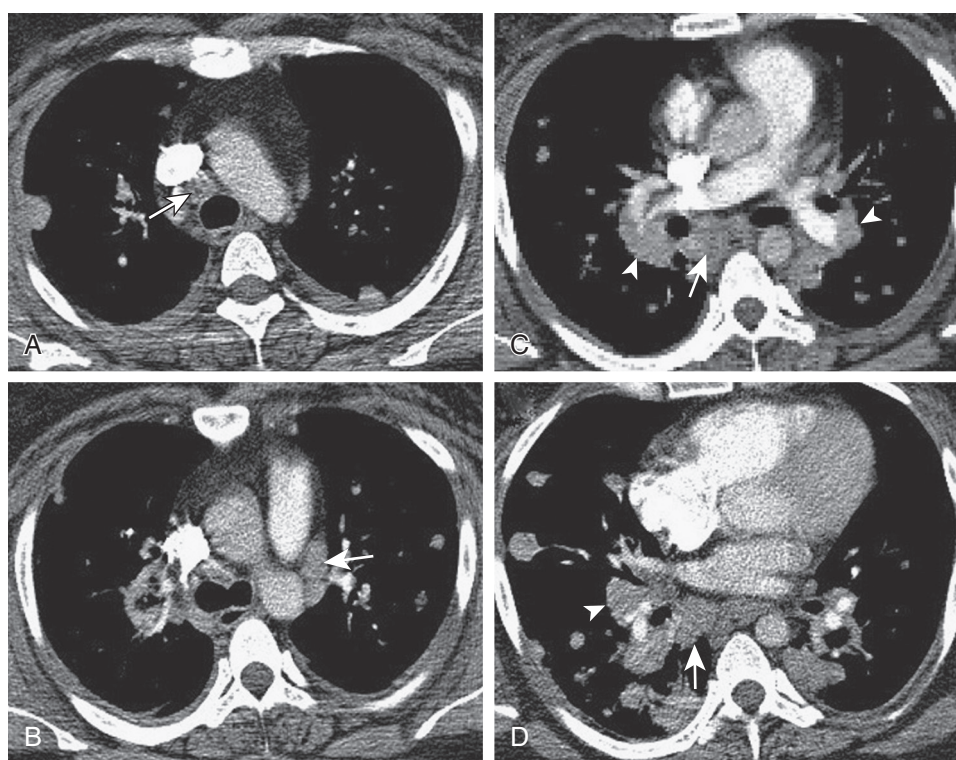
eFigure 60-5 Imaging of granulomatosis with polyangiitis: consolidation. A–D, Axial chest CT displayed in lung windows in a patient with granulomatosis with polyangiitis shows multifocal consolidation (*arrows*), somewhat resembling an organizing pneumonia. Note presence of air bronchograms in some of the opacities (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 60-6 Imaging of granulomatosis with polyangiitis: tracheobronchial stenoses. A and B, Axial chest CT displayed in soft tissue windows in a patient with granulomatosis with polyangiitis shows nodular, circumferential thickening of the trachea and bilateral mainstem bronchi (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 60-7 Imaging of granulomatosis with polyangiitis: upper respiratory tract ulceration. Axial (A) and coronal (B) sinus CT in a patient with granulomatosis with polyangiitis shows opacification of the maxillary sinuses bilaterally (*) and the sphenoid sinus (○). The nasal septum is completely eroded and essentially absent (the nasal septum should normally be located approximately between the two arrowheads). C, Axial contrast-enhanced axial T1-weighted MRI with fat saturation shows extensive inflammatory tissues in the nasopharynx (arrow) as well as absence of the nasal septum (the nasal septum should normally be located approximately between the two arrowheads). (Courtesy Michael Gotway, MD.)



eFigure 60-8 Imaging of granulomatosis with polyangiitis: lymphadenopathy. A–D, Enhanced chest CT shows bilateral peribronchial (arrowheads) and mediastinal (arrows) lymph node enlargement in a patient with granulomatosis with polyangiitis. Lung nodules are also visible (same patient as in eFig. 60-1). (Courtesy Michael Gotway, MD.)

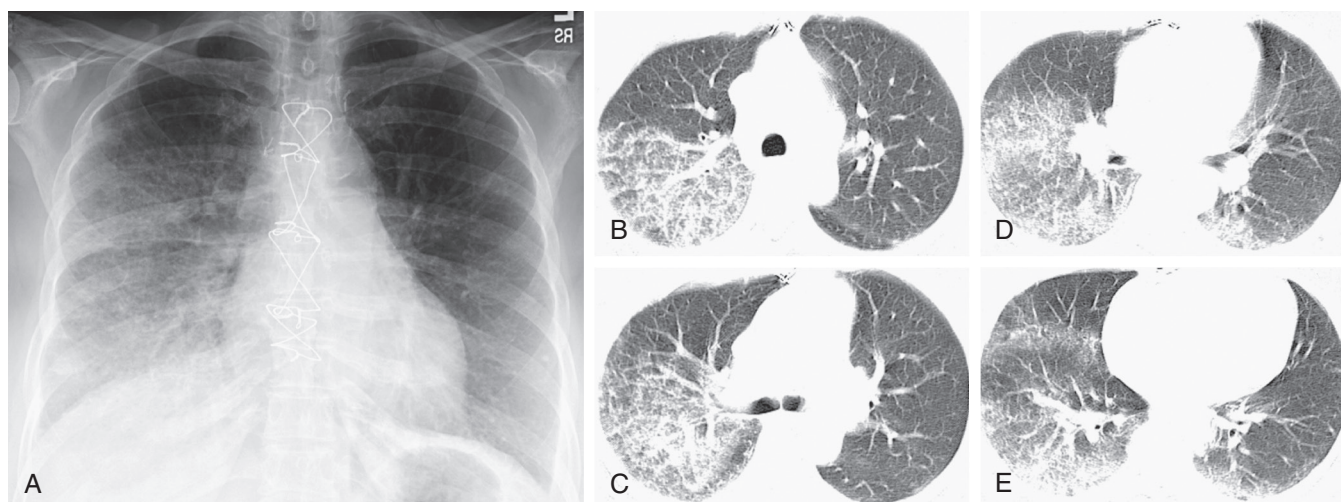


Figure 60-9 Imaging of eosinophilic granulomatosis with polyangiitis. **A**, Frontal chest radiograph shows multifocal hazy increased attenuation associated with a background of linear and reticular opacities, primarily affecting the right lung. **B–E**, Axial chest CT displayed in lung windows shows multifocal ground-glass opacity associated with linear and reticular opacities; these findings are consistent with pulmonary hemorrhage, but are ultimately nonspecific. (Courtesy Michael Gotway, MD.)

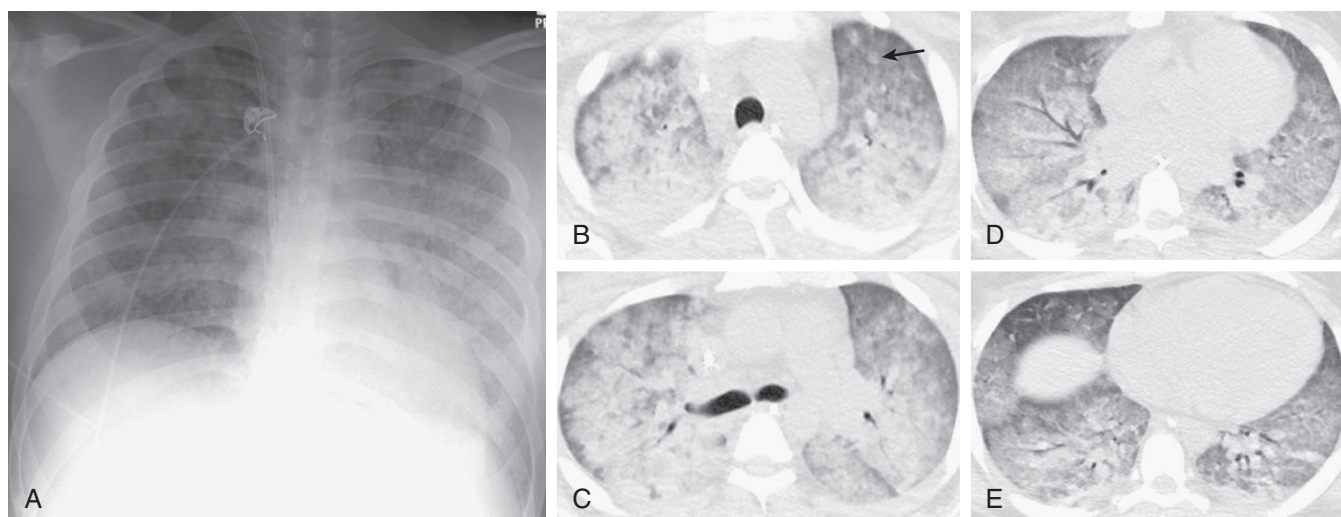


Figure 60-10 Imaging of microscopic polyangiitis. **A**, Frontal chest radiograph shows multifocal, bilateral hazy increased attenuation associated with a background of linear and reticular opacities, the latter best seen in the left lung. **B–E**, Axial chest CT displayed in lung windows shows multifocal ground-glass opacity, faintly forming poorly defined centrilobular nodules (*arrow*) in some locations, associated with linear and reticular opacities; these findings are consistent with pulmonary hemorrhage, but are ultimately nonspecific. (Courtesy Michael Gotway, MD.)

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PULMONARY VASCULAR ABNORMALITIES

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INTRODUCTION

Pulmonary vascular abnormalities are seen in a variety of acquired and congenital conditions. These structural defects include vascular communications that either are confined to the pulmonary circulation, as is the case with pulmonary arteriovenous malformations, or join the systemic to the pulmonary circulations, as with pulmonary sequestration. Aneurysmal dilations of the pulmonary artery and its branches are also considered in this chapter. Although all these conditions are rare, their diagnosis and treatment are important, because many are associated with complications that cause severe morbidity or mortality.

PULMONARY ARTERIOVENOUS MALFORMATIONS

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular structures that provide a direct capillary-free communication between the pulmonary arterial and pulmonary venous circulations, and hence a *right-to-left* (R-L) shunt. PAVMs are estimated by chest *computed tomography* (CT) scanning to affect 38 per 100,000 individuals (95% *confidence interval* [CI] = 18-76).¹ They range in size and complexity (Fig. 61-1, Fig. 61-2), and also include abnormal communications within the microvasculature (telangiectases). The true anatomic shunts of PAVMs are usually distinguished from the diffusion-perfusion defects that arise in patients with intrapulmonary vascular dilations secondary to the hepatopulmonary syndrome, which is fully described in Chapter 93.

Pulmonary arterial blood passing through these R-L shunts bypasses the alveoli and thus cannot be oxygenated, often leading to hypoxemia. In addition, the absence of a filtering capillary bed allows particulate matter to reach the systemic circulation, where it lodges in other capillary beds, including the cerebral circulation, resulting in embolic cerebrovascular accidents and brain abscesses. It is crucial for the pulmonologist to assimilate the recent data demon-

strating that—regardless of PAVM size—all patients with PAVMs evident on chest CT scan are at risk for paradoxical emboli. Importantly, recent data also confirm that most patients with clinically significant PAVMs do not have respiratory symptoms or profound hypoxemia. The incidence of major, usually neurologic, complications approaches 50% (Table 61-1), with nearly 13% incidence of cerebral abscess and 27% of embolic stroke or transient ischemic attack recorded in all series. These complications can be limited, if the underlying condition is recognized and treated, with embolization, the treatment of choice for almost all patients. Risk-benefit analyses are almost always in favor of treatment, although contraindications should be considered.

ETIOLOGY

PAVMs are most commonly attributed to the inherited vascular disorder *hereditary hemorrhagic telangiectasia* (HHT, or Osler-Weber-Rendu syndrome).³ This vascular condition is usually caused by mutations in the *ENG* gene coding for endoglin (HHT type 1), the *ACVRL1* gene coding for ALK-1 (HHT type 2), or the *SMAD4* gene (juvenile polyposis/HHT)—more details of the genetics of HHT are provided in the following section. In the absence of HHT, PAVMs may develop sporadically, as a result of surgical treatments for several forms of complex cyanotic congenital heart disease^{4,5} or after trauma.⁶ Sporadic PAVMs are usually single, and multiple PAVMs should raise particular suspicion that there is underlying HHT.^{3,7,8}

Hereditary Hemorrhagic Telangiectasia

HHT is a disorder of vascular development inherited as an autosomal dominant trait. Careful epidemiologic studies reveal a true incidence of 1 in 5000 to 8000 in France, Denmark, and Japan⁹⁻¹¹; The condition is subject to underreporting in men, lower socioeconomic groups and geographical areas.¹² Higher prevalences are described in isolated communities.^{9,13} PAVMs detected on chest CT affect at least 50% of HHT patients¹⁴ and are particularly common in *HHT type 1* (HHT1), with 85% of *ENG* mutation carriers demonstrating R-L shunts on contrast echocardiography.¹⁵

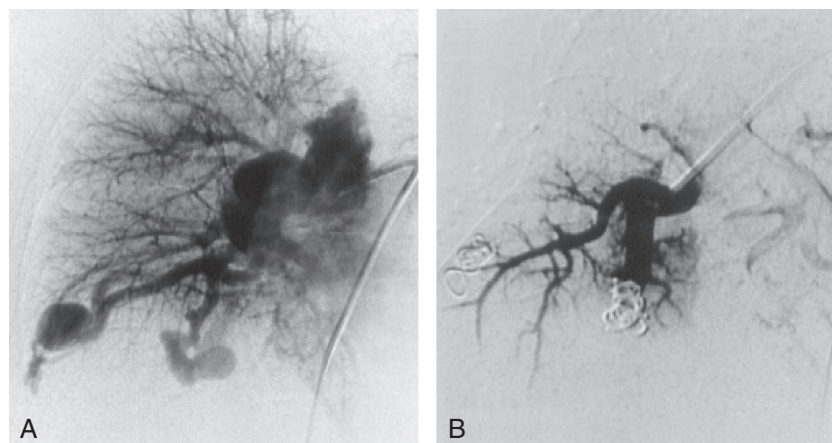


Figure 61-1 Macroscopic right lower lobe pulmonary arteriovenous malformations (PAVMs) before (A) and after (B) embolization. Note embolization coils and restored perfusion of pulmonary arterial branches in **B**. Similar PAVMs were present in the left lung. Embolization over an 18-month period reduced the right-to-left shunt from 32% to 3% and increased the arterial oxygen saturation from 78% to 92% at rest.



Figure 61-2 Diffuse small pulmonary arteriovenous malformations in a patient with a right-to-left shunt greater than 30% following maximal embolization. The patient declined transplantation; arterial oxygen saturation (erect) was unchanged at 78% to 79% over the next 25 years.

Clinical Features and Diagnosis. Most individuals with HHT have nosebleeds, but are otherwise often minimally symptomatic. Telangiectasias increase with age: by age 16 years, 71% of individuals will have developed some sign of HHT, increasing to more than 90% by age 40 years.^{3,16}

To permit a high level of clinical suspicion without leading to overdiagnosis, international consensus diagnostic criteria were developed based on four findings: (1) spontaneous recurrent nosebleeds, (2) mucocutaneous telangiectasias, (3) visceral involvement, and (4) an affected first-degree relative (Table 61-2).¹⁷ When three criteria are present, “definite HHT” can be diagnosed; with two criteria, most commonly family history and nosebleeds, “suspected

Table 61-1 Historical Features of Untreated Pulmonary Arteriovenous Malformations

	Mean (%)	Range (%)	Comment
RESPIRATORY			
Asymptomatic	49	25–58	Increasing with screening
Dyspnea	50	27–71	Decreasing with screening
Chest pain	12	6–18	Rarely due to PAVM
Hemoptysis	11	4–18	
Hemothorax	1	0–2	
Cyanosis	27	9–73	Decreasing with screening
Clubbing	28	6–68	Decreasing with screening
Bruit	31	3–58	Decreasing with screening
CENTRAL NERVOUS SYSTEM			
Cerebral abscess	13	0–25	
CVA/TIA	27	11–55	
CVA	14	9–18	>50% with CT/MR infarcts
TIA	22	6–36	
Migraine	45	38–57	

CVA, cerebrovascular accident; TIA, transient ischemic attack.
Data as commonly cited based on cases published 1948–1998.²

Table 61-2 Clinical Features of Hereditary Hemorrhagic Telangiectasia

Criteria	Approximate Frequency (%)	Comment
Epistaxes (nose bleeds)	90	
Mucocutaneous telangiectasia	80	
Gastrointestinal bleeding	25	
Pulmonary AVMs	~50	Dependent on genotype
Hepatic AVMs	30–70	Dependent on genotype
Cerebral AVMs	<10	
Spinal AVMs	<1	

AVMs, arteriovenous malformations (may also arise in sites not listed above, such as pancreas).

HHT” is diagnosed. With only one criterion, typically spontaneous nosebleeds, in a patient with neither a family history nor a first-degree relative of an HHT patient, and with no signs of the disease, the diagnosis of HHT is “unlikely.” A crucial issue for families (and medical practitioners) is that no child of a patient with HHT can be informed that he or she does not have HHT, unless the child has had a molecular diagnosis that demonstrates that he or she has not inherited the HHT-causing gene mutation for that family.

Genetics and Pathogenesis. HHT is a genetically heterogeneous condition. Three disease-associated genes have been identified. HHT1 is caused by mutations in *ENG*, encoding endoglin,¹⁸ and *HHT type 2* (HHT2) by mutations in *ACVRL1*, encoding *activin receptor-like kinase* (ALK-1).¹⁹ More rarely, mutations in *SMAD4* cause HHT, usually in association with juvenile polyposis/HHT.²⁰ An HHT-like syndrome is caused by mutations in the gene coding for *bone morphogenetic protein* (BMP) 9.²¹ There are at least two further unidentified genes that can cause classic HHT, that is, *HHT3* on chromosome 5q between *D5S2011* and *D5S2490* and *HHT4* on chromosome 7p between *D7S2252* and *D7S510*.^{22,23}

A body of evidence indicates that HHT mutations result in a nonfunctional allele and haploinsufficiency, which leads to a lack of sufficient protein for normal function. The most obvious mutations that will fail to generate a protein include entire gene deletions, start codon mutations, and mutations with no detectable mutant RNA. In addition, the majority of mutations reported on the HHT mutation database lead to premature termination codons, indicating that the mutated RNA species will undergo nonsense-mediated decay.²⁴ Although there have been suggestions that the telangiectasias/AVMs may develop at sites where there was a genetic “second hit,” it is believed that in most, if not all cases, HHT results from haploinsufficiency.

Phenotype-Genotype Correlations. Pulmonary AVMs are more common in patients with either HHT1 (*ENG*) or juvenile polyposis/HHT (*SMAD4*) than in HHT2 (*ACVRL1* mutations).²⁵⁻²⁹ A characteristic finding is that different members of the same HHT family display different patterns of disease. Recent data have identified a modifier gene that makes PAVMs more likely.³⁰ Although there was an initial suggestion that overall severity of disease is greater in HHT1 than HHT2,²⁹ this study predated the recognition of pulmonary hypertension (see later) and, in a later series, there was no difference in 90-month mortality.²⁵

Cellular Basis. The genes mutated in HHT encode proteins that mediate signaling by the *transforming growth factor-β* (TGF-β) superfamily. Superfamily ligands such as TGF-βs, activins, and BMPs affect cellular growth and differentiation through signal transduction cascades from transmembrane receptor complexes. Endoglin is a relatively endothelial-specific co-receptor for multiple receptor complexes of the TGF-β superfamily.^{31,32} ALK-1 represents an endothelial-specific type I receptor that structurally and mechanistically belongs to the BMP branch of type I receptors.³³ ALK-1 can associate with at least two type II receptors, BMPRII and TβRII.³⁴ In turn, TβRII can associate with

two different TGF-β type I receptors in endothelial cells (TβRI [also known as ALK-5] or ALK-1), activating different Smad pathways, and apparently resulting in opposing endothelial cell responses in terms of proliferation, migration, and proangiogenic or antiangiogenic gene expression.³⁴⁻³⁸ Recent HHT concepts include the “balance hypothesis,” whereby the HHT mutations modify the predominant endothelial TGF-β type I receptor, Smad pathway, and ultimately endothelial cell response³⁵⁻³⁸; and models incorporating BMP9 and BMP10, which are specific ALK-1 ligands that can also bind endoglin.³⁹⁻⁴⁴ The likelihood of BMP9 being the ligand contributing to HHT pathogenesis increased with the recent identification of an HHT-like syndrome caused by BMP9 mutations.²¹ How the disease gene mutations lead to the vascular pathology has proved difficult to unravel. Attention now focuses on aberrant vascular responses to injury-induced angiogenic stimuli; in this setting, the mutated genes in HHT appear to result in the inability of a blood vessel to mature appropriately.⁴⁵⁻⁴⁸

Cavopulmonary Shunts. In non-HHT patients, PAVMs commonly develop in those who have undergone surgical treatments of several forms of complex cyanotic congenital heart disease resulting in anastomoses between the *superior vena cava* (SVC) and *inferior vena cava* (IVC) and the pulmonary arteries.⁴ In the Glenn anastomosis, the SVC is redirected to provide the venous blood flow for the pulmonary arteries. Using angiography, PAVMs were detected in 31% of patients undergoing classic Glenn anastomoses after a mean follow-up of 6.8 years.⁴

The incidence of PAVMs increases substantially if microscopic AVMs detectable by contrast echocardiography are included⁴⁹; moreover, microscopic arteriovenous shunting may develop within 2 hours of the procedure.⁵⁰ Some have suggested that, following superior bidirectional cavopulmonary anastomosis (Kawashima procedure, in which almost all venous blood except the hepatic venous blood flow is redirected to the pulmonary arteries), the development of functional intrapulmonary shunts may be universal. Contrast-enhanced *magnetic resonance* (MR) angiography is emerging as a useful assessment modality for these patients.⁵¹

The key etiologic feature appears to be the route taken by hepatic venous flow, because PAVMs develop in the lung that receives no or minimal hepatic venous return, and regress if hepatic venous blood flow to the lung is restored.^{5,52-54} Serum levels of endostatin, a potent inhibitor of angiogenesis produced by the liver, drop after Glenn procedures ($n = 17$; 4.42 vs. 3.34 ng/mL; $P < 0.001$) (in which only SVC, not IVC, blood is directed to the lungs), but not after Fontan procedures ($n = 13$) (in which both SVC and IVC blood is directed to the lungs).⁵⁵ Because a decrease in endostatin may promote angiogenesis, the authors propose that the potential role of endostatin in the pathogenesis of PAVMs warrants further study.⁵⁵

PATHOPHYSIOLOGY

Anatomic Basis

Both macroscopic (see Fig. 61-1) and microscopic or diffuse PAVMs are recognized. In simple PAVMs, an aneurysmal

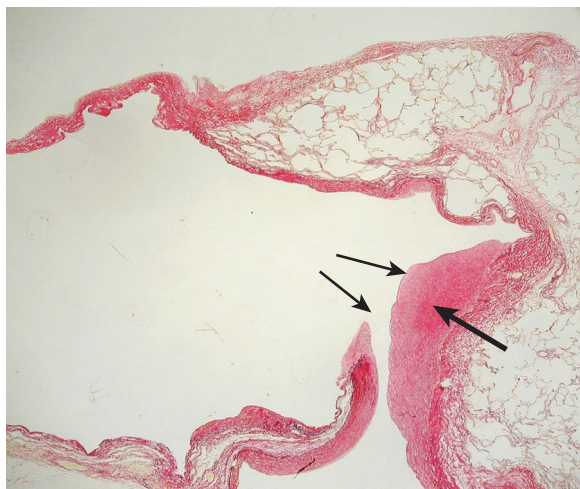


Figure 61-3 Histopathology of a pulmonary arteriovenous malformation that ruptured in pregnancy. Note site of rupture (narrow arrows) at lower border and region of endothelial intimal fibrous proliferation (thick arrow). (Shovlin CL, Sodhi V, McCarthy A, et al: Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia: suggested approach for obstetrics services. *Br J Obstet Gynaecol* 115:1108–1115, 2008.)

venous sac is supplied by a single artery and drained by a single vein. In complex PAVMs, a group of venous sacs are supplied by multiple vessels arising from adjacent segmental or subsegmental pulmonary artery branches and draining into multiple veins.^{56–58} They may be discrete (which is more common), or diffuse when a single segment,⁵⁹ or every segment of one or more lobes⁶⁰ are involved. The sacs are characterized by walls of varying degrees of thickness, even over relatively short segments, with disorganized adventitia. Medial thinning is observed, but areas of focal thickening with abundant elastin tissue and a varying contribution of smooth muscle cells are also prominent (Fig. 61-3).^{44,61}

PAVMs occasionally develop in the prenatal or perinatal period, and are present during childhood. In a series of 44 children (mean age 10.3 years, range 1 to 18 years), 20 (45%) had PAVMs detected by screening studies.⁶² PAVMs increase in size during puberty, in female patients during pregnancy,⁶³ and in the presence of pulmonary venous hypertension secondary to mitral stenosis or left ventricular dysfunction.⁶⁴ Pulmonary emboli can lead to temporary regression,⁶⁵ and on rare occasions, permanent spontaneous regression has been described.⁶⁶

Physiologic Attributes at Rest

Right-to-Left Shunt. PAVMs provide an anatomic R-L shunt, with the proportion of the cardiac output using the shunt pathways (shunt fraction) varying widely but reaching up to 60% in severe cases. In early series,^{67–71} mean R-L shunt fractions were generally higher (23% to 38%) than was found in later reports (8% to 13%),^{72–74} in which earlier diagnosis had taken place owing to more energetic screening procedures. Arterial PO_2 and arterial oxygen saturation (SO_2) are inversely related to the size of the R-L shunt fraction.^{75,76} The contribution of ventilation-perfusion mismatch to arterial hypoxemia in PAVMs is small, except in the occasional patient with significant coexisting lung disease.

Compensations for hypoxemia are usually highly successful. Chronic adaptations include secondary erythrocytosis which preserves the arterial oxygen content.^{77–79} Acute responses utilize increased cardiac output through heart rate (for acute falls in arterial oxygen content, e.g., on standing),⁷⁸ and stroke volume.^{67,80} which can preserve the oxygen pulse (oxygen utilized/delivered per heart beat) at rest and on exercise.⁸⁰

Pulmonary Hemodynamics. The absence of a microvascular network of capillary vessels in the PAVMs means that the pulmonary vascular resistance (PVR) of PAVMs is less than that of the surrounding normal lung. The effect on the overall PVR depends on the proportion of the cardiac output flowing through the shunt channels. In one study of eight patients with PAVM with large R-L shunt fractions (mean $31\% \pm 4\%$ [standard error]), mean PVR was 0.33 ± 0.08 mm Hg/L/min (normal 0.5 to 1.3 mm Hg/L/min) and pulmonary artery pressure (PPA) was 14 ± 0.6 mm Hg (normal 12 to 16 mm Hg), respectively.⁶⁷ PVR was low, despite normal PPA, because total pulmonary blood flow was high (8 ± 0.8 L/min [160% of predicted]). In later studies with smaller mean R-L shunt fractions (8.5% to 11.5%), mean pulmonary systolic and diastolic pressures have been in the normal range,^{72,74,81} and recent studies have focused on the occasional presence of coexisting pulmonary hypertension^{82–89} (see section on HHT-related pulmonary hypertension).

Pulmonary Function. Vital capacity is generally normal.^{68–72} There is no airflow obstruction unless a second pathology such as asthma or COPD is present.^{68,77} With large R-L shunts (>20%), the carbon monoxide diffusing capacity (DL_{CO}) is often moderately reduced (71% to 78%),^{68,71} but in the majority of patients with less R-L shunting, DL_{CO} is equal to or greater than 90% of predicted (interquartile range, 76% to 100%).⁷² Patients with the lowest DL_{CO} values generally have widespread and small vascular malformations.

Physiologic Consequences of Posture and Exercise

Posture. PAVMs are more common in the lower lobes than in the upper lobes.^{8,68} Hence, for gravitational reasons, the shunt fraction tends to increase when patients stand up; in one study, R-L shunt increased from 28.7% to 39% in eight patients upon standing.⁶⁹ Accordingly, arterial oxygen saturation falls. In 257 patients reported recently, 75 (29%) demonstrated orthodeoxia with an oxygen saturation fall of at least 2% on standing.⁷⁸ This was accompanied by an orthostatic tachycardia, with an age-adjusted pulse rise of 0.79 min^{-1} per 1% arterial SO_2 fall ($P < 0.001$).⁷⁸

Exercise. In the healthy lung during exercise, PVR falls to half its value at rest, attributed to dilation and recruitment of vessels in the pulmonary capillary bed. The effects of exercise on pulmonary hemodynamics in a PAVM-affected patient depend on the change in vascular resistance through the shunt channels in relation to the change in the resistance of the normal channels. In one group of eight patients with PAVM with severe arterial hypoxemia on exercise (arterial oxygen saturation $74\% \pm 3\%$), there was an

excessive increase in total pulmonary blood flow (142% of predicted) in relation to the observed *oxygen consumption* ($\dot{V}O_2$), resulting, in turn, in higher than predicted tissue oxygen delivery on exercise.⁶⁷

The change in arterial oxygen saturation from rest to exercise depends both on the change in the shunt fraction and the fall in mixed venous oxygen saturation on exercise. For patients with PAVM, overall, the fall in arterial oxygen saturation (rest to exercise) averaged 6% for mean shunts greater than 30%,^{67,70} 3% for mean shunts of 20% to 25%,^{68,70,72} and 1% to 2% for mean shunts less than 12%.⁷²

Overall, gas-exchange efficiency in terms of the *ventilatory equivalent* ($\dot{V}E/\dot{V}O_2$) is abnormally high on exercise; observed values are directly related to the exercise R-L shunt and inversely related to exercise arterial oxygen saturation.^{67,80}

Work capacity is well preserved in PAVM patients, even when arterial oxygen saturation on exercise is less than 80%.^{72,80} The adaptive responses are lost following correction of hypoxemia.^{77,80,90} In a recent study, despite higher arterial SO_2 , treated patients achieved similar work rates and similar peak oxygen consumption.⁸⁰ It is noteworthy that treated patients reset to virtually identical peak oxygen pulses and, in many cases, to the same point on the peak oxygen pulse/work-rate plot.⁸⁰

Pulmonary Hypertension

Pulmonary hypertension has been recognized in a number of patients with HHT.⁸¹⁻⁸⁹ The causes of pulmonary hypertension in HHT are diverse, as in the normal population. Two forms of pulmonary hypertension predominate in HHT: true pulmonary hypertension and postcapillary pulmonary hypertension seen in the context of high-output cardiac failure secondary to hepatic AVMs, a potentially reversible form of pulmonary hypertension. Mixed pictures are also observed.⁸¹ The frequency of pulmonary hypertension and hepatic AVMs differs with HHT genotype: pulmonary hypertension, and hepatic AVMs are more common in HHT type 2—due to *ACVRL1* mutations—than in other forms of HHT.^{86,88}

The overall prevalence of pulmonary hypertension in HHT is relatively low. Catheter-based studies in a group of 143 PAVM/HHT patients undergoing PAVM embolization, identified values for mean PPA as 13 (11 to 16) mm Hg, compared to normal values of 7 to 19 mm Hg.⁸¹ While PPA mean exceeded 20 mm Hg in 9 of 143 patients (6%), only 2 referred from services other than specialized pulmonary hypertension units had mean PPA values exceeding 35 mm Hg.⁸⁹ In one echocardiographic study of 68 HHT patients (ages 19 to 84 [mean 51] years), estimated systolic PPA values (40 to 58 mm Hg) were above the normal range in 9 (20.5%).⁸⁴ A separate study suggested pulmonary hypertension rates were higher (>30%) in hospitalized than in nonhospitalized patients.⁸⁹

CLINICAL FEATURES

Respiratory Symptoms

Dyspnea. Dyspnea is the respiratory symptom most commonly reported by PAVM patients, but this is present in less than 50% of all cases (see Table 61-1) and may not be

appreciated until after the condition has been treated. In one series of 219 consecutive patients, symptomatic dyspnea was generally only present when resting arterial oxygen saturations were less than 80%.^{74,81} Three subsequent studies showed no relationship between arterial SO_2 and dyspnea as self-reported (N = 165, arterial SO_2 78.5%-99%);⁷⁷ by Borg scales during cardiopulmonary exercise testing (N = 21, arterial SO_2 80%-96%);⁷⁸ or as self-reported during flight (N = 99; arterial SO_2 85%-99%).⁹¹ None of 75 consecutive patients demonstrating orthodeoxia reported platypnea (dyspnea on standing).⁷⁸

Hemoptysis. The fragile vessels in HHT should be more prone to hemorrhage than normal pulmonary vessels but, surprisingly, hemoptysis and hemothorax are relatively rare features for PAVMs (see Table 61-1), with two important exceptions: (1) with a spontaneous or postembolization systemic arterial blood supply to PAVM sacs,^{57,59,92} and (2) with pregnancy-associated changes.^{61,63} Both conditions place patients at higher risk of hemorrhage from PAVMs, which may be massive and life-threatening.

Chest Pain. Pleuritic chest pain of uncertain etiology may be described in up to 10% of PAVM patients (see Table 61-1). PAVM associations are likely to be overestimated, however, in series that do not correct for ascertainment bias of incidental PAVM detection following protocol-driven CT scans for suspected pulmonary embolism.

Strokes and Cerebral Abscess

PAVMs pose a substantial risk to patients because of paradoxical emboli leading to cerebral abscess or ischemic stroke,⁹³ as repeatedly reported in high proportions of patients in historical series (see Table 61-1).^{7,94,95} In more recent series, in which correction was made for ascertainment bias (i.e., diagnosis of PAVMs because of the presentation with stroke/abscess), rates for cerebral abscess were 7.8% to 9%^{74,96} and for ischemic stroke were 11.3% (Fig. 61-4).⁷⁴ Relative risks compared to control populations were particularly high in young adults.⁷⁴

Small studies using univariate analyses had suggested that neurologic complications were more common in patients with more severe PAVMs, defined by either PAVM size⁹⁷ or diffuse characteristics.⁵⁹ Paradoxical embolic events are more common in patients with the higher grade contrast echocardiography shunts that are more likely to be associated with visible PAVMs seen on CT.⁹⁸ Once PAVMs are sufficiently large for CT detection, or grade 3 shunts, there is little evidence that stroke risk is substantially influenced by further increase in shunt size^{74,76} or by conventional stroke risk factors (smoking, hypertension, diabetes mellitus, atrial fibrillation, and hypercholesterolemia).^{74,76} Ischemic strokes only occasionally develop following venous thromboemboli.^{65,74,76}

The strongest risk factor for ischemic stroke in the presence of PAVMs appears to be iron deficiency, with the risk of stroke falling by 0.96 for every 1 μ mol increase in serum iron.⁷⁶ Exuberant platelet aggregation to 5HT was proposed as a mechanistic link.⁷⁶ Two overlapping cohorts demonstrated that ischemic strokes were less common in patients with higher mean PPA^{74,76} and, once adjusted for PPA, marginally more frequent in patients with lower arterial SO_2 .⁷⁶

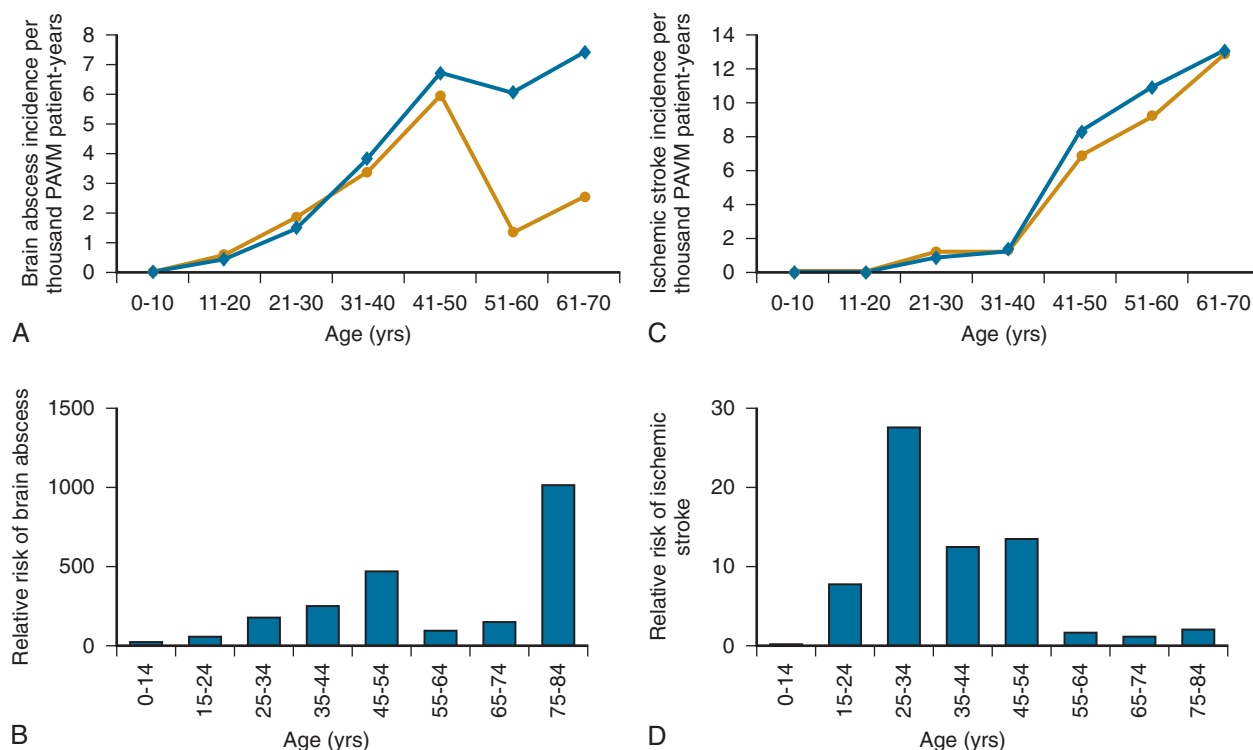


Figure 61-4 Age-specific incidence rates and relative risks of brain abscess and ischemic stroke. Age-specific incidence rates of brain abscess (A) and ischemic stroke (C) for all patients (diamonds/blue lines), and patients excluding ascertainment bias (solid circles/brown lines). Relative risk (fold increase) for brain abscess (B) and ischemic stroke (D) for pulmonary arteriovenous malformations patients, excluding individuals who presented because of their stroke/abscess. Brain abscess and stroke rates are compared to the general population. (Redrawn from Shovlin CL, Jackson JE, Bamford KB, et al: Primary determinants of ischaemic stroke and cerebral abscess are unrelated to severity of pulmonary arteriovenous malformations in HHT. *Thorax* 63:259–266, 2008.)

For cerebral abscess, there were strong associations with male gender and dental microorganisms⁷⁴; once adjusted for male gender, there was also an association between lower arterial SO_2 and brain abscess.⁷⁴

Other Neurologic Events

An excess of migraine was first noted in HHT populations.^{99,100} Multiple studies have now demonstrated that the risk of migraine in patients with HHT is approximately doubled if they have PAVMs,¹⁰¹⁻¹⁰⁶ and there is evidence that migraines improve following PAVM treatment.^{102,104} The theoretical basis for scuba diving–related stroke risks is discussed elsewhere.¹⁰⁷

Pregnancy

Pregnancy carries specific hazards for women with PAVMs,^{61,63,108-111} including for women who have been treated for PAVMs.⁶¹ In a study of 484 pregnancies in women with HHT and PAVMs, 1% of pregnancies (95% CI, 0.13% to 1.9%) resulted in maternal death.⁶¹ Maternal deaths have been attributed to PAVM hemorrhage (1% of pregnancies; 95% CI, 0.1% to 1.9%),⁶¹ cerebral hemorrhage,⁶¹ and pulmonary emboli. In four women, the severity of PAVMs associated with life-threatening hemorrhage could be evaluated: two had small PAVMs associated with normal arterial oxygen saturations and near-normal R-L shunts; none had evidence of pulmonary hypertension.⁶¹ In women experiencing a life-threatening event, prior awareness of HHT or of a diagnosis of PAVM was associated with improved survival ($P = 0.04$).⁶¹

DIAGNOSIS

Classic PAVM cases with large R-L shunts are easy to diagnose because of cyanosis, clubbing, a vascular bruit, and characteristic chest radiographs displaying lobulated masses and dilated feeding arteries and draining veins. Detection of smaller PAVMs, however, often requires a high degree of clinical suspicion.

Imaging

The classic appearance of a PAVM on chest radiography, chest CT, and catheter pulmonary angiography consists of a circumscribed, rounded, soft tissue nodule of any size associated with enlarged feeding and draining vessels (see Fig. 61-1, eFig. 61-1). Complex PAVMs are generally less well defined, although rounded nodular elements associated with prominent feeding arteries and draining veins are usually evident (eFig. 61-2). Diffuse lesions involving whole lung segments are seen as an area of generalized increased opacity with marked prominence of vascular markings but no discrete nodules. Before 2007, there was widespread opinion that the only PAVMs of clinical significance had feeding artery sizes larger than 3 mm, and the goals of many screening programs reflected this. Data presented in this era were that the chest radiograph was abnormal in 60% to 90% of instances.^{68,72,112} It is anticipated that the frequency of positive standard frontal radiographs will fall further as smaller PAVMs are sought (eFig. 61-3), in keeping with the recognition that these are an important cause of neurologic complications.^{74,76,97}

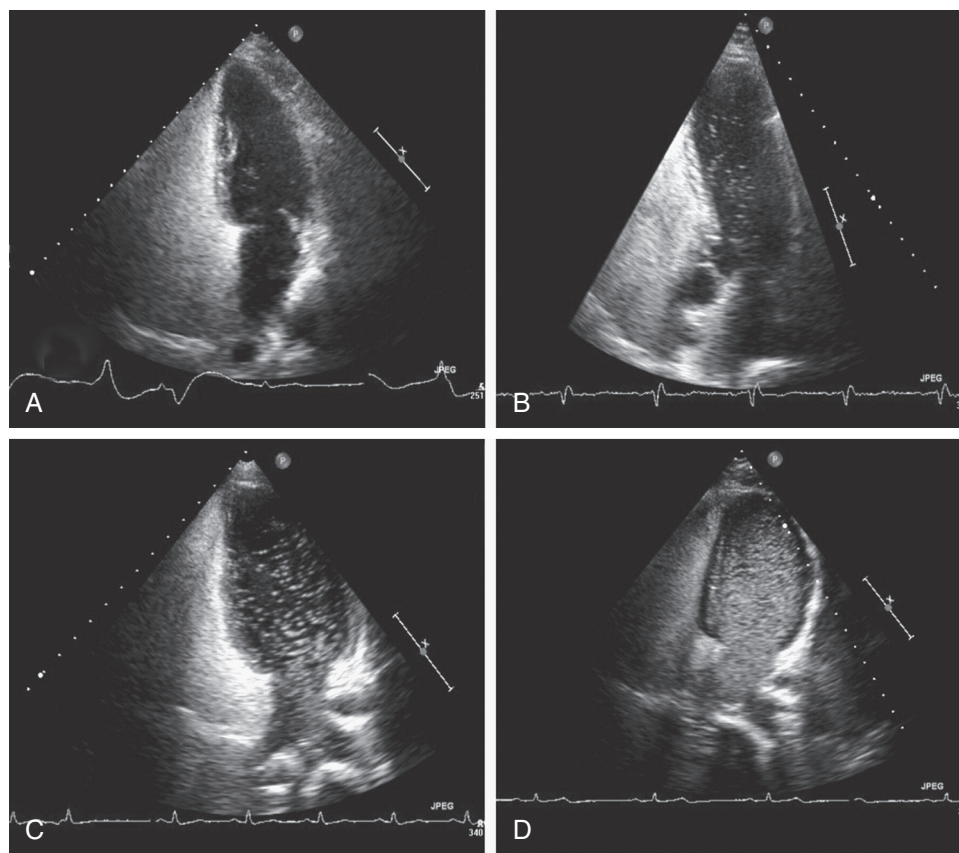


Figure 61-5 Contrast echocardiography showing different grades of left ventricular opacification. The grades shown are minimal (A), moderate (B), extensive (C), and extensive (D) with endocardial definition. The likelihood of detecting a pulmonary arteriovenous malformation on chest CT increases with higher grades of abnormality. (From Parra JA, Bueno J, Zarauza J, et al: Graded contrast echocardiography in pulmonary arteriovenous malformations. *Eur Respir J* 35:1281–1285, 2010. Reproduced with permission of the European Respiratory Society.)

Chest CT, without intravenous contrast medium, usually demonstrates the anatomy of PAVMs and their feeding vessels^{56,57,113} (see eFigs. 61-1C, 61-2C-F, 61-3C, and 61-4C, D, G, and H; see also eFig. 18-15); the radiation burden is greatly lessened and the resolution improved by the use of newer multislice CT protocols, which limit x-ray exposure to a single short breath-hold scan and which allow elegant multiplanar reconstructions of the images (see eFig. 18-15). MR imaging has been less effective than CT or pulmonary angiography in detecting small PAVMs with rapid blood flow.¹¹⁴ Methodology, though, is improving,¹¹⁵ and this modality does have the advantage that it provides no radiation exposure. But the frequency of its use may not increase as attention focuses on identification of the small CT-evident, yet clinically significant PAVMs (see also Chapter 18). Where there are difficulties with interpretation of dilated and apparent vascular structures, confirmation of R-L shunting may be helpful. A recent pictorial review highlights anatomic PAVM “mimics.”⁵⁸

Measurement of Right-to-Left Shunt

Classically, R-L shunts were calculated by measuring the arterial PO_2 in a patient breathing 100% oxygen, and by measuring ^{99m}Tc -macroaggregated albumin distribution to lung and kidney. R-L shunt measurements by either of these methods may confirm a diagnosis suspected on clinical grounds and provide useful follow-up data, but

neither is now generally used for diagnosis or follow-up of PAVMs.

Contrast Echocardiography. The method of *contrast echocardiography* (CE; synonym “echo-bubble”) demonstrates intrapulmonary shunts by tracing the circulatory transit of microbubbles generated by intravenously injected echocontrast material. Microbubbles seen in the left heart should therefore be the result of an R-L shunt, either cardiac (most commonly a patent foramen ovale) or pulmonary. Typically, with an intrapulmonary shunt such as a PAVM, the number of bubbles in the left heart increases after a matter of seconds (Fig. 61-5 and Video 61-1). The entry of bubbles is not affected by the cardiac cycle or respiration, and though influenced slightly by a Valsalva maneuver, this is in a more subtle manner to the changes observed with a patent foramen ovale.

CE consistently detects more intrapulmonary R-L shunting in HHT patients than any other PAVM screening modality.¹¹⁶⁻¹²⁵ False-negative results can result, but it was early reports demonstrating high sensitivity with no attendant radiation burden that led to current guidelines recommendations to use CE as the first-line method for PAVM screening.¹¹⁸

Presence of a positive shunt by echocardiography does not imply that a macroscopic PAVM will be found. Appreciable proportions of the general population exhibit intrapulmonary shunting; in one early study, intrapulmonary

shunts were found in 5 of 19 healthy subjects in whom contrast was injected directly into the pulmonary artery, thereby bypassing any intracardiac shunt.¹¹⁹ More recent studies using CE documented shunting in 6% to 7% of control subjects at rest,¹²⁰ rising to as high as 90% on exercise.¹²¹ Previous studies demonstrated a high frequency of false-positive results in which PAVMs were not identified by subsequent angiography, considered to be the “gold standard” for detection of PAVMs.^{112,119,123} For patients with endoglin mutations, a positive CE study only provided a positive predictive value for a treatable PAVM of 36.3%.¹⁵

Reassuringly, in the HHT-based research studies, no treatable PAVMs were found in individuals with negative CE studies, although these accounted on average for only 39% of screened individuals.¹¹⁹⁻¹²⁵ In one study of patients stratified by HHT mutations, 85% of those with endoglin mutations and 35% of those with *ACVRL1* mutations had a positive shunt by CE.¹⁵

Specialist groups have incorporated grading systems to examine whether clinically significant PAVMs could be excluded by low-grade positive CE studies (see Fig. 61-5). The broad grades of CE shunt severity range from grade 1 (found in at least 7% to 8% of the general population^{15,120,121}), to grades 3 and 4, which are more frequently associated with visible PAVMs seen on CT (see Fig. 61-3) and neurologic complications.⁹⁸ In a recent two-center study of 1038 patients undergoing PAVM screening, 530 (51%) had a positive CE shunt, but there was no enhanced stroke risk in patients with grade 1 shunts (<30 microbubbles per frame).⁹⁸ For patients with grade 2 (30 to 100 microbubbles per frame) or grade 3 (>100 microbubbles per frame) shunts, the odds ratios for cerebral ischemic event or brain abscess were 4.8 ($P = 0.03$) and 10.4 ($P = 0.002$), respectively.⁹⁸ In general, with increasing grade of abnormality on CE, the likelihood of finding a PAVM on CT and the risk of embolic events increase.

Screening Patients

The importance of screening programs for HHT is highlighted by the high proportions of patients with HHT/PAVM who are undiagnosed at the time of their PAVM-induced ischemic stroke or cerebral abscess (in one series, 66.7% and 64.3% respectively).⁷⁴

Screening modalities differ among PAVM centers, according to the expertise of the institution. Common to all programs are the policies of minimizing the radiation burden in an often young population and having a sensitive screen to detect all clinically significant and treatable PAVMs: the choice of study is usually chest CT or CE. With new generations of multislice chest CT scanners, diagnosis of clinically significant PAVMs can be made efficiently and quickly using a single-breath scan. Many specialized PAVM units with extensive CE expertise use CE as a first-line screen for PAVMs, reserving the radiation exposure of CT for patients with a positive CE shunt and, in some cases, with a CE shunt of a particular severity. At other institutions, CE is not used routinely because most CE studies yield positive results (see earlier discussion) and because of uncertainty about whether the published data provide sufficient confidence to withhold a CT, given the variability of CE-detected shunts with posture, Valsalva maneuvers, and repeat studies.¹⁰⁷ Some centers use pulmonary angiography as a tool to

confirm the diagnosis but, to reduce the radiation burden, we prefer to restrict angiography to therapeutic embolization sessions.

MANAGEMENT

A recent Cochrane database review concluded that randomized control trials of embolization of PAVMs have not been performed owing to ethical considerations, but that accumulated data from observational studies suggest embolization reduces morbidity.¹²⁶

Embolization

Percutaneous transcatheter embolization, which was introduced in 1978,^{127,128} is now the treatment of choice for the vast majority of patients.^{57,66,113,129-140} Vessels are considered for embolization when they are amenable to treatment, usually greater than 2 to 3 mm in diameter. The technique of embolization at our institution has been described previously.⁶⁶ The procedure is performed with antibiotic prophylaxis administered as a single dose 1 hour before angiography. Via a femoral venous approach, under local anaesthesia, pulmonary angiography is first performed using a pigtail catheter, which is then exchanged for a long 6-French straight sheath and a 5-French catheter combination. The feeding vessels to the PAVMs are selectively catheterized in turn and are occluded at the junction between the artery and venous sac with detachable metallic plugs and/or coils (eFigs. 61-4C-H and 61-5).

Amplatzer vascular plugs are rapidly becoming the preferred agent for PAVM embolization.¹³¹⁻¹³³ They have a number of important advantages over coils, including the ability to occlude the feeding vessel to a PAVM at the neck of the venous sac, the ability to occlude large diameter feeding arteries (measuring up to 1.2 mm in diameter) with single Amplatzer vascular plugs so that a larger number of PAVMs can be embolized in a single session (reducing radiation exposure), and the ability to occlude over a shorter length of vessel, thereby reducing the likelihood of occluding vessels supplying normal lung.¹⁰⁷

Long-Term Outcome. Anatomic long-term results of transcatheter embolization have been evaluated by several centers. After embolization, residual shunting through untreatable (<2 to 3 mm diameter) arterial feeding vessels is common (see eFig. 61-4H). Additionally, treated PAVMs may recanalize and/or reperfuse.^{57,113,132-135,138} Factors associated with reperfusion include a low number of coils, oversized coils, proximal placement of coils, and altered pulmonary hemodynamics (development of pulmonary hypertension or presence of hepatic AVMs).¹³⁴⁻¹³⁷ In one series of 192 PAVM patients in whom feeding arteries less than 3 mm in diameter were embolized,⁷⁴ 70% had residual disease, a finding supported by other studies (eTable 61-1).^{104,129,130} It has been recommended to use CT scans for 6-month and 1-to-3-years follow-up,¹¹⁸ but the recently documented radiation burden¹³⁷ calls this into question: In one series of 246 PAVM patients with HHT, CT scans accounted for 46% of the mean *cumulative effective dose* (CED).

Physiologic Outcome. Substantial improvement in oxygen saturation is the rule for patients with preembolization

eTable 61-1 Pre- and Postembolization Physiologic Results from Centers Treating Large Numbers of Patients with Pulmonary Arteriovenous Malformations

Center/Reference	No. Patients	R-L Shunt (%)		Arterial SO ₂ (%)		Residual Shunt Present (%)
		Pre	Post	Pre	Post	
BALTIMORE/YALE						
Pre–1983 ¹⁸²	10	44	24	76–80*	82–92*	
1978–1987 ⁸	76			79–83*	90–94*	
1978–1995 ¹¹⁷	45			85–89*	93–97*	
1978–2006 (subgroup diffuse) ⁴⁹	36					
Unilateral				87 ± 7	95 ± 3	
Bilateral				79 ± 8	85 ± 7	
HAMMERSMITH						
1984–1990 ⁷⁰	15	33	19	86 [†]	92 [‡]	
1987–1994 ⁶²	53	23	9	89	94	60
1994–1999 ⁶⁶	66	13	6	93	96	72
2006–2008 amp	69			94	96	
SAN FRANCISCO						
1986–1991 ⁶⁵	8	25	13	84–88*	92–96*	
NETHERLANDS						
1990–1995 ¹¹³	32	17	7	91–95*	93–97*	63
1988–2001 ¹⁸³	112					
DENMARK						
1994–1998 ¹¹⁴	12	21 [‡]	13 [‡]	266 mm Hg [§]	439 mm Hg [§]	73

*Arterial oxygen saturation (SO₂) values derived from arterial PO₂ measurements via standard oxygen dissociation curve.

[†]R-L shunt and arterial SO₂ measured in semirecumbent or supine posture.

[‡]Calculated from arterial PO₂ assuming hemoglobin concentration of 13.9 g/dL and C(a-v)O₂ = 4.4 mL/100 mL.

[§]Arterial PO₂ values breathing 100% oxygen.

hypoxemia (see eTable 61-1),^{71,77,81,129,138-140} with little effect on other pulmonary function measurements.^{68,72,75} Compensatory mechanisms reset; falls in hemoglobin restore arterial oxygen content to pre-embolization levels.⁷⁷ Stroke volume and cardiac output also fall after treatment of PAVMs,⁹⁰ and oxygen consumption at peak exercise is unchanged.⁸⁰

Clinical Outcome. Unsurprisingly exercise capacity, which is often relatively unimpaired before embolization,⁸¹ only improves in a subgroup of patients.⁷⁵ Concurrent cardiopulmonary disease was a predictor of improvement in one series of 98 treated patients.⁷⁷ Several studies have now demonstrated the clinical efficacy of embolization in improving stroke/abscess risk⁷⁴ and reducing the prevalence of migraine.^{102,104}

Risks of Embolization

In expert hands, embolization is efficacious and complications are rare, even though the procedure is not without risk. Successive series highlight a learning curve, and smaller series have higher complication rates. The most common complication is transient pleurisy in up to 10% of patients, particularly those with peripheral PAVMs. Higher rates are seen in patients with diffuse PAVMs.⁵⁹ The mechanism for the pleurisy is unknown, but it appears unrelated to pulmonary infarction.^{68,72} Angina is rare and is attributed to transient air bubble emboli, and has been reduced by technical advances reported in later series. There are occasional reports of long-term neurologic complications after embolization due to paradoxical emboli.¹⁴¹

Radiation Exposure. New data demonstrate that currently employed protocols can result in levels of radiation exposure that would be classified as harmful.¹³⁷ In a single center study of 246 PAVM patients (53 years mean age), the mean CED over an 11-year period was 51.7 mSv, and CED exceeded 100 mSv in 26 patients (11%).¹³⁷ Interventional procedures accounted for 51% of the CED.¹³⁷

Development of Systemic Arterial Supply. The risk of massive hemoptysis from PAVM sacs that persist after embolization and that acquire a systemic arterial collateral blood supply was first highlighted in a small series published in 1998.⁹² In view of the known importance of pulmonary-bronchial communications (see Systemic-to-Pulmonary Vascular Communications), systemic collaterals might be expected to develop to supply an area of the pulmonary capillary bed that had lost its pulmonary arterial supply as a result of embolization. Systemic supply is only of consequence if the fragile PAVM sac persists. None of the patients in Brillet and coworkers' series¹⁴² experienced hemoptysis, in contrast to the majority of those in a smaller series.⁹² To reduce the risk for development of systemic arterial collateral supply to any persistent sac, standard practice is to place embolization devices as close as possible to the neck of the malformation (see eFigs. 61-4C-H and 61-5).^{107,132} This is particularly difficult in patients with diffuse PAVMs, in whom sac persistence is inevitable. Expert institutions differ in the degree to which such PAVMs are embolized. At our institution, more limited embolization is undertaken and in the presence of ongoing neurologic symptoms

or hemoptysis, surgical resection is considered. Other approaches include dense packing of the most severely involved segmental arteries.⁵⁹

Development of Pulmonary Hypertension. PAVM embolization may be expected to elevate PPA, because PAVMs provide low-resistance pathways for pulmonary blood flow. Individual cases in which PPA increased both after embolization and after surgical resection are reported.^{71,81,143-147} In one series of 35 patients, there was no evidence of a sustained or acute change in PPA in the majority of patients and, in half, embolization led to a fall in PPA.⁸¹

Should embolization of PAVMs be performed in patients with severe preexisting pulmonary hypertension? This question was specifically addressed in light of lower stroke risk^{74,147} and data indicating that test balloon occlusion did not predict subsequent rise in PPA following definitive embolization.⁸¹ The main indications for PAVM embolization are to reduce the risk of paradoxical embolic stroke/brain abscess and, for individuals with hypoxemia, to improve dyspnea and exercise tolerance. The authors concluded that, for patients with preexisting severe pulmonary hypertension, the risks of PAVM embolization generally outweigh potential benefits.^{81,147} It was recognized that the most difficult judgments relate to individuals with severe pulmonary hypertension and major hemoptysis.^{81,147} Additionally, it is now recognized that higher PPA is one of the predictors for symptomatic improvement post embolization.⁷⁷

Nonembolization Options

There are circumstances when PAVMs cannot be treated by embolization, with the most common reason being that the feeding artery is too small (<2 mm diameter).

Surgery. Surgery remained the treatment of choice until the 1980s but was never the ideal solution for the multiple PAVMs of HHT; more recently, however, surgery has been a useful adjunctive therapy for selected cases. There may be times when small PAVMs are single or sufficiently localized for thoracoscopic resection when embolization is not feasible. At our institution, and elsewhere,¹⁴⁸ elective surgical treatments are reserved for patients demonstrating ongoing ischemic strokes or transient ischemic attacks following maximal embolization. In emergency situations, particularly associated with massive hemoptysis, lobectomy or pneumonectomy may be appropriate.^{61,148,149}

Lung transplantation has been undertaken in a few patients with severe hypoxemia secondary to diffuse disease.¹⁵⁰⁻¹⁵² The long-term complications of untreated PAVMs, however, are likely in most cases to be less than transplantation-associated morbidity and mortality. The three patients with PAVM in our clinic (one male, two female) who elected not to proceed with transplantation—after discussion of the risks at two different transplantation centers—have since remained stable over 20, 22, and 25 years, and one patient has had three successful pregnancies. In a retrospective series of 36 patients with diffuse PAVMs for whom follow-up data were available for a mean of 8.5 years (range, 0.12 to 26 years), 24 of the 27 survivors were working or studying full time; one of the deaths was transplantation associated.⁵⁹

Medical Management

Dental Issues. For patients with PAVMs and HHT, owing to the strong link between oral bacteria and cerebral abscess, antibiotic prophylaxis before dental and surgical procedures was recommended based on the endocarditis paradigm.¹⁵³⁻¹⁵⁵ The evidence for an association between oral microorganisms and brain abscess has since been strengthened.^{74,156} American Heart Association¹⁵⁷ and British National Institute for Health and Care Excellence¹⁵⁸ guidelines indicate that antibiotic prophylaxis is no longer required for most patients with structural heart disease at risk for infective endocarditis. This has led to confusion among dentists and medical practitioners caring for patients with PAVM. A recent article exploring why PAVM/HHT patients do not fall into the groups considered by the guidelines provided recommendations to reduce the risk of dental bacteremias, including the use of antibiotic prophylaxis before dental procedures.¹⁵⁹

Pregnancy. In view of the risks of PAVM growth and rupture during pregnancy, it is recommended that female patients be advised to defer pregnancy pending formal PAVM assessment and treatment. Pregnancies should be managed with close liaison between obstetricians, pulmonologists, and interventional radiologists, using appropriate “high-risk” obstetric management strategies.⁶¹ Patients and their medical practitioners should be alerted to the possibility of hemoptysis or sudden severe dyspnea that requires urgent admission and management: embolization in the second and third trimesters is feasible.^{61,160} The question of whether PAVM embolization should be offered to asymptomatic pregnant women differs between countries; at our institution it is not performed.⁶¹

Thromboembolic Risks. The American Stroke Association recommends antiplatelet agents for secondary prevention of ischemic stroke in PAVM patients.⁹³ Antiplatelet therapy can be considered on a case-by-case basis for patients, even if there is underlying HHT.¹⁶¹ Venous thromboemboli are common, associated with conventional venous thromboembolism risk factors and iron deficiency,¹⁶² and both prophylaxis and treatment with anticoagulants may be required, even when HHT is present.¹⁶¹

SYSTEMIC-TO-PULMONARY VASCULAR COMMUNICATIONS

ANATOMY

Communications between the systemic and pulmonary circulations are part of normal anatomy, in that terminal branches of the bronchial microcirculation communicate with peripheral pulmonary artery branches (Fig. 61-6A). These vessels are functionally important in preventing lung infarction in the great majority of cases of pulmonary embolic disease. Their presence may be detected during specialized functional scans such as contrast-enhanced, time-resolved perfusion MR imaging of regions of the lung in which hypoxic pulmonary vasoconstriction reduces pulmonary arterial supply; late filling might reflect the systemic arterial component.¹⁶³ In the presence of chronic intrapul-

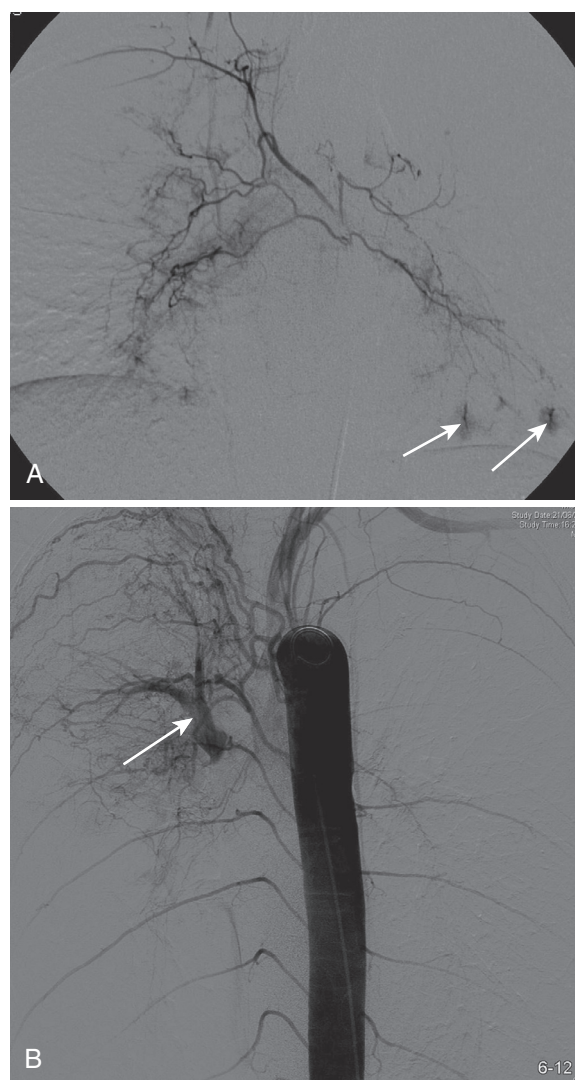


Figure 61-6 Catheter angiogram imaging of normal and abnormal bronchial circulations. **A**, Selective digital subtraction angiogram showing normal bronchial arteries. Normal peripheral pulmonary artery branches are opacified (arrows) via normal bronchopulmonary anastomoses. **B**, Digital subtraction descending aortogram in a patient with hemoptysis due to previous right apical tuberculosis. There is bronchial and nonbronchial systemic artery hypertrophy supplying the right upper zone, with retrograde opacification of the entire right upper lobe pulmonary artery (arrow) via enlarged bronchopulmonary anastomoses.

monary inflammatory disease, normal bronchopulmonary anastomoses enlarge considerably (Fig. 61-6B), increasing the perfusion pressure to the diseased lung, thereby increasing the likelihood of bleeding. Abnormal precapillary communications develop in multiple respiratory pathologies¹⁶⁴ especially when chronic inflammatory pulmonary disease is located peripherally and systemic supply is recruited transpleurally through dense inflammatory adhesions between the lung and the chest wall (eFig. 61-6 and Video 61-2). Direct communications between systemic arteries and the pulmonary circulation are also observed in several other settings (see later), such as when systemic arteries communicate with the pulmonary artery or its branch via the pulmonary ligament, which encloses the lung hilum. Intralobar sequestration (see Pulmonary Sequestration) is a developmental anomaly in which a systemic artery replaces a segmental pulmonary artery (see eFig. 18-18).

Adult (Acquired) Systemic-to-Pulmonary Communications

As noted, abnormally large systemic-to-pulmonary communications form part of the inflammatory response to the presence of chronically inflamed or necrotic lung tissue; the most frequent causes, according to Yoon and colleagues,¹⁶⁵ are pulmonary tuberculosis (usually chronic), aspergilloma (secondary to chronic sarcoidosis or tuberculosis), and bronchiectasis, including that caused by cystic fibrosis¹⁶⁶ (see Fig. 61-6B). Overlying pleural thickening provides transpleural access for systemic vessels arising from the intercostal (see eFig. 61-6), internal mammary, thyrocervical, axillary, and inferior phrenic arteries. For more proximal intrapulmonary disease, vascular hypertrophy and new vessel formation arise within the bronchial circulation.

Fetal and Perinatal Systemic-to-Pulmonary Artery Collaterals

During bronchial branching in the developing fetus, the dividing buds are supplied by a capillary plexus derived from the primitive aorta; this plexus later regresses as the growing lung advances and the developing pulmonary artery takes over. Between the 40th and 50th days of gestation, the lungs have a dual source of blood supply.^{166,167} Systemic-to-pulmonary artery collaterals arising from the proximal or distal part of the aortic arch persist in later gestation and were functional in 88 of 133 (66%) premature, very-low-birth-weight (<1500 g) infants, and declined with maturity, until, at 1 year of age, only 2 of the original 88 infants still had collaterals.¹⁶⁸

When present postnatally, these vessels, which provide additional L-R shunts, effectively function as a miniature patent ductus arteriosus, placing the neonate at higher risk for heart failure, which developed in 11% of infants with systemic-to-pulmonary artery collaterals in one series.¹⁶⁸

Aberrant Congenital Systemic-to-Pulmonary Communications

In addition to persistent fetal systemic-to-pulmonary artery collaterals, other congenital vascular anomalies are recognized but rarely cause problems. The systemic artery is usually the internal mammary or a coronary artery. Iskandrian and colleagues¹⁶⁹ reported 12 patients with coronary-to-pulmonary artery communications, mostly discovered accidentally during routine coronary angiography for chest pain. Large-flow congenital systemic-to-pulmonary artery collaterals characteristically present in the second or third decade of life with a continuous murmur similar to that of a patent ductus arteriosus. Hearne and Burbank¹⁷⁰ reviewed 11 reported cases of communications between an internal mammary artery and the pulmonary arteries; 8 cases were considered to be congenital, 2 traumatic, and 1 neoplastic in origin.

Cavopulmonary Anastomoses

Systemic-to-pulmonary artery collaterals are a feature of Glenn/Fontan circulations constructed surgically as a palliative correction for tricuspid atresia or a functionally univentricular heart,¹⁷¹ operations that are also associated with the development of PAVMs in the lung deprived of hepatic venous blood (see Cavopulmonary Shunts earlier). In a retrospective series by McElhinney and associates,¹⁷²

59% of 76 patients had systemic-to-pulmonary artery collaterals on follow-up catheterization at approximately 2.5 years; their presence, however, was not associated with a poorer outcome.

TREATMENT

Treatment requirements depend on the presence of symptoms. Even systemic-to-pulmonary artery collaterals derived from coronary arteries generally do not “steal” blood flow from the coronary artery.¹⁶⁹ Whereas earlier cases from series spanning 1947 to 1979 were treated with ligation of the vessels and resection of the lobe, more recent cases were left untreated. Treatment is now offered in three settings: (1) for hemoptysis, the most common complication of acquired systemic-to-pulmonary artery collaterals, (2) for heart failure, predominantly affecting neonates with persistent fetal collaterals,¹⁷⁰ and (3) for high-flow-induced pulmonary hypertension in patients with Fontan circulations.¹⁷²

Managements of Hemoptysis

Hemoptysis from systemic-to-pulmonary artery collaterals may be massive and require emergency management. Bronchoscopy may help localize the source of bleeding,¹⁷³ but chest CT performed during the aortic phase of contrast enhancement is usually more informative; CT angiograms document the underlying cause of bleeding in most instances and clearly demonstrate the presence or absence of hypertrophied bronchial (see eFig. 19-3) or nonbronchial systemic arteries.¹⁷⁴ In an emergency, angiography takes precedence, with a view to proceeding quickly to embolization of the bleeding vessels. In 1977, Rémy and associates¹⁷⁵ reported their results of selective bronchial artery angiography and embolization in 105 patients with hemoptysis.

Bronchial artery or collateral vessel embolization is carried out at angiography with particulate polyvinyl alcohol; it is a highly specialized interventional radiology technique (see eFig. 18-19).^{176,177} Complications are uncommon, but one of the most feared is that of a transverse myelitis, which may result if a spinal artery arising from an intercostal or bronchial artery is inadvertently embolized. The use of “superselective” coaxial catheters (3-French gauge), with peripheral placement of the tip in a stable position distal to normal arterial branches and without reflux after injection, has made the procedure much safer.¹⁷⁶⁻¹⁷⁸ In 80% to 90% of cases, immediate control of hemoptysis is achieved,¹⁷⁹ although 20% rebleed in the first 6 months, and a further 50% have significant hemoptysis on longer follow-up; repeat embolization is usually helpful in these individuals. While bronchial artery embolization is not curative and the risk of further hemoptysis is always present, embolization can be repeated several times.

Surgery is falling out of favor as first-line treatment for massive hemoptysis for three main reasons: (1) the patient's condition is often poor, (2) the disease is usually extensive and often bilateral, and (3) pleural thickening is present and traversed by extensive collateral vessels that often adhere the lung to the chest wall. In 10 series, the average perioperative mortality for pleuropulmonary aspergilloma resection was 9% (range 0 to 23%).¹⁸⁰ Increasingly, surgery is

confined to low-risk cases in which recurrent hemoptysis is a problem.

PULMONARY SEQUESTRATION

CLASSIFICATION

Pulmonary sequestration, also called bronchopulmonary sequestration, was first described by Pryce¹⁸¹ in 1946 and defined by him as “an abnormal artery from the aorta supplying a bronchopulmonary mass or cyst which is dissociated from the normally connected bronchial tree.” A distinction is usually made between intralobar sequestrations, which share a common visceral pleural investment with the adjacent normal lung tissue, and the much less frequent extralobar sequestrations, which have their own pleural lining that separates them from the remaining lung tissue. Both types have an abnormal systemic blood supply, most often from the thoracic aorta but, in roughly 20% of cases, the artery originates from the abdominal aorta; atypical origins of the feeding vessels, even from coronary arteries, are well described. The venous drainage in intralobar sequestrations is generally via a pulmonary vein whereas, in the extralobar variety, it is often via the azygos vein, but variations are common.¹⁸²

PATHOGENESIS

During bronchial branching, which is completed in humans 16 weeks after conception, the dividing buds are supplied by a capillary plexus derived from the primitive aorta; this plexus later regresses. Growth arrest locally of the pulmonary artery during bronchial division may disrupt maturation and tracheobronchial integrity, as well as lead to persistence of the blood supply from the aorta. The developing lung bud lies in close proximity to the developing foregut, from which it is derived, which explains the high incidence of associated foregut anomalies and linkage with congenital cystic adenomatoid malformation. In 1987, Clements and Warner¹⁸³ developed an alternative nomenclature and anatomic classification that unifies these embryologically related anomalies, many of which are now being diagnosed in utero (eFig. 61-7) owing to the extensive use of prenatal imaging studies.¹⁸⁴

CLINICAL FEATURES

Most patients with sequestrations are symptomatic, and the diagnosis is made in 50% to 60% before the age of 20. Diagnosis in adults older than 50 is uncommon, but a series of 17 patients was recently reported.¹⁸⁵ According to a 1979 review of 540 cases by Savic and colleagues,¹⁸⁶ 15% of patients are asymptomatic.

Typically, symptoms develop during infancy or childhood and are characterized by chronic cough and recurrent pneumonias and episodes of acute bronchitis, which are related to underlying progressive bronchiectasis, scarring, and cyst formation in the poorly communicating sequestered lung. Hemoptysis is also common. Chest radiographs classically show a basal opacity, usually on the left (eFig. 61-8), but the right lung base may also be involved

(eFig. 61-9); less commonly, sequestrations may involve more superior intrapulmonary anatomic units. Intralobar sequestrations, when uninfected, often appear as lucent lesions (eFig. 61-10). In contrast, extralobar sequestrations are most commonly encountered in infancy, appear solid at chest imaging (eFig. 61-11), and rarely become infected.

The diagnosis depends on demonstrating the anomalous systemic arterial blood supply that can reliably be shown by multislice chest CT techniques (Fig. 61-7, see eFigs. 61-8B-D, 61-9G-J, 61-10, 61-11, and 61-12; Video 61-3; and eFig. 18-18). MR angiography is also a valuable means of diagnosing sequestration (see eFig. 61-9G-J), and has the advantage of not involving ionizing radiation,¹⁸⁷ but this may be offset by longer imaging times when compared with CT, particularly in pediatric patients, in whom sedation is required.¹⁸²

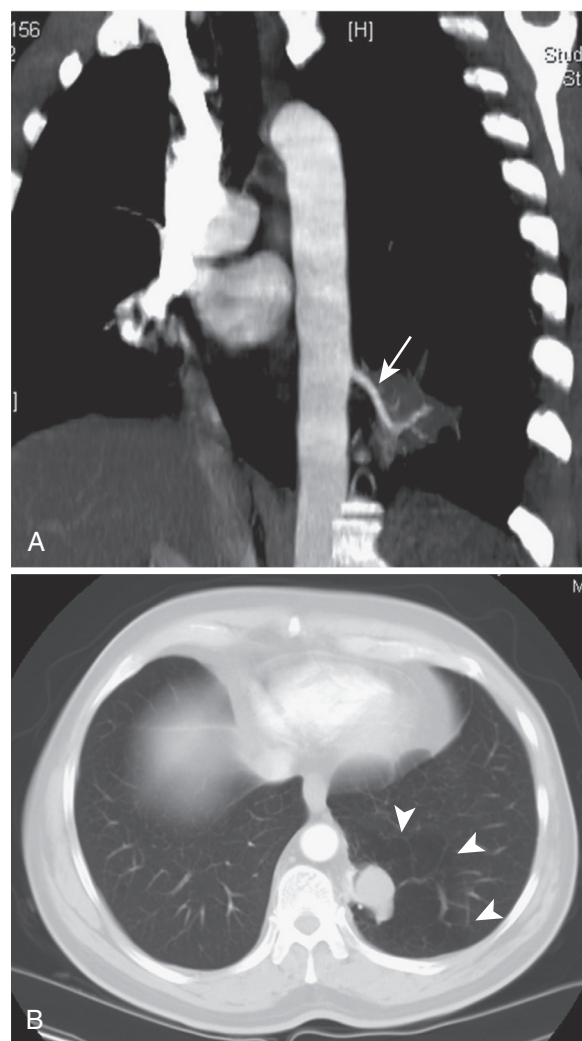


Figure 61-7 Pulmonary sequestration. The sequestration presented as a lung mass at the left lung base in an asymptomatic 55-year-old man (found on an employment radiograph). **A**, Coronal reformation from contrast-enhanced chest CT demonstrates the systemic arterial blood supply, which arises from the lower thoracic aorta (arrow) and supplies a soft tissue mass in the left lower lobe. **B**, Axial image on a lung window demonstrates the soft tissue mass with hyperinflation of the surrounding lung (arrowheads) due to disruption of the normal airway to this segment, resulting in air trapping.

TREATMENT

The recommended treatment of patients with symptomatic sequestrations is surgical removal of the affected lung, which often requires a lobectomy but which can sometimes be carried out by segmentectomy to conserve the normal portion of lung in patients with intralobar sequestrations. Recently, the feasibility of using video-assisted thoracic surgery has been demonstrated, but its final role in treatment is unknown.¹⁸⁸ A prerequisite of operative intervention is thorough definition of the origin and course of the aberrant arterial blood supply; Lee and coworkers¹⁸² believe also that an additional surgical advantage lies in the demonstration of the venous drainage pathways by chest CT examination. In patients in whom resection cannot be performed for technical reasons, ligation or embolization of the feeder artery is advised to prevent hemoptysis; embolization may also be performed preoperatively to help reduce blood loss.

PULMONARY VARICES

Pulmonary varices are uncommon and are generally only of importance in that they mimic other, more serious, pulmonary vascular anomalies. They are divided into congenital and acquired forms and are usually easily diagnosed on contrast-enhanced CT.

DIAGNOSIS AND TREATMENT

A *congenital pulmonary varix* represents a collateral intrapulmonary vein bypassing an atretic segment of normal pulmonary vein.^{58,189} This atretic segment is most commonly of a segmental or subsegmental vein, most commonly in the upper lobes, and the resultant intrapulmonary collateral vessel then courses through the lung, sometimes across a fissure, into the ipsilateral superior or inferior pulmonary vein (eFig. 61-13). This is not associated with pulmonary arterial hypertension and is not at risk for rupture.

Acquired pulmonary varices are described in association with long-standing severe mitral valve disease with associated pulmonary venous hypertension. Typically right-sided—thought to be due to the jet of regurgitant blood being directed towards this side—they have been reported as being at risk, not only for rupture with life-threatening hemorrhage but also for in situ thrombosis and resultant systemic thromboembolism. It has been suggested that there is a congenital weakness in the affected pulmonary vein wall, which allows the development of varices in response to pulmonary venous hypertension in these individuals, to explain the fact that they are rare whilst mitral valve disease is relatively common.

A second type of acquired pulmonary varix is seen in some patients in whom previous pulmonary tuberculosis or sarcoidosis has caused stenosis or occlusions of intrapulmonary venous branches and collateral veins have subsequently developed in order to bypass these areas. These collaterals typically cross fissures and are generally shorter and less well developed than the congenital form.⁵⁸ They do not appear to be associated with a risk for rupture and hemorrhage.

PULMONARY ARTERY ANEURYSMS

Pulmonary artery aneurysms (PAAs) are rare vascular anomalies. Historically they were classified as peripheral (predominantly tuberculous) or proximal (predominantly syphilitic). It is now recognized that PAAs can develop in a wide range of clinical settings and that the distinction between large and medium to small vessels is by no means absolute. Proximal PAAs tend to develop primarily due to inherited defects in the vascular wall, may be idiopathic⁵⁸ (eFig. 61-14) or result from trauma due to pulmonary hypertension or jets of blood impacting specific sites, such as immediately beyond a pulmonary valve stenosis (eFig. 61-15) or opposite a patent ductus arteriosus. They can also result from focal endovascular infection or vasculitis, or disease of the vasovasorum as in syphilis. Peripheral PAAs are more usually attributed to infection—either adjacent to an area of infected lung (as in tuberculous Rasmussen aneurysms) or due to endovascular seeding of infected foci—or to vasculitis. In many cases, more than one etiologic factor is present, and it is not clear whether an intrinsic vascular defect, endovascular trauma, or infection is primarily responsible for the development of the aneurysm. Multiple aneurysms should raise the possibility of underlying Behçet disease.

Pulmonary artery aneurysms are unstable structures: As the radius of the aneurysm increases, the wall tension becomes higher at any given level of intravascular pressure, thus increasing the dilating force via the Laplace relationship. Although only some aneurysms continuously dilate via this vicious circle until they rupture, all have the potential to do so. The main risks of these unstable structures are pulmonary hemorrhage—which may be life-threatening when they arise from any site—and dissection in the case of proximal lesions. In dissecting aneurysms, blood tracks through an intimal tear within the arterial wall. In false aneurysms (pseudoaneurysms), the blood breaches all the layers of the wall but is contained by the surrounding tissues or by clotting. If an aneurysm ruptures and is not contained in this way, blood may enter the bronchus sharing the common bronchovascular connective tissue sheath, causing hemoptysis and sometimes death from exsanguination.

ETIOLOGY AND PATHOGENESIS

In many cases, more than one etiologic factor is present. It is often not clear whether an intrinsic vascular defect, endovascular trauma, or infection is primarily responsible for the development of the aneurysm.

Infection

Small artery pseudoaneurysms are generally infective (mycotic) in origin, often mycobacterial or fungal. Pathologically, granulation tissue replaces a large part of the arterial wall. Tuberculosis and syphilis used to be the most common causes. Tuberculous Rasmussen aneurysms, classically described as the tortuous abnormal vasculature of tuberculous cavity walls, were seen in 4% of autopsies (45 of 1114) in patients with chronic pulmonary tuberculosis, and caused death in the majority of those patients in whom

they were present.¹⁹⁰ Rasmussen aneurysms remain important; in 1984, they were reported in approximately 5% of cases of massive hemoptysis.¹⁹¹ In contrast, in the current era of near universal treatment of syphilis, only 8 cases of untreated proximal syphilitic PAA were found in 109,571 autopsies.¹⁹²

Although the contribution of syphilis in particular has waned, infection remains a relatively common etiology, particularly secondary to tuberculosis or lung abscess. Other in situ pulmonary arterial wall infections result from endovascular seeding from right-sided heart valve vegetations, typically in chronic drug abusers,¹⁹³ or in one case, from *Candida* endocarditis introduced by a Swan-Ganz catheter.¹⁹⁴

Vascular Trauma

Large artery aneurysms have a variety of causes, the most common of which is congenital heart disease, especially patent ductus arteriosus; less common causes are pulmonary valve stenosis, atrial or ventricular septal defect, and Fallot tetralogy. The mechanism is thought to be trauma to the artery wall from jets of blood ejected at high velocity. External sources of trauma include penetrating injuries such as stab wounds¹⁹⁵ and tube thoracostomy.¹⁹⁶ Disruption of the arterial wall during inflation of pulmonary artery balloon catheters has led to a significant number of false aneurysms, particularly in patients with preexisting pulmonary hypertension or on anticoagulants, although this remains a rare complication.¹⁹⁷ Catheterization can cause a pseudoaneurysm if the vessel wall is lacerated by the catheter tip and bleeding is contained, temporarily or permanently, by the surrounding tissues (eFig. 61-16). Alternatively, a true aneurysm, with or without rupture, can develop if the catheter balloon is overinflated in a small branch of the pulmonary artery. Kearney and Shabot,¹⁹⁸ in a retrospective review of 32,442 patients requiring catheterization from 1975 to 1991, found that pulmonary artery rupture due to catheter balloon overinflation was associated with hemoptysis in 10 patients (0.03% incidence). The risk factors were both technical, related to peripheral placement and overinflation of the balloon, and pathophysiologic, the most important of which was age older than 60 years, which reflects the greater fragility of pulmonary arteries in older adults.

Weakness of the Arterial Wall

Vascular wall weakness may predispose to aneurysm formation. Large artery aneurysms have been reported in patients with giant cell arteritis,¹⁹⁹ and multiple aneurysms in Behçet syndrome (see eFig. 67-2) or the Hughes-Stovin syndrome.²⁰⁰ Pulmonary hypertension, when associated with atheromatous disease and cystic necrosis of the media, may lead to dissecting pulmonary artery aneurysms. Similarly, cystic necrosis and dissecting aneurysms are also caused by fibrillin deficiency in Marfan syndrome.²⁰¹

DIAGNOSIS AND TREATMENT

Pulmonary artery aneurysms usually come to light during the investigation of an unusual mass on a routine chest radiograph or during the workup for hemoptysis. Echocardiography (including transesophageal echocardiography),

CT scanning, and MR imaging are replacing angiography as first-line diagnostic investigations.²⁰² In the absence of hemoptysis, treatment should first be directed to the underlying cause (e.g., infection, vasculitis, pulmonary hypertension, and congenital heart disease). Such measures may not be possible in patients with hemoptysis in whom emergency treatment of the aneurysm is required. When the aneurysm does not include the pulmonary trunk or main pulmonary arteries, embolization is the treatment of choice using metal coils or detachable silicone balloons. Embolization is also becoming the preferred choice for large artery aneurysms.¹⁹⁹ When a pulmonary artery pseudoaneurysm is demonstrated, usually during selective bronchial arteriography that demonstrates a systemic artery-to-pulmonary artery shunt and pulmonary artery opacification, both bronchial and pulmonary artery embolization are likely to be necessary to control bleeding.²⁰³

Proximal aneurysms have been repaired by a variety of surgical techniques, including pulmonary artery banding or excision of the aneurysm and prosthetic patch replacement.²⁰⁴ Stents and grafts inserted endovascularly are likely to replace open heart surgery in some instances.²⁰⁵ Surgical resections in this group have been superseded because they result in excessive loss of parenchymal tissue and carry a high morbidity and mortality. Lung transplantation may be an option in patients with Group 1 idiopathic (primary) pulmonary arterial hypertension.²⁰⁶

Key Points

- Most pulmonary arteriovenous malformations are found in individuals with hereditary hemorrhagic telangiectasia, which is inherited as an autosomal dominant trait.
- Right-to-left shunting of blood through pulmonary arteriovenous malformations leads to hypoxemia, and paradoxical emboli that can present as cerebral abscess or ischemic stroke.
- Diagnosis is facilitated by CT techniques and contrast echocardiography.
- Embolization of pulmonary arteriovenous malformations with vascular plugs or coils decreases right-to-left shunting and the risk of paradoxical embolization. Small vessel malformations are difficult to close.
- Systemic to pulmonary communications are apt to be asymptomatic but may cause heart failure in neonates and hemoptysis in later life.
- Pulmonary sequestrations are supplied by an abnormal systemic artery, usually from the aorta, and lack a normal communication with the tracheobronchial tree. Symptoms, if they develop, may start at a young age and are characterized by cough and recurrent infections. Treatment is surgical removal.
- Pulmonary artery aneurysms are rare vascular abnormalities of varying etiology, whose major complication is hemoptysis. Diagnosis is usually made by CT and MR imaging. Treatment is directed at the underlying cause (infection, vasculitis, pulmonary hypertension, or congenital heart disease); hemoptysis is best treated by embolization.

Complete reference list available at ExpertConsult.**Key Readings**

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eFIGURE IMAGE GALLERY

The figures and videos in the imaging gallery are not those of the chapter authors but have been separately chosen by the Editor of Thoracic Imaging in this and other chapters as additional examples of the pathology discussed.

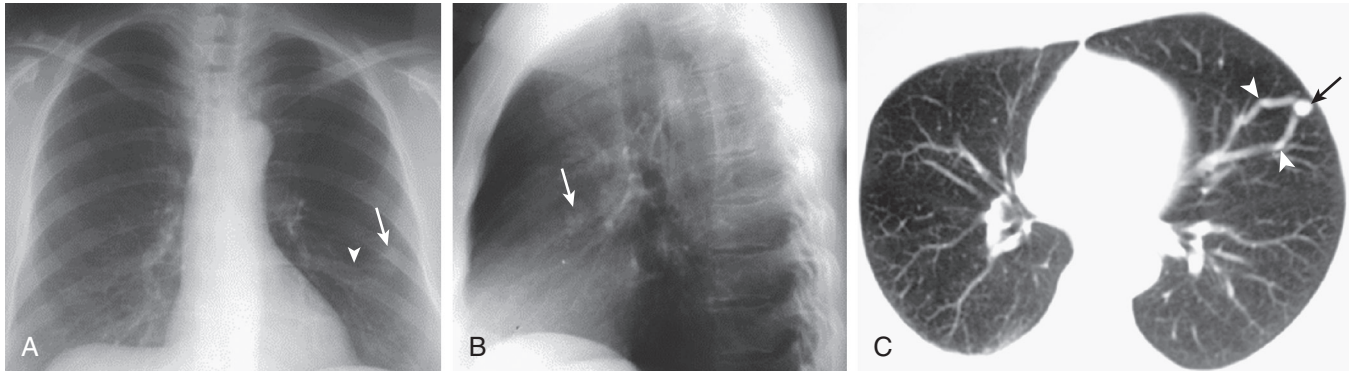


Figure 61-1 Simple arteriovenous malformation (AVM): chest radiographic and chest CT appearance. Frontal (A) and lateral (B) chest radiographs show a lobulated peripheral solitary pulmonary nodule (arrows), associated with a faint tubular opacity (arrowhead), which leads directly to the nodule. C, Axial chest CT displayed in lung windows shows that the peripheral solitary pulmonary nodule (arrow) is clearly associated with enlarged vessels (arrowheads); this morphology is diagnostic of AVM. On this single image, it is not possible to distinguish the feeding artery and draining vein, but following these vessels on more cranially located images allows the arterial supply and venous effluent to be distinguished. (Courtesy Michael Gotway, MD.)

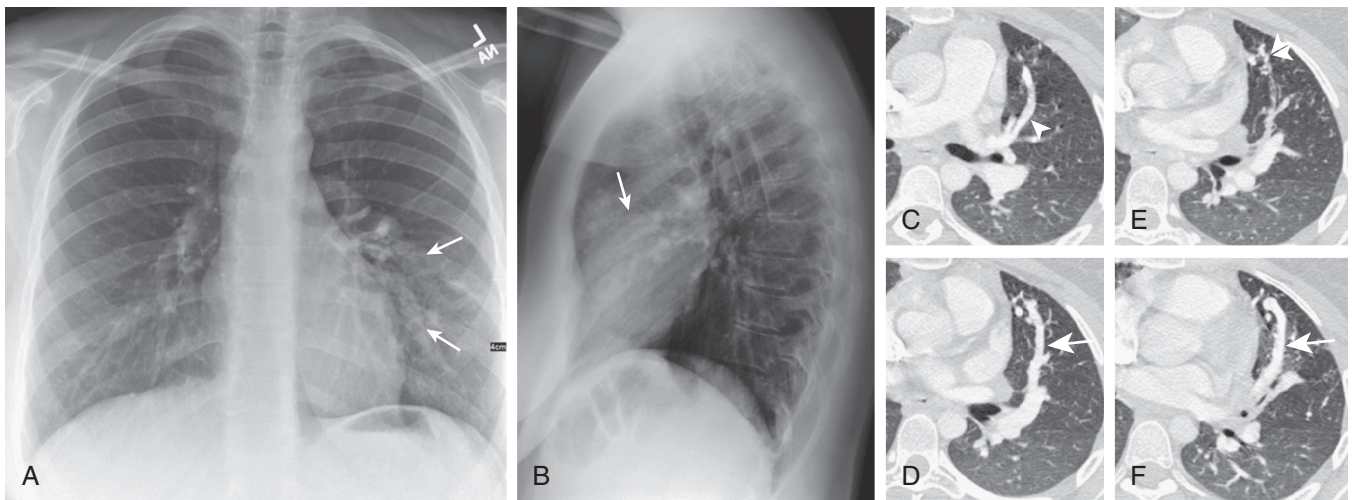


Figure 61-2 Complex arteriovenous malformation (AVM): chest radiographic and chest CT appearance. Frontal (A) and lateral (B) chest radiographs show several tubular-shaped left perihilar opacities (arrows) representing a combination of enlarged feeding arteries and draining veins. C-F, Axial chest CT displayed in lung windows shows an enlarged draining vein (single arrowhead, C) and two enlarged feeding arteries (arrows, D and F), supplying the AVM nidus (seen at the tip of the feeding artery in F). Lingular ground-glass opacities and small serpiginous structures (seen in F and double arrowhead, E, respectively) are consistent with increased pulmonary blood flow and small AVMs in this region. Several other feeding arteries were identified more inferiorly in the lingula as well. (Courtesy Michael Gotway, MD; case by Paul J. Conomos, MD, Arizona Pulmonary Specialists, Phoenix, AZ.)

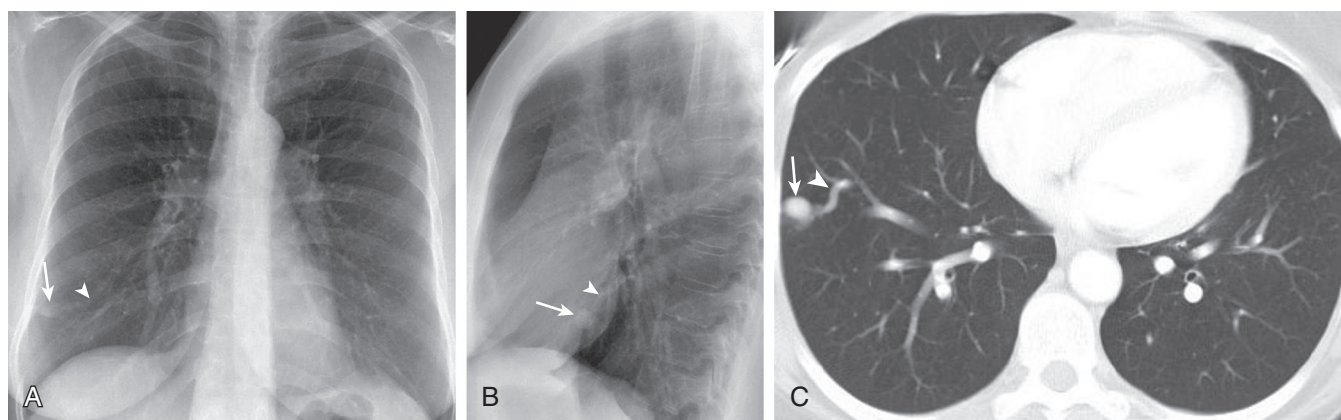


Figure 61-3 Relatively small arteriovenous malformation (AVM): chest radiography and chest CT appearance. Frontal (A) and lateral (B) chest radiographs show a circumscribed, peripheral, small right lower lobe pulmonary nodule (arrows). Note the serpiginous structure (arrowheads) closely associated with the nodule; this morphology is suggestive of AVM. C, Axial chest CT displayed in lung windows shows that the circumscribed peripheral right lower lobe nodule (arrow) is associated with a vessel (arrowhead) entering the nodule; this morphology is characteristic of AVM. (Courtesy Michael Gotway, MD.)

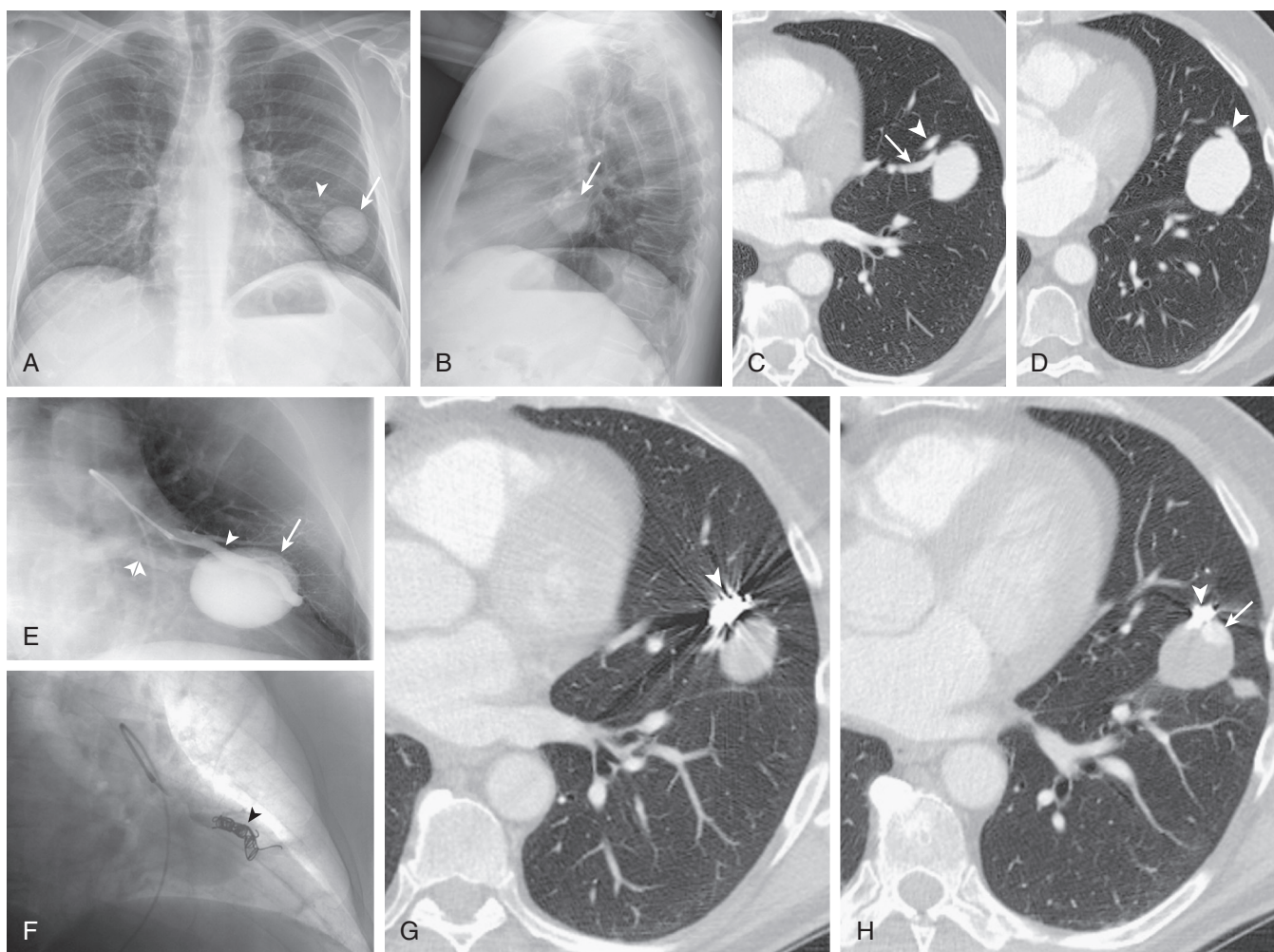
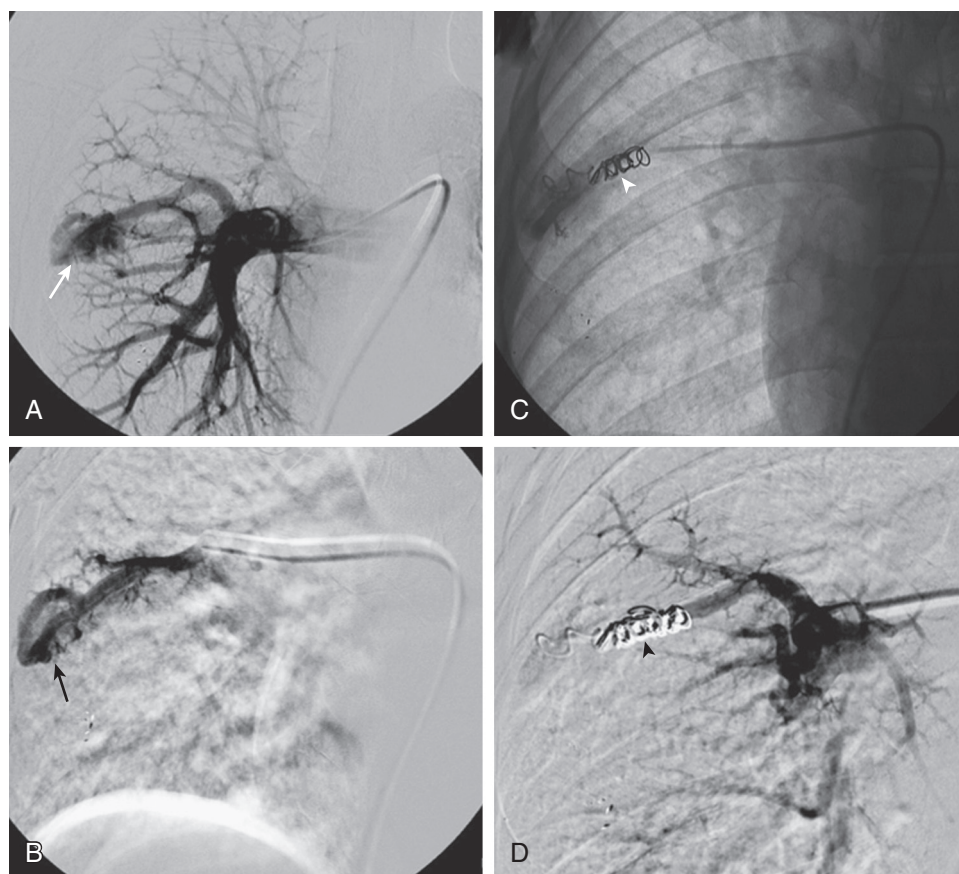
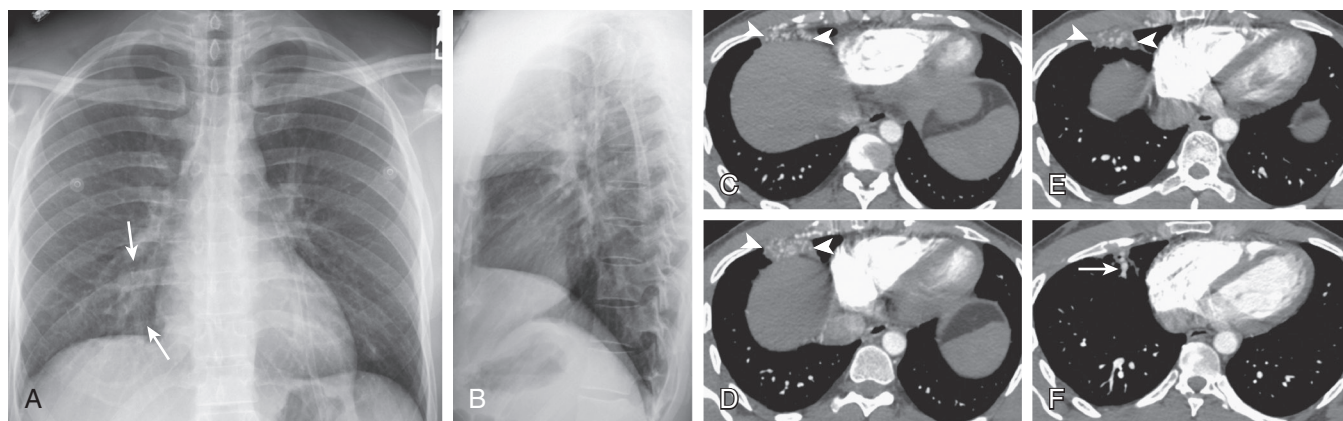


Figure 61-4 Percutaneous transcatheter embolization treatment for arteriovenous malformation (AVM). Pretreatment frontal (A) and lateral (B) chest radiographs show a circumscribed left base mass (arrow) representing an AVM; an enlarged tubular structure (arrowhead), representing a feeding vessel, is faintly seen. C and D, Axial enhanced chest CT shows the intensely enhancing AVM nidus as well as the feeding artery (arrowheads) and draining vein (arrow). E, Catheter pulmonary angiography shows selective catheterization of the feeding artery (arrowhead) and opacification of the vascular nidus (arrow); the draining vein (double arrowheads) is also visible. F, Catheter pulmonary angiography following embolotherapy shows placement of a metallic coil (arrowhead) in the feeding artery. G and H, Axial enhanced chest CT displayed in lung windows following percutaneous transcatheter embolization treatment for AVM shows the coil in the feeding artery (arrowheads). The majority of the AVM nidus now shows no enhancement (compare with C and D), although some residual enhancement in a portion of the nidus (arrow, H) is visible; this residual shunt was due to very small, untreated feeding arteries. (Courtesy Michael Gotway, MD.)



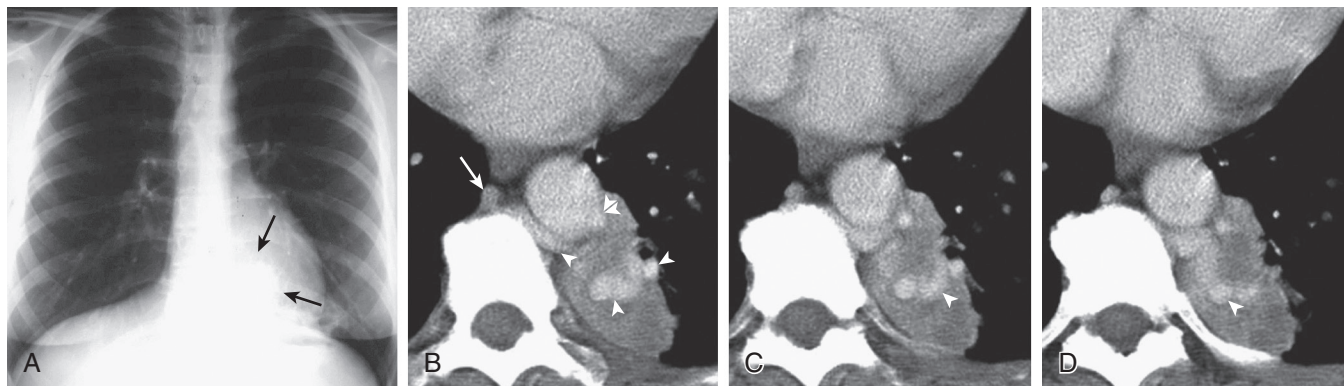
eFigure 61-5 Percutaneous transcatheter embolization treatment for arteriovenous malformation (AVM). **A** and **B**, Pretreatment catheter pulmonary angiography shows a peripheral right pulmonary AVM (arrows). **C** and **D**, Following treatment, a coil (arrowheads) is present within the pulmonary artery feeding the vascular nidus, and flow is no longer identifiable within the nidus of the AVM. (Courtesy Michael Gotway, MD.)



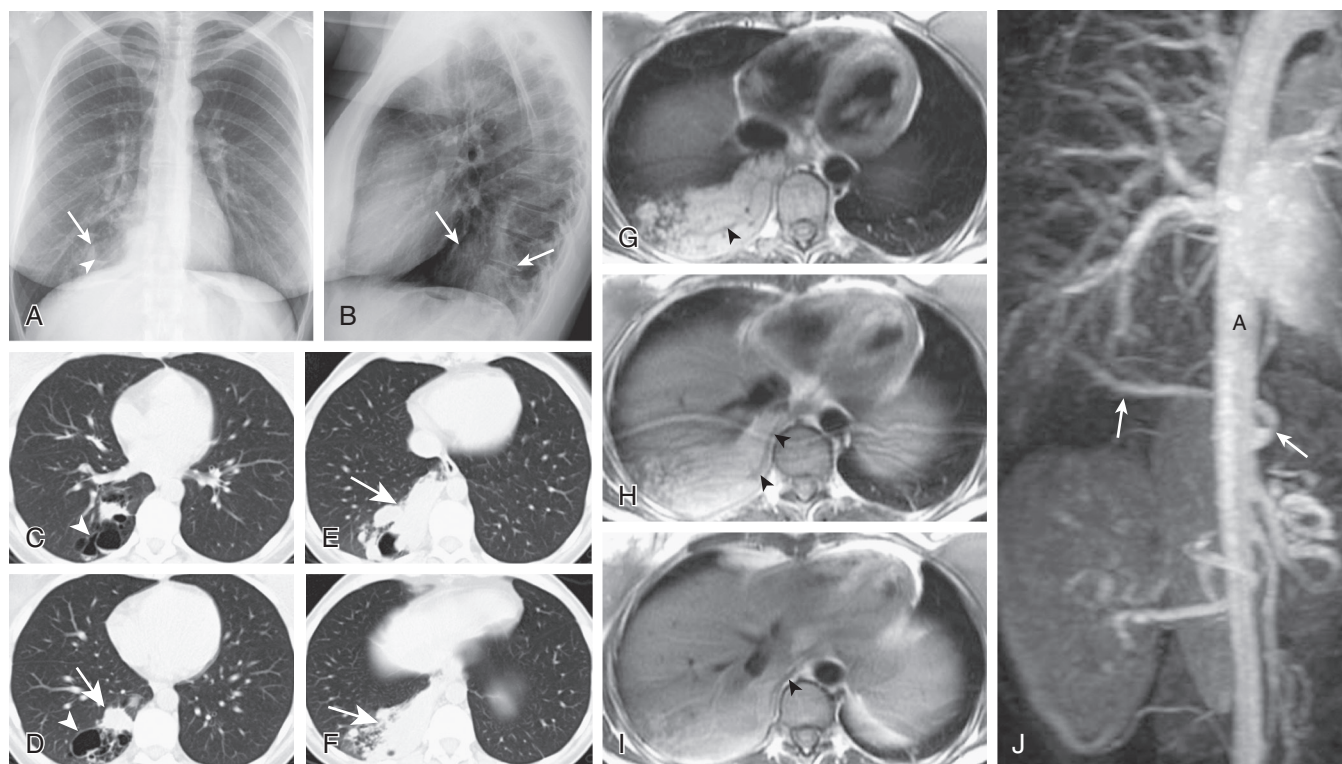
eFigure 61-6 Systemic-to-pulmonary vascular communication. Frontal (**A**) and lateral (**B**) chest radiographs show faint increased attenuation and prominent vessels in the medial right inferior lung (arrows). **C-F**, Axial chest CT scans displayed in soft tissue windows show prominent vessels within an area of consolidation in the inferior right middle lobe (arrowheads); these vessels derived from the intercostal and internal mammary arteries. More superiorly, the tangle of vessels within the right middle lobe consolidation can be traced to a point where they enter the lung and anastomose with a peripheral pulmonary artery (arrow, **F**) (see [Video 61-2](#) for the full study). (Courtesy Michael Gotway, MD.)



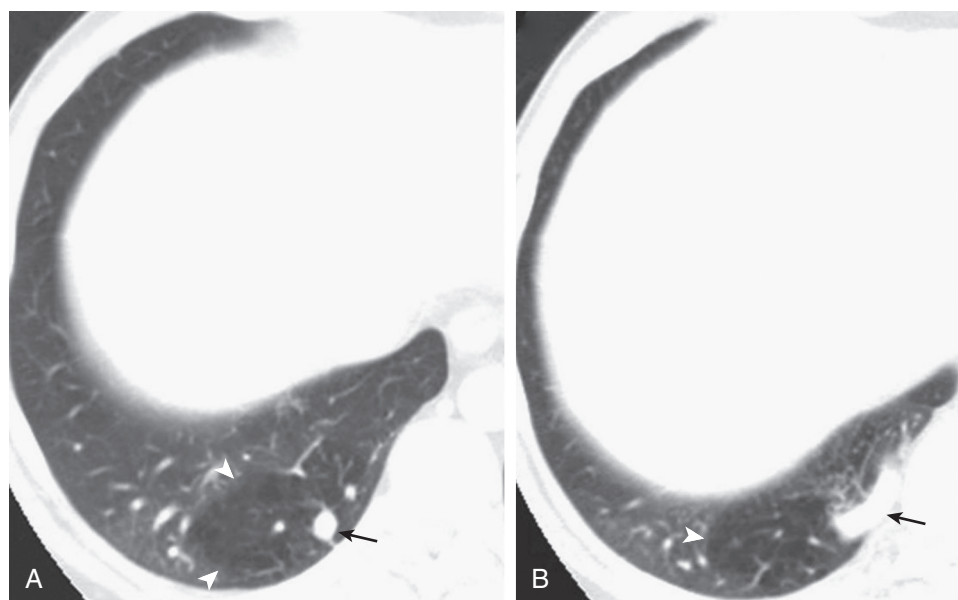
eFigure 61-7 In utero diagnosis of extralobar sequestration. Sagittal MRI shows a large, aberrant artery (*arrow*) arising from the descending thoracic aorta (*arrowheads*). This vessel supplied a solid mass identified at prenatal sonography, proven on resection performed following birth to represent extralobar sequestration. The fetus is in a “head-down” position. A, maternal anterior; B, fetal brain; P, maternal posterior. (Courtesy Michael Gotway, MD.)



eFigure 61-8 Left lower lobe intralobar sequestration: chest radiographic and chest CT appearance. A, Frontal chest radiograph in a young adult with a history of recurrent left lung pneumonias shows homogeneous masslike medial left base opacity (*arrows*). B–D, Axial enhanced chest CT displayed in soft tissue windows shows a medial left base soft tissue mass in contact with the pleura; an enlarged vein (*arrowheads*) draining to the systemic venous circulation is present. Azygos vein (*arrow*, B) is present. The systemic arterial supply arising from the descending thoracic aorta (*double arrowheads*) is visible. (Courtesy Michael Gotway, MD; case by W. Richard Webb, MD, Department of Radiology, University of California, San Francisco.)



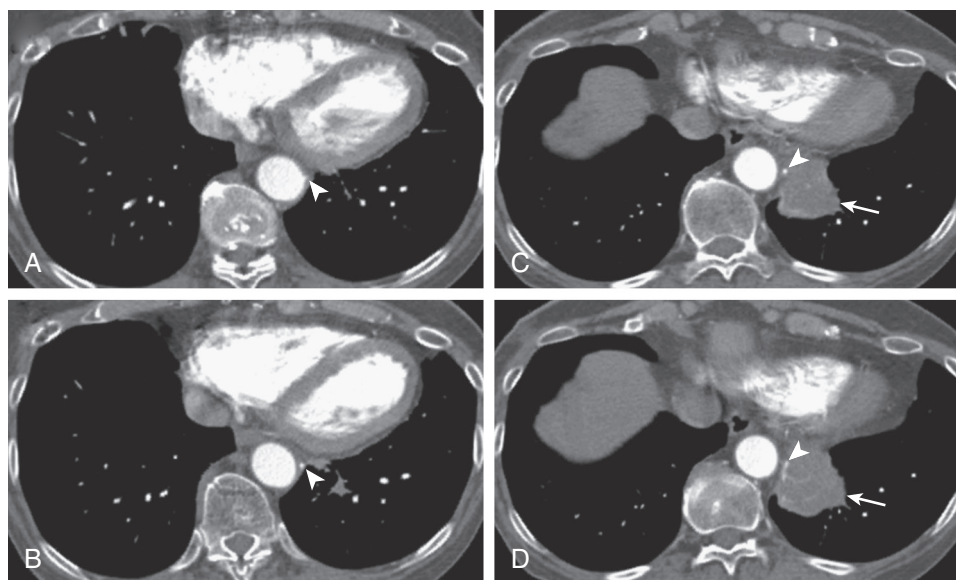
eFigure 61-9 Intralobar sequestration: right-sided location. Frontal (A) and lateral (B) chest radiographs show posteromedial right basal consolidation (arrows) with faint lucency (arrowhead). C-F, Axial chest CT displayed in lung windows shows posteromedial right base cystic change (arrowheads) and consolidation (arrows), typical of intralobar sequestration. This unenhanced chest CT did not adequately display the aberrant arterial supply to the sequestration. Axial unenhanced double inversion recovery (G-I) and oblique maximum intensity projected MR angiography (J) shows the posteromedial right basal consolidation as hyperintense, likely representing a combination of inspissated material and hemorrhage. The aberrant arterial supply is faintly seen as a hypointense linear structure (arrowheads) on the double inversion recovery images (G-I), but is well seen on the oblique coronal MR angiography images (arrows, J). The lesion was subsequently resected without complication. A, distal thoracic aorta. (Courtesy Michael Gotway, MD.)



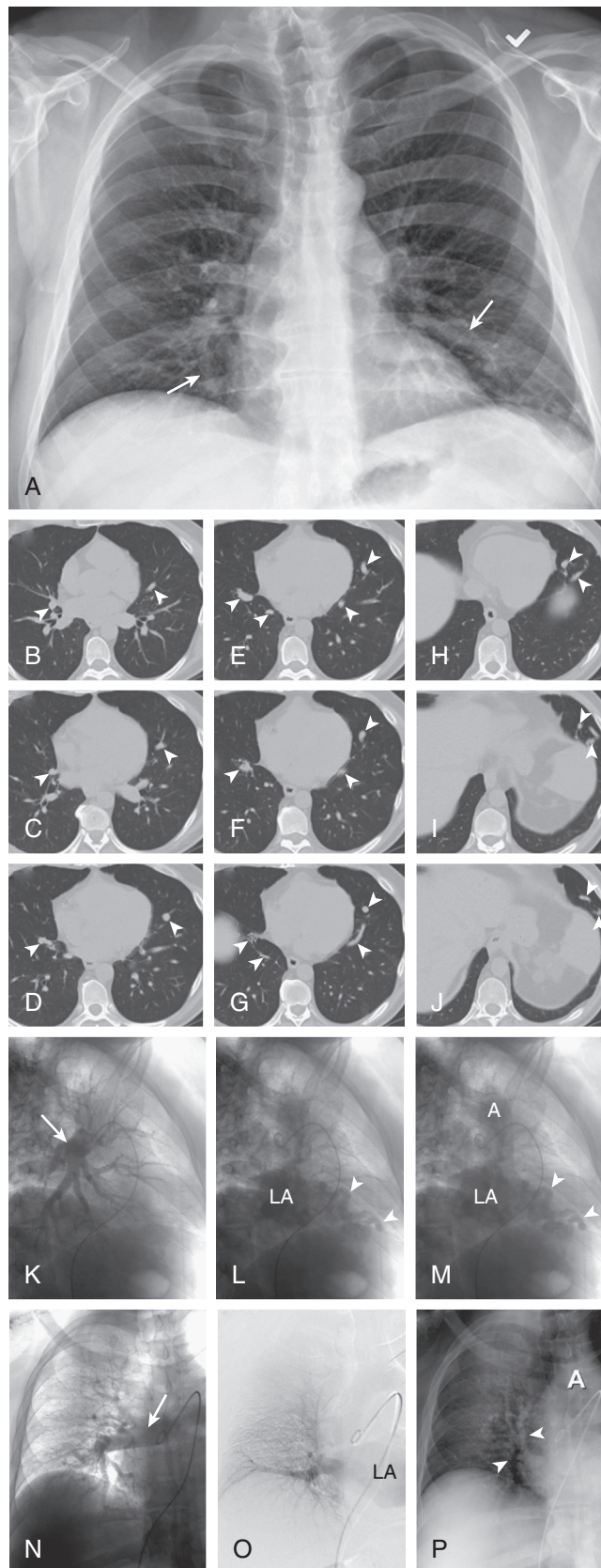
eFigure 61-10 Intralobar sequestration: lucent appearance. A and B, Axial chest CT displayed in lung windows shows a focal area of lucency in the posteromedial right lower lobe supplied by a large, anomalous artery (arrows) arising from the descending thoracic aorta; the appearance is typical of an uninfected intralobar sequestration. (Courtesy Michael Gotway, MD.)



eFigure 61-11 Left lower lobe extralobar sequestration: chest radiographic and chest CT appearance. **A**, Frontal chest radiograph in a neonate shows a left base mass (*arrow*) associated with contralateral shift of the heart and mediastinum. **B** and **C**, Axial enhanced chest CT confirms a solid mass at the left base (*arrows*) and reveals an anomalous artery (*arrowheads*) arising from the descending thoracic aorta supplying the lesion, establishing the diagnosis of extralobar sequestration. (Courtesy Michael Gotway, MD.)



eFigure 61-12 Intralobar sequestration: anomalous systemic arterial supply. **A-D**, Axial enhanced chest CT displayed in soft tissue windows shows a posteromedial left lower lobe solid mass (*arrows*) supplied by an anomalous artery (*arrowheads*) arising from the descending thoracic aorta; the appearance is typical of sequestration, usually intralobar when encountered in an adult patient (see [Video 61-2](#) for the full study). (Courtesy Michael Gotway, MD.)



eFigure 61-13 Congenital pulmonary varices: chest radiographic, chest CT, and angiographic appearance. **A**, Frontal chest radiograph shows prominent tubular structures (*arrows*) that could represent the vasculature supplying an arteriovenous malformation (AVM); note resemblance to eFig. 61-2A. **B-J**, Axial chest CT displayed in lung windows shows bilateral serpiginous structures (*arrowheads*) consistent with enlarged vessels. In this circumstance, no vascular nidus, typical of an AVM, can be identified, and the enlarged vessels showed no arterial connection; they were all traceable to the left atrium. Catheter pulmonary angiography left pulmonary artery injection (**K-M**) and right pulmonary artery injection (**N-P**) show normal pulmonary arteries (*arrows*) during the early arterial phase of the injection; no enlarged artery supplying a vascular nidus could be identified. The venous phase of the injection (**L, M, O, and P**) shows opacification of the left atrium (LA) and subsequent opacification of the pulmonary varices (*arrowheads*) leading to the left atrium. A, aortic arch. (Courtesy Michael Gotway, MD.)

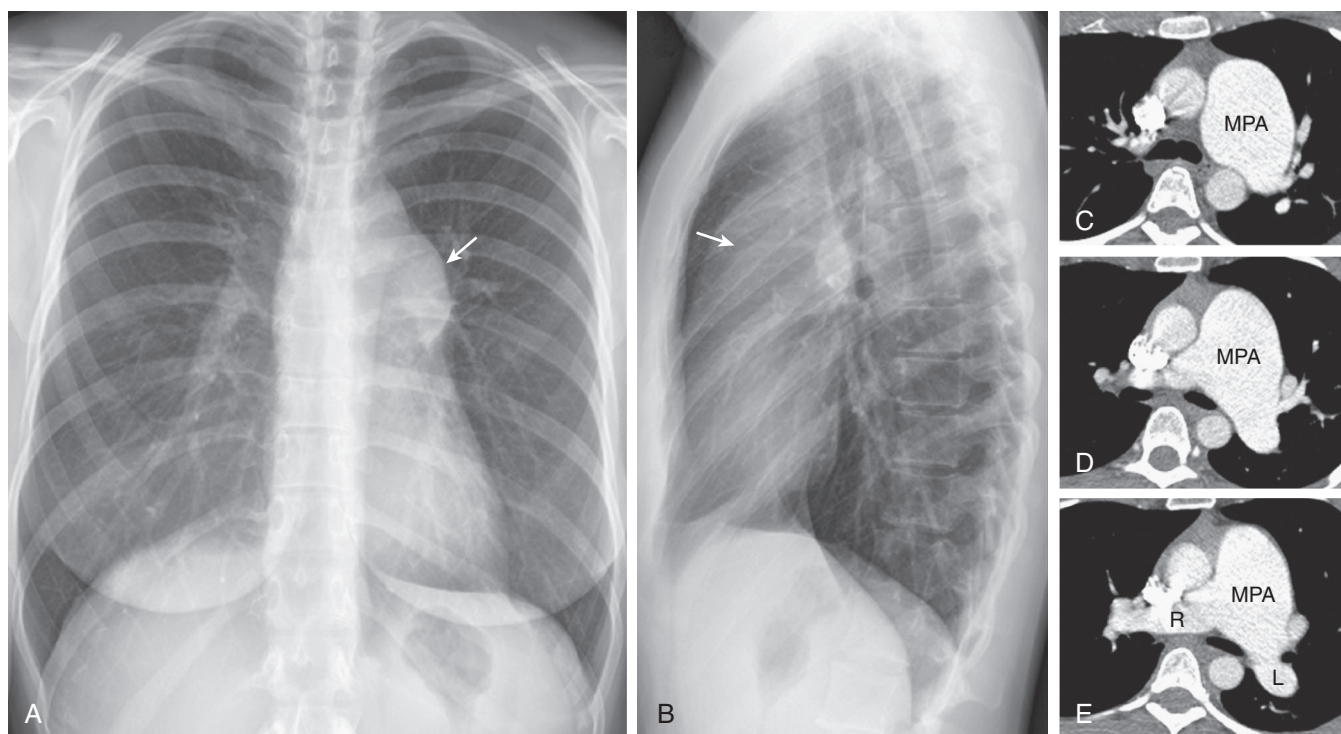


Figure 61-14 Main pulmonary artery aneurysm: chest radiographic and chest CT findings. Frontal (A) and lateral (B) chest radiographs show enlargement of the main pulmonary artery (arrows). C-E, Axial enhanced chest CT confirms enlargement of the main pulmonary artery (MPA), consistent with an aneurysm, with normal caliber right (R) and left (L) pulmonary arteries. The main pulmonary artery aneurysm was idiopathic; no specific etiology could be identified despite a thorough investigation. (Courtesy Michael Gotway, MD.)

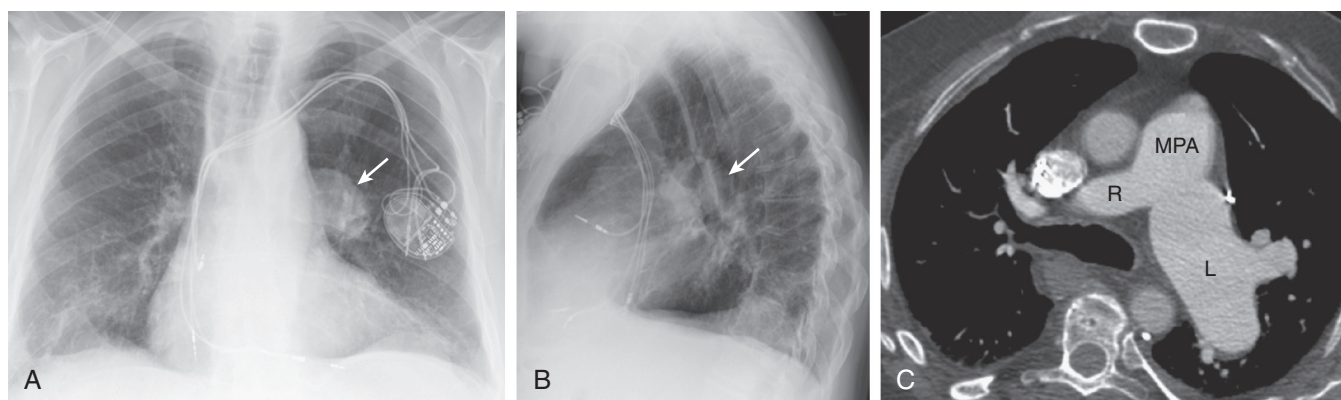
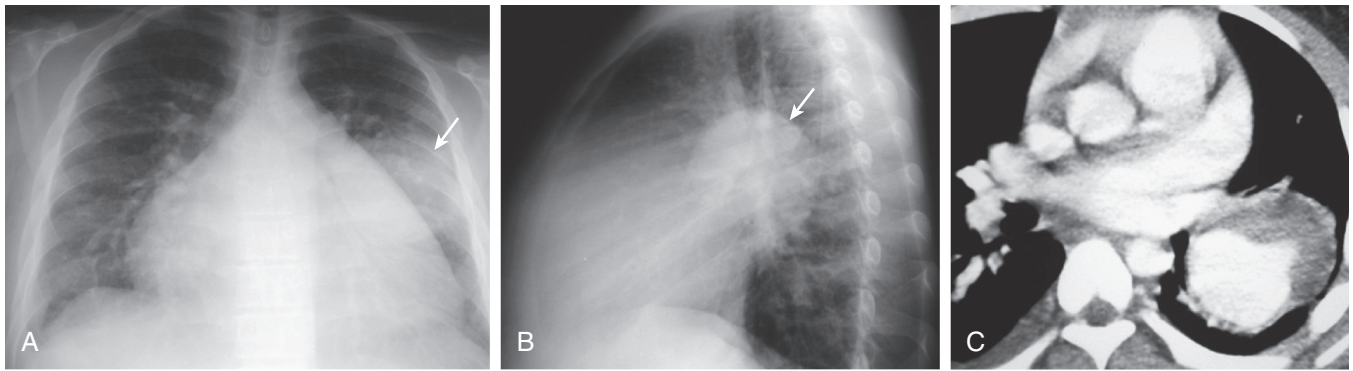


Figure 61-15 Left pulmonary artery aneurysm due to valvular pulmonic stenosis: chest radiographic and chest CT findings. Frontal (A) and lateral (B) chest radiographs show enlargement of the left pulmonary artery (arrows). C, Axial enhanced chest CT confirms enlargement of the left (L) pulmonary artery, consistent with an aneurysm, with normal caliber right (R) pulmonary artery. MPA, main pulmonary artery. (Courtesy Michael Gotway, MD.)



eFigure 61-16 Traumatic left pulmonary artery aneurysm: chest radiographic and chest CT findings. Frontal (A) and lateral (B) chest radiographs show a large, round left perihilar structure (*arrows*). Cardiomegaly is present, and the patient had known congenital heart disease that required a recent intensive care unit stay, during which a pulmonary arterial catheter was placed. C, Axial enhanced chest CT shows a large lesion enhancing similar to other vascular structures, representing an aneurysm of the left pulmonary artery; note low attenuation peripheral thrombus. Review of the chest radiographs obtained while the patient was in the intensive care unit showed the tip of the catheter in the left pulmonary artery approximately in this location. (Courtesy Michael Gotway, MD.)

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INTRODUCTION**PATHOPHYSIOLOGY OF PULMONARY EDEMA**

Increased Pressure Edema
Increased Permeability Edema

DIAGNOSIS

Clinical Assessment
Measurement of Lung Water
Measurement of Barrier Function

TREATMENT

Emergency Therapy
Increased Pressure Edema
Increased Permeability Edema

OUTCOME

Resolution of Pulmonary Edema
Overview

INTRODUCTION

Pulmonary edema—defined as excessive extravascular water in the lungs—is a common and serious clinical problem. Pulmonary edema can be life-threatening, but effective therapy is available to rescue patients from the deleterious consequences of disturbed lung fluid balance, which usually can be identified and, in many instances, corrected. Because rational and effective therapy depends on understanding basic principles of normal and abnormal liquid, solute, and protein transport in the lungs, this chapter begins with a brief overview of the major factors that govern fluid and protein filtration in healthy lungs before focusing on the pathophysiology of pulmonary edema. Next, the chapter discusses diagnosis, treatment, and resolution of pulmonary edema. Chapters 6 and 9 also provide additional information about the regulation of fluid balance in the lungs, and Chapter 100 includes details about the onset and management of acute lung injury and acute respiratory distress syndrome, as currently defined and subsequently discussed.

PATHOPHYSIOLOGY OF PULMONARY EDEMA

Pulmonary edema results when fluid is filtered into the lungs faster than it can be removed from them. Accumulation of fluid has serious consequences on lung function because gas exchange is greatly impaired in fluid-filled alveoli. Lung structure relevant to the forces governing fluid and protein movement in healthy lungs and lungs with pulmonary edema has been the subject of classic and more recent reviews.¹⁻⁶

There is always a net outward flux of fluid and protein crossing from the vascular space into the interstitium in the lungs, first, because the prevailing driving forces normally cause filtration out of the bloodstream and, second, because the microvascular endothelium is a permeable barrier that varies in its leakiness. Lung lymph flow, which represents the flow of fluid leaking across the microvascular barrier, normally is less than 0.01% of total lung blood flow. The

term *microvascular bed* (or *barrier*), is used throughout this chapter to refer to sites of fluid exchange. In addition to the vast interconnecting network of capillaries embedded in the alveolar walls, fluid is exchanged across capillaries in the interstitium at alveolar wall junctions (*corner vessels*) and across small interstitial arteries and veins.

The essential factors that govern fluid exchange in the lungs are expressed in the Starling equation for the microvascular barrier:

$$J_v = L_p S [(P_c - P_i) - \sigma_d (\pi_c - \pi_i)]$$

where J_v is the net fluid-filtration rate (volume flow) across the microvascular barrier; L_p is the hydraulic conductivity (“permeability”) of the microvascular barrier to fluid filtration (a measure of how easy it is for water to cross the barrier); S is the surface area of the barrier; P_c is the pulmonary capillary (microvascular) hydrostatic pressure; P_i is the interstitial (“perimicrovascular”) hydrostatic pressure; π_c is the capillary (microvascular) plasma colloid osmotic (or oncotic) pressure; π_i is the interstitial (perimicrovascular) fluid osmotic pressure; and σ_d is the average osmotic reflection coefficient of the barrier (a measure of how effective the barrier is in hindering the passage of solutes from one side of the barrier to the other).

The microvascular hydrostatic pressure is the principal force that causes fluid filtration in the lungs. If blood was not flowing through the lungs, the opposing hydrostatic and osmotic forces on either side of the microvascular barrier would be equal, their sum would be zero, and there would be no filtration. The pumping action of the heart causes blood to flow through the lungs and generates the microvascular hydrostatic pressure that establishes the steady-state values of the other driving pressures that cause filtration of fluid.^{5,7}

According to the Starling equation, the difference between the prevailing transmural hydrostatic pressures ($P_c - P_i$) and the colloid osmotic pressures ($\pi_c - \pi_i$) provides the “driving force” for fluid filtration. The actual amount of filtrate that forms at any given driving force is determined by the integrity of the barrier to filtration, which is reflected in the conductivity (L_p) and reflection (σ_d) coefficients. The equation predicts the development of two fundamentally different kinds of pulmonary edema: (1) *increased pressure*

Table 62-1 Safety Factors That Protect the Lungs Against Interstitial and Alveolar Edema Accumulation

1. Lung lymphatic system
2. Resorption into blood vessels
3. Drainage into the mediastinum
4. Drainage into the pleural space
5. Extremely low alveolar epithelial barrier permeability
6. Low alveolar surface tension (surfactant)
7. Active transport by alveolar and distal airway epithelial cells

pulmonary edema—when the net result of the driving forces increases, fluid filtration is forced across the barrier at a rate that exceeds removal by lymphatic drainage, and (2) *increased permeability pulmonary edema*—when the normal barriers to fluid filtration are damaged, typically by some form of injury, conductance of liquid and protein in the lungs is allowed to increase. A third type of pulmonary edema is caused by impaired lymphatic drainage of filtered fluid, but this has less clinical relevance than the other two types. The lymphatic drainage of the lungs provides a vital means for removing filtered fluid and proteins from the perimicrovascular interstitial space, as discussed later.^{5,7}

Because the healthy microvascular barrier is permeable, the alveolar barrier must serve as the principal protection against the accumulation of pulmonary edema. Fluid and protein do not normally move into alveoli because the alveolar epithelial barrier has a low permeability even to small molecules (similar to cell membrane permeability); in addition, any fluid that is filtered is continuously being pumped back into the interstitium by alveolar epithelial cells,² drained away from the alveolar walls through the interstitium, and removed by lymphatic vessels and the lung microcirculation.

The several factors (Table 62-1) that normally protect the lungs against edema have been called *safety factors*. Under normal conditions, the lymphatic system pumps filtered fluid and protein out of the lungs as rapidly as they are formed, even when filtration of fluid and protein from the bloodstream into the interstitium is increased. Increases in fluid and protein filtration across the microvascular barrier also can be drained away from the alveolar walls down the prevailing pressure gradient into the loose peribronchovascular connective tissue or can be resorbed directly into blood vessels.⁴ The lung lymphatics can increase their pumping capacity manifold, particularly when the microvascular wall has been injured.⁵

When the usual driving forces are upset by higher hydrostatic pressure, the increase in filtration of water across the microvascular barrier is much larger than that in protein flux because the microvascular barrier has a low protein conductance. This results in dilution (“wash-down”) of interstitial protein concentration and, thereby, an increase in the balance of the protein osmotic pressure opposing the higher hydrostatic pressure (because plasma protein concentration remains high). Furthermore, the interstitial gel also becomes hydrated and the exclusion volume for protein decreases, either because of swelling or because its composition changes as hyaluronan is washed out from the interstitium, reducing the concentration of protein by expanding the available volume.

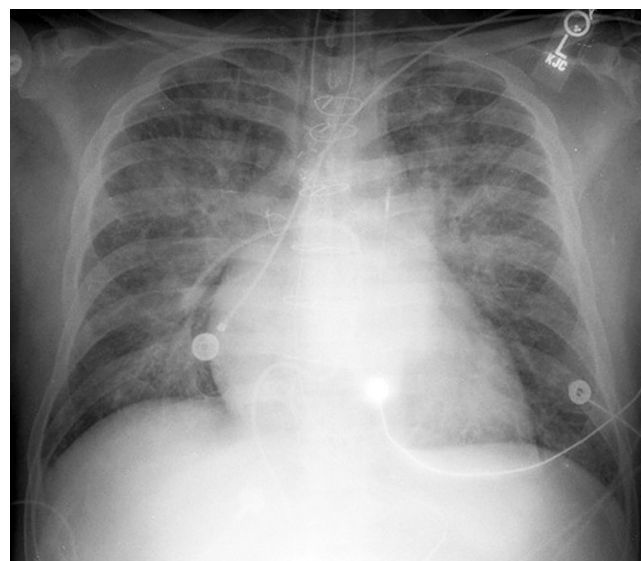


Figure 62-1 Frontal chest radiograph in a 55-year-old man with increased pressure edema due to heart failure. The heart is enlarged and bilateral perihilar linear and ground-glass opacity are present. This distribution is often referred to as a “butterfly” pattern and is commonly seen with chronic volume overload. (Courtesy Michael Gotway, MD.)

The protein osmotic pressure safety factors work only when the microvascular barrier is normal—as in increased pressure edema. In contrast, if the endothelial barrier is injured and its functional integrity is compromised—as in increased permeability edema—barrier conductance increases and the osmotic reflection coefficient decreases, making this safety factor much less effective or even completely ineffective. The compliance of the interstitial space also protects the lungs against edema. Increases in interstitial volume result in only small elevations of interstitial pressure until the interstitial volume is large. This maintains the hydrostatic driving pressure across the alveolar barrier suitably low. When interstitial pressure within the lungs rises to greater than pleural pressure, fluid flows across the visceral pleura into the pleural space, where its effects on lung function are relatively minor. Pleural fluid is drained by lymphatics in the parietal pleural and, even when pleural liquid accumulates, does not flow back from the pleural space into the lungs. Fluid that does accumulate in the alveoli is pumped out by active ion transport.² There are several mechanisms that can up-regulate the rate of alveolar fluid clearance (see Chapter 9).

In summary, pulmonary edema results from increases in either driving pressures (increased pressure edema) or barrier conductance (increased permeability edema) or both combined. What distinguishes between the two types is barrier permeability, which is normal in increased pressure edema but leaky in increased permeability edema. Fluid flow into the lungs is driven across the barrier in both types of edema according to the prevailing pressures.

INCREASED PRESSURE EDEMA

Increased pressure pulmonary edema (Fig. 62-1) is caused by an increase in the net sum of driving forces for fluid filtration into the lungs. The essential feature of this edema is

that the barriers to fluid and protein flow into the lungs are functionally intact. Increased pressure edema is often called *cardiogenic, high-pressure, or hydrostatic pulmonary edema*.

Pathophysiology

The flow of fluid and protein into the lungs increases when the sum of driving pressures is elevated. If the rate of fluid accumulation exceeds the rate at which it can be removed, increased pressure edema results. Because the barriers limiting fluid and protein flow into the lungs are intact, the lungs are protected against edema by the prevailing (normal) safety factors. Especially important is the ability to protect against increases in the principal driving pressure, lung microvascular hydrostatic pressure. Because of the low protein conductance of the microvascular barrier, fluid flow increases much more than protein flow when microvascular hydrostatic pressure rises. Interstitial protein concentration is diluted both by this higher fluid flow relative to protein flow and by a diminished exclusion volume for proteins as the interstitial gel is hydrated and swells. Lower interstitial protein concentration, owing to washout of interstitial proteins, results in lower perimicrovascular protein osmotic pressure and thereby a greater protein osmotic pressure difference across the barrier, which opposes any rise in hydrostatic pressure. In experimental animals, slightly less than 50% of an increase in hydrostatic pressure is offset by the increase in osmotic pressure difference.^{7,8} Increased pressure edema may be gradual in onset and progression because any elevation in microvascular hydrostatic pressure is attenuated by a rise in protein osmotic pressure difference across the microvascular barrier, owing to a decline in interstitial protein osmotic pressure.

The consequences of increased pressure edema on lung mechanics and gas exchange (Table 62-2) depend on how much edema accumulates.⁹ Deliberate dehydration of healthy subjects increases lung volumes and improves tests of ventilatory function.¹⁰ Early in the development of pulmonary edema, increases in hydrostatic pressure result in enlargement of the intrapulmonary blood volume, as

vessels, including capillaries, are both recruited and distended, which causes the *diffusing capacity of the lung* (DL_{CO}) to increase above normal; similarly, arterial *oxygen pressure* (PO_2) may rise because ventilated units are better perfused when vascular pressures increase.¹¹ The small reversible changes in airflow resistance and dynamic compliance, unaffected by vagotomy, in congested lungs appear to be due to reflex bronchoconstriction responses, but only when baseline bronchial tone is normal.¹²

When interstitial edema is present, closing volume may be increased and maximum expiratory airflows may be decreased. These changes were originally thought to be due to a decrease in caliber of small airways caused by compression by rising volume and pressure in the peribronchovascular connective tissue spaces. This effect would have to be in airways larger than bronchioles, because bronchioles and smaller airways do not have loose connective tissue sheaths¹ and their diameter is a function of lung volume, not transpulmonary pressure. Arterial PO_2 often falls as a result of ventilation-perfusion mismatching, but gas exchange is not seriously compromised until the alveoli are flooded.

With alveolar flooding, lung volumes are diminished.¹⁰ This is most marked in measurements of vital capacity, with inspiratory capacity affected more than expiratory capacity. Airways may close at higher than normal distending pressures, resulting in trapping of larger volumes of gas in the lungs.¹¹ Lung compliance is reduced when alveolar edema is present because lung volume decreases. Gas exchange becomes severely compromised when flooded alveoli remain perfused, causing *right-to-left shunts*,¹² and there is an increase in *wasted ventilation* (ventilation of units in which there is decreased or absent perfusion).

Light and electron microscopic examination of human and animal lung tissue in increased pressure edema shows alveolar edema and hemorrhage; thickened interstitial compartments (especially large peribronchovascular fluid cuffs) with separated, dispersed collagen fibrils; and increased capillary surface area and volume.¹³ More intercellular vesicles can be seen, but otherwise there are no detectable changes in the ultrastructure of the vascular endothelium, and the gap widths at intracellular junctions are not different from those in normal lungs. Long-standing pulmonary edema (e.g., in patients with chronic mitral stenosis) can be associated with basement membrane thickening and increased distance between the alveoli and the capillaries; increases in fibroblasts, histiocytes, and bulky strands of collagenous fibers can be seen in the interstitium. Dogs with pacing-induced chronic congestive heart failure developed a significant increase in the threshold for high-vascular-pressure edema formation—about a 50% reduction in the amount of water and protein cleared across the lung microvascular endothelial barrier at high pulmonary vascular pressures—compared with control animals. Morphometric analysis of the alveolar-capillary barrier showed that endothelial, interstitial, and epithelial thicknesses were all increased compared with controls, indicating that remodeling may confer an increase in the resistance to development of high-pressure-induced alveolar edema. Alveolar type II cells may be more numerous than in normal lungs, and alveolar macrophages proliferate.¹⁴ Sites of chronic severe increased pressure edema may also become

Table 62-2 Effects of Vascular Congestion, Interstitial Edema, and Alveolar Flooding on Pulmonary Function and Lung Mechanics

VASCULAR CONGESTION

Increased diffusing capacity
Increased arterial PO_2
Decreased compliance
Bronchoconstriction

INTERSTITIAL EDEMA

Increased closing volume
Decreased maximal expiratory flow
Increased ventilation-perfusion mismatching
Decreased arterial PO_2

ALVEOLAR FLOODING

Increased closing volume (air trapping)
Increased vascular resistance
Decreased lung volume (especially vital and inspiratory capacities)
Decreased compliance
Decreased diffusing capacity
Right-to-left shunting of blood (severely compromised gas exchange)

Table 62-3 Mechanisms of Increased Pressure Pulmonary Edema**INCREASED LUNG MICROVASCULAR HYDROSTATIC PRESSURE**

Left ventricular dysfunction
 Mechanical obstruction of left atrial outflow
 Volume overload
 Pulmonary venous hypertension
 Overperfusion
 Increased lymphatic outflow pressure

DECREASED PERIMICROVASCULAR HYDROSTATIC PRESSURE

Inspiratory airway obstruction
 Increased alveolar surface tension

organized and fibrotic, may calcify, and may even result in bone formation.¹⁵

Mechanisms

By far the most common cause of increased pressure edema is elevated lung microvascular hydrostatic pressure. The influence of driving pressures would be greater than usual if either perimicrovascular hydrostatic pressure or protein osmotic pressure difference across the microvascular barrier was decreased. At the alveolar barrier, an increase in interstitial hydrostatic pressure, a decrease in alveolar hydrostatic pressure, or a decrease in osmotic pressure difference across the barrier could result in a greater sum of driving pressures. The possibilities are listed in Table 62-3.

Increased Microvascular Hydrostatic Pressure. Congestive heart failure is the most common cause of increased pressure edema. That is why increased pressure edema is often called “cardiogenic,” even though the heart is not always primarily involved. Elevated pressures in the pulmonary microvasculature are usually due to left-sided heart failure, with elevated left atrial pressures transmitted retrograde into the pulmonary circulation. Common causes are left ventricular dysfunction (e.g., caused by acute myocardial infarction, severe coronary insufficiency, tachyarrhythmias, bradyarrhythmias, cardiomyopathies, constrictive pericarditis, aortic stenosis or regurgitation, mitral regurgitation, coarctation of the aorta, rupture of chordae tendinae or intraventricular septum, systemic hypertension) or mechanical obstruction of the left atrial outflow tract (e.g., mitral stenosis, left atrial myxoma). Left atrial and pulmonary microvascular pressures can also be elevated by severe fluid volume overloading in a patient with a normal or diseased heart.

An unusual cause of increased microvascular hydrostatic pressure is pulmonary venous hypertension in the absence of left ventricular or atrial disease, which can arise if the pulmonary veins are contracted (e.g., by possible muscular sphincters), compressed, or obstructed (e.g., because of veno-occlusive disease or mediastinal fibrosis). Bronchial venous hypertension, in contrast, does not appear to significantly increase fluid filtration in the lungs.¹⁶

Increases in fluid filtration also can be associated with increases in vascular pressure proximal to the filtration sites in the lungs. For example, pulmonary hypertension, combined with depressed left ventricular function, has been implicated in the pathogenesis of cocaine-induced pulmo-

nary edema. Whether such increases lead to pulmonary edema depends on what happens to microvascular pressure. If high right-sided pressures are caused by increased resistance proximal to the main site of filtration in the lungs—as found in hypoxic pulmonary vasoconstriction of small arterial vessels,¹⁷ primary pulmonary hypertension, and pulmonary artery or valvular stenosis—pulmonary edema does not develop. Conversely, if the lung vascular bed is only partially constricted or obstructed, or if the vascular surface area is greatly decreased (e.g., by lung resection), higher flow in perfused vessels can lead to increased pressure edema,¹⁸ because microvascular pressures at the fluid exchange site are elevated in the overperfused lung. For example, pulmonary edema resulted in about 15% of patients after pneumonectomy and seemed to be exacerbated by administration of fresh frozen plasma,¹⁹ in part because intravascular volume is presumably increased by such transfusions. Any increase in blood flow through the lungs increases the pulmonary microvascular pressure at the fluid exchange sites even when pulmonary venous pressure remains constant.

The mechanism of an uncommon cause of pulmonary edema, *high-altitude pulmonary edema*,²⁰ which is also discussed in Chapter 77, may also be related, in part, to elevated pulmonary vascular pressures. As noted earlier, overperfusion of a restricted pulmonary vascular bed, even in the absence of hypoxia, causes increased pressure edema, not increased permeability edema.¹⁸ This can explain why some cases of high-altitude pulmonary edema are correctly classified as increased pressure pulmonary edema. Evidence from climbers studied at high altitude suggests that high intravascular pressures cause physical damage to vascular walls (so-called stress failure). In experimental animals, stress failure has been demonstrated after extreme, but sometimes transient, increases in pulmonary vascular pressures.²¹ Such structural failures need not happen in large numbers to explain an increase in permeability edema, because edema would form readily and in a quantity driven by the prevailing elevated vascular pressure.²² The suggestion has been made that high-altitude pulmonary edema results from the stress failure of overdistended, relatively thin-walled pulmonary arteries rather than from microvascular rupture,²³ which might help explain why the prevailing vasoconstriction does not seem to offer much protection to downstream vessels, why there are no reports of gradual progression through an indolent prodrome of increased pressure edema before stress failure results, and why high-altitude pulmonary edema is first detected radiographically in the central lung fields surrounding large vessels rather than in the lung bases and periphery.

Alternative mechanisms for the increased permeability in high-altitude pulmonary edema have been proposed. However, inflammatory responses in high-altitude pulmonary edema may be a consequence rather than a cause of the edema.²⁴ The rapid reversibility of high-altitude pulmonary edema with descent to lower elevation, oxygen therapy, or pharmacologic reduction of pulmonary vascular pressure is not characteristic of increased permeability pulmonary edema with coexisting inflammation.

*Neurogenic pulmonary edema*²⁵ also may be related in part to elevated pulmonary vascular pressures (Fig. 62-2). Measurements of edema fluid protein concentration relative to

plasma protein concentration in 12 patients with neurogenic pulmonary edema have been reported. Seven of the patients had ratios typical of increased pressure pulmonary edema, and the other five had ratios consistent either with increased permeability pulmonary edema or with late sampling during the resolution phase of increased pressure pulmonary edema, because edema fluid protein concentration

rises as fluid is reabsorbed from the alveoli at a faster rate than protein.

Decreased Perimicrovascular Hydrostatic Pressure.

The sum of driving pressures would increase if perimicrovascular hydrostatic pressure was greatly diminished, thereby resulting in an increase in fluid and protein filtration at the microvascular barrier in the lungs. Pulmonary edema has been described in circumstances in which this might happen. The best clinical example may be *postobstructive pulmonary edema* as a consequence of upper airway obstruction or its release, which can be caused, for example, by laryngospasm, endotracheal tube obstruction, foreign body aspiration, epiglottitis, croup, severe acute asthma, airway compression by tumors, strangulation, or hanging. High negative intrathoracic pressures generated by inspiratory attempts against the occluded airway are transmitted to the interstitium, promoting fluid movement into the interstitium. Mechanical effects on the cardiovascular system likely contribute to this kind of edema. High negative intrathoracic pressure causes increases in cardiac preload and afterload and in pulmonary blood flow, all of which increase the microvascular pressure that drives fluid out into the interstitium. In three patients with upper airway obstruction and pulmonary edema, all had low edema fluid protein concentration relative to plasma protein concentration (ratios of 0.44, 0.31, and 0.52), indicating increased pressure pulmonary edema.²⁶

Aspiration of air or fluid from the pleural space with consequent reexpansion of a collapsed lung could result in a decrease in perimicrovascular hydrostatic pressure as the lung expands to fill the thorax. So-called *reexpansion pulmonary edema* has been reported both in experimental animals²⁷ and in patients²⁸ after lung reexpansion (Fig. 62-3), but the high edema fluid protein concentration measured in three patients²⁹ indicated that reexpansion may result in an increased permeability edema rather than an increased

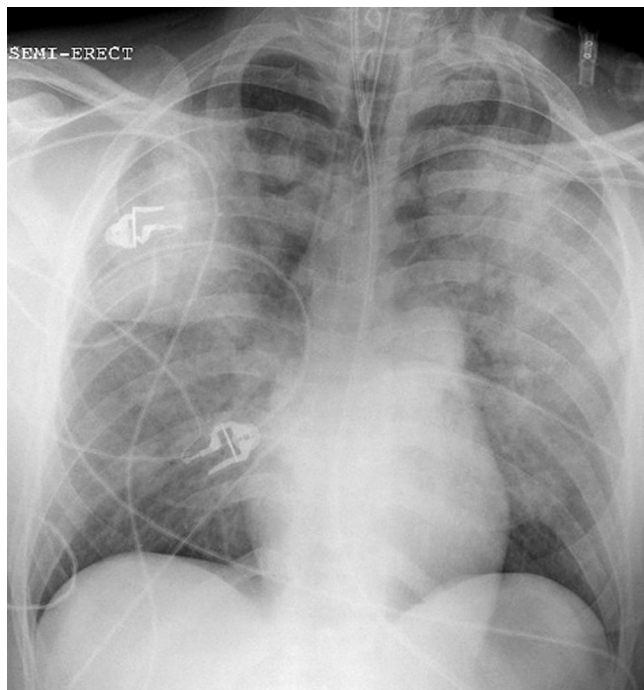


Figure 62-2 Frontal chest radiograph in a patient with subarachnoid hemorrhage and both increased intracranial pressure and neurogenic pulmonary edema. Multifocal bilateral consolidation and ground-glass opacity, somewhat upper lobe predominant, is present. The patient's volume status was normal and no clinical evidence of infection was present. (Courtesy Michael Gotway, MD.)

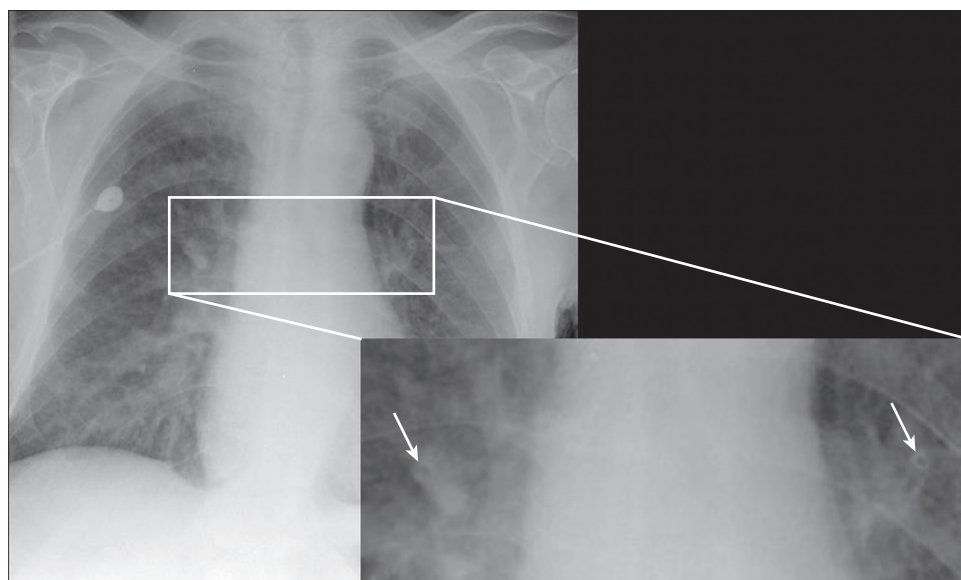


Figure 62-3 Frontal chest radiograph in a patient with increased pressure pulmonary edema showing peribronchial cuffing. Central vascular enlargement and indistinctness are present, associated with airway thickening best seen in end-on bronchi, such as the anterior segmental upper lobe bronchi. These findings are shown to advantage on the magnified, inset image (arrows). (Courtesy Michael Gotway, MD.)

pressure edema. However, another study of protein concentration in pulmonary edema fluid from patients with reexpansion edema indicates that hydrostatic mechanisms predominate.³⁰ The increased permeability hypothesis was supported in studies of rabbits with experimental reexpansion edema.³¹ Reperfusion injury is one of the causes of the pulmonary edema seen in transplanted lungs and appears to be predominantly an increased permeability edema.³²

If high alveolar surface tension was transmitted to the interstitium, perimicrovascular hydrostatic pressure would also be lowered, thereby increasing filtration across the microvascular barrier. Such an effect has been suggested by experimental findings in dog lungs.³³ The effect of alveolar surface tension on lung fluid balance is discussed later.

Decreased Transmural Protein Osmotic Pressure Difference. The sum of driving pressures would be increased if the protein osmotic pressure difference opposing the hydrostatic pressure difference across the microvascular barrier was decreased, either by lowering plasma protein concentration or by raising interstitial protein concentration, resulting in an increase in the sum of driving pressures for fluid and protein flow into the lungs. This theoretical mechanism of increased pressure edema has been the subject of study in experimental animals, with contradictory results.³⁴ When plasma protein osmotic pressure is low, the ability of the osmotic pressure gradient to widen in response to increased hydrostatic pressure is diminished, and edema accumulates at hydrostatic driving pressures lower than those needed to cause edema when protein concentration is normal.

Alveolar Barrier Function. If interstitial hydrostatic pressure was raised or if alveolar hydrostatic pressure or the osmotic pressure difference across the alveolar barrier was lowered, driving pressure for fluid and protein flow across the alveolar barrier would be elevated, resulting in increased pressure edema. Interstitial hydrostatic pressure rises as interstitial edema accumulates in the lungs.^{4,35} Increased interstitial hydrostatic pressure would raise the sum of driving pressures across the alveolar barrier and could drive edema formation across the alveolar or airway epithelium.

Greater pressure filtration across the alveolar barrier would also result from an increase in the sum of driving pressures if alveolar hydrostatic pressure was lowered. This is complicated by the interrelation between alveolar and interstitial hydrostatic pressures.^{4,36} A drop in alveolar hydrostatic pressure, which increases the sum of driving pressures across the alveolar barrier, also results in a lowering of interstitial hydrostatic pressure, which decreases the sum of driving pressures across the alveolar barrier but increases the sum of driving pressures across the microvascular barrier. Administration of a detergent aerosol resulted in loss of surfactant activity, higher alveolar surface tension, lower static compliance, atelectasis, and pulmonary edema; low protein concentration in alveolar edema fluid and left-hilar afferent lymph relative to plasma protein concentration indicated that this was an increased pressure type of pulmonary edema.³⁷ Because increased pressure edema can impair surface activity of dog lung extracts and isolated rabbit lungs, it is possible that changes in alveolar surface

tension may accelerate edema formation. However, the notion that changes in alveolar surface tension in edema lead to a self-perpetuating vicious circle of edema formation is not borne out clinically.

The only kind of clinical pulmonary edema caused by transmural osmotic pressure differences is near-drowning.³⁸ Seawater is three times more hyperosmotic (1000 mOsm) than plasma, so the volume of fluid in the air spaces after saltwater aspiration increases threefold to reach osmotic equilibrium, thus markedly increasing the alveolar edema already present owing to the volume of aspirated seawater itself in the alveoli. Osmotic equilibrium is reached in minutes as water is drawn from neighboring blood vessels into the alveoli by osmotic pressure.³⁹ Alveolar barrier function is not significantly compromised (unless perhaps the patient aspirates gastric contents or the seawater is contaminated or rich in particulate matter), and the alveolar edema is cleared rapidly (50% to 60% of excess alveolar fluid is cleared in 4 hours). Freshwater near-drowning proceeds in the opposite fashion: osmotic equilibrium is reached rapidly by flow of water out of the alveoli into the interstitium and bloodstream. Rapid water flux and hypotonicity can cause severe hemodilution, with hemolysis and fibrinolysis, as well as severe distortion of pulmonary ultrastructure, including damage to type I and type II cells, endothelial cell swelling, basement membrane detachment, and cell disruption. Both the alveolar epithelium and microvascular endothelium can thus be injured by the hypotonic fluid, leading to increased permeability pulmonary edema rather than a normal barrier type of pulmonary edema.

INCREASED PERMEABILITY EDEMA

Increased permeability pulmonary edema (Fig. 62-4) is caused by an increase in liquid and protein conductance across the barriers in the lungs. The essential feature of this edema is that the integrity of the barriers to fluid and protein flow into the lung interstitium and alveoli is altered from lung parenchymal damage. Increased permeability



Figure 62-4 Frontal chest radiograph in a patient with increased permeability edema. Bilateral consolidation, more prominent on the left, is present. The heart is not enlarged and no pleural effusions are present. No features typical of volume overload are evident. (Courtesy Michael Gotway, MD.)

edema is sometimes called *noncardiogenic pulmonary edema*, and the resulting clinical syndromes in humans—when explicitly defined (see later)—are referred to as *acute lung injury* (ALI) or, when severe, the *acute respiratory distress syndrome* (ARDS).⁴⁰

Pathophysiology

If the rate of fluid and protein accumulation from lung endothelial and epithelial barrier injury exceeds the rate at which it can be removed, increased permeability edema results. Because the barriers limiting fluid and protein flow into the lungs do not function normally when the lungs are injured, the lungs are not protected against edema by the usual safety factors. Although increases in fluid and protein filtration across the barriers are removed by lymphatics and drained away from the alveolar walls as in increased pressure edema, much more fluid and protein are filtered at any given sum of driving pressures because the barriers to their flow are much less restrictive than normal. Edema formation in injured lungs becomes extremely sensitive to driving pressures.²² Driving pressures are often increased when the lungs are injured because of the vasoconstrictive effects of inflammatory mediators such as thromboxanes, which may shift the main site of resistance to postcapillary venules, thus increasing hydrostatic pressure at the microvascular fluid exchange sites,⁶⁷ or because of effects on the heart as well as on the circulation. For example, elevated left atrial pressure, pulmonary venoconstriction, and an increase in cardiac output in sepsis can increase hydrostatic pressure at the microvascular fluid exchange sites.⁴¹

Because the endothelial-epithelial barrier becomes leaky, protective protein osmotic pressure differences are lost across them, driving pressure is unopposed by protein osmotic pressure, and even normal hydrostatic pressure results in significant fluid and protein extravasation into interstitial and alveolar spaces. The ability of the lymphatics to pump the excess filtrate away is increased when the lungs are injured. Maximal lung lymph flow increases more when the microvascular wall has been injured than when hydrostatic pressure alone is increased, but even this augmented lymphatic pumping capability is taxed at low driving pressures. If the epithelial barrier is injured, edema may accumulate readily in the alveoli, because most of the resistance to fluid and protein flow into the alveoli resides in the epithelial barrier.⁴² Increased permeability edema is often rapid in onset and progression because injured barriers offer much less resistance to flow and because hydrostatic driving pressure is unopposed by increases in osmotic pressure difference. Clinically, patients with increased permeability edema usually have a low intravascular hydrostatic pressure, commonly measured as a low or normal pulmonary capillary wedge pressure. In some cases, this reflects the low intravascular pressures associated with the underlying disease process (e.g., sepsis).

The consequences of increased permeability edema on lung mechanics and gas exchange depend on how much edema accumulates and how severe the causative lung injury is.⁴³ As with increased pressure edema, the major effects on pulmonary mechanics follow alveolar flooding. In experimental lung injury, functional residual capacity decreases as a consequence of alveolar flooding, and this loss of ventilated units accounted for virtually all the

observed decrease in static lung compliance.⁴⁴ *Computed tomography* (CT) has provided new insights into structure-function relationships in human ALI.⁴⁵ In its early stage, when alveolar edema predominates, the lungs are characterized by a homogeneous alteration of vascular permeability, and edema accumulates evenly in all lung regions with a nongravitational distribution. Increased lung weight due to edema causes collapse of lung regions along the vertical axis through the transmission of hydrostatic forces (compression atelectasis, caused by the weight of edema). Thus lung volume is lost mainly in the dependent lung, where the superimposed weight from above is greatest.

Measurements of pulmonary mechanics in mechanically ventilated patients with diffuse parenchymal lung damage showed decreased static lung compliance as a consequence of loss of ventilated lung. In addition, airflow resistance was increased as a result of decreased lung volume.⁴³ Bronchospasm may add to the increase in airflow resistance and can be substantially reversed by bronchodilator inhalation.⁴⁶ Chest wall compliance was reduced, probably because of alterations of intrinsic mechanical properties of the chest wall by abdominal distention, chest wall edema, and pleural effusion.⁴³ Different respiratory mechanical abnormalities and responses to *positive end-expiratory pressure* (PEEP) during mechanical ventilation were reported in patients with severe increased permeability edema originating from pulmonary disease (pneumonia with consolidation) or from extrapulmonary disease (associated with pulmonary edema and alveolar collapse).⁴⁷

Although the effects of surface forces on decreased lung compliance in patients with diffuse lung damage were thought to be small, results of experiments in isolated rabbit lungs indicated that increased permeability edema may result in more severe mechanical changes than equivalent degrees of increased pressure edema. Surfactant is thromboplastic, and coagulation may compound surfactant depletion when plasma proteins enter the air spaces. The injured lung may release substances that interfere with the normal low surface tension in the alveoli,⁴⁸ and activated *polymorphonuclear leukocytes* (PMNs) impair surfactant function in vitro and degrade the major surfactant apoproteins by proteolysis and oxidant-radical-mediated mechanisms.⁴⁹ Human lung surfactant obtained by *bronchoalveolar lavage* (BAL) of patients at risk for diffuse lung damage and patients with established injury is abnormal in chemical composition and functional activity.⁵⁰ Abnormalities also could be caused by interactions between surfactant and edema proteins, because plasma proteins (especially fibrin monomers but also fibrinogen and albumin) interfere with surfactant function. Proteinaceous edema fluid has been associated with surfactant inhibition in various experimental models.⁵¹ The role of surfactant in the development and treatment of diffuse parenchymal lung damage and the potential role for surfactant therapy are discussed in more detail later in this chapter.

Gas exchange is often severely compromised in increased permeability edema, owing both to intrapulmonary shunting of blood and to ventilation-perfusion inequalities.⁵² Patients with early lung injury typically have a marked increase in their pulmonary dead-space fraction, indicating that many ventilated lung units are not well perfused, although intrapulmonary shunting may also contribute to

the elevated dead space⁵³; this finding explains why minute ventilation rises to twice normal (12–16 L/min) at the onset of severe increased permeability edema. An elevated pulmonary dead-space fraction also has been reported in pediatric patients with widespread lung injury,⁵⁴ the mechanism for which may in part be explained by an increase in procoagulant and antifibrinolytic pathways in parenchymal damage.

The physiologic abnormalities associated with increased permeability edema are dominated by early alveolar flooding and depend on the severity and the duration of injury as well as its cause. Manifestations may resolve or worsen, but typically evolve in three pathologic patterns: exudative, proliferative, and fibrotic, usually in sequence. The earliest changes are marked by widespread alveolar and interstitial edema and hemorrhage. Injury to alveolar ducts may be particularly severe. Hyaline membranes, composed of precipitated plasma proteins, fibrin, and necrotic debris, can be seen. The alveolar epithelium may be more extensively damaged than the vascular endothelium, even if the underlying insult is blood-borne. Widespread, local areas of alveolar destruction, particular of type I alveolar epithelial cells, alternate with normal-appearing alveoli. The injured alveolar epithelium is swollen, disorganized, discontinuous, and often lifted off the exposed, but usually intact, basement membranes, which are covered by hyaline membranes. Type II cells are nearly always less severely damaged than type I cells, because their thin squamous cytoplasmic extensions, distant to the nucleus covering the thin side of the alveolar-capillary barrier, are frequently most gravely affected. The interstitium is widened by edema (especially in peribronchovascular cuffs) and may have leukocytes, platelets, red blood cells, fibrin, and debris (especially near the alveolar walls). The microvascular endothelium is often relatively preserved, usually showing little other than irregular focal thickening as a result of cytoplasmic swelling or vacuoles and greater numbers of luminal leukocytes, although frank swelling of endothelial cells may be seen on ultrastructural histology.

The exudative phase is followed by a proliferative phase, which begins within the 5 to 7 days after the onset of injury.⁵⁵ The relative contributions of the original insult, repair processes, and effects of therapies to this and subsequent phases are not well known, but some of the abnormalities after the initial exudative phase were related to the effects of traditional modes of mechanical ventilation that used tidal volumes between 12 and 15 mL/kg predicted body weight.⁵⁶ In the proliferative phase, some of the edema fluid has been reabsorbed from the air spaces. Fibrin may be prominent in alveoli and interstitium, and there is infiltration with inflammatory cells and fibroblasts. The alveolar epithelium is often cuboidal, made up largely of proliferating type II cells. The air-blood barrier can be thickened by interstitial and epithelial enlargement. The pulmonary vascular bed may be partially or completely disrupted, and structural alterations may reduce its surface area.

A final stage may follow, often about 10 to 14 days after the initial insult, in which fibrotic changes of the alveolar ducts, alveoli, and interstitium predominate: alveoli may be obliterated, alveolar walls coalesced, and functional lung units lost. Less commonly, the lungs show emphysema-like bullous changes.⁵⁵ Pulmonary function test results in

Table 62-4 Clinical Disorders Associated with Increased Permeability Edema

Infections
Aspiration
Trauma
Hemodynamic disturbances
Drugs, medications
Hematologic disorders
Neurologic disorders
Miscellaneous disorders

5-year survivors of severe increased permeability edema usually return to normal or near-normal values, but exercise limitation and both physical and psychological quality of life are apt to remain compromised.^{57,58}

Mechanisms

The major types of clinical conditions that have been associated with increased permeability edema are listed in Table 62-4. The most common causes are pneumonia, sepsis, gastric aspiration, and major trauma. The lungs are injured via either the airways or the bloodstream. The exact mechanisms by which diffuse lung injury leads to increased permeability edema have been the subject of intense investigation in humans, animal models, and cellular systems.⁵⁶ Human studies have provided descriptive data about events in the air spaces before and after the onset of lung injury. Studies using BAL in patients before and after the onset of diffuse lung damage have shown that there is a major acute inflammatory response that begins before lung injury is clinically recognized, peaks during the first 1 to 3 days of clinical involvement, and then resolves slowly over the next 7 to 14 days in patients who remain intubated.^{57,59} These studies have shown the complexity of the evolving inflammatory responses, which are characterized by the accumulation of acute response cytokines and their inhibitors, oxidants, proteinases and antiproteinases, lipid mediators, growth factors, and collagen precursors involved in the repair process.^{57,60-66} Extensive efforts have been made to find single biologic markers that predict the onset or the outcome of diffuse parenchymal lung injury, but these have met with only limited success.^{67,68}

Hypotheses about mechanisms of lung injury have been tested in animal models and in vitro studies, and several reviews have summarized the findings.^{56,69} The existing animal models do not completely reproduce all of the various aspects of different injuries in humans, in part because human injuries typically evolve over a longer period of time than can be studied in the laboratory. In addition, the lungs of humans are exposed not only to the initial injurious insult but also to the therapies that are used for treatment, such as mechanical ventilation. Experiments with isolated cells have been useful to test specific concepts, but the complexity and redundancy of intact biologic systems are not reproduced in simplified experimental systems. Most experimental work purposely limits a study to a single causative agent; however, this turns the reality of clinical complexity into the simplicity of a single experimental pathway. Increased permeability edema in humans is likely to be caused by interactions between a number of different pathways acting in parallel or in series.

Studies in isolated organs and small animals in which hemodynamic variables are not measured can be difficult to evaluate because indices of lung injury, usually measured by the appearance of markers in lungs, lavage fluid, or perfusate, are not determined solely by the barrier function of the microvasculature. For example, when the vascular endothelium is injured, movement of fluid and protein from the vascular space into the lungs is extremely sensitive to hydrostatic driving pressures and surface area for filtration,²² and the effects of experimental interventions may be caused by changes in these parameters and not solely by changes in microvascular barrier function. The effects of microvascular driving pressures and surface area can be difficult to evaluate even in large, instrumented animals. Data from experimental animal models suggest that there are at least two broad categories of mechanisms of increased permeability edema: those that are *direct* (i.e., not requiring intermediary mechanisms, with injury a direct result of contact between an offending substance and lung tissue) and those that are *indirect* (i.e., requiring the participation of intermediary mechanisms, such as host defenses). These categories overlap because, once the lungs are injured, inflammatory responses may compound the primary mechanism of injury. Three major hypotheses about the mechanism of increased permeability pulmonary edema have been proposed, and are interrelated. A recent review provides specific information on animal models of experimental lung damage and an American Thoracic Society Consensus Conference provided further recommendations.⁶⁹

DIAGNOSIS

The diagnosis of moderately and, especially, severely advanced pulmonary edema, particularly when caused by heart failure, is usually fairly easy. Unraveling the cause of other kinds of pulmonary edema may not be so straightforward, particularly in patients with increased permeability edema.

CLINICAL ASSESSMENT

Definitions

Newcomers interested in the history of catastrophic lung disease should remember the clinical anecdotes that began to surface as far back as the 1950s, 1960s, and 1970s showing that little by little survival from what had been known as “shock lung,” “Danang lung,” and “adult respiratory distress syndrome” represented a gigantic medical-technical-operational breakthrough. Previously, virtually *all* such egregiously wounded or injured casualties died. (The name *adult* changed to *acute* respiratory distress syndrome, but the familiar acronym ARDS remained.) Subsequently, the number of survival miracles steadily increased, but mortality remained high.

Conceptually, ALI comprise a continuum of lung damage ranging from trivial to severe or lethal. For decades and by general agreement, the term “ARDS” has defined the most grievously afflicted victims of the syndrome. In 1988, an “expanded definition” with numerical grading of ARDS was proposed,⁷⁰ and 6 years later it was recognized that the

term ALI could be “applied to a wide spectrum of this continuum of pathologic process so as to acknowledge and define it”⁷¹; moreover, the term ARDS continued to represent the most severe end of the ALI spectrum of damage.

To satisfy clinical and epidemiologic needs, three different definitions of lung damage have been widely used, but each has its shortcomings: the Acute Lung Injury Score,⁷⁰ the *American-European Consensus Conference* (AECC) definition,⁷¹ and a recent revision of the AECC definition termed the “Berlin Definition of ARDS.”⁷²

The Lung Injury Score (Table 62-5) provides an assessment of the severity of lung injury, taking into account supportive therapy, such as mechanical ventilation with PEEP and oxygen supplementation.⁷⁰ This score is important because not all lung injuries are of equal severity and severity changes over time. In this scoring system, ARDS defines only the most severe injuries (those that yield a score >2.5); milder lung injuries, termed mild-to-moderate, may have a better prognosis and may differ from ARDS in other important aspects. This scoring system has been used widely in clinical research and clinical trials.

The American-European Consensus Conference Definition⁷¹ (Table 62-6) has four elements: (1) timing (onset

Table 62-5 Components and Individual Values of the Lung Injury Score

1. CHEST RADIOGRAPH SCORE	VALUE
No alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrants	2
Alveolar consolidation confined to 3 quadrants	3
Alveolar consolidation in all 4 quadrants	4
2. HYPOXEMIA SCORE	
PaO ₂ /Fio ₂ ≥ 300	0
PaO ₂ /Fio ₂ 225–299	1
PaO ₂ /Fio ₂ 175–224	2
PaO ₂ /Fio ₂ 100–174	3
PaO ₂ /Fio ₂ < 100	4
3. PEEP SCORE (WHEN VENTILATED)	
PEEP ≤ 5 cm H ₂ O	0
PEEP 6–8 cm H ₂ O	1
PEEP 9–11 cm H ₂ O	2
PEEP 12–14 cm H ₂ O	3
PEEP ≥ 15 cm H ₂ O	4
4. RESPIRATORY SYSTEM COMPLIANCE SCORE (WHEN AVAILABLE)	
Compliance ≥ 80 mL/cm H ₂ O	0
Compliance 60–79 mL/cm H ₂ O	1
Compliance 40–59 mL/cm H ₂ O	2
Compliance 20–39 mL/cm H ₂ O	3
Compliance ≤ 19 mL/cm H ₂ O	4
The final value is obtained by dividing the aggregate sum by the number of components that were used.	
	SCORE
No lung injury	0
Mild to moderate lung injury	0.1–2.5
Severe lung injury (ARDS)	>2.5

ARDS, acute respiratory distress syndrome; PaO₂/Fio₂, arterial oxygen tension to inspired oxygen concentration ratio; PEEP, positive end-expiratory pressure.

From Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 138:720–723, 1988.

Table 62-6 American-European Consensus Conference Definition of Acute Lung Injury and Acute Respiratory Distress Syndrome**TIMING**

Acute

OXYGENATION (REGARDLESS OF PEEP LEVEL) $\text{PaO}_2/\text{FiO}_2 \leq 300$ = acute lung injury $\text{PaO}_2/\text{FiO}_2 \leq 200$ = acute respiratory distress syndrome**CHEST RADIOGRAPH**

Bilateral opacities on frontal view

PULMONARY ARTERY WEDGE PRESSURE

<18 mm Hg when measured, or

No clinical evidence of left atrial hypertension

Table 62-7 Berlin Definition of ARDS

Mild	$\text{PaO}_2/\text{FiO}_2$	200–300 mm Hg
Moderate	$\text{PaO}_2/\text{FiO}_2$	100–199 mm Hg
Severe ARDS	$\text{PaO}_2/\text{FiO}_2$	<100 mm Hg

must be “acute”); (2) oxygenation (arterial PO_2/FiO_2 [fractional concentration of oxygen in inspired gas] <300 mm Hg, regardless of the level of PEEP, for the diagnosis of ALI to be made, and arterial $\text{PO}_2/\text{FiO}_2 \leq 200$ mm Hg, regardless of PEEP level, for the diagnosis of ARDS to be made); (3) chest radiograph (bilateral opacities seen on frontal view); and (4) pulmonary artery wedge pressure (<18 mm Hg when measured, or no clinical evidence of left atrial hypertension).

The third explication, the Berlin Definition,⁷² simply subdivides ARDS into three categories of severity: mild, moderate, and severe, based on the arterial PO_2/FiO_2 ratio (Table 62-7). Initially, so-called ancillary variables—severity of chest radiographic findings, minimum PEEP level, respiratory system compliance, and standardized minute volume—were considered for inclusion, but finally discarded. Of interest, the term “acute lung injury” was abandoned. Mortality increases successively as arterial PO_2/FiO_2 ratio worsens in mild, moderate, and severe ARDS.

Another recent method of defining and grading the severity of clinically meaningful lung damage, first in a single center⁷³ and then in 21 others,⁷⁴ is what has been called the *Lung Injury Prediction Score*, or LIPS, whose goal is to improve the early identification of patients at high risk for development of serious early or impending lung injuries. Both risk factors (predisposing conditions, such as pneumonia, severe sepsis, trauma, and aspiration) and risk modifiers (e.g., alcohol abuse, hypoalbuminemia, and use of supplementary oxygen), have each been graded numerically to yield a combined LIPS value, which has an impressively high negative predictive value (0.96 to 0.98) but a much lower positive predictive value (0.14 to 0.23).⁷⁵ A more recent study showed that diffuse alveolar damage was observed in fewer than half the patients having clinical criteria for ARDS, but was more frequent (69%) in those with ARDS lasting more than 72 hours.⁷⁶

The current working definitions all have useful attributes, but fail to link any particular clinical feature to any

particular change in the structure or function of the relevant barriers in the lungs or to the degree of pulmonary edema. What defines the ALI-ARDS continuum in a meaningful way is the altered barrier permeability to protein in the lungs, the structural damage to the lung microvascular endothelial and alveolar epithelial barriers, and the consequent excess lung water content. In the future as research studies progress, these clinical definitions may need to be supplemented with biologic markers (see next section) and pathologic findings (when available) to help categorize ALI and ARDS into more specific disease entities.

Symptoms and Signs

The clinical manifestations of pulmonary edema vary with its severity and depend on the underlying pathophysiology and the extent to which excess edema fluid has accumulated in the lungs. Characteristic symptoms comprise dyspnea, cough, and tachypnea. Wheezing, when audible, may present a problem in differential diagnosis, but patients with typical asthma generally do not have other symptoms and signs of congestive heart failure or pulmonary edema.⁷⁷ Once alveoli have flooded, the diagnosis of pulmonary edema is not subtle. Patients with alveolar edema usually have severe respiratory distress with tachypnea and cough that is often productive of frothy and sometimes blood-tinged edema fluid. Crackles and rhonchi are heard over the lung fields and wheezing may be present. The patient may be cyanotic if alveolar flooding has seriously compromised gas exchange.

Development of pulmonary edema is often slow and progressive in increased pressure pulmonary edema because the alveoli are protected by the normal safety factors (see Table 62-1). In contrast, in increased permeability edema, alveolar flooding and symptoms of respiratory distress often happen rapidly. Edema that develops suddenly (or unexpectedly) sometimes is called “flash pulmonary edema,” which usually pertains to the rapid development of high-pressure edema, after protective safety factors have been surmounted.

Because pulmonary edema is always a sign of an underlying pathologic process, its cause must be identified so that effective therapy can be directed at the underlying problem producing abnormal transvascular fluid and solute flow into the lungs. Increased pressure edema is most often caused by cardiac failure from systolic dysfunction with impaired myocardial contractility and thus is usually accompanied by a history of heart disease; manifestations include signs and symptoms of any of the many causes of chronic and acute congestive heart failure, such as coronary insufficiency, hypertension, valvular heart disease, and severe volume expansion. Elevated jugular venous pressure, cardiac enlargement, gallop rhythms, heart murmurs, arrhythmias, large tender liver, and peripheral edema almost always suggest an underlying abnormality of cardiac function. However, pulmonary edema may be the only manifestation of silent myocardial infarction or diastolic dysfunction of the left ventricle.⁷⁸

History and physical examination may also be helpful in differentiating between increased pressure and increased permeability pulmonary edema, because most patients in the latter category usually do not have signs or symptoms of underlying cardiac disease. The cause of increased

permeability edema may be suggested by a history of exposure (e.g., to toxic gases or chemicals, near-drowning, drug ingestion, trauma), the clinical setting (e.g., sepsis, pneumonia, emesis, seizures, pancreatitis), or the physical findings (e.g., chest trauma, long bone fractures, coma, shock). Because infections, including the sepsis syndrome, are the leading causes of increased permeability edema in patients, a thorough search must be made for signs and symptoms of infection. Pulmonary and intra-abdominal sources are the most common sites of involvement, and all patients should be examined carefully, with special attention being paid to abdominal, rectal, and pelvic examinations.

Diagnostic Studies

Laboratory and other diagnostic studies are often helpful but, by the time many of the results are found to be abnormal, the diagnosis is usually obvious. Appropriate cultures for microorganisms and toxicology screens of blood and urine are useful in identifying underlying causes of increased permeability edema. Examination of sputum or tracheal aspirate, bronchoscopy with protected-specimen brushing, or mini-BAL are all useful in diagnosing pneumonia in ventilated patients, even those who are being treated with antimicrobial drugs.⁷⁹⁻⁸² Lung biopsy can sometimes provide a specific diagnosis in critically ill patients,⁸³ but the results often are not helpful because lung injuries caused by diverse underlying conditions have similar histologic appearances and because specific therapies may not be available.

In the special case of pulmonary edema suspected to be caused by saltwater near-drowning, measurement of plasma magnesium level can help determine whether a patient has aspirated or swallowed seawater, or both. Severe hypermagnesemia has been reported following aspiration of ordinary seawater and, especially, highly concentrated saltwater from the Dead Sea.⁸⁴

Chest Radiographs

The plain chest radiograph is the most practical laboratory study available for the detection of pulmonary edema.^{85,86} Disadvantages are that chest radiographs are insensitive to small changes in lung water and are only semiquantitative.¹ An additional limitation is that chest radiographs are not consistently helpful in distinguishing increased pressure edema from increased permeability edema.^{85,87} These disadvantages are offset by the advantages that chest radiographs are noninvasive, inexpensive, easily repeatable, readily available, and free of serious side effects (apart from a small amount of radiation).

Before alveolar flooding, plain chest radiographs typically show distended vascular shadows (particularly in the upper lung fields), enlargement and loss of definition of hilar structures, development of septal lines (Kerley lines) (Fig. 62-5; Video 62-1, loss of peribronchial and perivascular definition or cuffing) (Fig. 62-6), and perihilar haze indicating the presence of interstitial pulmonary edema. Acinar shadows, often confluent and creating irregular, patchy increases in lung density that obscure vascular markings, indicate the presence of alveolar edema. Air bronchograms may be observed in severe edema. Because the radiographic signs of interstitial and alveolar edema are determined by gas and blood volumes and their distribution in the lungs



Figure 62-5 Frontal chest radiograph in a patient with increased pressure pulmonary edema from heart failure showing alveolar edema and bilateral consolidation. Note presence of air bronchograms. (Courtesy Michael Gotway, MD.)

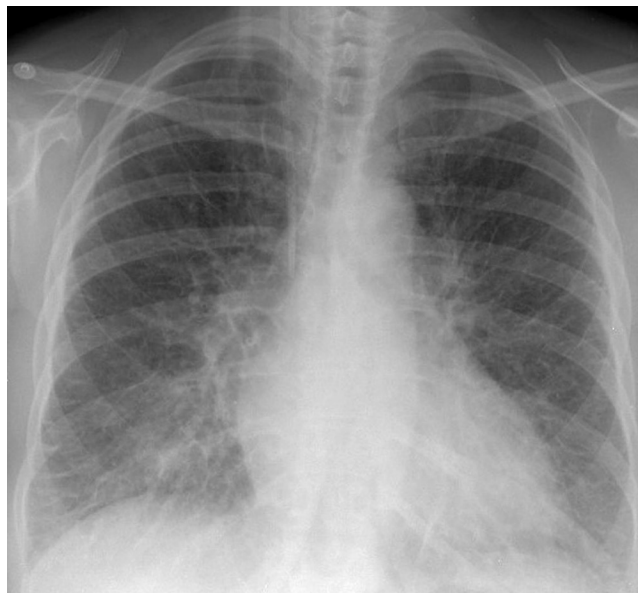


Figure 62-6 Frontal chest radiograph in a 56-year-old woman with increased pressure pulmonary edema from chronic heart failure showing interlobular septal thickening. Thin linear opacities are best seen in the inferolateral thorax, particularly on the right, representing thickened interlobular septae, or Kerley B lines. See the chest CT scan for this patient in Video 61-1. (Courtesy Michael Gotway, MD.)

in addition to the presence of edema, the recognition and quantitation of edema are not precise, and the radiographic appearance of edema is strongly influenced by the lung volume at the time the film is made. The chest radiograph score is an integral part of the Lung Injury Score and the revised Berlin Definition, but the interpretation of chest radiographs is not well standardized and significant interobserver variations have been reported.⁸⁸ One recent approach for scoring the chest radiograph and accounting for atelectasis correlated well with lung weight in lungs that were studied from brain-dead potential organ donors.⁸⁹

Arterial Blood Studies

The arterial PO_2 , arterial PCO_2 , and pH are the most informative laboratory indicators of overall pulmonary function in patients with pulmonary edema. Arterial blood studies are not sensitive to early edema. Interstitial pulmonary edema does not usually affect oxygen uptake in the lungs beyond modest hypoxemia caused by ventilation-perfusion mismatching. In contrast, alveolar flooding seriously compromises gas exchange, resulting in right-to-left shunting of blood from ongoing perfusion of alveoli that cannot be ventilated because they are fluid filled or collapsed. In two studies of groups of patients with increased permeability edema from lung injury, oxygenation appeared to depend more on the vasoconstrictive ability of the pulmonary circulation—owing to the ability to reduce perfusion of damaged and edematous areas of the lungs—than on the amount of edema present.^{90,91}

In patients hospitalized for acute cardiogenic pulmonary edema, arterial PCO_2 may be low, especially in the early stages, when tachypnea results in alveolar hyperventilation; arterial PCO_2 may also be within the normal range or elevated, the latter indicating alveolar hypoventilation, which can be caused by underlying lung disease, increased metabolic production of carbon dioxide (perhaps related to increased work of breathing), increased wasted ventilation (ventilation of poorly perfused alveoli), or mechanical impairment caused by weak respiratory muscles.⁹² An elevation in the pulmonary dead space fraction in the first 24 hours after development of severe increased permeability edema identifies patients with a higher risk for survival, particularly if the dead space fraction is greater than 0.60.⁵³

When pulmonary edema is severe or the lungs have been injured, many patients develop metabolic acidosis as a result of tissue hypoxia, increased work of breathing, intrinsic lung lactate production, or all of these.⁹³ Attempts to correct acidosis with parenteral bicarbonate administration usually are not necessary; rather, the underlying cause must be identified and treated appropriately. Maintenance of a satisfactory systemic blood pressure is crucial. Respiratory acidosis caused by alveolar hypoventilation can be treated either by noninvasive ventilation or by invasive mechanical ventilation with endotracheal intubation. Metabolic acidosis can be partially corrected by alleviating hypoxemia and improving cardiac function; the possibility of underlying disease amenable to surgery (e.g., intestinal ischemia or infarction, perforation of a viscus) or pancreatitis should be considered.

Measurement of Pulmonary Edema Fluid Protein Concentration

When florid pulmonary edema is present, measurement of protein concentrations in both simultaneously collected edema fluid (suctioned through an endotracheal tube) and plasma provides a rapid, noninvasive method for distinguishing increased pressure edema from increased permeability edema.⁹⁴ Because the microvascular barrier is functionally intact in increased pressure edema, plasma proteins remain largely confined to the intravascular space, and edema fluid protein concentration is low relative to plasma protein concentration (the ratio of edema fluid to plasma protein concentration is generally <0.65). In con-

trast, in increased permeability edema, when the microvascular barrier is injured, plasma proteins leak in high concentrations into the vascular space, which raises edema fluid protein concentration high relative to plasma protein concentration (ratio of edema fluid to plasma protein concentration generally >0.75). Intermediate values (between 0.65 and 0.75) may indicate that both types of edema are present and suggest the relative contributions of each.

Measurement of the ratio of edema fluid to plasma protein concentrations has been shown to be a simple method for separating the two different pathophysiologic types in numerous reported series of patients with pulmonary edema.⁹⁵⁻⁹⁸ Three studies indicated that an increasing protein concentration in serial measurements of edema fluid in increased permeability edema was a good sign, reflecting an intact epithelial barrier and net removal of edema fluid from the alveoli.^{97,98} There is new evidence that the edema fluid to plasma protein ratio has prognostic value as well as diagnostic value.⁹⁹ Such measurements need to be correlated with the patient's clinical condition, because an increasing protein concentration in edema fluid over time might also mean that increased permeability edema was complicating what had been increased pressure edema or that the lungs were injured more severely or more extensively as time passed.

Edema fluid can be collected by inserting a standard 14- to 18-gauge catheter through an endotracheal tube and advancing it into a wedged position in the distal air spaces (similar to the procedure for wedging a fiberoptic bronchoscope). Gentle suction is applied as the catheter is slowly withdrawn, and fluid is collected in a small trap. Several attempts may be needed; if no fluid can be suctioned, the clinician should try changing the patient's position. Samples grossly contaminated with airway secretions, which have a very low protein concentration, less than 1 g/dL, such as mucus, pus, and debris, should be discarded. The protein concentration in the edema fluid and the plasma can be measured by the clinical laboratory or estimated quickly at the bedside from the protein scale of a handheld refractometer.

Standard BAL using fiberoptic bronchoscopy or mini-BAL (with a wedged suction catheter) have been used as research and diagnostic tools that may also yield useful information about the cellular biochemical and microbial composition of the air space,¹⁰⁰ but lavage is not useful as a method to measure alveolar protein concentration, because the instilled saline dilutes alveolar fluid by approximately 50- to 100-fold, depending on the method.⁶⁷

MEASUREMENT OF LUNG WATER AND BARRIER FUNCTION

In theory, measurement of the quantity of water or edema fluid in the lungs could be useful in detecting early pulmonary edema and in assessing its clinical course and response to treatment; however, no optimal technique is available. Methods in use or under investigation focus on either measurement of lung density or equilibration of tracers with water in the lungs.^{1,101} Interest in such measurements assumes that accurate knowledge about lung water content would be useful in diagnosis and would be beneficial in the treatment of patients with pulmonary edema. Recent work

with a single thermal indicator for measuring extravascular lung water has shown promise based on some studies, although the actual clinical utility has not been convincingly proven.¹⁰²

Barrier Function

Clinical distinction between increased pressure edema and increased permeability edema is difficult,^{103,104} because transvascular fluid flow into the lungs can be abnormal long before lung water content increases greatly. In theory, the two types of edema can be separated on the basis of differences in barrier function. Detection of increased transvascular fluid flow into the lungs and measurement of barrier integrity might be more helpful than measurement of lung water content in edema. A simple and practical method exists to evaluate barrier integrity (edema fluid protein concentration measurements, discussed earlier), and several methods have been studied to detect early edema and changes in barrier function. However, not one is in routine clinical use.

Biologic Markers of Lung Injury

Potential biologic markers of imminent increased permeability edema from various kinds of lung injury have been the subject of many studies and comprehensive reviews.^{67,105,106} Naturally, considerable interest revolved around finding a simple blood, urine, or BAL test that could identify patients who are destined to develop or who are already in the earliest stages of increased permeability edema, or that could predict the outcome of patients with injured lungs. To be of clinical use, such a marker would have to be both practical and inexpensive to measure as well as sensitive and specific for the detection of lung injury. An extensive search has been made for a reliable biologic marker for the detection of early or impending lung injury comparable to the decisive clinical role played by troponin measurements for diagnosing acute myocardial infarction. The long-sought diagnostic nirvana for increased permeability edema remains distant.

Several studies from multicenter clinical trials have reported the independent predictive value of some plasma markers for mortality and other clinical outcomes in patients with increased permeability edema from various lung injuries. The biologic markers of greatest predictive value are surfactant protein D,¹⁰⁷ interleukin-6 and interleukin-8,¹⁰⁸ von Willebrand factor antigen,¹⁰⁹ soluble tumor necrosis factor- α receptors I and II,¹¹⁰ intercellular adhesion molecule-1,¹¹¹ protein C and plasminogen activation inhibitor-1,^{112,113} and the receptor for advanced glycation end products.^{114,115} Because increased permeability edema follows a wide variety of insults that range in severity, and because many abnormalities detected in increased permeability edema are found in other severe illnesses of diverse etiology that do not involve the lungs, it seems unlikely that any single marker will be found that unequivocally identifies the risk or the presence of severe lung injury. Increased attention is being given to the sensitivity and specificity of combinations of markers. In support of this approach, one recent study found that combinations of three plasma biomarkers had a statistically significant better prognostic value for predicting death than the use of standard clinical predictors alone.⁶⁸

Currently, the latest intriguing biologic marker of increased permeability edema, angiopoietin-2, an endothelial growth factor and potent regulator of vascular permeability, plays a role in several different clinical conditions, including malignancies, liver failure, malaria, chronic kidney disease, heart failure, and sepsis. Heightened interest in angiopoietin-2 followed the observation that levels in patients with sepsis were “markedly elevated within the first hour of clinical care,” correlated with disease severity, rose further in patients who died, and were predictors of shock or death.¹¹⁶ Moreover, these observations have been broadened by using angiopoietin-2 values to predict the development of increased permeability edema from lung injuries in a wide spectrum of critically ill patients; combining angiopoietin-2 levels with the Lung Injury Prediction Score (described previously) improved the resulting receiver operating curve characteristics compared with each curve separately.⁷⁵ Clearly, additional studies of larger numbers of patients and outcomes are needed to bolster these observations.

TREATMENT

Treatment of pulmonary edema often requires vigorous life-saving measures, followed by specific therapy directed at the factors that led to accumulation of water in the extravascular spaces of the lungs. Rational therapy also requires an accurate diagnosis and an understanding of the nature of the underlying disease state and of the strategies that might prove useful in limiting further edema accumulation and that favor fluid removal from the lungs.^{117,118}

EMERGENCY THERAPY

Patients with alveolar edema are frequently severely ill and require immediate treatment for acute respiratory failure. The basic principles of treatment of hypoxemic respiratory failure are discussed in Chapter 100. Essential requirements for patients with pulmonary edema include preservation of the airway, and provision of satisfactory alveolar ventilation and arterial blood oxygenation. Maintenance of arterial blood pressure is indispensable. Reliable means of monitoring and sustaining oxygen saturation and blood pressure in rescue operations and ambulance travel are now widely used. Ventilatory management in patients with florid alveolar flooding and severe gas exchange abnormalities, regardless of cause, requires emergent endotracheal intubation, high inhaled oxygen concentrations, and PEEP. After stabilization, obligatory lung-protective strategies are introduced in patients with increased permeability edema (see later discussion); in contrast, increased attention is being directed at noninvasive ventilatory methods (discussed later) that hasten improvement in respiratory distress and metabolic disturbances in patients with increased pressure edema, nearly always from congestive heart failure, but have no effect on short-term mortality.

INCREASED PRESSURE EDEMA

In increased pressure pulmonary edema, the common goal of therapy is to reduce the transudation of fluid into the

lungs. Because the rate of edema formation increases exponentially with increases in pulmonary vascular pressures,⁷ hydrostatic pressure control is crucial for successful therapy. Therapy must be clearly goal oriented, responsive to the underlying pathophysiology, and frequently reassessed until the patient is stable.

General Principles

The acute recognition and management of increased pressure pulmonary edema, exemplified by congestive heart failure, has been the subject of comprehensive reviews.^{5,6,8,119,120} With increased pressure edema, the goal of therapy is to reduce the hydrostatic pressure causing edema formation in the lungs. The major objective is to achieve a net negative fluid balance without adversely affecting myocardial performance. The work of the heart must be reduced as much as possible by restricting physical activity and preventing pain and anxiety, which act to increase cardiac work by increasing sympathetic tone. As the heart fails, cardiac performance is reflexly preserved by progressive increases in vascular volumes that act to increase cardiac stroke volume and work (the Frank-Starling mechanism). This compensatory increase in preload of the left ventricle results in pulmonary venous hypertension and raises the driving pressure for fluid filtration out of the pulmonary microcirculation. As heart failure worsens, cardiac output falls, pulmonary and systemic venous pressures rise, systemic vascular resistance increases, and edema, in the lungs and in the periphery, becomes the major manifestation of compromised cardiac function.

In patients with increased pressure edema, a reduction of vascular volume and an increase in cardiac output decrease the driving pressure for edema formation. Because the normal safety factors protecting the lungs from edema driven by high filtration pressures are intact, the pressure need be lowered only toward normal. At pulmonary capillary wedge pressures less than 20 mm Hg, fluid filtration in the lungs usually should not be sufficient to cause pulmonary edema. Patients with severe cardiac failure may tolerate higher pressures—because baseline barrier permeability is lowered in the lungs and lymphatic removal capability is increased—and may require such pressures to maintain cardiac output. Therapy is directed at reducing the work the heart must perform and at increasing the heart's efficiency for the work it must do including, in some patients with severe hydrostatic pulmonary edema, the use of positive-pressure mechanical ventilation. The resolution of alveolar edema in these patients is not simply a function of lowering lung vascular pressures; other mechanisms that augment alveolar fluid clearance are important.¹²⁰

Most patients with acute pulmonary edema caused by cardiac failure have systolic dysfunction from weakened contractility, but approximately 30% of patients have diastolic dysfunction. Cardiac contraction is normal, but relaxation is impaired. Because the ventricle does not relax normally, end-diastolic pressure is increased, thereby increasing hydrostatic pressure in the lung microcirculation. Acute diastolic dysfunction producing pulmonary edema is now recognized as a common manifestation of acute myocardial ischemia or uncontrolled hypertension. Other causes include diabetes mellitus, aortic stenosis,

infiltrative cardiomyopathies, endocardial fibroelastosis, hypothermia, septic shock, elevated thoracic pressures from mechanical ventilation, and pericardial effusion. Causal or aggravating conditions should be corrected (e.g., revascularization for coronary artery disease, control of systemic hypertension). The goal of therapy in acute diastolic dysfunction is to lower elevated filling pressures (by the cautious use of diuretics and nitrates) without significantly reducing cardiac output. These patients are prone to develop hypotension in response to diuretics and nitrates because adequate cardiac output depends on elevated filling pressures in the heart. Because systolic function is normal, positive inotropic agents do not help and can actually aggravate ischemia.

In the setting of acute increased pressure pulmonary edema, it is especially important to identify and treat correctable causes of heart failure. Acute myocardial infarction, ongoing myocardial ischemia, arrhythmias, valvular lesions, systemic hypertension, ventricular septal rupture, rheumatic or other inflammatory myocarditis, digitalis intoxication, pulmonary embolism, infection, thyrotoxicosis, or severe anemia may have caused the heart to fail and must be corrected. Cardiac patients presenting with pulmonary edema may not complain of chest pain, but most of them have significant coronary artery disease, and pulmonary edema may be the only manifestation of silent myocardial ischemia.

Morphine Sulfate

The sovereign emergency therapy for acute cardiogenic pulmonary edema has long been morphine sulfate, 5 to 10 mg, or its equivalent, given intravenously slowly over several minutes, taking care to avoid hypotension. Morphine is an extremely useful drug in the treatment of heart failure, because it is a potent vasodilator as well as a central nervous system sedative and because it does not depress myocardial contractility. Its vasodilating effects can substantially reduce pulmonary capillary pressure and may improve depressed cardiac output. The work of the heart is lessened by the vasodilating, bradycardic, and sedative effects of morphine. Cautiously administered morphine usually does not cause respiratory failure or aggravate existing carbon dioxide retention associated with acute pulmonary edema, but the patient must be closely watched if he or she is not intubated and receiving assisted ventilation. Hypotension following morphine administration indicates that too much drug was given or that the intravascular volume is lower than suspected; prompt administration of naloxone (Narcan) should quickly correct the disturbance.

Decreasing Venous Return

If sophisticated medical care is not immediately available, two useful age-old remedies for increased pressure pulmonary edema can be lifesaving. First, rotating tourniquets can reduce intrathoracic blood volume—and thereby pulmonary perfusion pressure—by trapping blood in the extremities, away from the pulmonary circulation. Tourniquets, or blood pressure cuffs inflated to less than systolic pressure, are applied to three of the four extremities and rotated every 15 minutes. The purpose is to decrease venous return, not to stop all blood flow to the extremities. Care must be taken that the tourniquets are rotated and that

venous return from any extremity is not obstructed for more than 45 minutes at a time. A study of patients with left ventricular dysfunction following myocardial infarction showed trapping by tourniquets of considerable blood volume in the periphery, but variable and sometimes unfavorable effects on left ventricular function.¹²¹ Second, removal of 100 to 500 mL of bloody by phlebotomy¹²² can be used to reduce blood volume in acute pulmonary edema from congestive heart failure when the patient is not in shock and when drugs and supportive care are not immediately available.

Ventilatory Strategies

Most patients hospitalized with increased pressure edema suffer from acute or chronic heart failure and require oxygen treatment to ensure satisfactory arterial blood oxygenation. Depending on the prevailing severity of oxygen deficiency, patients with mild abnormalities may require only supplementary oxygen administered through a nasal catheter or simple mask; those with moderate oxygen deficiency may be helped with noninvasive methods of oxygen administration. Finally, profound gas exchange abnormalities require endotracheal intubation with high oxygen concentrations and elevated end expiratory pressures.

Today, after many studies, noninvasive ventilation—by either continuous positive airway pressure or noninvasive intermittent positive-pressure ventilation—has proved beneficial for the treatment of acute cardiogenic pulmonary edema; both methods cause more rapid improvement in respiratory distress and metabolic abnormalities than standard oxygen treatment.¹²³ The two types of noninvasive ventilation are similar in their clinical benefits, but have no effect on short-term mortality.¹²⁴ Properly used noninvasive ventilation spares many patients from the ordeal of endotracheal intubation, but when cardiogenic pulmonary edema is severe and worsening, intubation is immediately indicated.^{125,126}

Right Heart Catheterization

In 1970, Drs. HJC Swan and William Ganz¹²⁷ introduced the balloon flotation catheter into clinical medicine for measurements of right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure, and for assessment of cardiac output and oxygen saturation values in the right heart chambers. Pulmonary artery catheters are reasonably easy to use but training is essential. Naturally, residents and fellows, as well as seasoned attending physicians in cardiology, critical care, surgery, and anesthesiology, joined the rush to insert Swan-Ganz catheters and learn about their benefits.

The good news is that these same eager young trainees and veteran doctors did indeed learn a gigantic amount of cardiovascular and respiratory physiology that most doctors knew little or nothing about before the advent of pulmonary artery catheterization.¹²⁸ As knowledge concerning hemodynamics became everybody's business, new conceptual models for the management of acute myocardial infarction, heart failure, and cardiogenic shock based on readily obtained hemodynamic data produced new clinical insights and research rewards. Similar approaches explored the mysteries of sepsis, septic shock, and postoperative complications, and how to differentiate increased pressure from

increased permeability edema. Novel hemodynamic concepts were enhanced by the use of new and increasingly potent diuretics and vasoactive and inotropic drugs.

The bad news, of course, was that the stampede “to swan” led to considerable overuse and abuse of pulmonary arterial catheterization.¹²⁹⁻¹³³ Technical competence and professional know-how sometimes suffered, and would-be experts did not always know how to interpret the information. But the Swan-Ganz bandwagon kept rolling on and did not slow down until well into the 1990s, when authorities began to question whether or not the unrestricted use of balloon flotation catheters in patients with acute myocardial infarction was warranted. Although the outcomes of early clinical trials were not definitive, they raised considerable doubts, and it was finally recognized that pulmonary artery catheterization had no place in the routine management of acute myocardial infarction.¹³⁴

Subsequently, the prevailing certainty that monitoring pulmonary capillary wedge pressure, and cardiac output, rather than central venous pressure, would optimize both control of volume status and regulation of vasopressor and inotropic treatment was challenged and put to the test. A large NHLBI-sponsored clinical trial of 1000 patients concluded that “[pulmonary artery catheterization]-guided therapy did not improve survival or organ perfusion and complications were higher than [central venous catheterization]-guided therapy.”¹³⁵

The latest (2013) information on the use of balloon flotation catheters for adult patients in intensive care comes from the Cochrane Central Register of Controlled Trials.¹³⁶ The authors concluded “that the use of a [pulmonary artery catheter] did not alter the mortality, general [intensive care unit] or hospital [length of stay], or cost for adult patients in intensive care.” As usual, experience and clinical judgment is essential.

It must be said and emphasized—now that the old controversies have been largely clarified—that several incontrovertible indications for Swan-Ganz catheterization endure unchallenged and remain commonly employed, particularly in the diagnosis and monitoring of cardiovascular diseases.¹²⁸ Alternative methods of hemodynamic monitoring, such as the Pulse Index Continuous Cardiac Output device,¹³⁷ are being designed and evaluated, but there remains an important role for balloon flotation catheters for critically ill adult patients.

Specific Pharmacologic Therapy

After emergency treatment has been instituted and the patient's condition stabilized, three major therapeutic options—vasodilators, diuretics, and inotropic agents—need to be considered and administered when appropriate. The goal of therapy with these agents is to lower the hydrostatic pressure at the filtration sites in the pulmonary vascular bed while maintaining adequate systemic delivery of oxygen. The choice of therapy is dictated by the patient's condition and the cause of the pulmonary edema.

Vasodilators. Depending on their specific therapeutic indications, vasodilators are used for hypertension, congestive heart failure, and angina. Several medications are available, usually in combination and usually as part of a long-term treatment regimen. Vasodilators are useful

pharmacologic agents for the treatment of acute increased pressure pulmonary edema, because their effects happen rapidly, usually in minutes. Through dilation of veins, vascular capacitance is increased and blood is redistributed peripherally, thereby lowering the driving pressure for fluid filtration in the lungs; through dilation of arteries, systemic vascular resistance (cardiac afterload) falls, cardiac output and stroke volume increase, and the heart works more efficiently. In addition to morphine, three classes of vasodilators may be useful in pulmonary edema: venodilators (e.g., nitrates), arteriolar dilators (e.g., phentolamine, hydralazine), and mixed dilators (e.g., nitroprusside).

The most common side effects of vasodilators such as dizziness, especially when standing, are related to low blood pressure. Tolerance to vasodilators may require revision of long-standing therapy.

Diuretics. Patients with symptoms of pulmonary edema, especially from increased vascular pressure, usually benefit from administration of diuretic agents, a standard means of initial therapy.¹³⁸ These drugs may exert a modest immediate effect by increasing venous capacitance and decreasing the relative perfusion of flooded alveoli (acting as vasodilators), but their principal mechanism of action is to increase sodium and water excretion by the kidneys.¹³⁹ The resultant diuresis causes a decrease in left ventricular volume and pressure and thereby a reduction in left atrial pressure and the pressure at the filtration sites in the lungs. Among the potent loop diuretics administered by slow intravenous injection, furosemide is highly effective and generally regarded as the agent of choice. Dozens of different dosage regimens of furosemide have been and are still being used to treat symptomatic patients with pulmonary edema from acute congestive heart failure. One such regimen consists of a loading dose of 40 to 80 mg followed by a continuous infusion at 10 to 20 mg/hr; if there is no response in an hour, the loading dose is repeated and the infusion rate is doubled. Equivalent doses of other loop diuretics (bumetanide, torsemide, or ethacrynic acid) have essentially the same effects.

Decades of clinical experience have documented that intravenous administration of loop diuretics nearly always result in prompt diuresis and symptomatic relief. Nevertheless, information about safety and efficacy is lacking and optimal use of diuretics in heart failure management needs much further study and improvement.¹⁴⁰

If the patient is hypotensive or in frank shock, diuretics are seldom of benefit, because poor renal perfusion limits any effects they might have on kidney function. In this circumstance, continuous venovenous ultrafiltration can reduce intravascular volume even in patients who require vasopressors for blood pressure support.

If the patient has severely diseased kidneys, diuresis may not be an option. In this circumstance, continuous arteriovenous hemofiltration with or without counter-current dialysis¹⁴¹ or venovenous ultrafiltration¹⁴² should be considered. These techniques represent considerable advances over traditional hemodialysis, which was often impossible in hemodynamically unstable patients (especially those with low cardiac output or hypotension), and peritoneal dialysis, which was both slow and poorly tolerated. Hemofiltration can be instituted, maintained, and managed suc-

cessfully by well-trained intensive care unit nurses and physicians, and it is not complicated by hypotension because the circuits have small volumes and pressures are low. Considerable fluid (<200 to 300 mL/hr) can be removed when needed, with the amount being titrated to the patient's cardiovascular status.

Inotropic Agents. Patients with cardiogenic shock and other cardiac catastrophes that lower systemic blood pressure often require inotropic agents as a temporary life-saving measure. In quite a different therapeutic category, patients with systolic heart failure and pulmonary edema with impaired cardiac contractility were at one time also thought to benefit from inotropic agents by increasing cardiac output and lowering the driving pressure for fluid filtration in the lungs. Although the use of pharmacologic agents to improve myocardial contractility seems rational, current opinion states that "inotropic therapies in the [systolic heart failure] population have universally failed to live up to their expectations."¹⁴³ Palliative inotropic treatment has its occasional indications, but other options such as combination implantable cardioverter-defibrillator and cardiac resynchronization may also provide benefits.¹⁴⁴

When present, increased pressure pulmonary edema is an important associated feature of impaired myocardial contractility, has proven difficult to treat, and has a poor prognosis; individualized diagnostic fine-tuning may transiently improve clinical outcome, but results remain modest at best. Older methods, however, are being supplanted by advanced techniques of coronary reperfusion, mechanical support with intra-aortic balloon pumps or ventricular-assist devices, expanded use of extracorporeal membrane oxygenators for severe respiratory failure, and improvements in heart and/or lung transplantation.

INCREASED PERMEABILITY EDEMA

As already emphasized, the strategy for managing patients with increased permeability pulmonary edema caused by various types of severe lung injury differs from that for patients with increased pressure pulmonary edema in two crucial respects: first, the endothelial and epithelial barriers are damaged in permeability edema, whereas they are usually normal in high-pressure edema; and second, when barriers are damaged, edema develops even at low driving pressures. The goals of therapy (Table 62-8) are to treat the underlying cause of acute lung damage, to provide support while the repair phase begins, to use a lung-protective ventilator strategy that will not worsen the lung injury, and to reduce as much as possible the driving pressures for fluid movement across the injured barriers into the lungs.

General Principles

The cause of lung injury may not always be apparent, and when the cause is not obvious, it should be assumed to be infection: the most common treatable underlying cause of increased permeability edema. Although the patient is often seriously ill, diagnostic studies must be performed to identify a possible source of infection, so that appropriate drainage and antimicrobial therapy can be instituted. Plain chest radiographs are seldom helpful. Abdominal sonograms and CT scans can be diagnostically useful. Sepsis

Table 62-8 Acute Lung Injury: Important Principles of Management**MINIMIZE EDEMA ACCUMULATION**

Ensure lowest possible pulmonary microvascular pressure
Reduce vascular volume

FIND AND TREAT INFECTION**PROVIDE SUPPORTIVE THERAPY**

Administer oxygen
Use lung-protective ventilation
Optimize blood pressure and cardiac output

DO MORE GOOD THAN HARM

Avoid hypotension
Avoid volume overload
Avoid oxygen toxicity
Avoid infection

from intra-abdominal infection is common and may be especially difficult to identify. Many of these infections require surgical drainage if antimicrobial drug therapy is to be effective. Because specific therapy for increased permeability is not usually available—unless the cause is a treatable infection—supportive therapy is extremely important. The initial concerns are to support ventilation and circulation. Patients with increased permeability edema may be hemodynamically unstable, and ventilatory support can be complicated by hypotension or frank shock; PEEP, which is usually required for adequate oxygenation, may compound the problem by impeding venous return to the heart and decreasing cardiac function.

Patients with low pulmonary capillary wedge pressures (<10 mm Hg) or central venous pressure (<4 mm Hg) and systemic hypotension require fluid resuscitation to support blood pressure and end-organ perfusion. If the patient has active, ongoing blood loss or the hemoglobin concentration is low (<7 g/dL), packed red blood cells are effective, not only to expand intravascular volume and restore blood pressure, but also to increase the oxygen-carrying capacity of the blood. Patients who are not bleeding and who have normal hemoglobin concentrations should be resuscitated with crystalloid solutions. Because the barriers restricting colloid movement from the vascular space into the lungs are not functioning normally in injured lungs, protein osmotic pressure differences favoring fluid movement into the vascular space cannot be established in the lungs; therefore there is no advantage to fluid resuscitation with colloid solutions.

Patients with hypotension that does not respond to fluid resuscitation or who have normal (>10 mm Hg) or elevated pulmonary capillary wedge pressure require vasopressors or positive inotropic agents. For patients with septic shock, generalized vasodilation resulting in low systemic vascular resistance is the major hemodynamic abnormality.¹⁴⁵ Nor-epinephrine is the most commonly used vasopressor to support blood pressure, but dopamine is also widely used.

Aggressive hemodynamic support of critically ill patients can be detrimental if the complications of therapies become more harmful than the underlying disease itself. Strategies to increase systemic oxygen delivery (e.g., with inotropes, intravascular fluids, and blood transfusions) or to achieve

supranormal values for the cardiac index or normal values for mixed venous oxygen saturation did not improve mortality when applied to all critically ill patients, but did improve outcome in patients with sepsis who were treated very early in their course.^{146,147} One ARDS Network clinical trial showed that, in patients without shock, as defined by lack of need for vasopressor treatment, a strategy to restrict fluids to reduce intravascular pressures improved clinical outcomes by reducing the duration of mechanical ventilation in patients with ALI; of note, pressure measurements from both central venous and pulmonary artery catheters provided equally useful guidelines for fluid restriction, but pulmonary artery catheterization was associated with significantly increased complications.¹⁴⁸

A multicenter, randomized, controlled clinical trial of transfusion requirements in critically ill patients with euvolemia after initial treatment compared a restrictive strategy of transfusing red blood cells if the hemoglobin concentration dropped to less than 7 g/dL versus a more liberal strategy of maintaining hemoglobin concentration greater than 10 g/dL. Restricting transfusion requirements to maintain hemoglobin concentration at 7 to 9 g/dL was at least as effective and was possibly superior to the strategy of giving transfusions to maintain hemoglobin concentration at 10 to 12 g/dL; the sole possible exception to this policy included patients with active coronary ischemic syndromes, such as acute myocardial infarction and unstable angina.¹⁴⁹

Lung-Protective Ventilator Strategies

In experimental animals, ventilation with high tidal volumes increases vascular filtration pressures and produces stress fractures of microvascular endothelium, alveolar epithelium, and basement membrane.^{150,151} The resulting injury appears to be due to the combination of large tidal excursions at high lung volumes coupled with elevated airway pressures: so-called *volutrauma*. Because the evidence from animal studies and small clinical trials provided compelling experimental rationale,^{152,153} investigations were performed to test the potential benefit of lower tidal volumes and reduced airway pressures versus standard (high) tidal volumes and elevated pressures. A large NHLBI-sponsored multicenter trial was stopped prematurely after the enrollment of 861 patients with well-defined ALI-ARDS. The trial compared “traditional” ventilator management using initial tidal volumes of 12 mL/kg of ideal body weight with plateau pressures of 50 cm H₂O or less, with lower tidal volumes of 6 mL/kg with airway plateau pressures limited to 30 cm H₂O or less: “Mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes—31% vs. 39.8%, $P = .007$ —and the number of days without ventilator use during the first 28 days after randomization was greater in this group—(mean \pm SD), 12 ± 11 vs. 10 ± 11 ; $P = .007$.”¹⁵⁴

The results of this seminal trial and several follow-up studies have transformed the management and outcome of patients with ARDS,¹⁵⁵⁻¹⁵⁸ and are being successfully applied to critically ill patients without ARDS.^{159,160} The protocol for implementing the lung-protective ventilatory strategy is detailed in Table 100-3 and further discussed in Chapter 100.

Interestingly, results from an Italian study showed that a low tidal volume strategy in ARDS patients attenuated inflammatory responses in both the lungs and bloodstream, as measured by a reduction in neutrophil and cytokine concentrations in BAL fluid and a reduction in cytokines in circulating blood.¹⁶¹ Other studies have confirmed that low tidal volume lung-protective ventilation is associated with reduction in inflammatory markers in the lung.¹⁶² In addition, alveolar epithelial injury is probably reduced, considering the decline in surfactant protein D levels (a type II epithelial cell marker) and the receptor for advanced end glycation product (a type I epithelial cell marker) in the plasma of patients treated with the lung-protective ventilatory strategy.^{115,163}

In addition to use of the lung protective ventilatory strategy, several adjuncts in small numbers of patients have been proposed to supplement treatment of critically ill patients, including prone positioning,¹⁶⁴ extrapulmonary gas exchange (oxygenation, carbon dioxide removal, or both), liquid ventilation, tracheal gas insufflation, permissive hypercapnia, and high-frequency ventilation. Additional discussion of these modalities is provided in Chapter 100.

Specific Pharmacologic Therapies

Several therapeutic agents, which are listed in Table 62-9, have been studied in patients with various forms of lung injury and sepsis. None of these agents have shown any benefit on mortality in large-scale, prospective, randomized, controlled clinical trials, including a recent trial of statins in ARDS.^{164a}

Whether or not newer anti-inflammatory therapies will be useful in patients with increased permeability edema from damaged lung barriers remains an important question. Although inflammatory reactions can damage tissue, it is important to remember that inflammation plays an important beneficial role in the elimination of invading microorganisms. Because inflammatory pathways are redundant, blocking any one inflammatory mediator (or even multiple mediators) may have little or no effect on the overall inflammatory response. If the mechanisms of lung injury differ after various clinical events, the application of therapy directed at one particular mechanism would not be appropriate until most or all of the underlying mechanisms have been recognized and treated successfully.

Table 62-9 Therapeutic Agents Tested in Increased Permeability Pulmonary Edema^{164a}

Corticosteroids
Ibuprofen
Nitric oxide
Prostaglandin-E ₁ (PGE ₁)
Liposomal prostaglandins E ₁ and E ₂
Surfactant
Antiendotoxin and antitumor necrosis factor antibodies
Platelet-activating factor receptor antagonist
Interleukin-1 receptor antagonist
Ketoconazole
N-acetylcysteine
Oxothiazolidine carboxylate
Pentoxifylline
Beta-adrenergic agonists
Statins

Corticosteroids. Of all the possible pharmacologic agents used to treat critical lung injuries, corticosteroids have the longest history. Despite a seemingly compelling rationale for their use in the setting of increased permeability edema from sepsis, four separate prospective, randomized, double-blind, placebo-controlled trials of high-dose methylprednisolone therapy failed to show any benefit.¹⁶⁵ Corticosteroid therapy did not prevent the development of well-characterized ALI or decrease its incidence in patients with the sepsis syndrome; neither did it hasten the reversal of ARDS, lower mortality, or improve respiratory function. Moreover, use of corticosteroids was associated with both a greater 14-day mortality rate in patients who developed critical lung injury and an increased frequency of associated infections. Corticosteroids also were ineffective in the sepsis syndrome and may have caused harm.¹⁶⁶

One exception may be the *fat embolism syndrome*. A prospective, randomized, double-blind, placebo-controlled trial of corticosteroid treatment in 64 patients with long bone fractures showed that high-dose methylprednisolone effectively prevented the development of the fat embolism syndrome.¹⁶⁷ Fat embolism is an uncommon clinical syndrome that is usually described in single case reports from orthopedists; corticosteroid treatment has not been routinely used and thus far a large-scale multicenter, randomized trial does not seem warranted.

The generally disappointing results of corticosteroid trials in patients with early or impending lung injury have not discouraged further investigations; rather, ongoing studies indicate that corticosteroids might be beneficial in subsets of patients or when given at a particular time (e.g., during the proliferative phase) or for a more sustained period.¹⁶⁸ Results of studies of corticosteroid therapy late in the course of ARDS (so-called rescue therapy) were encouraging, and a small (24-patient), randomized, double-blind, placebo-controlled clinical trial in patients with severe ARDS whose Lung Injury Score had failed to improve by the seventh day of respiratory failure showed improvement in lung injury and other organ dysfunction scores, as well as reduced mortality in treated patients.¹⁶⁹ However, an NHLBI-sponsored trial of corticosteroid therapy (methylprednisolone 2 mg/kg) beginning on day 7 to 21 of ARDS showed no reduction in 60- or 180-day hospital mortality in patients treated with corticosteroids compared with placebo.¹⁷⁰ In addition, there were important neuromuscular complications in patients treated with methylprednisolone. One study suggested potential benefit with steroids in severe lung injury although the design of the trial was suboptimal.¹⁷¹

Neuromuscular Blocking Agents. Experience to date has been limited and randomized clinical trials inconclusive concerning both the efficacy of neuromuscular blocking agents in the treatment of ARDS and their association with intensive care unit-acquired muscular weakness. In 2010, a randomized-controlled trial showed improvement in the adjusted 90-day survival and time off the ventilator in patients receiving cisatracurium compared with placebo.¹⁷² A new systematic review and meta-analysis, which included three trials, all from the same French research group, reevaluated the potential benefit of 48-hour intravenous infusions of cisatracurium besylate; short-term infusion of

this neuromuscular blocking agent significantly improved mortality rate and lowered the risk for barotrauma, but had no effect on the length of mechanical ventilation among survivors.¹⁷³ Data on risk of intensive care unit-acquired weakness were inconclusive. Further studies are needed to settle this pending issue.

OUTCOME

The outcome of patients with pulmonary edema depends on which of the two major pathophysiologic categories of edema formation is involved. Until recently, much less was known about the resolution of pulmonary edema than about its formation. Water—and any extravasated proteins and cellular debris—must be removed from the alveoli and the interstitial spaces to restore the lungs to their pristine, healthy condition. Edema fluid clears from the lungs via five routes: lymphatics, airways, blood vessels, pleural space, and mediastinum; in contrast, cellular debris and particulate matter must be removed from the alveoli by macrophage uptake or through the airways.

RESOLUTION OF PULMONARY EDEMA

The considerable advances in our understanding of the clearance of fluid and solute from the alveoli have been the subject of several reviews.^{2,174,175,175a} Active sodium and chloride transport across the alveolar epithelial barrier into the interstitium drives edema fluid removal from the air spaces (see Chapter 9). The uninjured alveolar epithelium has a remarkable ability to clear fluid from the air spaces rapidly: for example, serial edema fluid protein concentration measurements relative to simultaneous plasma protein concentrations in a saltwater near-drowning patient showed that 50% to 60% of the excess alveolar fluid in the lungs was removed over the course of just 4 hours.³⁸ In experimental studies in rabbits, instillation of 4 mL/kg of seawater into the lungs resulted in a 300% increase in alveolar fluid volume in less than 5 minutes—owing to the movement of mainly pure water driven by osmotic forces from the plasma into the hyperosmolar (881 ± 29 mOsm) instillate—80% of which was cleared from the alveoli in 6 hours.³⁹

Equivalent volumes of iso-osmotic (292 ± 6 mOsm) saline instilled into rabbit lungs were cleared at a similar rate. In neither circumstance was there evidence of injury to the alveolar epithelial barrier, which is more resistant than the endothelial barrier to a wide range of injuries, including ischemia, alveolar and intravenous endotoxin and bacteria, intravenous oleic acid, acid aspiration, saltwater aspiration, hyperoxia, intratracheal bleomycin, septic and hypovolemic shock, and rewarming after severe hypothermia. Even after mild to moderate alveolar injury, the capacity to transport salt and water is often preserved. In severe injury, however, when the barrier is disrupted, the capacity to clear edema is lost, and the vascular endothelium becomes the limiting barrier between the vascular system and the air spaces. Clinically, the capacity to remove some alveolar edema fluid—as indicated by increase in the edema fluid to plasma protein concentration ratio in the first 4 to 12 hours after the development of increased permeability edema—is a favorable prognostic finding associ-

ated with a mortality of only 20%. In contrast, the inability to resorb alveolar edema fluid early in the course of severe lung injuries was associated with a mortality of nearly 80%.⁹⁷ Of interest, a larger and more recent study confirmed these results.⁹⁸ Thus the functional capability of the alveolar epithelial barrier in acute increased permeability edema may be a useful prognostic index, perhaps because it serves as a marker of the severity and extent of lung injury.

The barrier function may also be manipulated in certain settings. Lung Na^+ , K^+ -ATPase activity was increased in rats recovering from experimental thiourea-induced increased permeability pulmonary edema.¹⁷⁶ Moreover, alveolar fluid clearance can be increased by salmeterol in uninjured ex vivo human lung,¹⁷⁷ and experimental studies have shown that alveolar fluid clearance can be increased pharmacologically (e.g., by catecholamines), even in the presence of increased permeability edema with alveolar flooding.² These observations raise the potential of therapy to hasten the resolution of alveolar edema, although an increase in alveolar clearance requires an intact alveolar epithelial barrier.

Because clearance of protein from flooded alveoli is much slower (1% to 2%/hr) than clearance of protein-free fluid (10% to 20%/hr),^{178,179} the protein left behind becomes concentrated. The increase in protein concentration in the alveoli as protein-free fluid is resorbed does not slow fluid clearance, because precipitated protein exerts no osmotic pressure and the concentration of soluble macromolecules is too small to counteract the differences in ion concentration resulting from transepithelial transport. Removal of edema fluid from flooded alveoli may be slowed if the fluid clots, which can be seen especially when lung vascular permeability is increased. Edema fluid may clot because, following extravasation of plasma into the air spaces, the clotting system may be activated by surfactant or macrophage-derived procoagulants.

Fluid cleared from alveolar spaces into the alveolar interstitium can leave the lungs by flowing into the lymphatic capillaries or by moving down the prevailing pressure gradient into the loose peribronchovascular connective tissue spaces or directly into the pleural space. Large amounts of fluid in the air spaces may be partially cleared into peribronchovascular cuffs through the hypothesized “leaky” terminal-airway epithelium,^{180,181} leaving alveolar fluid and solute behind to be cleared more slowly through the more impermeable alveolar epithelium.

Most of the interstitial water in pulmonary edema is in the peribronchovascular loose connective tissue spaces rather than in the alveolar walls. Because the lymphatic capillaries are arranged to drain only the alveolar wall interstitium, this route for edema removal is not available for most interstitial water. A study in goats showed that lung lymph originated mainly from alveolar wall interstitial fluid, and the contribution of the lung lymphatic system to the clearance of interstitial edema in bronchoalveolar cuffs and interlobular septa was small. The maximum possible contribution by lung lymphatics to the clearance of interstitial edema liquid was less than 10%, and airway loss of liquid by evaporation was about twice the rate of lymphatic clearance.¹⁸² In a study of in situ perfused sheep lungs with experimental low- and high-protein pulmonary edema, during recovery from pulmonary edema, interstitial liquid

was resorbed into the circulation in inverse proportion to its protein concentration, and only a very small fraction of interstitial edema was cleared by the lung lymphatics during recovery from either type of edema.¹⁸³ Some fluid from the loose peribronchovascular interstitium may drain directly into the bloodstream by crossing the walls of blood vessels in the lungs.

A study of isolated sheep lungs made edematous by raising vascular pressures showed that the primary route of edema clearance was by vascular resorption; 60% of filtered water was cleared over 3 hours, 42% by reabsorption into the bloodstream and 18% by lymphatic, pleural, and mediastinal drainage.¹⁸⁴ Edema may also drain into the pleural space. Pleural effusions are fairly common in increased pressure pulmonary edema—found in about 25% to 50% of patients and usually on the right side when unilateral—but are present in increased permeability as well—in about 35% of patients.¹⁸⁵⁻¹⁸⁷ Formation and removal of pleural effusions are discussed in detail in Chapter 79. As much as 25% to 30% of pulmonary edema fluid may leave the lungs through the pleural space.^{186,188} A significant portion of the interstitial edema probably follows the prevailing pressure gradient in the lungs to drain into the mediastinum to be removed by neighboring lymphatics.

Short-term alveolar protein clearance appears to proceed primarily by paracellular diffusion and is size dependent.⁶ Most proteins are cleared intact rather than being degraded into smaller fragments. The general consensus is that transcytosis (transport via vesicles) is not a major mechanism for clearing bulk quantities of albumin or other proteins from the alveolar space. Over the long term, cellular mechanisms, principally phagocytosis and catabolism by macrophages, account for most protein clearance from the alveolar space.⁵⁶ Insoluble, precipitated proteins are removed in this way. Macrophages are also ultimately responsible for removing senescent and dead PMNs and other debris. The small ciliated surface area of the distal air spaces seems to indicate that the mucociliary route could account for only a minor fraction of alveolar protein clearance, although proteins might reach the mucociliary escalator along currents in the alveolar fluid layer. Even so, removal would be very slow: the half-time for mucociliary clearance of particles from the alveolar space is more than 4 weeks. Complete clearance of alveolar protein from pulmonary edema by any route is slow.⁶

Little is known about the mechanisms and signals that regulate endothelial barrier function or how increased endothelial permeability returns to normal¹⁸⁹; on the other hand, the mechanisms for resolution of lung inflammation are beginning to be understood.⁵⁶

Increased Pressure Edema

The outcome of increased pressure pulmonary edema is determined by the underlying cause and the treatment used to correct it. Because the great majority of cases of increased pressure edema are caused by heart disease, outcome is largely determined by the patient's underlying cardiac function. Patients with pulmonary edema uncomplicated by acute myocardial infarction do reasonably well with an annual mortality rate of less than 10%.¹⁹⁰ However, when acute myocardial infarction supervenes, the prognosis

worsens, although coronary vascular reperfusion therapy, using thrombolytics and coronary angioplasty with stent placement, has considerably improved survival. Typically, patients who recover from increased pressure pulmonary edema caused by chronic congestive cardiac failure require long-term outpatient management aimed at preventing recurrent episodes.¹⁹¹

Some patients develop increased pressure pulmonary edema from noncardiac causes. Most cases are iatrogenic, being related to excessive, sometimes inadvertent, volume overload or to the use of drugs such as cocaine that impair cardiac function.¹⁹² Pulmonary edema associated with congenital or acquired heart disease is an uncommon but important problem in pregnancy, but pulmonary edema without heart disease is, perhaps, even more frequent. As discussed in Chapter 96, pregnancy complicated by pulmonary edema is occasionally caused by tocolytic treatment,¹⁹³ fluid overload, or preeclampsia.

Increased Permeability Edema

The outcome of increased permeability pulmonary edema from both ARDS and forms of milder lung injury is determined by its underlying cause and extent of lung injury, the presence of comorbidities, and the particular treatment strategy employed. The reported mortality rates range from 20% to 60% depending on the specific etiologic factor, but yearly ARDS mortality rates reported from a single institution in the period between 1983 and 1993 showed a significant decrease in patients younger than 60 years and in those with sepsis syndrome.¹⁹⁴ Recent trends in ALI mortality from 1996 through 2005 in 2451 mechanically ventilated patients enrolled in the NHLBI ARDS Network showed “clear temporal improvement in survival”; in 1996-1997, mortality was 35% and steadily declined to a low of 26% in 2004-2005.¹⁹⁵ Furthermore, 60-day mortality decreased even further to 22% in adult patients in the most recent ARDS Network clinical trials, despite an increased severity of illness.¹⁹⁶ Using the NHLBI-consensus definition in patients from Iceland, the incidence of ARDS almost doubled from 1988 to 2010, whereas hospital mortality decreased from 50% in 1988-1992 to 33% in 2006-2010; conversely, the 10-year survival of ARDS patients was only 68% compared with 90% in the reference population.¹⁹⁷

Patients with sepsis have significantly higher mortality rates than patients with other clinical disorders associated with the development of increased permeability edema.¹⁹⁸ Mortality, also, is much higher in patients with chronic liver disease¹⁹⁹ or with histories of chronic alcohol abuse than in other predisposing conditions. Besides damaging the liver, chronic ethanol ingestion may reduce alveolar type II cell glutathione content and impair surfactant synthesis and secretion.²⁰⁰ In general, mortality from ARDS increases with increasing age, which conforms to both data and expectations.²⁰¹ Patients with uncommon self-limited causes of injury, including venous air and fat embolism, isolated lung contusion and other trauma, massive blood transfusions, postictal pulmonary edema, and heroin pulmonary edema (Fig. 62-7), and those with milder degrees of edema have a greater chance of survival and edema often clears rapidly.

As pointed out, since at least during the 1980s, survival from increased permeability has steadily improved, but

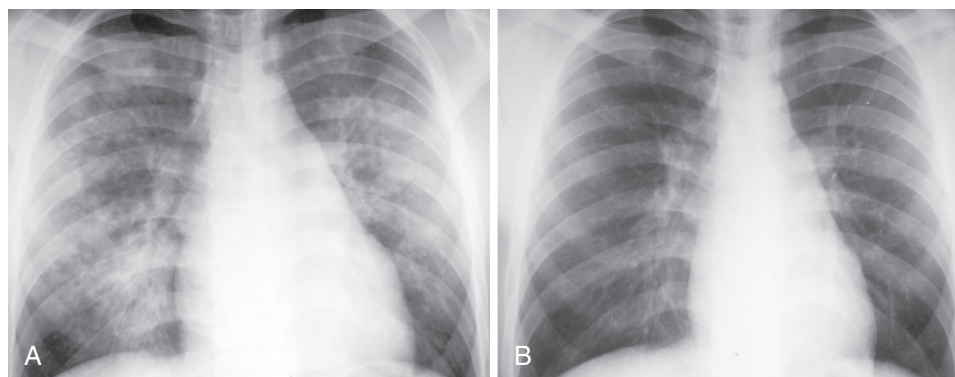


Figure 62-7 Frontal chest radiographs in a 22-year-old patient with heroin-induced increased permeability edema. Frontal chest radiograph performed at the time of presentation (**A**) shows patchy bilateral peribronchial thickening and consolidation, somewhat more prominent and nodular on the right. The vascular pedicle is narrow, and no features suggestive of volume overload are present. Frontal chest radiograph 24 hours later (**B**) shows complete clearing of lung opacity. Increased permeability edema may resolve rapidly if the initiating agent of lung injury is transient and mild and the chronic phase of parenchymal lung injury (type II cell hyperplasia, fibrosis, connective tissue deposition, vascular remodeling) does not develop. (Courtesy Michael Gotway, MD.)

long-term sequelae pose increasing problems. In decades past, based on short-term follow-up studies, survivors of ARDS seemed to do well; many had normal chest radiograph results, minimal or no complaints of dyspnea on exertion, normal lung volumes and airflow measurements, and normal resting and exercise arterial blood gas findings, including shunt fraction. Although the numbers of patients and the duration of follow-up may have left some doubt about the final outcome, an apparent paradox has taken place. Mortality from ARDS has clearly decreased over the past decades, whereas long-term survivors seem to have suffered worsening physical, cognitive, and mental health.

The post-ARDS return of pulmonary function test results to normal or near-normal values may, in fact, have obscured a significant deterioration of health-related quality of life. Disabling symptoms from muscle wasting, weakness, and fatigue were consistent with reduced 6-minute walk distances that changed little during the first 12 months in previously high-functioning, mostly young subjects.⁵⁷ Cognitive and emotional function was significantly impaired in “all” surviving post-ARDS patients at hospital discharge, 78% of whom remained symptomatic after 12 months. Furthermore, psychological sequelae such as anxiety, depression, and posttraumatic stress disorder persisted in 20% to 40% of survivors.⁵⁸ The roles played by treatment of ARDS with corticosteroids and neuromuscular blocking are not clear-cut, but neither agent appears to be a major factor.

Healing involves a fibroproliferative response in a subset of ARDS survivors, which seems to begin early in the course of increased permeability edema,²⁰²⁻²⁰⁴ perhaps as a consequence of ventilator-induced lung injury before the era of lung-protective ventilation²⁰⁵ (Video 62-2). How much of this problem is due to disease and how much to treatment is not known, but a fibroproliferative reaction portends a poor prognosis, either increased mortality or prolonged ventilation dependence. It might also be possible to accelerate reconstitution of alveolar structure in injured lungs; for example, keratinocyte growth factor (fibroblast growth factor-7),²⁰⁶ has been effective in several preclinical models of ALI²⁰⁷ and is now being tested in a phase 2 trial. More information about repair and healing should open new pos-

sibilities for therapy, including a better understanding of how lung progenitor cells may play a role in lung repair and regeneration.^{208,209}

OVERVIEW

Among the significant advances since the late 1960s has been the acquisition of important new knowledge concerning the physiology of fluid, solute, and protein transport in healthy and diseased lungs. Pulmonary edema—the abnormal accumulation of extravascular fluid in the lung—is a pathologic state that arises when fluid is filtered into the lungs faster than it can be removed. The many causes of pulmonary edema have been grouped into two main pathophysiologic categories: (1) increased pressure edema that results from an increase in the hydrostatic or protein osmotic forces (or both) that act across the barriers that normally restrict movement of fluid and solutes in the lungs; (2) increased permeability edema that results from damage to the normal barrier properties of lung endothelium and/or epithelium. Although these two different types of pulmonary edema share many features, they can usually be distinguished clinically and they have different treatment requirements and prognoses; differentiation is made possible by careful clinical, radiologic, and physiologic evaluation, but both increased permeability and increased pressure edema often coexist.

Increased pressure pulmonary edema typically has one of two cardiac origins, either from new-onset acute myocardial infarction or from inadequately treated and/or refractory heart failure, most commonly caused by coronary heart disease, but many other sources are possible. Revascularization techniques for acute and chronic manifestations of coronary heart disease have dramatically improved prognosis and long-term outcome. Acute cardiogenic pulmonary edema is becoming scarce and should become even scarcer. However, more attention is currently being paid to the acute complications of cardiovascular disease than to its chronic therapeutic requirements. Nevertheless, therapy of chronic heart disease has huge clinical payoffs and much more should be done to ensure satisfactory blood pressure control, regulate dyslipidemias, and manage anticoagulants, starting with aspirin.

There have been major advances in the treatment of increased permeability edema, largely due to the successful early application of lung-protective ventilatory strategies in patients with clinical lung injury. A low tidal volume (6 mL/kg ideal body weight) coupled with a plateau pressure limit (<30 cm H₂O) is still the only therapy proven to reduce mortality in patients with well-defined ALI and ARDS. Short-duration infusion of neuromuscular blockade agents show promise in severe ARDS, but further studies are needed for confirmation. New insights into the pathogenesis of various causes of increased permeability pulmonary edema suggest that other therapies may also prove to lower mortality in this common syndrome of severe acute respiratory failure.

Key Points

- The two main categories of pulmonary edema are (1) increased pressure edema from an increase in the hydrostatic or protein osmotic forces (or both) that act across the barriers that normally restrict movement of fluid and solutes in the lungs and (2) increased permeability edema from damage to the normal barrier properties of lung endothelium and/or epithelium.
- An evaluation of the cause of pulmonary edema should include a detailed history, thorough physical examination, and selected laboratory data, including a chest radiograph, electrocardiogram, cardiac enzymes, and, in some patients, microbiologic cultures, an echocardiogram, and, occasionally, pulmonary artery catheterization.
- Increased permeability pulmonary edema may be complicated by the presence of elevated pulmonary intravascular pressures, especially from coexisting cardiac failure or volume overload.
- Treatment for cardiogenic pulmonary edema should include the immediate administration of supplemental oxygen, morphine (usually), and pharmacologic measures to reduce preload.
- The diagnosis of increased permeability pulmonary edema should always include a thorough search for a treatable infection.
- Patients with increased permeability edema and, increasingly, other forms of ventilatory failure, require intubation and lung-protective ventilation, using 6 mL/kg tidal volume and less than 30 cm H₂O plateau pressure.

Complete reference list available at *ExpertConsult*.

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INFILTRATIVE AND INTERSTITIAL LUNG DISEASES

63

IDIOPATHIC INTERSTITIAL PNEUMONIAS

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Familial Pulmonary Fibrosis

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Acute Interstitial Pneumonia

Cryptogenic Organizing Pneumonia

Idiopathic Lymphocytic Interstitial Pneumonia

Idiopathic Pleuroparenchymal Fibroelastosis

INTRODUCTION

The term *interstitial lung disease* (ILD), in general, implies the clinical manifestation of inflammatory-fibrotic infiltration of the alveolar walls (septa) resulting in profound effects on the capillary endothelium and the alveolar epithelial lining cells (Fig. 63-1). Under normal conditions, small numbers of interstitial macrophages, fibroblasts, and myofibroblasts reside within the interstitium. Other components of the interstitium include the matrix proteins of the lung, consisting of collagen-related macromolecules and the noncollagenous proteins such as fibronectin and laminin.

In many of ILDs, interstitial fibrosis follows injury to the gas-exchanging units. This injury increases alveolar permeability, enabling the serum contents to enter the alveolar spaces resulting in airspace abnormalities in addition to the interstitial changes. Fibroblastic proliferation and excessive

collagen deposition, the histologic hallmarks of ILD, either result directly from the initial injury, from the inflammatory cell response that releases proinflammatory and profibrotic cytokines, or from the regenerative and reparative processes taking place at the epithelial and endothelial surfaces. Moreover, fibroblastic proliferation and collagen accumulation also takes place within airway and alveolar lumina and walls of small airways (alveolar ducts, respiratory bronchioles, and terminal bronchioles).

ILDs include many entities that injure the lung parenchyma, producing diseases with similar clinical, radiographic, and physiologic features. Some develop in the setting of other conditions, such as connective tissue disease; others are idiopathic. The primary goal of the clinician is to determine the cause or underlying disease whenever possible and, if not, at least a diagnosis that allows prognostication and a management plan.

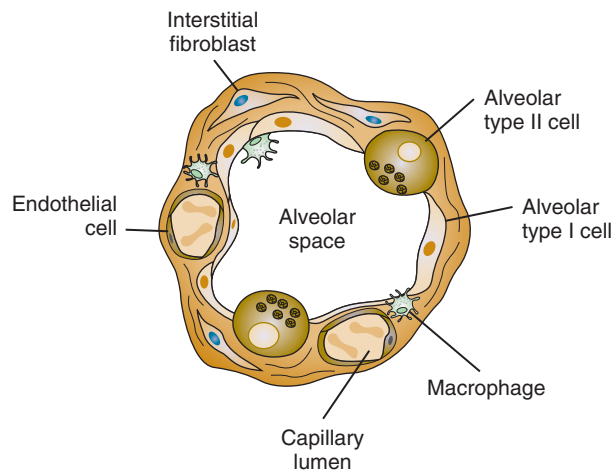


Figure 63-1 Schematic depiction of the lung parenchyma surrounding an alveolar space. The major cells that line and lie within the interstitial space are identified.

CLINICAL AND HISTOLOGIC CLASSIFICATION OF INTERSTITIAL LUNG DISEASE

The exact prevalence and incidence of ILDs are unknown. Studies suggest a prevalence of 81/100,000 for men compared with 67/100,000 for women.^{1,2} Similarly, the overall incidence of ILD is slightly more common in men (32/100,000/yr) than in women (26/100,000/yr) and increases with age. For example, among men and women 75 years of age or older, the prevalence of *idiopathic pulmonary fibrosis* (IPF) was 250/100,000 and the incidence was 160/100,000/yr.¹

ILDs can be classified according to clinical, histopathologic, or radiologic parameters. A clinical classification of ILDs is shown in [Table 63-1](#).³ Although the diagnosis of ILD due to occupational exposure, a medication, or a connective tissue disease may be obvious, primary and idiopathic ILDs can be difficult to diagnose on clinical grounds alone. This chapter presents an approach for the

Table 63-1 Clinical Classification of Interstitial Lung Diseases (ILDs)

IDIOPATHIC FIBROTIC DISORDERS

Acute interstitial pneumonitis (Hamman-Rich syndrome)
Idiopathic pulmonary fibrosis/usual interstitial pneumonia
Familial pulmonary fibrosis
Respiratory bronchiolitis/desquamative interstitial pneumonitis
Cryptogenic organizing pneumonia
Nonspecific interstitial pneumonia
Lymphocytic interstitial pneumonia (Sjögren syndrome, connective tissue disease, AIDS, Hashimoto thyroiditis)
Autoimmune pulmonary fibrosis (inflammatory bowel disease, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia)

CONNECTIVE TISSUE DISEASE-ASSOCIATED ILDs

Scleroderma
Polymyositis-dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Primary Sjögren syndrome
Ankylosing spondylitis
Behçet syndrome

TREATMENT-RELATED OR DRUG-INDUCED ILDs

Antibiotics (nitrofurantoin, sulfasalazine, cephalosporins, minocycline, ethambutol)
Antiarrhythmics (amiodarone, angiotensin-converting enzyme inhibitors, tocainide, β -blocking agents)
Anti-inflammatories (gold, penicillamine, nonsteroidal anti-inflammatory agents, leflunomide, TNF- α inhibitors)
Anticonvulsants (phenytoin, fluoxetine, carbamazepine, antidepressants)
Chemotherapeutic agents (mitomycin C, bleomycin, alkylating agents, busulfan, cyclophosphamide, chlorambucil, melphalan, methotrexate, azathioprine, cytosine arabinoside, BCNU [carmustine], CCNU [lomustine] procarbazine, nilutamide, interferon- α , paclitaxel, interleukin-2)
L-tryptophan
Dopaminergic drugs (bromocriptine)
Radiation
Oxygen toxicity
Paraquat
Bacille Calmette-Guérin
Narcotics

HEREDITARY ILDs

Gaucher disease
Niemann-Pick disease
Hermansky-Pudlak syndrome
Neurofibromatosis

OTHER CAUSES OF ILD

Aspiration
Exogenous lipid pneumonia
Lymphangitic carcinomatosis
Adenocarcinoma with lepidic pattern or mucinous type (formerly called bronchoalveolar carcinoma)
Pulmonary lymphoma

PRIMARY (UNCLASSIFIED) ILDs

Sarcoidosis
Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
Amyloidosis
Pulmonary vasculitis
Lymphangioleiomyomatosis (with or without tuberous sclerosis)
Acute respiratory distress syndrome
AIDS
Bone marrow transplantation
Postinfection
Eosinophilic pneumonia
Alveolar proteinosis
Diffuse alveolar hemorrhage syndromes
Pulmonary veno-occlusive disease
Alveolar microlithiasis
Metastatic calcification

OCCUPATIONAL AND ENVIRONMENTAL ILDs

Inorganic

Silicosis asbestosis
Hard-metal pneumoconiosis
Coal workers' pneumoconiosis
Berylliosis
Talc pneumoconiosis
Siderosis (arc welder)
Stannosis (tin)

Organic (hypersensitivity pneumonitis)

Bird breeder's lung
Farmer's lung

(For complete listing, see Chapter 64)

Table 63-2 Histologic Patterns in Interstitial Lung Diseases and Their Disease Associations

Histologic Patterns	Clinical Associations
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis; connective tissue diseases (uncommon); asbestosis; hypersensitivity pneumonitis; chronic aspiration pneumonia; chronic radiation pneumonitis; Hermansky-Pudlak syndrome; neurofibromatosis
Nonspecific interstitial pneumonia	Idiopathic; connective tissue diseases; drugs; hypersensitivity pneumonitis; resolving diffuse alveolar damage; AIDS; infections
Diffuse alveolar damage	Acute interstitial pneumonia (Hamman-Rich syndrome); acute respiratory distress syndrome; drugs (cytotoxic agents, heroin, cocaine, paraquat, ethchlorvynol, aspirin); toxic gas inhalation; radiation therapy; oxygen toxicity; connective tissue disease; infections (<i>Legionella</i> , <i>Mycoplasma</i> , viral)
Organizing pneumonia	Cryptogenic organizing pneumonia; organizing stage of diffuse alveolar damage; organizing infections (e.g., influenza) as part of diffuse alveolar hemorrhage; drugs (amiodarone, cocaine); infections; connective tissue diseases; hypersensitivity pneumonitis; eosinophilic pneumonia; granulomatosis with polyangiitis (Wegener)
Desquamative interstitial pneumonia/respiratory bronchiolitis	Cigarette smoking; idiopathic; connective tissue diseases; primary pulmonary Langerhans cell histiocytosis; asbestosis; hard-metal pneumoconiosis (cobalt); Gaucher disease; Niemann-Pick disease; Hermansky-Pudlak syndrome; drugs (nitrofurantoin, amiodarone)
Lymphocytic interstitial pneumonia	Idiopathic; hypogammaglobulinemia; autoimmune diseases, including Hashimoto thyroiditis, lupus erythematosus, primary biliary cirrhosis, Sjögren syndrome, myasthenia gravis, chronic active hepatitis; AIDS; allogeneic bone marrow transplantation
Eosinophilic pneumonia	Idiopathic acute and chronic; tropical filarial eosinophilia; parasitic infections; allergic bronchopulmonary aspergillosis; eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome); hypereosinophilic syndrome; AIDS
Alveolar proteinosis	Pulmonary alveolar proteinosis; acute silicosis; aluminum dust; AIDS; myeloproliferative disorder
Diffuse alveolar hemorrhage (with capillaritis)	Granulomatosis with polyangiitis (Wegener); microscopic polyangiitis; systemic lupus erythematosus; polymyositis; scleroderma; rheumatoid arthritis; mixed connective tissue disease; lung transplantation; drugs (retinoic acid, propylthiouracil, dilantin); Behçet disease; cryoglobulinemia; Henoch-Schönlein purpura; pauci-immune glomerulonephritis; immune complex glomerulonephritis
Amyloid deposition	Primary amyloidosis; multiple myeloma; lymphocytic interstitial pneumonia, lymphoma
Granuloma	Sarcoidosis; hypersensitivity pneumonitis; pulmonary Langerhans cell histiocytosis; intravenous talcosis; berylliosis; lymphocytic interstitial pneumonia; infections

evaluation of these patients with emphasis on *idiopathic interstitial pneumonias* (IIPs). An alternative method of histopathologic classification depends on the pattern of injury found on lung biopsy. As seen in Table 63-2, dissimilar clinical entities may result in similar histologic appearances.

The number of ILDs is daunting, but they are linked by many common features: clinical presentation, radiographic appearance, physiologic abnormalities, and, in some instances, histologic findings. Nevertheless, a specific diagnosis can be made in many patients from the results of a careful history and certain laboratory tests. Bronchoscopy with *bronchoalveolar lavage* (BAL) and, often, transbronchial biopsy are useful in the diagnosis of some causes of interstitial infiltration. Thoracoscopic or open-lung biopsy is required for a definitive diagnosis of the remaining cases. Further information about many of the specific members of the interstitial disease family in this section is found in Chapters 65 through 68. Additional discussion of other causes of ILD is found elsewhere in the book: the pneumoconioses in Chapter 73, hypersensitivity pneumonitis in Chapter 64, and drug-induced pulmonary disease in Chapter 71.

CLINICAL, RADIOLOGIC, AND PHYSIOLOGIC FEATURES OF INTERSTITIAL LUNG DISEASES

The hallmarks of an ILD are progressive dyspnea and cough, an abnormal chest radiograph, and impaired pul-

monary function tests.³ However, 5% to 10% of symptomatic patients eventually diagnosed as having ILD have normal chest radiographs at the time of presentation. There are also dyspneic patients with or without abnormal chest radiographs in whom routine pulmonary function tests (flows, volumes, and diffusing capacity) are normal. Some patients with ILD (e.g., sarcoidosis) on chest imaging may have no associated symptoms or pulmonary function abnormalities. Exercise testing, which stresses the cardiopulmonary system and measures gas exchange, may unmask abnormalities in these situations. Furthermore, *high-resolution computed tomography* (HRCT) scans and BAL can detect abnormalities in the presence of normal radiographs and physiologic tests in patients at high risk for development of ILD, such as those with connective tissue disease, asbestos exposure, or hypersensitivity pneumonitis, and those taking drugs known to injure the lung.

PAST HISTORY

ILD developing in a patient with an established connective tissue disease is obvious; however, there are patients in whom the lung disease precedes the more typical manifestations of the associated systemic disease by months to several years.

Occupational and Environmental History

The occupational and environmental history is of obvious importance. It should be thorough and detailed because a long latency period may occasionally exist between exposure and the appearance of clinical impairment and

disability. The exposure may have been of short duration but high intensity. Hypersensitivity pneumonitis, which can manifest either as recurrent acute or subacute pneumonitis or as an insidious form with slowly progressive dyspnea, must be excluded (see Chapter 64). A growing list of occupational and environmental antigens can cause granulomatous pneumonitis.

Drug History

A review of the medications used in the recent and distant past is important. Uncommonly, lung disease may appear weeks to years after the drug has been discontinued (see Chapter 71). Aspiration (often silent) of gastric contents because of *gastroesophageal reflux* (GER) can lead to the insidious development of ILD,⁴⁻⁶ as can the nocturnal use of oily nose drops or use of mineral oil as a laxative.⁷

Smoking History

Determining any history of tobacco use is important. More than 90% of patients with *pulmonary Langerhans cell histiocytosis* (PLCH) of the lung are smokers at the time of diagnosis; this is also true for respiratory bronchiolitis.⁸ Of patients with Goodpasture syndrome who smoked, 100% had diffuse alveolar hemorrhage, whereas only 20% of a nonsmoking group had pulmonary disease in addition to the renal involvement.⁹ Tobacco use also appears to enhance the development of interstitial fibrosis in an asbestos-exposed population. The risk of asbestosis in exposed smokers was 13 times that in a nonsmoking asbestos-exposed cohort. Most patients with IPF have a history of tobacco abuse. Conversely, hypersensitivity pneumonitis infrequently appears in the active smoker. Also, the incidence of sarcoidosis is lower in smokers.

Family History

Familial associations (with an autosomal dominant pattern) have been identified in cases of IPF, sarcoidosis, tuberous sclerosis, and neurofibromatosis; Niemann-Pick disease, Gaucher disease, and Hermansky-Pudlak syndrome are inherited in an autosomal recessive fashion⁶⁻⁸ (see “[Familial Pulmonary Fibrosis](#)” later).

GENDER

There are ILDs with a sex predilection. Lymphangioleiomyomatosis arises almost exclusively in women. In addition, many connective tissue diseases more commonly affect women. Occupational causes are more likely in men. However, transmission of inorganic dust, either from clothes or by living in the vicinity of a manufacturing or mining facility, has resulted in asbestosis and berylliosis in women, children, and men not employed in the industry.

SYMPTOMS

Progressive *dyspnea* is usually the most common symptom, but cough can be prominent, particularly in those patients with lymphangitic carcinomatosis in which the bronchial lymphatic channels are infiltrated.

Cough is a prominent symptom in ILDs, especially those that affect small airways or are bronchiolocentric in location, such as sarcoidosis, respiratory bronchiolitis, organiz-

ing pneumonia, PLCH, and hypersensitivity pneumonitis. In some ILDs such as IPF, cough can be debilitating.

Wheezing, an unusual symptom in ILD, has been reported with lymphangitic carcinomatosis, chronic eosinophilic pneumonia, respiratory bronchiolitis, and hypersensitivity pneumonitis.

Substernal chest pain, an unusual complaint for most ILDs, is frequent in sarcoidosis. *Pleuritic-type chest pain* may accompany connective tissue and drug-related ILDs. The sudden appearance of *chest pain* due to a pneumothorax can be the presenting manifestation or complicate preexisting PLCH, lymphangioleiomyomatosis, tuberous sclerosis, or neurofibromatosis.

Hemoptysis is typical for the diffuse alveolar hemorrhage syndromes, lymphangioleiomyomatosis, pulmonary veno-occlusive disease, and long-standing mitral valve disease. However, alveolar hemorrhage may be present without hemoptysis. Hemoptysis in a patient with an established ILD raises the possibility of a complicating malignancy.

Symptoms in patients with ILD are present for months to years and progress at varying rates. Several interstitial reactions are acute (days to several weeks). These are often confused with atypical pneumonias because they cause diffuse radiographic opacities and may be associated with fever. Included are *acute interstitial pneumonia* (AIP; Hamman-Rich syndrome), acute eosinophilic pneumonia, some cases of hypersensitivity pneumonitis, occasionally drug-related ILDs, some cases of organizing pneumonia, the diffuse alveolar hemorrhage syndromes, and the acute immunologic pneumonias seen with connective tissue diseases.

PHYSICAL FINDINGS

The most typical physical finding is bibasilar inspiratory crackles. Crackles are less likely in the granulomatous diseases. Bilateral inspiratory crackles may also be present in a symptomatic patient with a negative chest radiograph. Clubbing of the digits, which in most cases indicates advanced fibrotic disease, is a common finding in patients with the idiopathic or familial forms of pulmonary fibrosis. However, the appearance of digital clubbing in a patient with an established case of ILD could indicate an underlying bronchogenic carcinoma. With advanced fibrosis causing chronic hypoxemia, clinical signs of pulmonary hypertension and cor pulmonale appear. Attention to potential extrapulmonary physical findings or other manifestations may reveal a specific diagnosis ([Table 63-3](#)).

RADIOLOGIC FEATURES

Although standard chest radiography is not as sensitive for detection of ILD as the HRCT scan, it is the logical starting point and the initial way of identifying and defining disease.

Chest Radiography

Ziskind and coworkers¹⁰ classified diffuse lung diseases according to the pattern on chest radiographs—alveolar filling and primarily interstitial patterns (reticular or nodular). Although *computed tomography* (CT) scanning has supplanted the chest radiograph in the assessment of diffuse parenchymal lung diseases, it is still useful to recognize these radiographic patterns.

Table 63-3 Extrapulmonary Physical Findings and Clinical Manifestations in Interstitial Lung Diseases

Finding	Examples
Systemic hypertension	Connective tissue disease; neurofibromatosis; some diffuse alveolar hemorrhage syndromes
Erythema nodosum	Sarcoidosis; connective tissue disease; Behçet syndrome
Maculopapular rash	Drug-induced; amyloidosis; lipoidosis; connective tissue diseases; Gaucher disease
Heliotrope rash	Dermatomyositis
Albinism	Hermansky-Pudlak syndrome
Discoid lupus	Systemic lupus erythematosus
Neurofibroma	Neurofibromatosis
Telangiectasia	Scleroderma
Raynaud phenomenon	Connective tissue disease
Cutaneous vasculitis	Systemic vasculitides; connective tissue disease
Subcutaneous nodules	Neurofibromatosis; rheumatoid arthritis
Calcinosis	Dermatomyositis; scleroderma; amyloidosis
Uveitis	Sarcoidosis; Behçet syndrome; ankylosing spondylitis
Scleritis	Systemic vasculitis; systemic lupus erythematosus; scleroderma; relapsing polychondritis; sarcoidosis
Keratoconjunctivitis sicca	Lymphocytic interstitial pneumonia (Sjögren syndrome)
Salivary gland enlargement	Sarcoidosis, lymphocytic interstitial pneumonia (Sjögren syndrome)
Peripheral lymphadenopathy	Sarcoidosis; lymphangitic carcinomatosis; lymphocytic interstitial pneumonia; lymphoma
Hepatosplenomegaly	Sarcoidosis; pulmonary Langerhans cell histiocytosis; connective tissue disease; amyloidosis; lymphocytic interstitial pneumonia
Pericarditis	Radiation pneumonitis; connective tissue disease; systemic vasculitis
Myositis	Connective tissue disease; drugs (L-tryptophan)
Bone involvement	Pulmonary Langerhans cell histiocytosis; sarcoidosis; Gaucher disease; lymphangitic carcinomatosis
Arthritis	Connective tissue disease; systemic vasculitis; sarcoidosis
Diabetes insipidus	Pulmonary Langerhans cell histiocytosis; sarcoidosis
Glomerulonephritis	Systemic vasculitis; connective tissue disease; Goodpasture syndrome; sarcoidosis
Nephrotic syndrome	Amyloidosis; drug-induced (gold, penicillamine); systemic lupus erythematosus
Renal mass	Lymphangioleiomyomatosis; tuberous sclerosis

Table 63-4 Interstitial Lung Diseases Producing an Alveolar Filling Pattern on Chest Radiograph

Alveolar proteinosis (proteinaceous fluid)
Adenocarcinoma with lepidic pattern or mucinous type (formerly called bronchoalveolar carcinoma) (malignant cells)
Bronchioloalveolar metastases (malignant cells from pancreas, breast)
Pulmonary lymphoma (malignant lymphocytes)
Lymphocytic interstitial pneumonia (lymphoplasmacytic cells)
Alveolar sarcoid (lymphocyte-macrophage alveolitis or confluent granuloma)
Desquamative interstitial pneumonia (macrophages)
Diffuse alveolar hemorrhage (red blood cells; hemosiderin-filled macrophages)
Eosinophilic pneumonia (eosinophils, macrophages; lymphocytes)
Alveolar microlithiasis (calcium-phosphate microliths)
Organizing pneumonia (Masson bodies)
Exogenous lipid pneumonia (lipid-filled macrophages)
Acute hypersensitivity pneumonia (lymphoplasmacytic cells)

Alveolar Filling Pattern. Alveolar filling (Table 63-4) is recognized by a homogeneous opacity that can be diffuse or patchy and is characterized by confluent nodules with ill-defined outer borders, air bronchograms, and obliteration or silhouetting of normal structures such as the diaphragm,

heart, and intrapulmonary blood vessels (Fig. 63-2). Another feature occasionally seen with alveolar filling is the air alveologram, which represents small areas of uninflated lung in an area of incomplete consolidation, manifesting on the chest radiograph (Fig. 63-3) as small lucent areas within areas of increased lung opacity due to consolidation. So-called “acinar rosettes,” also referred to as “acinar nodules” or “air space nodules,” may be seen when alveolar filling is present and represent centrilobular or peribronchial nodules, rather than actual opacification of individual acini. Several have associated hilar adenopathy (e.g., sarcoidosis, pulmonary lymphoma). In patients with alveolar proteinosis, sparing of the lung parenchyma immediately adjacent to the diaphragm is seen. In chronic eosinophilic pneumonia, the pattern has been referred to as the radiographic negative of pulmonary edema because the alveolar opacities are most prominent in the periphery. A similar alveolar pattern has also been reported in some patients with organizing pneumonia (Fig. 63-4).

Interstitial Pattern. Radiographic interstitial opacities become apparent when the interstitial compartment becomes infiltrated and widened by inflammatory cells, excessive collagen, granulomatous inflammation, or smooth muscle proliferation. In other instances, malignant cells or amyloid deposits expand this compartment. These opacities appear as nodules, linear reticular opacities, or a

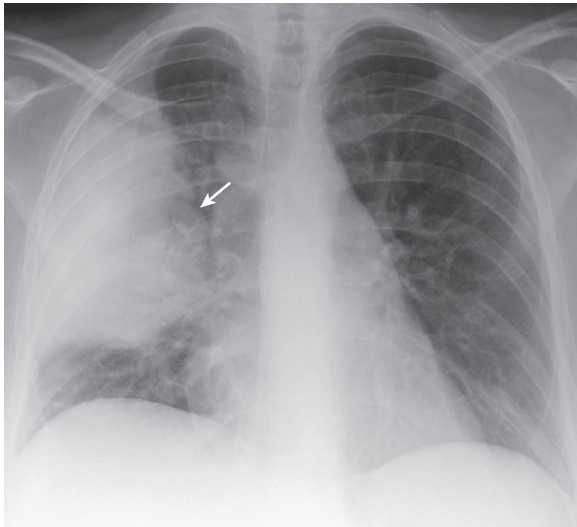


Figure 63-2 Frontal chest radiograph illustrating an alveolar filling pattern, or air-space consolidation. This homogeneous opacity obscures vascular margins, tends to extend to the pleural surfaces and is often associated with air bronchograms (*arrow*). This patient had pneumococcal pneumonia, but an alveolar filling radiographic pattern can be seen in patients with several interstitial lung diseases (see [Table 63-4](#)). (Courtesy Michael Gotway, MD.)

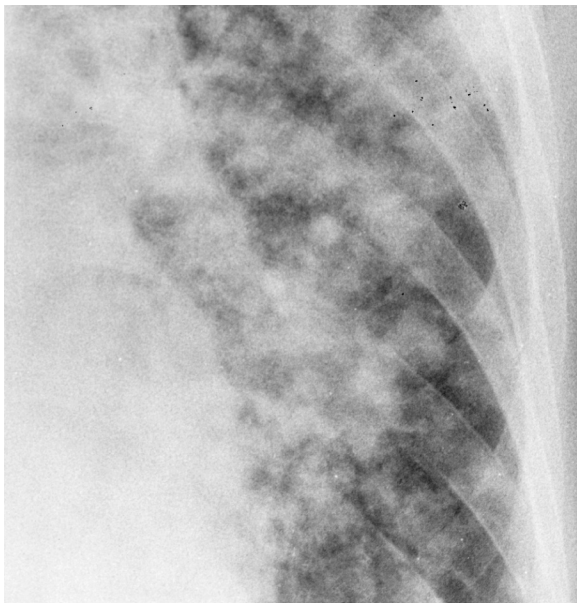


Figure 63-3 Detailed view of chest radiograph showing alveolar opacities with ill-defined nodules and distal air alveolograms. This patient had adenocarcinoma (formerly called bronchoalveolar) carcinoma, but this pattern can be seen in several interstitial lung diseases (see [Table 63-4](#)).

combination of linear shadows and nodules (“reticulonodular” opacities).

Nodular Pattern. Nodules of varying size characterize granulomatous lung diseases. Miliary nodules accompany infectious granulomas and noninfectious granulomas (e.g., sarcoidosis, PLCH, and hypersensitivity pneumonitis) and some malignant diseases (e.g., melanoma, hypernephroma, and lymphoma) ([Fig. 63-5](#)). However, linear opacities possibly representing an underlying cellular interstitial infiltrate are also visible.

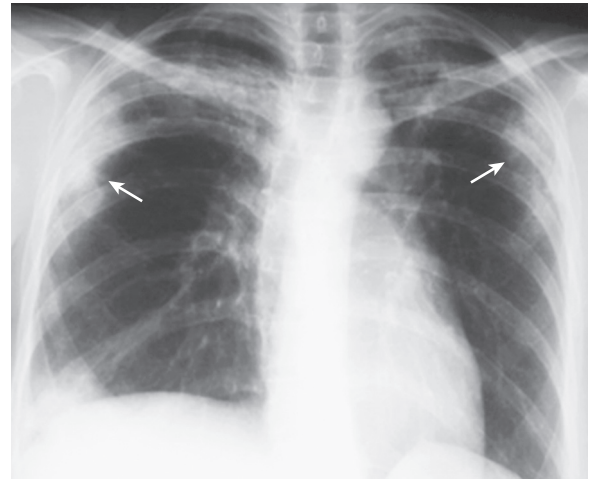


Figure 63-4 Frontal chest radiograph showing subpleural, upper lobe consolidation in a patient with chronic eosinophilic pneumonia (arrows). A similar pattern may be seen in organizing pneumonia. (Courtesy Michael Gotway, MD.)

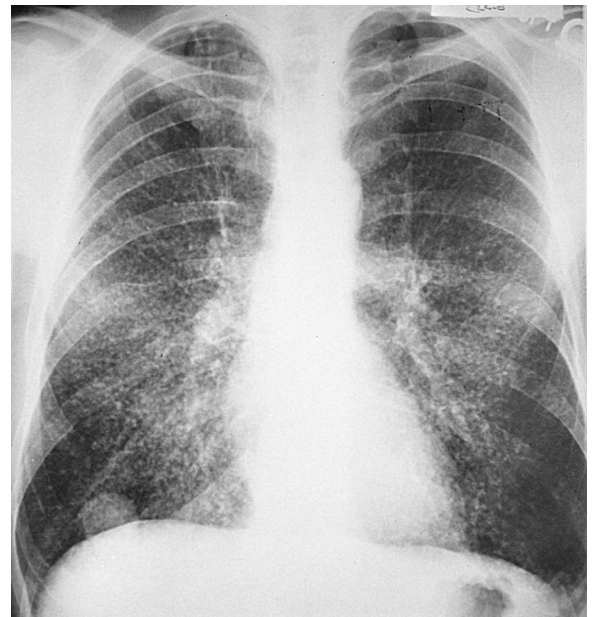


Figure 63-5 Frontal chest radiograph showing circumscribed small interstitial-appearing “miliary” nodules. A nodule is also present in the right lower lobe. This patient had metastatic malignant melanoma, but this pattern can also be seen in sarcoidosis, pulmonary Langerhans cell histiocytosis, and hypersensitivity pneumonitis.

Linear or Reticular. Linear or reticular interstitial changes are seen in most ILDs ([Fig. 63-6](#)). It is typical for many ILDs (e.g., IPF, the connective tissue diseases, asbestosis, cytotoxic drug-induced disorders) to have the greatest concentration of the reticular opacities in the lower lung zones. The term *radiographic honeycomb lung* refers to a reticular and cystic pattern that correlates with the histologic “honeycombing.” These small cystic structures, which are best seen in the lower and peripheral lung zones, indicate an underlying advanced fibrotic change ([Fig. 63-7](#)).

A criticism of the alveolar-interstitial classification is that a mixed pattern is often found. For example, interstitial fibrosis may eventually be superimposed on a disease

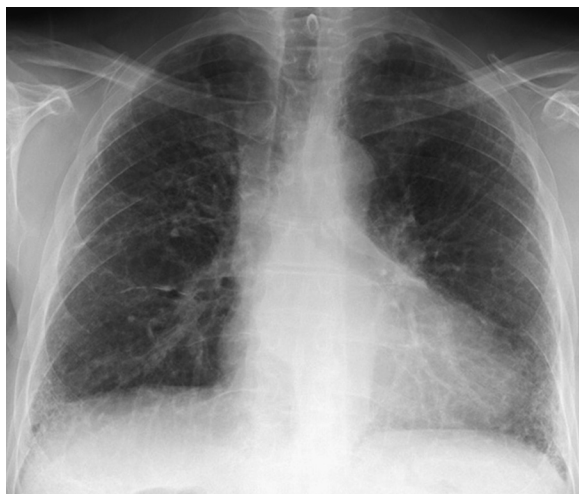


Figure 63-6 Frontal chest radiograph in a patient with idiopathic pulmonary fibrosis. Peripheral basal predominant reticulation is seen consistent with fibrotic lung disease. Note diminished lung volumes. (Courtesy Michael Gotway, MD.)

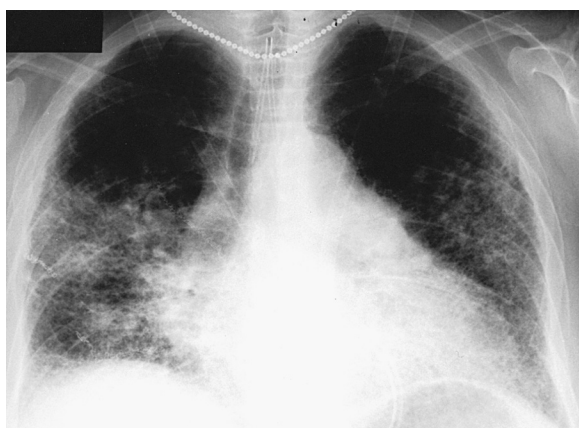


Figure 63-7 Frontal chest radiograph showing characteristic features of honeycomb lung. A network of 2- to 3-mm cystic spaces is distributed throughout the lung fields. This patient with end-stage idiopathic pulmonary fibrosis also had pulmonary hypertension and was receiving oxygen through a transtracheal catheter.

that was primarily alveolar, such as alveolar proteinosis, diffuse alveolar hemorrhage, eosinophilic pneumonia, or organizing pneumonia. Sarcoidosis, a disease characterized by interstitial granuloma, can be alveolar in appearance due to either coalescence of granulomas with compression of adjacent lung or a lymphocyte-macrophage alveolitis. Dense fibrosis from any fibrotic lung disease can compress adjacent lung, producing homogeneous shadows. The appearance of alveolar opacities during the course of an ILD may represent renewed activity of the primary disease, superimposed infection, or development of adenocarcinoma.^{11,12}

Other Radiographic Features. Several distinctive patterns may accompany the interstitial changes and may point to a diagnosis (Table 63-5). There are a group of interstitial diseases, often granulomatous, in which the radiographic changes are more prominent in the upper lung zones (Fig. 63-8). Some interstitial diseases are bronchiolocentric, resulting in either maintenance or expansion of the lung volume. If an ILD is superimposed on emphysema, the lung volumes are often preserved. The majority of ILDs result in a gradual reduction of the lung volumes. In fact, lower lobe volume loss and traction bronchiectasis are typical for the advanced stages of these diseases.^{11,13} Short horizontal lines at the lung periphery (Kerley B lines), representing thickened interlobular septa, are seen after obstruction of the pulmonary lymphatics (Fig. 63-9). Pneumothorax is often the presenting manifestation of PLCH or lymphangioleiomyomatosis. Diaphragmatic pleural calcification in a patient with interstitial opacities is indicative of asbestos exposure. Pleural thickening and pleural effusion may complicate the course of the connective tissue-associated ILDs. Chronic hypoxemia results in radiographic evidence of pulmonary hypertension.

Computed Tomography

Conventional chest radiographic assessment for ILD may miss up to 10% of cases.¹⁴ Conventional CT, obtained using 8- to 10-mm slices, offers little more for the detection of

Table 63-5 Radiologic Features of Interstitial Lung Diseases

Feature	Diseases
Upper zone—predominant disease	Radiation pneumonitis; neurofibromatosis; chronic sarcoidosis; pulmonary Langerhans cell histiocytosis; silicosis; coal workers' pneumoconiosis; chronic hypersensitivity pneumonitis; chronic eosinophilic pneumonia; ankylosing spondylitis; nodular rheumatoid arthritis; berylliosis; drug-induced (amiodarone, gold, bischloroethyl carmustine nitrosourea [carmustine]); radiation
Increased lung volumes	Lymphangioleiomyomatosis (with or without tuberous sclerosis); chronic sarcoidosis; pulmonary Langerhans cell histiocytosis; neurofibromatosis
Radiologic honeycomb lung	Idiopathic pulmonary fibrosis; connective tissue disease; asbestosis; drug-induced; lymphocytic interstitial pneumonia; chronic aspiration pneumonia; hemosiderosis; Hermansky-Pudlak syndrome
Pneumothorax	Pulmonary Langerhans cell histiocytosis; lymphangioleiomyomatosis (with or without tuberous sclerosis); neurofibromatosis
Kerley B lines	Lymphangitic carcinomatosis; lymphangioleiomyomatosis; left atrial hypertension (mitral valve disease, veno-occlusive disease); lymphoma; amyloidosis
Lymphadenopathy	Sarcoidosis; lymphoma; lymphangitic carcinomatosis; lymphoid interstitial pneumonia; berylliosis; amyloidosis; Gaucher disease
Pleural disease	Lymphangitic carcinomatosis; connective tissue disease; asbestosis (pleural calcification); lymphangioleiomyomatosis (chylous effusion); drug-induced (nitrofurantoin, radiation); sarcoidosis
Eggshell calcification of lymph nodes	Silicosis; sarcoidosis; radiation

radiographic-negative ILD. HRCT, obtained with a section thickness of less than 2 mm, enables better visualization of fine parenchymal detail and therefore the detection of early air space filling or interstitial change (Fig. 63-10). In cases of suspected ILD with negative conventional radiography, it is important to perform HRCT in the prone and supine positions. Dependent lung density can mask interstitial change, and vascular engorgement of the dependent portion of lung mimics septal thickening on supine imaging. Abnormalities that persist on prone imaging are indicative of disease.

In patients with abnormal chest radiographs, the diagnostic accuracy increases with HRCT evaluation. In cases of IPF, peripheral reticular opacities, lower zone subpleural honeycombing, and traction bronchiectasis are seen (Fig. 63-11).^{15,16} In the connective tissue diseases, asbestosis,

and some drug-induced ILD, the results on HRCT, as on chest radiography, are indistinguishable from those of IPF or *nonspecific interstitial pneumonia* (NSIP). In scleroderma, a disease in which the prevalence rate of ILD approaches 100% in autopsy series, HRCT detects disease in 45% to 75% of patients when conventional radiography is negative.^{17,18}

In sarcoidosis, in addition to the hilar and mediastinal adenopathy, nodules deposited along bronchovascular bundles and interlobular septa, air space filling due to the lymphocyte-macrophage alveolitis, and linear densities secondary to fibrotic scarring can be seen (Fig. 63-12). In patients with hypersensitivity pneumonitis, air space-filling centrilobular nodules and linear opacities without adenopathy are present. The HRCT can be normal in symptomatic patients with biopsy-proved hypersensitivity pneumonitis.¹⁹ In patients with PLCH, the combination of centrilobular nodules and cysts, most prominent in the upper lobes and occasionally accompanied by a pneumothorax, is



Figure 63-8 Uncomplicated silicosis. Frontal chest radiograph shows upper and mid lung predominant small nodules. Note that some of these nodules are calcified. (Courtesy Michael Gotway, MD.)

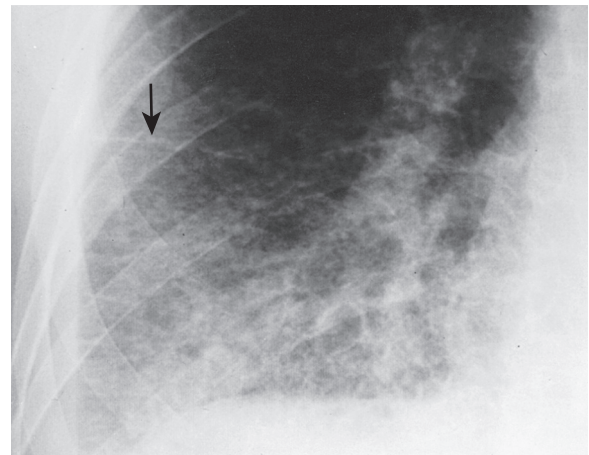


Figure 63-9 Lymphangitic carcinomatosis. Detailed view of right lung shows Kerley B lines (arrow) and pleural effusion.

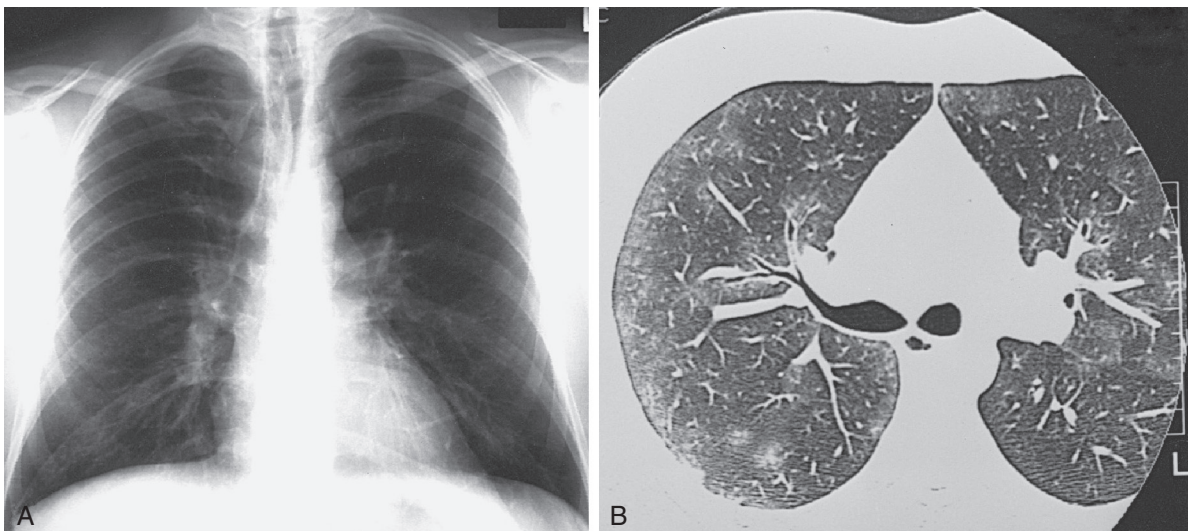


Figure 63-10 Hypersensitivity pneumonitis. **A**, Normal chest radiograph from a 45-year-old man with established hypersensitivity pneumonitis. At the time, his arterial oxygen pressure while breathing room air was 48 mm Hg. **B**, High-resolution chest CT image of the same patient demonstrates patchy ground-glass areas of air space-filling opacities.



Figure 63-11 Advanced idiopathic pulmonary fibrosis. High-resolution CT image shows extensive honeycomb changes.

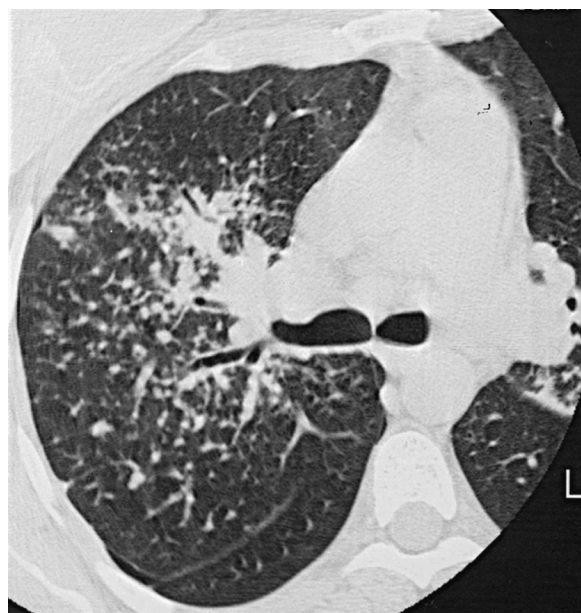


Figure 63-12 Sarcoidosis. High-resolution CT image shows hilar lymphadenopathy and nodular disease.

characteristic (Fig. 63-13). In earlier PLCH, coalescence of the nodules produces an air space–filling pattern.

In lymphangioleiomyomatosis, the HRCT is typical, revealing rounded, thin-walled cysts throughout (Fig. 63-14). A pneumothorax or pleural effusion (chylous) may accompany this change. Identical findings are present in lymphangioleiomyomatosis associated with tuberous sclerosis. Lymphangitic carcinomatosis produces a beaded-chain appearance of the interlobular septa that correlates with Kerley B lines seen with conventional radiography. In asbestos-related disease, noncalcified pleural plaques and early ILD are often difficult to detect, and the HRCT is more sensitive than conventional chest radiography.

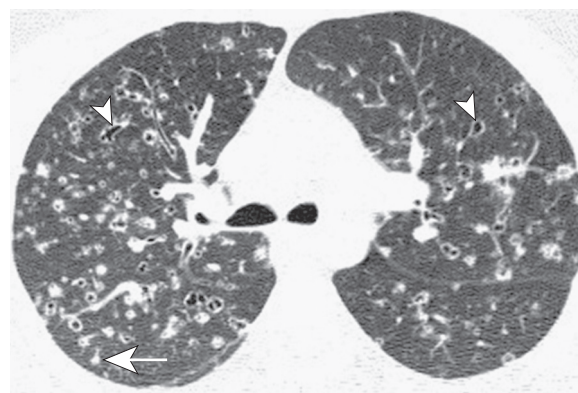


Figure 63-13 Pulmonary Langerhans cell histiocytosis. High-resolution CT image shows centrilobular nodules (arrow) and cyst formation (arrowheads). (Courtesy Michael Gotway, MD.)

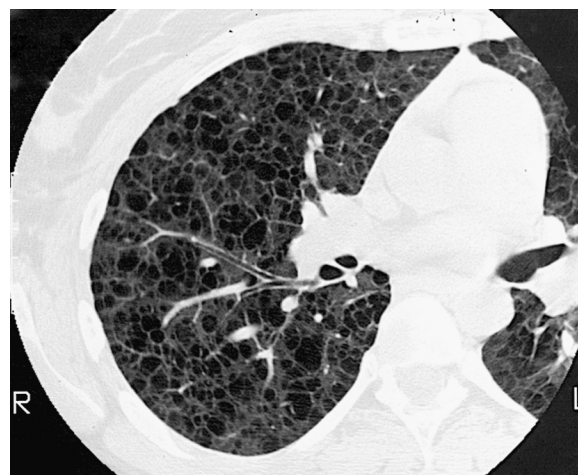


Figure 63-14 Lymphangioleiomyomatosis. High-resolution CT image shows characteristic thin-walled cysts throughout the parenchyma.

FUNCTIONAL ASSESSMENT

In ILD, there are characteristic alterations of the lungs' mechanical properties and impairment of gas exchange at the alveolar–capillary interface. Assessment of ventilatory function and the mechanical properties of the lungs, as well as gas exchange, particularly during exercise, are vital components of the initial evaluation of patients with suspected ILD. In addition, serial measurements of function enable the physician to determine progression of the disease and the effects of therapeutic intervention.

Ventilatory Function

Ventilatory function tests provide an indirect index of alterations to the impedance to respiration offered by the elastic resistance to distention of the lungs and the frictional resistance to airflow in the tracheobronchial tree. Clinically, alterations of the mechanical properties of the respiratory system are also reflected in the pattern of breathing that is adopted by the patient. These patients tend to breathe rapidly and shallowly because a larger tidal volume would require an inordinate increase in work of breathing to overcome the greatly increased elastic resistance.

Elastic Resistance

ILD is associated with an increase in elastic resistance (or decreased compliance), and this can be seen in a plot of the static transpulmonary pressure (i.e., at points of no flow) at differing decrements of lung volume from *total lung capacity* (TLC) to residual volume. In most patients with ILD, the plot of the volume-pressure relationship of the lungs is characteristically shifted downward and to the right, with a reduced slope (i.e., compliance is low) and a markedly increased coefficient of elastic recoil (maximum elastic recoil pressure, TLC). Conversely, as is demonstrated in Figure 63-15, there is significant variation in the position of the volume-pressure curve in patients with IPF and sarcoidosis,²⁰ and the correlation between alterations of the elastic properties (and lung volume compartments) and the degree of fibrosis present is poor. This is, at least in part, a consequence of the impact of smoking, which appears to

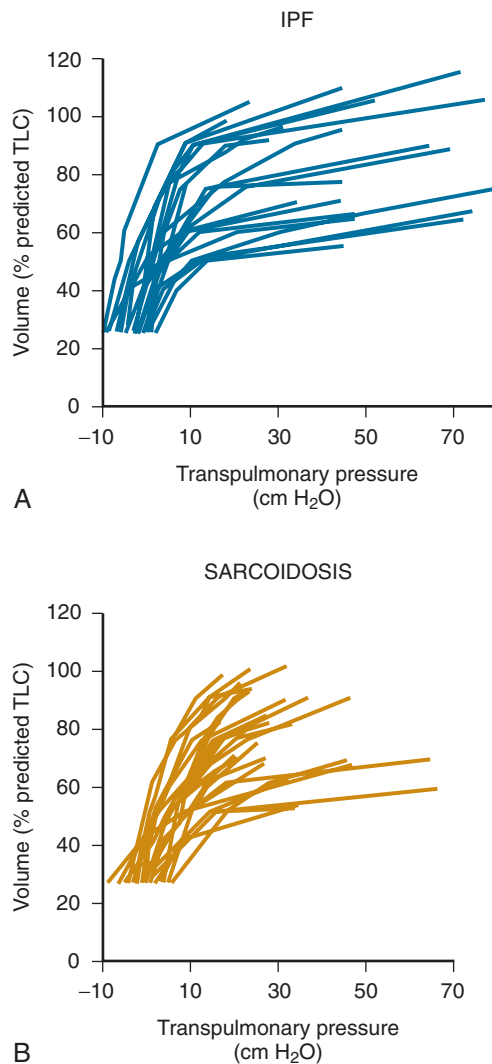


Figure 63-15 Multiple recordings show volume-pressure characteristics in patients with idiopathic pulmonary fibrosis (IPF) (A) and sarcoidosis (B). Note the marked variation of position and shape in both disorders. TLC, total lung capacity. (Redrawn from Hanley ME, King TE Jr, Schwarz MI, et al: The impact of smoking on mechanical properties of the lungs in idiopathic pulmonary fibrosis and sarcoidosis. *Am Rev Respir Dis* 144:1102, 1991.)

differ in the two disorders. In patients with IPF who smoke, the volume-pressure curve is shifted upward and to the left, whereas in patients with sarcoidosis who smoke, it is shifted downward and to the right.²⁰

Measurements of lung volume reflect changes in position of the volume-pressure curve of the lungs. This is because alterations of the elastic recoil of the lung or chest wall disturb the balance between the elastic forces of the lungs, which act in an expiratory direction, and those of the chest wall, which act in an inspiratory direction. In patients with ILD, the TLC, functional residual capacity, and residual volume are generally reduced (Fig. 63-16). A lower than expected TLC (and vital capacity) in association with a normal functional residual capacity and a greater than expected residual volume generally reflects a mixed restrictive and obstructive disorder. However, because maximum effort is necessary to determine the inspiratory capacity and the expiratory reserve volume, a less than maximal inspiration or expiration, either because of weak respiratory muscles or because of poor effort, leads to the same findings. Similar considerations apply to the vital capacity, which is often used as an index of alterations of elastic resistance. In addition, as can be seen in Figure 63-16, a low vital capacity is not specific for restrictive disorders because it is also lower than expected in patients with airflow limitation (because of an increased residual volume).

Flow Resistance

Measurement of lung volume is important when evaluating airflow resistance. This can be assessed directly from the relationship between the rate of airflow and the resistive component of the transpulmonary pressure.

In clinical practice, various indirect measures of flow resistance can be used: the *forced expiratory volume in 1 second* (FEV₁); the mean expiratory flow rate between 25% and 75% of the forced vital capacity (FEF_{25%-75%}); the maximal expiratory flow rate (\dot{V}_{max}) at a particular proportion (such as 75%, 50%, or 25%) of the *forced vital capacity* (FVC) (from a flow-volume curve); the FEV₁/FVC ratio;

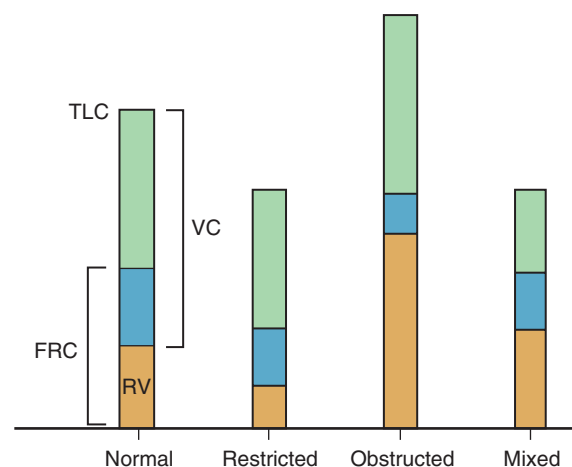


Figure 63-16 Bar graphs show total lung capacity (TLC) and its subdivisions in healthy persons (normal) compared with the typical abnormalities found in patients with restrictive disorders, obstructive disorders, and mixed disorders. FRC, functional residual capacity; RV, residual volume; VC, vital capacity. (Redrawn from Cherniack RM: Pulmonary function testing. Philadelphia, 1992, WB Saunders, p 212.)

or the FEV₁-to-vital capacity ratio. Low flow rates or a low FEV₁/FVC ratio (i.e., <70% of predicted) is believed to indicate expiratory airflow limitation. However, like airway resistance, \dot{V}_{\max} values depend on the diameter of the airways, which is influenced by the lung volume. The FEV₁/FVC ratio will be overestimated, and the degree of flow limitation underestimated, in the patient who does not exhale fully because of severe dyspnea or muscular weakness, pain, or poor effort.

Airflow resistance is not generally thought to be increased in ILD. As is seen in Figure 63-17, \dot{V}_{\max} is low in ILD, not because of an increase in flow resistance but rather because of the low lung volumes at which the flow is being measured. In fact, in uncomplicated ILD, \dot{V}_{\max} values are greater than expected at any particular lung volume because the lung elastic recoil pressure, which is the driving pressure for flow in the peripheral airways, is increased.¹⁹ As a corollary, a \dot{V}_{\max} lower than expected at a particular lung volume in a patient who is suffering from a restrictive

disorder indicates an increase of flow resistance in the more peripheral airways. An increase in peripheral airway resistance has been reported in patients with IPF, hypersensitivity pneumonitis, and asbestos exposure.

Gas Exchange

Alterations of gas exchange are readily assessed by analysis of the arterial oxygen pressure (PO₂) and carbon dioxide pressure (PCO₂) and calculation of the alveolar-arterial PO₂ difference ((A-a)PO₂), both at rest and during exercise.

In patients with ILD, arterial blood analysis while at rest usually reveals hypoxemia and an increased (A-a)PO₂, along with hypocapnia. In addition, the diffusing capacity for carbon monoxide (DL_{CO}) is reduced, primarily because of a reduction in the alveolar-capillary surface available for gas exchange. The disturbance of gas exchange generally accompanies abnormalities in ventilatory function,²¹ but gas exchange may be normal at rest in a significant number of patients. Similarly, the resting DL_{CO} may be only slightly reduced in patients who demonstrate a mild restrictive disorder or normal gas exchange while at rest, or both.

The DL_{CO} is generally greater than expected in those cases associated with recent pulmonary hemorrhage because the red blood cells in the pulmonary alveoli take up carbon monoxide readily. Sequential measurements of the DL_{CO} within minutes may aid in the establishment of the diagnosis of alveolar hemorrhage.²² When there is fresh blood in the alveolar spaces, each successive DL_{CO} value will be lower as the hemoglobin in the alveoli becomes saturated with carbon monoxide.

Exercise

In most patients, gas exchange is disturbed during exertion, even in those with normal gas exchange at rest. Assessment of gas exchange during exercise provides the best correlation with the severity of disease²³ and is probably the most important physiologic determination in patients with ILD (see Chapter 26).

In general, patients with the most severe restrictive disease have the poorest exercise tolerance. As is shown in Figure 63-18, ventilation generally rises excessively during exercise and may approach the ventilatory ceiling. Characteristically, the respiratory frequency rises inordinately with increasing exercise loads because of the increased work that would be required to overcome the elastic resistance of the lungs if the tidal volume were to increase.

The excessive ventilation is frequently preferentially distributed to areas of lung that have normal compliance but diminished perfusion (i.e., high ventilation-perfusion ratio); as a result, unlike the normal response, the calculated dead space (V_D) and the ratio of dead space to tidal volume (V_D/V_T) rise in association with rapid, shallow breathing. The increase in cardiac output with exercise and the rapid transit of blood through the pulmonary capillaries along with its redistribution in the lungs lead to a greater maldistribution of ventilation-perfusion ratios. This results in a rise in (A-a)PO₂ and a fall in arterial PO₂ (Fig. 63-19). Except for heavy exercise, when the transit through the circulation is exceptionally rapid, it is unlikely that a reduced ability of oxygen to diffuse across a thickened alveolar-capillary membrane plays a significant role in the hypoxemia.

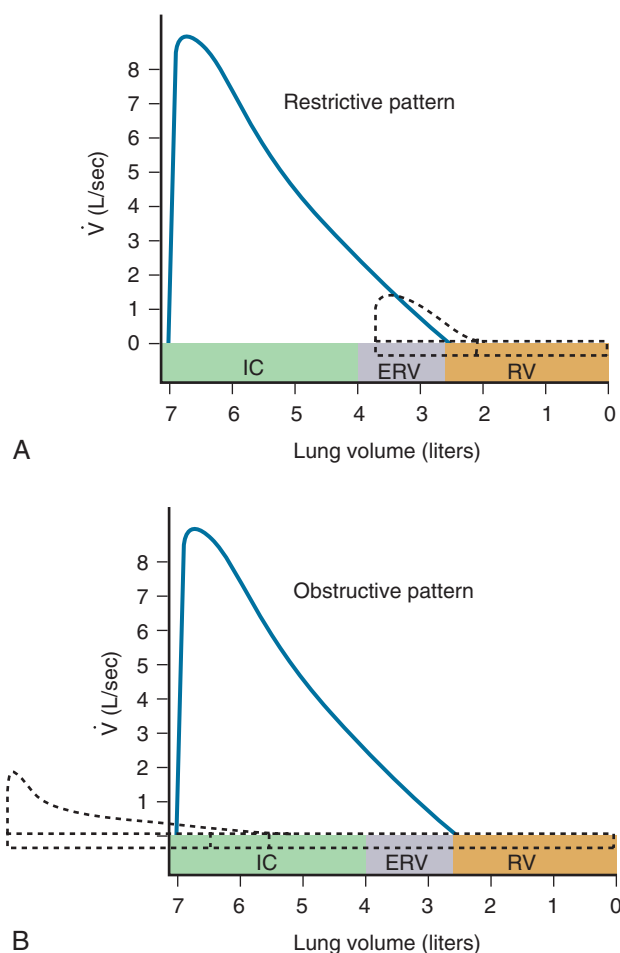
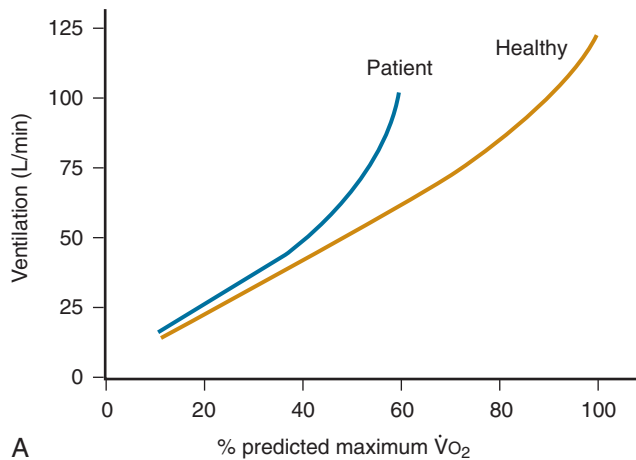
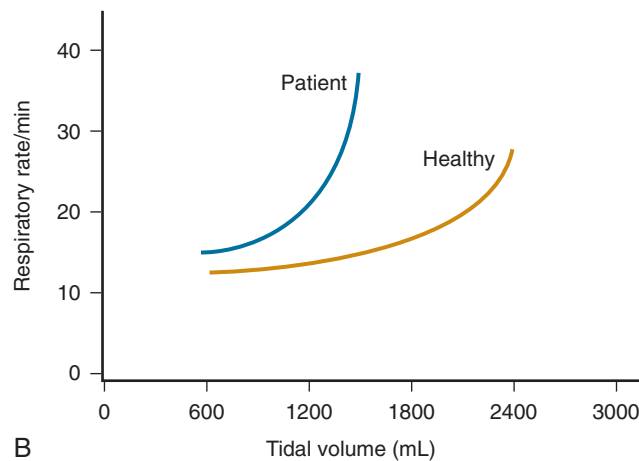


Figure 63-17 Schematic flow-volume curves in a healthy person (solid line) are compared with those in patients (dotted lines) with a restrictive disorder (A) and with an obstructive disorder (B). Lung volume is reduced in the restrictive disorder, and maximum expiratory flow rates are low because they are achieved at low lung volumes. Flow rates are higher than expected at low lung volumes because the driving pressure (lung elastic recoil) is increased. ERV, expiratory residual volume; IC, inspiratory capacity; RV, residual volume; \dot{V} , flow. (Redrawn from Cherniack RM: Pulmonary function testing. Philadelphia, 1992, WB Saunders, p 218.)



A



B

Figure 63-18 Schematic curves show the ventilatory response (**A**) and respiratory rate (**B**) during increasing exercise workloads expressed as a percentage of the predicted maximum oxygen uptake ($\dot{V}O_2$) in a healthy person and in a patient with idiopathic pulmonary fibrosis. (Redrawn from Cherniack RM: Pulmonary function testing. Philadelphia, 1992, WB Saunders, p 248.)

LABORATORY FINDINGS

Table 63-6 summarizes the results of laboratory tests that suggest or support the diagnosis of a specific ILD.

BRONCHOALVEOLAR LAVAGE

BAL is a technique employed to sample the distal airways via the instillation of sterile saline through a wedged fiberoptic bronchoscope. After aspiration, the contents, which are thought to represent the cellular, immunologic, and biochemical milieu of the alveolar structures, can be analyzed. The results of BAL for the evaluation of ILD have been difficult to interpret because of the lack of standardized techniques for both the performance of the procedure and the subsequent analysis of the data.²⁴⁻²⁶ Furthermore, in some of the earlier studies, correlative data between BAL and lung biopsies were not obtained. Often, the treatment or smoking status of the patient was not considered. A multicenter publication has set forth the methods of performing

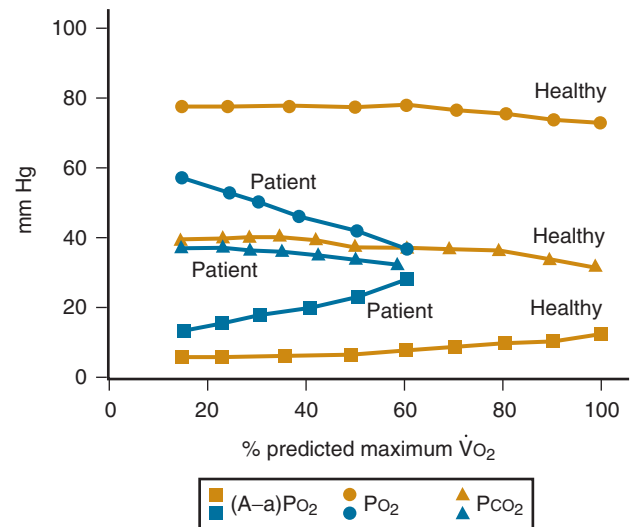


Figure 63-19 The changes in arterial PO_2 (circles), alveolar-arterial PO_2 difference ($(A-a)PO_2$, squares), and arterial carbon dioxide pressure (PCO_2 , triangles) during increasing exercise workloads expressed as the percentage of predicted maximum oxygen uptake ($\dot{V}O_2$) in a healthy person and a patient with idiopathic pulmonary fibrosis. Testing was performed at an altitude of 5280 feet. (Redrawn from Cherniack RM: Pulmonary function testing. Philadelphia, 1992, WB Saunders, p 249.)

and analyzing the results of BAL.²⁷ This study involved a large cohort of normal subjects of varying age and race who were compared with patients with documented ILD. Smoking affects the BAL results of both normal subjects and patients by amplifying the macrophage and eosinophil populations.²⁷

BAL is a useful investigative tool in many ILDs. Cytologic analysis of BAL specimens can be diagnostic for lymphangitic carcinomatosis, adenocarcinoma, and pulmonary lymphoma. If the eosinophil level exceeds 40% (normal, <2%), eosinophilic pneumonia is usually the cause of the diffuse pulmonary infiltration. BAL eosinophilia of a lesser degree may be found with some connective tissue diseases, IPF, or organizing pneumonia.

The finding of periodic acid-Schiff-positive lipoproteinaceous bodies in the BAL was originally thought to be diagnostic for pulmonary alveolar proteinosis but has proved to be nonspecific. In cases of diffuse alveolar hemorrhage, red blood cells and hemosiderin-laden macrophages dominate the lavage specimen. Sequential BAL samples show an increase in red cells and in its bloody appearance (see Fig. 67-3).

BAL lymphocytosis (>35% lymphocytes) predominates in some diseases. Sarcoidosis and hypersensitivity pneumonitis are most common. Others include *lymphocytic interstitial pneumonia* (LIP), pulmonary lymphoma, berylliosis, and some drug-induced ILDs. Smaller but increased percentages of lymphocytes (normal range, 10%–15%) can be seen with these entities in addition to a number of other ILDs, including IPF, organizing pneumonia, connective tissue diseases, and some pneumoconioses.²⁸ In patients with suspected asbestos-related disease, one or more asbestos bodies per high-powered field in the BAL specimen indicate significant exposure, although this does not establish the diagnosis of asbestosis. Because of the vertical gradient of asbestos bodies recovered in the lungs of patients with asbestosis, if

Table 63-6 Laboratory Findings in Interstitial Lung Diseases

Finding	Diseases
Leukopenia	Sarcoidosis; connective tissue disease; lymphoma; drug-induced
Leukocytosis	Systemic vasculitis; hypersensitivity pneumonitis; lymphoma
Eosinophilia	Eosinophilic pneumonias; sarcoidosis; systemic vasculitis; drug-induced (sulfa, nitrofurantoin, methotrexate)
Thrombocytopenia	Sarcoidosis; connective tissue disease; drug-induced; Gaucher disease; idiopathic pulmonary fibrosis
Hemolytic anemia	Connective tissue disease; sarcoidosis; lymphoma; drug-induced; idiopathic pulmonary fibrosis
Normocytic anemia	Diffuse alveolar hemorrhage syndromes; connective tissue disease; lymphangitic carcinomatosis
Urinary sediment abnormalities	Connective tissue disease; systemic vasculitis; drug-induced
Hypogammaglobulinemia	Lymphocytic interstitial pneumonia; granulomatous lymphocytic interstitial lung disease
Hypergammaglobulinemia	Connective tissue disease; sarcoidosis; systemic vasculitis; idiopathic pulmonary fibrosis; asbestosis; silicosis; lymphocytic interstitial pneumonia; lymphoma
Serum autoantibodies	Connective tissue disease; systemic vasculitis; sarcoidosis; idiopathic pulmonary fibrosis; silicosis; asbestosis; lymphocytic interstitial pneumonia
Serum immune complexes	Idiopathic pulmonary fibrosis; lymphocytic interstitial pneumonia; systemic vasculitis; connective tissue disease; pulmonary Langerhans cell histiocytosis
Serum angiotensin-converting enzyme	Sarcoidosis; hypersensitivity pneumonitis; silicosis; acute respiratory distress syndrome; Gaucher disease
Antibasement membrane antibody	Goodpasture syndrome
Antineutrophil cytoplasmic antibody	Systemic vasculitis

lavage is used to document previous asbestos exposure, samples should be obtained from a basal segment of one of the lower lobes. A diagnosis of berylliosis is confirmed when lavaged lymphocytes undergo proliferation after exposure to beryllium *in vitro*.

In the BAL recovered from patients with PLCH, all inflammatory cells are increased even though their percentages remain unchanged. Electron microscopy demonstrates increased numbers of Langerhans cells. This monocyte, which is thought to be central in the pathogenesis, has a typical pentilaminar body (Birbeck granule) in the cytoplasm, as revealed by electron microscopy. Langerin and CD1a are specific diagnostic markers for Langerhans cells.²⁹ Langerhans cells have been described in other fibrotic lung diseases, but not in numbers equivalent to those of PLCH.³⁰

Other applications of BAL include assessment of disease status and the prediction of therapeutic responsiveness. For example, in both the connective tissue diseases and IPF, BAL lymphocytosis is associated with a cellular histology (as opposed to fibrosis) and an improved response to treatment. Furthermore, the overall survival rate in these patients is increased. Conversely, the combination of lavage neutrophilia and eosinophilia without lymphocytosis often portends progressive unresponsive disease. In sarcoidosis, a disease characterized by increases in the number of T-helper (CD4⁺) lymphocytes in the lung, it has been suggested that clinical deterioration may be expected if the BAL lymphocyte level exceeds 28%; however, more recent data indicate that the level of BAL lymphocytes has no value in predicting the clinical outcome in sarcoidosis.

Another role for BAL is in the assessment of potential ILD in populations at risk. For example, in patients with scleroderma and rheumatoid arthritis in whom clinical, radiologic, and physiologic evidence of ILD is lacking, BAL studies have revealed increases in inflammatory cell populations.

HISTOLOGIC DIAGNOSIS

The final step in the evaluation of a patient with ILD is to decide whether tissue is necessary for diagnosis. As previously noted, the diagnosis of connective tissue, occupational, or drug-related ILD is often obvious after a careful history has been taken. In cases of idiopathic and primary ILD (see Table 63-1), the diagnosis may not be as obvious, although clinical, laboratory, and radiologic findings are often suggestive. Furthermore, the diagnosis of IPF, a commonly encountered ILD, in many cases can be established only by lung biopsy.

Transbronchial Biopsy

As a matter of practicality, transbronchial biopsy can be performed during the bronchoscopy for BAL. Transbronchial biopsy is relatively safe and is often diagnostic of sarcoidosis, diffuse malignancy, alveolar proteinosis, or eosinophilic pneumonia. Other entities are less frequently confirmed by this procedure. A transbronchial biopsy interpretation, which describes only inflammation, fibrosis, or both, is not evidence for IPF or any other entity listed in Table 63-1. Furthermore, even in clinically confirmed cases of connective tissue or drug-induced ILD, several different histologic patterns may evolve (see Table 63-2), and surgical lung biopsy is often undertaken to predict prognosis and therapeutic responsiveness, particularly if BAL and HRCT are inconclusive.

Surgical Lung Biopsy

If the transbronchial biopsy, clinical, and BAL data are inconclusive and the patient is not at high risk, a video thorascopic or open-lung biopsy should be performed. Moreover, there is a poor correlation between the results of transbronchial and open-lung biopsies unless the transbronchial biopsy yields a specific diagnosis. Therefore, when the transbronchial biopsy is inconclusive and a definitive

diagnosis is required, open or thoracoscopic lung biopsy is indicated.³¹

DIAGNOSIS AND MANAGEMENT OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

IIPs represent a heterogeneous group of diffuse parenchymal lung diseases characterized by varying patterns of inflammation and fibrosis.^{32,33} This group of lung diseases represents a subset of ILDs and comprises seven clinical-radiologic-pathologic entities that are sufficiently different from one another to be designated as separate diseases.³² The classification, diagnosis, understanding of the pathogenic mechanisms, and management of IIPs continue to evolve.^{34,35} As a group, they can be distinguished from other forms of ILD by clinical methods including history, physical examination, chest radiologic and laboratory studies, and pathology. It is crucial for clinicians to be aware that the

histologic pattern underlying these IIPs can be encountered in subjects with known causes for their lung disease (e.g., connective tissue diseases, smoking, drugs). Thus, *usual interstitial pneumonia* (UIP) can be seen not only in patients with IPF but also in patients with rheumatoid arthritis as a form of rheumatoid arthritis-associated ILD.^{33,36} In addition, the interstitial pneumonia patterns are associated with varying degrees of specificity with respect to etiology. For example, *respiratory bronchiolitis-associated ILD* (RB-ILD) in most patients is caused by smoking, whereas organizing pneumonia can be associated with a broad spectrum of causes including infections, aspiration, drug reactions, connective tissue disorders, eosinophilic lung disease, and many others.^{31,37-41} Tables 63-7 and 63-8 provide an overview of the key clinical and pathologic features of the IIPs.

IDIOPATHIC PULMONARY FIBROSIS

IPF is the most common form of IIP and accounts for 25% to 30% of ILDs.^{2,42-44} IPF is a well-defined clinical entity with

Table 63-7 Contrasting Pathologic Features of Idiopathic Interstitial Pneumonias

Features	UIP	DIP	RB-ILD	AIP	NSIP	COP
Temporal appearance (age of lesion)	Variegated	Uniform	Uniform	Uniform	Uniform	Uniform
Interstitial inflammation	Scant	Scant	Scant	Scant	Usually prominent	Usually moderate
Fibrosis/honeycombing	Patchy	Variable, diffuse, moderate	Variable, focal, mild	Typically no, but may evolve to fibrosis	Variable, diffuse	No
Fibroblast proliferation	Fibroblast foci prominent	No	No	Diffuse	Occasional, diffuse, or rare fibroblast foci	Within airways and air spaces (Masson bodies)
Honeycomb change	Yes	No	No	No	Rare	No
Intra-alveolar macrophage accumulation	Occasional, focal (smokers)	Yes, diffuse	Peribronchiolar	No	Occasional, patchy	Foamy macrophages common
Hyaline membranes	No	No	No	Occasional, focal	No	No

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; UIP, usual interstitial pneumonia.

Adapted from Katzenstein ALA, Myers JL: Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 157:1301–1315, 1998; and King TE Jr: Idiopathic interstitial pneumonia. In Schwarz MI, King TE Jr, editors: *Interstitial lung diseases*, ed 4. Hamilton, Ontario, 2003, BC Dekker, pp 701–786.

Table 63-8 Contrasting Clinical Features of Idiopathic Interstitial Pneumonias

Features	UIP	DIP	RB-ILD	AIP	NSIP	COP
Mean age at onset (yr)	60s	40s	40s	50s	50s	50s
Onset	Insidious	Insidious	Insidious	Acute	Subacute, insidious	Acute or subacute
History of cigarette smoking	About two thirds	Most	Most	Not known	Uncommon	About half
Mortality rate (mean survival)	68% (5–6 yr)	27% (12 yr)	0%	62% (1–2 mo)	≈25% in 10 yr	10% in 5 yr
Response to steroids	Poor	Good	Good	Poor	Good	Excellent
Complete recovery possible	No	Yes	Yes	Yes, rarely	Yes	Yes (≤70% of patients)

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; UIP, usual interstitial pneumonia.

Adapted from Katzenstein ALA, Myers JL: Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 157:1301–1315, 1998; and King TE Jr: Idiopathic interstitial pneumonia. In Schwarz MI, King TE Jr (eds): *Interstitial lung diseases*, ed 4. Hamilton, Ontario, Canada, 2003, BC Dekker, pp 701–786.

characteristic clinical, radiographic, physiologic, and pathologic manifestations but is also a diagnosis of exclusion (i.e., UIP of unknown cause).^{16,45} The exact prevalence of this condition is unknown. In a recent study using narrow case-finding criteria, the prevalence ranged from 0.8 to 65/100,000 individuals; comparable figures for incidence were 0.4 to 27/100,000 persons.⁴³ Extrapolating these rates to the overall U.S. population, prevalence was estimated to be 14/100,000 (incidence, 7/100,000). Both the prevalence and the incidence of IPF increase markedly with age.⁴³

Clinical Features

IPF is a disease of middle age, usually seen in patients between 50 and 70 years of age. Patients with familial pulmonary fibrosis tend to present at a younger age; otherwise, it is quite uncommon for a patient to present before the age of 40.⁴⁶⁻⁴⁸ The typical patient presents with the insidious onset of exertional breathlessness and a nonproductive cough. Constitutional symptoms are uncommon, but weight loss, fever, fatigue, myalgias, or arthralgia is occasionally present. Although patients may present with only a nonproductive cough, all patients experience dyspnea with exertion as the disease progresses. Most patients have these symptoms for months to years before definitive evaluation, usually around 12 to 18 months.

The physical examination is rarely normal. Most patients have bibasilar late inspiratory fine crackles (Velcro crackles) on chest examination. Clubbing of the fingers is seen in 40% to 75% of patients and is a late finding in the disease course. Cardiac examination is usually normal except in the middle or late stages of the disease, when findings of pulmonary hypertension (e.g., augmented P2, right-sided lift, tricuspid regurgitation, and S3 gallop) and cor pulmonale may become evident. Similarly, cyanosis is a late manifestation indicating advanced disease. Spontaneous pneumothorax or pneumomediastinum is rare.

Blood and Serologic Studies

An elevated erythrocyte sedimentation rate, low-level antinuclear antibodies titer positivity (≥ 40 and $< 1:320$), and elevated rheumatoid factor (> 60 IU/mL) have been identified in some of these patients.⁴⁹ Hemoglobin level along with leukocyte and differential counts are usually normal.

Chest Imaging Studies

Chest Radiography. The typical finding in patients with IPF is peripheral reticular opacities with a netlike appearance of linear or curvilinear densities, with predominance at the lung bases (Fig. 63-20). A coarse reticular pattern or multiple cystic or honeycombed areas (i.e., coarse reticular pattern with translucencies measuring 0.3 to 1 cm in diameter) are radiographic findings that correlate with advanced disease and poor prognosis (see Figs. 63-6 and 63-7). Chest radiographic evidence of reduced lung volumes is usually present unless there is associated obstructive airway disease, as can be seen in smokers.

Pleural abnormalities are uncommon in IPF; their presence should suggest another diagnosis, such as collagen vascular disease (especially rheumatoid arthritis or systemic lupus erythematosus), mitral valve disease, conges-

tive heart failure, asbestosis, infection, drug-induced lung disease, or lymphangitic carcinomatosis (see Table 63-5).

Computed Tomography Scan. CT plays a major role in the evaluation of pulmonary parenchymal diseases, especially IPF.^{16,50,51} HRCT is useful in the differentiation of IPF from other ILDs, the determination of the extent and severity of disease activity, and, most importantly, the detection of disease, especially in patients with normal or minimal change on chest radiography. HRCT findings in IPF include a marked peripheral (subpleural) distribution of the interstitial opacities. The involvement is patchy, with areas of reticulation intermingled with areas of normal tissue, often associated with cystic spaces 2 to 4 mm in diameter (see Fig. 63-11). Early disease appears as patchy, predominantly peripheral, subpleural reticular opacities (eFig. 63-1) and minor degrees of honeycomb change. In more advanced disease, a more diffuse reticular pattern in the lower lung zones with thickened interlobular septa and intralobular lines progresses to traction bronchiectasis and subpleural fibrosis (eFig. 63-2).^{50,51} The predominantly basal nature of these abnormalities is often readily appreciated with coronal imaging (eFig. 63-3).

One of the key findings indicating the diagnosis of IPF is the presence of honeycomb cysts in a basilar subpleural distribution (eFig. 63-4). Honeycomb changes appear on the HRCT scan as variably sized cystic spaces that share walls and frequently stack on one another in several layers.^{50,51} Ground-glass opacities are common but of mild severity and characteristically much less extensive than the reticular pattern. Architectural distortion, which reflects lung fibrosis, is often prominent.

Combined lower lobe pulmonary fibrosis and upper lobe emphysema has been recently described as a new CT-defined syndrome (eFig. 63-5, Video 63-1) (Fig. 63-21).^{52,53} Smoking appears to be the predominant risk factor for this disorder. Patients with this entity are primarily males with a mean age of 65 years who have relatively preserved lung volumes but marked reductions in DL_{CO} on pulmonary function testing. Limited data suggest that these patients with IPF and coexisting emphysema are more likely to require long-term oxygen therapy, to develop pulmonary hypertension, and to have a worse outcome than those without emphysema.^{52,53}

HRCT Correlation with Physiologic Data in ILD. Identification of a relationship between pulmonary function testing and HRCT findings remains incomplete. FVC, DL_{CO}, arterial PO₂ measured at peak exercise, and oxygen desaturation during exercise are the physiologic parameters that best correlate with the global extent of disease on HRCT.^{21,54} In one study, DL_{CO} was the physiologic characteristic most highly correlated with HRCT findings.⁴¹ Serial HRCT scanning showed that the changes over time in the total extent of the disease were similar to those changes observed in DL_{CO} and FVC.⁵⁵

Ability of HRCT Scanning to Diagnose ILD. HRCT plays an important role but has not replaced lung biopsy in the diagnosis and assessment of most ILDs. In the case of IPF, connective tissue diseases (particularly scleroderma) and asbestosis may cause a similar HRCT appearance (except

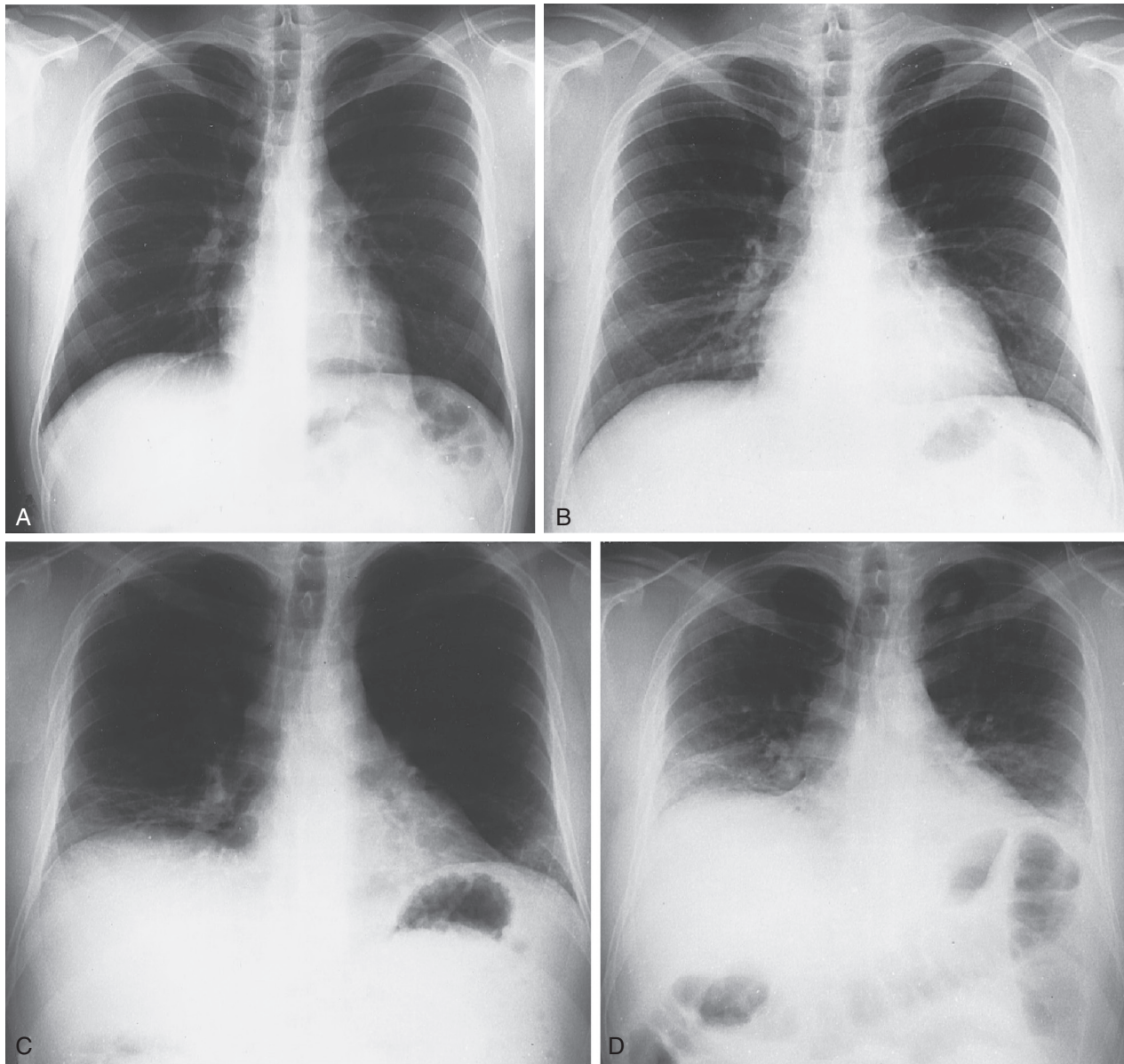


Figure 63-20 Serial chest radiographs from a patient with idiopathic pulmonary fibrosis. **A**, The frontal chest radiograph was obtained at the time of onset of breathlessness with exercise and mild cough. The chest appears normal. **B**, The follow-up film reveals progressive loss of lung volume and bibasilar, predominantly reticular opacities. The patient had stopped regular exercise because of breathlessness with exertion. **C**, Progressive changes are evident, with severe loss of lung volume. Predominantly in the lower lung zone are seen diffuse, bilateral, coarse reticular opacities typical of the radiographic appearance of the middle to late stage of pulmonary fibrosis. **D**, Continued disease progression is evident, with honeycombing and pulmonary hypertension. Open-lung biopsy revealed usual interstitial pneumonia with extensive fibrosis and histologic honeycombing. Treatment with corticosteroids and cyclophosphamide (Cytoxan) was started, but the patient experienced a progressive decline in functional status and died 6 months after lung transplantation.

for the presence of parenchymal bands of fibrosis and pleural plaques seen in patients with asbestosis).⁵⁶ Patients with chronic hypersensitivity pneumonitis can have similar reticular opacity or honeycombing, but often accompanied by a mosaic pattern, centrilobular nodules, and lack the bibasilar predominance seen in IPF (eFig. 63-6).^{57,58}

Studies evaluating the ability of HRCT scanning to diagnose IPF accurately have found that HRCT significantly increases the level of diagnostic confidence. In general, the sensitivity for a confident diagnosis is low ($\approx 48\%$) but the specificity is high ($\approx 95\%$).⁵⁹⁻⁶³ The accuracy of a confident diagnosis of IPF made on HRCT by a trained observer appears to be about 90%.^{57,64-66} Less experienced observers

are substantially less accurate than experienced observers.⁶⁴ An HRCT pattern highly suggestive of the diagnosis of IPF is associated with a poor prognosis.⁶⁷ Of those with a histopathologic diagnosis of UIP, those with basilar honeycombing have a worse survival than those without honeycombing.^{68,69} In a multivariate analysis of a large multicenter trial, it was found that extent of reticulation and honeycombing on HRCT is an important independent predictor of mortality in patients with IPF.⁵⁵

Other Imaging Techniques

Gallium Scanning. Lung scanning with radioactive gallium (^{67}Ga) is a noninvasive test for staging the

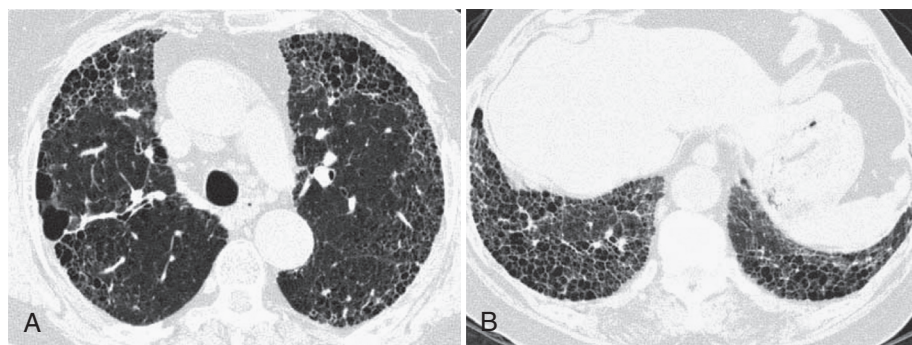


Figure 63-21 Combined pulmonary fibrosis and emphysema. CT images from a 69-year-old woman with a 12-month history of worsening cough and dyspnea. She is a current heavy smoker. **A**, Upper zones of the lungs show emphysema and mild patchy peripheral reticular opacities. **B**, Lower zones of the lungs show emphysema and architectural distortion with patchy peripheral reticular opacities and extensive honeycombing lesions.

“alveolitis” found in ILDs, particularly sarcoidosis.⁷⁰⁻⁷² However, ^{67}Ga lung scanning is not recommended in the routine evaluation of IPF because inflammation is not a prominent feature, the scan is difficult to interpret, the findings are not specific, and a negative scan does not exclude disease.

Ventilation-Perfusion Lung Scanning. Ventilation-perfusion lung scanning is not recommended as a routine part of the evaluation. In most parenchymal diseases, ventilation-perfusion scanning reveals an inhomogeneous reduction of blood flow, ventilation, or both.⁷² There are two types of perfusion abnormalities in IPF: nonsegmental inhomogeneities, probably due to a localized loss of the capillary bed, most often in the lower lobes; and increased perfusion of the upper lung zones, resulting from pulmonary hypertension, which induces an upward shift in the gradient of capillary perfusion. Ventilation scans often reveal patchy, nonsegmental areas of decreased ventilation, reflecting regions of airway obstruction or alveolar destruction. Patchy areas of high and low ventilation-perfusion matching are usually seen, with a few areas of well-maintained ventilation-perfusion matching. These findings of mismatching of ventilation and blood flow help explain the hypoxemia and high $\text{V}_\text{D}/\text{V}_\text{T}$ ratio found in many of these patients at rest.

Magnetic Resonance Imaging for Differentiating Inflammation and Fibrosis. Magnetic resonance imaging (MRI) has several advantages over CT, including lack of ionizing radiation and ability to identify tissue characteristics at a nuclear level that may allow for novel assessments of lung function and microstructure.⁷³ Ten patients with IPF and 16 with NSIP were examined by comparing 3-T MRI of the lung to the morphologic findings on surgical biopsy.⁷⁴ Compared with fibrotic areas, inflammation-predominant areas showed an early enhancement pattern on dynamic studies and a high-signal intensity on T2-weighted triple-inversion black-blood turbo spin-echo images compared with fibrotic areas. These results indicate that qualitative analysis of MRIs may be helpful for differentiating inflammation- and fibrosis-predominant lesions.

Imaging of Fibrogenesis by Positron Emission Tomography. The putative role of physiologic imaging using

^{18}F -2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scans in IPF has been explored in few patients without clear results.^{75,76} In general, the lungs of patients with IPF appear to show increased uptake of FDG on PET (eFig. 63-7). Some studies have suggested that cis-4- ^{18}F -fluoro-L-proline [^{18}F -proline] may be a reliable marker for fibrosis formation. This radioligand has been tested in patients with IPF.^{55,77} PET acquisition was performed 1, 2, and 3 hours after injection of ^{18}F -proline. Surprisingly, low uptake of ^{18}F -proline was found in the lungs of all patients with IPF. The highest uptake was seen at 2 hours postinjection, with a decline at 3 hours past injection. The authors speculate that this low uptake may be due to the slow nature of fibrogenesis or to the relatively low dose of proline that can be used. Further research is necessary to know if imaging through PET has a role in the diagnosis or prognosis of ILDs.

Pulmonary Function Tests

The lung volumes (TLC, functional residual capacity, and residual volume) are reduced in IPF. Early on, the lung volumes may be normal, especially in patients with superimposed *chronic obstructive pulmonary disease* (COPD). Lung volumes are higher in smokers with IPF compared with those who have never smoked.²⁰ As mentioned previously, a group of smokers develop a combined IPF and emphysema and show almost normal lung volumes, even in advanced disease.^{52,53} Expiratory flow rates (FEV_1 and FVC) may be decreased because of the reduction in lung volume, but the FEV_1/FVC ratio is maintained. Because of the increased static elastic recoil found in these patients, flow rates (at any given lung volume) are often increased (see Figs. 63-15A and 63-17).

Patients with IPF are tachypneic, with rapid shallow breaths, probably because of increased work of breathing. This rapid respiratory rate presumably results from altered mechanical reflexes, caused by the increased elastic load, vagal mechanisms, or both, because no defined chemical basis for the hyperventilation has been identified (see Fig. 63-18).

The DL_{CO} is reduced, often before the loss of lung volume. The decrease in the DL_{CO} results from both a contraction of the pulmonary capillary volume and the presence of ventilation-perfusion abnormalities. Resting arterial blood gases are usually abnormal, revealing hypoxemia and

respiratory alkalosis. The major cause of resting hypoxemia is ventilation-perfusion mismatching; it is not due to either impaired oxygen diffusion, as was originally suspected, or to anatomic shunts. With exercise, the (A-a)PO₂ widens, and the arterial PO₂ and oxygen saturation fall. During maximal exercise, 20% to 30% of the exercise-induced widening of the (A-a)PO₂ may be caused by some impairment of oxygen diffusion. Importantly, the abnormalities identified at rest do not accurately predict the magnitude of the abnormalities seen with exercise (see Fig. 63-19). In addition, gas exchange during exercise has been demonstrated to be a sensitive parameter for following the clinical course.

In patients with IPF, a highly significant correlation has been reported between the 6-minute walk distance (6MWD) test and DL_{CO}, as well as $\dot{V}O_{2\max}$; the 6MWD is a strong predictor of mortality.⁷⁸ The 6MWD test is difficult to perform in patients with advanced lung disease, however, and variability is common.

The 15-steps Climbing Oximetry Test has been found useful for estimating ventilatory reserve in patients with COPD and for predicting postoperative complications of lung resection. In a recent study, it was shown that the desaturation measured by the 15-steps Oximetry Test in IPF patients is comparable with the desaturation measured by the cardiopulmonary exercise test and the 6MWD test, suggesting it may be a reliable tool for monitoring IPF progression and for evaluating the need for oxygen supplementation.⁷⁹ This test may serve as a surrogate marker of $\dot{V}O_{2\max}$ and an alternative to the 6MWD test in this setting.⁸⁰

During exercise, patients with IPF increase their minute ventilation primarily by increasing their respiratory frequency (see Fig. 63-18). This method of increase differs from that in normal subjects, in whom ventilation increases during mild exercise by an increase in the tidal volume (VT) rather than respiratory rate. Thus, patients with IPF have elevated minute ventilation during exercise that is in part related to the increase in VD. In addition, the VD/VT ratio is increased at rest and is maintained or decreases only slightly with exercise. Occasionally, the VD/VT ratio increases in ILDs that have a prominent pulmonary vascular component, such as scleroderma or PLCH.

Pulmonary Hemodynamics

Recent evidence suggests *pulmonary hypertension due to IPF* (PH-IPF) is relatively common and may contribute substantially to functional status, quality of life, morbidity, and mortality.⁸¹⁻⁸⁵ (See Chapter 59.) The prevalence of PH complicating the course of patients with IPF has been reported in between 32% and 85% of patients, being more frequent in advanced disease.⁸⁵ The most appropriate method to detect PH noninvasively is transthoracic (Doppler) echocardiography. Unfortunately, echocardiography may be inaccurate in estimating pulmonary arterial systolic pressure in patients with ILD.⁸⁶ Right heart catheterization is the “gold standard” for the hemodynamic evaluation of the pulmonary circulation and diagnosis of PH but is an invasive technique. Right heart catheterization may be necessary, however, to document the severity of PH and potential right ventricular dysfunction. Abnormalities in gas exchange and exercise capacity seem to have a significant

association with PH-IPF. Thus, exaggerated exercise oxygen desaturation, out-of-proportion reduction of DL_{CO}, and supplemental oxygen requirement should raise suspicion of (and may be a useful surrogate for) the presence of underlying PH.^{83,85} Brain natriuretic peptide concentrations predicted moderate to severe PH with 100% sensitivity and high specificity (89%) in a small cohort of patients with pulmonary fibrosis.⁸⁷ This study requires further validation.

Pathologic vascular findings in IPF consist of changes in the arteries, arterioles, and venules, as well as destruction of the capillary bed.⁸⁸ Adventitial thickening around the pulmonary vessels reflects an increase of connective tissue. Smooth muscle cells hypertrophy and proliferate, and collagen and elastin accumulate in the media of the small muscular pulmonary arteries. Distal pulmonary arterioles become muscularized (see Fig. 59-4E,F). In addition, there may be extensive intimal hyperplasia, fibrosis, and reduplication of the inner elastic lamina in the small muscular pulmonary arteries in IPF. Increased hemosiderin deposition and alveolar septal capillary density have been associated with higher right ventricular systolic pressure (as assessed by transthoracic echocardiography) and may represent histologic correlates of pulmonary hypertension in IPF.⁸⁹

Supplemental oxygen is the most obvious choice for prevention or treatment of PH; however, there are no data supporting favorable effects of oxygen on survival in PH-IPF. Vasodilators agents are currently being studied, but one must recognize that decreased physiologic vasoconstriction in low ventilation-perfusion lung units may worsen shunt and hypoxemia in IPF.^{84,85,90}

Endothelin-1 (ET-1) receptor antagonists have been useful in patients with other types of pulmonary hypertension, mostly in primary PAH or PAH associated with connective tissue disease. Clinical trials in PH-IPF are ongoing (Table 63-9). Prostacyclin (*prostaglandin I₂* [PGI₂]) analogues used via inhalation could maintain (or even improve) ventilation-perfusion matching and could have a beneficial effect targeting PH. In one study, inhaled iloprost decreased mean pulmonary artery pressure without changes in shunt flow,⁹¹ suggesting the utility of selective pulmonary vasodilation in patients with PH-IPF. Sildenafil, a phosphodiesterase-5 inhibitor, promotes vasodilation and decreases smooth muscle proliferation and vascular remodeling. In an open-label study of treatment with sildenafil for 3 months in a small cohort of patients with PH-IPF, a modest but significant improvement in 6MWD was noticed.⁹² In a subsequent randomized clinical trial, sildenafil therapy did not show a benefit for the primary outcome (increase in 6MWD of 20% or more), but a small yet significant improvement was noted in arterial oxygenation, diffusing capacity, dyspnea, and quality of life.⁹³ Several other randomized clinical trials are currently ongoing (see Table 63-9) to learn whether any therapies will be useful in PH-IPF (see Chapter 59).

Abnormalities during Sleep

Many patients with IPF, especially those with low daytime arterial oxygen saturation or a history of snoring during sleep, develop sleep disturbances characterized by reduced rapid eye movement sleep, lighter and more fragmented

Table 63-9 Ongoing Clinical Trials in Patients with Idiopathic Pulmonary Fibrosis

Drug	Aim/Mechanism of Action	Sponsor	ClinicalTrials.gov Identifier
QAX576	It may down-regulate IL-13	Novartis	NCT00532233
FG-3019	It blocks CTGF	FibroGen	NCT00074698
Macitentan	Inhibitor of ET-1	Actelion	NCT00903331
Bosentan	Indicated for PAH	UCLA; Actelion	NCT00625469
Pirfenidone	Antifibrotic effects in vitro and in experimental models	InterMune	NCT01366209
Zileuton	Inhibitor of leukotrienes	University of Michigan	NCT00262405
Gleevec (imatinib mesylate)	Tyrosine kinase inhibitor	Daniels, Craig E., MD, Novartis	NCT00131274
Octreotide (somatostatin analogue)	Anti-inflammatory and antifibrotic properties in vitro and in vivo	Institut National de la Santé et de la Recherche Médicale, France	NCT00463983
GC1008	Antibody that neutralizes TGF- β	Genzyme	NCT00125385
Inhaled IFN- γ	Antifibrotic effects	New York University School of Medicine; National Center for Research Resources, Stony Brook University; Respironics	NCT00563212
Inhaled IFN- γ	Same as previous	New York University School of Medicine	NCT00212563
Tetrathiomolybdate	Copper chelating agent	University of Michigan; Coalition for Pulmonary Fibrosis	NCT00189176
Nintedanib	Inhibits profibrotic growth factors	Boehringer Ingelheim Pharmaceuticals	NCT01335177
NAC alone	Effect of the antioxidant NAC	NHLBI	NCT00650091
Thalidomide	Indicated for cough. Suppresses functional up-regulation of sensory fibers within the respiratory tract	Johns Hopkins University	NCT00600028
Sildenafil	Indicated for PAH	UCLA and Pfizer	NCT00625079
Sildenafil	Indicated for PAH	NHLBI; Pfizer	NCT00517933
Sildenafil	Indicated for PAH	Department of Veterans Affairs	NCT00359736
Inhaled iloprost	Indicated for PAH; secondary purpose: to evaluate antifibrotic properties	Actelion	NCT00109681
CNTO 888	Phase II study	Centocor	NCT00786201
Losartan	An antagonist of angiotensin type 1 receptor	H. Lee Moffitt Cancer Center and Research Institute; NCI	NCT00879879
IFN- α lozenges	Reduce the frequency and severity of coughing	Amarillo Biosciences; Texas Tech University Health Sciences Center	NCT00690885
Inhaled carbon monoxide	Decrease serum level of MMP7	Brigham and Women's Hospital	NCT01214187
Tralokinumab	Binds IL-13	MedImmune	NCT01629667
Lysophosphatidic acid receptor antagonist	Antifibrotic effects in vitro and in experimental models	Bristol-Myers-Squibb	NCT01766817
Simtuzumab	<i>Lysyl-oxidase-like 2</i> (LOXL2) inhibitor	Gilead Sciences	NCT01769196
SAR156597	IL-4 and IL-13 inhibitor	Sanofi	NCT01529853
STX-100	Integrin $\alpha\beta 6$ inhibitor	Stromedix	NCT01371305
Sirolimus	Reduces the number of circulating fibrocytes	University of Virginia	NCT01462006

CTGF, connective tissue growth factor; ET-1, endothelin-1; ET-A, endothelin receptor A; IFN- γ , interferon- γ ; IFN- α , interferon- α ; IL-13, interleukin-13; NAC, N-acetylcysteine; NCI, National Cancer Institute; NHLBI, National Heart, Lung, and Blood Institute; PAH, pulmonary arterial hypertension; TGF- β , transforming growth factor- β ; UCLA, University of California, Los Angeles.

sleep, and hypoxemia during rapid eye movement sleep.^{94,95} Severe hypoxemia can be seen in the absence of obstructive sleep apnea or changes in breathing pattern. Tachypnea persists during sleep. Identification and correction of the sleep disturbance may reduce morbidity and improve quality of life and patient survival. In one study, obstructive sleep apnea was confirmed in two thirds of IPF patients with complaints suggestive of sleep apnea.⁹⁶ An increased body mass index and a significant impairment in pulmonary function testing may be predictors of obstructive sleep apnea in this population.⁹⁶

Histopathology

The gross appearance of the lungs in IPF reveals a distinctive nodular pleural surface, sometimes resembling cirrhosis of the liver, due to contraction of the fibrotic septa. The histopathologic pattern in IPF is UIP. UIP is characterized by a pattern quite distinguishable even on low-power magnification because of its characteristic heterogeneous, predominantly subpleural and paraseptal distribution (Fig. 63-22). This striking heterogeneous appearance is characterized by the presence of small areas of residual normal or nearly normal lung tissue interspersed among extensively

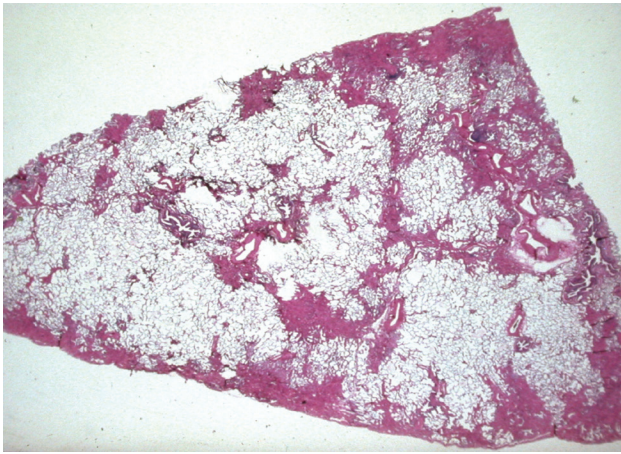


Figure 63-22 Usual interstitial pneumonia pattern often shows a striking subpleural distribution. This low-power photomicrograph is from an area without the usual remodeling of the lung architecture with cystic (honeycomb) changes. The visceral pleura is at the bottom of the image. (Courtesy Thomas V. Colby, MD, Mayo Clinic, Scottsdale, AZ.)

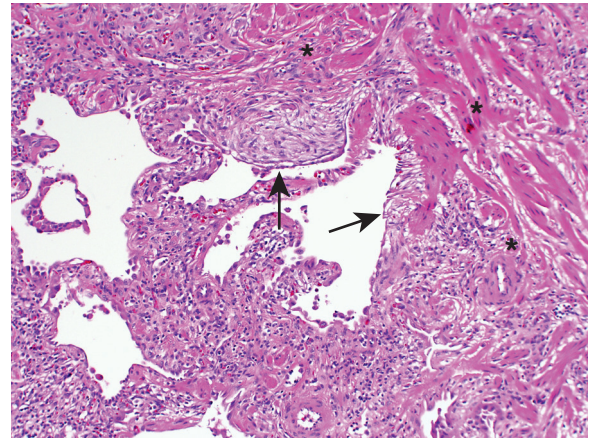


Figure 63-24 Photomicrograph of usual interstitial pneumonia. Two fibroblastic foci of loose organizing connective tissue (arrows) are seen adjacent to an area of dense fibrosis (asterisks). (Courtesy Thomas V. Colby, MD, Mayo Clinic, Scottsdale, AZ.)

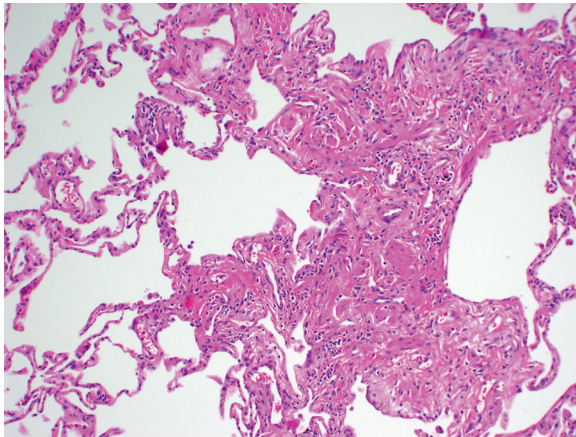


Figure 63-23 Photomicrograph of usual interstitial pneumonia. Residual lymphoplasmacytic inflammation and collagen deposition is seen broadening alveolar walls. (Original magnification $\times 10$.)

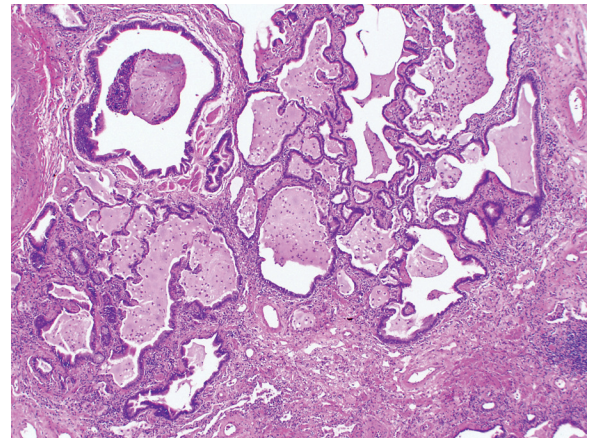


Figure 63-25 Photomicrograph of honeycomb lung in idiopathic pulmonary fibrosis. There is total disruption of the lung architecture by bands of fibrous tissue forming cystic spaces. The spaces are lined by metaplastic epithelium. (Original magnification $\times 10$.)

scarred parenchyma, which may show microscopic honeycombing characterized by enlarged air spaces lined by bronchiolar epithelium, often filled with mucin and variable numbers of inflammatory cells with abutting areas of active proliferation of fibroblasts and myofibroblasts (Figs. 63-23, 63-24, and 63-25).^{16,33,36} These discrete areas of fibroblastic proliferation have been termed *fibroblastic foci* and are essential to the histopathologic diagnosis of UIP³⁶ (see Fig. 63-24). Fibroblastic foci are composed of small dome-shaped collections of spindle-shaped fibroblasts and myofibroblasts within myxoid stroma, covered by hyperplastic alveolar lining cells. Generally, interstitial inflammation is minimal in UIP; if inflammation is present in significant amounts, the diagnosis of UIP in IPF should be reconsidered and other causes of a UIP pattern such as chronic HP and collagen vascular disease should be reconsidered. However, chronic inflammation, lymphoid aggregates with germinal centers, and even acute inflammation may be prominent around honeycomb areas, likely related to poor clearance from the areas of scarred lung.³⁶

Bronchogenic carcinoma (all histologic types) has been identified with increased frequency in advanced IPF (eFig. 63-8).⁹⁷⁻⁹⁹ It has been postulated that carcinoma arises from the metaplastic bronchiolar epithelium that develops in these patients, but the pathogenic mechanisms are unclear. Interestingly, a number of the reported cases have been reported in patients with familial IPF.

Etiologic Factors and Pathogenic Mechanisms

The inciting factors in the development of IPF are unknown. A widely held hypothesis is that this disorder develops in susceptible individuals following some unknown stimuli. Inciting agents initiate an uncontrolled cascade of events that evolve to the fibrotic process. Smoking presents the most significant association with IPF, particularly for individuals who were ever smokers, with *odds ratios* (ORs) varying from 1.6 to 9.4.¹⁰⁰ The same association has been found in familial pulmonary fibrosis. In a family-based case-control study of familial pulmonary fibrosis, Steele and colleagues⁴⁷ identified 111 families, with 309 affected and 360

unaffected individuals. Adjusting for age and gender, ever smoking was strongly associated with pulmonary fibrosis (OR, 3.6; 95% confidence interval [CI], 1.3-9.8). Some occupational and environmental exposures—primarily to wood and metal dusts—have also shown increased association with IPF.⁴⁷ The presence of Epstein-Barr virus found in some patients has led to speculation that chronic viral infection might play a role in the etiology of IPF,¹⁰¹ but this virus has also been found in other fibrotic lung diseases, as well as in many controls. A higher incidence of *gastroesophageal reflux* (GER) has been found in patients with IPF.¹⁰² GER is frequent, however, in the normal population, as well as in patients with other advanced lung diseases, including cystic fibrosis, COPD, and fibrosis associated with scleroderma.¹⁰³

The role of host genetic factors and their interactions with environmental factors leading to IPF is unknown. Numerous gene polymorphisms have been examined, and only a few of them have demonstrated a confirmed (usually weak) association. Moreover, putative associations have not generally been corroborated in independent cohorts. Interestingly, two recent studies performed in independent cohorts suggest that a common polymorphism in the promoter region of an airway mucin gene *MUC5B* may be associated with familial pulmonary fibrosis and idiopathic pulmonary fibrosis, although the link with disease pathogenesis is unknown.¹⁰⁴⁻¹⁰⁶ It has been suggested that this polymorphism in *MUC5B* may be associated with improved survival.¹⁰⁷ Additional studies have shown that the *MUC5B* promoter polymorphism is associated with ILD in the general population, and it does not appear to be influenced by cigarette smoking.¹⁰⁸

An important advance in our understanding of ILD has been the recognition that UIP appears to be a distinct pathophysiologic entity characterized by minimal inflammation and chronic fibroproliferation due to abnormal parenchymal wound healing.^{109,110} This paradigm suggests that the pathologic process of UIP is the result of persistent remodeling (abnormal wound healing) of the lung parenchyma. Multiple “microinjuries” damage and activate alveolar epithelial cells, which in turn provoke a profibrotic microenvironment.¹¹¹ Alveolar epithelial cells secrete growth factors and induce migration and proliferation of fibroblasts and differentiation into myofibroblasts. Aggregates of subepithelial fibroblasts-myofibroblasts (fibroblastic foci) and alveolar epithelial cells produce matrix-metalloproteinases 2 and 9 that may increase basement membrane disruption and allow fibroblast-myofibroblast migration into the alveolar spaces. In addition, alveolar epithelial cells induce an antifibrinolytic environment in the alveolar spaces, enhancing wound clot formation. Current evidence suggests that the tissue-factor-dependent extrinsic pathway is the predominant mechanism by which the coagulation cascade is locally activated in the lungs of patients with pulmonary fibrosis.¹¹² Both intra-alveolar and interstitial myofibroblasts secrete extracellular matrix proteins, mainly collagens. An imbalance between interstitial collagenases and tissue inhibitors of metalloproteinases provokes the progressive deposition of extracellular matrix.¹¹³ Signals responsible for myofibroblast apoptosis seem to be absent or delayed in UIP, increasing cell survival.¹¹⁴ These myofibroblasts produce angiotensinogen and hydrogen peroxide that

have been implied in alveolar epithelial cell death, further impairing reepithelialization.^{115,116} Although the molecular mechanisms that lead to end-stage pulmonary fibrosis in the IIPs are poorly understood, data support this “abnormal wound healing” hypothesis in UIP.^{45,111,117} At least in part, the abnormal communication between alveolar epithelial cells and myofibroblasts may be provoked by an aberrant recapitulation of embryologic programs.¹¹⁸⁻¹²⁰

One of the intriguing observations regarding IPF is that the disease is clearly associated with aging; it usually appears in individuals older than 50 years, reaching a peak in subjects of 60 to 65 years old. In this context, two recent studies have shown that mutations in the genes encoding telomerase components are implicated in familial pulmonary fibrosis.^{121,122} It has also been shown that patients with sporadic IPF have shorter leukocyte telomeres than age-matched controls and that some of them (10% to 25%) had telomere lengths below the first percentile for their age.^{123,124} Importantly, it was also determined that IPF patients had short telomeres in alveolar epithelial cells, suggesting that these cells may be the main lung culprit of this pathologic process.¹²³ Telomeres play a central role in cell fate and aging by adjusting the cellular response to stress and growth stimulation on the basis of previous cell divisions and DNA damage; their shortening has been associated with aging and several diseases.^{125,126}

Diagnosis

The most definitive method of establishing a diagnosis is by surgical lung biopsy, but the presence of typical features of a UIP pattern on HRCT may obviate the need for biopsy.^{32,59,127} Thoracoscopic or open-lung biopsy is indicated because it provides an accurate diagnosis; it excludes neoplastic and infectious processes that occasionally mimic chronic, progressive interstitial disease; it may also identify a more treatable process than originally suspected (e.g., chronic hypersensitivity pneumonitis); and it provides a better assessment of disease activity.^{16,31,32,128} Studies have addressed the accuracy of the combined clinical and radiographic diagnosis of IPF.^{59,61} In both studies, clinicians were blinded to the results of the surgical lung biopsies, which were used as the gold standard for diagnosis. The positive predictive value of a confident clinical diagnosis of IPF was 87% and 96% among pulmonologists and radiologists with specific expertise in ILD, respectively.¹²⁹ The clinical diagnosis of IPF had a sensitivity of 62% and a specificity of 97% compared with the radiologic diagnosis, which had a sensitivity of 70% and a specificity of 90%.⁶¹ As recognition of the HRCT features has improved, it has been suggested that—in the appropriate clinical setting and with radiologist expert in IPF diagnosis—the predictive value of HRCT for the diagnosis of IPF is good, even in patients with *possible* UIP pattern on HRCT (i.e., meeting ATS/ERS criteria for IPF but with 5% or less honeycombing on HRCT).¹³⁰

Collectively, these studies argue that, when the clinical and radiographic diagnoses are consistent, IPF can be confidently diagnosed. They also demonstrate, however, that this consistency is present in only about half of patients with biopsy-confirmed UIP. Furthermore, experts in the field performed these studies and it is unclear how the outcome would vary with community physicians less familiar with these processes. In this context, significant

disagreement has been reported regarding the diagnosis of IIPs between physicians based in communities compared with those in academic centers.¹³¹ Importantly, community physicians were more likely to make a diagnosis of IPF, which has important implications, because individual patients with other ILDs (e.g., hypersensitivity pneumonitis, NSIP, or collagen vascular disease–associated ILD) are more likely to respond to immunosuppressive treatment, whereas patients with IPF should be referred, whenever possible, for participation in clinical therapeutic trials or for evaluation for lung transplant. In addition, this study also confirms that a multidisciplinary team approach among clinicians, radiologists, and pathologists improves interobserver agreement and enhances diagnosis specificity.¹³¹

Staging of Disease Activity and Predicting Outcome

The long-term survival in IPF is distinctly poor, with only a 20% to 30% survival 5 years after the time of diagnosis.^{16,32,45,132-134} However, the rate of progression is variable. Attempts to predict who will respond to treatment have been largely disappointing primarily because the disease is relentlessly progressive with all the therapies used until now.

Clinical Features. Younger patients tend to have less fibrosis than do older patients, and younger patients and women survive longer than older patients and men. In a recent study, it was found that the percentage of monthly worsening in oxygen saturation is high in males, suggesting differences in disease progression according to gender.¹³⁵ Current smoking (i.e., at the time of presentation) was associated with improved survival in patients with IPF, whereas heavy smoking (i.e., higher number of pack-years) was associated with a worse prognosis.²³ In addition, pulmonary fibrosis combined with emphysema and the accelerated variant of IPF that display the worst survival seems to be more frequent in smokers.^{52,53,136} The *Medical Research Council* (MRC) Chronic Dyspnea Score estimated at the time of diagnosis is predictive of survival and may aid clinicians in assessing the prognosis of new cases of IPF.¹³⁷

Serum Studies. The presence of immunologic markers, including autoantibodies, elevated sedimentation rates, circulating immune complexes, and increased serum immunoglobulins, has not been shown to correlate with the overall natural history of IPF.

Serum *surfactant protein* (SP)-A and SP-D have prognostic value for mortality in patients with IPF.¹³⁸ A recent study showed that after controlling for known clinical predictors of mortality, an increased serum SP-A level is a strong and independent predictor of early mortality among patients with IPF. A prediction model containing SP-A and SP-D was substantially superior to a model with clinical predictors alone.¹³⁹ Also, serum CCL18 concentrations seem to have a predictive value in IPF with higher mortality observed in patients with concentrations above 150 ng/mL.¹⁴⁰

Chest Radiography and High-Resolution Computed Tomography Scanning. A general pattern of evolution is seen with serial chest radiography. The early changes include hazy opacities with reduction in lung volumes that

progress to a reticular pattern and finally end in coarser, cystic areas of honeycombed lung (eFig. 63-9). Unfortunately, the chest radiograph is not a useful monitor of the degree and extent of lesions. In fact, the only radiographic abnormality that correlates with the histologic pattern is honeycombing (eFig. 63-10). Furthermore, chest radiography may demonstrate no changes despite clinically apparent physiologic deterioration. Another major problem with using chest radiography to follow the disease course or to estimate the stage of disease is that there is considerable interobserver variability in the interpretation of these studies.

HRCT scanning in IPF may be useful in staging disease activity. The finding of a higher extent of ground-glass opacities and a lower extent of reticular opacities on the initial HRCT identifies those patients with early disease (see eFig. 63-1) who are the most likely to survive longer and respond (if transiently) to corticosteroids.¹⁴¹ Patients with a typical HRCT appearance of UIP experience the highest mortality.⁶⁷

It was shown by univariate logistic regression analysis that a greater extent of fibrosis by HRCT predicted a greater short-term mortality during follow-up.¹⁴² The multivariate logistic regression analysis showed that the single best predictor of mortality during follow-up was the visual extent of fibrosis on CT images, and there was little additional predictive power to be gained from the more quantitative measures.¹⁴²

Pulmonary Physiologic Tests. Reductions in the vital capacity correlate with the degree of fibrosis present and show a relationship with the overall histologic derangements.^{143,144} A significant reduction in the vital capacity (<50% of predicted) is associated with pulmonary hypertension and a reduced 2-year survival. Patients with normal DL_{CO} values usually do not have significant gas exchange abnormalities, whereas patients with DL_{CO} below 70% of predicted frequently have such changes at rest or with exercise. Survival is longer in patients with a more normal DL_{CO} (>45% of predicted value). A marked reduction of the DL_{CO} and resting hypoxemia are associated with pulmonary hypertension and decreased survival.

Patients with advanced disease and severe fibrosis have greater abnormalities of the $(A-a)PO_2$ when compared with those with early disease and preserved lung architecture. When compared with other indices of lung function, alterations in gas exchange during exercise correlate best with histopathologic findings. Serial measurements of gas exchange during exercise also appear to be the best predictors of survival. It has been demonstrated that the predictive ability of serial changes in physiology varies when patients are stratified by the presence/absence of desaturation during a baseline 66-minute walk test; for patients with baseline saturation less than 88%, the strongest observed predictor of mortality was serial change in DL_{CO} and, for patients with saturation greater than 88% during their baseline walk test, serial decreases in FVC and increases in desaturation area significantly predicted subsequent mortality.¹⁴⁵ In summary, pulmonary function testing is useful in establishing the presence of impairment in IPF and following its course and response to therapy. The severity of the initial abnormalities in FVC, DL_{CO} , arterial PO_2 , and

(A–a)PO₂, as well as oxygen desaturation on a 6MWD test,⁷⁸ correlate with poorer survival. Likewise, changes in DL_{CO}, TLC, FVC, arterial PO₂, oxygen saturation, and (A–a)PO₂ during follow-up are predictive of survival time after adjustment for baseline values.^{144,146}

Bronchoalveolar Lavage. It has been suggested that the BAL cellular constituents reflect the state of the pulmonary inflammatory response. Unfortunately, many studies have failed to demonstrate a clear distinction between diseases on the basis of the predominant cell type present in the lavage specimens. IPF is characterized by a severalfold increase in the total number of inflammatory cells recovered from the respiratory tract with an increase in the percentage of neutrophils and eosinophils.^{16,26} Studies evaluating the association of BAL fluid cellular constituents and mortality have yielded conflicting results about the prognostic value of BAL and were limited by the size of the study cohort and duration of follow-up.¹⁴⁷

Turner-Warwick and Haslam¹⁴⁸ found that patients who failed to improve had elevated neutrophil and eosinophil counts throughout their course. More recent findings tend to confirm these findings, suggesting that an elevated percentage of neutrophils in the BAL may be an independent predictor of early mortality among persons with IPF.¹⁴⁹ The impact was most important in the first year of follow-up and attenuated with time.

In one study, it was found that SP-A is reduced in IPF, and decreases in its concentration referenced to total phospholipid (a marker of surfactant to normalize to the surface sampled by lavage and recovery) predict an adverse clinical outcome and poorer survival.¹³⁸

Histopathology. Until recently, no specific histologic feature, other than end-stage fibrosis and honeycombing, has been shown to correlate with survival in UIP.^{23,109} It has been proposed that the earliest and most characteristic manifestation of ongoing lung injury in UIP is the development of multiple fibroblastic foci.^{36,150} The prognostic significance of these aggregates of fibroblasts and myofibroblasts in surgical lung biopsies from patients with IPF is unclear, and several studies have given contradictory results.^{151–155} The effect of sample size, tissue sampling bias, and the different techniques for assessing the number of foci may account for these results. In general, detailed quantification of fibroblast foci on surgical lung biopsies may not be a consistent predictor of patient survival in this disease.

Prediction Models. Several investigators have attempted to identify parameters that best predict the clinical course and prognosis of IPF.^{78,145,146,156,157} Individual changes in dyspnea score, TLC, FVC, arterial PO₂, oxygen saturation, or (A–a)PO₂ over 6 and 12 months may be useful as surrogate end points in monitoring therapeutic efficacy in individual patients. Prediction models based on combining multiple baseline clinical, radiologic, or physiologic measurements have been derived from large groups of carefully selected patients with IPF and appear to perform well as predictors of outcome.^{23,157} Using hierarchical multivariable analysis of clinical, radiologic, and extensive physiologic variables, King and associates²³ developed a model that allows clinicians to make more precise prognostic estimations about

patients with IPF. This model included the parameters of age, smoking history, clubbing, extent of profusion of interstitial opacities, presence or absence of pulmonary hypertension on the chest radiograph, percent predicted TLC, and arterial PO₂ at the end of maximal exercise. Although the clinical, radiologic, and physiologic score is an accurate predictor of survival in IPF, it requires both detailed radiographic analysis and exercise physiologic measurements, neither of which is readily available to many physicians. This may limit its utility as a predictor of survival for those in general practice.

Wells and coworkers¹⁵⁷ identified a composite physiologic index closely reflecting the morphologic extent of pulmonary fibrosis while accounting for the extent of emphysema (a finding commonly present in smokers with IPF). The composite physiologic index correlated strongly with extent of disease on CT and mortality and was more accurate than any individual pulmonary function test.¹⁵⁷ However, its value in clinical practice appears limited.

Recently, Ley and colleagues¹⁵⁸ proposed a multidimensional prognostic staging system for IPF using only commonly measured clinical and physiologic variables (age, gender, FVC, and DL_{CO}). A simple-to-use staging system such as this may help inform prognosis and guide management decisions such as those about the appropriate timing of lung transplantation.

Outcome and Causes of Death. Clinical deterioration in patients with IPF is expected. Most patients experience episodes of worsening shortness of breath, decreased exercise tolerance, or other decline in functional status during the course of their illness.¹⁴³ Disease progression may be difficult to distinguish from disease-associated complications and adverse effects of therapy.¹⁵⁹ Death rates are higher in men, higher with increasing age, and highest in the winter, even when infections are excluded.¹⁴³ Frequent hospitalizations for respiratory problems are common events and are often associated with death.^{143,160,161}

In a study of 42 consecutive patients who died with IPF over a 9-year period, autopsies showed that IPF by itself was the immediate cause of death in half of the patients either from an acute exacerbation (see “Acute Exacerbations of Idiopathic Pulmonary Fibrosis” later) or from the gradual progression of the disease.¹⁶² Other respiratory causes of death included pneumonia and aspiration. Cardiovascular disease including arrhythmia, myocardial infarction, and severe cor pulmonale was found to be the cause of death in 20% of subjects. Evidence of pulmonary hypertension was present on autopsy in 45% of patients and was the immediate cause of death in two of them. Pulmonary embolism appears to be relatively common in IPF lung transplant recipients, although its prevalence is unknown.¹⁶³ Importantly, it has been shown that patients with IPF have a higher prevalence of coronary artery disease.¹⁶⁴ Also, patients with clinically stable IPF exhibit not only right ventricular diastolic and systolic dysfunction but also impaired left ventricular diastolic filling, while the systolic function is preserved.¹⁶⁵

Therapeutic Approach

IPF is a progressive and fatal disorder without spontaneous remission, and no therapy to date has been shown to be

effective.^{16,45,166} Although the natural history of IPF has not been appropriately defined, data thus far suggest the median survival after diagnosis, with or without treatment, is 2 to 3 years.^{16,133,134,143} Any therapy of IPF, regardless of the agent used, requires at least 1 year before its effectiveness can be assessed.

Corticosteroids. Although corticosteroids alone were the mainstay for the treatment of IPF for many years, there was never any randomized, placebo-controlled study to support their use.^{167,168} The use of anti-inflammatory therapies in this disease was based on the concept that a chronic inflammatory infiltrate led to progressive extracellular matrix deposition. However, the response to corticosteroid treatment in IPF has been almost uniformly poor.¹⁶⁹ In addition, significant complications can result from corticosteroid therapy, affecting the quality of life. Currently, there is no indication for the use of corticosteroids alone in the treatment of IPF.

Immunomodulatory and Antifibrotic Agents. Because of the poor responsiveness of IPF to corticosteroids, immunomodulatory agents (azathioprine or cyclophosphamide alone or in combination with corticosteroids) have been tried.¹⁷⁰⁻¹⁷³

Several adequate randomized, controlled clinical trials of sufficient numbers of patients with IPF have been performed using putative “antifibrotic” drugs, but none thus far has shown significant improvements in outcome. Combination therapy with prednisone, azathioprine, and *N-acetylcysteine* (NAC) was suggested as a reasonable choice for patients with mild to moderate disease.¹⁷⁴ However, a recent study showed the combination therapy (prednisone, azathioprine, and NAC) to be associated with an increased rate of death and hospitalizations compared with placebo.¹⁷⁵ In this three-arm study of patients with mild to moderate impairment in lung function, combination therapy was compared with NAC alone and placebo. Enrollment into the combination therapy group was halted when an interim analysis revealed increased rate of death and hospitalization compared with placebo. These results argue against the use of such combination therapy in patients with IPF. The comparison of NAC alone versus placebo is ongoing.

AZATHIOPRINE. Azathioprine is a purine analogue that appears to act by the substitution of purines in DNA synthesis and by inhibiting adenine deaminase, which affects lymphocyte functions. Although older studies suggested azathioprine and low-dose prednisone might be useful in the treatment of patients with IPF,¹⁷¹ this drug alone or combined with corticosteroids is not currently indicated for this disorder.

N-ACETYLCYSTEINE. In a double-blind, randomized, placebo-controlled multicenter study, it was found that NAC, a molecular precursor to the naturally occurring antioxidant glutathione, added to prednisone and azathioprine at a dose of 600 mg three times daily, preserves vital capacity and DL_{CO} better than does prednisone and azathioprine alone after approximately 1 year of follow-up.¹⁷⁴ No mortality benefit was identified in this study. A placebo-controlled study of NAC administered orally alone in an IPF population does not support its use for the preservation

of FVC in IPF patients with mild-to-moderate physiologic abnormalities.¹⁷⁶

CYCLOPHOSPHAMIDE. Cyclophosphamide was formerly used as a second-line drug in patients who either failed or could not tolerate corticosteroid treatment. Cyclophosphamide is an alkylating agent of the nitrogen mustard group that is absorbed orally and activated in the liver to several cytotoxic compounds. Its mode of action is the depletion of lymphocytes, thereby suppressing lymphocyte function. The recommended dose is 2 mg/kg/day given orally as a single dose, usually with oral prednisone at 0.25 mg/kg/day. Few data are available on the length of therapy. However, a large retrospective study of well-defined, matched patients with IPF suggested that treatment with combined corticosteroid and cyclophosphamide therapy does not improve survival compared with untreated patients.¹⁷⁰

In addition, cyclophosphamide therapy also has severe side effects including leukopenia, thrombocytopenia, hematuria secondary to hemorrhagic cystitis, gastrointestinal symptoms (including anorexia, nausea, and vomiting), bone marrow suppression, azoospermia and amenorrhea, infection, and the development of a hematologic malignant disease.

Other Agents. A number of other immunosuppressive or putative antifibrotic agents have been reported in individual cases or in small groups of patients with IPF without success. In vitro studies suggest several mechanisms by which *colchicine* may interrupt the processes of collagen synthesis and deposition; it may have anti-inflammatory effects as well. On the basis of these mechanisms of action, colchicine has been used as a potential therapeutic agent in IPF, but there are no data affirming the efficacy of colchicine in IPF.¹⁷⁷⁻¹⁷⁹ *Penicillamine* inhibits collagen synthesis by interfering with collagen cross-linking and is a suppressor of T-cell function. Limited studies have not shown efficacy in IPF.¹⁷⁹ *Captopril* inhibits the angiotensin-converting enzyme and completely abrogates Fas-induced apoptosis in human alveolar epithelial cells. It has also been shown to inhibit fibroblast proliferation in vitro and reduce the fibrotic lung response in vivo. A retrospective study failed to demonstrate a beneficial effect of ACE inhibitors on survival of patients with IPF.¹⁸⁰

Recently, the efficacy of thalidomide therapy in suppressing cough in patients with IPF was evaluated in a 24-week, randomized, double-blind, two-period crossover trial of 98 participants. Thalidomide therapy was associated with improved cough and quality of life in patients with IPF. A larger trial is planned to confirm the beneficial effects observed in this trial.

New Therapeutic Approaches. On the basis of new knowledge about the pathogenic mechanisms involved in IPF and on the poor results obtained with immunosuppressive drugs, newer immunomodulatory or antifibrotic agents have been tried in patients with IPF.

PIRFENIDONE. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a novel antifibrotic and anti-inflammatory agent that inhibits the progression of fibrosis in animal models. Several clinical trials showed promise in stabilizing the lung function and reducing the number of patients who

experienced acute exacerbation of their disease.^{181,182} A randomized clinical trial from Japan noted a difference in progression-free survival in favor of the high-dose pirfenidone group compared with placebo.¹⁸³ Two additional international randomized clinical trials of pirfenidone have since been completed enrolling 435 and 344 IPF patients, respectively.¹⁸⁴ In one of these trials, pirfenidone achieved the primary end point of absolute change from baseline in percent-predicted FVC. The second trial did not meet this same primary end point. A recent phase 3 randomized, double-blind, placebo-controlled trial evaluating pirfenidone in patients with IPF observed reduced disease progression as reflected by better lung volume, improved exercise tolerance, and better progression-free survival.¹⁸⁵ Pirfenidone has been approved for the treatment of IPF in the United States, Europe, and Japan.

NINTEDANIB. Nintedanib (BIBF-1120) is a tyrosine kinase inhibitor that targets the platelet-derived growth factor receptor, vascular endothelial growth factor receptors, and fibroblast growth factor receptors.¹⁸⁶ A 12-month, randomized, double-blind, placebo-controlled, phase 2 trial with 432 IPF patients was recently completed and included four groups assigned to different doses of BIBF-1120.¹⁸⁷ The primary end point was annual rate of decline in FVC. A trend toward a reduction in the decline of lung function with fewer acute exacerbations and preserved quality of life was associated with the highest-dose (150 mg twice daily) regimen of BIBF-1120. In two recent replicate Phase III, multinational, randomized, placebo-controlled, parallel-group trials (INPULSIS-1 and INPULSIS-2), nintedanib slowed disease progression by significantly reducing the rate of decline in FVC.¹⁸⁸ Nintedanib has been approved for the treatment of IPF in the United States.

INTERFERON- γ . A large, controlled trial with *interferon* (IFN) γ -1b noted no difference in the primary end point (progression-free survival) or in most secondary end points.¹⁸⁹ In patients defined as having milder disease (FVC > 55%; defined post hoc), a potential survival benefit was suggested.¹⁹⁰ However, a much larger controlled trial (826 patients) with survival as the primary end point was recently discontinued due to a lack of efficacy. The overall mortality was 14.5% in the IFN γ -1b and 12.7% in the placebo group.¹⁹¹ A trial using IFN- γ as a nebulized mist is now ongoing (see Table 63-9).

ENDOTHELIN-RECEPTOR ANTAGONISTS. ET-1 contributes to the fibrotic phenotype of fibroblasts and is a downstream mediator of profibrotic responses to *transforming growth factor- β* (TGF- β).¹⁹² In a rat model, it was found that ET-1 is involved in the pathogenesis of lung fibrosis and that blockage of its receptors reduces the fibrosis.¹⁹³ *Bosentan* is a dual ET-1 receptor antagonist (ET_A and ET_B) that has been shown to be effective in the treatment of idiopathic PAH. In a large, randomized, multinational, double-blind, placebo-controlled trial in patients with IPF, bosentan did not show an improvement over placebo with respect to 6MWD (primary end point), but patients treated with this drug showed a tendency to delayed time to death or disease progression, a predefined secondary end point. A surprising and unexplained finding was that this treatment effect was significant in the subset of patients who underwent surgical lung biopsy for confirmation of diagnosis. In a subsequent prospective double-blind, placebo-controlled trial, 616

patients with IPF confirmed by surgical lung biopsy and without extensive honeycombing on HRCT were randomized 2:1 (bosentan to placebo).¹⁹⁴ Bosentan was well tolerated, but there was no difference in the treatment groups in primary end points (time to IPF worsening or death). There were no treatment effects on health-related quality of life or dyspnea.

ETANERCEPT. The introduction of targeted biologic agents directed against *tumor necrosis factor- α* (TNF- α) has represented a novel and exciting avenue for the treatment of a variety of diseases. Elevated levels of this cytokine have been detected in experimental lung fibrosis and in patients with IPF as well. The effect of etanercept, a recombinant soluble human TNF receptor that binds to TNF and neutralizes its activity in vitro, was explored in IPF patients.¹⁹⁵ Sixty-five patients (etanercept, $n = 34$; placebo, $n = 31$) completed the 48 weeks of treatment. No statistically significant differences were observed between treatment groups in the three primary end points: changes in FVC%, DL_{CO}%, and the (A-a)PO₂ (at rest) at 48 weeks. However, this can be due in part to the modest number of subjects included in the trial. In posthoc analysis, using rate of disease progression by death or absolute reduction in FVC (L), a tendency favoring etanercept was observed.

IMATINIB. Imatinib is a competitive tyrosine-kinase inhibitor developed in late 1990s that inhibits BCR-Abl tyrosine kinase, the constitutively active fusion product in chronic myelogenous leukemia.¹⁹⁶ It also inhibits tyrosine kinase for platelet-derived growth factor, c-Kit, and stem cell factor. Imatinib is used in the treatment of Philadelphia chromosome-positive chronic myeloid leukemia, c-kit-positive gastrointestinal stromal tumors, and other proliferative disorders. Imatinib has also been shown to be capable of blocking the TGF- β pathway and preventing bleomycin-mediated pulmonary fibrosis in an animal model.¹⁹⁷ A multicenter clinical trial comparing imatinib with placebo over 96 weeks in 119 patients was completed with the primary endpoint defined as time to progression (with progression defined as a 10% decline in percent predicted FVC from baseline) or time to death. There was no effect of imatinib therapy on the change in FVC or survival.¹⁹⁸

ANTICOAGULANTS. Excessive coagulant activity is thought to play a role in orchestrating fibrotic responses to tissue injury.¹⁹⁹ In 2005, Kubo and colleagues reported anticoagulant therapy was associated with better survival in a nonblinded prospective study of 56 IPF patients assigned to prednisolone alone or prednisolone plus anticoagulant therapy.^{199a} There appeared to be a substantial reduction in mortality associated with acute exacerbations of IPF. A subsequent randomized, double-blind, placebo-controlled study failed to show benefit of anticoagulant therapy in patients with progressive IPF.²⁰⁰ The study was terminated when an interim analysis showed an increase in mortality for those randomized to warfarin and a low likelihood of benefit. Ongoing clinical trials are summarized in Table 63-9.

TREATMENT OF GASTROESOPHAGEAL REFLUX. There is equipoise about how aggressively to pursue the diagnosis of gastroesophageal reflux and how aggressively to treat gastroesophageal reflux in patients with IPF. However, growing evidence suggests that there is a clinical benefit to treatment of gastroesophageal reflux with *proton pump inhibitors*

(PPIs) or *histamine-receptor-2* (H₂) blocker, despite concerns about the risks to medical treatment with PPIs (e.g., increased risk for community-acquired or hip fracture).^{6,102,201,202} Lee and coworkers²⁰¹ have shown that IPF patients taking antiacid treatment at baseline had a smaller decrease in FVC than did those not taking antacid treatment, less evidence of radiologic fibrosis, and a longer survival time.⁶ It is unknown if other measures used in the management of gastroesophageal reflux, such as lifestyle modifications (e.g., small meals, avoidance of certain foods and alcohol), other pharmaceutical interventions (e.g., prokinetics), or surgical barrier creation (e.g., Nissen fundoplication), have a role in the treatment of patients with IPF.^{202,203}

Lung Transplantation (see Chapter 106)

Since the late 1980s, lung transplantation has been used for the management of a wide range of severe lung disorders with progressive disease unresponsive to pharmacologic treatment, with evidence supporting quality of life and survival benefit for lung transplant recipients. The American Thoracic Society has published guidelines for the selection of IPF patients who should be considered potential transplant candidates.²⁰⁴

Unfortunately, given the scarcity of donors and the aging and disease complications of IPF patients, transplantation is indicated only in carefully selected patients. Early referral for consideration of transplant is highly desirable. It allows an orderly process for assessment, management of areas of concern, and patient education before active listing.²⁰⁴ Transplantation should be considered for patients who have signs or symptoms of progressive disease (including oxygen desaturation at rest or with exercise) with failure to improve or maintain lung function while being pharmacologically treated.²⁰⁴

According to the 2012 *International Society for Heart and Lung Transplantation/United Network of Organ Sharing* (ISHLT/UNOS) International Registry, the 1-year and 5-year survival rates following lung transplantation for IPF were 84% and 48%, respectively.^{205,206} One study compared survival of patients receiving transplantation for IPF ($n = 82$) with survival of patients receiving transplantation for non-IPF diagnoses ($n = 387$).²⁰⁷ Survival estimates after transplantation for IPF were 95%, 73%, 56%, and 44% at 30 days and 1, 3, and 5 years, slightly but significantly worse than for matched non-IPF patients. Survival for double- versus single-lung transplantation for IPF patients was 81% versus 67% at 1 year and 55% versus 34% at 5 years. These findings suggest survival after lung transplantation for IPF is worse than for other indications and that survival may be improved by double-lung transplant.²⁰⁷ However, a subsequent study using the UNOS data showed no difference between patients who had single- and double-lung transplant when adjusted for baseline differences.²⁰⁸

Regular review of patients on the waiting list is required to detect complications that may affect suitability for transplantation. Unfortunately, many IPF patients die while waiting. In this context, the lung allocation score was restructured in 2005 and replaced by an algorithm based on survival probability on the waiting list and after transplantation. The aim was to decrease the number of patients who die while on the waiting list. A recent study shows that

recipient diagnoses changed, with an increase in IPF and a decrease in emphysema and cystic fibrosis.²⁰⁹

Rehabilitation

Twelve weeks of combined inpatient and home-based rehabilitation programs (respiratory muscle training and bicycle riding to the limits of the patient's tolerance) has been shown to improve the quality of life and sensation of dyspnea in patients with ILD.²¹⁰ Pulmonary rehabilitation has also been shown to improve 6MWD and fatigue.²¹¹ The beneficial effects of pulmonary rehabilitation appear to be more pronounced in patients with worse baseline functional status.²¹²

Acute Exacerbations of Idiopathic Pulmonary Fibrosis

Some patients with IPF may experience a rapid deterioration in respiratory status after a period of relative stability.^{143,213,214} This acute worsening may be related to viral or bacterial infection, aspiration, or thromboembolic event. A growing body of evidence, however, indicates that many of these acute, clinically significant episodes are of unknown etiology; these have been termed *acute exacerbations of IPF*.²¹³ The overall incidence of acute exacerbations in the IPF population remains unknown but has been suggested to range from 5% to 10%.^{213,215} An analysis of the cause of death in the placebo arm of a large randomized clinical trial, however, showed that almost half of the deaths were acute in their onset after a period of decompensation that lasted 4 weeks or less, suggesting that acute exacerbations may be more frequent than usually believed.¹⁶¹ A recent study suggested the 1- and 3-year incidences of acute exacerbation in IPF to be 14% and 21%, respectively.²¹⁶

There is no established consensus on the diagnosis of acute exacerbation of IPF. Most definitions include a combination of the following data (over < 4 weeks): (1) severe worsening of dyspnea; (2) worsening hypoxemia (i.e., a fall in arterial $PO_2 > 10$ mm Hg); (3) new radiographic opacities, usually bilateral ground-glass opacities and consolidation superimposed on the reticular/honeycomb IPF pattern (eFig. 63-11); and (4) absence of an alternative explanation, such as infection, left heart failure, or pulmonary embolism.²¹⁶⁻²¹⁹ It has been suggested that the pattern of the new ground-glass opacities may differ in the patients with acute exacerbation and that these differences might have prognostic implications.^{219,220} Although radiographs of most patients typically show ground-glass attenuation at the periphery, near areas of underlying honeycombing, some demonstrate a multifocal or diffuse pattern (see Fig. 63-11) in previously uninvolved areas. Such cases seem to have a worse prognosis than patients with only peripheral involvement.²²¹ Biopsies or autopsies of most of these patients show *diffuse alveolar damage* (DAD) superimposed on underlying UIP. Occasionally, other patterns of acute lung injury may be seen, such as organizing pneumonia and extensive fibroblastic foci.^{217,218,222} Cell profiles on BAL usually show an increase in neutrophils or in both neutrophils and lymphocytes.

The etiology and pathogenesis of the acute exacerbations remain unknown. Disordered epithelial cell integrity, acute inflammation, excessive cytokines and matrix metalloproteinases, and an antifibrinolytic alveolar milieu

are all likely involved. Increased levels of *interleukin-8* (IL-8) and α -defensin have been reported in some patients, suggesting the importance of neutrophils.²¹³ Exaggerated levels of serum ST2 protein, an orphan receptor with unknown natural ligand, have also been reported.²²³ Importantly, ST2 is preferentially expressed on *type 2 T helper* (Th2) polarized cells expressing predominantly IL-4, IL-5, or IL-10 in vitro and ex vivo, indicating a role for activated (predominantly Th2) lymphocytes.²²⁴ More recently, antibodies to annexin-1 were detected in the sera and BAL from half of patients with acute exacerbation of IPF, supporting the hypothesis that pulmonary epithelial apoptosis may be important in this pathologic event.²²⁵

Once infections and other causes of worsening have been excluded, treatment has generally consisted of enhanced immunosuppression with pulse doses of methylprednisolone (0.5 to 1 g/day). Some studies have also reported the use of additional immunosuppression with cyclophosphamide or cyclosporine, but no convincing evidence of benefit has been demonstrated. Unfortunately, no data from controlled trials have proved the efficacy of any treatment for this condition.²²⁶

FAMILIAL PULMONARY FIBROSIS

The clinical, radiographic, physiologic, and morphologic manifestations of familial IPF are indistinguishable from the sporadic form of the disease.^{47,48,227} There may be a slight male predominance, and women tend to have a more favorable prognosis.^{47,48,228,229} It is estimated that familial cases account for 0.5% to 2.2% of all patients with IIPs, with a prevalence of 1.34 cases/10⁶ population in the United Kingdom.²²⁹ In Finland, it was estimated that the prevalence for familial IPF was 5.9/million population.²³⁰ The familial form explained 3.3% to 3.7% of all Finnish cases of IPF diagnosed according to the revised American Thoracic Society/European Respiratory Society international guidelines. Geographic clustering of patients with familial IPF has been noted, suggesting a “recent founder effect,” the nonrandom genetic sampling when a population derives from a small number of individuals.^{229,230} Importantly, familial pulmonary fibrosis has been associated with multiple pathologic subsets of the IIPs: *desquamate interstitial pneumonia* (DIP),²³¹ LIP,²³² and UIP.²²⁸

The genetic basis of familial pulmonary fibrosis is unclear and probably involves several genes. Thomas and associates²²⁸ showed that mutations in the SP-C gene (*SFTPC*) are associated with familial DIP and NSIP and may cause type II cellular injury. The authors hypothesized that the presence of two different pathologic diagnoses in affected relatives sharing this mutation indicates that in this kindred, these diseases may represent pleiotropic manifestations of the same central pathogenesis.²²⁸ Multiple heterozygous mutations in *SFTPC* have been reported in association with children suffering from ILD (DIP or NSIP), including familial and sporadic cases.^{233,234} In addition, a deficiency of SP-C has been described in a small kindred suffering from a poorly defined form of interstitial pneumonitis, despite no sequence variation in *SFTPC*.²³⁵ Taken together, these findings support a model in which misfolded pro-SP-C or SP-C can cause type II alveolar cell injury that results in ILD.²³⁵ As previously mentioned, germline mutations in the essen-

tial telomerase genes, *TERT* and *TERC*, leading to abnormal telomere shortening, are the causal genetic defect in about 15% of pulmonary fibrosis families. In the Finnish families, *ELMOD2*, a functionally uncharacterized gene, was identified as a novel candidate susceptibility gene.²³⁶

Steele and colleagues⁴⁷ evaluated 111 families with two or more cases of IIP among first-degree family members having 309 affected and 360 unaffected individuals. Older age, male gender, and having ever smoked cigarettes were associated with the development of IIP. Evidence of aggregation of disease was highly significant among sibling pairs, and 20 pedigrees demonstrated vertical transmission, consistent with autosomal dominant inheritance.⁴⁷

NONSPECIFIC INTERSTITIAL PNEUMONIA

NSIP originated as a histopathologic categorization reserved for surgical lung biopsies not demonstrating a clearly identifiable pattern, notably UIP, OP, LIP, and DAD among the IIPs.²³⁷ The histopathologic pattern of NSIP is found in a wide variety of diseases of known cause (e.g., hypersensitivity pneumonitis, drug-related, *acquired immunodeficiency syndrome* [AIDS], and collagen-vascular diseases).²³⁸ Moreover, many patients diagnosed with idiopathic NSIP meet the case definition of undifferentiated connective tissue disease, suggesting that idiopathic NSIP might actually be an autoimmune disease.^{239,240} In addition, it is estimated that up to 15% to 20% of patients who present with a chronic ILD either have an occult connective tissue disease or subsequently develop a clinically overt connective tissue disease. In this particular group of patients, the initial clinical presentation may be essentially indistinguishable from that of several IIPs (especially NSIP and less commonly UIP).²⁴¹

Clinical Features

The presentation is quite similar to that of other forms of idiopathic interstitial pneumonias (see [Tables 63-7](#) and [63-8](#)). Most patients are middle-aged adults with a subacute onset of symptoms approximately 8 months before diagnosis.^{133,237,238} In contrast to IPE, two thirds of the patients are women and, unlike patients with IPE, 70% are never smokers.²³⁸ Cough and dyspnea are the main clinical manifestations. Serologic abnormalities (antinuclear antibodies and rheumatoid factor) are common. BAL findings do not discriminate between UIP and NSIP and have no prognostic value.²⁴²

Chest Imaging Studies

Chest Radiography. In patients with early NSIP, the chest radiograph may be normal. In advanced disease, bilateral reticular or hazy opacities ([eFig. 63-12](#)) are the most prominent abnormality. The lower lung lobes are more frequently involved, but an obvious apical-basal gradient, as seen in UIP, is usually absent.^{237,238}

Computed Tomography Scan. In a recent review of 61 cases of confirmed idiopathic NSIP, the parenchymal abnormalities predominantly involved the lower lungs in the craniocaudal dimension. The most common HRCT features were a reticular pattern, traction bronchiectasis, and lobar volume loss.²³⁸ Ground-glass attenuation was present in



Figure 63-26 Nonspecific interstitial pneumonia. High-resolution chest CT image shows bilateral, patchy, ground-glass opacities without evidence of subpleural honeycombing.

nearly half of the cases (Fig. 63-26). Other findings in advanced NSIP include subpleural cysts (eFig. 63-13). Compared with those of UIP, these cysts are smaller and limited in extent.²⁴³ The major CT differential diagnosis for NSIP is UIP. Favoring the diagnosis of NSIP are the following findings: homogeneous lung involvement without an obvious apical-basal gradient, extensive ground-glass opacities, a finer reticular pattern, and micronodules. Importantly, during follow-up, ground-glass opacities in NSIP patients usually do not evolve to areas of honeycombing. By contrast, progression of ground-glass opacities to honeycombing is common in UIP and indicates irreversible fibrosis.²⁴⁴

Pulmonary Function Tests

Pulmonary function testing typically shows a restrictive ventilatory defect and gas-exchange abnormalities.

Pathologic Features

The histopathologic pattern of NSIP is characterized by temporally and spatially homogeneous lung involvement. This homogeneity is a key feature in differentiating the NSIP pattern from the UIP pattern. It is characterized by varying degrees of inflammation and fibrosis, with some cases having a primarily chronic inflammatory/cellular pattern (cellular NSIP) but most cases revealing a mixed cellular-fibrotic pattern (fibrotic NSIP)^{237,238} (Figs. 63-27 and 63-28). Cellular NSIP exhibits uniform alveolar septal infiltrates of lymphocytes and plasma cells. Neutrophils, eosinophils, and histiocytes are inconspicuous. Although NSIP may have significant fibrosis, it usually appears temporally uniform; fibroblastic foci and honeycombing, if present, are rare. Fibrotic NSIP can be difficult to distinguish from UIP, and significant interobserver variability among expert histopathologists exists.¹³⁴

Differential Diagnosis

Clinically, the most common diagnosis confused with fibrotic NSIP is IPF.^{34,133,237,238} It is essential that the pathologist not use terms like “UIP” or “NSIP” unless the defined criteria are met because some degree of fibrosis and inflammation is common in many ILDs and sampling error can be

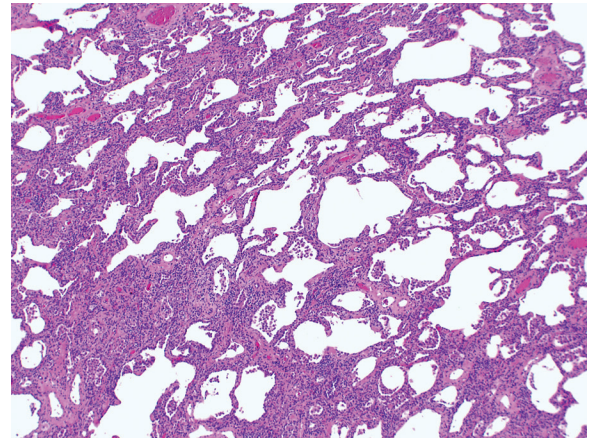


Figure 63-27 Photomicrograph of nonspecific interstitial pneumonia. Note the lymphoplasmacytic cells expanding the interstitial compartment. Alveolar macrophages are present also. (Original magnification $\times 10$.)

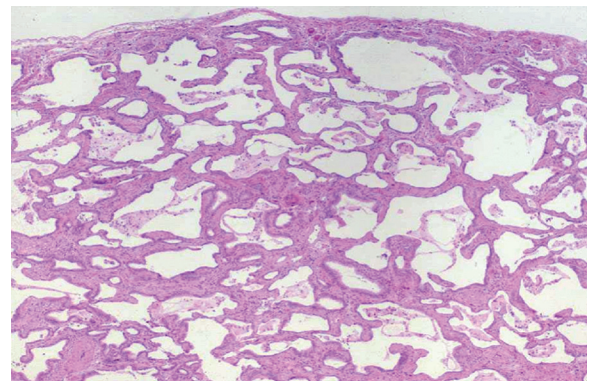


Figure 63-28 Photomicrograph of nonspecific interstitial pneumonia with a mixed cellular-fibrotic pattern. The alveolar walls are thickened by dense collagen and a few lymphocytes and plasma cells. The fibroblastic foci that are commonly found in the usual interstitial pneumonia pattern are not present in this lesion.

an issue, especially in small/inadequate surgical biopsies. Importantly, most biopsies showing an NSIP pattern are seen in patients who may have other conditions: an ill-defined or inadequately evaluated connective tissue disease, drug-induced ILD, chronic hypersensitivity pneumonitis, resolving acute lung injury (pneumonia or acute respiratory distress syndrome), or organizing pneumonia.^{32,150,245-249} The NSIP pattern on surgical lung biopsy should prompt the clinician to revisit the clinical data, carefully looking for these conditions.

Although it has been suggested that NSIP may represent early UIP, and while there is some histologic overlap and difficulties for pathologists in individual cases, this possibility is unlikely for several reasons. NSIP seems to develop predominantly in nonsmoking women, whereas UIP develops in smoking men.²³⁸ Early UIP (as well as advanced UIP) does not have significant inflammation but rather has scattered fibroblast foci. Finally, the patchwork pattern that is so characteristic of UIP is not seen in NSIP, and therefore, one would have to postulate that during progression, some areas of NSIP reverted to normal, whereas others evolved into fibrosis to become UIP.³⁶

Clinical Course and Outcome

Several retrospective studies indicate the survival rate of patients with idiopathic NSIP is significantly higher than those with UIP.^{133,134,237,238,250} This difference persists even after adjusting for age, gender, smoking history, and physiologic variables. Those patients with a purely cellular pattern on biopsy demonstrate the longest survival, indicating that prognosis depends primarily on the extent of fibrosis.^{150,238} In those patients who show an NSIP pattern in one lobe and a UIP pattern in another, the survival is similar to those with UIP. In NSIP, corticosteroids combined with azathioprine may be more effective than corticosteroids alone.

RESPIRATORY BRONCHIOLITIS–ASSOCIATED INTERSTITIAL LUNG DISEASE/DESQUAMATIVE INTERSTITIAL PNEUMONIA

Respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) and DIP are related and, in some cases, inseparable conditions because most cases appear to represent different stages of the same process.^{251–253} These diseases represent a distinct clinical syndrome found in current heavy smokers. The term *respiratory bronchiolitis–associated interstitial lung disease* is more anatomically accurate because it conveys important pathogenic implications compared with the older term “desquamative interstitial pneumonia.” Both (primarily RB-ILD) account for 15% to 20% of biopsied patients with IIPs (see [Tables 63-7](#) and [63-8](#)).^{254,255} Importantly, respiratory bronchiolitis is an accurate histologic marker of cigarette smoking, and it may be found many years after smoking ceases.²⁵⁶ The level of cytoplasmic pigmentation of macrophages and the presence of peribronchial fibrosis correlate with the pack-year smoking history.²⁵⁶ Moreover, it was recently reported that those with significant lifetime secondhand smoke exposure, especially in the previous 12 months, have significant increases in ground-glass opacities on HRCT, suggesting an early or subclinical respiratory bronchiolitis/DIP.²⁵⁷ Furthermore, RB/DIP-like histologic changes (1) are exceedingly common in PLCH, (2) may be sufficiently severe to cause the appearance of ground-glass opacities on HRCT, and (3) correlate with the cumulative exposure to cigarettes smoked.²⁵⁸ Although cigarette smoking is considered the main cause of RB-ILD/DIP, genetic abnormalities of surfactant function, specifically mutations in the genes coding for SP-B, SP-C, ABCA3, account for an increasing number of ILDs including DIP.^{259,260} In addition, DIP can be observed in various occupational or drug^{38,39,255} exposures.^{38,255,261}

Clinical Features

RB-ILD and DIP primarily afflict cigarette smokers between the third and the sixth decades of life.^{38,39,255} There is a male preponderance, with men affected nearly twice as often as women. Patients with either RB-ILD or DIP commonly present with insidious exertional dyspnea and persistent nonproductive cough. Less frequently, patients with DIP experience fatigue and weight loss. Coarse, bibasilar end-inspiratory crepitations are frequent findings on physical examination, whereas finger clubbing is uncommon.

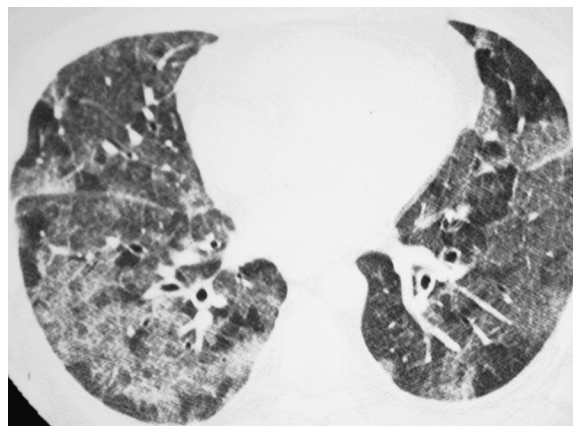


Figure 63-29 Desquamative interstitial pneumonia. Axial high-resolution CT shows patchy, multifocal ground-glass opacity associated with areas of interlobular septal thickening and intralobular interstitial thickening. (Courtesy Michael Gotway, MD.)

Chest Imaging Studies

Chest Radiography. The chest radiograph is insensitive for detection of RB-ILD and is often normal. Sometimes, bronchial wall thickening or reticular opacities can be seen ([eFig. 63-14](#)). Chest radiographs of DIP ([eFig. 63-15](#)) are nonspecific and usually reveal bilateral ground-glass opacities. Middle and lower lung field involvement with normal-appearing lung volumes predominates.^{38,39,255} Air bronchograms can be found when this process surrounds the airways. The honeycomb pattern is rare.

Computed Tomography Scan. The key HRCT features of RB-ILD include central bronchial wall thickening proximal to segmental bronchi, peripheral bronchial wall thickening distal to segmental bronchi, centrilobular nodules ([eFig. 63-16](#)), and areas of ground-glass opacity.^{253,262,263} ([Fig. 63-29](#)). Ground-glass opacifications may be diffuse or patchy, without basal or peripheral predominance.^{253,263,264} The predominant abnormality in DIP ([eFig. 63-17](#)) is the bilateral, moderately symmetrical, peripheral, and predominantly basal ground-glass attenuation. Tiny thin-walled cysts ([eFig. 63-18](#)) are noted within the ground-glass opacities in 30% to 60% of cases.^{265–267} A honeycombing pattern is rarely found.^{38,263,265,267}

There is occasional overlap in appearances between RB-ILD and DIP, although the ground-glass attenuation of DIP is usually more extensive, and nodules are infrequent or absent.²⁶⁸

Bronchoalveolar Lavage

BAL fluid in patients with RB-ILD/DIP is characterized by mild to moderate increases in total cell numbers, moderate to marked eosinophilia (a feature that in the absence of biopsy might raise the consideration of chronic eosinophilic pneumonia), and moderate neutrophilia.^{265,268}

Pulmonary Function Tests

Pulmonary function testing may be normal but usually shows mild to moderate restriction, normal or slightly reduced diffusing capacity, and mild hypoxemia.^{38,39,268} A mixed obstructive-restrictive pattern is common, although there may be an isolated increase in residual volume.

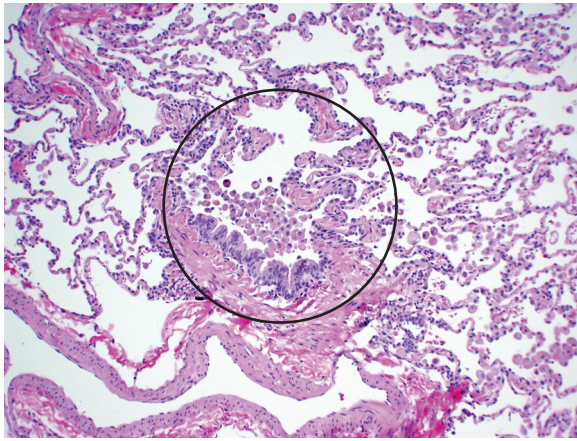


Figure 63-30 Photomicrograph of respiratory bronchiolitis. There is an ectatic small airway (circle), with thickened walls and extension of the bronchiolar metaplastic epithelium into the immediately surrounding alveoli. Intraluminal macrophages are also present within the peribronchiolar alveolar spaces.

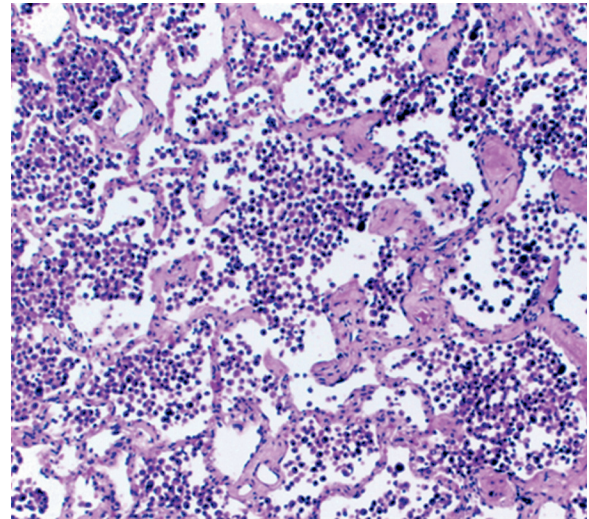


Figure 63-31 Photomicrograph of desquamative interstitial pneumonia. Characteristic dense collections of macrophages are seen filling alveolar lumens. (Original magnification $\times 100$.)

Pathologic Features

The cardinal feature of RB-ILD is the accumulation of alveolar macrophages within the bronchioles, including the terminal and respiratory bronchioles, variably extending into alveolar ducts and alveoli.^{37,254,256,269} In contrast to RB-ILD, DIP shows a much more widespread and uniform filling of all alveoli, although in any given biopsy one can find low-power fields showing only RB-ILD type changes and others typical of DIP. This histologic observation supports the close association of RB-ILD and DIP. Macrophages are characterized by glassy eosinophilic cytoplasm, usually with brown and finely granular pigmentation (representing constituents of cigarette smoke).^{32,254,268,269} There is often a chronic inflammatory cell infiltrate in bronchiolar and surrounding alveolar walls. The changes are patchy at low magnification and have a distinctly bronchiolocentric distribution without the associated diffuse involvement and interstitial pneumonia necessary for a diagnosis of DIP (Fig. 63-30).²⁵⁴

Bedrossian and coworkers²⁷⁰ coined the term *DIP-like reaction* to identify prominent intra-alveolar macrophage accumulation around space-occupying pulmonary lesions. This DIP-like reaction can be seen in a number of other processes, including pulmonary Langerhans cell histiocytosis, drug reactions (e.g., amiodarone), chronic alveolar hemorrhage, eosinophilic pneumonia, pneumoconioses (e.g., talcosis, hard-metal disease, asbestosis), obstructive pneumonias, and exogenous lipid pneumonia.^{8,271} In these cases, however, the DIP-like reaction is usually focal, without the uniform involvement of lung parenchyma seen in true cases of RB-ILD/DIP.

As mentioned, the histologic hallmark of DIP is the uniform filling of the alveolar spaces by cohesive clusters of numerous pigmented alveolar macrophages, including occasional multinucleated cells, eosinophils, and lymphocytes.^{254,271} Alveolar septa are thickened by a sparse inflammatory infiltrate and lined by uniform hyperplastic type II pneumocytes. Peribronchiolar lymphoid hyperplasia is seen in the majority of cases (Fig. 63-31).^{254,271}

The majority of DIP cases show a difference in the degree of pathologic change from one lobule to the next in a given biopsy specimen. Some degree of architectural destruction is usually observed. Akira and colleagues²⁶⁷ have pointed out the presence of dilated alveolar ducts and bronchioles and/or pulmonary cysts, which corresponded to cystic spaces on HRCT.²⁶⁵

Clinical Course and Outcome

Because there has not been a longitudinal study of a large group of subjects, the clinical course and prognosis of patients with RB-ILD are unknown. Most studies suggest a favorable response to smoking cessation and the use of corticosteroids, with documented improvement in lung function and chest radiographs²⁶⁹; few deaths secondary to progressive lung disease have been reported.³⁹

Patients with the DIP stage of this process also have a good prognosis. Carrington and associates²⁶¹ reported a 28% mortality after an average survival of 12 years. Other studies have shown similar results, but additional study of a larger number of subjects is necessary.^{38,263,267,269} In another study, symptomatic improvement (i.e., improved cough, dyspnea, or both) with prednisone treatment was noted in 24% of patients with DIP and 55% of patients with RB-ILD.³⁸ Objective improvement with prednisone treatment, as evidenced by improvement in pulmonary function measurements or parenchymal opacities seen on chest radiography or CT scans, was noted in 33% of patients with DIP and 64% of patients with RB-ILD.³⁸ Unfortunately, these positive responses tended to be transient in half of the patients with tapering and discontinuation of prednisone treatment. Patients can regress back to the baseline status even in the absence of smoking.³⁸

Nevertheless, because smoking plays a major role in the pathogenesis, smoking cessation is always indicated in these patients. In a recent study, both clinical symptoms and DL_{CO} improved significantly following smoking cessation, as did ground-glass opacities and centrilobular nodules seen on the initial HRCT examination.²⁷² Corticosteroids

may be required in refractory or recurrent cases but should not be instituted in the absence of smoking cessation.

ACUTE INTERSTITIAL PNEUMONIA

AIP is a rare, fulminant form of lung injury that presents acutely (days to weeks from onset of symptoms), usually in a previously healthy individual.²⁷³⁻²⁷⁵ AIP likely represents a subset of cases of idiopathic acute respiratory distress syndrome and is what Hamman and Rich²⁷⁶ described and termed “acute diffuse interstitial fibrosis” (see [Tables 63-7](#) and [63-8](#)).

Clinical Features

Most patients are older than 40 (mean age, 50 years; range, 7 to 83 years).^{273,274} Men and women are equally affected, and cigarette smoking does not seem to increase the risk for development of AIP. A prodromal illness, usually lasting 7 to 14 days before presentation, is common. The clinical signs and symptoms include fever, cough, and shortness of breath. Routine laboratory studies are nonspecific and generally not helpful.

Chest Imaging Studies

Chest Radiography. Diffuse, bilateral, air space opacification is seen on chest radiograph ([eFig. 63-19](#)).²⁷⁷⁻²⁷⁹

Computed Tomography Scan. The typical HRCT features of AIP are bilateral, multifocal or diffuse areas of ground-glass opacity and consolidation, usually without pleural effusion ([eFig. 63-20](#)).^{50,51,60,277} A predominantly subpleural distribution may be seen. These radiographic findings are similar to those seen in the acute respiratory distress syndrome; however, patients with AIP are more likely to have a symmetrical, bilateral distribution with a lower lobe predominance.²⁸⁰ In the early phase of AIP, ground-glass opacities and less extensive areas of consolidation are the dominant CT pattern, reflecting the presence of alveolar septal edema and hyaline membranes.⁵¹ During the organizing phase of the disease, HRCT findings consistent with evolving fibrosis are often present, including traction bronchiectasis, reticular opacities, and architectural distortion.²⁸¹ In this phase, consolidations resulting from intra-alveolar fibrosis may also be present. Mild honeycombing, usually involving less than 10% of the lung, may be seen on CT.²⁷⁷

Pulmonary Function Tests

Most patients have moderate to severe hypoxemia and develop respiratory failure.²⁷³⁻²⁷⁵

Pathologic Features

A surgical lung biopsy is required to confirm the diagnosis of AIP.^{32,254,273} The histopathologic pattern seen in AIP is DAD, which can be categorized into an early exudative phase, an organizing phase, and a chronic phase, depending on the timing of the biopsy in relation to the lung insult. DAD develops after an acute injury to the alveolar capillary basement membranes.^{273,275} DAD is common and also seen in immunosuppressed patients who have received cytotoxic drugs or who have developed diffuse infectious pneumonias, as well as in a number of other settings.²⁸²⁻²⁸⁴

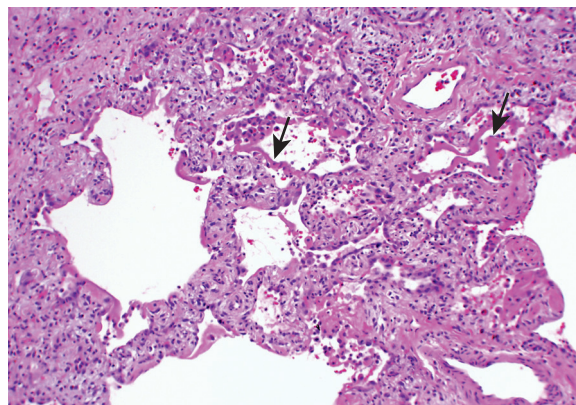


Figure 63-32 Photomicrograph of acute interstitial pneumonia shows diffuse alveolar damage. Note the hyaline membranes (arrows) within alveolar spaces and edema and inflammatory cell infiltration of the alveolar wall. (Original magnification $\times 10$.)

After the endothelial-epithelial injury, there is leakage of serum proteins and red blood cells into the alveolar spaces. The alveolar epithelium becomes necrotic and is sloughed, and the interstitium becomes edematous. Hyaline membranes, recognized as eosinophilic debris and consisting of necrotic epithelial cells, protein, and fibrin, form within alveolar spaces ([Fig. 63-32](#)). In the reparative or organizing stage of DAD, there is proliferation and hyperplasia of the alveolar type II epithelial cells, often showing nuclear enlargement and prominent nucleoli. Extensive fibroblast proliferation is a dominant finding in the organizing phase; proliferating fibroblasts and myofibroblasts within a myxoid basophilic matrix may be seen within alveolar septa or in the alveoli (resembling organizing pneumonia).²⁵⁴ Fibrin thrombi are often present. In some cases, these pathologic changes may resolve, but in others, perhaps due to protracted or repeated parenchymal injury, irreversible fibrosis and honeycomb lung result.

Clinical Course and Outcome

Treatment is largely supportive and consists of mechanical ventilation and oxygen supplementation.^{273,274,279,282} Corticosteroids seem to be effective in the early phase of disease. According to most studies, the mortality from AIP appears to be high (>50%), with the majority of patients dying within 3 months of presentation.^{273-275,279} Most survivors of AIP experienced recurrences and chronic, progressive ILD.²⁷⁹ However, a lower hospital mortality (12.5%) with no evidence of either recurrent or progressive disease has been also described.²⁸⁵

CRYPTOGENIC ORGANIZING PNEUMONIA

Organizing pneumonia (OP) can be cryptogenic (i.e., COP) or result from various forms of lung injuries (e.g., postinfectious, drug related, connective tissue disease related, post-transplant, hypersensitivity pneumonitis, radiation, or aspiration of particulate matter). COP is a specific clinicopathologic syndrome characterized by a “pneumonia-like” illness, with excessive proliferation of granulation tissue inside the alveolar spaces associated with chronic inflammation in the surrounding alveoli.^{32,33,40} The pathologic process may also involve the small airways (*bronchiolitis*

obliterans with organizing pneumonia [BOOP]) (see Tables 63-7 and 63-8). There are no major differences in clinical features of COP and secondary OP.²⁸⁶⁻²⁸⁸ OP may also be seen accompanying other histopathologic patterns (e.g., UIP). The diagnosis of COP is reserved for isolated OP in patients without an identifiable associated disease. The term *idiopathic BOOP* historically encompassed COP but is no longer recommended for this idiopathic condition.³²

Clinical Features

The incidence of COP is similar in both men and women.²⁸⁷ The mean age at presentation is about 50 to 55 (range, 21 to 80). Patients with COP are frequently specific about the timing of their disease onset. This is because the disease onset is recent (usually < 2 months) and is often dramatic, with the development of a flulike illness characterized by cough, mild dyspnea, fever, malaise, fatigue, and weight loss. Physical examination usually discloses focal sparse crackles but may be almost normal. Finger clubbing is rare.

Routine laboratory studies are nonspecific. A leukocytosis without increase in eosinophils is seen in approximately half the patients. The initial erythrocyte sedimentation rate is frequently elevated in patients with COP.

Chest Imaging Studies

Chest Radiography. The radiographic manifestations are distinctive, usually including unilateral or bilateral patchy consolidations that resemble pneumonic opacities in the presence of normal lung volumes (eFig. 63-21).^{50,289} A peripheral distribution of the opacities, similar to that thought to be “virtually pathognomonic” for chronic eosinophilic pneumonia, is commonly seen in COP.^{288,290,291} Irregular linear or nodular interstitial opacities are rarely present as the only radiographic manifestation (eFig. 63-22).²⁹² Honeycombing is rare and is seen only as a late manifestation in the few patients with progressive disease. Other radiographic abnormalities, such as pleural effusion, pleural thickening, hyperinflation, and cavities, are uncommon.

Computed Tomography Scan. CT scans of the lung reveal patchy air space consolidation, small nodular opacities, and bronchial wall thickening and dilation, most frequently in the periphery of the lung and often in the lower lung zones^{55,289,290,292} (Fig. 63-33, Video 63-2). Frequently, the CT findings are far more extensive than are expected by review of the chest radiograph. These opacities tend to migrate and decrease in size, even without treatment (eFig. 63-23). The CT finding of consolidation is associated with partial or complete resolution, whereas reticular opacities are associated with persistent or progressive disease (eFig. 63-24).²⁹³ Sometimes, COP shows unique findings such as the reversed halo sign (eFig. 63-25), which is defined as central ground-glass opacity surrounded by more dense air space consolidation of crescentic and ring shapes. This sign is seen in around 20% of patients with COP.²⁹⁴ The presence of enlarged nodes is less common in COP than in the other IIPs.²⁹⁵

Focal OP has been described as a discrete form of COP and presents as an isolated focal lesion on chest imaging.²⁹⁶⁻²⁹⁸ Many of these patients are asymptomatic,

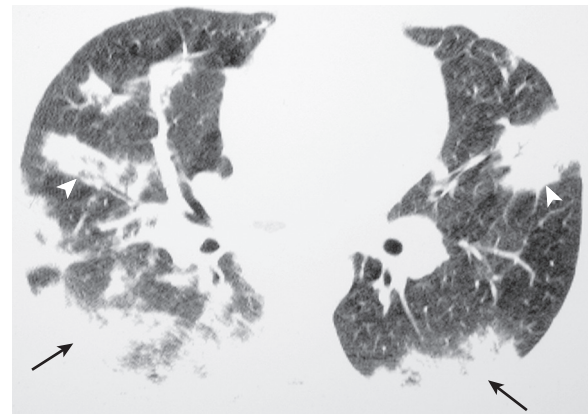


Figure 63-33 Cryptogenic organizing pneumonia. Axial CT shows areas of peripheral (arrows) and peribronchovascular (arrowheads) consolidation. (Courtesy Michael Gotway, MD.)

and the lesion is discovered by chest radiograph or CT. It may be suspected to be a putative lung cancer because most patients have a smoking history and are middle-aged or older.²⁹⁸

Pulmonary Function Tests

Pulmonary function is usually impaired, with a restrictive defect being most common, although an obstructive defect (FEV₁/FVC ratio < 70%) is found in almost one fifth of subjects with COP, mostly in current or former smokers.^{287,299} Gas-exchange abnormalities are extremely common, with resting and exercise arterial hypoxemia. The DL_{CO} is reduced (<80% of predicted) in three fourths of patients.

Bronchoalveolar Lavage

An increase in lymphocytes (20% to 40%), neutrophils (10%), and eosinophils (5%), with the level of lymphocytes higher than that of eosinophils, is the most common pattern at differential cell count.²⁸⁷ BAL lymphocytes are activated and the CD4/CD8 ratio is usually decreased. An increase of plasma cells and/or mast cells may also be seen.

Pathologic Features

The diagnosis of COP depends on both the clinical setting and the finding of the characteristic pathologic features. Intraluminal fibroblastic buds, also called Masson bodies, seen in respiratory bronchioles, alveolar ducts, and alveoli are the most prominent feature.^{32,250,300} Other pathologic features include foamy cells in the alveolar spaces, prominent type II cell hyperplasia, interstitial infiltrates, and fibrinous exudates.

OP is recognized by the appearance in the small airways of intraluminal collections of proliferating fibroblasts and myofibroblasts in a mucopolysaccharide-rich matrix. It is most prominent in the alveolar ducts but extends distally to the alveolar lumina and proximally to the bronchioles (Fig. 63-34). These Masson bodies may also extend from one alveolus to the next through the interalveolar pores, giving a characteristic “butterfly pattern.”²⁸⁷ OP can also show an interstitial lymphoplasmacytic infiltrate and hyperplasia of the type II epithelial cells. The organizing process, which may extend into the bronchioles, produces an intraluminal polypoid bronchiolitis obliterans (Fig. 63-35). OP represents a common reparative response to injury seen in a

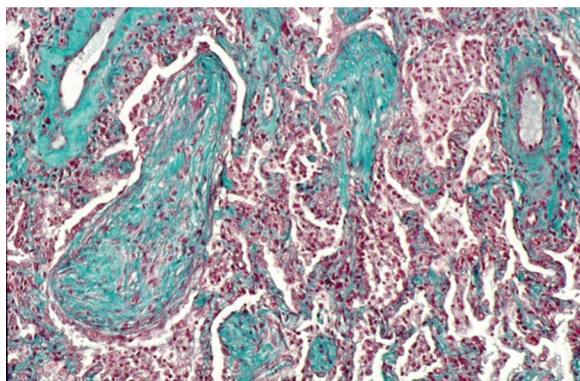


Figure 63-34 Photomicrograph indicates organizing pneumonia. Immature connective tissue and proliferating fibroblasts appearing blue/green (pentachrome stain) (also called Masson bodies) are present in alveolar ducts and alveolar spaces, and there is an interstitial infiltrate consisting of mononuclear cells. (Original magnification $\times 40$.)

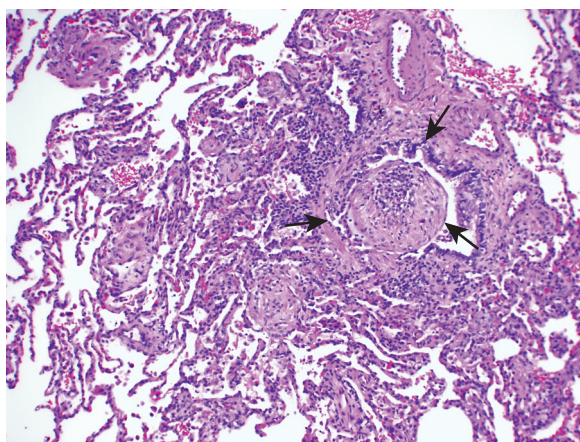


Figure 63-35 Photomicrograph of organizing pneumonia. There is a typical inflammatory polyp extending into the lumen of a terminal bronchiole (arrows). (Original magnification $\times 40$.)

variety of ILDs, infectious pneumonias, and many other processes. If the injury is unresponsive to treatment, progression to irreversible fibrosis and a honeycombed lung can result.

Clinical Course and Outcome

Corticosteroid therapy results in complete clinical, radiologic (eFig. 63-26), and physiologic recovery in two thirds of patients.²⁸⁷ One third demonstrates recurrent or persistent disease. Secondary OP (e.g., OP associated with connective tissue diseases), is less likely to respond to corticosteroids. In general, clinical improvement is rapid, within several days or a few weeks. Occasionally, recovery is quite dramatic. Patients can relapse when the corticosteroids are withdrawn, usually within 1 to 3 months. Most relapsed patients will improve when retreated with corticosteroids.³⁰¹ It has been suggested that COP may also respond to macrolide therapy, but studies are scanty.³⁰² A few patients may improve spontaneously over 3 to 6 months.^{287,303} A seasonal (early spring) presentation of COP with relapse every year at the same period has been reported.³⁰⁴ Few of the patients with COP die as a result of this illness, but those prone to develop a rapidly progressive

Table 63-10 Diseases Associated with Lymphocytic Interstitial Pneumonitis

AUTOIMMUNE DISEASE

Sjögren syndrome
Primary biliary cirrhosis
Myasthenia gravis
Hashimoto thyroiditis
Pernicious anemia
Autoimmune hemolytic anemia
Systemic lupus erythematosus

DISEASE WITH DYSPROTEINEMIA

Hypogammaglobulinemia
Polyclonal gammopathy

INFECTIONS

Human immunodeficiency virus
Epstein-Barr virus
HTLV-1
Legionella pneumonia
Tuberculosis

MISCELLANEOUS

Celiac sprue
Diphenylhydantoin
Allogeneic hematopoietic stem cell transplantation
Surfactant protein C deficiency

HTLV-1, human T-cell lymphotropic virus type 1.

Adapted from Cosgrove GP, Fessler MB, Schwarz MI: Lymphoplasmacytic infiltrations of the lung. In Schwarz MI, King TE Jr, editors: *Interstitial lung diseases*, ed 4. Hamilton, Ontario, Canada, 2003, BC Decker, p 827.

fatal form of OP have a clinical course similar to AIP.³⁰⁵ In such patients, the diagnosis is usually delayed or missed.

The majority of cases of focal OP are cryptogenic, do not recur after surgical resection, and do not require corticosteroid therapy.^{298,306,307}

IDIOPATHIC LYMPHOCYTIC INTERSTITIAL PNEUMONIA

LIP is an uncommon pathologic pattern characterized by the presence of widespread, monotonous sheets of lymphocytic infiltration in the interstitium of the lung.³⁰⁸⁻³¹⁰ Idiopathic LIP is rare and, in addition to being differentiated from other IIPs, it must be distinguished from other lymphocytic infiltrations in the lung, notably lymphomas, and ILDs associated with prominent lymphoid infiltrates such as collagen vascular diseases (especially Sjögren syndrome); dysproteinemia; drug reactions; hypersensitivity pneumonitis; immunodeficiency syndromes (e.g., HIV, combined variable immunodeficiency); and hematopoietic stem cell transplantation. The LIP pattern is far more common as a secondary disease in association with systemic disorders and most of the prior reports on LIP included such cases (Table 63-10).³¹¹⁻³¹⁴

Clinical Features

Patients most commonly present with progressive dyspnea and cough, although they may also have weight loss, pleuritic pain, arthralgias, and fever.³⁰⁸⁻³¹⁰ Bibasilar crackles are present on chest auscultation in most patients. Digital clubbing is usually absent and cyanosis is a rare physical finding. Extrapulmonary findings related to the underlying disease process may be present.

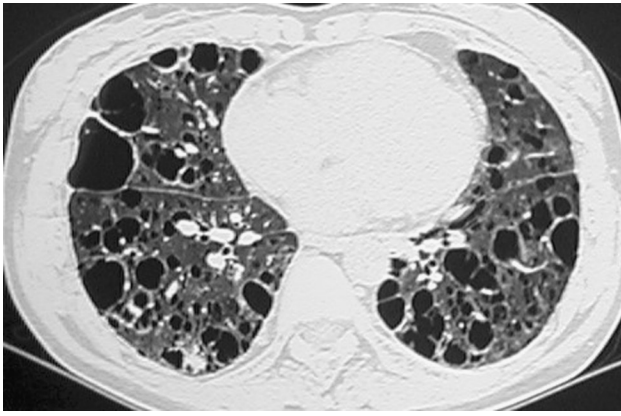


Figure 63-36 Lymphocytic interstitial pneumonia. High-resolution CT image shows diffuse cysts.

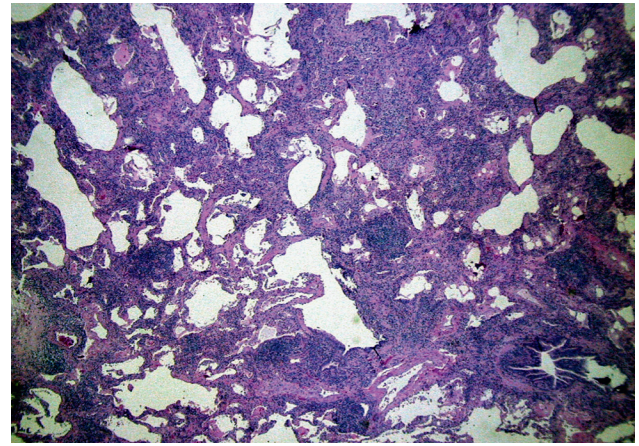


Figure 63-37 Photomicrograph of lymphocytic interstitial pneumonia. A diffuse lymphoid infiltrate extends through the pulmonary interstitium. (Original magnification $\times 10$.)

Chest Imaging Studies

Chest Radiography. The chest radiograph is nonspecific, with reticular opacities (eFig. 63-27) being the most frequent abnormality. A mixed alveolar-interstitial pattern appears as the disease progresses because of the coalescence of the opacities. Cysts, honeycombing, and pulmonary hypertension are also late manifestations.³¹⁵ Pleural effusions are infrequent and suggest a complicating lymphoma.

Computed Tomography Scan. The main parenchymal abnormalities on the initial CT scan consisted of ground-glass attenuation (eFig. 63-28), thickening of interlobular septa, centrilobular nodules (eFig. 63-29), thin-walled perivascular cysts, and air space consolidation (see eFig. 63-28)^{55,313} (Fig. 63-36). In contrast to the subpleural, lower lung cystic changes in UIP, the cysts of LIP are usually within the lung parenchyma throughout the mid lung zones and presumably result from air trapping due to peribronchiolar cellular infiltration.³¹³⁻³¹⁵ The cysts may be seen in up to 80% of patients and are typically few in number, measuring less than 3 cm in diameter. On follow-up CT, most patients improve, although several show increased extent of disease (eFig. 63-30). With the exception of cysts, the parenchymal opacities are reversible.³¹⁴ New cysts develop in a few patients; these develop mainly in areas with centrilobular nodules on initial CT. Honeycombing has been seen on follow-up CT in several patients in areas of previous air space consolidation on the initial CT.³¹⁴

Pulmonary Function Tests

A restrictive defect including reduced FVC, elevated FEV₁/FVC, and reduced TLC is commonly seen and is often associated with a reduction in the DL_{CO} and arterial hypoxemia.³⁰⁸⁻³¹⁰

Bronchoalveolar Lavage

A striking T-cell lymphocytosis is seen on BAL.³⁰⁹

Pathologic Features

Surgical lung biopsy is generally required for the diagnosis. The lymphocytic infiltration is usually extensive and severe, involving the alveolar septa and peribronchiolar and perivascular interstitium^{32,33,308} (Fig. 63-37). Reactive lymphoid follicles are often present and distributed along the peribronchiolar regions. The lymphocytes are polytypic (both B and T cells may be found), distinguishing them from the monotypic lymphocytic infiltrates characteristic of pulmonary lymphoma. The number of plasma cells and macrophages is also increased in these infiltrates.

LIP is distinguished from DIP and NSIP by the marked density of the lymphoid infiltrate in the former, although there are no precise criteria.^{32,33,308} Other features include the interstitial accumulation of macrophages, noncaseating granulomas, perivascular amyloid deposits, and germinal lymphoid centers.

LIP is distinguished from DIP and NSIP by the marked density of the lymphoid infiltrate in the former, although there are no precise criteria.^{32,33,308} Other features include the interstitial accumulation of macrophages, noncaseating granulomas, perivascular amyloid deposits, and germinal lymphoid centers.

Clinical Course and Outcome

The clinical course of idiopathic LIP is unknown. In cases in which LIP is associated with another disease, the underlying disease largely determines the outcome. In many case reports, marked improvement or complete resolution has followed corticosteroid therapy.³⁰⁹⁻³¹¹ However, patients can progress to pulmonary fibrosis, cor pulmonale, and death despite therapy. Infection is a common complication, especially in those with an associated dysproteinemia.³⁰⁹⁻³¹² Progression to pulmonary or systemic lymphoma appears to be rare and it is likely that, in this group of patients, malignant lymphoma was present from the outset.^{310,312,316,317}

IDIOPATHIC PLEUROPARENCHYMAL FIBROELASTOSIS

Idiopathic pleuroparenchymal fibroelastosis is another rare form of IIP and is characterized by a fibrotic process involving the pleura and subjacent parenchyma with a predominantly upper lobe distribution.³¹⁸⁻³²⁰ Patients with idiopathic pleuroparenchymal fibroelastosis present with exertional dyspnea with or without cough. A history of repeated lower respiratory tract infections may be elicited in some of these patients.³²⁰

CT features consist of bilateral irregular pleuroparenchymal thickening resulting from the fibrotic process and is more prominent in the upper and middle zones (eFig. 63-31).^{318,320,321} Histopathologic features include intra-alveolar fibrosis with septal elastosis.³¹⁸⁻³²⁰

The majority of patients with idiopathic pleuroparenchymal fibroelastosis experience disease progression. In a report by Reddy and colleagues,³²⁰ 5 of 10 patients died within 2 years of diagnosis. Prednisone treatment even with additional immunosuppressive therapy did not appear to have a beneficial effect.

Key Points

- Interstitial lung diseases include inflammatory and fibrotic diseases that ultimately disrupt the alveolar-capillary interface, leading to hypoxemia.
- Interstitial lung diseases arise in many diverse clinical settings, including connective tissue disease; occupational, environmental and drug exposures; and primary pulmonary disorders.
- In some patients, correlation of the clinical context (detailed history and examination along with relevant laboratory results) and radiologic features can establish the likely diagnosis.
- Ultimately, histopathologic examination of lung tissue (more often by surgical lung biopsy than bronchoscopic biopsy) may be necessary to confirm a specific diagnosis in interstitial lung disease.
- Idiopathic interstitial pneumonias are a subgroup of interstitial lung diseases of unknown etiology and are associated with variable radiologic features, response to therapy, and clinical course.
- Idiopathic pulmonary fibrosis is the most common of the interstitial lung diseases and is progressive, irreversible, and usually fatal with a portion of these deaths attributed to the phenomenon of “acute exacerbation.”
- The U.S. Federal Drug Administration has approved pirfenidone and nintedanib for the treatment of idiopathic pulmonary fibrosis.
- *Nonspecific interstitial pneumonia* (NSIP) is characterized by diffuse, temporally, and geographically homogeneous cellular infiltrates (cellular NSIP) or fibrosis (fibrotic NSIP). NSIP is often associated with collagen vascular diseases, drug-induced disease, and hypersensitivity pneumonitis among others. In general, patients with NSIP (especially cellular NSIP) fare better than those with idiopathic pulmonary fibrosis.

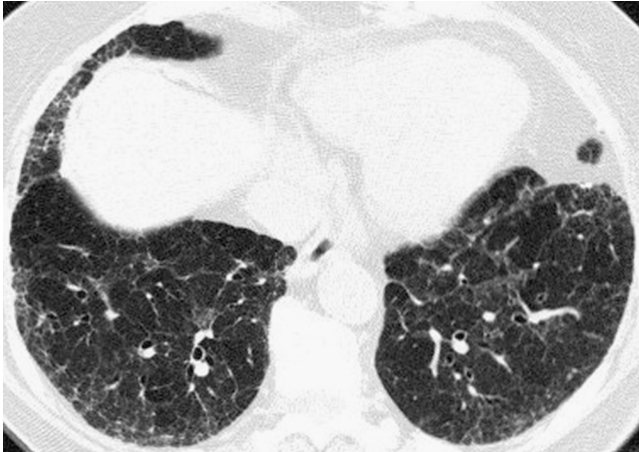
- Respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonia are smoking-related in most patients.

Complete reference list available at **ExpertConsult**.

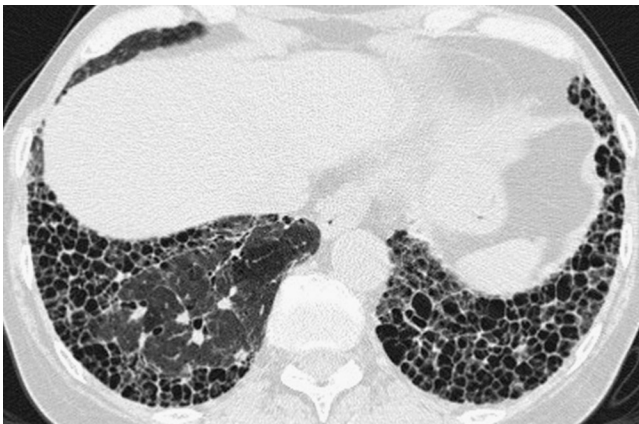
Key Readings

- American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias: This joint statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 165:277–304, 2002.
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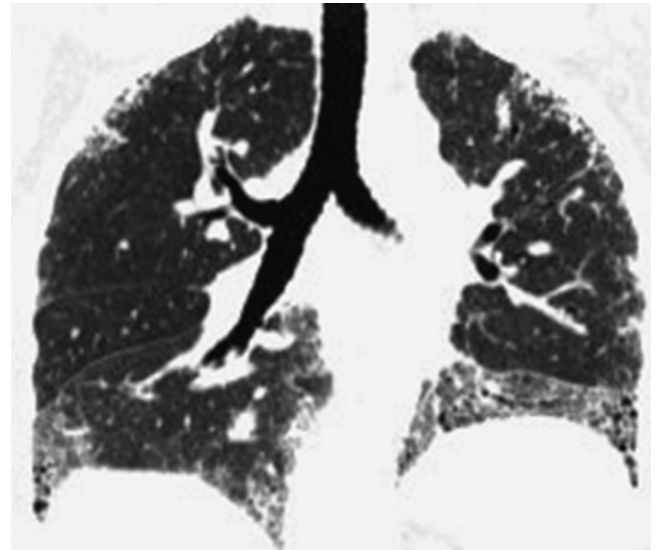
eFIGURE IMAGE GALLERY



eFigure 63-1 CT of “early” usual interstitial pneumonia/idiopathic pulmonary fibrosis. Axial chest CT through the lung bases shows subpleural reticulation and architectural distortion with areas of traction bronchiectasis, but no discrete honeycombing is visualized. (Courtesy Michael Gotway, MD.)



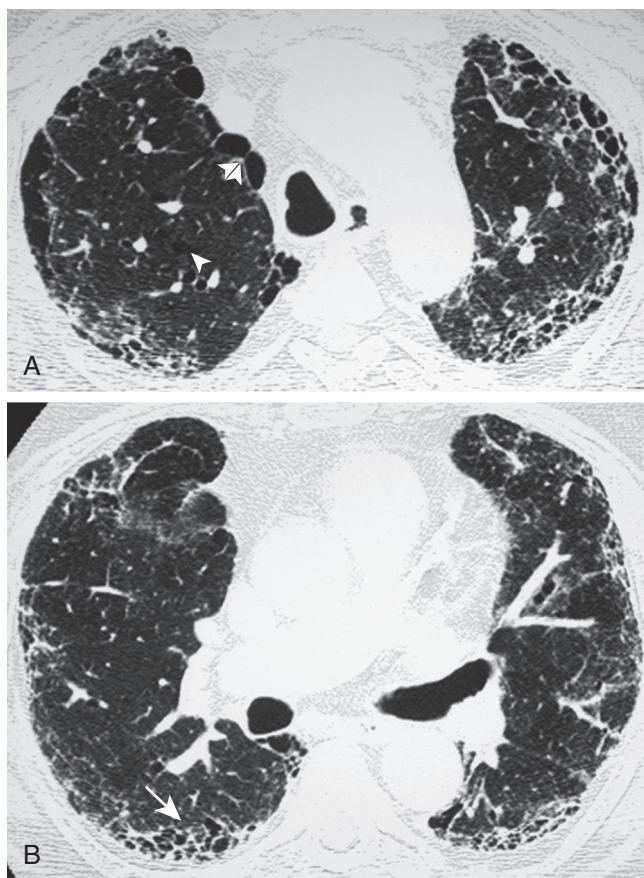
eFigure 63-2 CT of advanced IPF. Axial chest CT through the lung bases shows extensive basal and subpleural honeycombing. (Courtesy Michael Gotway, MD.)



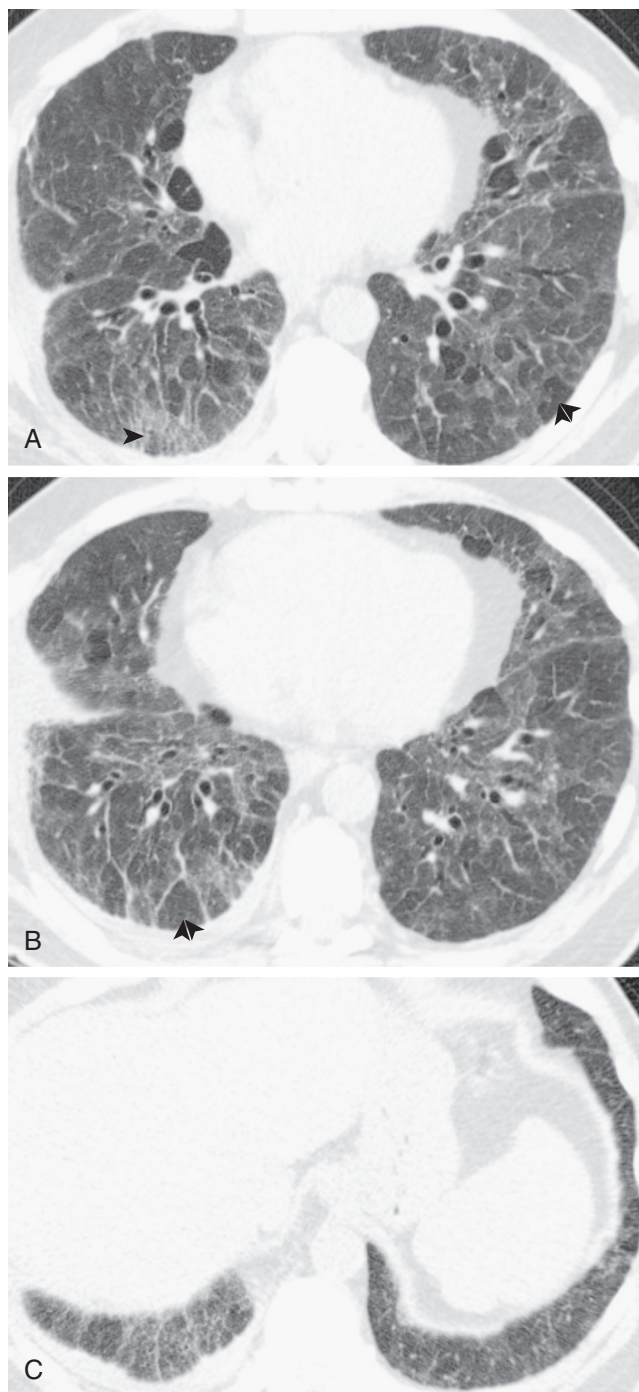
eFigure 63-3 Value of coronal CT for demonstrating the basal distribution of pulmonary findings in interstitial pneumonia/idiopathic pulmonary fibrosis. Coronal chest CT shows subpleural reticulation and basal predominant honeycombing. This single image captures the basal predominant nature of the high-resolution CT (HRCT) findings in patients with idiopathic pulmonary fibrosis. (Courtesy Michael Gotway, MD.)



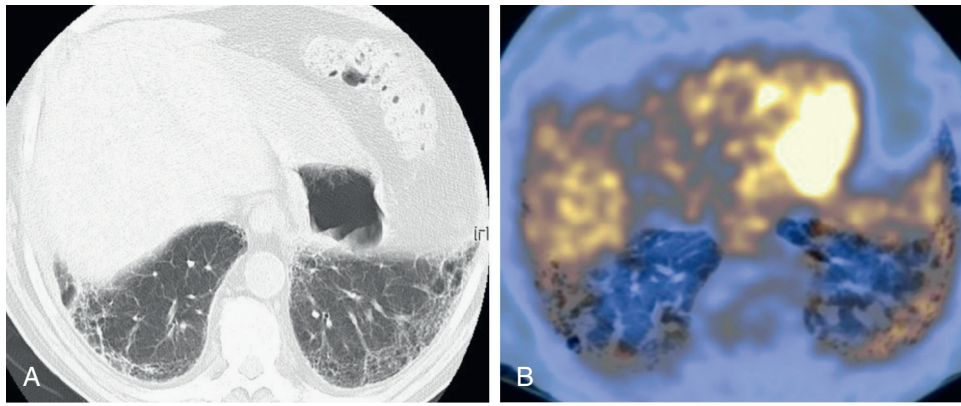
eFigure 63-4 Honeycombing on HRCT in usual interstitial pneumonia/idiopathic pulmonary fibrosis. Axial prone chest CT through the lung bases shows extensive subpleural cystic change consistent with honeycomb lung. Note how the cyst walls are visible, are mildly thickened (measuring 1 to 2 mm), and share walls with one another. (Courtesy Michael Gotway, MD.)



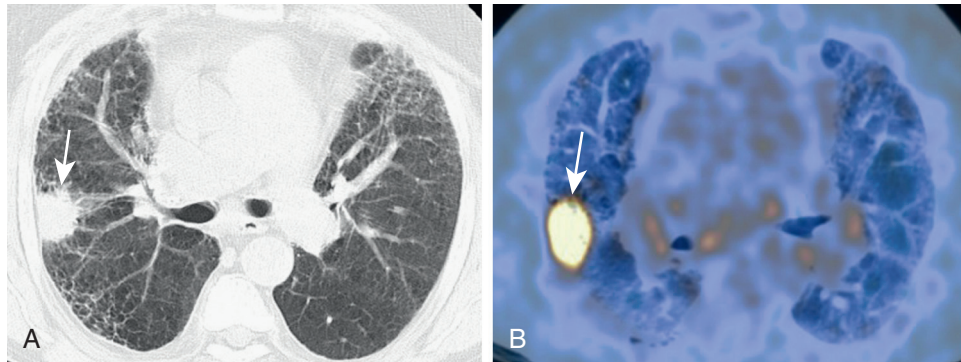
eFigure 63-5 CT of combined pulmonary fibrosis and emphysema. Axial chest CT through the upper lungs (**A**) and lung bases (**B**) shows centrilobular (*single arrowhead*) and paraseptal (*double arrowheads*) emphysema, with basal predominant reticulation, architectural distortion, and honeycombing (*arrow*), the latter consistent with interstitial pneumonia/idiopathic pulmonary fibrosis. (See [Video 63-1](#) for another example from a different patient.) (Courtesy Michael Gotway, MD.)



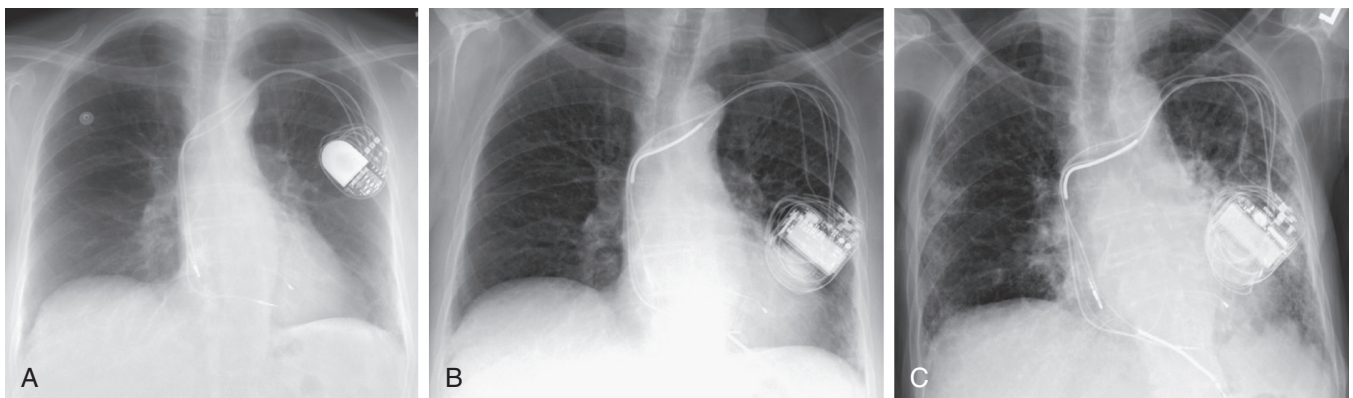
eFigure 63-6 CT of chronic hypersensitivity pneumonitis. Axial chest CT performed through the mid (**A**) and lower lungs (**B**) and extreme bases (**C**) shows relative basal sparing of pulmonary abnormalities compared with more cranial imaging levels, typical of hypersensitivity pneumonitis; this relative basal sparing is a useful feature for differentiating hypersensitivity pneumonitis from idiopathic pulmonary fibrosis. Other features of hypersensitivity pneumonitis are also evident, including ground-glass opacity (*single arrowhead*) and areas of lobular air trapping (*double arrowheads*), the latter consistent with small airway obstruction. Architectural distortion is present, consistent with the presence of fibrosis in this patient with chronic hypersensitivity pneumonitis. (Courtesy Michael Gotway, MD.)



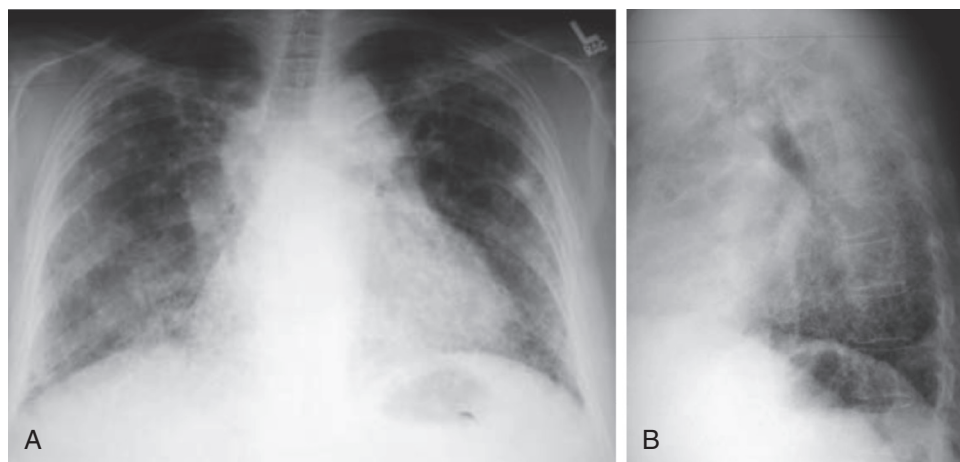
eFigure 63-7 PET-CT of idiopathic pulmonary fibrosis. Axial chest CT (**A**) shows basal, subpleural reticulation, traction bronchiectasis, and trace honeycombing representing idiopathic pulmonary fibrosis. Fused image from PET-CT (**B**) shows increased tracer utilization within the areas of fibrotic lung disease. Tracer uptake anteriorly represents cardiac activity. (Courtesy Michael Gotway, MD.)



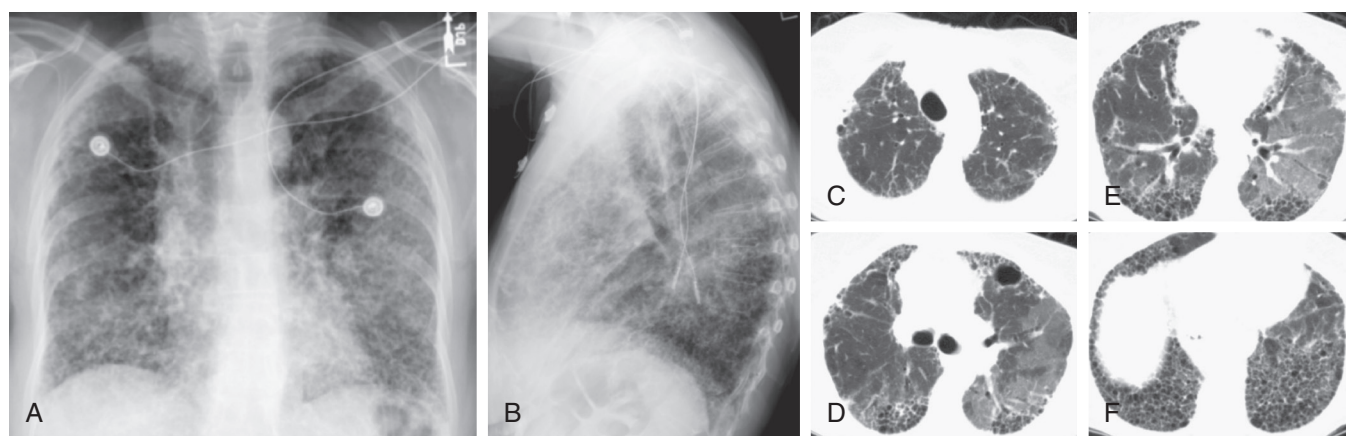
eFigure 63-8 CT and PET-CT in idiopathic pulmonary fibrosis with coincident lung carcinoma. Axial chest CT (**A**) shows basal, subpleural reticulation and traction bronchiectasis representing idiopathic pulmonary fibrosis. A subpleural nodule (arrow, **A**) is present, representing lung carcinoma. Fused image from PET-CT (**B**) shows increased tracer utilization within the nodule (arrow, **B**), as well as faint tracer uptake within the areas of fibrotic lung disease. (Courtesy Michael Gotway, MD.)



eFigure 63-9 Progression of fibrosis on chest radiography in idiopathic pulmonary fibrosis. Serial chest radiographs performed in 2004 (**A**), 2008 (**B**), and 2012 (**C**) show progressive development of linear and reticular abnormalities predominating in the mid and lower lungs, consistent with progressive fibrotic changes in a patient with idiopathic pulmonary fibrosis. (Courtesy Michael Gotway, MD.)



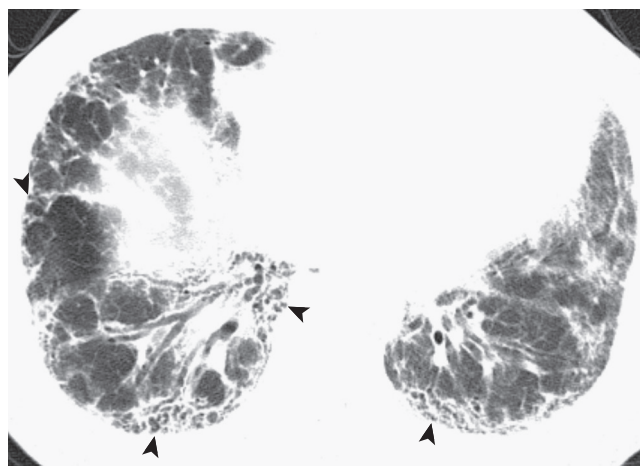
eFigure 63-10 Honeycombing on chest radiography in idiopathic pulmonary fibrosis. Frontal (A) and lateral (B) chest radiographs show peripheral predominant reticulation and linear opacities consistent with fibrotic changes in a patient with idiopathic pulmonary fibrosis. Note the cystic appearance best seen in the posterior and inferior lungs on the lateral chest radiograph (B); these cystic spaces represent honeycombing. (Courtesy Michael Gotway, MD.)



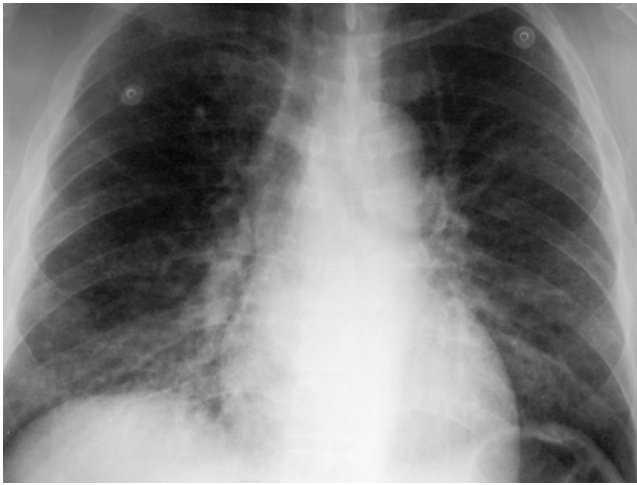
eFigure 63-11 Chest radiography and CT of accelerated interstitial pneumonia in idiopathic pulmonary fibrosis. Frontal (A) and lateral (B) chest radiographs show multifocal, bilateral reticular abnormalities, with cystic change most evident in the posterior and inferior lung bases on the lateral radiograph (B), consistent with fibrotic changes in a patient with idiopathic pulmonary fibrosis. In addition to these findings, more widespread areas of increased attenuation as well as a generalized nodular appearance are evident. Axial chest CT images in the upper (C), mid (D), and lower (E) lungs, as well as the extreme lung bases (F), show peripheral predominant fibrotic changes consistent with idiopathic pulmonary fibrosis. However, extensive areas of ground-glass opacity are evident, particularly in the left mid (D) and lower (E) lungs, and are consistent with an acute lung injury pattern and not fibrosis. (Courtesy Michael Gotway, MD.)



eFigure 63-12 Chest radiography of nonspecific interstitial pneumonia. Frontal chest radiograph shows patchy, bilateral areas of increased attenuation associated with faint areas of underlying reticulation; lung volumes are relatively preserved. (Courtesy Michael Gotway, MD.)



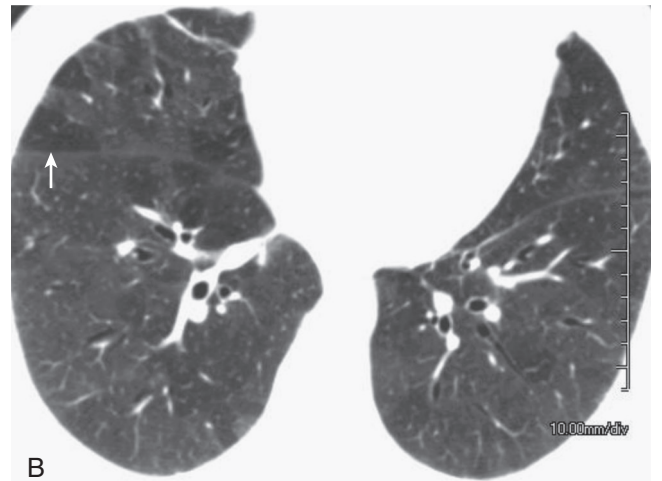
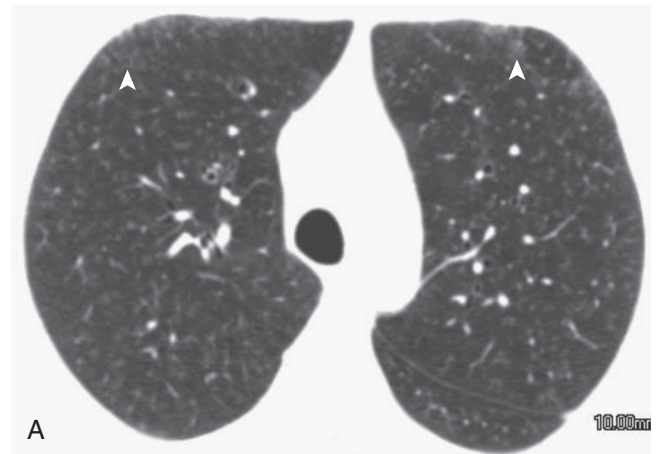
eFigure 63-13 CT showing subpleural cystic change in nonspecific interstitial pneumonia. Axial chest CT performed through the lung bases in a patient with fibrotic nonspecific interstitial pneumonia shows coarse peripheral reticulation, traction bronchiectasis, and peripheral cystic change (arrowheads). (Courtesy Michael Gotway, MD.)



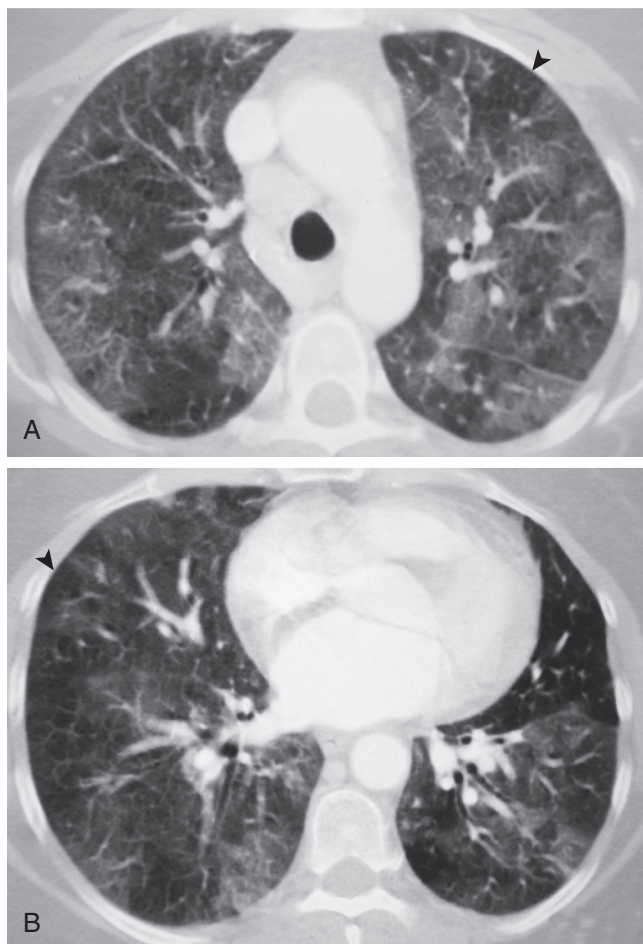
eFigure 63-14 Chest radiography of respiratory bronchiolitis-interstitial lung disease. Frontal chest radiograph shows multifocal, bilateral, linear and reticular abnormalities predominating in a perihilar and infrahilar distribution. Lung volumes are preserved. The appearance is nonspecific. (Courtesy Michael Gotway, MD.)



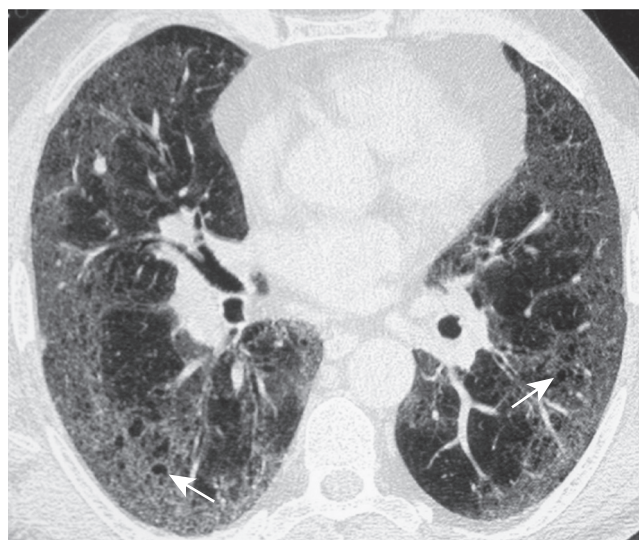
eFigure 63-15 Chest radiography of desquamative interstitial pneumonia. Frontal chest radiograph shows multifocal, bilateral, peripherally distributed linear and reticular abnormalities associated with peripheral left midlung consolidation. The appearance is nonspecific. (Courtesy Michael Gotway, MD.)



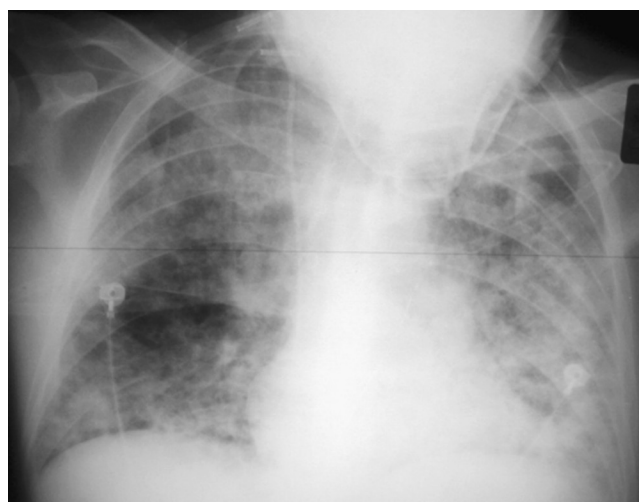
eFigure 63-16 CT of respiratory bronchiolitis-interstitial lung disease. Axial chest CT performed through the upper (A) and lower (B) lobes shows small, centrilobular ground-glass opacity nodules (arrowheads) predominantly in the upper lobes. Patchy, bilateral inhomogeneous lung opacity is visualized in the lower lobes, consisting of some mild increased attenuation, representing ground-glass opacity, and areas of decreased attenuation, representing mosaic perfusion, resulting from lobular air trapping (arrow). (Courtesy Michael Gotway, MD.)



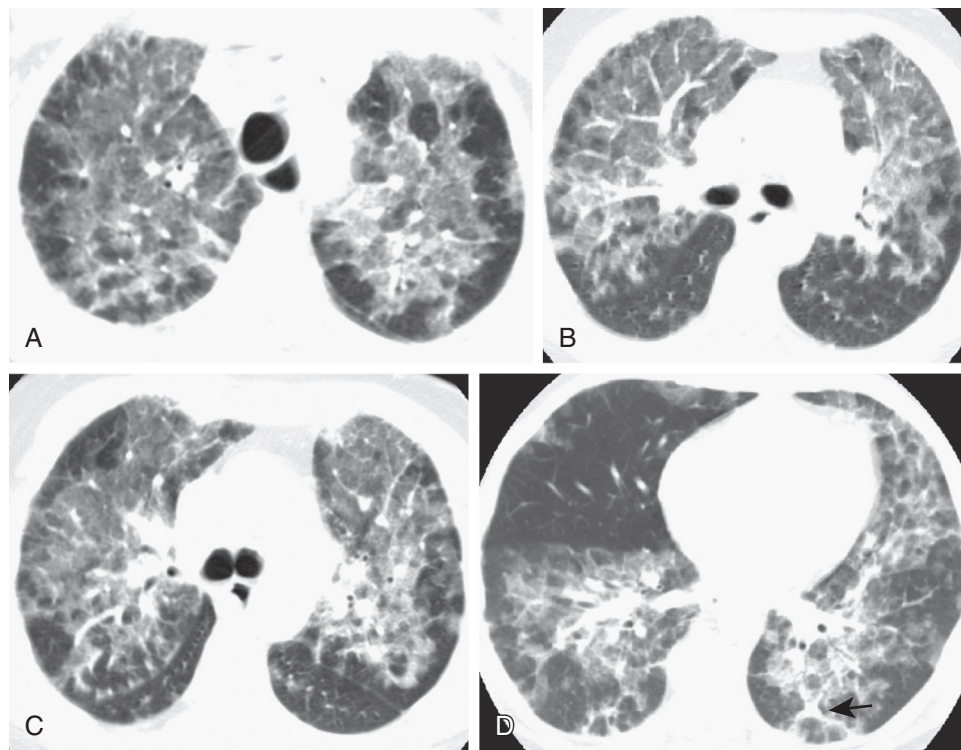
eFigure 63-17 CT of desquamative interstitial pneumonia. Axial chest CT performed through the upper (**A**) and lower (**B**) lobes shows multifocal, patchy areas of ground-glass opacity associated with fine reticular opacities. Areas of lobular low attenuation are present (*arrowheads*). (Courtesy Michael Gotway, MD.)



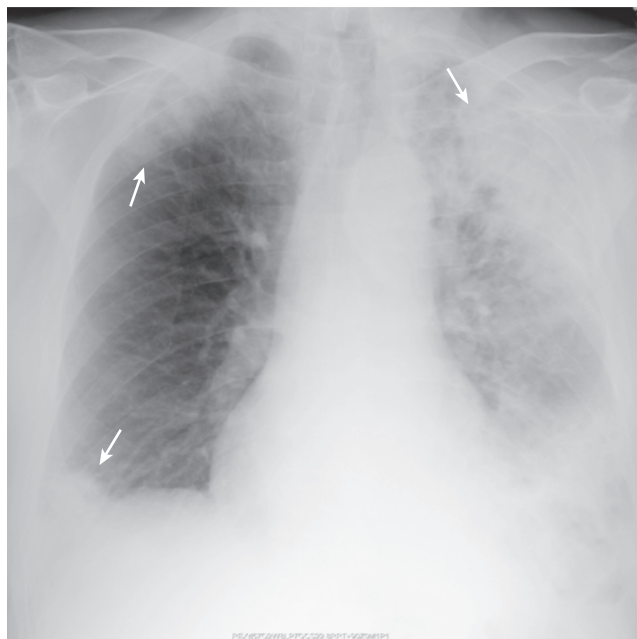
eFigure 63-18 CT showing small cystic foci in desquamative interstitial pneumonia. Axial chest CT shows multifocal, patchy areas of peripherally located ground-glass opacity associated with fine reticular opacities. Small cystic foci (*arrows*) are present. (Courtesy Michael Gotway, MD.)



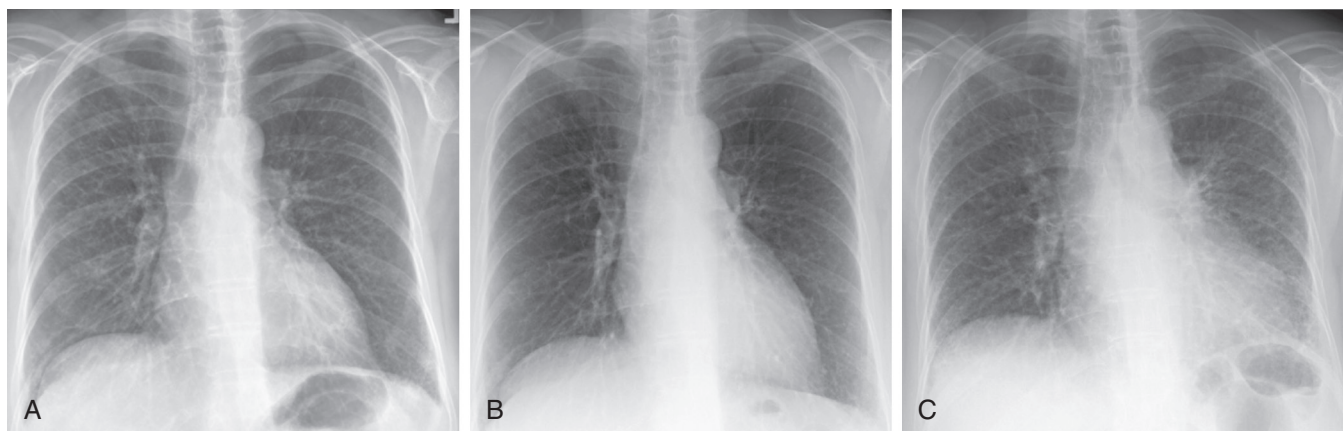
eFigure 63-19 Chest radiography in acute interstitial pneumonia. Frontal chest radiograph shows extensive, multifocal, bilateral consolidation. The imaging appearance is nonspecific and could be caused by numerous conditions. (Courtesy Michael Gotway, MD.)



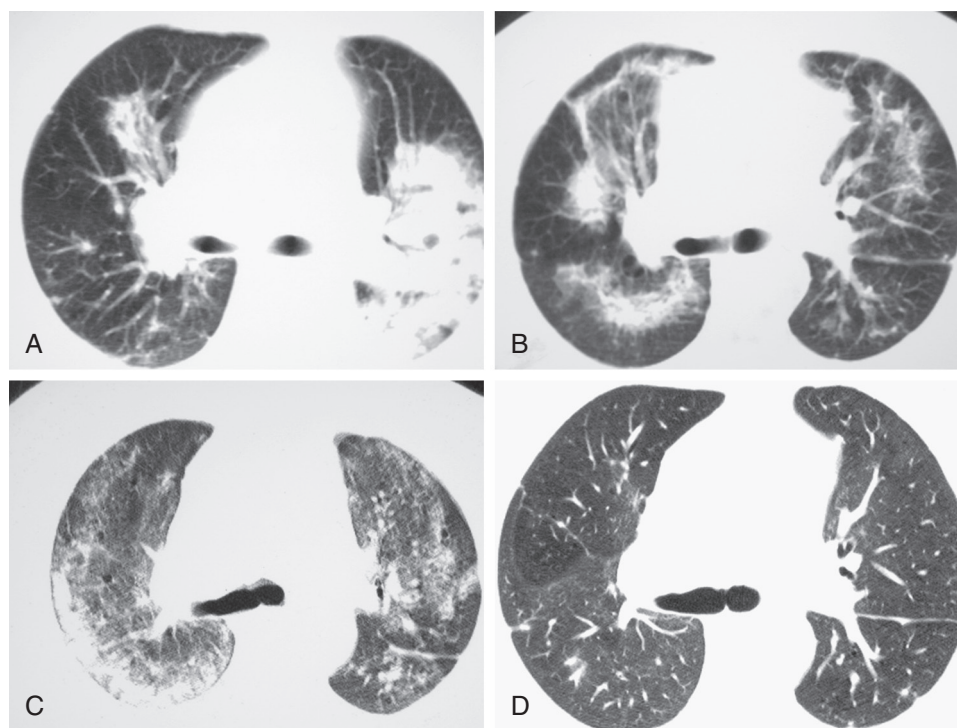
eFigure 63-20 CT of acute interstitial pneumonia. Axial chest CT images performed through the upper (**A**), mid (**B** and **C**), and lower (**D**) lobes show extensive, multifocal bilateral areas of bronchovascular thickening, ground-glass opacity, reticulation, and areas of bandlike consolidation (*arrow*). The imaging appearance is nonspecific and could be caused by numerous conditions. (Courtesy Michael Gotway, MD.)



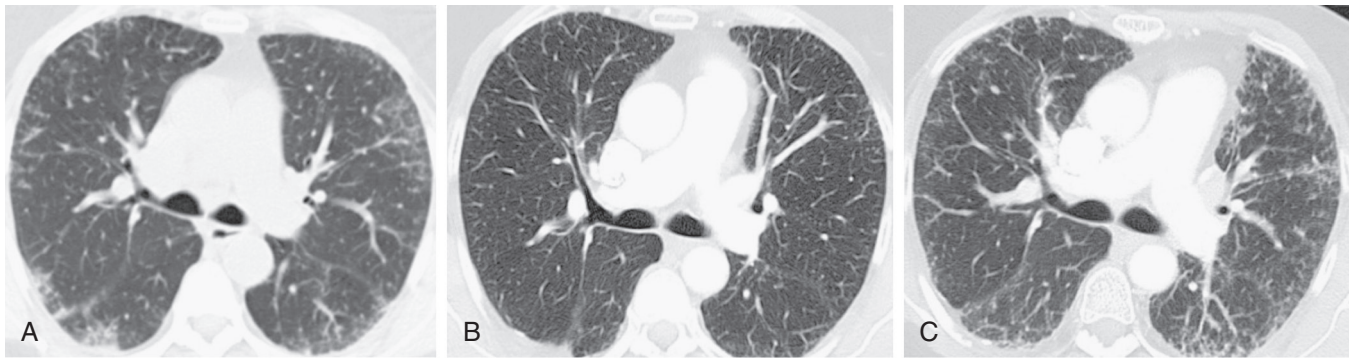
eFigure 63-21 Chest radiography of cryptogenic organizing pneumonia. Frontal chest radiograph shows multifocal, bilateral, peripherally distributed areas of consolidation (*arrows*). (Courtesy Michael Gotway, MD.)



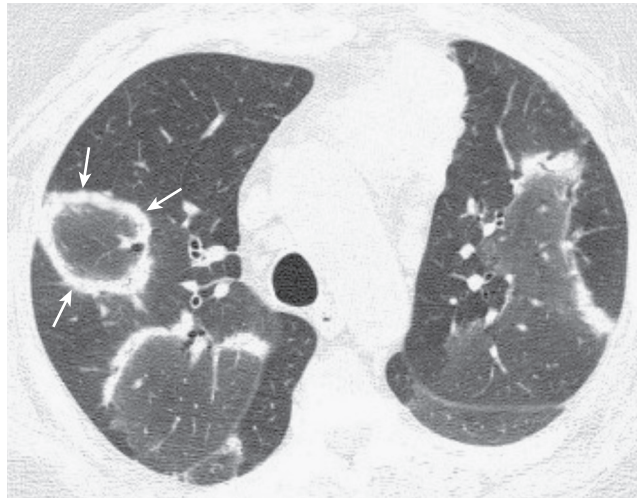
eFigure 63-22 Reticular appearance on chest radiography in cryptogenic organizing pneumonia. Frontal chest radiograph obtained at presentation (A), 2 years later following corticosteroid therapy (B), and 4 years following presentation and after corticosteroid therapy withdrawal (C), shows peripheral reticulation and interstitial thickening at presentation (A) that regresses following corticosteroid therapy (B). After withdrawal of corticosteroid therapy, when the patient again presented with symptoms, the reticulation and interstitial thickening has recurred. See CT of same patient in [eFigure 63-24](#). (Courtesy Michael Gotway, MD.)



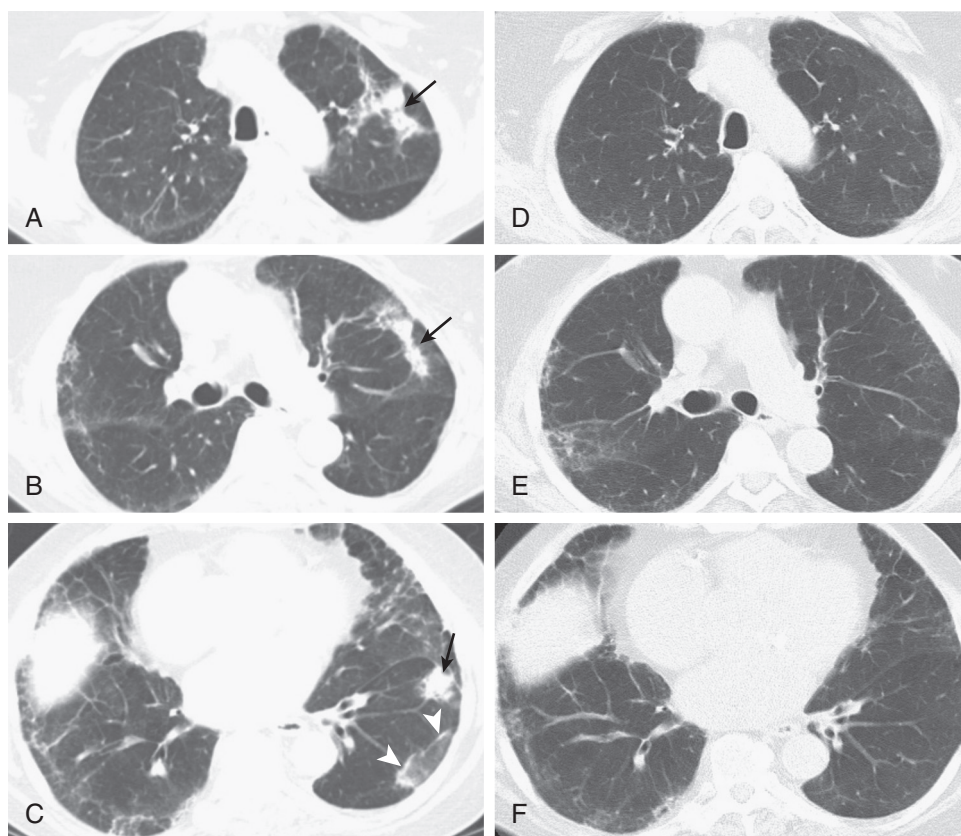
eFigure 63-23 CT of migratory opacities in cryptogenic organizing pneumonia. Axial chest CT performed at presentation (A), 6 months following presentation (B), 1 year following presentation (C), and following corticosteroid treatment (D). Image at presentation (A) performed through the midlungs shows extensive left lung consolidation and mild right lung consolidation. Six months after presentation (B), the left lung abnormalities have regressed and new right lung opacity is now present; note how the opacities have migrated peripherally compared with (A). Image performed 1 year following presentation (C) shows that the right lung consolidation has migrated into a frankly subpleural position. Image performed following corticosteroid therapy (D) shows complete resolution of lung opacity. (Courtesy Michael Gotway, MD.)



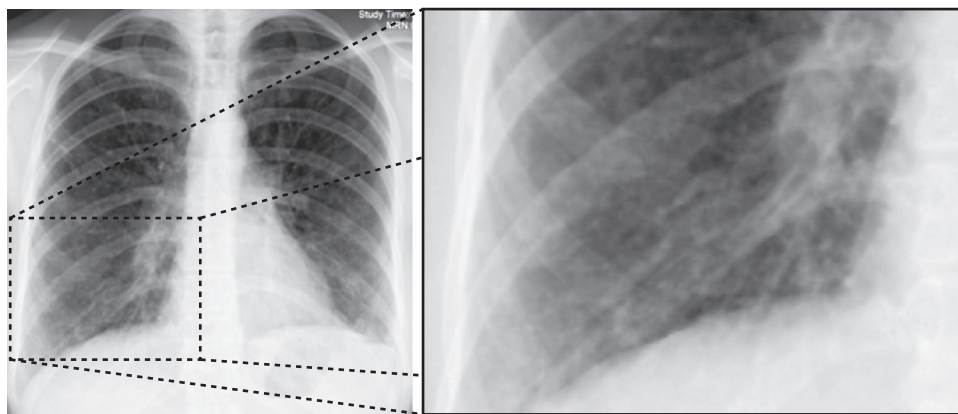
eFigure 63-24 Reticular appearance on CT in cryptogenic organizing pneumonia. Axial chest CT performed through the midlungs, obtained at presentation (**A**), 2 years later following corticosteroid therapy (**B**), and 4 years following presentation and after corticosteroid therapy withdrawal (**C**), shows peripheral reticulation and interstitial thickening at presentation (**A**) that regresses following corticosteroid therapy (**B**). After withdrawal of corticosteroid therapy, when the patient again presented with symptoms, the reticulation and interstitial thickening has recurred. See chest radiograph of same patient in eFigure 63-22. (Courtesy Michael Gotway, MD.)



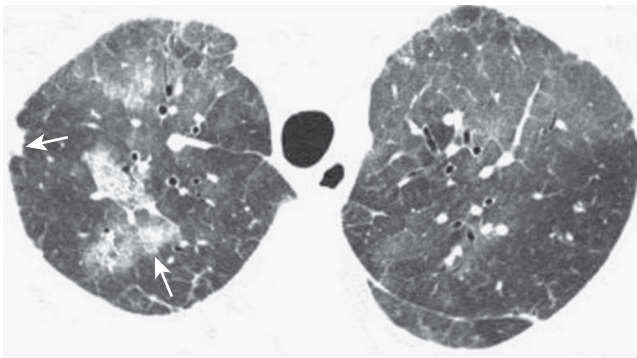
eFigure 63-25 CT of the "reverse ground-glass halo" ("atoll") sign in organizing pneumonia. Axial chest CT performed through the midlungs shows bilateral opacities characterized by peripheral consolidation with internal mild increased attenuation, the latter representing ground-glass opacity. One of the opacities shows a complete ring of peripheral consolidation (*arrows*), whereas other opacities show a partial ring or curvilinear appearance. (Courtesy Michael Gotway, MD.)



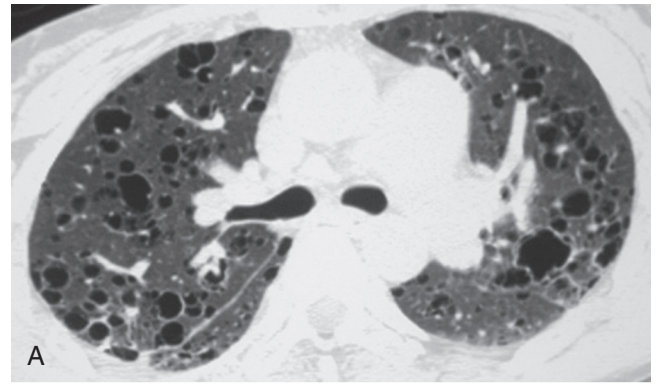
eFigure 63-26 CT of organizing pneumonia following corticosteroid therapy. Axial chest CT performed through the upper (**A**), mid (**B**), and lower (**C**) lungs at presentation shows patchy bilateral reticular opacities with foci of bandlike (*arrows*, **A** and **B**) and nodular (*arrow*, **C**) consolidation, representing foci of organizing pneumonia. Note the left lower lobe “reverse ground-glass halo” (“atoll”) sign (*arrowheads*) (**C**). Axial chest CT performed through the upper (**D**), mid (**E**), and lower (**F**) lungs following corticosteroid therapy shows resolution of the foci of consolidation. (Courtesy Michael Gotway, MD.)



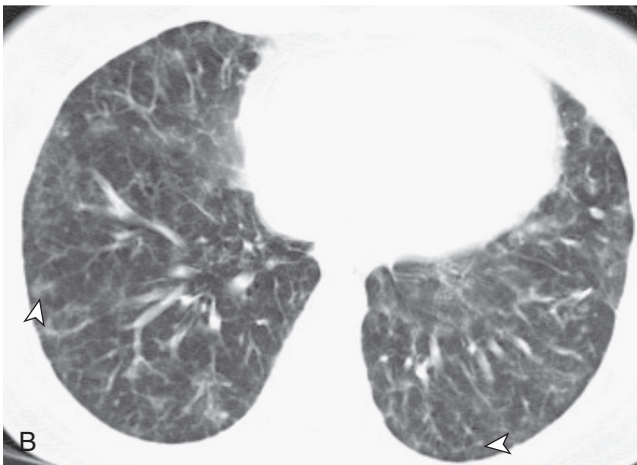
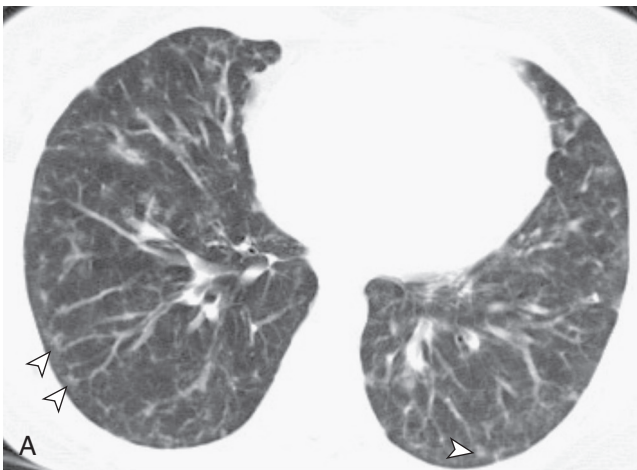
eFigure 63-27 Chest radiography of lymphocytic interstitial pneumonia. Frontal chest radiograph shows bilateral perihilar and infrahilar linear and reticular abnormalities with relative preservation of lung volumes. These findings are best appreciated in the detail image of the right lower lobe. The imaging appearance is nonspecific and could result from numerous etiologies. (Courtesy Michael Gotway, MD.)



eFigure 63-28 CT showing ground-glass opacity and consolidation in lymphocytic interstitial pneumonia. Axial chest CT performed through the upper lobes shows patchy, multifocal, bilateral areas of ground-glass opacity and consolidation (*arrows*). The imaging appearance is nonspecific and could result from numerous etiologies, including infection, hypersensitivity pneumonitis, and hemorrhage, among other possibilities. (Courtesy Michael Gotway, MD.)



eFigure 63-30 CT showing progression of cysts in lymphocytic interstitial pneumonia. Axial chest CT performed through the midlungs (**A**) shows numerous, variably sized, thin-walled cysts. Axial chest CT performed just under 2 years later (**B**) shows progression in cyst size and number. (Courtesy Michael Gotway, MD.)



eFigure 63-29 CT showing ground-glass opacity centrilobular nodules in lymphocytic interstitial pneumonia. Axial chest CT performed through the lower lobes shows patchy, bilateral bronchovascular thickening as well as small, ground-glass opacity centrilobular nodules (*arrowheads*). (Courtesy Michael Gotway, MD.)

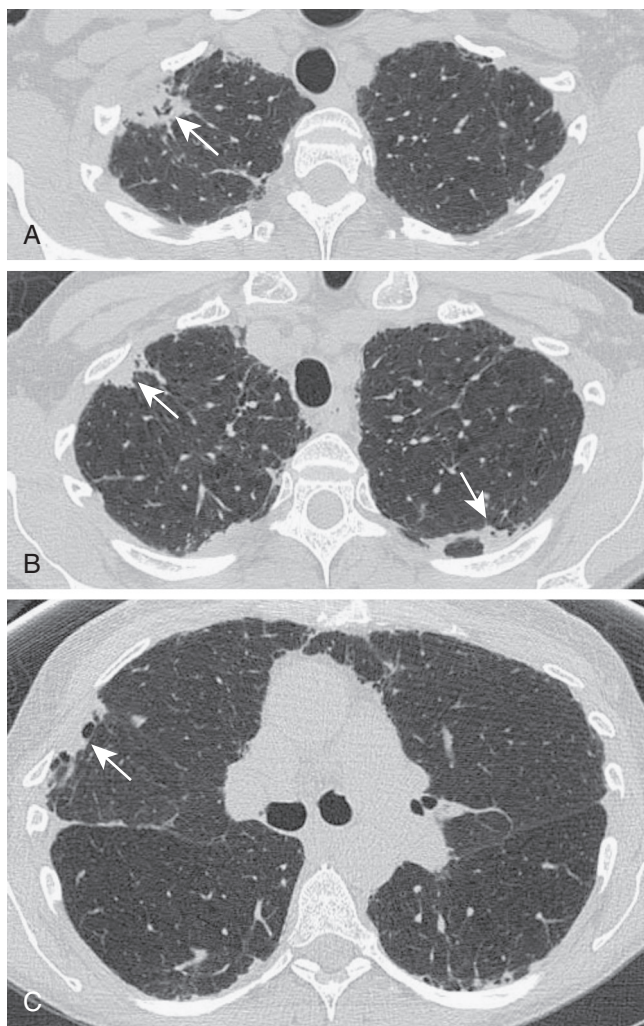


Figure 63-31 CT of idiopathic pleuroparenchymal fibroelastosis. Axial chest CT performed through the upper (A and B) lobes and midlungs (C) shows bilateral, subpleural areas of consolidation (*arrows*), associated with cystic change and bronchiolectasis. (Courtesy Michael Gotway, MD.)

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INTRODUCTION**ETIOLOGY**

Microbial Agents
Animal Proteins
Chemical Sensitizers

EXPOSURE SETTINGS AND RISK FACTORS**EPIDEMIOLOGY****CLINICAL PRESENTATION****IMMUNOPATHOGENESIS**

Host Factors

HISTOPATHOLOGY**CLINICAL FEATURES**

Signs and Symptoms
Lung Function
Imaging
Bronchoalveolar Lavage and Other
Laboratory Testing

DIAGNOSING HYPERSENSITIVITY PNEUMONITIS

Exposure History
Antibody Testing

Bronchoalveolar Lavage

Lung Biopsy

Inhalation Challenge

NATURAL HISTORY AND PROGNOSIS**TREATMENT**

Antigen Avoidance
Pharmacologic Therapy

PREVENTION**INTRODUCTION**

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, constitutes a spectrum of granulomatous, interstitial, bronchiolar, and alveolar-filling lung diseases resulting from repeated inhalation of and sensitization to a wide variety of organic aerosols and low-molecular-weight chemical antigens. Increasing recognition of the ubiquity of environmental antigen exposures and improved diagnostic tools have led to identification of cases and outbreaks of HP in a wide variety of occupational and environmental settings. The disease is a lymphocyte-driven process that manifests in a range of clinical phenotypes.

HP remains a diagnostic challenge because of the spectrum of clinical findings and the lack of a simple gold standard for diagnosis. The diagnosis depends on a strong clinical index of suspicion, a careful exposure history, and the integration of imaging and histopathologic findings. By themselves, these findings are nonspecific and may mimic a variety of other chest illnesses. HP is usually treatable if the exposure is recognized and antigen is effectively avoided. Unrecognized or untreated illness may lead to permanent airway reactivity, emphysema, and interstitial fibrosis.

ETIOLOGY

The list of specific agents that cause HP is extensive, and new exposure circumstances and disease entities continue to be described. The distinctive and often colorful disease names for HP can be organized more simply into three major categories of causal antigens: microbial agents, animal proteins, and low-molecular-weight chemicals (Table 64-1). There are also increasing numbers of pharmacologic agents that have been shown to cause hypersensitivity reactions in the lung, but the mechanisms and nature of these drug reactions are distinct from those of classic HP and are covered elsewhere under the subject of drug-induced lung diseases (see Chapter 71).

MICROBIAL AGENTS

Microbial organisms, including bacteria and fungi, are common in indoor environments. Warm, moist environments often provide ideal circumstances for the amplification and proliferation of microbial antigens that, if aerosolized and inhaled, can cause lung disease in a susceptible and previously sensitized host.

Bacteria have adapted to a wide variety of ecologic habitats and segregate under different physical and chemical conditions in indoor and outdoor environments. Thermophilic actinomycetes in hay are associated causally with the prototypical example of HP, *farmer's lung disease* (FLD), first described in 1932. These bacteria are ubiquitous in the environment and thrive in 50°C to 55°C temperatures and moist conditions. They secrete enzymes that facilitate decay of vegetable matter, but that can also cause immunologic lung reactions when inhaled. In addition to hay, thermophilic bacteria can be found in sugar cane (bagassosis) and mushroom compost (mushroom worker's lung) and can contaminate ventilation and humidification systems (humidifier lung) where temperatures can reach 60°C and stagnant water is present. Indoor bacteria that thrive at lower temperatures also can cause HP, and case reports have been associated with *Bacillus* spp. in contaminated wood dust, *Klebsiella* spp. in humidifiers, and *Epicoccum* spp. associated with moisture from a basement shower. Nontuberculous mycobacteria are an increasingly recognized cause of HP, mainly from workplace and recreational exposure to hot tub aerosols, but also from exposure to nontuberculous mycobacteria contaminants in shower heads.¹ There have also been outbreaks of HP from exposure to indoor swimming pools, termed "lifeguard lung," and to metalworking fluid aerosols contaminated with nontuberculous mycobacterial antigens.²⁻⁵

Exposure to fungal antigens is implicated in some HP cases.⁶ Components of fungi capable of becoming airborne include spores, mycelial fragments, metabolites and partially degraded substrates, and toxins. Among the interior sites for mold growth are garbage containers, food storage

Table 64-1 Etiologic Categories of Hypersensitivity Pneumonitis, with Examples**MICROBIAL AGENTS****Bacteria**

Examples: *Thermophilics*, *Bacillus subtilis*, *Klebsiella*, *Epicoccum nigrum*, nontuberculous mycobacteria

Fungi

Examples: *Aspergillus*, *Penicillium*, *Cladosporium*, *Trichosporon*, *Alternaria*, *Aureobasidium*, *Cephalosporium* species, *Absidia corymbifera*, *Eurotium amstelodami*, *Wallemia sebi*

ANIMAL PROTEINS

Examples: Bird proteins, fish meal, rat urine, mollusk shell, wheat weevil, silkworm larvae

CHEMICAL SENSITIZERS

Examples: Isocyanates, acid anhydrides, pyrethrum, Pauli's reagent (sodium diazobenzene sulfate)

areas, wallpaper, upholstery, areas of increased moisture such as shower curtains, window moldings, window air conditioners, damp basements, and emissions from cool mist vaporizers. Many fungal species have been associated causally with HP.⁷ *Aspergillus* spp. have been associated with HP in soy sauce brewers; bird breeders; farmers; compost, sawmill, mushroom, greenhouse, tobacco, cane mill, grain, and brewery workers; and in those exposed to contaminated esparto grass used in the production of ropes, canvas, sandals, mats, baskets, and paper paste. Similarly, *Penicillium* spp. may cause HP in cork workers, cheese workers, peat moss processors, laboratory workers, farmers, onion and potato sorters, sausage makers, and tree cutters.⁸ *Alternaria*, *Cladosporium*, *Aureobasidium*, *Paecilomyces*, *Fusarium*, and many other fungal species have been associated with HP in sawmill workers, tree cutters, hardwood processors, chicory leaf handlers, and other wood and plant handlers.^{9,10} There are several case reports of musical instruments (trombone and saxophone player's lung) contaminated with fungal species that caused HP in their users.^{11,12} A case of childhood HP from *Aureobasidium* contamination of indoor hydroponic cultivation has been described, with marked improvement with removal of the offending plants.¹³ Summer-type HP, the most prevalent form of HP in Japan, is caused by seasonal mold contamination (mainly *Trichosporon asahii*, formerly *Trichosporon cutaneum* serotype II) in the home, often from moldy wood flooring.^{14,15} Domestic fungal exposure associated with decaying wood and damp walls in inner city dwellings is the most common cause of HP in Australia.¹⁶ There, multiple fungal species were identified in the homes of individuals with disease, suggesting that sensitizing microbial exposures may be complex mixtures and that disease is not always attributable to a single, well-defined exposure.

ANIMAL PROTEINS

Particulates from a variety of animal sources can cause HP when inhaled. Exposure to bird protein antigens, first described in 1960, is the most clinically important and well recognized and is referred to as "bird breeder's" or "bird fancier's lung." Avian antigens are complex high- and low-molecular-weight proteins found in the feathers, droppings, and serum of turkeys, chickens, geese, ducks, parakeets (budgerigars), parrots, pigeons, doves, love birds, canaries,

and even native birds and are highly immunogenic.¹⁷ Immunoglobulins, particularly *immunoglobulin* (Ig) A and IgG, are released from birds' feathers, creating a fine dust called "bloom." Flying birds such as pigeons and parakeets produce the largest amount of bloom and are the birds most often associated with HP.¹⁸ Pigeon fancier's lung may also be caused by IgG secreted on pigeon intestinal mucin.^{19,20} Highest exposures to respirable avian antigens are associated with cleaning out bird lofts, cages, and coops. Indirect and apparently trivial antigen exposures also have been associated with avian HP. Goose feather duvets, down comforters and pillows, feathers used for making fishing lures, and those contained in decorative wreaths have all been associated with HP.²¹ These findings suggest that avian antigens are extremely potent inducers of immunologic lung disease, and a careful search for their presence must be included in the history taking of patients with suspected HP. These antigens can also be highly resistant to degradation, and antigenic similarity across various bird species mandates a thorough removal of all bird and feather products for a patient with bird fancier's lung.^{22,23} Even with extensive cleanup following removal of birds from indoor environments, antigen exposure may persist for months to years, perhaps explaining the lack of improvement in some patients with this form of HP.²⁴

There are several other animal exposures less commonly associated with HP. Animal handlers, including laboratory and veterinary workers, can develop HP from exposure to inhaled proteins in serum and excreta from rats and gerbils. Inhalation of grain dust infested with the wheat weevil *Sitophilus granarius* can cause a form of HP known as "miller's lung." Sericulturists engaged in silk production can develop HP from exposure to larval secretions and cocoon particulates.²⁵ Production workers exposed to mollusk shell dusts during cutting and polishing to make buttons may develop HP.²⁶

CHEMICAL SENSITIZERS

HP from inhalation exposure to low-molecular-weight chemicals is probably less common than from the other causes. Isocyanates are used for large-scale production of polyurethane polymers for flexible and rigid foams, as elastomers, adhesives, and surface coatings, and in two-part paints and are becoming increasingly recognized as a cause of HP.^{27,28} Acid anhydrides used in plastics, paints, and epoxy resins have been associated with an HP-like syndrome.²⁹ Rare case reports of HP have been described from exposure to the pesticide pyrethrum; from Pauli's reagent (sodium diazobenzene sulfate) used in chromatography; from copper sulfate in Bordeaux mixture used to spray vineyards; and from the enzyme phytase used as a cattle feed additive.³⁰ Other chemical exposures reported to cause HP include formaldehyde, dimethyl phthalate, and styrene, the latter used in boat manufacturing.^{31,32}

EXPOSURE SETTINGS AND RISK FACTORS

Although the acute symptoms of HP are often attributed to intense, intermittent antigen exposure whereas more

subtle, insidious symptoms are thought to result from lower level, more prolonged exposure, the paucity of environmental exposure data provides little insight into dose-response relationships. Insight into exposure-response relationships is further complicated by the fact that the latency period between exposure to an environmental antigen and onset of HP symptoms may vary from a few weeks to years.

Environmental risk factors—including particle size and solubility; antigen type and concentration; exposure duration, frequency, and intermittency; use of respiratory protection; and variability in work practices—may influence disease prevalence, latency, and severity. FLD is most common in late winter, when stored hay is used to feed cattle, and in regions with heavy rainfall and harsh winter conditions, where feed is likely to become damp and therefore an ideal substrate for microbial proliferation. A seasonal variation in specific antibody levels has been described in patients with pigeon breeder's disease, with a peak in antibody production during late summer, when highest exposures were associated with the sporting season.³³ There is wide geographic variability in the spectrum of indoor mold contaminants, where moist or humid environments foster growth.³⁴ Thus the most common forms of HP show both seasonal and geographic variation.

EPIDEMIOLOGY

The worldwide prevalence of HP is unknown. Reported disease incidence, prevalence, and attack rates vary widely and depend on the populations studied, the nature and intensity of antigen exposure, the case definition chosen, and variable host factors. In Europe, HP constitutes 4% to 13% of all interstitial lung diseases.³⁵ Epidemiologic studies of agricultural workers and bird fanciers suggest that HP is quite common in some high-risk occupational settings. Questionnaire surveys of farming communities found prevalence rates ranging from 2.3% to 20%. Country-wide reporting systems that collect data on clinically confirmed HP in Finnish farmers showed a mean annual incidence rate of 44 per 100,000; a Swedish study showed a rate of 23 per 100,000.³⁶ The reported prevalence of pigeon breeder's disease varies between 1 and 100 per 1000 breeders.³⁷ Rates of avian HP in the United Kingdom averaged 0.9 cases per 100,000 person-years between the years 1991 and 2003.³⁸ Fewer data exist on the prevalence of HP in workers exposed to chemical antigens. Isocyanate-induced HP was identified in 8 (4.8%) of 167 workers employed in a wood chipboard manufacturing plant.³⁹ Of the cases in which a causative agent was identified, 17% were due to various chemical agents, with isocyanates the most frequently reported.⁴⁰

HP can present in infants and children, although the incidence and prevalence are unknown. Avian proteins are the most common antigen associated with HP in the pediatric population. In one study of 86 pediatric HP cases, 70 were caused by birds.⁴¹ HP should be considered in the differential diagnosis of children with recurrent febrile respiratory illnesses and in those with unexplained interstitial lung disease.⁴² Parents should be questioned carefully regarding potential antigen exposures in the home,

school, and avocational settings such as indoor recreation centers.

CLINICAL PRESENTATION

HP is a syndrome marked by lung inflammation in response to an inhaled antigen in a sensitized host. However, the nature of the immune response and the associated clinical manifestations vary because of differences in the intensity of antigen exposure, the chronicity of antigen exposure, and individual host factors. Historically, three distinct clinical phenotypes have been recognized: acute, subacute, and chronic HP. *Acute* HP refers to the development of respiratory insufficiency or failure within hours after intense exposure to an antigen to which the patient has been previously sensitized. In contrast, patients with *subacute* HP have a more insidious presentation, in which symptoms develop over weeks to months, and for which the antigen concentration is likely lower than acute HP. Although pulmonary symptoms may be quite limiting, respiratory failure is not a typical feature of subacute HP. Historically, *chronic* HP described disease activity lasting beyond several months. In its current usage, chronic HP refers to findings of pulmonary fibrosis. For clarity and precision, we refer to this clinical phenotype as *chronic fibrotic* HP. It is thought to be due to prolonged exposure to low levels of antigen, and patients with this phenotype present with an even more insidious onset of symptoms. Signs of active inflammation on imaging or histologic findings are variable in chronic fibrotic HP.

There are limitations to these descriptors of clinical phenotypes. Subacute disease may persist and evolve to a chronic process, with or without fibrosis. In addition, there can be overlap. On imaging and histopathologic examination, subacute and chronic fibrotic changes frequently coexist. The recurrence of high-level exposures leading to acute HP events may be superimposed on a background of subacute or chronic fibrotic HP. While acknowledging these limitations, we discuss the features of HP based on these phenotypes because they work reasonably well to capture distinct immunopathologic processes and their clinical correlates.

IMMUNOPATHOGENESIS

The pathogenesis of HP is complex and for all three clinical phenotypes involves (1) repeated antigen exposure, (2) immunologic sensitization of the host to the antigen, and (3) immune-mediated damage to the lung. Even with these shared features, each phenotype has distinguishing features. These are addressed later, acknowledging that the immunopathologic features have been best defined for subacute disease.

The *bronchoalveolar lavage* (BAL) cellular profile of acute HP demonstrates a robust acute alveolitis in which an influx of neutrophils, peaking 48 hours after exposure, is followed by an increase in CD4⁺ lymphocytes.⁴³ Although early neutrophil accumulation is associated with the onset of systemic symptoms and pulmonary abnormalities, there are limited data on the nature and extent of neutrophil activity in the pathophysiologic characteristics of acute HP. The subsequent increase in lymphocytes is observed

between 48 and 72 hours and is due to both cellular redistribution from peripheral blood to lung and lymphocyte proliferation locally. The accumulation and expansion of CD8⁺ lymphocytes can lag that of CD4⁺ lymphocytes, and the ratio of CD4⁺/CD8⁺ cells, although often decreased in subacute HP, is less predictable in acute disease.^{44,45} Alveolar macrophages demonstrate an activated phenotype and produce reactive oxygen species that are thought to contribute to alveolar damage.⁴⁶ Cytokines and chemokines released from lymphocytes and antigen-presenting cells contribute to the proinflammatory milieu and perpetuate the inflammatory response. This response continues until antigen is cleared or until intrinsic mechanisms down-regulate the immune response. Although a pathogenic role for immune complex deposition (a type III hypersensitivity reaction) has been considered for acute HP, this remains to be established.²³

In subacute HP, robust engagement of adaptive immune responses is reflected in a pronounced BAL lymphocytosis, composed of CD4⁺ and CD8⁺ cells. Cell-mediated type IV hypersensitivity inflammation, the delayed type of hypersensitivity involving CD4⁺ T cells stimulating CD8⁺ cells to destroy targets, is central to the pathogenesis.⁴⁷ Interstitial and peribronchiolar lymphocyte accumulation and granuloma formation are predominate findings. The ratio of CD4⁺/CD8⁺ cells is often low, although not always.⁴⁸ Whether this is due to preferential expansion or survival of CD8⁺ lymphocytes in HP is not clear.⁴⁵ Similarly, the contribution of a cytotoxic effect of CD8⁺ lymphocytes to the pathophysiologic changes of HP remains poorly defined.^{49,50} CD4⁺ lymphocytes in HP polarize to a *type 1 T helper* (Th1) phenotype. Cytokines secreted by Th1 lymphocytes and macrophages, including interferon- γ , tumor necrosis factor- α , and interleukin-18, promote granuloma formation.⁵¹

The pathogenesis of chronic fibrotic HP is incompletely understood. Low-level antigen exposure, leading to subclinical disease, may permit the development of occult fibrosis in patients who are not alerted by symptoms to alter their exposure. However, it is not known to what extent fibrosis in HP develops as a sequela of nonresolving subacute HP or if it is a categorically discrete subtype in which the immune response is less inflammatory and more profibrotic from the outset. In either case, cellular profiles provide insight into possible mechanisms of disease; in chronic HP, effector T-cell function is lost, a shift toward a profibrotic Th2 lymphocyte profile is noted, and a higher CD4⁺/CD8⁺ ratio is often observed.⁵² Polarization of CD4⁺ lymphocytes to a Th2 phenotype may be important for the fibrotic response. In an animal model of HP, mice genetically programmed for enhanced Th2 activity were more likely to develop pulmonary fibrosis.⁵ In a study of patients with HP, those with fibrotic disease had a higher percentage of lymphocytes with Th2 properties compared to patients with subacute disease. More work is needed to understand both the early inflammatory events of chronic HP and the role of lymphocyte polarization and macrophage activity in the development of fibrosis. These patients often have an insidious clinical presentation, presenting with well-established fibrosis. In such cases the early immune events that proceeded and potentially promoted fibrogenesis are unable to be ascertained in retrospect.

HOST FACTORS

Following antigen exposure, more people develop precipitating antibodies than develop symptomatic HP. Susceptibility to or protection from HP may be explained in part by genetic polymorphisms.⁵³ Polymorphisms in the major histocompatibility complex and in tumor necrosis factor- α are associated with the development of HP.⁵⁴⁻⁵⁶ Within the major histocompatibility complex, polymorphisms of human leukocyte antigen genes and of the transporters associated with antigen processing 1 (*TAP1*) gene have been associated with increased risk for HP.^{54,55,57-59} Several polymorphisms have also been associated with decreased disease risk. Overexpression of GATA3, a regulator of Th2 differentiation, attenuates disease perhaps by correcting the Th1 immune response.⁶⁰ Variants in the tissue inhibitor of metalloproteinase-3 also appears to be protective.^{61,62}

Nongenetic host factors are also important disease determinants. HP develops more frequently in nonsmokers than in smokers. Compared with former and never smokers, pigeon fanciers who smoked had lower levels of serum IgG and IgA antibodies to pigeon proteins; this suggests that factors associated with cigarette smoking depress both T-cell-dependent and T-cell-independent responses to inhaled antigens.⁶³ In an experimental HP model, nicotine exposure was associated with reductions in cellular responses, lymphocyte and total cell counts in BAL, and lung tissue inflammation.⁶⁴ Other studies have shown that smoking induces relative increases in lung macrophages and decreases in lymphocytes and dendritic cells, perhaps promoting more effective clearance of antigens from terminal airways.^{65,66}

In addition to the risk factors for developing disease, variations in immune responses due to patient characteristics are also important determinants of the clinical phenotype of HP. Although HP is more common in nonsmokers, the prognosis is poorer in those with HP who smoke. In one study, smokers with FLD had more frequent illness recurrence, had lower percent predicted vital capacity, and had poorer 10-year survival in comparison with nonsmokers with FLD.⁶⁷ Smokers are more likely to have insidious than acute symptoms, which may delay clinical recognition. In addition to smoking status, age may play a role in the phenotype of disease, where immune responses change with age. In a study of clinical features of patients with nonacute HP, those who developed fibrosis were significantly older than those who did not develop fibrosis.⁶⁸

HISTOPATHOLOGY

The histopathologic features of acute HP are poorly understood, because biopsies in this setting are generally not performed. When available, results of biopsies show lymphocytic interstitial infiltrates and a neutrophilic and lymphocytic alveolitis. Foci of eosinophilic infiltrates can also be observed. Granulomas, which take days to weeks to develop, are not apparent in new-onset acute HP.

The histopathologic findings of subacute HP have been better characterized than those of acute HP. The classic histologic triad includes (1) cellular bronchiolitis, (2) interstitial mononuclear cell infiltrates, and (3) scattered, small,

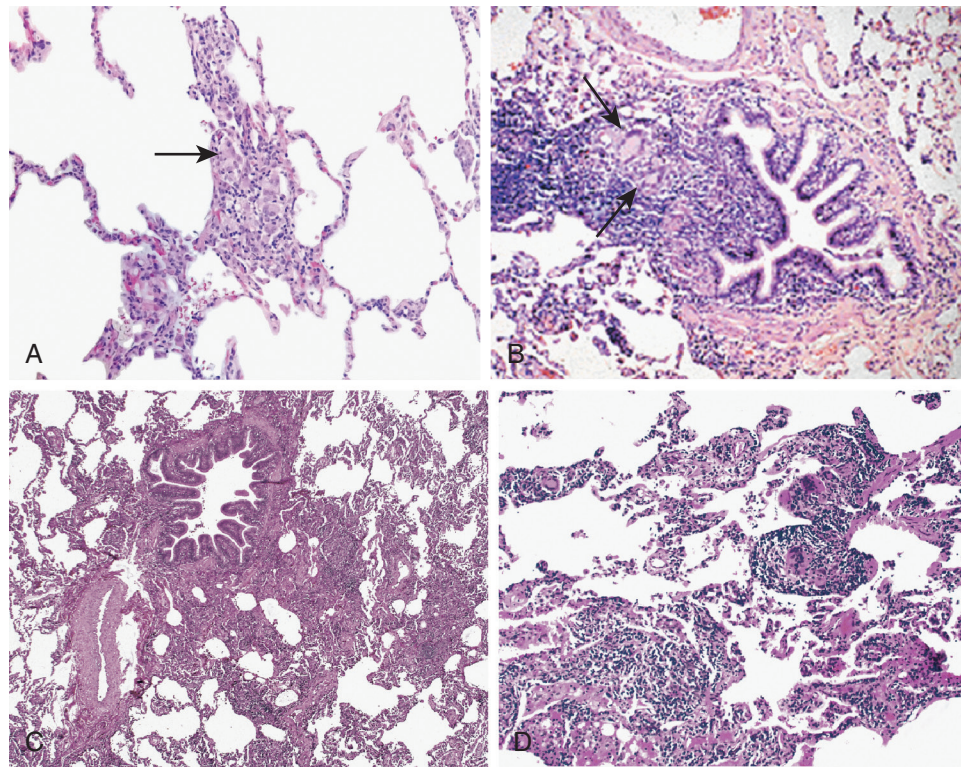


Figure 64-1 Granulomatous involvement seen in hypersensitivity pneumonitis. **A**, Several poorly formed non-necrotizing granulomas are present (arrow). **B**, Airway-centered interstitial fibrosis is seen together with giant cells (arrows). **C**, A bronchiolocentric distribution may be evident, as indicated by the presence of a terminal bronchiole or by some degree of nodularity to the infiltrates at low magnification. **D**, Multinucleate giant cells may also be seen in the interstitium and constitute a helpful feature at low magnification in drawing the eye to features meriting closer examination.

non-necrotizing granulomas (Fig. 64-1).⁶⁹ A cellular bronchiolitis in which lymphocytes and plasmacytes infiltrate respiratory bronchioles is a hallmark of subacute HP. The interstitial lymphocytic infiltrate is most prominent in peribronchiolar areas, although its distribution may be more uniform and thus similar to *nonspecific interstitial pneumonia* (NSIP); in such cases, coexisting granulomas are a helpful distinguishing feature.⁷⁰ Granulomas in HP are often distinct from those of sarcoidosis, although granuloma characteristics alone should not be used to distinguish these two diseases. Except in hot tub lung, in which granulomas may be well formed, HP granulomas tend to be smaller, less numerous, and more loosely organized than sarcoid granulomas.⁷¹ Because they seldom hyalinize, HP granulomas often resolve after antigen clearance and avoidance.⁷² Granulomas in HP form in bronchiolar walls and alveolar tissue. Whereas constrictive bronchiolitis is an uncommon finding, focal areas of organizing pneumonia have been observed in subacute HP.⁷²

The chronic fibrotic form of HP is characterized by airway-centered interstitial fibrosis and giant cells, often with minimal or absent granulomatous inflammation (see Fig. 64-1B).⁷² Bridging fibrosis may be observed between peribronchiolar and perilobular areas. Organizing pneumonia, cellular NSIP, fibrotic NSIP, and usual interstitial pneumonia with honeycombing and fibroblast foci are well-described patterns variably observed in chronic fibrotic HP.⁷²⁻⁷⁴ Coexisting histopathologic features that support a diagnosis of HP over other clinical entities include the

presence of granulomas, giant cells, bridging fibrosis, or chronic bronchiolitis. When the histopathologic features remain equivocal, additional clinical data must be considered in confirming the diagnosis.^{70,73-75}

Acute exacerbations have been reported in chronic fibrotic HP. Histopathologic findings from lung biopsies obtained during such exacerbations reveal diffuse alveolar damage, akin to findings in acute exacerbations of idiopathic pulmonary fibrosis.⁷⁶ It is not clear how often such exacerbation events in HP are due to antigen reexposure or to a complication of the underlying fibrotic process.

CLINICAL FEATURES

SIGNS AND SYMPTOMS

Acute HP typically begins hours after antigen exposure, with the abrupt onset of flulike respiratory and constitutional symptoms, including cough, dyspnea, chest tightness, fevers, chills, malaise, and myalgias. Symptoms may be accompanied by physical findings of fever, tachypnea, tachycardia, and inspiratory crackles on lung examination. A peripheral blood leukocytosis with neutrophilia and lymphopenia may be present. Eosinophilia is unusual. If antigen exposure ceases, symptoms of acute HP typically begin to resolve within days. Subacute HP has a more insidious presentation, in which progressive dyspnea on exertion and decreased activity tolerance are common. Cough is variably

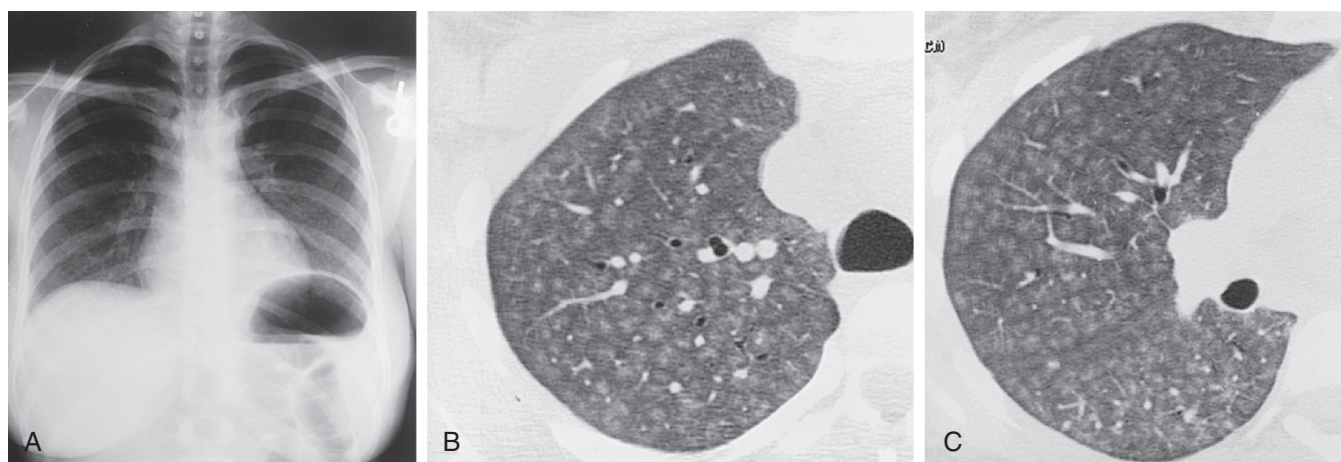


Figure 64-2 Acute hypersensitivity pneumonitis. **A**, Chest radiograph of a patient with HP shows diffuse micronodules. **B**, High-resolution (1.5-mm thin section) CT (HRCT) image through the lung of the same patient shows profuse centrilobular micronodules. **C**, HRCT scan of a different patient with bird breeder's lung shows diffuse ground-glass attenuation with reticular opacities and centrilobular micronodules.

present. Although there may be low-grade fevers and weight loss, systemic symptoms are not as prominent or as prevalent in subacute HP as in acute HP.⁷⁷ On lung examination, inspiratory crackles are common, and squeaks are variably present. Alternatively, the lung examination findings may be entirely normal.⁷⁷ Patients with chronic fibrotic HP often present with slowly progressive dyspnea on exertion and a nonproductive cough; they may uncommonly report wheezing, sputum production or chest tightness.^{77,78} Weight loss, if present, is often mild, and patients may report fatigue and decreased stamina. Similar to subacute HP, fever and other systemic symptoms are not as prominent in chronic fibrotic HP as in acute HP. Examination may reveal hypoxemia, at rest or with exertion, and basilar crackles are common. Cyanosis and right-sided heart failure can be seen in severe fibrotic disease. Digital clubbing, when present, is associated with a poorer prognosis.⁷⁹

LUNG FUNCTION

Complete *pulmonary function tests* (PFTs), including lung volumes, spirometry, and diffusing capacity for carbon monoxide, should be obtained in all patients with suspected HP who are clinically stable enough for testing. Although PFT results may be normal, most often abnormalities are detected, although none are specific for HP. A reduction in the diffusion capacity is common in all HP phenotypes and may be the most sensitive pulmonary function alteration. Lung function abnormalities in HP are classically restrictive.^{76,80} Alternatively, obstruction or mixed deficits may be observed. The response to bronchodilators is variable, and HP should be considered in the differential diagnosis of nonsmokers presenting with either fixed or reversible obstruction. Obstruction in HP may be more common in those with fibrosis, where periairway fibrosis may contribute to airflow impairment.⁸⁰ Nonspecific bronchial hyper-reactivity on methacholine challenge can be observed.⁸¹ An exercise-induced decrease in arterial oxygen saturation is an early sign of functional impairment in patients with mild disease. In patients with significant airway or parenchymal involvement, gas exchange abnormalities can be significant

with exercise or may be evident at rest. After an initial assessment, serial PFTs should be followed to assess response to therapy and to guide treatment decisions until recovery or stability of lung function is achieved. In acute HP, lung function typically normalizes after recovery from the acute event. In subacute HP, lung function may normalize if permanent damage has not ensued. In chronic fibrotic HP, however, lung function may be permanently and severely impaired.

IMAGING

In acute HP, chest imaging typically reveals diffuse ground-glass opacities, although a fine micronodular pattern may also be observed (Fig. 64-2).^{82,83} Ground-glass opacities reflect underlying alveolitis; although they can be seen in any stage of HP, ground-glass opacities are the predominant finding in acute HP.⁸⁴ Paralleling the clinical response, radiographic abnormalities in acute HP resolve over days to weeks if further exposure is avoided (eFig. 64-1).

In subacute HP, the imaging manifestations include ground-glass opacities, centrilobular nodules (eFig. 64-2A and B), and mosaic attenuation.^{85,86} These findings are best appreciated on *computed tomography* (CT) imaging (see eFig. 64-2C and D).^{87,88} Occasionally the centrilobular nodules may be small (≤ 3 mm) and circumscribed and may be referred to as “micronodules” (eFig. 64-3), although the diagnostic and prognostic significance of this designation is unclear. Similar to acute HP, ground-glass opacities reflect an underlying alveolitis. Accompanying cellular bronchiolitis manifests as centrilobular nodules (see eFigs. 64-2B, C and 64-3C-E; Video 64-1A) and “air trapping” (see Video 64-1B). Mosaicism due to air trapping is common in HP, in which hyperlucent areas are the result of hypoxic vasoconstriction and decreased arterial blood flow in hypoventilated regions^{78,87} (Fig. 64-3). Air trapping is best assessed by comparing inspiratory (see Video 64-1A) and expiratory CT images (see Video 64-1B), where expiratory views accentuate hyperlucent areas.⁸⁹ Lung cysts, similar to those described in lymphoid interstitial pneumonia, have been reported in HP (see eFig. 69-8).⁹⁰ Hilar or mediastinal

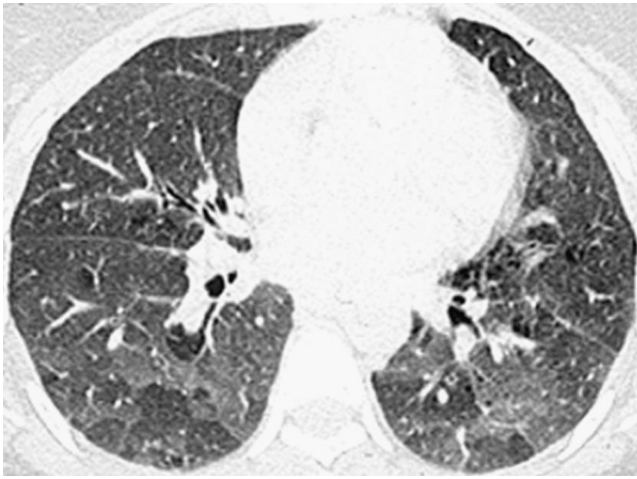


Figure 64-3 Hypersensitivity pneumonitis. Bilateral, diffuse ground-glass opacities with mosaic perfusion reflect alveolitis and bronchiolitis, respectively.

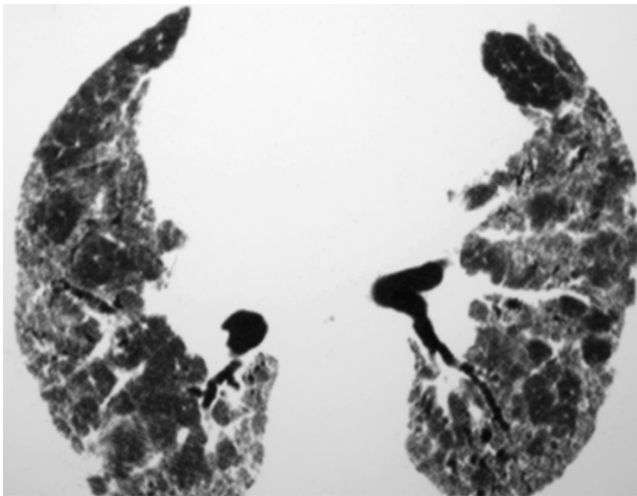


Figure 64-4 Chronic fibrotic hypersensitivity pneumonitis. Areas of ground-glass opacity admixed with a few small areas of fairly normal-appearing lung are associated with extensive reticulation, traction bronchiectasis, and architectural distortion.

lymphadenopathy rarely is seen at chest radiography. In contrast, mild mediastinal lymphadenopathy, typically involving only a few nodes, is variably observed on CT imaging in any subtype of HP.

In chronic fibrotic HP, although radiographic findings of subacute HP are often also present, fibrotic changes predominate. The chest radiograph often reveals volume loss, architectural distortion, and fibrotic lines (eFig. 64-4A). CT findings include volume loss, traction bronchiectasis, fibrotic reticular or linear opacities, and honeycombing (Fig. 64-4; see eFig. 64-4B-D). Usual interstitial pneumonia and fibrotic NSIP are well-recognized radiographic patterns of chronic fibrotic HP, and CT imaging alone is often unreliable in differentiating chronic fibrotic HP from other fibrotic interstitial lung diseases, with an accurate diagnosis in only 50% of patients in one series.⁹¹ The degree of fibrosis on CT is associated with a poorer prognosis in patients with HP (see Fig. 64-4).^{92,93} Notably, in chronic fibrotic FLD, emphy-

sema not related to smoking is a more common radiographic finding than fibrosis.^{94,95}

BRONCHOALVEOLAR LAVAGE AND OTHER LABORATORY TESTING

Typically, acute and subacute HP are characterized by a marked increase in BAL white blood cell count and a BAL lymphocytosis (30% to 70%), often with a CD8⁺ lymphocyte predominance; this is less true in fibrotic HP. The absolute number of macrophages is similar to that in controls, although their percentage is reduced because of the high percentage of lymphocytes. These typical findings notwithstanding, the BAL cellular profile may vary considerably, depending on the stage of illness and on the time since the last antigen exposure. There appears to be little correlation between BAL findings and other clinical abnormalities, including radiographic changes, pulmonary function, and the presence of precipitating antibodies.

Mild serum elevations in erythrocyte sedimentation rate, C-reactive protein level, and immunoglobulins of IgG, IgM, or IgA isotypes are variable findings. Rheumatoid factor can be elevated.⁷¹ However, antinuclear antibodies and other autoantibodies rarely are detected and, if found, suggest an underlying connective tissue disease.

DIAGNOSING HYPERSENSITIVITY PNEUMONITIS

A number of diagnostic criteria for HP have been proposed, but there remains no gold standard test or approach.⁷⁶ One widely cited set of criteria includes these findings: (1) symptoms compatible with HP, (2) evidence of exposure to an appropriate antigen by either the history or antibody testing results, (3) symptom periodicity that correlates with recurrent antigen exposure, (4) imaging findings compatible with HP, (5) a lymphocytosis on BAL, and (6) histopathologic features compatible with HP. A diagnosis of HP is made by the presence of at least four of these, in addition to findings of crackles on lung examination, a reduction in the diffusion capacity, and/or hypoxemia, and when other diseases have been appropriately ruled out.⁹⁶ Although widely used, these criteria have not been validated. A subsequent clinical prediction model found the following features to be highly predictive of active HP: (1) exposure to a potential HP antigen, (2) positive antibody testing to the offending antigen, (3) episodic symptoms, (4) symptom onset within hours of antigen exposure, (5) crackles on lung examination, and (6) weight loss.⁹⁷ This model was developed from a cohort of patients with either HP or non-HP lung disease and was validated in a follow-up cohort of patients with HP. Patients with chronic fibrotic HP were not included, and applicability of this prediction model to patients with this phenotype is unknown. More recently, a published algorithm emphasized the importance of CT changes typical of HP, lymphocytosis on BAL, and positive antibodies in the setting of antigen exposure in order to diagnose HP without a surgical lung biopsy.⁴ The various proposed sets of criteria, models, and algorithms have in common an emphasis on the constellation of clinical,

radiographic, and biopsy findings in the context of the exposure history to arrive at a diagnosis of HP (Table 64-2). In addition, other diseases that have clinical features similar to HP need to be considered and excluded (Table 64-3).

EXPOSURE HISTORY

A thorough and detailed history remains the cornerstone of HP diagnosis (Table 64-4). A temporal relationship between symptoms and particular activities can be identified in some cases of acute and subacute HP and is particularly suggestive of the diagnosis, although such a

relationship is often not clinically apparent. Recurrent episodes of otherwise unexplained respiratory and systemic symptoms should prompt consideration of HP and a careful search for relevant exposures. In some cases, exposure may be frequent or sustained enough that discrete fluctuations in clinical status associated with exposure will not be evident.

Antigen exposures capable of causing HP can take place in almost any indoor environment under appropriate circumstances, and a simple job title cannot be used to exclude potential risk. The work history should include a chronology of current and previous occupations, with a description

Table 64-2 Typical Clinical Features of Acute, Subacute, and Chronic Hypersensitivity Pneumonitis

Diagnostic Approach	Acute HP	Subacute HP	Chronic Fibrotic HP
Time course of presentation	<ul style="list-style-type: none"> Acute onset of symptoms hours to days after exposure Exposure to high antigen concentration often recognized 	<ul style="list-style-type: none"> Subtle onset of symptoms over weeks to months Periodicity of symptoms corresponding to intermittent exposure may be evident 	<ul style="list-style-type: none"> Insidious onset of respiratory symptoms Clinical periodicity is often lacking
Symptoms	<ul style="list-style-type: none"> Dyspnea at rest, chest tightness, cough Pronounced systemic symptoms, including diffuse aches and fevers 	<ul style="list-style-type: none"> Dyspnea on exertion, cough, chest tightness Fatigue, low-grade fevers, myalgias are common but variable 	<ul style="list-style-type: none"> Dyspnea on exertion, \pm cough Fever and aches are less pronounced; weight loss and fatigue may be common
Examination findings	<ul style="list-style-type: none"> Fever, tachypnea, tachycardia, hypoxemia Crackles and dyspnea, or lung examination may be normal 	<ul style="list-style-type: none"> \pm Hypoxemia Crackles, or lung examination may be normal 	<ul style="list-style-type: none"> Hypoxemia Crackles, or lung examination may be normal
Gas exchange findings	<ul style="list-style-type: none"> Exertional desaturation 	<ul style="list-style-type: none"> Decreased ventilatory capacity Exertional desaturation 	<ul style="list-style-type: none"> Decreased ventilatory capacity Exertional desaturation
Serum precipitins	<ul style="list-style-type: none"> Negative results do not rule out disease, but a positive precipitins result helps confirm relevant antigen exposure 		
Chest CT imaging	<ul style="list-style-type: none"> Diffuse GGOs 	<ul style="list-style-type: none"> Air trapping GGOs Centrilobular nodules 	<ul style="list-style-type: none"> \pm Features of subacute HP Peribronchiolar and reticular fibrosis
Bronchoalveolar lavage	<ul style="list-style-type: none"> Increased neutrophils Lymphocytosis (develops over 24–72 hr of exposure) 	<ul style="list-style-type: none"> Lymphocytosis CD4/CD8 is often < 1 	<ul style="list-style-type: none"> Lymphocytosis and an altered CD4/CD8 ratio are variably observed
Findings on surgical lung biopsy	<ul style="list-style-type: none"> Biopsies are rare in acute disease but when done reveal neutrophilic and lymphocytic infiltrates involving bronchioles and alveolar interstitium 	<ul style="list-style-type: none"> Lymphocytic bronchiolitis Interstitial lymphocytic infiltrates Small, loose granulomas—bronchiolar walls, alveolar septa Foci of organizing pneumonia may be present 	<ul style="list-style-type: none"> \pm Features of active inflammation Peribronchiolar fibrosis Interstitial fibrosis, \pm bridging features UIP or NSIP are less common

GGO, ground-glass opacity; HP, hypersensitivity pneumonitis; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

Table 64-3 Differential Diagnosis of Hypersensitivity Pneumonitis*

	Clinical Presentation	BAL Lymphocytosis	Histopathology
Asthma	++	+	–
Sarcoidosis	++	++	+
Inhalation fever (e.g., ODS)	++	–	–
Viral/mycoplasma pneumonias	++	+	–
Mycobacterial infections	++	++	+
Fungal infections	+	+	+
Other ILD (collagen vascular, IPF)	+	+	+
Chronic beryllium disease	+	++	+
Toxic fume inhalation	+	–	–

*Designations reflect other illnesses compared with hypersensitivity pneumonitis (acute, subacute, or chronic presentation). ++, very similar; +, similar; –, dissimilar.

BAL, bronchoalveolar lavage; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ODS, organic dust toxic syndrome.

Table 64-4 Components of an Occupational and Environmental History for Patients with Suspected Hypersensitivity Pneumonitis**OCCUPATIONAL HISTORY**

Chronology of current and previous occupations (with major attention to employment activities within the past several years)
 Description of job processes and specific work practices (including recent changes in production processes or practices)
 List of specific chemicals, dusts, and other aerosol exposures (e.g., grain dust; animal handling; food and plant processing; cooling towers, fountains, and other water sprays; metalworking fluids)
 Review of safety data sheets (SDS or MSDS) to identify known chemical sensitizers
 Review of industrial hygiene evaluations or environmental testing at the workplace
 Symptom improvement away from work or worsening with specific workplace exposures
 Presence of persistent respiratory or constitutional symptoms in exposed coworkers
 Use of respiratory protection at work

ENVIRONMENTAL AND RESIDENTIAL HISTORY

Pets and other domestic animals (especially birds)
 Hobbies and recreational activities (especially those involving chemicals, feathers or fur, plant materials, and organic dusts)
 Presence of humidifiers, dehumidifiers, evaporative coolers, clothes dryers vented indoors, and other humidity sources
 Use of hot tubs or saunas
 Leaking or flooding indoors
 Water damage to carpets or furnishings
 Visible fungal growth or reports of musty or moldy odors
 Feather pillows, comforters, or bedding
 Similar symptoms in other family members or home occupants

MSDS, Material Safety Data Sheet; SDS, Safety Data Sheet.

of specific work processes and exposures. The environmental history should explore exposure to animal proteins, particularly birds or feathers; hobbies such as gardening and lawn care, which may involve sensitizing chemical exposures like pyrethrums; recreational activities, for example, use of hot tubs, indoor swimming pools, or saunas from which microbial bioaerosols can be generated; use of humidifiers, cool mist vaporizers, and humidified air conditioners, which can be sources of microbial bioaerosols; moisture indicators such as leaking, flooding, or previous water damage to carpets and furnishings; and visible mold or mildew contamination in occupied spaces, sometimes with musty or moldy odors.

Although a suggestive exposure history is included in most published diagnostic criteria, in many cases a causal antigen is not identified. This may be the result of inadequate occupational and environmental history taking or because of exposure to a novel causative antigen. In fibrotic HP, antigen exposure may no longer be ongoing, and, even in the setting of complete exposure histories, up to 30% of cases have no causal exposure identifiable.⁹⁸

ANTIBODY TESTING

In general, precipitating and other antibody tests are neither sensitive nor specific for HP.⁹⁹ When positive, antibody tests can be helpful in confirming the diagnosis in bird breeder's lung and in other circumstances in which the putative antigen has been identified. In a study from France where an antigen panel containing common local microbial

agents was tested in patients with HP and compared to healthy control farmers, sensitivity and specificity were quite good.⁷ However, antibody testing is not recommended as a screening tool because, in exposed populations, positive test results have a poor specificity for disease.¹⁰⁰ The finding of specific IgG-precipitating antibodies indicates exposure sufficient to generate a humoral immunologic response, but it is not strongly associated with disease. In a large series of patients with bird fancier's HP, where 92% had positive serum IgG antibodies, 87% of controls who were similarly exposed to birds but did not develop HP also had positive precipitins.⁷⁷ More sensitive assays such as the enzyme-linked immunosorbent assay and electrosyneresis to detect specific IgG antibodies may lead to confusion because of decreased specificity.⁷ However, there may be false-negative results, and negative precipitins should not be used to exclude the diagnosis. False-negative results can be due to poorly standardized antigens, improper quality controls, insensitive immunologic techniques, the wrong choice of antigen, or underconcentrated sera. In addition to these test parameters, serum precipitins may disappear over time after exposure ceases or may be undetectable in patients with low-level antigen exposure.¹⁰¹ In cases of complex microbial bioaerosol exposures, disease may not be a reaction to one organism alone but a cumulative reaction to a number of airborne antigens, which may not be reflected in available laboratory antigen panels. Therefore, despite advances in detection of serum antibodies, challenges in their use and interpretation persist.¹⁰² In addition, skin tests for both immediate and delayed-type hypersensitivity reactions are not helpful in the diagnosis of HP.^{100,103,104}

BRONCHOALVEOLAR LAVAGE

BAL is a generally safe and sensitive tool to confirm the presence of alveolitis in patients with HP. In nonsmoking patients with radiographic evidence of an active inflammatory disease process, a lack of BAL lymphocytosis argues against HP. Even in predominantly fibrotic HP, the relative and absolute lymphocyte count is still often elevated, albeit less so than in acute and subacute disease.^{68,105} Although BAL lymphocytosis is a sensitive finding in HP, it is not specific. Similar to the formation of precipitating antibodies, individuals exposed to HP antigens may develop a lymphocytic alveolitis but have no symptoms or other clinical abnormalities. In addition, the lymphocytosis may persist for years after apparent removal from antigen exposure and despite improvement in other clinical parameters, limiting its utility as a tool to follow the course and progression of disease or to assess adequacy of antigen avoidance.¹⁰⁶

LUNG BIOPSY

When the risk-benefit ratio is reasonable, obtaining 8 to 10 transbronchial biopsy samples may be a prudent approach to increasing the diagnostic yield in patients undergoing bronchoscopy for initial HP evaluation. Interstitial lymphocytic inflammation and granulomas can be seen; however, appreciation of the prototypical airway-centered inflammation in subacute HP usually requires a surgical lung biopsy.¹⁰⁷ Although yields of transbronchial biopsies are unpredictable, when positive they may spare a more

invasive surgical lung biopsy. Surgical lung biopsy is indicated in patients without sufficient clinical criteria for a definitive diagnosis or to rule out other diseases that require different management.¹⁰⁸ Surgical lung biopsy is also often helpful to differentiate fibrotic HP from other fibrotic interstitial lung diseases.^{68,74,75,97} Because findings may be patchy or sparse, diagnostic yield increases if biopsies are taken from multiple lobes.¹⁰⁹ In spite of some histologic findings that are highly suggestive of HP, the potential for overlap in the appearance of HP and other interstitial lung diseases often makes pathologic changes without clinical correlation insufficient for diagnosis.^{109a} Special stains and cultures are important to distinguish HP from infectious granulomatous conditions, including fungal and mycobacterial diseases. HP typically differs from sarcoidosis in the finding of inflammatory infiltrates at interstitial sites distant from granulomas and in the morphologic characteristics and distribution of granulomas. Interstitial infiltrates in sarcoidosis, if present, are seen in the vicinity of granulomas, which are well formed and perilymphatic.

INHALATION CHALLENGE

The use of laboratory inhalation challenge in the diagnosis of HP is limited by the lack of standardized antigens and techniques. Inhalation of an aerosolized antigen suspected to be causative is most helpful when acute symptoms and clinical abnormalities are part of the disease presentation and are likely to arise within hours after exposure. Inhalation challenge also may be helpful in the evaluation of new potential HP agents, though it is not widely available or standard practice at most clinical centers. Interpretation of results is often difficult, and routine inhalation challenge is not recommended in most patients with suspected HP.

NATURAL HISTORY AND PROGNOSIS

In acute HP, symptoms of fever, chills, and cough usually disappear within days after exposure ceases. Malaise, fatigue, and dyspnea may persist for several weeks. There is usually rapid improvement in lung vital capacity and diffusing capacity for carbon monoxide in the first few weeks after an acute attack, but mild abnormalities in pulmonary function often persist for several months.¹¹⁰ In general, recovery from acute HP is expected, and avoidance of antigen exposure is associated with a favorable long-term outcome. Some patients, after recovering from acute HP, remain without pulmonary impairment in spite of recurrent antigen exposure.¹¹¹ Conversely, the disease may progress despite removal from exposure.¹¹² Although uncommon, continued symptoms and/or progressive lung disease have been reported after recurrent acute attacks or even after a single severe attack.¹¹²

The subacute and chronic fibrotic forms of HP, with insidious symptoms and more subtle, progressive clinical abnormalities, are often recognized later in the course of illness and consequently have a poorer prognosis than acute disease. HP can result in asthma, emphysema, and

interstitial fibrosis (eFig. 64-5). In a study of Finnish farmers meeting strict diagnostic criteria for FLD, the risk for asthma necessitating medication was found to increase within the first 3 years after a diagnosis of FLD, with significantly higher asthma prevalence rates in the population with FLD at 5-year follow-up compared with the reference population.¹¹³ Emphysema is also associated with FLD. In a case-control study of 88 farmers with FLD, emphysema was found in 23% (in 18% of nonsmoking and 44% of smoking FLD patients).¹¹⁴ Recurrent attacks of FLD were associated with risk for developing emphysema. In another study of farmers with FLD, 50% had residual disease, and obstruction from emphysema was the most common clinical finding.¹¹⁵ Whereas emphysema is more common in chronic FLD, interstitial fibrosis is a more common outcome in chronic bird breeder's lung. When compared to patients with FLD, patients with HP from avian antigens appear to have a higher risk for developing fibrotic lung disease and poorer associated long-term survival rates.

No functional or biochemical marker exists to predict resolution or progression of HP. The BAL lymphocytosis may persist for years after removal from exposure and despite clinical recovery. Age at diagnosis, duration of antigen exposure after onset of symptoms, and total years of exposure before diagnosis had predictive value in the likelihood of recovery from pigeon breeder's lung disease.¹¹⁶ Patients with fibrotic disease have a significantly worse prognosis overall compared to those with nonfibrotic HP.^{85,93,117} The type of fibrotic features in HP may also correlate with prognosis; usual interstitial pneumonia and fibrotic NSIP findings are associated with worse long-term survival compared to cellular NSIP and other fibrotic histopathologic patterns.¹¹⁸ Diffuse alveolar damage can complicate the course of HP. Similar to idiopathic pulmonary fibrosis, these events in HP are often labeled an "exacerbation" of disease and are associated with a poor prognosis.¹¹⁹

A 23-year population-based study undertaken to investigate the mortality of HP showed that overall age-adjusted death rates increased between 1980 and 2002.¹²⁰ The authors suggest that this may be due to the concomitant decline in smoking rates in the United States and better disease recognition from use of thoracoscopic lung biopsy for diagnosis.¹²⁰ The risk for death increases with age, with rates of 0.01 per million in the 15- to 24-year-old group, compared with 0.80 per million in the 65-year-old and older group of patients with HP.^{68,92,121} Exacerbations of chronic fibrotic HP from diffuse alveolar damage are also associated with an increased risk for death.¹²²

TREATMENT

Ongoing antigen exposure can lead to progressive disease and potentially irreversible lung damage. Thus early diagnosis and avoidance of exposure are the mainstays of treatment. Importantly, the inability to identify an offending antigen has been shown to be independently associated with shortened survival.¹²³ In some cases, antigen avoidance does not lead to disease resolution, and cases of more advanced chronic HP may progress despite exposure

cessation. Pharmacologic therapy is an important adjunct in some cases.

ANTIGEN AVOIDANCE

On-site investigation of the implicated work or home environment by an experienced industrial hygienist may be helpful in cases in which the exposure history is uncertain, particularly when disease is progressive. Inspection of a suspect residence requires skill in assessing for sources of moisture intrusion and microbial contamination, including familiarity with air-handling systems. Recommendations for removal of contaminated furnishings along with other remediation strategies have not been systematically assessed for efficacy, though such efforts are frequently implemented.³⁴ Affected patients often inquire about the need for mold sampling. However, quantitative bioaerosol sampling for indoor microbial antigens is time-consuming and expensive and requires an experienced industrial hygienist and analytical laboratory. Even when properly performed, results are often difficult to interpret. Negative results should not be used to disprove disease or exposure.

In cases of home humidifier and hot tub lung, removal of the contaminated source is usually straightforward in eliminating ongoing exposure. However, in bird fancier's disease, bird removal is not enough, and a more comprehensive effort to eliminate residual feathers and droppings is essential. Avian antigens can be found in homes without birds if wild bird excrement is deposited heavily outside the house and tracked in on shoes. Avoidance of exposure by eliminating the offending antigen from the environment may be difficult in some circumstances. In five homes monitored serially after bird removal, antigen levels measured by inhibition enzyme-linked immunosorbent assay only gradually declined despite environmental control measures, including removal of the bird and rug cleaning, with high antigen levels still detectable at 18 months in one home.²⁴

When elimination of the antigen is not feasible or the etiologic agent is not identified, exposure avoidance may be accomplished by removing the affected individual from the likely antigen-containing environment. This approach may be simple and adequate for recovery. However, the social consequences and economic disruption to the affected individual may preclude strict abstinence from exposure. When antigen exposure avoidance is likely to be inadequate, regular follow-up of pulmonary function, chest imaging, and symptoms is essential to assess response to treatment and to direct efforts to mitigate ongoing antigen exposure.

Elimination of a causative antigen from the patient's environment is the first step not only in treatment but also in prevention of hypersensitivity diseases in others who may be exposed. For example, maple bark disease and bag-assosis are now quite rare in the United States after changes in the handling of organic material, resulting in diminished opportunity for microbial growth. Removal of damaged and colonized areas, disinfection, and elimination of conditions leading to seasonal mold contamination have been effective in preventing recurrence of summer-type HP in Japan.¹²⁴ Outbreaks of HP traced to microbial contamination

of ventilation systems were controlled by extensive modification and replacement of the systems and corresponding work areas.¹²⁵

PHARMACOLOGIC THERAPY

For acute attacks of HP, systemic corticosteroids are often prescribed, although controlled clinical trials are lacking. In cases in which pulmonary function abnormalities are minor, the clinical status is stable, and spontaneous recovery is likely with removal from exposure, corticosteroids are probably unnecessary. Given the paucity of treatment studies and the known side effects of systemic corticosteroids, clinical judgment and careful medical follow-up must guide individual patient management. Corticosteroid use in acute HP has not been shown to alter long-term outcomes. However, prednisone is often given in more severe cases, typically beginning at 60 mg/day, plus supplemental oxygen for hypoxemia and other appropriate supportive measures. Prednisone usually is continued for 4 to 6 weeks until there is significant symptomatic and functional improvement. If there is objective improvement, a gradual taper to minimum sustaining doses should follow; otherwise, corticosteroids should be tapered and discontinued.

For subacute and chronic fibrotic HP, the effect of corticosteroids on the course of disease has received limited study. In a study of pigeon breeders with HP, there were no significant clinical outcome differences between patients who were treated with corticosteroids and those who were not; the mean time for improvement or normalization of pulmonary function after treatment and removal from exposure was 3.4 months.¹¹⁶ In patients with subacute HP, 3 to 6 months of daily, slowly tapering prednisone may be adequate for disease remission. However, in those with progressive or persistent inflammatory HP, sustained corticosteroid treatment may be necessary. In a patient presenting with what appears to be end-stage chronic fibrotic HP, it may be worth a short trial (2 to 3 months) of prednisone with pretreatment and posttreatment PFTs to assess for a component of treatable disease. Although empiric, inhaled corticosteroids and β -agonists may be helpful in patients with HP manifested by symptoms of chest tightness and cough and with airflow limitation on pulmonary function testing. Nonsteroidal immunosuppressives such as mycophenolate mofetil and azathioprine have been used in patients with refractory HP, but efficacy has not been assessed in clinical trials, and reports of clinical response are lacking.¹²⁶ Antimycobacterial therapy is generally not required in patients with hot tub lung. Lung transplantation may be a last resort in patients with advanced fibrotic HP.

PREVENTION

Recognition of an index case of HP is often a sentinel health event, indicating the need for further investigation and intervention in the environment where others may be at risk and where opportunities for prevention may be identified. For example, efforts to reduce the risk for metalworking fluid-related HP have included enclosure of machining

operations, improved ventilation and other engineering controls to decrease metalworking fluid aerosols, and targeted worker training.¹²⁷

Indoor microbial contamination often is related to problems with control of moisture and, to a lesser extent, temperature. Source control and dilution should be used when appropriate to reduce indoor contaminants. Source control includes preventing leaking and flooding; removing stagnant water sources; eliminating aerosol humidifiers, hot tubs, and vaporizers; and maintaining indoor relative humidity below 70%. Optimal approaches for disinfection and maintenance to prevent hot tub lung remain unknown. If humidifiers are used, frequent cleaning and water changes minimize the risk for microbial growth. Dilution of contaminants can be achieved by increasing the amount of outdoor air in a building, and high-efficiency filters can be added to the ventilation system to help improve recirculated air quality. Work practices recommended to reduce the prevalence of FLD include efficient drying of hay and cereals before storage, use of mechanical feeding systems, and better ventilation of farm buildings. Education of potentially exposed workers in the use of work practices to minimize antigen inhalation and in early symptom recognition may be helpful.¹²⁸

In a few studies the efficacy of various types of respirators has been evaluated in preventing antigen sensitization and disease progression in sensitized individuals.¹²⁹ In bird breeders with HP, serum antibody levels declined by 65% over 14 months in those wearing respirators in comparison with no decline in antibody levels in those without respirators; no data were reported on changes in symptoms or pulmonary function in the two groups.¹²⁹ In another study, use of high-efficiency respirator masks resulted in nearly normal reactivity scores, including a composite of clinical, serologic, and pulmonary function indices, upon antigen rechallenge.¹³⁰ Adherence with long-term mask use is often poor, because most respirators are uncomfortable and cumbersome and interfere with communication. Dust respirators offer substantial but, in some cases incomplete, protection against organic dusts and are not recommended as preventive measures in sensitized individuals.

Key Points

- Hypersensitivity pneumonitis (HP) is a complex syndrome caused by an immunologic reaction to a variety of inhaled antigens, and the clinical findings, disease severity, and natural history are heterogeneous.

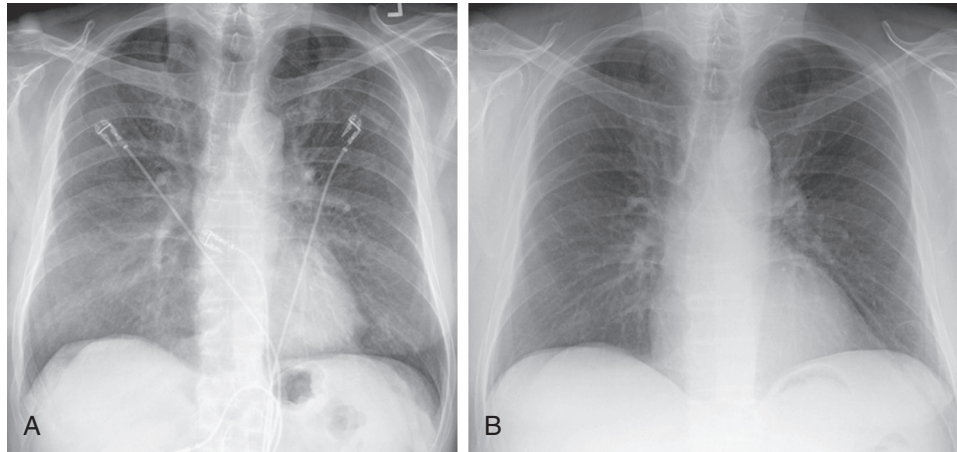
- Individuals with mild or subacute HP often escape early detection or are misdiagnosed as suffering from viral illnesses or asthma.
- Only a small proportion of exposed individuals develops clinically significant HP; even fewer develop chronic fibrotic HP.
- Genetic and host factors such as smoking status play a role in determining an individual's risk for disease.
- A high index of suspicion for the diagnosis of HP in patients with a compatible clinical presentation should prompt a comprehensive exposure history focused on microbial, bird, and low-molecular-weight chemical antigens.
- There is no gold standard test for HP; the exposure history, clinical assessment, and radiographic and physiologic findings help establish the diagnosis.
- Although the prognosis for recovery may be excellent with early disease recognition and exposure removal, patients with chronic fibrotic or emphysematous manifestations of HP often have a poor prognosis.

Complete reference list available at *ExpertConsult*.

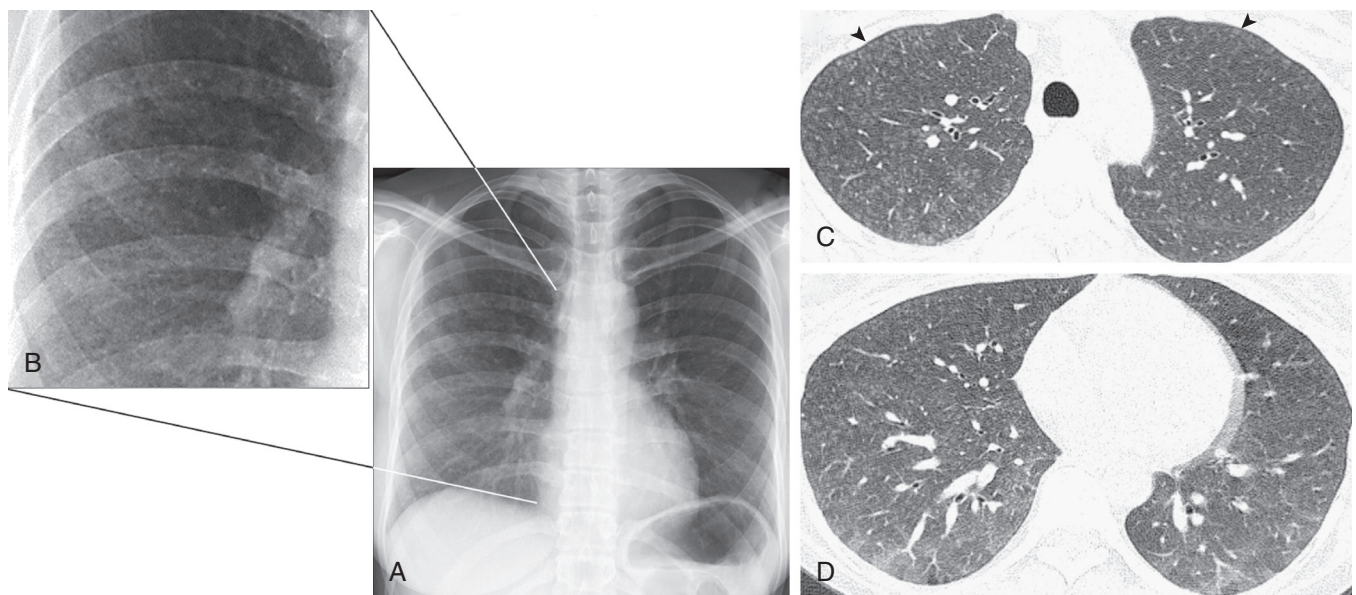
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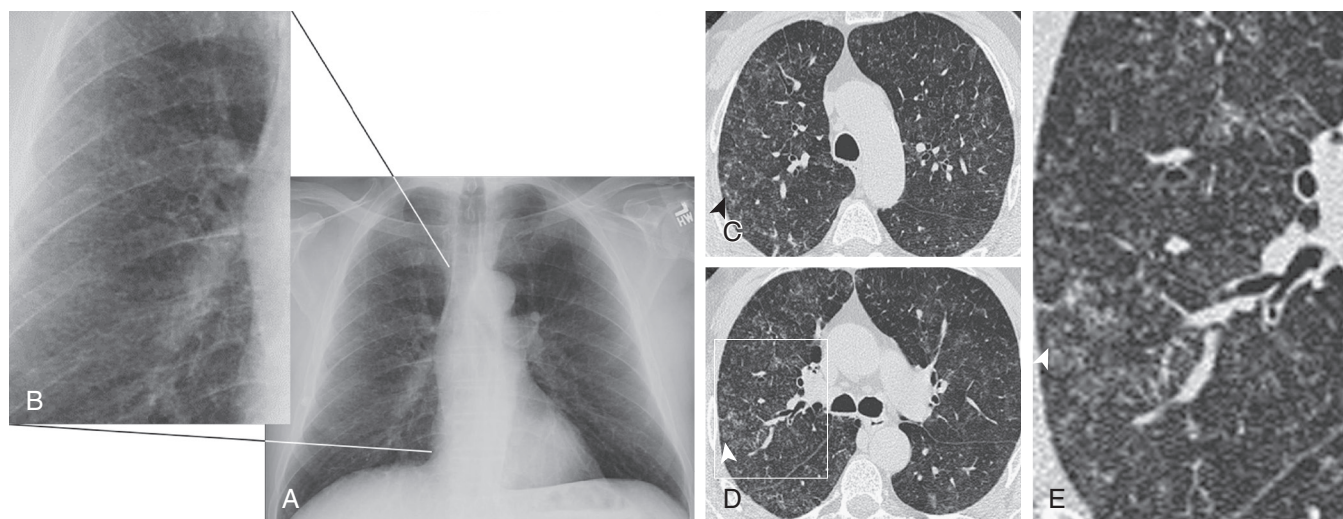
eFIGURE IMAGE GALLERY



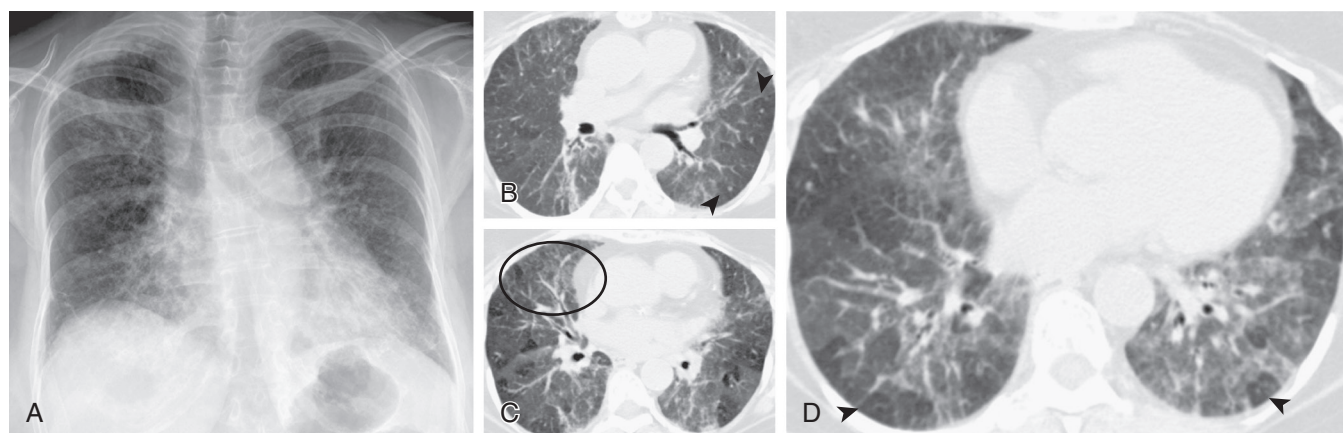
eFigure 64-1 Resolution of hypersensitivity pneumonitis following removal of offending antigen. **A**, Frontal chest radiograph in a patient with shortness of breath and bronchoscopic biopsy and chest CT evidence of hypersensitivity pneumonitis (HP). The frontal chest radiograph shows bilateral areas of faintly nodular increased attenuation and ground-glass opacity. A humidifier was the suspected etiologic agent and was removed, and the patient was treated with corticosteroid therapy. **B**, Frontal chest radiograph performed after the patient had dramatic clinical improvement, 1 month after the radiograph in **A**, shows resolution of the poorly defined areas of ground-glass opacity; the chest radiograph now appears normal. (Courtesy Michael Gotway, MD.)



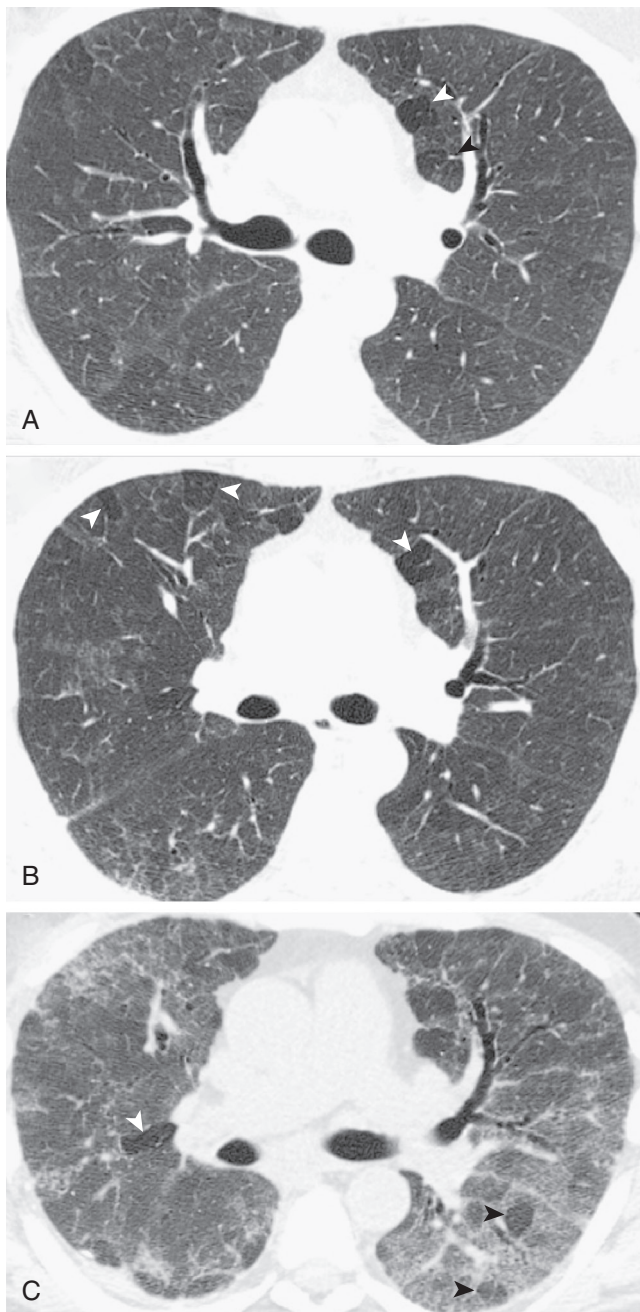
eFigure 64-2 Subacute hypersensitivity pneumonitis (HP): centrilobular opacities at chest radiography and CT. **A**, Frontal chest radiograph in a patient with many birds shows numerous, very small, poorly defined nodular opacities. The pulmonary opacities are best seen in the right midlung detail image (**B**). **C** and **D**, Axial CT images through the upper (**C**) and lower (**D**) lungs show diffuse, small, poorly defined ground-glass opacity centrilobular nodules (arrowheads). (Courtesy Michael Gotway, MD.)



eFigure 64-3 Subacute hypersensitivity pneumonitis (HP): micronodules at CT. **A**, Frontal chest radiograph demonstrating diffuse interstitial disease. Interstitial changes are highlighted in the right midlung detail image (**B**). **C** and **D**, Axial CT images through the upper (**C**) and mid (**D**) lungs show patchy, bilateral ground-glass opacities associated with small, solid nodules (arrowheads). **E**, Magnified image from **D** of posterior right upper lobe shows the micronodules (arrowhead) to advantage. (Courtesy Michael Gotway, MD.)



eFigure 64-4 Chronic fibrotic hypersensitivity pneumonitis (HP): imaging findings. **A**, Frontal chest radiograph shows multifocal, bilateral, midlung predominant linear and reticular opacities consistent with fibrotic lung disease. The imaging findings are not specific, but the absence of a clear basal and subpleural distribution argues against an idiopathic interstitial pneumonia as the cause. **B–D**, Axial chest CT displayed in lung windows shows multifocal, bilateral inhomogeneous lung opacity with areas of decreased attenuation (arrowheads) representing mosaic perfusion, with a noticeable lobular configuration (arrowheads, **D**). Patchy areas of ground-glass opacity, in some areas with micronodule formation (oval, **C**), are present. Areas of somewhat normal-appearing lung parenchyma are also seen. The combination of normal lung parenchyma, areas of mosaic perfusion, and ground-glass opacity with associated features of fibrotic lung disease is typical of fibrotic chronic HP. (Courtesy Michael Gotway, MD.)



eFigure 64-5 Progression of hypersensitivity pneumonitis (HP) over time from alveolitis toward fibrotic lung disease. **A**, Axial HRCT image shows minimal bilateral inhomogeneous lung opacity, with a few areas of faintly seen lobular low attenuation (*arrowheads*), which may suggest a small airway obstructive process, but the findings are subtle. **B**, Axial HRCT image performed 2 years after **A** shows more apparent inhomogeneous lung opacity with more clearly visible areas of lobular low attenuation (*arrowheads*); faintly ground-glass opacity is developing also. **C**, Axial HRCT performed 4 years after **A** shows extensive ground-glass opacity and reticulation associated with areas of lobular low attenuation (*arrowheads*).

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INTRODUCTION**SYSTEMIC SCLEROSIS (SCLERODERMA)**

Epidemiology and Risk Factors
 Chemically Induced Scleroderma-like Disorders
 Pulmonary Manifestations
 Pulmonary Vascular Disease in Systemic Sclerosis
 Other Pulmonary Complications
RHEUMATOID ARTHRITIS
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SYSTEMIC LUPUS ERYTHEMATOSUS

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POLYMYOSITIS AND DERMATOMYOSITIS

Epidemiology and Risk Factors
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MIXED CONNECTIVE TISSUE DISEASE**UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE**

RELAPSING POLYCHONDritis
BEHÇET SYNDROME
ANKYLOSING SPONDYLITIS
MARFAN SYNDROME

INTRODUCTION

The lung may be involved in all *connective tissue diseases* (CTDs). The involvement is often subclinical, but its true extent may be masked by exercise limitation due to musculoskeletal features of the CTD. Patterns of lung involvement vary considerably within each CTD. The differential diagnosis is made even wider by inclusion of the drug-induced pulmonary reactions (Table 65-1) and the opportunistic infections secondary to therapy for the lung disease (Table 65-2), which may present with features indistinguishable from diffuse lung disease.

It is not surprising that the lung is involved frequently in CTDs because these are systemic syndromes, but it is disappointing that little is known about the true incidence and prevalence of lung disease because of a dearth of well-controlled, prospective, unselected series. Imprecision of nomenclature has also confused the issue. With this background, the aims of this chapter are to highlight the ways in which the lung may be involved in the most common CTDs and to indicate, when appropriate, the most usual pattern of lung disease for each CTD, with an emphasis on approaches to diagnosis and efficient management.

Interstitial lung disease (ILD) has been evaluated in much more detail in systemic sclerosis than in other CTDs, probably because patients with systemic sclerosis tend to be managed at referral centers. Controlled treatment data in ILD are largely confined to patients with systemic sclerosis. Therefore, the clinical presentation, prognostic evaluation, and management of ILD, covered in the systemic sclerosis section, can be broadly applied to the other CTDs and are not discussed in detail elsewhere in the chapter.

SYSTEMIC SCLEROSIS (SCLERODERMA)

The preliminary criteria for classification of *systemic sclerosis* (SSc) require that one major or two or more of three minor criteria be present (Table 65-3).¹ The skin changes may affect the entire extremity or the face, neck, and trunk (thorax and abdomen). Scleroderma is traditionally classified on the basis of the extent of skin disease. Limited disease can involve the face, but the trunk and limbs proximal to the elbows and knees are spared. Diffuse disease can involve any part of the body.

EPIDEMIOLOGY AND RISK FACTORS

The incidence of SSc is approximately 2 to 20/100,000/yr, with a peak incidence in the fourth to sixth decades. The prevalence is 30 to 120/100,000, with a 3:1 to 8:1 female preponderance.² Mortality rates have been remarkably consistent over the years, varying from 0.9 to 1.5/million for men and 2.1 to 3.8/million for women in the United States. The disease is present worldwide.

Although scleroderma clusters in families with other autoimmune disease, there are few reports of first-degree relatives having SSc. The importance of genetics to SSc is illustrated by a study of Choctaw Indians residing in southeastern Oklahoma. The prevalence of SSc in full-blooded Choctaws is roughly 1:200, which is significantly higher than is found in non-full-blooded Choctaws (1:3000) and strikingly higher than the global prevalence of SSc in other Native Americans in Oklahoma (1:10,000).³

Genetic involvement in the disease has been determined by the identification of chromosomal abnormalities and by

Table 65-1 Drug Toxicity: Patterns of Lung Disease That Have Been Reported as Adverse Effects of Drugs Commonly Used to Treat Connective Tissue Diseases

Pulmonary Effect	Penicillamine	Methotrexate	Gold	Cyclophosphamide	Sulfasalazine
Hypersensitivity pneumonitis		+	+		
Pulmonary infiltrate with eosinophilia		+	+		+
Interstitial pulmonary fibrosis			+	+	
Obliterative bronchiolitis	+		+		
Organizing pneumonia	+	+	+		+
Pleural effusion, thickening		+		+	+
Alveolar hemorrhage, vasculitis	+				+

Table 65-2 Immunosuppressive Therapy: Common Drugs Used in the Treatment of the Major Pulmonary Complications of Connective Tissue Diseases

Drug	Dose	Duration	Comments	Monitoring
Azathioprine	2.5 mg/kg/day Maximum 200 mg/day	Continuous	<ul style="list-style-type: none"> Maximal effect may not be evident for 6–9 mo but has better adverse effect profile than cyclophosphamide. May be used long term. Starting dose 50 mg daily with monitoring full blood count in case of thiopurine methyltransferase deficiency; maintenance dose from 1 mo. 	Full blood count Liver function tests
Cyclophosphamide, oral	2 mg/kg/day	Variable	Oral cyclophosphamide may be used continuously or substituted at 3 mo for azathioprine because of more favorable adverse effect profile in DLD.	Full blood count Liver function tests Urinalysis for blood
Cyclophosphamide, IV	15 mg/kg monthly for 1–6 mo	Variable	<ul style="list-style-type: none"> IV therapy for rapid induction of remission at 2–4 mg/kg/day for 3–4 days, especially for vasculitis Pulsed IV cyclophosphamide may be given at 1- to 3-mo intervals with better adverse effect profile and lower long-term cumulative dose, particularly in nonvasculitic disease 	Full blood count Liver function tests Urinalysis for blood
Cyclosporin A	5 mg/kg/day	Continuous	<ul style="list-style-type: none"> Bioavailability variable, thus blood monitoring necessary. May be used in combination with prednisolone. 	Blood pressure Urea and creatinine Cyclosporin A level
Mycophenolate mofetil	1–3 g/day	Continuous	<ul style="list-style-type: none"> Increasingly favored as best second line therapy, usually in combination with low dose prednisolone. Usually well tolerated with gastrointestinal symptoms the major side effects. 	Full blood count Liver function tests
Methotrexate	7.5–25 mg/wk	Continuous	<ul style="list-style-type: none"> Little information to support use except as second-line therapy. Pulmonary toxicity may be limiting. 	Full blood count Liver function tests
Prednisolone	1 mg/kg/day or 20 mg alternate days	Continuous	Prednisolone used alone in high dose for cellular DLD and then titrated to control. In conjunction with immunosuppressants, the low-dose regimen is used.	Blood pressure Blood glucose Weight Bone densitometry
Methylprednisolone	500–1000 mg	3–5 days	Used for aggressive induction of remission, particularly for vasculitis or acute pneumonitis, then followed by maintenance therapy of prednisolone or prednisolone plus immunosuppressive agent.	

DLD, diffuse lung disease; IV, intravenous(ly).

studies of the major histocompatibility complex genes. Although many of the early studies were serologic, more recently, polymerase chain reaction technology has been employed. With this latter approach, an association between diffuse lung disease and *human leukocyte antigens* (HLAs)—HLA-DR3, HLA-DR52a, HLA-DRB1*11, and HLA-DPB1*1301—has been recognized.^{4,5}

CHEMICALLY INDUCED SCLERODERMA-LIKE DISORDERS

A variety of agents are known to induce SSc-like disease, often with lung involvement, including D-penicillamine, tryptophan, bleomycin, pentazocine, and (particularly in men) the industrial agents vinyl chloride, benzene, toluene,

Table 65-3 Systemic Sclerosis (Scleroderma)**CRITERIA FOR DIAGNOSIS*****Major**

Thickening of the skin of the hands

Minor

Sclerodactyly (i.e., the changes of the major criterion but limited to the fingers)
 Digital pitting scars or loss of substance from the finger pad: depressed areas at tips of fingers or loss of digital pad tissue as a result of ischemia
 Bibasilar pulmonary fibrosis

LUNG MANIFESTATIONS

Interstitial pulmonary fibrosis
 Organizing pneumonia
 Isolated pulmonary vascular disease
 Aspiration pneumonia (secondary to esophageal dysmotility)
 Chest wall restriction

*The major or ≥ 2 minor criteria required for diagnosis.

and trichloroethylene.⁶ Silica exposure increases the odds ratio of SSc, and silicosis increases the rate even further.⁷ The toxic oil syndrome, first recognized in Madrid in 1981, results from ingestion of an adulterated cooking oil containing rapeseed oil denatured with aniline.⁸ This provokes a scleroderma-like syndrome with pulmonary involvement. The association with silicone breast implants is unproved.

PULMONARY MANIFESTATIONS

More is known about the pulmonary complications associated with SSc than with any other CTD. Pulmonary involvement has emerged as the major cause of excess morbidity and mortality in SSc.⁹ The patterns of lung disease with which SSc may present are variable and are shown in Table 65-3.

Interstitial Pulmonary Fibrosis

Pathogenesis. There are several distinct, but related, aspects of pathogenesis.

PREDISPOSITION. There is good evidence that individuals are predisposed genetically to develop SSc, and there are emerging markers that define risks for diffuse lung disease. Class II major histocompatibility complex associations increase the risk of interstitial pulmonary fibrosis in SSc. The relative risk is increased if the anti-DNA topoisomerase (Scl-70) antibody is present. Recent studies have shown that there is an association between Scl-70 and an allele of the major histocompatibility complex *DPB1* gene.

The genetic susceptibility probably results in injury and an immune response. It has been shown that there are highly restricted T-cell responses to epitopes of DNA topoisomerase 1, both in healthy individuals and in those with SSc. Thus, in individuals with Scl-70-responsive T-cell clones, the autoantibody may be responsible for driving the immune response. In the lung, there is an accumulation of “memory-type” CD45 Ro lymphocytes and secondary lymphoid follicles with true germinal centers within lung biopsy samples.¹⁰ Furthermore, the T cells present within the lung express cytokines of both the *T helper 1* (Th1) and the *T helper 2* (Th2) subsets.¹¹ Genetic susceptibility is also

relevant to noninflammatory mediators on the basis of recent genome-wide association studies.^{12,13}

INFLAMMATION AMPLIFICATION. A wide variety of cytokines identified in *bronchoalveolar lavage* (BAL) fluid clearly contribute to the cascade of inflammation in the lungs.¹⁴ The most striking of these are interleukin-8 (neutrophil chemoattractant and activator), *tumor necrosis factor- α* (TNF- α ; an early cytokine involved in many pathologic processes), macrophage inflammatory protein-1 α (important in neutrophil chemotaxis), and RANTES (*regulated on activation normal T cell expressed and secreted*; important in T-cell and eosinophil recruitment and activation). It is clear, therefore, that the downstream events of the initiation result in the release of a number of proinflammatory cytokines that are responsible for further recruitment and activation of inflammatory cells at disease sites.

FIBROGENETIC FACTORS. The hallmark of SSc in both lung and skin is the accumulation of connective tissue matrix cells and proteins.^{15,16} Many factors have been studied in this regard, and a wide variety of growth factors have been identified. Perhaps the most striking of these is connective tissue growth factor, which appears to depend on *transforming growth factor- β* (TGF- β) for up-regulation and has a potent effect on collagen production, as evidenced by collagen gel retraction studies.^{17,18} TGF- β is found in high amounts in the lungs of patients with SSc¹⁹ and, when TGF- β signaling is inhibited, minor epithelial injury leads to extensive fibrosis.²⁰ *Endothelin* (ET)1 and coagulation cascade proteins are also present in high amounts in BAL fluid.^{15,21} Fibroblasts from patients with lung disease exhibit dysregulated type I collagen biosynthesis and impaired messenger RNA down-regulation. The balance of ET receptors (A and B) is modified in the lungs of patients with scleroderma, with a consistent decrease in ETA and an increase in ETB receptors.^{16,22} ET1 may contribute to epithelial-mesenchymal transition of airway epithelial cells, resulting in fibrosis.²³

EPITHELIAL DAMAGE. Although a key pathogenic event in idiopathic ILD, epithelial damage has been relatively underemphasized in disease models of pulmonary fibrosis in CTD. Abnormally rapid clearance of an epithelial tracer (DTPA, see later) and elevated serum KL6 levels, specific markers of alveolar epithelial damage, correlate with the severity of pulmonary involvement and are predictive of pulmonary disease progression in SSc.^{24,25} The intratracheal instillation of normal saline in a mouse strain with SSc features (including skin fibrosis and other universal characteristics) leads to lung injury and fibrosis, with evidence of epithelial injury on electron micrographic studies, attenuated type II pneumocyte proliferation, and persistence of the myofibroblast population after injury.^{26,27} Chronic microaspiration, believed to happen in many patients with SSc,²⁸ is a plausible trigger of recurrent epithelial injury.

A number of parallel events result in the development of lung injury and subsequent fibrosis. It is simplistic to target any one of these as being the important factor, but there seems little doubt that the key cytokines in the cascade include TNF- α (because it appears early in disease and has been shown in animal models to be a pivotal factor in lung fibrosis)²⁹ and TGF- β receptor (which up-regulates collagen gene expression and is important in connective tissue growth factor release). Other important cytokines may

include hepatocyte growth factor and insulin-like growth factor-II.^{30,31} The balance of Th1 to Th2 cytokines is also key because, when the shift is in favor of Th2 cytokines, such as in idiopathic pulmonary fibrosis, the prognosis is worse and there is a much higher eosinophil influx into the lung, in comparison with patients with SSc, in whom the Th1/Th2 ratio is balanced and there is less eosinophil influx per unit lung involvement.¹¹

Clinical Features

The prevalence of lung disease in SSc depends on the method used for detection. Symptoms or signs of lung disease are common. Dyspnea is present in roughly 55% of patients (range, 21% to 80%).³² Cough, a less frequently reported symptom, tends to be dry and nonproductive. Hemoptysis is rare but may complicate carcinoma or bronchial telangiectasia.³³ Fine crackles are heard at the lung bases and are of a “Velcro” character. Pleural rub is almost never heard. Pleuritic chest pain is uncommon. Pneumothorax is even less common. Digital clubbing is extremely rare. Secondary pulmonary hypertension with appropriate clinical features of right ventricular strain, raised jugular venous pressure, and ankle edema may be seen during the terminal stages of the disease.

The lung is involved more commonly in patients with diffuse rather than limited cutaneous SSc, but the extent of skin involvement does not correlate with lung function changes. Patients are often without symptoms, even with moderate pulmonary function impairment, but in other cases, exertional dyspnea is present when ILD is trivial or absent, due to pulmonary vascular limitation, cardiac involvement, musculoskeletal problems, general debility, loss of fitness, or a variable combination of these factors. Rarely, scleroderma of the chest wall may cause extrathoracic restriction.

Lung disease may be the first manifestation of SSc. In this setting, a history of Raynaud phenomenon is often helpful. In addition, careful examination of the capillaries in the nail beds reveals the typical feature associated with scleroderma: abnormal loops associated with capillary “dropout” (Fig. 65-1A). The presence of autoantibodies, particularly antinuclear antibodies, is helpful in suggesting a CTD etiology (Table 65-4).

Imaging

Chest radiographic abnormalities are present in 25% to 67% of patients, and lung function is impaired in up to 90%, although a large subset of patients has only a minor reduction in gas transfer or diffusing capacity (DL_{CO}). Chest radiography typically shows a reticular pattern in the lung bases and periphery in early disease. There is obvious loss of volume with more extensive reticular shadowing in more advanced disease. In this situation, honeycombing may be present (Fig. 65-1B).

Computed tomography (CT) has revolutionized the interpretation of the pattern and extent of disease. Disease is localized to the lung periphery, appearing earliest at the bases and posteriorly (Fig. 65-1C and D, eFigs. 65-1, 65-2, and 65-3). As disease becomes more advanced, it progresses superiorly, centrally, and anteriorly. Esophageal dilation is common, which can be helpful in the diagnosis if the lung disease is the first manifestation of the systemic disease (Fig. 65-1C and D).³⁴ The pattern may be “ground-glass” (reflecting either fine intralobular fibrosis or a more cellular histopathology) or an overtly fibrotic “reticular” pattern, consisting of intersecting linear abnormalities, often associated with traction bronchiectasis.³⁵ Honeycomb change is present in up to one third of cases but is usually limited in extent.³⁶

CT extent correlates moderately well with lung function variables, particularly measures of DL_{CO} .^{36a} In the absence of overt pulmonary hypertension, individuals with SSc are less hypoxemic than those with idiopathic pulmonary fibrosis, once the extent of disease on CT has been taken into account, a difference that has been ascribed to a relative absence of new vessel formation in abnormal lung in SSc.³⁷ The extent of individual patterns (ground-glass vs. reticular) is associated with the type of inflammatory cell found in BAL. More extensive reticular (consistent with more fibrosis) disease is associated with high neutrophil numbers, and this influx appears to be associated primarily with more extensive lung disease.³⁸

Gallium scans provide no added value. Technetium-99m-labeled *diethylenetriaminepentaacetic* (DTPA) acid clearance has been used in some medical centers to identify early disease and predict prognosis.³⁹ A more rapid clearance of

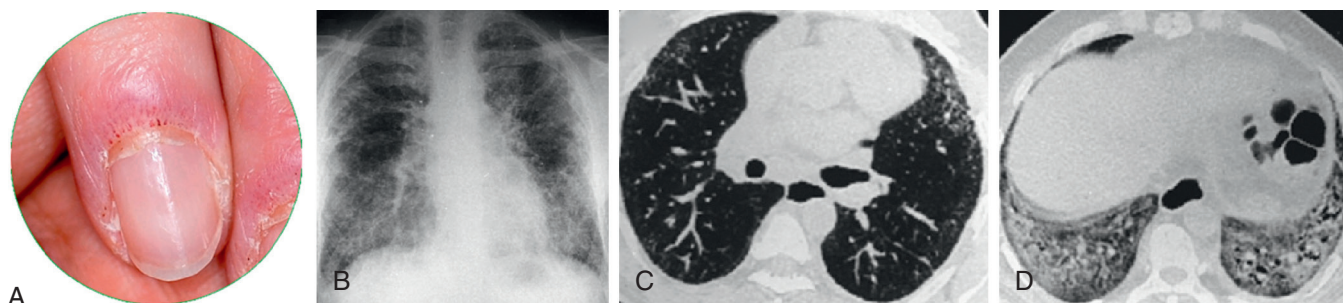


Figure 65-1 Radiographic appearances in patients with systemic sclerosis. **A**, Nail bed showing abnormal capillary loops in the cuticle. **B**, Chest radiograph from a patient with systemic sclerosis. Note the widespread, predominantly peripheral pattern of reticular opacities. The heart borders and the diaphragm are obscured. **C**, CT scan taken at a level just below the carina in a patient with systemic sclerosis. Note the peripheral reticular pattern that in this case is more prominent anteriorly. In this patient with subtle disease, the dilated esophagus is a clue as to the true cause of the fibrosing lung disease. **D**, CT scan taken at the level of the diaphragm in a patient with more extensive interstitial pulmonary fibrosis in the context of systemic sclerosis. Note in particular the dilated airways, indicating that the apparent “ground-glass”/consolidation pattern is dense fibrosis. Again, the dilated esophagus indicates that this disease is likely to be part of systemic sclerosis. (A, Adapted from Iaccarino L, Ghirardello A, Bettio S, et al: The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun* 48–49:122–127, 2014, Fig. 1; B–D, Courtesy Michael Gotway, MD.)

Table 65-4 Autoantibodies in Connective Tissue Disease

CTD	Autoantibody	Target	Comments
SSc	Anticentromere	Centromere proteins (CENP A-F)	20%–40% total SSc, wide racial variation 70%–80% limited cutaneous variant with pulmonary hypertension
	Scl-70	DNA topoisomerase 1	28%–70% total SSc, wide racial variation; >30% diffuse cutaneous disease with ILD
	PM-Scl	—	Scleroderma-myositis overlap syndromes
	Antinucleolar Ku	RNA polymerase-1 DNA binding proteins	8%–20% SSc suggests poorest 10-yr survival, renal crisis Scleroderma-myositis overlap syndromes
Rheumatoid arthritis	Rheumatoid factor	IgG	Seropositive disease more frequent with pulmonary nodules
	Antinuclear antibody Histone	— Histone proteins	— 5% rheumatoid vasculitis
SLE	dsDNA	dsDNA	50%–75%, strong association with nephritis
	ANA	—	90%–95%
	Ro/La	RNA transcription factors	60%/20%
	Histone	Histone proteins	>90% drug-induced lupus, 20%–30% primary SLE
	Sm	—	10% whites and 30% African Americans and Chinese
MCTD	Lupus anticoagulant	Phospholipid	20%–30%
	U1-RNP	Small nuclear proteins	Myositis overlap syndromes (10% SSc)
DM/PM	U2-RNP	—	Myositis, SLE, SSc
	Jo-1	Histidyl tRNA synthetase	20%–30% inflammatory myopathy but 50%–100% when associated with diffuse fibrosing lung disease
	PL-7	Threonyl tRNA synthetase	<3% antisynthetase syndrome
	PL-12	Alanyl tRNA synthetase	<3% antisynthetase syndrome
	EJ	Glycyl tRNA synthetase	<2% antisynthetase syndrome
	OJ	Isoleucyl tRNA synthetase	<2% antisynthetase syndrome
	Mi-2	Nuclear proteins	<8% DM, associated with acute onset of classic DM
	Ku	Nuclear proteins	Associated with myositis-CTD overlap syndromes
Antiphospholipid syndrome	Anticardiolipin	Membrane phospholipids	Disease diagnosis depends on presence of clinical features
	Lupus anticoagulant	—	—
Relapsing polychondritis	Anticardiolipin	Cartilage Collagen	Unknown sensitivity
Sjögren syndrome	Ro (SS-A)	RNA transcription factors	40%–50% primary Sjögren syndrome (25%–30% SLE)
	La (SS-B)	—	50% Sjögren (10% SLE)

ANA, antinuclear antibody; CTD, connective tissue disease; DM/PM, dermatomyositis/polymyositis; dsDNA, double-stranded DNA; IgG, immunoglobulin G; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; tRNA, transfer RNA.

this tracer from the air spaces into the circulation is indicative of a loss of epithelial cell integrity. A persistently rapid clearance rate confers an increased risk of subsequent lung function deterioration, and a persistently normal clearance rate predicts lung function stability.

Lung Function Tests

The interstitial pulmonary fibrosis of SSc is characterized by a restrictive ventilatory defect, which results in reduced pulmonary compliance, vital capacity, and total lung capacity. Residual volume is decreased. DL_{CO} is reduced and may be the only abnormality in early disease. Blood gas analysis usually reveals a normal or reduced *arterial oxygen pressure* (PO_2), reflecting regional vasoconstriction in diseased lung, with a normal or low *arterial carbon dioxide pressure* (PCO_2). In the absence of pulmonary hypertension, hypoxemia is seldom marked until late in the disease process.

There have been a number of studies of the rate of decline of lung function in SSc.^{40,41} In one study of 38 patients with SSc, the mean loss of vital capacity was 100 mL per year (20 to 30 mL/yr being the normal rate of decline).⁴¹ A second study showed that vital capacity loss was greater in patients who had evidence of an active alveolitis on BAL.³⁰ Lower *forced vital capacity* (FVC) within 3 years of disease onset predicts decline in pulmonary function.⁴² Rates of

decline are often higher within the first few years of onset of SSc, emphasizing the importance of identifying lung disease early.

Exercise lung function testing increases ventilation-perfusion mismatching and also increases diffusion abnormalities resulting in hypoxemia and widening of the alveolar-arterial oxygen difference. Minute ventilation increases generally as a consequence of increased respiratory rate rather than tidal volume. Dead space ventilation may increase with exercise, with a rise in the dead space-to-tidal volume ratio. For a given degree of lung involvement defined by CT, abnormalities on exercise gas exchange are more severe in patients with idiopathic pulmonary fibrosis than in those with interstitial pulmonary fibrosis in association with SSc.³⁷

Bronchoalveolar Lavage

BAL may identify alveolitis in SSc before the onset of pulmonary symptoms.⁴³ A neutrophil alveolitis has been described by some authors to predict more progressive disease.^{40,44,45} However, it has been shown that an increase in neutrophils reflects an increase in the extent of disease on CT, particularly of the reticular pattern; thus, this increase is likely a marker of more extensive disease rather than an independent index of progressive disease.^{38,46,47}

BAL should not be used alone to determine whether treatment should be started. Many patients with apparently normal BAL findings may exhibit progressive disease. BAL is, therefore, not recommended routinely for the diagnosis or monitoring of SSc-related interstitial disease.

Biopsy

Surgical lung biopsy is virtually never required in the diagnosis of SSc-related interstitial disease unless clinical and CT findings are atypical for ILD in SSc and an alternative diagnosis is suspected. No useful additional information is provided by transbronchial biopsy. Pathologically, the most prevalent pattern is nonspecific interstitial pneumonia, with thickening of the alveolar walls with inflammatory cells (mononuclear cells, granulocytes, and plasma cells); connective tissue matrix cells; and proteins combined with intra-alveolar inflammation (predominantly by macrophages), type II pneumocyte proliferation, and vascular obliteration. The distribution is subpleural and basal and is maximal in posterior segments, with the macroscopic findings of the lung surface taking on a fine nodular, “cirrhotic” appearance in the early stages and honeycombing with more advanced disease.⁴⁵ This pattern differs from usual interstitial pneumonia in exhibiting a homogeneous pattern of pathology (eFig. 65-4). Much less commonly, the usual interstitial pneumonia pattern of histopathology is seen. One of the hallmarks of usual interstitial pneumonia is a heterogeneous appearance, with normal alveoli seen in the same section as areas of extensive alveolar remodeling (areas of fibroblastic proliferation and dense fibrosis).⁴⁸ Crucially, outcome does not differ materially. In idiopathic disease, the usual interstitial pneumonia pattern of injury is associated with a worse outcome compared with the nonspecific interstitial pneumonia pattern.^{48a} However, in SSc, outcome is not related to the histologic pattern in the largest series,⁴⁵ although there is evidence in a smaller series that some patients with usual interstitial pneumonia pattern have a progressive course.⁴⁹ Overall, surgical biopsy data do not provide sufficient prognostic information to justify the procedure in SSc.

Electron microscopy shows early endothelial and epithelial cell injury, even without abnormalities on light microscopy. Autopsy studies show diffuse lung disease in up to 80% of cases and pulmonary vascular disease in up to 30% (eFig. 65-4C). In some patients with a more accelerated course of disease, histopathologic examination has shown a diffuse alveolar damage pattern.⁵⁰

Serologic Investigations

Although SSc is traditionally defined on the basis of the extent of the skin disease, as outlined previously, the pattern of autoantibodies appears to be a much stronger determinant of the associated internal organ involvement.^{51,52} Antinuclear antibodies are found in 90% to 100% of patients with SSc (roughly 30% of normal individuals have antinuclear antibodies at a titer of 1:40). Three major autoantibodies include anti-centromere, seen in 57% of patients with limited cutaneous disease; anti-topoisomerase (Scl-70), seen in 40% of patients with diffuse disease; and PM-Scl, seen in a small fraction of cases in association with the polymyositis overlap syndrome. It is rare to have both Scl-70 and anti-centromere antibodies. Diffuse lung disease

is rare in the presence of anti-centromere antibodies, and a protective role for this autoantibody has been argued but not substantiated. Interstitial pulmonary fibrosis is strongly associated with the Scl-70 antibody and with diffuse scleroderma. Limited cutaneous disease associates with vascular disease and the anti-centromere antibody. Both forms of lung disease may progress to pulmonary hypertension. Other autoantibody studies have shown associations with organ involvement, including a nucleolar pattern associated with diffuse lung disease and pulmonary hypertension⁵³; the antibody against B23, a nucleolar phosphoprotein, associated with pulmonary hypertension and the presence of the anti-fibrillarin antibody; and anti-Th/To antibodies associated with pulmonary hypertension and diffuse lung disease.

Prognosis

Although crude mortality rates are 3.9%/yr for men and 2.6%/yr for women, lung disease remains the most common cause of death in patients with SSc.⁵⁴ In one series, lung disease accounted for 21% of all deaths.⁵⁵ There is also an increased risk of lung cancer in SSc. With the widespread use of *high-resolution computed tomography* (HRCT), mild or trivial ILD (see eFigs. 65-1, 65-3A) is detected in many SSc patients, leaving the clinician with difficult decisions as to whether to introduce therapy or to observe carefully without immediate intervention. This dilemma is most frequently confronted in SSc but is also increasingly encountered in other CTDs. In overtly severe ILD, the decision to treat is straightforward. However, the majority of SSc patients have milder lung involvement, and a reliable means of discriminating between stable and progressive ILD would be useful in management. On the basis of clinical series and accumulated experience, prognostic evaluation should focus on three main considerations.

The decision to treat patients with SSc is most strongly influenced by the extent of disease at presentation, as judged by lung function tests (particularly FVC and DL_{CO}), and the extent of disease on CT. A simple staging system using CT extent (above and below 20%) and FVC at presentation (above and below 70%), the *United Kingdom Raynaud's and Scleroderma Association* (UKRSA) staging system, is highly discriminatory for both progression and death (Fig. 65-2).⁵⁶ The prognostic value of the UKRSA staging system has been confirmed,⁵⁷ and the severity thresholds were virtually identical to those found to identify the likelihood of a treatment effect in the first controlled study of oral cyclophosphamide in SSc.⁵⁸

The selection of patients in need of treatment is also influenced by the duration of systemic disease. The greatest risk of ILD progression is during the first 4 years of SSc. Early declines in FVC are strongly predictive of subsequent severe ILD,⁵⁹ which most often develops in the first 4 years.⁶⁰ Put simply, in SSc and other CTDs, the early development of mild to moderate ILD is a marker of likely rapid disease progression, which should reduce the threshold for initiating therapy.

Finally, evidence of recent disease progression is an important justification for treatment. It should be acknowledged that the long-term prognostic value of observed disease progression has not been quantified in SSc or, indeed, in other CTDs. However, declines in lung function

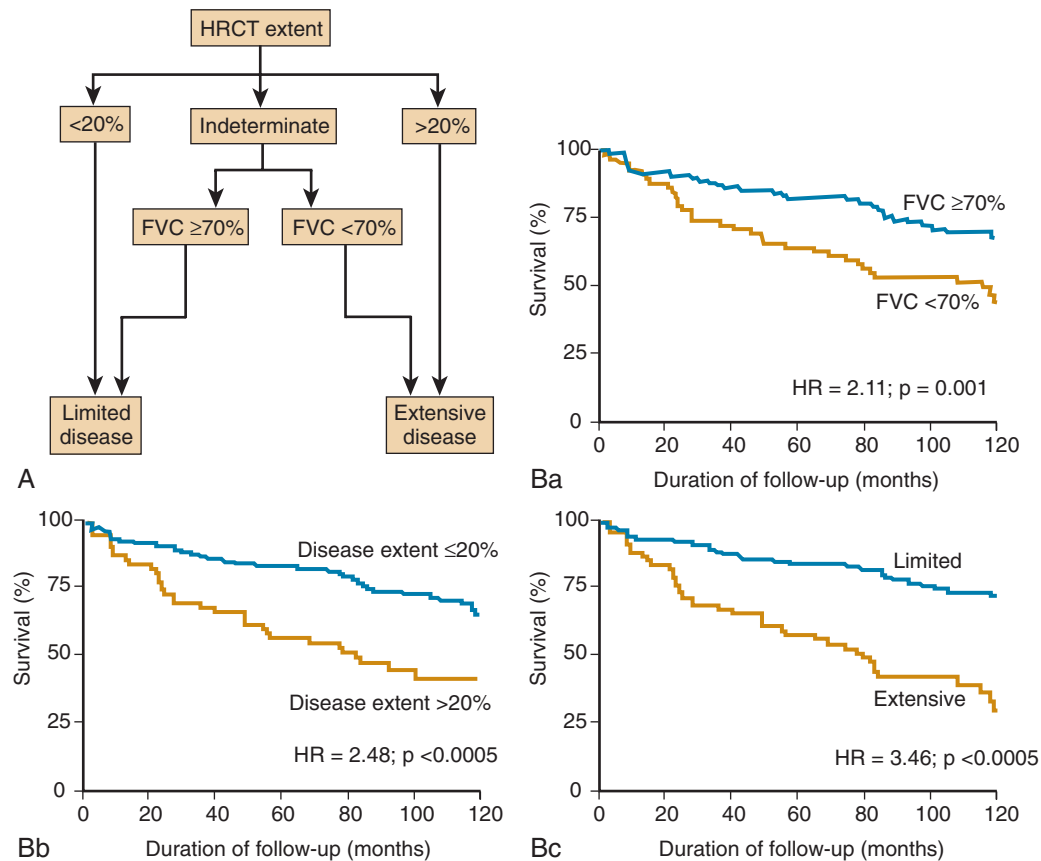


Figure 65-2 Staging algorithm for interstitial lung disease due to systemic sclerosis. **A**, Flow diagram of limited/extensive staging system with use of high-resolution CT (HRCT) scores and pulmonary function test data. Identification of overtly minimal/limited disease is based on disease extent threshold of 20% on HRCT versus severe/extensive disease that is identified by HRCT disease extent greater than 20%. In cases with an indeterminate extent of disease on HRCT, a forced vital capacity (FVC) threshold of 70% is used to separate the cases into limited or extensive disease. The HRCT scans are scored at five levels for total disease extent, extent of reticulation, proportion of ground glass, and coarseness of reticulation. **B**, Survival compared between patient subgroups with **(Ba)** FVC levels above and below a threshold value of 70%; **(Bb)** HRCT disease extent above and below a threshold value of 20%; and **(Bc)** limited disease (HRCT extent ≤ 10%, or when HRCT extent was 10% to 30%, FVC ≥ 70%) versus extensive disease (HRCT > 30%, or when HRCT extent was 10% to 30%, FVC < 70%). (Data from Goh NS, Desai SR, Veeraraghavan S, et al: Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 177:1248–1254, 2008.)

variables, especially FVC, have consistently been predictive of long-term mortality in other forms of pulmonary fibrosis and these observations can reasonably be extrapolated to CTDs.

Although no overall treatment algorithm of ILD has been devised to integrate the duration of systemic disease, evidence of recent progression, and the severity of disease, consideration of all three factors provides a basis for rational treatment decisions. More recently, attention has focused on refining the selection of appropriate SSc patients with pulmonary fibrosis to participate in controlled treatment trials. In order for treatment effects to be demonstrated, it is necessary to enroll patients with progressive disease: the UKRSA staging system has recently been endorsed for this purpose by an expert group.⁶¹ Biomarker data might, in principle, be used, both in clinical prognostication and to select patients for trial involvement, but at present, despite promising preliminary data, no single biomarker is currently fit for routine use.

Treatment

A wide variety of treatments for interstitial pulmonary fibrosis in SSc have been explored.^{62,63} Most of these include

immunosuppression. A number of uncontrolled reports suggested an advantage of treatment with cyclophosphamide, together with prednisolone, to improve lung function and prognosis.^{64,65} The Scleroderma Lung Study demonstrated a small but significant benefit of oral cyclophosphamide compared with placebo for FVC, skin scores, and quality of life and dyspnea scores at 12 months.⁵⁸ The oral cyclophosphamide treatment regimen used most commonly is 2 mg/kg/day orally up to a maximum of 150 mg with moderately low dosages of prednisolone at 10 mg/day or 20 mg every other day. Close scrutiny with full blood counts, liver function tests, and urine testing for evidence of hemorrhagic cystitis is necessary.

Intravenous cyclophosphamide may have a better safety profile.⁶⁶ Studies of intravenous cyclophosphamide (750 to 1000 mg/m²) given at 2- to 4-week intervals for 6 to 12 months tended toward significance, as judged by CT and pulmonary function data.^{67,68} The similarity in the amplitude of treatment effects in the Scleroderma Lung Study⁵⁸ and a smaller placebo-controlled trial of intravenous cyclophosphamide⁶⁸ prompted the European League Against Rheumatism to state that “in view of the results from two high-quality RCTs and despite its known toxicity,

cyclophosphamide should be considered for treatment of SSc-ILD.”⁶⁹ However, it cannot be emphasized too strongly that in SSc and in other CTDs alike, careful selection of patients with severe or progressive lung disease is required, given the toxicity associated with intense immunosuppressive therapy.

In controlled trials,^{58,68} treatment effects largely consisted of the prevention or reduction in progression of lung disease, as judged by serial lung function trends, with the greatest benefit seen in patients with extensive fibrotic disease,⁵⁸ endorsing the important principle of intervention in irreversible fibrotic lung disease, with the primary aim of achieving stabilization, as opposed to regression of disease. However, in the Scleroderma Lung Study, after the cessation of active treatment, therapeutic benefits were transient.⁷⁰ Longer-term treatment approaches have not been evaluated in controlled studies. In SSc and in other CTDs, oral immunosuppressive agents that are less toxic than cyclophosphamide have been widely used, including azathioprine, methotrexate, and mycophenolate mofetil, on the basis of accumulated clinical experience and small retrospective case series.⁷¹⁻⁷³ The most convincing data were generated in a recent retrospective series of 100 CTD patients, in which treatment with mycophenolate mofetil was well tolerated and was associated, on average, with stabilization of pulmonary fibrosis over a number of years.⁷⁴

Controlled treatment data in SSc (and in other CTDs) have been confined to immunomodulatory strategies. Novel antifibrotic agents with documented treatment effects in idiopathic pulmonary fibrosis (e.g., antioxidant therapy,⁷⁵ pirfenidone⁷⁶) have not been evaluated in CTD. A well-conducted placebo-controlled trial of bosentan in SSc pulmonary fibrosis was definitively negative.⁷⁷ A study of interferon- α showed a greater deterioration in lung function at 1 year than with placebo.⁷⁸ With bone marrow transplantation in severe progressive SSc, significant improvements in lung function variables are seen in some cases.^{79,80} The most promising pilot data apply to the use of rituximab in SSc-ILD^{81,82} and, more convincingly, in polymyositis-dermatomyositis,⁸³ especially when given as rescue therapy in CTD patients with severe progressive disease despite high-dose corticosteroid and immunosuppressive therapy.^{84,84a} However, the use of rituximab in lung disease in SSc and other CTDs is currently unclear.

The question of *Pneumocystis* prophylaxis is not resolved. Some medical centers use cotrimoxazole three times a week if immunosuppressive agents are being given.

It has been observed that steroid therapy is associated with scleroderma renal crisis, both with moderate to high-dose therapy (≥ 15 mg/day prednisone or equivalent)⁸⁵ and, more recently, with prednisolone doses of less than 10 mg daily.⁸⁶ However, confounding by severity cannot be excluded, as patients with more aggressive systemic disease are more likely to receive corticosteroids, although occasional cases of renal crisis are undoubtedly linked to high-dose corticosteroid therapy.⁸⁷ Thus, low-dose steroid therapy remains justified as an invaluable adjunct to the treatment of lung disease, although renal function should be monitored.

End-stage lung disease has been treated with single-lung transplantation provided there is no evidence of disease activity in other organs and no major esophageal dysfunc-

tion. With careful selection of patients, outcome with transplantation may differ little from that in individuals with idiopathic diffuse lung disease, although it should be understood that perceived contraindications to lung transplantation due to systemic disease activity vary widely between transplant units. In terminal disease, consideration must be given to oxygen therapy, treatment of supervening heart failure, and infection and advanced care planning, with palliative care specialists often having an invaluable input.

PULMONARY VASCULAR DISEASE IN SYSTEMIC SCLEROSIS

Unlike the other CTDs, vascular involvement in SSc is caused by concentric fibrosis of small arterioles replacing the normal intima and media, but the plexiform lesions and fibrinoid necrosis of primary pulmonary hypertension are not seen. Isolated vascular disease arises mainly in the limited form of SSc. Associated features are those of the CREST syndrome (*calcinosis*, *Raynaud phenomenon*, *esophageal dysmotility*, *sclerodactyly*, and *telangiectasias*) with prominent telangiectasia, esophageal disease, abnormal nail fold capillaries (dilated capillaries and dropout of capillary loops), and a positive anti-centromere antibody. Chest radiography, CT scanning, and BAL are all normal. Lung function studies show an isolated or disproportionate fall in DL_{CO} , quantified by a decline in DL_{CO} adjusted for the alveolar volume (DL_{CO}/VA or K_{CO}) or a rise in the FVC/ DL_{CO} ratio. Although routine annual echocardiography has been advocated in all SSc patients, recent data suggest that the above-gas transfer variables can reasonably be used to select patients for echocardiography.⁸⁸ When damage to the pulmonary vascular bed is extensive (gas transfer $< 50\%$ of predicted), the risk of pulmonary hypertension increases.⁸⁹ Mortality rates increase with increasing pulmonary hypertension^{90,91} (see also Chapter 58).

Doppler echocardiography has been shown to correlate with measurements of pulmonary artery pressures made at right heart catheterization. Qualitative features found on echocardiography may also suggest pulmonary hypertension even in the absence of a tricuspid regurgitant jet that precludes measurement of the gradient across the tricuspid valve and, thus, an estimate of pulmonary artery pressure. These qualitative features include right ventricular dilation and right ventricular hypertrophy. Overall, echocardiography is moderately sensitive for the diagnosis of *pulmonary arterial hypertension* (PAH; 47% to 88%).^{92,93} However, echocardiography is less accurate at borderline and mild levels of pulmonary hypertension. Stress (exercise) echocardiography may be able to identify preclinical PAH.^{94,95} NT-proBNP, released from cardiac ventricles in response to stretch, is elevated in SSc and inversely related to gas transfer. Elevated NT-proBNP levels may predict the development of pulmonary hypertension in SSc.^{96,97} Worse functional class and impaired DL_{CO} predict worse outcomes in scleroderma-associated PAH.^{97a}

Although there are a number of emerging therapeutic options, optimal treatment of pulmonary vascular disease (see Chapter 58) in SSc has not yet been defined. Calcium channel antagonists have been used historically, but the dosage required to reduce pulmonary vascular limitation often causes unacceptable drops in left-sided pressures and

peripheral edema. Prostacyclin analogues cause potent pulmonary and systemic vasodilation and inhibit platelet aggregation. Intravenous and subcutaneous prostacyclin analogues have been shown to lead to improved pulmonary vascular resistance, pulmonary pressure, and 6-minute walk distances in the acute and longer term.⁹⁸⁻¹⁰⁰ Exact dosage regimens need to be validated, however. Inhaled iloprost may also improve exercise capacity and cardiopulmonary hemodynamics.¹⁰¹ Oral ET1 receptor antagonists have been shown to improve exercise capacity and hemodynamics in patients with PAH and CTD (including SSc).¹⁰²⁻¹⁰⁴ Sildenafil, a phosphodiesterase-5 inhibitor, leads to an improvement in exercise capacity and hemodynamics in patients with PAH (including patients with SSc).^{105,106} The correct balance of these therapies, including combination therapy, is yet to be determined in controlled studies. It should also be stressed that targeted therapy for PAH should never be introduced without the prior performance of a right heart catheter study because rapidly fatal pulmonary edema may result from occult left ventricular dysfunction due to involvement by SSc or unrelated cardiac disease. Emerging therapies, such as the platelet-derived growth factor antagonist imatinib, show promise in animal studies.¹⁰⁷

OTHER PULMONARY COMPLICATIONS

Classical aspiration pneumonia is uncommon, particularly considering the prevalence of esophageal dysfunction in SSc. It is not yet clear whether microaspiration from reflux may in some cases serve as an important cofactor leading to progression of lung disease and, therefore, active treatment of symptomatic reflux is advisable. Pleural disease is uncommon. Rarely, the extent of skin tightness over the chest wall produces an extrinsic restriction of ventilation. Occasionally, the first manifestation of pulmonary parenchymal disease is organizing pneumonia. This responds well to corticosteroid therapy, as does organizing pneumonia in other contexts.

RHEUMATOID ARTHRITIS

The American Rheumatism Association revised criteria for the classification of *rheumatoid arthritis* (RA) require that at least four of the criteria listed in Table 65-5 be satisfied for a minimum of 6 weeks.¹⁰⁸

EPIDEMIOLOGY AND RISK FACTORS

The reported incidence of RA ranges from 0.2 to 3/1000 person-years (<0.5/1000 person-years in most surveys), with a rising incidence with increasing age into the seventh decade. In adult whites, the prevalence of RA ranges from 0.5% to 2%, with a male-to-female ratio between 1:2 and 1:4. Depending on disease severity (as judged by disability scales and the need for long-term corticosteroid therapy), the age-matched mortality rate of RA is up to twofold higher than in the general population, with this increased mortality being attributed to cardiorespiratory complications.^{109,110} The prevalence of RA is similar throughout the world. Evidence in support of a genetic predisposition

Table 65-5 Rheumatoid Arthritis

CRITERIA FOR DIAGNOSIS*

Morning stiffness (lasting at least 1 hr)
Arthritis (soft tissue swelling or fluid) of 3 or more joints (PIP, MCP, wrist, elbow, knee, ankle, MTP joints)
Arthritis of hand joints (swelling of at least 1 wrist, MCP, or PIP joint)
Symmetrical arthritis (i.e., simultaneous arthritis of the same joints on both sides of the body)
Rheumatoid nodules
Serum rheumatoid factor positivity (at a level such that < 5% of normal controls are positive)
Radiographic hand or wrist changes typical of rheumatoid arthritis

LUNG MANIFESTATIONS

Interstitial pulmonary fibrosis
Organizing pneumonia
Obliterative bronchiolitis
Follicular bronchiolitis
Bronchiectasis
Vasculitis
Nodules
Pleural disease
Lymphocytic interstitial pneumonia
Drug induced

*At least 4 criteria for a minimum of 6 weeks.

MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

includes familial and twin clustering and associations between RA and HLA-DRB1 alleles.¹¹¹ Hormonal factors may play a role, judging from the female preponderance of RA and a reduced incidence during pregnancy. Infectious agents and socioeconomic factors have not been shown to be etiologically important.

PULMONARY MANIFESTATIONS

Pleuropulmonary manifestations are multiple and are listed in Table 65-5 and shown in Fig. 65-3.

Interstitial Pulmonary Fibrosis

The interstitial pulmonary fibrosis of RA has a male predominance (male-to-female ratio, 3:1).¹¹² High titers of rheumatoid factor¹¹³ and the presence of rheumatoid nodules^{114,115} are associated with an increased prevalence of pulmonary fibrosis in RA. Smoking is a risk factor for the development of overt pulmonary fibrosis in RA^{113,116} and has also been associated with subclinical disease.^{117,118} In the presence of HLA-DR susceptibility genes, smoking is strongly associated with development of anti-citrulline-positive RA.^{116,116a-c} It has been suggested that the seropositive RA actually starts in the lungs.¹¹⁹

In early disease, a lymphocytic interstitial infiltrate is often the predominant abnormality,¹²⁰ and prominent peribronchiolar follicles, containing aggregates of lymphocytes with germinal centers, are often seen.¹²¹ In long-standing disease, fibrosis predominates, often resulting in cystic changes or honeycombing. It is difficult to estimate the exact prevalence of subcategories of interstitial pulmonary fibrosis because, in historical series, histologic descriptions of "interstitial fibrosis" have not been detailed. Both non-specific interstitial pneumonia and usual interstitial pneumonia are present in significant proportions of patients

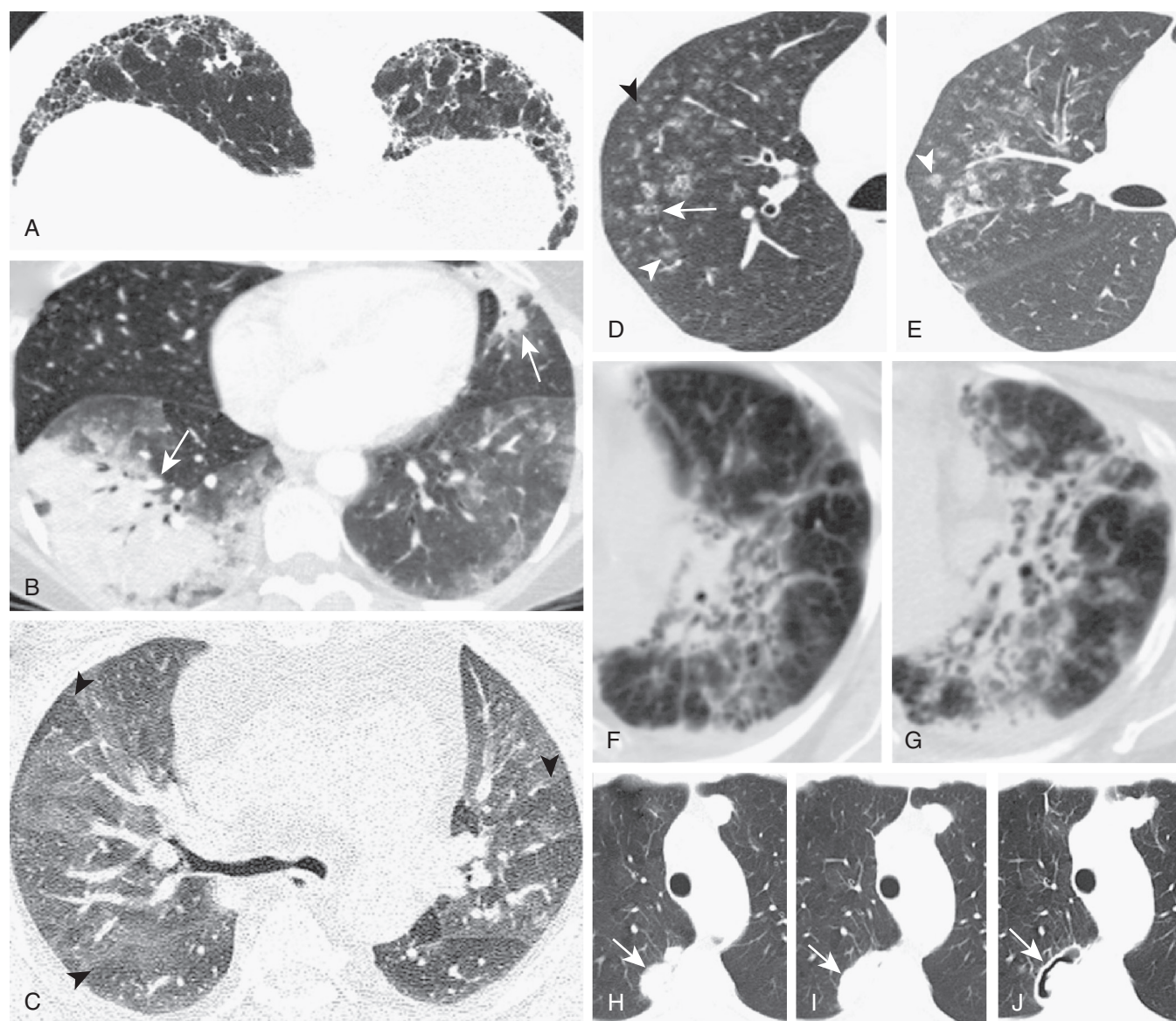


Figure 65-3 Rheumatoid arthritis–associated pulmonary abnormalities shown on axial chest CT. **A**, Usual interstitial pneumonia pattern (UIP). Axial prone high-resolution CT (HRCT) image shows basal, subpleural coarse reticulation, architectural distortion, and honeycombing identical to the UIP pattern in patients with idiopathic pulmonary fibrosis. **B**, Organizing pneumonia. Axial HRCT image shows bilateral peripheral consolidation (arrows). **C**, Bronchiolitis obliterans. Axial supine HRCT image shows extensive, multifocal, bilateral areas of low attenuation (arrowheads) reflecting air trapping due to small airway obstruction. **D** and **E**, Axial supine HRCT images show centrilobular ground-glass opacity nodules (arrowheads) in the right upper lobe, some of which show early cavitation (arrow), shown on biopsy to represent follicular bronchiolitis. **F** and **G**, Axial supine HRCT images show bronchiectasis in the left upper lobe, progressing over the 4-year interval between the two studies. **H–J**, Axial supine HRCT images show progressive enlargement of a rheumatoid nodule (arrows) over 1 year (**H** and **I**), with cavitation developing 3 years later (**J**). (Courtesy Michael Gotway, MD.)

with interstitial fibrosis^{122,123} (eFig. 65-5A). Usual interstitial pneumonia is associated with a better outcome in CTD than in an idiopathic setting.^{48,124,125} However, in RA, usual interstitial pneumonia is associated with a worse outcome than nonspecific interstitial pneumonia.^{126,127} Furthermore, usual interstitial pneumonia has a worse outcome in RA than in other CTDs.¹²⁸

However, even taking this fact into account, the outcome in RA patients with usual interstitial pneumonitis in the above series was somewhat better than the outcome in idiopathic pulmonary fibrosis, in keeping with trends observed in the histologic series of Park.¹²⁵ However, it is also clear that a subset of RA patients with usual interstitial pneumonia have a progressive course similar to that in idiopathic

pulmonary fibrosis, especially when HRCT appearances are similar to those in classical idiopathic pulmonary fibrosis (see Figs. 65-3A and 18-23), with predominantly basal subpleural honeycomb change and little or no ground-glass attenuation.¹²⁹

In general, surgical lung biopsies are not performed for prognostic indications in CTD. In pulmonary fibrosis in RA, it is not clear that knowledge of the histologic pattern adds usefully to HRCT assessment in prognostic evaluation, although surgical biopsies are performed in some centers. Minor pulmonary fibrosis is common in RA; in one open-lung biopsy series performed in the previous century in volunteers with RA (some without clinical evidence of ILD), pulmonary fibrosis was seen in 60% of patients.¹³⁰

Reductions in DL_{CO} are found in 40% of unselected RA patients.¹³¹ However, radiologically overt pulmonary fibrosis is found in only 1% to 5% of RA patients (based on three large chest radiographic series).^{114,117,132} In the largest prospective series reported to date, 150 consecutive patients were screened for pulmonary disease.¹³³ Of these, 19% had CT evidence of interstitial fibrosis, which was often subtle; 43% of those with interstitial abnormalities also had emphysematous bullae. Chest radiography identified abnormalities in only 14% of the whole cohort, but physiologic abnormalities were seen in 82% (gas transfer) and 14% (restrictive pattern of ventilatory defect).¹³³ Disease severity as judged by CT generally reflects functional impairment.¹³⁴⁻¹³⁶

The most frequent symptom is exertional dyspnea, although this may be masked by a general loss of mobility due to systemic disease. The clinical picture is usually identical to that of idiopathic pulmonary fibrosis, with bilateral, predominantly basal crackles and tachypnea, cyanosis, and right heart failure in advanced disease. Finger clubbing, which is occasionally striking, is more prevalent than in other CTDs. Severe progressive disease requiring hospitalization may be associated with cor pulmonale and respiratory failure and has a poor prognosis, with a 5-year survival rate of less than 50%.⁵³ A subgroup of patients has more indolent disease that progresses little during prolonged follow-up. A strong predictor of clinical decline is a gas transfer less than 55% of predicted at presentation.¹³⁷

Organizing Pneumonia

Organizing pneumonia is characterized by plugs of granulation tissue in the air spaces distal to and including the terminal bronchioles, associated with lymphocytic infiltration within well-preserved bronchiolar walls and the surrounding lung interstitium. Organizing pneumonia has a very different profile from the entity of bronchiolitis obliterans (also found in RA), with a clinical presentation of pneumonia (as opposed to airflow obstruction), multifocal consolidation on chest radiograph and CT (see [Figure 65-3B](#)), a restrictive functional defect, and a much higher chance of responsiveness to corticosteroids than bronchiolitis obliterans (with a good outcome in 15 of the first 17 reported cases).¹³⁸ Organizing pneumonia is more common in RA than in other CTDs (with the exception of inflammatory myopathy and mixed connective tissue disease). In a series of 40 patients with RA undergoing open-lung biopsy, organizing pneumonia (6 cases) had a prevalence similar to that of interstitial fibrosis (5 cases),¹³⁹ although organizing pneumonia might have been overrepresented owing to an acute presentation (and thus a perceived need to reach a definitive histologic diagnosis). The good prognosis generally seen in organizing pneumonia has been emphasized in the medical literature, but a minority of RA patients with organizing pneumonia progress to respiratory failure and death despite treatment.

Bronchiolitis Obliterans

Bronchiolitis obliterans (BO) in RA has now been described in numerous case reports and small series. BO (synonymous with obliterative bronchiolitis and constrictive bronchiolitis) is characterized histologically by destruction of the bronchiolar wall by granulation tissue, effacement of

the lumen, and eventual replacement of the bronchiole by fibrous tissue. There is circumstantial evidence to suggest that, in some cases, BO may be preceded by an inflammatory exudate; prominent bronchiolar inflammation may be found in patients with the shortest symptomatic course.¹⁴⁰ The expression of HLA antigens B40 and DR1 is increased in BO associated with RA (but not in isolated BO).¹⁴¹

In early descriptions, the hallmark of BO was a rapidly progressive, often fatal, course; however, because clinician awareness of the disease was then low, patients with advanced and progressive disease were undoubtedly overrepresented. There is great heterogeneity in the speed of progression, with some patients having indolent disease¹⁴²; the use of CT in RA patients with suspected pulmonary complications has now identified a subgroup with occult bronchiolitis (see [Fig. 65-3C](#)), often admixed with ILD. The prevalence of unsuspected BO in unselected RA patients remains uncertain, with unexplained airflow obstruction identified in a significant minority (including many nonsmokers) in one study¹⁴³ but no increase in the prevalence of pulmonary function abnormalities suggestive of isolated small airway disease in two subsequent controlled series.^{144,145}

Two major associations with the development of BO in RA have been reported. It is likely that secondary Sjögren syndrome is an important predisposing factor, being associated with BO in five of six RA patients in one series¹⁴²; the spectrum of histologic abnormalities in these cases, ranging from peribronchiolar lymphocytic infiltration to small airway destruction, was analogous to changes seen in the parotid gland in Sjögren syndrome. As the presence or absence of Sjögren syndrome is not documented in many case reports of BO in RA, the etiologic importance of Sjögren syndrome in this context remains uncertain.

More contentious is the reported association between BO and the use of penicillamine, first reported in the late 1970s.¹⁴⁶ After a number of case reports and small series, a significantly higher prevalence of BO was identified in RA patients who took penicillamine (3 of 133) than in other RA patients (0 of 469) in a large cohort.¹⁴⁰ It is possible that the development of BO and the use of penicillamine are both markers of more aggressive RA and are linked for this reason; however, BO developed less than 1 year after penicillamine was begun in 19 of the first 20 cases,¹⁴⁰ and thus the association is unlikely to be entirely spurious. Because BO has been reported in many RA patients not taking penicillamine, it is likely that an underlying predisposition to BO in RA is unmasked by penicillamine (which disrupts collagen linkage and thus interferes with tissue repair). A relationship between BO and gold therapy has been suggested but is not endorsed by recent clinical experience.

Follicular Bronchiolitis

Follicular bronchiolitis (FB) is characterized by external compression of bronchioles by hyperplastic lymphoid follicles, with variable lymphocytic infiltration of the bronchiolar wall ([eFig. 65-5B](#)). FB is associated more commonly with RA than with other CTDs¹⁴⁷ and is often found incidentally at lung biopsy in RA patients with interstitial pulmonary fibrosis. No causative mechanism has been identified, and it is unclear whether FB predisposes to the subsequent development of BO. When found in isolation, FB simulates ILD,

with reticular or nodular opacities on chest radiography and a pattern of functional impairment that may be restrictive or obstructive. Clinically significant isolated FB is rare in RA, but its recognition is important because a response to corticosteroid therapy, although not the rule, is much more likely than in BO; in six of the first nine reported cases, disease stabilized or regressed with treatment.¹³⁸ In a CT study of patients with histopathologically proven FB, the most prominent features were centrilobular (see Fig. 65-3D and E) and peribronchial nodules together with patchy ground-glass increases in attenuation in a bronchocentric distribution.¹⁴⁸

Bronchiectasis

The prevalence of bronchiectasis is higher in RA than in other CTDs. One literature review identified 289 patients with bronchiectasis associated with RA reported since 1928; however, because respiratory symptoms preceded the systemic manifestations of RA in 90%, it is likely that chance association accounts for a high proportion of early reported cases.¹⁴⁹ Although associated with long-standing RA in one study,¹⁵⁰ on prospective evaluation of 50 RA patients, bronchiectasis was present on 30% of CT scans (see Fig. 65-3F and G).¹⁵¹ Bronchiectasis in RA is not associated with more aggressive systemic disease and is often clinically silent, with little or no sputum production and a less progressive and disabling course than in patients with idiopathic bronchiectasis.

Pulmonary Vasculitis

It is surprising that pulmonary vasculitis is reported only rarely in RA, given the relatively high prevalence of systemic vasculitis in the disease. Pulmonary hypertension resulting from pulmonary vascular disease (as opposed to extensive pulmonary fibrosis) is uncommon, although occasional cases of pulmonary vasculitis have been found at autopsy.¹⁴⁷ Similarly, diffuse alveolar hemorrhage is a rare complication of RA.

Pulmonary Rheumatoid Nodules

Pulmonary rheumatoid nodules may be single or multiple, are found on chest radiography in less than 1% of RA patients,¹¹⁵ and are usually associated with rheumatoid nodules elsewhere in the body.¹⁵² Occasionally pulmonary rheumatoid nodules precede the development of systemic disease. Nodules are circumscribed, with central necrotic material contained by palisading epithelioid cells and surrounded by fibrosis and lymphocytic infiltration (eFig. 65-5C). Nodule cavitation occasionally causes hemoptysis, and pneumothorax may result from the rupture of subpleural nodules. Diffuse infiltration by small nodules leading to respiratory failure has been reported.¹⁵³ However, nodules generally present as asymptomatic abnormalities on imaging (see Fig. 65-3H-J) and may vary in size according to underlying rheumatoid activity; thus, when solitary, their growth as judged by chest radiography may simulate malignancy. Caplan syndrome consists of the association of single or multiple nodules with coal workers' pneumoconiosis, which is often trivial, in keeping with the suggestion that nodule formation results from a hypersensitivity reaction to inhaled coal dust perhaps amplified by immunologic overactivity.

Pleural Disease

Pleural disease is seen at autopsy in approximately 50% of patients,¹¹⁵ and 20% give a history of pleuritic chest pain¹⁵⁴ (eFig. 65-5D). However, pleural effusions are found in less than 5%,^{113,114} usually in men,¹⁵² and are frequently asymptomatic, often being identified on routine chest radiography. In a minority, pleuritic pain and fever are prominent, and the exclusion of empyema (which may be more prevalent in RA) is required. Occasionally, effusions may develop acutely in association with pericarditis or exacerbations of arthritis; more typically, radiographic abnormalities are chronic, often remaining unchanged for years. The fluid is an exudate, with a low glucose level (correlating poorly with serum glucose),¹⁵⁵ a low pH, and usually, a predominant lymphocytosis (although a neutrophilia is occasionally found). Pleural fluid rheumatoid factor levels tend to mirror serum levels and have little independent diagnostic value.

Other Pulmonary Complications

Other pulmonary complications of RA are rare. Lymphocytic interstitial pneumonia is an occasional finding at lung biopsy¹³⁹ and responds variably to corticosteroid therapy. Apical fibrosis mimicking the lung disease of ankylosing spondylitis has been reported.¹⁵⁶ Extensive apical cavitation in the absence of nodules or other causes of fibrocavitary disease (including tuberculosis) has been described in a handful of cases and may follow a fulminant course.¹⁵⁷ Pulmonary amyloidosis has been reported occasionally. The incidence of secondary pulmonary hypertension increases with time from diagnosis.¹⁵⁸ Lower respiratory tract infection is increased in frequency in RA; bronchopneumonia is a common terminal event, accounting for 15% to 20% of deaths in RA patients.^{159,160} An increase in lung cancer has been reported in RA patients.¹⁶¹

Drug-Induced Pulmonary Disease

Drug-induced pulmonary disease is a particular problem in RA because of the widespread use of methotrexate in routine clinical practice, and lung disease has been reported in 3% to 18% of RA patients treated with methotrexate.^{162,163} Methotrexate pneumonitis is potentially life threatening. It presents with cough, dyspnea, fever, widespread crackles, and pulmonary opacities on chest radiography and CT (see eFig. 71-4), which may be focal or diffuse.¹⁶⁴ Although the presentation is sometimes explosive, more often, the onset is subacute (with symptoms evolving for up to 2 months before diagnosis)¹⁶⁴; 50% of cases are diagnosed within 4 months of initiation of methotrexate therapy. Because the clinical and radiographic features are nonspecific, methotrexate-induced lung disease should always be suspected in the treated patient presenting with progressive lung disease. Unfortunately, histologic findings are nonspecific, although finding a prominent lymphocytic infiltration increases the likelihood of methotrexate pneumonitis.¹⁶⁵ There is conflicting evidence on whether preexisting lung disease predisposes to lung injury caused by methotrexate, but the published evidence does not suggest that functional impairment is an absolute contraindication to its use (although particular caution is warranted when pulmonary reserve is grossly compromised, and patients with previous methotrexate toxicity should

not be retreated).^{164,166} Pulmonary methotrexate toxicity is associated with a mortality rate of 15% to 20%¹⁶⁴; because the lymphocytic component of disease is wholly or partially reversible, immediate withdrawal of methotrexate and the early institution of steroid therapy are warranted.

Pulmonary toxicity in RA has also been documented with sulfasalazine, gold therapy, and penicillamine (discussed earlier; see Chapter 71). Pulmonary opacities (due to organizing pneumonia) associated with sulfasalazine most commonly present in the upper lobes; this side effect is rare in RA, with only a handful of cases reported (most cases were reported in ulcerative colitis).¹⁶⁷ Pulmonary disease induced by gold takes the form of alveolar opacities adjacent to bronchovascular bundles, best demonstrated by high-resolution CT, and often associated with fever or skin rash, relatively low rheumatoid factor titers, and a BAL lymphocytosis.¹⁶⁸ In most patients with sulfasalazine or gold toxicity, lung disease largely regresses with withdrawal of the agent and corticosteroid therapy.

There have been a number of reports of rapidly progressive ILD associated with anti-TNF- α therapies, including etanercept and infliximab, although there are divergent views on whether these reports are truly indicative of drug toxicity or reflect the selective use of these therapies in more aggressive RA. The range of reported toxicity ranges from infection (with particular focus on reactivation of tuberculosis), undoubtedly a true association, to interstitial disease and vasculitis.^{169,170} Leflunomide has also been associated with pulmonary rheumatoid nodules and interstitial disease.^{171,172}

Acute Exacerbations of Interstitial Lung Disease

Acute exacerbations of ILD, representing the development of diffuse alveolar damage, are less prevalent in CTD than in idiopathic pulmonary fibrosis. In both settings, presenting features include worsening dyspnea over 2 to 4 weeks, new ground-glass opacities on HRCT (eFig. 65-6), and the absence of infection or other overt causes of decline.¹⁷³ Acute exacerbations are more common in RA than in other CTDs (see eFig. 65-6), with a high early mortality.¹⁷⁴⁻¹⁷⁶ Triggers of acute exacerbations have not been identified in RA and there is currently no proven therapy, although high-dose corticosteroid therapy is usually given.

PULMONARY FUNCTION TESTS

Patterns of functional impairment in RA have been variable in unselected populations, with predominant airflow obstruction a frequent finding in one cohort¹⁴³ but reductions in DL_{CO} ascribed to occult interstitial fibrosis in at least 40%.¹³¹ Inconsistencies in published data can be ascribed to the confounding effects of smoking and variations in the type and severity of associated pulmonary disease. Airflow obstruction may result from bronchiectasis or BO. Interstitial pulmonary fibrosis, organizing pneumonia, and lymphocytic interstitial pneumonia give rise to restrictive defects.

RADIOLOGIC FEATURES

In chest radiographic series of unselected patients with RA, appearances indicative of ILD are found in 1% to 5% of

cases.^{113,114,132,135} In interstitial pulmonary fibrosis, appearances are indistinguishable from idiopathic pulmonary fibrosis in a minority of cases, with symmetrical basal interstitial opacification in limited disease and diffuse coarse reticular abnormalities in extensive disease. In the majority of cases, CT appearances are intermediate between those of idiopathic pulmonary fibrosis (see Fig. 65-3A) and nonspecific interstitial pneumonia or are suggestive of the latter pattern.¹⁷⁷ Ground-glass opacity, consisting of a patchy or diffuse increase in lung density, is likely to denote inflammatory histologic appearances or fine intralobular fibrosis, as in other fibrosing lung diseases. Rheumatoid nodules (see Fig. 65-3H-J) are usually radiologically discrete and small but are often multiple and may reach up to 7 cm in diameter; in Caplan syndrome, nodules appear in crops, often grow rapidly, and may cavitate. Other chest radiographic findings in RA include focal consolidation (in organizing pneumonia [see Fig. 65-3B], infectious pneumonia, and lung disease induced by methotrexate); focal areas of hyperinflation (in BO [see Fig. 65-3C]); and pleural thickening or effusion.

The cardinal CT feature of organizing pneumonia is patchy bilateral air space consolidation (often with associated ground-glass attenuation), which is often predominantly subpleural¹⁷⁸ but may have a bronchovascular distribution (see Fig. 65-3B).¹⁷⁹ Small nodules (≤ 1 cm in diameter) are common in organizing pneumonia; small pleural effusions and limited fibrosis (probably resulting from prolonged untreated inflammation) are occasional findings.

In bronchiolitis, bronchiolar structures are occasionally visualized directly on CT as centrilobular (see Fig. 65-3D and E), micronodular opacities and peripheral branching structures, denoting marked thickening of the bronchiolar wall; this appearance may be most frequent in FB.¹⁸⁰ In BO, areas of reduced lung density in a patchy distribution ("mosaic perfusion," see Fig. 65-3C) are associated with a reduction in the caliber of pulmonary vessels in areas of decreased attenuation, indicative of regional hypoxic vasoconstriction in areas of severe bronchiolitis. Bronchiectasis and bronchial wall thickening on CT are common in constrictive bronchiolitis.

TREATMENT OF PULMONARY COMPLICATIONS

The treatment of ILD has usually consisted of corticosteroid therapy, with or without immunosuppressive agents. However, when CT appearances are similar to those of idiopathic pulmonary fibrosis, immunomodulation, and especially high-dose corticosteroid therapy, should be used with caution due to the recent documentation of major toxicity with this approach in idiopathic pulmonary fibrosis.¹⁸¹ It can reasonably be argued that in this context high-dose steroid therapy should be largely confined to those with suspected supervening drug-induced lung toxicity or diffuse alveolar damage. Owing to small numbers, regimens have remained anecdotal. Organizing pneumonia and methotrexate pneumonitis often respond well to treatment. Regression of disease is highly variable in FB and lymphocytic interstitial pneumonia and is virtually never seen in BO. Lung function may improve in response to treatment in interstitial pulmonary fibrosis, but a more realistic goal

Table 65-6 Systemic Lupus Erythematosus**CRITERIA FOR DIAGNOSIS***

Malar rash
 Discoid rash
 Photosensitivity skin rash
 Oral or nasopharyngeal ulceration
 Nonerosive arthritis involving ≥ 2 peripheral joints
 Serositis (pleuritis or pericarditis)
 Renal disorder (persistent proteinuria or cellular casts)
 Neurologic disorder (unexplained seizures or psychosis)
 Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
 Immunologic disorder (positive LE cell, anti-DNA antibody, anti-Sm antibody, false-positive syphilis serology)
 Elevated antinuclear antibodies

LUNG MANIFESTATIONS

Acute lupus pneumonitis
 Interstitial pulmonary fibrosis
 Pulmonary vasculitis
 Diffuse alveolar hemorrhage
 Pulmonary hypertension
 Shrinking lung syndrome
 Antiphospholipid antibody syndrome
 Organizing pneumonia
 Pleural disease

*Minimum of 4 criteria required.
 LE, lupus erythematosus.

in most cases is to prevent further progression of disease, especially when lung disease is extensive.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an inflammatory multisystem disorder of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis. The 1982 revised American College of Rheumatology criteria for the diagnosis of SLE require that a minimum of four of the criteria listed in Table 65-6 be satisfied (although SLE is sometimes diagnosed with fewer than four criteria).¹⁸²

EPIDEMIOLOGY AND RISK FACTORS

SLE appears throughout the world; the reported prevalence ranges from 12 to 50/100,000 population, and the incidence ranges from 1.8 to 7.6/100,000 population/yr.¹⁸³ There is a six- to ten-fold female excess, and the disease is three times more common in African Americans than in whites. The 5-year survival rate exceeds 90%, but the mortality rate is three times higher than in the general population. Support for a genetic contribution to disease includes a high prevalence in monozygotic twins, familial clustering, and associations among SLE and HLA-DR2, HLA-DR3, and the C4A null allele.¹⁸⁴ No infectious or other environmental factor has been shown to play a major etiologic role.

PULMONARY MANIFESTATIONS

Pleuropulmonary manifestations of SLE are listed in Table 65-6.

Diffuse Lung Disease

Diffuse lung disease on lung biopsy or at autopsy has been reported in 4%, 33%, and 70% of SLE patients.¹⁸⁵⁻¹⁸⁷ These striking inconsistencies undoubtedly reflect major variations in the histologic diagnostic criteria. In the series with the highest prevalence, trivial interstitial thickening was categorized as “pulmonary fibrosis” but likely represented the minor residuum of infection or inflammatory complications of SLE. Only 3% of SLE patients have clinical evidence of diffuse lung disease at the onset of systemic disease, and a disease resembling interstitial pulmonary fibrosis (eFig. 65-7) develops during follow-up in less than 5%.¹⁸⁸ Risk factors for pulmonary fibrosis in SLE include increasing age, pneumonitis, and anti-RNP antibodies.¹⁸⁹

Interstitial Pneumonia. The clinical presentation (dyspnea, cough, predominantly basal crackles, a restrictive lung function defect or isolated reduction in DL_{CO} , basal opacities on chest radiography) is similar to idiopathic pulmonary fibrosis. Features not typical of idiopathic pulmonary fibrosis include variably associated pleuritic pain, a paucity of patients with morphologically extensive or functionally severe lung fibrosis, and the frequent presence of enlarged peribronchiolar lymphoid follicles at lung biopsy (although other histologic findings are similar to usual interstitial pneumonia). Partial regression of disease with corticosteroids in 9 of 14 cases in one series¹⁹⁰ suggests that an empirical trial of therapy is usually warranted.

Acute Lupus Pneumonitis. Although seen in less than 2% of SLE patients, acute lupus pneumonitis is often life threatening, with a mortality rate of more than 50% (once respiratory failure has supervened) despite treatment.¹⁹¹ The predominant histologic feature of diffuse alveolar damage is nonspecific, and it has been argued that acute lupus pneumonitis is merely a manifestation of aspiration or bacterial infection.¹⁸⁵ However, well-documented striking responses to corticosteroids and immunosuppressive agents after antibiotic failure suggest strongly that the disorder is a true, albeit rare, entity.

Acute lupus pneumonitis is not to be confused with organizing pneumonia, discussed elsewhere in this chapter and reported in only a handful of adult patients with SLE, or with lymphocytic interstitial pneumonia, described in a small number of patients with SLE.

Extrapulmonary Restriction

Extrapulmonary restriction, resulting in exertional dyspnea, a restrictive functional defect, and marked decrease of DL_{CO} , is a well-recognized complication of SLE. The “shrinking lung syndrome” was first described in patients with severe restriction and a marked reduction in lung volume on chest radiography, and it is generally ascribed to diaphragmatic weakness (Fig. 65-4).¹⁹² However, the use of sniff pressures to evaluate diaphragmatic strength may be confounded by concurrent lung restriction or airflow obstruction; in one study, with the use of alternative methods to evaluate diaphragmatic function, the characteristic restrictive defect was attributed to an “unspecified restriction in chest wall expansion.”¹⁹³ No treatment of proven efficacy currently exists, although a handful of patients have improved in

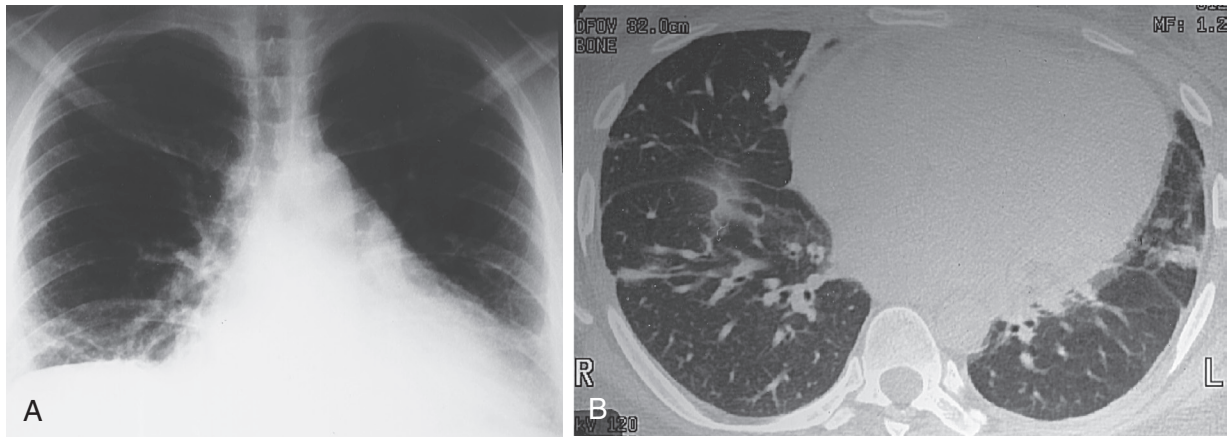


Figure 65-4 Systemic lupus erythematosus. **A**, Chest radiograph from a patient with systemic lupus erythematosus shows marked elevation of both hemidiaphragms, in keeping with “the shrinking lung syndrome.” **B**, On a CT scan from the same patient as in **A**, linear abnormalities are seen that denote subsegmental atelectasis resulting from regional hypoventilation (due to diaphragmatic weakness). The heart is enlarged.

association with corticosteroid or immunosuppressive therapy.¹⁹⁴ The disorder is almost always self-limited, although sometimes it is severe.

Diffuse Alveolar Hemorrhage (see Chapter 67)

Although seen more frequently in SLE than in other CTDs, diffuse alveolar hemorrhage is rare in SLE. The typical presentation of acute dyspnea and extensive pulmonary opacities on imaging (eFig. 65-8, see eFig. 67-4) may mimic acute lupus pneumonitis, especially in the absence of hemoptysis.¹⁹⁵ Diffuse alveolar hemorrhage is often life threatening, with a mortality rate of approximately 50%, similar to that of acute lupus pneumonitis; however, because the two diseases are both treated empirically with corticosteroid and immunosuppressive therapy, the important differential diagnosis is opportunistic infection. Patients with SLE have underlying defects in most arms of the immune system and are at added risk of fulminant infection with the use of corticosteroids or immunosuppressive agents.¹⁹⁶ In this context, a misdiagnosis of acute lupus pneumonitis or diffuse alveolar hemorrhage may lead to a potentially disastrous increase in immunosuppression. Thus, the performance of BAL to exclude opportunistic infection may be crucial in SLE patients with unexplained extensive pulmonary opacities. Treatment responses in both acute lupus pneumonitis and diffuse alveolar hemorrhage have been observed with intravenous immunoglobulins, plasmapheresis, and rituximab.¹⁹⁷⁻¹⁹⁹

Pulmonary Hypertension

Pulmonary hypertension was once considered rare in SLE, but it is now reported with increasing frequency²⁰⁰ and has a 2-year survival rate of less than 50% in severe disease. Abnormalities indicative of subclinical pulmonary hypertension are found on echocardiography in 10% of SLE patients, usually in association with Raynaud phenomenon,²⁰¹ and thus, it is likely that, in many cases, pulmonary hypertension results from vasoconstriction rather than pulmonary vasculitis (which is seldom identified in SLE); in autopsied patients with pulmonary hypertension, overt vasculitis is rare (see also Chapter 58).

Important alternative mechanisms for pulmonary hypertension include vasculitis and thromboembolism.²⁰² Thromboembolism has a high prevalence in SLE, especially in patients with antiphospholipid antibodies (which cross-react with coagulation factors).^{203,204} In a 1993 study of 842 SLE patients, immunoglobulin G anticardiolipin antibodies were present more frequently than immunoglobulin M antibodies (24% vs. 13%), but both were associated with a 30% prevalence of thrombosis (as opposed to 10% in other SLE patients).²⁰⁵ Patients with antiphospholipid antibody syndrome also have a higher incidence of impaired lung function than normal controls.²⁰⁶ In view of the multiplicity of mechanisms potentially responsible for pulmonary hypertension, vasodilators and anticoagulation have all been advocated empirically for patients with the pulmonary vascular disease of SLE. Corticosteroid or immunosuppressive agents may be effective therapy for SLE-associated pulmonary hypertension.²⁰² In a small series of patients given chronic epoprostenol, measures of pulmonary hypertension, pulmonary vascular resistance, and exercise capacity all improved.²⁰⁷

Pleural Disease

Pleural disease is the most common pulmonary manifestation of SLE. Clinical or radiographic evidence of pleural involvement is seen in 20% of patients at the onset of systemic disease and in at least 50% at some time²⁰⁸ (with pleural abnormalities at autopsy in 50% to 100%). Pleural disease is often asymptomatic, but pleuritic pain may be recurrent or intractable. Pleural fluid is usually serosanguineous (but occasionally hemorrhagic) and exudative, with a neutrophilia in patients with pleurisy but a predominant lymphocytosis in chronic effusions.²⁰⁸ The nonspecific histologic appearance of fibrinous pleuritis is not diagnostically useful. The identification of lupus erythematosus cells has largely fallen out of favor because technical difficulties greatly reduce the sensitivity of the test in confirming that a pleural effusion is due to SLE.²⁰⁹ The measurement of pleural fluid antinuclear antibody titers may be more diagnostically useful when the etiology of pleural disease is in doubt²¹⁰ (see also Chapter 79).

SJÖGREN SYNDROME

Sjögren syndrome is an autoimmune disorder characterized by lymphocytic infiltration of the lacrimal, salivary, conjunctival, and pharyngeal mucosal glands, with variable involvement of extraglandular tissue. The cardinal clinical features of keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) may exist in isolation (primary Sjögren syndrome, typically seen in women older than age 40) but are more often associated with CTDs such as RA, SSc, or SLE (secondary Sjögren syndrome). Sicca symptoms are common in lung disease, however, and need to be carefully evaluated.²¹¹ Variable diagnostic criteria are used internationally; in one proposed diagnostic algorithm, sicca symptoms are mandatory, with supportive evidence including ocular signs (positive Schirmer test testing reduced tear formation, rose bengal score > 3 for staining of damaged conjunctiva and cornea), typical histologic appearances on salivary gland biopsy, antibodies to Ro (SS-A) or La (SS-B), or reduced salivary flow.²¹²

EPIDEMIOLOGY AND RISK FACTORS

The reported prevalence of primary Sjögren syndrome ranges from 0.5% to 3.0%. The etiology of the disease is unknown. Some evidence suggests a genetic predisposition, including familial clustering and an association with HLA-Dw2 and HLA-Dw3, but no environmental triggers have been identified.

PULMONARY MANIFESTATIONS

Pulmonary involvement is common in Sjögren syndrome. In early series, primary and secondary Sjögren syndromes were combined; it is likely that many of the pulmonary abnormalities seen in secondary Sjögren syndrome were ascribed to the underlying CTD. Careful evaluation of patients with primary Sjögren syndrome has shown that cough and dyspnea are common,²¹³ with objective evidence of pulmonary abnormalities in approximately one fourth of cases.²¹⁴ Lung involvement usually consists of lymphocytic infiltration similar to that seen in salivary glands and resulting in tracheobronchial disease or ILD, depending on whether involvement is limited to secretory glandular tissue or more widespread. However, population studies of respiratory involvement in Sjögren syndrome have been hampered by variations in diagnostic criteria, failure to discriminate between primary and secondary Sjögren syndrome, and failure to control for confounding features such as drug treatment and smoking. Lung manifestations include diffuse lung disease and tracheobronchial disease.

In a CT study of 35 patients, the most prevalent findings were large and/or small airway disease ($n = 19$) and diffuse lung disease ($n = 12$, including 7 in whom the features were suggestive of lymphocytic interstitial pneumonia). The patterns of physiologic abnormalities were consistent with the predominant CT pattern.²¹⁵

Diffuse Lung Disease

Although often asymptomatic, diffuse lung disease in Sjögren syndrome may present with cough, dyspnea,

crackles on auscultation, reticular or nodular opacities on chest radiography, and a restrictive pattern of functional impairment. Interstitial involvement can be classified as pulmonary fibrosis, lymphocytic interstitial pneumonia, or lymphoma (eFig. 65-9). Pulmonary fibrosis has been reported in up to 10% of patients with primary Sjögren syndrome²¹⁶ and most frequently takes the form of fibrotic nonspecific interstitial pneumonia (eFig. 65-9A).²¹⁷ Although a presentation typical of extensive or progressive interstitial pulmonary fibrosis is rare and interstitial disease in Sjögren syndrome is often regarded as clinically insignificant, Gardiner and coworkers²¹⁶ found that patients with primary Sjögren syndrome complaining of dyspnea ($\approx 10\%$) have a high prevalence of histologic abnormalities (fibrosis or lymphocytic infiltration) on transbronchial biopsy.²¹⁶ A 10-year follow-up study of 30 patients showed that most patients do not develop progressive lung disease, although the total gas transfer level fell significantly in seven cases.²¹⁸ In a recent report of 105 patients with primary Sjögren syndrome and diffuse lung disease, diagnosed between 1976 and 2005, there was a striking female preponderance (91%) and a twofold increase in mortality, compared with patients without lung involvement. Diffuse lung disease tended to develop early in the disease course with a cumulative incidence of 10% at 1 year after the diagnosis of systemic disease.²¹⁹

Lymphocytic interstitial infiltration may take the form of lymphocytic interstitial pneumonia, pseudolymphoma (extensive pulmonary lymphocytic infiltration with the formation of lymphoid follicles, eFig. 65-9E), or pulmonary lymphoma (eFig. 65-9F and G). Lymphocytic interstitial pneumonia, historically believed to be the most common diffuse lung disease in Sjögren syndrome,²²⁰ is characterized by a diffuse lymphocytic infiltrate, with or without histiocytes and multinucleated giant cells, most prominent around bronchioles. Regression of disease with corticosteroids, in isolation or in combination with immunosuppressants, is highly variable. There are recent anecdotal reports of responses to rituximab. Pseudolymphoma, characterized by pulmonary infiltration, may regress spontaneously and often responds well to corticosteroid therapy; however, some patients progress to pulmonary lymphoma. The prevalence of lymphoma is increased 40- to 50-fold in Sjögren syndrome²²¹; pulmonary lymphoma has a highly variable clinical and radiographic presentation, with the spectrum of disease ranging from diffuse interstitial involvement to discrete (often perihilar) masses (eFig. 65-9F and G).

Organizing pneumonia has been reported in Sjögren syndrome (eFig. 65-9D) but is less common than in RA or polymyositis. A response to corticosteroid therapy is usual but not invariable.

Tracheobronchial Disease

Tracheobronchial disease may take the form of loss of mucous secretion in the trachea (xerotrachea), chronic bronchitis, or small airway disease. Xerotrachea develops in up to 25% of patients with primary Sjögren syndrome and consists of atrophy of tracheobronchial mucous glands in association with a lymphoplasmacytic infiltrate, manifesting clinically as a relentless dry cough and endobronchial inflammation at bronchoscopy.²²² It is likely that similar histologic abnormalities in bronchi and bronchioles account

Table 65-7 Polymyositis with Dermatomyositis**CRITERIA FOR DIAGNOSIS**

Symmetrical proximal muscle weakness
 Muscle biopsy specimen showing myositis
 Elevation of serum skeletal muscle enzymes
 Characteristic electromyographic pattern of myositis
 Typical rash of dermatomyositis

LUNG MANIFESTATIONS

Interstitial pulmonary fibrosis
 Acute pneumonitis (with diffuse alveolar damage)
 Organizing pneumonia
 Aspiration pneumonia
 Pulmonary vasculitis and alveolar hemorrhage
 Respiratory muscle weakness

for an increased prevalence of bronchial hyperresponsiveness, reported in 40% to 60% of patients with primary and secondary Sjögren syndrome.²²³

Subclinical bronchiolitis may be common in Sjögren syndrome. In the ILD of Sjögren syndrome, lymphocytic infiltration is more prominent around small bronchioles, resulting in a BAL lymphocytosis²²⁴; thus, it is likely that the occasional cases of isolated lymphocytic bronchiolitis, presenting with a clinical picture of COPD, represent a more limited form of lymphocytic infiltration. The evaluation of airflow at low lung volumes in unselected patients with primary and secondary Sjögren syndrome has demonstrated a high prevalence of small airway dysfunction²¹³; aerosol penetration from central airways to the lung periphery is reduced, indicating small airway obstruction.²²⁵ These abnormalities, indicating either BO or mucous plugging, may contribute to an increased prevalence of bronchopneumonia but do not evolve into severe BO (which is not generally a feature of Sjögren syndrome, except in occasional cases with associated RA). FB has been reported in a handful of patients with primary Sjögren syndrome but may be more frequently seen in secondary Sjögren syndrome; in a number of reported cases of FB associated with RA, the presence of Sjögren syndrome is not explicitly excluded. FB and diffuse bronchiolar lymphocytic infiltration may be part of the same spectrum of disease, but the relationship between the two disorders is uncertain.

POLYMYOSITIS AND DERMATOMYOSITIS

The defining criteria for *polymyositis* (PM) and *dermatomyositis* (DM) are listed in Table 65-7. For PM, a definite diagnosis is made if the first four features are present, a probable diagnosis is made if any three of the first four features are present, and a possible diagnosis is made if any two of the first four features are present. For DM, the typical rash must be present, plus any three of the first four for a definite diagnosis, two of the first four for a probable diagnosis, and one of the first four for a possible diagnosis (Bohan and Peter's criteria).²²⁶

The skin problems of DM include the presence of scaly cutaneous eruptions affecting extensor surfaces of the finger joints (Gottron tubercles or papules) (Fig. 65-5A) and



Figure 65-5 Skin changes seen in dermatomyositis. **A**, Gottron papules. A discrete scaly rash is seen over the extensor surfaces of the joints. **B**, Heliotrope rash. Named after a lilac-like flower with purple petals, this purplish rash and associated edema particularly involve the eyelids. (Adapted from Iaccarino L, Ghirardello A, Bettio S, et al: The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun* 48–49:122–127, 2014, Fig. 1.)

the characteristic edema and violaceous or purplish, heliotrope rash that involves and surrounds the eyelids (see Fig. 65-5B). Proximal muscle weakness tends to be insidious, progressive, and painless, affecting head, neck, and limb girdles and eventually involving the muscles of the tongue and pharynx and the respiratory muscles. Pulmonary complications arise in approximately 45% of patients and are the most frequent cause of death.

EPIDEMIOLOGY AND RISK FACTORS

The inflammatory myopathies are relatively rare, affecting 2 to 10/100,000 population, with a female-to-male predominance of 2.5:1 and with a bimodal age distribution peaking in childhood and in the fourth to fifth decades. DM appears to have a higher expression of HLA-B8/DR3, HLA-B14, and HLA-B40, whereas PM associates with HLA-B8/DR3 and in African Americans with HLA-B7 and HLA-DRw6.²²⁷ There are multiple manifestations of lung disease, as listed in Table 65-7. The presence of diffuse lung disease has been associated with two HLA haplotypes: HLA-DRB1*1302-DQA1*0102-DQB1*0604 and HLA-DRB1*0405-DQA1*03-DQB1*0401.²²⁸ In combined series, the prevalence of diffuse lung disease can be up to 64%. The disease may also present with pulmonary symptoms, and, in one series, this was the case in 21 of 70 patients.²²⁹ The

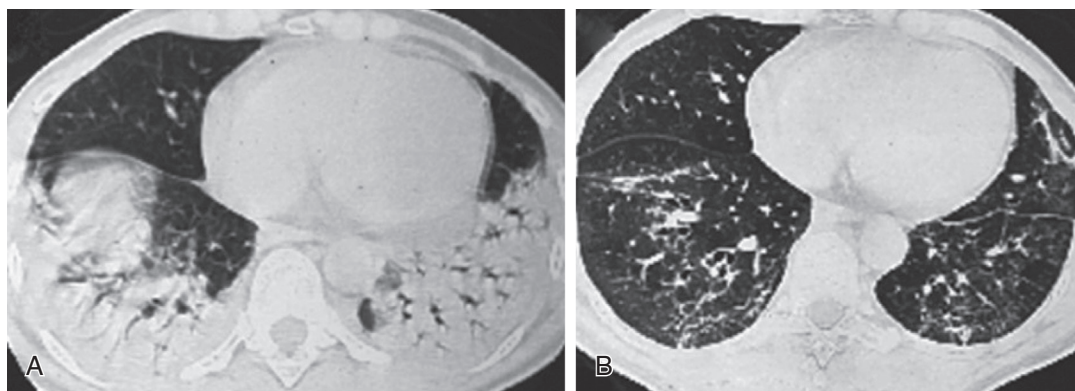


Figure 65-6 Organizing pneumonia in polymyositis. **A**, CT scan shows dense consolidation that denotes organizing pneumonia in a patient with polymyositis. As shown in this example, the disease tends to be most prominent posteriorly in the lower lobes. **B**, After treatment, the dense consolidation has regressed, but there is extensive residual linear opacification, representing residual fibrosis and resulting in traction bronchiectasis on the right and a restrictive functional defect. (Courtesy Michael Gotway, MD.)

prevalence of lung disease varies from series to series, and often the respiratory symptoms are masked by muscle fatigue. Nonetheless, pulmonary complications of the disease can be a frequent cause of death.

PULMONARY MANIFESTATIONS

Diffuse Lung Disease

Diffuse lung disease is the most common problem encountered in the context of DM with PM and may develop in up to 32% of patients.²³⁰ The prevalence of diffuse lung disease may be less common in patients with amyotrophic DM, a small subgroup of patients with the rash of DM but not the muscle involvement, and is three to five times more common in women than men, most commonly presenting in the fifth decade. The natural history and treated course of diffuse lung disease often mimics that of idiopathic fibrotic nonspecific interstitial pneumonia and, in many cases, a major component of organizing pneumonia, admixed with fibrotic abnormalities, is a prominent early feature, both histologically and on HRCT²³¹⁻²³³ (Fig. 65-6). However, in a distinct minority of cases with supervening diffuse alveolar damage (eFig. 65-10), the onset is subacute, rapidly progressive, and often resistant to treatment.²³⁴ The histopathologic features associated with these forms of presentation include nonspecific interstitial pneumonia and usual interstitial pneumonia in patients with an interstitial pulmonary fibrosis pattern, diffuse alveolar damage in the acute pneumonitis, and organizing pneumonia.²³⁵⁻²³⁷ In a large series of 70 patients, Douglas and colleagues²²⁹ reported that 82% of patients who were biopsied had the nonspecific interstitial pneumonia pattern of histopathology. One report described an acute presentation of pulmonary capillaritis with alveolar hemorrhage in association with PM.²³⁸

Clinical Features. The clinical features of diffuse lung disease in PM with DM depend on the nature of the lung process. Dyspnea and nonproductive cough are the most common presenting symptoms. Breathlessness on exertion without wheeze is common and, if the myopathy is severe, orthopnea may be striking. Hemoptysis may develop if there is capillaritis. Pleural disease is uncommon. Pulmonary involvement can develop before the systemic disease or at any time in the disease course. There is no correlation

between the severity of pulmonary parenchymal involvement and the systemic musculoskeletal manifestations. Rarely, patients present acutely with or progress rapidly to acute respiratory failure.

Imaging. Chronic diffuse lung disease is associated with peripheral reticular opacities, particularly in the lung bases as for interstitial pulmonary fibrosis. Acute pneumonitis can result in ground-glass opacification on chest radiography and alveolar hemorrhage with areas of consolidation.

High-resolution CT is more sensitive and specific than chest radiography, highlighting the distributions of the different processes. CT findings include thickened interlobular septa, linear opacities, ground-glass opacification (see eFig. 65-10), and patchy consolidation. A combination of consolidation with a peripheral reticular pattern is highly characteristic.²³⁹ Traction bronchiectasis and honeycombing are less common. The consolidation may evolve into a reticular pattern.²⁴⁰ DM and PM are well-recognized paraneoplastic phenomena, so it is sometimes difficult to determine which condition presented first.²⁴¹ Screening for occult carcinoma is recommended with mammography, abdominal CT, pelvic ultrasonography, and tumor markers.

Pulmonary Function. Lung function tests show a restrictive ventilatory defect with reduced gas transfer. In recent hemorrhage or marked myopathy, there may be a disproportionate preservation of the DL_{CO} . However, it must be remembered that acute hemorrhage can present in the context of previous chronic disease, so the DL_{CO} may be normal or subnormal but elevated from a level that was previously lower. Severe reduction in DL_{CO} is associated with increased mortality.

Bronchoalveolar Lavage. BAL lymphocytosis and neutrophilia have been described in diffuse lung disease associated with DM/PM. The significance of BAL is debated, but it appears that neutrophilia on BAL is associated with clinical deterioration.²⁴²

Laboratory Tests. Several studies have reported no association between creatine kinase levels and respiratory disease. In fact, the presence of a low creatine kinase has been associated with more rapidly progressive diffuse lung disease.^{243,244} Studies of autoantibodies have highlighted

the association between the presence of antibodies to aminoacyl-transfer RNA (tRNA) synthetases, inflammatory myopathies, and diffuse lung disease.²⁴³ These antibodies help define the clinical antisynthetase syndrome: the coexistence of myositis, diffuse lung disease, and arthritis. The most common autoantibody is Jo-1 (a cytoplasmic antihistidyl tRNA synthetase), found in 20% to 30% of patients with inflammatory myopathy and correlating strongly with the presence of diffuse lung disease. Jo-1 antibodies are present in 50% to 100% of cases of inflammatory myopathy and diffuse lung disease, in contrast to less than 5% of patients without diffuse lung disease. A variety of novel autoantibodies have been described with affinity for other tRNA synthetase molecules: PL-12, PL-7, EJ, OJ, and Ku.²⁴⁵

Other Pulmonary Manifestations

Muscular weakness may lead to aspiration pneumonia in up to 20% of patients and is usually associated with dysphagia. Respiratory muscle weakness and hypercapnic respiratory failure develop in up to 25% of patients, although severe respiratory failure requiring ventilatory support is less common. Bilateral diaphragmatic paralysis has been reported.

Treatment of Pulmonary Complications

Diffuse lung disease is a serious complication of DM/PM and is associated with increased mortality.²⁴⁶ The clinical course and prognosis of DM/PM-associated diffuse lung disease is heterogeneous and depends on the histologic pattern of disease. The decision to treat and the choice of therapy, therefore, need to be individualized. Corticosteroids are the preferred initial therapy. Oral prednisolone (0.75 to 1 mg/kg/day) is usual, but intravenous corticosteroids are required in more severe or rapidly progressive disease. Immunosuppressive therapy may be used in patients who are steroid resistant or experiencing adverse effects from corticosteroids. There are some reports of efficacy of cyclophosphamide,^{247,248} cyclosporine A,²⁴⁹ and azathioprine.^{250,251} In refractory cases, methotrexate and intravenous immunoglobulin should be considered. Mycophenolate has been shown to be safe and effective in treatment of the systemic disease, but no controlled studies have yet been performed in DM/PM-related lung disease. As discussed earlier, in pilot studies, rituximab is promising treatment for the anti-synthetase syndrome,²⁵² including for patients with life-threatening disease refractory to other immunomodulatory therapies.²⁵³

MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD) is defined by the presence of features of SLE, SSc, and PM (Sjögren syndrome may also be seen) in association with high titers (>1:1600) of autoantibody directed against the extractable nuclear antigen U1-RNP.^{254,255} Criteria that have been suggested for the diagnosis of MCTD include the presence of antibody to the U1 ribonuclear protein together with the clinical features of hand edema, synovitis, Raynaud phenomenon,

acrosclerosis, and myositis. At least three of these clinical features are needed in addition to the autoantibody finding. A fourth clinical feature is required if the initial three are Raynaud phenomenon, edema, and acrosclerosis. The difference between MCTD and overlap syndrome may be semantic, but the former often presents more acutely and with greater specificity for U1-RNP. MCTD may differentiate into specific rheumatologic diseases. This differentiation may be genetically determined.²⁵⁶

Other overlap syndromes are reported in which clinical features of more than one CTD are present in the same patient. Although MCTD tissue disease remains the most clearly definable, other overlap syndromes are seen both with and without typical autoantibody association. Of the former, overlapping clinical features found in association with U2-RNP and U3-RNP and the tRNA synthetase-associated diseases (see earlier) can be considered to be part of an overlap syndrome. Antibodies to PM-Scl, KU, and U2-RNP are associated with overlaps of SSc and PM.²⁵⁵

The prevalence of MCTD is unclear, but it is estimated at 1 in 10,000, with a 9:1 female preponderance, most frequently presenting in the fourth decade. Pleuropulmonary complications are seen in 20% to 85% of patients, but diffuse lung disease (most commonly a nonspecific interstitial pneumonia CT pattern) is the most common lung complication.²⁵⁷ In a CT study of 41 patients, the major abnormalities were ground-glass opacities in all, subpleural micronodules in 40 of 41, and nonseptal linear opacities in 32 of 41.²⁵⁸ Pleural effusions develop in patients with other clinical features of SLE and are usually small, are exudative, and often resolve spontaneously. Pulmonary hypertension may also develop.²⁵⁹ Respiratory muscle weakness, diffuse alveolar hemorrhage, and small airway disease are less common complications.

Survival is difficult to quantify owing to the heterogeneity of disease. Individual disease course tends to be similar to that of the CTD most closely resembled in that patient. Survival is better if the diffuse lung disease is associated with U1-RNP positivity than with no U1-RNP. Treatment depends on the nature of the lung disease and is identical to the approaches used for the other CTDs. Pleural effusions are often responsive to corticosteroids. A combination of low-dose prednisolone and an immunosuppressant (such as cyclophosphamide or azathioprine) is generally used to treat interstitial fibrosis, with an approach similar to that for SSc.

UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

Up to 25% of patients with autoimmune features do not fulfill American College of Rheumatology criteria for a specific CTD, and a large proportion never progress to a “differentiated” CTD. ILD may complicate undifferentiated connective tissue diseases,²⁶⁰ with little known about the prognosis or treatment of ILD in this context. However, attention has recently focused on this patient subgroup²⁶¹ as CTD is eventually diagnosed in approximately 15% of patients presenting with idiopathic interstitial pneumonia^{262,263} and in 30% of patients with idiopathic NSIP.²⁶⁴

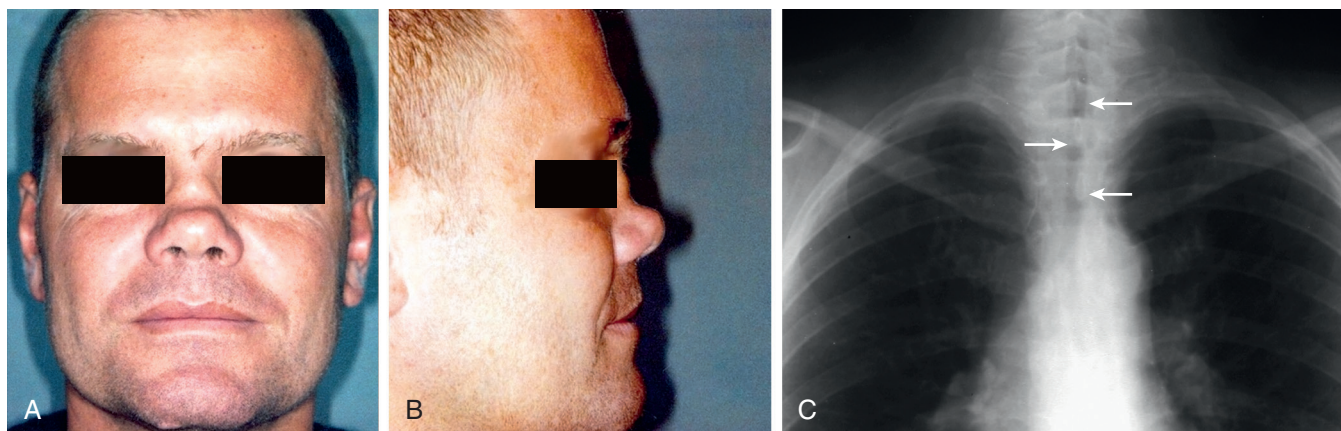


Figure 65-7 Relapsing polychondritis. **A** and **B**, Saddle nose deformity indicating loss of cartilage of the nose due to inflammatory deterioration of cartilage structure. In this 42-year-old man, destruction of the nasal septum led to restriction of ventilation with collapse of the internal nasal valves during a rapid inspiration. **C**, Relapsing polychondritis: chest radiographic appearance. Focused frontal chest radiograph shows smooth sagittal narrowing of the trachea (arrows). (**A** and **B**, From Haug MD, Witt P, Kalbermatten FD, et al: Severe respiratory dysfunction in a patient with relapsing polychondritis: should we treat the saddle nose deformity? *J Plast Reconstr Aesthet Surg* 62:e7–e10, 2009, Fig. 3; **C**, Courtesy Michael Gotway, MD.)

The view that all patients with idiopathic NSIP have undifferentiated CTD was based on findings in a small patient cohort, in which broad diagnostic criteria for undifferentiated CTD were used, including highly nonspecific features such as weight loss, gastroesophageal reflux, and a high erythrocyte sedimentation rate.²¹¹ However, with use of the more specific diagnostic criteria of Mosca²⁶⁵ in a subsequent larger retrospective series, criteria for undifferentiated UCTD were met in only 31% of patients with idiopathic NSIP and in 13% of patients with IPF.²⁶⁶ The presence of undifferentiated CTD had no effect on outcome in this series and in other reports of idiopathic interstitial pneumonia, the presence of antinuclear antibodies²⁶⁷ and the presence of a sign or symptom of CTD in combination with a non-specific autoantibody²⁶⁸ had no prognostic significance. However, it remains possible that a more exact definition of the entity “interstitial pneumonitis with autoimmune features,” currently being developed by an expert group, may have future management implications.

RELAPSING POLYCHONDritis

Relapsing polychondritis is a rare disease characterized by recurrent progressive cartilaginous inflammation. The episodic and painful inflammation results eventually in the widespread degeneration of cartilaginous structures. The diagnosis of relapsing polychondritis requires the presence of three or more of the following clinical features²⁶⁹: bilateral auricular chondritis; nonerosive, seronegative inflammatory polyarthritis; nasal chondritis; ocular inflammation; respiratory tract involvement (either upper or lower respiratory tract); cochlear with or without vestibular abnormality; and positive biopsy specimen. The presence of anticartilage antibodies may be helpful in the diagnosis.

The condition affects men and women equally and has a peak incidence between ages 40 and 60. It is considered an autoimmune process, and autoantibodies have been found directed against cartilage and type II collagen. A weak association with HLA-DR4 has been reported.²⁷⁰ Diagnosis is

chiefly clinical but can be confirmed at biopsy of affected cartilage, including tracheal rings.

Relapsing polychondritis is usually multifocal, affecting cartilage of the ear (85% to 94%), nose (54% to 57%) (Fig. 65-7A and B), upper respiratory tract (31% to 48%), and ribs. In addition, patients frequently suffer ocular inflammation, nonerosive arthropathy (52%), and vestibulocochlear dysfunction.^{269,271} Relapsing polychondritis may be associated with a wide range of other conditions, especially CTD and vasculitis. Approximately 30% of patients have a preexisting CTD.

Respiratory involvement probably accounts for around 10% of deaths in this condition. Up to 25% of cases present with focal or generalized respiratory tract involvement. The larynx and upper trachea are the most common focal areas involved, but large or small airways may also be affected. Laryngotracheal involvement is a poor prognostic determinant. Destruction and obstruction of the glottis, trachea, and bronchi may lead to airway stricture, collapse, and distal infection.²⁷² Pulmonary parenchymal disease is rare, with the exception of pulmonary vasculitis.

The site of cartilaginous involvement determines the clinical presentation. Upper airway involvement typically presents with wheezing and hoarseness. Lung function testing shows diminution in maximal inspiratory (large, extrathoracic airways) and expiratory (smaller, intrathoracic airways) flow rates, suggesting airway collapse. Static recoil pressures are preserved. Chest radiography may show ectopic airway cartilage calcification or large airway narrowing (see Fig. 65-7C) but is often insensitive. However, high-resolution CT scanning shows tracheal ring thickening, airway wall attenuation, and calcification (Fig. 65-8A, see Fig. 18-32). Postexpiratory CT scanning, using either scanning at the completion of a forced vital capacity maneuver (see Fig. 65-8B) or cine scanning during such a maneuver, shows extensive tracheobronchial collapsibility and can help to localize the large airway disease.²⁷³ Bronchoscopy may show endobronchial inflammation or stenosis and is useful in the exclusion of mechanical obstruction. Endobronchial biopsy may be diagnostic but is insensitive.

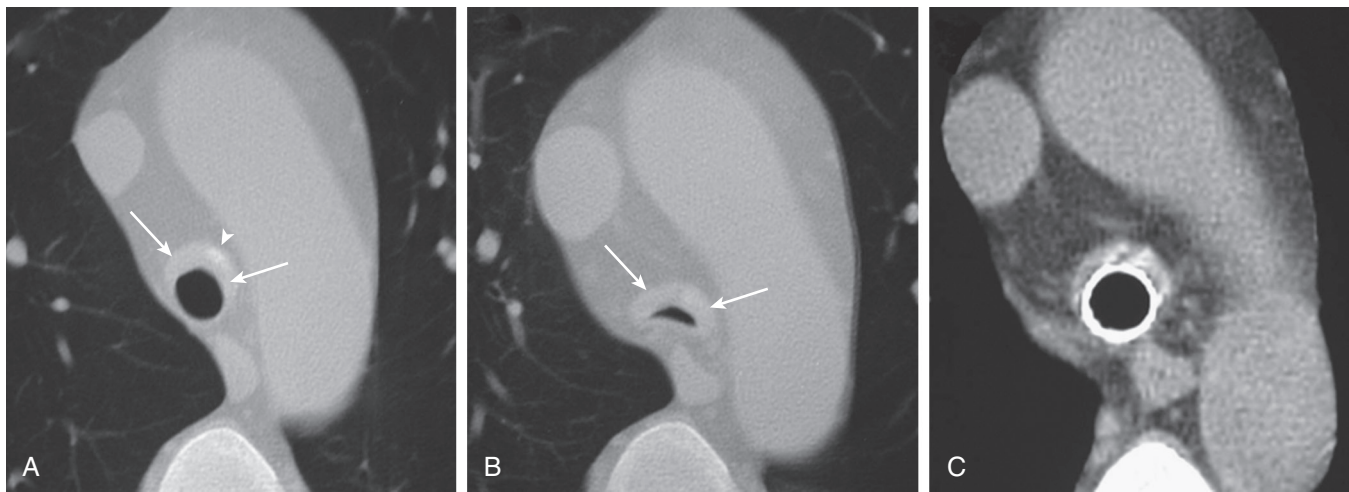


Figure 65-8 Relapsing polychondritis: chest CT appearance. **A**, Axial unenhanced chest CT shows thickening of the anterior two thirds of the trachea (arrows), with sparing of the posterior tracheal membrane; this pattern is typical of relapsing polychondritis. A small focus of calcification is present in the anterior tracheal wall at the 1 o'clock position (arrowhead). **B**, Axial postexpiratory HRCT image shows extensive tracheal collapse (arrows), consistent with tracheomalacia, and typical of relapsing polychondritis. **C**, Treatment of relapsing polychondritis with a self-expandable endoluminal metallic stent shows patency of the tracheal lumen. (Courtesy Michael Gotway, MD.)

Laryngoscopy and bronchoscopy are associated with risk of acute airway compromise, however.²⁷²

Treatment depends on disease severity. Mild cases may be controlled with nonsteroidal anti-inflammatory drugs, but troublesome relapses may require short-term high-dose corticosteroid therapy. In acute airway involvement, high-dose intravenous corticosteroid is used. In one large review of 159 reported cases, three fourths of the patients required chronic corticosteroid therapy, which in that series, decreased the frequency, duration, and severity of flare-ups but did not prevent disease progression.²⁷⁴ Steroid-resistant lesions have been treated with immunosuppressive agents such as cyclophosphamide. Despite short-term improvement with steroid and immunosuppressive therapy, relapse and disease progression are common. More recently, there have been a number of reported responses to biologic agents, including TNF- α antagonists, anti-IL-6 therapy, and rituximab, with efficacy or partial efficacy in more than half of cases.^{275,276} Currently, biologics cannot be recommended as first-line therapy but may have an important role in cases refractory to corticosteroids and as steroid-sparing agents. Tracheostomy and stenting are occasionally indicated, but other surgical treatment is difficult owing to the diffuse nature of involvement and risk of relapse.²⁷⁷ In one study, the use of multiple, self-expandable stents (see Fig. 65-8C) via fiberoptic bronchoscopy in five patients requiring mechanical ventilation resulted in improvement in four patients who were all able to live without mechanical ventilation for up to 20 months.²⁷⁸ Newer self-expanding silicone stents have been used with variable effect in palliative cases.²⁷⁹ Intraluminal stents may be complicated by hemorrhage, tracheal erosion, ulceration, or airway obstruction, however. Survival has been reported at 94% at 8 years.²⁸⁰

BEHÇET SYNDROME

Behçet syndrome is found predominantly in the countries bordering the Mediterranean Sea. Prevalence estimates

Table 65-8 Behçet Syndrome

CRITERIA FOR DIAGNOSIS
Major (required)
Recurrent aphthous ulceration at least 3 times in a 12-mo period
Minor (2 of 4)
Recurrent genital ulceration
Ocular disease
Skin lesions (erythema nodosum, skin ulcers)
Positive pathergy test (a 2-mm erythematous papule or pustule at the prick site 48 hr after the application of a sterile hypodermic 20- to 22-gauge needle that obliquely penetrated avascular antecubital skin to a depth of 5 mm)

approach 80 to 370/100,000 population in Turkey. Men and women are affected equally, and age of onset is usually in the second or third decade. There is an association between the HLA-B51 allele and, more controversially, more severely affected patients; relative risk of HLA-B51 carriers is roughly 13:1 in Turkey. Herpes simplex type 1 and streptococci have been suggested as causative agents.²⁸¹ Diagnosis requires the development of recurrent oral ulceration at least three times in a 12-month period and the presence of two of the four minor features listed in Table 65-8.²⁸² Mucocutaneous ulceration is the clinical hallmark, with aphthous oral and genital ulceration seen in almost all patients. Other cutaneous features include erythema nodosum, an acneiform rash, and papular lesions of cutaneous vasculitis. Uveitis is the major cause of morbidity, but systemic vasculitis may affect all systems.

Pulmonary involvement is seen in 1% to 7% and tends to affect HLA-B51-positive younger males (<25 years) more severely. The major pulmonary manifestations are pulmonary vasculitis,²⁸³ pulmonary artery aneurysms, arterial and venous thromboses, pulmonary infarction, organizing pneumonia, and pleurisy.²⁸⁴ Symptoms include dyspnea, chest pain, and recurrent hemoptysis that can be massive and fatal.²⁸⁵

The cardinal histologic feature is vasculitis affecting arterial and venous vessels of all sizes. Pulmonary arterial aneurysms are surrounded by inflammatory infiltrates and have thickened intima and degeneration of the elastic lamina with thrombosis. Behçet syndrome may be accompanied by arterial and venous thromboses, pulmonary infarcts, and occasionally, pleural effusion.²⁸⁶ The radiographic abnormalities are nonspecific but may include the features of small airway disease, pulmonary hemorrhage, vascular occlusion, or mass lesions representing arterial aneurysm(s) (see eFig. 67-2).^{287,288} Prognosis is variable. The disease course is relapsing remitting. Pulmonary artery aneurysm carries the worst prognosis, with a 2-year survival of 70%.

Treatment is complex and depends on presentation. Steroids and immunosuppressive agents are used to control vasculitis, particularly in cases of pulmonary artery aneurysm, in which eventual regression is sometimes observed. Cyclosporin A and FK506 have been successful in some patients.²⁸⁴ Anticoagulants may be required for control of thrombosis but should be used only if immunosuppression is insufficient because there is a significant risk of hemorrhage. However, controlled data are lacking and accumulated experience mostly relates to the treatment of systemic disease, including orogenital ulceration, and must be applied to pulmonary disease with caution. Acknowledging this caveat, the major recent change in treatment has been the increasing use of anti-TNF therapy, found to be efficacious for oral ulceration and skin lesions in a randomized controlled trial²⁸⁹ and endorsed for eye disease, neurologic disease, and gastrointestinal disease by a position paper, based on a definitive review of uncontrolled treatment data.²⁹⁰ For pulmonary artery aneurysms, pulmonary embolization and surgical resection have been reported to be successful, but surgical treatment of aneurysms can result in aneurysms at the anastomosis site.²⁹¹

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a seronegative spondyloarthritis developing in 0.05% to 1.5% of the general population and is associated with the major histocompatibility antigen HLA-B27.²⁹² The prevalence of AS is higher in white males, with a male-to-female ratio of 10:1. The cardinal site of disease is the vertebral column. As the disease progresses, inflammation leads to fibrosis and ossification, with ankylosis of the vertebral joints. Peripheral joint arthritis is seen in approximately one third of patients, and extra-articular features include aortic regurgitation, uveitis, pulmonary disease, and extrapulmonary restriction.

Lung disease, mainly upper zone fibrosis, can be present in up to 30% of case series but fibrobullous disease is less common (see Figs. 98-16 and 98-18). In a series of 2080 patients with AS, this pattern was seen in only 1% to 2% of patients.²⁹³ Limited ILD, small airway disease, bronchiectasis, and paraseptal emphysema are frequently present even when chest radiographic appearances are normal.²⁹⁴⁻²⁹⁶ In another study, abnormalities were seen in 15 of 21 patients, comprising thickened interlobular septa (33%), bronchial wall thickening (29%), pleuropulmonary abnormalities (29%), and linear septal thickening (29%).²⁹⁷ Pulmonary

involvement, often subclinical, is an early manifestation of AS.²⁹⁸ A subclinical lymphocytic alveolitis may be evident with BAL.²⁹⁹ Histologically, lung abnormalities consist of a variable mixture of lymphocytic infiltration, fibrosis, and bullous change. On chest radiography, diffuse reticular opacities in the upper zones are usually symmetrical and are seldom extensive except in patients with severe spinal disease³⁰⁰ or a long history of AS.²⁹³ However, apical fibrosis occasionally may precede the development of extrapulmonary disease. No proven treatment exists to prevent the development of apical fibrosis; resistance to corticosteroid therapy is the rule.

Cavities may develop within distorted fibrotic apical tissue and are sometimes colonized by mycobacteria or fungi, especially *Aspergillus fumigatus* (see Fig. 98-18), which are isolated in up to 60% of AS patients with apical cavitation.³⁰¹ Life-threatening hemoptysis is an occasional complication of mycetoma formation within cavities and may be controllable by bronchial artery embolization; the resection of a mycetoma is a treatment of last resort owing to the high prevalence of postoperative bronchopleural fistula or empyema. Advanced apical fibrosis is often associated with apical pleural thickening, but pleural disease is seldom seen adjacent to normal lung parenchyma elsewhere in the thorax. There is an increased ($\leq 10\%$) prevalence of pneumothorax in AS patients with apical fibrosis,²⁹³ probably due to subpleural bullous degeneration in advancing disease.

Extrapulmonary restriction due to immobilization of the chest wall (costovertebral ankylosis) is an occasional complication of AS. Extrapulmonary restriction is often asymptomatic and associated with surprisingly little impairment in pulmonary function, perhaps because the diaphragm is able to make a major contribution in the presence of a high resting volume. Lung volumes may be mildly reduced, but gas transfer is almost always preserved in the absence of parenchymal disease.³⁰²

MARFAN SYNDROME

Marfan syndrome (MS) is an autosomal dominant condition of variable penetrance affecting approximately 5/100,000 population. MS is characterized by abnormalities of fibrous connective tissue with abundant type I collagen (in some cases due to mutations on chromosome 15), especially in the skeleton (long limbs, arachnodactyly, pectus excavatum, kyphoscoliosis), eyes (subluxation of the lens), and cardiovascular system (aortic or mitral regurgitation, aortic aneurysm). The reduced life expectancy of MS is largely attributable to cardiac complications; there is no effective treatment to reverse disease or slow progression.

Respiratory complications can be subdivided into pulmonary and extrapulmonary abnormalities. Ten percent to 15% of patients with MS have pulmonary involvement. The most common pulmonary complication is pneumothorax (often recurrent and bilateral). The high prevalence of pneumothorax in MS of 5% to 10%³⁰³ (>100-fold higher than in the general population) can be ascribed to the rupture of subpleural bullae. Localized bulla formation with a predilection for the lung apex³⁰⁴ is an occasional striking finding in young patients. Emphysema is present on

chest radiography in the majority of MS patients with pneumothoraces.^{303,305} Lung histologic appearances in MS are poorly characterized, but in a small series of patients with absent or minimal smoking histories, a pattern of distal acinar emphysema was evident in all cases.³⁰⁶ Generalized emphysema in nonsmoking patients with MS may become evident at any age and is sometimes fatal in childhood.³⁰⁷ Underlying apical fibrosis has been reported in a handful of cases. Other less frequent parenchymal manifestations include congenital malformations of the middle lobes (which may be absent or rudimentary) and an increased prevalence of bronchopneumonia.³⁰³

Thoracic cage involvement is present in greater than 50% of MS patients. Isolated pectus excavatum in MS is seldom associated with significant impairment in lung function. However, occasionally kyphoscoliosis is associated with fatal cor pulmonale.³⁰⁸ It is likely that nocturnal desaturation amplifies hypoxemia due to kyphoscoliosis. Increased upper airway collapsibility during sleep is common in MS, accounting for an association between MS and obstructive sleep apnea.³⁰⁹

Key Points

- In connective tissue diseases, the lung can be involved by a wide variety of patterns of pathology, from the trachea to the parenchyma to the pleura.
- Sometimes, pulmonary manifestations may precede the systemic features of the connective tissue diseases.
- Often, combinations of patterns exist that raise the likelihood that connective tissue disease is the underlying problem. Some patterns of lung disease are more common in one connective tissue disease than the others. Specific pathologic entities that are seen in

these diseases do not generally follow the same course as their idiopathic counterparts.

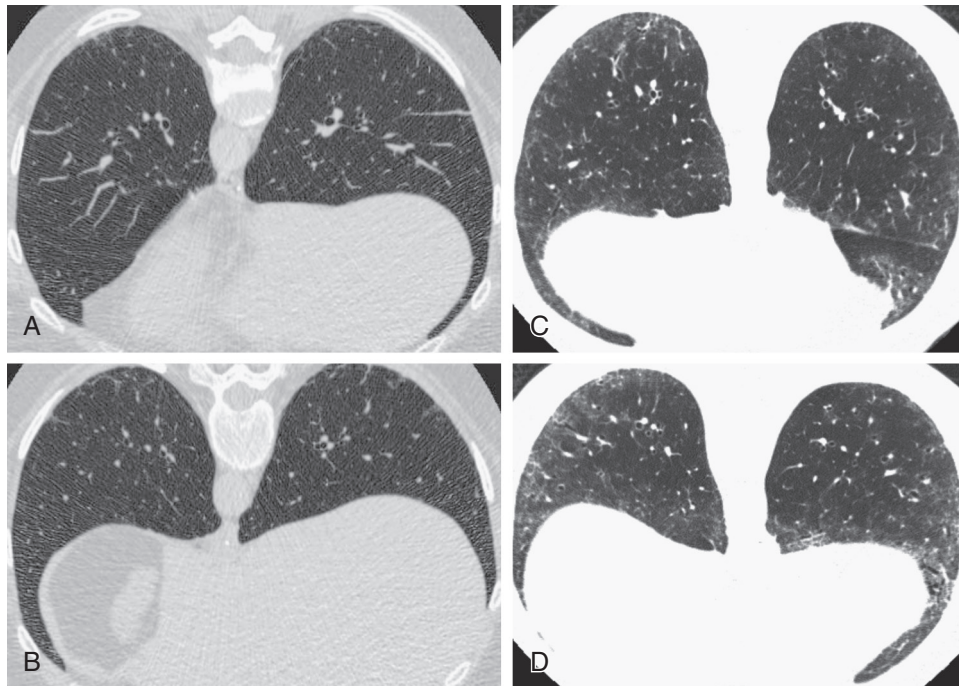
- Common drugs used in the treatment of connective tissue diseases may result in major pulmonary complications.
- Increasing recognition of the pulmonary manifestations of these protean disorders is resulting in better outcomes.

Complete reference list available at *ExpertConsult*.

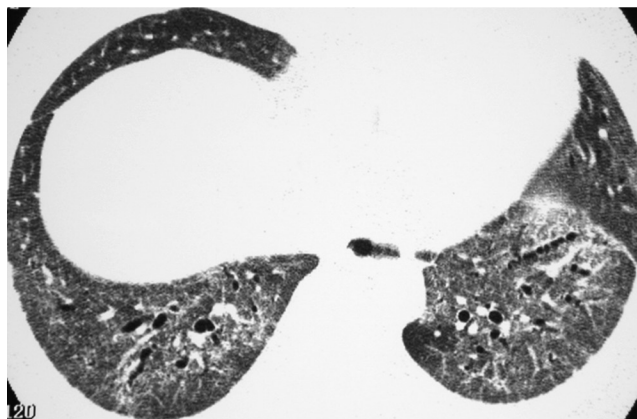
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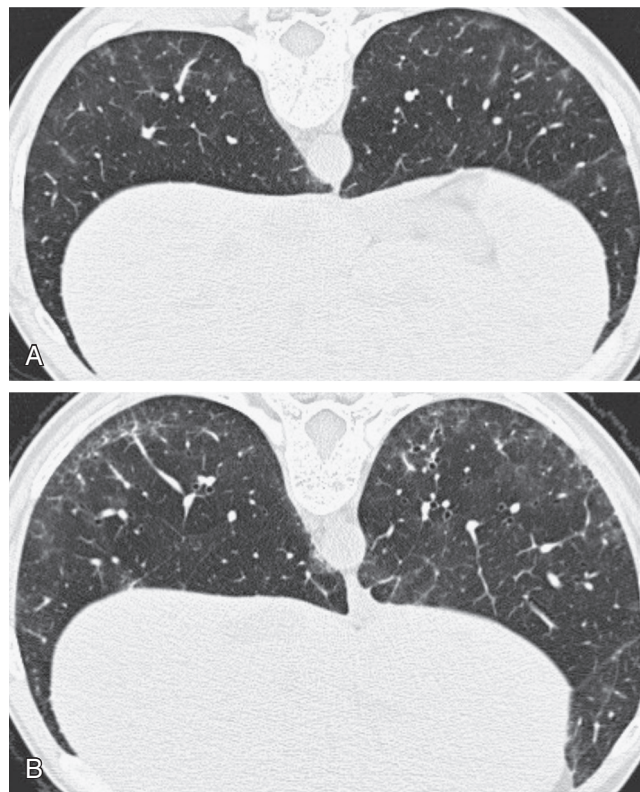
eFIGURE IMAGE GALLERY



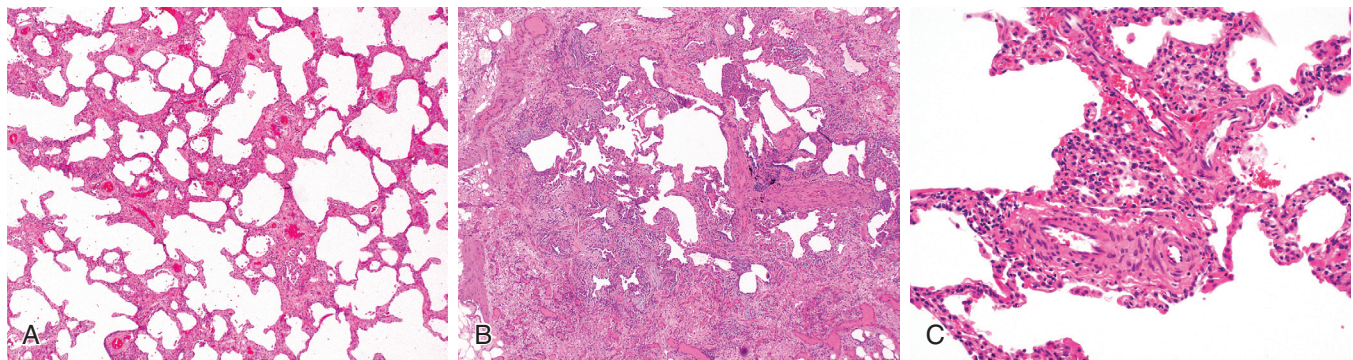
eFigure 65-1 High-resolution CT (HRCT) of mild systemic sclerosis lung disease. **A and B,** Axial prone HRCT imaging in a patient with scleroderma shows mild, faint reticulation. **C and D,** Axial prone imaging in a patient with scleroderma shows some faint reticulation, with more prominent subpleural ground-glass opacity. (Courtesy Michael Gotway, MD.)



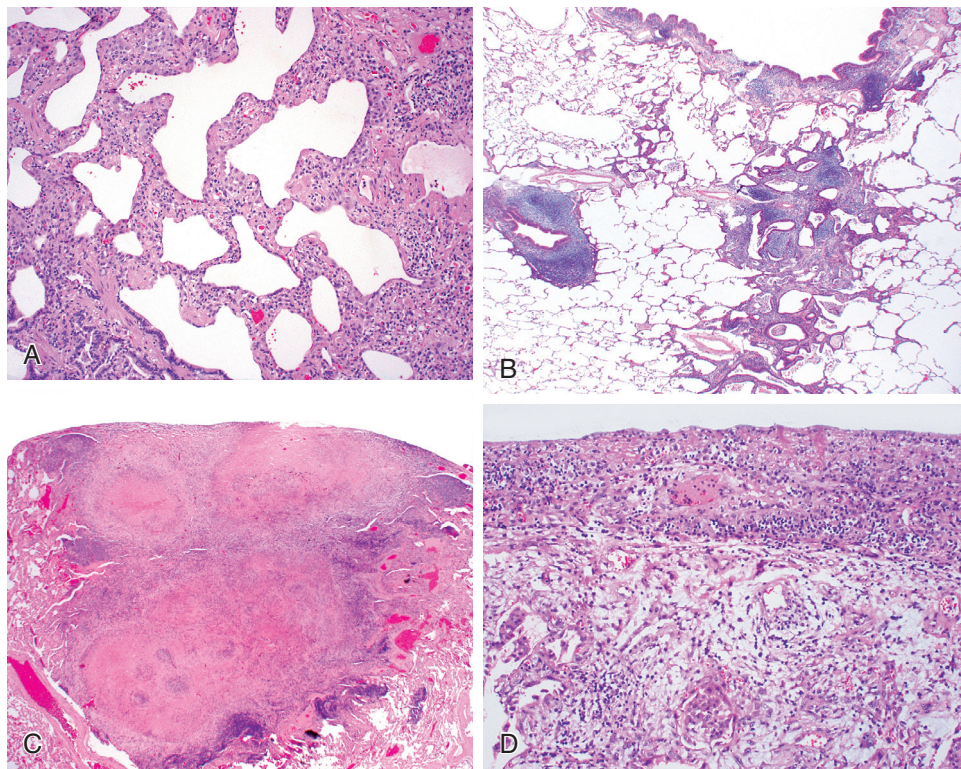
eFigure 65-2 High-resolution CT (HRCT) of moderate systemic sclerosis lung disease. Axial supine HRCT imaging shows moderate basal, subpleural ground-glass opacity associated with reticulation. The pattern is identical to idiopathic nonspecific interstitial pneumonia. (Courtesy Michael Gotway, MD.)



eFigure 65-3 High-resolution CT (HRCT) of progressive systemic sclerosis lung disease. **A**, Axial prone HRCT image shows faint, subpleural basal ground-glass opacity. **B**, Axial prone HRCT image 1 year following **A** shows worsening of basal, subpleural ground-glass opacity and reticulation. (Courtesy Michael Gotway, MD.)



eFigure 65-4 Progressive systemic sclerosis (PSS). **A**, The interstitial fibrosis of PSS is typically paucicellular and diffuse, with preservation of underlying lung architecture. **B**, When fibrosis is more advanced, distinction from usual interstitial pneumonia (of idiopathic pulmonary fibrosis) may be difficult on morphologic grounds. **C**, Pulmonary hypertensive changes may be present and deserve careful attention because this is a major cause of mortality in scleroderma patients with lung disease. (From Leslie KO, Wick MR: Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series, ed 2. Philadelphia, 2011, Elsevier, Figs. 7-39 and 7-40.)



eFigure 65-5 Rheumatoid arthritis (RA) lung disease. **A,** Variable interstitial fibrosis is typical and often resembles the fibrotic form of nonspecific interstitial pneumonia. **B,** Most of the lymphoid aggregations in RA are present around the terminal airways (“follicular bronchiolitis” when lymphoid germinal centers are prominent), but lymphoid follicles may also be present in the pleura. **C,** Typical rheumatoid nodules may appear in RA lung and must be distinguished from lesions seen with infection and in granulomatosis with polyangiitis. **D,** The presence of chronic pleuritis should always raise the possibility of RA in the differential diagnosis. (From Leslie KO, Wick MR: Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series, ed 2. Philadelphia, 2011, Elsevier, Figs. 7-38 and 7-35.)

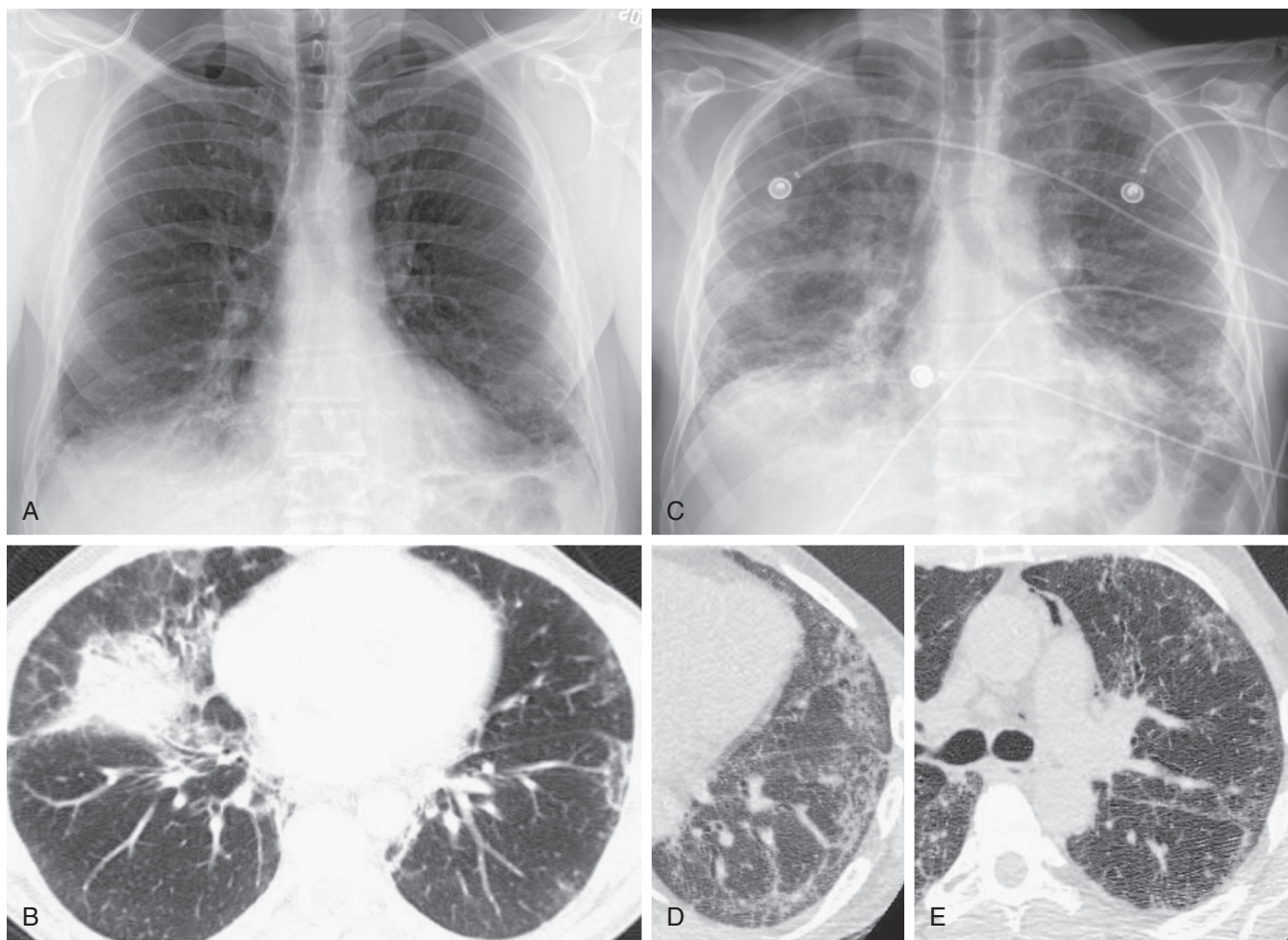
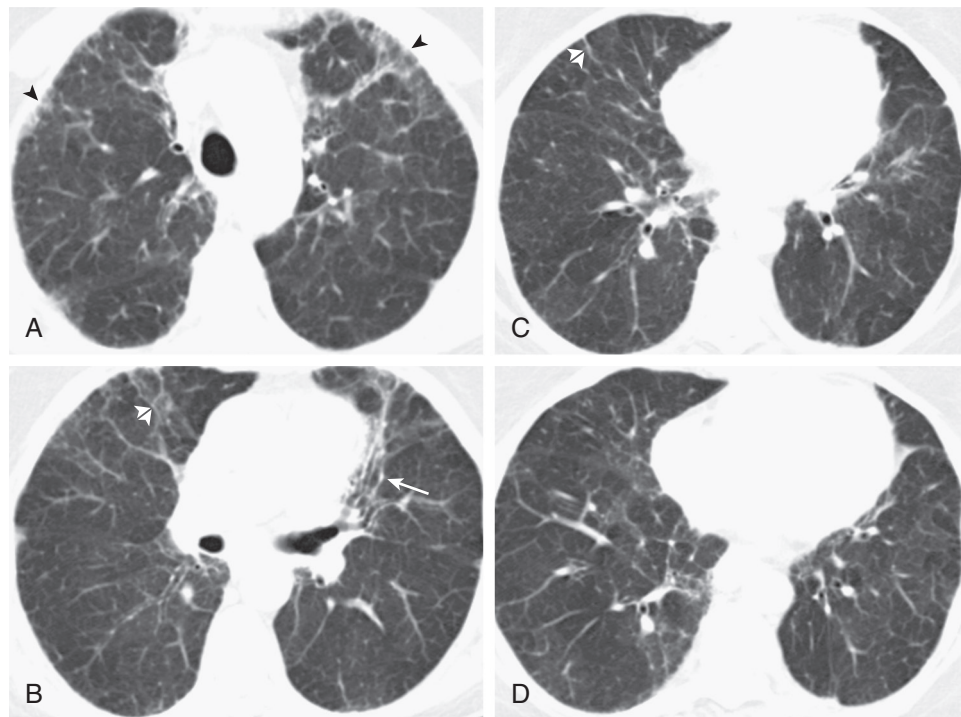
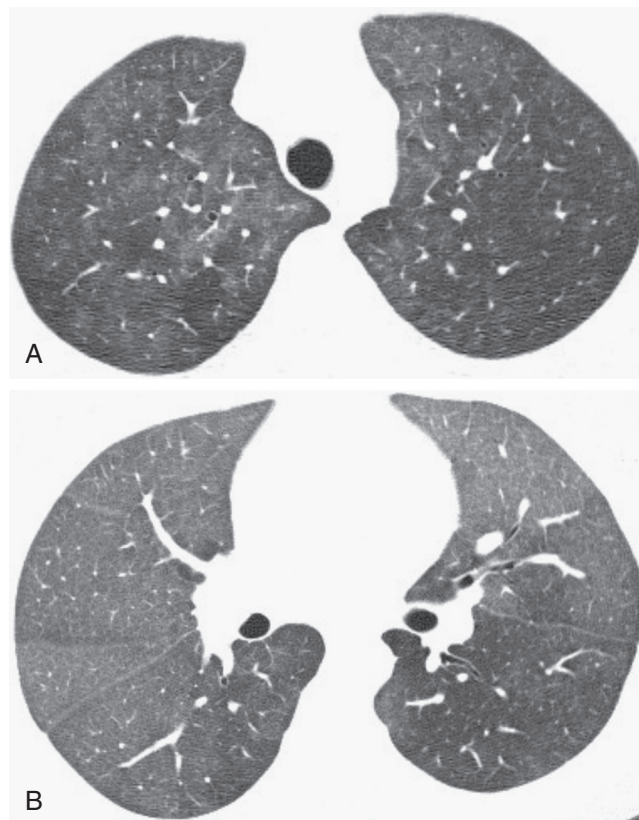


Figure 65-6 High-resolution CT (HRCT) of accelerated interstitial pneumonia in a patient with rheumatoid arthritis. **A**, Frontal chest radiography shows basal reticulation and linear opacities consistent with interstitial lung disease in the setting of rheumatoid arthritis. **B**, Axial supine HRCT image shows basal reticulation, patchy subpleural ground-glass opacity, and traction bronchiectasis. **C**, Frontal chest radiography performed several years following **A** and **B**, when the patient developed severe shortness of breath, shows diminished lung volumes with development of extensive bilateral opacities. **D**, Axial supine HRCT image focused on the left base shows progression of the basal lung abnormalities seen previously; similar findings were now also present in the mid and upper lungs (**E**). Surgical lung biopsy showed diffuse alveolar damage. The pneumomediastinum was postoperative in nature. (Courtesy Michael Gotway, MD.)



eFigure 65-7 High-resolution CT (HRCT) of diffuse interstitial fibrosis in systemic lupus erythematosus. A–D, Axial supine HRCT images show multifocal, bilateral, patchy areas of reticular and linear opacities, including interlobular septal thickening (*double arrowheads*), associated with ground-glass opacity (*arrowheads*) and mild architectural distortion. Mild traction bronchiectasis (*arrow*) is evident. The findings are nonspecific, but surgical lung biopsy showed features suggestive of a connective tissue disorder (enlarged peribronchiolar lymphoid follicles). (Courtesy Michael Gotway, MD.)



eFigure 65-8 High-resolution CT (HRCT) of diffuse alveolar hemorrhage in systemic lupus erythematosus. A and B, Axial supine HRCT images show multifocal bilateral ground-glass opacity, with a somewhat centrilobular nodular appearance in the upper lobes (**A**). (Courtesy Michael Gotway, MD.)

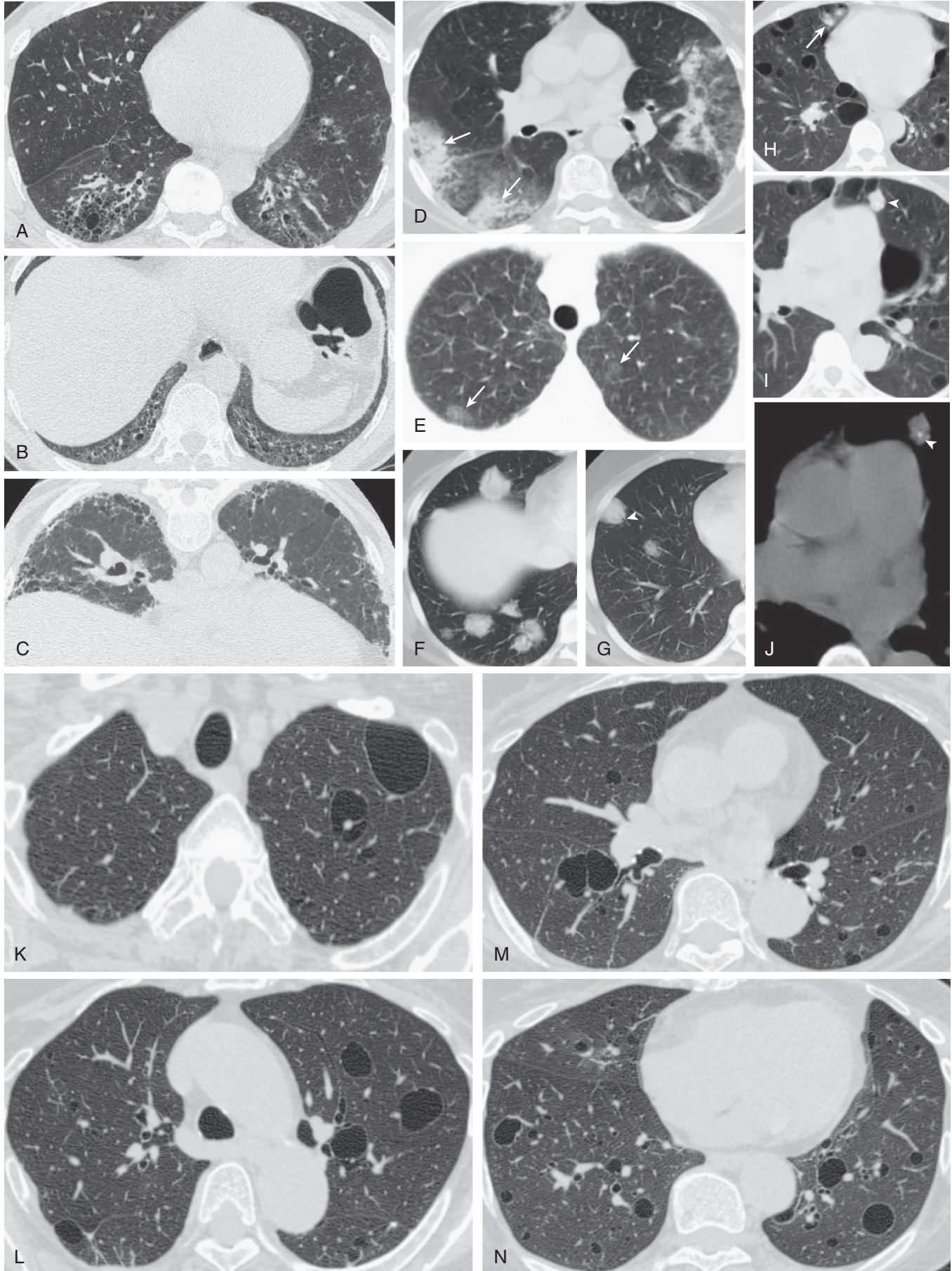
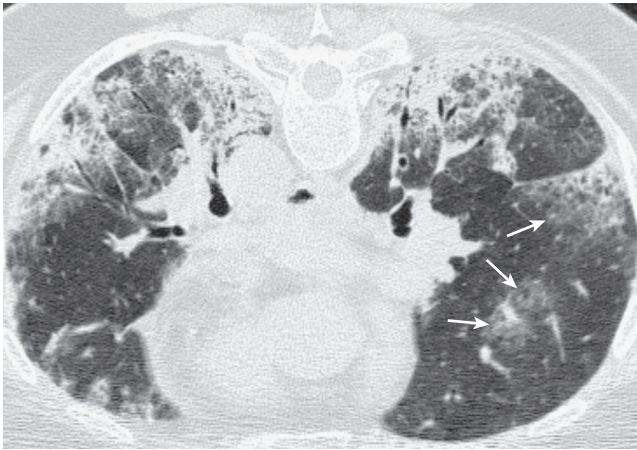


Figure 65-9 Spectrum of Sjögren-related pulmonary abnormalities. **A** and **B**, Axial supine high-resolution CT (HRCT) images show basal reticulation, mild ground-glass opacity, and traction bronchiectasis in the subpleural lower lobes, consistent with a nonspecific interstitial pneumonia pattern. **C**, Axial prone HRCT image shows coarse basal reticulation, subpleural cystic change, and traction bronchiectasis, consistent with a usual interstitial pneumonia pattern. **D**, Axial supine HRCT image shows peripheral consolidation (arrows) consistent with an organizing pneumonia pattern. **E**, Axial supine HRCT image shows several poorly defined ground-glass opacity nodules (arrows), representing lymphocytic interstitial pneumonia. This appearance is nonspecific and can be seen with other lymphoproliferative disorders that may be encountered in Sjögren patients, including follicular bronchiolitis, nodular lymphoid hyperplasia, and even MALT lymphoma. **F** and **G**, Axial supine HRCT image shows multiple, bilateral poorly defined pulmonary nodules found to represent MALT lymphoma. Note the air bronchograms associated with one of the nodules (arrowhead), indicating the bronchiolocentric nature of the process. **H** and **I**, Axial supine HRCT images show multiple thin-walled cysts and small nodules (arrow), one of which shows a small focus of calcification (arrowhead) on the images displayed in soft tissue windows (**J**). **K–N**, Axial supine HRCT images in a patient with Sjögren syndrome show multiple, bilateral, thin-walled cysts with normal intervening lung parenchyma. (Courtesy Michael Gotwax, MD.)



eFigure 65-10 Diffuse alveolar damage superimposed on pulmonary interstitial abnormalities in a patient with polymyositis-dermatomyositis. Axial prone high-resolution CT image shows patchy, subpleural reticulation and areas of consolidation, consistent with a mixture of nonspecific interstitial pneumonia and organizing pneumonia injury patterns. Patchy areas of ground-glass opacity, spatially separated from the subpleural process, represent areas of diffuse alveolar damage. (Courtesy Michael Gotway, MD.)

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Lung Imaging
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Eyes
Skin
Nervous System
Heart
Ears, Nose, and Throat

Parotid Gland
Liver and Spleen
Joints
Peripheral Lymph Nodes
Endocrine Glands
Blood

TREATMENT OF SARCOIDOSIS

Anti-inflammatory Medications
Management of Extrapulmonary Disease
Antifibrotic Therapy
Supportive Care
Management of Complications of Sarcoidosis

INTRODUCTION

Sarcoidosis has been defined as a multisystem granulomatous disorder of unknown cause.¹ Sarcoidosis affects the lung in over 90% of cases but can affect any part of the body. For many patients the disease is self-limited and resolves within 2 to 5 years.² However, a chronic form of the disease can lead to significant morbidity and some mortality.^{3,4} Glucocorticoids are usually effective for treating the disease; however, because long-term treatment may be required, steroid-sparing agents are often used.⁵

EPIDEMIOLOGY

Sarcoidosis is a worldwide disease, but it is more common in some parts of the world and within certain ethnic groups. Figure 66-1 summarizes the reported rates of sarcoidosis around the world.⁶ In the United States the disease appears to be more common in the southeastern part of the country.

Sarcoidosis is rare before adulthood.⁷ Pediatric sarcoidosis is usually diagnosed in patients older than 10 years, with a peak in the 13- to 15-year-old age group.⁸ When it does present in childhood, there is a different clinical phenotype with mostly eye (uveitis), skin, and joint involvement, although lung involvement is commonly identified when lung imaging studies are performed.⁹ The clinical appearance of juvenile-onset sarcoidosis resembles that of the adult type of the disease.^{10,11} As in adults, the most common finding in childhood sarcoidosis is a chest radiograph with abnormal findings (>90% at onset, with stage I in two thirds of the subjects).¹² Although previously felt to be a disease mostly of young adults, it has been increasingly diagnosed in older patients. In the United States, half of the patients are older than age 40.¹³ There appear to be two peaks of age of onset, 20 to 29 years and 60 to 65 years.^{7,13,14}

Sarcoidosis is believed to be more common in women compared to men at a ratio of less than 2 : 1.^{7,15}

ETIOLOGY

Although sarcoidosis was first described as a distinct clinical entity more than 140 years ago, its cause remains unknown. It is rational to expect that the immunopathogenesis of sarcoidosis is similar to that of other granulomatous diseases. That is, some antigen is encountered and phagocytized by an antigen-presenting cell. The antigen-presenting cell then processes the antigen and presents it, via a *human leukocyte antigen* (HLA) class II molecule, to a restrictive set of T-cell receptors on a T lymphocyte, usually of the CD4⁺ class.^{16,17} This interaction results in a polarization of the T lymphocytes to a type 1 T-helper phenotype, which is followed by monocyte recruitment, T-cell proliferation, and differentiation leading to the development of the sarcoidosis granuloma. In this process a myriad of cytokines and chemokines is released, but the relative importance of most of them is unclear.

POTENTIAL ANTIGENS

Because many infections induce a granulomatous response, infectious pathogens have been implicated as potential causes of sarcoidosis. However, because sarcoidosis responds to immunosuppressive therapy, it is unlikely that sarcoidosis represents an invasive infection; it is nonetheless possible that a host response to an infectious antigen, even if the infecting organism is dead, may induce a granulomatous response. For example, propionibacteria, including *Propionibacterium acnes*, the common acne bacterium, have also been implicated as a cause of sarcoidosis. Propionibacterial DNA has been detected within granulomatous lymph nodes

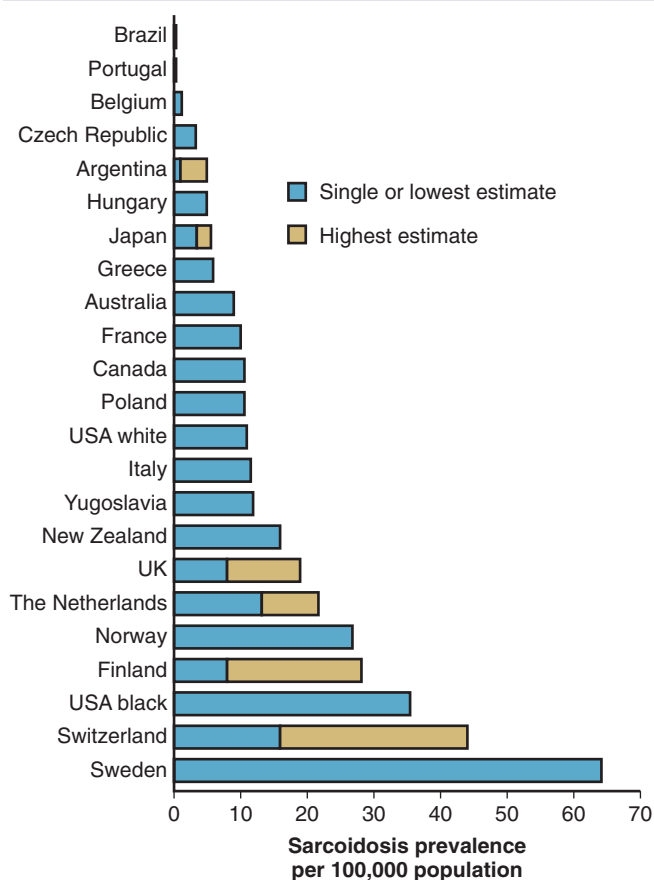


Figure 66-1 Prevalence of sarcoidosis around the world. (Adapted from Denning DW, Pleuvry A, Cole DC: Global burden of chronic pulmonary aspergillosis complicating sarcoidosis. *Eur Respir J* 41:621–626, 2013. doi: 10.1183/09031936.00226911, published ahead of print June 27, 2012. Reproduced with permission of the European Respiratory Society.)

of Japanese sarcoidosis patients.¹⁸ These findings have not been corroborated, however, in subsequent studies outside of Japan.¹⁹

Mycobacteria have been implicated as a potential cause of sarcoidosis. More than two dozen studies have assessed the presence of mycobacterial DNA and RNA in sarcoidosis tissues.²⁰ A meta-analysis has suggested that 26% of sarcoidosis tissues have evidence of mycobacterial DNA that is 9- to 19-fold greater than in nonsarcoidosis control tissues.²¹ However, quantitative polymerase chain reaction comparing lung tissue from sarcoidosis patients, controls, and those with tuberculosis in an area in which tuberculosis is endemic (China) found that the copies of mycobacteria DNA identified in the tissue from sarcoidosis patients were at levels similar to those of control tissues and 1000-fold less than in the tissues of patients infected with *Mycobacterium tuberculosis*.²² It is therefore not clear that mycobacterial DNA is consistently higher in the tissues of patients with sarcoidosis.

The protein mycobacterial catalase-peroxidase has been identified in human sarcoidosis tissue and has been shown to induce an immunoglobulin G antibody response in 12 of 25 sarcoidosis patients compared to purified protein derivative–negative controls.²³ Subsequent studies have demonstrated a T-lymphocyte response to mycobacterial catalase-peroxidase both in the peripheral blood and bronchoalveolar lavage (BAL) of sarcoidosis patients.^{20,24,25}

Environmental and occupational exposures may also be associated with sarcoidosis.^{26,27} Combustible wood product exposure may be associated with sarcoidosis, because the incidence and prevalence of sarcoidosis in firefighters far exceeds that of emergency medical technicians who travel to the same fires.²⁸ In addition, a relationship between wood stove/fireplace exposure and the development of sarcoidosis has been documented.²⁹ An increased incidence of a sarcoidosis-like granulomatous lung process was found in firefighters and first responders involved in the World Trade Center disaster who were exposed to large amounts of debris during a prolonged period.^{30–32} It is not clear, however, whether patients exposed to World Trade Center debris exhibit the same clinical features as patients with non–World Trade Center–related sarcoidosis.

An increased incidence of sarcoidosis has been found in individuals exposed to metals, in particular, titanium,³³ metalworking, metal machining,³³ and photocopier toner (that contains silicates, iron, and copper).³⁴ Analysis of lung biopsy specimens from pulmonary sarcoidosis patients has revealed various metals, including silicates, aluminum, and titanium.³⁵ Sarcoidosis has also been associated with several additional occupations and exposures, including hairdressers,³⁶ health care workers,³⁷ agricultural employment,²⁷ insecticide use at work,²⁷ work environments with mold or mildew,²⁷ industrial organic dust exposure, educators, and workers of suppliers of building materials, hardware, and gardening materials.²⁶ Many of these exposures may, in and of themselves, cause granulomas. Many of the sarcoidosis cases associated with environmental exposure to respirable material are of isolated pulmonary sarcoidosis.³⁸ It is not clear whether these are truly cases of sarcoidosis or of “sarcoid-like” conditions (e.g., hypersensitivity pneumonitis).

GENETIC ASPECTS

There is compelling evidence that sarcoidosis is the result of environmental triggers acting upon an immunogenetically susceptible host.³⁹ The importance of genetics in the development of sarcoidosis is further supported by evidence of familial clustering of the disease.^{40–42}

Because HLA class II molecules and T-cell receptors appear integral to the immunopathogenesis of sarcoidosis,¹⁷ various polymorphisms of these molecules have been examined for their association with sarcoidosis. Indeed, some HLA polymorphisms have been found to be associated with sarcoidosis.⁴³ Most of these associations appear in specific ethnic groups and have not been universal.⁴⁴ In addition, some HLA polymorphisms appear to protect against sarcoidosis,⁴⁴ whereas others are associated with certain clinical phenotypes.^{45–48} The presence of *HLA-DRB1*03* in a Swedish sarcoidosis cohort was strongly associated with a Löfgren syndrome phenotype and also with disease resolution.^{49,50} Thus the presence or absence of *HLA-DRB1*03* could provide clinical prognostic information in the near future.

Although not studied as extensively as HLA molecules, specific arrangements of T-cell receptors have also been associated with sarcoidosis. A restricted use of T-cell receptor α and β chain variable gene segments on T cells in the lungs of sarcoidosis patients has been identified.⁵¹

Non-HLA class II genes have also been shown to be associated with sarcoidosis. HLA class I polymorphisms have been associated with sarcoidosis susceptibility.⁵¹ In a study of German families the *butyrophilin-like 2* (*BTNL2*) immunoregulatory gene explained 23% of the sarcoidosis risk in that population.⁵² Other genome-wide approaches have implicated regions associated with sarcoidosis in chromosome 5 in an African American population⁵³ and mutations in the annexin 1 gene in a German population.⁵⁴ Gene-wide assays have been used to identify other potential associations.⁵⁵ Bioinformatic analyses of global gene expression (“pathway analysis”) identified a dominant network regulated by signal transducer and activator of transcription-1 as the most significantly associated with sarcoidosis in a study of lung and lymph nodes⁵⁶ and identified genes associated with type 1 T-helper cells, type 17 T-helper cells, signal transducer and activator of transcription-3, and interleukin-21 in sarcoidosis skin tissue.⁵⁷

SARCOIDOSIS AS THE RESULT OF IMMUNE SYSTEM EXHAUSTION

Chen and colleagues⁵⁸ demonstrated intense expression and wide distribution of serum amyloid A within the sarcoidosis granuloma that surpassed that found in all other granulomatous diseases examined. Serum amyloid A appeared to have originated from macrophages and giant cells within the sarcoid granuloma. These authors postulated that serum amyloid A could bind to matrix proteins and thereby consolidate a poorly soluble protein aggregate to form a nidus for granuloma formation. Serum amyloid A may disrupt the clearance of an antigen within the granuloma that allows for its persistence. Therefore sarcoidosis may relate not only to certain exposures or antigens but also to failure of effective antigen clearance. The granulomatous inflammation in sarcoidosis may result from a prolonged immunogenic response to a persistent antigen resulting in “immune system exhaustion.”⁵⁹

Evidence for a potential role of immune system exhaustion from chronic stimulation as an integral mechanism in the formation of the sarcoid granuloma is beginning to emerge. Invariant natural killer T cells have been found to be depleted in sarcoidosis, and this is postulated to be the result of functional exhaustion.⁵⁹ *T regulatory* (Treg) cells have been found to be increased in the BAL of several granulomatous diseases,^{60,61} including sarcoidosis.^{61,62} Increased Treg cells in the BAL of sarcoidosis is associated with more active disease.^{61,62} Treg cells may induce anergy and mollify the immune response. However, recent data suggest that there is an anergic response in CD4 T cells in sarcoidosis that is not reversed by Treg cell depletion.⁶³ This suggests that CD4 T-cell exhaustion may be a primary event in sarcoidosis.

DIAGNOSTIC APPROACH

Histologic evidence of granulomatous inflammation *alone* is inadequate for the diagnosis of sarcoidosis because alternative causes of granulomatous inflammation need to be excluded. Additionally, with rare exceptions (see later), clinical findings without histologic confirmation of granuloma-

tous inflammation are inadequate to secure the diagnosis of sarcoidosis.

Figure 66-2 outlines the approach to the diagnosis of sarcoidosis. This process usually involves a review of clinical information, histologic examination of tissue for the presence of granulomatous inflammation, and exclusion of known causes of granulomatous inflammation.⁶⁴

CLINICAL DATA COLLECTION

One can never be certain of the diagnosis of sarcoidosis. Similar to other diseases, sarcoidosis may be considered as the probable diagnosis if clinical data exceed a certain “threshold” so that the diagnosis is plausible. Table 66-1 outlines clinical findings that are often used to gauge the likelihood of the diagnosis of sarcoidosis. For most patients the clinical information suggests the diagnosis, but a tissue biopsy is usually indicated to enhance the probability of sarcoidosis.

Patients with sarcoidosis may present with no symptoms. This is more common in white than black patients.⁶⁵ Therefore sarcoidosis should be considered in asymptomatic patients with hilar adenopathy, mediastinal adenopathy, and/or diffuse parenchymal opacities on lung imaging.⁶⁵⁻⁶⁷ An inquiry should be made about a family history of sarcoidosis because the prevalence rate of sarcoidosis is much higher in first-degree relatives of sarcoidosis patients than in the general population.⁴¹ Sarcoidosis is more common in nonsmokers than in smokers in most studies.^{27,68,69}

In addition, patients should be questioned concerning potential exposures that may cause diseases that may mimic sarcoidosis. Specifically, a history of active tuberculosis, latent tuberculosis infection, and tuberculosis exposure should be obtained. The possibility of beryllium exposure should be explored because chronic beryllium disease can mimic sarcoidosis radiographically⁷⁰ and histologically.^{71,72} Chronic beryllium disease has been misdiagnosed as sarcoidosis in up to 40% of cases.⁷³ Because most patients are unaware of potential exposures to beryllium, it is important to ask about work industries where exposure to beryllium is plausible, including aerospace, nuclear weapons, electronics, jewelry, sporting goods, ceramics, and dental.⁷⁴ Furthermore, minimal beryllium exposure may lead to significant disease.^{75,76} Hypersensitivity pneumonitis, which may mimic sarcoidosis, is a granulomatous pulmonary disease resulting from exposure to numerous agents (see Chapter 64).

EVIDENCE OF EXTRAPULMONARY INVOLVEMENT

At presentation, 95% of sarcoidosis patients have clinical evidence of pulmonary involvement, and more than 40% have evidence of involvement in the skin, liver, peripheral lymph node, or eye.¹³ Therefore evaluation for involvement of these organs should be performed in any patient being evaluated for possible sarcoidosis.

RADIOGRAPHIC FINDINGS

Bilateral hilar adenopathy on chest radiograph suggests the diagnosis of sarcoidosis, especially if the patient has no

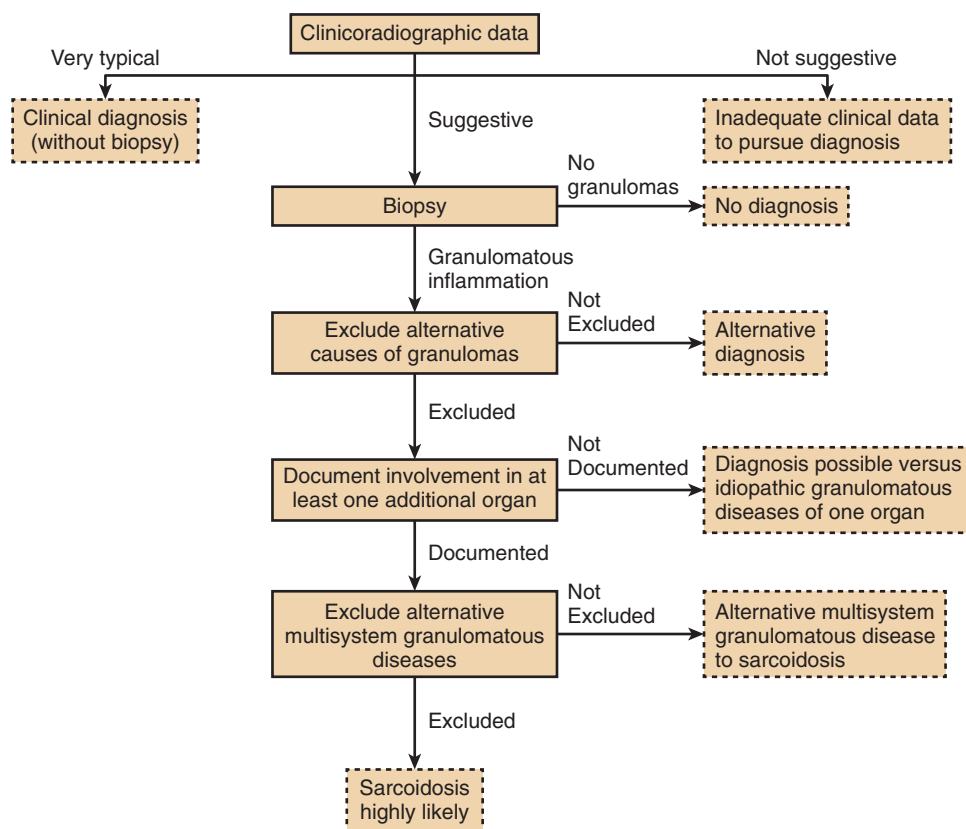


Figure 66-2 Diagnostic algorithm for sarcoidosis. The figure outlines the diagnostic approach for sarcoidosis with consideration of clinical information and tissue biopsy demonstration of granulomatous inflammation as well as exclusion of known causes of granulomatous inflammation (see text for details). (Adapted from Judson MA: The diagnosis of sarcoidosis. *Clin Chest Med* 29:415–427, 2008.)

Table 66-1 Clinical and Chest Imaging Data Supporting or Weakening the Likelihood of Sarcoidosis

	Supports	Weakens
Demographics	<ul style="list-style-type: none"> U.S. African American Northern European 	<ul style="list-style-type: none"> Age < 18 years
Medical history	<ul style="list-style-type: none"> Nonsmoking No symptoms (in patients with BHA on chest radiograph) Positive family history of sarcoidosis Symptoms involving ≥ 2 organs commonly involved with sarcoidosis (e.g., lung and eyes) 	<ul style="list-style-type: none"> Exposure to tuberculosis Exposure to organic bioaerosol Exposure to beryllium Intravenous drug abuse
Laboratory data	<ul style="list-style-type: none"> Elevated serum angiotensin-converting enzyme level, especially if > 2× ULN Elevated serum calcium level Elevated serum alkaline phosphatase level Leukopenia 	
Radiographic findings	<ul style="list-style-type: none"> Chest radiograph: bilateral hilar adenopathy (especially if without symptoms) High-resolution computed tomography: disease along the bronchovascular bundle 	

2× ULN, two times the upper limit of normal; BHA, bilateral hilar adenopathy.

Adapted from Judson MA: The diagnosis of sarcoidosis. *Clin Chest Med* 29:415–427, 2008.

fever, night sweats, or weight loss.^{66,67} The chest radiograph often demonstrates concomitant enlargement of the right paratracheal lymph nodes⁷⁷ (Fig. 66-3). Scadding⁷⁸ defined four patterns of the chest radiograph findings: stage 1, with adenopathy alone (see Fig. 66-3); stage 2, adenopathy and parenchymal opacities (Fig. 66-4); stage 3, opacities alone (Fig. 66-5); and stage 4, fibrosis (Fig. 66-6).

Findings on chest *high-resolution computed tomography* (HRCT) may be more specific for the diagnosis of sarcoidosis than those found on chest radiography (see Figs. 66-3 to

66-6). Typical HRCT findings that suggest sarcoidosis include parenchymal nodules and opacities that represent conglomerations of these nodules that have a perilymphatic distribution along the bronchovascular bundles as well as in subpleural locations.⁷⁹⁻⁸¹

SERUM MARKERS FOR DISEASE

Angiotensin-converting enzyme (ACE) is produced in the epithelioid cell of the sarcoid granuloma, and *serum ACE*

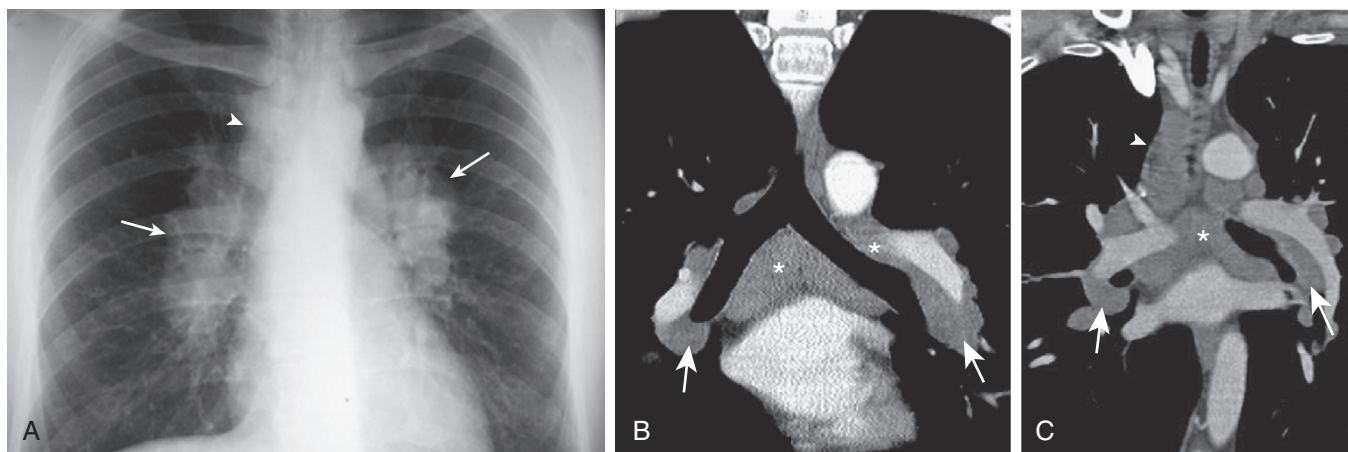


Figure 66-3 Sarcoidosis: Scadding stage 1. **A**, Frontal chest radiograph shows symmetric, bilateral peribronchial (arrows) and right paratracheal lymphadenopathy (arrowhead), typical of sarcoidosis. **B** and **C**, Contrast-enhanced chest CT confirms the presence of symmetric, bilateral peribronchial (arrows) and right paratracheal (arrowhead) lymphadenopathy, as well as enlargement of other mediastinal lymph nodes (*). (Courtesy Michael Gotway, MD.)

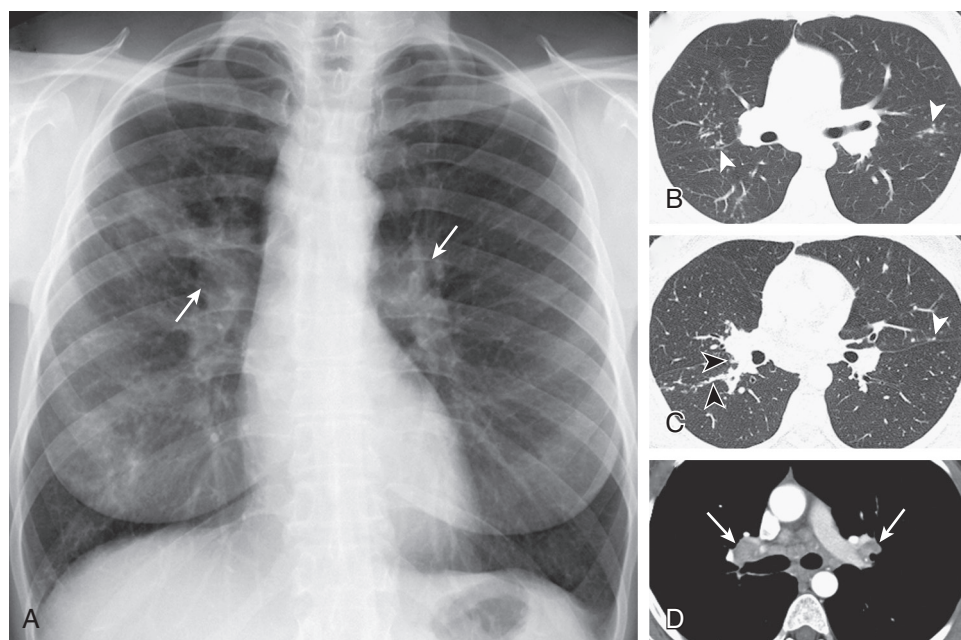


Figure 66-4 Sarcoidosis: Scadding stage 2. **A**, Frontal chest radiograph shows symmetric, bilateral peribronchial lymph node enlargement (arrows) as well as small, well-defined nodules best visualized in the right suprahilar region. The oblong opacity in this area represents a conglomeration of granulomatous inflammation. **B-D**, Axial enhanced chest CT displayed in lung (**B** and **C**) and soft tissue (**D**) shows small, circumscribed nodules distributed along the fissural surfaces (white arrowheads, **B** and **C**) and soft tissue (black arrowheads, **C**), the latter resulting in a “beaded” appearance of the pulmonary vessels. Chest CT also confirms the presence of peribronchial lymph node enlargement (arrows, **D**). (Courtesy Michael Gotway, MD.)

(SACE) levels may reflect the total body burden of sarcoidosis granulomas.⁸² Although SACE has been suggested as a diagnostic test for sarcoidosis,⁸³ elevated SACE levels alone are inadequately sensitive or specific to diagnose or exclude the disease. In a review of 14 studies encompassing 4195 patients concerning the diagnostic accuracy of SACE for sarcoidosis, the sensitivity was 77% (range, 41% to 100%) and the specificity was 93% (range, 83% to 99%).⁸⁴ The likelihood of sarcoidosis increases with higher SACE levels,^{84,85} and SACE levels greater than two times the upper limit of normal are rarely seen in other diseases and not seen in cancer or lymphoma.^{83,86} Polymorphisms of the *ACE* gene also influence the SACE level and likely alter the

diagnostic accuracy of SACE measurements in individual patients.⁸⁷ In addition, none of these polymorphisms have been shown to be associated with increased incidence or worsening of the disease.⁸⁸ Furthermore, the differences of these polymorphisms between the white and African American populations suggest that the role of the polymorphism of the *ACE* gene is population dependent, and this explains the reported racial difference in the relationship between SACE levels and the polymorphism.

Other serum markers have been studied in sarcoidosis. These include serum chitotriosidase, which has been shown to be elevated in a small cohort of Italian sarcoidosis patients. Higher serum levels may be associated with a

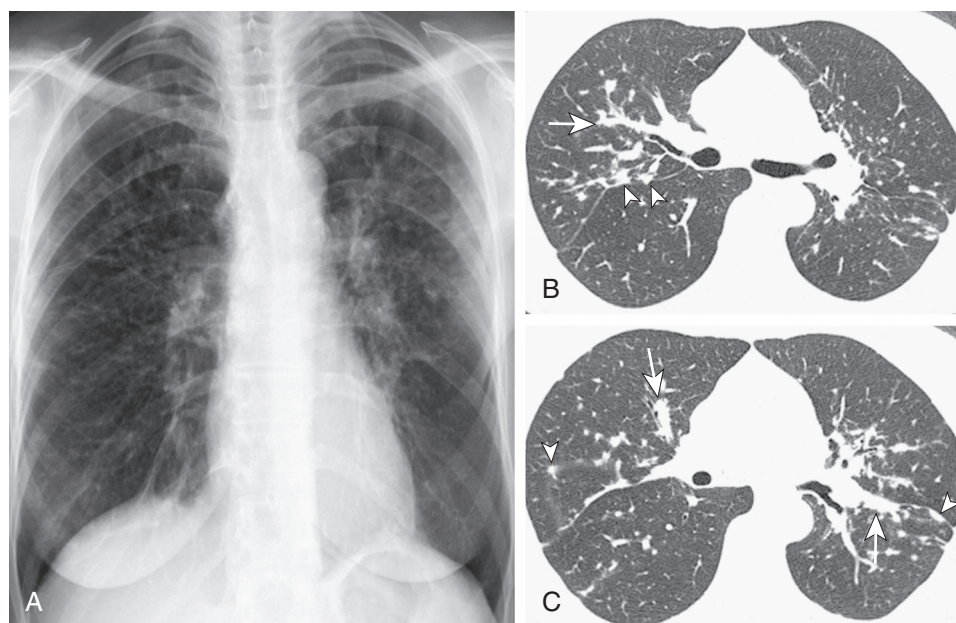


Figure 66-5 Sarcoidosis: Scadding stage 3. **A**, Frontal chest radiograph shows upper lobe–predominant nodular opacities with little evidence of architectural distortion to suggest associated parenchymal fibrosis. No clear evidence of peribronchial or mediastinal lymph node enlargement is present. Mild prominence of the left hilum is due to parenchymal opacity projected over this region, as shown at chest CT. **B** and **C**, Axial chest CT displayed in lung windows shows small, circumscribed nodules distributed along the fissural surfaces (*arrowheads*), as well as along the more central peribronchovascular interstitium (*arrows*), the latter resulting in a “beaded” appearance of the pulmonary vessels. Additional chest CT images also confirmed the lack of significant peribronchial and mediastinal lymph node enlargement. (Courtesy Michael Gotway, MD.)

worse prognosis.^{89,90} The soluble interleukin-2 receptor is a marker of T-cell activation and found to be elevated in sarcoidosis patients.^{90,91} In small studies it was an effective measure of disease activity.^{79,91} The value of these biomarkers regarding diagnosis and prognosis needs to be verified by larger multinational trials.

TISSUE EXAMINATION

With the exception of the rare instances in which the clinical findings are highly specific for sarcoidosis, the diagnosis requires a tissue biopsy (see Fig. 66-2). Our approach to the selection of a biopsy site is summarized in Figure 66-7. It is in the patient's best interest that the biopsy be minimally invasive and associated with the least morbidity. For these reasons, superficial biopsy sites are preferred compared to visceral organs.⁹² Even in patients suspected to have sarcoidosis on the basis of obvious thoracic or abdominal disease, a thorough skin, conjunctival, lacrimal gland, and peripheral lymph node examination should be performed. The patient should be questioned about the presence of scars or tattoos (see Fig. 66-14D), because sarcoidosis skin nodules have a predilection to form in these areas.

When there is no clinical evidence that a superficial site is involved with sarcoidosis, a biopsy is usually attempted in an organ in which sarcoidosis involvement is suspected. This is very often the lung, because the lung is involved in more than 90% of sarcoidosis patients early in the course of the disease.^{13,93} Bronchoscopy is the most commonly used procedure to obtain tissue from the lung. More invasive techniques such as mediastinoscopy are reserved for cases in which bronchoscopy was not diagnostic. Video-assisted thoracoscopic biopsy is rarely needed to confirm the diagnosis of sarcoidosis.

Bronchoscopy

The bronchoscope allows for several different samples, including the *transbronchial biopsy* (TBB), endobronchial biopsy, and *transbronchial needle aspiration* (TBNA). The yield of TBB for the diagnosis of pulmonary sarcoidosis ranges from 60% to 97% depending on the number of biopsy specimens taken and the presence of parenchymal disease on chest imaging studies.⁹⁴⁻⁹⁶ Endobronchial biopsy results may be positive in up to 60% of patients with pulmonary sarcoidosis.^{97,98} Biopsy results are more frequently positive in individuals with abnormal-appearing airways but may provide the diagnosis even from normal-appearing airways.⁹⁷ Furthermore, endobronchial biopsy can be performed with TBB and increases the yield for sarcoidosis above that using TBB alone.

TBNA has been extensively evaluated as a diagnostic approach for pulmonary sarcoidosis over the last decade. The diagnostic yield is in the range of 80%.⁹⁹ The use of endobronchial ultrasonography has been shown to be superior to blind TBNA in two randomized trials.^{100,101} The yield for TBNA is much higher for patients with adenopathy on chest radiograph (stage 1 or 2), whereas the yield for TBB is higher for those with a stage 3 pattern on the chest radiograph.^{101,102} The use of on-site cytopathologic examination allows for rapid review of the TBNA specimen, and, if the TBNA is diagnostic, the bronchoscopist may not need to proceed to TBB.¹⁰³

Bronchoalveolar Lavage

Examination of inflammatory cells from BAL fluid is sometimes used as a complementary test for the diagnosis of pulmonary sarcoidosis.¹⁰⁴ The diagnostic accuracy of the percentage of lymphocytes and the ratio of CD4/CD8

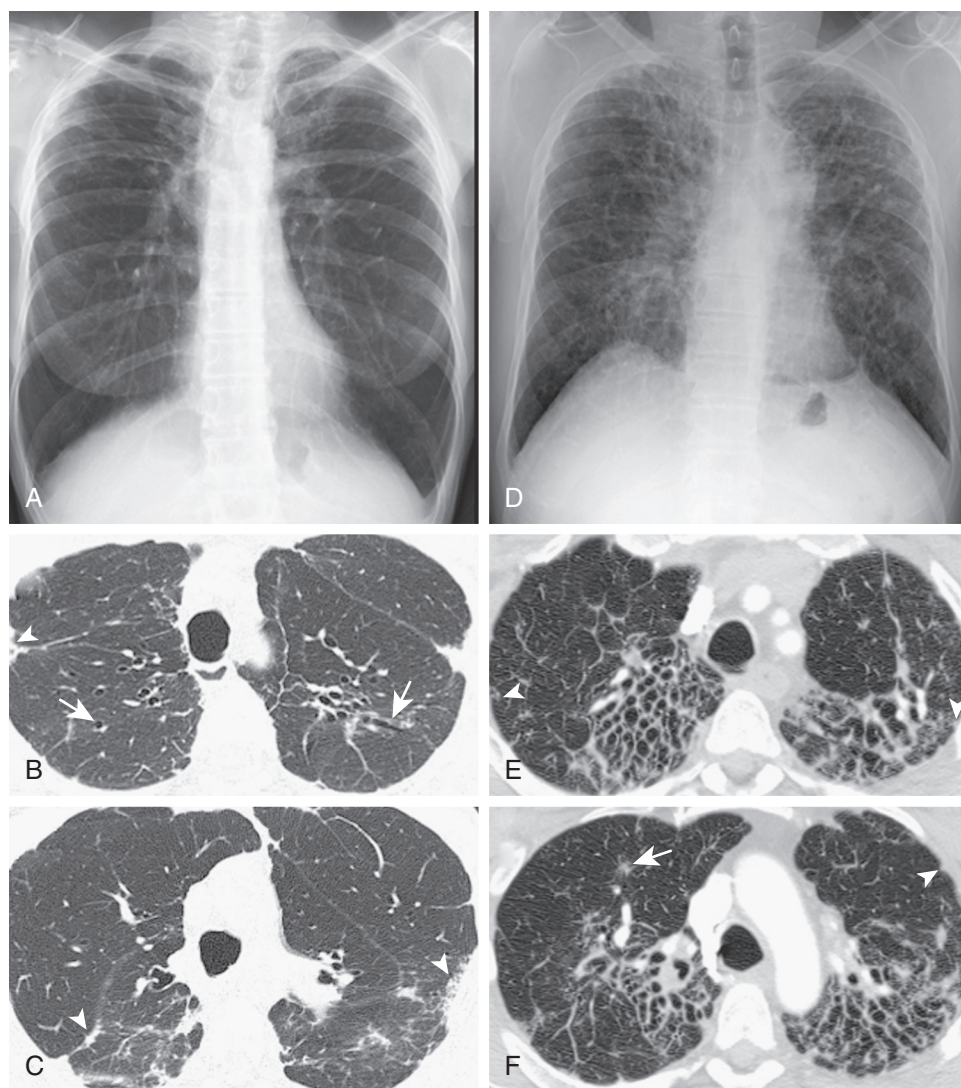


Figure 66-6 Sarcoidosis: Scadding stage 4 (findings in two patients). **A**, Frontal chest radiograph shows upper lobe linear and reticular opacities associated with architectural distortion consistent with a fibrosing process; note bilateral superior hilar retraction. There is little pleural abnormality, typical of granulomatous inflammation due to sarcoidosis as opposed to granulomatous infections. **B** and **C**, Axial chest CT displayed in lung windows shows patchy, upper lobe linear opacities associated with architectural distortion and traction bronchiectasis (*arrows*). Subpleural and perifissural nodular opacities (*arrowheads*) are present. **D**, Frontal chest radiograph in a patient with advanced lung parenchymal fibrosis related to sarcoidosis shows extensive upper lobe linear and reticular opacities associated with architectural distortion, again without significant pleural abnormality. Nodular interstitial thickening is also evident. **E** and **F**, Axial chest CT displayed in lung windows shows extensive biapical traction bronchiectasis with peribronchovascular interstitial thickening (*arrow*, **F**) and perifissural nodularity (*arrowheads*). (Courtesy Michael Gotway, MD.)

lymphocyte subpopulations in BAL has been assessed. In general, BAL lymphocytosis (>15% lymphocytes) has a 90% sensitivity for the diagnosis of sarcoidosis,¹⁰⁴⁻¹⁰⁶ although the specificity is lower. Other conditions leading to a BAL lymphocytosis must be excluded, including infections such as tuberculosis and fungal infections, lymphoma, and hypersensitivity pneumonitis.^{106,107} A BAL lymphocytosis of more than 60% and presence of mast cells is more common in hypersensitivity pneumonitis than in sarcoidosis.¹⁰⁵ The BAL CD4/CD8 ratio is increased more than 3.5 times in 50% to 60% of pulmonary sarcoidosis patients. However, the specificity of the BAL CD4/CD8 ratio criterion has approached 95% in some¹⁰⁶⁻¹⁰⁸ but not all¹⁰⁹ studies. Some have advocated that the BAL CD4/CD8 criterion is diagnostic of sarcoidosis when there are concomitant chest imaging findings compatible with sarcoidosis¹⁰⁴; however, these criteria have not been formally tested. Like other

studies, BAL provides supportive evidence for the diagnosis of sarcoidosis. In addition, BAL samples can be tested along with bronchial washings for evidence of fungal or mycobacterial infection.¹¹⁰

Extrapulmonary Tissue Biopsy

Granulomas can be detected histologically in any organ that is involved with sarcoidosis.⁹² The biopsy of neural tissue and the heart are particularly problematic because of the potential morbidity associated with these procedures. Because patients with neurosarcoidosis will have extraneural sarcoidosis nearly 90% of the time,¹¹¹ most patients have extraneural disease from which a biopsy specimen can be obtained. Although endomyocardial biopsy is a fairly specific test for cardiac sarcoidosis in the proper clinical setting, its sensitivity is very low.¹¹² For this reason, endomyocardial biopsy is rarely performed for the diagnosis of sarcoidosis.

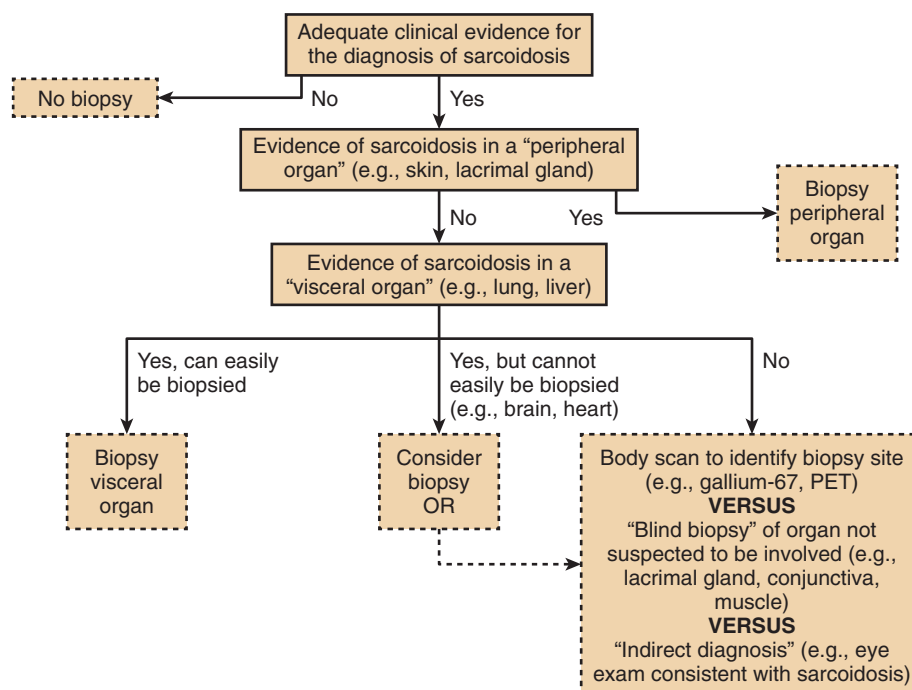


Figure 66-7 Diagnostic approach to selecting a biopsy site for pathologic confirmation of granulomatous inflammation consistent with sarcoidosis. This approach emphasizes (1) selection of a relatively noninvasive biopsy site when possible; (2) biopsy of a site suspected to be clinically involved unless the biopsy would be highly invasive; (3) consideration of alternate approaches when no obvious organ involvement is demonstrated or the only organs with potential involvement would require very invasive biopsies.

Table 66-2 Clinical Presentations That May Be Assumed to Be Sarcoidosis without Tissue Confirmation Provided Additional Data Does Not Suggest an Alternative Diagnosis

- Lupus pernio
- Löfgren syndrome⁴⁹
 - Bilateral hilar adenopathy on chest radiograph
 - Erythema nodosum skin lesions
 - Periarticular inflammation or arthritis of the ankles with or without erythema nodosum
- Heerfordt syndrome¹¹³ (parotitis, uveitis, facial palsy and fever)
 - Uveitis
 - Parotitis
 - Fever (often)
- Bilateral hilar adenopathy on chest radiograph without symptoms
- Positive panda sign (parotid and lacrimal gland uptake) and lambda sign (bilateral hilar and right paratracheal lymph node uptake) on gallium-67 scan¹¹⁶

Adapted from Judson MA: The diagnosis of sarcoidosis. *Clin Chest Med* 29:415–427, 2008.



Figure 66-8 Erythema nodosum. Tender red nodules or lumps, usually seen on both shins, are caused by inflammation of the fat cells under the skin.

Often, imaging studies are used as surrogate tests for the diagnosis of neurosarcoidosis and cardiac sarcoidosis. Such studies should be interpreted cautiously because their specificity depends upon associated clinical evidence for sarcoidosis, which should almost always include previous biopsy confirmation of granulomatous inflammation of unknown cause in another organ (see later). Also, the specificity of imaging studies for neurosarcoidosis and cardiac sarcoidosis is unknown.

Clinical Phenotypes Suggestive of Sarcoidosis

In some cases the clinical presentation of sarcoidosis is so specific that the diagnosis can be made without performing a confirmatory tissue biopsy. These presentations are listed in Table 66-2.⁶⁴ In patients with these presentations, one

may consider performing a bronchoscopy to rule out other possible causes, including infection. In patients in whom a bronchoscopy is not diagnostic, the presence of factors in Table 66-2 may help bolster confidence for the diagnosis of sarcoidosis. Lupus pernio (see Fig. 66-14A) is an indurated, raised skin lesion that is characteristically found on the ears, cheeks, and nose (see later); it is considered highly specific for sarcoidosis. Löfgren syndrome initially included only patients with erythema nodosum of lower legs or forearms (Fig. 66-8). However, periarticular inflammation or arthritis of the ankles with or without erythema nodosum has been added to the expanded definition of Löfgren syndrome.⁴⁹ Uveoparotid fever, also known as Heerfordt syndrome is unusual but specific for the diagnosis of sarcoidosis.¹¹³

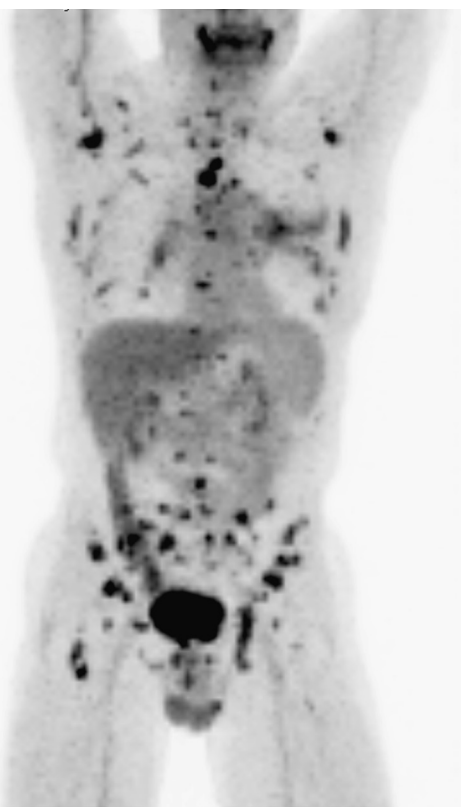


Figure 66-9 Positron emission tomography (PET) scan demonstrating both lung parenchymal and mediastinal nodal uptake. Also demonstrated are several extrapulmonary lymph nodes and other areas with increased activity.

Other Diagnostic Approaches

On some occasions the diagnosis of sarcoidosis is suspected on clinical grounds although no specific organ can be found to biopsy. This would include patients presenting with disease of the eye, brain, or heart that is consistent with sarcoidosis but does not provide a safe site for biopsy. There is no established approach for this situation. Total body imaging such as ^{18}F -fluorodeoxyglucose positron emission tomography (PET)^{114,115} or gallium-67 scanning¹¹⁶ has been proposed in such cases to identify an organ for biopsy (Fig. 66-9), although no rigorous analysis of this approach has been undertaken. Another suggested approach in this situation is to biopsy organs that are commonly affected, even in the absence of symptoms or other clinical findings suggestive of sarcoidosis involvement of that organ. Conjunctival biopsies have been performed in this situation, and the yield has ranged from 27% to 55% in patients without ocular symptoms.¹¹⁷⁻¹¹⁹ In vivo confocal microscopy of the conjunctiva can detect multinucleated giant cells without the need for a biopsy, a noninvasive approach that has been advocated to confirm granulomatous inflammation in sarcoidosis patients.¹²⁰ Liver biopsy demonstrates granulomas in 24% to 78% of sarcoidosis patients, even when they have no symptoms attributable to the liver and have normal serum liver function test results.^{121,122} However, hepatic granulomas are not specific for sarcoidosis so that clinical evidence of extrahepatic sarcoidosis must be present for the diagnosis to be secure.¹²³ Andonopoulos and colleagues¹²⁴ found that gastrocnemius muscle biopsy revealed granulo-

mas in 22 consecutive patients without muscle symptoms who had bilateral hilar adenopathy on chest radiograph. However, most of these patients had strong clinical evidence of sarcoidosis; furthermore, this procedure is fairly invasive.

Another test to consider when sarcoidosis is suspected on clinical grounds although no specific organ is identified to biopsy is the Kveim-Siltzbach test. This test is only available in selected centers and may be indicated when chest imaging studies are normal (e.g., in cases of uveitis of unknown origin, hypercalciuria, hepatic granulomatous disease, suspected neurosarcoidosis, or recurrent erythema nodosum).¹ This test involves the intradermal inoculation of a suspension of splenic tissue from spleen that was involved with sarcoidosis.¹²⁵ If a skin nodule develops at the inoculation site in 4 to 6 weeks, it is biopsied. A biopsy demonstrating noncaseating granulomatous inflammation is highly specific for the diagnosis of sarcoidosis.¹²⁶ The Kveim-Siltzbach test has a false-negative rate of 20% to 40%. The sensitivity and specificity of the test vary depending on the spleen that is used to prepare the Kveim-Siltzbach reagent and the duration of disease. Transmission of infective agents is possible if the antigen is poorly prepared or controlled.¹

PATHOLOGIC FINDINGS

Granulomatous inflammation is necessary to establish a diagnosis of sarcoidosis in most cases; however, the finding of granulomas is not sufficient for the diagnosis of sarcoidosis (Fig. 66-10).^{1,64} Meticulous histologic examination with appropriate staining of all biopsy specimens should be performed to search for known causes of granulomatous inflammation, such as mycobacteria, fungi, parasites, and foreign material (e.g., talc).

Although there are no specific histologic features that are diagnostic of sarcoid granulomas, there are certain features that suggest this diagnosis. The sarcoid granuloma usually consists of a compact (organized) collection of mononuclear phagocytes (macrophages and epithelioid cells).¹²⁷ Typically there is no necrosis within the sarcoid granuloma; however, on occasion, there is a small to moderate amount of necrosis. Usually, giant cells fuse within the sarcoid granuloma to form multinucleated giant cells. These granulomas are typically surrounded by lymphocytes in the periphery. A variety of inclusions may be present within the sarcoid granuloma, including asteroid bodies, Schaumann bodies, birefringent crystals, and Hamazaki-Wesenberg bodies; however, these inclusions are neither specific nor diagnostic for sarcoidosis (Fig. 66-11).¹²⁷ In particular, birefringent crystals within the sarcoid granuloma may lead to a misdiagnosis of talc granulomatosis.⁷² Care must be taken to ensure that the crystal morphologic features and size are compatible with intravenously injected talc to ensure the diagnosis of talc granulomatosis.

Sarcoidosis has been defined as a multisystem granulomatous disorder of unknown cause.¹ The fact that the disease is “multisystem” implies that there should be evidence of granulomatous inflammation in at least two organs for the diagnosis of sarcoidosis to be secure. However, the biopsy of a second organ is not routinely performed. Of note, there are some conditions that appear to be distinct

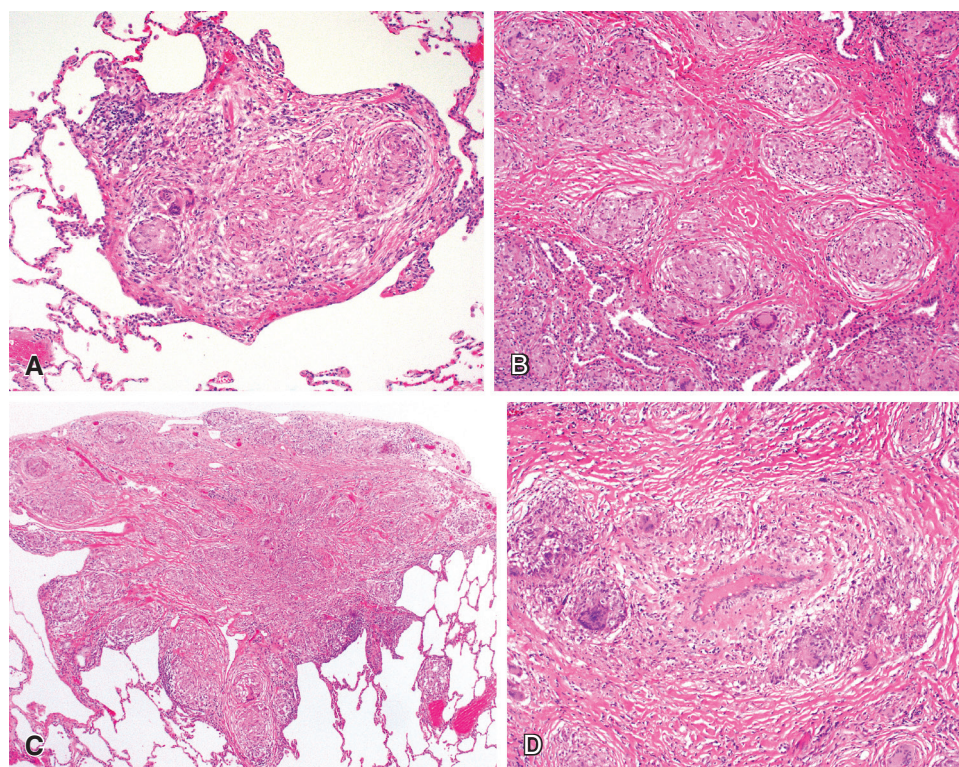


Figure 66-10 Sarcoidosis. **A**, The characteristic pathologic lesion of pulmonary sarcoidosis is the non-necrotizing (immune) granuloma. **B**, Granuloma within sclerotic fibrosis. **C**, Granulomas distributed along lymphatic routes in the pleura, within the intralobular septa, and along the bronchovascular bundles. This image is diagnostic of sarcoidosis, but berylliosis should always be included as a diagnostic possibility. **D**, Perivascular granulomas embedded in sclerosis are commonly seen. Despite this potential for vasocentric growth, pulmonary hypertension is an uncommon complication of sarcoidosis. (Adapted from Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach*, ed 2, Philadelphia, 2011, Elsevier, Figs. 7-75 and 7-78.)

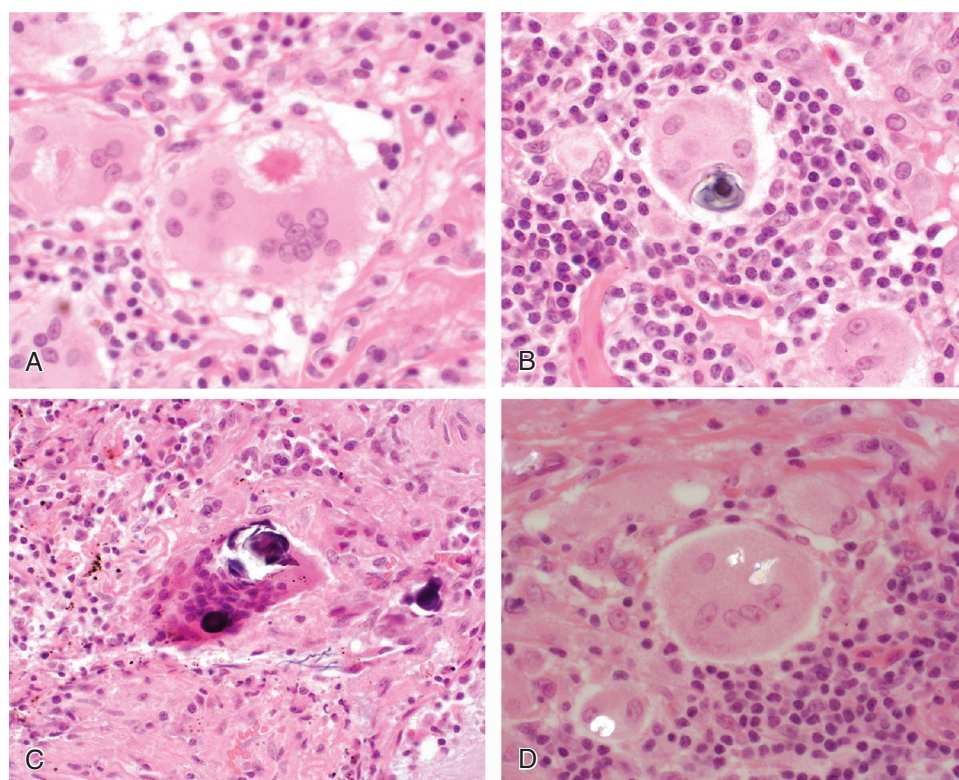


Figure 66-11 Sarcoidosis. Multinucleate giant cells characteristically are present, often accompanied by a variety of distinctive (but not specific) cytoplasmic inclusions. **A**, Asteroid body. **B**, Schaumann body. **C**, Schaumann (conchoidal) bodies. **D**, Schaumann body in polarized light. (Adapted from Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach*, ed 2, Philadelphia, 2011, Elsevier, Fig. 7-79.)

from sarcoidosis in which granulomatous disease seems to be limited to a single organ (e.g., idiopathic granulomatous hepatitis,^{128,129} and idiopathic panuveitis¹³⁰).

OTHER IDIOPATHIC MULTIORGAN GRANULOMATOUS DISEASES

There are other multiorgan granulomatous syndromes that should be considered in the differential diagnosis of sarcoidosis. These include infections, such as tuberculosis.

Blau syndrome consists of granulomatous iritis, arthritis, and skin rash.^{131,132} The disease is a genetic disorder¹³³ and has an autosomal dominant pattern of inheritance with variable penetrance.^{131,132} In contrast to sarcoidosis, most cases present before 12 years of age. Blau syndrome is considered a separate entity from childhood sarcoidosis on the basis of a lack of visceral (e.g., pulmonary) involvement, mode of inheritance, and absence of Kveim-Siltzbach skin test reactivity.^{131,134} Also, the Blau gene has not been found in sarcoidosis patients.¹³⁵

The *granulomatous lesions of unknown significance* (GLUS) syndrome consists of granulomatous inflammation in the liver, spleen, bone marrow, and lymph nodes, a benign course, and a tendency for recurrence. The GLUS syndrome is thought to be distinct from sarcoidosis because (1) elevated SACE levels are not found, (2) hypercalcemia is not found, (3) the Kveim-Siltzbach test results are negative, and (4) immunotyping of the T lymphocytes in the GLUS syndrome granulomas is different from that in sarcoidosis granulomas.^{136,137}

Necrotizing sarcoid granulomatosis is a systemic granulomatous vasculitis.^{138,139} Because of vascular involvement, necrosis is a prominent feature, unlike in most cases of sarcoidosis. Although the lung is commonly involved, extrapulmonary involvement is also common.¹⁴⁰ It is debated whether necrotizing sarcoid granulomatosis is a distinct clinical entity or a form of systemic sarcoidosis.¹⁴⁰⁻¹⁴²

EVALUATION OF PULMONARY DISEASE

The evaluation of pulmonary disease in sarcoidosis patients relies on three major determinants: pulmonary function, chest imaging, and symptoms. There have been several instruments developed in all three of these areas. The pulmonologist uses pulmonary function testing and chest imaging as a method to measure lung involvement. However, the patients' major concerns are how they feel and how their lung disease affects their quality of life. Dyspnea and cough are the major reasons for treatment of pulmonary sarcoidosis.

PULMONARY FUNCTION

A significant proportion of sarcoidosis patients will have normal spirometry findings and lung volumes at the time of diagnosis.^{13,93} Over time, some of these patients will develop a restrictive pattern, with reduction of lung volumes.^{3,143}

However, a significant proportion of sarcoidosis patients have obstructive lung disease.¹⁴⁴ The *diffusing capacity for carbon monoxide* (DL_{CO}) is a more sensitive measure of early interstitial lung disease¹⁴⁵ and often predicts a reduction in exercise capacity.^{145,146} A disproportionately reduced DL_{CO} (compared to lung volumes) may also be an indicator of sarcoidosis-associated pulmonary hypertension.^{147,148}

Clinical pulmonary exercise testing may be useful in assessing dyspnea in sarcoidosis patients.¹⁴⁵ Patients with normal lung function test results may still have abnormalities in exercise testing.¹⁴⁹ However, exercise testing is not well standardized and relatively cumbersome to perform. The *6-minute walk distance* (6MWD) test has been widely used to assess exercise capacity.¹⁵⁰ In sarcoidosis a reduction in 6MWD has been found to correlate with reduced *forced vital capacity* (FVC), fatigue, and quality-of-life measures.¹⁴⁶ A reduced 6MWD and oxygen desaturation have been found in patients with sarcoidosis-associated pulmonary hypertension.^{151,152} However, several factors besides cardiopulmonary function influence the 6MWD test, including muscle strength, joint disease, and neurologic symptoms.^{150,153}

LUNG IMAGING

Chest Radiograph

The findings on the routine chest radiograph have been classified into several stages, originally proposed by Scadding (see earlier).⁷⁸ The Scadding chest radiographic stages correlate with prognosis. Those with stage 1 (see Fig. 66-3) have a more than 80% chance of resolution of hilar adenopathy 2 to 5 years after presentation, whereas those with stage 3 have less than a 30% chance of resolving to a normal chest radiograph. Fibrotic changes (stage 4) do not resolve. The limitation of chest radiographic staging is that it does not characterize extrapulmonary manifestations of sarcoidosis. In addition, there is significant variability in the classification of radiographic stages even among experienced radiologists.¹⁵⁴

An alternative to monitoring the chest radiograph by Scadding staging is to compare chest radiographs serially over time. This is what is commonly done in clinical practice. The change in the chest radiograph has been shown to have good reproducibility and correlates with changes in pulmonary function.^{155,156} In one study the kappa coefficient for comparison reading was much better than for the Scadding scoring system.¹⁵⁴

Another method for scoring the chest radiograph developed by Muers and coworkers¹⁵⁷ is similar to a scoring system used for pneumoconiosis. It was shown that the portion of this score that assessed reticulation was able to detect changes after corticosteroid therapy¹⁵⁸ and after treatment with infliximab.¹⁵⁹ The scoring system was reproducible with a good kappa coefficient.¹⁵⁴ However, the scoring is tedious and does not appear practical for routine clinical practice.

Chest Computed Tomography Scanning

As noted earlier, chest *computed tomography* (CT) imaging, including HRCT, has proved useful in the diagnosis of sarcoidosis (see Figs. 66-3 to 66-6).¹⁶⁰ A scoring system for CT

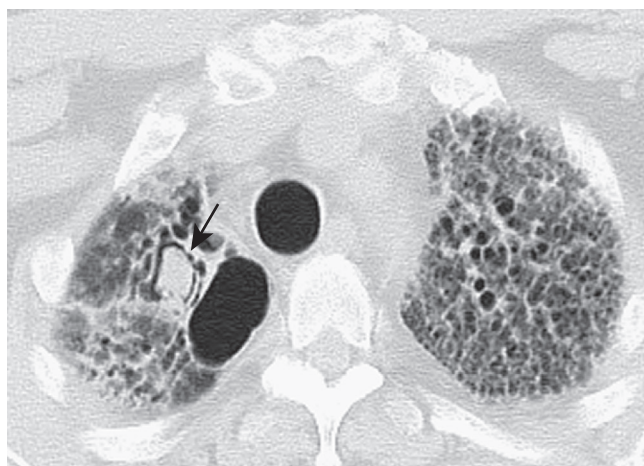


Figure 66-12 Aspergilloma in sarcoid. High-resolution CT demonstrating upper lobe fibrosis with presence of an aspergilloma in the right upper lobe (arrow).

scans in sarcoidosis has been described⁷⁹ and has been suggested to assess severity of disease.¹⁶¹ However, it is unclear what features of the CT scan are important for the management of the disease. Some HRCT scan features do correlate with physiologic impairment in sarcoidosis; for example, honeycombing is associated with a reduced DL_{CO} and an increased alveolar-arterial PO_2 difference,^{162,163} and peribronchial thickening may lead to airway obstruction and air trapping.^{164,165} HRCT is also useful in defining the extent of bronchiectasis and the presence of complications, such as aspergilloma (Fig. 66-12).¹⁶⁶

Radionuclide Scanning

Radionuclide scanning has been used as an aid in the diagnosis of sarcoidosis and the assessment of organ involvement.¹¹⁵ Early studies focused on the gallium scan as a method of identifying inflammation.^{167,168} The presence of extrapulmonary disease was often useful in identifying potential areas to biopsy. In addition, uptake in the parotid and lacrimal glands ("panda sign") and/or right paratracheal and bilateral hilar areas ("lambda sign") were highly supportive of the diagnosis of sarcoidosis.¹¹⁶ Octreotide scanning has also been used as a marker of lung inflammation in sarcoidosis.¹⁶⁹

The detection of radioactive glucose uptake by PET scan has been widely applied to malignant conditions, including lung cancer and lymphoma. PET scan activity can also be quite enhanced in sarcoidosis, demonstrating diffuse activity in the lungs, mediastinal lymph nodes, and other parts of the body (see Fig. 66-9).^{114,115} The PET scan has proved useful in identifying potential areas for biopsy in those suspected of sarcoidosis.¹¹⁴ It has also been found to demonstrate ongoing activity in patients who are receiving immunosuppressive therapy and may suggest that the disease will relapse when therapy is withdrawn.^{170,171} Patients with increased PET uptake in the pulmonary parenchyma have been shown to have active disease by virtue of changes in their pulmonary function.¹⁷² In this study, sarcoidosis patients with increased parenchymal PET uptake who were treated showed a significant improvement in their FVC and DL_{CO} , and those who were not treated showed a significant fall in DL_{CO} ; those without increased

PET parenchymal activity had no change in FVC and DL_{CO} without therapy, indicating inactive disease.¹⁷² In a study comparing PET to gallium scans, the PET scan was found to be more sensitive and reproducible.¹⁷³ Because the PET scan is more widely available and can be performed in 1 day rather than the 2 days necessary for gallium scanning, the PET scan is preferred, provided that there are no issues with reimbursement. Imaging of the heart for detection of cardiac sarcoidosis can be performed with either PET or magnetic resonance imaging (MRI) scanning¹⁷⁴; cardiac MRI appears to be more sensitive and specific.¹⁷⁵ However, cardiac MRI requires special expertise to interpret and is usually contraindicated once a defibrillator or pacemaker has been placed.

HEALTH-RELATED QUALITY OF LIFE

Sarcoidosis has been associated with impaired *health-related quality of life* (HRQOL),¹⁷⁶⁻¹⁷⁸ and treatment of sarcoidosis has been associated with changes in HRQOL.¹⁷⁸ However, the results of studies have been discordant. Corticosteroids have demonstrated improvement,¹⁷⁹ no change,¹⁸⁰ or worsening¹⁷⁷ in the short form 36, a general quality-of-life instrument. The Saint George Respiratory Questionnaire, which was originally developed as a measure of HRQOL in chronic obstructive pulmonary disease,¹⁸¹ has also been used for several interstitial lung diseases, including idiopathic pulmonary fibrosis and sarcoidosis.^{182,183} Improvements in the Saint George Respiratory Questionnaire results have been reported for patients with sarcoidosis-associated pulmonary hypertension who have been treated with pulmonary hypertension therapy.^{184,185} In addition, two sarcoidosis-specific quality-of-life instruments have been developed: the Sarcoidosis Health Questionnaire¹⁸⁶ and the King's Sarcoidosis Questionnaire.¹⁷⁶

Fatigue is a common complaint in sarcoidosis patients.^{187,188} It has been reported by more than half of sarcoidosis patients in both Europe and the United States.¹⁸⁹ Although fatigue is reported by patients with both pulmonary and extrapulmonary sarcoidosis, it is more common in the latter.¹⁹⁰ Fatigue may persist long after other evidence of disease has regressed.¹⁸⁸ There are several fatigue scales that are not specific for a particular disease^{187,190,191}; however, the Fatigue Assessment Scale is a sarcoidosis-specific fatigue questionnaire.¹⁹² The questionnaire appears to have a good correlation with general fatigue questionnaires in some^{191,193} but not in all¹⁹⁴ studies. The Fatigue Assessment Scale has been found to improve in sarcoidosis patients treated with infliximab.¹⁹⁵

Depression is a common underdiagnosed problem in sarcoidosis patients.^{196,197} The prevalence of depression ranged from 25% to 60% of the subjects and may contribute to a poorer quality of life.^{196,198} Consequently, a referral for a psychiatric or psychological evaluation and counseling should be considered for many sarcoidosis patients.

Sarcoidosis-associated pulmonary hypertension (SAPH) can develop from a variety of mechanisms, including left ventricular diastolic dysfunction, pulmonary arterial vasculitis, pulmonary veno-occlusive disease, pulmonary fibrosis, and hypoxia.¹⁹⁹ The overall incidence of pulmonary hypertension in sarcoidosis appears to be 5% to 15%.^{147,152,200,201} In patients with moderate to severe symptoms, the

Table 66-3 Organ Involvement in Sarcoidosis

	Charleston (%)	Cincinnati (%)
Female	66	71
African American	66	43
SPECIFIC ORGAN INVOLVEMENT		
Lungs	89	88
Eye	23	33
Skin	32	33
Liver	20	13
Neurologic	9	14
Cardiac	4	5

Organ involvement in more than 2700 patients seen at two large clinics.

Standardized criteria for diagnosis were the same in each clinic, and only definite or probable involvement was recorded.

Charleston data from Judson MA, Boan AD, Lackland DT: The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis* 29:119–127, 2012. Cincinnati data are unpublished.

prevalence of pulmonary hypertension has been reported to be 50% or greater.^{148,202–204} Precapillary pulmonary hypertension is the most common cause of SAPH, but left ventricular diastolic dysfunction is present in a significant proportion of cases.^{201,204} The survival of patients with precapillary SAPH is significantly worse than for those with diastolic dysfunction.²⁰⁴

EXTRAPULMONARY SARCOIDOSIS

Sarcoidosis is a multiorgan disease. Pulmonary involvement has been reported in over 90% of cases in most large series.^{13,93,205} However, several other organs are commonly affected with the disease. Table 66-3 lists organ involvement as detected by two large clinics in the United States with a total of more than 2700 patients.²⁰⁵ Both of these groups used the same standardized criteria for organ involvement and listed only those organs with definite or probable disease.²⁰⁶ Patients may have undetected organ involvement. For example, liver biopsies performed in patients without symptomatic liver disease may still demonstrate granulomatous inflammation in up to half of the cases.^{121,207}

EYES

The eyes are involved in about a third of patient in the United States and Europe. Eye disease is more common in African Americans and in women.^{13,205} In Japan up to 80% of sarcoidosis patients have eye disease.²⁰⁸ Table 66-4 lists some of the more common ocular manifestations of sarcoidosis.²⁰⁹ It is recommended that all sarcoidosis patients undergo an ocular examination by a specialist at the time of initial evaluation.¹ Uveitis is the most common manifestation of ocular sarcoidosis and at times can be clinically silent. Anterior uveitis typically presents acutely, with pain, photophobia, lacrimation, and redness, but may have a more chronic course. Posterior uveitis is typically gradual in onset and is more likely to affect vision. Conjunctival nodules are another common, although usually asymptomatic, presentation. In fact, the diagnosis of sarcoidosis can sometimes be made with conjunctival biopsy, even in patients without any ocular symptoms. Patients with ocular

Table 66-4 Types of Eye Involvement in Sarcoidosis

Uveitis: anterior, intermediate, posterior
Optic neuropathy
Adnexal and orbital disease
Lacrimal glands: enlargement, sicca syndrome, dacryocystitis
Orbital mass
Scleral involvement
Glaucoma
Cataracts

Adapted from Baughman RP, Lower EE, Kaufman AH: Ocular sarcoidosis. *Semin Respir Crit Care Med* 31:452–462, 2010.



Figure 66-13 Cutaneous sarcoidosis. Arm of patient with chronic cutaneous sarcoidosis demonstrating maculopapular lesions.

sarcoidosis may develop complications from eye involvement, such as sicca syndrome, glaucoma, and cataracts. Cataracts and glaucoma can also be a complication of either local or systemic corticosteroid treatment. Although less common, lacrimal gland enlargement is a characteristic finding. Vigilance for ocular involvement is extremely important, because approximately 10% of patients with sarcoid-associated uveitis develop blindness in at least one eye.

SKIN

Cutaneous involvement is also encountered in about a third of sarcoidosis patients.²¹⁰ Skin manifestations include maculopapular lesions, papules, hyperpigmentation, and hypopigmentation (Fig. 66-13).²¹¹ Lupus pernio is an indurated facial lesion that is specific for sarcoidosis (Fig. 66-14).²¹² It is more common in patients of African descent. It is usually chronic²¹³ and can be resistant to usual therapy.²¹⁴ Erythema nodosum, as noted earlier, is often, but not always, associated with a good prognosis.⁴⁹ In particular, patients of African descent with erythema nodosum will often have chronic disease.²¹⁵ Other cutaneous involvement may appear as patches, plaques, violaceous areas, localized alopecia, ichthyotic areas, subcutaneous nodules, ulcers, and pustules.

NERVOUS SYSTEM

Neurosarcoidosis develops in less than 10% of patients. Neurologic disease can involve the spinal cord or just the cranial nerves.^{216–218} The most sensitive method of detecting



Figure 66-14 Cutaneous sarcoidosis lesions. **A**, Lupus pernio. Violaceous nodular plaques on the nose, cheek and lip. **B**, Lupus pernio. Violaceous swelling of distal digits. **C**, Papular sarcoidosis. Multiple papules in a periorbital distribution. **D**, Cutaneous sarcoidosis presenting as pink indurated areas within and around a tattoo. (Adapted from Marchell RM, Judson MA: Chronic cutaneous lesions of sarcoidosis. *Clin Dermatol* 25:295–302, 2007.)

disease is MRI with gadolinium because neurologic lesions will often enhance.^{218,219} Spinal fluid analysis can be helpful, because it may demonstrate a lymphocytosis and elevated protein level.²¹⁹ An elevated level of ACE in spinal fluid has been reported to be specific for neurosarcoidosis, but a sensitivity as low as 50% has been reported.²²⁰ In patients with neurosarcoidosis, especially those who present as isolated neurosarcoidosis,²²¹ one has to consider multiple sclerosis.²²² Patients with sarcoidosis can develop optic neuritis, with or without uveitis.²²³ It is important to distinguish these patients from multiple sclerosis, because neurosarcoidosis patients will often improve with treatment, including with anti-tumor necrosis factor (TNF) treatments such as infliximab.^{223,224}

HEART

Sarcoidosis can directly cause an infiltrative cardiomyopathy with two major manifestations: arrhythmias and reduced ejection fraction. The detection of cardiac sarcoidosis can be difficult.²²⁵ The presence of cardiac symptoms, including palpitations and syncope, is a sensitive but not specific screening for sarcoidosis. Echocardiography and 24- to 48-hour cardiac monitoring are useful supplemental tests for screening.¹⁷⁴ Table 66-5 summarizes the prevalence, sensitivity, and specificity for cardiac sarcoidosis of screening tests by themselves or in combination.¹⁷⁴ Currently imaging with MRI and/or PET scanning is felt to be the most specific for diagnosing cardiac sarcoidosis.²²⁵ The arrhythmias, especially ventricular arrhythmias, remain a potential cause of death in cardiac sarcoidosis.²²⁶ However, implantable defibrillators have markedly reduced the mortality from this manifestation.^{227,228} Therefore patients with potential cardiac sarcoidosis should be screened for ven-

Table 66-5 Screening for Cardiac Sarcoidosis: Diagnostic and Prognostic Value of Outpatient Testing

Abnormalities on Baseline Testing	Prevalence	Sensitivity	Specificity
History of cardiac symptoms	12 (19%)	46%	95%
ECG	3 (5%)	8%	97%
Holter monitor	13 (21%)	50%	97%
Echocardiogram	8 (13%)	25%	95%
Any screening variable	29 (47%)	100%	87%
Two or more variables	7 (11%)	25%	97%
Three or more variables	1 (2%)	4%	100%
All variables abnormal	0 (0%)		

A study of 62 consecutive patients with sarcoidosis evaluated for cardiac sarcoidosis with symptoms (palpitations, presyncope, or syncope) and a series of tests. Based on cardiac MRI and PET scanning studies, 24 patients were diagnosed with cardiac sarcoid; the sensitivity and specificity of various screening variables individually or in combination are shown. ECG, electrocardiogram; MRI, magnetic resonance imaging.

Adapted from Mehta D, Lubitz SA, Frankel Z, et al: Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest* 133:1426–1435, 2008.

tricular arrhythmias and evaluated by a specialist for the need for defibrillator implantation.^{228a}

EARS, NOSE, AND THROAT

The salivary glands can be involved in sarcoidosis, resulting in severe xerostomia, otitis media, vestibular symptoms, or hearing loss. Nasal and paranasal sinus involvement presents with nonspecific symptoms, including nasal congestion,

postnasal drip and sinus pressure, headaches, and infections. Lupus pernio, nasal deformities such as saddle nose deformity, and nasal mucosal abnormalities such as friability with crusting, bleeding, and submucosal nodules may accompany these symptoms. Rarely, the submucosal nodules may erode through the hard or soft palate, resulting in oral ulcerations or fistulous tracts. Other rare complications of nasal and sinus disease include epiphora (chronic tearing due to intranasal lacrimal tract outlet obstruction), anosmia (loss of the sense of smell due to direct involvement of the olfactory epithelium or obstruction of the olfactory cleft), and mass lesions with intraorbital or intracranial invasion. Definitive diagnosis relies on biopsy evidence of granulomatous inflammation and exclusion of other infections and inflammatory causes (e.g., fungal or mycobacterial infection, rhinoscleroma, or vasculitis). There are a number of management strategies for sinonasal sarcoidosis, depending on disease severity and location.

PAROTID GLAND

Parotid enlargement is a classic but rare disease feature. Heerfordt syndrome, or uveoparotid fever, is characterized by parotid enlargement with fever, facial palsy, and anterior uveitis.

LIVER AND SPLEEN

Liver involvement is common in sarcoidosis.²²⁹ The usual pattern seen in the serum chemistry results is an elevated alkaline phosphatase level and sometimes elevated transaminase levels.^{121,207} Imaging of the liver with contrast CT scan can be supportive of the diagnosis. Liver biopsy will usually detect granulomatous disease, even in patients with no symptoms or blood chemistry abnormalities.^{121,207,230} Splenic involvement is also rarely symptomatic, but is common, as determined by studies of fine-needle aspiration biopsies. Rarely, splenomegaly can be massive and may cause thrombocytopenia or other cytopenias.

JOINTS

Arthralgias are common in patients with Löfgren syndrome; other forms of sarcoidosis less commonly demonstrate joint involvement. Arthralgias are noted by 25% to 39% of patients, but deforming arthritis is rare. Between 3% and 13% of patients display bony involvement, although the increasing use of MRI may increase future estimates of the frequency of osseous sarcoidosis. Classically, if the bones are involved, plain radiographs or MRI will demonstrate bone cysts in the phalanges, although virtually any bone can be affected.

Symptomatic muscle involvement, characterized by nodules, acute myositis, or chronic myopathy, is rare; however, in systemic sarcoidosis without clinical manifestations of muscle disease, 20% to 75% of cases are found to have granulomas on muscle biopsy.

PERIPHERAL LYMPH NODES

Hilar and mediastinal lymphadenopathy is common (up to 90% of patients). However, peripheral lymphadenopathy is

not as common (5% to 30%). The nodes are typically nontender, mobile, and located in the cervical, axillary, epitrochlear, and inguinal regions.

ENDOCRINE GLANDS

Hypercalcemia or hypercalciuria has been reported in up to 30% of sarcoidosis patients.^{231,232} The most common mechanism is from excessive levels of 1,25-dihydroxyvitamin D due to autonomous 1- α -hydroxylase activity.^{233,234} Levels of 1,25-dihydroxyvitamin D may be elevated despite low levels of 25-hydroxyvitamin D.²³¹ There are other causes of hypercalcemia in sarcoidosis, including hyperparathyroidism.²³¹ Hypercalcemia in sarcoidosis patients can be associated with renal failure, which may reverse with treatment of the hypercalcemia.²³⁵

BLOOD

Hematologic abnormalities are seen in up to 40% of patients (e.g., anemia, leukopenia, lymphopenia, or a combination of these). Bone marrow involvement or splenic enlargement with platelet destruction may rarely cause thrombocytopenia.

TREATMENT OF SARCOIDOSIS

Most patients with sarcoidosis show evidence of disease remission within 3 years of diagnosis with few or no long-term consequences. However, up to one third of patients have persistent disease, which causes significant organ impairment. Few patients die from sarcoidosis (<5%), with death usually the result of cardiac or neurologic involvement or of respiratory failure due to pulmonary fibrosis.

The treatment of sarcoidosis requires consideration of sarcoidosis-related inflammation, the complications of the disease, and the complications of therapy. Table 66-6 lists these aspects of the disease and potential treatments, when they have been reported, with the level of evidence to support their use in sarcoidosis.^{236,237}

ANTI-INFLAMMATORY MEDICATIONS

Because sarcoidosis patients are frequently asymptomatic and many will have spontaneous resolution of their sarcoidosis within 6 months of diagnosis,¹⁵⁸ not all patients require initial therapy.^{158,238,239} The usual decision to treat patients is based on symptoms and, with regard to pulmonary sarcoidosis, when there is a concomitant decline in pulmonary function.²³⁸

Corticosteroids remain the most widely used, well-documented, and most effective treatment for sarcoidosis.^{5,240,241} The reported initial dose of corticosteroids varies widely. McKinzie and colleagues have found that, in some patients, there was a significant improvement in FVC in less than a month with an average daily dose of prednisone of 20 mg.²⁴² Once the patient has had improvement, the dose of drug is usually tapered to minimize toxicity but to maintain the benefit from the initial induction of response. In some cases, patients may relapse when treatment is reduced, requiring an increase in dosage.²⁴³ Patients

Table 66-6 Treatment for Sarcoidosis*

Anti-inflammatory treatment	
Acute disease	
Glucocorticoids	1A
Hydroxychloroquine	2B
Methotrexate	2A
Chronic disease	
Glucocorticoids	1B
Methotrexate	1A
Azathioprine	1B
Leflunomide	1B
Mycophenolate	1C
Infliximab	1A
Adalimumab	1C
Hydroxychloroquine	2B
Refractory disease	
Infliximab	1A
Adalimumab	1C
Fibrotic disease	
When criteria for treatment are met	
Oxygen therapy	1C
Lung transplantation	1B
Pulmonary rehabilitation	1C
Complications of disease	
Pulmonary hypertension	
Bosentan	1A
Ambrisentan	2B
Sildenafil	1B
Tadalafil	2B
Inhaled iloprost	2B
Prostacyclin	2B
Fatigue	
Methylphenidate	1C
Dexmethylphenidate	1A
Armodafinil	1A
Complications of disease/therapy	
Aspergillomas	
Azole therapy	1C
Intracavitary amphotericin	1B
Resection (when tolerated)	1C

*NOTE: The grading scheme classifies recommendations as strong (grade 1) or weak (grade 2), according to the balance among benefits, risks, burdens, and possibly cost, and the degree of confidence in estimates of benefits, risks, and burdens. The system classifies quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to factors that include the study design, the consistency of the results, and the directness of the evidence.²³⁷

may also relapse after the drug is withdrawn, so a slow withdrawal over the course of months is usually recommended.²⁴⁴ Even those patients treated with glucocorticoids for 2 or more years have at least a 50% chance of relapse when drug is withdrawn.^{245,246}

Patients who do not respond to the equivalent of prednisone 40 mg daily are considered refractory to standard treatment and can be considered for alternative therapy. However, such patients are relatively rare.

For patients who are started on therapy, a significant percentage will require long-term treatment beyond 2 years.^{158,238,239,244,247} Corticosteroid-sparing agents and alternative agents are often considered in these patients because significant cumulative toxicities from corticosteroids are common. For many of the nonsteroidal immunosuppressive agents, there are evidence-based recommendations for monitoring patients while being treated for pulmonary disease.²⁴⁸

The antimalarial agents, chloroquine and hydroxychloroquine, have been reported to be effective in treating certain aspects of extrapulmonary disease,^{249,250} such as cutaneous and sinonasal disease.^{249,251} They have also proved useful in treating hypercalcemia²⁵² and may be more effective in treating sarcoidosis-associated fatigue than other anti-inflammatory agents.¹⁸⁹ The major toxicity encountered with antimalarial agents has been ocular. Hydroxychloroquine appears to have a lower rate of ocular toxicity. However, routine screening is still recommended.²⁵³⁻²⁵⁵ For most patients, 400 mg a day of hydroxychloroquine appears to be safe. In the most recent recommendations, the dose needs to be modified only for those of short stature.²⁵⁵

Methotrexate is a commonly used steroid-sparing cytotoxic agent for sarcoidosis.^{240,256} Methotrexate has been shown to be effective in remitting and persistent disease. It has also been shown to be effective in ocular,^{209,257} cutaneous,²⁵⁸⁻²⁶⁰ sinus,^{261,262} and neurologic disease.^{263,264} A major potential toxicity of methotrexate and other cytotoxic drugs is bone marrow suppression. The effect is dose dependent. There are evidence-based and expert opinion recommendations for monitoring patients while receiving methotrexate therapy.^{248,265}

Azathioprine is another cytotoxic agent commonly used in chronic sarcoidosis. Limited data suggest that it is as effective as methotrexate but results in greater toxicity.²⁶⁶ It has been shown to be effective in pulmonary²⁶⁷ and extrapulmonary disease.^{261,268,269} A recent report of increased morbidity and mortality for patients with idiopathic pulmonary fibrosis receiving azathioprine suggests that the full dosage of the drug should be used with caution in patients with advanced fibrotic disease.²⁷⁰

Leflunomide is an antimetabolite similar in action to methotrexate originally developed for treating rheumatoid arthritis.²⁷¹ It has been reported to be effective in treating sarcoidosis either alone or in combination with methotrexate.^{272,273} Compared to methotrexate, leflunomide has less gastrointestinal toxicity, although it has a similar rate of liver function test result abnormalities.²⁷¹ Leflunomide can produce pulmonary toxicity, but at a lower rate than with methotrexate.^{274,275} Leflunomide can also cause a peripheral neuropathy, which usually resolves with discontinuation of the drug.^{276,277}

Mycophenolate analogues have been increasingly employed to treat inflammatory lung diseases.^{278,279} They have been reported to be as effective as a steroid-sparing agent for those with persistent disease, especially neurosarcoidosis.^{280,281} Whereas mycophenolate treatment has less bone marrow toxicity and hepatotoxicity, it is still associated with significant gastrointestinal and infectious complications.²⁸²

Infliximab is a chimeric monoclonal antibody directed against TNF. It was first reported to be effective in treating refractory sarcoidosis in 2001.^{283,284} The drug has been widely used for various forms of refractory disease, including pulmonary, skin, eye, and neurologic disease.²⁸⁵⁻²⁸⁹ Two double-blind placebo-controlled trials have shown a benefit of infliximab when used in addition to maintenance therapy.^{159,180} The drug has also proved to be effective for some patients with extrapulmonary disease.²⁹⁰ In a large retrospective study of patients with lupus pernio, infliximab

was superior to all other treatment options.²¹⁴ It has also proved to be useful in treating refractory neurosarcoidosis.^{281,291} Infliximab is not a cure for sarcoidosis. Adverse effects of the drug may be considerable, and a high rate of relapse has been reported when the drug is withdrawn within a year of treatment.²⁹²

The toxicity of infliximab includes an allergic reaction to the chimeric antibody, which can manifest as an acute reaction, including anaphylaxis, vasculitis, or a subacute, lupus-like reaction.²⁹³ In addition, along with the other anti-TNF antibodies, infliximab has also been associated with a high risk for the reactivation of tuberculosis.²⁹⁴ The risk appears to be lower with the TNF receptor antagonist etanercept.^{294,295} Adhering to guidelines for screening and treating latent tuberculosis can significantly reduce this risk for reactivation.²⁹⁶ Testing for latent tuberculosis with skin testing may not be adequate in sarcoidosis, because anergy is a common problem.²⁹⁷ An interferon- γ release assay seems to be more reliable for screening for latent tuberculosis in anergic or immunosuppressed patients.²⁹⁸ The anti-TNF treatments may be contraindicated in patients with advanced congestive heart failure because of an apparent increased mortality rate in such patients treated with infliximab.²⁹⁹ However, infliximab has been used successfully in treating cardiomyopathy due to sarcoidosis.^{56,300,301} Finally, there may be an increased risk for malignancy with the use of anti-TNF agents. In rheumatoid arthritis, a meta-analysis found an increase in nonmelanoma skin cancers only.³⁰² However, another study suggested a potential increased risk for lymphoma, although the relative risk was not significantly different from that for controls.³⁰³ Thus the risk for developing cancer in sarcoidosis patients treated with anti-TNF therapy is unknown, and one should remain cautious regarding this risk when using this class of drugs.

Adalimumab, a totally humanized anti-TNF antibody, has been reported to be effective in treating some sarcoidosis cases.^{289,304-306} Compared to infliximab, it appears to have a lower response rate and takes longer to demonstrate effectiveness.²⁸⁸ This may be due to the relatively lower doses of drug initially used. When used at a higher induction and maintenance dose, for example, adalimumab has been shown to be more effective in treating Crohn disease.³⁰⁷ This higher dose of the anti-TNF antibody may be necessary to achieve clinical response in sarcoidosis, but it remains unclear how often these increased doses need to be employed.³⁰⁸ A potential dose-dependent effect may explain the failure of a recently completed trial of golimumab, another humanized monoclonal anti-TNF antibody.

Etanercept is a TNF receptor antagonist and has been reported to be effective in some cases of refractory sarcoidosis.³⁰⁹ However, the drug was not found to be effective in an open-label trial of pulmonary sarcoidosis³¹⁰ or in a placebo-controlled double-blind randomized controlled trial of ocular sarcoidosis.³¹¹

Interestingly, patients treated with anti-TNF therapy can develop a granulomatous disease that is indistinguishable from sarcoidosis.^{312,313} The mechanism of this reaction is unknown, but possible mechanisms include rebound TNF production or alteration of the function of Treg cells.³¹⁴ As noted earlier, abnormalities of Treg cells have been described in sarcoidosis.^{60,61} Of note, there are several new anti-inflammatory therapies being evaluated in sarcoidosis.⁵

MANAGEMENT OF EXTRAPULMONARY DISEASE

In general the treatment of extrapulmonary disease is similar to the treatment of pulmonary disease. However, there are a few special considerations. For ocular disease, local therapy with topical steroids, periocular steroid injections, and steroid implants may be sufficient to control disease.²⁰⁹ However, use of corticosteroids may cause cataract formation or glaucoma. Therefore the use of a cytotoxic agent, such as methotrexate, is considered desirable early in the management of chronic ocular sarcoidosis.^{257,289} For cutaneous sarcoidosis, patients may often respond to hydroxychloroquine or local steroid therapy.^{251,315} However, lupus pernio responds significantly more often to infliximab than to corticosteroid or cytotoxic therapy.³¹⁶ Neurologic disease often requires more intense treatment with either higher doses of corticosteroids and/or cytotoxic treatments.²⁶³ Anti-TNF treatment may be particularly helpful in the treatment of refractory neurosarcoidosis.^{281,317}

ANTIFIBROTIC THERAPY

Patients with significant pulmonary fibrosis from sarcoidosis have an increased mortality.¹⁶³ To date there is limited understanding of the pathophysiologic mechanisms that underlie fibrosis, a lack of potential therapies for pulmonary fibrosis in general, and no specific therapy reported to be effective for the fibrotic component of sarcoidosis.³¹⁸

SUPPORTIVE CARE

Supportive care is a mainstay of therapy, especially for patients with severe dyspnea, hypoxemia, and pulmonary hypertension (see later).³¹⁹ Supportive therapy, as is common in other fibrotic lung diseases, includes facilitation of mucociliary clearance and treatment of infections associated with bronchiectasis, supplemental oxygen, and pulmonary rehabilitation when appropriate.³²⁰

MANAGEMENT OF COMPLICATIONS OF SARCOIDOSIS

Pulmonary Hypertension

For precapillary *sarcoidosis-associated pulmonary hypertension* (SAPH), several pulmonary hypertension agents have been studied. Table 66-7 lists some of the studies specifically designed to determine the efficacy of treatment. These include the prostanoids, including intravenous prostacyclin^{321,322} and inhaled iloprost.¹⁸⁴ Long-term use of intravenous epoprostenol was associated with prolonged clinical improvement in some cases.³²¹ The endothelin receptor antagonists have also been reported to be safe in treating SAPH.^{185,323,324} A double-blind, placebo-controlled study demonstrated significant improvement of pulmonary hemodynamics for SAPH patients treated with bosentan but not for those treated with placebo.³²⁵ Sildenafil has also been shown to improve hemodynamics in patients with SAPH.³²⁶

For several of the studies cited in Table 66-7, the response to treatment for SAPH was in pulmonary hemodynamics and/or quality of life.^{184,185,326} In part that was because the

Table 66-7 Treatment of Sarcoidosis-Associated Pulmonary Hypertension

Class	Therapy	Significant improvement	Improvement Seen in Some Cases
Prostanoids	Epoprostenol ³²² Epoprostenol ³²¹ Iloprost ¹⁸⁴		Improved hemodynamics Improved hemodynamics Improved hemodynamics and HRQOL
Endothelin receptor antagonists	Bosentan ³²⁵ Ambrisentan ¹⁸⁵	Improved hemodynamics	Improved HRQOL
Phosphodiesterase-5 inhibitors	Sildenafil ³²⁶		Improved hemodynamics
Combination therapy	<ul style="list-style-type: none"> Sildenafil plus bosentan Sildenafil plus inhaled iloprost Sildenafil plus bosentan plus inhaled iloprost Epoprostenol plus bosentan³⁴⁸ 	Improved hemodynamics	Improved 6MWD

HRQOL, health-related quality of life; 6MWD, 6-minute walk distance.

studies examined patients after only a relatively short period, usually 4 months. In one study that evaluated SAPH patients after more prolonged therapy, there was not only improvement in hemodynamics, but also improvement in 6MWD.³²³ However, that improvement in 6MWD was seen only in those with mild to moderate restrictive disease and was unusual in those patients with a FVC of less than 50% of predicted value.

Fatigue

As noted earlier, fatigue is a common manifestation of sarcoidosis.¹⁸⁷ Fatigue can be associated with several factors, including diabetes, depression, and sleep apnea.^{327,328} Sleep apnea is a common problem in sarcoidosis patients, especially in those patients who have been treated with glucocorticoids.³²⁸⁻³³⁰ However, even after treatment of sleep apnea, fatigue may persist.¹⁹³

Fatigue may be severely debilitating but is not life-threatening. As a result, the benefits associated with treatment of fatigue should always be weighed against the risks associated with the side effects. Neurostimulants such as methylphenidate have been reported to be effective in treating sarcoidosis-associated fatigue.³³¹ In a double-blind, placebo-controlled crossover trial of dexamethylphenidate, sarcoidosis-associated fatigue was 30% lower during active treatment than during placebo treatment.¹⁹¹ A limitation of methylphenidate is the short half-life of the drug, often requiring an afternoon dose, which may lead to insomnia. The drug armodafinil is a neurostimulant-like drug that, in a double-blind, placebo-controlled crossover trial, was found to reduce fatigue significantly more than placebo.¹⁹³

There is a relationship between small fiber neuropathy and fatigue.³³² Several agents have been used with varying success in sarcoidosis-associated small fiber neuropathy. Neuropathic agents are often the initial drugs of choice. These agents, however, have limited efficacy. In refractory cases the anti-TNF agents should be considered. Intravenous gamma globulin treatment was reported to be effective in one small retrospective series.³³³ Other treatments are currently being studied.³³⁴

Aspergilloma

Fungal infections, especially aspergilloma, are a serious complication of advanced fibrotic sarcoidosis and are usually associated with immunosuppressive therapy.^{6,163,335-337}

Aspergillomas may lead to fatal hemoptysis. The risks and benefits of medical and surgical therapy vary with the manifestations of disease and the patient's pulmonary status. Therefore the approach to therapy must be individualized. In patients with good pulmonary function, surgical resection can be offered to prevent or treat potentially life-threatening hemoptysis and is usually curative. The medical treatment of aspergillomas includes azole therapy.^{6,338,339} The evidence regarding the efficacy of long-term antifungal therapy for chronic cavitary pulmonary aspergillosis is based upon small case series and open-label noncomparative studies.^{338,340} Limited data suggest that intracavitary amphotericin may be effective on a short-term basis in treating selected cases of aspergillomas in sarcoidosis patients.³⁴¹

Bone Health

Because sarcoidosis patients often have high levels of vitamin 1,25-dihydroxyvitamin D there usually is no reason for supplementation of vitamin D.³⁴² However, bisphosphonates can improve osteopenia or osteoporosis in sarcoidosis patients.³⁴³

Lung Transplantation

Lung transplantation has been successfully performed in sarcoidosis patients.³⁴⁴ Patients may develop granulomas in the transplanted lung,³⁴⁵ but this does not generally alter the clinical outcome of transplant recipients, because post-transplant immunosuppression is often adequate treatment for the sarcoidosis.³⁴⁶ One should focus on treating superimposed infections, because they are common complications of the bronchiectasis seen in fibrotic sarcoidosis and they may be one of the events leading to acute decompensation.³⁴⁷

Key Points

- Sarcoidosis is characterized by an enhanced granulomatous response to an unknown antigen.
- Although many patients with sarcoidosis have resolution of their disease within 2 years, a significant proportion have chronic disease—with roughly a quarter of all patients still requiring systemic therapy more than 2 years after diagnosis.

- Genetic polymorphisms have been shown to be associated with clinical outcome in some cases.
- The diagnosis of sarcoidosis relies on recognition of a clinical pattern consistent with disease, exclusion of other conditions that can cause granulomatous inflammation and, in most cases, a biopsy demonstrating granulomas.
- Identification of extrapulmonary disease is important not only to identify other potential causes of morbidity in sarcoidosis but also to help bolster confidence in the diagnosis.
- Fatigue, chest discomfort, and depression are conditions that lead to poor quality of life for patients with chronic sarcoidosis.
- Systemic treatment of sarcoidosis, usually initially with glucocorticoids, is indicated when the patient has symptoms. Steroid-sparing agents are most useful for patients with chronic disease or those encountering toxicity with glucocorticoids.

Complete reference list available at *ExpertConsult*.

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ALVEOLAR HEMORRHAGE AND RARE INFILTRATIVE DISEASES

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INTRODUCTION

DIFFUSE ALVEOLAR HEMORRHAGE

Definition

Clinical Presentation

Classification Schema

Diagnostic Approach

Specific Causes

RARE INFILTRATIVE DISORDERS OF THE LUNG

Neurofibromatosis

Hermansky-Pudlak Syndrome

Dyskeratosis Congenita

Gaucher Disease

Niemann-Pick Disease

Pulmonary Alveolar Microlithiasis

INTRODUCTION

This chapter discusses *diffuse alveolar hemorrhage* (DAH) and includes other rare infiltrative disorders of the lung. DAH is a serious condition characterized by widespread intra-alveolar hemorrhage that originates from the pulmonary microcirculation (arterioles, capillaries, and venules). DAH can be seen in many different diseases, often as the presenting manifestation.

The second section of the chapter discusses several rare infiltrative disorders of the lung, including neurofibromatosis, Hermansky-Pudlak syndrome, dyskeratosis congenita, Gaucher disease, Niemann-Pick disease, and pulmonary alveolar microlithiasis.

DIFFUSE ALVEOLAR HEMORRHAGE

Unlike the more common forms of pulmonary hemorrhage that result from focal lesions (e.g., necrotizing pneumonia, bronchitis, bronchiectasis, malignancy, pulmonary infarction, arteriovenous malformation), DAH affects the majority of the alveolar capillary surface. DAH is a medical emergency that often results in acute respiratory failure and death. Pulmonologists must be prepared to identify DAH promptly, diagnose the underlying disease that is causing it, and institute appropriate medical therapy.

DEFINITION

DAH is defined on clinical grounds: diffuse pulmonary opacities with varying degrees of respiratory failure, a falling hemoglobin level, and progressively bloody return (or with increasing red blood cell counts) on sequential *bronchoalveolar lavage* (BAL). The pathologic process is characterized by the intra-alveolar accumulation of erythrocytes (Fig. 67-1). There can be evidence of chronicity with the accumulation of intra-alveolar hemosiderin-containing macrophages, erythrophagocytosis, and collections of free interstitial hemosiderin,¹⁻³ findings that help distinguish DAH from acute biopsy-related bleeding. Other histologic features of DAH include hyperplasia of the type II alveolar epithelial lining cells, intra-alveolar organization (organiz-

ing pneumonia), mononuclear cell infiltration of the alveolar interstitium, and small thrombi in the alveolar capillaries and venules.¹⁻⁵

Patients with DAH may demonstrate neutrophilic inflammation of the alveolar interstitium known as pulmonary or alveolar *capillaritis* (Fig. 67-2).⁶ Capillaritis is commonly associated with endothelial edema, injury, and localized fibrinoid necrosis.⁴ Characteristically there is infiltration of the alveolar septa with neutrophils, many of which are undergoing leukocytoclasia and appear fragmented and pyknotic. Fragmentation of these cells leads to accumulation of nuclear dust in the lung parenchyma. Capillaritis is a small vessel vasculitis of the lung and is central to the pathogenesis of many cases of DAH. This small vessel injury and necrosis leads to the loss of integrity of the shared epithelial-endothelial alveolar basement membrane, resulting in extravasation of red blood cells into the alveolar lumina. DAH can also result from all causes of *diffuse alveolar damage* (DAD) (i.e., cytotoxic drug, allogeneic [bone marrow transplantation]), and can also result from bland (noninflammatory) injuries (i.e., mitral stenosis).

CLINICAL PRESENTATION

History and Physical Examination

The clinical presentation of DAH includes hemoptysis, alveolar opacities on chest radiograph, and anemia.⁷ However, there are cases that show only one or two of these features; the absence of classic features does not exclude DAH. In up to 33% of cases, hemoptysis is initially absent. Other symptoms are nonspecific (e.g., dyspnea, cough, chest pain, fever), although in some cases, disease-specific symptoms (e.g., sinusitis, rash, arthritis) may be present. In general, symptoms are usually of short duration, present from days to several weeks, and may be recurrent. The lung examination is nonspecific, with inspiratory crackles common but not universal. There may also be physical findings suggesting a systemic disease.

Radiology and Laboratory Evaluation

Laboratory evaluation usually reveals anemia and leukocytosis. Serum creatinine levels may be elevated. BAL reveals a bloody return that, with each aliquot returned from the same location, becomes progressively more bloody

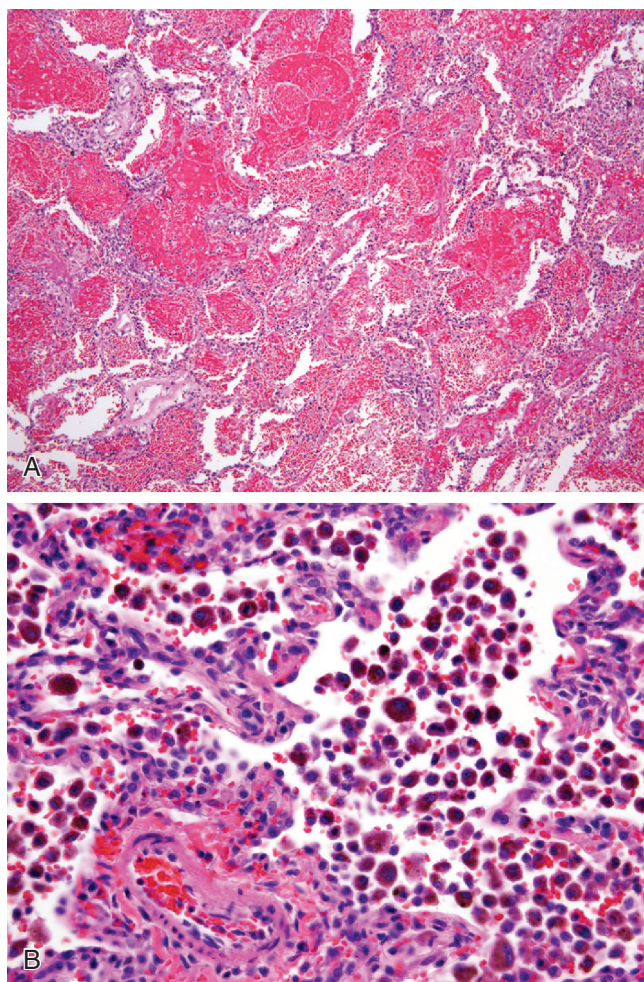


Figure 67-1 Histopathologic findings of diffuse alveolar hemorrhage. **A**, In acute diffuse alveolar hemorrhage, the alveoli show filling and distention by red blood cells admixed with fibrin. **B**, Chronic alveolar hemorrhage shows numerous hemosiderin-filled macrophages within air spaces. The alveolar septa may show mild fibrosis. (Courtesy Dr. Kirk Jones, University of California, San Francisco.)

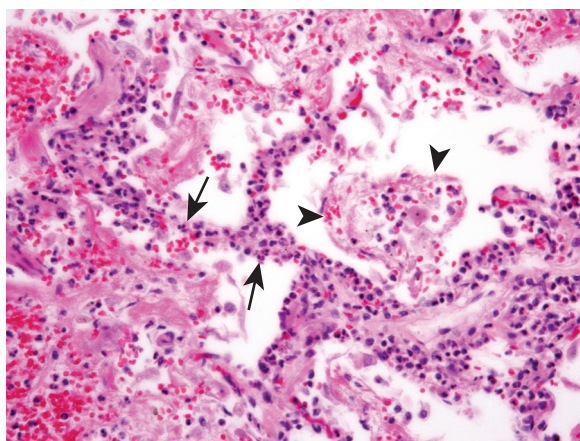


Figure 67-2 Histopathologic findings of diffuse alveolar hemorrhage accompanied by pulmonary capillaritis. Capillaritis is identified by accumulation of neutrophils (see *arrows*) within alveolar septa with accompanying fibrinoid necrosis and adherent alveolar fibrin within air spaces (*arrowheads*). (Courtesy Dr. Kirk Jones, University of California, San Francisco.)

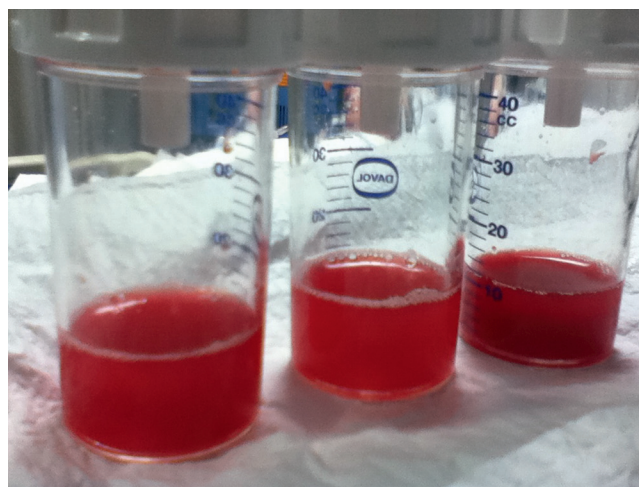


Figure 67-3 Sequential bronchoalveolar lavage (BAL) showing increasing bloody appearance diagnostic of diffuse alveolar hemorrhage. These BAL, sequential in order from left to right, were obtained from the same location of the lung in a patient with granulomatosis with polyangiitis (Wegener granulomatosis). (Courtesy Dr. Sixto Arias, Johns Hopkins University.)

(Fig. 67-3). BAL shows increased sequential red blood cell counts even in patients who do not present with hemoptysis. On examination of the sediment, there is a predominance of red blood cells and hemosiderin-containing macrophages.

The chest radiograph in DAH shows varying degrees of diffuse alveolar opacities (Fig. 67-4; see eFigs. 60-3A, 60-9A, 60-10A, and Fig. 91-4A).⁸ High-resolution computed tomography (HRCT) imaging is more sensitive for radiographic abnormalities and generally shows bilateral ground-glass opacities or patchy consolidation, and occasionally centrilobular nodules. Nonetheless, it is important to recognize that the HRCT appearance of pulmonary hemorrhage is variable and not specific for a particular cause (Fig. 67-5; see eFigs. 60-3B-E, 60-9B-E, 60-10B-E, and Fig. 91-4B-D). With recurrent and chronic disease, reticulation may appear, providing evidence of interstitial fibrosis. Interlobular septal thickening (Kerley B lines) (eFig. 67-1) may occasionally be present in cases of mitral stenosis and pulmonary veno-occlusive disease. There are reports of an obstructive lung disease developing after recurrent episodes of DAH secondary to alveolar capillaritis.

Physiology

If measured, there are restriction and gas exchange abnormalities, particularly in chronic cases. In acute DAH an increase in the *diffusing capacity for carbon monoxide* (DL_{CO}) is often present, attributed to the increased binding of carbon monoxide to intra-alveolar hemoglobin.⁹ This will generally resolve in 48 to 72 hours, as hemoglobin is degraded into hemosiderin.¹⁰ Varying degrees of hypoxemia result from the ventilation-perfusion abnormalities produced by the alveolar hemorrhage, and patients often require ventilatory support.

CLASSIFICATION SCHEMA

There is no consensus classification schema for DAH, although clinical, histopathologic, and etiologic approaches have all been suggested.^{7,11} One approach is presented here

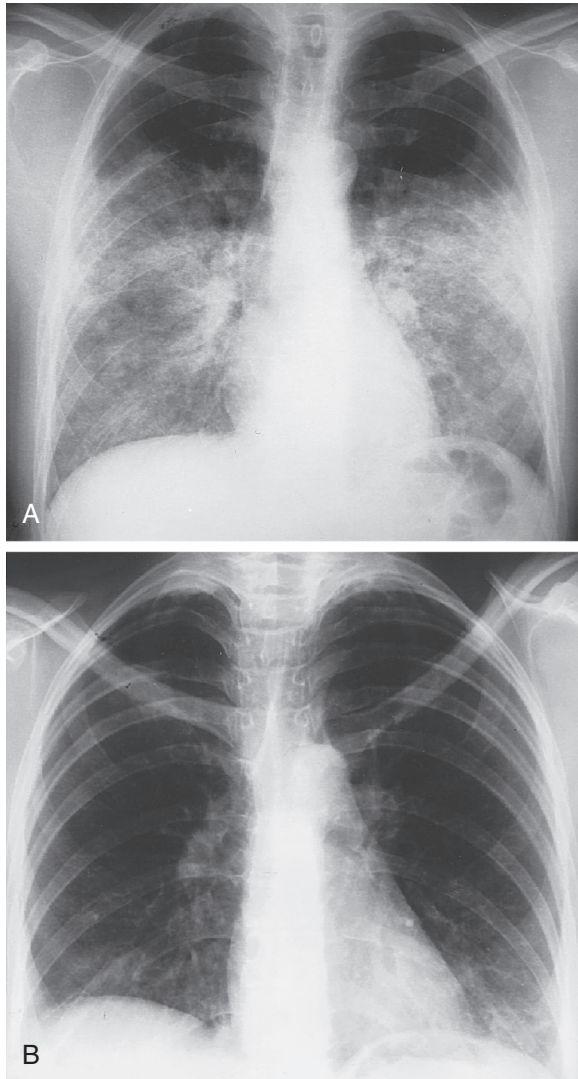


Figure 67-4 Diffuse alveolar hemorrhage (DAH). Chest radiographs show diffuse alveolar opacities in a patient with microscopic polyangiitis (**A**) and in a patient with granulomatosis with polyangiitis (Wegener granulomatosis) (**B**).

(Table 67-1). The various causes of DAH are diverse; any source of injury to the alveolar microcirculation may contribute. The pathogenesis of DAH due to capillaritis is thought to be due to one of the following scenarios: (1) the direct effects of autoantibodies on the alveolar capillary endothelium, as in *granulomatosis with polyangiitis* (GPA; Wegener granulomatosis) or *microscopic polyangiitis* (MPA), (2) the effects of antibody directed against the alveolar basement membrane (e.g., Goodpasture syndrome or *anti-glomerular basement membrane antibody* [ABMA] disease), (3) immune complex-mediated injury (e.g., *systemic lupus erythematosus* [SLE], Henoch-Schönlein purpura), or (4) direct alveolar injury.¹²

The most common causes of DAH are the systemic vasculitides, in particular GPA (Fig. 67-6). Other vasculitides are also implicated, including MPA and isolated pulmonary capillaritis. A review of 34 cases of DAH found that vasculitis accounted for about half of the cases, followed by Goodpasture syndrome (13%), *idiopathic pulmonary hemosiderosis* (IPH; 13%), and connective tissue disease (13%).¹

DIAGNOSTIC APPROACH

There are two steps to the diagnosis of DAH: identification of DAH and identification of its underlying cause. Both are essential to the timely evaluation of this life-threatening condition.

Diagnosis of Diffuse Alveolar Hemorrhage

The diagnostic considerations for patients presenting with DAH are broad. A thorough history and physical examination looking for evidence of potential associated conditions (e.g., connective tissue disease, symptoms/signs of systemic vasculitis, anticoagulant medications) is essential, and initial studies should include a HRCT scan of the chest, complete blood count, and examination of the urine sediment. If DAH is a possibility, fiberoptic bronchoscopy should be performed immediately.

Bronchoscopy with BAL is essential to the accurate identification of DAH. Sequential BAL specimens should be obtained and sent for cell count and differential, with an increasing red blood cell count considered consistent with the diagnosis. Quantitative scoring of the hemosiderin concentration in alveolar macrophages obtained by BAL cytologic examination has a sensitivity for the diagnosis of DAH as well.¹³ Importantly, BAL serves to rule out other diagnostic considerations such as infection, acute hypersensitivity pneumonitis, acute eosinophilic pneumonia, and pulmonary alveolar proteinosis.

Diagnosis of Underlying Cause

Once DAH is identified, the underlying cause must be determined. Table 67-2 summarizes the differential clinical and laboratory features of some of the more common causes of DAH. In some cases, the cause is clear (e.g., history of SLE, drug exposure). In others, a detailed laboratory evaluation is required. The presence of proteinuria and an abnormal urinary sediment (red blood cells and red blood cell casts) suggests an underlying glomerulonephritis consistent with the diagnosis of systemic vasculitis, Goodpasture syndrome, some connective tissue diseases, or rarely infection.^{13a} Vasculitis is associated with the presence of *antineutrophil cytoplasmic antibodies* (ANCA) directed against either proteinase 3 (*cytoplasmic ANCA* [c-ANCA]) or myeloperoxidase (*perinuclear ANCA* [p-ANCA]).¹⁴ Elevation of the c-ANCA level is seen in GPA, whereas elevation of p-ANCA is seen with MPA, pauci-immune glomerulonephritis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), and sometimes isolated pulmonary capillaritis. However, there can be crossover.¹⁵

The diagnosis of Goodpasture syndrome is established by the presence of serum ABMA. DAH due to SLE is accompanied by reduced serum complement levels as well as the presence of antinuclear and native anti-DNA antibodies in the serum. Henoch-Schönlein purpura is characterized by the formation of *immunoglobulin A* (IgA) immune complexes present in the circulation and also bound to tissue.¹⁶

Role of Surgical Lung Biopsy and Renal Biopsy

For the diagnosis of DAH, BAL is generally sufficient. For identifying the underlying cause of the DAH, clinical and serologic findings are usually sufficient¹; surgical lung biopsy may be useful but is often nonspecific. However,

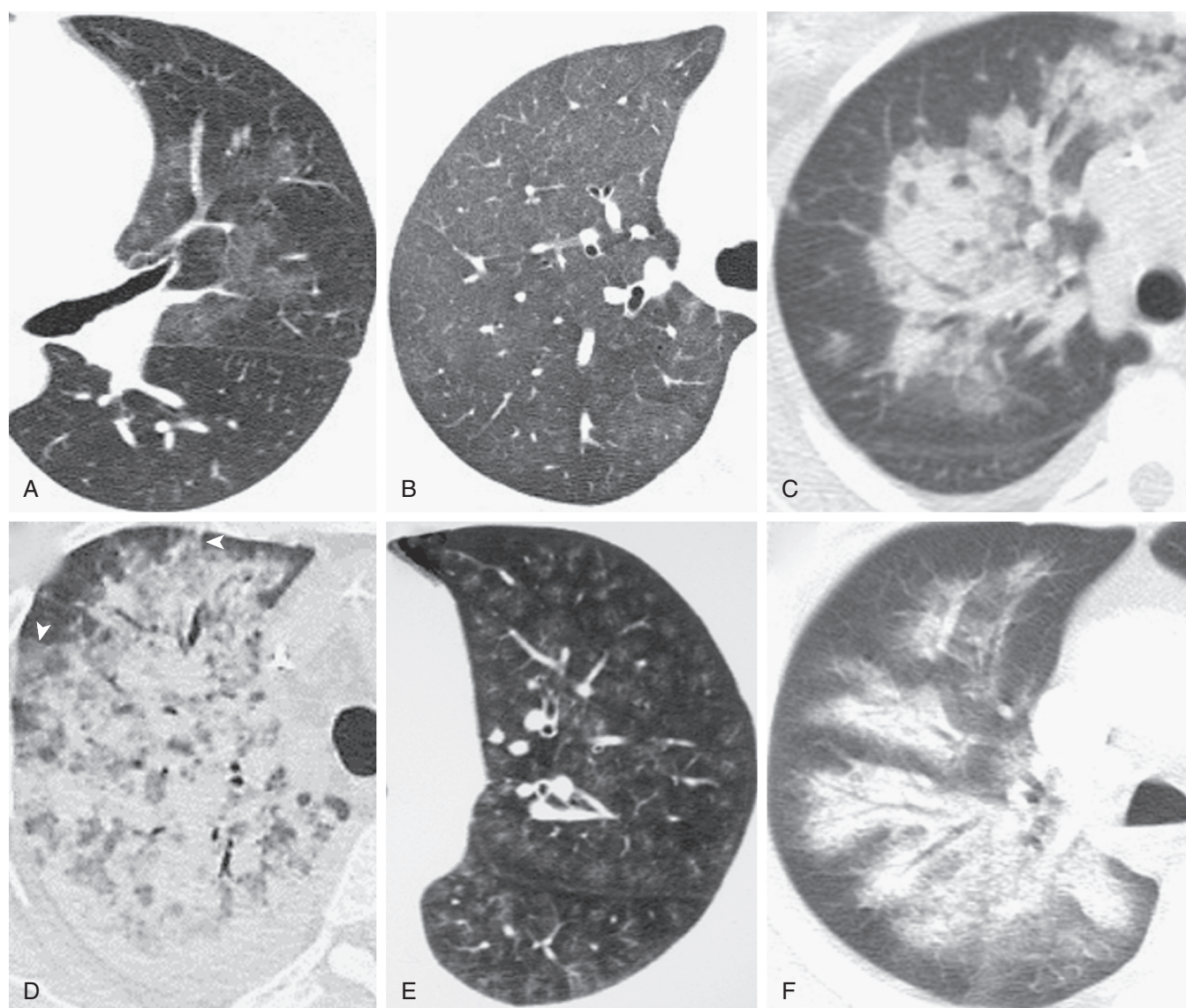


Figure 67-5 High-resolution CT (HRCT) appearance of diffuse alveolar hemorrhage (DAH). Axial chest CT images in different patients with various causes for DAH showing the variable CT manifestations of pulmonary hemorrhage. The features of DAH on HRCT are nonspecific and can be seen with any cause. **A**, Patchy, geographic ground-glass opacity in a patient with granulomatosis with polyangiitis (GPA) (Wegener granulomatosis). **B**, Vague, extensive multifocal ground-glass opacity in a patient with systemic lupus erythematosus. **C**, Dense consolidation with air bronchograms in a patient with microscopic polyangiitis. **D**, Consolidation and ground-glass opacity with a background of linear opacities representing interlobular septal thickening (arrowheads) in an over-anticoagulated patient undergoing antiplatelet therapy. **E**, Hazy ground-glass opacity in a patient with hemosiderin-laden macrophages on bronchoalveolar lavage, with presumed idiopathic hemosiderosis. **F**, Extensive peribronchovascular thickening and peribronchial consolidation and ground-glass opacity in a patient with GPA. Solid centrilobular nodules can also be a manifestation of pulmonary hemorrhage. (Courtesy Michael Gotway, MD.)

surgical lung biopsy should be considered for isolated DAH without an obvious cause.

When serologic findings are equivocal and vasculitis or Goodpasture syndrome is under consideration, renal biopsy may be appropriate because these conditions are more easily confirmed by kidney biopsy, even in the absence of clinically evident renal involvement.¹⁷ Moreover, renal biopsy may provide useful information regarding the activity and chronicity of renal involvement that may help guide therapy.

Therapeutic Approach

The most important first step in management is to identify the underlying cause and begin specific treatment when available, for example, by stopping suspected drugs or expo-

sure, treating infection, and reversing excess anticoagulation. Patients with severe hemoptysis require general supportive therapy that is based on the degree of bleeding.

Systemic glucocorticoids, with additional immunosuppressive therapy, are the mainstay of therapy for the DAH syndrome associated with systemic vasculitis, connective tissue disease, ABMA disease (Goodpasture syndrome), and isolated pulmonary capillaritis. The common approach is to begin intravenous pulse methylprednisolone (500 to 1000 mg in divided doses daily) for up to 5 days followed by gradual tapering and then maintenance on an oral preparation. The decision to add immunosuppressive therapy (cyclophosphamide or azathioprine) is dependent upon the severity of the illness, the responsiveness to glucocorticoids, and the underlying disease. Our practice is to begin

intravenous cyclophosphamide (0.75 g/m² if renal function is relatively normal). Careful attention must be given to the nadir of the peripheral white blood cell count. Oral therapy is usually started in approximately 2 weeks if neutropenia does not develop.

Plasma exchange is used in the treatment of DAD associated with ABMA disease or occasionally for refractory vasculitis syndromes or DAH associated with a connective tissue disease.¹⁸ A role for intravenous immunoglobulin or rituximab in patients with DAD remains to be defined. *Recombinant activated factor VII* (rFVIIa) has been used with variable success.^{18a-18c}

Table 67-1 Causes of Diffuse Alveolar Hemorrhage

VASCULITIS

Granulomatosis with polyangiitis (Wegener granulomatosis)
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Isolated pulmonary capillaritis
Mixed cryoglobulinemia
Behçet syndrome
Henoch-Schönlein purpura
Pauci-immune glomerulonephritis
Antiphospholipid antibody syndrome

IMMUNOLOGIC

Goodpasture syndrome (ABMA disease)
Connective tissue disease associated
Immune complex-associated glomerulonephritis
Acute pulmonary allograft rejection
Celiac disease

COAGULATION DISORDERS

IDIOPATHIC PULMONARY HEMOSIDEROSIS

OTHER

Drugs/toxins
Diffuse alveolar damage
Mitral stenosis
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Lymphangioleiomyomatosis/tuberous sclerosis

DIFFUSE INFILTRATIVE LUNG DISEASES

SPECIFIC CAUSES

Vasculitis (see Chapter 60)

Granulomatosis with Polyangiitis (Wegener Granulomatosis). GPA is a systemic vasculitis that commonly involves the upper and lower respiratory tracts and kidneys. Other organs (e.g., eyes, skin) may be involved. DAH secondary to pulmonary capillaritis can either complicate an established case of GPA or represent the initial manifestation of the disease. Pulmonary capillaritis can be the sole pulmonary parenchymal histologic finding, or it can be seen in combination with the more typical pathologic

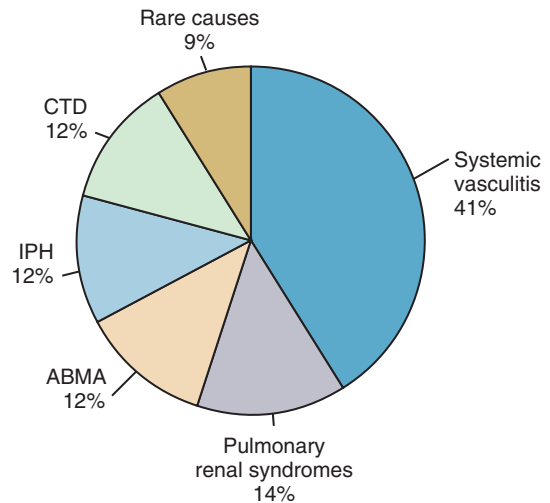


Figure 67-6 Causes of diffuse alveolar hemorrhage. A retrospective review of 34 cases of diffuse alveolar hemorrhage found systemic vasculitis to be the most common cause (14 cases: 5 definite granulomatosis with polyangiitis [Wegener granulomatosis], 6 probable, and 3 unclassifiable), followed by unclassifiable pulmonary renal syndromes (5 cases), Goodpasture syndrome (ABMA disease) (4 cases), idiopathic pulmonary hemorrhage (IPH) (4 cases), connective tissue disease (CTD) (4 cases: 2 systemic lupus erythematosus, 1 rheumatoid arthritis, 1 juvenile rheumatoid arthritis), and other rare causes (3 cases: 2 idiopathic glomerulonephropathy, 1 immunoglobulin A nephropathy). ABMA, anti-glomerular basement membrane antibody. (Data from Travis WD, Colby TV, Lombard C, Carpenter H: A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. *Am J Surg Pathol* 14:1112–1125, 1990.)

Table 67-2 Clinical Differentiation of Common Diffuse Alveolar Hemorrhage Syndromes

Syndrome	Renal	Arthritis	Skin	ANA	dsDNA	C	ABMA	c-ANCA (PR3)	p-ANCA (MPO)	Histopathology; IF
Granulomatosis with polyangiitis (Wegener granulomatosis)	+	+	+	±	±	NI	–	+	–	Capillaritis; ± granular
Microscopic polyangiitis	+	+	+	±	±	NI	–	–	+	Capillaritis; no deposits
Isolated pulmonary capillaritis	–	–	–	–	–	NI	–	–	–	Capillaritis; none
Goodpasture syndrome (ABMA disease)	+	–	–	–	–	NI	+	–	–	Bland or capillaritis; linear IgG
Systemic lupus erythematosus	+	+	±	+	+	Low	–	–	–	Bland or capillaritis; granular IgG
Idiopathic pulmonary hemosiderosis	–	–	–	–	–	NI	–	–	–	Bland; none

ABMA, anti-glomerular basement membrane antibody; ANA, antinuclear antibody; C, complement; c-ANCA (PR3), cytoplasmic antineutrophil cytoplasmic antibody (anti-proteinase 3); dsDNA, anti-double-stranded DNA antibody; IF, immunofluorescence; IgG, immunoglobulin G; NI, normal; p-ANCA (MPO), perinuclear antineutrophil cytoplasmic antibody (antimyeloperoxidase).

features of GPA. Surgical lung biopsies from 87 patients with GPA revealed capillaritis in 31%, but in only 3 was it an isolated finding.⁵ In another series, capillaritis was present in 17% of 35 patients, but never as an isolated finding.¹⁹ In a postmortem study of 22 patients, capillaritis was the sole histologic feature in 3 and was seen in conjunction with the more typical granulomatous vasculitis in 7 cases.²⁰ The typical histologic features of GPA are granulomatous inflammation, small and medium vessel vasculitis, and parenchymal geographic necrosis. When DAH is present alone (see eFig. 60-3), without the characteristic histologic features, sinusitis (see eFig. 60-7), or nodular/cavitary lung lesions (see eFigs. 60-1, 60-2, 60-4, and 60-5), differentiation from MPA is difficult.

The specific diagnosis depends on the ANCA pattern, with c-ANCA suggesting the diagnosis of GPA. The characteristic histologic and clinical features of GPA may appear months to years after the initial presentation of DAH and capillaritis.²¹ Circulating endothelial cells are present in GPA and MPA. The presence of circulating endothelial cells may serve as a novel marker of active ANCA-positive vasculitis.²²

Alveolar hemorrhage is often subclinical and recurrent in GPA (as well as in MPA), suggested by the presence of hemosiderin-laden macrophages on BAL. This pattern of frequently recurring DAH is more typical of the ANCA-associated vasculitides and SLE than of nonvasculitic diseases such as rheumatoid arthritis.²³

More than 40 cases of GPA with only DAH and pulmonary capillaritis have been described. Early mortality is 37% and is most often due to acute respiratory or renal failure.^{5,19-21,24,25} Renal disease in the form of a focal segmental necrotizing glomerulonephritis (Fig. 67-7), a cutaneous leukocytoclastic vasculitis, and arthritis often accompany the DAH. Treatment with high-dose corticosteroids and cyclophosphamide has been the recommended initial therapy, which, for DAH of GPA, depending on the severity of the disease, is usually administered intravenously. The role of plasmapheresis is still unclear, but it is often initiated if renal failure is present. Azathioprine may be substituted for cyclophosphamide after remission.²⁶ Recurrences of DAH and other disease manifestation with

tapering of the drug are to be expected. Disease activity can be monitored by the erythrocyte sedimentation rates, ANCA levels, serial DL_{CO} determinations, and microscopic urine examinations. The role of rituximab specifically for the treatment of DAH complicating the vasculitides has not been studied, but it is equal to any other therapy in maintaining remission.²⁷ As previously stated, the differentiation of GPA with DAH from MPA is at times difficult because the clinical presentation, lung histologic features, and serologic findings can be identical.²⁷ In fact, the response to treatment and the tendency for recurrences are similar. The differentiation can be established only after the development of the more typical upper airway disease and pathologic features of GPA.

Microscopic Polyangiitis. MPA has been considered the small vessel variant of polyarteritis nodosa. When present, it is a frequent cause of pulmonary capillaritis and DAH (see eFig. 60-10).^{4,6,21,28-31} MPA is distinguishable from polyarteritis nodosa by the absence of medium-sized blood vessel involvement, the absence of asthma and systemic hypertension, and the relative sparing of the abdominal viscera. DAH has only rarely been documented with polyarteritis nodosa.³²

The most consistent pathologic feature in MPA is a focal segmental necrotizing glomerulonephritis, the renal lesion common to all systemic vasculitides. The lungs are involved by capillaritis in 20% to 30% of cases.³¹ The alveolar hemorrhage tends to be severe and is often life-threatening. Other manifestations include fever, weight loss, cutaneous vasculitis, myalgias, arthralgias, diarrhea, and gastrointestinal bleeding from mucosal vasculitis that is often visible by direct examination, peripheral neuropathy, and in a few cases, sinusitis.^{31,33,34} As with other vasculitides, the erythrocyte sedimentation rate is elevated, and nonspecific increases of serum rheumatoid factor and antinuclear antibody levels are found. Although circulating immune complexes are present in 45% of cases, tissue localization of these complexes is difficult to detect (pauci-immune). Anti-DNA antibodies and hypocomplementemia, findings suggestive of SLE, are absent. A positive serum p-ANCA strongly supports the diagnosis. Antibodies to hepatitis B and C antigens are present in 33% of cases.³⁵

Treatment consists of either oral or intravenous corticosteroids combined with cyclophosphamide or azathioprine.²⁶ Adjuvant treatment with plasmapheresis is recommended by some authors, but its additional efficacy is difficult to determine.³¹ Outcome with early initiation of therapy for MPA is generally good, with a 65% rate of 5-year survival. However, the presence of DAH contributes to an early mortality rate of 25%.^{4,6,21,28-31} There is a tendency for recurrence with tapering of the medications. Factor VIIa has been used successfully with dramatic effects in cases of uncontrolled alveolar hemorrhage.³⁶

The transition to pulmonary fibrosis and restrictive ventilatory impairment after recurrent DAH has been described,¹⁰ and fibrotic lung disease has been reported as the presenting manifestation of MPA.³⁷ There have been three cases of persistent, severe, irreversible airway dysfunction after recurrent episodes of DAH that complicated MPA.³⁸ It is postulated that the combination of recurrent vascular obliteration from capillaritis and the release of

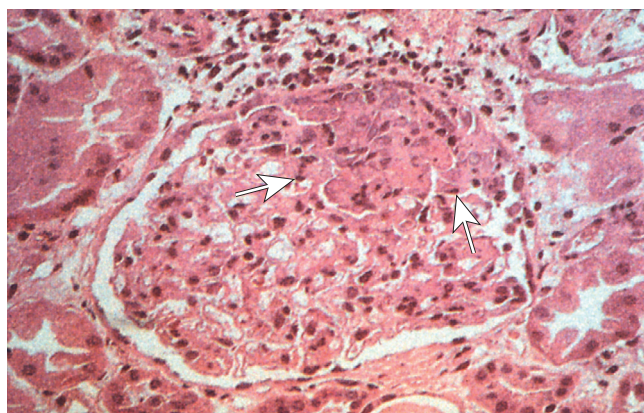


Figure 67-7 Granulomatosis with polyangiitis. Histopathologic findings of a renal biopsy specimen demonstrate focal segmental necrotizing glomerulonephritis. The focal lesion represents an area of fibrinoid necrosis (arrows). (×40 original magnification).

neutral proteases and oxygen radicals from the overwhelming and recurrent burden of neutrophils causes permanent damage to the alveolar septa and results in emphysema.

Isolated Pulmonary Capillaritis. Isolated pulmonary capillaritis is a small vessel vasculitis confined to the lungs and without concomitant systemic involvement.³⁹ There are two forms: one with serum p-ANCA positivity and the other without any positive serologic testing.^{39,40} In one series the latter type was the most frequent cause of pulmonary capillaritis and DAH.³⁹ Direct immunofluorescent studies of the lung in these patients have been negative (pauci-immune). Although respiratory failure necessitating ventilatory support was frequent, response to corticosteroids and cyclophosphamide was good, and only one of eight patients died. Recurrences appeared in two subjects. During a 4-year follow-up period, clinical or serologic evidence for a systemic vasculitis or connective tissue disease did not appear.

Isolated forms of pulmonary capillaritis causing DAH must be distinguished from IPH, which is not associated with pulmonary capillaritis, as well as lung-limited forms of Goodpasture syndrome, the initial presentation of a collagen vascular disease, primary antiphospholipid antibody syndrome, and mitral stenosis. All patients who present with unexplained DAH should have an echocardiogram and undergo surgical lung biopsy.

Mixed Cryoglobulinemia. Mixed cryoglobulinemia is a systemic vasculitis that is recognized by the presence of purpura, arthritis, hepatitis, and glomerulonephritis. It is thought to be an immune complex–induced disease, with most cases linked to hepatitis C (and less commonly hepatitis B) viral infection. Cutaneous vasculitis appearing as raised purpura is the clinical hallmark of this disease. Histologically, there is a perivascular polymorphonuclear infiltration with tissue extravasation and fragmentation in the dermis (leukocytoclastic vasculitis). The renal disease is a proliferative glomerulonephritis with positive granular immunofluorescence. Interstitial lung disease consisting of inflammation and fibrosis of the alveolar walls is the most common pulmonary manifestation.⁴¹ There are two published cases of DAH with pulmonary capillaritis that complicated mixed cryoglobulinemia.^{42,43} rFVIIa failed to control DAH in a patient with cryoglobulinemic vasculitis.^{18a}

Behçet Syndrome. Behçet syndrome is a chronic relapsing illness characterized by oral and genital ulceration, iridocyclitis, thrombophlebitis, and a multisystem disease consisting of a cutaneous vasculitis, arthritis, and meningoencephalitis.⁴³ Immune complexes have been identified in the serum of active cases as well as in the lung and other organs.^{44,45}

The thorax is involved in 5% to 10% of cases of Behçet syndrome. The pulmonary disease is typically a small vessel vasculitis affecting capillaries, venules, and arterioles. The renal disease is a focal segmental necrotizing vasculitis, as is seen in other systemic vasculitides. Immune complexes composed of IgG and complement have been identified in small pulmonary vessels in several cases.^{44,45} In addition to alveolar hemorrhage, involvement of larger vessels can lead to aneurysms of the pulmonary (eFig. 67-2) and bronchial

arteries, the latter potentially eroding into bronchi, causing massive pulmonary hemorrhage and death.^{46,47} Another potential cause for pulmonary hemorrhage in Behçet syndrome is pulmonary arterial occlusion with infarction.⁴⁵ A review of 28 cases of pulmonary involvement in Behçet syndrome emphasized several points: pulmonary complaints consisting of cough, hemoptysis, chest pain, and fever were more common in men than in women; 39% of patients died of pulmonary hemorrhage, usually within 6 years of the first episode of hemoptysis.⁴⁸ Other studies have confirmed the seriousness of this complication regardless of its cause.^{46,47} Treatment consists of corticosteroids and immunosuppressive therapy.⁴⁹ Treatment with anti-tumor necrosis factor therapy has shown dramatic results in case reports.⁵⁰

Henoch-Schönlein Purpura. Henoch-Schönlein purpura, primarily a disease of children, also can be seen in adults.⁵¹ Adults typically present with palpable purpura (leukocytoclastic vasculitis) and glomerulonephritis.¹⁶ The joints and gastrointestinal tract are commonly involved. Pulmonary involvement is unusual. In several large series, pulmonary disease, except for transient chest radiographic opacities, was not mentioned.¹⁶ There have been documented cases of DAH with pulmonary capillaritis in patients with Henoch-Schönlein purpura.^{52,53} In one, IgA immune complexes were present in the alveolar septa.⁵² It is postulated that IgA immune complexes, which are present in the serum and kidneys of these patients, are responsible for the tissue damage that results in the clinical syndrome.⁵⁴ Corticosteroids were used in both cases and are generally recommended.

Pauci-immune Glomerulonephritis. Pauci-immune glomerulonephritis is one of three types of isolated renal vasculitides (the other two being immune complex–mediated glomerulonephritis and Goodpasture syndrome). Pauci-immune glomerulonephritis lacks any immunoreaction product except for minimal accumulation of fibrin. It is histologically and immunologically similar to the glomerulonephritis of MPA and GPA and is considered to represent a form of renal-limited vasculitis.²¹ Up to 50% of affected patients develop pulmonary capillaritis and DAH, and a smaller number develop a full-blown systemic vasculitis indistinguishable from MPA. Another indication that pauci-immune glomerulonephritis represents a limited form of vasculitis is the presence of serum p-ANCA in these patients. Because clinical manifestations are often limited to the lung and kidney, it can be confused with Goodpasture syndrome.^{21,54} Pauci-immune glomerulonephritis is distinguished by the absence of circulating basement membrane antibodies in the serum and by the negative findings on renal immunofluorescence studies. Treatment with high-dose corticosteroids plus immunosuppressive therapy with either cyclophosphamide or azathioprine is recommended.

Immunologic

Goodpasture Syndrome. Whether the case reported by Goodpasture in 1919⁵⁵ describes the syndrome that bears his name is questionable. He described an 18-year-old man who died 6 weeks after an influenza infection and was

found to have DAH, pleuritis, glomerulonephritis, splenic infarctions, and vasculitis of the small intestines. In 1965 an *anti-glomerular basement membrane antibody* (ABMA)—now identified as an antibody against the NC1 domain of the $\alpha 3$ chain of type IV collagen—was identified in the kidneys and lungs of some patients with DAH and glomerulonephritis.^{56,57} The diagnosis of Goodpasture syndrome, also known as *ABMA disease*, is reserved for cases of DAH and glomerulonephritis in which this antibody appears in the serum, is bound to kidney and/or lung basement membranes in a linear manner by immunohistochemistry, or both.²¹

At least 90% of patients with Goodpasture syndrome have circulating ABMA.⁵⁸ The level of ABMA is not generally considered an accurate index of disease activity, although higher levels have been associated with more severe renal disease. In 60% to 80% of cases, the lung and renal disease appear simultaneously; in 5% to 10%, only the lung is affected; and in the remainder, renal disease exists by itself.^{59,60} It is clear that ABMA is pathogenetic; however, the stimulus for its production remains unknown. The clinical onset of Goodpasture syndrome has been temporarily related to infection with influenza A2 as well as to other respiratory infections, hydrocarbon exposure, and tobacco use.^{61–63} The presence of histocompatibility *human leukocyte antigen* (HLA)-DRw2 and HLA-B7 (90% and 60%, respectively) in patients with Goodpasture syndrome indicates that susceptible individuals are predisposed to disease that is often severe and progressive.^{64,65} It is interesting to note that, in some experimental models, the introduction of ABMA produces renal but not pulmonary disease; for the antibody to deposit in the lung, an additional injury is required that increases alveolar-capillary permeability.^{66,67}

Men are more commonly affected (60% to 80% of patients), and the concentration of cases is greatest between the ages of 20 and 30 years.^{68,69} In older cases, the sex distribution is equal and the disease tends to be limited to the kidney.⁶² Interestingly, DAH is more common in patients who smoke.⁶² The alveolar permeability is increased in most smokers, and this is thought to be an important factor leading to DAH.⁶¹ In one study, 100% of smokers with Goodpasture syndrome developed both DAH and glomerulonephritis, whereas only 20% of nonsmokers developed DAH.⁶² Resumption of cigarette smoking by patients who are in remission can result in recurrent episodes of DAH. Exposure to volatile hydrocarbons (e.g., petroleum products, turpentine, toluene, and pesticides) is associated with initiation, as well as exacerbations, of DAH.^{59,60,70,71}

Symptoms most often refer to the lungs and consist of hemoptysis, cough, and dyspnea. Fatigue caused by iron-deficiency anemia and renal failure may predominate. Microscopic hematuria, proteinuria, and increases in the serum creatinine level are often present, but gross hematuria with hypertension is unusual. The diffusing capacity may be increased during periods of active bleeding and is considered to be a useful monitor of new or recurrent DAH.⁷² An increase of 30% above baseline is highly suggestive of an intra-alveolar hemorrhage, and this increase may precede pulmonary symptoms or radiographic changes. Chest radiography often reveals patchy air space abnormalities (eFig. 67-3A and B). HRCT scanning (see eFig. 67-3C) typically shows ground-glass opacities and

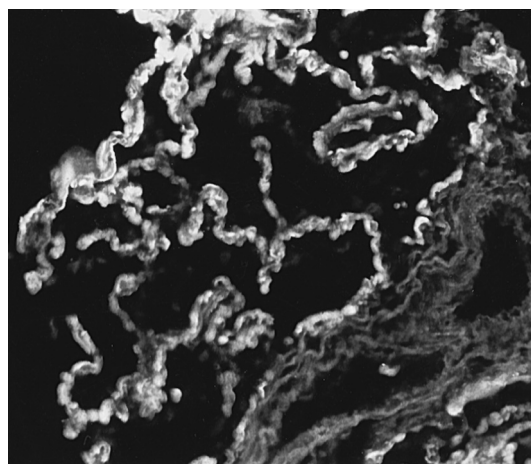


Figure 67-8 Goodpasture syndrome (ABMA disease). Immunofluorescence study demonstrates linear staining of immunoglobulin G in the alveolar walls in a patient with Goodpasture syndrome (ABMA disease) ($\times 10$ original magnification).

consolidation and is more sensitive for DAH than is chest radiography.⁷³

Pulmonary capillaritis is present in some cases of Goodpasture syndrome, but the usual histologic appearance is bland pulmonary hemorrhage.⁷¹ Alveolar wall necrosis, which is seen with systemic vasculitis, is not a feature of Goodpasture syndrome. The renal histologic findings are a focal segmental necrotizing glomerulonephritis with crescent formation. The major distinction between Goodpasture syndrome and the other rapidly progressive glomerulonephritides is the presence of an uninterrupted linear deposition of immunoglobulin and complement along the glomerular basement membrane (Fig. 67-8). Identical findings are present on alveolar basement membranes.⁷⁴ Even when DAH dominates the clinical picture (i.e., there is no evidence of renal disease), renal biopsy will still reveal the typical linear staining.⁷⁵

In the minority of patients without clinically evident renal involvement, DAH responds to oral or intravenous corticosteroids. Glomerulonephritis, if present, appears resistant to corticosteroid monotherapy. The combination of plasmapheresis (3 to 6 L daily for 2 weeks), corticosteroids, and cytotoxic drugs is effective, particularly in patients who do not have oligoanuria and do not require dialysis.^{76–80} The combination of cyclophosphamide or azathioprine with corticosteroids leads to a dramatic fall in circulating ABMA, and oliguric dialysis-dependent subjects have responded to the point at which dialysis could be discontinued.^{80,81} Anuric patients do not respond well to this combination therapy, and dialysis and renal transplantation are often necessary.⁸¹ Case reports of successful treatment of refractory, life-threatening Goodpasture syndrome with mycophenolate mofetil and anti-CD20 monoclonal antibody have been reported.^{82,83} Bilateral nephrectomy no longer has a role in the management of Goodpasture syndrome.

Over time, the survival rate in Goodpasture syndrome has improved from 80% mortality at 6 months (half dying from DAH and the rest from renal insufficiency) to approximately 50% at 2 years.⁶⁹ With the aggressive treatment approach described previously, it is estimated that the

5-year survival rate exceeds 80%, and fewer than 30% of patients require long-term dialysis. DAH is the usual cause of death, often being precipitated by a concomitant infection.⁶⁰ There has been spontaneous remission in cases without clinical evidence of renal disease, although this is not usual.⁸⁴ The most useful prognostic information comes from the kidney. Clinically, oliguric or anuric renal failure reduces the survival rate to 50% at 6 months. Histopathologically, less than 30% involvement of the glomeruli on biopsy predicts significant therapeutic response and improved survival. When 70% or more of glomeruli have formed crescents in conjunction with renal insufficiency, renal failure is progressive and often unresponsive to therapy, eventually necessitating dialysis.⁸¹

Connective Tissue Disease. Among the connective tissue diseases, DAH is most commonly seen in SLE (eFig. 67-4).^{21,85-87} It is unusual for DAH to be the initial manifestation of SLE, in contrast to acute lupus pneumonitis, which is often the initial manifestation.^{88,89} Most patients with DAH have active lupus nephritis.⁸⁶ The onset of alveolar hemorrhage can be dramatic, producing severe gas-exchange abnormalities and necessitating mechanical ventilation. Reduced complement levels and increased serum titers of serum antinuclear antibodies confirm the diagnosis.

DAH must be distinguished from other causes of hemoptysis in SLE, specifically acute lupus pneumonitis. Acute lupus pneumonitis presents with fever, cough, and dyspnea. In 50% of cases, this is the initial manifestation of SLE.⁸⁹ It is an inflammatory condition, characterized histologically by organizing pneumonia, DAD, cellular nonspecific interstitial pneumonia, and occasionally, intra-alveolar hemorrhage. Although hemoptysis may accompany acute lupus pneumonitis, significant reductions of the hemoglobin level are not to be expected. Unlike DAH, pleural and pericardial effusions are common in acute lupus pneumonitis. Other diagnostic considerations in the patient with suspected DAH include infectious pneumonias and pulmonary infarction associated with deep venous thrombosis with or without a circulating lupus anticoagulant.^{90,91}

Histopathologic examination of DAH in patients with SLE generally reveals capillaritis, but bland pulmonary hemorrhage and DAD have been described.^{89,92} Granular deposits of IgG and complement (C3) are commonly found in the alveolar interstitium and within the walls of intra-alveolar blood vessels (Fig. 67-9).^{85,92-94} Capillaritis and immune complex deposition do not necessarily overlap. In one series of four patients with SLE and massive DAH associated with pulmonary capillaritis, only two demonstrated immune complexes by light and electron microscopic techniques.⁹⁵

Treatment of DAH caused by SLE includes high-dose intravenous corticosteroids as well as azathioprine or cyclophosphamide. rFVIIa administered via local intrapulmonary route may be an effective treatment option for DAH in SLE patients.^{18b} Plasmapheresis has been combined with chemotherapy in some cases, but its utility is unknown.⁸⁶ Broad-spectrum antibiotic coverage is recommended because of some evidence that infection may trigger the hemorrhage.⁸⁶ DAH is associated with a 50% mortality rate in SLE and can be recurrent in survivors.^{88,92-96} Death is caused by massive hemorrhage, concurrent infection, or renal or central nervous system disease.

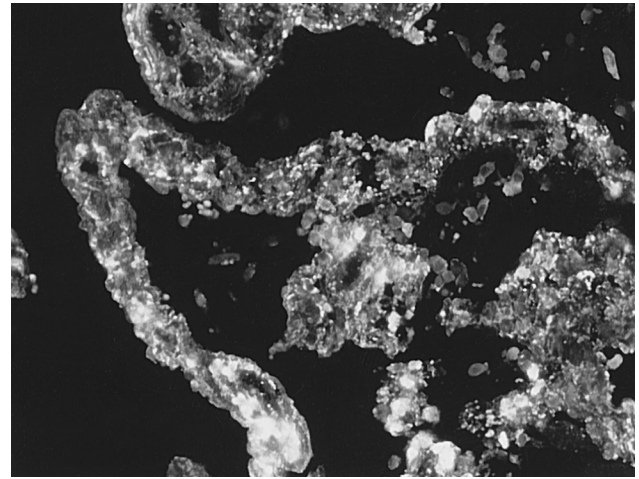


Figure 67-9 Systemic lupus erythematosus. Immunofluorescence study demonstrates granular deposition of immunoglobulin G in the alveolar walls of a patient with systemic lupus erythematosus and diffuse alveolar hemorrhage ($\times 40$ original magnification).

Rarely, DAH and glomerulonephritis develop in patients with rheumatoid arthritis,⁹⁷ scleroderma,⁹⁸ or mixed connective tissue disease. Isolated DAH with capillaritis has also been described in polymyositis, rheumatoid arthritis, and mixed connective tissue disease.^{99,100} In polymyositis, DAH was the presenting manifestation, and in rheumatoid arthritis and mixed connective tissue disease, DAH and capillaritis followed the primary diagnosis (2 to 20 years).^{99,100} The absence of a systemic vasculitis in these cases, including glomerulonephritis, was unexpected.

Immune Complex–Related Crescentic Glomerulonephritis. Immune complex–related crescentic glomerulonephritis is rarely accompanied by capillaritis and DAH.^{1,101} Although the kidneys demonstrate granular immune deposits, immune complexes are not found in lung tissue.

Acute Pulmonary Allograft Rejection. Pulmonary capillaritis and DAH have been reported after lung transplantation for a variety of underlying diseases.¹⁰² The suspected acute vascular rejection can develop weeks to months after the transplantation and may be the only histopathologic manifestation of allograft rejection. This represents a serious immunologic complication that threatens survival. In addition to standard anti-inflammatory therapy with corticosteroids and cytotoxic agents, plasmapheresis may be effective.

Coagulation Disorders

Coagulation disorders associated with DAH include disseminated intravascular coagulation,¹⁰³ idiopathic thrombocytopenic purpura,¹⁰⁴ thrombotic thrombocytopenic purpura,¹⁰⁵ acquired vitamin K deficiency,¹⁰⁶ and antiphospholipid antibody syndrome.¹⁰⁷ Uniquely among coagulation disorders, primary antiphospholipid antibody syndrome–associated DAH is often associated with capillaritis (eFig. 67-5).¹⁰⁸

All anticoagulant medications have been associated with DAH, including warfarin (Coumadin) and its derivatives,¹⁰⁹⁻¹¹¹ thrombolytics,^{112,113} agents targeting the platelet glycoprotein IIb/IIIa,¹¹⁴⁻¹¹⁶ and clopidogrel.¹¹⁷ In most

iatrogenically anticoagulated patients, correction of the coagulation defect resolves the DAH. It has been suggested that patients using coumarins with confirmed DAH are at risk for the development of fibrosing interstitial pneumonitis.¹¹⁸

DAH is common in patients with acute leukemia who have undergone induction chemotherapy and are thrombocytopenic (eFig. 67-6).¹¹⁹⁻¹²¹ Although thrombocytopenia surely contributes to the DAH, these patients also have evidence of DAD due to chemotherapy, oxygen toxicity, and infection that likely plays a central role.

Idiopathic Pulmonary Hemosiderosis

IPH is predominantly a disease of children, but adults represent about 20% of cases.^{120,121} It is a diagnosis of exclusion,^{122,123} and efforts to rule out other causes of DAH are essential. Among adults, men are more often affected, and there are reports of familial cases.¹²⁴ Some cases have been described in the setting of celiac disease, and serum IgA levels are increased in 50% of cases.^{125,126} The pathogenesis of IPH is not understood. Some cases may be secondary to environmental exposures, such as *Stachybotrys atra*, a toxigenic fungus that has been potentially linked to several cases of otherwise idiopathic alveolar hemorrhage.¹²⁷

Recurrent hemoptysis due to DAH is the rule, ranging from intermittent blood-streaked sputum to life-threatening hemorrhage. Fever, cough, substernal chest pain, and fatigue secondary to iron-deficiency anemia are also reported. In selected pediatric cases, lymphadenopathy and hepatosplenomegaly are found. Renal disease is absent. In chronic recurrent disease, progressive dyspnea, finger clubbing, inspiratory crackles, and pulmonary fibrosis appear. Pulmonary function testing reveals a restrictive ventilatory defect with an increase in the DL_{CO} during periods of active bleeding. Chest imaging reveals diffuse ground-glass opacity (eFigs. 67-7 and 67-8) and ill-defined centrilobular nodules, the typical appearance of pulmonary hemorrhage of any cause.¹²⁸ Measurements of serum antibodies reveal the absence of alternative causes.

In adult cases, lung tissue is required to exclude the entity of isolated pulmonary capillaritis. The histologic examination of the lung in IPH reveals bland alveolar hemorrhage with hemosiderin accumulation.^{123,129} There is hyperplasia of type II alveolar epithelial cells with capillary dilation and tortuosity. The iron content of the lung is increased, and it is the hemosiderin deposition in the interstitium that is thought to be the basis for collagen proliferation and parenchymal fibrosis. Pulmonary immune complexes are absent, differentiating IPH from isolated pulmonary Goodpasture syndrome. Electron microscopic studies indicate degeneration of type I alveolar epithelial cells with exposure of and breaks in the basement membrane and discontinuity of the alveolar capillary structure.^{127,128} Although nonspecific, these findings indicate a form of DAD.

Clinical benefit and recovery from the acute hemorrhage after corticosteroid therapy have been reported, but long-term benefit is unlikely.^{123,130} Azathioprine has been successful in several cases.^{129,131,132} Approximately 25% of patients are free of disease after the initial episode. Another 25% are free of active disease but have persistent dyspnea and anemia, and another quarter have persistent active disease that leads to fibrosis and severe restrictive lung

disease. The rest have unresponsive disease with continued hemorrhage and death from respiratory failure. In those with persistent disease, the average survival is 3 to 5 years.^{123,130} Adults have a better prognosis than children. Lung transplantation is controversial in this disease because IPH has been reported to recur after bilateral lung transplantation.¹³³

Other Causes of Diffuse Alveolar Hemorrhage

Drugs/Toxins. There are many drugs that have been reported to cause DAH.^{133a} Anticoagulants have been discussed previously. Most DAH due to drugs or toxins is associated with DAD. This has been reported with abciximab, amiodarone, azathioprine, carbamazepine, cyclosporine, ara-C, dextran, docetaxel, fludarabine, hydralazine, methotrexate, radiographic contrast media, retinoic acid, sirolimus, tumor necrosis factor- α , and valproate.¹³⁴

A few drugs have been associated with DAH and capillaritis, including tretinoin, propylthiouracil, phenytoin, and mitomycin.¹³⁵⁻¹³⁹ DAH due to these drugs may also be associated with crescentic glomerulonephritis and elevated ANCA levels.

Penicillamine can result in DAH and an immune complex-mediated glomerulonephritis. Glomerular capillaries display a granular (as opposed to a linear) immunofluorescent pattern for IgG and C3.¹⁴⁰⁻¹⁴² Cases have appeared after as much as 20 years of treatment. Some authors have called this a drug-induced Goodpasture syndrome, but the pattern of immunoglobulin deposition in the kidney differentiates this entity. Treatment with immunosuppressive therapy and even plasmapheresis may be required.¹⁴³

Trimellitic anhydride is used for the manufacture of paints, epoxy resins, and plastics. DAH has been reported after the inhalation of fumes or dry powder, generally during spraying of this product on heated surfaces.¹⁴⁴⁻¹⁴⁶ Antibodies to trimellitic anhydride in the serum and a latent period of 1 to 3 months both support an immunologic basis for this syndrome. Long-term physiologic impairment is unusual if further exposure is avoided.

Diffuse Alveolar Damage. DAD is the underlying histopathologic feature of acute lung injury, and it has a variety of causes (Table 67-3). In DAD the interstitium of the lung becomes edematous, and the type I alveolar epithelial lining cells are sloughed. There is neutrophilic inflammation and fibroblastic proliferation. Hyaline membranes (eosinophilic strands of necrotic cells, protein, and fibrin) develop adjacent to the injured alveolar walls. In severe cases, red blood cells may enter the alveolar space as a result of injury to the alveolar-capillary interface, resulting in DAH. The neutrophilic inflammation in DAD-associated DAH is not as intense as it is in pulmonary capillaritis.

Mitral Stenosis. Mitral stenosis can be clinically silent and, over time, can result in substantial pulmonary venous hypertension. In some cases this can lead to the development of DAH.¹⁴⁷ The presentation can be dramatic, with massive hemoptysis arising from the rupture of engorged bronchial varicosities that develop as a result of long-standing left atrial hypertension. Less severe DAH may be recurrent and is often misdiagnosed, leading to chronic

Table 67-3 Causes of Diffuse Alveolar Damage**ACUTE RESPIRATORY DISTRESS SYNDROME**

Sepsis
 Pneumonia (e.g., bacterial, viral, *Pneumocystis jirovecii*)
 Trauma
 Aspiration
 Massive transfusion
 Drugs (e.g., cytotoxic/chemotherapeutic agents, antibiotics)

CONNECTIVE TISSUE DISEASE**DIFFUSE LUNG DISEASE**

Acute interstitial pneumonia
 Acute exacerbation of idiopathic pulmonary fibrosis

RADIATION THERAPY**TOXIC INHALATION**

Smoke
 Ozone
 Heavy metal fumes

interstitial fibrosis. Radiographic findings consist of central ground-glass abnormalities and, in chronic cases, reticular abnormalities (eFig. 67-9).¹⁴⁸ Repair or replacement of the stenotic mitral valve prevents recurrence.

Pulmonary Veno-occlusive Disease. *Pulmonary veno-occlusive disease* (PVOD) is a rare cause of pulmonary hypertension due to fibrous obliteration of small pulmonary veins and venules. PVOD affects men and women equally and involves all age-groups, most commonly children and young adults.¹⁴⁹⁻¹⁵¹ Patients with PVOD present with dyspnea, syncope, and, when severe, physical findings suggestive of cor pulmonale. Because PVOD is a postcapillary cause of pulmonary hypertension, paroxysmal nocturnal dyspnea, orthopnea, and DAH can be seen.

Right heart catheterization cannot easily distinguish PVOD from precapillary pulmonary hypertension because the pulmonary capillary wedge pressure is generally normal. Imaging shows signs of pulmonary hypertension; in some cases, interstitial opacities with septal thickening (see Fig. 58-3) suggesting congestion as well as ground-glass abnormality from alveolar hemorrhage may be seen. Pleural effusions are common.

Pulmonary function studies reveal a reduced DL_{CO} with preservation of lung volumes, a physiologic picture similar to that found in other causes of pulmonary hypertension. Definitive diagnosis is achieved by lung biopsy, which demonstrates fibrous intimal obliteration of small pulmonary veins and venules, acute or recanalized thrombi, and hemosiderosis (Fig. 67-10).

Most cases of PVOD are idiopathic, but it has been reported after chemotherapy (e.g., carmustine, mitomycin, bleomycin) for malignant disease, bone marrow transplantation, and associated with connective tissue disease.¹⁵²⁻¹⁵⁹ A mutation in the *bone morphogenetic protein receptor II gene* (BMP2), a gene associated with many cases of primary pulmonary hypertension, has been identified in a patient with idiopathic PVOD, suggesting a potential etiologic role.¹⁶⁰

The use of pulmonary vasodilators in the treatment of PVOD is complicated and potentially harmful. Modest improvements with nifedipine and epoprostenol have been

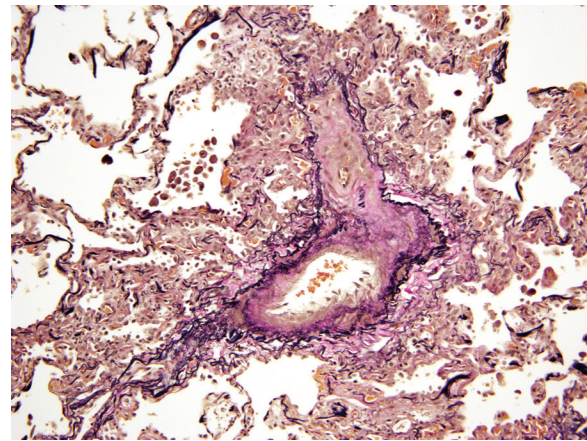


Figure 67-10 Histopathologic findings of pulmonary veno-occlusive disease. An elastic tissue stain (elastic van Gieson) shows marked intimal sclerosis with venous narrowing. These cases may show mild interstitial chronic inflammation and air space accumulation of hemosiderin-filled macrophages (hemosiderosis). (Courtesy Dr. Kirk Jones, University of California, San Francisco.)

reported, but there have also been cases of these agents precipitating massive pulmonary edema and death.^{161,162} Any trial of vasodilator therapy should be performed during right heart catheterization in an appropriate hospital setting. A few patients have had clinical responses to prednisone and azathioprine.^{163,164} Anticoagulation for PVOD has been recommended based on the potential role of thrombosis in the pathogenesis of PVOD and on limited data suggesting efficacy in patients with primary pulmonary hypertension. Anticoagulants should generally be avoided in patients who have had DAH.

Pulmonary Capillary Hemangiomatosis. Pulmonary capillary hemangiomatosis is a rare cause of pulmonary hypertension that can be associated with severe and recurrent DAH.¹⁶⁵⁻¹⁶⁷ It is seen across age and gender. Patients universally present with dyspnea, often with evidence of right heart failure. Hemoptysis develops in roughly one third of cases during the course of the disease.¹⁶⁵ Imaging findings are nonspecific, with chest radiography often showing nonspecific diffuse or bibasilar predominant reticular (eFig. 67-10A) and nodular opacities, with interlobular septal thickening less common than seen with PVOD. Chest *computed tomography* (CT) may show multifocal or diffuse, poorly defined centrilobular ground-glass opacity nodules (eFig. 67-11; see eFig. 67-10B) and evidence of pulmonary arterial hypertension. Pulmonary function test results are mixed, with both obstructive and restrictive changes described.¹⁶⁵ As with PVOD, right heart catheterization generally reveals a normal pulmonary capillary wedge pressure.

Pulmonary capillary hemangiomatosis is characterized by a proliferation of pulmonary capillaries, which infiltrate the interstitial, bronchial, and vascular structures of the lung (Fig. 67-11).¹⁶⁶ The exact mechanism of pulmonary hypertension and DAH is unclear, but mechanical rupture of hemangiomatous vessels in the setting of pulmonary arterial and venous occlusion and/or thrombosis is likely responsible. Treatment of pulmonary capillary hemangiomatosis with pulmonary vasodilators is generally

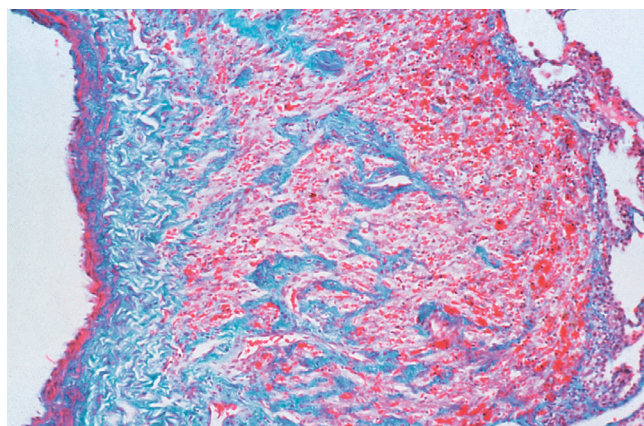


Figure 67-11 Histopathologic findings of pulmonary capillary hemangiomatosis. There is capillary proliferation in the wall of this large pulmonary vein (×100 original magnification).

contraindicated because worsening pulmonary edema and death have been reported as a result.^{168,169} In a few reports, treatment with recombinant interferon-alfa-2a may have led to stabilization or improvement.^{165,170} Mean survival after diagnosis is usually 3 years, although successful treatment with lung transplantation has been reported.¹⁶⁵

Lymphangioleiomyomatosis and Tuberous Sclerosis. Lymphangioleiomyomatosis and tuberous sclerosis share a common pathobiology involving proliferation of smooth muscle in pulmonary interstitial, lymphatic, bronchial, and vascular structures (see Chapter 69 for a full discussion of these diseases).¹⁷¹⁻¹⁷³ Involvement of the pulmonary vasculature commonly results in episodes of alveolar hemorrhage. This alveolar bleeding is often focal; DAH is unusual. Pathologic specimens of the lung in lymphangioleiomyomatosis and tuberous sclerosis typically demonstrate focal areas of hemorrhage and hemosiderin deposition.

RARE INFILTRATIVE DISORDERS OF THE LUNG

NEUROFIBROMATOSIS

There are two clinically and genetically distinct forms of neurofibromatosis termed “neurofibromatosis 1” and “neurofibromatosis 2.” Lung disease is generally associated with neurofibromatosis 1, also known as von Recklinghausen disease.¹⁷⁴ Neurofibromatosis 1 is an autosomal dominant disease caused by mutations in the *NF1* gene at 17q11 and is characterized clinically by the appearance of cutaneous café au lait spots, subcutaneous neurofibromas, and Lisch nodule in the iris. The thoracic manifestations of neurofibromatosis are listed in Table 67-4. Interstitial lung disease arises in 10% to 20% of affected patients, with dyspnea appearing between the third and the sixth decades.¹⁷⁵⁻¹⁷⁹ Lower zone interstitial disease is the rule, with bullous disease eventually appearing in the upper zones.¹⁸⁰ Physiologic testing early in the course of the disease reveals restrictive ventilatory impairment, but with time, an obstructive lung disease supervenes, because the fibrotic

Table 67-4 Thoracic Manifestations of Neurofibromatosis

LUNG PARENCHYMAL

Interstitial lung disease
Metastatic neural tumor

MEDIASTINAL

Meningocele
Vagal nerve neurofibroma

CHEST WALL

Subcutaneous neurofibromas
Rib notching (inferior) from intercostal neurofibroma
Kyphoscoliosis
Apical neurofibroma (Pancoast syndrome)

process in the lung involves not only the interstitium but also the small airways. Histopathologic examination reveals cellular and fibrotic interstitial pneumonia.¹⁷⁵ Scar carcinoma has been reported as a complication of neurofibromatosis.¹⁷⁸

HERMANSKY-PUDLAK SYNDROME

Hermansky-Pudlak syndrome is an autosomal recessive disorder characterized by oculocutaneous albinism and bleeding, found predominantly in inhabitants of Puerto Rico and southern Holland.¹⁸¹⁻¹⁸³ The biochemical defect is unknown, although putatively responsible genes have been identified and several mutations have been reported.¹⁸⁴ In patients with this disease, there is an accumulation of a chromolipid ceroid (related to lipofuscin) in the reticuloendothelial system. This results in partial tyrosine-negative albinism and a qualitative platelet defect. In addition, granulomatous colitis and progressive pulmonary fibrosis develop.

The interstitial lung disease is more common in women and develops during the second through fourth decades.¹⁸² It progresses slowly and is unresponsive to treatment. Spirometry and measurement of lung volumes reveal restrictive lung disease. Chest radiography shows reticular opacities that progress to radiographic honeycombing over time. The histologic appearance is one of extensive interstitial fibrosis with filling of the alveolar spaces by ceroid-containing macrophages. These macrophages are identified in BAL and by subsequent staining with the Fontana-Masson silver reduction technique. No effective medical treatment of the interstitial lung disease has been reported.¹⁸⁵

DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DKC) is a rare inherited condition consisting most generally of mucocutaneous features, including nail dystrophy, skin pigmentation, and oral leukoplakia.^{186,187} Mutations in the genes encoding telomerase and telomere maintenance have been identified in nearly 50% of patients with this disease. Most patients with DKC are male, suggesting an X-linked pattern of inheritance.¹⁸⁸ Telomere length is important to control of cell division, and shortening of telomeres (either due to aging or inherited abnormalities) eventually leads to cellular senescence. In

DKC this most commonly manifests as bone marrow failure (isolated cytopenias to aplastic anemia).

Pulmonary fibrosis has been described in patients with DKC.¹⁸⁹ This was initially described in patients following bone marrow transplant and may have been the result of increased susceptibility to chemotherapy-related pulmonary toxicity.¹⁹⁰ Since that time, additional cases of pulmonary fibrosis in patients with DKC have been reported.¹⁹¹ There is little information on the histopathologic appearance of these cases. Approximately 11% of deaths in one cohort were due to pulmonary complications, with another 11% of deaths due to pulmonary complications of bone marrow transplantation.¹⁹¹

GAUCHER DISEASE

Gaucher disease results from a deficiency in the enzyme glucocerebrosidase, a central component of ganglioside catabolism. The infantile form of Gaucher disease, a hereditary disorder that is most common in Ashkenazi Jewish persons, is uniformly fatal because of central nervous system involvement. However, the adult form (type 1 disease) is relatively benign and is associated with good long-term survival. This condition presents with hepatosplenomegaly, anemia, thrombocytopenia, long-bone erosions, and an increase in serum acid phosphatase level. It is an autosomal recessive disease, the pathologic hallmark being the Gaucher cell. The Gaucher cell is a reticuloendothelial cell with a foamy cytoplasm due to the accumulation of glucocerebrosides. This leads to an excessive deposition of glucocerebrosides in the reticuloendothelial system, bone marrow, central nervous system, and occasionally the lung.

Pulmonary disease develops in only a small minority of adult cases.¹⁹²⁻¹⁹⁴ Parenchymal disease, which consists of radiographically visible small nodules, appears during the first 3 decades of life. Pathologic examination reveals conglomerate masses of glucocerebroside-filled macrophages in the alveolar spaces and infiltrating the interstitium. Remarkably, there is limited to no acute or chronic inflammation or fibrosis. In addition to interstitial lung disease, affected patients are susceptible to lung infection. A single case of pulmonary hypertension from diffuse small vessel obstruction by these cells has been reported.¹⁹⁵ Although enzyme replacement (glucocerebrosidase) has therapeutic promise for many of the manifestations of Gaucher disease, the interstitial lung disease appears unresponsive.¹⁹⁶

NIEMANN-PICK DISEASE

Niemann-Pick disease results from a deficiency of sphingomyelinase that causes accumulation of sphingomyelin in the cells of the reticuloendothelial and central nervous systems.¹⁹⁷ As in Gaucher disease, there is an infantile form of Niemann-Pick disease that is rapidly fatal. The adult form (type B disease), which appears during the second and third decades, is relatively benign, presenting with hepatosplenomegaly, hemostatic defects, platelet dysfunction, and occasionally, cerebellar ataxia. Interstitial lung disease, which appears as diffuse nodular opacities on imaging (eFig. 67-12), is usually asymptomatic, although a mild restrictive ventilatory defect and reduced diffusing capacity

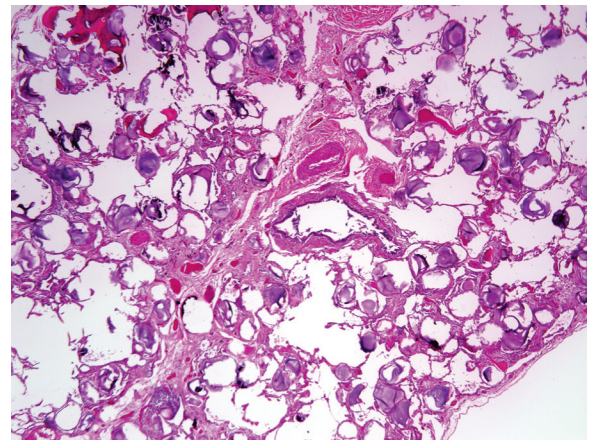


Figure 67-12 Histopathologic findings of pulmonary alveolar microlithiasis. Alveolar spaces are filled by lamellated, rounded microliths. (Courtesy Dr. Kirk Jones, University of California, San Francisco.)

have been reported.^{198,199} As in Gaucher disease, collections of foamy alveolar macrophages are found on lung biopsy. Bronchial casts can be observed as a feature of Niemann-Pick disease, and extraction of bronchial casts and whole-lung lavage may facilitate clinical and radiologic improvement in such patients.²⁰⁰

PULMONARY ALVEOLAR MICROLITHIASIS

Pulmonary alveolar microlithiasis is an idiopathic rare disease in which concretions composed of calcium and phosphorus collect in alveolar spaces (Fig. 67-12).^{201,202} In more than 50% of cases, a familial association is found.²⁰³ A systemic disorder of calcium metabolism has not been identified, and the serum calcium and phosphate levels are normal. Most authors believe that the responsible mechanism is an inborn error of calcium metabolism that is confined to the lung and leads to precipitation of the salts.

Most cases of pulmonary alveolar microlithiasis are diagnosed during the third through fifth decades. Among familial cases, women are affected more often than men, but there is an equal distribution among the sporadic cases.^{203,204} Cough and dyspnea are the most common presenting symptoms. Expectorated microliths have been reported.²⁰¹ Inspiratory crackles, finger clubbing, and signs of cor pulmonale may be present in more advanced disease.

The chest radiograph is characteristic and shows diffuse bilateral calcific opacities with predilection for the lower lung zone (eFig. 67-13A). This opacity is alveolar, producing air bronchograms and radiographic obliteration of the heart borders, pulmonary vessels, and diaphragmatic surfaces.²⁰⁵ Chest CT (see eFig. 67-13B-I; Video 67-1) often demonstrates widespread intra-alveolar calcified nodules with a lower lobe and subpleural predominance, although early disease can be less conspicuous (Fig. 67-13).^{206,207} Pulmonary function remains normal or only slightly impaired for a prolonged period after disease detection.²⁰⁸ With time, the alveolar walls become fibrotic, and a restrictive ventilatory defect with a reduced DL_{CO} develops. Technetium-99m bone scintigraphy or transbronchial lung biopsy can provide confirmation of the diagnosis.^{209,210} Treatment is supportive. Whole-lung lavage has been tried without benefit.²¹¹

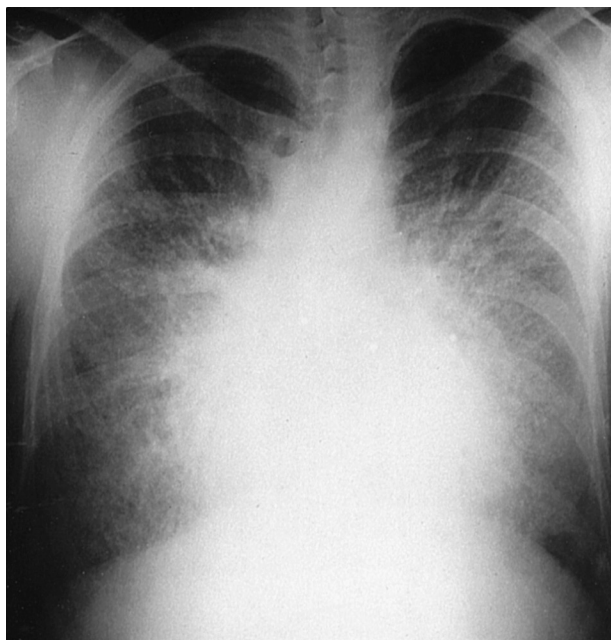


Figure 67-13 Pulmonary alveolar microlithiasis. Chest radiograph showing the widespread intraalveolar deposition of calcium-containing microliths, with a lower lobe predominance.

Key Points

- *Diffuse alveolar hemorrhage* (DAH) is a medical emergency that often results in acute respiratory failure and death.
- The classic clinical presentation of DAH includes hemoptysis, alveolar opacities on chest radiograph, and anemia.
- Many of the disorders causing DAH appear to be immunologically mediated, either through injury to the capillary basement membrane by specific autoantibody or through deposition of immune complexes.

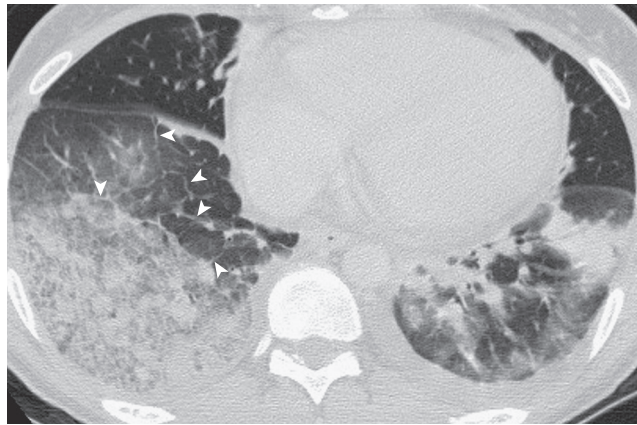
- Bronchoscopy with serial bronchoalveolar lavage is essential to the accurate identification of DAH.
- Many cases of DAH demonstrate neutrophilic inflammation of the alveolar interstitium known as capillaritis.
- The presence of proteinuria and an abnormal urinary sediment (red blood cells and red blood cell casts) suggests an underlying glomerulonephritis consistent with the diagnosis of systemic vasculitis or Goodpasture syndrome (anti-glomerular basement membrane antibody disease).
- Accurate diagnosis is essential because aggressive treatment with corticosteroids, cytotoxic agents, rituximab, and plasmapheresis (alone or in combination) is often helpful.

Complete reference list available at *ExpertConsult*.

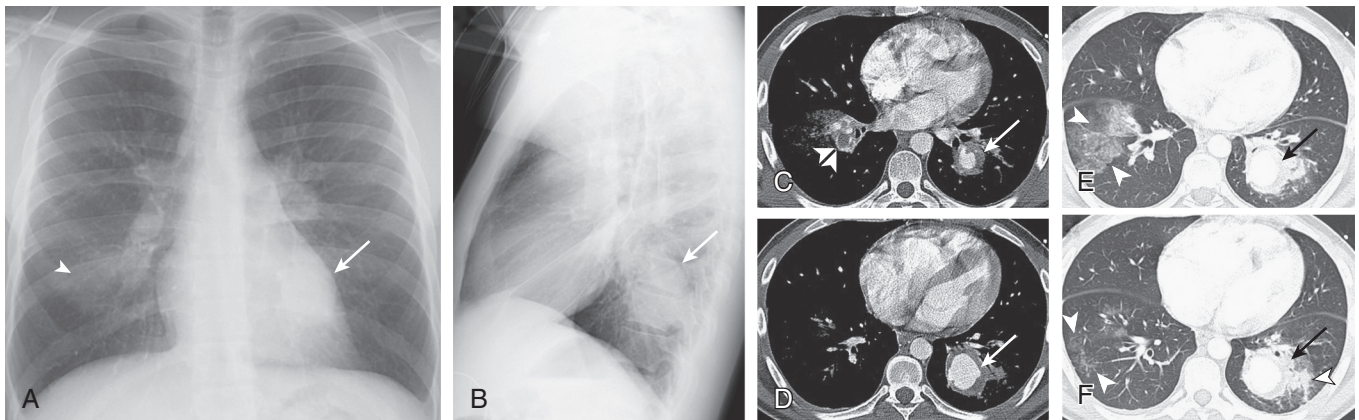
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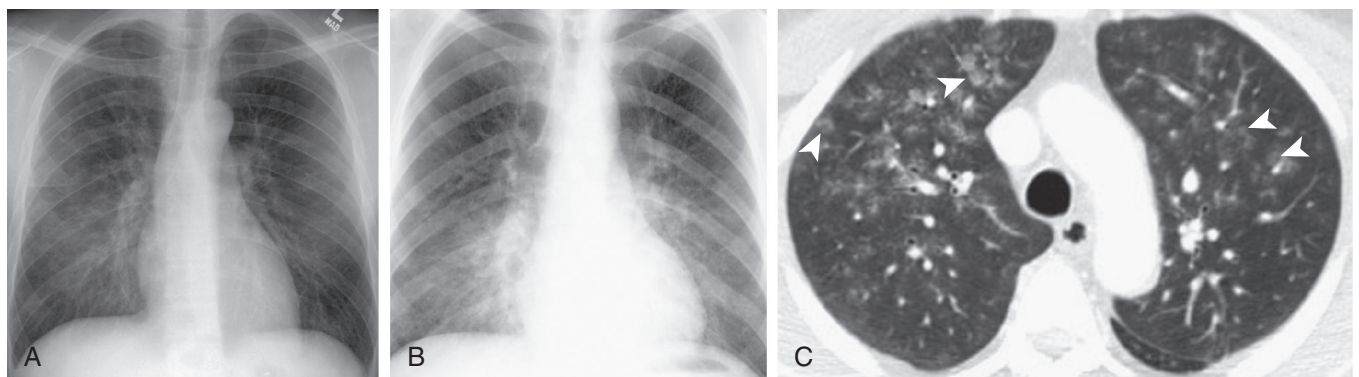
eFIGURE IMAGE GALLERY



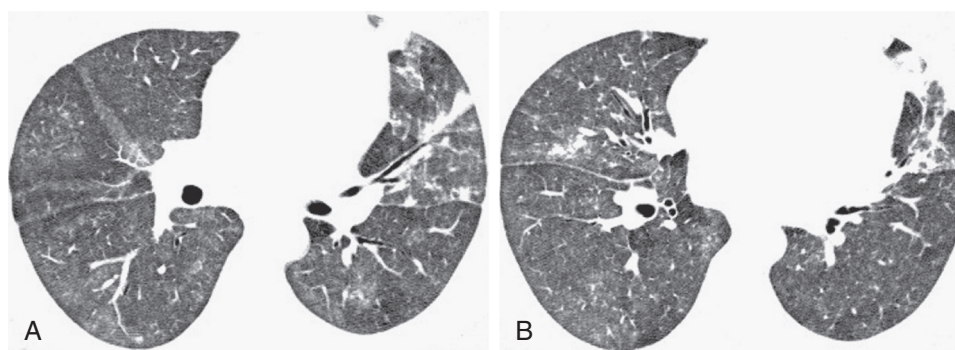
eFigure 67-1 Diffuse alveolar hemorrhage with smooth interlobular septal thickening. Axial chest CT image displayed in lung windows shows multifocal ground-glass opacity and consolidation associated with smooth linear opacities (*arrowheads*), representing interlobular septal thickening. (Courtesy Michael Gotway, MD.)



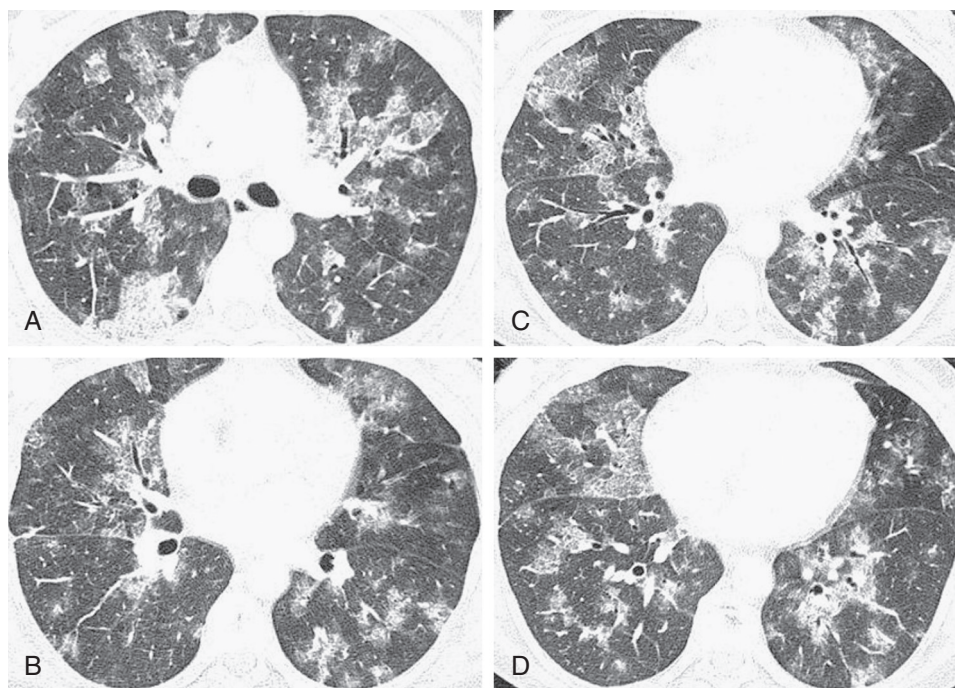
eFigure 67-2 Behçet disease: chest radiographic and chest CT manifestations. Frontal (**A**) and lateral (**B**) chest radiographs show left hilar enlargement associated with a left lower lobe mass (*arrow*) representing a pulmonary artery aneurysm as well as patchy areas of ground-glass opacity best seen in the right lower lobe (*arrowhead*), reflecting pulmonary hemorrhage. **C-F**, Axial enhanced chest CT displayed in soft tissue (**C** and **D**) and lung (**E** and **F**) windows shows a left lower lobe pulmonary artery aneurysm (*arrow*). Thrombosis is seen in the caudal portion of a right pulmonary artery aneurysm (*double arrowhead*, **C**). Ground-glass opacity (*single arrowheads*, **E** and **F**) represents hemorrhage surrounding the pulmonary artery aneurysms. (Courtesy Michael Gotway, MD.)



eFigure 67-3 Diffuse alveolar hemorrhage in Goodpasture syndrome (ABMA disease): chest radiography and chest CT findings. **A** and **B**, Frontal chest radiographs of two different patients with Goodpasture syndrome show multifocal bilateral, hazy ground-glass opacity representing pulmonary hemorrhage. These findings are slightly denser and more prominent in the perihilar area in the second patient (**B**). **C**, Axial chest CT displayed in lung window (same patient as in **A**) shows multifocal, poorly defined ground-glass opacity centrilobular nodules (*arrowheads*), reflecting recurrent pulmonary hemorrhage. (Courtesy Michael Gotway, MD.)



eFigure 67-4 Diffuse alveolar hemorrhage in systemic lupus erythematosus: chest CT findings. A and B, Axial chest CT displayed in lung windows shows multifocal, poorly defined ground-glass opacity and lingular consolidation, reflecting pulmonary hemorrhage. The findings are not specific for the cause of the hemorrhage, because diffuse alveolar hemorrhage from any cause can manifest in this fashion. (Courtesy Michael Gotway, MD.)



eFigure 67-5 Diffuse alveolar hemorrhage in antiphospholipid antibody syndrome: chest CT findings. A–D, Axial chest CT displayed in lung windows shows multifocal, poorly defined ground-glass opacity associated with mild, smooth interlobular septal thickening, reflecting multifocal pulmonary hemorrhage. (Courtesy Michael Gotway, MD.)

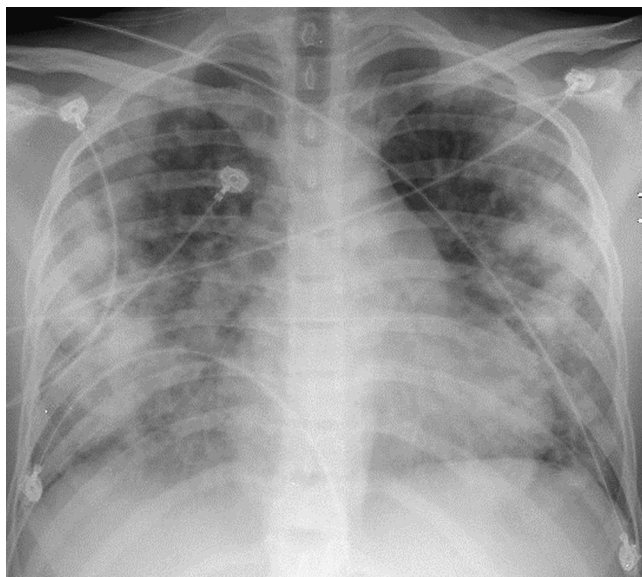


Figure 67-6 Diffuse alveolar hemorrhage in acute leukemia. Frontal chest radiograph shows multifocal, bilateral, peripherally predominant consolidation, proven to represent diffuse alveolar hemorrhage. (Courtesy Michael Gotway, MD.)

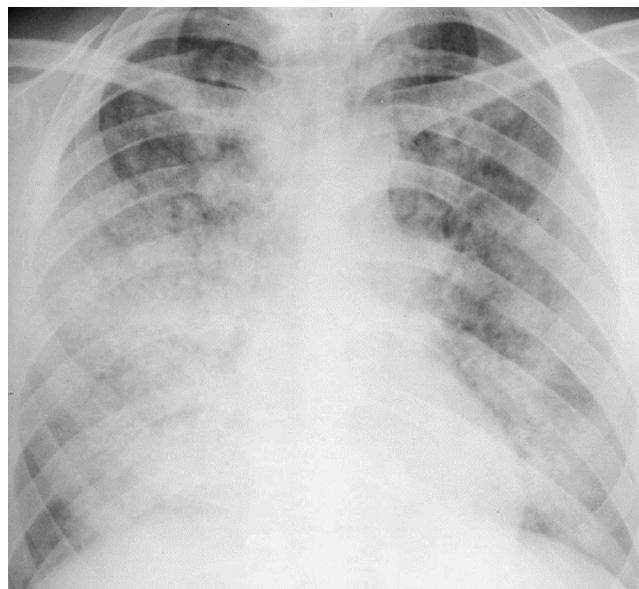


Figure 67-7 Idiopathic pulmonary hemosiderosis syndrome. Frontal chest radiograph shows multifocal, bilateral, dense consolidation, proven to reflect diffuse alveolar hemorrhage. (Courtesy Michael Gotway, MD.)

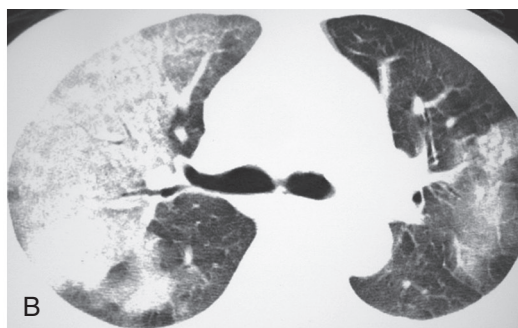
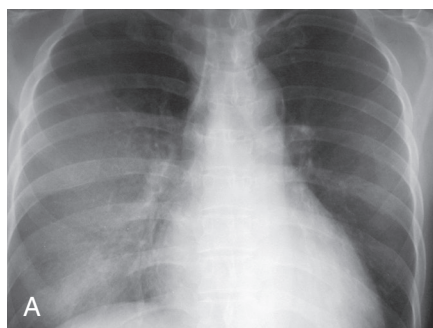


Figure 67-8 Idiopathic pulmonary hemosiderosis syndrome: chest radiography and chest CT findings. **A**, Frontal chest radiograph shows multifocal, bilateral, right-greater-than-left ground-glass opacity found to reflect pulmonary hemorrhage. **B**, Axial chest CT displayed in lung window shows multifocal, bilateral ground-glass opacity associated with smooth interlobular septal thickening, typical of alveolar hemorrhage, correlating with the chest radiographic findings. (Courtesy Michael Gotway, MD.)

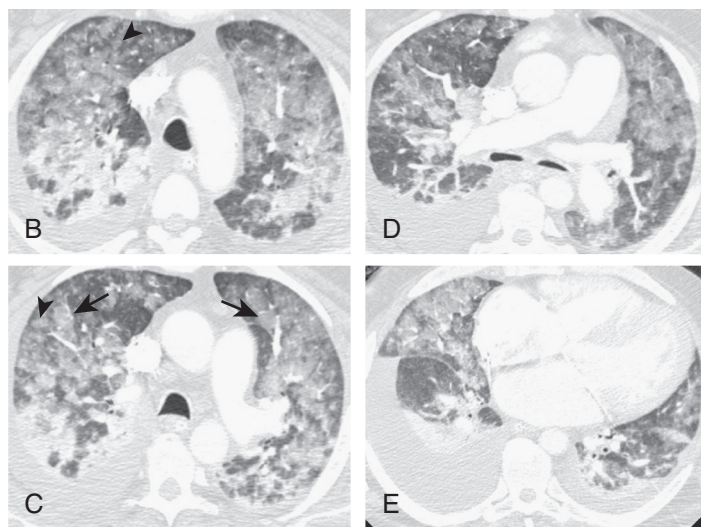
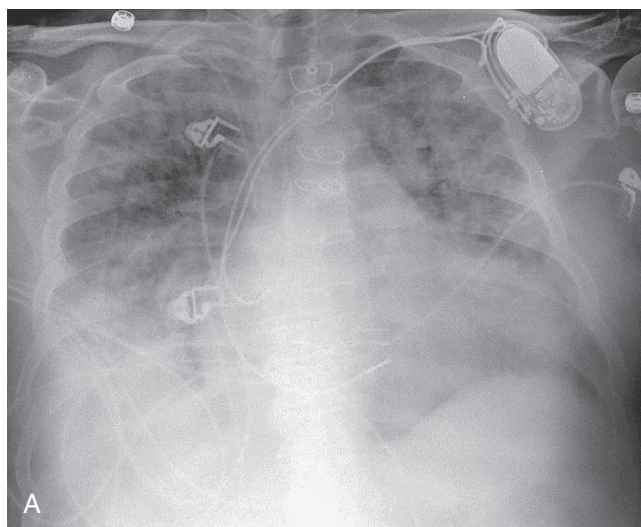
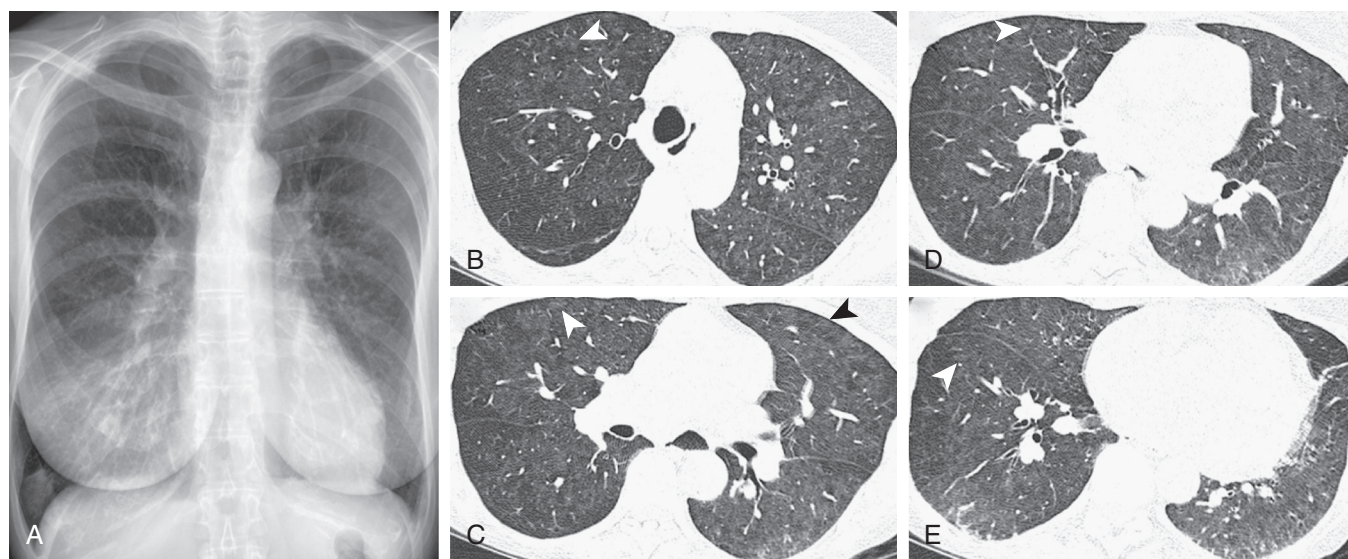
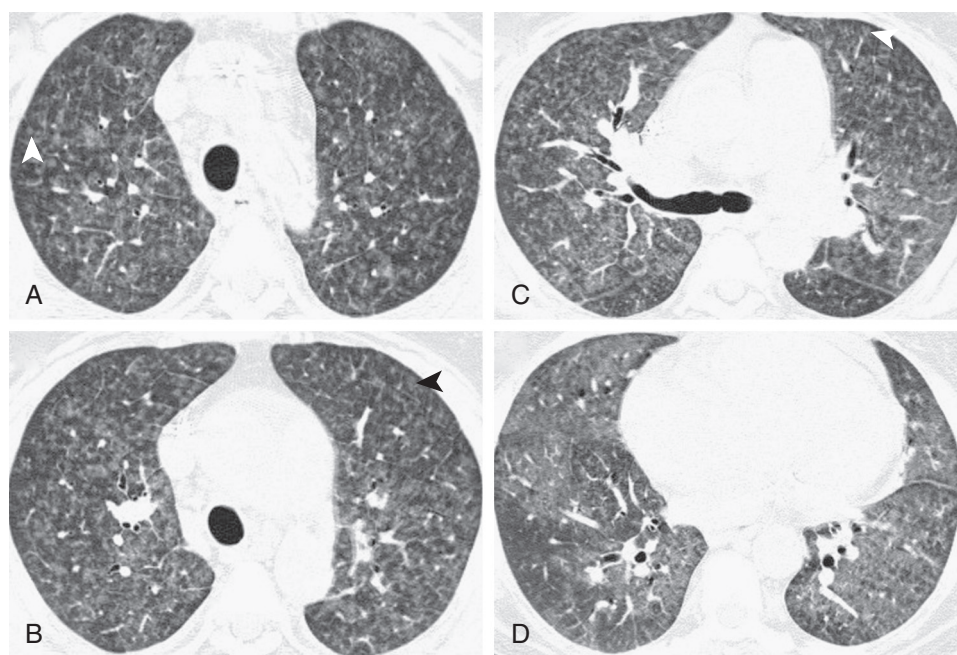


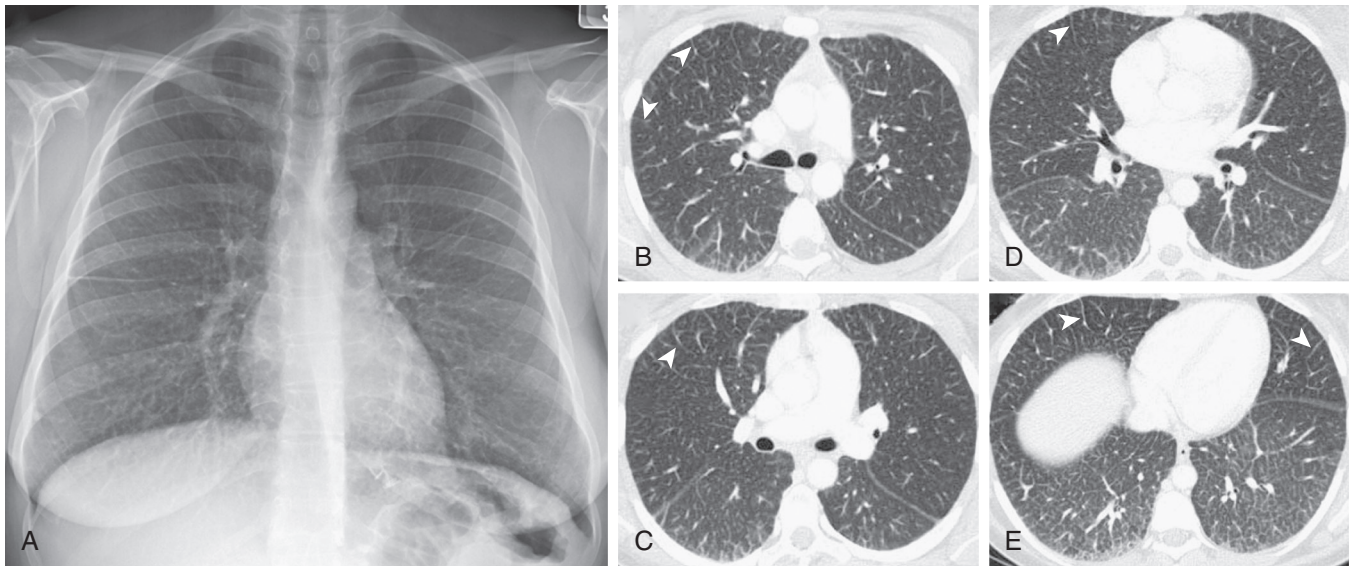
Figure 67-9 Diffuse alveolar hemorrhage in a patient with mitral stenosis. **A**, Frontal chest radiograph shows extensive bilateral consolidation and peribronchovascular infiltration in a patient with cardiomegaly and sternotomy. **B–E**, Axial chest CT displayed in lung windows shows multifocal areas of ground-glass opacity, in some areas centrilobular (*arrowheads*) and in others more lobular (*arrows*). Areas of consolidation and pleural effusions are also present. The appearance is very suggestive of, though not specific for, pulmonary hemorrhage. (Courtesy Michael Gotway, MD.)



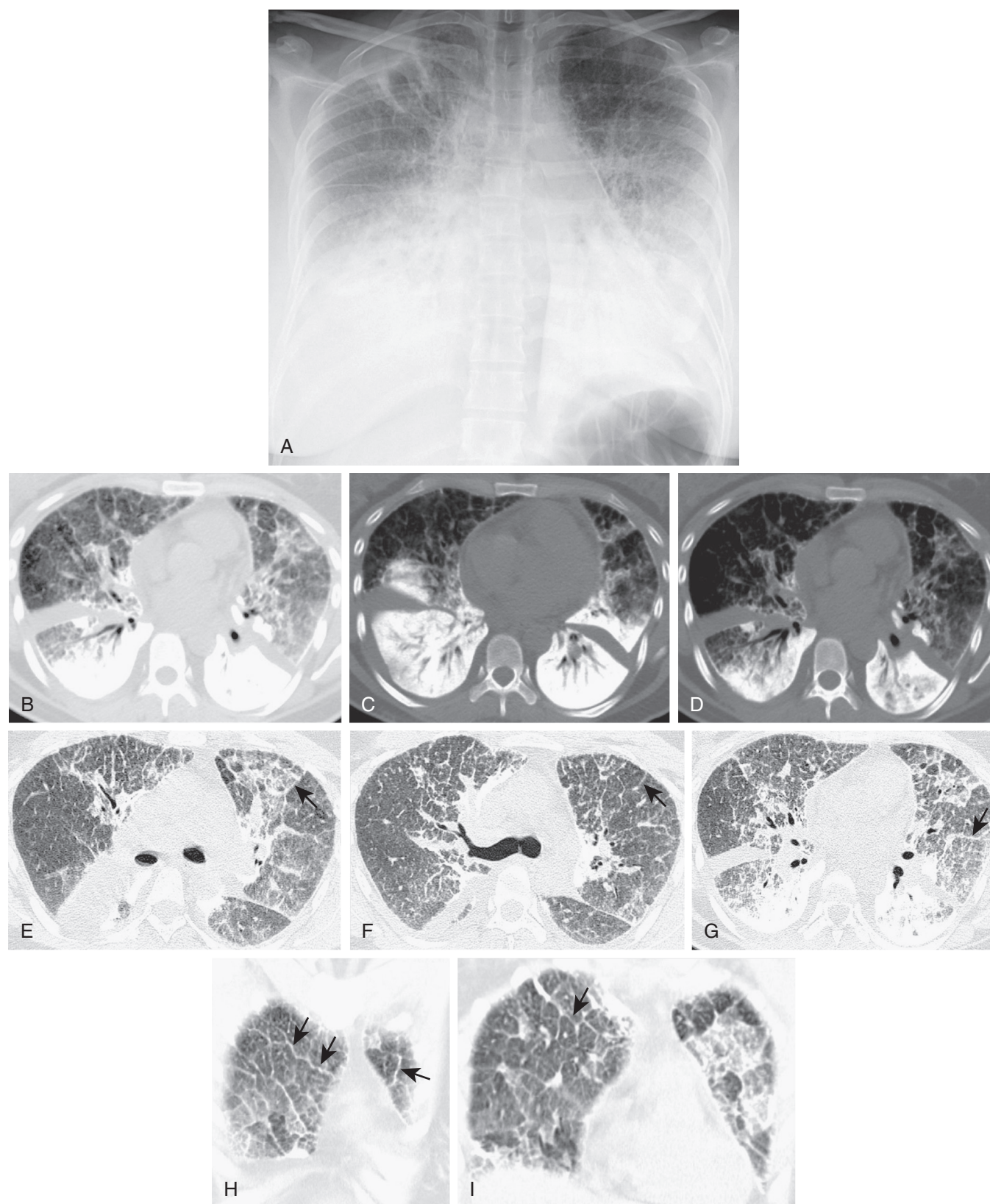
eFigure 67-10 Pulmonary capillary hemangiomatosis: chest radiography and chest CT findings. Frontal chest radiograph (A) and axial chest CT displayed in lung windows (B–E) show multifocal, bilateral ground-glass opacity, in some areas with a centrilobular appearance (arrowheads). (Courtesy Michael Gotway, MD.)



eFigure 67-11 Pulmonary capillary hemangiomatosis: chest CT findings. A–D, Axial chest CT displayed in lung windows shows multifocal, bilateral ground-glass opacity centrilobular nodules (arrowheads). The ground-glass opacity is more confluent-appearing in the bases (D). (Courtesy Michael Gotway, MD.)



eFigure 67-12 Niemann-Pick disease: chest radiographic and chest CT findings. **A**, Frontal chest radiograph in a 34-year-old patient with Niemann-Pick disease type B shows fine, symmetric, basal predominant reticulation. Lung volumes are normal, and no pleural disease is evident. **B–E**, Axial chest CT displayed in lung windows shows smooth interlobular septal thickening (*arrowheads*), becoming particularly pronounced in the bases bilaterally. (Courtesy Dr. Eric A. Jensen, Mayo Clinic, Arizona.)



eFigure 67-13 Pulmonary alveolar microlithiasis: chest radiographic and chest CT findings. **A**, Frontal chest radiograph shows bilateral, extensive, hyperattenuating basal consolidation associated with extensive linear opacity radiating from the hila. A right apical cavity (a finding unrelated to pulmonary alveolar microlithiasis) is present. **B–D**, Axial chest CT displayed in lung (**B**) and bone (**C** and **D**) windows shows calcified basal consolidation. Extensive interlobular septal thickening, in some areas hyperattenuating, is present. **E–G**, Axial high-resolution chest CT displayed in lung windows shows the extensive interlobular septal thickening (*arrows*), which is also seen to advantage on the coronal reformatted images (**H** and **I**). (From Panse PM, Jensen EA, Gruden JF, Gotway MB: Pulmonary parenchymal consolidation at thoracic CT: clues to a specific diagnosis. *Clin Pulm Med* 21[2]:104–106, 2014.)

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INTRODUCTION**EOSINOPHIL BIOLOGY****GENERAL FEATURES OF EOSINOPHILIC PNEUMONIAS**

Historical Perspective

Clinical Presentation

Pathology

Diagnosis

EOSINOPHILIC LUNG DISEASE OF UNDETERMINED CAUSE

Idiopathic Chronic Eosinophilic Pneumonia

Idiopathic Acute Eosinophilic Pneumonia

Eosinophilic Granulomatosis with Polyangiitis

Hypereosinophilic Syndrome

Idiopathic Hypereosinophilic Obliterative Bronchiolitis

EOSINOPHILIC LUNG DISEASE OF DETERMINED CAUSE

Eosinophilic Pneumonias of Parasitic Origin

Eosinophilic Pneumonias of Other Infectious Causes

Allergic Bronchopulmonary Aspergillosis and Related Syndromes

DRUG-, TOXIC AGENT-, AND RADIATION-INDUCED EOSINOPHILIC PNEUMONIAS

Drugs

Radiation Therapy

MISCELLANEOUS LUNG DISEASES WITH ASSOCIATED EOSINOPHILIA

Organizing Pneumonia

Asthma and Eosinophilic Bronchitis

Idiopathic Interstitial Pneumonias

Langerhans Cell Histiocytosis

Lung Transplantation

Other Lung Diseases with Occasional Eosinophilia

INTRODUCTION

The eosinophilic lung diseases are a group of disorders (Table 68-1) characterized by the presence and presumed pathogenetic role of eosinophils in the disease processes. They are mainly represented by the eosinophilic pneumonias, which are defined by a prominent infiltration of the lung parenchyma by eosinophils. The other eosinophilic lung diseases mainly involve the airways, as in the allergic bronchopulmonary mycoses and hypereosinophilic obliterative bronchiolitis. Asthma, in which the eosinophil plays an important role, is not discussed in this chapter.

EOSINOPHIL BIOLOGY

The role of the eosinophil in homeostasis function, physiology, and pathophysiology has become better appreciated in recent years.¹⁻³ Eosinophils are multifunctional leukocytes implicated in innate and adaptive immunity, including numerous inflammatory reactions to parasitic helminth, bacterial, and viral infections.³ They have been especially credited with a beneficial role in parasitic infestation; however, results from in vivo infection studies have given conflicting results.⁴

The eosinophil^{1-3,5} matures in the bone marrow under the action of cytokines and especially of *interleukin* (IL)-5 (involved in the differentiation of eosinophil precursors), IL-3, and *granulocyte-macrophage colony-stimulating factor* (GM-CSF) and the activation of transcription factors including *Adbl-GATA-1*. The eosinophil then circulates in the blood for about 1 day before being attracted into tissues by complex processes including adhesion and attraction, diapedesis, and chemotaxis, where it undergoes apoptosis unless survival factors are present.

Major advances have been made in the understanding of molecular and intracellular pathways regulating eosinophil

differentiation, priming, activation, degranulation, and mediator secretion (with especially the role of vesicle-associated membrane proteins in the regulation of granule fusion in eosinophils).⁵ The eosinophil contains two types of intracytoplasmic granules. The larger granules, characterized by an electron-dense crystalloid matrix, contain the characteristic cationic proteins, which have direct toxicity to the heart, brain, and bronchial epithelium. The smaller amorphous granules contain arylsulfatase and acid phosphatase. Activation of the eosinophil results in degranulation with the extracellular release of the eosinophil-specific proteins, including *major basic protein* (MBP), eosinophil cationic protein, eosinophil-derived neurotoxin, and the enzymatic protein *eosinophil peroxidase* (EPO). The finding of vacuoles in the cytoplasm of the eosinophil and ultrastructural evidence of loss of electron density from the central core of the granules (inversion or disappearance of core density) morphologically characterizes the process of degranulation. Eosinophils also release proinflammatory cytokines, arachidonic acid-derived mediators, enzymes, reactive oxygen species, and matrix metalloproteases. They express a variety of surface proteins, including adhesion molecules, apoptotic signaling molecules, chemokines, complement receptors, chemotactic factor receptors, cytokine receptors, and immunoglobulin receptors. The release of toxic substances in itself contributes to the pathophysiology of eosinophilic disorders.

Many biologic properties of the eosinophil are directed by *T helper* (Th) lymphocytes, but the eosinophil interacts in many allergic or inflammatory processes with other cells including mast cells and basophils, endothelial cells, macrophages, platelets, and fibroblasts. Eosinophils are capable of regulating mast cell function and histamine release. Activated eosinophils express the major histocompatibility complex II protein *human leukocyte antigen*, (HLA)-DR, and possess the ability to participate in numerous immune functions, including antigen presentation and secretion of an

Table 68-1 Classification of the Eosinophilic Lung Diseases**EOSINOPHILIC LUNG DISEASE OF UNDETERMINED CAUSE**

Idiopathic eosinophilic pneumonias
 Idiopathic chronic eosinophilic pneumonia (ICEP)
 Idiopathic acute eosinophilic pneumonia (IAEP)
 Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
 Hypereosinophilic syndrome (HES)
 Idiopathic hypereosinophilic obliterative bronchiolitis

EOSINOPHILIC LUNG DISEASE OF DETERMINED CAUSE

Eosinophilic pneumonias of parasitic origin
 Tropical eosinophilia
Ascaris pneumonia
 Eosinophilic pneumonia in larva migrans syndrome
Strongyloides stercoralis infection
 Eosinophilic pneumonias in other parasitic infections
 Eosinophilic pneumonias of other infectious causes
 Allergic bronchopulmonary aspergillosis and related syndromes
 Allergic bronchopulmonary aspergillosis
 Other allergic bronchopulmonary syndromes associated with fungi or yeasts
 Bronchocentric granulomatosis
 Drug-, toxic agent-, and radiation-induced eosinophilic pneumonias
 Drugs (typical, occasional, or exceptional eosinophilic pneumonia)
 Toxic agents (toxic oil syndrome, L-tryptophan)
 Eosinophilic pneumonia induced by radiation therapy to the breast

MISCELLANEOUS LUNG DISEASES WITH POSSIBLE ASSOCIATED EOSINOPHILIA

Organizing pneumonia
 Asthma and eosinophilic bronchitis
 Idiopathic interstitial pneumonias
 Langerhans cell histiocytosis
 Lung transplantation

array of cytokines capable of promoting effector T-cell proliferation. In addition, eosinophils are implicated in the regulation of Th1/Th2 balance, through synthesis of IL-4, promotion of IL-4, IL-5, and IL-13 secretion by CD4⁺T cells, as well as the synthesis of indoleamine 2,3-dioxygenase (indirectly promoting Th1 apoptosis). Identification of the immune and multifunction properties of the eosinophil has changed the view on eosinophils, from a terminal effector cell in allergic airway diseases to the current paradigm of eosinophils being involved in the initial stages of disease development.⁶ In addition, abnormalities in the T-cell receptor repertoire and T-cell clonotype of *bronchoalveolar lavage* (BAL) lymphocytes and peripheral blood lymphocytes might contribute to the pathophysiology of eosinophilic lung diseases.⁷⁻⁹

Recruitment of the eosinophil to the lung mostly implicates IL-5 and the eotaxin subfamily of chemokines (itself regulated by the Th2 cell–derived IL-13 cytokine). Release of toxic granule proteins and lipid mediators by eosinophils may contribute to tissue damage and dysfunction. Although histopathologic lesions related to the release of toxic granule proteins and lipid mediators in eosinophilic pneumonias are largely reversible with treatment, tissue damage and remodeling with fibrosis (partly through the release of transforming growth factor- β by eosinophils) associated with eosinophil infiltration can take place, especially in the bronchial mucosa, as in *allergic bronchopulmonary aspergillosis* (ABPA) and in *eosinophilic granulomatosis with polyangiitis* (Churg-Strauss syndrome) (EGPA [CSS]). Corticosteroids are the most effective agents for dramatically reducing

eosinophilia in the blood and tissues by shortening the half-life of cytokines such as eotaxins and inhibiting the cytokine-dependent survival of eosinophils.

Major impediments in eosinophil research are the inability of murine eosinophils to degranulate either in vivo or in vitro in contrast with human eosinophils that differentially release their granule proteins after contact with different stimuli and the limits of animal models in mimicking human eosinophilic lung disease. The availability of humanized anti-IL-5 antibody, which lowers eosinophil levels in the blood and in the lung in humans, as well as of genetically engineered mice such as those deficient in IL-5 or in eosinophils, has contributed to a better understanding of the pathogenic role of eosinophils.¹⁰ Recent advances in eosinophil biology and drug design have led to the design of a variety of potential therapeutic agents that target eosinophil-specific molecules and which are the focus of active research in patients with hypereosinophilic diseases.¹¹ The most promising targets currently being investigated include IL-5 and IL-5R, CD2 binding protein, *immunoglobulin E* (IgE), and IL-4/IL-13 receptor, with a few agents already evaluated or routinely used clinically.

GENERAL FEATURES OF EOSINOPHILIC PNEUMONIAS

HISTORICAL PERSPECTIVE

In 1952, Reeder and Goodrich¹² published a series of cases describing pulmonary “infiltration with eosinophilia,” including probable *idiopathic chronic eosinophilic pneumonia* (ICEP) and EGPA. Crofton and coworkers¹³ published in the same year a series of 16 cases of “pulmonary eosinophilia” with a review of 450 cases from the literature and proposed the following classification:

1. Simple pulmonary eosinophilia (Löffler syndrome), defined by mild symptoms and transient opacities.
2. Prolonged pulmonary eosinophilia characterized by radiographic shadows persisting for longer than 1 month.
3. Tropical eosinophilia.
4. Pulmonary eosinophilia with asthma (a rather heterogeneous category).
5. Polyarteritis nodosa.

The authors mentioned “a continuum from the simple and transient abnormalities of Löffler syndrome to the severe and often fatal manifestations of polyarteritis nodosa.” Churg and Strauss had reported in 1951¹⁴ the eponym syndrome of “allergic granulomatosis, allergic angiitis, and periarteritis nodosa,” and Carrington and colleagues¹⁵ described in 1969 the syndrome of ICEP. McCarthy and Pepys¹⁶ later reported 27 cases of “cryptogenic pulmonary eosinophilias,” 2 of whom developed systemic vasculitis.

CLINICAL PRESENTATION

Eosinophilic pneumonia is a pneumonia where the eosinophils are the most prominent inflammatory cells on histopathologic examination. Other inflammatory cells,

especially lymphocytes and neutrophils, are often associated, but eosinophils clearly predominate. In clinical practice, the eosinophilic pneumonias may be separated into two main etiologic categories: (1) those in which a definite cause is found or (2) those of undetermined origin, that is, idiopathic (with the eosinophilic pneumonia being either solitary or included in a systemic disorder such as EGPA).

A definite cause must be carefully investigated in any patient with eosinophilic pneumonia because it has practical consequences (e.g., stopping a drug responsible for iatrogenic eosinophilic pneumonia or treating a parasitic infection). When no cause is identified, the eosinophilic pneumonias may usually be included within well-characterized and individualized syndromes.

The eosinophilic pneumonias may manifest by different clinico-radiologic syndromes, namely Löffler syndrome, chronic eosinophilic pneumonia, or acute eosinophilic pneumonia, mostly differing from one another by the pattern of disease onset. Extrapulmonary manifestations accompanying eosinophilic pneumonia are the hallmark of EGPA and, to a lesser extent, *hypereosinophilic syndromes* (HESs), drug reactions, or infections, especially parasitic infections. The vast majority of cases of eosinophilic pneumonia respond dramatically to corticosteroid treatment and heal without significant sequelae.

PATHOLOGY

Histopathologic studies of eosinophilic pneumonia have mainly been done in patients with ICEP,^{15,17,18} which was initially diagnosed by open-lung biopsy. The pathologic features described in ICEP may be considered as a common denominator of all categories of eosinophilic pneumonias, whatever their origin. Occasionally, pathologic studies in eosinophilic pneumonias of known cause have further shown some specific features, such as a possible distinctive distribution of lesions (e.g., bronchocentric distribution in ABPA) or the presence of causal agents such as parasites or fungal hyphae.

In ICEP, the alveolar spaces are filled with eosinophils (Fig. 68-1). Macrophages are also present with some mul-

tinucleated giant cells scattered in the infiltrate; these may contain eosinophilic granules or Charcot-Leyden crystals.¹⁵ An associated interstitial inflammatory cellular infiltrate is invariably present, consisting of eosinophils, lymphocytes, plasma cells, and histiocytes. A proteinaceous and fibrinous exudate accompanies the cellular eosinophilic infiltrate. Some eosinophilic microabscesses may be observed (foci of necrotic intra-alveolar eosinophils surrounded by macrophages or epithelioid cells with palisading arrangement). Morphologic (especially electron microscopic) and immunohistochemical studies have shown eosinophil degranulation within the site of eosinophilic pneumonia.¹⁹ The global architecture of the lung remains intact, without necrosis or fibrosis.

Organization of the alveolar inflammatory exudate is a rather common finding,¹⁵ suggesting some possible overlap between ICEP and organizing pneumonia. However, intraluminal organization in the distal air spaces is only sparse and never prominent in ICEP. Mucus plugs obstructing the small airways may be present in ICEP.¹⁵ A mild *non-necrotizing* vasculitis involving both small arteries and venules is common, with perivascular cuffing and a few cells infiltrating the arterial media (Fig. 68-2).

The distribution of eosinophilic pneumonia is generally diffuse. However, it may be more focal in some cases, and the lesions may have an angiocentric or bronchiolocentric distribution in some etiologic groups of eosinophilic pneumonia. The hilar lymph nodes associated with ICEP contain many eosinophils, and lymphoid hyperplasia is present.¹⁵

In *idiopathic acute eosinophilic pneumonia* (IAEP), the pathologic pattern includes intra-alveolar and interstitial eosinophilic infiltrates, diffuse alveolar damage, intra-alveolar fibrinous exudates, organizing pneumonia, and non-necrotizing vasculitis (Fig. 68-3).²⁰

DIAGNOSIS

In clinical practice, the diagnosis of eosinophilic pneumonia is suspected in patients presenting with respiratory

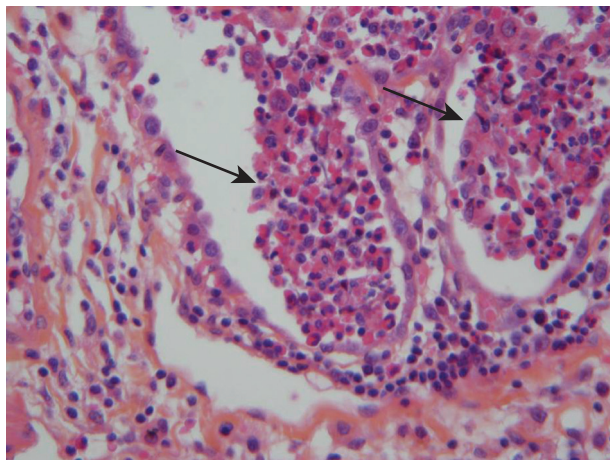


Figure 68-1 Eosinophilic pneumonia. There is an accumulation of eosinophils (arrows) within the alveoli. (Courtesy Françoise Thivolet-Béjui, MD, Department of Pathology, Louis-Pradel Hospital and Claude Bernard University, Lyon, France.)

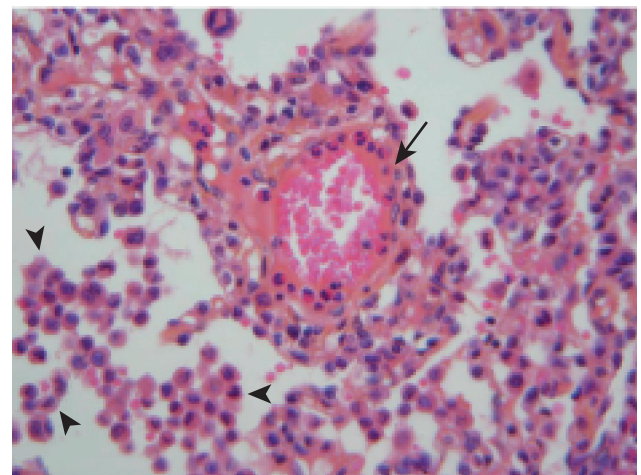


Figure 68-2 Eosinophilic pneumonia. Eosinophils have infiltrated the arteriolar wall (non-necrotizing vasculitis) (arrow) and are present within the alveoli (arrowheads). (Courtesy Françoise Thivolet-Béjui, MD, Department of Pathology, Louis-Pradel Hospital and Claude Bernard University, Lyon, France.)

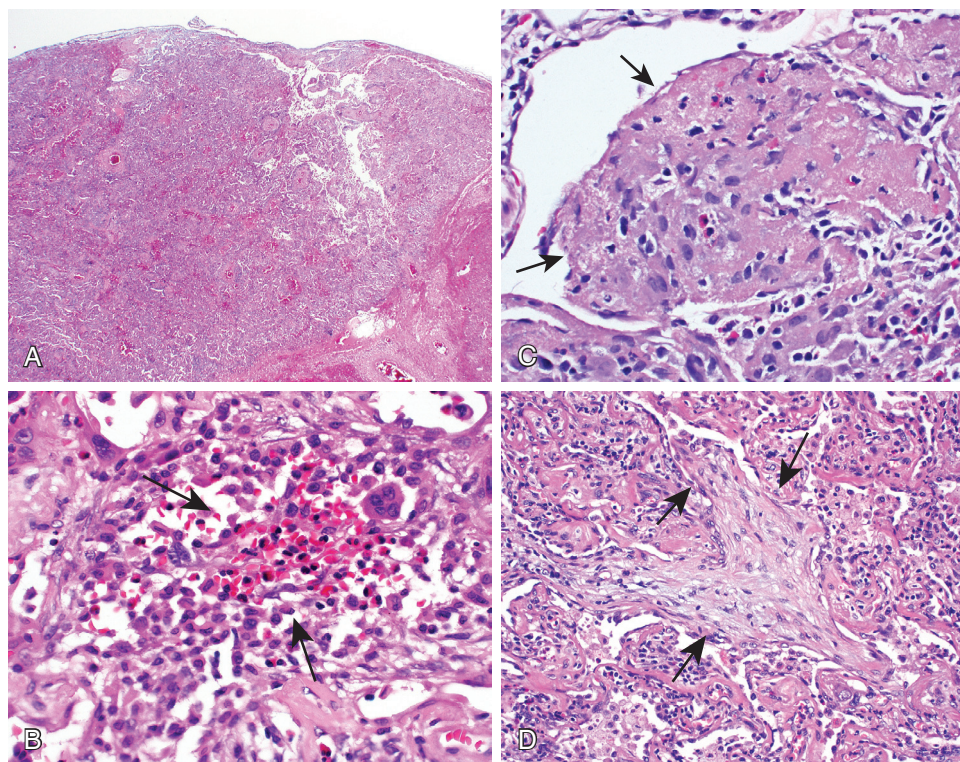


Figure 68-3 Acute eosinophilic pneumonia. **A**, In acute eosinophilic pneumonia, the alveolar spaces are diffusely filled with eosinophils and plump eosinophilic macrophages, sometimes with an associated mild interstitial pneumonia. In this low power view, multiple alveolar spaces are completely filled up to the pleural surface. **B**, Eosinophilic microabscesses (arrows) may be present. **C**, Fibrinous air space exudates (arrows) are commonly present, typically with admixed eosinophils, as seen in this specimen. **D**, Organizing pneumonia pattern with repair may also be seen (arrows). (From Leslie KO, Wick MR: Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series, ed 2. Philadelphia, 2011, Elsevier, Figs. 7-56 and 7-58.)

symptoms (dyspnea, cough, or wheezing); pulmonary opacities at chest imaging; and the demonstration of eosinophilia in the peripheral blood or, preferably, in the lung. Importantly, *blood eosinophilia* is defined by an eosinophil blood count greater than $0.5 \times 10^9/L$ ($500/\mu L$) and *hyper-eosinophilia* by an eosinophil blood count greater than $1.5 \times 10^9/L$ ($1500/\mu L$) on two examinations at least 1 month apart, and/or tissue hypereosinophilia.²¹

Although pathologic examination of the lung has been the “gold standard” to define eosinophilic pneumonia, surgical lung biopsy is almost abandoned and video-assisted thoracoscopic lung biopsy is seldom necessary. Transbronchial lung biopsy may show characteristic features of eosinophilic pneumonia, but the small size of the specimen usually does not allow morphologic evidence of a possible etiologic process.

BAL has become a widely accepted noninvasive surrogate of lung biopsy for the diagnosis in a patient with *high-resolution computed tomography* (HRCT) features of eosinophilic pneumonia, although no study has definitely established a correlation between increased eosinophils at differential cell count and the finding of eosinophilic pneumonia at lung pathology. In normal subjects, BAL eosinophilia is lower than 1% of cells at differential count.²² In contrast, BAL eosinophilia greater than 40% is found mainly in patients with chronic eosinophilic pneumonia, whereas BAL eosinophilia between 3% and 40% (and especially between 3% and 9%) may be found in various conditions, such as idiopathic pulmonary fibrosis, interstitial lung disease associated with connective tissue disorders,

hypersensitivity pneumonitis, sarcoidosis, radiation pneumonitis, asthma, pneumoconioses, and infection.²³

A conservative cutoff of 40% of eosinophils in the BAL has been adopted for the diagnosis of ICEP in clinical studies,^{24,25} and a cutoff of 25% has been proposed for the diagnosis of IAEP.²⁶ For clinical practice, our recommendation is that a diagnosis of eosinophilic pneumonia is supported by alveolar eosinophilia when the eosinophils (1) are the predominant cell population (macrophages excepted) and (2) represent more than 25% and preferably more than 40% of the differential cell count in the BAL.

Although BAL is usually a safe procedure, it may not always be mandatory in typical cases with both radiographic pulmonary opacities and peripheral blood eosinophilia, although alternative diagnoses can be considered (such as bacterial or parasitic pneumonia, or pulmonary opacities related to Hodgkin disease). However, diagnosing eosinophilic pneumonia on the sole finding of blood eosinophilia and pulmonary opacities requires markedly elevated eosinophilia ($>1 \times 10^9/L$ and preferably $1.5 \times 10^9/L$; >1000 and preferably $1500/\mu L$) together with typical clinicoradiologic features, because the finding of peripheral blood eosinophilia does not prove that the observed pulmonary opacities correspond to eosinophilic pneumonia. For example, BAL may occasionally be omitted for the diagnosis of Löffler syndrome (as it is seen in ascariasis), with rather mild and nonspecific cough and wheezes, transient pulmonary opacities at chest radiography, and frank blood eosinophilia. Conversely, peripheral blood eosinophilia may be missing in patients who have already received systemic

corticosteroids, and it is often absent at presentation in IAEP. Nevertheless, BAL is recommended to confirm the diagnosis of eosinophilic pneumonia in most cases.

Once the diagnosis of eosinophilic pneumonia has been made, a thorough evaluation is necessary to investigate possible causes, such as parasitic infection or drug or toxic exposure, and to classify the case into one of the possible clinical entities (see Table 68-1).

EOSINOPHILIC LUNG DISEASE OF UNDETERMINED CAUSE

ICEP is characterized by a progressive onset of symptoms over a few weeks with cough, increasing dyspnea, malaise, and weight loss, whereas IAEP presents as an acute pneumonia (similar to acute lung injury or *acute respiratory distress syndrome* [ARDS]) with frequent respiratory failure necessitating mechanical ventilation. Both conditions are idiopathic.

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA

Idiopathic chronic eosinophilic pneumonia (ICEP) was first described in detail by Carrington and colleagues,¹⁵ in a series of nine patients, and further confirmed and detailed by several series^{18,25,27-29} and numerous case reports.

Clinical Features

ICEP arises predominantly in women (with a 2:1 female-to-male ratio).^{18,25} Although ICEP may develop in young people,^{30,31} only 6% of patients are younger than 20 years old.^{18,31a} The incidence of ICEP peaks in the fourth decade,¹⁸ with a mean age of 45 years at diagnosis.²⁵ A vast majority of patients with ICEP are nonsmokers,^{18,25,28} suggesting that smoking might be protective. A prior history of atopy is found in about half of the patients, with allergic rhinitis in 12%¹⁸ to 24%,²⁵ drug allergy in about 10%,^{18,25} nasal polyps in 5%¹⁸ to 13%,²⁵ urticaria in 10%,²⁵ and eczema in 5%.²⁵

Prior asthma is present in up to two thirds of the patients.^{17,18,24,25,28,29} Asthma may also develop concomitantly with the diagnosis of ICEP in 15% of patients or develop after ICEP in 13%.²⁴ The presentation of ICEP is similar in asthmatic and nonasthmatic patients with the exception of higher total IgE in the former group.²⁴ ICEP may develop while asthmatic patients are on a desensitization program, but there is no proof that desensitization may contribute to the development of ICEP. Asthma often gets worse after the development of ICEP and requires long-term oral corticosteroid treatment even in the absence of recurrence of the eosinophilic pneumonia.²⁴

The onset of ICEP is progressive, with a mean interval between the onset of symptoms and the diagnosis of 4 months in one series.²⁵ The most common respiratory symptoms are cough, dyspnea, and chest pain.^{18,25} Dyspnea is usually not severe initially, although the necessity for mechanical ventilation after several months of progression of disease has occasionally been reported.³² Hemoptysis is rare but has been reported in up to 10% of cases.^{18,25}

Wheezes at physical examination are found in one third of patients¹⁸ and crackles in 38%.²⁵ Upper respiratory tract symptoms of chronic rhinitis or sinusitis are present in about 20% of patients.²⁵

Systemic symptoms and signs are often prominent, with fever, weight loss (>10 kg in about 10%). Asthenia, malaise, fatigue, anorexia, weakness, and night sweats are also common.

Imaging

The imaging features of ICEP are characteristic, although they may overlap with those found in cryptogenic organizing pneumonia (see Chapter 63). Peripheral opacities on chest radiography are present in almost all cases^{15,18,25,33-36} and are migratory in a quarter of the cases.²⁵ They usually consist of alveolar opacities with ill-defined margins, with a density varying from ground-glass to consolidation (Fig. 68-4, eFig. 68-1). The classic pattern of “photographic negative or reversal of the shadows usually seen in pulmonary edema,”³⁵ highly evocative of ICEP,³⁵ is seen in only one fourth of patients.¹⁸

Characteristic imaging features of ICEP are better described at HRCT (Fig. 68-5). Whereas the opacities are bilateral in at least 50% of cases at chest radiography,^{18,28} the proportion of bilateral opacities may increase up to 97.5% at HRCT.²⁵ Characteristic opacities predominate in the upper lobes^{18,25,33} and are peripheral, with generally coexisting ground-glass and consolidation opacities at HRCT (Video 68-1).^{25,34,37,38} Midzone distribution of opacities and centrilobular nodules are present in less than 20% of cases.³⁸ Consolidation with segmental or lobar atelectasis may be seen.³⁴ Septal line thickening is common (see Video 68-1).³⁷ On corticosteroid treatment, consolidation and ground-glass opacities rapidly show a decrease in size and extent (eFig. 68-2), with possible change from consolidation to ground-glass opacities or inhomogeneous opacities, and later to streaky or bandlike opacities parallel to the



Figure 68-4 Idiopathic chronic eosinophilic pneumonia. Chest radiograph of a patient with idiopathic chronic eosinophilic pneumonia shows bilateral alveolar opacities predominating in the upper lobes.

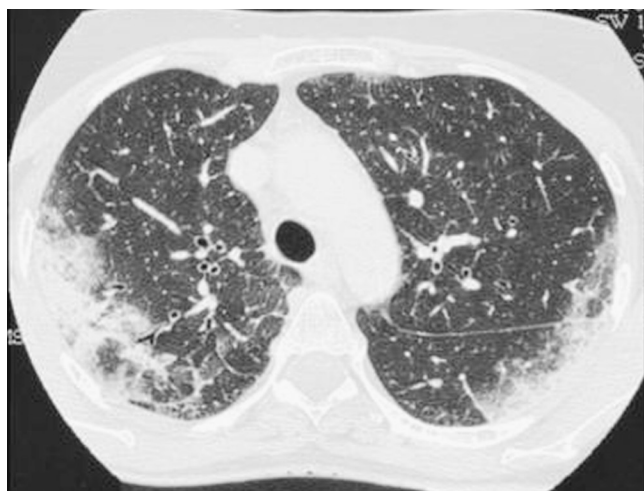


Figure 68-5 Idiopathic chronic eosinophilic pneumonia. Axial chest CT scan of a patient with idiopathic chronic eosinophilic pneumonia shows bilateral symmetrical peripheral alveolar opacities.

chest wall.³⁴ Cavitory lesions are extremely rare and should lead to reconsideration of the diagnosis. Contrary to organizing pneumonia, the reverse halo or atoll sign (i.e., central ground-glass opacity surrounded by denser consolidation in a crescentic circle or ring) is rare. Compared with IAE, in which pleural effusions are seen in the majority (see later), small pleural effusions are present in only 10% of cases of ICEP at HRCT and mediastinal lymph node enlargement in 17%.²⁵

Laboratory Studies

Peripheral blood eosinophilia over 6% was present in 88% of 111 cases in one literature review,¹⁸ with a mean percentage of blood eosinophils at differential count of 26%. The mean blood eosinophilia was $5.5 \times 10^9/L$ (5500/ μL) in our series, with eosinophils representing a mean of 32% of the total blood leukocyte count.²⁵ Because peripheral blood eosinophilia is often a diagnostic criterion of ICEP, the proportion of patients with ICEP and possible normal peripheral blood count is unknown.

Erythrocyte sedimentation rate is increased, and C-reactive protein level is elevated.^{18,25,28} Total blood IgE level is increased in about half of cases and greater than 1000 IU/mL in 15% (normal < 100 IU/mL).²⁵ Circulating immune complexes have been reported in ICEP in about one third of patients.²⁵ Antinuclear antibodies may occasionally be present.²⁵ Urinary eosinophil-derived neurotoxin level indicating active eosinophil degranulation is markedly increased.³⁹

Bronchoalveolar Lavage

BAL has replaced lung biopsy for the diagnosis of ICEP. Alveolar eosinophilia is a characteristic and constant feature in ICEP,^{25,40} with a mean of 58% at differential cell count.²⁵ Alveolar eosinophilia may be associated with an increased percentage of neutrophils, mast cells, and lymphocytes.²⁵ BAL eosinophil cell count drops within a few days under corticosteroid treatment.⁴¹ Sputum eosinophilia may also be present.^{13,29}

BAL eosinophils of patients with ICEP show activation features such as the release of eosinophil proteins, which

are taken up by macrophages.⁴² Eosinophil cationic protein⁴³ and eosinophil-derived neurotoxin⁴³ are increased in BAL fluid of patients with ICEP. Expression of HLA-DR in a patient with ICEP was present on 86% of alveolar eosinophils in contrast to 7% of blood eosinophils, suggesting compartmentalization of eosinophilic activation within the lung.⁴⁴ BAL lymphocytes are characterized by an accumulation of CD4⁺ T cells that express activation surface antigens of memory T cells (CD45RO⁺, CD45RA⁻, CD62L⁻),⁴⁵ and may present clonal rearrangement of the T-cell receptor repertoire.^{8,46} Recruitment of eosinophils to the lung involves various chemokines, which contribute to suppress Fas-induced apoptosis of eosinophils.⁴⁷

Differential Diagnosis

Although ICEP is not a systemic disease, isolated and moderately severe extrapulmonary manifestations, including arthralgias, repolarization (ST-T) abnormalities on the electrocardiogram, pericarditis, altered liver biologic tests, eosinophilic lesions at liver biopsy, mononeuritis multiplex, diarrhea, skin nodules, immune complex vasculitis in the skin, and eosinophilic enteritis, have been reported occasionally.^{15,25,48} Such manifestations suggest an overlap between ICEP and EGPA. Eosinophilic pneumonia similar to ICEP may be a presenting feature of EGPA^{49,50} with patients often receiving corticosteroid treatment, which may prevent the development of overt systemic vasculitis. In a series of ICEP with especially high frequency of extrapulmonary signs (30%), some of which were quite evocative of EGPA, none of the patients treated with corticosteroids developed characteristic EGPA or HES on follow-up.⁴⁸

Lung Function Tests

Lung function tests in ICEP show an obstructive ventilatory defect in about half the patients^{18,25} and a restrictive ventilatory defect in half the cases.²⁵ Hypoxemia defined by an arterial oxygen pressure arterial (PO₂) of 75 mm Hg or less was present in 64% of patients in a series²⁵; CO transfer factor (diffusing capacity DL_{CO}) was less than 80% of predicted in 52%, and transfer coefficient (DL_{CO} per unit alveolar volume) was less than 80% of predicted in only 27%. An increased alveolar-arterial oxygen difference has been reported in 90% of cases.¹⁸ The impaired lung function tests normalize under treatment in most patients.¹⁸ However, a ventilatory obstructive defect may develop over time in some patients, especially those with a markedly increased BAL eosinophilia at initial evaluation.⁵¹

Treatment and Prognosis

The natural course of untreated ICEP is not well known because most patients receive corticosteroids with a dramatic response.¹⁸ ICEP may spontaneously resolve,^{18,25} and death directly resulting from ICEP is exceedingly rare. Symptoms improve within 1 or 2 weeks of corticosteroid treatment and even within 48 hours in about 80%²⁵ of cases. Pulmonary opacities on chest radiography clear rapidly (eFig. 68-3). They disappeared within 1 week in 69% of patients in our series of patients treated with a mean initial dose of 1 mg/kg/day, and almost all patients treated with corticosteroids had a normal chest radiograph at their last follow-up visit.²⁵

The optimal dose of corticosteroids is not established, but the usual doses vary between 20 and 60 mg/day. Our current recommendation is to start with 0.5 mg/kg/day of prednisone, with slow tapering over 6 to 12 months based on clinical evaluation and blood eosinophil cell count. Most patients require prolonged treatment (i.e., >6 months) because of relapse while decreasing below a daily dose of 10 to 15 mg/day of prednisone, or after stopping the corticosteroid treatment. In one series, 58% of cases relapsed after corticosteroids had been discontinued and 21% while the corticosteroids were being tapered.¹⁸ In our series, half of the patients relapsed after the corticosteroids had been weaned (with a mean delay of 72 weeks) or were being tapered (the mean dose of corticosteroids at the time of relapse was 11 mg/day).²⁵ Relapses in the same areas of the lungs or in different areas²⁵ respond well to resumed corticosteroid treatment; a dose of 20 mg/day of prednisone is usually sufficient to treat the relapses.

The clinical series in which follow-up is available clearly show that most patients need very prolonged corticosteroid treatment: in our series with a mean 6.2 years of follow-up, only 31% were weaned at the last control visit.²⁵ Respiratory symptoms may be due to asthma or to ICEP relapse. Relapses of ICEP are less frequent in patients with asthma, possibly because they often receive inhaled corticosteroids after stopping oral corticosteroids.^{24,25} Inhaled corticosteroids might thus help in reducing the maintenance dose of oral corticosteroids, although they are not sufficient when given as monotherapy.⁵² Long-term steroid use may lead to osteoporosis. Omalizumab, a recombinant humanized monoclonal antibody against IgE, has been suggested in case reports to prevent recurrence of ICEP and to spare oral corticosteroids^{53,54}; however, caution must be exerted given recent reports of omalizumab-associated EGPA.^{55,56} Mepolizumab, a monoclonal antibody against IL-5, has not yet been evaluated in patients with ICEP.

IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA

Idiopathic acute eosinophilic pneumonia (IAEP) differs from ICEP by its acute onset, the severity of hypoxemia, the usual lack of increased blood eosinophils at presentation contrasting with frank eosinophilic alveolitis at BAL (BAL differential count with $\geq 25\%$ eosinophils or predominance of eosinophils in open lung biopsy), and the absence of relapse after clinical recovery.^{20,26,29,57-60} Because fever and bilateral opacities on chest radiograph are present in all patients, IAEP is often misdiagnosed as infectious pneumonia and its frequency may therefore be underestimated. The absence of hypersensitivity to drugs, historical or laboratory evidence of infection, and other known causes of acute eosinophilic lung disease are additional diagnostic criteria.²⁶ Current diagnostic criteria of IAEP are listed in Table 68-2.⁶¹

Clinical Features

The average age at presentation is about 30 years,^{26,60} but IAEP may develop in patients age 20 or younger³⁰ and in older patients.⁶⁰ In contrast with ICEP, it is seen almost exclusively in males,⁶² and most patients have no prior asthma history.²⁹

Table 68-2 Diagnostic Criteria for Idiopathic Acute Eosinophilic Pneumonia

1. Acute onset of febrile respiratory manifestations (≤ 1 mo duration before consultation)
2. Bilateral diffuse opacities on chest radiography
3. Hypoxemia, with PaO_2 on room air < 60 mm Hg, and/or $\text{PaO}_2/\text{FiO}_2 \leq 300$ mm Hg, and/or oxygen saturation on room air $< 90\%$
4. Lung eosinophilia, with $> 25\%$ eosinophils on BAL differential cell count (or eosinophilic pneumonia at lung biopsy)
5. Absence of infection or of other known causes of eosinophilic lung disease (especially exposure to a drug susceptible to induce pulmonary eosinophilia)

Adapted from Allen JN, Pacht ER, Gadek JE, Davis WB: Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N Engl J Med* 321:569–574, 1989; and Cottin V, Cordier JF: Eosinophilic pneumonias. *Allergy* 60:841–857, 2005.

Importantly, most patients seem to have been exposed to dust or cigarette smoke within the days before onset of disease. Some patients had peculiar outdoor activities, such as cave exploration, plant repotting, wood pile moving, smokehouse cleaning, motocross racing in dusty conditions, indoor renovation work, gasoline tank cleaning, and explosion of a tear gas bomb.^{26,60} One case was also reported in a New York City firefighter exposed to World Trade Center dust.⁶³

A causative role of cigarette smoke seems established because IAEP has developed soon after the initiation of smoking (especially when starting with large quantities) in numerous patients,⁶⁴⁻⁶⁹ and challenge with cigarette smoking was positive in some of them,^{64-67,69} but tolerance may develop in patients who resume smoking.⁶⁵⁻⁶⁷ Flavoring components of smoked cigars have been suspected.⁷⁰ Recent alterations in smoking habits (e.g., beginning to smoke, restarting, or increasing the number of cigarettes smoked daily) especially within 1 month (median delay, 2 weeks) seem to play a major role in the onset of “idiopathic” AEP.^{62,69} Passive smoking has also been reported to cause AEP.⁷¹ It is likely that inhalation of tobacco smoke or of any nonspecific injurious agent may initiate or contribute to the development of IAEP in individuals intrinsically prone to develop eosinophilic reactions to inhaled nonspecific causative agents. Increased levels of $\beta(1 \rightarrow 3)$ -D-glucan (a major component of the cell wall of most fungi and also one of the components of cigarette smoke) have been reported in BAL fluid of patients with IAEP.⁶⁸

IAEP develops acutely in previously healthy individuals, with symptoms at presentation consisting of cough, dyspnea, fever, and chest pain. It may also develop subacutely over a few weeks,²⁰ with no clinical difference between patients seen in a time interval of less than 7 days or 7 to 31 days from the first symptoms to the diagnosis of IAEP.⁶⁰ More than half of patients present with acute respiratory failure.⁶² Abdominal complaints and also myalgias have been reported.²⁶ At physical examination, tachypnea and tachycardia are present, with crackles or, less often, wheezes on auscultation.

Imaging

The chest radiograph shows bilateral opacities, with mixed alveolar or interstitial opacities (eFig 68-4A-B, G).^{26,58-60} In contrast with ICEP, bilateral pleural effusion and Kerley B

lines are common.²⁶ The chest radiograph returns to normal within 3 weeks (see eFig. 68-4L),^{26,58} with pleural effusions being the last abnormality to disappear.²⁶

At chest CT imaging, ground-glass opacities and air space consolidation are the most common patterns of parenchymal lesions, with poorly defined nodules and interlobular septal thickening seen in a majority of patients; pleural effusion is present in at least two thirds of patients and is usually bilateral (see eFig. 68-4C-E, H-K).^{26,36,58,60,72} We consider that bilateral pleural effusion and interlobular septal thickening are highly characteristic of IAEP in a patient with eosinophilic pneumonia; in addition, they should raise the suspicion of IAEP in a patient considered to have infectious pneumonia.

Laboratory Studies

In contrast with ICEP, the white blood cell count at presentation usually shows an increased leukocyte count with a predominance of neutrophils, with eosinophils only rarely higher than $0.3 \times 10^9/L$ ($300/\mu L$), but the eosinophil count often rises to high values later during the course of disease,^{26,29,60} a retrospective finding suggestive of IAEP. Eosinophilia is also present in the pleural fluid^{26,65,73} and sputum.²⁹

The IgE level may be elevated in some patients,^{73,74} and serum IgG and especially IgG2 and IgG4 levels may be reduced during the active phase of disease as compared with controls,⁷⁴ although with limited diagnostic value. Serum levels of *thymus and activation-regulated chemokine* (TARC/CCL17), KL6, or exhaled nitric oxide are often increased in IAEP as opposed to other causes of acute lung injury or infectious pneumonia; these biomarkers are not specific for IAEP, however.^{75,76}

Bronchoalveolar Lavage

Given the usual lack of initial blood eosinophilia, BAL is the key to the diagnosis of IAEP, showing an average percentage of 37%²⁶ to 54%⁶⁰ eosinophils on the differential cell count, with sterile bacterial cultures. Lymphocyte and neutrophil counts can be moderately increased. After recovery, eosinophilia in the BAL may persist for several weeks.⁷⁷ We consider that the finding of eosinophilia greater than 25% at BAL may obviate the need for lung biopsy for diagnosis, at least in immunocompetent patients.

Lung Function Tests

Hypoxemia may be severe and refractory to breathing 100% oxygen, suggesting right-to-left shunting in some patients.^{57,60} A majority of patients fit the definition of ARDS of various severity (e.g., acute onset of respiratory failure not fully explained by cardiac failure or fluid overload, with objective exclusion of hydrostatic edema); bilateral opacities (not fully explained by effusions, lobar/lung collapse, or nodules); and an arterial PO_2/FIO_2 (fractional inspired oxygen concentration) < 300 mm Hg with positive end-expiratory pressure or continuous positive expiratory pressure greater than or equal to 5 cm H_2O .⁷⁸ Mechanical ventilation, either noninvasive or with intratracheal intubation, was necessary in a majority of patients in earlier series.^{26,60} More recent series have shown that the severity of IAEP is more varied than originally reported.⁶² In contrast with ARDS, shock is extremely unusual^{79,80} and extrapulmonary organ failure is not seen. FIO_2 may be decreased

within a few hours of steroid treatment in many patients initially requiring oxygen.²⁶

When performed in less severe cases, lung function tests have shown a mild restrictive ventilatory defect with normal *forced expiratory volume in 1 second*–to–*forced vital capacity* (FEV_1/FVC) ratio and reduced transfer factor (diffusing capacity).⁷⁴ Alveolar-arterial oxygen gradient is increased.²⁶ Lung function tests performed after recovery are normal in most patients, with possible ventilatory restriction in some of them.^{26,81,82}

Lung Biopsy

Lung biopsy is seldom necessary when BAL is performed. When done, it shows acute and organizing diffuse alveolar damage together with interstitial alveolar and bronchiolar infiltration by eosinophils, intra-alveolar eosinophils, and interstitial edema.^{20,26,79,83}

Treatment and Prognosis

Recovery without corticosteroid treatment has been reported,^{60,75} and therefore improvement concomitant with corticosteroid treatment cannot be considered a diagnostic criterion of IAEP. However, when a diagnosis of IAEP is made, corticosteroid treatment is usually started with initially intravenous methylprednisolone and later changed to oral therapy that can be tapered over 2 to 4 weeks.²⁶ The patient generally responds to corticosteroids within 3 days (see eFig. 68-4L)⁶² and can be rapidly weaned from the ventilator and from oxygen supplementation. The chest radiograph normalizes within 1 week in 85% of patients, but mild pulmonary opacities and pleural effusion may still be present on chest *computed tomography* (CT) at 2 weeks.⁶² One recent study of 137 patients suggested that a treatment duration of 2 weeks may be sufficient, with an initial daily dose of 30 mg of prednisone (or 60 mg of intravenous methylprednisolone every 6 hours in patients with respiratory failure).⁶² Recovery is rapid with no significant clinical or imaging sequelae, and with no relapse after stopping corticosteroid treatment, in contrast with ICEP where relapse is common.

Although IAEP often presents clinically like acute lung injury or ARDS, its prognosis is far better. The key to the diagnosis is finding eosinophilia on BAL because blood eosinophilia is usually absent initially. A careful search for a cause of AEP is mandatory, and infectious agents must be sought for in BAL fluid by cultures and appropriate staining.⁸⁴⁻⁸⁶ Drug-induced AEP must also be carefully excluded. Identification of causative tobacco or environmental exposures is key to preventing rare recurrences that in most cases are due to resumption of cigarette smoking after smoking cessation.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

History and Nomenclature

The first reliable case of *eosinophilic granulomatosis with polyangiitis* (EGPA) was reported by Lamb⁸⁷ in 1914. Churg and Strauss¹⁴ described in 1951 the eponymous syndrome, mainly from autopsied cases. They described characteristic pathologic features consisting of granulomatous extravascular lesions, as well as necrotizing, inflammatory, and

granulomatous vascular changes, with an inflammatory exudate rich in eosinophils. The most frequent site of inflammation was the heart. In approximately half of the cases, a pneumonic process was found, with an eosinophil-rich exudate mixed with giant cells in the acute stage.

In the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis,⁸⁸ CSS was included in the group of small vessel vasculitides. In 2012, the nomenclature of the systemic vasculitides was revised at the International Chapel Hill Consensus Conference.⁸⁹ The eponym CSS was replaced by the terminology of eosinophilic granulomatosis with polyangiitis to achieve nomenclature symmetry with microscopic polyangiitis and with granulomatosis with polyangiitis (Wegener), which are the pulmonary *antineutrophil cytoplasmic antibody* (ANCA)-associated vasculitides, together with single-organ, ANCA-associated vasculitis.

EGPA is defined as an eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract and a necrotizing vasculitis predominantly affecting small to medium vessels, associated with asthma and eosinophilia. It is acknowledged that the disease may be confined to a limited number of organs, especially the upper or lower respiratory tract.⁸⁹ This terminology reminds us that EGPA is indeed a vasculitis; however, not all patients with EGPA have robust criteria of documented systemic vasculitis or the presence of ANCA.⁹⁰ ANCAs are present in approximately 40% of the cases. ANCAs are more frequent when glomerulonephritis is present, and most patients with

documented necrotizing glomerulonephritis have ANCAs.⁹¹ Therefore the current revised terminology and classification may require further refinement.

Pathology

Because the diagnosis is now made earlier in the course of disease, lung biopsy is seldom necessary, and patients may receive corticosteroids before overt vasculitis has developed. The pathologic lesions of EGPA currently observed^{92,93} only rarely comprise all the characteristic features on a single biopsy from one organ. When typical features are present, both vasculitis (necrotizing or not, involving mainly the medium-sized pulmonary arteries) and granulomatous eosinophilic infiltration are seen (Fig. 68-6A-B). The extravascular granuloma consists of palisading histiocytes and giant cells (see Fig. 68-6C). Diffuse pulmonary hemorrhage with capillaritis can develop (see Fig. 68-6D). When present, the eosinophilic pneumonia in EGPA is similar to ICEP. The early (prevasculitic) phase of EGPA is characterized by eosinophilic infiltration of the tissues without vasculitis (perivascular eosinophils are commonly found).

Clinical Features

The clinical features of EGPA have been well defined.⁹⁴⁻⁹⁹ It is a rare systemic disease, which presents especially in adults younger than 65^{98,100}; it has been occasionally reported in children and adolescents.^{100a} There is no sex predominance. The mean age of onset of vasculitis ranges from 38 to 49 years.^{98,101}

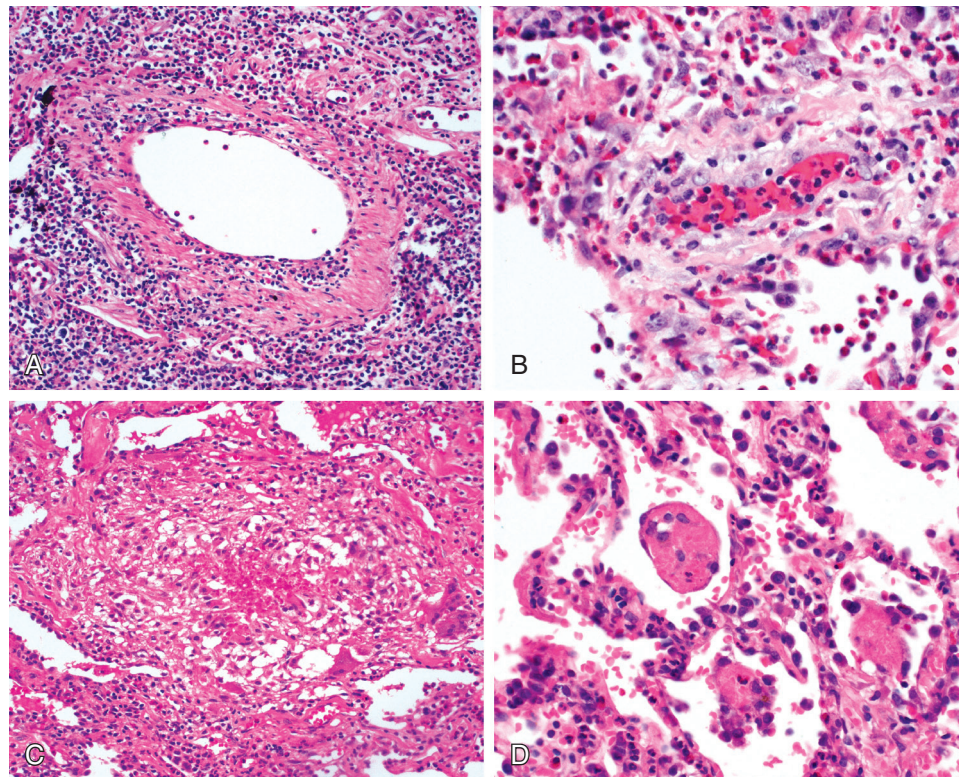


Figure 68-6 Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (EGPA) **A**, Vasculitis. A medium-sized artery infiltrated by eosinophils and scattered lymphocytes. **B**, Vasculitis. A venule infiltrated by eosinophils. Note fibrin and eosinophils in surrounding air spaces. **C**, Eosinophilic granulomas. Characteristic "allergic granuloma" is readily apparent. Note the vaguely palisaded histiocytes at the periphery of eosinophilic necrosis (center). Multinucleate giant cells may be present and typically have a brightly eosinophilic cytoplasm. **D**, Pulmonary hemorrhage. Diffuse pulmonary hemorrhage with capillaritis can be seen in EGPA. Capillaritis is demonstrated here, associated with aggregated air space fibrin and eosinophils. (From Leslie KO, Wick MR: Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series, ed 2. Philadelphia, 2011, Elsevier, Figs. 10-27, 10-29, and 10-28.)

Asthma, generally severe and becoming rapidly corticosteroid dependent, presents at a mean age of about 35.⁹⁸ It usually precedes the onset of vasculitis by 3 years and up to 9 years.^{94,98,101,102} The interval between asthma and the onset of vasculitis may be much longer in rare cases,¹⁰² or they may be contemporaneous.¹⁰¹ The severity of asthma typically increases progressively until the vasculitis develops, but it may attenuate when the vasculitis flourishes and further increase once the vasculitis recedes.^{98,102}

Chronic rhinitis is present in about three quarters of cases of EGPA^{98,103,104} and is often accompanied by relapsing sinusitis and/or polyposis, with eosinophilic infiltration seen on histopathology.¹⁰⁵ Paranasal sinusitis has been reported in 61% of patients.⁹⁴ Crusty rhinitis may be present, but the rhinitis in EGPA is distinctly much less severe than in granulomatosis with polyangiitis, with septal nasal perforation or saddle nose deformation being unusual.

Asthenia, weight loss, fever, arthralgias, and myalgias (all of which are unusual in simple asthma) often herald the development of the extrapulmonary manifestations of vasculitis.

Heart damage, which may be severe and lead to cardiac failure or sudden death,^{94,98,99,101,102,106} results especially from eosinophilic myocarditis and much less commonly from coronary arteritis.^{107,108} Cardiac involvement is often insidious and asymptomatic and, thus may be recognized only when left ventricular failure and dilated cardiomyopathy have developed. Heart failure may require heart transplantation,^{108a} but eosinophilic vasculitis may recur in the transplanted heart. However, myocardial impairment and coronary arteritis may markedly improve with corticosteroid treatment, thus necessitating a strict cardiac evaluation in any patient with suspected EGPA, including electrocardiogram, echocardiography, serum level of troponin, and *magnetic resonance imaging* (MRI) of the heart.¹⁰⁹ The main practical difficulty is the absence of a gold standard to diagnose clinically relevant myocardial involvement. Cardiac MRI can frequently demonstrate late enhancement of the myocardium¹¹⁰⁻¹¹²; however, it remains difficult to differentiate irreversible lesions representing scarring from active inflammation requiring intense immunosuppression; the combination of cardiac MRI with positron emission tomography may be useful but deserves further study.¹¹³

Pericarditis with limited effusion at echocardiography is common; tamponade is rare. In contrast with the idiopathic HES, endomyocardial involvement is not a common feature. Patients with EGPA are at greater risk of venous thromboembolic events.¹¹⁴

Peripheral neurologic involvement mainly consists of mononeuritis multiplex, present in 77% of patients,⁹⁴ or asymmetrical polyneuropathy, with sudden onset of painful, focal or multifocal weakness or sensory loss, generally in the lower extremities. Cranial nerve palsies and central nervous system involvement are rare. Digestive tract involvement is present in 31% of cases⁹⁴ and usually manifests as isolated abdominal pain, but intestinal or biliary tract vasculitis may be present. Other digestive manifestations include diarrhea; ulcerative colitis; gastroduodenal ulcerations; perforations (esophageal, gastric, intestinal); digestive hemorrhage; and cholecystitis. Cutaneous lesions, which present in about half of patients,⁹⁴ mainly consist of palpable purpura of the extremities, subcutaneous nodules (especially of the scalp and extremities), erythematous rashes, and urticaria. Renal involvement presents in 26% of cases and is usually mild,⁹⁴ in contrast with the other ANCA-associated vasculitides.

Imaging

Pulmonary opacities corresponding to eosinophilic pneumonia represent the most typical abnormalities on chest radiograph and have been reported in large series with a frequency of 37%⁶⁹ to 72% (see [eFig. 60-9A](#)).^{98,115} The pulmonary opacities are usually noted at presentation, but the chest radiograph remains normal throughout the course of the disease in some patients. The pulmonary opacities usually consist of ill-defined opacities, sometimes migratory, transient, and of varying density.^{98,102,116-118} In contrast to *granulomatosis with polyangiitis* (GPA), pulmonary cavitary lesions are extremely unusual. Pleural effusion (usually mild) and phrenic nerve palsy may be observed.

The pulmonary opacities on thin-section chest CT mainly consist of areas of ground-glass attenuation (see [eFig. 60-9B-E](#)) or air space consolidation, with peripheral predominance or random distribution ([Fig. 68-7](#)); centrilobular nodules are more frequent than in patients with ICEP³⁸; less common findings include bronchial wall thickening or dilation, interlobular septal thickening (see [eFig. 60-9B-E](#)),

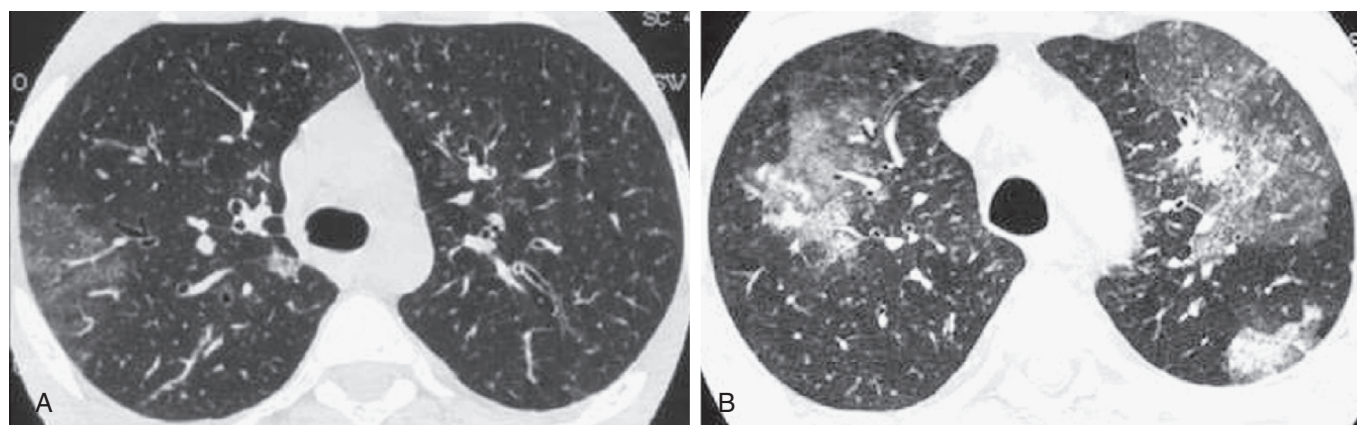


Figure 68-7 Eosinophilic granulomatosis with polyangiitis. Axial chest CT scan of patients with eosinophilic granulomatosis with polyangiitis shows ground-glass opacity of the right upper lobe (**A**) and bilateral central and peripheral opacities with varying density (**B**).

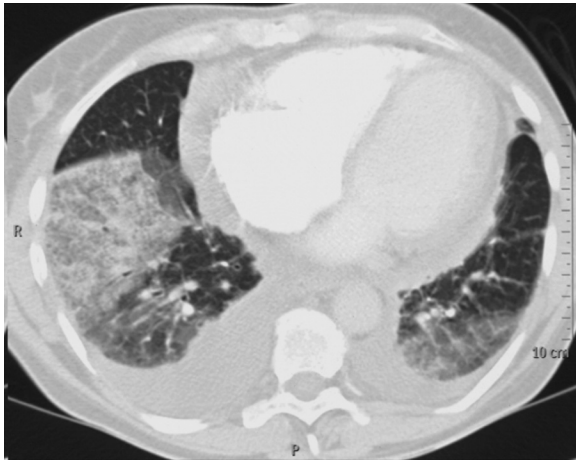


Figure 68-8 Eosinophilic granulomatosis with polyangiitis. Axial chest CT scan of a patient with eosinophilic granulomatosis with polyangiitis, with lung consolidation and ground-glass opacities corresponding to eosinophilic pneumonia. In addition, pericardial effusion and bilateral pleural effusions are present due to cardiomyopathy.

hilar or mediastinal lymphadenopathy, pleural effusion, or pericardial effusion^{36,117-119} (Fig. 68-8). When present, pleural effusion should lead one to consider both inflammatory eosinophilic exudate and transudate with cardiomyopathy as a possible cause. Because these abnormalities are nonspecific, a correct diagnosis of EGPA was made on CT in only 44% of 111 patients with eosinophilic lung diseases.³⁶

Laboratory Studies

Peripheral blood eosinophilia is a major feature of EGPA that usually parallels the activity of the vasculitis. Blood eosinophils are generally between 5 and $20 \times 10^9/L$ (5000 to 20,000/ μL), but they may reach higher values.^{94,98,102} Blood eosinophilia often disappears dramatically after the initiation of corticosteroid treatment (which may thus cause the absence of eosinophilia if blood tests are not done before starting corticosteroid treatment). Eosinophilia, sometimes greater than 60%, is found on BAL differential cell count¹²⁰ and in pleural fluid when present.¹²¹

The ANCAs reported in about 40% of patients are mainly *perinuclear antineutrophil cytoplasmic antibodies* (p-ANCAs) with myeloperoxidase specificity (much less often *cytoplasmic antineutrophil cytoplasmic antibody* [c-ANCA] with proteinase 3 specificity).^{94,101,122-124} Serum IgE levels are markedly increased. The erythrocyte sedimentation rate and C-reactive protein level are increased, and anemia is common. High levels of urinary eosinophil-derived neurotoxin have been reported, and these might represent an activity index of disease.¹²⁵ Serum IgG4, CCL17/TARC, CCL26/Eotaxin-3 levels are elevated in active disease, but these have not been validated as biomarkers.¹²⁶⁻¹²⁹

Pathogenesis

The pathophysiology of EGPA is not established. EGPA may be considered as an autoimmune process involving T cells, endothelial cells, and eosinophils. Recent studies have identified possible defects in regulatory CD4⁺, CD25⁺, or CD4⁺CD25⁻ T-cell lymphocytes (producing IL-10 and IL-2) in EGPA (as compared with ICEP), possibly influencing progression and prognosis of disease.¹³⁰ Clonal CD8⁺/V β ⁺ T-cell

expansions with effector memory phenotype, showing markers of cytotoxic activity and consistent with a hypothesis of persistent antigenic stimulation, were found in peripheral blood lymphocytes by flow cytometry combined to analysis of *T-cell antigen receptor* (TCR)- γ gene rearrangement.^{131,132,132a} T-cell receptor-C beta gene rearrangement were reported.⁹ Some triggering or adjuvant factors (such as vaccines or desensitization) have been suspected to play a role in EGPA.^{133,134} The hypothesis of defective apoptosis pathways in eosinophils has not been confirmed.¹³⁵

Although a family history of atopy and allergic rhinitis is often present, evidence of allergy (demonstration of specific IgE with corresponding clinical history) is present in less than one third of patients; when present, allergy in EGPA mainly consists of perennial allergies, especially to *Dermatophagoides*, with seasonal allergies less frequent than in asthmatic patients without EGPA.¹³⁶ A genetic predisposition to develop EGPA has been demonstrated in patients carrying the major histopathology complex DRB4 allele¹³⁷ and perhaps in certain families.¹³⁸

Other possible triggering factors include *Aspergillus*, allergic bronchopulmonary candidiasis, *Ascaris*, bird exposure, or smoked cocaine. Drug-induced eosinophilic vasculitis with pulmonary involvement has been reported in the past with sulfonamides used together with antiserum, and later with diflunisal,¹³⁹ macrolides,¹⁴⁰ and diphenylhydantoin.¹⁴¹ EGPA has also been reported in asthmatic patients treated with omalizumab, an anti-IgE antibody.¹⁴²⁻¹⁴⁵

The possible responsibility of leukotriene-receptor antagonists (montelukast, zafirlukast, pranlukast) in the development of EGPA has generated much debate.^{101,146-150} Although the association between leukotriene receptor antagonists and EGPA is now established, there is conflicting evidence whether it is the result of confounding by indication or a genuine causal association.^{56,149} Whether the association is coincidental, whether some cases of smoldering EGPA flare because of reducing oral or inhaled corticosteroids and/or adding leukotriene receptor antagonists, or whether these drugs really exert a role on the pathogenesis of the vasculitis is not established. A possible mechanistic link has been proposed.¹⁵¹ However, EGPA may follow montelukast treatment in the absence of preexisting disease, may recur on rechallenge with leukotriene receptor antagonists, and may remit on withdrawal of this treatment without modifying the corticosteroid and/or immunosuppressive therapy.^{147,149} At least one recent study indicates that a causal relationship cannot be totally dismissed.¹⁵² We therefore consider that leukotriene receptor antagonists should be avoided in any asthma patient with eosinophilia and/or extrapulmonary manifestations compatible with smoldering EGPA.

Diagnosis

The diagnosis of EGPA may be difficult because the clinician nowadays is more often faced with patients presenting with early and mild signs corresponding to the so-called formes frustes of EGPA, which are more or less suppressed by corticosteroid treatment for asthma and which may later be unmasked, especially when treatment is reduced or stopped.

The evolution of EGPA usually follows three stages: asthma and rhinitis; tissue eosinophilia (such as a pulmonary disease resembling ICEP); and extrapulmonary

Table 68-3 Distinct Phenotypes of Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

	Vasculitic Phenotype	Tissular (Tissue) Phenotype
Respective frequency	≈40%	≈60%
ANCA	Present (mostly p-ANCA with anti-MPO specificity)	Absent
Predominant clinical features	Glomerular renal disease Peripheral neuropathy Purpura	Cardiac involvement (eosinophilic myocarditis) Fever
Predominant histopathologic features	Biopsy-proven vasculitis	Eosinophilic pneumonia

ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; p-ANCA, perinuclear antineutrophil cytoplasmic antibody.

Adapted from Sable-Fourtassou R, Cohen P, Mahr A, et al: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 143:632–638, 2005; and Sinico RA, Di Toma L, Maggiore U, et al: Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum* 52:2926–2935, 2005.

eosinophilic disease with vasculitis. Diagnostic difficulties thus largely depend on the stage of disease at which the patient is seen. Although systemic disease is necessary to consider a diagnosis of EGPA, it is extremely important that the diagnosis be established before severe organ involvement (especially cardiac) is present.

There are currently no established diagnostic criteria for EGPA. Lanham and associates⁹⁸ have proposed three diagnostic criteria including (1) asthma, (2) eosinophilia exceeding $1.5 \times 10^9/L$ ($1500/\mu L$), and (3) systemic vasculitis of two or more extrapulmonary organs. According to the classification criteria (which are not *diagnostic* criteria, however) of the American College of Rheumatology,¹⁵³ a sensitivity of 85% and a specificity of 99.7% are obtained if four or more of the six following criteria are present in a patient with proven systemic vasculitis: asthma; eosinophilia greater than 10% on differential blood cell count; mono-neuritis (including multiplex) or polyneuropathy; fluctuating opacities on chest radiography; bilateral maxillary sinus abnormalities; or presence of extravascular eosinophils on a biopsy including a vessel. However, these diagnostic and classification criteria were proposed before ANCAs were available. In the future, the presence of ANCA will probably be considered a major diagnostic criterion when present, and provisional diagnostic criteria have been proposed.⁹⁰ A pathologic diagnosis of EGPA is desirable, but not mandatory, in patients with characteristic clinical features and marked eosinophilia. The skin, nerve, and muscle are the most common sites where a pathologic diagnosis of vasculitis may be obtained.⁹⁴ Biopsy of the cutaneous lesions is the most common and simple procedure to obtain pathologic evidence of vasculitis. Lung biopsy is seldom done. Transbronchial biopsies usually do not show vasculitis or granulomata.

Differential Diagnosis

The borders separating EGPA from the other ANCA-associated vasculitides and the other eosinophilic syndromes are sometimes difficult to establish. An overlap between ANCA-negative EGPA and unclassified systemic eosinophilic disease is possible. An eosinophilic variant of granulomatosis with polyangiitis has been described.¹⁵⁵ Concurrent EGPA and pulmonary opacities and temporal arteritis (either with or without giant cells, either eosinophilic or not) have been described.¹⁵⁶ Distinguishing between mild EGPA and ICEP with minor extrathoracic symptoms may also be difficult, especially in the absence of

typical polyangiitis features. Some mild vasculitis (non-necrotizing) is common on pathologic examination of the lung in patients with ICEP.¹⁵ ICEP may further progress to EGPA.⁴⁹ In addition, some cases of “limited” EGPA have been reported,¹⁵⁷ including those solely involving the lung or the heart. *Formes frustes* of EGPA often consist of cases in which the disease has been controlled to a greater or lesser extent by corticosteroids given for asthma. Other cases are difficult to classify as either EGPA or idiopathic HES. Careful clinical analysis, the presence of ANCA, the finding of a vasculitis and granulomas on biopsy, and molecular biologic analysis (in the cases of idiopathic HES) help in determining the final diagnosis.

Interestingly, recent studies have demonstrated that ANCA status may characterize two distinct clinical phenotypes in EGPA^{123,124,158,158a} (Table 68-3). Hence patients *with* ANCA, representing approximately 40% of patients, have a *vasculitic phenotype* of disease with an increased frequency of extracapillary glomerular lesions, peripheral neuropathy, purpura, and biopsy-proven vasculitis. Conversely, EGPA patients *without* ANCA have a *tissue* phenotype of disease with more frequent cardiac and pulmonary involvement (and fever). The latter might conceivably represent a variant of the HES with systemic manifestations.^{123,159} The vasculitic phenotype of EGPA is more frequent in patients carrying the major histopathology complex DRB4 allele.¹³⁷ The ANCA-negative EGPA is associated with the *IL10*-3575/1082/592 TAC haplotype (part of the ancient haplotype IL-10.2 correlated with increased IL-10 expression). Thus genetic predisposition may affect the phenotype of EGPA.

Treatment and Prognosis

Corticosteroids are the mainstay of treatment of EGPA and suffice in a large number of cases.^{98,160,161} Initial methylprednisolone pulses, for 1 to 3 days, are useful in the most severe cases, then oral treatment is started, usually with 1 mg/kg/day of prednisone. Treatment is prolonged for several months with progressive reduction of doses. Relapses are common, and asthma often persists (or reappears if it had disappeared during high-dose corticosteroid treatment). Distinguishing relapse or persistence of so-called difficult asthma from relapse or persistence of EGPA requires precise evaluation, taking into account the levels of blood eosinophils (generally $< 1 \times 10^9$ but $< 1000/\mu L$ in asthma without EGPA relapse) and occasionally new systematic manifestations.

Cyclophosphamide therapy should be added to corticosteroids in patients with manifestations that could result in mortality or severe morbidity.¹⁶² A retrospective study^{160,163} of patients with either polyarteritis nodosa or EGPA identified four factors associated with higher mortality: age older than 65, cardiac symptoms (based on easily detectable clinical parameters), gastrointestinal involvement, and renal insufficiency, whereas ear, nose, and throat symptoms were associated with a lower risk of death.¹⁶³ Cardiomyopathy is the main predictor of mortality in multivariable analysis,¹⁵⁸ especially in cases of heart failure.¹⁶⁴ Older age at diagnosis is also associated with a poor prognosis.^{158,165} The risk of relapse of the vasculitis is higher in patients with ANCA¹⁵⁸ and lower in patients with baseline eosinophils $> 3 \times 10^9/L$ ($>3000/\mu L$).¹⁶⁵

The combination of immunosuppressors with corticosteroids improved disease control, despite associated infections (which could be decreased by using bolus instead of oral cyclophosphamide administration).^{166,167} Mortality was associated with disease severity, and treatment with cytotoxic agents did not prevent relapses.¹⁶⁸ Although the optimal duration of therapy remains to be determined, 12 cyclophosphamide pulses were better able to control the disease than a 6-pulse regimen in patients with EGPA and at least one poor prognosis factor at onset.¹⁶⁹ Corticosteroid treatment alone for EGPA patients without poor prognostic factors at onset is efficient, with about half of the patients achieving complete remission without relapse.¹⁷⁰ Therefore immunosuppressive therapy (most commonly with intravenous pulses of cyclophosphamide) in addition to corticosteroids is warranted in patients with poor prognostic factors at onset and especially heart failure.^{113,165} Maintenance therapy with oral azathioprine or intramuscular methotrexate in addition to corticosteroids may be useful in patients who relapse when taking less than 20 mg/day or more of prednisone.

Subcutaneous interferon- α was successfully used mainly in EGPA patients with severe disease.¹⁷¹ High-dose intravenous immunoglobulins, cyclosporin A, and rituximab¹⁷²⁻¹⁷⁵ have been used successfully in case reports or short series. The anti-IgE omalizumab has been used successfully in patients with EGPA to treat persistent asthma^{176,177}; however, it does not control the systemic disease, and careful clinical monitoring is warranted. Mepolizumab has a glucocorticoid-sparing effect, reduces exacerbations, and improves asthma control in patients with eosinophilic asthma requiring daily oral glucocorticoid therapy.^{177a,177b} Mepolizumab is under evaluation as a potential therapy in EGPA.^{178,179}

The prognosis of EGPA has improved considerably over time,¹⁵⁸ with almost 80% of patients alive at 5 years¹⁶⁰ and 97% alive at 5 years in one recent series of EGPA without poor prognostic factors.¹⁸⁰ Most deaths during the first year of treatment are due to cardiac involvement.¹⁸¹ In one series, EGPA did not appear to confer increased mortality, a rather surprising finding.¹⁰¹ As most patients continue to take oral corticosteroids over the long term, treatment-related side effects cause significant morbidity.¹⁸⁰ In addition, airflow obstruction due to uncontrolled asthma is present despite corticosteroids in many patients during follow-up, and persistent airflow obstruction may develop.^{182,183} Airflow obstruction may not respond to

inhaled bronchodilators but may be partly reversible with increased oral corticosteroid treatment.¹⁸²

HYPEREOSINOPHILIC SYNDROME

The definition of the “idiopathic” *hypereosinophilic syndrome* (HES) proposed by Chusid and coworkers¹⁸⁴ in 1975 included (1) a persistent eosinophilia greater than $1.5 \times 10^9/L$ ($1500/\mu L$) for longer than 6 months, or death before 6 months associated with the signs and symptoms of hyper-eosinophilic disease; (2) a lack of evidence for parasitic, allergic, or other known causes of eosinophilia; and (3) presumptive signs and symptoms of organ involvement, including hepatosplenomegaly, organic heart murmur, congestive heart failure, diffuse or focal central nervous system abnormalities, pulmonary fibrosis, fever, weight loss, or anemia. The 14 cases they reported¹⁸⁴ included 2 patients with “prolonged benign hypereosinophilia,” 3 with eosinophilic leukemia, and 1 with possible EGPA. The later published cases of the idiopathic HES also proved heterogeneous, although patients with typical chronic disease shared some common complications, especially cardiac involvement. The diagnosis of HES is now considered in patients with blood hypereosinophilia ($>1.5 \times 10^9/L$ [$1500/\mu L$]) on at least two occasions in the absence of other etiologies for the eosinophilia.

Pathogenesis

In contrast with common hypereosinophilia, which is usually a reactive nonclonal process (as in parasitic disorders), several studies demonstrated that HES may result from a clonal proliferation of lymphocytes producing eosinophilopoietic chemokines (“lymphocytic variant” of HES), or from the clonal proliferation of the eosinophil cell lineage itself (“myeloproliferative variant” of HES, also referred to as *chronic eosinophilic leukemia*).¹⁸⁵⁻¹⁹⁰ The term *idiopathic* should probably be abandoned in the classification of HES¹⁹¹ and may be appropriate only for the proportion of cases that cannot at present be classified in either category. In such genuinely idiopathic cases, innovative diagnostic tools such as the quantitative assessment of the *Wt1* transcript in peripheral blood may help to differentiate HES from other causes of eosinophilia of determined cause.¹⁹²

The “lymphocytic variant” of HES, which may account for about 30% of patients with HES, results from the production of chemokines (especially IL-5) (which promote the accumulation of eosinophils) by clonal Th2 lymphocytes (as demonstrated by clonal rearrangement of the TCR) bearing an aberrant immunologic phenotype (such as CD3⁺CD4⁺). Lymphocyte phenotyping to detect a phenotypically aberrant T-cell subset by flow cytometry and analysis of the rearrangement of the TCR genes in search of T-cell clonality should be performed on the peripheral blood (and bone marrow). The observation of increased IL-5 expression from cultured T cells can also demonstrate that the observed eosinophilia is caused by an expanded population of T cells.¹⁹³ Serum levels of IgE are elevated as a consequence of IL-4 and IL-13 production by Th2 lymphocytes.^{191,194,195} Serum levels of IL-5 and TARC are increased.¹⁹⁶ Most reported patients were recruited from dermatology clinics and had papules or urticarial plaques infiltrated by lymphocytes and eosinophils (and in some of them, a cutaneous

T-cell lymphoma or the Sezary syndrome was ultimately present). In such cases, the HES may be considered as a premalignant T-cell disorder.^{194,195,197}

The “myeloproliferative variant” of HES (or chronic eosinophilic leukemia), accounting for 20% to 30% of cases, is caused by a constitutively activated tyrosine kinase fusion protein created by fusion of *FIP1L1-PDGFR* as a consequence of an interstitial chromosomal deletion of a region in the long arm of chromosome 4 (q12) not detectable by karyotype analysis.^{198,199} Hepatomegaly, splenomegaly, mucosal ulcerations, severe cardiac manifestations resistant to corticosteroid treatment, anemia, thrombocythemia, increased serum vitamin B₁₂, leukocyte alkaline phosphatase and serum tryptase, and circulating leukocyte precursors are common and suggestive of the diagnosis, whereas cutaneous manifestations are infrequent. A pronounced mastocytosis (lacking *KIT* mutations) is frequent. The diagnosis is confirmed by chromosomal rearrangement analysis and transcript study of the *FIP1L1-PDGFR* fusion gene (or nested polymerase chain reaction analysis), which should be systematically performed in patients with HES. The presence of the *FIP1L1-PDGFR* rearrangement is sufficient for the diagnosis of myeloproliferative HES. Presence of the causative deletion can also be demonstrated using FISH probes to the gene *CHIC2* encompassed in the deleted sequence.¹⁹³ The fusion protein transforms hematopoietic cells and is inhibited by imatinib, a tyrosine kinase inhibitor originally used to treat chronic myelogenous leukemia, other chronic myeloproliferative diseases, and gastrointestinal stromal tumors (also characterized by aberrant constitutively activated tyrosine kinases). Imatinib proved efficient for several months in treating HES in patients refractory to corticosteroids, hydroxyurea, and/or interferon- α . One patient relapsed due to a mutation in *PDGFR* conferring resistance to imatinib (thus demonstrating that the *FIP1L1-PDGFR*- α fusion protein is the target of imatinib). Interestingly, IL-5 overexpression is necessary in mice to induce a condition similar to HES, suggesting that additional mechanisms may cooperate with the *FIP1L1-PDGFR* fusion gene in disease etiology.²⁰⁰

Clinical Features

The pulmonary involvement in patients with eosinophilia of clonal origin has not been studied extensively and especially has not been examined in cases classified according to the previously discussed two variants. However, lung or pleural involvement, although uncommon, has been mentioned in some cases^{194,195,201} in patients with clonal lymphoid proliferations. The following data derived from older studies including cases with the two previously mentioned variants of HES may therefore need reevaluation in the future, and the prevalence of pulmonary involvement might be much lower than previously considered.

The HES is more common in men than in women (9:1), and appears between 20 and 50 years.²⁰² The onset is generally insidious, with eosinophilia discovered incidentally in 12% of the patients.²⁰³ The mean eosinophil count at presentation was $20.1 \times 10^9/L$ (21,000/ μL), with an average highest value of $44.4 \times 10^9/L$ (44,000/ μL) in one series.²⁰⁴ Extremely high values of eosinophilia, in excess of $100 \times 10^9/L$ (100,000/ μL), are found in some patients.¹⁸⁴

The main presenting symptoms are weakness and fatigue (26%), cough (24%), and dyspnea (16%).²⁰³ One quarter of the patients may have asthmatic symptoms.²⁰⁵ Severe coughing attacks were present in 40% of the cases in one series²⁰⁴ with no other mention of bronchopulmonary disease. In another series,²⁰⁶ cough was also the predominant feature, with bronchospasm and pulmonary opacities in 11/40 patients each. Cardiovascular involvement, present in 58% of the patients,²⁰² is a major cause of morbidity and mortality. Fibrotic thickening of the endocardium by collagen-rich connective tissue (endomyocardial fibrosis) is characteristic of cardiac disease in HES,^{203,207} which differs from the cardiac involvement seen in EGPA.¹⁰⁷ Endomyocardial fibrosis is preceded by an initial acute necrotic stage followed by a thrombotic process (eFig. 68-5).²⁰² Cardiac manifestations include dyspnea, congestive heart failure, mitral regurgitation, and cardiomegaly.^{203,206} Echocardiography demonstrates the classic features of HES consisting of mural thrombus, ventricular apical obliteration, and involvement of the posterior mitral leaflet.²⁰⁸ The other manifestations of HES²⁰² include neurologic manifestations (thromboemboli, central nervous system dysfunction, and peripheral neuropathies) and cutaneous manifestations (erythematous pruritic papules and nodules, urticaria, and angioedema).^{202,209}

Imaging

Pulmonary involvement is present in about 40% of patients^{184,203} and includes pleural effusion, pulmonary emboli, and interstitial opacities. Chest CT findings in five patients consisted of small nodules with or without a halo of ground-glass attenuation and focal areas of ground-glass attenuation mainly in the lung periphery.²¹⁰ In another series, pulmonary radiologic manifestations varied but most commonly consisted of patchy ground-glass opacities and consolidation.²⁰⁵ CT findings are therefore poorly specific.³⁶ Some of the observed pulmonary imaging changes may correspond to pulmonary edema resulting from cardiac involvement rather than genuine eosinophilic lung involvement.

Laboratory Studies

Only mild eosinophilia at BAL contrasting with high levels of eosinophilia in the blood has been reported in patients with the HES,^{211,212} suggesting that eosinophilia may be compartmentalized in some patients with HES. Serum levels of mast cell tryptase may be elevated, and dysplastic mast cells may be found in the bone marrow, with some patients meeting minor criteria for systemic mastocytosis.²¹³

Treatment and Prognosis

Imatinib has become the first-line therapy in patients with the myeloproliferative variant of HES, especially (but not exclusively) when the *FIP1L1-PDGFR* fusion protein is present.^{198,199} Response to imatinib is more frequent, yet not restricted to, patients carrying the *FIP1L1-PDGFR*- α fusion protein.²¹⁴ Imatinib can be stopped without relapse in some patients, whereas in others low-dose imatinib is necessary to maintain long-term remission.²¹⁵ Corticosteroids may be used, especially in the “lymphocytic variant” of HES (with response in only about half of the patients).^{206,216} The anti-IL-5 antibody mepolizumab has recently been

shown to be beneficial as a corticosteroid-sparing agent in HES patients negative for the *FIP1L1-PDGFR* fusion gene and requiring 20 to 60 mg/day of prednisone to maintain a stable clinical status and a blood eosinophil count of less than $1 \times 10^9/L$ ($<1000/\mu L$).²¹⁷⁻²¹⁹ Other treatments include chemotherapeutic agents (hydroxyurea, vincristine, etoposide); cyclosporin A^{202,204,216}; and interferon- α either as monotherapy²²⁰⁻²²³ or in association with hydroxyurea, particularly in the myeloproliferative variant.^{224,225}

Whereas the 3-year survival was only 12% in the first published series,¹⁸⁴ the prognosis has improved markedly in later series with about 70% survival at 10 years,²⁰³ 80% survival at 5 years, and 42% at 10 and 15 years, respectively.²⁰⁶ It is fascinating that advances in molecular biology may result in direct clinical benefit and provide a better prognosis for patients with an up-to-now almost untreatable disease.

IDIOPATHIC HYPEREOSINOPHILIC OBLITERATIVE BRONCHIOLITIS

A distinct entity coined *hypereosinophilic obliterative bronchiolitis* has been recently identified¹⁵⁴ and is defined by the following provisional working criteria: (1) blood eosinophil cell count greater than $1 \times 10^9/L$ ($>1000/\mu L$) and/or bronchoalveolar lavage eosinophil count greater than 25%; (2) persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids; and (3) eosinophilic bronchiolitis at lung biopsy and/or direct signs of bronchiolitis (centrilobular nodules and branching opacities) on chest CT (Fig. 68-9).¹⁵⁴ Before this description, biopsy-proven isolated cases of eosinophilic bronchiolitis had been reported.^{226,227,227a} The blood eosinophil cell count is elevated (with a mean of $2.7 \times 10^9/L$ ($2700/\mu L$), and the mean eosinophil differential percentage at BAL was 63% in our series. Airflow obstruction is often severe but reversible with oral corticosteroid therapy in all cases. Whitish tracheal and bronchial granulations or bronchial ulcerative lesions can be present with prominent eosinophilia at bronchial biopsy.¹⁵⁴ Clinical and functional manifestations often recur when oral prednisone is tapered to less than 10 to 15 mg/

day. It is hypothesized that unrecognized and/or smoldering hypereosinophilic obliterative bronchiolitis might be a cause of irreversible airflow obstruction in chronic eosinophilic respiratory diseases. In addition to the idiopathic presentation, a similar condition of hypereosinophilic obliterative bronchiolitis can be encountered in patients with asthma, ABPA, or EGPA or may be induced by drugs, especially minocycline.¹⁵⁴

EOSINOPHILIC LUNG DISEASE OF DETERMINED CAUSE

EOSINOPHILIC PNEUMONIAS OF PARASITIC ORIGIN

The eosinophilic pneumonias related to parasite infestation probably represent the most common cause of eosinophilic pneumonia in the world. Parasitic eosinophilic pneumonia arises mainly in humans following infection by helminths (large multicellular worms) and especially nematodes (roundworms; see eFig. 39-1). The parasites may or may not be found at pathologic examination of the lung when performed (see also Chapter 39).

Tropical Eosinophilia

Clinical Features. Tropical eosinophilia²²⁸ is a syndrome characterized by severe spasmodic bronchitis, leukocytosis, and high blood eosinophilia. The clinical manifestations present mainly in the second and third decades of life, with a male predominance. It has been reported mostly in Indians and occasionally in patients originating from India or Asia and living in North America or in Europe.^{229,230} Tropical pulmonary eosinophilia is one of the most common causes of cough in tropical areas with endemic filariasis.²³¹ Patients develop a dry, hacking cough exacerbated at night (especially between 1 and 5 AM) and often associated with dyspnea and expiratory wheezing. Associated fever, loss of weight, and anorexia are common. Eosinophils, and sometimes Charcot-Leyden crystals, are present in the sputum. The chest radiograph can reveal patchy bilateral opacities and small nodules (see eFig. 39-2A and B, Fig. 39-2A and B).

Pathogenesis. Tropical eosinophilia caused by the filarial nematodes *Wuchereria bancrofti* and *Brugia malayi* is endemic in the tropical and subtropical areas of coastal regions of Asia, the southern and western Pacific, and Africa (less commonly in South and Central America). The adult worms reside in the lymphatic vessels, leading to lymphatic obstruction with subsequent elephantiasis. Humans are infected by infective larvae deposited in the skin by mosquitoes, which develop into mature worms within 6 to 12 months. First-stage larvae or microfilariae released from the fecund female's uterus circulate in the bloodstream from where they are ingested by the mosquitoes.

Patients with tropical pulmonary eosinophilia do not usually have clinical features of lymphatic filariasis. Microfilariae are usually not found in the blood or the lung. The circulating microfilariae are trapped in the lung vasculature where they release their antigenic contents, further triggering the inflammatory pulmonary reaction. The

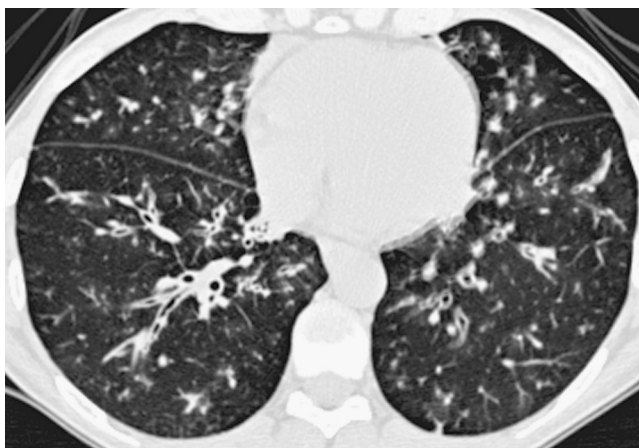


Figure 68-9 Idiopathic hypereosinophilic bronchiolitis. Axial chest CT scan of a patient with idiopathic hypereosinophilic bronchiolitis shows bronchial wall thickening, peripheral tree-in-bud and branching pattern, and central bronchiectasis with mucoid impaction.

clinical features of tropical pulmonary eosinophilia largely result from an immune response of the host to the parasites.²³²

Although blood eosinophilia is high at the early stage (<2 wk) of pulmonary disease, no prominent eosinophilic infiltration is found in the lung. Eosinophilic pneumonia is seen later (1 to 3 months), with the formation of eosinophilic abscesses and granulomatous lesions characterized by the presence of foreign body giant cells, fibroblasts, and epithelioid cells; prominent eosinophilic infiltration is present at the periphery of the granuloma. Cases left untreated for 5 years or more eventually show pulmonary fibrosis with histiocytic infiltration.

Laboratory Studies. Blood eosinophilia is prominent, with more than $2 \times 10^9/L$ ($>2000/\mu L$) in all cases and up to $60 \times 10^9/L$ ($>60,000/\mu L$) in some cases.²³³ IgE levels are increased. Antifilarial IgG antibodies are increased, as in all patients with filariasis. BAL shows intense alveolitis with a mean percentage of 54% of eosinophils with marked degranulation.²³⁴ High levels of eosinophil-derived neurotoxin are present in the BAL.²³⁵ In patients treated with diethylcarbamazine, BAL eosinophils drop within 2 weeks; blood eosinophils also decrease rapidly upon treatment.²³⁴

Persisting irregular basilar opacities are present in about two thirds of patients after 1 year. A “reticulonodular pattern” on chest CT is present in a majority of patients, with other features consisting of bronchiectasis, air trapping, and mediastinal lymphadenopathy.

Lung function tests show a restrictive ventilatory defect, with a reversible obstructive ventilatory defect and hypoxemia in about a quarter of the patients.^{236,237}

Because microfilariae are not detectable in the blood, the diagnosis is made in patients with residence for several months in an endemic area by the combination of the clinical, epidemiologic, and laboratory features, including blood eosinophilia persisting for weeks with an absolute eosinophil count in the blood greater than $3 \times 10^9/L$ ($3000/\mu L$), IgE levels exceeding 10,000 ng/ μL (4200 IU/mL; normal <100 IU/mL), and markedly increased antifilarial IgG. Diagnosis is further supported by clinical improvement in the weeks following treatment. The diagnostic criteria of tropical pulmonary eosinophilia include cough worse at night; residence in a filarial endemic area; eosinophil count greater than 3300/ μL ; and clinical and hematologic response to diethylcarbamazine.²³⁸

Treatment. Diethylcarbamazine is the only effective drug for tropical pulmonary eosinophilia; corticosteroids in addition to diethylcarbamazine may be beneficial.

Ascaris Pneumonia

Pulmonary opacities with eosinophilia (Löfller syndrome) may develop during the migration of the larvae of the parasite through the lung.

Ascaris lumbricoides is the most common helminth infecting humans, especially children, in the tropical and subtropical areas. Mature females in the human intestine release large numbers of eggs expelled with stools, which may survive for several months or years. The disease is transmitted through food or water contaminated by human feces. The infective larvae formed within eggs develop in the

small intestine, penetrate through the intestinal wall, and migrate via the venous circulation to the lungs, where they break out into the alveoli. They then migrate through the bronchi and trachea, are swallowed, and mature into adult worms in the small intestine.

Pulmonary manifestations develop during larval migration to the lungs. Usually, pulmonary symptoms are mild, with cough and wheezing, transient pulmonary opacities (see eFig. 39-1), and blood eosinophilia. Transient fever is present in the majority of patients, with possible pruritic eruption at the time of respiratory symptoms. Blood eosinophilia may be as high as $22 \times 10^9/L$ ($22,000/\mu L$).²³⁹ Symptoms spontaneously resolve in a few days, whereas blood eosinophilia may remain elevated for several weeks. The diagnosis may be made by finding larvae in the sputum or gastric aspirates but is more usually made by the delayed finding of the worm or ova in the stool within 3 months of the pulmonary manifestations.

Intestinal ascariasis is treated with oral mebendazole, 100 mg twice a day for 3 days, or albendazole, 400 mg once.²⁴⁰

Eosinophilic Pneumonia in Larva Migrans Syndrome

Visceral larva migrans²⁴¹ is a zoonotic infection caused in humans by *Toxocara canis*, a parasite infecting many dogs and other canines. Toxocariasis is found in all temperate and tropical areas of the world. Eggs released by female worms pass in the feces of infected dogs, and the soil of public playgrounds in urban areas is therefore often contaminated with eggs of *Toxocara*. Children playing in contaminated areas may become infected, especially when they practice geophagia. Ingested eggs hatch in the intestine, migrate through the portal circulation, and invade the liver, lung, and other organs. However, in humans, the development of the parasite is blocked at the larval stage.

Visceral larva migrans presents predominantly in children, the majority of whom remain asymptomatic and undiagnosed. When symptomatic, patients present with fever, pulmonary manifestations, seizures, and fatigue. Pulmonary manifestations in about 80% of cases consist of cough, wheezes, and dyspnea; pulmonary opacities on chest radiography are present in approximately half the patients with pulmonary symptoms.²⁴¹ Severe pulmonary involvement, which is seen in about 15% to 20% of cases, may benefit from corticosteroids.²⁴²

Although uncommon in adults, toxocariasis may be severe^{243,244} and necessitate mechanical ventilation. Patients present with fever, dyspnea, and pulmonary opacities on chest radiography. Wheezes or crackles are present at pulmonary auscultation. Blood eosinophilia may be present initially or may develop only in the following days. Eosinophils are increased in the BAL differential cell count.

The diagnosis of toxocariasis is difficult because a positive serodiagnosis may be caused by residual antibodies that do not have any diagnostic significance. IgM antibodies can be found throughout the course of helminthiasis and are not diagnostic of recent infection.²⁴⁵

Visceral larva migrans usually requires only symptomatic treatment, the use of antihelmintics being controversial. Corticosteroids seem beneficial in cases with severe pulmonary involvement.

***Strongyloides stercoralis* Infection**

Strongyloides stercoralis is an intestinal nematode that may cause severe autoinfection in immunocompromised patients. It is widely distributed in the tropics and subtropics. Human infection is acquired through the skin by contact with the soil of beaches or mud. Then larvae pass through the circulation to the lungs, where they break into alveoli, ascend the trachea, are swallowed, and reside in the small intestine where they mature. Females deposit eggs that hatch into larvae that pass with feces. Eosinophilia is usually present in recently infected patients, but it is often absent in disseminated disease.²⁴⁶ *S. stercoralis* infection may persist for years and give rise thereafter to severe disseminated strongyloidiasis, which may affect all organs (hyperinfection syndrome), especially with immunosuppression from any cause.

Löffler syndrome develops when larvae migrate through the lungs after acute infection (see eFig. 68-6A). Peripheral blood eosinophilia, in association with pneumonia, bronchospasm, or bronchitis and abdominal pain or diarrhea, suggests strongyloidiasis in patients living, or having traveled, in endemic areas.

About 20% of hospitalized patients with strongyloidiasis have coexisting chronic lung disease.²⁴⁷ Patients with chronic obstructive pulmonary disease (COPD) or asthma receiving corticosteroids and immunocompromised patients are at risk of hyperinfection syndrome. Eosinophilia may or may not be present. Cough, wheezing, and dyspnea are associated with bilateral patchy opacities. Rhabditiform larvae may be recovered by BAL or bronchial washing^{248,249} or in the sputum.²⁵⁰

Diagnosis of strongyloidiasis depends on the demonstration of larvae in the feces or in sputum and BAL fluid (see Fig. 39-1B-C). Immunodiagnostic assays by ELISA methods may be useful for diagnosis and screening. Because of the risk of hyperinfection syndrome that persists for years, all infected patients are treated when diagnosed (ivermectin 200 µg daily for 2 days and repeated 2 weeks later).

Eosinophilic Pneumonias in Other Parasitic Infections

The dog hookworm *Ancylostoma brasiliense* causing cutaneous helminthiasis (creeping eruption) may produce simple pulmonary eosinophilia in 50% of cases. Pulmonary manifestations develop after the seventh day of cutaneous eruption. The human hookworms *Ancylostoma duodenale* and *Necator americanus* are other possible causes of Löffler syndrome.

In early acute schistosomiasis (due to infection with either *Schistosoma haematobium* or *S. mansoni*), patients may develop transient, multiple, small pulmonary nodules on chest radiography (best seen on chest CT scan) and eosinophilia²⁵¹ (see eFig. 68-6B). In chronic schistosomiasis, embolization of ova in small arteries in the lungs results in granuloma formation, occlusion and remodeling of pulmonary arteries, and further pulmonary hypertension mediated by portopulmonary hypertension.^{252,253} The granuloma comprises lymphocytes, eosinophils, and giant cells. A post-treatment eosinophilic pneumonitis (also called lung shift, verminous pneumonia, and reactionary Löffler-like pneu-

monitis) may develop.²⁵⁴ It could result from parasitic antigen release following treatment.

The filarial parasite of dog *Dirofilaria immitis* (the pulmonary fluke) may occasionally develop into adult worms in the human lungs after inoculation of infective larvae by mosquitoes (eFig. 68-6C). It may manifest by eosinophilic pulmonary opacities on chest imaging studies (see Fig. 39-3).

Other parasites causing rare pulmonary manifestations with eosinophilia include *Paragonimus westermani* (see Fig. 39-4 and eFig. 39-3), *Trichomonas tenax*, *Capillaria aerophila*, and *Clonorchis sinensis* (see eFig. 68-6D).

EOSINOPHILIC PNEUMONIAS OF OTHER INFECTIOUS CAUSES

Pulmonary infection with eosinophilia has been reported with the fungi *Coccidioides immitis* (see eFigs. 37-5 through 37-12), *Bipolaris australiensis*, *Aspergillus niger*, and *Bipolaris spicifera*. BAL eosinophilia has been reported in *Pneumocystis jirovecii* pneumonitis in patients with acquired immunodeficiency syndrome (see eFigs. 90-11 through 90-20). Bacterial or viral pulmonary infection (e.g., tuberculosis, brucellosis, respiratory syncytial virus, influenza infection) may occasionally be a cause of eosinophilic pneumonia.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS AND RELATED SYNDROMES

Allergic Bronchopulmonary Aspergillosis

ABPA^{254a} is distinct from the other pulmonary manifestations due to the fungus *Aspergillus* such as invasive pulmonary aspergillosis developing in immunocompromised patients, aspergilloma developing in preexistent pulmonary cavities, or *Aspergillus fumigatus*-associated asthma.²⁵⁵ However, ABPA may be associated with chronic necrotizing aspergillosis.²⁵⁶ ABPA is characterized by asthma, eosinophilia, and bronchopulmonary manifestations with bronchiectasis secondary to a complex allergic and immune reaction to the presence of *Aspergillus* colonizing the airways in susceptible hosts who are unable to clear the respiratory epithelium of inhaled fungal spores. ABPA develops in 1% to 2% of adults with previous asthma present for several years (with a prevalence of 1% to 2%) and also in up to 7% to 10%^{257,258} of patients in large series of cystic fibrosis. ABPA may be associated with allergic *Aspergillus* sinusitis,^{259,260} which has been considered as a sinus equivalent of ABPA²⁶⁰⁻²⁶⁵ and results in a syndrome called *sinobronchial allergic aspergillosis*. Recently, cases of ABPA have been reported in patients with COPD^{266,267}; however, this association seems to be exceedingly rare despite impaired mucociliary clearance in COPD.

Pathogenesis. ABPA results from an immune and inflammatory reaction in the bronchi and the surrounding parenchyma in response to antigens from *Aspergillus* growing in mucous plugs in the airways of asthmatics. The immunologic response of the host includes—but is not restricted to—both type I hypersensitivity mediated by IgE antibodies and type III hypersensitivity with the participation of IgG and IgA antibodies and of a Th2 CD4⁺ T cell-mediated

immune response accompanied by sustained IL-17 expression.²⁶⁸ Over time, the associated inflammatory reaction results in damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma.^{269,270}

ABPA may have an environmental (and especially occupational) dimension, as suggested by a study of workers in the bagasse-containing sites in sugar cane mills, where ABPA was diagnosed in 7% of workers who had chronic respiratory problems.²⁷¹

Interestingly, an increased prevalence of heterozygotic *cystic fibrosis transmembrane conductance regulator* (CFTR) gene mutations has been reported in non-cystic fibrosis patients with ABPA or sinobronchial allergic mycosis,^{272,273} suggesting that CFTR gene mutations could be involved in the development of these conditions without overt cystic fibrosis. Genetic susceptibility to develop ABPA has also been suggested by association with a polymorphism within the IL-4 receptor α -chain gene²⁷⁴ and association with HLA-DR subtypes.²⁷⁵ Infection with nontuberculous mycobacteria may be seen with increased frequency in patients with ABPA.²⁷⁶ ABPA has been reported after infliximab therapy for sarcoidosis.²⁷⁷

Diagnostic Criteria. The classical diagnostic criteria include asthma, history of pulmonary opacities, proximal bronchiectasis, elevated serum IgE, and immunologic hypersensitivity to *A. fumigatus* such as immediate reaction to prick test for *Aspergillus* antigen, precipitating antibodies against *A. fumigatus*, and elevated specific IgE against *A. fumigatus*.^{278,279} Other common findings in patients with ABPA include the expectoration of mucous plugs, the presence of *Aspergillus* in sputum, and late skin reactivity to *Aspergillus* antigen.²⁷⁸ In patients with ABPA, typical proximal bronchiectasis may be absent; such cases are designated ABPA seropositive.²⁸⁰ Revised criteria have recently been proposed to account for some of the components that may be more important than others (Table 68-4).²⁸¹ A high index of suspicion should be maintained in patients with

particularly severe asthma, and yet those with negative *Aspergillus fumigatus*-specific IgE are unlikely to have ABPA.²⁸¹

About 40 antigenic components can bind with IgE antibodies, of which 22 recombinant *Aspergillus* allergens (named *Asp f1* to *Asp f22*) are identified.²⁸⁰ Specific antibodies to recombinant *Asp f4* and *Asp f6* may be the most helpful for diagnostic purposes.²⁸²

Five stages of ABPA have been distinguished: acute, remission, recurrent exacerbations, corticosteroid-dependent asthma, and fibrotic end stage. However, a newly proposed staging system merits evaluation.²⁸¹ Pulmonary opacities or peripheral blood eosinophilia may be present only during the acute phase or recurrent exacerbations of the disease.

Imaging. Damage to the large bronchi is a major feature of ABPA, with mucous plugs containing *Aspergillus* obstructing the airways with subsequent atelectasis and bronchial wall damage. Proximal bronchiectasis (in the medial half of the lung from the hilum to the chest wall) predominates in the upper lobes and is well visualized on chest CT.²⁸³⁻²⁸⁶ However, proximal bronchiectasis (see Fig. 48-10) lacks both sensitivity and specificity and further represents a complication of ABPA and not a diagnostic criterion of early disease.²⁸¹ Muroid impaction of high attenuation, mosaic attenuation, centrilobular nodules, and tree-in-bud opacities are also commonly seen (see Figs. 48-3 and 48-11). In asthmatic patients, the presence of bronchiectasis affecting three or more lobes, centrilobular nodules, and muroid impaction on CT scan is highly suggestive of ABPA (Fig. 68-10)²⁸⁷; because of its characteristic imaging presentation, the correct diagnosis of ABPA was made on CT scan in 84% of cases of ABPA in a series of patients with eosinophilic lung diseases.³⁶ The CT imaging pattern may be classified as serologic ABPA (without bronchiectasis), ABPA with bronchiectasis, ABPA with high-attenuation mucus, and ABPA with pleuropulmonary

Table 68-4 Newly Proposed Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis

Predisposing conditions	<ul style="list-style-type: none"> ■ Bronchial asthma ■ Cystic fibrosis
Obligatory criteria (both should be present)	<ul style="list-style-type: none"> ■ Type I <i>Aspergillus</i> skin test positive (immediate cutaneous hypersensitivity to <i>Aspergillus</i> antigen) or elevated IgE levels against <i>Aspergillus fumigatus</i> ■ Elevated total IgE levels (>1000 IU/mL)*
Other criteria (at least 2 of 3)	<ul style="list-style-type: none"> ■ Presence of precipitating or IgG antibodies against <i>A. fumigatus</i> in serum ■ Radiographic pulmonary opacities consistent with ABPA† ■ Total eosinophil count >500 cells/μL in steroid-naïve patients (may be historical)

*If the patient meets all other criteria, an IgE value < 1000 IU/mL may be acceptable.

†The chest radiographic features consistent with ABPA may be transient (i.e., consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (i.e., parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis).

From Agarwal R, Chakrabarti A, Shah A, et al: Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 43:850–873, 2013.

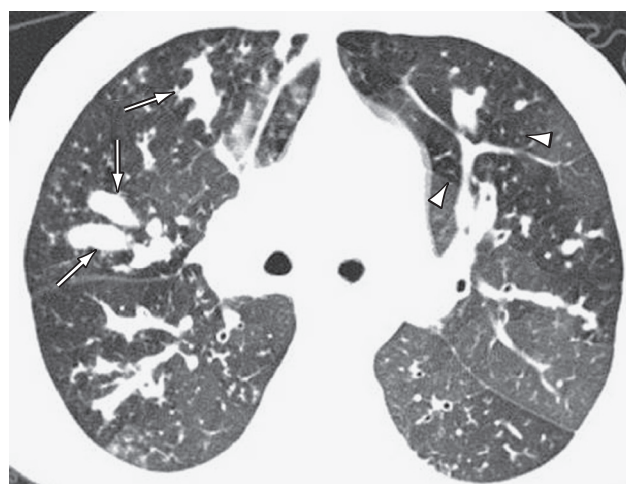


Figure 68-10 Allergic bronchopulmonary aspergillosis. Axial CT scan of a patient with allergic bronchopulmonary aspergillosis shows central bronchiectasis with mucoid impaction (arrows). Diffuse bilateral inhomogeneous lung opacity is present, with areas of low attenuation throughout the pulmonary parenchyma (arrowheads) representing mosaic perfusion resulting from a combination of large and small airway inflammation.

fibrosis.²⁸¹ In a series of patients with serologic ABPA, central bronchiectasis did not develop during follow-up,²⁸⁸ suggesting that it may correspond to a variant rather than an early stage of disease. Although surgery is seldom warranted, eosinophilic pneumonia may be found in resection specimens from patients with asthma and ABPA with chronic pulmonary consolidation.^{283,289}

The initial stage of ABPA is characterized on imaging by either fleeting opacities due to eosinophilic pneumonia or mucus plugging with ensuing segmental, lobar, or even whole-lung atelectasis. Fever is present. Blood eosinophilia is generally greater than $1 \times 10^9/L$ ($>1000/\mu L$). Sputum and expectorated plugs contain eosinophils and Charcot-Leyden crystals. Serum levels of TARC are elevated and might be used as a marker for identification and monitoring of ABPA.^{290,291} Mucoid bronchial impaction is typically characterized by a V-shaped lesion with the vertex pointing toward the hilum and atelectasis.²⁹² The diagnosis is rarely made at the early acute stage.

Treatment. Management decisions in ABPA are generally based on low-level evidence. In addition to conventional treatment of severe asthma (i.e., high-dose inhaled corticosteroids and long-acting bronchodilators), the treatment of ABPA mainly relies on corticosteroids during exacerbations, with long-term corticosteroids maintained only in patients with frequent symptomatic attacks or evidence of progressive lung damage. Treatment of episodes of pulmonary consolidation may prevent the progression of ABPA to the fibrotic end stage.²⁹³ Inhaled corticosteroids may reduce the need for long-term oral corticosteroids. Oral itraconazole is a useful adjunct to corticosteroids, allowing reduction of the doses of corticosteroids.^{294,295} A double-blind, randomized, placebo-controlled 16-week study indicated that patients with corticosteroid-dependent ABPA generally benefit from concurrent itraconazole treatment; improvements included the immunologic and physiologic criteria and the corticosteroid dose, but there was no significant effect on pulmonary opacities.²⁹⁶ Another randomized study with itraconazole demonstrated that subjects receiving itraconazole had a decrease in sputum eosinophils, sputum eosinophil cationic protein levels, serum IgE levels, and serum IgG levels to *A. fumigatus* and had fewer exacerbations than patients receiving placebo.²⁹⁷ Uncontrolled studies further suggest that itraconazole is potentially useful in ABPA patients with cystic fibrosis.^{298,299} On the basis of these data, the use of itraconazole may be effective in approximately 60% of ABPA patients with asthma²⁹⁹ and is recommended.³⁰⁰ Duration of itraconazole therapy is not standardized; however, treatment is generally continued for a minimum of 4 to 6 months. Itraconazole interacts with many medications and may further induce adrenal insufficiency^{301,302}; oral prednisone and inhaled beclomethasone or ciclesonide should be preferred to oral methylprednisolone and budesonide or fluticasone to reduce interactions.²⁹⁹ Measuring total serum IgE level may be helpful for monitoring therapy. Clinical and radiologic improvement along with a 25% or greater decline in serum total IgE level signifies satisfactory response to therapy.²⁸¹

Treatment with an anti-IgE recombinant antibody omalizumab may be useful in some cases³⁰³⁻³⁰⁵ and in short series,^{306,307} with possibly fewer episodes of exacerbation

and reduction of steroid dose. The appropriate dosing, however, is unknown in the setting of ABPA with IgE levels that exceed 1000 IU/mL. Pulses of intravenous corticosteroids have also been used to treat exacerbations. The newer agents voriconazole and posaconazole have been successfully used in ABPA only in isolated case reports, especially in cystic fibrosis but with no proven benefit as compared with itraconazole.³⁰⁸⁻³¹⁰ Sustained improvement has been reported following administration of nebulized liposomal amphotericin B in patients with ABPA that was difficult to control using the standard treatment regimen.^{311,312}

Other Allergic Bronchopulmonary Syndromes Associated with Fungi or Yeasts

A similar syndrome of allergic bronchopulmonary disease may be produced by other fungi or yeasts.^{313,313a} The frequency of this condition is far less than that of ABPA. The diagnosis is difficult due to the necessity to document for sensitization to the specific fungi.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis³¹⁴ has been described as an inflammatory and destructive process beginning within the bronchiolar walls and further extending into the surrounding parenchyma with a peribronchiolar distribution of the lesions.³¹⁵ The granulomatous inflammatory process destroys both the mucosa and the walls of the bronchioles, and the necrotic areas resulting from the destroyed bronchioles are often surrounded by palisading histiocytes. Scattered fungal hyphae may be demonstrated by the Grocott silver stain in some patients. A dense inflammatory infiltrate is, in most cases, present in the peribronchial tissue. In asthmatic patients with bronchocentric granulomatosis, eosinophils compose the major proportion of the infiltrate. Other possible changes include vascular inflammation and mucoid impaction.^{315,316}

About half the patients with bronchocentric granulomatosis at lung pathologic examination are asthmatics who further present with fever and cough. A peripheral blood eosinophilia is common, generally greater than $1 \times 10^9/L$ ($>1000/\mu L$).^{315,316} The radiographic features consist of masses (eFig. 68-7), alveolar opacities or pneumonic consolidation, or reticulonodular opacities, which predominate in the upper lobes and are unilateral in a majority of patients.^{317,318} Most of these patients fulfill the criteria for ABPA, and those treated with corticosteroids have an excellent prognosis, although recurrences are common.³¹⁵ Eosinophilia is usually not conspicuous when bronchocentric granulomatosis develops in patients without asthma (an infectious cause is found in some cases).

DRUG-, TOXIC AGENT-, AND RADIATION-INDUCED EOSINOPHILIC PNEUMONIAS

DRUGS

More than 80 drugs have been reported to cause eosinophilic pulmonary opacities and especially acute eosinophilic pneumonia (Table 68-5). However, the causality has not been established in many case reports and thus the number

Table 68-5 Drugs That May Cause Acute Eosinophilic Pneumonia

Ampicillin	Mefenamic acid
Cannabis	Minocycline
Chloroquine	Nomifensine
Cocaine (snorted)	Progesterone
Daptomycin	Pyrimethamine-sulfadoxine
Ethambutol	Risperidone
Excipients and vehicle	Sertraline
Fludarabine	Tacrolimus
Fluoxetine	Tobacco smoking, cigarette smoke
Gemcitabine	Tryptophan
Heroin	Venlafaxine
Infliximab	

Data from www.pneumotox.com.

of drugs that can reliably be considered as a common cause of drug-induced eosinophilic pneumonia is much smaller. Drugs causing eosinophilic pneumonia are mainly nonsteroidal anti-inflammatory drugs and antibiotics. The online database www.pneumotox.com is a reliable reference in the evaluation of suspected cases, providing a list of causative drugs for which eosinophilic lung disease has been published.

Drug-induced eosinophilic lung disease may present in three main clinical settings: (1) patients taking a drug for several months (or years) for the treatment of chronic disease who progressively develop increasing dyspnea with cough and mild fever; (2) asymptomatic patients who are found to have an interstitial lung disease by routine chest radiography; (3) patients who present with acute eosinophilic pneumonia sometimes requiring mechanical ventilation. Associated extrapulmonary iatrogenic manifestations, especially cutaneous rashes, fever, or nausea, may be present. Severe cases may present as *drug reaction with eosinophilia and systemic symptoms* (DRESS).^{319,320}

All the drugs taken in the weeks or months preceding the clinical syndrome must be carefully recorded in any patient presenting with eosinophilic pneumonia, including illicit drugs (cocaine, heroin), the intake of which is often denied by the patient.

Simple pulmonary eosinophilia also called Löffler syndrome (with transient pulmonary opacities), chronic eosinophilic pneumonia, and acute eosinophilic pneumonia have all been reported as drug-induced syndromes. Systemic eosinophilic vasculitis involving the lung (and thus closely resembling EGPA) has also been reported.^{141,321}

The regression of eosinophilic lung disease after stopping the drug is the best clue for an iatrogenic reaction. However, this may take a long time and, therefore, in many reported cases, corticosteroids have been given concomitantly with drug withdrawal, so the responsibility of the drug cannot be definitely established. The only absolute proof of the drug responsibility would be obtained by its reintroduction with ensuing relapse of pneumonia, but this may be dangerous and thus unethical if done only for scientific purposes. Careful reintroduction of a drug presumed to be the cause of eosinophilic pneumonia may be considered with careful monitoring only when no alternative treatment for a serious disease is available.

Presentation of eosinophilic drug-induced pneumonia is generally nonspecific. Although, in most cases, patients present with pulmonary manifestations compatible with

ICEP (with the exception of possible associated pleural effusion and extrapulmonary manifestations including cutaneous rash), other patients present with features characteristic of IAEP. Therefore, in any case of “idiopathic” eosinophilic pneumonia, an iatrogenic cause must be systematically considered.

The eosinophilia-myalgia syndrome, which developed in 1989 in the United States, was related to the intake of contaminated preparations of L-tryptophan. It manifested with frequent dyspnea and cough, myalgia, fatigue, rash, paresthesia, swelling, and muscle weakness, with interstitial lung disease or opacities on chest CT in 13% of cases,³²² and peripheral blood eosinophilia. The outcome was favorable, especially in patients receiving corticosteroids.³²²⁻³²⁴ A new case has been reported recently after the sale of L-tryptophan has been authorized again.³²⁵

Ingestion of denatured cooking oil was the cause of the toxic oil syndrome, which affected about 20,000 people in Spain in 1981.³²⁶ This scleroderma-like disorder was characterized by an interstitial-alveolar pattern on chest imaging and eosinophilia during the first 4 months.

RADIATION THERAPY

Chronic eosinophilic pneumonia may develop after radiation therapy for breast cancer.^{327,328} It was seen in women with a history of asthma or allergy, at a median time of 3.5 months and up to 10 months after completion of radiotherapy for breast cancer (one case has been reported six years after completion of radiation therapy).³²⁹ Dyspnea and cough were the main presenting symptoms, with pulmonary opacities at imaging being unilateral (involving the irradiated lung) or bilateral, and possibly migratory. All patients had blood eosinophilia of $1.0 \times 10^9/L$ (1000/ μL) or greater and/or eosinophilia greater than 40% on the BAL differential cell count. Patients rapidly improved with oral corticosteroids without sequelae, but some patients relapsed after treatment withdrawal. This syndrome is similar to the organizing pneumonia syndrome primed by radiation therapy to the breast,³³⁰ with eosinophilic pneumonia developing preferentially in patients with asthma or atopy. Eosinophilic pneumonia may also develop on radiation therapy preferentially in patients with a preexisting Th2-oriented lymphocyte response,^{327,331,332} together with yet unidentified additional factors.

MISCELLANEOUS LUNG DISEASES WITH ASSOCIATED EOSINOPHILIA

Eosinophilia in blood and/or in BAL has been reported in some pulmonary disorders in which eosinophilic pneumonia is not a major finding.

ORGANIZING PNEUMONIA

Organizing pneumonia is defined by the presence of buds composed of inflammatory cells, fibroblasts, and connective tissue within the lumen of distal air spaces. It may be secondary to various causes (such as infection or drug-induced reactions) or be cryptogenic. The typical clinical and

imaging features (patchy alveolar opacities) of organizing pneumonia may closely mimic ICEP.³³³ Furthermore, pathologic overlap of organizing pneumonia and ICEP may be encountered, with foci of organizing pneumonia in ICEP, and eosinophils in organizing pneumonia. In some cases, organizing pneumonia may represent the evolution of an untreated CEP.³³³ Eosinophilia in BAL may be present in cryptogenic organizing pneumonia, but it is usually less than 20% at differential cell count.

ASTHMA AND EOSINOPHILIC BRONCHITIS

Infiltration of the airways by eosinophils is common in the eosinophilic pneumonias but may also be an isolated phenomenon. The eosinophil is considered to play a major role in the pathogenesis of asthma.³³⁴ Eosinophilic inflammation of the airways present in the submucosa and epithelium of patients with asthma is correlated with severity of asthma.³³⁵ BAL has shown mildly increased levels of eosinophils (usually <5%) on differential cell count in asthmatics, with the increase in eosinophils in the alveolar samples less than in bronchial samples.³³⁶ Interestingly, although eosinophilic infiltration of the bronchi is common in the eosinophilic pneumonias, asthma is not a constant feature in such disorders. The eosinophilic phenotype of asthma has recently been the focus of particular attention because substantial eosinophilic airway inflammation (often with little or no increase in the peripheral blood eosinophil numbers) is a marker of steroid-responsive disease, is associated with a high risk of exacerbations, and may be targeted by specific inhibitors, including the anti-IL-5 humanized monoclonal antibodies mepolizumab and reslizumab, and a monoclonal antibody to the IL-5 receptor (IL5RA) benralizumab.³³⁷ Furthermore, some patients present with asthma and important blood hypereosinophilia (i.e., >1 and especially $>1.5 \times 10^{-9}/L$ (1500/ μL) or alveolar eosinophilia (>25% and especially >40%), a condition tentatively labeled “hypereosinophilic asthma.”^{338,339} Hypereosinophilic asthma is generally severe, frequently requires high-dose inhaled or even oral corticosteroids, and may progress to EGPA, ABPA, or ICEP.

Eosinophilic bronchitis (without asthma) with a high percentage of eosinophils (about 40%) in sputum is a cause of chronic cough responsive to corticosteroid treatment,³⁴⁰ with normal lung function and absence of bronchial hyperactivity.^{341,342} It is not accompanied by eosinophilic pneumonia. The observed values of sputum eosinophils are often much higher in eosinophilic bronchitis than in asthma.³⁴² The *FIP1L1-PDGFR* fusion gene has been reported in one patient with eosinophilic bronchitis.³⁴³ Treatment is based on inhaled corticosteroids.^{340,344} Treatment with an antagonist of the eotaxin tissue receptor CCR3, the receptor for eotaxin and other chemokines, may be beneficial.³⁴⁵ Eosinophilic bronchitis is distinct from bronchial asthma, although it may in rare cases evolve over time to irreversible airflow obstruction without asthma or to genuine asthma.^{346,347}

IDIOPATHIC INTERSTITIAL PNEUMONIAS

Mildly increased levels of eosinophils may be found in the BAL differential cell count in the idiopathic interstitial pneumonias (idiopathic pulmonary fibrosis, nonspecific

interstitial pneumonia, cryptogenic organizing pneumonia, desquamative interstitial pneumonia). Increase of BAL eosinophils is associated with a poor outcome.³⁴⁸⁻³⁵⁰ Focal eosinophilic pneumonia has been reported in cases of usual interstitial pneumonia,³⁵¹ and focal findings of eosinophils are a minor feature of nonspecific interstitial pneumonia.³⁵²

LANGERHANS CELL HISTIOCYTOSIS

Pulmonary Langerhans cell histiocytosis (also designated as eosinophilic granuloma or pulmonary histiocytosis X) results from the proliferation of Langerhans cells. The pulmonary pathologic lesions consisting of nodules often assuming a bronchiolocentric stellate shape are composed of Langerhans cells with variable numbers of eosinophils, plasma cells, and lymphocytes. Eosinophils usually present in the initial active stage of disease contribute to the “eosinophilic granuloma.” Numerous in about 25% of cases, they are usually situated at the periphery of the lesions. The eosinophils are rare or absent at the chronic stage of disease.

LUNG TRANSPLANTATION

Eosinophilic alveolitis in lung transplant recipients may be indicative of acute rejection (tissue eosinophilia is involved in rejection after renal, cardiac, hepatic, and pancreatic transplantation). BAL eosinophilia of 2% or greater is associated with a poor outcome in lung transplantation.³⁵³ However, pulmonary eosinophilia in lung transplant recipients may also result from infectious agents such as *Aspergillus*, *Pseudomonas*, or coxsackievirus.³⁵⁴

OTHER LUNG DISEASES WITH OCCASIONAL EOSINOPHILIA

Blood eosinophilia and tissue eosinophilia may be present in sarcoidosis but are usually mild.³⁵⁵ Pulmonary eosinophilia developed in two patients after transplantation for sarcoidosis, with bronchiolitis obliterans syndrome developing after resolution of pulmonary eosinophilia.³⁵⁶ Eosinophilic pneumonia was reported in a patient with gastric cancer producing GM-CSF and IL-5.³⁵⁷

Key Points

- Eosinophilic lung disease may manifest clinically with varying severity, ranging from chronic or transient opacities with mild symptoms to the acute severe eosinophilic pneumonia resembling acute lung injury or acute respiratory distress syndrome and necessitating mechanical ventilation.
- Blood eosinophilia greater than 1×10^9 eosinophils/L (and preferably $>1.5 \times 10^9/L$ or 1500/ μL) is of considerable help for suggesting the diagnosis. However, blood eosinophilia may be absent (as in the early phase of idiopathic acute eosinophilic pneumonia or when patients are already taking corticosteroids).
- On bronchoalveolar lavage, high eosinophilia (>25%, and preferably >40%) may be considered diagnostic of eosinophilic pneumonia in a compatible setting.

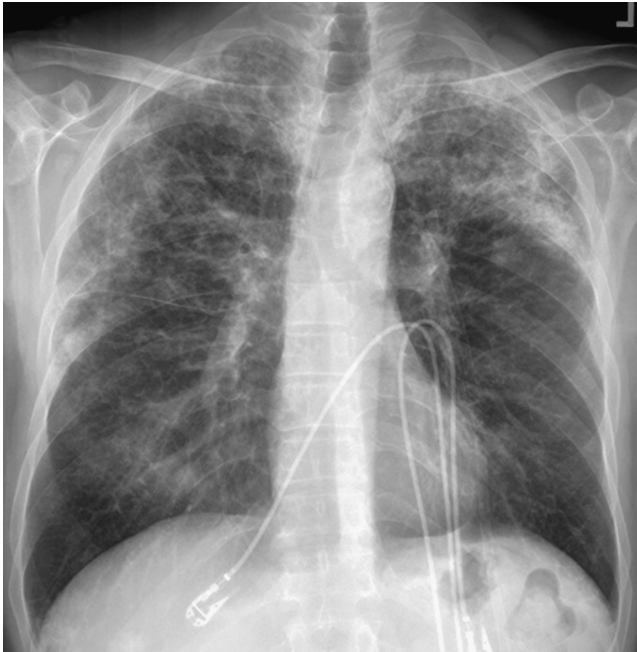
- Inquiry concerning drug intake must be meticulous (www.pneumotox.com), and any suspected drug should be withdrawn.
- Consideration of parasitic causes must take into account the travel history or residence and the epidemiology of parasites.
- When present, extrathoracic manifestations raise the suspicion of a systemic eosinophilic disease such as *eosinophilic granulomatosis with polyangiitis* (Churg-Strauss syndrome) (EGPA) or *hypereosinophilic syndrome* (HES), whereas airflow obstruction can be found in hypereosinophilic asthma, allergic bronchopulmonary aspergillosis, idiopathic chronic eosinophilic pneumonia, EGPA, or in the recently identified syndrome of hypereosinophilic obliterative bronchiolitis.
- Corticosteroids remain the cornerstone of symptomatic treatment for eosinophilic disorders, with a generally dramatic response, but relapses are common when tapering the doses or after stopping treatment. Cyclophosphamide is necessary in patients with EGPA and poor prognostic factors.
- Imatinib has proved effective in the treatment of the myeloproliferative variant of HES.

Complete reference list available at *ExpertConsult*.

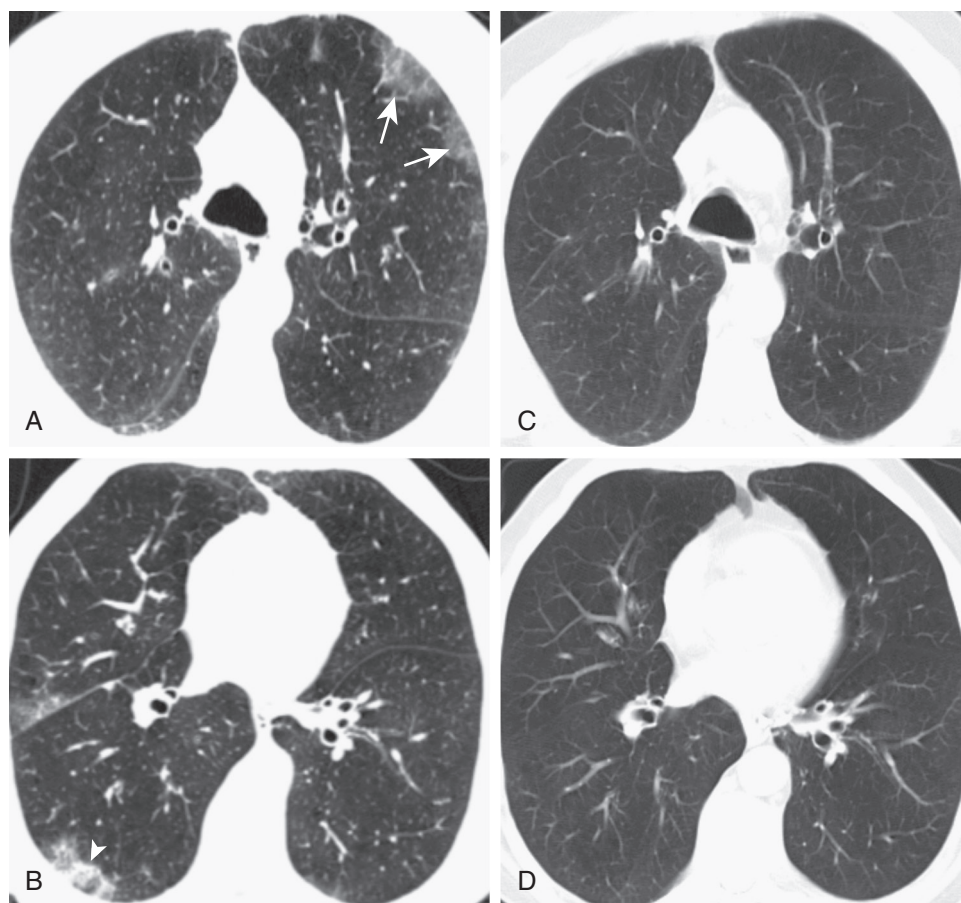
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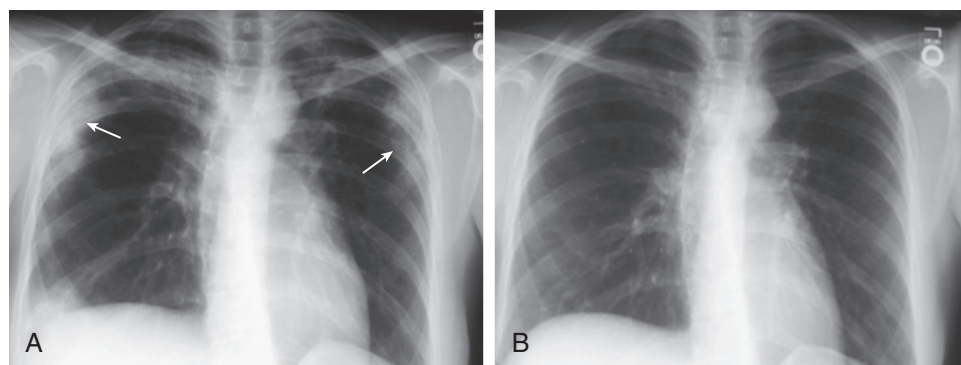
eFIGURE IMAGE GALLERY



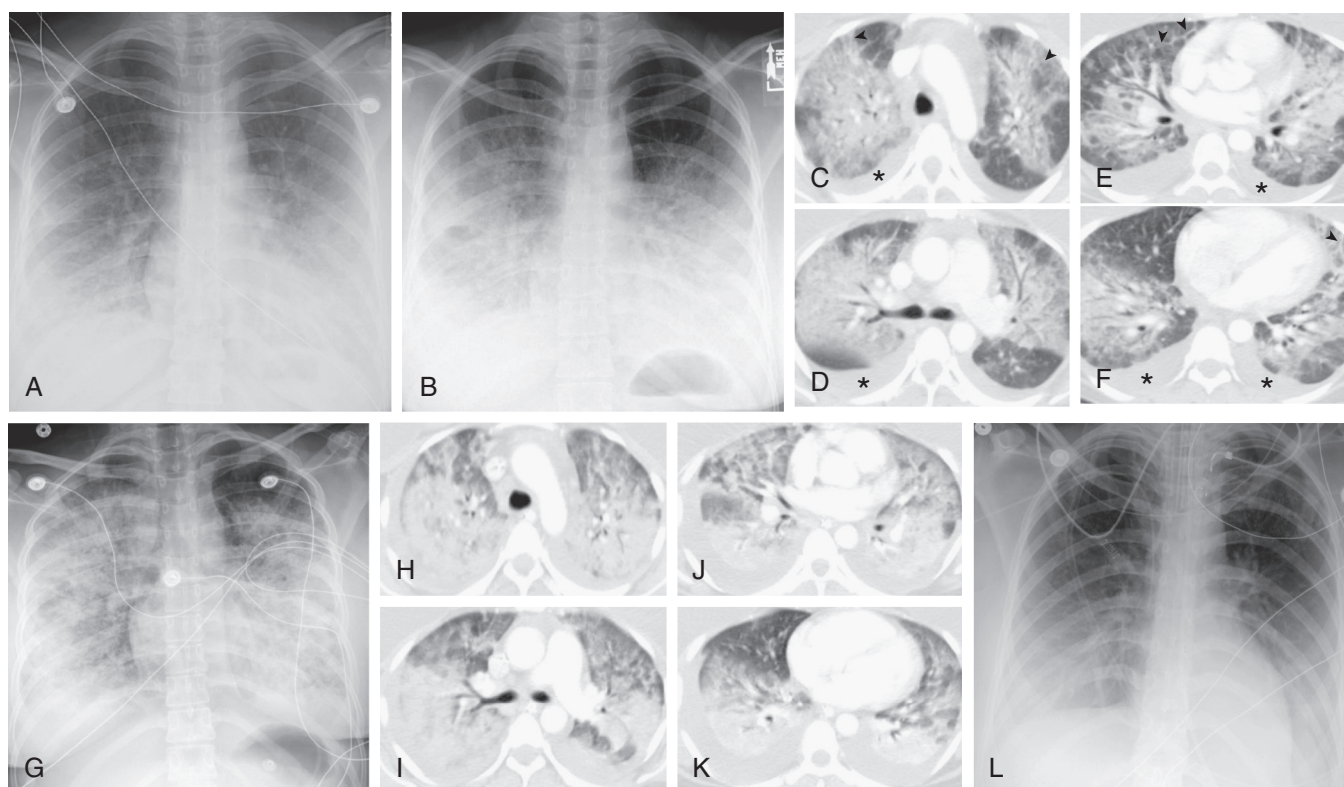
eFigure 68-1 Idiopathic chronic eosinophilic pneumonia: chest radiographic findings. Frontal chest radiograph in a patient with chronic eosinophilic pneumonia shows bilateral, upper lobe predominant peripheral consolidation and bronchovascular thickening (see [Video 68-1](#) for chest CT for this patient). (Courtesy Michael Gotway, MD.)



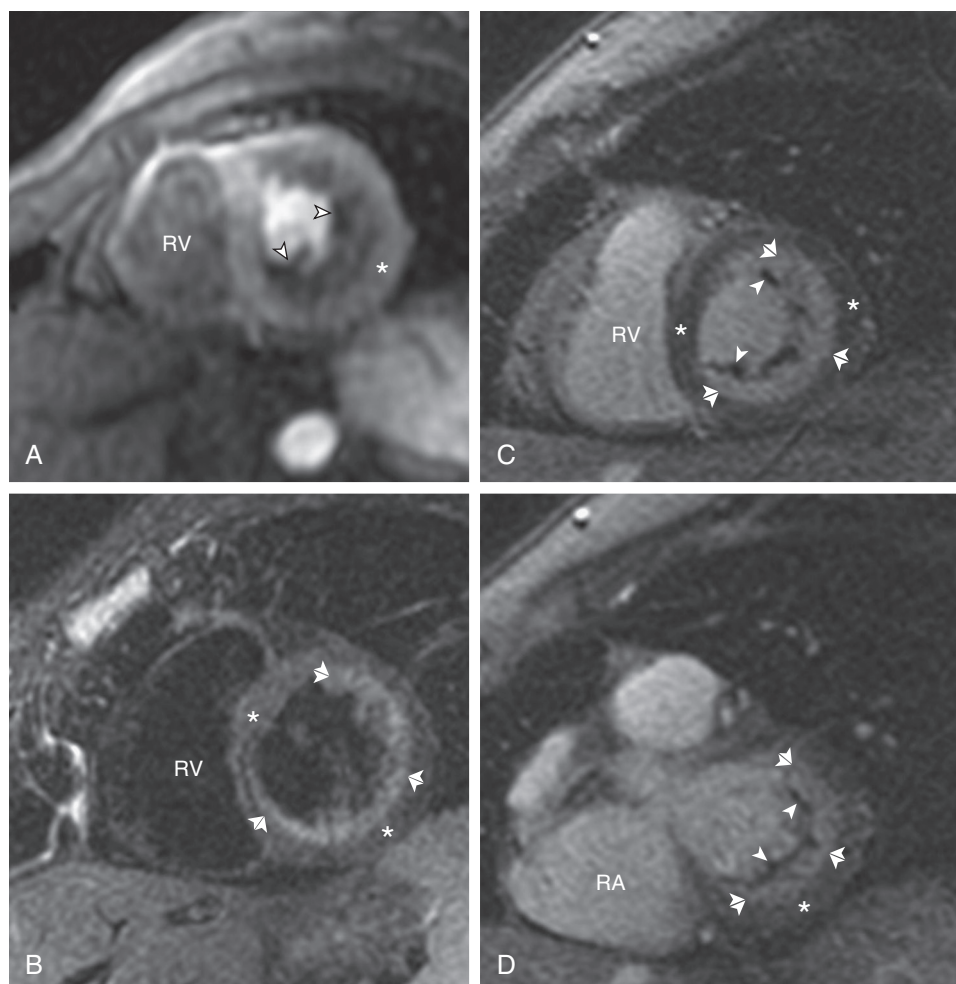
eFigure 68-2 Idiopathic chronic eosinophilic pneumonia: clearing following corticosteroid therapy at chest CT. **A** and **B**, Axial chest CT in a patient with chronic eosinophilic pneumonia, displayed in lung windows, shows patchy, bilateral areas of subpleural ground-glass opacity (*arrows*) and consolidation (*arrowhead*). **C** and **D**, Axial chest CT displayed in lung windows following corticosteroid therapy shows resolution of the areas of ground-glass opacity and consolidation. (Courtesy Michael Gotway, MD.)



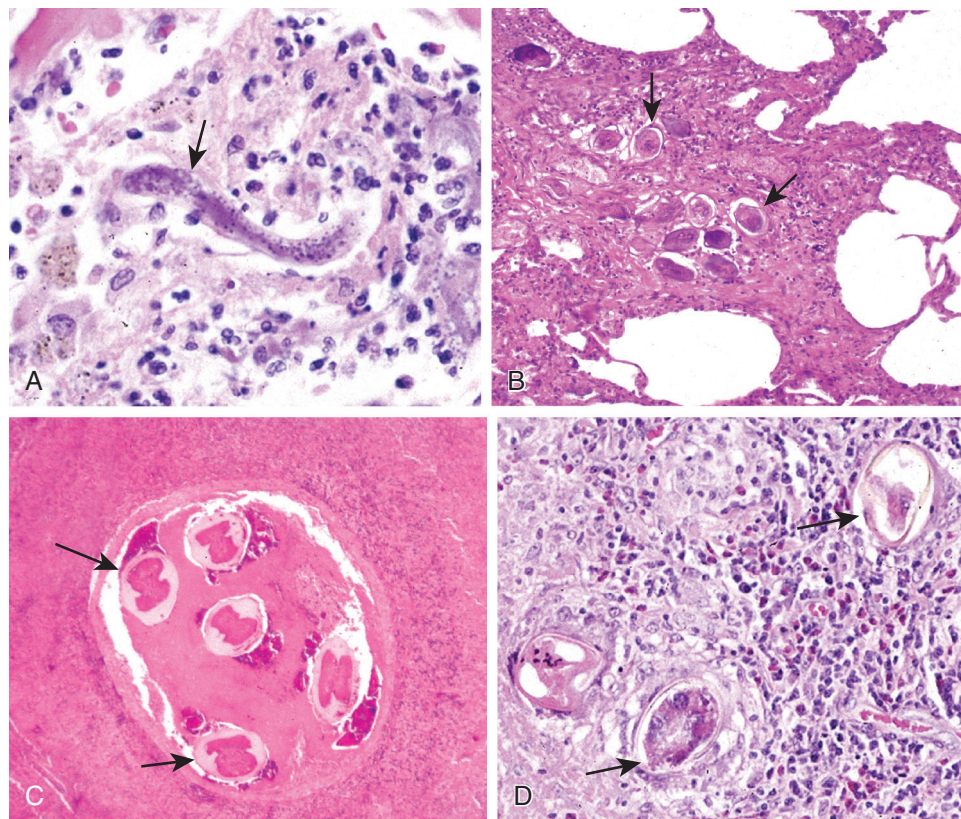
eFigure 68-3 Idiopathic chronic eosinophilic pneumonia: clearing following corticosteroid therapy at chest radiography. **A**, Frontal chest radiograph in a patient with chronic eosinophilic pneumonia shows the typical appearance of upper lobe, bilateral, subpleural consolidation (*arrows*). **B**, Frontal chest radiography following corticosteroid therapy shows clearing of the consolidation. (Courtesy Michael Gotway, MD.)



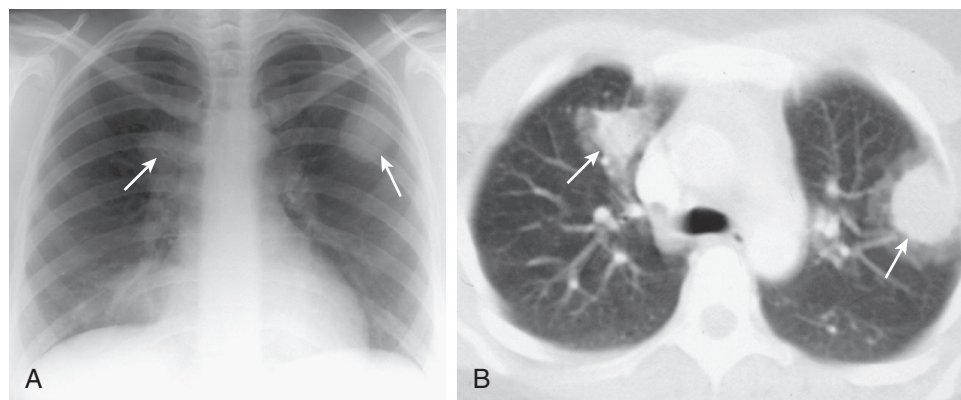
eFigure 68-4 Idiopathic acute eosinophilic pneumonia: chest radiographic and chest CT findings with evolution. **A**, Frontal chest radiograph in a 31-year-old previously healthy, immunocompetent, nonsmoking woman, performed on the first day of hospitalization, shows bilateral, symmetrical, mid- and lower lung-predominant opacities with preserved lung volumes, normal mediastinal width, and no clear pleural effusions. The patient initially complained of cough and was treated with broad-spectrum antibiotics but worsened, developing shortness of breath and fever. **B**, Frontal chest radiograph performed on the second day of hospitalization shows progression of the bilateral pulmonary opacities. **C–F**, Axial chest CT displayed in lung windows on the third hospital day shows symmetrical, bilateral, diffuse air space consolidation and ground-glass opacity with a background of smooth interlobular septal thickening (*arrowheads*). Small symmetrical bilateral pleural effusions (*) are seen. **G**, Frontal chest radiograph on the third hospital day shows continued progression in bilateral and now extensive air space consolidation. **H–K**, Axial chest CT displayed in lung windows after the patient suffered profound oxygen desaturation, requiring transfer to the intensive care unit and intubation, shows progression in the bilateral ground-glass opacity and consolidation with slight enlargement of the pleural effusions. **L**, Frontal chest radiograph performed 6 days after hospitalization, following administration of corticosteroids initiated after bronchoscopy with BAL revealed abundant eosinophilia, shows marked clearing of the bilateral air space opacities. The patient remains intubated, but her respiratory status continued to improve rapidly and she was subsequently extubated and then discharged home 5 days later. (Images courtesy Paul Conomos, MD, Arizona Pulmonary Specialists, Phoenix. From Gotway MB, Conomos PJ: Rapidly progressive pulmonary opacities on thoracic imaging studies. *Clin Pulmon Med* 15:300–303, 2008, Fig. 5).



eFigure 68-5 Cardiac involvement in hypereosinophilic syndrome: cardiac MRI findings showing the characteristic “three-layered” appearance of endomyocardial fibrosis. **A**, Short-axis, first-pass perfusion image shows extensive low-signal, nonenhancing thrombus (*arrowheads*) within the left ventricle, adjacent to the enhanced left ventricular cavity, internal to the left ventricular muscle (*). **B**, Short-axis triple inversion recovery image (a fluid and inflammation-sensitive sequence) shows diffuse high signal involving the severely thickened endomyocardium (*double arrowheads*), internal to the normal-appearing, intermediate signal left ventricular musculature (*). **C** and **D**, Short-axis, inversion-recovery-prepared, fast-gradient echo late gadolinium enhancement images (obtained 10 minutes following the intravenous administration of gadolinium), at the base of the heart, show the hypointense thrombus (*single arrowheads*) associated with extensive enhancement of the inflamed (and possibly fibrotic) and markedly thickened endomyocardium (*double arrowheads*), interposed between the low signal thrombus (*single arrowheads*) and normal-appearing left ventricular muscle (*). RA, right atrium; RV, right ventricle. (Images courtesy Philip A. Araoz, MD, Department of Radiology, Mayo Clinic, Rochester MN.)



eFigure 68-6 Parasites in the lung. **A**, Filariform larva of *Strongyloides stercoralis* (arrow) penetrating into alveolar space with associated inflammation. **B**, Schistosoma eggs in lung parenchyma (arrows). **C**, Dirofilarial nodule, with worm remnants (arrows) in organizing thrombosed vessel. **D**, *Paragonimus westermani* with yellowish refractile eggs (arrows) in eosinophil-rich exudates. (Modified from Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, Figs. 6-115, 116, 118A, and 119.)



eFigure 68-7 Bronchocentric granulomatosis: chest radiographic and chest CT findings. **A**, Frontal chest radiograph performed in a 20-year-old nonsmoking woman with pleuritic chest pain shows bilateral, upper lobe pulmonary nodules and masses (arrows). **B**, Axial chest CT displayed in lung windows shows the lesions at chest radiography to be somewhat poorly defined, with faint, surrounding ground-glass opacity halos (arrows). Percutaneous biopsy of the dominant left upper lobe lesion showed only necrotizing granulomatous inflammation without evidence of malignancy. Subsequently, surgical lung biopsy was performed and showed bronchocentric granulomatosis. The patient's symptoms and lesions resolved following corticosteroid therapy, and she suffered no recurrences during 5 years of follow-up. (Courtesy Michael Gotway, MD.)

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PROGRESSION AND PROGNOSIS**FUTURE CLINICAL TRIALS IN****LYMPHANGIOLEIOMYOMATOSIS**

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare neoplastic disease characterized by a genetic association with the neurocutaneous syndrome, *tuberous sclerosis complex* (TSC), marked female gender predominance, cystic destruction of the lung, and progressive respiratory failure. Symptoms and signs include dyspnea on exertion, recurrent pneumothorax, abdominal tumors including renal *angiomyolipomas* (AMLs) and lymphangiomyomas, and chylous fluid accumulation in the chest and abdomen.^{1,2}

LAM was first reported in a patient with TSC who presented with bilateral spontaneous pneumothorax in 1918³ and in a patient without TSC in 1937.⁴ In the 1950s through the late 1960s, there were solitary case reports or small case series that fostered a varied and confusing pathologic nomenclature in the literature. Cornog and Enterline,⁵ for example, described six cases of “lymphangioleiomyoma” in 1966 and reviewed 14 prior cases in the literature with similar pathology that had been termed “lymphangioma,” “lymphangiomyoma,” “lymphangiopericytoma,” “leiomyomatosis,” “lymphangiomatosis malformation,” and “intrathoracic angiomatous hyperplasia.” Since the late 1970s, larger case studies have better defined the natural history, pathologic classification, and clinical presentation of LAM.^{6–14} Moreover, in the past 2 decades, synergistic interactions between pulmonary investigators, tuberous sclerosis geneticists, *Drosophila* biologists, and patient advocacy groups have resulted in truly remarkable progress in our understanding of the molecular and cellular basis of LAM,¹⁵ as well as the development of a targeted therapy.

EPIDEMIOLOGY

LAM is seen both in the setting of *tuberous sclerosis complex* (TSC-LAM) and in a sporadic form in patients who do not have germline mutations in TSC genes or the clinical syndrome of TSC (sporadic LAM, or S-LAM) (Table 69-1).^{1,2}

TSC is an autosomal dominant genetic disorder associated with development of hamartomas and dysplastic lesions in several organs, including cortical tubers, giant cell astrocytomas, and subependymal nodules in the central nervous system; angiofibromas, shagreen patches, and ash leaf macules of the skin; and AMLs and cysts of the kidney.¹⁶ The cystic lung changes seen in patients with TSC are typically presumed to be due to LAM but, because the lung is not routinely biopsied in this population, other etiologies are also possible. There have been a number of case reports of biopsy-proven LAM in women with TSC, as well as in a few in men with TSC.^{17–19} In cross-sectional studies from tertiary referral centers, TSC-LAM has been reported in about 10% of men and 30% of women with TSC^{20–22}; although a recent screening study suggested that age-dependent development of cystic change in women with TSC results in an estimated LAM prevalence of up to 80% by age 40.²³ Symptomatic TSC-LAM is almost entirely restricted to women. In S-LAM, in contrast, lesions of the skin and brain are absent, and manifestations that accompany the pulmonary cystic changes include only renal and extrarenal AMLs and smooth muscle infiltration and obstruction of the lymphatic system. A clinical presentation consistent with S-LAM, including biopsy documentation and negative germ line TSC mutation analysis, has been reported in a single male without clinical evidence of TSC.²⁴

Careful epidemiologic analyses of the ethnic and racial distribution of LAM have not been performed. Although the biases introduced by the rarity of the illness, the protean presentation, and the disproportionate reporting of patients with LAM in large series from the United States, Europe, and Asia^{9–12,14} might suggest a predilection of the disease for whites and Asians, it is likely that all races are affected and that countries and populations with the greatest access to health care resources are overrepresented in these studies.

Harknett and colleagues²⁵ determined that LAM was diagnosed in 3.4 to 7.8 women per million across seven

Table 69-1 Comparison of TSC-LAM and S-LAM

	TSC-LAM	S-LAM
Estimated no. patients worldwide	150,000	10,000-30,000
Reported in males	+	+(one)
Reported in children	+	+
Ascertainment	Screening, dyspnea, pneumothorax	Dyspnea, pneumothorax, chylothorax, incidentally on CT
Germline TSC mutations	+	—
Inheritable	+	—
TSC1/TSC2 mutations reported	33%/66%	0%/100%
Renal angiomyolipomas	93% Bilateral 81% Multiple 60%	33% Bilateral 19% Multiple 6%
Hepatic angiomyolipomas	33%	2%
Lymphangiomyomas	9%	29%
MMPH	+ (~12%)	Very rare, if ever (~1%)
CNS/skin/eye/cardiac lesions	+	—
Retroperitoneal, thoracic adenopathy	Rare	+
Dyspnea	Less common	More common
Chylothorax	Uncommon	33%
Pneumothorax	Less common	66%
Respiratory failure	Less common	More common

CNS, central nervous system; CT, computed tomography; LAM, lymphangiomyomatosis; MMPH, multifocal micronodular pneumocyte hyperplasia; S-LAM, sporadic lymphangiomyomatosis; TSC, tuberous sclerosis complex.

different countries.²⁵ The authors did not stratify patients by the presence or absence of TSC, but it is likely that both S-LAM and TSC-LAM populations were included in the estimate. Extrapolation of this prevalence range to the 3.4 billion women on earth results in a predicted global LAM population ranging from 11,600 to 26,500 diagnosed patients.

LAM often presents in a protean manner and it is likely that the disease is severalfold more common than these numbers suggest. Considering that the live birth prevalence of TSC is estimated to be 1/10,000 to 1/12,500 persons and that TSC affects both genders equally,²⁶ the estimated worldwide prevalence of TSC is approximately 1.1 million to 1.5 million people (assuming a world population of 7 billion people), with roughly half of them being women. If one estimates that cystic pulmonary changes consistent with LAM are found in one third of women with TSC,²⁰⁻²² the global prevalence of TSC-LAM is about 150,000 to 200,000 women, or upwards of 60 TSC-LAM cases per million women in the general population.

Although screening of TSC populations identifies a subset of LAM patients who have a range of cystic change in the lung from very mild to severe, the degree of cystic profusion is often mild or moderate,²³ and pulmonary manifestations appear to reach clinical significance in only about 5% to 10% of patients with TSC-LAM.²⁷ TSC-LAM is certainly

underrepresented in large trials, registries, and databases: patients with TSC-LAM made up only about 14.7% of the 230 patients who enrolled in the *National Heart, Lung, and Blood Institute* (NHLBI) LAM Registry²⁸ and 9.5% of patients who are listed in the LAM Foundation database (Sally Lamb, personal communication, The LAM Foundation, Cincinnati). Although TSC-LAM is predicted to be 10-fold more common than S-LAM, most patients with LAM (85% to 90%) who seek medical attention with adult pulmonary specialists have S-LAM. This observation is consistent with the notion that TSC-LAM identified through screening is often a milder disease than S-LAM, which typically reaches attention through progressive dyspnea or pneumothorax/chylothorax. It is also possible that other TSC comorbidities may overshadow the pulmonary manifestations of TSC-LAM and hinder TSC-afflicted patients from seeking medical care for their lung disease.

GENETIC AND MOLECULAR BASIS OF TUBEROUS SCLEROSIS COMPLEX AND LYMPHANGIOLEIOMYOMATOSIS

INHERITANCE

Approximately two thirds of new TSC cases arise from de novo mutations, which happen during embryogenesis. Familial TSC, which results from inheritance of germline mutations, accounts for one third of new cases.²⁹ There have been several reports of familial TSC-LAM,^{20,30} but mother-daughter transmission of S-LAM has never been reported.

MOLECULAR PATHOGENESIS

Our understanding of the genetic and molecular basis of TSC and LAM has increased substantially since the late 1990s. The most significant findings have included that LAM is a neoplastic and metastatic process, that LAM is caused by mutations in TSC genes,³¹ and that dysregulation of the Akt signaling pathway plays a central role in LAM cell growth, motility, and survival.^{32,33}

Tumor Suppressor Proteins Control Cell Growth

Clinicians have long recognized that the cystic lung disease in women with TSC is pathologically indistinguishable from that in women with S-LAM.^{5,34} However, the demonstration that S-LAM and TSC-LAM are genetically linked was reported only relatively recently.³⁵ The lag period in our understanding may have been due, in part, to the failure to appreciate that a nonfamilial disease could share a common genetic basis with a heritable disease. There are several precedents for this phenomenon among the class of diseases known as tumor suppressor syndromes (including neurofibromatosis and von Hippel-Lindau syndrome), of which TSC is a member.

Tumor suppressor proteins regulate orderly cell growth and differentiation by sensing the surrounding environment, transmitting signals to the nucleus, and directly affecting transcription, translation, survival, or cell division.

In the classic “two-hit” paradigm,³⁶ a mutant copy of a tumor suppressor gene is inherited from one parent and a tumor or dysplastic lesion develops when the second “good” parental copy of the tumor suppressor gene is inactivated through a random, somatic mutation. This first (inherited) hit, often a point mutation or a small insertion or deletion, results in heterozygosity for the allele (i.e., one good copy and one mutant copy). The second mutational event is usually a large deletion, resulting in the loss of a chromosomal segment and *loss of heterozygosity* (LOH) (two mutant copies). A *polymerase chain reaction* (PCR) technique can be used to detect LOH for the allele caused by the deletion. When both copies of a tumor suppressor gene contain critical mutations, the protein produced by the gene becomes defective or deficient, protein function is lost, and cell growth, survival, and synthetic function become dysregulated.

The Tuberous Sclerosis Complex Proteins Regulate Signaling through the Akt Pathway

TSC is caused by inactivating mutations in either of the two known TSC loci, *TSC1* on chromosome 9q34³⁷ or *TSC2* on chromosome 16p13.³⁸ The proteins encoded by *TSC1* and *TSC2* are hamartin and tuberlin, respectively (Fig. 69-1).

More information on Akt pathway signaling is available online at *ExpertConsult*.

Genetic mutations that result in the absence or dysfunction of tuberlin or hamartin, such as is seen in patients with tuberous sclerosis and LAM, ultimately cause constitutive activation (phosphorylation) of S6 and eIF4E, two proteins that are intimately involved in the regulation of protein translation, as well as Rho kinase, which regulates intracellular trafficking, cell adhesion, and cell movement. The end result is the inappropriate stimulation of protein synthesis, cell motility, and cell growth.³³ Multiple mTOR effectors and mTOR itself were found to be highly phosphorylated in tumors of rats,⁴⁶ mice,⁴⁷ and humans⁴⁸ with mutations in TSC genes. Sirolimus, a microbial product that inhibits mTOR activity, extinguishes phosphoS6 staining and causes widespread apoptosis in the rat renal tumors.⁴⁶

Tuberous Sclerosis Complex Mutations Are Found in the Lung and Kidney Lesions of Patients with Sporadic Lymphangioleiomyomatosis

Tuberous sclerosis patients have germline mutations in TSC genes, but patients with S-LAM do not.⁴⁹ Smolarek and coworkers⁵⁰ first implicated TSC genes in the pathogenesis of S-LAM by finding that LOH for *TSC2* was present in the renal AMLs and lymph nodes of patients with S-LAM. Proof that the loss of tuberlin function was responsible for lung disease in LAM was provided by Carsillo and colleagues, who demonstrated the presence of missense and protein

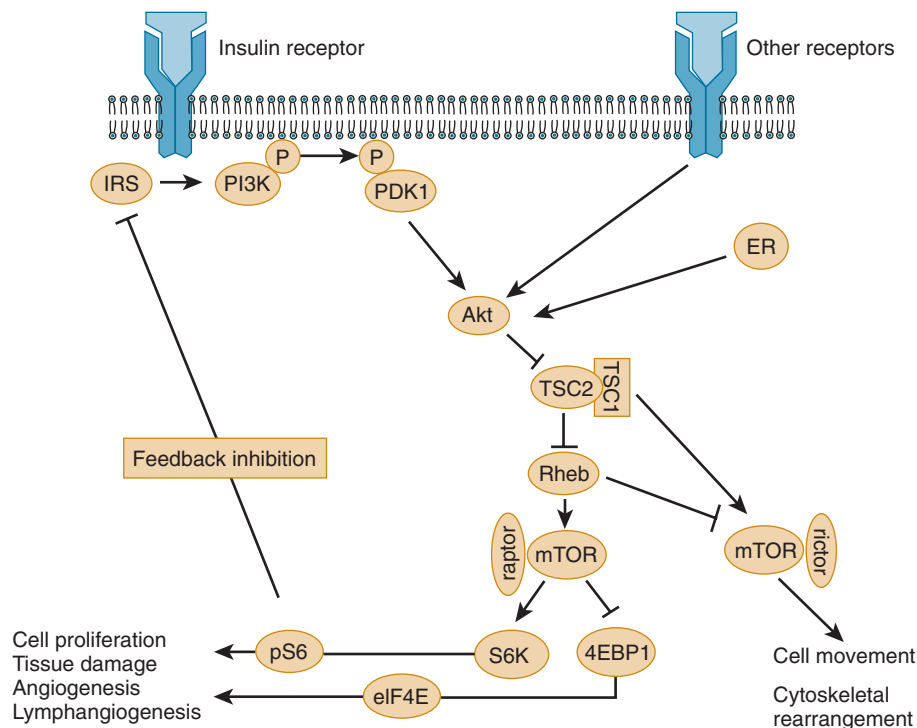


Figure 69-1 Tuberous sclerosis proteins regulate signaling through the Akt growth and protein translation pathway. The binding of a ligand to a growth factor receptor (e.g., the insulin receptor) activates phosphatidylinositol-3-kinase (PI3K) followed by Akt. Activated pAkt phosphorylates tuberous sclerosis complex-2 (TSC2), which blocks its GTPase-activating protein (GAP) activity. When not phosphorylated, TSC2 complexed with TSC1 functions as a GAP for Rheb, maintaining Rheb in an inactivated Rheb-GDP state. Activated Rheb (Rheb-guanosine triphosphate [GTP]) is therefore abundant when TSC1 or TSC2 is missing or defective, or when TSC2 is phosphorylated. Rheb GTP activates mTOR, in a manner that is potentiated by the availability of amino acids, phosphatidic acid, and adenosine triphosphate, and blocked by the absence of these substrates or the presence of sirolimus. Activated mTOR complexed with raptor phosphorylates downstream targets S6K and 4E-BP1. pS6K phosphorylates S6 and 4E-BP1 releases eIF4E, which together activate the cellular translational machinery and promote cell growth. S6 also feeds back to inhibit upstream signaling, which restrains cell growth and “malignant” cellular behavior. Activated mTOR complexed with rictor signals through a divergent pathway to control cytoskeletal dynamics and cell movement through Rho kinases. (Adapted from Kwiatkowski DJ: Rhebbing up mTOR: new insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. *Cancer Biol Ther* 2:471–476, 2003.)

Hamartin has no informative homologies with other proteins in the National Center for Biotechnology Information database, whereas tuberin has a domain with *GTPase-activating protein* (GAP) homology.³⁹

Until recently, little was known about the function of TSC proteins other than that they modulate cell growth. In 1999, it was reported that the enlarged eye cell phenotype of the mutant fruit fly, *Gigas*, was the result of genetic inactivation of the fly homologue for tuberin.⁴⁰ The loss of tuberin results in a defect in cell cycle control, which causes cells to repeat S phase without entering M phase. Several laboratories subsequently reported that tuberin and hamartin regulate signaling through the PI3K/PKB(Akt)/S6K pathway, which controls cellular size and proliferation.⁴¹⁻⁴³

Our understanding of the function and positioning of the TSC proteins in the Akt/S6K pathway has been a rapidly evolving process, and the available data to date are modeled

in [Figure 69-1](#). Tuberin and hamartin associate into a complex that functions as a master regulator for the kinase, mTOR, or mammalian target of rapamycin (sirolimus), through an intermediate G protein called Rheb.^{44,45} The intact tuberin/hamartin complex acts as a GAP for Rheb, maintaining the protein in an inactivated, nonphosphorylated state (Rheb-GDP). Phosphorylation of tuberin by Akt inactivates the GAP activity of the tuberin/hamartin complex, increases the abundance of Rheb-GTP, drives association of mTOR with raptor (and mLST8 and PRAS40, not shown) to form the mTORC1 complex, and results in phosphorylation and activation of downstream kinases mTOR, S6K, and the initiation factor *4E-binding protein* (4E-BP1). The association of mTOR with raptor (and mSIN1 and mLST8, not shown) to form mTORC2 results in activation of ROCK and rho kinase, cytoskeletal rearrangement, and cell movement.

truncating *TSC2* mutations associated with LOH in the abnormal lung and kidney tissue of patients with S-LAM.³⁵ Samples taken from the normal regions of lung and the kidney in those patients did not exhibit TSC mutations.⁴⁹ These findings were subsequently confirmed in 21 patients by Sato and associates,⁵¹ A single patient with S-LAM caused by *TSC1* mutations has been described to date.^{35,51,52} These data indicate that somatic mutations in either *TSC2* or *TSC1* alleles after conception cause S-LAM and result in defects or deficiency in tuberlin or hamartin. *TSC1* and *TSC2* mutations have both been described in TSC-LAM, although *TSC2* mutations are more common.^{20,53}

GENETIC EVIDENCE SUGGESTS THAT LYMPHANGIOLEIOMYOMATOSIS IS A METASTATIC NEOPLASM

Cornog and Enterline⁵ were the first to suggest that, despite their benign appearance, cells that make up the LAM lesion represent a clonal, neoplastic proliferation of smooth muscle cells. The demonstration of LOH in the lung, kidney, and lymph node lesions in patients with LAM indicated that Cornog and Enterline's suspicions regarding neoplasia and clonality were correct.⁵⁰ Carsillo and colleagues³⁵ further demonstrated that the mutations present in the cells of the kidney tumor and lung lesion of a given individual with S-LAM were identical, suggesting that they arise from a common precursor.

A model for LAM has been proposed in which the lung is infiltrated as a consequence of benign metastasis of LAM cells from a remote and, as yet unidentified, source such as the bone marrow, the lymphatic system,⁵⁴ the uterus,⁵⁵ or AMLs.⁵⁶ Reports of recurrence of LAM in the donor lung of patients with LAM who had undergone lung transplantation are also consistent with this metastatic theory⁵⁷⁻⁶⁰; in two cases, the source of lung metastases were proven to arise from the recipient by genetic and molecular techniques.^{60,61} These data contradicted earlier reports that the recurrent lesions were derived from donor cells,^{57,58} but in retrospect, the initial studies were limited by the spatial resolution that can be achieved with the immunohistochemical techniques used to colocalize cellular markers. Cells containing LOH for TSC genes have been isolated from the blood of patients with LAM,⁶² consistent with dissemination through the systemic circulation.

Other rare diseases that result from metastases of benign smooth muscle cells in women include leiomyomatosis peritonealis disseminata,⁶³ intravenous leiomyomatosis,⁶⁴ and benign metastasizing leiomyomatosis.⁶⁵ The metastatic theory of LAM suggests possible novel approaches for treatment based on preemptive removal of the source, once its identity is known.³¹

ROLE OF LYMPHANGIOGENESIS AND LYMPHATIC SPREAD IN DISSEMINATION OF LYMPHANGIOLEIOMYOMATOSIS

Approximately 30% of patients with LAM have axial abdominal or thoracic lymphadenopathy.⁶⁶ In some cases, LAM is restricted to the retroperitoneum, abdomen, or pelvis and is associated with normal lung parenchyma or only a very few lung cysts, consistent with regional spread from a subdiaphragmatic source.⁶⁷ Clusters of cells in the

chylous pleural fluid of patients with LAM were first described by Valensi⁶⁸ in 1973. Later, Itami and coworkers⁶⁹ demonstrated that the clusters originated in the dilated lymphatic system and were composed of alpha smooth muscle actin–positive spindle cells enveloped by a single layer of endothelial cells. They suggested that LAM cell clusters could be used diagnostically to obviate the need for biopsy in patients with chylous manifestations of LAM. Data from Japan provide additional evidence that a likely source and mechanism of spread of LAM may be through the lymphatic circulation.^{54,70,71} In a small autopsy series, Kumasaka and colleagues^{54,72} described the presence of LAM cell clusters enveloped by lymphatic endothelial cells budding from the walls of lymphatic vessels and in the lumen of lymphatic channels and the thoracic duct.

Induction of lymphangiogenesis appears to play an important role in this process, based on abundant expression of lymphatic endothelial markers such as *podoplanin* (D2-40), LYVE-1, *vascular endothelial growth factor* (VEGF) receptor 3 (VEGFR-3), VEGF-C, and VEGF-D.⁷² Several laboratories have reported that VEGF-D is elevated more than threefold to eightfold in the serum of patients with LAM, a finding that is useful for distinguishing LAM from other cystic lung diseases and for predicting response to therapy.⁷³⁻⁷⁹ LAM clusters are found in the lymphatic lumen, in regions between axial lymph nodes (retroperitoneal, mediastinal, and left venous angle) that are infiltrated with LAM cells, and in chylous fluids of patients with chylous ascites and chylothorax.^{54,72,73,80,81} LAM cell clusters enter the venous circulation at the insertion of the thoracic duct into the junction of the left internal jugular and subclavian veins and disseminate throughout the pulmonary capillary bed. LAM cell clusters impacted in the lung vasculature proliferate and invade, perhaps through a novel mechanism called “invasion-independent metastasis.”^{82,83}

ROLE OF ESTROGEN

Estrogen-containing drugs have been implicated in the worsening of LAM. Estrogen may play a role in LAM cell migration, infiltration, proliferation, or secretion of destructive proteases.^{33,84} Estrogen regulates the transcription of many genes, and there is some evidence that estrogen can modulate signaling through the Akt pathway.^{84,85} Estrogen-mediated activation of the ERK pathway promotes activation of the late response gene *FRA1*, which is associated with epithelial mesenchymal transition.⁸⁶ Akt activation, in turn, enhances the efficiency of *FRA1* translation through the phosphorylation of the S6K1-dependent eucaryotic translation factor, 4b. Estrogen was shown to promote pulmonary metastases and enhanced survival of *TSC2*-deficient cells in mice.⁸⁷ Collectively, these data suggest that targeting the E2-ERK pathway in combination with the mTORC1 pathway may be an effective combination therapy strategy for LAM.

MECHANISMS OF MATRIX REMODELING IN LYMPHANGIOLEIOMYOMATOSIS

Cystic destruction of the lung parenchyma causes progressive decline in lung function in patients with LAM, and proteases are believed to play a major role in the process.

In addition, multiple growth factors are abundant in LAM, which induce proliferation, suppress apoptosis and support fibrosis. Targeting the systems that promote proteolytic and fibroproliferative responses are possible therapeutic strategies for the future.



More information on matrix remodeling Akt pathway signaling is available online.

CLINICAL FEATURES

LAM usually presents during the reproductive years, with a mean age at the onset of symptoms in the early to mid-30s.^{8,9,14,100} Although new diagnoses of LAM have been reported in patients as young as 12 years,^{101,102} documented cases of the disease before menarche are rare. A number of reports in the literature describe women in whom the diagnosis was made after menopause and in the ninth decade of life.^{8,9,14,100,103-106} LAM does not appear to be smoking-related, because the majority of patients in the largest case series were nonsmokers.^{9,12,14}

Because LAM is rare and the symptoms are often nonspecific, the diagnosis is often delayed, with a mean interval between the onset of symptoms and diagnosis of 5 to 6 years.^{8,11,14,107} Initial incorrect diagnoses in these series typically included bronchial asthma, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, sarcoidosis, diffuse panbronchiolitis (in Asia), and even idiopathic interstitial pneumonias including idiopathic pulmonary fibrosis.

In the patients reported by Urban and associates,¹⁴ exertional dyspnea and spontaneous pneumothorax were the initial symptoms in 49% and 46% of patients, respectively. During the course of the illness, dyspnea developed in 87% of patients, and pneumothorax developed in 68% of patients. The first pneumothorax precedes the diagnosis of LAM in 82% of patients; in fact, most patients have two pneumothoraces before the diagnosis is made.^{108,109} In patients with LAM who have a pneumothorax, the likelihood of an ipsilateral or contralateral recurrence is greater than 70%.^{7,11,14,109} Pneumothorax most likely results from the rupture of subpleural blebs, but whether the event is triggered by progressive degradation of connective tissue matrix or airflow obstruction and overdistention of distal air spaces, or both, is unclear.

Other signs and symptoms of LAM, which may be present at the onset or may develop during the course of the disease, include fatigue, cough, hemoptysis (rarely massive), chest pain, and symptoms related to reflux of chylous fluid into pleural (33% of patients) and extrapleural locations, such as the peritoneum (chylous ascites) or pericardium (chylopericardium), airway (chyloptysis), and genitourinary tract (chyluria and chylous metrorrhagia). Fistulous communication in the gut can result in protein-losing enteropathy. Chylous pulmonary parenchymal congestion was recently described in patients with LAM and should be considered in the differential of subacute worsening of oxygenation or shortness of breath.¹¹⁰ It is likely that the chylous complications of LAM result from obstruction of lymphatic channels due to infiltration by smooth muscle cells.

AMLs, unusual hamartomas composed of fat, smooth muscle, and abnormal blood vessels, may arise in virtually any location in the chest and abdomen but are most

common in the kidney (eFig. 69-1). About 29% to 33% of patients with S-LAM have renal AMLs, compared with about 88% to 93% of patients with TSC or TSC-LAM.^{20,28} AMLs are more commonly unilateral and solitary in patients with S-LAM, and more commonly bilateral and multiple in patients with TSC-LAM (see eFig. 69-1).⁶⁶ Blood vessels in AMLs are often tortuous and aneurysmal and are composed of cells with normal genotype and cells with TSC mutations.¹¹¹ Spontaneous hemorrhage into AMLs may produce severe flank or abdominal pain, acute hypotension, and/or anemia, occasionally in association with circulatory collapse. Renal cysts are seen occasionally in patients with LAM; in TSC-LAM, polycystic kidney disease may develop due to a contiguous gene deletion of *PKD1* which is immediately adjacent to *TSC2* on chromosome 16.¹¹²

Lymphangiomyomas are tumor-like masses characterized by smooth muscle (LAM cells) and endothelial proliferation of lymphatic vessels and lymph nodes in the mediastinum, retroperitoneum, and lung. Not uncommonly, LAM presents as retroperitoneal masses, including cystic lymphangiomyomas (eFig. 69-2) or lymph nodes with hypodense centers, which mimic necrotizing lymphomas, ovarian or renal cancers, or other malignancies.^{113,114}

There have been case reports of exacerbation of LAM associated with birth control pill use¹¹⁵ or during pregnancy.¹¹⁶⁻¹²⁰ In a group of 69 patients with sporadic LAM, pulmonary symptoms began during pregnancy in 9 of the 46 patients (20%) with a history of pregnancy before or at the time of diagnosis.¹⁴ In this same group, a marked exacerbation of previously diagnosed pulmonary LAM was observed in two (14%) patients during pregnancy.¹²¹ The effect of pregnancy or exogenous estrogen use on LAM has not been systematically studied.

PHYSICAL EXAMINATION

The physical examination in LAM is often nonspecific. Lung auscultation is usually uninformative but may reveal rhonchi or wheezing in some patients.^{9,11,14} Crackles are unusual and should raise suspicion for chylous pulmonary congestion. Clubbing is not a feature of LAM, despite being reported in 3% and 5% of patients in two larger case series.^{9,11} Physical examination may also reveal evidence of pleural effusion, ascites, or pneumothorax, if present. Careful dermatologic, ocular, and dental surveys should be performed for evidence of TSC, including facial angiofibromas, subungual fibromas, palpable dysplastic cutaneous lesions called shagreen patches, hypomelanotic macules including those with ash leaf or confetti configurations, retinal hamartomas, and dental pitting.¹⁶

IMAGING STUDIES

The chest radiograph in patients may appear relatively normal (eFig. 69-3), even late in the disease, or may suggest hyperinflation only. As the disease progresses, the chest radiograph often demonstrates diffuse, bilateral, and symmetric reticulonodular opacities (eFig. 69-4), cysts (eFig. 69-5), bullae, or a “honeycomb” or somewhat “pseudofibrotic” appearance (eFig. 69-6).^{9,14} Pleural effusion and pneumothorax (eFig. 69-7) may also be apparent (Fig.

The spectrum of metalloproteinases that are aberrantly expressed in LAM has not been fully characterized, but *matrix metalloproteinase* (MMP)-2 is the most abundant of those studied to date. Overexpression of MMP-1, MMP-9, MT1-MMP, and MMP-14 has also been reported,⁸⁸ and serum levels of MMP-9 are elevated in patients with LAM.⁸⁹ MMP-1, MMP-2, and MMP-9 are able to degrade elastin, consistent with the loss and degradation of elastic fibers seen in LAM.⁸⁸ Zhe and associates have proposed that increased expression of serum response factor may lead to MMP activation⁹⁰⁻⁹³ and down-regulation of *tissue inhibitor of metalloproteinase* (TIMP-3) in LAM cells,⁹⁰ leading to an imbalance of proteases and protease inhibitors. Abundant expression of cathepsin K has been reported in LAM, suggesting a possible pathogenic role of this protein in tissue destruction.⁹⁴

Basic fibroblast growth factor (bFGF) is a potent mitogenic factor for smooth muscle cells, myofibroblasts, and fibroblasts. LAM lesions have also been reported to contain abundant tryptase-positive mast cells, which express bFGF and receptors *Bek* (FGFR-2) and *Flg* (FGFR-1), as well as chymases, renin, angiotensin-converting enzyme, and angiotensin receptors type I and type II.^{95,96} *Insulin-like growth factors* (IGFs) are involved in normal pulmonary development and in the pathogenesis of smooth muscle cell proliferation. IGF-I, IGF-II, IGF-I receptor, *IGF-binding protein* (IGFBP)-1, IGFBP-2, IGFBP-4, IGFBP-5, and IGFBP-6 are expressed in lung tissue of patients with LAM.⁹⁷ Carelli and coworkers⁹⁸ showed that *TSC2*^{-/-} human smooth muscle cells derived from AMLs express the apoptosis inhibitor protein survivin when exposed to IGF-1. Transforming growth factor- β 1, a profibrotic cytokine, is enriched in highly cellular areas of the LAM lesion.⁹⁹

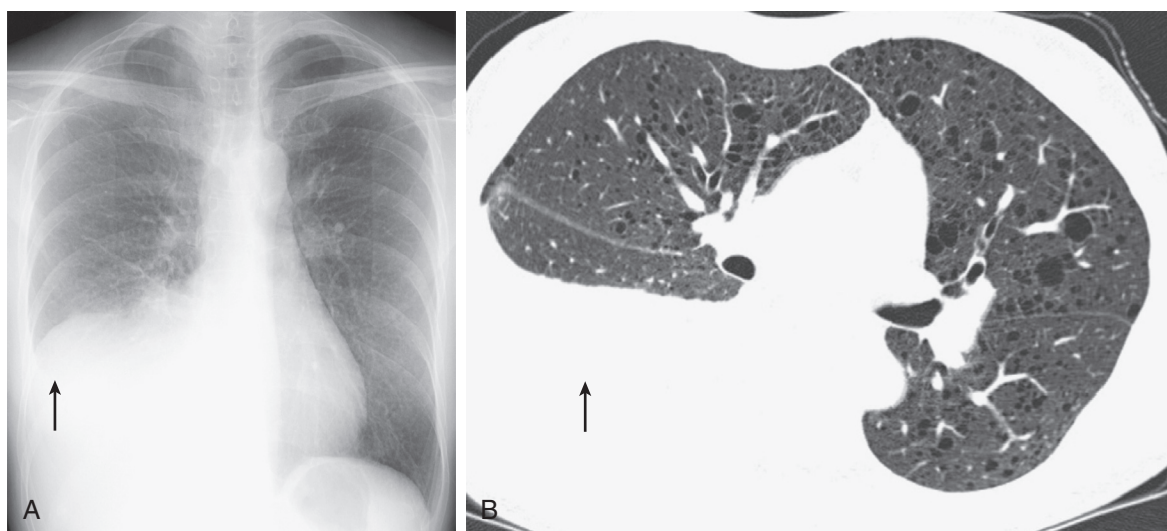


Figure 69-2 Sporadic LAM with chylothorax. Chest radiograph (A) and high-resolution CT (B) of a 40-year-old woman with sporadic LAM. Diffuse cystic changes and a right-sided chylothorax (arrows) are present.

69-2). Preservation of lung volumes in the presence of increased interstitial markings is a radiographic hallmark of LAM that helps distinguish it from most other interstitial lung diseases (see eFigs. 69-3A, 69-4, 69-5A, and 69-6A), in which alveolar septal and interstitial expansion tend to increase the lung's elastic recoil properties and decrease lung volumes.

The *high-resolution computed tomography* (HRCT) chest scan is much more sensitive than the chest radiograph in detecting cystic parenchymal disease and is almost always abnormal at the time of diagnosis, even when the chest radiograph and pulmonary function assessments are normal.^{9,11,14,122} The typical CT shows diffuse round, bilateral, thin-walled cysts of varying sizes ranging from 1 to 45 mm in diameter (see Fig. 69-2; see eFigs. 69-1C, 69-2C, 69-3B through D, 69-5B, 69-6B, and 69-7B).^{11,14} The numbers of cysts varies in LAM from a few (see eFig. 69-7B) to almost complete replacement of the normal lung tissue (see eFig. 69-5B). The profusion of cysts tends to be milder in patients with TSC-LAM than S-LAM, perhaps explained in part by ascertainment of patients with TSC-LAM earlier in the disease process by screening.¹²³

The morphology of the cysts is useful in differentiating LAM from other cystic lung diseases (Fig. 69-3). In *emphysema*, dilated airspaces often have internal structure, such as septae or a “centrilobular dot” consistent with a vessel, features virtually never seen in LAM. In addition, in emphysema, the borders of the lucent spaces are difficult to discern, whereas in LAM, cyst walls are thin but easily perceptible. *Langerhans cell histiocytosis* cysts (see eFig. 54-37) have thick walls and the cystic spaces are bizarre in shape. *Birt-Hogg-Dubé* (BHD) cysts tend to predominate in the lower lobes, while LAM cysts are distributed diffusely. *Lymphocytic interstitial pneumonia* cysts can closely resemble those of LAM, but are often larger, more varied in size, and bounded by eccentric vessels. Blinded expert radiologists can correctly identify LAM among a pool of CT scans consisting of a variety of other cystic lung diseases about 72% of the time.¹²⁴ Pleural effusions are seen on CT in 12% of patients with S-LAM and 6% of patients with TSC-LAM. Other CT

features include linear densities (29%), hilar or mediastinal lymphadenopathy (9%), pneumothorax, lymphangiomyomata (see eFig. 69-2), and thoracic duct dilation.^{11,14} Ground-glass opacities (12%) suggest the presence of interstitial edema due to lymphatic congestion (Fig. 69-4).

In patients with TSC, nodular densities on HRCT may represent *multifocal micronodular pneumocyte hyperplasia* (MMPH) made up of clusters of hyperplastic type II pneumocytes^{23,125,126} (Fig. 69-5; see eFig. 56-2). MMPH may be present in males or females with TSC in the presence or absence of LAM, but not in patients with S-LAM.¹²⁷ MMPH is not typically associated with physiologic or prognostic consequences, but one case of respiratory failure due to MMPH has been reported.¹²⁸

Chu and associates¹¹ reported that ventilation-perfusion scans were abnormal in 34 of 35 women with LAM. The most common abnormality was nonspecific diffuse heterogeneity, usually grossly matched. These authors also described an “unusual,” “speckling pattern” on the perfusion images in 74% of patients, consisting of “small, often peripheral collections of radioisotope.”

LAM and AML lesions do not typically exhibit increased uptake of ¹⁸F-fluorodeoxyglucose on PET scanning.^{129,130} Other neoplasms (or sources of inflammation) should therefore be considered in known or suspected LAM cases in which FDG-PET results are positive.¹²⁰

Abnormalities on abdominal imaging, such as renal AML (see eFig. 69-1A and B) and enlarged lymphatic structures, are also common in LAM (Figs. 69-6 and 69-7). Fat density within a renal mass is pathognomonic of AMLs (see eFig. 69-1A and B). AMLs are more prevalent and more frequently bilateral and large in patients with TSC-LAM than in patients with S-LAM, and AML size correlates with the prevalence of pulmonary cysts in patients with TSC.²⁰ Avila and associates¹²³ reported the results of CT imaging in 256 patients with S-LAM and 67 patients with TSC-LAM who were referred to the National Institutes of Health. Renal AMLs were present in 32% of patients with S-LAM and 93% of patients with TSC-LAM. Hepatic AMLs (see eFig. 69-1A) were present in 2% of patients with S-LAM and 33% of

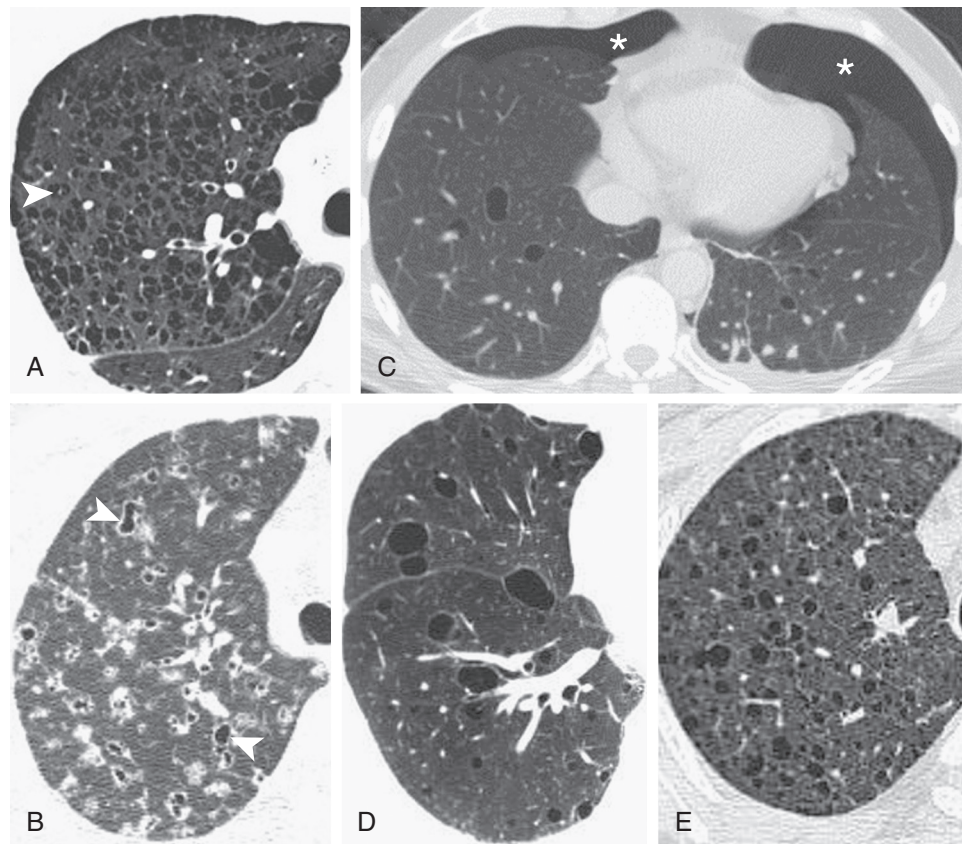


Figure 69-3 LAM cystic lung disease mimics. **A**, Centrilobular emphysema—note lack of a true cyst wall and the presence of the centrilobular artery (arrowhead) with the cystic region. **B**, Pulmonary Langerhans cell histiocytosis—note “bizarre-shaped” cysts (arrowheads) and numerous nodules. **C**, Birt-Hogg-Dubé syndrome—note lower lobe predominance of cysts. Spontaneous pneumothorax (*) is present bilaterally. **D**, Lymphocytic interstitial pneumonia—the cysts in this disorder may closely simulate LAM, particularly when no other infiltrative parenchymal findings coexist. **E**, LAM, presented for comparison. Note the relatively uniform, thin-walled appearance of the cysts with normal-appearing intervening lung parenchyma. (Courtesy Michael Gotway, MD.)



Figure 69-4 Interstitial pulmonary edema due to lymphatic obstruction/congestion. In patients with cystic change seen on high-resolution CT that is otherwise typical for LAM, the ground-glass appearance (arrows), often together with chylous effusions, lymphadenopathy, and/or lymphangiomyomas, may be indicative of pulmonary lymphatic congestion due to chylous reflux. This entity should be considered in the differential of worsening dyspnea or hypoxemia and is amenable to treatment with sirolimus. Other considerations include bronchospasm, which is present in up to 20% of patients with LAM, and intrapulmonary shunts.

patients with TSC-LAM. Ascites was uncommon, seen in fewer than 10% of patients with LAM. Abdominal lymphangiomyomas (see eFig. 69-2B), often containing both cystic and solid components, were seen in 29% of patients with S-LAM and 9% of patients with TSC-LAM.

Central nervous system abnormalities, such as cortical or subependymal tubers and astrocytomas, are common in patients with TSC, including those with TSC-LAM, but are not found in women with S-LAM. Moss and associates¹³¹ reported that women with S-LAM and TSC-LAM may have an increased incidence of meningioma, but the significance of that finding has been challenged.¹³²

PULMONARY FUNCTION TESTING

Pulmonary function testing in patients with LAM may be normal or may reveal obstructive, restrictive, or mixed patterns, with obstructive physiology being the most common abnormality. Quality controlled lung function data were collected prospectively by the NHLBI Registry,²⁸ a 5-year study of patients with LAM in centers around the United States. Spirometry revealed obstructive changes in about 57% of patients and normal results in 34%.²⁸ Restriction, defined as a total lung capacity less than the lower limit of

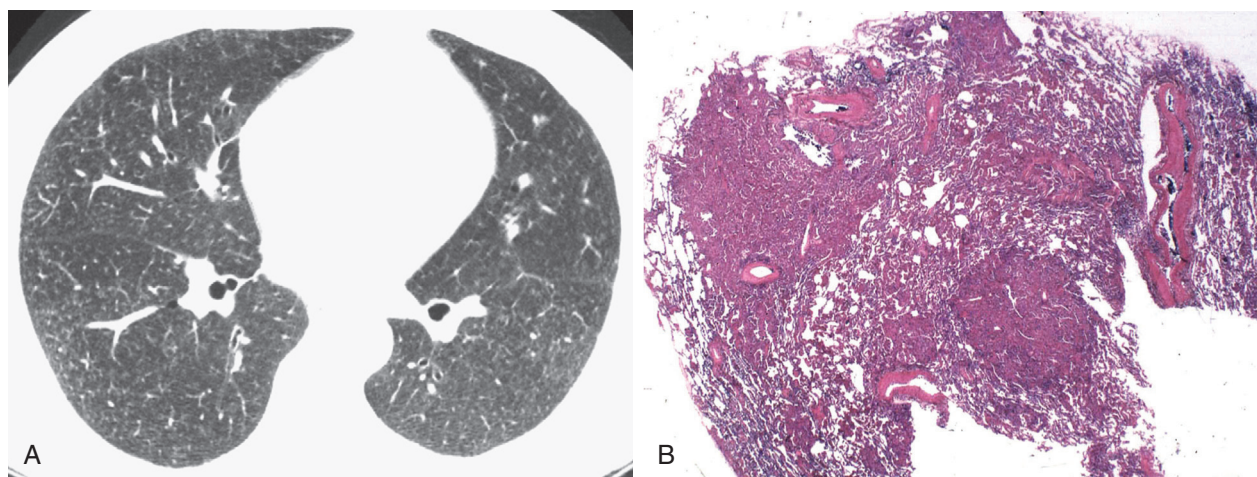


Figure 69-5 Radiographic and histopathologic presentation of multifocal micronodular pneumocyte hyperplasia (MMPH). **A**, High-resolution chest CT of a patient with MMPH reveals miliary nodules throughout both lungs. **B**, The low-power view of lung biopsy from a patient with MMPH reveals diffuse nodular proliferation of alveolar type II cells.

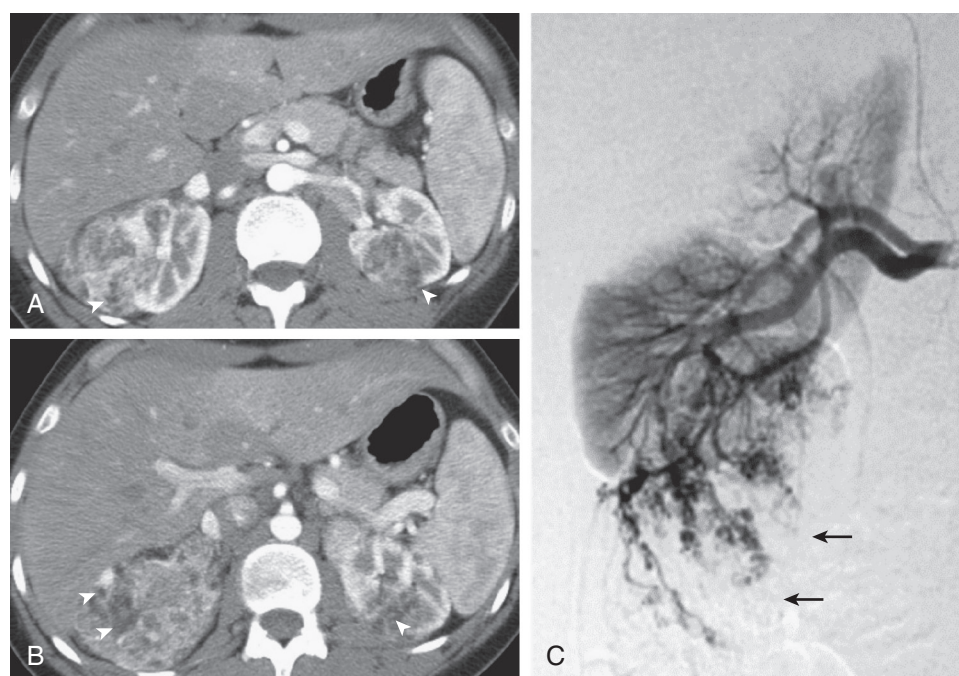


Figure 69-6 Angiomyolipoma. Axial abdominal CT scans (**A** and **B**) and angiography (**C**) of a renal angiomyolipoma in a 16-year-old female with sporadic LAM. Note the tumor (arrow) in the right kidney. (**A** and **B**, Courtesy Dr. Shoji Samma, Nara Prefectural Nara Hospital, Japan.)

normal, was seen in 11%. Hyperinflation was unusual, present in about 6%. The average residual volume was 125% of predicted when measured by plethysmography, but was only 103% of predicted determined with gas dilution methods, suggesting significant air trapping in non-communicating airspaces. Approximately 25% of patients with obstructive physiology may demonstrate bronchodilator responsiveness.¹² The obstructive physiologic defect in LAM is primarily attributable to airflow obstruction and, to a lesser degree, to a modest increase in lung compliance.¹³³

The most common finding on initial pulmonary function testing in various case series was abnormal gas transfer, as assessed by the *diffusing capacity for carbon monoxide* (DL_{CO}), described in 82% to 97% of patients.^{8,9,11,14} It is not unusual

for DL_{CO} to be reduced out of proportion to *forced expiratory volume in 1 second* (FEV_1).¹² Reduction in DL_{CO} and increase in residual volume are generally considered to be the earliest physiologic manifestations of LAM.

Crausman and colleagues¹³⁴ studied the mechanism of exercise limitation in 16 patients with LAM. They concluded that poor exercise performance was primarily due to airflow obstruction and increased dead-space ventilation caused by pulmonary vascular disease or extensive cystic change. Cardiopulmonary exercise testing in a much larger cohort of patients with LAM revealed a reduced *maximal oxygen consumption* ($\dot{V}O_{2max}$) and anaerobic threshold in 217 patients.^{135,136} Exercise-induced hypoxemia was found even in patients who did not have resting abnormalities in

FEV₁ and DL_{CO}. In most patients, exercise was thought to be ventilation limited, owing to airflow obstruction and increased dead-space ventilation.

Disease progression is usually accompanied by a progressive obstructive ventilatory defect, and decline in FEV₁ is the most commonly used parameter to monitor disease progression. Although resting pulmonary hypertension appears to be unusual in LAM, pulmonary arterial pressure often rises with low levels of exercise, related in part to hypoxemia.¹³⁶ Zafar and colleagues¹³⁷ reported an increase in intraparenchymal shunts in dyspneic patients with LAM, which may contribute to resting and exercise hypoxemia.

Taveira-DaSilva and coworkers¹² correlated lung function testing with lung histology in 74 patients. They reported that a positive bronchodilator response was associated with a predominantly solid pattern of lung lesions as

opposed to a cystic pattern. They also found that the DL_{CO} correlated with the lung histology score, a quantification of the extent of involvement with cystic lesions and LAM cells. FEV₁ and DL_{CO} were the best predictors of $\dot{V}O_{2\max}$.

PATHOLOGY

Grossly, LAM lungs are enlarged and diffusely cystic, with dilated air spaces as large as several centimeters in diameter^{7,138} (Fig. 69-8). Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of the lung parenchyma, airways, lymphatics, and blood vessels associated with areas of thin-walled cystic change. LAM lesions often contain an abundance of lymphatic channels, forming an anastomosing meshwork of slitlike spaces lined by endothelial cells. LAM cells generally expand interstitial spaces without violating tissue planes but have been observed to invade the airways, the pulmonary artery, the diaphragm, aorta, and retroperitoneal fat, to destroy bronchial cartilage and arteriolar walls, and to occlude the lumen of pulmonary arterioles.⁷

There are two major cell morphologies in the LAM lesion: small spindle-shaped cells and cuboidal epithelioid cells.¹³⁹ LAM cells stain positively for smooth muscle actin, vimentin, desmin, and, often, estrogen and progesterone receptors (Fig. 69-9). The cuboidal cells within LAM lesions also react with a monoclonal antibody called HMB-45, developed against the premelanosomal protein gp100, an enzyme in the melanogenesis pathway.¹³⁹ This immunohistochemical marker is very useful diagnostically, because other smooth muscle–predominant lesions in the lung do not react with the antibody.¹⁴⁰ The spindle-shaped cells of the LAM lesion are more frequently proliferating cell nuclear antigen–positive than the cuboidal cells, consistent with a

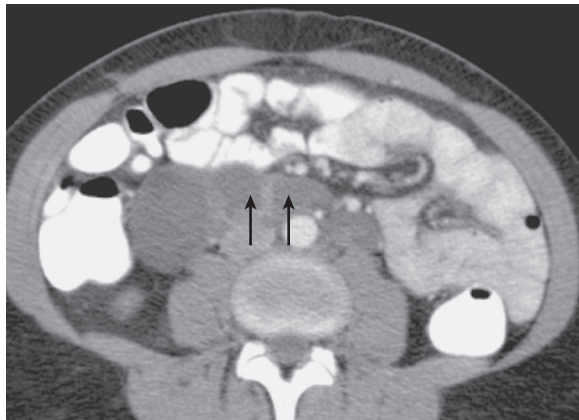


Figure 69-7 Abdominal CT of cystic lymphangiomyomas (arrows) and retroperitoneal lymphadenopathy in a patient with LAM.

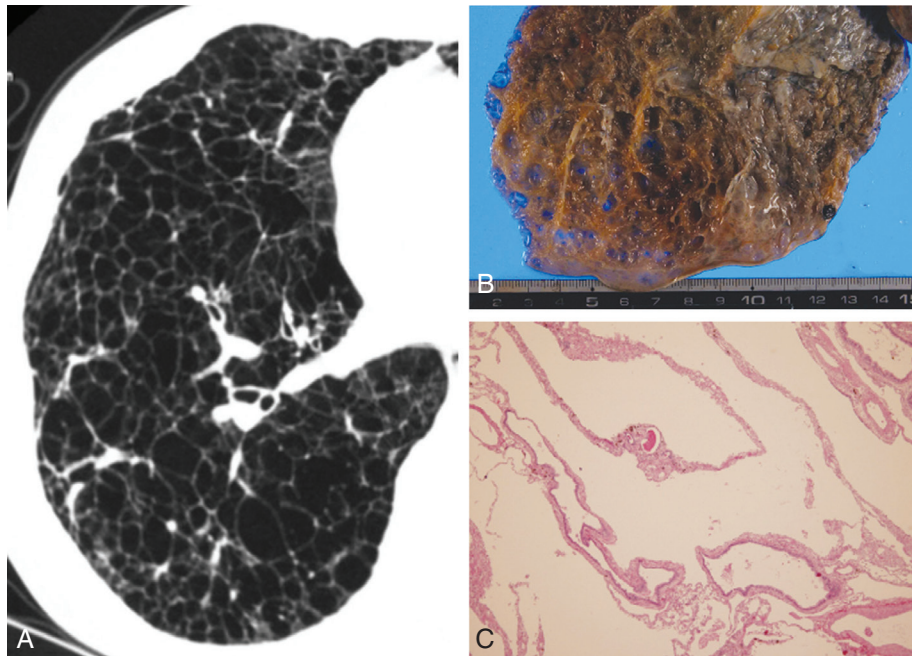


Figure 69-8 Pathologic appearance of LAM. HRCT (A) and pathologic gross specimen (B) of the autopsied lung of a 57-year-old woman with sporadic LAM. C, Microscopy with low magnification (H&E) staining. Extensive cystic changes are evident in the terminal stages of LAM. (Courtesy Dr. Masanori Kitaichi, National Hospital Organization, Kinki-Chuo Chest Medical Center, Osaka, Japan.)

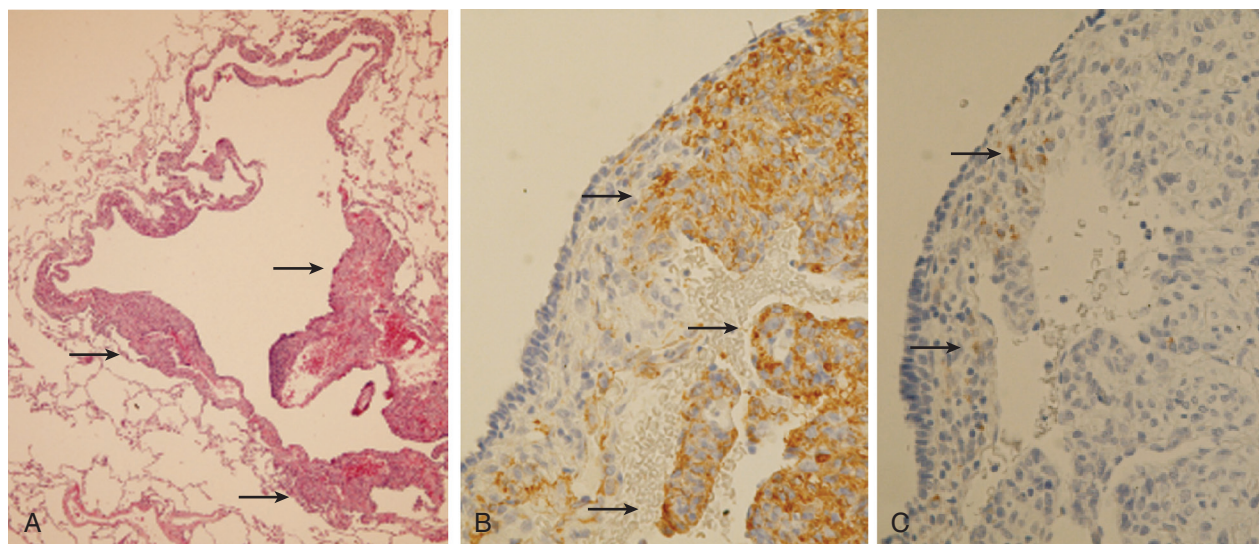


Figure 69-9 Histopathology of a lung specimen from a 32-year-old woman with sporadic LAM. **A**, Smooth muscle cell proliferation (arrows), cystic change, and distorted pulmonary architecture characteristic of LAM (H&E staining). **B**, LAM nodule immunostained with alpha smooth muscle actin (arrows). **C**, Scattered positive LAM cells immunostained with HMB-45 (arrows). (Courtesy Dr. Masanori Kitaichi, National Hospital Organization, Kinki-Chuo Chest Medical Center, Osaka, Japan.)

proliferative phenotype.¹³⁹ Compared with cigar-shaped normal smooth muscle cells, spindle-shaped LAM cells contain less abundant cytoplasm and are less eosinophilic. Estrogen and progesterone receptors are also present in LAM lesions,^{141,142,142a} but not in adjacent normal lung tissue.¹⁴³ LAM lesions express lymphatic markers LYVE-1, PROX1, podoplanin and VEGFR-3.^{143a} The smooth muscle-like cells of AMLs are morphologically and immunohistochemically similar to LAM cells, including reactivity with antibodies directed against actin, desmin, vimentin, and HMB-45 as well as estrogen and progesterone receptors.^{144,145} Unlike the dilated air spaces in emphysema, the cystic spaces found in LAM may be partially lined with hyperplastic type II cells.¹⁴⁶

DIAGNOSIS

The diagnosis of LAM usually follows CT scanning of the chest, often triggered by one of four presentations: chronic dyspnea on exertion, new onset or recurrent pneumothoraces, chylous effusion, or incidental cysts found on scans of the chest, heart, or abdomen done for other reasons. When based on dyspnea, diagnoses such as obstructive pulmonary diseases (e.g., asthma or chronic bronchitis) are often erroneously made first, resulting in delays in the diagnosis of LAM for up to several years. The time to diagnosis is typically shorter following pneumothorax or chylous effusion, but most patients have more than one pneumothorax before the diagnosis is made.^{108,109} Cardiac and abdominal CT scans performed for other indications can detect cystic change in the lung and lead to performance of a dedicated chest CT and a diagnosis of LAM.

CLINICAL DIAGNOSIS

In the proper clinical context, a confident, clinical diagnosis of LAM may be established based on radiographic

findings.¹⁴⁷ For instance, classic LAM cystic changes on HRCT of the lung along with a chylothorax documented by thoracentesis or CT evidence of fat-containing renal masses consistent with AMLs establishes the diagnosis with a high degree of certainty. There are rare exceptions, however, because lymphomas can present with pulmonary cystic change and chylothorax, and Birt-Hogg-Dubé (BHD) syndrome (see Fig. 69-3) can present with pulmonary cystic change, and AMLs, albeit rarely.¹⁴⁸ Pulmonary cystic change in a nonsmoking woman with TSC is consistent with LAM and does not usually require biopsy. In smoking patients with or without TSC, the diagnoses of pulmonary emphysema and Langerhans cell histiocytosis¹⁴⁹ (see Fig. 69-3; see eFig. 54-37) must be seriously considered. Serologies for Sjögren syndrome antibody A (SS-A) and B (SS-B) should be obtained to investigate follicular bronchiolitis and lymphocytic interstitial pneumonitis; alpha₁ antitrypsin should be measured to exclude emphysema caused by antitrypsin deficiency.¹⁵⁰ Serum VEGF-D is elevated threefold to eightfold in patients with LAM,⁷¹ but not in patients with pulmonary emphysema, Langerhans cell histiocytosis, lymphangiomatosis, or BHD and is useful in differentiating LAM from these disorders.⁷⁴ A serum level of VEGF-D of at least 800 pg/mL in a patient with typical cystic change on HRCT establishes the diagnosis of LAM with a sensitivity and specificity of 60% and 100%, respectively.⁷⁶

To aid in diagnosis of LAM, a dedicated CT of the abdomen may be obtained to screen for AMLs, lymphangiomomas, uterine masses, and chylous ascites. Renal AMLs can be identified radiographically based on the presence of fat (see eFigs. 69-1A and B); biopsy may be required to rule out renal cell carcinoma in the rare cases in which renal masses are solid appearing and do not contain fat.

DIFFERENTIAL DIAGNOSIS

The primary differential diagnoses in patients with a smoking history include Langerhans cell histiocytosis and

pulmonary emphysema. The morphology of the cysts can be helpful in differentiating these disorders from LAM; in emphysema (see Fig. 69-3), the cysts are devoid of distinct walls and, in Langerhans cell histiocytosis (see Fig. 69-3; see eFig. 54-37), the cysts are thicker walled, mid and upper lung zone predominant, and more irregularly shaped.¹²⁴ Diffuse subcentimeter nodular changes are often present in Langerhans cell histiocytosis (see eFig. 54-38), but can also be seen in TSC-LAM, where they usually represent MMPH.¹²⁷ Other cystic lung diseases that can mimic LAM and that should also be considered include Sjögren syndrome,¹⁵¹ Castleman disease, follicular bronchiolitis and lymphocytic interstitial pneumonitis (see Fig. 69-3), *Pneumocystis jirovecii* pneumonia (see eFigs. 90-14 and 90-15), recurrent respiratory papillomatosis (see eFigs. 54-29 through 54-32), hyper IgE syndrome, hypersensitivity pneumonitis (eFig. 69-8),¹⁵² amyloidosis (see eFig. 54-35), lymphoma, light chain deposition disease,¹⁵³ and bronchopulmonary dysplasia/barotrauma.^{150,154} Note that a few scattered thin-walled cysts may normally be encountered on HRCT studies, particularly in older individuals.¹⁵⁵ Recently, diffuse thin-walled cysts seen on HRCT have been described in a small number of patients with various small airway obstructive disorders, including asthma.¹⁵⁶ Thin-walled cystic lung lesions can also be associated with metastatic genitourinary neoplasms (eFig. 69-9) including endometrial stromal cell sarcoma,¹⁵⁷ low-grade leiomyosarcomas and angiosarcomas (eFig. 69-10), cystic fibrohistiocytic tumor, and cystic benign metastasizing leiomyoma (eFig. 69-11).⁶⁵

BHD syndrome¹⁵⁸ can be difficult to distinguish from LAM. BHD is a rare tumor suppressor syndrome associated with spontaneous pneumothorax, skin lesions, bland, peripheral and subpleural pulmonary cysts devoid of smooth muscle infiltration (see Fig. 69-3; Fig. 69-10), and inherited renal neoplasms. Mutations in the folliculin gene (*FLCN*) cause defects or deficiency in a protein of unknown function called *folliculin* and result in BHD syndromes of renal tumors, lung cysts, and skin lesions, or familial spontaneous pneumothorax.^{159,160} It appears that BHD is also associated with aberrant signaling through the Akt pathway, but the loss of regulation is upstream of mTOR.

Chylous diseases that involve the thorax, including lymphangiomatosis, lymphangiectasis, and lymphatic dysplasia,¹⁶¹⁻¹⁶⁴ may also be confused with LAM, although they do not typically produce cystic change in the lung.

LUNG BIOPSY

The diagnosis of LAM is most definitively established by lung biopsy. HMB-45 staining is highly specific for LAM and can be used to differentiate LAM from other causes of smooth muscle proliferation in the lung including idiopathic pulmonary fibrosis, benign metastasizing leiomyoma, and leiomyosarcoma. Bronchoscopic diagnosis, using transbronchial biopsies with appropriate immunohistochemical staining and expert interpretation, represent a viable alternative to surgical biopsy in some cases.¹⁶⁵ Recent small series suggest the yield of transbronchial biopsy may exceed 60% and, although the numbers of patients studied in these cohorts precludes definite conclusions regarding safety, there were few complications reported.¹⁶⁶⁻¹⁶⁹ In one large series from China, transbronchial biopsy was used to make the diagnosis in 49 of 97 patients with pathologic confirmation.¹⁶⁹ Video-assisted thoracoscopic lung biopsy remains the “gold standard” for making the diagnosis of LAM, although with proper application of diagnostic guidelines, VEGF-D testing, abdominal imaging, and transbronchial biopsy, fewer than 15% to 20% of patients should require a surgical approach. A proposed algorithm for the diagnostic approach to a patient with suspected LAM is presented (Fig. 69-11). Clarity regarding the diagnosis of LAM facilitates discussions regarding life planning, pregnancy, birth control, pneumothorax management, and candidacy for trials, and is increasingly important in the era of effective but side-effect prone therapies.

TRIALS AND TREATMENT

The remarkable gender restriction in LAM, although unexplained, has provided the rationale for the empirical antiestrogen strategies that have dominated the approach to LAM for the past several decades. The results have been generally disappointing and, because proper trials with hormonal therapies have never been conducted, there remain no proven therapies for LAM based on antagonism of estrogen action. Bilateral oophorectomy has not been demonstrated to slow the rate of decline in lung function in LAM.^{8,9,14} Enthusiasm for the use of progesterone, which became the standard of care following a single positive outcome published in a case report in 1987,¹⁰⁰ has likewise waned over

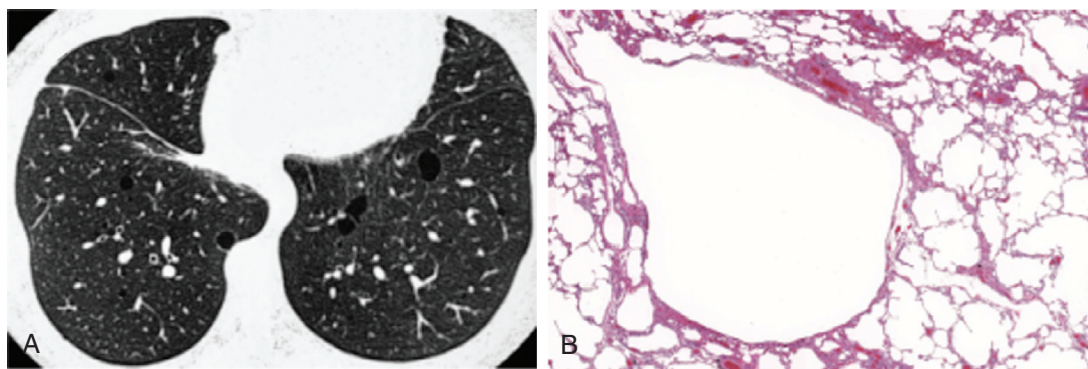


Figure 69-10 Birt-Hogg-Dubé syndrome. HRCT (A) and histopathologic (B; H&E staining) presentation of the lung cysts. This 58-year-old patient had repeated bilateral pneumothoraces and a family history of pneumothorax in a brother, son, and daughter. In the cyst wall, there is a lack of smooth muscle infiltration. (Courtesy Dr. Takashi Ogura, Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan; and Tamiko Takemura, Japanese Red Cross Medical Center, Tokyo, Japan.)

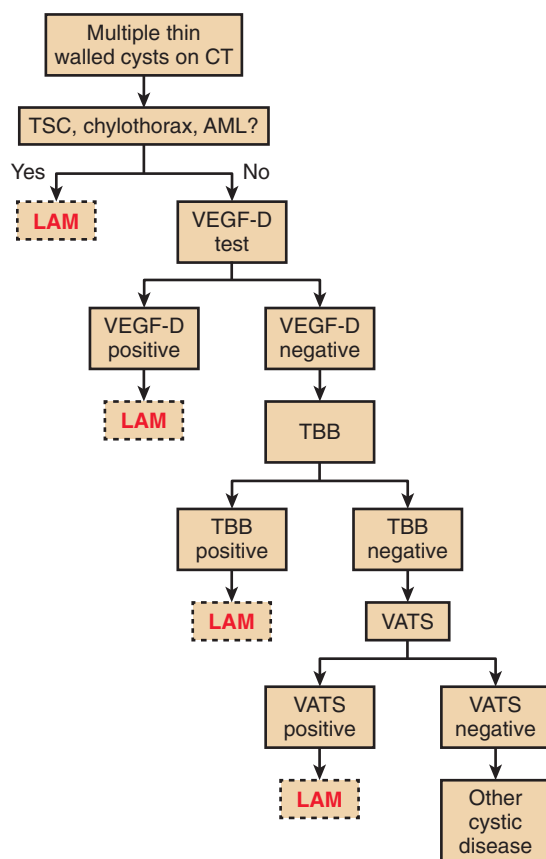


Figure 69-11 Proposed diagnostic algorithm for LAM. LAM should be considered in the differential of thin-walled multicystic lung disease. In a patient with typical CT changes, a confident clinical diagnosis of LAM can be made if tuberous sclerosis, chylothorax, a lymphangiomyoma, or an angiomyolipoma are present. For patients without these features, a serum VEGF-D level greater than 800 pg/mL is also diagnostic for LAM. If VEGF-D is negative, transbronchial biopsy, cytologic examination of pleural fluid, or thin needle biopsy of abdominal or thoracic masses can be useful for obtaining a pathologic diagnosis without surgery. Video-assisted thoracoscopic biopsy can be employed if the aforementioned approaches are uninformative, and will distinguish LAM from other mimics including emphysema, Langerhans cell histiocytosis, and lymphocytic interstitial pneumonitis/follicular bronchiolitis. AML, angiomyolipoma; TBB, transbronchial biopsy; TSC, tuberous sclerosis complex; VATS, video-assisted thoracoscopic surgery; VEGF-D, vascular endothelial growth factor D.

time. In a retrospective study of 275 patients, Taveira-DaSilva and associates¹⁰⁷ found that progesterone treatment failed to slow the decline in FEV₁. In fact, in that study, intramuscular or oral progesterone therapy was associated with an accelerated rate of decline in DL_{CO} compared with that in untreated patients. In another study, the rate of decline in FEV₁ and DL_{CO} was no different in patients treated with the gonadotropin-releasing hormone agonist triptorelin for 3 years than in a well-characterized cohort of historical controls.¹⁷⁰ Other case series of gonadotropin-releasing hormone agonist treatment have yielded conflicting results.¹⁷¹⁻¹⁷³ Use of gonadotropin-releasing hormone agonist is therefore not routinely recommended, except perhaps in patients who suffer recurrent, cyclical shortness of breath, chest discomfort, or pneumothoraces during menstruation. There is no proven role for corticosteroids, immunomodulatory cytotoxic agents, or ovarian irradiation in the treatment of LAM.

SIROLIMUS

Sirolimus had been shown to silence S6 phosphorylation and to induce apoptosis, necrosis, and regression of renal cystadenomas in TSC mutant rats and of hepatic tumors of TSC heterozygous null mice.^{174,175} Goncharova and colleagues¹⁷⁶ reported abundant S6 phosphorylation and unregulated cell proliferation in LAM cells isolated from explanted LAM lungs harvested at lung transplant. They further demonstrated that sirolimus blocked the hyperphosphorylation of S6 in cultured LAM cells and restored orderly cell growth.

The discovery of the importance of the mTOR pathway in LAM and preclinical studies in TSC animal models formed the basis for phase I/II trials of sirolimus in patients with tuberous sclerosis and LAM (*Cincinnati Angiomyolipoma Sirolimus Trial* [CAST]; NCT00457964).¹⁷⁷ In this open-label study, 25 patients with AMLs, including 6 patients with S-LAM, 12 with TSC-LAM, and 7 with TSC alone, were treated for 1 year with sirolimus and followed with serial magnetic resonance imaging studies of the kidneys, chest CT scans, and pulmonary function tests. Of the 20 patients still enrolled at 1 year, AML volume shrank by an average of 47%; of the 11 patients with LAM still enrolled at 1 year, the FEV₁ and forced vital capacity (FVC) increased by 118 mL and 390 mL, respectively. The residual volume fell by 440 mL, and cyst volume percent, a measurement of the fraction of the pulmonary parenchyma occupied by cysts, tended to decline on therapy.¹⁷⁸ Parameters that did not change included total lung capacity, 6-minute walk distance, and DL_{CO}. There were a number of adverse events while patients were taking the study agent, including mouth ulcers, cholesterol elevations, and hospitalizations for pneumonia, diarrhea, cellulitis, pyelonephritis, palpitations, and mucositis.

In the second year of the trial, patients were observed off the study agent at 6-month intervals. At the 2-year point, the average AML volume had increased again to 86% of baseline, although in 25% of patients, AML size remained below 70% of baseline; FEV₁ and FVC had declined at rates that are generally consistent with those of untreated patients with LAM,¹⁷⁹ but remained 62 mL and 364 mL above baseline, respectively; residual volume remained 333 mL below baseline, indicative of durable reduction in gas trapping. Similar results were seen in subsequent trials.^{180,181}

On the basis of the unexpected lung function response in the 11 patients with LAM, and a higher than expected rate of adverse events, a pivotal trial was designed to determine the risks and benefits of sirolimus in patients with LAM. The *Multicenter International LAM Efficacy of Sirolimus* (MILES) trial was a randomized, double-blind, controlled trial of sirolimus in 89 women with LAM and abnormal lung function (FEV₁ < 70% predicted).¹⁸² During the 1-year treatment period, lung function (FEV₁) stabilized on sirolimus, while declining by about 11% in the placebo group. Sirolimus also improved some measures of quality of lung and functional performance. In the observation year off therapy, lung function decline resumed in the sirolimus group and paralleled that in the placebo group. At baseline, serum VEGF-D was elevated by more than fivefold (relative to healthy

volunteers⁷³) in both groups. VEGF-D remained stable in the placebo group but, in the sirolimus group, VEGF-D decreased by more than 50%. When sirolimus was withdrawn, VEGF-D increased toward baseline again.⁷⁵ The sirolimus-induced decreases in VEGF-D are intriguing in light of the strong lymphangiogenic phenotype observed in LAM and marked improvement in chylous effusions and lymphangiomyoma volume seen in patients with LAM with lymphatic involvement.¹⁸³ Adverse events were common during the treatment period and were more prevalent in the sirolimus group. There was no increase in risk of infection, however, and the frequency of serious adverse events was balanced between the groups.

Collectively, the data suggest sirolimus therapy stabilizes lung function and improves some measures of quality of life in patients with LAM. The fact that decline resumes when the drug is withdrawn indicates that the therapy is suppressive and does not result in durable remission. One explanation for the beneficial but transient effects on lung function and tumor volume seen in CAST, MILES, and other trials is that the drug may shrink cells, attenuate tumor cell infiltration, or inhibit proliferation within the organs, but does not induce apoptosis of LAM cells. It is possible that mTOR inhibitors must be given continuously to maintain cellular homeostasis and avoid AML regrowth and lung function decline; indeed, there is early evidence of sustained benefit from longer-term therapy.¹⁸⁴

GENERAL RECOMMENDATIONS—TREATMENT AND MANAGEMENT

The MILES trial supports the use of about 2 mg/day of sirolimus in patients with LAM with an FEV₁ of less than 70% predicted. Lower-dose sirolimus (approximately 1 mg/day), used frequently in Japan (primarily for financial reasons), appears to be effective as well.^{184a} A single open label trial suggests that patients with rapidly declining lung function who are referred for transplantation may also benefit.¹⁸⁵ In several case reports and one small series,¹⁸⁴ sirolimus has been reported to be effective for the treatment of chylous fluid collections and lymphangiomyomas. Although sirolimus has been successfully used to treat recurrent LAM after lung transplantation,¹⁸⁶ routine use of sirolimus as first line immunosuppression is not recommended. Use in the immediate postoperative periods is associated with bronchial anastomotic dehiscence.^{186a} High serum VEGF-D is associated with baseline markers of disease severity, including need for oxygen, bronchodilator responsiveness, and reductions in FVC and DL_{CO}, and predicts disease progression and treatment response.⁷⁵ All other things being equal, a high baseline VEGF-D may tip the balance toward treatment in a patient being considered for sirolimus therapy. Early administration of long-term, low-dose suppression with sirolimus is an appealing strategy to prevent progression of LAM, but trials to determine the safety and efficacy of this approach are needed.

Other Therapeutic Considerations

Estrogen-containing medications may have adverse effects¹¹⁵ and are contraindicated. Agents that antagonize the effects of estrogen have not been proven to be effective.

A trial of bronchodilators should be considered in patients with LAM, because up to 17% to 25% of patients with LAM have bronchodilator-responsive airflow obstruction.^{11,28} Oxygen should be administered to maintain oxyhemoglobin saturations of greater than 90% with rest, exercise, and sleep. Bone densitometry should be considered in all patients who are immobilized and/or on antiestrogen therapies, and appropriate therapy instituted for osteoporotic patients. Proper attention should be paid to cardiovascular health following natural or induced menopause. Pulmonary rehabilitation seems to be particularly rewarding in this young, motivated population with obstructive lung disease, but studies to assess the effect of this intervention on exercise tolerance, conditioning, and quality of life have not been done.

GENERAL RECOMMENDATIONS—SCREENING

Sporadic LAM

Primary spontaneous pneumothorax, the most common cause of pneumothorax in young adults, happens primarily in smokers. Hagaman and colleagues¹⁸⁷ estimated that 5% of 24- to 52-year-old nonsmoking women who present with a sentinel pneumothorax have LAM and argue that HRCT screening of women in this demographic is cost effective, to the extent that it facilitates early pleurodesis that prevents recurrences.¹⁸⁷ We recommend screening in this population.

Tuberous Sclerosis–Associated LAM

HRCT screening of women with TSC identifies cystic changes in about 20% of subjects younger than 30 years old and 80% of subjects older than 40 years old.²³ The *Tuberous Sclerosis Alliance* (TSA)^{188,189} and the *European Respiratory Society* (ERS)¹⁴⁷ recommend a screening chest CT after age 18. For patients without pulmonary symptoms, the ERS recommends repeating the chest CT screen at age 30, while the TSA recommends repeat screening every 5 to 10 years. Once cysts are detected, the pace of TSC-LAM progression should be determined via HRCT testing every 2 to 3 years accompanied by annual pulmonary function and 6-minute walk testing, at least until trends are established.^{188,189} The percentage of women with TSC and cystic change on CT who become symptomatic due to LAM is generally thought to be small, probably less than 10%, but 6 of 48 (12.5%) patients with TSC-LAM in the Cudziolo study eventually succumbed to their lung disease.²³ Although cystic changes are found in approximately 10% of adult men with TSC,^{190,191} symptomatic LAM in males is very rare,¹⁸ and screening is not recommended.

The diagnosis and management issues that should be addressed in patients with LAM are outlined in [Table 69-2](#).

PREGNANCY

Patients should be advised that pregnancy has been reported to result in exacerbations of LAM in some cases.¹¹⁶⁻¹²⁰ However, risk associated with pregnancy in LAM has not been rigorously studied and decisions regarding the advisability of pregnancy should be made on an individual basis.

Table 69-2 Recommended Interventions, Studies and Immunizations in Patients with LAM**INTERVENTIONS/RECOMMENDATIONS**

Stop smoking
 Stop all estrogen-containing medications
 Counsel regarding pregnancy and air travel
 Inform patient of symptoms/management of pneumothorax, chylothorax
 Consider bronchodilator therapy
 Consider oxygen therapy
 Refer large angiomyolipomas (>4 cm in diameter) for possible embolization
 Refer for transplant evaluation for FEV₁ < 30%, disabling dyspnea, or profound hypoxia

STUDIES

High-resolution CT of the chest
 Pulmonary function testing (every 6 to 12 months)
 Serum levels of alpha₁-antitrypsin level, SS-A, SS-B, VEGF-D
 Abdominal CT, MRI, or ultrasound for angiomyolipoma (every 6 to 12 months)
 Rule out TSC with head CT or MRI, dermatologic, and ophthalmologic examinations
 Resting, nocturnal, exercise oximetry; 6-minute walk test
 Bone densitometry
 Consider transbronchial biopsy

INDICATIONS FOR LUNG BIOPSY

Cystic pulmonary change without corroborating features of known TSC or angiomyolipomata. In smokers, lung biopsy may be required to distinguish LAM from emphysema and Langerhans cell histiocytosis.

IMMUNIZATIONS

Flu shot and Pneumovax

CT, computed tomography; FEV₁, forced expiratory volume in 1 second; LAM, lymphangioleiomyomatosis; MRI, magnetic resonance imaging; SS-A, Sjögren syndrome antibody A; SS-B, Sjögren syndrome antibody B; TSC, tuberous sclerosis complex; VEGF-D, vascular endothelial growth factor D.

Women in whom LAM is diagnosed during pregnancy have high rates of pneumothorax, miscarriage, and premature birth.¹²¹ In a survey of 318 patients who indicated on their LAM Foundation intake forms that they had had at least one pregnancy, 163 patients responded to a second survey focusing on lung collapse.¹⁶² A total of 38 patients reported such an event, consistent with an incidence of pneumothorax in pregnancy of at least 10% (38 of 318). In a third of patients, the pneumothorax during pregnancy led to the diagnosis of LAM. Pneumothoraces were almost twice as frequent on the right as on the left, and four women presented with bilateral spontaneous pneumothorax. Most pneumothoraces took place during the second and third trimesters. This study and others^{14,108} suggest that pregnancy is associated with pleural complications in patients with LAM. Unfortunately, the more pressing question of whether pregnancy accelerates the decline in lung function in LAM may never be fully addressed, because so few women with a known LAM diagnosis choose to become pregnant and patients in whom LAM is diagnosed during pregnancy rarely have baseline pulmonary function tests available.

AIR TRAVEL

Whether patients with LAM are at increased risk for pneumothorax during air travel is controversial. Pollock-BarZiv

and coworkers¹⁹² found that 35% of patients with LAM had been advised by their physician to avoid air travel because of the theoretical risk for lung cyst rupture associated with atmospheric pressure changes during flight. In a survey of 276 patients who answered an LAM Foundation questionnaire, there were eight cases of radiographically documented pneumothorax associated with 454 flights. In five cases, however, symptoms that were consistent with pneumothorax may have been present before boarding. Other symptoms and signs, including anxiety (22%), chest pain (12%), shortness of breath (14%), cyanosis (2%), and hemoptysis (0.4%), were noted in 10% to 20% of flights. The conclusion from the study was that, although there were adverse events during flight in patients with LAM, air travel is well tolerated by most patients with LAM. A recent study of 281 patients with LAM who had routine chest radiograph after traveling to the National Institutes of Health identified seven with acute pneumothorax. There was no difference in the incidence of pneumothorax in patients who traveled by ground versus air. The conclusion was that pneumothorax with air travel was related to the high incidence of pneumothorax in the disease rather than the air travel itself.¹⁹³

In advising patients with LAM about air travel, it is reasonable to consider several factors, including a history of frequent or recent pneumothoraces, and the overall extent of cardiopulmonary impairment. Patients with poor cardiopulmonary reserve may tolerate even small pneumothoraces poorly. It is prudent for patients with LAM to seek medical evaluation including a chest radiograph before boarding a plane if pleuritic chest pain or unexplained shortness of breath is present. Hypoxemia during flight presents independent risks. Patients should consult with their physicians regarding recommendations for on-board oxygen use. In most cases, however, air travel in patients with LAM should not be restricted.

PLEURAL DISEASE

Pneumothoraces in patients with LAM tend to recur, especially after conservative management such as observation, aspiration, or simple tube thoracostomy. Over 65% of patients with LAM develop pneumothorax during the course of their illness, averaging 3.5 pneumothoraces per affected patient over a lifetime.¹⁰⁹ Risk of pneumothorax appears to correlate with the size of cysts.¹⁹⁴ The LAM Foundation Pleural Consensus Group advocated for the use of a pleural symphysis procedure with the first pneumothorax, given the greater than 70% chance of recurrence.¹⁰⁹ Chemical sclerosis, mechanical abrasion, talc poudrage, and pleurectomy have been effective in patients with LAM. However, for reasons that are not well explained, failure rates after pleurodesis are surprisingly high, higher than in any other chronic lung disease.

Chyle does not generally cause pleural inflammation or fibrosis, and small stable chylous effusions rarely require intervention once the diagnosis of LAM is made. Shortness of breath may mandate drainage, however, in some cases repeatedly. Pleural symphysis may be required to prevent nutritional and lymphocyte deficiencies that can result from repeated taps or persistent drainage. Chemical

pleurodesis is generally an effective therapy for chylothorax, as is mechanical abrasion and talc poudrage.¹⁹⁵

PULMONARY TRANSPLANTATION

Urban and associates¹⁴ reported the outcome of transplant in 13 patients (associated with renal transplant in 1). The mean interval between time of onset of LAM and transplant was 7.8 ± 5.2 years (range, 2.1 to 16.8 years). Mean FEV₁ before transplant was 0.57 ± 0.15 L. Boehler and colleagues¹⁹⁶ conducted a retrospective survey on 34 patients with LAM who had undergone lung transplant. The actuarial survival after 2 years was 58%, which is similar to other lung disease categories. The incidence of perioperative bleeding appeared to be higher, especially in patients with extensive pleural adhesions related to prior pleural procedures, as were complications of pneumothorax and postoperative chylothorax. The United Network of Organ Sharing recorded 126 transplants for LAM from 1989 through 2007, including 77 double-lung transplants and 49 single-lung transplants. The 1-, 3-, and 5-year survival rates for single-lung transplants were 87%, 73%, and 61%; and for double-lung transplants were 92%, 83%, and 77%, respectively. These survival rates are equal to or better than those for other disease groups transplanted in the same time frame. There have been four case reports of recurrence of LAM in the donor allograft.^{58-60,197} The recurrences did not appear to contribute to death in any of these patients and, at the present time, the risk of recurrence should not be considered in judging the candidacy of patients for transplant. More than half of patients with LAM who have undergone lung transplantation have had a prior history of unilateral or bilateral pleural fusion procedures and, although postoperative bleeding risk is increased, the operative mortality and long-term survival do not appear to be adversely affected.^{109,196}

As with other obstructive lung diseases, referral for lung transplantation should be considered when the FEV₁ falls to less than 30% of the predicted value. Some patients who fail to meet this criterion may qualify based on other factors that profoundly affect quality of life, such as disabling dyspnea or problems maintaining oxygen saturation despite high levels of supplemental oxygen. Although the question of single- versus double-lung transplantation has not been directly studied in LAM, double-lung transplantation produces better functional outcomes in other types of obstructive lung disease.¹⁹⁸ However, double-lung transplantation is not always feasible owing to the limited availability of organs and the urgency of the procedure in some patients.

ANGIOMYOLIPOMAS

Renal AMLs may require embolization or cauterization for control of bleeding, a complication that is thought to be more common when the diameter of the tumor exceeds 4 cm.¹⁹⁹ Others contend that the extent of aneurysmal change determines bleeding risk. Serial abdominal imaging should be performed to assess AML size at 6- to 12-month intervals, at least until trends in growth are clear. Nephron-sparing partial resections may be considered for very large tumors.²⁰⁰ Nephrectomy is sometimes required for tumors

with intravascular extension or other reasons, but is rarely the approach of choice for AMLs that can be managed by less invasive means. Everolimus has recently been approved by the U.S. Food and Drug Administration for the treatment of AMLs.²⁰¹

PROGRESSION AND PROGNOSIS

Progressive airflow obstruction typically develops in patients with LAM. In a cohort of patients in the United Kingdom, 10 years after symptom onset, 55% of 77 patients were breathless when walking on flat ground and 10% were housebound.²⁰² The average annual rate of decline in FEV₁ and DL_{CO} in 275 patients studied in a single laboratory at the NHLBI was 75 ± 9 mL and 0.69 ± 0.07 mL/min/mm Hg, respectively.¹⁷⁹ In other series from Europe, the rate of decline in FEV₁ was considerably higher, estimated at approximately 100 to 120 mL/yr.^{14,203,204} In the MILES trial, patients in the placebo group lost 134 mL/yr. There was some evidence in these studies that rate of decline in lung function correlates with initial DL_{CO}, with menopausal status, and with progesterone treatment. Indeed, in the placebo cohort from the MILES trial, the rate of decline in premenopausal patients was fivefold higher than the rate in postmenopausal patients (200 mL/yr vs. 40 mL/yr, respectively).¹⁸² In patients with mild disease, the development of pneumothorax appears to correlate with a faster rate of decline in FEV₁.¹⁹⁴ A positive bronchodilator response, which was associated with a lower FEV₁, was found to be a predictor of more rapid rate of decline in FEV₁ over time.¹² High baseline VEGF-D also correlates with disease progression and treatment response.⁷⁵

Survival estimates vary widely, appear to be dependent on mode of presentation or ascertainment, and have generally trended upward over the past few decades, probably due to earlier recognition through more widespread use of CT scanning. The data from early, large case series indicate that 38% to 78% of patients are alive at 8.5 years from the time of disease onset.^{8,9} Urban and associates¹⁴ reported a 91% probability of survival at 8.5 years, 79% at 10 years, and 71% at 15 years. For Japanese patients who presented with pneumothorax as the sentinel event, Hayashida and colleagues¹³ reported that 5-, 10-, and 15-year survival probabilities were 95%, 89%, and 89%, whereas for those who presented with dyspnea, survival rates were only 85%, 60%, and 47%. Matsui and coworkers²⁰⁵ found that the actuarial survival rate, based on time from lung biopsy to death or transplant, was 85% and 71% after 5 and 10 years, respectively. These investigators also developed a lung histology scoring system based on semiquantitative analyses of smooth muscle cell infiltration and cystic change, which correlated with survival. Other negative prognostic indicators that have been reported include a reduced FEV₁/FVC, increased total lung capacity, and a predominantly cystic, rather than smooth muscle hyperplastic, histology.⁹ There are no prognostic data available for TSC-LAM, but the survival of patients identified through screening is almost certainly more favorable than that of patients who present with dyspnea.^{20,22} In a population-based cohort ascertained by surveying patients registered with the LAM Foundation, the median survival was 29 years.²⁰⁶

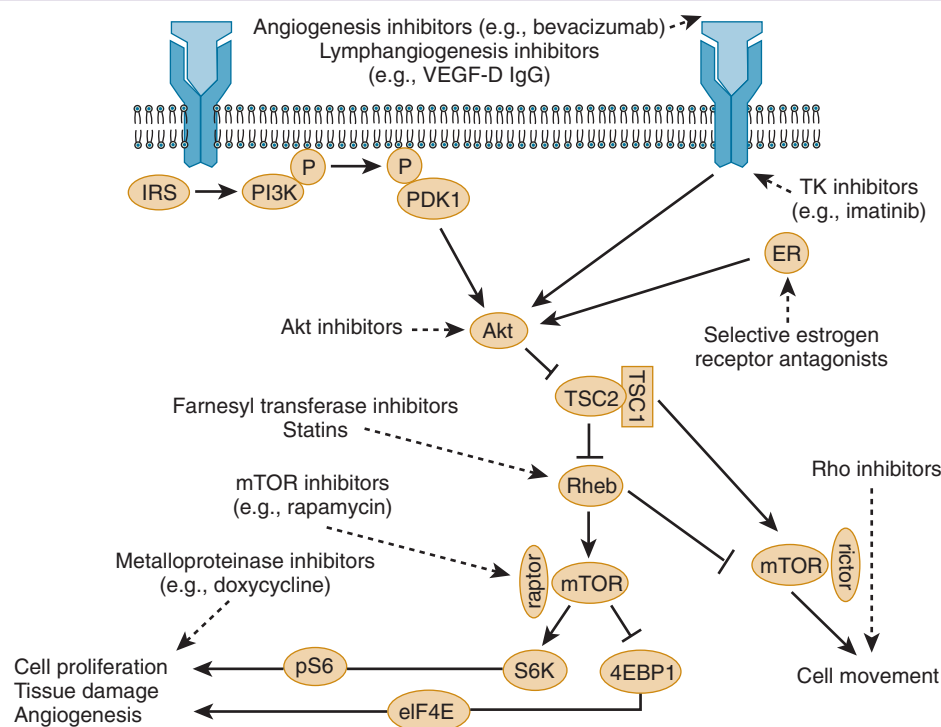


Figure 69-12 Future therapeutic targets for LAM. Knowledge of the signaling pathways that are dysregulated in patients with LAM has revealed a number of promising molecular targets for intervention. The constitutive activation of mTOR drives the inappropriate phosphorylation of S6 (pS6) when the *TSC1* or *TSC2* gene is missing or defective, as is seen in patients with LAM. pS6 (and eIF4E) drives protein translation and inappropriate cellular proliferation, but also feeds back to inhibit the activation of immunoreactive secretin (IRS) and the downstream effector Akt. This feedback loop control can be defeated by the activation of Akt through other routes, such as the platelet-derived growth factor (PDGF) and estrogen receptor pathways (which may partly explain the gender restriction in LAM). In this regard, tyrosine kinase (TK) inhibitors such as imatinib and selective estrogen antagonists may have special utility in LAM to block alternative activation of Akt. mTOR inhibitors such as sirolimus and everolimus block mTOR signaling, and statins and farnesyl transferase inhibitors block Rheb translocation to the membrane by inhibiting the lipid modification of the protein. Patients with LAM express elevated levels of the lymphangiogenic growth factor, vascular endothelial growth factor D (VEGF-D), which is currently being studied as a target in metastatic malignancy trials. Angiogenesis inhibitors such as bevacizumab and anti-VEGF-D or VEGFR-3 antibody may block blood and lymphatic vessel recruitment required for tumor maintenance, respectively, and metalloproteinase inhibitors such as doxycycline may block lung matrix degradation that plays a role in tumor implantation, spread, and tissue destruction. Cell migration, infiltration, and metastasis are controlled by a rapamycin-insensitive mTOR pathway, but may be susceptible to inhibition by rho kinase inhibitors.

FUTURE CLINICAL TRIALS IN LYMPHANGIOLEIOMYOMATOSIS

Progress in the understanding of the genetic and molecular basis of LAM has suggested a number of potential candidate therapies beyond allosteric mTOR inhibitors that may be appropriate for single agent- or combination therapy-based testing in clinical trials (Fig. 69-12). These include PI3K kinase pathway inhibitors, mTOR kinase inhibitors, Rheb and Rho inhibitors (e.g., farnesyltransferase inhibitors and statins), estrogen antagonists (e.g., gonadotropin-releasing hormone agonists), selective estrogen response modifiers, selective estrogen receptor down-regulators (e.g., Faslodex), prolactin inhibitors, aromatase inhibitors (e.g., letrozole), tyrosine kinase inhibitors (e.g., imatinib mesylate, nintedanib), metalloproteinase inhibitors (e.g., doxycycline, marimastat, batimastat), angiogenesis inhibitors (e.g., bevacizumab), and lymphangiogenesis inhibitors (e.g., anti-VEGF-D antibody, VEGFR3 antibody, pazopanib). Many of these drugs have been approved by the U.S. Food and Drug Administration or are in development for other indications.

Key Points

- *Lymphangioleiomyomatosis* (LAM) is a progressive cystic lung disease that is strikingly more prevalent in women and that most commonly presents with dyspnea on exertion and/or pneumothorax, and less commonly with chylothorax, hemoptysis, or incidentally discovered abdominal masses or pulmonary cysts.
- LAM is a metastasizing neoplasm, arising from an unknown source, associated with infiltration of lung with benign appearing smooth muscle cells and cystic parenchymal destruction.
- The diagnosis of LAM can be established on clinical grounds, using consensus guidelines and the diagnostic biomarker, serum VEGF-D, but may require transbronchial biopsy, cytologic evaluation of chylous fluid, thin needle aspirates from abdominal lesions, or, less commonly, surgical tissue confirmation.
- LAM is associated with tuberous sclerosis mutations that activate mTOR and promote growth and lymphangiogenesis, whether the mutations are in the germline in the heritable genetic disease tuberous sclerosis

or caused by somatic (non-germline) mutations in the sporadic form of the disease.

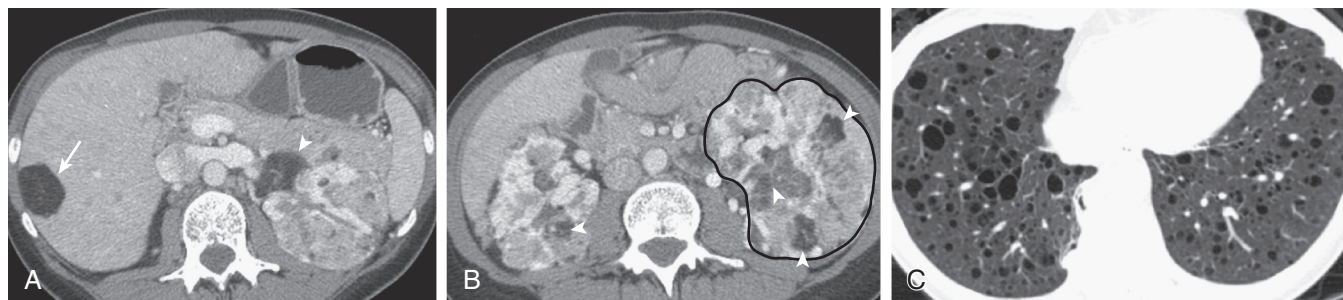
- Sirolimus is an effective treatment for LAM that should be considered in patients with abnormal lung function, rapid decline in FEV₁ or DL_{CO}, recurrence after lung transplant, or chylous complications.
- The clinical course of LAM is highly variable, but is generally slowly progressive, with 10-year survival of approximately 80% to 90% and a median survival after the onset of symptoms approaching 30 years.

Complete reference list available at *ExpertConsult*.

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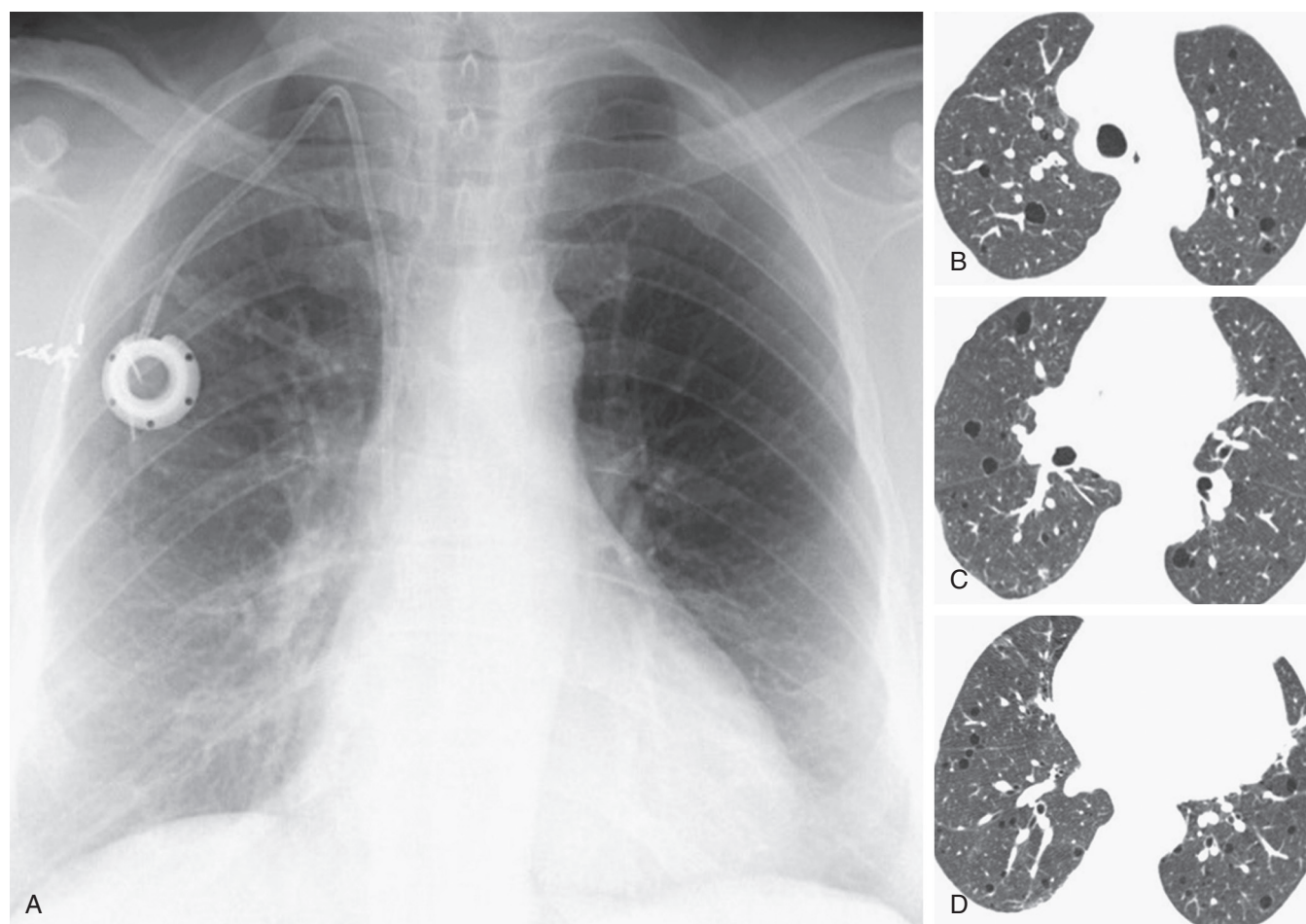
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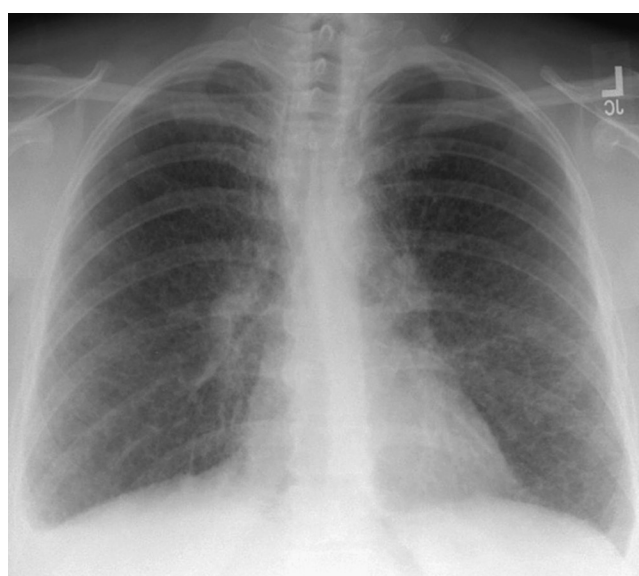
eFigure 69-1 Angiomyolipomas in LAM. **A** and **B**, Axial contrast-enhanced chest CT through the upper abdomen shows bilateral renal enlargement (left kidney outlined in black in **B**). Numerous areas of fat density (*arrowheads*, **A** and **B**) representing angiomyolipomas are present. Hepatic angiomyolipomas (arrow, **A**) are also evident. **C**, Axial chest CT displayed in lung windows shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, which is typical of LAM. (Courtesy Michael Gotway, MD.)



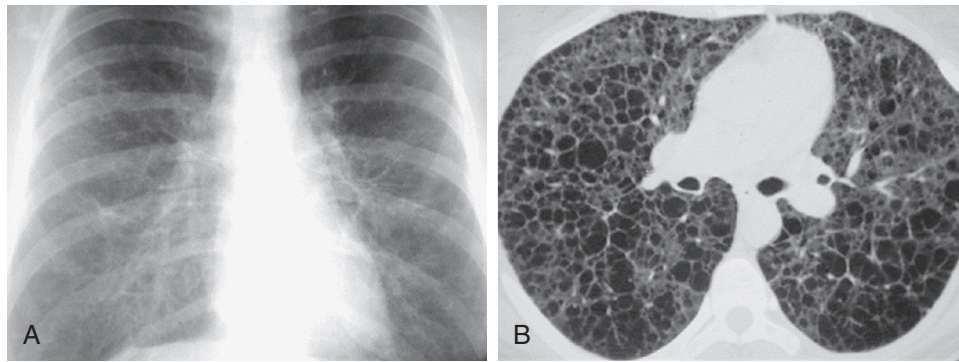
eFigure 69-2 Lymphangiomyomas in LAM. Axial chest CT through the upper thorax (**A**) and axial chest CT through the pelvis (**B**) show circumscribed, faintly septated, low attenuation structures (*arrows*) representing lymphangiomyomas. **C**, Axial chest CT displayed in lung windows shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of LAM. (Courtesy Diego Ruiz, MD, Palo Alto Medical Clinic.)



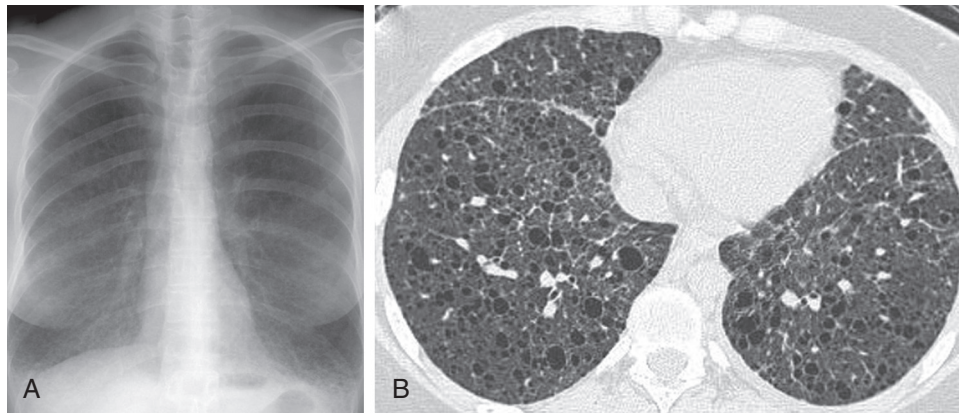
eFigure 69-3 Relatively unremarkable chest radiographic appearance in LAM. **A**, Frontal chest radiograph in a patient with LAM shows relatively few abnormalities, with no findings specifically suggesting the diagnosis of LAM. Nonspecific mild right perihilar linear and reticular opacities are present. **B** through **D**, Axial chest CT displayed in lung windows shows bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of LAM. The presence of comparatively fewer and smaller cysts in this patient likely contributes to the understated nature of the appearance on the chest radiograph (compare to [eFigs. 69-4, 69-5A, and 69-6A](#)). (Courtesy Michael Gotway, MD.)



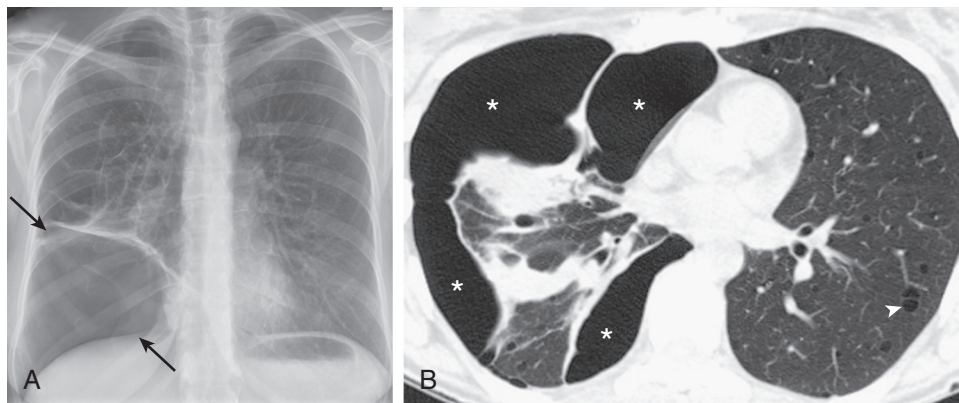
eFigure 69-4 LAM—linear/reticular appearance on chest radiograph. Frontal chest radiograph in a patient with LAM shows diffuse, bilateral, symmetric linear and reticular opacities suggesting a disorder infiltrating the pulmonary interstitium. The appearance of interstitial lung disease on chest radiograph in patients with LAM may result from superimposition of the walls of the cysts characteristic of this disorder, in addition to actual interstitial space expansion resulting from lymphatic dilation and diffuse nodular proliferation of type II cells. (Courtesy Michael Gotway, MD.)



eFigure 69-5 LAM—typical imaging appearance. **A**, Frontal chest radiograph in a patient with LAM shows increased lung volumes associated with bilateral linear and reticular opacities, faintly seen to represent the walls of the cysts typical of LAM. **B**, Axial chest CT shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of LAM. (Courtesy Michael Gotway, MD.)



eFigure 69-6 “Honeycomb” or “pseudofibrotic” appearance of LAM at imaging. **A**, Frontal chest radiograph shows bilateral linear and reticular opacities, somewhat resembling interstitial/fibrotic lung disease, especially in the bases. The large lung volumes, however, strongly argue against a fibrotic interstitial pneumonia. **B**, Axial chest CT displayed in lung windows shows numerous bilateral, uniform-appearing, thin-walled cysts with relatively normal-appearing intervening lung, typical of LAM. The numerous overlapping cyst walls contribute to the “interstitial” appearance on radiography. This appearance in the bases can superficially resemble fibrotic lung disease. (Courtesy Michael Gotway, MD.)



eFigure 69-7 Spontaneous pneumothorax in LAM. **A**, Frontal chest radiograph shows a basal predominant right-sided pneumothorax (arrows). **B**, Axial chest CT displayed in lung windows shows the pneumothorax (*); thin-walled left lower lobe cysts (arrowhead), typical of LAM, are present. (Courtesy Michael Gotway, MD.)

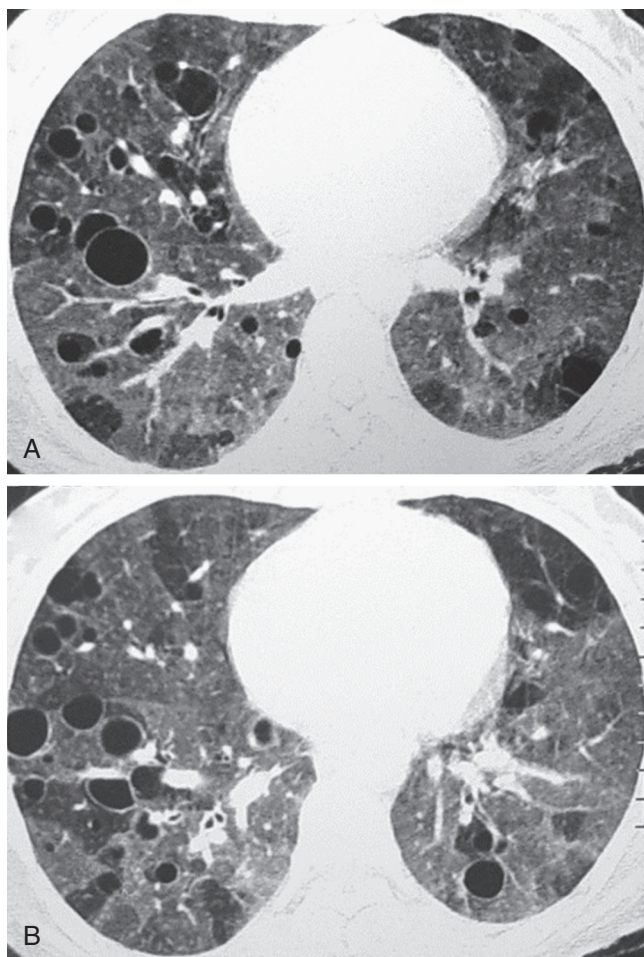
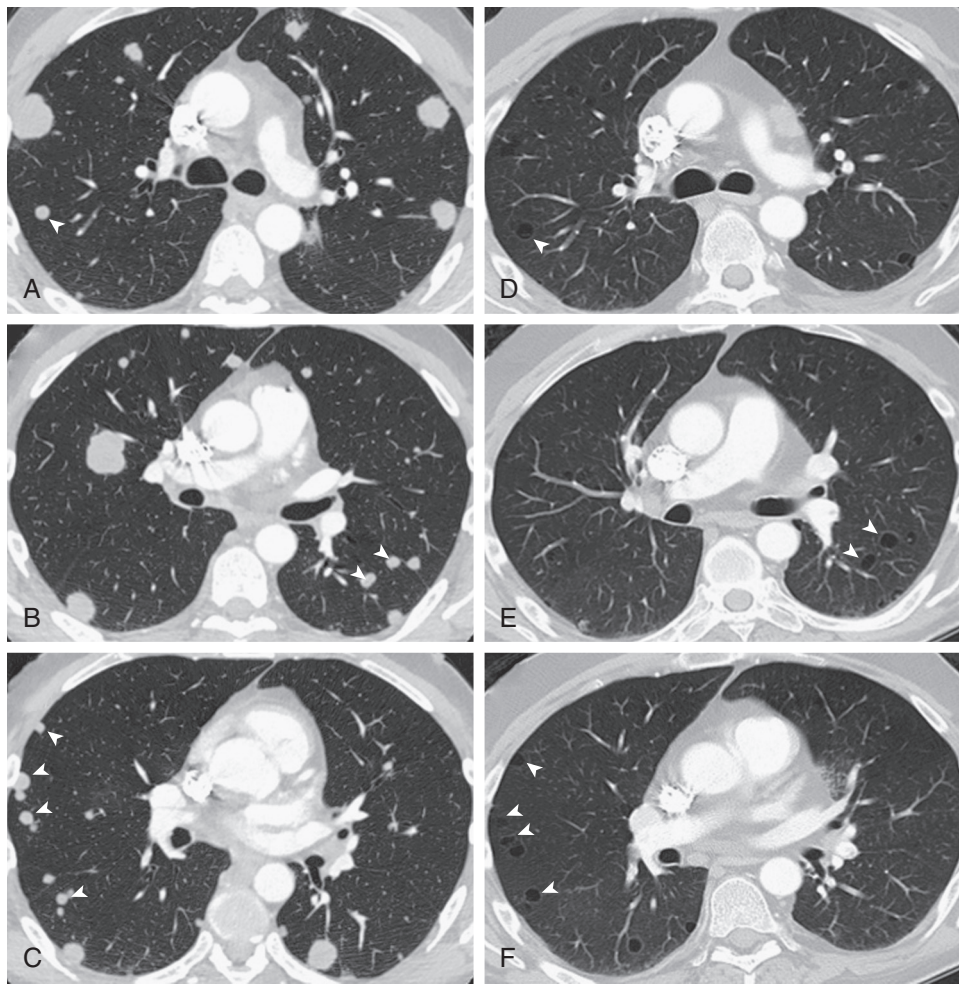
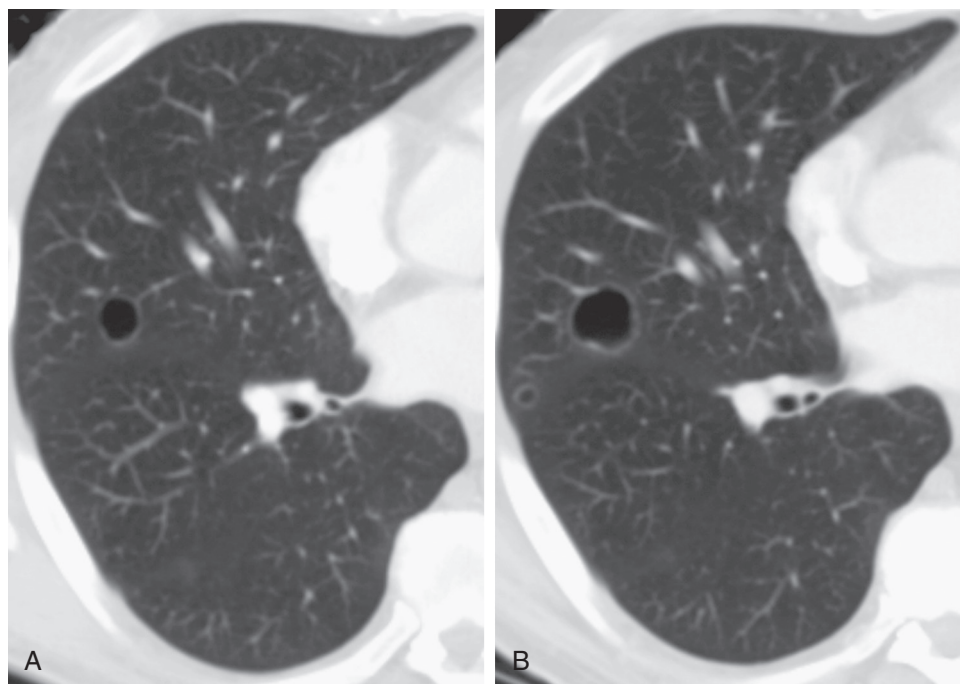


Figure 69-8 Thin-walled cystic lung disorders simulating LAM: diffuse cystic lung disease in hypersensitivity pneumonitis. A and B, Axial chest CT displayed in lung windows shows patchy areas of ground-glass opacity associated with numerous thin-walled cysts in a patient with proven hypersensitivity pneumonitis. (Images courtesy Alejandro Gómez-Gómez, Hospital Central Dr. Ignacio Morones Prieto, Facultad de Medicina, San Luis Potosí, SLP, México).



eFigure 69-9 Thin-walled cystic lung disorders simulating LAM: cystic metastatic disease. **A–C,** Axial chest CT displayed in lung windows at diagnosis shows numerous, variably sized, bilateral solid lung nodules (*arrowheads*), representing pulmonary metastatic disease from testicular carcinoma. **D–F,** Axial chest CT following therapy for metastatic testicular carcinoma shows many of the solid nodules have evolved into thin-walled cysts (*arrowheads*). While the appearance at follow-up (**D–F**) may simulate more common causes of diffuse cystic lung disease, such as LAM and lymphocytic interstitial pneumonia, the clinical context (particularly the gender in this particular circumstance) and serial evolution from nodular lung disease readily provide differentiation from typical cystic lung disorders. (Courtesy Michael Gotway, MD.)



eFigure 69-10 Thin-walled cystic lung disorders simulating LAM: cystic metastatic disease. **A** and **B**, Axial chest CT displayed in lung windows in a patient with metastatic angiosarcoma shows several thin-walled cysts, ultimately shown to reflect metastatic angiosarcoma. (Images courtesy Diego Ruiz, MD, Palo Alto Medical Clinic.)

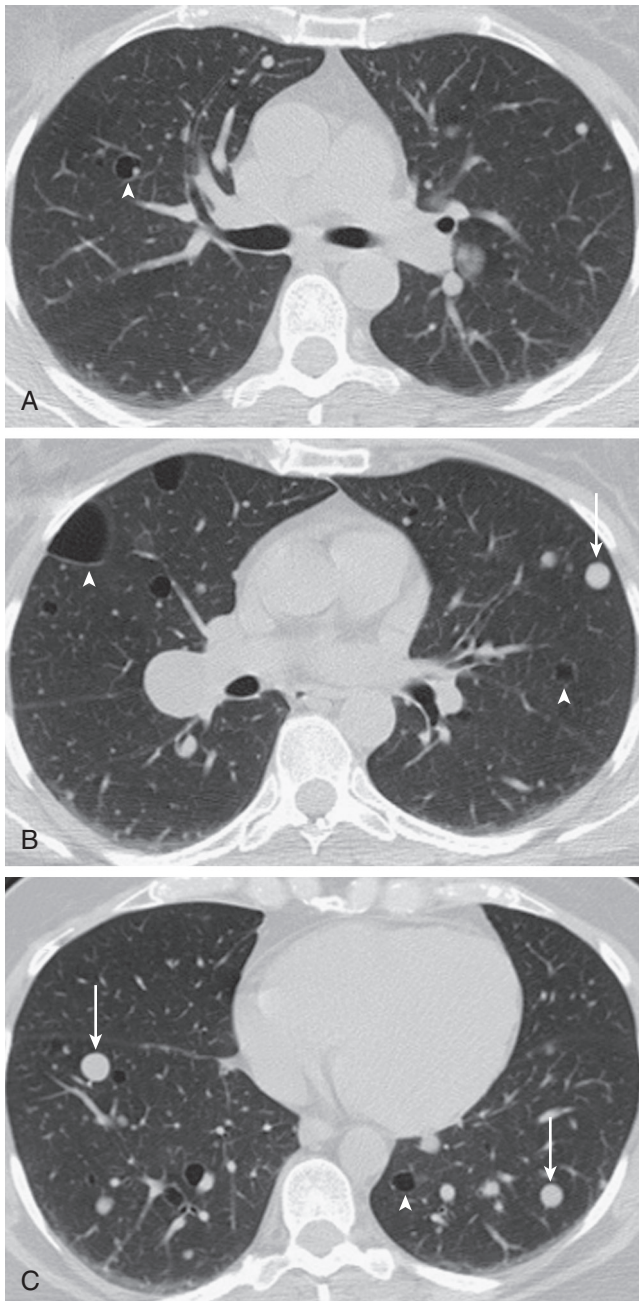


Figure 69-11 Thin-walled cystic lung disorders simulating LAM: cystic benign metastasizing leiomyoma. A–C, Axial chest CT displayed in lung windows shows several bilateral thin-walled cysts (*arrowheads*) and solid, circumscribed nodules (*arrows*). The cysts evolved from solid nodules on serial examinations. Biopsy showed benign metastasizing leiomyoma. (Courtesy Michael Gotway, MD.)

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PULMONARY ALVEOLAR PROTEINOSIS SYNDROME

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by abnormal alveolar surfactant accumulation and hypoxemic respiratory insufficiency. It arises in a heterogeneous group of mechanistically distinct diseases usefully divided into disorders of surfactant *production* or surfactant *clearance*.¹⁻³ Disorders of production include *pulmonary surfactant metabolic dysfunction* (PSMD) disorders caused by mutations in genes encoding surfactant proteins or genes encoding proteins involved in surfactant production. Disorders in clearance can be further divided into *primary* PAP caused by disruption of *granulocyte/macrophage colony-stimulating factor* (GM-CSF) signaling and *secondary* PAP caused by another disease or condition that disrupts alveolar macrophage surfactant clearance.

Recent advances including reports of several large cohorts⁴⁻⁷ have greatly improved our understanding of PAP pathogenesis, epidemiology, clinical subtypes, prognosis, and natural history and have resulted in new methods to diagnose, evaluate, and treat patients.^{2,8} Importantly, research on this rare and fascinating syndrome has identified the critical role of GM-CSF in alveolar macrophage ontogeny, pulmonary surfactant homeostasis, alveolar structural integrity, host defense, pulmonary and systemic inflammation, and autoimmunity. Further, studies involving GM-CSF-deficient mice identified new treatment approaches for common diseases such as asthma and rheumatoid arthritis. This chapter reviews the pathogenesis, classification, epidemiology, presentation, and therapy of PAP.

PATHOGENESIS

SURFACTANT COMPOSITION AND HOMEOSTASIS

Surfactant is a complex mixture of 90% phospholipids and 10% surfactant proteins that functions at the air-liquid-alveolar wall interface to reduce surface tension, thereby preventing alveolar collapse. It is produced in type II alveolar epithelial cells, secreted into the alveolar space, and cleared by either recycling or catabolism by type II cells or uptake and catabolism by alveolar macrophages. Surfactant composition, production, and homeostasis are reviewed in Chapter 8. Studies in animals and humans in which the pathogenesis of PAP has been elucidated have identified GM-CSF as a critical regulator of surfactant homeostasis (Fig. 70-1).

GRANULOCYTE/MACROPHAGE COLONY-STIMULATING FACTOR

GM-CSF is a 23-kD cytokine that signals via cell surface receptors comprising a GM-CSF-binding, low-affinity α chain (CDw116) and a nonbinding, affinity-converting β chain (CD131).^{9,10} Although neither chain has intrinsic signaling activity,¹¹ the β chain constitutively binds *Janus kinase 2* (JAK2),¹¹ a tyrosine kinase involved in cytokine signaling. Ligand binding causes the formation of $\alpha\beta$ JAK2 multimers and activation of JAK2, resulting in phosphorylation of α ¹² and β chains, activation of other kinases,¹¹ and initiation of signaling via multiple pathways^{11,13} including the *signal transducer of activation and transcription-5* (STAT5).¹⁴

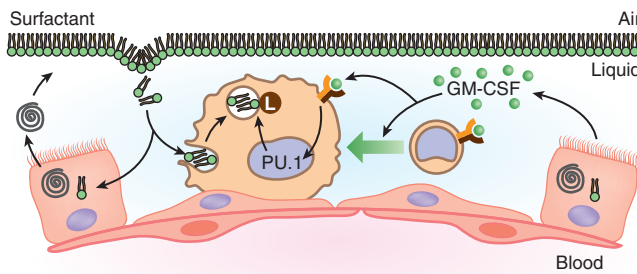


Figure 70-1 Schematic of pulmonary surfactant homeostasis within an alveolus of a healthy individual. Surfactant lipids and proteins are synthesized in type II alveolar epithelial cells and secreted into the alveolar space. Extracellular surfactant contributes to the surfactant layer present at the air-liquid interface, which plays a critical role by reducing surface tension within the alveolus. Surfactant lipids and proteins are removed from the extracellular surfactant by uptake and recycling in type II cells or by uptake and catabolism in alveolar macrophages. Granulocyte-macrophage colony-stimulating factor (GM-CSF), a critical regulator of surfactant catabolism in alveolar macrophages, functions by binding to heterologous receptors on alveolar macrophages and stimulating surfactant catabolism via the transcription factor PU.1. GM-CSF is also critical for stimulating the terminal differentiation of precursors into mature alveolar macrophages.

MURINE MODELS OF DISORDERED SURFACTANT HOMEOSTASIS

GM-CSF-deficient (*Csf2*^{KO}) mice provided the first clue to the pathogenesis of PAP. Although neither production of surfactant by type II cells nor its uptake by alveolar macrophages was altered,^{15,16} clearance of surfactant by alveolar macrophages was impaired.¹⁷ Pulmonary GM-CSF,^{18,19} acting via the transcription factor PU.1,²⁰ coordinately regulated surfactant catabolism; cell adhesion; expression of Fc receptors, mannose receptors, and other receptors; phagocytosis; bacterial killing; and Toll-like receptor-4 signaling.²⁰ GM-CSF was identified as a critical regulator of the terminal differentiation of alveolar macrophages in mice.

GM-CSF receptor β chain-deficient (*Csf2rb*^{KO}) mice develop PAP indistinguishable from that of GM-CSF-deficient mice.²¹ Because transplantation of wild-type bone marrow corrected PAP in these mice, myeloid cells, and not lung resident epithelial cells, were identified as the cellular site of pathogenesis.²² A biomarker of PAP in these mice (increased serum GM-CSF) suggested the means that led to identification of hereditary PAP caused by *CSF2RA* and *CSF2RB* mutations in children.²³⁻²⁵ Importantly, *Csf2rb*^{KO} mice and children with *CSF2RA* or *CSF2RB* mutations develop a lung disease that is identical in every respect including lung pathology (surfactant-filled alveoli, preserved architecture); cytopathology (oil red O-stained macrophages, cell debris); alveolar macrophage biomarkers (reduced messenger RNA [mRNA] for PU.1, *peroxisome proliferator-activated receptor- γ* [PPAR- γ], ABCG1); and BAL biomarkers (increased surfactant proteins/lipids, turbidity, cytokines [GM-CSF, M-CSF, MCP-1]) and clinical course (progressive surfactant accumulation). Studies in these mice have identified *pulmonary macrophage transplantation* (PMT) as a novel therapeutic approach for hereditary PAP.²⁶

Mice deficient in ABCG1, a transmembrane protein mediating cellular cholesterol efflux, accumulate cholesterol in alveolar macrophages and type II cells and develop pulmonary lipidosis, indicating ABCG1 may be important in surfactant homeostasis.²⁷ Importantly, ABCG1 expression is decreased in alveolar macrophages from GM-CSF-deficient mice, patients with autoimmune PAP,²⁸ GM-CSF receptor-deficient mice, and patients with hereditary PAP (unpublished data). Conditional disruption of PPAR- γ (a known transcriptional regulator of ABCG1) specifically in alveolar macrophages also disrupts surfactant clearance.²⁹

Together, murine studies suggest the pathogenesis of primary PAP, both autoimmune and hereditary, may involve disruption of a pathway including GM-CSF, PU.1, PPAR- γ , and ABCG1 that is critical for surfactant clearance by alveolar macrophages.

In secondary PAP, several models have shed light on the pathogenesis. For example, reduction of alveolar macrophage numbers by chemical depletion increases surfactant pool size³⁰ and inhalation of respirable silica results in alveolar proteinosis.³¹

In addition to these models of surfactant clearance, murine models of abnormal surfactant production called PSMD disorders develop lung diseases faithfully recapitulating their respective human diseases. They are clinically, histologically, and biochemically distinct from PAP in GM-CSF-deficient mice and have improved the understanding of surfactant homeostasis. For example, SP-B-deficient mice develop respiratory failure at birth. Studies in these mice showed that SP-B is critical in the post-translational processing of SP-C, organization of surfactant phospholipids in lamellar bodies, formation of tubular myelin in alveoli, generation of surfactant films capable of reducing surface tension, and lung function during the early postnatal period.³²⁻³⁴ ABCA3-deficient mice develop respiratory failure at birth,³⁵ and studies in these mice established ABCA3 as critical to lamellar body formation and pulmonary surfactant biogenesis.³⁶

Other murine models have been shown to develop PAP and are providing insights to surfactant homeostasis including murine models of severe combined immunodeficiency,³⁷ pulmonary overexpression of *interleukin* (IL)-4³⁸ or IL-13,³⁹ and SP-D-deficiency.⁴⁰

ROLE OF GM-CSF AUTOANTIBODIES IN PRIMARY PAP

In 1999, Nakata's group first identified neutralizing GM-CSF autoantibodies in the BAL fluid and serum of idiopathic, now called *autoimmune*, PAP patients.^{41,42} Multiple subsequent studies confirmed that high levels of GM-CSF autoantibodies are associated with idiopathic PAP but not with secondary PAP, other lung diseases, PSMD disorders, or healthy individuals (Fig. 70-2).^{1-3,43,44} In one study, the concentration of GM-CSF autoantibodies in 158 idiopathic PAP patients was 113 ± 7 $\mu\text{g/mL}$,^{1,43} while levels were less than 1 $\mu\text{g/mL}$ in patients with secondary PAP, PSMD disorders, or other lung diseases.¹ GM-CSF autoantibodies are composed of IgG, predominantly of the IgG1 and IgG2 subclasses; are highly specific for GM-CSF; have a high binding affinity (20 ± 7.5 pM); and are capable of neutralizing GM-CSF at levels up to many thousands times higher than

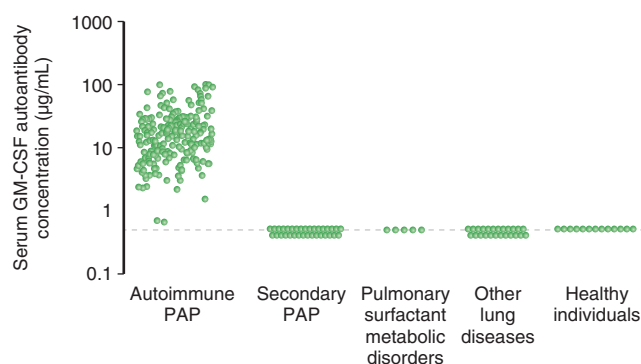


Figure 70-2 Serum antibodies to GM-CSF are elevated in autoimmune pulmonary alveolar proteinosis (PAP). Serum GM-CSF autoantibody levels in individuals with autoimmune PAP ($n = 223$), secondary PAP ($n = 33$), pulmonary surfactant metabolic dysfunction ($n = 5$), other lung diseases ($n = 24$), and in healthy controls ($n = 13$). The detection limit of the assay was $0.5 \mu\text{g/mL}$ of serum. (Some of these data were reported in Inoue Y, Trapnell BC, Tazawa R, et al: Characteristics of a large cohort of autoimmune pulmonary alveolar proteinosis patients in Japan. *Am J Respir Crit Care Med* 177:752–762, 2008.)

the physiologic concentrations of GM-CSF in vivo.^{41,43,45} Notwithstanding these important observations, GM-CSF autoantibodies have been reported at low frequency in healthy people and in patients with autoimmune diseases without evidence of PAP; in addition, GM-CSF comprises the dominant anti-cytokine activity in pharmaceutical immunoglobulin prepared from healthy individuals.^{46,47} In a more recent study utilizing multiple detection methods, GM-CSF autoantibodies were demonstrated in all of 72 healthy individuals with no prior exposure to exogenously administered GM-CSF, albeit at low levels (median [interquartile range] = 1.04 [0.63 to 1.7] $\mu\text{g/mL}$ serum).⁴⁵ Another confusing observation was that in patients with PAP, serum GM-CSF autoantibodies did not correlate with disease severity.⁴⁴

To prove that GM-CSF autoantibodies were critical to the pathogenesis of idiopathic PAP and not a related but unimportant epiphenomenon, GM-CSF autoantibodies from these patients were isolated in pure form (i.e., a single band on SDS gels) and used to immunize healthy nonhuman primates. Results demonstrated unequivocally that GM-CSF autoantibodies reproduced the cardinal molecular and cellular features of PAP, including surfactant-filled alveoli with preserved wall architecture, foamy alveolar macrophages, alveolar macrophage biomarkers (reduced PU.1, PPAR- γ , and ABCG1 mRNA), and BAL biomarkers (increased SP-D and turbidity).^{48,49} Evaluation of GM-CSF autoantibodies isolated from the immunized primates or directly from patients has similar bioactivity.⁴⁸ Together with the clinical studies in humans, these data provided strong evidence that GM-CSF autoantibodies were in fact the pathogenic driver in idiopathic PAP, which is now recognized as *autoimmune PAP*.⁴⁸ Neutrophils from the immunized primates also had impaired phagocytosis similar to defects reported in these patients, in GM-CSF deficient mice, and in normal human neutrophils incubated with purified GM-CSF autoantibodies in vitro.⁵⁰ Using the CD11b stimulation index assay (see later), GM-CSF signaling in immunized primates was found to decrease inversely with GM-CSF autoantibody concentration at values below 5 mcg/mL and was zero at higher values, thus defining the critical threshold concentration

needed to block GM-CSF signaling.⁴⁹ In a translational study using this assay, a similar relationship and threshold were observed in humans.⁴³ Thus seemingly discrepant observations (i.e., the critical role of GM-CSF autoantibodies in PAP pathogenesis and the lack of correlation between their concentration and disease severity) were reconciled by the hypothesis that a critical threshold level of GM-CSF autoantibodies was needed to reduce GM-CSF bioactivity sufficiently to impair surfactant clearance.⁴⁷

GM-CSF autoantibodies are polyclonal and directed at epitopes throughout the GM-CSF molecule.⁴³ Evaluation of 19 monoclonal autoantibodies from 6 patients demonstrated that they use multiple immunoglobulin V genes and targeted at least four non-overlapping epitopes on GM-CSF, suggesting that GM-CSF is driving the autoantibodies and not a B-cell epitope on a pathogen cross-reacting with GM-CSF.⁵¹

The observations that GM-CSF stimulation of neutrophil functions is impaired in autoimmune PAP and GM-CSF deficient mice provides a further explanation for the increased infection risk in PAP caused by disruption of GM-CSF signaling. Further, the inverse correlation between GM-CSF autoantibody levels and neutrophil function (phagocytosis) in healthy people suggests a potential physiologic role for these autoantibodies, such as scavenging free GM-CSF, which can function as a proinflammatory cytokine. Supporting this concept, using methods capable of detecting GM-CSF, whether bound by GM-CSF autoantibody or not, serum GM-CSF concentrations in healthy people ($3048 \pm 484 \text{ pg/mL}$ serum, $n = 11$) are much higher than previously reported, and more than 99% is bound to GM-CSF autoantibodies both in healthy individuals and in PAP patients.⁴⁵

GENETIC FACTORS

A series of reports have now established hereditary PAP as a newly described genetic disease caused by genetic mutations in *CSF2RA* or *CSF2RB*, which encode GM-CSF receptor α or β chains, respectively (Fig. 70-3).^{23-25,52,53} In some cases, the genes have been cloned, the defects reproduced in vitro, the signaling abnormalities studied in detail,²³⁻²⁵ and the results used to develop several novel biomarker-based diagnostic tests (see later). One particularly useful test, serum GM-CSF, was used to identify a number of patients with hereditary PAP due to mutations in the GM-CSF receptors and is capable of identifying patients with defects in either chain of the receptor.^{23-25,54} Of importance to the pathogenesis of PAP, in families with two siblings carrying the same function-impairing GM-CSF receptor gene mutation, the older sibling had minimal disease while the younger sibling had more extensive disease, suggesting another factor besides loss of GM-CSF signaling is important in determining disease severity in hereditary PAP.²⁴ Several genetic factors associated with hematologic disease and secondary PAP have been identified including mutations in the gene encoding the transcription factor GATA2, as well as in GMCSF receptor chain genes.^{54a,79}

Mutations in three genes encoding surfactant proteins, *SFTPB*, *SFTPC*, and *ABCA3*, disrupt surfactant production and function and cause respiratory disease in neonates,

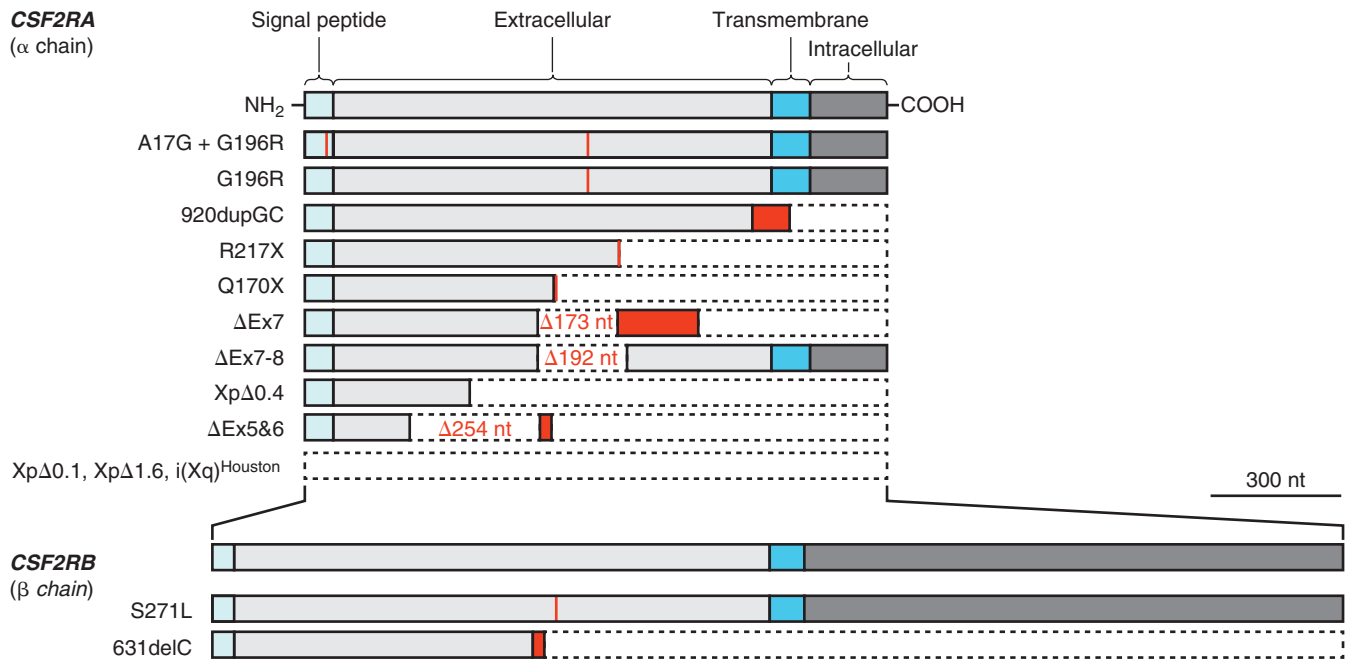


Figure 70-3 Genetic mutations in *CSF2RA* and *CSF2RB* and corresponding GM-CSF receptor α and β chain abnormalities associated with the development of hereditary pulmonary alveolar proteinosis. For each gene, a schematic of the normal protein is shown above to indicate regions corresponding to the signal peptide, extracellular domain, transmembrane spanning domain, and intracellular domain. Shown below each normal protein are the abnormal proteins caused by genetic mutations (indicated) known to cause hereditary PAP. (Some data are from Suzuki T, Sakagami T, Young LR, et al: Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. *Am J Res Crit Care Med* 182:1292–1304, 2010.)

children, and older individuals.⁵⁵⁻⁵⁸ See Chapter 8 for additional information on pulmonary surfactant. SP-B and SP-C are hydrophobic peptides that reside within the surfactant phospholipid layer, which functions to reduce surface tension at the alveolar air/liquid interface,³⁴ whereas ABCA3 likely transports lipids, including phosphatidylcholine, cholesterol, sphingomyelin, and phosphatidylglycerol, into lamellar bodies in alveolar type II cells, where the surfactant complex is assembled, processed, and stored.

SFTPB is a small gene (9.7 kb) encoding a 79-amino acid, hydrophobic protein. Infants homozygous for recessive loss-of-function mutations in *SFTPB* develop respiratory failure and die shortly after birth.^{59,60} In contrast, individuals heterozygous for SP-B deficiency alleles have normal lung function.⁶¹ More than 30 mutations have been identified to date in fewer than 100 infants with SP-B deficiency.^{58,62} Two thirds have an insertional frameshift mutation caused by the replacement of a single nucleotide by three nucleotides at codon 121 (designated 121ins2). Among infants with SP-B deficiency, approximately 60% are homozygous for the 121ins2 mutation, 25% are heterozygous for this and another function-altering allele, and 15% have other mutations. SP-B deficiency is associated with the aberrant processing and secretion of an immature SP-C peptide, which may contribute to the respiratory failure associated with hereditary SP-B deficiency.⁶³

SFTPC is a small gene (3 kb) encoding a 35-amino acid hydrophobic protein. Known mutations in *SFTPC* are expressed in a dominant fashion and are associated with interstitial lung disease in neonates, children, and adults.^{58,64-67} Twenty-five percent of individuals with SP-C-associated lung disease have a point mutation in *SFTPC* causing the substitution of threonine for isoleucine at codon

73 (I73T).⁶⁵ Immunohistochemical analysis of lung tissue from an infant with the I73T mutation demonstrated normal staining patterns for pro-SP-B, SP-B, and pro-SP-C. Although infants with this mutation can present with respiratory distress syndrome, most children with the mutation become symptomatic with interstitial lung disease beyond the newborn period.^{65,68}

ABCA3 is a large gene (80 kb) encoding a 1704-amino acid protein. Autosomal recessive mutations in *ABCA3* can result in fatal surfactant deficiency in neonates^{69,70} and chronic respiratory insufficiency in older children.⁷¹ Function-altering mutations in *ABCA3* result in surfactant that is deficient in phosphatidylcholine and has decreased function, suggesting that *ABCA3* has an important role in pulmonary surfactant phospholipid homeostasis.⁷² A relatively common missense point mutation in *ABCA3* causing the substitution of a valine for glutamic acid at codon 292 (E292V) is associated with chronic interstitial lung disease in older children who are heterozygous for this and a different function-altering mutation on the other *ABCA3* allele.⁷¹

NKX2.1 is essential for expression of SP-B, SP-C, and *ABCA3*. Haploinsufficiency of the gene encoding for the transcription factor *NKX2.1* (also known as thyroid transcription factor 1 or TTF1) causes a complex phenotype in neonates that includes, albeit variably, hypothyroidism, brain abnormalities, and acute and chronic lung disease.^{73,74}

Although the lung diseases associated with mutations in *SP-B*, *SP-C*, *ABCA3*, and *NKX2.1* disrupt surfactant homeostasis, cause varying degrees of surfactant accumulation (i.e., PAP), and are often cited as hereditary forms of PAP in the medical literature, they are distinguished from disorders of surfactant clearance by their surfactant dysfunction (i.e., functionally abnormal surfactant), histopathologic

Table 70-1 Underlying Systemic Disorders Reported in Association with Pulmonary Alveolar Proteinosis

Disease Category/Underlying Disease	Reference
HEMATOLOGIC DISORDERS	76
Acute lymphocytic leukemia	78
Acute myeloid leukemia	79
Aplastic anemia	145
Chronic lymphocytic leukemia	146
Chronic myeloid leukemia	147
Myelodysplastic syndromes	77
Multiple myeloma	148
Lymphoma	75
Waldenstrom macroglobulinemia	149
NONHEMATOLOGIC MALIGNANCIES	
Adenocarcinoma	150
Glioblastoma	150
Melanoma	151
IMMUNE DEFICIENCY AND CHRONIC INFLAMMATORY SYNDROMES	
Acquired immunodeficiency syndrome	152
Amyloidosis	153
Agammaglobulinemia	154
Fanconi syndrome	145
Juvenile dermatomyositis	155
Lysinuric protein intolerance	80
Renal tubular acidosis	156
Severe combined immunodeficiency disease	157
CHRONIC INFECTIONS	
Cytomegalovirus	158
<i>Mycobacterium tuberculosis</i>	159
<i>Nocardia</i>	160
<i>Pneumocystis jirovecii</i> (formerly <i>carinii</i>)	161

abnormalities (gross parenchymal derangement and interstitial disease), and clinical course. Consequently, the term *pulmonary surfactant metabolic dysfunction* (PSMD) disorders has been proposed for this group of genetic disorders.

DISEASE ASSOCIATIONS

PAP has been reported in association with various medical conditions believed to cause the disorder, resulting in use of the term *secondary* PAP.^{1,2} Systemic disorders associated with secondary PAP include malignant and other hematologic diseases, nonhematologic malignancies, immune deficiency syndromes, chronic inflammatory syndromes, and chronic infections (Table 70-1). In the past, chronic myelogenous leukemia and myelodysplastic syndrome were the most frequently reported hematologic disorders associated with PAP.^{2,75-77} In one single-institution study, PAP was reported in 5.3% of patients with hematologic malignancies and in 8.8% of those who were neutropenic.⁷⁶ Of possible pathogenic significance, 9 of 10 patients in one study were neutropenic when PAP developed and, in most, PAP recovered spontaneously after bone marrow engraftment. In another, PAP developed during a period of neutropenia that resolved after treatment with granulocyte colony-stimulating factor.⁷⁸ In a third report, PAP developed in three patients with acute myeloid leukemia with GM-CSF receptor abnormalities, including reduced levels of the β chain (three of three) and undetectable α chain (two of three).⁷⁹ PAP has been found in about 10% of patients with lysinuric protein intolerance, an ultra-rare inherited

Table 70-2 Pulmonary Exposures Associated with Pulmonary Alveolar Proteinosis

Exposure Category/Agent	Reference
DUSTS (INORGANIC)	
Aluminum	90, 91
Cement	162
Silica	87, 88
Titanium	92
Indium	93
ORGANIC DUSTS	
Agricultural	163
Bakery flour	87
Fertilizer	87
Sawdust	86
FUMES	
Chlorine	87
Cleaning products	87
Gasoline/petroleum	87
Nitrogen dioxide	164
Paint	92
Synthetic plastic fumes	87
Varnish	87

disorder caused by defective cationic amino acid transport.^{80,81} Secondary PAP has been reported in association with various forms of immunodeficiency, including thymic alymphoplasia,⁸² immunoglobulin A deficiency,⁸³ solid organ transplantation,⁸⁴ and acquired immunodeficiency syndrome.⁸⁵

Although the mechanism(s) responsible for secondary PAP are poorly studied, two common themes have emerged when considered in the context of the critical role of alveolar macrophages in surfactant homeostasis. Conditions reducing either the numbers or functions of alveolar macrophages would be expected to reduce the capacity of resident alveolar macrophages to clear surfactant from the lung surface.

ENVIRONMENTAL FACTORS

PAP has been associated with inhalation exposure to environmental agents including cigarette smoke, a wide variety of organic and inorganic dusts, fumes, and gases (Table 70-2). Epidemiologic studies (see later) document that PAP is more common in smokers. Five of the 27 original patients reported by Rosen and colleagues⁸⁶ had been exposed to wood dust. Most reports implicating other environmental exposures are single cases or small retrospective series and, in general, have not established a causal relationship between the exposure and development of PAP. One early report on 138 PAP patients found that half had significant exposure to dust and fumes, of which the most common exposure was to inhaled silica, noted in 10 individuals.⁸⁷ With the advent of occupational protective equipment in the workplace, this form of “acute silicoproteinosis”^{88,89} is rare. Other case reports document the association of PAP with exposure to aluminum dust,⁹⁰ cellulose fibers, cement dust, titanium dioxide,^{91,92} indium-tin oxide,⁹³ and nitrogen dioxide. The link between silica and PAP is supported by studies in rats demonstrating that inhalation of silica particles disrupts surfactant homeostasis, resulting in increased

surfactant accumulation.^{31,94} In five separate large series of patients with PAP,^{2,4-7} a history of dust exposure, when data were available, was present in 26% to 54% of patients.⁷ Further research is necessary to determine what role environmental inhalation exposure plays in the pathogenesis of PAP.

MECHANISMS OF DISRUPTION OF SURFACTANT HOMEOSTASIS

In mice, a series of observations has established GM-CSF as a critical regulator of pulmonary surfactant homeostasis, including the following: (1) surfactant homeostasis requires the presence of GM-CSF in the lung, and PAP develops in the absence of either pulmonary GM-CSF or its receptor; (2) surfactant accumulation in GM-CSF-deficient mice is caused by decreased catabolism by alveolar macrophages and not by increased production; (3) pulmonary GM-CSF is required for normal expression of transcription factor PU.1 in alveolar macrophages, and enforced (i.e., retroviral-mediated) expression of PU.1 restores surfactant catabolism in alveolar macrophages from GM-CSF knockout mice; and (4) surfactant homeostasis can be restored in GM-CSF receptor β -deficient mice by transplantation of bone marrow from a wild-type mouse.

Primary PAP (Autoimmune and Hereditary)

In humans, studies elucidating the pathogenesis of autoimmune and hereditary PAP show that GM-CSF is also critical for surfactant homeostasis in humans. Supportive data include (1) GM-CSF autoantibodies (a) are present at high levels only in autoimmune PAP, (b) can be isolated in pure form, (c) cause PAP after injection into healthy primates, and (d) retain biologic activity after injection^{48,49}; (2) GM-CSF autoantibodies neutralize vastly higher amounts of GM-CSF than is present physiologically⁴³; (3) in PAP patients, PU.1 expression is reduced in alveolar macrophages and increased by GM-CSF therapy⁹⁵; (4) disruption of GM-CSF signaling by *CSF2RA* or *CSF2RB* mutations causes lung disease histopathology indistinguishable from that of GM-CSF knockout mice and autoimmune PAP in humans^{23-25,52,53}; (5) reduced expression of GM-CSF receptor β on leukocytes is associated with PAP in children and with development of PAP in leukemia patients⁷⁹; and (6) disorders that transiently reduce numbers and/or functions of alveolar macrophages are temporally related to the development and resolution of secondary PAP in humans.⁷⁸

Available evidence suggests that GM-CSF regulates myeloid cell functions similarly in humans and mice. GM-CSF knockout mice and autoimmune PAP patients have remarkable similarity in (1) pulmonary histopathologic appearance of the lung; (2) cytologic and ultrastructural appearance of alveolar macrophages; (3) elevation of certain cytokines (monocyte chemotactic protein-1, macrophage colony-stimulating factor); (4) the pattern of differential impairment of various neutrophil functions; and (5) the increased incidence of pulmonary and extrathoracic secondary infections.

The pathogenic mechanism in primary PAP is (1) disruption of GM-CSF signaling to alveolar macrophages, either by the absence of GM-CSF (observed in mice, but not yet in humans); (2) disruption of GM-CSF signaling by mutations

in the GM-CSF receptor proteins (in mice and humans), or (3) disruption of GM-CSF by an autoimmune attack that neutralizes GM-CSF, eliminating GM-CSF bioactivity and myeloid cell stimulation in vivo (in humans and nonhuman primates). GM-CSF, via PU.1, regulates catabolism of surfactant in alveolar macrophages (in mice and possibly humans). Surfactant accumulation in PAP is due to reduced clearance by alveolar macrophages, but the precise mechanism is unknown. Because pulmonary surfactant is internalized into macrophages by endocytosis and catabolized in phagolysosomes, it is possible that interruption of GM-CSF signaling blocks the translocation of endocytosed surfactant to lysosomes. Such a mechanism has been demonstrated for adenovirus internalized by macrophages from GM-CSF-deficient mice, in which PU.1 redirects adenovirus-containing endosomes to lysosomes for destruction. Alternatively, GM-CSF deficiency may result in a key enzyme deficiency. Potentially supporting this possibility are data related to the *peroxisome proliferator-activated receptor- γ* (PPAR- γ), a ligand-activated transcription factor regulating genes involved in lipid metabolism and other pathways.⁹⁶ PPAR- γ messenger RNA and protein are expressed in alveolar macrophages in healthy individuals, decreased in PAP patients, and increased by GM-CSF therapy of PAP patients.⁹⁵ CD36, a lipid scavenger receptor regulated by PPAR- γ , is regulated in a similar pattern. However, PPAR- γ deficiency has been noted in several other disorders, including sarcoidosis, acute respiratory distress syndrome, and asthma, where there have been reports of surfactant abnormalities.⁹⁷ Further studies are required to determine the mechanism by which interruption of GM-CSF signaling leads to reduced catabolism of surfactant by alveolar macrophages.

Secondary PAP

The mechanisms involved in secondary PAP, although less well supported by experimental data, likely involve reduced numbers or functions of alveolar macrophages. This would decrease the surfactant clearance capacity of resident alveolar macrophages and is supported by data demonstrating a temporal relationship of the onset and resolution of PAP with the suppression and restoration of myeloid cells in hematologic disorders. Other secondary mechanisms of PAP—for example, due to inhalation of toxic fumes and dusts—are less clear. Presumably, they would involve a reduction in the ability of alveolar macrophages to clear surfactant. However, because overexpression of certain cytokines (IL-4, IL-13) or decreased expression of some *surfactant proteins* (SP-D) also increases surfactant production in mice, other potential mechanisms appear possible.

Pulmonary Surfactant Metabolic Dysfunction

Mechanisms of PSMD involve mutations in genes of the surfactant synthetic pathway, including *SFTPB*, *SFTPC*, *ABCA3*, *NKX2.1*, and likely others, and result in the production of biochemically and functionally abnormal surfactant. These disorders have a lung histopathology and clinical course that is markedly different from PAP caused by interruption of GM-CSF signaling. Further, the pathophysiology arises from surfactant deficiency rather than surfactant excess as in PAP. Thus it may be appropriate to consider these disorders as distinct from PAP and not part of a spectrum of PAP.

NOMENCLATURE AND CLASSIFICATION

Since PAP was first described as a lung disease “of the filling of the alveoli by a PAS-positive proteinaceous material, rich in lipid,”⁸⁶ it has become recognized as a syndrome caused by distinct diseases¹ and is reported in the medical literature using numerous terms, resulting in a nomenclature that is redundant, inconsistent, and confusing. Terms have been based on the biochemical characteristics of the accumulated material (e.g., alveolar proteinosis, phospholipidosis); pathogenesis (e.g., silicoproteinosis, idiopathic); disease category (e.g., primary vs. secondary); and timing of symptom onset (e.g., congenital, acquired) and are redundant (e.g., idiopathic PAP, acquired PAP, pulmonary alveolar lipoproteinosis, phospholipoproteinosis, alveolar lipoproteinosis, alveolar proteinosis, alveolar phospholipidosis, and alveolar lipophosphoproteinosis). Confusion arises from use of the same term for different diseases. For example, the term *congenital PAP* has been used for the disease caused by mutations in *SFTPB*, which is uniformly fatal at birth and caused by surfactant deficiency, and also for the disease caused by GM-CSF receptor deficiency that presents in children, is caused by surfactant accumulation, and can be treated successfully.

The foregoing discussion underscores the need for a classification and nomenclature that will facilitate clear communication about disorders of homeostasis necessary for clinical training, disease management, and research. On the basis of initial discussions of a global task force assembled by the Rare Lung Diseases Consortium, a simplified classified scheme is proposed (Table 70-3).

Disorders of surfactant homeostasis are separated into disorders of reduced *clearance* (PAP) or abnormal *production* (PSMD). PAP is further subdivided into primary and secondary categories, depending on whether it is due to a primary disturbance of GM-CSF signaling or secondary to another disease, respectively. *Primary PAP* is composed of several specific disease mechanisms: an autoimmune disease

caused by GM-CSF autoantibodies (autoimmune PAP) or a genetic disease caused by mutations in *CSF2RA* or *CSF2RB*. A third disease, caused by GM-CSF deficiency, exists in mice and is predicted but not yet observed in humans. *Secondary PAP* arises in association with several disease categories, including hematologic disorders, malignancy, immune deficiency syndromes, chronic inflammatory disorders, and chronic infections (see Table 70-1), as well as in association with certain inhalation exposures, especially silica (sandblasters) (see Table 70-2). PSMD disorders are those arising from mutations in genes of the surfactant synthesis pathway, including *SFTPB*, *SFTPC*, *ABCA3*, *NKX2.1*, and likely others that have yet to be identified.⁵⁶ These disorders are included in a new classification of interstitial lung disease in young children.⁹⁸

The plethora of terms used to report on the PAP syndrome are not recommended for continued use and should be replaced with the term *pulmonary alveolar proteinosis*. Terms referring to clinical presentation (i.e., acquired PAP, congenital PAP) should not be used when the underlying disease is known. For example, “SP-B deficiency” is far more informative than “congenital PAP” and more consistent with its pathogenesis as a disorder of surfactant deficiency (PSMD) rather than excessive surfactant accumulation (PAP). When the cause is unknown, the term *unclassified PAP* is preferred over “idiopathic PAP” because the latter is currently understood to be the disorder caused by high levels of GM-CSF autoantibodies.

EPIDEMIOLOGY

Disorders of surfactant homeostasis are found in worldwide distribution but are rare. Since the initial description of PAP, more than 1000 cases of primary or secondary PAP^{2,4,23,86,99} and substantially fewer cases of PSMD^{55-58,64,65,69,71,100-102} have been reported in the medical literature (Table 70-4). A comprehensive meta-analysis of 410 separate cases of PAP representing all clinical subtypes found that patients were more likely to be male (male-to-female ratio = 2.65:1.0) and that males predominated among smokers (male-to-female ratio = 2.78:1.0) but not among nonsmokers (male-to-female ratio = 0.69:1.0).² These results suggested that the high proportion of males among PAP patients may be explained by their higher frequency of tobacco use. This study also found the median age at diagnosis to be 39 years (39 in men and 35 in women).

Autoimmune PAP has been studied in several ways to establish its epidemiology. A large national, multicenter, registry-based study of PAP was recently conducted in Japan and identified 223 patients with autoimmune PAP.⁴ This study reported a male predominance (male-to-female ratio = 2.1:1.0) and found that males predominated among smokers (male-to-female ratio = 9.3:1.0) but not among nonsmokers (male-to-female ratio = 0.6:1.0).⁴ The median age at the time of diagnosis was 53 years (52 in men and 55 in women). The prevalence was similar in nine nonoverlapping geographic regions encompassing the entirety of Japan, and the case rate correlated closely with the regional population size. This result suggests the absence of an effect of climate or geography on the prevalence. Further

Table 70-3 Classification of Diseases Associated with Disruption of Surfactant Homeostasis

CLINICAL CATEGORY/DISEASE

Primary PAP

GM-CSF autoimmunity
CSF2RA mutations
CSF2RB mutations
GM-CSF mutations (mice)

Secondary PAP

Hematologic disease
Nonhematologic malignancy
Immune deficiency syndromes
Chronic inflammatory syndromes
Chronic infections

Pulmonary Surfactant Metabolic Dysfunction Disorders

SFTPB mutations
SFTPC mutations
ABCA3 or NKX2.1 mutations

GM-CSF, granulocyte-macrophage colony-stimulating factor; PAP, pulmonary alveolar proteinosis.

Table 70-4 Comparison of Demographic and Epidemiology Data Among Five Large Series of Pulmonary Alveolar Proteinosis Patients

	Seymour ² (n = 410)	Inoue ⁴ (n = 233)	Xu ⁵ (n = 241)	Bonella ⁶ (n = 70)	Campo ⁷ (n = 81)
Age at Diagnosis (mean, range)	39 (30–46)	51 (41–58)	42 (na)	43 (18–78)	40 (26–54)
Ratio Male/Female	2.6	2.0	2.2	1.3	2.0
Primary PAP (%)	na	90	na	91	90
Secondary PAP (%)	na	10	na	9	4
Time to diagnosis (mo)	7 (3–19)	10 (4–36)	na	9 (1–36)	11 (0–27)
Spontaneous remitters (%)	6	5	na	5	7
Smoking habits (%)					
Never	28	43	—	21	36
Previous	na	29	—	30	42
Current	na	29	—	49	22
Dust exposure (%)	na	26	na	54	32

supporting this, autoimmune PAP is seen in a worldwide distribution. An intensive screening within the Niigata prefecture in Japan (population 2.41 million) estimated the incidence and prevalence of autoimmune PAP to be 0.49 ± 0.13 and 6.2 per million, respectively.⁴ This registry found that, among noncongenital cases of PAP, 89.9% of cases were autoimmune, 9.7% were secondary, and 0.4% were unclassified. In a meta-analysis of 1045 primarily adult PAP patients in five recent series,⁷ the mean age at diagnosis was similar in 4 out of 5 series (ranging from 39 to 43) and slightly older in the Japanese series (mean age of 51). In all series, males prevailed over females, with a ratio ranging from 1.3:1 to 2.6:1. The interval between onset of symptoms and diagnosis was similar (ranging from 7 to 11 months). Importantly, between 21% and 43% of PAP patients were never-smokers, indicating that PAP is not simply a smoking-related disease.

Hereditary PAP is caused by various genetic mutations in *CSF2RA* or *CSF2RB* genes (see Fig. 70-3) and usually presents in children between the ages of 1.5 and 11 years, although it has been observed to present in adults aged 29 and 35 years.^{23-25,52,53}

Secondary PAP accounts for not more than 10% of all PAP cases in adults^{2,4} and develops as a consequence of an underlying disease (see Table 70-1) or environmental exposure (see Table 70-2). Thus the prevalence of secondary PAP is estimated to be approximately 0.34 per 100,000 individuals in the general population. Historically, hematologic malignancy was the most common cause of secondary PAP, accounting for up to 5.3% of cases.⁷⁶ However, in a recent study, myelodysplastic syndrome accounted for 65% of cases.¹⁰³ Secondary PAP arises as a function of the underlying clinical disorder and, in some cases, can resolve with successful treatment of the underlying disorder.

PSMD disorders develop in individuals with mutations in the genes involved in surfactant synthesis: *SFTPB*, *SFTPC*, *ABCA3*, and *NKX2.1*, as discussed earlier. The incidence of SP-B deficiency is estimated to be approximately 1 per 1.5 million births. Among infants with respiratory distress syndrome of unknown etiology, mutations appear more commonly in *ABCA3* than in *SFTPB*.⁵⁶ The prevalence of the common disease-associated mutations in the *SFTPB* (121ins2), *SFTPC* (I73T), and *ABCA3* (E292V) genes are

Table 70-5 Frequency of Symptoms Among Patients with Autoimmune Pulmonary Alveolar Proteinosis*

Symptom	Frequency (%)
Dyspnea	54
Cough	23
Sputum production	4
Other	4
None (asymptomatic)	31

*Data for a contemporaneous group composed of 220 patients.

From Inoue Y, Trapnell BC, Tazawa R, et al: Characteristics of a large cohort of autoimmune pulmonary alveolar proteinosis patients in Japan. *Am J Respir Crit Care Med* 177:752–762, 2008.

not well established. However, a recent study in ethnically diverse cohorts from Missouri, Norway, South Korea, and South Africa ($n = 420$) found the population-based frequencies of these mutations to be rare ($<0.4\%$). Further, E292V was present in 3.8% of newborns with respiratory distress syndrome, suggesting it imparts an increased genetic risk for this syndrome.⁵⁵

CLINICAL PRESENTATION

Autoimmune PAP presents as progressive dyspnea of insidious onset unless secondary infection is also present, in which case fever, cough, and rarely hemoptysis may also be present. The frequency of various symptoms was recently evaluated in a large contemporaneous cohort in Japan (Table 70-5). This nonspecific presentation may lead to months or years of misdiagnosis as “asthma” or “chronic bronchitis.” The symptoms are frequently milder than expected from the radiographic findings, which should raise the suspicion of PAP. The physical examination is nonspecific and is frequently normal despite a grossly abnormal chest radiograph but may include basilar crackles. Cyanosis is seen in severe cases; hemoptysis and fever are rare. Clubbing is not a feature of autoimmune PAP or of hereditary PAP. In the Japanese national PAP registry cohort, 31% of patients with marked radiologic manifestations were asymptomatic.⁴

Hereditary PAP caused by mutations in GM-CSF receptor genes (*CSF2RA* or *B*) presents as insidious, progressive, dyspnea-like autoimmune PAP, usually in children.^{23,24,52,53} Thus, whereas this disease is newly described, rare, and necessarily less well studied, it appears similar to autoimmune PAP, except that it is a disease of children instead of adults.

Secondary PAP usually arises in an individual with an underlying systemic disorder such as a hematologic malignancy/disease.^{75,76,78,99,104,105} It can be seen in the context of neutropenia or myeloid cell dysfunction related to the underlying disorder and can resolve with successful treatment of the underlying disorder.

PSMD disorders can present as a spectrum of lung disease ranging from respiratory distress syndrome in neonates and infants to interstitial lung disease in children, adolescents, and adults, depending on the exact nature of the underlying genetic mutations. SP-B deficiency typically presents as respiratory distress immediately after birth.^{59,68,106} *ABCA3* mutations can result in fatal respiratory distress syndrome in neonates and interstitial lung disease in infants, children, and adolescents.^{69,71,102,107} SP-C mutations can present as interstitial lung disease in children and adults.^{58,64,66,67,101}

EVALUATION AND DIFFERENTIAL DIAGNOSIS

RADIOGRAPHIC APPEARANCE

The chest radiograph in autoimmune PAP and secondary PAP of hematologic origin typically reveals bilateral patchy or diffuse air-space consolidation or hazy ground-glass opacity (eFig. 70-1) similar in appearance to that of pulmonary edema but without the other radiographic signs of left heart failure.^{86,108} Other patterns can include mixed alveolar, interstitial (eFig. 70-2), or nodular opacities and asymmetrical or focal abnormalities (eFig. 70-3), but dense consolidation with air bronchograms is uncommon. Lymphadenopathy, cardiomegaly, and effusions are not features of PAP. The chest radiograph in hereditary PAP is similar but may be normal early in the clinical course or in mild cases.²³ The diagnostic value of the chest radiograph is limited by its lack of specificity.

Conventional chest *computed tomography* (CT) scans demonstrate bilateral areas of consolidation with poorly defined margins (Fig. 70-4).^{109,110} High-resolution chest CT (eFig. 70-4) is superior to both conventional CT and chest radiography in the assessment of the pattern and distribution of abnormalities and may demonstrate lesions even when the radiograph is normal. The distribution of disease is variable and may reflect heterogeneity of underlying disease causing PAP. Several features are noteworthy. Areas of *ground-glass opacification* (GGO) often have sharply defined straight and angulated margins, giving them a “geographic” appearance. The sharp margination usually reflects lobular or lobar boundaries. A pattern of fine overlapping lines forming 3- to 10-mm polygonal shapes can be seen in the majority of cases. Superimposition of these two patterns gives an appearance that has been described as “crazy paving,” which is *characteristic but not diagnostic*

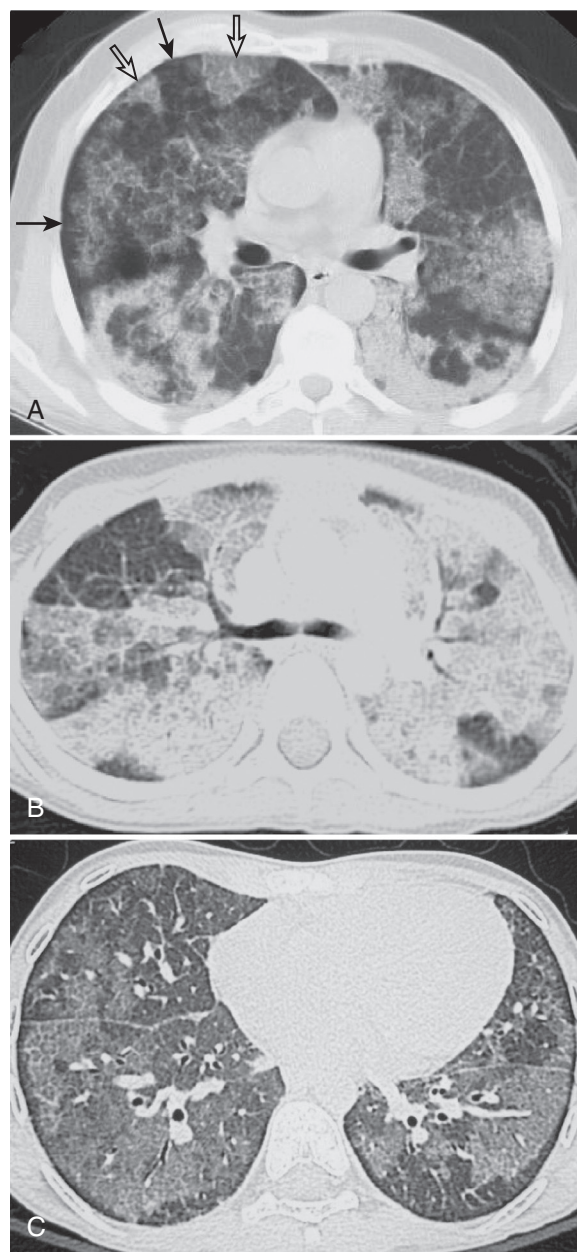


Figure 70-4 CT of different forms of PAP. CT of the chest illustrating differences in the radiographic appearance of the lungs in autoimmune PAP (A), hereditary GM-CSF receptor (α chain) dysfunction (B), and secondary PAP in a child with lysinuric protein intolerance (C). Note the juxtaposition of highly abnormal secondary lobules (open arrows), adjacent to more normal-appearing secondary lobules (solid arrows). This is referred to as a “geographic” pattern and is common in autoimmune PAP. It is also seen in hereditary PAP due to GM-CSF receptor dysfunction. Opacities that are more homogeneous and less geographic are more common in secondary PAP (C).

of PAP (eFig. 70-5).¹¹¹ Notably, crazy paving can also be seen in hypersensitivity pneumonitis, *Pneumocystis jirovecii* pneumonia, minimally invasive adenocarcinoma/lepidic invasive adenocarcinoma (formerly bronchioloalveolar carcinoma), lymphangitic carcinomatosis, cardiogenic pulmonary edema/acute lung injury, and lipoid pneumonia (eFig. 70-6). One study reported that a geographic appearance with crazy paving is more commonly seen in autoimmune than secondary PAP.¹¹²

Findings on the chest radiograph and high-resolution chest CT correlate with a restrictive ventilatory defect, reduced diffusing capacity, and hypoxemia.¹¹⁰ Quantitative CT measurements of ground-glass opacities, lung weight, and gas volume may be useful in following patients with PAP.¹¹³

PULMONARY FUNCTION TESTING

The results of pulmonary function testing may be normal or, in more advanced disease, may show a restrictive ventilatory defect with mild impairment of the forced vital capacity and total lung capacity and a disproportionate, severe reduction of the diffusing capacity for carbon monoxide.^{2,4} Arterial blood gases show mild to severe hypoxemia, an increased alveolar-arterial PO₂ gradient, compensated respiratory alkalosis depending on the degree of disease progression, and absence of hypercarbia. The shunt fraction is elevated when compared with patients with other diffuse lung diseases.¹¹⁴ Six-minute walk testing typically reveals early desaturation.

BRONCHOSCOPY, BRONCHOALVEOLAR LAVAGE, AND TRANSBRONCHIAL BIOPSY

Bronchoscopic airway examination is unremarkable in PAP. In contrast, *bronchoalveolar lavage* (BAL) specimens usually reveal characteristic gross, cytopathologic, and biochemical findings highly suggestive or diagnostic of PAP. In autoimmune, hereditary, and secondary PAP but not PSMD, the BAL fluid has a “milky” or “waxy” appearance and sediment forms on standing (Fig. 70-5). Cytologic examination of periodic acid–Schiff–Papanicolaou-stained specimens reveals the BAL fluid and sediment contains granular, acellular, lipoproteinaceous material,¹¹⁵ cells, and fat globules. Strikingly, cytopsin preparations reveal alveolar macrophages engorged with intracytoplasmic lipid droplets

imparting a foamy appearance by light microscopy (Fig. 70-6). Electron microscopic examination of the sediment reveals the presence of tubular myelin, lamellar bodies, and fused membrane structures characteristic of pulmonary surfactant. The BAL cell differential in autoimmune PAP may be normal or reveal the presence of increased pulmonary lymphocytes composed of increased numbers of CD4⁺ and CD8⁺ cells.¹¹⁶ Cultures of bronchoscopic washings and BAL are important to rule out infection.

Biochemical analysis of BAL fluid reveals increased amounts of phospholipids and proteins, similar in composition to that of surfactant from healthy individuals.¹¹⁷ Surfactant proteins are variably increased in the BAL fluid in PAP.

SURGICAL LUNG BIOPSY

Because of the diagnostic accuracy of BAL, lung biopsy is generally not necessary to make the diagnosis of PAP but may be indicated when the diagnosis is in doubt or secondary PAP is suspected. Macroscopically, the cut surface of lung biopsy specimens in autoimmune and hereditary PAP reveals a geographic pattern of 2- to 3-cm grayish-yellow regions of firm consolidation that exudes fatty material (eFig. 70-7). Microscopically, alveoli and terminal airways are filled with a fine eosinophilic material that stains strongly for surfactant proteins (see Fig. 70-6). The alveolar wall and interstitial architecture are relatively well preserved, but lymphocyte infiltration and occasionally fibrosis can be seen. The vasculature appears normal. Electron microscopy, which is seldom necessary, reveals characteristic, concentrically laminated surfactant structures (lamellar body inclusions) within the granular material and in alveolar macrophages.¹¹⁸ Importantly, although a lung biopsy can establish the presence of PAP syndrome, it cannot identify the disease responsible (e.g., autoimmune or hereditary PAP, Fig. 70-6E and F, respectively), which has important implications for newer therapies.

LABORATORY STUDIES

Routine laboratory studies are usually normal in PAP. Serum lactate dehydrogenase is typically elevated in proportion to lung disease severity, although this finding is nonspecific.^{2,114} Serum levels of SP-A, SP-B, SP-D, C-reactive protein, and *Krebs von den Lungen protein-6* (KL-6), a mucin-like protein (MUC1), are increased in PAP and correlate with lung disease severity.^{4,44,119} However, all of these biomarkers can be elevated in other lung diseases.^{120,121} Thus although not useful in diagnosis, these biomarkers may be useful in monitoring disease activity in patients with PAP. For example, KL-6 has been reported to outperform arterial PO₂ and LDH in predicting disease progression and need for therapy in autoimmune PAP.¹²²

Several biomarker-based tests are effective for the diagnosis of disease-specific PAP. The most well established is the serum-based GM-CSF autoantibody ELISA test.^{1,45,50,123,124,124a} Although serum GM-CSF autoantibodies are present at low levels in healthy people,⁴⁵ a high serum level is diagnostic of autoimmune PAP. In a recent validation study (MICEPAP) conducted in the United States, Germany, Italy, and Japan, both the sensitivity and



Figure 70-5 Whole-lung lavage fluid. Saline (A) compared to the whole-lung lavage fluid from a patient with autoimmune PAP (B). The lavage fluid, which was allowed to settle overnight in the refrigerator, shows a “milky” appearance and dense sediment.

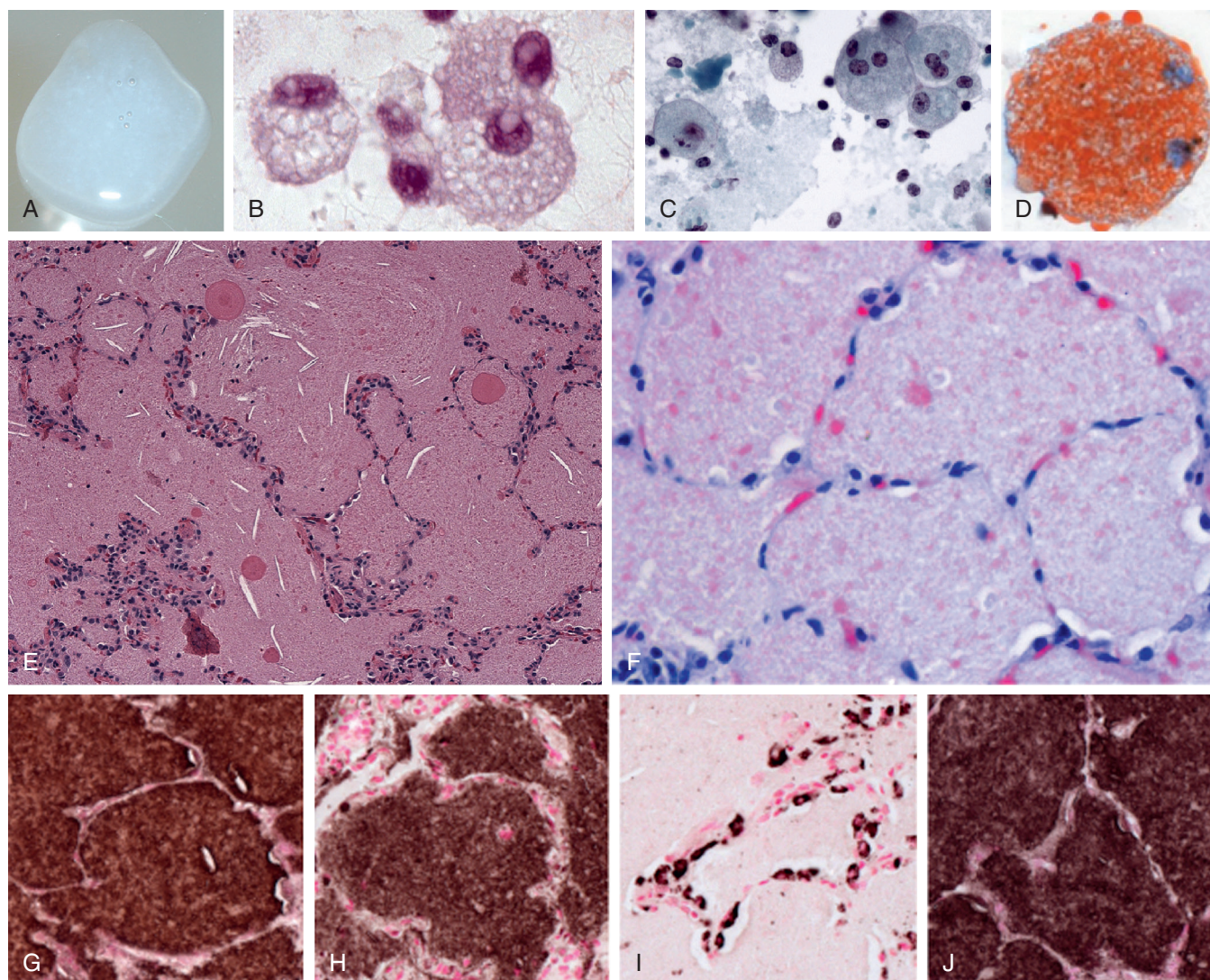


Figure 70-6 Appearance of sputum, sputum cytology, and lung histopathology in PAP due to disruption of GM-CSF signaling. **A**, Gross appearance of freshly expectorated sputum from a patient with uncomplicated autoimmune PAP. **B**, Sputum smear after staining with periodic acid–Schiff reagent. **C**, Sputum smear after staining with Papanicolaou reagent. Note the appearance of large, foamy-appearing alveolar macrophages in **B** and **C**. **D**, Alveolar macrophage stained with Oil Red O. **E**, Histopathologic appearance of an open-lung biopsy in autoimmune PAP after periodic acid–Schiff staining. Alveoli are filled with amorphous, acellular eosinophilic material and also cholesterol clefts and eosinophilic bodies. Alveolar wall architecture is well preserved. **F–J**, Histopathologic appearance of an open-lung biopsy in hereditary PAP caused by *CSF2RA* gene mutations after staining with hematoxylin and eosin (**F**), or immunostaining for SP-A (**G**), mature SP-B (**H**), pro-SP-C (**I**), or SP-D (**J**). (**F–I** from Suzuki T, Sakagami T, Rubin BK, et al: Familial pulmonary alveolar proteinosis caused by mutations in *CSF2RA*. *J Exp Med* 205:2703–2710, 2008.)

specificity of a recently improved assay were found to be 100%.¹²⁵ Furthermore, an international *monoclonal GM-CSF autoantibody reference standard* (MCRS) was developed to help standardize test results from the few laboratories that currently perform the test. When the GM-CSF autoantibodies are at levels close to the diagnostic threshold, measurement of GM-CSF signaling in whole blood is useful and can be done by measuring the ability of exogenous GM-CSF to bind GM-CSF receptors on leukocytes and stimulate an increase in cell surface CD11b (the CD11b stimulation index test)⁵⁰ or an increase in STAT5 phosphorylation (the STAT5-phosphorylation index test).¹²⁶ Both assays give similar results (a large increase in healthy people and no change in autoimmune PAP), but the latter is more robust and reliable. Measurement of the serum concentration of GM-CSF by ELISA is a useful screening

test to identify patients with hereditary PAP in whom GM-CSF signaling is disrupted not by GM-CSF autoantibodies but by GM-CSF receptor dysfunction.^{23,127} Various molecular and genetic tests are available to determine the specific abnormality in hereditary PAP and PSMD.^{24,25}

APPROACH TO DIAGNOSIS

The timely diagnosis of PAP requires a high degree of clinical suspicion, and PAP should be suspected in patients with dyspnea of insidious onset and typical chest CT findings. In previously healthy adults with these findings, an abnormal serum GM-CSF autoantibody test is usually sufficient to establish the diagnosis of autoimmune PAP.¹²⁵ An abnormal GM-CSF signaling test, either the *STAT5 phosphorylation index* (STAT5-PI) or the *CD11b stimulation index*

(CD11b-SI) test, confirms the diagnosis. Pulmonary function testing may be helpful if the disease is moderate or severe but is normal (except for DL_{CO}) in many patients.³ Although BAL cytology or a surgical or transbronchial lung biopsy can establish the presence of PAP syndrome, none can identify the underlying disease.⁹⁹ An open-lung biopsy is usually not necessary, but a biopsy may still be useful if the diagnosis is unclear or if secondary PAP is suspected to rule out disorders that have radiologic, cytologic, or pathologic features similar to PAP.

In younger patients in whom PAP is suspected, the presentation can be helpful. SP-B deficiency presents as respiratory failure at birth. ABCA3 dysfunction can present similarly or as interstitial lung disease in infants, children, and adolescents. SP-C dysfunction presents as interstitial lung disease in children and adults. Although autoimmune PAP usually presents in adults, it has been seen in children as young as 3 years and can readily be diagnosed by blood test without the need for a lung biopsy. Hereditary PAP often presents in children between the ages of 1.5 and 11 but can present as late as age 35. In hereditary PAP, the serum GM-CSF autoantibody test is normal and the GM-CSF signaling tests, STAT5-PI (CD11b-SI), and serum GM-CSF tests are abnormal.²³⁻²⁵ These blood-based tests are useful in evaluating young patients and should be employed to minimize the use of more invasive procedures.

The diagnostic workup of individuals with disorders of surfactant homeostasis, including PAP and PSMD disorders, consists of routine clinical evaluations, biomarker evaluations, and genetic tests capable of distinguishing among autoimmune PAP, secondary PAP, hereditary PAP caused by receptor dysfunction, and PSMD disorders (Fig. 70-7).

NATURAL HISTORY

No longitudinal studies of the clinical course of PAP have been reported. However, cross-sectional evaluations of PAP cohorts in Japan, China, Germany, and Italy have recently been reported (see Table 70-4).⁴⁻⁷ In Seymour and Presneill's comprehensive meta-analysis of PAP, the actuarial survival rates for 343 patients with acquired PAP were $78\% \pm 8\%$ at 2 years, $75\% \pm 8\%$ at 5 years, and $68\% \pm 9\%$ at 10 years.² More than 80% of the deaths attributable to PAP during a 5-year period took place during the first 12 months after diagnosis. This study reported that, of the 69 deaths, death was caused by respiratory failure from PAP in 47 patients (72%), uncontrolled infection in 13 (20%), and unrelated causes in 5 cases (8%). In a contemporaneous cross-sectional cohort study of 223 autoimmune PAP patients in Japan, there were no deaths over the 5-year period of the study.⁴ Autoimmune PAP follows one of three patterns: progressive deterioration, stable disease, or spontaneous resolution.² Secondary PAP may have a far worse prognosis than autoimmune PAP: A recent study of 40 individuals with secondary PAP diagnosed premortem reported a median survival of less than 20 months from diagnosis.¹⁰³

SECONDARY INFECTIONS

Multiple reports document increased infections in PAP by microbial pathogens ranging from community- and hospital-acquired organisms to *Nocardia* spp. (eFig. 70-8) or opportunistic organisms.² GM-CSF-deficient mice also have increased mortality from infection and increased susceptibility to a wide variety of microbial pathogens, including

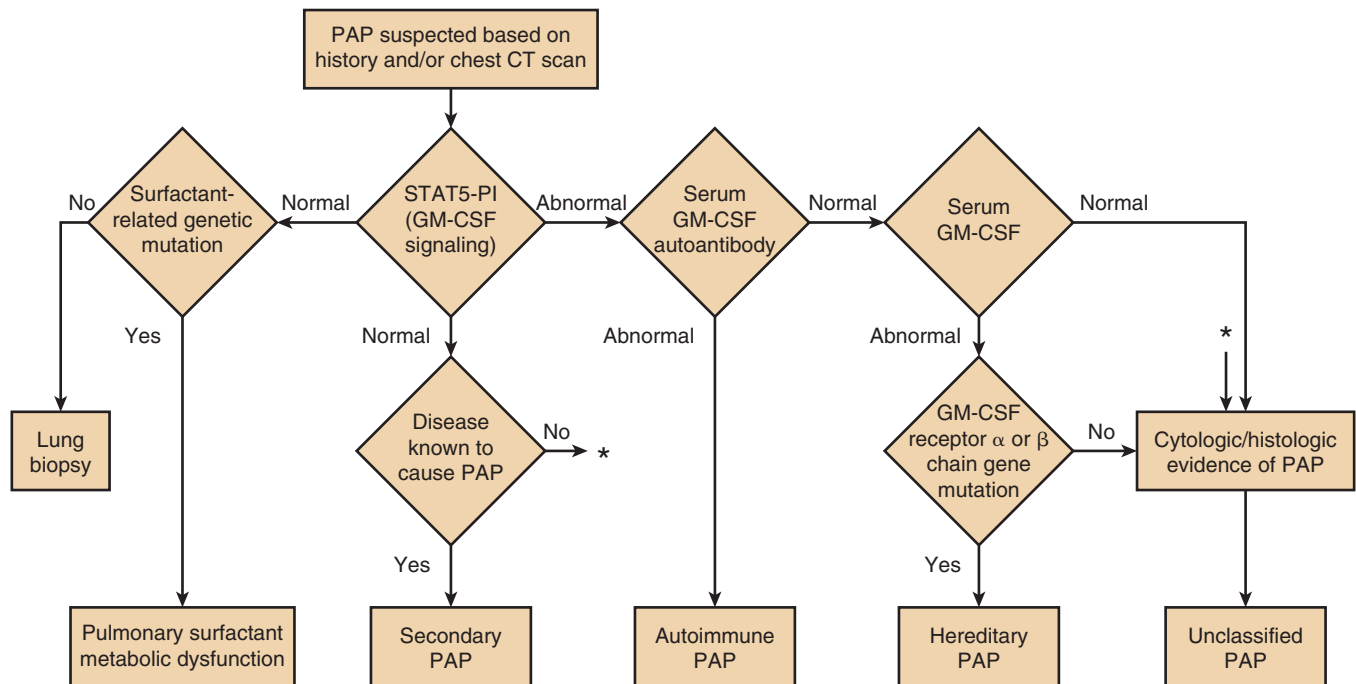


Figure 70-7 Diagnostic algorithm for evaluation for individuals with PAP syndrome. In hereditary PAP caused by mutations in GM-CSF receptor genes *CSF2RA* or *CSF2RB*, further GM-CSF signaling tests are necessary to confirm and identify the specific nature of the defect. See text for details. STAT5-PI, STAT5 phosphorylation index. *, links decision tree in algorithm.

bacteria, fungi, and mycobacteria (eFig. 70-9). Further, myeloid cells from both patients with autoimmune PAP and GM-CSF-deficient mice have defects in innate immune functions, including phagocytosis, generation of reactive oxygen species, inflammatory signaling, and bacterial killing.^{20,45,50,123,128} In both GM-CSF-deficient mice and PAP patients, infections can arise in the lungs and at extrathoracic locations, consistent with a systemic immune defect caused by disruption of GM-CSF signaling.

PULMONARY FIBROSIS

Pulmonary fibrosis has been reported in association with PAP and has been reproduced in animal models of exposure to inhaled silica.^{31,118} Further, exposure to oxygen or repeated *whole-lung lavage* (WLL) has been suggested as potentially contributing to fibrosis. However, although not adequately studied, “end-stage lung disease” or irreversible scarring of the lung is rarely associated with PAP.

SPONTANEOUS RESOLUTION

Spontaneous improvement of PAP (eFig. 70-10) was noted in Rosen’s initial report.⁸⁶ In subsequent case series, spontaneous resolution was described in 5% to 8% of patients (see Table 70-4).⁴⁻⁷

TREATMENT

Various therapeutic strategies have been proposed for PAP. WLL emerged early and served as the standard therapy for nearly 5 decades, albeit with some refinements. Novel therapeutic approaches have recently been developed based on recognition of the critical role of GM-CSF in surfactant homeostasis and of the neutralizing GM-CSF autoantibodies in PAP pathogenesis. These novel approaches include GM-CSF augmentation, plasmapheresis, and anti-B lymphocyte therapy. Each is discussed briefly as follows.

AUTOIMMUNE PAP

Whole-Lung Lavage

Originally developed by Ramirez in the early 1960s, WLL is a procedure performed under general anesthesia in which large volumes (commonly 20 to 30 L, but up to 50 L) of saline are infused sequentially into each lung to “wash out” the accumulated surfactant lipids and proteins while the other lung is mechanically ventilated.¹²⁹⁻¹³¹ A number of procedural variations have been tested (although none systematically), including the use of mechanical chest percussion, prone positioning, variation in the volume of infusate, and use of a hyperbaric chamber. Notwithstanding improvements, WLL has not been standardized with respect to the method (i.e., volume infused, use of mechanical percussion, the end point of an individual lavage procedure); indications for its use; methods for evaluating the treatment effectiveness; or timing of repeated procedures. The end point used clinically for terminating lung lavage in the operating room is a clearing of the appearance of the lavage effluent. No studies have systematically evaluated the procedure, its

utilization in clinical practice, or the efficacy or durability of clinical responses. Notwithstanding, among practitioners, it is widely believed to improve symptoms, radiographic findings, and gas exchange in PAP patients.^{132,133}

Although WLL is safe in the vast majority of individuals, complications include hypoxemia, pneumonia, sepsis, acute respiratory distress syndrome, hydrothorax, pneumothorax, and pneumomediastinum (eFig. 70-11). The procedure should not be performed in a patient with an active microbial lung infection because this can result in sepsis and shock. Bronchoscopic segmental or lobar lavage has been proposed as a safe alternative in patients in whom WLL under general anesthesia is considered risky due to severe hypoxemia.¹³⁴ Other alternatives include performance in a hyperbaric chamber¹³⁵ and use of complete cardiopulmonary bypass.¹³⁶

A comprehensive literature review identified 231 individuals for whom sufficient WLL data were available and reported that lavage was associated with increased overall 5-year survival ($94 \pm 2\%$ with lavage [$n = 146$] versus $85 \pm 5\%$ without lavage [$n = 85$]; $P = 0.04$).² This study also reported that the median number of WLL procedures performed was two and that 70% of patients underwent the procedure within 5 years of diagnosis. Among 55 individuals undergoing the procedure, the median duration of benefit was 15 months and only 20% of patients remained free of recurrence at 3 years. Among 41 patients with adequate available data, arterial PO₂ improved by 20.1 mm Hg after WLL (Table 70-6). The improvement in other pulmonary function test parameters was less impressive. More than 95% of patients respond to WLL; however, a small fraction of patients did not respond despite aggressive lavage. Improvement results from the physical removal of the accumulated surfactant and can be evident within hours of completion of therapy.

In practice, the indications for WLL therapy include dyspnea, exercise intolerance, and a desire to reduce the requirement for supplemental oxygen therapy. Reasonable indications for performing the procedure may include dyspnea limiting activities of daily living, arterial PO₂ less

Table 70-6 Therapeutic Response to Whole-Lung Lavage Therapy of Adults with PAP

Parameter	N	Mean Change ± SD	95% CI of the Mean	P Value*
Arterial PO ₂ (mm Hg)	41	20.1 ± 14.3	15.6 to 24.6	<0.0001
(A–a)PO ₂ (mm Hg)	21	–30.6 ± 18.0	–38.8 to –22.4	<0.0001
FEV ₁ (L)	33	0.26 ± 0.47	0.09 to 0.42	<0.0034
VC (L)	40	0.50 ± 0.54	0.33 to 0.67	<0.0001
DL _{CO} (mL/mm Hg per minute)	25	4.4 ± 4.5	2.6 to 6.3	<0.0001

*Value is for the comparison of paired postlavage with prelavage data for individual patients for each parameter for only those patients with available data using a two-sample t-test.

(A–a)PO₂, alveolar-arterial difference in oxygen tension; CI, confidence interval; DL_{CO}, diffusing capacity of carbon monoxide; FEV₁, forced expiratory volume in 1 second; PAP, pulmonary alveolar proteinosis; VC, vital capacity.

From Seymour JF, Presneill JJ: Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med* 166:215–235, 2002.

than 60 mm Hg while breathing room air, significant desaturation (>5%) on exercise,⁷ and a shunt fraction greater than 10% to 12%.

Granulocyte/Macrophage Colony-Stimulating Factor

GM-CSF therapy of PAP was first shown to be effective in a single patient in 1995.¹³⁷ A follow-up study in 14 autoimmune PAP patients receiving GM-CSF by subcutaneous injection in escalating doses (5 to 20 µg/kg/day) over a 3-month period reported an overall response rate of 43%.¹³⁸ A subsequent study in 21 autoimmune PAP patients receiving GM-CSF by subcutaneous administration in escalating doses (5 to 18 µg/kg/day) for 6 to 12 months reported an overall response rate of 48% as defined by a 10 mm Hg or greater improvement in room air arterial PO_2 .¹³⁹ Several case studies have reported similar findings. In aggregate, results indicate that (1) subcutaneous GM-CSF therapy of autoimmune PAP may result in objective improvement in about 50% of patients, (2) the therapeutic response is variable among patients, (3) the therapeutic response depends on the dose and duration of treatment, and (4) there is a lag of about 8 weeks before a therapeutic response is seen. These studies have not demonstrated a consistent change in the GM-CSF autoantibody level.

Aerosolized GM-CSF therapy of autoimmune PAP has been tested in small studies using daily inhaled doses of GM-CSF ranging from 125 to 500 µg per patient per day.¹⁴⁰ In one larger study in 50 autoimmune PAP patients, 35 patients with unremitting/progressive disease received aerosolized GM-CSF therapy initially at an “induction” higher dose (250 µg on days 1 to 8 of 14, ×6 cycles) followed by a lower “maintenance” (125 µg on days 1 to 4 of 14, ×6 cycles).¹⁴¹ In this study, which excluded patients who improved spontaneously during an initial observation period and thus only evaluated patients with unremitting/progressive disease, the overall response rate was 62%. Results suggested that delivery of GM-CSF by aerosol induced a higher clinical response rate than by the subcutaneous route. Furthermore, whereas both routes appeared to be safe, local site reactions and other minor problems were noted in 85% of patients receiving subcutaneous GM-CSF, while no treatment-related side effects were noted with inhaled GM-CSF. In another retrospective study of 12 individuals, administration of up to 500 µg bid every other week by aerosol resulted in complete remission in two patients and an overall response rate of 92%.^{141a} Currently, nonhuman toxicology studies of inhaled GM-CSF therapy are under way to help define the safety of this promising therapeutic approach for autoimmune PAP.

Rituximab and Other Approaches

Other therapeutic strategies aimed at reducing the level of GM-CSF autoantibodies, including plasmapheresis and B-lymphocyte depletion, have been tried in a few patients. One study evaluating a single cycle of rituximab therapy in 10 patients gave promising results,¹⁴² but further studies are necessary before any useful conclusions can be drawn about the potential utility of this theoretically attractive strategy. Lung transplantation has been performed successfully in a 41-year-old patient with PAP (probably autoimmune PAP), but the disease recurred 3 years later.¹⁴³

HEREDITARY PAP

WLL is the standard therapy for hereditary PAP caused by *CSF2RA* or *CSF2RB* mutations.^{23,24} Bone marrow transplantation has been tried without success in one child.⁵³ Recently, gene correction and pulmonary macrophage transplantation have shown promising results in a mouse model of hereditary PAP.²⁶

SECONDARY PAP

Secondary PAP, in some cases caused by hematologic disorders, can resolve with resolution of the underlying disorder. Nonresolving secondary PAP can be effectively treated with WLL. However, this has not been well studied.

PULMONARY SURFACTANT METABOLIC DYSFUNCTION DISORDERS

Therapy of these disorders depends on the disease and presentation; care is generally supportive and includes assessment of need for supplemental oxygen and nutritional support. In very young children, WLL is extremely challenging and of uncertain efficacy, and an adapted technical approach to airway management is required during lavage.¹⁴⁴ Neonates may show transient improvement with exogenous surfactant administration. Lung transplantation can be considered in cases of SP-B deficiency and in severe and progressive disease from *ABCA3* mutations.

GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

ETIOLOGY

Autoimmune PAP, the most common PAP disease, has a well-explained pathogenesis even though its etiology remains obscure. Although it has been established that GM-CSF, via PU.1, is critical for surfactant homeostasis in humans and that GM-CSF autoantibodies mediate the pathogenesis of autoimmune PAP, the precise mechanism by which loss of GM-CSF signaling reduces surfactant clearance by alveolar macrophages is unknown. The immunopathology of autoimmune PAP, while of particular interest, is largely unexplored.

In contrast, secondary PAP is less well studied in terms of pathogenesis, but in some cases the etiology (i.e., loss of alveolar macrophages in hematologic disorders and after chemotherapy) seems clear.

Hereditary PAP also has a clear etiology (i.e., genetic mutations in *CSF2RA* or *CSF2RB*). However, the pathogenesis beyond the loss of GM-CSF signaling is unclear.

PSMD disorders have a clear etiology and continue to provide important information regarding surfactant production and processing.

CLINICAL PRACTICE GUIDELINES

Standardized clinical practice guidelines for pulmonary alveolar proteinosis are necessary. WLL has been in use for

nearly 5 decades, yet no studies have prospectively evaluated the indications for, timing of, or methods to monitor outcomes of the procedure. Nor has the procedure itself been standardized with respect to volume of infusate, use of mechanical percussion, hyperbaric oxygen, position or repositioning of the patient during the procedure, or objective methods for terminating the procedure.

NOVEL THERAPEUTIC APPROACHES

Results of clinical trials suggest that inhaled GM-CSF in patients with autoimmune PAP is safe and effective. However, existing results have not defined the optimal dose, timing, or duration of administration, which could potentially improve the current response rate. Nor has the mechanism underlying the therapeutic effect been determined. It is puzzling why administration of GM-CSF to these patients does not result in any increase in GM-CSF autoantibody levels, but this appears to be the case. Further research is necessary to evaluate other therapies, including plasmapheresis, anti-B lymphocyte therapy, and combination therapies. Examples of the latter include combining WLL with aerosolized GM-CSF to improve the benefit from lavage and combining plasmapheresis and anti-B lymphocyte therapy to deplete GM-CSF autoantibodies.

Key Points

- *Pulmonary alveolar proteinosis* (PAP) constitutes a group of heterogeneous diseases and is characterized by surfactant accumulation in alveoli due to either impaired surfactant clearance by alveolar macrophages or abnormal surfactant production.
- The molecular pathogenesis is now known in most cases: mechanisms include (1) disruption of GM-CSF signaling by GM-CSF autoantibodies (autoimmune PAP, ≈85% of cases) or GM-CSF receptor mutations (hereditary PAP, ≈5% of cases), (2) disruption of alveolar macrophage numbers or functions by a separate disease (secondary PAP, ≈5% of cases), and (3) disruptions of surfactant amount or function by mutations resulting in abnormal surfactant production (pulmonary surfactant metabolic dysfunction disorders, ≈5% of cases).
- PAP can present in men, women, and children of all ethnic backgrounds and in all geographic locations and has an estimated overall prevalence of 7 to 10 per million in the general U.S. population and globally.
- The patient with PAP typically presents with progressive dyspnea of insidious onset with or without cough but, if infection is also present, may also have fever, diaphoresis, or hemoptysis.
- The natural history depends on the disease responsible. In autoimmune PAP, the clinical course varies and includes respiratory failure and death in a small fraction, slowly progressive/stable disease in most, and spontaneous improvement in 6% to 8% of patients.
- Characteristic (but nondiagnostic) chest CT findings and bronchoalveolar lavage results are used to diag-

nose PAP syndrome but cannot identify the disease causing it. However, new blood tests (including GM-CSF autoantibody level, GM-CSF signaling assays [e.g., STAT5-PI], and serum GM-CSF) currently available as clinical research tests can identify the PAP-causing disease in more than 95% of cases.

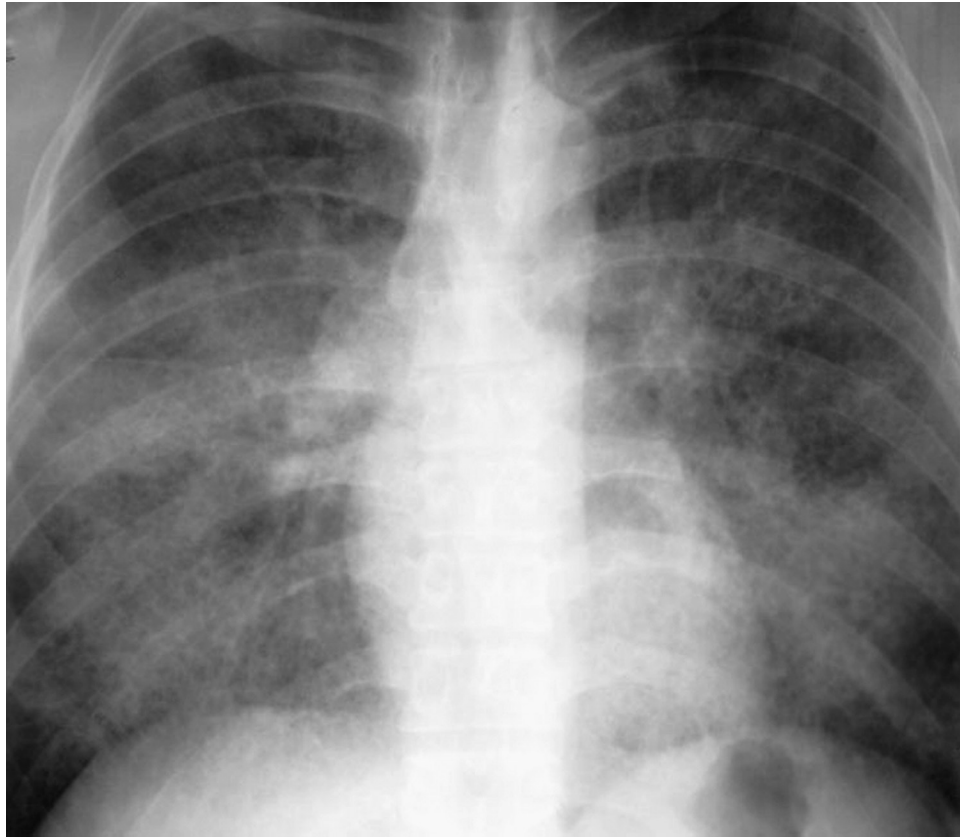
- Whole-lung lavage is the current standard therapy for autoimmune PAP, hereditary PAP, and some (myelodysplasia) but not all (silica-induced) forms of secondary PAP, but it is not useful in pulmonary surfactant metabolic dysfunction disorders. GM-CSF, particularly by inhalation, and rituximab are promising experimental therapeutic approaches under active study.

Complete reference list available at *ExpertConsult*.

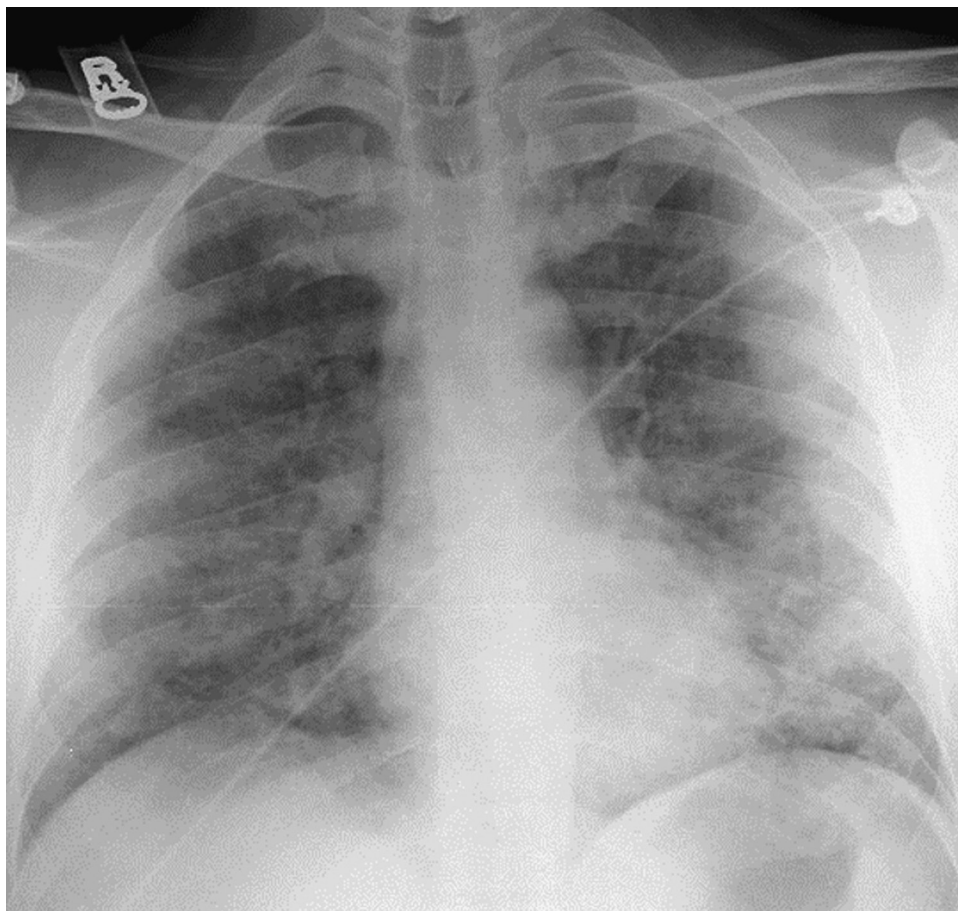
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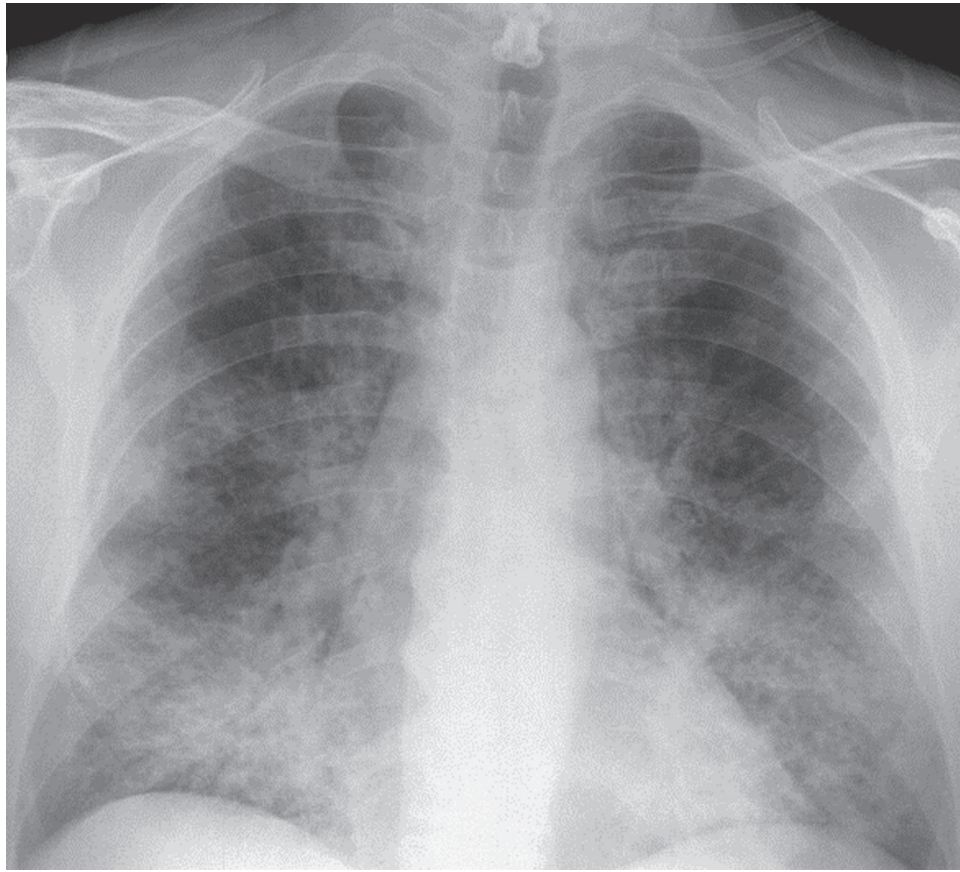
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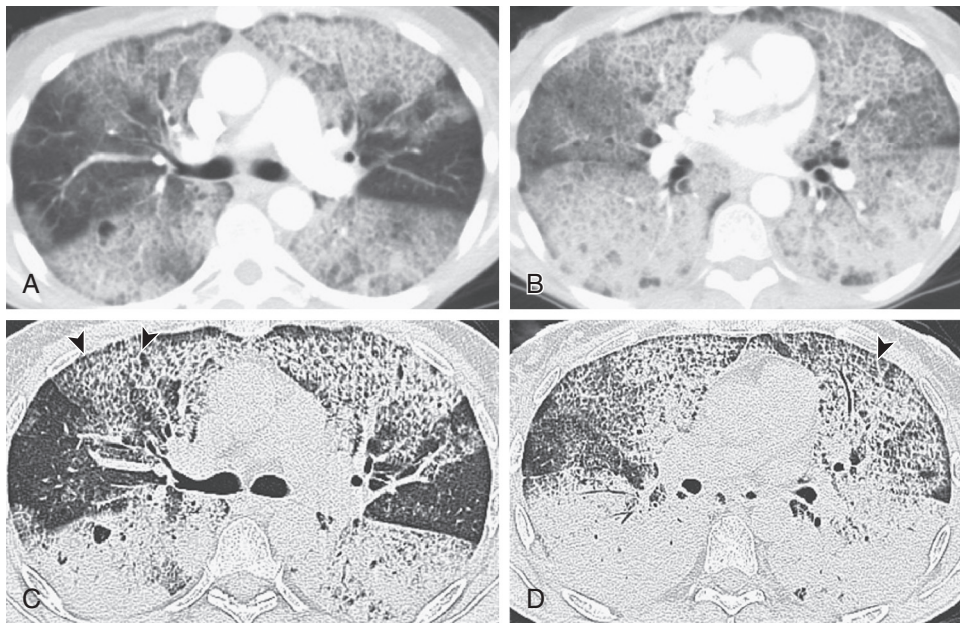
eFigure 70-1 Pulmonary alveolar proteinosis (PAP): typical chest radiographic findings. Frontal chest radiograph shows bilateral ground-glass opacity associated with a prominent, underlying linear and reticular pattern. Note the normal heart size and mediastinal width, both of which argue against increased pressure pulmonary edema. (Courtesy Michael Gotway, MD.)



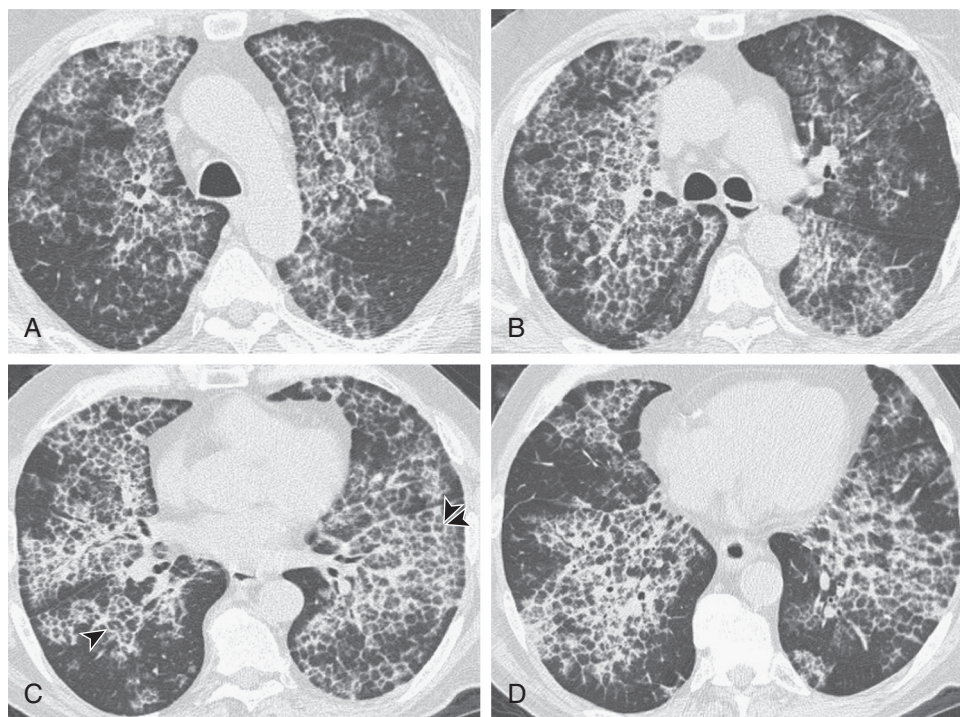
eFigure 70-2 PAP: typical chest radiographic findings. Frontal chest radiograph shows multifocal, bilateral, poorly defined, somewhat linear-appearing opacities suggesting a diffuse interstitial lung process. (Courtesy Michael Gotway, MD.)



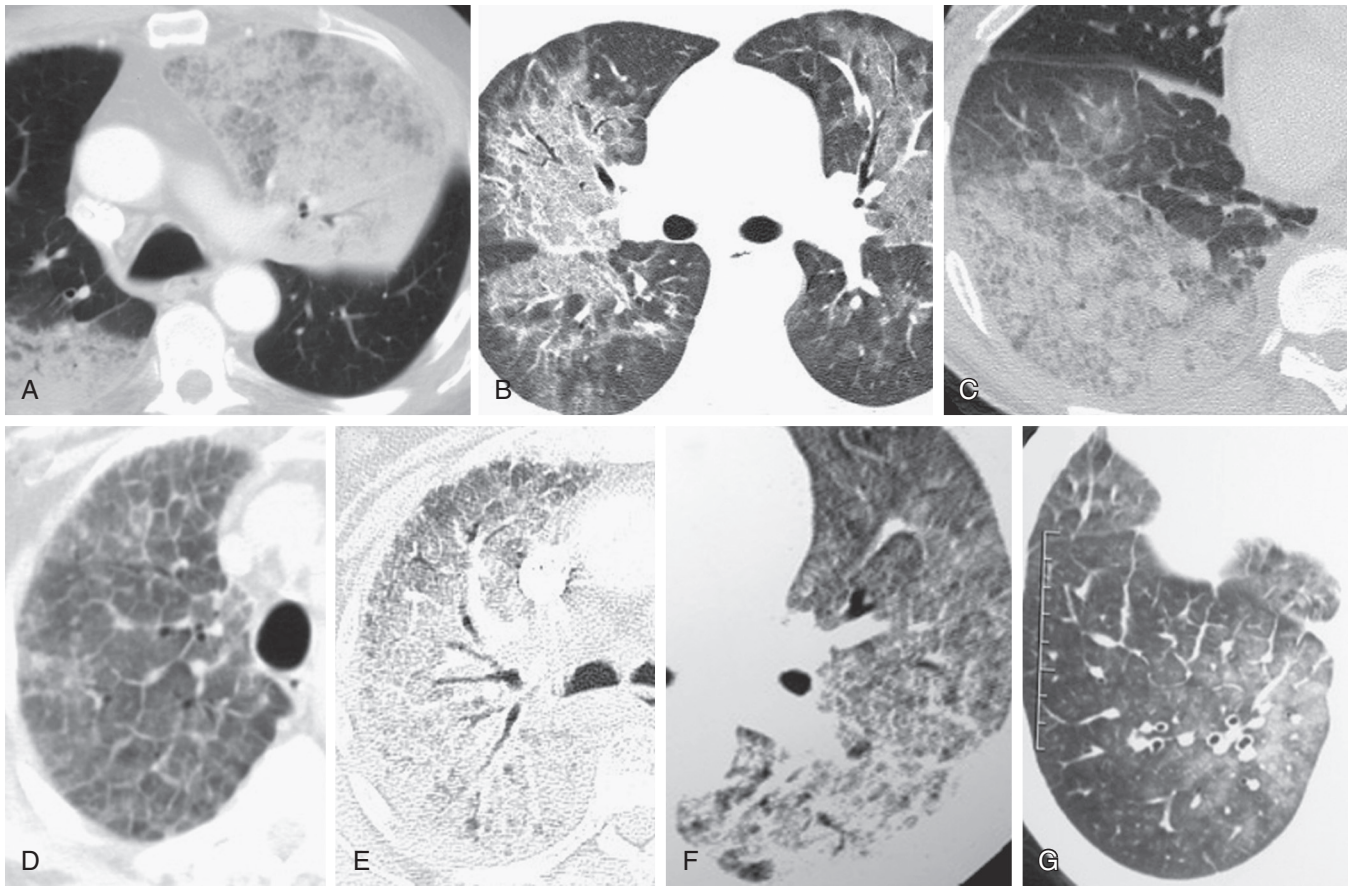
eFigure 70-3 PAP: somewhat atypical chest radiographic findings. Frontal chest radiograph shows multifocal bilateral linear opacities and peribronchovascular thickening, with more focal opacity in the right lung base. High-resolution CT of this patient is shown in [eFigure 70-5](#). (Courtesy Michael Gotway, MD.)



eFigure 70-4 PAP: "routine" versus high-resolution chest CT findings. **A** and **B**, Axial chest CT reconstructed at 5-mm section thickness displayed in lung windows shows multifocal, bilateral ground-glass opacity associated with interlobular septal thickening. **C** and **D**, Axial high-resolution chest CT performed 24 hours following **A** and **B** shows the smooth interlobular septal thickening, associated with fine intralobular opacities, to advantage. The combination of ground-glass opacity and smooth interlobular septal thickening is consistent with a "crazy paving" appearance. (Courtesy Michael Gotway, MD.)



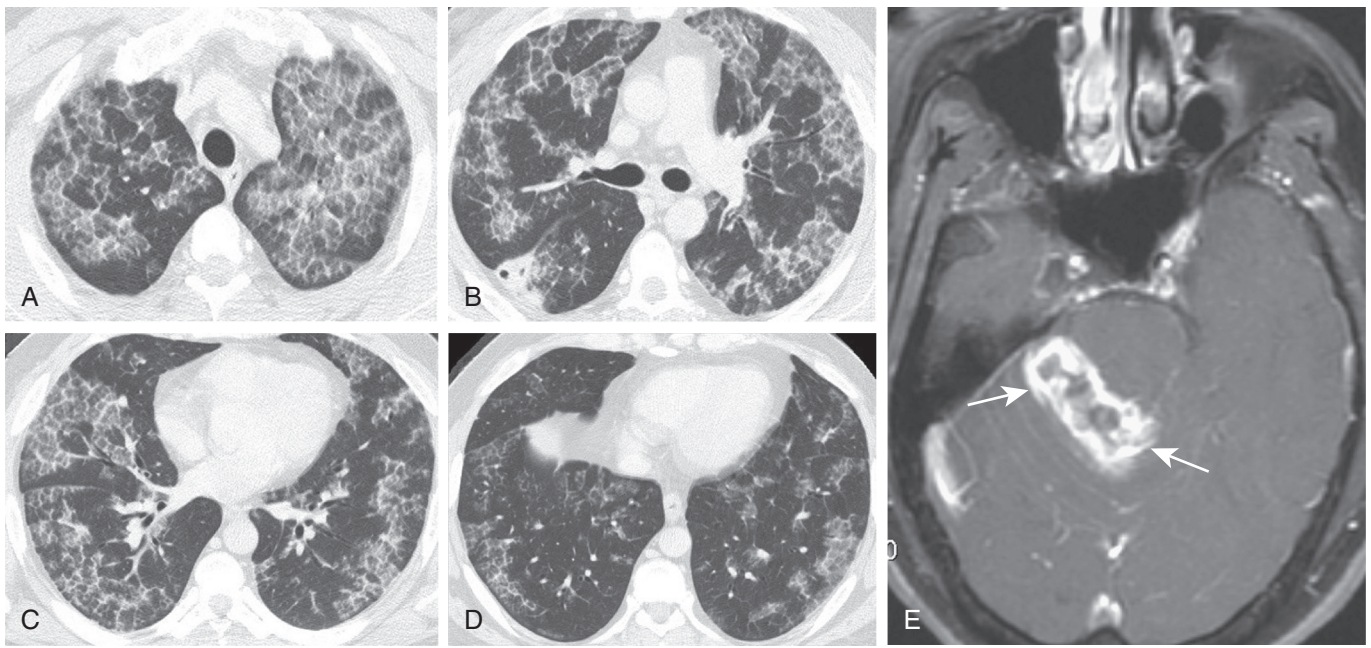
eFigure 70-5 PAP: high-resolution chest CT findings. A–D, Axial high-resolution CT displayed in lung windows shows patchy, multifocal, bilateral areas of ground-glass opacity associated with smooth interlobular septal thickening (*arrowhead* in **C**) associated with fine intralobular lines, with a sharp, geographic, often nonanatomic demarcation between normal and abnormal-appearing lung, consistent with the “crazy paving” pattern. Note the appearance of “polygons” (*double arrowhead*, **C**), representing the secondary pulmonary lobule outlined by the smoothly thickened interlobular septae. (Courtesy Michael Gotway, MD.)



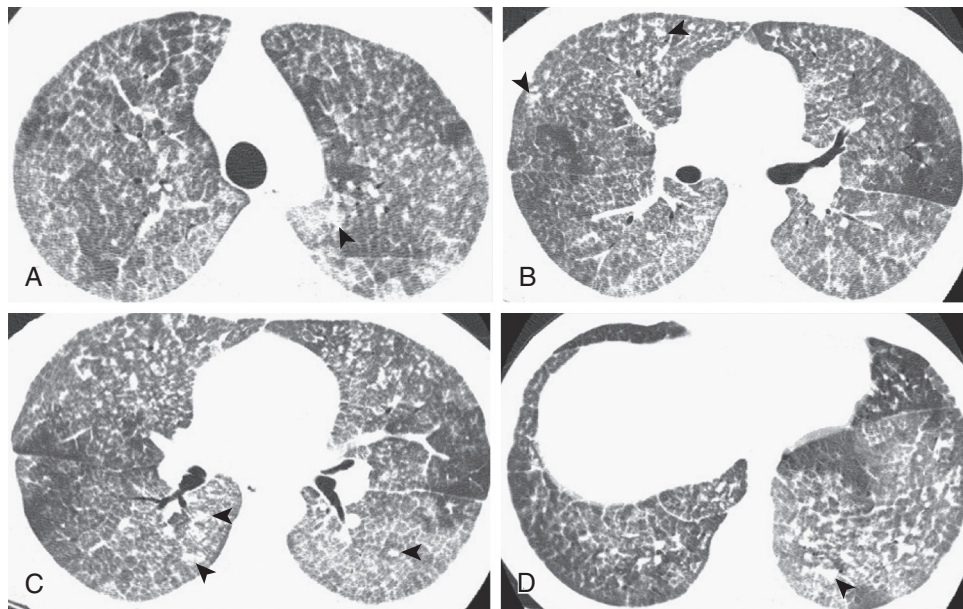
eFigure 70-6 “Crazy-paving” mimics at chest CT. **A**, Invasive mucinous adenocarcinoma with lepidic growth (formerly referred to as multicentric mucinous bronchioloalveolar carcinoma); **B**, lipoid pneumonia; **C**, pulmonary hemorrhage; **D**, acute fibrinous and organizing pneumonia; **E**, noncardiogenic edema; **F**, acute eosinophilic pneumonia; **G**, increased pressure pulmonary edema. To some extent, all these cases show the combination of ground-glass opacity with smooth interlobular septal thickening, consistent with “crazy paving,” although, as is often the case, conditions other than pulmonary alveolar proteinosis that produce a crazy paving pattern at chest CT have a qualitatively distinct appearance. Compare these CT images with [eFigures 70-4, 70-5, 70-8A-D, and 70-10](#). (Courtesy Michael Gotway, MD.)



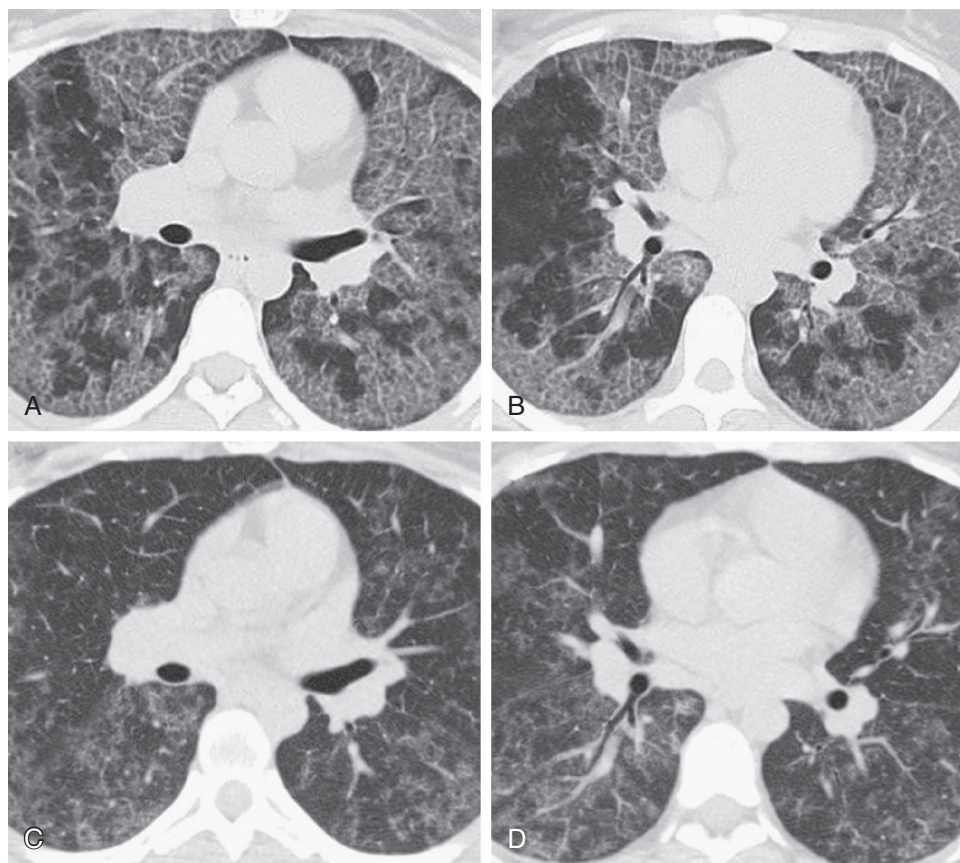
eFigure 70-7 PAP: gross pathologic findings. Multifocal focal areas of yellowish firm consolidation (*arrows*) are present, representing an exudate of fatty material. These findings are associated with smoothly thickened interlobular septae (*arrowheads*).



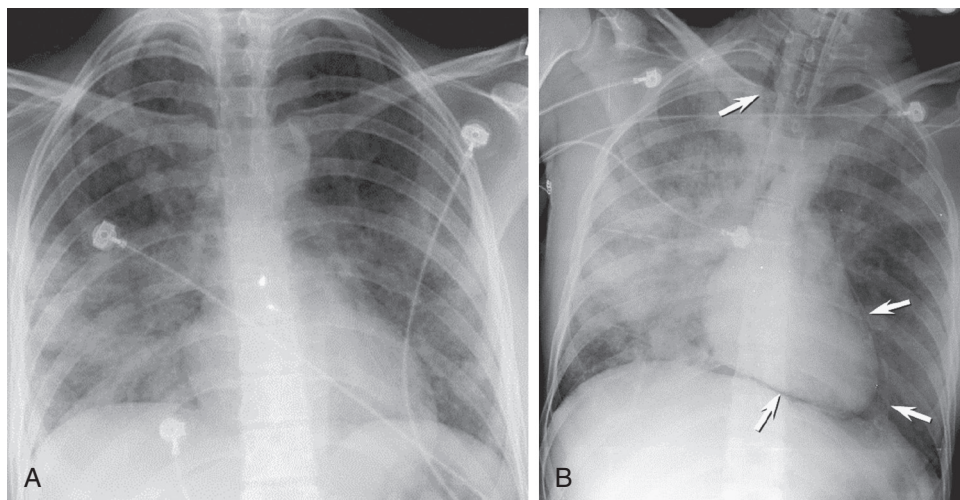
eFigure 70-8 PAP: infectious complications. A–D, Axial high-resolution CT displayed in lung windows shows the classic “crazy paving” appearance of pulmonary alveolar proteinosis. E, Axial contrast-enhanced brain MRI shows a peripherally enhancing lesion in the right cerebellopontine angle (arrows), representing a *Nocardia asteroides* brain abscess. (Courtesy Michael Gotway, MD.)



eFigure 70-9 PAP: infectious complications. A–D, Axial chest CT displayed in lung windows shows the classic “crazy-paving” appearance of pulmonary alveolar proteinosis, with numerous superimposed small nodules (arrowheads), the latter reflecting disseminated nontuberculous mycobacterial infection. (Courtesy Michael Gotway, MD.)



eFigure 70-10 Spontaneous improvement in a patient with pulmonary alveolar proteinosis. **A** and **B**, Axial high-resolution CT obtained at the time of initial diagnosis shows the typical appearance of “crazy paving.” **C** and **D**, Axial chest CT obtained 1 year following **A** and **B** shows spontaneous reduction in multifocal ground-glass opacity; the patient had not undergone any specific therapy for pulmonary alveolar proteinosis. (Courtesy Michael Gotway, MD.)



eFigure 70-11 PAP: whole-lung lavage complication. **A**, Frontal chest radiograph obtained before whole-lung lavage shows multifocal, patchy bilateral ground-glass opacity and consolidation associated with linear and reticular abnormalities, consistent with pulmonary alveolar proteinosis. **B**, Frontal chest radiograph obtained following whole-lung lavage procedure shows development of pneumomediastinum (arrows). (Courtesy Michael Gotway, MD.)

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DRUG-INDUCED PULMONARY DISEASE

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INTRODUCTION

CHEMOTHERAPEUTIC AGENTS

Antibiotic-Derived Agents
Alkylating Agents
Antimetabolites
Podophyllotoxins
Vinblastine
All-*Trans* Retinoic Acid
Irinotecan and Topotecan
Targeted Therapy

ANTIMICROBIAL AGENTS

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Miscellaneous Antimicrobial Drugs

ILLICIT DRUGS

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Methylphenidate

Cocaine

Talc Granulomatosis

CARDIOVASCULAR DRUGS

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ANTI-INFLAMMATORY AGENTS

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Biologic Agents
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DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

INHALANTS

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Tocolytic-Induced Pulmonary Edema
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Methysergide, Bromocriptine, and Cabergoline
Dextran
Amphetaminergic Agents
Esophageal Variceal Sclerotherapy
Phenytoin
Dantrolene

INTRODUCTION

Adverse drug reactions have been the object of intense scrutiny since the early 1990s and have been recognized as a top safety priority by health care quality improvement organizations across the United States.¹ A groundbreaking report published in 1999 by the Institute of Medicine only intensified this attention by suggesting that medical errors, including medication errors, may be responsible for 98,000 patient deaths per year in the United States.² Specifically, medication errors and preventable adverse drug events may injure 1.5 million people and cost billions of dollars annually. Up to 2% to 5% of hospitalized patients may have non-preventable adverse drug reactions.³ The classification of drug reactions includes allergic or hypersensitivity reactions, overdosage, intolerance, idiosyncratic reaction, side effects, and secondary effects.

We know relatively little about the pharmacokinetic properties of drugs in individual patients. Many drug-related injuries are not reproducible in animals and therefore cannot be studied in depth. Moreover, if a drug administered in the therapeutic dose range caused an adverse reaction in most of the patients who received it, the drug would not be usable. Indeed, only a small percentage of the population develops pulmonary toxicities to otherwise successful drugs. Nevertheless, drug-induced pulmonary diseases represent a significant problem and are likely underrecognized. It is estimated that less than 5% of all adverse drug-induced pulmonary diseases and overall less than 1% of serious and unexpected events are formally reported to the U.S. Food and Drug Administration (FDA).¹ The number of drugs associated with pulmonary toxicity is steadily increasing.⁴ By 2009, more than 350 drugs have

been identified to cause adverse pulmonary reactions. These reports are of various nature and quality, ranging from clear toxicities established in large series to isolated case reports. Some of these medications are listed in Table 71-1. To minimize mortality and significant morbidity, it is incumbent on the clinician to keep in mind at least the more common drugs that may induce pulmonary disease.⁵⁻⁸

Four mechanisms of drug injury to the lungs are recognized: (1) oxidant injury, such as during chronic nitrofurantoin ingestion; (2) direct cytotoxic effects (and these effects may be aggravated by oxidant injuries); (3) deposition of phospholipids within cells, such as those produced by cationic amphiphilic drugs such as amiodarone; and (4) immune-mediated injury through drug-induced *systemic lupus erythematosus* (SLE).^{6,9-13} Although extensive investigation has been undertaken to look for other forms of immune system–mediated injury, only the SLE induced by drugs has been proven.

CHEMOTHERAPEUTIC AGENTS

Chemotherapeutic agents are extensively used in solid and hematologic malignancies but are also increasingly employed for their immunosuppressive properties in the management of various inflammatory disorders. Because of the severity of the diseases in which they are employed, higher risks for potential adverse lung reactions are typically tolerated, and as such, pulmonary complications of chemotherapy are common in this clinical setting. It is, however, a diagnostic challenge for the clinician who must determine the responsibility of the chemotherapeutic agent, usually on the basis of a diagnosis of exclusion, and decide

Table 71-1 Classification of Drug-Induced and Related Pulmonary Diseases by Type of Medication

CHEMOTHERAPEUTIC	CARDIOVASCULAR
Cytotoxic	Amiodarone*
Azathioprine	Angiotensin-converting enzyme inhibitors
Bleomycin	Anticoagulants
Busulfan	β-Blockers*
Chlorambucil	Dipyridamole
Cyclophosphamide	Flecainide
Etoposide	Protamine*
Interleukin-2	Tocainide
Melphalan	
Mitomycin C*	
Nitrosoureas	ILLICIT
Procarbazine	Heroin*
Vinblastine	Methadone*
Zinostatin	Methylphenidate
	Cocaine
Noncytotoxic	Talc granulomatosis
Bleomycin*	INHALANT
Cytosine arabinoside*	Aspirated oil
Gemcitabine*	Oxygen*
Methotrexate*	
Procarbazine*	INTRAVENOUS
	Blood products*
ANTIBIOTIC	Sodium morrhuate*
Amphotericin B*	Ethiodized oil (lymphangiogram)
Nitrofurantoin	
Acute*	MISCELLANEOUS
Chronic	Appetite suppressants
Sulfasalazine	Bromocriptine
	Complement-mediated leukostasis*
ANTI-INFLAMMATORY	Dantrolene
Acetylsalicylic acid*	Hydrochlorothiazide*
Gold	Methysergide
Interferons	Radiation
Leukotriene antagonists	Systemic lupus erythematosus (drug-induced)
Methotrexate	Tocolytic agents*
Nonsteroidal anti-inflammatory agents	Tricyclics*
Penicillamine*	L-Tryptophan
ANALGESIC	
Placidyl*	
Propoxyphene*	
Salicylates*	

*Typically present as acute or subacute respiratory insufficiency.

whether or not to discontinue it, with the risk of depriving his or her patient of a potentially life-saving therapy.

Oncology patients are prone to a number of pulmonary complications irrespective of their chemotherapy regimen, including opportunistic infections, atypical presentations of common lung infections, radiation-induced lung injury, cardiogenic or noncardiogenic pulmonary edema, and, of course, metastatic lung involvement. The various presentations of drug-induced pulmonary disease must be rapidly differentiated from these other etiologies whose clinical presentations, including fever and diffuse radiographic abnormalities, may be extremely similar to chemotherapy-induced pulmonary reactions. As combination regimens are generally the rule, it can become difficult to incriminate one agent over the other. Chemotherapy-associated pulmonary reactions have become a major problem, particularly in relation to therapeutic regimens containing bleomycin, methotrexate, cyclophosphamide, and a host of newer agents (Table 71-2).

Table 71-2 Selected Chemotherapeutic Agents with Associated Pulmonary Toxicities

ANTIBIOTIC-DERIVED AGENTS	PODOPHYLLOTOXINS
Bleomycin	Etoposide
Mitomycin C	Paclitaxel
	Docetaxel
ALKYLATING AGENTS	NOVEL ANTITUMOR AGENTS
Busulfan	All-trans retinoic acid (ATRA)
Cyclophosphamide	Gefitinib (Iressa)
Chlorambucil	Erlotinib (Tarceva)
Melphalan	Imatinib (Gleevec)
	Dasatinib
ANTIMETABOLITES	IMMUNE MODULATORY AGENTS USED IN MALIGNANCY
Methotrexate	Interferons
6-Mercaptopurine	Interleukin-2
Azathioprine	Tumor necrosis factor-α
Cytosine arabinoside	
Gemcitabine	
Fludarabine	
NITROSOUREAS	OTHER MISCELLANEOUS CHEMOTHERAPY AGENTS
Bischloroethyl nitrosourea (BCNU)	Procarbazine
Chloroethyl cyclohexyl nitrosourea (CCNU)	Zinostatin
Methyl-CCNU	Vinblastine

Consistent criteria for drug-induced lung disease have not been officially established. Uncertainty that a given respiratory complication is linked to a particular drug is generally present. Confirmation with rechallenge is to be avoided because it is often neither practical nor generally ethical. Hence the diagnosis of cytotoxic lung damage rests on an appropriate history of drug exposure, histologic evidence of lung injury, and the exclusion of other causes of the lung damage. There is no single diagnostic test or tissue biopsy that can definitively confirm the diagnosis of chemotherapy-associated lung disease. Thus a careful and thorough evaluation to eliminate the possibilities of other conditions producing these effects, particularly infection, is warranted. It is estimated that 10% to 20% of patients undergoing some type of chemotherapy will develop respiratory symptoms directly related to their treatment.^{8,14} Thus the clinician should maintain a high index of suspicion and carefully screen for other competing causes of pulmonary injury that may affect these immune-compromised patients.

The clinical presentation of many chemotherapy drug effects is quite similar, with the exception that some present more acutely, whereas others tend to be more insidious in their onset. In general, nonproductive cough, dyspnea, and often fever begin weeks to years after the agent is first administered. Occasionally, symptoms may present acutely, as in the case of hypersensitivity reactions or infusion reactions. Symptoms may also manifest years after discontinuation of the drug, perhaps reactivated by radiotherapy, a process called “radiation recall.” Fever is common with most chemotherapeutic drug-induced pulmonary injury, but it may not be consistently present, and chills are usually absent. Weight loss may be present. The chest radiograph in cases of chemotherapy-induced lung disease may be unremarkable for days or weeks before showing typical changes of a diffuse interstitial infiltrative pattern. Alternatively, there may be a diffuse mixed alveolar-interstitial

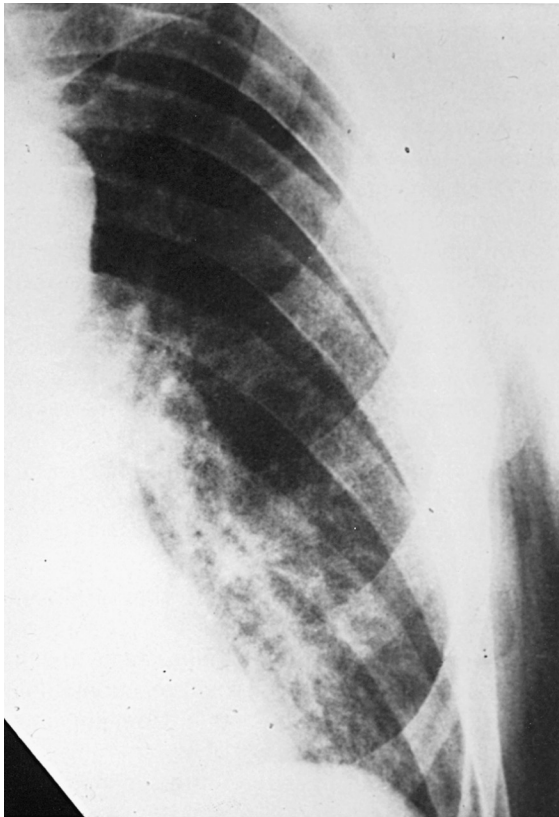


Figure 71-1 Cytotoxic pattern of drug-induced lung disease. A close-up chest radiograph showing an alveolar interstitial pattern that is characteristic but not diagnostic of cytotoxic lung disease.

pattern, which may occasionally be useful in recognizing early drug effects (Fig. 71-1). Auscultation of the lungs will frequently reveal crackles, which are also nonspecific. In some instances, pleural effusions may be present during adverse drug reactions, but not consistently.

Pulmonary function studies are abnormal in almost all patients with cytotoxic drug-induced lung disease when compared with pretreatment testing. The *carbon monoxide diffusing capacity* (DL_{CO}) may decrease before reduced volumes are detected. In addition, this decrease in DL_{CO} may precede the onset of symptoms and radiographic changes by days or weeks.¹⁴ In several prospective investigations, diffusing capacity has been used to detect early onset of pulmonary reactions, at which time the agents are discontinued to minimize progression into overt clinical disease.¹⁵ *Bronchoalveolar lavage* (BAL) may be another means of assessing early lung damage from these drugs; however, the results are often variable. In general, the greatest utility of BAL is to exclude infection.

ANTIBIOTIC-DERIVED AGENTS

Bleomycin

Bleomycin is an antibiotic chemotherapeutic agent that was isolated in 1966 from *Streptomyces verticillus*. Its pulmonary toxicity was recognized early and has since been one of the main factors limiting its use in the clinical

setting. The incidence of bleomycin lung toxicity ranges anywhere from 0% to 46%; pulmonary function testing and chest radiographs reveal that 20% of patients treated with bleomycin develop overt pulmonary disease, and up to 3% die from pulmonary consequences of bleomycin therapy.^{14,16}

The mechanisms by which bleomycin exerts its antineoplastic effects are diverse. Direct cytotoxic effect, prevention of neoangiogenesis by the tumor, stimulation of the production of various cytokines, and free radical generation via formation of a complex between ferrous iron and oxygen are likely the most important.¹⁷⁻²⁰ The latter effect may explain increased bleomycin toxicity with high fractions of inspired oxygen. This is often a problem during anesthesia and in the postoperative recovery period.^{21,22} This sensitivity to supplemental oxygen may persist for months and, perhaps, years after discontinuation of the drug. Perhaps one of the most consistent features of bleomycin-induced lung disease is the concept of cumulative toxicity. The incidence of pulmonary toxicity is significantly greater in those who have received a cumulative dose of greater than 450 units, with a 10% death rate in those having received a total dose greater than 550 units of bleomycin. However, doses as little as 50 units may occasionally be enough, especially when other synergic factors are present. Rapid rates of delivery by the intravenous route may also play a role, and slower infusion rates, as well as intramuscular injections, have been recommended.

Bleomycin is metabolized primarily by the kidneys. Hence renal failure predisposes to impaired metabolism of the drug and increased toxicity. It is also inactivated by an enzyme, bleomycin hydrolase, present in most tissues except for the lungs and skin. The lack of a detoxifying enzyme in the skin may explain the scleroderma-like skin changes occasionally observed with bleomycin. Radiotherapy is itself a common cause of pulmonary complications and is also thought to promote the generation of free radicals, toxic to both the tumor cells and surrounding tissues. The concomitant use of bleomycin and radiotherapy may be synergistic. Treatment with bleomycin may reactivate prior radiation-induced lung disease, a process called *radiation recall*, as mentioned earlier as an example of a delayed drug reaction. Pulmonary toxicity is also increased in patients older than 70 and in those with preexisting lung disease. There is good evidence that pediatric patients may also be at increased risk, with 70% of children treated with bleomycin for rhabdomyosarcoma developing pulmonary toxicity in one study.²³ Impaired or immature ability to process free radicals and inadequate kidney function may explain these differences. Finally, bleomycin toxicity may be synergistically increased by several other chemotherapeutic agents.

Although of uncertain value, determination of pretreatment DL_{CO} and its frequent monitoring have been suggested in an attempt to predict subsequent clinical deterioration. A progressive fall in the DL_{CO} should prompt withdrawal of further bleomycin administration.²⁴ Vital capacity and pulmonary capillary blood flow may be better predictors of lung toxicity.²⁵ In addition, the enhanced sensitivity of *computed tomography* (CT) scanning may also be useful in establishing an early diagnosis of bleomycin pneumonitis. In one series of 100 patients receiving bleomycin, chest CT scans

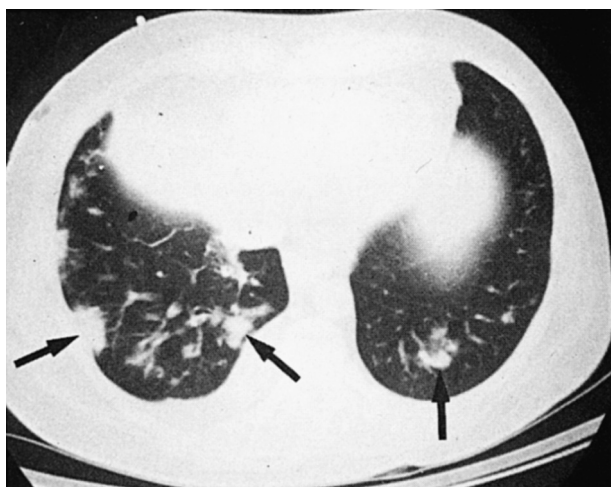


Figure 71-2 Bleomycin-induced lung disease. A chest CT scan of bleomycin pneumonitis showing a nodular pattern (arrows). The histologic features of this form of bleomycin-induced lung injury are typical of organizing pneumonia.

were abnormal in 38%, whereas the chest radiographs were abnormal in only 15%.²⁶ Serial imaging studies are not recommended in the absence of specific symptoms.

Other forms of bleomycin-induced lung disease have been described, albeit less commonly. Hypersensitivity reactions (eFig. 71-1) are possible with an association of fever and peripheral blood or BAL eosinophilia.^{14,15} Discontinuation of bleomycin and initiating corticosteroids usually bring about rapid reversal of this hypersensitivity variant of bleomycin pneumonitis.

An additional rare, but clinically important, presentation of bleomycin pneumonitis is that of nodular pulmonary lesions mimicking tumor metastasis (Fig. 71-2).²⁷ These reactions to bleomycin have been described in the setting of lymphoma or seminoma, requiring surgical biopsy to differentiate bleomycin-associated lung injury from recurrence of the primary malignancy. Although bleomycin pulmonary toxicity may reflect diffuse alveolar damage (eFig. 71-2A), these nodular lesions from bleomycin often exhibit the histologic pattern of organizing pneumonia (see eFig. 71-2B).⁶ Pneumothorax and pneumomediastinum have also been described.

In suspected cases of bleomycin lung toxicity, discontinuation of the drug is warranted. Administration of corticosteroids is often recommended. It would seem prudent to pay particular attention to avoid high fractions of inspired oxygen and concomitant radiotherapy and to monitor the kidney function carefully during the duration of treatment. One study demonstrated that, if the patient survives the acute injury from bleomycin, pulmonary findings might improve substantially over time (see eFig. 71-1).²⁸ However, if significant fibrosis is present, the process may progress insidiously despite the administration of corticosteroids. Histologic, end-stage bleomycin pneumonitis may appear similar to the usual interstitial pneumonia pattern.

Mitomycin C

Mitomycin C is another antibiotic chemotherapeutic agent associated with pulmonary toxicity, which shares features

similar to those induced by bleomycin. It has been employed in the management of bladder tumors, lung cancer, anal cancer, metastatic breast carcinoma, metastatic liver tumors, and esophageal malignancies. One series estimated the incidence of mitomycin-induced pneumonitis to be approximately 8%, with two additional series suggesting the incidence ranged from 12% to as high as 39%.^{29,30} Similar to bleomycin-induced lung toxicity, the cumulative dose appears associated with the incidence of pulmonary manifestations in a linear fashion, with pulmonary fibrosis unlikely at doses less than 30 mg/m². Again, high fraction of inspired oxygen and radiotherapy may exacerbate this phenomenon. Concomitant administration of other chemotherapeutic agents such as bleomycin, doxorubicin, or cyclophosphamide may enhance pulmonary toxicity.

The symptomatology, imaging abnormalities, and histologic findings of mitomycin-induced pneumonitis are similar to those of other alkylating drug toxicities. However, it has been suggested that the DL_{CO} may not fall before the onset of clinical symptoms, making it an unreliable predictor of overt lung disease.³⁰ In addition, a favorable response to corticosteroid therapy has also been quite dramatic in many of these patients, possibly greater than in other forms of chemotherapy-associated lung injury.

In addition to mitomycin-induced pneumonitis, there are reports of an unusual reaction to mitomycin C consisting of microangiopathic hemolytic anemia with associated noncardiogenic pulmonary edema and renal failure, in particular when associated with 5-fluorouracil.³¹ This may be associated with pulmonary hypertension. Most of these patients developed side effects between 6 and 12 months after beginning mitomycin C chemotherapy. Up to one half of these patients evolve into the *acute respiratory distress syndrome* (ARDS), with mortality as high as 95% in some series. The mortality in patients with mitomycin C-associated hemolytic uremic syndrome who do not develop acute respiratory distress syndrome is still in the range of 50%. In some instances, this unusual drug reaction appears to be precipitated by blood transfusions. Microangiopathic changes are present in the lungs and kidneys with intimal hyperplasia of the arterioles, along with prominent nuclear atypia of the capillary cells and capillary fibrin thrombi. Treatment is essentially supportive, with initiation of plasma exchange with or without dialysis and corticosteroids when deemed appropriate.

Pulmonary veno-occlusive disease (PVOD) has also been rarely reported in patients receiving mitomycin C. In one case report, PVOD was confirmed on autopsy.³²

Other Antibiotic Chemotherapeutic Agents

A variety of other antibiotic chemotherapeutic agents have been associated with respiratory complications, although the nature of combined chemotherapeutic regimens makes it difficult to attribute the responsibility to one drug instead of another. *Doxorubicin* is an anthracycline agent notorious for causing cumulative cardiotoxicity with possible cardiogenic pulmonary edema. Rare cases of interstitial pneumonias have also been described, usually in combination with other drugs, typically with mitomycin C. Organizing pneumonia has rarely been reported. Infusion reactions with dyspnea may be observed in 5% to 10% of patients treated with pegylated liposomal doxorubicin. *Epirubicin* is

a similar compound with fewer side effects. Pulmonary complications are rare but may be seen in conjunction with other chemotherapeutic agents. *Mitoxantrone* is an anthracenedione inhibitor of topoisomerase II used in the treatment of multiple sclerosis, acute lymphoid leukemia, acute myeloid leukemia, breast cancer, liver cancer, non-Hodgkin lymphoma, and prostate cancer. Rare cases of subacute interstitial pneumonias have been described. *Actinomycin D* has also been associated with reactivation of prior radiation pneumonitis.²³

ALKYLATING AGENTS

Busulfan

Busulfan has been used for the management of chronic myeloproliferative disorders. It was discovered in 1961 and found to be responsible for significant pulmonary toxicity shortly after. The average duration from the initiation of therapy to the onset of respiratory symptoms is roughly 3.5 years, ranging between 8 months and as late as 10 years. However, busulfan pulmonary toxicity can develop as soon as 6 weeks following initiation of therapy. The incidence of busulfan pulmonary toxicity is estimated to be 6%, with a reported range of 2.5% to 43%.³³ The mortality rate is extremely high, in the range of 80%.²³ No effective therapy has been identified, and discontinuation of the drug with or without initiation of corticosteroid therapy, although recommended, is of unclear value. No obvious aggravating factors have been identified, except perhaps the concomitant administration of other chemotherapeutic agents or radiotherapy. Age and cumulative dose do not seem to play any important role.

Dyspnea, fever, and cough begin in a more insidious fashion with busulfan than with many other chemotherapy lung toxicities. Such symptoms have even been reported to begin months after busulfan therapy has been discontinued. The chest radiograph in busulfan toxicity reveals a combined alveolar and interstitial process to a greater degree than in other chemotherapy reactions. This is likely due to a high degree of desquamation of injured epithelial cells into the alveolar spaces. This alveolar debris may be so extensive as to suggest pulmonary alveolar proteinosis in some patients receiving busulfan. This form of alveolar proteinosis is more refractory to therapeutic lavage than is idiopathic pulmonary alveolar proteinosis. Busulfan-induced pulmonary toxicity is characterized by the presence of acute lung injury with associated atypical type II pneumocytes with markedly enlarged pleomorphic nuclei and prominent nucleoli (eFig. 71-3).

Cyclophosphamide

Cyclophosphamide is widely included in combination chemotherapy for hematologic malignancies and solid tumors. It is also used in the treatment of granulomatous polyangiitis. The incidence of pulmonary toxicity is estimated at around 1%, although accumulating evidence suggests that it may be much more common. A case series from a large tertiary referral center only identified six patients older than 20 in whom cyclophosphamide was the only factor contributing toward pulmonary injury.³⁴ Clinical features of cyclophosphamide-associated pulmonary toxicity include

fever, dyspnea, cough, gas-exchange abnormalities, parenchymal opacities, and pleural thickening. Two patterns of cyclophosphamide-induced lung toxicity have been described. First, there can be an early-onset pneumonitis within the first 1 to 6 months after institution of therapy. This form generally responds to withdrawal of cyclophosphamide. In contrast, there may also be a late-onset pneumonitis that may develop after months or even years of therapy and result in progressive lung fibrosis and bilateral pleural thickening. This late-onset variety unfortunately has minimal response to withdrawal of cyclophosphamide or to corticosteroid therapy.³⁴ The dose of cyclophosphamide and development of lung disease are not clearly related. Supplemental oxygen and radiotherapy may increase the likelihood of lung manifestations. Likewise, concomitant administration of other agents such as bleomycin, and perhaps carmustine, in preparation before bone marrow transplantation seems to accentuate the phenomenon. There have also been rare reports of rechallenge with cyclophosphamide without subsequent recurrence of the pulmonary toxicity. For obvious reasons, this is generally not recommended.

Chlorambucil

This agent has been prescribed primarily for chronic lymphocytic disorders. The clinical presentation, chest radiographic abnormalities, and histologic features of chlorambucil-associated pneumonitis are remarkably similar to those described in other alkylating agent–induced pulmonary toxicities.⁸ Cumulative doses in excess of 2 g seem to increase the risk significantly. The presentation is usually insidious, happening 6 months to a year or more after the start of therapy. Surveillance of lung function, particularly DL_{CO}, may be of benefit in anticipating which patients will deteriorate and require discontinuation of the agent. Few data are available on the efficacy of corticosteroid therapy in chlorambucil-related lung toxicity.

Melphalan

Melphalan has been enlisted in the treatment of multiple myeloma. There have been relatively few well-documented cases of pulmonary toxicity associated with melphalan.³⁵ The course of melphalan-associated pulmonary injury varies from acute to more subacute in tempo. Patients present with insidious to abrupt onset of dyspnea, cough, and frequently fever. There are no particular clues for predicting which patients will develop side effects. The incidence of pulmonary side effects from melphalan must be generally low, in view of the fact that this agent has been widely employed in the long-term management of myeloma.

Ifosfamide

Ifosfamide is structurally related to cyclophosphamide and has been used in the treatment of a variety of solid tumors, including lung, testicular, and breast cancer. Case reports of subacute interstitial pneumonias can be found in the literature, although the responsibility of ifosfamide remains unclear, as it was used in combination with other chemotherapeutic agents such as docetaxel. One case of fatal acute pneumonitis primarily due to ifosfamide has been reported. A case of methemoglobinemia has also been

described, presumably secondary to the interaction between 4-thioifosfamide, a metabolite of ifosfamide, and glutathione and resultant oxidative stress.³⁶

Other Alkylating Agents

Procarbazine is primarily used in the treatment of Hodgkin lymphoma and glioblastoma multiforme. Rare cases of interstitial pneumonias have been reported, sometimes characterized by significant eosinophilia suggesting a hypersensitivity reaction. Progression to widespread and irreversible fibrosis seems rare.³⁷

Oxaliplatin has been associated with laryngeal dysesthesia and was thought to be responsible for the development of diffuse alveolar damage, often in association with 5-fluorouracil. More typically, there can be severe anaphylactic reactions during infusion of the drug in about 1.3% of the cases. Eosinophilic pneumonia has also been rarely reported.^{38,39}

Temozolomide is a second-generation alkylating agent now considered standard of care as an adjuvant therapy for glioblastoma in association with radiotherapy. It is also used in the treatment of metastatic melanoma. Few respiratory side effects have been described, mainly pharyngitis, sinusitis, cough, upper respiratory tract infection, and dyspnea. Pneumonitis was found in up to 4.8% of patients in Phase II trials. One case of organizing pneumonia that resolved after discontinuation of treatment was described.⁴⁰

Chlorozotocin, an alkylating agent used in the treatment of neuroendocrine tumors, has been associated with several cases of mild pneumonitis. All cases resolved with discontinuation of the drug and administration of corticosteroids.⁴¹

ANTIMETABOLITES

Methotrexate

Methotrexate is present in many combination regimens for malignancies and is also used extensively for nonmalignant conditions, including psoriasis and rheumatoid arthritis. It interferes with the metabolism of folic acid, hence specifically targeting replicating cells and leading to a variety of well-described adverse effects, including bone marrow suppression, mucositis, alopecia, and gastrointestinal manifestations. Pulmonary toxicity is thought to develop in about 10% of all patients treated but is fortunately rarely fatal. Dyspnea, nonproductive cough, and fever usually commence a few days to several weeks after initiation of therapy. However, in rare cases, symptoms may be observed a few months or years after onset of therapy.⁴²

Methotrexate-associated pneumonitis (eFig. 71-4) is almost always reversible with or without the addition of corticosteroids. Eosinophilia is seen in at least half of the cases, and the disease is therefore believed to represent a hypersensitivity reaction.¹⁴ The intriguing feature of this reaction is that the drug may be reinstituted following resolution of methotrexate pneumonitis without necessarily triggering a subsequent recurrence of symptoms or findings.⁴³ In about one third of the patients, weakly formed granulomas are identified in lung biopsy, which is unusual in other forms of chemotherapy-associated lung disease (eFig. 71-5).⁶ Hilar lymphadenopathy is occasion-

ally present, and this might mimic the manifestations of sarcoidosis. There is no cellular atypia, such as is seen in many other cytotoxic drug toxicities.

The chest radiograph tends to reveal a homogeneous opacity throughout all lung fields. Hilar adenopathy or pleural effusion is seen in at least 10% to 15% of patients with methotrexate lung toxicity. In distinct contrast to most of the other chemotherapy-induced pulmonary toxicities, prospective investigations of patients receiving methotrexate have not demonstrated a diminished DL_{CO} that might predate subclinical toxicity. In addition, pulmonary toxicity in response to methotrexate does not appear to be dose related. There have been a few reports of fatal reactions either from intrathecal methotrexate or from oral ingestion after previous intrathecal injections. Two other important manifestations associated with methotrexate should be mentioned. Opportunistic infections related to T-cell deficiency need to be excluded, in particular *Pneumocystis* pneumonia, which has been reported in a number of patients receiving methotrexate, either alone or in combination with corticosteroids.⁴⁴ Peculiar Epstein-Barr virus-related lymphomas that typically resolve after discontinuation of treatment have also been reported and may be directly related to an alteration in immune surveillance induced by methotrexate (as seen in posttransplantation lymphoproliferative disorders). The clinical presentation, chest radiography, and other clinical features can be quite similar to methotrexate lung.⁴⁴

Azathioprine and 6-Mercaptopurine

More than two dozen case reports of azathioprine-associated pneumonitis have been reported. However, the net overall incidence must be low, considering the widespread use of this agent for neoplastic and non-neoplastic conditions.³⁵ Nevertheless, the possibility of an azathioprine pneumonitis must be considered in any individual receiving this agent. Azathioprine is metabolized to 6-mercaptopurine, and there have been a handful of reports detailing cytotoxic interstitial pneumonitis in association with this metabolite.⁵ However, most of these patients have also received other agents that potentially could be implicated in the lung injury described.

Cytosine Arabinoside

Cytosine arabinoside (ara-C) is a cytotoxic agent used to induce remission in acute leukemia and other hematologic malignancies before bone marrow transplantation. Intensive ara-C treatment regimens have been associated with rapidly fatal noncardiac pulmonary edema (Fig. 71-3).⁵ Histologic examination of lung tissue during ara-C pulmonary toxicity reveals substantial accumulation of intra-alveolar proteinaceous material without the cellular atypia and mononuclear infiltration described with other cytotoxic drugs. In two large series, 13% to 28% of the patients with toxicity developed respiratory distress during the administration of the drug, and nearly one half developed symptoms within a month of completing drug administration. The mechanism underlying this reaction is unknown, and the associated mortality is high. Treatment for ara-C pulmonary toxicity is largely supportive, with mechanical ventilation, careful management of fluid status, and surveillance for superimposed infectious complications.

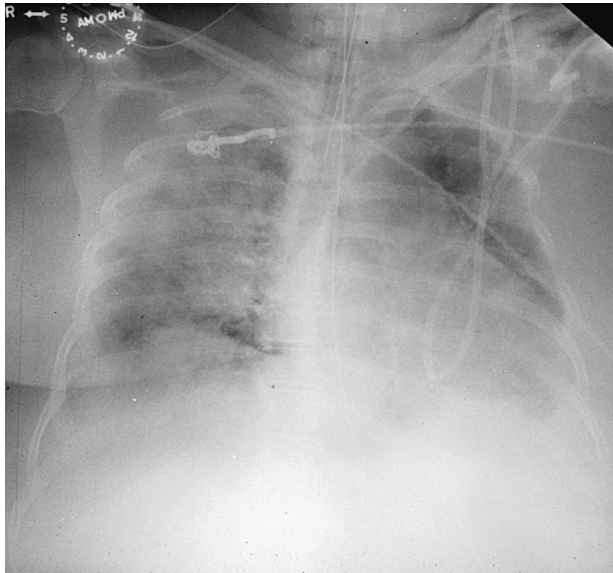


Figure 71-3 Cytosine arabinoside-induced lung disease. A chest radiograph of a 44-year-old woman showing acute noncardiac pulmonary edema that resulted from cytosine arabinoside-induced lung disease. Histologic examination typically demonstrates intense intra-alveolar proteinaceous material forming hyaline membranes, but little other reaction.

Gemcitabine

Gemcitabine is a pyrimidine analogue, with structure and activities similar to ara-C. It is highly active against non-small cell lung cancer, as well as breast, pancreatic, and ovarian cancers. It is usually well tolerated, with the most prevalent toxicity being bone marrow suppression, as well as nausea, rash, transaminase elevation, and edema in some cases. The incidence has probably been underestimated. Dyspnea has been reported in 10% of treated patients, with severe dyspnea reported in up to 5%.⁴⁵⁻⁴⁷ Noncardiogenic pulmonary edema is thought to develop in 0.1% to 7% of all patients treated.⁴⁸ There are three major patterns of respiratory involvement in gemcitabine-related pulmonary toxicity. The first pattern is a nonspecific, self-limiting dyspnea reported within hours to days of treatment. A second, relatively uncommon, pattern is that of an acute hypersensitivity reaction with bronchospasm. A third pattern of severe respiratory involvement is occasionally seen. This is a severe idiosyncratic reaction with profound dyspnea and pulmonary opacities that may progress to life-threatening respiratory insufficiency within hours of infusion (Fig. 71-4). Most cases of gemcitabine-related pulmonary toxicity resolve with discontinuation of this drug. In cases of severe symptoms, discontinuation of the agent along with institution of corticosteroids, careful fluid management, and diuretic therapy may be warranted.⁴⁵ Cases of diffuse alveolar hemorrhage, pulmonary veno-occlusive diseases, and thrombotic microangiopathy have also been described.

Fludarabine

Fludarabine, another nucleoside analogue, is widely employed in the management of chronic lymphoproliferative disorders. The incidence of pulmonary toxicity related to fludarabine has been estimated to be approximately 8.6% in a series of 105 patients.⁴⁹⁻⁵¹ Affected individuals experi-

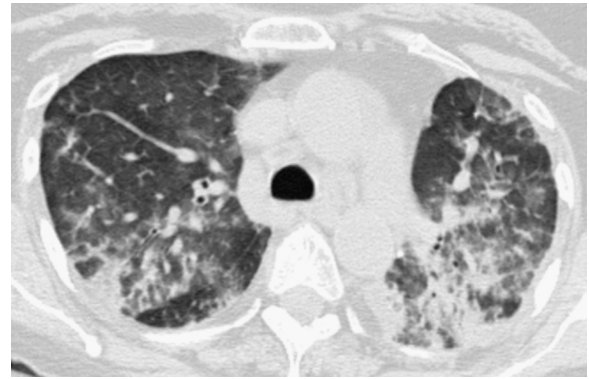


Figure 71-4 Gemcitabine-induced lung disease. A chest CT image of an individual with gemcitabine-induced lung disease. The pattern is a mixed alveolar and interstitial infiltration.

ence dyspnea as early as 3 days after the first round of chemotherapy, though later onset of pulmonary symptoms has also been reported. The chest radiograph reveals either interstitial or mixed alveolar-interstitial opacities. Nodular opacities have also been described. As is often the case with chemotherapeutic agents, particular attention should be given to the possibility of opportunistic infections. Most patients respond to discontinuation of the drug and receive symptomatic and objective benefits from additional corticosteroid therapy.

Piritrexim

Piritrexim is an oral inhibitor of the dihydrofolate reductase used in the treatment of parasitic infections, psoriasis, and transitional cell carcinoma. It is closely related to methotrexate, and pulmonary toxicity has been observed in up to 14% of patients.⁵²

Nitrosoureas

Nitrosourea compounds have a role in the treatment of gliomas and other central nervous system tumors, as well as in conditioning protocols preceding autologous bone marrow stem cell transplantation. Pulmonary toxicity related to nitrosoureas is well recognized and represents one of the most common side effects of these agents.⁵³ In particular, *bischloroethyl nitrosourea* (BCNU, carmustine) has been described to induce both acute-onset pulmonary injury (see eFig. 91-13) and delayed-onset pulmonary fibrosis, with a predilection for the upper lobes.⁵³ The incidence of pulmonary toxicity associated with the administration of BCNU varies from 1.5% to 20% and is dose related, with up to a 50% incidence of lung disease in those receiving a total dose of greater than 1500 mg/m². However, there have also been reports of pulmonary effects with much lower doses. The duration of therapy before the onset of pulmonary toxicity for the acute variant of nitrosourea lung injury has generally ranged from 6 months to 3 years. There appears to be a synergistic effect with cyclophosphamide, radiation therapy, and possibly other chemotherapeutic agents. The outcome may be unpredictable and sometimes fatal. There have been fewer case reports of pulmonary toxicity with *methyl-chloroethyl cyclohexyl nitrosourea* (methyl-CCNU) and *chloroethyl cyclohexyl nitrosourea* (CCNU). Apparently, fever is less commonly associated with this form

of pulmonary toxicity than with many other chemotherapeutic drugs. Therapy usually consists of withholding the offending agent and institution of corticosteroids, which has variable and often only transient beneficial effects.⁵⁴

A long-term complication of BCNU toxicity is upper lobe fibrosis that may appear many years after the completion of chemotherapy. O'Driscoll and colleagues⁵⁵ followed 17 patients for up to 17 years, and 12 of the 17 (71%) developed delayed upper lobe fibrosis. The fibrosis is insidious in onset and, once discovered, appears to be intractably progressive. Corticosteroid therapy has not proven to be effective in delayed BCNU upper lobe fibrosis. Another unusual reported complication that is almost exclusively associated with nitrosourea compounds is pneumothorax.⁵⁶ This may be related to the upper lobe fibroblastic changes present in patients with BCNU lung toxicity.

Cases of pulmonary fibrosis have also been reported with other nitrosourea agents, including lomustine (CCNU), semustine (methyl-CCNU), fotemustine (CENU), and chlorozotocin (DCNU). Pneumothoraces have rarely been described with these agents.

PODOPHYLLOTOXINS

Etoposide and Teniposide

Etoposide (VP-16), a topoisomerase II inhibitor, has been widely used in combination chemotherapy for non-small cell and small cell lung carcinoma. Despite its extensive use, only a few cases of etoposide-associated pulmonary toxicity have been reported.⁵⁷ Toxicity may become apparent shortly after the first round of chemotherapy, although most of the associated cases present after prolonged treatment. Tissue examination reveals features of alveolar edema, diffuse alveolar damage, and atypical type II pneumocytes. Therapy consists of withdrawal of the agent and administration of corticosteroids, which provide variable improvement. In addition, etoposide may increase the intracellular levels of methotrexate and thus, the combination of methotrexate and etoposide may synergistically increase the likelihood of adverse reactions.

Teniposide, another podophyllotoxin agent, is also associated with hypersensitivity reactions in 3.6% to 6.5% of the cases. This toxicity may present with dyspnea, bronchospasm, and hypertension.⁵²

Paclitaxel

Paclitaxel is a highly potent chemotherapeutic agent used in the treatment of lung, breast, and ovarian carcinomas. Well-documented cases of pulmonary toxicity induced by paclitaxel can be found in the literature, but the frequency is unclear. Patients may complain of respiratory symptoms including cough, dyspnea, wheezing, and chest tightness within minutes of administration of the drug, suggesting a type I hypersensitivity reaction. Immunoglobulin E antibodies against paclitaxel itself or perhaps its vehicle, Cremophor EL, are thought to be responsible.⁵⁸ This reaction may be seen in up to 30% of patients, and premedication with corticosteroids is sometimes considered. Reticular and nodular opacities have been reported on chest radiographic studies.⁵⁹ Cases of transient pulmonary opacities and suspected interstitial pneumonitis have also been described

(eFig. 71-6). The true incidence of lung toxicity directly related to paclitaxel is not well understood. A prospective study of lung function in 33 patients receiving paclitaxel with carboplatin (an agent with little lung toxicity) in the setting of nonthoracic malignancy revealed an isolated decrease in DL_{CO} without other clinical or radiographic evidence of pulmonary toxicity.⁶⁰ In other studies, conducted on patients with lung carcinoma, significant early and late pulmonary toxicity has been noted in 10% and 68% of patients, respectively.^{61,62} Attributing the toxicity directly to paclitaxel is confounded by the underlying thoracic neoplasm, as well as other cytotoxic agents used in these patients.⁶¹ Nonetheless, clinicians should be aware of the potential of paclitaxel impairing pulmonary function.

Docetaxel

Docetaxel (Taxotere) is another taxane compound that has activity in the treatment of breast and non-small cell lung cancer. Occasional pulmonary toxicity based on a hypersensitivity reaction has been observed.⁶³ These patients have responded rapidly to corticosteroid therapy. A small case series has suggested that the combination of docetaxel and gemcitabine has a particular propensity to induce severe pulmonary toxicity.⁶⁴ Some patients may develop capillary leak syndrome with peripheral edema, noncardiogenic pulmonary edema, and/or pleural effusions.^{65,66} The severity of fluid retention can be reduced by prophylactic treatment with corticosteroids.⁶⁷

VINBLASTINE

Vinblastine, a vinca plant alkaloid, is one of the oldest chemotherapeutic agents still in use. Vinblastine continues to be included in a wide variety of chemotherapeutic regimens for hematologic and solid malignancies. Traditionally, vinblastine was thought to have little if any pulmonary toxicity. However, reports have associated vinblastine with pulmonary complications when it is combined with other agents, particularly mitomycin C. This combination has been complicated by bronchospasm, interstitial pneumonitis, and a noncardiac pulmonary edema.^{68,69}

ALL-TRANS RETINOIC ACID

All-trans retinoic acid (ATRA) has been employed in acute promyelocytic leukemia, in which it promotes differentiation of myeloid precursors and stimulates the maturation of leukemic cells, thereby promoting remission. It has also been reported to reduce disseminated intravascular coagulation and hemorrhagic complications during promyelocytic leukemia. The main complication limiting its use is the development of the differentiation syndrome (previously called retinoic acid syndrome) in up to 25% of patients treated. This syndrome consists of diffuse edema, pleuro-pericardial effusions, and noncardiogenic pulmonary edema that may evolve into a generalized capillary leak syndrome (eFigs. 71-7 and 71-8). Hypotension and acute renal failure are commonly present. Toxicity may manifest suddenly between days 2 and 21 of treatment. Its pathogenesis remains elusive, but it is thought to result from a massive release of cytokines from newly mature myeloid cells and adhesion of granulocytes to the pulmonary

endothelium. Indeed, high leukocyte counts have been associated with an increased incidence of the syndrome in some, but not all, studies. In addition, multiple hemorrhagic complications have also been described. In one study, 9 of 35 patients with promyelocytic leukemia receiving ATRA developed respiratory distress.⁷⁰ Intravenous corticosteroid therapy seemed to be of benefit to these patients. On the basis of these observations, an additional study has suggested that the incidence of ATRA-associated pulmonary complications may be reduced to roughly 10% through the use of preventative treatment with oral corticosteroids.

The mortality associated with ATRA-induced pulmonary toxicity is estimated at around 9%. Tissue examinations of lungs affected by ATRA have revealed interstitial infiltration with maturing myeloid cells. However, the overall spectrum of the ATRA-associated pulmonary syndrome is continuing to evolve and includes the presence of myeloid cells and blasts in BAL fluid, nodular pulmonary opacities, pulmonary leukostasis, noncardiogenic pulmonary edema, ARDS, Sweet syndrome, and diffuse alveolar hemorrhage.⁷¹

IRINOTECAN AND TOPOTECAN

Irinotecan, a semisynthetic camptothecin, has been employed for advanced colorectal cancer either alone or in combination with 5-fluorouracil, as well as in some lung cancer trials. Early studies of irinotecan in Japan documented a 1.8% incidence of pneumonitis.⁷²⁻⁷⁴ In those studies, clinical features included dyspnea, fever, and reticulonodular pulmonary opacities. Empirical corticosteroids were recommended, but some patients progressed to fatal respiratory failure. In subsequent U.S. trials, cough and dyspnea were described in roughly 20% of treated patients.⁷⁵ However, many of these patients had intrathoracic malignancies. The reported incidence of serious pulmonary toxicity related to irinotecan was much lower in these subsequent trials ($\approx 0.4\%$).⁷⁵ Radiotherapy and preexisting lung disease may increase the risk. Nonetheless, cases of serious irinotecan-associated interstitial pneumonitis have been reported in the United States. Patients with preexisting pulmonary disease may be at enhanced risk.

Topotecan is a similar agent and has rarely been reported to induce pulmonary toxicity, including cases of diffuse alveolar damage and constrictive bronchiolitis.

TARGETED THERAPY

Monoclonal Antibodies

As our understanding of the pathogenesis of malignant processes continues to increase, the identification of specific target tumoral antigens has led to the development of specific immunotherapeutic tools, including monoclonal antibodies. Several new molecules have emerged as potentially beneficial adjunct agents in a variety of neoplastic processes.

Bevacizumab. Bevacizumab (Avastin) is a monoclonal antibody targeting the vascular endothelial growth factor, and designed to inhibit tumoral neoangiogenesis. It has been used in conjunction with conventional chemothera-

peutic agents in the treatment of metastatic colon, renal cell cancer, breast cancer, sarcoma, ovarian cancer, glioblastoma, and nonsquamous non-small cell lung cancers. It is associated with hemorrhagic complications including fatal pulmonary hemorrhage thought to result from extensive tumor necrosis. These complications have been predominantly seen in patients with squamous cell lung cancer. Although it may seem counterintuitive, bevacizumab is thought to increase the incidence of thromboembolic disease by twofold. This may be secondary to vascular injury with secondary exposure of the underlying endothelium with secondary activation of the coagulation cascade. Cases of thrombotic microangiopathy with hypertension and acute renal failure have also been described. Cases of congestive heart failure have also been described, mostly in association with anthracycline agents, raising questions about this reported association.⁷⁶ Tracheoesophageal and bronchoesophageal fistulas have been described in patients treated with bevacizumab for lung cancer.⁷⁷⁻⁷⁹

Cetuximab and Panitumumab. Cetuximab and panitumumab are two monoclonal antibodies directed against the *epidermal growth factor receptor* (EGFR) that are increasingly used in treatment of a number of neoplasms. Both have been associated with rare pulmonary toxicity. Interstitial lung disease has been reported in 0.4% of patients with cetuximab, and there may be infusion reactions with bronchospasm and hoarseness in 23% of the cases. With panitumumab, there may be similar infusion reactions, which may be severe in 1% of the cases. Panitumumab has now been associated with an increasing number of interstitial lung disease and pulmonary fibrosis cases. The interstitial lung disease has been found to be fatal in some cases, so if toxicity becomes apparent, panitumumab should be stopped and steroids should be considered.^{80,81}

Trastuzumab and Ado-Trastuzumab Emtansine. Trastuzumab selectively binds the *human epidermal growth factor receptor-2* (HER-2) protein and is an adjuvant treatment of metastatic HER-2-positive breast cancer. As seen with other monoclonal antibodies, infusion reactions may present in 15% of the cases and are potentially associated with angioedema, fever, and bronchospasm. Trastuzumab reactions may also present as an acute or subacute interstitial pneumonia in approximately 0.5% of the cases, with a mortality rate estimated at 0.1%.⁸² An increasing number of case reports suggest that interstitial pneumonia is likely a rare but real toxicity of trastuzumab. Ado-trastuzumab is an antibody-drug conjugate that contains trastuzumab and a cytotoxic microtubule inhibitor. It is also used in breast cancer and has been associated with acute pneumonitis. The incidence is low at 0.8% to 1.2% but may be life-threatening, so if pneumonitis develops, ado-trastuzumab should be discontinued.⁸³

Rituximab. Rituximab is an anti-CD20 chimeric monoclonal antibody approved in 1997 for the treatment of non-Hodgkin lymphoma. Its ever-increasing indications have led to an exponential increase in its use in a variety of diverse conditions from autoimmune inflammatory diseases to posttransplantation lymphoproliferative disorders. The most common side effect of rituximab is an infusion

reaction in more than 50% of patients. Symptoms include fever, chills, dyspnea, hypotension, rhinitis, urticaria, pruritus, and a sensation of throat and tongue swelling. Slowing or stopping the rituximab infusion may help resolve the symptoms. Corticosteroids are occasionally required. Other pulmonary complications of rituximab appear fairly rare overall. A review of the literature in 2007 only identified 16 cases of interstitial lung disease assumed to be secondary to rituximab use. Specific patterns of lung injury have also been described in pathologic specimens, including diffuse alveolar hemorrhage and desquamative interstitial pneumonia, but the experience is often limited to isolated case reports.⁸⁴

Tyrosine Kinase Inhibitors

Gefitinib. Gefitinib (Iressa) is a selective EGFR tyrosine kinase inhibitor used in patients with advanced non-small cell lung cancer and EGFR-activating mutations. Acute interstitial pneumonia has been associated with this drug, and the overall incidence of gefitinib-associated interstitial lung disease may be in the range of 1%, with a mortality rate approaching 30%.^{85,86} The most common presentation is acute dyspnea with or without cough or fever.⁸⁵ The median onset of symptoms was 24 to 31 days in Japanese and 42 days in American patients.⁸⁵ Diffuse ground-glass opacities and multifocal airspace consolidation have been reported on CT scan.⁸⁷ Tissue examination demonstrates diffuse alveolar damage, interstitial inflammation with or without fibrosis, and organizing pneumonia.^{86,88-90} Although some patients respond to withdrawal of the agent and institution of corticosteroid therapy, others progress to fulminant respiratory insufficiency. Hence the clinician needs to remain mindful of this pulmonary complication of gefitinib therapy and discontinue the agent if symptoms and radiographic abnormalities develop. The benefit of corticosteroids is unclear.

Erlotinib. Erlotinib (Tarceva), another EGFR antagonist, is used widely in the United States for the treatment of advanced lung adenocarcinomas with EGFR mutations. Erlotinib has also been rarely associated with pulmonary toxicity including fatalities.⁹¹⁻⁹³ Patients who have undergone lung biopsy have shown organizing pneumonia or diffuse alveolar damage.⁹³ The presentation is similar to most drug-induced lung injury with dyspnea, cough, and low-grade fever. The median time to toxicity is 47 days.⁹¹ Treatment is supportive with removal of the drug. The benefit of corticosteroids is unclear.

Imatinib. Imatinib (Gleevec) is an inhibitor of the Bcr-Abl, KIT, and *platelet-derived growth factor receptor* (PDGFR) tyrosine kinases. It is used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors.⁹⁴ Fluid retention causing peripheral, periorbital, and pulmonary edema is a common complication.⁹⁵⁻⁹⁷ There have been cases reported of pulmonary infiltration with eosinophilia or acute interstitial pneumonia.^{94,98-101} Symptoms of dyspnea, cough, and low-grade fever develop at a median time of 49 days.¹⁰² Radiographic studies have shown ground-glass opacities, consolidation, or nodular opacities. BAL findings demonstrate lymphocytes, foamy macrophages, and, in some cases, eosinophilia.^{101,103,104}

Peripheral eosinophilia has also been demonstrated.¹⁰³ Lung biopsies have demonstrated interstitial inflammation and fibrosis, alveolitis, and pulmonary alveolar proteinosis.^{99,103,104} Treatment is removal of the drug and, in many cases, corticosteroids. Rechallenge of the drug does not always cause recurrence of the lung injury, so physicians must carefully consider alternative agents and the risk and benefit of rechallenge.^{103,105}

Dasatinib. Dasatinib is a Bcr-Abl tyrosine kinase inhibitor that is used to treat Philadelphia chromosome-positive chronic myeloid leukemia. Dasatinib is associated with pleural effusions, pulmonary hypertension, and pulmonary parenchymal abnormalities. Pleural effusions have been reported in 10% to 35% of patients treated.¹⁰⁶⁻¹¹⁰ Effusions are mostly lymphocytic and exudative. Concomitant lung disease and higher initial daily dose were risk factors for development of pleural effusions.¹⁰⁸ Treatment of the pleural effusions is unclear but has included glucocorticoids, diuretics, thoracentesis, and discontinuation of dasatinib.^{106,108,111,112} Pulmonary arterial hypertension is a rare complication of dasatinib use with symptom onset after 8 to 48 months of therapy.¹¹³⁻¹¹⁷ Presenting symptoms included tachypnea, exertional dyspnea, fatigue, and peripheral edema.¹¹³⁻¹¹⁷ Dasatinib therapy should be discontinued if pulmonary hypertension develops, and there should not be a rechallenge of the drug.¹¹³⁻¹¹⁷ Pneumonitis is another rare complication of dasatinib. In one study of patients treated with dasatinib, 40 (23%) patients developed a lung abnormality.¹¹⁸ The lung changes resolved or partially resolved in all 9 patients with parenchymal abnormalities.¹¹⁸ Discontinuation of dasatinib resulted in resolution in 5 patients, and glucocorticoids were used in 1 patient with complete resolution.¹¹⁸ Rechallenge with dasatinib can be considered in patients with parenchymal abnormalities.¹¹⁸

Bosutinib. Bosutinib is another tyrosine kinase inhibitor that targets Bcr-Abl and is used to treat Philadelphia chromosome-positive CML. Like dasatinib, pleural effusion is the most common pulmonary toxicity.¹¹⁹

Sunitinib and Sorafenib. Sunitinib and sorafenib are small molecule tyrosine kinase inhibitors that block the intracellular domain of the *vascular endothelial growth factor* (VEGF) receptor. Sunitinib is used to inhibit angiogenesis in the treatment of gastrointestinal stromal tumors and renal cell cancer. Sunitinib has been reported to cause dyspnea and cough.¹²⁰ Pulmonary embolism has also rarely been reported. Sorafenib is used to inhibit angiogenesis in renal cell carcinoma and unresectable hepatocellular carcinoma. Pulmonary toxicity has been reported during sorafenib use with diffuse pulmonary opacities, dyspnea, cough, and fever.¹²¹ Although a rare toxicity, it was fatal in some patients, so the drug should be stopped immediately if pulmonary toxicity is suspected.¹²¹

Immunomodulatory Agents

Interferons. Interferons have been used in a wide variety of malignant, infectious, and inflammatory disorders. Interferon-alfa and interferon-beta have been employed in the treatment of hairy cell leukemia, myeloma, T-cell

lymphoma, chronic myelogenous leukemia, malignant pleural effusions, melanoma, renal cell carcinoma, and Kaposi sarcoma. Interferon-gamma has been included in investigative trials for mesothelioma, non-small cell lung carcinoma, and idiopathic pulmonary fibrosis.

Administration of interferons has been associated with a variety of pulmonary reactions. For instance, interferon- α has been linked to severe exacerbation of bronchospasm in patients with preexisting asthma.¹²² In addition, a granulomatous reaction indistinguishable from sarcoidosis (eFig. 71-9) has been described in relation to interferon therapy.¹²³ These toxicities usually respond to either reduction or withdrawal of the interferon treatment with or without the addition of corticosteroids. Noncaseating granulomas have been documented in the lung, lymph nodes, liver, and skin of affected patients.

Interferon-associated interstitial lung disease has also been reported.¹²⁴ Dyspnea and cough are observed and bilateral opacities are present on chest radiography. A CD8-predominant lymphocytic response is found in the BAL fluid, and a cellular interstitial pattern is present on histology. In some cases, interferon therapy has also been associated with an organizing pneumonia pattern.¹²⁵ Most affected patients respond to discontinuation of the interferon and administration of corticosteroids. Recently, interferon-gamma has been used in idiopathic pulmonary fibrosis. A series has been reported in which four patients with advanced idiopathic pulmonary fibrosis developed acute hypoxemic respiratory failure during interferon-gamma treatment.¹²⁶ This was not responsive to corticosteroids and was fatal in three cases. Interferon-gamma is also associated with a high incidence of severe radiation pneumonitis when it is used in multimodality therapy for non-small cell lung carcinoma.

Rapamycin Analogs. Sirolimus was initially developed as an antifungal agent isolated from *Streptomyces hygroscopicus*. It is a macrolide antibiotic inhibitor of the mammalian target of rapamycin (mTOR) with antiproliferative and immunosuppressive properties essentially used to prevent rejection in solid-organ transplantation and as a coating agent in drug-eluting stents. It is currently under investigation for the treatment of lymphangiomyomatosis.¹²⁷ Several patterns of drug toxicity have been described with sirolimus, including the subacute onset of interstitial pneumonitis (eFig. 71-10) (which usually resolves after discontinuation of therapy), an organizing pneumonia injury pattern, and diffuse alveolar hemorrhage. Rare cases of alveolar proteinosis and granulomatosis have also been reported. Typically, these pulmonary complications are reversible after discontinuation of therapy, but occasionally they represent a difficult diagnostic challenge in an immunosuppressed population prone to a variety of opportunistic infections.¹²⁸

Everolimus is a similar inhibitor of the mTOR pathway that has been used as an immunosuppressive agent in solid-organ transplantation and in treatment of renal cell cancer and neuroendocrine tumors. Several types of pulmonary toxicity have been described, including organizing pneumonia and the subacute onset of interstitial pneumonitis.¹²⁹ The interstitial pneumonitis has been reported in varying severity. In one report of interstitial lung disease while

receiving everolimus, four patients underwent BAL, which demonstrated lymphocytosis; two patients also had increased eosinophil counts.¹³⁰ Transbronchial biopsies from three of the patients demonstrated interstitial lymphocytic inflammation and septal thickening.¹³⁰ Treatment may involve observation in mild cases but can require discontinuation of the drug and initiation of glucocorticoids in severe cases.^{131,132} The use of glucocorticoids is of unclear benefit.

Temsirolimus is active against a variety of solid tumors, including endometrial cell carcinoma, breast cancer, and neuroendocrine tumors. It is FDA-approved for the treatment of advanced renal cell carcinoma. In a retrospective review of 22 patients treated with temsirolimus, eight patients (36%) developed pulmonary complications. Half of these patients were symptomatic. On radiographic studies, two different patterns of involvement were identified consisting of ground-glass opacities or alveolar consolidation. Pneumonitis has recurred in some cases with rechallenge.¹³³ Discontinuation of the drug is advised.^{134,135}

ANTIMICROBIAL AGENTS

NITROFURANTOIN

Acute Reaction

Nitrofurantoin pneumonitis may be one of the most common drug-induced pulmonary diseases.¹³⁶⁻¹³⁸ Acute pulmonary reactions are probably underestimated. The incidence has been estimated to be anywhere from 1 in 550 to 1 in 5400 individuals.¹³⁸ The mechanism of the acute nitrofurantoin reaction is unknown.

The typical reaction begins a few hours to several days after initiation of therapy. It appears to be much more common in women, perhaps due to the increased use of this drug in women. Fever is present in the majority of cases, dyspnea is almost always present, and cough is present in about two thirds of cases. Other incidental findings include leukocytosis and eosinophilia in one third and an elevation in sedimentation rate in nearly one half of cases. Imaging shows either an alveolar or an interstitial process or both. The reaction may be unilateral or asymmetrical and is generally most prominent at the bases. Pleural effusion has been found in one third of patients, most commonly unilaterally. Bronchospasm has been reported in a number of cases, but its incidence is unknown; it may happen in the absence of pulmonary parenchymal or pleural disease.¹³⁸

The treatment consists of discontinuing the medication and providing supportive care. It is not known whether corticosteroids accelerate the resolution, and there is probably no indication for their use. There is also no role for rechallenge to confirm the diagnosis. Nitrofurantoin-induced SLE with pleuropulmonary disease and positive antinuclear antibody has also been reported.

Chronic Reaction

There is no clinical overlap between the acute and chronic pulmonary reaction to nitrofurantoin. Chronic reactions are far less common than acute pulmonary reactions. In chronic reactions, fever and eosinophilia are much less common.¹³⁷⁻¹³⁹ The onset of dyspnea and cough is usually

insidious, beginning after 6 months to many years of continuous or intermittent use of nitrofurantoin. These reactions are more common in women.

Chest imaging shows a diffuse interstitial process.^{138,139} There is no associated bronchospasm or obstructive airway disease. Pulmonary function testing demonstrates a restrictive pattern. BAL usually shows a lymphocytic reaction. Histologic analysis of lung tissue shows inflammatory cells and fibrosis. Clinically, radiologically, and histologically, this condition often mimics other forms of interstitial lung disease, including usual interstitial pneumonia or nonspecific interstitial pneumonia patterns (eFig. 71-11).

The literature varies as to the utility of corticosteroids. Our experience is that they are almost always required for significant resolution. Others imply that the opacities resolve spontaneously on discontinuation of the medication.¹³⁹ Our policy is to observe the patient for 2 to 4 months after discontinuing nitrofurantoin and then repeating the imaging and pulmonary function studies. If there is no improvement, a trial of corticosteroids is given.¹⁴⁰

SULFASALAZINE

Sulfasalazine is an antimicrobial drug that has been used for many years for the treatment of inflammatory bowel disease.¹⁴¹ There appear to be two separate types of adverse pulmonary reactions: one is a pulmonary opacity with eosinophilia, and the other an organizing pneumonia pattern of pulmonary injury. After 1 to 8 months of continuous therapy, patients experience the onset of cough, dyspnea, and, in about half of cases, fever. The chest radiograph shows a variable pattern of lung opacities, ranging from upper lobe alveolar opacities to a diffuse interstitial process. More than half of the patients have significant blood eosinophilia. Resolution is seen within 1 week to 6 months after discontinuing the drug and, if necessary, adding corticosteroids. Sulfasalazine is metabolized to 5-aminosalicylic acid and sulfapyridine, both of which have been implicated in eosinophilic pneumonitis. In cases of suspected sulfasalazine-associated pulmonary disorders, it is important to keep in mind that inflammatory bowel disease has been associated with a variety of pulmonary abnormalities independent of sulfasalazine use. Inflammatory bowel disease has been independently linked to airway inflammation, interstitial lung disease including an organizing pneumonia pattern of pulmonary injury, neutrophilic necrotic pulmonary nodules, and serositis. Most of these disorders respond to corticosteroid therapy.

MISCELLANEOUS ANTIMICROBIAL DRUGS

There are many scattered reports of unusual reactions to various antimicrobial drugs. In view of the wide use of these agents, the incidence is extremely small. Many of these reactions appear to be pulmonary opacities with eosinophilia (eFig. 71-12). The polymyxin and aminoglycoside antibiotics are known to produce respiratory muscle weakness when they reach an excessive level in the blood.¹⁴² Antibiotics can reach toxic levels in the blood in patients to whom these drugs are given by direct instillation into the peritoneal or pleural space, in persons with renal failure, or in patients receiving them together with a muscle-relaxing

agent at the time of general anesthesia. These effects are reversible with physostigmine. The combined administration of amphotericin B with granulocytes may predispose some patients to transient deterioration in pulmonary function.¹⁴³

ILLICIT DRUGS

HEROIN

Although nitrofurantoin appears to be the prescribed drug with the most commonly reported adverse pulmonary effects, heroin pulmonary edema may be the most common drug-induced pulmonary disease worldwide. Hospitals in all major cities of the United States receive hundreds of patients with heroin pulmonary edema. Heroin is diacetylmorphine and, because of its increased lipid solubility, it crosses the blood-brain barrier much more readily than morphine. There are several postulated mechanisms of heroin-induced noncardiac pulmonary edema. These include a direct toxic effect on the alveolar-capillary membrane, leading to an increased permeability and extravasation of fluid into the alveolar spaces; a neurogenic response to central nervous system injury; an allergic or hypersensitivity reaction; and an acute hypoxic effect on the alveolar-capillary membrane in association with secondary increased permeability.

Heroin can cause pulmonary edema with the first intravenous use of the drug. It is believed that the effects of heroin are related to the dose. However, the exact dose is almost always unknown. Up to 40% of addicts hospitalized for acute drug overdose have acute pulmonary edema with severe hypoxemia and hypercapnia. The noncardiac pulmonary edema is indistinguishable at the outset from other forms of ARDS. The pulmonary capillary wedge pressure is usually within normal range. Typically, symptoms of dyspnea and somnolence begin within minutes of the intravenous "push," but reports of delayed onset of hours and even a few days have been published. The patient hypoventilates, becoming hypoxemic and hypercapnic. The pupils are small. Auscultation of the lungs discloses crackles. Imaging (see Fig. 62-4) typically shows changes of noncardiac pulmonary edema. Acidosis can be metabolic and respiratory.

Up to one half of these patients vomit and aspirate, which may complicate interpretation of the chest radiograph and later lead to secondary bacterial infection. Infection should be suspected if the pulmonary opacities do not clear within 24 to 48 hours of treatment. Other pulmonary abnormalities include septic emboli from infected thrombophlebitis or tricuspid endocarditis. Treatment consists of assisted ventilation using positive end-expiratory pressure, oxygen, and intravenous naloxone to reverse the respiratory depression. This is usually sufficient treatment for the noncardiac pulmonary edema, which will reverse with time. Corticosteroids are unnecessary. Because up to half of these patients have aspirated and have bacterial infections, appropriate use of antimicrobial drugs is indicated.

Bronchiectasis and necrotizing bronchitis in chronic heroin abusers have been reported. These may be more sequelae of recurrent gastric aspiration than the effects of

heroin, with or without pulmonary edema. Pulmonary function is abnormal in patients with pulmonary edema. Even after the radiographic clearance of the edema and the return of the lung volumes to normal, a reduction in the DL_{CO} may persist. In chronic abusers of heroin and other illicit intravenous drugs, pulmonary function abnormalities are more likely to be related to talc granulomatosis (see later) than to sequelae of a single acute injury.

METHADONE

Pulmonary sequelae similar to those associated with heroin have been reported with methadone and likely have similar mechanisms. Treatment is the same as for heroin-induced sequelae. Noncardiac pulmonary edema has been reported in cases of both oral and intravenous overdose of methadone.

METHYLPHENIDATE

Methylphenidate may have more serious adverse side effects than either heroin or cocaine.^{144,145} Methylphenidate can be abused either intravenously or orally. In one series of methylphenidate abuse, all 22 patients had chest pain and wheezing and most had abnormal pulmonary function tests and hemoptysis.¹⁴⁴ In another series, severe panlobular emphysema (eFig. 71-13) was found in 7 patients at autopsy.¹⁴⁵

COCAINE

Cocaine use remains a major problem throughout the world, and there are increasing reports of adverse pulmonary effects from both intravenous and inhalation use of the drug. These are over and above the known cardiac effects of cocaine, which produces left ventricular failure with pulmonary congestion and edema. The principal effects of cocaine are infection and aspiration, noncardiac pulmonary edema (eFig. 71-14), particulate embolization, talcosis, diffuse alveolar damage, diffuse alveolar hemorrhage (eFig. 71-15), intra-alveolar eosinophilic infiltration, lung mass with or without cavitation, and an organizing pneumonia pattern of lung injury (Table 71-3).^{146,147}

TALC GRANULOMATOSIS

Talc (magnesium silicate) and other agents, such as cellulose, are used as fillers in many medications intended for oral use. Addicts who abuse oral medications such as

meperidine, methadone, methylphenidate, amphetamines, and tripeleminamine often crush the tablets, mix them with various solutions, and inject them intravenously. This results in the insidious onset of granulomatous interstitial fibrosis, granulomatous pulmonary arterial occlusion, or both.¹⁴⁶⁻¹⁴⁸ In large series of consecutive autopsies done on addicts, depending on the type of addiction, the incidence of talc granulomatosis ranges from 15% to 80%.

Dyspnea is the major symptom, with cough in some patients; in more advanced stages of pulmonary hypertension, there may be exercise-induced syncope, right-sided heart failure, and even sudden death. Chest radiography may be normal in up to half of patients with proven talc granulomatosis. Pulmonary function studies characteristically show a low diffusing capacity before any other abnormalities are evident. Imaging in patients with injection granulomatosis may show diffuse micronodular densities varying in size between 1 and 3 mm (eFig. 71-16), which may mimic alveolar microlithiasis or hypersensitivity pneumonitis. Pulmonary opacities resulting from injection talcosis may show hyperattenuation at chest CT (eFig. 71-17). Therapy with corticosteroids provides little consistent improvement.

Histologically, the pulmonary tissue demonstrates granulomatous changes, with multinucleated giant cells, mononuclear inflammatory cells, lymphocytes, and fibrosis. Talc is detected by the presence of strongly birefringent crystals (using polarized light) within the granulomas (eFig. 71-18). BAL fluid shows an increased lymphocytosis and sometimes contains intracellular and free talc.

CARDIOVASCULAR DRUGS

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors are widely used for control of hypertension and in the management of congestive heart failure. Soon after their introduction, these agents were associated with nonproductive cough and more rarely with angioneurotic edema. Dry cough develops in 5% to 20% of patients on ACE inhibitors, being reported with captopril, enalapril, lisinopril, and virtually all other ACE inhibitors. The mechanism of ACE inhibitor-induced cough likely involves accumulation of kinins and substance P, which are degraded by ACE and other endopeptidases. The cough generally is reported in the first few weeks after beginning therapy but may not be appreciated for a number of months. ACE-induced cough is usually benign but can be quite annoying and causes the discontinuation of these agents in half of the patients affected. Exacerbation of bronchospasm has been associated with ACE inhibitors only on rare occasions. Fortunately, most patients can be switched to other classes of drugs. Rechallenge with a different ACE antagonist is not recommended as the cough will usually return. Cough generally abates within 4 days of discontinuation of the agent, providing confirmation of the diagnosis. Of note, selective angiotensin receptor antagonists have much lower incidence of dry cough compared with ACE inhibitors and may represent a therapeutic option for many patients.

Table 71-3 Principal Effects of Cocaine

Infection and aspiration leading to noncardiac pulmonary edema
Particulate embolization
Talcosis
Diffuse alveolar damage
Alveolar hemorrhage
Intra-alveolar eosinophilic infiltration
Lung mass with or without cavitation
Organizing pneumonia

ACE inhibitors cause angioedema much less frequently; this condition is reported in 0.1% to 0.2% of patients receiving ACE inhibitors. This complication usually arises within hours to, at most, 1 week after initiating therapy, and can be life-threatening. This reaction may be mediated by bradykinins but may also involve autoantibodies and complement system activation. Treatment is supportive and consists of airway protection. Although frequently used, epinephrine, antihistamines, and corticosteroid administration are of unclear value. The ACE inhibitor must be discontinued and future use avoided in these patients.

AMIODARONE

Amiodarone has significant benefit for ventricular and supraventricular dysrhythmias in patients who do not respond to most other antiarrhythmic agents. This drug is associated with a number of side effects, which include corneal microdeposits (in nearly 100% of the patients); peripheral neuropathy; liver dysfunction; thyroid dysfunction, including hypothyroidism and hyperthyroidism; and bluish pigmentation of the skin. However, the most serious side effect is an interstitial pneumonitis, which develops in up to 6% of patients and may be fatal.

The mechanism of amiodarone toxicity is unknown, but the toxicity is dose related and has distinctive histologic features. The histologic findings generally include foamy alveolar macrophages and type II pneumocytes containing lamellar inclusions. The incidence of pulmonary toxicity from amiodarone varies widely but probably averages 4% to 6% of those patients on the drug.^{11,149} The majority are men, but this may be related to increased use in men. Symptoms consist of insidious dyspnea, nonproductive cough, and occasionally a low-grade fever without chills, followed by subtle chest radiographic findings, which initially may be asymmetrical or even limited to the upper lobes. If the drug is continued, the process may diffusely involve the lungs with an interstitial or alveolar process. Pleural effusion is uncommon. Pleuritic chest pain exists in about 10% of patients. Crackles may be heard, but it is difficult to be certain whether these are due to pulmonary edema, because congestive heart failure is common in these patients. In about 20% of patients with amiodarone pneumonitis, the presentation will be acute, mimicking pneumonia (eFig. 71-19).

On laboratory studies, there is a normal to mildly elevated leukocyte count, generally no eosinophilia, and an elevated sedimentation rate, with little or no reactivity to antinuclear antibody. Pulmonary function studies disclose a decrease in the total lung capacity and DL_{CO} , as well as hypoxemia. There may be an increased predisposition to amiodarone pneumonitis if either pulmonary function or imaging findings are abnormal before administration of the drug begins.

The majority of the patients who develop amiodarone pneumonitis have been taking the drug for at least a month, and some for a few years. Most are receiving at least 400 mg/day. However, there have been a number of reports of amiodarone pneumonitis in patients taking as little as 200 mg/day. There are also reports of patients receiving 200 mg/day for months or even years and not developing amiodarone pneumonitis until the dose is boosted for better control

of the arrhythmia. Generally, the systemic side effects from amiodarone, such as peripheral neuropathy and liver dysfunction, correlate with the serum levels, but this is not necessarily the case with the pulmonary toxicity. Perhaps the greater phospholipid turnover in the lung explains the greater chance for lung toxicity from amiodarone. The diagnosis of amiodarone pneumonitis is one of exclusion.

Normally, amiodarone pneumonitis is thought to be primarily an interstitial or alveolar process (or both) sometimes mimicking eosinophilic pneumonitis with peripheral opacities (eFig. 71-20), but there are a number of reports of confluent lesions and other patterns (eFig. 71-21). Many of these lesions represent an organizing pneumonia injury pattern (see eFig. 71-23D).^{150,151} Chest CT imaging can further define these processes because amiodarone, being an iodinated compound, is radiopaque and, on a CT scan, the amiodarone pneumonitis lesions are denser than the surrounding soft tissue in the chest wall (Fig. 71-5, eFig. 71-22). This latter finding may help support the diagnosis.

Treatment consists of drug withdrawal and leads to a variety of responses. Some patients who were not treated with corticosteroids have died of pulmonary fibrosis and respiratory failure. Others have died in spite of being treated with corticosteroids. The majority respond to discontinuation of the drug and addition of corticosteroids (see eFigs. 71-19 and 71-21), which are usually required for a period of at least 2 and perhaps 6 months or longer. There are many case reports of patients who continued on amiodarone because it was the only drug that controlled their arrhythmia and who at the same time were given corticosteroids to suppress their pneumonic reaction.¹⁵²

Initially, it was believed that tissue confirmation was necessary to establish a diagnosis, although stopping the drug and adding corticosteroids may offer a presumptive diagnosis if the process clears. BAL produces variable results.¹¹ The presence of foamy macrophages in lavage fluid or on biopsy only confirms exposure to the drug; their presence alone

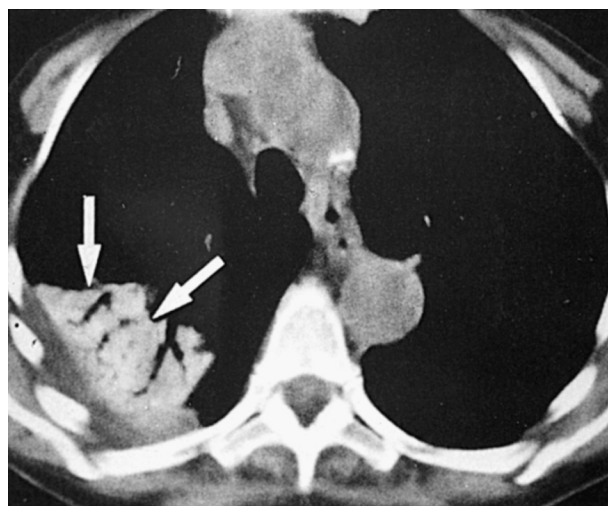


Figure 71-5 Amiodarone-induced lung disease. A chest CT scan showing confluent pulmonary masses (arrows) from amiodarone pneumonitis. Note that the masses are appreciably denser than the surrounding soft tissue in the chest wall in this CT scan obtained without contrast.

Table 71-4 Drugs or Treatment Associated with the Induction of Organizing Pneumonitis

Bleomycin	Interferons
Amiodarone	Methotrexate
Gold	Mitomycin C
Penicillamine	Cyclophosphamide
Sulfasalazine	Cocaine
Radiation	

does not necessarily indicate amiodarone toxicity. Their absence does not exclude the diagnosis, however. Although not used frequently in recent years, a positive ^{67}Ga scan can be highly suggestive of an inflammatory pneumonitis rather than congestive heart failure. If the diagnosis has not been established, the clinician must decide whether to proceed with an open-lung biopsy to rule out other disease processes or to consider diminishing the dose or discontinuing the drug, or adding corticosteroids, or both. A lung biopsy usually reveals the foamy macrophages and epithelial cells, as well as variable inflammatory cell infiltration (eFig. 71-23). The histopathologic patterns of amiodarone-induced pulmonary injury vary, with the most common pattern of injury being a cellular interstitial pneumonia (see eFig. 71-23). However, some patients may exhibit an organizing pneumonia injury pattern (Table 71-4, see eFig. 71-23D). Reductions in sedimentation rate following discontinuation or reduction of amiodarone dosage may be of further value in establishing the diagnosis.

There are reports that patients on amiodarone can develop a postoperative ARDS, an injury that begins 18 to 72 hours after surgery. Several of these patients have died as a result.^{153,154} In a recent population-based study, amiodarone was responsible for approximately 2.7% of cases of acute lung injury.¹⁵⁴ It has been postulated that the high fraction of inspired oxygen given during the operation and the postoperative period contributes to this complication.

PROTAMINE

Protamine sulfate is used to reverse the anticoagulant effects of heparin following cardiovascular surgical procedures. Systemic hypotension is not uncommon following administration of this drug. However, there have been a number of cases of noncardiogenic pulmonary edema within minutes to 1 or 2 hours after the administration of the drug.¹⁵⁵ It is frequently associated with an anaphylactic reaction and bronchospasm, an increase in pulmonary artery pressure with normal wedge pressure, and hypotension. In at least half of the patients there is a history of previous use of protamine, either in a similar situation or as protamine zinc insulin. Skin testing can confirm the sensitization. Therapy is supportive, including reintubation if the patient has been extubated, assisted ventilation with high inspired oxygen concentrations, administration of high-dose corticosteroids, and treatment of hypotension with an α -adrenergic agonist. In patients whose skin test is positive to protamine or who have a history of reaction to protamine, intravenous hexadimethrine can be used to reverse the effects of heparin.

β -ADRENERGIC ANTAGONISTS

β -Adrenergic antagonists are among the most commonly prescribed drugs. β -Adrenergic receptors can be divided into excitatory β_1 -receptors, located in the heart, and inhibitory β_2 -receptors, located in the bronchi. The β -adrenergic blockers, or β -blockers, are competitive antagonists.

Propranolol was the first β -adrenergic antagonist introduced. It was quickly recognized that it had adverse effects on individuals with known obstructive lung disease. Studies have also demonstrated that propranolol increased airway resistance in normal persons and in asymptomatic asthmatic patients.¹⁵⁶ Thus this agent should be avoided in all patients with known obstructive lung disease, even those who are asymptomatic. The following β -adrenergic antagonists, presented in decreasing order of bronchoprovocation potential, are available for clinical use in the United States: propranolol, timolol, nadolol, metoprolol, atenolol, and labetalol.¹⁵⁷

Two features of β -adrenergic antagonists predict their potential for bronchoprovocation: their cardioselectivity and their intrinsic sympathomimetic activity. Generally, cardioselectivity is the more important of the two in avoiding bronchoconstriction; if the drug is cardioselective, it has little effect on the inhibitory β -receptors located in the bronchial walls. Propranolol, timolol, and nadolol have essentially no cardioselectivity and thus have a higher bronchoprovocation potential. Metoprolol has some cardioselectivity, and atenolol has considerable cardioselectivity, making atenolol one of the drugs of choice in an individual with obstructive airway disease who needs a β -adrenergic antagonist. The other mechanism important in avoiding bronchoconstriction with β -adrenergic antagonists is intrinsic sympathomimetic activity; pindolol has strong intrinsic sympathomimetic activity, accounting for its lower bronchoprovocation potential. As an exception to the rule, labetalol is unique in that it has the lowest bronchoprovocation potential despite not having cardioselectivity or intrinsic sympathomimetic activity. It does have combined α - and β -antagonist effects. Thus it is assumed that its α -adrenergic antagonist potential causes it to be bronchoprotective.

Thus, among the seven drugs listed, atenolol and then metoprolol and probably labetalol are the three that can be used with relative safety in persons with obstructive lung disease, if absolutely necessary. However, these should always be given in conjunction with an aerosolized β_2 -adrenergic agent. Calcium channel blockers may be a good alternative to β -blocking drugs, if indicated, because they also may have some bronchodilating capabilities.

The same findings have been described in asthmatic patients receiving timolol eye drops for glaucoma. There are many case reports of the adverse effects of topical ocular timolol, including a number of fatal cases of status asthmaticus.¹⁵⁸ Topically applied timolol is absorbed through the conjunctiva and bypasses the liver, resulting in a higher serum concentration than when given orally. A novel ocular β -adrenergic antagonist, betaxolol, has been shown to be safer in patients with known airway disease. There are scattered reports of β -blocker-associated interstitial pneumonitis.¹⁵⁹ Propafenone is an additional membrane-stabilizing antiarrhythmic agent that is structurally similar to propranolol and has the potential to aggravate bronchospasm.¹⁶⁰

TOCAINIDE AND FLECAINIDE

Tocainide is used in the treatment of refractory ventricular arrhythmias. There are more than 100 known cases of acute interstitial pneumonitis beginning 3 weeks to several months after initiation of therapy.¹⁶¹ The response to discontinuing the drug is good; corticosteroids may be necessary in some cases. Flecainide, another antiarrhythmic agent, has been reported to be associated with the ARDS and an interstitial lymphocytic pneumonitis.^{35,162}

ANTI-INFLAMMATORY AGENTS

ASPIRIN

Anti-inflammatory agents are among the most commonly used drugs, and many have pulmonary side effects. Aspirin is the most commonly used drug in the world. In the United States, there are more than 200 proprietary drugs that contain aspirin. It is estimated that up to 5% of asthmatics are sensitive to aspirin; ingestion may cause fatal aggravation of bronchospasm.¹⁶³ The exact cause of aspirin-sensitive asthma is unknown. One theory is that, by inhibiting cyclooxygenase, aspirin and similar compounds prevent the generation of cyclooxygenase products such as the prostaglandins. If certain individuals are reliant on the bronchodilator activity of prostaglandins such as prostaglandin E₂, their inhibition could cause bronchospasm. The aspirin-asthma triad consists of asthma, rhinitis, and nasal polyposis. Almost always there are other associated side effects, such as cutaneous rashes and gastrointestinal symptoms. These adverse reactions are not dose related because they can develop with very small doses. Salicylates can induce noncardiac pulmonary edema in cases of overdose when the serum salicylate level is greater than 40 mg/dL.

OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Most of the nonsteroidal anti-inflammatory agents can produce the same side effects as aspirin, including aggravation of asthma, noncardiac pulmonary edema, drug-induced SLE, and pulmonary opacities with eosinophilia. Naproxen may be more commonly associated with an opacity and eosinophilia than are the other agents.¹⁶⁴ A few agents can cause hypervolemia and, in turn, pulmonary edema through the mechanism of increased sodium retention through the kidneys.

Penicillamine

Penicillamine is used to treat Wilson disease, rheumatoid arthritis, and cystinuria and has been associated with pulmonary toxicity. There are three possible pulmonary complications with the use of penicillamine with no apparent overlap: penicillamine-induced SLE, bronchiolitis obliterans, and Goodpasture syndrome. Penicillamine-induced SLE may induce pneumonitis, alveolitis, and sometimes pleural effusion. Penicillamine-associated bronchiolitis obliterans is probably underestimated in its incidence and severity. Corticosteroids have little benefit in treating this

condition, which usually presents in an advanced state. There have also been several case reports of penicillamine-associated Goodpasture syndrome with diffuse alveolar hemorrhage.¹⁶⁵ If recognized early enough, appropriate therapy with hemodialysis, plasmapheresis, and immunosuppression may prevent a serious outcome.

Leflunomide

Several new agents have in recent years been found to be efficacious in the treatment of inflammatory conditions with a considerably improved safety profile when compared with the previous regimens used. Leflunomide received its FDA approval in 1998 and is currently used to treat rheumatoid arthritis and psoriatic arthritis. It is a pyrimidine synthesis inhibitor, which exerts mainly an immunomodulating effect, although it was also found to exert significant anti-inflammatory effects. Its main described adverse effect is liver toxicity, and it may act synergistically with methotrexate. Several patterns of lung injury have been observed with leflunomide, mostly consisting of hypersensitivity reactions. In a postmarketing surveillance study, significant lung toxicity was identified in 61 of 5053 patients, with 24 patient deaths directly related to the pulmonary complications. Preexisting lung disease and, to a lesser degree, loading dose, a smoking history, and low body weight have been identified as independent risk factors. A case-control study also showed a higher incidence of lung toxicity in those with prior lung disease but suggested that was because higher-risk patients were more likely to receive leflunomide.¹⁶⁶ True hypersensitivity pneumonias have also been reported in case series, as defined by interstitial opacities associated with ill-defined granulomas.¹⁶⁷ Nonspecific opacities with or without eosinophilia have also been reported. Diffuse alveolar hemorrhage and pulmonary alveolar proteinosis are rarely encountered. Cholestyramine wash-out therapy has been shown to treat leflunomide-induced pneumonitis; oral cholestyramine binds the drug and its metabolites, removes them from the body, and greatly shortens their otherwise long half-life.¹⁶⁸

BIOLOGIC AGENTS

These agents have truly revolutionized the management of a number of chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis. *Antitumor necrosis factor- α* (TNF- α) medications such as infliximab (a chimeric monoclonal antibody targeting TNF- α), etanercept (a soluble TNF- α receptor), or adalimumab (recombinant monoclonal antibody targeting TNF- α) have been used with various success in these conditions by directly interfering with the first steps of the inflammatory cascade. Not unexpectedly, infections are a major complication of these treatments—tuberculosis, in particular, may easily reactivate in a context of impaired T-cell immunity. Tuberculosis skin tests or interferon-gamma release assays for *Mycobacterium tuberculosis* are mandatory before initiation of treatment. Extrapulmonary manifestations seem relatively common (40 of 70 patients in an initial report), with most cases reported in areas with a low incidence of tuberculosis, perhaps because these drugs tend to be used in more developed countries. Interestingly, other

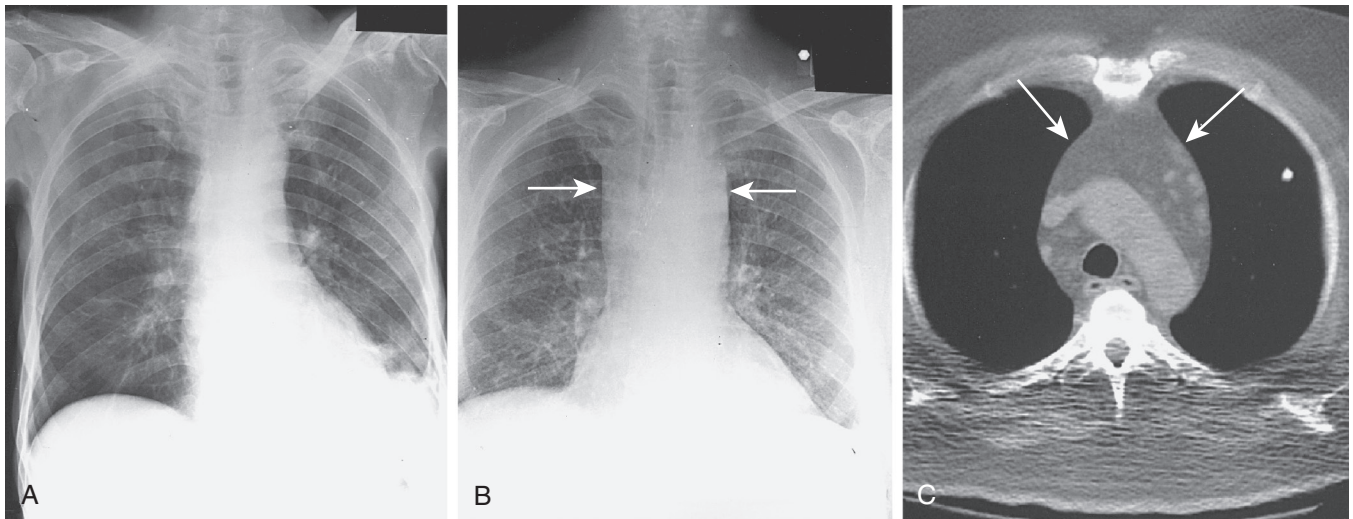


Figure 71-6 Mediastinal lipomatosis in response to corticosteroids. **A**, Chest radiograph before systemic corticosteroid administration. **B**, Chest radiograph after corticosteroid administration shows widened mediastinum (arrows). **C**, Chest CT scan shows mediastinal lipomatosis, with radiographic fat density (arrows) surrounding the great vessels and tracheal shadows.

opportunistic infections, including fungal lung infections, although described, are less of a concern with these agents. Multiple patterns of lung injury have been described with infliximab, including acute hypersensitivity reactions with or without eosinophilia, nonspecific interstitial pneumonitis, *de novo* usual interstitial pneumonia (UIP), or exacerbation of rheumatoid arthritis–associated UIP and vasculitis.¹⁶⁹ Two other anti-TNF- α medications, adalimumab (eFig. 71-24) and etanercept, have also been described in association with pulmonary fibrosis, but these associations are relatively weak and mainly based on isolated case reports.^{170,171} Etanercept has also been associated with pulmonary granulomatous inflammation.¹⁷²

LEUKOTRIENE ANTAGONISTS

The potent antiasthma agents, zafirlukast, montelukast, and pranlukast, have been associated with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).¹⁷³⁻¹⁷⁵ A number of cases have been described with patients exhibiting pulmonary opacities, cardiomyopathy, and eosinophilia while receiving zafirlukast. A systematic review of the cases reported in the literature identified 62 cases of eosinophilic granulomatosis with polyangiitis after initiation of leukotriene antagonists.¹⁷⁵ Although some of the cases may have had preexisting eosinophilic granulomatosis with polyangiitis, many demonstrated a temporal relationship to the leukotriene antagonist.¹⁷⁵ As a leukotriene antagonist is added to an asthmatic treatment regimen, corticosteroids are frequently tapered, suggesting that some of the effects of adding leukotriene antagonists are actually effects of tapering corticosteroids. However, a small number of these patients were not receiving oral or inhaled corticosteroid at the time the medication was added. Eosinophilic granulomatosis with polyangiitis developed 6 to 18 months after initiation of the leukotriene antagonist. Remission of the signs and symptoms were noted with removal of the leukotriene antagonist with or without escalation of treatment. It is currently unknown whether these medications

actually trigger these reactions or whether they are unmasking a preexistent infiltrative eosinophilic disorder.¹⁷⁵ In either event, the pulmonary reaction responds to discontinuation of the leukotriene antagonist and reinstitution of corticosteroids.

CORTICOSTEROIDS

Corticosteroids given in immunosuppressive doses are well known for predisposing to the development of opportunistic infections. A most unusual adverse effect of corticosteroids is mediastinal lipomatosis, the deposition of mediastinal fat, which produces a widening of the mediastinum that mimics lymphadenopathy or other neoplasms (Fig. 71-6). Clinically, these patients have a cushingoid appearance, with rounded facies and a “buffalo hump.” The same kind of fat that deposits in the buffalo hump can deposit in the mediastinum. The chest radiograph does not show the lumpiness usually expected with adenopathy. Chest CT can usually make this diagnosis by establishing fat density throughout the mediastinal mass (see Fig. 71-6). Mediastinal lipomatosis does not necessitate tapering corticosteroids because the fat does not compromise vital structures.

DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

Of more than 50 drugs associated with SLE, only 5 regularly induce antinuclear antibodies in patients taking them: hydralazine, procainamide, isoniazid, phenytoin, and penicillamine and only a small percentage of the patients on these drugs develop the clinical lupus-like syndrome. It is thought that patients who develop antinuclear antibodies to these drugs are *slow acetylators*, with a slower rate of metabolism of the offending drug. Symptoms almost always begin insidiously after the patient has been taking the drug for many months or even years. Systemic signs and

symptoms of polyarthralgia, myalgia, fever, pleurisy, and cutaneous lesions are common. However, renal disease is uncommon, possibly because complement is not as often involved in the drug-induced form of SLE compared with the spontaneous type.

The antinuclear antibody assay is positive in all patients with drug-induced SLE. However, the test for antinative (anti-double-stranded) DNA is negative. The complement level may or may not be abnormal. A Coombs test is positive in about one third of patients. An elevated erythrocyte sedimentation rate and hypergammaglobulinemia are common nonspecific findings.

The chest radiographic findings of the drug-induced form of the disease are indistinguishable from spontaneous-onset SLE and include pleural effusions in one third of patients, basilar opacities, pneumonitis with atelectasis, and apparent cardiomegaly from pericardial effusion. Pleural fluid glucose is normal or at least correlates with the blood glucose levels.

The symptoms usually resolve once the drug is discontinued. However, occasionally it is necessary to add corticosteroids for more rapid resolution of disabling symptoms. If the offending drug cannot be discontinued for clinical reasons, the lowest dose should be used, along with the addition of corticosteroids.

INHALANTS

OIL

Aspirated oil can produce a variety of pulmonary diseases, ranging from an asymptomatic solitary nodule to diffuse disease with severe respiratory insufficiency.^{176,177} Most commonly, however, the disease presents in an asymptomatic individual with an incidental finding of an abnormal chest radiograph that mimics a more serious process such as bronchogenic carcinoma. Because patients rarely consider oily nose drops, oily eye lubricants, and mineral oil as medications, they rarely volunteer that they are taking oil-containing medications.

There are three types of oil: mineral oils, neutral oils, and animal fats. Mineral oils are the most commonly aspirated oils. Oily droplets are taken up by macrophages that eventually die and release the oil, which in turn inhibits ciliary activity. Thus the oil is not expectorated and the cycle is repeated. Eventually, the oil incites a fibrotic or granulomatous reaction. Neutral or vegetable oils (e.g., olive or castor oil) do not elicit a local reaction and can be removed by expectoration. Animal fats (e.g., milk, butter) are rapidly hydrolyzed, with the liberated fatty acids producing tissue necrosis and subsequent fibrosis. The diagnosis can be established with the demonstration of oil in the lung tissue. CT and magnetic resonance imaging have been used in diagnosing lipid-induced opacities.¹⁷⁶ The "CT angiogram" sign, defined by the ability to distinguish the pulmonary vasculature within an area of consolidation, was once thought to be fairly specific for lipid pneumonitis but may be seen in a variety of unrelated conditions. Treatment involves the discontinuation of the oil-containing medication. With discontinuation, progression is unlikely.

OXYGEN

Exposure to high concentrations of oxygen may contribute to or aggravate the ARDS. There are two theories as to the mechanism of oxygen-induced pulmonary disease. The first is that a high fraction of inspired oxygen induces formation and release of free oxidant radicals. These short-lived molecules damage DNA, destroy lipid membranes, and inactivate intracellular enzymes.¹⁷⁸ The other theory is that hyperoxia produces a direct injury to endothelial cells and type I epithelial cells, which results in alveolar-capillary leak.¹⁷⁹

Studies in volunteers breathing 100% oxygen for 6 to 48 hours produced variable effects, but some developed a tracheobronchitis, with symptoms of substernal burning, chest tightness, and nonproductive cough. It also produced a reduction in vital capacity and DL_{CO} . The development of tolerance to hyperoxia appears to be related to the ability of the individual to increase the production of antioxidants, a mechanism that may be determined genetically.

The sequelae of oxygen toxicity are separable into two phases, the acute, or exudative, phase and the subacute proliferative phase; however, there is considerable overlap between the two phases, with the proliferative phase beginning after the fourth to seventh day. The exudative phase begins within 48 to 72 hours, depending on the fraction of inspired oxygen, and is associated with perivascular, interstitial, and alveolar edema with atelectasis, as well as alveolar hemorrhage. This phase appears to be reversible.

The proliferative phase is characterized by progressive resorption of exudates and hyperplasia of type II cells. This is followed by the deposition of collagen and elastin in the interstitium and hyaline membrane deposition. This is usually an irreversible phase. Clinically, hypoxemia and diminished compliance progress, requiring a greater fraction of inspired oxygen and assisted ventilation, further aggravating the problem. Imaging shows an alveolar-interstitial pattern in an irregular distribution, with evidence of moderate loss of volume from patchy atelectasis.

There is no clinical way of diagnosing oxygen toxicity. A lung biopsy specimen may show changes consistent with oxygen toxicity, but the primary value of the biopsy is to exclude other causes of lung injury. Keeping the arterial PO_2 less than 80 mm Hg or the inspired fraction of oxygen below 0.40 to 0.50 minimizes the likelihood of oxygen toxicity. Barotrauma and ventilator-induced injury may accompany and be indistinguishable from oxygen toxicity.

MISCELLANEOUS DRUGS/AGENTS

RADIOGRAPHIC CONTRAST MEDIUM-INDUCED LEUKOSTASIS

The symptoms and signs produced by complement-induced granulocyte aggregation associated with radiographic contrast media are frequently attributed to an allergic reaction and may cause noncardiac pulmonary edema. Anaphylaxis as a cause can be eliminated by the absence of urticaria or other rash, and by the absence of significant laryngeal edema or bronchospasm. Histologic examination of the lungs demonstrates aggregates of granulocytes obstructing

microscopic pulmonary arterioles and capillaries. These findings can be overlooked if not carefully sought or if the autopsy or examination of lung tissue is not done within a few hours of the reaction.

Clinically, the onset of symptoms of dyspnea and hypoxemia begins within a few minutes to an hour of the injection of the radiographic contrast medium. There is not necessarily a history of an allergic reaction to iodine. Treatment is supportive and includes a trial of high-dose corticosteroids, although this may be ineffective.

The activation of complement and, in turn, the generation of C5a stimulates granulocytes to aggregate and to adhere to endothelium, releasing proteases and toxic oxygen compounds. These, in turn, produce endothelial damage and capillary leakage. One study found high postmortem plasma histamine levels, which were thought to represent mast cell activation.¹⁸²

TOCOLYTIC-INDUCED PULMONARY EDEMA

Tocolytics are agents that have been widely used in the treatment of premature labor. The most commonly used drugs are terbutaline, albuterol, ritodrine, and other β -mimetic drugs. There are many reports of these agents inducing pulmonary edema in otherwise healthy women. The incidence varies from 0.5% to 5%. Predisposing factors include the use of corticosteroids, twin gestation, fluid overload (particularly with saline), and anemia. The β -mimetic drugs typically stimulate β_2 -adrenergic receptors, increase the maternal pulse rate and the cardiac output, and produce peripheral vasodilation. Hemodilution can be detected by a drop in the hemoglobin, hematocrit, and albumin. The blood pressure may drop as a result of the peripheral vasodilation.

A typical clinical scenario is as follows. In spite of the tocolytic agent, labor continues; the tocolytic agent is then stopped, and corticosteroids are added to accelerate fetal lung maturation. With the discontinuation of the tocolytic, the vasodilated vessels return to normal tone. During delivery, uterine contractions lead to autotransfusion. The increased venous tone and the increased blood volume can then lead to pulmonary edema, usually in the postpartum period.

There are conflicting reports of the wedge pressure ranging from normal to elevated. In one study, patients with an elevated wedge pressure had normal left ventricular function by echocardiography. At this point, it is uncertain whether the pulmonary edema is truly cardiac or noncardiac in origin.

The treatment is oxygen and diuresis. In certain cases, consideration has been given to resuming the tocolytic agent to recreate the previous peripheral vasodilation. Corticosteroids aggravate the situation by their mineralocorticoid effect, which promotes fluid retention. The differential diagnosis includes aspiration of gastric contents, left-sided heart failure, amniotic fluid embolism, and overtransfusion.

HYDROCHLOROTHIAZIDE

More than 40 reported cases of acute onset of diffuse pulmonary opacities are associated with hydrochlorothiazide.¹⁸⁰

It may begin with the first dose or days later; 90% of cases have been reported in women who take the drug intermittently rather than daily, presumably for fluid retention. Symptoms consist of fairly rapid onset of dyspnea that clears 48 to 72 hours after discontinuing the drug. A low-grade fever may be present. Eosinophilia and antinuclear antibodies are not present. The chest radiograph shows diffuse bilateral alveolar-interstitial opacities. In the few cases studied, the pulmonary capillary wedge pressure was normal.

METHYSERGIDE, BROMOCRIPTINE, AND CABERGOLINE

Methysergide, bromocriptine, and cabergoline are structurally similar and produce similar pleuropulmonary reactions. Methysergide is now rarely used to treat vascular headaches because there are better alternative drugs. Bromocriptine and cabergoline are used for the treatment of Parkinson disease. The pleuropulmonary disease produced by both of these agents has an insidious onset. The predominant feature is pleural thickening and effusion, which is reversible by discontinuing the medication. Effusions are rarely large, are not commonly associated with pleuritic pain, and may show lymphocytosis.¹⁸¹

DEXTRAN

Hyskon is a low-molecular-weight dextran that is capable of producing a noncardiac pulmonary edema.¹⁸² It is used principally in hysteroscopic surgery, most often for improving fertility, during which the endometrial cavity is distended with approximately 500 mL of low-molecular-weight dextran. The incidence of noncardiac pulmonary edema increases significantly if more than 500 mL is used, endometrial surfaces are excessively irritated, or the procedure lasts more than 45 minutes. In addition to noncardiac pulmonary edema, coagulopathy can also develop.

AMPHETAMINERGIC AGENTS

In the 1960s, excess cases of pulmonary hypertension were associated with the potent anorexigen aminorex fumarate. More recently, pulmonary hypertension has been associated with dexfenfluramine, fenfluramine, and phenteramine.¹⁸³ Valvular heart disease has also been associated with these agents.¹⁸⁴ Although these agents were removed from the market in 2004, a careful drug history must be taken to exclude this possibility in patients presenting with dyspnea, cardiovascular symptoms, or heart murmurs because manifestations typically persist despite discontinuation of the drugs. A retrospective study on 340 patients with pulmonary hypertension identified a history of stimulant use in 29% of them, including methamphetamine, amphetamine, and cocaine, emphasizing the importance of seeking this part of history that may not be easily volunteered by the patients.

ESOPHAGEAL VARICEAL SCLEROTHERAPY

Esophageal variceal sclerotherapy with either sodium morrhuate, sodium tetradecyl sulfate, or ethanolamine oleate

can lead to multiple abnormalities. Typically about 1 mL of one of these substances is injected into or around the varices, and up to 15 to 20 injections are made during a single procedure. Chest radiographs performed shortly after the procedure were abnormal in 85% of the cases at the Mayo Clinic, but this was rarely of clinical significance.¹⁸⁵ Pleural effusion was seen in about 25% of patients, mediastinal widening in 33%, atelectasis in 12%, and pulmonary opacities in 9%. Fever, chest pain, and difficulty in swallowing were common after the procedure but were rarely serious.

In the literature, pleural effusion has been described in up to 50% of the patients; most of these patients were asymptomatic.¹⁸⁵ Effusions were more common when a large volume of fluid was injected and the volume per site was increased. Serious complications such as mediastinitis or frank esophageal rupture are rare but should be suspected if the fever persists for more than 24 hours, the pleural effusion is large, or chest pain persists. ARDS happens in less than 1% of the patients undergoing sclerotherapy.

PHENYTOIN

There has been much confusion in the literature as to whether or not phenytoin produces parenchymal pulmonary disease and mediastinal adenopathy. Reports in the affirmative have been followed by a more detailed patient study refuting the possibility of pulmonary parenchymal disease.^{186,187} The only two phenytoin-induced pulmonary diseases are drug-induced SLE and a few rare cases of hypersensitivity pneumonitis that show a predominance of lymphocytes found in the BAL fluid or biopsied tissue. The fact that phenytoin is one of the more commonly used drugs over extremely long periods of time and that it has not shown an obvious relationship for the induction of significant pulmonary disease makes it unlikely that there is a true relationship of any consequence.

DANTROLENE

Dantrolene is a long-acting skeletal muscle relaxant used in treating patients with spastic neurologic disorders.¹⁸⁸ There have been several case reports of chronic pleural effusion or pericarditis, or both, associated with this drug. Peripheral blood eosinophilia was seen in some patients who were taking dantrolene.

Key Points

- The frequency of drug-induced pulmonary toxicity may be underestimated because the diagnosis is one of exclusion in the vast majority of cases. Clinicians must maintain a high index of suspicion that unexplained pulmonary disease may be caused by medications.
- Most associations are based on anecdotal reports and circumstantial evidence.
- Potential mechanisms of lung injury include (1) oxidative injury, (2) direct cytotoxic effect, (3) accumulation of phospholipids, and (4) immune-mediated injury.
- Chemotherapy-induced lung toxicity should always be considered in the differential diagnosis of diffuse lung opacities because virtually all histopathologic presentations have been described.
- Even in situations in which cumulative toxicity is an issue, screening via serial imaging or physiologic studies is rarely helpful.
- Most drug-induced pulmonary reactions are reversible if the drug is stopped. If necessary, additional measures such as judicious use of corticosteroids may be helpful.
- Rechallenging the patient with the suspected drug is often dangerous and generally not indicated.
- If there is a question of whether or not a medication may be the cause of a particular pulmonary abnormality, one option is to call the medical director of the drug manufacturer, listed in the *Physicians' Desk Reference*. In addition, a useful website can be accessed at <http://www.pneumotox.com>.

Complete reference list available at ExpertConsult.

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eFIGURE IMAGE GALLERY

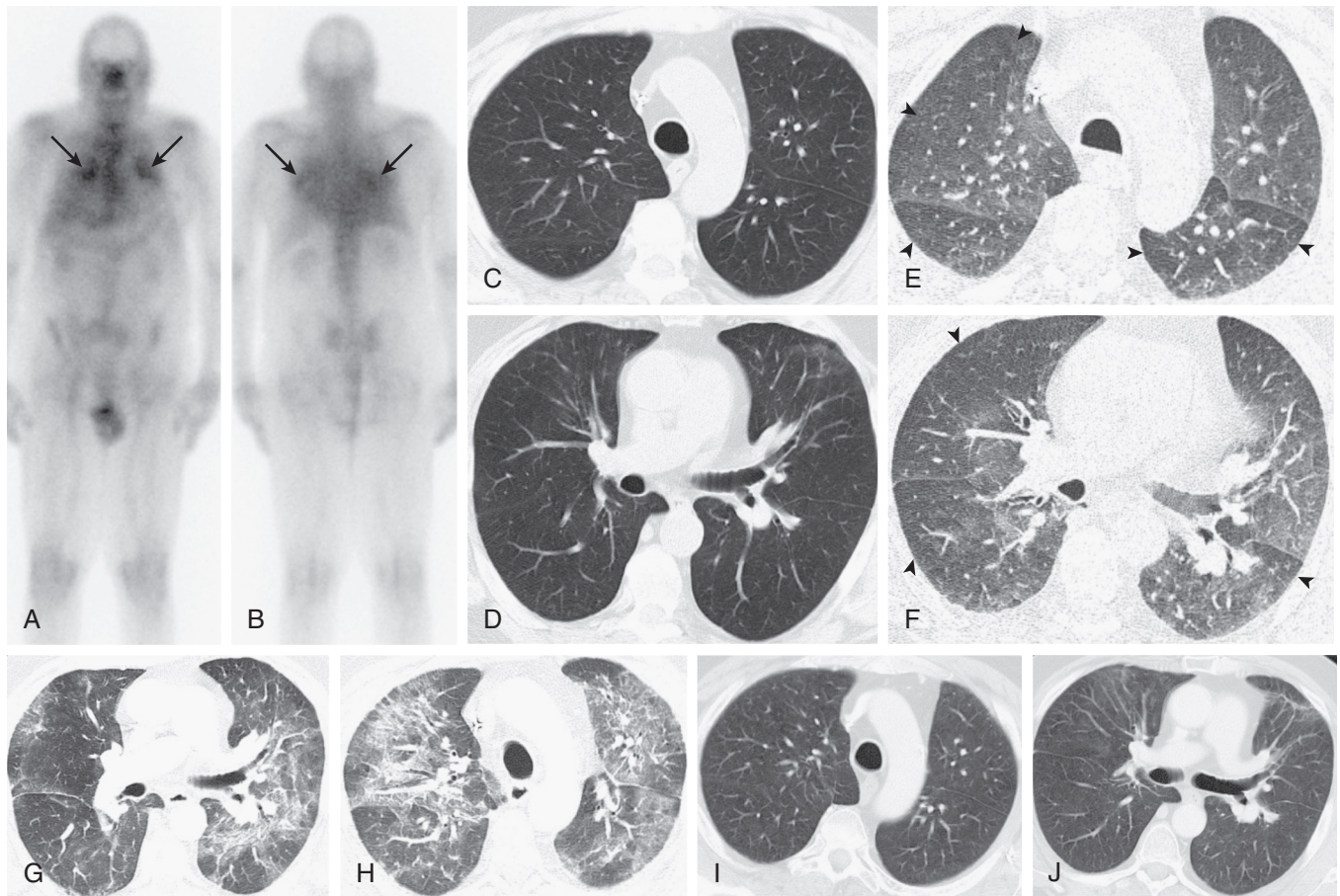
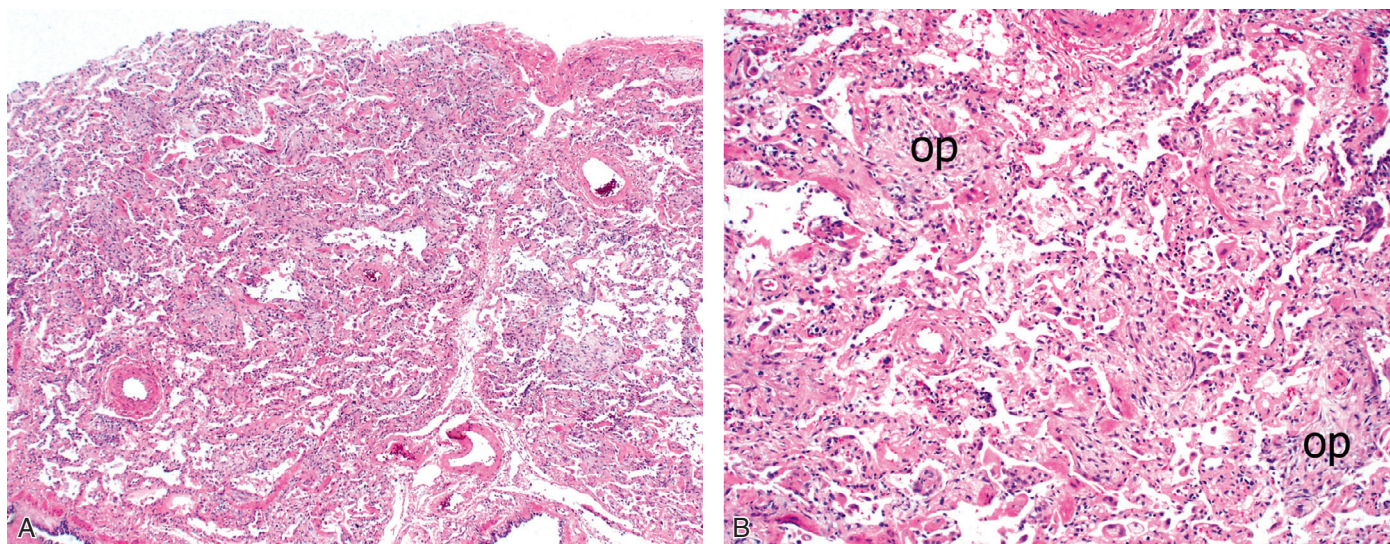
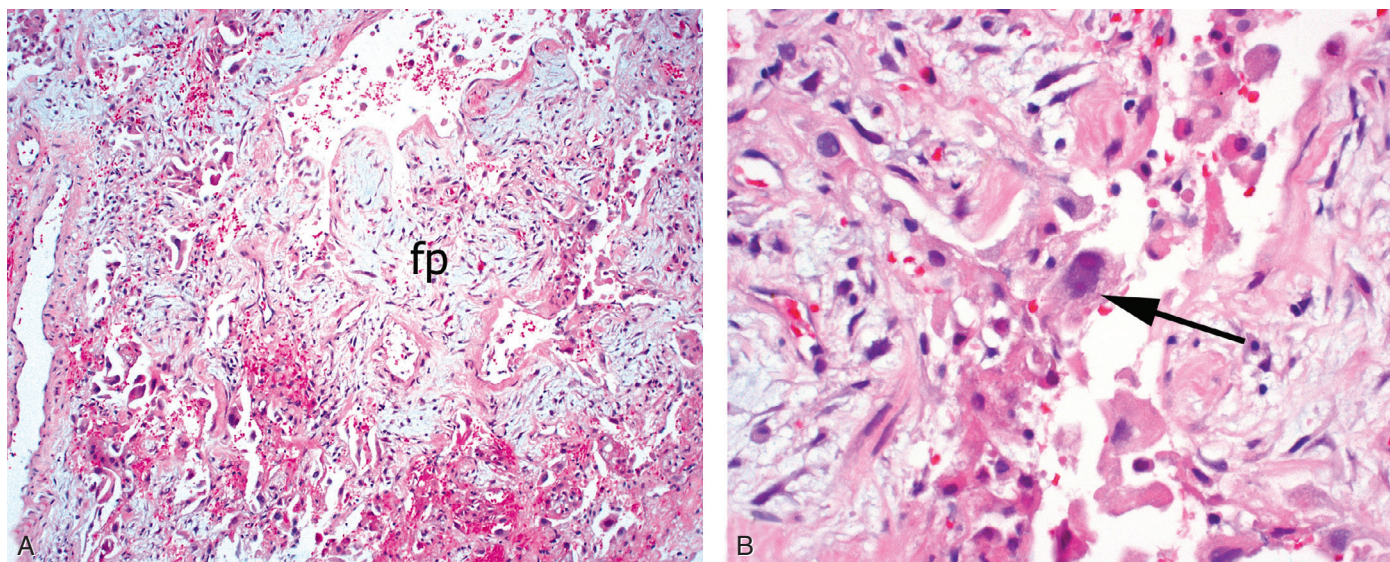


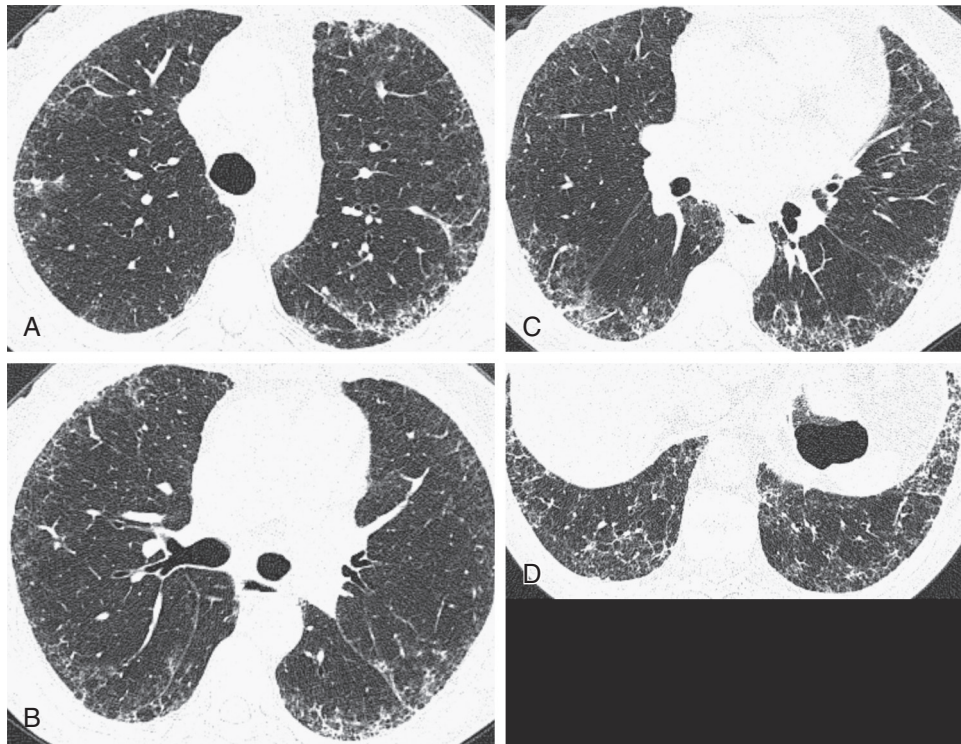
Figure 71-1 Bleomycin-induced lung injury; hypersensitivity reaction. Anterior (A) and posterior (B) planar ⁶⁸Ga scintigraphic images in a patient with Hodgkin lymphoma treated with bleomycin shows increased uptake in the lungs (arrows) in a symmetric, bilateral distribution. C–F, Axial chest CT obtained at the same time as the nuclear study (A and B) shows little evidence of an infiltrative abnormality on inspiratory images (C and D). On expiratory imaging, areas of decreased lung attenuation (E and F, arrowheads) are evident, representing air trapping and suggesting a small airway obstructive process. This pattern suggests bronchiolitis obliterans but can rarely be seen with hypersensitivity reactions. G and H, Axial chest CT obtained 2 weeks following (C–F) shows interval development of multifocal, bilateral areas of ground-glass opacity and reticulation; this pattern is consistent with an acute lung injury pattern, although the presence of the small airway obstruction, as shown on the initial CT (C–F), suggests a combined infiltrative and obstructive disorder, which is typical of a hypersensitivity reaction. Evaluation for infection and pulmonary hemorrhage was unrevealing. I and J, Axial chest CT following withdrawal of bleomycin, obtained 4 months following (C–F), shows clearing of the infiltrative lung opacity with minimal anterior lung scarring remaining. (Courtesy Michael Gotway, MD.)



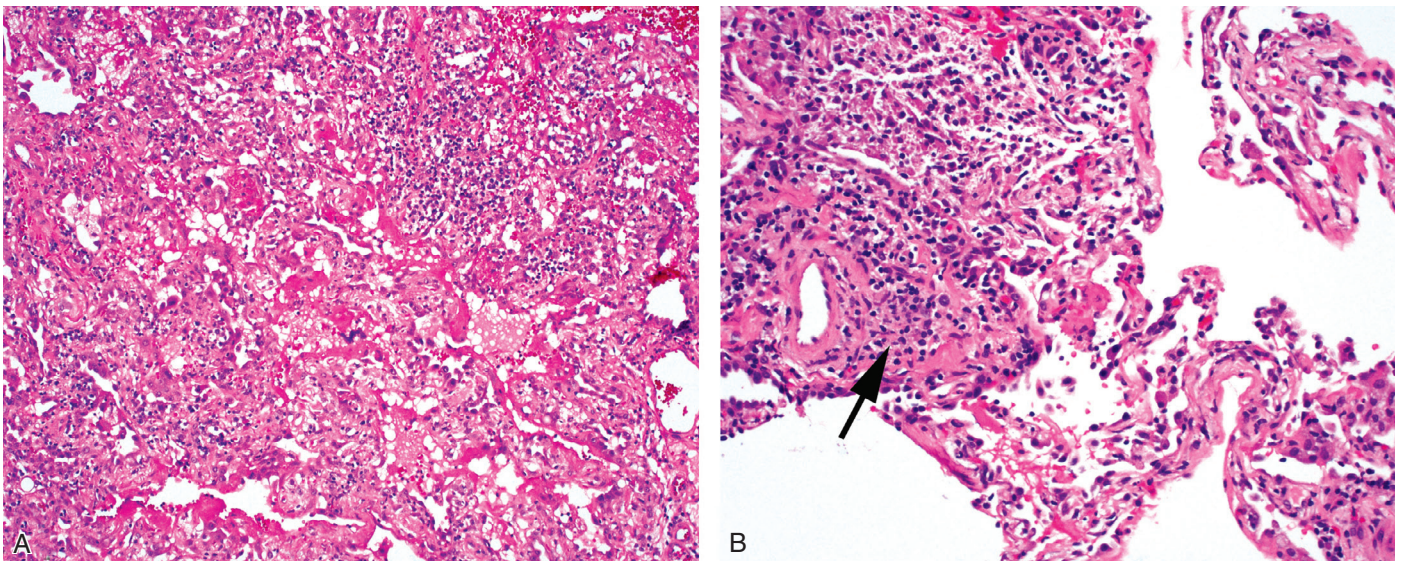
eFigure 71-2 Histopathologic patterns of bleomycin-induced pulmonary injury. **A**, Diffuse alveolar damage from bleomycin toxicity. **B**, Reactive type II cells and organizing pneumonia (*op*) are commonly found. (From Cheung Y, Graziano P, Leslie KO: Acute lung injury. In Leslie KO, Wick MR, editors: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 117–137, Fig. 5-28.)



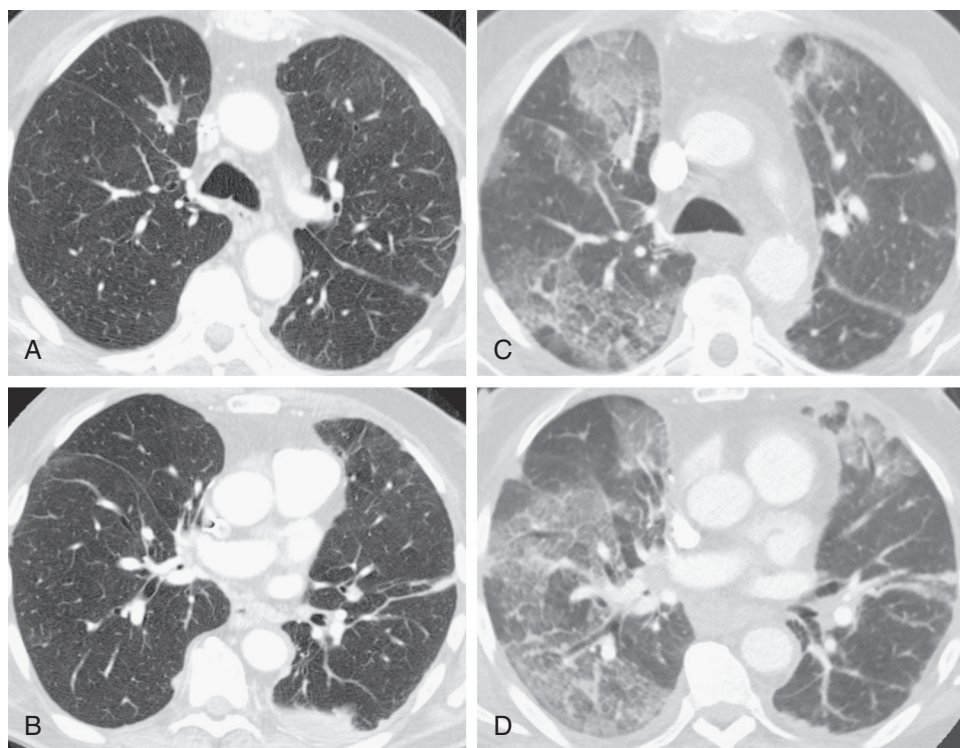
eFigure 71-3 Diffuse alveolar damage from busulfan toxicity. **A**, Busulfan can produce diffuse injury characterized by the presence of prominently atypical type II cells. In this case, prominent interstitial organization with edematous fibroblastic proliferation is seen (*fp*), and hyaline membranes are evident. **B**, Reactive type II cells may appear alarmingly atypical (*arrow*). (From Cheung Y, Graziano P, Leslie KO: Acute lung injury. In Leslie KO, Wick MR, editors: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 117–137, Fig. 5-29.)



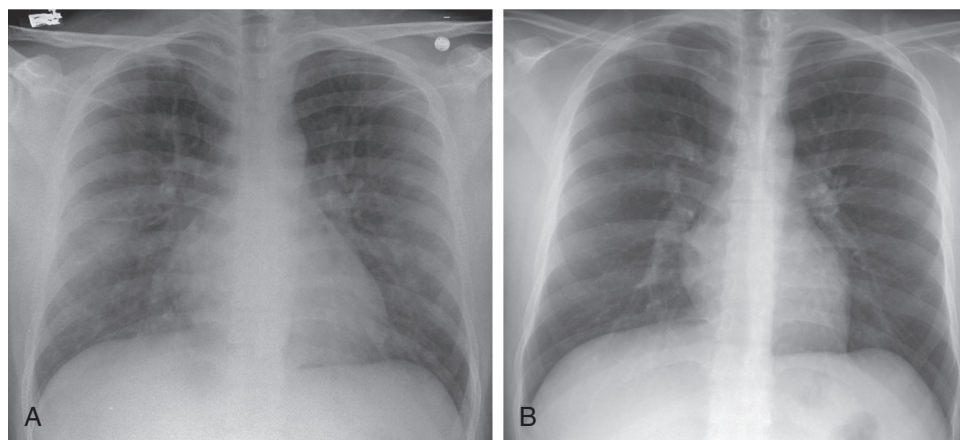
eFigure 71-4 Methotrexate-induced lung injury; non-specific interstitial pneumonia pattern. A–D, Axial chest CT in a patient receiving methotrexate shows bilateral basal and peripheral predominant linear and reticular abnormalities associated with architectural distortion and mild traction bronchiectasis; the pattern resembles fibrotic nonspecific interstitial pneumonia. (Courtesy Michael Gotway, MD.)



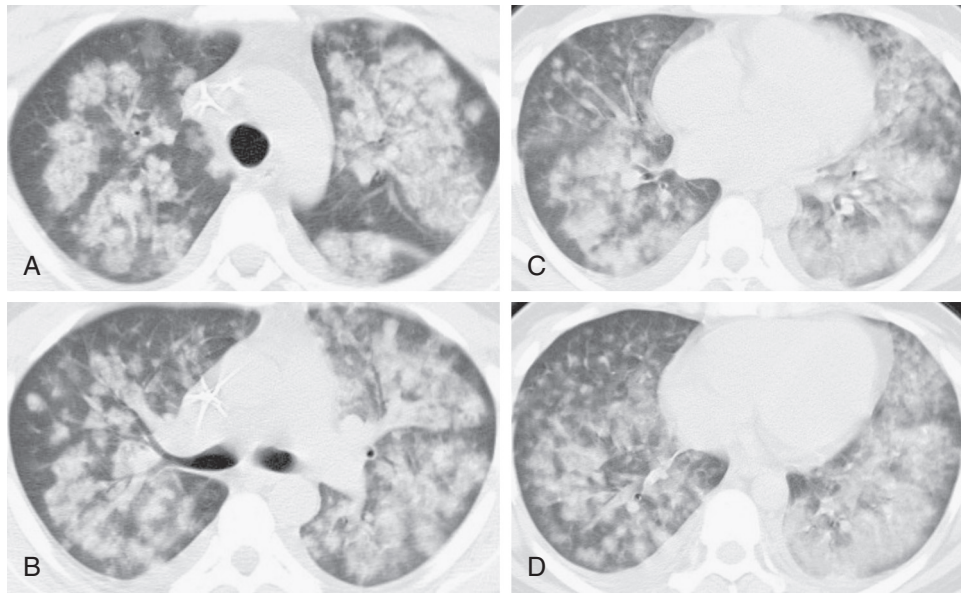
eFigure 71-5 Diffuse alveolar damage (DAD) from methotrexate toxicity. A, Methotrexate produces small, poorly formed granulomas in subacute and chronic manifestations of lung toxicity. B, Early aggregations of macrophages may be seen resembling poorly formed granulomas in cases in which DAD is the manifestation of injury, but these are not required for the diagnosis (*arrow*). (From Cheung Y, Graziano P, Leslie KO: Acute lung injury. In Leslie KO, Wick MR, editors: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 117–137, Fig. 5-31.)



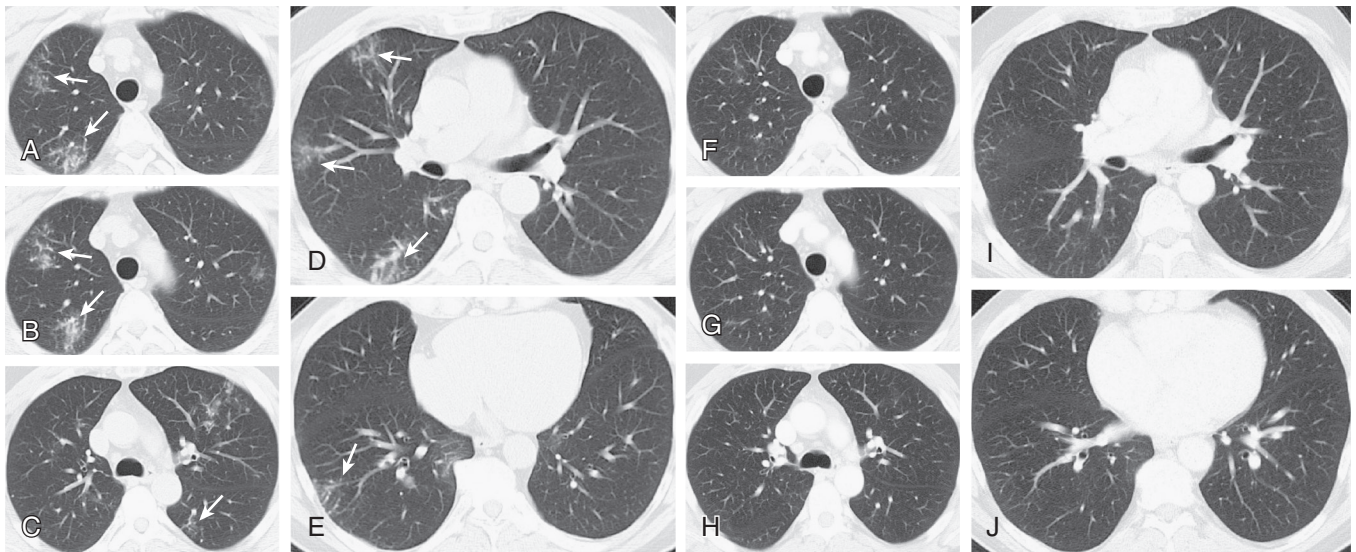
eFigure 71-6 Paclitaxel-induced pulmonary injury. **A** and **B**, Axial chest CT in a patient with non-small cell lung carcinoma at the onset of paclitaxel therapy. **C** and **D**, Axial chest CT performed 2 weeks following initiation of paclitaxel therapy shows interval development of multifocal ground-glass opacity associated with reticulation. No evidence of infection or pulmonary hemorrhage could be found. The CT appearance is consistent with an acute lung injury pattern. (Courtesy Michael Gotway, MD.)



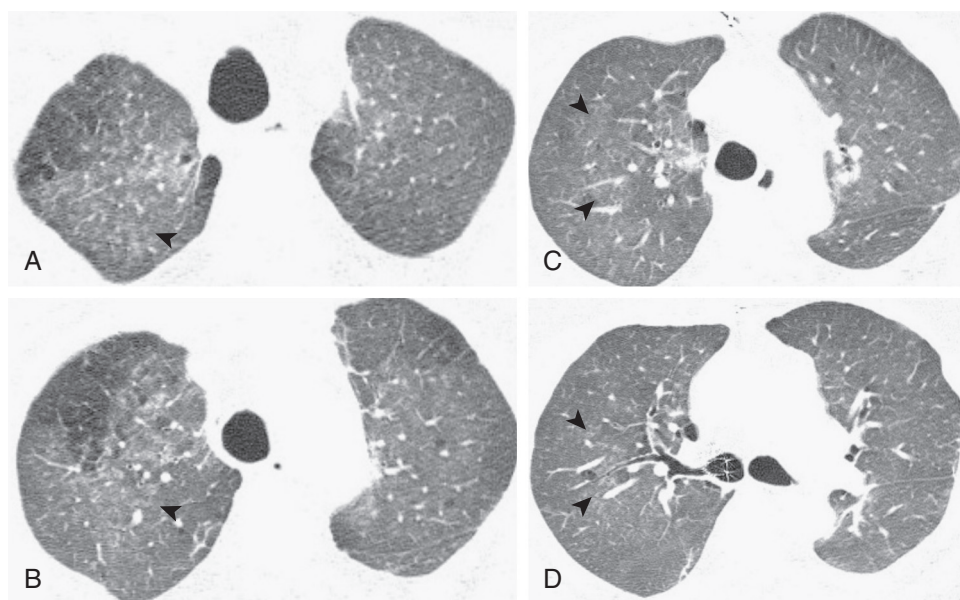
eFigure 71-7 All-trans retinoic acid (ATRA) syndrome in a patient treated for acute promyelocytic leukemia: chest radiographic findings. **A**, Frontal chest radiograph performed shortly following initiation of therapy, when the patient developed renal insufficiency and peripheral edema, shows multifocal bilateral opacities consistent with an acute lung injury, or “capillary leak,” pattern. **B**, Frontal chest radiograph following withdrawal of therapy and corticosteroid treatment shows resolution of findings. (Courtesy Michael Gotway, MD.)



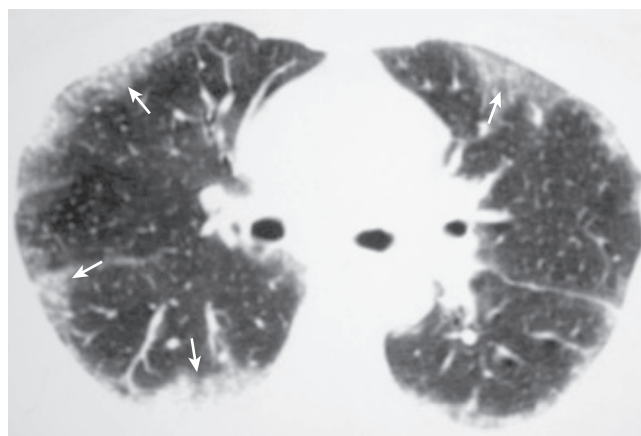
eFigure 71-8 All-trans retinoic acid (ATRA) syndrome in a patient treated for acute promyelocytic leukemia: chest CT findings. A–D, Axial chest CT displayed in lung windows shows multifocal, bilateral areas of nodular ground-glass opacity resembling pulmonary hemorrhage, although no hemorrhage was found at bronchoscopy. The pattern is nonspecific but consistent with acute lung injury. The abnormalities resolved following cessation of all-trans retinoic acid therapy and corticosteroid treatment, and no infection was ever found. (Courtesy Michael Gotway, MD.)



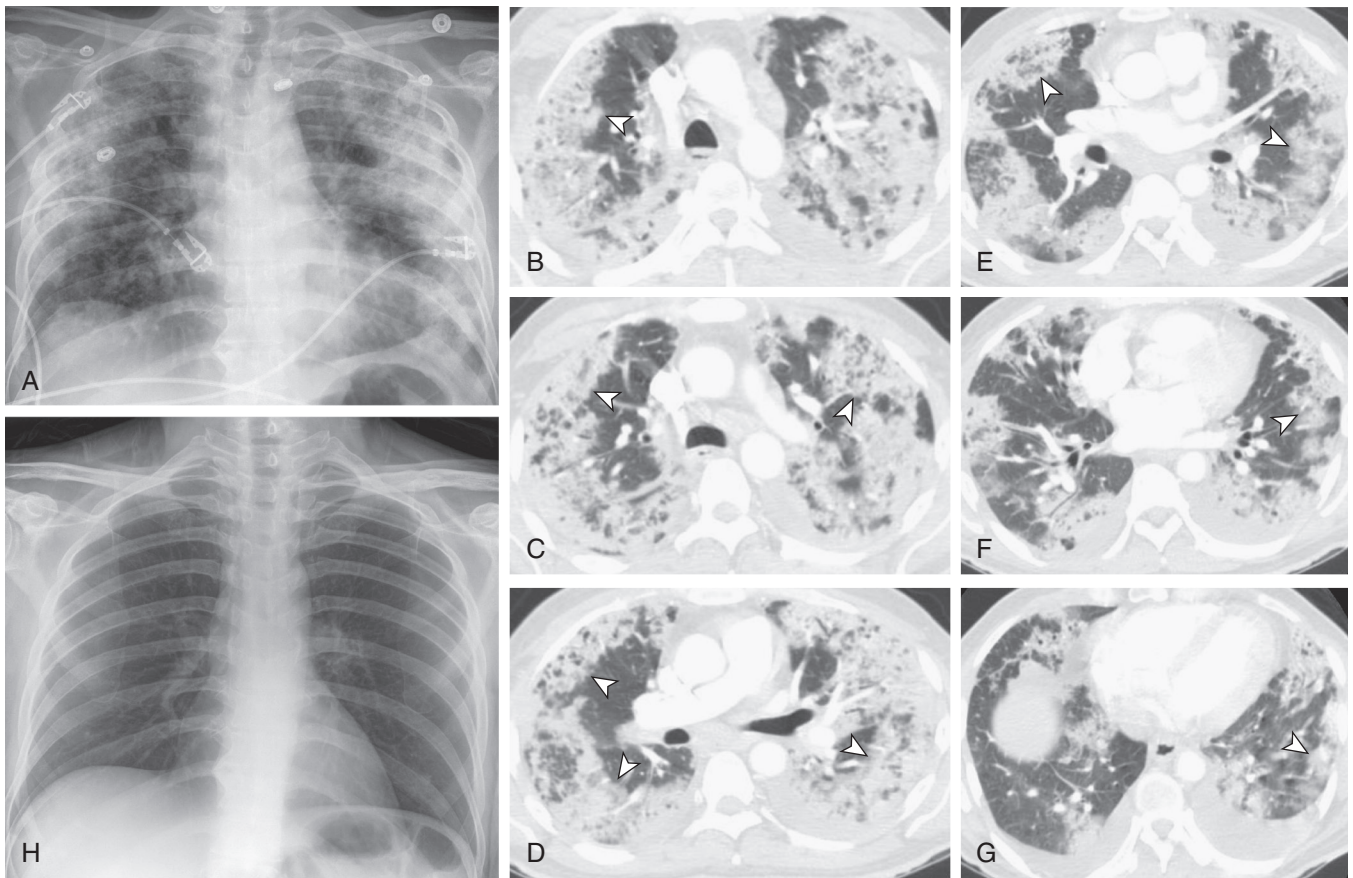
eFigure 71-9 Interferon-induced sarcoid-like reaction. A–E, Axial chest CT in a patient with renal cell carcinoma treated with interferon-alfa shows multifocal, bilateral, patchy nodules (arrows) distributed along the bronchovascular bundles and fissural surfaces, typical of the appearance of sarcoidosis. No infectious etiology was found, and the findings worsened on repeat evaluation. F–J, Axial chest CT performed following withdrawal of interferon-alfa therapy shows resolution of the small nodules. (Courtesy Michael Gotway, MD.)



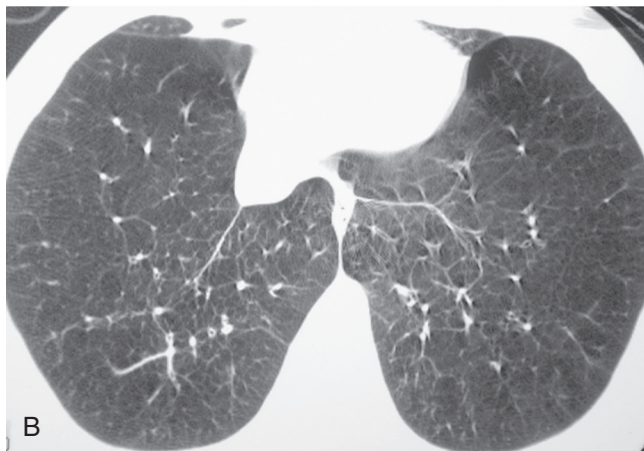
eFigure 71-10 Sirolimus-induced interstitial pneumonitis in a lung transplant recipient. A–D, Axial chest CT shows poorly defined, faintly nodular areas of ground-glass opacity (*arrowheads*) in the mid and upper lungs bilaterally. Extensive evaluation revealed no evidence of infection or hemorrhage, and the abnormalities resolved following withdrawal of sirolimus therapy. (Courtesy Michael Gotway, MD.)



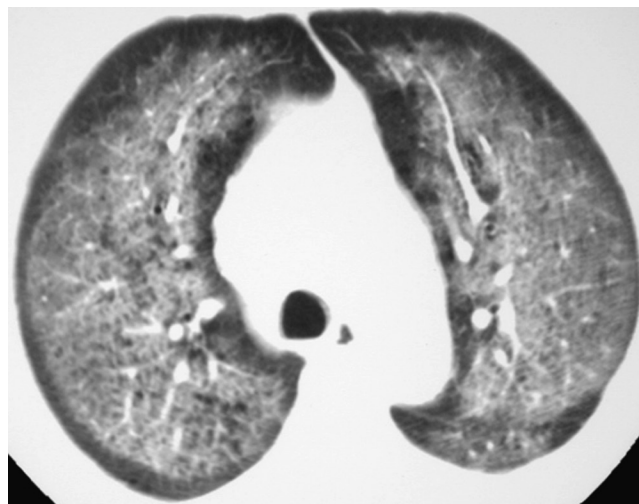
eFigure 71-11 Nitrofurantoin-induced interstitial pneumonitis. Axial chest CT in a patient undergoing nitrofurantoin therapy shows bilateral, patchy, subpleural ground-glass opacity and reticulation (*arrows*) consistent with a nonspecific interstitial pneumonia lung injury pattern. (Courtesy Michael Gotway, MD.)



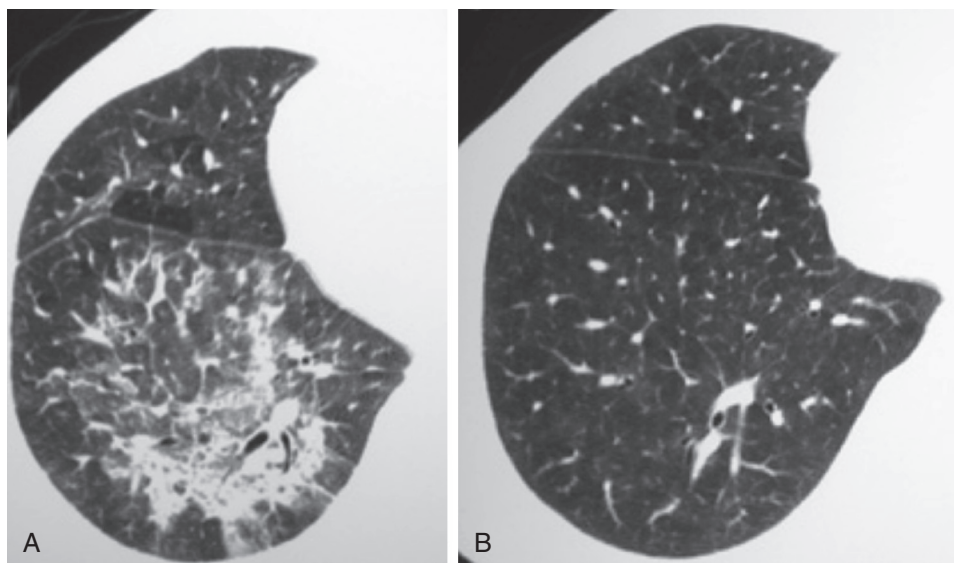
eFigure 71-12 Antibiotic-induced eosinophilic pneumonia lung injury pattern. **A**, Frontal chest radiograph in a patient receiving daptomycin shows bilateral, peripheral lung consolidation. **B–G**, Axial chest CT performed shortly following the chest radiograph shown in (**A**) reveals multifocal, bilateral, noticeably peripherally distributed areas of ground-glass opacity, consolidation, and reticulation (*arrowheads*). Bronchoscopy demonstrated pulmonary eosinophilia, without hemorrhage, and no evidence of infection was found. **H**, Frontal chest radiograph performed following discontinuation of daptomycin shows complete resolution of the pulmonary abnormalities. (Courtesy Michael Gotway, MD.)



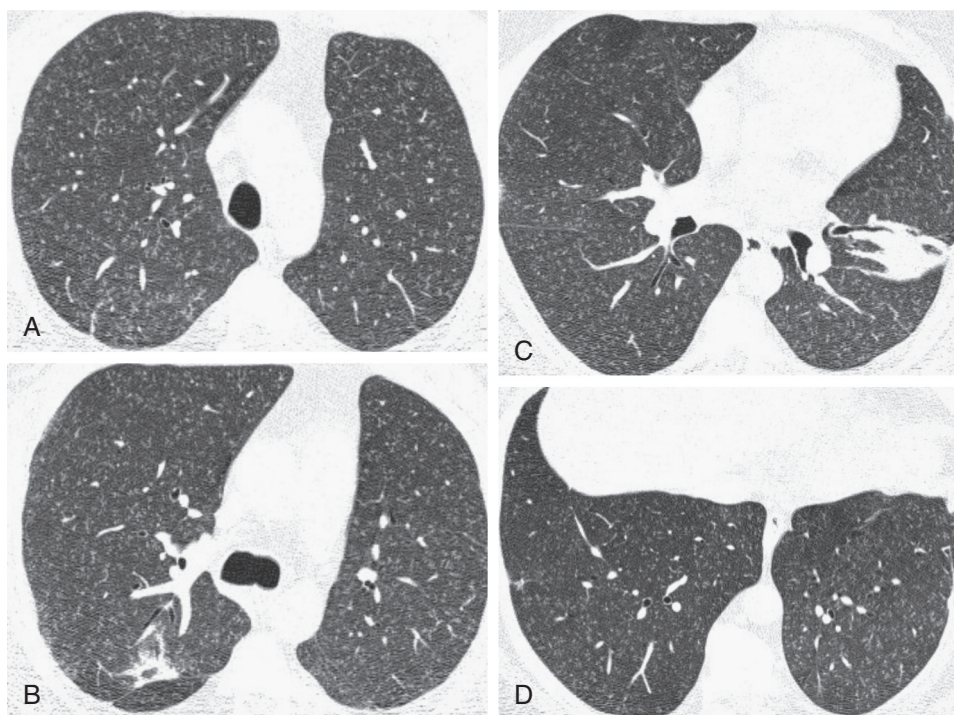
eFigure 71-13 Panlobular emphysema in a patient abusing methylphenidate. **A**, Frontal chest radiograph in a 40-year-old woman with respiratory failure, known to abuse methylphenidate intravenously, shows enormous lung volumes. Note diaphragmatic flattening. **B**, Axial chest CT through the lung bases shows diffuse low attenuation and simplification of pulmonary architecture, consistent with panlobular emphysema. (Courtesy Michael Gotway, MD.)



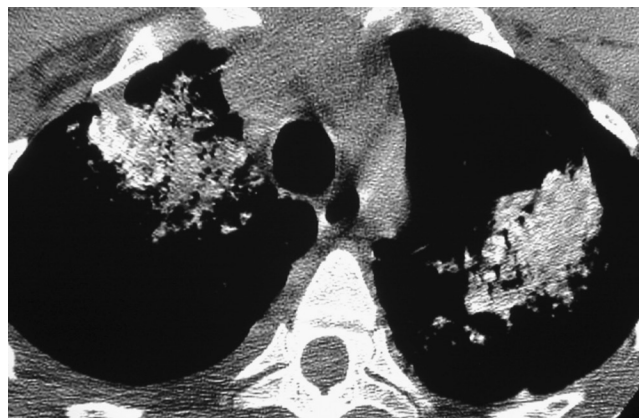
eFigure 71-14 Noncardiogenic edema following cocaine inhalation. Axial chest CT performed in a patient who developed severe shortness of breath and cough following crack inhalation shows multifocal bilateral ground-glass opacity with peripheral sparing. No evidence of infection was noted. (Courtesy Michael Gotway, MD.)



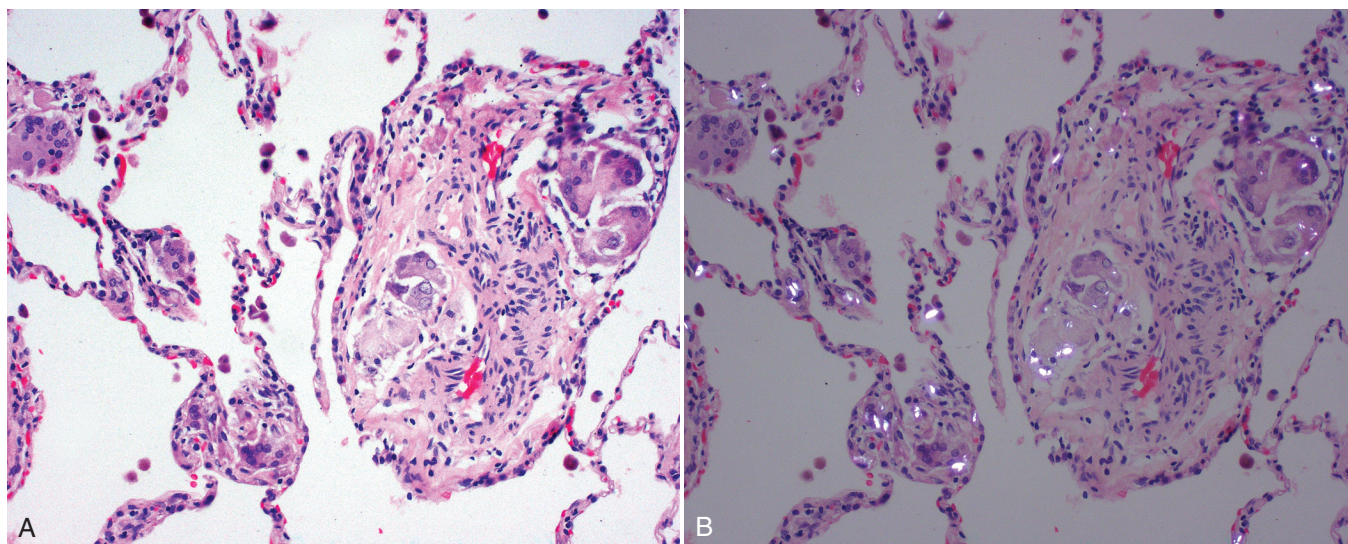
eFigure 71-15 Pulmonary hemorrhage following cocaine inhalation. **A**, Axial chest CT performed in a patient complaining of shortness of breath and cough following crack inhalation shows patchy right lower lobe ground-glass opacity with interlobular septal thickening, consistent with hemorrhage; the latter was confirmed at bronchoscopy. **B**, Repeat axial chest CT 3 weeks following (**A**) shows clearing of the right lower lobe pulmonary hemorrhage. (Courtesy Michael Gotway, MD.)



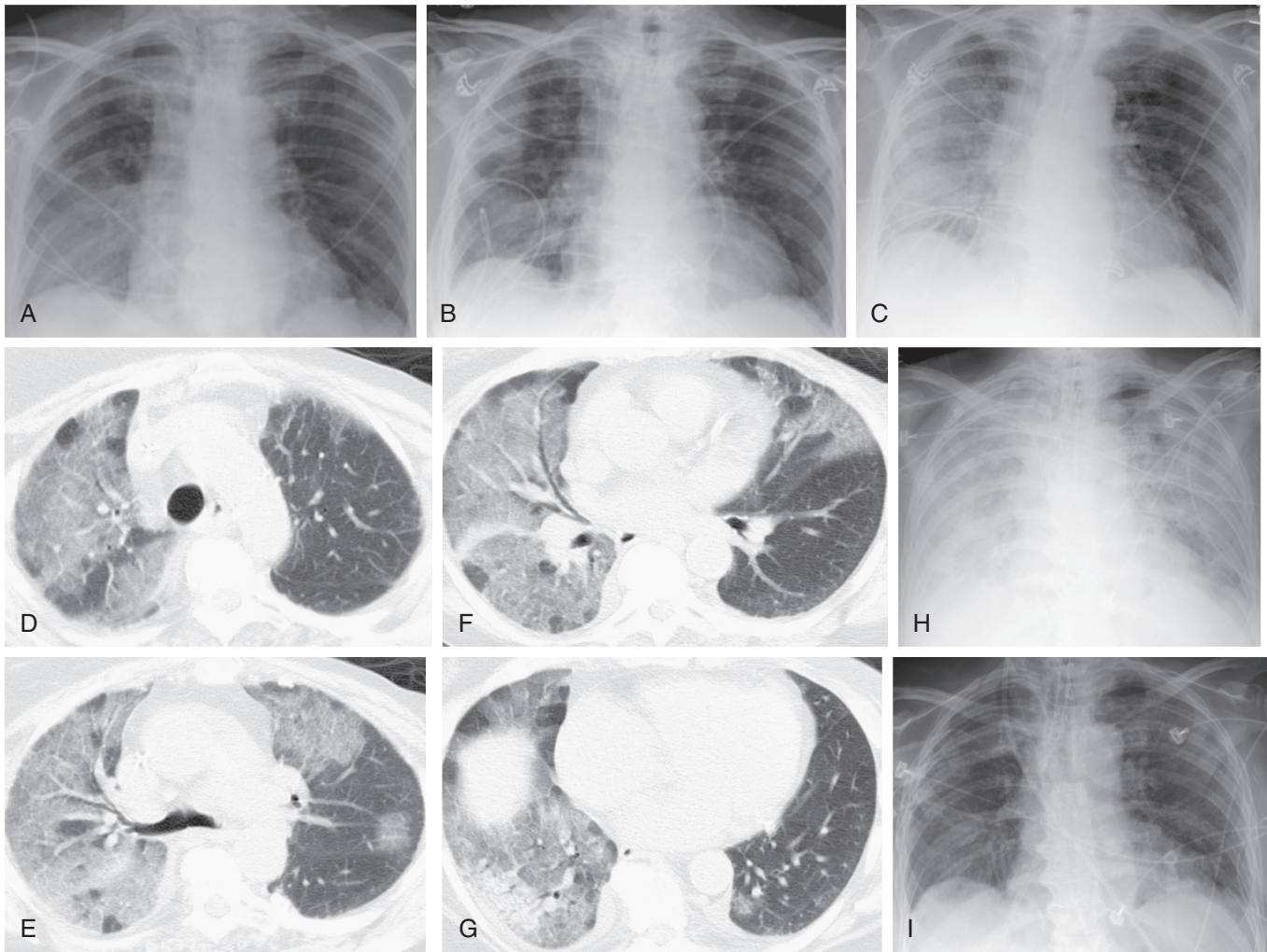
eFigure 71-16 Injection cellulose granulomatosis in a patient injecting Vicodin tablets intravenously. **A–D**, Axial chest CT in an injection drug user shows numerous, diffusely distributed, bilateral ground-glass opacity nodules; the appearance closely resembles subacute hypersensitivity pneumonitis. Surgical lung biopsy showed a perivascular foreign body giant cell reaction with granulomas and polarizable refractive crystals consistent with cellulose. (Courtesy Michael Gotway, MD.)



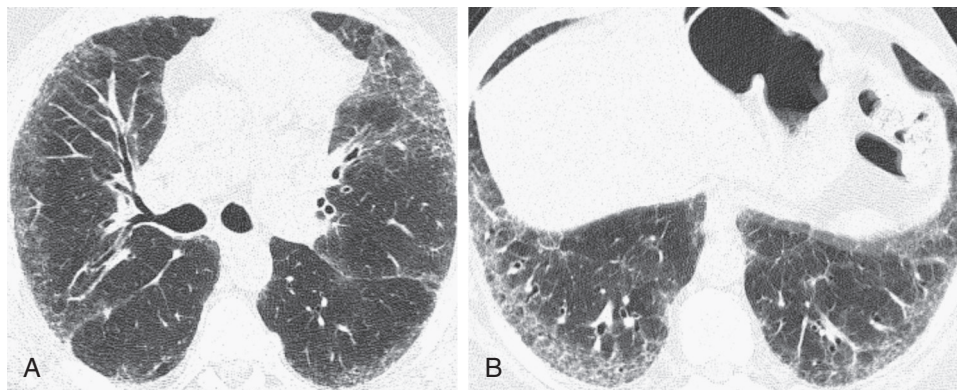
eFigure 71-17 Injection talcosis. Axial chest CT displayed in soft tissue windows performed on an intravenous drug abuser shows bilateral mass-like opacities consistent with injection talc granulomatosis. (Courtesy Michael Gotway, MD.)



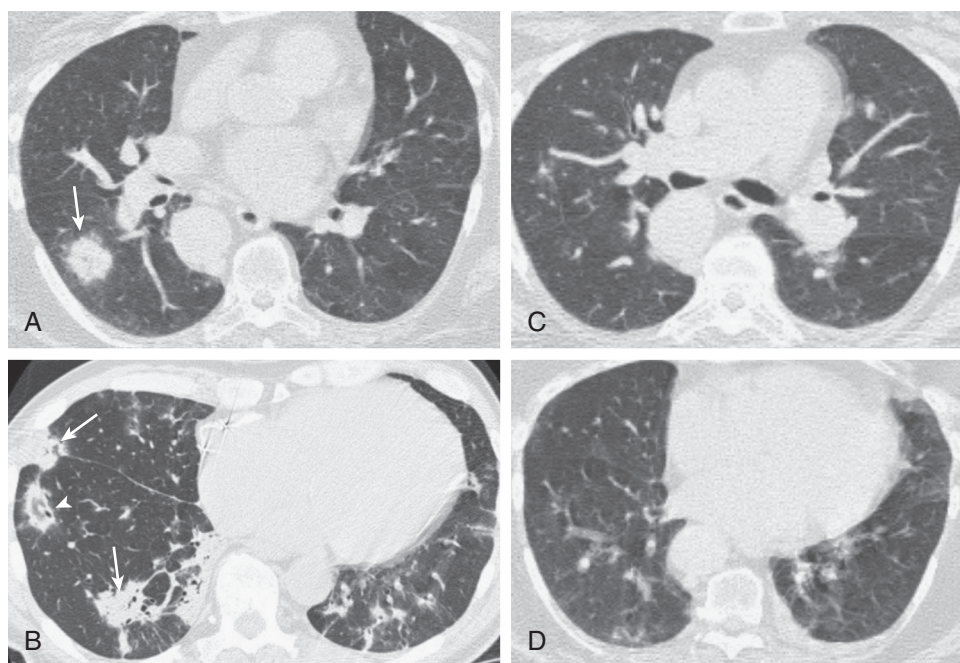
eFigure 71-18 Intravenous drug abuse-induced particulate foreign body reaction. **A**, Normal light microscopy appearance. **B**, Polarized light. A perivascular interstitial foreign body-type granulomatous reaction is associated with prominent vascular changes, as seen here. (From Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 117–137, Fig. 7-73.)



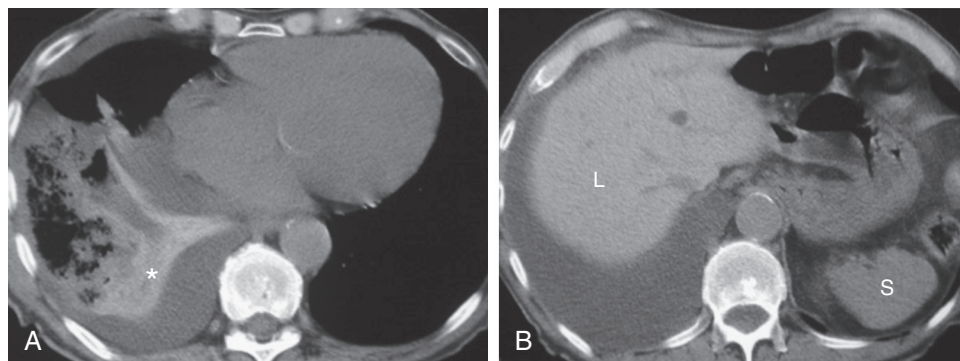
eFigure 71-19 Acute amiodarone pulmonary toxicity. **A**, Frontal chest radiograph performed in a patient with supraventricular tachycardia recently loaded with amiodarone shows right lower lung opacity thought to reflect pneumonia. The patient was treated presumptively for pneumonia with broad-spectrum antibiotics. **B**, Frontal chest radiograph performed several days following **(A)** shows slight improvement in right lower lung opacity, but new right upper lobe opacity is now present. **C**, Follow-up frontal chest radiograph shows progression of the right lung abnormalities despite a normal intravascular volume and broad-spectrum antibiotic therapy. **D–G**, Axial chest CT displayed in lung windows shows multifocal, bilateral ground-glass opacities associated with fine reticulation and subpleural right lower lobe consolidation, but no features to suggest fibrosis. The findings are consistent with an alveolitis or hemorrhage but are nonspecific. **H**, Follow-up frontal chest radiograph shows continued worsening of bilateral lung opacities. **I**, Frontal chest radiograph performed several days following discontinuation of amiodarone shows significant improvement in bilateral lung opacities. (Courtesy Michael Gotway, MD.)



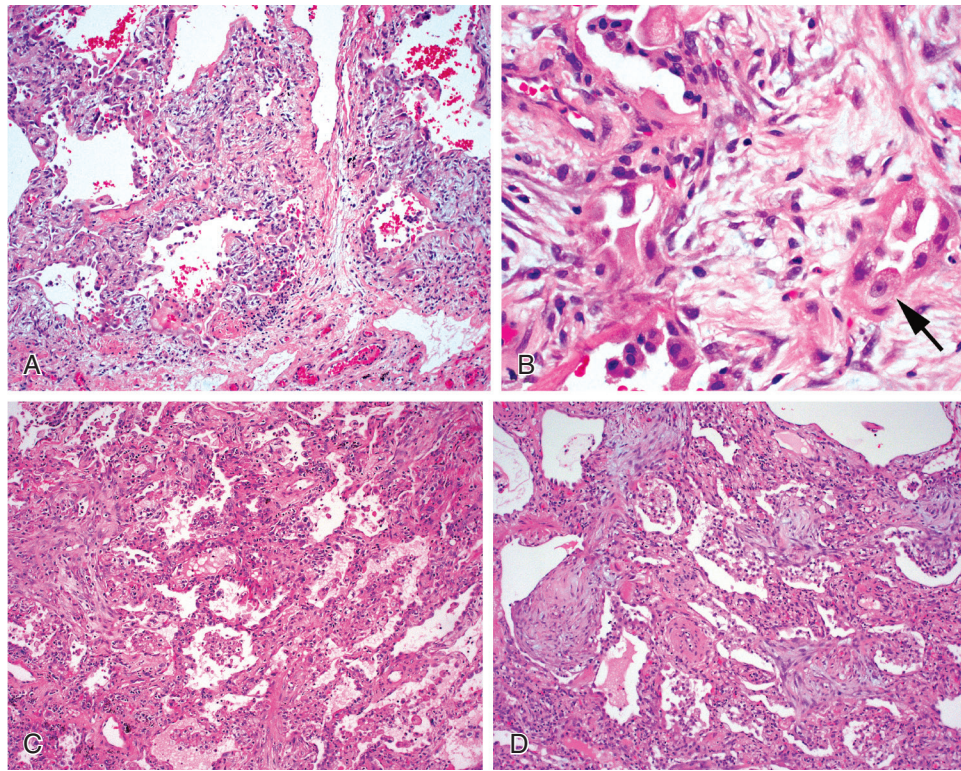
eFigure 71-20 Amiodarone pulmonary toxicity: nonspecific interstitial pneumonia pattern. **A** and **B**, Axial chest CT displayed in lung windows performed for a patient receiving chronic amiodarone therapy shows bilateral, subpleural fine intralobular interstitial thickening and ground-glass opacity; the appearance resembles a nonspecific interstitial pneumonia lung injury pattern. (Courtesy Michael Gotway, MD.)



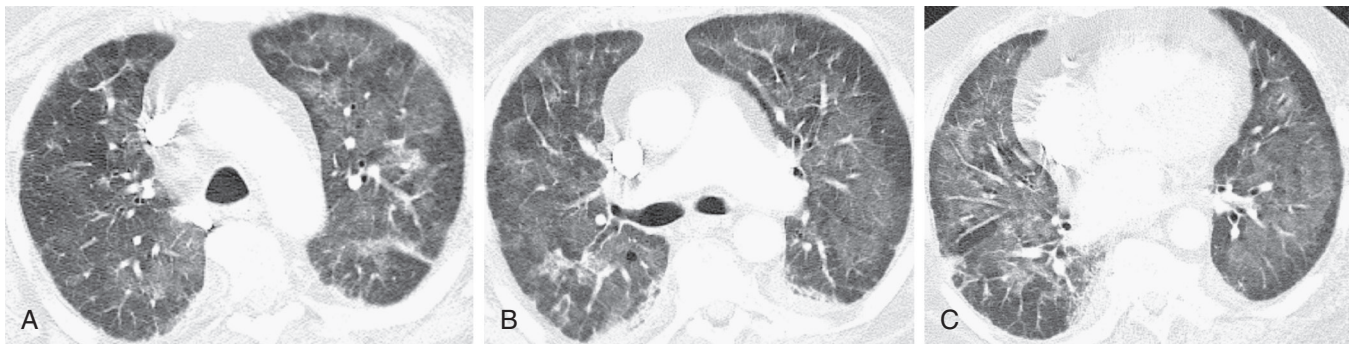
eFigure 71-21 Amiodarone pulmonary toxicity: nodular organizing pneumonia pattern. **A** and **B**, Axial chest CT displayed in lung windows performed for a patient receiving chronic amiodarone therapy shows right lung nodules (*arrows*) associated with air bronchograms; one nodule shows ground-glass opacity surrounded by consolidation (**B**, *arrowhead*), consistent with the "reverse ground-glass halo" sign, or "atoll" sign, suggestive of organizing pneumonia. **C** and **D**, Axial chest CT performed following discontinuation of amiodarone therapy and implementation of corticosteroid treatment shows near complete resolution of the nodules. (Courtesy Michael Gotway, MD.)



eFigure 71-22 Amiodarone exposure: high attenuation lung consolidation. **A**, Axial chest CT performed in a patient taking amiodarone for an atrial arrhythmia shows high attenuation right lower lobe consolidation (*), consistent with amiodarone exposure. **B**, Axial chest CT through the upper abdomen shows increased attenuation of the liver parenchyma (L) relative to the spleen (S), also consistent with amiodarone exposure. (Courtesy Michael Gotway, MD.)



eFigure 71-23 Amiodarone toxicity. **A**, Scanning magnification of amiodarone-induced diffuse alveolar injury. **B**, The finely vacuolated macrophages in type II cells are clearly evident (*arrow*). **C**, The most common pathologic change seen in amiodarone toxicity is a cellular interstitial pneumonia associated with prominent intra-alveolar macrophages whose cytoplasm shows fine vacuolation. **D**, In some patients with amiodarone toxicity, an organizing pneumonia pattern develops, resulting in a mass effect on thoracic imaging studies. (From Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 117–137, Figs. 5-32, 7-64, 7-66A.)



eFigure 71-24 Adalimumab-induced lung injury. **A–C**, Axial chest CT in a patient with rheumatoid arthritis undergoing adalimumab therapy shows multifocal bilateral ground-glass opacity with reticulation, consistent with an acute lung injury pattern. (Courtesy Michael Gotway, MD.)

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ENVIRONMENTAL AND OCCUPATIONAL HAZARDS

72

ASTHMA IN THE WORKPLACE

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WORK-EXACERBATED ASTHMA

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INTRODUCTION

Work-related asthma (WRA) is a major public health concern due to its high prevalence and societal burden. WRA is a broad term indicating that asthma is worsened by the workplace.¹ WRA encompasses *occupational asthma* (OA), which is asthma caused by a specific agent at the workplace and *work-exacerbated asthma* (WEA), which corresponds to asthma exacerbated by nonspecific stimuli at the workplace but not caused by it (Fig. 72-1).²

Several definitions of OA have been proposed. The most recent has been published in the latest American College of Chest Physicians Consensus statement on WRA³: “Occupational asthma refers to de novo asthma or the recurrence of previously quiescent asthma (i.e., asthma as a child or in the distant past that has been in remission) induced by either sensitization to a specific substance (e.g., an inhaled protein [*high-molecular-weight* (HMW) protein of > 10 kD] or a chemical [*low-molecular-weight* (LMW) agent]), at work, which is termed sensititizer-induced OA, or by exposure to an inhaled irritant at work, which is termed irritant-induced OA.”

Sensitizer-induced OA has also been defined as “asthma with a latency period,” suggesting the presence of an underlying immunologic mechanism responsible for a latency period from the beginning of the occupational exposure to the onset of asthma symptoms.⁴

Irritant-induced (occupational) asthma (IIA), also called “OA without a latency period” or “nonimmunologic OA,”⁵ encompasses a wide spectrum of asthma phenotypes related to irritant mechanisms, as opposed to OA caused by immunologic mechanisms. The rapid onset of asthma within a few hours after a single exposure to high levels of irritant substances (i.e., acute-onset IIA or *reactive airways dysfunction syndrome* (RADS)⁶ is the best typified phenotype of IIA, whereas for other clinical phenotypes (e.g., “low-dose reactive airways dysfunction syndrome,” “not-so-sudden IIA,” or “IIA with latency”)^{7-13,13a} the causal relationship with workplace irritant exposures remains uncertain.

WEA has received growing attention during the past decade. The latest definition of WEA has been proposed by the American Thoracic Society Task Force on WEA² and consists of four criteria:

- There is preexisting or concurrent asthma. The onset of asthma may have predated current employment or happened first while at the worksite of interest but was not caused by specific exposures within that workplace.
- An increased frequency of asthma symptoms, medication use, or health care utilization is temporally associated with work. Medical test results may document more frequent abnormalities.
- Workplace exposures or conditions that can exacerbate asthma exist.
- Occupational asthma (asthma caused by a specific, identified workplace exposure) is unlikely.

In spite of these clear definitions, differentiating those conditions is often difficult in clinical practice. An accurate diagnosis is crucial because the diagnosis of this condition can result in a change of career and/or some financial compensation. This chapter reviews the epidemiology, pathophysiology, diagnosis, management, prevention, and socioeconomic impacts of sensitizer-induced OA, IIA, and WEA.

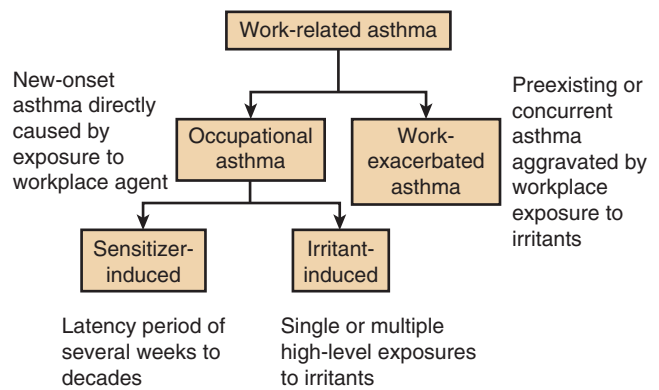


Figure 72-1 Categorization of work-related asthma into subsets based on the cause and timing of the asthma.

SENSITIZER-INDUCED OCCUPATIONAL ASTHMA

EPIDEMIOLOGIC ASPECTS

Estimates of the frequency of OA have been derived from various sources, including cross-sectional and longitudinal studies of high-risk workforces, occupational disease registries, voluntary notification programs, and population-based surveys. A pooled analysis of data published up until 2007 indicated that 17.6% of all adult-onset asthma is attributable to workplace exposures.¹⁴

Cross-sectional surveys of workforces exposed to sensitizing agents reported highly variable prevalence rates of OA, but these estimates are largely affected by the criteria used to identify the disease and selection biases. Prospective cohort studies reported incidence rates ranging from 1.8 to 4.1 cases of OA per 100 person-years among workers exposed to laboratory animals,¹⁵ wheat flour,¹⁶ and latex gloves.¹⁷ Incidence rates derived from notification schemes and compensation statistics in various countries ranged from 24 to 174 new cases per million active workers per year.¹⁸⁻²⁴ Differences from one country to another may result from geographic differences in industrial activities, as well as the heterogeneity in diagnostic criteria and data collection procedures.

The European Community Respiratory Health Survey II provided higher estimates of 250 to 478 incident cases of work-attributable asthma per million people per year.^{25,26} These data suggest that the disease remains largely unrecognized, although population surveys are affected by the lack of confirmation of OA through objective tests.

CAUSAL AGENTS

A large number of substances (>400) used at work can cause immunologically mediated OA.²⁷ They are usually categorized into HMW and LMW agents (Table 72-1). HMW

Table 72-1 Principal Agents Causing Occupational Asthma

Agent		Occupation/Industry
HIGH-MOLECULAR-WEIGHT AGENTS		
Cereals, flour	Wheat, rye, barley, buckwheat	Flour mills, bakers, pastry makers
Latex	Proteins from the Hevea tree	Health care workers, laboratory technicians
Animals	Mice, rats, cows, seafood	Laboratory workers, farmers, seafood processing
Enzymes	α-Amylase, maxatase, alcalase, papain, bromelain, pancreatin	Baking product production, bakers, detergent production, pharmaceutical industry, food industry
LOW-MOLECULAR-WEIGHT AGENTS		
Isocyanates	Toluene diisocyanate (TDI), methylene diphenyl-diisocyanate (MDI), hexamethylene diisocyanate (HDI)	Polyurethane production, plastic industry, insulation, molding, spray painting
Metals	Chromium, nickel, cobalt, platinum	Metal refinery, metal alloy production, electroplating, welding
Biocides	Formaldehyde, glutaraldehyde, quaternary ammonium compounds	Health care workers, cleaners
Persulfate salts	Hair bleach	Hairdressers
Acrylates	Cyanoacrylates, methacrylates, di- and tri-acrylates	Adhesives, dental and orthopedic materials, sculptured fingernails, printing inks, paints and coatings
Acid anhydrides	Phthalic, trimellitic, maleic, tetrachlorophthalic anhydrides	Epoxy resin workers
Reactive dyes	Reactive black 5, pyrazolone derivatives, vinyl sulphones, carmine,	Textile workers, food industry workers
Woods	Red cedar, iroko, obeche, oak, and others	Sawmill workers, carpenters, cabinet and furniture makers

agents are (glyco)proteins from plant and animal origins. LMW agents include chemicals, metals, and wood dusts. The intrinsic characteristics of occupational agents that determine their sensitizing potential remain largely uncertain. However, LMW agents causing OA are typically highly reactive electrophilic compounds that are capable of combining with hydroxyl, amino, and thiol functionalities on airway proteins. Quantitative structure-activity relationship models have identified a number of reactive groups that are associated with a high risk of respiratory sensitization (e.g., isocyanate [$\text{N} = \text{C} = \text{O}$], carbonyl [$\text{C} = \text{O}$], and amine [NH_2]), particularly when two or more groups are present within the same molecule.²⁸

Actually, a handful of agents (i.e., flour, diisocyanates, latex, persulfate salts, aldehydes, animals, wood dusts, metals, enzymes) usually account for the majority (50% to 90%) of reported cases of OA.^{24,29} Nevertheless, the distribution of causal agents may vary widely across geographic areas, depending on the pattern of industrial activities.¹⁸⁻²⁴ The highest incidence of OA is seen in bakers and pastry makers, other food processors, spray painters, hairdressers, wood workers, health care workers, cleaners, farmers, laboratory technicians, and welders.

PATHOPHYSIOLOGY

The pathophysiology of sensitizer-induced OA often involves an *immunoglobulin E* (IgE)-dependent mechanism. This mechanism is encountered mainly with HMW agents. Although specific IgE has also been encountered in OA due to LMW agents (e.g., platinum salts, trimellitic anhydride, other acid anhydrides), the production of specific IgE antibodies or the upregulation of IgE receptors has not been identified in the majority of cases of OA induced by LMW agents.³⁰

Immunologic, IgE-mediated

The pathophysiology of OA induced by IgE-dependent agents is similar to allergic asthma unrelated to work. HMW agents act as complete antigens and induce the production of specific IgE antibodies, whereas the LMW occupational agents that are likely to induce specific IgE antibodies do so by acting as haptens and binding with proteins to form functional antigens. The role of specific IgE is still controversial in isocyanate-induced asthma.³¹ The presence of specific IgE to isocyanates seems a good predictor of isocyanate-induced OA (specificity 89% to 100%),³ whereas specific IgG seems to be mostly associated with exposure to isocyanates.³² However, whether isocyanate-induced asthma is an IgE-mediated disease is still a matter of debate.³¹

Immunologic, non-IgE mediated

Cell-mediated reactions are likely to play an important role in OA due to LMW agents. Although the predominant immune response to chemical respiratory allergens may be of the *type 2 T helper* (Th2) type, other cells may play important support or regulatory roles. CD4- and CD8-positive T cells and different cytokines such as *interleukin* (IL)-1, IL-4, IL-5, IL-6, and IL-15 have been found in biopsies,³³ *bronchoalveolar lavage* (BAL), and the sputum of patients with isocyanate-induced asthma.³² Neutrophils are also likely to

be involved in isocyanate-induced asthma as shown by an increase in myeloperoxidase and IL-8 after exposure to *toluene diisocyanate* (TDI).³⁴ A mixed Th1/Th2 cytokine production has been observed in subjects with red-cedar-induced asthma.³⁵ Furthermore, a *specific-inhalation challenge* (SIC) test induced a mixed Th2/Th1 response in which CD8⁺ cells were the main producers of *interferon* (IFN)-gamma.³⁶

There is evidence that isocyanates can stimulate human innate immune responses by up-regulating immune pattern-recognition receptors of monocytes and increasing the chemokines that regulate monocyte/macrophage trafficking (*macrophage migration inhibitory factor* [MIF], *monocyte chemoattractant protein-1* [MCP-1]).³⁷ Furthermore, repetitive antigenic stimulation of diisocyanate asthmatic peripheral blood mononuclear cells induced the synthesis of *tumor necrosis factor* (TNF)- α , and MCP-1,³⁸ but not IL-4 or IL-5.³⁰

RISK FACTORS

OA results from the complex interaction between environmental and individual susceptibility factors (Table 72-2).²⁹

Environmental Factors

The intensity of exposure to sensitizing agents is currently the best identified and the most important environmental risk factor for the development of OA. There is strong evidence supporting a dose-response relationship between the level of exposure to HMW agents and the development of IgE-mediated sensitization and OA. Such a dose-response relationship has also been documented for some LMW agents, such as platinum salts, acid anhydrides, and isocyanates. Noteworthy, exposure-response relationships may be affected by individual susceptibility factors and the timing of exposure. For instance, the role of genetic susceptibility markers, such as certain HLA class II alleles, may become more apparent at low levels of exposure to occupational agents.³⁹ The incidence of WRA symptoms is consistently higher within the first 1 to 4 years of exposure to HMW agents, and exposure-response gradients are more clearly documented in this early period of exposure.¹⁵

A number of studies indicate that cigarette smoking can increase the risk of IgE-mediated sensitization to some HMW and LMW agents, but the evidence supporting an association between smoking and the development of clinical OA is still weak. The role of other environmental cofactors, such as nonrespiratory routes of exposure and concomitant exposure to endotoxin and pollutants at work, remains largely uncertain.

Host-Related Factors

Atopy has been consistently demonstrated as an important host risk factor for the development of IgE sensitization and OA, but only for HMW agents. Preexposure sensitization to common allergens that are structurally related to workplace allergens, such as exposure to pets in laboratory animal workers, could be a stronger risk factor for OA than atopy.

Prospective cohort studies suggested that the presence of nonspecific bronchial hyperresponsiveness^{40,41} and rhinitis^{41,42} before entering exposure to HMW occupational agents is an independent risk factor for subsequent IgE

Table 72-2 Potential Risk Factors for the Development of Occupational Asthma

Risk Factor	Evidence	Agents/Settings
ENVIRONMENTAL FACTORS		
High level of exposure	Strong Moderate	HMW agents LMW agents: platinum salts, acid anhydrides, isocyanates
Cigarette smoking	Moderate Weak	(For IgE sensitization) Laboratory animals, snow crab, prawn, salmon, psyllium, green coffee, enzymes, acid anhydrides, platinum, reactive dyes (For clinical OA) Laboratory animals, enzymes
Skin exposure	Weak	Isocyanates
HOST-RELATED FACTORS		
Atopy	Strong Weak	HMW agents LMW agents: platinum, acid anhydrides
Genetic markers		
HLA class II alleles	Moderate	LMW agents: isocyanates, red cedar, acid anhydrides, platinum salts HMW agents: laboratory animals, latex
Antioxidant enzymes*	Moderate	Isocyanates
SNPs of α -T catenin	Moderate	Isocyanates
TLR4 polymorphisms	Weak	Laboratory animals
IL-4 receptor alpha and IL13 polymorphisms	Weak	Isocyanates
Preexisting nonspecific bronchial hyperresponsiveness	Moderate	HMW agents (laboratory animals, flour, latex)
Work-related rhinitis	Strong	Laboratory animals
Gender (female)	Weak	Snow crab processors

*Glutathione-S-transferase and N-acetyltransferase.

HMW, high-molecular-weight; IL, interleukin; LMW, low-molecular-weight; OA, occupational asthma; SNPs, single nucleotide polymorphisms; TLR4, Toll-like receptor-4.

sensitization to these allergens. On the other hand, there is strong evidence that the development of occupational rhinitis during exposure is associated with an increased risk for the development of OA.^{43,44} However, the proportion of subjects with occupational rhinitis who will develop OA remains unknown. Among workers exposed to laboratory animals, the predictive value of work-related nasal symptoms on the subsequent development of probable OA was only 11.4% over a follow-up period of 30 to 42 months.

Certain HLA class II molecules (i.e., HLA-DR, HLA-DQ, and HLA-DP alleles), which are involved in the presentation of processed antigens to T lymphocytes, were found to confer either susceptibility or protection against OA due to various LMW and HMW occupational allergens.⁴⁵ There is also some suggestion that genes associated with Th2-cell differentiation (i.e., polymorphism of the IL-4 receptor alpha-chain, *IL13*, and *CD14* [C159T] genes) could play a role in the development of OA. Genes involved in the protection against oxidative stress, such as *glutathione-S-transferase* (GST) and *N-acetyltransferase* (NAT), have been associated with an increased risk of isocyanate-induced OA (i.e., *GSTM1* null genotype and slow N-acetylator phenotypes) or a protective effect (i.e., *GSTP1**Val/Val allele). Overall, the currently available information indicates that genetic markers have a low predictive value in identifying susceptible workers. In addition, there is convincing evidence that a wide variety of environmental factors can interact with genetic determinants to affect disease susceptibility.

DIAGNOSIS

The diagnosis of OA is difficult to establish. A comprehensive and integrated approach including the assessment of occupational history, clinical symptoms, and functional

and inflammatory characteristics at baseline and in response to exposure to occupational agents needs to be undertaken in order to achieve an accurate diagnosis. This approach is summarized in [Figure 72-2](#). Each step of the investigation has substantial limitations that may be attenuated by the combination of several tests.⁴⁶ The validity of the different diagnostic tests and their practical limitations and advantages are summarized in [Table 72-3](#).

OA should be suspected in every adult with new-onset asthma. Although the respiratory symptoms (e.g. wheezing, dyspnea, chest tightness, cough, and sputum production) are similar to those encountered in *non-WRA* (NWRA), in OA, their appearance and severity is usually modulated by the work exposure. The symptoms can start at the beginning of the work shift or toward its end or even after working hours with remission or improvement during weekends and holidays. Rhinitis is associated with respiratory symptoms in the majority of cases of OA and often precedes the respiratory symptoms, especially with exposure to HMW agents. Although a thorough clinical and occupational history must be carefully recorded, the diagnosis of OA cannot be made only on the basis of a compatible history, which has a low positive predictive value.⁴⁷

A good occupational history must detail not only the current employment and exposure but also the past employments and exposures. The work history (current and past employments), the symptoms (nature and temporal relationship to work), as well as the potential risk factors, need to be recorded.⁴⁸ The substances to which the worker is potentially exposed at work can be checked against a comprehensive list of agents recognized as causing OA, and the person's employment can be searched on the list of at-risk occupations.³ *Material safety data* (MSD) sheets can be requested from the workplace and may be of help in clarifying the presence of a workplace sensitizer. If the content of

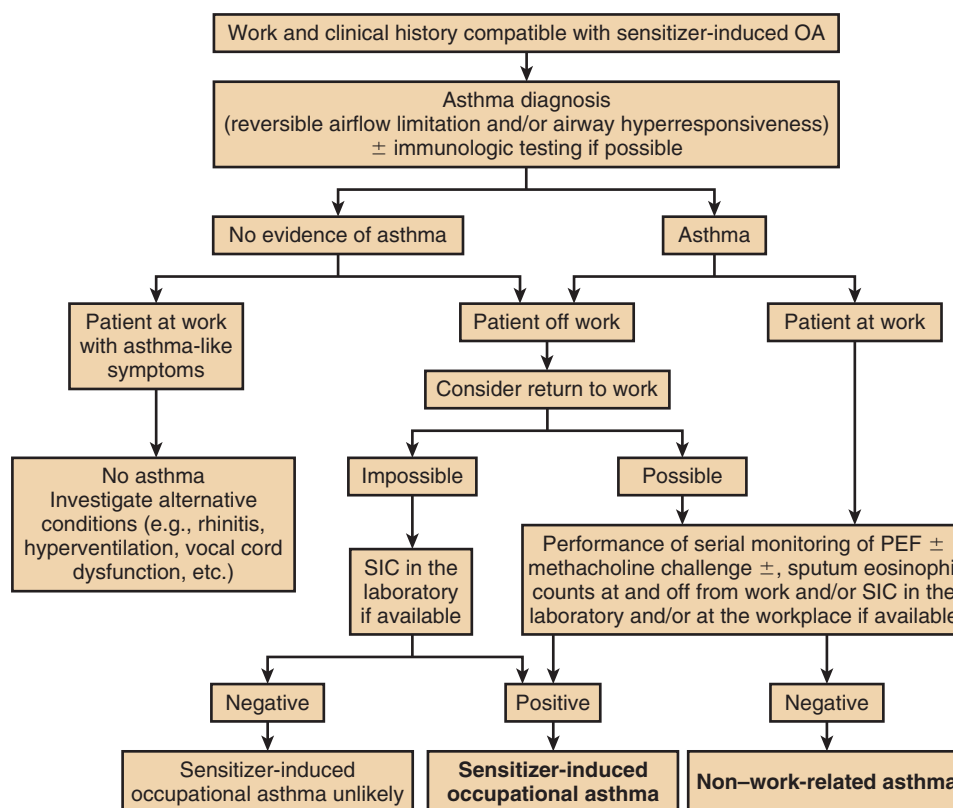


Figure 72-2 Diagnostic approach in the investigation of sensitizer-induced occupational asthma. OA, occupational asthma; PEF, peak expiratory flow rates; SIC, specific inhalation challenge.

the causal agent is less than 1%, it may not be listed in the MSD. If available, the occupational health record and the industrial hygiene record from the company should also be reviewed. A list of *agents* responsible for OA can be found at: http://www.asthme.csst.qc.ca/document/Info_Gen/AgenProf/Bernstein/BernsteinAng.htm.

A list of *occupations* in which the exposure to those agents is encountered can be found at: [http://www.asthme.csst.qc.ca/document/Info_Med/IdCauses/Bernstein/Occupational Asthma-Agents by occupation.pdf](http://www.asthme.csst.qc.ca/document/Info_Med/IdCauses/Bernstein/Occupational%20Asthma-Agents%20by%20occupation.pdf).

Once the history has been obtained, the diagnosis of asthma should be confirmed by documenting reversible airflow limitation and/or airway hyperresponsiveness. However, the lack of airway hyperresponsiveness does not exclude the diagnosis of OA in subjects who have been removed from exposure. Immunologic testing is useful in demonstrating a sensitization of the worker to the suspected agent. Although the negative predictive value of these tests is high in the case of HMW, they are limited by the lack of standardized commercially available reagents for skin and in vitro tests. Skin-prick tests are seldom useful when LMW agents are suspected.

The work-relatedness of asthma should be assessed through serial measurements of *peak expiratory flow* (PEF) and/or nonspecific bronchial hyperresponsiveness at work and off work and/or specific inhalation challenges in the laboratory or at the workplace.

Assessing airway responsiveness is an important step in the investigation of OA. It may confirm not only the diagnosis of asthma but also the improvement of airway responsiveness after a period away from work, which may support

the diagnosis of OA. However, additional studies assessing the predictive positive and negative values of serial measures of nonspecific bronchial hyperresponsiveness at and away from work for diagnosing OA are required to know the diagnostic performance of this test. Nonetheless, normal airway responsiveness after a period at work at which time the workers experience their respiratory symptoms makes the diagnoses of OA and asthma improbable. In this case, an alternative diagnosis should be investigated.³

As said, a serial measurement of PEF at work and away from work has been found to be useful in confirming OA.⁴⁸ The minimum period of PEF monitoring should be 2 weeks at work with a significant exposure to the suspected causative agent and a similar period away from work, unless significant changes are recorded earlier at work. Asthma treatment should be kept constant throughout the period of monitoring. However, similarly to common asthma, compliance with PEF monitoring has been shown to be poor and the results may be falsified if an electronic PEF meter is not used.⁴⁹

SIC tests consist of exposing the subjects to the suspected occupational agent in the laboratory and/or at the workplace.^{50,50a} These tests are considered to be the reference tests, but they are time consuming and require specialized facilities available in only a few centers. Specific-challenge tests are useful when (1) the diagnosis of OA remains in doubt after serial monitoring of PEF or airway responsiveness; (2) a patient clearly has OA, but the causal agent needs to be identified; (3) a new agent is suspected of causing OA; and (4) the patient cannot be returned to the incriminated workplace. A false-negative response may be obtained if the wrong agent is used or if the exposure

Table 72-3 Advantages and Limitations of the Diagnostic Tests Used in the Investigation of Occupational Asthma

Diagnostic Tests	Advantages and Limitations
Assessment of nonspecific bronchial hyperresponsiveness	<ul style="list-style-type: none"> ■ Simple, low cost. ■ Confirms the diagnosis of asthma. ■ Low specificity for diagnosis of OA. The absence of airway hyperresponsiveness does not exclude the diagnosis of OA in subjects who have been removed from the workplace.
Immunologic tests	<ul style="list-style-type: none"> ■ Easy to perform, low cost. ■ Commercial extracts are available (skin prick tests or specific IgE for HMW agents). ■ Measurement of specific IgE available for some LMW agents (anhydrides, acids, isocyanates, aldehydes), but low sensitivity. ■ Lack of standardization for the majority of occupational allergens except for latex. ■ Can identify the sensitization but not necessarily the disease.
PEF monitoring	<ul style="list-style-type: none"> ■ Low cost. ■ Requires the workers' collaboration. ■ Low adherence (<60%). ■ Possible falsification of results. ■ Requires 2 weeks at and away from work, which is not always possible. ■ Impossible to perform when the worker has been removed from work. ■ No standardized method for interpreting the results. ■ Interpretation of the results requires experience.
Specific-inhalation challenges in the laboratory	<ul style="list-style-type: none"> ■ Confirmation of the diagnosis of OA when the test is positive. ■ False-negative tests are possible. ■ Costly. ■ Available in a small number of centers worldwide.
Specific-inhalation challenges at the workplace	<ul style="list-style-type: none"> ■ Exclude diagnosis if negative when performed in the usual work conditions. ■ Requires usual work conditions. ■ Costly.
Noninvasive measures of airway inflammation	<p>Sputum cell counts</p> <ul style="list-style-type: none"> ■ Impossible to falsify ■ Bring additional evidence to the diagnosis of OA ■ Costly ■ Not widely available ■ Does not confirm or exclude the diagnosis of OA by itself <p>Exhaled NO</p> <ul style="list-style-type: none"> ■ Easy to perform ■ Inconsistent results ■ Difficult to interpret ■ Affected by many different factors

conditions are not comparable with those in the workplace. SICs have been shown to be safe and induce rarely severe asthmatic reactions requiring administration of systemic steroids.^{50b}

Noninvasive measures of airway inflammation are increasingly used during the investigation of OA. There is evidence that OA is associated with an increase in the sputum eosinophil percentage during periods at work and a decrease after removal from exposure.^{51,52} In settings where this tool is available, it may complement the current investigation of OA. Although the measurement of *fractional exhaled nitric oxide* (FeNO) is easier to obtain than sputum cell counts, the current evidence does not show a clear benefit of using FeNO in the investigation of OA.⁵³ The interpretation of an increased FeNO is more difficult than sputum differential cell counts due to its lack of specificity, as well as the potential confounding factors that may influence the results. However, recent evidence shows a high specificity of this test in subjects exposed to HMW agents.⁵⁴ Whether the monitoring of FeNO should be used in some phenotypes of OA remains to be determined.⁵⁴ Making an accurate diagnosis of OA is crucial due to the significant social and financial consequences associated with this diagnosis.

OUTCOME AND MANAGEMENT OF SENSITIZER-INDUCED ASTHMA

According to recent systematic reviews of the existing data, the complete avoidance of exposure to the causal agent remains the optimal treatment of immunologic OA.^{55,56} Although a reduction of exposure to the agent can be considered as an alternative option, the limited available evidence indicates that this option is less beneficial than complete cessation of exposure because it is associated with a lower likelihood of asthma improvement and a higher risk of worsening.⁵⁷

Immunotherapy has only been tested in workers with allergy and/or OA to HMW agents for which an IgE-dependent reaction has been demonstrated. Immunotherapy has been mainly tested in health care workers allergic to latex.⁵⁸ Although immunotherapy can reduce cutaneous and respiratory symptoms in health care workers allergic to latex, this treatment can induce systemic reactions in a large number of treated subjects.⁵⁹ Small or uncontrolled studies have reported an improvement of allergic and respiratory symptoms after immunotherapy to some selected agents (cereal,⁶⁰ sea squirt,⁶¹ laboratory animal,⁶² and wood⁶³). However, whether immunotherapy can alter the

course of OA in the long term remains to be determined. Further studies need to be conducted before immunotherapy can be recommended for the treatment of OA to HMW agents.

A few case reports provided some suggestion that treatment with the anti-IgE omalizumab could improve asthma control in subjects with flour-induced OA, who remain exposed to the causal work environment, although further prospective investigations are required in subjects who choose to continue exposure.³

Clinicians should be aware that OA is not always reversible after cessation of exposure to the sensitizing agent. Asthma symptoms and *airway hyperresponsiveness* (AHR) persist in approximately 70% of the patients with OA several years after removal from the offending environment.⁶⁴ Besides environmental interventions, the pharmacologic treatment of OA should follow the clinical practice guidelines for asthma.⁶⁵

Primary prevention aims at preventing the development of immunologic sensitization to workplace agents and subsequent OA.^{3,66} Primary preventive strategies should focus on the control of workplace exposures because there is strong evidence supporting a dose-response relationship between the level of exposure to sensitizing agents and the development of OA. The control of exposure can be achieved through a panel of measures that include the elimination of agents with a known sensitizing potential whenever feasible: (1) the modification of sensitizing materials (e.g., encapsulation of detergent enzymes); (2) the substitution of highly sensitizing agents by materials with lower asthmagenic potential (e.g., nonvolatile oligomers of diisocyanates, latex gloves with a lower content in powder and protein allergens); (3) engineering changes to the workplace (e.g., exhaust ventilation, enclosure of industrial processes); (4) information and education of workers and employers on safe work practices; and (5) the use of personal protective equipment for specific tasks.^{67,68} Another approach is to identify susceptible individuals at the time of preemployment examination and exclude them from employment or from high-risk jobs. This strategy is inefficient and unduly discriminating because the currently identified markers of individual susceptibility (see Table 72-2) offer only a low positive predictive value for the development of OA, especially when these markers, such as atopy, are highly prevalent in the general population.³ Nevertheless, physicians caring for adolescents with asthma and allergic diseases may offer useful advice regarding careers in which their underlying atopic status increases the risks for work-related sensitization to HMW agents.⁶⁹

Secondary prevention of sensitizer-induced OA involves the detection of the disease process at an early (preferably preclinical) stage to modify the disease process through appropriate interventions to eliminate exposure. The rationale underlying secondary prevention is the consistent finding that the outcome of OA is better with an early diagnosis and milder disease at the time of removal from exposure.^{64,70} Increasing awareness of the disease among workers and health professionals is a key step to enhance the recognition of OA because the condition still remains underdiagnosed and inappropriately investigated.⁷¹ There is recent evidence that appropriately designed surveillance

programs are effective in identifying OA in subjects with less severe asthma and a more favorable outcome.⁷²

A few observational studies and historical data indicate that prevention is effective in reducing the incidence of OA and occupational rhinitis caused by natural rubber latex in health care workers,⁷³ enzymes in the detergent industry,⁷⁴ flour,⁷⁵ laboratory animals,⁷⁶ and isocyanates.⁷² However, available data do not distinguish the relative effect of the diverse components of prevention strategies because they are usually implemented as multicomponent programs targeting education, control of exposure, and medical surveillance.

SOCIOECONOMIC IMPACT

Studies worldwide have shown that OA is associated with substantial financial consequences for affected workers and society as a whole.^{77,78} There is growing evidence that WRA is associated with more severe asthma^{79,80} and with a higher health care resource utilization⁸¹ as compared with asthma unrelated to work. In addition, OA generates higher indirect costs than nonoccupational asthma because the former condition most often requires job changes to either avoid or reduce exposure to the causative agent.⁸² Follow-up studies of workers with OA have consistently documented that the condition is associated with a high rate of prolonged unemployment, ranging from 18% to 69%, and a reduction in work-derived income in 44% to 74% of affected workers.⁸³ A poorer socioeconomic outcome is associated with the need for a complete avoidance of exposure to the sensitizing agent, a lower level of education, an older age, and lack of effective job retraining programs.⁸³

Because the specific bronchial hyperreactivity to occupational agents almost never completely disappears, workers with OA should be considered as permanently and completely disabled for jobs involving exposure to the sensitizing agent that caused their OA.⁸⁴ They should be thoroughly informed about the possibilities for compensation, and established cases should be reported to the appropriate public health authorities, according to national regulations. Evaluation of physiologic impairment should take into account the characteristic features of asthma and should be based on the level of airway obstruction, the degree of nonspecific bronchial hyperresponsiveness, and the intensity of medication required for controlling asthma.³

IRRITANT-INDUCED ASTHMA

EPIDEMIOLOGIC ASPECTS

Surveillance programs conducted in various countries indicated that RADS and IIA account for 5% to 18% of all reported cases of WRA.⁸⁵ However, few population-based surveys have addressed the impact of acute inhalation incidents on the global burden of asthma. The longitudinal part of the European Community Respiratory Health Survey found that reported acute inhalation incidents were associated with a higher risk of new-onset asthma.²⁶ Several cross-sectional studies revealed that asthmatic individuals more often report a history of a single high-level exposure to irritant cleaning products than healthy controls.⁸⁶⁻⁸⁸ A

longitudinal study of rescue and recovery workers exposed to high levels of alkaline dust during and after the World Trade Center disaster showed an increased risk of new-onset asthma in the follow-up period of 5 to 6 years, particularly in the first months after exposure.⁸⁹

Longitudinal workforce-based studies have documented an increased risk of asthma among workers with repeated exposures to high levels of chlorine, ozone, and sulphur dioxide in metal production and pulp mill workers.⁹⁰⁻⁹² Exposures to high levels of irritants in the workplace are called “gassings” and are often recalled by workers in epidemiologic studies. Few epidemiologic studies have supported the role of repeated and/or chronic exposure to lower levels of irritant compounds at work in the development of asthma, with the exception of workers exposed to cleaning agents.⁹³ In these populations, the frequent use of chlorine bleach and ammonia has been associated with an increased risk of asthma.^{86,94} A spectrum of exposures to irritant agents are likely to induce different clinical presentations of asthma ranging from RADS, when subjects are exposed to high concentrations of irritants agents, to “low-dose reactive airways dysfunction syndrome,” “not-so-sudden IIA,” or “IIA with latency” when subjects are exposed to irritants at lower concentrations. However, “low-level” irritant-induced asthma cannot currently be reliably diagnosed in the individual worker.

PATHOPHYSIOLOGY

Several factors may influence the pulmonary responses to irritants, such as the intensity of exposure, physical properties (e.g., vapor pressure, solubility), and the chemical reactivity.⁹⁵ Although many irritants are odorous and pungent, it is worth remarking that odor is not related to toxicity. The resulting biologic effect will depend on the depositing of the irritant in the upper and/or lower airways. Water-soluble irritants and particles with an aerodynamic diameter larger than 5 μm are predominantly deposited in the upper respiratory tract and proximal airways. Water-insoluble agents and particles of 0.5 to 5 μm can reach the distal airways and alveoli, often without causing much sensory irritation (see Chapters 11 and 75).

The development of acute IIA has been associated with a wide variety of high-level exposures to irritant fumes, gases, sprays, or even dusts (Table 72-4).⁹⁶ Typically, the exposure is caused by spills of volatile compounds, accidental releases of irritants under pressure, accidental fire with release of complex mixtures of thermal degradation products, or inadvertent reduction of the air ventilation rate in a confined space.⁹⁵ The nature and concentrations of inhaled irritants generated during workplace exposure incidents are most often unavailable.

Inhaled irritants provoke epithelial cell damage and persistent inflammatory response and airway remodeling, although the precise pathophysiologic mechanisms leading to persistent asthma remain largely speculative.⁹⁵ Bronchial biopsy samples obtained after a high-level exposure to irritants revealed marked epithelial desquamation, inflammatory changes with predominance of lymphocytes, airway remodeling, and collagen deposition in the bronchial wall.^{97,98} Similar changes have been described in animal models.⁹⁹⁻¹⁰¹ Two studies provided information on the long-

Table 72-4 Examples of Exposures Causing Acute Irritant-Induced Asthma

Exposure	Examples
Gases	Chlorine (e.g., released by mixing sodium hypochlorite with acids), chloramines (released by mixing sodium hypochlorite with ammonia), sulfur dioxide, nitrogen oxides, dimethyl sulfate
Acids	Acetic, hydrochloric, hydrofluoric, hydrobromic acids
Alkali	Ammonia, calcium oxide (lime), hydrazine
Biocides	Formalin, ethylene oxide, fumigating agents, insecticides (sodium methyldithiocarbamate, dichlorvos)
Halogenated derivatives	Bromochlorodifluoromethane (fire extinguisher), trifluoromethane, chlorofluorocarbons (CFC, thermal degradation products of freons), uranium hexafluoride, hydrogen and carbonyl fluoride
Solvents	Perchloroethylene
Fumes	Diesel exhaust, paint fumes, urea fumes, fire smoke, iodine compounds (iodine and aluminium iodide, hydrogen iodide), diethylaminoethanol (corrosion inhibitor)
Sprays	Paints (not specified), floor sealant (aromatic hydrocarbons)
Dusts	World Trade Center alkaline dust, calcium oxide (lime)
Potential sensitizers	Isocyanates, phthalic anhydride

term outcome of airway inflammation and remodeling in a large series of subjects with acute IIA.^{98,102} Both showed an inflammatory profile similar to what has been described in sensitizer-induced OA after removal from exposure, with an increase of eosinophils in some patients or neutrophils in others. However, in patients with IIA, subepithelial fibrosis was more prominent than in those with sensitizer-induced asthma. Altogether, in IIA, the pathologic changes observed during the acute phase are consistent with an acute toxic injury, whereas the long-term phase is similar to sensitizer-induced OA.

RISK FACTORS

The environmental and host factors that determine the initiation and persistence of IIA remain largely unknown. A relationship between the level of exposure assessed qualitatively by industrial hygienists and the prevalence of nonspecific bronchial hyperresponsiveness has been documented in subjects who had been exposed to a spill of acetic acid.¹⁰³ In a follow-up survey of pulp mill workers exposed to high levels of chlorine, the severity of gassing incidents, as evidenced by hospital emergency department visits, was a more significant risk factor for the persistence of nonspecific bronchial hyperresponsiveness than was the number of incidents.¹⁰⁴ The development of IIA did not appear to be associated with smoking and atopy.^{103,104} Among the World Trade Center rescue and cleaning workers, the main risk factors for the development of a respiratory disease were the presence on the site during the first 48 hours and the duration of exposure during rescue and cleaning.¹⁰⁵ Smoking was a predisposing or an additive risk factor, whereas atopy was identified as a risk factor for upper, but not for lower, airway disease.

Table 72-5 Diagnostic Criteria for the Reactive Airways Dysfunction Syndrome (i.e., Acute Onset Irritant-induced Asthma)

1. Absence of preexisting asthma symptomatology or a history of asthma in remission
2. Onset of asthma symptoms after a single specific inhalational exposure or accident
3. Exposure to an irritant vapor, gas, fume, or smoke in high concentration
4. Onset of asthma symptoms within minutes to hours and less than 24 hours after the exposure
5. Presence of airflow limitation with a significant bronchodilator response or nonspecific bronchial hyperresponsiveness to histamine/methacholine
6. Exclusion of other pulmonary disorders that can explain the symptoms or simulate asthma

Adapted from Brooks SM, Weiss MA, Bernstein IL: Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 88(3):376–384, 1985; Brooks SM, Bernstein IL: Irritant-induced airway disorders. *Immunol Allergy Clin North Am*. Nov31(4):747–768, 2011; Tarlo SM, Balmes J, Balkissoon R, et al: Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. *Chest* 134(3 Suppl):15–41S, 2008.

DIAGNOSIS

RADS (i.e., acute IIA) is characterized by the onset of asthma symptoms within 24 hours after a single, most often accidental, high-level exposure to a wide variety of irritant substances in subjects without preexisting asthma. Brooks and coworkers proposed stringent clinical and functional criteria for the diagnosis of this condition (Table 72-5).^{3,6} The presence of asthma should be substantiated by spirometry demonstrating airflow limitation with a significant bronchodilator response or nonspecific bronchial hyperresponsiveness to methacholine or histamine. Conditions with similar clinical manifestations, such as irritant-induced vocal cord dysfunction, should be carefully considered.³ The causal role of the workplace exposure can be documented with a reasonable level of confidence by the strong temporal association between an inhalation accident and the rapid onset of asthma symptoms. Such cases should be considered as “definite” IIA. Nevertheless, the World Trade Center tragedy brought new insights by suggesting that asthma can develop insidiously over a few months after a massive exposure to a complex mixture of alkaline dust and combustion products.^{106,107} In subjects who reported multiple high-level exposures to irritants, though less clearly massive than in RADS, the causal relationship can be supported by the documentation of repeated symptomatic inhalation accidents requiring medical care or reports to first aid units or occupational health services. These subjects should be regarded as having “probable” IIA.

There are some clinical features that clearly distinguish acute IIA from sensitizer-induced OA. Unlike sensitizer-induced OA, acute IIA does not require a latency period of exposure before the appearance of asthma, but an apparent latency period can be present in IIA that develops after multiple high-level exposures. Subjects with IIA do not develop WRA symptoms after reexposure to low concentrations of the irritant that initiated the symptoms because they are not “sensitized” to the offending agent. However, subjects with acute IIA may experience WRA symptoms because

their nonspecific bronchial hyperresponsiveness makes them more susceptible to irritant stimuli at work. The development of specific bronchial hypersensitivity has been documented after a single, intense exposure to some LMW chemicals.¹⁰⁸ Conversely, known sensitizers can induce IIA when inhaled at high concentrations.^{109,110} In such instances, specific inhalation challenges with the suspected agent may be useful in distinguishing IIA from sensitizer-induced-OA.

In the clinical reports that described the onset of asthma after repeated, often daily exposure to “moderate” levels of respiratory irritants at work, the evidence supporting the work-relatedness of asthma was weak and relied on the following findings: (1) a history of adult onset of asthma (or even the reactivation of a previously quiescent asthma⁹); (2) a history of repeated exposure to irritants; and (3) the absence of an identified sensitizer in the subject’s working environment. Distinguishing IIA attributed to repeated, moderate level exposures from coincidental asthma that is not work-related is elusive on a clinical basis. The possibility of “chronic/delayed-onset IIA” can only be inferred from epidemiologic studies documenting an increased risk of adult-onset asthma in certain occupations that are associated with frequent “moderate/excessive” exposures to irritant compounds.

OUTCOME AND TREATMENT

The few available data on the outcome of IIA indicate that it is quite similar to what has been described in subjects with sensitizer-induced OA after avoidance of exposure to the causal agent. Nonspecific bronchial hyperresponsiveness can improve over several years after an acute symptomatic inhalation accident.^{104,111} On the long term, however, about three quarters of subjects with acute IIA show persistent nonspecific bronchial hyperresponsiveness and require treatment with inhaled corticosteroids.¹¹²

Limited data exist on the management of IIA, and they are mainly related to case reports of acute IIA.¹¹³ There is some evidence that subjects with IIA benefit rapidly from treatment with oral and/or inhaled corticosteroids, although the dose and duration of treatment remains unknown. Unlike workers with sensitizer-induced OA, those with acute IIA may be able to continue in their usual jobs with appropriate asthma management, although they may subsequently experience worsening of their asthma symptoms on exposure to irritants at work, which may substantially reduce their capacity to work in polluted or dusty environments. The management of IIA may be further complicated by associated disorders, such as chronic rhinitis, perceived intolerance to multiple chemicals, and post-traumatic stress syndrome, which can result from an accidental exposure to irritant substances at work.^{89,112,114}

PREVENTION

Prevention of IIA should be primarily aimed at eliminating the risk of high-level exposures that can cause asthma. Such strategies should be directed toward the control of exposures to safe levels by occupational hygiene measures such as containment and adequate ventilation. Continuous monitoring of airborne concentrations of potential

respiratory irritants and alarm systems to detect peak exposures may be appropriate in some settings. An important component of prevention is the implementation of workers' educational programs on safe handling of chemicals, effective use of personal protective equipment, and measures to take in the event of an accident at work.

WORK-EXACERBATED ASTHMA

EPIDEMIOLOGIC ASPECTS

The prevalence of WEA reported in the literature varies according to the definition and the type of settings (clinical vs. epidemiologic) in which the WEA was assessed. Twelve studies have provided overall estimates of prevalence of WEA. These studies were conducted in the general population or in general health care settings in seven countries. The definition of asthma was not consistent and included physician-diagnosed asthma as determined from self-reports or medical records, or diagnosis based on an objective measurement of pulmonary function.^{115,116} Some of the studies reported prevalence as a percentage of all adults with asthma, and others as a percentage of all working adults with asthma. The prevalence of WEA from these 12 studies ranged from 13% to 58%, with a median of 21.5%. In the study where WEA was diagnosed according to changes in PEF between periods at and away from work, the prevalence of WEA was 14% in asthmatic workers.¹¹⁷ The most recent systematic review of the literature estimates that 21.5% of the cases of asthma are exacerbated by conditions at the workplace.² Therefore, although the prevalence varies quite widely from one study to another due to the definition and the population of interest, the prevalence of WEA can be estimated to be around 20% of the adult asthma population, which constitutes a substantial proportion of the whole asthmatic population.

PATHOPHYSIOLOGY

The pathophysiology of WEA is likely to be largely dependent on the type of triggers inducing asthma exacerbations. There is no reason to believe that the pathophysiology of WEA is different from the pathophysiology of asthma exacerbations observed in NWRA when the triggers are common allergens. When triggers consist of irritant agents, it is likely that the pathophysiology resembles what is seen in IIA. An airway epithelium injury is likely to play a pivotal role, and the injury intensity of the epithelial layer may be correlated with the respiratory function impairment as demonstrated in New York firefighters who intervened on 9/11.¹¹⁸ In murine models of chlorine exposure, oxidative stress plays a pivotal role in the pathogenesis of this condition and the administration of antioxidants can mitigate the epithelial damage.¹¹⁹ As shown in the animal models of chlorine exposure, the extent of the damage is likely to depend on the dose of the irritant agent inhaled.

WORK EXPOSURES ASSOCIATED WITH WORK-EXACERBATED ASTHMA

The identification of exposures associated with WEA has been reported either in studies that recorded the agents to

which the subjects with WEA were exposed in clinical settings, surveillance programs, or worker compensation programs or by using a risk-set approach, testing associations between occupational exposures and WEA while controlling for potential confounders. The studies assessing individual cases of WEA were performed mainly in North America¹²⁰⁻¹²⁸ or Europe.¹²⁹ The most commonly described agents were chemicals, dust, smoke, paints, and cleaning products. Although less frequently encountered than these agents, physical factors such as exercise,¹²⁸ temperature,¹²⁰ or emotional stress¹²¹ have also been reported to be associated with WEA.

DIAGNOSIS OF WORK-EXACERBATED ASTHMA

WEA should be suspected in all patients whose asthma is difficult to control, in patients who complain of a worsening of their symptoms, or in those who require an increase of their asthma medication when at work.³

Before establishing a diagnosis of WEA, the diagnosis of asthma needs to be confirmed by objective measures. Most asthma guidelines recommend the performance of spirometry, both prebronchodilator and postbronchodilator in order to show a FEV₁ reversibility of 12% with an absolute increase of at least 200 mL.¹³⁰ In the absence of a reversible airflow limitation, the measurement of airway hyper-responsiveness can confirm the diagnosis of asthma. The lack of objective confirmation of the diagnosis of asthma can lead to misdiagnosis in 30% of cases.¹³¹ Furthermore, nonspecific respiratory symptoms are frequent and can mimic asthma in workers exposed to a dusty or irritant environment.¹³²

The diagnosis of WEA relies on the demonstration of (1) a relationship between asthma exacerbations and occupational exposures or (2) poor asthma control during periods at work, along with (3) the determination that OA is unlikely. Asthma exacerbations or loss of asthma control can be documented by a change in the frequency and severity of asthma symptoms or by the need for an increase in asthma medications. Asthma exacerbations can also be documented by the need for emergency visits or hospitalizations or by changes in respiratory function at work. Serial PEF monitoring can show increased variability during periods at work compared with periods away from work.¹³³ Identifying the factors that trigger asthma symptoms is important to not only confirm the diagnosis of WEA but also decrease or remove the adverse environmental conditions at the workplace. Identifying multiple triggers is common because the workers are frequently exposed to several agents concomitantly.

Although there are limited data concerning the management of WEA, professional organizations have advised minimizing exposures at work and optimizing standard medical management for asthma (e.g., pharmacologic treatment, avoidance of symptom triggers).^{3,134} Although there is clear evidence that a persistent exposure to the occupational agent that caused their asthma is detrimental for workers with OA,⁵⁵ the impact of continuing exposure to triggers for WEA has not been well studied and thus is unknown at this time. There is limited evidence that workers with OA may have a greater improvement in their lung function and asthma control than subjects with WEA when removed from exposure.¹³⁵⁻¹³⁷

DIFFERENTIATING WORK-EXACERBATED ASTHMA FROM NON-WORK-RELATED ASTHMA OR OCCUPATIONAL ASTHMA

A few studies have compared workers with WEA to adults with NWRA. The clinical characteristics of workers with WEA did not differ greatly from adults with NWRA. Some studies reported that workers with WEA tended to be older,^{135,138} while others found an increased proportion of smokers in subjects with WEA.⁸¹ No specific risk factors have been clearly identified for WEA.

Workers with WEA are often difficult to differentiate from asthmatic subjects with OA, especially in cases who report a new onset of asthma while in the current workplace. The studies that compared subjects with WEA and OA report discrepant findings that can be explained by the different populations studied (general population vs. tertiary clinics). On the basis of U.S. cases that fulfilled the surveillance case definitions set by the *Sentinel Event Notification System for Occupational Risks* (SENSOR), Goe and colleagues¹³⁹ found that subjects with WEA were more likely to be female, young, nonwhite, and nonsmokers. These findings were not confirmed in the studies where WEA cases were from a referral clinic and defined by a worsening of asthma symptoms when at work and a negative SIC to the suspected agent(s).^{52,140}

Lemière and colleagues¹³⁷ found that after adjusting for age, asthma control, and FEV₁, the diagnosis of WEA was associated with more frequent prescriptions of inhaled corticosteroids, a noneosinophilic phenotype, and a trend toward a higher proportion of smokers than the diagnosis of OA.

The timing of the onset of asthma with respect to the start of employment at the workplace does not necessarily differentiate WEA from OA; for example, Larbanois and colleagues¹⁴⁰ defined WEA by the presence of WRA symptoms and a negative SIC and showed that only 7% of the 71 WEA subjects had asthma before employment. Also, onset of asthma before employment in the workplace of interest does not preclude the diagnosis of OA. Workers with previously diagnosed asthma can become sensitized to a new

agent at their workplace and develop OA. An increase in asthma symptoms or severity is usually noticed at this time.

In both WEA and OA, there is a worsening of asthma symptoms when at work with an improvement when removed from exposure. Serial PEF monitoring can show a greater variability during periods at work compared with periods away from work in both types of cases, and the PEF variability is greater in subjects with OA than with WEA.¹³³ However, in clinical practice, the difference in the magnitude of PEF variability does not allow differentiating WEA from OA.

SIC testing can be performed to diagnose OA, with a positive result considered indicative of OA. Although there can be false-negative tests, a negative SIC favors the diagnosis of WEA. In several clinical studies, the definition of OA and WEA relied on the positivity or negativity, respectively, of SIC.⁵² However, those tests are not available in the majority of settings.

An eosinophilic phenotype is more frequently found in subjects with OA compared with WEA. Workers with OA usually show an increase in eosinophilic inflammation when exposed to the agents to which they are sensitized. In contrast, workers with WEA had no increase in eosinophilic inflammation when at work compared with periods away from work or during exposure to the suspected agents in the laboratory.⁵²

Table 72-6 summarizes demographic, clinical, functional, and inflammatory differences between subjects with WEA and subjects with NWRA or OA.

SOCIOECONOMIC IMPACT OF WORK-EXACERBATED ASTHMA

WRA has a major impact on workers and society as a whole. The workers tend to experience asthma symptoms interfering with their work productivity and causing absenteeism. Although there are no current data on absenteeism in subjects with WEA while at work, the cost related to reduced workforce participation, restrictions in job duties, loss of work days (“absenteeism”), or decreased effectiveness while at work (“presenteeism”) is likely to be substantial.

Table 72-6 Characteristics of Work-Exacerbated Asthma (WEA) in Comparison with Non-Work-Related Asthma and Occupational Asthma

Characteristics	Compared with Adults with Non-Work-Related Asthma	Compared with Adults with Occupational Asthma
Gender	Similar ^{135,138} or predominance of men in subjects with WEA ⁸¹	Similar ⁸¹ or greater number of women in subjects with WEA ¹³⁹
Age	Older ^{135,138}	Similar or younger ¹³⁹
Race	More nonwhite ¹³⁵	More nonwhite ¹³⁹
Education	Less ¹³⁵	N/A
Smoking habits	More likely to have smoked cigarettes ¹³⁵	More smokers ⁸¹
Asthma severity	More asthma exacerbations requiring emergency department visits or hospitalizations in workers with WEA, ⁸¹ More days with asthma symptoms, more severe asthma based on self-report ¹³⁵	Same number of asthma exacerbations requiring emergency department visits or hospitalizations ¹³⁷ Greater need of ICS in subjects with WEA ¹³⁷
Functional characteristics	Similar FEV ₁ , PC ₂₀ ⁸¹	Less PEF variability when at work in subjects with WEA compared with OA ¹³³ PC ₂₀ may be lower in subjects with WEA ¹⁴⁰
Airway inflammation	Neutrophilic inflammation inconsistently found depending on the study ^{51,52}	Less likely to have eosinophilic airway inflammation ^{52,137}

ICS, inhaled corticosteroids; OA, occupational asthma; PEF, peak expiratory flow rate.

Presenteeism is the term used to describe employees who are physically present at their jobs but experience decreased productivity because of illness or other barriers to performance. Unproductive workers who are present at work seem to represent even higher costs than those who are absent.¹⁴¹ In addition to the decreased work productivity, the workers have to seek medical care, go to the emergency department, or be hospitalized.

If one examines all of WRA, the 2001 and 2002 data from Breton and colleagues¹⁴² showed that the subjects who reported suffering from WRA in the United States were 4.8 times more likely to report having an asthma exacerbation, 4.8 times more likely to visit the emergency department at least once, and 2.5 times more likely to visit their physician for an asthma exacerbation in the previous 12 months compared with individuals with NWRA. Lemièrre and colleagues⁸¹ confirmed those data showing that 341 subjects with WRA followed in a tertiary Canadian clinic had more visits to the clinic for asthma (4.1 vs. 1.2 $P < 0.05$) and hospitalizations for asthma (0.04 vs. 0.008 $P < 0.05$) during the year preceding their diagnosis than 381 subjects with NWRA. In a recent cohort study of subjects with WRA followed in two Quebec tertiary clinics, Lemièrre and colleagues showed that the health care-related costs were similar between WEA and OA but 10-fold greater than the costs related to NWRA in the year preceding the assessment of those subjects in tertiary clinics.¹³⁷

Although the cost of OA decreased significantly after the diagnosis was made and the patients were removed from exposure, the cost of WEA following the diagnosis did not decrease significantly. In the few studies in which the work disruption of subjects with WEA was evaluated, it was reported to be similar to OA.^{136,140} There is a high rate of unemployment in workers with WEA (30% to 50%),^{140,143} which is equivalent to subjects with OA. Job changes are frequent in subjects affected with WEA. The reduction in earnings seems to be similar in WEA and OA.¹⁴⁰ Overall, WEA exerts a large socioeconomic impact on workers and society by using a large amount of health care resources and inducing substantial disruption of work.

Key Points

- The workplace environment can lead to the development of different types of *work-related asthma* (WRA), including occupational asthma (i.e., asthma caused by work through either immunologic [sensitizer induced] or nonimmunologic [irritant induced] mechanisms) and work-exacerbated asthma (i.e., preexisting or coincident asthma exacerbated by nonspecific stimuli at work).
- WRA represents a significant public health concern due to the high-prevalence, long-term respiratory

health consequences, and socioeconomic consequences for affected workers and society.

- For subjects with sensitizer-induced occupational asthma, the recommended treatment is complete avoidance of the causal agent, although the rate of recovery is low, especially when the diagnosis is delayed.
- The diagnosis of sensitizer-induced occupational asthma should be established with the highest level of accuracy by performing a comprehensive investigation in order to avoid unwarranted removal from exposure.
- Unlike those with sensitizer-induced occupational asthma, subjects with irritant-induced occupational asthma do not develop work-related asthma symptoms after reexposure to low concentrations of the irritant that initiated the symptoms.
- Irritant-induced asthma is characterized by early onset after exposure; however, irritant-induced asthma can also develop insidiously over a few months after a massive exposure to a complex mixture of alkaline dust and combustion products, as shown in the World Trade Center disaster.
- *Work-exacerbated asthma* (WEA) should be suspected in all patients whose asthma is difficult to control and in patients who complain of a worsening of their symptoms or who require an increase of their asthma medication when at work.
- Workers with WEA are often difficult to differentiate from asthmatic subjects with occupational asthma, especially in cases who report a new onset of asthma while in the current workplace.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION

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HARD-METAL DISEASE**SILICON CARBIDE (CARBORUNDUM) PNEUMOCONIOSIS****NEW PNEUMOCONIOSES****INTRODUCTION****DEFINITIONS**

The *Encyclopedia of Occupational Health and Safety* of the International Labour Organization (ILO)¹ defines pneumoconiosis as “the accumulation of dust in the lungs and the tissue reactions to its presence.” The main reaction to mineral dust in the lungs is fibrosis. Not included in the definition of pneumoconiosis are conditions such as asthma, *chronic obstructive pulmonary disease* (COPD), and hypersensitivity pneumonitis, which do not require dust to accumulate in the lungs.

ACCUMULATION OF DUST IN THE LUNG AND TISSUE REACTIONS

The *deposition* of dust in the lungs depends on the size and geometric and aerodynamic properties of the particles. Particle clearance is determined by the mucociliary escalator and cellular mechanisms, in particular, the macrophage (see Chapter 12). Dust *accumulation* in the lungs is determined by deposition and clearance. The biologic *response* depends on the amount and duration of the accumulation and the nature of the dust. Tissue responses to inorganic dusts depend on particle size and the biologic activity of the dust, which in turn depends on its surface chemical and

physical properties.¹ Some dusts, such as coal, are relatively inert and may accumulate in considerable amounts with minimal tissue response; others, in particular silica and asbestos, have potent biologic effects. Parenchymal responses include nodular fibrosis (the classic example is the silicotic nodule), diffuse fibrosis (the classic example is asbestosis), and macule formation with focal emphysema (the classic example is the coal dust macule).² Irregular and mixed fibrotic patterns have been described as a consequence of mixed exposures involving other mineral dusts or fibers in addition to silica dust exposure.³ For any given dust exposure, the severity of the tissue reaction appears to be related to the cumulative lung dust burden.

EXPOSURE-RESPONSE RELATIONSHIPS

In epidemiologic studies, the dust burden in the lung can be assessed only indirectly. However, at an individual level, exposure can be estimated more directly from the job history, from the engineering history of the plant, including the efficiency of dust control, and from environmental measurements.

The demonstration of exposure-response relationships has implications for clinical practice. For instance, a clinical diagnosis of pneumoconiosis is strengthened greatly when there has been exposure to dust levels known to be associated with an increased risk of disease. Although

exposure-response relationships generally describe the events in a work force, there may be heavily exposed individuals who remain unaffected and lightly exposed individuals with disease. Thus, environmental standards such as threshold limit values set by the *American Conference of Government and Industrial Hygienists* (ACGIH) are levels that if respected throughout an individual's working life, are unlikely to be associated with disease. However, dust sampling may be problematic and even in a workplace where average dust concentrations are below the threshold limit value, nearly half the samples exceed this value.⁴ Thus, a clinician should not reject the diagnosis of pneumoconiosis solely on the grounds that exposure was too remote, too short, or in a workplace where the threshold limit value was maintained. The subject in question may be unusually susceptible, may have had an unusual exposure profile, or may retain more dust than others similarly exposed.

CHEST IMAGING

The ILO standard films for the descriptive interpretation of the radiologic appearance of diffuse parenchymal lung disease⁵ were originally developed for epidemiologic studies of occupational lung disease but may also be used for clinical interpretation. The 2011 ILO guidelines accommodate the use of digital images, and a set of standard digital images is available. Apart from improving consistency in the reading of parenchymal disease, which is notoriously subject to reader variability, they enable the clinician to set an individual case in the context of the available epidemiologic information.⁵ Small opacities in the parenchyma are classified by shape and size: p, q, or r for rounded opacities (diameter, <1.5 mm, 1.5 to 3 mm, or >3 mm, respectively) and s, t, or u for irregular opacities (width, <1.5 mm, 1.5 to 3 mm, or >3 mm, respectively). Profusion category (or concentration) is read on a 12-point scale (0/–, 0/0, 0/1, up to 3/2, 3/3, and 3/+) in comparison with the standard radiographs. Large opacities are classified as category A (for one or more such opacities with a diameter > 1 cm but not exceeding a combined diameter of 5 cm), category B (one or more opacities > 5 cm in diameter and whose combined area does not exceed one upper zone), and category C (>B). Provision is made to grade pleural thickening for width ($a \leq 5$ mm, $b > 5$ mm but < 10 mm, and $c \geq 10$ mm) and extent (1 = up to one quarter, 2 = one quarter to one half, and 3 = over one half of the lateral chest wall). The extent of pleural calcification is also graded, and there are provisions for comment on other features.

In the United States, the *National Institute of Occupational Safety and Health* (NIOSH) administers the National Coal Workers' Health Surveillance Program, which provides coal miners with the opportunity of a periodic medical examination. The program incorporates quality control in terms of radiographic technique and reading procedures using the ILO classification and reader training. This involves training seminars for physicians who may qualify as "A" readers (i.e., attended the seminars) or "B" readers, who passed a comprehensive examination on the basis of 120 radiographs read into the ILO classification.

Conventional chest radiographs or digital images are the cornerstone of surveillance for pneumoconiosis in the

workplace. *Computed tomography* (CT) and *high-resolution computed tomography* (HRCT) have revolutionized clinical case evaluation. CT and HRCT are able to characterize lung and pleural lesions, as well as their extent and confluence, and are considerably more sensitive than the conventional chest radiograph. The role of magnetic resonance imaging in the diagnosis of pneumoconiosis is limited, but the technique has been used to differentiate between pleural plaques and mesothelioma.⁶ *Positron emission tomography* (PET) scans have been used to detect pulmonary neoplasms in the presence of pneumoconiosis,⁷ but increased metabolic activity in lesions of progressive massive fibrosis,⁸ in benign lung nodules in coal workers' pneumoconiosis,⁹ and in mediastinal nodes in patients with pneumoconiosis¹⁰ limit the usefulness of the technique. The chest radiograph remains the accepted method for surveillance and assessment because of its wide availability, acceptable cost and radiation dose, and the standardization of its reading.

CLINICAL ISSUES, LUNG FUNCTION, AND PRINCIPLES OF MANAGEMENT

The clinician is faced with two main tasks when evaluating a case of suspected pneumoconiosis. *First*, the clinician must assess the nature of the disease process, including its site (airways or pulmonary parenchyma or pleura) and its extent, as well as to determine whether it has decreased the individual's performance in particular for his or her current job (evidence of impairment or disability). Assessment of impairment is based on symptoms and measurements of pulmonary function at rest and during exercise where indicated (see Chapters 25 and 26). Pneumoconiosis may be associated with apparently normal lung function or with a predominantly obstructive, restrictive, or mixed pattern of dysfunction. In the individual case, interpretation of results in terms of lung function profiles is usually done by the use of reference or predicted values. These may, however, be misleading given that those who undertake dusty occupations on average have higher initial spirometry and lung volumes than the general population, on whom most predicted values are based.¹¹ Thus, it is not appropriate to minimize the functional significance of pneumoconiosis on the grounds of apparently normal lung function. Assessment of disability is made in the wider context of whether the subject is fit for his or her job and, thus, requires expert knowledge of the job content.

Second, the clinician needs to determine whether there has been environmental or occupational exposure of duration, intensity, and character sufficient to account in full or in part for the patient's present condition. For this task, the key tool is the occupational history, which can be completed with the addition of the often extensive knowledge that the worker can provide concerning his or her occupations, the materials handled, and the processes involved. Because pneumoconiosis is a reaction to retained dust, it may appear and progress after exposure has ceased¹²; hence, the importance of a complete exposure history, including student summer jobs, military service, and short-term jobs. In addition, in industrialized countries, between 25% and 60% of men and up to 30% of women report exposure to dust or fumes at work,¹³ further testimony to the fact that an occupational history is as essential as the smoking history in the

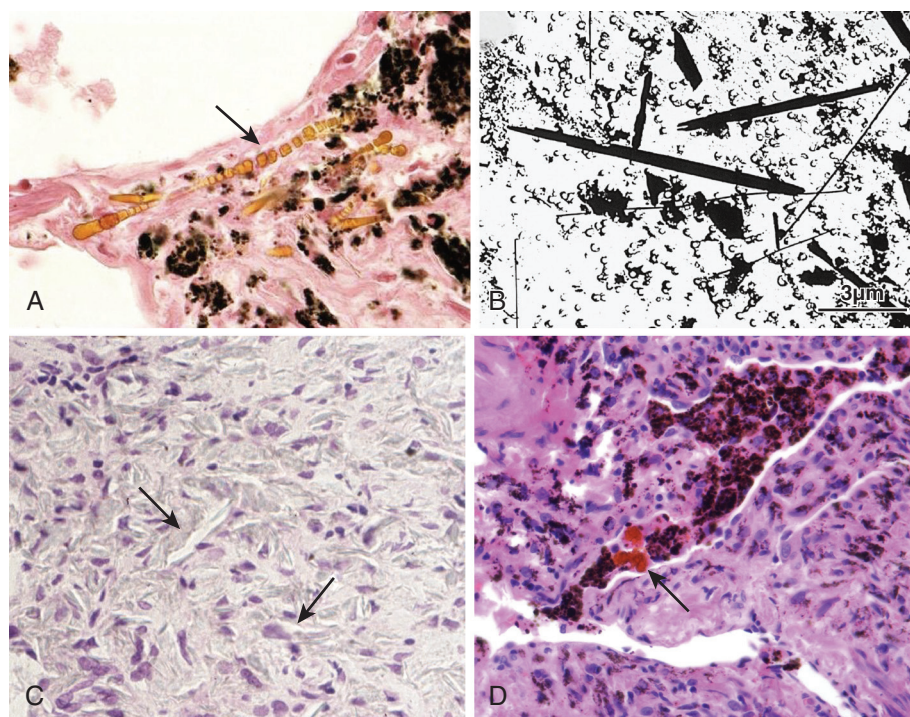


Figure 73-1 The putative agent in the lung tissue in four cases of pneumoconiosis. **A**, Typical asbestos body (arrow) in the lung of a crocidolite asbestos miner with asbestosis, from South Africa. **B**, Lung digest from the case of a 67-year-old long-term chrysotile miner with asbestosis from the Thetford area, photographed on a filter of pore diameter 0.2 mm (pores are evident as small punched-out areas in the photograph). The thin fibers were identified as chrysotile using morphologic criteria and energy-dispersive x-ray spectrometry (EDS). The thick fibers were identified as tremolite by EDS. In this mining area, there is a small amount of tremolite in the mined ore that accumulates preferentially in the lung tissue.¹ Amphiboles such as crocidolite, amosite, and tremolite most frequently form the core of asbestos bodies. For each asbestos body found in lung tissue, the number of uncoated fibers is at least several orders of magnitude greater. **C**, Lung section from a 53-year-old man who worked in a mica milling factory. The mica (arrows) appears as birefringent (bright white) elongated particles. **D**, Lung from a foundry worker shows amorphous black carbon particles and a cluster of rounded iron-coated particles (arrow). Particle clusters like this are frequently seen in the lung sections of welders and foundry workers who have had exposure to iron dusts and fumes. (**A**, **C**, and **D**, Courtesy National Institute for Occupational Health, South Africa; **B**, courtesy Drs. Bruce Case and R. S. Fraser, Department of Pathology, and Dr. Patrick Sébastien, formerly of the School of Occupational Health, McGill University, Montreal.)

practice of respiratory medicine. On occasions, it may be necessary to establish occupational exposure on the basis of analysis of biologic material (sputum, *bronchoalveolar lavage* [BAL], transbronchial or open-lung biopsy specimen) for the putative dust or its breakdown products. This is particularly so in cases in which the exposure is remote and the exposure history incomplete or unreliable. **Figure 73-1** presents examples of cases in which the putative dust was demonstrated in the pathologic specimens. The case record described in the legend for **Figure 73-9** is an example of the use of lung dust burden measurements in establishing attributability.

Tuberculosis was a common complication of pneumoconiosis in the early part of the 20th century. Although now relatively rare in industrialized countries, tuberculosis remains an important issue in industrializing countries and has increased dramatically, especially in South Africa, in response to the *human immunodeficiency virus* (HIV) epidemic.¹⁴

Pneumoconiosis does not regress and may appear and progress only after work exposure ceases.¹² In general, the worker with pneumoconiosis should have no further occupational dust exposure.

The physician has the legal responsibility to report all cases of pneumoconiosis.¹² The diagnosis of pneumoconiosis reflects a failure of environmental controls in the work-

place that may require intervention by an appropriate authority. There are differences in disease notification practice and compensation legislation among states and among countries, and physicians should be aware of the appropriate procedures in the location of their practice.

EPIDEMIOLOGY AND IMPLICATIONS FOR CLINICAL PRACTICE

Information on the distribution of these diseases within and between work forces and the factors that influence distribution provides the scientific base that the physician uses to reach a diagnosis, set prognosis, and plan management. Thus, knowledge of pneumoconiosis rates in the industries located in the local area assists the physician in diagnosis. Likewise, determining prognosis depends on work force-based information, on knowing which factors influence disease progression favorably and unfavorably, and the likely effect of further exposure even at low levels.

In the discussion that follows, the various types of pneumoconioses are considered separately with respect to occupations at risk, pathophysiology and epidemiology, as well as the clinical issues of diagnosis, prognosis, and management. On all continents and in many countries, a substantial proportion of individuals is exposed to dust at work and therefore potentially at risk for pneumoconiosis.¹³

Table 73-1 Industries and Occupations at Risk for Silicosis

Industries with Examples	Occupations Implicated
MINING, TUNNELING, AND EXCAVATING	
Underground: gold, copper, iron, tin, uranium, civil engineering projects	Miner, driller, tunneler, developer, stoper*
Surface: coal, iron, excavation of foundations	Mobile rig drill operator
Quarrying	
Granite, sandstone, slate, sand, chinastone/clay	Driller, hammerer, digger
Stonework	
Granite sheds, monumental masonry	Cutter, dresser, driller, polisher, grinder, mason
FOUNDRIES	
Ferrous and nonferrous metals	Molder, knockout man, fettler, [†] coremaker, caster
ABRASIVES	
Production: silica flour, metal polish, and sandpapers, fillers in paint, rubber, and plastics	Crusher, pulverizer, and mixer; workers in the manufacture of abrasives
Sandblasting: oil rigs, tombstones, denim	Operators of high-speed jets
CERAMICS	
Manufacture of pottery, stoneware, refractory bricks for ovens and kilns	Workers at any stage of process if products are dry
OTHERS	
Glass making, boiler scaling, traditional crafts, stone grinders, gemstone workers, dental technicians, concrete reconstruction	

*Stoper, a miner who works in a steplike excavation made in a step vein in a mine.

[†]Fettler, a worker who cleans the machines in the mill and sands and grinds imperfections from metal castings.

Lists of occupations and jobs at risk are never exhaustive (Table 73-1) but are a guide for use in general office practice. For those in occupational health or occupational medicine practice, reference should be made to one of the more specialized texts that describe the occupations at risk in greater detail.

SILICOSIS

DEFINITION

Silicosis is a fibrotic lung disease attributable to the inhalation of crystalline silica usually in the form of quartz and, less commonly, as cristobalite and tridymite.^{1,15,16} Amorphous silica is relatively nontoxic; silicates such as asbestos, mica, and talc evoke a different type of pulmonary response and are considered separately.

INDUSTRIES AND OCCUPATIONS STILL AT RISK

Silicosis is an ancient disease that continues to be a major disease worldwide in men and women exposed to silica dust in a variety of occupations.^{1,17} Table 73-1 provides some common examples of industries in which workers are at risk for silica exposure. Construction, surface, and under-

ground rock drilling have all been subjects of Alert documents from NIOSH. Foundries are also a main source of silica dust. More recent reports have shown a silicosis risk for workers involved with the repair, rehabilitation, or demolition of concrete structures¹⁸ including roads.¹⁹ Less common occupations associated with silicosis include workers producing stressed denim by sandblasting,²⁰ stone carvers,²¹ granite countertop manufacturers,^{22,22a} dental technicians,^{22b,22c} and jewelers using chalk molds.²³ Many of the current cases of silicosis come from industries using relatively new technology that, if unaccompanied by modern controls, may result in exposures to finer dust particles than in traditional industries and jobs. Many “new” types of pneumoconiosis often turn out to be silicosis in an industry not previously thought to be at risk or a mixed dust pneumoconiosis in which silica is implicated with other dusts.

Silicosis is often the result of exposure in the remote past and not in the current workplace. The risks for silicosis depend on the levels of exposure and, although this can be controlled, there is evidence that dust levels may be monitored inappropriately and that the sampling accuracy may be poor in many workplaces.²⁴

Outbreaks of silicosis and death from the disease continue to be reported worldwide,^{12,21,24} even in countries with developed legislative systems and environmental surveillance programs, such as the United States,²⁵ Canada,²⁶ Europe,²⁷ and South Africa.²⁸ U.S. data show that the rate of decline in deaths from silicosis has lessened after 1995 with an increased proportion of deaths in the age group younger than 45 years. These data indicate “that intense overexposures to respirable crystalline silica continue to occur despite the existence of legally enforceable limits.”¹⁷ In China 23 million workers are exposed to silica, while in the United States, NIOSH has estimated that at least 1.7 million workers are exposed to silica, of whom between 1500 and 2360 will develop silicosis each year. Cases of silicosis have also been reported following general environmental exposure^{29,30} and in agricultural workers.^{31,32}

PATHOLOGY

Three clinicopathologic types of silicosis have been described: *chronic silicosis*, which typically follows exposure, measured in decades rather than years, to respirable dust usually containing less than 30% quartz; *accelerated silicosis*, which follows shorter, heavier exposure; and *acute silicosis* (silicoproteinosis), which follows intense exposure to fine dust of high silica content, such as that found in sandblasting industries, for periods measured in months rather than years.^{2,15}

Chronic silicosis is the most common form of the disease. The hallmark of chronic silicosis is the silicotic nodule, one of the few agent-specific lesions in pathology (Fig. 73-2A and B; eFig. 73-1). Silicotic nodules develop first in the hilar lymph nodes³³ and may be confined to this area; they may become encased in calcification and impinge on or erode into airways. The disease process next involves the lung parenchyma. It is usually bilateral, predominantly involving the upper zones.

In accelerated silicosis, the changes are similar to those seen in chronic silicosis. However, the nodules develop

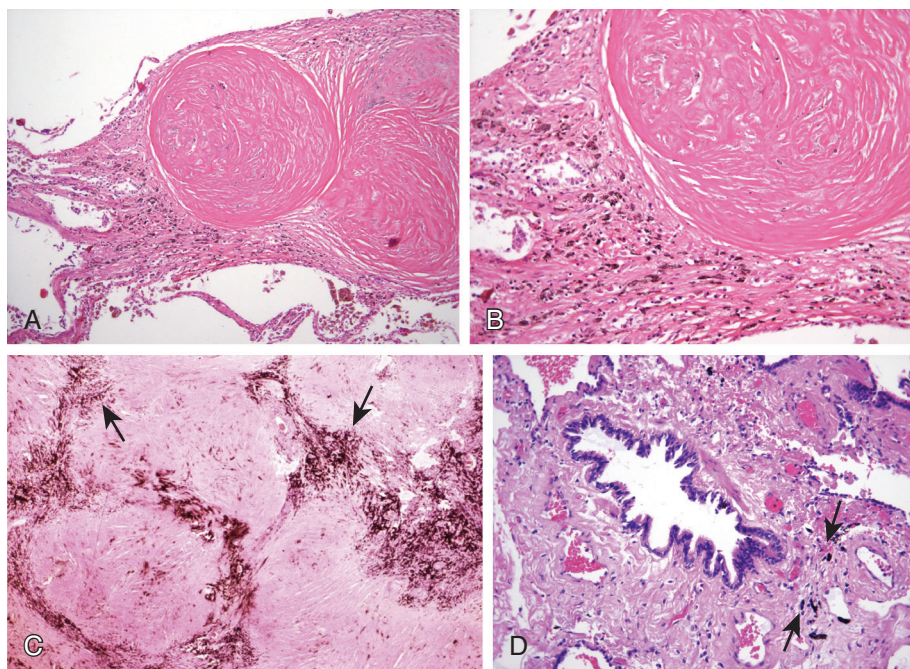


Figure 73-2 Pathologic lesions of chronic silicosis. **A**, Silicotic nodule characterized by a central zone of a cellular hyalinized collagen with a whorled appearance and a peripheral zone of dust-laden macrophages. **B**, Silicotic nodule at higher magnification to show these characteristics to better advantage. **C**, Progressive massive fibrosis shows confluent silicotic nodules and aggregates of dust-laden macrophages (arrows). **D**, Mineral dust small airway disease characterized by peribronchiolar fibrous tissue containing a moderate amount of pigment (arrows). (Courtesy National Institute for Occupational Health, South Africa.)

sooner (after 3 to 10 years of exposure), may be more widely distributed in the lung, and are more cellular than fibrotic.

With disease progression in both chronic and accelerated silicosis, the nodules may become confluent, leading to the development of *progressive massive fibrosis* (PMF) (see Fig. 73-2C), also known as *complicated silicosis*. These lesions, which are at least 1 cm in diameter (and often larger), usually involve the upper lobes. They tend to obliterate lung structure and may cavitate, which may be an indication of tuberculosis.² *Rheumatoid nodules* may also develop in the setting of silicosis and may be seen in subjects with rheumatoid arthritis or high levels of circulating rheumatoid factor.² There may be silicotic nodules in the background. Rheumatoid nodules are less frequently associated with silica than with coal dust exposure (see subsequent discussion).

Acute silicosis shows all the features of pulmonary alveolar proteinosis (see Chapter 70). Silica particles and various biomarkers of tissue reaction can be identified in the proteinaceous material from the alveolar spaces and in lavage material.

The lungs of exposed individuals, whether or not they show silicosis, also may demonstrate the features of other diseases associated with occupational dust exposure, such as chronic bronchitis and emphysema. The pathologic features are similar whether associated with occupational exposure to dusts and fumes encountered in the workplace or with exposure to tobacco smoke. Small airway abnormalities, including fibrosis and pigmentation of respiratory bronchioles (see Fig. 73-2D), are seen in association with exposures to a variety of mineral dusts including those responsible for silicosis.³⁴

Silicotic nodules may also develop in the cervical and abdominal lymph nodes and, occasionally, in the liver, spleen, and bone marrow.¹²

PATHOGENESIS

The pathogenicity of silica dust is dependent on the physical, mechanical, and chemical properties of the particles. A review of this topic summarizes the processes whereby silica produces inflammation and fibrogenesis in the lung.³⁵ However, the cellular mechanisms that initiate and drive the process of inflammation and fibrosis are not fully understood. There is agreement that freshly fractured silica, such as that generated during sandblasting, is more toxic to the alveolar macrophages than is “aged” silica, presumably because of its increased redox potential. Other minerals, particularly clay components, may adhere to the surfaces of silica particles, producing “coated” silica that is less toxic than uncoated silica dust. This may explain the relatively nonfibrogenic response to silica in coal and hematite miners and the observation that the incidence of silicosis is decreased by concomitant exposure to other dusts. Silica particles smaller than 5 μm reach the lower respiratory tract and may enter the alveoli. The intensity of the exposure determines the nature of the lung injury.

Tumor necrosis factor- α (TNF- α) and *interleukin 1* (IL-1) play an important role in the initiation of silicosis, and experimental inhibition of these cytokines has been shown to prevent silicosis. Growth factors, including *transforming growth factor- β* (TGF- β), are important in fibrogenesis (and also have been implicated in carcinogenesis) in association with silica.^{36,37} A review describes the immune response to

silica in more detail and the role of innate and adaptive immunity.³⁸ Although the major determinant of silicosis is the level of exposure to silica-containing dust, individual susceptibility to the disease may play a role in its development and severity.^{39,40}

EPIDEMIOLOGY: SECULAR TRENDS AND THEIR IMPLICATIONS FOR THE CLINICIAN

Over the course of the 20th century, silicosis changed from a rapidly fatal disease to an indolent and disabling disorder. Reasons include improved environmental controls, falling rates of tuberculosis, and the advent of drug therapy for tuberculosis. Nevertheless, there is still well-warranted concern that this avoidable disease will remain a significant cause of morbidity¹² and mortality in the 21st century.^{41,42} The prevalence of silicosis is difficult to estimate, given the large number of industries at risk (see Table 73-1), the transient labor force in industrializing and industrialized countries, and the frequent appearance (and progression) of disease after the worker has left the work force.^{43,44} Despite the progress made, silicosis has been reported in workers from a variety of industries in persons starting work after 1970, and reported cases have been estimated to under-represent the total cases of silicosis substantially.⁴⁵ In calculating an individual's risk for silicosis, duration and intensity of exposure are of primary interest but peak exposure also may be important.⁴⁶ The physician should never dismiss the diagnosis of silicosis when that diagnosis is suggested by clinical and radiologic features, even when exposure appears to have been insignificant or in an occupation not known to be associated with silicosis.

TUBERCULOSIS

The association between silicosis and tuberculosis has long been recognized. Rates for active tuberculosis in silicotic subjects range from two- to thirty-fold more than those in the same workforce without silicosis.⁴⁷ Factors that influence the development of tuberculosis in the subject with silicosis include the severity and type of disease (the risk is considerably higher in patients with acute and accelerated silicosis),¹⁵ the prevalence of tuberculosis in the population from which the work force was drawn, as well as their age, general health, and HIV status.⁴⁷⁻⁴⁹ Exposure to silica, without silicosis, may also predispose individuals to tuberculosis.^{47,48}

Tuberculosis is characterized by necrotizing epithelioid granulomas. These are never seen with silicosis alone. Although *Mycobacterium tuberculosis* is the usual organism, nontuberculous mycobacteria account for a large proportion of the mycobacterial disease in populations in which nontuberculous mycobacterial disease is common.^{12,50} Smoking has been shown to increase the risk for the development of tuberculosis in those with silicosis.⁵¹ There is some evidence to suggest that those with silicosis are also at risk for fungal infections.⁵²

AIRFLOW OBSTRUCTION AND CHRONIC BRONCHITIS

COPD and chronic bronchitis are common manifestations of long-term occupational exposure to environments con-

taminated by silica dust and can develop in silica-exposed individuals with or without silicosis.^{12,53-55} Small airway abnormalities, including fibrosis and pigmentation of respiratory bronchioles (see Fig. 73-2D), are also seen in association with exposures to a variety of mineral dusts including silica.³⁴ In South African gold miners, the estimated *additional* loss of lung function attributable to mine dust exposure without invoking silicosis or tuberculosis is an average of 208 mL of forced vital capacity over a 30-year working life (in excess of the expected loss of 400 to 500 mL over 30 years in normal men with age).⁵⁶ In a study of adolescents and young adults working in a stone-crushing plant, lung function changes were interpreted as evidence for impaired lung growth that was attributed to their high respirable crystalline silica exposure.⁵⁷ Smoking can potentiate the effect of silica dust on airflow obstruction.⁵⁴

CONNECTIVE TISSUE DISEASES, RENAL DISEASE, AND CARDIOVASCULAR DISEASE

Associations have been reported between exposure to silica and certain connective tissue diseases including progressive systemic sclerosis, systemic lupus erythematosus, and as previously mentioned, rheumatoid arthritis.^{12,58} Epidemiologic evidence indicates that the prevalence of rheumatoid arthritis is increased in those with exposure to silica and in those with silicosis.⁵⁹ Systemic sclerosis has been shown to be associated with silicosis⁵⁹ but may also be associated with silica dust exposure without silicosis.¹² The evidence for an association between lupus erythematosus and silicosis is strongest for acute or accelerated silicosis but is inconclusive for chronic silicosis.^{12,59}

Renal disease has been reported in silica-exposed workers. Some studies have implicated an immune complex glomerulitis or a direct toxic effect of silica.^{12,59,60} Silicosis has been linked with *antineutrophil cytoplasmic antibody* (ANCA) positivity and possibly with vasculitis.^{58,61}

Cardiovascular disease may also be associated with silica exposure. A recent report of a cohort of 74,040 silica-exposed workers found an increased mortality compared with nonexposed workers; cardiovascular disease was the major cause of death.⁶²

LUNG CANCER

The association between silicosis and lung cancer has been difficult to establish because of the high prevalence of smoking in silica-exposed workers and because of frequent concomitant radon exposure.¹² Studies of non-radon-exposed, nonsmoking workers with silicosis suggest a clear relationship between silicosis and lung cancer, but there remains some doubt as to whether silica exposure, in the absence of silicosis, carries an increased risk for lung cancer.^{12,59,62-65,65a}

CLINICAL FEATURES

The symptoms and signs of chronic silicosis may be minimal. The main symptom is breathlessness but, in chronic silicosis, in the absence of other respiratory disease, even this symptom may be absent. It is not unusual for a patient with chronic silicosis to present without symptoms

for assessment of an abnormal chest radiograph. The appearance of breathlessness may mark the development of a complication such as PMF or tuberculosis or may reflect associated airway disease. Cough and sputum production are common symptoms and usually relate to chronic bronchitis but may reflect the development of tuberculosis or lung cancer. Chest pain is not a feature of silicosis nor are systemic symptoms such as fever and weight loss, which should be attributed to tuberculosis or lung cancer until proved otherwise. Clubbing is also not a feature of silicosis and should raise concern about lung cancer.

In accelerated and acute silicosis, the time scale of symptom evolution is in years or months rather than in decades. In acute silicosis, breathlessness may become disabling within months, followed by impaired gas exchange and respiratory failure.

RADIOGRAPHIC FEATURES

Uncomplicated silicosis is characterized by the presence of small rounded opacities on the chest radiograph,^{1,15} as

graded in the ILO classification (as described previously).⁵ In general, there is a good correlation among dust exposure, the amount of dust in the lungs, the lung pathology, and the chest radiograph.⁶⁶ However, occasionally, even advanced silicosis, determined by histology, may not be apparent on a chest radiograph.⁶⁷

Silicotic nodules are usually symmetrically distributed and tend to appear first in the upper zones (Fig. 73-3), later, although not invariably, involving other zones (eFig. 73-2). Enlargement of the hilar nodes may precede the development of the parenchymal lesions. Eggshell calcification, when present, is strongly suggestive, although not pathognomonic, of silicosis (Fig. 73-4; see also Fig. 73-3, eFig. 73-3).

PMF is characterized by the coalescence of small rounded opacities to form larger lesions (eFig. 73-4A); they are graded on the ILO scale according to size and extent (categories A to C). CT assessment is superior to the chest radiograph in not only assessing the presence and extent of silicotic nodulation but also revealing early conglomeration (eFig. 73-4-E; Videos 73-1 and 73-2).⁶⁸ With time, the mass

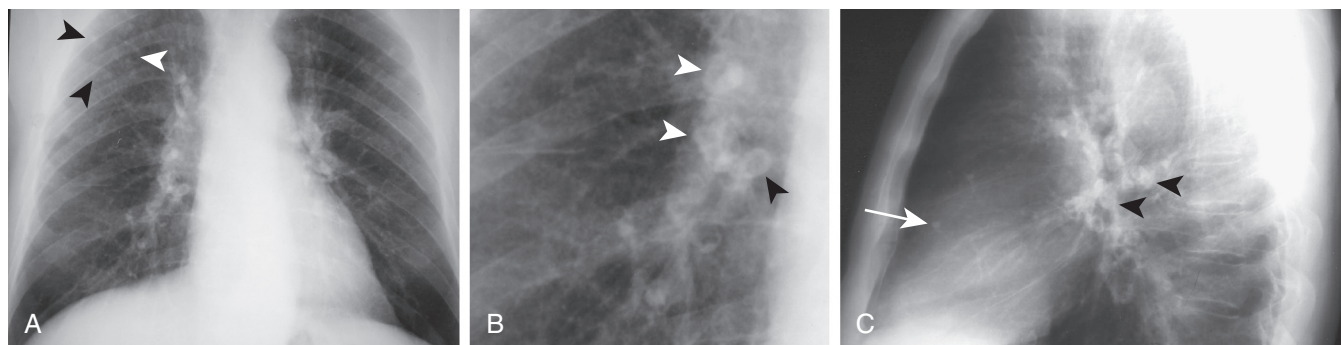


Figure 73-3 Radiographic patterns of silicosis. **A**, Posteroanterior chest radiograph shows predominantly upper zone but, atypically, asymmetrical nodularity (arrowheads). **B**, Detail image shows the “eggshell” calcification of the hilar lymph nodes (arrowheads). This latter feature strongly suggests that the nodular opacities in the lung parenchyma on this chest radiograph represent silicosis, notwithstanding the patient’s history of 30 years of underground work in a coal mine. **C**, Lateral view shows the eggshell calcification (arrowheads) and also a larger and probably calcified nodule situated anteriorly and a small calcified parenchymal lung nodule (arrow). These latter features are compatible with a healed primary tuberculous focus and, if this is supported by a positive test for tuberculosis, a course of treatment for latent tuberculosis infection should be offered. (Courtesy Dr. J. H. M. MacGregor, University of Calgary.)

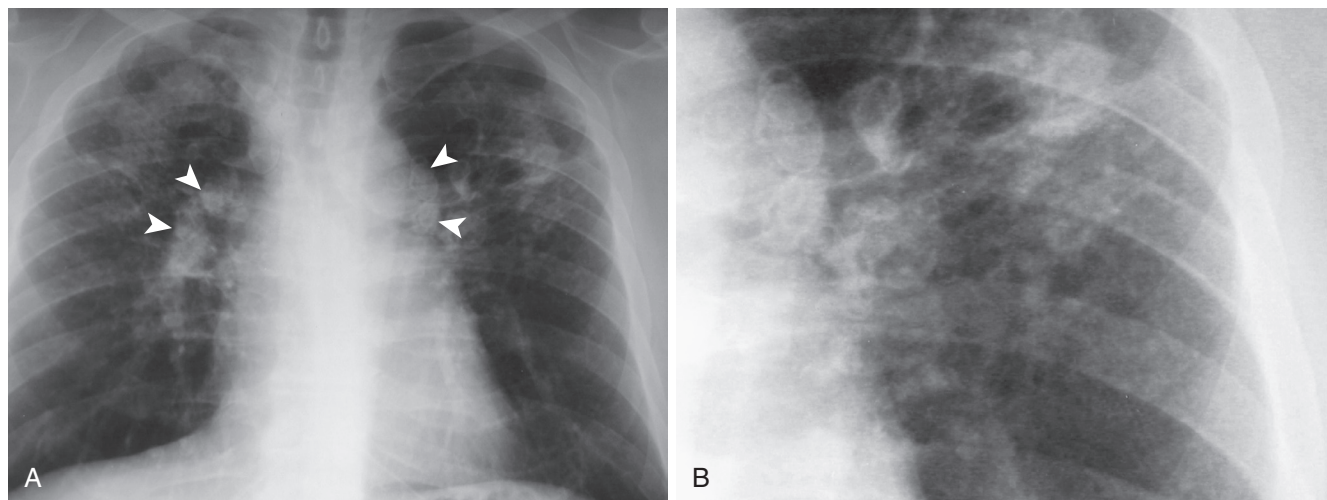


Figure 73-4 Progressive massive fibrosis. **A**, Posteroanterior radiograph shows features of progressive massive fibrosis (PMF) with “eggshell” calcification of the mediastinal and peribronchial nodes (arrowheads), in keeping with complicated silicosis, in a man who had shoveled sand in a glass factory. **B**, Detail view shows the PMF with a background of smaller nodules and the eggshell calcification. (Courtesy Dr. J. H. M. MacGregor, University of Calgary.)

lesions tend to contract, usually to the upper lobes, leaving hypertranslucent zones at their margins (eFigs. 73-5 and 73-6) and often at the lung bases. In this process, small rounded opacities, previously evident, may disappear, resulting in a picture that must be distinguished from tuberculosis. The rapid development of several large lesions suggests rheumatoid silicosis, but new lesions, especially if cavitated, should be regarded as evidence of mycobacterial disease. Acute silicosis is characterized radiologically by diffuse changes that usually display an air space and interstitial pattern rather than the usual nodularity.⁶⁹


LUNG FUNCTION

The lung function profile is determined by the extent of silicosis, as well as associated or concomitant airway and vascular changes. In chronic silicosis, spirometric tests (*forced expiratory volume in 1 second* [FEV₁], FEV₁/forced vital capacity [FVC]) usually reflect airflow limitation.¹² Reduction in *diffusing capacity of carbon monoxide* (DL_{CO}) is generally apparent in more advanced chronic silicosis and probably reflects associated emphysema.⁷⁰

In the accelerated and acute forms, functional changes are more marked and progression is more rapid. In acute silicosis, lung function shows a restrictive defect and impairment of gas exchange, which leads to respiratory failure.

DIAGNOSIS AND COMPLICATIONS

Silicosis is diagnosed on the basis of a history of exposure and the characteristic radiographic changes.¹⁵ Problems arise when the history of exposure is remote, forgotten, or missed or has taken place outside a recognized occupation. Occasionally, the radiologic features are unusual; examples include the presence of hilar lymphadenopathy or of large lung opacities in the absence of typical small nodules. Detection of silica in BAL material may suggest the diagnosis. Lung biopsy may be necessary to distinguish progressive massive fibrosis or other atypical features from lung cancer, tuberculosis, and other diagnoses. Biopsy material should be submitted for microanalysis for dust including silica.

Less common complications include cor pulmonale, spontaneous pneumothorax, broncholithiasis, and tracheobronchial obstruction from enlarged calcified hilar nodes.¹⁵ The diagnosis of active tuberculosis in the silicotic subject may be more difficult than in the nonsilicotic subject but, in general, a good sample of sputum or sputum induced by nebulized hypertonic saline sent for mycobacterial culture provides the diagnosis. The presence of cough, hemoptysis, weight loss, fever, or any new radiologic feature (eFig. 73-7) should be pursued with culture of sputum or BAL fluid or with culture and histologic examination of tissue. In many instances, it is the chest imaging rather than the clinical features that gives the first indication of tuberculosis in the presence of silicosis (see eFig. 73-7,  Video 73-3), but it should be noted that those with silicosis are also at risk for extrapulmonary tuberculosis.⁴⁷

MANAGEMENT AND CONTROL

Once established, the fibrotic process of chronic silicosis is thought to be irreversible. Management of the individual

case is thus directed toward preventing progression and the development of complicated disease. A change in occupation to an environment free of silica-containing dust should be advised. The disease will generally progress even without further exposure,^{43,44} but the rate of deterioration may be reduced.

Interventions to interrupt the inflammatory process that leads to chronic silicosis including the inhalation of aluminum or polyvinylpyridine-N-oxide and oral tetrandrine have not been shown to be successful. There is currently interest in the use of lung lavage to remove silica from the lung, but a favorable impact on progression of acute or chronic silicosis has not been demonstrated. Treatment of all forms of silicosis should be directed toward control of mycobacterial disease. This is especially true for acute and accelerated silicosis and silicosis in workers with HIV infection.^{15,49} All subjects with silicosis should have a tuberculin skin test or an *interferon-γ* (IFN-γ) release assay⁷¹ and, if positive in the absence of evidence of tuberculosis, be offered treatment for latent tuberculosis infection (see Chapter 35).

The interaction between silica exposure and smoking in the development of COPD, tuberculosis,⁵¹ and lung cancer makes it important to implement smoking-cessation programs in the workplace.

Because acute and accelerated silicosis carry such a poor prognosis and tend to arise in younger subjects,⁷² consideration should be given for lung transplantation in such cases (see Chapter 106).

The most important aspect of the management of silicosis relates to its prevention. To achieve this, a sustained effort must be made to increase awareness of silicosis. Recent deaths from silicosis in younger subjects in the United States have been reported after exposure in the construction and manufacturing sectors, with none from mining.⁷² Deaths of young people sandblasting denim²⁰ are a reminder that there is often a lack of awareness of the hazards of silica outside the traditional occupations associated with silicosis.

COAL WORKERS' PNEUMOCONIOSIS

DEFINITION AND OCCUPATIONS AT RISK

Coal workers' pneumoconiosis (CWP) is a distinct pathologic entity resulting from the deposition of coal dust in the lungs.^{1,2,4} The tissue reactions to deposits of dust include the *coal macule* and *coal nodule* (simple CWP) and PMF (complicated CWP)² (Fig. 73-5).

The main occupation at risk for CWP is coal mining, an industry that in the 1970s employed approximately 250,000 people in the United Kingdom and a comparable number in Western Europe.¹³ Approximately 175,000 coal miners were employed in the United States in 1986; since then, there had been a steady decrease in the number to approximately 80,000 in 1999 but, in 2011, the number increased to 143,437.⁷³ It has been estimated that there are 6 million coal miners in China. Coal is also mined in Eastern Europe, India, and on the African, Australian, and South American continents. With mechanization, output and

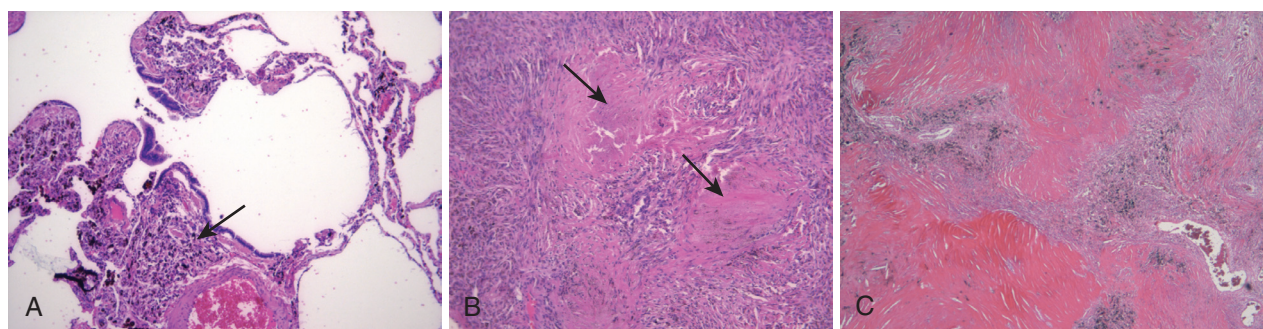


Figure 73-5 Pathologic lesions of coal workers' pneumoconiosis: examples from South African coal miners. **A**, Coal macule shows an aggregation of dust and dust-laden macrophages in the wall of a distal airway in which reticulin and a few collagen fibers were demonstrated. **B**, Coal nodule consists of dust and dust-laden macrophages and dense, irregular depositions of collagen (arrows). This lesion would be palpable. Associated focal emphysema was also evident. **C**, Progressive massive fibrosis with coalescence of nodules and dense collagen deposition. (Courtesy National Institute for Occupational Health, South Africa.)

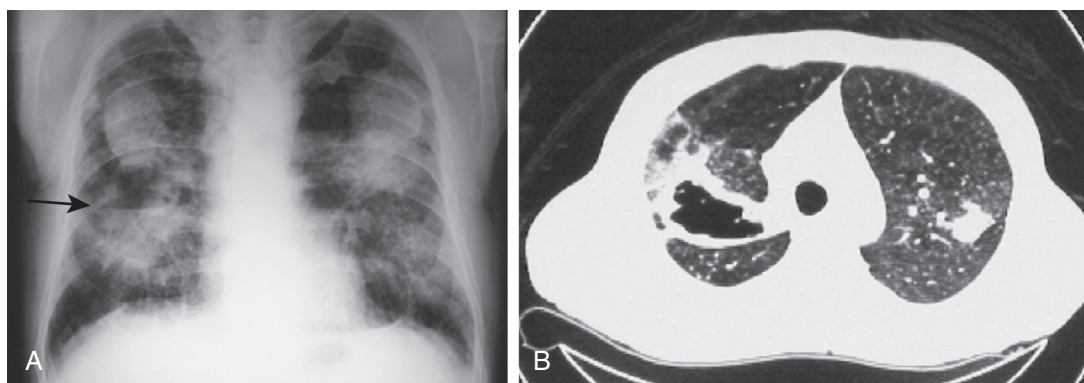


Figure 73-6 Progressive massive fibrosis (PMF). **A**, Chest radiograph shows PMF with evidence of cavitation with an air-fluid level in the right lower lung (arrow). This image represents complicated coal workers' pneumoconiosis. **B**, Chest CT shows the background nodularity and the lesions of PMF with cavitation on the right. (Courtesy Dr. J. H. M. MacGregor, University of Calgary.)

potential for dust exposure have increased. Former and current coal workers are likely to continue to be seen with CWP. Surface coal miners are also at risk for pneumoconiosis but are not always included in surveillance programs.⁷⁴

Coal mine dust contains a variable amount of quartz depending on the nature of ore-bearing rock, the size of the coal seam, and the processes used to mine the seam (including the degree of mechanization). Coal miners may also develop silicotic nodules when the coal seams are in hard rock. Silicosis is more common in mines with a high grade or *rank* of coal (see later in “*Pathogenesis*”) and in workers such as roof bolters who work outside of the coal seams.^{2,4} Current evidence shows that coal mining, even in the absence of CWP, is associated with chronic bronchitis, chronic airflow limitation,^{4,75,76} and emphysema.^{2,4,77}

Other occupations at risk for exposure to coal or carbon dust include coal trimming (which involves loading and stowing coal in stores or ships' holds), the mining and milling of graphite in carbon plants, the manufacture of carbon electrodes, and the manufacture and use of carbon black.

PATHOLOGY

The primary lesion in CWP is the coal macule, which can be seen (although not palpated) on macroscopic examination as a small (≤ 4 mm) pigmented lesion, distributed

initially in the upper lobes, although the lower lobes may subsequently become involved.² On microscopic examination, the coal macule consists of a stellate aggregation of dust and dust-laden macrophages around respiratory bronchioles, with reticulin fibers and a variable amount of collagen (see Fig. 73-5).² Focal emphysema, a form of centriacinar emphysema, forms within and around the coal macule, and together they form the characteristic lesion of CWP.² The coal nodule is a palpable lesion that, in addition to dust-laden macrophages and reticulin, contains a substantial number of haphazardly arranged collagen fibers.² Coal nodules, which result from exposure to coal dust admixed with silica, are usually present in association with coal macules.¹ Classic silicotic lesions are seen in approximately 12% of U.S. coal miners² and form when lung dust residue contains 18% or more quartz. Other features include subpleural dust deposits, enlargement of the hilar and mediastinal nodes and, on occasion, tattooing of the parietal pleural lymphatic channels by coal dust.

PMF (complicated CWP) is defined as a fibrotic pneumoconiotic lesion 1 cm or greater in diameter. These bulky, often irregular, well-defined, heavily pigmented rubbery black tissue masses usually appear in a background of severe simple CWP. PMF usually develops in the posterior segment of the upper lobes or apical segments of the lower lobes and is typically bilateral (Figs. 73-6 and 73-7). Microscopically, the lesions contain the same elements as the coal nodule (see Fig. 73-5C). They may impinge on and

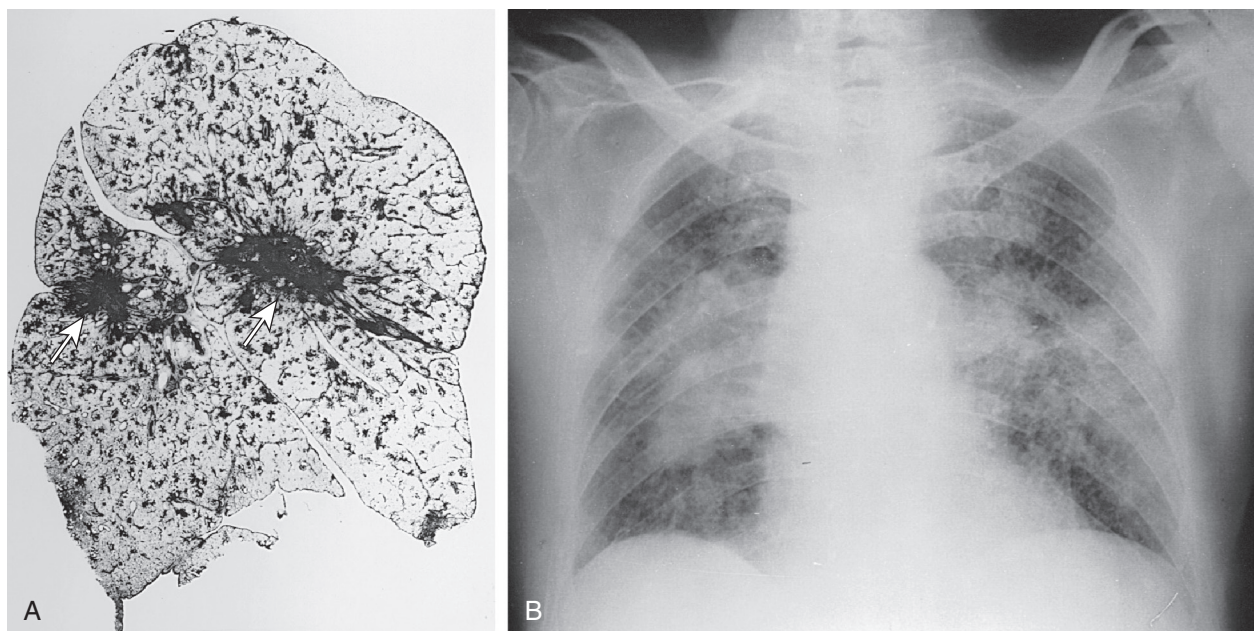


Figure 73-7 Progressive massive fibrosis (PMF). **A**, Whole-lung section of a 71-year-old Appalachian coal miner. The miner was a nonsmoker and had worked for 28 years underground, primarily at face work (directly involved in mining at the face surface of the mine). The midsagittal section of the left lung shows massive lesions in the superior segment of the lower lobe and in the central area of the upper lobe (arrows). PMF is seen against a background of simple nodular and macular coal workers' pneumoconiosis. In several areas, there is evidence of coalescence of nodules. There is mild focal emphysema associated with the coal dust macules. **B**, Chest radiograph shows features of PMF against a background of nodularity. The mass lesion on the right shows the propensity of PMF to move toward the hilum. The opacities are somewhat atypical given their predominantly lower lung location. (Case from the National Institute of Occupational Safety and Health W. Laqueur collection, courtesy Drs. V. Vallyathan and F. H. Y. Green.)

obliterate airways and vessels and cross interlobar fissures. Cavitation is not uncommon, probably as a consequence of ischemic necrosis, given that vascular obliteration is common within areas of PMF.

Rheumatoid pneumoconiosis,² one variant of which is called Caplan syndrome, is a form of CWP associated with rheumatoid arthritis or a rheumatoid diathesis. It is characterized by nodules that are larger than coal nodules and have smoother borders. Pigmentation is arranged in concentric laminations and, relative to PMF lesions, they contain little dust. These lesions may cavitate or calcify. The microscopic features are similar to those described for the rheumatoid silicotic lesion (see earlier discussion under the "Pathology" of "Silicosis"). Active areas in the nodules contain dust-laden macrophages, lymphocytes, polymorphonuclear leukocytes, and plasma cells. When activity ceases, they may collapse or calcify. Rheumatoid pneumoconiosis lesions were originally described in Welsh coal miners and are reported in Belgian coal miners but are uncommon in North American coal miners.

Diffuse interstitial fibrosis has also been reported in coal miners; the fibrosis may contain black carbon pigment and may appear similar to the *usual interstitial pneumonia* (UIP) pattern. However, it has a relatively benign clinical course compared with that of the same condition in the general population.²

PATHOGENESIS

The risk for CWP increases with the intensity and duration of exposure to coal dust. The effect of coal on the lung is

also related to its rank, a measure of the degree of metamorphosis and which is based on its carbon content. Anthracite ranks highest (93% carbon), followed by bituminous, sub bituminous, and lignite, with the lowest carbon content (60% to 70%).^{2,4} In epidemiologic studies, CWP is more common in mines of high-rank coal than in those of low-rank coal. This may relate to the greater relative surface area of the coal dust particles, higher surface free radicals, and more frequent presence of silica in the high-rank, rather than the low-rank, coal.^{2,4} The coal dust macule and nodule are ascribed to the accumulation of large amounts of relatively inert dust in the lung. As the lung burden of dust increases, alveolar macrophages are activated and reactive oxygen species are released. These in turn trigger the release of cytokines, including interleukins and TNF, which set in motion the processes of inflammation and fibrogenesis that are responsible for the development of pneumoconiosis and also trigger the release of proteases, which contribute to the associated emphysema. The fibrosis, however, is considerably less intense and extensive than that evoked by the more bioactive dusts, such as silica and asbestos.

Although the exact pathogenic mechanisms underlying the development of PMF remain in doubt, these lesions are thought to relate to the amount of coal dust accumulated in the lung, the proportion of inhaled silica in the dust and its surface bioactivity, individual immunologic and genetic factors, and whether tuberculosis is present.^{2,4,40} Of these factors, the total dust burden appears to be the most important. In addition, there are striking differences in rates of simple pneumoconiosis and PMF among different coal pits,

mining areas, and countries,^{2,4,40} suggesting that other characteristics of the dust particles, including their shape, size, composition, bioactivity, and durability in lung tissue, also contribute to the risk of developing CWP and PMF.

EPIDEMIOLOGY AND NATURAL HISTORY

Early studies of coal miners suggested that the occupation of coal mining and even the presence of CWP were not associated with higher mortality rates. These studies probably did not take the healthy worker effect into account, and more recent studies have shown that exposure to coal dust is associated with increased mortality.^{78,79} Overall, in the United States, the mortality associated with CWP decreased by 36% from 1982 to 2000 compared with 1968 to 1981,⁸⁰ but more recent data showed an increase in years of potential life lost before the age of 65 years since 2002.⁸¹

Although the rates of CWP had been falling steadily in the United States and Europe, new cases continue to be detected^{1,25,73,82} and the diseases associated with coal dust have shown an increase since 1995 notwithstanding apparent adherence to the current dust standard.^{73,83-85} The presence of PMF is associated with more severe adverse effects on the health and life expectancy of coal miners than those of simple CWP, and recent data show a sharp increase in the finding of PMF in U.S. underground coal miners.^{85a} Risk factors for PMF include the presence and stage of CWP, the intensity of dust exposure, and the age of the subject.⁸⁶ The role of silica in the development of PMF is controversial but is generally believed to be important.^{2,4,87} A study of coal miners with rapidly progressive CWP suggests that silica exposure might be a marker for the development of PMF. Risk factors for rapid progression of CWP included working at the face in smaller mines, younger age, and mining in eastern Kentucky and western Virginia.^{82,88,89}

RHEUMATOID PNEUMOCONIOSIS

Rheumatoid pneumoconiosis (Caplan syndrome) was originally described as a variant of PMF in coal workers on the basis of its distinctive radiologic features. Active arthritis or circulating rheumatoid factor were commonly associated with rheumatoid pneumoconiosis.¹ At present, most evidence suggests that the presence of rheumatoid arthritis, a predisposition to rheumatoid disease, or both is a host factor that modifies the response of an individual to coal mine dust exposure. Conversely, dust exposure does not appear to be a risk factor for rheumatoid arthritis.¹ CWP does not appear to have an association with other connective tissue disorders.

ROLE OF SILICA

Although it is recognized that silica does not play a primary role in the causation of CWP, coal miners, especially those mining anthracite, may develop the lesions of silicosis. When present, silicosis is usually associated with CWP.² Although combined exposure to silica and coal dust may produce less silicosis than would a similar pure exposure to silica, silica exposure is nevertheless thought to contribute to the risk of developing PMF.⁴

AIRFLOW OBSTRUCTION AND CHRONIC BRONCHITIS

The association between coal mining and obstructive lung disease has now been confirmed by several longitudinal studies that show that airflow can be limited from coal dust exposure independently from CWP and that the effect becomes comparable with that of smoking at exposure levels at which there is a risk for CWP.^{4,55,90}

Mucus hypersecretion (chronic bronchitis) is common in coal workers but does not appear to play a direct role in their development of COPD. Mucus hypersecretion will generally resolve after withdrawal from dust exposure as it does after smoking cessation. Bronchial hyperresponsiveness appears to predispose coal workers to develop COPD.

TUBERCULOSIS AND CANCER

Mycobacterial infection, either by *M. tuberculosis* (see eFig. 73-7) or nontuberculous mycobacteria, has not been demonstrated to be more common in association with CWP in the absence of silicosis.⁹¹ Most evidence suggests that the occupation of coal mining is not associated with lung cancer; however, two recent studies have reported an association between lung cancer and coal mining.^{91a,91b} An increased risk of stomach cancer has been documented,^{2,4,92} but this was not apparent in a 23-year follow-up study of 8899 coal miners.⁷⁸

CLINICAL FEATURES

Simple CWP is regarded as a disease state without symptoms or physical signs. The diagnosis is based on the radiologic features. The symptoms of cough and sputum reported by most coal miners are likely to be the consequence of dust-induced chronic bronchitis.⁵⁵ Breathlessness on effort is usually caused by associated chronic airflow limitation or by the development of PMF.⁴ Respiratory impairment and disability develop as PMF progresses, although patients with category A PMF (lesions 1 to 5 cm in diameter) may be asymptomatic. Lesions of PMF that impinge on airways may cause abnormal breath sounds. Large or bilateral PMF lesions may be associated with hypoxemia and right heart failure. The presence of new lung lesions with rheumatoid arthritis, subcutaneous rheumatoid nodules, or positive rheumatoid factor raises the possibility of rheumatoid pneumoconiosis. The lung lesions may or may not develop concomitantly with joint disease.

CHEST RADIOGRAPHY

The hallmark of simple CWP on the chest radiograph is the presence of small rounded opacities in the lung parenchyma (eFig. 73-8).^{1,5} (See the discussion of chest radiographs in the "Introduction" to this chapter.) Coal macules are usually associated with small (<1.5 mm) p nodules on the chest radiograph, but the radiograph may show no nodularity with mild to moderate grades of CWP. Large amounts of coal dust in the lungs are found in association with small, rounded p nodules. When the larger q and r nodules are visible radiologically, this usually reflects the

presence of coal nodules and a higher proportion of quartz in the lungs.⁹³

Because the chest radiograph has been shown to be insensitive to the presence of macules and nodules,⁹³ in individual cases, CT may be useful. Small rounded opacities are usually seen first in the upper zones and involve the other zones at a later stage. The nodule profusion is closely related to the lung dust content at autopsy.⁹³ Small irregular opacities also appear in a profusion up to 1/0 in association with increasing age and smoking and, in coal workers, may relate to coexisting fibrosis and emphysema. Small rounded opacities probably never regress, but the presence of emphysema appears to reduce the reading of profusion on the chest radiograph. Some enlargement of hilar nodes is usual, but eggshell calcification is unusual. In a recent report, the presence of small irregular shadows indicating the presence of interstitial fibrosis has been described as a feature in those with exposure to coal dust and the same report disputes the conventional view that nodular opacities in CWP are predominantly in the upper lung zones.⁷³

PMF is diagnosed radiologically when the parenchymal opacities exceed 1 cm in diameter, a cutoff point that is arbitrary in what is obviously a continuous process, as shown by the pathologic demonstration of PMF without associated radiologic features.⁹³ Conversely, approximately one third of cases diagnosed as PMF on the radiograph have been shown, at autopsy, to represent other lesions, including tumors, rheumatoid nodules, or tuberculosis scars.⁹³ PMF lesions are more common in the upper lobes, are situated posteriorly, and are usually well demarcated from the adjacent lung. As PMF becomes more advanced, the lesions are nearly always bilateral (see Figs. 73-6 and 73-7). They may take on bizarre shapes, cavitate, or calcify. As the lesions shrink toward the hilum or to the apex, bullous lesions may be seen in the surrounding lung.

Lesions seen on the chest radiograph in rheumatoid pneumoconiosis are similar to those of PMF but are usually multiple and peripherally located. The lesions, which range in diameter from 0.5 to 5.0 cm, may appear within weeks. These lesions generally appear in the presence of lesser degrees of nodule profusion than are usual for PMF. They may cavitate, contain fluid levels, and show some calcification surrounding the cavity. In some cases, the lesions disappear, often completely, but may be followed at a later date by a fresh crop of lesions. The ILO classification of radiographs provides a special notation for lesions thought to be rheumatoid pneumoconiosis.⁵

LUNG FUNCTION

The controversy regarding the association between simple CWP and abnormal lung function has persisted largely because coal dust has been shown to cause both obstructive lung disease⁹⁴ and pneumoconiosis. In general, it is probably true that simple CWP is a condition with little demonstrable effect on lung function. In part, this may be due to the health selection effect into a dusty job.⁵⁵ Small irregular opacities and PMF have each been shown to be associated with abnormal lung function.^{4,95} Lung function deficits in complicated CWP include reduction in FVC and FEV₁, increased *total lung capacity* (TLC) and residual volume, and decreased DL_{CO} (particularly in the presence of

mixed rounded and irregular opacities). Similar changes have also been noted in nonsmoking coal miners without CWP.⁴ Pulmonary hypertension may develop in proportion to the reduction of the vascular bed associated with advanced PMF.

DIAGNOSIS, COMPLICATIONS, AND MANAGEMENT

A history of occupational exposure to coal and a chest radiograph are the fundamental elements in the diagnosis of CWP. A CT scan of the chest may be used to demonstrate evidence of CWP when the features on the radiograph are inconclusive.

There are no data to suggest that CWP alone carries an increased risk for mycobacterial infection, either tuberculous or nontuberculous, but treatment of latent tuberculosis infection should be considered for coal workers who are thought to have had significant silica dust exposure or who have evidence of silicosis. Other complications include rheumatoid nodules, which are associated more commonly with coal mining than with gold mining exposure, and scleroderma, in which the opposite is true. Most evidence suggests that the occupation of coal mining is not associated with a risk of lung cancer, but some data suggest and some data refute an increased risk of stomach cancer.^{4,78}

The principles of management are those summarized in the “Introduction” to this chapter and elaborated in the section on “Silicosis.” Subjects with radiologic disease of profusion category 1 or greater should be advised to change their occupation to one in which they are no longer exposed to dust because of their risk of developing PMF. Management of other dust-related, smoking-related, or dust- and smoking-related diseases, such as chronic bronchitis and emphysema, is less straightforward. Smoking-cessation counseling should be given on general principles. Although there are no data to show any interaction between smoking and CWP, both coal mining and smoking have the capacity to cause COPD.⁷⁷

ASBESTOS-RELATED FIBROSIS OF THE LUNGS (ASBESTOSIS) AND PLEURA

ASBESTOS MINERALS

History and Uses

Asbestos is an ancient mineral exploited by humans from prehistoric times because of its durability and heat resistance and its fibrous nature, which enabled it to be spun.^{1,96} Commercial use of asbestos grew with mechanization; growth was exponential between the two world wars. Annual production peaked over 5 million tons in 1976 and stabilized at approximately 4 million tons in the early 1980s. Production began to fall in Europe and North America only in the late 1980s, when the ill health effects of exposure became a matter of increasing public concern.¹ In 2010, the world consumption of asbestos, mainly chrysotile, was estimated to have been 2 million tons. By contrast, annual

world production of the nonasbestos mineral silicates is approximately 30 million tons. The use of substitutes has increased proportionately as the use of asbestos has been restricted or banned, although in 2012, only 54 countries had banned or severely restricted the use of asbestos. On the African, Asian, and South American continents, asbestos continues to be in demand as a cheap, durable material for use in water reticulation and in housing projects for their rapidly urbanizing populations, and in many countries, the consumption of asbestos remains high and is increasing.⁹⁷

The word *asbestos* (meaning “unquenchable” in Greek) is used currently as a collective term for naturally occurring mineral silicates of the serpentine and amphibole group. Despite different origins and physical and chemical properties, these silicates have in common a fibrous habit, that is, they form naturally in bundles from which fibers can be easily separated.

As a basis for standard setting, the *Occupational Safety and Health Administration* (OSHA) defines a fiber as a particle more than 5 μm in length with an aspect ratio equal to or greater than 3:1.

Table 73-2 lists some of the mineral silicates found in human lung tissue and gives a general indication of their commercial uses. From the point of view of health effects, the most important are asbestos fibers and man-made mineral fibers. Biologic potency (and disease-producing potential) depends in general on dose delivered to the target organ, fiber dimensions, and durability in the lung tissue. The role of each of these parameters may not be the same for all fibers and all disease entities. Nonfibrous particles greater than 10 μm seldom reach the lung parenchyma, whereas fibers up to 200 μm can be found in the lungs if their diameter is less than 3 μm .²

Sources of Human Exposure

Table 73-2 gives a list of the more common sources for human exposure to asbestos.¹ The discussion that follows deals mainly with exposure to asbestos fibers; the principles, however, apply equally to exposure to other fibers.

In industrialized countries, and increasingly in industrializing countries, human exposure is most likely to be *occupational* and may happen in mining, milling, transporting, manufacturing, and applying or using raw fiber or manufactured products. In World War II, a major source of exposure was in the naval shipbuilding, repair, or refitting industries; in the post–World War II period, major sources of exposure were in the construction and transport industries, although exposures in shipbuilding, repair, or refitting continued to pose risks. Asbestos-containing materials in post–World War II buildings include boards, panels, surfacing, insulation, tile and floor covering, roofing, and caulking. Workers are thus exposed in maintenance operations or demolition of plants and buildings in which asbestos-containing materials have been used. Other sources of human exposure are during the removal of asbestos lagging or insulation from ships or buildings and the disposal of industrial waste, such as the dumps of defunct asbestos plants. In most industrialized countries, these sources of exposure have diminished in response to heightened public awareness and control regulations. However, as recently as 2004, the U.S. Department of Labor estimated that 1.3

million workers remained exposed to asbestos in the workplace, notably in construction and general industry in the United States⁹⁸ and, in a more recent report, ongoing asbestos exposure is also attributed to local and imported, asbestos-containing goods.⁹⁹ Data do suggest that asbestos exposure has decreased, although a recent study from the United States comparing those examined between 1980 and 1992 and those examined between 1993 and 2005 found an unexplained increase in crocidolite fibers in the lungs from 819 subjects with lung cancer, malignant mesothelioma, and asbestosis.¹⁰⁰

Indirect occupational exposure, also called *bystander exposure*, describes the exposure of those whose trades require them to work in the vicinity of others who are working directly with asbestos or asbestos-containing materials. Examples are carpenters and welders who may work in close contact with insulators and ladders who mix asbestos on site, often in closed spaces. Workers were often indirectly exposed in the shipbuilding, repair, and refitting industries and the construction industries.

Domestic exposure happened primarily as a consequence of fiber-laden work clothes being brought home. Domestic exposure still accounts for a small proportion of cases of asbestos-related disease, mainly pleural, and is reported to have accounted for up to 15% of malignant mesothelioma in one U.K. study.¹⁰¹ Given the long incubation period of this tumor (from 20 to 40 years), domestic exposure is likely to be the source of cases presenting well into the 21st century.

Environmental and residential exposure takes place as a consequence of living in the neighborhood of asbestos mines, mills, or plants.¹⁰² This source of exposure was first dramatically brought to medical attention in 1960 in a report of a cluster of 31 cases of malignant mesothelioma among residents and crocidolite asbestos miners of the Northwest Cape, South Africa.¹⁰³ New cases were reported from this area until 1995, and because occupational and environmental exposure continued until the 1970s, cases were expected to continue and to increase up to and beyond 2010.¹⁰⁴ A cohort study comparing the mortality experience of more than 4500 women living in the vicinity of the Quebec chrysotile mines with that of 1.375 million women from 60 reference areas in the province found seven deaths from mesothelioma in women living in the asbestos mining area and none in the reference population.¹⁰² Vermiculite mined from Libby, Montana, and shipped around the country was found to be contaminated with asbestos fibers. Residents of Minneapolis who had lived near waste piles of Libby vermiculite and who had never worked in the vermiculite industry have been found to have a high prevalence of asbestos-related pleural disease, greater if they ever played in or had contact with the waste piles.¹⁰⁵ Similar waste piles associated with the remote processing of Libby vermiculite are estimated to exist in 250 sites across the United States. A community-based study in Libby found that localized pleural abnormalities were associated with restrictive pulmonary function.¹⁰⁶ Environmental exposures from nonindustrial sources have been documented among residents of rural areas in Eastern Europe where the soil is contaminated with various fibers.¹⁰⁷ In addition, there have been epidemics of asbestos-related pleural disease, nonmalignant and malignant, among residents of

Table 73-2 Mineral Silicates That Have Been Found in Human Lung Tissue*

Mineral: Group and Form	Location of Major Deposits, Commercial or Other	Main Commercial Uses and/or Other Sources of Human Exposure
ASBESTOS MINERALS		
Serpentine		
Chrysotile [†] (white asbestos)	Canada (Quebec, British Columbia, Yukon, Newfoundland [‡]), Russia, China (Szechwan), Brazil, Mediterranean countries (Cyprus, Corsica, Greece, Italy), southern Africa (South Africa, Zimbabwe, Swaziland)	Brake lining, shipbuilding and repair, polishing of precious stones, stone cutting, whetstone cutting, foundry operations (mainly for insulation) Asbestos cement products (pipes, gutters, tiles, roofing); insulation, fireproofing, reinforced plastics (fan blades, electric switchgear); textiles; friction materials; paper products; filters, spray-on products
Amphibole		
Crocidolite (blue asbestos)	South Africa (Northwest Cape [‡]), western Australia [‡]	Used in combination, mostly in cement but also in some of the products listed above
Amosite (brown asbestos)	South Africa (Northern Province, former Transvaal)	
Anthophyllite	Finland [‡]	Filler in rubber and plastics
Tremolite	Contaminates ore in certain talc, iron, and vermiculite mines (e.g., Libby, MT); also found in some agricultural soils	May or may not be removed in processing; has rural domestic uses (e.g., stucco)
Cummington-grunerite	Contaminates ore in certain iron mines (often not fibrous)	No commercial use
NONASBESTOS MINERAL SILICATES		
Clay minerals (usually fine-grained, powder-like) such as kaolin and montmorillonite (bentonite)	40 countries, including China, United States (Georgia, North Carolina), United Kingdom (Cornwall), Germany, Egypt, Japan	Functional filler in paper, plastic, bricks and cement, rubber, paint, etc.; fire clays, refractories, ceramics, lubricants
Attapulgite and sepiolite	United States (Georgia, Florida), Spain, Australia, South Africa	Oil absorbants; pesticide carriers; pet litter
Talcs (usually platelike but can roll into scrolls)	United States (Vermont, Montana, New York, California), Italy, Spain, Norway, China, Japan, Korea, Canada	Ceramics; paper making; cosmetics; pharmaceuticals; animal feed; fertilizer; anticaking; paints; varnishes; plastic reinforcer
Micas (Usually Flaky) Muscovite	United States (North Carolina, Georgia, and other states), France, Spain, China, India, Italy	Filler in plastics, drill sites, special paints; refractories; semiconductors; insulation; anticorrosion materials; welding rods
Vermiculite (expands when heated)	South Africa, United States (Montana, Virginia), Australia, Kenya	Absorbents (horticulture); plasters; boards; insulation; fire resistance
Wollastonite (exists as needles or fibers in limestones)	United States (California, New York), Japan, former USSR, Finland, Mexico, Australia	Filler/flux in ceramic industry; used in latex and oil-based paint; in welding fluxes; asbestos substitute in hardboard, insulation, and brake linings
Zeolite (fibrous), e.g., Erionite [§]	Turkey (Cappadocia and Anatolia regions) [§] ; noncommercial deposits	Houses constructed in erionite rock; soil-containing fibers mixed with tremolite; sepiolite used in stucco and plaster
Other (mainly nonfibrous)	Worldwide (in filling of lava cavities); mined in 16 countries, including several in Europe, the United States, and Japan	Pollutant and radioactive waste control; also used in catalysts, adsorbents, conditioners
MAN-MADE MINERAL FIBERS		
Glass wool and filament, rock wool, slagwool, ceramic fiber	Production in factories around the world	Many uses previously reserved for asbestos: glass filament used in mats, lamination, yarns; glass-rock and slagwool used as insulation in buildings and in car and naval construction; ceramic fiber used in reinforced cloth, disks, brakes, gaskets, board, and paper; high-performance ceramic fiber used in jet engines, spacecraft

*The list is not exhaustive, and the reader should consult other sources^{1,2,170,171} for further information. Asbestos minerals invariably exhibit the fibrous habit; nonasbestos mineral silicates also may do so. Most silicate deposits are mineralogically heterogeneous, as are most of the commercial forms of the minerals.¹⁷⁰

[†]Accounts for more than 90% of the world's commercial production; other fibers still used in combination with chrysotile.

[‡]Mining no longer in operation.

[§]One of three epidemics of mesothelioma in Turkish villages implicated erionite; in the other two, tremolite and/or chrysotile were implicated.¹⁰⁷ As of 2012, 54 countries have prohibited the use of asbestos or severely restricted its use, but in all countries, exemptions are allowed for certain uses. A prohibition decree was adopted to be enforced in the European Community in 2005.

Turkish villages whose homes were constructed in erionite tuff rock or who used erionite and tremolite in stucco and plaster¹⁰⁷ and in Da-yao, southwestern China, where crocidolite is present in the soil.^{102,108} A major concern since the 1980s has been the potential risk of exposure to occupants of public (including schools), commercial, and residential buildings constructed during the post-World War II period, when asbestos-containing materials were widely used in construction. A health review mandated by the U.S. Congress concluded that exposure in buildings was less by an order of magnitude than that encountered in the workplace except for custodians and others responsible for building maintenance.¹⁰⁹ The report also provided estimates of lifetime cancer risk (see “[Asbestosis, Asbestos Exposure, Lung Cancer, and Mesothelioma](#)” later).

Fate of Inhaled Fibers

Accumulation of fibers in the lung is the outcome of exposure, deposition, clearance, and retention, all processes that depend on fiber dimensions and the level, intensity, and profile of exposure.¹¹⁰⁻¹¹² Clearance of fibers from the lung is greater for short and for chrysotile fibers than for long and amphibole fibers.¹¹³ Retention of fibers is inhomogeneous, with more fibers being found in the lung regions with shorter pathways and greater accumulations of longer fibers with asbestosis than in lungs in which only airway lesions have developed.¹¹³ Fibers equal to or less than 3 μm are phagocytosed by activated macrophages and then translocated to lymphatic channels. Longer fibers are incompletely phagocytosed, often by more than one macrophage, and become the core of what were originally called *asbestos bodies* because of their association with asbestos exposure. Although most coated fibers in human lungs have been shown to contain asbestos (usually amphibole) when subjected to radiographic diffraction analysis,^{2,96} the term *ferruginous bodies* has been suggested to underline the fact that other mineral fibers may undergo coating in human lungs. (For a discussion of the translocation of fibers to the pleural space, see Chapters 79 and 82.)

In the lungs of exposed individuals, the number of uncoated, or bare, fibers (visible only on electron microscopy) exceeds the number of coated fibers (*asbestos* or *ferruginous* bodies), visible by light microscopy, by 5- to 10,000-fold.¹¹⁵ For many years, the coated asbestos fiber, *asbestos body*, has been considered the hallmark of exposure, past or current, no doubt because of its distinctive structure and because it was readily visible under the light microscope. The presence of more than one coated fiber has been cited (and challenged) as a necessary criterion for the pathologic diagnosis of asbestosis even in a subject with an appropriate exposure history.¹¹⁵ Asbestos bodies may be found in sputum or in BAL fluid when lung tissue levels are high. They are also more commonly found when exposure has been recent and to amphibole rather than chrysotile fibers.^{2,116,117} BAL fluid may also show characteristic cellular, biochemical, and mineralogic features in workers exposed to asbestos and especially in those with asbestosis.¹¹⁸

Exposure versus Dose-Response Relationships

Epidemiologic studies have consistently demonstrated exposure-response relationships for asbestos-related paren-

chymal lung fibrosis.¹¹⁹ There are differences in the exposure-response relationships between industrial sectors, which probably reflect the fiber size (smaller fibers causing more lung disease) and the nature of the fibers, their retention, and their biopersistence in lung tissue (amphiboles causing more disease than chrysotile). For asbestos-related pleural disease, exposure-response relationships can also usually be demonstrated, but the residence time of the dust in the lungs is more important than the cumulative exposure.^{111,114} Mineralogic analysis has also shown that the degree of fibrosis correlates with fiber concentration, both in chrysotile- and in amosite-exposed workers. The toxicity of mineral fibers is determined by their physical and aerodynamic properties, which determine deposition and retention. Also relevant in fibrogenesis and probably in carcinogenesis is the solubility of the fibers (which determines their survival in lung tissue), their surface properties and electrical charge (which may affect their toxicity for cell membranes and the formation of free radicals), and the length-to-width aspect ratio (which may affect cellular toxicity).^{2,35}

ASBESTOSIS (PULMONARY PARENCHYMAL FIBROSIS)

Pathology and Pathogenesis

Asbestosis tends to be prominent in the lower lobes and subpleural areas. The lesions of mild asbestosis are found at scattered sites and usually consist of foci of peribronchiolar fibrosis¹²⁰ with local chronic interstitial inflammation, accumulation of macrophages in the air spaces, and proliferation of type II pneumocytes. Second- and third-order bronchioles and alveolar ducts tend to be involved as the disease progresses and the fibrosis spreads to involve the alveolar interstitium (Fig. 73-8A). When disease is advanced, the lungs are small, streaks of fibrosis outline lobar and interlobar septa, and the visceral pleura is invariably thickened. Honeycombing may be prominent subpleurally and in the lower lobes. Unlike in silicosis, the tracheobronchial lymph nodes do not show characteristic changes and progressive massive fibrosis is unusual.¹¹⁵ Advanced asbestos-related fibrosis is distinguishable from advanced fibrosis due to any other cause only by the presence of asbestos bodies or uncoated asbestos fibers (Fig. 73-8B).²

In general, the grade of pulmonary fibrosis relates to the fiber burden carried by the lungs.² On the basis of animal and human data,^{35,121,122} asbestosis is thought to commence with an alveolitis that may resolve if the fiber burden is low and the fibers are cleared. If the fiber load is low but retained, a nonprogressive distal airway lesion, mineral dust-induced peripheral airway disease, may develop.^{35,113,120-122} If the dust load retained is high and phagocytosis of fibers by alveolar and interstitial macrophages is incomplete, fibronectin is released together with other proinflammatory and cytotoxic agents such as free oxygen radicals. These interact with and recruit fibroblasts to the site of the injury, where they proliferate and lay down collagen. If sustained, this leads to irreversible damage, loss of alveolar spaces, and the development of chronic interstitial lung fibrosis, asbestosis.¹¹³

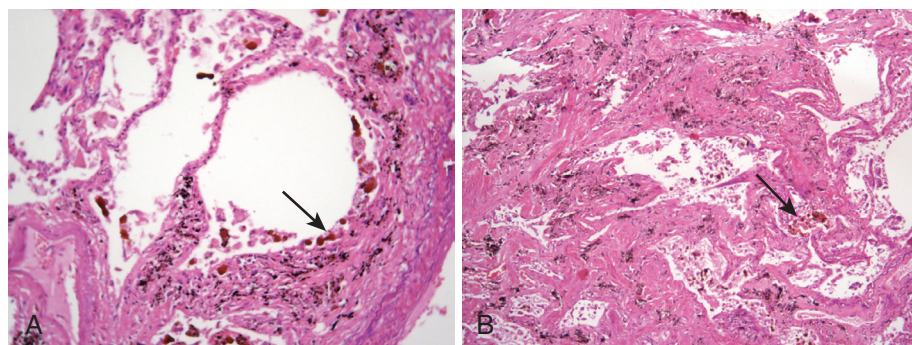


Figure 73-8 Pathologic features of asbestosis: examples from South African asbestos workers. **A**, Asbestos bodies (arrow) with commencing fibrosis. The architecture of the surrounding lung parenchyma is preserved. **B**, Diffuse interstitial fibrosis with destruction of the lung architecture and honeycombing; asbestos bodies are seen in the air spaces and interstitial tissue (arrow). (Courtesy National Institute for Occupational Health, South Africa.)

Epidemiology and Natural History

Clinical asbestosis is becoming less frequent and less severe as exposure levels in workplaces around the world are increasingly meeting currently recommended control levels.^{111,123} However, in the United States, although mortality rates for the other pneumoconioses (CWP and silicosis) are declining, the rate for asbestosis increased possibly by as much as 10-fold between 1968 and 1999^{25,80} and is not expected to decrease before 2024.¹²⁴ A similar trend was apparent in Australia,¹²⁵ while in the United Kingdom and Canada, rates of certification of death or disability from asbestosis were reported to be falling.^{126,127} However, a recent report from the United Kingdom shows that, while other pneumoconioses were becoming less common, the incidence of asbestosis in the United Kingdom continued to rise until 2005 and decreased only slightly since that time.¹²⁸ With low-level exposure to asbestos, the interval between exposure and disease increases.¹¹¹ The pattern of exposure also determines the nature of the disease. In occupations in which exposure is intermittent but of high intensity, the ratio of pleural-to-parenchymal radiologic abnormalities may exceed 20, whereas in occupations in which workers are more consistently exposed, the ratio of pleural-to-parenchymal abnormalities is closer to 2 : 1.^{111,129} Exposure at a young age is an independent determinant of both attack and progression rates of parenchymal and pleural radiologic abnormalities, suggesting that residence time of dust in the lung is important in their pathogenesis.^{111,129,130} Other determinants of progression are level and duration of exposure, cumulative exposure, and fiber type; asbestosis is more frequent after exposure to the amphiboles, crocidolite and amosite, or mixtures of amphibole and chrysotile than to chrysotile alone.¹¹¹ Once established, radiologic asbestosis will usually progress.¹²⁹ Radiologic asbestosis may appear and progress long after exposure ceases; in a study of chrysotile miners and millers in Quebec, appearance and progression rates of 31% and 9%, respectively, were recorded for pleuroparenchymal disease over an average follow-up period of 17 years after exposure.^{111,129} Progression in the absence of further exposure relates to cumulative exposure up to the time of leaving work.^{111,130} Genetic features appear to play a role in determining the development and extent of asbestos-induced lung fibrosis.^{111,131,132}

Smoking deserves comment because of its role as a universal risk factor for respiratory disease, both malignant and nonmalignant. There is some evidence that the milder grades of radiologic small irregular opacities on the ILO classification may be caused by smoking. Pathologic studies do not show evidence of an association between asbestosis grade and smoking,¹³³ although there is evidence to suggest that smoking enhances the retention of fibers in the lungs.^{2,133}

Clinical Features

Asbestosis is characteristically associated with dyspnea. Dyspnea often precedes other evidence of disease and, therefore, may be underrated by the physician because of its subjective nature. However, the consistency of its relationship to exposure levels¹¹¹ suggests that it is related to early parenchymal asbestosis. Persistent dry cough is reported commonly, almost as frequently as dyspnea in some series,^{114,134} and has been attributed to the stimulation of lung receptors. Chest tightness or pain, or both, are not uncommon and may be caused by acute asbestos-associated pleural reactions.

Basal crackles, an early and distinctive feature of asbestosis, are fine, crisp, persistent sounds, often heard first over axillary and basal regions and then more generally as the disease advances.⁹⁸ Other sounds, including coarse crackles and rhonchi, reflect airway disease that may be related to cigarette smoking or to dust in the occupational environment.¹³⁵ Clubbing of the fingers and, occasionally, the toes develops in some subjects. Late manifestations include respiratory and circulatory failure, and these, with cancer, are common causes of death.

Radiographic Features

The posteroanterior chest radiograph remains a key tool in the initial clinical diagnosis of asbestosis and in the health surveillance of exposed workers. The ILO classification⁵ uses the term “small irregular opacities” to describe the irregular linear shadows that develop in the lung parenchyma and obscure the normal bronchovascular arborization pattern seen in disease-free lungs. The parenchymal opacities are usually seen first in the lower lateral zones (eFig. 73-9). As their profusion increases, the borders of the heart may be obscured (eFig. 73-10). Small rounded

opacities are unusual when the exposure has been primarily to fibers but are more likely to be seen in workers who also have had silica exposure (e.g., asbestos cement workers).^{1,19}

Early fibrotic changes are better visualized by HRCT with supplementary prone images (eFig. 73-11),¹¹⁸ particularly for subpleural parenchymal changes that may be obscured by overlying pleural fibrosis on the chest radiograph (eFig. 73-12).¹³⁶ Visceral pleural thickening of the interlobar fissures is common.¹¹⁴ Changes in the parietal pleura (see later) are also common, and the presence of pleural plaques (particularly if they are bilateral) (see eFig. 73-12) or of pleural thickening provides additional evidence that the parenchymal disease is asbestos related. Hilar node enlargement is not a feature of asbestosis, and PMF lesions, including rheumatoid pneumoconiosis, are less common than in workers exposed to coal or silica. The radiologic features of well-developed disease seldom present a diagnostic problem, whereas the detection of less advanced disease may require the use of ILO films and HRCT. The CT scan is also useful in characterizing localized pleuropulmonary lesions, including rounded atelectasis (eFig. 73-13A-D, Video 73-4), which must be distinguished from lung cancer because it usually presents as a solid localized lesion (Fig. 73-9). HRCT can also identify coexisting lung disease such as emphysema and distinguish subpleural fat from pleural thickening and plaques (eFig. 73-14).

Lung Function

Established asbestosis is often, but certainly not always, associated with a restrictive lung function profile; reduced FVC, *total lung capacity* (TLC) and DL_{CO} . In studies of exposed populations, a substantial proportion of subjects (up to half in some series)¹²⁹ exhibit a mixed or obstructive function profile in keeping with the parallel development of airway

and parenchymal effects of working in dusty occupations contaminated by mineral dusts.⁷⁵ When repeated lung function tests are used to assess progression of disease, simple volume measurements such as FVC appear to be the most useful.^{96,129,137}

Diagnosis and Complications

Criteria for diagnosis depend on the purpose for which a diagnosis is required. Clinical diagnosis depends on establishing the presence, extent, and nature of pulmonary fibrosis and whether the exposure has been of a duration and intensity sufficient to put the individual at risk for developing asbestosis. The fewer the features, the less certain the diagnosis is; the more trivial the exposure, the less likely it is to be causal. When radiologic or lung function changes are marginal, other imaging, including CT or HRCT, may be helpful. In the absence of what appears to be an adequate exposure history, it may be appropriate to perform a biopsy of the lung to establish the nature of the disease and the presence and burden of asbestos in the lung. Sputum analysis may be useful for identifying asbestos bodies as an indication of lung dust burden but is far less sensitive than BAL.^{98,118,138} Diagnosis of asbestosis for the purpose of legal attribution calls for greater certainty and the use of criteria that vary according to the legal administrative system involved. Most published criteria consider histopathology as the best means of establishing the diagnosis.¹¹³ In its absence, the following criteria are proposed: (1) a reliable history of asbestos exposure; (2) an appropriate lag time between exposure and detection; (3) evidence of lung fibrosis on the chest radiograph or HRCT scan; (4) a restrictive pattern of lung function; (5) bilateral fixed inspiratory crackles; and (6) clubbing of the fingers or toes, or both. Of these, history of exposure and radiographic evidence are considered essential and the others confirmatory.¹¹³

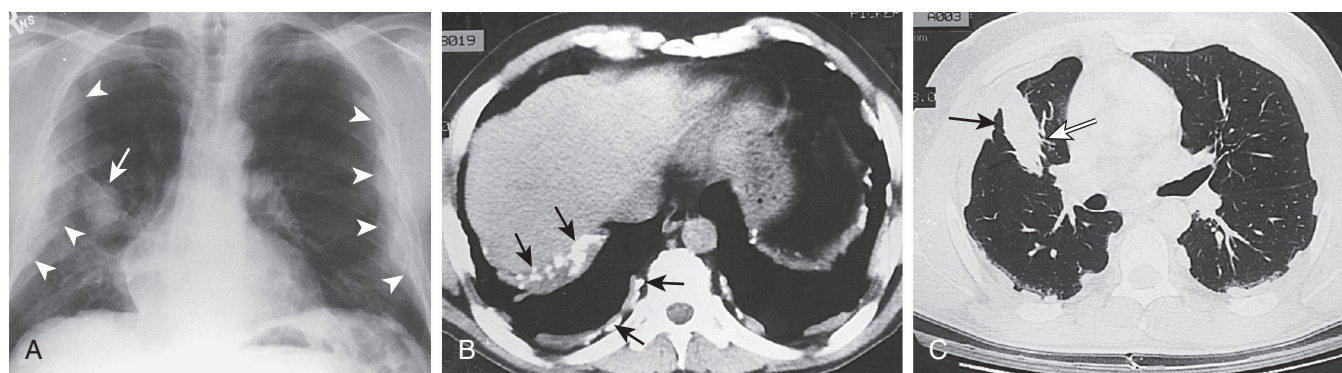


Figure 73-9 Asbestos-related pulmonary parenchymal and pleural disease (bilateral pleural fibrosis and atypical rounded atelectasis) in a 50-year-old man. The patient had worked as an electrician since the age of 17 years, first in construction for 10 years (with known exposure to asbestos), then briefly on naval ships during World War II, and in a chemical plant (with known exposure to talc) for the past 20 years. His exercise tolerance was excellent and his only complaint was a dry cough. Chest radiographic abnormalities had been noted 4 years previously. **A**, Posteroanterior chest radiograph shows bilateral diaphragmatic plaques, extensive bilateral pleural thickening (arrowheads), and a circumscribed lesion in the right mid-lung zone that had increased in size over the past year (arrow). **B**, On CT, the pleural plaques were shown to be much more extensive than appeared from the chest radiograph. Many plaques (arrows) were calcified. In addition, HRCT revealed bands of subpleural fibrosis related to the pleural plaques or thickening, or both. Lung volumes and carbon monoxide diffusing capacity were greater than 100% and 98% of predicted values, respectively. Because the circumscribed lesion (arrow in **C**) had enlarged over the past year, it was removed surgically. The lesion, which was nonmalignant, consisted of pleural, subpleural, and interstitial fibrosis. Analysis of lung digest revealed the following: 36 asbestos bodies/mg of dry lung tissue and 7570 fibers/mg of dry lung tissue, more than half of which were asbestos fibers and less than 1% of which were talc. These findings implicated his earlier, rather than his more recent, occupational exposures as the cause of his pleural disease. (Dr. J. Kosiuk, Department of Radiology, Royal Victoria Hospital, Montreal, carried out the radiographic studies; Dr. A. Dufresne, School of Occupational Health, McGill University, carried out the lung dust analyses.)

The individual with asbestosis is at increased risk for cancer of the lung^{139,140} and, by virtue of asbestos exposure, is also at risk for mesothelioma. Working in a dusty occupation also puts the worker at risk for developing COPD.⁷⁵ Tuberculosis and rheumatoid pneumoconiosis are uncommon complications of asbestosis.

Asbestosis, Asbestos Exposure, Lung Cancer, and Mesothelioma (see Chapters 52 and 82)

In 1977 the *International Agency for Research on Cancer* (IARC) classified asbestos as a human carcinogen, the target sites being lung, larynx, and pleura.¹³⁹ Since that date, a considerable body of evidence has accumulated in support of this view that lung cancer is associated with asbestos exposure with or without asbestosis,¹⁴¹⁻¹⁴³ although there are still dissenting views.² The lung cancer risk is enhanced by cigarette smoking, and the independent and joint impacts of smoking, asbestos exposure, and asbestosis are discussed in a recent paper in which smoking and asbestos exposure are described as having an additive effect, whereas smoking and asbestosis have a “supra-additive” effect on the risk of dying from lung cancer.¹⁴⁴ This report shows a substantial fall in the risk for lung cancer when asbestos-exposed insulator workers stop smoking; the risk is halved at 10 years after stopping smoking and is reduced to that of a nonsmoker after 30 years.¹⁴⁴ Other factors influencing the risk of lung cancer in exposed workforces include industry (risk greater in the textile vs. the asbestos cement industry), fiber type (risk greater when exposure is to amphibole, crocidolite, amosite or tremolite, or mixed amphibole-chrysotile than when it is only to chrysotile), and fiber dimensions (longer fibers are more carcinogenic than shorter fibers).^{113,145}

The introduction of workplace dust exposure controls has resulted in an increase in the emergence of cancer as opposed to asbestosis as an important cause of death in asbestos-exposed individuals. This is explained by the fact that the asbestos-dust burden is much lower in cases of lung cancer than it is in cases of asbestosis. For instance, in chrysotile miners in Quebec, the fiber concentrations in those dying of asbestosis versus those dying of lung cancer versus those nonexposed were 30 versus 13 versus 2 million chrysotile fibers per gram dry lung tissue; for those engaged in trades with asbestos exposure in the Pacific Northwest, where amosite was the dominant fiber, the equivalent figures were 10.0 versus 1.0 versus 0.7 million fibers per gram of dry lung tissue.¹³³ All histologic cell types of lung cancer have been shown to be associated with asbestos exposure, which further supports the direct role of asbestos, independently from asbestosis, as a carcinogen.¹⁴⁶

Of great concern to the public has been the risk of cancer from attending school or working in a building constructed with asbestos-containing materials. The lifetime risk for premature cancer death from exposure at school from age 5 to 18 years has been estimated at 6 per million exposed and, for working in an office building with asbestos-containing material, at 4 per million exposed; these risks are compared with a risk of 2000 per million for 20 years employed in a workplace conforming to 0.1 fiber/mL, the current permissible exposure limit proposed by OSHA.¹⁰⁹ Malignant mesothelioma has been reported in school

teachers; population studies have failed to show an increase in the incidence of mesothelioma in relation to the use of asbestos in buildings.¹⁰⁹

PLEURAL PLAQUES

Pathology and Pathogenesis

Pleural plaques are distinctive, smooth, white, raised lesions with irregular borders usually found on the parietal and rarely on the visceral pleura (eFig. 73-15). They may vary from small to extensive and are usually nonadherent to the lung. Common sites are the posterolateral midzones, where they may follow the rib contour, and on the diaphragm. They are less commonly found on the pleura adjacent to the mediastinum and pericardium and, rarely, in the apices and costophrenic sulci.¹¹⁴ On microscopic section, pleural plaques consist of avascular, acellular, laminated collagen fibers arranged parallel to the surface or in whorls, with hyaline changes and occasional fibroblasts. Macroscopic calcification is common, and microscopic calcification is extremely common, especially in the parietal lesions. The lesions are usually covered by mesothelium. Fine asbestos fibers are seen on electron microscopy.¹¹⁴ The lungs of patients from the general population who have plaques have been shown to contain a 50- to 250-fold excess of long, thin, mainly amphibole fibers.² In asbestos miners and millers in Quebec and in those engaged in the Pacific Northwest trades that involve exposure to asbestos, the lung burden is similar to that seen in association with lung cancer (see earlier).¹¹⁴ Pleural plaques are thought to develop after the movement of fibers into the pleural space (see also Chapter 82). Once the fibers are within the pleural space, macrophage and cellular interactions may determine fiber localization and plaque formation. In the absence of macrophages, the pleural reaction tends to be disorganized and diffuse.¹⁴⁷ The parietal location may be due to the fact that for fibers, as for macrophages, the only exit from the pleural space is via stomata that communicate directly with the parietal pleural lymphatic channels. Pleural fibrosis and pleural plaques may have the same pathogenesis.²

Clinical Features

Pleural plaques, in the absence of parenchymal disease, often do not cause signs and symptoms and are usually detected as an incidental finding on a routine chest radiograph. Their visualization depends on their thickness and the orientation of the x-ray beam. Only a modest proportion of those seen at autopsy are detected on posteroanterior chest radiographs (see eFigs. 73-9, 73-10, 73-12A); oblique views increase the yield. CT and HRCT scans can identify plaques at an earlier, less well-developed stage (eFig. 73-13B-E) and can differentiate plaques from extrapleural fat pads. In the past, pleural plaques have been labeled as “visiting cards” for asbestos exposure, implying that they had no impact on lung function at rest or on effort. In fact, in epidemiologic studies, lung volumes (mainly vital capacity and FVC) of those with pleural plaques are on average modestly but consistently reduced.¹⁰⁶ The DL_{CO} is generally normal.^{114,129,137} Increasingly, too, it is recognized that in some individuals, pleural plaques may be associated with

disability.¹⁴⁸ The underlying mechanism may be inhibition of inspiratory capacity during exercise, resulting in an increase in the work of breathing.

Epidemiology

Pleural plaques continue to be the most frequent and often the only manifestation of asbestos exposure,^{114,127,149} and asbestos exposure is the most common cause of pleural plaques. Bilateral pleural plaques are more likely to be associated with asbestos exposure than unilateral plaques, for which other causes should be considered.⁹⁸ Age and residence time of dust in the lungs are determinants of these distinctive pleural lesions¹¹⁴; smoking is considered to be a determinant by some¹ but not in general.¹¹⁴ Domestic and residential exposures have been implicated in the production of pleural plaques (see earlier, the discussion of human exposure in the section on “Asbestos Minerals”), with remarkably high rates for pleural calcification ($\leq 30\%$) being described in some rural communities in the eastern Mediterranean countries of Corsica, Greece, Cyprus, and Turkey.¹⁰⁷ Environmental (nonoccupational) exposure to the asbestos-contaminated vermiculite from Libby, Montana, has also been reported in at least one of the several U.S. sites where this material has been processed.¹⁰⁵ Of greater concern to the patient and the clinician is the prognostic significance of plaques. In one study, they were associated with alveolitis, as reflected in bronchoalveolar cell counts¹⁴⁷ and, by implication, with an increased likelihood of developing parenchymal disease. The results of a Swedish cohort mortality study involving 1596 men were interpreted as showing that pleural plaques on the chest radiograph indicated significant exposure to asbestos, as well as an increased risk of mesothelioma and possibly also for lung cancer.¹⁵⁰ This risk raises the question of screening chest radiographs in those with pleural plaques, a topic that remains controversial in the absence of clear evidence of benefit.^{98,150}

PLEURAL FIBROSIS AND VISCEROPARIETAL REACTIONS

Pathology

Like pleural plaques, pleural fibrosis and visceroparietal pleural reactions may be localized or diffuse and may vary in thickness from a milky discoloration of the lung surface to a thick, white peel encasing much of one or both lungs. The interlobar fissures are commonly involved. Visceral pleural disease may be severe even in the presence of minimal parenchymal reaction.^{114,115} Occasionally, a localized pleural reaction may fold on itself and the surfaces adhere, trapping the underlying lung and leading to a well-defined pleuroparenchymal lesion or pseudotumor, also called *rounded atelectasis*¹¹⁴ (see Fig. 73-9, eFig. 73-13). Asbestos bodies and fibers are usually found in the visceral pleura, the underlying parenchyma, or both,¹¹⁴ and the lung dust burden usually reflects the occupational exposure; however, fiber counts are considerably less than those seen in asbestosis.

Epidemiology

Like pleural plaques, pleural fibrosis and visceroparietal reactions may be found in the absence of radiologic

parenchymal fibrosis and are increasing in frequency.¹¹⁴ The exposures implicated (see Table 73-2) are often short, heavy, remote, and related to amphiboles. Latency is usually long, 34 years in a recent report,¹⁵¹ reflected in the fact that these reactions relate to time since first exposure (a proxy for residence time of dust in the lung) and not to cumulative exposure dose.¹¹⁴ Pleural fibrosis has been reported in association with environmental exposures from mining operations (see previous discussion under “Sources of Human Exposure”) in Finland and South Africa and from nonmining (agricultural) operations in Bulgaria, Czech Republic, Slovakia, Poland, Greece, and Turkey. Epidemiologic studies are also consistent in showing that the presence of pleural fibrosis is associated with reduction in lung function, after any associated parenchymal fibrosis has been taken into account.^{114,129,137}

Diagnosis

Pleural fibrosis is less specific for asbestos exposure than are pleural plaques, and other causes need to be considered in the differential diagnosis. The diagnosis of asbestos-related pleural thickening is usually based initially on the chest radiograph. Clinical presentation, like that of pleural plaques, is often as an incidental abnormality detected on a routine chest radiograph. After careful inquiry, a remote history of exposure, often quite brief but usually heavy, can be obtained from the subject. Rounded atelectasis may present as a radiologic abnormality in an asymptomatic subject, usually with a clear history of exposure. Conversely, some subjects present with breathlessness¹¹⁴ or chest pain, or both, with or without a history of acute episodes, attributed to benign pleural effusions (see later). Pleural fibrosis restricts the movement of the lungs; in the absence of associated parenchymal disease, clinical signs may be minimal, even though functional impairment is detectable. Impairment may be modest even in the presence of severe pleural disease.^{114,129,152} In one study, any pleural abnormality was associated with an average deficit of 0.22 L and 0.40 L for FEV₁ and FVC, respectively,¹⁴⁸ but pleural fibrosis occasionally becomes severe enough to precipitate respiratory and cardiac failure and to require pleurectomy.^{114,153}

The radiologic and CT features of pleural fibrosis are discussed under “Pleural Plaques.” Given a history of exposure, obliteration of the costophrenic angle is likely to represent the residuum of asbestos pleural effusion.¹¹⁴ In rounded atelectasis, the CT scan is particularly useful in delineating the relationship of the rounded lesion to other pleural changes.¹³⁶ Nevertheless, the differential diagnosis of rounded atelectasis includes lung cancer and, in some cases, the diagnosis can be established only by surgery.

BENIGN ASBESTOS-RELATED PLEURAL EFFUSIONS

Benign asbestos-related pleural effusions may arise without evidence of prior pleural involvement from asbestos exposure or may mark an increase in the extent or severity of an already present pleural reaction. The term “benign” does not imply a lack of clinical significance but rather that the effusion is not associated with mesothelioma.¹¹⁴ Benign asbestos-related pleural effusions usually appear within 15

years of the first exposure, often after exposure has ceased,¹¹⁴ with a median of 38 years after first exposure to asbestos.¹⁵¹ They are more common in persons in their 20s and 30s and may be the most common manifestation of asbestos pleural disease in that age group. The episodes are usually transient and may be silent but may be associated with chest tightness and, occasionally, pleural pain, fever, and dyspnea.¹¹⁴ The effusion is usually small, exudative, and bloodstained² and contains leukocytes. Asbestos bodies are rarely found in the fluid, but they may be seen in the underlying parenchyma on biopsy.¹⁵⁴ The sedimentation rate is often raised.¹⁵⁴ Diagnosis is by exclusion, and suggested criteria include (1) an exposure history, (2) the absence of other causes, and (3) absence of tumor on a 3-year follow-up.¹¹³ Because cytologic examination of the pleural fluid is rarely conclusive, a thoracoscopic biopsy is usually required to exclude other causes; to establish the presence of fibers in the pleural fluid (rarely demonstrable), pleura (sometimes demonstrable), or the underlying lung parenchyma (not infrequently demonstrable); and to rule out malignancy, in particular malignant pleural mesothelioma. The usual pathologic findings in benign asbestos-related pleural effusion are those of chronic fibrous pleurisy with minimal cellularity.

The prognosis of benign asbestos-related pleural effusions is generally good; most clear spontaneously, whether it be the first episode or a recurrence. They may recur on the opposite side. Although pleural effusion is a common form of presentation for mesothelioma, there is no evidence that a benign effusion signals a future pleural malignancy. It appears rather to represent a stage in the evolution of asbestos-related pleural fibrosis and also carries a risk of developing parenchymal fibrosis (asbestosis).¹¹¹ The pathogenesis is unknown.² Both inflammatory effects by fibers in the pleura and a direct cytotoxic effect on the surface mesothelial layer have been invoked.¹¹⁴

MANAGEMENT, PREVENTION, AND HEALTH MONITORING

The principles guiding clinical management of all asbestos-related lung and pleural conditions are no different from those guiding management when there is no history of asbestos exposure. However, it is important to make the appropriate notification of a case of asbestos-related disease. Notification, together with any procedure related to compensation, depends on the local jurisdiction. Employment advice should be guided by knowledge of the impact of further exposure on the natural history of the disease processes^{114,115,129} and by the risks for developing additional asbestos-related disease. It is important to emphasize that, even in the absence of any further exposure, all nonmalignant asbestos-related diseases may progress due to the dust load already in the lungs.

No active treatment measures have been shown to influence the course of asbestosis. Patients with end-stage asbestosis have been the recipients of lung and heart-lung transplants, but technical difficulties may arise because of the associated pleural disease.

For the nonmalignant asbestos-related pleural disorders, the evidence is reasonably clear that those with pleural fibrosis are at greater risk for parenchymal fibrosis in the

future.¹¹¹ The presence of pleural fibrosis or pleural plaques is associated with increased risk for malignant pleural mesothelioma and lung cancer.¹⁵⁰ A document from the American College of Chest Physicians highlights areas in which there is and is not consensus regarding the health effects of asbestos exposure.¹⁵⁵

As a public health measure, an international ban on asbestos has been advocated for its control.¹⁵⁶ However, issues associated with an international ban, imposed by the industrialized world, include the lack of inexpensive alternatives for asbestos, especially important in the industrializing world, which currently accounts for much of the asbestos use, and the lack of studies comparable with those conducted on asbestos to examine the safety and effectiveness of substitutes, including man-made fibers.¹⁵⁷ Concern certainly still exists about the potential ill health effects of the man-made substitutes,^{157,158} and even though most data do not suggest that those exposed occupationally have an increased risk of lung cancer or mesothelioma,¹⁵⁹⁻¹⁶¹ recent studies report that exposure to mineral wool¹⁶² and refractory ceramic fibers^{162a} enhanced the risk of mesothelioma in asbestos-exposed workers.

The possible role of smoking in the initiation and progression of fibrotic parenchymal disease and its established role in multiplying the risk of lung cancer are strong indications for smoking-cessation advice to be given to the individual and for instituting smoking-cessation programs for workers in workplaces contaminated by asbestos dust. Quitting tobacco smoking should benefit the asbestos-exposed individual even more than the nonexposed individual because of the interaction of these two agents.¹⁶³

The mesothelioma risk may be expected to decline with time. Although in Europe and Australia, it had been estimated that rates would decline only by the second decade of the 21st century,^{164,165} a 2003 report from a British naval dockyard indicates that rates had already peaked in 1991 and have since fallen.¹⁶⁶ Similar trends have been observed in Sweden, where the rate in men peaked in 1995 and has subsequently fallen,¹⁶⁷ and in the Netherlands.¹⁶⁸ This improvement is attributed, at least in part, to the introduction of asbestos safety guidelines in the 1970s in the countries concerned.

NONASBESTOS MINERAL SILICATES AND LUNG DISEASE

Exposure to some of the nonasbestos mineral silicates listed in Table 73-2 has been associated with lung disease. Silicate dust particles are found in the lungs of most urban dwellers¹⁶⁹ and, in general, they appear to have low biologic activity.¹⁷⁰ Disease may develop after long, heavy exposure; initially, it is characterized by accumulation of dust-laden macrophages around respiratory bronchioles and, later, by fiber deposits with little mature collagen; the disease appears to progress in relation to lung dust burden.^{107,170,171} Silicates are used widely as filling materials (kaolin, talc, and chlorite); insulation (mica, vermiculite); and absorbents (attapulgite, sepiolite), among other uses.¹⁷⁰ The clay minerals, talcs and mica (also called phyllosilicates because of their sheet structure),¹⁷⁰ constitute an important group.

World production and use (estimated in 1991 as 5.3 million tons for talc alone) considerably exceeds that of the asbestos minerals, which peaked at 5 million tons in the late 1970s. Before a 1989 NATO Workshop, their toxicity as a group for humans had been little studied,¹⁷⁰ although three (talc, attapulgite, and sepiolite) had been evaluated for carcinogenic risk for humans by the IARC.¹⁷⁰ The information in this section is derived from the report of this workshop¹⁷⁰ and other sources.^{2,122,172} Talc and, more often, mica particles may form the core of ferruginous bodies. In general, the nonfibrous silicates have pulmonary effects similar to those caused by coal, unless they contain fibrous forms of these minerals or are contaminated by asbestos fibers, in which case their effects are closer to those produced by asbestos. The biologic effects of silica (quartz) may be modulated by the presence of silicates.

KAOLIN PNEUMOCONIOSIS

The lesions of kaolin pneumoconiosis tend to be cellular and dust packed.¹⁷⁰ In its simple form, this pneumoconiosis is not usually associated with clinical or lung function changes, but rarely, there may be interstitial fibrosis or PMF and impairment of lung function.² In 10 surveys of kaolin-exposed work forces, the radiologic prevalence of simple pneumoconiosis (mostly small round opacities) ranged from less than 1% to 26.3%, whereas complicated pneumoconiosis and pleural changes were unusual.¹⁷² In general, prevalence was related to level and duration of dust exposure and probably contamination by other materials, including silica. Although lung cancers have been mentioned in relation to kaolin exposure,^{7,173} no cohort mortality studies have been reported.

TALC PNEUMOCONIOSIS

The lesions of talc pneumoconiosis include peribronchial and perivascular interstitial accumulations of dust-filled macrophages, ill-defined nodular lesions in which birefringent talc crystals can be seen, and foreign body granulomas.^{2,170} In general, the disease evolves slowly and PMF is infrequent; tuberculosis may complicate the condition but might reflect concomitant silica exposure. Interstitial fibrosis also may develop. A granulomatous arteritis caused by talc embolism is described in those who use an intravenous route for talc-containing drug tablets (eFig. 73-16). Pleural changes, including plaques, are common; they are usually associated with mining exposures and may be due to contamination of mine dust by fibers (tremolite or anthophyllite).^{2,170} Reactions to talc can be difficult to distinguish from those caused by silica or by asbestos, which often contaminate or even predominate in industrial grade talc.² In six surveys of talc-exposed workforces, prevalence of small opacities ranged from less than 1% to 37%, the lower rates in some studies in which exposure was to pure talc and the higher rate in long-time workers.^{172,174} In three of seven cohort mortality studies in talc-exposed workers, excess deaths were recorded from nonmalignant respiratory disease, including pneumoconiosis. In addition, an excess of respiratory cancer mortality was found in five of the seven cohorts, but these findings must be interpreted with caution because they were based on only 13 or fewer deaths

in each cohort. In four of these, coexposure to other carcinogenic agents (mineral fibers, radon, silica) could have been implicated.¹⁷² Several cases of mesothelioma were reported but all in cohorts exposed to fiber-contaminated dusts.¹⁷²

MICA PNEUMOCONIOSIS

The lesions of mica pneumoconiosis comprise dust particles surrounded by reticulin but usually with relatively little cellular reaction, although there are case reports of interstitial fibrosis¹⁵⁶ in which granulomas also have been described.¹⁷² In three surveys of mica-exposed work forces, the prevalence of radiologic pneumoconiosis ranged from 1% to 44%, the latter work force being exposed to quartz-contaminated mica.¹⁷² No mortality studies have been reported, but there has been one case report of a peritoneal mesothelioma in a mica-exposed worker.¹⁷² Vermiculite, also a mica, does not appear to be toxic to the lungs of animals. However, in four surveys of vermiculite-exposed mine workers, the prevalence of radiologic pneumoconiosis ranged from less than 1% to 18% and of pleural changes from 3% to 28%; in a processing plant, rates were higher and were related to cumulative exposure.^{170,172} Pleural effusions and pleural thickening have been reported in mica-exposed work forces but are thought to relate to amphibole contamination of vermiculite. Vermiculite mined in Libby, Montana, has been found to be contaminated with asbestos and to be associated with asbestosis, mesothelioma, and lung cancer in former miners, millers, and processors. The material has been widely used as insulation in buildings, which has raised concern for those exposed through building maintenance and renovation.¹⁷⁵ A case report of fatal asbestosis 50 years after exposure to vermiculite from Libby in a California expansion plant emphasizes the risk from even brief but intense exposure to this material.¹⁷⁶ The lung biopsy fiber analysis showed 8 million fibers per gram of dry lung, a level certainly compatible with the diagnosis of asbestosis, of which 68% were tremolite. Pleural plaques had been noted on his chest film 10 years before evidence of interstitial lung disease became apparent. A recent report highlights the effects of environmental exposure to Libby vermiculite in one of many sites outside Montana where the material has been processed.¹⁰⁵

The authors of a 1990 review¹⁷² concluded that (1) there is little evidence that occupational exposure to pure kaolin, talc, mica, or vermiculite carries any important risk for health; (2) long and heavy exposure to kaolin and mica may result in low-grade radiographic changes, but clinically important pneumoconioses in work forces exposed to these phyllosilicates are likely to be the result of contamination by silica or asbestos fibers; (3) pleural lesions are common in talc-exposed workers but are probably caused by fiber contaminants; and (4) the increased rates of lung cancer or mesothelioma recorded in several exposed work forces probably result from exposure to silica or fiber contaminants of the ore or milled products.

MAN-MADE VITREOUS FIBERS

The production of *man-made vitreous fibers* (MMVFs), including glass fibers, mineral wool, refractory ceramic fibers, and

mineral fibers such as carbon graphite, Kevlar-Aramid, silicon carbide, and aluminum oxide has increased markedly since the restriction or banning of asbestos in several countries. As with asbestos fibers, determinants of MMVF toxicity are (1) their dimensions (greatest risk with fine, long fibers < 0.25 μm in diameter and > 8 μm in length); (2) their biopersistence, which can be altered in the production process according to the end use; and (3) dose to the target organ. MMVFs differ from asbestos fibers in being more soluble, less durable, and less biopersistent along a gradient: glass > rock > ceramic fibers.¹⁵⁹ Airborne levels in plants manufacturing MMVFs are commonly lower than 1 fiber/mL and lower in most applications except the application of insulation in confined spaces.¹⁷⁷ Airborne fiber diameters, with the exception of ceramic fiber, are generally large (1 mm) and thus nonrespirable. Despite their intensely irritating effects on skin and mucous membranes, there is no firm evidence that these fibers produce lung fibrosis, pleural lesions, or nonspecific respiratory disease in humans. Refractory ceramic fibers may, however, enhance the effects of smoking in producing airway disease.^{177,178} An increased standardized mortality ratio for lung cancer in several cohorts exposed to MMVFs is now thought to have been attributable to smoking.^{159,161} Nevertheless, several agencies have recommended exposures of 0.5 to 1 fiber/mL based on apparent excess working lifetime risk for lung cancer.¹⁷⁹ There is no evidence of an increased mesothelioma risk for MMVF workers¹⁶⁰ but, as mentioned earlier, a French report suggests that mineral wool enhances the risk for mesothelioma in workers also exposed to asbestos.¹⁶²

BERYLLIUM LUNG DISEASE

BERYLLIUM: USES, HUMAN TOXICITY, AND EXPOSURES

Beryllium is a rare metal that has many applications in modern industry because of its light weight, tensile strength, high melting point (1500° C), excellent alloying properties (beryllium-copper alloys are the most widely used), good thermal and electrical conductivity, resistance to corrosion, and ability to reduce the speed of nuclear fission.¹ Major sources are Argentina, Brazil, India, Zimbabwe, South Africa, and the United States. Its toxicity for humans was first recognized in Europe in the 1930s. In the United States, an epidemic of *chronic beryllium disease* (CBD) was recognized as a result of exposure in the fluorescent light industry during the 1940s, leading to discontinuation of its use in that industry and the institution of engineering controls in other industries handling beryllium.¹ Initially, a large number of cases of acute berylliosis, an acute, toxic pneumonitis, were documented but acute cases are now uncommon. Chronic berylliosis, a disease with features similar to those of sarcoidosis, continues to be reported. Cases arise from beryllium exposure in a wide variety of industries including the manufacture of alloys, ceramics, radiographic equipment, and vacuum tubes and in the extraction and smelting of beryllium. Cases have been reported from exposure to beryllium in dental laboratories, but there is no risk to those in dental offices nor to those who wear dental crowns or other completed products. The number of indi-

viduals potentially exposed in the United States in 1987 was estimated between 30,000 and 800,000 in the following industries: aerospace, electronics, ceramics, metal, including refining of scrap metal, nuclear (reactors, weapons), telecommunications, tool and die, and welding.¹⁸⁰ Cases of berylliosis have also been reported in residents living near a beryllium manufacturing facility¹⁸¹ and in a wife who laundered her exposed husband's clothing.¹⁸² Sarcoidosis-like granulomatous lung disease in firefighters involved with rescue work at the World Trade Center is of uncertain origin and might suggest berylliosis or another environmental cause for granulomatous lung disease.¹⁸³

PATHOLOGY AND IMMUNE PATHOGENESIS

CBD is a multisystem disorder characterized by noncaseating granulomas throughout the body, although their primary manifestation is in the lung.^{2,180} On pathologic examination, CBD is characterized by the presence of a lymphocytic (helper/inducer T cells) alveolitis, as well as noncaseating epithelioid granulomas indistinguishable from those of sarcoidosis (eFig. 73-17A and B). There is a variable amount of fibroblastic activity that progresses to interstitial fibrosis as the lesions mature. Granulomatous lesions may occasionally be found in other sites, including thoracic and abdominal lymph nodes, spleen, liver, kidneys, and adrenal glands.

Beryllium enters the body by inhalation and, occasionally, via the skin, where it acts as a specific antigen (alone or as a hapten through an IL-2 receptor pathway), leading to a proliferation of specific CD4 lymphocytes, release of lymphokines, and granuloma formation.¹ Because the agent persists in the lung, its slow release over time explains the appearance and progression of disease, even without further exposure.^{1,2} There is evidence for an underlying genetic basis for susceptibility to beryllium disease, linked to a major histocompatibility complex (MHC) class II marker (*human leukocyte antigen* [HLA]-DP β -1^{Glu69}) carrier status, which adds to the effect of the process (exposure) risk factor.^{184,185} Evidence for delayed hypersensitivity to beryllium may be assessed by the *in vitro beryllium lymphocyte proliferation test* (BeLPT) on lymphocytes from blood or BAL.¹⁸⁶ Although these reactions are thought to indicate exposure and sensitization, not disease, in one series, six of eight sensitized individuals had granulomas on transbronchial biopsy.¹⁸⁷

Beryllium is considered to be a human carcinogen, especially in the presence of beryllium lung disease; in 1993, the IARC classified beryllium as a class 1 human carcinogen.¹⁸⁸

CLINICAL FEATURES

Acute beryllium disease is uncommon, with clinical features including cough, chest pain, blood-tinged sputum, crackles, and patchy airspace disease on the chest radiograph. The disorder is associated with high, and usually accidental, exposure and may present with an acute syndrome with features of the acute respiratory distress syndrome or in a subacute form with features of pneumonitis.¹⁸⁹ CBD may follow an acute beryllium pneumonitis but more usually develops without antecedent events. The clinical

features of CBD are similar to those of pulmonary sarcoidosis, although extrapulmonary manifestations including hilar and mediastinal lymphadenopathy and splenomegaly are less common.^{180,190} There may be no associated symptoms,¹⁸⁶ but symptoms often include dyspnea, cough, chest pain, weight loss, fatigue, and arthralgias. Physical signs may include crackles, but signs of lung disease are often absent. Radiographic changes may precede the development of symptoms. The usual finding is ill-defined nodular or irregular opacities (eFig. 73-18A and B, Video 73-5); hilar lymphadenopathy (see eFigs. 73-18C and D) is seen in approximately 40% of cases but is usually mild.¹⁸⁰ In the later stages of the disease, patchy fibrosis is seen, with adjacent hyperinflation or distortion and extensive honeycombing. In CBD, in advanced disease, pulmonary function usually shows a restrictive defect but, in mild or moderate disease, may show features including obstruction or an isolated reduction in DL_{CO}.¹⁹¹ The clinical course of CBD is variable. Some cases remain stable, some relapse and remit, and some progress inexorably.¹⁸⁰

DIAGNOSIS AND MANAGEMENT

The diagnosis of CBD is based on documented exposure to beryllium, evidence of lung disease compatible with the diagnosis, and a positive BeLPT performed on blood or BAL fluid.¹⁹² The BeLPT allowed for the introduction of three categories of beryllium-associated disorders: beryllium sensitization (positive blood or BAL BeLPT but negative biopsy), subclinical beryllium disease (positive BeLPT and biopsy but no clinical or radiologic features of the disease), and chronic berylliosis (positive BeLPT and biopsy with clinical and radiologic features of disease).¹⁹²

Given the potentially long latency time for CBD and despite the generally lower exposures since the 1950s and its decreasing frequency, CBD still should remain in the differential diagnosis of sarcoidosis. Clusters of sarcoidosis in a workplace should alert the clinician to the possibility that these represent examples of chronic berylliosis. In this context, note should be made of the wide range of occupations associated with potential exposure to beryllium.

The most important step in case management is complete cessation of further exposure to beryllium, and this advice should also be given to exposed workers with a positive BeLPT, even in the absence of clinical and radiologic signs of disease, because of the high prevalence of lung granulomata associated with that finding.¹⁸⁷ Corticosteroid therapy has been recommended in CBD, and long-term steroid therapy is believed to alter the course of the disease favorably, although there are no reports of permanent cure.

HARD-METAL DISEASE

Hard-metal disease, first described in Germany in the 1940s, has now been reported from many countries. Hard metal is manufactured by a process called *sintering*, the fusing of a powder together at high temperature. In making hard metal, a powder of tungsten carbide powder (often with tantalum carbide or titanium carbide added) and 10% cobalt is pressurized and heated to 1500° C.¹ The resultant “hard metal” has diamond-like hardness, extreme strength,

and heat resistance; because of these qualities, hard-metal products have wide application in industry as drill tips (from dental to engineering drilling and diamond polishing), cutting and tunneling tools, grinding wheels, molds, jet engines, and ferromagnets. Humans are exposed in the manufacturing of hard-metal products and in their maintenance and use. The grinding of sintered pieces generates high dust and cobalt concentrations.

Work-related illness in hard-metal workers may be acute (rhinitis and asthma), subacute (hypersensitivity pneumonitis), or chronic (diffuse and progressive interstitial fibrosis).¹⁹³ The interstitial fibrosis is characterized by unusual multinucleated giant cells comprising alveolar type II cells and macrophages (eFig. 17-19), which can sometimes be recovered from BAL. The interstitial lung disease that has been described with exposure to both tungsten carbide products and in diamond polishers¹⁹⁴ is thought to be a hypersensitivity pneumonitis to cobalt, which reacts with metallic carbides to produce active oxygen species.¹⁹⁵ A genetic association with some HLA-DP alleles may also be implicated.¹⁹⁶ This affords a plausible explanation of why only a small proportion of those exposed develop disease. A 1998 industry-wide cohort study in 10 facilities in France documented an increased mortality from lung cancer associated with simultaneous exposure to cobalt and tungsten carbide.¹⁹⁷ A review of workplace surveys indicates that interstitial disease is rare, whereas airway diseases including bronchitis and asthma are more frequent.^{193,198} Both interstitial (eFig. 73-20 and Video 73-6) and airway disease may be seen in the same individual. Diagnosis is based on an exposure history, a compatible clinical presentation, and pathologic and mineralogic features on biopsy.^{193,199} Both tungsten carbide and cobalt have now been identified in the centrilobular fibrotic lesions associated with hard-metal lung disease.²⁰⁰ Prompt diagnosis and removal from exposure may reverse acute disease, including asthma, and prevent the development of chronic disease. There have been several reports of response to withdrawal from exposure and treatment with corticosteroids.² Prevention requires control of exposure; for monitoring workforce exposure, the measurement of urinary cobalt may be useful.

SILICON CARBIDE (CARBORUNDUM) PNEUMOCONIOSIS

Carborundum pneumoconiosis is associated with exposure in the manufacture of carborundum, a silicon carbide of extreme hardness used as an abrasive. Under current exposure levels, this is generally a mild and nonprogressive disorder.²⁰¹ There is, however, some evidence that those exposed to this material, which has a silica and a fibrous component, are at risk for pneumoconiosis associated with lung dysfunction^{202,203} and, possibly, for lung cancer.²⁰⁴

NEW PNEUMOCONIOSES

Lung diseases associated with exposure to metal-working fluids²⁰⁵; nylon, rayon, and polypropylene flock²⁰⁶; indium;

popcorn flavoring (diacetyl)²⁰⁷; and nano-particles have been described. A recent review details these diseases and lung disease associated with exposure to the burning and collapse of the World Trade Centers in New York.²⁰⁸

Key Points

- The population exposed to dust in the workplace is so large that an occupational history, including remote occupations, should be part of every respiratory assessment.
- Chest radiography and occupational history are the mainstays for the diagnosis of pneumoconiosis, although CT and lung biopsy may be necessary, especially for asbestosis.
- Because of the many interactions between smoking and dust, it is important to implement smoking-cessation programs in the workplace.
- Workers exposed to dust are at risk for developing *chronic obstructive pulmonary disease* (COPD) and chronic bronchitis. In some cases, they are also at risk for fibrosis and lung cancer.
- Silicosis is a risk in a wide range of new and older but less classic industries such as concrete rehabilitation, stone carving, and the sandblasting of denim jeans.
- Silica dust is a risk factor for tuberculosis and other mycobacterial lung diseases, lung cancer, COPD, and connective tissue diseases.
- Coal mining is ubiquitous and, with mechanization, continues to expose underground and surface miners to large amounts of dust; high rates of coal workers' pneumoconiosis are seen especially in small mining operations.
- Asbestos-related diseases will be seen for many decades because of the long latent period between exposure and disease and because asbestos is still widely encountered.

Complete reference list available at *ExpertConsult*.

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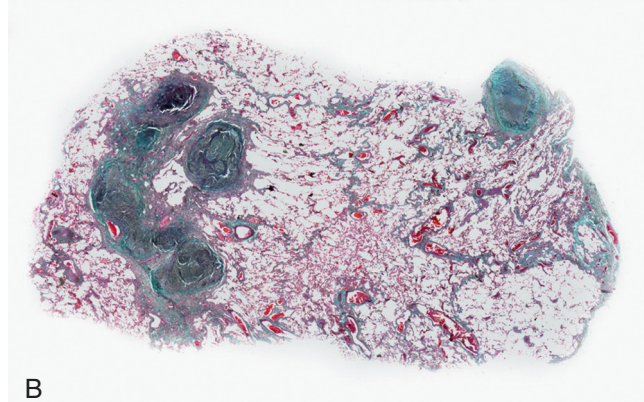
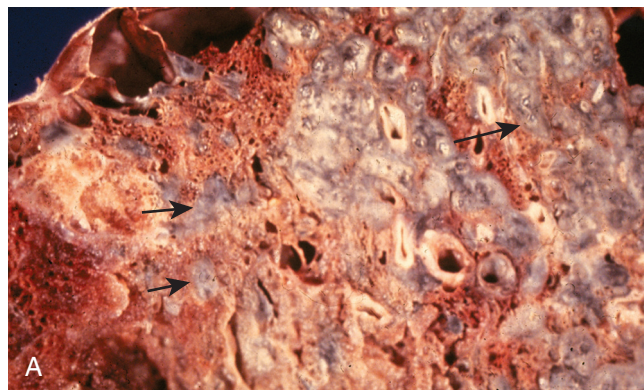
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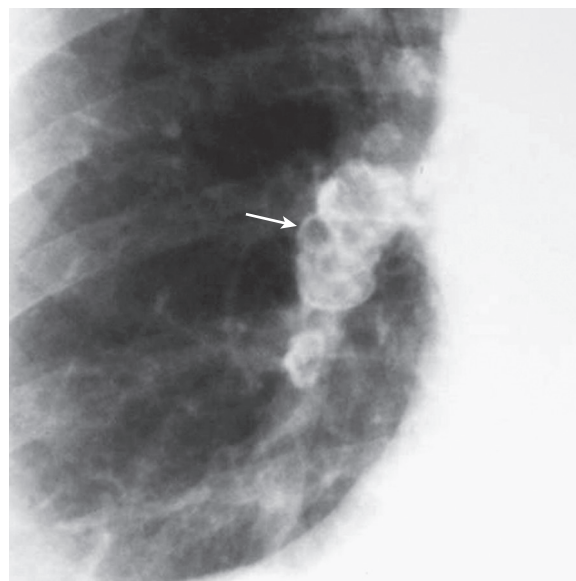
eFIGURE IMAGE GALLERY



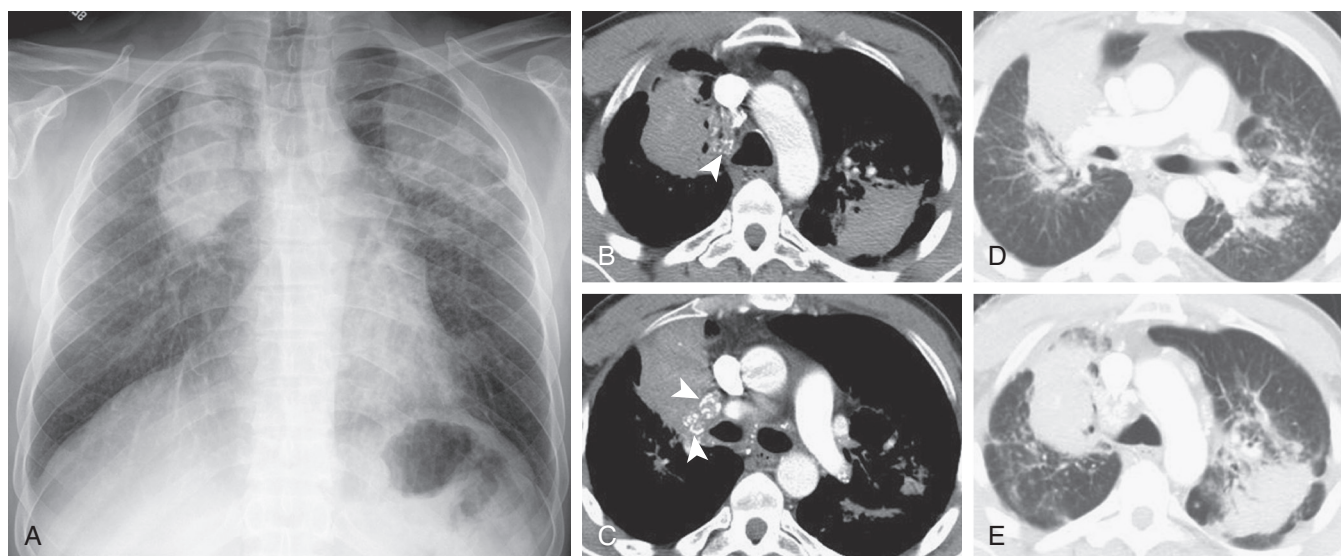
eFigure 73-1 Silicosis. **A**, In this gross specimen, circumscribed areas of nodular fibrosis are slate gray and of firm consistency (*arrows*). **B**, At low magnification, silicotic nodules are sharply circumscribed and densely collagenous (Masson trichrome stain). (Adapted from Butnor KJ, Roggli VL: Pneumoconioses. In Leslie KO, Wick MR: Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series, ed 2. Philadelphia, 2011, Elsevier, pp 311–338, Figs. 9-1 and 9-2.)



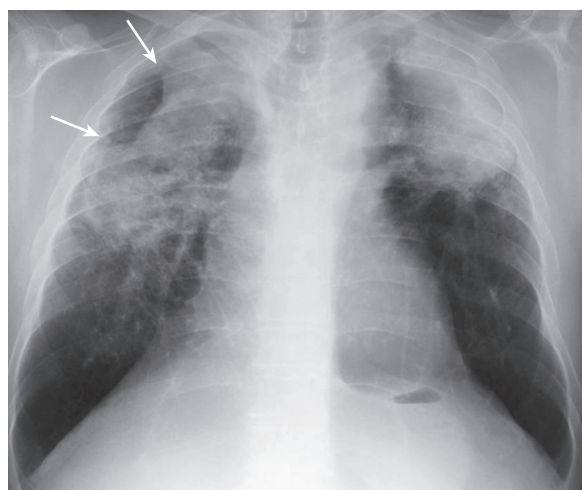
eFigure 73-2 Silicosis. Frontal chest radiograph in a patient with silicosis shows a somewhat atypical distribution of small, round lung opacities. In this patient, opacities are best seen in the mid- and lower lungs, rather than the more typically encountered upper and posterior lung location. (Courtesy Michael Gotway, MD.)



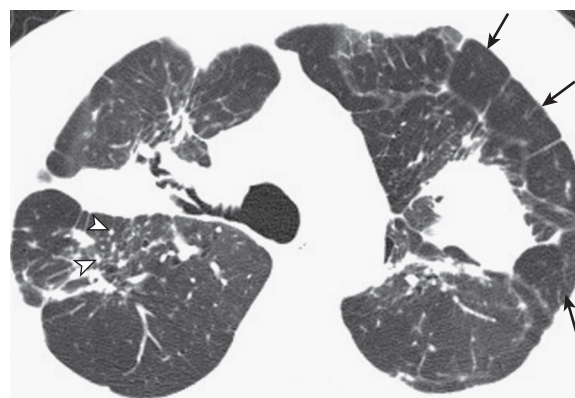
eFigure 73-3 Silicosis. Detail frontal chest radiograph in a patient with silicosis shows the typical appearance of "eggshell" lymph node calcifications (*arrow*). (Courtesy Michael Gotway, MD.)



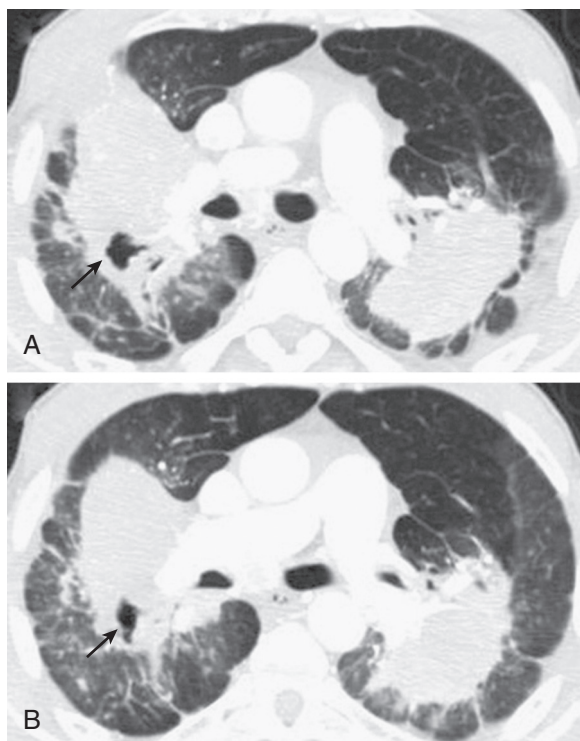
eFigure 73-4 Complicated silicosis: progressive massive fibrosis. **A**, Frontal chest radiograph shows upper lobe masses with a background of small nodules and linear and reticular opacities. Axial chest CT in soft tissue (**B** and **C**) and lung (**D** and **E**) windows shows the upper lobe masses and background of small, circumscribed nodules and lymph node calcifications (*arrowheads*). The associated videos ([Video 73-1](#), soft tissue windows, and [Video 73-2](#), lung windows) highlight the presence of calcification within the upper lobe masses, as well as the upper lobe distribution of the lung opacities. (Courtesy Michael Gotway, MD.)



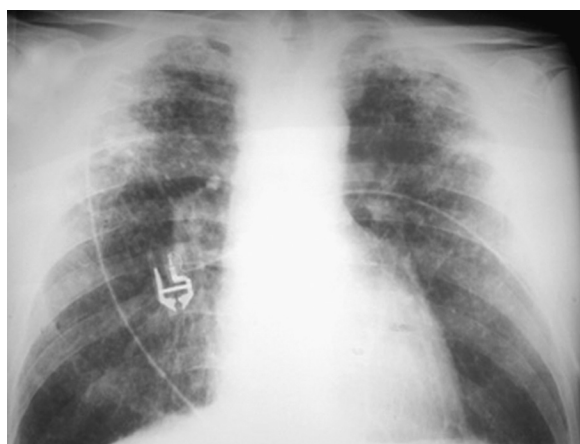
eFigure 73-5 Silicosis. Frontal chest radiograph in a patient with silicosis and progressive massive fibrosis shows bilateral upper lobe opacities with areas of hyperlucency (between *arrows*) left in the "wake" of the migration of the opacities toward the hila. (Courtesy Michael Gotway, MD.)



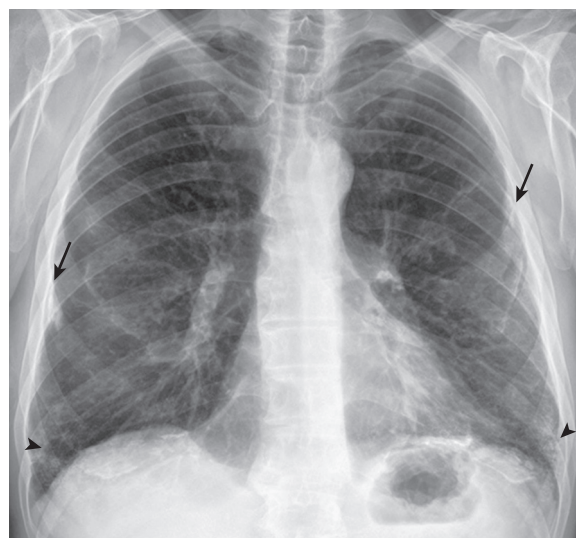
eFigure 73-6 Silicosis. Chest CT in a patient with silicosis and progressive massive fibrosis shows small nodules in the posterior upper lobes (*arrowheads*) consistent with silicosis, as well as upper lobe opacities representing progressive massive fibrosis. Note the area of hyperlucency and irregular air space enlargement (*arrows*) left in the "wake" of the migration of these opacities toward the hila. (Courtesy Michael Gotway, MD.)



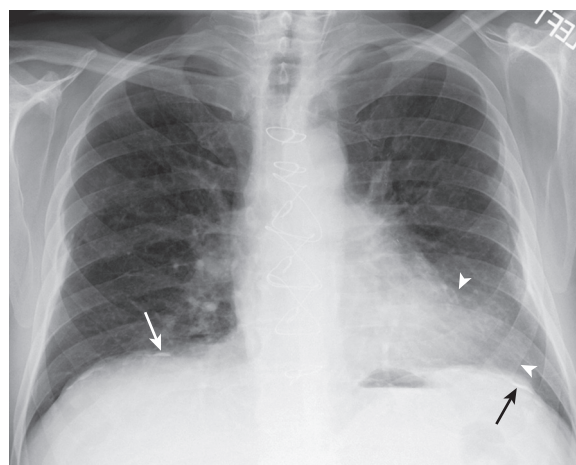
eFigure 73-7 Silicosis. A and B, Chest CT in a patient with silicosis and progressive massive fibrosis (same patient as eFig. 73-5, at a later time) shows development of cavitation within the posterior margin of the right upper lobe opacity (arrows) due to superimposed mycobacterial infection. See Video 73-3. (Courtesy Michael Gotway, MD.)



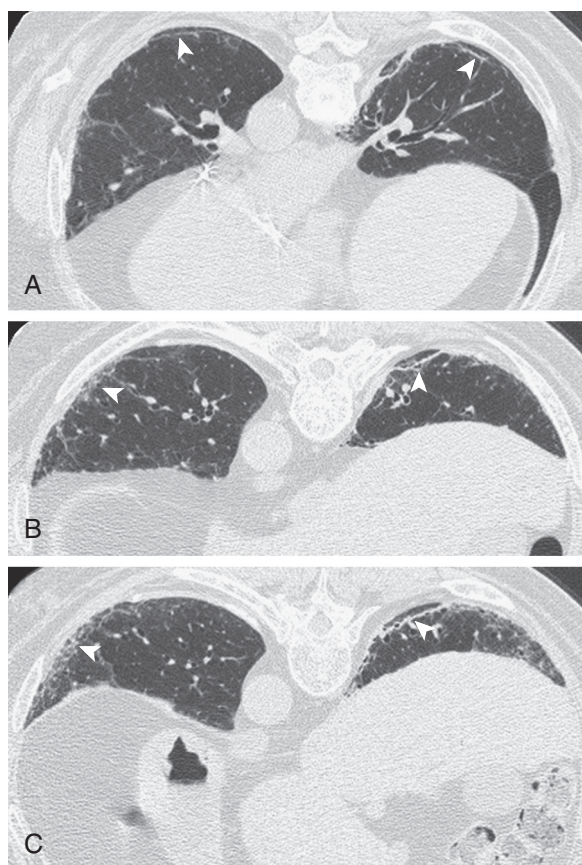
eFigure 73-8 Coal workers' pneumoconiosis. Frontal chest radiograph in a patient with simple coal workers' pneumoconiosis shows upper lobe predominant, circumscribed small nodules. The nodules are somewhat larger than is often seen in coal workers' pneumoconiosis, especially in the upper lobes, raising the possibility of superimposed silicosis. (Courtesy Michael Gotway, MD.)



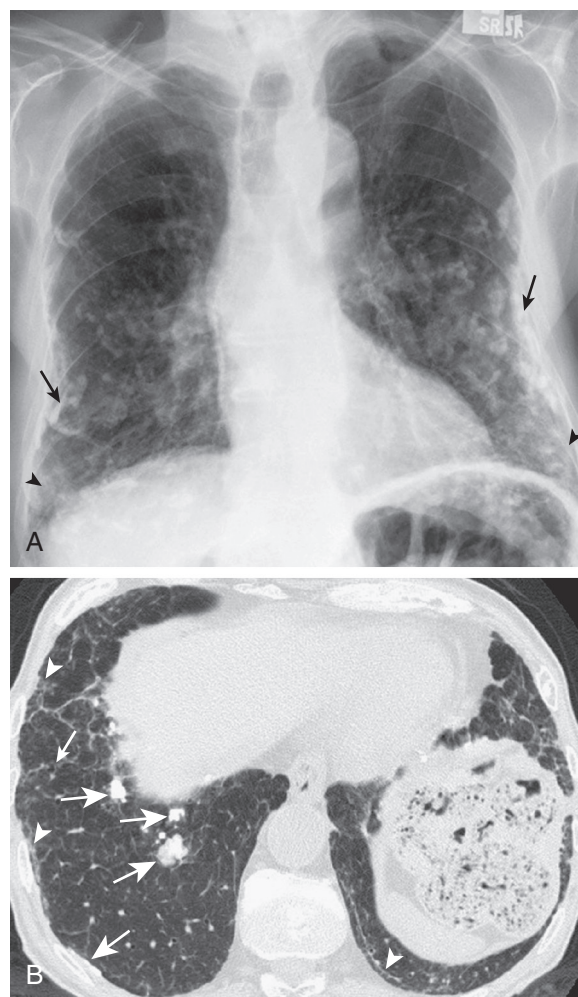
eFigure 73-9 Asbestosis. Frontal chest radiograph in a patient with asbestos exposure shows bilateral calcified pleural plaques (arrows) and fine, subpleural, bibasal linear and reticular opacities (arrowheads) consistent with fibrotic lung disease. (Courtesy Michael Gotway, MD.)



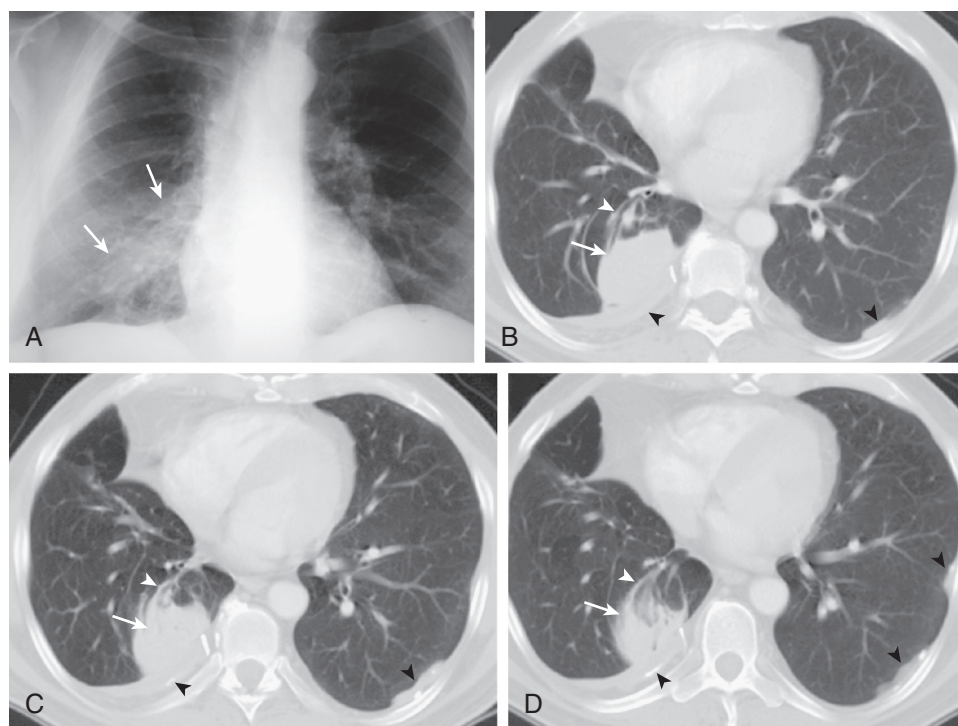
eFigure 73-10 Asbestosis. Frontal chest radiograph in a patient with asbestos exposure shows bilateral calcified pleural plaques (arrows) and obscuration of the left cardiac border (arrowheads), representing the "shaggy heart border sign" in asbestosis. (Courtesy Michael Gotway, MD.)



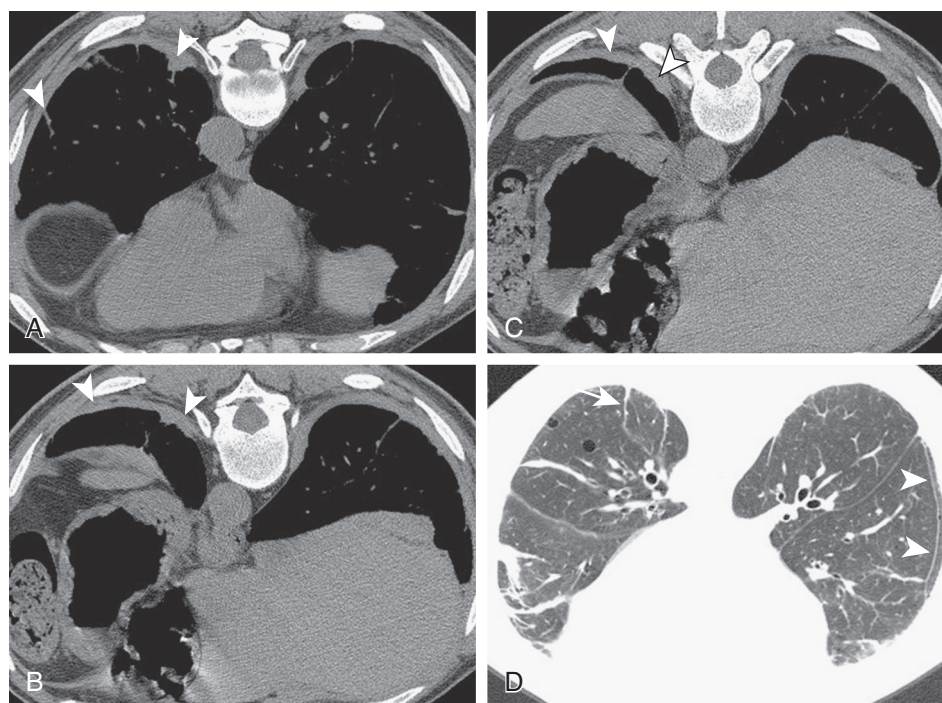
eFigure 73-11 Asbestosis. A–C, Axial prone high-resolution CT of the lung through the bases in a patient with asbestos exposure shows bilateral, subpleural linear and reticular opacities (*arrowheads*) consistent with asbestosis. (Courtesy Michael Gotway, MD.)



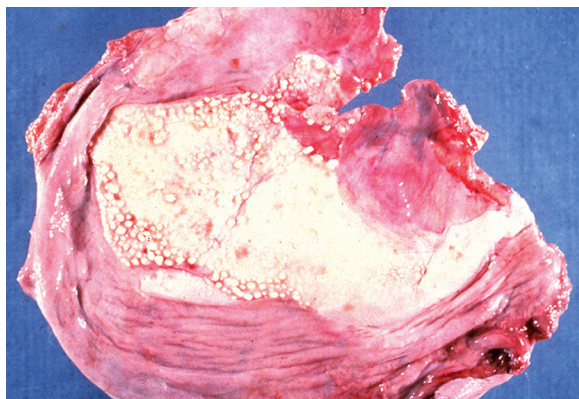
eFigure 73-12 Asbestosis. A, Frontal chest radiograph in a patient with asbestos exposure shows bilateral calcified pleural plaques (*arrows*) and faint basal linear and reticular abnormalities (*arrowheads*) suggesting possible fibrotic lung disease. The heavy pleural calcification limits assessment. B, Axial chest CT through the lung bases shows pleural calcifications (*large arrows*) and peripheral linear and reticular opacities (*arrowheads*) with mild traction bronchiectasis (*small arrow*), confirming fibrotic lung disease. (Courtesy Michael Gotway, MD.)



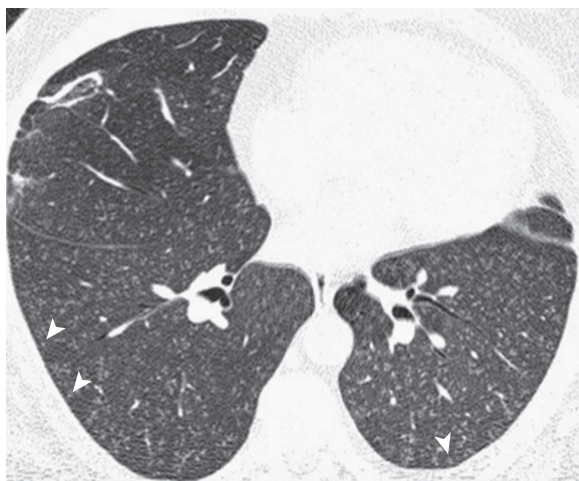
eFigure 73-13 Asbestos-induced pleural plaques and rounded atelectasis. **A**, Frontal chest radiograph in a patient with asbestos exposure shows a poorly defined right lower lobe opacity (arrows). **B–D**, Axial chest CT through the lung bases shows calcified and non-calcified pleural plaques (black arrowheads) and confirms the right lower lobe subpleural mass (arrows). The mass is in contact with abnormal pleura and is associated with a spiraling configuration of the bronchovascular bundles (white arrowheads) leading to the mass, as well as right lower lobe volume loss—these features are consistent with rounded atelectasis (see [Video 73-4](#)). (Courtesy Michael Gotway, MD.)



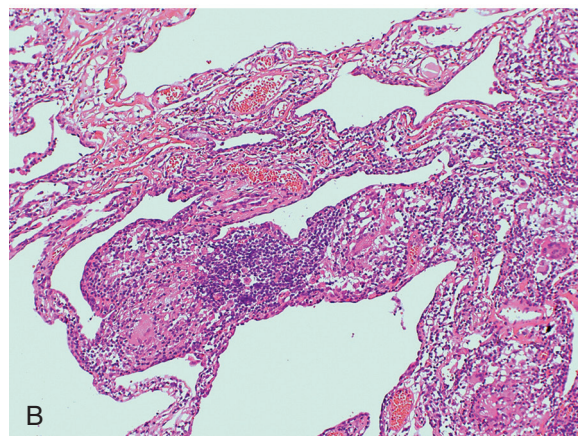
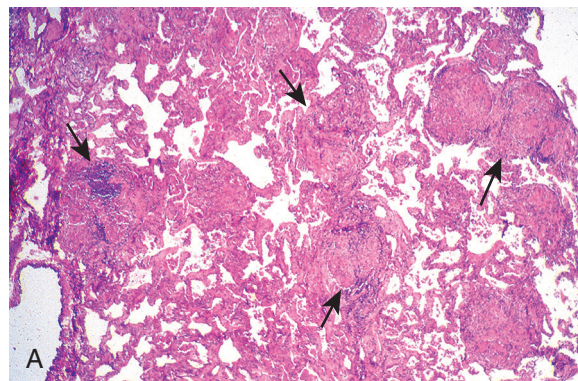
eFigure 73-14 Diffuse pleural thickening related to asbestos exposure. **A–D**, Axial prone chest CT in soft tissue (**A–C**) and lung (**D**) windows shows extensive contiguous pleural thickening (arrowheads **A–C**) extending continuously from the posteromedial thorax along the right lateral thorax. Image displayed in lung windows (**D**) shows other pulmonary parenchymal findings associated with asbestos exposure, such as parenchymal bands (arrow) and a subpleural line (arrowheads). (Courtesy Michael Gotway, MD.)



eFigure 73-15 Pleural plaque. The whitish plaque has been resected along with surrounding tissue and is viewed en face. Its gross appearance has been likened to that of candle wax drippings. (From Butnor KJ, Roggli VL: *Pneumoconioses*. In Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 311–338, Fig. 9-31).



eFigure 73-16 Talc granulomatosis. Axial chest CT in an injection drug user shows numerous small basal centrilobular opacities (arrowheads) found on biopsy to represent small talc granulomas. (Courtesy Michael Gotway, MD.)



eFigure 73-17 Chronic beryllium disease. **A**, The presence of numerous granulomas is characteristic of *chronic beryllium disease* (CBD) (arrows). **B**, In addition to granulomatous inflammation, there is a chronic interstitial inflammatory infiltrate. (From Butnor KJ, Roggli VL: *Pneumoconioses*. In Leslie KO, Wick MR: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 311–338 [Figs. 9-91 and 9-93].)

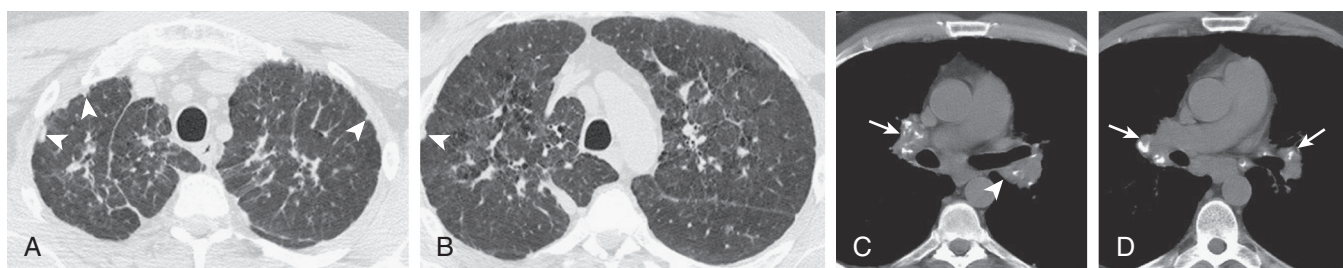


Figure 73-18 Chronic beryllium disease. **A** and **B**, Axial chest CT shown in lung windows shows subpleural nodules (*arrowheads*) associated with central bronchovascular thickening and architectural distortion. The appearance resembles sarcoidosis. **C** and **D**, Axial chest CT shown in soft tissue windows shows mild, symmetric, bilateral calcified lymph node enlargement (*arrows*). An uncalcified, mildly enlarged left retrobronchial lymph node (*arrowhead*, **C**) is present. The appearance is identical to sarcoidosis. [Video 73-5](#) shows the upper lobe distribution of the pulmonary parenchymal abnormalities to advantage. (Courtesy Michael Gotway, MD.)

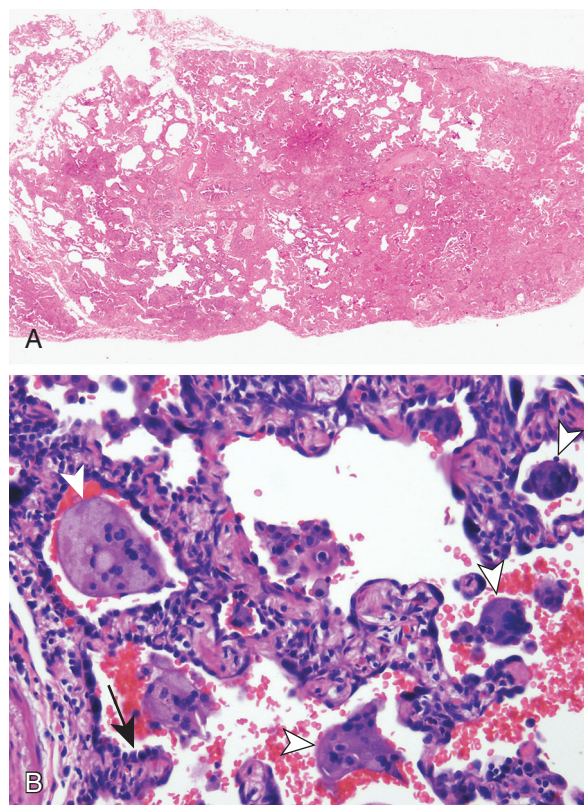


Figure 73-19 Hard-metal pneumoconiosis. **A**, At low magnification, the interstitium appears widened, accompanied by alveolar filling. **B**, This example demonstrates interstitial pneumonia with hyperplastic type II pneumocytes (*arrow*) and multinucleate giant cells (*arrowheads*) in alveolar spaces. (From Butnor KJ, Roggli VL: *Pneumoconioses*. In Leslie KO, Wick MR, editors: *Practical pulmonary pathology: a diagnostic approach: a volume in the pattern recognition series*, ed 2. Philadelphia, 2011, Elsevier, pp 311–338, Figs. 9-82 and 9-83.)

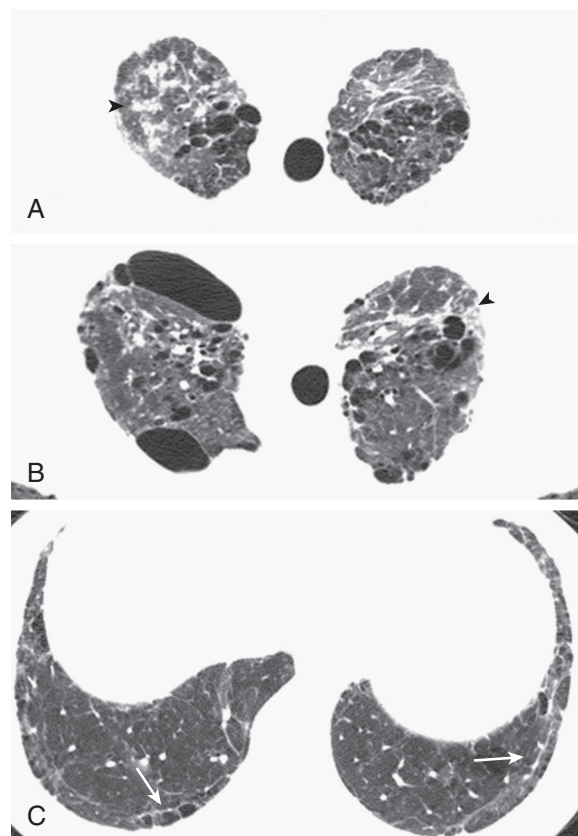


Figure 73-20 Hard-metal lung disease. **A–C**, Axial chest CT (**A** and **B**, prone, **C**, supine) in a 26-year-old man who was a saw sharpener shows upper lobe predominant linear and nodular opacities (*arrowheads*) associated with mild architectural distortion. Basal subpleural bands (*arrows*, **C**) are noted. Chest CT video ([Video 73-6](#)) shows the upper lobe distribution of the pulmonary parenchymal abnormalities to advantage. Extensive subpleural cystic change is present. The patient was a nonsmoker, and his urinary cobalt levels were abnormally elevated. Lung biopsy showed numerous foamy macrophages and multinucleated giant cells. (Courtesy Michael Gotway, MD.)

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INDOOR AND OUTDOOR AIR POLLUTION

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INTRODUCTION

Catastrophic air pollution events in the Meuse Valley of Belgium (1930), Donora, PA (1948), and London (1952) arose when air stagnation caused high levels of ambient pollutants, especially sulfur dioxide and particles. In each case, there was a marked increase in respiratory symptoms and mortality. These “fog disasters” provided incontrovertible evidence that air pollution can have immediate lethal consequences. Since this time, scientific investigations have uncovered myriad adverse respiratory health effects of air pollution, ranging from asthma exacerbation to respiratory mortality.

The respiratory system, because it is the portal of entry for air pollutants, suffers the major consequences of air pollution. This chapter reviews the key air pollutants, which are termed *criteria pollutants* by the U.S. *Environmental Protection Agency* (EPA), and how they affect the airways and lungs (Table 74-1). Both indoor and outdoor air pollution are considered. Respiratory health conditions that are most strongly linked with air pollution are reviewed.

AIR POLLUTANTS

POLLUTANTS—WHAT THEY ARE AND WHY THEY MATTER

Air pollution involves the contamination of the atmosphere by chemicals, particles, or biologic materials that causes human morbidity and mortality, damages other living organisms such as plants, or adversely affects the natural environment such as by reducing visibility. Pollutants can be emitted from mobile sources (e.g., vehicles), stationary

sources (e.g., factories, power plants, refineries), and indoor sources (e.g., building materials, gas stoves, passive smoking, cleaning products).¹⁻³

Toxic air pollutants (air toxics) are a subset of air pollutants that may cause cancer or other serious health effects such as birth defects. These substances, such as benzene and cadmium, produce primarily nonrespiratory effects despite entering the body via the respiratory tract.

The major types of air pollutants affecting the respiratory system are *particulate matter* (PM), *sulfur dioxide* (SO₂), *nitrogen dioxide* (NO₂) and *ozone* (O₃) (Table 74-2). The principal sources of these pollutants are mobile and stationary sources. Ozone is a secondary pollutant that arises from the action of sunlight on nitrogen oxides and hydrocarbons present in motor vehicle exhaust. It is a major component of photochemical pollution or “smog.” The respiratory health effects of these pollutants are considered later in the chapter. Two other air pollutants, *carbon monoxide* (CO) and lead, which also enter via the respiratory tract, have primarily nonpulmonary toxicity and are not considered further in this chapter.

Indoor air quality has assumed increasing importance. As levels of outdoor ambient air pollution have decreased in many areas throughout the United States, the relative impact of indoor air pollution has increased. Moreover, North American residents spend the majority of their time indoors, increasing their exposure to indoor air pollutants.^{4,5} At the same time, changes in home and office building construction have resulted in lower air exchange rates, increasing the levels of pollutants emitted indoors.⁶ In the developing world, indoor air pollution due to biomass smoke from domestic cooking and heating is a major source of morbidity and mortality.⁷

GENERAL PROPERTIES, SOURCES, AND DISTRIBUTION OF POLLUTANTS

PM, sulfur oxides, NO₂, and O₃ are the most widely encountered pollutants that cause adverse pulmonary health effects.¹⁻³

PM is an important pollutant. In the western United States and many other areas of the world, particulate pollution is not driven by the combustion of sulfur-containing fuels. Atmospheric particulate air pollution arises from a variety of sources, including both natural (e.g., sea spray, windblown dust) and synthetic (e.g., power plants, motor vehicles) sources.^{8,9} Moreover, particulate material that enters the atmosphere can be primary (particles emitted directly) or secondary (particles formed by complicated chemical reactions happening in the atmosphere and involving gas-phase precursors such as SO₂ and nitrogen oxides). In North America, secondary particles comprise most of the fine-particle pollution.

Table 74-1 National Primary Air Quality Standards in the United States (Criteria Pollutants)

Pollutant	Standard*	Averaging Period
Particulate matter < 10 µm (PM ₁₀)	150 µg/m ³	24 hr
Particulate matter < 2.5 µm (PM _{2.5})	12 µg/m ³ 35 µg/m ³	1 yr 24 hr
Sulfur dioxide	75 ppb (214 µg/m ³) 500 ppb (1430 µg/m ³)	1 hr 3 hr
Nitrogen dioxide	100 ppb (188 µg/m ³) 53 ppb (100 µg/m ³)	1 hr 1 yr
Ozone	75 ppb (100 µg/m ³)	8 hr
Lead	0.15 µg/m ³	Rolling 3-mo average
Carbon monoxide	9 ppm (10 mg/m ³) 35 ppm (40 mg/m ³)	8 hr 1 hr

*Where two standards are listed, the first is the primary air quality standard set by the U.S. Environmental Protection Agency to protect health. The second standard listed is the so-called secondary standard, which is set to protect welfare.

Ppb, parts per billion; ppm, parts per million.

In epidemiologic studies, researchers have defined the size of particles in terms of aerodynamic diameter because most particles have irregular shapes with geometric diameters that cannot be easily measured. The aerodynamic diameter is the diameter of a perfect sphere of unit density (1 g/mL) that has the same aerodynamic properties (e.g., settling velocity) as the particle in question. Larger particles are filtered in the nose and throat, but particles less than 10 µm in diameter (i.e., PM₁₀) can be deposited in the respiratory tract.^{8,9} Fine particles, which are less than 2.5 µm in diameter (PM_{2.5}), penetrate to the alveoli, and ultrafine particles (PM_{0.1}) can pass through the alveoli and spread to other organs.

Size also determines how far particles travel and persist in the environment. Fine particles can travel for long distances and remain in the atmosphere for days to weeks; “coarse” particles (>2.5 to 10 µm) travel for rather short distances and have atmospheric half-lives of minutes to hours.¹⁰ Ultrafine particles are typically generated from combustion processes and have short atmospheric half-lives. For example, the concentration of ultrafine particles emitted from motor vehicles on a major roadway has a rapid falloff with distance from the roadway; the concentration is back down to the background level at or beyond 300 m.¹⁰

Fine particles (PM_{2.5}) are composed mainly of varying amounts of water and several major components (sulfates, acids, nitrates, elemental carbon, organic carbon, and trace metals) depending on sources.¹¹ They are directly emitted during combustion but are also formed from gases by nucleation, condensation, or liquid-phase reactions. Coarse particles (PM_{10-2.5}) are composed primarily of crustal (rock, soil), biologic (pollen, spores), and industrial components; they are formed primarily by mechanical processes that produce small particles from larger particles.

SO₂ is produced by the combustion of sulfur contained in fossil fuels such as coal and crude oil. The major sources of SO₂ pollution are power plants, oil refineries, smelters, and paper pulp mills. In the United States, SO₂ levels are generally higher in the Northeast and Midwest because sulfur-containing coal is used in power plants. Sulfur dioxide itself is a clear, highly water-soluble gas, so it is effectively absorbed by the mucosal surfaces of the upper airways. A small proportion of inhaled SO₂ reaches the distal regions

Table 74-2 Major Pollutants Associated with Adverse Pulmonary Effects

Pollutant	Outdoor Sources	Indoor Sources	Adverse Effects
Particulate matter	Motor vehicle exhaust, power plants	Tobacco and wood smoke	Exacerbations of asthma and chronic obstructive pulmonary disease, increased cardiopulmonary mortality
Sulfur oxides	Power plants, oil refineries, smelters	Kerosene space heaters	Bronchoconstriction
Nitrogen oxides	Motor vehicle exhaust, power plants, oil refineries	Gas stoves and furnaces, kerosene space heaters	Airway injury (respiratory bronchiolitis), impaired lung defenses, enhanced response to allergens
Ozone	Motor vehicle exhaust	Aircraft cabins, welding, copiers, ozone generators	Airway injury (respiratory bronchiolitis), decreased lung function, exacerbations of asthma, enhanced response to allergen
Radon	None	Residential basements	Lung cancer
Polycyclic aromatic hydrocarbons	Diesel exhaust	Tobacco smoke	Lung cancer

of the lungs, but susceptible persons such as those with asthma may still suffer adverse respiratory health effects.^{12,13} The SO₂ released into the atmosphere does not, however, remain uniquely in the form of a gas; rather, it undergoes chemical reactions with water, trace metals, and other pollutants to form particulate aerosols. The nature of particles generated from sulfur-containing fuels varies geographically, but sulfuric acid and various metallic, acidic, and ammonium sulfates are commonly present. The mixture of sulfur oxides and small particles may be blown great distances from its source, undergoing continuous transformation from gas to particle phase and ultimately becoming “acid rain” capable of profoundly affecting flora and fauna.¹⁴

NO₂ is rapidly generated from nitrogen oxides, which are produced whenever there is combustion, and motor vehicles and power plants are the major sources of this pollutant. The areas with the highest concentrations of NO₂ tend to be the downtown cores of large cities where there are major roadways and traffic congestion. Because NO₂ tracks well with traffic emissions, it is often considered a marker of traffic-related air pollution in epidemiologic studies. NO₂ reacts with oxygen to generate O₃ and nitric oxide, but this is a bidirectional reaction so that O₃ levels tend to be lower in areas where NO₂ is concentrated. Thus, O₃ levels tend to be lower in neighborhoods adjacent to major roadways.

O₃ arises primarily from the action of sunlight on emissions from internal combustion engines of motor vehicles.¹⁵ The most important of these emissions are unburned hydrocarbons (so-called *volatile organic compounds* or VOCs) and nitrogen oxides. In the atmosphere farther away from traffic sources, ultraviolet irradiation of the mixture of VOCs and NO₂ results in a complex series of chemical reactions, producing O₃, alkyl nitrates, peroxyacyl nitrates, alcohols, ethers, acids, peroxyacids, and other organic and inorganic compounds that exist in both gas and particulate aerosol phases.¹⁵ This mixture of pollutants typifies the “smog” found in areas with large numbers of automobiles and abundant sunlight, such as the Los Angeles basin.

Because O₃ and NO₂ are the gases present in the highest concentration in smog and they clearly cause toxic effects in animals and humans, they have been the oxidant pollutants most extensively studied. Both gases are relatively insoluble and poorly absorbed by the upper airways. A high proportion of the inhaled dose therefore reaches the peripheral portion of the lungs and can cause injury at any site from the upper airways to the alveoli.^{16,17}

Outdoor urban air contains a number of known lung carcinogens, including *polycyclic aromatic hydrocarbons* (PAHs), *n*-nitroso compounds, and asbestos. The concentrations of these carcinogens in ambient air, however, are quite low. Diesel exhaust, in particular, contains particles with PAHs as constituents. Epidemiologic studies have provided consistent evidence of an excess risk of lung cancer in workers exposed to diesel exhaust; it is listed by the International Agency on Cancer Research as a known human carcinogen.^{18–21} Several large population-based epidemiologic studies have also linked lung cancer to long-term exposure to PM, SO₂, and O₃ pollution.^{22–26}

Although most attention has been given to pollutants present in outdoor air, it is now apparent that elevated

concentrations of airborne contaminants are common inside homes, public buildings, and other indoor micro-environments.^{6,27} In developed countries, there are point sources of pollution indoors, such as secondhand tobacco smoke and gas stove use, that greatly increase the concentration of pollutants compared with outdoor air. In developing countries, biomass fuels are still burned indoors in poorly efficient stoves for cooking and heating. Biomass smoke is a mixture of gases and PM that is similar to tobacco smoke with the exception that it does not contain nicotine. Both indoor and outdoor pollution must be considered when assessing the total health effects of air pollution.

MECHANISMS OF DEFENSE AGAINST AIR POLLUTION-RELATED RESPIRATORY EFFECTS

The respiratory system, which encounters myriad particles and gases daily, has evolved an effective defense system for removing impurities from inhaled air. The various mechanisms of defense are interrelated and work in a coordinated manner. A perturbation of any defense mechanism, whether because of congenital deficiency, disease, or the effect of an inhaled pollutant itself, may result in the breakdown of the coordinated defense system and the development of disease.

DEPOSITION OF AND CLEARANCE OF PARTICLES (see Chapter 11)

The size of particles determines their site of deposition in the respiratory tract.²⁸ Large particles (diameter > 10 µm) are efficiently removed in the nose by simple filtration via the cilia. Those particles that are not removed by filtration will largely be deposited by a process termed *impaction*. The pathway through the nose, mouth, and branching airways is tortuous. Because inhaled particles cannot easily change direction to follow the abrupt changes in the pathway of airflow, they impact on the mucosa of the upper and lower respiratory tract. Airway bifurcations are especially prone to particle impaction. The complementary mechanisms of filtration and impaction are efficient, so few particles more than 10 µm reach the lower respiratory tract.

Smaller particles are less affected by filtration and impaction; the sites of their deposition are more determined by the processes of sedimentation and diffusion.²⁸ Sedimentation is the tendency for particles to fall at a constant rate under the influence of gravity. It is strongly influenced by particle density, particle diameter, and the viscosity of the surrounding gas. As air moves deeper into the lung, the airflow rate decreases and particles fall out of the air stream under the influence of gravity. Sedimentation is the predominant mechanism for deposition of particles of intermediate size (0.5 to 3.0 µm) in the smaller bronchi, bronchioles, and alveoli.

The smallest particles (<0.5 µm), however, are deposited by the mechanism of diffusion. These particles have random (Brownian) motion and will impact the airway mucosa in

the terminal bronchioles and alveoli, removing them from the stream of inspired air.

The pattern of breathing can influence the deposition of particles. A higher respiratory rate increases the velocity of airflow, promoting impaction of particles in the more proximal airways. Conversely, increased tidal volume results in deeper lung penetration by particles; when the respiratory rate is slow, there is more time for diffusion and sedimentation to deposit particles in the distal airways and alveoli.

After particles are deposited in the tracheobronchial tree, cough and mucociliary clearance are the most important mechanisms of defense. Cough is most effective for clearing particles that are deposited in the larger, more central airways. It is provoked by stimulation of afferent nerves that are most densely present in the mucosa of the larynx and branching points of the tracheobronchial tree, at which particles are most likely to be deposited.²⁹

The “mucociliary escalator” is a critical system for clearing particles that are deposited in the tracheobronchial tree; it operates over the respiratory tract from the proximal trachea to the terminal bronchioles. The mucus blanket is the product of secretion by goblet cells and serous cells of the epithelium and by the mucus cells and serous cells of the submucosal glands. The mucus blanket is propelled mouthward by the coordinated beating of epithelial cell cilia. The effective removal of particles by the mucociliary system thus requires secretion of glycoproteins by specialized secretory cells, maintenance of liquefaction by the transport of water and solute by airway epithelial cells, and coordinated function of airway cilia. Impairment of any of these functions, whether by congenital or acquired diseases affecting mucus or water secretion (e.g., cystic fibrosis, chronic bronchitis) or ciliary function (e.g., dysmotile cilia syndrome), leads to longer residence of particles in the airway and a greater likelihood of adverse health effects.

Some particles will be deposited in the distal airway and alveoli, beyond the reach of the mucociliary escalator. The central mechanism for clearing these particles involves the alveolar macrophage, which phagocytoses particles that are deposited in the gas-exchanging parts of the lung and either digests them or migrates to the respiratory bronchiole and ascends the mucociliary escalator. A smaller number of particle-laden macrophages migrate to peribronchial or perivascular connective tissue, which is a slow method of clearance that takes many weeks. Because macrophages are the primary phagocyte for inhaled PM, the carbon content of macrophages has been used as a biomarker of exposure to particulate pollution in epidemiologic studies.³⁰

GASES—DEPOSITION AND DAMAGE ARE FUNCTIONS OF SOLUBILITY

For gaseous pollutants such as O₃, NO₂, and SO₂, the site of deposition in the respiratory tract is largely a function of water solubility. For highly soluble gases, the nose serves an important defensive function because the air inhaled transnasally is passed over the large, irregular surface of the turbinates. The promotion of turbulent flow prolongs contact with the mucosal surface, increasing adsorption. Under conditions of quiet breathing, when most air is inspired transnasally, the concentration of SO₂ that reaches

the glottis is less than 2% of the concentration inspired at the nose.³¹ The more rapid the inspiratory flow rate, the smaller the proportion of SO₂ removed. Furthermore, the mouth is substantially less efficient at absorbing gases than is the nose, and the proportion of air inhaled through the mouth increases as the ventilatory demands of exercise rise. Therefore, the dose of a soluble pollutant delivered to the lower airways is increased by exercise for three reasons: the inspiratory flow is higher, the proportion inhaled through the mouth is increased, and the total quantity inhaled over time is greater. The importance of the level of ventilation, which depends on the level of exercise, and of the oral-nasal distribution of breathing has perhaps best been shown in studies of the bronchoconstrictor response to SO₂, in which the responses are greatest during oral breathing and smallest during nasal breathing.³² In addition, people with obstructive nasal disease also appear to be at greater risk for adverse respiratory effects of soluble pollutant gases.

OXIDATIVE STRESS

Air pollution, especially particles and O₃, can increase the oxidative burden to the lung. To minimize oxidant damage to biologic molecules, the human lung has an integrated antioxidant system of enzymatic and expendable soluble antioxidants. This system includes several antioxidant defense mechanisms that detoxify reactive products or convert them to products that are quenched by other antioxidants. If the oxidant burden is sufficiently great, the reactive species may overwhelm or inactivate the antioxidant system. An imbalance between the production of *reactive oxygen species* (ROS) and reactive nitrogen species and antioxidant capacity leads to a state of “oxidative stress” that contributes to the pathogenesis of several respiratory diseases.^{33–35}

When imbalance exists, the excess oxygen species induce a cellular stress response that activates a number of the redox-sensitive signaling cascades. This initial response is mediated in large part through the transcription factor nuclear factor erythroid 2–related factor 2, which leads to transcriptional activation of more than 200 antioxidant and detoxification enzymes that are collectively known as the phase 2 response.³⁶ Examples of phase 2 enzymes include heme oxygenase 1, glutathione-S-transferase isoenzymes, NADPH quinone oxidoreductase, catalase, superoxide dismutase, and glutathione peroxidase. If phase 2 responses fail to prevent a further increase in ROS production, major cellular components, including membrane lipids, protein, carbohydrates, and DNA, will be damaged and inflammation and tissue damage may ensue.

Oxidative stress-induced proinflammatory effects are mediated by the redox-sensitive mitogen-activated protein kinase and nuclear factor-κB cascades that are responsible for the expression of cytokines, chemokines, and adhesion molecules.³⁷ Cytotoxic effects are associated with mitochondrial membrane damage, which leads to release of factors that induce apoptosis of lung cells.³⁸ Pathophysiologic consequences of pollutant-induced oxidant injury include airway inflammation leading to clinical exacerbation of asthma, increased susceptibility to infection, enhanced allergic responses, and, if repetitive or chronic, airway remodeling.

METHODS OF STUDYING THE HEALTH EFFECTS OF AIR POLLUTION

In order to develop sound public policy aimed at protecting the public from the adverse health effects of pollutants, scientific studies are necessary both to elucidate the health effects of various pollutants and to define the threshold level at which the risk substantively increases. The scientific basis of public policy is based on several lines of evidence: epidemiologic studies of the association between air pollution and disease in the population, controlled human exposure studies conducted in the laboratory, studies of the effects of pollutants on lung structure and function in animals, and in vitro studies of toxicity. Each of these study designs has advantages and disadvantages, and none alone can provide irrefutable proof of harmful effects from a particular pollutant under naturalistic conditions of exposure (Table 74-3). Air quality standards are based, therefore, on the coherence of evidence provided by epidemiologic, clinical, animal, and in vitro research and are set to provide a margin of safety to protect susceptible subgroups of the general population.

EPIDEMIOLOGIC STUDIES

Epidemiologic studies have a major role in the evaluation of air pollution-related health effects because they involve “real-world” exposures of human subjects. The strengths of epidemiologic studies include the ability to evaluate a wide array of health effects and representative sampling of the larger population. These studies, however, have to address issues of confounding and other sources of bias. Moreover, epidemiologic studies, although they play a key role in support for regulatory intervention, do not provide mechanistic data; human, animal, and cellular toxicologic data are required to understand mechanistic pathways.

For each putative pollution-related health effect, evidence must be compiled from published literature, synthesized, and evaluated for the likelihood of a causal effect. Typically, the guidelines for evaluating whether a particular pollutant (e.g., PM) causes a specific respiratory disease

(e.g., *chronic obstructive pulmonary disease* [COPD]) are those introduced by Sir Austin Bradford Hill³⁹ and used by the U.S. Surgeon General beginning in 1964. These include strength of the association, consistency of the association, specificity of the association, temporal relationship, coherence, biologic plausibility, and exposure-response gradient. Using this approach to evaluate the strength of the evidence provides a sound basis for regulatory decisions.

The issue of confounding must be addressed in epidemiologic studies of air pollution-related health effects. It is often difficult to be sure that all confounders (e.g., cigarette smoking, occupational exposures, socioeconomic status) have been identified and controlled. The use of daily time-series studies that correlate daily average air pollution levels (e.g., PM_{2.5}) with daily counts of a health outcome (e.g., deaths) is one method that provides good control of confounders that do not change over relatively short time periods.^{40,41}

Another difficulty with epidemiologic studies is that most outdoor environments include a complex mixture of pollutants. Assessing the effects of individual pollutants, one by one, might miss the effects of the mixture. A related issue is “multicollinearity,” which arises because air pollutant concentrations are correlated with one another, making it difficult to parse out the individual health effects of each pollutant. Sophisticated statistical modeling attempts are used to address these potentially confounding issues, but they remain challenges to valid inferences.^{42,43,43a}

Another major challenge to air pollution epidemiologic studies is exposure assessment. Many studies estimate individual exposure by mapping each individual subject’s home (and sometimes schools or workplaces) relative to stationary pollution monitors. Recent advances have also allowed investigators to conduct personal monitoring of exposure to specific pollutants, but expense and other logistical considerations may make this infeasible.⁴⁴ Choosing the metric of exposure that is most relevant to disease causation requires careful consideration. With O₃, for example, the 8-hour average from 10 AM to 6 PM may be most appropriate because the EPA air quality standard uses an 8-hour averaging time and these hours reflect the impact of photochemistry on O₃ precursors emitted from motor vehicles during the morning commute. In contrast, shorter peak exposures would be more appropriate for assessing the

Table 74-3 Methods for Studying Air Pollution

Method	Strengths	Weaknesses
Epidemiologic study	<ul style="list-style-type: none"> Representative sample of general population Naturalistic exposure Broad range of pollutants Wide range of health outcomes Study of susceptible subgroups 	<ul style="list-style-type: none"> Chance, bias, confounding are threats to study validity Difficulty separating effects of individual pollutants when present as multipollutant mixtures Usually no information on biologic mechanisms
Controlled human exposure study	<ul style="list-style-type: none"> Rigorous experimental design Elimination of bias and confounding Systematic control of exposure levels Study of susceptible subgroups 	<ul style="list-style-type: none"> Acute effects do not necessarily predict chronic effects Limited range of exposures and outcomes evaluated
Animal study	<ul style="list-style-type: none"> Best method for evaluating impact of pollutants on structure and function of lung Dose-response relationship (from minimal level producing health effects to death) 	<ul style="list-style-type: none"> Large interspecies response to pollutants Applicability to humans often uncertain
In vitro study	<ul style="list-style-type: none"> Elucidate cellular mechanisms Rigorous experimental control 	<ul style="list-style-type: none"> Limited to available cell lines Applicability to intact human organism often uncertain

effect of SO₂ on exacerbations of asthma. Whether a time “lag” between onset of exposure to the pollutant and onset of the health outcome (e.g., one or several days) should be considered is also an important question.

CONTROLLED HUMAN EXPOSURE RESEARCH

Experimental studies expose human subjects to pollutants under carefully controlled conditions. Such studies can rigorously evaluate the impact of a single pollutant or a mixture such as diesel exhaust on acute responses such as lung function or airway inflammation. In addition to documenting the acute health effects of pollution, controlled human exposure studies can evaluate the minimal concentration of a pollutant that causes reduction in lung function or other acute responses. These studies can also evaluate the effects of pollutants on susceptible subgroups of the population, such as on adults with asthma. Moreover, measurement of biomarkers of inflammation, oxidative stress, and other pathophysiologic processes can provide mechanistic insights.

A major advantage of controlled human exposure studies is the (near) elimination of confounding and bias because exposures are experimentally induced and carefully controlled. Because these studies evaluate acute effects, however, they cannot, by themselves, be easily extrapolated to the effects of more chronic or recurrent exposure. The finding that a brief exposure to O₃ causes acute decrements in lung function does not, for example, necessarily indicate that prolonged or repeated exposure will lead to the development of COPD. However, controlled human exposure studies, when combined with epidemiologic and animal toxicologic studies, can provide important data for establishing the causal effect of pollution on a respiratory health outcome.

ANIMAL RESEARCH

Animal studies offer the most effective way to investigate the impact of air pollution on lung structure. In addition, animal studies permit assessment of the effects of a range of concentrations so that a dose-response curve can be constructed for outcomes ranging from the first measurable change in lung function or structure until death. Animal studies also afford a unique opportunity to dissect the pathogenetic mechanisms of pollution-related health effects.

The major limitation of animal studies is the large interspecies variations in response to pollutants. As such, applicability of animal studies to humans, especially for dose-response relationships, may not always be clear. Rodents, for example, can tolerate relatively high levels of O₃ without developing structural injury to the lungs, whereas rhesus monkeys develop injury at levels approaching ambient concentrations.⁴⁵ Moreover, common human lung diseases, such as asthma and cystic fibrosis, have not been fully reproduced in animals, precluding study of these susceptible subgroups for pollution-related effects.

IN VITRO RESEARCH

Exposure of cell cultures to specific air pollutants has helped to elucidate the mechanisms of lung injury, inflammation,

and other adverse respiratory health effects. Specifically, cell culture systems have been used to study the impact of particulate and other air pollutants on inflammatory cytokines, oxidative stress, DNA damage, and cytotoxicity.⁴⁶⁻⁵² Cultures of bronchial and alveolar epithelial cells, monocytes, dendritic cells, and other cell lines have been useful for studying the mechanisms of air pollution on the respiratory system.^{52a}

AIR POLLUTION STUDIES—PUTTING IT ALL TOGETHER

In sum, there is no single study design or discipline that can establish the health effects of air pollution and provide the basis for regulation. Epidemiologic studies are required because they evaluate the impact of real-world air pollution on respiratory health outcomes among the general population. The limitations of epidemiologic studies usually mean that coherence of epidemiologic findings with those of experimental data from controlled human exposure, animal, and in vitro studies is required to provide a sufficient weight of evidence to support regulatory policy.

INDOOR AIR POLLUTION

Indoor air quality has been increasingly recognized as an important determinant of human health. As levels of outdoor ambient air pollution have decreased throughout the developed world, and because residents of these countries spend the majority of their time indoors, the relative impact of indoor air pollution has increased.⁵ To characterize personal exposure to air pollution, indoor air quality must be taken into account (Table 74-4).

SOURCES OF INDOOR POLLUTION

The concentrations of indoor air pollutants depend on both indoor and outdoor emission sources (Fig. 74-1).^{6,27,53} Outdoor emission sources determine outdoor pollution concentrations, which, in turn, affect indoor air quality.⁵⁴ The degree of penetration of outdoor pollution into the indoor environment depends largely on the rate of air infiltration from outdoors to indoors.⁵⁵ The rate of air infiltration is a complex function of the “tightness” of building construction and insulation, building location and orientation,

Table 74-4 Indoor Air Pollutants

Category of Pollutant	Indoor Pollution Source
Combustion (e.g., NO ₂ , CO, PM _{2.5} , PAHs)	Secondhand smoke Gas stoves, ovens, heaters, and fireplaces Wood smoke (stoves, fireplaces) Kerosene heaters Candles and incense
Building materials (e.g., formaldehyde, volatile organic compounds)	Plywood Particle board Carpeting Paints
Cleaning materials (e.g., ammonia gas, chlorine gas, chloramine)	Bleach, ammonia, detergents

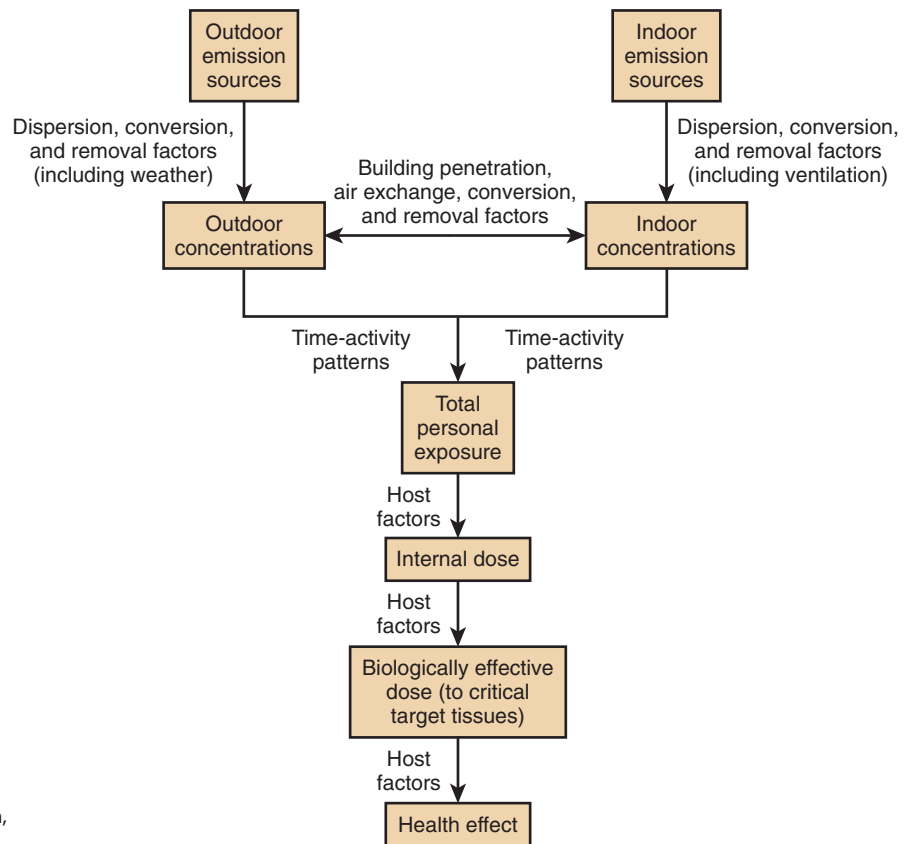


Figure 74-1 Relationships among outdoor pollution, indoor pollution, and health effects.

number of exterior walls and windows, surrounding terrain and barriers, wind speed and direction, indoor-outdoor temperature gradient, and ventilation system type (e.g., heating, ventilation, air-conditioning system) and efficiency.^{6,27,55}

Time-activity patterns will influence personal exposure. The relative time spent indoors versus outdoors will affect the contribution of indoor pollutants to total personal exposure. Time spent in specific locations within the home will affect exposure to particular pollutants, as the distribution of indoor pollutant concentrations will vary among different zones of a building, especially for pollutants generated indoors.⁵⁵ In addition, activity level will affect metabolic rate and ventilatory rate, which will also influence personal exposure to indoor pollutants.

INDOOR COMBUSTION: MAJOR SOURCE OF INDOOR AIR POLLUTION

The major source of indoor pollution is from combustion, particularly *secondhand smoke* (SHS) exposure, gas stove use, and wood burning in stoves and fireplaces. Kerosene space heaters are also an important source of indoor air pollution. Table 74-4 shows the major indoor pollutants that are released from these sources and are associated with adverse pulmonary effects.

SECONDHAND SMOKE AND OBSTRUCTIVE LUNG DISEASE

SHS is perhaps the best known and studied indoor pollutant. Strong evidence implicates it as a cause of lung cancer,

coronary heart disease, and decreased life span.⁵⁶⁻⁵⁸ In addition to these adverse health effects, SHS contains respiratory irritants, such as SO₂, ammonia, acrolein, and formaldehyde.⁵ SHS is a complex mixture containing thousands of gas-phase and particulate substances. Homes where smoking is allowed have PM_{2.5} levels up to 10 times higher than nonsmoking homes.⁵⁹ Workplace exposures can be even higher, especially in bars and casinos.

Passive smoking has also been linked with allergic phenomena, such as elevated serum immunoglobulin E levels.⁶⁰ As a consequence, SHS has the potential to induce new cases of asthma through irritant or sensitizing mechanisms. The results of multiple studies provide evidence that SHS exposure is causally associated with new-onset asthma among children.^{5,61,62}

Exposure to SHS also appears to be associated with new-onset asthma in adulthood. Cross-sectional, case-control, and cohort studies have suggested a link between SHS exposure and adult-onset asthma.⁶²⁻⁷⁰ SHS exposure in the workplace, in particular, appears to be related to adult asthma induction.⁶⁹

Beyond asthma induction, SHS exposure is a likely cause of asthma exacerbation in both children and adults.⁵ Parental smoking causes increased symptoms, poorer pulmonary function, and other indicators of worsened asthma control among children with established asthma.^{62,71} Similarly, SHS exposure, both at home and at work, appears to cause asthma exacerbation among adults.⁷²⁻⁷⁸ Moreover, the negative impact of SHS exposure on pulmonary function appears to be greater among adults with asthma than in the general population.^{72,79}

Exposure to SHS may also cause respiratory symptoms and impaired lung function among nonasthmatic individuals.^{67,72,80-82} In a cohort of older adults, lifetime home and workplace exposure to SHS was associated with a more rapid decline of lung function during a decade of follow-up.⁸³ Studies of bartenders who had high occupational exposures to SHS have revealed a strong link between SHS and poorer respiratory health. Since smoke-free workplace laws have been implemented in several different locations around the world, bartenders and restaurant workers have experienced a reduction of respiratory symptoms and improved lung function.^{79,84,85}

Emerging evidence now suggests that SHS exposure may also be a cause of COPD independent of personal cigarette smoking.^{85a} A population-based study from the United States found that both cumulative home and work SHS exposure was associated with a greater risk of COPD, controlling for potential confounders.⁸⁶ A recent study from China found that self-reported cumulative lifetime SHS exposure at home and work was related to a greater risk of COPD.⁸⁷ Other epidemiologic studies also support an association between SHS exposure and the development of COPD.^{67,88-92} Among patients with established COPD, SHS exposure may increase the risk of respiratory symptoms, poor health status, and disease exacerbations.⁹³⁻⁹⁵

GAS STOVE EXPOSURE: CAUSE OF ASTHMA EXACERBATION?

Cross-sectional epidemiologic studies demonstrate an increased risk of childhood asthma in homes with gas stoves, which are a major source of indoor NO₂, compared with homes with electric stoves,^{96,97} although a recent birth cohort study did not.⁹⁸ In adults with established asthma, a prospective panel study found an association between gas stove use and increased risk of respiratory symptoms, restricted activity, and emergency department visits.⁹⁹ Another time-series analysis found a negative impact of gas stove use on daily peak expiratory flow and respiratory symptoms.¹⁰⁰ In contrast, a longitudinal U.K. cohort study found no effect of gas stove exposure on persistence of adult asthma or on respiratory symptoms among asthmatics¹⁰¹; the European Community Respiratory Health Survey investigators found no clear link between gas stoves and asthma symptoms.¹⁰² Moreover, a prospective cohort study of adults with asthma found no impact of gas stove exposure on asthma outcomes^{77,103} and, in a population-based sample of U.S. adults, no association between gas stove exposure and pulmonary function impairment was observed.¹⁰⁴ Overall, the evidence has not been sufficient to implicate gas stove use as an exacerbating factor in preexisting adult asthma. Among children with asthma, however, there is stronger evidence of a deleterious effect of indoor NO₂ exposure and poorer asthma control.^{105,106}

WOOD SMOKE EXPOSURE—RESPIRATORY HEALTH EFFECTS

Wood smoke, which is produced from domestic fireplace or wood stove use, contains potent respiratory irritants such as formaldehyde, acrolein, nitrogen oxides, and SO₂. It is also a major source of particulate air pollution.¹⁰⁷ Exposure

to extremely high wood smoke levels has been linked with respiratory problems. After a work shift, forest firefighters experience an acute decrement in pulmonary function.¹⁰⁸ Similarly, wildland fires have been associated with increased respiratory symptoms and health care utilization for respiratory problems.¹⁰⁹ In developing countries, wood smoke from domestic cooking and heating in poorly ventilated homes has been associated with chronic bronchitis and COPD.^{6,94,110,111,111a} The exposure levels in such settings are extremely high and are likely the major cause of COPD in women in the developing world, who tend not to smoke cigarettes.¹¹⁰ Cooking with other biomass fuels, such as crop residues or dung, and with coal can also lead to chronic respiratory symptoms and airflow obstruction.¹¹¹ Cooking with wood and/or charcoal has been associated with risk of COPD in developed countries as well.

The respiratory health effects of residential biomass smoke exposure on asthma are not as clear. Previous studies have reported conflicting results.^{77,99,105,112-115} However, an analysis from the International Study of Asthma and Allergy in Children, which included more than 250,000 children from over 31 countries, did find an association between use of an open fire for cooking and prevalence of asthma symptoms and reported asthma.¹¹⁶ Exposures to wood smoke in developed countries are usually at much lower levels than in countries where a large proportion of the population cooks on open fires, so it is less clear how such exposures contribute to asthma burden.

RESPIRATORY EFFECTS OF KEROSENE HEATER USE

Kerosene heaters can substantially increase indoor levels of fine particles (PM_{2.5}), sulfate aerosol (SO₄²⁻), and acidic aerosol (H⁺), as well as CO.¹¹⁷ Kerosene is similar to diesel fuel in chemical composition. The existing evidence, however, is inconclusive about whether kerosene heater use is a cause of respiratory and asthma symptoms in developed countries.^{96,105,117-119} In developing countries where kerosene may also be used for lighting using inefficient wick lamps, this fuel has been associated with increased risk of respiratory infections, especially tuberculosis.^{120,121}

OTHER INDOOR POLLUTANTS—"TOXIC" INDOOR ENVIRONMENT

Besides indoor combustion, there are many other sources of indoor pollutants. Building materials, such as plywood or particle board, and carpeting can emit formaldehyde; furniture may release formaldehyde and *volatile organic compounds* (VOCs); paints, cleaning compounds, and photocopiers may release VOCs; and radon can arise from soil sources.^{6,27} Cleaning with bleach and other compounds can release chlorine and ammonia gas, which are airway irritants. Combination of bleach and ammonia or other nitrogen sources can also produce chloramine, which may induce upper and lower respiratory tract symptoms.¹²² Of these substances, radon exposure has been associated with lung cancer.¹²³ Exposure to chlorine, chloramine, and VOCs may be linked with respiratory symptoms, some of which suggest asthma, but further evidence is necessary before final conclusions can be drawn.^{122,124,125}

OUTDOOR AIR POLLUTION— ADVERSE RESPIRATORY EFFECTS OF SPECIFIC POLLUTANTS

PARTICULATE MATTER

Since the catastrophic air pollution events of the Meuse Valley, Donora, and the London Fog, hundreds of epidemiologic studies have examined the health impacts of particulate air pollution. There is strong and consistent evidence that particulate pollution causes premature death, which is principally from cardiovascular and respiratory causes.^{22,26,126-130} Both short-term exposure, measured as daily fluctuation of particulate pollutant levels, and longer-term chronic exposures have been linked with mortality. In particular, the Harvard Six Cities Study and the American Cancer Society study have provided key insights into the long-term health impacts of particulate air pollution. Evidence linking PM₁₀ and PM_{2.5} to mortality is robust but particularly strong for PM_{2.5}. Although particulate pollution is strongly correlated with other pollutants, such as SO₂, PM has a strong independent effect on mortality.

PM increases respiratory symptoms. For example, exposure to PM has been associated with lower respiratory tract symptoms among children, such as cough, wheezing, or shortness of breath.¹³¹⁻¹³³ Children with asthma are especially vulnerable.^{134,135-138} Adults with asthma who are exposed to higher levels of PM have an increased risk of health care utilization for exacerbations.^{139,140}

PM is also associated with poorer lung function, both in children and in adults. The Children's Health Study conducted in Southern California, which followed thousands of children over many years, found that fine particulate pollution was linked to a reduced rate of lung function growth.¹⁴¹⁻¹⁴³ Another study used carbon content of airway macrophages as a biomarker of individual exposure to PM derived from fossil fuel; there was a dose-dependent inverse association between the carbon content of airway macrophages and lung function, including *forced expiratory volume in 1 second* (FEV₁), in children.³⁰ Because it used an airway-related biomarker of particulate exposure, this study provides key support for the connection between particulate exposure and impaired lung function in children. In adults, particulate pollution has also been linked to poorer lung function and increased risk of COPD, which may reflect decreased growth of lung function in childhood or accelerated decline subsequently.^{94,141,144,145} In support of a link between particulate pollution and COPD, other studies have linked ambient particle exposure to a greater risk of hospitalization and death from COPD.^{139,140,146-148}

Importantly, a reduction in particulate air pollution translates to improved pulmonary function and a longer life span for the population. A Swiss study (SAPALDIA) examined the association between the 11-year change in air quality and lung function decline among a large sample of adults.¹⁴⁹ A PM₁₀ reduction of 10 µg/m³ was associated with a decreased rate of annual decline of FEV₁. To address the impact of declining PM_{2.5} levels on mortality, another study examined 211 metropolitan counties throughout the United States from approximately 1980 to 2000.¹²⁸ A decrease in PM_{2.5} of 10 µg/m³ was associated with a mean

increase in life expectancy of 0.61 years, after taking into account measures of sociodemographic and smoking factors. During the 2 decades of the study, the average life expectancy increased 2.72 years. The authors estimated that up to 15% of this improvement in life span could be attributed to declining particulate pollution levels. In the Harvard Six Cities Study, declining fine particle levels were also shown to be associated with reduced mortality in the United States.¹²⁶

Another important component of particulate pollution is diesel exhaust. Diesel exhaust from heavy-duty trucks and diesel-engine cars is a major contributor to particulate air pollution in many parts of the world. Diesel exhaust particles have a central carbon core and adsorbed organic compounds, including *polycyclic aromatic hydrocarbons* (PAHs) and other known carcinogens. Occupational exposure to diesel exhaust among truck drivers, railroad workers, and miners has been associated with an elevated risk of lung cancer.¹⁸⁻²¹ Toxicologic studies have confirmed the carcinogenic properties of diesel exhaust.²¹

Diesel exhaust exposure can cause acute deterioration of lung function among persons with asthma. A randomized crossover study randomly assigned adult subjects with mild to moderate asthma to walk along Oxford Street in London at lunchtime (the busiest shopping street, in which only diesel powered buses and taxis are allowed) or in Hyde Park.¹⁵⁰ Fine and ultrafine particle levels were approximately three times higher on Oxford Street than in Hyde Park. The maximal decline in FEV₁ was much greater for subjects walking on Oxford Street than in Hyde Park, and sputum biomarkers of neutrophilic inflammation were also increased after the street walks. Other studies indicate that diesel exhaust may favor a Th2 immune response, further connecting this form of particulate pollution with allergic disease and asthma.^{151,152} Diesel exhaust contains PAHs that have been shown to worsen asthma outcomes, potentially through an epigenetic mechanism to decrease T regulatory cell function.¹⁵³

SULFUR DIOXIDE

The major source of sulfur oxides in the ambient environment is the combustion of sulfur-containing fossil fuels such as coal and crude petroleum. SO₂ is the most important of the gas-phase *sulfur oxides* (SO_x) in terms of both atmospheric chemistry and health effects. Sulfur oxides are usually considered to include *sulfur trioxide* (SO₃) and gas-phase *sulfuric acid* (H₂SO₄), but neither is present in the atmosphere in concentrations that result in substantial human exposures except when there are industrial or transportation accidents. Sulfur dioxide is regulated by the EPA as a criteria pollutant. A newly recognized source of exposure to SO₂ that has been associated with acute health effects is volcanic emissions.¹⁵⁴

Bronchoconstriction is the primary acute effect of SO₂ and is likely mediated by chemosensitive receptors in the tracheobronchial tree. In particular, persons with asthma are most sensitive to the effects of SO₂, which may result from preexisting airway inflammation that leads to enhanced release of mediators, alterations in the autonomic nervous system, and exaggerated response of the chemosensitive receptors.^{155,156} Multiple controlled human

exposure studies have observed symptomatic bronchoconstriction in exercising asthmatics following 5- to 10-minute exposures to SO₂ at concentrations that are similar to those found in ambient air.^{157,158} In the published studies, 5% to 30% of relatively healthy asthmatic subjects experienced moderate or greater decrements in lung function (>100% increase in specific airway resistance or >15% decrease in FEV₁) with exposures to SO₂ concentrations of 200 to 300 ppb during exercise (compared with the current EPA standard of 75 ppb over a 1-hour averaging time).^{32,158} At concentrations of 400 ppb or greater, a greater percentage (20% to 60%) of exercising asthmatic individuals experienced SO₂-induced bronchoconstriction. A clear concentration-response relationship has been demonstrated following exposures to SO₂ at concentrations between 200 and 1000 ppb, in terms of both increasing severity of effect and proportion of asthmatic individuals affected. Individuals without asthma do not typically experience bronchoconstriction at these levels.

The results of multiple epidemiologic studies show associations between short-term exposures (generally 24-hour averages) to ambient SO₂ and respiratory morbidity. These studies were conducted in areas where the mean ambient 24-hour average SO₂ concentration ranged from 1 to 30 ppb, with maximum values ranging from 12 to 75 ppb. Several multicity studies and single-city studies have found an association between 24-hour average SO₂ concentrations and respiratory symptoms in children, particularly those with asthma.¹⁵⁹⁻¹⁶² Generally consistent associations have also been observed between ambient SO₂ concentrations and lung function decrements and health care utilization for all respiratory causes, particularly among children and older adults (≥65 years), and for asthma.¹⁶³⁻¹⁶⁷

The observed associations of asthma symptoms and lung function changes with 24-hour average SO₂ exposures in epidemiologic studies may be due to short-term peak exposures similar to the 5- to 10-minute exposures that have produced symptomatic bronchoconstriction in controlled human exposure studies. In other words, the effects of SO₂ on respiratory symptoms and lung function observed in human experimental studies using peak exposures are coherent with the increased emergency department visits and hospital admissions observed in epidemiologic studies. To protect asthmatic individuals from acute episodes of bronchoconstriction, in 2010 the EPA added a 1-hour ambient air quality standard for SO₂ of 75 ppb.

Because SO₂ and PM_{2.5} are both emitted from the combustion of sulfur-containing fuels such as coal and heating oil, epidemiologic studies of SO₂ need to address potential confounding by this and other co-pollutants. In studies that have evaluated multipollutant models, the effect of SO₂ on respiratory health outcomes appears to be robust and independent of the effects of gaseous co-pollutants, including NO₂ and O₃, but the effect of SO₂ is not always found to be independent of PM.^{165,168}

Several studies have assessed the effects of decreases in SO₂ concentrations on respiratory symptoms due to air quality regulations. In eastern Germany, a marked decline in ambient SO₂ concentrations (90% across the decade of the 1990s) was associated with a decrease in the prevalence of respiratory symptoms.¹⁶⁹ During the study period, however, concentrations of other ambient air pollutants

also decreased, including that of PM, which was approximately 60% lower. In a similar study of the effect of a 1990 regulation requiring use of low-sulfur fuel for power generation and on-road vehicles in Hong Kong, large reductions in ambient SO₂ concentrations of up to 80% were associated with reduced respiratory symptoms; in this study, reductions in ambient PM were less than 20%.¹⁷⁰ Although the improved respiratory symptoms observed in both of these intervention studies may be partially attributable to declining concentrations of air pollutants other than SO₂, the results nevertheless provide support for a causal relationship between SO₂ and respiratory health.

NITROGEN DIOXIDE

The term *oxides of nitrogen* (NO_x) includes all forms of oxidized nitrogen compounds, including *nitric oxide* (NO), *nitrogen dioxide* (NO₂), and all other oxidized nitrogen-containing compounds formed from NO and NO₂. NO_x is emitted by combustion sources mainly as NO with smaller quantities of NO₂. Motor vehicles and electric utilities are the two largest NO_x sources in the United States. NO is the primary NO_x species emitted from most combustion sources but is rapidly converted to NO₂; thus, NO₂ is the focus of most health effects studies. NO₂ is another of the criteria pollutants regulated by the EPA to protect public health. It is an oxidant gas like O₃ but less potent. Although high concentrations sometimes found in silos are well known to cause the acute and sometimes lethal pulmonary edema of “silo filler’s disease,”¹⁷¹ the much lower levels of NO₂ in outdoor air had not been definitively linked to adverse health effects in epidemiologic studies until the past decade. When it became apparent that indoor concentrations of NO₂ often exceeded outdoor concentrations, particularly in homes equipped with gas stoves, research interest focused on the possibility that exposure to NO₂ in indoor air might increase the frequency of respiratory infections, in part because of animal studies showing that exposure increased risk of infection.¹⁷²

Controlled human exposure studies provide evidence for increased airway responsiveness to both nonspecific and specific challenges in asthmatic subjects after short-term exposure to NO₂. The results of several older studies suggested that short-term (30- to 60-minute) exposures to NO₂ at concentrations in the range of 100 to 300 ppb may cause increased airway responsiveness to nonspecific bronchoconstrictor agents such as methacholine and histamine.¹⁷³ More recent studies involving allergen challenge in asthmatics suggest that NO₂ may enhance both allergen-induced bronchoconstriction and inflammatory responses after exposures as low as 260 ppb NO₂ for 30 minutes during rest.^{174,175}

Evidence from a number of epidemiologic studies supports an association between ambient NO₂ and respiratory morbidity, especially among persons with asthma. In particular, a study that evaluated the effect of an intervention that reduced indoor exposure to NO₂ from gas heaters provided evidence of improvement in respiratory symptoms in asthmatic children.¹⁷⁶ Studies using community ambient monitors to assign exposures to NO₂ also found associations between ambient NO₂ and respiratory symptoms in asthmatic children.^{10,159} Positive associations were observed in

cities where the 24-hour average ambient concentrations were within the range of typical large U.S. urban areas. The results of multipollutant models generally showed that the NO₂ associations were robust after adjustment for co-pollutants including O₃, PM, and CO.

Multiple epidemiologic studies have shown positive associations between short-term ambient NO₂ concentrations and emergency department visits and hospital admissions for respiratory causes, especially asthma.^{168,177-179} These associations are particularly consistent for children and older adults (age 65+ years) when considering all respiratory diseases as the outcome and, for children and adults of all ages when considering asthma as the outcome.

In addition to the epidemiologic evidence that short-term exposure to ambient NO₂ can cause respiratory morbidity, long-term exposure to NO₂ has been associated with decreased rate of growth of lung function. Results from the longitudinal Children's Health Study indicated that decrements in lung function growth were substantial for boys and girls who lived in southern California communities with relatively high annual average ambient NO₂.¹⁴¹ The mean annual NO₂ concentrations in the communities ranged from approximately 5 to 40 ppb, well below the current EPA national ambient air quality standard of 53 ppb as an annual average. Similar associations have also been found for PM, inorganic (mostly nitric) acid vapor, and proximity to traffic (<500 m) in this cohort; the high correlation among traffic-related pollutants makes it difficult to determine the independent effect of NO₂ on lung function growth.^{141,180}

Of interest, the results of several studies, including two from the Children's Health Study, suggest that long-term residential exposure to NO₂ is associated with increased risk of developing asthma in children.^{181-183,183a} However, it may be that NO₂ itself is not the causal agent, but rather that NO₂ concentrations are a good marker of exposure to the traffic pollution mixture.¹⁸²

Because short-term exposures to NO₂ can induce greater airway responsiveness among asthmatic subjects in human experimental studies and are associated with respiratory outcomes, especially asthma, in epidemiologic studies, there is coherent evidence to support a short-term averaging time for air quality standards to control this pollutant. To protect individuals with asthma from acute exacerbations, the EPA promulgated a new 1-hour ambient air quality standard for NO₂ of 100 ppb in 2010.

OZONE

O₃ is a colorless, pungent, relatively water-insoluble gas that, together with other photochemical oxidants and fine particles, forms "smog." Tropospheric, or ground-level, O₃ is an environmental air pollutant and is distinct from the stratospheric O₃ found at altitudes of greater than 10 km (6.2 miles) above the earth's surface. O₃ is generated by a series of sunlight-driven reactions involving NO_x and VOCs from predominantly mobile (i.e., motor vehicle) but sometimes stationary sources. The meteorologic conditions that tend to foster the generation of O₃ are typically present from late spring to early fall. O₃ reaches peak concentrations typically in mid-afternoon, after both the morning rush hour and several hours of bright sunlight. Because of its high

chemical reactivity, ambient O₃ tends not to penetrate well into buildings. However, indoor sources of O₃ include office equipment with electric motors or ultraviolet light, such as photocopy machines, and electrostatic devices, such as air purifiers and ion generators.

Although O₃ has long been associated with southern California smog, many other areas of North America also experience high concentrations of this pollutant, especially Houston, Mexico City, and cities in the eastern United States and Canada during the summer months. In these areas, there are many days each year when the current EPA national ambient air quality standard for O₃ is exceeded.

Ozone is a potent oxidant and is capable of reacting with a variety of extracellular and intracellular molecules. When ozone reacts with unsaturated lipids, free radicals and toxic intermediate products that can lead to cellular damage or cell death are generated.¹⁸⁴ Direct cytotoxicity is a major mechanism of O₃-induced tissue injury; secondary damage from the inflammatory response likely also plays a role.

Dosimetric studies indicate that much of the inhaled O₃ is deposited in the upper and proximal lower airways.¹⁸⁵ However, because of its relative water insolubility, a considerable fraction will penetrate to the distal airways and alveoli. At the tissue level, the dose is highest at these sites.¹⁸⁶ Increased inspiratory flow, as would be seen with exercise, may overwhelm the upper airway "scrubbing mechanisms" and cause greater deposition of O₃ in the distal lung.¹⁸⁷

Most of the research on the health effects of O₃ has focused on short-term exposure. In controlled human exposure studies, O₃ inhalation by healthy subjects causes decrements in FEV₁ and FVC that correlate with concentration, exposure duration, and minute ventilation.¹⁸⁸⁻¹⁹⁰ These decrements in lung function are primarily a result of decreased inspiratory capacity rather than airway obstruction. The mechanism of the decreased inspiratory capacity appears to be neurally mediated involuntary inhibition of inspiratory effort involving stimulation of C fibers in the lungs.¹⁹¹ Somewhat surprisingly, older subjects and those who are cigarette smokers demonstrate lower O₃-induced decrements in pulmonary function than younger, healthy subjects.¹⁹² The acute decrements in pulmonary function induced by O₃ usually resolve within 24 hours. Statistically significant decrements in FEV₁ have been demonstrated in healthy subjects with exposures during exercise to concentrations below the current U.S. air quality standard.¹⁹³

Respiratory symptoms (e.g., substernal chest discomfort, cough, wheeze, dyspnea) are correlated with these decrements in pulmonary function.¹⁹⁰ Another adverse effect of short-term exposure to O₃ is enhanced airway responsiveness to nonspecific stimuli such as methacholine and histamine.¹⁹⁰ This effect may persist longer than the acute decrements in lung function and may be seen even in individuals who do not experience a decline in their FEV₁.

Ozone exposure may induce adverse respiratory consequences through a variety of mechanisms. These include nasal inflammatory changes, injury to type I alveolar cells, ciliated airway epithelial cell injury, infiltration of the airway mucosa by neutrophils, and increased bronchoalveolar lavage fluid neutrophils and inflammatory mediators.¹⁹⁴⁻¹⁹⁶

Airway inflammation has been demonstrated after exposure to ambient concentrations with exercise, including levels below the current U.S. air quality standard.^{193,197}

The effects of chronic O₃ exposure in humans have not been adequately defined. It has been hypothesized that chronic exposure would lead to structural changes; however, to date, most toxicologic studies involving rodents have failed to demonstrate structural damage after long-term exposure to ambient concentrations. However, studies with rhesus monkeys have shown that O₃ exposure of neonatal rhesus monkeys led to abnormal development of conducting airways, especially with coexposure to house dust mites.¹⁹⁸ In addition, some epidemiologic studies, but not all, suggest that long-term residence of children in a high ambient O₃ environment can lead to remodeling of the small airways.^{141,199,200}

Multiple epidemiologic studies show that high ambient O₃ concentrations are associated with an increased rate of asthma attacks and increased respiratory-related hospital admissions/emergency department visits for respiratory disease.^{201,202} The biologic plausibility of these findings is supported by the results of controlled human exposure studies showing that O₃ increases nonspecific airway responsiveness, asthmatic subjects have a greater inflammatory response to exposure, and specifically sensitized asthmatic subjects have enhanced bronchoconstrictor responses to inhaled allergen.^{203,204} In addition to the exacerbation of preexisting asthma, some evidence exists that exposure to O₃ could induce new cases of asthma; for example, children playing outdoor sports in polluted areas of the Los Angeles basin have a threefold to fourfold increased risk of asthma.²⁰⁵

Both short-term and long-term exposures to O₃ have been associated with increased risk of mortality; this has been reported in both Europe and the United States.²⁰⁶⁻²⁰⁸ Although this effect was first reported for respirable PM, both O₃ and fine PM are capable of generating oxidative stress and local inflammation deep in the lung. Similar to what has been observed in PM mortality studies, it appears that elderly people with preexisting heart and lung disease represent the group at greatest risk for O₃-related death. If excess oxidative stress is a critical step in a pathway that leads to early mortality in individuals with heart and lung disease, it is not surprising that exposure to both ambient O₃ and PM is associated with increased risk. Of additional concern, several studies have suggested that young adults living in southern California have increased oxidative stress and cytogenetic damage compared with those living in northern California, perhaps related to differential exposure to O₃.^{209,210}

In summary, tens of millions of persons in the United States are exposed to levels of O₃ above the current U.S. national ambient air quality standard. This exposure is capable of inducing both acute decrements in lung function and respiratory symptoms. Although these effects are transient, acute respiratory tract injury and inflammation can also be induced by short-term exposure to ambient concentrations of O₃. Exacerbations of asthma and increased risk of death of the elderly appear to be the most important health effects of short-term exposure. The long-term consequences of O₃-induced acute injury and inflammation are not well understood, but there is epidemiologic evidence consistent with airway remodeling.

Key Points

- Although the hazard of air pollution for human health has been recognized for less than a century, great progress has been made in defining the sources, properties, and distribution of pollutants. More recently, the importance of indoor air pollution has become clear.
- Epidemiologic studies, taken together with controlled human exposure studies, animal studies, and in vitro studies, have delineated many of the serious respiratory and cardiovascular health effects of air pollution. Significant questions remain, however, about the impact of multiple pollutants acting together, the effect of pollution on susceptible populations, and the minimum ambient levels at which the risk of health effects increases. Further research is needed to answer these important questions.
- Great progress has been made in clearing the air in the United States and other developed countries, but levels of indoor and outdoor pollutants remain higher than is desirable for human health. In developing countries, a major source of air pollution is biomass smoke from domestic heating and cooking, which may be the world's leading cause of obstructive lung disease among women.
- Further research that addresses the important remaining questions in air pollution, especially the question of what are safe thresholds for air pollutants of concern, including biomass smoke, will inform future policy efforts to protect public health.

Complete reference list available at *ExpertConsult*.

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ACUTE RESPONSES TO TOXIC EXPOSURES

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INTRODUCTION

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INTRODUCTION

This chapter focuses on the acute effects on the lung after exposure to toxic substances. As used in this chapter, *acute* indicates short-term exposures (minutes to hours), with the initial onset of pulmonary responses within a similarly rapid time period. Generally, the relevant toxicant exposures are of high intensity, far in excess of recommended safety limits for population-wide environmental levels or even workplace-permissible limits. In this chapter, the *target organ* discussed for the toxicants is the lung. Importantly, *target organ* does not equate with *route of exposure*. For most acute exposures, inhalation is the route of delivery leading to the lung injury. Because ingestion may also lead to lung injury, paraquat and hydrocarbon, examples of ingested toxins with severe acute target organ effects on the lung, are included in this chapter. However, in some instances, inhalation may be the route of delivery for the toxicant and yet the primary target organ is not the lung (e.g., solvent inhalation that causes central nervous system depression). Inhalation exposures leading to nonpulmonary illnesses are not addressed here.

Moreover, this chapter does not address brief exposures inducing acute responses mediated by anamnestic (i.e., allergic or other immune-mediated) mechanisms. These responses require prior exposures that have already led to sensitization, such as hypersensitivity pneumonitis (see Chapter 64) or occupational asthma (see Chapter 72). There are also a number of toxicants causing unusual pulmonary syndromes after subacute (days to months) as opposed to acute exposure. Some of these syndromes have emerged in recent years associated with new technologies or novel toxicants, such as diacetyl-caused popcorn worker's lung and other flavor industry workers' diseases linked to this chemical,^{1,2} "flock workers' lung" caused by short synthetic textile fibers,^{3,4} and "Ardystil lung," a dye chemical-induced organizing pneumonia.^{5,6} Although beyond the scope of this chapter, some of these syndromes are discussed elsewhere.

PATHOGENESIS OF LUNG INJURY FROM INHALED TOXICANTS

PATTERNS OF RESPONSE TO IRRITANT INHALATION

Acute lung toxicity results from a variety of exposures but, nonetheless, is manifest by a narrow repertoire of injury (Table 75-1). Irritant toxic substances can be encountered in various physical states relevant to their inhalational properties. Such states include *gases*, *vapors* (i.e., the gaseous form of a substance that is a liquid or a solid at normal temperatures and pressures), and *fumes* (i.e., solid material, often metals, of small particle size suspended in a gaseous medium (most < 1.0 μm and many < 0.1 μm). *Aerosols* encompasses a mix of potential states (i.e., liquid droplets or fine particulates dispersed in a gaseous medium; *smoke* is a subset of aerosol resulting from incomplete combustion).

These various classes of exposures include heterogeneous toxic agents that are capable of causing extensive cell injury throughout the upper and lower respiratory tract. The primary location of respiratory tract injury and the onset of clinical symptoms are partly dependent on the solubility of the gas, vapor, fume, or aerosol involved and, in the case of fumes or aerosols, particle or droplet physical characteristics. Other factors that determine the injury pattern following exposure include (1) amount of the toxic substance inhaled, (2) duration of exposure to the inhalant, (3) concentration of the inhalant in the ambient air, (4) other physical properties (such as pH or chemical reactivity), and (5) a variety of host factors, such as age, use of respiratory protection, and comorbid illness. Overwhelming exposures to any irritant inhalant, however, can cause extensive damage throughout the respiratory tract.

Ammonia⁷ and sulfur dioxide⁸ are examples of substances that are highly soluble in water. Such highly soluble substances cause immediate irritation of the conjunctival mucosa and upper airways. In contrast, oxides of nitrogen,⁹

Table 75-1 Major Clinical Scenarios of Pulmonary Responses Shortly After Acute Toxicant Exposure

Clinical Scenario	Exemplar Exposures	Additional Comments
Mucous membrane and airway irritation (burning eyes, nose, and throat; laryngospasm and bronchospasm) with or without lower lung injury (pulmonary edema, diffuse alveolar damage)	Chlorine, chlorine dioxide, chloramine; bromine; sulfur dioxide; acid aerosols (sulfuric, hydrochloric, hydrofluoric); ammonia; zinc chloride (smoke bombs)	At low exposures, mucous membrane irritation may be the sole effect; with heavy exposure, lower lung injury may be seen.
Lower lung injury (pulmonary edema, diffuse alveolar damage) with little or no mucous membrane irritation or airway effects	Nitrogen dioxide, phosgene, ozone, cadmium fume, mercury vapor, nickel carbonyl, fluorocarbon (waterproofing)	Exposure can be inadvertent or occult with presentation delayed 24–48 hr
Self-limited flulike illness with fever and leukocytosis beginning 6–12 hr after a clear exposure history	Zinc oxide fume, heavy organic dust inhalation, polymer fume, endotoxin	The presence of hypoxemia or lung injury indicates another diagnosis
Foreign substance ingestion followed by pneumonitis	Hydrocarbon aspiration, exogenous lipid pneumonia, paraquat fibrosis	Heavy aerosol inhalation can cause lipid pneumonia; paraquat can also be absorbed through the skin

ozone,¹⁰ and phosgene¹¹ have relatively low water solubility. For this reason, exposure to one of these agents may *not* be characterized by immediate symptoms of mucous membrane irritation. This may lead to more prolonged exposure and delay in seeking medical attention. Both more and less soluble irritant exposures can lead to distal lung injury, but in the case of highly soluble materials, a history of severe upper respiratory symptoms should precede the presentation of distal airway and alveolar damage.¹²

Irritants reaching the lower respiratory tract, either because of their inherent physical characteristics or because of exposures that overwhelm the absorptive capacity of the upper airway, can injure both the lung epithelium and its endothelium. Pathophysiologically, irritant injury at this level leads to a nonspecific pattern of diffuse alveolar damage similar to that seen from a variety of different causes (see Chapter 15). The pathologic changes in fatal cases of irritant lung injury include focal and confluent areas of edema with protein-rich fluid in the alveolar spaces, hyaline membrane formation, and denudation of the alveolar epithelium. In addition, mucous membranes of the bronchial and bronchiolar walls may be destroyed or denuded. Some pulmonary hemorrhage may be seen in irritant lung injury but is typically not the dominant clinical-pathologic manifestation; prominent pulmonary hemorrhage should raise suspicion of other toxicant- or nontoxicant-mediated syndromes¹³ (see Chapter 67).

On the cellular level, respiratory tract injury may be mediated through the deposition or formation of an acid, alkali, free radical, or other reactive chemical species. The precise cellular mechanisms of injury from irritant inhalants have not been fully delineated even for relatively common irritants such as chlorine or even the chemical warfare agent phosgene, substances for which a great deal of human and experimental animal data exist.^{14–17}

OTHER PATTERNS OF RESPONSE

Acute irritant inhalation injury is the predominant, but not the only, pathophysiologic mechanism underlying acute toxic lung syndromes. In contrast to the anatomic distribution commonly seen in water-soluble, irritant chemical-related inhalant injury, it may be difficult to delineate a descending, hierarchical pattern from upper airway to lower lung injury following exposure to a diverse group of

other agents. Many of these exposures, as with the water-soluble irritants, also lead to acute lung injury via nonimmunologic mechanisms (clinically, acute respiratory distress syndrome; pathologically, diffuse alveolar damage), as detailed subsequently in this chapter. Other toxicant exposures produce various other syndromes of respiratory tract injury, such as heavy metal pneumonitis,¹⁸ hydrocarbon aspiration,¹⁹ or paraquat lung injury.^{20,21} The inhalation fever syndromes are an exception in that they do not involve obvious lung injury; the pathophysiology of this group of self-limited acute lung syndromes appears to be cytokine-mediated.²²

GENERAL MANAGEMENT PRINCIPLES

Symptoms and signs of acute inhalation injury can be delayed in onset. Following removal from exposure while safeguarding the rescuing personnel, the next most important management decisions include protection of the airway (i.e., preemptive intubation may be required to prevent precipitous airway obstruction from progressive airway edema) and treatment of hypoxemia. The nasopharynx and larynx may manifest injuries earliest because they are exposed to the highest concentrations of inhaled water-soluble toxicants. The upper airway may also be a primary target organ due to angioedema in selected toxicant ingestions.²³ Within a few hours after exposure, progressive airway edema, mucopurulent sputum production, and bronchorrhea may develop. Bronchoconstriction, peribronchial edema, and bronchial mucosal sloughing may produce atelectasis. In the distal airways and alveoli, epithelial and endothelial injury leads to permeability-induced edema, which can manifest ranging from mild interstitial edema to diffuse alveolar damage. Pulmonary edema may be rapid following high-concentration toxicant exposure or delayed up to 24 to 48 hours. Pneumothorax and pneumomediastinum can be acute complications of respiratory tract injury due to chemical toxicants.^{24–29} Diffuse alveolar damage after severe acute toxic lung injury should be managed consistent with the basic management of acute lung injury due to other causes. This extends to the role of protective ventilation strategies.³⁰ Concomitant airway injury with acute

bronchospasm often warrants treatment with bronchodilators because of the airway obstruction.

A beneficial role for systemic corticosteroids in the acute phase of irritant and other chemically mediated forms of acute injury to the lungs has not been established, by either controlled trials in humans or studies using experimental animal models.^{31,32} Inhaled steroids are more likely to have a better risk-benefit ratio in the therapy of acute inhalation injury (e.g., in the context of bronchospasm and concomitant use of bronchodilators, taking acute smoke inhalation injury as a paradigm).³³ Despite the lack of controlled evidence of efficacy, anecdotal reports of benefits from systemic corticosteroid use continue to appear.²⁸ Prophylactic antibiotic drugs have not proved to be efficacious in toxic lung injury; antibiotics should be reserved for those patients with clinical evidence of infection, including ventilator-associated pneumonia.^{34,35} To date, convincing data do not support the use of other pharmacologic agents, such as antioxidants, in the generic treatment of toxic chemical lung injury, although this is the subject of active experimental research.^{31,36}

There are certain exposure-specific management issues that do occasionally arise. In paraquat-induced lung injury, for example, oxygen toxicity is a particular concern because of the specific mechanism of action of paraquat (i.e., high concentrations of oxygen may lead to more severe lung injury).²⁰ In paraquat as well, immunosuppressive therapy has been of particular interest and has yielded some promising data but remains to be confirmed in randomized, controlled studies.²¹ In the case of certain metal toxins, chelation may have a therapeutic role, as is addressed later in relation to the specific exposures involved. Inhalation fever is self-limited, so the principal clinical management issue is to exclude other exposures with more serious outcomes.²²

CHRONIC SEQUELAE AND RESIDUAL EFFECTS

Among persons surviving symptomatic exposure to acute irritants, there may be persistent structural and functional effects. Long-term consequences to the upper airways (nose, pharynx, and larynx) can be sequelae of acute inhalational exposures; upper airway complaints including chronic rhinitis (*reactive upper airway dysfunction syndrome* [RUDS]), anosmia, and vocal cord dysfunction have been reported.³⁷⁻⁴⁰

Follow-up studies of more homogeneous populations evaluated after inhalation injury (with only a minority experiencing severe injury) suggest that airflow obstruction and nonspecific airway hyperresponsiveness are the most common persistent abnormalities of the conducting airways after irritant injury. Even so, epidemiologic data suggest that only a minority of those exposed will experience these outcomes.⁴¹⁻⁴³ The term *reactive airway dysfunction syndrome* (RADS) has been applied to the persistence of airway reactivity after acute exposure to respiratory irritants.⁴⁴⁻⁴⁷ The more general term *irritant-induced asthma* has also been used to describe this condition.^{48,49} Insofar as this syndrome represents a form of work-related asthma, it is addressed in Chapter 72.

Chronic injury to the lower airways and lung parenchyma are unusual sequelae of acute inhalational exposure. Long-term follow-up evaluation after recovery from acute respiratory distress syndrome due to heterogeneous causes (predominantly associated with sepsis) suggests that residual deficits in lung volumes, airflow, and gas exchange may persist long after recovery.⁵⁰ *Bronchiolitis obliterans* (BO),⁵¹⁻⁵⁸ bronchiectasis,^{7,57,59-62} and organizing pneumonia^{63,64} may all develop but are rare complications. Irritants, in particular nitrogen oxide and related exposures, have long been known to cause BO.⁶⁵ Yet even with nitrogen dioxide, BO is an infrequent event; for example, only 1 case was found in a series of 20 moderate to severe exposures.⁵² Pathologically, irritant-induced BO is usually characterized by intrabronchial granulation tissue (to which the term *proliferative bronchiolitis obliterans* is sometimes applied), as opposed to constrictive (obliterative) BO. The latter appears to be the pathologic correlate of diacetyl-caused popcorn worker's lung² and has been reported in one case of BO following exposure in the World Trade Center disaster,⁶⁶ in a case series of Iraq and Afghanistan military veterans (although no single toxic exposure has been implicated),⁶⁷ and in association with styrene-fiberglass boat construction, presumably with indolent rather than acute exposure.⁶⁸ In addition to residual obstructive ventilatory deficits, restrictive deficits may also result from severe irritant inhalation injury.^{59,69} There is also some indication that an isolated reduction in residual volume may be noted in the follow-up of such cases.^{70,71} Finally, nonspecific respiratory complaints after acute inhalation events can be a somatic manifestation of psychological processes and can be further complicated by *posttraumatic stress disorder* (PTSD) comorbidity.⁷²⁻⁷⁵

SPECIFIC EXPOSURES (Table 75-2)

CHLORINE, CHLORAMINES, HYDROCHLORIC ACID, AND RELATED CHEMICALS

Among the toxic agents causing pulmonary responses, *chlorine* is a common and potent irritant inhalant accounting for substantial human morbidity.^{15,76,77} Common forms of exposure include industrial leaks,^{78,79} environmental releases primarily during transport,^{80,81} water purification,⁸² swimming pool-related events,^{83,84} household cleaning product misadventures,⁸⁵ and even homemade chemical bombs⁸⁶ or intentional terrorist use.⁸⁷ In the form of a yellow-green acrid gas, industrial and environmental releases typically present clear-cut exposure histories. Because the gas is heavier than air, higher contamination can be expected in low-lying areas (hence, its use in trench warfare in World War I).⁸⁸ However, other environmental conditions may supervene. Examples include one well-documented case of the gas rising along the heated outside wall of a factory where rooftop workers were exposed.⁷⁸ In another case, chlorine initially collected in a basement but then was sucked up into the central heating system of a dormitory.⁸⁹

The history of exposure to chlorine may be less straightforward when the chlorine is generated after *de novo* generation from chlorine-containing products. Chlorine gas

Table 75-2 Selected Toxic Agents Causing Pulmonary Responses After Acute Exposure

Agent	Common Exposure Scenarios	References
Acid aerosols	Plating; microelectronics; other manufacturing	110, 125–129
Acrolein	Structural or wildland fires; other combustion	269, 270
Ammonia	Industrial refrigeration leaks; fertilizers	7, 294, 298
Brevetoxin	Aerosolization of “red tide” toxin	285, 287
Bromine	Water treatment; chemical manufacturing	58, 299–302
Cadmium fume	Flame cutting of soldered or sheet metal materials	168–172
Chloramines and nitrogen trichloride	Bleach + ammonia mix; chlorination + ammonia	90–92
Chlorine gas	Gas leak; water treatment; bleach + acid mix	14, 76–85
Chlorine dioxide	Pulp paper bleaching	116, 117
Crowd control agents (tear gas)	Military and police training and operations	157–160
Dimethyl sulfate	Industrial chemical yielding sulfuric acid	123, 124
Fluorocarbon polymers	Overheating polymers	131, 198, 204
Fluorocarbon sprays	Waterproofing and related aerosol sprays	236–240
Hydrocarbons	Aspiration of low-viscosity materials, “fire-eating”	19, 246, 248, 253, 255
Hydrogen sulfide	Sewers and manure pits; fossil fuel and geothermal production	306, 309–311
Mercury vapor	Gold extraction, heating cinnabar	174–181
Methyl bromide	Pesticide fumigant	304, 304
Methyl isocyanate	Pesticide manufacturing	312, 314
Methyl isothiocyanate	Breakdown product of metam sodium fumigant	315, 316
Mustard gas	Chemical warfare agent	59, 141–143
Nickel carbonyl	Nickel processing, metal reclamation	182–186
Nitrogen dioxide	Silage; combustion; explosives; welding; nitric acid mixes	9, 52, 104, 105, 108
Organic dusts/aerosols	Contaminated dust or bioaerosol generation	22, 217, 222, 223
Organophosphates	Pesticide application; chemical warfare	131, 132
Ozone	Bleaching; water treatment; plasma welding	10
Paraquat	Herbicide skin contamination or ingestion	20, 259
Phosgene	Chlorinated solvent breakdown by-product	11, 16
Phosphine	Fumigation with aluminum or zinc phosphide, microelectronics	330–332
Sulfur dioxide	Refrigeration; cement manufacture; mining; pulp paper mills	8, 118–120
Tributyltin (bis[tributyltin] oxide)	Paint additive for mold inhibition	196
Vanadium	Ore processing; fossil fuel by-product, catalyst use	192, 193
Zinc chloride	Smoke bombs (“white smoke”)	162, 166
Zinc oxide fume	Welding galvanized steel; brass casting	199, 200, 216

can be generated from liquid bleach containing hypochlorite or from dry powdered bleach containing chlorinated phosphate. In either liquid or powdered bleaches, the chlorine gas is liberated on contact with acids in common household products containing muriatic (i.e., hydrochloric), phosphoric, or hydrofluoric acid⁸⁵ or in industrial settings.⁴³ In contrast, mixing chlorine-containing products with ammonia leads to release of chloramines (monochloramine [NH₂Cl] and dichloramine [NHCl₂]) and related chemicals, especially nitrogen trichloride (NCl₃), chemicals whose irritant effects are attributed to in situ pulmonary reactions releasing chlorine, hypochlorous acid, and ammonia.^{85,90,91} In swimming pools, inadvertent mixing of the chlorinated water with nitrogen donors can also happen, with potential irritant effects attributed to nitrogen trichloride in particular.^{90,92} Chloramines evolved from chlorine and ammonia mixing should not be confused with Chloramine-T (sodium-N-chlorine-p-toluene sulfonamide), a disinfectant that can act as a chemical sensitizer leading to allergic asthma and other anamnestic responses.⁹³

Irritant effects after inhalation of *hypochlorite* aerosols in confined spaces without a history of combining products (not an uncommon scenario when cleaning bathrooms) can also be associated with irritant effects. Similarly, in certain industrial operations, hydrochloric (hydrogen chloride in water) or hypochlorous acid aerosols are also respiratory irritants. Chlorine exposure can also take place in specific industrial processes that use inorganic chlorine derivatives; worthy of particular mention are chlorine dioxide (used in pulp paper processing),⁹⁴ chlorinated silanes (gases used in microelectronics),⁹⁵ reactive metal halides (e.g., titanium or antimony chlorides),¹⁸ and thionyl chloride (which breaks down to yield hydrogen chloride and sulfur dioxide).^{54,96}

For chlorine and related chemicals, the acute respiratory response corresponds to the effective dose delivered to the lungs. For chlorine, as for irritant gases generally, the dose response has been presumed to be equivalent for any given cross-product of concentration and exposure time (Haber law), although experimental data indicate that this

relationship may be more variable.⁹⁷ All of these compounds appear to share a final common toxic pathway. As noted in the general discussion of acute toxicant inhalation, water solubility is an important determinant of the dose reaching the lower airways. For chlorine, chlorine dioxide, chloramines, and nitrogen trichloride, their lower solubility favors deeper penetration with a more effective delivered dose compared with an equivalent inhalation of agents with a higher solubility such as acid aerosols. However, exposure to any of these compounds is associated with some degree of immediate mucous membrane and upper airway irritation. In fact, the absence of acute irritant effects is not clinically consistent with chlorine gas or related exposures.

Chlorine inhalation may manifest any of the full spectrum of respiratory tract irritant effects, from minor mucosal responses to upper airway responses to diffuse alveolar damage.^{78-88,98} Persistent airway hyperresponsiveness after irritant exposure has been associated particularly with chlorine gas and chlorine-containing products, although this association may have more to do with the frequency of exposure to chlorine rather than to any particular effect of chlorine on the airways.^{14,43,48,49} Human experimental studies are inconsistent as to whether persons with underlying airway hyperreactivity may be more sensitive to chlorine.^{99,100}

Use of inhaled bronchodilators and inhaled steroids may be indicated for both acute and residual bronchospasm following chlorine inhalation, consistent with general principles of management addressed previously. Although several case reports and series have touted the potential benefits of nebulized sodium bicarbonate inhalation in the acute treatment of chlorine or chloramine inhalation, the efficacy of this intervention has never been assessed in a controlled trial.^{91,100,101} One small controlled trial administered inhaled bicarbonate 3 months or more after exposure in irritant-induced asthma and described some benefit.¹⁰²

OXIDES OF NITROGEN, OZONE, SULFUR DIOXIDE, AND ACID AEROSOLS

These inhalants are major air pollutants; the effects of low-level exposure are discussed in detail in Chapter 74. When they are inhaled in high concentrations, these irritants cause acute lung injury. Because of their lower solubility and thus their lower incidence of upper airway symptoms, ozone¹⁰ and, even more commonly, nitrogen dioxide, may be associated with a longer exposure with a greater predilection for lung injury.¹⁰³ Nonetheless, with sulfur dioxide and acid aerosols, despite their high solubility, a sufficient intensity of exposure can also lead to diffuse alveolar damage.

High-intensity exposure to *oxides of nitrogen* can take place through decomposition of organic matter and other sources. Examples of exposure scenarios include nitrogen dioxide-induced lung injury among farmers (also known as silo filler's disease),^{52,104,105} use of internal combustion engines in enclosed spaces (with large outbreaks associated with ice resurfacing equipment used in indoor skating rinks),^{9,106-108} thermal degradation of polymers (e.g., in structural fires),³⁴ toxic gas produced by the detonation of explosives,^{56,109} the release of gas through reactions of

nitric acid breakdown in air or in reaction with metals or organic materials,¹¹⁰⁻¹¹² welding by-products, particularly when "gas-shielded" techniques are employed (manual inert gas welding or tungsten inert welding),¹¹¹ and the release of compressed nitrogen dioxide gas.¹¹⁴ Historically, the detonation of explosives has been one of the most important sources of exposure to nitrogen oxides.¹⁰⁹ Nitric oxide, an inhalant used therapeutically, breaks down to nitrogen dioxide in the presence of oxygen and, thus, must be monitored with appropriate delivery devices to avoid exposure to the potentially toxic nitrogen dioxide.¹¹⁵

High-intensity occupational ozone exposure is unusual, but it can happen with welding conditions similar to those associated with oxides of nitrogen.¹¹³ More recently, ozone in water treatment and in pulp paper bleaching has also emerged as a health issue; in the latter industry, there is often concomitant exposure to chlorine dioxide.^{116,117}

Important sources of high-level sulfur dioxide exposure include mining and ore refining,⁸ Portland cement manufacturing,¹¹⁸ sulfur treatment of fruit,¹¹⁹ and industrial releases.¹²⁰ Historically, sulfur dioxide has been and continues to be important in sulfite process pulp paper processing, where acute gas releases are superimposed on chronic lower-level exposure.^{116,117,121} In the past, sulfur dioxide was also a common refrigerant.¹²²

In ambient air pollution, sulfuric acid is an acid aerosol of primary concern; in various occupations, sulfuric acid can also be encountered at high levels. Workers can be exposed to sulfuric acid through both direct use and the breakdown of a highly toxic industrial chemical, dimethyl sulfate.^{123,124} A number of other inorganic and organic acid vapors and aerosols are also important potential causes of acute lung injury, including chromic,¹²⁵ acetic,¹²⁶ formic,¹²⁷ and hydrofluoric acids.^{112,128,129} *Hydrofluoric acid* (hydrogen fluoride) inhalation, in addition to nonspecific irritant effects, can induce clinically significant hypocalcemia, which is thought to result from the formation of insoluble calcium fluoride.¹³⁰ People can be exposed to hydrofluoric acid in manufacturing of both microelectronics and phosphate fertilizers, in household use of hydrofluoric acid rust removal agents (the mixture of which with hypochlorite bleach can evolve both chlorine and hydrogen fluoride), and in the incomplete combustion (pyrolysis) of fluorinated polymers.¹³¹ Exposure to hydrogen fluoride is a chronic problem in the aluminum smelting industry.¹³² Hydrogen fluoride is also released as a breakdown product of sulfur hexafluoride, an electrical insulating liquid chemical used in equipment.¹³³

MILITARY AND CROWD CONTROL AGENTS

Overview

Unfortunately, chemical warfare agent exposures are not of mere historical interest.^{88,134,135} Not only can sporadic exposures result from contact with discarded ordinance,¹³⁶ but more importantly, exposure can be widespread through the use of chemical warfare agents in acts of terrorism or in conventional military conflicts. Such risks have raised the specter that the diagnosis and management of such toxicants will again become clinically relevant. There have been a number of reviews of the general aspects of this

question.¹³⁷⁻¹³⁹ The goal of this section is to address individual chemical agents, including other military and crowd control agents that are not warfare chemicals per se, focusing on their respiratory target organ toxicity. Biologic warfare agents of relevance to the respiratory tract are covered elsewhere (see Chapter 40).

Sulfur Mustard

Of the major World War I chemical weapons, only sulfur mustard (so called “mustard gas,” although not a true gas in physical state) has been used “militarily” since World War II. Classified as a vesicant because of blistering induced by skin contact, mustard gas inhalation causes severe respiratory injury. Largely on the basis of the Iranian experience of their Iraqi war veterans, sulfur mustard survivors can exhibit residual tracheobronchitis, asthma, bronchiectasis, bronchotracheomalacia, BO, and fibrosis.^{59,140-143} Nitrogen mustards were sulfur mustard derivatives originally developed for military purposes but later applied medically; nonetheless, occupationally related acute lung injury has been reported through industrial release.¹⁴⁴

Phosgene

Another World War I toxic gas, phosgene, is currently encountered as a chemical industry process chemical and as a thermal breakdown product or ultraviolet photoreactant of chlorinated solvents (e.g., methylene chloride).^{11,145} An occult cause of exposure can be inadvertent phosgene production from welding metals “degassed” with solvents.¹¹³ Phosgene is the prototypic deeply penetrating inhalant exhibiting a delayed onset of symptoms (12 to 24 hours after exposure).^{17,30,146,147,147a}

Chloropicrin

Chloropicrin, another World War I gas, is a low-threshold irritant currently encountered in chemical manufacturing and as a component of fumigants.¹⁴⁸⁻¹⁵⁰

Neurotoxicants

The modern chemical warfare armamentarium is dominated by systemic toxicants developed from organophosphate pesticides (which are discussed later in “Pharmacologic Syndromes”); the nerve agent “VX” is prototypical.^{151,152} These highly lethal neurotoxins have important respiratory effects, including manifestations of both muscarinic receptor stimulation (bronchorrhea and bronchospasm) and nicotinic receptor depolarization blockade (respiratory muscle paralysis); treatment is based on reversing enzyme inhibition and countering the effects of acetyl cholinesterase excess.¹⁵³

Chloroacetophenone (Mace), Other Tear Gas Agents, and Zinc Chloride

Crowd control agents (“tear gases”), as opposed to the war gases, are intended to incapacitate persons via immediate mucous membrane irritation.¹⁵⁴ The agents in greatest use worldwide are chloroacetophenone (“mace”) and ortho-chlorobenzamalonitrile.^{155,156} In addition to their mucous membrane effects, these agents have also been implicated in lower respiratory injury and even in persistent effects following high-intensity exposures (e.g., in enclosed buildings).¹⁵⁷⁻¹⁶⁰ Unlike tear gas, exposure to smoke bomb releases

(sometimes referred to as “white smoke”) can cause severe lower respiratory injury by exposure to the potent respiratory irritant, zinc chloride fume, created through a pyro-technic reaction between hexachloroethane and zinc oxide.^{161,162} Military, police, and others who are exposed, often during ill-conceived training exercises, are at risk.^{27,161-166}

TOXIC METALS

Overview

Inhalation of certain metal fumes or metal vapors can cause an acute pneumonitis.¹⁸ Dangerous exposures to toxic metal fumes arise, in part, because these agents are not immediately irritating, analogous to the delayed symptoms after phosgene or nitrogen oxide gas inhalation. Patients typically present in respiratory distress 12 to 48 hours after exposure. Indeed, the exposure history often remains occult unless aggressively pursued. Metal pneumonitis from these materials also can include fever as a clinical manifestation of this toxic syndrome. However, the term *metal fume fever* should not be used in this context.¹⁶⁷ The toxic mechanism generalizable in heavy metal pneumonitis is presumed to be inhibition of enzymatic and other critical cellular functions.

Cadmium, Mercury, and Nickel

The three metals most important clinically in lung injury are cadmium, mercury, and nickel (the latter in the form of nickel carbonyl). For cadmium, exposure typically takes place through welding, brazing (high-temperature soldering) or flame-cutting metal, or working with molten metal under conditions of inadequate ventilation.¹⁶⁸⁻¹⁷¹ In welding, brazing, and flame-cutting, the usual source of cadmium is the welding rod, brazing solder, or a metal coating, rather than the base metal itself.¹¹³ In areas of the world where jewelry is made at a cottage industry level, cadmium use in silver-working can present a particular exposure risk.^{172,173}

High levels of the relatively volatile metal mercury can be generated effectively from many nonenclosed operations, most notably through heated metal reclamation processes (e.g., home refining of mercury-gold amalgams or even reclaiming of mercury from electronic equipment).¹⁷⁴⁻¹⁸¹ Exposure has also been reported after burning mercury sulfide (Chinese red cinnabar) and mercuric oxide for medicinal purposes.¹⁷⁹ Chelation treatment has not been shown to be effective in heavy metal pneumonitis due to mercury.

Nickel carbonyl is an organic metal derivative and potent pulmonary toxicant, with exposure during nickel refining, during manufacturing processes in which it is used as a catalyst or intermediate, or during metal recycling or reclaiming operations.¹⁸²⁻¹⁸⁶ A case report of fatal nickel fume inhalation from a metal spraying operation that was nickel carbonyl free suggests that under certain conditions inorganic nickel can also cause acute lung injury.¹⁸⁷ Although specific metal chelators have been advocated in nickel-related lung injury, the evidence in support of this in clinical practice (i.e., after illness is manifest) is equivocal. The agent dithiocarb (diethyldithiocarbamate) has been

used as a chelating antidote for nickel carbonyl pneumonitis, on the basis of supportive animal data, although its benefits are most clear-cut when administered soon after exposure (e.g., before the time clinical illness would be manifested); disulfiram has been suggested as a potential alternative treatment, although experimental data to support this practice are weak as well.¹⁸⁸

Other Metals

Other metals, including antimony, manganese, and beryllium, are sometimes cited as causes of acute lung injury consistent with metal pneumonitis, but there are few reports in the past 50 years providing documentation of such disorders.⁷ A recent case report implicated copper dust inhalation with acute lung injury.¹⁸⁹ Osmium tetroxide is a potent respiratory irritant with terrorist weapon potential; fortunately, to date experience with human inhalation exposure has been limited.¹⁹⁰ Cerium oxide is another metallic exposure of theoretical concern because of its potential use as a fuel additive and its capacity to cause acute inhalation injury experimentally.¹⁹¹

Two other metal compounds are well-documented bronchial irritants in humans. Vanadium (typically as a metal oxide), which is encountered in metal processing and, in lower concentrations, as a fossil fuel by-product, causes acute bronchitis.¹⁹² Among boilermakers, vanadium-rich fuel oil ash is suspected to be a key exposure related to acute respiratory symptoms.¹⁹³ In a single case report, high-intensity exposure to ash from an oil-burning furnace was associated with diffuse alveolar damage; although vanadium was detectable in the residue, the toxic mechanism in this case was unclear.¹⁹⁴ In another case report, vanadium (as vanadyl pyrophosphate) was linked to pneumonitis.¹⁹⁵ Tributyltin (bis[tributyltin] oxide) is an organotin compound, which is an organic compound with one or more molecules of tin. Tributyltin, which is employed as a mildew and mold retardant, is also an acute airway irritant.¹⁹⁶

METAL FUME FEVER, POLYMER FUME FEVER, ORGANIC DUST TOXIC SYNDROME, AND OTHER INHALATION FEVERS

There are a number of febrile flulike pulmonary syndromes reflecting similar clinical responses to a diverse group of acute inhalational exposures.^{22,197} Their hallmark is chills, fever, malaise, and myalgia with onset 4 to 8 hours after intense inhalation of fumes or organic dusts.^{22,167,198} Common respiratory complaints include cough or mild dyspnea, but findings of chest radiographic opacities or hypoxemia are inconsistent with this disorder. Peripheral leukocytosis usually accompanies the syndrome; bronchoalveolar lavage shows a marked influx of neutrophils.¹⁹⁹⁻²⁰¹ These syndromes all are self-limited, resolving clinically within 12 to 48 hours. Inhalation fevers share a common feature of tachyphylaxis, with a blunted response to daily repeated inhalation (and hence the name “Monday morning fever” among both brass founders and cotton mill workers).^{22,202,203}

Signs or symptoms of pneumonitis should suggest alternative, more serious diagnoses, such as cadmium pneumonitis,^{169,170} hypersensitivity pneumonitis (see Chapter 64), active infection (in the case of water-source aerosols), or

inhalation of more toxic temperature-dependent fluoropolymer combustion by-products (which include hydrogen fluoride and perfluorobutylene [PFIB], which is more toxic than phosgene).^{204,205,205a} Toxic pneumonitis due to fluorocarbon-containing aerosol sprays is an exposure scenario distinct from polymer fume fever from exposure to fluoropolymer combustion by-products or from acute lung injury and are dealt with separately (see later).

Metal fume fever is associated with zinc oxide inhalation from welding galvanized metal or brass working.²⁰⁶ There is only limited clinical evidence that other metals (magnesium and copper) are capable of causing a similar response,^{167,207} and experimental data further discount magnesium as a potential cause of fume fever.²⁰⁸ Zinc oxide fume rarely has also been purported to cause an acute lung pattern in case reports of welding-related illness, but the likelihood of cadmium or nitrogen dioxide co-exposures make this uncommon association questionable.²⁰⁹ Further, controlled experimental human exposure data do not support this as a zinc oxide inhalation effect.²⁰⁰

Polymer fume fever is associated with thermal breakdown products of fluoropolymers (e.g., Teflon and related materials).^{198,210-212} The pathophysiologic mechanisms underlying the metal and polymer fume fever syndromes have not been established, but research suggests that pulmonary cytokines may play a key role.²¹³⁻²¹⁶

Organic dust toxic syndrome (ODTS) is associated with inhalation of materials contaminated with thermophilic bacteria and fungal spores, including wood chips,²¹⁷ straw,²¹⁸ silage,²¹⁹ seeds,²²⁰ grains and flour,²²¹ and textile raw materials.²⁰³ The increasing industrialization of agricultural processes, especially the use of animal confinement techniques or so-called *concentrated animal feeding operations* (CAFOs), is an additional source of exposure leading to ODTS, although these same settings also can produce irritant gases such as hydrogen sulfide and ammonia.^{222,223} ODTS has gone by various names, including pulmonary mycotoxicosis,²²⁴ silo unloader's syndrome,²¹⁹ and mill fever.²²⁵ One of the best documented historical outbreaks of ODTS was among individuals who worked with contaminated cotton mattresses.²⁰³ Inhalation of aerosols from contaminated water sources produces a self-limited febrile syndrome similar to ODTS. Some of these outbreaks are attributable to inhalation of *Legionella* species without actual infection (i.e., without clinical evidence of pneumonia) and are referred to as “Pontiac fever.”²²⁶⁻²²⁸ Contaminated aerosols causing inhalation fever syndromes can originate from saunas or hot tubs,^{229,230} commercial (industrial) humidifying systems,^{231,232} and metal machining cooling fluids.²³³ Along with these heterogeneous exposure scenarios, a variety of different names have been used for these syndromes, including humidifier fever,²³² sump bay fever,²³⁴ and bath water fever.²²⁹ As with ODTS, many of the same occupational and environmental conditions can lead to or be concomitant with cases of hypersensitivity pneumonitis and, more specific to waterborne aerosols, active respiratory infection. In addition to its self-limited nature, a key characteristic differentiating an outbreak of inhalation fever from other syndromes is its relatively high attack rate over a fairly short time period. As with metal fume fever and polymer fume fever, cytokines are presumed to be key mediators of the ODTS and water-borne aerosol-related

inhalation fevers, with endotoxin and related factors being key exposure variables.^{22,235}

FLUOROCARBON AEROSOL SPRAY PNEUMONITIS

Acute lung injury following inhalation exposure to commercial fluorocarbon-containing aerosol products is an important emerging syndrome first reported in the early 1990s.²³⁶ This syndrome is distinct both from fluoropolymer fume fever as previously discussed and from exposure to irritant by-products from higher-temperature thermal breakdown of such polymers. A key feature of fluorocarbon aerosol pneumonitis is the onset of symptoms within several hours after using a spray product containing fluorocarbon polymers. Exposure can take place in an occupational setting (e.g., construction) or, commonly, from use of over-the-counter products. These exposures can be relatively brief, with varying degrees of ventilation; importantly, exposure need not be in an enclosed space. Victims usually do not recall previous exposure; there is nothing in the condition to suggest a hypersensitivity mechanism. Application of multiple types of fluorocarbon-containing products have been linked to outbreaks; although waterproofing leather and fabric sprays have dominated the reports, other products include floor stain protector, rust-proofing spray, grout sealer, and ski wax.²³⁶⁻²⁴³ The clinical presentations manifest a range of severity consistent with varying degrees of non-specific acute lung injury; management is based on standard support care. The various descriptive labels for this condition, such as “horse rug lung” and “hill walkers’ lung,” can obscure the consistent pattern of the syndrome.^{239,244}

HYDROCARBON PNEUMONITIS AND “FIRE-EATER’S” LUNG

Hydrocarbon pneumonitis can follow oral ingestion of hydrocarbons and associated hydrocarbon aspiration. In the pediatric high-risk age group, aspiration can take place during ingestion from non-tamper-proof containers typically involving mineral spirits, mineral seal oil (common in furniture polish), lamp oil, kerosene (paraffin), turpentine (pine oil), gasoline, and lighter fluid.^{19,245-247} In adults, hydrocarbon aspiration associated with fuel syphoning represents an occupational hazard among diesel-powered heavy equipment and tractor operators.^{248,249} Even though these substances have systemic toxic effects such as central nervous system depression, life-threatening complications of ingestion are predominantly the result of concomitant hydrocarbon aspiration and subsequent pulmonary compromise, making the lung the target organ of concern in hydrocarbon ingestion. Pneumatocele is a recognized complication of hydrocarbon pneumonitis.²⁵⁰ In contradistinction to aspiration hydrocarbon pneumonitis, the toxicity of hydrocarbon (solvent) vapor inhalation manifests primarily in either central nervous system or cardiac effects. Major pulmonary target organ damage associated with acute hydrocarbon exposure by inhalation is unusual but has been reported.²⁵¹ Importantly, the lung also appears to be the target organ for the toxicity of intravenously administered hydrocarbons, an unusual but well-documented suicidal scenario.²⁵²

“Fire-eater’s lung” is an important variant of hydrocarbon pneumonitis.^{253,254} This syndrome typically involves adolescents or young adults becoming exposed through mishap during flame-blowing performances using a variety of different flammable materials. In addition to kerosene and gasoline, the toxicants include jet fuel and, in France, an aromatic hydrocarbon-enriched petroleum-distillate called “kerdan.”^{255,256} There has also been a case of citronella oil aspiration in a fire-eater.²⁵³ As with hydrocarbon pneumonitis in children, fire-eater’s lung can also be complicated by pneumatocele.²⁵⁷ Although the term *acute lipoid pneumonia* has been used to refer to the fire-eater’s lung syndrome, as well as in other acute aspirations, this is a misnomer.²⁵⁸

In both childhood and adult pneumonitis, hydrocarbons are aspirated at the time of the initial ingestion or subsequently with vomiting. The low viscosity of an ingested hydrocarbon is considered a major factor promoting aspiration, presumably for mechanical reasons.^{19,246} Although it has been theorized that hydrocarbon toxicity may involve disruption of surfactant, the chemical pneumonitis of the syndrome appears to be nonspecific.

PARAQUAT

Paraquat is a widely used herbicide and a potent toxin. Ingestion, rather than inhalation, is the typical route of exposure associated with human toxicity. There have been systemic reactions following skin exposure after direct exposure to the skin (e.g., soaking of the skin with paraquat) or when the skin integrity has been breached (e.g., preexisting skin lesions or burn). The theoretical risk of smoking contaminated materials has never been established.

Most paraquat deaths result from suicidal intent.^{20,259,260} Paraquat ingestion is a relatively uncommon method of suicide in the United States, but its incidence is greater in a number of other countries, perhaps related to patterns of crop utilization and ease of access.^{259,261} Although paraquat ingestion leads to acute gastrointestinal tract necrosis and multiorgan failure, the lung is the target organ for toxicity among those surviving the immediate postingestion period. Diquat, a related dipyridyl herbicide, does not cause the lung injury associated with paraquat, although poisoning can lead to renal failure and cerebral hemorrhage.²⁶²

The pulmonary toxicity of paraquat, in contrast to its gastrointestinal effects, does not reflect caustic irritant injury. The major lung effect of paraquat toxicity is the development of pulmonary edema, usually observed 24 to 48 hours after ingestion. The pulmonary edema may evolve to a condition resembling acute respiratory distress syndrome, associated with histopathologic findings similar to those of diffuse alveolar damage, which may progress to an accelerated, chemically induced pulmonary fibrosis. After stabilization following acute multiorgan toxic effects, disease progression is marked by rapidly worsening respiratory distress, hypoxemia, and a restrictive ventilatory defect, with decreased lung compliance and diffusing capacity, ending in death from ventilatory failure within days to weeks.^{20,259} Survivors may demonstrate modest and slow improvement in lung function.²⁶³

The mechanism of paraquat toxicity is attributed to the generation of superoxide radicals that may be partly iron dependent. Consistent with an oxidant mechanism, supplemental oxygen and radiation therapy may worsen the outcome; there are no known antidotes for paraquat poisoning, and enhanced elimination as by hemoperfusion has not demonstrated a clear benefit.^{20,259} Plasma paraquat levels can be determined and may have a use in predicting outcome.²⁶⁴ Data suggest a possible therapeutic benefit from immunosuppression, but this awaits confirmation through controlled clinical trials.^{21,259} Death results from multiorgan failure, which usually happens within 1 to 2 weeks but may be observed up to 6 weeks after ingestion.

SMOKE INHALATION

The generic term *smoke inhalation* includes potential exposure to a wide array of substances because of the complex chemistry of heat decomposition and pyrolysis.^{34,265} *Pyrolysis* refers to the thermal decomposition of organic material without the involvement of oxygen and is a common component of burning buildings where oxygen is limited. Pyrolysis produces a variety of gases and a physical product such as charcoal. Although anoxia from carbon monoxide, cyanide, and oxidants represents a major manifestation of toxic insult from acute smoke inhalation, this nonpulmonary target organ effect is not covered here. However, a number of chemical irritants produced as pyrolysis by-products do have significant potential pulmonary toxicity. In contrast to thermal injury to the respiratory tract, which is typically limited to upper airways, with laryngeal edema the major potential medical management problem,^{266,267} inhalation of the smoke from fires can affect the entire respiratory tract through irritant injury.

In certain cases, irritant chemicals from fires are released as preformed substances but, most commonly, the toxins are formed *de novo*. These irritants are produced by the thermal degradation of both natural and synthetic polymers. The predominant by-products of heat breakdown are determined by the nature of the polymers consumed, temperature of the fire, and availability of oxygen.²⁶⁸

Generally, polymers do not break down to their monomer precursors, although residual monomers can be evolved under certain circumstances. For example, when polyvinyl chloride is burned, hydrogen chloride is released rather than the monomer, vinyl chloride. Many of the specific chemical irritants that can be released as common thermal breakdown by-products are addressed elsewhere in this chapter. These include the following: hydrochloric acid (hydrogen chloride), hydrofluoric acid (hydrogen fluoride), and other acids; ammonia; phosgene; and oxides of nitrogen. The zinc chloride “smoke” of smoke bombs (in contrast to the heterogeneous character of “natural smoke”) is also discussed separately.

Aldehydes merit specific attention. They are a common cause of high-intensity irritant lung injury from the smoke from fires. These chemicals include formaldehyde, acetaldehyde, and acrolein. The most severe irritant, *acrolein* ($\text{CH}_2 = \text{CHCHO}$), is least familiar to most health care providers. Acrolein, a highly reactive chemical and key toxicant in smoke inhalation injury, is formed as an important pyrolysis product of both synthetic (e.g., acrylic) and natural poly-

mers.^{269,270} In addition to *de novo* formation as a combustion by-product, acrolein is also intentionally manufactured and used as a pesticide; its use as an aquatic herbicide to facilitate water flow in irrigation canals can lead to human inhalation exposure with irritant effects.²⁷¹

The general considerations concerning irritant exposure discussed previously, including air concentration and water solubility, come into play in smoke inhalation. These factors are further complicated by the potential interactive effects of multiple simultaneous exposures, as well as the modifying impact of physical cofactors such as airborne respirable particulates (e.g., soot) that may serve as adsorbent carriers facilitating deep lung penetration. In practice, detailed exposure data delineating the irritant contents of a specific smoke exposure are rarely available. Information that may help to elucidate exposure conditions include identity of the products involved (e.g., specific synthetic polymers, if known), history of inhalation within an enclosed or confined space, evidence of thermal injury, and carboxyhemoglobin and methemoglobin levels as markers of inhalation severity based on other concomitant exposures (carbon monoxide and oxidants).

Firefighters (both urban and wildland) and nonoccupationally exposed victims of irritant smoke inhalation have proved to be important groups in which to study acute inhalational syndromes. Large-scale conflagrations (e.g., urban “wildland” fires^{271a,271b}) can expose substantial numbers of people to irritant combustion by-products, as can smoke drift from intentional burning of agricultural residue. Studies of such populations after smoke inhalation have demonstrated acute and persistent airflow obstruction and increased nonspecific airway hyperresponsiveness.²⁷²⁻²⁸⁰ Bronchiectasis and BO have both been associated with combustion by-product exposure.^{55,57} The acute respiratory effects and potential sequelae of exposure to the plume generated by the destruction of the World Trade Center may relate to other factors such as alkaline (high-pH) dust from concrete, gypsum, and glass fibers, rather than to standard smoke particulate.²⁸¹

PHARMACOLOGIC SYNDROMES

Certain natural and synthetic chemical exposures affect the lung by specific mechanisms consistent with known pharmacologic actions. These chemicals are site-specific for key cellular functions leading to adverse respiratory effects. As noted previously, the most potent chemical warfare agents act through acetyl cholinesterase inhibition, with profound impacts on respiratory function.^{151,152} Similar, albeit less potent, agents have widespread use as agricultural chemicals. Both organophosphate and carbamate pesticides lead to respiratory compromise as a principal toxic effect. For example, in one case series, a considerable number of poisonings from these pesticides led to respiratory failure, accompanied by a high case-fatality rate; in contrast, all the patients without concomitant respiratory failure survived.²⁸²

Inhaled capsaicin, of interest as a research tool to study substance P-mediated effects, is associated with cough in occupational settings (e.g., in chili pepper processing).²⁸³ When used as a “personal defense spray,” respiratory irritation has been reported, although ocular problems are more

common.^{284,284a} Brevetoxin is a toxin produced by dinoflagellates associated with “red tides.” Environmental inhalation exposure from airborne aerosols of red tide due to wind and surf action causes cough, sneeze, and wheeze.²⁸⁵⁻²⁸⁷ For lifeguards, brevetoxin health effects represent a source of occupational respiratory morbidity, including work loss.²⁸⁸ The toxin appears to act by stimulating sodium channels in the lung. Respiratory irritation may also be a manifestation of *Pfiesteria* dinoflagellate toxin inhalation (although potential neurotoxicologic effects have been of more concern).^{289,290}

OTHER INHALANT EXPOSURES

Ammonia

Anhydrous ammonia is a gas at room temperature and ambient pressure, although ammonia is more commonly encountered in aqueous form, as in cleaning solutions. Potential sources of ammonia gas exposure include incidents in the chemical industry and in hazardous transportation, commercial refrigeration systems, and farming (e.g., fertilizer).^{7,291-295} Anhydrous ammonia has also been released from illicit methamphetamine laboratory operations, although such exposures are often in the context of conflagrations with concomitant thermal burns and other coexposures.^{296,297} Ammonia has prominent irritant warning properties (such as burning eyes). It is linked with lung injury chiefly in settings of overwhelming exposure or where immediate escape has not been possible. Both asthma and bronchiectasis have been documented after ammonia exposure.^{7,294} Acute ammonia exposure has also been reported to have residual upper airway effects, including decreased olfactory acuity.³⁷ Death may result from laryngeal edema and airway obstruction, acute pulmonary edema, or complications of the pneumonic process (e.g., bacterial superinfection). A case of lung transplantation within a year after ammonia inhalation has been reported.²⁹⁸

Bromine and Methyl Bromide

Bromine is an irritant halogen. It is usually handled as a liquid rather than as a gas, but it vaporizes readily. Sources of bromine exposure other than environmental releases include chemical synthesis and water purification.^{58,299-302} Bromine is a more potent irritant than chlorine and approximately 100 times more irritating than ammonia.³⁰³ *Methyl bromide* is a major industrial fumigant with far-greater potential for public exposure. Methyl bromide is also a potent respiratory irritant, but the central nervous system may represent the more important target organ in typical exposures.^{304,305}

Hydrogen Sulfide

Hydrogen sulfide is a common by-product of petroleum extraction and refining, as well as a potential hazard from the breakdown of organic materials (hence, its common name, “sewer gas”); overexposure can result from work in confined spaces, submersion in manure pits,³⁰⁶ or proximity to geothermal and volcanic sources.³⁰⁷ Hydrogen sulfide is a respiratory irritant, but it is an even more potent cytotoxic asphyxiant, impairing cytochrome oxidase and cellular respiration. Therefore, in cases of severe hydrogen sulfide exposure, rapid cardiovascular collapse and death often

overshadow any pulmonary organ effects, although an acute lung injury pattern can be present in those surviving long enough to receive intensive supportive care; irritant symptoms as a predominant feature may be of greater relevance in lower-intensity exposures.^{306,308-311}

Methyl Isocyanate and Methyl Isothiocyanate

Methyl isocyanate (MIC) use is restricted to a narrow industrial application in the synthesis of pesticides. The mass fatalities at Bhopal, India, make MIC an important toxin for historical reasons. The toxicity of MIC was the result of its severe irritant properties leading to pulmonary edema.³¹²⁻³¹⁴ No cyanide-mediated mechanism was involved. Methyl isothiocyanate, a breakdown product of the soil fumigant metam sodium, is an irritant chemically related to MIC that was also involved in a mass exposure episode, although less severe than the MIC release at Bhopal, and has also been associated with respiratory symptoms following agricultural application.^{315,316} The isocyanates associated with urethane, such as *toluene diisocyanate* (TDI), *diphenylmethane diisocyanate* (MDI), and *hexamethylene diisocyanate* (HDI), are pulmonary irritants but are primarily of concern because of their induced sensitization (see Chapter 72).

MISCELLANEOUS EXPOSURES

A number of other occupational and environmental agents result in acute pulmonary syndromes. Examples of such exposures include diethylaminoethanol and cyclohexylamine (both anticorrosive boiler additives)^{317,318}; amitrole and glyphosphate (both common herbicides)^{319,320}; sodium azide (used in a variety of chemical applications but important as a potential inhalant through automobile airbag deployment)³²¹; diazomethane, which is explosive but also highly toxic to the lung with a delayed onset similar to that of nitrogen dioxide^{322,323}; diborane (an irritant gas used in manufacturing microelectronic equipment)^{324,325}; barium (inhalation can cause bronchospasm and respiratory muscle weakness in addition to life-threatening hypokalemia)³²⁶; and hydrogen selenide (an irritant gas used in several industrial processes, as well as being a potential metal processing by-product).^{327,328} A recent outbreak of severe lung injury in Korea was linked to the room humidifier water being treated with two biocides: *polyhexamethyleneguanidine* (PHMG) and oligo(2-(2-ethoxy)ethoxy-ethyl) guanidinium chloride.^{329,329a}

Phosphine is an important agricultural fumigant with pulmonary and systemic toxicity that is generated on site as a gas given off by moisture coming in contact with solid form aluminum or zinc phosphide (e.g., in grain storage facilities or railway grain transport cars, where bystanders can be exposed).^{330,331} Ingestion of the parent material by animals can also lead to exposure among treating veterinary personnel.³³² Phosphine also has industrial applications, particularly in the production of microelectronics. Acetic anhydride (used in making epoxy and other resins) has also been associated with acute lung injury following acute inhalation.³³³ A distinctly different pattern of injury is associated with a related epoxy chemical, trimellitic anhydride, which causes severe pulmonary hemorrhage after subacute exposure.¹³ Carbon dioxide, although a bulk asphyxiant and not a respiratory irritant, causes shortness

of breath and induces tachypnea; people can be exposed through natural geologic sources and dry ice sublimation in an enclosed space.³³⁴⁻³³⁶ Baby (talcum) powder inhalation can cause a pediatric acute pneumonitis within hours of heavy exposure; infant inhalation of nontalcum powders has also led to pneumonitis.³³⁷⁻³³⁹ Paraphenylenediamine is a dye used to color hair and can also be admixed with henna as a temporary tattooing agent; its ingestion as an agent of self-harm is common in Asia and Africa. In addition to rhabdomyolysis and renal damage, this chemical has a particular propensity to cause angioedema leading to airway obstruction.²³

Naturally occurring sources of exposure can also be associated with acute and subacute lung responses, although these syndromes are poorly characterized. Epidemiologically, *Stachybotrys chartarum* (atra) mold growth in water-damaged residential structures was initially linked to a cluster of cases of pulmonary hemorrhage in infants, although the association was later retracted in a follow-up review by the U.S. Centers for Disease Control and Prevention.^{340,341} Other case reports have occasionally linked other molds or mold by-products with lung injury (as opposed to self-limited ODTs, discussed previously).³⁴²

Lycoperdonosis is a potentially severe, acute pulmonary syndrome following intentional inhalation (sometimes as a natural medicinal treatment) of puffball mushroom (*Lycoperdon*) spores; in addition to human illness, fatal inhalation in pet dogs is a well-characterized veterinary syndrome.³⁴³⁻³⁴⁵ The pathophysiology of the syndrome is not understood, but its high attack rate with heavy exposure suggests a toxic rather than an allergic or infective mechanism.

Key Points

- Short-term inhalation exposures to toxic substances have important effects on the lung as the target organ for damage.
- Acute lung toxicity results from a variety of exposures but, nonetheless, is manifest by a narrow repertoire of injury.
- Although modified by the solubility and other physical properties of the toxic agent, injury largely depends on the intensity and duration of exposure.
- Extensive injury can lead to acute pulmonary edema and diffuse alveolar damage.
- Specific exposures of importance include chlorine, oxides of nitrogen, sulfur dioxide, acid aerosols, toxic metal fumes, and pyrolysis by-products.
- Aside from acute irritant or toxic lung insult leading to airway injury and diffuse alveolar damage, other patterns of acute responses include the inhalation fevers (which are self-limited and appear to be cytokine-mediated) and certain target-specific effects, such as those elicited by cholinesterase inhibition.
- Exposure by *ingestion* of some substances (e.g., hydrocarbons and paraquat) can cause important acute pulmonary target organ toxicity.

Complete reference list available at *ExpertConsult*.

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Useful Resources for Information about Specific Toxins

- National Library of Medicine's TOXNET (<http://toxnet.nlm.nih.gov/>) is a web-based collection of resources covering toxicology, chemical safety, environmental health, and related areas.
- The Household Products Database (<http://householdproducts.nlm.nih.gov/>) is a consumer guide that provides information on the potential health effects of chemicals contained in more than 7000 common household products used inside and around the home.
- Tox Town (http://toxtown.nlm.nih.gov) is an interactive guide to commonly encountered toxic substances, public health, and the environment.
- TOXMAP (http://toxmap.nlm.nih.gov) is an interactive mapping site that helps users explore the geographic distribution of certain chemical releases, their relative amounts, and their trends over time.
- Haz-Map (http://hazmap.nlm.nih.gov) is an occupational health database designed for health and safety professionals and for consumers seeking information about the health effects of exposure to chemicals and biologics at work.
- WISER (Wireless Information System for Emergency Responders) (http://wiser.nlm.nih.gov) is a system designed to assist first responders in hazardous material incidents.

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THORACIC TRAUMA**INTRODUCTION**

Among trauma victims, thoracic trauma is the second most common cause of death in the field and the third most common cause of death in patients who make it to the hospital. In civilian trauma, the most common mechanism is blunt trauma and the most frequently encountered injuries (i.e., hemothorax and pneumothorax) are seen in 20% of patients.¹ The majority require only tube thoracostomy for definitive treatment; however, up to 15% of these patients will require operative intervention,¹ whether immediate (resuscitative), urgent, or delayed. Overall mortality in patients with thoracic trauma is about 10%, with a low Glasgow Coma Scale score exerting the strongest influence on mortality.¹ Additional predictors of poor outcomes include increasing age, mechanism of blunt injury, increasing number of ribs fractured, and concomitant long bone extremity fractures.¹

INDICATIONS FOR RESUSCITATIVE THORACOTOMY

Patients who arrive without signs of life may benefit from *emergency department thoracotomy* (EDT) or “resuscitative” thoracotomy depending on the amount of time elapsed since the loss of vital signs (<15 minutes for penetrating trauma; <10 minutes for blunt trauma).^{2,3} The goal of this procedure is to restore spontaneous circulation by rapid repair of intrathoracic injuries or release of pericardial tamponade, and occlusion of the descending thoracic aorta to divert perfusion to the brain and heart. Internal cardiac massage with injection of intracardiac medications may also be indicated. In cases of bronchovenous air embolism, clamping of the pulmonary hilum prevents further propagation. Because resuscitative thoracotomy should always proceed to the operating room for definitive repair, it should not be attempted without a surgeon immediately available. Rhee and colleagues reported that the overall survival rate after EDT is 7.4%, with a survival rate of 15% among all patients with penetrating injuries and 35% among patients with penetrating cardiac injuries.⁴ On the contrary, survival rates are very low (2%) after blunt traumatic arrest.⁴

It is important to perform an initial cardiac ultrasound, because EDT can be considered futile if asystole is the presenting rhythm and pericardial tamponade is absent.³ In patients with appropriate indications, aggressive efforts are justified, because functional long-term outcomes in survivors are excellent. More than half of survivors are discharged home from the hospital, and more than 75% have normal cognition, are ambulatory, and have no evidence of posttraumatic stress disorder.⁵ However, inappropriate EDT results in no survival benefit, wasted use of resources, and exposure of health care workers to needle-stick and bone fragment injuries.⁶

INDICATIONS FOR URGENT THORACOTOMY

Commonly accepted indications for urgent thoracotomy include any of the following: initial chest drain output of 1500 mL; greater than 1500 mL output in the first 24 hours after injury; more than 200 mL bloody output per hour for 3 consecutive hours; massive air leak (present during all phases of respiration, associated with inability to reexpand the lung or affecting ventilation secondary to loss of tidal volume); or hypotension.⁷ Rarely, a patient has sudden cardiovascular collapse or new neurologic symptoms, typically after the patient is placed on positive pressure ventilation, that are consistent with air embolism and require urgent thoracotomy.

INDICATIONS FOR DELAYED THORACOTOMY

Delayed thoracotomy is performed several days after injury in stable patients, usually for retained hemothorax, trapped lung, persistent air leak, or rib fixation (discussed later).

THORACIC CAGE INJURIES**Rib Fractures**

Rib fractures are seen in 10% of hospitalized trauma patients.^{8,9} The morbidity of rib fracture pain is underappreciated; one third of patients require hospitalization for pain control, and pneumonia develops in another third of these patients.¹⁰ The true incidence of rib fractures is likely higher, in that, a supine chest radiograph is, at best, about

Table 76-1 Chest Wall Trauma Scoring System

Age (years)	Number of Rib Fractures
<45 = 1 point	<3 = 1 point
45-65 = 2 points	3-5 = 2 points
>65 = 3 points	>5 = 3 points
Score: _____	Score: _____
Pulmonary Contusion	Bilateral Rib Fractures
None = 0 points	No = 0 points
Mild = 1 point	Yes = 2 points
Severe = 2 points	Score: _____
Bilateral = 3 points	
Score: _____	
Total Score: _____	

From Pressley CM, Fry WR, Philp AS, Berry SD, Smith RS. Predicting outcome of patients with chest wall injury. *Am J Surg* 204:910-914, 2012.

50% sensitive for detecting rib fractures. Chest *computed tomography* (CT) (eFig. 76-1) is much more sensitive and can also evaluate for other occult injuries.⁸ In general, ribs tend to fracture at their weakest structural point (the posterior angle) or directly at the point of impact.¹¹ They are rarely the sole injury, and 50% of patients with rib fractures have other significant injuries.¹⁰ In a patient with lower rib injury (9th through 12th), abdominal solid organ injury (spleen or liver) should be ruled out.

Pressley and colleagues developed a simple scoring system based on initial clinical findings (age, number of fractured ribs, severity of *pulmonary contusion* [PC], unilateral vs. bilateral rib fractures), to predict the likelihood of requiring mechanical intubation or *intensive care unit* (ICU) admission¹² (Table 76-1). The authors found that a patient with a score of 7 or 8 had a high probability of death, need for ICU admission, and a need for mechanical ventilation. Similarly, a score of greater than 5 predicted the need for a longer hospital stay and prolonged mechanical ventilation. Other studies found that an increasing number of rib fractures correlates to increasing *ICU length of stay* (LOS), hospital LOS, and mortality.^{13,14}

Treatment for the vast majority of patients with rib fractures is supportive care, consisting of aggressive pain control and pulmonary rehabilitation. Deep breathing facilitates clearance of secretions to reduce the incidence of pneumonia. Analgesic options include oral analgesics (including opioids), intermittent intravenous analgesics, patient-controlled analgesia, *thoracic epidural analgesia* (TEA), intrapleural blocks, intercostal blocks, and thoracic paravertebral blocks.¹⁵ Non-opioid analgesic options include acetaminophen, nonsteroidal anti-inflammatory drugs (including ketorolac), anticonvulsants such as gabapentin, and topical lidocaine patches.¹⁶ Numerous small, single-center trials have reported that pain control with TEA, compared with intravenous opioids, results in superior outcomes as measured by less pain, improved pulmonary function, fewer ventilator days, fewer infections, fewer pulmonary complications, shorter ICU LOS, and shorter hospital LOS.¹⁷⁻²⁴ Furthermore, TEA may also attenuate the postinjury inflammatory response.^{22,25} At present, TEA is the preferred analgesic modality for pain secondary to blunt

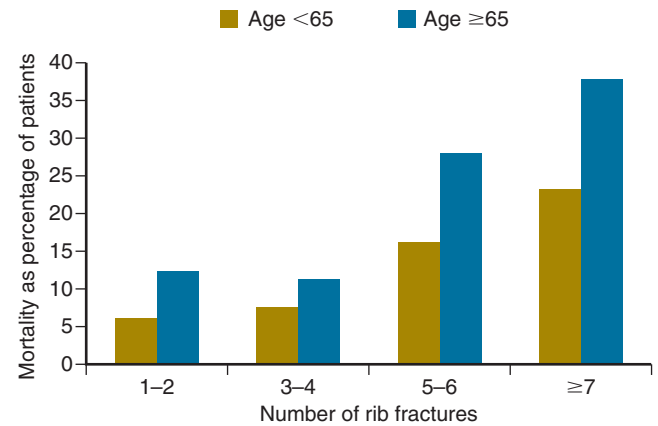


Figure 76-1 Relationship between the number of rib fractures and mortality. In a retrospective study of patients admitted to trauma centers, mortality increased with increasing number of rib fractures, an easily quantifiable measure of trauma severity. At each number of rib fractures, mortality for those older than 65 years was greater than that for those younger than 65. (From Stawicki SPG, Michael D, Hoey, Brian A, et al: Rib fractures in the elderly: a marker of injury severity. *J Am Geriatr Soc* 52:805-808, 2004.)

thoracic injury.²⁶ However, TEA is underused, with studies reporting less than 30% TEA use in eligible patients.²⁷ Epidural analgesia is not without risk, though, and side effects include hypotension, epidural hematoma, urinary retention, and epidural abscess.

Interestingly, a recent pooled meta-analysis did not find any benefit of TEA for duration of mechanical ventilation, ICU LOS, hospital LOS, or mortality.²⁸ For epidural analgesia to be of benefit, appropriate patient selection is paramount. Although absolute number of fractured ribs is predictive of the need for TEA, it is important to examine the patient carefully to determine whether pain is severe enough to cause respiratory embarrassment. In fact, one review reported that epidural analgesia was associated with *increased* complications and prolonged LOS in older patients.²⁹

Another underused analgesic option is the *thoracic paravertebral block* (TPVB) or paravertebral catheterization, which is easy to learn, has a greater than 90% success rate, and has a low incidence of side effects.^{30,31} When successful, TPVB has been shown to improve pain scores and pulmonary function tests.³² TPVB provides unilateral pain relief and thus is usually used only for patients with unilateral rib fractures; however, it is also useful when there are contraindications to TEA, such as coagulopathy, spinal fractures, or altered mental status.

In addition to pain control, a formalized multidisciplinary pathway that includes aggressive respiratory therapy and nutritional support has been shown to decrease ventilator days, LOS, infectious morbidity, and mortality among patients older than age 45 years with more than four fractured ribs.³³

Older patients with rib fractures are at especially high risk for complications: 15% require intubation, and pneumonia develops in up to 31%³⁴⁻³⁶ (Fig. 76-1). In patients older than age 45 years, morbidity sharply increases when more than four ribs are fractured.³⁷ Bulger and coworkers reported that patients older than 65 years with fractured ribs have double the morbidity and mortality rates compared with

younger patients with similar injuries.²⁷ Bedside vital capacity measurement can predict hospital LOS and identify those patients requiring discharge to an extended care facility.³⁸

Nonunion results in a small percentage of rib fractures and can manifest as chronic pain and discomfort.¹⁰ Typically, follow-up demonstrates that a significant proportion of patients have chronic persistent pain and impairment of both work and personal life.³⁹ In one study, patients with rib fractures had more disabilities at 30 days after injury than did patients with chronic medical illness. These patients with rib injuries missed an average of 70 days of work.⁴⁰ Two months after injury, more than 75% of patients with rib fractures reported some form of disability.⁴¹ Interestingly, the single most important predictive factor for long-term disability after rib injury was the initial intensity of pain. The total number of rib fractures and injury on both sides was not predictive.⁴¹

Flail Chest. A flail chest, also known as “stoved-in” or “crushed” chest, is the most severe form of blunt thoracic injury (see Chapter 98). The mortality associated with flail chest is up to 40%.⁴² Radiographically, it is defined as three or more consecutive ribs fractured in at least two locations. Clinically, a flail chest manifests as paradoxical incursion (rather than excursion) of the “floating segment” of chest wall during inspiration (Videos 76-1 and 76-2). Due to the significant energy transfer required to produce this injury, flail chest is almost universally accompanied by PC.

The management of flail chest has evolved over the past half century. Previously, it was believed that the paradoxical chest wall movement was the cause of the respiratory failure and hypoxia. Now, it is understood that the respiratory impairment is due to the underlying pulmonary parenchymal injury. Historically, efforts were focused on correcting the paradoxical motion through external stabilization (“sandbagging”), and later, “internal pneumatic stabilization” (i.e., positive pressure ventilation).^{43,44} Hence, in the mid-twentieth century, the predominant treatment method for all patients with flail chest was mechanical ventilation. Starting in the mid 1970s, some physicians found that these patients could be adequately managed without ventilatory support. It was at this time that it was recognized that the underlying PC rather than the chest wall instability was the driving factor in outcome.⁴⁵ Currently, less than half of patients with flail chest require mechanical ventilation.⁴⁶ Abnormal gas exchange, not chest wall movement, should drive the decision to mechanically ventilate a patient with flail chest.⁴⁷

In the modern management of flail chest, optimal pain control is paramount. According to the Eastern Association for the Surgery of Trauma practice management guidelines, TEA is the preferred pain treatment modality in the treatment of flail chest.⁴⁸ When an epidural catheter is contraindicated, TPVB may be considered. If mild to moderate respiratory compromise is present, a trial of noninvasive ventilation in conjunction with TEA may be considered before proceeding to endotracheal intubation. However, in the absence of respiratory embarrassment, mechanical ventilation to treat paradoxical chest wall motion is not recommended.

Surgical fixation of the “floating” chest wall segment has been practiced for decades in Europe and Asia, but is underused in the United States, likely due to a combination of relative unfamiliarity with the procedure itself and unfamiliarity with the evidence supporting the procedure. In a survey of trauma surgeons, orthopedic surgeons, and thoracic surgeons, only 26% had ever performed or assisted on the procedure and most were unaware of the published randomized trials supporting its use.⁴⁹ European and Asian studies report clinical benefit, yet the quality of evidence is poor and consists mainly of small, observational single-center studies.⁵⁰⁻⁵² To date, three randomized controlled studies and a meta-analysis evaluating surgical fixation in patients with flail injury have been published supporting rib fracture fixation.⁴³ Tanaka and colleagues reported that patients who underwent internal fixation of their fractured ribs benefited by less mechanical ventilation, lower incidence of pneumonia, shorter ICU LOS, improved pulmonary function, and quicker return to employment.⁵³ Granetzny and coworkers also reported decreased need for mechanical ventilation, shorter ICU LOS, and lower incidence of pneumonia in patients randomized to operation.⁵⁴ Most recently, Marasco and associates demonstrated decreased ICU LOS and decreased need for tracheostomy in patients randomized to operative repair of flail chest, with no difference in duration of invasive mechanical ventilation.⁴⁶ The optimal time for operative intervention is currently unknown and no trial has compared surgical fixation with modern nonoperative management with TEA and chest physiotherapy. An economic analysis based on reported incidences of complications and outcomes concluded that, despite the additional cost of surgery, rib fixation for flail chest remained cost-effective compared with nonoperative management.⁵⁵

Numerous techniques are described for rib fracture fixation, including the use of wire suture, staples, metal or absorbable plates, and screws.¹⁰ A case-control study reported by de Moya and colleagues concluded that rib fracture fixation significantly decreased the need for analgesia.⁵⁶ Infection of rib fixation hardware is uncommon, reported to be approximately 2%.¹⁰

Rescue therapies such as single lung ventilation and high-frequency oscillatory ventilation may be considered when traditional mechanical ventilation fails to improve oxygenation. However, there is no evidence to support routine use of these treatment modalities.

The long-term outcome of flail chest managed nonoperatively is marked by disability, with 70% of patients reporting dyspnea and more than 50% reporting chronic chest wall pain.^{48,57} Less than half of patients are able to return to work.⁵⁸

Sternal Fractures. The most common cause of sternal fracture is motor vehicle crash (eFig. 76-2).⁵⁹ The presence of sternal fractures has traditionally been considered a marker of injury severity, especially in previous decades when seatbelt use was not as widespread. As such, some advocate for hospital admission and close monitoring to rule out other serious injuries, such as blunt cardiac injury. Others report that sternal fracture, ipso facto, is not a significant cause of morbidity or mortality, and many believe that morbidity is mainly attributable to other associated

injuries.⁵⁹⁻⁶² With increasing seatbelt use, the incidence of sternal fractures has increased while mortality has decreased.^{63,64}

In the initial workup of a patient with sternal fracture, it is important to rule out a blunt cardiac injury with a 12-lead electrocardiogram and serum troponin level. Arrhythmias, ST changes, heart block, signs of ischemia, and elevated troponin levels are considered abnormal screening tests and should be followed by a confirmatory echocardiogram; normal findings on electrocardiogram and initial troponin level essentially exclude the diagnosis of blunt cardiac injury.⁶⁵ Nuclear medicine studies are not useful in the diagnostic workup of blunt cardiac injury. As in rib fractures, adequate pain control is paramount in the treatment of sternal fractures. Sternal fracture fixation is rarely indicated.

Clavicle Fractures. The clavicle is an S-shaped bone that acts as a strut between the shoulder and the axial skeleton. It protects the apex of the lung, brachial plexus, and subclavian vessels. Clavicle fractures follow direct impact to the extremity or chest, and account for 44% of all fractures to the shoulder girdle.⁶⁶

Fractures of the middle third are the most common, accounting for 69% to 81% of all clavicular fractures.⁶⁶ Diagnosis of clavicle fractures requires some type of imaging, usually radiography, although many are only visualized on CT. Special radiographic views can be ordered to improve the evaluation for subtle fractures, fracture displacement, or sternoclavicular joint dislocations (eFigs. 76-3 and 76-4). These views include axillary views, 45-degree cephalic tilt, or a serendipity view, which is a 40-degree cephalic tilt.

Treatment generally is nonoperative, with a sling or figure-of-eight brace, and 2 to 6 weeks of immobilization, as well as avoidance of heavy lifting and contact sports for 4 to 6 months. Operative treatment is indicated for all open fractures, skin tenting that will result in an open fracture, and any neurovascular compromise. A recent Cochrane meta-analysis of eight trials involving 555 patients examined the difference between conservative treatment and surgical fixation among patients with fractures of the middle third of the clavicle. Unfortunately, due to heterogeneity between the studies and overall high risk of bias, no strong conclusions can be made and the authors concluded that the decision to operate must be made on a case-by-case basis.⁶⁷

LUNG PARENCHYMA INJURIES

Pulmonary Contusion

PC is a common injury, with an incidence of 30% to 75% in patients suffering blunt thoracic injury⁴⁸ and up to 17% of all trauma admissions. PC is most common after a blunt mechanism of injury, but can also manifest adjacent to a missile tract through lung parenchyma. At the microscopic level, the contused lung displays edema, alveolar and intraparenchymal hemorrhage, and atelectasis, which results in intrapulmonary shunting, ventilation-perfusion mismatch, and decreased lung compliance. This manifests as hypoxemia, hypercarbia, and increased work of breathing. The

full effects of PC may not be obvious immediately; however, clinically significant PC becomes apparent within 24 hours. The natural history of PC is progressive dysfunction over the first few days and resolution within a week.⁶⁸

Severe PC can produce systemic effects. Animal studies demonstrate that after unilateral contusion, there is capillary leak in both ipsilateral and contralateral sides. Both lungs develop increased edema and accumulation of inflammatory cells.⁶⁹ Inflammatory cytokines are increased both locally and systemically, and there is evidence of global immune dysfunction.⁷⁰⁻⁷³ Additionally, PC primes the immune system for an exaggerated response to a subsequent second hit, such as infection^{69,74} (Fig. 76-2). Trauma patients with PC have twice the rate of ventilator-associated pneumonia as those without PC.⁷⁵ At 6 years after injury, more than half of patients with PC have evidence of lung fibrosis on CT scan,⁷⁶ and long-term lung function can be compromised.³⁹

Because not all PCs are clinically significant, several authors have attempted to identify factors predictive of outcome. De Moya and associates developed a simple scoring system, combining the initial CT findings, Glasgow Coma Score, and number of fractured ribs, to predict the need for

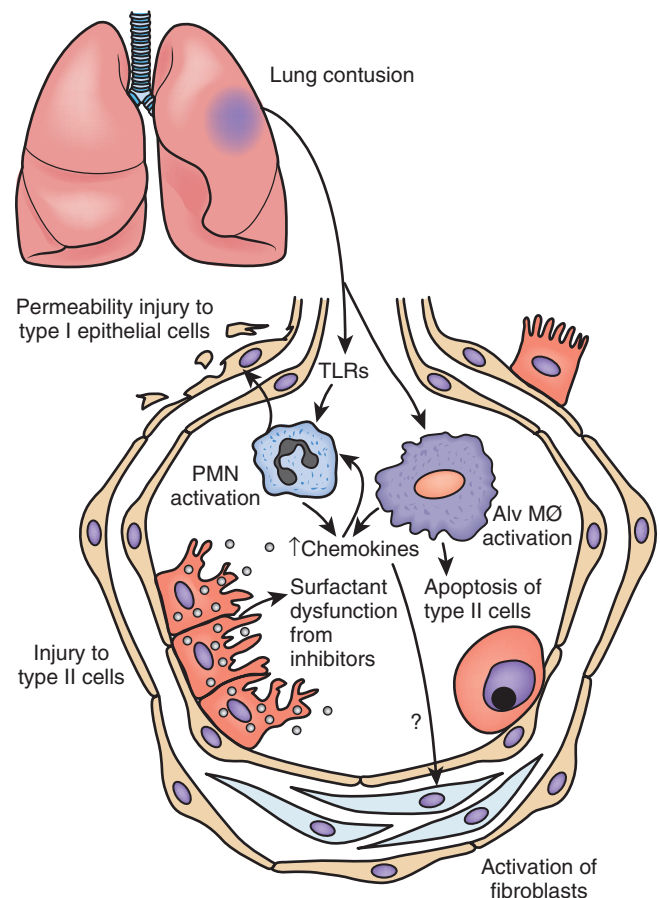


Figure 76-2 Inflammatory effects following pulmonary contusion. In the diagram, the potential interactions of the cells and mediators of the innate inflammatory response to contusion are shown. While this inflammatory mechanism may amplify the injury of the contusion, it may also provide potential targets for therapeutic intervention. TLRs, Toll-like receptors. (From Raghavendran K, Notter RH, Davidson BA, et al: Lung contusion: inflammatory mechanisms and interaction with other injuries. *Shock* 32:122–130, 2009.)

mechanical ventilation. Interestingly, in this study, less than one third of all PCs were evident on the initial chest radiograph (eFig. 76-5).⁷⁷ Other authors have questioned the significance of “occult” PC (i.e., apparent only on CT, eFig. 76-6). In a prospective study of 255 patients with PC, Deunk and colleagues reported that patients with occult PC fared no worse than those without PC, while those with PC seen on both chest radiograph and chest CT scan had significantly worse outcomes.⁷⁸ Others have attempted to correlate PC size (as a percentage of total lung volume) with outcomes. Studies have demonstrated that patients with PC volume greater than 20% of total lung volume are at increased risk for requiring mechanical ventilation, developing pneumonia, and developing *acute respiratory distress syndrome* (ARDS).⁷⁹

At this time there is no well-supported intervention to treat PC, and management consists mainly of supportive care and avoidance of iatrogenic injury. Steroids are not recommended and prophylactic antibiotics are strongly discouraged. Four decades ago, Trinkle and coworkers recognized that crystalloid administration increased PC size while diuresis decreased PC size.⁸⁰ Pharmacologic therapies being investigated include arginine vasopressin and dexmedetomidine.⁸¹ A recent animal study reported that dexmedetomidine infusion in a PC model improved hemodynamic parameters, decreased inflammatory infiltration, limited the extent of lung damage, and abrogated pulmonary edema.⁸² In patients with early, severe hypoxemia (arterial $PO_2/FIO_2 < 200$), a trial of noninvasive ventilation may be attempted in order to decrease the need for intubation; however, the development of pneumothorax must be carefully monitored.^{83,84} In animal studies, the application of positive end-expiratory pressure has been shown to decrease the size of PCs. Small clinical studies have reported that recruitment maneuvers are successful in improving aeration (“open lung” strategy).⁸⁵ In patients with PC, the use of airway pressure release ventilation has been reported to decrease the incidence of ventilator-associated pneumonia; however, experience and evidence is limited.⁷⁵ For severe, unilateral PC, lung isolation ventilation may be considered.⁸⁶ The use of rescue therapies such as high-frequency

oscillatory ventilation, surfactant administration, prone positioning, and extracorporeal membrane oxygenation for the treatment of PC is poorly studied and considered experimental at this time.⁸⁷⁻⁹⁰

In the management of PC, the patient should be resuscitated to maintain signs of adequate tissue perfusion. Once this has been achieved, however, meticulous attention should be paid to the avoidance of excessive fluid administration, to the point of using a pulmonary artery catheter if necessary to help guide diuretic therapy.⁴⁸ Aggressive pulmonary toilet and adequate analgesia are paramount in preventing pneumonia.

Pulmonary Laceration

Pulmonary laceration reflects tearing of the pulmonary parenchyma that disrupts the alveolar walls. Pulmonary lacerations result from several mechanisms, such as alternate compression and decompression of the chest wall or from a sudden, rapid increase in intrathoracic pressure with a closed glottis leading to high intra-alveolar pressure that produces shearing of pulmonary parenchymal tissue. Alternatively, pulmonary laceration may also result from direct puncture of lung tissue by a fractured rib, missile, or stab wound, or from shearing of lung tissue fixed by previously formed pleural adhesions. The disrupted pulmonary tissue fills with blood and/or air and manifests on thoracic imaging as one or more pulmonary parenchymal cavities (eFig. 76-7), appearing as gas-fluid levels, frequently with surrounding pulmonary consolidation and ground-glass opacity related to hemorrhage and atelectasis.

While only a small fraction of patients with thoracic injury ultimately require urgent thoracotomy, of those that proceed to surgery, about one third may require lung resection, usually to remove severely injured lung tissue, to control hemorrhage, or to remove irreparable proximal bronchus injuries.⁹¹ The extent of resection can range from simple, nonanatomic “wedge” resection, to formal anatomic lobectomy, to the extremely morbid pneumonectomy. For the majority of penetrating injuries, lung-sparing techniques such as simple suture or “tractotomy” are sufficient⁹¹⁻⁹³ (Fig. 76-3). Not surprisingly, there is a

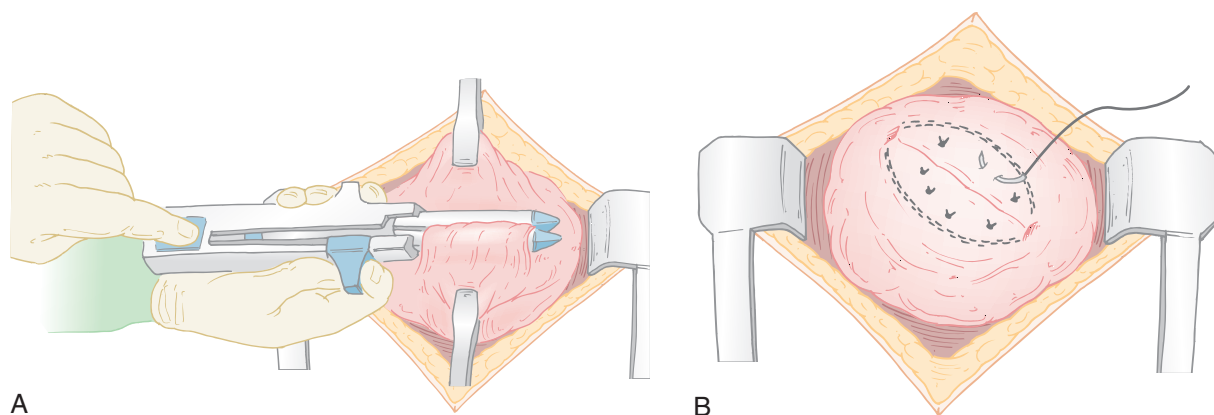


Figure 76-3 Lung-sparing “tractotomy” in which the tract of the penetrating injury is rapidly opened and injured vessels and bronchi ligated. **A**, The stapling device is advanced through the orifices of the entry and exit wound and is then closed and fired to staple the lung on either side and to open the tract (“tractotomy”) for visualization of the injured vessels and bronchi. **B**, The tractotomy exposes the bleeding vessels, which are then selectively ligated. The tractotomy approach preserves lung by avoiding wedge resection, lobectomy, or pneumonectomy. (From Asensio JA, Demetriades D, Berne JD, et al: Stapled pulmonary tractotomy: a rapid way to control hemorrhage in penetrating pulmonary injuries. *J Am Coll Surg* 185:486–487, 1977.)

stepwise increase in mortality with increasing extent of lung resection for trauma: wedge resection (19%), lobectomy (27%), and pneumonectomy (53%).

While most healthy patients can tolerate a wedge resection or lobectomy, pneumonectomy imposes a tremendous physiologic burden and patients may succumb to right ventricular failure. Using a porcine model, Cryer and colleagues demonstrated that pulmonary vascular resistance increases up to 500% within 4 hours after pneumonectomy.⁹⁴ Postoperative complications in survivors are common, and include pneumonia, bronchopleural fistula, empyema, or erosion into the pulmonary artery.

Bronchopleural Fistula

A bronchopleural fistula is a direct connection between the bronchus and atmosphere by way of the pleural space and tube thoracostomy. While most heal spontaneously, a persistent bronchopleural fistula may seriously impair the ability to ventilate a patient secondary to loss of tidal volume through the fistula. It is believed that air flowing through the fistula impedes healing and therefore medical therapies are aimed at reducing bronchopleural fistula flow.

Nonsurgical treatments include minimizing airway pressures (via lower tidal volumes, positive end-expiratory pressure, and inspiratory time), application of positive intrapleural pressure through the chest tube, isolated contralateral lung ventilation, dependent positioning of the side with the bronchopleural fistula, and use of high-frequency oscillatory ventilation.⁹⁵⁻⁹⁷ Bronchoscopy is useful to identify the injury directly (proximal) or the affected bronchial segment (distal). A balloon is used to occlude the segments sequentially until a reduction in air leak is noted. Once the affected bronchus is identified, agents such as silver nitrate, cyanoacrylate-based agents, gelatin, fibrin, and even fishing weights have been applied to occlude the bronchial segment and close the fistula.⁹⁸⁻¹⁰² Bronchopleural fistula refractory to medical therapy for more than 7 days may require pleurodesis or operative intervention.

Miscellaneous

Pneumothorax. Pneumothorax, air within the pleural cavity, is present in 40% and 20% of blunt and penetrating thoracic trauma patients, respectively (see Chapter 81).¹⁰³ The clinical consequence of pneumothorax ranges from asymptomatic to the most life-threatening manifestation, “tension” pneumothorax, whereby progressive air trapping in the thorax results in a contralateral mediastinal shift, compression or kinking of the superior vena cava/inferior vena cava, and a precipitous drop in preload and cardiac output (Fig. 76-4). Clinically, this form of “obstructive” shock manifests as hypotension and hypoxia, and should be treated with immediate thoracic decompression, either with needle thoracostomy or tube thoracostomy. Current recommendations from the Advanced Trauma Life Support program¹⁰⁴ are to insert the needle in the mid-clavicular line at the second intercostal space; however, some authors have questioned the efficacy of inserting the needle in this location and recommend instead inserting the needle in the mid-axillary line at the fifth intercostal space because of decreased chest wall thickness in this location.¹⁰⁵ Additionally, lateral needle insertion avoids potentially life-threatening hemorrhagic complications such as laceration

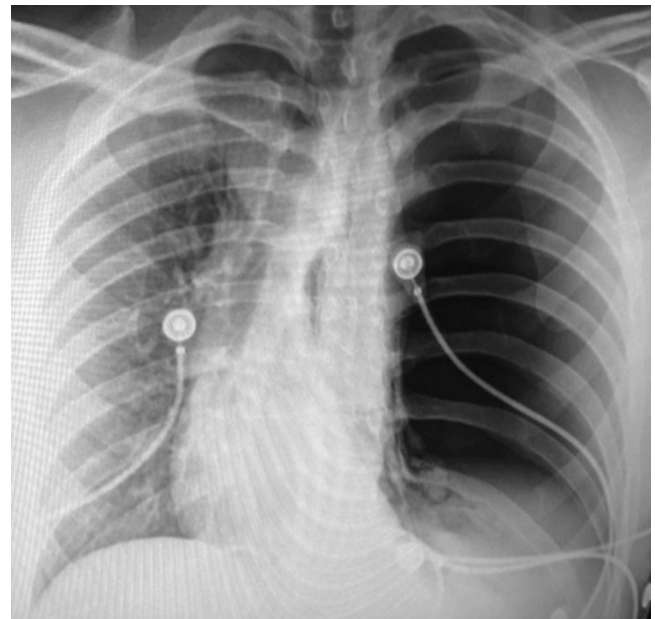


Figure 76-4 Tension pneumothorax. The free air in the left hemithorax is associated with a shift of the mediastinum into the right chest, depression of the hemidiaphragm, and widening of the intercostal spaces. Hypotension follows due to impairment of venous return to the right heart, both by the high intrathoracic pressure and perhaps mechanical compression or kinking of the superior vena cava. Immediate decompression is required.

of the internal mammary artery, subclavian artery, or pulmonary artery.^{106,107} Others recommend inserting a chest tube at the outset instead of a needle due to frequent failure rates associated with the latter.¹⁰⁸

An open pneumothorax, or “sucking” chest wound, is a special form of pneumothorax whereby a defect in the chest wall permits air entry through the wound with diaphragmatic movement. If the size of the wound approaches the size of the trachea, this may significantly hamper ventilation, because air preferentially enters through the wound.¹⁰⁹ Before operative repair, the wound should be covered with a flutter (“Heimlich”) valve or an occlusive dressing with one side open to allow air egress.

For less severe pneumothorax, the decision to drain the pleural cavity should be made based on the degree of respiratory compromise and the potential for enlargement to a tension pneumothorax. Managed without tube thoracostomy, it is estimated that the average pneumothorax absorption rate is 1.25% per day.¹¹⁰ Clinical significance of a pneumothorax depends not only upon the absolute size of the pneumothorax, but also on the preinjury condition of the patient (e.g., presence of chronic obstructive pulmonary disease) and other associated injuries. Chest tube insertion is not without risk, and modern series report a 15% to 20% incidence of tube-related complications, with an additional 15% requiring more chest tubes after suboptimal placement^{111,112} (Fig. 76-5). One rare but potentially fatal complication following pneumothorax drainage is reexpansion pulmonary edema¹¹³ (Fig. 76-6). Prophylactic antibiotics for the duration of dwell time of the chest tube are not recommended.¹¹⁴

An “occult” pneumothorax is defined as a pneumothorax which can only be visualized on chest CT scan; it is not

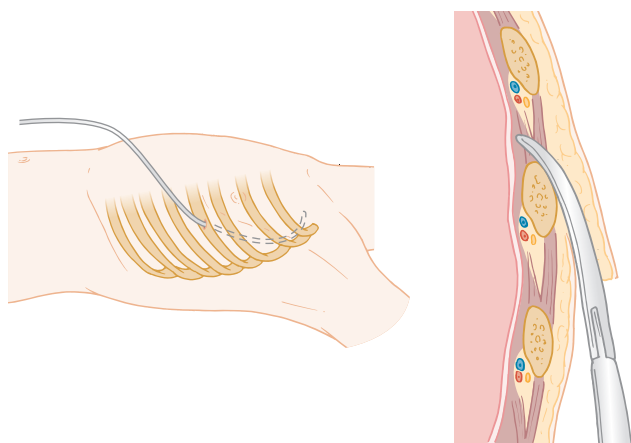


Figure 76-5 Tube thoracostomy placement. Diagram showing the placement of a thoracostomy tube in the mid-axillary line; the tube is directed anteriorly for drainage of a pneumothorax. (From Van Way CW III, Buerk CA: Surgical skills in patient care. St. Louis, 1978, CV Mosby.)

detectable on chest x-ray nor is it suspected on clinical examination (Fig. 76-7). “Occult” pneumothorax is present in up to 12% of seriously injured patients^{115,116} and, in an era of liberal CT scanning, comprise more than 50% of all pneumothoraces diagnosed in injured patients.¹¹⁷ Supine portable chest radiographs have been consistently shown to be only 50% sensitive for the detection of pneumothorax. Ultrasonography has been shown to be more sensitive than chest radiography for the detection of pneumothorax.¹¹⁸⁻¹²⁷ Subtle findings on supine chest radiograph suggestive of pneumothorax include the “deep sulcus” sign (Fig. 76-8).

The management of “occult” pneumothorax has evolved over the past 3 decades from mandatory tube thoracostomy for all “occult” pneumothoraces, progressing to selective drainage for only those patients undergoing positive pressure ventilation,¹²⁸ to selective drainage for all patients.^{115,128} In a large, multicenter observational study involving 569 patients with “occult” pneumothorax across 16 trauma

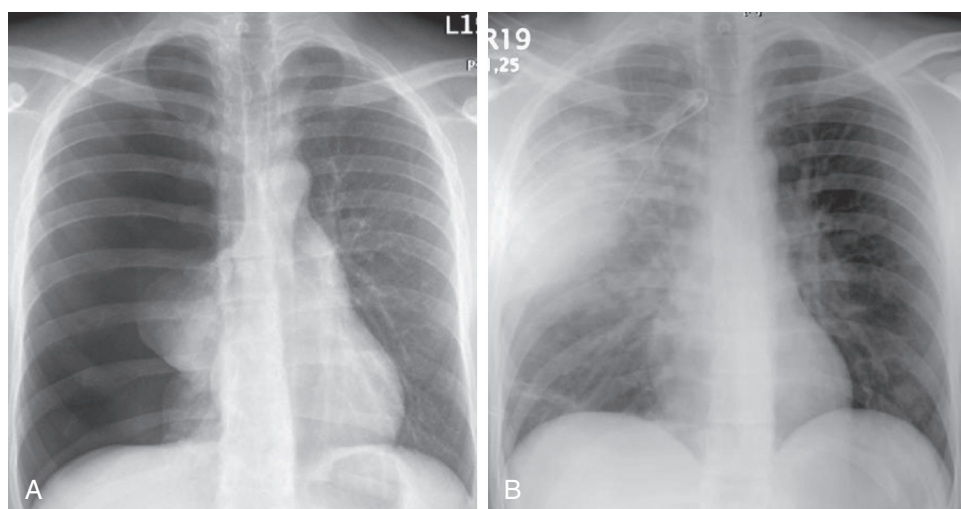


Figure 76-6 Reexpansion pulmonary edema. **A**, A pneumothorax can be seen on the right with a subtotal lung collapse. **B**, The same patient after expansion of the lung following placement of a thoracostomy tube. Peripheral right upper lobe opacity is now present, consistent with the development of reexpansion injury and edema in that region of lung. (From Malota M, Kowarik MC, Bechtold B, Kopp R: Reexpansion pulmonary edema following a post-traumatic pneumothorax: a case report and review of the literature. *World J Emerg Surg* 6:32, 2011.)

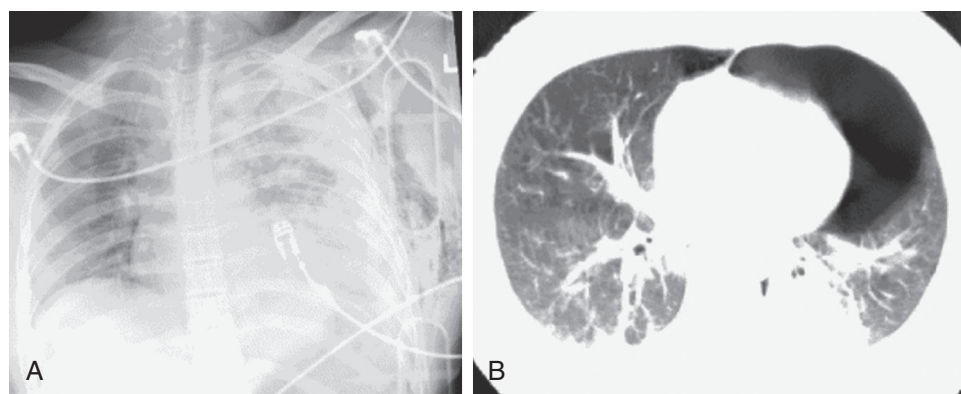


Figure 76-7 Occult pneumothorax. **A**, Anteroposterior supine chest radiograph of blunt trauma victim. There is no obvious pneumothorax. **B**, CT scan reveals a large occult left-sided pneumothorax. (From Ball CG, Hameed SM, Evans D, et al: Occult pneumothorax in the mechanically ventilated trauma patient. *Can J Surg* 46:373–379, 2003.)

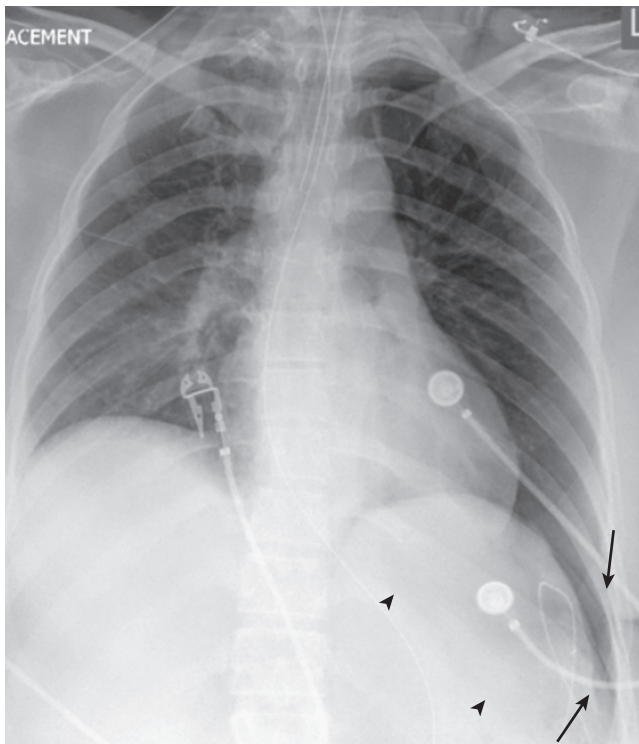


Figure 76-8 Deep sulcus sign on chest radiograph. In this supine patient, a pneumothorax on the left can be recognized by the depth of the diaphragmatic sulcus on the left compared with the right (arrows). There is also lucency overlying the left hemidiaphragm, representing air anterior and lateral to the left hemidiaphragm and seen as an air-tissue interface (arrowheads).

centers, Moore and colleagues reported that 21% required immediate tube thoracostomy. Of the remaining patients, however, only 6% overall failed observation and required tube thoracostomy for pneumothorax enlargement, respiratory distress, or development of hemothorax. In this series, 14% of patients on positive pressure ventilation required tube thoracostomy. Importantly, no patient who failed observation experienced an adverse event resulting from delay of chest drainage.¹²⁹

After drainage, standard management of the chest tube entails serial chest radiographs to document resolution of the pneumothorax. A bedside clinical examination should be performed to rule out an ongoing air leak, which is usually secondary to persistent alveolar-pleural fistula.¹³⁰ Air leaks may be graded according to increasing severity: forced expiratory, expiratory, inspiratory, and continuous. The vast majority of posttraumatic air leaks in stable patients are forced expiratory (coughing) or expiratory and almost all resolve with time and patience.¹³⁰ Typically, the chest tube is placed at 20 cm H₂O suction and “advanced” to water seal before removal. It is customary to obtain a chest radiograph after transitioning to water seal and after chest tube removal to monitor for pneumothorax reappearance. Pneumothorax recurs after chest tube removal in 11% to 24% of cases; however, if the pneumothorax is small and stable and the patient is asymptomatic, observation is frequently successful.^{131,132} It is common practice to allow up to 24 hours between changes in chest tube management, however Schulman and associates reported that

changes may be made at shorter intervals, because clinically significant recurrent pneumothorax appeared within 3 hours.¹³³

Accumulating evidence suggests that smaller 14- to 16-French “pigtail” catheters are equally effective as traditional large-bore chest tubes (28- to 40-French), require less dissection, can be placed by the Seldinger technique, and may be less painful.^{134,135}

Hemothorax. A hemothorax is blood in the pleural cavity that can cause a wide range of symptoms from minor discomfort to life-threatening situations (eFig. 76-8). In general, hemothorax evident on supine chest radiograph should be drained immediately, because these typically represent volumes of at least 200 mL. Similar to “occult” pneumothorax, “occult” hemothoraces also exist and the decision to drain an “occult” hemothorax should take into consideration the amount of blood present and the morbidity of chest tube insertion.

The initial treatment of hemothorax is tube thoracostomy. Based on the volume of initial output, the next step may be either urgent thoracotomy or observation. If the source of bleeding is the pulmonary parenchyma, hemostasis is usually achieved by complete expansion of the lung because the pulmonary circulation is a low pressure circuit. Bleeding from lacerated intercostal or internal mammary arteries is likely to persist and may require urgent thoracotomy for definitive hemostasis. Indications for urgent thoracotomy include hemodynamic instability, 1500 mL initial chest tube output, greater than 1500 mL over a 24-hour period, or greater than 200 mL/hr blood drainage for 3 consecutive hours.¹³⁶ Hemothorax secondary to major thoracic vascular structures (e.g., aorta, pulmonary artery) almost universally requires emergent thoracotomy for hemodynamic instability.

Assuming adequate drainage and resolution of the hemothorax, it is customary to “advance” the chest tube to water seal before removal, similar to the chest tube management for a simple pneumothorax (see earlier). An additional factor to consider is the daily volume of bloody chest tube drainage. While there are no standardized guidelines or recommendations, the majority of trauma surgeons advance a chest tube once the daily output decreases to between 100 mL and 300 mL per day.

The evacuation of a hemothorax can be incomplete in up to 20% of cases and can be frustrating to deal with.^{132,137,138} Untreated, a stagnant hemothorax may evolve into empyema or fibrothorax (“trapped lung”), two morbid complications.¹³⁹ Additional chest tube placement is usually ineffective for clot evacuation.

Early *video-assisted thoracic surgery* (VATS) (less than 5 days after injury), compared with delayed operation or additional chest tubes, has been reported to decrease hospital LOS and decrease conversion to open thoracotomy.^{140,141} According to the Eastern Association for the Surgery of Trauma guidelines, there is level 1 evidence that a retained hemothorax should be treated with early VATS, and not insertion of a second chest tube. VATS should be considered within 3 to 7 days of hospitalization because this reduces the risk for infection and the requirement for thoracotomy (level 2 evidence). Retained hemothorax less than 300 mL by chest CT scan may be observed.¹⁴² Currently, intrapleural

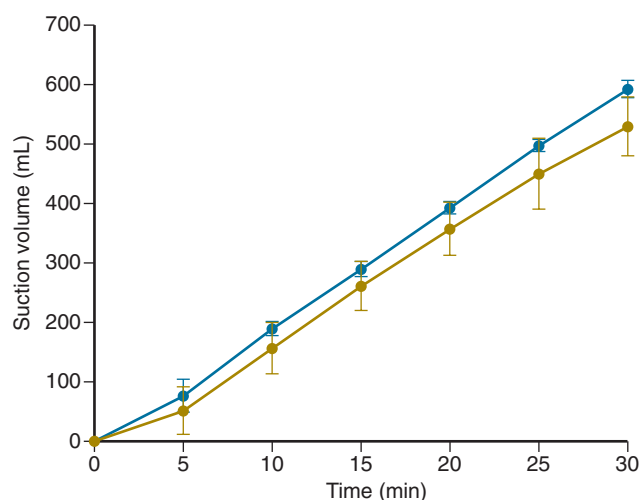


Figure 76-9 Comparison of fluid dynamics between two different sizes of pleural drains. The smaller drain (19-French, blue) is as effective as the larger one (28-French, brown) in draining fluid. (From Niinami H, Tabata M, Takeuchi Y, Umezumi M: Experimental assessment of the drainage capacity of small silastic chest drains. *Asian Cardiovasc Thorac Ann* 14:223–226, 2006.)

thrombolytics are considered second line treatment after VATS and can be considered in subacute hemothoraces to improve drainage.^{143,144}

Over the past decade, there has been a trend toward using smaller chest tubes for evacuating hemothorax.¹³⁵ When comparing the standard 36-French to 40-French chest tube with 28-French to 32-French tubes, Inaba and colleagues found that the initial drainage volume and total indwelling time were similar and there were no differences between groups in tube-related complications or the need for additional interventions.¹⁴⁵ A recent animal study of flow dynamics provides even further evidence to support that smaller tube size is equally effective for hemothorax evacuation. Niinami and coworkers reported that a 19-French fluted silicone drain is capable of draining 11 L/hour¹⁴⁶ (Fig. 76-9). Similarly, Kulvatunyou and colleagues reported that a 14-French “pigtail” catheter seems to drain blood as effectively as larger bore traditional chest tubes, with a similar incidence of complications.¹⁴⁷

Chylothorax. Traumatic chylothorax is an uncommon entity that results from disruption of the thoracic duct. Chylothorax presents as a milky pleural effusion upon resumption of oral intake and the diagnosis is confirmed by finding triglyceride levels greater than 110 mg/dL with or without lymphocytes predominating.¹⁴⁸ Initial treatment involves lung reexpansion and parenteral nutrition, with the possible addition of octreotide. If these measures fail, thoracic duct embolization or operative intervention is warranted.¹⁴⁹ However, the optimal duration of nonoperative management is unknown.

Pneumatocele/Intraparenchymal Hematoma. Also termed a *posttraumatic pulmonary pseudocyst*, a pneumatocele is an atraumatic cavitory lesion within the parenchyma following a pulmonary laceration (eFig. 76-9). Asymptomatic patients may be managed expectantly and most resolve within several weeks. For infectious complications, antibiotic

ics and CT-guided catheter drainage may be attempted. Operative resection (VATS or thoracotomy) may be necessary if less invasive measures fail.

TRACHEOBRONCHIAL INJURIES

Tracheobronchial injuries present in one of two ways, depending upon site, size, and communication with the pleural cavity: they are either immediately apparent, requiring immediate attention (11%), or they are very subtle and difficult to diagnose.^{150,151} Two thirds are unrecognized for more than 24 hours and, in 10%, there is no evidence of thoracic injury on physical examination or radiographs.¹⁵⁰ In this second group of patients, there is no discernible morbidity associated with delayed repair. Death is usually not from the tracheobronchial injury itself, but instead from fatal injuries to adjacent vascular structures.¹⁵² Even with complete transection, the robust peritracheal connective tissue can splint the tracheal fragments, maintaining airway continuity. Blunt force likely injures the tracheobronchial tree by one of three mechanisms: rupture from tracheal compression against the rigid vertebral column, rupture from increased airway pressures due to compression of the chest with a closed glottis, or laceration from shearing forces.¹⁵³

The majority of tracheobronchial injuries take place within 2.5 cm of the carina, with main stem bronchial injuries comprising the majority (86%).^{150,153} Clinically, the patient may have dyspnea (the most common symptom), hoarseness, stridor, hemoptysis, crepitus, or respiratory distress. Radiographically, the “fallen lung” sign, first described by Oh and associates in 1969, is a highly specific finding for this injury. This sign manifests when the patient has a pneumothorax. When pneumothorax is present without tracheobronchial injury, the lung falls *toward* the hilum (central displacement), whereas with tracheobronchial injury, the transected lung falls *away* from the hilum (peripheral displacement) (Fig. 76-10). CT scanning may demonstrate bronchial wall discontinuity (eFig. 76-10 and Video 76-3) or mediastinal emphysema. A tracheal or proximal bronchus injury should be suspected with pneumomediastinum or with a pneumothorax refractory to chest drainage. Bronchoscopy is the most effective method of diagnosis.

Although the treatment for large or life-threatening tracheobronchial injuries is immediate repair, selective intubation beyond the injury alone (or even observation alone) may be successful in carefully selected patients with small or partial thickness injuries.^{7,154}

Delayed complications of unrecognized injury include bronchopleural fistula, atelectasis, bronchiectasis, and postobstructive pneumonia as well as more serious sequelae such as mediastinitis or cervical abscess.

DIAPHRAGM INJURIES

Diaphragmatic injury is a rare but morbid injury, presenting in less than 1% of blunt trauma and associated with a 21% overall mortality rate.¹⁵⁵ More than 90% are seen after motor vehicle crashes. Two thirds of diaphragm injuries develop on the left, perhaps because the liver cushions the impact on the right side. Because of the significant force

required to rupture the diaphragm, these injuries are almost universally accompanied by other organ injuries, such as lung (77%), liver (52%), spleen (32%), and stomach (19%).¹⁵⁵

The physical examination is inaccurate for the diagnosis of diaphragmatic injuries. For most victims of penetrating injury, there is no sign unique to diaphragmatic injury. For patients following blunt trauma, dyspnea and pain are common but nonspecific. Chest radiography is diagnostic in fewer than half of those with injury to the left hemidiaphragm (eFig. 76-11) and in only 17% of those with injury



Figure 76-10 “Fallen lung” sign. Chest radiograph obtained 6 hours after initial presentation of acute dyspnea in an 8-year-old boy. Bilateral pneumothorax, more prominent on the right, is seen. Pneumomediastinum and soft tissue emphysema are observed. The right lung is seen to be collapsed inferior to the hilum (fallen lung sign), usually a sign of complete rupture of the main bronchus. A thoracostomy tube has been inserted on the right, yet a large right pneumothorax remains. (From Savas R, Alper H: Fallen lung sign: radiographic findings. *Diagn Interv Radiol* 14:120–121, 2008.)

to the right hemidiaphragm¹⁵⁶ (Fig. 76-11). CT scan has a very high sensitivity for blunt diaphragmatic rupture. Imaging signs of injury include: a nasogastric tube terminating above the diaphragmatic contour, discontinuity of the hemidiaphragm, herniation of the viscera into the thorax (eFig. 76-12), diaphragmatic thickening (eFig. 76-13), the “hump sign,” the “band sign,” the “dependent viscera sign” (eFig. 76-14), the “collar sign” (eFig. 76-15), and the “dangling sign.”^{157,158}

All acute diaphragmatic injuries should be surgically repaired. The natural history of traumatic diaphragmatic hernias is poorly studied, but it is presumed that the tendency is to enlarge over time, with progressive herniation of abdominal viscera into the chest due to the negative intrathoracic pressure and positive intra-abdominal pressure. For left-sided penetrating thoracoabdominal wounds, if there is no immediate indication for operative exploration, it is recommended to perform a diagnostic laparoscopy, because 20% will have diaphragm injuries.^{159,160}

BLAST LUNG INJURY

INTRODUCTION

An increasing frequency of terrorist bombing attacks worldwide has resulted in a large number of civilian blast injuries.¹⁶¹ Blast victims require a standard trauma workup as recommended by Advanced Trauma Life Support. Additionally, such victims may also present with a set of pulmonary injuries unique to the blast mechanism.¹⁶²

Victims of blast injuries manifest different injuries depending on the type of the bomb, the location of detonation, and whether the targets were military or civilian. Typically, military victims have different injuries from civilian victims. Military personnel are young and healthy, and usually have body armor that protects their thoracic and abdominal organs, whereas civilian victims range from children to older adults and are not wearing body protection. Thus civilian victims present with more thoracic/lung

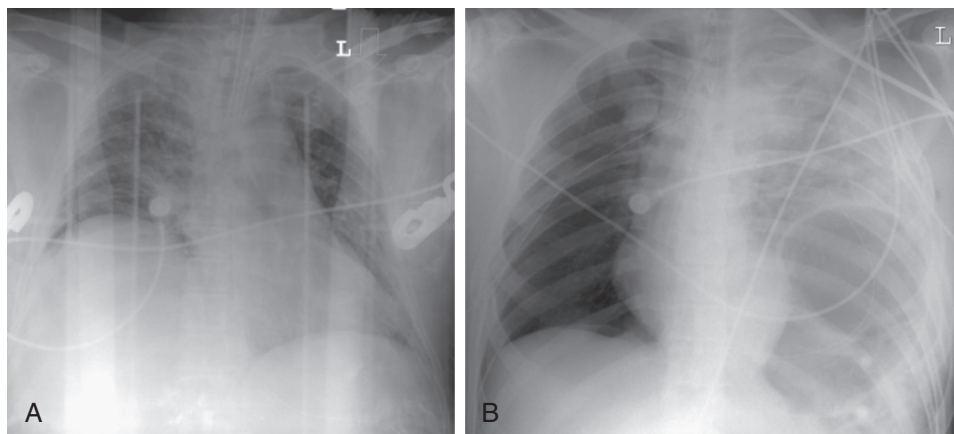


Figure 76-11 Hemidiaphragmatic injury in the setting of trauma. A, Right hemidiaphragmatic injury. Frontal chest radiograph shows apparent elevation of the right hemidiaphragm, generally a nonspecific finding. However, in the setting of trauma, diaphragmatic injury with herniation of the liver into the thorax manifests similarly, as in this example. B, Left hemidiaphragmatic injury. Frontal chest radiograph shows herniation of the stomach into the left thorax, consistent with a large tear of the left hemidiaphragm.

and abdominal injuries than military victims. As a general rule, blast injury victims suffer multiple blunt and penetrating injuries, including traumatic amputations. Injuries from blast detonations are classified into the following categories: (1) primary; (2) secondary; (3) tertiary; and (4) quaternary.¹⁶²

PRIMARY BLAST INJURIES

Primary blast injuries result from overpressure effects of the blast wave (see later). The blast typically injures organs that have interfaces between different densities, such as air and tissue, or water and air. Examples include pulmonary barotrauma, tympanic membrane ruptures, gastrointestinal contusions/perforations, and traumatic amputations. Previously, tympanic membrane rupture was used as a marker of severity of illness from the blast wave. However, recent studies show that tympanic membrane rupture is not a reliable marker of severity, demonstrating poor sensitivity and specificity.¹⁶³ Instead, markers of severe blast injury include the following: (1) >10% total body surface area burns; (2) skull/facial fractures; (3) penetrating injuries to the head/torso.¹⁶³

SECONDARY BLAST INJURIES

Secondary blast injuries result when penetrating injuries are caused by flying debris, such as bomb fragments from the explosive device and fragments of bone and teeth from the bomber and victims. There are case reports of these biologic fragments transmitting hepatitis B.^{164,165} Theoretically, transmission of hepatitis C and HIV are also possible.

TERTIARY BLAST INJURIES

Tertiary blast injuries result when victims are physically propelled into hard surfaces by the force of the blast wave. Crush injuries from falling debris also fit into this category.

QUATERNARY BLAST INJURIES

Quaternary blast injuries encompass all other explosion-related effects such as burns, asphyxia, radiation poisoning, toxins, psychological trauma, and exacerbation of underlying medical conditions.

PHYSICS OF THE BLAST WAVE

Explosions result when a chemical reaction transforms a solid or liquid into gas within a very short time period, resulting in a massive release of energy. The explosion releases most of its energy as a “blast wave,” a positive pressure front that travels faster than the speed of sound.¹⁶⁶ As a result, victims feel the blast wave before hearing the explosion. In the open-air, the blast wave behaves in a predictable manner based on the physics of wave motion.¹⁶⁷

Detonations within confined spaces or under water cause blast waves that are accentuated and deadlier.^{162,164} Under these conditions, blast waves are reflected back from surfaces with a different density, such as walls or air-water interfaces. The reflected wave superimposes and amplifies the outgoing blast wave, causing a higher intensity and

thus much deadlier blast wave. Furthermore, the blast wave can reflect back from surfaces at an angle greater than 40 degrees, augmenting the incoming wave and creating a new blast wave. This phenomenon is known as a “mach stem formation.”¹⁶⁸ Studies have shown that explosions detonated in corners can result in explosions that are up to eight times deadlier than explosions in the open air.¹⁶⁴

Damage to the human body results when the blast wave transmits energy directly to the body. This energy is transmitted unevenly through body tissues and, as described, reflects back upon encountering changes in density. As a result, the majority of damage is done at interfaces of different tissue densities. For example, pulmonary blast injuries result when the blast wave rapidly changes in amplitude upon entering and exiting the multiple air- and fluid-filled structures within the lungs. Other air/tissue interfaces include the gastrointestinal tract, tympanic membranes, and extremities, where greatly disparate density planes, such as joints with air, soft tissue, and bones all reside within a small space. The mechanisms causing these injuries can be classified physiologically into distinct categories: (1) spalling forces, (2) implosion forces, and (3) inertia forces.^{162,167}

Spalling Forces

Spalling forces result when the blast wave displaces and fragments one tissue into another tissue, usually the higher density tissue into the lower density tissue. For example, spalling forces cause the forcible movement of blood from the capillaries into the alveoli, causing alveolar hemorrhage.

Implosion Forces

Implosion forces result when the highly compressed edge of the blast wave enters the victim. This results in gas that rapidly compresses and reexpands causing injury. For example, implosion forces cause barotrauma by compressing and reexpanding the air in the alveoli. Furthermore, this rapid change in air density can cause an air embolism by entering the circulatory system.

Inertia Forces

Inertia forces result when the blast wave causes the different tissue densities to absorb different amounts of energy. This results in the different tissues moving at different velocities. The resulting shearing of tissue planes causes massive injuries, typically traumatic avulsions/amputations.

Blast lung injury results from the combination of all the forces described above. After the initial damage to the architecture of the alveoli, pulmonary hemorrhage ensues. The free hemoglobin in the alveoli leads to the formation of free radicals, worsening edema and an early inflammatory response.^{169,170} This leukocyte accumulation and release of inflammatory cytokines leads to further epithelial cell damage over 12 to 24 hours, as well as endothelial cell damage over 24 to 56 hours. This inflammatory cascade results in a lung injury syndrome characteristic of ARDS.

Histologic examination of the lung damaged by blast injury reveals perivascular edema, extensive alveolar hemorrhage during the first 12 hours, and then further epithelial cell damage and detachment from the basement membrane.^{169,170}

MANAGEMENT OF BLAST LUNG INJURY

Initial management of patients with blast lung injury should follow standard local trauma protocols and Advanced Trauma Life Support teaching. Survivors of the blast wave with primary blast lung injury have a mortality rate of 11% and represent a group of patients with very severe injuries.

Clinical features include shortness of breath, cough, chest pain, hemoptysis, cyanosis, and tachypnea. Hypoxemia is a typical finding, but may not develop until after the first few hours following presentation. One case series found that only 28% of patients had hypoxemia on initial presentation.¹⁷⁰

All patients with suspected blast lung injury should receive a chest radiograph as soon as possible. Radiographic findings of blast injury may include not only the classic “bat wing” appearance on chest radiograph but also subcutaneous emphysema; pneumothorax; pulmonary interstitial emphysema; pneumopericardium; pneumomediastinum; and pneumoperitoneum.

The general treatment for primary blast lung injury patients is similar to the treatment for the ARDS patient. This includes limiting fluid administration to decrease the chance of pulmonary edema and the use of low-tidal-volume “lung-protective” ventilation with permissive hypercapnia to minimize peak and plateau airway pressures.¹⁷¹ Refractory cases can be considered for rescue treatments for ARDS, such as inhaled nitric oxide, inhaled prostaglandins, and open-lung ventilation strategies. However, caution should be used when considering extracorporeal membrane oxygenation. The underlying pathophysiology of blast lung involves alveolar hemorrhage and, as a result, there are reports that the required anticoagulation for extracorporeal membrane oxygenation results in catastrophic pulmonary hemorrhage.¹⁷²

In the rare case of air embolism from the blast lung injury, treatment aims to prevent further air emboli. The patient is placed in the left lateral decubitus position, with the head down and feet up in an attempt to contain the air embolism at the apex of the left ventricle. Peak pressures during positive-pressure ventilation should be minimized and hyperbaric therapy considered. The diagnosis is a clinical one because CT scans, echocardiography, and observation of retinal air bubbles on fundoscopic exams are unreliable.¹⁶²

Patients that survive blast lung injury typically have excellent long-term pulmonary outcomes. One study found that, one year after the injury, survivors had normal pulmonary exams, with minimal pulmonary complications.¹⁷³

INITIAL MANAGEMENT AND DIAGNOSTIC APPROACH TO THE THORACIC TRAUMA PATIENT

The assessment of every trauma patient begins with the time-honored “ABCs”—airway, breathing, and circulation. In case of suspected tension pneumothorax, pleural decompression should precede intubation. A complete physical exam should follow the ABCs, with special attention paid to the presence of decreased breath sounds, distended neck veins, subcutaneous emphysema, and upper extremity pulse or neurologic deficits.

If there is a concern for thoracic injury and the patient has stable vital signs, workup can begin with a chest radiograph and thoracic ultrasound. The ultrasound should be considered as an extension of the physical examination, and a careful survey of the pericardium and bilateral thoracic cavities should be performed on every patient. Large or clinically significant pneumothoraces or hemothoraces should be treated immediately with tube thoracostomy prior to leaving the trauma bay of the emergency department. Depending upon the chest radiograph and ultrasound findings, a chest CT scan or bronchoscopy may be required to delineate injury further.

Key Points

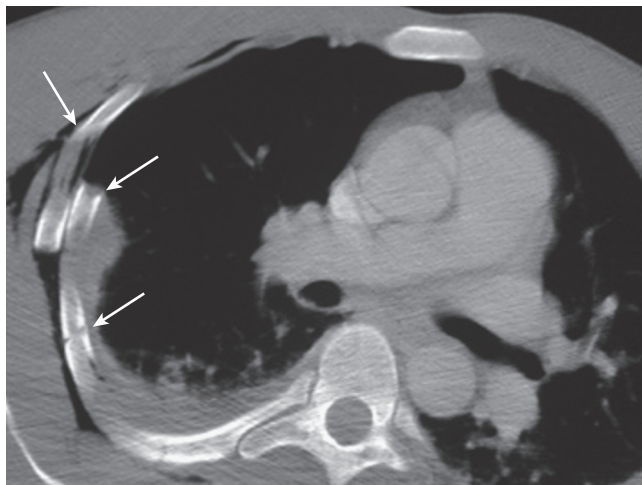
- The majority of patients with pneumothorax and hemothorax may be adequately managed by tube thoracostomy alone.
- The cornerstone of treatment for rib fractures and flail chest is pain control.
- Pulmonary contusion is a major driver of morbidity and can cause systemic immune dysfunction.
- Occult pneumothorax may be safely managed with observation, even in patients on positive pressure ventilation.
- Blast lung injury is a unique form of lung injury, which is most commonly seen in survivors of closed-space explosions.
- The diagnosis of blast lung injury is based on clinical observations and confirmed by plain chest radiograph. Lung injury is the leading cause of late blast mortality.
- Management of blast lung injury is predominantly supportive and closely approximates the treatment of acute respiratory distress syndrome.

Complete reference list available at **ExpertConsult**.

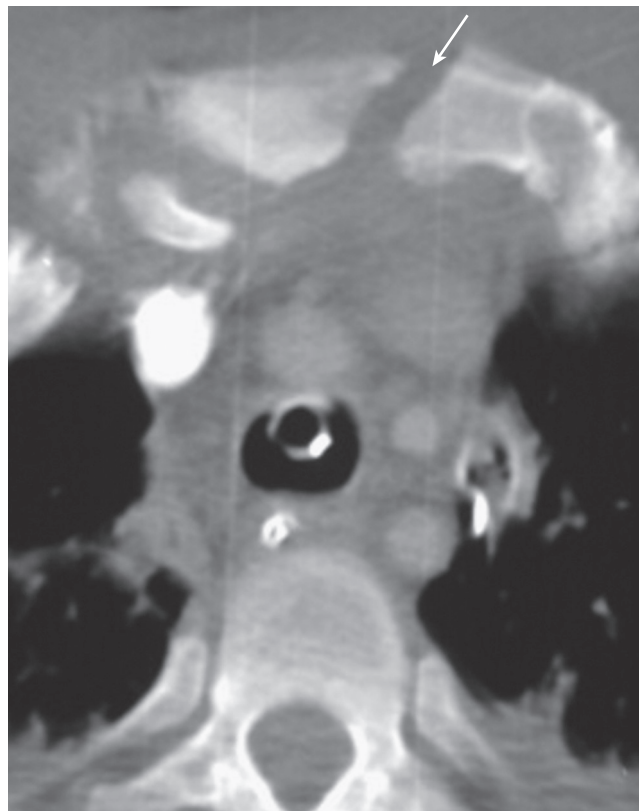
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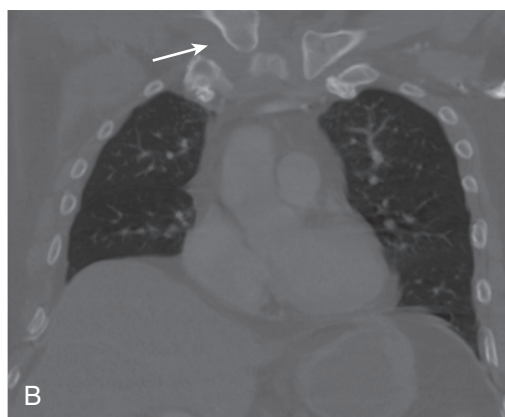
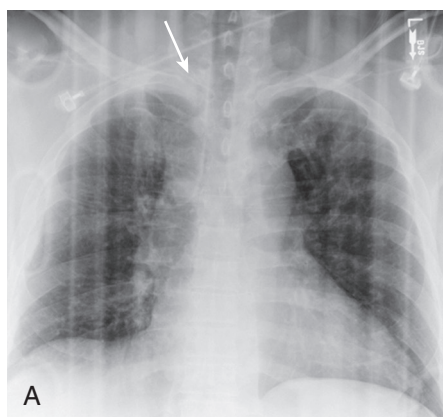
eFIGURE IMAGE GALLERY



eFigure 76-1 Blunt thoracic traumatic injury: rib fracture. Axial enhanced chest CT scan shows displaced right-sided rib fractures (*arrows*). (Courtesy Michael Gotway, MD.)



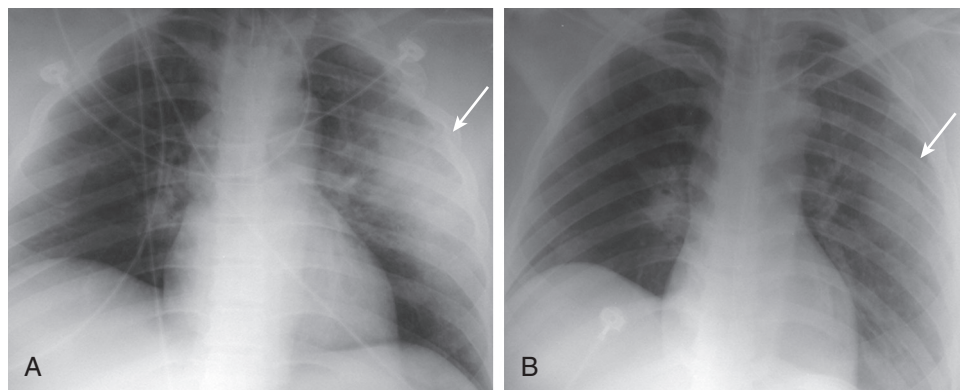
eFigure 76-2 Blunt thoracic traumatic injury: manubrial fracture. Axial chest CT scan shows a fracture line (*arrow*) through the manubrium, resulting from a motor vehicle collision. (Courtesy Michael Gotway, MD.)



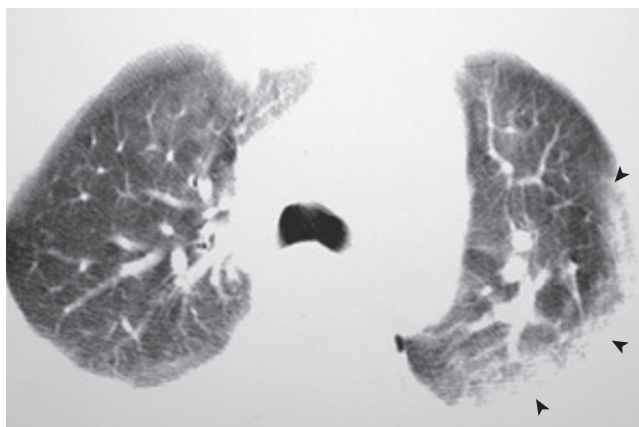
eFigure 76-3 Blunt thoracic traumatic injury: sternoclavicular dislocation. **A**, Frontal chest radiograph of a patient who fell from height shows subtle displacement of the medial head of the right clavicle (*arrow*); compare with the normally positioned left clavicular head. **B**, Coronal enhanced chest CT scan displayed in bone windows shows superior dislocation of the medial head of the right clavicle (*arrow*). (Courtesy Michael Gotway, MD.)



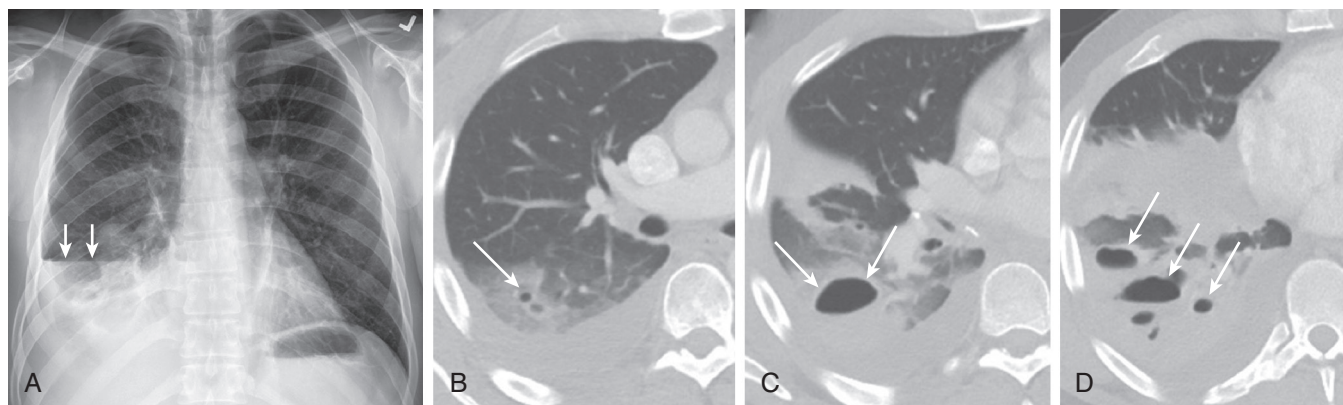
eFigure 76-4 Blunt thoracic traumatic injury: sternoclavicular dislocation. Axial chest CT scan in a patient following a motor vehicle collision shows posterior dislocation of the right clavicular head (*arrow*). Note the normally positioned left clavicular head (*arrowhead*) and the normal sternoclavicular joint space (*). (Courtesy Michael Gotway, MD.)



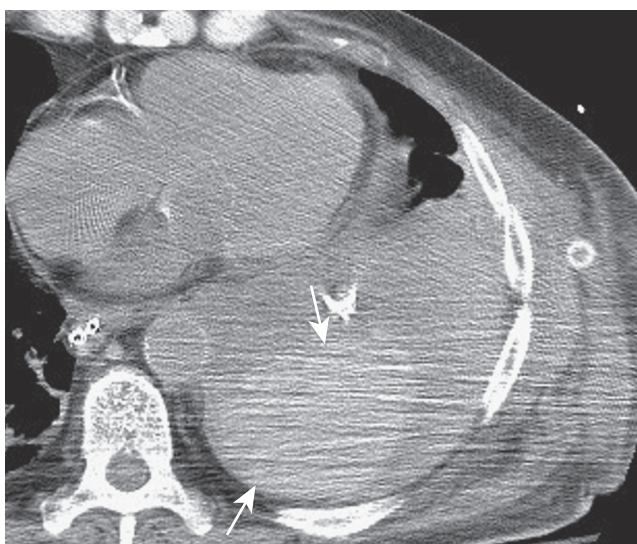
eFigure 76-5 Blunt thoracic traumatic injury: pulmonary contusion on chest radiograph. **A**, Frontal chest radiograph performed at emergency room presentation in a patient following a motor vehicle collision shows homogeneous peripheral left lung consolidation (*arrow*), consistent with contusion. **B**, Frontal chest radiograph performed 24 hours following presentation (**A**) shows significant improvement in the left lung contusion (*arrow*). (Courtesy Michael Gotway, MD.)



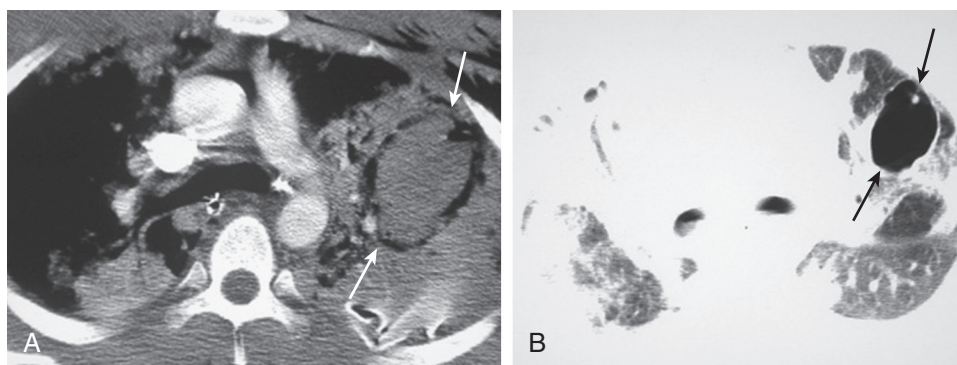
eFigure 76-6 Blunt thoracic traumatic injury: pulmonary contusion on chest CT scan. Axial chest CT scan performed in a patient following blunt thoracic traumatic injury shows homogeneous, nonsegmental, peripheral left upper lobe ground-glass opacity and consolidation (*arrowheads*), typical of pulmonary contusion. (Courtesy Michael Gotway, MD.)



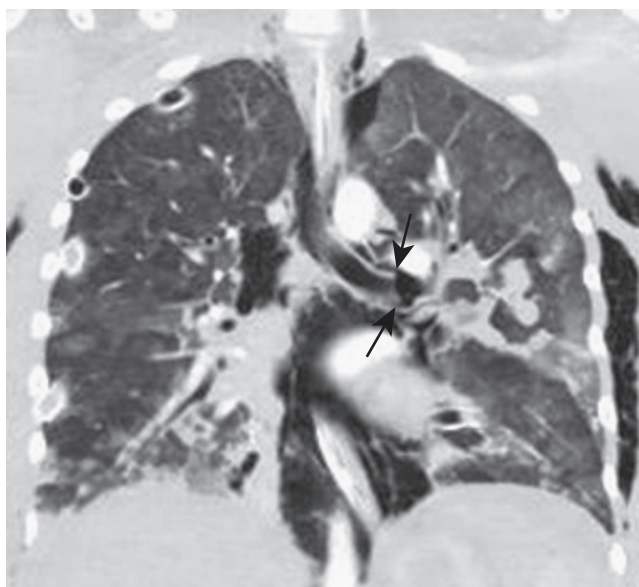
eFigure 76-7 Blunt thoracic traumatic injury: pulmonary laceration. **A**, Frontal chest radiograph performed in a patient following a motor vehicle collision shows right lower lobe consolidation containing an air-fluid level (arrows). **B–D**, Axial chest CT scan displayed in lung windows shows numerous right lower lobe areas of cavitation (arrows) associated with surrounding consolidation, consistent with pulmonary laceration. (Courtesy Michael Gotway, MD.)



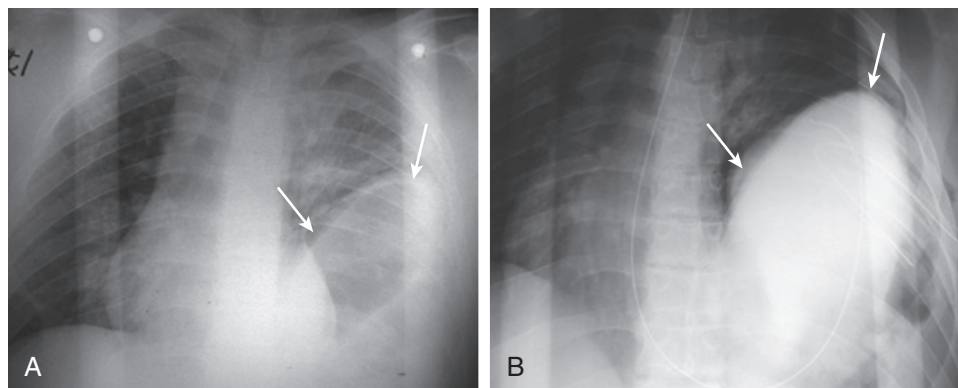
eFigure 76-8 Blunt thoracic traumatic injury: hemothorax. Axial chest CT scan shows a left pleural effusion containing a masslike area of high attenuation (arrows), representing retracting clot within a hemothorax. (Courtesy Michael Gotway, MD.)



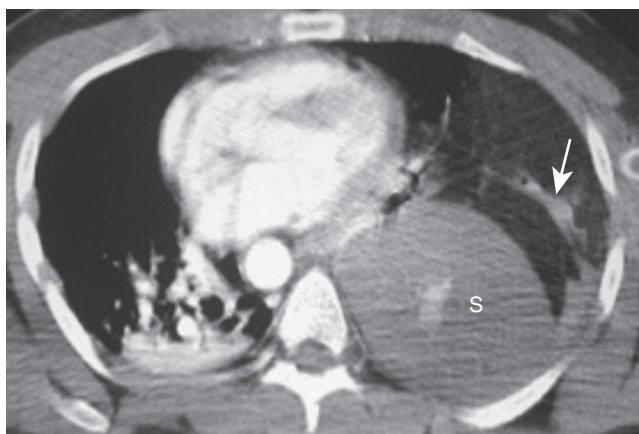
eFigure 76-9 Blunt thoracic traumatic injury: hematoma with pneumatocele development. **A**, Axial chest CT scan performed in a patient following blunt traumatic thoracic injury shows a left upper lobe mass (arrows) with surrounding lucency, the latter consistent with cavitation. The material within the cavity is blood, consistent with hematoma. **B**, Axial chest CT displayed in lung windows performed 3 weeks following (A) shows evacuation of the contents of the left upper lobe cavity, revealing a thin-walled cyst (arrows). This lesion spontaneously closed over the ensuing month, consistent with a pneumatocele. (Courtesy Michael Gotway, MD.)



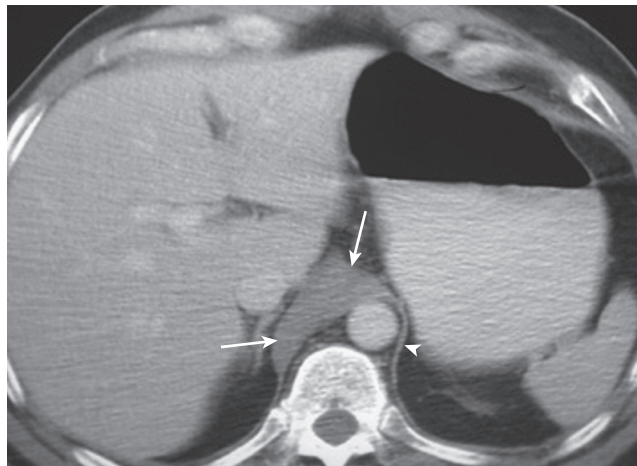
eFigure 76-10 Blunt thoracic traumatic injury: tracheobronchial injury. Coronal chest CT displayed in lung windows performed in a patient following a high-speed motor vehicle collision shows extensive subcutaneous emphysema and pneumomediastinum, both hallmarks of airway injury. The left mainstem bronchus is fractured (*arrows*), with gas collecting around the area of airway injury. The associated video ([Video 76-3](#)) shows the extensive pneumomediastinum, subcutaneous emphysema, and medial left apical pneumothorax as well as multifocal lung parenchymal injuries. (Courtesy Michael Gotway, MD.)



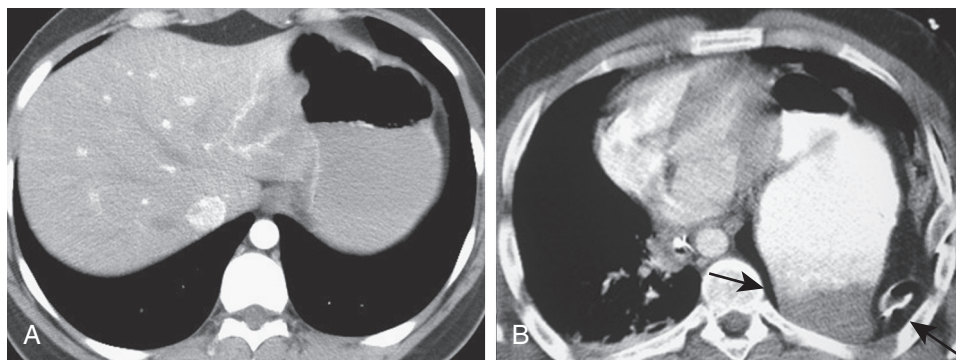
eFigure 76-11 Blunt thoracic traumatic injury: diaphragmatic injury on chest radiography. **A**, Front chest radiograph obtained in a patient after a motor vehicle collision shows intrathoracic herniation of the stomach (*arrows*). **B**, Frontal chest radiograph obtained following chest CT, for which oral contrast was administered, shows the contrast filling the intrathoracic stomach (*arrows*). (Courtesy Michael Gotway, MD.)



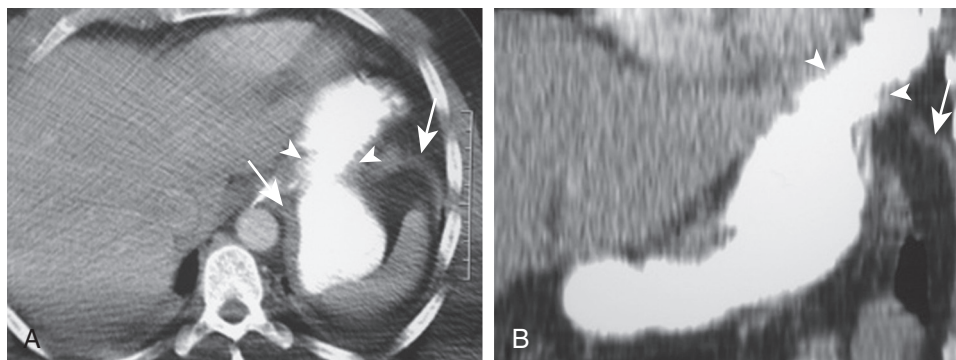
eFigure 76-12 Blunt thoracic traumatic injury: diaphragmatic injury presenting as intrathoracic visceral herniation. Axial chest CT scan performed in a patient following blunt traumatic injury shows intrathoracic herniation of the spleen (S) as well as other contents of the left upper quadrant, including the colon (*arrow*), consistent with a very large left diaphragmatic tear. (Courtesy Michael Gotway, MD.)



eFigure 76-13 Blunt thoracic traumatic injury: diaphragmatic injury presenting as diaphragmatic thickening (the “thick crus” sign). Axial chest CT scan performed in a patient following blunt traumatic injury shows thickening of the right diaphragmatic crus (arrows), due to retraction of this structure following right diaphragm injury. Compare the right diaphragm crus thickness with the normal left diaphragm crus (arrowhead). (Courtesy Michael Gotway, MD.)



eFigure 76-14 Blunt thoracic traumatic injury: diaphragmatic injury presenting as the “dependent viscera” sign. **A**, Normal appearance of the thoracoabdominal junction. Note the abdominal contents are positioned within the central portion of the image at this level, with the thoracic contents positioned peripherally. **B**, Axial chest CT scan performed in a patient following blunt traumatic injury shows that the abdominal viscera (stomach and left upper quadrant fat, arrows) rests against the posterior chest wall. Normally, as shown in (**A**), the lung parenchyma and pleura occupy this location. The positioning of abdominal viscera against the posterior chest wall near the thoracoabdominal junction at chest CT is referred to as the “dependent viscera” sign and represents intrathoracic visceral herniation, usually due to fairly large diaphragmatic tears. (Courtesy Michael Gotway, MD.)



eFigure 76-15 Blunt thoracic traumatic injury: diaphragmatic injury presenting as the “collar” sign. **A**, Axial enhanced chest CT scan shows focal constriction of the stomach (arrowheads) as it enters the thorax through a small left hemidiaphragmatic tear (arrows, left hemidiaphragm). **B**, Coronal reformatted CT image shows the focal constriction of the stomach as it passes through the small diaphragmatic defect (arrowheads) to advantage; this focal constriction is referred to as the “collar” sign (arrow, left hemidiaphragm). (Courtesy Michael Gotway, MD.)

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INTRODUCTION**ADAPTATION TO HIGH ALTITUDE**

Pulmonary Adaptation
 Cardiovascular Adaptation
 Hematologic Adaptation
 Tissue Adaptation
 Central Nervous System Adaptation

Fluid Homeostasis and Renal Function**CHANGES IN COMMON SEA-LEVEL ACTIVITIES AT HIGH ALTITUDE**

Sleep
 Exercise
MALADAPTATION

Problems of Lowlanders on Ascent to High Altitude

Problems of High-Altitude Residents**PREEXISTING ILLNESS AND HIGH ALTITUDE**

Respiratory Diseases
 Altitude-Illness Medications and Underlying Medical Diseases

INTRODUCTION

Nearly 100 million people live at altitudes greater than 2500 m, primarily in the Rocky Mountains of North America, the Andes Mountains of South America, the Ethiopian Highlands of East Africa, and the Himalaya Mountains of South-Central Asia. These people have developed the ability to live and reproduce at elevations as high as 5000 m, but in some cases, develop chronic medical problems attributable to their high-altitude residence. In addition to long-term residents, many lowlanders venture to high altitude for work and recreation. These more acute exposures also pose the hazards of acute altitude illnesses or altitude-related exacerbations of preexisting diseases. With growing awareness of such risks, persons are seeking advice on traveling to these regions. It is, therefore, imperative that the counseling physician be able to provide guidance about minimizing risks and managing problems.

This chapter reviews the normal adaptive processes that take place in response to high altitude, specifically the compensatory changes in the transport of oxygen from the air to the tissues in the setting of decreased barometric pressure. Acute and chronic adaptation are discussed, and factors determining the limits of adaptation and performance at high altitude are explored. Also reviewed are the consequences of maladaptation—the acute and chronic illnesses of high altitude—and strategies for managing these situations are discussed. Finally, an approach to the traveler with underlying medical problems who is planning a trip to high altitude is presented.

ADAPTATION TO HIGH ALTITUDE

The *partial pressure of oxygen* (PO_2) diminishes as oxygen moves from air to the tissues. Ventilation, regional matching of ventilation and blood flow, diffusion of oxygen from air to the blood, transport within the circulation, diffusion of oxygen from blood into the tissue, and metabolism in the mitochondria are all links in this oxygen transport chain. As altitude increases, the barometric pressure declines (Table 77-1); as a result, PO_2 at every step in this chain is lower than it would be at sea level. Compensatory processes take place at each step in the chain at different rates to raise

PO_2 and maintain adequate oxygen delivery, thereby facilitating tolerance of the hypoxic environment.

The process of adaptation is vitally important to survival at high altitude. Whereas a person who makes a sudden ascent from sea level to the summit of Mt. Everest (8848 m) by helicopter, for example, would become unconscious within minutes and die soon thereafter, a climber using an appropriately slow ascent rate can complete the climb without obvious effects because of the body's adaption to the hypoxic environment. Since the latter half of the nineteenth century, researchers have investigated the full spectrum of these adaptive responses, creating a vast literature that has been reviewed extensively by Swenson and Bartsch¹ and West and colleagues.² A summary of the key features of the adaptive responses to high altitude follows.

PULMONARY ADAPTATION**Control of Ventilation**

Acute Response. Upon acute exposure to hypoxia, alveolar ventilation increases. This response, the *hypoxic ventilatory response* (HVR), minimizes the drop in alveolar PO_2 (Fig. 77-1). Individuals vary in this response, which subsequently plays an important role in adaptation, maladaptation, and performance at high altitude. Large increases in ventilation are generally not seen until the arterial PO_2 falls below 60 mm Hg and, at any given altitude, ventilation continues to increase over weeks, in a process called *ventilatory acclimatization*. At extreme elevations, the increase in minute ventilation can be dramatic, representing a large metabolic cost. Data obtained from several individuals just below the summit of Mt. Everest (at 8400 m, barometric pressure approximately 272 mm Hg) revealed an average arterial PCO_2 of 13 mm Hg. As a result, despite an inspired PO_2 of only 47 mm Hg, the mean arterial PO_2 was maintained at roughly 30 mm Hg.³

The HVR is mediated by peripheral chemoreceptors in the carotid body. Neural discharge from the whole carotid sinus nerve is related hyperbolically to decreasing arterial PO_2 ,⁴ and surgical ablation of carotid body input (e.g., carotid endarterectomy or bilateral carotid body resection for intractable dyspnea) results in loss of the ventilatory response to acute hypoxia.⁵

Table 77-1 U.S. Standard Atmosphere: Altitude, Barometric Pressure, and Inspired Partial Pressure of Oxygen*

Altitude (meters)	Altitude (feet)	Barometric Pressure (mm Hg)	Inspired PO ₂ (mm Hg)
0	0	760	159
1000	3280	674	141
2000	6560	596	125
3000	9840	526	110
4000	13,120	463	97
5000	16,400	405	85
6000	19,680	354	79
8000	26,240	268	56
8848	29,028	253	43

*Values except 8848 m, are taken for mid-latitude (45°N). There is greater variation at higher latitudes.

Modified with permission from Altman PL, Dittmer DS, editors: *Respiration and circulation*. Bethesda, 1971, pp 12–13.

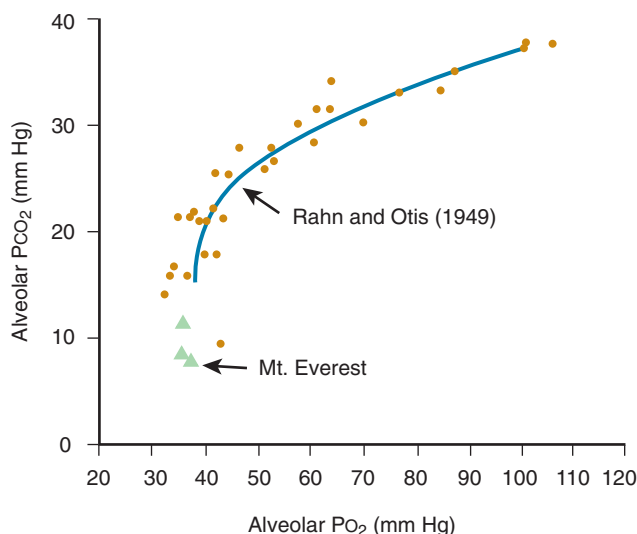


Figure 77-1 Oxygen-carbon dioxide diagram demonstrating the alveolar gas composition in acclimatized subjects at high altitude. Solid circles represent data collected by Rahn and Otis (Rahn H, Otis AB: Man's respiratory response during and after acclimatization to high altitude. *Am J Physiol* 157:445–449, 1949), while the triangles are measurements from three altitudes on Mt. Everest. At extreme altitudes, marked hyperventilation maintains alveolar PO₂ at approximately 35 mm Hg. (From West JB, Hackett PH, Maret KH, et al: Pulmonary gas exchange on the summit of Mt. Everest. *J Appl Physiol* 55:678–687, 1983.)

In response to a relatively constant hypoxic stimulus, ventilation increases over time (Fig. 77-2). With initial exposure and the subsequent acute rise in minute ventilation, arterial PCO₂ at the medullary and peripheral chemosensors decreases and depresses the ventilatory response.⁶ Subsequently, over days, ventilation increases and continues to rise for months.⁷ The classic explanation for this ongoing increase was that the slower renal compensation for the respiratory alkalosis permitted near full realization of the hypoxic stimulus to ventilation. However, blood pH reveals that hypocapnic alkalemia persists as ventilation increases, suggesting that other mechanisms beyond renal compensation, which is completed within 3 to 4 days, must be responsible for this change. It was proposed that a rela-

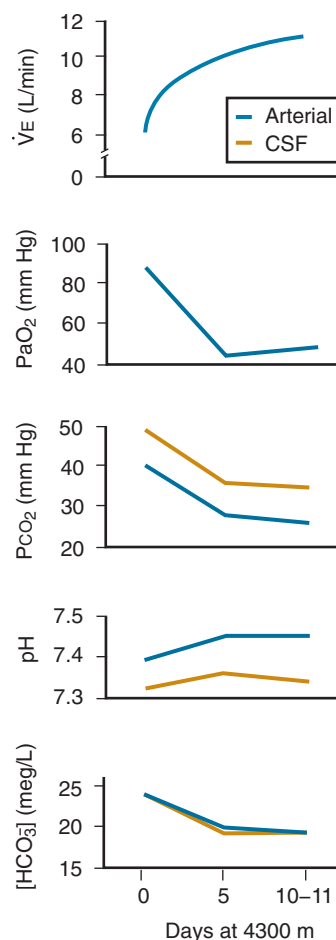


Figure 77-2 Ventilatory acclimatization during 10- to 11-day sojourn to 4300 m. Ventilation continues to increase as cerebrospinal fluid acid-base alterations parallel plasma changes. HCO₃⁻, bicarbonate; PaO₂, arterial oxygen tension; PCO₂, carbon dioxide tension; V_E, minute volume of ventilation. (From Forster HV, Dempsey JA, Chosy LW: Incomplete compensation of CSF [H⁺] in man during acclimatization to high altitude [4300 m]. *J Appl Physiol* 38:1067–1072, 1975.)

tive acidosis in the *cerebrospinal fluid* (CSF) and at medullary chemosensors triggers the increased ventilation but lumbar CSF remains alkaline during high-altitude (3100 m) sojourns of up to 3 weeks, while during deacclimatization, hyperventilation persists even when arterial PCO₂ and blood and CSF pH have returned toward normal.⁸ The pH of brain interstitial and intracellular fluid has also failed to show changes that could account for the increase in ventilation.⁹ These results suggest that some mediator other than hydrogen ion sustains the hyperventilation during a high-altitude sojourn. One possible mediator may be erythropoietin signaling in the brain via erythropoietin receptors.¹⁰ Another factor that would promote progressive hyperventilation is an increase over time in carotid body sensitivity to hypoxia.¹¹

Intermittent Hypoxic Exposure. The sustained increase in ventilation generally pertains to exposures lasting days to weeks. Shorter intermittent exposures also affect ventilatory responses to both oxygen and carbon dioxide.¹² Studies have focused on the “dose” and frequency of the hypoxic stimulus necessary to induce a physiologic response. For example, 8 hours of exposure to isocapnic and poikilocapnic

(i.e., varying PCO_2) hypoxia (end-tidal $PO_2 = 55$ mm Hg) increases the chemosensitivity to carbon dioxide compared to controls,¹³ while a 1 hr/day exposure to a simulated 4500-m altitude was associated with increased HVR, ventilatory equivalents (\dot{V}_E/\dot{V}_{O_2}), and arterial SO_2 during post-exposure hypoxia.¹⁴

Chronic Ventilatory Adaptation. Long-term high-altitude residents have lower ventilation and higher arterial PCO_2 than acclimatized lowlanders at the same elevation and have blunted ventilatory responses to acute hypoxia.¹⁵ The blunted response arises in conjunction with carotid body hypertrophy and may be an adaptive phenomenon in which the disadvantage of the lower arterial PO_2 is offset by the decreased work of breathing associated with lower ventilation.

Pulmonary Function and Mechanics

On ascent, lung function changes in several ways. Vital capacity decreases in the first 24 hours and remains depressed at high altitude.¹⁶ Proposed mechanisms for a lower vital capacity include increased interstitial fluid volume, resulting in airway narrowing, gas trapping, and delayed emptying of some lung units,¹⁶ pulmonary vascular engorgement,¹⁷ decreased respiratory muscle strength,¹⁸ and reduction in lung compliance by hypocapnia.¹⁹ In addition, peak expiratory flow rates are increased and airway resistance is reduced.²⁰ The lower airway resistance is presumably due to decreased air density, which counteracts any narrowing of airways due to hypoxia and hypocapnia.

In contrast, vital capacity is increased in high-altitude residents compared to that in nonnative residents,²¹ with the magnitude of the increase dependent on the length of stay at high altitude. Those born and raised at high altitude develop larger vital capacities than those who move to high altitude later in life.²²

Gas Exchange

Ventilation and Perfusion Matching. The increase in ventilation during acute hypoxia is matched by increased cardiac output and pulmonary perfusion. Additionally, alveolar hypoxia triggers *hypoxic pulmonary vasoconstriction* (HPV), which increases pulmonary vascular resistance. These changes cause redistribution of blood flow to areas of the lung that are usually less well perfused at sea level and may, thereby, improve \dot{V}_A/\dot{Q} matching and optimize gas exchange.

Diffusion. Several factors limit diffusion of oxygen from the alveolus to blood at high altitude. Decreasing barometric pressure lowers alveolar PO_2 , which, in turn, decreases the pressure gradient for diffusion such that at altitudes above 2500 m even the estimated pulmonary capillary transit time at rest of 0.75 second may not be adequate for end-capillary equilibration of oxygen; diffusion limitation is exacerbated during exercise due to the shortened transit time of blood across the pulmonary capillary and the greater fall in mixed venous PO_2 . Because the low arterial PO_2 lies on the steep portion of the oxygen-hemoglobin dissociation curve, a small decrease in PO_2 will result in a proportionately greater drop in pulmonary capillary oxygen content than at sea level. West and Wagner²³ modeled these

factors for the summit of Mt. Everest ($P_B \sim 250$ mm Hg) and found that alveolar-capillary equilibration of oxygen is far from complete (Fig. 77-3).

With long-term residence at high altitude, the diffusing capacity of the lung increases, although the mechanism for this increase remains unclear. When compared to

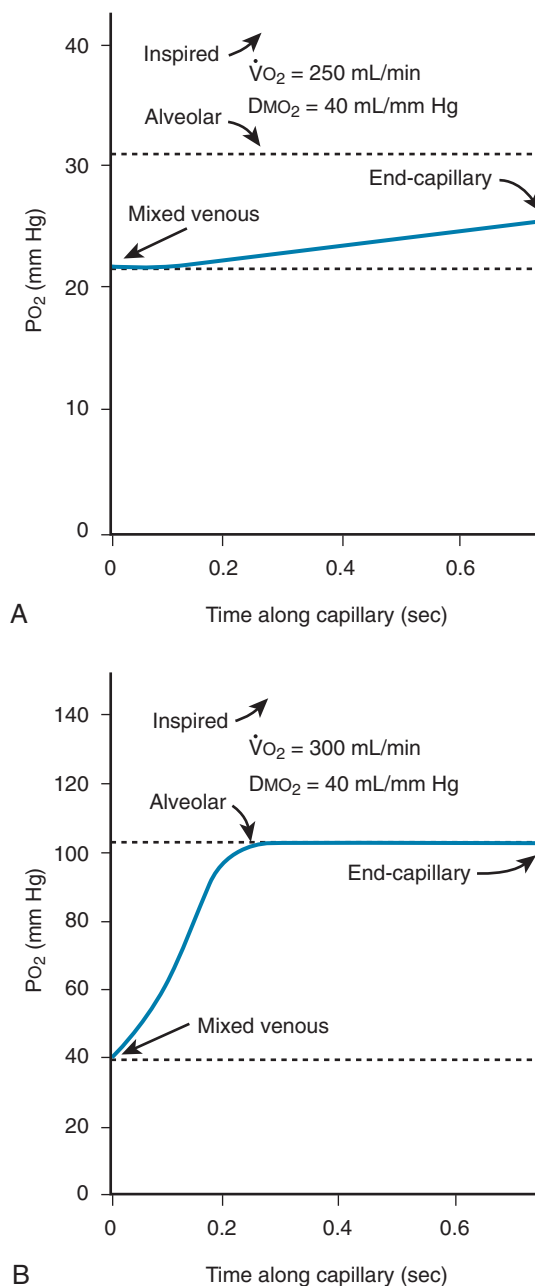


Figure 77-3 Comparison of the calculated time course of oxygen tension (PO_2) in the pulmonary capillary of a climber at rest on the summit of Mt. Everest (A) (barometric pressure = 250 mm Hg, inspired $PO_2 = 43$ mm Hg) to sea-level values (B) (barometric pressure = 760 mm Hg, inspired $PO_2 = 150$ mm Hg). At sea level, there is adequate time for equilibration of alveolar and end-capillary oxygen, whereas at extreme altitude, even at rest, when transit time for the red blood cell is presumably similar to that at sea level, full equilibration is not realized, resulting in end-capillary blood that is not fully saturated. \dot{V}_{O_2} , oxygen consumption; DMO_2 , diffusion capacity of the alveolar capillary membrane. (From West JB, Wagner PD: Predicted gas exchange on the summit of Mt. Everest. *Respir Physiol* 42:1–16, 1980.)

sojourners, high-altitude residents have a lower $(A - a)PO_2$ difference, increased diffusing capacity, and despite having lower ventilation, a higher arterial PO_2 at rest and during exercise.^{24,25}

CARDIOVASCULAR ADAPTATION

Cardiac Response

With acute hypoxia and decreased arterial oxygen content, cardiac output increases in an effort to maintain oxygen delivery so that, for any given work rate, cardiac output is higher than at sea level. After about 1 week, the relationship between cardiac output and work rate returns to that seen at sea level. The increase in cardiac output is explained largely by an increase in heart rate rather than a change in stroke volume. In fact, stroke volume actually declines upon initial exposure to high altitude and remains lower than sea-level values despite acclimatization. The lower stroke volume is not due to depressed myocardial function, according to studies that reveal evidence of preserved cardiac contractility in hypoxia²⁶; instead, it is likely due to diminished preload from a reduction in plasma volume. Systemic blood pressure increases in sojourners upon acute exposure to high altitude, likely due to increased sympathetic activity,²⁷ but decreases over time. In fact, in as few as 1 to 2 years after moving to high altitude, many people have lower systemic pressure, likely secondary to a vasodilatory effect of hypoxia on systemic arterial smooth muscle.

Hemodynamic Response

At high altitude, low alveolar PO_2 triggers vasoconstriction in the pulmonary vasculature, a response known as *hypoxic pulmonary vasoconstriction*, or HPV. Pulmonary artery pressure increases minimally until the alveolar PO_2 drops below 70 mm Hg, at which point a more marked rise ensues (Fig. 77-4). There is, however, substantial interindividual variability in this response.²⁸

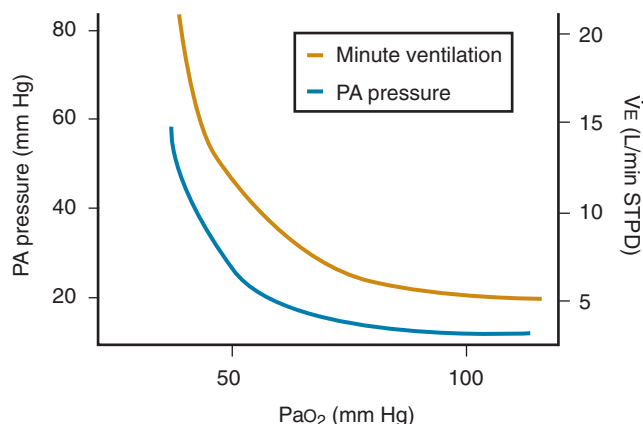


Figure 77-4 Relationship of arterial oxygen tension (PaO_2) to minute ventilation (\dot{V}_E) and pulmonary arterial (PA) pressure. Although there is variability among individuals, both the ventilatory and the pulmonary vascular response do not increase until arterial PO_2 falls below 70 mm Hg. (From Reeves JT, Wagner WW Jr, McMurtry F, et al: Physiological effects of high altitude on the pulmonary circulation. In Robertshaw D, editor: *International review of physiology: environmental physiology III*. Baltimore, 1979, University Park Press, pp 289–310.)

Chronic hypoxic exposure results in even greater increases in pulmonary vascular resistance and pulmonary hypertension due to pulmonary vasoconstriction, hyperviscosity from polycythemia, and extensive vascular remodeling due to smooth muscle hypertrophy and collagen proliferation. The precise time course of these changes is not clear. In a 40-day simulated ascent of Mt. Everest (Operation Everest II), Groves and coworkers²⁹ exposed individuals to progressively lower inspired oxygen tensions and demonstrated an increase in pulmonary vascular resistance of more than threefold. Interestingly, after the 40 days, breathing 100% oxygen did not return the pulmonary vascular resistance to the sea-level baseline. This result suggests that the vasculature can remodel in just a few weeks. Depending on the severity of changes, particularly the degree of intimal fibrosis, reversal of pulmonary hypertension may require months or years at low altitude.³⁰

HEMATOLOGIC ADAPTATION

Erythropoietic Response

Hemoglobin concentration increases within 1 to 2 days of ascent and continues to rise for a number of weeks. The initial rise is due to hemoconcentration from a diuresis; further changes are due to increased red blood cell production, a result of hypoxia-mediated release of erythropoietin by the kidneys. Serum erythropoietin levels increase within 24 to 48 hours of ascent, and then decline over 3 weeks as acclimatization progresses.³¹ Both red blood cell volume and total blood volume increase. The erythropoietic response ceases on descent and hematocrit returns to sea-level values in approximately 3 weeks.

Although hematocrit generally increases with altitude, there is interindividual variability in the responses of both sojourners³² and highlanders.³³ Similar variability is seen among different highland populations, which may be genetically determined³⁴: Andean natives demonstrate greater erythropoiesis than either Himalayan or Ethiopian highlanders.³⁵ Whether greater erythropoiesis in Andean natives is secondary to genetic factors, environmental exposures, such as high levels of cobalt in and around mining regions,³⁶ or an up-regulation of the erythropoietic response to the renal sensing of hypoxia³⁷ is not clear.

While increasing hemoglobin concentration can augment arterial oxygen content, it may also impair oxygen delivery, in that, as the hematocrit approaches 60%, viscosity increases sufficiently to impair cardiac output and limit perfusion of the microvasculature.

Oxygen-Hemoglobin Affinity

Oxygen transport by blood is also influenced by the oxygen affinity of hemoglobin, as defined by the shape and position of the oxygen-hemoglobin dissociation curve. An important feature of the oxygen-hemoglobin relationship is the manner in which the dissociation curve steepens as arterial PO_2 falls below 60 mm Hg. As a result, with ascent to high altitude, arterial PO_2 falls into a range in which the oxygen content of hemoglobin drops precipitously with only small decreases in PO_2 .

To mitigate the potentially large impact on oxygen delivery, adaptations take place in the oxygen-hemoglobin

relationship. For example, with initial exposure to high altitude and the resultant respiratory alkalosis, the dissociation curve shifts to the left. This shift enhances oxygen loading in the lungs and increases arterial oxygen content but comes at the expense of potentially decreased oxygen off-loading in the tissues. Over time, the curve shifts back to the right in response to increased 2,3-diphosphoglycerate concentrations and renal compensation for the respiratory alkalosis and improves oxygen off-loading in the tissues.

Coagulation

Hemostasis has not been shown to change in a consistent manner, with conflicting results regarding the effect of high altitude on platelet counts, bleeding times, and markers of thrombin and fibrin formation.³⁸⁻⁴⁰ Increased fibrinogen levels and prolonged clot lysis times in patients with *high-altitude pulmonary edema* (HAPE)⁴¹ have been taken as evidence that thrombosis and platelet aggregation may contribute to this disease. Bartsch and associates,⁴² however, performed careful longitudinal studies while subjects were developing HAPE and concluded that platelet and coagulation changes had no causative role. Thromboembolic risk at altitude may be linked to the underlying coagulopathy,⁴³ but more work is necessary on this question.

TISSUE ADAPTATION

At the final stage of oxygen delivery, oxygen moves from plasma to the site of oxidative phosphorylation in the mitochondria. Driving pressures of 10 mm Hg may be needed for movement from capillary plasma to the cytoplasm while driving pressures of only 1 to 2 mm Hg are necessary for diffusion from cytoplasm to the mitochondria. At sufficiently high altitudes, the capillary P_{O_2} may fall to levels at which diffusion from plasma into the mitochondria is impaired. Structural and biochemical responses (e.g., diminished muscle fiber size that reduces diffusion distance from blood to mitochondria, increased myoglobin concentration, and increased levels or activity of enzymes involved in oxidative metabolism) help overcome this problem. Much of this structural and metabolic adaptation may be driven by gene transcription via hypoxia inducible factors 1 and 2, which are known to regulate many hundreds of genes involved in tolerance to hypoxia, such as erythropoietin, vascular endothelial growth factor, nitric oxide synthase, and numerous enzymes in intermediary metabolism.⁴⁴ Finally, recent evidence indicates that many cells express cytoglobins, heme proteins with oxygen-binding and transport characteristics similar to myoglobin, which may be up-regulated in hypoxia and play a role in adaptive responses.⁴⁵

CENTRAL NERVOUS SYSTEM ADAPTATION

Cerebral Blood Flow

On acute exposure, hypoxia triggers an increase in cerebral blood flow that is, in part, offset by hypocapnic-mediated cerebral vasoconstriction; the net result is a modest increase in cerebral blood flow,⁴⁶ which appears to be equally distributed between white and gray matter.⁴⁷ The acute cerebrovascular response may be biphasic in nature with an initial

decrease in cerebral blood flow due to acute hypocapnia followed by a subsequent increase triggered by arterial hypoxemia.⁴⁸ After 4 to 5 days, cerebral blood flow decreases but is still 13% greater than the sea-level value.⁴⁶ This increase in cerebral blood flow helps maintain oxygen delivery when arterial oxygen content is at its lowest until other adaptive mechanisms take effect and raise arterial oxygen content.

Cerebral Function

As one ascends, motor, sensory, and complex cognitive abilities are progressively impaired. New tasks are learned with difficulty at 3048 m, and simulated altitudes of 6100 m result in a decrement in sensory, perceptual, and motor performance. Short-term memory is impaired in climbers ascending without supplemental oxygen to 8500 m or higher.⁴⁹ Even acute, modest decreases in arterial SO_2 to 85% impair mental concentration and fine motor coordination; a further decrease to 75% results in poor judgment, irritability, and decreased muscle function.

It is difficult to predict which individuals will experience neurologic dysfunction at high altitude, but combined data from a field study on Mt. Everest and a chamber study simulating an ascent of Mt. Everest (Operation Everest II), demonstrated that individuals with a high HVR and higher arterial SO_2 had more pronounced neuropsychometric dysfunction.⁵⁰ One explanation for these findings is that those with a more brisk HVR might have greater hypocapnic cerebral vasoconstriction and, consequently, lower cerebral oxygen delivery.

A recent study in which brain *magnetic resonance imaging* (MRI) was performed on climbers who had ascended to summits between 5895 and 8848 m demonstrated evidence of subcortical lesions suggestive of small infarctions.⁵¹ The study did not correlate these findings with symptoms or signs of neurologic dysfunction and did not include follow-up studies to determine whether these lesions resolved, but the results raise the question as to whether high-altitude exposure causes permanent cerebral injury and whether the observed dysfunction at high altitude persists over time. Existing evidence suggests that the transient deterioration in learning, memory, and expression of verbal material return to baseline within 1 year but that fine motor coordination problems may persist for longer periods of time.^{50,52}

Cellular Adaptive Mechanisms

As with cytoglobin up-regulation in peripheral tissues, intracerebral expression of neuroglobin, another protein related to hemoglobin and myoglobin, is increased during hypoxic stress and may play a role in limiting neuronal dysfunction or injury.⁵³

FLUID HOMEOSTASIS AND RENAL FUNCTION

Upon ascent to high altitude, there is diuresis and natriuresis and, as with the HVR, these peripheral chemoreceptor-mediated responses vary almost 10-fold between individuals over the first 24 to 48 hours at altitude.⁵⁴ Following acclimatization, further gains in elevation may lead to additional diuresis and natriuresis.⁵⁵ The mechanism underlying this observed diuresis and natriuresis is not clear, but it does not

appear to result from changes in renin, angiotensin, aldosterone, or atrial natriuretic peptide levels. In acute hypoxia, urinary protein excretion increases twofold to threefold, and with high-altitude illness, urinary protein excretion increases further.

CHANGES IN COMMON SEA-LEVEL ACTIVITIES AT HIGH-ALTITUDE

SLEEP

Difficulty sleeping is a common problem at high altitude. In studies examining pharmacologic prophylaxis for *acute mountain sickness* (AMS), for example, more than 70% of people receiving placebo reported poor-quality sleep.⁵⁶ In addition to subjective impressions of sleep impairment, there is objective evidence of poor sleep, with increased arousals, changes in sleep architecture, and an increased incidence of periodic breathing (Video 77-1).⁵⁷ In addition, it is during sleep that both sojourners and natives experience the most severe hypoxemia, because steep, transient drops in oxygen saturation often accompany apneic periods.

The mechanisms underlying periodic breathing at high altitude have been reviewed elsewhere.⁵⁸ The consensus is that sleep eliminates most cortical influences on respiration, leaving hypoxemia via carotid chemoreceptors as the prominent drive. The effect of hypoxia-induced changes in PCO_2 on hypoxic drive may set up oscillations of ventilation in a poorly damped system. At moderate altitudes (<3000 m), this periodic breathing diminishes over several days as ventilatory acclimatization proceeds, but at higher altitudes periodic breathing persists for long periods of time.⁵⁹

Periodic breathing during sleep at high altitude can be eliminated by breathing supplemental oxygen (Fig. 77-5) and can be reduced through the use of respiratory stimulants such as acetazolamide.⁶⁰ A review of trials of acetazolamide in AMS prophylaxis demonstrates that sleep was also improved in the acetazolamide groups compared to the placebo groups.^{56,61} More recently, the benzodiazepine class drug temazepam has also been shown to reduce the incidence of periodic breathing and improve measures of sleep quality without a negative effect on next-day reaction

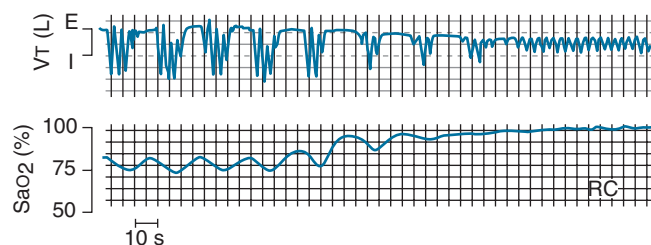


Figure 77-5 Periodic breathing in lowlander at 5400 m during sleep while breathing ambient air (left half of tracings) and oxygen (right half of tracings). Upper panel is tidal volume (VT, inspiration downward), and lower panel is arterial oxygen saturation (SAO_2 , %). (From Lahiri S, Maret K, Sherpa MG: Dependence of high-altitude sleep apnea on ventilatory sensitivity to hypoxia. *Respir Physiol* 52:281–301, 1983.)

times or maintenance of wakefulness.⁵⁹ Gamma aminobutyric acid receptor agents, including zolpidem and zaleplon, can also improve sleep quality and sleep architecture, but there is no evidence that either agent decreases periodic breathing.⁶²

EXERCISE

Exercise at high altitude is different in many important respects from exercise at sea level.

Maximal Work

With acute and prolonged hypoxic exposures, maximal oxygen consumption ($\dot{V}O_{2max}$) and work capacity are decreased relative to sea-level values.^{63,64} $\dot{V}O_{2max}$ decreases about 10% per 1000 m of altitude gain so that, at approximately 0.5 atm, $\dot{V}O_{2max}$ is about half of its sea-level value and, at 0.33 atm (as at the summit of Mt. Everest), $\dot{V}O_{2max}$ is about 23% of that at sea level. Because maximum oxygen uptake is decreased at altitude, maximum minute ventilation and heart rate at peak exercise are also reduced compared to their sea-level values (Fig. 77-6).⁶³

Ventilation

Because of the decrease in air density and the lower amount of oxygen, greater ventilation is required to achieve the same oxygen uptake at high altitude. As a result, the ventilatory response to exercise is augmented at altitude compared to sea level.⁶³ For example, with a sojourn to 6300 m, the ventilation for a given metabolic rate (the ventilatory equivalent, $\dot{V}E/\dot{V}O_2$) is almost four times as great as at sea level. The increase is a function of both the altitude attained

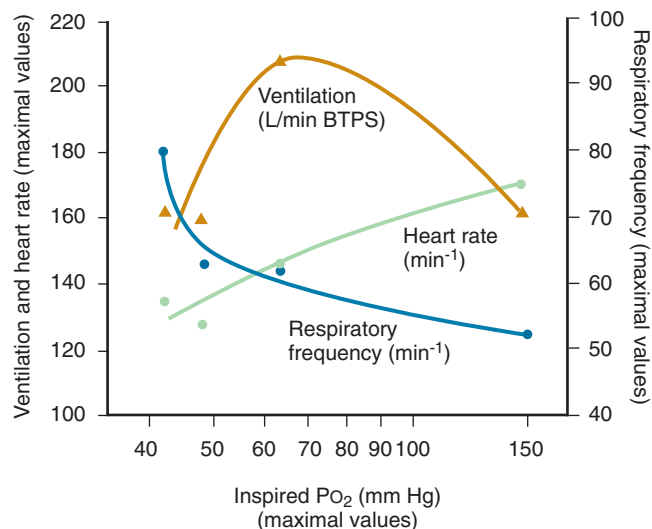


Figure 77-6 Maximal ventilation ($\dot{V}E_{max}$), respiratory frequency, and heart rate versus inspired PO_2 . At a PO_2 of 64 mm Hg (equivalent to an elevation of 6300 m), $\dot{V}E_{max}$ is increased to a maximum of over 200 L/min because of the stimulation to ventilation from hypoxia as well as a decreased density of the inspired air, whereas at a PO_2 of 43 mm Hg (equivalent to an elevation more than 8000 m such as on Mt. Everest), $\dot{V}E_{max}$ is decreased, probably as a result of a diminished metabolic demand from low work rates. Respiratory frequency continues to increase. Maximum heart rate decreases with increasing altitude. (From West JB, Boyer SJ, Graber DJ, et al: Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol* 55:688–702, 1983.)

and the strength of the individual's HVR.⁶⁵ The increase in ventilation comes at a price, however. At extreme altitude, the oxygen cost of breathing during exercise may be as high as 40% of the overall metabolic rate and may result in allocation of cardiac output to respiratory muscles that could otherwise be dedicated to muscles of locomotion. Extreme dyspnea with exercise may affect the intensity and duration of exercise; with rest, dyspnea typically resolves rapidly.

Gas Exchange

Unlike at sea level, where arterial oxygen saturation remains constant with increasing workloads in most normal individuals, it decreases with increasing workloads following either short⁶⁶ (Fig. 77-7) or long duration high-altitude exposures.⁶³ Alveolar hypoxia decreases the driving gradient for diffusion while pulmonary capillary transit time is shortened as a result of the increase in cardiac output, thereby creating a true diffusion limitation (see Fig. 77-3). \dot{V}_A/\dot{Q} mismatching may also contribute to the observed gas exchange abnormalities⁶⁶; nonuniform hypoxic pulmonary vascular response may lead to interstitial pulmonary fluid accumulation, which, in turn, creates \dot{V}_A/\dot{Q} heterogeneity and impairs gas exchange.

Cardiovascular Response

For any given *submaximal* work rate, cardiac output and heart rate are higher during exercise at altitude compared to sea level. With acclimatization, cardiac output at submaximal workloads returns to sea-level values while the heart rate remains elevated. However, *maximal* exercise capacity and peak heart rate and cardiac output at altitude are reduced relative to sea-level values. With acclimatization, maximal exercise capacity is not restored to sea-level

values over time and maximum cardiac output, heart rate, and stroke volume all remain decreased.²⁶

Pulmonary artery pressures reach high levels during exercise at high altitudes.²⁹ Whether these high pressures limit exercise capacity at altitude is not clear. On the one hand, because cardiac output is maintained at levels appropriate for the work rates attained, the increase in pulmonary vascular resistance in healthy sojourners to high altitude would not appear to limit exercise. However, in a field study of acclimatized individuals,⁶⁷ administration of the phosphodiesterase inhibitor sildenafil prior to a maximum exercise test at 5245 m lowered pulmonary artery systolic pressure and improved maximum exercise capacity compared to placebo, but other studies have not confirmed this.⁶⁸ Alternatively sildenafil improves arterial oxygenation, which may explain the greater exercise capacity.⁶⁹ Thus, it remains unresolved whether the rise in pulmonary artery pressures contributes to limiting exercise capacity at high altitude.

Exercise Performance at High Altitude

The effect of altitude on exercise performance varies based on the type of activity and the duration of stay at high altitude. Performance for running events of less than 2 minutes' duration at less than 3000 m altitude is not impaired and may even be slightly improved because of decreased air density and resistance. Performances in events of longer duration are predictably diminished and can be restored only part way to sea-level capacity with prolonged stays at high altitude. Finally, as noted earlier, maximum oxygen consumption, peak heart rate, and peak minute ventilation are reduced at high altitude. Regardless of the duration of stay or the intensity of training, these values do not return to sea-level values.

Training at High Altitude

There is considerable interest in whether living and training at high altitude improves performance at lower elevations. In the past, many elite endurance athletes relocated to and trained at moderate altitudes of 2000 to 2500 m, but the beneficial effects on performance after return to sea level were generally not realized, because athletes could not attain the same maximum speeds and power output during training at altitude that they needed to reach during their sea-level races. More recently, interest has been raised in using intermittent hypoxic exposure as an alternative means to apply the benefits of high-altitude acclimatization to sea-level performance. For example, Beidleman and colleagues⁷⁰ found that intermittent exposure to 4300-m altitude for 3 weeks improved speed and endurance in trained cyclists. In their landmark study, Levine and coworkers⁷¹ studied four well-matched groups of athletes: (1) those who lived low and trained low (1350 m), (2) those who lived low and trained high (3000 m), (3) those who lived high and trained high, and (4) those who lived high and trained low. The group that lived high and trained low seemed to have gained the benefit of hypoxic conditioning while not losing the intensity of training sessions. This advantage was presumably due to the modestly elevated hemoglobin from the altitude exposure, although there was individual variability in the erythropoietic response that correlated with improvement in performance.⁷²

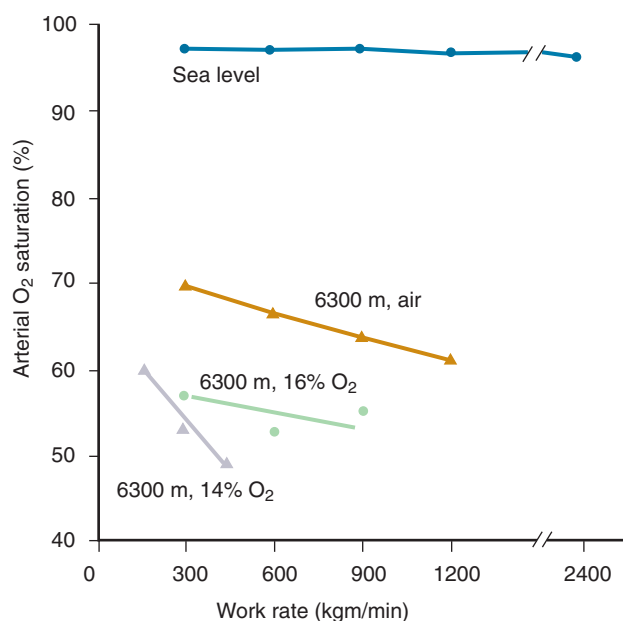


Figure 77-7 Arterial oxygen saturation with exercise at altitude. Arterial oxygen saturation (%) does not decrease with exercise at sea level but drops progressively with higher workloads at greater altitudes. There is a diffusion limitation of oxygen transfer across the alveolar-hemoglobin interface. (From West JB, Boyer SJ, Graber DJ, et al: Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol* 55:688–702, 1983.)

Because of the limited access to high altitude for many athletes, recent interest has focused on “bringing the mountain to the athlete”⁷³ by having the athlete spend time each day in oxygen-depleted tents that can be set up in their home or training center. The key question that has emerged from this practice and the studies noted, however, is this: What “dose” of hypoxic exposure and what level of athletic capacity is necessary to see a benefit in sea-level performance? A review of studies on the topic concluded that athletes needed to reside at 2000–2500 m for at least 4 weeks for at least 22 hours/day in order to derive physiologic benefit from the live high–train low model.⁷³ However, a recent placebo-controlled trial in which elite athletes were blinded to whether they were in the “live high” group found no benefit to this strategy.⁷⁴

MALADAPTATION

The physiologic adaptations described earlier give most individuals the ability to tolerate high-altitude exposure. Regardless of the ultimate altitude achieved, however, individuals who ascend too rapidly to altitudes above 2500 m may display maladaptive responses and develop one of three forms of acute altitude illness: AMS, HAPE, and *high-altitude cerebral edema* (HACE). Because the risk of such illnesses decreases as individuals spend more time at altitude, long-term residents are not susceptible to these problems. However, several forms of chronic altitude illness, chronic mountain sickness and right heart failure, can affect these populations and represent important public health concerns.

PROBLEMS OF LOWLANDERS ON ASCENT TO HIGH ALTITUDE

Susceptibility to Altitude Illness

The incidence and severity of acute altitude illness depend on several factors, including the rate of ascent, the length of stay, and individual susceptibility. A trip to and from high altitude on the same day poses much less risk than an overnight stay because hypoxia is accentuated during sleep and because more prolonged exposure is associated with the overnight stay. Susceptibility to altitude illness varies considerably among individuals but, for a single individual, the symptoms are often reproducible given the same rate of ascent and other circumstances. Whereas men and women are equally susceptible to AMS,^{75,76} younger adults⁷⁵ and the obese⁷⁶ may be slightly more vulnerable. Recent trips to high altitude⁷⁷ and residence at moderate altitude (>1900 m)⁷⁸ have a protective effect. Of note, being in good physical condition does not exert any protective effect.⁷⁹ There are insufficient data regarding whether preexisting chronic illnesses increase susceptibility.

At present, there are no adequate means to predict who will get sick upon ascent to high altitude. Variables such as the HVR⁸⁰ and arterial oxygen saturation during hypoxic exposure⁸¹ have been proposed as useful predictors for developing AMS, but have not been validated in further studies, while specific genetic markers that reliably predict susceptibility have also yet to be identified.⁸² Richalet and

colleagues⁸³ have proposed a model to identify patients with risk factors for severe high-altitude illness, but this prediction tool requires the use of cardiopulmonary exercise testing under hypoxic conditions to identify susceptible individuals and, as a result, can be difficult to implement on a wide basis.

HAPE-susceptible individuals have been shown to have intense HPV and exaggerated pulmonary vascular responses to resting hypoxia and normoxic exercise,^{28,64} but this relationship has not been validated in prospective studies. In the end, the only useful predictive tool remains the patient's prior experience at high altitude, particularly when the ascent rate and altitude of the prior and planned sojourns are similar.

Acute Mountain Sickness

AMS is the most common form of acute altitude illness, affecting 22% to 50% of travelers to altitudes between 1850 and 4240 m.^{75,76} Because of increasing awareness of the risks of altitude illness among the general population, incidence rates have likely fallen in commonly traveled regions, but very high incidence rates (up to 70%) continue to be reported with rapid ascents to high elevations in certain regions such as Mt. Kilimanjaro.⁸⁵

Clinical Presentation. AMS is marked by the presence of headache plus one or more other symptoms including lassitude, insomnia, anorexia, nausea, dizziness, and, in severe cases, vomiting, although recent debate has developed as to whether headache is required for diagnostic purposes.^{86,87} Symptoms do not start immediately upon ascent and, instead, come on over many hours following arrival at altitudes above 2400 m (8000 feet), with the elevation at which symptoms begin varying significantly between individuals. Although many people complain of a sense of oppression in the chest, there is rarely any respiratory distress when the patient is at rest.

There are no characteristic physical examination findings in AMS, although crackles on auscultation and peripheral edema have been documented in some reports.^{88,89} No consistent changes are seen in body temperature, with some studies reporting a mild increase in temperature⁹⁰ and others reporting a decrease of 1.7°C with no change in metabolic rate.⁹¹ Oxygen saturation values may be lower in individuals with AMS compared to those who remain healthy,^{92,93} but AMS can still be seen in those with what would be considered normal oxygenation at a particular altitude.

The symptoms and signs of AMS are nonspecific and other causes must be considered on the differential diagnosis, including dehydration, hypothermia, hyponatremia, exhaustion, alcohol hangover, carbon monoxide poisoning, and respiratory or cerebral infections. The diagnosis is based solely on the clinical history and there are no confirmatory laboratory tests. For a diagnosis of AMS and not the more severe HACE, the patient must have normal neurologic and mental status examinations.

Natural Course of Untreated AMS. In a study of Indian soldiers⁸⁸ airlifted to 3300 to 5500 m, incapacitating illness lasted 2 to 5 days but full recovery often took longer; 38% recovered fully within 3 days, 40% were still ill after 1 week,

and 13% had symptoms after 1 month. In tourists sleeping at a lower altitude (2700 m), symptoms lasted an average of 15 hours (range: 6 to 94 hours).⁹⁴ Most individuals tolerate or treat their own symptoms as the illness resolves over 1 to 3 days, but some persons with AMS seek medical help or are forced to descend. HACE or HAPE develops in a small percentage of those with AMS, especially when ascent is continued despite illness.

Pathophysiology. Current concepts of pathophysiology emphasize the cerebral etiology of AMS. In severe illness, elevated intracranial pressure and cerebral edema have been noted on neurologic imaging⁹⁵ and brain biopsy.⁸⁸ Brain MRI studies⁹⁵ have demonstrated swelling in the white matter and none in the gray matter in patients with HACE, a finding that suggests the edema is vasogenic in origin and initially confined to the white matter. Brain MRI also shows slightly increased brain volume and decreased intracerebral CSF volume in patients with AMS than in those without symptoms.⁹⁶ Subsequent studies revealed conflicting data, with some reporting no evidence of changes consistent with cerebral edema⁹⁷ and others⁹⁸ showing evidence of mild increases in brain volumes and evidence of cytotoxic edema in subjects with mild to moderate AMS. It has been suggested that development of AMS may depend to some extent on the ability to shift CSF out of the cranium, and those individuals with smaller ventricles and CSF spaces may be at a disadvantage. This argument, referred to as the “tight-fit” hypothesis, might explain the increased susceptibility of younger persons, because age-related increases in the volume of sulci in older persons may provide more room to accommodate mild brain swelling.⁹⁹

Although evidence suggests that cerebral edema plays a role in severe AMS, it remains unclear whether this causes milder forms of the disease. There is only one study of intracranial pressure in subjects with early AMS, and it failed to demonstrate an increase in CSF pressure.⁹⁹ Because headaches arise early in AMS at a time when edema and significant increases in intracranial pressure are unlikely, alternative explanations should be considered. The classic explanation that the headache and other symptoms of AMS are due to cerebral vasodilation alone seems unlikely, because the severity of AMS symptoms has not been shown to correlate with middle cerebral artery blood flow velocity.¹⁰⁰ Limited evidence that sumatriptan, a 5-HT₁ receptor agonist, can prevent AMS¹⁰¹ or treat high-altitude headaches¹⁰² suggests that abnormal cerebrovascular reactivity or neuropeptide responses play a role in AMS pathophysiology. Another explanation is that hypoxia-induced changes in the blood-brain barrier alter permeability to plasma compounds with potential neurotoxicity or irritation. In studies in animals and cell cultures, hypoxia has been shown to mediate increased permeability of the blood-brain barrier to large molecules, but this has not been observed in humans.⁹⁸ The mechanism underlying these blood-brain barrier changes is unclear, but factors such as oxygen free radical species and vascular endothelial growth factors have been proposed as possible contributors.^{103,104}

The findings in severe AMS of possible cerebral edema, peripheral edema, and proteinuria also suggest that there may be a defect in salt and water homeostasis and an increase in capillary permeability. AMS-susceptible indi-

viduals have elevated aldosterone and antidiuretic hormone levels when compared with controls, while persons acclimatizing well exhibit diuresis, net water loss, and low antidiuretic hormone values.¹⁰⁵ A relatively recent study confirmed the findings regarding antidiuretic hormone but found no difference in aldosterone levels between healthy controls and those with AMS.¹⁰⁶ These alterations in hormone levels cannot be attributed to a generalized increase in systemic capillary permeability or endothelial cell dysfunction, in that subjects with and without AMS demonstrate no differences in the global transvascular escape of labeled protein.¹⁰⁷

Hypoventilation may also contribute to the development of AMS. Acetazolamide and theophylline, two medications with respiratory stimulant properties, prevent the disorder^{61,108} and a brisk increase in ventilation on ascent to altitude has been associated with a lower incidence of AMS.⁸⁰ At the same time, however, prospective studies have not demonstrated a correlation between a lower HVR measured before ascent and the development of AMS at high altitude.¹⁰⁹ Bartsch and coworkers¹⁰⁹ demonstrated that relative hypoventilation developed in subjects with early AMS compared to well-adapting subjects, suggesting that the blunted HVR was a response to AMS rather than a cause.

Prevention. Appropriate pharmacologic and nonpharmacologic measures to prevent or ameliorate AMS have been described in recently published guidelines.¹¹⁰ Because overly rapid ascent to high elevation is the leading risk factor for altitude illness, gradual ascent, with rest days for acclimatization, is considered the single best way to prevent all forms of altitude illness. It is recommended that above 3000 m, individuals should increase their sleeping elevation by no more than 300 to 500 m per night and should take an acclimatization day and sleep at the same elevation a second night every 3 to 4 days or after any large gain in elevation. Only a single study has attempted to study the benefits of slow ascent in a randomized, controlled manner,¹¹¹ and strict adherence to published recommendations may be difficult due to a variety of logistical factors. Travelers should avoid overexertion. They should refrain from heavy alcohol consumption or narcotic medication use, particularly before bedtime, in order to avoid hypoventilation, which can exacerbate the hypoxemia of high altitude. These strategies have never been subjected to rigorous study but represent common sense measures in light of the known physiologic changes at altitude.

Pharmacologic means can also be used to prevent AMS. The most commonly used medication for this purpose is acetazolamide.^{61,75} Its principal action is renal carbonic anhydrase inhibition, which causes a bicarbonate diuresis and a metabolic acidosis, which, in turn, stimulates ventilation, increases alveolar PO₂, and enhances oxygen off-loading in the tissues. In effect, the drug speeds natural acclimatization by accelerating the pace of ventilatory adaptation by several days. Actions of acetazolamide on carbonic anhydrase elsewhere in the body, such as the peripheral and central chemoreceptors, may also contribute to its preventive role.¹¹²

Debate persists about the proper dose of acetazolamide,¹¹³ but most published resources continue to recommend a

Table 77-2 Dosing and Use of Altitude Illness Medications in Normal Persons and in Patients with Underlying Disease

Medication	Dose in Normal Individuals	Liver Disease	Chronic Kidney Disease	Other Major Dosing Issues
Acetazolamide	AMS prevention: 125 or 250 mg bid AMS treatment: 250 mg bid	Use is contraindicated	Avoid use in patients with GFR < 10 mL/min, metabolic acidosis, hypokalemia, hypercalcemia, and hyperphosphatemia or recurrent nephrolithiasis	Avoid in patients on long-term high-dose aspirin or with ventilatory limitation (FEV ₁ < 25% predicted) Caution in patients with documented sulfa allergy Avoid concurrent use of topiramate
Dexamethasone	AMS prevention: 4 mg bid or 2 mg qid HACE treatment 8 mg once followed by 4 mg every 6 hours	No contraindication; no dose adjustments necessary	No contraindication; no dose adjustments necessary	Expect elevated blood glucose values when used in diabetic patients Avoid in patients at risk for peptic ulcer disease or upper gastrointestinal bleeding Caution in patients at risk for amebiasis or strongyloidiasis
Nifedipine	HAPE prevention: 20 to 30 mg of sustained release version every 12 hours HAPE treatment: 20 to 30 mg of sustained release version every 12 hours	Reduced dose required (10 mg bid)	No contraindication; no dose adjustments necessary	Caution in patients taking medications metabolized by CYP450 3A4 and 1A2 pathways Caution during concurrent use with other antihypertensive medications
Tadalafil	HAPE prevention: 10 mg bid HAPE treatment: Unknown	Child's class A and B: Maximum 10 mg daily Child's class C: Do not use tadalafil	Dose adjustments necessary if GFR < 50 mL/min. If GFR 30–50 mL/min, use 5-mg dose, maximum 10 mg in 48 hr. If GFR < 30 mL/min, no more than 5 mg	Increased risk for gastroesophageal reflux Caution in patients taking medications metabolized by CYP450 3A4 pathway Avoid concurrent use of nitrates or α -blockers
Sildenafil	HAPE prevention: 50 mg every 8 hours HAPE treatment: Unknown	Dose reductions recommended. Starting dose 25 mg tid Avoid use in patients at risk for variceal bleeding	Dose adjustments necessary if GFR < 30 mL/min	Increased risk for gastroesophageal reflux Caution in patients taking medications metabolized by CYP450 3A4 pathway Avoid concurrent use of nitrates or α -blockers
Salmeterol	HAPE prevention: 125 μ g bid HAPE treatment: No established role in HAPE treatment	Insufficient data	No contraindication; no dose adjustments necessary	Avoid concurrent use of β -blockers, monoamine oxidase inhibitors or tricyclic antidepressants Possible adverse effects in coronary artery disease patients prone to arrhythmia

AMS, acute mountain sickness; FEV₁, forced expiratory volume in 1 second; GFR, glomerular filtration rate; HACE, high-altitude cerebral edema;
HAPE, high-altitude pulmonary edema

dose of 125 to 250 mg twice a day^{96,110} (Table 77-2). Acetazolamide is well tolerated with the most common side effect being paresthesias involving the hands, feet, and lips. There may be nausea and drowsiness, and carbonated beverages may taste flat, probably secondary to the inhibition of hydration of carbon dioxide on the palate. Acetazolamide has a sulfonamide moiety and shares the cautions common to all sulfa drugs. The likelihood of a cross reaction is low (approximately 7% to 10%),¹¹⁴ but case reports describe fatal anaphylactic reactions in people with documented sulfa allergy who received acetazolamide.¹¹⁵

For patients who do not tolerate or cannot take acetazolamide, dexamethasone is an effective alternative for AMS prophylaxis.¹¹⁶ Studies comparing dexamethasone and acetazolamide have revealed approximately equal effectiveness of the two drugs in preventing AMS.¹¹⁷ Dexametha-

sone does not speed the acclimatization process and may be associated with reappearance of symptoms if it is abruptly discontinued. Suggested doses are listed in Table 77-2.

As noted earlier, theophylline can prevent AMS but given the narrow therapeutic window of the medication, it should not be used for this purpose. Conflicting results have been reported regarding the effects of ginkgo biloba on AMS prevention,^{118,119} likely as a result of variable production standards between manufacturers,¹²⁰ and as a result, the supplement should not be used for AMS prophylaxis. Recent attention has also focused on a potential role for ibuprofen in AMS prevention,¹²¹ but it has yet to be proven superior to acetazolamide for this purpose and is not part of standard recommendations at this time.¹¹⁰

In most cases, pharmacologic prophylaxis is not necessary, in that a slow ascent is usually sufficient to prevent

AMS. Pharmacologic prophylaxis may be reserved for those with a known increased risk for altitude illness, as for people with known susceptibility to AMS who are returning to altitudes at which they have been sick in the past, people flying into high-altitude destinations (e.g., La Paz, Bolivia), or people whose work mandates a rapid ascent (e.g., rescue teams).¹¹⁰

Treatment. In general, descent leads to resolution of all forms of altitude illness. Patients with mild illness may not require descent, however, and often recover by remaining at the same elevation and resting for a period of time. In more severe illness, descent is indicated and should continue until symptoms resolve. How much descent is required varies depending on the severity of the case; less severe illness may resolve with descent of only 300 m while more severe illness may require further drops in altitude. At times, because of field conditions, descent may not be feasible and alternative treatments are necessary. Severely ill patients can be placed on supplemental oxygen if gas tanks or an oxygen concentrator are available or “low altitude” can be brought to the patient through the use of lightweight portable hyperbaric chambers (Fig. 77-8). These chambers can be pressurized to 2 psi and mimic a descent of approximately 1500 m. By means of a foot pump, sufficient gas flow is maintained to keep the carbon dioxide concentration low and the oxygen concentration close to 21%.¹²² Studies demonstrate that the chamber is as effective as administering supplemental oxygen with an FIO_2 of 0.26 to 0.3, although the therapy is difficult to implement with claustrophobic individuals or those who are vomiting. As with oxygen therapy, relief of symptoms is generally immediate, but long treatment times are needed in severe illness and to ensure sustained improvement upon removal from the chamber.¹²²



Figure 77-8 A portable hyperbaric chamber used to treat severe altitude illness when supplemental oxygen is not available or descent is not feasible. The sick individual is placed in the bag, which is then closed using an air-sealed zipper. A foot pump is used to inflate the bag and increase the barometric pressure within it. Visual contact is maintained through plastic windows in the wall of the bag while verbal communication can be maintained across the wall of the bag. Once inflated to the target pressure, the bag must be pumped on a continual basis to maintain the target pressure and ensure adequate ventilation. Depending on the pressure to which the bag is raised, it is possible to simulate a descent of 2000 to 5000 feet (600 to 1500 m) for the individual inside the bag. (Copyright Andrew Luks, MD.)

Acetazolamide can ameliorate symptoms of AMS and improve arterial oxygenation,¹²³ while aspirin,⁸⁸ ibuprofen,¹²⁴ and acetaminophen¹²⁴ have been shown to treat the headache associated with AMS. Prochlorperazine is useful for treating nausea and vomiting and, unlike some other antiemetics, may actually increase rather than depress ventilation.¹²⁵ Even if it is not being used for AMS prophylaxis, dexamethasone should be part of the high-altitude traveler's medical kit, especially in remote areas of the mountains, because rapid treatment of evolving symptoms with dexamethasone may keep the patient ambulatory, allowing a rapid descent without need for an expensive evacuation.

High-Altitude Cerebral Edema

HACE is a potentially fatal form of acute altitude illness defined by the onset of mental status changes and/or ataxia in a person with AMS, or by the presence of both neurologic signs in a person without AMS who has recently ascended to altitude. It usually develops at higher altitudes than AMS.

In addition to ataxia and altered level of consciousness, many people develop an incapacitating headache, persistent nausea and vomiting, and debilitating lassitude. Affected individuals may also develop one of many neurologic symptoms and signs including papilledema, visual changes, cranial nerve palsies, bladder dysfunction, abnormal reflexes, paresthesias, pareses, aphasia, clonus, hallucinations, seizures, and behavioral changes.⁷⁵ If the disease is not recognized and treated promptly, coma and death may ensue.

While incidence rates of 0.53% to 1.25% have been reported,^{88,126} the true incidence is difficult to assess because the boundary of progression from AMS may be hard to define and the symptoms and signs may be similar to those of cerebral hypoxia secondary to severe hypoxemia from pulmonary edema. The differential diagnosis includes all other causes of encephalopathy, such as carbon monoxide poisoning, hypertensive crisis, severe cerebral hypoxia secondary to HAPE, meningitis, hypoglycemia, moderate to severe hypothermia, and migrainous encephalopathy. Because HACE is generally a problem of global neurologic dysfunction marked by gradual onset over a period of hours, a sudden onset and/or presence of focal neurologic deficits, high temperature, or neck stiffness should prompt consideration of alternative diagnoses. Diagnosis in the field is based on the clinical history and clinical examination. Heel-to-toe walking along a straight line is an effective test for the presence of ataxia (Video 77-2). When advanced diagnostic modalities are available, MRI reveals a pattern of reversible increased T2-weighted signal in the corpus callosum and, in particular, the splenium, which may help differentiate HACE from other conditions.⁹⁵

In persons who die of HACE, pathology reports reveal gross cerebral edema.¹²⁷ Findings include swelling and flattening of the cerebral gyri, compression of the sulci, herniation of cerebellar tonsils and uncus, small petechial hemorrhages, and venous and sinus thromboses. Brain MRI performed in patients with nonfatal HACE also reveals evidence of hemosiderin deposition, a finding consistent with the presence of microhemorrhages.¹²⁸

The definitive treatment for HACE is descent, although recovery is not as rapid as in AMS and HAPE, and descents

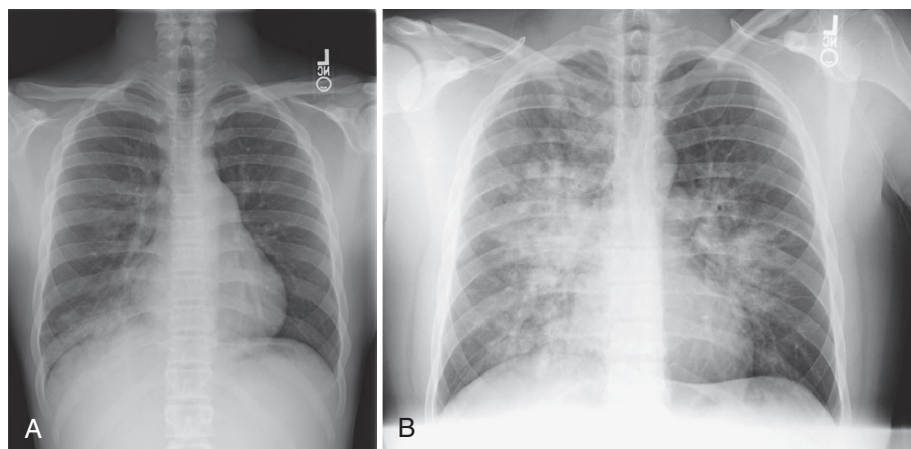


Figure 77-9 High-altitude pulmonary edema. **A**, Typical chest radiographic appearance of high-altitude pulmonary edema in a 15-year-old boy. Note that the edema is unilateral and predominantly right sided. **B**, Severe high-altitude pulmonary edema in a 27-year-old man. Note the normal heart size and the presence of bilateral opacities in this case. (Courtesy of Peter Hackett.)

of more than 1000 m may be necessary. If descent is not possible, oxygen or hyperbaric therapy may be lifesaving temporizing measures. In the only study of therapy, severe neurologic symptoms and signs responded to furosemide and betamethasone, although the drugs were not studied separately or in a prospective manner.⁸⁸ Dexamethasone is now routinely used in HACE management (see Table 77-2). Mannitol and glycerol have been suggested for treatment but are difficult to use safely in the field due to lack of adequate monitoring of serum osmolality and volume status and should only be used in a hospital or clinic setting.

High-Altitude Pulmonary Edema

HAPE is the most common cause of death from high-altitude illness. It was previously misdiagnosed as pneumonia, bronchitis, or congestive heart failure until reports by Hultgren and colleagues⁸⁴ and Houston¹²⁹ revealed it to be a distinct form of noncardiogenic pulmonary edema.

Clinical Presentation. HAPE typically manifests within 2 to 4 days of ascent to altitudes above 2400 m (8000 feet), most commonly beginning on the second night. In the early stages of the disease, decreased exercise performance develops and individuals require increasing amounts of time to recover from exertion. Individuals also complain of fatigue, weakness, and a persistent dry cough; symptoms of AMS may also be present. As the disease worsens, individuals become short of breath with minimal exertion. Dyspnea at rest, audible chest congestion, and production of pink frothy sputum are late findings in severe disease. Even in the absence of concurrent HACE, severe hypoxemia may produce mental changes, ataxia, and altered levels of consciousness.

On physical examination, the patient often appears better than one would expect based on blood gases and radiographic findings. There may be a low-grade fever to 38.5°C, as well as tachycardia and tachypnea. Crackles are initially heard in the right mid-lung fields and then more diffusely as the disease worsens. Generalized pallor and nail bed cyanosis may be noted. Radiographs and computed tomogra-

phy scans show patchy, alveolar opacities, which may be limited to one area (the right lung field predominating initially) or generalized, depending on illness severity (Fig. 77-9). Arterial blood gases reveal severe hypoxemia. In a study at 4559 m, for example, individuals with HAPE had a mean arterial PO_2 of 23 ± 3 mm Hg and an average saturation of $48 \pm 8\%$ versus 40 ± 5 mm Hg and $78 \pm 7\%$ for healthy controls.¹³⁰ Pulmonary artery pressure is high, but pulmonary wedge pressure is normal and heart size is not increased.⁸⁴

Pathologic Findings. A total of 22 autopsies have been reported in persons dying of HAPE.^{88,131} A red cell-rich proteinaceous exudate with hyaline membranes is characteristic. All had some areas of pneumonitis with neutrophil accumulation but no evidence of bacterial accumulation. Pulmonary veins were not dilated. Most reports mention capillary and arteriolar thrombi, fibrin deposits, hemorrhage, and infarcts.

Bronchoalveolar lavage samples obtained within the first 24 hours of ascent to 4559 m have demonstrated an increase in red blood cells and protein but an absence of inflammatory mediators and neutrophils,¹³² whereas samples obtained later in the disease process show even more protein, neutrophilia, and evidence of inflammation marked by such inflammatory mediators as leukotriene B_4 and thromboxane B_2 ,¹³³ as well as interleukin-1, -6, and -8, and tumor necrosis factor- α .¹³⁴

Possible Mechanisms. HAPE is a form of noncardiogenic pulmonary edema. Left ventricular function and pulmonary capillary wedge pressure remain normal. Although the mechanisms underlying HAPE remain incompletely understood, it appears that elevated pulmonary artery pressures play a central role in the process, in that multiple investigations have shown that affected individuals have markedly elevated pulmonary artery pressures compared to healthy controls.^{84,135}

HAPE-susceptible individuals have exaggerated HPV, which likely accounts for their elevated pulmonary artery

pressures; multiple studies demonstrate that HAPE-susceptible individuals have abnormally high pulmonary artery pressure responses during hypoxic breathing, during normoxic and hypoxic exercise, and on ascent to high altitude before the onset of edema.^{28,136} A lower HVR^{137,138} and slightly lower lung volumes¹³⁸ may also contribute to increased pulmonary artery pressure by increasing alveolar hypoxia and reducing the number of recruitable vessels. Finally, evidence suggests that increased sympathetic tone¹³⁹ and alterations in vasoactive mediators (*endothelin* [ET-1], *nitric oxide* [NO]) produced by pulmonary endothelial cells¹⁴⁰ may also lead to stronger HPV.

The levels of ET-1, a potent endothelial-derived pulmonary vasoconstrictor, are elevated in HAPE-susceptible individuals¹⁴⁰ and correlate with a rise in pulmonary artery pressures, whereas the levels of NO, a universal vasodilator, are lower in HAPE-susceptible subjects.¹⁴¹⁻¹⁴³ Bailey and colleagues¹⁴⁴ confirmed lower levels of NO in HAPE subjects at high altitude and also provided evidence of increased free radicals in the pulmonary circulation during HAPE, which might contribute to development of the disorder. Thus, an inherent imbalance of vasoconstrictors (ET-1) and vasodilators (NO) may constitute an important predisposing factor in HAPE-susceptible subjects, an imbalance that provides potential avenues for therapeutic intervention.

Given the central importance of elevated pulmonary artery pressures in the pathogenesis of HAPE, how do these elevated pulmonary artery pressures cause fluid accumulation when patients with severe pulmonary hypertension at sea level do not typically have pulmonary edema? Hultgren¹⁴⁵ has suggested that edema results from uneven hypoxic vasoconstriction, resulting in overperfusion of the microvasculature in areas of the lung where arteriolar vasoconstriction failed to protect downstream vessels. Uneven perfusion is suggested clinically by the typical patchy radiographic appearance (see Fig. 77-9) and by MRI studies in persons breathing hypoxic gas mixtures,¹⁴⁶ which demonstrates greater heterogeneous regional perfusion in HAPE-susceptible subjects.

The leak in overperfusion edema may be due to *capillary stress failure* in which high shear forces cause biomechanical stress and injury in the precapillary arterioles and capillaries.¹⁴⁷ The mechanisms by which high pressures and shear stress lead to a high permeability-type leak may involve a continuum of pressure-related phenomena by which plasma and even red cells move from the intravascular space to the interstitium and subsequently into the alveolar space. At lower levels of pressure elevation, stretch on collagen and other supporting extracellular matrix elements may induce dynamic and quickly reversible changes in barrier permeability,¹⁴⁸ which with greater duration and further pressure elevation, may lead to capillary rupture and alveolar hemorrhage as seen in severe cases of HAPE.

Although the data largely establish a mechanical basis for HAPE, interest in the role of inflammation arose when bronchoalveolar lavage studies in patients with HAPE demonstrated increased cellularity and the presence of chemotactic (leukotriene B₄) and vasoactive (thromboxane B₂) mediators compared to controls.¹³³ Whether the inflammation was a primary or secondary phenomenon was clarified in a study by Swenson and colleagues,¹³² in which bron-

choalveolar lavage was performed in HAPE-susceptible individuals and normal controls within the first 24 hours of arrival at 4559 m, earlier than the lavage samples were obtained in the other studies. At this early time, although the lavage fluid demonstrated high protein and red blood cell content, the levels of which correlated with pulmonary artery pressures measured by echocardiography (Fig. 77-10), there was no evidence of cytokine expression or neutrophil recruitment. These findings solidified the notion

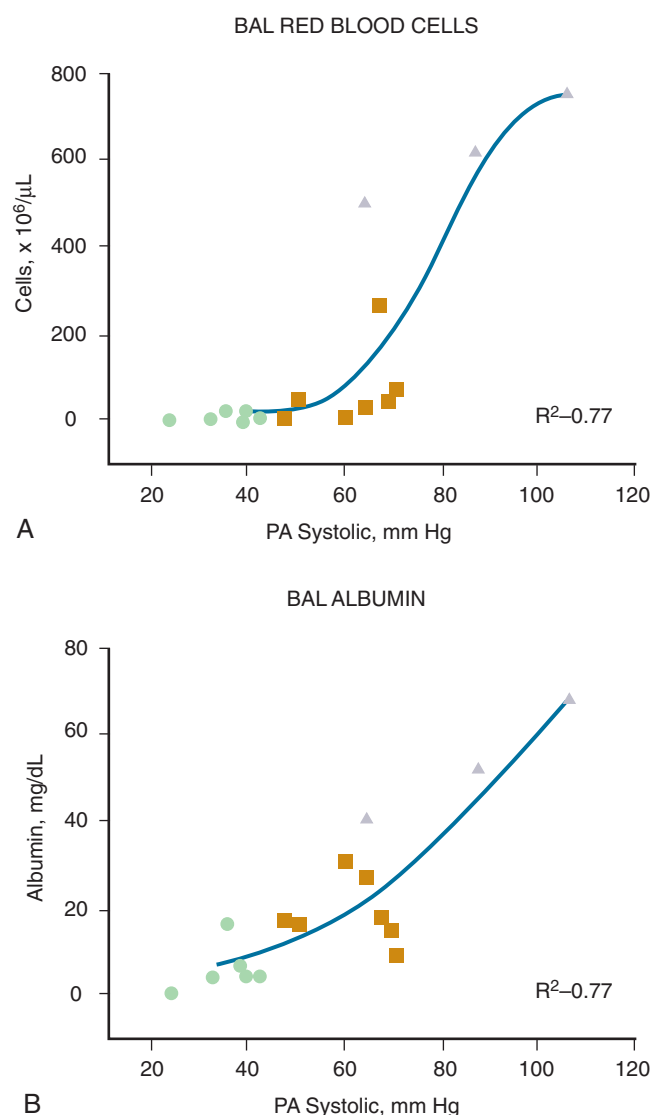


Figure 77-10 The relationship between pulmonary artery pressure (PA) measured by echocardiography and the number of red blood cells and the concentration of albumin in bronchoalveolar lavage (BAL) fluid of normal and HAPE-susceptible individuals at sea level and at 4559 m. The circles in the lower left of both panels show normal values for red blood cells and albumin at low altitude (490 m). Squares indicate HAPE-susceptible individuals at 4559 m who were not experiencing HAPE at the time of bronchoscopy; triangles indicate HAPE-susceptible individuals at 4559 m who were clinically considered to have HAPE at the time of bronchoscopy. Correlation coefficients are provided for the best fit curves of the data at high altitude. (From Swenson ER, Maggiorini M, Mongovin S, et al: Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. *J Am Med Assoc* 287:2228–2235, 2002.)

that HAPE starts as a result of high intravascular pressure, not due to an inflammatory process.

Although inflammation is not the primary factor in most cases, it may still play a role in certain situations. Respiratory viral infections have been shown to predispose to HAPE in children,¹⁴⁹ and there are anecdotal reports of viral infections preceding HAPE in adults. This suggests that viral infections may trigger inflammation, which makes the microvascular endothelium more vulnerable to increased pressures. This potential role for upper respiratory tract infections and subsequent inflammation may account for the cases of HAPE seen at surprisingly low altitudes (1500 to 2400 m).¹⁵⁰

Changes in fluid transport dynamics in the lung may also contribute to HAPE. Hypoxia has been shown to decrease alveolar transepithelial sodium transport¹⁵¹ and alveolar fluid clearance,¹⁵² which are known to be important in normal lung fluid balance. In subsequent studies in humans that have examined transepithelial potential differences across the nasal mucosa as a model of alveolar epithelial function, lower transepithelial nasal potentials in normoxia have been demonstrated in HAPE-susceptible individuals versus nonsusceptible controls, which was attributed to decreased sodium transport by the epithelial sodium channel.¹⁵³ A subsequent study confirmed the difference in nasal potential between HAPE-susceptible individuals and controls in normoxia, but could not attribute these differences to alterations in epithelial sodium channel activity.¹⁵⁴ Transalveolar sodium transport can be increased by β_2 -receptor stimulation, and a field study has reported successful prevention of HAPE with inhalation of salmeterol, a long-acting β_2 -agonist.¹⁵³ However, given the multiple actions of this drug, including increased ventilatory response to hypoxia, and tightening of cell-to-cell contacts, the contribution of enhanced alveolar fluid clearance to the study's positive outcome remains uncertain.¹⁵⁵ Finally, ET-1 has been shown to impair alveolar fluid clearance by 65% in a rat model,¹⁵⁶ providing another potential mechanism by which it might contribute to HAPE in humans.

Allemann and colleagues¹⁵⁷ documented an increased incidence of patent foramen ovale in HAPE-susceptible individuals at low and high altitude compared to healthy controls and argued its presence may increase the risk of HAPE. It is not clear, however, whether the patent foramen ovale actually causes HAPE or is a sequela of the prior marked rises in pulmonary artery pressure during sojourns to high altitude or during normoxic exercise seen in HAPE-susceptible individuals.¹⁵⁸

Finally, it has been proposed that HAPE is a form of neurogenic pulmonary edema, in that the presence of red blood cells, the spectrum of serum proteins in HAPE lavage fluid, and the absence of architectural damage are all features seen in this other form of noncardiogenic pulmonary edema.¹⁵⁹ Sympathetically mediated pulmonary venous constriction is thought to play a large role in neurogenic pulmonary edema,¹⁶⁰ while as noted earlier, increased sympathetic activity may play a role in HAPE¹³⁹ and α -adrenergic blockade has been shown to decrease pulmonary artery pressure in HAPE.¹⁶¹ What is lacking in HAPE, however, is the severe neurologic injury typically seen in neurogenic pulmonary edema. Although some HAPE patients have concurrent AMS or HACE, this is usually far less severe than

the profound central nervous system alterations (e.g., subarachnoid hemorrhage) in most cases of neurogenic pulmonary edema.

Prevention. The nonpharmacologic preventive measures previously described for AMS also apply to HAPE, with a slow ascent being the most important strategy. Because unrecognizable subclinical pulmonary edema might be converted to clinical edema by exercise, subjects should avoid overexertion before acclimatization, especially when fatigued. Nifedipine, a calcium channel blocker that attenuates HPV, is effective in preventing HAPE in subjects with a past history of the illness.¹⁶² Because the incidence of HAPE is low, prophylactic nifedipine should be reserved for known susceptible individuals. A single study established that high-dose inhaled salmeterol augments alveolar fluid clearance and may be useful for prophylaxis,¹⁵³ although very high doses (2.5 times those used in asthma management) were used in the study and may be associated with side effects that affect patient tolerance. More recently, Maggiorini and coworkers¹⁶³ demonstrated that tadalafil, a phosphodiesterase inhibitor with pulmonary vasodilatory properties, can also prevent disease in known susceptible individuals. An unexpected finding of this study was that dexamethasone was also effective in this regard. Subsequent studies have established that dexamethasone decreases estimated pulmonary artery pressure following ascent to 4559 m,¹⁶⁴ but because the mechanism of action remains unclear and clinical experience with dexamethasone for HAPE prophylaxis remains limited, it has not become part of standard HAPE prevention protocols.¹¹⁰ Recommended doses for these medications are provided in Table 77-2.

Treatment. Proper treatment depends on the severity of the illness and the immediate setting. For patients in remote locations with limited access to care, the first priority is descent to lower elevation. The patient's level of exertion should be limited during descent because exertion may increase pulmonary artery pressure and worsen the pulmonary edema. If HAPE is diagnosed early, recovery is rapid with descents of only 500 to 1000 m, and the victim may be able to reascend cautiously 2 or 3 days later. If descent is not feasible due to weather or other factors, supplemental oxygen or a portable hyperbaric chamber should be an urgent priority.¹⁶⁵ If neither option is available, positive pressure mask ventilation may improve oxygenation although the effect on outcomes has not been established.¹⁶⁶

Given the reduced margin for error in remote settings, the use of a pulmonary vasodilator such as nifedipine is warranted regardless of whether supplemental oxygen is available. The data supporting this practice are limited, however, and the recommendation is based largely on extensive clinical experience. A single study¹⁶⁷ demonstrated that nifedipine can be used to manage HAPE in the absence of descent or supplemental oxygen but this study was small and lacked a control group. Other pulmonary vasodilators such as tadalafil and sildenafil have not been studied for HAPE treatment but reports in the literature indicate clinicians are using them for this purpose, often in conjunction with calcium channel blocker therapy.¹⁶⁸ Given the absence of data supporting benefit and the risk of

provoking systemic hypotension, concurrent use of two pulmonary vasodilators should be avoided. Such warnings have not been heeded in the field setting,¹⁶⁹ where almost every available pharmacologic modality is often given when most patients, except for the most critically ill, would likely do well with just rest and supplemental oxygen.

In less remote settings such as at ski resorts, treatment with bed rest and oxygen may be sufficient and evacuation to lower elevations may be unnecessary. In well-selected patients with mild disease and adequate support by family or friends to monitor their clinical course, it may even be feasible to send them home or to their hotel with supplemental oxygen rather than evacuating them to a hospital.¹⁷⁰ Complete resolution of the edema may require 24 to 72 hours of oxygen therapy at the altitude of onset whereas moving the patient to a lower altitude results in more rapid improvement. Pulmonary vasodilators can be added in patients who worsen or fail to improve with conservative measures. There are no data comparing nifedipine to phosphodiesterase inhibitors, although there is more clinical experience with the less expensive nifedipine. A single case series documented the use of continuous positive airway pressure to relieve dyspnea in patients with HAPE,¹⁵⁰ but there are no controlled data to suggest this improves outcomes. Because temperatures as high as 38.5°C have been described in HAPE, a finding of elevated temperature should not prompt administration of antibiotics unless the clinical picture is consistent with pneumonia. Patients who do not improve on an appropriate regimen should be investigated for other causes of hypoxemia and lung infiltrates.

PROBLEMS OF HIGH-ALTITUDE RESIDENTS

Chronic Mountain Sickness

First described in Andean dwellers by Monge¹⁷¹ in 1928 and often referred to as Monge disease, *chronic mountain sickness* (CMS) is a commonly described form of chronic altitude illness. It is seen in persons born and living at high altitude as well as in lowlanders who move to high altitudes and stay for prolonged periods of time, generally more than 1 year. Excessive erythrocytosis, defined as a hematocrit above 60% to 70% or more than two standard deviations above the average value for healthy residents at a given high altitude, is an essential characteristic of this syndrome whose severity can be graded based on criteria stipulated in a recent consensus report.¹⁷²

There are geographic and ethnic differences in the prevalence of CMS. It is rarely found in natives of the Tibetan plateau but is frequently encountered in the Andes, in the North American Rockies, and in other mountainous regions where lowlanders have moved as in, for example, Han Chinese who have been relocated to Tibet.¹⁷³⁻¹⁷⁵ The reason for these regional differences is only speculative, but it is thought to be secondary to more advantageous adaptations that the Tibetans have undergone because of their greater duration of existence on the Tibetan plateau compared with that of the Andeans. Especially relevant may be that Tibetans have much less HPV and erythrocytosis compared with other high-altitude populations. These may potentially be markers of more successful adaptation over a much longer period of time.

Clinical Presentation. Symptoms of CMS are similar to those found in persons suffering polycythemia at low altitude: headache, dizziness, lethargy, impaired memory and mentation, and poor sleep. Subsequent investigations reveal cyanosis, plethoric appearance, and elevated hematocrit and hemoglobin. The diagnosis can be established only by eliminating all other causes of polycythemia. Indeed, much confusion in the literature regarding incidence and other aspects of CMS may be due to inadequate validation of the diagnosis. Monge¹⁷¹ and Leon-Velarde and colleagues,¹⁷⁶ for example, noted a high frequency of bronchial complications in patients with CMS, whereas Kryger and coworkers¹⁷³ found evidence of lung disease in 50% of those with CMS in Leadville, Colorado. Indeed, when viewed as a syndrome, it is possible that many cases represent an interaction between some underlying chronic lung disease, high altitude, and, perhaps, heavy metal toxicity.³⁶

Pathophysiology. The likely initiating factors for CMS are a blunted HVR and relative hypoventilation. Hypoventilation increases alveolar hypoxia and arterial hypoxemia. Alveolar hypoxia, in turn, triggers more HPV and greater pulmonary hypertension while arterial hypoxemia leads to increased erythropoietin secretion and more red blood cell production.^{173,177,178} With exercise, rapid interstitial fluid accumulation has also been noted in patients in CMS,¹⁷⁹ which may also contribute to hypoxemia.

The precise cause and effect relationships between hypoventilation, polycythemia, and CMS are not entirely clear, however. For example, polycythemia has been shown to blunt ventilatory responses,^{180,181} while hypoxia itself may contribute to the ventilatory depression, as evidenced by an increase in ventilation in some natives with CMS when given supplemental oxygen. It should also be noted that HPV may not solely be a function of increased alveolar hypoxia because patients with CMS also have been noted to have accentuated pulmonary artery pressure responses to modest exercise when compared with healthy individuals living at the same elevation,¹⁸² a phenomenon also seen in HAPE-susceptible patients as noted earlier.

While the excessive polycythemia of CMS is likely due to greater hypoxemia, the actual hematocrit is often higher than expected for the measured arterial SO_2 ,¹⁸³ suggesting that affected individuals may have exaggerated erythropoietic responses to a given hypoxic stimulus.¹⁷⁷ Severe nocturnal desaturation also may contribute to the development of polycythemia, as suggested by investigations in the Rocky Mountains that revealed greater hypoxemia during sleep in patients with CMS than in healthy controls.¹⁸⁴ Finally, Jefferson and coworkers³⁶ found that a majority of subjects with CMS and excessive erythrocytosis in an Andean mining community had detectable serum concentrations of cobalt, a heavy metal known to stimulate renal erythropoietin production. This may help explain the higher incidence of CMS in high-altitude regions where mining is common.

Once present, polycythemia may also contribute to the pulmonary vascular issues noted earlier, because the increase in viscosity leads to increased pulmonary vascular resistance. Along with impairments in gas exchange and pulmonary vascular changes resulting from HPV, the onset

of polycythemia represents a turning point in CMS that ultimately leads to the clinical deterioration and demise of these patients.^{175,185}

Treatment. The key to treating CMS is to decrease the red cell mass. Improving oxygenation and thereby reducing the hypoxic stimulus for red blood cell production is the most physiologic approach to achieving this goal. Although relocation to a lower altitude is the definitive means to achieve these goals, this approach is not acceptable for many patients and other treatments are often employed. Phlebotomy has long been used, but despite the common practice and prompt subjective improvement, long-term benefits have not been well documented. Low-flow oxygen during sleep is probably effective, especially for those with marked sleep desaturation. Older data suggest that, by virtue of its ability to stimulate ventilation and increase alveolar PO₂, medroxyprogesterone, may be effective at decreasing hematocrit and treating CMS,¹⁸⁶ while more recent data indicate acetazolamide is an inexpensive, safe, and effective intervention.¹⁸⁷ Daily use of angiotensin-converting enzyme inhibitors can also suppress erythropoietin secretion and decrease the need for phlebotomy.¹⁸⁸

High-Altitude Pulmonary Hypertension

An alternative form of altitude-related disease in long-term residents has now been described in areas outside the Andes Mountains. Referred to as high-altitude pulmonary hypertension, it is marked by pulmonary hypertension and cor pulmonale *without* polycythemia. According to a recent consensus panel,¹⁷² high-altitude pulmonary hypertension is present if a resident at altitudes above 2500 m has a mean pulmonary artery pressure greater than 30 mm Hg or a systolic pulmonary artery pressure greater than 50 mm Hg, right ventricular hypertrophy, right heart failure, and moderate hypoxemia without excessive erythrocytosis (hemoglobin less than 21 g/dL in men and less than 19 g/dL in women). There is considerable overlap between this disease and subacute mountain sickness, a syndrome of pulmonary hypertension and right heart failure seen in lowlanders after weeks to months at high altitude,¹⁸⁹ with the major difference being the time spent at high altitude by the affected individual. There is also some debate as to whether this truly represents a separate entity from CMS or is simply a variant of the same disease.¹⁷⁸

Affected individuals present with dyspnea, cough, cyanosis, peripheral edema, and physical examination findings consistent with right heart failure. Right axis deviation, right ventricular hypertrophy, and P-pulmonale may be present on the electrocardiogram while chest imaging reveals right ventricular and right atrial enlargement and prominence of the pulmonary arteries.¹⁷² The pulmonary hemodynamics are similar to those seen in patients with CMS.¹⁷⁸ The optimal treatment for the disorder is relocation to lower elevation but, as in CMS, descent may not be feasible and pharmacologic options may be necessary. Unfortunately, aside from a small placebo-controlled trial that demonstrated that a 3-month course of the phosphodiesterase inhibitor sildenafil lowered pulmonary artery pressure by a modest amount (approximately 6 to 7 mm Hg)

and improved 6-minute walk distance,¹⁹⁰ larger studies of this and other pulmonary vasodilators are lacking. No formal treatment protocols exist at this time.

Reentry Pulmonary Edema

Some persons living for years at high altitude who descend to lower altitudes may develop HAPE on reascent. The phenomenon has been most often observed in Peru, where, due to the ease of air travel, high-altitude residents can return from sea level to high altitude quite rapidly. Cases have also been reported in Leadville, Colorado, but reports are conspicuously absent from Nepal and Tibet, possibly because rapid return to high altitude is often less readily available. Authors have suggested that the incidence of HAPE on reascent may be higher than during initial ascent by sojourners,¹⁹¹ but data on true incidence are lacking; children and adolescents may be more susceptible than adults.¹⁹¹ It has been postulated that the increased muscularization of pulmonary arterioles that develops with chronic high-altitude exposure generates an inordinately high pulmonary artery pressure on reascent, causing the edema. Aside from a study by Marticorena and Hultgren,¹⁹² which demonstrated that treatment with bed rest alone may be sufficient in mild to moderate cases, no treatment trials have been conducted for reentry HAPE and the disorder should be managed in the same way as for HAPE in unacclimatized lowlanders.

PREEXISTING ILLNESS AND HIGH ALTITUDE

Given the prevalence of many common diseases, such as hypertension and *chronic obstructive pulmonary disease* (COPD) in the general population, it is likely that many high-altitude travelers have some underlying medical condition. This situation raises two important questions: (1) Will the underlying disease predispose these individuals to high-altitude illness? (2) Will the added stress of hypoxia at high altitude worsen control of their underlying problems? To date, few studies have examined what happens to people with respiratory and other diseases when they visit high-altitude destinations, and even fewer data are available about how to treat them before and after their exposure. Several major categories of respiratory diseases are discussed in following paragraphs, while other major disease categories including heart disease,¹⁹³ renal disease,¹⁹⁴ and diabetes¹⁹⁵ are reviewed elsewhere.

RESPIRATORY DISEASES

High-altitude exposure poses several challenges to patients with lung disease that have been reviewed extensively elsewhere.¹⁹⁶ Several major forms of lung disease are considered in brief here.

Chronic Obstructive Pulmonary Disease and Interstitial Lung Disease

The drop in barometric pressure and subsequent fall in inspired PO₂ place patients with severe COPD and interstitial

lung disease at risk for arterial desaturation, particularly with exertion. Patients with moderate to severe COPD ($FEV_1 < 1.5$ L) and interstitial lung disease should undergo pre-travel assessment of their risk for hypoxemia and need for supplemental oxygen using one of several possible strategies, including prediction rules that take into account arterial blood gases^{197,198} and pulmonary function testing at sea level, cardiopulmonary exercise testing,¹⁹⁹ or exposure to simulated hypoxic conditions using the hypoxia altitude simulation test.²⁰⁰ For patients in whom the predicted value of arterial PO_2 falls below 50 mm Hg—the same threshold used for determining supplemental oxygen needs on commercial air flight—home oxygen should be prescribed and the prescription filled at the patient's destination (e.g., a ski resort town). An alternative strategy in patients with less severe disease is to have them monitor their own pulse oximetry using a portable handheld device with instruction to have a prewritten home oxygen prescription filled if their saturation falls below certain thresholds.²⁰¹ Patients with COPD should travel with their controller medications and a supply of rescue medications in case their condition is exacerbated. Because safety of patients with COPD or interstitial lung disease sleeping at altitude above 3000 m is unknown, such patients should sleep at elevations lower than 3000 m.

Asthma

Changes in air temperature, humidity, and density may alter lung mechanics and airflow obstruction in patients with asthma, but field data demonstrate that mild, well-controlled asthmatic patients have decreased bronchial responsiveness at elevations as high as 5000 m²⁰² and tolerate ascents as high as 6410 m without significant changes in their symptoms.^{203,204} Patients must have their asthma under good control before any trip to high altitude and should travel with both their controller medications and an adequate supply of rescue inhalers and prednisone for use in case of an exacerbation.

Pulmonary Vascular Disease

In patients with pulmonary hypertension, low alveolar oxygen tensions provoke HPV and increase pulmonary artery pressure, which in turn may lead to either acute right heart failure or HAPE. No systematic studies have examined this issue but several case reports and case series have documented HAPE in patients with pulmonary hypertension secondary to anatomic or nonanatomic causes.²⁰⁵ Patients with known or suspected pulmonary hypertension should undergo echocardiography to measure pulmonary artery pressures. Travel to high altitude should be avoided in patients with moderate to severe disease, although the threshold used to proscribe travel is not clear. The available evidence suggests that mean pulmonary artery pressures of about 40 mm Hg are sufficient to increase the incidence of HAPE but a wide range of pressures have been documented in case reports of this phenomenon at high altitude.²⁰⁵ Patients with less severe disease should use nifedipine and should be encouraged to monitor their pulse oximetry using either a handheld device or by periodically visiting a local clinic. Patients with congenital absence of a pulmonary artery should also avoid high-altitude travel, because these

individuals are known to be susceptible to HAPE.²⁰⁶ Whether the same risks are present in patients following pneumonectomy has not been established but the prudent course is for such patients to avoid high-altitude exposure as well.

Sleep Apnea

Although the decrease in barometric pressure and air density at high altitude might lead one to expect a decrease in the severity of obstructive sleep apnea in this environment, recent field studies suggest that obstructive sleep apnea persists following ascent to 2950 m and is accompanied by a marked increase in the number of central apneas as well as impaired performance on simulated driving tasks, increased systolic blood pressure, and more frequent cardiac arrhythmias.²⁰⁷ Given these issues, it would be prudent for people with moderate to severe obstructive sleep apnea to travel to high altitude with their continuous positive airway pressure machine, assuming that reliable access to power sources can be arranged. If logistical issues prevent the use of continuous positive airway pressure, acetazolamide (250 mg twice daily) can decrease the apnea-hypopnea index, improve sleep efficiency and subjective insomnia, and blunt the rise in systolic pressure during sleep at altitudes as high as 2590 m.²⁰⁸

Thromboembolic Disease

Although many case reports document arterial or venous thromboembolic events at high altitude, a review of the cases reveals that most events were reported in people with underlying coagulopathy.¹⁹⁶ There remains no compelling evidence that the risk of thromboembolism is increased in normal individuals at high altitude. As a result, there is no need to screen for thrombophilia in asymptomatic persons before high-altitude travel and no indication to start anticoagulation in those not previously on such medication. Efforts should be made to maintain mobility and good hydration throughout the trip. The international normalized ratio may change with trips to and from altitude,²⁰⁹ and patients on warfarin should consider obtaining follow-up international normalized ratio values upon returning from a long sojourn or periodically during prolonged stays at a new altitude.

ALTITUDE-ILLNESS MEDICATIONS AND UNDERLYING MEDICAL DISEASES

As noted earlier, acetazolamide, dexamethasone, nifedipine, and the phosphodiesterase inhibitors play a large role in the prevention and treatment of high-altitude illness. The efficacy and safety of these medications has largely been established on the basis of studies in healthy individuals with no underlying medical disease. However, given the increasing numbers of people traveling to high altitude, it is possible that many of those using these medications for management of altitude illness will have underlying medical problems or will be using other medications that cause adverse drug interactions. Practical guidelines for the selection and dosing of the altitude illness medications in such patient populations are reviewed elsewhere²¹⁰ and are summarized in Table 77-2.

Key Points

- At every step of the oxygen transport chain, important adaptations maintain oxygen delivery in the setting of lower ambient oxygen levels. However, the magnitude of these changes varies between individuals and affects individual tolerance of this environment.
- Various aspects of sleep, including respiratory patterns, sleep architecture, and subjective impressions of sleep quality, are altered and contribute to poor sleep at high altitude.
- Maximum exercise capacity is reduced at high altitude and does not recover to sea-level baseline values even with prolonged time and acclimatization at high altitude.
- An overly rapid ascent to high elevation is the primary reason acute altitude illness develops, and a gradual ascent is the best nonpharmacologic means for prevention.
- Acute mountain sickness is the most common form of acute altitude illness and is marked by the onset of headache plus one or more other symptoms, including lightheadedness, gastrointestinal upset, fatigue, and poor sleep several hours following ascent to high altitude.
- High-altitude cerebral edema and high-altitude pulmonary edema are uncommon forms of severe acute altitude illness in which mortality is possible but avoidable with prompt recognition and initiation of treatment.
- Long-term high-altitude residents are generally not susceptible to acute forms of high-altitude illness but are at risk for two forms of chronic altitude illness, namely chronic mountain sickness and high-altitude

pulmonary hypertension, for which the optimal form of treatment is relocation to lower elevation.

- High-altitude travelers with underlying medical problems should undergo pretravel assessment to evaluate whether the underlying disease process may be worse at high altitude. The choice and dose of prophylactic medications may require adjustment based on the patient's underlying medical issues.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION

Increased Pressure
Water Immersion
Thermal Exposure
Energy Needs for Diving

EQUIPMENT

Open-Circuit Scuba
Closed-Circuit Rebreather Scuba
Surface-Supplied Equipment

**DISORDERS RELATED TO DIVING:
NOMENCLATURE****PRESSURE EFFECTS: BOYLE'S LAW**

Relation of Gas Volume to Depth
Barotrauma

**DISSOLVED INERT GAS EFFECTS:
HENRY'S LAW**

Inert Gas Kinetics
Inert Gas Supersaturation in Tissues
Decompression Sickness

**INERT GAS NARCOSIS
OXYGEN TOXICITY****MEDICAL QUALIFICATIONS FOR
DIVING**

Exercise Requirements
Disorders Causing Sudden
Unconsciousness
Pulmonary Disorders
Cardiac Disorders

DROWNING

Pathophysiology
Clinical Presentation
Treatment
Prognosis

INTRODUCTION

Diving and work in compressed air have produced occupational exposure to hazardous environments for over 100 years. In the past 60 years, diving has become a recreation for millions of individuals throughout the world. Any physician may encounter a recreational diver for an illness related to a diving exposure or for medical clearance for diving. Occasionally a physician may be confronted with an acute medical emergency related to diving exposure, such as decompression sickness, arterial gas embolism, or drowning. This chapter provides a basis for initiating treatment, seeking consultation, or furthering education in this interesting area of environmental medicine.

INCREASED PRESSURE

Underwater exposure results in increasing pressure directly proportional to depth (Table 78-1). There is also exposure to pressure in hyperbaric chambers, pressurized tunnels and caissons used for underwater construction, and underwater habitats. As depth increases, the diver breathes gas of increased density using breathing equipment that provides oxygen and allows for elimination of carbon dioxide. Increased depth and pressure also lead to decreases in gas volume and an increased amount of gas dissolved in body tissues. The terms *atmosphere* (ATM) and *atmosphere absolute* (ATA) both refer to pressure; ATM, however, can be used as a relative term (33 feet of water depth is equivalent to 1 ATM of water), whereas ATA is always used for absolute pressure (33 feet of water depth is equivalent to 2 ATA). ATA is the term used in this chapter and is always used for equations, such as Boyle's law.

WATER IMMERSION

Intrathoracic blood volume increases with water immersion.¹ Increased hydrostatic pressure during immersion prevents blood from pooling in the peripheral veins,

increases transdiaphragmatic pressure, and increases venous return.^{2,3} The magnitude of the increase in intrathoracic blood volume during immersion with the head above water has been estimated to be 700 mL.² The central blood shifts result in an increase in cardiac output² and an increase in central venous pressure. The increase in intrathoracic blood volume causes a diuresis because of release of natriuretic hormones and suppression of antidiuretic hormone.

THERMAL EXPOSURE

Most diving takes place in water colder than skin temperature, and the diver loses heat throughout the dive. Hypothermia happens rapidly in the absence of protective garments even in relatively warm water (e.g., 22° to 23° C). Cold stress evokes thermogenic responses, reflected by a rise in *oxygen consumption* ($\dot{V}O_2$) upon exposure to cold water to generate additional body heat and minimize core temperature change. Cold water diving also leads to peripheral vasoconstriction; the magnitude of the vasoconstriction is dependent on body core temperature, which, in turn, is affected by the amount of thermal protection and the water temperature. Heat loss is inhibited in divers doing moderate work in water above 30° C, and, in this situation, hyperthermia can develop.

ENERGY NEEDS FOR DIVING

A scuba (*self-contained underwater breathing apparatus*) diver swimming underwater at a speed of 1.0 knot (about 100 feet/min or 1.15 miles per hour or 1.85 km per mile) consumes about 25 mL of oxygen per kilogram per minute (Fig. 78-1).^{4,5} A diver with a maximum $\dot{V}O_2$ of 40 mL/kg per minute would tolerate swimming at 1.3 knots for a few minutes but would become extremely tachypneic to compensate for lactate production. For a diver with a maximum $\dot{V}O_2$ of 40 mL/kg per minute, sustainable swimming speed, working at 50% of maximum capacity, would be about

Table 78-1 Pressure Equivalents for Altitude and Depth

	Feet	ATA	mm Hg	psi
Altitude above sea level	12,000	0.636	483	9.3
	8000	0.742	564	10.9
	4000	0.863	656	12.7
Sea level	0	1	760	14.7
Depth in seawater	33	2	1520	29.4
	66	3	2280	44.1
	99	4	3040	58.8
	132	5	3800	73.5

ATA, atmosphere absolute; psi, pounds per square inch.

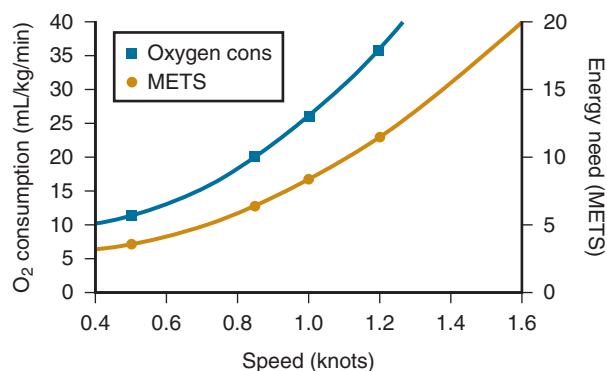


Figure 78-1 Oxygen consumption and metabolic equivalents (METs) are shown for underwater swimming. The speed is shown in knots; one knot is one nautical mile per hour. One knot = 100 feet per min = 1.15 miles per hr = 1.85 km per hr. (Data from Navy Department: *U.S. Navy diving manual*, vol 1, rev 3: Air diving. Publication No. NAVSEA 0994-LP-001-9110. Washington, DC, 1996, U.S. Navy Department.)

0.9 knots or 90 feet/min, whereas the diver with a maximum $\dot{V}O_2$ of 25 mL/kg per minute would be able to sustain a swimming speed of only approximately 0.55 knots or 55 feet/min. Safety considerations suggest that the sport diver should be able to tolerate a sustained workload of about 20 mL/kg per minute (50% of maximum).^{4,5} Poorly conditioned divers can experience severe dyspnea under even mildly stressful conditions that exceed their anaerobic threshold.

EQUIPMENT

OPEN-CIRCUIT SCUBA

The most commonly used breathing equipment in diving is the open-circuit scuba. This equipment (Fig. 78-2) consists of a metal cylinder containing compressed air connected to a pressure regulator that lowers pressure to ambient pressure. This device delivers ambient-pressure air only when inhalation is initiated and allows flow that matches the minute volume of the diver. Expired air is released directly into the surrounding water. A typical scuba cylinder can supply approximately 2100 L of air at the surface (1 ATA). This volume is reduced in direct proportion to ambient pressure. For example, at a depth of 66 feet of seawater or 3 ATA pressure, the effective volume of air is decreased to 700 L. With a minute ventilation of 20 L/min, this air

OPEN-CIRCUIT SCUBA

CLOSED-CIRCUIT REBREATHING

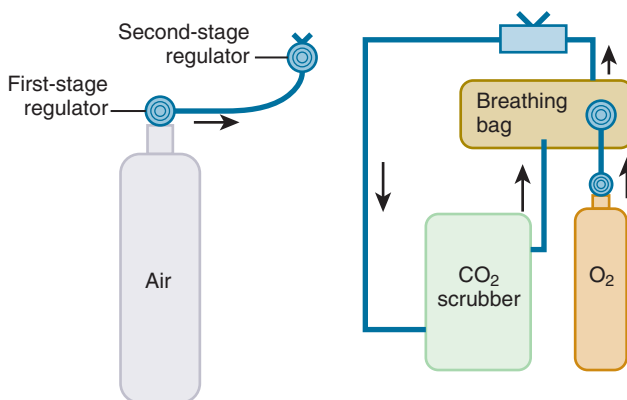


Figure 78-2 Two types of self-contained diving systems. The open-circuit scuba is the system commonly used for recreational diving. Air is exhaled into the surrounding water. Rebreather systems allow exhaled breathing gas to be recycled through a carbon dioxide scrubber, mixed with additional breathing gas, and returned to the diver through a breathing bag. Breathing gas is replenished via a demand valve. This system can be used with 100% oxygen or oxygen-enriched air mixtures. Other forms of rebreather systems contain separate oxygen and inert gas supplies, and mixing is controlled with a small computer to maintain a constant oxygen partial pressure.

supply would last 105 minutes at the surface but only 35 minutes at 66 feet of seawater. Open-circuit scuba is usually limited to depths above 200 feet because of limited air supply, nitrogen narcosis, and oxygen toxicity.

CLOSED-CIRCUIT REBREATHING SCUBA

The self-contained rebreather uses a carbon dioxide absorbent to remove exhaled carbon dioxide and replenishes only the oxygen used. Inert gas is conserved by recycling the exhaled gas through the carbon dioxide absorbent and then adding oxygen before the gas is rebreathed (see Fig. 78-2). Little gas is released into the surrounding water, oxygen can be carried in volumes adequate for several hours of exposure, and gas consumption is independent of depth. Although use of closed-circuit scuba in the past was confined to commercial and military divers, such systems now are becoming popular among recreational divers.

SURFACE-SUPPLIED EQUIPMENT

Commercial diving often employs this form of equipment. The diver breathes compressed air or other gas mixtures pumped from the surface to the helmet. The diving helmet is attached at the collar to a diving suit so that air flows from the helmet into the suit to maintain an air layer for thermal protection. Modern systems contain a demand mask built into the helmet.

DISORDERS RELATED TO DIVING: NOMENCLATURE

Golding and coworkers⁶ described disorders related to supersaturation of inert gases in tissues with subsequent bubble formation as *decompression sickness* (DCS). They

described a systemic form of DCS that involves the central nervous system, the lungs, and the circulation (“serious,” type II) and a nonsystemic (peripheral) form that involves the skin, bones, and joints (“minor,” type I). *Arterial gas embolism* is named separately based on its relationship to pulmonary barotrauma. Francis and Smith⁷ suggested the term *decompression illness* for these two disorders because they can be clinically difficult to separate and require similar therapy.

PRESSURE EFFECTS: BOYLE’S LAW

RELATION OF GAS VOLUME TO DEPTH

Boyle’s law states that, if the temperature of a fixed mass of an ideal gas is kept constant, volume and pressure are inversely related. Consequently, when the pressure is doubled, the volume is reduced to one half of the original volume. Because the gas volume is proportional to the absolute pressure, the volume change from the surface to 33 feet of seawater (from 1 to 2 ATA) is greater than the change from 33 to 66 feet (from 2 to 3 ATA).

BAROTRAUMA

With increased pressure, volume in the lungs, middle ear, paranasal sinuses, and gastrointestinal tract are reduced. Displacement of tissues into the diminishing volume of these spaces may cause tissue injury and dysfunction of the organ involved. Barotrauma can affect a paranasal sinus with an occluded orifice, a residual air pocket left between a tooth filling and the base of the tooth, or the air space within a diving mask.

Pulmonary Barotrauma and Arterial Gas Embolism

The gas a diver breathes is pressurized to the ambient pressure so that pressure gradients from the breathing supply to the airways are not altered as the diver descends. Behnke⁸ and Polak and Adams⁹ described lung barotrauma in ascending divers due to inadequate exhalation during ascent and overexpansion of the lungs. Later studies provided further insight into mechanisms and prevention of pulmonary barotrauma.¹⁰ After breathing compressed air, persons who ascend to the surface from depths as shallow as 4 feet can experience pulmonary barotrauma.

Pathophysiology. Under experimental conditions, transpulmonary pressures (i.e., the difference between intratracheal and intrapleural pressures) of 95 to 110 cm H₂O are sufficient to disrupt the pulmonary parenchyma and force gas into the interstitium.¹⁰ Extra-alveolar gas will migrate through perivascular sheaths to cause mediastinal emphysema and pneumothorax.¹⁰ Gas can also dissect into the retroperitoneum and into the subcutaneous tissues of the neck. Extra-alveolar gas can pass into ruptured blood vessels, travel to the left side of the heart, and enter the arterial circulation as gaseous emboli. The dissemination of gas bubbles throughout the arterial circulation causes injury to other organ systems and to skeletal muscle, which is evident by a rise in serum creatine kinase level.¹¹

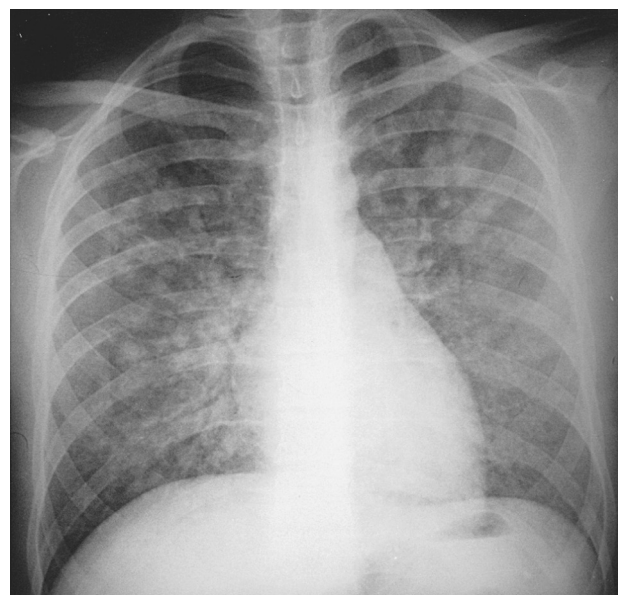


Figure 78-3 Chest radiograph from a diver who experienced near drowning. The diffuse pulmonary edema pattern is suggestive of water aspiration.

Pulmonary barotrauma can be seen in divers who would not be considered at risk for lung overpressure. Occult lung disease may contribute to unexplained barotrauma and cerebral air embolism.¹² Epidemiologic studies have not demonstrated a significant relationship between asthma and an increased risk for pulmonary barotrauma.¹³

Clinical Manifestations of Arterial Gas Embolism.

The brain is commonly involved. Within minutes of surfacing, the diver can experience loss of consciousness, hemiplegia, stupor, and confusion. Seizures, vertigo, visual disturbances, sensory changes, headache, and circulatory collapse are common. Most individuals fully recover if they are promptly recompressed.¹⁴

When they lose consciousness in the water, victims of arterial gas embolism frequently drown. Chest radiographs (Fig. 78-3) may show a diffuse lung edema pattern. About 5% of patients immediately develop apnea, unconsciousness, and cardiac arrest. This catastrophic course results from filling of the heart and great vessels with air. Many of these individuals are unresponsive to cardiopulmonary resuscitation and advanced life support measures.¹⁵ A report of 31 patients with cerebral air embolism from diving included the following findings: 25% demonstrated pneumomediastinum; 10%, subcutaneous emphysema; 6%, pneumocardium; 3%, pneumoperitoneum; and 3%, pneumothorax. Fifty-two percent had pulmonary opacities indicating associated drowning.¹⁶

Mediastinal emphysema is generally associated with mild substernal pain that may be exacerbated by inspiration, coughing, or swallowing. Unless massive, this condition is not usually associated with circulatory compromise. On physical examination a crunching sound synchronous with cardiac action may be auscultated (the Hamman sign). The chest radiograph confirms the diagnosis. No treatment is usually necessary.

Subcutaneous emphysema causes swelling and crepitus in the base of the neck and supraclavicular fossa, sore throat, hoarseness, and dysphagia. Radiographs may be helpful in detecting subtle cases, but *computed tomography* (CT) scans are more sensitive and can be useful to confirm the diagnosis of barotrauma in doubtful cases. Extra-alveolar gas that ruptures into the pleural space will cause a pneumothorax. Laboratory evaluation may show an elevated hematocrit level and elevation of several serum enzyme levels.¹⁷ Treatment for arterial gas embolism requires recompression in a hyperbaric chamber (see later).

Middle Ear Barotrauma

Middle ear barotrauma is the most common diving-related disorder encountered in divers.¹⁸ The middle ear undergoes barotrauma when the eustachian tube is blocked during descent and the middle ear space cannot equilibrate with the increasing ambient pressure. The tympanic membrane is displaced inward and may rupture. The middle ear may fill with blood from engorged mucous membranes. Infection and hearing loss are complications. Symptoms during descent include pain in the affected ear that increases with depth. Relief of pain without proper equalization of the middle ear pressure usually indicates that the tympanic membrane has ruptured. Cold water entering the middle ear when the tympanic membrane ruptures may cause vertigo because of unilateral vestibular stimulation. Late complications include bacterial otitis media, serous otitis media, and chronic tympanic membrane perforation.¹⁸ In rare cases of middle ear barotrauma, the facial nerve is injured by the increased pressure and a temporary facial paralysis results.¹⁹ A modified Valsalva maneuver is commonly used to equilibrate middle ear pressure. Because middle ear barotrauma causes edema and hemorrhage in the middle ear, equalization is usually impossible to achieve until healing is complete. The presence of middle ear barotrauma usually prohibits diving until it is resolved.

Alternobaric Vertigo. Vertigo may develop on ascent when the reduction of middle ear pressure is not uniform in both ears. The pressure imbalance causes differential stimulation of the labyrinths, resulting in what is called *alternobaric vertigo*. The sensation of vertigo may persist for 1 to 2 hours after diving and gradually disappears without therapy. Symptoms are similar to labyrinthitis and can include nausea, vomiting, and generalized malaise. Some subjects may be particularly susceptible to alternobaric vertigo if they have had previous injury or infection of the labyrinths. In susceptible individuals, use of moderate doses of antihistamines or decongestants may prevent symptoms. The disorder must be differentiated from vestibular DCS, which is usually associated with deeper, prolonged diving.

Inner Ear Barotrauma

Inner ear barotrauma may develop on descent in divers who perform a forceful Valsalva maneuver to equalize middle ear pressure. When the eustachian tube is blocked, middle ear pressure becomes progressively more negative relative to ambient pressure.^{18,20} When a Valsalva maneuver is then performed, intrathoracic pressure, central venous pressure, spinal fluid pressure, and inner ear pressure rise above ambient pressure, thereby increasing the

gradient between the inner ear perilymph and the middle ear. The round or oval window can rupture, and perilymph can then leak from the inner ear to the middle ear.

Symptoms include vertigo, nausea, vomiting, tinnitus, and loss of hearing on the affected side. Severity may vary, and some divers complain of hearing loss, tinnitus, or vertigo only after diving.

Treatment varies from conservative therapy to surgical repair of the round or oval window. Vertigo and nausea can be treated with benzodiazepine medications. Tinnitus and reduced hearing may become chronic, particularly if no treatment is provided. Divers who exhibit clinical evidence of inner ear barotrauma with intact round and oval windows may have a pressure injury to the organ of Corti and the vestibular system.²¹

Inner ear DCS may be seen within 2 hours of surfacing and may include vertigo and hearing loss.²² The mechanism is poorly understood but may involve formation of bubbles in the inner ear or embolism of systemic bubbles. Divers with inner ear DCS have been reported to have a higher prevalence of *patent foramen ovale* (PFO), a condition that increases risk for right to left shunts of air bubbles and thus of decompression events; such an association suggests that the inner ear DCS may also result from air emboli.^{23,24} The proper therapy for inner ear DCS is hyperbaric recompression.

Sinus Barotrauma

When a sinus orifice is occluded, pressure within the sinus becomes negative with respect to ambient pressure, and mucosal blood vessels become engorged and eventually rupture. Pain over the affected sinus during descent and epistaxis on ascent are usual symptoms. Headache following a dive may indicate sphenoid sinus barotrauma. Treatment includes decongestants and maneuvers to drain the affected sinus. Persistence of blood in the sinus may result in bacterial sinusitis. Prevention is accomplished by avoiding diving with congestion of the nasopharynx and prudent use of decongestants. If a maxillary sinus orifice is occluded, the maxillary branch of the trigeminal nerve may be compressed during ascent and result in infraorbital paresthesias that usually resolve in 2 to 3 hours.²⁵

Less Common Forms of Barotrauma

Facial barotrauma (mask squeeze) happens in the area of distribution of the diving mask. Facial edema, ecchymoses, and conjunctival hemorrhages can be noted after diving. Retro-orbital hematoma and diplopia have been described as complications.^{26,27} The disorder is self-limiting; no treatment is needed.

Tooth barotrauma leading to severe toothache results when air pockets under fillings or in areas of decay become compressed on descent. Careful dental work prevents this disorder.²⁸

Gastrointestinal barotrauma results when air enters the stomach during diving due to faulty breathing apparatus or by air swallowing. On ascent the expanding air will distend the stomach or intestine. Gastric distention can occlude the esophageal-gastric junction and prevent eructation. Distention of the stomach may cause stomach rupture and pneumoperitoneum.²⁹ The diver experiences abdominal pain, which increases during ascent. Treatment

Table 78-2 Characteristics of Inert Gases*

Gas	Molecular Weight	Lipid Solubility [†]	Water Solubility	Narcotic Potential [‡]
Helium	4	0.015	0.009	0.23
Neon	20	0.019	0.009	0.28
Hydrogen	2	0.036	0.018	0.55
Nitrogen	28	0.067	0.013	1.00
Argon	40	0.140	0.026	2.32

*Solubility of the various gases in lipid is related to their narcotic potential.

Helium is the least, and argon the most, narcotic gas in the list.

[†]Expressed as gas volume/solute volume at 1 bar.

[‡]Values relative to nitrogen.

Adapted from Bennett PB: Inert gas narcosis and HPNS. In Bove AA, editor: *Bove and Davis' diving medicine*, ed 4, Philadelphia, 2004, WB Saunders, pp 225–240.

requires surgical repair of the ruptured viscus. Divers with previous gastric surgery may be prone to gastric air trapping.³⁰

DISSOLVED INERT GAS EFFECTS: HENRY'S LAW

INERT GAS KINETICS

Gases dissolve in tissues, fats, and water according to Henry's law: $Q = c \cdot P$, where c , a solubility coefficient, and P , the partial pressure of the gas, determine the quantity (Q) of dissolved inert gas. Increased ambient pressure increases dissolved gas concentration in the tissues. The partial pressure of the gas and the solubility of the gas in the specific tissue (Table 78-2) determine dissolved gas content. Although Henry's law determines the amount of gas in the tissue, there is a finite time required for equilibrium to be achieved. Factors that affect the rate of entry include blood flow and the rate of diffusion of gases into the tissue. Tissue gas concentration follows an asymptotic curve in which the tissue gas concentration approaches the maximum concentration for the given pressure after time has elapsed. Similar kinetics control the washout of inert gas from tissues when ambient pressure is reduced. Different body compartments have different gas exchange characteristics.³¹

Because most diving is of short duration (i.e., minutes to hours) and shallow (i.e., in depths shallower than 200 feet), only a few tissue compartments reach equilibrium based on Henry's law. Divers can return to the surface from these short-duration dives by following a schedule of ascent based on depth and time.³¹ When diving exposure is long enough, all tissues reach equilibrium at the new ambient pressure and are fully saturated with inert gas. Divers can spend prolonged periods (weeks) under pressure, with all tissues saturated at the increased pressure, without serious physiologic changes.³²

INERT GAS SUPERSATURATION IN TISSUES

When the diver ascends after breathing pressurized gas, tissues become supersaturated with gas. When the degree

of supersaturation becomes excessive, dissolved gas will leave solution and form free gas. Recent studies suggest that blood microparticles may act as a nidus for bubble formation in blood.³³

DECOMPRESSION SICKNESS

Excess supersaturation causes dissolved gases to change phase to the gaseous form.³⁴ Expansion of gases in blood and tissues on ascent results in damage and dysfunction of tissues and organs and venous gas embolism to the lungs. DCS is the disorder caused by damage to organs and tissues as a result of free gas production.

Bert³⁵ first described the pathophysiology of DCS. Subsequent investigators in the early twentieth century concluded from autopsies on divers and caisson workers that DCS is caused by free gas in blood and tissues.³⁶ Based on free gas volume and location, they were able to explain the variety and severity of the symptoms. Paralysis resulted from free gas in the spinal cord, cerebral dysfunction was thought to result from free gas in the brain, and dyspnea was associated with free gas in the pulmonary circulation. Muscle and joint pain may be due to free gas in ligaments, fascia, periosteum, marrow, or nerve sheaths.

Hallenbeck and colleagues³⁷ described effects of free gas in blood and tissues that were not caused by mechanical obstruction. Subsequent studies identified clotting and platelet activation, intravascular coagulation, plasma leakage from the intravascular space, hemoconcentration, and hypovolemia as manifestations of surface effects of the bubbles.³⁸ Venous gas emboli are commonly present before overt symptoms of DCS appear.³⁹ Free gas and tissue injury result in activation of the inflammatory cascade.⁴⁰ The inflammatory response causes fluid to leak into the interstitial tissues of the systemic and pulmonary vascular beds.⁴¹

Factors Affecting Risk for Decompression Sickness

The use of ultrasonography for intravascular bubble detection has provided insight into the presence of bubbles following diving.⁴² Many divers demonstrate venous gas emboli but no manifestations of DCS. The concept of a threshold or dose-response effect has been postulated, wherein a certain volume of free gas is needed to produce the clinical disorder and lesser amounts are asymptomatic.⁴³ Venous bubbles in asymptomatic divers and aviators are associated with increased risk for developing DCS after diving or altitude exposure.^{44,45} Exercise and temperature during decompression are considered to be risk factors for DCS. Breath-hold divers can develop DCS from frequent repetitive dives.^{45a}

Symptoms can be prevented by keeping the degree of supersaturation below a certain level.⁴⁶ The concept of a critical pressure ratio is the basis for most decompression tables used to prevent DCS. The body can be considered as a set of tissue compartments with different rates of gas uptake and elimination.⁴⁶ Although these tissues do not represent discrete anatomic structures, they provide a convenient means for understanding the kinetics of inert gas exchange. In most decompression schedules, stops during ascent are selected to avoid excess supersaturation in tissues with specific gas-exchange rates (Fig. 78-4). Decompression procedures are well defined for air and other mixtures of

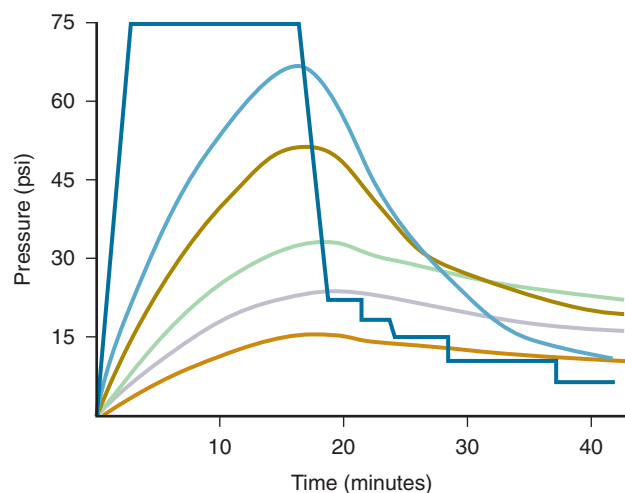


Figure 78-4 Theoretical nitrogen gas concentrations are expressed in units of pressure for an exposure of 75 psi (5.1 ATA) following the depth-time profile indicated by the heavy line. Curves are shown for five theoretical tissue compartments with different rates of gas exchange. Gas concentrations increase to different levels in the different tissue compartments during exposure to pressure. When pressure is reduced, gas concentrations in the different tissue compartments fall at different rates. Stops during return to baseline allow tissue concentration to fall to a safe level of supersaturation before reducing pressure further. (Data from Boycott AE, Damant GCC, Haldane J: The prevention of compressed air illness. *J Hyg [Cambridge]* 8:342–443, 1908.)

nitrogen and oxygen; helium and oxygen; nitrogen, helium, and oxygen (trimix); hydrogen and oxygen; and a few rare earth gases such as argon and neon.

Patent Foramen Ovale. Moon and coworkers⁴⁷ reported 30 patients with a history of DCS who were studied with echocardiography for identification of a PFO. Sixty-one percent of 18 patients with serious DCS had shunting, whereas a 25% prevalence was seen in normal volunteers. Wilmschurst and associates⁴⁸ identified a single patient with paradoxical gas embolism through an atrial septal defect and suggested that the atrial septal defect augmented symptoms of DCS. Moon and coworkers⁴⁹ evaluated 90 divers with previous DCS who were studied using echocardiography to detect right-to-left shunting through a PFO. Fifty-nine of 90 had experienced serious decompression symptoms, whereas 31 had experienced pain only or mild symptoms.

In the presence of a PFO, cerebral gas embolism can be caused by venous bubbles transiting a PFO.⁵⁰ Germonpré and associates⁵¹ found that divers with cerebral DCS have a high incidence of large PFO compared to control subjects. Billinger and colleagues⁵² demonstrated an increase in magnetic resonance imaging–detected brain objects in divers with a PFO. Honek and colleagues^{52a} demonstrated that a large PFO could increase risk of DCS in divers with exposures that resulted in significant venous gas emboli. The presence of a PFO may be associated with a twofold to fourfold increase in the risk for DCS.⁵³ The high prevalence of PFO in the population and the very low incidence of DCS suggest that a PFO can play only a minor role in the pathophysiology of DCS. There is no current need to close a PFO as a prophylactic measure.⁵⁴

Table 78-3 Frequency of Decompression Sickness (DCS) Symptoms in 100 Cases

Symptom	Percentage of All DCS Symptoms
Skin itch	4
Headache	11
Fatigue/malaise	13
Bone/joint pain	54
Spinal/back pain	11
Spinal/neurologic	22
Respiratory	21

Adapted from Navy Department: *U.S. Navy diving manual*, Vol 5, Rev 6: Diving medicine and recompression chamber operations (NAVSEA 0910-LP-106-0957), Washington DC, 2011. http://www.supsalv.org/00c3_publications.asp.

Age. A 10-year study by the U.S. Air Force on flight exposures ranging from 1500 to 30,000 feet shows a threefold increase in susceptibility to altitude DCS in aviators 42 years of age and older compared with those 18 to 21 years of age.⁵⁵ Carturan and colleagues⁵⁶ found a correlation between bubble formation, increased age, and decreased physical condition in sport divers. Klingmann and coworkers⁵⁷ reported an increased incidence of DCS in novice divers compared to more experienced divers. Blatteau and associates⁵⁸ reported that age and depth of dive exposure increased DCS risk.

Relation to Altitude. Exposure to altitudes above 18,000 feet (0.5 ATA) may result in free gas formation in tissues because of supersaturation of inert gases dissolved at atmospheric pressure.⁵⁹ Divers can develop free gas in tissues when going to higher altitude after diving even though they follow established protocols for ascent from depth to the surface. It is common for sport divers to fly in commercial aircraft (about 8000 feet equivalent altitude) shortly after diving.

Clinical Manifestations

Compared to sport and military divers, commercial divers have the highest incidence of DCS. Musculoskeletal DCS (type I) is the most common form. The incidence of DCS is about 1 in 5000 dives for the sport diver.^{60,61}

DCS can mimic a variety of other disorders (Table 78-3). Free gas entering the venous system will cause varying degrees of pulmonary vascular obstruction. A classic syndrome (“chokes”) manifested by chest pain, dyspnea, and cough is described.⁶² DCS is often associated with free gas in the blood and tissue injury that activates an inflammatory process, with damage to vascular endothelium, microvascular occlusion, and focal regions of tissue ischemia.⁶³ A common manifestation of DCS in divers is spinal cord dysfunction, usually at levels below the diaphragm.⁶⁴ Symptoms include paresthesias, muscle weakness, paralysis of the lower extremities, bowel or bladder incontinence, urinary retention, and sexual impotence.⁶⁵ A sudden ascent from deep depth (blowup) can cause a massive DCS syndrome with both cerebral and spinal neurologic symptoms, unconsciousness, hypovolemic shock, pulmonary edema, and a high mortality rate. A rare but important symptom

of serious (type II) DCS is sudden acute neurologic hearing loss and vestibular dysfunction. DCS of this type usually follows deep, prolonged diving exposures and, if untreated, can result in permanent deafness.⁶⁶

The musculoskeletal form of DCS is manifested by pain in the extremities and joints.^{67,68} Symptoms of local joint pain are often confused with pain from injuries, and the diagnosis of DCS may be missed. In some populations a high incidence of osteonecrosis is found in divers who have experienced musculoskeletal DCS in the distant past or who have experienced deep, prolonged exposures in caisson work,⁶⁸ as well as in diving instructors⁶⁹ and workers in commercial diving operations. An erythematous or purpuric skin rash (cutis marmorata) may also be a manifestation of DCS. A systematic method for diagnosing DCS is described by Grover and coworkers.⁷⁰

Diagnostic Testing

Chest radiography can be used to diagnose pneumothorax, pneumomediastinum associated with pulmonary overpressure accidents, and the pulmonary abnormalities associated with aspiration or capillary leakage associated with chokes. Chest or abdomen CT can be used to diagnose pneumothorax, pneumomediastinum, or pneumoperitoneum. In most cases it is not necessary to postpone recompression treatment in order to obtain radiographic studies. If pneumothorax is suspected, a chest radiograph can be helpful in making the decision to insert a chest tube. Neurologic and psychological testing may be useful in determining response to treatment when brain injury is present. Electronystagmography and audiography may be useful in distinguishing inner ear DCS from inner ear barotrauma. Inner ear DCS requires recompression, whereas inner ear barotrauma is managed with bed rest, avoidance of straining, and possibly surgical intervention. The circumstances causing the two syndromes are distinct (see earlier) and are helpful in the differential diagnosis. Central nervous system injury can be diagnosed by magnetic resonance imaging and correlated with clinical findings.^{71,72} Magnetic resonance images of the brain in divers with no history of decompression-related disorders are also found to be abnormal in some studies.⁷³

Treatment

The clinical manifestations of arterial gas embolism and DCS often overlap. The initial treatment of DCS and arterial gas embolism should always be a return to pressure by recompression in a hyperbaric chamber and administration of oxygen at increased ambient pressure.^{74,75} Fluid replacement and antiplatelet agents are also a part of the initial treatment. Once stabilized with pressure and oxygen, the patient must be decompressed slowly to permit the inert gas to be carried away from tissues by the circulatory system and then to be exhaled by the lungs. With early treatment, DCS and air embolism generally have an excellent prognosis for recovery. When treatment is delayed or when the injury is severe, there may be permanent injury to the brain or spinal cord.

Hyperbaric Therapy. Treatment of DCS and arterial gas embolism should be instituted with recompression as soon as possible after the injury.^{75a} A history and physical evaluation, including a neurologic examination and cognitive

assessment, should be obtained before treatment when possible. Therapy is provided in a hyperbaric chamber by a trained medical team. The usual practice is to follow the standard protocols for pressure treatment outlined in the *U.S. Navy Diving Manual*,⁵ which involves a pressure exposure equivalent to a 60-foot depth in seawater (60 fsw) using intermittent oxygen therapy.

Most practitioners use a hyperbaric treatment protocol lasting about 6 hours (see Table 6 in *U.S. Navy Diving Manual*⁵) for treatment of types I and II DCS. Recompression therapy for cutis marmorata resulting from DCS has been recommended by some, but most cases resolve spontaneously. Itching and erythema of the skin may also be noted following hyperbaric chamber exposures, but these skin findings alone do not require recompression therapy.

When a diver ascends from extreme depths with significant missed decompression, the practitioner may choose to use recompression tables that pressurize the diver to a "depth of relief," to use alternate gas mixtures (i.e., helium and oxygen), or to hold the diver for over 24 hours at a single depth to stabilize the medical status (saturation treatment).⁷⁴ For surface-supplied air and scuba divers, the principal treatment gases are oxygen and air. For treatment depths greater than 60 fsw, enriched nitrogen-oxygen (nitrox) or helium-oxygen (heliox) may also be used.

Repeated hyperbaric oxygen treatments can be given, although end points for repetitive therapy are not well defined. Treatments can be administered until no further change of symptoms is found or for a fixed number of exposures (e.g., five). Controlled trials to determine efficacy of repetitive treatments are not available. Treatment of arterial gas embolism follows similar protocols. Recompression to 60 fsw and oxygen therapy are usually successful.⁷⁶ Recompression to 165 fsw depth equivalent (6 ATA) is recommended if symptoms persist after recompression to 60 fsw.⁵

Supplemental Oxygen and Fluids. Early administration of 100% oxygen on the surface is thought to be beneficial for treating both DCS and arterial gas embolism.⁷⁷ Intravenous fluid administration also may be a useful initial treatment. Central nervous system injury may be exacerbated by hyperglycemia, and glucose-containing intravenous solutions should be administered cautiously. Measurements of hematocrit and urine specific gravity are useful to guide fluid replacement therapy.

Emergency Treatment

Because divers may be injured in areas remote from medical care, treatment measures should be instituted during transit to a hyperbaric chamber facility. Emergency treatment should include 100% oxygen by mask, aspirin 325 to 975 mg by mouth, and Ringer lactate (or normal saline) intravenously. One study of oxygen, aspirin, intravenous fluids, and hydrocortisone 1 to 2 g intravenously during transit to a hyperbaric chamber found that two thirds of the cases had a favorable outcome⁷⁸; however, it remains unproven whether emergency treatment alters long-term outcome. A favorable response to urgent care should not prolong transfer to the closest facility capable of providing recompression therapy.

INERT GAS NARCOSIS

Inert gas narcosis (nitrogen narcosis) results from breathing air at depths greater than 100 fsw.⁷⁹ Symptoms include loss of fine motor control and high-order mental skills, inappropriate response to emotional stress, hostility, and unconsciousness. Symptoms increase with increasing depth below 100 feet. At 300 to 400 fsw, unconsciousness may result from the anesthetic effect of nitrogen at this pressure. Fatigue, heavy work, and hypothermia can augment the narcotic effect of nitrogen. Symptoms disappear immediately on ascending to a shallow depth. Often there is amnesia for the events.⁷⁹ Narcotic potential varies among the inert gases (see [Table 78-2](#)).

OXYGEN TOXICITY

Oxygen toxicity in divers primarily affects the central nervous system.⁸⁰ Pulmonary oxygen toxicity is rare in diving but may be of some concern in prolonged hyperbaric oxygen treatments. Acute toxicity to the brain usually results when oxygen partial pressure exceeds 1.4 ATA. Higher partial pressures can be tolerated for brief periods. The affected diver may experience auditory or visual hallucinations and commonly suffers a grand mal seizure. When underwater, a seizure can lead to drowning. For example, a 32% oxygen mixture will expose a diver to 1.4 ATA of oxygen partial pressure at 111 fsw. Divers have been known to develop seizures when using this breathing gas at depths greater than this.

MEDICAL QUALIFICATIONS FOR DIVING

Military divers have the most stringent requirements, whereas recreational divers have the most relaxed requirements. Commercial divers, caisson and tunnel workers, and hyperbaric chamber workers all have unique standards. Disorders that limit cardiovascular or pulmonary function during exercise, physical deconditioning, metabolic disorders that limit exercise capacity, and certain physical handicaps can compromise diving safety.

EXERCISE REQUIREMENTS

Workloads in diving vary based on the type of diving (see previous). A diver swimming underwater at a speed of 1.0 knot consumes about 25 mL of oxygen per kilogram per minute.⁸¹ Safety considerations suggest that divers should tolerate a sustained workload of about 25 mL/kg/min to ensure safety under adverse diving conditions. Divers who do not achieve this level of fitness should avoid exposures that may require high levels of physical exertion.

DISORDERS CAUSING SUDDEN UNCONSCIOUSNESS

Seizure disorders are considered to be a contraindication to diving because a diver sustaining a seizure underwater is at

risk for drowning and may compromise the safety of others who attempt a rescue. A diving candidate with a history of a seizure disorder should be seizure-free without antiseizure medications for 4 years before being considered for diving.⁸² Insulin-dependent diabetes mellitus is considered a contraindication to commercial and military diving because of the risk for hypoglycemia. Special training has allowed safe diving for insulin-dependent sport divers.⁸³

PULMONARY DISORDERS

Asthma has been a subject of controversy in diving because of possible air trapping and pulmonary overinflation during ascent. Increased risk for pulmonary barotrauma has not been supported by clinical observation.⁸⁴ Criteria for safe diving by patients with a history of asthma include evidence that midexpiratory flow is not reduced after exercise by greater than 50%. A more detailed discussion of issues related to asthma and diving has been published.⁸⁵ Clinical and operational experience suggests that patients with a history of spontaneous pneumothorax or those with bullae or cysts may be at risk for a tension pneumothorax during diving. Treatment requires immediate decompression of the pleural space through an intercostal needle or chest tube and may be difficult at remote diving sites.

CARDIAC DISORDERS

Patients with coronary disease may develop angina pectoris, myocardial infarction, or sudden death while diving. The highest incidence of diving-related death from cardiovascular disease in divers is in the age range from 60 to 70 years.⁸⁶ Of 33 cases of sudden death while diving reported by the Divers Alert Network, 31 were attributed to coronary disease, 1 was related to a stroke, and 1 was related to aortic stenosis.⁸⁷ Screening of diving candidates for coronary disease is particularly important in the sport diving community, where candidates at increased risk for coronary disease due to age and chronic illness may present for training.

Diving candidates with atrial septal defects risk paradoxical embolism of gas bubbles that form in the venous circulation during decompression.⁷⁵ The presence of an atrial septal defect is considered to be a contraindication to diving. Compared to an atrial septal defect, a PFO appears to have a minor role in DCS, and prophylactic closure is not advised. A ventricular septal defect does not appear to produce a risk for paradoxical embolization of bubbles. Patients with a right-to-left shunt and arterial hypoxemia will normally have severely limited exercise capacity and should not dive. A detailed treatment of this topic can be found elsewhere.⁸¹

Diving-Induced Arrhythmias

Reflex bradycardia from diving has been described by a number of investigators⁸⁸ and may be related to the response to facial immersion and cooling found in diving mammals⁸⁹ as well as in humans. The autonomic adjustments to apneic diving in marine mammals appear to be an oxygen-conserving reflex, but this effect does not appear to be significant in humans. Drowning has been associated with the familial-inherited long QT syndrome in swimmers,⁹⁰ and the same risk is likely to apply to divers.

DROWNING

Drowning is reported as the leading cause of death in the approximately 100 to 150 scuba fatalities in the United States each year^{91,92}; however, sudden cardiac death or arterial gas embolism may be the precipitating factor or even the cause of death in many of these accidents.^{93,94} Historically the terms *drowning* and *near drowning* have been used to describe victims who either died or survived, respectively. It is simpler and preferable to use the term *drowning* for all individuals who suffer from submersion incidents.⁹⁵

Intentional hyperventilation before breath-hold diving is associated with drowning episodes. Hyperventilation reduces the arterial PCO₂, so the breath-hold breakpoint is prolonged sufficiently for hypoxemia to develop before the individual is forced to breathe. The hypoxemia in turn causes the individual to lose consciousness, and then drown.⁹⁶ This is termed “shallow water blackout.” Atrial and ventricular arrhythmias are known to happen during prolonged breath-holding experiments, but whether these arrhythmias play an important role in drowning incidents needs further study.⁹⁷

Hypothermia leading to drowning has been reported frequently; however, in diving fatalities this is unusual due to the almost universal use of thermal protection by divers. Hypothermia reduces a person’s ability to function until the point of unconsciousness or helplessness is reached.⁹⁸ At that time, for someone at the surface, the head falls into the water, resulting in drowning. Maximum breath-hold times can drop dramatically in cold water, further compromising the ability to survive in rough water when intermittently submerged. In rare circumstances, hypothermia can have a protective effect on the drowning victim (see later). Hypothermia is only one of many conditions that can precipitate drowning by causing unconsciousness. In the case of scuba diving incidents, contamination of the diver’s air supply with carbon monoxide produces rapid unconsciousness, and oxygen-induced seizures (see earlier) have been implicated as the cause of death in divers using oxygen-enriched air as a breathing mixture.

PATHOPHYSIOLOGY

Approximately 10% to 15% of drowning victims may not aspirate fluid during immersion.⁹⁹ To account for the lack of aspiration in these individuals, it has been hypothesized that reflex laryngospasm persists until reflex ventilatory activity ceases. However, review of early “dry” animal studies does not support the dry drowning hypothesis for fatal cases.¹⁰⁰ It is much more likely that these cases actually represent arrhythmic deaths. In these cases, if ventilation can be reestablished before injury secondary to hypoxemia happens, recovery is typically rapid and uneventful.

Unlike the victim without aspiration, the individual who aspirates remains hypoxemic, even after being removed from the fluid medium and after ventilation is reestablished. As a result, the period of hypoxemia is longer, and secondary damage to other organ systems is more likely.^{101,102} The continuing hypoxemia is due to direct lung injury from the aspirated fluid, which creates areas of low ventilation-perfusion ratio. With saltwater aspiration, it is believed that

hyperosmotic fluid causes transudation of fluid into alveoli, and the aspiration of debris (sand, diatoms, algae, etc.) causes a reactive exudate. As a result, alveoli become filled and are not ventilated. In freshwater aspiration, it is believed surfactant is washed out of the lungs, causing areas of focal alveolar collapse, leading to areas of low ventilation-perfusion ratio, and hypoxemia. These abnormalities persist until the lung damage resolves or until surfactant can be regenerated.

Victims often swallow large amounts of fluid during the drowning episode, so further decreases in ventilatory function may result from gastric distention. Vomiting and aspiration of gastric contents may further complicate the drowning episode. Hypoxemia and decreased alveolar ventilation produce a number of consequences. Arterial PCO₂ quickly rises, and pH quickly falls. Metabolic acidosis can be severe because the victim often struggles during the drowning episode. Finally, there may be cardiovascular collapse, resulting in cardiac arrest. If hypoxemia and decreased cardiac output persist long enough, anoxic cerebral damage can ensue.^{103,104} Although electrolyte disturbances are usually not a significant problem in drowning, the exception to this situation appears to be drowning victims in the Dead Sea, where electrolyte concentrations are greater than those in normal seawater.¹⁰³ The remaining specific consequence of drowning is aspiration pneumonia. The pathogens and the clinical picture of pneumonia associated with drowning have been reviewed extensively.¹⁰⁴

Because, in drowning, cardiac arrest is secondary to hypoxemia, it may be delayed by a significant amount of time. If the water in which the victim is immersed is cold enough, if the surface area-to-mass ratio of the victim is large enough, and if the victim swallows enough water, core temperature may decrease significantly; at low core temperatures the oxygen demands may be low enough that victims can occasionally survive even prolonged submersion.¹⁰⁵

CLINICAL PRESENTATION

The clinical presentation of drowning victims is highly variable. The patient who is unconscious and reported to be without vital signs at the site of the accident may be hemodynamically stable and neurologically intact in the emergency department, whereas the victim initially thought to be hemodynamically stable at the scene might deteriorate significantly before arrival at the hospital.

Cardiovascular System

Victims of significant drowning may suffer cardiac arrest and respond to on-scene resuscitative measures. Whether this represents premature cardiopulmonary resuscitation or a response to therapy is not certain. However, it is also not uncommon for a victim to be brought to the emergency department still requiring cardiopulmonary resuscitation. If the patient “responds” to cardiopulmonary resuscitation at the scene of the rescue with a stable rhythm or if the patient never suffers a cardiac arrest, supraventricular tachycardias are commonly seen. If the patient presents with a viable rhythm, it will most likely be supraventricular tachycardia secondary to hypoxemia and acidosis.¹⁰⁶ Patients with underlying cardiac disease may have a

Table 78-4 Average Blood Gas Measurements in Hospitalized Near Drowning Victims Breathing Room Air upon Admission

	pH	Paco ₂ (mm Hg)	PaO ₂ (mm Hg)	Base Excess (mEq)
Freshwater	7.26	38	66	−9
Seawater	7.37	36	56	−5
All	7.30	37	62	−7

Adapted from Modell JH, Davis JH, Giammona ST, et al: Blood gas and electrolyte changes in human near-drowning victims. *JAMA* 203:337–343, 1968.

primary cardiac arrest that may mimic a drowning episode.⁹³ The spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes may be greater than previously suspected.^{106,107} Pathologic diagnoses may be further complicated by terminal aspiration secondary to agonal breathing after cardiac arrest, and thus postmortem analyses that depend upon aspiration may be misleading.^{108,109}

Pulmonary System

Patients with water aspiration may present with few or no respiratory complaints or with severe pulmonary edema due to direct lung injury.¹¹⁰ Patients who have aspirated any significant quantity of water will likely have a widened alveolar-arterial oxygen gradient and anything from mild to severe hypoxemia. Arterial PCO₂ can be low or elevated depending on alveolar ventilation (Table 78-4). Chest radiographs can show patchy opacities, which are most common in the periphery or in the medial basal regions, or frank (noncardiac) pulmonary edema (see Fig. 78-3). The clinical course cannot be predicted with certainty by the radiographic picture of lung injury. Victims with clear-cut pulmonary difficulties may show minimal radiographic abnormalities, and those with minimal clinical injury may have severely abnormal radiographic pictures.

An interesting form of pulmonary edema found in divers was described by Wilmshurst and colleagues¹¹¹ and by Hampson and Dunford.¹¹² This is manifest as severe dyspnea while diving, associated with arterial hypoxemia, lung congestion, and a normal cardiovascular system. The syndrome may be related to negative-pressure pulmonary edema, a phenomenon well described in the anesthesia literature¹¹³; however, there is also evidence that there are multiple cardiovascular effects that may precipitate this syndrome.^{114,115}

Neurologic Status

The neurologic status of patients can also be quite variable. Severe permanent neurologic injury is the most devastating long-term consequence of the victim of a drowning episode.

TREATMENT

Restoration of normal neurologic function, although unusual, has been described even after prolonged drowning-induced cardiac arrest.¹¹⁶ Because cardiac arrest in this setting is invariably due to hypoxemia and acidosis, the first

goal must be to establish a reliable airway and to supply as high an inspired oxygen concentration as possible. Until the results of arterial blood gas determinations are available, 100% oxygen should be provided. Endotracheal intubation is the preferred method for establishing an airway. This approach needs to take into account the possibility of a concomitant unstable neck injury if there is associated trauma¹¹⁷ as well as the risk for the aspiration of gastric contents. However, without signs or a history of trauma, the risk for an unstable cervical spine injury is low.¹¹⁸

Patients with cardiac arrest due to drowning can have a profound metabolic acidosis. The doses of bicarbonate required to reverse such acidosis may be far larger than the doses recommended for patients suffering cardiac arrest from primary heart disease.¹¹⁹ If bicarbonate is to be given, arterial blood gas determinations are necessary to guide dosing. Concurrently a nasogastric tube should be inserted to decompress the stomach, and body temperature readings should be obtained to rule out hypothermia. In the presence of a significantly lowered body temperature, rewarming measures should be instituted. Once an adequate airway has been obtained and spontaneous cardiac activity achieved, an adequate arterial PO₂ must be established to ensure adequate oxygen delivery to the tissues. Occasional patients will have marked decreases in blood pressure and cardiac output. The initial therapy for hypotension of most causes is a trial of fluids, but, for a drowning victim with pulmonary edema, this may not be appropriate. As a result, this group of patients may require invasive hemodynamic monitoring. With knowledge of pulmonary artery wedge pressure and cardiac output, more rational decisions concerning the need for fluids or pressors can then be made. Isolated measurement of the central venous pressure is generally not an accurate method of judging intravascular volume status in the presence of noncardiac pulmonary edema. In the case of immersion pulmonary edema in a diver, the cause of hypoxemia is not water aspiration, and therapy should include diuretics to reduce lung congestion.¹¹²

Positive end-expiratory pressure is extremely effective in reversing the abnormal ventilation-perfusion relationships leading to hypoxemia. Usually only modest amounts of pressure are necessary to achieve adequate oxygenation. Positive end-expiratory pressure apparently does not alter the course of the underlying pulmonary injury but rather allows for adequate oxygenation while the lung is recovering. It also allows this recovery to take place at a level of inspired oxygen that is not in itself toxic to the lung.^{120,121} Usually the pulmonary injury resolves over a period of 48 to 72 hours, and ventilatory support in most circumstances is relatively brief, unless infection develops. Consequently, in patients who are able to tolerate it, nasal continuous or bilevel positive airway pressure may be a reasonable method for short-term ventilatory support. At present there are insufficient data to warrant the use of inverse-ratio ventilation in cases of drowning.¹²² It may be prudent to manage some drowning victims with high-flow oxygen delivery systems for relatively brief periods before resorting to more invasive methods of providing adequate oxygenation. Optimization of oxygen and carbon dioxide levels (as well as serum glucose level) is likely important to help manage concomitant neurologic injury as well.

The use of antibiotics in the drowning victim who aspirates ocean water or swimming pool water is generally necessary only for those individuals who become febrile, develop new pulmonary opacities, or develop purulent secretions.¹²³ Prophylactic antibiotics do not improve mortality or decrease morbidity.¹⁰³ Because most pulmonary infections in the near drowning victim appear to be hospital acquired, prophylactic antibiotics seem only to select for more resistant organisms.¹²⁴ If the victim aspirates heavily contaminated water with a known or suspected organism (as in the case of aspiration in a hot tub), the use of prophylactic antibiotics may be appropriate. A rare complication of drowning is the aspiration of sand or gravel.¹²⁵ Although bronchoscopy for the routine management of the drowning victim is probably not warranted, consideration of this procedure should be made when unexpected difficulties with mechanical ventilation arise.

Routine use of adrenocorticosteroids to treat the lung injury associated with near drowning is unwarranted. Experimental evidence with this form of aspiration, as well as others, strongly suggests that steroids do not improve the long-term outcome or short-term morbidity.¹²⁶ Artificial and animal-derived surfactants,¹²⁷ extracorporeal membrane oxygenation,¹²⁴ cardiopulmonary bypass,¹²⁸ and hypothermia¹²⁹ have also been used to treat the pulmonary injury associated with drowning. Any victim who has more than minimal respiratory symptoms, an abnormal chest radiograph, or abnormal arterial blood gas measurements should be observed, because pulmonary damage may not be clinically manifest for several hours after the incident.¹³⁰ Nearly all patients who will demonstrate significant problems of gas exchange will do so by 4 to 8 hours after the incident; therefore consideration for discharge from the emergency department may be appropriate in people who can be observed in this fashion.¹³¹ Indeed, current evidence suggests many victims can safely be sent home by lifeguards after a water rescue.¹⁰⁴

PROGNOSIS

The prognosis for the drowning victim depends mainly on the duration of immersion, the length of the anoxic period, and the degree of damage secondary to the anoxic episode. Patients who arrive at the hospital neurologically intact have an excellent prognosis and should survive neurologically unimpaired. An apparent (i.e., undocumented) cardiac arrest does not in itself suggest a poor outcome; however, cardiac arrest that persists through the period of initial first aid and transport to the hospital is a poor prognostic sign. The presence of spontaneous respirations on presentation to the emergency department following cardiac arrest in the field is a good prognostic sign.¹³² The duration of immersion correlates with the degree of damage secondary to the anoxic episode and therefore with the outcome. No prognostic test has proven to be a reliable basis for treatment decisions, and predictions concerning outcome cannot be made in the presence of severe hypothermia.

Key Points

- Middle ear barotrauma is the most prevalent diving injury, whereas pulmonary barotrauma, although uncommon, is the most severe form of barotrauma injury due to the risk for accompanying cerebral arterial gas embolism.
- Decompression sickness results when inert gas dissolved in the body at increased pressure forms free gas in blood and tissues upon decompression.
- Clinical manifestations of acute decompression sickness include disorders of the brain and spinal cord, musculoskeletal pain, chest pain, dyspnea, and skin rash seen up to 24 hours following an exposure to increased pressure.
- Treatment of decompression sickness and arterial gas embolism should be instituted with recompression in a hyperbaric chamber as soon as possible after the injury.
- Assessment for fitness for diving includes consideration of the type of diving (recreational, commercial, military) and a number of chronic disorders that can be aggravated by the diving environment. Because of the increased risk of arterial gas embolism, the presence of an atrial septal defect is considered to be a contraindication to diving.
- Although drowning without aspiration is theoretically possible, the majority of drownings are associated with aspiration of water into the lungs and an accompanying hypoxemia.
- Goals of therapy for a drowning victim include reversing hypoxemia with positive-pressure ventilation and oxygen, treating metabolic acidosis, managing accompanying cardiac arrhythmias, and administering antibiotics when indicated.

Complete reference list available at *ExpertConsult*.

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DISORDERS OF THE PLEURA

79

PLEURAL EFFUSION

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INTRODUCTION

The pleural space is bounded by two membranes, the visceral pleura covering the lung and the parietal pleura covering the chest wall and diaphragm. Into this space, normal liquid and protein enter from the systemic circulation and are removed by the parietal pleural lymphatics. Pleural pressure is subatmospheric and ensures inflation of the lung. Because the mesothelial boundaries are leaky, excess liquid can move across into this lower-pressure, high-capacitance space and accumulate as a pleural effusion. Thus, pleural effusions are common and of highly diverse etiologies; effusions can arise from the nearby pleural membranes or from more distant thoracic or abdominal organs. Depending on the protein and *lactate dehydrogenase* (LDH)

concentrations of the liquid, these effusions can be categorized initially as exudates or transudates. Exudative pleural effusions meet at least one of the following criteria, whereas transudative effusions meet none (Light's criteria): pleural fluid protein-to-serum protein ratio of more than 0.5, pleural fluid LDH-serum LDH ratio of more than 0.6, and pleural fluid LDH more than two thirds of the upper normal limit for serum. In this chapter, we discuss both the physiology and pathophysiology of liquid movement in the pleural space.

Other chapters cover the anatomy of the pleural membranes (see Chapter 1) and the pleural diseases related to pleural infections (see Chapter 80) and pleural tumors (see Chapter 82). In addition, pneumothorax, chylothorax, hemothorax, and fibrothorax are covered in Chapter 81.

This introductory chapter covers effusions in general with attention to transudates and those exudative effusions not caused by malignancy and infection.

PLEURA: FORM AND FUNCTION

The two pleural membranes meet at the hilar root of the lung. In the sheep, an animal with a pleural anatomy similar to humans, the surface area of the visceral pleura of one lung, including that invaginating into the lung fissures, is similar to that of the parietal pleura of one hemithorax, approximately 1000 cm².¹ The normal pleural space is approximately 18 to 20 μm in width, although it widens at its most dependent areas.¹ It has been shown that the pleural membranes do not touch each other and that the pleural space is a real, not a potential, space¹ (see Fig. 1-30).

It is likely that the primary function of the pleural membranes is to allow extensive movement of the lung relative to the chest wall. If the lung adhered directly to the chest wall, its expansion and deflation would be more limited. Encased in its slippery coat, the lung, although still coupled mechanically to the chest wall, is able to expand across a breadth of several intercostal spaces. Nonetheless, in clinical and experimental studies, pleural symphysis has not been associated with large abnormalities in lung function.^{2,3} The most common findings have been a decrease in volume of the affected lung and, in one study, of the opposite lung as well.⁴ If pleural thickening accompanies pleural symphysis, abnormalities of lung function may result more from fibrothorax than from obliteration of the pleural space alone.

The visceral pleura may also provide mechanical support for the lung: contributing to the shape of the lung, providing a limit to expansion, and contributing to the work of deflation. Because the submesothelial connective tissue is continuous with the connective tissue of the lung parenchyma, the visceral pleura may help to distribute the forces produced by negative inflation pressures evenly over the lung. In this way, overdistention of alveoli at the pleural surface may be avoided, lessening the chance of rupture and pneumothorax.

One recognized function of the pleural space is to provide a route by which edema can escape the lung.⁵ As has been shown in several experimental studies of either hydrostatic or increased-permeability lung edema,^{6,7} the pleural space can function as an additional safety factor protecting against the development of alveolar edema. The formation of transudative effusions in patients with congestive heart failure apparently reflects the movement of edema from the lung to a space where its effects on lung function are relatively small.

EMBRYOLOGY AND ANATOMY

By 3 weeks' gestational age, the pleural, pericardial, and peritoneal spaces begin to form from the mesoderm and, by 9 weeks, the pleural cavity has become separated from both the pericardial and peritoneal spaces.⁸ Various cysts, diverticulae, and defects can result from incomplete partitioning

of the three mesodermal spaces. As the lung develops, the lung buds invaginate into the visceral pleura and henceforth retain a pleural covering.

The pleural membranes are smooth, glistening coverings for the constantly moving lung. Overlying each pleural membrane is a single cell layer of mesothelial cells. These cells can vary in shape from flat to cuboidal or columnar, perhaps on the basis of the degree of stretching of the underlying submesothelial tissue. These cells, the most numerous of the pleural space, may have a variety of functions important to pleural biology.⁹ Mesothelial cells can secrete the macromolecular components of the extracellular matrix and organize them into mature matrix, phagocytose particles, produce fibrinolytic and procoagulant factors, and secrete neutrophil and monocyte chemotactic factors that may be important for inflammatory cell recruitment into the pleural spaces. The mesothelial cells also produce cytokines such as transforming growth factor-β, epidermal growth factor, and platelet-derived growth factor, cytokines that are important in pleural inflammation and fibrosis.

On their surface are microvilli, which are irregularly distributed over the pleural surfaces. Although microvilli presumably exist to increase surface area for metabolic activity, the function of these prominent features is unknown. Mesothelial cells produce hyaluronan but not mucin, express keratin microfilaments, stain negatively with epithelial-specific antibodies (Ber-EP4, B72.3, Leu.M1, and CEA), and stain positively for calretinin and mesothelin—all features that are important for histochemical and immunohistochemical identification of the cells in pleural effusions.^{10,11}

The cells lie on a thin basement membrane overlying a varying region of connective tissue containing mostly collagen and elastin. Although the parietal pleural connective tissue layer is of a consistent thickness, the visceral connective tissue layer varies greatly. In a single individual, the visceral pleura varies from a thinner layer at the cranial region to a thicker layer at the caudal region.¹² Interestingly, among mammalian species, whereas the parietal pleura is constant, the visceral pleura varies greatly (see Fig. 1-31). Analysis of the constituents of the visceral pleura has shown that there is more collagen relative to elastin than is found in the lung parenchyma, a finding consistent with a mechanical role for the pleura.¹³ This connective tissue layer contains blood vessels and lymphatics and joins with the connective tissue of the lung. The submesothelial tissue has been shown to have mechanical strength and to contain various growth factors that can support cell growth, suggesting that mesothelium could function as a repair and regenerative material.¹⁴

BLOOD SUPPLY

The parietal pleura is supplied by intercostal arteries¹⁵ (Fig. 79-1A). In humans and other large mammals, the visceral pleura is exclusively supplied by the bronchial circulation, which drains into pulmonary veins¹² (Fig. 79-1B). The drainage route via pulmonary veins may have contributed to earlier confusion about whether the visceral pleural blood supply was from a systemic (bronchial) or pulmonary circulation. Both pleurae in humans therefore have a systemic circulation, although the visceral pleural bronchial

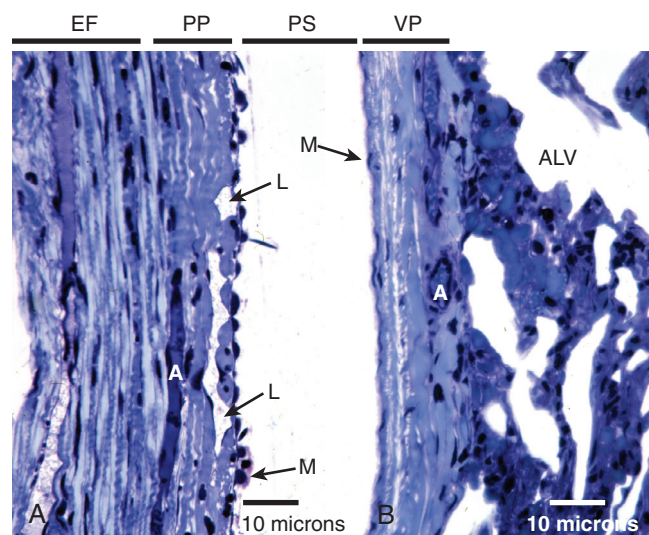


Figure 79-1 Light micrograph showing the parietal and visceral pleurae of the sheep, an animal with a similar pleural anatomy to that of humans. Both membranes are covered by a single layer of mesothelial cells (M). **A**, The parietal pleura (PP) is the layer of loose connective tissue between the pleural space (PS) and the dense connective tissue of the endothoracic fascia (EF). Within the loose connective tissue are blood microvessels (A) from the intercostal arteries and lymphatic lacunae (L), which open into the pleural space via stomata. **B**, The visceral pleura (VP) lies between the pleural space (PS) and the alveoli (ALV). The blood supply to the visceral pleura is via the bronchial arteries (A), which drain into pulmonary veins. The pleura contains dense bands of elastin and collagen. (Reproduced with permission from Staub NC, Wiener-Kronish JP, Albertine KH: Transport through the pleura: physiology of normal liquid and solute exchange in the pleural space. In Chrétien J, Bignon J, Hirsch A editors: *The pleura in health and disease*. New York, 1985, Marcel Dekker, pp 174–175, courtesy Marcel Dekker, Inc.)

circulation may have a slightly lower perfusion pressure than the parietal pleural intercostal circulation because of its drainage into a lower-pressure venous system.

LYMPHATICS

If one injects carbon particles into the pleural space as a visible marker of lymphatic drainage pathways, one later finds that the black carbon has been taken up into lymphatics on the parietal side, not the visceral side (Fig. 79–2) (see Fig. 1-32C). The visceral pleura has extensive lymphatics, but they do not connect to the pleural space¹² (see Fig. 1-27). Demonstrated in rabbits, sheep, and now in man, the parietal pleural lymphatics connect to the pleural space via stomas, holes of 8 to 10 μ m in diameter that are formed by discontinuities in the mesothelial layer where mesothelium joins to the underlying lymphatic endothelium (see Fig. 1-32A and B).^{16–18} The stomas can accommodate particles as large as erythrocytes. In various experimental studies, these lymphatics have been shown to be the major route of exit of liquid from the pleural space.¹⁹ From the stomas, liquid drains to lacunae, spider-like submesothelial collecting lymphatics, which then drain to infracostal lymphatics, to parasternal and periaortic nodes, to the thoracic duct, and into the systemic venous system. Lymphoid cells have been described lying within aggregates underneath morphologically different mesothelial cells, forming raised structures called *Kampmeier foci* that may have an immune function, as shown for the peritoneal space.⁹

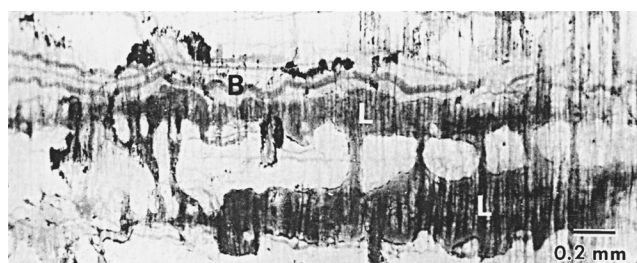


Figure 79-2 Macroscopic photograph of lymphatic lacunae in the parietal pleura over an intercostal space. Colloidal carbon was instilled into the pleural space to label the draining lymphatics. When one looks down on the pleura, the lymphatic lacunae (L) appear as broad cisterns. B, blood vessel. (Original magnification $\times 39$.) (Reprinted by permission of Wiley-Liss, a division of Wiley and Sons, Inc., copyright owner. From Albertine KH, Wiener-Kronish JP, Staub NC: The structure of the parietal pleura and its relationship to pleural liquid dynamics in sheep. *Anat Rec* 208:406, 1984.)

NERVE SUPPLY

The parietal pleura contains sensory nerve fibers, supplied by the intercostal and phrenic nerves, and has long been thought to be the major site of pain sensation in the pleura. The costal and peripheral diaphragmatic regions are innervated by the intercostal nerves, and pain from these regions is referred to the adjacent chest wall. The central diaphragmatic region is innervated by the phrenic nerve, and pain from this region is referred to the ipsilateral shoulder. The visceral pleura has more recently been shown to have sensory nerve fibers that may participate in pain or other sensations such as dyspnea.²⁰ In addition, pleural adhesions may contain pain fibers and contribute to post-thoracotomy or postpleurodesis pain.²¹

PHYSIOLOGY OF THE PLEURAL SPACE

NORMAL PLEURAL LIQUID AND PROTEIN TURNOVER

In the past 10 to 20 years, a consensus has developed that normal pleural liquid arises from the systemic pleural vessels in both pleurae, flows across the leaky pleural membranes into the pleural space, and exits the pleural space via the parietal pleural lymphatics^{22,23} (Fig. 79-3). In this way, the pleural space is analogous to other interstitial spaces of the body. There are several lines of evidence for this view.

1. Intrapleural pressure is lower than the interstitial pressure of either of the pleural tissues. This pressure difference constitutes a gradient for liquid movement into but not out of the pleural space.
2. The pleural membranes are leaky to liquid and protein. Whether tested in vitro^{24,25} or in situ,^{26,27} the pleura offers little resistance to liquid or protein movement.
3. Mesothelial cells express various transporters and aquaporins, but these have not been shown to have a role in reabsorption of effusions.^{28,29} Although normal pleural liquid has been reported to be alkaline with a higher bicarbonate than plasma, there is no evidence for mesothelial participation in generating a bicarbonate gradient. If indeed the mesothelial layer is leaky, it is difficult

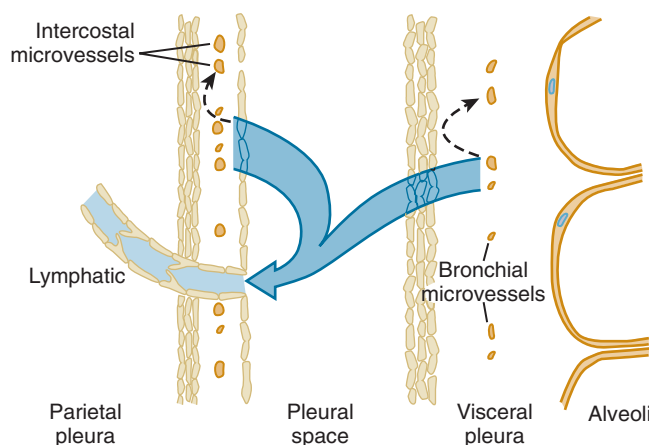


Figure 79-3 Schema showing normal pleural liquid turnover. The initial microvascular filtrate in the parietal and visceral pleura is partly reabsorbed (dashed arrows). The remaining low-protein interstitial liquid flows across the leaky pleural mesothelial layers into the pleural space. The pleural liquid exits the pleural space via the parietal pleural lymphatic stomata. (Reproduced with permission from Staub, NC, Wiener-Kronish JP, Albertine, KH: Transport through the pleura: Physiology of normal liquid and solute exchange in the pleural space. In Chrétien J, Bignon J, Hirsch A, eds: *The pleura in health and disease*, New York, 1985, Marcel Dekker, p. 182, courtesy Marcel Dekker.)

to explain how mesothelial cells could maintain such a gradient. (The bicarbonate difference could also be explained by a passive distribution of ions across a semi-permeable membrane, a phenomenon called the *Donnan equilibrium*.)

4. The entry of pleural liquid is slow and compatible with known interstitial flow rates. By noninvasive studies of the equilibration of radiolabeled albumin, the entry rate of pleural liquid is approximately 0.01 mL/kg per hour in a sheep, or about 0.5 mL hourly or 12 mL a day in a grown man.³⁰ The half-time of pleural liquid turnover in sheep and rabbits is 6 to 8 hours.^{30,31}
5. The protein concentration of normal pleural liquid is low in sheep³⁰ and probably in humans, which implies sieving of the protein across a high pressure gradient. The protein concentration of sheep pleural liquid (10 g/L, 1 g/dL) and pleural-to-plasma protein concentration ratio (0.15) are similar to those of filtrates from high-pressure systemic vessels. By comparison, a filtrate from low-pressure pulmonary vessels has a higher protein concentration (45 g/L, 4.5 g/dL) and ratio (lymph-to-plasma protein concentration ratio 0.69).³²
6. The majority of liquid exits the pleural space by bulk flow, not by diffusion or active transport. This is evident because the protein concentration of pleural effusions remains constant as the effusion is absorbed, as is expected with bulk flow. If liquid were absorbed by diffusion or active transport, proteins would exit at a slower rate and the protein concentration would progressively increase. In addition, erythrocytes instilled into the pleural space are absorbed intact and in almost the same proportion as the liquid and protein.¹⁹ This indicates that the major route of exit is via holes large enough to accommodate sheep erythrocytes (6 to 8 μ m diameter). The only possible exit is via the parietal pleural stomas (10 to 12 μ m diameter) into the pleural lymphatics. Of note, these lymphatics have a large capacity for

absorption. When artificial effusions were instilled into the pleural space of awake sheep, the exit rate (0.28 mL/kg per hour) was nearly 30 times the baseline exit rate (0.01 mL/kg per hour).¹⁹

PLEURAL PRESSURE

The pleural pressure in humans is approximately -5 cm H₂O at midchest at functional residual capacity and -30 cm H₂O at total lung capacity.³³ If the compliance of the lung decreased, pleural pressures at the same lung volumes would be more negative. In one study of patients undergoing thoracentesis, those with more negative pleural pressures had a smaller improvement in lung volume than those with less negative pressures, presumably reflecting the presence of underlying diseased, noncompliant lung.³⁴

Although the pleural space pressure is subatmospheric, gases do not accumulate there. The sum of all partial pressures of gases in capillary blood is approximately 700 mm Hg, or 60 mm Hg below atmospheric ($P_{H_2O} = 47$, $P_{CO_2} = 46$, $P_{N_2} = 570$, and $P_{O_2} = 40$ mm Hg). The subatmospheric pressure of dissolved gases in capillary blood helps to maintain the pleural space free of gas and facilitates absorption of any gas that does enter the pleural space. Of note, to increase the gradient favoring absorption of gas, one can lower the partial pressure of nitrogen in the blood by having a patient breathe increased concentrations of inspired oxygen. The oxygen displaces alveolar nitrogen, thereby lowering the partial pressure of nitrogen in capillary blood; because of the limited absorption of oxygen due to the plateau of the oxygen-hemoglobin dissociation curve, however, the increase in inspired oxygen does not add greatly to the partial pressure of oxygen in capillary blood.

PATHOPHYSIOLOGY OF THE PLEURAL SPACE

PLEURAL EFFUSIONS

For pleural liquid to accumulate to form an effusion, it is likely that *both* the entry rate of liquid must increase and the exit rate must decrease. If only the entry rate increased, it would require a sustained rate more than 30 times normal to exceed the reserve lymphatic removal capacity; if the exit rate decreased, it would take more than a month at the normal entry rate of 12 mL per day to produce an effusion detectable by chest radiograph.²³ Thus, in the clinical setting, it is most likely that excess pleural liquid accumulates due to changes in *both* entry and exit rates.

Increased entry of liquid may result from increased filtration across systemic or pulmonary capillaries or entry of another liquid (e.g., chyle, cerebrospinal fluid, urine, intravenous fluid from a displaced catheter). Decreased exit of liquid may result from interference with lymphatic function (e.g., obstruction of the parietal pleural stomas, inhibition of lymphatic contractility, infiltration of draining parasternal lymph nodes, or elevation of the systemic venous pressure into which the lymph drains).²³ There are few studies on the rate of removal of liquid in humans; however, decreases in lymphatic clearance have been confirmed in patients with tuberculous and malignant effusions,³⁵ and

in those with the yellow nail syndrome, a disease of lymphatic function.³⁶ In some cases, it is likely that the same disease process acts to increase entry and reduce exit of liquid whereas, in other cases, different disease processes may act cooperatively to produce an effusion.

To determine the origin of effusions, a classic and useful distinction is between transudates and exudates (see “[Separation of Exudates from Transudates](#)” later).³⁷ Transudates form by leakage of liquid across an intact capillary barrier, owing to increases in hydrostatic pressures or decreases in osmotic pressures across that barrier. Transudates generally indicate that the pleural membranes are not themselves diseased. Exudates generally form from leakage of liquid and protein across an altered capillary barrier with increased permeability. The protein ratio, LDH ratio, and absolute pleural LDH concentration constitute Light’s criteria.

Transudates include various low protein liquids that arise from noninjured capillary beds. The majority of transudates and, in fact the majority of all effusions, are caused by congestive heart failure. These transudates have been shown to form mainly from leakage of edema across normal pulmonary capillaries into the pulmonary interstitium; this interstitial edema can then move toward the pleural space and across the leaky visceral pleura into the pleural space.^{6,38} Other transudates, those associated with the nephrotic syndrome or atelectasis, may form because of altered pressures (osmotic or hydrostatic) across the pleural capillaries. Some transudates, usually small, may develop primarily because of an isolated decrease in exit rate.³⁹ Hepatic hydrothorax and effusions from peritoneal dialysis develop when liquid flows from the peritoneal space into the lower pressure pleural space across macroscopic holes in the diaphragm. Finally, other *very* low protein fluids such as urine or cerebrospinal fluid or intravenous liquids may find their way to the pleural space if their normal course is disrupted.

Exudates arise from injured capillary beds, either in the lung, pleura, or adjacent tissues. Most exudates, such as those associated with pneumonia or *pulmonary embolism* (PE), probably form following lung inflammation and injury when a high-protein lung edema leaks into the pleural space. Another large category of exudates arises from pleural injury due to inflammation, infection, or malignancy. Exudates can also form when exudative liquid in the mediastinum (esophageal rupture or chylothorax), retroperitoneum (pancreatic pseudocyst), or peritoneum (ascites with spontaneous bacterial peritonitis or Meig syndrome) finds its way into the lower-pressure pleural space.

As stated, for either transudates or exudates, lymphatic obstruction may contribute to the accumulation of the effusion. Nonetheless, because lymphatic clearance does not alter the pleural fluid protein concentration, the protein concentration gives information about the *formation* of the fluid, not its *removal*.²³

EFFECTS OF PLEURAL EFFUSIONS ON LUNG AND CARDIAC FUNCTION

In the presence of a space-occupying liquid in the pleural space, the lung recoils inward, the chest wall recoils outward, and the diaphragm is depressed inferiorly and is sometimes inverted.⁴⁰ If the lung and chest wall have

normal compliances, the decrease in lung volume accounts for approximately a third of the volume of the pleural effusion, and the increase in the size of the hemithorax accounts for the remaining two thirds. As a result, lung volumes are reduced by less than the pleural effusion volume. If the lung is otherwise normal, there is no evidence that an effusion causes significant hypoxemia, presumably because ventilation and perfusion decrease similarly. In fact, in one study, mild hypoxemia present before thoracentesis worsened significantly *after* thoracentesis,⁴¹ when perfusion presumably was restored while ventilation remained inadequate. In another study using multiple inert gas techniques to quantify V/Q distributions, pleural effusion was associated with a small intrapulmonary perfusion shunt (6.9%) that did not change significantly when measured again 30 minutes after thoracentesis of approximately 700 mL (6.1%).⁴² Draining pleural effusions in patients with refractory hypoxemia on mechanical ventilation may improve oxygenation,⁴³ although there is no consensus on the indications for thoracentesis in this setting.⁴⁴ It appears therefore that the effects of pleural effusion and thoracentesis on oxygenation are variable and may depend on the underlying lung function.

Large pleural effusions may impair cardiac function, most likely by decreasing the distending pressures on the cardiac chambers and cardiac filling. In a study of 27 patients with large effusions occupying more than half the hemithorax, clinical and echocardiographic findings of cardiac tamponade were identified in most patients. These findings, including elevated jugular venous pressure, pulsus paradoxus, right ventricular diastolic collapse, or flow velocity paradoxus, resolved in all patients when studied again 24 hours after thoracentesis of more than 1 L.⁴⁵ Large pleural effusions, especially left-sided effusions, should be considered as potentially reversible causes of cardiac dysfunction.⁴⁶ Thoracentesis of a unilateral effusion (mean value 1.5 L) has also been shown to improve exercise tolerance.⁴⁷

Common symptoms of patients with effusions are pleuritic chest pain, cough, and dyspnea. It appears that the three symptoms are due to different causes. Pleuritic chest pain derives from inflammation of the parietal pleura and possibly the visceral pleura. Occasionally, this symptom is accompanied by an audible or palpable pleural rub, reflecting the movement of abnormal pleural tissues ([Audio 16-11](#)). Cough may be induced by distortion of the lung, in the same way as cough follows lung collapse from a pneumothorax. Dyspnea is most likely caused by the mechanical inefficiency of the respiratory muscles that are stretched by the outward displacement of the chest wall and the downward displacement of the diaphragm.⁴⁰ After the removal of large amounts of pleural liquid, dyspnea is generally relieved promptly, although the reduction in pleural liquid volume is associated with only small increases in lung volume and little improvement, or an actual decrease, in PO_2 . In one study, nine patients underwent removal of more than 1800 mL of pleural liquid and, despite increases in vital capacity of only 300 mL, all patients experienced immediate relief of dyspnea.⁴⁸ Although the vital capacity changed little, patients could generate a more negative pleural pressure at the same lung volume after thoracentesis than before, indicating an improved efficiency of the

respiratory muscles following the return of the chest wall and diaphragm to a more normal position after thoracentesis. Another related explanation is that dyspnea is due to the inversion of the diaphragm caused by the weight of the pleural effusion, and that dyspnea is promptly relieved when thoracentesis allows the restoration of a dome-shaped diaphragm.⁴⁹ It appears that mechanical effects of a pleural effusion account for dyspnea and for the rapid relief of dyspnea after removal of pleural liquid.

APPROACH TO PATIENTS WITH PLEURAL EFFUSION

Physical findings of a pleural effusion include dullness to percussion, decreased breath sounds, egophony at the upper level of the effusion, and decreased tactile fremitus. With large effusions, signs can include asymmetrical chest expansion or even bulging of the intercostal spaces. A systematic review concluded that the most useful physical findings were dullness to percussion and decreased tactile fremitus⁵⁰ (see Chapter 16).

The possibility of a pleural effusion should be considered in any patient with an abnormal chest radiograph. Increased opacity on chest radiography is frequently attributed to a parenchymal process when it actually represents pleural fluid. Free pleural fluid gravitates to the most dependent part of the thoracic cavity, which is the posterior costophrenic sulcus when the patient is upright. Therefore, if the posterior costophrenic angle is blunted or if the posterior part of the diaphragm is not visible on the lateral chest radiograph, bilateral decubitus chest radiographs (see Figs. 18-7 and 18-9) or an ultrasonic examination (see eFig. 18-21) of the pleural space should be obtained to ascertain whether free pleural fluid is present. If the distance between the inside of the thoracic cavity and the outside of the lung is less than 10 mm, the pleural effusion is not likely to be clinically significant and, in any case, will be difficult to obtain by thoracentesis. If the distance is greater than 10 mm, an effort should be made to determine the cause of the pleural effusion.

DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSION

Many different diseases may have an accompanying pleural effusion (Table 79-1). The vigor with which various diagnoses are pursued should depend on the likelihood that the person has that particular disease. Table 79-2 shows rough estimates of the annual incidence of the most common causes of pleural effusions. Congestive heart failure and cirrhosis are responsible for almost all transudative pleural effusions. Pneumonia, malignant pleural disease, PE, and gastrointestinal disease account for at least 90% of all exudative pleural effusions.

SEPARATION OF EXUDATES FROM TRANSUDATES

A diagnostic thoracentesis should be performed on nearly every patient with free pleural fluid that measures more

Table 79-1 Differential Diagnoses of Pleural Effusions

TRANSUDATIVE PLEURAL EFFUSIONS	Collagen vascular diseases
Congestive heart failure	Rheumatoid pleuritis
Pericardial disease	Systemic lupus erythematosus
Hepatic hydrothorax	Drug-induced lupus
Nephrotic syndrome	Immunoblastic lymphadenopathy
Peritoneal dialysis	Sjögren syndrome
Urinothorax	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Myxedema	Granulomatosis with polyangiitis (Wegener)
Central venous occlusion	Post-cardiac injury syndrome
Subarachnoid-pleural fistula	Post-coronary artery bypass surgery
Veno-occlusive disease	Fontan procedure
Bone marrow transplantation	Asbestos exposure
iatrogenic	Sarcoidosis
	Uremia
EXUDATIVE PLEURAL EFFUSIONS	Meigs syndrome
Neoplastic diseases (see Chapter 82)	Ovarian hyperstimulation syndrome
Metastatic disease	Yellow nail syndrome
Mesothelioma	Drug-induced pleural disease
Primary effusion lymphoma	Nitrofurantoin
Pyothorax-associated lymphoma	Dantrolene
Infectious diseases (see Chapter 80)	Methysergide
Pyogenic bacterial infections	Bromocriptine
Tuberculosis	Procarbazine
Actinomycosis and nocardiosis	Amiodarone
Fungal infections	Dasatinib
Viral infections	Radiation therapy
Parasitic infections	Electric burns
Pulmonary embolism	Iatrogenic injury
Gastrointestinal disease	Hemothorax (see Chapter 81)
Esophageal perforation	Chylothorax (see Chapter 81)
Pancreatic disease	
Intra-abdominal abscesses	
Diaphragmatic hernia	
Postabdominal surgery	

Table 79-2 Approximate Annual Incidence of Various Types of Pleural Effusions in the United States

Type of Effusion	Incidence
Congestive heart failure	500,000
Pneumonia (bacterial)	300,000
Malignant disease	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	50,000
Pulmonary embolism	150,000
Viral disease	100,000
Post-coronary artery bypass surgery	60,000
Cirrhosis with ascites	50,000
Gastrointestinal disease	25,000
Collagen vascular disease	6000
Tuberculosis	2500
Asbestos exposure	2000
Mesothelioma	1500

Adapted with permission from Light RW: Pleural diseases, ed 6. Philadelphia, 2013, Lippincott Williams & Wilkins.

than 10 mm on the decubitus radiograph, ultrasound, or chest *computed tomography* (CT) scan. If the patient has obvious congestive heart failure, consideration can be given to postponing the thoracentesis until the heart failure is treated. However, if the patient is febrile or has pleuritic chest pain or if the effusions are not of comparable size on both sides, thoracentesis should be performed without delay.

Thoracentesis is a safe procedure when performed by an experienced operator. Because of the small-bore needle required, it can be safely performed in patients with coagulopathies and thrombocytopenia⁵¹ and in patients on positive mechanical ventilation.⁵² Descriptions of technique emphasize proper positioning of the patient, identification of the area of decreased tactile fremitus that is a sensitive physical finding for the level of the effusion, and adequate local anesthesia of parietal pleura and the skin. The needle should run over the top of the rib to avoid the neurovascular bundle that travels in each intercostal space. Of note, this bundle travels in the middle of the intercostal space from the spine for approximately 5 to 6 inches (13 cm) before taking its safer position beneath the upper rib (eFig. 79-1; also see eFig. 19-1E).⁵² Thus, one should avoid thoracentesis medial to the midclavicular line.

Complications from thoracentesis include pneumothorax and hemothorax (see eFig. 19-1). Estimates of each complication from prospective studies are low (2% to 6% for pneumothorax; 1% for hemothorax), with only half of the pneumothoraces requiring chest thoracostomy.⁵³ Pneumothorax is often associated with procedural events such as aspiration of air, multiple needle passes, and development of new symptoms. The risk for pneumothorax appears to be higher in patients with prior radiotherapy to the chest, multiple prior thoracenteses, or the use of vacuum bottles. In an uncomplicated thoracentesis that is well tolerated by the patient, there appears to be no value for routine chest radiography postprocedure. In addition, routine post-thoracentesis radiographs rarely show new findings.⁵³ Thoracentesis may be safer when guided by ultrasound, although, given the safety of the procedure in uncomplicated cases and the cost or inaccessibility of ultrasound, ultrasound can be selected for higher-risk procedures. For example, it would be appropriate to use ultrasound guidance for thoracentesis on small or multiloculated effusions, in patients with poor lung function or bullous lung disease, and in patients on positive pressure ventilation^{52,54} (see Chapter 20).

The first question that should be answered with the diagnostic thoracentesis is whether the patient has a transudative or an exudative pleural effusion (see “Pleural Effusions” earlier). The identification of transudates or exudates is made by analysis of the levels of protein and *lactate dehydrogenase* (LDH) in the pleural fluid and the serum. Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none³⁷: (1) pleural fluid protein/serum protein greater than 0.50; (2) pleural fluid LDH/serum LDH greater than 0.60; and (3) pleural fluid LDH greater than two thirds of the upper normal limit for serum. If none of these criteria is met, the patient has a transudative pleural effusion and the pleural surfaces can be ignored while the congestive heart failure, cirrhosis, or nephrosis is treated. In the rare cases

where malignancy has been associated with a transudate, extrapleural effects of the tumor or other causes such as concurrent congestive heart failure are the most likely cause as evidenced by the rarity of a positive cytology in those effusions.^{23,55}

These criteria may misidentify a transudative effusion as an exudative effusion in up to 25% of cases. If a patient appears to have a transudative effusion clinically, additional tests can be assessed to verify its transudative etiology. If the difference between the protein concentration of serum and pleural exceeds 3.1 g/dL or if the difference between the albumin concentration of serum and pleural exceeds 1.2 g/dL, the patient in all probability has a transudative effusion.⁵⁶ If pleural concentrations of *N-terminal probrain natriuretic peptide* (NT-BNP) are elevated (>1300 pg/mL), the patient likely has a transudate from a cardiac cause.⁵⁷

Most studies dichotomize pleural effusions into transudates or exudates on the basis of a single cutoff point. An alternative approach recommended by Heffner and coworkers⁵⁸ is to use likelihood ratios for identifying whether a pleural fluid is a transudate or an exudate. The idea behind this approach is that the higher a value (e.g., the pleural fluid LDH), the more likely the effusion is to be an exudate, and the lower the value, the less likely the effusion is to be an exudate. When these likelihood ratios are used in conjunction with pretest probabilities using Bayes theorem, posttest probabilities can be derived. The difficulty in using this approach is that estimates of pretest probabilities vary significantly from physician to physician. Moreover, most physicians do not understand the mathematics involved. Nonetheless, this approach does emphasize that it is important to take into consideration the absolute value of the measurements. Very high or very low measurements are almost always indicative of exudates and transudates, respectively, while values near the cutoff levels can be associated with either transudates or exudates and can be considered *indeterminate*.

When dealing with a patient who has a high likelihood of having a transudative pleural effusion, the most cost-effective use of the laboratory is to order only protein and LDH levels on the pleural fluid and obtain other laboratory tests only if the fluid turns out to be an exudate. In one study, of 320 pleural fluid specimens submitted for analysis, 83 were found to be transudative.⁵⁹ For these 83 effusions, 725 additional laboratory tests had been ordered, increasing both cost and the incidence of false-positive tests (7/9). If one suspects initially that the patient has an exudate or if the fluid turns out to be an exudate, specimens can be sent for cytology, amylase, glucose, cell count and differential, and cultures.

DIFFERENTIATING EXUDATIVE PLEURAL EFFUSIONS

Once it has been determined that the patient has an exudative pleural effusion, one should attempt to determine which of the diseases listed in Table 79-1 is responsible for the effusion, remembering that pneumonia, malignancy, and PE account for the great majority of all exudative pleural effusions. In all patients with undiagnosed exudative pleural effusions, the appearance of the fluid should be noted and the pleural fluid protein and LDH levels (if not already

obtained), glucose level, differential cell count, and microbiologic and cytologic studies should be obtained.⁶⁰ In selected patients, other tests on the pleural fluid, such as pH, amylase level, antinuclear antibody level, rheumatoid factor level, *adenosine deaminase* (ADA), lipid analysis, and so forth, may be of value. It is certainly not cost effective, however, to obtain all these tests routinely on patients with undiagnosed exudative pleural effusions.

Appearance of Pleural Fluid

The gross appearance of the pleural fluid should always be described and its odor noted. If the pleural fluid smells putrid, the patient has a bacterial infection (probably anaerobic) of the pleural space. If the fluid smells like urine, the patient probably has a urinorhorrax. If the pleural fluid is bloody, a pleural fluid hematocrit should be obtained. If the pleural fluid hematocrit is greater than 50% that of the peripheral blood, the patient has a hemothorax and the physician should strongly consider inserting chest tubes to monitor the rate of bleeding. If the pleural fluid hematocrit is less than 1%, the blood in the pleural fluid has no clinical significance. If the pleural fluid hematocrit is between 1% and 50%, the patient most likely has malignant pleural disease, a PE, or a traumatically induced pleural effusion.⁶¹

If the pleural fluid is turbid, milky, or bloody, the fluid should be centrifuged and the supernatant examined. If the pleural fluid is turbid when originally obtained and the turbidity clears with centrifugation, the turbidity is due to cells or debris in the pleural fluid; if the turbidity persists after centrifugation, the patient probably has a chylothorax (see Fig. 81-8, eFig. 81-8, Video 81-1) or a pseudochylothorax (eFig. 79-2A). These two entities can be differentiated by the patient's history, examination of the sediment for cholesterol crystals (see eFig. 79-2B), and lipid analysis of the supernatant. With chylothorax, the disease process is acute, the pleural surfaces are not thickened, there are no cholesterol crystals present, and the pleural fluid triglyceride level is usually above 110 mg/dL (1.24 mmol/L). With pseudochylothorax, the disease process is usually chronic, the pleural surfaces are usually thickened, there may be cholesterol crystals, and the pleural fluid triglyceride level is usually not elevated. (For further discussion of chylothorax and pseudochylothorax, see Chapter 81.)

Pleural Fluid Protein

The pleural fluid protein level tends to be elevated to a comparable degree with all exudative pleural effusions and is therefore not generally useful in the differential diagnosis of an exudative pleural effusion. However, if the protein level is above 5.0 g/dL, the likelihood of the diagnosis of tuberculous pleurisy is increased. If the pleural fluid protein level is very low (<0.5 g/dL), the patient probably has a urinorhorrax, an effusion secondary to peritoneal dialysis, a leak of cerebrospinal fluid into the pleural space, or an effusion secondary to the misplacement of a central intravascular line.

Pleural Fluid Lactate Dehydrogenase

Whereas pleural liquid protein and LDH arise from filtration from serum and thus serve as indicators of vascular permeability, LDH, as an intracellular enzyme, also may indicate

the degree of cell turnover within the pleural space. Nonetheless, the pleural fluid LDH level is increased to a comparable degree in patients with all categories of exudative pleural effusions and therefore is of no utility in the differential diagnosis of exudative pleural effusion.³⁷ Likewise, the pleural fluid LDH isoenzymes are of limited use in the differential diagnosis of exudative pleural effusions. However, pleural fluid LDH concentration should be measured every time a diagnostic thoracentesis is performed, because the level of LDH in the pleural fluid reflects the degree of inflammation in the pleural space. If the pleural fluid LDH concentration increases with serial thoracentesis, the degree of inflammation in the pleural space is worsening and the physician should be more aggressive in pursuing the diagnosis. Alternatively, if the pleural fluid LDH level decreases with serial thoracentesis, the pleural disease is resolving and observation of the patient is indicated.⁶² When an effusion meets exudative criteria on the basis of LDH but not protein, the effusion is usually malignant or parapneumonic.³⁷

Pleural Fluid Glucose

A low glucose concentration probably indicates the coexistence of two abnormalities: a thickened, infiltrated pleura leading to an impaired diffusion of glucose into the pleural space plus increased metabolic activity leading to increased glucose utilization within the pleural space. The glucose level should be measured in all undiagnosed exudative pleural effusions because the demonstration of a reduced pleural fluid glucose level (<60 mg/dL, 3.3 mmol/L) narrows the diagnostic possibilities to seven: parapneumonic effusion, malignant effusion, tuberculous effusion, rheumatoid effusion, hemothorax, paragonimiasis, or *eosinophilic granulomatosis with polyangiitis* (EGPA, Churg-Strauss).⁶² If a patient with a parapneumonic effusion has a pleural fluid glucose level below 40 mg/dL (2.2 mmol/L), tube thoracostomy should be considered. Many patients with rheumatoid pleural effusions have a pleural fluid glucose level below 30 mg/dL (1.7 mmol/L).⁶³ In contrast, most patients with pleural effusion secondary to *systemic lupus erythematosus* (SLE) will have a pleural fluid glucose level above 80 mg/dL (4.4 mmol/L).⁶⁴ Patients with malignant pleural disease and a low pleural fluid glucose level usually have a positive pleural fluid cytology. In addition, their prognosis is poor, with a mean survival of less than 2 months.^{65,66}

Pleural Fluid White Cell Count and Differential

Pleural liquid that is submitted for white cell count and differential should be sent in a tube with an anticoagulant to prevent the cells from clumping.⁶⁷ In the normal pleural space, the cell count has been reported to be 1700 cells/ μ L.⁶⁸ In effusions, the cell count has limited diagnostic value. A pleural fluid white blood cell count of 1000/ μ L roughly separates transudative from exudative pleural effusion, whereas a pleural fluid white blood cell count above 10,000/ μ L is most common with empyemas and parapneumonic effusions but is also seen with pancreatitis, PE, and collagen vascular diseases and, occasionally, with malignancy and tuberculosis.⁶¹

The differential cell count on the pleural fluid is much more useful than the white cell count itself. The normal

pleural space contains predominantly macrophages (75%) followed by lymphocytes (23%).⁶⁸ A change in differential from this normal distribution provides a clue to the underlying disease process. For the pleural fluid differential cell count, the cells should be partitioned into the following categories: polymorphonuclear leukocytes, eosinophils, small lymphocytes, mesothelial cells, and other mononuclear cells. Pleural effusions due to an acute disease process such as pneumonia, PE, pancreatitis, intra-abdominal abscess, or early tuberculosis contain predominantly polymorphonuclear leukocytes. Pleural effusions due to a chronic disease process contain predominantly mononuclear cells.

Pleural fluid eosinophilia (10% or more eosinophils by differential count) is most commonly due to air or blood in the pleural space. *Interleukin-5* (IL-5) appears to be an important factor because the number and percentage of eosinophils in the pleural space are closely correlated with the pleural liquid IL-5 levels.⁶⁹ Occasionally, no pleural fluid eosinophils are found in the initial thoracentesis, but many eosinophils are seen in a subsequent thoracentesis most likely due to entry of air or blood caused by the initial thoracentesis.⁷⁰ With traumatic hemothorax, pleural fluid eosinophilia does not appear until the second week. The eosinophilia appears to be due to production of IL-5 by CD4⁺ T cells within the pleural space⁷¹ and has been associated with a type 2 innate immune response following a pneumothorax.⁷² At times, the pleural fluid eosinophilia associated with a hemothorax can lead to eosinophilia in the peripheral blood.⁷³ The bloody pleural effusion complicating PE frequently contains many eosinophils.⁷⁴ With pneumothorax, pleural eosinophilia appears within 3 days of the pneumothorax and reaches a peak after 6 days.⁷⁵

After excluding air or blood as the underlying cause, the etiologies of 392 cases of eosinophilic pleural effusions have been reported as follows: idiopathic 40%, malignancy 17%, parapneumonic 13%, tuberculosis 6%, PE 4%, transudates 8%, and other 13%.⁷⁶ If the etiology of the eosinophilia is not evident, several unusual diagnoses should be considered. Benign asbestos pleural effusions are frequently eosinophilic. In one series, 15 of 29 patients (52%) with benign asbestos pleural effusions had pleural fluid eosinophilia.⁷⁰ Patients with pleural effusions secondary to drug reactions (nitrofurantoin or dantrolene) typically have pleural fluid eosinophilia.⁶² The pleural fluid of patients with pleural paragonimiasis is typically eosinophilic with low glucose, low pH, and high LDH level.⁷⁷ EGPA is the only other disease that produces this constellation of pleural fluid findings.⁷⁸

Mesothelial cells line the pleural cavities. It is unusual to find mesothelial cells in effusions due to tuberculosis. However, the absence of mesothelial cells is also common with other conditions in which the pleura becomes coated with fibrin, such as a complicated parapneumonic effusion.

Lymphocytic pleural effusions by definition contain more than 50% small lymphocytes. Most lymphocytic pleural effusions are due to malignancy or tuberculosis. Ninety of 96 exudative pleural effusions (94%) in two series with more than 50% small lymphocytes were due to tuberculosis or malignant disease.^{61,79} Because these two diseases can be diagnosed with needle biopsy of the pleura, the presence of

pleural fluid lymphocytosis should alert the physician to consider needle biopsy of the pleura for diagnosis. In general, separation of pleural lymphocytes into T and B lymphocytes has not been useful diagnostically because most lymphocytic effusions contain a predominance of T cells (CD4⁺) whether the diagnosis is malignancy or tuberculosis.⁸⁰ Such partitioning can be useful diagnostically, however, when a diagnosis of chronic lymphocytic leukemia or lymphoma is suspected. With these diseases the pleural lymphocytes are usually of B-cell origin.⁸¹

Pleural Fluid Cytology

A pleural fluid specimen from every patient with an undiagnosed exudative pleural effusion should be sent for cytopathologic studies. The first pleural fluid cytologic study is positive for malignant cells in up to 60% of the effusions caused by pleural malignancy.⁶¹ If three separate specimens are submitted, up to 90% with pleural malignancy have positive cytopathology. The percentage of cases in which cytologic study of the pleural fluid establishes the diagnosis of a malignant pleural effusion ranges from 40% to 87%.^{61,82,83} The frequency of positive pleural fluid cytologic tests is dependent on the tumor type. For example, less than 25% of patients with Hodgkin disease have positive cytology,⁸⁴ whereas most patients with adenocarcinomas have positive cytology.⁸³ The percentage of positive diagnoses is higher if both cell blocks and smears are prepared by standard protocols and examined by an experienced cytologist.⁸⁵ Each additional sample may increase diagnostic yield in part by providing a higher percentage of fresher cells as older degenerated cells are largely removed by the earlier thoracenteses. During thoracoscopy, pleural lavage has been found to increase the diagnostic yield, perhaps by harvesting more fresh cells for analysis.⁸⁶ The percentage of positive diagnoses is obviously dependent on the skill and experience of the cytologist. Immunohistochemical stains of malignant cells are used to confirm a diagnosis and to specify tumor type, with many new markers available and being used in panels for optimal diagnostic efficacy.^{11,85,87} Cytology can provide enough DNA to assess mutational analysis for *epidermal growth factor receptor* (EGFR) activating mutations when extremely sensitive techniques including next-generation sequencing are used.^{88,89}

Other Diagnostic Tests for Malignancy

Cytology may be nondiagnostic either because of a problem of specificity (e.g., the malignant cells cannot be differentiated from reactive mesothelial cells and “atypical” benign cells) or because of a problem of sensitivity (e.g., the malignant cells are rare). Several assays are being evaluated for their ability to increase the specificity of cytology for diagnosis of malignancy.⁹⁰ *Fluorescent in situ hybridization* (FISH) with chromosome-specific probes can confirm abnormal numbers of specific chromosomes (aneuploidy), thereby confirming that abnormal cells are indeed malignant.⁹¹ Early findings of malignancy including DNA methylation can be detected by methylation-specific *polymerase chain reaction* (PCR)⁹² and gene expression patterns can help distinguish mesothelioma and adenocarcinoma.⁹³ EGFR mutations can predict response to EGFR tyrosine kinase inhibitors. On the other hand, biomarkers have generally been disappointing due to nonspecificity. However, pleural

fluid mesothelin measurements hold promise for the diagnosis of mesothelioma; pleural mesothelin is more accurate than serum for mesothelioma, and a low value can be useful in excluding the diagnosis.^{94,95} However, routine use of mesothelin is not useful⁹⁵ (see Chapter 82).

Culture and Bacteriologic Stains

Pleural fluid from patients with undiagnosed exudative pleural effusions should be cultured for bacteria (both aerobically and anaerobically), mycobacteria, and fungi. Gram stain should also be obtained. In the case of a probable complicated parapneumonic effusion with an initial negative Gram stain, the sediment of the pleural fluid should be stained because the bacteria will be precipitated in the sediment along with the white blood cells and debris. The yield of bacterial culture can be increased by using blood culture bottle cultures in addition to standard cultures; in 62 patients with pleural infection, the added inoculation of a set of aerobic and anaerobic blood culture bottles increased the identification of pathogens from 38% to 59%.⁹⁶

One potentially useful adjunct is molecular detection of bacterial antigens or DNA. This may be especially useful in children for whom the yield from culture is often poor, presumably due to antibiotics given before the thoracentesis.⁹⁷ Such molecular tests can be rapid and more accurate. Antigen-based assays have shown promise in diagnosing empyema caused by *Streptococcus pneumoniae*^{98,99} and *Streptococcus pyogenes*.⁹⁷ Amplification and sequencing of bacterial 16S ribosomal RNA have identified bacteria in pleural empyema, showing in one study of adults that the bacteriology of pleural infections differed from that of pneumonia.¹⁰⁰ It is likely that use of species-specific PCR will become a more standard molecular test for a panel of organisms; it improves detection when compared with 16S PCR and has the potential to make specific diagnoses, although false-positive results are a potential limitation.¹⁰¹

OTHER DIAGNOSTIC TESTS FOR PLEURAL FLUID

Pleural Fluid pH and Pco₂

The pleural fluid pH can be reduced to less than 7.20 with 10 different conditions: (1) complicated parapneumonic effusion, (2) esophageal rupture, (3) rheumatoid pleuritis, (4) tuberculous pleuritis, (5) malignant pleural disease, (6) hemothorax, (7) systemic acidosis, (8) paragonimiasis, (9) lupus pleuritis, or (10) urinothorax.⁶² The decreased pleural fluid pH appears to result from lactic acid and carbon dioxide accumulation in the pleural fluid.¹⁰² The pleural fluid pH is most useful in determining whether chest tubes should be inserted in patients with parapneumonic effusions.¹⁰³ A fall in the pleural fluid pH appears to be a sensitive indicator that the patient has a highly inflammatory parapneumonic pleural effusion that will require drainage.

The routine measurement of pleural fluid pH is recommended only in patients with parapneumonic effusions. In general, pleural fluids with a low pH also have a low glucose¹⁰²; thus, pleural fluid glucose can be used as an alternative to the pH measurement. When the pleural fluid pH is used as a diagnostic test, it must be measured with the same care as arterial pH. The fluid should be collected

anaerobically in a heparinized syringe and placed on ice. If the sample is left open to air, a spuriously high pH value can be obtained because of the rapid loss of carbon dioxide. The pH must be measured with a blood gas machine; a pH meter or indicator paper is not sufficiently accurate.¹⁰⁴ Pleural fluid pH, but not glucose, may be significantly altered by residual air or lidocaine in the syringe.¹⁰⁵ In a 2012 study, 40% of pulmonologists did not appreciate that blood gas analysis was the only accurate method to measure pleural fluid pH and nearly 40% of pulmonologists incorrectly believed their laboratory was using blood gas analysis.¹⁰⁶ The pleural fluid glucose may be a preferable test when the accuracy of pH measurements cannot be assured.

Pleural Fluid Amylase

The pleural fluid amylase is elevated in patients with pleural effusions secondary to esophageal perforation, pancreatic disease, or malignant disease. However, because such a small percentage of effusions are due to esophageal perforation or pancreatic disease, the routine measurement of pleural fluid amylase is not indicated.¹⁰⁷ In the case of esophageal rupture, the origin of the amylase is the salivary glands.¹⁰⁸ In animal models of esophageal rupture, the pleural fluid amylase concentration is elevated within 2 hours of esophageal rupture.¹⁰⁹ In effusions due to pancreaticopleural fistulas, the amylase concentration is extremely high (>4000 IU/mL), reflective of the concentrations in pancreatic secretions.¹¹⁰ In approximately 10% of malignant effusions, the pleural fluid amylase level is mildly elevated. The site of the primary tumor in such patients is usually not the pancreas.¹¹¹ Malignancy can be differentiated from pancreatic disease with amylase isoenzymes because the amylase with malignant effusions is primarily of the salivary type.¹¹² Because lipase originates only from the pancreas, finding lipase in the pleural effusion should help identify the source as the pancreas.

Tests for Collagen Vascular Diseases

About 5% of patients with rheumatoid arthritis¹¹³ and 50% of patients with SLE¹¹⁴ have a pleural effusion sometime during the course of their disease. At times, the effusions may be the first manifestation of the disease; therefore, these diagnostic possibilities should be considered in patients with undiagnosed exudative pleural effusion.

Measurement of the *antinuclear antibody* (ANA) titer is the best screening test for lupus pleuritis, although it is now evident that a positive pleural fluid ANA is not specific for the diagnosis. Although all patients with lupus pleuritis have a positive pleural liquid ANA (>1:40), the finding of a positive ANA has been found in between 11% and 27% of all other effusions.¹¹⁵ Neither the titer of ANA, ratio of pleural-to-plasma ANA, or the pattern of staining has been found to increase the specificity for SLE.¹¹⁶ In fact, a positive pleural fluid ANA in patients without SLE may be associated with malignancy.¹¹⁶ In patients with SLE, the lack of ANA in pleural liquid may have a high negative predictive value; in patients with SLE and a pleural effusion of uncertain etiology, a lack of ANA (dsDNA, *extractable nuclear antigens* [ENA]) in the pleural fluid argues against the diagnosis of lupus pleuritis.¹¹⁷

When a rheumatoid pleural effusion is suspected, the clinical picture usually establishes the diagnosis. If any

question exists, the level of rheumatoid factor in the pleural fluid should be measured. Only patients with rheumatoid pleuritis have a pleural fluid rheumatoid factor titer equal to or greater than 1 : 320 and equal to or greater than the serum titer.¹¹⁸

Adenosine Deaminase

ADA, a product of activated lymphocytes, catalyzes the conversion of adenosine to inosine and is important for normal immune function. The pleural fluid ADA levels are elevated in almost all patients with tuberculous pleuritis but not with other conditions even when associated with lymphocytic effusions.¹¹⁹ Despite earlier concerns about false-negative values in HIV-positive patients, ADA remains a sensitive marker for tuberculous pleurisy in patients with HIV.¹²⁰ ADA levels can be elevated in other conditions and also in neutrophilic effusions; in one study, ADA above the cutoff (35 U/L) was seen in up to 40% of parapneumonic effusions and in half of effusions due to lymphoma.¹²¹ Because it is a highly sensitive test, the ADA can be a useful test to exclude the diagnosis of tuberculosis when the ADA level is low (<40 U/L).¹²²

Interferon Gamma

Interferon gamma, a T-cell lymphokine, may play a critical role in the effective clinical response to *Mycobacterium tuberculosis*. Pleural liquid interferon gamma is elevated almost exclusively in tuberculous effusions.¹²³ Interferon gamma appears to be as useful as ADA; because ADA is less expensive, ADA is generally preferred. Compared with ADA and interferon gamma, the interferon gamma release assays of pleural fluid, however, have not been shown to be of use in the diagnosis or exclusion of active pleural tuberculosis; these tests are not currently recommended for pleural fluid.¹²⁴⁻¹²⁶

Molecular Techniques for Diagnosis of *Mycobacteria tuberculosis*

Four molecular techniques are now available: PCR to detect specific mycobacterial DNA sequences in clinical specimens (pleural liquid or biopsy), nucleic acid probes to identify the organism in culture, restriction fragment length polymorphism to compare strains in epidemiologic studies, and gene-based susceptibility studies to screen for known genes associated with drug resistance.¹²⁷

In theory, PCR tests have great potential for providing a rapid, highly sensitive and specific diagnosis of mycobacterial infection. In practice, PCR amplification of clinical samples has been limited by a low sensitivity,¹²⁸ which may be due to degradation of the target DNA by sample processing or by inhibitors of amplification in clinical fluids. PCR amplification assays show a high specificity and thus, when positive, can help in making the diagnosis; however, because of their low sensitivity, they are not useful in excluding the disease.¹²⁹ Before wide application of PCR assays, considerations will also include its cost and current inability to identify antibiotic resistance of the organism. In the future, molecular techniques for diagnosis of tuberculosis and for other slow-growing microorganisms will likely prove increasingly important.

USEFUL RADIOGRAPHIC TESTS IN PATIENTS WITH SUSPECTED PLEURAL DISEASE

The possibility of a pleural effusion should be considered whenever a patient with an abnormal chest radiograph is evaluated. Two main factors influence the distribution of free fluid in the pleural space. First, the fluid collects in the most dependent part of the thoracic cavity because the lung is less dense than the pleural fluid. Second, because of their elastic recoil, the lobes of the lung generally maintain their traditional shape at all stages of collapse.

When the patient is upright, the fluid first accumulates between the inferior surface of the lower lobe and the diaphragm. If there is less than 75 mL of fluid, it may occupy only this position without overflowing into the costophrenic sinuses. When more fluid accumulates, it spills over into the posterior costophrenic angle and obliterates the posterior part of the diaphragm on the lateral projection. The possibility of a pleural effusion should be suspected whenever the posterior part of one or both diaphragms is obscured (see Fig. 18-9). The presence of a clinically significant amount of free pleural fluid can be excluded if both posterior costophrenic angles are clear. Pleural effusions on radiography can be missed in the setting of lower lobe consolidation and, in the setting of pneumonia, consideration should be given to seeking the presence of effusions with additional imaging.¹³⁰

When there are larger amounts of pleural fluid, the lateral costophrenic angle on the posteroanterior radiograph becomes blunted. Collins and associates¹³¹ demonstrated that at least 175 mL of pleural fluid had to be injected into the pleural space of cadavers before the lateral costophrenic angle was blunted. In some of their cases, more than 500 mL of pleural fluid could be present without blunting the lateral costophrenic angle. As more fluid accumulates, the entire outline of the diaphragm on the affected side is lost, and the fluid extends upward around the anterior, lateral, and posterior thoracic walls, producing opacification of the lung base and the typical meniscus shape of the fluid.

The changes just discussed are suggestive rather than diagnostic of the presence of pleural fluid. Lateral decubitus radiographs (see Figs. 18-7 and 18-9) or ultrasonic examination should be obtained in most instances when free pleural fluid is suspected. If the entire hemithorax is opacified, decubitus radiographs are of no use, because there is no air-containing lung in the hemithorax. The basis for the use of the lateral decubitus view is that free fluid gravitates to the most dependent part of the pleural space. When a patient is placed in the lateral recumbent position, the free pleural fluid on the dependent side accumulates between the chest wall and the lung (Fig. 79-4). As little as 5 mL of pleural fluid can be demonstrated with properly exposed decubitus radiographs.¹³² The amount of pleural fluid can be semiquantitated by measuring the distance between the inner border of the chest wall and the outer border of the lung (see Fig. 79-4). As already stated, when this distance is less than 10 mm, the amount of pleural fluid is small and a diagnostic thoracentesis is usually not attempted.

Pleural fluid may become encapsulated by adhesions anywhere between the parietal and the visceral pleurae or

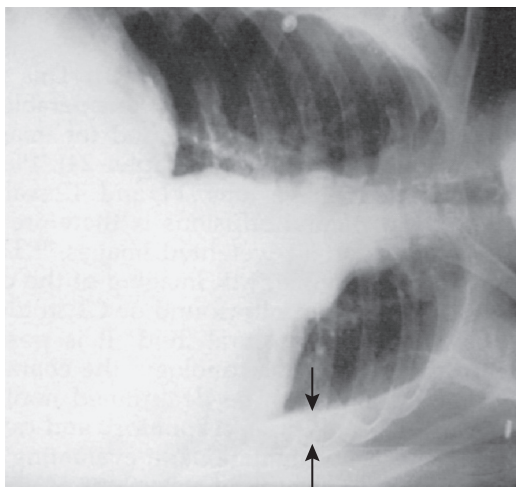


Figure 79-4 Left lateral decubitus chest radiograph demonstrating the presence of free pleural fluid. The amount of pleural fluid can be semiquantified by measuring the distance between the two arrows.

in the interlobar fissures. Pleural fluid loculates most frequently in association with conditions that cause intense pleural inflammation, such as with a complicated parapneumonic effusion or tuberculous pleuritis. When the loculation is situated between the lung and the chest wall, there is a characteristic radiographic picture. The loculation is “D” shaped with the base of the D against the chest wall and the smooth convexity protruding inward toward the lung (see Fig. 18-39). The absence of air bronchograms helps differentiate a loculated pleural effusion from a parenchymal process. A definite diagnosis of loculated pleural effusion is best established by ultrasonography or CT.

Ultrasound

One way to document and locate loculated pleural fluid is with ultrasound. In the presence of pleural fluid, the proximal echoes from the skin, intercostal muscles, and parietal pleura are separated from the distal echoes arising from the visceral pleura and the lung by a central echo-free space. The advantages of ultrasound over CT are the ease and speed with which the examination can be performed, the lack of ionizing radiation, the relatively low cost, and the ability to provide continuous guidance for thoracentesis or pleural biopsy.¹³³

The appropriate site for a thoracentesis can be identified using ultrasound.⁵² If a patient has a moderate or large effusion, the thoracentesis may be performed without ultrasound but large studies have shown a lower incidence of pneumothorax when ultrasound is used.¹³⁴ Ultrasound should definitely be used if no fluid is obtained on an initial attempt or if the effusion is small. When ultrasound is used to identify the site for thoracentesis, it is important to perform the thoracentesis at the time of the ultrasonic examination. If the skin is marked and the patient returned to his or her room, thoracentesis may be unsuccessful because the relationship between the skin and the pleural fluid may have changed. In addition, when the thoracentesis is performed at the time of the ultrasonic examination, there is immediate feedback that is valuable in improving the skill of the ultrasonographer (see Chapter 20).

Computed Tomography

Chest CT is currently the best way to visualize the pleural space.¹³³ Chest CT has its greatest utility in distinguishing parenchymal and pleural abnormalities.¹³⁵ With current protocols involving the rapid injection of intravenous contrast medium, the unaerated perfused lung parenchyma will enhance, whereas the pleural fluid will not.¹³⁶ The use of CT to discriminate transudates from exudates by their attenuation (Hounsfield units) has not been found to be clinically useful due to a great deal of overlap.¹³⁷

Chest CT is quite useful in distinguishing a parenchymal lung abscess located near the chest wall from an empyema with an air-fluid level. The most distinctive features are the margins of the abnormality. With empyema, the cavity walls are of uniform thickness both internally and externally (see eFigs. 80-2, 80-5) and the adjacent lung is usually compressed. The angle of contact with the chest wall may be obtuse (see eFig. 33-7B). In addition, most empyemas have a lenticular shape and demonstrate the “split pleura” sign (Fig. 79-5A see also eFigs. 80-2, 80-5).¹³⁸ With lung abscess, the walls of the cavity are not of uniform thickness and the adjacent lung is not compressed (see eFigs. 33-4, 33-13B and C, 33-21D and E). The angle of contact with the chest wall may be acute (Fig. 79-5B).

In diffuse pleural disease, chest CT is useful in distinguishing malignant from benign causes. Features associated with malignancy include circumferential pleural thickening, pleural nodules (see eFig. 53-5), parietal thickening greater than 1 cm, and mediastinal pleural involvement (see eFig. 53-4 and Video 79-1).¹³⁹ The distinction of metastatic disease from mesothelioma can be difficult, although hilar adenopathy is more common with metastatic disease.¹³³

CT pulmonary angiography (CTPA) has become a first-line imaging test for the evaluation of PE¹⁴⁰ (see Chapters 18 and Chapter 57). The evaluation of a patient with a pleural effusion for PE can begin with a Doppler ultrasound of the lower extremities. If the ultrasound identifies thrombus, the patient can then be treated for thromboembolic disease. If it is negative, the patient may still have a PE. In the past the standard approach was to proceed to lung ventilation-perfusion scanning. However, this has largely been replaced by CTPA. CTPA is highly sensitive and specific for pulmonary emboli in the proximal, segmental pulmonary arteries.¹⁴⁰ In contrast to ventilation-perfusion lung scanning, CTPA can establish alternate diagnoses as well. Where CTPA is not available, lung scanning can be used, perhaps after efforts to improve accuracy by withdrawing as much pleural liquid as possible. A diagnostic scan (normal or high probability) can then be used either to exclude the diagnosis or initiate anticoagulation. If nondiagnostic (e.g., of low or intermediate probability), the scan should be followed by pulmonary angiography.

Magnetic Resonance Imaging

At present, *magnetic resonance imaging* (MRI) of the chest is less satisfactory than ultrasound or CT in identifying the presence of pleural fluid.¹³³ It is possible that with improved MR technology, the characteristics of pleural fluid can be determined noninvasively. Respiratory and cardiac motion

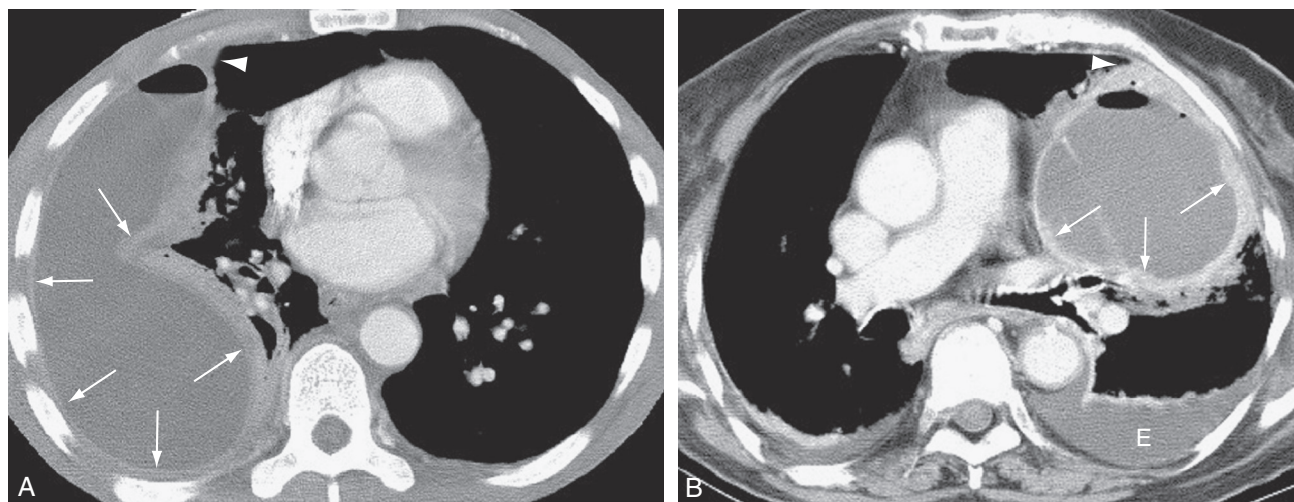


Figure 79-5 Typical CT features of a pleural empyema versus a lung abscess. **A**, Axial CT through the lower thorax in a patient with fever and pleuritic chest pain shows features typical of empyema, including the formation of obtuse angles between the lesion and chest wall (arrowhead), a lenticular shape, a smooth internal surface (arrows), and mass effect on surrounding structures (note leftward shift of the heart and great vessels). Note enhancement of the parietal and visceral pleura, representing the “split-pleura” sign (arrows) and the presence of an air-fluid level, indicating the presence of a broncho-pleural fistula. **B**, Axial CT through the mid thorax in a patient with fever and cough productive of foul-smelling sputum shows features typical of a pulmonary abscess, including the formation of acute angles between the lesion and chest wall (arrowhead); a round shape; a thick, irregular internal surface (arrows); and relatively little mass effect on surrounding structures, despite the large size of the lesion. The lack of mass effect results because pulmonary abscesses tend to destroy adjacent lung more than they displace it. An effusion, found to be an empyema (E), is also present.

is the major limitation in evaluating specific intensity patterns of fluid collections of various compositions. MRI may have current value in delineating malignancy in the pleural space and may be better than chest CT for determining chest wall or diaphragmatic invasion.

Positron Emission Tomography and PET/CT

Positron emission tomography (PET) visualizes tissues that are metabolically active by their concentration of the radioisotope ^{18}F -fluorodeoxyglucose. Because most malignant cells have a higher metabolic rate than nonmalignant cells, PET can help differentiate malignant from benign lesions, stage patients with malignancy, and identify recurrence.¹³³ Introduced in 1998, PET/CT integrates the metabolic information of PET with the detailed anatomic information of CT. Compared with CT or PET alone, PET/CT can allow detection of additional lesions, localize them more accurately, characterize them as highly likely to be malignant, and discriminate malignant from surrounding normal tissue¹⁴¹ (see Chapter 82).

INVASIVE TESTS IN PATIENTS WITH UNDIAGNOSED EXUDATIVE PLEURAL EFFUSIONS

In the patient with an undiagnosed exudative pleural effusion, several invasive tests might be considered, including blind or image-guided needle biopsy of the pleura, bronchoscopy, thoracoscopy or video-assisted thoracic surgery, and open biopsy of the pleura. It is important to remember that no diagnosis is ever established for approximately 20% of all exudative pleural effusions and that many resolve spontaneously, leaving no residua.^{122,142} In patients with undiagnosed exudative pleural effusions, three factors should influence the vigor with which one pursues the diagnosis with invasive tests. First, the symptoms and clinical

course of the patient. If symptoms are minimal or improving with time, a less aggressive approach is indicated. Second, the trend of the pleural fluid LDH level with time. If the pleural fluid LDH increases with serial thoracenteses, a more aggressive approach is indicated. Third, the attitude of the patient. If the patient is anxious about the cause of the pleural effusion, an aggressive approach should be taken. Furthermore, when an undiagnosed exudate resolves without treatment, two diagnoses should still be considered and excluded: PE and tuberculosis.

Needle Biopsy of the Pleura

Small specimens of the parietal pleura can be obtained with needle biopsy, often called *blind* or *closed needle biopsy*. The needles most commonly used for this procedure are the Cope needle and the Abrams needle.⁶² Because needle biopsy of the pleura is useful mainly to establish the diagnosis of malignant or tuberculous pleural effusions, this procedure should be considered when one of these diagnoses is suspected.

In malignant pleural disease, the needle biopsy of the pleura will be positive in 40% to 60% of patients.¹⁴²⁻¹⁴⁴ Overall, the yield from pleural fluid cytology tends to be higher, probably because it samples cells dislodged from the entire pleura, while the needle biopsy can only sample from a localized area. In one series of 281 patients with malignant pleural effusions, the pleural biopsy was positive in 43%, whereas the pleural fluid cytology was positive in 58%.¹⁴² In 7% the pleural biopsy was positive and the pleural fluid cytology negative.¹⁴² In a more recent study of 66 patients, although cytology was more likely to be positive than biopsy (69% vs. 48%), closed pleural biopsy added diagnoses in some cytology-negative patients.¹⁴⁴ A prudent approach to the patient with a suspected malignant pleural effusion is to obtain a pleural biopsy only if the cytology obtained at the time of the initial diagnostic thoracentesis

is nondiagnostic. If the CT shows pleural thickening or nodularity, an image-guided pleural biopsy is an excellent option.¹⁴⁵

Needle biopsy of the pleura has greater utility for the diagnosis of tuberculous pleuritis than of malignancy. The initial biopsy is positive for granulomas in 50% to 80% of patients.¹⁴⁶ The demonstration of granulomas on the pleural biopsy is virtually diagnostic of tuberculous pleuritis; caseous necrosis or acid-fast bacilli need not be demonstrated, although on rare occasions, fungal diseases, sarcoidosis, or rheumatoid pleuritis can produce granulomatous pleuritis. When tuberculous pleuritis is suspected, a portion of the pleural biopsy specimen should be cultured for mycobacteria. In one series of 21 patients with tuberculous pleuritis, either the microscopic examination or the biopsy culture was positive in 20 of the 21 patients (95%)¹⁴⁷; in a more recent series of 113 patients with tuberculous pleural effusion, the sensitivity of closed pleural biopsy (by showing granulomas on pathology or culture) was 92%.¹⁴⁸ If the initial biopsy is nondiagnostic and the patient has tuberculous pleuritis, a second biopsy will be diagnostic 10% to 40% of the time.^{146,149}

The greatest value of needle biopsy for a patient with tuberculosis is in obtaining material for culture of *M. tuberculosis* for the determination of drug susceptibility. Often, the presentation of a patient with a recent purified protein derivative conversion and an exudative pleural effusion with lymphocytosis is classic and unlikely to be due to any diagnosis other than tuberculous pleurisy. The diagnosis can be further supported by measurements, where available, of pleural fluid ADA or interferon gamma. In those cases, treatment for tuberculosis can be offered with confidence without needle biopsy confirmation. However, when the patient may have been exposed to drug-resistant organisms, needle biopsy will increase the likelihood of obtaining organisms for culture and is recommended. Sputum induction can also be useful for culturing the organism, even when only pleural involvement is suspected and the chest radiograph shows no pulmonary involvement; in this setting, sputum induction has been shown to have a yield similar to culture of the pleural biopsy (52% vs. 62%).¹⁵⁰ Medical thoracoscopy has a higher yield than blind needle biopsy for obtaining pleural material for culture. When different approaches were compared in the same 51 patients, thoracoscopy obtained a positive culture of *M. tuberculosis* in 76%, whereas the Abrams needle obtained a culture in 48%.¹⁵¹ If the need for obtaining positive cultures is high, the more invasive diagnostic tests including medical thoracoscopy may be preferred.

The two major complications of needle biopsy of the pleura are pneumothorax and bleeding. Pneumothoraces require a chest tube in only about 1% of pleural biopsies.^{142,152} It is likely that many pneumothoraces develop because of leakage of air through the biopsy needle and do not necessarily indicate puncture of the lung. A hemothorax can result from inadvertent biopsy of an intercostal artery or vein. In one older series, a fatal hemothorax was a complication in 2 of 227 biopsy procedures.¹⁵² The pleural biopsy needle can also be mistakenly inserted into the liver, spleen, or kidney, which can lead to hemorrhage in these organs. However, in general, bleeding complications are rare.

If no diagnosis is obtained after routine laboratory tests including cytology and one needle biopsy of the pleura, what can be said concerning the patient? Poe and coworkers¹⁵² followed 143 such patients for 12 to 72 months, during which time 29 patients were diagnosed with malignant pleural disease and one patient with tuberculous pleuritis. In all 29 cases in which malignancy was eventually diagnosed, the diagnosis of malignant neoplasm was suggested by clinical criteria such as weight loss, constitutional symptoms, or a history of previous cancer. These authors concluded that most patients with undiagnosed exudative pleural effusions in whom the clinical picture does not suggest malignancy are best managed by observation. In those with symptoms suggestive of malignancy, image-guided pleural biopsy or thoracoscopy are probably the procedures of choice.

Image-Guided Pleural Biopsy

In patients with pleural abnormalities consistent with malignancy, CT-guided cutting-needle biopsies may supplant closed pleural biopsy for diagnosis, where image-guided technology is available.¹⁵³ In a randomized study of 50 patients with suspected malignant pleural effusions with negative cytology, those randomized to image-guided biopsy were more likely to be diagnosed (87% sensitivity) than those randomized to blind pleural biopsy (47%).¹⁴⁵ In situations where the effusion is small and there is loculation or pleural thickening without an effusion, CT image-guided pleural biopsy is an excellent choice. PET/CT may increase the yield further by improving interpretation and selection of biopsy targets (see earlier).

Bronchoscopy

Another procedure that should be considered in the patient with an undiagnosed pleural effusion is bronchoscopy (see Chapter 22). If the patient has an associated parenchymal lesion or hemoptysis, fiberoptic bronchoscopy will provide a diagnosis in nearly 75%.¹⁵⁴ On the other hand, if the patient has neither a parenchymal abnormality nor hemoptysis, a diagnosis for the pleural effusion is established less than 10% of the time.¹⁵⁵ At present, chest CT should be performed in all patients with undiagnosed exudative pleural effusions. Bronchoscopy should then be performed only if the CT scan demonstrates parenchymal or obstructing airway abnormalities or if the patient has hemoptysis. At the time of bronchoscopy, special attention is paid to those portions of the lung in which the parenchymal abnormalities were demonstrated.

Thoracoscopy or Video-Assisted Thoracic Surgery

Thoracoscopy is discussed fully in Chapter 24. Thoracoscopy may be useful diagnostically in patients in whom the origin of a pleural effusion remains unclear after routine fluid analysis and needle biopsy of the pleura. In many cases, especially for the evaluation of malignancy, thoracoscopy may supplant needle biopsy because of a greater diagnostic yield and the added ability to provide a pleurodesis. Thoracoscopy can be performed by pulmonologists using local anesthesia and conscious sedation for direct visualization of the pleural surfaces, tissue sampling, and pleurodesis; thoracoscopy performed by thoracic surgeons, generally referred to as *video-assisted thoracic surgery* (VATS),

utilizes general anesthesia and single-lung ventilation by double-lumen intubation and allows greater access to the pleura and lung for surgical procedures.

Which patients with undiagnosed pleural effusions should undergo thoracoscopy? A diagnosis can be established in more than 90% of patients with malignancy including those with mesothelioma.¹⁵⁶ Moreover, talc can be insufflated at the time of the procedure and this will control the effusion in the majority of patients. Nonetheless, there are minor risks of the procedure, a need for post-procedure chest tube(s), and a procedure cost that should be considered. Thoracoscopy is therefore recommended for the patient with an undiagnosed pleural effusion after diagnostic thoracentesis and needle biopsy of the pleura in whom the diagnosis of malignancy is strongly suspected and in whom one wishes to establish this diagnosis.

Open Biopsy of the Pleura

Thoracotomy with direct biopsy of the pleura provides the best visualization of the pleura and the best biopsy specimens. Nowadays, the less invasive thoracoscopy can replace thoracotomy in most instances. The main indication for open pleural biopsy is progressive undiagnosed pleural disease that cannot be approached by or has failed to be diagnosed by thoracoscopy. In the past, for example, the diagnosis of malignant mesothelioma was usually made with open biopsy of the pleura, but now the diagnosis can be established in the majority of the cases with thoracoscopy.

It should be emphasized that open pleural biopsy does not always provide a diagnosis in patients with pleural effusions. Over the 11-year period from 1962 to 1972, 51 patients with pleural effusion at the Mayo Clinic had no diagnosis after an open pleural biopsy.¹⁵⁷ In 31 of these patients (61%), there was no recurrence of the pleural effusion, and no cause ever became apparent. However, 13 of the patients were eventually proved to have malignancy; 6 had lymphoma and 4 had malignant mesothelioma. Thus, observation of patients with undiagnosed pleural effusions is often warranted unless there is compelling reason to pursue the diagnosis of malignancy. Since the time of this study, there have been many improvements in diagnostic tests that may increase the diagnostic yield of invasive procedures and the treatment options available.

TRANSUDATIVE PLEURAL EFFUSIONS

Transudative pleural effusions frequently accompany many common clinical disorders. It is noteworthy that the primary abnormality in most cases of transudative pleural effusions originates in organs other than the pleura or lungs, especially the heart, liver, and kidneys. This association emphasizes the fact that although patients may visit their physicians for respiratory complaints, these symptoms may be caused by extrapulmonary disorders.

CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is probably the most common cause of pleural effusion.⁶² The incidence of pleural effusion

in patients with CHF is high. In one series of 60 patients with an exacerbation of stable CHF, chest CT scans demonstrated that 50 patients (83%) had a right-sided pleural effusion and 46 patients (77%) had a left-sided effusion. Approximately one third of the effusions had a volume that exceeded 700 mL.¹⁵⁸

Pathophysiology

The pleural fluid that accumulates with CHF is related to the clearance of pulmonary interstitial fluid across a leaky mesothelium into the pleural space.⁵ In studies in which sheep lungs were isolated in situ, volume loading led to an increased transudation across the lung into the pleural space.⁶ The pleural fluid had the same protein concentration as that of the lung lymph and the interstitial edema liquid in the lung. The volume of pleural fluid constituted about 25% of all edema formed in the lung.⁶ In the clinical situation, patients with CHF are much more likely to have a pleural effusion if there is radiologically apparent pulmonary edema.¹⁵⁹

Clinical Manifestations

Patients with pleural effusion resulting from CHF usually have symptoms and signs of heart failure, such as dyspnea on exertion, orthopnea, nocturia, peripheral edema, distended neck veins, crackles, and a cardiac gallop. The chest radiograph almost always reveals cardiomegaly in addition to the pleural effusion.

The pleural effusions seen with CHF tend to be bilateral, with larger effusions on the right (Fig. 79-6A). On CT imaging, interstitial and alveolar edema can often be detected by the presence of thickened septae and patchy opacities (Fig. 79-6B and Video 79-2). Thickened septa represent interstitial edema, as seen in edematous lungs frozen to demonstrate the location of edema; the interstitial edema is continuous with the interlobular septa and the subpleural space, from which the edema has been shown to move across the visceral pleura to the pleural space (Fig. 79-6C).⁶

In an autopsy study of 250 patients with CHF and pleural effusion, 88% of the patients had bilateral pleural effusions, with the mean volume of pleural fluid in the right pleural space (1084 mL) slightly greater than the mean volume of fluid in the left pleural space (913 mL).¹⁶⁰ Moreover, of the 35 patients who did have unilateral pleural effusions, 46% had either PE or pneumonia.¹⁶⁰ Weiss and Spodick¹⁶¹ reported that 73% of 51 patients with CHF had bilateral effusions, 19% had unilateral right-sided effusions, and 9% had unilateral left-sided effusions. In a study of 100 patients with bilateral pleural effusions, CHF was the most common contributor to effusions, but often the causes were multiple; in fact, most of the effusions were exudative and, of these, CHF was the second most common cause.¹⁶²

The reason that effusions are generally larger on the right side may lie in the fact that they originate from the larger lung on the right side.³⁹ In volume-overloaded sheep, the rate of liquid leakage from the right lung was higher than from the left, likely due to the larger volume and surface area of the right lung.⁶ In another study in awake sheep, there was no difference in the rate of absorption of effusions from the right and left pleural spaces,¹⁹ suggesting that differences in formation are the cause of the difference in size.^{19,39}

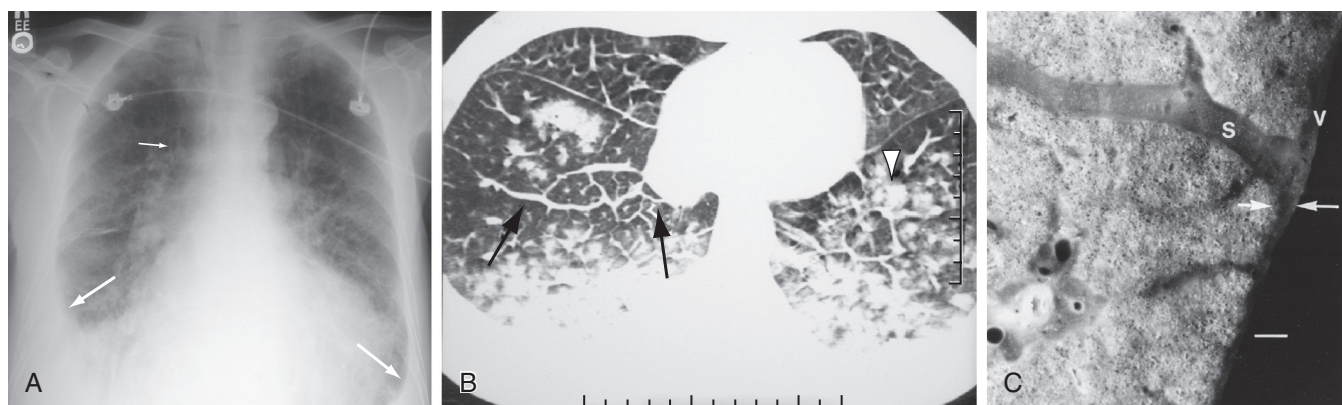


Figure 79-6 Effusion from congestive heart failure. **A**, Frontal chest radiograph in a patient with pulmonary edema shows cardiomegaly, bilateral pleural effusions (*larger arrows*), and central interstitial thickening, including Kerley A lines (*small arrow*). Note that the right effusion is slightly larger than the left effusion. **B**, Chest CT scan in a patient with pulmonary edema shows interstitial edema with bilateral, basilar centrilobular ground-glass opacity nodules (*arrowhead*) and smooth interlobular septal thickening (*arrows*). Bilateral pleural effusions are also present. **C**, Frozen sheep lung after volume loading showing edema as a continuous band (between *arrows*) from the interlobular septa (S) to beneath the visceral pleura (V), which it can cross to enter the pleural space. Horizontal bar = 1 mm. (**C**, Reproduced with permission from Broadus VC, Wiener-Kronish JP, Staub NC: Clearance of lung edema into the pleural space of volume-loaded anesthetized sheep. *J Appl Physiol* 68(6):2627, 1990.)

Although CHF is by far the most common cause of bilateral pleural effusions, an alternate explanation should be sought if there is no cardiomegaly. In one series of 78 patients with bilateral effusions but a normal-sized heart, only 4% of the effusions were caused by CHF.¹⁶³

Diagnosis and Management

The diagnosis is usually suggested by the clinical picture of CHF. A diagnostic thoracentesis should be performed if the pleural effusion is unilateral, if bilateral effusions are not comparable in size, if the patient is febrile, if the patient has pleuritic chest pain, or if the patient does not have cardiomegaly.⁶² If none of these conditions is met, one can treat the CHF and observe; if the effusions do not resolve in a few days, a diagnostic thoracentesis should be performed.

The pleural fluid from a patient with CHF is usually a transudate.³⁷ However, if the patient has been on diuretics, the pleural fluid protein and LDH ratios may be increased sufficiently that the pleural fluid meets Light's exudative criteria. A similar phenomenon has been described in the ascites literature.¹⁶⁴ The LDH ratio can also increase if intrapleural LDH increases due to injury from repeated taps and if serum LDH falls when diuresis reduces liver congestion.¹⁶⁴ Generally, if the effusion protein and LDH values meet Light's criteria for an exudate, it is only by a small amount.⁵⁸ The transudative nature of the pleural fluids can be established in such patients if the serum minus the pleural fluid protein level is greater than 3.1 g/dL or the serum minus the pleural fluid albumin level is greater than 1.2 g/dL.⁵⁶

Measurement of pleural fluid *N-terminal pro-brain natriuretic hormone* (NT-proBNP) is useful in this setting and may be more accurate, although more expensive, than the serum-to-pleural protein gradients for correctly classifying effusions from CHF.⁵⁷ Pleural fluid NT-proBNP is superior to BNP.⁵⁷ In a systematic review and meta-analysis of 10 studies, pleural fluid NT-pro-BNP was shown to be useful for the diagnosis of pleural effusions due to CHF; the studies used different threshold values, but, in this review, the authors proposed a threshold for diagnosis of 1500 ng/mL (the average level was > 6000 pg/mL).¹⁶⁵

Patients with CHF and pleural effusion should be treated with afterload reduction, diuretics, and inotropes as needed. When heart failure is successfully managed, pleural effusion usually resolves. If the patient is markedly dyspneic when first evaluated, a therapeutic thoracentesis to relieve the dyspnea should be considered. Rarely, despite intensive therapy of the CHF, a patient has persistent large effusions; if such patients are dyspneic and if their dyspnea is relieved by a therapeutic thoracentesis, consideration can be given to controlling the effusions with a pleurodesis using a sclerosing agent, such as doxycycline or talc slurry, or the insertion of an indwelling catheter.

HEPATIC HYDROTHORAX

The incidence of pleural effusions with cirrhosis is approximately 6%.^{166,167} The incidence appears to be much higher if ascites is present; however, in some patients with hepatic hydrothorax, no ascites can be detected, presumably because all ascitic fluid moves to the pleural space due to the prevailing pressure gradients and the low-resistance diaphragmatic defects.^{39,168}

Pathophysiology

The predominant mechanism leading to a pleural effusion in a patient with cirrhosis and ascites appears to be the movement of the ascitic fluid from the peritoneal cavity through defects in the diaphragm into the pleural space.¹⁶⁹ The decreased plasma osmotic pressure is only a secondary factor.

The diaphragmatic defects have been demonstrated in many ways. Lieberman and coworkers¹⁶⁶ introduced 500 to 1000 mL of air into the peritoneal cavity of five patients with cirrhosis, ascites, and pleural effusions and found that a pneumothorax developed in all patients within 48 hours. In addition, they were able to demonstrate air bubbles coming through an otherwise undetectable diaphragmatic defect at thoracoscopy in one of their patients. In two of their patients, diaphragmatic defects were demonstrated at postmortem examination.¹⁶⁶ By thoracoscopy, different types of defects have been documented such as blebs or

fenestrations¹⁷⁰ (eFig. 79-3). There are no normal direct lymphatic connections between the peritoneal and the pleural spaces. Thus, the connections between the spaces are either preexisting developmental defects or are defects caused by trauma or stretching.

Clinical Manifestations

The clinical situation in patients with pleural effusions from cirrhosis and ascites is usually dominated by the cirrhosis and ascites. At times, however, the presence of a large pleural effusion may produce severe dyspnea. The pleural effusion associated with cirrhosis and ascites is frequently large and can occupy the entire hemithorax. The large effusions form because the diaphragmatic defect permits fluid to flow from the peritoneal cavity into the pleural cavity until the pleural pressure approaches the peritoneal pressure. The pleural effusions are usually right sided (80%) but occasionally are left sided (17%) or bilateral (3%).¹⁶⁹

Diagnosis and Treatment

The diagnosis of hepatic hydrothorax is usually easily established from the clinical picture. If doubt exists, the diagnosis can be confirmed by scanning the chest after ^{99m}Tc sulfur colloid is injected into the peritoneal cavity.¹⁷¹ Both a paracentesis and a thoracentesis should be performed to confirm that the ascites and pleural fluid are both transudates. Xiol and associates¹⁷² performed thoracentesis on 60 patients with cirrhosis and ascites. The pleural fluid analysis yielded a diagnosis other than hepatic hydrothorax in 18 (30%) including 9 spontaneous bacterial pleuritis, 2 tuberculosis, 2 adenocarcinomas, 2 parapneumonic effusions, and 3 undiagnosed exudates.¹⁷² The protein level with hepatic hydrothorax in the pleural fluid is usually higher than that in the ascitic fluid but is still below 3.0 g/dL and the LDH is low.¹⁶⁶ If the polymorphonuclear cell count is greater than 500 cells/μL, the diagnosis of spontaneous bacterial pleuritis in conjunction with spontaneous bacterial peritonitis should be considered.¹⁷³

The initial management of the pleural effusion associated with cirrhosis and ascites should be directed toward treatment of the ascites. Chest tube insertion should be avoided because the ascitic fluid will also drain through the chest tube, which can lead to significant fluid and protein losses and even fatal cardiovascular collapse.¹⁶⁸ Instead, the patient should be given a low-salt diet and treated with diuretics, usually furosemide and spironolactone.

If diet and diuretics cannot control the effusion, the treatment of choice is liver transplantation.^{168,174} Patients with hepatic hydrothorax have been found to do well after transplant, at least as well as matched cirrhotic patients without hepatic hydrothorax; however, this condition does not yet merit higher priority for transplant.¹⁷⁵ The next best approach is probably implantation of a *transjugular intrahepatic portal systemic shunt* (TIPS). TIPS is usually effective in the management of hepatic hydrothorax. Kinasevitz and Keddis¹⁶⁸ summarized the literature on 115 patients who received TIPS for refractory hepatic hydrothorax and reported that the procedure controlled the hydrothorax in 80%, but 12% of the patients developed encephalopathy. In a study of TIPS with a long follow-up, 73 patients underwent TIPS with 59% complete response at 1 month and a

21% partial response; however, hepatic encephalopathy developed in 15% and 30-day mortality was 19%. Survival was associated with the pre-TIPS *Model for End-stage Liver Disease* (MELD) score: with a MELD less than 15, median survival was 875 days, and with a MELD greater than 15, it was 180 days.¹⁷⁶ If neither TIPS nor liver transplantation is feasible, the best alternative treatment is probably VATS with closure of the diaphragmatic defects and pleurodesis. Cerfolio and Bryant¹⁷⁷ performed this procedure on 41 patients and reported a success rate of 80%. Huang and colleagues¹⁷⁸ reported success in 10 patients using a pleural or mesh onlay to repair the diaphragmatic defects. Nonetheless, as pointed out in a recent review of 77 patients, the outcome for those who cannot undergo liver transplantation or TIPS is extremely poor.^{178a}

Spontaneous Bacterial Pleuritis

Spontaneous bacterial pleuritis is, by definition, infection of a preexisting hepatic hydrothorax in which a parapneumonic infection has been excluded. Originally termed spontaneous bacterial *empyema*, we prefer the term *pleuritis* to emphasize its similarity to spontaneous bacterial peritonitis and to indicate that its treatment does not require tube thoracostomy. The diagnosis of spontaneous bacterial pleuritis is made if the pleural fluid culture is positive, the pleural fluid neutrophil count is greater than 250 cells/μL, and a pneumonic process has been excluded; the diagnosis of *culture-negative* spontaneous bacterial pleuritis is made if the pleural fluid cultures are negative and the pleural fluid neutrophil count is greater than 500 cells/μL.¹⁷³ In one series in Spain, 16 of 120 patients (13%) admitted with a diagnosis of hepatic hydrothorax had a spontaneous bacterial pleuritis; 10 of 24 episodes (43%) of spontaneous bacterial pleuritis were not associated with bacterial peritonitis.¹⁷³ Appropriate treatment of spontaneous bacterial pleuritis requires systemic antibiotics, but tube thoracostomy does not appear to be necessary. It remains to be seen whether spontaneous bacterial pleuritis is common in the United States.

NEPHROTIC SYNDROME

There is a high incidence of pleural effusion in patients with the nephrotic syndrome. In one study of 52 patients, 21% had pleural effusions.¹⁷⁹ The mechanism responsible for the transudative pleural effusion associated with the nephrotic syndrome is probably the combination of decreased plasma osmotic pressure and increased hydrostatic pressure. The increased hydrostatic pressure is due to salt retention, which produces hypervolemia. The pleural effusions in patients with a nephrotic syndrome are usually bilateral and are frequently infrapulmonary in location.¹⁷⁹

A diagnostic thoracentesis should be performed in all patients with the nephrotic syndrome and a pleural effusion to prove that the pleural fluid is a transudate. Nonetheless, the possibility of PE should always be considered in patients with the nephrotic syndrome and a pleural effusion. In one series of 36 patients with the nephrotic syndrome, 22% had pulmonary emboli.¹⁸⁰ If the pleural fluid is an exudate, a CT pulmonary angiogram should be obtained.

The treatment of the pleural effusion associated with the nephrotic syndrome should be aimed at increasing the level

of protein in the serum by decreasing the protein loss in urine. If this is unsuccessful, pleurodesis with a sclerosing agent should be considered in selected patients who are symptomatic from the pleural effusion.

PERITONEAL DIALYSIS

Peritoneal dialysis is occasionally complicated by the development of an acute hydrothorax. In a review of 3195 patients receiving continuous ambulatory peritoneal dialysis in Japan, 1.6% developed a pleural effusion as a result of the movement of the dialysate from the peritoneal cavity into the pleural cavity.¹⁸¹ The effusion developed within 30 days of initiation of the dialysis in 50% of the patients, but 18% had been receiving dialysis for more than a year before the effusion developed.¹⁸¹ The effusions are right sided in about 90%.^{181,182}

The pleural fluid in these patients is characterized by a glucose level intermediate between that of the dialysate and the serum, a protein level below 10 g/L (1.0 g/dL), and a low LDH level. The LDH level is higher and the glucose level is lower in the pleural fluid than in the ascitic fluid.¹⁸² Although the communication closes spontaneously in some patients, a surgical approach is usually required if continuous ambulatory peritoneal dialysis is to be continued. The treatment of choice is probably thoracoscopy with closure of the diaphragmatic defects, followed by pleurodesis. Alternative treatments are pleurodesis alone or thoracotomy with repair of the diaphragmatic defects.

URINOTHORAX

Obstruction of the urinary tract resulting in a retroperitoneal urine collection (urinoma) can lead to a pleural effusion.¹⁸³ The mechanism by which the pleural fluid accumulates is unknown, but it is thought that this retroperitoneal urine collection drains along pressure gradients into the pleural space. The collection of fluid actually represents urine, and the pleural fluid smells like urine. Patients with urinothoraces have pleural fluid creatinine levels higher than those in serum, but about 10% of other effusions also meet this criterion.¹⁸³ When the urinary tract obstruction is relieved, the pleural effusion rapidly disappears.^{183a}

MYXEDEMA

A pleural effusion sometimes arises as a complication of myxedema. Most patients with myxedema and pleural effusion have a concomitant pericardial effusion. In one series of 25 patients with pericardial effusions secondary to myxedema, 13 of the patients (52%) had concomitant pleural effusion.¹⁸⁴ When the pleural effusion presents at the same time as a pericardial effusion, the pleural fluid is usually a transudate.¹⁸⁴ The isolated pleural effusion seen in conjunction with myxedema is generally borderline between a transudate and an exudate. Although the mechanism of formation of the effusion is unknown, a decrease in lymphatic function due to low thyroid levels may contribute.²³ Thyroid replacement is the obvious treatment for pleural effusions associated with myxedema.

PERICARDIAL DISEASE

Pleural effusion is commonly seen in patients with pericardial disease (Video 79-3). Few of these effusions have been characterized, but they can be transudative or exudative. In one series of 35 patients with constrictive pericarditis, 60% of the patients had radiologically demonstrable pleural effusions.¹⁸⁵ Weiss and Spodick¹⁸⁶ reviewed 124 patients with pericardial disease and found that 35 (28%) had a pleural effusion. Of the 35 patients, 21 had only a left-sided pleural effusion (eFig. 79-4), 2 had only a right-sided pleural effusion, and the remaining 12 were bilateral. However, in another series of 21 patients with constrictive pericarditis and pleural effusion, the pleural effusion was right sided only in 9 (43%) and bilateral in the remaining 12 (57%).¹⁸⁵

The mechanism responsible for the pleural effusion associated with pericardial disease is not clear. In constrictive pericarditis, one explanation for the effusions is that the pulmonary and systemic capillary pressures are elevated secondary to the pericardial disease, resulting in a transudative pleural effusion. However, one would expect these effusions to be bilateral. In inflammatory pericardial disease, however, the pleural effusion tends to be left sided (see eFig. 79-4) and, although the characteristics of the fluid have not been well described, it is probable that the effusion forms from extension of the pericardial inflammation to the adjacent pleura¹⁸⁶ or possibly from direct movement of the fluid across the pericardium into the pleural space.

OTHER CAUSES OF TRANSUDATIVE PLEURAL EFFUSIONS

A subarachnoid pleural fistula can develop, resulting in the accumulation of *cerebrospinal fluid* (CSF) in the pleural space. The pleural fluid looks like CSF with low protein and LDH levels. Subarachnoid pleural fistula can follow ventriculo-pleural shunting and with penetrating injuries, fractures, or surgery of the thoracic spine.⁶² If there is doubt about the diagnosis, measurement of the pleural fluid β_2 -transferrin is useful because only CSF contains this molecule.¹⁸⁷ The fistula rarely closes without surgical intervention.

Central venous obstruction can cause large, persistent transudative effusions, perhaps due to increases in venous pressure leading to increased formation of liquid and to decreases in lymphatic clearance. Venous obstruction as a cause of persistent transudative effusions should be considered in situations with prior instrumentation and has been reported from occlusions of the hemiazygos vein, brachiocephalic vein, and superior vena cava (eFig. 79-5). Relief of the obstruction can lead to resolution of the effusion.¹⁸⁸

Pulmonary veno-occlusive disease frequently has small pleural effusions.¹⁸⁹ The characteristics of the pleural fluid have not been described, but it is probably a transudate because the effusions are likely related to the increased pulmonary interstitial fluid. Patients with right failure secondary to pulmonary hypertension frequently have small bilateral pleural effusions.¹⁹⁰

PE has been reported to be associated with a transudative pleural effusion. However, in a study of the pleural fluid findings in patients with PE, all 60 pleural fluids were exudates.⁷⁴ Pleural amyloidosis is associated with transudative

effusions, probably due to a combination of heart failure and pleural infiltration with amyloid.¹⁹¹ Cytokines such as *vascular endothelial growth factor* (VEGF) may play a role because, in one series, three out of four patients with persistent pleural effusions due to primary systemic amyloid improved with treatment with an antibody against VEGF, bevacizumab.¹⁹²

EXUDATIVE PLEURAL EFFUSIONS

Exudative pleural effusions are common clinical problems. These effusions may develop as a result of inflammation, injury, or malignancy, which can involve the pleural surfaces, the adjacent lung, or more distant tissues, such as mediastinal or abdominal organs. Further discussion of effusions due to infections is presented in Chapter 80; special types of effusions (chylothorax and hemothorax) are discussed in Chapter 81; and effusions secondary to pleural tumors are presented in Chapter 82.

PULMONARY EMBOLISM

The diagnosis most commonly overlooked in the differential diagnosis of a patient with an undiagnosed pleural effusion

is PE. It has been estimated that at least 500,000 persons develop venous thromboembolism annually in the United States. Because at least 30% of patients with PE have an associated pleural effusion,¹⁹³ more than 150,000 pleural effusions secondary to PE should be diagnosed annually. Therefore, one should expect to see more cases of pleural effusion secondary to PE than to bronchogenic carcinoma. Nevertheless, in most large series, PE accounts for less than 5% of pleural effusions. The diagnosis and treatment of PE are discussed in Chapter 57.

Clinical Manifestations

Patients with PE can be divided into three categories, depending on their presenting symptoms: (1) pleuritic pain or hemoptysis, (2) isolated dyspnea, and (3) circulatory collapse. In the *Prospective Investigation of Pulmonary Embolism Diagnosis* (PIOPED) study, 56% of the patients with pleuritic pain or hemoptysis had pleural effusion and 26% of those with isolated dyspnea had pleural effusion, but none of the patients with circulatory collapse had pleural effusion.¹⁹³

Approximately 50% of patients with paraembolic effusions have parenchymal opacities seen on chest radiographs.¹⁹⁴ The opacities are usually in the lower lobes, are pleural based, and are convex toward the hilum. Paraembolic effusions are usually small (Fig. 79-7); in one series,

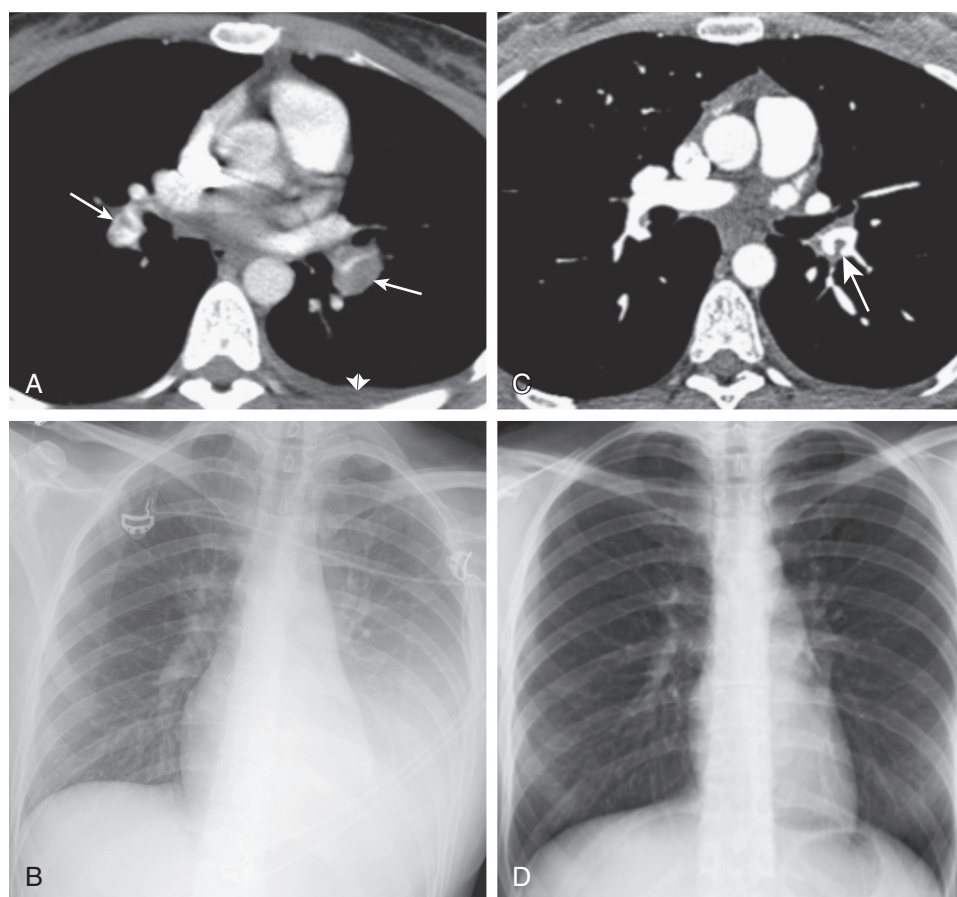


Figure 79-7 Pleural effusion related to acute pulmonary embolism. **A**, Axial CT pulmonary angiography shows bilateral acute pulmonary emboli (arrows); a trace left pleural effusion (double arrowheads) is present. **B**, Frontal chest radiograph obtained 5 days following the CT pulmonary angiogram (**A**) shows left basal consolidation with a large left pleural effusion. **C**, Axial CT pulmonary angiography performed more than 1 month after presentation, during treatment, shows near-complete resolution of the bilateral pulmonary emboli (arrow). **D**, Frontal chest radiograph obtained more than 1 month after presentation shows complete resolution of the left basal consolidation and pleural effusion. (See also [Video 79-4A](#) and [B](#).) (Courtesy Michael Gotway, MD.)

48 of 56 patients (86%) had only blunting of the costophrenic angle, and no patient had an effusion that occupied more than one third of a hemithorax.¹⁹³ The pleural effusions may be unilateral or bilateral. In one study of 63 patients with PE and pleural effusion, the effusions were bilateral in 16 (25%).¹⁹⁵ Interestingly, in studies using *CT pulmonary angiography* (CTPA) in patients suspected of having PE, those patients found to have PE were no more likely to have pleural effusions than those without embolism (50% vs. 58%¹⁹⁶; 57% vs. 56%¹⁹⁷). In another study using CTPA, those found to have PE were more likely to have pleural effusions (29/60 or 48%) than those without PE (76/225 or 34%); effusions tended to be small and few were large enough to warrant thoracentesis. Of note, effusions in those without PE were also common and similar to those in size and location to those in patients with PE.¹⁹⁸ Patients suspected of having PE likely have other underlying conditions that predispose them to pleural effusions, such as CHF or pneumonia.

Pleural fluid analysis is of limited value in establishing the diagnosis of paraembolic effusion because there is nothing characteristic about the fluid. The pleural fluid is almost always an exudate.⁷⁴ The pleural fluid red blood cell count exceeds 100,000/ μ L in less than 20% and is below 10,000/ μ L in at least 30%. The pleural fluid white blood cell count can vary from less than 100 to more than 50,000/ μ L. The differential white blood cell count may reveal predominantly polymorphonuclear leukocytes, eosinophils, or mononuclear cells.

Diagnosis

The diagnosis of PE is discussed in Chapter 57. The possibility of PE should be considered in every patient with a pleural effusion, even if the patient has obvious CHF. In an autopsy series of 290 patients with CHF and pleural effusion, 60 (21%) had PE.¹⁶⁰ When a paraembolic effusion is strongly suspected, the patient should be started on heparin treatment and a diagnostic test for PE should be performed before a thoracentesis is attempted.¹⁸⁹

In the patient with an undiagnosed pleural effusion for whom PE is suspected, CTPA appears to be the preferred test because it also provides information about the lung parenchyma, the mediastinum, and the pleural surfaces, which may provide clues to the etiology of the pleural effusion (see

Fig. 79-7) (Videos 79-4A and 79-4B). Another reason to obtain the CTPA rather than a perfusion scan in patients with pleural effusions suspected of having PE is that the presence of the effusion makes the lung scan more difficult to interpret.

Treatment

Treating the patient with a paraembolic effusion is the same as for any patient with PE (see Chapter 57). The presence of bloody pleural fluid is not a contraindication to the administration of heparin or, if indicated, thrombolytic therapy.¹⁹⁴ Paraembolic effusions usually reach their maximum size within the first 3 days.¹⁹⁹ If the effusion increases in size after this time, the patient probably has recurrent emboli, a pleural infection, or a hemothorax and a diagnostic thoracentesis should be performed. If the pleural fluid hematocrit value is greater than 50% of the peripheral hematocrit, a hemothorax is present. In this

instance, anticoagulation should be discontinued and tube thoracostomy should be performed.

ABDOMINAL DISEASES

Many abdominal diseases can cause pulmonary signs and symptoms. This section describes the most important of these disorders that cause pleural effusion.

Esophageal Perforation

The diagnosis of esophageal rupture should always be considered in the differential diagnosis of exudative pleural effusions because, if this condition is not rapidly treated, the mortality increases, with current estimates ranging between 30% and 60%. Approximately 60% of patients with esophageal perforation have a pleural effusion, whereas about 25% have a pneumothorax.²⁰⁰ The pleural effusion is usually left sided (Fig. 79-8), but it may be right sided or bilateral.

The esophagus most commonly perforates as a complication of esophagoscopy and is more likely when there is an attempt to remove a foreign body or to dilate an esophageal stricture.²⁰¹ Overall, the incidence of esophageal perforation with esophagoscopy examination is 0.15% to 0.70%.²⁰⁰ The insertion of a Blakemore-Sengstaken tube for esophageal varices can be complicated by esophageal rupture. Frequently, the diagnosis is missed in these patients because of the severity of their illness and the multiple coexisting problems.²⁰⁰ Esophageal perforation may also result from transesophageal echocardiography, foreign bodies, esophageal carcinoma, gastric intubation, chest trauma, chest surgery, or vomiting (Boerhaave syndrome). In a review of 120 consecutive patients with esophageal perforation from all causes, the incidence of pleural effusion was 52% and of pneumothorax, 11%.²⁰²

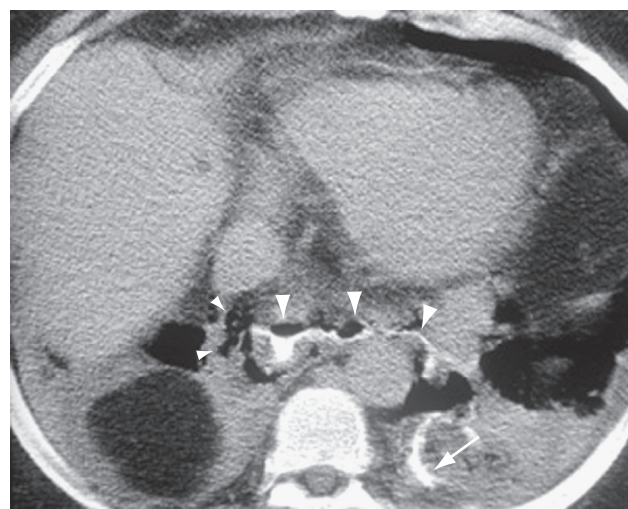


Figure 79-8 Effusion due to esophageal perforation. Axial CT through the lower thorax in a patient with chest pain shows pneumomediastinum (small arrowheads) and leakage of water-soluble oral contrast from the ruptured esophagus (large arrowheads) through the mediastinum into the left pleural space (arrow). (From Fadoo F, Ruiz DE, Dawn SK, et al: Helical CT esophagography for the evaluation of suspected esophageal perforation or rupture. *AJR Am J Roentgenol* 182:1177–1179, 2004.)

Clinical Manifestations. The symptoms associated with esophageal perforation result from the acute mediastinitis produced by contamination of the mediastinum by the oropharyngeal contents. Most of the morbidity from esophageal perforation is caused by infection of the mediastinum and the pleural space by the oropharyngeal bacterial flora.¹⁰⁹

A patient with an esophageal perforation is usually acutely ill. With a spontaneous rupture, there is frequently a sensation of tearing or bursting in the lower part of the chest or the epigastrium. The chest pain is characteristically excruciating and is often unrelieved by opiates. More than 50% of patients have small amounts of hematemesis. The presence of subcutaneous emphysema in the suprasternal notch is suggestive of the diagnosis. However, less than 10% of patients have subcutaneous emphysema within the first 4 hours of rupture.²⁰³ When the esophagus is perforated during esophagoscopy, the endoscopist generally does not realize it; however, the patients usually develop persistent chest or epigastric pain within a few hours after the procedure.

Diagnosis. The diagnosis of esophageal rupture should be considered in all acutely ill patients with an exudative pleural effusion. The best screening test for esophageal rupture appears to be the level of amylase in the pleural fluid.²⁰³ The pleural fluid amylase level is elevated owing to saliva, with its high amylase content, entering the pleural space.¹⁰⁸ The pleural fluid pH is usually decreased below 7.00 in patients with pleural effusion secondary to esophageal perforation due to the intense inflammatory response resulting from the mediastinitis and not the regurgitation of gastric juice into the pleural space. The demonstration of either squamous epithelial cells or food particles in the pleural fluid is highly suggestive of the diagnosis. Other findings suggestive of esophageal rupture are a chest tube output more than 500 mL/day and polymicrobial flora in the pleural fluid. The diagnosis is established when esophageal perforation is confirmed by contrast studies of the esophagus (see Fig. 79-8).

Treatment. Treatment of the esophageal rupture may range from nonoperative stenting to primary repair to esophagectomy depending on the underlying disease of the esophagus and the size of the rupture.²⁰² Mediastinitis from esophageal perforation and other causes is discussed in detail in Chapter 84.

Pancreatic Disease

Three different types of nonmalignant pancreatic disease can have an accompanying pleural effusion: acute pancreatitis, chronic pancreatitis with pseudocyst, and pancreatic ascites.

Acute Pancreatitis. In a study of 133 patients with their first attack of acute pancreatitis, 50% of the patients had a pleural effusion on chest CT scan.²⁰⁴ The effusion was bilateral in 51 (77%), unilateral left sided in 10 (15%), and unilateral right sided in 5 (8%). Patients with acute pancreatitis and a pleural effusion had more severe disease and a higher mortality rate than did those without effusions.²⁰⁴ The exudative pleural effusion accompanying acute pancreatitis results from the diaphragmatic inflammation and

transdiaphragmatic transfer of the exudative fluid arising from acute pancreatic inflammation.

The clinical picture is usually dominated by abdominal symptoms, including pain, nausea, and vomiting. However, at times, respiratory symptoms consisting of pleuritic chest pain and dyspnea may dominate the clinical picture. In addition to the small to moderate-sized pleural effusion, the chest radiograph may reveal an elevated diaphragm and basilar opacities. Demonstration of an elevated pleural fluid amylase level is highly suggestive of the diagnosis, but the diagnosis of esophageal rupture must be excluded. The pleural fluid is an exudate with predominantly polymorphonuclear leukocytes and a normal glucose level.

Chronic Pancreatic Pleural Effusion. Patients with chronic pancreatic disease sometimes have a large chronic pleural effusion. When the pancreatic ductal system is disrupted, a pseudocyst may form in the pancreas. A sinus tract may extend from the pseudocyst through the aortic or esophageal hiatus into the mediastinum. Once the sinus tract reaches the mediastinum, the process may be contained to form a mediastinal pseudocyst or it may rupture into one or both pleural spaces, resulting in a large chronic pleural effusion¹¹⁰ (Fig. 79-9).

The clinical picture of patients with chronic pancreatic disease and pleural effusion is usually dominated by chest symptoms, such as dyspnea, cough, and chest pain. Most patients do not have abdominal symptoms because the pancreaticopleural fistula decompresses the pseudocyst. The pleural effusion is usually massive and recurs rapidly after thoracentesis.¹¹⁰ The effusion is usually left sided but may be right sided or bilateral.

The key to the diagnosis is a markedly elevated pleural fluid amylase level, generally greater than 1000 IU/mL, while the serum level of amylase may be only mildly elevated. Patients with chronic pancreatic pleural disease are generally easily differentiated from those with malignant pleural effusion, who also may have an elevated pleural fluid amylase level, because the amylase level is much higher with the pseudocyst. In rare cases in which the differentiation is not obvious, the diagnosis can be made by measuring amylase isoenzymes because the amylase

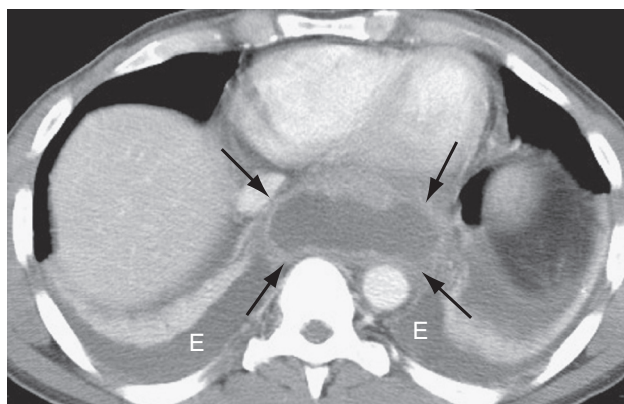


Figure 79-9 Effusion due to pancreatic pseudocyst. Axial CT image through the lower thorax in a patient with chronic pancreatitis shows bilateral pleural effusions (E) and a cystic mass in the mediastinum (arrows) representing a pseudocyst.

associated with malignancy is of the salivary, not the pancreatic, type.¹¹² Both ultrasound and CT are useful in establishing the diagnosis of pancreatic pseudocyst. Endoscopic retrograde cholangiopancreatography usually documents the fistulous tract or other pancreatic pathology.

Patients with chronic pancreatic pleural effusions should be given a trial of conservative therapy for 2 to 3 weeks that consists of nasogastric suction, no oral intake, suppression of pancreatic secretion with atropine, and repeated therapeutic thoracenteses.¹¹⁰ The administration of a continuous infusion of somatostatin may decrease the secretions through the fistula and facilitate closure.²⁰⁵ Conservative treatment is successful within 4 weeks in about 40% of patients. If conservative treatment fails, a laparotomy should be performed. The anatomy of the pancreatic ductal system should be assessed before surgery with endoscopic retrograde cholangiopancreatography or at the time of operation with operative pancreatography. If a sinus tract is found, it should be ligated or excised. The pancreas should be partially resected, drained with a Roux-en-Y loop, or both, depending on the pancreatographic findings.¹¹⁰ An alternative approach is to attempt percutaneous abdominal pseudocyst drainage by use of CT guidance. Decortication of the pleura may be necessary for some patients in order to remove the thick pleural peel created by the intense inflammation caused by the presence of pancreatic enzymes.

Pancreatic Pleural Effusion. Some patients with pancreatic disease develop ascites characterized by high amylase and protein levels. If such patients should happen to have or develop a defect in their diaphragm, they develop a large pleural effusion as a result of the flow of fluid from the peritoneal cavity to the pleural cavity. The treatment for pancreatic pleural effusion is the same as for pancreatic ascites, except serial thoracenteses rather than serial paracenteses are performed.

Intra-Abdominal Abscesses

Pleural effusions are frequently seen with intra-abdominal abscesses. The possibility of an intra-abdominal abscess should be considered strongly in any patient with an undiagnosed exudative pleural effusion containing predominantly polymorphonuclear leukocytes, particularly when there are no pulmonary parenchymal opacities. The mechanism responsible for the development of the exudative pleural effusion is probably diaphragmatic irritation.

Subphrenic abscess is the intra-abdominal abscess most commonly associated with a pleural effusion; pleural effusions develop in approximately 80% of patients with subphrenic abscess.²⁰⁶ The approximate incidence of effusions with other intra-abdominal abscesses is 40% in pancreatic abscesses, 30% in splenic abscess, and 20% in intrahepatic abscesses. With pancreatic abscess, the pleural fluid has a high amylase level.

Clinical Manifestations. Subphrenic abscess most commonly develops as a postoperative complication 1 to 3 weeks after intra-abdominal surgery.²⁰⁶ Splenectomy and gastrectomy are particularly likely to be complicated by left subphrenic abscess. There is no antecedent abdominal

surgery in approximately 10% of patients with subphrenic abscess.²⁰⁶ The abscess may result from perforation of the stomach, duodenum, appendix, colon, or a diverticulum, or from diverticulitis, cholecystitis, pancreatitis, or trauma. Most patients have fever, leukocytosis, and abdominal pain but, frequently, there are no localizing signs or symptoms.

Most patients with pyogenic intrahepatic abscesses have fever and anorexia. Abdominal pain is common and often not localized to the right upper quadrant. On physical examination, an enlarged, tender liver can be demonstrated. Laboratory tests reveal leukocytosis, anemia, elevated alkaline phosphatase levels, and hyperbilirubinemia.²⁰⁷

Pancreatic abscess usually follows an episode of acute pancreatitis. This diagnosis should be suspected if the patient does not respond to the initial therapy or if fever, abdominal pain, and leukocytosis develop within 3 weeks of the episode of acute pancreatitis. Splenic abscess is uncommon, usually seen in patients with systemic infection. Bacterial endocarditis is the most common underlying infection.

The pleural fluid that accumulates in patients with intra-abdominal abscesses is an exudate with predominantly polymorphonuclear leukocytes. The pleural fluid white blood cell count may exceed 50,000/ μ L, but the pleural fluid pH and glucose concentration usually remain above 7.20 and 60 mg/dL (3.33 mmol/L), respectively. Only rarely does the pleural fluid become infected.

Diagnosis and Treatment. The diagnosis of intra-abdominal abscess is best established with an abdominal CT scan (eFig. 79-6 and Video 79-5).²⁰⁸ The appropriate treatment for a patient with an intra-abdominal abscess and a pleural effusion is drainage of the abscess combined with parenteral antibiotics.

Abdominal Surgery

Approximately 50% of patients undergoing abdominal surgery develop a pleural effusion in the first few days after surgery.^{209,210} The incidence of postoperative pleural effusion is greater in patients undergoing upper abdominal surgery, in patients with postoperative atelectasis, and in patients with free abdominal fluid at surgery.^{209,210} The accumulation of pleural fluid within the first 72 hours after abdominal surgery is probably related to either diaphragmatic irritation or transdiaphragmatic movement of intra-abdominal fluid. A postoperative patient with a significant amount of pleural fluid, particularly when associated with fever, should have a diagnostic thoracentesis to rule out pleural infection as a cause of the effusion. In addition, the possibility of PE should be considered. If the effusion develops more than 72 hours after surgery, it is probably not related to the surgical procedure itself, and alternative explanations must be sought, such as PE intra-abdominal abscess, and hypervolemia.

Liver Transplantation

Most patients who undergo an orthotopic liver transplantation develop a pleural effusion after surgery. In one study, 68% of 300 patients undergoing liver transplantation developed a pleural effusion and the effusion occupied more than 25% of the hemithorax in 21 patients (7%).²¹¹ The

effusion was unilateral right sided in 153 and bilateral in 53. The effusions are large enough to require therapeutic thoracentesis or tube thoracostomy in approximately 10%.²¹¹ The natural history of these effusions is that they increase in size over the first 3 postoperative days and then gradually resolve over several weeks to several months. The pathogenesis of these effusions is probably related to injury or irritation of the right hemidiaphragm caused by the extensive right upper quadrant dissection. These pleural effusions can be largely prevented if a fibrin sealant is sprayed on the undersurface of the diaphragm around the insertion of the liver ligaments at the time of the transplantation.²¹²

Bilious Pleural Effusion

Bilious pleural effusions are due to a fistula from the biliary tree to the pleural space.²¹³ The fistula may be secondary to trauma, suppurative complications of biliary tract infections, or surgery, particularly when biliary obstruction is present. The diagnosis should be suspected in any patient with an obstructed biliary tract. The pleural fluid usually appears bilious but, at times, the diagnosis may depend on the demonstration that the ratio of pleural fluid to serum bilirubin is greater than 1.0. Appropriate treatment consists of reestablishment of biliary drainage. The incidence of empyema with bilious pleural effusion is approximately 50%. Most patients who have a bilious pleural effusion require decortication and diaphragmatic repair.⁶²

INFLAMMATORY DISEASES

Rheumatoid Pleuritis

The pleura is occasionally involved in the course of rheumatoid arthritis. Approximately 5% of patients with rheumatoid arthritis have a pleural effusion, and approximately 20% experience pleuritic chest pain.^{113,214} Rheumatoid pleurisy has a striking male predominance, despite the higher prevalence of rheumatoid disease in women; more than 10% of men, but less than 2% of women, with rheumatoid disease have a pleural effusion.^{113,214}

Clinical Manifestations. Almost all patients with rheumatoid pleural effusions are older than 35 years. Approximately 80% are men and approximately 80% have subcutaneous nodules. The pleural effusion usually develops only after the arthritis has been present for several years¹¹³ but, on rare occasions, a patient may present with a pleural effusion.

Patients with rheumatoid pleuritis may be asymptomatic or symptomatic with pleuritic chest pain, fever, or both,^{113,118} and some patients experience dyspnea secondary to the presence of pleural fluid. In most patients, the chest radiograph reveals a small or moderate-sized pleural effusion. In approximately 25% of patients, the effusion is bilateral.¹¹³ With time, the effusion may alternate from one side to the other or come and go on the same side. Other intrathoracic manifestations of rheumatoid disease are present in up to one third of patients.¹¹³

Diagnosis. The diagnosis is suggested by the clinical picture of rheumatoid arthritis and the presence of a pleural

effusion. The pleural fluid with rheumatoid pleuritis is distinctive, characterized by a glucose level less than 30 mg/dL (1.67 mmol/L), a high LDH level (>2 times the upper limit of normal), a low pH (<7.20), and a high rheumatoid factor titer (>1 : 320 and ≥ the serum titer).¹¹⁸ Occasionally, the pleural fluid glucose is not low when the patient is first seen, but serial pleural fluid glucose determinations reveal progressively lower pleural fluid glucose levels. Another interesting characteristic of rheumatoid pleural effusions is their tendency to contain cholesterol crystals or high levels of cholesterol.²¹⁵ A unique cytologic appearance of elongated macrophages, called “comet tail” cells, is also considered specific for the diagnosis²¹⁶ (eFig. 79-7).

With the characteristic pleural fluid findings, the primary alternative diagnosis to exclude is complicated parapneumonic effusion. The incidence of complicated parapneumonic effusion is high in patients with rheumatoid pleuritis,²¹⁷ so this differentiation is important. It is particularly important to examine the Gram stain of the pleural fluid and to culture the fluid both aerobically and anaerobically.

Prognosis and Treatment. The natural history of rheumatoid pleuritis varies. Most patients experience a spontaneous resolution within 3 months but, in the occasional patient, the effusion is persistent and massive pleural thickening may develop. No studies have demonstrated that anti-inflammatory therapy has any influence on the course of rheumatoid pleuritis. The results after intrapleural corticosteroids have been mixed.⁶² Decortication should be considered in patients with thickened pleura who are symptomatic with dyspnea. This procedure is particularly difficult in patients with rheumatoid pleuritis because it is not easy to develop a plane of dissection between the lung and the fibrous peel.

Lupus Pleuritis

Approximately 40% of patients with SLE or drug-induced lupus have a pleural effusion during the course of their disease.¹¹⁴

Clinical Manifestations. Most patients with lupus pleuritis have arthritis or arthralgias before the development of a pleural effusion. Almost all patients with lupus pleuritis have pleuritic chest pain, and most are also febrile. Lupus pleuritis frequently develops in association with an exacerbation of the underlying disease. The pleural effusions secondary to lupus are usually small and bilateral in about 50% of patients.²¹⁸

Many medications have been incriminated for producing drug-induced lupus erythematosus (see Chapter 71).⁶² Hydralazine, procainamide, isoniazid, phenytoin, and chlorpromazine are the ones most commonly associated with drug-induced lupus, but there are more than 70 other drugs that possibly induce lupus. For the latest information on possible drug reactions, including lupus reactions, an excellent online source is www.pneumotox.com. The presenting signs, symptoms, and radiographic abnormalities are similar, whether the pleuritis is due to spontaneous or to drug-induced lupus. The symptoms associated with drug-induced lupus characteristically abate within days of discontinuing the offending drug.

Diagnosis. The possibility of lupus pleuritis should be considered in any patient with an exudative pleural effusion of unknown cause. The pleural fluid can contain a predominance of either polymorphonuclear or mononuclear cells, depending on the timing of the thoracentesis in relation to the development of the symptoms.⁶⁴ Although it was believed in the past that elevated ANA titers in the pleural fluid were diagnostic of lupus pleuritis, it appears that such elevated titers are neither specific nor sensitive for diagnosing lupus pleuritis.^{115,219} The diagnosis is based primarily on the clinical picture and the serologic findings for lupus.

Treatment. In contrast to rheumatoid pleuritis, the pleuritis with systemic lupus responds to corticosteroid administration. It is recommended that patients with lupus pleuritis be treated with oral prednisone, with rapid tapering once the symptoms are controlled. At times, the effusion is large, is symptomatic, and does not respond to corticosteroid therapy. In such a situation, consideration should be given to chemical pleurodesis. Of course, if the patient has drug-induced lupus, the offending drug should be withdrawn.

OTHER INFLAMMATORY DISEASES

Pleural effusions occasionally develop in the course of eosinophilic granulomatosis with polyangiitis (Churg-Strauss), granulomatosis with polyangiitis (Wegener), and Sjögren syndrome, which are described in detail in other chapters. The pleural disease seen with these diseases constitutes a relatively minor portion of the clinical picture.

SARCOIDOSIS

The prevalence of pleural effusion with sarcoidosis (see Chapter 66) is about 1%.^{220,221} Patients with pleural effusion due to sarcoid usually have extensive parenchymal sarcoidosis and, frequently, extrathoracic sarcoidosis.²²⁰ The symptoms of pleural involvement with sarcoidosis vary; many patients have no symptoms, although an equal number have pleuritic chest pain or dyspnea.

The pleural effusions with sarcoidosis are usually small and are bilateral in approximately one third of cases. The pleural fluid is almost always an exudate, and its cell differential is characterized by predominantly small lymphocytes.^{220,221} In the patient with known sarcoidosis, one can attribute the presence of the pleural effusion to sarcoid only when other causes of exudative lymphocyte-predominant pleural effusions, such as tuberculosis, are excluded. The pleural effusion secondary to sarcoidosis may resolve spontaneously, or corticosteroid therapy may be required for its resolution.

ASBESTOS EXPOSURE


An otherwise unexplained pleural effusion may result years after exposure to asbestos, which may have been brief or intermittent, and in the immediate or distant past. Epler and coworkers²²² reviewed the medical histories of 1135 asbestos workers whom they had followed for several years and found that 35 (3%) of the workers had pleural effusions for

which there was no other ready explanation. The heavier the asbestos exposure, the more likely the patient is to develop a pleural effusion. The pleural effusion sometimes develops within 5 years of the initial exposure but, in one large series, the mean latency was 30 years.²²³

The pathogenesis of the pleural effusion arising after asbestos exposure is unknown.¹⁰ Asbestos fibers, both long and short, move from the lung to the pleural space and lodge in the parietal pleura, where they appear to be concentrated in specific locations that correlate with the lymphatic drainage. Their presence leads to a continuous low-grade inflammation. This chronic inflammation can both decrease the lymphatic clearance of the pleural space and increase the permeability of the capillaries in the parietal pleura; the combined effects could lead to the development of an exudative pleural effusion. An immune mechanism also has been invoked to explain the fluctuations in the degree of pleuritis with time.²²³

Clinical Manifestations. Patients with pleural effusion secondary to asbestos exposure have surprisingly few symptoms. In the series of Epler and coworkers,²²² 66% had no symptoms. The chest radiograph usually reveals a small to moderate-sized effusion, which is bilateral in about 10%. The pleural fluid is an exudate, and the pleural fluid differential can reveal either predominantly polymorphonuclear leukocytes or mononuclear cells. Interestingly, pleural fluid eosinophilia was present in 15 (52%) of the 29 patients with asbestos pleural effusions for whom pleural fluid differentials were reported.⁷⁰

Diagnosis. The diagnosis of benign asbestos effusion is one of exclusion. It requires the following criteria: history of direct or indirect exposure to asbestos; exclusion of other causes, notably infection, PE, and malignancy; and follow-up of at least 2 years to verify that the effusion is benign.²²³

The possibility of mesothelioma must be carefully considered and excluded, a process that may include thoracoscopic examination and biopsy (see [Video 82-4](#)). 

Prognosis. The natural history of the patient with an asbestos pleural effusion is one of chronicity, with frequent recurrences and sometimes the development of extensive fibrosis of the parietal pleura.²²² On average, the pleural effusion persists for 3 months but eventually clears and leaves no residual pleural disease. Massive pleural fibrosis develops in about 20% of patients, with ipsilateral blunting of the costophrenic angle in another 20%.²²² Rounded atelectasis also develops in about 10% of patients. There is no known treatment for asbestos pleural effusion. Further information about asbestos-induced lung disease is provided in Chapter 73.

UREMIA

Uremia may be complicated by a fibrinous pleuritis and pleural effusion.⁶² The pathogenesis of the pleural effusion associated with uremia is unclear. It is probably somewhat analogous to that for uremic pericarditis because more than half of the patients with uremic pleuritis also have uremic pericarditis ([eFig. 79-8](#)). The incidence of pleural effusions with uremia is approximately 3%. A close relationship does

not appear to exist between the degree of uremia and the development of a pleural effusion. The incidence of pleural effusion in patients who are receiving chronic hemodialysis is approximately 50% on chest CT scan. The etiologies of 100 effusions seen in hospitalized patients with uremia on hemodialysis in one study were as follows: heart failure, 46; uremia, 16; parapneumonic, 15; atelectasis, 11; and miscellaneous, 12.²²⁴ In another study of 76 patients with effusions on hemodialysis, uremia was considered the cause in 24%, while parapneumonic effusion (24%) and CHF (20%) were also common.²²⁵

The pleural effusion seen with uremia frequently occupies more than 50% of the hemithorax and is bilateral in about 20% of patients.²²⁶ More than 50% of patients are symptomatic from the pleural disease, with fever (50%), chest pain (30%), cough (35%), and dyspnea (20%) being the most common symptoms. The pleural fluid is an exudate that is frequently serosanguineous or bloody. The differential white blood cell count reveals predominantly lymphocytes.²²⁶ Pleural biopsy specimens invariably reveal chronic fibrinous pleuritis.

The diagnosis of uremic pleuritis is one of exclusion in the patient with chronic renal failure. After beginning dialysis, the effusion gradually disappears within 4 to 6 weeks in about 75% of patients. In the remaining patients, the effusion persists, progresses, or recurs. An occasional patient develops marked pleural thickening that may require decortication.

POST-CARDIAC INJURY SYNDROME

Post-cardiac injury syndrome (PCIS), also known as the post-pericardiectomy or the post-myocardial infarction (Dressler) syndrome, is characterized by combinations of pericarditis, pleuritis, and pneumonitis that develop after injury to the myocardium or pericardium.^{227,228} In one report, noncomplicated PCIS was defined as the presence of temperature greater than 100.5° F, patient irritability, pericardial friction rub, and a small pericardial effusion with or without pleural effusion following cardiac trauma; a complicated PCIS was defined as a noncomplicated PCIS plus the need for hospital readmission with or without the need for pericardiocentesis or thoracentesis.²²⁹ Imazio and colleagues²³⁰ have defined the PCIS as the presence of at least two of the following: fever without alternative explanation, pleuritic chest pain, pericardial friction rub, new or worsening pleural effusion, and new or worsening pericardial effusion. PCIS has been described after myocardial infarction (eFig. 79-9), cardiac surgery, blunt chest trauma, percutaneous left ventricle puncture, and implantation of a pacemaker.²²⁷ The incidence of PCIS is approximately 1% after myocardial infarction and is somewhat higher after cardiac surgery.⁶² The exact pathogenesis of this syndrome is unknown, but it appears to have an immunologic basis.

Clinical Manifestations. The syndrome typically develops about 3 weeks after the injury, but it can happen any time between 3 days and 1 year. The two cardinal symptoms are fever and chest pain. The chest pain often precedes the onset of fever and can vary from an agonizing crush to a dull ache. At times, it may have a pleuritic component. Most patients have a pericardial friction rub. Pulmonary opacities are present in about 50% of patients, and laboratory

evaluation reveals leukocytosis with an elevated erythrocyte sedimentation rate.

A pleural effusion arises in about two thirds of patients with PCIS.²²⁷ The pleural effusions are bilateral and small in most patients. The pleural fluid is an exudate that is frequently serosanguineous or bloody. The pleural fluid differential may reveal either predominantly polymorphonuclear leukocytes or mononuclear cells, depending on the acuteness of the process.²²⁷

Diagnosis. The diagnosis of PCIS should be considered in any patient who develops a pleural effusion after injury to the heart. The diagnosis of the syndrome is established by the clinical picture and by excluding CHF, PE, and pneumonia.

Treatment. PCIS usually responds to treatment with anti-inflammatory agents, such as aspirin, colchicine or indomethacin. Corticosteroids may be necessary in more severe cases.

POST-CORONARY ARTERY BYPASS SURGERY

More than 600,000 patients undergo CABG surgery in the United States each year. Because approximately 10% of patients who undergo CABG surgery will develop a pleural effusion that occupies more than 25% of their hemithorax in the subsequent month,²³¹ CABG surgery is one of the more common causes of pleural effusions in the United States. The prevalence of small pleural effusions is high following CABG surgery. In one study, the prevalence of pleural effusions in 47 patients as detected by ultrasound was 89% at 7 days, 77% at 14 days, and 57% at 30 days.²³² In a study of 349 patients post-CABG, the prevalence of pleural effusion on chest radiograph 30 days postoperatively was 62%; and 40 of the 349 patients (11%) had an effusion that occupied more than 25% of the hemithorax.²³¹ The pleural effusions after CABG surgery tend to be left sided or bilateral and, if bilateral, the effusion is usually larger on the left.²³¹

The primary symptom of a patient with a large pleural effusion post-CABG is dyspnea.²³¹ The presence of either chest pain or fever should alert the physician to an alternative diagnosis. When all patients with large pleural effusions after CABG surgery are considered, the effusions can be divided into those that are bloody and those that are serous. The bloody effusions are probably secondary to bleeding into the pleural space. They reach their maximal size within 30 days of surgery, are frequently associated with pleural fluid or peripheral eosinophilia or both, have a high pleural fluid LDH level,²³³ and respond to one or two therapeutic thoracenteses.²³³ In contrast, the cause of the serous pleural effusions is unknown. They tend to reach their maximal size more than 30 days after surgery, have more than 50% small lymphocytes, and have a relatively low pleural fluid LDH level.²³³ Most of these late effusions can also be managed with one or two therapeutic thoracenteses,²³¹ but some are refractory. It is unknown whether anti-inflammatory agents or diuretics are beneficial in the treatment of these effusions. A placebo-controlled, double-blind randomized study of 360 patients compared the effectiveness of colchicine with placebo in preventing postoperative effusions.²³⁴ These investigators reported that the patients

who received colchicine had a significantly lower incidence of pleural effusion (12.2% vs. 26.5%) and a significantly lower incidence of pericardial effusion (12.8% vs. 22.8%).

FONTAN PROCEDURE

With the Fontan procedure, an anastomosis is created between the superior vena cava, the right atrium, or the inferior vena cava and the pulmonary artery to bypass the right ventricle, usually because of tricuspid atresia or a univentricular heart. Pleural effusion develops in many patients after surgery and contributes significantly to postoperative morbidity. Pleural effusions are more likely in patients who have significant aortopulmonary collateral vessels before surgery; thus, Spicer and colleagues²³⁵ recommended that these vessels be embolized during preoperative angiography. The amount of pleural drainage postoperatively is decreased by about 50% if the Fontan circuit is fenestrated to allow shunt of deoxygenated blood to the systemic circulation.²³⁶ After the Fontan procedure, the pleural fluid is generally an exudate; some are chylothoraces. The treatment of choice for these effusions is usually insertion of a pleuroperitoneal shunt. Alternative treatments are creation of a late fenestration to create a right-to-left shunt or chemical pleurodesis.

DRUG REACTIONS

Lupus-like syndromes arise in conjunction with the administration of many different medications and have been discussed earlier in this chapter and in Chapter 71. Although there are case reports of pleural disease associated with administration of many drugs,²³⁷ the following drugs are known to induce pleural disease.

Nitrofurantoin

Pleuropulmonary reactions occasionally result from the administration of nitrofurantoin. Such reactions can have an acute or a chronic presentation.²³⁸ The acute presentation is seen within 1 month of initiation of therapy and is manifested by dyspnea, nonproductive cough, and fever. About 20% of patients have pulmonary opacities and an effusion, and about 3% have only an effusion. Most patients have both peripheral eosinophilia ($>350/\mu\text{L}$) and lymphopenia ($<1000/\mu\text{L}$).²³⁹ The chronic syndrome is seen when the patient has been taking nitrofurantoin for 2 months to 5 years and is much less common than the acute syndrome. Pleural effusion develops in less than 10% of patients and is typically accompanied by pulmonary opacities.²³⁸

The diagnosis of nitrofurantoin pleuropulmonary reaction should be suspected in all patients with a pleural effusion who are taking nitrofurantoin. If the drug is discontinued, the patient usually improves clinically within 1 to 4 days. The chest radiograph becomes normal within a week with the acute syndrome, whereas the time course is much longer for the chronic syndrome.²³⁸

Dantrolene

Dantrolene sodium is a long-acting skeletal muscle relaxant with a chemical structure similar to that of nitrofurantoin. Its administration can lead to the development of pleural or pericardial disease.²⁴⁰ The pleural effusion is unilateral and develops 2 months to 12 years after the initial administra-

tion of dantrolene. Patients may be febrile and may have pleuritic chest pain. The pleural fluid is an eosinophilic exudate with a normal glucose level.²⁴⁰ When dantrolene is discontinued, the patient improves symptomatically within days, but it may take several months for the pleural effusion to resolve completely.

Methysergide

The administration of methysergide can lead to a pleuropulmonary disease similar to that seen with nitrofurantoin.²⁴¹ Symptoms consisting of chest pain, dyspnea, and fever develop 1 month to 3 years after methysergide therapy is initiated. The chest radiograph commonly shows bilateral localized pleural effusions and pleural thickening.²⁴¹ When methysergide is discontinued, the symptoms of the patients improve. However, in one series of 13 patients, severe pleural fibrosis persisted in the two patients who had continued to take the drug for the longest period (18 and 36 months) after the onset of the pleurisy.²⁴¹

Ergot Alkaloids

The administration of ergot alkaloid drugs such as bromocriptine, ergotamine, dihydroergotamine, nicergoline, pergolide, and dopergine in the long-term treatment of Parkinson disease can lead to pleuropulmonary changes.²³⁷ As of 1988, a total of 23 patients had been reported. All the patients were men, and the drug had been taken for 6 months to 4 years before symptoms developed. Two to 5% of patients receiving long-term ergot alkaloid therapy develop pleuropulmonary disease. The incidence of pleural disease is higher if the patient has previous exposure to asbestos.²⁴² The chest radiograph reveals unilateral or bilateral pleural thickening or effusion in most patients. Analysis of the pleural fluid reveals an exudate with predominantly lymphocytes and frequently eosinophils.²⁴³ The natural history of pleuropulmonary disease during ergot alkaloid therapy is unclear. The disease progresses only in some of the patients who continue taking the drug.²⁴³

Procarbazine

There have been two detailed case reports of pleuropulmonary reactions consisting of chills, cough, dyspnea, and bilateral pulmonary opacities with pleural effusion after treatment with procarbazine, a chemotherapeutic drug.⁶² In both cases, symptoms developed within hours after procarbazine therapy, recurred with rechallenge, and resolved with discontinuation.

Amiodarone

Amiodarone is an antiarrhythmic that may produce severe pulmonary toxicity. Pleural effusions are seen as a manifestation of amiodarone toxicity, but they are uncommon. Most cases have concomitant parenchymal involvement, but cases have been reported in which there is none.²³⁷ The pleural fluid is an exudate and may have predominantly lymphocytes, macrophages, or polymorphonuclear leukocytes.²³⁷

Interleukin-2

Recombinant IL-2 is sometimes used in the treatment of malignancies, especially melanoma or renal cell carcinoma. One of the primary side effects of IL-2 administration is the development of pulmonary opacities and pleural effusions

that are probably related to a generalized capillary leak syndrome.⁶² The incidence of pleural effusion after IL-2 administration is approximately 50%.²³⁷ The characteristics of the pleural fluid have not been described. After the IL-2 therapy is stopped, the effusions tend to disappear. However, in one study, 17% of patient still had a pleural effusion 4 weeks after cessation of therapy.²⁴⁴

Dasatinib

Dasatinib is an inhibitor of multiple tyrosine kinase inhibitors, used primarily for treating adults with chronic myeloid leukemia with resistance to prior therapy. Use of dasatinib is associated with a high incidence of pleural effusion. Qunitas-Cardama and associates²⁴⁵ reported that the effusion developed in 35% of 135 patients receiving the drug, and about half the effusions occupied more than 25% of the hemithorax. The effusions were bilateral in 80% of the patients. The effusions were mostly exudates. The effusions resolved when dasatinib was discontinued or when steroids were administered. The effusions are less common when dasatinib is administered once rather than twice per day. Interestingly, pleural effusion has been associated with a better clinical response to dasatinib.^{245a}

MISCELLANEOUS

Lung Transplantation

With lung transplantation, the lymphatics that normally drain the lung are severed. Accordingly, the fluid that normally leaves the lung via these lymphatics drains through the pleural space. Pleural complications such as hemothorax, empyema, and persistent air leak contribute substantially to the postoperative morbidity and mortality.^{245b} The incidence of pleural effusions at 3 months after transplant is about 30% to 60%.^{246,247} The incidence of effusion at 12 months is less than 10%.²⁴⁷ The effusions are characteristically a lymphocyte-predominant exudate with a benign course.²⁴⁶ However, patients who develop complications after lung transplantation are likely to develop pleural effusions. In one study, pleural effusions were seen with 74% of 19 episodes of acute rejection, 88% of 8 instances of chronic rejection, 55% of 11 episodes of infection, and 75% of 4 instances of lymphoproliferative disease.²⁴⁸ (More details about lung transplantation are provided in Chapter 106.)

Meigs Syndrome

Meigs and Cass²⁴⁹ originally described a syndrome characterized by ascites and pleural effusion in association with solid benign ovarian tumors. Subsequently, it has become apparent that a similar syndrome can be seen with benign cystic ovarian tumors, with benign tumors of the uterus (fibromyomas), and with low-grade ovarian malignant tumors without evidence of metastases.⁶² The ascites appears to result from the secretion of large amounts of fluid by the tumors. VEGF may play an important role in the pathogenesis of the ascites and pleural fluid because VEGF levels are high in both the ascites and pleural fluid.²⁵⁰ It is thought that the pleural effusion results from the ascitic fluid passing through defects in the diaphragm into the pleural space.

Patients with Meigs syndrome usually have a chronic illness characterized by weight loss, pleural effusion, ascites, and a pelvic mass. It is important to realize that not all patients with this constellation of symptoms have a disseminated malignancy. Approximately 70% of the effusions are right sided, and 20% are bilateral. The pleural fluid is usually an exudate with a relatively low white blood cell count ($<1000/\mu\text{L}$) and is occasionally bloody. The level of CA-125 in the pleural fluid may be elevated, and this should not be taken as an indication of malignancy.²⁵⁰

The diagnosis of Meigs syndrome should be considered in all women who have a pelvic mass, ascites, and a pleural effusion. If the cytology of the pleural fluid is negative in such patients, a diagnostic laparoscopy or an exploratory laparotomy should be performed to determine whether there are peritoneal metastases. The diagnosis is confirmed when the ascites and pleural fluid resolve after the primary neoplasm is removed, usually within the first 2 weeks after surgery.

Endometriosis

An occasional patient with severe endometriosis presents with massive ascites. In one review, 10 of 27 patients (37%) also had a pleural effusion.²⁵¹ The effusions are usually right sided but may be bilateral. The pleural fluid is a bloody or chocolate-colored exudate. The serum carcinoembryonic antigen level may be elevated, suggesting ovarian carcinoma. Hormonal therapy, including gonadotropin-releasing hormone agonists, may be attempted, but frequently it is ineffective and many patients require total abdominal hysterectomy plus bilateral salpingo-oophorectomy.²⁵¹

Ovarian Hyperstimulation Syndrome

This syndrome is a serious complication of ovulation induction. The dramatic clinical picture is characterized by massive ovarian enlargement with multiple cysts, hemoconcentration, and the third-space accumulation of fluid.²⁵⁰ The full-blown syndrome may be complicated by renal failure, hypovolemic shock, thromboembolic episodes, acute respiratory distress syndrome, and death. Although the pathophysiology of this syndrome is incompletely understood, it is likely that the increased capillary permeability is due to the increased VEGF production by the ovarian granulosa cells in response to the exogenous human chorionic gonadotropin.²⁵⁰

Patients with the syndrome present within 2 to 3 weeks of receiving the human chorionic gonadotropin. Patients typically present with abdominal pain and distention, non-productive cough, and dyspnea caused by the ascites, pleural effusion, or both. The pleural effusion is usually bilateral, and the pleural fluid is an exudate with predominantly neutrophils and a relatively low LDH level. The treatment of severe cases requires restoration of intravascular volume, correction of electrolyte abnormalities, and venous thromboembolism prophylaxis.²⁵⁰

Trapped Lung

Effusions that are remarkably stable over time, recur after thoracentesis, and are resistant to diagnosis may be due to an underlying trapped lung (Fig. 79-10). Following an earlier episode of inflammation, a fibrous peel may form over the visceral pleura and can prevent the underlying

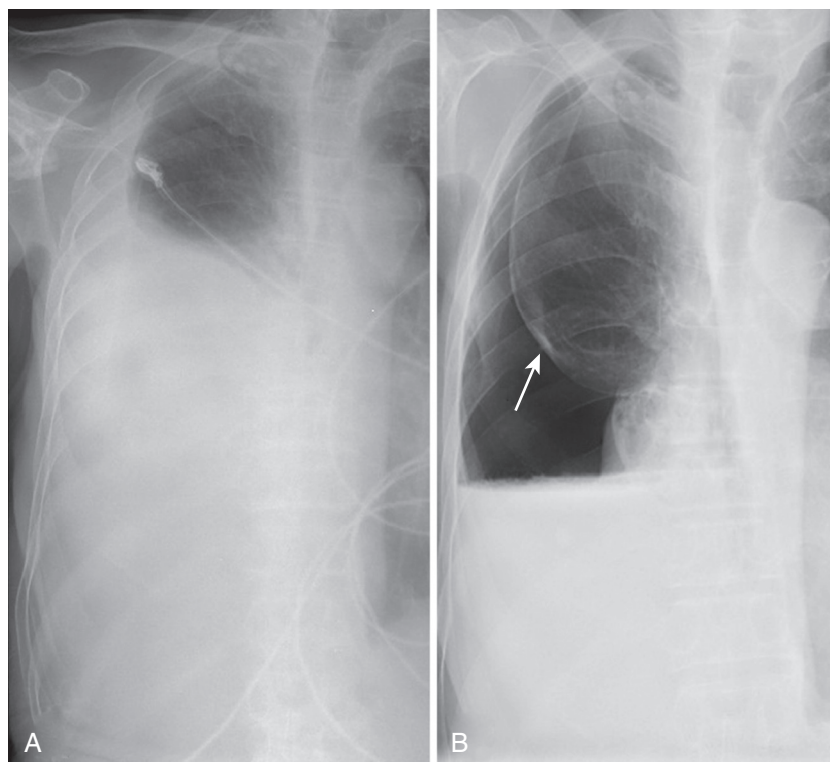


Figure 79-10 Effusion with trapped lung. Frontal chest radiograph (A) shows a large right pleural effusion. On a subsequent radiograph (B), the effusion has been partially drained revealing the underlying lung with some visceral pleural thickening (arrow). The lung failed to re-expand despite negative intrapleural pressures. The intrapleural air entered the pleural space from the atmosphere along the drainage tract.

lung from expanding fully, thereby “trapping” the underlying lung. The resulting negative pleural pressure leads to the development of a chronic pleural effusion.^{252,253}

Patients with a chronic pleural effusion secondary to trapped lung are often asymptomatic but may have symptoms of dyspnea. Symptoms of acute pleural inflammation, such as pleuritic chest pain and fever, are distinctly uncommon, but the patient often gives a history of such events in the past. One characteristic of the pleural effusion secondary to trapped lung is that the amount of fluid is quite constant from one study to another. With trapped lung, the pleural fluid is often a borderline exudate; the ratio of pleural fluid to serum protein is about 0.5, and the ratio of pleural fluid LDH to serum LDH is about 0.6.

The diagnosis of pleural effusion secondary to trapped lung should be suspected in any patient with a stable, chronic pleural effusion, particularly if the patient has a history of uremia, thoracic radiation, or prior thoracic surgery.²⁵³ The thickened visceral pleura can be demonstrated if 200 to 400 mL of air is injected into the pleural space at the time of a thoracentesis. At some institutions, pleural manometry is used routinely during a therapeutic thoracentesis; if the pleural pressure falls rapidly (more than 14 to 15 cm H₂O per liter pleural fluid removed), air is allowed to enter the pleural space to return the pleural pressure to a more normal range (−5 cm H₂O) so that an air-contrast chest CT scan can be obtained to evaluate the visceral pleura.²⁵³

The definitive therapy for trapped lung is thoracotomy with decortication. However, this major surgery is indicated only in patients who are symptomatic from the trapped lung. If the patient is asymptomatic or minimally symptomatic, the patient can be observed if the clinical

picture, pleural fluid findings, and pleural pressure measurements are all compatible with the diagnosis of trapped lung.

Yellow Nail Syndrome

This syndrome consists of the triad of deformed yellow nails, lymphedema, and pleural effusions. The three entities may become manifest at widely disparate times and therefore are not all concurrently present in every patient. The basic abnormality responsible for this syndrome appears to be hypoplasia of the lymphatic vessels^{254,255} or a decrease in function of lymphatics.²⁵⁶ The onset of the condition is after puberty (mean age of onset 53 in one study,²⁵⁷ 61 in another²⁵⁸), may be acquired,²⁵⁷ and may resolve without treatment.²⁵⁷

Typically, the nails are pale yellow to greenish in color and are excessively curved from side to side (eFig. 79-10). They are also thickened and may show transverse ridging or onycholysis (separation of nail from bed). The pleural effusions are bilateral in about 50% of cases and can be massive. Once a pleural effusion has developed with this syndrome, it tends to persist and recur rapidly after thoracentesis.²⁵⁴ The pleural fluid is usually an exudate with predominantly lymphocytes.²⁵⁴ The pleural fluid LDH tends to be relatively low relative to the pleural fluid protein level.⁶²

The diagnosis is usually established by the presence of the triad of pleural effusion, lymphedema, and yellow nails. The diagnosis may be difficult to establish if the pleural effusion is the first manifestation of the syndrome. There is no specific treatment for the syndrome but, if the effusion is large and producing symptoms, the effusion can be treated with pleurodesis or decortication/pleurectomy.^{258a}

Pleural Effusions Due to Misplaced Catheters

Both internal jugular and subclavian vein catheterization can be complicated by misplacement of the catheter tip into the mediastinum or pleural space that results in a large unilateral (eFig. 79-11) or bilateral pleural effusion. The pleural fluid may have the characteristics of the intravenous fluid, or it may be bloody from laceration of the blood vessels.²⁵⁹ If the patient is receiving lipids through a central line, the fluid may look chylous.²⁶⁰ The diagnosis of a misplaced central venous catheter should be considered in all patients with such lines who rapidly develop pleural effusions, and the patients should be evaluated by diagnostic thoracentesis.

In the past several years, the development of soft, flexible, small-bore polyurethane feeding tubes has made nasogastric and nasoenteric feeding more practical and comfortable for patients. However, misplacement of these tubes can lead to serious pleural complications. Pneumothorax is the most common complication, but infusion of the enteral formula into the pleural space or the development of an empyema, or both, are also common.²⁶¹ These small flexible tubes are inserted with a stylet in place that enables easier advancement of the device. However, with the stylet in place, the tubing becomes stiff enough that it can perforate structures relatively easily. The risk is much greater if the patient has an endotracheal tube in place or is obtunded.²⁶¹ To prevent these complications, these tubes should be inserted only by experienced persons, and the tube should be immediately removed if the patient starts coughing. The tube should not be advanced if resistance is felt and, before feeding is initiated, the position of the tip of the tube should be confirmed radiographically.²⁶² If enteral solutions enter the pleural space, tube thoracostomy should be performed to remove the solution. In addition, the patient should be carefully observed for the development of an empyema.²⁶¹

Key Points

- Entry of normal fluid into the pleural space is normally slow, consistent with that found in other interstitial spaces of the body. Exit of fluid is mainly via parietal pleural lymphatics, which have a large reserve capacity and can normally accommodate increases in fluid formation without the development of an effusion.
- Pleural effusions develop when disease or combinations of diseases lead to an increase in fluid entry into the pleural space and a decrease in removal from the pleural space; both changes are likely necessary for formation of an effusion.
- Excess fluid elsewhere in the body can move to and enter the pleural space due to (1) subatmospheric pleural pressure (−5 to −30 cm H₂O), (2) the leaky

mesothelial layer, and (3) the high capacitance of the pleural space.

- Transudates usually result from systemic changes in hydrostatic and/or osmotic pressures that lead to collection of a relatively low protein and *lactate dehydrogenase* (LDH) fluid, with a pleural/serum protein ratio < 0.5 and pleural/serum LDH < 0.6 and LDH less than two-thirds the upper limit of normal (Light's criteria).
- Transudates with a *very* low protein concentration (<0.5 g/dL) come from entry of cerebrospinal fluid, urine, peritoneal dialysis fluid, or intravenous fluids into the pleural space.
- Exudates result from a multitude of inflammatory, infectious, or malignant diseases, leading to an effusion with a relatively high protein and/or LDH concentration.
- Most transudates arise from congestive heart failure. When the cause is unclear or when the protein and LDH ratios are not clearly transudative, as can happen after diuresis, the pleural fluid N-terminal probrain natriuretic peptide is a sensitive and specific marker for a cardiac etiology.
- Most exudates arise from pneumonia, malignancy, or pulmonary embolism.
- No diagnosis is ever established for approximately 20% of all exudative pleural effusions and many resolve spontaneously, leaving no residua. The degree to which a diagnosis is pursued by invasive procedures will depend on the (1) symptoms and the clinical course of the patient, (2) trend of the pleural fluid LDH level with time, and (3) eagerness of the patient for a diagnosis.

Complete reference list available at [ExpertConsult](#).

Key Readings

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eFIGURE IMAGE GALLERY

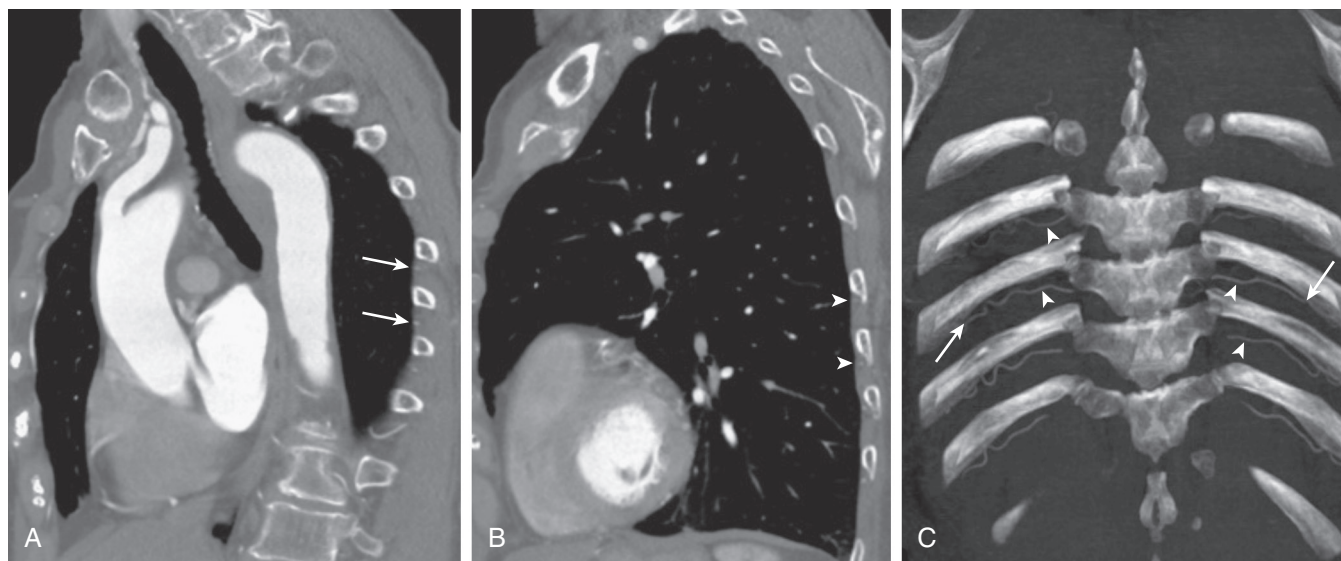


Figure 79-1 Intercostal arterial anatomy at enhanced chest CT. **A** and **B**, Sagittal enhanced chest CT medially (**A**) shows the presence of the intercostal arteries positioned in the middle of the intercostal space (*arrows*, **A**), compared with the position along the inferior margin of the rib more laterally (*arrowheads*, **B**). **C**, Coronal maximum intensity projected enhanced CT image shows the courses of the intercostal arteries, positioned in the middle of the intercostal space medially (*arrowheads*) and along the inferior margin of the rib more laterally (*arrows*). (Courtesy Michael Gotway, MD.)

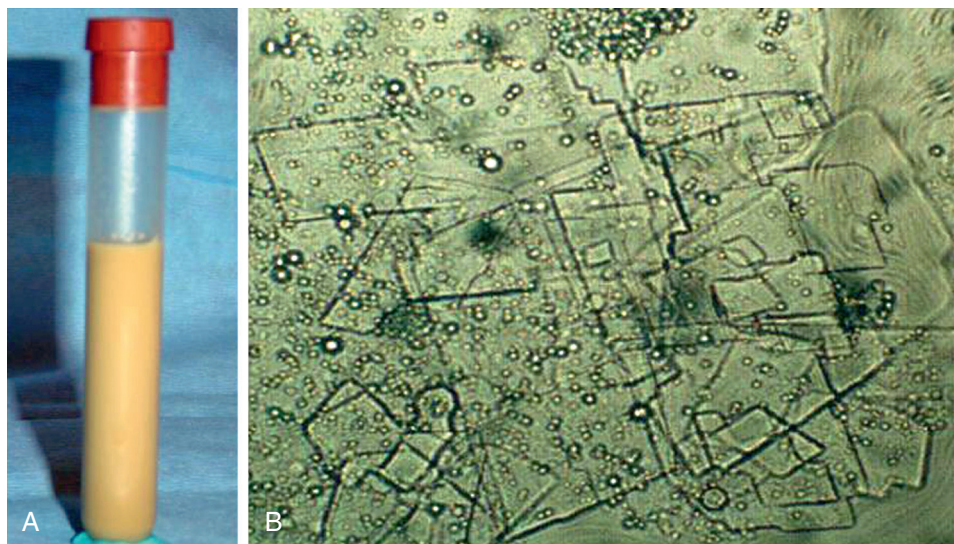


Figure 79-2 Pleural fluid from a patient with pseudochoylorax. **A**, The milky appearance of the pleural fluid persisted after the centrifugation. **B**, The presence of cholesterol crystals in microscopic examination of the pleural fluid established the diagnosis of pseudochoylorax. (From Kalomenidis I, Lee YCG: Chylorax, pseudochoylorax, LAM, and yellow nail syndrome. In Laurent GJ, Shapiro SD, editors: *Encyclopedia of respiratory medicine*. Waltham, MA, 2006, Academic Press, Fig. 2, p 392.)

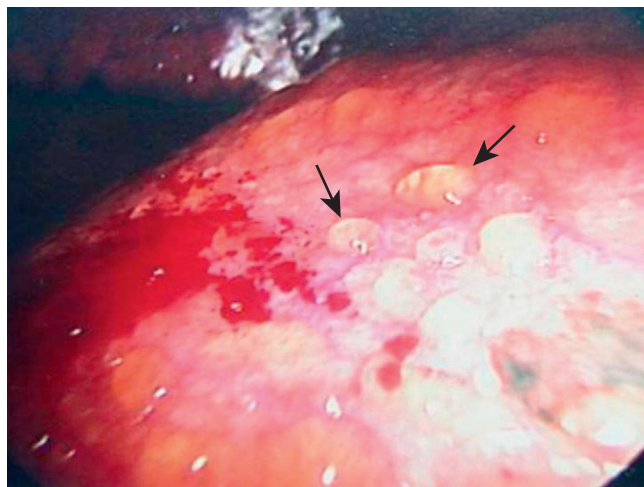


Figure 79-3 Porous diaphragm in a patient with hepatic hydrothorax. After aspiration of the pleural fluid, the diaphragm can be seen to be leaking fluid across the surface in many locations (arrows) as evidence of increased porosity. (From Huang PM, Chang YL, Yan CY, Lee YC: The morphology of diaphragmatic defects in hepatic hydrothorax: thoracoscopic finding. *J Thorac Cardiovasc Surg* 130:141–145, 2005. Fig. 3.)

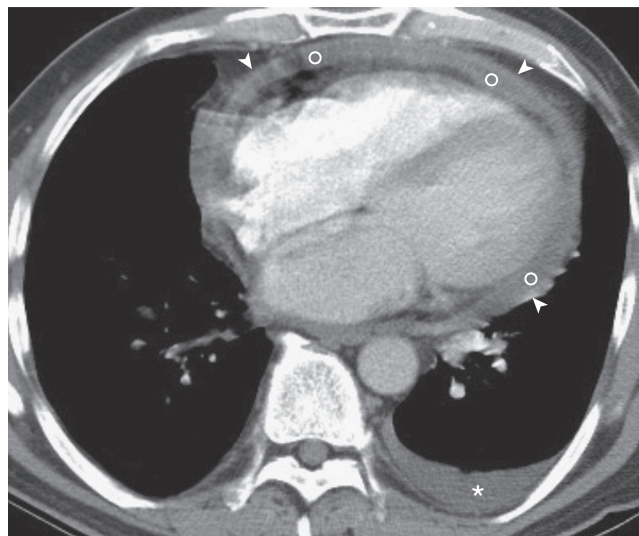


Figure 79-4 Acute pericarditis with left pleural effusion. Axial enhanced chest CT shows a small pericardial effusion (*) with smooth thickening of the pericardium (arrowheads). A small left pleural effusion (*) is present. (Courtesy Michael Gotway, MD.)

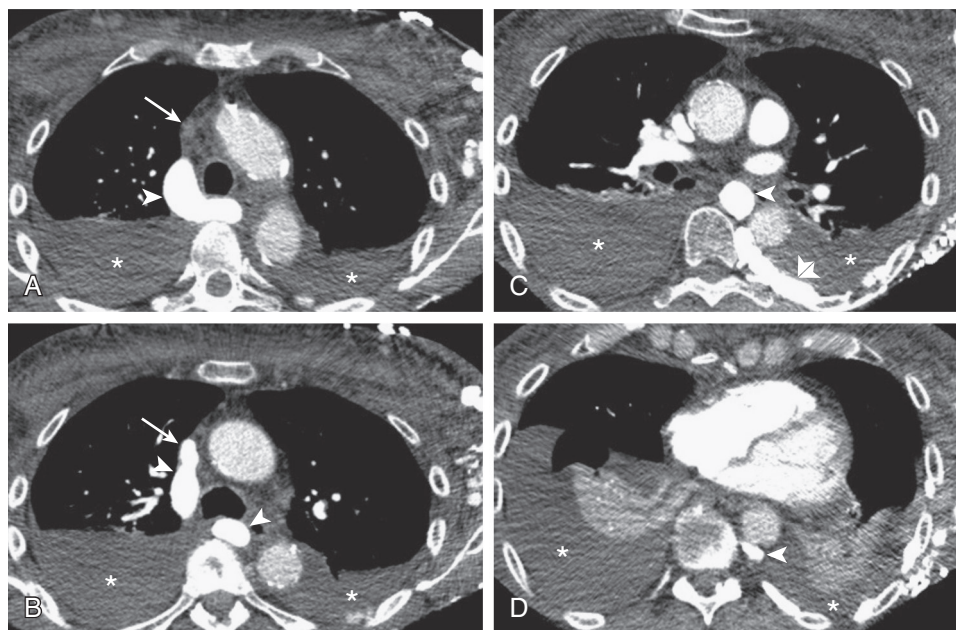
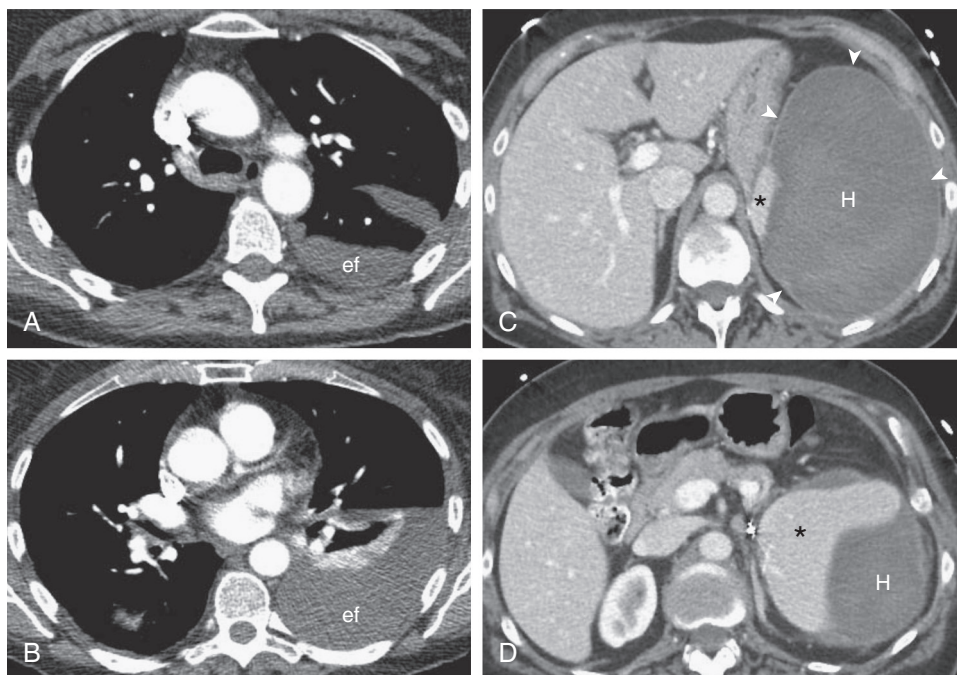
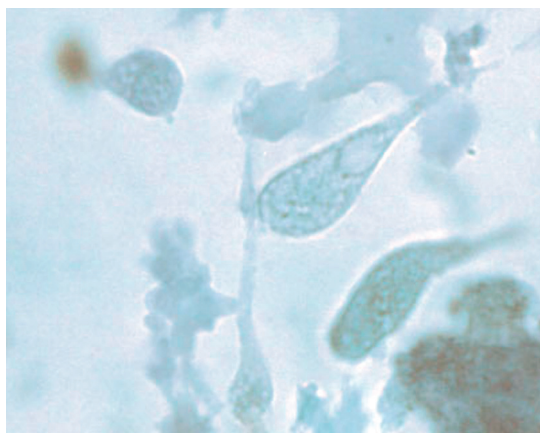


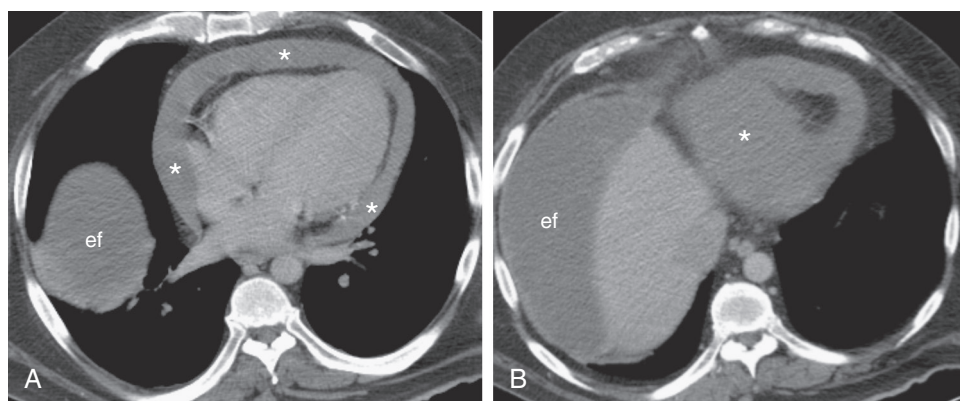
Figure 79-5 Pleural effusions associated with superior vena caval obstruction. A–D, Axial enhanced chest CT in a patient with superior vena caval stenosis following central venous catheter placement shows lack of enhancement of the narrowed superior vena cava (arrow, **A**). The superior vena caval stenosis is supraazygos in location, which results in intense enhancement of the azygos vein (arrowheads, **A–D**) due to retrograde flow through this vessel into the infraazygos portion of the superior vena cava (arrow, **B**). Marked enlargement and intense enhancement of left intercostal veins (double arrowheads, **C**), is present. Bilateral pleural effusions (*, **A–D**) are present. Extensive edema of the subcutaneous fat bilaterally is visible as well, and intensely enhancing left chest wall collateral veins are visible also. (Courtesy Michael Gotway, MD.)



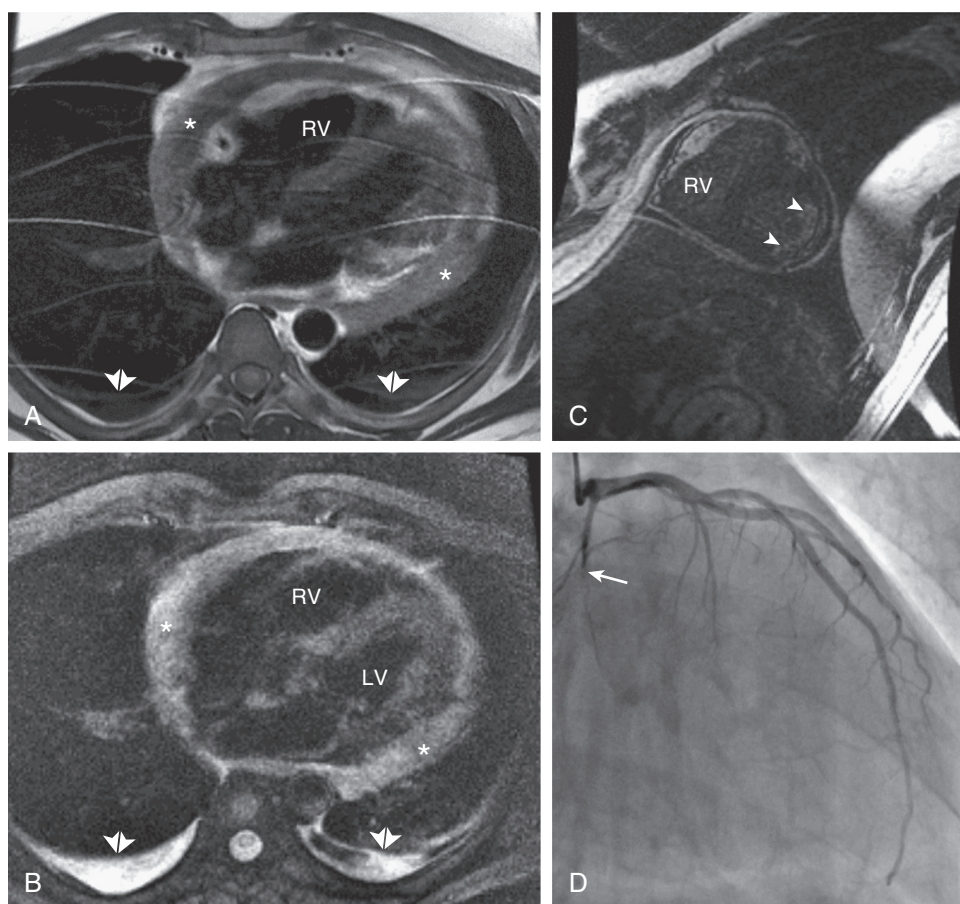
eFigure 79-6 Pleural effusion resulting from intraabdominal pathology. A and B, Axial enhanced chest CT shows a moderately large left pleural effusion (ef). C and D, Enhanced abdominal CT shows a large hypoattenuating structure reflecting a subcapsular splenic infected hematoma (H, arrowheads). Note that the abnormality compresses and deforms the spleen (*). (Courtesy Michael Gotway, MD.)



eFigure 79-7 Comet-shaped cell in rheumatoid arthritis. Cytologic examination of the pleural fluid of a 33-year-old woman with rheumatoid arthritis (RA) and a right pleural effusion. Papanicolaou stain showed elongated macrophages, with oval nuclei and tadpole-like tails. When seen, this feature, along with a granular amorphous background, has been described as characteristic of RA. (From Brucato A, Tombini V, Guffanti C: Clinical image: comet cells in rheumatoid arthritis. *Arthritis Rheumatol* 54:243, 2006. Illustration 1.)



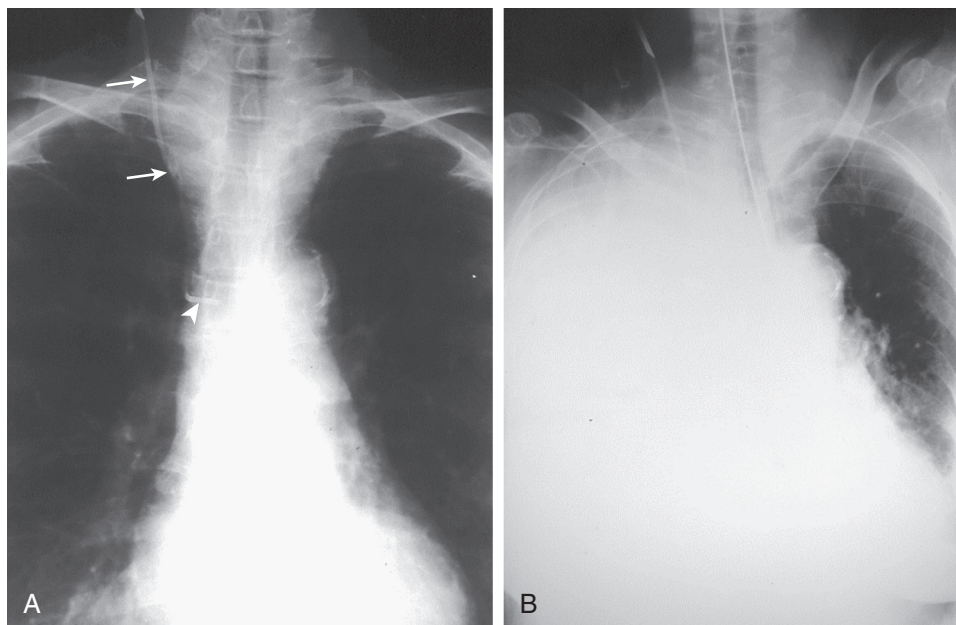
eFigure 79-8 Uremic pleural and pericardial effusions. **A** and **B**, Axial unenhanced chest CT in a patient in renal failure shows a moderate-sized pericardial effusion (*) and a loculated right pleural effusion (ef). The effusions improved following hemodialysis. (Courtesy Michael Gotway, MD.)



eFigure 79-9 Post-cardiac injury syndrome: pleural and pericardial effusions resulting from recent myocardial infarction. The myocardial infarction was unrecognized and the patient presented to MRI with a 3-week complaint of chest pain. **A** and **B**, Axial double (**A**) and triple (**B**) inversion recovery sequences show a moderate pericardial effusion (*). Small bilateral pleural effusions (double arrowheads) are present. **C**, Short axis segmented, T1-weighted inversion recovery late gadolinium enhancement sequence shows subendocardial enhancement (arrowheads) involving the basal and midcavity left ventricular muscle, consistent with myocardial infarction. **D**, Catheter coronary angiogram shows occlusion of the left circumflex coronary artery (arrow). LV, left ventricle; RV, right ventricle. (Courtesy Michael Gotway, MD.)



eFigure 79-10 Nails in a patient with yellow nail syndrome. Nails can be yellow or pale green and are thickened, smooth, and excessively curved from side to side. Nail growth is slow and the nail may separate from the nail bed (onycholysis). The abnormal nails and the formation of pleural effusions are thought to result from a deficit in lymphatic drainage. (From Habif TP: *Clinical dermatology: a color guide to diagnosis and therapy*, ed 5. Philadelphia, 2010, Mosby, Fig. 25-41.)



eFigure 79-11 Massive pleural effusion due to central venous catheter misplacement. **A**, Frontal chest radiograph following right internal jugular venous catheter placement shows the line projected over the expected course of the right internal jugular vein (arrows), although the catheter tip takes an unusual medial course inferiorly (arrowhead). **B**, Frontal chest radiograph performed after the total parenteral nutrition was delivered through the right neck catheter shows development of a massive right pleural effusion, proven to be the result of instillation of total parenteral nutrition fluid into the right pleural space due to the misplacement of the central venous catheter. (Courtesy Michael Gotway, MD.)

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INTRODUCTION**HISTORICAL PERSPECTIVE****INCIDENCE****EPIDEMIOLOGY****PATHOGENESIS****CLINICAL PRESENTATION****PLEURAL FLUID SAMPLING****BIOCHEMISTRY****MICROBIOLOGY****ANTIBIOTIC SELECTION AND DURATION****NUTRITION****EARLY RISK STRATIFICATION****IMAGING TECHNIQUE FOR PLEURAL INFECTION**

Radiology

Bronchoscopy

TUBE SIZE**FIBRINOLYTIC THERAPY****MONITORING RESPONSE TO MEDICAL MANAGEMENT****SURGICAL OPTIONS****SUMMARY****TUBERCULOUS PLEURITIS**

Pathogenesis

Clinical Manifestations

Pleural Fluid

Diagnosis

Treatment

ACTINOMYCOSIS**NOCARDIOSIS****FUNGAL INFECTIONS**

Aspergillosis

Blastomycosis

Coccidioidomycosis

Cryptococcosis

Histoplasmosis

*Pneumocystis jirovecii***VIRAL INFECTIONS**

Primary Atypical Pneumonia

Other Viruses

Acquired Immunodeficiency Syndrome

PARASITIC DISEASES

Amebiasis

Echinococcosis

Paragonimiasis

INTRODUCTION

Of the approximately 1 million cases of hospitalized pneumonia each year in the United States, around 60,000 will develop frank empyema. A further 25,000 are estimated to develop pleural infection for other reasons, including trauma and iatrogenic instrumentation.^{1,2} The annual estimated hospital cost for treating these cases is in excess of \$500 million.^{1,2} The morbidity and mortality rates in patients with pneumonia and associated pleural effusions are higher than for those in patients with pneumonia alone, with one study suggesting the increased relative risk for mortality was 3.4 times higher.³ There also appears to be a rising incidence of pleural infection internationally,⁴⁻⁶ but, despite continued advances in the management of this condition, morbidity and mortality have essentially remained static over the past decade.

HISTORICAL PERSPECTIVE

Infection of the pleural space is an ancient disease, with the earliest recorded description more than 5000 years ago⁷ and the first consistent description of its manifestations and treatment credited to the father of modern medicine, Hippocrates. Open thoracic drainage remained the standard treatment for pleural infection until the influenza pandemic of 1919; however, there was a 70% mortality rate associated with this treatment. In 1918 the U.S. Army Empyema Commission was formed to address the problem. They noted that dogs with empyema died more often if treated with early open drainage rather than delayed intervention, and the commission recommended using the closed-tube

drainage techniques described by Hewitt and Bulau.^{8,9} The commission's summary recommendations were: adequate pus drainage with a closed tube, avoidance of early open drainage, obliteration of the pleural space, and proper nutritional support. A landmark paper by Graham charted the successes seen during this time, with short-term mortality plummeting to 4%.¹⁰ These treatment principles, described almost 100 years ago, remain essentially unchanged to this day. The discovery of penicillin in the 1940s was a major advance that led to a further reduction in mortality. Surgical techniques beyond open drainage were developed in the late 19th century, with thoracoplasty described by Estlander¹¹ and Schede¹² and with decortication described by Fowler and Beck.¹³ It was only recently, however, that *video-assisted thoracic surgery* (VATS) was introduced and is being increasingly used today as the operation of choice in patients requiring surgery for their pleural infection.

INCIDENCE

There have been a number of recent reports from the United States, Canada, Europe, and Asia, all showing a dramatic increase in the incidence of pleural infection. This seems to be the case for both children and adults and, although most data are derived from developed-world populations, this pattern has been replicated around the globe.^{4,6,14-16} The incidence of pleural infection began to rise in the mid to late 1990s. This was captured by Grijalva and colleagues,⁶ who recently examined the trends in parapneumonic empyema in the United States over a 13-year period, demonstrating a doubling in the rates of empyema hospitalizations between

1996 and 2008, from 3.04 to 5.98 per 100,000. Similar results were demonstrated by a Canadian study, which also confirmed the significant disparity in empyema incidence between those 65 years of age and older (17 to 20 per 100,000) and those 19 years of age or younger (2 to 4 per 100,000).⁴

Mortality rates from empyema also seem to be on the rise. A study looking at the population of Utah showed a sixfold rise in mortality from the period 1950–1975 to the period 2000–2005.¹⁷ In a large series, inpatients were found to have a mortality up to 18% in the short term,¹⁸ with those in intensive care experiencing mortality as high as 41%.¹⁹ In a large multicenter trial from the United Kingdom, patients with an average age of 59 were shown to have a mortality rate 1 year after treatment for empyema between 8% and 20%.²⁰

The explanation for the increase in empyema incidence is not clear. With the introduction of the heptavalent pneumococcal conjugate vaccine in 2000, a reduction in pneumococcal empyema in children from serotypes covered by the vaccine may have led to an increase of cases caused by nonvaccine serotypes.²¹ This may account for an increase in adult infection with these serotypes. This, however, does not explain the increase in staphylococcal empyema seen in the series by Grijalva and associates.⁶

EPIDEMIOLOGY

Pleural infection is seen in patients of all ages but has a bimodal distribution, with a peak in childhood and a further rise in older adults. Men are affected twice as often as women,²² and this is illustrated in Figure 80-1, which shows the age and sex distribution of the large cohort of adult patients from the *Multicenter Intrapleural Sepsis Trial* (MIST) 1 study.²³ Pleural infection is also more common in those with diabetes, alcohol dependency, or drug addiction and those with rheumatoid arthritis.^{22,23} Poor dentition and aspiration have also been shown to be risk factors.¹⁸

The underlying etiology of pleural infection is varied, with most cases being of community origin. Although this

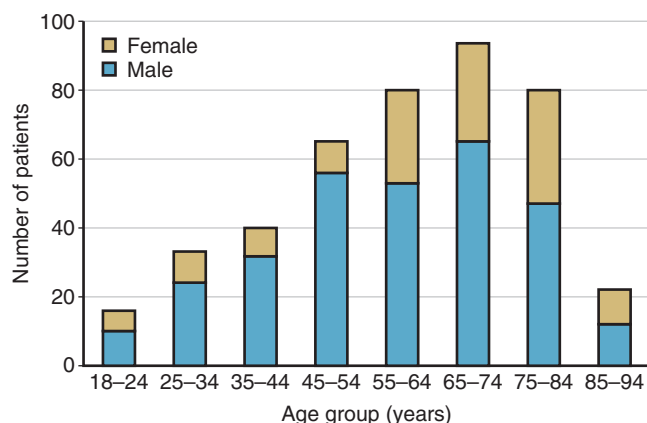


Figure 80-1 The age and sex distribution of pleural infection in adults in one large U.K. cohort. The disease is more common in males and the peak incidence in adults is in the 65- to 74-year-old age-range. (Data from Maskell NA, Davies CW, Nunn AJ, et al: U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 352:865–874, 2005.)

often results from a community-acquired pneumonia, a sizable proportion of cases show no evidence of consolidation on *computed tomography* (CT) imaging and are thought to have been acquired through hematologic spread or direct translocation from the oropharynx.²⁴ The next largest group are hospital-acquired pleural infections, which are often the result of prolonged hospital admissions for other initial reasons, or complications following surgery or invasive procedures. For example, pleural infections and other pleural complications are common after lung transplantation.^{24a} Other potential causes include direct (transdiaphragmatic) spread of abdominal sepsis, blunt or penetrating chest trauma, esophageal perforation, or rupture of a peripheral lung abscess into the pleural space.^{23,25,26}

PATHOGENESIS

The evolution of a pleural infection can be divided into three stages, which may overlap with each other. The first, *exudative* stage is characterized by the rapid outpouring of sterile pleural fluid into the pleural space. Some of this comes from the interstitial spaces of the lung and some from the parietal pleura because of increased permeability. The pleural fluid will have a low white blood cell count and *lactate dehydrogenase* (LDH) level, together with a normal glucose level and pH.^{27,28} At this stage chest tube drainage is rarely required, and antibiotics alone should suffice.

The second, *fibropurulent* stage evolves if bacteria invade the sterile exudative effusion. During this stage there is an accumulation of leukocytes, bacteria, and cell debris together with increased amounts of pleural fluid. Fibrin is then deposited over the visceral and parietal pleura, and there is a tendency at this stage for loculations to form within the pleural fluid, which may limit effective drainage of the effusion with a chest tube. The pleural fluid pH and glucose level will be lower, and the LDH level will rise, often dramatically.

The final *organization* stage is characterized by aggressive fibroblast growth over the pleural surfaces to form an inelastic membrane called the “pleural peel.” This is often extensive and reduces lung functionality considerably. The pleural fluid is often thick, consisting of pus and cellular debris.

Primary empyema instead arises by direct translocation from the oropharynx or by hematogenous spread. In this circumstance, bacteria invade the pleural space as the initial insult leading directly to the fibropurulent stage.

CLINICAL PRESENTATION

Although there have been some extremely unusual cases,⁴⁷ the classic presentation of prolonged pleural infection is difficult to separate from that of pneumonia, whereby patients suffer with dyspnea, cough, fever, malaise, and perhaps pleuritic chest pain.²⁹ In fact, a significant number of patients with pneumonia will go on to develop a parapneumonic effusion without a change in symptoms to offer clues to its existence. Furthermore, there is no symptomatic discriminator between patients with effusions determined to be uncomplicated or complicated.

An *uncomplicated* parapneumonic effusion is defined here as an effusion with a glucose level above 40 mg/dL, pH above 7.2, and negative Gram stain and culture without loculation on ultrasonography. A *complicated* parapneumonic effusion is either loculated on ultrasonography or has a glucose level below 40 mg/dL or a pH below 7.2. A high index of suspicion should be maintained for those patients who fail to improve within a few days of initiating antibiotic therapy³⁰ or who exhibit persistent fever or signs of sepsis, with further investigations following rapidly.³¹ With long-lasting infection, the course of patients with pleural infection can mimic the course of those with malignant processes, often with significant weight loss, sweats, and loss of appetite.

PLEURAL FLUID SAMPLING

Abnormal signs, symptoms, or blood test results in the context of a suggestive radiograph should lead to confirmation of the presence of an effusion and early sampling of the fluid. However, in a small retrospective series, Skouras and colleagues suggested that parapneumonic effusions less than 2 cm in thickness on chest CT scan can be treated with antibiotics without sampling because they are unlikely to become complicated or require intervention.³² Such patients would still require close monitoring and appropriate antibiotic therapy.

BIOCHEMISTRY

In cases where overt pus is revealed on initial aspiration, no further biochemical analysis is necessary, and chest tube placement is required. Microbiologic analysis is, however, still important in these cases.

Pleural fluid pH may be the best discriminator for a complicated pleural process during initial investigations, with many studies demonstrating better patient outcomes when drainage is instituted based on the early biochemical changes related to infection. In the meta-analysis by Heffner and coworkers,³³ the receiver operating characteristic for the diagnostic accuracy of pleural fluid pH showed that, if the pH was less than 7.2, a chest tube was likely to be necessary to resolve the pleural infection. A pH analysis (or glucose analysis) should therefore be performed in all cases where the diagnosis of pleural infection is being considered. The pH needs to be measured using a blood gas machine because pH strips and pH meters are not accurate enough to be of value.³⁴ Some institutions rely on the glucose concentration instead, finding it as useful a test and less prone to error.

Current guidelines therefore regard a pH of 7.2 as diagnostic of complexity, making this the definitive “cutoff” below which drainage should take place. It should be noted that fluid pH values may be appreciably altered by minor variations in sampling and processing techniques, which can therefore have significant effects on management strategy. In a study of pleural fluid pH, Rahman and associates reproduced several common scenarios that could result during testing. Even small amounts of residual heparin or local anesthetic in a sample syringe could dramatically

lower pH; residual air in the syringe could increase pH (if 1 mL of air was in the syringe with 2 mL of fluid, the pH rose by an average of 0.08). These errors represented a clinically significant change in over two thirds of patients.³⁵

As mentioned earlier, when pH measurements are not easily obtainable, a glucose level can be useful.³³ Samples should be collected in a blood glucose tube and sent to the laboratory, with a value of less than 2.2 mmol/L (40 mg/dL) indicating the need for chest tube drainage.^{33,35} It should be noted that pH and glucose level can also be low in malignant pleural effusions, rheumatoid pleural effusions, and pleural effusions secondary to esophageal rupture; therefore their value for guiding chest tube drainage should be restricted to the setting of parapneumonic effusions.

LDH measurements tend to be high in all cases of complicated parapneumonic effusions and empyema. LDH tends to rise rapidly as the pleural infection progresses through the fibropurulent and organizing stages of the disease. When a patient is being treated with antibiotics alone, a rising LDH on repeated thoracentesis may indicate that an effusion is not responding and chest tube drainage should be considered.

MICROBIOLOGY

The bacteriologic features of culture-positive pleural fluid have changed since the introduction of antibiotics. In the preantibiotic era, the commonest pathogens were *Streptococcus pneumoniae* or *Streptococcus haemolyticus*.³⁶ After this period, between 1955 and 1965, *Staphylococcus aureus* was the commonest causative organism, with the major shift in the frequency and type of causative organisms attributable to the introduction of antibiotics. There also appear to be global and regional differences in the frequencies and range of the causative organisms.

In a study of patients with pleural infection,³⁷ standard culture methods were combined with nucleic acid amplification to discern causative organisms, attaining a 74% overall identification rate. Cloning techniques were also applied to a small number of cases (3%), limited by cost. Nucleic acid amplification identified an organism in 38% of the culture-negative samples, with the same organism found by both culture and nucleic acid amplification (or cloning) in 35% of cases.

In this cohort of mostly community-acquired pleural infections (85%), the *Streptococcus anginosus* group (formerly *Streptococcus milleri* group) was the predominant species of bacteria. These and other gram-positive aerobes were implicated in 65% of cases, confirming the inherent differences in etiology of empyema compared to pneumonia. Other organisms included staphylococci (11%), gram-negative aerobes such as *Escherichia coli* (9%), and anaerobes (20%). Polymicrobial samples were identified in 20% of cases, but this may well underestimate the true incidence, as suggested by the results using cloning in the study and the fact that anaerobes, which have been identified in up to three quarters of cases of community-acquired pleural infection in other series, may have been underrepresented in this series.³⁸

Hospital-acquired pleural infections made up only 15% of this cohort overall but were quite different from the

Table 80-1 Summary of 2175 Culture-Positive Cases of Pleural Infection (including Both Hospital-Acquired and Community-Acquired Cases) in English Language Literature between 1996 and 2012

Organism—Aerobes (Gram-Positive)	Percent	Organism—Aerobes (Gram-Negative)	Percent	Anaerobes	Percent
<i>Streptococcus pneumoniae</i>	32	<i>Escherichia coli</i>	3	<i>Fusobacterium</i>	2
<i>Streptococcus milleri</i> group	10	<i>Klebsiella</i> spp.	3	<i>Bacteroides</i>	2
Other <i>Streptococcus</i> spp.	10	<i>Haemophilus influenzae</i>	1	<i>Peptostreptococcus</i>	6
<i>Staphylococcus aureus</i>	10	Other coliform spp.	2	<i>Prevotella</i>	1
<i>Streptococcus pyogenes</i>	2	<i>Proteus</i>	1	Mixed anaerobes	1
Methicillin-resistant <i>S. aureus</i>	2	<i>Enterobacter</i> spp.	2	Other	6
<i>Enterococcus</i> spp.	1	<i>Pseudomonas aeruginosa</i>	3		
Total	67		15		18

community-acquired pleural infections. Most (58%) cases were attributed to gram-negative organisms or staphylococci, with over 70% of the latter due to methicillin-resistant *S. aureus*.³⁷ A similar gram-negative predominance has been found among patients in the intensive care setting.¹⁹ The bacteriology of hospital-acquired pleural infection is therefore very different from that of community-acquired pleural infections and requires different empirical antibiotics at presentation. Table 80-1 summarizes the frequency of over 2000 culture-positive cases reported in the English literature between 1996 and 2012.

The use of blood culture bottles for culturing pleural fluid can increase yield; Menzies and colleagues³⁹ provided the first comparative, prospective evidence of increased microbiologic diagnostic yield in pleural infection using the BACTEC blood culture bottle system (Becton, Dickinson U.K.). Addition of blood culture bottle-inoculated pleural fluid at the bedside to standard pleural fluid culture increased microbiologic diagnostic yield by 21%, and, in a small proportion of cases (4%) where the standard culture was positive, use of the blood culture bottles suggested the presence of additional organisms that would alter antibiotic management. These findings are further supported by the lack of false-positive culture results from noninfected control samples. The standard cultures were positive in 29% of cases in which the pleural fluid cultured in blood culture bottle cultures were negative, suggesting potential organism preference for certain growth media. This study demonstrates a significant increase in diagnostic yield using a widely available and relatively inexpensive technique, suggesting that inoculation of pleural fluid into blood culture bottles should be added to standard pleural fluid culture routinely.

ANTIBIOTIC SELECTION AND DURATION

The initial empirical antibiotic selection at presentation should be based on whether the pleural infection is community acquired or hospital acquired. Hospital-acquired pleural infection has a different range of causative organisms and a considerably higher mortality (Fig. 80-2).

Because anaerobic bacteria are commonly seen in this setting and often fail to grow in culture, they should be

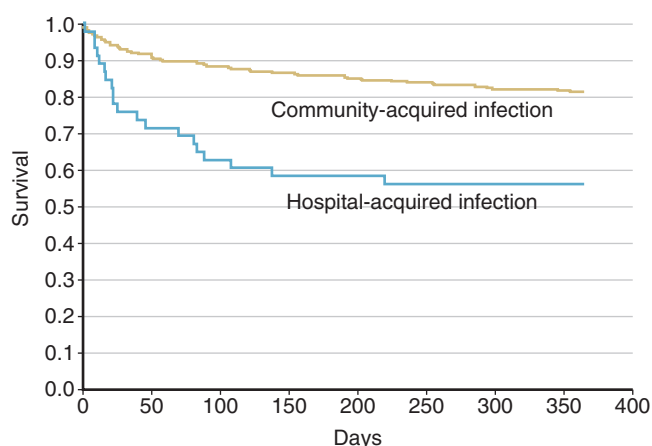


Figure 80-2 Survival following pleural empyema. Kaplan-Meier survival curves comparing community-acquired and hospital-acquired pleural infection in the Multicenter Intrapleural Sepsis Trial cohort, showing the significantly higher mortality rates in those with hospital-acquired pleural infection. (From Maskell NA, Batt S, Hedley EL, et al: The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med* 174:817–823, 2006.)

covered empirically in all cases of presumed pleural infection. Liaison with local microbiologists is invaluable in deciding the best combination of antibiotics to use, because resistance patterns vary significantly from one geographic region to the next.

There are no robust studies looking at the optimal duration of antibiotics for pleural infection. In our experience, if a patient is ill enough to require hospitalization, then intravenous antibiotics are usually indicated. When converted to an oral equivalent, perhaps before discharge, a further 1 to 3 weeks of antibiotics is commonly needed. The length of the antibiotic course is governed by the inflammatory markers (*C-reactive protein* [CRP]) and any ongoing, often mild fever, rather than by the radiologic appearance, which often lags behind clinical improvement.

The potential role of intrapleural antibiotics is not often considered and randomized, controlled trial data are lacking. Because most intravenous antibiotics penetrate into the pleural space in suitable concentrations, there is no current role for intrapleural antibiotic use in this setting. However, it should be noted that aminoglycosides do not penetrate the pleural space well and should be avoided.

NUTRITION

Patients with pleural infection, particularly those with empyema who have had a delayed presentation, suffer the protracted catabolic consequences of chronic infection. A low albumin level has been shown to be a marker of poor outcome in one large published series.⁴⁰ Addressing the patient's nutritional status at presentation is often overlooked and should be an early priority alongside tube drainage and the prescribing of suitable antibiotics. Early nutritional assessment should be seen as mandatory.

EARLY RISK STRATIFICATION

A reliable and sensitive clinical prediction model of poor outcome in pleural infection would enable clinicians to triage patients according to risk and to select the more aggressive and expensive therapies for patients who may otherwise have the poorest outcomes. To date, there are no robust validated methods for identifying high-risk patients at presentation with pleural infection. Selection for surgery has previously been based on duration of symptoms, pleural fluid purulence, size of infected pleural fluid collection, and the degree of parietal pleural thickening on imaging. In a cohort study of 85 sequential patients, clinical care was based on structured treatment guidelines to assess whether the generally accepted baseline predictors reliably identified patients at high risk. Only pleural fluid purulence had predictive power for a poor outcome, and this was insufficiently sensitive and specific to be of clinical value.⁴¹ In a second study, this finding was confirmed and predictors of residual pleural thickening were identified, although thickening was uncommon and not associated with clinical disability.⁴²

Although there are likely to be complex interactions between genetic and environmental factors that contribute to the development of pleural infection,²¹ these have not yet been determined. There are, however, certain patient risk factors, particularly chronic alcohol excess and intravenous drug use, which likely increase the risk because of aspiration of gastric contents. In addition to these, Chalmers and colleagues⁴³ described four other independent risk factors that seem to predict the development of pleural infection: serum albumin level below 30 g/L, serum CRP greater than 100 mg/L, platelet count above $400 \times 10^9/L$, and serum sodium level below 130 mmol/L. This study noted that none of the routinely employed pneumonia or sepsis scores were adequate in determining this outcome and suggested a score based on these six factors, although this still requires validation. Interestingly, patients with chronic obstructive pulmonary disease were found to be at lower risk for developing pleural infection, perhaps due to a background level of generalized inflammation causing an attenuated response to a pleural bacterial challenge.⁴⁴

For patients with confirmed pleural infection, those at greatest risk for poor outcome may be identifiable.⁴⁵ For the patients recruited to the U.K. MIST1 trial, an outcome score was developed and subsequently validated using a second cohort from the MIST2 trial. Of the 32 baseline characteristics analyzed, 5 presenting factors (age, serum urea level, serum albumin level, fluid purulence, and likely origin of

infection) could predict the eventual outcome, with patients divided into low-, medium-, or high-risk groups. Patients in the lowest risk group were found to have a mortality of less than 5% at 3 months, whereas those in the highest were found to have a mortality approaching 50% over the same time period. The main potential advantage of this stratification system is in allowing physicians to institute fibrinolytics or surgery earlier in the clinical presentation when they are perhaps more likely to be successful.

IMAGING TECHNIQUES FOR PLEURAL INFECTION

Radiologic tests are vital in the initial diagnosis and management of pleural infection. Chest radiography, CT, and ultrasonography are all useful tools in the management of patients with pleural infection.

RADIOLOGY

The presence of fever, pleuritic pain, and pleural effusion should always alert the physician to the possibility of pleural infection. Pleural fluid loculation can result in a D-shaped subpleural opacity (Fig. 80-3 and eFig. 80-1A) on chest radiography, which could be misinterpreted as a lung mass if one is not aware of this common appearance. In ventilated patients in the supine position, free fluid may track posteriorly and cause haziness of the hemithorax on the chest radiograph.

Thoracic ultrasonography (see eFig. 80-1) is advisable in all cases of suspected pleural infection because it can provide important information and it allows accurate chest tube placement into the most appropriate part of the pleural collection. Use of ultrasonography has also been shown to reduce iatrogenic injury.⁴⁶ Ultrasonography is also more accurate than CT imaging in detecting loculations and



Figure 80-3 Pleural empyema. Frontal chest radiograph showing the D-shaped opacity, suggesting an extraparenchymal process, which is commonly seen in cases of pleural infection.

septations and can detect the presence of small quantities of pleural fluid not visible on chest radiography.

Chest CT (see [eFig. 80-1H–K](#)), particularly contrast-enhanced chest CT ([eFig. 80-2](#)), is not necessary in all patients with pleural infection and should be reserved for those with persistent collections despite attempted chest tube drainage, those who may have a suspected proximal obstructing lesion, and those in whom surgery is being considered. It will provide detailed information about fluid loculation ([Video 80-1](#)), identify chest tube position, and differentiate between empyema and lung abscesses (see [eFig. 33-7B–E](#)) when there is diagnostic uncertainty ([Fig. 80-4](#) and [Table 80-2](#)).

Magnetic resonance imaging is usually reserved for those patients who are unable to undergo CT imaging or for persons at high risk from irradiation. It is very good at visualizing septations and loculations within the pleural fluid ([Fig. 80-5](#)).

BRONCHOSCOPY

Practitioners should be aware that a proximal obstructing lesion may be the cause of an empyema. Although uncommon (less than 4% in one large series), it should be considered in patients with a suggestive plain chest radiograph, especially one in which the mediastinum is shifted toward the side of the effusion, or in those failing to respond to

simple first-line management. A bronchoscopy and chest CT would be the investigations of choice if a bronchial obstruction is suspected. There is no role for routine bronchoscopy in all patients with pleural infection.

When an empyema is discovered distal to an obstructed bronchus, the underlying cause is usually malignancy. Once histologic confirmation has been obtained, relief of the obstruction with radiation therapy, laser resection, or stent insertion might allow the empyema to be treated effectively. Where this is not possible, prolonged oral antibiotics may be useful to prevent ongoing sepsis.

Table 80-2 Key Differences between the Radiographic Appearance of Pleural Infection and Lung Abscesses

Empyema	Lung Abscess
Lenticular shape	Rounded
Surrounding lung often compressed	Boundary between lung and fluid indistinct
Margins of collection create obtuse angles with chest wall	Makes contact with chest wall at acute angle
Thick smooth wall	Thick irregular wall
No vessels close by	Vessels seen passing through or near collection

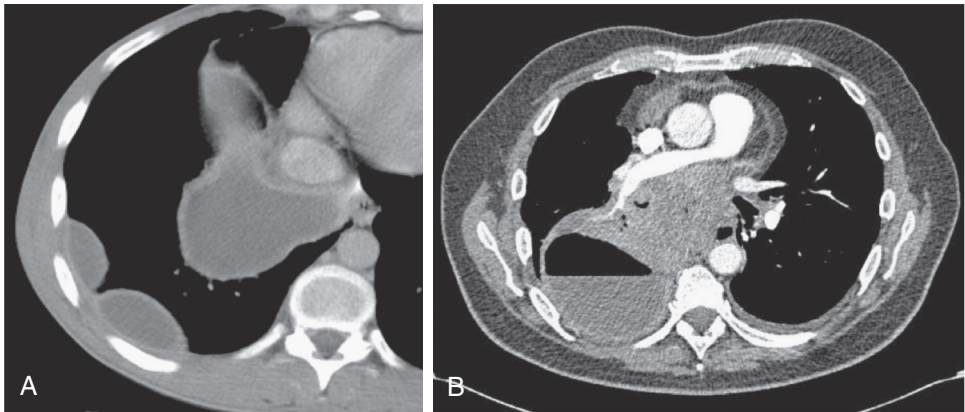


Figure 80-4 Contrast-enhanced chest CT enables discrimination of pleural from parenchymal lesions. **A**, Empyema. **B**, Lung abscess. Also see [Table 80-2](#) and Chapter 18 for features that differentiate between lung abscess and empyema.

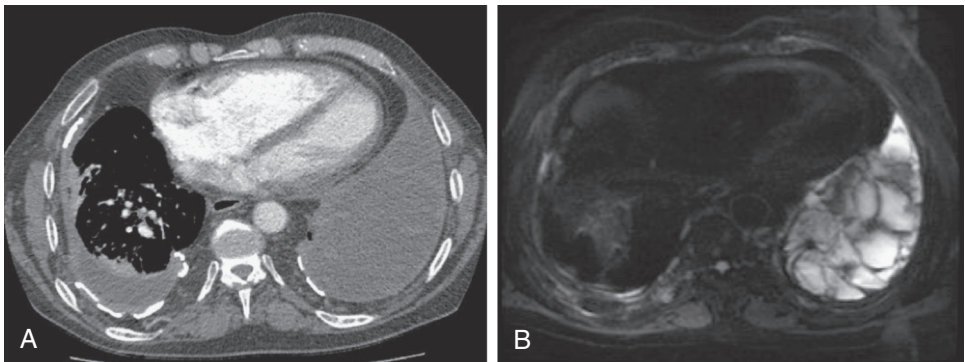


Figure 80-5 Magnetic resonance imaging (MRI) of pleural empyema. **A**, Contrast-enhanced chest CT revealing a complex, large left pleural fluid collection secondary to pleural infection. **B**, T2-weighted MRI in the same patient revealing the presence of multiple septations and loculations.

TUBE SIZE

Over the past decade there has been a shift away from large-bore catheters to small-bore chest tubes inserted by the Seldinger technique. This change in practice is not so much the result of large, well-conducted, randomized controlled trials but more to do with the relative ease of the technique and the benefits of the smaller drains, which cause the patient less pain during insertion and while in situ.⁴⁷

For cases of pleural infection, we recommend initial placement of a small-bore (12-French) chest tube under ultrasonographic guidance and then management with regular saline flushes to ensure that it does not become occluded. Guidelines recommend the instillation of 30 mL saline every 6 hours via a three-way stopcock. If this fails to drain the effusion effectively, a large-bore drain may occasionally be necessary. It is more common for tubes to be replaced not because of obstruction but because they have become dislodged or fall out as a result of failure to secure the chest tube correctly.

Although there are no randomized data comparing large-bore with small-bore chest tubes for pleural infection, one study reviewed the 405 patients who participated in the MIST trial. As part of the study, data were collected about the size of chest tube used. No difference between small- and large-bore tubes was found in the frequency with which patients either died or required thoracic surgery. However, those with larger chest tubes reported significantly more pain both at the time of insertion and while the drain remained in situ.⁴⁸

In another study of 103 patients with pleural infection, the small-bore chest tubes provided definitive treatment in 78% of cases,⁴⁹ similar to the success rates of two other series in which large-bore chest tubes were used.^{50,51} It should be noted that, in this study, radiologists guided tube placement, which almost certainly helped the result. With this in mind, we recommend that chest tubes should be placed under ultrasonographic guidance in the largest locule in a dependent part of the pleural effusion.

FIBRINOLYTIC THERAPY

The use of fibrinolytic agents to disrupt fibrinous pleural septations was first described by Tillett and Sherry in 1949,⁵² who used partially purified streptococcal fibrinolysin that contained both streptokinase and streptodornase (a DNase) to drain infected postoperative hemothoraces. It was associated with immunologic side effects and did not become routine practice.

Streptokinase is a proteolytic enzyme derived from a bacterial protein of group C β -hemolytic streptococci. It forms a complex with plasminogen that then converts additional circulating plasminogen to plasmin. Plasmin lyses fresh fibrin clot and digests prothrombin and fibrinogen. Because it is derived from a bacterial source, it is antigenic, unlike urokinase.

In a series of 24 patients, Davies and coworkers⁵³ began to allay fears regarding intrapleural thrombolysis, which was found to be safe and also led to improvements in clinical outcomes. Other studies tended to focus more on the use of

urokinase in loculated effusions, with benefits being demonstrated in terms of a reduction in treatment failure (as judged by surgical referral or death), reduced length of hospital stay, and better surgical outcomes.⁵⁴⁻⁵⁶ However, these studies were often small trials or case series, which limited their ability to be generalized.

The 2005 MIST1 trial²³ recruited 454 pleural infection patients from the United Kingdom to receive either intrapleural streptokinase or placebo. Entry criteria reflected real-world practice with a strong reliance on local physician diagnosis, antibiotic choice, chest tube use, and surgical referral. The trial was unable to show any significant benefit from the use of streptokinase in either surgical referral or death. There was also no improvement in the length of stay or in any signal in any subgroup analysis. However, a Cochrane review found that intrapleural fibrinolytics conferred benefit both in reduced treatment failure and reduced need for surgical intervention in pleural infection, but not reduced mortality.⁵⁷ The choice of streptokinase as the primary lytic may have contributed to these results, because its mechanism of action relies upon using a proportion of the intrapleural plasminogen to form an active complex before the rest can be converted to plasmin.⁵⁸ Nonetheless, the 2010 British Thoracic Society guidelines advised that intrapleural fibrinolytics should not be used routinely, but might be considered in select cases.⁵⁹

Following this, in the blinded, 2-by-2 factorial MIST2 trial,²⁰ 210 patients with pleural infection were randomly assigned to receive one of four study treatments for 3 days: intrapleural *tissue plasminogen activator* (t-PA) and DNase, t-PA and placebo, DNase and placebo, or double placebo. The primary outcome was the change in pleural opacity, measured as the percentage of the hemithorax occupied by effusion on chest radiography on day 7 as compared with day 1. The mean (\pm SD) change in pleural opacity was significantly greater in the t-PA–DNase group than in the double placebo group ($-29.5\% \pm 23.3\%$ versus $-17.2\% \pm 19.6\%$; difference, -7.9%); the change observed with t-PA alone and with DNase alone ($-17.2\% \pm 24.3\%$ and $-14.7\% \pm 16.4\%$, respectively) was not significantly different from that observed with placebo. The frequency of surgical referral at 3 months was lower in the t-PA–DNase group than in the double placebo group (2 of 48 patients [4%] versus 8 of 51 patients [16%]; the odds ratio for surgical referral, 0.17, and was greater in the DNase group (18 of 46 patients [39%]) than in the placebo group (odds ratio, 3.56). Combined t-PA–DNase therapy was associated with a reduction in the hospital stay as compared with double placebo (difference, -6.7 days); the hospital stay with either agent alone was not significantly different from that with placebo.

The authors concluded that intrapleural t-PA–DNase therapy improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. Treatment with DNase alone or t-PA alone was ineffective; indeed, DNase monotherapy was associated with an increase in surgical referrals by a factor of 3. Reduction in the infected pleural fluid collection was roughly doubled with the use of the combination therapy (with clearing of approximately 30% of the ipsilateral hemithorax volume and about a 60%

reduction in the baseline pleural collection). This treatment was not associated with an excess of adverse events. In a report from eight centers, the use of tPA/DNase also showed benefit, although with some pain and bleeding, in those who did not respond to antibiotics and thoracostomy drainage.^{59a} In summary, this approach looks promising, although a larger trial is needed to confirm safety and guide physicians on which patient groups are likely to gain the most benefit.

MONITORING RESPONSE TO MEDICAL MANAGEMENT

Identifying patients who are not responding to medical management can be a challenging task. Improvements in the imaging appearance often lag behind clinical improvement and therefore, in our opinion, are not a good indicator of the need for further intervention. The best markers of response to medical management include a falling CRP (halving in value and ideally falling to below 100 mg/L), the settling of a spiking temperature, and clinical signs associated with resolution of sepsis. If these markers are all improving, then further interventions with additional chest tubes or surgery rarely becomes necessary.

When patients look as if they have avoided surgery by the narrowest of margins, prolonged oral antibiotics (for 4 to 6 weeks) and close follow-up as outpatients with monitoring of the chest radiograph and CRP is advised.

SURGICAL OPTIONS

Patients are usually referred for surgical intervention after initial medical treatment failed or if they presented late with highly organized empyemas that demonstrate significant pleural thickening and loculation. Practice varies, with some centers having an extremely low threshold for early surgery.⁶⁰ The point at which medical management is deemed to have “failed” is necessarily ill defined, but one important indicator would be signs of ongoing sepsis despite attempted chest tube drainage and adequate antibiotic therapy. Another important consideration is the risk for long-term respiratory embarrassment without the removal of the fibrin and loculated fluid.

Modern surgical options are varied and may be tailored to the individual. VATS typically requires general anesthetic and single-lung ventilation but can be performed under local anesthetic in patients deemed too high risk for a general anesthetic (Fig. 80-6 and Video 80-2). Although originally used for thorough pleural débridement,⁶¹ VATS can now be used to perform decortication in particularly advanced or chronic empyema, although this latter situation may reduce the chance of successful outcome.⁶² Despite this, overall success rates for VATS, measured by resolution of sepsis and clinical stability, exceed 85%.

Open decortication for empyema was formerly a mainstay of treatment, but its role is likely to become increasingly marginalized as VATS surgery becomes commonplace.⁶³ It is therefore now used when less invasive approaches have failed. Decortication following thoracotomy allows com-

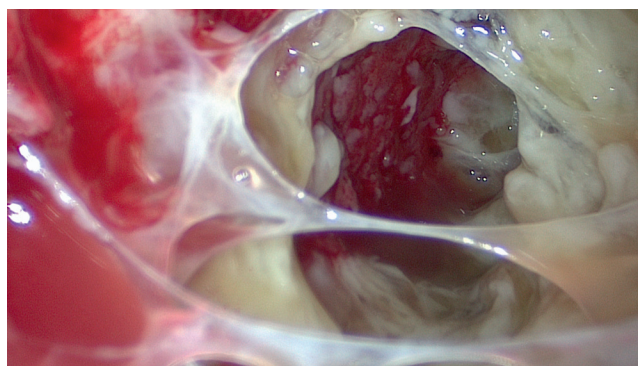


Figure 80-6 Empyema in a 26-year-old woman at the time of video-assisted thoracic surgery (see Video 80-2).

plete mobilization of the lung, which is particularly useful in cases of trapped lung.⁶⁴ A study from 1996 described a mortality of about 3% for this operation.⁶⁵

When managing patients with pleural infection in the acute stages, decortication should only be considered for the control of pleural infection. Decortication should not be performed just to remove thickened pleura because such thickening usually resolves spontaneously over the subsequent 4 to 6 months.

For patients who have recurrent or particularly complex empyema, small prosthetic devices may be inserted between the ribs to maintain a drainage route. The more permanent way to achieve this effect is to perform an open-window drainage. This involves the resection of two or three ribs to create a direct opening to the thoracic cavity, which affords the opportunity to pack the pleural space.⁶⁶ The advantage of this open flap (Eloesser flap, eFig. 80-3) is that it creates a skin-lined fistula that provides drainage without tubes. Should methods such as these fail, a thoracomyoplasty may become necessary, whereby a large muscle is used to pack the thoracic cavity. This is usually reserved for patients with bronchopleural fistulas (see eFig. 80-3B), trapped lung, or postoperative empyema.⁶⁴

A more conservative approach, which may be applied in highly selected patients who have high risks for surgery, is the insertion of an indwelling pleural catheter together with long-term oral antibiotic therapy.⁶⁷ In our experience, this approach can occasionally be extremely useful and would certainly warrant further research.

SUMMARY

The worldwide incidence of pleural infection due to bacteria is rising, with a changing spectrum of causative organisms and underlying etiology. Early recognition and instigation of simple therapies such as antibiotics, nutritional supplements, and chest drainage remains the cornerstone of good management. For patients who have incomplete drainage, intrapleural fibrinolytic therapy with t-PA combined with DNase appears to offer a good alternative to surgical intervention. However, further trials are needed in this area to ascertain its place in the treatment algorithm. Meanwhile, minimally invasive surgical intervention such as VATS is being practiced more widely, and

frailer patients are increasingly being offered definitive surgical intervention, under local anesthetic if necessary.

TUBERCULOUS PLEURITIS

In many parts of the world, the most common cause of an exudative pleural effusion is *tuberculosis* (TB). However, in the United States, tuberculous pleuritis is relatively uncommon, with only 7549 cases reported in the 10 years from 1993 to 2003; the number of cases of pleural TB constituted 3.6% of the total number of cases of TB seen over this period.⁶⁸ In some African countries, the incidence of pleural involvement in TB appears to be much higher because the percentage of patients with TB who have a pleural effusion exceeds 30%.⁶⁹ The effect of *human immunodeficiency virus* (HIV) on the incidence of tuberculous pleurisy is still uncertain; in some studies HIV appears to increase the incidence, and in others it does not.⁶⁹ Some authors suggest that pleural TB in those with HIV has a different pathogenesis compared to the disease in those without HIV,⁷⁰ but the confusion may in part be due to the state of immunocompromise. The prevalence of tuberculous pleurisy is also higher in patients with CD4 counts above 200 cells/ μ L than in those with CD4 counts below 200 cells/ μ L,⁷¹ in keeping with the understanding of the role of delayed hypersensitivity in the development of the effusion.

A pleural effusion as a manifestation of TB has been likened to a primary chancre as a manifestation of syphilis. Both are self-limited and of little immediate concern, but both may lead to serious disease many years later. Most instances of pleural effusion secondary to TB resolve spontaneously; however, if patients are not treated with antituberculous therapy, they have about a 50% likelihood of developing active TB in the subsequent 5 years.⁷⁷

PATHOGENESIS

A tuberculous pleural effusion can either be a sequel to a primary infection acquired 3 to 6 months previously or represent reactivation TB. A molecular epidemiologic study confirmed that tuberculous pleurisy is usually an early manifestation of TB infection.⁷² Delayed hypersensitivity appears to play a large role in the pathogenesis of tuberculous pleuritis. In sensitized animals, the intrapleural injection of tuberculin protein results in the rapid appearance of an exudative pleural effusion.⁷³ When the animals are given antilymphocyte serum, the development of the effusion is suppressed. The observation that pleural fluid cultures are negative in approximately 80% of patients with tuberculous pleuritis supports the contention that delayed hypersensitivity also plays a large role in the development of tuberculous pleural effusions in humans. Although delayed hypersensitivity to tuberculin protein is believed to be primarily responsible for tuberculous pleuritis, about one third of patients with tuberculous pleuritis have a negative tuberculin skin test result when first evaluated. The negative skin test is thought to be due to the sequestration of circulating purified protein derivative-reactive lymphocytes in the pleural space or suppressor cells, either adherent monocytes or Fc-bearing lymphocytes, that are found in the blood but not in the pleural space.⁷³

CLINICAL MANIFESTATIONS

Tuberculous pleuritis presents as an acute illness in about two thirds of cases and as a chronic illness in the remaining one third. The acute illness is marked by cough and chest pain in about 75% of patients and often mimics a bacterial pneumonia with parapneumonic effusion (eFig. 80-4). The chronic form is characterized by low-grade fever, weakness, and weight loss.

Effusions secondary to tuberculous pleuritis can present in a similar fashion as malignant effusions, being almost always unilateral, and usually small to moderate in size, although they may be large (eFig. 80-5), to the point of occupying the entire hemithorax. Up to 86% of patients will have coexisting parenchymal disease (eFig. 80-6; see eFigs. 80-4 and 80-5). In such patients the pleural effusion is almost always on the side of the parenchymal opacity and invariably indicates active parenchymal disease. It is likely that, even in cases with no radiographic evidence of parenchymal involvement, the effusion is associated with a subpleural focus of infection. Evidence to support this contention is provided by a study in which the yield of sputum induction for *Mycobacterium tuberculosis* was as high in patients with no radiographic evidence of parenchymal involvement (55%) as in those with evidence of parenchymal disease (45%).⁷⁴

PLEURAL FLUID

The pleural fluid from patients with tuberculous pleuritis is an exudate that usually contains predominantly small lymphocytes, although, in a series from 2012, 17% of confirmed cases were found to have less than 50% lymphocytes in pleural fluid.⁷⁵ In around 11% of cases, the fluid will have a polymorphonuclear leukocyte predominance, with this more likely to be the pattern in the earlier stages of the disease.⁷⁶ The pleural fluid glucose level is usually similar to that of serum, but it can also be reduced. A pleural fluid protein level above 5.0 g/dL is suggestive of tuberculous pleuritis, perhaps due to the intense inflammation and leakiness of the pleural capillaries.

DIAGNOSIS

The possibility of tuberculous pleuritis should be considered in every patient with an undiagnosed exudative pleural effusion, even though only a small percentage of such effusions are due to TB in the United States.⁷⁷ For the past 40 years, the most common way to establish the diagnosis of tuberculous pleuritis has been with biopsy of the pleura, and this remains the “gold standard” test. However, in recent years, pleural fluid tests have been developed that may be useful in establishing or excluding the diagnosis of tuberculous pleuritis.⁷⁷ Those that have found the most utility, especially in combination, are (1) the level of *adenosine deaminase* (ADA) in the pleural fluid, (2) the level of interferon- γ in the pleural fluid, and (3) polymerase chain reaction for mycobacterial DNA. All patients should have at least one of these tests performed on their pleural fluid. There was initial hope that interferon- γ release assays might be of diagnostic benefit when applied to pleural fluid,^{78,79} but this appears not to be the case.^{80,81} Other markers that

have been investigated include CRP,⁸² ADA2,⁸³ and tumor necrosis factor- α .⁸⁴

All patients with an undiagnosed exudative pleural effusion should undergo mycobacterial cultures of their pleural fluid. It has also been suggested that enhanced culture methods such as the Microscopic Observation Drug Susceptibility assay may have a role in diagnosing pleural TB without the need for biopsy.⁸⁵ An induced sputum sample should also be sent for smear and culture, because it will be positive in approximately 50% of patients.⁷⁴ If the culture of the fluid or sputum is positive, standard treatment for TB should be initiated. If culture is negative but one of the other tests is positive, the patient should also be treated for TB unless the patient has a disease that is known to be associated with a positive result, or if the index of suspicion is low for another reason. In areas with a high likelihood of resistant TB, one may be more inclined to obtain pleural tissue for cultures via needle biopsy of the pleura or thoracoscopy, if available. Thoracoscopic biopsies remain the ideal way of obtaining tissue but, if this resource is not available, then traditional blind pleural biopsy remains an important diagnostic modality,⁸⁶ especially when used in combination with ADA and differential cell count.⁸⁷ Blind pleural biopsy with an Abrams needle may be preferable to other forms of blind biopsy when ultrasonographic guidance is used.⁸⁸ If the patient does not respond to therapy, then further investigations for alternative causes are warranted.

TREATMENT

Patients with tuberculous pleuritis should be treated with antituberculous medications in the same treatment regimens as patients with pulmonary TB. With treatment, patients generally become afebrile within about 2 weeks, and the pleural effusion resolves within 6 weeks. On occasion the pleural effusion worsens after antituberculous therapy is initiated⁸⁹ or a pleural effusion develops while patients are being treated for parenchymal TB.⁹⁰ In these situations, the possibility of a wrong diagnosis must be considered, but paradoxical worsening can be seen with the correct diagnosis and appropriate antituberculous medications.^{89,90} Mild degrees of residual pleural fibrosis are present a year after therapy is begun in about 50% of patients. Some authors have used fibrinolytics during drainage of tuberculous effusions with good long-term improvement in the residual fibrosis.⁹¹ Despite this, the presence of fibrosis is not necessarily related to the initial pleural fluid findings and may be of limited clinical significance.

The role of systemic corticosteroids in the treatment of tuberculous pleuritis remains controversial. According to a literature review, there were insufficient data to support evidence-based recommendations regarding the use of adjunctive corticosteroids in persons with tuberculous pleurisy.⁹² Use of corticosteroids may be considered for those who are markedly symptomatic, but only after the institution of appropriate antituberculosis therapy. However, evidence suggests that their use in HIV-infected patients with TB pleuritis should be avoided due to the increased risk for Kaposi sarcoma.⁹³ Therapeutic thoracentesis is indicated if the patient has a moderate-sized or larger pleural effusion producing symptoms. Otherwise, complete

drainage of the pleural space does not appear to have a significant effect on the long-term outcome.⁹⁴

ACTINOMYCOSIS

More than 50% of patients with thoracic actinomycosis have pleural involvement.⁹⁵ In one series of 15 patients, 6 had pleural effusion and an additional 6 had marked pleural thickening.⁹⁵ The characteristic chest radiographic finding is a localized lung lesion extending to the chest wall with pleural thickening or effusion. The pleural fluid with actinomycosis may be either frank pus with predominantly polymorphonuclear leukocytes or serous fluid with predominantly lymphocytes.

The diagnosis of actinomycosis should be considered when a chronic infiltrative pulmonary lesion extends to adjacent lobes through intralobar fissures. The presence of chest wall abscesses or draining sinus tracts suggests the diagnosis, as do bone changes consisting of periosteal proliferation or bone destruction (see eFig. 33-23B). The definitive diagnosis is established with the demonstration of *Actinomyces israelii* by anaerobic cultures. Patients with pleural actinomycosis should be treated with high doses of penicillin or another suitable antimicrobial for prolonged periods. The management of the pleural effusion is similar to that for patients with any other bacterial pneumonia.

NOCARDIOSIS

Pleural effusions develop in roughly 50% of patients with pulmonary nocardiosis.⁹⁵ Patients with pleural effusion secondary to nocardiosis almost always have an associated parenchymal opacity (eFig. 80-7). The pleural fluid can range from serous fluid to frank pus, and pleural fluid cultures may or may not be positive. Because most patients who develop nocardiosis are immunosuppressed,⁹⁶ this diagnosis should be considered in the immunosuppressed patient with a parenchymal opacity and a pleural effusion. The diagnosis is usually established with aerobic cultures, although polymerase chain reaction has been successfully used in some cases.⁹⁷ Cultures should be observed for at least 2 weeks because *Nocardia asteroides* is a slow-growing organism. Patients with pleural nocardiosis should be treated with sulfonamides or suitable alternative antimicrobials, and the pleural effusion should be managed as any pleural effusion complicating a pneumonia.

FUNGAL INFECTIONS

Fungal infections of the lungs are discussed in Chapters 37 and 38. This section considers the pleural complications of aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis. In addition, *Pneumocystis jirovecii* has been included.

ASPERGILLOSIS

The pleural space occasionally becomes infected with *Aspergillus*, usually *Aspergillus fumigatus*.⁹⁸ Pleural aspergillosis

usually arises in one of two settings: in patients who were treated in the past with artificial pneumothorax therapy for TB and, less commonly, in patients following lobectomy or pneumonectomy, in which case a bronchopleural fistula is almost always present. Pleural aspergillosis has been described in a healthy individual.^{98a}

The diagnosis of pleural aspergillosis should be suspected in any patient with a history of artificial pneumothorax therapy for TB who has signs and symptoms of a chronic infection, such as weight loss, malaise, low-grade fever, and chronic cough. The chest radiograph reveals increasing degrees of pleural thickening and usually an air-fluid level in the pleural space, indicating the presence of a bronchopleural fistula.⁹⁸ In some patients, fungal balls may be evident in either the lungs or the pleural space. The diagnosis is confirmed by the demonstration of *Aspergillus* on fungal cultures of the pleural fluid. Patients with pleural aspergillosis almost always have positive precipitin blood test results for antibodies against *Aspergillus*.

The optimal treatment for pleural aspergillosis is likely to be a combination of surgical removal of the involved pleura and resection of the involved lobe or the entire ipsilateral lung and concomitant medical therapy, which may take the form of systemic therapy or topical antifungal treatment. Lung resection is usually necessary because the infection tends to invade and destroy the underlying lung. Surgery, if appropriate, should be performed as early as possible to avoid progressive destruction of the lung. Some patients with pleural aspergillosis are too debilitated to undergo a major surgical procedure. Such patients should undergo open drainage (Eloesser flap) with daily insertion of gauze impregnated with amphotericin B.⁹⁹

Systemic medical treatment is usually given both before and after surgery. A potential regimen is an initial 2- to 4-week period of therapy with amphotericin B, followed by longer-term administration of a more modern agent such as an azole. Treatment should continue for at least 6 months, although some patients may require much longer periods of treatment.¹⁰⁰ Topical pleural antifungal treatment may be used as an adjunct to systemic therapy.¹⁰¹

BLASTOMYCOSIS

Infection with *Blastomyces dermatitidis* produces a pleural effusion in about 10% of patients, and an additional 40% or more have pleural thickening.¹⁰² Patients with pleural blastomycosis have signs and symptoms similar to those of tuberculous pleuritis. The pleural fluid is usually an exudate with predominantly small lymphocytes, although polymorphonuclear leukocytes may predominate. Because pleural biopsy results may reveal noncaseating granulomas, one should consider the diagnosis of blastomycosis in patients with a clinical picture compatible with tuberculous pleuritis and granulomas on pleural biopsy. The diagnosis is established by demonstrating the organism in secretions, pleural fluid, or histologic sections. Patients with pleural blastomycosis should be treated with itraconazole or amphotericin B.

COCCIDIOIDOMYCOSIS

Two types of pleural disease are seen in association with coccidioidomycosis. The first is associated with a

primary benign infection and may or may not have concomitant parenchymal involvement. The second develops when a coccidioidal cavity ruptures to produce a hydropneumothorax.

Primary Coccidioidomycosis

The incidence of pleural effusion in hospitalized patients with primary coccidioidomycosis is about 15%.¹⁰³ Most patients are febrile and have pleuritic chest pain. The pleural effusion is almost always unilateral and can occupy more than 50% of the hemithorax.¹⁰³ There is a coexisting parenchymal opacity in about 50% of patients. The pleural fluid is an exudate containing predominantly small lymphocytes and frequently eosinophils.¹⁰³ At times the pleural fluid can be pus.¹⁰³ Pleural fluid cultures are positive for *Coccidioides immitis* in about 20%, with poor results also from polymerase chain reaction.¹⁰⁴ Cultures of pleural biopsy specimens, however, are almost always positive. Most patients with primary coccidioidomycosis and pleural effusion require no systemic therapy. The complement fixation titers are usually high in patients with coccidioidal pleural effusion, and a high titer alone should not be used as an indication for treatment. Only patients with prolonged or severe symptoms, evidence of dissemination, or those at a high risk for dissemination should be considered for first-line treatment with an azole.

Rupture of Coccidioidal Cavity

Hydropneumothoraces develop in 1% to 5% of patients with chronic cavitary coccidioidomycosis (see Fig. 37-6). The rupture of the cavity into the pleural space is usually heralded by the development of an acute illness with systemic signs of toxicity. These patients should undergo tube thoracostomy immediately to drain the air and fluid from the pleural space. Most patients require a thoracotomy with a partial or total lobectomy, and most require some degree of decortication.⁷⁷

CRYPTOCOCCOSIS

Pleural involvement with cryptococcosis appears to result from extension of a primary subpleural cryptococcal nodule into the pleural space. About 50% of patients with pleural cryptococcosis have disseminated disease, and most have an accompanying parenchymal abnormality. Most patients who have a cryptococcal pleural effusion are immunosuppressed, and many of the patients have *acquired immunodeficiency syndrome* (AIDS).¹⁰⁵ The pleural fluid is an exudate, usually with a predominance of small lymphocytes.

Not all patients with pleural cryptococcosis require treatment with systemic antifungal therapy.⁷⁷ Treatment should be initiated in patients with cryptococcal antigen in their blood or cerebrospinal fluid; in immunosuppressed patients, including those with AIDS; and in those with enlarging effusions, especially if pleural cell counts and LDH concentrations are increasing.⁷⁷

HISTOPLASMOSIS

Pleural effusion is rare with histoplasmosis. In one review of 259 patients with pulmonary histoplasmosis, only one had a pleural effusion.¹⁰⁶ Patients with pleural effusions

secondary to histoplasmosis usually have a subacute illness characterized by low-grade fever and pleuritic chest pain. The chest radiograph usually reveals an opacity or a subpleural nodule in addition to the pleural effusion.¹⁰⁷ The pleural fluid is usually a lymphocytic-predominant exudate, and the pleural biopsy may reveal noncaseating granulomas. No systemic treatment is usually necessary for a pleural effusion secondary to histoplasmosis because the effusion normally resolves spontaneously over several weeks. Systemic therapy should be administered if the effusion persists more than 3 to 4 weeks or if the patient is immunosuppressed.

PNEUMOCYSTIS JIROVECI

Pleural effusions are rare in patients with *P. jirovecii* pneumonia, but they have been reported. There is, however, no evidence to support the routine testing of pleural fluid for *P. jirovecii* except in the severely immunocompromised.¹⁰⁸ When there are pleural effusions, they appear to be an extension of the pulmonary process, and concurrent pneumothoraces are common (see eFig. 90-15). The pleural fluid is an exudate with a relatively low protein level but an LDH level above the upper normal limit for serum. At times, organisms can be visualized in the pleural fluid.

VIRAL INFECTIONS

Viral infections account for a sizable percentage of undiagnosed exudative pleural effusions. However, the diagnosis is rarely established because it usually depends on the isolation of the virus or the demonstration of a significant increase in antibody titers to the virus. These studies are not routinely obtained on patients with undiagnosed pleural effusions.

PRIMARY ATYPICAL PNEUMONIA

The incidence of pleural effusions with so-called primary atypical pneumonia (usually caused by *Mycoplasma* or viruses) is as high as 20%.¹⁰⁹ The effusions associated with atypical pneumonia are usually small, are exudative, and contain predominantly neutrophils. If there is sufficient fluid, as described earlier, thoracentesis should be performed to exclude a complicated parapneumonic effusion.

OTHER VIRUSES

Viral infection is probably responsible for a much higher percentage of pleural effusion without parenchymal opacities than is generally recognized. In one epidemic, 559 soldiers in Turkey had an acute febrile illness characterized by pleuritic chest pain and a mononuclear cell–predominant pleural effusion without parenchymal opacities. No pathogens were demonstrated, and it was assumed that this self-limited disease was due to a virus, although serologic studies were not performed.¹¹⁰

Almost all patients with the hantavirus pulmonary syndrome have a pleural effusion. Initially the fluid is a transudate, probably resulting from cardiac dysfunction, but subsequently the fluid becomes exudative.¹¹¹ Almost all

patients with severe cases of dengue hemorrhagic fever also have pleural effusions. Pleural effusions have also been reported to result from infection with hepatitis, infectious mononucleosis, respiratory syncytial virus, influenza viruses, measles after the administration of inactivated virus vaccine, cytomegalovirus, herpes simplex virus, and Lassa fever virus. Pleural effusions have not been a major feature of infection with Ebola virus.^{111a}

ACQUIRED IMMUNODEFICIENCY SYNDROME

Pleural effusions are seen in patients with AIDS but are less common than are parenchymal opacities. In one series of 1225 consecutive hospital admissions of patients with AIDS in Jacksonville, Florida, the incidence of pleural effusion was 15%.¹¹² The distribution of the diseases responsible for pleural effusions in patients with AIDS varies widely. In series from industrialized countries that included predominantly intravenous drug users, the most common cause is parapneumonic effusions; in series with predominantly homosexuals, the most common cause is Kaposi sarcoma; in series from Africa, the most common cause is TB. Other causes of pleural effusions in patients with AIDS include primary effusion lymphoma (see eFig. 90-37), *P. jirovecii*, opportunistic infections, renal failure, and congestive heart failure.

A patient with AIDS and parapneumonic effusions should be managed as any patient with a parapneumonic effusion would be managed, recognizing that the incidence of complicated parapneumonic effusion is higher in patients with AIDS.¹¹³ The incidence of pleural effusion with pulmonary Kaposi sarcoma is approximately 50% (eFig. 80-8). Most patients with a pleural effusion due to Kaposi sarcoma have bilateral parenchymal opacities (see eFig. 80-8B). The diagnosis of pleural involvement is difficult and often depends on the demonstration of pulmonary Kaposi sarcoma, either by bronchoscopic examination, high-resolution CT, or thoracoscopy. The pleural fluid is an exudate that is usually serosanguineous or hemorrhagic. Pleural fluid cytologic examinations are invariably negative with pleural Kaposi sarcoma; pleural biopsy results are also usually negative because the parietal pleura is not involved.

Patients with AIDS with an exudative pleural effusion should have a diagnostic thoracentesis that includes bacterial, mycobacterial, and fungal cultures and measurement of the pleural fluid ADA level. If this does not establish a diagnosis, consideration should be given to performing thoracoscopy, at which time a pleurodesis may be considered in symptomatic patients.

PARASITIC DISEASES

Parasitic infections of the lungs are discussed in Chapter 39. Those that may also involve the pleura—amebiasis, echinococcosis, and paragonimiasis—are also considered in this section.

AMEBIASIS

About 20% of patients with amebic liver abscess will develop pleuropulmonary complications.¹¹⁴ Pleural effusions arise

by two different mechanisms. First, an amebic liver abscess may irritate the diaphragm and produce a sympathetic pleural effusion in a manner analogous to that caused by a pyogenic liver abscess. Second, a pleural effusion develops when an amebic liver abscess ruptures into the pleural space through the diaphragm (see eFig. 33-29).¹¹⁵

The sympathetic effusion in amebic liver abscess is more common than rupture of an abscess through the diaphragm.¹¹⁵ The pleural fluid has not been well characterized. The diagnosis can be established by positive gel diffusion, indirect hemagglutination, or enzyme-linked immunosorbent assay tests, the results of which are positive in more than 98% of patients with extraintestinal invasive amebiasis.¹¹⁵ Patients with amebic abscess and a sympathetic pleural effusion should be treated with antiamebic drugs.

The transdiaphragmatic rupture of an amebic liver abscess is usually heralded by an abrupt exacerbation of pain in the right upper quadrant and may be accompanied by a tearing sensation.¹¹⁴ Shortly thereafter, progressive respiratory distress, sepsis, and occasionally shock develop. The pleural effusion is frequently massive, with opacification of the entire hemithorax and shift of the mediastinum to the contralateral side.¹¹⁴ The diagnosis of amebic abscess with transdiaphragmatic rupture is suggested by the discovery of “anchovy paste”-or “chocolate sauce”-like pleural fluid on diagnostic thoracentesis. Patients with transdiaphragmatic rupture should undergo urgent tube thoracostomy. The patients should also be treated with the same antiamebic drugs recommended for patients with amebic sympathetic effusions, such as metronidazole. Although the pus in amebic empyema is sterile,¹¹⁶ because bacterial infection of the pleural space complicates the process in about one third of patients, bacterial cultures of the pleural fluid should be obtained routinely. If bacterial infection is present, appropriate antibiotic therapy should be initiated.

ECHINOCOCCOSIS

Pleural involvement with hydatid disease can develop in one of three situations: (1) a pulmonary hydatid cyst may rupture into the pleural space, (2) a hepatic hydatid cyst or rarely a splenic cyst may rupture through the diaphragm into the pleural space, or (3) a hydatid cyst may slowly enlarge into the pleural space.¹¹⁷ When a cyst ruptures into the pleural space, either an empyema or a pneumothorax can result.¹¹⁷ In a series of 474 patients with pulmonary hydatid disease, 6% had pleural thickening or effusion.¹¹⁸

When a hydatid cyst ruptures into the pleural space, the patient develops acute symptoms, with sudden tearing chest pain, dyspnea, and shock from the antigenic challenge to the body. The cyst frequently also ruptures into the tracheobronchial tree, producing a bronchopleural fistula with a hydropneumothorax that may become secondarily infected.¹¹⁷

The diagnosis of pleural echinococcosis is established either by the demonstration of echinococcal scolices with hooklets in the pleural fluid or in the pleural biopsy specimen, or by a combination of serologic testing and radiology.

Lobulated cystic lesions in the pleural space may be seen on CT or magnetic resonance imaging.¹¹⁶ Eosinophils are frequently present in the pleural fluid unless it is secondarily infected. Patients with pleural echinococcosis should be immediately subjected to thoracotomy to remove the parasite, to excise the original cyst, and to close the bronchopleural fistula.¹¹⁷ Patients with hydatid cysts should be treated with antiprotozoal therapy if all the cysts cannot be removed, or if a cyst has ruptured. An alternative nonsurgical approach is PAIR therapy (puncture, aspiration, injection, and reaspiration), although this can cause allergic reactions.¹¹⁶

PARAGONIMIASIS

Pleural disease is common with paragonimiasis. In one series of 71 patients, 43 (61%) had pleural disease, including 20 with unilateral pleural effusions, 6 with bilateral pleural effusions, 6 each with unilateral and bilateral hydropneumothorax, and 5 with pleural thickening.¹¹⁹ Paragonimiasis can be found in natives of the United States who have never left the country.

Patients with pleural paragonimiasis present with a chronic illness. There is a concomitant parenchymal opacity in about 50% of patients. The pleural fluid in patients with pleural paragonimiasis is characteristic. It is an exudate with a glucose level of less than 10 mg/dL (0.56 mmol/L), an LDH level of more than three times the upper limit of normal for serum, a pH below 7.10, and a differential revealing a high percentage of eosinophils.¹²⁰ In addition, cholesterol crystals¹²⁰ or chyle¹²¹ may be present. Pleural paragonimiasis is one of only two conditions in which the pleural fluid is characterized by a low pH, a low glucose level, and many eosinophils; the other is eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Usually there are no ova in the pleural fluid.

The diagnosis of pleural paragonimiasis is strongly suggested by the unique pleural fluid findings, although in some cases lung biopsy may become necessary. The diagnosis is established definitively by demonstrating the typical operculated eggs in sputum, stool, or pleural fluid. A complement fixation titer above 1 : 8 for *Paragonimus westermani* is strongly suggestive of the diagnosis.¹²⁰ The treatment for paragonimiasis is discussed in Chapter 37.

Key Points

- The incidence of pleural infection is increasing globally in both adults and children for unclear reasons.
- Standard bacterial cultures are positive only in approximately 60% of pleural infection cases. Blood culture bottles can be combined with standard cultures to increase the yield.
- Community-acquired pleural infection is caused by a different range of organisms than hospital-acquired pleural infection and should be treated with different empirical antibiotics at presentation.
- The cornerstones of pleural infection management remain intravenous antibiotics, adequate drainage of the pleural collection, and adequate nutrition.

- A parapneumonic effusion with a pH of less than 7.20, a glucose level below 40 mg/dL, or significantly loculated pleural collection generally requires chest tube drainage to resolve the pleural sepsis.
- Surgical techniques such as video-assisted thoracic surgery have become widely available and can be offered to most patients if less invasive approaches are unsuccessful.
- Intrapleural tissue plasminogen activator plus DNase has been shown to improve the chest radiographic evidence of empyema and to decrease hospital length of stay. Its role needs to be evaluated further before its routine use can be recommended.

Complete reference list available at *ExpertConsult*.

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eFIGURE IMAGE GALLERY

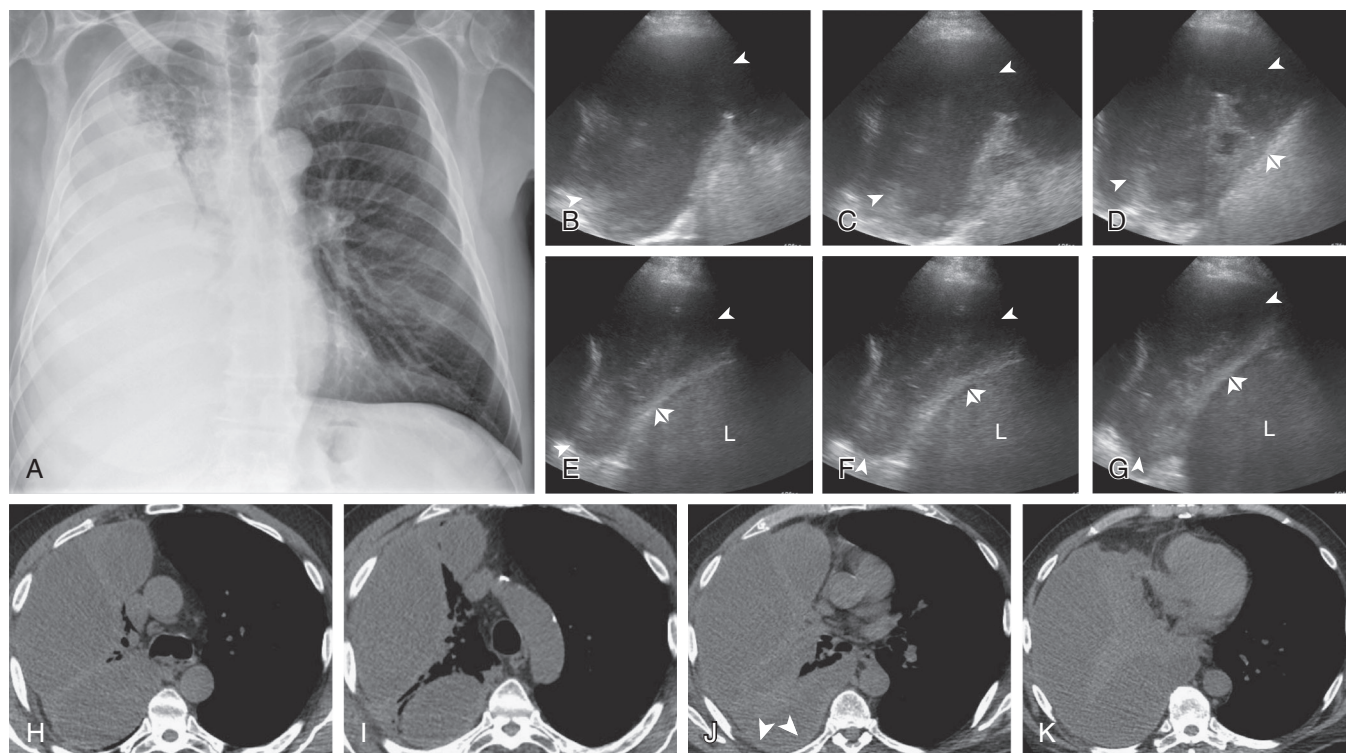
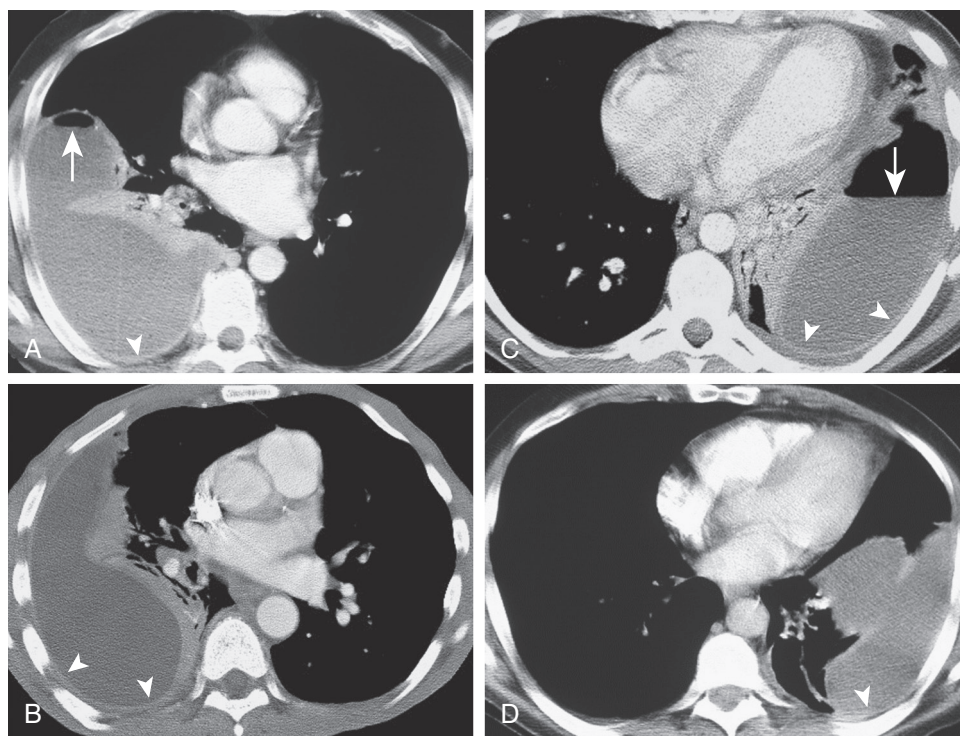
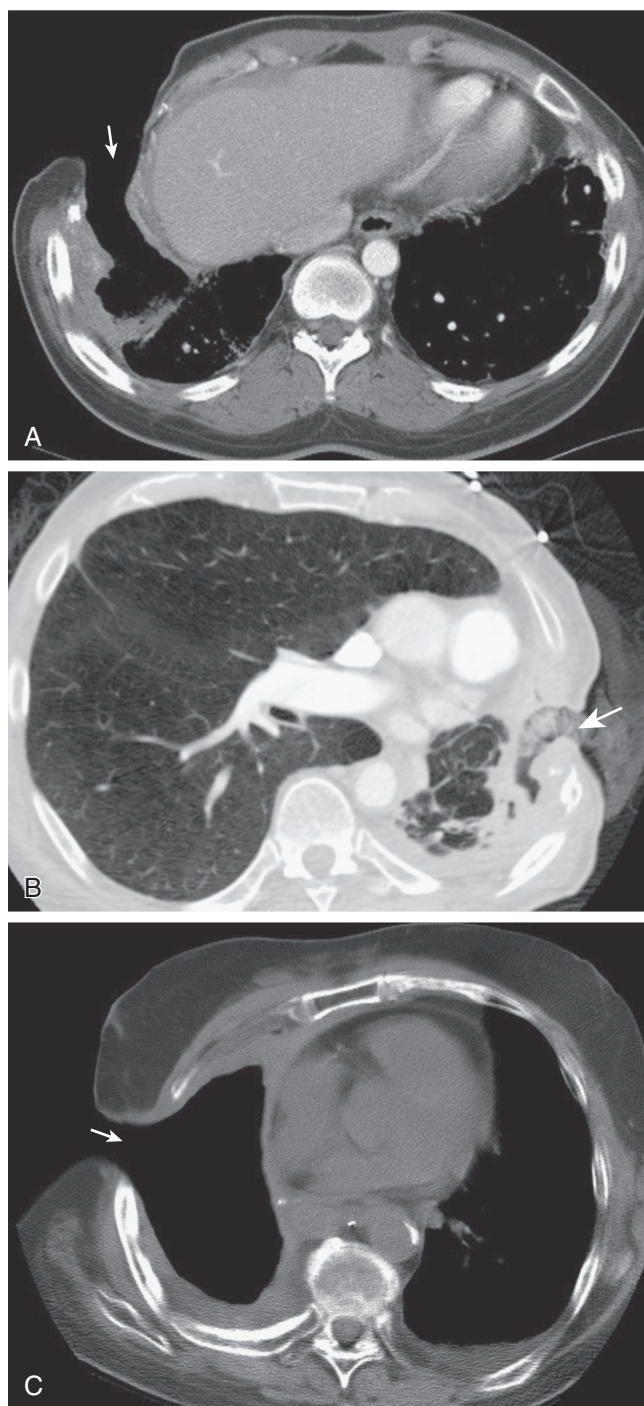


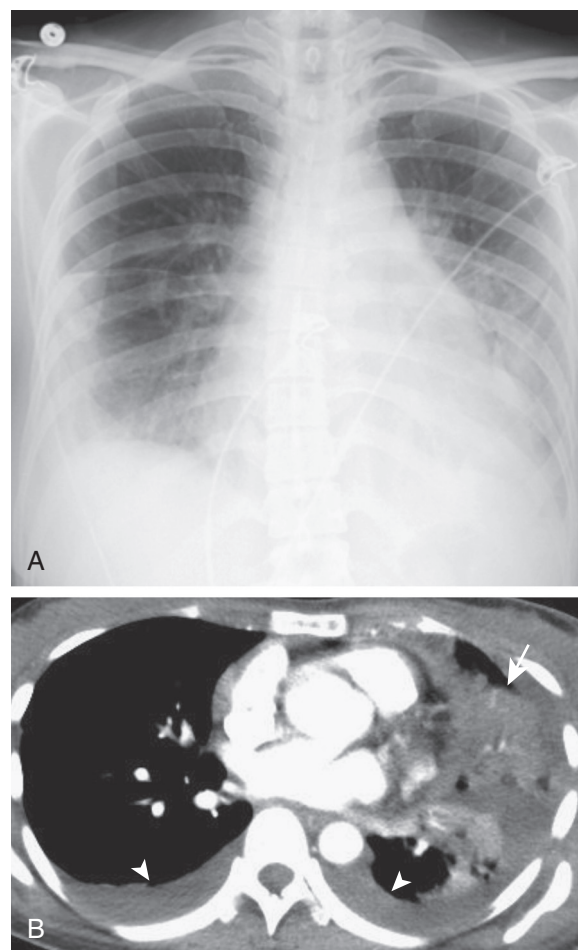
Figure 80-1 Empyema: chest radiographic, ultrasonographic, and chest CT appearance. **A**, Frontal chest radiograph shows a large, homogeneous opacity, without air bronchograms, occupying the right thorax. **B–G**, Axial ultrasonographic images show a heterogeneous but predominantly hypoechoic collection (*single arrowheads*) in the right pleural space. The right diaphragm (*double arrowheads*) is visible; the complex fluid collection resides cranial to the diaphragm. The liver (L) is seen caudal to the complex fluid collection and diaphragm. Ultrasonographically guided thoracentesis yielded 250 mL yellow, cloudy fluid. The minimal amount of fluid that could be withdrawn was due to the presence of multiple loculations. **H–K**, Axial unenhanced chest CT shows multiloculated right pleural fluid associated with areas of smooth pleural thickening (*arrowheads*). Pleural fluid culture subsequently grew *Streptococcus intermedius*. (Courtesy Michael Gotway, MD.)



eFigure 80-2 Empyema: enhanced chest CT appearance. A–D, Contrast-enhanced chest CT in four different patients with empyema shows loculated pleural fluid collections with foci of smooth pleural thickening (*arrowheads*). Two of the cases (**A** and **C**) show gas-fluid levels (*arrows*), both before intervention, suggesting bronchopleural fistula. (Courtesy Michael Gotway, MD.)



eFigure 80-3 Eloesser flap: chest CT appearance. A–C, Axial enhanced (A and B) and unenhanced (C) chest CT images in three separate patients who underwent the Eloesser flap procedure, one for chronic empyema (A), one for treatment of bronchopleural fistula (B), and the other as part of surgery for mesothelioma (C). All three images show a clear connection between the thorax and exterior (arrow). The patient with mesothelioma (C) shows concentric pleural thickening. (Courtesy Michael Gotway, MD.)



eFigure 80-4 Tuberculous pneumonia and effusion presenting similarly to bacterial pneumonia and parapneumonic effusion. A, Frontal chest radiograph shows nonspecific left perihilar opacity and a hazy right base with increased attenuation. Left lower lobe consolidation obscuring the diaphragm is also present. The imaging findings are very nonspecific. B, Enhanced chest CT shows lingular (arrow) and left lower lobe consolidation with small, symmetric, nonspecific pleural effusions (arrowheads). Although the chest CT findings were ultimately shown to be due to *Mycobacterium tuberculosis*, the imaging findings are not specific for that diagnosis. (Courtesy Michael Gotway, MD.)

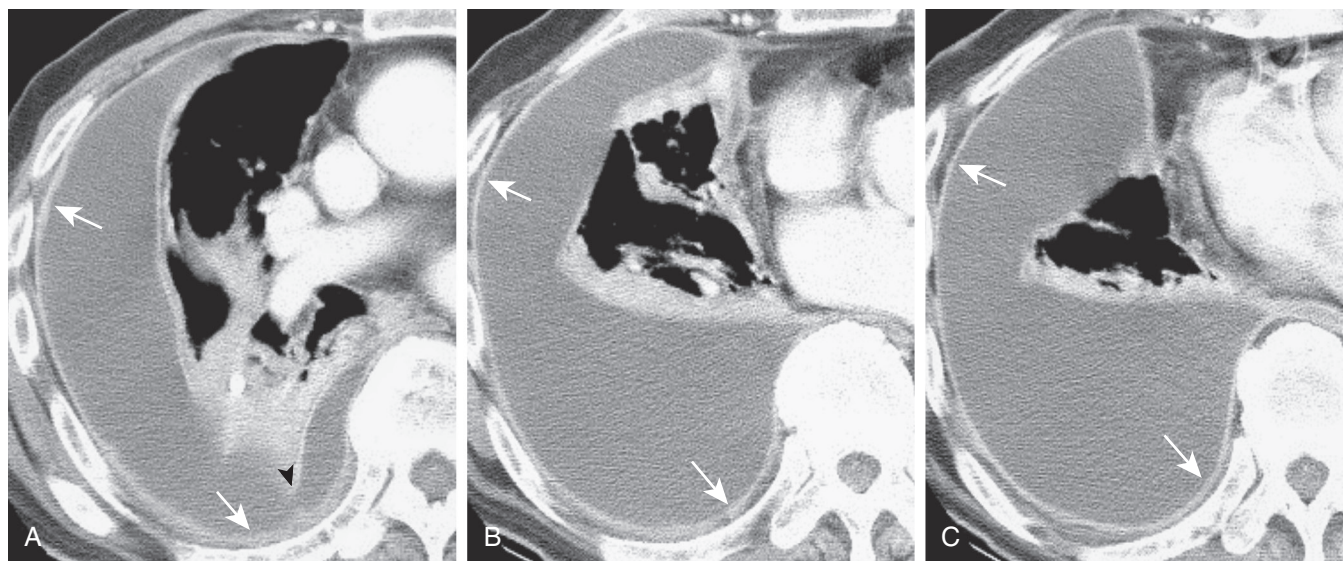


Figure 80-5 Tuberculous empyema: chest CT findings. A–C, Axial enhanced chest CT shows a large right pleural effusion with loculation (*arrowhead*), and smooth pleural thickening (*arrows*). The nondependent morphologic features and lenticular shape (seen in **A**), loculation (*arrowhead*), and smooth pleural thickening, representing the “split-pleura” sign, are all suggestive of empyema but are not specific for tuberculosis. (Courtesy Michael Gotway, MD.)

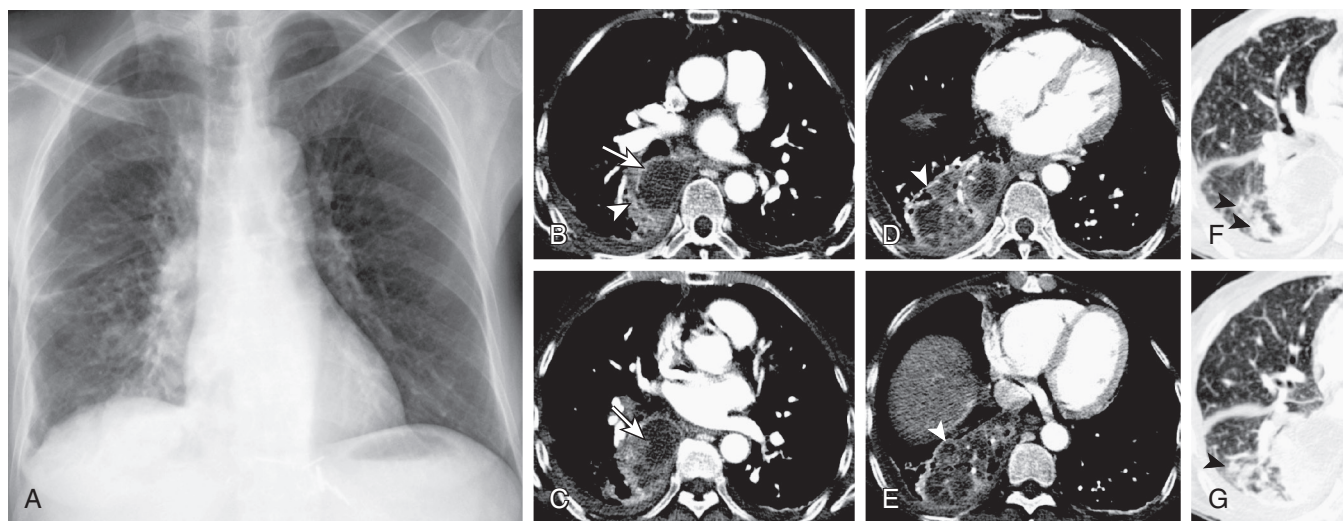
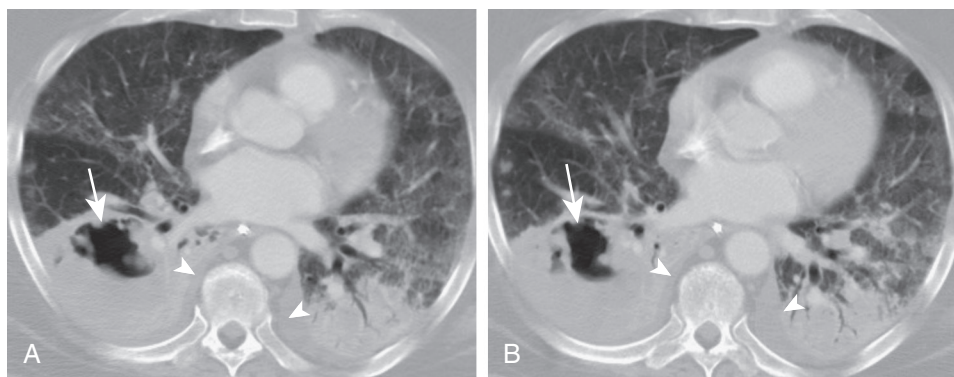
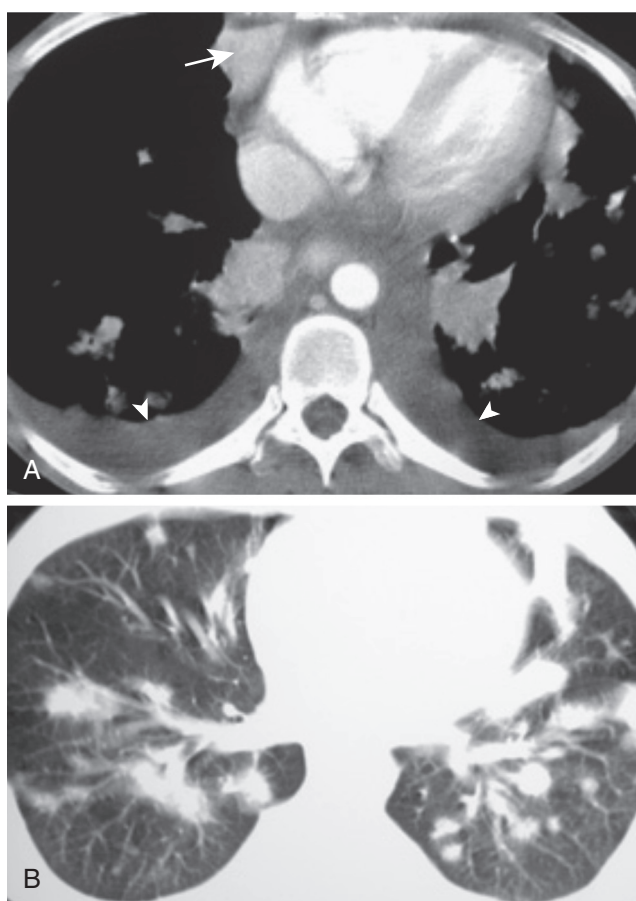


Figure 80-6 Tuberculous empyema: chest radiographic and chest CT findings. A, Frontal chest radiograph shows nonspecific medial right base consolidation. B–G, Enhanced chest CT displayed in soft tissue (B–E) and lung (F and G) windows shows a loculated, medial right thoracic pleural fluid collection (*arrow*) consistent with empyema. Necrotic and nodular medial right lower lobe lung parenchymal opacity (*arrowheads*) represents tuberculous infection. (Courtesy Michael Gotway, MD.)



eFigure 80-7 *Nocardia asteroides* pulmonary infection with pleural effusion. **A** and **B**, Axial enhanced chest CT displayed in lung windows shows bilateral lower lobe consolidation, cavitory on the right (*arrows*). Trace bilateral, nonspecific pleural effusions (*arrowheads*) are present. (Courtesy Michael Gotway, MD.)



eFigure 80-8 Pleural effusions in Kaposi sarcoma. **A** and **B**, Axial enhanced chest CT displayed in soft tissue (**A**) and lung (**B**) windows shows small, symmetric, bilateral pleural effusions (*arrowheads*). Enhancing right cardiophrenic angle lymphadenopathy (*arrow*) is present. The typical appearance of bilateral, patchy, poorly defined peribronchial nodular opacities is readily appreciated on the lung window images (**B**). (Courtesy Michael Gotway, MD.)

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PNEUMOTHORAX, CHYLOTHORAX, HEMOTHORAX, AND FIBROTHORAX

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Treatment

INTRODUCTION

A pneumothorax is present when there is air in the pleural space. Pneumothoraces are classified as *spontaneous pneumothoraces*, which develop without preceding trauma or other obvious cause, and *traumatic pneumothoraces*, which develop as a result of direct or indirect trauma to the chest, including diagnostic or therapeutic maneuvers (*iatrogenic pneumothoraces*). Spontaneous pneumothoraces are subclassified as *primary* or *secondary*. A *primary spontaneous pneumothorax* (PSP) presents in an otherwise healthy person without underlying lung disease. A *secondary spontaneous pneumothorax* (SSP) complicates an underlying lung disease, most commonly *chronic obstructive pulmonary disease* (COPD).

Most pleural effusions prove to be either an exudate or a transudate according to the criteria provided in Chapter 79. Occasionally the liquid contents turn out to be chyle, pseudo-chyle, or blood. This chapter describes the pathogenesis and clinical manifestations of chylothorax, pseudochylothorax, and hemothorax. Fibrothorax, the sequela of chronic organizing pleural disease of any origin, is also considered.

PATHOPHYSIOLOGY OF PNEUMOTHORAX

In normal subjects the pressure in the pleural space is negative with respect to the alveolar pressure during the entire respiratory cycle. The pressure gradient between the alveoli and the pleural space—the transpulmonary pressure—is the result of the inherent elastic recoil of the lung. During spontaneous breathing, the pleural pressure is also negative with respect to the atmospheric pressure. The functional residual capacity, or resting end-expiratory volume of the lung, is the volume at which the inherent outward pull of the chest wall is equal to, but opposite in direction to, the inward pull (recoil) of the lung.¹

When a communication develops between an alveolus or other intrapulmonary air space and the pleural space, air will flow from the alveolus into the pleural space until there is no longer a pressure difference or until the communication is sealed. Similarly, when a communication develops through the chest wall between the atmosphere and the pleural space, air will enter the pleural space until the pressure gradient is eliminated or the communication is closed. The influence of a pneumothorax on the volume of the

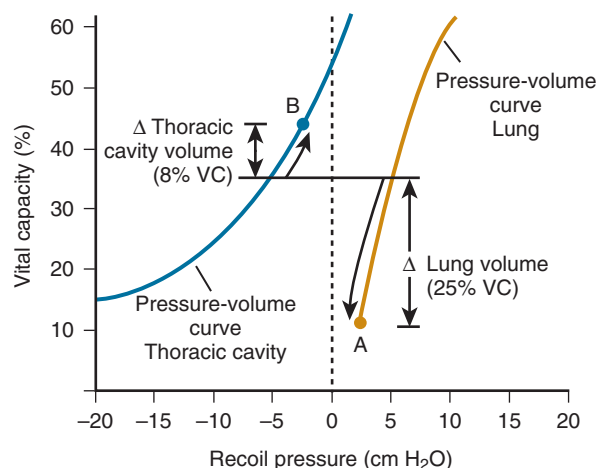


Figure 81-1 Influence of a pneumothorax on the volumes of the lung and hemithorax. In this illustration the pneumothorax has caused the intrapleural pressure to rise from -5 to -2.5 cm H_2O . The lung and thoracic cavity move on their respective pressure-volume curves to new volumes for the lung (A) and thoracic cavity (B). Note that the volume of the hemithorax becomes larger as the volume of the lung becomes smaller. The changes in volumes of the hemithorax and lung are unequal because of the differences in the slopes of two pressure-volume curves. VC, vital capacity. (Redrawn from Light RW: *Pleural diseases*, ed 4, Philadelphia, 2001, Lippincott Williams & Wilkins, p 286.)

hemithorax and the lung is illustrated in Figure 81-1. In this example, sufficient air has entered the pleural space to elevate the pleural pressure from -5 to -2.5 cm H_2O , so that the transpulmonary or recoil pressure has decreased from 5 to 2.5 cm H_2O . The amount of air necessary to effect this change in the pleural pressure can be seen to be equal to 33% of the patient's vital capacity: most of this pleural air (25% of the vital capacity) is accounted for by air displaced from the lung, and the rest is accounted for by the expansion of the thoracic cavity along its pressure-volume curve (by 8% of the vital capacity). The rise in the pleural pressure also causes a shift of the mediastinum to the contralateral side, an enlarged hemithorax, and a depressed hemidiaphragm. These findings are expected and do not necessarily indicate that a tension pneumothorax is present.¹

The main physiologic consequences of a pneumothorax are a decrease in the vital capacity (as illustrated in Fig. 81-1) and the arterial PO_2 . In patients with PSP, the decrease in the vital capacity is usually well tolerated. If the lung function of the patient is abnormal before the development of the pneumothorax, however, the decrease in vital capacity may lead to respiratory insufficiency with alveolar hypoventilation and respiratory acidosis.

Most patients with a pneumothorax have a reduced arterial PO_2 and an increase in the alveolar-arterial oxygen tension difference. In a series of 12 patients with spontaneous pneumothorax, the arterial PO_2 was below 80 mm Hg in 9 (75%) and was below 55 mm Hg in 2 patients, both of whom had SSP.²

The reduction in arterial PO_2 appears to be due to the creation of regions of the lung both with low ventilation-perfusion ratios and with absent ventilation (shunt), and occasionally due to alveolar hypoventilation. Norris and coworkers² reported that the average right-to-left shunt in their 12 patients with spontaneous pneumothorax was more than 10%. Larger pneumothoraces were associated

with greater shunts. When the pneumothorax occupied less than 25% of the hemithorax, the shunt was not increased.²

After air is evacuated from the pleural space, the arterial PO_2 usually improves, but the improvement may take several hours. Norris and colleagues² evacuated the pleural air from three patients with an initial shunt above 20%; within 90 minutes, the shunt had decreased below 10%, but it nonetheless remained above 5% in all patients. The delay in improvement may be related to the duration of the pneumothorax and the time necessary to expand collapsed alveoli.

PRIMARY SPONTANEOUS PNEUMOTHORAX

INCIDENCE

A study from Britain reported an incidence of spontaneous pneumothorax as 24.0 and 9.8 per 100,000 per year for men and women, respectively,³ and about one half of the pneumothoraces were PSPs. This extrapolates to an annual incidence of 22,500 in the United States.

ETIOLOGIC FACTORS

PSP, which develops in an otherwise healthy person without known lung disease, is traditionally believed to result from rupture of a subpleural emphysematous bleb often located in the apex of the lung.⁴ Blebs can be found in more than 75% of patients undergoing thoracoscopy for treatment of PSP.⁴ The pathogenesis of these subpleural blebs and the trigger(s) of their rupture are unclear. Such blebs have been attributed to congenital abnormalities, inflammation of the bronchioles, and disturbances of the collateral ventilation.⁴ There is a strong association between smoking and the development of a PSP. When four separate series of patients with PSP are combined, 461 of 505 patients (91%) with PSP were smokers or ex-smokers.¹ The risk for a spontaneous pneumothorax is related to the level of cigarette smoking. In men the relative risk for a pneumothorax is 7 times higher in light smokers (1 to 12 cigarettes per day), 21 times higher in moderate smokers (13 to 22 cigarettes per day), and 102 times higher in heavy smokers (>22 cigarettes per day) than in nonsmokers.⁵ It is probable that smoking-induced disease of small airways contributes to the development of the subpleural blebs.

Patients with PSP tend to be taller and thinner than control persons. In one study, military recruits with a pneumothorax were on average 2 inches taller and 25 pounds lighter than the typical military recruit.¹ An increased length of the chest may contribute to the formation of the subpleural blebs. Because pleural pressure falls about 0.20 cm H_2O per centimeter of vertical height, pleural pressure will be more negative at the apex of the lung in taller persons; accordingly, the alveoli at their lung apex are subjected to a greater mean distending pressure. Over an extended period, this could lead to the formation of subpleural blebs in subjects genetically predisposed to bleb formation.

The risks for PSP can be inherited. The Birt-Hogg-Dubé syndrome is an autosomal dominant condition characterized by an increased incidence of spontaneous pneumothorax (see Fig. 69-10), benign skin tumors, and renal tumors.⁶ The genetic abnormality resides on chromosome 17p11.2 and involves mutations in the folliculin gene.⁶ Approximately 40% of patients with the mutation will have a pneumothorax.⁶ Pneumothorax is also more frequent in those with the Marfan syndrome and homocystinuria.

The traditional concept was that air leaked from one bleb supplied by a single airway. More recent data have challenged this concept; a study using inhaled fluorescein suggested that air may leak from more areas than just the blebs,⁷ raising the possibility of “pleural porosity,” in which the air leaks from multiple pores on the visceral pleura. Endobronchial one-way valve studies also found that occlusion of multiple segmental bronchi are necessary to stop air leaks.⁸ This suggests that air is leaking either via multiple sites, via collateral ventilation, or both.

CLINICAL MANIFESTATIONS

PSP most commonly happens to those in their early 20s, and rarely after age 40. PSP usually develops while the patient is at rest, and rarely during heavy exercise.¹

Chest pain and dyspnea are the main symptoms. The chest pain, often acute, is usually localized to the side of the pneumothorax. Rarely, Horner syndrome can develop, probably from traction on the sympathetic ganglion associated with the mediastinal shift.

Vital signs are usually normal, with the exception of a moderate tachycardia. A tension pneumothorax should be suspected if tachycardia (>140 beats/min), hypotension, cyanosis, or electromechanical dissociation is present. The side with pneumothorax may be larger than the contralateral side and move less during the respiratory cycle. Tactile fremitus is absent, the percussion note is hyperresonant, and the breath sounds are absent or reduced on the affected side. In those with a right-sided pneumothorax, the lower edge of the liver may be shifted inferiorly. With a large pneumothorax, the trachea may be shifted toward the contralateral side.

DIAGNOSIS

The diagnosis is usually suggested by the clinical history and physical examination and established by demonstrating a pleural line on the chest radiograph (Fig. 81-2). A visceral pleural line can be distinguished from other lines such as skinfolds by the following criteria. This line is defined by air density on both sides of the line, whereas a skinfold is really an edge without air density on either side. A pleural line should generally be sharp and well defined, whereas a skinfold is often poorly defined, at least on one side. A pleural line can be followed continuously, roughly paralleling the chest wall inner contour so that, in the upright patient, it caps the apex of the lung (assuming no adhesions) and often tapers toward the lung base; a skinfold usually is not continuous, often fades at both ends, and often does not follow an anatomically sensible configuration. Finally, a

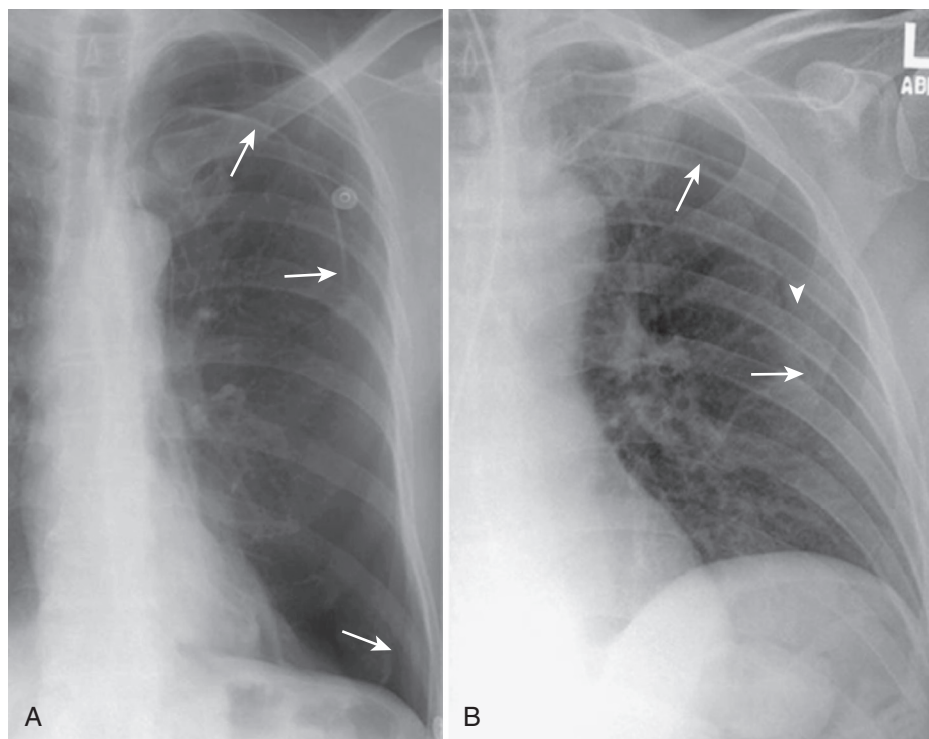


Figure 81-2 Distinguishing a pneumothorax from a skinfold. **A**, Chest radiograph of a pneumothorax. The pleural line has lucency on either side, representing air in the pleural space on one side of the line and air in the lung on the other. The line is sharply demarcated and can be traced along its course (lower arrow). No blood vessels can be seen beyond the superior (upper arrow) and lateral (middle arrow) extent of the line. **B**, Chest radiograph of a skinfold (arrows) that could be mistaken for a pneumothorax. The border is more of an edge, with lucency on only one side. The edge is poorly defined and cannot be followed continuously (lower arrow). Blood vessels can be traced beyond the border of the fold (arrowhead).

pleural line should not be crossed by lung vessels, whereas a skinfold can show lung vessels beyond its edge (eFig. 81-1).

In doubtful cases, lateral decubitus films (with the affected side up, eFig. 81-2), ultrasonography, or *computed tomography* (CT) (see Fig. 76-7) may facilitate the diagnosis. Expiratory films (see Fig. 18-5) are only slightly more sensitive than inspiratory films in detecting pneumothoraces and are not routinely recommended.⁴ A small pleural effusion is associated with a PSP in approximately 15% of cases and is manifested radiographically as an air-fluid level (eFig. 81-3; see eFig. 81-2). The pleural fluid frequently contains a large percentage of eosinophils.⁹ On rare occasions, spontaneous pneumothorax is complicated by brisk pleural bleed, producing a hemopneumothorax.¹⁰ Emergency surgery is indicated if the patient is hemodynamically compromised.¹⁰

When one is managing a patient with a pneumothorax, the amount of lung collapse should be estimated. One can first measure the lung and hemithorax “diameter”: the distance from the lung root to the visceral pleural line (lung diameter) or to the chest wall (hemithorax diameter). Because the volumes of the lung and the hemithorax are roughly proportional to the cube of their diameters, one can estimate the degree of collapse (percent pneumothorax, or PTX%) by measuring average diameters of the lung and the hemithorax, cubing these diameters, and using the following equation, known as the Light index¹:

$$\text{PTX}\% = 100\% \times [1 - (\text{diameter of the lung} / \text{diameter of the hemithorax})^3]$$

There is an excellent correlation ($r = 0.84$) between the Light index and the amount of air that can be aspirated from a pneumothorax.¹¹

RECURRENCE RATES

Following a PSP, a patient is at risk for recurrence particularly in the months immediately after the first episode. One study¹² followed 153 PSP patients for a mean of 54 months and reported that 39% had a recurrent ipsilateral pneumothorax, most within the first year. Interestingly, 15% also developed a pneumothorax on the contralateral side.

There have been several attempts to predict who will develop recurrent pneumothorax. Patients who are tall, patients with a low body mass index, and those who continue to smoke are more likely to have a recurrence.¹³ Patients who have blebs or bullae or both on high-resolution CT scan are also more likely to have a recurrence.¹⁴ Once a patient has had one recurrence, the risk for another recurrence increases to more than 50% if no measure is taken to prevent the recurrence.¹

TREATMENT

There are two goals to managing a patient with a PSP: to rid the pleural space of air and to prevent recurrence. Treatment options include observation, supplemental oxygen, simple aspiration, simple tube thoracostomy, tube thoracostomy with instillation of a pleurodesing agent, thoracoscopy with oversewing of the blebs and pleurodesis, and open thoracotomy. When selecting treatment for any given patient, it should be remembered that PSP is mainly a

nuisance and rarely life-threatening. Published guidelines, such as from the American College of Chest Physicians¹⁵ and the British Thoracic Society,¹⁶ have emphasized the lack of controlled studies on the treatment of pneumothorax.¹⁵

Observation

Once the communication between the alveoli and the pleural space is eliminated, the residual air in the pleural space will be gradually reabsorbed, albeit slowly. Kircher and Swartzel¹⁷ estimated that 1.25% of the volume of the hemithorax is absorbed each 24 hours. For a patient with a 20% pneumothorax, it will take 16 days for pleural air to be absorbed spontaneously. Supplemental oxygen may increase the rate of pleural air absorption (see the next section).

Supplemental Oxygen

In pneumothorax, gases move in and out of the pleural space from the capillaries in the visceral and parietal pleura. The movement of each gas depends on the gradient between its partial pressure in the capillaries and in the pleural space, the blood flow per unit surface area available for gas exchange, and the solubility of each gas in the surrounding tissues. Normally the sum of all the partial pressures in the capillary blood with a patient breathing room air is about 706 mm Hg (PN₂, 573; PH₂O, 47; PCO₂, 46; and PO₂, 40 mm Hg). If it is assumed that the pleural pressure is approximately 0 when there is a pneumothorax, then the net gradient for gas absorption is only 54 mm Hg (760 – 706). If the patient is placed on 100% oxygen, however, the sum of all the partial pressures in the capillary blood will probably fall below 200 mm Hg (the PN₂ will approach 0, whereas the PO₂ will remain <100 mm Hg). The net gradient for gas absorption will exceed 550 mm Hg, or be 10 times greater than it was with the patient breathing room air.¹

Administration of humidified 100% oxygen to rabbits with experimentally induced pneumothoraces increased the rate of absorption by about sixfold.¹⁸ In subsequent studies in patients with a spontaneous pneumothorax, administration of high concentrations of supplemental oxygen increased the rate of absorption by fourfold.¹⁹ It is recommended that hospitalized patients with any type of pneumothorax who are not subjected to aspiration or tube thoracostomy be treated with high-flow supplemental oxygen.

Simple Aspiration

The initial treatment for most patients with PSP greater than 15% of the volume of the hemithorax should be simple aspiration.^{16,20} This procedure is successful in about 60% of patients with PSP. If successful, simple aspiration avoids hospitalization, and there is less pain from the smaller tube. The recurrence rates appear to be similar after simple aspiration and after tube thoracostomy.^{16,20}

With this procedure, a relatively small needle (≈16 gauge) with an internal polyethylene catheter is inserted into the second anterior intercostal space at the mid-clavicular line after local anesthesia. An alternative site is selected if the pneumothorax is loculated or if adhesions are present. After the needle is inserted, it is extracted, leaving the catheter tip in the pleural space. A three-way stopcock and a

60-mL syringe are attached to the catheter. Air is manually withdrawn until no more can be aspirated. The catheter is then occluded for several hours. If the chest radiograph confirms that there has been no recurrence, the catheter is removed and the patient is discharged. Alternatively, the patient can be observed overnight or can be discharged with a Heimlich one-way valve attached to the catheter.^{20a} If the total volume of air aspirated exceeds 4 L and no resistance has been felt, it is assumed that there has been no reexpansion, and alternative procedures are initiated.

Patients with their first PSP should be managed initially with simple aspiration on an outpatient basis. Consideration can be given to overnight observation in hospital for those who reside a long distance from the hospital. Patients should return in 24 to 72 hours for a follow-up chest radiograph. If aspiration is unsuccessful, then either thoracoscopy or tube thoracostomy should be undertaken.²¹ In one study the intrapleural administration of 300 mg of minocycline after a successful pneumothorax aspiration decreased the incidence of subsequent PSP recurrence from 49% to 29%.²² Simple aspiration is not recommended for patients with secondary spontaneous pneumothoraces or with recurrent PSPs.

Tube Thoracostomy

For the past several decades, most patients with PSP have been managed initially with tube thoracostomy. It is recommended if simple aspiration proves ineffective and thoracoscopy is not readily available. It rapidly results in the reexpansion of the underlying lung and does not require prolonged hospitalization. In one series of 81 patients treated with tube thoracostomy, the average duration of hospitalization was only 4 days (range, 3 to 6 days). Only 3 patients (4%) had persistent air leaks after several days of chest tube drainage.²³

Tube thoracostomy with relatively small tubes (8 to 16 French) or pigtail catheters (8 to 10 French) appear to be as effective as larger tubes.¹⁶ It is advisable to use a water-seal chamber and to avoid suction for the first 24 hours of tube thoracostomy to reduce the risks of reexpansion pulmonary edema.

After the lung has reexpanded and the air leak has ceased for 24 hours, the chest tube can be removed. Air leaks are present when there is bubbling through the water-seal chamber of the drainage system. If there is no bubbling on quiet respiration, the patient should be asked to cough. The absence of bubbling indicates there is no air leak. Whether clamping the tube to observe for the recurrence of pneumothorax before its removal is beneficial remains controversial.¹⁵ If there is a persistent air leak after 72 hours, consideration should be given to application of a blood patch (see later). If air leak persists over 72 hours after tube thoracostomy, thoracoscopy should be considered.

Tube Thoracostomy with Instillation of a Pleurodesing Agent

Efforts have been made to diminish the recurrence rates of PSP by injecting pleurodesing agents into the pleural space at the time of the initial episode. Thoracoscopy with stapling of blebs and pleural abrasion reduces the recurrence rate to less than 5%²⁴ and is the preferred option. Otherwise, pleurodesis with talc slurry or doxycycline can reduce the

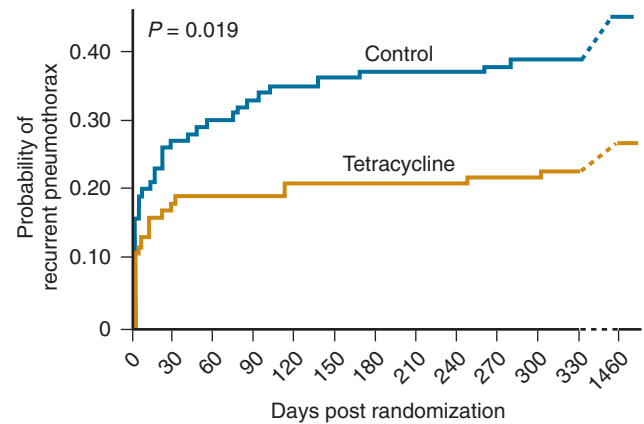


Figure 81-3 Pneumothorax recurrence. The probability of recurrent pneumothorax after assignment to the tetracycline group was lower than in the control group in the Veterans Administration cooperative study on spontaneous pneumothorax. (Redrawn from Light RW, O'Hara VS, Moritz TE, et al: Intrapleural tetracycline for the prevention of recurrent spontaneous pneumothorax. *JAMA* 264:2224–2230, 1990.)

recurrence rates from approximately 40% to 25% (Fig. 81-3).²⁵ Large-particle-size talc should be used to minimize the risks for acute lung inflammation.²⁶ A tetracycline derivative (e.g., doxycycline or minocycline) is preferred by some (see Chapter 82). Bleomycin is not recommended because it does not produce a pleurodesis in animals with a normal pleura²⁷ and has not been studied with pneumothorax in humans.

Autologous Blood Patch for Persistent Air Leak

The presence of a persistent air leak leads to prolongation of the hospitalization of patients with spontaneous pneumothorax. One inexpensive, noninvasive treatment for prolonged air leaks is the application of an autologous blood patch.^{28,29} Venous blood (50 to 100 mL) is drawn and promptly instilled intrapleurally, without anticoagulation, through a chest tube.²⁸ The chest tube should not be clamped because, with an ongoing air leak, there would be risk for tension pneumothorax. Elevating the tube (about 60 cm) keeps the blood within the pleural cavity without clamping. According to a review of the literature, the blood patch technique stopped the air leaks in 91.7% of 107 patients.²⁸ Whether blood patches prevent recurrence is unknown, although, in a small study ($n = 32$), no recurrences was found after a follow-up period of 12 to 48 months.³⁰

Thoracoscopy

Video-assisted thoracic surgery (VATS) is the treatment of choice of PSP if aspiration fails or if pneumothorax recurs (see Chapter 24). In a meta-analysis of 27 studies, the recurrence rate was only 5.4%.³¹ During VATS, attempts are made to eliminate the blebs (e.g., by endo-stapling or suturing³²) and to create a pleurodesis. Pleurodesis is probably best induced by pleural abrasion,^{33,34} but some recommend apical pleurectomy.³⁵ Bleb stapling without pleurodesis has a higher recurrence rate than bleb stapling with pleurodesis and is not recommended.

The most common complication after VATS for the treatment of PSP is a persistent air leak, seen in less than 5% of cases. VATS offers shorter hospitalization stays

(median, 3 days) and less morbidity when compared with thoracotomy.³¹

Medical thoracoscopy with talc insufflations (without stapling of blebs and pleural abrasion) has been tried.³⁶ In one study of 59 patients, this approach had a recurrence rate of 5% during a follow-up period of 5 years.³⁷ Controlled studies are needed to determine whether thoracoscopy is as effective as VATS.

Open Thoracotomy

When VATS is not available, open thoracotomy with oversewing of the blebs and pleural abrasion is a reasonable alternative. A transaxillary mini-thoracotomy can minimize the trauma and the length of the scar.³⁷ In a meta-analysis the recurrence rate after open thoracotomy was only 1.1% and significantly better than that for VATS.²⁴ Various methods have been used for scarification of the pleural surfaces, ranging from visceral and parietal pleurectomy to pleural abrasion with dry sponges. Because all appear to be similarly effective, pleural abrasion with dry gauze is recommended because it is less traumatic than pleurectomy and does not appear to interfere with a subsequent thoracotomy.

Summary of Treatment

Most patients with their first PSP should be managed initially with simple aspiration. Patients who fail aspiration should be managed with tube thoracostomy. If the air leak persists, VATS should be performed promptly, with endostapling of blebs and pleural abrasion to create a pleurodesis. When thoracoscopy is unavailable, a blood patch or an attempt at pleurodesis with a tetracycline derivative or talc can be tried. Thoracotomy is effective but involves longer hospitalizations and more postoperative morbidity. Patients with recurrent PSP should undergo VATS or thoracotomy.

SECONDARY SPONTANEOUS PNEUMOTHORAX

SSP, which develops in a patient with an underlying lung disease, is thus more serious than a primary pneumothorax because it further decreases the pulmonary function of a patient whose reserve is already diminished. In addition, the presence of the underlying lung disease makes diagnosis and management of the pneumothorax more difficult.

INCIDENCE

The incidence of SSP is similar to that of PSP.³⁸ There are an estimated 15,000 new cases of SSP annually in the United States. Men older than age 75 have the highest per capita rate of pneumothorax, 60 per 100,000 per year.³

ETIOLOGIC FACTORS

COPD is the most common underlying disease in patients with SSP, although almost every lung disease has been associated with SSP. In one series of 505 patients with SSP, 348

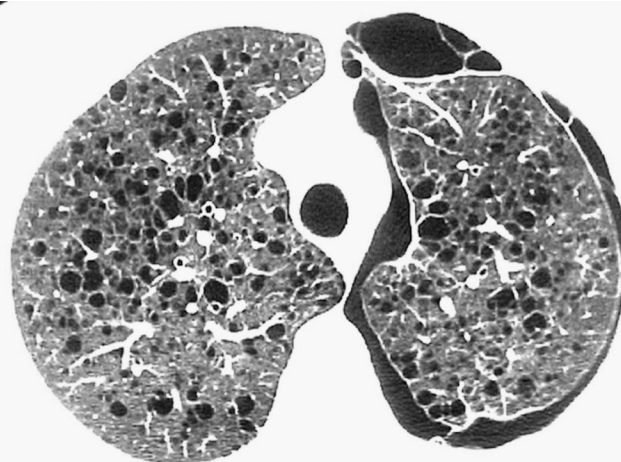


Figure 81-4 Chest CT scan of a patient with lymphangioleiomyomatosis. Note the numerous thin-walled cysts, rounded and relatively uniform in shape, and a pneumothorax on the left. (Courtesy Dr. Lisete Teixeira, University of Sao Paulo, Brazil.)

patients had COPD, 93 had tumors, 26 had sarcoidosis, 9 had tuberculosis, 16 had other pulmonary infections, and 13 had miscellaneous diseases.³⁹ Among patients with COPD, the incidence of SSP increases with progressive severity of the COPD. In the Veterans Administration cooperative study²⁵ on pneumothorax, 27% of the 229 participants had an FEV₁/FVC ratio below 0.40. One of the more common causes of SSP is *Pneumocystis jirovecii* infection in patients with *acquired immunodeficiency syndrome* (AIDS) (see eFig. 90-15).⁴⁰ There is also a high incidence in cystic fibrosis. Of the more than 28,000 patients on the Cystic Fibrosis Foundation registry, the incidence of pneumothorax was 3.4%.⁴¹ Patients with lymphangioleiomyomatosis (Fig. 81-4; see Chapter 69 and eFig. 69-7) and Langerhans cell histiocytosis (formerly histiocytosis X⁴²) (see Chapters 54 and 63) also have a high incidence of spontaneous pneumothorax.

CLINICAL MANIFESTATIONS

In general, the clinical features (dyspnea, chest pain, cyanosis, and hypotension) associated with SSP are more severe than those associated with PSP. In the Veterans Administration cooperative study, the mortality rate from pneumothorax was 1%.²⁵

DIAGNOSIS

The possibility of a pneumothorax should be considered in every patient with COPD who has a sudden increase in breathlessness and/or chest pain. Physical examination is not always helpful because patients with underlying disease may already have hyperexpanded lungs, decreased tactile fremitus, a hyperresonant percussion note, and distant breath sounds over both lung fields.

The demonstration of a pleural line on the chest radiograph can be difficult in radiographs of COPD patients because of their emphysematous lungs. Pneumothorax is therefore easily overlooked, particularly when the radiograph is overexposed. In patients with lung disease, the

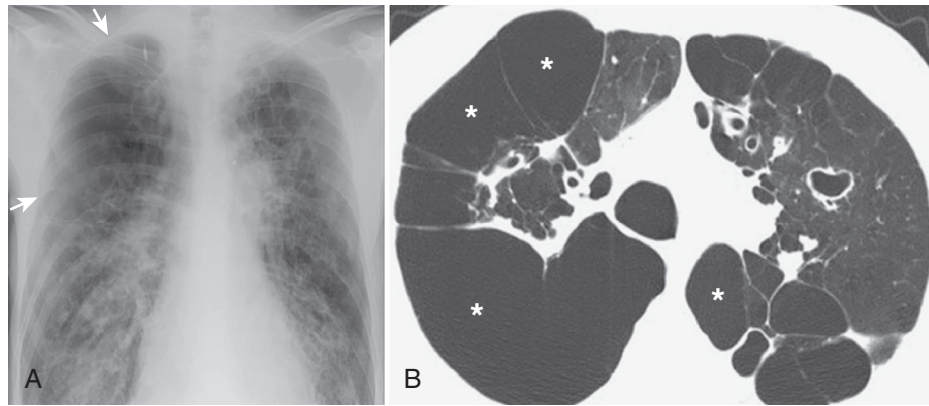


Figure 81-5 Bullae resembling pneumothorax. **A**, Frontal chest radiograph of a patient with cystic fibrosis and extensive bullous disease of the right apex that was initially mistaken for a pneumothorax. Note lucent area (arrows) within the right upper lung field. **B**, CT scan confirms the presence of bullae (*) and excludes pneumothorax.

radiographic appearance of the pneumothorax can be altered by the underlying abnormalities. Areas of normal lung collapse more evenly and completely than do diseased areas with large bullae or severe emphysema, which have decreased elastic recoil and may trap gas.

It is important to distinguish a SSP from a thin-walled bulla in patients with COPD. The apparent pleural line with a large bulla is usually concave toward the lateral chest wall because it represents the medial border of the bulla, whereas the pleural line with a pneumothorax is usually convex toward the lateral chest wall. CT scanning may be necessary to diagnose pneumothorax in a patient with COPD and to discriminate between pneumothorax and bullae (Fig. 81-5).

RECURRENCE RATES

The recurrence rates for SSPs are higher than those for PSPs whether or not measures are taken to prevent a recurrence. In observation studies over a 3- to 5-year period, the recurrence rates were shown to be higher in those with SSP ($\approx 45\%$) than in patients with PSP ($\approx 30\%$).^{12,25}

TREATMENT

Urgent evaluation is indicated for any patient suspected of having a SSP, because death has been reported before a chest tube can be inserted. Such deaths were reported in 3 of 57 patients (5%) with pneumothorax secondary to COPD⁴³ and in 3 of 15 patients (20%) with cystic fibrosis.⁴⁴ The high immediate mortality rate emphasizes the need for prevention of recurrences.

If one has time, the initial treatment for nearly every patient with a SSP should be tube thoracostomy. Simple aspiration is not recommended except in an emergency (see later) because it frequently is ineffective and cannot prevent recurrence. The evacuation of even a small pneumothorax can rapidly improve symptoms. In patients receiving mechanical ventilation, immediate chest tube drainage is needed because the pneumothorax is likely to enlarge.

In SSP the lung is more difficult to expand and air leaks persist longer when compared with PSP. In SSP caused by COPD, the median time for lung expansion is 5 days (versus

1 day for PSP),⁴³ and more patients require prolonged chest tube drainage. After 7 days of tube thoracostomy drainage, the lung remains unexpanded or the air leak persists in about 20% of patients with SSP.⁴³

Following thoracostomy, most patients with SSP should be considered for thoracoscopy. Thoracoscopy should certainly be performed in patients with a persistent air leak or an unexpanded lung after 72 hours of tube thoracostomy. If the lung expands and the air leak ceases within the first 72 hours, an attempt should be made to prevent a recurrence. For preventing recurrences, thoracoscopy is superior to chemical pleurodesis (recurrence rates of about 5% versus 20%, respectively).^{12,25} If thoracoscopy is unavailable/inappropriate, chemical pleurodesis should be performed (as discussed earlier) to prevent a recurrent pneumothorax. A blood patch can be considered if thoracoscopy is unavailable and the patient has a persistent air leak.⁴⁵ Thoracotomy is another alternative.

One consideration for patients with SSP is the effect that a pleurodesing agent might have on future lung transplantation. In 1998, however, a consensus conference statement on lung transplantation in cystic fibrosis stated that pleurodesis is not a contraindication to lung transplantation.⁴⁶ However, pleurodesis is likely to make future lung transplantation more difficult, and consultation with a transplant surgeon is advisable.

PNEUMOTHORAX SECONDARY TO PNEUMOCYSTIS IN PATIENTS WITH AIDS

Patients with AIDS and *P. jirovecii* infection have a relatively high incidence of spontaneous pneumothorax. Approximately 5% of patients with AIDS who receive prophylactic pentamidine will have a spontaneous pneumothorax. Most patients with AIDS who have a spontaneous pneumothorax have a history of *P. jirovecii* infection, many are taking prophylactic pentamidine, and most have a recurrence of *P. jirovecii* infection.^{1,40} The presence of multiple subpleural lung cysts or cavities, often associated with subpleural necrosis, may explain the high incidence of spontaneous pneumothorax¹ (see eFig. 90-15). After having one pneumothorax, the patient is likely to experience a contralateral pneumothorax. It should be noted that iatrogenic

pneumothoraces, particularly those related to mechanical ventilation or pulmonary procedures, are also common in patients with AIDS.^{1,40}

Perhaps due to the necrotic lung surrounding the ruptured cavity, the spontaneous pneumothorax associated with AIDS and *P. jirovecii* infection is notoriously difficult to treat. In one report of 20 patients, the median duration of tube thoracostomy was 20 days; 11 patients underwent pleurodesis, whereas 5 patients had thoracotomy.⁴⁷

Patients with AIDS and a spontaneous pneumothorax should be treated with tube thoracostomy. If the air leak persists for more than a few days, there are two options: a Heimlich valve or VATS. There is no literature on use of the blood patch technique in managing these patients. In general, the Heimlich valve is preferred because the patient can be managed as an outpatient.

If the air flow is too high for the Heimlich valve to maintain lung inflation, VATS can be performed. Wait⁴⁸ reported that 30 of 32 patients with AIDS and spontaneous pneumothorax were managed successfully with talc insufflation without endo-stapling. If operative intervention is planned, it should be carried out early to avoid prolonged hospitalization and morbidity.

PNEUMOTHORAX SECONDARY TO TUBERCULOSIS

Between 1% and 3% of patients hospitalized for pulmonary tuberculosis will have a pneumothorax⁴⁹ (eFig. 81-4). All such patients should be treated initially with tube thoracostomy. In one series of 28 patients, 7 of the 11 patients treated by observation or repeated pleural aspiration died,⁴⁹ compared with 1 of the 17 patients treated with tube thoracostomy (64% versus 6%, respectively). Antituberculous chemotherapy should be given concomitantly with the tube thoracostomy. Thoracoscopy or thoracotomy should be considered if the lung remains unexpanded or if there is an air leak after 7 days.⁵⁰

IATROGENIC PNEUMOTHORAX

Iatrogenic pneumothoraces are probably more common than PSPs and SSPs combined. Currently, the leading cause of iatrogenic pneumothorax is transthoracic needle aspiration (see Fig. 19-10). The incidence of iatrogenic pneumothorax with this procedure is about 25%, and about 10% of the patients with pneumothorax receive tube thoracostomy.¹ This procedure is more likely to result in a pneumothorax if the patient has COPD, if the lesion is deep within the lung, or if the angle of the needle route is wide (which may correlate with an increased number of passes).^{51,52} Various maneuvers such as positioning the patient with the biopsied side down or using the blood patch technique have not consistently proved useful in diminishing the incidence of pneumothorax. One paper did demonstrate a significant reduction in pneumothoraces if the puncture access was sealed by instillation of NaCl 0.9% solution during extraction of the guide needle.⁵³

Mechanical ventilation is another risk factor. In one early series of 553 patients undergoing mechanical ventilation, 4% developed a pneumothorax.⁵⁴ The frequency of the

pneumothorax was increased if the patient had aspiration pneumonia (37%), was treated with positive end-expiratory pressure (15%), had intubation of the right main-stem bronchus (13%), or had COPD (8%).⁵⁴ In another study, the incidence of pneumothorax in 725 patients with acute respiratory distress syndrome was 6.9%.⁵⁵ In patients with acute respiratory distress syndrome, the incidence of barotrauma is higher if the ventilator plateau pressure exceeds 35 cm H₂O or if the lung compliance is below 30 mL/cm H₂O. In patients with asthma, barotrauma rates were high and mortality was similarly high; now both have been reduced by low-pressure permissive hypercapnic ventilatory strategies.

Other common causes of iatrogenic pneumothorax (with approximate incidences) are thoracentesis (2.5%), pleural biopsy (8%), and transbronchial lung biopsy (6%) (eFig. 81-5). Iatrogenic pneumothorax also frequently complicates *cardiopulmonary resuscitation* (CPR). Other procedures associated with the development of an iatrogenic pneumothorax include subclavian (eFig. 81-6) or internal jugular vein catheterization, tracheostomy, intercostal nerve block, mediastinoscopy, liver biopsy, and the insertion of small nasogastric tubes.¹ Radiofrequency ablation is increasingly used to treat lung tumors and carries a high incidence of pneumothorax (≈30%).^{56,57} In a series of 137 procedures, 27 resulted in symptomatic pneumothoraces requiring chest tube drainage.⁵⁸ In another series, the risk for pneumothorax was associated with the number of tumors ablated, electrode positions, and the electrode trajectory through aerated lung.⁵⁷

DIAGNOSIS

Iatrogenic pneumothorax should be suspected in any patient treated by mechanical ventilation whose clinical condition suddenly deteriorates. A sensitive indicator of the development of a pneumothorax in such patients is increased peak and plateau pressures if the patient is on a volume-cycled ventilator or a decreased tidal volume if the patient is on a pressure-cycled ventilator.

The diagnosis should also be suspected in any patient who becomes more dyspneic after an intervention procedure that has been associated with development of a pneumothorax. Importantly symptoms from the pneumothorax may not be evident for 24 hours or longer after the procedure.⁵⁹ The diagnosis needs confirmation by ultrasound or radiographic imaging. In patients with extensive pulmonary opacities, there may be little evidence of lung collapse, but the air in the pleural space may instead be indicated by the “deep sulcus” sign (Fig. 81-6).

TREATMENT

The treatment of iatrogenic pneumothorax differs from that of spontaneous pneumothorax in that preventing recurrence is not an issue. If the patient has minimal/no symptoms and the pneumothorax is small (e.g., <15% of the volume of the hemithorax), the patient can be observed. The administration of supplemental oxygen increases resolution rate (see earlier section). Otherwise, the procedure of choice is simple aspiration with a plastic catheter,⁶⁰ as described for PSP. If simple aspiration fails,

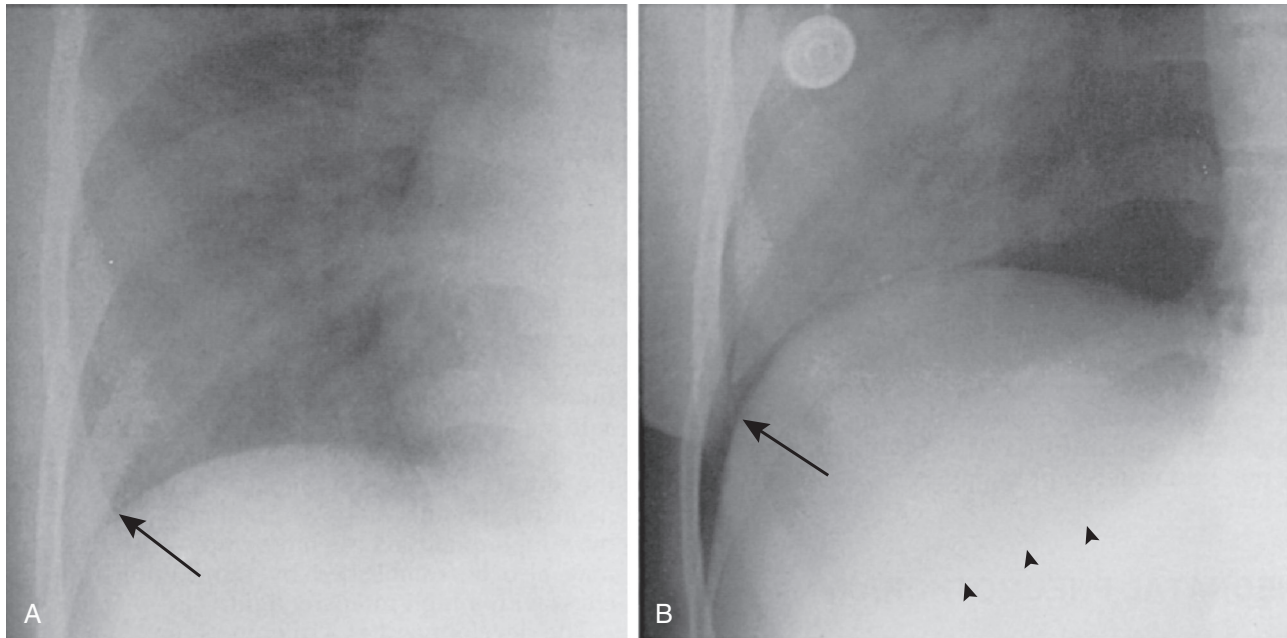


Figure 81-6 Appearance of pneumothorax in a supine patient. Detailed views of the right costophrenic angle from successive supine chest radiographs taken before (A) and after (B) the development of a pneumothorax. Both illustrations show diffuse infiltration in the right lower lung field. Note change in costophrenic angles (arrows) caused by air in the pleural space between the diaphragm and chest wall: the “deep sulcus” sign. Air in the anterior pleural space can also be recognized by an air-tissue interface (arrowheads).

tube thoracostomy should be performed. Small-bore chest tubes with Heimlich valves are quite effective in this situation.⁶¹

The management of patients with an iatrogenic pneumothorax secondary to positive-pressure mechanical ventilation should include urgent tube thoracostomy because tension pneumothorax can easily develop when the positive pressure forces air into the pleural space under high pressure until it exceeds atmospheric pressure. If the patient continues to receive mechanical ventilation, the chest tube should be left in place for at least 48 hours after the air leak stops. At times, a bronchopleural fistula is so large that a high percentage of the total inspired volume exits through the chest tube. The air exiting through the chest tube still provides effective ventilation, however, because it contains levels of carbon dioxide similar to those of exhaled gas.⁶² Two studies in adults^{63,64} have demonstrated that high-frequency ventilation does not consistently improve gas exchange or decrease air leak through the fistula.

TRAUMATIC (NONIATROGENIC) PNEUMOTHORAX

The incidence of pneumothorax after blunt trauma depends on the severity of the trauma. The incidence of pneumothorax exceeds 35% in some series.⁶⁵

MECHANISM

A traumatic pneumothorax can result from either penetrating or nonpenetrating chest trauma (see Figs. 76-4, 76-7, 76-8, and 76-10 and eFigs. 76-10 and 84-2). With penetrating chest trauma, the wound allows air to enter the

pleural space via the chest wall or via the visceral pleura from the tracheobronchial tree. With nonpenetrating trauma, a pneumothorax may develop if the visceral pleura is lacerated secondary to a rib fracture or dislocation. In the majority of patients with pneumothorax secondary to nonpenetrating trauma, however, there are no associated rib fractures. It is thought that the sudden chest compression abruptly increases the alveolar pressure, which may cause alveolar rupture. Air then enters the interstitial space and dissects toward either the visceral pleura or the mediastinum. A pneumothorax develops when either the visceral or the mediastinal pleura ruptures.

DIAGNOSIS AND TREATMENT

The diagnosis of pneumothorax is made by ultrasonography, chest radiography, or CT. A pneumothorax detectable on CT, but not on the chest radiograph, is called an *occult* pneumothorax¹ and accounts for about 40% of traumatic pneumothoraces⁶⁶ (see Fig. 76-7). In recent years, ultrasonography (see Chapter 20) performed by emergency department physicians or surgeons has been used increasingly to determine whether a pneumothorax is present.⁶⁶ Ultrasonography is more sensitive than supine chest radiographs in identifying pneumothoraces,^{66,67} but there are also false positives, particularly in patients with underlying lung diseases, especially COPD.⁶⁸

Most traumatic pneumothoraces should be treated initially with tube thoracostomy. If the patient has an occult pneumothorax or if the distance between the lung and chest wall does not exceed 1.5 cm, however, tube thoracostomy is probably not indicated unless the patient is receiving mechanical ventilation.⁶⁹ In one series, 333 patients with pneumothoraces less than 1.5 cm were initially managed without chest tubes, and only 33 (10%)

subsequently required tube thoracostomy.⁶⁹ When traumatic pneumothoraces are treated with tube thoracostomy, the lung usually expands and the air leak ceases within 24 hours.⁶⁹ If the leak persists for more than a few days, consideration should be given to performing thoracoscopy to identify and repair the site of the air leak.⁷⁰

Immediate thoracotomy is indicated for traumatic pneumothorax in two uncommon scenarios. The first is fracture of the trachea or a major bronchus (see eFig. 76-10 and 84-2), which usually presents together with an anterior/lateral fracture of one or more of the first three ribs and is associated with at least some hemoptysis.⁷¹ Fiberoptic bronchoscopy to search for a bronchial tear⁷¹ followed by its surgical repair usually restores full function of the distal lung.⁷¹

The second diagnosis to consider is traumatic rupture of the esophagus, which is almost always accompanied by a hydropneumothorax (see Fig. 84-7). A reliable screening test for esophageal rupture is measurement of the pleural fluid amylase concentration.⁷² If this level is elevated, contrast radiographic studies of the esophagus should be performed. It is important to establish the diagnosis of esophageal rupture expeditiously because the mortality approaches 100% if surgical treatment is not performed promptly.

AIR TRAVEL AND PNEUMOTHORAX

For patients who have suffered a pneumothorax, the Aerospace Medical Association suggests that flying be allowed 2 to 3 weeks after radiologic resolution of the pneumothorax.⁷³ One study of 12 patients with traumatic pneumothorax reported that the 10 patients who waited at least 14 days before travel were all asymptomatic in flight, whereas 1 of 2 patients who flew earlier than 14 days developed respiratory distress in flight with symptoms suggesting a recurrent pneumothorax.⁷⁴ However, a recent article suggested that patients who do not have a pneumothorax 48 hours after discharge can travel safely.^{74a}

NEONATAL PNEUMOTHORAX

A spontaneous pneumothorax is present shortly after birth in 1% to 2% of all infants, and the pneumothorax is symptomatic in approximately half of these.^{18,75} It is twice as common in male infants. Affected infants are usually full- or post-term and have a history of fetal distress requiring resuscitation or a difficult delivery with evidence of aspiration of meconium, blood, or mucus.¹⁸

There is a high incidence (19% in a series of 295 infants) of pneumothorax in infants with neonatal respiratory distress syndrome⁷⁶ (eFig. 81-7). Pneumothorax developed in 29% of those requiring intermittent positive-pressure ventilation with positive end-expiratory pressure, in 11% of those requiring continuous positive airway pressure, and in only 4% of those not requiring respiratory assistance.⁷⁶ In a series of more than 20,000 babies with birth weights between 401 and 1500 g (0.9 to 3.3 pounds) born in 1999, the incidence of pneumothorax was 6.3%, but, in those babies weighing less than 750 g (1.7 pounds), the incidence was 15%.⁷⁷

PATHOGENESIS

The development of a spontaneous neonatal pneumothorax is related to the mechanical problems of expanding the lung for the first time. During the first few breaths of life, the transpulmonary pressures average 40 cm H₂O, with occasional pressures as high as 100 cm H₂O.¹ At birth the alveoli usually open in rapid sequence, but, if bronchial obstruction is present from the aspiration of blood, meconium, or mucus, high transpulmonary pressures may lead to rupture of the lung. A transpulmonary pressure of 60 cm H₂O ruptures an adult lung,¹⁸ whereas a transpulmonary pressure of 45 cm H₂O ruptures a neonatal rabbit lung.¹

CLINICAL MANIFESTATIONS

With neonatal spontaneous pneumothorax, the signs vary from none to severe acute respiratory distress, depending on the size of the pneumothorax. With a small pneumothorax, there may be mild apneic spells with some irritability or restlessness. With a large pneumothorax, there may be severe respiratory distress with marked tachypnea, grunting, retractions, and cyanosis.¹⁸ In newborn babies the detection of pneumothorax by physical examination is often difficult because breath sounds are widely transmitted in the small neonatal thorax from the contralateral lung. The most reliable sign is a shift of the apical heart impulse away from the side of the pneumothorax.¹⁸ The diagnosis requires radiographic confirmation (see eFig. 81-7).

The development of a pneumothorax in a patient with neonatal respiratory distress syndrome is usually heralded by a change in the vital signs. In one series, cardiac arrest marked the development of the pneumothorax in 12 of the 49 patients; most of the other patients had a decrease in the blood pressure, pulse, or respiratory rate.⁷⁶ In another series, however, the earliest signs were an increase in the blood pressure, heart rate, or pulse pressure.⁷⁸ A pneumothorax in an infant with the neonatal respiratory distress syndrome is associated with mortalities exceeding 60% in some studies.

TREATMENT

An infant with a spontaneous pneumothorax who is asymptomatic or mildly symptomatic can be observed closely because the pneumothorax usually resolves within a few days. It is necessary to observe the patient closely in case the pneumothorax enlarges or a tension pneumothorax develops.¹⁸ Supplemental oxygen can hasten the resolution of the pneumothorax, but it should be administered with care because of the dangers of retrolental fibroplasia.¹⁸ Tube thoracostomy should be performed on any neonate who is more than mildly symptomatic. In one series of 76 infants with spontaneous pneumothorax, respiratory failure necessitated mechanical ventilation in 18, and pulmonary hypertension requiring either nitric oxide or extracorporeal membrane oxygenation developed in 7.⁷⁹ However, all the patients had complete resolution of their pulmonary compromise.⁷⁹ Tube thoracostomy should be performed in virtually all infants with the neonatal respiratory distress syndrome and pneumothorax, because the

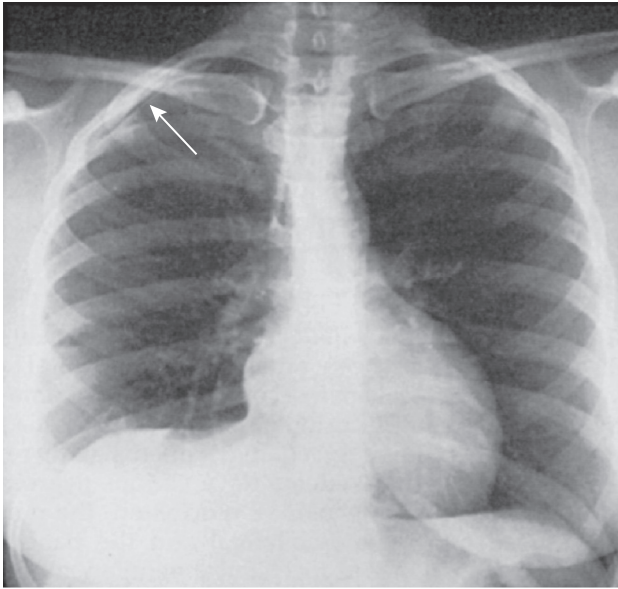


Figure 81-7 Catamenial pneumothorax. Frontal chest radiograph from a 32-year-old woman showing a small right-sided pneumothorax (arrow). This was the fourth episode with onset during menses. (Courtesy Dr. Lewis S. Lehman, San Francisco.)

pneumothorax further compromises the ventilatory status and tends to increase in size.

CATAMENIAL PNEUMOTHORAX

A catamenial pneumothorax is a pneumothorax that develops in conjunction with menstruation (Fig. 81-7). Up until 2004, 229 cases had been reported,⁸⁰ but it is probably underdiagnosed and underreported. With catamenial pneumothorax, respiratory symptoms usually develop within 24 to 48 hours of the onset of the menstrual flow.⁸¹ Most pneumothoraces are right sided, but left-sided and bilateral pneumothoraces have been reported.⁸¹ Catamenial pneumothoraces tend to be recurrent. On average, patients have approximately five pneumothoraces before the diagnosis is recognized.

PATHOGENESIS

The pathogenesis of catamenial pneumothorax is unclear. When the syndrome was initially described,⁸² it was hypothesized that air gained access to the peritoneal cavity during menstruation and then entered the pleural cavity through a diaphragmatic defect. In a subsequent review of 28 patients who had undergone thoracoscopy, endometriosis, primarily diaphragmatic, was present in 18 and diaphragmatic perforations or nodules were present in 21.⁸³ It has been suggested that, with diaphragmatic endometriosis, the endometrial tissue undergoes cyclical necrosis leading to a diaphragmatic defect.⁸⁴ These authors concluded that diaphragmatic abnormalities play a fundamental role in the pathogenesis of catamenial pneumothorax.^{83,84} Alternatively, endometriosis of the visceral pleura could lead to alveolar pleural air leaks during menstruation.

DIAGNOSIS AND TREATMENT

Any woman who has a spontaneous pneumothorax within the first 48 hours of her menstrual period should be suspected of having a catamenial pneumothorax. The treatment of catamenial pneumothorax is aimed at treating endometriosis, known or suspected, by suppressing the ectopic endometrium. This can be attempted by suppression of ovulation with oral contraceptives or by suppression of gonadotropins with danazol or gonadotropin-releasing hormone to produce a medical oophorectomy.⁸⁰ Alternative treatments include thoracoscopy with stapling of blebs, closure of diaphragmatic defects and parietal abrasion or pleurectomy, or pleurodesis.⁸⁰ In one series, 28 patients were treated with removal of the diaphragmatic perforation and pleurodesis at thoracoscopy plus suppression of gonadotropins, and the recurrence rate was still 32%.⁸³

TENSION PNEUMOTHORAX

A tension pneumothorax is present when the intrapleural pressure exceeds the atmospheric pressure throughout expiration and often during inspiration as well.¹ Most patients who develop a tension pneumothorax are receiving positive pressure to their airways, either during mechanical ventilation or during resuscitation.¹ For a tension pneumothorax to develop in a spontaneously breathing person, some type of one-way valve mechanism must be present so more air enters the pleural space on inspiration than leaves the pleural space on expiration, and thus air accumulates in the pleural space under positive pressure.¹

PATHOPHYSIOLOGY

The development of a tension pneumothorax is usually heralded by a sudden deterioration in the cardiopulmonary status of the patient. This is probably related to the combination of a decreased cardiac output due to impaired venous return and profound hypoxia due to ventilation-perfusion mismatches. In mechanically ventilated sheep, an induced tension pneumothorax (mean pleural pressure of +25 cm H₂O) reduced the cardiac output from 3.5 to 1.1 L/min.⁸⁵ The arterial PO₂ also fell from a baseline value of 159 to 59 mm Hg. Comparable reductions in cardiac output and oxygen saturation were seen in pigs⁸⁶ and in dogs⁸⁷ following induction of tension pneumothoraces. Similarly, in patients on mechanical ventilation who develop tension pneumothorax, there is a large drop in the cardiac output.⁸⁸

CLINICAL MANIFESTATIONS

Tension pneumothorax most commonly develops in patients receiving positive-pressure mechanical ventilation or CPR.⁸⁹ Occasionally a tension pneumothorax will evolve during the course of a spontaneous pneumothorax or during hyperbaric oxygen therapy. Tension pneumothorax can develop from improper connection of one-way flutter valves with small-caliber chest tubes.⁹⁰

The clinical picture of a tension pneumothorax is often characterized by respiratory distress, cyanosis, marked

tachycardia, and profuse diaphoresis, marked hypoxemia and sometimes respiratory acidosis.

Tension pneumothorax should be suspected in patients receiving mechanical ventilation who suddenly deteriorate. In this situation the peak pressures on the ventilator usually increase markedly if the patient is on volume-type ventilation, whereas the tidal volumes decrease markedly if the patient is on pressure-support ventilation.¹ Tension pneumothorax should also be suspected in any patient undergoing CPR in whom ventilation becomes difficult. In one series of 3500 autopsies, an unsuspected tension pneumothorax was found in 12 cadavers; 10 had received mechanical ventilation, and 9 CPR.⁹¹ Tension pneumothorax should also be suspected in patients with a known pneumothorax who deteriorate suddenly or in patients who have undergone a procedure known to cause a pneumothorax.

DIAGNOSIS AND TREATMENT

A tension pneumothorax is a medical emergency. One should not waste time to establish the diagnosis radiologically because the clinical situation and the physical findings usually strongly suggest the diagnosis¹ (see Fig. 76-4 and eFig. 81-7). The patient should immediately be given high-flow supplemental oxygen. Once the abnormal hemithorax is identified, a small (14- to 16-gauge) catheter with needle should be immediately inserted into the pleural space through the second anterior intercostal space.¹ The catheter should be left in place and in communication with the atmosphere until air ceases to exit through the syringe. Additional air can be withdrawn from the pleural space with the syringe and the three-way stopcock. The patient should be prepared for immediate tube thoracostomy.

REEXPANSION PULMONARY EDEMA

Unilateral pulmonary edema (*reexpansion pulmonary edema* [RPE]) may develop in certain patients whose lung has been rapidly reinflated after a period of collapse secondary to a pneumothorax or a pleural effusion. Patients with RPE have various degrees of hypoxia and hypotension. On occasion the pulmonary edema becomes bilateral, and the patient requires intubation and mechanical ventilation. On rare occasions the syndrome has been fatal, including in otherwise healthy, young persons. The incidence of RPE is probably relatively low because there were no instances of RPE in the Veterans Administration cooperative study of more than 200 patients with spontaneous pneumothorax.²⁵ In a retrospective study of 320 episodes of pneumothorax, RPE developed in 3 patients (1.0%).⁹² A literature review in 1988 revealed 53 cases of RPE edema, which was fatal in 11 (21%) cases.⁹³ This is likely an overestimation, because nonfatal cases are less likely to be reported and many patients are asymptomatic.⁹⁴

PATHOPHYSIOLOGY

RPE appears to be due to increased permeability of the pulmonary vasculature. In both experimental animals and

humans, the edema fluid has a high protein content, suggesting that edema forms because of increased capillary leak rather than increased hydrostatic pressure. It has been hypothesized that the mechanical stresses applied to the lung during reexpansion damage the capillaries and lead to pulmonary edema. Reperfusion injury due to reactive oxygen species is another possibility. However, several animal studies⁹⁵⁻⁹⁸ demonstrated that the administration of reactive oxygen species-scavenging compounds such as dimethylthiourea, catalase, or superoxide dismutase all partially inhibit the neutrophilic infiltration associated with the development of RPE but do not impressively decrease the amount of edema in the experimental situation. Moreover, neutrophil depletion does not affect the amount of edema. For these reasons, mechanical stress on the lung is currently considered to be the most likely cause of RPE.

In humans, most cases of RPE develop when the pneumothorax or pleural effusion has been present for at least 3 days and when negative pressure has been applied to the pleural space. Similar findings have been confirmed in experimental animal studies.

CLINICAL MANIFESTATIONS

Patients with RPE typically have pernicious coughing or chest tightness during or immediately after tube thoracostomy or large-volume thoracentesis. The symptoms usually progress for 12 to 24 hours, and serial chest radiographs reveal progressive ipsilateral pulmonary edema (see Fig. 76-6), which may progress to involve the contralateral lung. Treatment is primarily supportive, with the administration of supplemental oxygen and diuretics, and intubation and mechanical ventilation when necessary. One report suggested that the syndrome could be aborted if the patient is treated with continuous positive airway pressure within the first hour of the development of the syndrome.⁹⁸ Chest tubes should be placed to underwater-seal drainage if the syndrome develops to avoid further aggravation with suction.

PREVENTION

Because RPE can be fatal, it is important to prevent it when possible. The possibility of its development should be considered in any patient with a large pneumothorax or pleural effusion subjected to tube thoracostomy or thoracentesis. When tube thoracostomy is performed for spontaneous pneumothorax, the tubes should initially be connected to an underwater-seal drainage apparatus rather than to negative pleural pressure. If underwater-seal drainage does not cause reexpansion of the underlying lung within 24 to 48 hours, then negative pressure can be applied to the pleural space.¹

When a thoracentesis is performed, the procedure should be terminated if the patient develops tightness of the chest or experiences coughing. In a series of 941 thoracenteses, including 119 that drained more than 1500 mL, opacities consistent with RPE were noted in only two patients (0.2%) from whom 1000 and 1200 mL of pleural fluid had been removed; neither was symptomatic or required treatment.⁹⁹ Thus, RPE is rare and rarely clinically significant.

Patients should be monitored during thoracentesis for symptoms, and, although pleural manometry has been recommended to follow pleural pressures, such approaches have not yet been shown to alter the incidence of this rare complication.

CHYLOTHORAX

Pleural fluid can be milky or turbid. When this cloudiness persists after centrifugation, it is almost always due to high lipid content in the pleural fluid. High levels of lipid can accumulate in pleural fluid through two separate mechanisms. In one, chyle enters the pleural space following disruption of the thoracic duct, producing a chylothorax (chylous pleural effusion). In the second, large amounts of cholesterol or lecithin-globulin complexes accumulate in a pleural effusion to produce a pseudochylothorax (chyliform or cholesterol pleural effusion).¹⁰⁰ It is important to recognize and differentiate these two conditions because their etiology and management are completely different.

PATHOPHYSIOLOGY

A chylothorax forms when the thoracic duct, which carries dietary fat in the form of chylomicrons, becomes disrupted. Chylomicrons are formed in the intestine, after which they enter the intestinal lacteal vessels and are then transported to the cisterna chyli. The thoracic duct, a 2- to 3-mm-wide thin-walled conduit, leaves the cisterna chyli and passes through the aortic hiatus of the diaphragm on the anterior surface of the vertebral body between the aorta and the azygos vein into the posterior mediastinum. The thoracic duct then ascends extrapleurally in the posterior mediastinum along the right side of the anterior surface of the vertebral column. Between the level of the fourth and sixth thoracic vertebrae, the duct crosses to the left side of the vertebral column and continues cranially to enter the superior mediastinum between the aortic arch and the subclavian artery and the left side of the esophagus. As a result, rupture of the thoracic duct in its caudal portion tends to produce right-sided chylothoraces, and rupture of the cranial portion of the duct tends to produce left-sided chylothoraces.¹⁰⁰ Once the thoracic duct passes the thoracic inlet, it arches above the clavicle and passes anterior to the left subclavian artery, vertebral artery, and thyrocervical trunk to terminate in the region of the left jugular and subclavian veins.

Although the route just described is the typical one, there are wide anatomic variations throughout the course of the duct. For example, duplication or even triplication of the thoracic duct is present in 40% of the population. Also, many collateral vessels and lymphaticovenous anastomoses are known to exist. Presumably these channels transport the chyle to the blood following therapeutic ligation of the thoracic duct. The wide range of anatomic variation and the multiple collateral channels render the thoracic duct at risk for injury, especially during thoracic surgery.¹⁰¹

Chyle, the liquid drained from the thoracic duct, is a milky, opalescent fluid that usually separates into three layers on standing: a creamy uppermost layer containing chylomicrons, a milky intermediate layer, and a dependent

layer containing cellular elements. Chyle is bacteriostatic,¹⁰⁰ not irritating, and not known to induce pleural thickening.

The thoracic duct normally conveys between 1500 and 2500 mL of chyle daily. Ingestion of fat can increase the flow of lymph in the thoracic duct by two to tenfold for several hours. Ingestion of liquid, but not protein or carbohydrate, also increases the flow, whereas starvation decreases chyle flow. The primary cellular component of chyle is the T lymphocyte. Prolonged loss of chyle can result in severe nutritional depletion, dehydration, electrolyte loss, and hypolipidemia, as well as depletion of T- and B-cell lymphocytes and immunodeficiency.¹⁰⁰

ETIOLOGY

Chylothorax can result from traumatic (including surgical) and nontraumatic causes: their relative frequencies vary among series. In a summary of five separate series totaling 143 patients, greater than 50% of chylothoraces were caused by tumors, especially lymphoma (Video 81-1), followed by trauma.¹ However, a single institute series of 203 patients revealed trauma/surgery as the most common (50%) cause compared to nontraumatic causes (44%).¹⁰²

The unpredictable anatomy of the thoracic duct and associated accessory lymphatics makes them vulnerable to injury during cardiovascular or thoracic surgical procedures, especially those involving the posterior mediastinum. Esophagectomy, for example, is complicated by chylothorax in 1% to 4% of cases.¹⁰³ Overall, the incidence of chylothorax after cardiothoracic operations is low (0.5% to 2.5%).^{104,105} Surgical procedures that involve mobilization of the left subclavian artery are particularly likely to be complicated by chylothorax. Transplantation of the lung and heart (or both) can sever the lymphatic drainage and result in chylothoraces.¹⁰⁶ Chylothorax has been reported to complicate a wide range of other operations, including esophagoscopy, stellate ganglion blockade, thoracic sympathectomy, high translumbar aortography, lung resections, thyroid surgery, spinal surgery,¹ and even gastric banding.¹⁰⁷ Bilateral chylothoraces can develop following bilateral neck dissection.¹⁰⁸ Chylothorax is common after surgical repair of congenital diaphragmatic hernia (incidence, 4.6% in a series of 1383 patients), especially if patch repair or extracorporeal membrane oxygenation is employed. Most (>80%) patients can be treated conservatively, and mortality is not increased.¹⁰⁹ To aid in the identification of the thoracic duct during surgery, ingestion of cream (to increase the flow and size of the thoracic duct) before high-risk operations (e.g., esophagectomy) has been advocated.¹¹⁰

Nonsurgical trauma can also lead to chylothorax. The thoracic duct may be disrupted with penetrating injuries involving the neck or thorax. Nonpenetrating trauma in which the spine is hyperextended or a vertebra is fractured can lead to chylothorax, particularly if the injury follows shortly after the ingestion of a fatty meal. Less impressive traumas such as weight lifting, straining, severe bouts of coughing or vomiting, childbirth, and vigorous stretching while yawning have been associated with chylothorax.¹⁰⁰ Chylothoraces secondary to closed trauma are usually on the right side, with the site of rupture in the region of the 9th or 10th thoracic vertebra.

Chylothoraces can also arise from transdiaphragmatic movement of chylous ascites.¹¹¹ Causes of chylous ascites include many of the causes of chylothorax. In addition, cirrhosis may be a cause of chyloascites and associated chylothorax. These chylothoraces are transudative, probably from dilution by low-protein cirrhotic ascitic fluid.

There are many other causes of chylothorax, but all together they account only for a small percentage of all chylothoraces. Lymphangioleiomyomatosis (see also Chapter 69) and other lymphatic abnormalities, such as pulmonary lymphangiectasis, yellow nail syndrome, lymph node enlargement, and lymphangitis of the thoracic duct can result in chylothorax, as can tuberous sclerosis, amyloidosis, mediastinal fibrosis, lupus, and Gorham syndrome. Elevated pressure of the venous system into which the thoracic duct drains (e.g., superior vena caval or subclavian vein thrombosis/obstruction) is another cause of chylothorax.¹⁰⁰ In postsurgical patients, those with central venous thrombosis were five times more likely to develop chylothorax.¹¹² Chylothorax accounts for about one fifth of pleural effusions in patients with superior vena cava syndrome.¹¹³

Chylothorax with no identifiable cause (5% to 10% of all cases) is labeled *idiopathic*. Lymphoma, however, must be excluded.

Fetal and Neonatal Chylothorax

Fetal chylothorax is an uncommon but important condition that requires monitoring and management to avoid serious complications, including spontaneous abortion or death after birth.¹¹⁴ Fetal chylothoraces are often termed *primary* fetal pleural effusions, because no obvious cause can be identified in most cases.¹¹⁴ Congenital lymphangiectasis is a rare condition that can produce fetal chylothorax.¹¹⁵ Cytogenetic analysis of the cells (mainly lymphocytes) may help detect underlying chromosomal abnormalities.

Chylothorax is the most common type of neonatal pleural effusion,¹¹⁴ with an incidence estimated at 1:15,000. Of note, the pleural fluid remains clear rather than milky until milk feeding begins.¹¹⁴ It may be a result of persistent fetal chylothorax¹¹⁴ but can also be due to developmental abnormalities of the thoracic duct or its rupture from trauma during delivery.¹¹⁶ Increased venous pressure, especially from congenital heart diseases or from thrombosis of central venous catheters, is another recognized mechanism of neonatal chylothorax.¹¹⁴ In many cases the chylothorax is idiopathic.

Mutations of several candidate genes have recently been linked with congenital chylothorax, including *integrin α_9* (*ITGA9*) and β_1 (*ITGB1*), vascular endothelial growth factor receptor 3 (*FLT4*, and *FOXC2*). The integrin $\alpha_9\beta_1$ is widely expressed in smooth muscles and is a receptor for extracellular matrix proteins and vascular cell adhesion molecule-1. Animal studies suggested that the α_9 subunit is required for the normal development of the lymphatic system, including the thoracic duct. Mice with homozygous null mutation of the α_9 subunit develop large bilateral congenital chylothoraces.¹¹⁷ An autosomal inheritance of a heterozygous missense mutation (c.1210G>A, p.G404S) of *ITGA9* has been found in four of five fetuses with chylothoraces who did not respond to prenatal pleurodesis but not in those who responded.¹¹⁸

The gene for vascular endothelial growth factor C was found to be important in tumor-related lymphangiogenesis and chyloascites formation in mice bearing ovarian carcinoma. Chy-3-mutant mice, which carry a chromosomal deletion that includes *Vegfc*, develop hypoplastic dermal lymphatic drainage and resultant chyloascites and lymphedema.¹¹⁹ Transgenic mice with mutations in the *Pi3kca* (*phosphoinositide 3-kinase*) gene also develop defective lymphatics and chyloascites.¹²⁰ *Rasa1* (also known as p120 RasGAP) is a Ras GTPase-activating protein that functions as a regulator of blood vessel growth in adult mice and humans. In mice, systemic loss of *Rasa1* resulted in early lethality caused by chylothorax with underlying extensive lymphatic vessel hyperplasia and leakage.¹²¹

CLINICAL MANIFESTATIONS

The symptoms, physical findings, and radiographic features of chylothorax are the same as those encountered in patients with comparably sized pleural effusions of any cause. Pleuritic chest pain and fever are rare because chyle is not proinflammatory. Chylopericardium or chyloascites can be present concurrently.

With nontraumatic chylothorax, insidious onset of dyspnea on exertion is common. With traumatic chylothorax, there is usually a latent period of 2 to 10 days between the trauma and the clinical presentation of the pleural effusion.¹²² During this latent period, chyle may accumulate in the posterior mediastinum to form a chyloma—visible radiologically as a posterior mediastinal mass¹—which eventually ruptures into the pleural cavity, giving rise to a chylothorax.

Neonatal chylothorax may present with respiratory distress in the first few days of life. Fifty percent of the infants have symptoms within the first 24 hours, whereas 75% have symptoms by the end of the first week. Most neonatal chylothoraces are either right sided or bilateral, but rarely left sided.¹¹⁶ There is a high frequency of neonatal chylothoraces in infants with hydramnios.¹¹⁶ Fetal chylothorax is often diagnosed only on ultrasonography.

The main threat to life with chylothorax is from external drainage leading to inanition. The daily loss of 1.5 to 2.5 L of fluid rich in protein, fats, electrolytes, and lymphocytes will rapidly render patients malnourished and immunocompromised.

DIAGNOSIS

The distinctive white, odorless, milky appearance should suggest the diagnosis, though chylothorax must be differentiated from empyema and pseudochylothorax (Fig. 81-8). In empyema, the milky appearance is caused by suspended leukocytes and debris, which will sediment upon centrifugation, leaving a clear supernatant. In both chylous and chyloform pleural effusions, the milky appearance is caused by high lipid levels, and the supernatant will remain cloudy after centrifugation. The lipids in chyloform effusion are cholesterol or lecithin-globulin complexes rather than chylomicrons (as in chylothoraces).¹²³ It should be emphasized that the pleural fluid with chylothorax can occasionally be bloody or even clear yellow. In one series only 44% of chylothoraces were milky.¹²⁴



Figure 81-8 Chylothorax pleural fluid before and after low-fat diet. **A**, Milky appearance of a chylothorax, with a triglyceride level of greater than 700 mg/dL and cholesterol less than 70 mg/dL. **B**, Clear appearance of pleural fluid obtained after a low-fat diet, along with a reduced triglyceride level in the fluid. (From Scholz GA, Sirbu H, Anders K, et al: Persisting right-sided chylothorax in a patient with chronic lymphocytic leukemia: a case report. *J Med Case Rep* 5:492, 2011.)

Pleural fluid and serum triglyceride and cholesterol levels should be measured. Pleural fluid from a chylothorax usually has a triglyceride level above 110 mg/dL (1.24 mmol/L), a ratio of the pleural fluid to serum triglyceride level of greater than 1.0, and a ratio of the pleural fluid to serum cholesterol level of less than 1.0.¹¹¹ However, fasting may significantly reduce the triglyceride level in the pleural fluid and produce false-negative results.¹²⁵ If doubt persists after the lipid measurements, one approach is to feed the patient a high-fat meal before sampling the pleural fluid. Alternatively, the demonstration of chylomicrons in lipoprotein analysis of the pleural fluid confirms the diagnosis of chylothorax.¹²⁶ The latter is particularly valuable if the triglyceride level is in the equivocal range (50 to 110 mg/dL). Rarely, a pleural fluid triglyceride level of less than 50 mg/dL has been found in chylothorax. It is important to differentiate chylous from chyloform pleural fluid (see later).

Typical chylous effusions are lymphocyte-rich effusions with exudative protein levels but low lactate dehydrogenase

Table 81-1 Management of a Chylothorax

MAINTAINING NUTRITION AND REDUCING THE VOLUME OF CHYLE CIRCULATION

Dietary: medium-chain triglyceride diet or total parenteral nutrition
Octreotide

RELIEVING DYSPNEA BY REMOVING CHYLE FROM THE PLEURAL CAVITY

Thoracentesis (short term only)
Tube thoracostomy (short term only)
Pleuroperitoneal or pleurovenous shunting
Pleurodesis/indwelling pleural catheter

TREATMENT OF THE UNDERLYING DEFECT

Thoracic duct embolization
Ligation of the thoracic duct (thoracoscopy or thoracotomy)
Clipping or fibrin glue to the thoracic duct leak
Radiation therapy for mediastinal lymphoma

levels.¹²⁴ The electrolyte composition of chyle is similar to that of serum, and the protein content is usually around 3 g/dL. Transudative chylothorax is usually due to concurrent conditions (especially hepatic cirrhosis) known to produce transudates. An elevated lactate dehydrogenase level in chylothorax should raise concerns of concurrent conditions (e.g., infection).^{124,127} Magnetic resonance imaging can confirm the high fat signal, whereas chest CT may occasionally show low attenuation representing fat (eFig. 81-8 and Video 81-2) within the pleural effusion and support the diagnosis of chylothorax.

After establishing the diagnosis of a chylothorax, it is important to determine the cause. Because lymphoma is the most common (and treatable) cause of nontraumatic chylothorax, CT of the mediastinum and abdomen is mandatory to search for lymphadenopathy and is also useful in the diagnosis of lymphangioleiomyomatosis.

Bipedal lymphangiography or lymphoscintigraphy (e.g., with technetium-99m-labeled human serum albumin) is useful to help pinpoint the site of chyle leak along the thoracic duct.¹²⁸⁻¹³⁰ Direct lymph node puncture to inject dye is an alternative method favored by some.¹⁰¹ Lipiodol is an alternative dye that has some sclerosant effect and thus potential advantage in occluding the thoracic duct.¹⁰¹ Unenhanced magnetic resonance imaging¹³¹ or the combination of lymphoscintigraphy with three-dimensional magnetic resonance imaging can provide additional anatomic and functional details of the lymphatic channels.¹³² Pleural biopsy or thoracoscopy is not usually indicated in the workup of patients with a chylothorax because the pleura is generally not affected.

TREATMENT

General Approaches

Management strategies for chylothoraces should be directed toward (1) maintaining nutrition and reducing the flow of chyle, (2) relieving dyspnea by removing the chyle, and (3) closure of the defect (Table 81-1). No evidence-based guidelines exist for chylothorax management, which may in part depend on the clinical scenario (e.g., adult versus child,¹³³ traumatic versus nontraumatic) and the rate of chyle leak.

Maintaining Nutrition and Reducing the Flow of Chyle. The main dangers to the patient are malnutrition and immunodeficiency from removal of a large volume of chyle; hence it is important to initiate definitive treatment of the chylothorax promptly.

Regardless of the cause, closure of the thoracic duct leak may be facilitated by reducing the flow of chyle. This can be achieved by using parenteral hyperalimentation to provide nutrition. Alternatively, a low-fat diet with most fats in the form of medium-chain triglycerides can reduce chyle flow because the medium-chain triglycerides are absorbed directly into the blood¹⁰⁰ (see Fig. 81-8). Input from an experienced dietitian is recommended.

A range of compounds have been tested to hasten the closure of thoracic duct leak. Most studies have used octreotide (a somatostatin analogue) in postoperative pediatric patients in uncontrolled trials, but evidence on its use in adults and for nontraumatic chylothoraces is relatively scarce; large controlled studies are urgently needed. In a series of chylothoraces in 85 children, 85% responded to dietary manipulation. Somatostatin therapy was successful in half of the remaining 15% of cases, but no factors were identified to predict octreotide response.¹³⁴ The mechanism of its action is not clear but is believed to be related to a reduction of intestinal fat (especially triglyceride) absorption and increased fecal fat excretion.¹³⁵ Common side effects include flushing, nausea, and diarrhea. Other agents examined include etilefrine¹³⁶—a sympathomimetic drug that aimed to induce contraction of smooth muscles around the main thoracic duct—and factor XIII; the results of these agents need further verification.

Relieving Dyspnea by Removing Chyle. Thoracentesis or tube thoracostomy may be used initially, but every attempt should be made to minimize the duration of tube drainage to avoid malnutrition or immunosuppression.

Pleuroperitoneal shunts are advisable if the chylothorax fails to resolve quickly. This minimizes the risks for malnourishment or immunodeficiency because the lymph is not removed from the body. Some authors recommend pleuroperitoneal shunts as the first line of management as soon as the diagnosis is established. To date, most series on pleuroperitoneal shunts are based in pediatric populations. Pleuroperitoneal shunting is contraindicated if ascites is present and is less likely to be successful if the chylothoraces result from central venous thrombosis.¹³⁷ Redirection of the chyle back into the systemic circulation has been performed successfully via pleurovenous shunts.¹³⁸ Use of indwelling pleural catheters for ambulatory drainage of chylothoraces has been reported in several retrospective small series.¹³⁹

Closure of the Defect. With traumatic chylothorax, the defect in the thoracic duct frequently closes spontaneously. Conversely, nontraumatic chylothorax is more likely to require surgical intervention.¹⁴⁰ In one series ($n = 74$), chylothorax resolved with medical (nonsurgical) measures in 50% of traumatic but only 27% of nontraumatic cases. In addition, chylous effusion recurred more commonly in nontraumatic chylothorax (50% versus 13% in traumatic cases). Lymphatic imaging did not seem to materially influence management.¹⁴¹

If the pleuroperitoneal shunt is ineffective in draining the pleural space, or if the patient has a chest tube and the drainage of chyle continues unabated beyond 7 days, a more aggressive treatment plan is needed. In a series of 27 patients with chylothorax following lung resection, those with large-volume drainage (>500 mL per 24 hours) despite total parenteral nutrition were more likely to require reoperation.¹⁰⁵ In another series of patients with post-lung resection chylothorax, 13 of the 15 patients with lower initial drainage volume (mean, 300 mL/day) responded to conservative treatment, whereas only 6 of 11 patients with larger drainage volume responded.¹⁴²

Several options exist to control the chyle leak. Talc pleurodesis by slurry or poudrage has been successful in some reports.¹⁴³ Recently, lymphatic embolization and blockade¹⁰¹ has been shown in several series, with a complete or partial response rate of approximately 70%.¹⁴⁴⁻¹⁴⁶ The thoracic duct is punctured transabdominally via a peritoneal cannula under fluoroscopic guidance, and the duct is embolized with various devices (e.g., microcoils). In patients whose thoracic duct cannot be cannulated, disruption of the duct with needles may be sufficient to reduce or stop the chyle leak.¹⁴⁴ Retrograde embolization of the cisterna chyli has been attempted via a microcatheter passed through the thoracic duct for the treatment of chylous ascites.¹⁴⁷ Coils, gelatin sponge, and doxycycline have been used as embolization material.¹⁴⁷

Surgical repair of the thoracic duct defect should be considered if lymphatic embolization is unavailable or fails. Surgical ligation can often be achieved via VATS, but thoracotomy is sometimes required. Laparoscopic and laparotomy approaches have also been tried. The duct is ligated above and below the site of the leak or at the lowest point in the chest.¹⁴⁸ Various technical advances have been tried, including fibrin glue application around the leak,¹⁴⁹ use of robotic ligation,¹⁵⁰ and thermofusion of the thoracic duct using a computer-controlled diathermy system.¹⁵¹ Ligation of the thoracic duct by laparoscopy has also been attempted with success.¹⁵²

Ideally, the site of the leak should be identified preoperatively by lymphangiography or lymphoscintigraphy. The identification of the thoracic duct can also be facilitated with preoperative oral administration of cream.¹⁵³

If for technical reasons the thoracic duct cannot be successfully ligated during VATS, a pleurodesis (e.g., partial pleurectomy or talc insufflation) should be performed to obliterate the pleural space during the operation. Mediastinal radiation therapy was successful in a pilot study ($n = 7$) of post-thoracic surgery chylothorax.¹⁵⁴

Special Considerations

Nontraumatic Chylothorax. If the patient is known to have either lymphoma or metastatic carcinoma, the chylothorax can respond to mediastinal radiation. In one series, mediastinal radiation adequately controlled the chylothorax for the remainder of the patient's life in 68% of those with lymphoma and in 50% of those with metastatic carcinoma.¹⁵⁵ If radiation therapy fails, embolization, pleurodesis, or pleuroperitoneal shunting should be considered.¹⁵⁶

If the cause of a nontraumatic chylothorax is unknown, the initial management is similar to that for a patient with a traumatic chylothorax, as discussed previously. A

pleuroperitoneal shunt may be considered to allow time for a thorough evaluation. If chest CT and lymphangiography have normal findings, the chylothorax can be assumed to be due to minor trauma, and spontaneous closure can be expected within weeks.

Fetal and Congenital Chylothorax. Congenital chylothorax, diagnosed either in utero or after birth, can cause developmental abnormalities and at times be fatal.¹¹⁴ Congenital chylothorax was present in 3.2% of 598 patients with hydrops fetalis in one series, with a mortality of 5.9%.¹⁵⁷ If diagnosed in utero, maternal dietary restriction should be initiated.¹⁵⁸ Ultrasound-guided thoracentesis can be performed to evacuate the chylothorax,¹⁵⁹ because large effusions can cause pulmonary hypoplasia and respiratory distress at birth.¹¹⁴ If the chylothorax reaccumulates, pleuro-amniotic shunting should be considered.¹⁶⁰ In a small number of reported cases, ultrasound-guided intrapleural administration of OK-432¹⁶¹ or maternal blood¹⁶² has offered effective control of the chylothorax, presumably via creating a pleurodesis.

If the congenital chylothorax is diagnosed after birth, the baby should be treated conservatively with repeated thoracenteses to avoid respiratory compromise while nutrition is maintained by the parenteral route or with medium-chain triglycerides.¹⁶³ Feeding with centrifuged breast milk (which removes the fat content) was attempted in one small study.¹⁶⁴ Although the evidence supporting octreotide remains limited, it has a good safety profile and can be tried. If the chylothorax recurs after the third pleural aspiration, however, a pleuroperitoneal shunt should be placed. If the shunt is unsuccessful, thoracic duct ligation is recommended.¹¹⁴ In one study of congenital chylothoraces ($n = 10$), those with lower birth term and birth weight and whose drainage exceeded 50 mL/kg/day were more likely to fail to respond to conservative treatment and require surgery.¹⁶⁵

Pulmonary Lymphangioleiomyomatosis. Pulmonary lymphangioleiomyomatosis (LAM) is a rare condition, affecting mostly women of reproductive age, and is characterized by progressive dyspnea, recurrent pneumothoraces, and chylous effusions (see Chapter 69). The reported incidence of chylothorax in patients with LAM ranges from 10%¹⁶⁶ to 30%.¹⁶⁷ It can arise in both the sporadic and the tuberous sclerosis complex-associated types of LAM—the former is associated with a higher incidence of chylothorax.¹⁶⁶ Whereas the mean age of presentation of LAM is in the early 30s,¹⁶⁸ the mean age of presentation of chylothorax is in the early 40s.¹⁶⁶ The chylothorax is usually unilateral but can be bilateral¹⁶⁶ or associated with chyloascites. The chylothorax is thought to be the result of the combination of perilymphatic proliferation of smooth muscle leading to lymphatic obstruction and of infiltration of the lymph nodes in the mediastinum and retroperitoneal space by immature smooth muscle cells.¹⁶⁹ CT scan is usually diagnostic for LAM (see Fig. 8.1-4). Typical LAM cell clusters can also be found in the chylous pleural fluid.¹⁷⁰

The general principles for the management of a chylothorax secondary to LAM are similar to those for any non-traumatic chylothorax. The course of these chylothoraces is highly variable.¹⁶⁶ In some cases, simple thoracentesis for

symptomatic relief is adequate.¹⁶⁶ However, in two series combined, 12 of the 19 LAM patients with chylothoraces required either pleurodesis or thoracic duct ligation to control the reaccumulation of chyle.^{166,171} In one series, sirolimus successfully controlled the chylous effusions in 12 patients with improvement in lung function.¹⁷²

When considering use of pleurodesis, one should consider the potential impact on future lung transplantation, which is a treatment option for a proportion of patients with LAM (19% in one series¹⁷³). The morbidity and mortality of transplantation is already increased in these patients, especially from intraoperative bleeding¹⁷⁴ attributed to pleural adhesions from recurrent pneumothoraces, and pleurodesis may increase that risk. Although pleurodesis is not an absolute contraindication for future transplantation, a transplant surgeon should be consulted before subjecting LAM patients with a chylothorax to pleurodesis or surgical ligation of the thoracic duct.

PSEUDOCHYLOTHORAX (CHYLIFORM PLEURAL EFFUSIONS; CHOLESTEROL PLEURAL EFFUSIONS)

A pseudochylothorax (chyliform pleural effusion) may also produce milky turbid pleural fluid. The turbidity is related to high levels of cholesterol or lecithin-globulin complexes in the fluid. Pseudochylothoraces, with fewer than 200 reported cases in the literature,¹⁷⁵ are much less common than chylothoraces.

PATHOGENESIS

Although pseudochylothorax was first reported over a century ago, its precise pathogenesis remains unknown. Most patients with a pseudochylothorax have pleural surfaces that are markedly thickened and sometimes calcified, and the effusion is usually long-standing. It appears that, if an exudative effusion persists for a lengthy period—months to years—in a fibrotic area of grossly thickened pleura, it has a high tendency to become enriched with cholesterol.¹⁰⁰ However, increasing reports of pseudochylothoraces without chronic pleuritis or grossly thickened pleura challenge the traditional belief.¹⁷⁶

Most of the cholesterol in chyliform pleural effusions is associated with high-density lipoproteins, in contrast to the cholesterol in acute exudates, which is mostly bound to low-density lipoproteins.¹⁷⁷ It has been hypothesized that, during acute inflammation, there is increased filtration of cholesterol into the pleural fluid.¹⁷⁷ In addition, the cholesterol can originate from degeneration of erythrocytes and leukocytes that enter the pleural space as part of the underlying disease process.¹⁷⁸ The thickened pleura inhibits the exit of cholesterol out of the pleural space.¹⁷⁷ Serum cholesterol levels and systemic cholesterol metabolism appear to be normal in patients with pseudochylothorax.

Chyliform pleural effusions are most commonly seen after tuberculous pleurisy (54%), including those cases treated with artificial pneumothorax. Successful treatment

of an acute tuberculous pleurisy does not preclude the development of a pseudochylothorax.¹⁷⁵ Pseudochylothorax can develop in association with chronic rheumatoid pleurisy (9% of pseudochylothoraces) and rarely with paragonimiasis and trauma (including thoracic surgery).¹⁷⁹

CLINICAL MANIFESTATIONS

Pseudochylothorax commonly but not inevitably develops in patients with long-standing pleural effusions. The mean duration of the effusion is 5 years before it turns chyliform, but much shorter times of onset have been reported.^{176,180} Many patients with chyliform pleural effusions are asymptomatic or at least no more symptomatic than before they developed the pleural effusion. Symptoms, if present, are usually related to the underlying disease process or to the pulmonary restriction produced by the effusion and the thickened pleura. In some cases the effusion gradually enlarges with time, with resultant progressive dyspnea.¹⁰⁰

DIAGNOSIS

The pleural effusion is often chronic and associated with thickened or calcified pleura. The fluid is milky, and the differential diagnoses of chylothorax and empyema need exclusion (see earlier). Presence of cholesterol crystals in the fluid defines a pseudochylothorax. The cholesterol crystals give a distinct satin-like sheen to the pleural fluid and microscopically have a typical rhomboid appearance. Not all patients with chyliform pleural effusion have cholesterol crystals in their pleural fluid; however, most have an elevated pleural fluid cholesterol level (>250 mg/dL, or 6.45 mmol/L).¹ Pleural fluid triglyceride levels can be high in pseudochylothorax. CT chest scan can reveal a layering of fat in nondependent sites.¹⁸¹

TREATMENT

Tuberculosis should always be considered in patients with a pseudochylothorax, although tuberculous pseudochylothorax is usually culture negative.¹⁷⁵ We advise drainage only in symptomatic cases and treating with antituberculous chemotherapy only those patients with positive stain or culture for tuberculosis and those with enlarging effusions of suspected tuberculous origin (see Chapter 35).

When the patient's exercise capacity is limited by breathlessness, a therapeutic thoracentesis should be performed and may improve exercise tolerance.¹⁷⁸ Thoracentesis can be difficult because of the frequently thickened pleura and negative intrapleural pressure.¹⁰⁰ Limited evidence exists to support surgical decortication, which should be considered only if the patient is symptomatic and the underlying lung is believed to be functional.

HEMOTHORAX

Hemothorax is the presence of blood in the pleural space, specifically when the hematocrit of the pleural fluid is greater than or equal to 50% of that of the peripheral blood.¹ When bloody pleural fluid is obtained with a diagnostic thoracentesis, the hematocrit should always be

measured. Frequently, even though the pleural fluid appears to be pure blood, the hematocrit of the fluid is below 5%.¹

TRAUMATIC HEMOTHORAX

Blood may enter the pleural space from injury to the chest wall, diaphragm, lung, blood vessels, or mediastinum. On entering the pleural space, the blood coagulates rapidly, but, presumably as a result of the physical agitation produced by movement of the heart and lungs, the clot may be defibrinated, rendering it liquid and unable to clot again. Loculation may develop early in the course of hemothorax.

Diagnosis

The diagnosis of traumatic hemothorax should be suspected in any patient with penetrating or nonpenetrating trauma of the chest (Fig. 81-9; see eFig. 76-8). It should be emphasized that the hemothorax may not be apparent on the initial chest radiograph. In one series of 130 patients with hemothorax secondary to nonpenetrating trauma, the hemothorax was not appreciated on the initial chest radiograph in 24% of the patients.¹⁸² Although the hemothorax was missed in some of the patients because the initial radiograph was obtained with the patient supine, other patients had no evidence of a hemothorax on the erect radiograph.¹⁸²

The CT scan is more sensitive than the chest radiograph in detecting hemothoraces. In a study of 103 patients with blunt trauma,⁶⁵ chest CT detected a hemothorax in 21 patients (20%) in whom the routine chest radiograph showed no pleural fluid. When patients experience severe thoracic trauma, a CT scan of the chest is indicated for its ability to identify hemothorax, as well as pneumothoraces, lung contusion, and bone fractures.⁶⁵

Ultrasonography is now used in many emergency departments and was comparable to initial chest radiograph in detecting hemothoraces in one study ($n = 240$, specificity

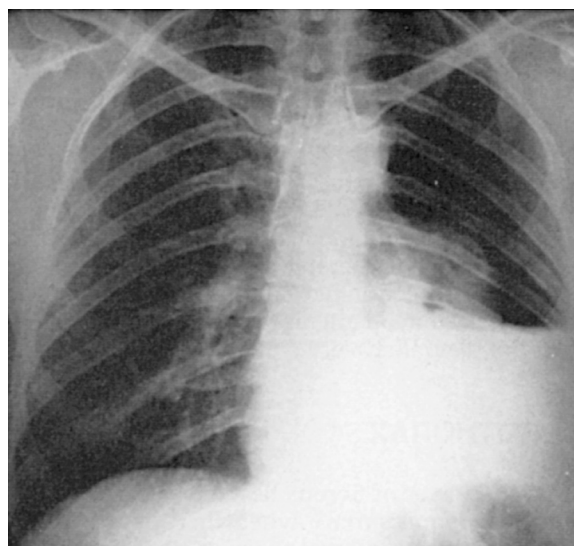


Figure 81-9 Frontal chest radiograph from a patient who suffered multiple injuries in an automobile accident. The patient had a hemothorax. With the prompt institution of tube thoracostomy, the air and blood were evacuated from the pleural space and the chest radiograph was normal 1 week later.

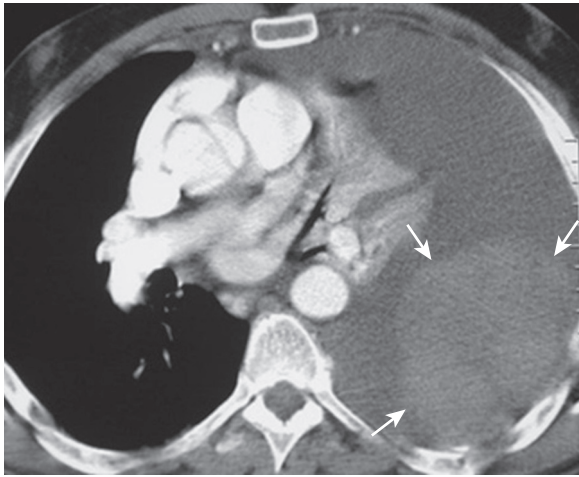


Figure 81-10 Axial CT scan of a patient with a large left hemothorax. The hyperdense region (arrows) indicates a retracted thrombus. Occasionally, unclotted erythrocytes can settle to the dependent area, creating a “fluid-fluid level,” representing the so-called hematocrit sign (see eFig. 81-9B).

100% and sensitivity 96%).¹⁸³ On CT scans, hyperdensity, due to the high hemoglobin content of retracted clot or sedimented blood, may point toward a hematoma (Fig. 81-10).¹⁸⁴

Delayed hemothorax was reported in one third of 36 patients at 18 hours to 6 days following the initial blunt trauma, especially those with multiple or displaced rib fractures.¹⁸⁵ However, in another series of 100 patients with penetrating thoracic trauma, none developed a hemothorax after 3 hours.¹⁸⁶

A patient with a traumatic hemothorax should undergo immediate tube thoracostomy, which helps evacuate the blood from the pleural space, brings the two pleural surfaces into apposition (which some believe may retard bleeding), enables quantification of the blood loss, and may decrease the incidence of subsequent empyema. The blood drained from the pleural space may be autotransfused, although contents of a hemothorax have a lower concentration of hemoglobin and coagulation factors than fresh blood.¹⁸⁷

Wherever possible, chest tubes should be inserted under image guidance to avoid injuring the ipsilateral hemidiaphragm, which may be elevated because of other causes such as atelectasis or phrenic nerve paralysis. Large-bore chest tubes have traditionally been recommended to avoid clotting of the blood, although this has not been proven. Observational series have shown no significant differences in clinical outcomes in patients treated with drains of 28 to 32 French (compared with those treated with 36 to 40 French).¹⁸⁸ Chest tubes should be removed as soon as they stop draining or cease to function to reduce risks of pleural infection.

No precise threshold exists for the amount of pleural bleeding that should trigger surgical intervention; however, if the bleeding is greater than 200 mL/hr with no signs of slowing, surgery must be considered. VATS has largely replaced thoracostomy as the procedure of choice,¹⁸⁹ with thoracotomy reserved only for massive acute hemorrhages. No relationship between timing of VATS and success rate was identified in a study of 328 patients. Independent

predictors of the need for thoracostomy (and failure of VATS) included diaphragm injury, retained hemothorax greater than 900 mL, and not administering antibiotics for initial chest-tube placement.¹⁹⁰

In a series of patients with active hemothorax, those with drainage above 200 mL/hr were subjected to contrast-enhanced CT scan, which identified sites of bleeding intercostal arteries. Subsequent transcatheter arterial embolization successfully stopped the bleeding.¹⁹¹

Complications

The four main potential pleural complications of traumatic hemothorax are the retention of clotted blood in the pleural space, pleural infection, pleural effusion, and perhaps fibrothorax. In one retrospective series, 24 (1.4%) of 1728 chest trauma patients had a residual hemothorax.¹⁹² Most patients with small to moderate amounts of clotted blood remaining in their pleural space have no residual pleural abnormalities even if no intervention is undertaken.¹⁹³ If more than 30% of the hemithorax is occupied by clotted blood, the hemothorax should be evacuated. Decisions regarding thoracoscopic evacuation should not be made from the plain chest radiograph alone and require CT studies.¹⁹⁴ VATS is the mainstay of management, and conversion to thoracostomy is seldom required.¹⁸⁹ The clotted blood should be evacuated within 7 days because after this time it begins to become organized and is much more difficult to remove.¹⁸⁹ In a prospective, randomized trial, VATS was more effective than thoracostomy tube drainage for removing retained hemothoraces. In this study, both the length of hospital stay (7 vs. 3.6 days) and the duration of tube drainage (4.5 vs. 2.5 days) were shorter in the group receiving VATS.¹⁹⁵ In another series, thoracoscopic evacuation performed within 3 days of admission was associated with a lower operative difficulty score (and shorter operation time) and shorter inpatient stay, compared with patients operated at later time points.¹⁹²

Once the source of the bleeding is controlled, intrapleural administration of fibrinolytic agents (e.g., streptokinase or urokinase) may be safe in patients with hemothorax and retained clots, according to several descriptive studies.¹⁹⁶ However, there have been no comparative studies to confirm the efficacy of fibrinolysis versus conservative management or surgical evacuation.

Empyema develops in 1% to 4% of all patients with traumatic hemothoraces,^{193,197} especially for those admitted in shock or those who have gross pleural contamination, associated abdominal injuries, or prolonged pleural drainage.^{193,197} For those with posttraumatic retained hemothorax, the risk for empyema was as high as 26.8% in a multicenter prospective study ($n = 328$).¹⁹⁸ The presence of rib fractures, Injury Severity Score of 25 or higher, and the need for additional interventions to evacuate retained blood from the thorax were predictors of empyema. Prophylactic antibiotics (e.g., cefazolin 500 mg every 6 hours until tube removal) can decrease the incidence of pleural infection,¹⁹⁹ which should be treated similarly as postpneumonic pleural infection (see Chapter 80).

In more than 10% of patients with a traumatic hemothorax, a pleural effusion will develop after the chest tubes are removed.^{193,197} Most such pleural effusions resolve spontaneously, leaving no residual pleural abnormalities. It is

important to perform a diagnostic thoracentesis in such patients, however, to verify sterility.

It is thought that fibrothorax develops in less than 1% of patients with hemothorax. Fibrothorax appears to develop more frequently when a hemopneumothorax is present or when a hemothorax becomes infected. The definitive treatment for fibrothorax is decortication. Decortication for fibrothorax should be delayed for several months after the injury, however, to allow time for spontaneous resolution of the pleural thickening, which is often considerable.

IATROGENIC HEMOTHORAX

The most common cause of iatrogenic hemothorax is thoracic surgery,²⁰⁰ but perforation of a central vein or artery by a percutaneously inserted catheter²⁰¹ is also common. Iatrogenic hemothorax can also follow thoracentesis (eFig. 81-9), pleural biopsy, chest tube insertion, percutaneous lung aspiration or biopsy (see eFig. 19-1), transbronchial biopsy, endoscopic esophageal variceal therapy, or CPR. Patients with iatrogenic hemothoraces should be managed, as are patients with traumatic hemothoraces, with chest tubes and thoracoscopy or thoracotomy as needed.

NONTRAUMATIC HEMOTHORAX

Nontraumatic hemothoraces are distinctly uncommon. The most common cause is malignant pleural disease, and the second most common cause is a complication of anticoagulation therapy for pulmonary embolization.²⁰² The cause of the hemothorax in some patients remains unknown despite exploratory thoracotomy.

A spontaneous hemothorax may result from rupture of an abnormal intrathoracic blood vessel, such as subpleural arteriovenous malformations, aneurysm of the aorta or pulmonary artery, patent ductus arteriosus, or coarctation of the aorta. Other causes of a spontaneous hemothorax include a complication of bleeding disorders (such as hemophilia or thrombocytopenia), a complication of spontaneous pneumothoraces, bronchopulmonary sequestration, thoracic endometriosis, varicella pneumonia, or intrathoracic extramedullary hematopoiesis. Spontaneous hemothorax is a rare but potentially life-threatening complication of neurofibromatosis, either from aneurysmal changes in large arteries (e.g., aorta) or from dysplastic changes in small vessels.


Mediastinal tumors can also produce a spontaneous large hemothorax, which can be bilateral. Blood can also accumulate in the pleural space because of pathologic conditions of abdominal organs, such as rupture of a splenic artery aneurysm through the diaphragm, pancreatic pseudocysts, and rupture of hepatocellular carcinomas.

Hemothoraces can complicate anticoagulant therapy (warfarin²⁰³ or heparin—low molecular weight²⁰⁴ or unfractionated²⁰²) or intrapleural fibrinolytic therapy.²⁰³ The hemothorax usually becomes apparent 4 to 7 days after anticoagulation therapy is initiated, but it may happen much later. When the hemothorax develops, the coagulation study results may be within the acceptable therapeutic range.²⁰²

Chest tubes should be inserted into patients with spontaneous hemothorax to remove the blood from the pleural

space and to quantify the rate of bleeding. If brisk (>100 mL/hr) bleeding persists, emergency thoracotomy should be performed.

FIBROTHORAX

Pleural fibrosis usually follows intense inflammation of the pleura; however, the mechanisms following the inflammatory process leading up to fibrosis are unclear (Video 81-3). Profibrotic cytokines, especially *transforming growth factor-β* (TGF-β), probably play a significant role. In various animal models, TGF-β, administered directly or via vector transfection, induces pleural fibrosis, and anti-TGF-β antibodies can inhibit pleural adhesion formation in empyema.²⁰⁵

A fibrothorax most commonly develops as a complication of an empyema or a hemothorax, but can also complicate tuberculosis, collagen vascular diseases, uremia, paragonimiasis, drug reactions, and other pleural injuries. The pleura can also be involved in systemic fibrotic diseases such as nephrogenic systemic fibrosis and immunoglobulin G4-related sclerosing disease.²⁰⁶ Pleural fibrosis can be idiopathic, and isolated familial cases have been reported.²⁰⁷

Whereas tuberculous pleuritis is common, fibrothorax is a rare complication.²⁰⁸ In one study, restrictive functional sequelae were found in 10% of 81 patients with tuberculous pleuritis, but were mostly mild.²⁰⁹ Neither the early drainage of the pleural effusion²¹⁰ nor the use of systemic corticosteroids²¹¹ has significant impact on subsequent development of pleural thickening or restrictive lung function in patients with tuberculous pleuritis. Pleural fluid inflammatory markers are, at best, weak predictors of eventual pleural thickening.²⁰⁹

Asbestos exposure may also lead to a fibrothorax (also called diffuse pleural thickening), which is usually bilateral.²¹² In these cases, extensive fibrosis of the visceral pleura develops, together with areas of adhesion with the parietal surfaces, thus obliterating the pleural space.²¹² Diffuse pleural thickening is known to follow benign asbestos pleural effusions, and it has been suggested that this is a necessary precursor of fibrothorax.²¹³ In one series of 44 patients with diffuse pleural thickening, half had a history of benign asbestos effusion; conversely, 54% of those who had a benign asbestos effusion had residual pleural thickening.²¹³ Diffuse pleural thickening is usually,²¹² but not inevitably, associated with heavy asbestos exposure (see eFig. 73-14), and its incidence increases with increasing time since first exposure.²¹³ The pleural fibrosis is often progressive, resulting in restrictive lung defects, especially if the costophrenic angle is obliterated.²¹⁴

Pleural fibrosis (with or without concurrent pulmonary fibrosis) can also develop with the use of ergot alkaloids (e.g., bromocriptine, pergolide, and methysergide).^{203,215} It has been suggested that subjects with asbestos exposure may be more susceptible to bromocriptine-induced pleural fibrosis.²¹⁶ Onset of dyspnea from ergot-induced pleural fibrosis is usually insidious and in the majority of cases presents at least 6 months after starting the medication.²⁰³ The pleural thickening is usually bilateral but can be unilateral and may be associated with pleuritic pain. Constitutional symptoms and elevated serologic inflammatory markers have also been reported.²¹⁵ In the case of

bromocriptine, the fibrothorax will stop progressing on cessation of the drug use, and may regress,²⁰³ though complete resolution is rare. Corticosteroids are often administered, but their effectiveness has never been established.²⁰³ Pleural fibrosis is often bilateral (if due to systemic causes) and may be associated with concurrent peritoneal fibrosis.²¹⁷

Idiopathic pleuroparenchymal fibroelastosis is a group of disorders recently reported.²¹⁸⁻²²¹ It is characterized by progressive fibrotic thickening of the pleura and subpleural parenchyma, often in the upper lobes, and not associated with any known causes of fibrothorax. Dyspnea, cough, and recurrent infections are common.²¹⁸

Carbon nanotubes, which have many features similar to asbestos fibers, have caused alarm recently by being shown to stimulate significant pleural and subpleural/lung fibrosis in animal studies.²²² These nanotubes have high tensile strength and high length-width ratio and, upon inhalation, can migrate from distal alveoli to the pleural cavity.^{223,224} The long-term safety of carbon nanotubes, especially in humans, is under intensive research.

Although pleural fibrosis is usually an undesirable event, it is commonly used therapeutically (pleurodesis) to control pleural effusions and pneumothoraces. Pleurodesis is the iatrogenic induction of pleural fibrosis, leading to symphysis of the visceral and parietal pleurae to obliterate the pleural space to prevent fluid or air reaccumulation.²²⁵ Interestingly, pleurodesis has no major impact on pulmonary function, even after decades. A retrospective review of young patients treated 22 to 35 years ago for spontaneous pneumothoraces showed that those who received talc pleurodesis ($n = 80$) had a higher incidence of pleural thickening on radiographs, but minimal restrictive changes in their lung function when compared with those treated by simple drainage ($n = 34$).²²⁶ Several small human and animal studies also revealed no significant impairment in

lung volumes and gas exchange at rest or during exercise following pleurodesis.²²⁵ Such observations imply that, for a fibrothorax to be clinically significant, it must involve either very extensive pleural fibrosis (in excess of therapeutic pleurodesis) or concomitant parenchymal fibrosis.

DIAGNOSIS

In one large population screening study of over 70,000 subjects, pleural thickening was reported in 3.6% of radiologic examinations.²²⁷ The diagnosis of fibrothorax can typically be made from the radiographic findings plus a history of a predisposing cause (e.g., an old injury or infection) (eFigs. 81-10 to 81-12). Radiologically, a peel of uniform thickness surrounds the lung. Calcification, which is frequently seen on the inner aspect of the peel (Fig. 81-11; see eFig. 81-12), can provide an indicator by which the thickness of the peel may be accurately measured. Apparent pleural thickening can be seen, especially in obese subjects (body mass index > 30), presumably the result of extrapleural fat deposition.²²⁸ A CT scan can easily discriminate between fat and thickening.

A CT scoring system that quantifies the thickness of the pleura and the fractional circumference of the hemithorax involved (as well as other pleural changes, such as rounded atelectasis and pleural plaques) has been shown to correlate with impairment in pulmonary function measures (especially total lung capacity and diffusing capacity).²²⁹

Routine pulmonary function testing usually reveals mild to severe restrictive ventilatory dysfunction.²¹³ In the case of asbestos-induced diffuse pleural thickening, the restriction arises from inflammatory involvement of the costal surfaces of the diaphragm and lower costal pleura, thus producing a pleurodesis that limits the movement of both the diaphragm and rib cage during inspiration.²³⁰ The

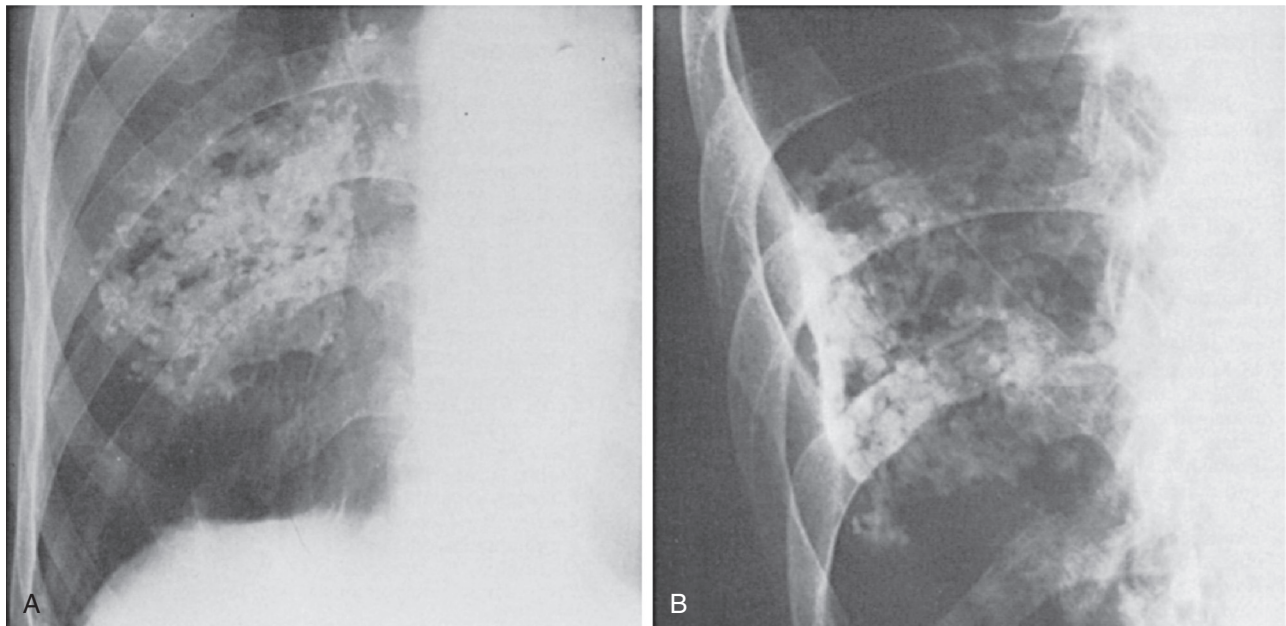


Figure 81-11 Fibrothorax. Detailed views from frontal (A) and oblique (B) chest radiographs of a 62-year-old man showing a localized fibrothorax with calcified plaque on the right. The patient had a right-sided empyema 32 years before. (From Hinshaw HC, Murray JF: *Diseases of the chest*, Philadelphia, 1980, WB Saunders, p 912.)

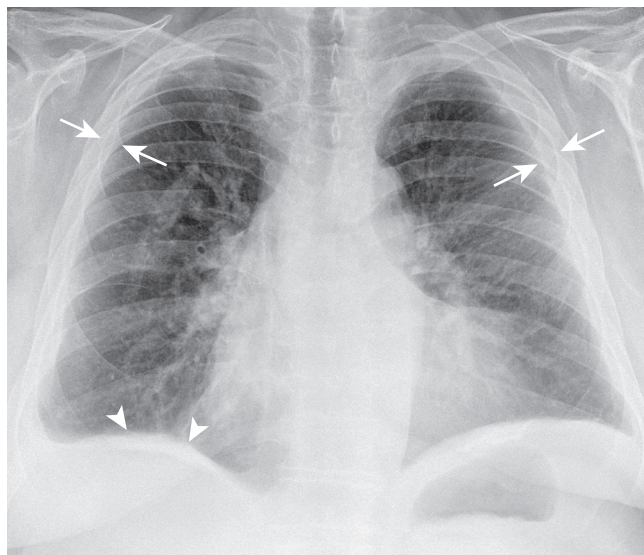


Figure 81-12 Diffuse pleural thickening. Chest radiograph of a man with a strong history of asbestos exposure, progressive dyspnea, and a restrictive picture on pulmonary function testing. The radiograph showed bilateral diffuse pleural thickening (between arrows), blunting of the costophrenic angles, and calcified diaphragmatic plaque on the right (arrowheads).

reduction in rib cage expansion is the main cause of restriction, because the diaphragm can still contribute by flattening of its dome on inspiration.²³⁰ In one study, 95% of patients with asbestos-induced diffuse pleural thickening complained of exertional dyspnea.²³¹ Objective reduction of exercise work capacity had also been shown.²³²

Pulmonary function may be severely compromised in patients with an extensive fibrothorax (Fig. 81-12). With marked pleural thickening, the hemithorax becomes contracted, the intercostal spaces narrow, and the mediastinum may be displaced ipsilaterally. In severe, especially bilateral cases of fibrothorax, hypercapnic respiratory failure may develop and may necessitate noninvasive ventilation.²³³

TREATMENT

It should be emphasized that patients with a recent hemothorax, empyema, or tuberculous pleuritis frequently show marked spontaneous improvement in their symptoms and the degree of pleural thickening in the 3 to 6 months after the acute episode.²³⁴ Patients with a fibrothorax should avoid drugs that can induce pleural fibrosis.

Decortication—surgical removal of the fibrous peel from the pleural surface—has been attempted to treat fibrothorax. However, the degree of improvement after decortication varies, with many series showing disappointing results.^{235,236} Success in part depends on the condition of the underlying lung. If the underlying lung is normal, the vital capacity may improve after decortication, but, if there is extensive parenchymal disease, the vital capacity may even decrease. The duration of the fibrothorax does not predict outcome. Surgical morbidity and mortality are not insignificant.²³⁷ Therefore decortication should be considered only in patients with significant pleural fibrosis (with

relatively preserved underlying lung parenchyma) whose quality of life is limited by exertional dyspnea. The results of decortication in patients with bilateral fibrothoraces secondary to asbestos exposure have been disappointing, probably a result of concomitant pulmonary fibrosis.²³⁸

Key Points

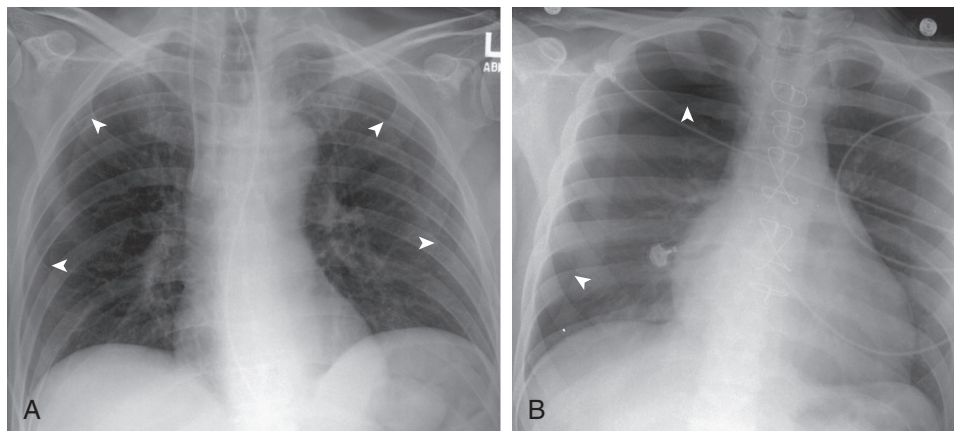
- Simple aspiration is the recommended first step of air evacuation in most cases of primary spontaneous pneumothorax.
- Secondary spontaneous pneumothorax is potentially life-threatening, and prevention of recurrence should be considered even at the first episode of pneumothorax.
- Chylothorax is characterized by milky fluid and the presence of chylomicrons. Early intervention to control the chylothorax is advocated because prolonged drainage of chylous effusion can lead to malnutrition.
- Pseudochylothorax is characterized by cholesterol crystals and should be differentiated from chylothorax because the etiology and management are different.
- A traumatic hemothorax should be drained and, if the bleeding rate is greater than 200 mL/hr, intervention targeting the underlying bleeding site by surgical or interventional radiologic means should be considered. Traumatic hemothorax can be complicated by retention of clotted blood in the pleural space, pleural infection, pleural effusion, and perhaps fibrothorax.
- Pleural thickening may improve spontaneously during the 3 to 6 months after acute hemothorax, empyema, or tuberculous pleuritis. Decortication should be considered only if the pleural thickening has been present for several months and if the patient has significant exertional dyspnea.

Complete reference list available at [ExpertConsult](#).

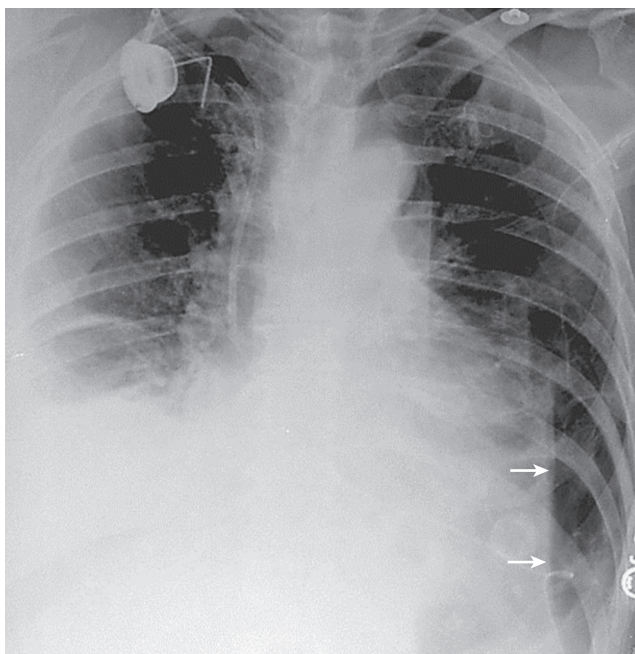
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eFIGURE IMAGE GALLERY



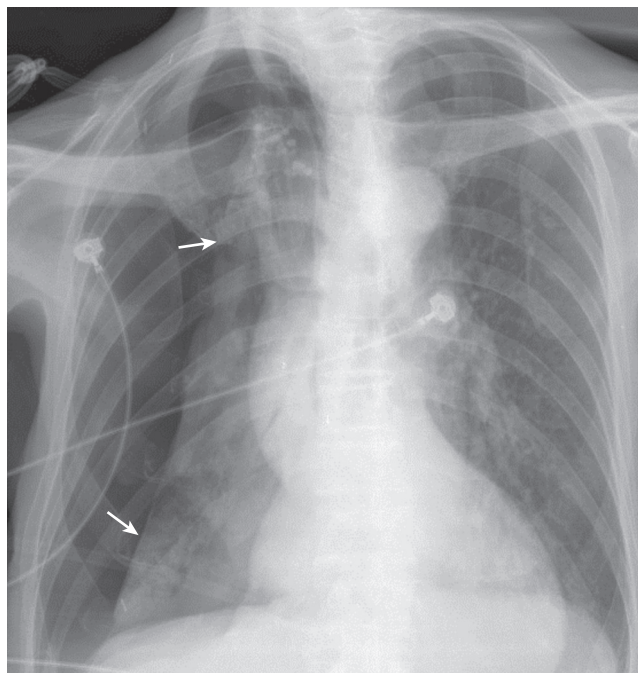
eFigure 81-1 Skinfold versus pneumothorax. **A**, Frontal chest radiograph in a patient with bilateral skinfolds simulating pneumothorax shows “edges” peripherally overlying the periphery of both lungs, but there is no increased lucency beyond the margins of the edges (i.e., the edge is not outlined by air or gas density on both sides), nor are the edges well defined (*arrowheads*). Furthermore, the edges “stop” rather than cap the apex of the lung, and vessels extend beyond the margin of the edges. **B**, Pneumothorax presenting as a “line” in the peripheral right thorax (*arrowheads*). Note that there is increased lucency lateral to the line (representing air or gas on both sides of the line), that the line is well defined, and that the line extends completely medially. (Courtesy Michael Gotway, MD.)



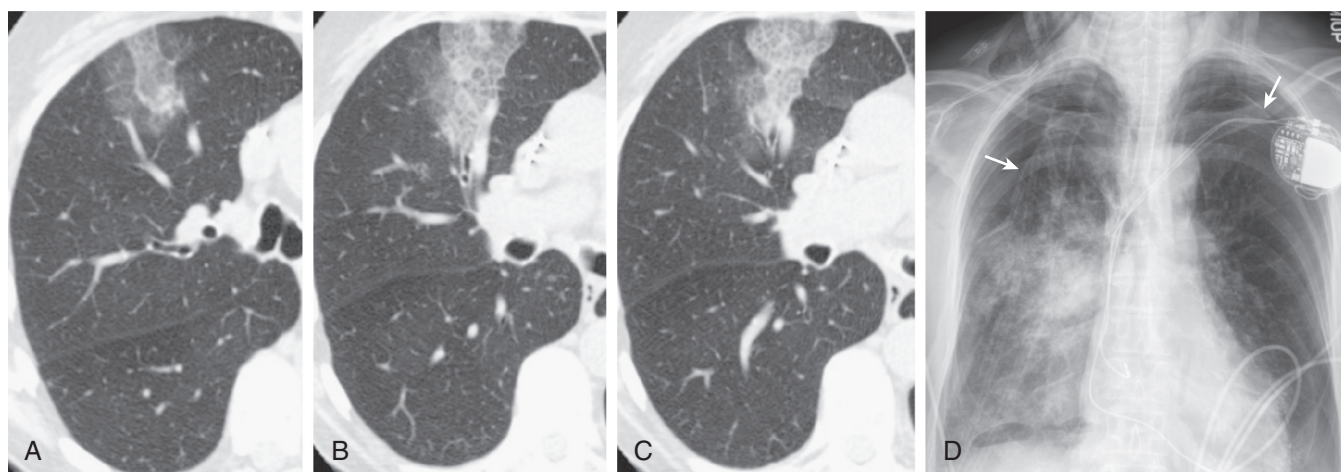
eFigure 81-2 Pneumothorax detection using decubitus radiography. Right lateral decubitus chest radiograph shows an air-fluid level (*arrows*) in the left lower thorax, representing a hydro-pneumothorax in the nondependent thorax. (Courtesy Michael Gotway, MD.)



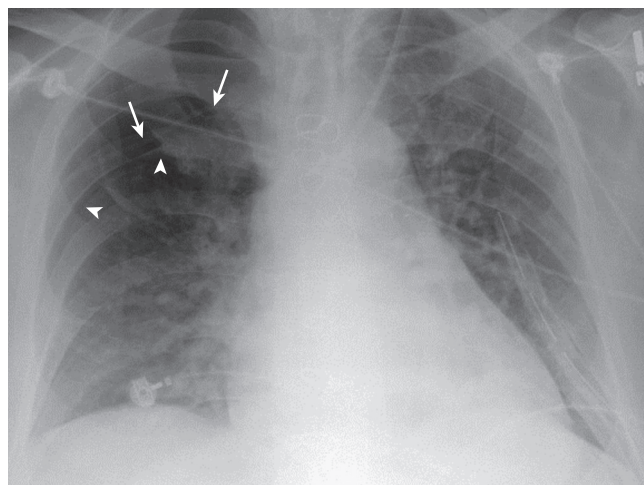
eFigure 81-3 Hydropneumothorax. Frontal chest radiograph shows a large left pneumothorax with a gas-fluid level (*arrowheads*) inferiorly, consistent with hydropneumothorax. (Courtesy Michael Gotway, MD.)



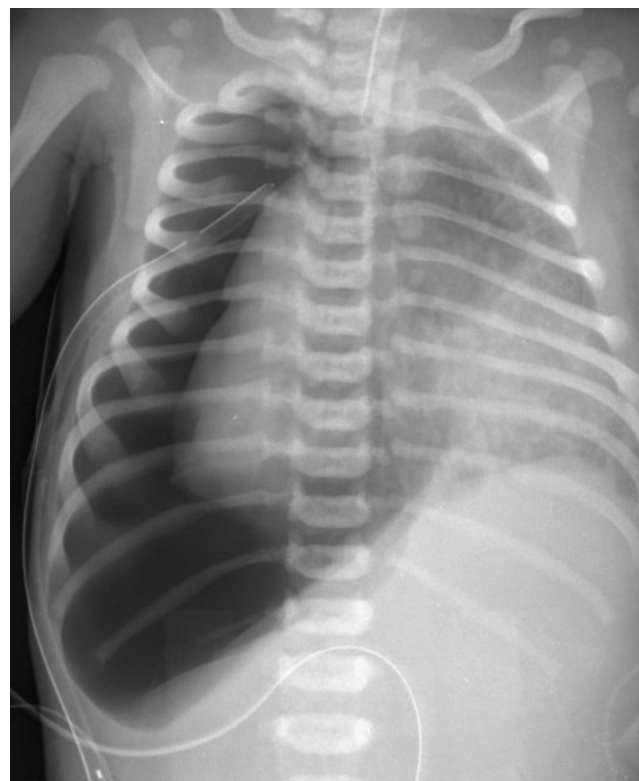
eFigure 81-4 Pneumothorax (*arrows*) in a patient with *Mycobacterium tuberculosis* infection. Note the multiple calcifications at the right apex, indicating the presence of a chronic lung disease, shown in this patient to be reactivation of pulmonary tuberculosis. (Courtesy Michael Gotway, MD.)



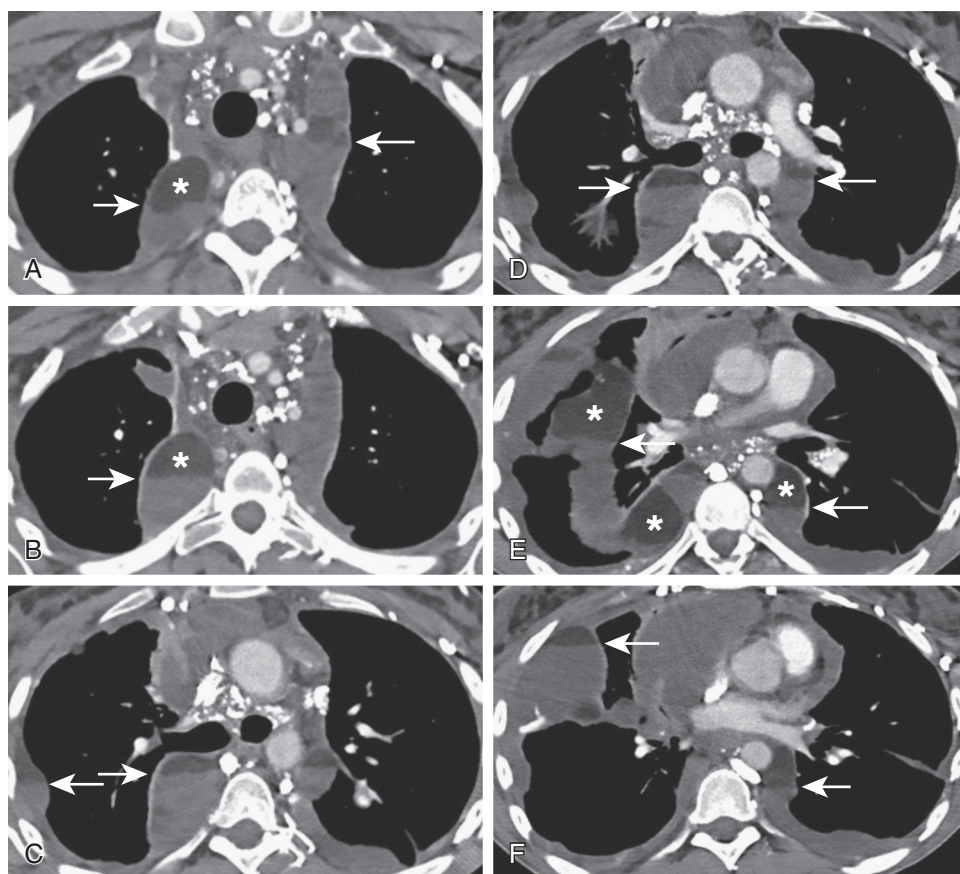
eFigure 81-5 Pneumothorax following bronchoscopy with transbronchial biopsy. A–C, Axial chest CT shows an unusually shaped ground-glass opacity lesion in the anterior segment of the right upper lobe. This lesion had been slowly enlarging on two prior CT scans over the previous year. D, Frontal chest radiograph following bronchoscopy with transbronchial biopsy shows bilateral pneumothoraces (arrows). The right upper lobe lesion remained undiagnosed, although the patient recovered. (Courtesy Michael Gotway, MD.)



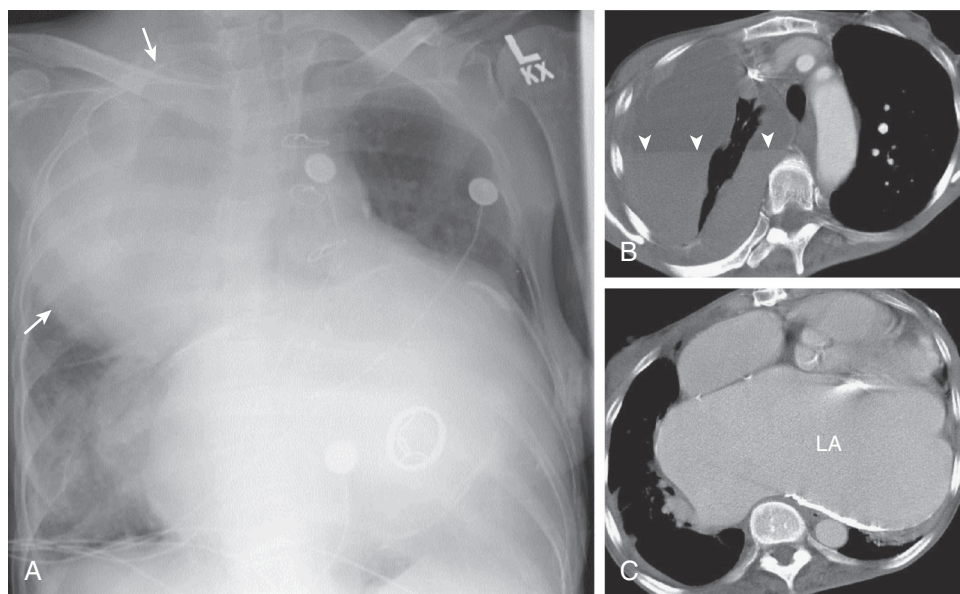
eFigure 81-6 Latrogenic pneumothorax. Moderate right pneumothorax (arrowheads denote pleural line) following placement of a right subclavian central venous catheter (arrows). (Courtesy Michael Gotway, MD.)



eFigure 81-7 Neonatal tension pneumothorax. Frontal chest radiograph in an infant with respiratory distress of the newborn shows a large right pneumothorax, despite thoracostomy tube placement, associated with eversion of the right hemidiaphragm. (Courtesy Michael Gotway, MD.)



eFigure 81-8 Chest CT of chylothorax. A–F, Axial enhanced chest CT in a patient with chylothorax shows gross fat (*) in the pleural space bilaterally, associated with numerous fat-fluid levels (arrows). The patient had anemia of chronic disease with upper extremity thrombosis and chronic chylothoraces and chylous ascites of unknown cause. (Courtesy Michael Gotway, MD.)



eFigure 81-9 Iatrogenic hemothorax following thoracentesis. A, Frontal chest radiograph in a patient with rheumatic heart disease, treated with anticoagulation, shows a large, homogeneous opacity in the superior right thorax (arrows) that developed following thoracentesis for right pleural effusion. Note prosthetic mitral valve. B, Axial enhanced chest CT shows a hematocrit level (i.e., blood-fluid level [arrowheads]; the dependent high attenuation is the heavier blood elements settling dependently). C, Note enlarged left atrium (LA) with wall calcification. (Courtesy Michael Gotway, MD.)

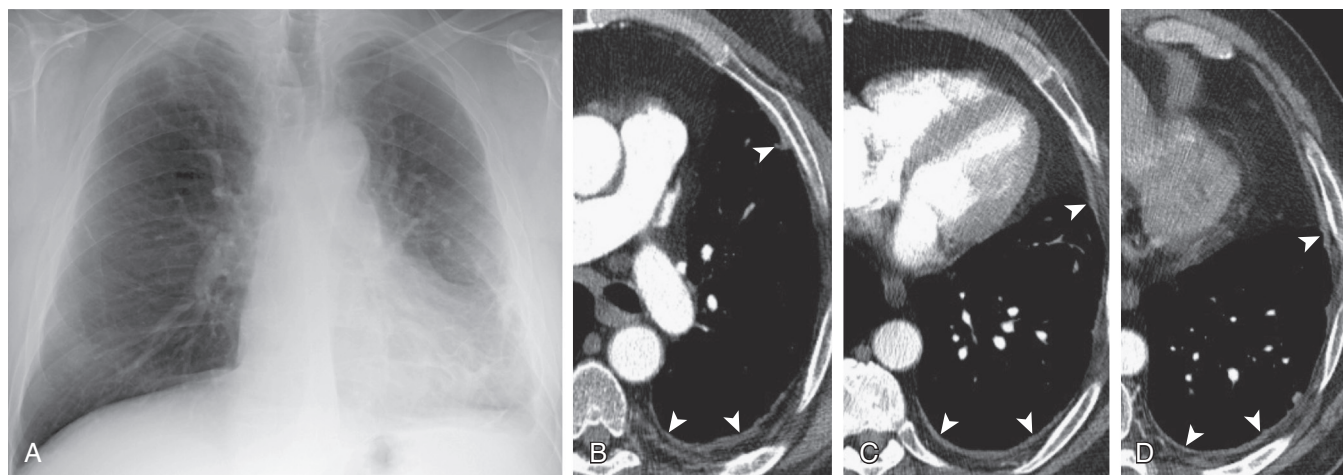


Figure 81-10 Minimal fibrothorax. **A**, Frontal chest radiograph shows pleural and parenchymal scarring in the left lung base. Mild left lung volume loss is present. **B–D**, Axial enhanced chest CT shows minimal irregular pleural thickening (*arrowheads*) without pleural liquid in the posterior and lateral left thoracic base. The patient was largely asymptomatic. (Courtesy Michael Gotway, MD.)

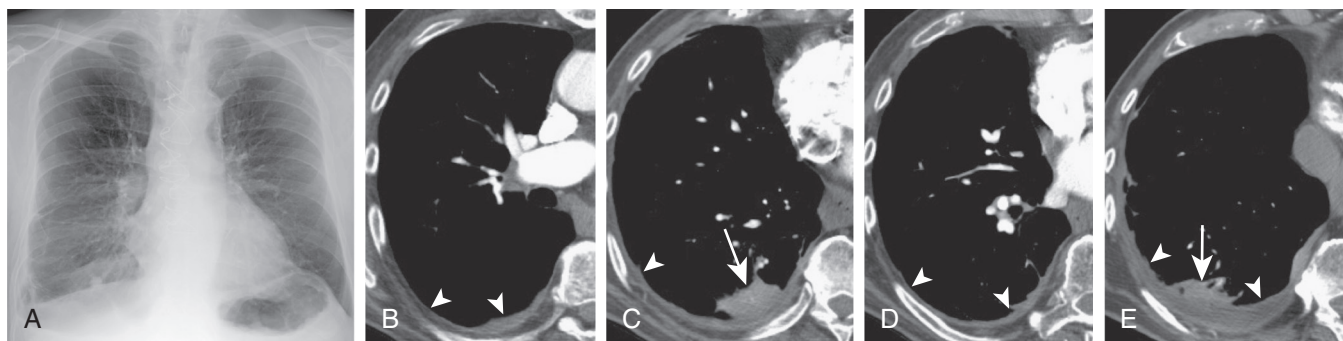


Figure 81-11 Mild-to-moderate fibrothorax. **A**, Frontal chest radiograph shows pleural and parenchymal scarring in the right lung base. Mild right lung volume loss is present. **B–E**, Axial enhanced chest CT shows mild-to-moderate irregular pleural thickening (*arrowheads*) with some low attenuation suggesting pleural liquid, in the right posterior thoracic base. Associated round atelectasis (*arrows*) is present. The pleural thickening developed following sternotomy and was presumed to be related to cardiovascular surgery. The patient had mild-to-moderate restrictive ventilatory impairment. (Courtesy Michael Gotway, MD.)

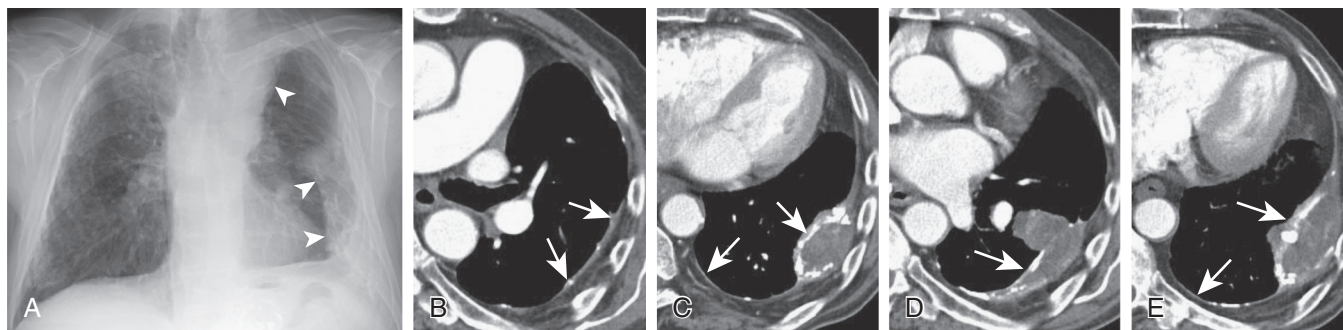


Figure 81-12 Severe partially calcified fibrothorax. **A**, Frontal chest radiograph in a patient with prior tuberculosis infection shows extensive left pleural opacity (*arrowheads*) associated with calcification. Left thoracic volume loss is present, and a calcified right fibrothorax is also evident. **B–E**, Axial enhanced chest CT displayed in soft tissue windows shows extensive, partially calcified left fibrothorax (*arrows*). This finding had been stable for more than 6 years, although the patient did have chronic, severe ventilatory impairment. (Courtesy Michael Gotway, MD.)

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INTRODUCTION**METASTATIC PLEURAL DISEASE**

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SOLITARY FIBROUS TUMOR OF THE PLEURA**PRIMARY EFFUSION LYMPHOMA****PYOTHORAX-ASSOCIATED LYMPHOMA****INTRODUCTION**

Tumors of the pleural space can be primary or secondary. The secondary tumors from metastatic spread of malignancy are the most common and are discussed first. Pleural metastatic disease is estimated to affect 200,000 persons per year in the United States and represents the second most common cause of exudative pleural effusion (after infection).¹ Unfortunately, because it represents metastatic spread, the treatment goal is that of palliation, not cure. Survival is poor, with a median of 4 months.² The primary tumors of the pleural space are less common. The most common primary tumor, malignant mesothelioma, affects approximately 15,000 persons per year worldwide and 3000 per year in the United States, and its incidence is growing.¹ Interestingly, despite its grim reputation, mesothelioma offers better survival than does metastatic pleural disease, with a median survival of 12 months.³ Although curative treatments are not yet available, progress is being made. Other rare but interesting tumors such as solitary fibrous tumor of the pleura, primary effusion lymphoma, and pyothorax-associated lymphoma are discussed.

METASTATIC PLEURAL DISEASE**TYPES OF TUMOR**

Certain tumors appear to have a predilection for metastasis to the pleura, particularly lung cancer, breast cancer, and lymphomas, and less commonly gastrointestinal and genitourinary malignancies (Table 82-1). In approximately half the cases of metastatic pleural disease, the patient will have an associated pleural effusion, most often exudative.⁴ However, in up to 10% of the malignant pleural effusions, the tumor of origin is never identified.⁵

The pattern of metastatic spread can provide some clues to the identity of the primary tumor. Whereas malignant mesotheliomas generally originate on the parietal pleura and then spread to the visceral pleura, metastases due to bronchogenic carcinoma or other cancers usually are first found on the visceral pleura and then spread to the parietal

pleura; they are rarely found exclusively on the parietal pleura.^{4,6} In addition, in most cases of bronchogenic carcinoma, the side of a malignant effusion is usually the same as the tumor of origin, with 17 out of 24 cases ipsilateral in one autopsy series.⁶

CLINICAL FEATURES

The most common symptom associated with a malignant pleural disease is dyspnea, most often from the presence of a pleural effusion (see Chapter 79 for further discussion). Cough is also a symptom that may be due to the presence of a pleural effusion. If the effusion is the cause of these symptoms, both dyspnea and cough can be relieved promptly by thoracentesis. When a thoracentesis fails to relieve these symptoms, tumor infiltration of lung or pleura or another medical condition should be suspected. Chest pain can often be described as a dull ache; this may indicate involvement of the chest wall and sensory neurons of the parietal pleura and chest wall although, with the recognition that sensory fibers lie in the visceral pleura, chest pain may not necessarily mean invasion of the chest wall.⁷ In one series, 34% of patients with a malignant pleural effusion described a dull chest ache, and 24% described pleuritic chest pain.⁸ This differed from those patients with benign causes of their effusions, who were more likely to describe pleuritic chest pain.⁸ Systemic symptoms may include malaise and anorexia.

MALIGNANT PLEURAL EFFUSIONS

Malignant pleural disease can exist without pleural effusion (Video 82-1). In autopsy studies of patients with malignancy, malignant pleural disease was found *without* an effusion in 40%⁶ to 45%⁴ of cases. It is increasingly recognized that malignant cells can reach the pleural space without effusion because lavage of the pleural space before resection of lung cancer in those without effusion can have positive cytologic results (see eFigs. 18-35 and 53-5). In one study of more than 1200 patients with lung cancer without effusion undergoing curative surgical resection, 5.3% had positive pleural cytologic findings on lavage at the time of

thoracotomy before resection.⁹ In fact, positive cytologic results on pleural lavage have poor prognostic significance and may be incorporated into future modifications of the *tumor-node-metastasis* (TNM) staging system; some have advocated using adjuvant chemotherapy in those with positive cytologic findings on preresection pleural lavage.¹⁰ The development of a malignant effusion may depend on the ability of the tumor cells themselves to secrete bioactive mediators or their ability to initiate inflammatory, angiogenic, or fibrinolytic processes in the normal tissues.¹¹

Lung cancer is the most common cause of malignant pleural effusions¹² (see Table 82-1). Lung cancer and breast cancer together account for more than half of all malignant pleural effusions. Of the histologic types of bronchogenic cancers, adenocarcinomas are most frequently associated with malignant pleural effusions, but effusions may be seen with all types.¹³

Breast cancer is the second most common cause of malignant pleural effusions.^{12,14} The time course of development of the effusion from the time of initial diagnosis of breast cancer is usually 2 years but can be up to 20 years. The

effusion usually is ipsilateral to the site of the original tumor (50%) but can also be contralateral (40%) and less commonly bilateral (10%).¹⁵

Lymphoma is the third most common cause in most series¹² but is possibly the most common cause in young adults.¹⁴ Pleural effusions are common in both non-Hodgkin (eFig. 82-1) and Hodgkin lymphoma.¹⁶ In patients with non-Hodgkin lymphoma, approximately 16% will develop malignant effusions, and most will have the effusion at the time of initial diagnosis in association with evidence of disease elsewhere.¹⁷ The high yield of pleural fluid cytologic studies suggests frequent invasion of the pleural space.¹⁸ In some patients with non-Hodgkin lymphoma, chylothorax may also develop; in one analysis of 88 patients with chylothorax, 12.5% were due to lymphoma, all non-Hodgkin lymphoma.¹⁹ In Hodgkin lymphoma, effusions may be caused by hilar or mediastinal lymph node involvement as well as pleural involvement.¹⁶ In one study of 110 patients presenting with Hodgkin lymphoma, effusions were present in 26 (24%); these were equally unilateral or bilateral. The presence of effusion was more common in those with higher-stage disease, extranodal involvement, and bulky mediastinal disease.²⁰

Malignancies probably produce pleural effusions by both increasing the entry of liquid and decreasing the normal exit of liquid (Table 82-2) (see Chapter 79). The entry of liquid can increase by several mechanisms: (1) increased permeability of the pleural vessels by direct invasion of tumor cells, inflammatory and vasoactive cytokines (e.g., *vascular endothelial growth factor* [VEGF]), or injury (e.g., radiation-induced); (2) increased permeability of *pulmonary* vessels by infection, pulmonary embolism, or pulmonary infarct with movement of liquid from lung to pleural space; (3) increased hydrostatic forces due to venous obstruction or hypoproteinemia; and (4) entry of other sources of liquid such as chyle from a disrupted thoracic duct. The exit of liquid from the pleural space can decrease by several mechanisms that would reduce lymphatic drainage: (1) infiltration of parietal pleural lymphatics or mediastinal lymph nodes, (2) lowered pleural pressure due to atelectasis

Table 82-1 Primary Tumors Responsible for Malignant Pleural Effusion

Primary Tumor Site	Total (%)
Lung	37.5
Breast	16.8
Lymphoma	11.5
Gastrointestinal	6.9
Genitourinary	9.4
Other	7.3
Unknown	10.7

A compilation of data from five different reports with a total of 2040 patients. The "other" category includes ovarian carcinoma, sarcomas, uterine and cervical carcinomas, and other carcinomas.

From Antunes G, Neville E, Duffy J, Ali N: BTS guidelines for the management of malignant pleural effusions. *Thorax* 58:ii29–ii38, 2003.

Table 82-2 Physiologic Mechanisms (Neoplastic and Paraneoplastic) by Which Malignancy May Cause Pleural Effusions

Means of Increasing Liquid	Mechanism	Site/Source	Examples
Increased entry	Increased vascular permeability	Pleural vessels	Invasion by tumor Cytokines (e.g., VEGF) Injury (e.g., radiation)
		Pulmonary vessels	Infection (e.g. postobstructive pneumonitis) Cytokines/injury
	Increased vascular hydrostatic gradient	Pleural vessels	Decreased pleural pressure (e.g., atelectasis) Increased venous pressure (e.g., SVC syndrome) Decreased plasma osmotic pressure (e.g., hypoproteinemia)
		Thoracic duct	Chylothorax
Decreased exit	Increased resistance to lymphatic flow	Pleural lymphatics Lymph nodes	Infiltration of parietal pleura Infiltration of mediastinal lymph nodes
	Increased gradient opposing lymphatic flow		Decreased pleural pressure (e.g., atelectasis) Increased venous pressure (e.g., SVC syndrome)

Both an increase in entry and a decrease in exit are likely required to produce a stable pleural effusion. "Paraneoplastic" refers to mechanisms taking place outside the pleural space.

SVC, superior vena cava; VEGF, vascular endothelial growth factor.

Adapted from Broadbush VC: Physiology: fluid and solute exchange in normal physiological states. In Light R, Lee Y, editors: *Textbook of pleural diseases*, ed 2, London, 2008, Hodder Arnold Publishers, pp 43–48.

from bronchial obstruction, or (3) elevated central venous pressure, as from superior vena cava syndrome. We suspect that several factors combine to form a pleural effusion in association with malignancy.²¹ The malignancy alone may be sufficient to tip the balance between the entry and exit of liquid toward accumulation of excess pleural liquid. Alternatively, the malignancy may alter the balance gradually without the development of an overt effusion because lymphatic clearance can handle the excess influx; the advent of another nonmalignant condition, such as heart failure or pneumonia, may then tip the balance and precipitate the appearance of a symptomatic pleural effusion. In these cases, malignancy may contribute to but not be the sole cause of the effusion.²¹ The combination of different processes may explain how malignancy can be associated with transudative effusions, for example, if malignancy interferes with lymphatic clearance and a separate transudative process increases entry of fluid into the pleural space.²² In the same way, malignancy may lead to bilateral effusions; in a prospective study of bilateral effusions, malignancy was found to be a common contributing cause along with other processes.²³

In several animal studies, bioactive molecules involved in angiogenesis and permeability, such as VEGF, have been identified that may play key roles in accumulation of effusions in malignancy.¹¹ An important role of VEGF is supported by the finding that, in patients with malignant effusions due to non-small cell lung cancer, increased pleural fluid VEGF is also associated with poor survival.²⁴ Understanding the mechanisms of effusion formation could lead to new therapeutic approaches such as inhibition of VEGF or the VEGF receptor or interfering with their effects on permeability and angiogenesis. In fact, some clinical responses to anti-VEGF therapy have been observed, and clinical trials are ongoing to determine whether such therapy targeted to VEGF (e.g., bevacizumab or cediranib) can control malignant effusions.^{25,26}

PLEURAL FLUID ANALYSIS

The pleural fluid from malignant effusions is almost always an exudate. The effusion may meet exudative criteria by the *lactate dehydrogenase* (LDH) (either the ratio or the absolute level) only and not by protein criteria.²⁷ Such an observation may indicate that an increased cell turnover and cell lysis is the source of the elevated LDH, whereas an increased vascular permeability needed to produce pleural fluid with increased protein concentration is not present. In some studies, approximately 5% of malignant effusions are found to be transudates.²⁸ In most of these cases, the primary cause of these “malignant” transudative effusions appears to be congestive heart failure or other known cause of a transudate (e.g., superior vena cava syndrome, volume overload), whereas the malignancy has a secondary, contributing role.²⁸ Malignancy could be the primary cause of a transudate if, for example, the malignancy interfered with lymphatic absorption of pleural liquid.²¹ In such cases, one could imagine that normal pleural liquid would accumulate until it formed a transudate. In one interesting case report, a patient with metastatic colon cancer but without other comorbid conditions presented with transudative pleural effusions and negative cytologic results; within 1 month,

the effusions were exudative with positive cytologic findings.²⁹ Biopsy showed parietal pleural lymphatic infiltration, suggesting that the initial transudative effusion was caused by blockage of pleural liquid lymphatic clearance, and that the later exudative effusion was caused by invasion of the pleural space.

The effusion may be grossly bloody; indeed, malignant disease is the most common cause of bloody effusions.³⁰ However, about half of malignant effusions are not bloody in appearance and have pleural fluid red blood cell counts under 10,000 cells/ μ L.³⁰ On cell differential, a predominance of lymphocytes is usual, but a mononuclear or eosinophilic predominance does not exclude the diagnosis. The presence of pleural fluid eosinophilia (>10% eosinophils) has been thought to be unusual in malignant effusion and to argue against the diagnosis.³¹ However, in a more recent study of 460 effusions, 20% of the eosinophilic effusions were found to be malignant; of note, 20% of noneosinophilic effusions were also found to be malignant, showing not only that eosinophilic effusions could be malignant but also that the presence of eosinophilia did not alter the likelihood of malignancy.³² Eosinophilia in many of these situations may be caused by other factors, such as the prior entry of air or blood into the pleural space. In another study in which care was taken to study only the initial thoracentesis to avoid artifacts due to prior entry of air or blood, eosinophilia was present in 12.6% of all effusions tapped, and the presence of eosinophilia did not differentiate malignant from benign causes.³³

The pleural glucose concentration is lower than 60 mg/dL in approximately 20% of malignant pleural effusions.³⁴ Effusions with a low glucose level also tend to have a low pleural pH and may have a larger tumor burden in the pleural space. It would therefore be expected that those patients with a low pleural glucose level or pH would have a shorter survival and a poorer response to pleurodesis, as has been reported.^{35,36} However, other studies have found that pleural fluid pH may not be an accurate predictor of survival^{37,38} and may also fail to predict which patients will respond to a pleurodesis.^{37,39} Therefore neither the pleural fluid pH nor the glucose level should be relied upon for selecting patients for pleurodesis. In fact, for survival, the best predictor may not lie in the pleural space; in one study the best criteria for predicting survival was the Karnofsky score, a scale from 0 to 100 based on results of the history and physical examination.³⁸

Pleural fluid amylase concentration is elevated in 10% of patients with malignant pleural effusions.⁴⁰ However, the origin of the amylase is not the pancreas, as shown by its identification as salivary rather than pancreatic amylase.⁴¹ In one series of consecutive effusions, a very high amylase concentration in malignant pleural fluid (>600 IU/L) was a poor prognostic factor.⁴⁰

RADIOGRAPHIC EVALUATION

The size of malignant effusions may vary greatly. Some may be small, amounting to a few milliliters and only causing blunting of the costophrenic angle, whereas others are large enough to obscure the hemithorax. In fact, malignancy is the most common cause of effusions that are either large, opacifying two thirds of the hemithorax, or

massive, opacifying the entire hemithorax (eFig. 82-2A; see eFig. 82-1A). In one retrospective series of 766 patients, malignancy was found as the cause of 55% of large and massive effusions⁴²; the other causes were pleural empyema and tuberculous effusions. Of these large malignant effusions, most were caused by lung or breast cancer. Interestingly, cytologic examination was no more likely to be positive in these large/massive effusions than in smaller ones (63% yield from large effusions; 53% from small).⁴²

If the effusion is large, it is important to note the position of the mediastinum. It is expected that, in an uncomplicated situation, the mediastinum will be shifted away from a large effusion (see eFig. 82-2A). If the mediastinum is midline, one can suspect one of two things: (1) the pleural pressures are equal on the two sides, implying that significant lung collapse is present and offsetting the increase in pressure expected from the presence of the effusion, or (2) the mediastinum is fixed in position and cannot shift in response to a pressure differential. If the mediastinum is shifted toward the side of the effusion, the pressure is most likely lower on the side of the effusion than on the other side (Video 82-2); in that case, the lung must be unable to expand fully in response to this abnormally low pressure. Because the lung is restricted from expanding or is trapped, due either to main-stem bronchial obstruction or to infiltration by tumor (see eFig. 82-2B), it is unlikely to reinflate with chest tube thoracostomy. In situations where the mediastinum is shifted toward a massive effusion, placement of chest tubes is not recommended. Instead, a bronchoscopy would be a reasonable next step to investigate for bronchial obstruction as a possible reason for the failure of lung expansion.

Computed tomography (CT) has the advantage of providing reasonably detailed information about the pleural surfaces, as well as information about the lung parenchyma, chest wall, and mediastinum. Thus one obtains clues about the identity of the tumor of origin as well as staging information. The typical features found in malignant pleural disease are pleural thickening (>1 cm), irregularity, and nodules (Fig. 82-1 and eFig. 82-3; also see eFigs. 18-35 and 53-5). In a prospective CT study of 40 patients with suspected malignant effusions, these pleural characteristics discriminated well between malignant and benign disease, with a sensitivity for malignancy of 84% and a specificity of 100%.⁴³ In a larger CT study of 211 consecutive patients with effusions, the most specific findings for malignancy were pleural nodules and nodular thickening.⁴⁴ Pleural thickening alone was not as specific and was seen in malignancy as well as empyema. Although the presence of pleural nodules was highly specific, it was not sensitive because only 17% of malignant effusions had associated pleural nodules. Interestingly, half of the patients with malignant effusions had no pleural abnormalities on the CT; other CT findings such as the presence of a pulmonary mass, chest wall involvement, large mediastinal nodes, and hepatic metastases suggested malignancy (Video 82-3).⁴⁴ Even minimal pleural effusions may represent malignant involvement; in patients with lung cancer, a minimal (<10 mm thick) effusion on CT has been shown to be a poor prognostic factor; these minimal effusions were thought to indicate early malignant involvement of the pleural space or of the mediastinal lymph nodes.⁴⁵

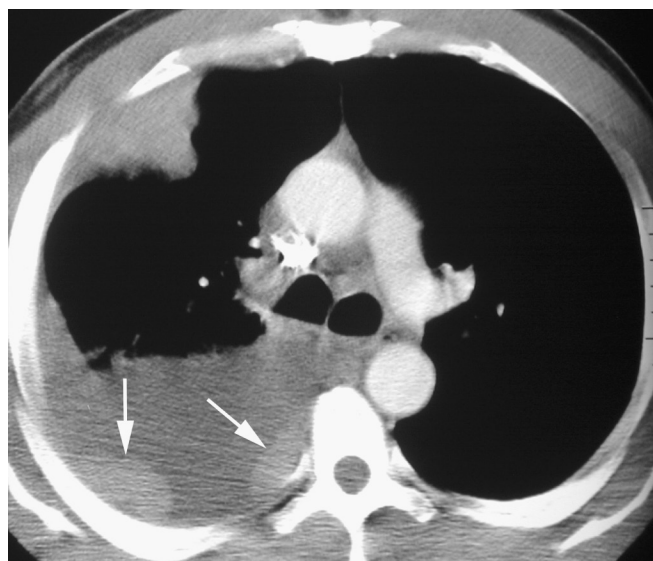


Figure 82-1 Metastatic adenocarcinoma. Axial contrast-enhanced chest CT shows right pleural effusion associated with enhancing nodular masses (arrows) emanating from the parietal pleura, later shown to be metastatic adenocarcinoma.

Magnetic resonance imaging (MRI) is not advocated for routine evaluation of malignant effusions. However, its excellent soft-tissue contrast may be useful for detailed evaluation of tumor invasion.⁴⁶ It may be particularly useful in evaluating the chest wall and pleura in the apices of the hemithoraces.

Positron emission tomography with ¹⁸F-fluorodeoxyglucose (PET) can be very useful for differentiating benign pleural abnormalities from malignancy⁴⁷ and provides useful information for staging in cases of documented malignancy (see eFig. 53-4). However, it may not always be able to differentiate pleural malignancy from benign pleural inflammation, such as that due to talc pleurodesis⁴⁸ (Fig. 82-2). In a patient with a history of talc pleurodesis, PET/CT can allow correlation of the increased uptake with areas of increased attenuation characteristic of talc deposits.⁴⁹

DIAGNOSIS

Cytologic examination is reportedly diagnostic in approximately 60% of patients,⁵⁰ but the diagnostic yield varies with the type of tumor, extent of tumor involvement of the pleural space, and the skill and experience of the cytologist (see Chapter 79). Cytologic results are more likely to be positive in adenocarcinoma than in squamous cell lung cancer, for example, perhaps because adenocarcinoma is more often located peripherally and has a greater tendency to invade the pleural space.³⁰ Interestingly, cytologic yield does not vary greatly with the size of the effusion; as mentioned, in one study, cytologic results were positive as often in large or massive effusions (63%) as in small or moderate-size effusions (53%).⁴²

Immunohistochemical staining of cell blocks can be quite useful for diagnosis. Certain markers such as thyroid transcription factor 1 have a high specificity for a lung primary tumor, whereas GATA3 has been proposed as a sensitive and specific immunostain for breast cancer.⁵¹

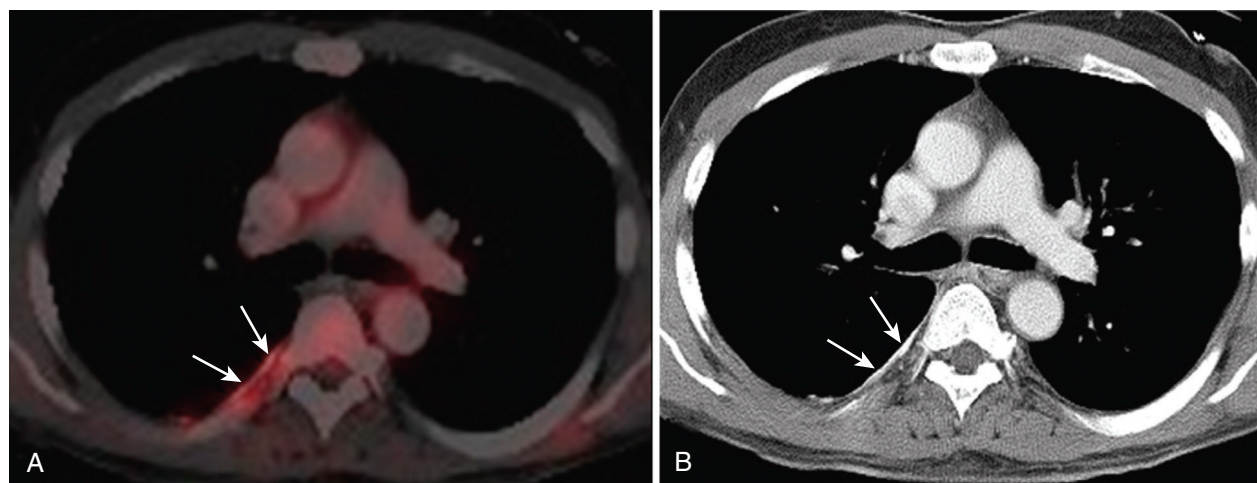


Figure 82-2 Increased PET activity at site of talc pleurodesis. **A**, A PET/CT scan obtained in a patient with a prior talc pleurodesis for recurrent pneumothorax shows increased pleural uptake (arrows). **B**, The axial chest CT image confirms that the area of increased PET uptake corresponds to an area of high attenuation characteristic of talc deposits.

Cytologic specimens can be used for sequencing for mutations of *epidermal growth factor receptor* (EGFR),⁵² and, with highly sensitive sequencing such as next-generation sequencing, such markers may be detected even when cytologic examination reveals a low percentage or even no malignant cells.⁵³

Biopsy may be necessary when cytologic examination is negative or indeterminate. In the past, closed (or “blind”) pleural biopsy was performed as a next step in cases where cytologic results were negative. However, the patchy involvement of the parietal pleura by malignancy appears to make closed pleural biopsy a “hit-or-miss” technique, and, not surprisingly, image-directed biopsies have been shown to be more accurate. In one randomized study comparing CT-guided biopsy with closed pleural biopsy using an Abrams needle, CT-guided biopsy was significantly more sensitive (87% versus 47%) with a better negative predictive value (80% versus 44%).⁵⁴ Thoracoscopy is a well-tolerated procedure that permits excellent visualization of the entire pleural surface (see Chapter 24 and eFig. 53-5B). Directed biopsies of suspicious areas lead to a correct identification of metastatic pleural disease in nearly 100% of cases.⁵⁵ This technique has additional advantages, including the ability to provide large biopsy specimens for immunohistochemical and genetic analysis for molecular markers (e.g., EGFR) if needed, to provide information about the gross appearance of tumor, to provide information for staging, to lyse adhesions, and to drain the pleural space for talc pleurodesis. It is worth remembering that metastatic disease may be diagnosed by fine-needle aspirates of abnormal lymph nodes in the cervical, supraclavicular, or other regions or by biopsies of mediastinal nodes guided by endoscopic or endobronchial ultrasonography, bypassing invasive tests directed at the pleural space.

Molecular markers for malignancy may be identified as the molecular biology of cancer is better understood. Biomarkers in pleural fluid would potentially assist the cytologic diagnosis (see Chapter 79). Unfortunately, biomarkers have had indeterminate sensitivity and specificity, leading to overlap between malignant and nonmalignant conditions. One approach has been to combine tumor markers to

improve diagnostic yield, although one may predict malignancy as well by using clinical characteristics (time of symptoms more than 1 month, absence of fever, serosanguineous fluid, and chest CT findings of malignancy).⁵⁶ For mesothelioma, detecting the molecule mesothelin, a product of mesothelial cells, may have diagnostic utility in certain circumstances (see “[Mesothelioma](#)” section, later). Interestingly however, pleural liquid mesothelin levels are elevated in many patients with malignant effusions other than mesothelioma, whereas the mesothelin level is not elevated in benign effusions. Thus a high mesothelin level is strongly suggestive of the presence of some sort of malignancy.⁵⁷

The future of diagnosis may include genetic analysis, either for features of malignancy (DNA methylation, mutations, microsatellite, telomerase, aneuploidy) or in the genetic expression fingerprint (microarray) characteristic of tumors.^{58,59} As discussed earlier, genetic testing of pleural cells may lead to the selection of therapy; for example, finding an EGFR mutation in malignant pleural cells may predict response to appropriate EGFR tyrosine kinase inhibitors, such as erlotinib or gefitinib.^{52,53,60} High-throughput sequencing technology, a by-product of the Human Genome Project, enables rapid sequencing of either the whole genome or the small percentage of the genome that codes for expressed genes (i.e., the exome). Because all cancers are unique, it is hoped that this might lead to patient-specific markers and therapies (e.g., construction of specific vaccines that “drive” the host immune system to attack that patient’s cancer).⁶¹

THERAPY AND PALLIATION

The therapeutic and palliative approach to malignant pleural effusions is guided by several factors ([Table 82-3](#)). The options are several and of increasing invasiveness. First of all, the clinician should determine whether the effusion is causing either dyspnea or cough, symptoms that can be due to the volume of the effusion and its effect on lung and cardiac function (see Chapter 79). Symptomatic effusions require an effort to control the effusion, usually by obliterating the pleural space or by draining the effusion, either

Table 82-3 Options for Control of Symptomatic Malignant Effusions

Option	Patient Eligibility and Considerations
Chemotherapy	Chemoresponsive tumor
Thoracentesis	Slowly recurring effusion Used for patients with very short life expectancy
Pleurodesis Via chest tube Via thoracoscopy	Lung able to reinflate Can free up lung tacked down by adhesions, obtain biopsies Thoracoscopy must be available
Indwelling tunneled catheter	Good outpatient situation Good for trapped lung
Pleuroperitoneal shunt	Patient able to operate pump Good for trapped lung Excellent for chylothorax
Pleurectomy Via thoracoscopy Via thoracotomy	When other less invasive options have failed Good patient status and life expectancy

internally or externally. Important issues that help the clinician decide on the approach are the ability of the lung to reinflate fully, the clinical status of the patient, and the availability of approaches such as thoracoscopy. The overall goal is to provide the greatest relief of symptoms using the least invasive, least morbid, and least expensive therapy. Management issues mainly focusing on palliation have been addressed in guidelines from the European Respiratory Society/American Thoracic Society and the British Thoracic Society.^{12,62,63}

Systemic therapy with chemotherapy may be considered, as dictated by the primary malignancy. Malignant pleural effusions that may respond to chemotherapy include those due to breast cancer, small cell lung cancer, and lymphoma.^{15,64,65} Radiation therapy may be useful for treatment of the primary tumor or to treat local areas of chest wall invasion but is limited by the radiosensitive organs adjacent to the pleura, such as the lung and heart. As stated previously, the most common and most debilitating symptom caused by malignant effusions is dyspnea, and control of dyspnea can often be the primary focus of palliative therapy.

Repeated thoracentesis to remove a symptomatic effusion may be used in those unusual circumstances when the fluid reaccumulates slowly and the patient prefers this approach. Nonetheless, most malignant effusions recur rapidly and would need frequent drainage, making this approach useful in only a few cases, such as in a patient with a very short life expectancy.

Chemical pleurodesis can be considered when the lung can reinflate so it comes in contact with the parietal pleura. Even if reinflation is incomplete, as long as the lung can cover a large part of the parietal pleura, pleurodesis may still be effective at preventing the recurrence of large symptomatic effusions and can be considered.⁶³ Pleurodesis with talc is successful in most (70% to 100%) cases⁶⁶ and is more effective than pleurodesis with other agents, including tetracycline and bleomycin.^{62,66} Talc pleurodesis can be painful

and, in a small percentage of patients, can lead to pulmonary edema and acute respiratory failure.¹ Evidence suggests that the smaller talc particles (<10 µm) can exit the pleural space and distribute systemically; in a randomized study, pleurodesis with graded talc (with most particles less than 10 µm removed) was associated with fewer complications than a mixed talc that included small particles.⁶⁷ Alternative sclerosing agents have been investigated, but currently talc is the preferred agent. Nonetheless, there is significant variability in the practice of pleurodesis, as shown in a survey of pulmonologists in five countries.⁶⁸ Other agents include tetracycline, bleomycin, iodopovidone, nitrogen mustard, *Corynebacterium parvum*, and silver nitrate.⁶⁶

Talc can be delivered to the pleural space by instillation as a slurry through a chest tube or by insufflation as a powder (poudrage) during thoracoscopy. Talc slurry can be given via small or large chest tubes, without rotation of the patient. Prospective trials have shown no benefit of standard large-bore tube over small-bore tubes (12 French) for pleurodesis, although talc was used in a minority of these patients,⁶⁹ and no benefit from rotation of patients as determined by instillation of radiolabeled talc and by outcome.⁷⁰ In outpatients, instillation of talc slurry through small-bore catheters followed by removal of chest tubes in 24 hours has shown promise.⁷¹ Talc slurry and talc poudrage have been compared in a prospective, randomized trial and have been found to be similar in efficacy; 71% of patients had a successful 30-day outcome following talc slurry and 78% following poudrage.⁷² Interestingly, for the subgroup of patients with breast or lung cancer, poudrage may have been better than slurry (82% success with poudrage versus 67% with slurry).⁷² Thoracoscopy or video-assisted thoracic surgery also has the ability to drain the pleural space completely at the time of talc poudrage and lyse adhesions, which may allow more success in selected patients.

Chronic indwelling tunneled catheters have been shown to be effective alternatives to chemical pleurodesis, even leading to a symphysis and removal of catheters in many patients. The catheter is inserted under local anesthesia, and the patient drains the effusion via a daily or every-other-day protocol as an outpatient. This approach may be the only alternative when pleurodesis is not possible, as, for example, when the lung cannot reexpand. It has now been recognized that not only can the indwelling catheters control symptoms but, in many cases, they can induce a symphysis, allowing the tube to be removed without recurrence of the effusion. In a review of 263 patients with malignant pleural effusions treated with indwelling tunneled pleural catheters until drainage was less than 50 mL/day, the catheters could be removed in 58% of patients.⁷³ The average indwelling time for the catheter overall was 29 days. The success of the catheter alone was greater in those with breast and gynecologic tumors (70% to 72%), those without a history of chest wall irradiation, those with positive cytologic results, and those with complete reexpansion of the underlying lung.⁷³ An added benefit of this outpatient approach is a reduction in hospitalization time, a particularly attractive feature for a palliative procedure. In the first randomized controlled trial comparing the indwelling catheter versus talc pleurodesis, 106 patients with malignant pleural effusion were treated with an indwelling

pleural catheter inserted as an outpatient procedure or talc slurry via a chest tube as an inpatient procedure.⁷⁴ There was not much difference between the approaches: both relieved dyspnea and had a similar quality of life. More patients in the talc group underwent further pleural procedures (22% versus 6%), and more patients in the catheter group experienced adverse events. Nonetheless, the near equivalence of outcomes indicated that patient preference might guide treatment choice.⁷⁴ A combination of techniques can also be used; in a pilot study, patients with malignant pleural effusions underwent thoracoscopy with talc poudrage and placement of a tunneled indwelling pleural catheter.⁷⁵ For the 30 patients, the pleurodesis was effective in 92% and the catheter could be removed in less than 8 days. Such combinations of approaches could potentially enhance efficacy without increasing hospital stay or adverse events.

Pleuroperitoneal shunting is another alternative for palliation when the lung cannot reexpand or pleurodesis is unsuccessful but is reserved primarily for patients with chylous effusions. It can be considered as a temporary measure while other treatments for the malignancy are initiated. Although it is a more invasive procedure, the pleuroperitoneal shunt allows the redirection of chyle into the abdomen, where it can presumably be absorbed via different routes, and thus minimizes depletion of protein and lymphocytes. Improvement in dyspnea is achieved in most patients (95%).⁷⁶ Of note, the external pump chamber must be manually compressed several times each day to move the pleural fluid into the peritoneal space.

Pleurectomy via thoracotomy can achieve a pleural symphysis. However, with the advent of effective alternatives such as pleurodesis and indwelling pleural catheters, pleurectomy cannot be recommended.

PROGNOSIS

The overall prognosis is poor for most patients with malignant pleural effusions. In an analysis of several studies with a total of over 400 patients, the median survival was 4.0 months.² The survival varied by tumor of origin; patients with malignant effusions from lung cancer had a median survival of 3.0 months, whereas those with pleural effusions from cancer of the breast had 5.0 months, from mesothelioma 6.0 months, and from lymphoma 9.0 months. When used to predict survival for any individual patient, pleural fluid pH or glucose level is not sufficiently robust.² One of the strongest predictors appears to be the Karnofsky performance scale; in a prospective trial of 85 consecutive patients with malignant pleural effusions referred for thoracoscopic pleurodesis, those with a Karnofsky score above 70 had a median survival of 13.2 months, whereas those with a score below 30 had a median survival of 1.1 months.³⁸ Interestingly, in this study, when compared to other measures such as pleural fluid pH, glucose level, or extent of carcinomatous involvement of the pleural surface, performance scoring was the only significant predictor of survival.

The life expectancy of patients with lung cancer and malignant pleural effusion has affected the revised staging classification of malignant pleural effusions⁷⁷ (see Chapter 53). In the sixth edition of the TNM classification, effective

since 1997, malignancy of the pleural space was considered a T4 lesion, with a similar prognosis as other invasive lesions, and patients were staged as IIIB. However, in a comprehensive reassessment of staging and its effect on survival, patients with malignant pleural effusions were found to have a poorer prognosis than other T4M0 patients (8 months versus 13 months) and to be more similar to patients with metastatic disease to the other lung (10 months).⁷⁷ In the revised staging system, pleural malignancy (malignant effusions or pleural nodular malignancy) is considered along with contralateral lung nodules as intrathoracic metastatic disease (M1a). Intrathoracic metastatic disease (M1a) is classified separately from extrathoracic metastatic disease (M1b) because of a somewhat better prognosis.⁷⁷

MESOTHELIOMA

INCIDENCE AND ETIOLOGY

Malignant pleural mesothelioma is uncommon but can no longer be considered rare with almost 3000 cases per year diagnosed in the United States alone. The number of cases is anticipated to continue to increase in the United States and Western Europe until approximately 2020⁷⁸ because of the increase in occupational exposures to asbestos and asbestos-containing products after World War II. During the heyday of excitement about asbestos, asbestos was viewed as a modern breakthrough because it was cheap and yet provided good insulation and fire resistance and was able to be woven or molded into thousands of different products. Asbestos was even used in such products as toothpaste⁷⁹ and cigarette filters!⁸⁰ Unfortunately, after extensive use in industry and in building materials, asbestos fibers were discovered to be harmful. It appears that their mechanisms of action are multiple⁸¹ (see later).

After 2020, the number of cases is anticipated to plateau and then gradually decline in Western countries because of the reduction in occupational exposures caused by restrictions on asbestos use, worker protection, and asbestos abatement efforts that were instituted from the mid-1970s to 1990s. In those industrialized countries where the control of asbestos was delayed by several decades, as in Japan, the “epidemic” of mesothelioma may also be delayed by several decades. Unfortunately, asbestos continues to be mined, and its use is actually increasing to high levels in many developing countries, with little environmental controls, raising the specter of a fresh new era of asbestos-related diseases.⁸² Globally there is a great disparity in asbestos use, with some countries adopting “asbestos bans” and others using asbestos without regulation. Interestingly, the United States does not have a ban, although asbestos use has fallen to less than 1% of its historical peak.⁸³ In countries with unregulated use of asbestos, the incidence of malignant mesothelioma is expected to reach high levels in the future. Asbestos-induced lung cancer will also be expected to increase because of the multiplicative effects of asbestos inhalation (including chrysotile) and cigarette smoking⁸⁴ (see Chapter 52).

Those with significant asbestos exposure and increased rates of mesotheliomas include workers in the asbestos

industry, insulators, pipe fitters, shipyard workers, brake mechanics, railroad workers, construction workers, carpenters, plumbers, electricians, painters, nonasbestos miners, welders, machinists, manufacturers of mineral products, and workers who perform maintenance and repair in buildings with asbestos insulation.⁸⁵ In addition, it is not uncommon to see women with mesothelioma whose only clear asbestos exposure was from exposure to their spouses' contaminated clothing. Children who have been incidentally exposed can develop mesothelioma in early adult life.

Besides those who mined or milled asbestos (the "first wave") and those who worked with asbestos in industry (the "second wave"), there is now a third wave of those exposed inadvertently to asbestos during short-term or low-level exposure in the home or workplace.⁸⁶ The most common inadvertent exposure is thought to be during home renovations, a source that may be causing an increasing incidence of mesothelioma.⁸⁶ Incidence may also rise because of population exposures such as from the dust that settled after the collapse of the World Trade Center.⁸⁷ In addition, the use of nanoparticles and nanotubes raises concerns for unforeseen toxic effects analogous to those of asbestos, although this has not been proven.^{88,89}

Other causes of mesothelioma have been postulated. There has been a great deal of controversy as to whether a simian virus (SV40) that contaminated the polio vaccine administered from 1955 through 1961 may be contributing to the development of mesotheliomas in the United States and other countries. SV40 is an intriguing candidate because it can immortalize cells by binding and inactivating both the retinoblastoma protein and p53, key control steps for proliferation and apoptosis, respectively. In a review of 15 studies, mesothelioma tissues were 17 times more likely to have evidence of SV40 compared to control tissues.⁹⁰ In cell and animal studies, SV40 may cooperate with asbestos in inducing damage and generating mesothelioma.⁹¹ However, in humans, a causal relationship has not been established, and epidemiologic studies to date have not shown an increase in the incidence of mesotheliomas in populations exposed to this virus.^{92,93} Further complicating the analysis is the recognition that the presence of SV40 DNA sequences alone does not prove its role in tumor development; to be oncogenic, viral proteins must be expressed and impair the function of cell proteins necessary for normal cell function. At this time, SV40 is still a subject of intense discussion, more as a possible co-carcinogen with asbestos than as a primary cause of mesothelioma. See arguments addressing the evidence for⁹⁴ and against⁹⁵ SV40 as a cause of mesothelioma.

Cigarette smoking is not associated with an increased incidence of mesotheliomas.⁹⁶ Silica or man-made vitreous fibers (rock/slag wool and fiberglass) have not been found to be associated with occupational mesotheliomas.^{97,98} Excess cases of mesotheliomas have been identified in oil refinery workers; this risk was once thought to be due to exposure to petroleum oil and its products but is now attributed to occupational asbestos exposure.⁹⁹ Ionizing radiation may be a cause or may contribute to development of mesothelioma; a small increased risk for mesothelioma has been described in patients exposed to the contrast medium

Thorotrast (containing thorium dioxide), to radiation therapy, and to low-level radiation as atomic energy workers.¹⁰⁰

Environmental asbestos exposures are also associated with the development of mesothelioma. Low-dose exposure in large populations may produce only "background" levels of asbestos in lung tissue but, because of the large number of individuals exposed in that way, may lead to an increase in the number of mesothelioma cases (similar to widespread exposure to sunlight and melanoma development). In Turkey an extraordinarily high incidence of mesothelioma is found in certain villages in central Turkey with exposure to erionite dust, a nonasbestos crystalline fibrous form of the mineral zeolite.¹⁰² Erionite is now recognized to be in many locations, including in the western United States, and may be a future hazard due to the use of erionite-containing gravels on some roadways.^{102,103}

Finally, chronic inflammation of the pleura as seen in familial Mediterranean fever has been postulated to cause mesothelioma. At least four cases of mesothelioma have been reported in patients with this disease, presumably due to recurrent serositis.¹⁰⁴ Asbestos may still be an underlying cause or contributing factor in patients without a clear occupational exposure given that fiber burden studies suggest that most urban dwellers have some asbestos fibers in their lungs.¹⁰⁵

Although millions of workers have been exposed to significant amounts of asbestos, only a few develop mesothelioma, making it likely that there are genetic factors that increase susceptibility. Supporting the notion of genetic susceptibility is the identification of multiple clusters of this disease in families,¹⁰⁶ although clusters may also be explained by common environmental exposure to asbestos. Nonetheless, in the Cappadocian region of Turkey, where exposure to erionite is widespread, the susceptibility to mesothelioma appears to be inherited in an autosomal dominant pattern.¹⁰⁷ Mesothelioma susceptibility genes have been reported using genome-wide association studies.¹⁰⁸ Some familial clustering of mesothelioma has been found to be due to a germline *BAP1* (BRCA1-associated protein-1) mutation, a discovery that links predisposition to mesothelioma with predisposition to other tumors such as uveal melanoma, although this familial feature is uncommon in mesothelioma.¹⁰⁹

GENETIC CHARACTERISTICS

The three tumor suppressor genes most frequently implicated in mesothelioma are *CDKN2A* (or *P16INK4A-P14ARF*), the *neurofibromatosis type 2* (*NF2*) gene, and the *BAP1* ubiquitination-related gene.¹¹⁰ (For discussion of genetic abnormalities in lung cancer, see Chapter 51.) Studies of cytogenetics and loss of heterozygosity show consistent losses of chromosomal regions, suggesting that these regions may contain genes for key tumor suppressors. Losses are consistently found in regions 1p, 3p, 6q, 9p, 13q, 15q, and 22q. Oncogenes or growth-promoting genes suspected to play a role in mesothelioma include those coding for c-Myc and for growth factors or growth factor receptors (e.g., platelet-derived growth factor, EGFR). Gene expression profiling and high-throughput, next-generation sequencing

are beginning to be explored and will likely provide additional insights into genetic abnormalities critical for mesothelioma; genetic discoveries may also provide prognostic information, help with diagnosis, guide therapy, and suggest future therapeutic approaches.¹¹¹⁻¹¹³

Action of Fibers at the Pleura

The long latency period between exposure to asbestos and development of mesothelioma suggests that multiple genetic abnormalities are required. Unlike the situation for bronchogenic carcinoma, where the natural history can be studied by repeatedly accessing the bronchial epithelium, the pleural space is not easily sampled, making the natural history of mesothelioma more opaque.¹¹⁴ Many pleural diseases can be caused by asbestos fibers, including plaques, rounded atelectasis, fibrosis, and benign asbestos pleurisy.¹¹⁵ Of these, mesothelioma has the longest latency.

Due to their long thin shape, asbestos fibers are inhaled deep into the lung and translocate from the lung to the pleural space and accumulate at the parietal pleura, where they can interact with mesothelial cells over decades.¹¹⁴ The fibers have been found to accumulate at particular spots, where carbon also accumulates, seen at thoracoscopy as “black spots”; these spots probably correspond to sites of lymphatic clearance of pleural fluid and cells.¹¹⁶ The fibers are ingested by macrophages, inducing a chronic inflammation within the lung and pleura. The fibers may also be internalized by mesothelial cells, where they can interfere with chromosome segregation, leading to chromosome damage, and generate reactive oxygen species via their iron content, leading to oxidant injury to DNA.¹¹⁷ From cell and animal studies, it appears that asbestos can injure the chromosomes both by generating reactive oxygen species that damage DNA and by mechanical breakage of chromosomes.¹¹⁸ In the process, the cells develop unregulated proliferation and an increased resistance to apoptosis.¹¹⁹ The combination of chronic inflammation and chromosomal and DNA damage may explain their potent carcinogenic effect. Loss of key genetic areas containing tumor suppressors may be critical steps in generating mesothelioma. If SV40 contributes to this process, it may be by binding and inactivating key regulators of cell growth and survival, retinoblastoma and p53 proteins.

CLINICAL FEATURES

The mean age at presentation is 60 years because of the long latency (usually 30 to 40 years) from the time of first exposure to asbestos to the development of clinically evident disease.⁷⁸ The incidence is higher in men, presumably because more men have worked in asbestos-related trades.

Symptoms and physical findings are generally not specific for the disease. Most patients present with nonpleuritic chest pain or dyspnea.¹²⁰ Compared to that of metastatic pleural diseases, the pain from mesothelioma can be severe, aching, and often very difficult to control. Less common complaints are cough, fevers, chills, sweats, and fatigue. Fatigue, cachexia, and pain are common in advanced disease. Physical examination is usually remarkable only for signs related to the presence of a pleural effusion or

mass. Later in the course of disease, one can often appreciate volume loss and decreased mobility of the chest wall on the side of the primary tumor. Occasionally the tumor may extend directly into the chest wall and be detected as a tender or nontender chest wall mass.

Laboratory findings are also nonspecific and include anemia and thrombocytosis. Thrombocytosis (platelets > 400,000/ μ L) can be seen in 40% of patients, may be due to production by the tumor of interleukin-6, and augurs a poor prognosis.^{121,122} Measurement of mesothelin in serum shows promise for the diagnosis of mesothelioma and for monitoring of disease progression.¹²³

RADIOGRAPHIC EVALUATION

The most common findings on chest radiograph are a moderate to large unilateral pleural effusion or unilateral pleural thickening (nodular or smooth)¹²⁰ (Fig. 82-3 and Video 82-4). In a study of 99 patients with malignant mesothelioma, the most common finding on CT was a rindlike extension of tumor on the pleural surfaces (eFig. 82-4) (70%).¹²⁴ Other findings included circumferential lung encasement by multiple nodules (eFig. 82-5) (28%), pleural thickening with an irregular margin between the lung and pleura (26%), and pleural thickening with pleural-based nodules (20%). Invasion of soft tissues and the chest wall (eFig. 82-6) with rib destruction may also be seen (Video 82-5). As the disease progresses and the lung becomes more encased with tumor, there is often volume loss with a shift of the mediastinum toward the side of the primary tumor (see Fig. 82-3). Signs of lymphatic metastasis may be seen (eFig. 82-7) but are more commonly evident late in the course of disease. Further tumor progression may lead to invasion into the contralateral chest. It is important to note that pleural plaques are often not visible; only 28% have radiographically apparent plaques (eFig. 82-8).¹²⁵ Large mediastinal lymph nodes are more consistent with metastatic disease than with mesothelioma. Mediastinal adenopathy on chest radiographs or CT as the initial



Figure 82-3 Mesothelioma. Axial chest CT scan shows diffuse right pleural thickening (arrows) associated with marked volume loss in the right thorax. Note the presence of mediastinal pleural involvement (arrowhead).

presentation of mesothelioma has been reported but is exceedingly rare,¹²⁶ although PET scanning often identifies active nodes that are normal in size and shape on imaging.¹²⁷ Radiographic features that favor the diagnosis of malignant mesothelioma over metastatic pleural disease were found by multivariate analysis to include rindlike pleural involvement, mediastinal pleural involvement, and pleural thickness more than 1 cm.¹²⁴

Some clinicians prefer MRI (eFig. 82-9) over CT for staging and preoperative evaluation because, as reported in one study, MRI may demonstrate extent of disease and in particular chest wall and diaphragmatic invasion better than CT¹²⁸ (Fig. 82-4). However, this has not yet been shown to confer an important clinical advantage. In an earlier study, Heelan and coworkers¹²⁹ also found MRI superior in detection of tissue invasion in these areas; nonetheless, they found no improvement in staging and no alteration in therapy due to its use.

PET and particularly PET/CT shows promise as a tool to differentiate benign from malignant disease and as an adjunctive tool for staging (Fig. 82-5; see eFigs. 82-4E-H and 82-5C). In a comparison of different diagnostic imaging techniques in patients with mesothelioma who then underwent surgery, PET/CT was more accurate than PET, CT, or MRI alone.¹³⁰ It is hoped that functional assessment by PET may also be useful for stratifying patients by prognosis¹³¹ and for monitoring response to therapy.¹³²

In patients being considered for an extensive debulking procedure such as extrapleural pneumonectomy (in which the entire pleura is removed along with ipsilateral pericardium, diaphragm, and lung), every effort should be made to define the extent of disease, in particular to exclude patients with unsuspected extension beyond the pleura. A combination of the imaging techniques may be necessary for determining the best approach to the patient.¹³³ Imaging alone may be insufficient; for patients being evaluated for surgery, even for those with negative imaging, the preoperative workup will often include additional studies such as endoscopic ultrasonography with biopsy of suspicious nodes or thoracoscopic visualization of the contralateral

pleura or peritoneum (see “Surgical Therapy” section, later).¹³⁴

DIAGNOSIS

The role of pleural fluid cytologic examination in establishing a diagnosis is controversial, with some groups demonstrating a high level of diagnostic specificity and others demanding tissue histopathologic analysis.¹³⁵⁻¹³⁷ Patterns of gene expression by microarray in cytologic samples may also help with diagnosis.¹³⁸ The only serum biomarker that is clinically useful is serum mesothelin, which, in the serum,

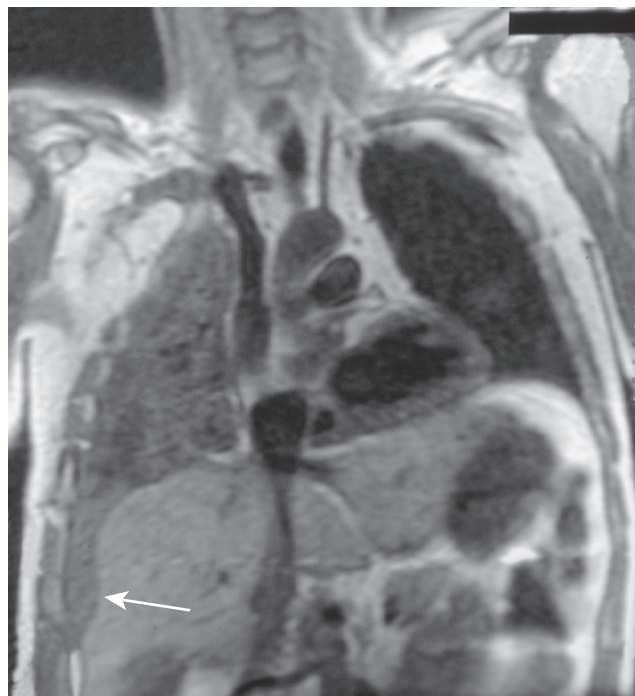


Figure 82-4 Mesothelioma. Magnetic resonance imaging of the same patient as in Figure 82-3 with malignant mesothelioma showing invasion across the diaphragm by tumor (arrow).

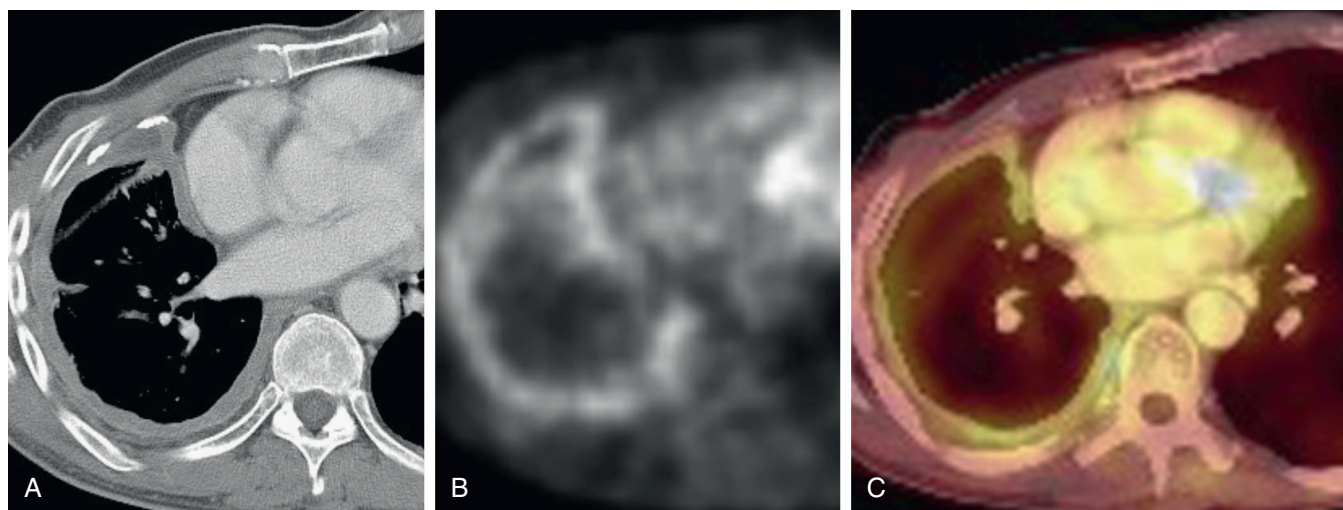


Figure 82-5 Malignant pleural mesothelioma: PET/CT appearance. **A**, Axial enhanced chest CT shows extensive, nearly circumferential right pleural thickening associated with volume loss affecting the right thorax. **B**, PET, and **(C)** fused PET/CT images show extensive metabolic activity within the tumor, correlating with the location of the pleural thickening seen at CT. (Courtesy Michael Gotway, MD.)

has a high specificity (over 90%) but only a 50% sensitivity for the diagnosis.¹³⁹ Other biomarkers such as hyaluronic acid, osteopontin, and fibulin 3 lack specificity.^{139a} The high specificity of mesothelin means that a patient with an undiagnosed effusion and an elevated serum mesothelin level has a high likelihood of having mesothelioma. Mesothelin biomarker levels in pleural fluid may also be useful in diagnosis.¹⁴⁰

Closed pleural biopsy often misses malignant tissue, though the yield may be improved using CT or ultrasonographic guidance. In one study in which patients were randomly assigned to closed pleural biopsy or CT-guided biopsy, mesothelioma was diagnosed by closed pleural biopsy with a sensitivity of 55% (6/11) and by CT-guided biopsy with a sensitivity of 89% (8/9); although the difference was not significant because of small numbers, a similar diagnostic advantage of CT-guided biopsy was found for other pleural malignancies.⁵⁴ With current immunohistochemical stains, mesothelioma can usually, though not always, be differentiated from metastatic adenocarcinoma. It is often harder to differentiate mesothelioma from the benign mesothelial cell hyperplasias that often accompany inflammatory processes in the pleura. In uncertain cases, surgical biopsy is required to establish a definitive diagnosis. A surgical biopsy not only provides larger specimens for immunohistochemistry and perhaps electron microscopy, but also provides critical information about the biologic behavior of the tumor. The behavior of mesotheliomas is unique in that they usually start on the parietal pleural surface with multiple colonies of cells that coalesce and spread to the visceral pleura. Distant metastases are generally a very late finding. In contrast, metastatic adenocarcinomas are usually more prominent on the visceral pleural surface and are often associated with distant metastasis.

The preferred technique for surgical biopsy is thoracoscopic biopsy (see Chapter 24). Not only does thoracoscopy have the advantage of obtaining large samples, but also it permits the drainage of effusions and the freeing up of a trapped lung.¹⁴¹ In addition, if the lung is not trapped, talc can be insufflated at the end of the procedure to achieve a pleurodesis. The location of the insertion site of the thoracoscope is an important consideration if tumor debulking is attempted in the future because of the tendency of mesotheliomas to seed biopsy and chest tube sites.¹³⁵ Misdiagnosis with thoracoscopy has rarely been reported and, in those cases, was thought to be due to adhesions preventing access to the primary tumor.¹⁴² If thoracoscopy cannot be performed, an incisional biopsy has an equally high diagnostic yield.

Talc insufflation has been reported to have a greater than 95% success rate of preventing recurrent pleural effusion in this setting¹⁴³ (see [Video 24-5](#)). Talc pleurodesis does not apparently interfere with later attempts at surgical debulking. However, talc pleurodesis does interfere with any intrapleural therapy that might be considered, as in clinical trials of gene therapy, so this should be considered before pursuing pleurodesis. Talc pleurodesis can also confound interpretation of PET, which can show increased activity in areas of talc deposition for long periods of time following pleurodesis⁴⁸ (see [Fig. 82-2](#)). In such cases, PET/CT may be helpful by localizing the increased activity on PET to areas of increased attenuation on CT due to talc.⁴⁸

PATHOLOGIC FEATURES

The dilemma for the pathologist can be in differentiating mesothelioma both from metastatic adenocarcinoma and from nonmalignant reactive mesothelium. Use of a panel of immunohistochemical stains is now standard for the diagnosis of mesothelioma, including antibodies that stain positively for mesothelioma (calretinin, cytokeratin 5/6, WT1) and those that stain negatively (e.g., adenocarcinoma-specific stains such as CEA, MOC-31, B72.3, Ber-EP4).^{144,145} The actual panel of antibodies used may depend on the differential diagnosis under consideration.¹⁴⁵ Ultrastructural features seen with electron microscopy that are typical of mesothelioma include cytoplasmic tonofilaments and long, sinuous, branching microvilli; in contrast, the microvilli of adenocarcinomas are relatively short, wide, and straight.¹⁴⁶ Nowadays electron microscopy is rarely if ever used because immunohistochemistry is faster, cheaper, and more useful; if needed, electron microscopy to detect microvilli may also be performed on formalin-fixed tissue from paraffin blocks.¹⁴⁵ Although a variety of immunohistochemical stains have been used to differentiate mesothelioma from adenocarcinoma, none is specific, especially with poorly differentiated tumors. Sarcomatous and biphasic mesothelioma raise special issues, usually in differentiating from other sarcomatous tumors.¹⁴⁴

PROGNOSIS AND STAGING

The median survival for patients with malignant mesothelioma is between 9 and 12 months from the time of diagnosis.^{147,167} Regardless of therapy, patients with the epithelial cell type do best, and those with the sarcomatous cell type the worst, with mixed or biphasic usually falling between the two other types.¹⁴⁷ In two separate studies, age, male gender, performance status, leukocytosis, and presence of chest pain were associated with a worse prognosis.^{121,148}

Staging is an issue for those patients in whom surgery is contemplated and continues to be controversial. Before the proposal of a TNM-based staging system by the *International Mesothelioma Interest Group* (IMIG),¹⁴⁹ there had been at least six other systems proposed for staging of mesotheliomas. None of the six was clearly shown to predict survival, including the most widely used Butchart staging system.¹⁵⁰ The IMIG TNM-based staging system is organized in a manner similar to the system currently in use for non-small cell carcinoma of the lung ([Table 82-4](#)). Further surgical studies at Memorial Sloan Kettering supported the prognostic value of this system.^{151,152} For example, patients with stage I disease had a median survival of 30 months, and those with stage IV had a median survival of 8 months.¹⁵² However, the Brigham group found it less useful for determination of surgical resectability and have proposed yet another staging system that is also widely used¹⁵³ ([Table 82-5](#)). It should be noted that this staging system requires resection to determine the involvement of surgical margins, limiting its applicability mostly to postsurgical staging. A new staging system is being devised by the *International Association for the Study of Lung Cancer* (IASLC) and the IMIG, which have assembled a large, multicenter, and international database of patients; an initial analysis

Table 82-4 International Mesothelioma Interest Group Staging System for Malignant Pleural Mesothelioma

T1	Tumor limited to ipsilateral parietal pleura
T1a	No involvement of visceral pleura
T1b	Some scattered foci involving visceral pleura
T2	Tumor involving entire ipsilateral pleura, both visceral and parietal Plus, invasion of diaphragmatic muscle Or, confluent involvement of visceral pleura, including the fissures Or, invasion from visceral pleura into pulmonary parenchyma
T3	Tumor locally advanced but potentially resectable
T4	Tumor locally advanced but technically unresectable
NX	Regional nodes cannot be assessed
N0	No lymph node metastasis
N1	Metastasis to ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastasis to subcarinal or <i>ipsilateral</i> mediastinal nodes
N3	Metastasis to <i>contralateral</i> mediastinal or internal mammary nodes, or to any supraclavicular node
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present
Stage	Description
Stage I	
Ia	T1aN0M0
Ib	T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0 Any N1M0 Any N2M0
Stage IV	Any T4 Any N3 Any M1

From Rusch V, Group IMI: A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest* 108:1122–1128, 1995.

Table 82-5 The Brigham Staging System for Malignant Pleural Mesothelioma

Stage	Description
Stage I	Completely resectable
Stage II	Positive surgical margins and/or intrapleural adenopathy*
Stage III	Local extension and extrapleural disease
Stage IV	Distant metastasis

*Intrapleural adenopathy is any node present in the resected pleural envelope.

From Sugarbaker DJ, Norberto JJ, Swanson SJ: Surgical staging and work-up of patients with diffuse malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 9:356–360, 1997.

indicates that the staging using the tumor and nodal descriptors effectively describes prognosis.¹⁵⁴

Staging systems may be supplemented by prognostic scoring systems that do not require surgical staging. Prognostic scoring systems proposed by the European Organisa-

tion for Research and Treatment of Cancer and by the Cancer and Leukemia Group B incorporate performance status, histopathology, and other laboratory studies.¹²¹ A change in biomarker levels may be an accurate prognostic feature.¹⁵⁵

APPROACH TO THERAPY

The best therapy for mesothelioma is not known. In part because mesothelioma is unusual and dispersed internationally, there have been fewer randomized, controlled trials than are commonplace for other tumors. Guidelines for therapy have been proposed by the European Respiratory Society,¹⁵⁶ by the Asbestos Diseases Research Institute of Australia,¹⁵⁷ and by the National Comprehensive Cancer Network.¹⁵⁸

Surgical Therapy

The two potential goals of surgical therapy for mesothelioma are palliation of symptoms and debulking of tumor with therapeutic intent. Many believe that therapy should follow the paradigm of treatment developed for ovarian cancer because of the similarities in biologic behavior of the cancer and similar embryologic origin of the cells of the primary tumor.¹⁵⁹ In both diseases, surgical resection alone does not prevent disease recurrence. However, the approach of surgical debulking followed by systemic chemotherapy has shown significant success for the treatment of ovarian cancer. For surgical debulking of mesotheliomas, two surgical approaches are commonly employed, *pleurectomy with decortication* (P/D) or *extrapleural pneumonectomy* (EPP). P/D removes all gross disease from all pleural surfaces and preserves the underlying lung; in recommendations from the IASLC and IMIG, an “extended” P/D is proposed for the situation in which the diaphragm or pericardium is also resected.¹⁶⁰ EPP entails en bloc removal of the lung along with surrounding parietal pleura, pericardium, and diaphragm, with the pericardium and diaphragm then replaced by synthetic grafts. These are all technically challenging procedures and should be performed only by surgeons with extensive experience. EPP is especially difficult and was originally associated with an unacceptably high morbidity of 30%. However, with advances in surgical, anesthetic, and critical care techniques, and more exacting patient selection, experienced centers now report mortality rates of less than 4%, a rate comparable to standard pneumonectomy.¹⁶¹ Both P/D and EPP are accomplished through an extended posterolateral thoracotomy and, as mentioned earlier, previous talc pleurodesis is not a contraindication to either procedure.

Preoperative evaluation of patients considered for surgery includes a thorough assessment of tumor stage, cardiac function, and pulmonary function. Most surgery is confined to those with the epithelial cell morphologic features. If debulking surgery is to be of benefit, it is essential that tumor is at an early stage and confined to one hemithorax. Chest CT and MRI are the usual first steps in staging. MRI is preferred by some centers for assessment of transdiaphragmatic extension of tumor (see Fig. 82-4), and many now request PET or PET/CT as well (see Fig. 82-5 and eFigs. 82-4E–H and 82-5C). Recognition that mediastinal lymph node involvement is a poor prognostic sign has

prompted centers to require either cervical mediastinoscopy, endoscopic ultrasonography, or endobronchial ultrasonography with biopsy of suspicious nodes before EPP. Even with negative findings on imaging studies, some groups perform extensive surgical staging with mediastinoscopy and laparoscopy because mesothelioma often spreads through the diaphragm to the peritoneum.¹³⁴

For patients who successfully complete such extensive screening, a few large series suggest that surgical debulking procedures may provide a survival advantage. In the first studies in which both surgeries were performed, it appeared as if pleurectomy was superior, with better survival than EPP.^{151,162} However, in a follow-up report, the same investigators found that there was no difference in median survival between the two surgical debulking procedures.¹⁵² Both series showed that failure after pleurectomy is more often local, whereas failure after EPP is more often extrathoracic. These results underscore the difficulty in eradicating mesothelioma with surgery alone.

Based on such studies showing that surgery alone is insufficient to cure mesothelioma, Sugarbaker and colleagues¹⁶¹ at the Brigham and Women's Hospital developed a strategy of tumor debulking using EPP followed by chemotherapy and high-dose radiation therapy to destroy residual tumor cells. This strategy was reported to yield a median survival of 19 months and 5-year survival of 15%.¹⁶¹ However, patients with all three positive variables (an epithelial cell type, clean margins after resection, and negative lymph nodes) had a median survival of 51 months and a 5-year survival of 46%. Of note, patients with sarcomatous cell type did especially poorly. These results, although exciting, have been criticized for selection bias. Given the lack of prospective randomized studies comparing surgery with or without adjuvant therapy to medical management or supportive care, the therapeutic or even palliative benefit of surgical debulking followed by chemotherapy and radiation therapy remains unknown. Some critics point out that there are some long-term survivors without treatment and that surgery may actually harm patients without improving survival.¹⁶³ For example, in one unrandomized prospective study, 52 patients receiving surgery and other treatments (chemotherapy or radiation therapy) were compared to 64 patients without treatment. Although the treatments were felt to provide palliation, there was no significant difference in survival between treated and untreated patients.¹⁶⁴ Until randomized studies are performed, the best treatment plan for patients with mesothelioma will remain unknown.

Surgical debulking has been combined with a variety of other cytoreductive approaches to destroy residual tumor cells on the surface of the thoracic cavity, including hyperthermia and photodynamic therapy, without convincing success. At this time, the value of surgical debulking and adjunctive measures such as hyperthermia, photodynamic therapy, chemotherapy, immunotherapy, and radiation therapy is not known. It may be that an approach of debulking followed by some modality to eradicate residual tumor will improve outcome. The issue of radical surgery for mesothelioma has again entered the medical literature.^{165,166} However, until randomized trials are undertaken and a consensus is reached on staging, both of which are difficult to achieve, this will not be known with confidence.

Chemotherapy

There are two main regimens that are used in mesothelioma. The most commonly used now includes the multitargeted antifolate drug pemetrexed with a platinum drug such as cisplatin. The use of this combination was compared to cisplatin alone in a large Phase III study of 456 patients.¹⁶⁷ Response rates were significantly better in the pemetrexed-cisplatin arm than in the cisplatin-alone arm (41.3% versus 16.7%), and survival was significantly better as well (median survival, 12.1 months versus 9.3 months). Importantly, the addition of folic acid and vitamin B₁₂ significantly reduced toxicity without altering survival benefit.¹⁶⁷ The other regimen used commonly is the false nucleotide gemcitabine with a platinum agent. Nearly half of the patients on this doublet regimen noted symptom improvement, 33% had a partial response, and 60% had stable disease; no survival benefit was demonstrated compared to historical controls.¹⁶⁸

Newer Agents under Study

Studies of the molecular biology of mesothelioma and the cellular mechanisms leading to a malignant phenotype have led to the identification of several possible therapeutic targets for treatment of this disease. Some of these are under investigation in clinical trials (see www.clinicaltrials.gov). Monoclonal antibodies labeled with toxins targeted to the protein mesothelin on the surface of mesothelioma cells have produced some major responses in immunotoxin trials.¹⁶⁹

Radiation Therapy

Despite evidence from *in vitro* studies,¹⁷⁰ the clinical experience reported by radiation oncologists suggests that mesothelioma is an especially radioresistant tumor. In addition, radiation of the involved chest is limited by the presence of radiosensitive organs and the extensive nature of the tumor. As a consequence, its use appears limited to adjunctive therapy for patients who have undergone EPP and to palliative treatment of painful chest wall lesions. Prophylactic chest wall irradiation may reduce the incidence of chest wall recurrences at incision sites, but there is no consensus on its use and randomized controlled trials are needed.¹⁷¹ An area of active ongoing research is the role of high-dose hemithorax irradiation after EPP for early-stage disease. In carefully staged patients, this approach has resulted in a marked reduction in local tumor recurrences, although nearly one half of patients subsequently developed isolated distant metastases.¹⁷²

Immunotherapy

It is known that an immune response, although weak, is induced by mesothelioma.¹⁷³ This knowledge has prompted a number of investigators to study different ways of strengthening that response. The intrapleural instillation of cytokines is limited by the short half-life of most cytokines, necessitating repeated injections or continuous infusion via a pleural catheter. In studies reported in the early 1990s, intrapleural interferon- γ twice weekly for 2 months was reported to induce a response rate of 56% in early-stage disease.¹⁷⁴ A continuous intrapleural infusion of interleukin-2 induced a partial response in 4 of 21 patients

and an overall survival of 16 months.¹⁷⁵ In both cases, side effects were minimal and consisted primarily of fever and constitutional symptoms. Studies in animals suggest that interferons have an antiproliferative effect on mesothelioma cells and enhance the cytotoxic effect of cisplatin. The results from these studies led to the development of a Phase II trial of cisplatin-doxorubicin and interferon alpha-2b in advanced malignant mesothelioma.¹⁷⁶ The overall response was modest; however, severe myelosuppression was seen in most patients, limiting the application of this treatment.¹⁷⁶ Patient-specific vaccines have been studied, as have other immunotherapies, and this remains a very active area of research.^{177,178}

Gene Therapy

Gene therapy may be particularly suited to use in mesothelioma because the disease is usually localized to a space that can be reached relatively easily and offers a large surface area for gene transfer.¹⁷⁹ Strategies that have been investigated for the treatment of mesothelioma include mutation compensation, molecular chemotherapy, and genetic immunopotential. Mutation compensation attempts to block or replace abnormally expressed genes. The best example of this in mesothelioma is compensation for the absence of p16 gene expression, a consistent abnormality in mesothelioma. Reexpression of p16 using an adenoviral vector improved survival in a murine model of mesothelioma.¹⁸⁰ Molecular chemotherapy is a technique of genetically modifying cells to make them susceptible to a drug. For example, an adenoviral vector containing the herpes simplex thymidine kinase gene has been injected into the pleural space of patients; the virus is taken up by mesothelial cells, and the herpes simplex thymidine kinase gene product causes the cells to metabolize ganciclovir to a toxic by-product. In humans, such approaches have been limited by patchy viral uptake and the development of immunity to the virus.¹⁸¹ Genetic immunopotential employs the genetic induction of an inflammatory antitumor response.^{182,182a}

Palliative Therapy

Pain is common and often disabling. Invasion of the chest wall can cause localized somatic pain, intercostal nerve invasion or vertebral invasion can cause neuropathic pain, and lung invasion may cause diffuse visceral pain. Opioids, such as liquid morphine plus sustained-release morphine, are the mainstay of pain control. Somatic pain may respond to nonsteroidal anti-inflammatory drugs, and neuropathic pain may benefit from an anticonvulsant such as carbamazepine or valproate sodium. Some patients require procedural pain relief as from intrathecal analgesia or nerve block. Cordotomy, the creation of a lesion in the lateral spinothalamic tract in the anterolateral spinal cord, has been evaluated in a systemic review; although cordotomy appeared to be safe and effective, further study and a national registry were recommended.¹⁸³

Dyspnea and cough are often due to large pleural effusions or from tumor spread. The approach to palliation has been described for malignant pleural effusions earlier in this chapter, and some of these options are applicable to the effusions due to mesothelioma as well (see Table 82-3).

Pleurodesis with talc is an option if a patent pleural space is not needed in the future, as for intrapleural therapy in the setting of a clinical trial. Talc pleurodesis is reasonably effective and a relatively inexpensive agent for this task. As described earlier, it can be administered as a slurry through a chest tube or as a powder during thoracoscopy with equal effect. Regardless, with either technique, the affected lung must be capable of expanding so that the visceral and parietal pleura are in contact. Placement of a tunneled pleural catheter for chronic pleural drainage is another option for these patients, as described for malignant pleural effusions earlier.

Psychosocial care is also very important in palliation given the fear, anger, and suffering associated with the disease.^{184,185} When patients exposed to asbestos are eligible for compensation, physicians can provide that information to patients; in a study in the United States, physicians often missed the opportunity to inform their patients about compensation and legal redress.¹⁸⁶

CHEMOPREVENTION AND SCREENING

The existence of populations with known exposure to asbestos suggests that an effective chemoprevention strategy could reduce the incidence of mesothelioma.¹⁸⁷ As of yet, chemoprevention efforts in asbestos-exposed populations have not shown efficacy.¹⁸⁸

Screening of high-risk populations has the potential of detecting early lesions that could respond better to therapy. Screening trials of high-risk populations are ongoing to determine the value of routine low-dose CT scanning.¹⁸⁹ Serum mesothelin testing has a significant early pickup rate (15% to 40%), but it is not sensitive enough for use as a marker for early-stage mesothelioma; biomarkers with greater sensitivity are needed.¹⁹⁰

Additional information on clinical and basic research concerning mesothelioma can be found in reports of the biannual meetings of the IMIG.¹⁹¹ Independent websites include the National Cancer Institute (www.nci.nih.gov), Oncolink (Abramson Cancer Center, University of Pennsylvania; www.oncolink.com), and, for referral of patients for ongoing National Institutes of Health-sponsored studies, www.clinicaltrials.gov.

SOLITARY FIBROUS TUMOR OF THE PLEURA

Solitary fibrous tumors are mesenchymal tumors that can arise not only in the pleura but throughout the body.¹⁹² The term *solitary fibrous tumor* is now used in preference to earlier terms such as *benign mesothelioma* or *localized mesothelioma* for several reasons: to distinguish it clearly from malignant mesothelioma, to acknowledge that it may contain malignancy within it, and also to recognize that its cellular origin is more likely from pluripotent fibroblasts than from mesothelial cells.^{193,194} These localized tumors of the pleura are rarer than malignant mesotheliomas, accounting for 8% of all benign pathologic processes of the chest and 10% of all pleural neoplasms.¹⁹⁵ More than 50%

cause no symptoms and are identified as an incidental finding on radiographic examination.¹⁹⁶ When symptoms do arise, they are usually chronic and related to the mechanical effects of the tumor. Most commonly noted are cough, dyspnea, and chest pain.^{193,197}

Paraneoplastic syndromes are associated with this tumor. Hypertrophic osteoarthropathy has been described in 14%¹⁹⁷ to 19%¹⁹³ of patients and usually resolves over a few months following resection of the tumor.¹⁹³ Hypoglycemia has been described in between 4%¹⁹³ and 14%¹⁹⁷ of patients with solitary fibrous tumors, although the percentage may be overestimated because the hypoglycemia may be the factor that brings the patient to medical attention. The hypoglycemia arises from the production by the tumor of insulin-like growth factor 2, which has insulin activity peripherally and at the liver.¹⁹⁸ As in the case of other non-islet cell tumors associated with hypoglycemia, the hypoglycemia can be treated best by full resection of the tumor.¹⁹⁹ If this is not possible or if there is a delay while awaiting surgical resection, patients have been treated successfully with corticosteroids, which can suppress insulin-like growth factor 2 production.¹⁹⁹

Most solitary fibrous tumors arise from the visceral pleura, but some arise from the parietal.¹⁹⁷ In cases where they appear within the lung parenchyma, the tumor border may be attached to the pleura via a pedicle or stalk (see eFig. 56-11). They are usually round and firm with clear borders and can grow to be several centimeters in diameter. On cut section, the tumor has a fibrous whorled appearance with occasional calcification, hemorrhage, and central necrosis. Cells are elongated and spindle shaped on histologic examination. By immunohistochemistry, the solitary fibrous tumor can be distinguished from malignant mesothelioma by its staining for vimentin and CD34 (a hematopoietic progenitor cell antigen) and its lack of staining for keratin.^{197,200}

Imaging evaluation usually reveals a solitary circumscribed lesion (Fig. 82-6; see eFigs. 56-7, 56-8, 56-10, and 56-11). It rarely may occupy the entire hemothorax (see

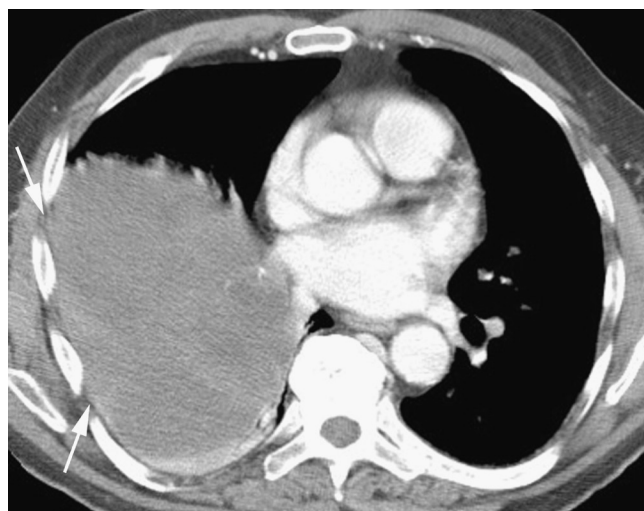


Figure 82-6 Solitary fibrous tumor of the pleura. Axial CT image shows a large, somewhat heterogeneous mass in the right lower chest with extensive chest wall contact (arrows).

eFig. 56-9), but the average size is about 6 cm. In one study, most of the masses appeared to have an atypical appearance for pleural-based tumors in that they appeared to form an acute angle with the chest wall on radiographic examinations (eFig. 82-10).²⁰¹ This may be due to the size of the lesions and the tendency for them to hang from a pedicle into the lung.²⁰¹ In some cases, the mass may be mobile due to the pedicle, and occasionally movement can be documented using decubitus views. CT or MRI may reveal heterogeneous areas of enhancement in some larger tumors that correlate pathologically with areas of cystic necrosis and hemorrhage (see eFigs. 56-7 and 56-9). All have contours that are smooth or lobulated without evidence of invasion into underlying tissues. Occasionally dense calcification is seen.²⁰² MRI findings are consistent with a fibrous tumor with low signal on T1- and T2-weighted images (see eFigs 56-7C and D).²⁰³ There is little information about the use of PET to differentiate solitary fibrous tumors from malignant mesothelioma. However, the few cases in the literature support the finding of low or absent uptake of ¹⁸F-fluorodeoxyglucose on PET imaging of the solitary fibrous tumor (see eFig. 56-10C).²⁰⁴

The diagnosis is strongly suggested by the chest radiograph and CT scan. If a paraneoplastic syndrome is present together with a large tumor of the pleural space, the diagnosis of solitary fibrous tumor is likely. Needle biopsy may be unhelpful and, even if malignancy is present within a portion of the tumor, may miss the areas of concern. Surgery is advised in most cases both for diagnosis by excision and for definitive treatment.

Surgical resection will be curative in most cases. When the tumor arises from the visceral pleura, surgical resection may involve wedge resection or lobectomy. Recurrences have been documented many years after resection, sometimes with malignant transformation (see eFigs. 56-12 and 56-13).^{193,205} Annual chest radiographs are recommended to follow these patients after resection. Sometimes return of a paraneoplastic syndrome can accompany a recurrence of the solitary fibrous tumor.¹⁹⁷

Treatment of recurrent tumors can be difficult if re-resection is not possible. Current approaches targeting VEGF and angiogenesis pathways have shown promise.¹⁹²

PRIMARY EFFUSION LYMPHOMA

Primary effusion lymphoma (PEL) is a type of high-grade B-cell lymphoma that grows within the serous body cavities (pleural, peritoneal, and pericardial) without a detectable tumor mass (Fig. 82-7), although occasionally it may arise in extracavitary tissues.²⁰⁶ Because of its tropism for serosal spaces, it is considered one of the entities within the group of body cavity lymphomas.²⁰⁷ PEL is a body cavity lymphoma caused by the *human herpesvirus 8* (HHV8),²⁰⁷ the same virus that is the cause of Kaposi sarcoma. Most cases of PEL are found in homosexual men with advanced *human immunodeficiency virus* (HIV) disease. In a few cases, PEL has also been described in HIV-negative patients, usually elderly persons of Eastern European/Mediterranean descent, in an epidemiologic pattern similar to that of HIV-negative, classic Kaposi sarcoma.²⁰⁷ Many PELs in HIV-positive patients

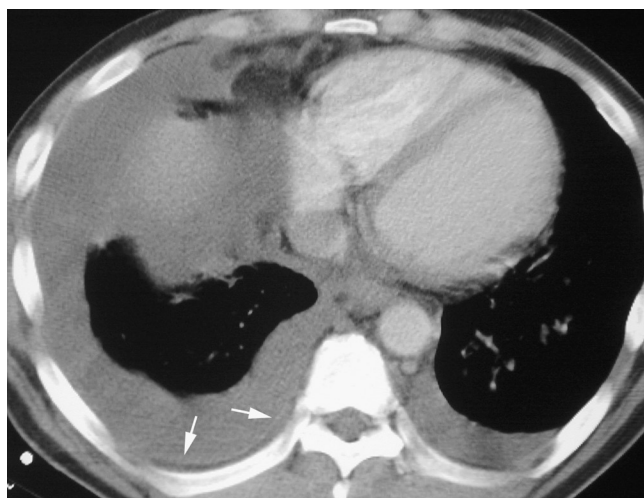


Figure 82-7 Primary effusion lymphoma. On axial CT, the malignancy is manifest in bilateral effusions. Arrows indicate a minimally thickened parietal pleura, without nodularity.

display a coinfection with *Epstein-Barr virus* (EBV),²⁰⁷ suggesting a cooperative etiologic role between HHV8 and EBV. Nonetheless, the HHV8 is thought to be the primary etiologic factor, and the identification of HHV8 is required for the diagnosis of PEL.²⁰⁷

PEL tends to be a late manifestation of HIV infection. Therefore PEL should be considered in patients with advanced HIV disease with large exudative lymphocytic effusions. Chest CT scans will show a small degree of pleural thickening, without a tumor mass or mediastinal adenopathy²⁰⁸ (see Fig. 82-7). Pleural fluid may have a very elevated LDH level.¹⁹⁴ Cytologic examination will show pleomorphic large lymphocytes and suggest the diagnosis. The lymphocytes stain negatively for B- and T-cell antigens.²⁰⁹ Identification of HHV8 can be performed by extracting DNA from involved tissues followed by Southern blot analysis, by in situ hybridization of slides from paraffin-embedded samples, and by in situ reverse transcriptase polymerase chain reaction of cytologic smears or cell blocks.²¹⁰

Prognosis is poor, with survival reported between 6 months²⁰⁹ and 9 months²¹¹; prognosis may vary depending on the number of body cavities involved.²¹¹ Treatment is usually attempted with a CHOP-like regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) and, if the patient is HIV positive, with antiretroviral therapy.²¹² Some patients have shown benefit from antiretroviral therapy alone, suggesting that immune reconstitution can be effective against the lymphoma.²¹² As more is learned of the life cycle of HHV8, there is hope for specific therapy targeting the causative virus.²⁰⁹

PYOTHORAX-ASSOCIATED LYMPHOMA

Pyothorax-associated lymphoma (PAL) is an HHV8-negative lymphoma associated with EBV.²⁰⁷ It is a high-grade non-Hodgkin lymphoma arising as a mass in the pleural space of patients with long-standing chronic pleural inflamma-

tion usually following artificial pneumothorax for pleuropulmonary tuberculosis.²¹³ This entity is mainly seen in Japan but has also been reported in Western countries.^{213,214} The few series available report a strong association with EBV, with 70% of tumors having evidence of EBV in one study.²¹⁵ The cell type is usually B cell with frequent plasmacytoid features, but occasionally an aberrant dual B/T phenotype may be seen.²¹⁴ As opposed to PEL, which is associated with systemic immunodeficiency as from HIV or old age, PAL is associated with a local pleural immunosuppression and antigenic stimulation.²⁰⁷

A relatively large review of 106 patients with PAL in Japan showed the median age at the time of diagnosis to be 64 years (range, 46 to 82).²¹⁵ In these patients, there was at least a 20-year history of pyothorax (mean, 37 years, maximum, 64 years), and patients were predominately male (12:1). All had a history of chronic inflammation of the pleura, due to either artificial pneumothorax for treatment of pulmonary tuberculosis (80%) or tuberculous pleuritis (17%). Fever and/or back pain were the common symptoms on presentation, and chest radiograph or CT scan showed a localized pleural mass in an area of chronic pleural disease.²¹⁶ PET scans have been reported as showing intense uptake in the mass.²¹⁷ There are no large series evaluating specific treatments for this disease. In some reports, it appears that patients may do better with radiation therapy than with chemotherapy.^{218,219} In the review of 106 patient records, patients underwent a variety of treatments, including surgical resection, chemotherapy with CHOP-like regimen, or radiation therapy.²¹⁵ Patients appeared to respond initially to chemotherapy, but the clinical outcome was poor, with a 5-year survival of 22%.²¹⁵ In one patient undergoing treatment, the serum EBV load measured by a quantitative real-time polymerase chain reaction correlated well with tumor size, suggesting that monitoring of the serum EBV load might be helpful in the management of EBV-positive patients with this disease.²¹⁹

Key Points

- Malignant effusions are most commonly due to lung cancer, followed by breast cancer and lymphoma.
- Malignant effusions are often diagnosed by cytologic examination (60% of cases), with a high yield for adenocarcinoma and a low yield for squamous cell carcinoma. If cytologic results are negative, image-guided biopsy and thoracoscopy have a high yield (80% to 100%) for the diagnosis.
- Malignancy may involve the pleural space without formation of an effusion. In the seventh edition of tumor-node-metastasis staging for lung cancer, pleural malignancy with or without effusion is now classified as a metastatic lesion (M1a, intrathoracic metastasis).
- Palliation of malignant pleural effusions may include repeated taps, talc pleurodesis, or indwelling catheter drainage, with the choice depending on the life expectancy of the patient and whether the lung can reexpand. Indwelling catheter drainage can be an outpatient procedure and leads to symphysis and catheter removal in many patients.

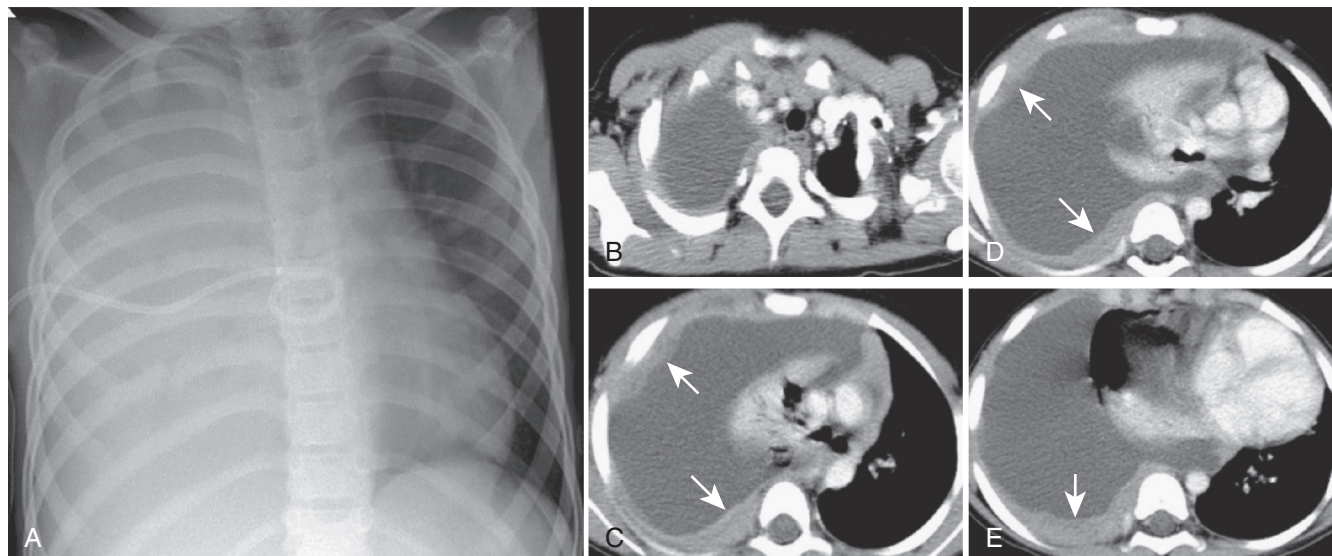
- Pleural mesothelioma should be considered in any patient with a persistent undiagnosed exudate, especially if there is a history of exposure to asbestos, chest pain, a rindlike nodular thickening of the pleura, and involvement of the mediastinal pleura. Diagnosis may be suggested by an elevated mesothelin level in serum or pleural fluid but will require biopsy, often by thoracoscopy, for adequate tissue for panels of immunohistochemical stains.
- Pleural mesothelioma has been shown in a large prospective randomized trial to respond to cisplatin plus pemetrexed; although not studied in a randomized trial, surgery may play a role in debulking and as a part of multimodality therapy including chemotherapy and radiation therapy.
- Solitary fibrous tumors of the pleura are mesenchymal tumors that can involve the visceral pleura and are usually treated successfully with resection.
- *Primary effusion lymphoma* (PEL) and *pyothorax-associated lymphoma* (PAL) arise in the pleural space, the first presenting without a mass and the second as a mass. PEL is associated with systemic immunosuppression from HIV and is caused by human herpesvirus 8; PAL is associated with long-standing pleural inflammation and is associated with Epstein-Barr virus.

Complete reference list available at *ExpertConsult*.

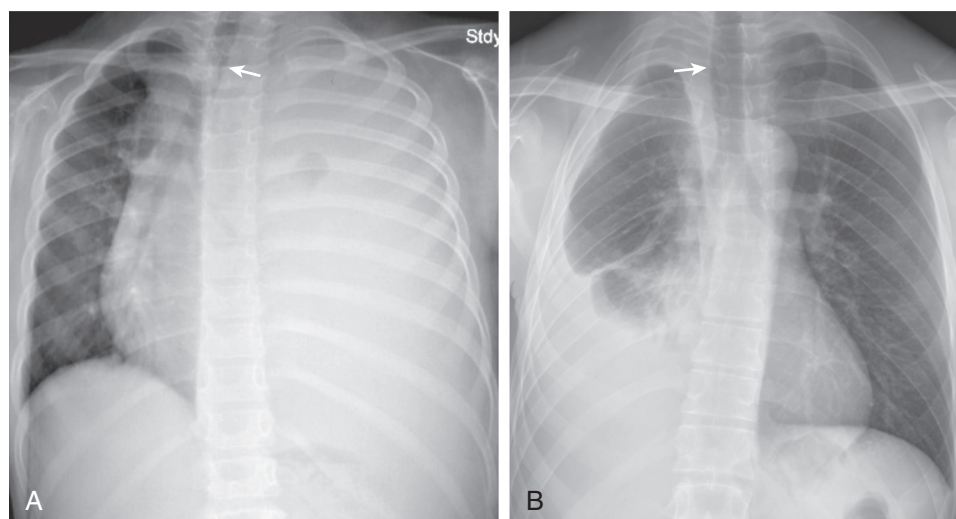
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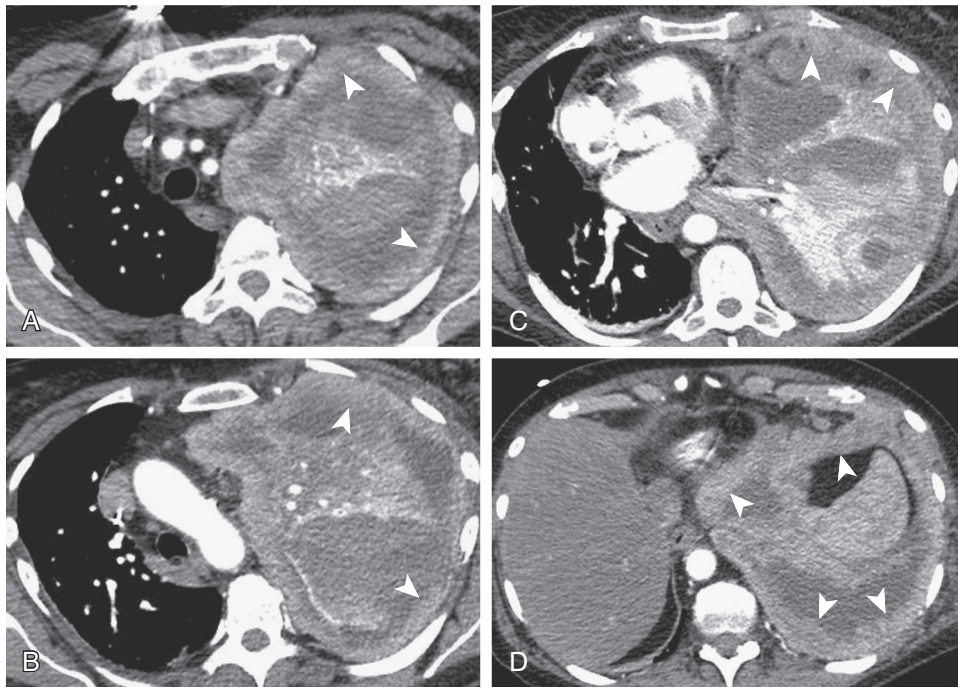
eFIGURE IMAGE GALLERY



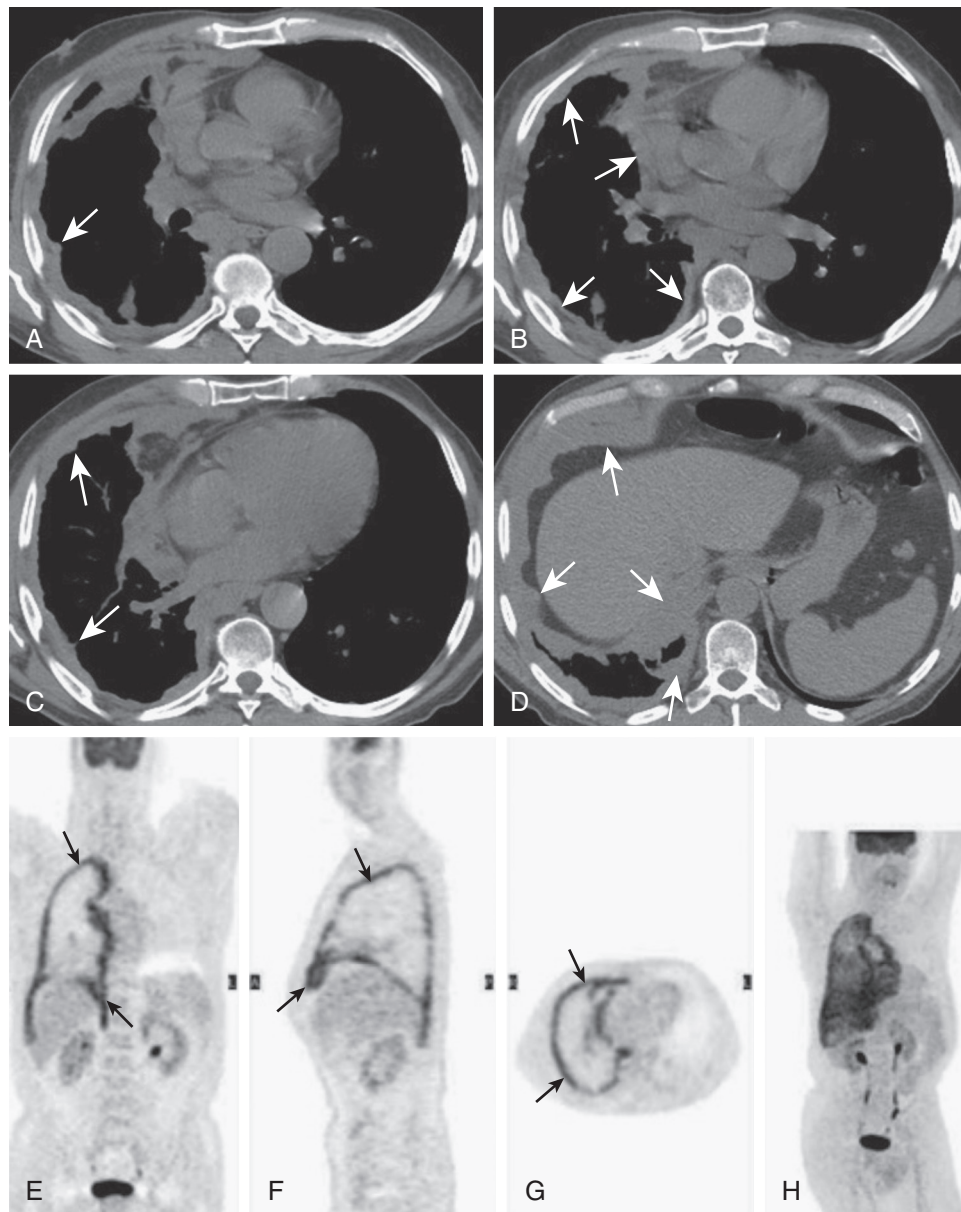
eFigure 82-1 Pleural effusion due to lymphoma. **A**, Frontal chest radiograph shows complete opacification of the right hemithorax due to a massive right pleural effusion. **B–E**, Axial enhanced chest CT shows a large right pleural effusion associated with prominent multifocal pleural thickening (arrows). (Courtesy Michael Gotway, MD.)



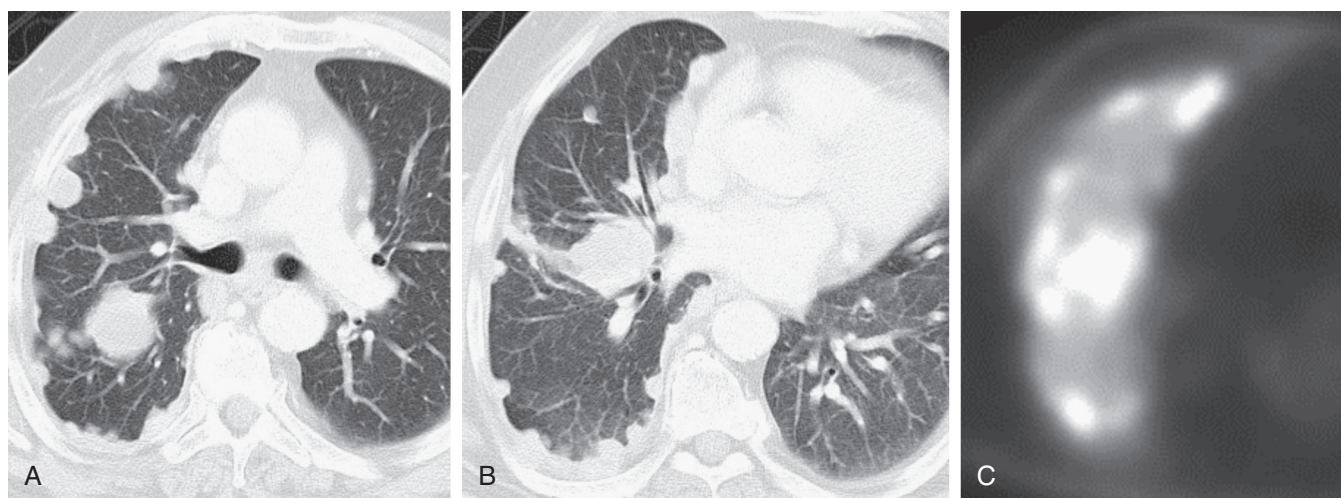
eFigure 82-2 Pleural effusion effect on mediastinal position. **A**, Frontal chest radiograph in a patient with a large left effusion shows *contralateral* shift of the cardiomeastinal structures; note rightward displacement of trachea (arrow). **B**, Frontal chest radiograph in a patient with a moderate right pleural effusion shows slight *ipsilateral* shift of the cardiomeastinal structures; note slight rightward displacement of trachea (arrow). The right pleural effusion in this patient was due to metastatic mucinous adenocarcinoma. (CT and PET imaging for this patient is shown in eFig. 53-4.) (Courtesy Michael Gotway, MD.)



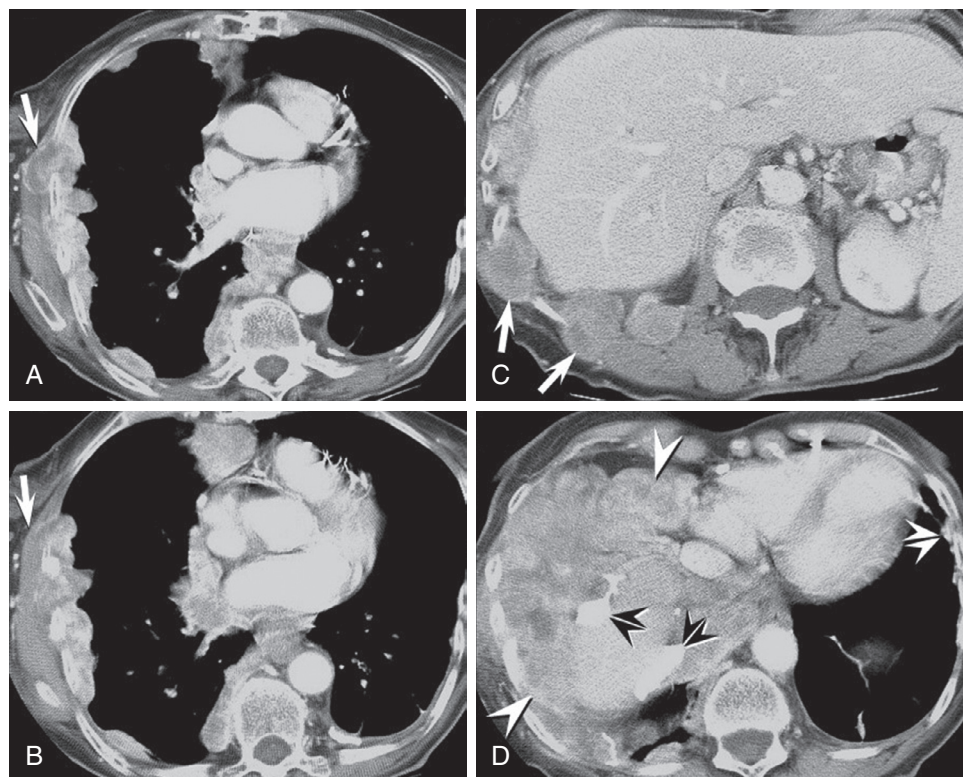
eFigure 82-3 Chest CT appearance of malignant pleural disease. A–D, Axial enhanced chest CT shows extensive, nodular, circumferential pleural thickening (*arrowheads*) due to metastatic bronchogenic malignancy. (Courtesy Michael Gotway, MD.)



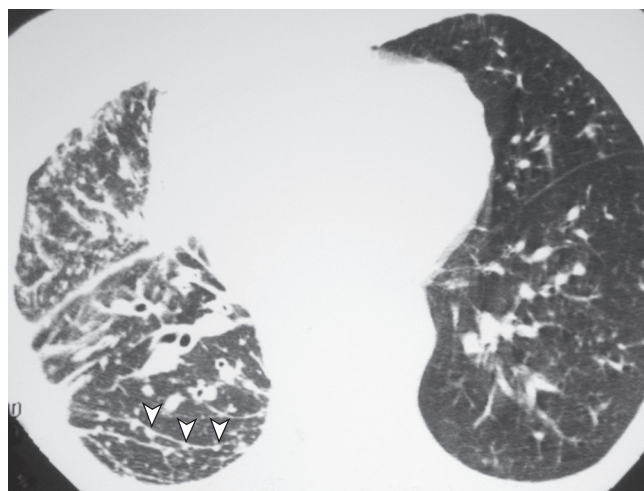
eFigure 82-4 Malignant pleural mesothelioma: chest CT and PET/CT appearance. A–D, Axial unenhanced chest CT shows extensive, circumferential, nodular pleural thickening (*arrows*) associated with mild right thoracic volume loss. E–H, Coronal (E and H), sagittal (F), and axial (G) PET images show intense metabolic activity circumferentially involving the right pleura (*arrows*), correlating with the chest CT findings. (Courtesy Michael Gotway, MD.)



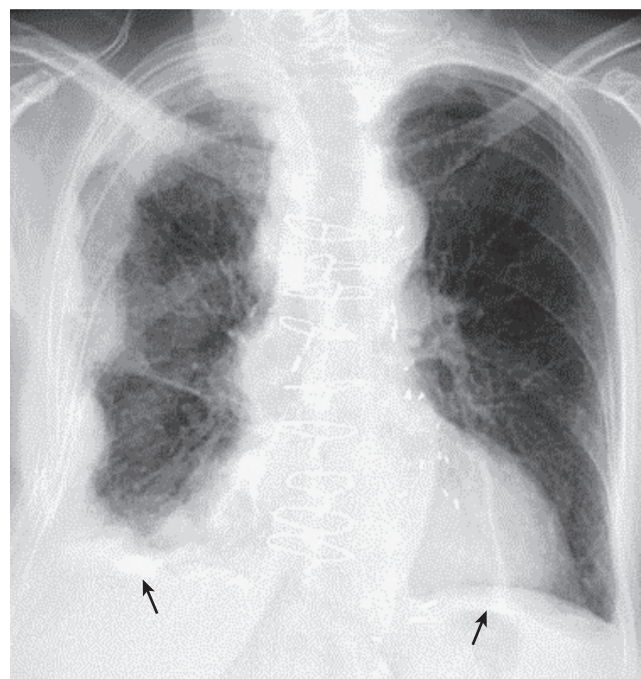
eFigure 82-5 Malignant pleural mesothelioma: pleural nodules. A and B, Axial chest CT displayed in lung windows shows large nodules nearly circumferentially involving the right pleura. C, Axial PET image shows extensive metabolic activity within the nodules. (Courtesy Michael Gotway, MD.)



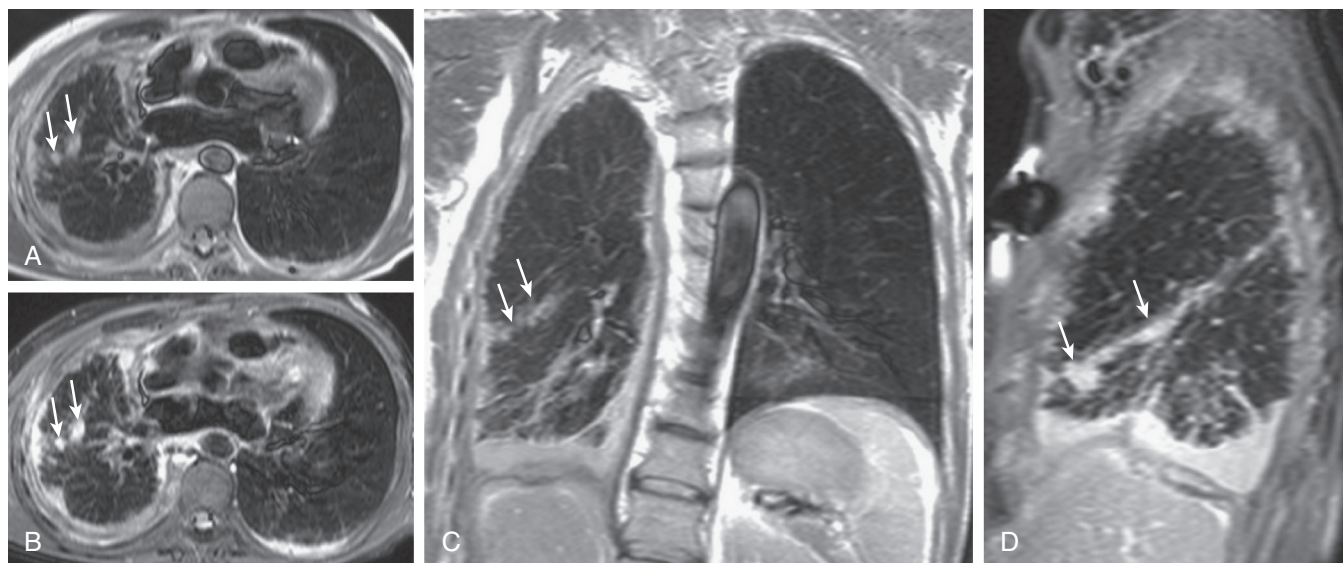
eFigure 82-6 Malignant pleural mesothelioma: chest wall and diaphragm invasion. A–D, Axial enhanced chest CT shows extensive, nodular right pleural thickening with extension of the pleural disease into the adjacent chest wall (arrows). Extensive nodular soft tissue thickening involving the basal pleura and right hemidiaphragm (arrowheads) is present, and partially calcified pleural plaques (double arrowheads), representing asbestos-related pleural disease, are seen bilaterally. (Courtesy Michael Gotway, MD.)



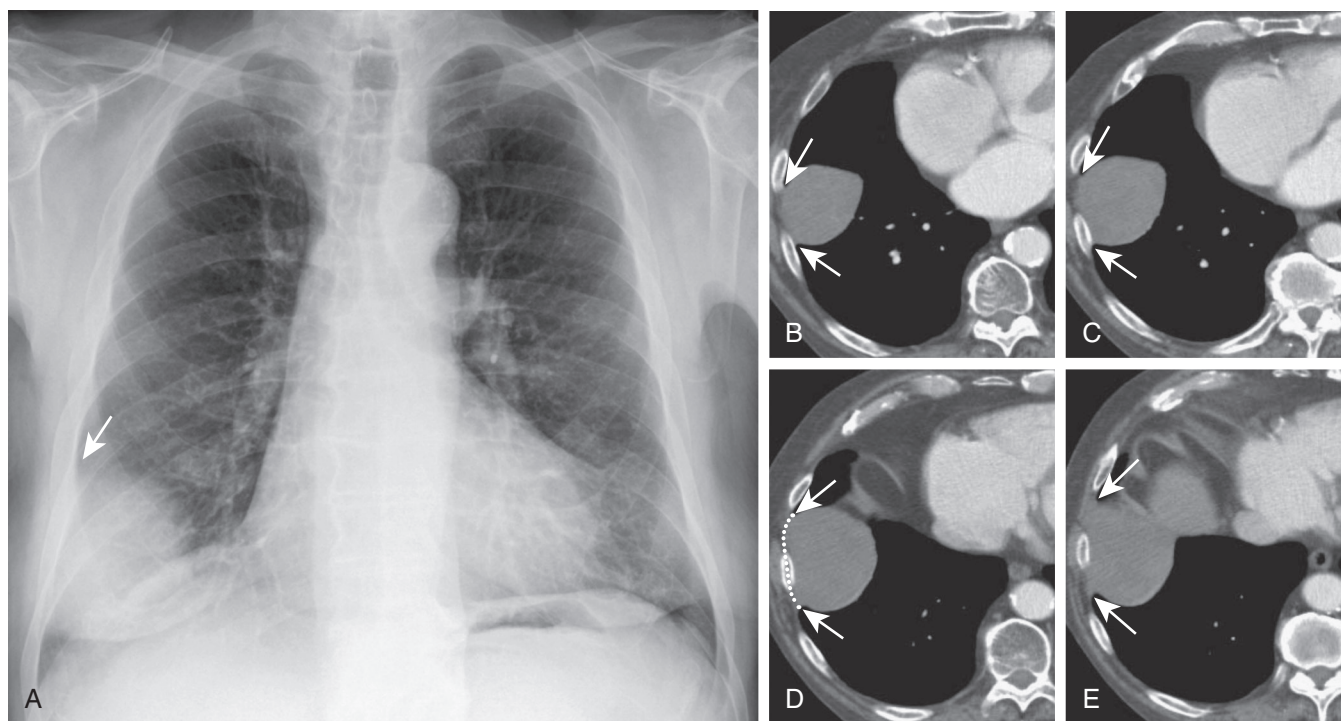
eFigure 82-7 Malignant pleural mesothelioma: lymphatic metastases. Axial chest CT displayed in lung windows shows volume loss affecting the right thorax associated with extensive interstitial thickening. Clear nodular interlobular septal thickening (*arrowheads*) is present. (Courtesy Michael Gotway, MD.)



eFigure 82-8 Malignant pleural mesothelioma complicating asbestos-related pleural disease. Frontal chest radiograph shows extensive nodular pleural thickening affecting the right pleura associated with mild volume loss affecting the right lung. Calcified diaphragmatic pleural plaques (*arrows*), reflecting asbestos-related pleural disease, are present. (See chest CT for this patient in eFig. 82-6.) (Courtesy Michael Gotway, MD.)



eFigure 82-9 Malignant pleural mesothelioma: magnetic resonance imaging appearance. **A** and **B**, Axial T1-weighted imaging before (**A**) and following (**B**) intravenous contrast administration shows enhancing circumferential right pleural thickening with clear nodularity involving the right major fissure (*arrows*). Coronal unenhanced (**C**) and sagittal fat saturation enhanced (**D**) T1-weighted images show extensive pleural thickening and enhancement with a nodular appearance involving the right major fissure (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 82-10 Solitary fibrous tumor of the pleura creating acute angles with the chest wall. **A**, Frontal chest radiograph shows a focal, circumscribed right peripheral chest mass creating an acute angle (*arrow*) at its cranial point of contact with the chest wall. **B–E**, Axial enhanced chest CT shows a circumscribed, homogeneous mass abutting the right inferior chest wall, creating acute angles (*arrows*) with the chest wall, raising the possibility of a location within the subpleural lung rather than the chest wall. The long length of contact of the lesion with the chest wall (*dotted lines, D*), favors a chest wall origin. Tissue sampling showed fibrous tumor of the pleura. (Courtesy Michael Gotway, MD.)

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DISORDERS OF THE MEDIASTINUM

83

MEDIASTINAL TUMORS AND CYSTS

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Additional figures and videos are available online at ExpertConsult.

INTRODUCTION

The mediastinum is the region in the chest between the pleural cavities that contains the heart and other thoracic viscera, except the lungs. Interest in the mediastinum as a separate body region stems from the diversity and importance of the structures it contains and the multiplicity of disease processes by which it can be affected. The mass lesions that arise in the mediastinum represent a heterogeneous group of benign and malignant processes that defy easy categorization. The nonspecific clinical manifestations of most of these disorders and the relative inaccessibility for tissue sampling result in considerable challenges to the clinician evaluating mediastinal disease. This chapter

describes the normal anatomy and contents of the mediastinum, the clinical manifestations produced by mediastinal disease, and the means available for diagnostic investigation. It then describes the features of specific mediastinal tumors and cysts and outlines an overall clinical approach to the evaluation of mediastinal disease. The focus of the discussion of pathology is on lesions that arise primarily in the mediastinum; lung cancer is discussed as it pertains to findings in the mediastinum.

NORMAL ANATOMY OF THE MEDIASTINUM

The anatomy of the mediastinum is divided into anterior, middle, and posterior compartments.¹ This three-compartment model is consistent with embryonic development of the region and with the characteristic distribution of individual disorders encountered clinically. The anatomic relationships of the mediastinal viscera and tissue

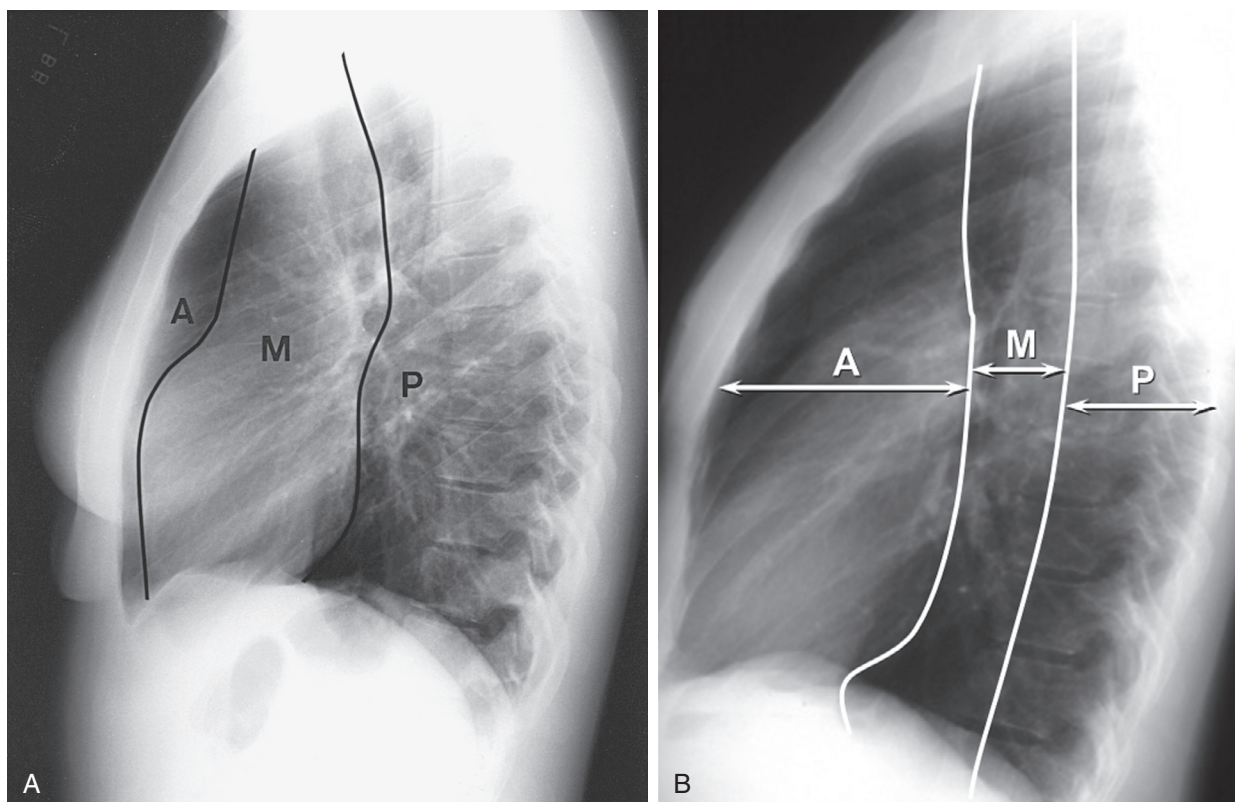


Figure 83-1 Mediastinal compartments. **A**, By *anatomic* convention, the mediastinum is divided into anterior (A), middle (M), and posterior (P) compartments, as outlined on this lateral chest radiograph. **B**, Another method was developed to facilitate constructing an accurate differential diagnosis for mediastinal masses detected at chest radiography. Using this *radiologic* method, the anterior mediastinal compartment (A) is defined as the tissues residing anterior to a line drawn along the anterior aspect of the trachea and extended along the posterior cardiac margin, from the thoracic inlet to the diaphragm. The posterior mediastinal compartment (P) is defined as structures residing posterior to a line drawn 1 cm posterior to a line drawn along the anterior margins of the thoracic vertebrae; the middle mediastinal compartment (M) consists of those tissues residing between these two lines. (From Whitten CR, Khan S, Munneke GJ, Grubnic S: A diagnostic approach to mediastinal abnormalities. *Radiographics* 27:657–671, 2007.)

planes are best appreciated on axial images such as are shown schematically on a lateral chest radiograph in Fig. 83-1.²

The anterior compartment consists of everything anterior and superior to the heart; its boundaries are the sternum, the first rib, and an imaginary curved line following the anterior heart border and brachiocephalic vessels from the thoracic inlet to the diaphragm. Within the anterior compartment lie the thymus gland, any substernal extensions of the thyroid and parathyroid glands, and lymphatic tissue (Table 83-1).

The middle compartment, dorsal to the anterior mediastinum, extends from the lower edge of the anterior heart border along the diaphragm and then cranial along the posterior heart border and posterior wall of the trachea. It contains the heart, the pericardium, the aortic arch and its major branches, the innominate veins and *superior vena cava* (SVC), the pulmonary arteries and hila, the trachea, and several groups of lymph nodes. In addition, the phrenic and upper vagus nerves course through the middle mediastinal compartment.

The posterior compartment occupies the space between the back of the heart and trachea and the front of the posterior ribs and paravertebral gutters. It extends from the diaphragm cranial to the first rib. In it are the esophagus, descending aorta, azygos and hemiazygos veins,

Table 83-1 Normal Mediastinal Contents

ANTERIOR COMPARTMENT

Thymus gland
Substernal extensions of thyroid and parathyroid glands
Lymphatic vessels and lymph nodes
Connective tissue

MIDDLE COMPARTMENT

Heart
Pericardium
Aortic arch and great vessels
Innominate veins and superior vena cava
Pulmonary arteries
Trachea and main bronchi
Hila
Lymph nodes
Phrenic and upper vagus nerves
Connective tissue

POSTERIOR COMPARTMENT

Esophagus
Descending aorta
Azygos and hemiazygos veins
Paravertebral lymph nodes
Thoracic duct
Vagus nerves (lower portions)
Sympathetic chains
Connective tissue

paravertebral lymph nodes, and thoracic duct. The lower portions of the vagus nerve and sympathetic chains also lie within the posterior mediastinum.

CLINICAL PRESENTATIONS OF MEDIASTINAL DISEASE

MEDIASTINUM IN PATIENTS WITH MALIGNANCY

The most common reason that clinicians evaluate the mediastinum is in the staging of patients with lung cancer, because the extent to which the mediastinum is involved is crucial to management.³ Staging of lung cancer is discussed in greater detail in Chapters 21 and 53. Careful preoperative evaluation of the mediastinum is critical in determining a patient’s candidacy for surgical resection or other treatment modalities.^{4,5}

Nonthoracic malignancies also may metastasize to the mediastinum. This is particularly common in tumors originating in the head and neck, the esophagus, the genitourinary tract, the breasts, and the skin (malignant melanoma).

ASYMPTOMATIC MASS

The majority of mediastinal masses are discovered incidentally—at least half of all mediastinal masses are asymptomatic and detected by chest radiography performed for unrelated reasons. About 80% of such asymptomatic masses are benign, whereas more than half of those that produce symptoms are malignant.⁶⁻⁸

COMPRESSION OR INVASION OF ADJACENT TISSUES

Symptoms in patients with mediastinal mass lesions are usually caused by compression or invasion of adjacent intrathoracic structures.^{6,7} Chest pain, from traction on mediastinal tissues, tissue invasion, or bone erosion, is common. Cough may be due to extrinsic compression of the trachea or bronchi, erosion into the airway, and sometimes postobstructive pneumonia. Hemoptysis, hoarseness, or stridor also may be part of the clinical presentation. Invasion or inflammation of the pleural surface may produce a pleural effusion, and cause pain and dyspnea. Compression or direct invasion of the esophagus may lead to dysphagia. Rarely, anterior mediastinal tumors can cause pericarditis or pericardial tamponade, and masses in the middle mediastinum can produce right ventricular outflow obstruction and cor pulmonale.

The SVC is especially vulnerable to extrinsic compression and obstruction because it is thin-walled and has low intravascular pressure. The SVC syndrome results from increased venous pressure in the upper thorax, head, and neck⁹ and is characterized by dilation of collateral veins in the upper portion of the thorax and neck, edema and plethora of the face, neck, and upper torso, and suffusion and edema of the conjunctiva (see Fig. 53-5A and B). Neurologic symptoms such as headache, disturbance of consciousness, and visual distortion, may be present. Symptoms are exacerbated

in the supine position. Numerous benign causes of SVC syndrome are described,¹⁰ but bronchogenic carcinoma (Video 83-1 and eFig. 83-1) and lymphoma (Video 83-2 and eFig. 83-2) are now the most common etiologies.^{11,12}

The compression or invasion of nerves may result in hoarseness from involvement of the recurrent laryngeal nerve, Horner syndrome from involvement of sympathetic ganglia, dyspnea from involvement of the phrenic nerve causing diaphragmatic paralysis, tachycardia from involvement of the vagus nerve and clinical manifestations of spinal cord compression.

SYSTEMIC SYMPTOMS AND SYNDROMES

Fever, anorexia, weight loss, and other systemic symptoms are nonspecific features of malignancy and inflammation that may manifest in patients with mediastinal disease.

In addition, primary mediastinal tumors are associated with a wide array of distinctive systemic syndromes (Table 83-2).^{6,7,13-15} Some typically have endocrine activity, such as intrathoracic goiter, which may present with thyrotoxicosis. Cushing syndrome is associated with thymomas and carcinoid tumors. Thymomas are classically associated with myasthenia gravis (Video 83-3 and eFig. 83-4), in addition to other systemic syndromes. Patients with human chorionic gonadotropin-secreting germ cell tumors may manifest with gynecomastia; patients with pheochromocytoma may present with hypertension. Hypercalcemia may be a presenting abnormality observed in patients with parathyroid adenoma and lymphoma. Hypoglycemia in patients with certain pleural tumors, teratomas, fibrosarcomas, and neurosarcomas is also believed to be the result of tumor products with endocrine activity.

Table 83-2 Systemic Syndromes Associated with Mediastinal Masses

Syndrome	Associated Conditions
ENDOCRINE EFFECTS	
Hypothyroidism or hyperthyroidism	Mediastinal goiter
Hypercalcemia	Parathyroid adenoma, lymphoma
Hypertension	Pheochromocytoma, ganglioneuroma, chemodectoma
Cushing syndrome	Carcinoid, thymoma
Hypoglycemia	Mesenchymal tumor
Gynecomastia	Germ cell tumor
Diarrhea	Ganglioneuroma, neuroblastoma
AUTOIMMUNE EFFECTS	
Opsomyoclonus	Neuroblastoma
Myasthenia gravis	Thymoma
Red cell aplasia	Thymoma
Myocarditis	Thymoma
Hypogammaglobulinemia	Thymoma
CONGENITAL SYNDROMES	
Neurofibromatosis	Neurofibroma
Multiple endocrine neoplasia	Parathyroid adenoma, pheochromocytoma
UNKNOWN CAUSES	
Alcohol-induced pain	Hodgkin lymphoma
Fever and night sweats	Lymphoma

IMAGING THE MEDIASTINUM

The mediastinum is relatively inaccessible for examination or exploration. Accordingly, imaging studies play an important role in the initial evaluation of mediastinal disease. These include conventional radiographic studies, *computed tomography* (CT), *magnetic resonance imaging* (MRI), trans-thoracic and endoscopic ultrasonography, PET, and other radionuclide studies.

CONVENTIONAL RADIOGRAPHIC TECHNIQUES

Most mediastinal abnormalities are first detected by standard posteroanterior and lateral chest radiographs, and certain mediastinal mass lesions have characteristic findings (Table 83-3). For example, teratomas are usually ante-

rior and may contain areas of calcium (sometimes teeth or bone), fat, and soft tissue. Neural tumors lie posteriorly and have sharply delineated margins. Bronchogenic cysts tend to lie against the trachea, carina, or main bronchus. These findings give clues to the possible origin of a mediastinal mass, but further imaging evaluation is usually required.

In the appropriate clinical settings, contrast studies remain important diagnostic tools in mediastinal disease. Barium esophagrams can demonstrate extrinsic compression, esophageal diverticulum, tumor invasion, or fistula formation.⁶ Angiography can identify vascular compression or invasion, can define the vascular supply of tumors, and can sample blood for hormonal localization of certain tumors. Myelography may help delineate intraspinal extension of posterior mediastinal tumors and differentiate neurogenic neoplasms from meningoceles. For the most part, these techniques have been supplanted by CT and MRI.

COMPUTED TOMOGRAPHY

CT imaging is the mainstay of radiographic evaluation of the mediastinum, because this modality can firmly determine the anatomic location, morphology, and tissue density of a mass. The transaxial plane of CT is well suited for assessment of mediastinal structures, most of which are oriented perpendicularly to this plane. Administration of intravenous contrast helps delineate vascular structures as they relate to a mass and other mediastinal structures. Easily identified CT patterns include the high density of calcified tissue and contrast-enhanced blood vessels, and the characteristic low density of fat (Fig. 83-2).¹⁶ Normal anatomic variations and fluid-filled cysts can be distinguished confidently from bulky solid masses, which may be irregularly bordered and possess necrotic areas. Additionally, the site of origin of mediastinal masses can be better identified.¹⁷ Characteristic CT findings in a variety of mediastinal disorders have been described (see Table 83-3). For example, the specificity of the CT appearance of teratomas (Video 83-4, eFigs. 83-9 and 83-10), thymolipomas (Video 83-5 and eFig. 83-11), and omental fat herniation (Video 83-6 and eFig. 83-12) is 100%, but the overall accuracy of CT for predicting the diagnosis of all mediastinal masses is less than 50%.¹⁶

Lymph nodes are readily identifiable on CT scan and can be categorized by size and morphology. Mediastinal lymph nodes greater than 1 cm in diameter in the short axis are considered to be abnormally enlarged and are suspicious for malignancy in the proper clinical context. Mediastinal lymph nodes greater than 2 cm in diameter are virtually always abnormal. In the most recent systematic review of studies on the use of CT in mediastinal staging of lung cancer, the median sensitivity and specificity for identifying metastatic lymph nodes using the greater than 1 cm criteria were 55% and 81%, respectively,¹⁸ similar to what was previously reported by Gould and coworkers.¹⁹ However, even in series of patients with proven bronchogenic carcinoma, benign findings were present in 10% to 37% of lymph nodes that were either larger than 2 cm in diameter or had evidence of central necrosis.^{20,21}

Even though CT cannot reliably distinguish between benign and malignant disease, it remains the initial imaging procedure of choice for the evaluation of the mediastinum

Table 83-3 Characteristic Radiographic Findings in Mediastinal Disease

Feature	Likely Etiology
Bulky mass on initial presentation	Anterior: lymphoma, germ cell tumor, thymoma or thymic carcinoma Posterior: neurogenic tumor
Teardrop-shaped mass within interlobar fissure	Pericardial or bronchogenic cyst
Fat density on CT scan	Mediastinal lipomatosis or lipoma
Calcification in mass	In rim of mass: Cystic thymoma or thyroid adenoma Aneurysm Silicosis ("eggshell" calcification) In center of mass: Thyroid adenoma Teratoma
Teeth or bone	Teratoma
Phleboliths	Hemangioma
Air-fluid level in mass	Esophageal disease Diaphragmatic hernia Developmental cyst Cystic teratoma Abscess
Mass with associated parenchymal opacity	Granulomatous inflammation/infection Metastatic bronchogenic carcinoma Lymphoma with direct extension into lung Esophageal abnormality with aspiration pneumonitis Bronchial compression by primary mediastinal mass
Mass with associated pleural effusion	Metastatic malignancy with pleural involvement Granulomatous inflammation of lymph nodes
Superior vena cava obstruction	Recent onset: Bronchogenic carcinoma Lymphoma Catheter-associated thrombosis Long-standing: Mediastinal fibrosis
Erosion or destruction of bone	Arterial aneurysm Tumors of peripheral nerves or sympathetic ganglia Meningocele
Spine or rib deformity	Enteric cyst

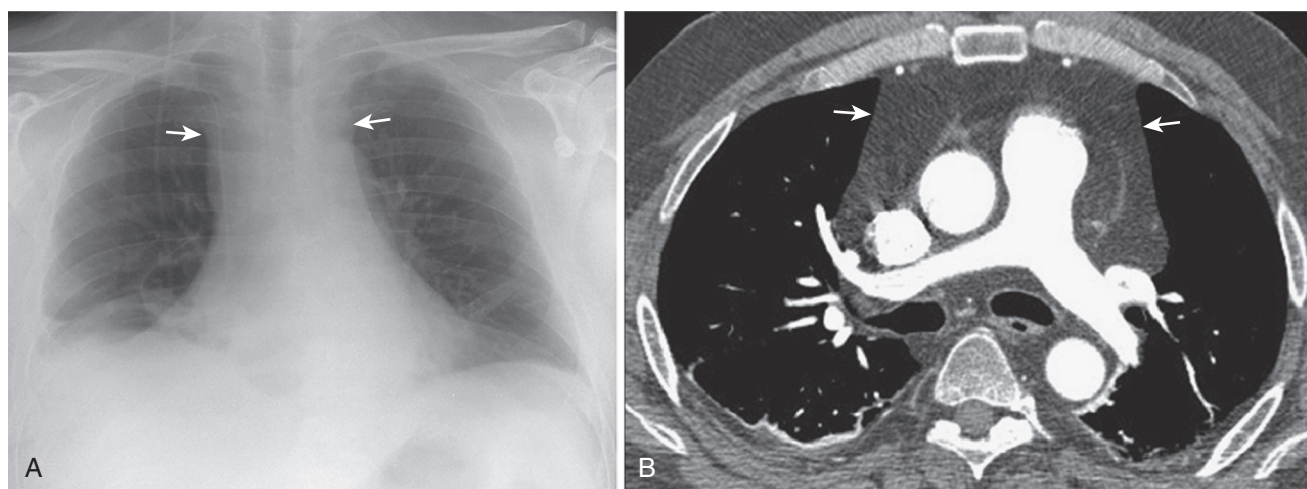


Figure 83-2 Mediastinal lipomatosis. Chest radiograph (A) showing diffuse mediastinal widening (arrows) and chest CT scan (B) showing extensive fat deposition (arrows) in the anterior mediastinum in a patient with mediastinal lipomatosis.

in patients with a primary mediastinal mass¹³⁻¹⁵ or with suspected lung cancer.²² CT can precisely define the mediastinal anatomy and guide subsequent invasive diagnostic and staging procedures, or can confirm a clinical suspicion of extensive mediastinal involvement or visceral organ invasion that precludes curative resection.

MAGNETIC RESONANCE IMAGING

Although much less frequently used than CT in evaluating mediastinal lesions, MRI offers several potential advantages over CT. MRI assesses tissues by measuring radiofrequency-induced nuclear resonance emissions, and the better contrast resolution over CT is advantageous in evaluating soft tissue structures and tissue boundaries (Fig. 83-3).²³⁻²⁶ Blood vessels are identifiable without the need for contrast enhancement (Fig. 83-4) (Videos 83-7A and B), thus MRI can provide an alternative to patients who cannot be given iodinated contrast material required by CT. Ionizing radiation exposure is also eliminated.²⁷

MRI has utility in evaluating neurogenic tumors, and it may also be useful in evaluating thymoma and distinguishing it from congenital cyst or thymic carcinoma.²⁸ MRI can be helpful for defining anatomy before surgical resection of superior sulcus tumors or those invading the mediastinum, chest wall, or diaphragm.^{4,22}

Whereas CT is more commonly used for routine staging of lung cancer, MRI may be useful for defining anatomy in special circumstances, such as before surgical resection of superior sulcus tumors or tumors invading the mediastinum, chest wall, or diaphragm.^{5,23} A large multicenter study comparing CT and MRI in patients with lung cancer found similar accuracy for the detection of mediastinal node involvement, but MRI was superior for detecting direct mediastinal tumor invasion (Video 83-8 and eFig. 83-15; see also Chapter 18).²⁹ Diffusion-weighted MRI distinguished between malignant and benign mediastinal lesions based on apparent diffusion coefficient levels with a sensitivity of 95% and specificity of 87% in a study of 53 mediastinal lesions,²⁴ with evidence of lower apparent diffusion coefficient values indicating a slower diffusion of water molecules in the malignant lesions. However, the use



Figure 83-3 Magnetic resonance lymphogram of the thoracic duct. The normal course of the thoracic duct can be seen crossing diagonally through the lower mediastinum from the patient's right to left and then ascending along the left mediastinum to reach the subclavian vein. In this case the duct is somewhat more dilated and tortuous than normal due to the presence of hepatic cirrhosis. (From Takahashi H, Kuboyama S, Abe H, et al: Clinical feasibility of noncontrast-enhanced magnetic resonance lymphography of the thoracic duct. *Chest* 124:2136–2142, 2003.)

of MRI to establish malignancy or benignity requires further study.

ULTRASONOGRAPHY

Ultrasonography can confirm the cystic nature of mediastinal masses, but it cannot readily distinguish between benign and malignant cystic lesions. Both transthoracic and endoscopic ultrasound probes are useful in the evaluation of mediastinal disease in the context of guiding endoscopic biopsy procedures.³⁰

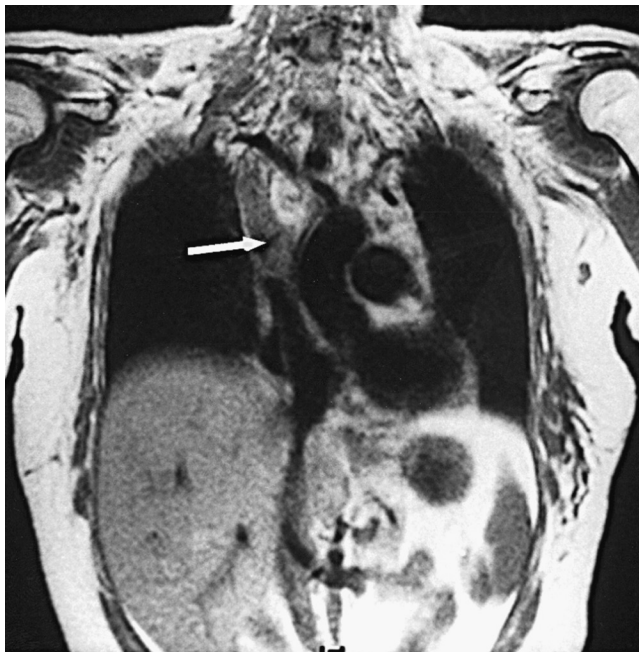


Figure 83-4 Magnetic resonance imaging of superior vena cava syndrome. A 52-year-old woman with multiple myeloma experienced symptoms of superior vena cava (SVC) obstruction following placement of an indwelling central venous catheter in preparation for bone marrow transplantation. Vertically oriented structures are clearly discernible, and black “flow void” is present within the heart and great vessels. The SVC is completely obstructed by thrombus (arrow).

NUCLEAR IMAGING

Nuclear imaging studies rely on the localization of markers based on specific metabolic or immunologic properties of the target tissue to provide a functional image of a lesion. The spatial resolution of radionuclide scans is relatively poor, but the overall diagnostic accuracy may be high if a sufficiently specific probe is available. Nuclear studies offer the potential to identify a primary malignancy and identify distant metastases with a single scan of the entire body.

PET is a widely used nuclear imaging technique that relies on high-energy photon-emitting probes, such as ^{18}F -fluorodeoxyglucose (FDG), which are chemically trapped within metabolically active neoplastic cells. The result is a high signal-to-background ratio and excellent spatial resolution for a functional image of a tumor (Fig. 83-5). More recently, use of combined and co-registered PET and CT images has allowed for more accurate anatomic localization of the lesions in question but at the cost of lower specificity and increased false-positive results.^{18,31}

The use of PET in the evaluation of the mediastinum is largely focused on metastatic disease from thoracic malignancies, because it is useful in staging and preoperative planning for lung cancer. In the evaluation of suspected lung cancer, PET can identify metastatic foci in the mediastinum and extrathoracic sites and help determine the optimal biopsy approach that will make a histologic diagnosis as well as stage the disease.³² Despite widespread use of PET scanning, standardized quantitative criteria for defining an abnormal scan are lacking, and accuracy is far from perfect.³³ False-positive results can be caused by granulomatous, inflammatory, or infectious conditions. FDG-PET

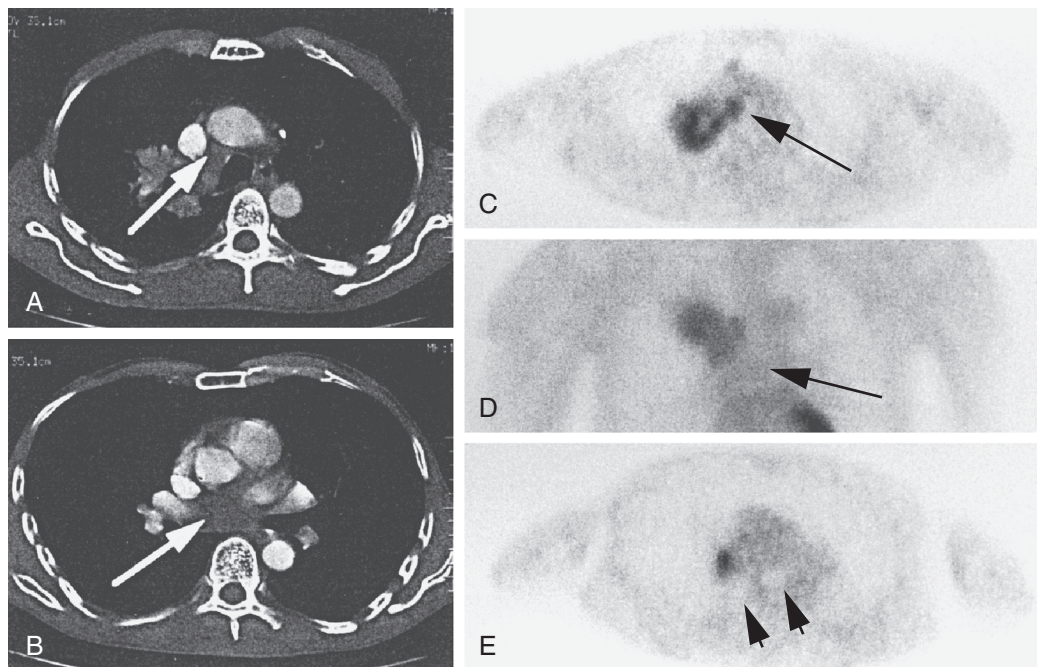


Figure 83-5 Chest CT and PET scans of a patient with right upper lobe squamous cell carcinoma. The primary tumor and right paratracheal adenopathy (A) and subcarinal adenopathy (B) are evident on the standard CT images (arrows). PET images reveal probe uptake in the primary tumor and right paratracheal nodes on axial (C) (arrow) and coronal (D) views, but not in the subcarinal node on coronal (D) (arrow) and axial (E) views. The arrowheads in E point to the main bronchi. At mediastinoscopy, the right paratracheal nodes were found to be malignant, and the subcarinal nodes were enlarged but benign. (From Vansteenkiste JF, Stroobants SG, De Leyn PR, et al: Mediastinal lymph node staging with FDG-PET scan in patients with potentially operable non-small cell lung cancer: a prospective analysis of 50 cases. *Leuven Lung Cancer Group. Chest* 112:1480–1486, 1997.)

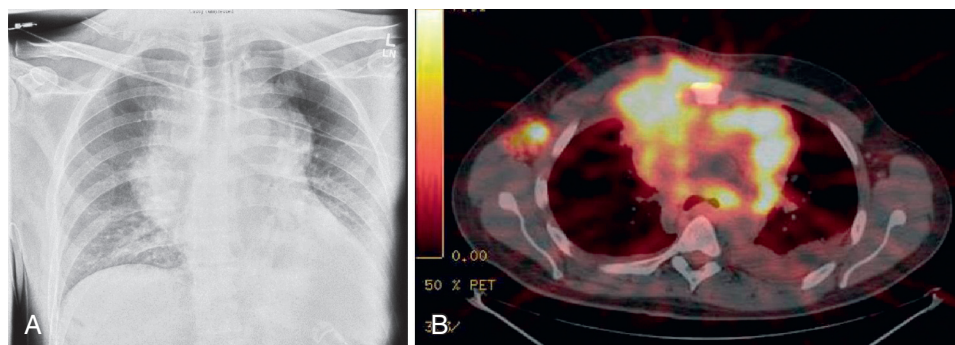


Figure 83-6 Mediastinal lymphoma. **A**, Chest radiograph of a 36-year-old man with gray zone lymphoma presenting as a bulky mediastinal mass. **B**, PET-CT scan performed before initiation of treatment shows a hypermetabolic anterior mediastinal mass with invasion of the chest wall and pectoralis muscles as well as involvement of axillary lymph nodes.

has been shown to be more accurate than CT for mediastinal staging of lung cancer with a sensitivity of 80% and a specificity of 88% in an updated meta-analysis¹⁸; when lymph nodes are enlarged by CT criteria, sensitivity increases while specificity decreases.¹⁹ Mediastinal lymph node sampling is warranted in the setting of a positive PET scan if the findings of mediastinal involvement would alter the subsequent surgical approach (see Chapters 21 and 53).

The utility of PET for the evaluation of primary mediastinal lesions is not as well established as it is for metastatic disease. FDG-PET may differentiate between thymoma and thymic carcinoma,³⁴ but has low sensitivity in differentiating between nonaggressive and aggressive subtypes of thymoma.²⁸ It is not used routinely for staging of thymoma. However, PET is considered standard of care in the pretreatment workup and follow-up of mediastinal lymphoma (Fig. 83-6). FDG-PET also plays a role in detecting residual post-chemotherapy malignant germ cell tumors, specifically seminomas, of the mediastinum. There is little role for PET in evaluating neurogenic tumors.³⁵ Hypermetabolic lesions in the mediastinum may also represent sarcoidosis, mycobacterial and fungal infection, or brown fat.

Other nuclear medicine techniques for the evaluation of the mediastinum include radioiodine scanning for the detection of ectopic thyroid tissue; a positive result is pathognomonic for that condition.⁶ This approach must be planned carefully because iodinated contrast administered intravenously for a CT scan may prevent the uptake of radioiodine for several weeks or more.

TECHNIQUES FOR OBTAINING MEDIASTINAL TISSUE

Definitive diagnosis of most mediastinal masses requires the evaluation of a tissue sample. However, biopsy of mediastinal tissue should be reserved for instances when diagnostic results will influence subsequent treatment. The decision to perform a biopsy rather than surgical resection is based on the presumptive diagnosis. If definitive surgical resection is the treatment choice regardless of the results of a biopsy, then a “diagnostic delay” should be avoided.

Available approaches for biopsy of mediastinal lesions include needle aspiration and biopsy via transbronchial,

percutaneous, or transesophageal approaches. Surgical biopsies are obtained by more invasive procedures including mediastinoscopy and thoracoscopy.

IMAGE-GUIDED BIOPSY

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

For evaluation of mediastinal adenopathy or other lesions in the middle mediastinum, *transbronchial needle aspiration* (TBNA) via the fiberoptic bronchoscope offers a less invasive option to surgical mediastinoscopy. Although few significant complications have been reported, the sensitivity of blind TBNA is low, ranging from 14% to 50%.³⁶⁻³⁸

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a recent technology that has significantly improved the ability of pulmonologists to diagnose and stage non-small cell lung cancer in a minimally invasive manner. With the advent of a curvilinear ultrasound probe integrated at the end of the bronchoscope, TBNA with a 22-gauge needle can be performed under real-time ultrasonographic guidance. The ability to visualize the area of interest as well as adjacent vascular structures has vastly improved diagnostic yields.³⁹⁻⁴¹ Upper and lower paratracheal, subcarinal, and hilar lymph nodes are readily accessible by EBUS-TBNA, as is any mediastinal or hilar lesion that is adjacent to the large airways. EBUS-TBNA has the advantage over mediastinoscopy in accessing the posterior subcarinal lymph nodes as well as hilar nodes or masses, in addition to being an ambulatory procedure with lower associated health care costs.⁴²

While the efficacy of EBUS-TBNA is now firmly established in the evaluation of lung cancer, there is also an increasing role for the initial evaluation of isolated mediastinal adenopathy due to other conditions such as sarcoidosis. In a randomized controlled trial of 50 patients with clinically suspected sarcoidosis due to the presence of mediastinal and hilar adenopathy, the diagnostic yield of EBUS-TBNA was superior to blind TBNA, with a sensitivity of 83% and specificity of 100%.⁴³ In a prospective trial of 77 patients with isolated mediastinal adenopathy, a specific diagnosis of sarcoidosis, tuberculosis, lymphoma, or other malignancy was made in 67 of them, thus obviating the need for a more invasive surgical mediastinoscopy.⁴⁴

EBUS-TBNA can be useful in providing a definitive diagnosis of primary or recurrent lymphoma; however, its role in the initial diagnosis of mediastinal lymphoproliferative disorders is controversial because the amount of tissue provided may not be adequate for histologic subtyping.^{44,45}

Endoscopic Ultrasound-Guided Needle Aspiration and Biopsy

Endoscopic ultrasound (EUS)–guided sampling relies on the placement of biopsy needles that are passed through the working channel of a gastroscope.⁴⁶ The proximity of the esophagus to mediastinal sites relatively inaccessible to mediastinoscopy, such as the posterior subcarinal lymph nodes, makes this approach particularly useful in selected cases. EUS-guided biopsy has similar sensitivity as PET for determining inoperability in lung cancer and, importantly, superior specificity (100% vs. 72%).⁴⁷ In selected cases, it can confirm the presence of mediastinal metastases and thereby obviate the need for surgical staging procedures.⁴⁸

Percutaneous Needle Aspiration and Biopsy

Percutaneous needle aspiration and biopsy of mediastinal masses, usually in the anterior compartment, can be performed using ultrasound or, more often, CT guidance⁴⁹ (Fig. 83-7). Percutaneous needle aspiration of the mediastinum has acceptable morbidity and yields comparable to those from percutaneous biopsy of pulmonary lesions. As with TBNA, serious bleeding is seldom encountered,⁴⁹ and accurate diagnosis of a wide variety of lesions has been reported.

SURGICAL BIOPSY

Mediastinoscopy

Mediastinoscopy allows direct inspection and biopsy of lymph nodes or other masses in the superior portion of the anterior mediastinum.⁵⁰ Cervical mediastinoscopy provides access to the paratracheal and subcarinal lymph nodes, whereas an anterior mediastinotomy (otherwise known as

an anterior or parasternal mediastinoscopy) provides access to the lymph nodes in the aortopulmonary window. Although more invasive than a percutaneous or endobronchial approach, mediastinoscopy has the advantage of providing the entire lymph node for histologic examination, rather than the cellular aspirates or small tissue fragments produced by needle biopsy techniques. Mediastinoscopy is most frequently used in the staging of bronchogenic carcinoma,⁵¹ but has utility in evaluating mediastinal adenopathy or mass lesions of other etiologies. Either frozen section or imprint cytology methods can provide rapid, accurate results and facilitate immediate decisions about the feasibility of curative resection.^{52,53}

Mediastinal anatomy from the perspective of the surgeon performing a mediastinoscopy is different from that based on the lateral chest radiograph as described earlier. For mediastinoscopy, structures are considered according to whether they lie anterior, posterior, or immediately to the right or left of the trachea.² Mediastinoscopy is performed using general anesthesia, but is typically an outpatient procedure when subsequent thoracotomy is not planned to follow immediately.⁵⁴

Mediastinoscopy is safe and well tolerated. Complications of mediastinoscopy include pneumothorax, hemorrhage, recurrent laryngeal nerve or phrenic nerve paralysis, injury to the trachea, esophageal perforation, thoracic duct laceration, air embolism, and mediastinitis.

Video-Assisted Thoracoscopic Surgery

Biopsies of mediastinal lymph nodes can also be performed by *video-assisted thoracoscopic surgery* (VATS). VATS provides access to the hilar nodes and inferior pulmonary ligament lymph nodes on both sides. Additionally, on the right side, VATS can provide access to the right paratracheal lymph nodes and subcarinal nodes. Left-sided VATS can provide access to the aortopulmonary nodes. VATS can also be a tool for the evaluation of pleural and lung abnormalities in the management of mediastinal diseases. After dissection through the mediastinal pleura, mediastinal lymph nodes can be sampled to aid in the staging of malignancies such as esophageal carcinoma and for the diagnosis and resection of primary mediastinal tumors and cysts.⁵⁵⁻⁵⁸ VATS requires a general anesthetic, chest tube placement at the conclusion of the procedure, and typically a limited stay in the hospital.

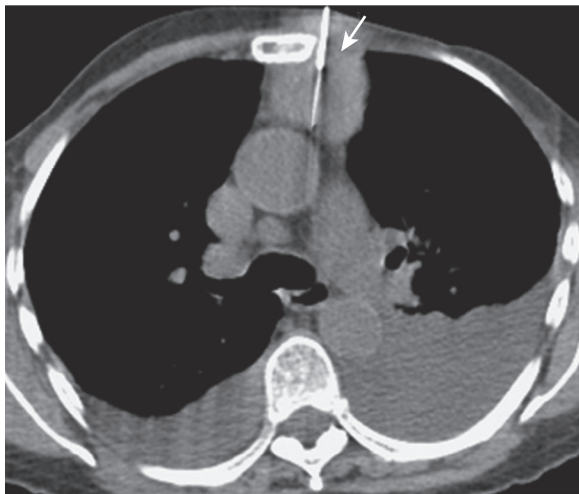


Figure 83-7 CT-guided needle aspiration of an anterior mediastinal mass. The image shows the needle entering the mass by passing lateral to the sternum and medial to the internal mammary vessels (arrow, left internal mammary artery). Associated findings include a pretracheal lymph node and bilateral pleural effusions.

MEDIASTINAL MASS

CLASSIFICATION

Mediastinal masses are considered primary, that is, arising solely from structures within the mediastinum, or secondary, usually as metastatic disease from intrathoracic or extrathoracic malignancy.

The most practical clinical classification of primary mediastinal masses groups together lesions that are characteristically found in the anterior, middle, or posterior mediastinal compartments (Table 83-4), with the recognition that such a simplified scheme overlooks the fact that mediastinal masses will not necessarily respect anatomic borders. Masses found within any of the mediastinal compartments

Table 83-4 Disorders Presenting as a Mass in the Mediastinum

Anterior Mediastinum	Middle Mediastinum	Posterior Mediastinum
Thymic neoplasms	Lymphadenopathy	Neurogenic tumors
Germ cell tumors	Reactive and granulomatous inflammation	Meningocele
Teratoma	Metastasis	Esophageal lesions
Seminoma	Angiofollicular lymphoid hyperplasia (Castleman disease)	Carcinoma
Nonseminomatous germ cell tumors	Lymphoma	Diverticula
Embryonal cell carcinoma	Developmental cysts	Diaphragmatic hernia (Bochdalek)
Choriocarcinoma	Pericardial cyst	Miscellaneous
Lymphoma	Foregut duplication cysts	
Hodgkin lymphoma	Bronchogenic cyst	
Non-Hodgkin lymphoma	Enteric cyst	
Thyroid neoplasms	Others	
Parathyroid neoplasms	Vascular enlargements	
Mesenchymal tumors	Diaphragmatic hernia (hiatal)	
Lipoma		
Fibroma		
Lymphangioma		
Hemangioma		
Mesothelioma		
Sarcoma		
Diaphragmatic hernia (Morgagni)		
NUT midline carcinoma		

may be due to lesions more commonly found in another mediastinal compartment or due to those that have extended from another area in the mediastinum (Fig. 83-8).

In a series of 400 consecutive patients with a primary mediastinal lesion,⁵⁹ 25% had a primary cystic lesion and 42% had a malignant lesion. The anterior compartment was the most common compartment for a lesion, which was more likely to be malignant, followed by the posterior and then middle compartments. Although two thirds of mediastinal masses are benign, the likelihood of malignancy depends on the location, age of the patient, and presence or absence of symptoms.^{60,61} In a series of 38 patients with malignant mediastinal tumors, 31 had at least one sign or symptom.⁶¹

INCIDENCE

The true incidence of primary mediastinal masses is difficult to ascertain. In a study of more than 9000 patients in a lung cancer CT screening trial, the prevalence of an incidentally detected mediastinal mass was 0.77%; on follow-up annual screening, the incidence was 0.01%.⁶² Historically, thymomas and developmental cysts were the most common masses found in adults, followed by neurogenic tumors and lymphoma, based on the collection by Silverman and Sabiston of nearly 2400 cases from the literature (Table 83-5).⁶ More recent series suggest a similar pattern,^{8,63} although Cohen and associates⁸ have observed both a rising incidence of mediastinal masses in general and an increasing proportion of lymphoma and malignant neurogenic tumors over the course of their 45-year survey. Neurogenic tumors, thymomas, and developmental cysts account for about 60% of all mediastinal masses. Lymphomas and germ cell tumors such as teratoma and seminoma account for about 25%, and a large number of other lesions, both benign and malignant, constitute the remaining 15%.⁸

SPECIFIC MEDIASTINAL TUMORS AND CYSTS

LESIONS OF THE ANTERIOR MEDIASTINUM

Thymic Neoplasms

Thymoma is the most common neoplasm arising in the anterior mediastinum^{6,7,17,64} and is increasingly recognized in the course of thorough evaluations of patients with myasthenia gravis.⁶ It remains a rare tumor, with an overall incidence of 0.13 per 100,000 person-years in the United States.⁶⁵ The peak incidence of thymomas is between the ages of 40 and 60 years and is higher in Asians and African Americans, with equal gender predilection.

Although most thymomas are not biologically aggressive, about one third of thymomas found have already invaded their capsules. Advanced disease involves extension into local structures and transdiaphragmatic extension into the abdomen and pericardial involvement, but lymphogenous and hematogenous metastases are rare.⁶¹ The histologic classification remains a subject of debate and revision.²⁸ The current World Health Organization classification system, which is based on histologic features, does not accurately predict clinical outcome, thus treatment of patients has been based historically on the presence and degree of tumor invasion into microscopic and local structures. Most clinicians use the Masaoka clinical staging system, which is based on the degree of invasion of the tumor through the capsule into adjacent structures.⁶¹ Moran and colleagues recently proposed a new staging system in which the overall prognosis and recurrence is based on extent of tumor infiltration.⁶⁶ Currently the *International Thymic Malignancies Interest Group* (ITMIG) and the *International Association for the Study of Lung Cancer* (IASLC) are collaborating on developing a new TNM-based classification system, which is expected in 2017.^{66a}

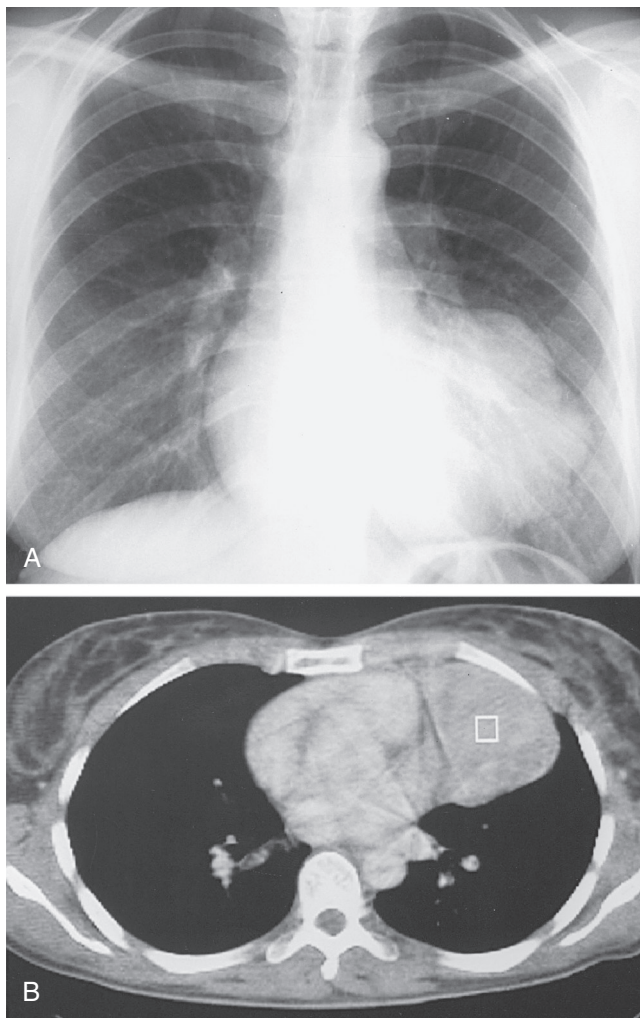


Figure 83-8 Thymoma. Typical findings on chest radiograph (A, frontal view) and chest CT (B) showing a mass presenting in the anterior and middle mediastinum. At surgery, this mass proved to be a benign thymoma, originating in the anterior mediastinum and extending by a slender stalk into the middle compartment. (Courtesy Dr. Robert Stevens, Wenatchee, WA.)

Clinically, the majority of patients with thymoma are asymptomatic, while one-third of patients will present with nonspecific chest pain, cough, or dyspnea due to local tumor effects.⁶⁷ Forty to 70% have at least laboratory evidence of one or more of the two dozen systemic “parathymic” syndromes that have been recognized.⁶ Thymomas are associated with numerous systemic syndromes, most of which appear to be autoimmune in origin.^{6,7,14} The most familiar of these is myasthenia gravis, reported in 10% to 50% of patients with thymoma⁶ and thought to be due to autoantibodies to the postsynaptic acetylcholine receptor.^{68,69} Other associated syndromes include pure red blood cell aplasia, myocarditis, and hypogammaglobulinemia. Patients with thymoma also have an increased incidence of collagen vascular disease, Whipple disease, and malignancy elsewhere in the body.

On chest radiography, thymomas appear as an ovoid, smooth or lobulated unilateral mass near the junction of the heart and great vessels (Fig. 83-9).⁷⁰ Compared with thymic hyperplasia, which is typically symmetrical,

Table 83-5 Relative Frequencies of Mediastinal Masses in Adults and Children*

Lesion	Adults (%)	Children (%)
Thymoma	19	—
Developmental cysts	21	18
Bronchogenic	7	8
Pericardial	7	<1
Enteric	3	8
Other cysts	4	2
Neurogenic tumors	21	40
Lymphoma	13	18
Germ cell tumors	11	11
Endocrine (thyroid, parathyroid, carcinoid)	6	—
Mesenchymal tumors	7	9
Primary carcinoma	—	—
Other malignancies	3	4

*Based on Silverman and Sabiston's review of reported mediastinal masses in 1950 adults and 437 children.

Data from Silverman NA, Sabiston DC Jr: Mediastinal masses. *Surg Clin North Am* 60:757-777, 1980.

thymoma usually distorts the gland's normal shape and extends to one side.⁷¹ On CT scan, most thymomas present as a solid 5- to 10-cm anterior mediastinal mass outlined by fat; up to one third of thymomas contain cystic, necrotic, or hemorrhagic areas that enhance heterogeneously. Contrast CT is necessary for the staging of thymoma, specifically for discerning vascular involvement. MRI can help distinguish benign cysts from a cystic thymoma or thymic carcinoma. At this time, nuclear medicine has little role in the evaluation of thymoma. Due to their relatively indolent nature, most thymomas have low FDG uptake, which limits the utility of PET imaging to discern a benign from a malignant thymic mass.^{28,61}

The mainstay of therapy for thymomas is surgical resection, which provides the best chance for an optimal prognosis.⁶¹ Adjunctive treatment with postoperative radiotherapy is typically provided,^{7,64,72} and the addition of preoperative or adjuvant chemotherapy appears promising for more advanced stages.⁷³⁻⁷⁵

Patients whose tumors are fully encapsulated with no evidence of invasion can expect postoperative survival equal to that of the general population. Invasive tumors have a poorer prognosis, with 50% to 77% 5-year and 30% to 55% 10-year survival.⁷⁶ Thymoma recurs after resection in nearly a third of patients.⁷⁶ The largest and most recent retrospective survey of thymic tumors from the European Society of Thoracic Surgeons database showed that higher Masaoka stage (with evidence of invasion), incomplete resection, and nonthymoma histology were factors in recurrence and worsening survival.^{76a}

Thymic carcinoma is an aggressive epithelial malignancy that invades locally and frequently metastasizes.^{77,78} This rare cancer develops predominantly in middle-aged men, who present with symptoms of cough, dyspnea, and chest pain as well as nonspecific systemic symptoms.⁶¹ On imaging, thymic carcinomas are heterogeneous masses with areas of necrosis and calcifications. They are highly FDG-avid on PET scan.^{28,34} The prognosis, which depends

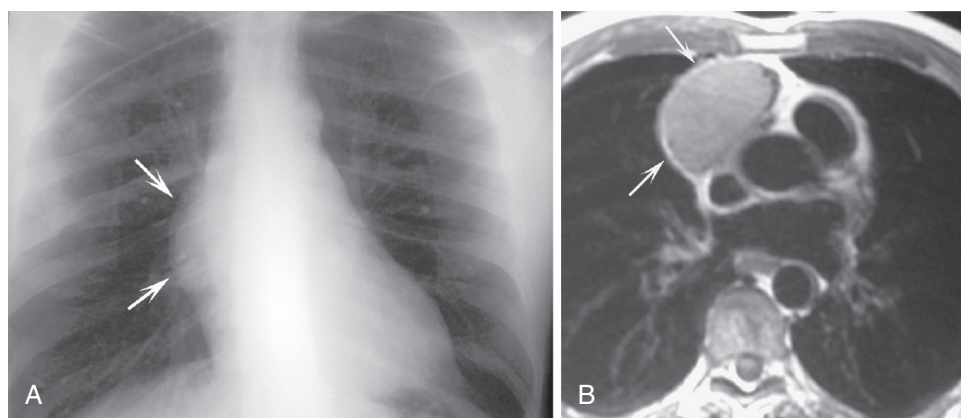


Figure 83-9 Thymoma. **A**, Frontal chest radiograph shows a smoothly margined mass along the right side of the mediastinum (arrows). **B**, Axial magnetic resonance T1-weighted image through the base of the heart shows that the mass (arrows) is slightly hyperintense compared to the skeletal muscle and resides within the anterior mediastinum. Note the smooth, well-defined margins of the mass, consistent with an encapsulated thymoma.

on the histologic grade and the anatomic stage, is generally poor. Surgical resection is the treatment of choice; chemotherapy and radiation therapy are advocated for unresectable disease.

Carcinoid tumors occasionally arise in the thymus.^{79,80} They may cause Cushing syndrome and be associated with multiple endocrine adenomatosis. Locally invasive carcinoids may be difficult to resect completely, but characteristically have a prolonged clinical course.⁶ Interestingly, the thymus is also a common site for mediastinal Hodgkin lymphoma, and normal thymic tissue may enlarge following chemotherapy for lymphoma (a process termed *thymic rebound*) (eFig. 83-25), mimicking recurrence of the primary disease.⁸¹ Other thymic mass lesions include benign conditions such as thymic hyperplasia (eFig. 83-26), thymic cysts, and lipothymomas (see Video 83-5 and eFig. 83-11).⁸²

Germ Cell Tumors

Approximately 10% to 12% of primary mediastinal masses are derived from multipotent germ cells that migrated abnormally during early embryonic development.^{6,7,83,84} These neoplasms are classified into three groups: benign teratoma, seminoma, and nonseminomatous germ cell tumors.⁸⁴

Teratomas, the most common germ cell tumors, are by definition made up of tissues foreign to the area in which they arise. Ectodermal derivatives predominate, but structures originating in all three primary germ cell layers may be found. *Dermoid cyst* refers to a lesion that contains only the epidermis and its derivatives. Teratomas arise most often in young adults, but have been reported in all age groups; men and women are affected with equal frequency. Most patients with teratomas have symptoms caused by the tumor; only about a third are asymptomatic.^{6,85} Usual symptoms are pain, cough, and dyspnea. Teratomas can rupture into the pleural space or into the pericardium. If the tumor erodes into a bronchus, the patient may have hemoptysis or even expectorate differentiated tissue such as hair (trichoptysis) or sebaceous material.⁸⁵

On chest radiographs, teratomas appear smooth, rounded, and circumscribed if they are cystic. Solid lesions can appear lobulated and asymmetric. On CT scans (see Video 83-4 and eFig. 83-10), soft tissue, fat, and calcifica-

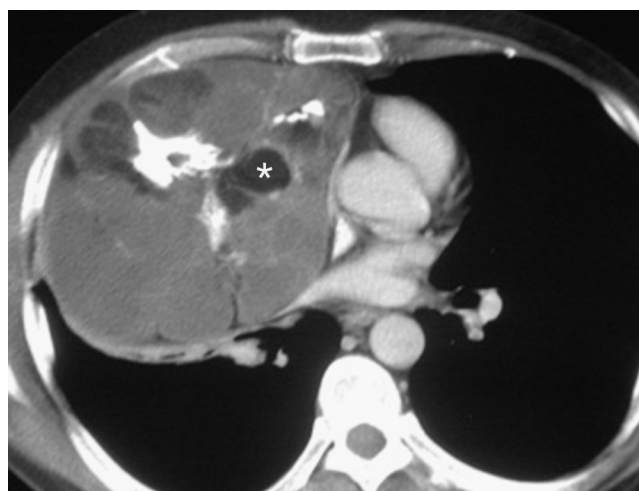


Figure 83-10 Teratoma. Axial CT image through the base of the heart shows a large right-sided anterior mediastinal mass with heterogeneous attenuation. Elements of calcium, soft tissue, and fat (*) are present. The presence of fat within an anterior mediastinal mass is most consistent with teratoma.

tion (occasionally, fully formed teeth and bone) can be identified, rendering this one of few mediastinal tumors that can be diagnosed confidently before operation¹⁶ (Fig. 83-10). All teratomas should be resected due to malignant potential and effects of impingement on adjacent vital structures. In malignant teratoma, adjuvant combination chemotherapy may result in improved survival.⁸⁶

Seminomas and nonseminomatous germ cell tumors are malignant and nearly always cause symptoms. These lesions appear as a large anterior mediastinal mass on chest imaging (Video 83-9 and eFig. 83-29). Seminomas are seen almost exclusively in men, usually in the third decade of life.⁷ Most patients seek medical attention because of chest pain, dyspnea, cough, hoarseness, or dysphagia. Seminomas are aggressive malignant tumors that extend locally and metastasize distantly, usually to skeletal structures. The tumor can obstruct the SVC. They may secrete human chorionic gonadotropin, but not alpha-fetoprotein. Factors associated with a poor prognosis include age older than 35 years, SVC obstruction, supraclavicular, cervical, or hilar

adenopathy, and fever.^{87,88} Seminomas are extremely radiosensitive and may respond dramatically to chemotherapy, even in cases with dissemination.^{84,89} With aggressive cisplatin-based regimens, long-term survival for all mediastinal seminomas is approximately 80%.^{84,90}

Nonseminomatous mediastinal germ cell tumors include embryonal cell carcinoma and choriocarcinoma.^{6,7,87} Like seminoma, these tumors develop mainly in men in the third and fourth decades and are usually symptomatic. These malignancies carry a poorer prognosis relative to cancers arising from the gonads.⁸⁴ Embryonal cell carcinoma is also called endodermal sinus or yolk sac tumor (Video 83-10 and eFig. 83-30). These highly aggressive tumors often secrete human chorionic gonadotropin, alpha-fetoprotein, or carcinoembryonic antigen. Human chorionic gonadotropin may also produce clinical manifestations, such as gynecomastia, in 50% of patients.⁷ Associations have been noted with Klinefelter syndrome⁹¹ and with hematologic malignancy.⁹² Most patients present with disseminated disease, and the prognosis has been less favorable than in seminoma.⁷ Cisplatin-based treatment regimens have markedly improved the outcome, with more than 50% of patients achieving long-term survival.^{84,92} Long-term survival may also be possible in those who undergo a complete surgical resection following chemotherapy.⁹³ Even disseminated and refractory malignant germ cell tumors may respond to aggressive chemotherapy⁹⁴ and salvage regimens involving bone marrow transplantation.^{95,96}

Lymphoma

Lymphoma is an important cause of mediastinal mass, and is distinguished from other mediastinal lesions in that management is primarily medical, not surgical. In most series, lymphoma represents between 10% and 20% of mediastinal masses in both adults and children.^{6-8,63} Lymphomas are the most common anterior and middle mediastinal masses in children; a majority of pediatric patients with *Hodgkin lymphoma* (HL) and half of those with *non-Hodgkin lymphoma* (NHL) present with a mediastinal mass.⁹⁷ HL has a bimodal distribution, arising in adolescents and young adults as well as in those older than 50, whereas NHL arises most commonly in older adults.

Primary mediastinal B-cell lymphoma (PMBL) is a distinct subset of NHL that has a similar clinical presentation as classic HL of the nodular sclerosing subtype.⁹⁸ Both present in the third or fourth decade of life and tend to affect females. These tumors present as a bulky anterior mediastinal mass involving the thymus (see Fig. 83-6). SVC syndrome is a common presentation of PMBL, less so for HL (see Video 83-2 and eFig. 83-2), which can involve the hilar nodes and lung parenchyma.⁹⁹ However, there are distinct and nonoverlapping histologic features. HL is characterized by the Hodgkin/Reed Sternberg cell in a nodular growth pattern with a specific immunophenotype of CD30+, CD45-, and CD15+ in 85% of cases. PMBL is histologically characterized by an infiltrate of large cells in a diffuse pattern with an immunophenotype of a mature B lymphocyte expressing CD20. A B-cell lymphoma that exhibits histologic features of both PMBL and HL has been named "gray zone lymphoma."¹⁰⁰

Distinguishing HL from PMBL is important for guiding therapy, thus tissue biopsy is indicated. The current stan-

dard of treatment for early stage, bulky mediastinal disease is combined modality therapy, consisting of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and radiation. Optimal therapy for nonbulky mediastinal HL is controversial; recent clinical trials suggest no difference in overall survival but an increase in risk for disease progression with chemotherapy alone.^{101,102} The benefits of radiation therapy must be balanced with the risk for serious late complications, including pulmonary fibrosis, cardiovascular disease, and secondary malignancies such as breast and lung cancer.¹⁰⁰

PMBL is treated with immunochemotherapy, which includes rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-based regimens, followed by radiation. Whereas these standard dose regimens have a cure rate of up to 75%, more recent evidence has shown that dose intensity may improve outcomes in PMBL. DA-EPOCH (dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone, rituximab) has been shown to confer an overall survival of 97% without the need for radiation treatment in the majority of patients.¹⁰³ The prognosis of HL and NHL has improved strikingly in the past 2 decades as staging of the disease has been refined and as more effective and less toxic combinations of radiotherapy and chemotherapy have evolved. With new chemotherapy regimens, radiotherapy may not be a necessary part of the treatment plan for PMBL.^{103a} PET scan, which is often used to restage aggressive lymphomas, appears to have a high negative predictive value and may be helpful for clinicians in deciding when to omit radiotherapy after primary chemotherapy; this is being investigated in an ongoing clinical trial.^{103b,103c} Effective salvage regimens including bone marrow transplantation have been developed to treat relapsed disease. HL is curable in approximately 75% of patients, although late toxicities of treatment contribute significantly to mortality.

Thyroid Lesions

In surgical series, ectopic thyroid glands account for fewer than 10% of mediastinal masses but, in clinical practice, these are probably more common. Thyroid tissue within the mediastinum is of two distinct origins. Most commonly, a cervical goiter extends subternally into the anterior mediastinum.¹⁰⁴ Primary intrathoracic goiter, presumably originating from an embryonic nest of heterotopic thyroid tissue, is rare. Most such goiters are in the anterior mediastinum, but they may arise in the middle or posterior mediastinum as well.^{6,7} Intrathoracic goiter presents predominantly in middle aged or older women. Although it is usually asymptomatic, goiter may cause hoarseness, cough, or swelling of the face and arms. Intrathoracic thyroid tissue is easily recognized by radioactive iodine scanning,¹⁰⁵ as long as the scan is completed before intravenous iodinated contrast injection, which may block iodine uptake for weeks. It may be suspected on the basis of high radiodensity on CT scans, particularly after iodinated contrast injection.^{106,107} Treatment is surgical resection.

Parathyroid Lesions

Mediastinal parathyroid tissue accounts for up to 10% of cases of hyperparathyroidism, and the mediastinum is the most common site for ectopic parathyroid adenomas in

surgically resistant hyperparathyroidism.¹⁰⁸ Half of ectopic parathyroid adenomas lie in the anterior mediastinum, usually near the thymus. Parathyroid cysts may enlarge sufficiently to appear as a mass on the chest radiograph and to produce symptoms, but ectopic tissue may be difficult to locate.¹⁰⁹ Evaluation of the lesion is typically conducted using CT angiography, ultrasound, MRI, and the sensitive technetium-99m sestamibi scanning.¹¹⁰ Selective arteriography and venous sampling for parathormone levels have largely been supplanted by sestamibi radionuclide scanning.¹¹⁰ Parathyroid adenomas are cured by complete resection, and resection via VATS is increasingly advocated.⁵⁵ Parathyroid carcinoma may be functional, resulting in varying degrees of hyperparathyroidism, but is also locally invasive and may metastasize.¹¹¹ Cure is possible with aggressive surgical management¹¹² that may be guided by imaging and functional localization studies.¹¹³

Mesenchymal Tumors

Included in this group of unusual mediastinal masses are lipomas, fibromas, mesotheliomas, and lymphangiomas (see Table 83-4).⁶ They arise from connective tissue, fat, smooth muscle, striated muscle, blood vessels, or lymphatic channels and can be found in any region of the mediastinum. Histologically and clinically, they are not substantially different from their counterparts elsewhere in the body. Unless the lesion is very large, the presence of symptoms usually indicates that the lesion is malignant.^{6,17}

Lipoma is the most common mesenchymal tumor of the mediastinum and is most often located in the anterior mediastinum. It may be encapsulated or unencapsulated, appearing as a smooth and rounded lesion with well-defined margins. The characteristic low density of lipomas on CT images (Fig. 83-11) permits a confident diagnosis unless there is associated heterogeneity, invasion of surrounding tissues, or poor demarcation of the mass's perimeter, in which case malignancy (liposarcoma or lipoblastoma) or teratoma must be excluded.¹⁷ Considerably more common than lipoma is mediastinal lipomatosis, or generalized overabundance of histologically normal unencapsulated fat (see Fig. 83-2).¹¹⁴ Mediastinal lipomatosis appears on the conventional radiograph as a smooth widening or bulging of normal mediastinal contours, and its low homogeneous CT density confirms the diagnosis.¹⁷ Mediastinal lipomatosis does not compress or displace other mediastinal structures.

Sarcomas involving the mediastinum are rare but, if present, are likely to be due to nerve sheath sarcoma, spindle cell sarcoma, leiomyosarcoma, or liposarcoma.¹¹⁵ Prior radiation therapy appears to be a predisposing factor in some cases.¹¹⁶ Primary mediastinal sarcoma is a rare entity that affects adults; it can present with distant metastases¹¹⁷ and tends to have an aggressive course.

Primary Carcinoma

Numerous rare neoplasms of the mediastinum have been described in larger case series of mediastinal tumors as well as in isolated case reports.^{7,118} Case series up through the 1980s report primary carcinoma of the mediastinum as comprising 1% or fewer of the cases of malignant neoplasms found in the anterior mediastinum.^{59,143} Since these case series, very little regarding primary carcinoma of the

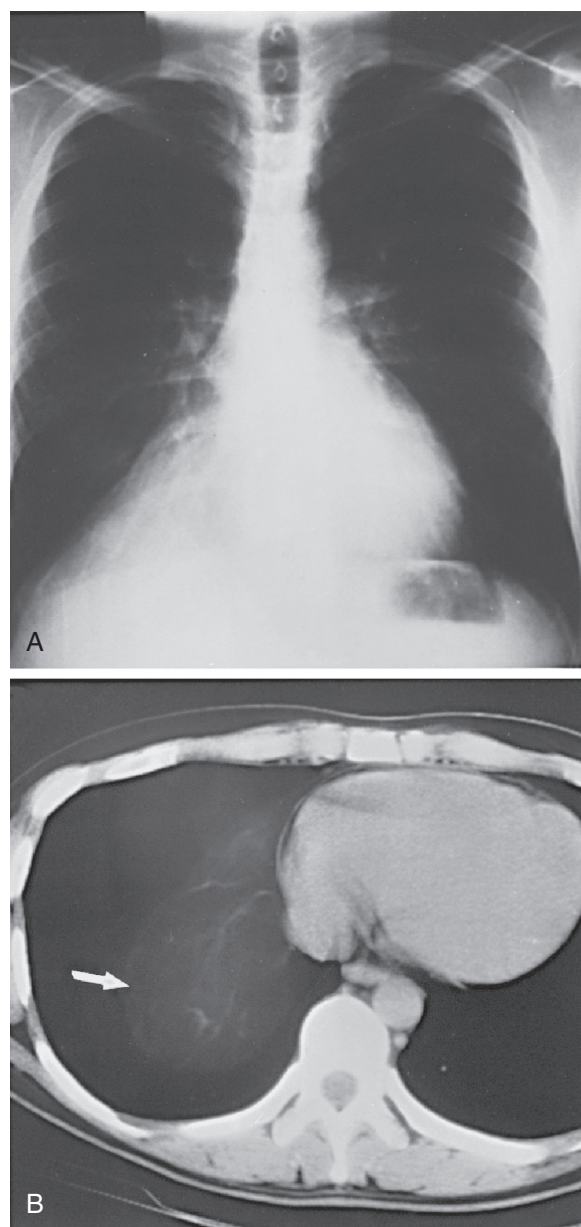


Figure 83-11 Lipoma. **A**, Chest radiograph of a 31-year-old man showing an abnormality at the right cardiophrenic angle noted as an incidental finding. **B**, Axial chest CT demonstrates a well-circumscribed homogeneous fat-density mass characteristic of a mediastinal lipoma extending into the right hemithorax (arrow).

mediastinum as a specific disease has been reported. It is possible that these tumors represented a heterogeneous group of metastatic carcinoma of unknown origin, or otherwise unclassifiable disease.

In the 1990s, cases of young patients with a highly aggressive carcinoma presenting in the mediastinum and other midline structures were reported; these tumors were found to have t(15;19) translocations, resulting in a *BRD4-NUT* fusion oncogene,^{119,120} which was first described in 2003. These NUT midline carcinomas are uniformly fatal, presenting as large masses with local mass effects and distant metastases. The advent of molecular targets in cancer treatment make this discovery a potential

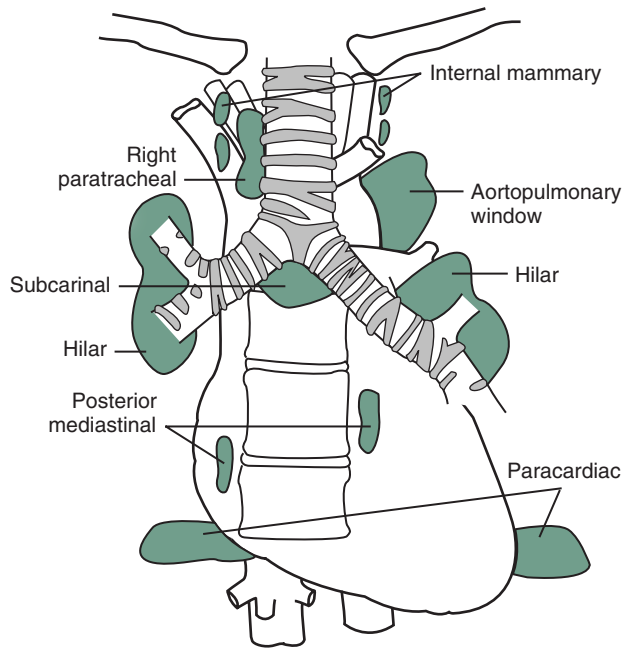


Figure 83-12 Simplified schematic diagram depicting mediastinal lymph node groups. (Redrawn from McLoud TC, Meyer JE: Mediastinal metastases. *Radiol Clin North Am* 20:453–468, 1982.)

therapeutic target in undifferentiated or poorly differentiated epithelioid malignancies.

LESIONS OF THE MIDDLE MEDIASTINUM

Enlargement of Lymph Nodes

Numerous classifications exist for the mediastinal lymph nodes, including the most recently accepted classification by the International Association for the Study of Lung Cancer.¹²¹ Figure 83-12 presents a simplified grouping of the main mediastinal nodes that corresponds to findings on chest radiography and CT scans.¹²² Most authors consider 1-cm diameter at the short axis to be the upper limit of normal.¹⁸

Evaluating the mediastinum in the context of staging lung cancer is discussed elsewhere in the textbook (see Chapter 53). Mediastinal lymph node enlargement is most often due to lymphoma,¹²³ metastatic cancer,¹²² granulomatous inflammation, such as that caused by sarcoidosis, or infection. Infection should be considered when the adenopathy is associated with a pulmonary opacity. Tuberculosis is a notable cause of mediastinal adenopathy that can mimic sarcoidosis or malignancy and should be suspected in a host with known tuberculosis risk factors, such as recent known exposure or residence in an endemic area.¹²⁴ Fungal infections that cause granulomas, particularly histoplasmosis, may present with mediastinal and hilar adenopathy in the absence of a pulmonary opacity.¹²⁵

Numerous less common causes of mediastinal adenopathy are described, including Castleman disease or angiofollicular lymphoid hyperplasia. Mediastinal adenopathy is common in HIV-infected patients and is usually caused by infection, although adenopathy may also be caused by lymphoma, Kaposi sarcoma, and other noninfectious processes.¹²⁶

Developmental Cysts

Developmental cysts of various sorts comprise 10% to 20% of all mediastinal masses.^{6,127} Most can be identified as bronchogenic, enteric, or pericardial.⁶ Bronchogenic and enteric cysts are often referred to as *foregut duplication cysts* because of their origin from aberrant portions of the ventral and dorsal foregut, respectively.

Bronchogenic cysts are found near large airways, often just posterior to the carina (Fig. 83-13), although they may be attached to the esophagus or even lie inside the pericardial space.⁶ The cyst wall often contains cartilage and respiratory epithelium. Most are discovered incidentally and cause no symptoms; however, they may communicate with the tracheobronchial tree and become infected¹²⁸; enlarge sufficiently to cause airway obstruction,¹²⁹ pulmonary artery compression,¹³⁰ or hemodynamic collapse¹³¹; or rupture.¹³² Enteric or enterogenous cysts are similar in location and appearance to bronchogenic cysts, but have digestive tract epithelium. They are relatively uncommon in adults, but are the most common cysts found in infants and children, in whom they may be associated with spinal extension and malformations of the vertebral column (called “neurenteric” cysts). Enteric cysts can occasionally be multiple and associated with duplications of other portions of the gastrointestinal tract.

Pericardial cysts account for about one third of cystic masses in adults, but are much less common in children (see Table 83-5). They lie against the pericardium, diaphragm, or anterior chest wall in the right cardiophrenic angle. Rarely, pericardial cysts may communicate with the pericardial space. Although typically harmless, pericardial cysts may enlarge enough to cause right ventricular outflow obstruction,¹³³ or they may rupture and hemorrhage to cause pericardial tamponade¹³⁴ or sudden cardiac death.¹³⁵

Developmental cysts can usually be identified by CT (see Fig. 83-13A) or ultrasonography, and the diagnosis may be confirmed by aspiration cytology. MRI is valuable for confirming the cystic nature of these lesions (see Fig. 83-13B-D). Pericardial cysts can be followed with serial imaging and need not be resected unless they cause symptoms. Bronchogenic cysts can also be followed conservatively if asymptomatic¹³⁶; however, most authorities favor resection for purposes of diagnosis and to reduce the potential for complications.^{128,132} Alternatives to thoracotomy include therapeutic aspiration^{137,138} and thoroscopic or mediastinoscopic excision.^{56,139,140}

LESIONS OF THE POSTERIOR MEDIASTINUM

Neurogenic Tumors

The vast majority of tumors in the posterior mediastinum represent neoplasms arising from neural tissues,^{6,7} historically accounting for about 20% of adult cases and twice that proportion in children (see Table 83-5). Neurogenic tumors appear radiographically as a unilateral paravertebral mass.^{6,141,142} Clinical manifestations include chest pain from nerve or bone erosion, dyspnea secondary to tracheal compression, and neurologic deficits resulting from spinal cord compression by intraspinal tumor extension. In addition, many neurogenic tumors are hormonally active. MRI

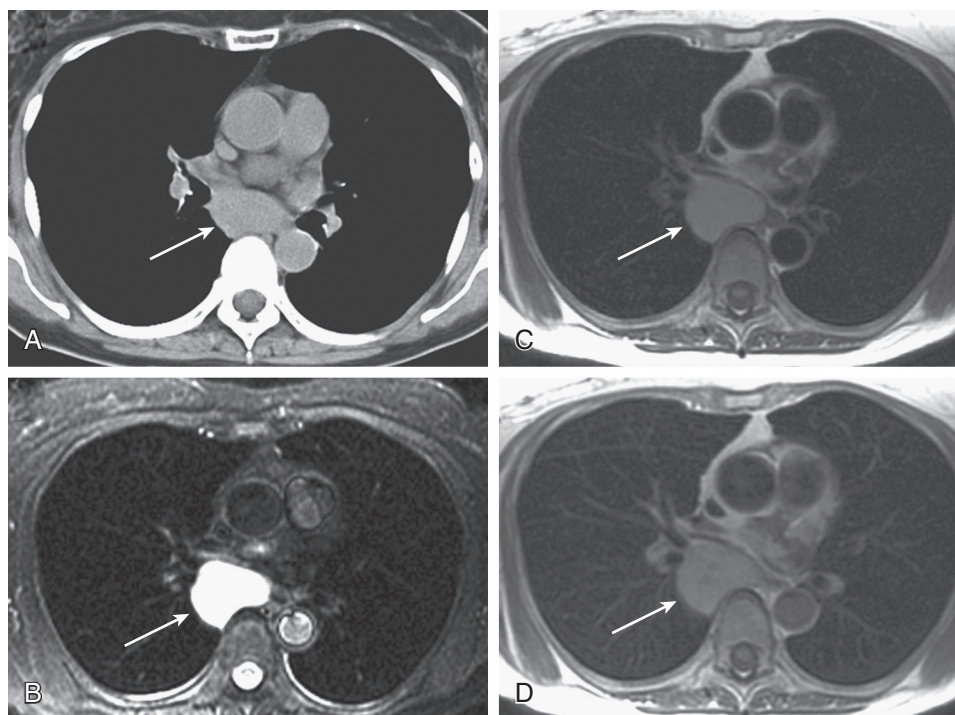


Figure 83-13 Bronchogenic cyst. Axial unenhanced chest CT (**A**) shows a mildly hyperattenuating structure (*arrow*) in the subcarinal space. Axial triple inversion-recovery (TIR) MRI (**B**) and axial unenhanced double inversion-recovery (DIR) image (**C**) show the same lesion (*arrows*). Note the very high signal on the fluid-sensitive TIR image (**B**), consistent with fluid, and the mildly increased signal on the unenhanced DIR image (**C**), consistent with proteinaceous or hemorrhagic fluid; the latter mechanism also accounts for the hyperattenuating appearance on CT. Enhanced DIR MRI (**D**) shows no enhancement of the lesion (*arrow*) following intravenous gadolinium administration, typical of a foregut duplication cyst. (Courtesy Michael Gotway, MD.)

Table 83-6 Neurogenic Tumors of the Mediastinum

NEOPLASMS ARISING FROM PERIPHERAL NERVES

Neurofibroma
Neurilemoma (schwannoma)
Neurosarcoma

NEOPLASMS ARISING FROM SYMPATHETIC GANGLIA

Ganglioneuroma
Ganglioneuroblastoma
Neuroblastoma

NEOPLASMS ARISING FROM PARAGANGLIONIC TISSUE

Pheochromocytoma
Paraganglioma (chemodectoma)

is usually indicated when there is suspicion for a neurogenic lesion. Although the majority of neurogenic tumors are benign, surgical resection is indicated to alleviate local symptoms from mass effects of the tumor.

Neurogenic tumors are classified by site of origin: peripheral nerves, sympathetic ganglia, or paraganglionic tissue (Table 83-6). Tumors arising from peripheral nerves include neurofibromas, neurilemmomas, and neurosarcomas. Neurofibromas contain both nerve sheath cells and nerve elements and are the most common tumor of this group. They are incompletely encapsulated and may grow quite large, producing symptoms by compression of nerves or other structures. Mediastinal neurofibroma may be one manifestation of von Recklinghausen disease (neurofibromatosis). As with these tumors found elsewhere in the body, neurofi-

bromas may eventually transform into the malignant neurosarcoma in 10% to 15% of patients.⁷

Neurilemoma, or schwannoma (Videos 83-11A and B, and eFig. 83-43), is another common neurogenic tumor that arises from the neural sheath. Most often seen in the third to fifth decade of life, neurilemoma usually causes no symptoms and appears as a well-circumscribed, homogeneous density on chest radiography (Fig. 83-14A).^{6,7} It is always completely encapsulated and does not invade surrounding tissues, although neurilemmomas may extend into intervertebral foramina (Fig. 83-14B and C). Treatment of both neurilemoma and solitary neurofibroma is resection.

Malignant tumors of nerve sheath origin are also known as malignant neurofibroma, malignant schwannoma, or neurogenic fibrosarcoma. These tumors behave aggressively, with both local invasion and distant metastasis. Half arise in patients with neurofibromatosis.¹⁵ Treatment requires wide excision and usually adjuvant radiation.¹⁵

Tumors arising from nerve cells in sympathetic ganglia generally affect children and display a spectrum of neoplastic behavior ranging from ganglioneuroma, a benign tumor, to the malignant tumors ganglioneuroblastoma and neuroblastoma. Ganglioneuromas cause symptoms merely by mass effect, and are usually cured by surgical excision. Ganglioneuroblastomas have intermediate behavior and can invade locally but are less likely to metastasize.⁷ Neuroblastoma rapidly displaces and invades adjacent structures and may be widely metastatic at the time of presentation.^{143,144} These tumors often elaborate endocrine peptides and

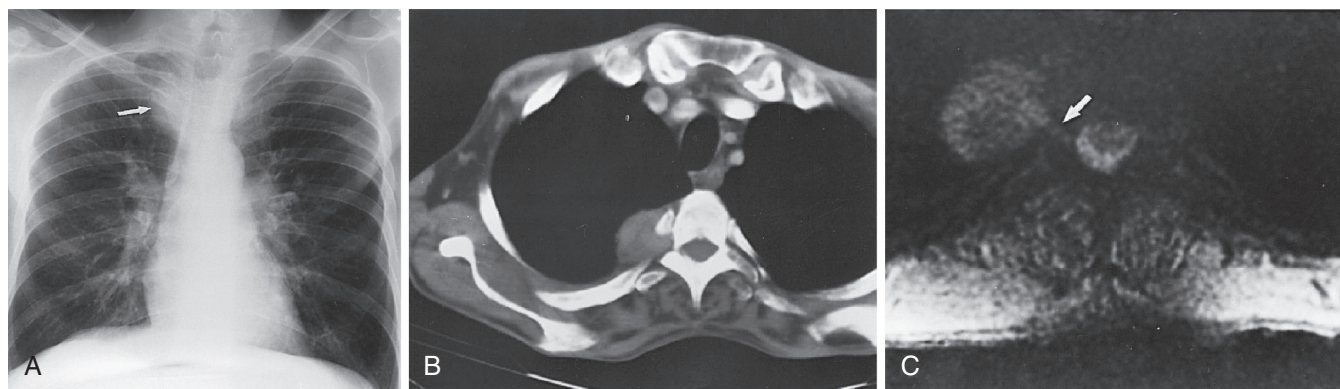


Figure 83-14 Series of imaging studies of a 64-year-old asymptomatic man with a surgically proved neurilemoma, or schwannoma. **A**, Frontal chest radiograph showing an incidental finding of a discrete mass behind the right clavicular head (arrow). **B**, Axial chest CT showing homogeneous, well-circumscribed appearance and posterior location adjacent to the vertebral column. **C**, Magnetic resonance image showing extension of the tumor into the intervertebral foramen (arrow).

catecholamines, and are associated with diarrhea, fever, anorexia, and weight loss.⁶ The propensity to produce catecholamines is used to advantage by promoting tumor uptake of the catecholamine precursor ¹²³I- or ¹³¹I-*meta*-iodobenzylguanidine (MIBG) for purposes of diagnosis, identification of distant tumor metastases, and treatment.^{145,146} Treatment of neuroblastoma involves using escalating multimodality therapy strategies that are based on the risk for disease progression.¹⁴⁷

Neoplasms arising from paraganglionic or chemoreceptor tissue include pheochromocytomas, which are found rarely in the mediastinum and are indistinguishable clinically and histologically from their counterparts in the abdomen, and paragangliomas (chemodectomas). Paragangliomas may secrete catecholamines just as do pheochromocytomas and thus may also be detected and perhaps treated with MIBG.¹⁴⁸ They appear benign under the microscope and seldom metastasize, but spread locally in an aggressive fashion and thus have high morbidity and mortality rates.⁶

MISCELLANEOUS MEDIASTINAL MASSES

Benign Lesions

Pancreatic pseudocysts may extend into the mediastinum, usually through the aortic or esophageal hiatus.^{7,149,150} They have been reported in all three mediastinal compartments. Hydatid cysts also arise rarely in the mediastinum.⁷ The posterior mediastinum is occasionally the site of a thoracic duct cyst.^{6,63} Also, extramedullary hematopoiesis (Video 83-12 and eFigs. 83-44 and 83-45) in patients with chronic hemolytic anemia may appear as a mediastinal mass, often in a posterior location. Meningoceles, outgrowths of the spinal meninges that protrude along the course of a spinal nerve, can produce posterior mediastinal masses.

Vascular Masses and Enlargements

Although not technically masses, a variety of vascular lesions must be considered in the differential diagnosis of a mediastinal mass seen on the chest radiograph.^{7,151} These include poststenotic aortic dilation, aneurysms (Video 83-13 and eFig. 83-46) or tortuosity of the aorta

and great vessels, aortic coarctation, innominate vein and SVC aneurysm, persistent left vena cava, azygos (Video 83-14 and eFig. 83-48) and hemiazygos vein enlargement, anomalous pulmonary venous return, pulmonary venous varix, and varices associated with portal hypertension (eFig. 83-49).¹⁵² Idiopathic dilation of the pulmonary trunk and pulmonary arterial hypertension of any cause may appear as a mediastinal mass, and traumatic aortic transection or more subtle vascular injuries may result in mediastinal hematoma.

Angiography has been the traditional means of diagnosing mediastinal masses of vascular origin but, in most cases today, CT imaging with intravenous contrast provides a more convenient diagnosis.^{153,154} MRI may permit definitive diagnosis without radiation or contrast exposure.

Diaphragmatic Hernia

Omental fat (Video 83-15 and eFig. 83-50; see also Video 83-6 and eFig. 83-12) or other abdominal contents may protrude through the diaphragm via several potential routes, producing mediastinal mass lesions in any compartment.¹⁷ A hernia through the foramen of Morgagni (eFig. 83-50) produces a cardiophrenic angle mass, usually on the right side in the anterior mediastinum. Bochdalek hernia (eFig. 83-51), in the posterior mediastinum, generally appears on the left side, presumably because the liver prevents herniation on the right. Herniation of fat around the esophagus is believed to precede hiatal hernia formation; either may appear as a mediastinal mass on chest radiography. Fine linear opacities are often demonstrable in diaphragmatic fat herniations on CT imaging. These are thought to represent omental vessels within the hernia, and they may help differentiate a hernia from a lipoma.¹⁷

GENERAL APPROACH TO A MEDIASTINAL MASS

INITIAL EVALUATION

With the advent of advanced imaging techniques such as CT, MRI, and nuclear imaging, the evaluation of a mediastinal mass is best made in a multidisciplinary setting

involving the pulmonologist or internist, a radiologist, and a thoracic surgeon. The differential diagnosis of a mediastinal mass depends significantly on patient demographics, the presence of clinical symptoms, as well as the anatomic location, size and morphology. For a mediastinal mass that is found incidentally, the primary concern for a clinician is to determine whether it is benign or malignant, and, if benign, whether it has the potential to cause local symptoms. At a minimum, a chest CT scan with contrast should be obtained to evaluate any mediastinal mass detected by conventional radiography. This narrows the differential diagnosis and suggests further imaging or a diagnostic and/or therapeutic procedure. A stable appearance, in comparison to older films, can obviate the need for further investigation in selected patients. A few benign lesions in the mediastinum can be diagnosed with confidence based on clinical information and CT scan appearance; such benign lesions include vascular lesions, extramedullary hematopoiesis, pericardial cysts and developmental cysts, and mediastinal lipomatosis. Suspected mediastinal thyroid tissue can be confirmed by radioactive iodine scans.

SURGICAL MANAGEMENT

In most cases, the optimal diagnostic and therapeutic maneuver is surgical resection of the mass.¹⁵⁵ The decision to perform a biopsy versus resection is thus based on the presumptive diagnosis after imaging. A suggested approach for evaluation is shown in Figure 83-15.

In the anterior mediastinum, well-encapsulated lesions are resected, whereas biopsy will be performed in those situ-

ations where there is a high degree of suspicion for lymphoma. Biopsy is also preferred for locally invasive or frankly unresectable anterior mediastinal lesions. Biopsy options for anterior lesions include CT-guided needle biopsy and anterior mediastinotomy. Cervical mediastinoscopy is less useful for anterior mediastinal masses because the anterior mediastinal mass is not near the pretracheal plane. Interventions by VATS are generally reserved for those lesions that are amenable to resection. Definitive resection of anterior mediastinal masses can be performed by VATS, median sternotomy, or a transcervical approach (e.g., Cooper thymectomy). A robotic VATS approach has gained in popularity in recent years for resection of anterior mediastinal masses.

In the middle mediastinum, the majority of masses in adults are malignant, the most common being lymphoma or metastatic disease. Hence for lesions in the middle mediastinum, biopsy is the typical initial approach. Biopsy can be performed by either CT-guided needle techniques, EBUS or EUS-TBNA, or by mediastinoscopy or VATS. Given the proven sensitivity and negative predictive value of EBUS-TBNA, this is the preferred sampling option. When benign-appearing cystic lesions are found by diagnostic imaging, the lesion is removed by either VATS or open thoracotomy.

In the posterior mediastinum, most lesions are resected either with a VATS or thoracotomy approach. A thoracotomy is preferred if there is any suggestion of malignancy (to ensure free resection margins), size greater than 5 cm, or presence of inflammation or infection that can obscure dissection planes. Surgical experience plays a large part in determining the technique utilized for intervention.

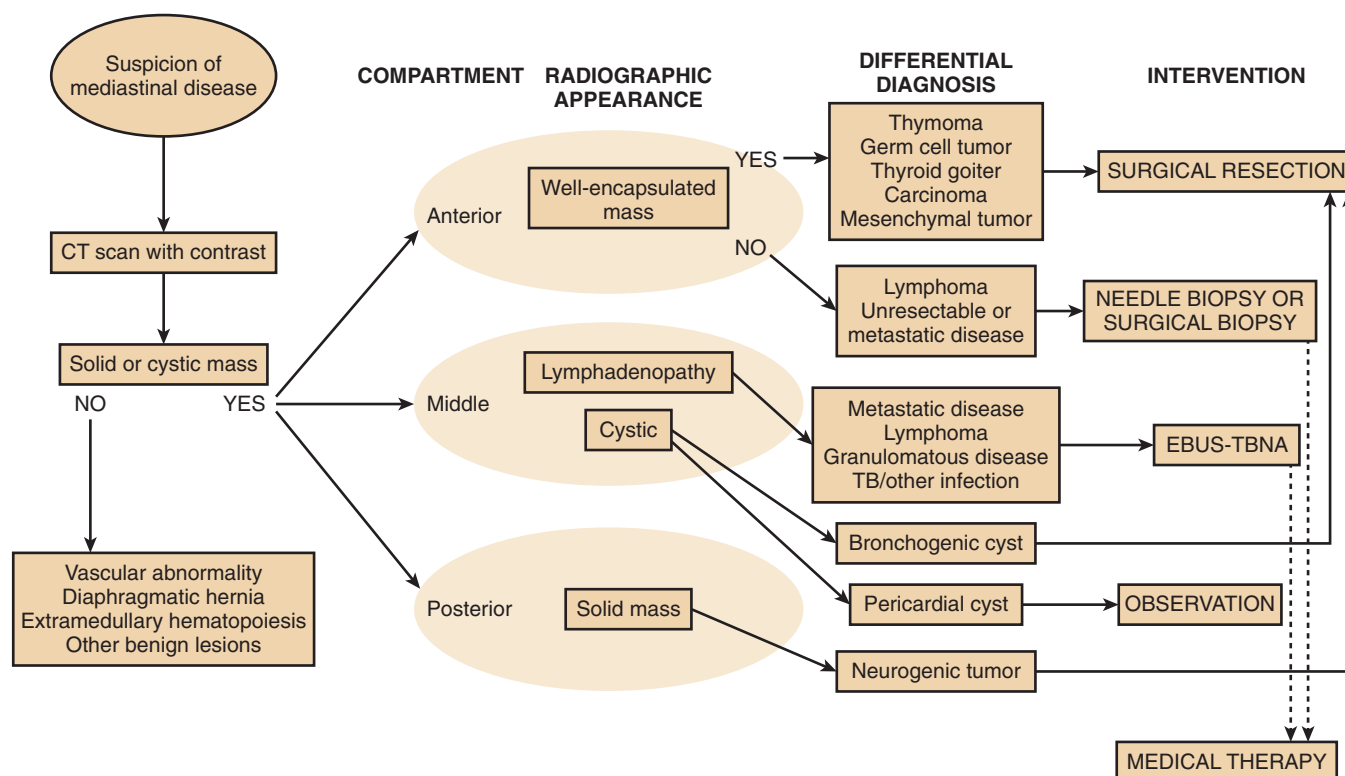


Figure 83-15 A suggested algorithm for the diagnostic approach to mediastinal masses.

ACKNOWLEDGMENTS

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Key Points

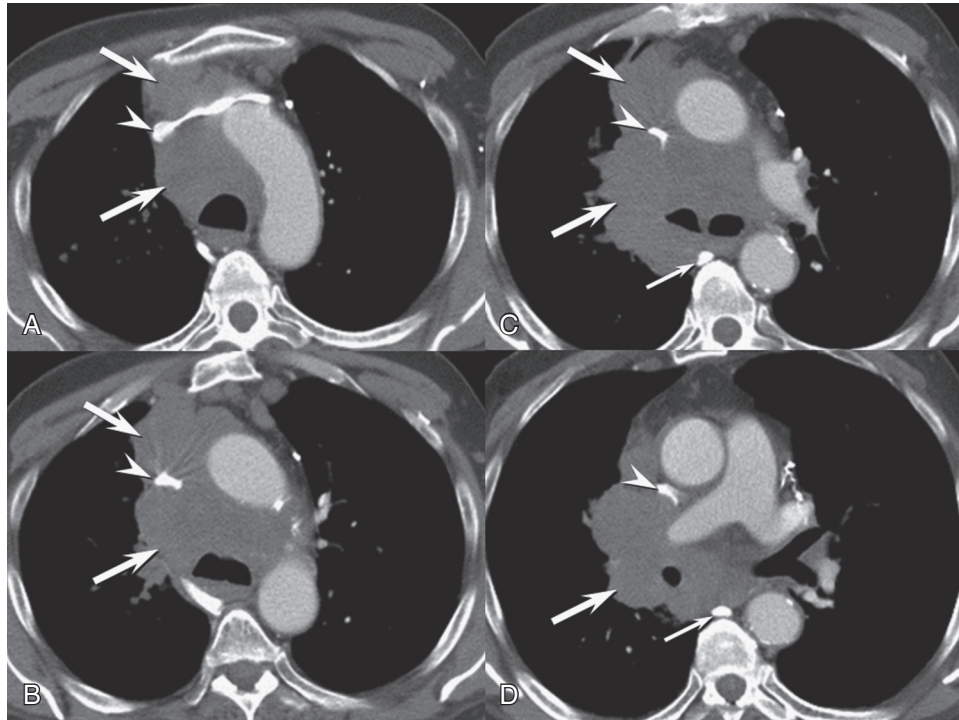
- The mediastinum, which contains thoracic viscera in the center of the chest, can be divided into three compartments based on anatomic boundaries that can be seen on a lateral chest radiograph: anterior, middle, and posterior.
- While the majority of mediastinal masses are benign, the likelihood of a mediastinal mass being malignant depends on the compartment of the mediastinum, patient factors, and the presence of symptoms. Symptomatic masses are more likely to be malignant.
- The most common mediastinal masses in the anterior compartment include thymomas, germ cell tumors, and lymphoma. The middle compartment includes lymphadenopathy and benign developmental cysts. Isolated mediastinal adenopathy may represent sarcoidosis, tuberculosis, lymphoma, lung cancer, or metastatic disease from an extrathoracic malignancy. The posterior compartment includes mainly neurogenic tumors.
- Most mediastinal tumors and cysts should be surgically removed due to potential for malignancy and local compressive and invasive effects on adjacent vital structures.

Complete reference list available at *ExpertConsult*.

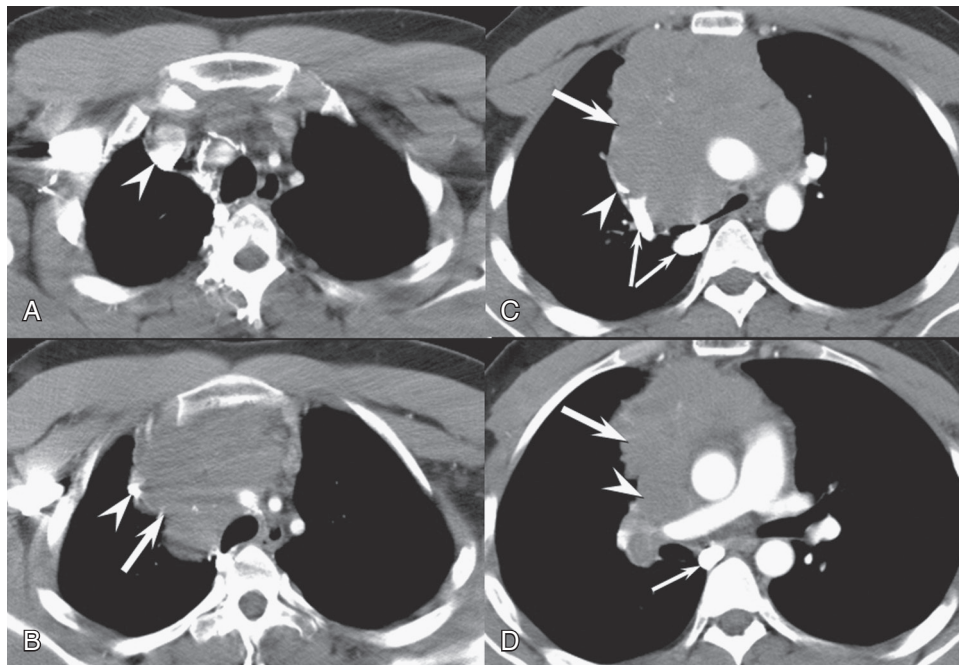
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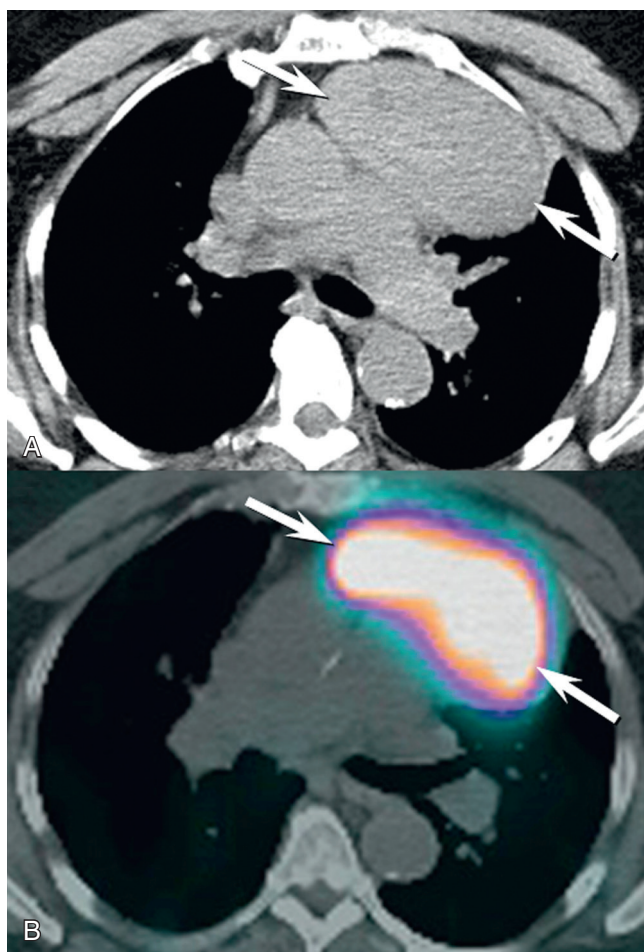
eFIGURE IMAGE GALLERY



eFigure 83-1 Axial contrast-enhanced chest CT in a patient with bronchogenic carcinoma and superior vena cava syndrome shows a confluent mediastinal mass (arrows) occupying the anterior and middle mediastinum, compressing the superior vena cava (arrowheads), resulting in collateral circulation through the azygos vein (small arrow). See [Video 83-1](#) for the full study. (Courtesy Michael Gotway, MD.)



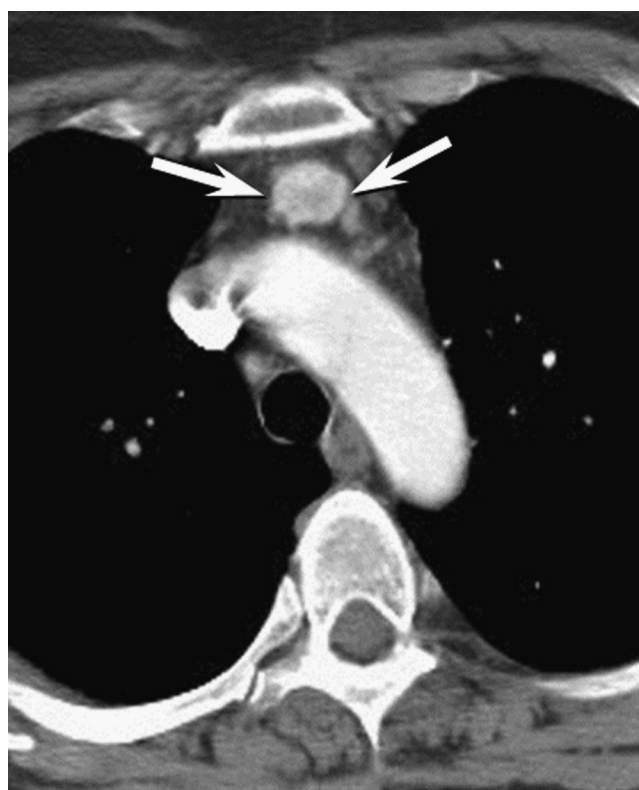
eFigure 83-2 Axial contrast-enhanced chest CT in a patient with lymphoma and superior vena cava (SVC) syndrome shows a confluent mediastinal mass (arrows, B–C) occupying the anterior and middle mediastinum, compressing the SVC (arrowheads, C–D), resulting in collateral circulation through the azygos vein (small arrows). The caudal SVC is occluded (arrowhead in D). The arrowheads in A and B show the enhanced right brachiocephalic vein, distended in A, and compressed and laterally displaced adjacent to the mediastinal mass in B. See [Video 83-2](#) for the full study. (Courtesy Michael Gotway, MD.)



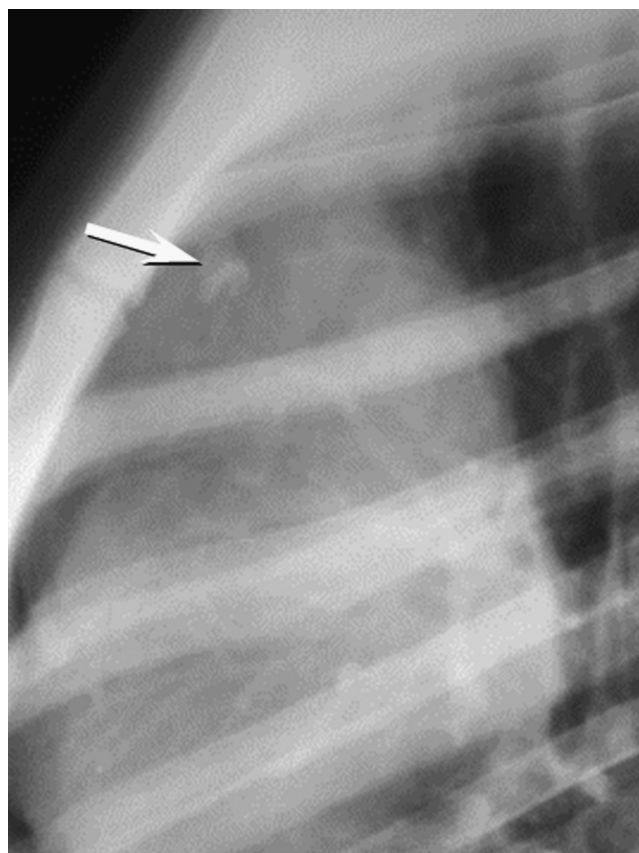
eFigure 83-3 Axial unenhanced chest CT (**A**) and fused ^{18}F FDG-PET image (**B**) in a patient with Cushing syndrome shows an anterior mediastinal mass (*arrows*) in a patient with thymic neuroendocrine malignancy (e.g., thymic carcinoma). (Courtesy Michael Gotway, MD.)



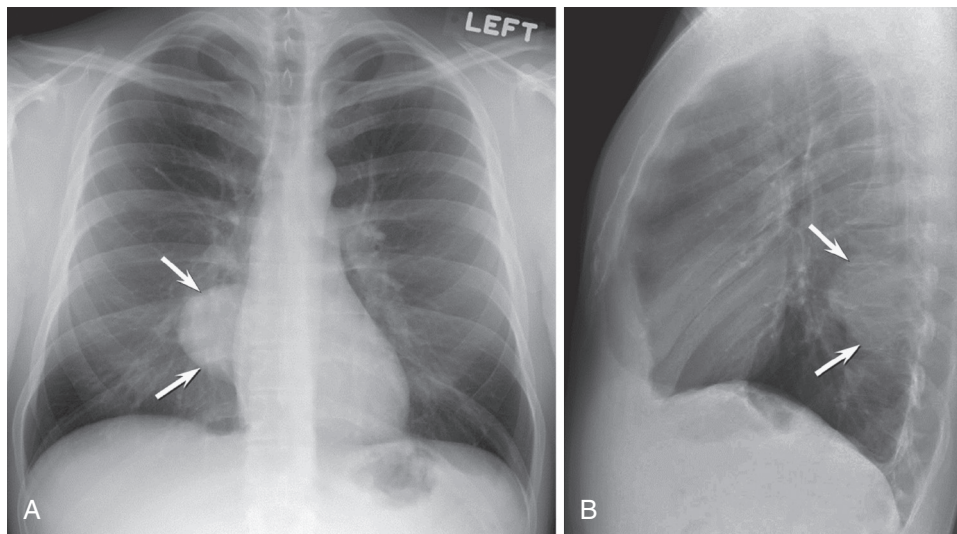
eFigure 83-4 Axial enhanced chest CT in a patient with myasthenia gravis shows an anterior mediastinal mass (*arrow*) representing thymoma. See [Video 83-3](#) for the full study. (Courtesy Michael Gotway, MD.)



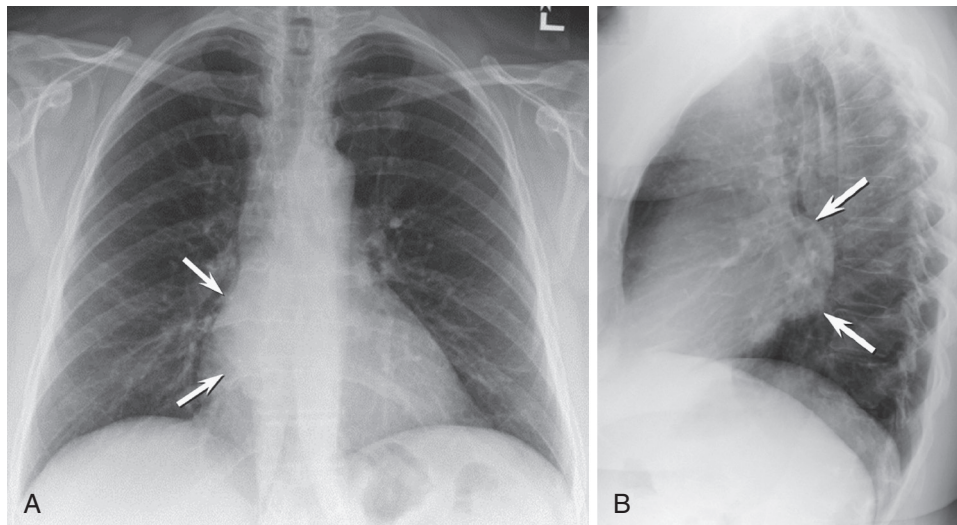
eFigure 83-5 Axial enhanced chest CT in a patient with recurrent hyperparathyroidism following previous parathyroidectomy shows an intensely enhancing anterior mediastinal mass (*arrows*) representing an ectopic parathyroid adenoma. (Courtesy Michael Gotway, MD.)



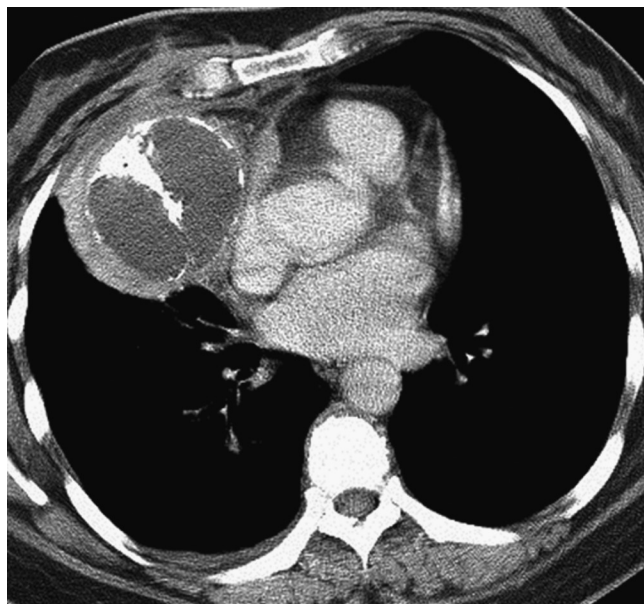
eFigure 83-6 Detail lateral chest radiograph in a patient with teratoma shows a tooth (*arrow*) in the anterior mediastinum. (Courtesy Michael Gotway, MD.)



eFigure 83-7 Posterior mediastinal mass due to a neurogenic neoplasm. Frontal (A) and lateral (B) chest radiographs show a circumscribed right-sided mass (arrows). On the frontal projection (A), note the interface between the mass with the mediastinum—the lesion has significant contact with the mediastinum, evidenced by the lack of visualization of the medial border of the lesion. The appearance is consistent with a posterior mediastinal lesion. The lateral radiograph (B) shows the lesion (arrows) projected over the spine, also indicative of a posterior mediastinal location. (Courtesy Michael Gotway, MD.)



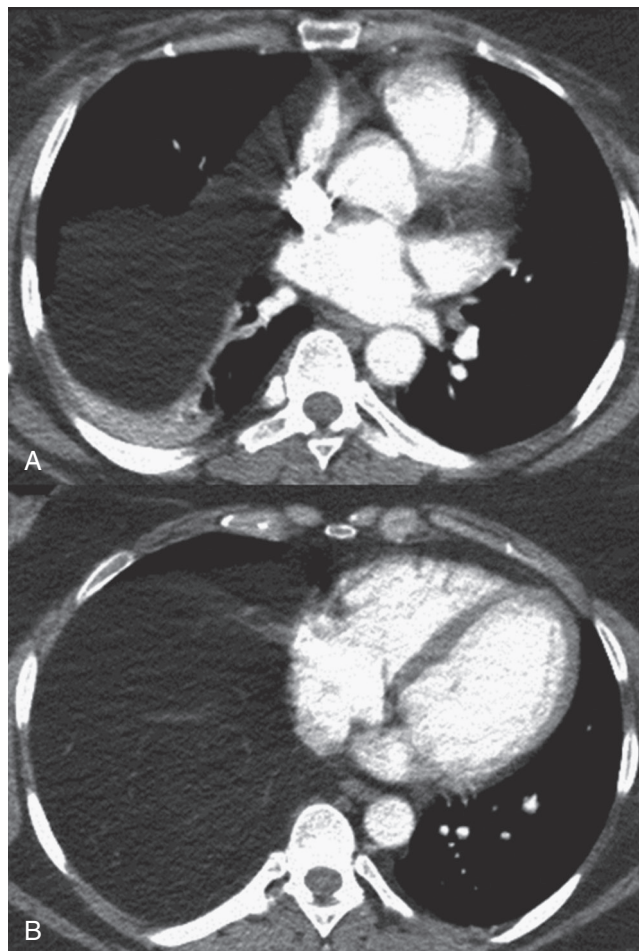
eFigure 83-8 Middle mediastinal mass due to a bronchogenic cyst. Frontal (A) and lateral (B) chest radiographs show a circumscribed right-sided mediastinal mass (arrows). The lateral projection (B) shows the mass is related to the subcarinal space—the most common location for mediastinal bronchogenic cysts. (Courtesy Michael Gotway, MD.)



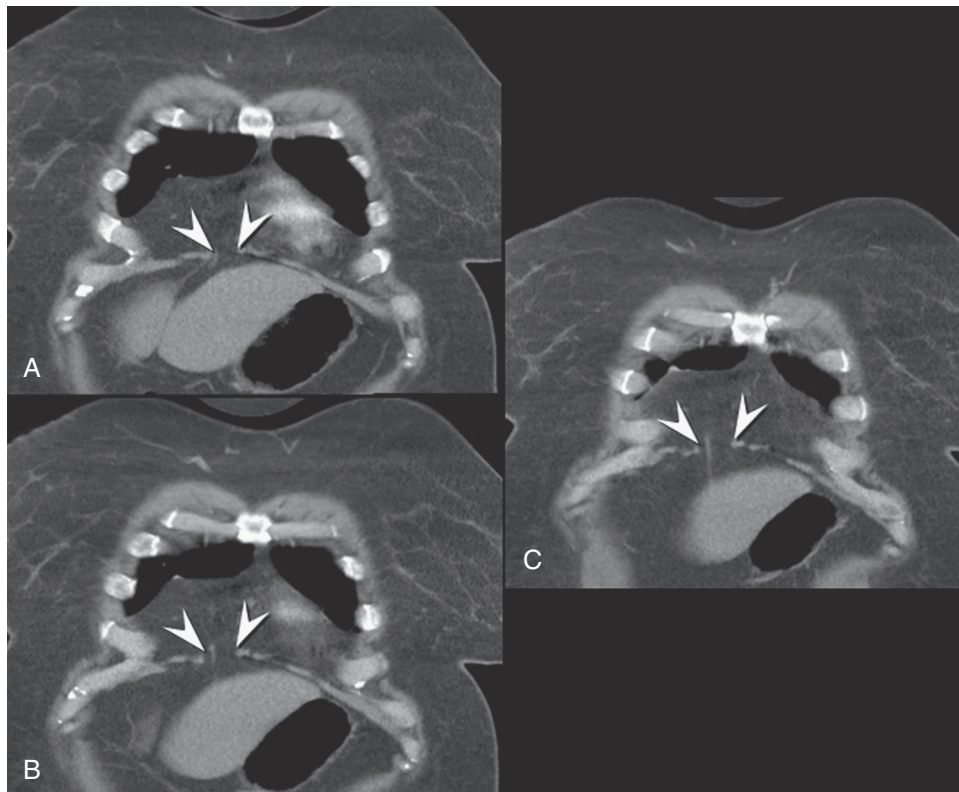
eFigure 83-9 Axial enhanced chest CT in a patient with an anterior mediastinal teratoma shows the excellent visualization of calcium within the lesion. (Courtesy Michael Gotway, MD.)



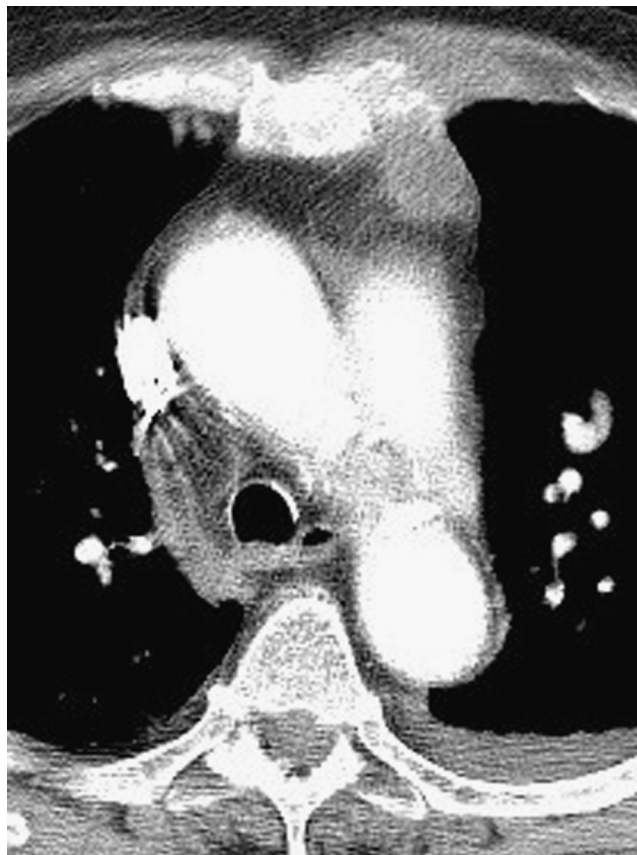
eFigure 83-10 Axial enhanced chest CT in a patient with an anterior mediastinal teratoma shows the excellent visualization of low attenuation fat and hyperattenuating calcium within the lesion. See [Video 83-4](#) for the full study. (Courtesy Michael Gotway, MD.)



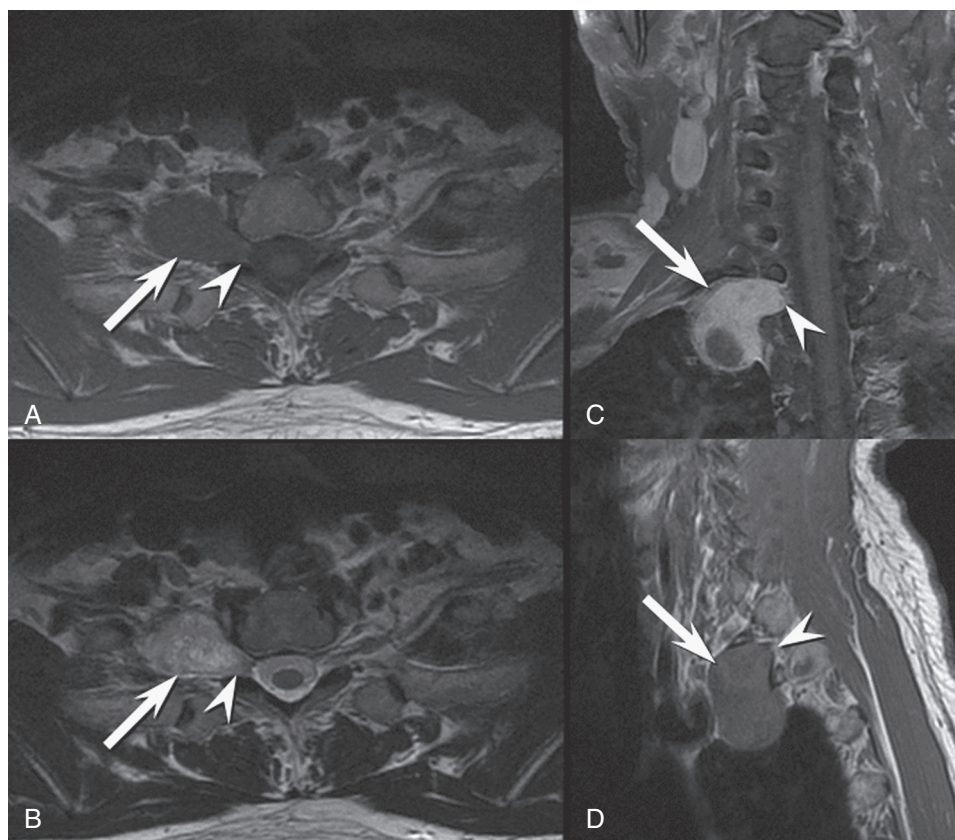
eFigure 83-11 Thymolipoma. Axial enhanced chest CT through the mid (A) and lower (B) thorax shows a fatty mass occupying the right mediastinum. See [Video 83-5](#) for the full study. (Courtesy Michael Gotway, MD.)



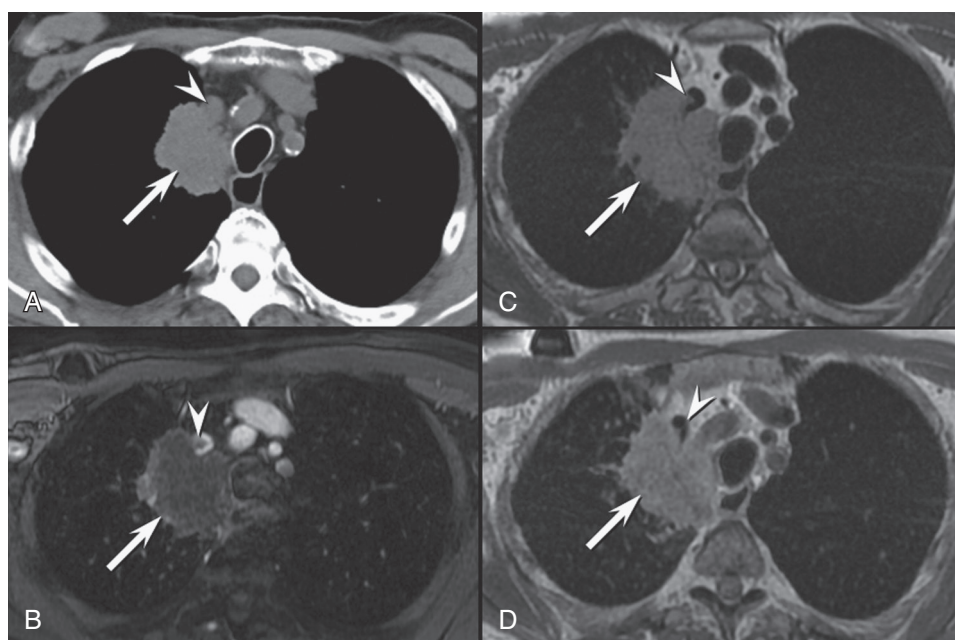
eFigure 83-12 Omental fat hernia due to foramen of Morgagni hernia. Coronal enhanced chest CT through the anterior thorax shows a fatty mass occupying the right mediastinum, arising from the abdomen and extending through a diaphragmatic defect (*arrowheads*) into the thorax. A vessel accompanying the fat herniation is clearly visible in **C**. See [Video 83-6](#) full the full study. (Courtesy Michael Gotway, MD.)



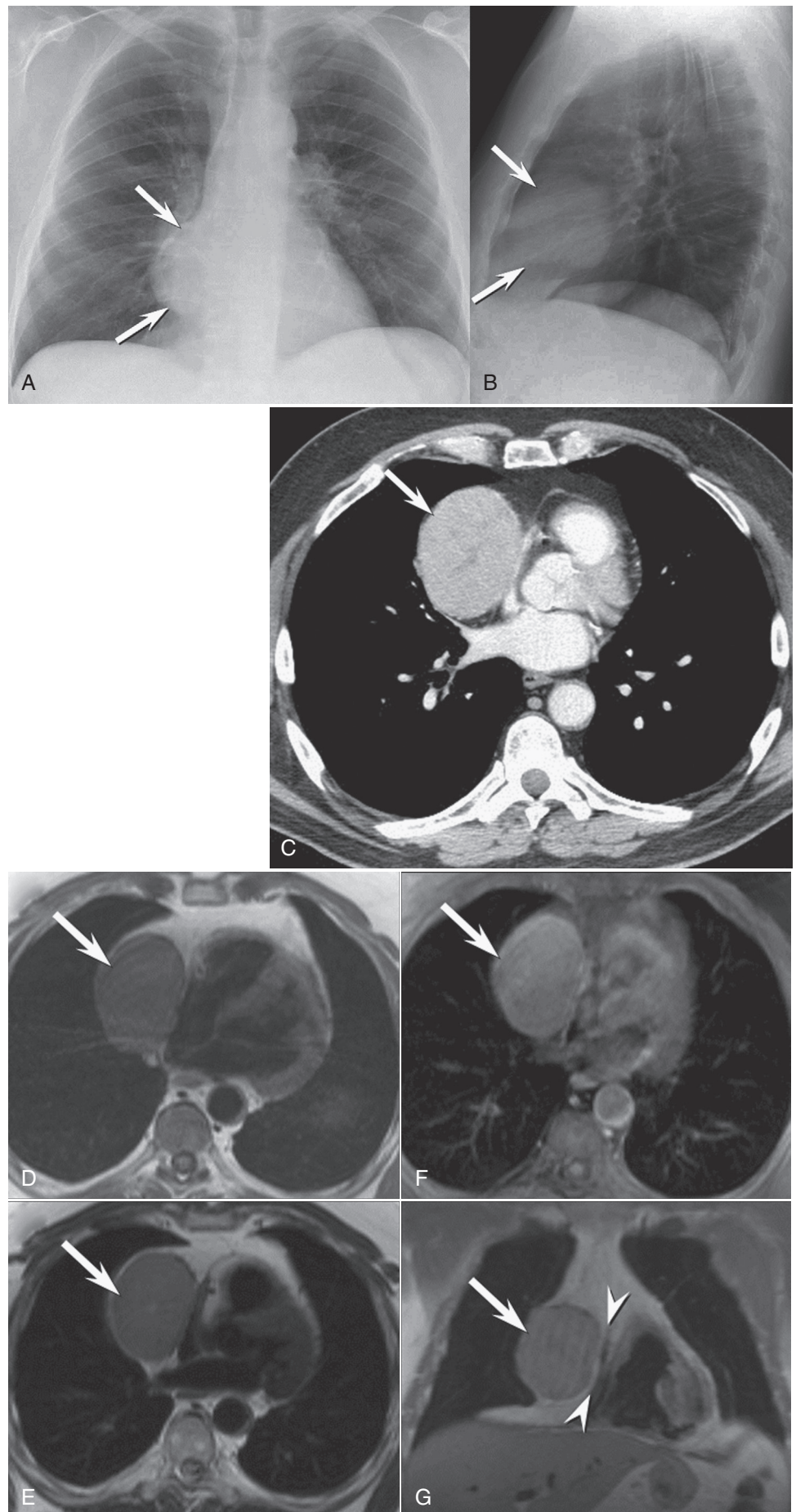
eFigure 83-13 Axial enhanced chest CT in a patient with breast cancer shows left internal mammary lymphadenopathy. (Courtesy Michael Gotway, MD.)



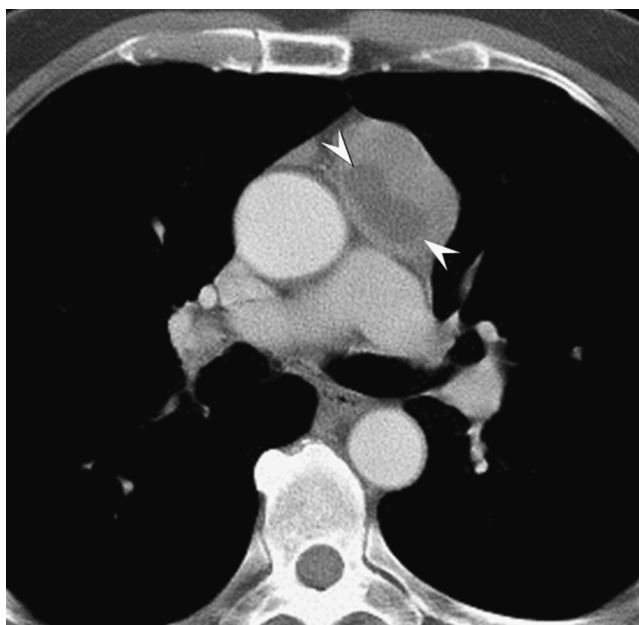
eFigure 83-14 Neurogenic tumor on magnetic resonance (MR) imaging. Axial thoracic T1-weighted (**A**), T2-weighted (**B**), coronal enhanced T1-weighted (**C**), and sagittal unenhanced T1-weighted (**D**) MR images show a neurogenic tumor (*arrows*). Note the tumor extension from the neural foramen (*arrowheads*). The lesion shows increased signal on T2-weighted images (**B**) and intense contrast enhancement (**C**). (Courtesy Michael Gotway, MD.)



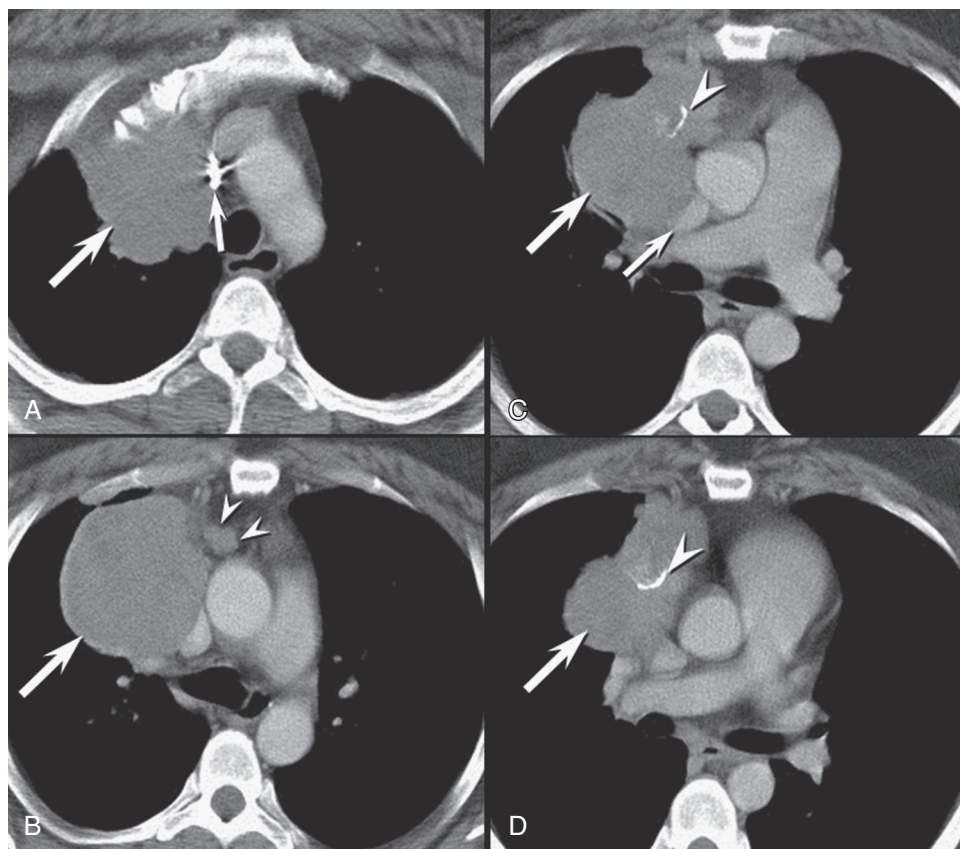
eFigure 83-15 Utility of magnetic resonance imaging (MRI) for determining mediastinal involvement in bronchogenic malignancy. **A**, Axial unenhanced chest CT shows a medial right upper lobe bronchogenic malignancy (*arrow*, **A**) with extensive contact with the mediastinum, especially the right brachiocephalic vein (*arrowhead*, **A**). **B**, Axial thoracic steady-state free precession, unenhanced (**C**) and enhanced (**D**) T1-weighted MRI shows extension of the neoplasm (*arrows*, **B–D**) into the mediastinal fat with invasion of the right brachiocephalic vein, evidenced by the small intravascular nodule (*arrowheads*, **B–D**). See [Video 83-8](#) for the full study of part **B**. (Courtesy Michael Gotway, MD.)



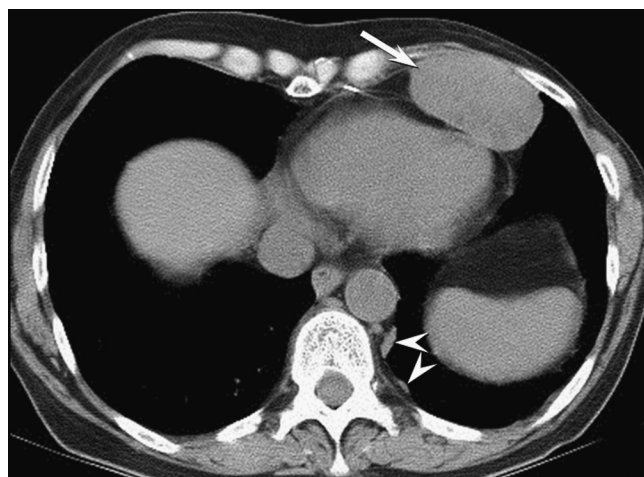
eFigure 83-16 Typical appearance of thymoma at thoracic imaging. Frontal (A) and lateral (B) chest radiographs show a smoothly circumscribed mediastinal mass (arrows) at the level of the junction of the heart and great vessels. The obscuration of the right heart border on the frontal projection (A) and the presence of the mass overlying the heart on the lateral projection (B) indicates that the mass is adjacent to the heart. C, Axial enhanced chest CT shows the smoothly circumscribed, enhancing mediastinal mass. Axial T1-weighted (D) T2-weighted (E), enhanced, fat saturation T1-weighted (F), and coronal T1-weighted (G) images show the mediastinal lesion (arrows) to advantage. In particular, the indolent nature of the mass, evidenced by the maintained fat plane between the mass and pericardium (arrowheads, G) is well shown. The lesion shows intermediate-to-slightly-decreased signal on T2-weighted imaging (E), consistent with the cellular nature of the neoplasm. (Courtesy Michael Gotway, MD.)



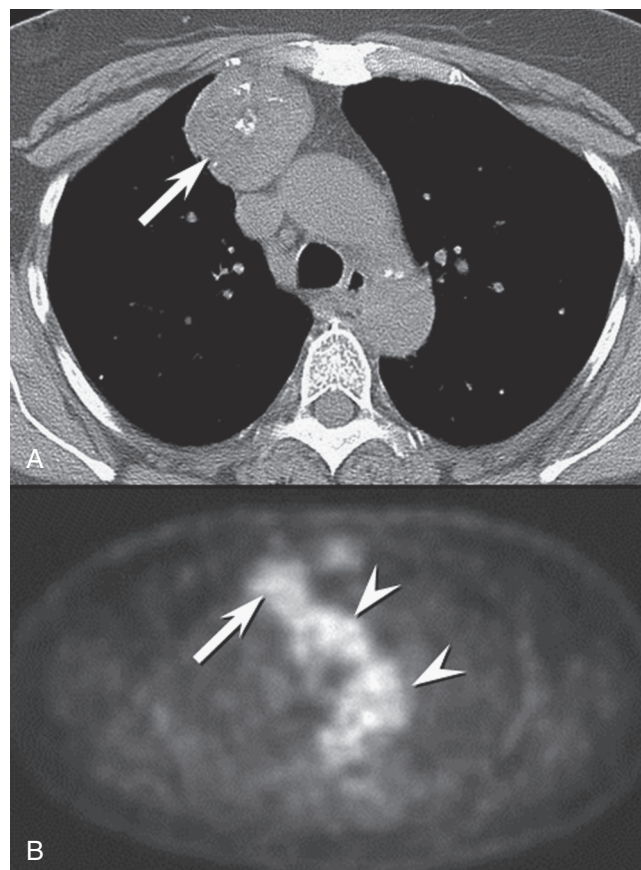
eFigure 83-17 Cystic degeneration within a thymoma. Axial enhanced chest CT shows an enhancing anterior mediastinal mass containing internal low attenuation (*arrowheads*) consistent with cystic change or necrosis. (Courtesy Michael Gotway, MD.)



eFigure 83-18 Utility of chest CT for thymic neoplasm staging. A–D, Axial enhanced chest CT shows a lobulated mass (*large arrows, A–D*) with foci of calcification (*arrowheads, C and D*). The CT scan shows features consistent with an aggressive neoplasm, including lobulation, mediastinal fat infiltration, regional lymphadenopathy (*double arrowhead, B*), and marked vascular compression (*small arrows, A and C*). Compare the appearance of this aggressive neoplasm with the more indolent lesion shown in e-Fig. 83-16. (Courtesy Michael Gotway, MD.)



eFigure 83-19 Utility of chest CT for thymic neoplasm staging. Axial chest CT shows a circumscribed anterior mediastinal mass (*arrow*) in contact with the pericardium. While the circumscribed nature of the lesion initially suggests a relatively indolent neoplasm, potentially amenable to surgical resection, chest CT also shows pleural nodules (*arrowheads*) in the left lower medial thorax, representing intrathoracic metastatic disease. (Courtesy Michael Gotway, MD.)



eFigure 83-20 Limited utility of ^{18}F FDG-PET for thymic neoplasm evaluation. **A**, Axial unenhanced chest CT shows an anterior mediastinal mass (*arrow*) consistent with a thymic neoplasm; note calcification within the lesion. **B**, ^{18}F FDG-PET image shows modest glucose utilization within the tumor (*arrow*), but the degree of tracer uptake does not exceed that of mediastinal blood pool (*arrowheads*). In general, tracer activity must exceed that seen within mediastinal blood pool to confidently suggest a malignant process. (Courtesy Michael Gotway, MD.)

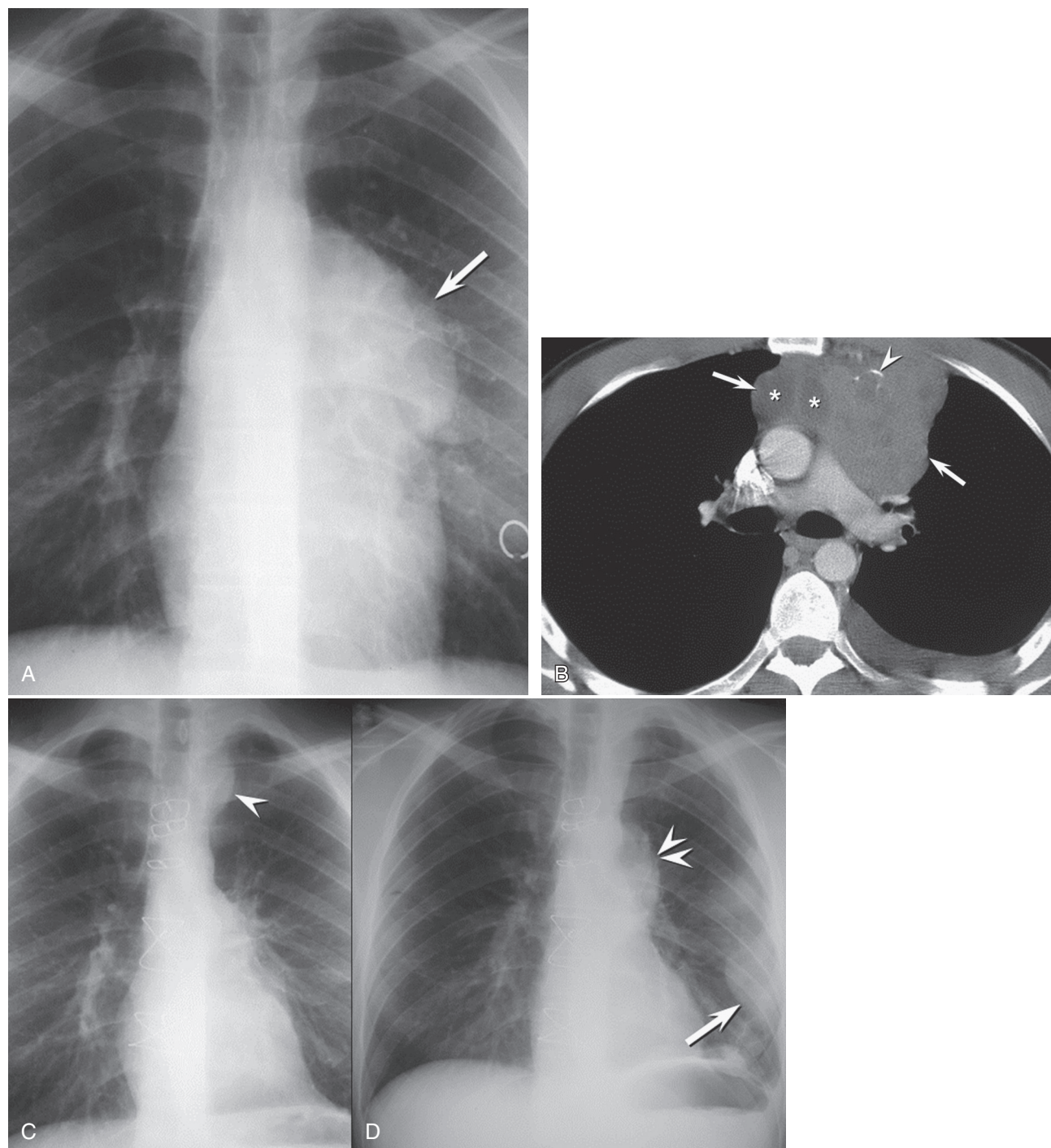
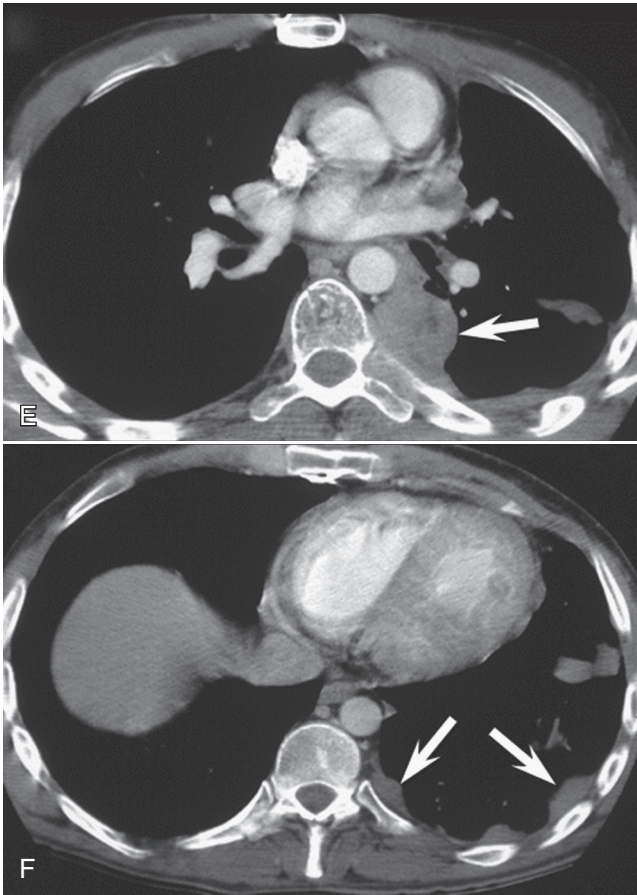
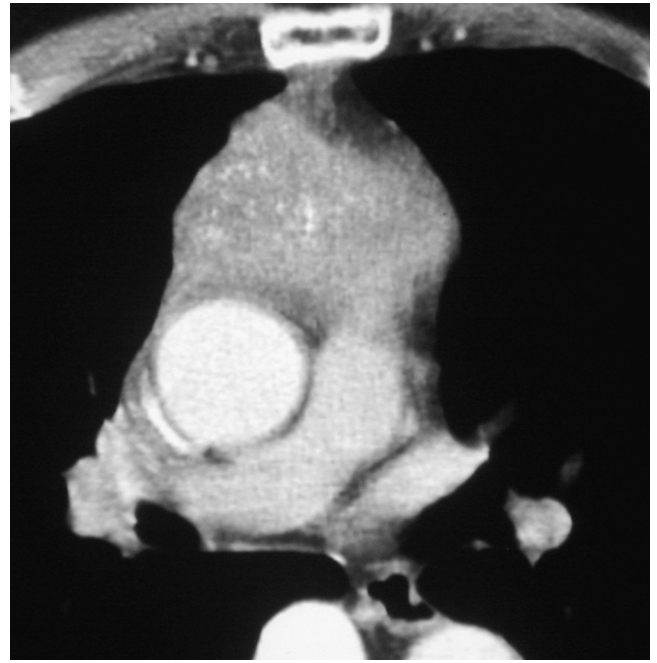


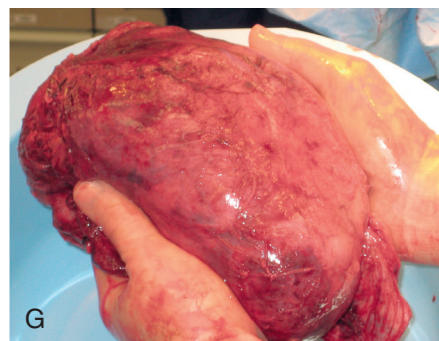
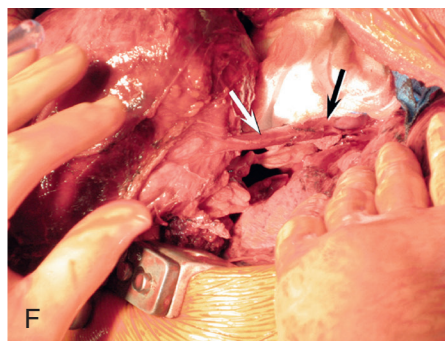
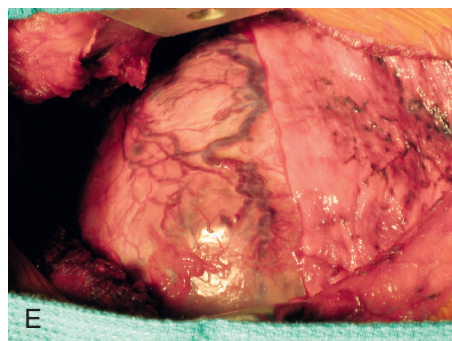
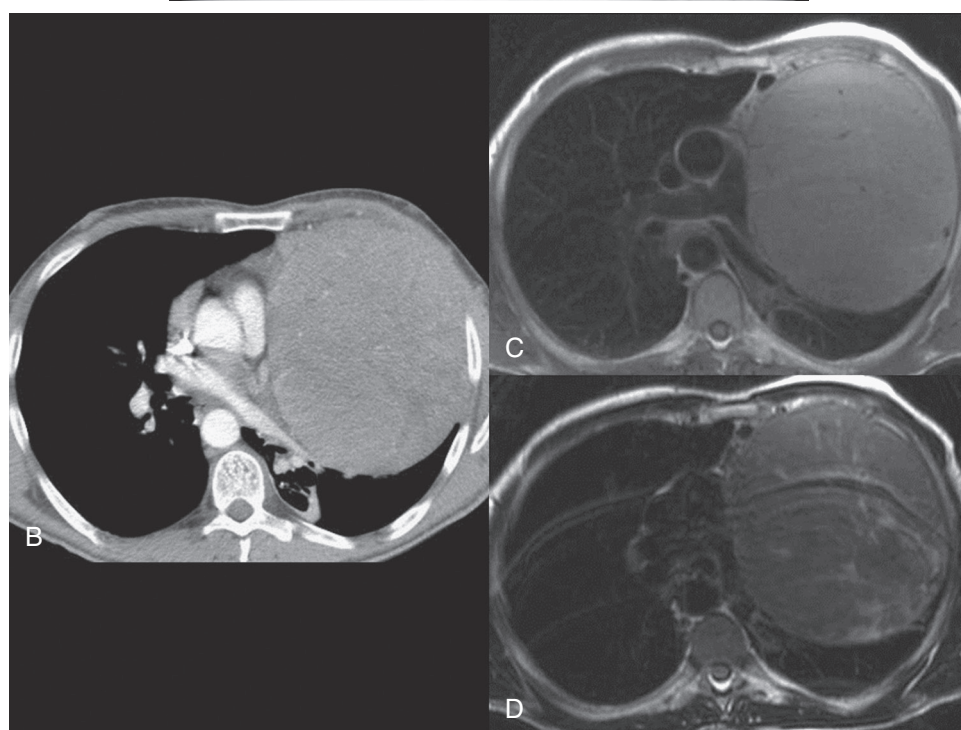
Figure 83-21 Thymic neoplasm recurrence. Frontal chest radiograph (A) and enhanced chest CT (B) at presentation show a left-sided mediastinal mass (arrows) subsequently shown to represent thymic neoplasia; note the lobulation, cystic change (*), vascular compression and displacement, and calcification (arrowhead) on CT scan (B), all suggestive of an aggressive neoplasm. C, Frontal chest radiograph performed months following resection of the thymic neoplasm shows a new lesion abutting the posterior mediastinal surface of the left superior thorax (C, arrowhead), consistent with tumor recurrence. D, Frontal chest radiograph several months following C shows an enlarging mediastinal mass (double arrowheads) and enlarging pleural metastatic deposits (arrow, D).



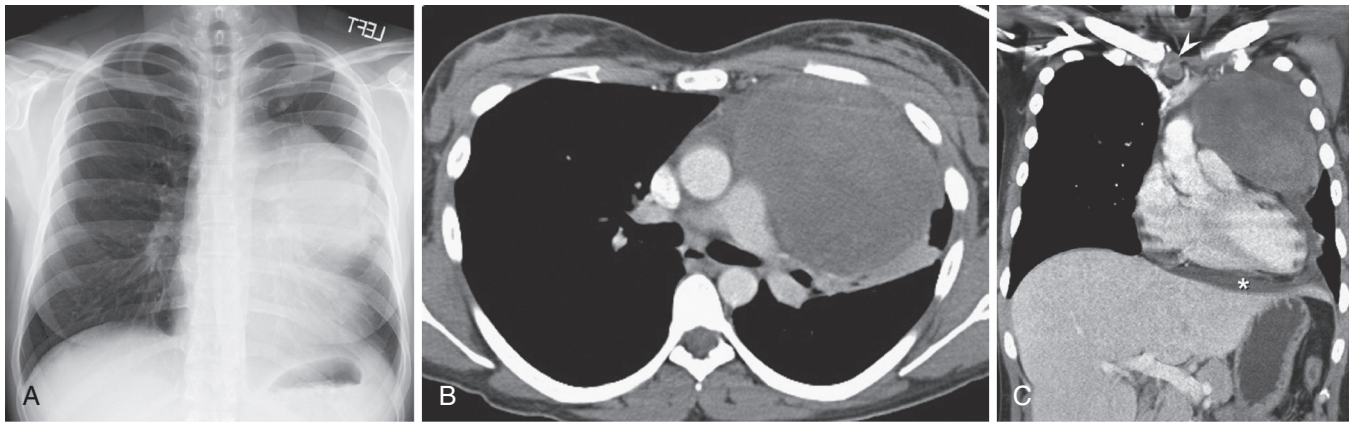
eFigure 83-21, cont'd E and F, Enhanced chest CT confirms pleural metastatic disease (*arrows*). (Courtesy Michael Gotway, MD.)



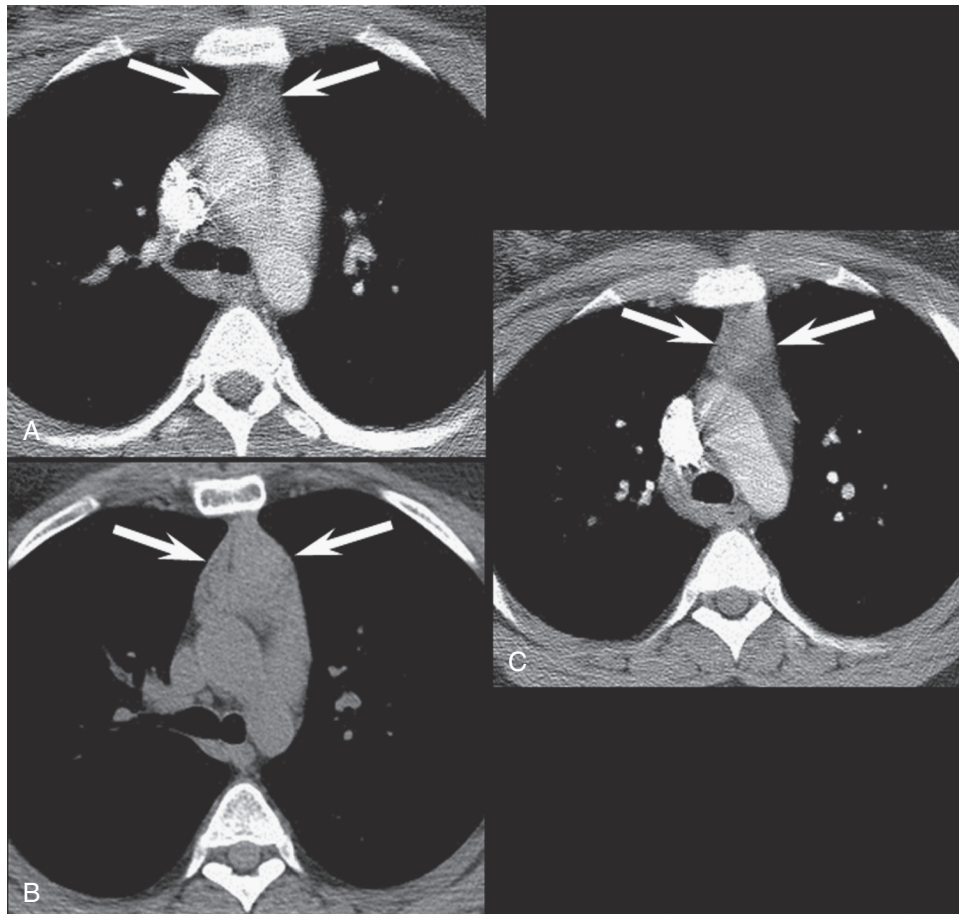
eFigure 83-22 Chest CT scan of thymic carcinoma. Focused axial enhanced chest CT shows a lobulated anterior mediastinal mass with foci of stippled calcification and extensive contact between the mass and vessels, in particular with obliteration of the fat plane between the mass and main pulmonary artery. (Courtesy Michael Gotway, MD.)



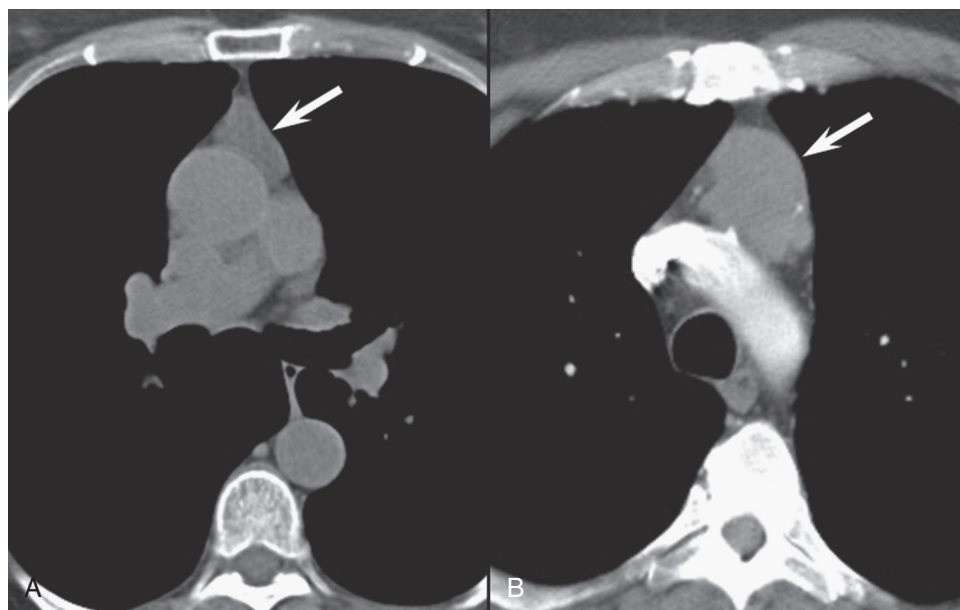
eFigure 83-23 Neuroendocrine thymic malignancy (“thymic carcinoid tumor”). **A**, Frontal chest radiograph shows a smoothly circumscribed left-sided anterior mediastinal mass. **B**, Axial enhanced chest CT scan shows a solid, homogeneously enhancing left-sided anterior mediastinal mass with contralateral mediastinal shift, but no other overtly aggressive features. Axial double inversion recovery T1-weighted (**C**) and T2-weighted (**D**) magnetic resonance images also show the lesion and its mass effect, but no locally invasive behavior. The T2-weighted (**D**) image shows intermediate signal within the lesion, indicative of a relatively cellular neoplasm. The small “black dot” anterior and medial to the mass represents a flow void within an enlarged mediastinal vein. **E** and **F**, Intraoperative view of the lesion during resection shows the large vein on the surface of the neoplasm; this vascular pedicle (arrows, **F**) was identified at surgery and ligated. **G**, Photograph of the resected specimen. (A to D, Courtesy Michael Gotway, MD; E to G, intraoperative photographs courtesy Andrew H. Goldstein, MD.)



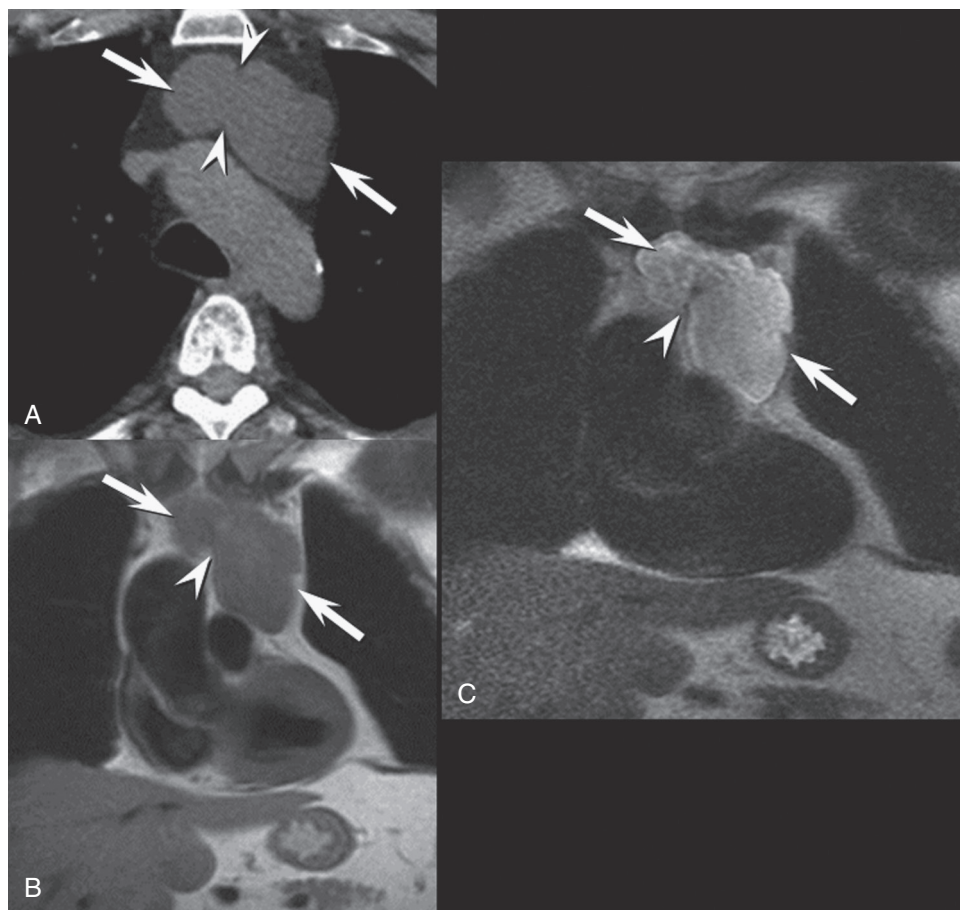
eFigure 83-24 Hodgkin lymphoma involving the thymus. **A**, Frontal chest radiograph shows a large left-sided anterior mediastinal mass. Axial (**B**) and coronal enhanced (**C**) chest CT scans show a minimally lobulated slightly inhomogeneous left-sided anterior mediastinal mass. The appearance is similar to thymic neoplasia. The pericardial effusion (*) and regional necrotic lymph node enlargement (arrowhead) are indicative of an aggressive process. (Courtesy Michael Gotway, MD.)



eFigure 83-25 Thymic "rebound" hyperplasia. **A**, Enhanced chest CT in a young patient with breast malignancy at time of diagnosis shows minimal soft tissue mixed with fat (arrows), consistent with normal residual thymus. **B**, Axial unenhanced chest CT shows marked increase in the soft tissue within the anterior mediastinum (arrows) several months following chemotherapy, consistent with "thymic rebound." The appearance can be difficult to distinguish from neoplasia. **C**, Enhanced chest CT 1 year after **B** shows return to a more normal appearance of the thymus (arrows). (Courtesy Michael Gotway, MD.)



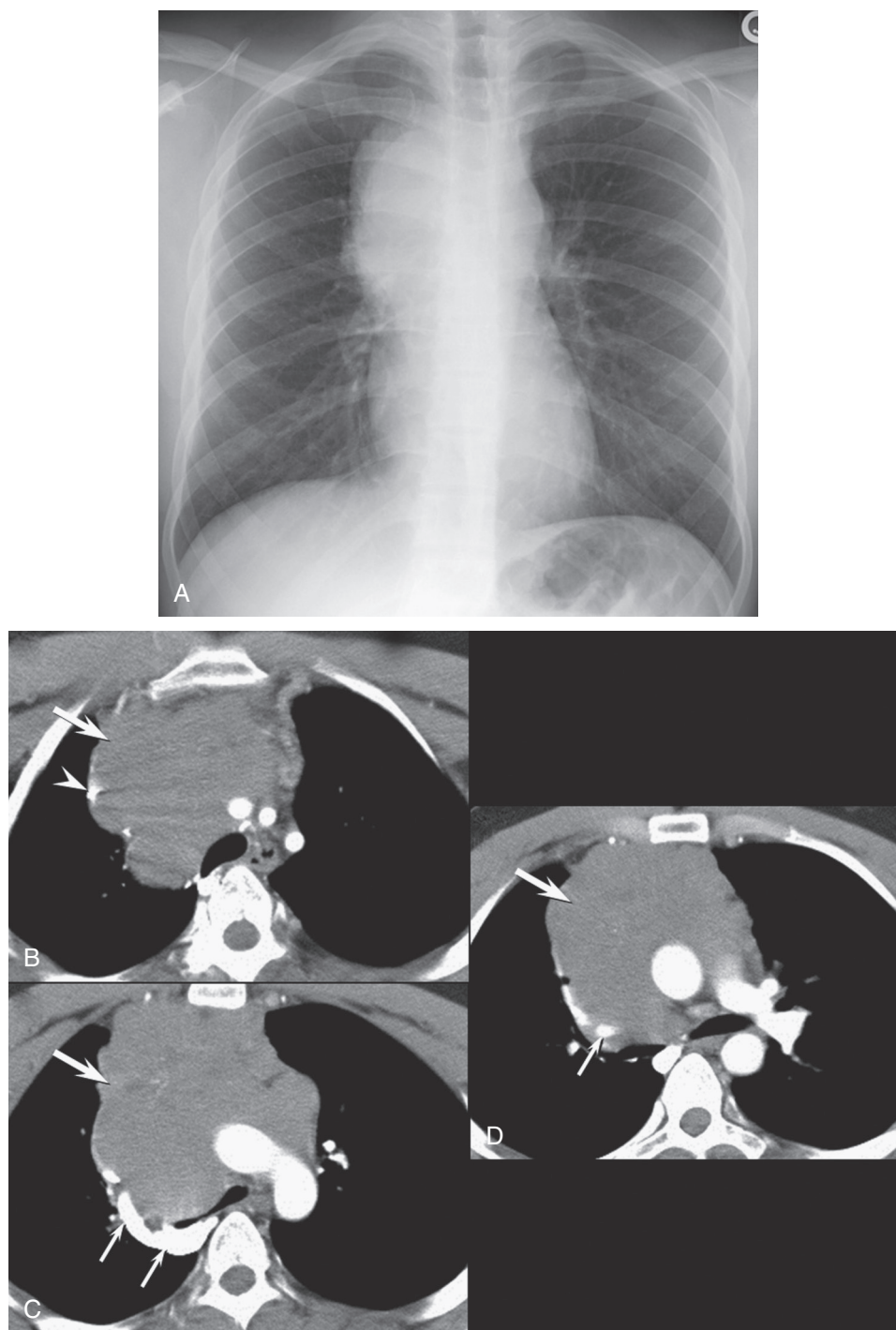
eFigure 83-26 Thymic hyperplasia versus thymoma. **A**, Unenhanced chest CT in a patient with thymic hyperplasia shows a homogeneous low attenuation, smoothly circumscribed anterior mediastinal lesion (*arrow*) consistent with thymic hyperplasia; note the morphology of this lesion still resembles normal thymus. This appearance contrasts with **B**, the lobulated, irregular appearance of thymoma (*arrow*). (Courtesy Michael Gotway, MD.)



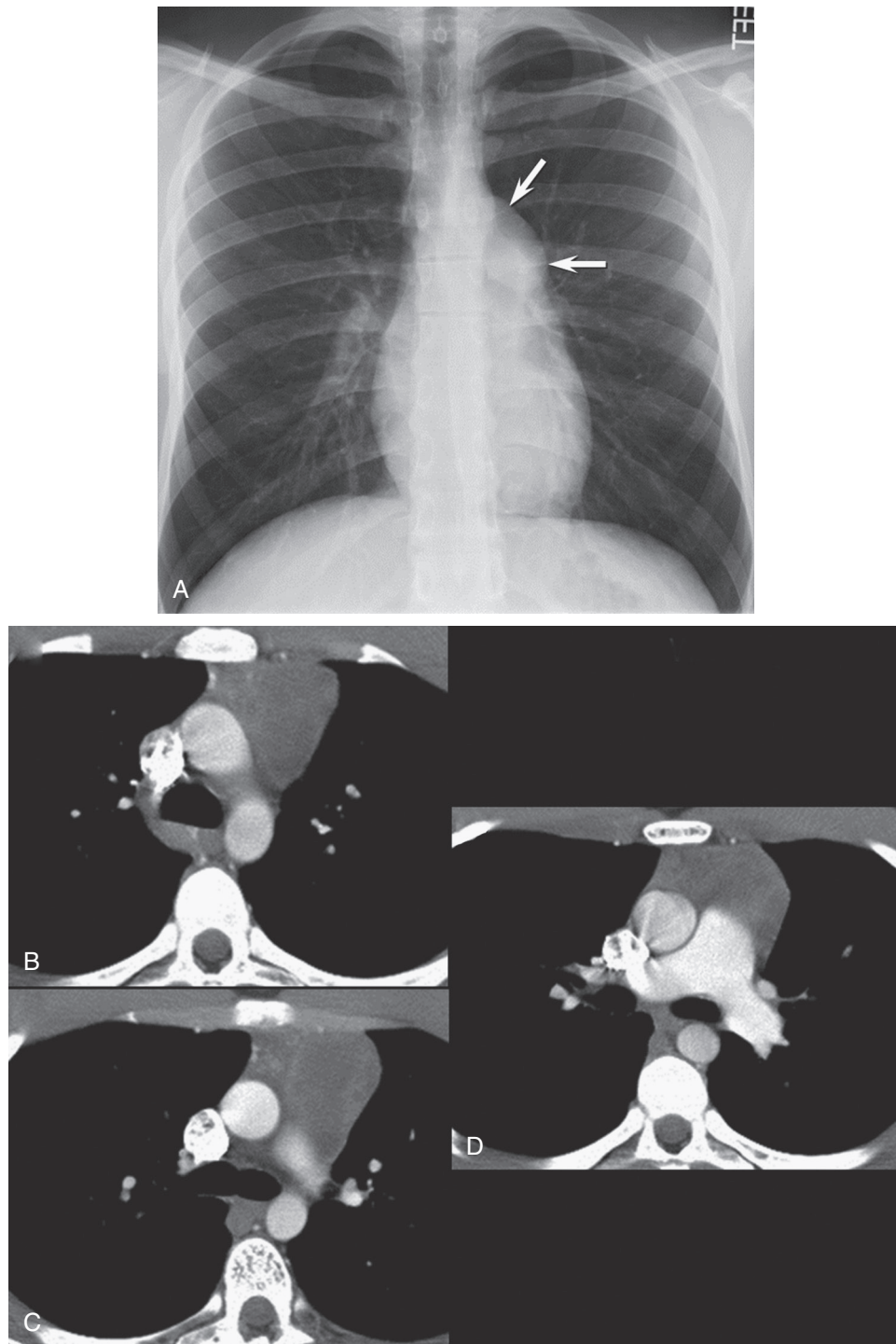
eFigure 83-27 Thymic cyst. **A**, Axial unenhanced chest CT shows a homogeneously (water density) low attenuation anterior mediastinal lesion (*arrows*). Note the cleft in the lesion (*arrowheads*); this morphology is reminiscent of the normal bilobed thymus. Coronal double inversion recovery unenhanced T1-weighted (**B**) and fast spin-echo T2-weighted magnetic resonance (**C**) images show low and high signal, respectively, within the lesion (*arrows*), consistent with fluid. This lesion has remained stable for a number of years. Both images show the cleft within the lesion (*arrowheads*). (Courtesy Michael Gotway, MD.)



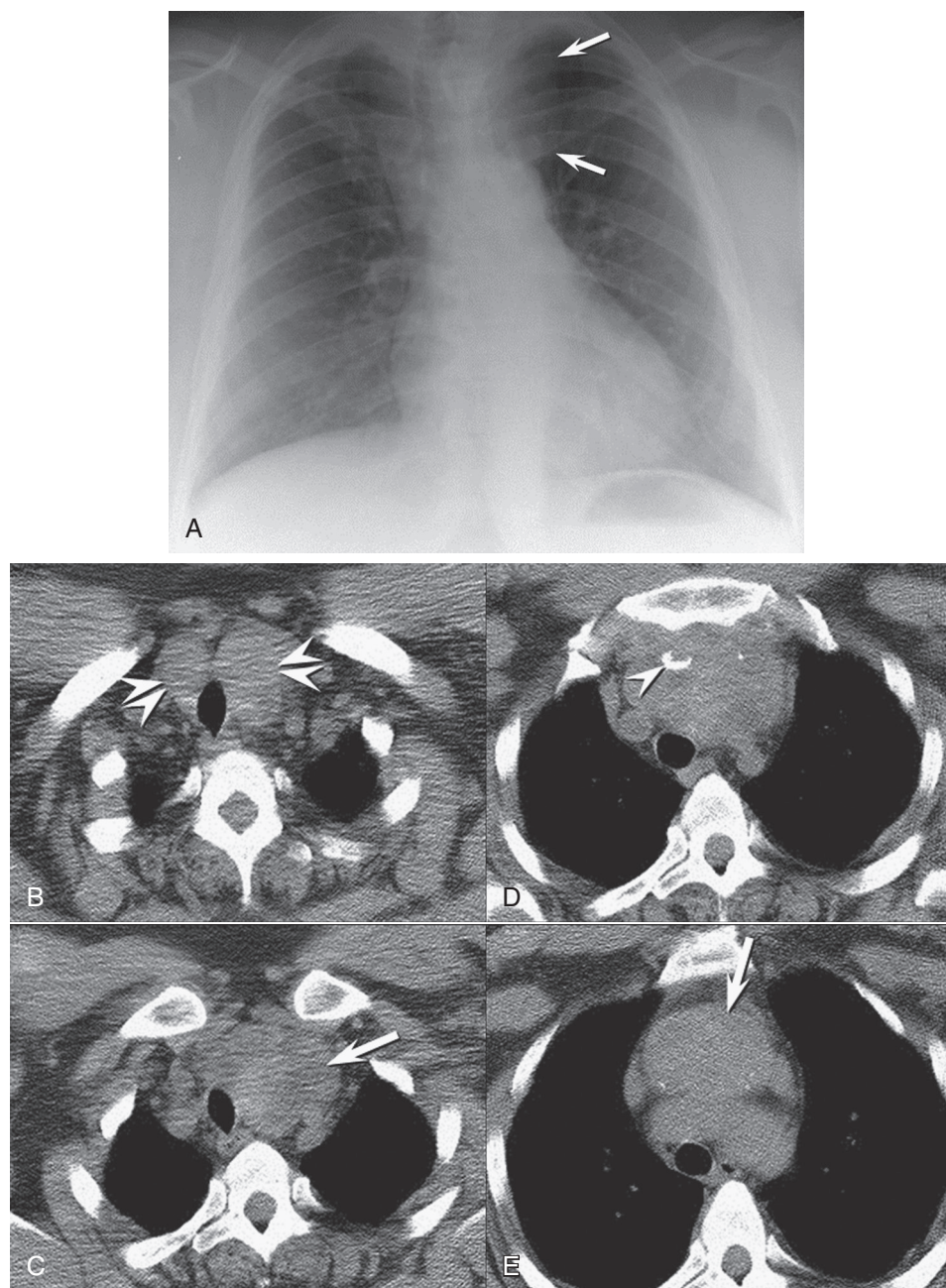
eFigure 83-28 Teratoma. Frontal chest radiograph shows a large right-sided mediastinal mass, representing teratoma. (Courtesy Michael Gotway, MD.)



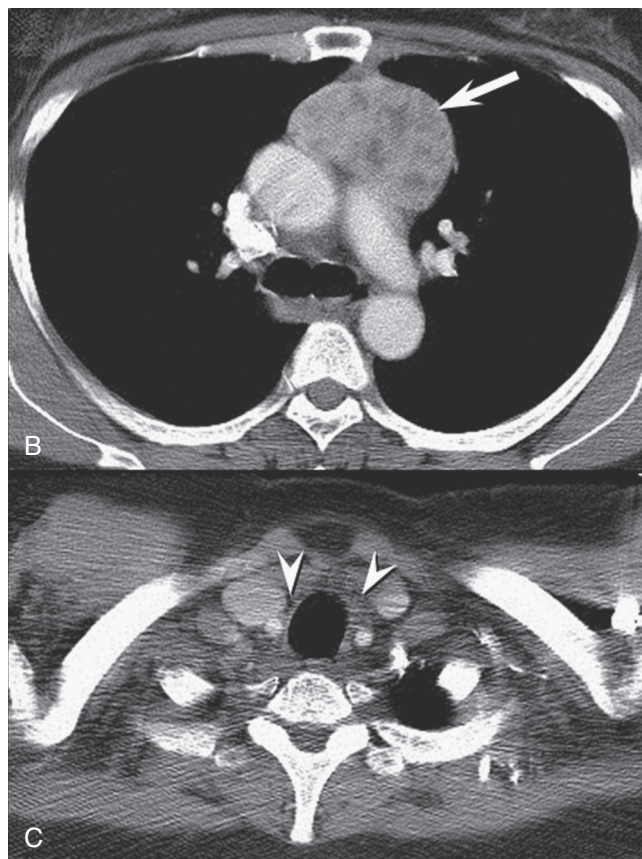
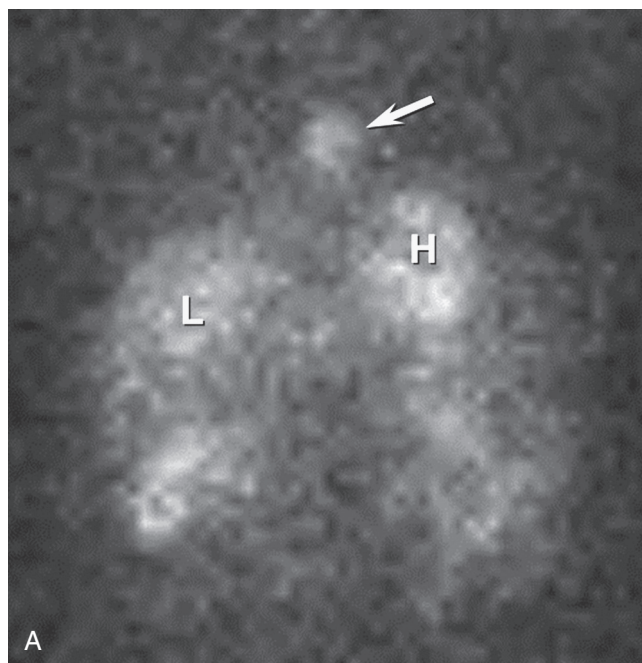
eFigure 83-29 Seminoma. **A**, Frontal chest radiograph shows a large right-sided mediastinal mass. **B–D**, Axial enhanced chest CT scans show a mildly inhomogeneous, lobulated mass (*arrows*) with compression and displacement of the right brachiocephalic vein (*arrowhead*), resulting in extensive azygos vein (*small arrows*, **B** and **C**) collateral circulation. See [Video 83-9](#) for the full study. (Courtesy Michael Gotway, MD.)



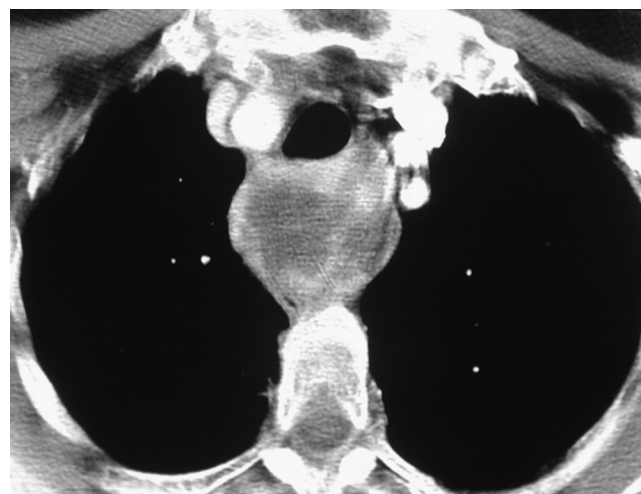
eFigure 83-30 Embryonal cell carcinoma. **A**, Frontal chest radiograph shows a circumscribed left-sided anterior mediastinal mass (*arrows*). **B-D**, Axial enhanced chest CT shows a heterogeneous anterior mediastinal mass that obliterates fat planes with the adjacent vessels. Internal low attenuation within the tumor, as seen in the example, is more commonly encountered as non-seminomatous mediastinal germ cell neoplasms than seminomas. See [Video 83-10](#) for the full study. (Courtesy Michael Gotway, MD.)



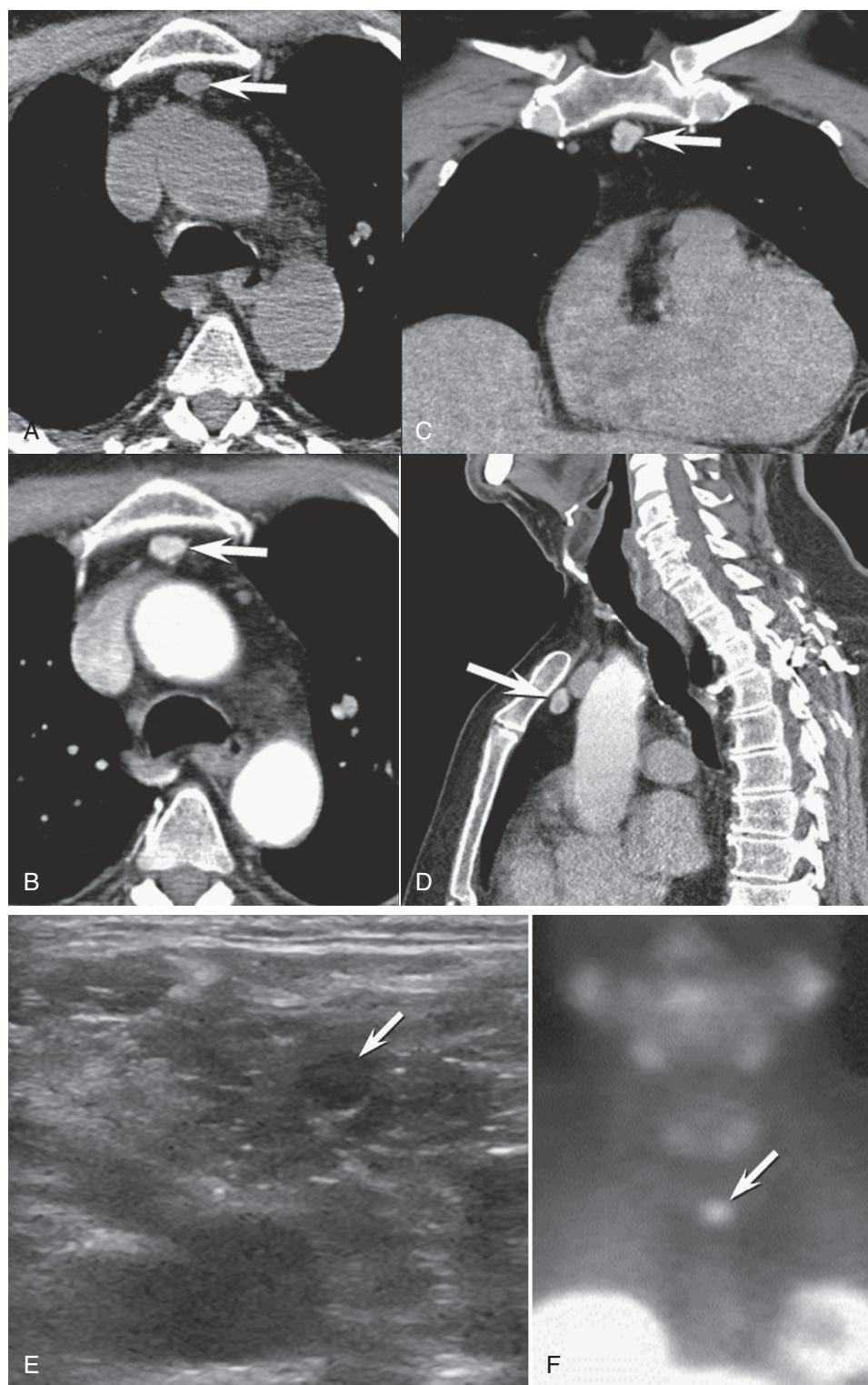
eFigure 83-31 Anterior mediastinal extension of a thyroid goiter. **A**, Frontal chest radiograph shows widening of the superior mediastinum with rightward shift of the trachea resulting from a mediastinal mass (*arrows*). The superior mediastinal widening extends into the base of the neck. **B–E**, Axial unenhanced chest CT shows enlargement of the cervical thyroid gland (*double arrowheads*, **A**). The anterior superior mediastinal mass (*arrows*, **C** and **E**) extends from the base of the neck, originating from, and in contact with, the cervical thyroid gland. The mass contains calcification (*single arrowhead*, **D**), a common finding in thyroid goiters. Continuity of a mediastinal lesion with the cervical thyroid gland is key for confidently establishing a mediastinal mass as thyroidal in origin. (Courtesy Michael Gotway, MD.)



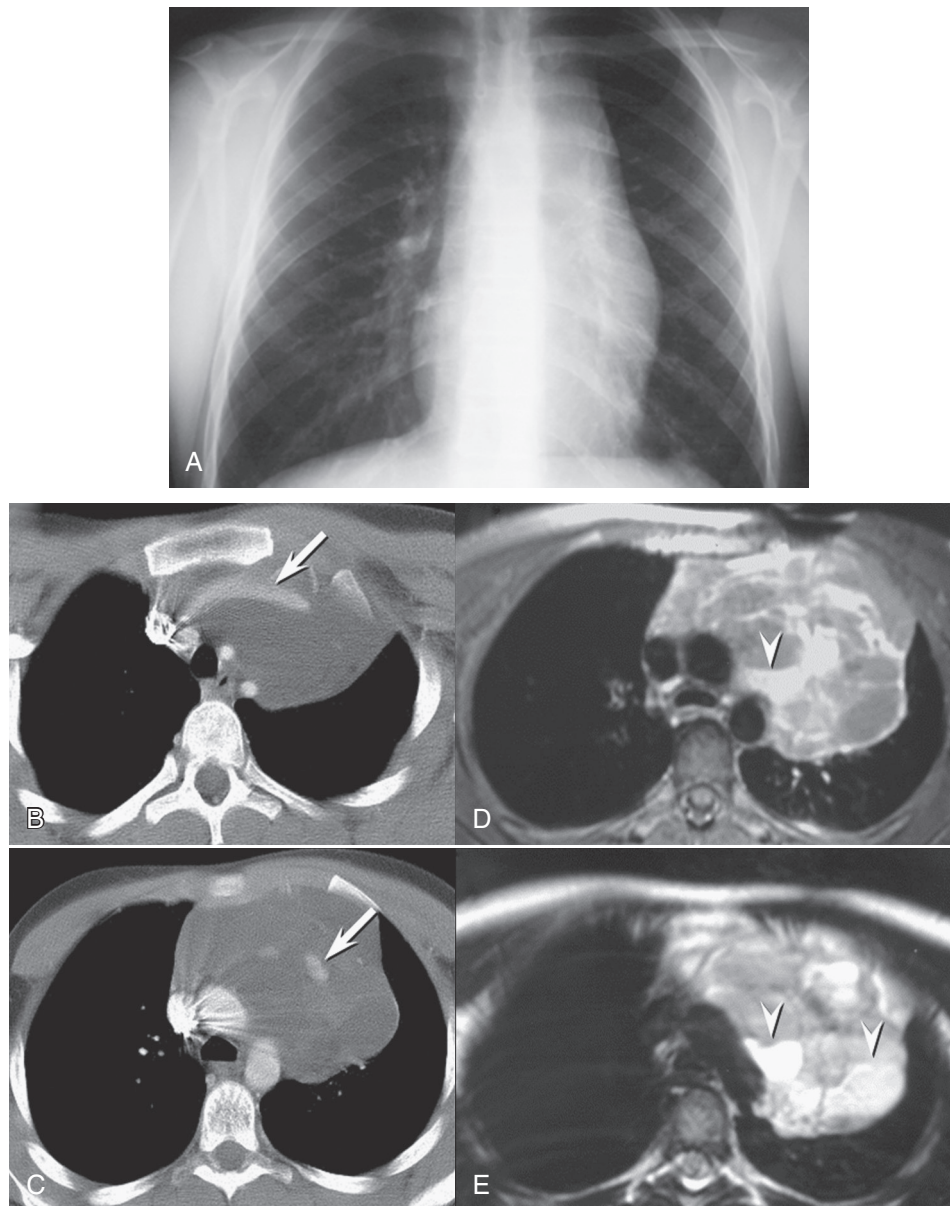
eFigure 83-32 Ectopic mediastinal thyroid tissue. **A**, Planar frontal 99m-technetium sestamibi scintigraphy shows faint tracer uptake within the mediastinum (*arrow*), separate from the heart (H) and liver (L). Axial enhanced chest CT shows a heterogeneously enhancing anterior mediastinal mass (*arrow*). **C**, Axial CT image through the cervicothoracic junction shows absence of a normal thyroid gland (*arrowheads*, **C**). (Courtesy Michael Gotway, MD.)



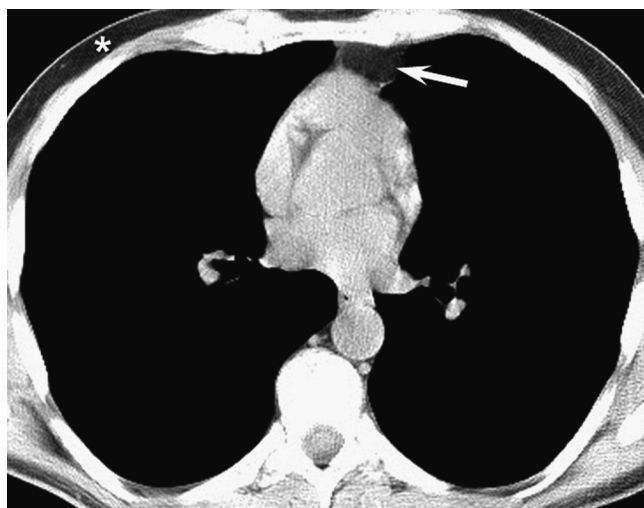
eFigure 83-33 Middle mediastinal extension of a thyroid goiter. Axial enhanced chest CT shows a peripherally hyperenhancing mass with central necrosis posterior to the trachea. This lesion was in contact with thyroid tissue at the base of the neck, establishing it as mediastinal goiter extension. (Courtesy Michael Gotway, MD.)



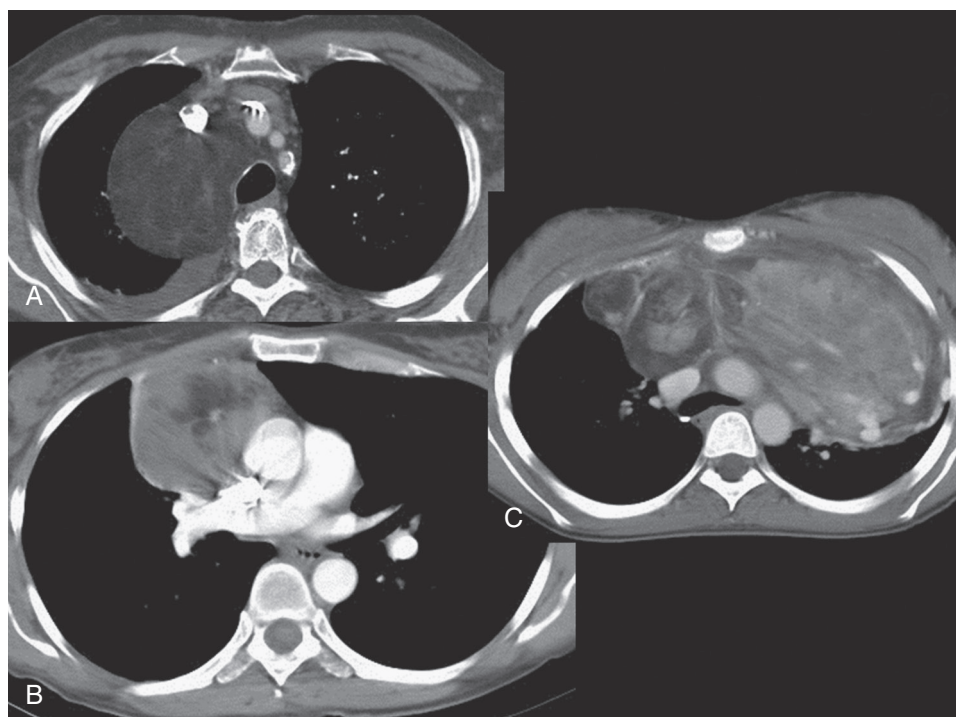
eFigure 83-34 Ectopic anterior mediastinal parathyroid adenoma. Axial unenhanced (**A**) and axial (**B**), coronal (**C**), and sagittal (**D**) enhanced chest CT shows an intensely enhancing lesion (*arrow*) in the anterior mediastinum. **E**, Transverse sonography performed at the level of the suprasternal notch shows a hypoechoic nodule (*arrow*) corresponding to the CT abnormality. **F**, Planar frontal 99m-technetium sestamibi scintigraphy shows avid tracer accumulation within the anterior mediastinal lesion (*arrow*), confirming ectopic parathyroid adenoma. (Courtesy Michael Gotway, MD.)



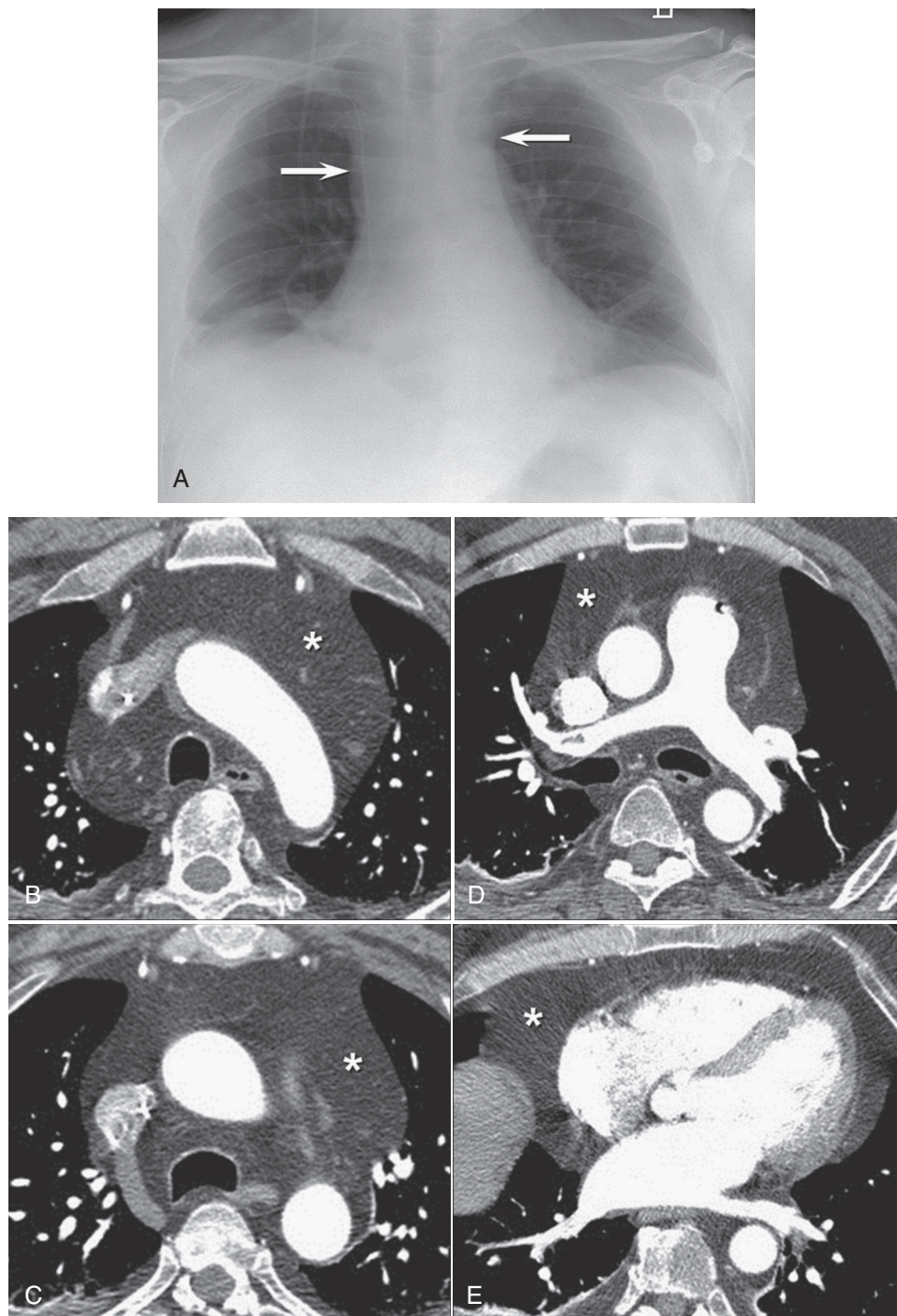
eFigure 83-35 Mediastinal lymphangioma. Frontal chest radiograph in a 13-year-old boy shows a circumscribed left mediastinal mass without mediastinal shift. **B** and **C**, Axial enhanced chest CT shows an anterior and superior low attenuation mediastinal lesion surrounding, but not compressing, the left brachiocephalic vein (*arrows*); this behavior indicates that the lesion is relatively “soft.” Axial fat saturation T1-weighted (**D**) and T2-weighted (**E**) magnetic resonance images show a mass with heterogeneous signal intensity containing multiple fluid-fluid levels (*arrowheads*). The dependent signal within the areas of fluid-fluid level formation is bright on both T1- and T2-weighted images, consistent with blood. (Courtesy Michael Gotway, MD.)



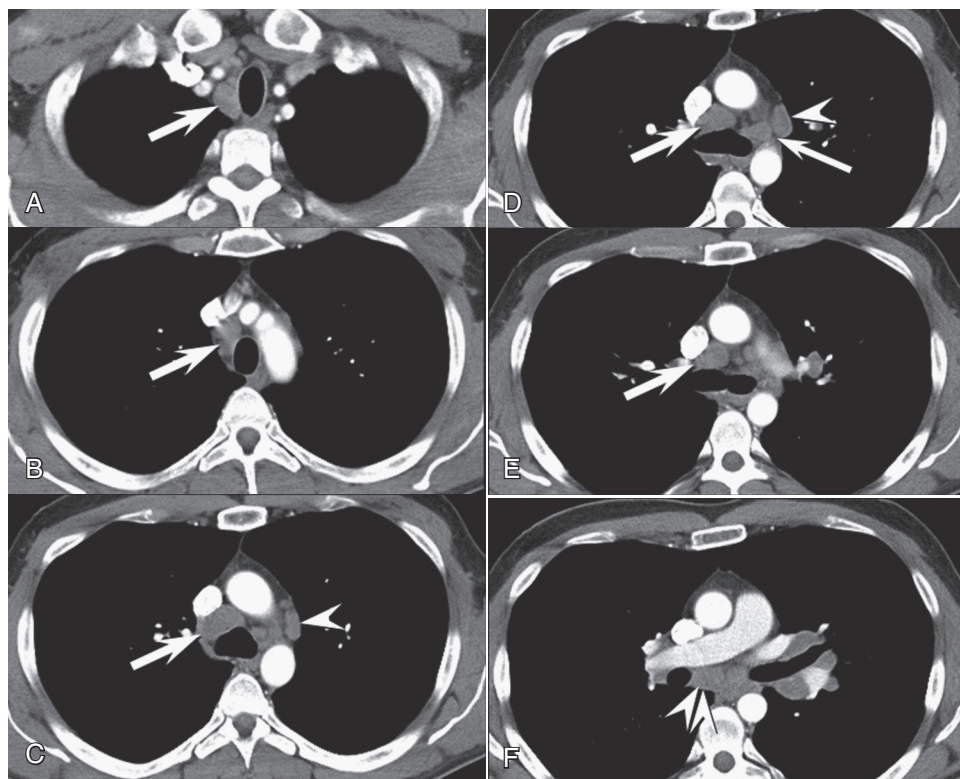
eFigure 83-36 Anterior mediastinal lipoma. Axial enhanced chest CT shows an encapsulated fat-containing lesion (*arrow*) consistent with a small lipoma. (Courtesy Michael Gotway, MD.)



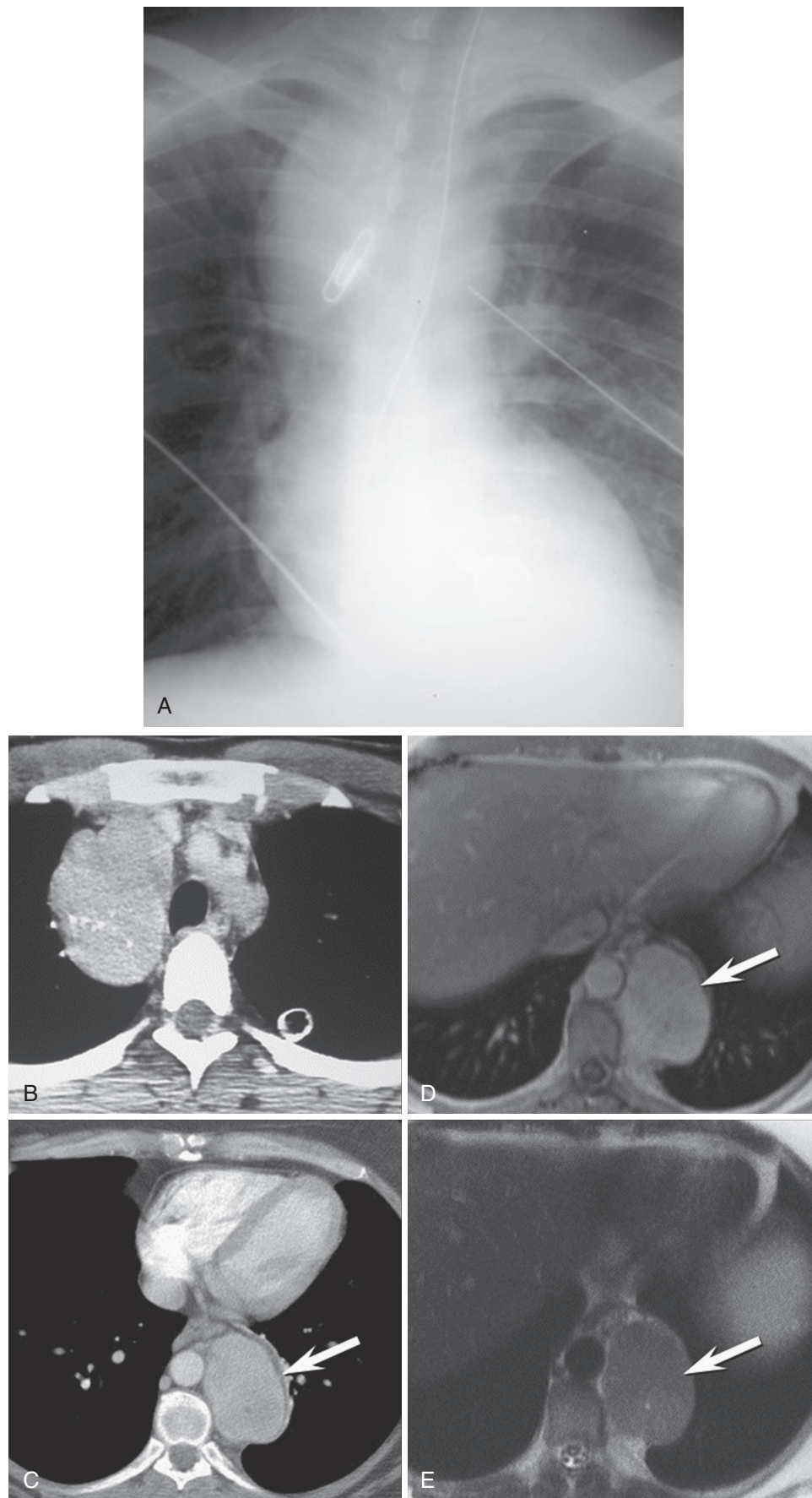
eFigure 83-37 Mediastinal liposarcoma. **A**, Axial chest CT shows a predominantly fatty attenuating mass, representing well-differentiated liposarcoma. **B**, Axial chest CT shows a mediastinal mass again containing fat, but with considerably more soft tissue than the well-differentiated lesion in **A**, representing moderately differentiated mediastinal liposarcoma. **C**, Axial chest CT shows a large inhomogeneous mass containing fat, but also with soft tissue components and extensive vascularity, representing poorly differentiated mediastinal liposarcoma. (Courtesy Michael Gotway, MD.)



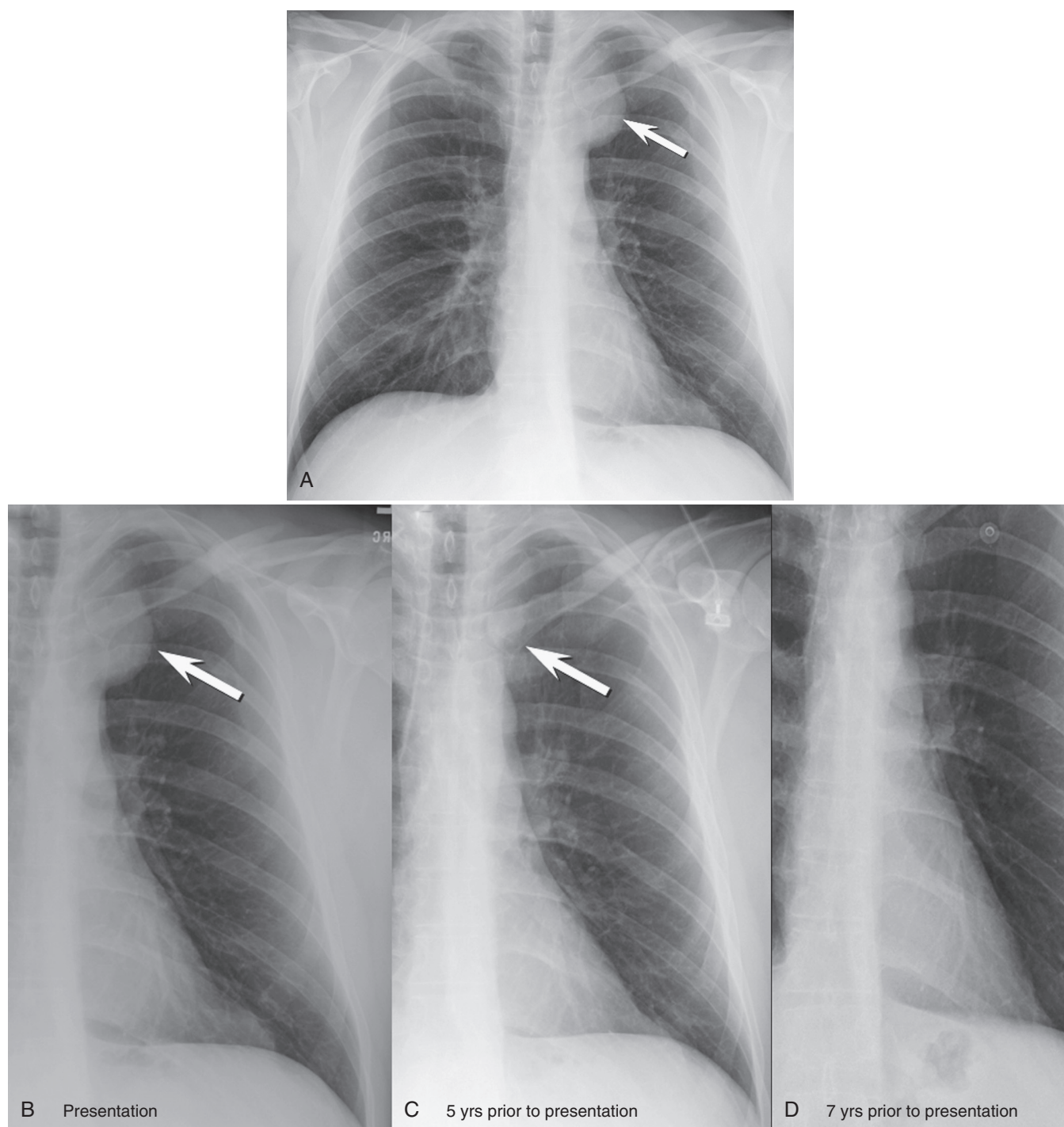
eFigure 83-38 Mediastinal lipomatosis. **A**, Frontal chest radiograph shows widening of the superior mediastinum (*arrows*), but the contours of the mediastinum are not lobulated, nor is the mediastinum abnormally dense. **B–E**, Axial enhanced chest CT shows abundant, unencapsulated mediastinal fat (*) on both sides of midline, without significant nodularity. (Courtesy Michael Gotway, MD.)



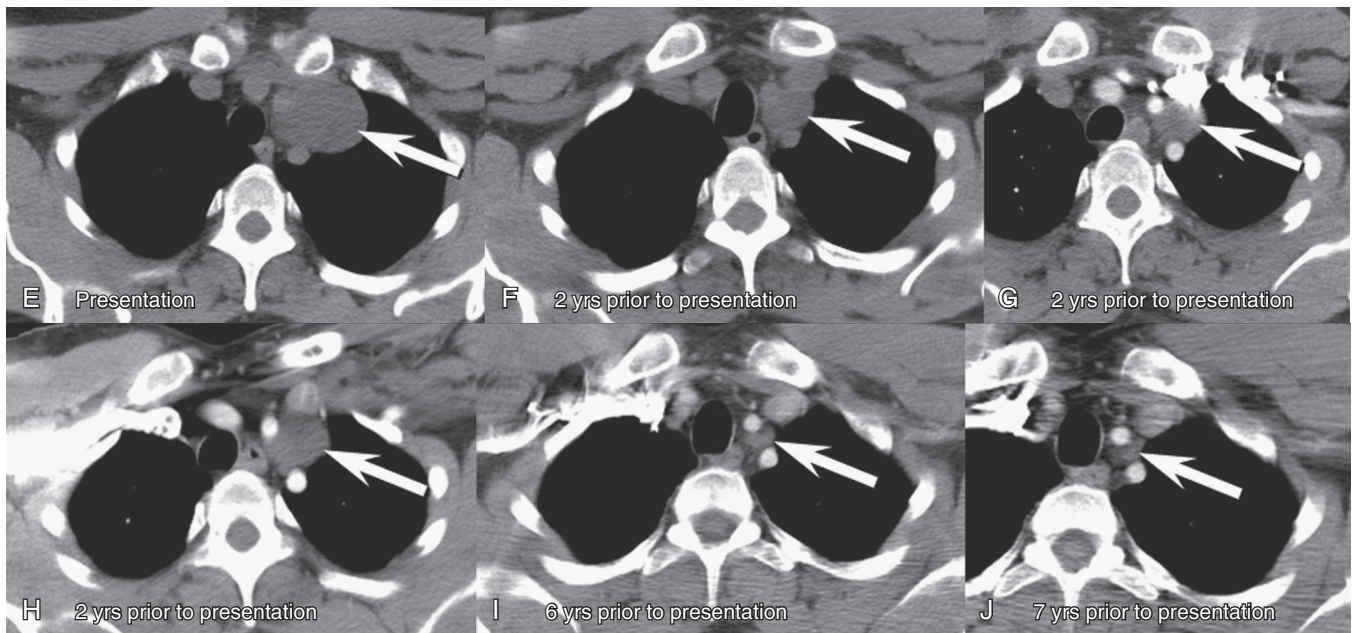
eFigure 83-39 Mediastinal lymphadenopathy in a patient with sarcoidosis. A–F, Axial enhanced chest CT shows mildly enlarged lymph nodes in multiple mediastinal stations: **A**, highest right paratracheal nodes (station 1R, *arrow*); **B**, upper right paratracheal nodes (station 2R, *arrow*), **C–E**, lower right paratracheal nodes (station 4R, *arrows*); **D**, lower left paratracheal nodes (station 4L, *thin arrow*, **D**) and aortopulmonary window nodes (station 5, *arrowhead*, **D**); **F**, subcarinal nodes (station 7, *double arrowheads*, **F**). (Courtesy Michael Gotway, MD.)



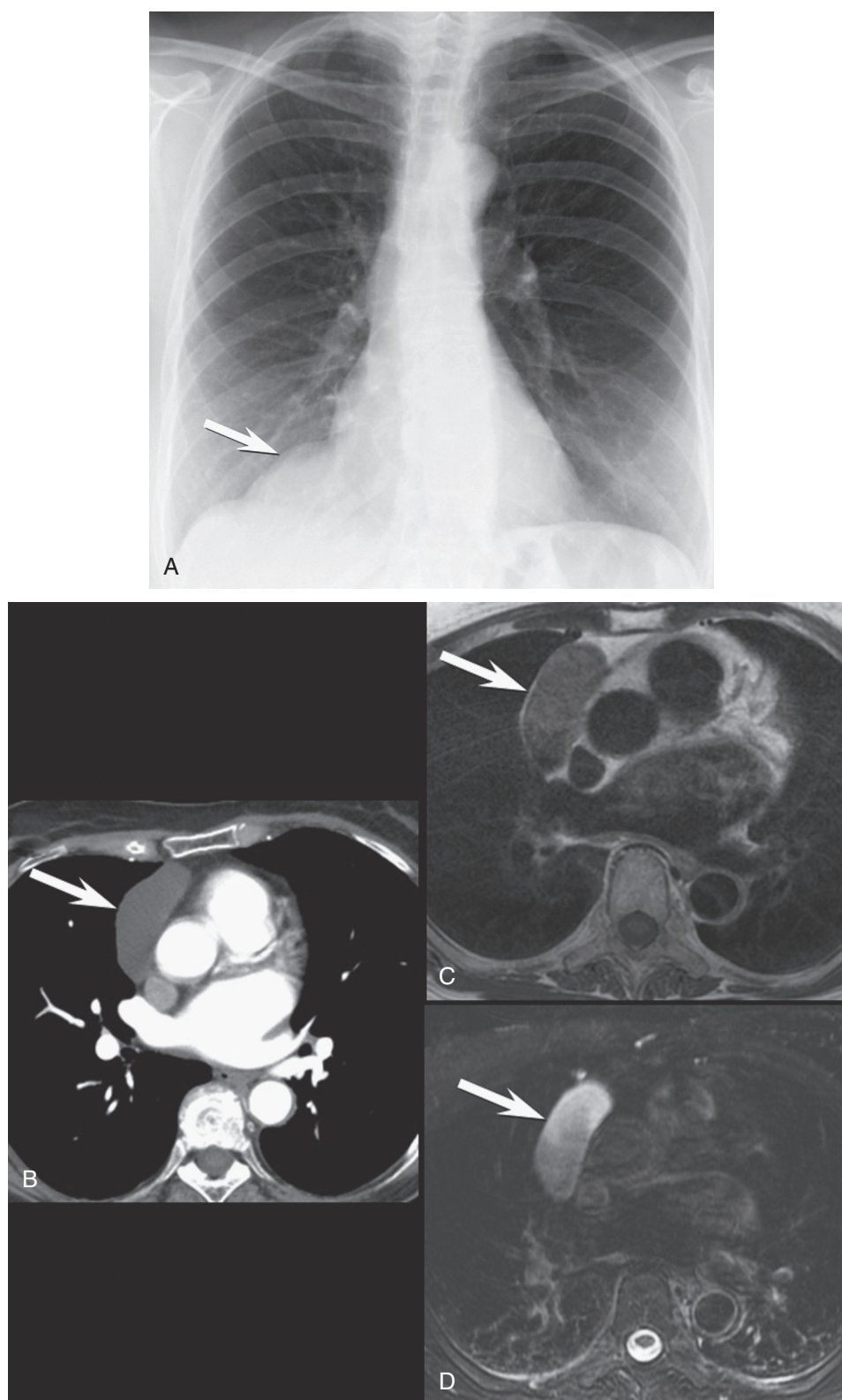
eFigure 83-40 Angiofollicular lymphoid hyperplasia (Castleman disease). **A**, Frontal chest radiograph shows a right paratracheal mass in a patient with an anterior chest wall stab wound, with penetrating entry site on the skin marked by a paper clip. **B**, Axial enhanced chest CT shows an enhancing right paratracheal mass with small foci of calcification, shown to reflect angiofollicular lymphoid hyperplasia at surgical resection. **C**, Axial enhanced chest CT (**C**), T1-weighted (**D**) and T2-weighted (**E**) magnetic resonance images in a different patient show a posterior mediastinal mass (arrows) shown to reflect angiofollicular lymphoid hyperplasia at surgical resection. (Courtesy Michael Gotway, MD.)



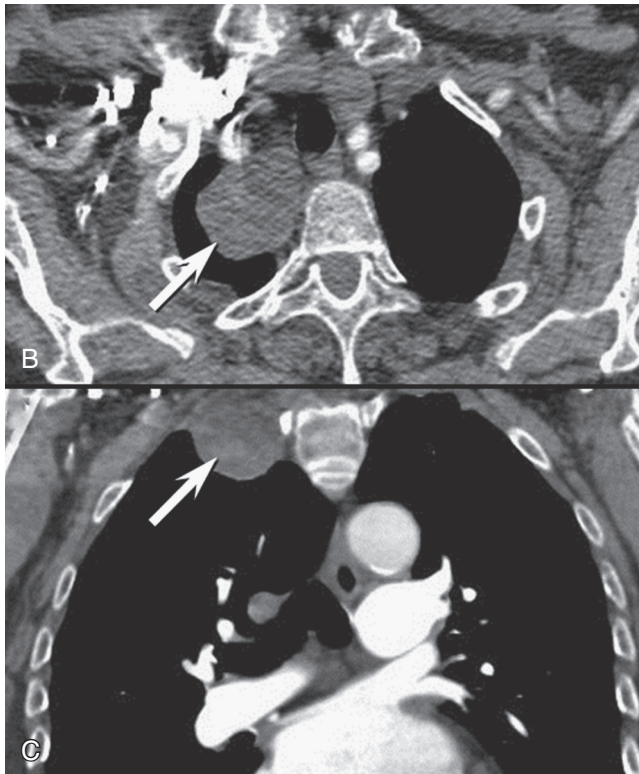
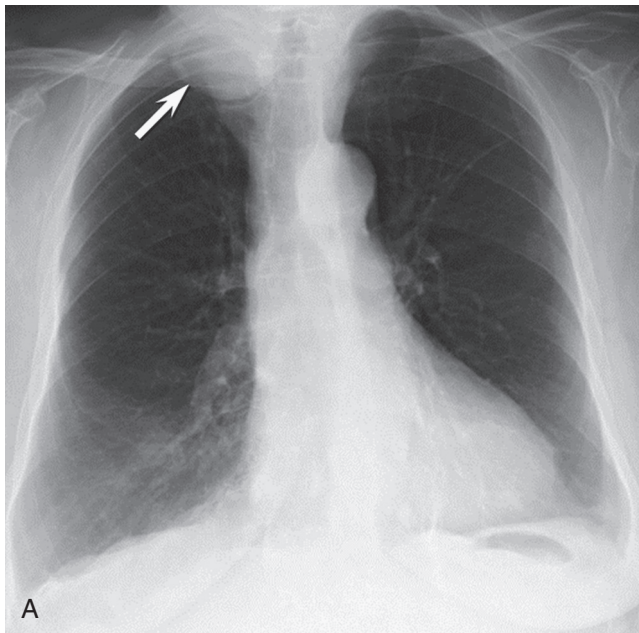
eFigure 83-41 Growth of a bronchogenic cyst over time. **A**, Frontal chest radiograph shows a smoothly circumscribed lesion (*arrow*) in the left superior mediastinum. **B–D** Retrospective review of serial chest radiographs obtained over the previous 7 years shows slow enlargement of the lesion.



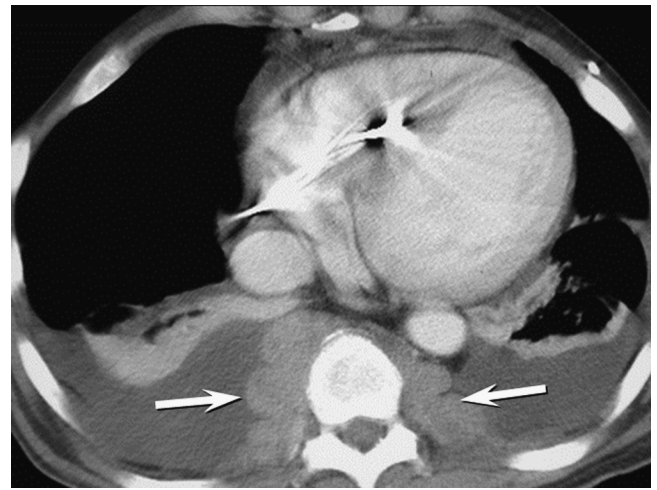
eFigure 83-41, cont'd E-J, Axial chest CT shows serial enlargement of the lesion over a 7-year period. (Courtesy Michael Gotway, MD.)



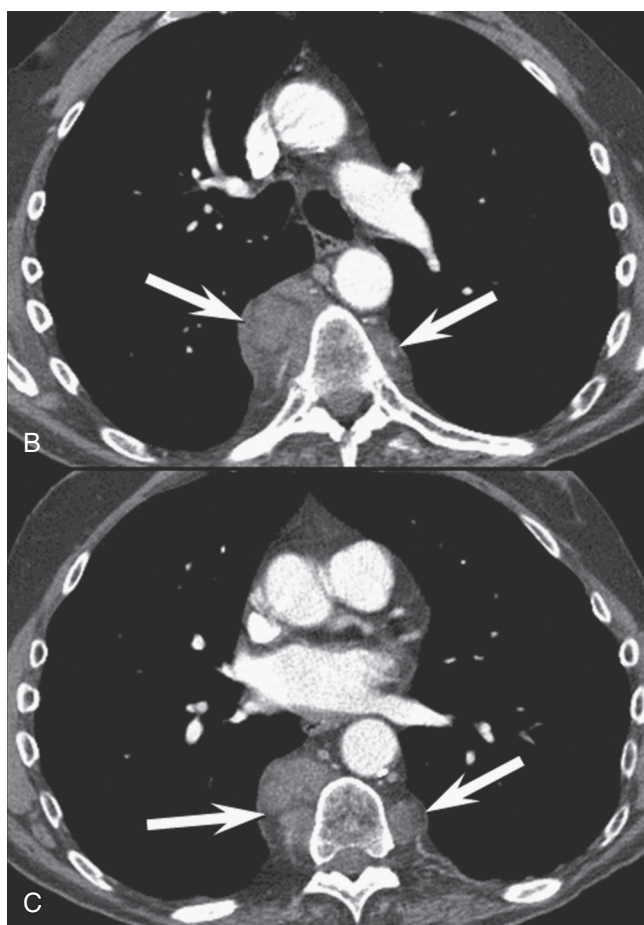
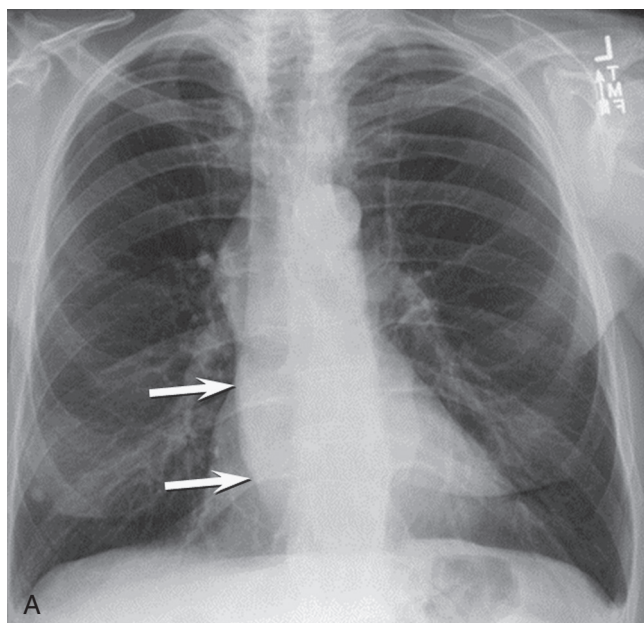
eFigure 83-42 Pericardial cyst. **A**, Frontal chest radiograph shows a smoothly circumscribed right cardiophrenic angle mass (*arrow*). **B**, Axial enhanced chest CT shows a homogeneous water density mass (*arrow*) abutting the right pericardium. Axial double inversion recovery T1-weighted (**C**) and axial triple inversion recovery (**D**) magnetic resonance images show fluid signal within the mass (*arrows*). Triple inversion recovery sequences (**D**) suppress fat signal, with water signal appearing bright (note the high signal of the cerebrospinal fluid posteriorly). The slight “shading” of the signal intensity posteriorly within the pericardial cyst may reflect debris or hemorrhage. (Courtesy Michael Gotway, MD.)



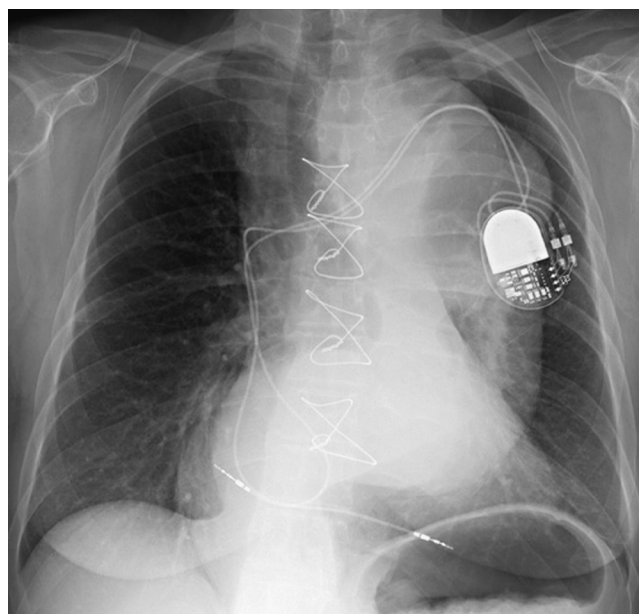
eFigure 83-43 Schwannoma. **A**, Frontal chest radiograph shows a smoothly circumscribed lesion (*arrow*) at the right thoracic apex. The extensive contact with the chest wall and lack of visualization of the superior border of the lesion (often referred to as the “incomplete border” sign) are consistent with a non-lung parenchymal origin. Axial (**B**) and coronal (**C**) enhanced chest CT shows a homogeneous low-attenuation lesion (*arrows*) in contact with the right superior mediastinum and chest wall. The lesion was shown to reflect schwannoma. See [Video 83-11](#) for the full studies. (Courtesy Michael Gotway, MD.)



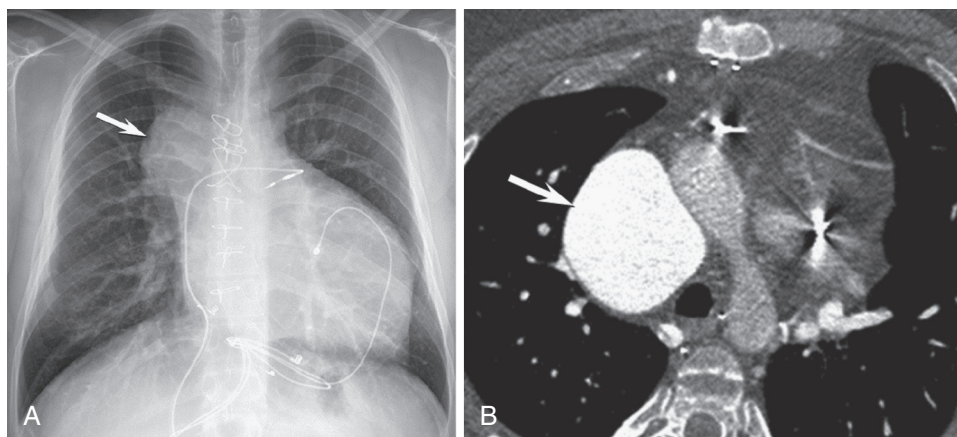
eFigure 83-44 Extramedullary hematopoiesis. Enhanced chest CT in a patient with thalassemia shows enhancing paravertebral soft tissue (*arrows*), representing extramedullary hematopoiesis. (Courtesy Michael Gotway, MD.)



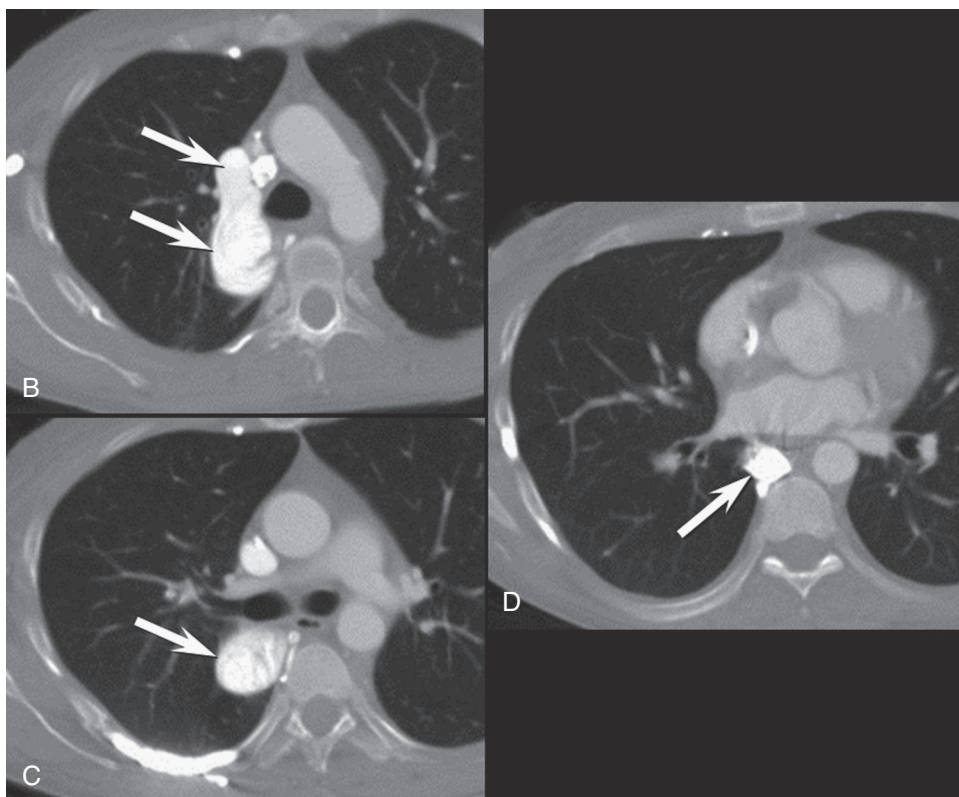
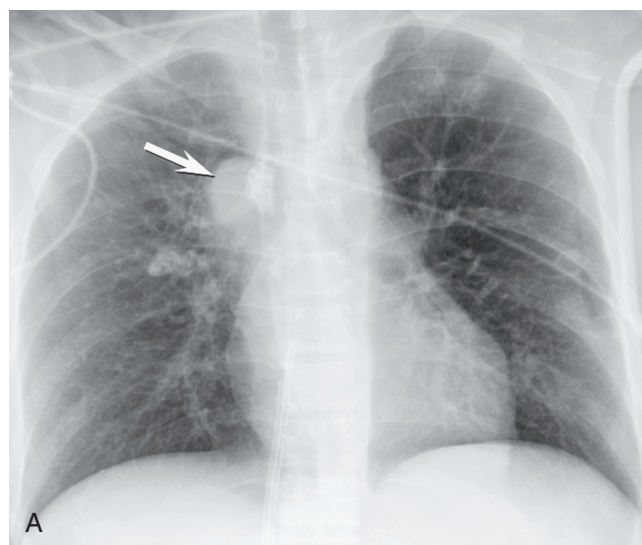
eFigure 83-45 Extramedullary hematopoiesis containing fat. **A**, Frontal chest radiograph in a patient with anemia shows an abnormal right-sided posterior mediastinal contour (*arrows*); a similar abnormal contour can be appreciated in the left retrocardiac region. The posterior mediastinal location is suggested by the relatively long contour abnormality without obscuration of the right heart border or lateral displacement of the right hilum. **B** and **C**, Axial enhanced chest CT shows bilateral posterior mediastinal masses (*arrows*) mixed with some areas of low attenuation, the latter consistent with fat. See [Video 83-12](#) for the full study. (Courtesy Michael Gotway, MD.)



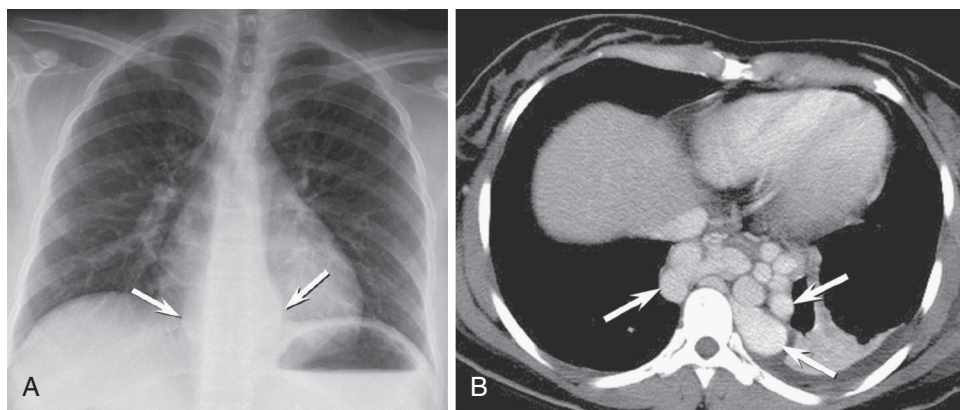
eFigure 83-46 Mediastinal mass caused by aortic aneurysm. Frontal chest radiograph shows a huge left-sided mediastinal mass without visualization of a normal thoracic aorta. See [Video 83-13](#) for an enhanced chest CT showing a huge aneurysm of the descending thoracic aorta with mural thrombus. (Courtesy Michael Gotway, MD.)



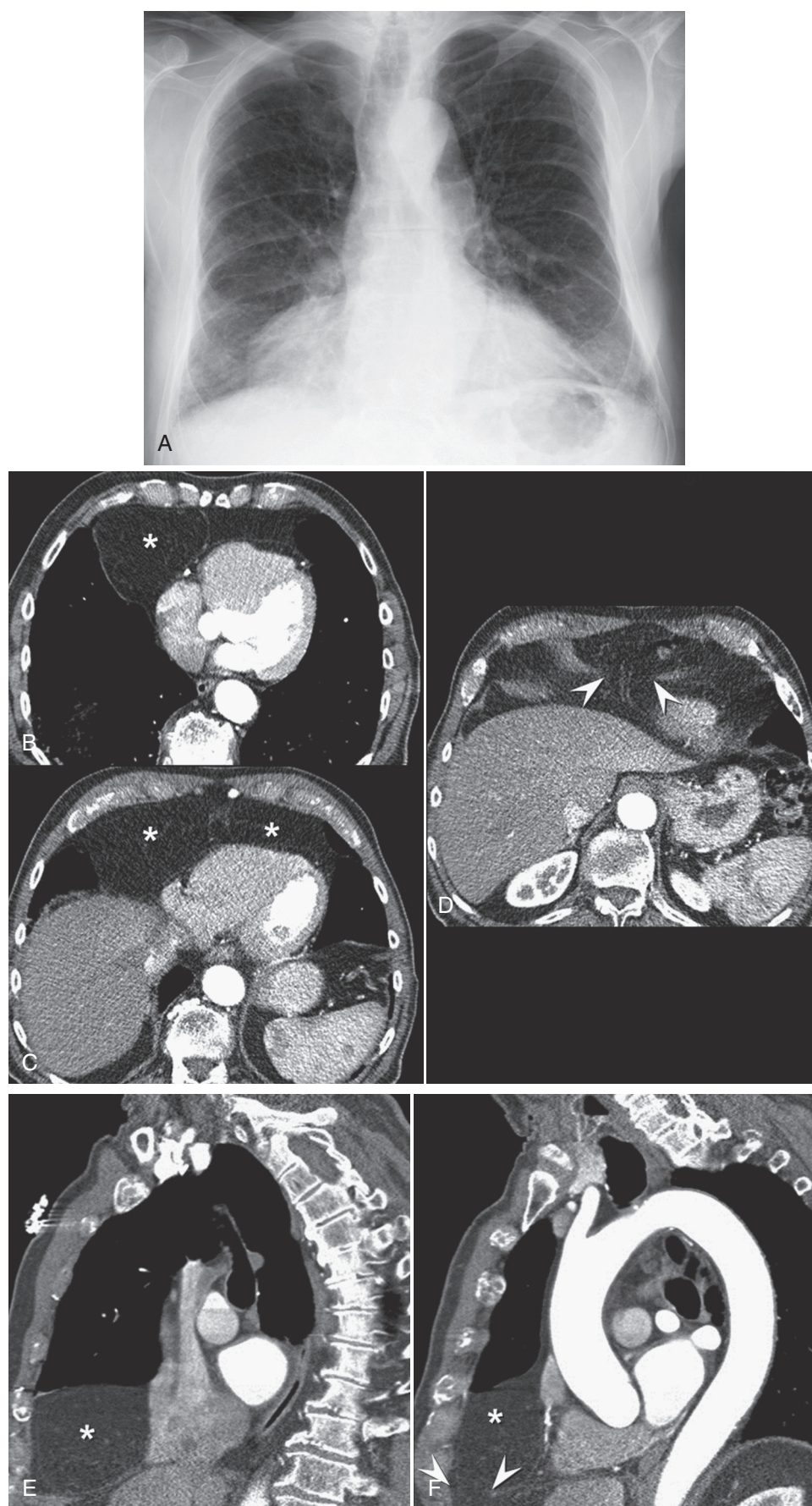
eFigure 83-47 Mediastinal mass caused by superior vena cava aneurysm. **A**, Frontal chest radiograph shows a right-sided mediastinal mass (*arrow*). Patient had undergone Glenn shunt (SVC-to-PA) for double outlet right ventricle. **B**, Axial enhanced chest CT shows a 6-cm aneurysm of the superior vena cava (*arrow*). (Courtesy Michael Gotway, MD.)



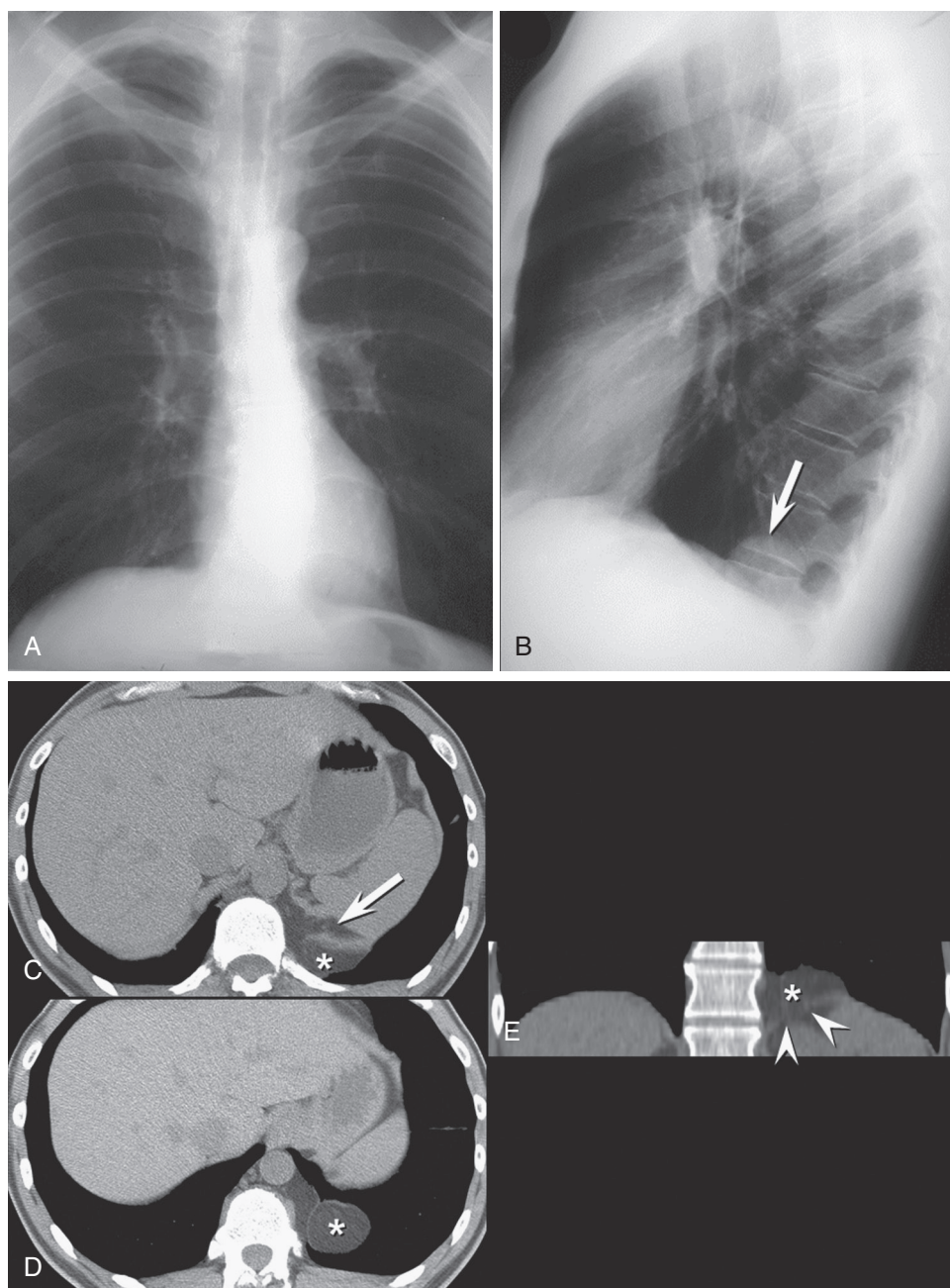
eFigure 83-48 Mediastinal mass caused by enlargement of the azygos vein. **A**, Frontal chest radiograph shows a mass (*arrow*) in the right tracheobronchial angle; this is the normal position of the anterior portion of the azygos vein. **B–D**, Axial enhanced chest CT shows dense contrast enhancement of the enlarged azygos vein (*arrows*). See [Video 83-14](#) for the full study. (Courtesy Michael Gotway, MD.)



eFigure 83-49 Mediastinal mass caused by esophageal varices. **A**, Frontal chest radiograph shows bilateral paraspinal line displacement (*arrows*) consistent with a posterior mediastinal mass. **B**, Axial enhanced chest CT shows that the posterior mediastinal mass is caused by periesophageal varices (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 83-50 Foramen of Morgagni hernia. **A**, Frontal chest radiograph shows a smoothly circumscribed right cardiophrenic angle mass. Axial (**B-D**) and sagittal (**E** and **F**) enhanced chest CT scans show that the right cardiophrenic angle mass (*) contains fat and originates within the abdomen, herniating into the thorax through an anteromedial diaphragmatic defect (*arrowheads*, **D** and **F**). Note that vessels, seen as thin linear hyperattenuating streaks, can be seen accompanying the fat herniation (**D**). See [Video 83-15](#) for the full axial study. (Courtesy Michael Gotway, MD.)



eFigure 83-51 Foramen of Bochdalek hernia. Frontal (**A**) and lateral (**B**) chest radiographs show a smoothly circumscribed contour abnormality along the posterior left diaphragm (*arrow, B*). The finding is difficult to appreciate on the frontal chest radiograph (**A**), but is readily seen on the lateral projection (*arrow, B*). Axial (**C** and **D**) and coronal (**E**) unenhanced chest CT shows that the lesion (*) consists entirely of fat, originating from the abdomen and extending into the posteromedial thorax through a diaphragmatic defect (*arrow, C, and arrowheads, E*). (Courtesy Michael Gotway, MD.)

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PNEUMOMEDIASTINUM AND MEDIASTITIS

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INTRODUCTION

GENERAL ANATOMIC CONSIDERATIONS

PNEUMOMEDIASTINUM

Pathophysiology
Clinical Settings and Syndromes
Clinical Manifestations and Diagnosis
Approach to Management

MEDIASTITIS

Acute Mediastinitis
Chronic Granulomatous Mediastinitis and
Mediastinal Fibrosis

INTRODUCTION

Pneumomediastinum and mediastinitis are disorders that involve the potential spaces and tissues of the mediastinum. Although both may be present at the same time, for example, after esophageal rupture, the term *pneumomediastinum* usually refers to the presence of aberrant air in the mediastinum without accompanying infection and *mediastinitis* refers to infection or inflammation regardless of the presence of air. These conditions are seen in a variety of unique clinical circumstances. Both tend to result from either breaches in the integrity of mediastinal structures or the spread to mediastinal structures from elsewhere in the body. Thus, anatomic considerations are similar for the two processes. However, the pathophysiology, clinical settings, management approaches, and clinical impact of pneumomediastinum and mediastinitis are quite different and are discussed separately.

GENERAL ANATOMIC CONSIDERATIONS

The mediastinum is traversed by the trachea and the esophagus, which are air-filled structures in direct communication with the outside world and may contain colonizing microorganisms. In addition, mediastinal lymph nodes drain the airways and lung parenchyma where inhaled organisms, antigens, and dusts are encountered. Consequently, entry of air or inflammatory and infectious materials into the mediastinum is readily accomplished by breaches in the integrity of these mediastinal structures or when materials deposited in the airways or distal lung are transported through the lymphatic system.

How air enters and moves through the mediastinum can be understood by referring to the soft tissue compartments of the neck, thorax, and abdomen, as illustrated in [Figure 84-1](#). The visceral space surrounding the trachea, esophagus, and great vessels in the neck continues into the chest to envelop the mediastinal viscera and passes through the diaphragm with the esophagus to communicate with the retroperitoneal space. This same space extends along the vessels and airways of the pulmonary hilum to merge with the distal bronchovascular sheaths (see [Fig. 84-1](#)).¹

Thus, it is possible for air or inflammation that reaches these tissue planes to dissect and spread to involve any of the mediastinal structures.

PNEUMOMEDIASTINUM

Pneumomediastinum consists of air or other gas in the mediastinum. Also known as *mediastinal emphysema*, it is one of several forms of aberrant extra-alveolar air that include subcutaneous emphysema, pulmonary interstitial emphysema, pneumopericardium, pneumoperitoneum, pneumoretroperitoneum, pneumocephalus, and pneumorachis (air in the spinal canal). Pneumothorax, the most common life-threatening form of extra-alveolar air, is discussed elsewhere (see Chapter 81).

Pneumomediastinum and subcutaneous emphysema were first recognized during childbirth. In her “Observations” of 1617 (as cited by Gordon²), Louise Bourgeois, midwife to the queen of France, wrote, “I saw that she tried to stop crying out, and I implored her not to stop, for fear that her throat might swell.” The first formal medical documentation of pneumomediastinum and subcutaneous emphysema during labor was by Simmons in 1784, and this association was reported in more than 130 patients by 1927.² Over the next 2 decades, Hamman^{3,4} had thoroughly established the clinical features of spontaneous pneumomediastinum and Macklin and Macklin⁵ had elegantly elucidated its pathophysiology. Little has been added to the pioneering descriptions of these investigators, but pneumomediastinum and other forms of extra-alveolar air are seen today in a greater variety of clinical circumstances. These include mechanical ventilation and other situations in critical care, decompression injury diving, chest trauma, and asthma.¹

PATHOPHYSIOLOGY

The pathophysiology of pneumomediastinum depends on the clinical circumstances in which it is encountered. Pneumomediastinum most commonly results from alveolar rupture but can also result from air escaping from the upper respiratory tract, intrathoracic airways, or gastrointestinal tract. Gas can be generated by certain infections, and outside air can reach the mediastinum after trauma or

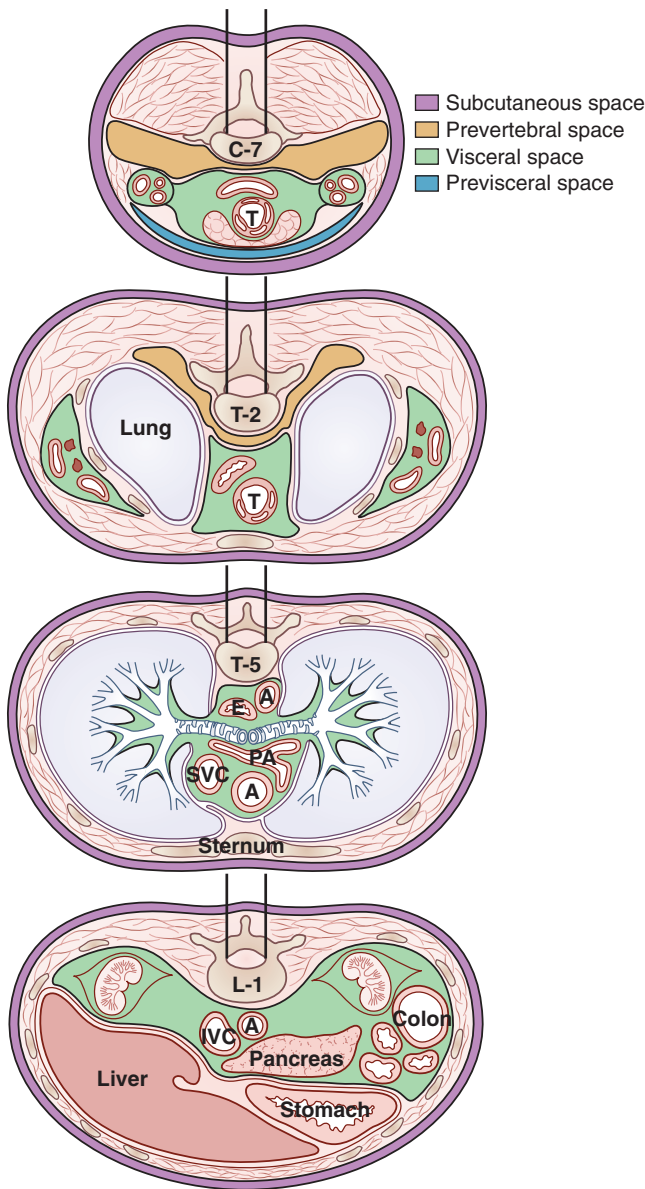


Figure 84-1 Mediastinal compartments. Soft tissue compartments of the mediastinum (at levels of T2 and T5) in relation to those of the neck (at level of C7) and the upper abdomen (at level of L1) demonstrate continuity of the visceral space (shown in light green). A, aorta; E, esophagus; IVC, inferior vena cava; PA, pulmonary artery; SVC, superior vena cava; T, trachea. (Redrawn from Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema: pathophysiology, diagnosis, and management. *Arch Intern Med* 144:1447–1453, 1984.)

surgery. These potential sources for mediastinal emphysema are summarized in [Table 84-1](#) and discussed in the following sections.

Air Originating from the Upper Respiratory Tract

Mediastinal air dissecting downward from the head and neck can originate in several ways. Retropharyngeal abscess is a long-established cause of gas in the neck, but other infections including dental abscess, cervical adenitis, salivary gland infection, tonsillitis, and osteomyelitis of the facial bones can also produce this finding.^{1,6} Odontogenic infections are said to be the most common of these.⁷

Dental extractions or drilling can be followed by pneumomediastinum. Passage of air into the soft tissues from the socket of an extracted tooth can be increased dramatically if positive pressure is applied at the mouth—as illustrated by the case of a soldier whose neck swelled on resumption of his duties as a bugler immediately after a tooth extraction.⁸

Injury to the paranasal sinuses, orbit, mandible, and other facial bones adjacent to the upper airways can provide access of air to the fascial planes of the neck, especially following nose blowing. Surgical procedures involving the upper respiratory tract may produce air in the neck via breaches in either the oropharyngeal mucosa or the trachea. For instance, pneumomediastinum and subcutaneous emphysema are common after tracheotomy; these findings were noted in 13% of cases in one prospective series in adults.⁹

Pneumomediastinum can also arise following traumatic attempts at endotracheal intubation or after overinflation of the endotracheal tube cuff when the hypopharyngeal mucosa or membranous trachea is injured ([eFig. 84-1](#)).¹⁰ Tracheal injury and esophageal rupture leading to pneumomediastinum can also happen when air is forced into the open mouth.^{11,12}

Air Originating from the Intrathoracic Airways

Blunt thoracic trauma, particularly deceleration injury as sustained in motor vehicle crashes, may lacerate or fracture the trachea or main bronchi and allow air to enter the mediastinum ([eFig. 84-2](#) and [Video 84-1](#); see [eFig. 76-10](#) and [Video 76-3](#)).¹³ Although the trachea may be damaged proximally, the majority of such injuries are within 3 cm of the carina, probably owing to the relative fixation of the airway at the carina and the development of a shearing force when the more mobile parts are displaced by the sudden impact.

Other potential sources of mediastinal air from the major intrathoracic airways include perforation by an aspirated foreign body and erosion by bronchogenic or esophageal neoplasm. Visceral perforation is associated more frequently with esophagoscopy than with bronchoscopy. However, the increasing use of bronchoscopic biopsy techniques and therapies for bronchial obstruction render this source for mediastinal air increasingly likely.

Air Originating in the Lung Parenchyma

Most instances of pneumomediastinum are the result of alveolar disruption. Alveoli may be disrupted after direct injury to the lung parenchyma, which allows air to escape from torn alveoli and terminal bronchioles, after surgery, when air can escape from cut surfaces, or when the lung is nicked in the course of central venous access procedures, or percutaneous or transbronchial lung biopsy. The majority of cases of alveolar disruption leading to pneumomediastinum, however, is from “spontaneous” alveolar rupture.

Mechanism of “Spontaneous” Alveolar Rupture. Disruption of alveolar walls and entry of air into the bronchovascular bundle can result when a pressure gradient becomes sufficient to disrupt the alveolar walls at their bases and force air into the pulmonary interstitium, as depicted in [Figure 84-2](#).^{1,5,14} Although it has been speculated that an increase in intra-alveolar pressure alone was

Table 84-1 Origins of Air in the Mediastinum**UPPER RESPIRATORY TRACT**

Head and neck infection (odontogenic, salivary glands, cervical adenitis, tonsillitis, peritonsillar abscess, osteomyelitis of facial bones)
 Fractures (involving paranasal sinuses, orbit, mandibles, other facial bones)
 Other mucosal disruption (trauma, surgery, attempted endotracheal intubation)
 Dental procedures (extractions, air-turbine drilling)

INTRATHORACIC AIRWAYS

Blunt or penetrating chest trauma
 Foreign body
 Iatrogenic (bronchoscopy, bronchial brushing, transbronchial biopsy, needle aspiration)
 Neoplasm

LUNG PARENCHYMA

Direct disruption of alveoli (penetrating trauma, surgery, transbronchial biopsy, needle aspiration)
 "Spontaneous" alveolar rupture (between alveolus and adjacent bronchovascular bundle)

GASTROINTESTINAL TRACT

Esophageal perforation
 Via pneumoperitoneum or pneumoretroperitoneum (gastric or intestinal perforation, diverticulitis, pneumatosis cystoides intestinalis, endoscopy, biopsy, infection)

EXTERNAL TO THE BODY

Penetrating trauma to neck or chest
 Surgical procedures (tracheotomy, mediastinoscopy, sternotomy)
 Via subcutaneous emphysema in association with chest tube insertion

INFECTION WITH GAS-PRODUCING ORGANISMS

Acute bacterial mediastinitis
 Head and neck infections

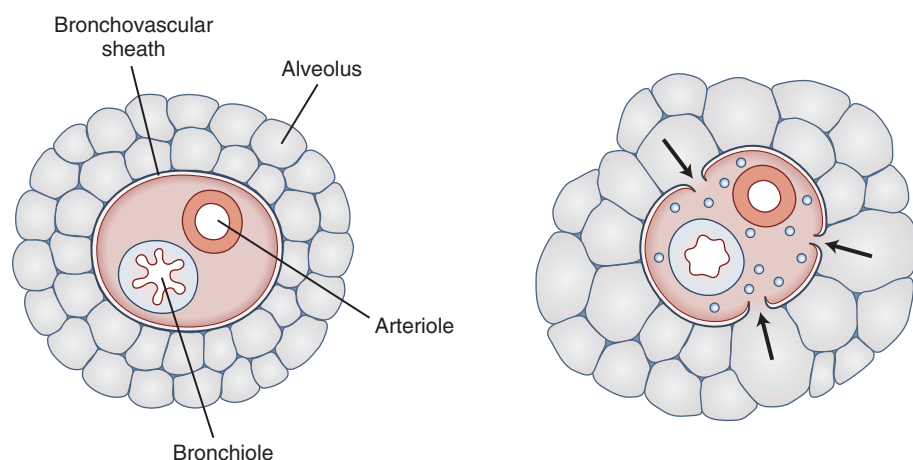


Figure 84-2 Extra-alveolar air movement into the bronchovascular bundle. Schematic diagram shows the mechanism of alveolar rupture across the bronchovascular sheath resulting from a pressure gradient between them. (Redrawn from Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema: pathophysiology, diagnosis, and management. *Arch Intern Med* 144:1447–1453, 1984.)

capable of producing alveolar rupture, animal experiments have demonstrated that an increase in alveolar volume, due to increased *transpulmonary* pressure, is a more important determinant of disruption of the alveolar walls.¹⁵ This finding may explain the rarity of alveolar rupture following coughing and sneezing; contraction of muscles of the chest and abdominal walls counter the transient high intra-alveolar pressures, and transpulmonary pressures and alveolar volume do not increase.¹⁶

With decompression, when there are decreases in external pressure, high alveolar volumes undoubtedly contribute to alveolar rupture.^{16,17} The mechanism of alveolar rupture presumably relates to overdistention due to the expansion of gas trapped in the lungs during ascent.^{18,19}

Underlying disease of the lungs is probably also important. Pneumomediastinum and other forms of extra-alveolar air arising from the lung are almost always associated with parenchymal abnormalities in the affected lung both during mechanical ventilation^{16,20} and during spontaneous ventilation.^{1,5}

Spread of Air following Alveolar Rupture. Entry of air into the bronchovascular bundle, as depicted schematically in Figure 84-2, produces pulmonary interstitial emphysema (eFig. 84-3). This is the initial consequence of alveolar

rupture and may be the only overt manifestation of extra-alveolar air. According to Munsell,²¹ Laennec called this condition "interlobular emphysema." Because the mean pressure in the mediastinum, like that in the pleural space, is always somewhat negative with respect to the pressure in the pulmonary parenchyma, the pressure difference causes air to move toward the mediastinum.²² This is illustrated in Figure 84-3 and convincingly described in the 1944 paper by Macklin and Macklin,⁵ which first confirmed the sequence in experimental animals:

The first step ... was air passing through numerous minute ruptures in the strained bases of the alveoli of the overinflated region into the underlying vascular sheaths. The air bubbles, at the very first minute, moved along the vascular sheaths, coalescing and gaining in size. This streaming of air through the pulmonic interstitium reminded one of the flow of a river that ever increases in size by addition of new tributaries as it proceeds on its course. Reaching the root of the lung, the train of air bubbles passed into and distended the mediastinum. With continued insufflation an actual overflow into the retroperitoneum, anterior mediastinum and subcutaneous tissues of the root of the neck and axillae occurred. In extreme cases the mediastinal wall ruptured, producing a pneumothorax.

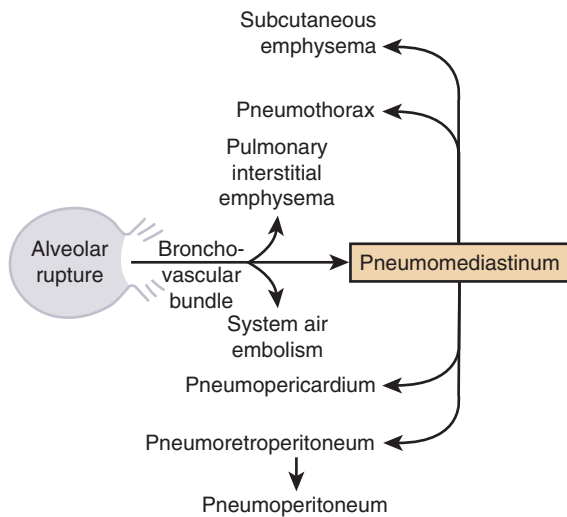


Figure 84-3 Extra-alveolar air movement throughout the body. The movement of air from alveoli to extra-alveolar sites showing the likely sequence for development of the different forms of extra-alveolar air following alveolar rupture.

These classic observations have since been confirmed in more recent studies but, conceptually, little has been added.

Entry of Air into the Pleural Space. Once in the mediastinum, air follows the path of least resistance and may rupture through the delicate mediastinal fascia and overlying pleura into the pleural space. This model is supported by observations that, in animal experiments, lower sustained inflation-hold pressures were required to produce pulmonary interstitial emphysema than to create a pneumomediastinum or pneumothorax and that, in most mechanically ventilated patients in one clinical series, pneumomediastinum preceded pneumothorax.²³ Another proposed mechanism for pneumothorax suggests that air dissects toward the periphery of the lung rather than toward the mediastinum and ruptures via subpleural blebs through the visceral surface of the lung. Which of these mechanisms most often accounts for “spontaneous” pneumothorax is uncertain.

Entry of Air into the Abdomen. Extra-alveolar air originating from disrupted alveoli may appear below the diaphragm as either pneumoperitoneum or pneumoretroperitoneum (eFig. 84-4).²⁴ To reach the retroperitoneal space, air from the mediastinum usually travels via the loosely packed paraesophageal connective tissue across the diaphragm. The retroperitoneal air may then break through the peritoneum to enter the peritoneal space.

Air Originating in the Gastrointestinal Tract

Mediastinal air can also originate from the gastrointestinal tract, either above or below the diaphragm. In *Boerhaave syndrome*, rupture of the esophagus allows air and other material to enter the mediastinum (eFig. 84-5).²⁵ In this circumstance, pneumomediastinum is accompanied by acute mediastinitis, as discussed later in this chapter. Pneumomediastinum can also result from esophageal perforation during upper gastrointestinal endoscopy²⁶ or following

the ingestion of a caustic such as paraquat²⁷ or lye (sodium hydroxide). Spontaneous pneumomediastinum is a rare presentation of achalasia.²⁸

Rarely, air or other gas originating in the retroperitoneal space can spread to the mediastinum.¹ Retroperitoneal causes of pneumomediastinum include perforation of a duodenal ulcer, ulcerative colitis, colonic diverticulitis (see eFig. 84-4), pneumatosis cystoides intestinalis, “rectal barotrauma”²⁹ and procedures such as sigmoidoscopy, colonoscopy, and barium enema.³⁰

Air Originating from External and Miscellaneous Sources

Pneumomediastinum can arise from air entering the body from external sources, particularly if positive pressure is applied at the subcutaneous tissue planes. Air can reach the mediastinum via the cervical soft tissues during tracheotomy,⁹ via the chest wall during arthroscopic shoulder surgery,³¹ or via the extremities as a result of industrial accidents.³² Mediastinal air can also arise from a pneumothorax by an unusual mechanism: air in the pleural space can reach the subcutaneous tissues via a tube thoracostomy tract, can dissect to the neck, and can then penetrate down into the mediastinum. Pneumomediastinum has also been observed following the insufflation of air into the peritoneal cavity for tuberculosis treatment,³³ during the course of modern era laparoscopy,³⁴ and via the female genital tract during pelvic examination,³⁵ douche,³⁶ postpartum exercise,³⁷ or blowing into the vagina,³⁸⁻⁴⁰ especially during pregnancy.⁴¹

Gas can form in the mediastinum during acute bacterial mediastinitis caused by gas-producing microbes. More commonly, however, pneumomediastinum associated with mediastinitis is due to communication with the gastrointestinal tract (as in Boerhaave syndrome), respiratory tract (as in necrotizing pneumonia), or outside air (as in traumatic or poststernotomy mediastinitis). These conditions are described in more detail later in this chapter.

CLINICAL SETTINGS AND SYNDROMES

Pneumomediastinum can be categorized as spontaneous or secondary. *Spontaneous* pneumomediastinum develops without an obvious etiology but may nonetheless have a predisposing condition or precipitating factor. Spontaneous pneumomediastinum is most frequently seen in young adults and is usually a benign, self-limited condition. In contrast, *secondary* pneumomediastinum arises from a specific pathologic event such as barotrauma from mechanical ventilation, intrathoracic or iatrogenic trauma, infection, or other acute conditions. Compared to spontaneous pneumomediastinum, secondary pneumomediastinum carries higher morbidity and mortality, likely due to the underlying etiology. Thus, in cases without an obvious precipitant, it is important to investigate for possible underlying causes of secondary pneumomediastinum (Table 84-2).⁴²

Spontaneous Pneumomediastinum

Predisposing Conditions. Underlying lung diseases are present in 25% to 44% of patients with spontaneous pneumomediastinum, as shown in two cohorts.^{42,43} Of those with lung disease, more than half had evidence of

Table 84-2 Spontaneous and Secondary Pneumomediastinum

Spontaneous	Secondary
VOLUNTARY ALTERATION IN BREATHING PATTERN	BAROTRAUMA
Marijuana smoking and cocaine inhalation	Mechanical ventilation
Pulmonary function testing	Noninvasive mechanical ventilation
Mountain climbing—"voluntary pressure breathing"	Manual ventilation during resuscitation, anesthesia, or transport
Wind instrument playing	Equipment malfunction or misconnection in anesthesia or oxygen therapy
Yelling, shouting, and singing	Heimlich maneuver
INVOLUNTARY ALTERATION IN BREATHING PATTERN	Deceleration injury
Childbirth	INVASIVE PROCEDURES
Vomiting	Esophageal perforation
Seizures; status epilepticus	Endobronchial needle aspiration
Violent coughing; sneezing; hiccupping	
Heavy lifting; athletic competition	
Straining at stool	
INTRINSIC AIRWAY AND LUNG DISEASE	
Asthma	
Atelectasis	
Bronchiolitis	
Pneumonia	
Influenza	
Measles	
Tuberculosis	
Silicosis	
Foreign body	
Tumor	

interstitial lung disease (eFig. 84-6). Other parenchymal diseases associated with pneumomediastinum include atelectasis,⁵ bronchiolitis,^{44,45} pneumonia,^{46,47} influenza,^{5,21} measles,⁴⁸ and hematogenous tumor metastases.⁴⁹

Obstructive lung diseases, especially acute asthma, are a well described predisposing factor leading to pneumomediastinum. On rare occasions, pneumomediastinum during asthma exacerbations can lead to life-threatening respiratory and hemodynamic compromise.^{50,50a} Although chest radiographs are not routinely obtained during attacks of asthma, pneumomediastinum was noted in 5.4% of 479 radiographs of children admitted with asthma attacks.⁵¹

Cigarette smoking has been implicated as a predisposing factor in spontaneous pneumomediastinum, although the mechanism is unclear.^{42,52}

Precipitating Factors. Voluntary manipulations of the breathing pattern can sometimes lead to alveolar rupture. "Voluntary pressure breathing," a practice originally proposed for fliers during World War II, consisted of slow, deep inhalations followed by forced exhalation through tightly pursed lips. This maneuver was also advocated by some mountain climbers as a means of getting more oxygen into the blood. However, this maneuver may lead to alveolar rupture. Patients with pneumomediastinum reported by Vosk and Houston⁵³ were members of the same climbing party who had both practiced "voluntary pressure breathing" during ascent.

Inhalational drug use is commonly cited as a precipitating factor in spontaneous pneumomediastinum.^{43,52} A typical example is pneumomediastinum after vigorous straining against a closed glottis during marijuana smoking⁵⁴ or after inhaling free-base cocaine,^{55,56} during which users sometimes add additional external airway pressure by having an accomplice blow vigorously into their mouths through a cardboard tube.⁵⁷ Of note, given the direct toxic effect of cocaine on lung parenchyma, some authors argue that pneumomediastinum following cocaine inhalation should be considered secondary.⁵² Recreational inhalation of nitrous oxide from disposable canisters was also reported as a cause of pneumomediastinum in two college fraternity brothers.⁵⁸

Involuntary manipulations of the breathing pattern are more common precipitating factors than voluntary maneuvers. Such causes of pneumomediastinum include straining or exertion such as during childbirth²; vomiting in association with bulimia,⁵⁹ hyperemesis gravidarum,⁶⁰ and diabetic ketoacidosis⁶¹; and prolonged straining during convulsive seizures,⁶² athletic competition,^{63,64} and violent coughing,⁶⁵ sneezing, hiccupping; and straining at stool.^{1,5} It is reasonable to expect that any activity producing large momentary swings in intrathoracic pressure could result in alveolar rupture leading to pneumomediastinum.

No Predisposing Condition or Precipitating Factor.

Although a history of a potential predisposing event or disease process is elicited in most patients with "spontaneous" pneumomediastinum, a few cases have been described without such associations and are known as *Hamman syndrome*. Hamman's original patient was a 51-year-old physician in whom no predisposing factor could be identified.³ Hamman later reported several additional cases of truly "idiopathic" pneumomediastinum; in modern series, cases have been reported despite normal lung parenchyma as determined by chest *computed tomography* (CT).^{3,66}

Secondary Pneumomediastinum

Mechanisms for secondary pneumomediastinum include blunt thoracic trauma, perforation of the esophagus or other viscus from invasive procedures, or unusual cases due to pathology in the neck, thorax, or abdomen,^{66a} as described previously.

Barotrauma. Barotrauma during mechanical ventilation accounts for up to one third or more of cases of secondary pneumomediastinum in recent studies.⁴² Alveolar rupture during positive-pressure ventilation is thought to result from overdistention in an area with abnormal airways or lung parenchyma. Subsequent dissection of air proximally toward the mediastinum results in pneumomediastinum, and rupture through the mediastinal pleura leads to the development of pneumothorax. Before the era of low tidal volume ventilation, barotrauma developed in almost a one fourth of mechanically ventilated patients and was associated with high mortality.²³ Historically, large delivered tidal volumes and high levels of positive end-expiratory pressure were thought to predispose mechanically ventilated patients to barotrauma, but these associations were likely related to the severity of the underlying lung disease.^{16,67,68} Gammon and others have shown the *acute*

respiratory distress syndrome (ARDS) was the condition most commonly associated with barotrauma and, among ventilated patients, was the only independently associated risk factor for barotrauma.^{23,69} Ventilator settings, including tidal volume, peak and plateau airway pressures, have not been found to be associated with barotrauma in a heterogeneous population of mechanically ventilated patients.⁷⁰ Although rates of barotrauma in low tidal volume (6 mL/kg) lung-protective ventilation strategies are reported to be the same as in traditional tidal volumes (12 mL/kg) in large clinical trials,⁶⁸ the overall rate of barotrauma appears to be lower when compared with historical references and clinician experiences.^{23,68}

Noninvasive forms of positive-pressure ventilation are less often associated with barotrauma than is conventional mechanical ventilation. This is probably because of the lower airway pressures used and the less severe lung diseases being treated. For instance, continuous positive airway pressure applied by mask was associated with pneumomediastinum in only 1 of 331 applications of this therapy, as cited in one review.⁷¹

Air or oxygen inadvertently insufflated under high pressure, as for example during manual ventilation during cardiopulmonary resuscitation, is especially likely to cause barotrauma. Improperly connected oxygen tubing preventing exhalation has resulted in life-threatening barotrauma,⁷² as have similar errors following anesthesia and surgery.^{73,74}

Deceleration injury, even when there is no open chest wound or displaced rib fracture, can cause barotrauma. Although such deceleration injuries most commonly result from motor vehicle accidents, they can also follow blows to the chest or falls into water with the glottis closed.^{14,75} Pneumomediastinum has also been caused by resuscitation using the Heimlich maneuver.⁷⁶

Infections. Infectious etiologies of secondary pneumomediastinum include mediastinitis with gas-forming organisms, *Pneumocystis jirovecii* pneumonia patients infected with human immunodeficiency virus (eFig. 84-7), or pneumonia with cavitary lesions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms, Physical Signs, and Laboratory Findings

Chest pain is the most common symptom reported by patients with pneumomediastinum.^{1,66} It has been reported in the majority of patients with “spontaneous” pneumomediastinum and may account for some cases of unexplained acute chest pain in otherwise healthy young people.^{66,77} The pain is characteristically substernal in location and aggravated by movement, breathing, and position changes. It often radiates to the back, shoulder, or arm. Discomfort may extend into the neck, and retropharyngeal or perilaryngeal air dissection may give rise to dysphagia or dysphonia, with characteristic muffled voice. Dyspnea and cough are also common symptoms.⁶⁶ In half of the cases, physical examination reveals palpable crepitation in the neck and supraclavicular area,⁷⁷ and cyanosis and neck vein distention have also been observed.²¹ *Hamman sign*, or Hamman’s

crunch,^{21,78} is a crunching or clicking sound synchronous with the heartbeat, heard over the precordium, and increased in intensity during inspiration and in the left lateral decubitus position.^{1,21,79} It has been described as similar to the noise produced by rubbing two rubber balloons together.²¹ Although considered by Hamman to be pathognomonic for the presence of mediastinal air, it can occasionally be heard in other circumstances such as with pneumothorax without radiographic evidence for pneumomediastinum.¹

Low-grade fever, along with mild to moderate leukocytosis,^{1,21} likely results from reactive inflammation associated with air dissecting in the mediastinum. In one series, leukocyte counts were reported to be greater than 10,000/mm³ in 16 of 23 patients and greater than 20,000/mm³ in 5 of 23, returning to normal without treatment within 1 to 2 days.²¹

Electrocardiographic changes are seen in some cases of pneumomediastinum without evidence of other cardiac abnormalities.²¹ The electrocardiogram may show diffusely low voltage, nonspecific axis shifts, ST-T wave changes, and ST segment elevation in the lateral precordial leads.²¹ These changes are also observed in association with pneumothorax and may be in part related to physical displacement of mediastinal structures.

Radiographic Features

Pneumomediastinum is most often detected by chest radiography and the finding of pneumomediastinum may be the first manifestation of extra-alveolar air. The diagnosis is usually made by demonstrating a thin line of radiolucency, best seen along the left heart border (Fig. 84-4 and eFig. 84-8A; see eFig. 84-5A).¹ Other common signs are the highlighting of the aortic arch, which is surrounded by increased radiolucency, and the “continuous diaphragm”

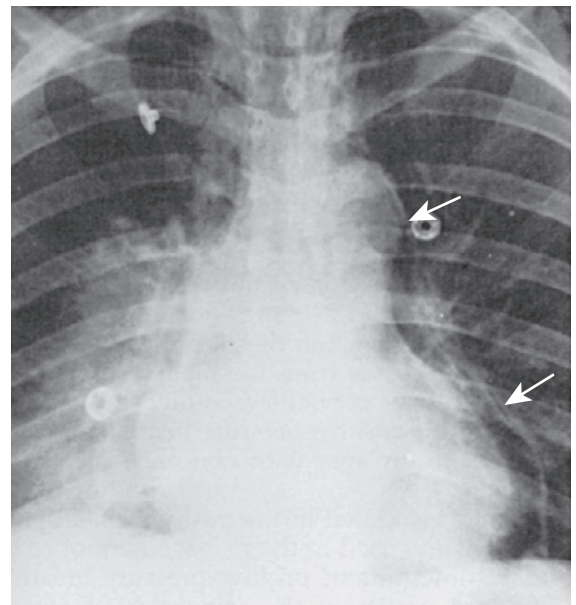


Figure 84-4 Pneumomediastinum. Chest radiograph of a 47-year-old man in whom mediastinal emphysema developed while he was hospitalized for treatment of right lower lobe pneumonia; image shows displacement of the mediastinal pleura by air (arrows).

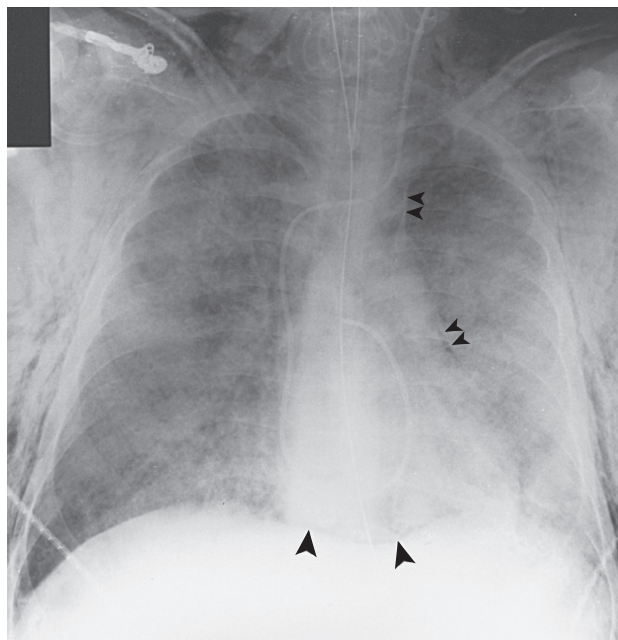


Figure 84-5 Pneumomediastinum. The “continuous diaphragm” sign in a patient with pneumomediastinum that developed during mechanical ventilation for acute respiratory distress syndrome. An unbroken radiolucent line (*large arrowheads*) is visible from one hemidiaphragm to the other, rendering the inferior heart border clearly visible. Air is also present in the mediastinum (*small arrowheads*) and in the soft tissues of the shoulders, neck, and chest wall.

sign,⁸⁰ an unbroken radiolucent line extending from one hemidiaphragm to the other beneath the heart (Fig. 84-5 and see eFig. 84-8B). Mediastinal air may be easier to see on films obtained with the patient in lateral projection, which may demonstrate retrosternal air or vertical lucent streaks outlining the aorta, pulmonary artery (the so-called ring-around-the-artery sign; see eFig. 84-8C and D), or other mediastinal structures.¹ Less commonly encountered chest radiographic findings of pneumomediastinum include the “extrapleural air” sign (see eFig. 84-8E and F), Nacle-rio’s “V” sign (see eFig. 84-8G), elevation of the residual thymus (typically in younger patients, referred to as the *thymic spinnaker-sail sign*; see eFig. 84-8H-J), and air or gas trapped within the pulmonary ligament (see eFig. 84-8K). Distinguishing between mediastinal emphysema and a small pneumothorax may be difficult. Film obtained with the patient in the lateral decubitus position may show air rising to the most elevated portion of the thorax if it is free to move in the pleural space, whereas mediastinal air moves little with changes in position.⁸¹ Other chest radiographic findings that may mimic the appearance of pneumomediastinum include an unusual appearance of the major (oblique) fissure (eFig. 84-9), medial bullae, and Mach bands (eFig. 84-10).

Subcutaneous emphysema is readily detected as streaks or pockets of air outlining the tissue planes in the neck or chest. It often outlines the tissue compartments of the chest wall, clearly identifying the pectoral muscles. Both subcutaneous emphysema and pneumomediastinum are common findings in patients on mechanical ventilators,^{82,83} being present in 7% of cases in one early series (Fig. 84-6).⁸² These signs of alveolar rupture during positive-pressure

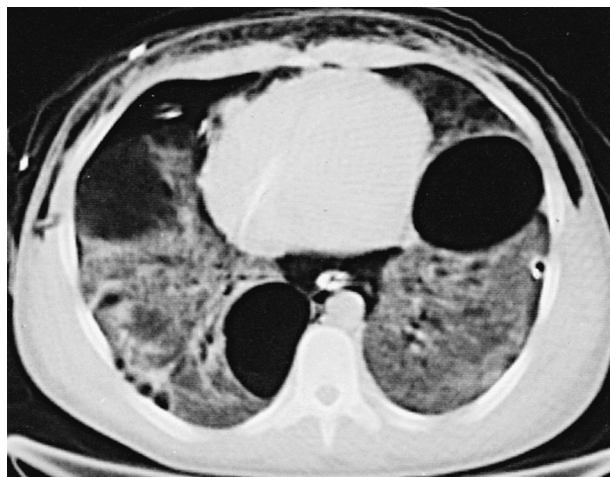


Figure 84-6 Pneumomediastinum. CT of the chest shows pneumomediastinum associated with extensive subcutaneous emphysema in a patient undergoing mechanical ventilation for acute respiratory distress syndrome. Mediastinal air is seen in both the middle and the posterior mediastinal compartments.

ventilation are important clinical danger signals, because pneumothorax may develop in at least half of these patients.^{23,83}

Chest CT is more sensitive than chest radiographs for detecting aberrant air in all its forms and should be considered when important management decisions rest on a given distinction or when the underlying cause is not evident.⁸¹ This is especially true in patients with pneumomediastinum due to blunt trauma, in which only 15% could be detected by chest radiographs.⁸⁴

APPROACH TO MANAGEMENT

Natural History

In most cases of pneumomediastinum, air spreads throughout the mediastinum and vents out of the thorax into the subcutaneous tissue planes.¹ Subcutaneous emphysema can become massive and prove distressing to both patient and physician, but it is seldom dangerous. Subcutaneous air collections will resolve spontaneously without surgical decompression once the primary air leak has sealed. Complete resolution of subcutaneous emphysema usually requires a couple of weeks, and hence counseling patients who are clinically stable is an important component of its management.

Management of Spontaneous Pneumomediastinum

Treatment of predisposing or precipitating factors of spontaneous pneumomediastinum is usually followed by gradual resolution of the aberrant air. Supplemental oxygen may hasten reabsorption, but specific therapy for pneumomediastinum is rarely needed. Most cases resolve with conservative management alone.^{85,85a}

In rare instances pneumomediastinum can produce life-threatening cardiovascular collapse.^{2,5,86} An early, well-documented incident was described by Laënnec more than 150 years ago, as related by Munsell.²¹ The great French clinician was called to see a small boy who had been

run over by a dung cart: Laënnec describes how his 4-year-old patient was placed in a tent with a candle for light. With the boy in extremis, Laënnec inserted sharp sticks into the boy's neck, supraclavicular areas, and anterior portion of the chest; a rapid, large outpouring of air extinguished the candle and the boy recovered. Modern medicine can add little more to this emergency decompression regimen except for the substitution of needles for sticks.

Most experienced clinicians reserve invasive therapy for cases of increasing airway impingement or cardiovascular compromise (eFig. 84-11). In these instances, small infraclavicular venting incisions seem to be the most prudent initial approach.⁸⁷

Management of Pneumomediastinum During Positive-Pressure Ventilation

The appearance of mediastinal or subcutaneous air in a patient receiving positive-pressure ventilation should prompt an assessment of the patient's physiologic response as well as the ventilator status. Immediate discontinuation of positive-pressure ventilation is usually not feasible, but adjustments to the ventilator can diminish the tendency of air to enter the mediastinum and reduce the risk of developing pneumothorax. Delivered tidal volumes should be reduced if possible. Positive end-expiratory pressure should be reduced or discontinued. Occult positive end-expiratory pressure, or "auto-PEEP," can augment air leakage and, if present, should be reduced.⁸⁸ Finally, bronchospasm and other potentially reversible contributors to air trapping during mechanical ventilation should be treated. Cough suppression should be considered.

Tracheobronchial disruption causing extra-alveolar air requires prompt diagnosis and surgical repair.¹³ This condition should be considered in a patient with blunt thoracic trauma in the presence of extensive soft tissue emphysema, airway bleeding, or nonresolving pneumothorax (see eFig. 84-2).^{1,14} Tracheobronchial disruption is certain if, on chest radiography, the collapsed lung tissue appears to have fallen away from the hilum (see Fig. 76-10).⁸⁹ When these findings are present, the patient should be taken to the operating room, where the first step is emergent bronchoscopy to confirm the diagnosis.¹ Performing the bronchoscopy in the operating room allows for immediate surgical intervention once confirmed. An exception can be made in the scenario of a trauma patient who is intubated and clinically stable with a pneumomediastinum found on CT imaging that could represent either an artifact or a small tear in the tracheobronchial tree. In these stable patients, one can do a quick bedside bronchoscopy to confirm the diagnosis which, if confirmed, would necessitate immediate operating room availability. However, these are situations which must be closely coordinated with thoracic surgery to ensure there is no delay in intervention.

MEDIASTINITIS

The term *mediastinitis* encompasses a number of loosely related processes that induce inflammation of mediastinal structures. Most forms of mediastinitis are infectious, and variations in their clinical presentation depend largely on the chronicity of the underlying process rather than on the

specific microbial cause. *Acute* mediastinitis is usually dramatic in presentation and requires prompt recognition and treatment. *Chronic* mediastinitis encompasses a spectrum that ranges from active granulomatous infection to end-stage fibrosis. The paucity of recent literature on these subjects reflects the relative rarity of mediastinitis. Nonetheless, recognition of mediastinitis and its forms is important because of its devastating morbidity and mortality.

ACUTE MEDIASTINITIS

Acute mediastinitis was once a rare and usually fatal condition seen after rupture of the esophagus from forceful vomiting (see eFig. 84-11) or in conjunction with penetrating trauma. With the advent of endoscopic procedures and cardiac surgery via median sternotomy, acute mediastinitis is now most commonly encountered as an iatrogenic complication and may vary in clinical presentation. Relatively indolent infections may be termed "suppurative" rather than "acute." In either case, a distinction is drawn between these disorders and chronic "granulomatous" and "fibrosing" mediastinitis.

The following discussion characterizes the clinical picture and management of acute mediastinitis according to the mechanism of access to the mediastinum (Table 84-3).

Mediastinitis Resulting from Visceral Perforation

Boerhaave syndrome refers to esophageal rupture associated with forceful vomiting (see eFigs. 84-5 and 84-11), classically after overeating or excessive drinking. It is the most familiar example of acute mediastinitis,^{90,91} although no longer the most common. Unilateral or bilateral hydro-pneumothorax is common and quickly progresses to empyema (Fig. 84-7). Spontaneous esophageal rupture can be difficult to diagnose and may be mistaken for an abdominal catastrophe especially in the patient who may not be

Table 84-3 Acute Mediastinitis: Etiologies and Clinical Settings

PERFORATION OF A THORACIC VISCUS

Esophagus

Forceful vomiting (Boerhaave syndrome)
Direct penetrating trauma
Impacted foreign body
Instrumentation: esophagoscopy; sclerotherapy; esophageal obturator airway
Erosion: carcinoma; necrotizing infection

Trachea or Main Bronchi

Direct penetrating trauma
Instrumentation: diagnostic bronchoscopy; therapeutic bronchoscopy; intubation
Foreign body
Erosion of carcinoma

DIRECT EXTENSION OF INFECTION FROM OUTSIDE MEDIASTINUM

Retropharyngeal space; odontogenic
Pancreatitis
Lung; pleura; pericardium
Lymph node
Paraspinal abscess

MEDIASTINITIS AFTER CARDIOTHORACIC SURGERY

INHALATIONAL ANTHRAX

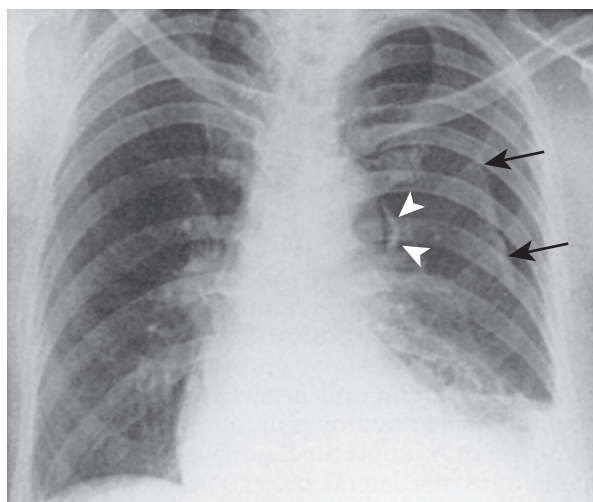


Figure 84-7 Esophageal perforation. Chest radiograph of a 64-year-old woman 16 hours after traumatic perforation of the esophagus showing a subtle lucency along the lateral aortic arch (arrowheads) representing pneumomediastinum. In addition, left-sided pneumothorax (arrows) and pleural effusion are evident."

able to relate a clear history. During a violent vomiting episode, the pressure in the esophagus can increase to the point at which it overcomes the tensile strength of the normal esophageal wall. The most common location of perforation is the lower left posterolateral wall, where the muscle bundles in the longitudinal layer of the esophagus can separate, allowing a bubble of mucosa to protrude into the mediastinum and burst.

In the classic description of acute mediastinitis related to esophageal rupture, the onset is sudden and dramatic. Patients complain of severe, unrelenting substernal chest pain which is worsened by breathing or coughing, and may report a sense of impending doom. The pain may be referred into the neck and ear if there is involvement of the superior mediastinum. Radicular pain that radiates around the chest and between the scapulae suggests involvement of the posterior or inferior mediastinum. Symptoms and signs of systemic toxicity—high fevers, chills, tachycardia, and tachypnea—are prominent. Examination may reveal supraclavicular fullness, tenderness over the sternum or sternoclavicular joints, crepitus, and other signs of mediastinal and subcutaneous emphysema. Hamman sign is characteristic but not always present. Tracheal deviation, jugular venous distention, and other signs of compression of mediastinal structures may appear later in the clinical course. These features are typical after spontaneous esophageal rupture as seen in Boerhaave syndrome, but may not be present in less acute settings.

While still rare, esophageal perforation during diagnostic or therapeutic endoscopic procedures is an important cause of acute mediastinitis in the contemporary era.⁹² Diagnostic upper endoscopy causes a perforation at a rate of less than 0.03%.⁹³ Therapeutic maneuvers, such as dilation of strictures (eFig. 84-12) and endoscopic mucosal resection, have a much higher risk of perforation, from 2% to 6%.⁹³ Additionally, therapy of malignant lesions is more likely to be complicated by perforation than that of benign lesions.⁹⁴

The esophageal obturator airway and swallowed foreign bodies can also perforate the esophagus, particularly if their

use is intended to induce injury. One series describes six prison inmates who swallowed hypodermic needles fashioned in the shape of "stars" to win temporary reprieves from incarceration.⁹⁵ All required surgical management. Accidental or intentional ingestion of caustic solutions such as paraquat or lye also can lead to esophageal perforation.²⁷

The diagnosis of esophageal perforation depends on an appropriate degree of clinical suspicion. On chest radiograph, the hallmarks are diffuse mediastinal widening and the presence of air in the mediastinum and adjacent soft tissues. Mediastinal air-fluid levels may be seen, and pneumothorax or hydropneumothorax may be present. CT can delineate these abnormalities more clearly. Passage of ingested contrast material into the periesophageal or pleural space may be observed.^{96,97}

Frank uncontained esophageal perforation requires prompt surgical repair, drainage of the mediastinum and often the pleural spaces, and administration of appropriate antibiotics.^{98,99} Percutaneous catheter drainage of mediastinal abscesses, under CT guidance, has been used when the infection is localized and the clinical setting is less urgent (see eFig. 84-12E-H). In a series describing 51 patients 3 died before intervention could be accomplished, 31 underwent standard thoracotomy and repair leading to 11 deaths, and 17 highly selected patients with minimal contamination were managed successfully with targeted drainage and antibiotic therapy.¹⁰⁰

If esophageal perforation due to endoscopy is detected early, morbidity and mortality can be avoided with prompt treatment. Clips may be used to repair small perforations endoscopically if detected immediately. In selected cases, esophageal perforation can be contained using endoscopically placed stents.^{101,102} In addition, a surgeon should be involved as soon as a perforation is detected and broad-spectrum antibiotics should be administered.⁹³ The rate of recovery is high when perforations are repaired within 24 hours.

Complications of acute mediastinitis after esophageal rupture may include localized abscess formation, extensive pleural empyema, and persistent esophagocutaneous fistulas. A prolonged course is usual, and reexploration may be necessary to ensure adequate drainage. Reported mortality has varied due to differences in patient selection and management approaches. Timing of surgical drainage has been of prime importance in determining the clinical outcome. Modern series reporting the use of consistently aggressive surgical management cite up to 90% survival after spontaneous esophageal rupture.^{103,104}

Bronchoscopic airway perforation and migration of indwelling central venous catheters are other iatrogenic causes of mediastinitis. Bronchoscopy is a much less frequently reported cause of mediastinitis than esophagoscopy.¹⁰⁵ However, increasing use of laser and mechanical endobronchial procedures, often performed in the setting of malignancy, with chronic airway colonization or postobstructive pneumonia, add to the likelihood of potential mediastinal complications. Mediastinitis has been reported after endobronchial ultrasound-guided transbronchial needle aspiration, but is overall a rare event.¹⁰⁵ Intravascular catheters may be another source of acute mediastinitis when the catheter tip erodes through the vessel wall into

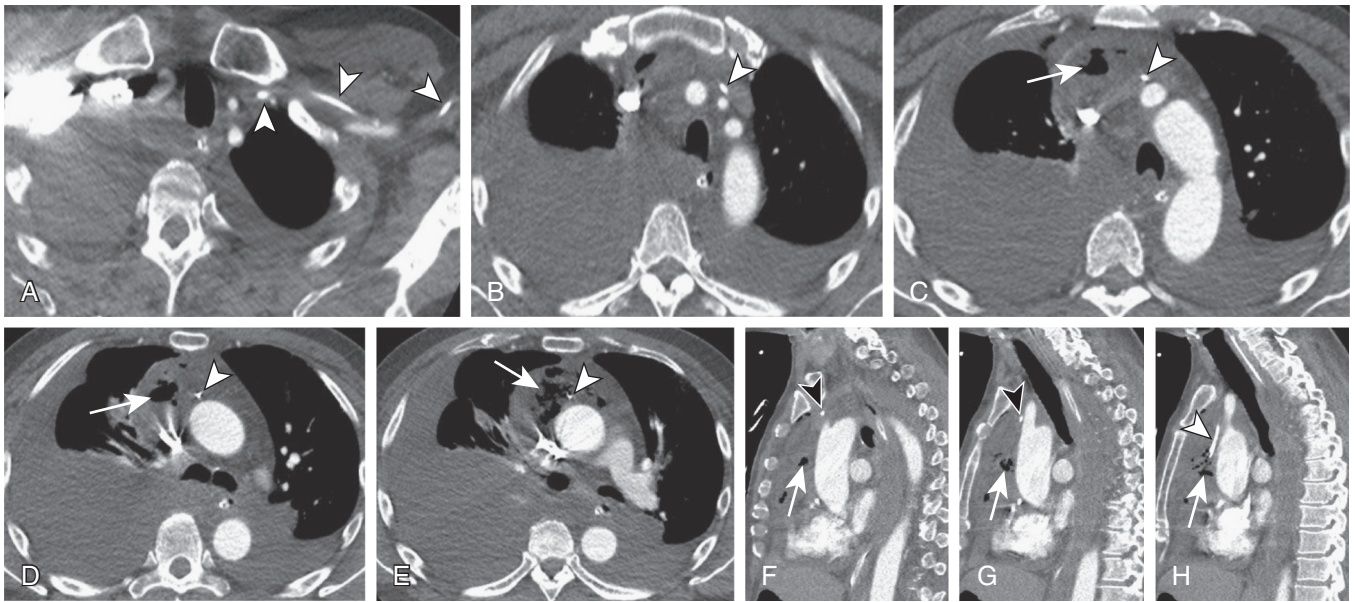


Figure 84-8 Venous perforation of a peripherally inserted venous catheter with entry into the mediastinum. Axial (A–E; see [Video 84-2](#)) and sagittal (F–H) enhanced chest CT show a left upper extremity peripherally inserted venous catheter (arrowheads) coursing through the left subclavian and brachiocephalic veins (arrowheads, A–C), but then coursing caudally into the anterior mediastinum (arrowheads, D and E). A mediastinal gas collection (arrows) represents a developing abscess. (Courtesy Michael Gotway, MD.)

the mediastinum ([Fig. 84-8](#) and [Video 84-2](#)). Instillation of hyperosmotic,¹⁰⁶ vesicant, or vasoactive substances via these catheters may induce a chemical, rather than an infectious, inflammation.

Direct Extension of Infection from Extramediastinal Sites

Descending necrotizing mediastinitis is infection that has extended directly into the mediastinum from a head and neck source.¹⁰⁷ Periodontal, peritonsillar, odontogenic, or pharyngeal infection may extend to the mediastinum via the prevertebral, visceral, or pretracheal spaces or carotid sheaths,^{6,108} although the usual route is via the retropharyngeal space to the posterior mediastinum ([Fig. 84-9](#)).^{109,110} Recent studies demonstrate a shift from odontogenic infection to pharyngeal infection as the most common source of descending necrotizing mediastinitis.^{107,111,112} Most infections are mixed, with both aerobic and anaerobic organisms; purulent pleural and pericardial involvement is common.¹⁰⁷ Mediastinal infection of this type rapidly leads to sepsis and multiorgan failure and carries a high mortality rate.^{109,110,113,114} High preoperative mortality is most strongly related to a delay in diagnosis.¹¹⁵

In addition to the clinical signs described previously for acute mediastinitis after esophageal perforation, patients with descending necrotizing mediastinitis may have widening of the retropharyngeal space, with or without associated air-fluid levels, anterior displacement of the tracheal air column, and loss of the normal cervical spine lordosis on lateral films of the neck. CT of the neck and chest are usually definitive ([Fig. 84-10](#)).¹⁰⁹

Successful treatment of descending necrotizing mediastinitis depends on early recognition and diagnosis, prompt antibiotic administration, and timely and aggressive surgical drainage. Multiple surgical approaches are available for mediastinal drainage and the choice of procedure depends

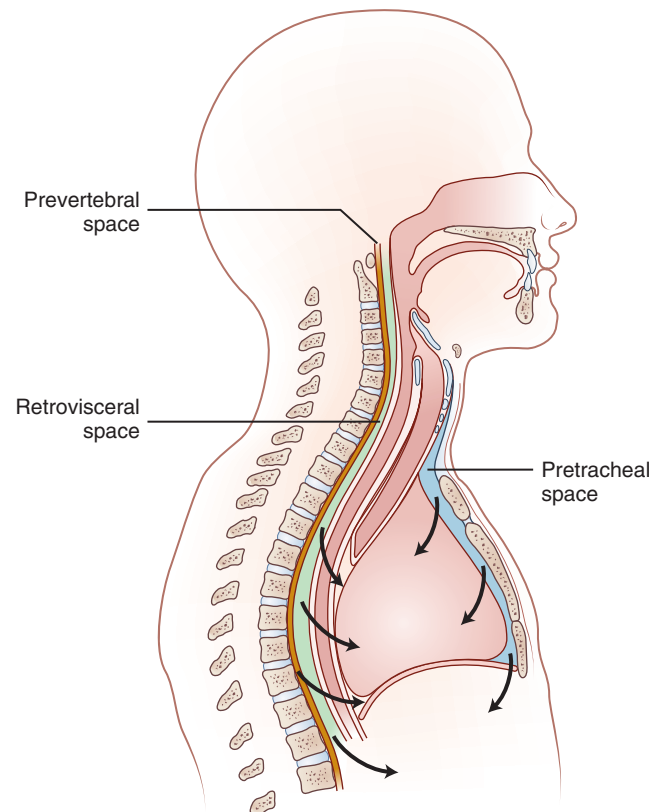


Figure 84-9 The three deep spaces of the neck and their communication with the mediastinum. (Redrawn from Freeman RK, Vallières E, Verrier ED, et al: Descending necrotizing mediastinitis: an analysis of the effects of serial surgical debridement on patient mortality. *J Thorac Cardiovasc Surg* 119:260–267, 2000.)

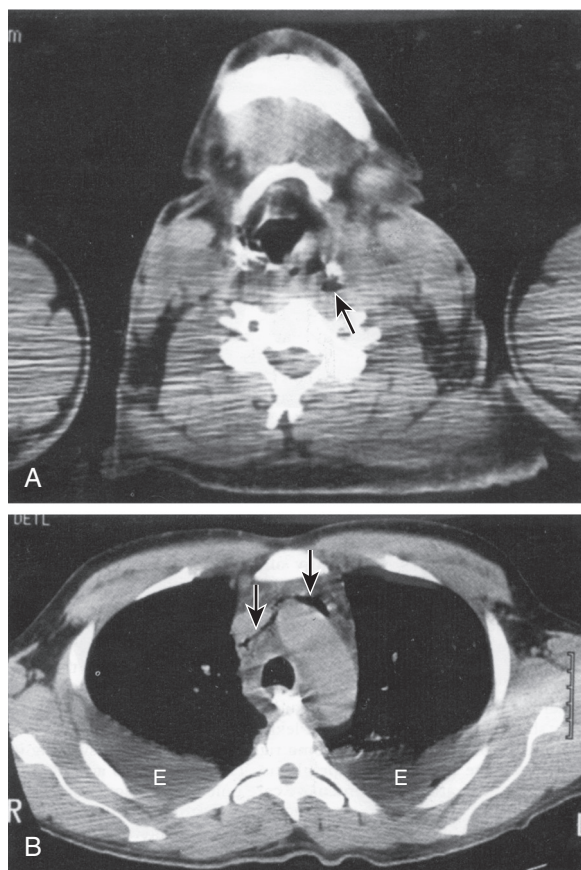


Figure 84-10 Chest CT of a 35-year-old man with descending necrotizing mediastinitis. **A**, At the level of the hyoid bone in the neck, there is gas in the retropharyngeal soft tissues (arrow) with parapharyngeal space inflammatory stranding. **B**, At the level of the aortic arch in the chest, there is gas outlining the great vessels (arrows). There are inflammatory changes in the paratracheal tissues, and bilateral pleural effusions (**E**). (From Corsten MJ, Shamji FM, Odell PF, et al: Optimal treatment of descending necrotizing mediastinitis. *Thorax* 52:702–708, 1997.)

on the extent of involvement and the patient's condition.¹¹⁵ A cervical approach is used for drainage of disease localized in the upper mediastinum, although most surgeons now advocate for transthoracic exploration and debridement if there is any suspicion of diffuse disease.^{107,112} This more aggressive approach is supported by findings of Corsten and coworkers¹⁰⁹ that the mortality rate of patients treated with cervical drainage alone was 47% compared with 19% when thoracic mediastinal drainage was added. Routine serial postoperative cervicothoracic CT imaging and aggressive reexploration and drainage guided by these imaging findings appear to reduce the mortality of this condition even further.¹¹⁰ In a recent series of 17 patients, in whom transthoracic surgery was performed within a median time frame of 6 hours after radiographic diagnosis, only one patient experienced an early death.¹¹⁴

Although video-assisted thoracic surgery and other percutaneous drainage procedures have been described and may be appropriate in early-stage disease, open surgical drainage and irrigation remains the standard approach. Direct extension of infection from elsewhere in the chest is a rare cause of acute mediastinitis. Such extension can be associated with eroding neoplasms, with anterior chest wall and neck infections in injection drug users, or as a compli-

cation of vertebral or costal tuberculous infection. Penetrating chest injuries may result in acute mediastinitis, especially if the wound causes visceral perforation or is grossly contaminated, or if there has been a delay in reaching medical attention. In such instances, the diagnosis of acute mediastinitis may not be apparent if the patient has other serious injuries.

Pancreatitis has been reported to extend into the mediastinum, presenting as mediastinal widening with the clinical picture of acute mediastinitis. Spread in such a circumstance is presumably via the aortic and esophageal hiatuses. Both gastric and esophageal ulcers have been reported as causes of mediastinitis, sometimes eroding into the pericardium.

Mediastinitis After Cardiothoracic Surgery

Mediastinitis after cardiac surgery^{116,117} and after heart and heart-lung transplantation is another significant form of acute mediastinitis of iatrogenic etiology in the modern era.¹¹⁸⁻¹²⁰

The incidence of mediastinal infection after cardiac surgery has been variously reported at 0.4% to 5.0% but, in a more recent series, the reported rate was less than 1%.¹²¹ Post-sternotomy mediastinitis has become a substantial clinical problem, not because of a high case incidence but rather because cardiac surgery via median sternotomy has become such a widely used procedure.

Risk factors that appear to predispose to development of mediastinitis after cardiac surgery include underlying comorbidities such as diabetes mellitus and obstructive lung disease, as well as advanced age.^{121,122,122a} Perioperative risk factors include shaving rather than clipping for hair removal, the use of bilateral internal mammary artery grafts, a longer duration of the surgical procedure and perfusion time, greater use of cautery or bone wax, low cardiac output state in the early postoperative period, and greater amounts of postoperative bleeding. The incidence of postoperative mediastinitis appears to be increased further if reoperation is required to control bleeding, if multiple valve replacement accompanies coronary artery bypass, or if the patient requires more than 48 hours of mechanical ventilation postoperatively.

Careful infection control measures and scrupulous aseptic technique in the operating room remain important means of prevention.¹²¹ The prophylactic intranasal application of mupirocin ointment has been shown to reduce by 50% the rate of *Staphylococcus aureus* nosocomial infections in carriers who undergo major surgery,¹²³ leading to the suggestion that it be used routinely.

The bacteriology of postoperative mediastinitis parallels that of early prosthetic valve endocarditis. *Staphylococcus epidermidis* and *S. aureus* have been the most frequent isolates in several series,^{124,125} and as many as 40% of cases have mixed infections.¹²⁴ Methicillin-resistant *Staphylococcus aureus* is a relatively uncommon but virulent cause.¹²⁶ Rare organisms include anaerobes and gram-negative bacilli,^{124,127} *Candida* species,^{124,128} and nontuberculous mycobacteria (especially *Mycobacterium chelonae* and *Mycobacterium fortuitum*).¹¹⁶

Acute mediastinitis presenting after cardiac surgery tends to be less devastating than that seen in the settings described previously, perhaps because it remains relatively

localized longer and tends to be recognized earlier. Typically, the clinical course consists of fever and systemic signs, followed by bacteremia and local signs of wound infection.¹²⁹ Drainage from the sternotomy incision and other localizing findings are present in the great majority of patients.^{124,129,130}

The diagnosis is usually made at the time of reexploration of the sternotomy wound and rests on a high clinical suspicion in the appropriate setting. CT is particularly helpful in identifying and discerning soft tissue swelling, fluid collections, and sternal erosion or dehiscence (eFig. 84-13).¹³¹ However, because swelling and fluid collections are common in the early postoperative period, their significance is much more clear when they persist or develop after 14 days.^{131,132} Patients with fever, positive blood cultures, and wound abnormalities in the post-sternotomy period should be evaluated surgically. As in other settings, therapy for post-sternotomy mediastinitis consists of administration of systemic antibiotics and early surgical exploration with débridement and drainage.^{121,124,133,134} Reported mortality from mediastinitis after cardiac surgery varies considerably. These patients typically require multiple surgical procedures and eventual coverage of the wounds with vascularized muscle flaps. Currently, most patients survive, with mortality rates of 20% to 40%.^{121,129} Hospitalization of survivors is usually prolonged by this complication.¹³⁵

“Primary Mediastinitis”: Inhalational Anthrax

Anthrax, caused by infection with *Bacillus anthracis*, is primarily a disease of cattle, sheep, and goats and is most prevalent in the Middle East, although it is now recognized as an important disease of bioterrorism (see Chapter 40). Clinical syndromes are classified by primary site of infection: cutaneous, gastrointestinal, injectional, or inhalational. The most common form of anthrax, the cutaneous form, is contracted by direct inoculation usually from handling hides or hair from infected animals. Gastrointestinal anthrax is due to ingestion of meat contaminated with anthrax spores. Recently, injectional anthrax has emerged as a severe soft tissue infection seen in heroin users in the United Kingdom and Europe.¹³⁶

Inhalational anthrax, or *wool sorter's disease*, is contracted by inhaling *B. anthracis* spores from animal sources. Anthrax spores inhaled into the distal air spaces are ingested by alveolar macrophages and transported to the mediastinal lymph nodes, where they induce a hemorrhagic mediastinitis, followed by bacteremia, overwhelming sepsis, and shock. Mortality is high, even with aggressive supportive care.¹³⁷⁻¹³⁹ Virulence of the anthrax bacillus is related to the production of two toxins, called *lethal* and *edema* toxins, as well as a capsule that resists phagocytosis.¹³⁶ Sporadic anthrax is fortunately rare, with one report documenting only two confirmed cases in this country in 25 years.¹⁴⁰ However, anthrax has remained a very real concern because of its devastating clinical effects and its ominous potential as an agent of biologic warfare and bioterrorism.^{138,139,141,142} In 1979, there was an outbreak of 42 cases after the accidental release of weapons-grade anthrax in Sverdlovsk, Russia.¹⁴¹ In the fall of 2001, this potential was realized when *B. anthracis* spores were intentionally dispersed through the U.S. Postal Service system, resulting in an outbreak of 11 cases of cutaneous anthrax and 11 cases of inhalational anthrax.^{143,144}

Modern clinical knowledge of inhalational anthrax has been largely derived from these limited outbreaks. Patients typically experience a biphasic illness with an initial flulike illness lasting 2 to 4 days and characterized by fever, malaise, myalgias, and nonproductive cough. This is followed by a fulminant phase of acute mediastinitis, with respiratory distress, chest pain, cyanosis, and hemodynamic instability.^{138,139,143,144} Once septic shock has developed, it is usually resistant to aggressive supportive measures.¹³⁶ The chest radiograph and chest CT typically show mediastinal widening and pleural effusions (see Fig. 40-2).¹⁴⁵ A triad of hemoconcentration, widened mediastinum, and altered mental status are characteristic of inhalational anthrax and help distinguish it clinically from community-acquired pneumonia.¹³⁶ The diagnosis is established by demonstration of gram-positive, boxcar-shaped bacilli in tissue or body fluid specimens or in the blood buffy coat. A direct fluorescent antibody test, polymerase chain reaction, and serologic tests are available for confirmation.

Historically, inhalational anthrax has been a devastating disease even with appropriate treatment: 12 of 13 well-documented sporadic cases in the United States had fatal outcomes.¹³⁷ In the 2001 bioterrorism outbreak, prompt diagnosis and initiation of antibiotic therapy plus aggressive drainage of mediastinal and pleural collections resulted in the survival of 6 of the 11 patients.¹⁴⁴

The cornerstone of treatment is prompt antibiotic administration upon first suspicion of anthrax. Recommended initial treatment options include ciprofloxacin or doxycycline with a second agent, either clindamycin or penicillin.¹³⁶ Anthrax is resistant to third- and fourth-generation cephalosporins. Most patients in the bioterrorism outbreak were treated with multiple agents including a fluoroquinolone.¹⁴³ For postexposure prophylaxis, ciprofloxacin or doxycycline orally as well as immunization with antitoxin antibodies is recommended.^{136,146}

CHRONIC GRANULOMATOUS MEDIASTITIS AND MEDIASTINAL FIBROSIS

Chronic granulomatous mediastinitis and mediastinal fibrosis are two manifestations of chronic mediastinal disease. Disorders falling along the continuum from active granulomatous mediastinitis to pure mediastinal fibrosis have been identified by a variety of terms in the literature—mediastinal adenitis, mediastinal granulomatosis, sclerosing mediastinitis, mediastinal collagenosis, fibrosing mediastinitis, and idiopathic fibroinflammatory lesion of the mediastinum—but conceptually, all these entities may be thought of as variations of a common process (Fig. 84-11).

Etiologies and Pathophysiology

In North America, the majority of cases of granulomatous mediastinitis are caused by histoplasmosis; worldwide, tuberculosis is the most common etiology.¹⁴⁷⁻¹⁵⁰ Histoplasmosis and tuberculosis together account for 83% of the confirmed diagnoses.^{147,151} Granulomatous infection is the usual cause of mediastinal fibrosis (see Fig. 84-11).

The most important noninfectious etiology of chronic mediastinal disease is sarcoidosis, which accounts for 11% of the cases of granulomatous mediastinitis of known

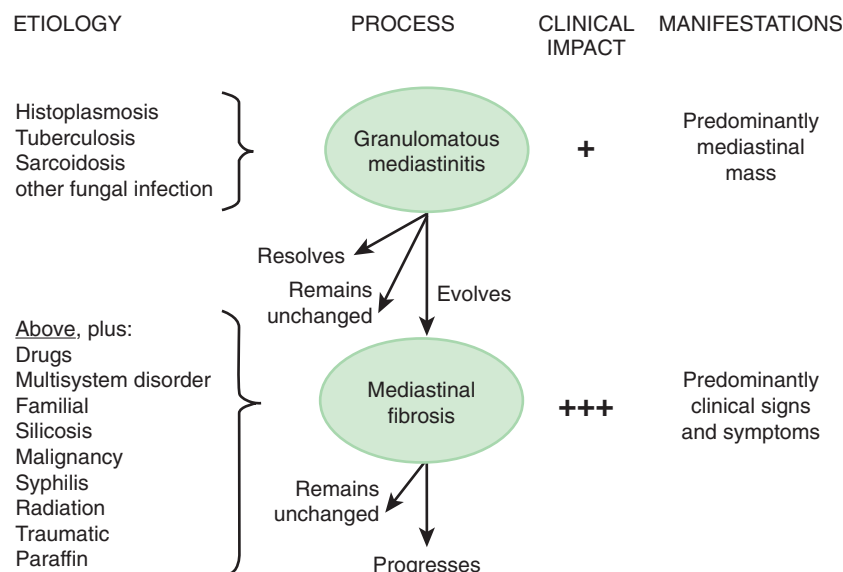


Figure 84-11 Pathophysiologic relationships between granulomatous mediastinitis and mediastinal fibrosis.

cause.¹⁴⁷ Methysergide, a drug once used in the control of severe vascular headache, is well-known for causing mediastinal fibrosis. Other reported noninfectious causes of mediastinal fibrosis include silicosis,¹⁵² paraffin (as a late complication of plumbage for tuberculosis), and traumatic mediastinal hematoma.¹⁵³ Nodular sclerosing Hodgkin lymphoma may also masquerade as mediastinal fibrosis.¹⁵⁴ Mediastinal irradiation has been reported to cause mediastinal fibrosis with superior vena caval and bronchial obstruction.¹⁵⁵

The genesis of chronic mediastinal disease is most easily understood using histoplasmosis or tuberculosis as an example. Infection begins as a primary focus in the lung, which spreads to mediastinal lymph nodes and induces mediastinal adenitis and periadenitis. Eventually, a cluster of caseating lymph nodes breaks down into an irregular mass, heals by fibrous encapsulation and, in some cases, undergoes dense calcification. The thickness of the fibrotic capsule is the main determinant of the clinical picture: when 2- to 5-mm in thickness, it has little clinical impact, whereas, if the capsule reaches 6 to 9 mm, it can invade or interfere with adjacent tissues.^{148,156} This benign localized “healing” process produces physiologically important effects because of the compact nature of the mediastinum and the importance and vulnerability of its structures (Fig. 84-12). Whether either of these concepts or some other mechanism is responsible, it is evident that the host response plays an important role.

The symptoms and physiologic effects of this process are determined by the location of the involved lymph nodes. Most commonly, the involved lymph nodes are in the right perihilar region (eFig. 84-14); perhaps this predilection for a right-sided location accounts for the high prevalence of superior vena cava (SVC) obstruction in chronic mediastinitis. Later, in instances in which the process progresses to generalized fibrosis, the entire upper portion of the mediastinum may be involved.

Clinical Manifestations

On the continuum from active granulomatous mediastinitis to mediastinal fibrosis, the former tends to be asymptomatic

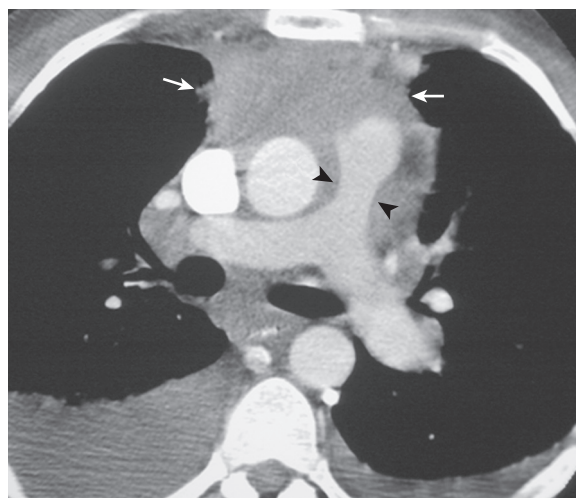


Figure 84-12 Mediastinal fibrosis. Axial CT through the main pulmonary artery shows abnormal soft tissue infiltrating the mediastinum (arrows), compressing the main pulmonary artery (arrowheads). The presence of mass effect on vessels and bronchi is characteristic of mediastinal fibrosis.

and to be discovered incidentally by chest radiography; the latter tends to cause clinical manifestations.⁷⁸ In 52 patients with mediastinal fibrosis and evidence of histoplasmosis reviewed by Loyd and associates,¹⁵⁷ initial symptoms included cough in 41%, dyspnea in 32%, hemoptysis in 31%, and chest pain in 23%. Clinical manifestations develop either because the fibrotic process invades or compresses mediastinal structures or because a calcified mass erodes into adjacent structures. These manifestations can be grouped into those related to involvement of the SVC, the airways, the esophagus, the major pulmonary vessels, and mediastinal nerves.

Superior Vena Cava Obstruction. SVC obstruction has been the most frequent complication of granulomatous mediastinitis and mediastinal fibrosis in some series.^{147,158} Although most patients with SVC obstruction have malignancy (see eFigs. 83-1 and 83-2), benign causes account for about 3% to 6% of large published series,^{159,160} of which

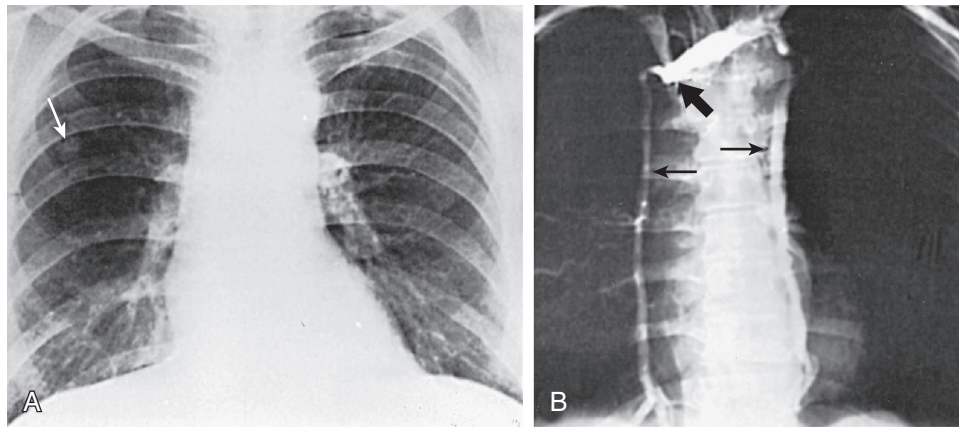


Figure 84-13 Mediastinal fibrosis (in this instance from histoplasmosis) with superior vena cava obstruction and extensive collateral circulation. **A**, Frontal chest radiograph shows smooth widening of the superior mediastinum with a peripheral granuloma in the right lung (arrow). **B**, Imaging following rapid injection of contrast material into an antecubital vein shows complete obstruction of the superior vena cava (thick arrow), with filling of the internal mammary veins bilaterally (thin arrows). (From Fraser RG, Paré JAP, Paré PD, et al: *Diagnosis of diseases of the chest*, vol II, ed 3. Philadelphia, 1989, WB Saunders, p. 955.)

most are due to granulomatous mediastinitis or mediastinal fibrosis.¹⁵⁵ SVC obstruction can develop at any stage of granulomatous or fibrotic involvement; in Schowengerdt and coworkers' series,¹⁴⁷ SVC obstruction was present in 77% of symptomatic patients with granulomatous mediastinitis and in 52% of symptomatic patients with mediastinal fibrosis.

The typical presentation is SVC syndrome.¹⁶¹ Because obstruction develops gradually, collateral channels tend to divert much of the venous flow (Fig. 84-13). Therefore, symptoms may be less prominent than might be expected and may improve with time.¹⁵⁰ However, even chronic SVC obstruction can cause serious complications such as hemorrhage from esophageal varices, recurrent upper extremity thrombophlebitis, and postphlebotic syndrome. Less commonly, the inferior vena cava or azygos vein can be involved.¹⁴⁷ Thoracic duct obstruction is rare¹⁴⁷ but can produce chylothorax and its associated clinical manifestations.

Airway Involvement. Airway complications including dyspnea, cough, and hemoptysis were the most common clinical manifestations of chronic mediastinal disease in several series^{78,157} and constituted the most common indication for surgical intervention.⁷⁸ Any of the main airways may be compromised, but involvement of the right middle lobe is reported as most frequent and is often accompanied by features of the right middle lobe syndrome. A rare complication, bronchoesophageal fistula, may be heralded by simultaneous hemoptysis and hematemesis.¹⁶²

Esophageal Involvement. Esophageal involvement can include extrinsic compression, traction diverticula, disturbances of esophageal motility, or bleeding. Symptoms of dysphagia, chest pain, and eructation can result.¹⁴⁷

Pulmonary Vascular Involvement. Mediastinal fibrosis can involve major vessels on either side of the heart¹⁴⁷⁻¹⁴⁹ and, if so, the prognosis can be serious. Progressive obstruction of one or both main pulmonary arteries can result in pulmonary hypertension, cor pulmonale, and refractory right-sided heart failure (see eFigs. 37-1 and 54-22).¹⁶³

Stenosis of proximal pulmonary veins can cause a clinical picture similar to that of severe valvular mitral stenosis, with pulmonary venous hypertension and recurrent episodes of hemoptysis. Pulmonary venous hypertension can be unilateral when the veins from only one lung are involved and, thus, may result in unilateral pulmonary edema and fibrosis (see eFig. 37-1). Occasionally fibrotic changes involving the pulmonary parenchyma may be the result of previous pulmonary infarction when significant vascular compression is present (see eFig. 54-22). With flow-limiting systemic venous stenoses, collateral vessels are frequently abundant (see eFig. 54-21).

Mediastinal Nerve Involvement. Entrapment or compression of the mediastinal nerves can cause a variety of disorders. Hoarseness can result from involvement of the recurrent laryngeal nerve,^{147,149} diaphragmatic paralysis from involvement of one or both phrenic nerves, Horner syndrome from impingement on autonomic ganglions or nerves, and persistent tachycardia from damage to the vagus nerve.

Diagnosis and Management

In most instances, surgical exploration is necessary to distinguish between benign and malignant causes of SVC syndrome, localized mediastinal mass, or other manifestations of chronic mediastinitis. Occasionally, prior radiographs documenting an unchanged appearance or dense calcification within the mass permits a confident diagnosis without surgery.

Chest radiographs are abnormal in most patients. Granulomatous mediastinitis more often presents as a localized mass, usually in the right paratracheal area, and the later fibrotic state more frequently produces generalized widening of the superior portion of the mediastinum, but these characteristics vary.^{149,150} Mass lesions tend to be smooth and lobulated,¹⁵⁰ and contrast studies in cases of SVC obstruction typically show the affected area to be smooth and tapered,¹⁴⁹ in contrast to the more ragged appearances usually seen with cancer. In some cases, the mediastinum is normal in appearance on standard chest radiographs, and venography or chest CT is necessary to demonstrate the

anatomic basis of a clinically evident obstruction (see eFigs. 54-21 and 54-22).¹⁵⁰ Magnetic resonance imaging may be useful in assessing vascular compromise beyond what is shown on CT scan.¹⁶⁴

The role of specific medical therapy for granulomatous mediastinitis or mediastinal fibrosis is unclear.⁷⁸ Some evidence suggests that selected cases with active inflammation associated with histoplasmosis may benefit from antifungal therapy,^{158,165} but specific indications, if any, for antifungal therapy remain unknown. A similarly conservative approach should be taken to tuberculosis-related mediastinal complications, unless sputum or tissue samples are positive for mycobacteria or convincing clinical evidence of active tuberculosis is present.

The clinical manifestations of this disease appear to be the result of host factors as much as the infection itself. Accordingly, therapy has also been directed at the host inflammatory response. Anecdotal reports of treatment of mediastinal and retroperitoneal fibrosis with corticosteroids have reached opposite conclusions.^{166,167} It appears that diffuse forms of fibrosis may be more likely to respond to anti-inflammatory therapy.¹⁶⁸ As in the case of antimicrobial therapy, the appropriate role for anti-inflammatory therapy for granulomatous mediastinitis and mediastinal fibrosis is at present unknown.¹⁶⁹

At the time of exploration for diagnosis, some surgeons advise removal of as much of the inflammatory or fibrous mass as possible in order to reduce its bulk and perhaps diminish its later impact on adjacent tissues.¹⁶⁹ Surgical debulking is tedious and associated with significant morbidity and mortality. However, there have been anecdotal case reports of surgical intervention being successful in these patients.⁷⁸ Surgery to bypass an obstructed vena cava is technically difficult and not always effective, although this may still be considered in the setting of bleeding esophageal varices or recurrent upper extremity thrombophlebitis. Endovascular stent placement is another option (see eFig. 54-21).¹⁷⁰ Obstruction of major pulmonary vessels is a poor prognostic sign and, for this complication, therapeutic options are limited, with surgical reconstruction, angiographic dilation, and stent placement only rarely being successful.¹⁷¹

ACKNOWLEDGMENTS

The authors wish to acknowledge the contributions of David J. Pierson, MD, who wrote this chapter for the first and second editions, and coauthored this chapter with DRP for the third edition. These earlier chapters contain more extensive historical references.

Key Points

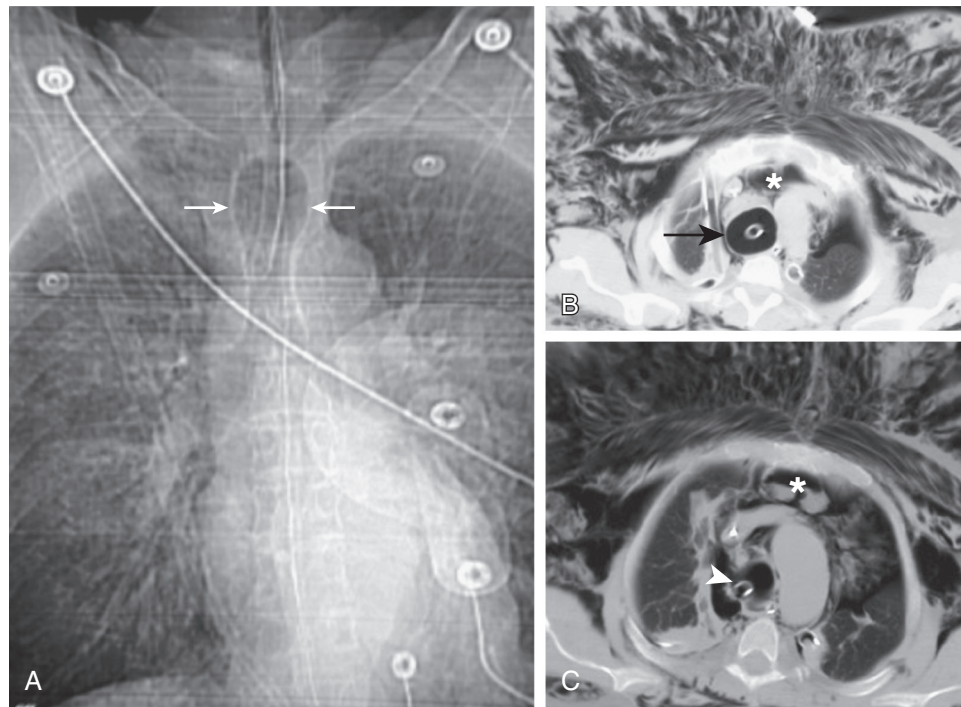
- Pneumomediastinum refers to the presence of air or other gas in the mediastinum, which usually originates from alveolar rupture in the lungs but may arise from the upper respiratory tract or the gastrointestinal tract.
- Treatment of pneumomediastinum depends primarily on successful management of the underlying disease process. Rarely, direct intervention is needed to decompress air in the mediastinum.
- Acute mediastinitis is usually a sudden and severe disease that is now most commonly caused by perforation of the esophagus during endoscopic procedures and infectious complications after surgical procedures with sternotomy incisions.
- All forms of acute mediastinitis are life-threatening and require prompt diagnosis, imaging, surgical drainage, and antimicrobial treatment.
- Chronic mediastinitis results from granulomatous inflammation of the mediastinum, most commonly due to histoplasmosis and its fibrotic sequelae. Complications include bronchial obstruction, superior vena cava syndrome, esophageal compression, and pulmonary vessel obstruction.
- Management of chronic mediastinitis is aimed at relief of these mechanical complications. The role of anti-inflammatory and antimicrobial therapy is at present unclear.

Complete reference list available at [ExpertConsult](#).

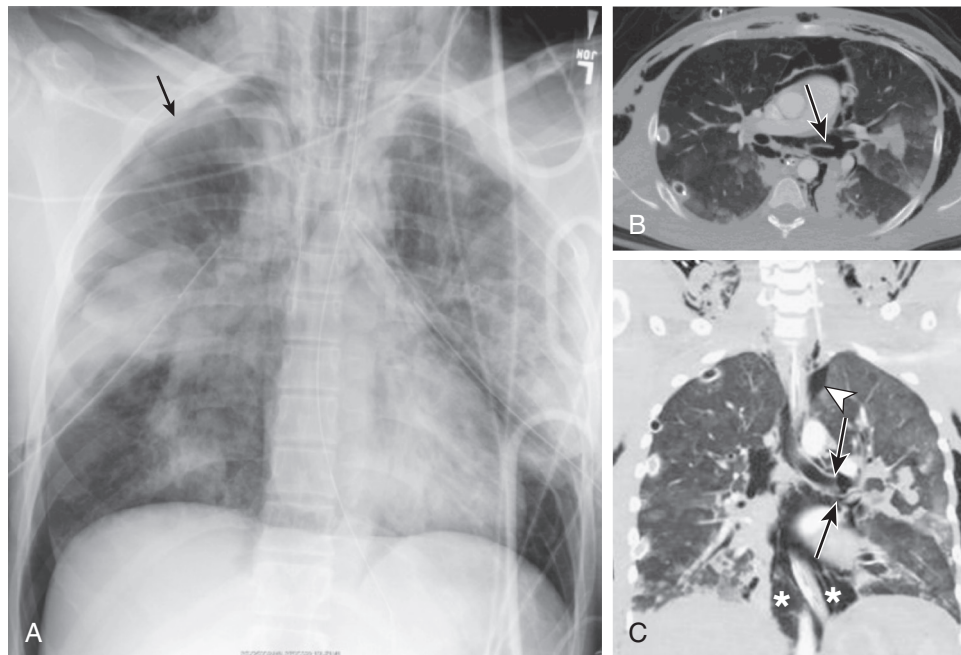
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eFIGURE IMAGE GALLERY



eFigure 84-1 Pneumomediastinum resulting from tracheal perforation from an endotracheal tube. **A**, Scout view performed before chest CT shows overdistention of the endotracheal tube cuff with focal tracheal dilation (arrows). Subcutaneous emphysema and pneumomediastinum are present. **B** and **C**, Axial chest CT displayed in lung windows performed at the level of the aortic arch shows focal dilation of the trachea (arrow, **B**), with the endotracheal tube exiting the right posterolateral trachea at the site of tracheal perforation (arrowhead, **C**). Pneumomediastinum (*) and subcutaneous emphysema are present. (Courtesy Michael Gotway, MD.)



eFigure 84-2 Left main-stem bronchial fracture following motor vehicle collision. **A**, Frontal chest radiograph shows subcutaneous emphysema with pneumomediastinum with a right apical pneumothorax (arrow) and a “deep sulcus” sign, also on the right. A left pneumothorax has been addressed with a left thoracostomy tube, although clinically a persistent air leak from this tube was present. **B** and **C**, Axial (see [Video 76-3](#)) and coronal (see [Video 84-1](#)) chest CT displayed in lung windows shows subcutaneous emphysema with pneumomediastinum (*) with a complete fracture of the left mainstem bronchus (arrows). A residual left apical pneumothorax (arrowhead in **B**) remains. (Courtesy Michael Gotway, MD.)

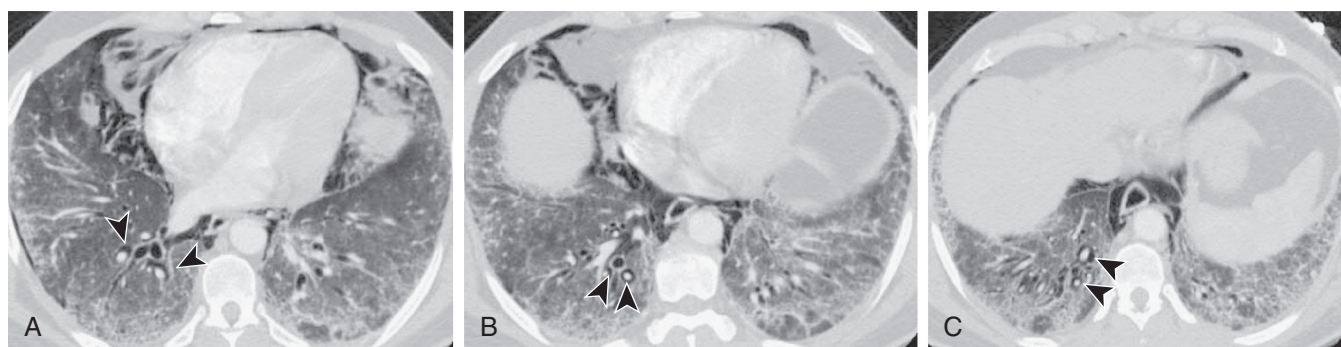


Figure 84-3 Pulmonary interstitial emphysema: chest CT appearance. A–C, Axial chest CT displayed in lung windows shows gas collections (*arrowheads*) surrounding the right lower lobe segmental and subsegmental arteries and airways, creating the appearance of a lucent “halo” around these structures, representing pulmonary interstitial emphysema. The pulmonary interstitial emphysema in this patient was spontaneous, although associated with an undiagnosed interstitial lung process, and was presumed to reflect peripheral alveolar rupture. (Courtesy Michael Gotway, MD.)

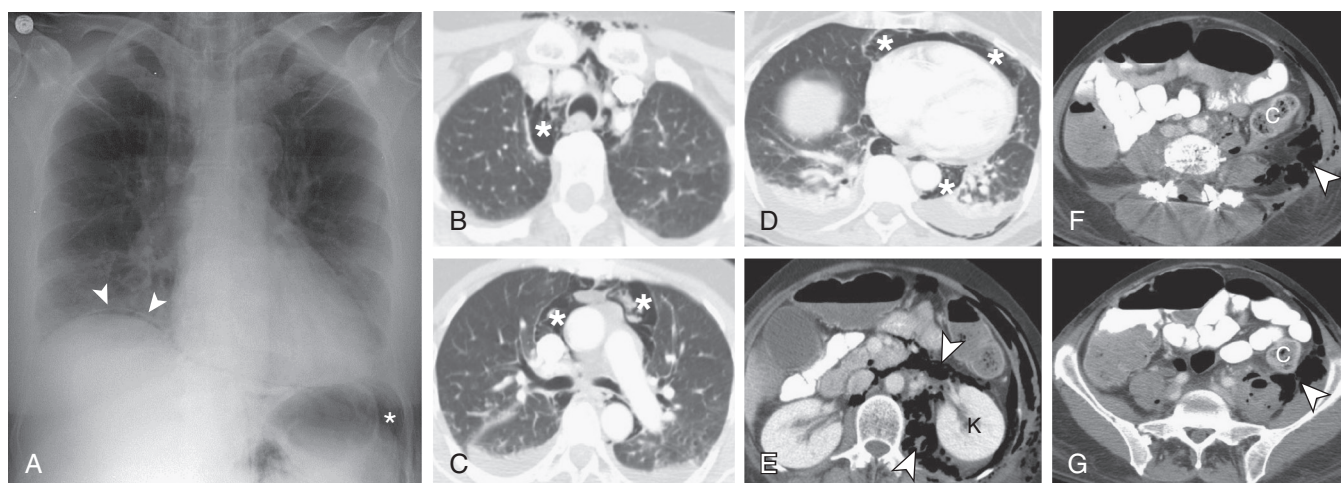


Figure 84-4 Pneumomediastinum resulting from a subdiaphragmatic source—perforated diverticulitis. A, Frontal chest radiograph shows free intraperitoneal gas outlining the right diaphragm (*arrowheads*), as well as extraluminal gas in the left upper quadrant (*). Left upper quadrant subcutaneous emphysema is also present. Axial CT performed through the thorax (B–D) and abdomen and pelvis (E–G) shows pneumomediastinum (*) extending from pneumoretroperitoneum (outlining the left kidney [K], in panel E, and arrowheads, E–G) resulting from perforated diverticulitis involving the descending colon (C, in panels F and G). (Courtesy Michael Gotway, MD.)

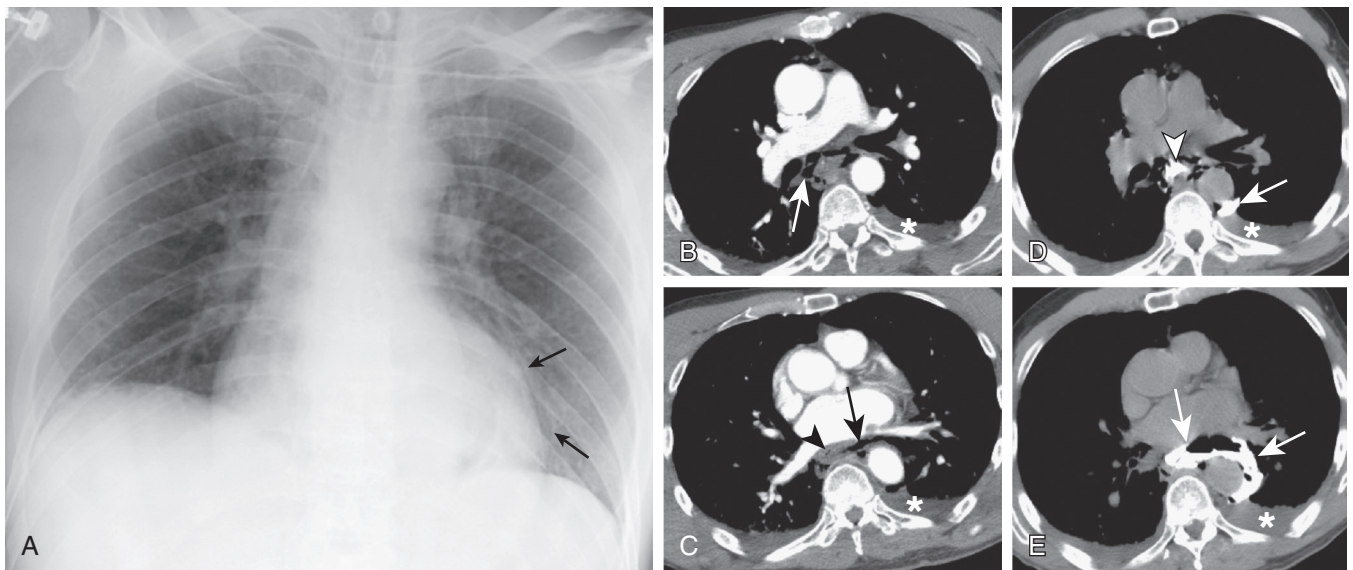


Figure 84-5 Esophageal rupture (Boerhaave syndrome): imaging findings. **A**, Frontal chest radiograph in a patient with chest pain shows pneumomediastinum, evidenced by elevation of the left mediastinal pleura, producing a gas lucency between the left heart border and medial left lung (*arrows*). Axial chest CT initially performed following intravenous contrast, prior to oral contrast administration (**B** and **C**), and after administration of oral contrast (**D** and **E**) shows pneumomediastinum (*arrows*, **B** and **C**) in close proximity to the esophagus (*arrowhead*, **C**). Left pleural effusion (*) is evident. Following administration of oral contrast (**D** and **E**), the contrast material can be seen to distend the esophagus (*arrowhead*, **D**) subsequently opacifying the areas of pneumomediastinum (*arrows*, **D** and **E**) extending toward the left pleural space, confirming an esophageal source for the perforation. (Courtesy Michael Gotway, MD.)

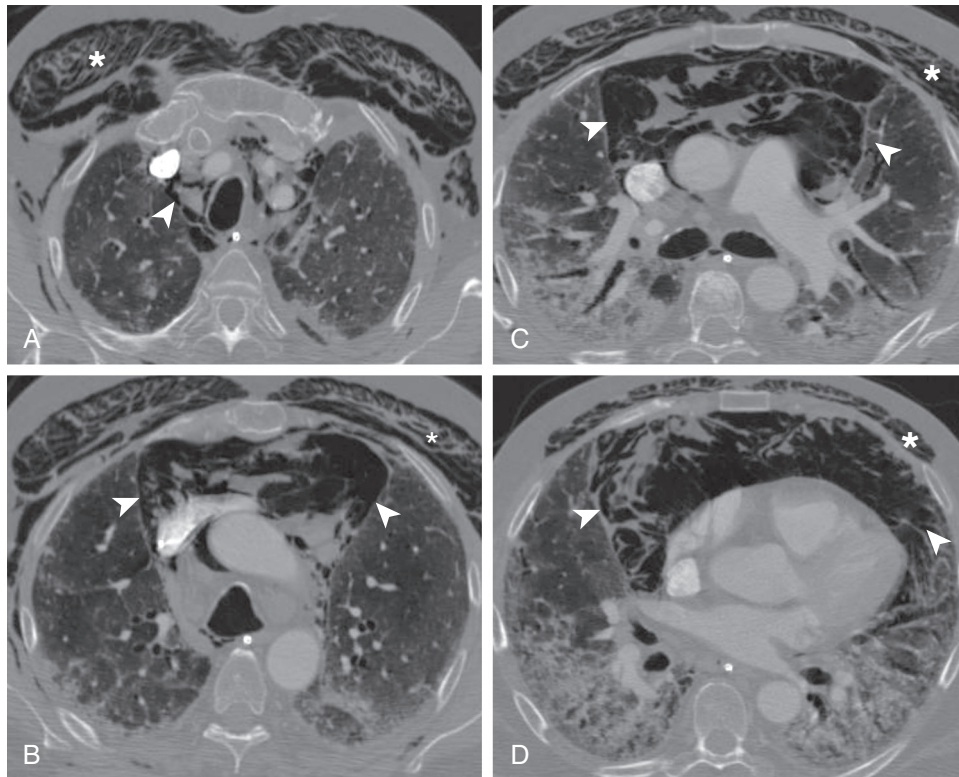
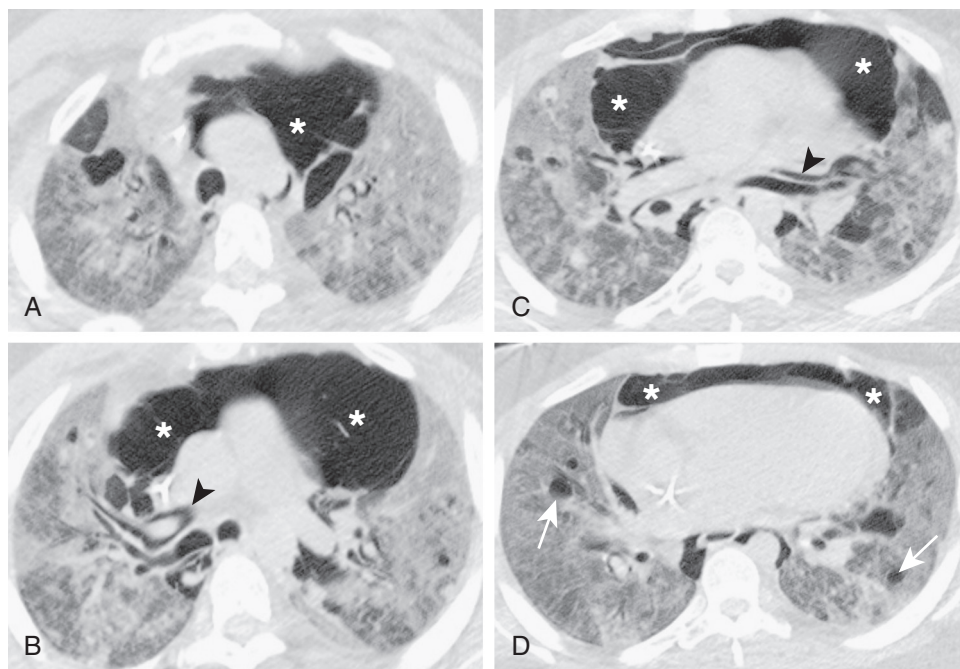


Figure 84-6 Spontaneous pneumomediastinum in a patient with interstitial lung disease. **A–D**, Axial chest CT displayed in lung windows shows extensive pneumomediastinum (*arrowheads*) and subcutaneous emphysema (*). Patchy bilateral basal predominant reticulation and architectural distortion represent fibrotic lung disease, with areas of more upper lobe predominant ground-glass opacity shown to reflect diffuse alveolar damage at surgical lung biopsy performed subsequently. The diffuse alveolar damage developed acutely, superimposed on the chronic fibrotic lung disease. (Courtesy Michael Gotway, MD.)



eFigure 84-7 Pneumomediastinum in a patient with AIDS and *Pneumocystis jirovecii* pneumonia. A–D, Axial chest CT shows diffuse ground-glass opacity associated with thin-walled cysts (arrows), representing pneumatoceles in the setting of *Pneumocystis jirovecii* pneumonia. Extensive pneumomediastinum (*) is present. Pneumomediastinum outlining the right upper lobe pulmonary artery (arrowhead, B) and interstitial emphysema, anterior to the left mainstem bronchus (arrowhead, C) are seen. (Courtesy Michael Gotway, MD.)

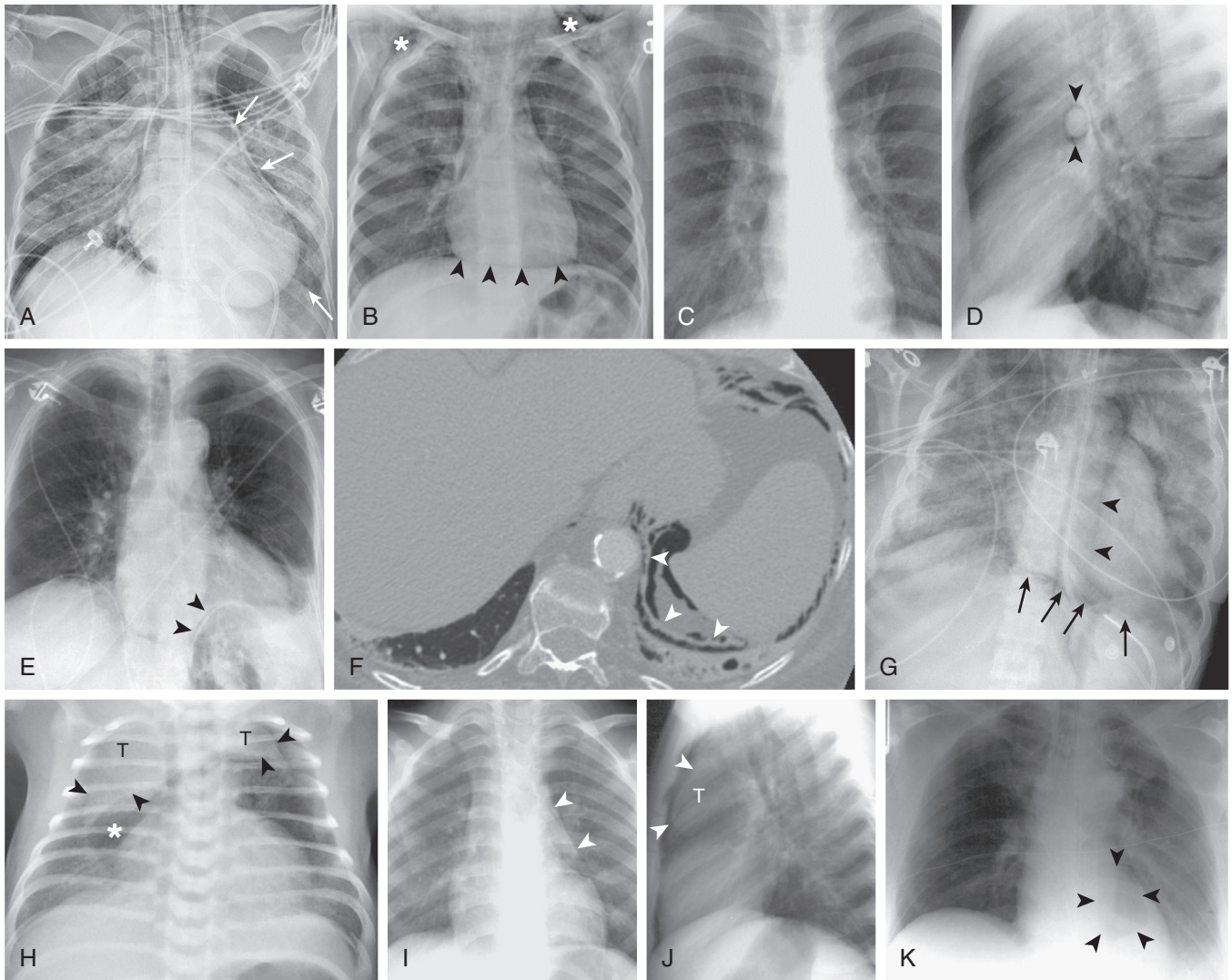
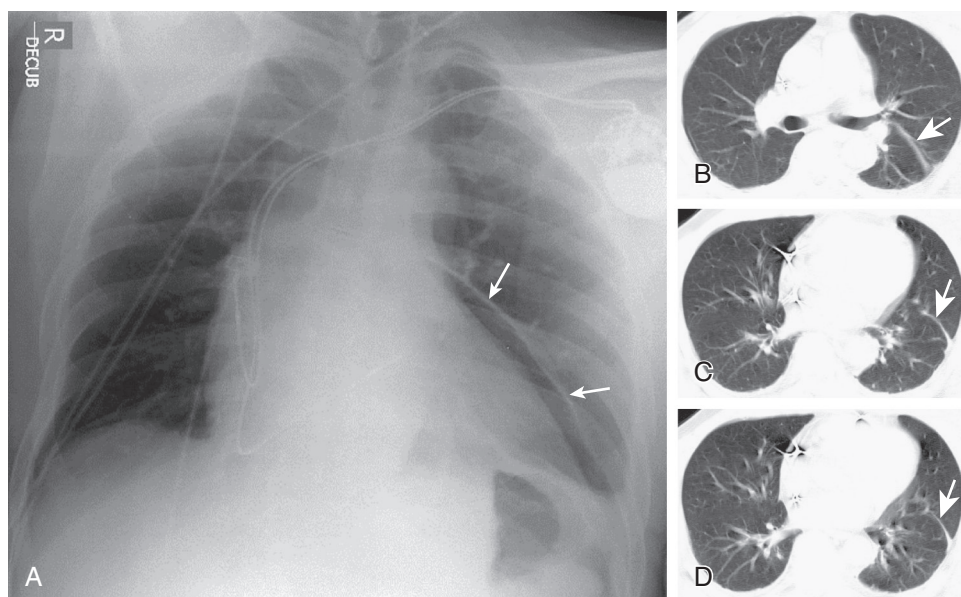
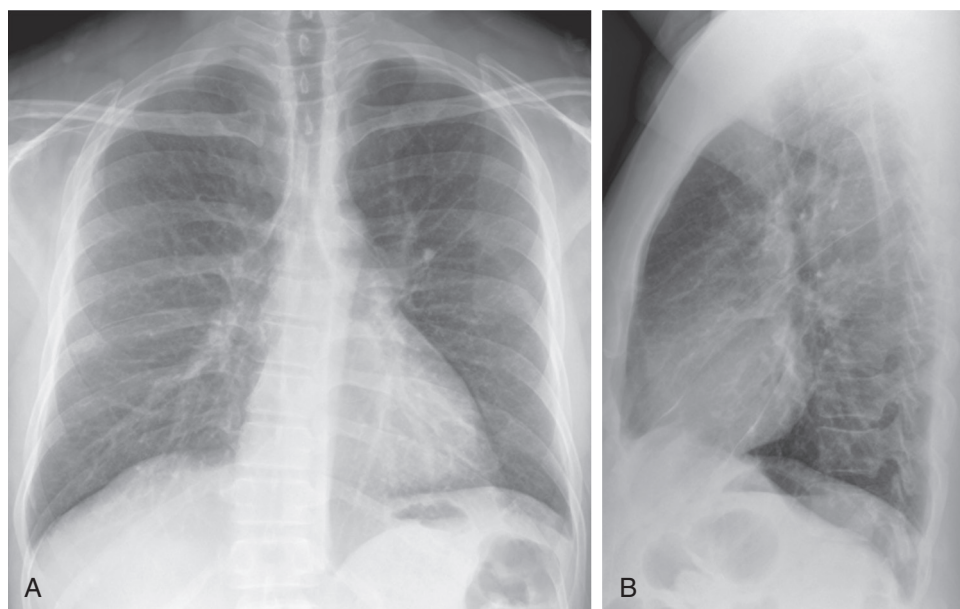


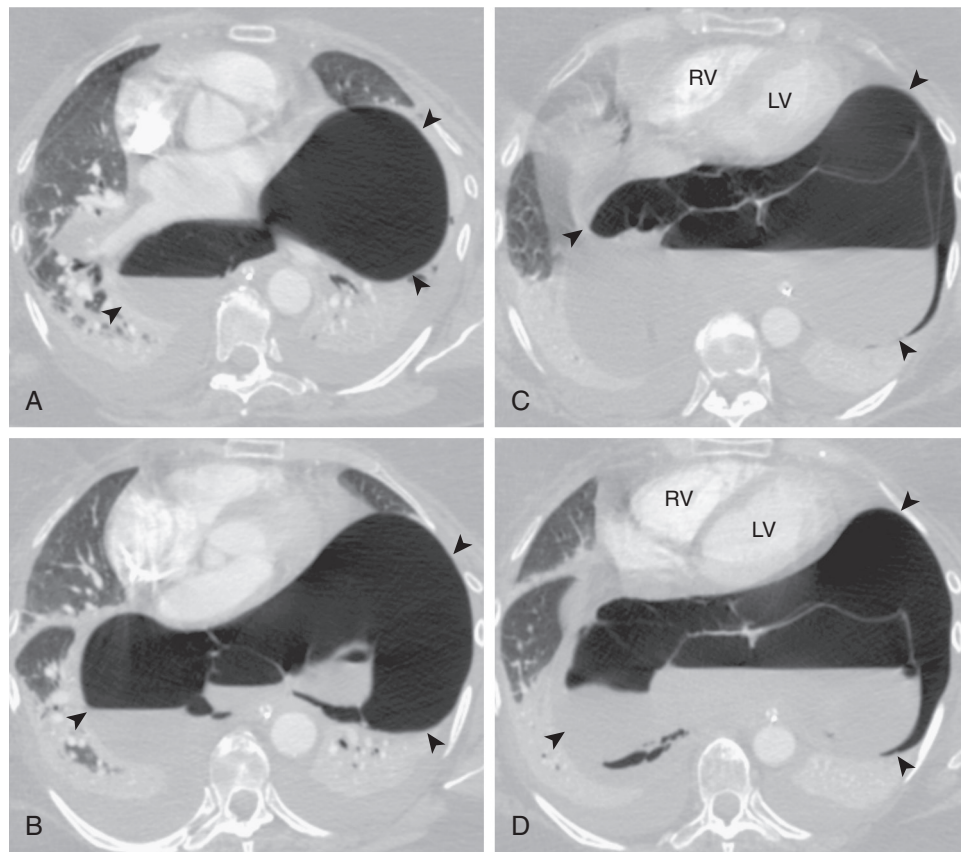
Figure 84-8 Chest radiographic findings of pneumomediastinum. **A**, Frontal chest radiograph shows abnormal lucency interposed between the left cardiac border and left mediastinal pleura (*arrows*) due to the presence of mediastinal gas. Gas outlines the superior mediastinum and extends into the neck as well. **B**, The "continuous diaphragm" sign. Frontal chest radiograph shows a linear gas lucency between the heart and diaphragm (*arrowheads*), rendering the diaphragm visible where it is normally obscured because of contact with the inferior pericardium and heart. **C** and **D**, Chest radiographic findings of pneumomediastinum: "ring-around-the-artery" sign. **C**, Frontal chest radiograph shows few features that allow the confident diagnosis of pneumomediastinum. **D**, Lateral chest radiograph shows gas surrounding and sharply outlining the extrapericardial segment of the right pulmonary artery (*arrowheads*). **E** and **F**, Chest radiographic findings of pneumomediastinum: the "extrapleural air" sign. **E**, Frontal chest radiograph shows gas lucency separating the diaphragm from the combined parietal and visceral pleural layers (*arrowheads*). **F**, Axial chest CT displayed in lung windows shows gas, representing pneumomediastinum outlining both sides of the medial left hemidiaphragm (*arrowheads*). **G**, Chest radiographic findings of pneumomediastinum: Naclerio's "V" sign. Frontal chest radiograph shows lucency extending along the descending thoracic aorta (*arrowheads*) and extending laterally between the parietal pleura and medial left hemidiaphragm, intersecting gas lucency along the latter (*arrows*). Other chest radiographic features of pneumomediastinum, such as sharp outlining of the aortic arch and left mediastinum, are evident. **H**, Chest radiographic findings of pneumomediastinum: elevation of the thymus causing the "thymic spinnaker-sail" sign. Frontal chest radiograph in an infant shows abnormal mediastinal lucency that forms an interface (*arrowheads*) with superior mediastinal tissue, representing the thymus (*T*); note that the gas lucency "elevates" the thymus. **I** and **J**, Frontal and lateral chest radiographs in an older child show gas lucency along the left mediastinum (*arrowheads*) on the frontal projection (**I**), and sharply outlining (*arrowheads*) the thymus (*T*) on the lateral projection (**J**). **K**, Chest radiographic findings of pneumomediastinum: gas in the pulmonary ligament. Frontal chest radiograph shows triangular gas lucency in the retrocardiac area (*arrowheads*), the apex of which points superiorly. This finding resolved on repeat chest radiography 1 week later. (Courtesy Michael Gotway, MD.)



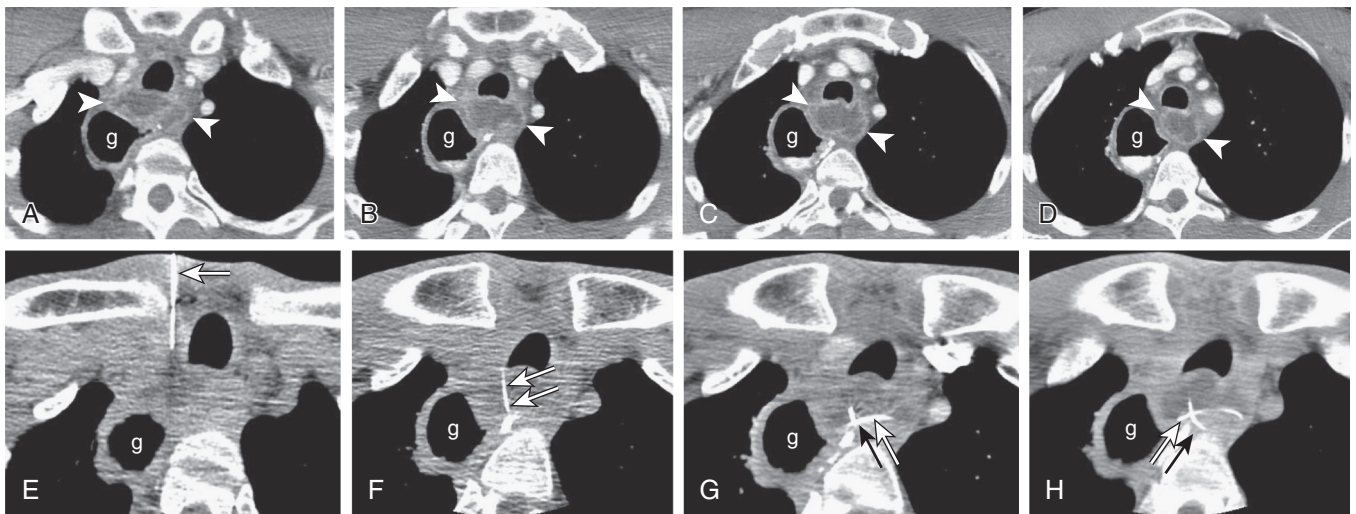
eFigure 84-9 Pneumomediastinum mimics at chest radiography: unusual appearance of a thickened left major (oblique) fissure. **A**, Frontal chest radiograph shows a curvilinear opacity (*arrows*) in the left mid-lung. The lucency between this opacity and the left cardiac border creates the appearance of pneumomediastinum. **B–D**, Axial chest CT displayed in lung windows shows that the left mid-lung opacity is caused by thickening of the left major (oblique) fissure (*arrows*), which is posteriorly rotated due to volume loss in the left lower lobe. (Courtesy Michael Gotway, MD.)



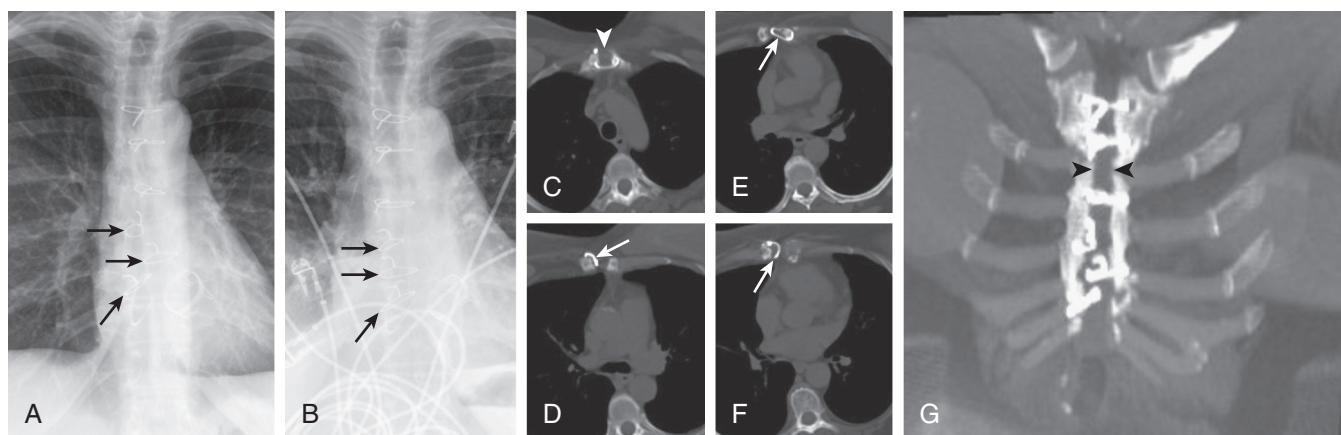
eFigure 84-10 Pneumomediastinum mimics at chest radiography: Mach bands. **A**, Frontal chest radiograph shows prominent lucency along the left cardiac border. No other features of pneumomediastinum are present. **B**, Lateral radiograph reveals no evidence of pneumomediastinum. The finding is due to a Mach band. Mach bands are alternating light and dark lines that are seen at the border between objects of differing contrast, optical density, or luminance, and are created by the process of lateral inhibition in retinal cells. This process effectively results in enhancement of the border between objects with differing optical densities. (Courtesy Michael Gotway, MD.)



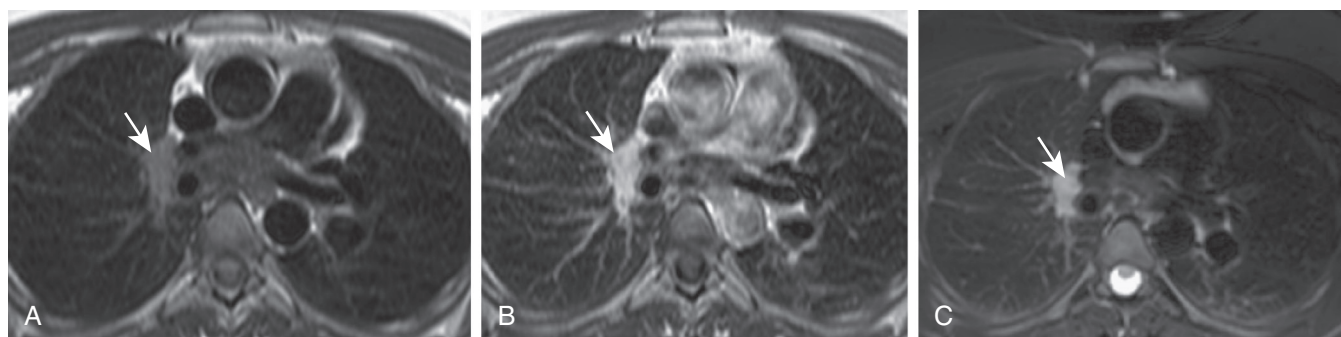
eFigure 84-11 Tension pneumomediastinum. A-D, Axial chest CT images displayed in lung windows show a large gas collection with numerous internal loculations in the middle mediastinum (arrowheads) resulting from esophageal perforation. The gas collection exerts significant mass effect on the heart, compressing and distorting the ventricles. Mediastinitis from the esophageal rupture was present, and the mediastinal gas and fluid was decompressed through placement of several thoracostomy tubes followed by repair of the esophageal laceration. LV, left ventricle; RV, right ventricle. (Courtesy Michael Gotway, MD.)



eFigure 84-12 Mediastinal abscess: CT findings. A-D, Axial contrast-enhanced chest CT displayed in soft tissue windows shows an enhancing fluid collection (arrowheads) in the mediastinum, representing an abscess that was seen after attempted dilation of a stricture following esophageal resection and gastric pull-through. E-H, CT images of the percutaneous drainage of the mediastinal abscess. Axial chest CT obtained during percutaneous drainage of the mediastinal abscess shows placement of a coaxial needle (arrow, E) into the anterior margin of the abscess through a paratracheal approach. Subsequent images (F-H) show a wire (double arrows) coiling in the abscess, over which a small drainage catheter was placed. g, intrathoracic stomach following gastric pull-through. (Courtesy Michael Gotway, MD.)



eFigure 84-13 Sternal dehiscence: imaging findings. **A**, Frontal chest radiograph obtained at presentation in a patient complaining of increasing chest pain and tenderness several months after a sternotomy. **B**, Frontal chest radiograph obtained shortly after the sternotomy, prior to symptoms, is shown for comparison. Note migration of sternal wires (*arrows*) on the presentation image (**A**) compared with **B**. **C–F**, Axial unenhanced chest CT shows that the sternal wires have “pulled through” the sternum (*arrows*), resulting in marked widening of the space between the two sternal halves (*arrowhead*). **G**, Coronal unenhanced chest CT shows sternal widening (*arrowheads*). (Courtesy Michael Gotway, MD.)



eFigure 84-14 Mediastinal fibrosis: MR appearance of right peribronchial involvement. Axial T1-weighted spin-echo images before (**A**) and after (**B**) intravenous contrast administration show an enhancing soft tissue mass in the right peribronchial region (*arrows*). **C**, Axial short tau inversion recovery image (a sequence designed to suppress signal from fat and highlight signal from fluid, such as edema; note increased signal in the cerebrospinal fluid posteriorly) shows increased signal within the actively inflamed right peribronchial tissue (*arrow*). Biopsy showed fibrotic material. (Courtesy Michael Gotway, MD.)

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DISORDERS OF SLEEP AND CONTROL OF BREATHING

85

CONTROL OF BREATHING AND UPPER AIRWAYS DURING SLEEP

RICHARD L. HORNER, PhD • ATUL MALHOTRA, MD

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INTRODUCTION

Problems with breathing are the root cause of the most common and serious of the sleep disorders. Such breathing problems are associated with a wide range of poor health outcomes including high blood pressure, heart attacks, stroke, diabetes, obesity, and altered brain function. This chapter is structured around several clinically oriented key concepts that relate to understanding the control of breathing and the upper airway during sleep. The key concepts are rooted in basic physiologic principles that are first presented, and these are followed by their application to the spectrum of clinical sleep-related breathing problems. To facilitate understanding of such sleep-related breathing problems further, we present several “perturbations” that importantly impact respiratory function during sleep. We also stress that although each perturbation is defined individually, several such perturbations can coexist in any one person to predispose to respiratory dysfunction. Such respi-

ratory dysfunction can manifest itself either specifically in sleep, or it can be present in wakefulness and made worse by sleep. Ultimately, it is the interaction of these perturbations with mechanisms of respiratory control in sleep that critically impact overall clinical course, stability, and long-term outcome.

WAKEFULNESS AND SLEEP

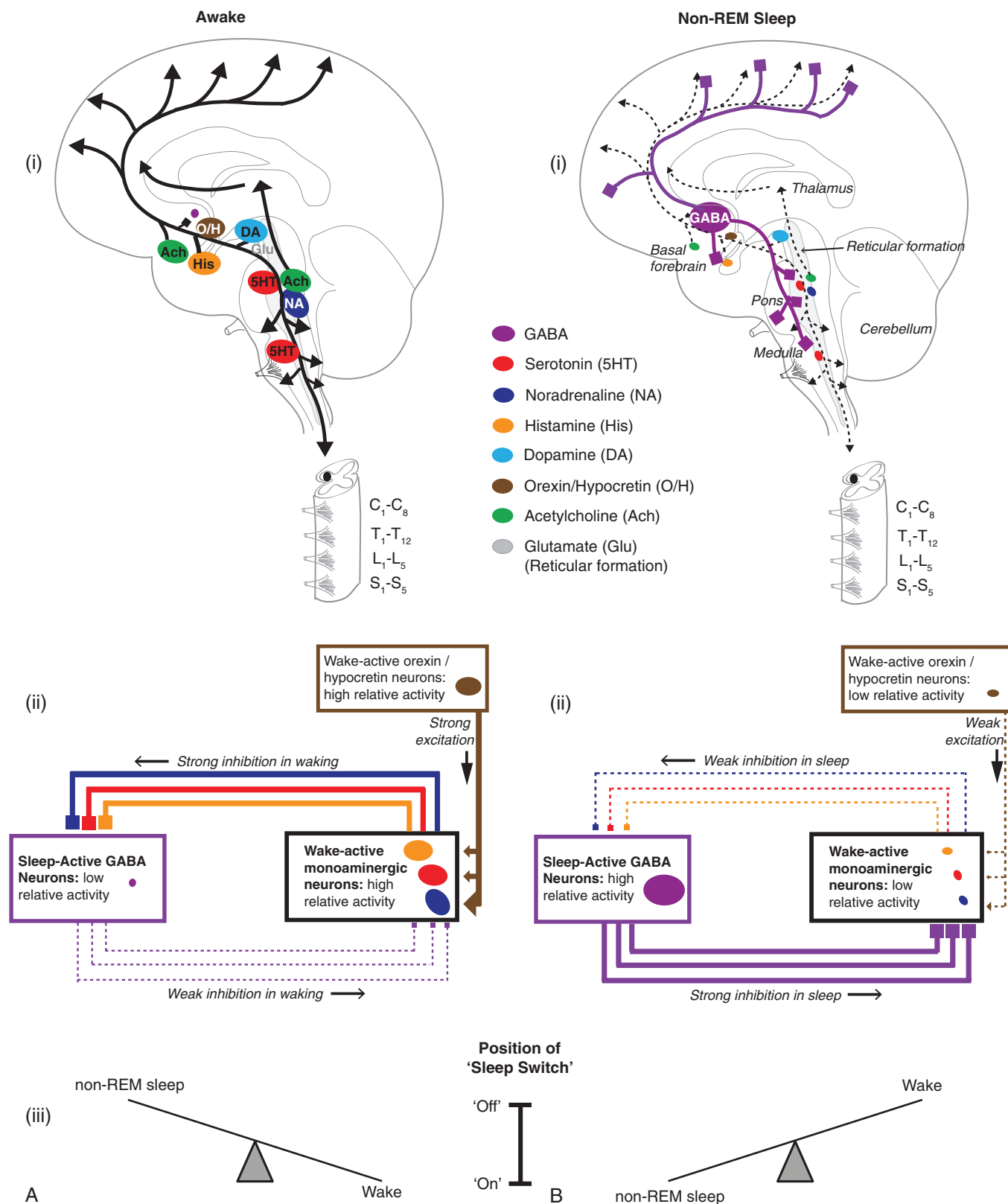
Some of the key brain circuits that generate the states of wakefulness, *non-rapid eye movement* (non-REM) sleep, and REM sleep are summarized in this section. Knowledge of these mechanisms leads to understanding the principle of the “sleep switch.”^{1,2} This principle is then used to explain how the common, serious, and at times life-threatening problems associated with sleep and drug-induced brain sedation and respiratory depression can work through common brain pathways.

GENERATION OF WAKEFULNESS AND SLEEP

Wakefulness

Figure 85-1A illustrates some of the main neuronal clusters involved in the regulation of brain activity in wake-

fulness and sleep. Serotonin, noradrenaline, histamine, dopamine, orexin (also named hypocretin), acetylcholine, and glutamate-containing cell groups collectively contribute to the brain activation of wakefulness. Such brain activation manifests as relatively low-voltage and fast-wave



activity in the *electroencephalogram* (EEG), and resting motor tone in the electromyogram recorded from postural muscles.

Some of the neuronal clusters that significantly contribute to the brain activation of wakefulness include dorsal and caudal raphe neurons located in the pons and medulla, respectively (serotonin-containing); the locus coeruleus (noradrenaline-containing); the tuberomammillary nucleus (histamine-containing); the ventral periaqueductal gray (dopamine-containing); the perifornical region of the lateral hypothalamus (orexin/hypocretin-containing); the pedunculopontine and laterodorsal tegmental nuclei in the pons as well as regions of the basal forebrain (acetylcholine-containing); and several of the aforementioned cell clusters plus distributed neurons in what has been commonly termed the *reticular formation* (glutamate-containing).

Non-REM Sleep

Non-REM sleep is often thought of as the “restorative” nondreaming phase of sleep. It is promoted and sustained by a system of neurons that inhibit the brain-arousal systems of wakefulness (see Fig. 85-1B). The chief cell groups that comprise this non-REM sleep-active inhibitory system include neurons in the ventrolateral preoptic area and anterior region of the hypothalamus, and regions of the basal forebrain. The cell groups that comprise this non-REM sleep-active inhibitory system synthesize and secrete the inhibitory amino acid *gamma-aminobutyric acid* (GABA) and the neuropeptide galanin. GABA is one of the chief inhibitory neurotransmitters in the brain. The direct GABA-mediated inhibition of the brain arousal systems identified in the section “Wakefulness” and Figure 85-1A, in combination with activation of cortically projecting inhibitory GABA neurons (see Fig. 85-1B), is responsible for the relatively higher-voltage and slower-wave EEG activity that typifies non-REM sleep.

REM Sleep

REM sleep, on the other hand, is associated with the dreaming phase of sleep and is accompanied by paralysis (atonia) of the skeletal musculature, effects that can also impact breathing. There are two major circuits involved in REM sleep generation (Fig. 85-2). The activation of these circuits produces the defining signs of REM sleep: (1) low-voltage

and fast-wave EEG activity and (2) suppression of postural motor tone. Important for the changes in EEG activity is reactivation of the cholinergic cell groups in the pons and basal forebrain that were relatively inactivated during non-REM sleep (see Fig. 85-2). The *spinal* motor activity in REM sleep is suppressed through recruitment of descending neural circuits that involve glycine (principally) and GABA (see Fig. 85-2). However, the periods of major suppression of upper airway muscle activity that are also seen in REM sleep do not seem to involve the same mechanism. The genioglossus muscle activity in REM sleep is suppressed through two additional processes: (1) *disfacilitation* (i.e., withdrawal of excitatory inputs), mediated principally by reduced noradrenaline and serotonin excitation at the hypoglossal motor pool, and (2) *inhibition* mediated by a newly identified muscarinic receptor mechanism linked to G protein-coupled potassium channels.³ The latter is illustrated in Figure 85-2, with the circuitry further explained in “Breathing and Its Control.”

THE “SLEEP SWITCH”

There are *mutually opposing* interactions between the wakefulness-promoting neuronal systems (see Fig. 85-1A) and the non-REM sleep-promoting neuronal systems (see Fig. 85-1B). This organization leads to wakefulness being associated with both a relatively *high level* of activity in the wake-promoting neuronal arousal systems *combined with* a relatively *low level* of activity in the opposing sleep-promoting GABA system (see Fig. 85-1A, panel ii). In contrast, non-REM sleep is associated with both a relatively *high level* of activity in the sleep-promoting GABA system *combined with* a relatively *low level* of activity in the opposing wake-promoting neuronal arousal systems (see Fig. 85-1B, panel ii).

The mutually opposing interactions between the wake-promoting and sleep-promoting neuronal systems produces a situation wherein the brain is in a stable state when *either* one of the respective neuronal systems dominates. This arrangement constitutes the “*sleep switch*”, in which the position of the switch is stable in either state because when one side is active the alternate state is simultaneously inhibited (see Fig. 85-1). In non-REM sleep, for example, the activation of GABA neurons reinforces their own activation via

Figure 85-1 Schema showing the main neuronal groups and their organizational interactions for generating the brain states of wakefulness (A) and non-rapid eye movement (non-REM) sleep (B). Shown (i) are the major neuronal clusters whose ascending projections are responsible for producing the electrocortical arousal of wakefulness and whose descending projections influence brain-stem autonomic networks and spinal motor activity. Non-REM sleep is generated when these wakefulness-generating systems are inhibited by clusters of neuronal groups containing the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The organizational structure for the maintenance of wakefulness and non-REM sleep, and the switch between the two states, are also shown (ii and iii). Mutual inhibitory interactions between wakefulness and sleep-promoting neuronal groups lead to the “switch” being stable in either position, thus producing consolidated periods of sleep at night and wakefulness during the day. The propensity to transition to a consolidated period of sleep at night (and later a consolidated period of wakefulness in the morning) is linked to the circadian-mediated decrease (then the later increase) in body temperature: the decrease in body temperature activates the GABA sleep-promoting neuronal systems, whereas the increase deactivates them. The non-REM sleep-active GABA neuronal groups include those in the ventrolateral preoptic region of the thalamus, as well as those in the basal forebrain and anterior hypothalamus. The relative position and sizes of neuronal groups are shown for visual clarity and are not meant to represent their strict anatomic positions. Relatively high levels of neuronal activity are represented by *large symbols and solid lines*, whereas relatively low levels of neuronal activity are represented by *small symbols and dashed lines*. Inhibitory neuronal projections from cell groups are indicated by **■**, and excitatory projections by *solid arrowheads*. See text for further details. (Adapted from Horner RL: Emerging principles and neural substrates underlying tonic sleep-state-dependent influences on respiratory motor activity. *Philos Trans R Soc Lond B Biol Sci* 364, 2553–2564, 2009; Horner RL: Central neural control of respiratory neurons and motoneurons during sleep. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine*. St. Louis, 2011, Elsevier Saunders, pp. 237–249; Horner RL: Respiratory physiology. In Kushida C, editor: *Encyclopedia of sleep*, vol. 1. Waltham, MA, 2013, Academic Press, pp. 517–524; Saper CB, Scammell TE, Lu J: Hypothalamic regulation of sleep and circadian rhythms. *Nature* 437:1257–1263, 2005. © Richard L. Horner, PhD, University of Toronto.)

REM Sleep Generation and Motor Suppression

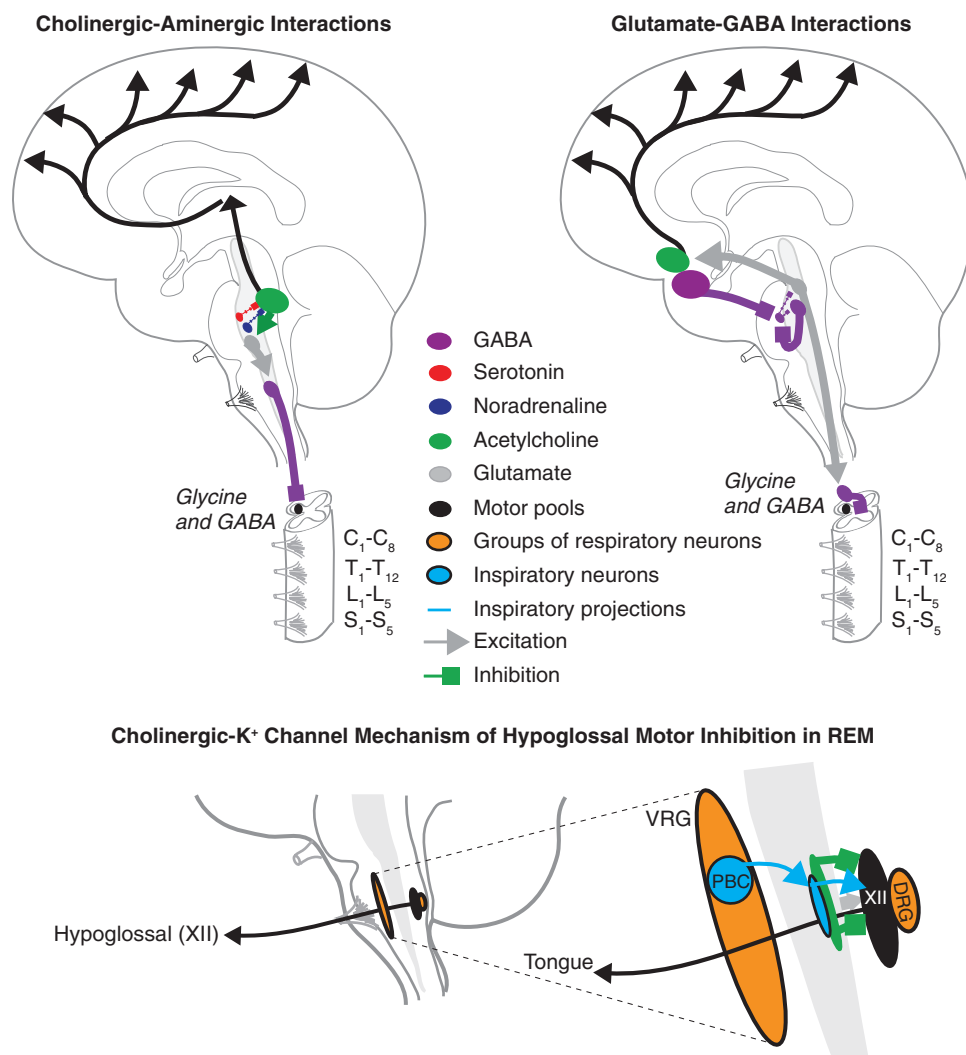


Figure 85-2 Schema showing the main neuronal groups and their organizational interactions for generating the brain state of REM sleep. There are currently two explanations of REM sleep generation: one involving interactions of cholinergic and aminergic cell clusters (*top left*) and the other involving interactions of glutamatergic and GABAergic cell clusters (*top right*). Although the finer details are discussed in the text, the upshot is that each can explain the cardinal features of REM sleep: (1) ascending cortical activation and (2) descending spinal motor inhibition. The inhibition of spinal motor activity in REM sleep appears different. For the hypoglossal motor pool, for example, which innervates the musculature of the tongue via cranial nerve XII, a cholinergic mechanism mediates the strong motor inhibition of REM sleep. This inhibition counteracts the inspiratory drive to this motor pool that originates from the ventral respiratory group (VRG) via the pre-Bötzinger complex (PBC) and premotoneurons in the lateral reticular formation (the latter two indicated as inspiratory neurons and color coded in *blue*). The dorsal respiratory group (DRG) is also shown for completeness. The hypoglossal motor pool also receives tonic state-dependent drive from the reticular formation (color coded in *gray*). Inhibitory neuronal projections are indicated by ■, and excitatory projections by solid arrowheads. See text for further details. GABA, Gamma-aminobutyric acid. (© Richard L. Horner, PhD, University of Toronto.)

inhibition of the wake-active neuronal systems at the same time.

EFFECTS OF COMMON NEURODEPRESSIVE DRUGS ON BRAIN AROUSAL STATE

The reciprocally opposing wakefulness and sleep-promoting neuronal systems identified in sections, “*Generation of Wakefulness and Sleep*” and “*Sleep Switch*,” essentially alter the brain arousal state via the associated changes in the balance of excitatory and inhibitory neurotransmitters in the critical brain regions identified in [Figure 85-1](#). The

balance of these brain neurochemicals, however, is not only changed across natural states of wakefulness and sleep, but also the balance is changed in *predictable ways* by the ingestion of commonly used neurodepressive drugs. Such drugs include benzodiazepines, imidazopyridines (nonbenzodiazepine sedative hypnotics), barbiturates, ethanol, and some general anesthetics that are either inhalational (e.g., isoflurane) or injectable (e.g., propofol or etomidate). All these agents interact with binding sites on GABA_A receptors that enhance neuronal inhibition at sites where GABA would otherwise be acting.⁴ There are several sites within the endogenous sleep-wake circuitry identified in [Figure](#)

85-1 where such neurodepressive drugs act to depress the brain arousal state and promote sedation and/or loss of consciousness.⁴ Such agents, therefore, effectively “tip the balance” within the endogenous sleep-wake circuitry “toward” sedation and “away” from brain arousal.

The principle of the *sleep switch* can also be used to understand that the depression of brain arousability that is seen in both natural sleep and with neurodepressive drugs is the product of *two* mechanisms. The first is the augmentation of inhibitory GABAergic influences and the second is the concomitant depression of arousal-related stimulatory influences (see Fig. 85-1B, panel ii). There is a dual effect because these inhibitory and excitatory mechanisms cannot operate independently because of their inherent interconnectedness. This principle has further implications for understanding sleep- and drug-induced respiratory depression.

APPLICATION TO SLEEP AND DRUG-INDUCED RESPIRATORY DEPRESSION

The organization of the sleep switch and its application to understanding sleep and drug-induced brain sedation (see “Effects of Common Neurodepressive Drugs on Brain Arousal State”) also has direct applications to understanding respiratory depression. The respiratory network and its associated control systems are themselves influenced by the same state-dependent arousal/sleep systems illustrated in Figures 85-1 and 85-2. Such wakefulness and sleep-dependent neuronal systems also have significant projections to the respiratory network.

Accordingly, during both natural sleep and in the presence of many commonly used sedative and anesthetic drugs, there is both augmentation of the GABAergic inhibitory system and corresponding reductions in excitatory influences from the brain arousal systems (as outlined in “Effects of Common Neurodepressive Drugs on Brain Arousal State”). The net result is a tipping of the balance in the sleep switch toward low brain arousability *plus* alteration of drives to the respiratory network. As further outlined in “Breathing and Its Control,” these state-dependent drives affect the musculature particularly of the upper airways, thus predisposing to obstructive sleep apneas and hypopneas in susceptible individuals.⁵ In essence, the brain functions as a gain-setting device for breathing by altering brain neurochemistry of the key elements of respiratory control: the respiratory neurons, the motoneurons, and the sites involved in the reflex modulation of breathing (see “Breathing and Its Control”).

BREATHING AND ITS CONTROL

The complexity of the brain-stem respiratory network can be distilled to three essential elements:

1. *Respiratory neurons* that generate respiratory rhythm and drive the expression of rhythmic activity in other components of the respiratory network.
2. *Respiratory motor pools* that innervate and activate the primary and secondary muscles of breathing. The primary respiratory muscles are so designated because

they *generate* airflow (e.g., the diaphragm). In contrast, the secondary (accessory) muscles of breathing do not generate airflow but either significantly modulate its passage (e.g., pharyngeal muscles that maintain a patent upper airway) or otherwise support the act of breathing (e.g., the intercostal muscles that contribute to the maintenance of lung volume).

3. *Chemosensors* that detect alterations in blood gases and elicit a physiologic response. In the case of hypoventilation during sleep, for example, the appropriate physiologic response includes *both* an attempted chemoreceptor-mediated increase in ventilation *and* arousal from sleep. The importance of arousal from sleep is critical to survival in some situations when the ventilatory response is futile by itself, for example, shaking off a suffocating blanket in the case of a sleeping infant to prevent asphyxia and risk of sudden infant death syndrome.

The following sections identify the key circuits that generate breathing and control its regulation.

RESPIRATORY NEURONS

Organization

Figure 85-3 illustrates the main components of the respiratory network generating respiratory rhythm and motor activation. The *ventral respiratory group* (VRG) contains Bötzing complex (expiratory) neurons, pre-Bötzing complex (inspiratory) neurons, rostral ventral respiratory group (predominantly inspiratory) neurons, and caudal ventral respiratory group (predominantly expiratory) neurons. The *dorsal respiratory group* (DRG) contains mainly inspiratory neurons. The DRG and its associated regions of the nucleus of the solitary tract are also the projection sites for afferents important to the reflex control of breathing: the carotid and aortic chemoreceptors and baroreceptors, and lung vagal afferents.

The brain stem also includes motoneurons of the hypoglossal and trigeminal motor nuclei that innervate muscles important to the maintenance of upper airway patency (see Fig. 85-3).⁵ Regions of the nucleus ambiguus also contain motoneurons that innervate the muscles of the larynx and pharynx via the vagus, glossopharyngeal, and accessory nerves. Respiratory neurons in the pons (not shown) also modulate the activity of medullary respiratory neurons.

Respiratory Rhythm and Motor Activation

Figure 85-3 also illustrates that some respiratory neurons are identified as *propriobulbar*, that is, neurons that project to, and influence the activity of, other medullary respiratory neurons but themselves do not project to motoneurons.⁵ Others are identified as *bulbospinal respiratory pre-motoneurons*, that is, neurons that project to spinal motoneurons, which in turn innervate the respective respiratory pump and abdominal muscles of breathing.

Inspiration

A particularly important propriobulbar respiratory neuronal group is the pre-Bötzing complex. This region plays a key role in generating the fundamental respiratory rhythm

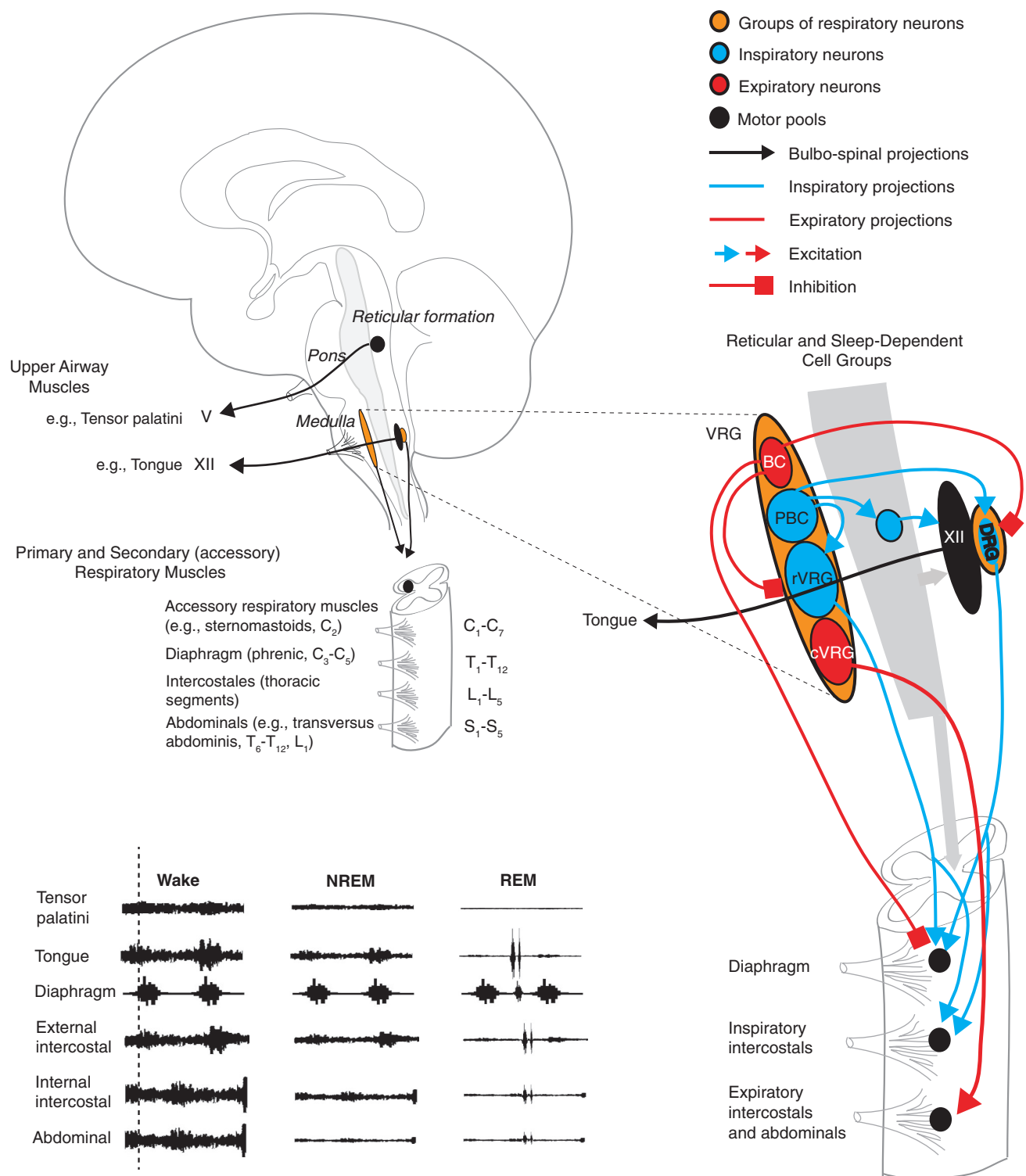


Figure 85-3 Schema showing some of the main neuronal groups and their organizational interactions for the generation of efferent motor output to different respiratory muscles. On the upper left are shown the main neuronal groups and selected motor pools innervating the muscles of the upper airway and the primary and secondary (accessory) muscles of the respiratory pump. On the right, at higher magnification, are shown the main clusters of neurons comprising the ventral and dorsal respiratory groups (VRG and DRG, respectively), and their projections to other neurons comprising the respiratory network. The innervation of the hypoglossal motor pool by state-dependent neurons of the reticular formation is also shown. See text for further details on the relevance of this latter point. At the lower left, the electromyographic activities of various respiratory-related muscles are also shown: palatal, tongue, diaphragm and the accessory, intercostal, and abdominal respiratory muscles. Note that the level of respiratory-related and tonic activities varies for different muscles, with some muscles such as the tensor palatini expressing mainly tonic activity and others, like the tongue and intercostals, expressing both tonic and respiratory activity. This relative balance of tonic and respiratory-related activity can change across sleep-wake states; with tonic activity being typically suppressed in sleep. The onset of muscle activity with respect to the diaphragm is shown by the dashed line. BC, Bötzinger complex; cVRG, caudal VRG; PBC, pre-Bötzinger complex; rVRG, rostral VRG. See text for further details. (Adapted from Horner RL: Emerging principles and neural substrates underlying tonic sleep-state-dependent influences on respiratory motor activity. *Philos Trans R Soc Lond B Biol Sci* 364, 2553–2564, 2009; Horner RL: Central neural control of respiratory neurons and motoneurons during sleep. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine*. St. Louis, 2011, Elsevier, Saunders, pp. 237–249; Horner RL: Respiratory physiology. In Kushida C, editor: *Encyclopedia of sleep*, vol. 1. Waltham, MA, 2013, Academic Press, pp. 517–524. © Richard L. Horner, PhD, University of Toronto.)

in mammals.⁶ Pre-Bötzinger complex neurons drive activation of bulbospinal neurons of the DRG and VRG during inspiration, which then activate spinal inspiratory phrenic and intercostal motoneurons (see Fig. 85-3). Inactivation of pre-Bötzinger complex neurons in animal models leads to ataxic breathing and central apneas, especially in sleep.^{7,8} The pre-Bötzinger complex is also a critical site mediating respiratory rate depression by opioids.⁹

Expiration

In expiration, the expiratory neurons of the Böttinger complex inhibit inspiratory pre-motoneurons and motoneurons (see Fig. 85-3). Also, in expiration, the caudal ventral respiratory group neurons increase excitability of spinal expiratory motoneurons (see Fig. 85-3), although this excitation does not necessarily manifest as demonstrable expiratory muscle activation at rest.

Respiratory Rhythm Generation and Central Apneas

The automatic and nonconscious rhythm of breathing is ultimately generated by the intrinsic membrane properties and connections of the individual neurons that comprise the respiratory network. Essential to expression of this rhythmicity, however, is provision of a sufficient level of underlying tonic excitation. Key sources of tonic excitation are from the aforementioned wakefulness-dependent neural systems (see Fig. 85-1) as well as the peripheral and central chemoreceptors (Fig. 85-4).

An important physiologic principle that emerges from identification of the necessity and sufficiency of tonic exci-

tation for respiratory rhythm generation is that removal of such tonic excitation can abolish respiratory rhythm. Sleep or neurodepressive drugs (see Fig. 85-1), or reduced chemoreceptor inputs (see “Breathing Is Dependent on Feedback Regulation in Sleep”), can each lead to cessation of respiratory rhythm and development of central sleep apneas.

RESPIRATORY MOTOR POOLS AND MUSCLE ACTIVITY

Respiratory Muscles Vary in the Degree of Their Relationship to Breathing

Different respiratory muscles express varying degrees of respiratory-related activity and/or tonic (i.e., nonrhythmic, continuous, or background) activation. The diaphragm, for example, is almost exclusively respiratory-related while the palatal, tongue, intercostal, and abdominal muscles express both respiratory and tonic activities, to varying degrees. The physiologic basis for this variation is that the respiratory neurons that ultimately drive the respective respiratory muscles themselves vary in the strength of their relationship to breathing.¹⁰ Some respiratory neurons, for example, are almost exclusively driven by respiratory rhythm-generating neurons and are weakly influenced by other inputs. In contrast, there are some respiratory neurons that are weakly influenced by respiratory rhythm-generating neurons but more strongly influenced by tonic nonrespiratory inputs.¹⁰ Such tonic nonrespiratory inputs can arise from the sleep state-dependent cell groups identified in Figure 85-1.

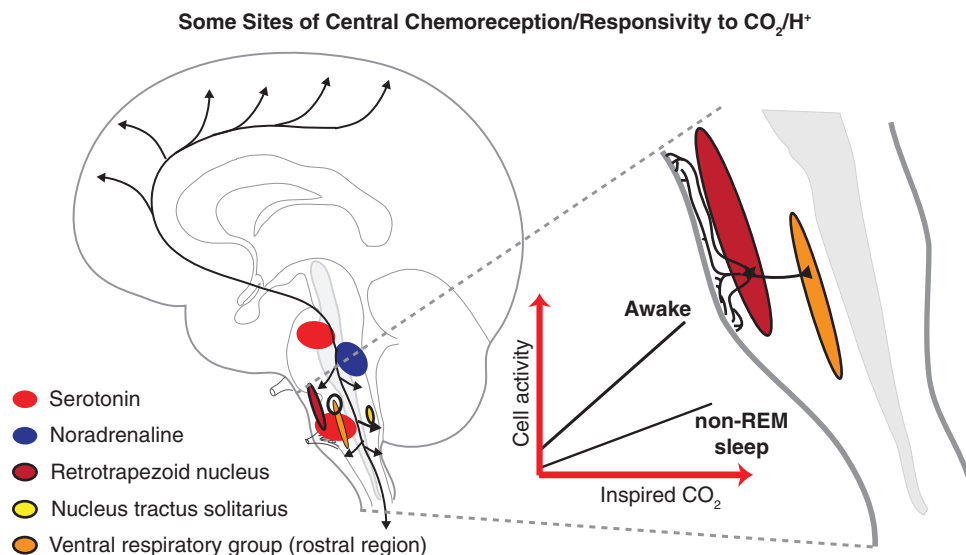


Figure 85-4 Sites of chemoception/responsivity to changes in CO_2/H^+ in the brain. Some of these sites are intimately associated with regulation of brain arousal in sleep and wakefulness (e.g., serotonin and noradrenaline containing cell clusters; see Fig. 85-1). Other sites are intimately associated with respiratory neuronal activity and reflex responses (e.g., nucleus tractus solitarius and ventral respiratory group; see Fig. 85-3). A key site that is intrinsically sensitive to alterations in CO_2/H^+ is the retrotrapezoid nucleus located near the ventral surface of the medulla. This region of the brain is magnified in the panel on the right. Branching dendrites from retrotrapezoid neurons “taste” the cerebrospinal fluid at the medullary surface and are activated by increased CO_2 (lowered H^+). Activity related to CO_2/H^+ influences several brain regions, including the ventral respiratory group, so driving breathing. The inset shows the response of a brain-stem serotonergic neuron to increases in inspired CO_2 . There are several features of note: (1) baseline activity (i.e., at zero inspired CO_2) is higher in wakefulness than in sleep, in keeping with Figure 85-1; (2) the neuronal activity at any given inspired CO_2 is greater in wakefulness than in sleep; (3) the slope (gain) of response is also greater in wakefulness than in sleep. Together, these three features parallel the overall respiratory responses to CO_2 as measured by changes in ventilation (compare with Fig. 85-7). © Richard L. Horner, PhD, University of Toronto.)

Effects of Sleep

The identification of respiratory neurons and motoneurons that vary in the strength of their relationship to breathing assumes greater significance because of the physiologic principle identified by John Orem from Texas Tech University.¹⁰ Those respiratory neurons that are most strongly driven by respiratory rhythm-generating neurons are *least* affected by the transition from wakefulness to non-REM sleep. In contrast, those respiratory neurons that are more strongly influenced by tonic nonrespiratory inputs are *most* affected by the change from wakefulness to sleep. In the latter case, activity within certain respiratory muscles can cease or be markedly depressed during sleep, especially those showing prominent tonic muscle activity in wakefulness, such as the muscles of the upper airway and chest wall (see Fig. 85-3). The key physiologic and clinical implications of this effect are identified in “Upper Airway Motor Tone and Compensatory Reflex Responses are Particularly Sensitive to Depression In Sleep”; the loss of the tonic input to muscles of the upper airway is one of the major reasons for the suppression of upper airway muscle activity in sleep and the susceptibility to obstructive sleep apneas.

CHEMOSENSORS AND CHEMOREFLEXES

Location and State-Dependence of Responses

Arterial O_2 and CO_2 levels are regulated by peripheral chemoreceptors located at the bifurcation of the common carotid arteries, and central chemoreceptors located in the brain. More specifically, the central chemoreceptors are located close to the ventral surface of the medulla in the caudal region of the retrotrapezoid nucleus (see Fig. 85-4).¹¹ Cells in this region of the retrotrapezoid nucleus are intrinsically sensitive to changes in CO_2/H^+ . These CO_2/H^+ sensitive neurons have dendrites that extend to the ventral medullary surface by which they sense the pH of the surrounding cerebrospinal fluid. They also have axons that project to the rostral region of the VRG by which they drive respiratory network activity.

In addition to the retrotrapezoid nucleus, some of the wakefulness-active/sleep-inactive cell groups identified in Figure 85-1, such as serotonergic and noradrenergic neurons, are also responsive to alterations in CO_2/H^+ levels (see Fig. 85-4). For any given inspired CO_2 , the activity and responsivity (i.e., slope of response) of such neurons is reduced in sleep compared to wakefulness. As identified in later sections, this change in cell activity in response to hypercapnia from wakefulness to sleep parallels the change in overall ventilatory response.

INTEGRATIVE PHYSIOLOGIC MECHANISMS UNDERPINNING RESPIRATORY DYSFUNCTION AND INSTABILITY DURING SLEEP

The aim of this section is to integrate the key concepts and principles identified in the preceding sections in order to

identify the variety of mechanisms that can predispose to respiratory dysfunction in sleep.

BREATHING IS DEPENDENT ON FEEDBACK REGULATION IN SLEEP

Principle

A prevailing level of tonic excitation into the respiratory network is essential to drive respiratory rhythm and muscle activation (see “Respiratory Rhythm Generation and Central Apneas”). The brain arousal systems of wakefulness (see Fig. 85-1) provide a major source of such excitation to modulate breathing volitionally and/or non-volitionally, together termed *behavioral* influences or the “wakefulness stimulus” to breathing.¹² Figure 85-5 illustrates that such behavioral influences on respiratory network activity are reduced or withdrawn as one moves from wakefulness to non-REM sleep. As a result, the respiratory system becomes *dependent* upon feedback regulation in non-REM sleep to sustain sufficient activity.

Tonic activity of the peripheral and central chemoreceptors is *normally* sufficient to sustain effective breathing in non-REM sleep. The key consequence of the organization identified in Figure 85-5, however, is that *any* reduction or defect in feedback chemoreceptor control, for *any* reason, causes severe respiratory disturbance in non-REM sleep, a time when the stimulatory effects of wakefulness on the respiratory system are withdrawn. Interestingly, compared with the situation in non-REM sleep, in REM sleep, the heightened state of brain arousal (see Fig. 85-3) can restore sufficient nonspecific behavioral drives to the respiratory network to restore breathing.

Application

Hypocapnia is a potential cause of central apnea. Interestingly, hypocapnia, by itself, is not sufficient to elicit central

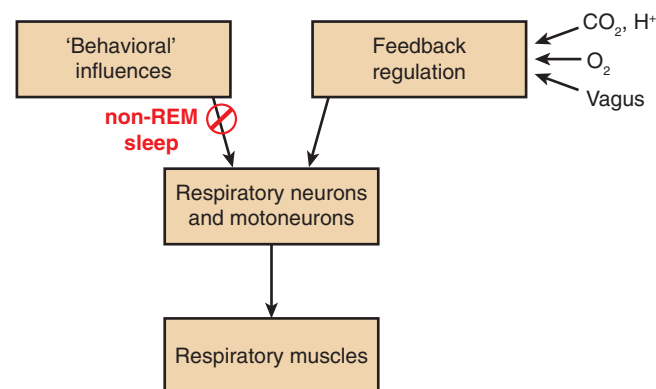


Figure 85-5 Conceptual model showing that efferent output from respiratory neurons and motoneurons is controlled by behavioral influences and feedback regulation. Feedback regulation includes control by CO_2/H^+ , O_2 levels, and responses to mechanical and ventilatory events in the airways and lung via the vagus nerves. Notably, behavioral influences are significantly reduced or withdrawn in non-REM sleep. The physiologic principle that arises from this effect is that breathing is essentially *dependent* on metabolic (CO_2 and O_2) control in non-REM sleep. The consequence is that *any* defect in metabolic control, for *any* reason, causes severe respiratory disturbance in sleep, but not necessarily in wakefulness. Behavioral influences include both volitional and nonvolitional (but wakefulness-dependent) mechanisms that influence breathing. (© Richard L. Horner, PhD, University of Toronto.)

apneas in wakefulness or in REM sleep because of the concomitant presence of behavioral influences on breathing. However, in non-REM sleep, hypocapnia can elicit central apneas because the stimulatory effects of brain arousal (i.e., behavioral influences) to the respiratory network are absent. This critical combination of factors, that is, hypocapnia and absence of behavioral influences to breathing in non-REM sleep, removes two of the crucial sources of tonic drives to the brain-stem network that normally generate and sustain breathing. Hypocapnia may be present at the onset of sleep as a result of chronic hyperventilation in wakefulness caused, for example, by heightened chemoreceptor drive (e.g., resulting from congestive heart failure) or by exaggerated behavioral influences on breathing (e.g., caused by anxiety). Hypocapnia at sleep onset can also result from the transient hyperventilation caused by sleep disturbance and brief arousal from sleep: the hyperventilation predisposing to unstable breathing by depleting the CO_2 reserve (defined in “Loop Gain and its Importance”). In these settings of hypocapnia, central apneas may become clinically important in non-REM sleep.

As a second example of the importance of tonic stimulation, patients with *congenital central hypoventilation syndrome* (CCHS) who have a defect in chemoreception exhibit major disturbances of ventilation in non-REM sleep but ventilate normally during wakefulness and during REM sleep. In more than 99% of CCHS patients, mutations have been found in the *paired-like homeobox 2b* (*PHOX2B*) gene, a gene expressed by neurons involved in peripheral and central chemoreception. The fact that *PHOX2B* is not expressed by respiratory neurons can perhaps explain the ability of these patients to breathe in wakefulness, because the mutation does not affect respiratory neurons. Rather, the state of wakefulness itself provides sufficient excitatory drive to the respiratory system to mask the major defect in chemoreceptor activity caused by the *PHOX2B* mutation. The ability of the CCHS patients to breathe normally in REM sleep further reinforces the principle that the relatively high levels of brain activation inherent to REM sleep (see Fig. 85-2) can provide sufficient restoration of behavioral drives to the respiratory network to reinstitute breathing.

As a final example that highlights the powerful effect of wakefulness as an independent driver of respiratory activity, it is noted that deep non-REM sleep and anesthesia are the most vulnerable states for respiratory rate depression by opioids at the pre-Bötzinger complex.⁹ In this situation breathing can be sustained by wakefulness even when opioids are present at the pre-Bötzinger complex, a key site for respiratory rhythm generation in mammals. However, loss of this important wakefulness stimulus to breathing can lead to hazardous respiratory depression in non-REM sleep and anesthesia. This example further emphasizes the principle that wakefulness per se can provide sufficient excitatory drive to the respiratory system to mask (at least partially) otherwise significant defects in respiratory control, in this case defects induced by drugs. The clinical relevance of this principle is that sedating agents can be deemed well tolerated in the initially alert patient but, when the stimulating effects of wakefulness are withdrawn during sleep, the patient may suffer significant respiratory depression (i.e., “crash”). Such a scenario is particularly dangerous when patients with sleep-related breathing problems

use opioids for pain management, especially if taken in combination with benzodiazepines and/or alcohol at home.

LOOP GAIN AND ITS IMPORTANCE

Principle

Loop gain is an engineering term that describes the overall gain, or sensitivity, of a feedback control system. A high gain system responds quickly and vigorously to any given perturbation; a low gain system responds slowly and weakly. The factors contributing to overall loop gain are *plant gain* and *controller gain* (Fig. 85-6). Plant gain largely reflects the effectiveness of breathing to eliminate CO_2 , that is, how much a given change in ventilation itself affects arterial CO_2 . Controller gain largely reflects chemoresponsiveness, for example, how much a given change in arterial CO_2 itself affects ventilation.

Overall, a high loop gain promotes ventilatory instability because it predisposes to a situation whereby a small perturbation in ventilation can trigger cessation of breathing because the change of the arterial PCO_2 makes it more likely to reach the *apnea threshold* (see Fig. 85-6). Loop gain is defined and quantified as the magnitude of the response to a given disturbance in breathing (e.g., hyperpnea) divided by the magnitude of the causal disturbance itself (e.g., an apnea, a sigh). If loop gain is less than 1, then the system corrects itself (i.e., breathing normalizes), but if loop gain is 1 or greater, then the system remains unstable. In the latter case, a large ventilatory response to a particular perturbation in breathing can itself become a subsequent disturbance, and so precipitate persistent instability. Overall, an increase in plant and/or controller gains can destabilize breathing because they lower the effective CO_2 reserve, that is, the amount by which an increase in ventilation lowers arterial PCO_2 to the chemical apnea threshold¹³ (see Fig. 85-6).

Application

There are several situations whereby altered plant and/or controller gains can predispose to sleep-disordered breathing. For example, when there is low functional residual capacity, dead space, or metabolic CO_2 production, a given increase in ventilation more effectively lowers arterial PCO_2 toward the apnea threshold. This is because in each situation there is an increase in plant gain and a corresponding increased tendency to unstable breathing by virtue of the effectively reduced CO_2 reserve¹³ (see Fig. 85-6C). Interventions such as nasal continuous positive airway pressure or positive end-expiratory pressure can help stabilize breathing in this context by increasing both functional residual capacity and dead space, thereby effectively reducing plant gain. Subtler distinctions between steady state and dynamic plant gains are discussed elsewhere.¹⁴ Similarly, patients with alveolar hypoventilation secondary to central nervous system disturbances or neuromuscular weakness are also predisposed to unstable breathing in sleep. This predisposition is also explained by virtue of their lowered CO_2 reserve, despite having an elevated resting arterial PCO_2 , due to a shift to the right in their equilibrium position for resting breathing¹³ (see orange symbol on Fig. 85-6C). Patients with heart failure also experience unstable breathing during

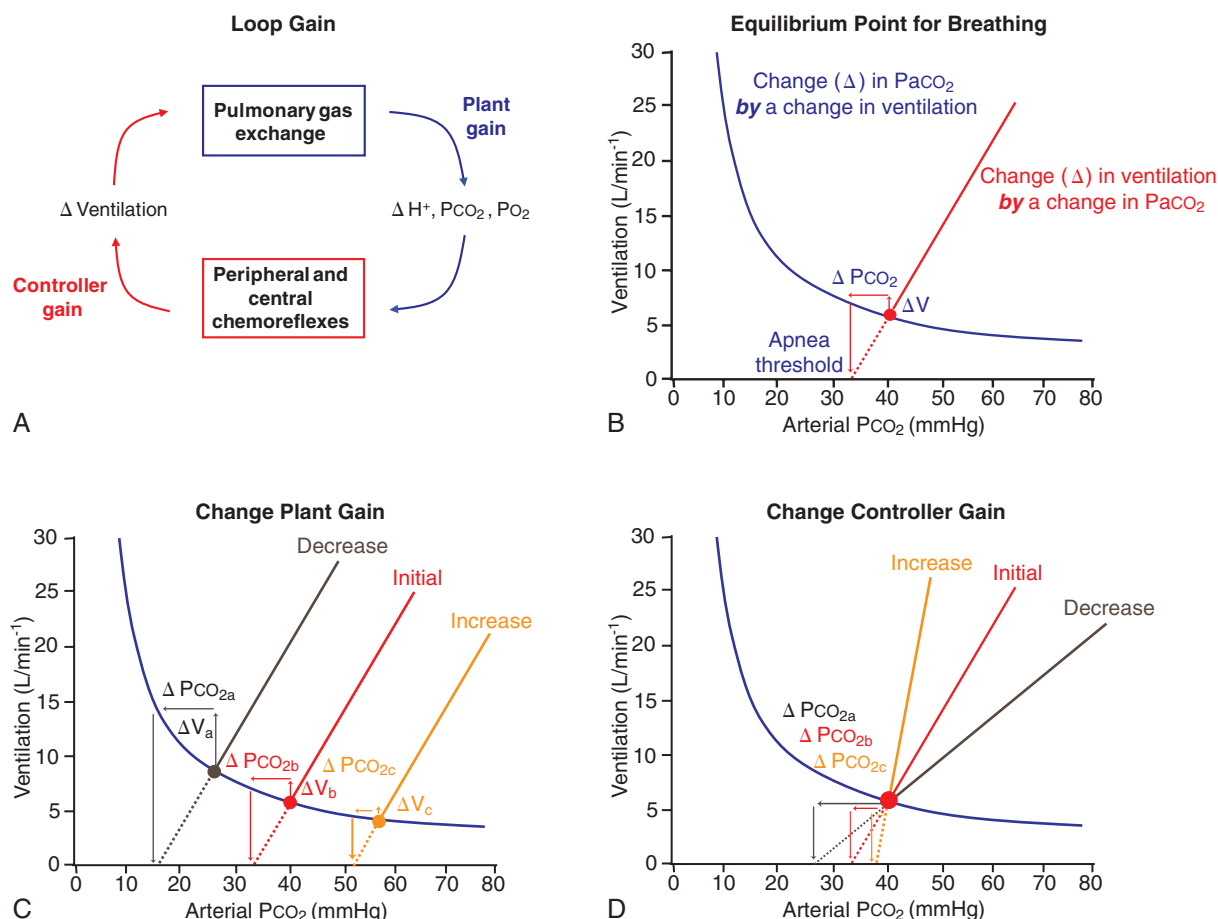


Figure 85-6 Schema to illustrate how loop gain (comprised of plant and controller gains) determines the equilibrium point for breathing and influences breathing stability/instability. **A**, Pulmonary gas exchange changes ventilatory variables, which themselves influence breathing. *Plant gain* largely reflects the effectiveness of ventilation to eliminate CO_2 (e.g., with a low functional residual capacity, low dead space, or low metabolic rate). *Controller gain* is largely a result of chemoresponsiveness (e.g., increased in heart failure). **B**, The equilibrium point for stable breathing is illustrated by the red symbol (●). This equilibrium point for resting breathing sits at the intersection of the ventilatory response to increased arterial PCO_2 (red line) and the change in arterial PCO_2 that results from a change in ventilation (the metabolic hyperbola, blue line). Reductions in arterial PCO_2 reduce ventilation according to the ventilatory response (dashed red line), until apnea is seen (the *apnea threshold*). The magnitude of the increase in ventilation that lowers arterial CO_2 to the apnea threshold is termed the CO_2 reserve. **C** and **D**, The predisposition to unstable breathing based upon the equilibrium position for resting breathing and the apnea threshold. Decreases in plant or controller gains produce a situation in which a larger increase in ventilatory disturbance is necessary to deplete the CO_2 reserve before apnea (**C** and **D**, brown line). In contrast, increases in plant or controller gains produce a situation in which a smaller increase in ventilatory disturbance is necessary to deplete the CO_2 reserve before apnea (**C** and **D**, orange line). The physiologic principle that arises from this effect is that the predisposition to ventilatory instability and disordered breathing in sleep is significantly determined by the plant and controller gains. For example, patients with alveolar hypoventilation secondary to central nervous system disturbance or neuromuscular weakness are predisposed to periodic breathing in sleep despite having an elevated resting arterial CO_2 (point ● in **C**). Likewise, patients with heart failure who have sympathetic nervous system-mediated increases in chemoreflex responsiveness are also predisposed to periodic breathing in sleep (point ● in **D**). (Adapted from Philipson EA, Bowes G: Control of breathing during sleep. In Cherniack NS, Widdicombe JG, editors: *Handbook of physiology*, section 3, control of breathing, part 2, the respiratory system, vol. II, Bethesda, MD, 1986, American Physiological Society, pp. 649–689; Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP: Pathophysiology of sleep apnea. *Physiol Rev* 90:47–112, 2010. © Richard L. Horner, PhD, University of Toronto.)

sleep. In these patients, the increased chemoresponsiveness associated with heart failure-induced sympathetic nervous system activation leads to increased controller gain and again a diminished CO_2 reserve (see Fig. 85-6D).

AROUSAL FROM SLEEP: A CONSEQUENCE AND CAUSE OF RESPIRATORY DISTURBANCE

Principle

The ventilatory responses to hypoxia and hypercapnia are fundamental to the homeostatic regulation of arterial blood gases. These ventilatory responses are reduced in non-REM

sleep compared to wakefulness, and are further reduced in REM sleep¹⁵ (Fig. 85-7). The threshold level of hypercapnia to provoke arousal from sleep is similar, on average, between non-REM and REM sleep in humans, whereas the level of asphyxial hypoxia (e.g., hypoxia of the type experienced in obstructive sleep apnea) often elicits arousal at lower arterial oxygen saturations in REM sleep than non-REM sleep¹⁵ (see Fig. 85-7). Isocapnic hypoxia, however, is generally a weak stimulus to elicit arousal from sleep and the threshold is similar, on average, between non-REM and REM sleep.¹⁵

The normal decrease in ventilation from wakefulness to sleep usually results in trivial changes in arterial O_2 saturation because the starting arterial PO_2 is on the flat portion

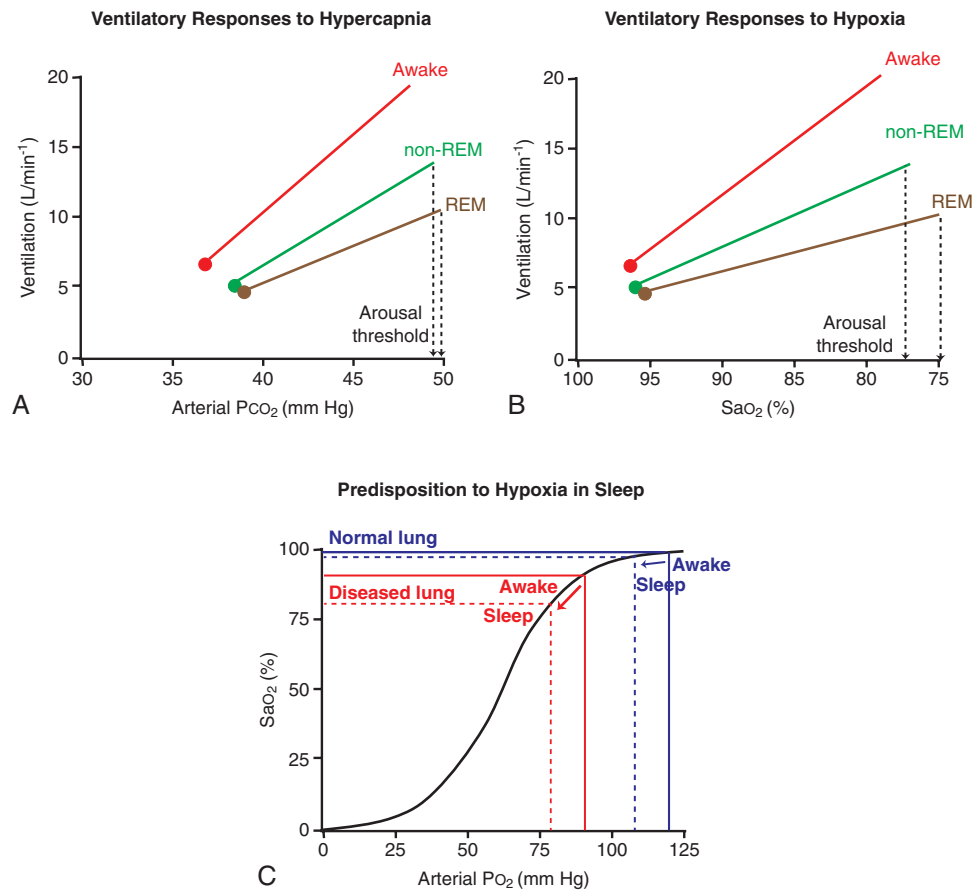


Figure 85-7 Summary graphs showing the ventilatory and arousal responses to hypercapnia (A) and hypoxia (B). Note: (1) The decrease in basal ventilation from wakefulness (●) to non-REM (●) and REM (●) sleep; (2) ventilation is greater in wakefulness at any given elevated arterial CO₂ or lowered arterial oxygen saturation (SaO₂) compared to non-REM sleep and REM sleep; (3) the slope (gain) of the ventilatory responses to hypercapnia and hypoxia is also greater in wakefulness than in non-REM sleep and is most depressed in REM sleep. Also shown are the thresholds for hypercapnia (A) and asphyxial hypoxia (B) to elicit arousal from sleep (see text for additional details). The figure also illustrates the relationship between the starting (waking) arterial partial pressure of O₂ and the magnitude of the decrease in SaO₂ from wakefulness to sleep (C). Normal decreases in ventilation from wakefulness to sleep lead to normal decreases in arterial PO₂ but only modest or trivial decrease in SaO₂ in sleep, because the starting arterial PO₂ is on the flat portion of the oxyhemoglobin dissociation curve (blue lines, C). Such a situation, for example, typically would be experienced by individuals living at sea level, or in individuals with healthy lungs and/or with normal ventilation and lung perfusion. The same magnitude of decrease in ventilation and arterial PO₂ from wakefulness to sleep, however, can lead to a large decrease in SaO₂ if an individual is initially hypoxic and therefore initially positioned on the steep portion of the dissociation curve (starting SaO₂ of about 90%). For clinical relevance see text. (Adapted from Douglas NJ: Respiratory physiology: understanding the control of ventilation. In Kryger MH, Roth T, Dement WC, editors: *Principles and practice of sleep medicine*. St. Louis, 2011, Elsevier, Saunders, pp. 250–258; Thompson SR, Ackermann U, Horner RL: Sleep as a teaching tool for integrating respiratory physiology and motor control. *Adv Physiol Educ* 25:101–116, 2001; Horner RL: Pathophysiology of obstructive sleep apnea. *J Cardiopulmon Rehabil Prev* 28:289–298, 2008; Horner RL: Respiratory physiology. In Kushida C, editor: *Encyclopedia of sleep*, vol. 1. Waltham, MA, 2013, Academic Press, pp. 517–524. © Richard L. Horner, PhD, University of Toronto.)

of the oxyhemoglobin dissociation curve. However, there can be a larger decrease in arterial O₂ saturation from wakefulness to sleep if an individual is *initially* hypoxemic and therefore initially positioned on the steep portion of the dissociation curve (see Fig. 85-7). This situation can be seen with an individual at altitude, with lung disease, or with depressed ventilation and/or impairments in breathing for *any* reason. The physiologic principle that arises from these relationships is that *any* situation that lowers arterial PO₂ in wakefulness for *any* reason (e.g. altitude, lung disease) predisposes to worsening hypoxemia in sleep, *especially* in REM sleep.

Application

Interactions between the ventilatory responses to hypercapnia and hypoxia, and arousal from sleep, can provoke unstable breathing and central apneas. Figure 85-8 outlines

these interactions using the ventilatory responses to hypercapnia as the example (see legend for additional details specific to Fig. 85-8). As a general rule, however, the same predisposition to unstable breathing during arousal from sleep also applies to the ventilatory responses to hypoxia or to combined hypercapnia and hypoxia (i.e., asphyxia as seen in sleep-disordered breathing). The physiologic principle that arises from these interactions is that *any* separation of equilibrium points for stable breathing in wakefulness and non-REM sleep for *any* reason can lead to unstable breathing and central apneas at sleep onset, especially when sleep onset follows a perturbation to breathing such as arousal from sleep (see Fig. 85-8). Such a separation could be seen in one or more clinically relevant scenarios. For example, the equilibrium point for waking ventilation could shift to the left in situations of acute or chronic hyper-ventilation caused by anxiety, congestive heart failure, or

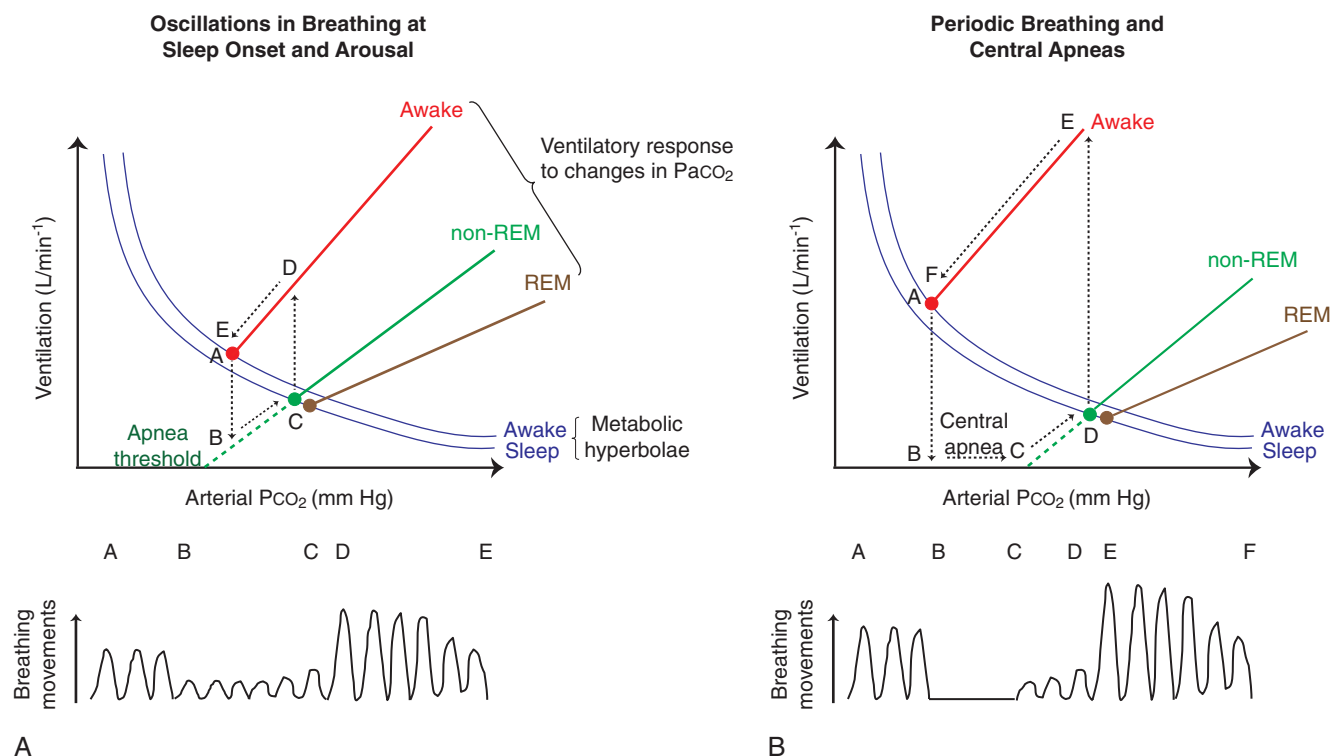


Figure 85-8 Schema to illustrate how interactions between the ventilatory responses to hypercapnia and transitions between sleep and wakefulness can provoke unstable breathing and central apneas. The equilibrium point for stable breathing in wakefulness is illustrated by point A (●) in the left graph. This equilibrium point intersects the ventilatory response to increased arterial PCO_2 (red line) and the change in arterial PCO_2 that results from a change in ventilation (the metabolic hyperbola, blue line). The ventilatory response to increased arterial PCO_2 in non-REM and REM sleep are also shown (green and brown lines, respectively). Also shown is how a decrease in arterial PCO_2 in non-REM sleep can result in reduced ventilation and eventually apnea (dashed green line). At sleep onset, the arterial PCO_2 that was previously present in wakefulness (point A) produces lesser ventilation in sleep according to the extrapolation of the ventilatory response to CO_2 in sleep (dashed green line, point B). This decrease in ventilation is out of proportion to metabolic rate so ventilation progressively increases toward the new sleeping equilibrium position (point C, ●). If the patient arouses from sleep, then the arterial PCO_2 that represents the equilibrium point for breathing in sleep (●) now represents a hypercapnic stimulus according to the ventilatory response to CO_2 in wakefulness, such that ventilation increases dramatically (points C to D). The elevated level of ventilation at point D is out of proportion to the prevailing metabolic rate so ventilation progressively decreases toward the waking equilibrium position (points D to E, ●). The cycle of waxing and waning of ventilation with the waxing and waning of wakefulness and sleep continues until sleep is established. The physiologic principle that arises from this effect is that any separation of equilibrium points in wakefulness and non-REM sleep (● and ●), for any reason can lead to periodic breathing and central apneas at sleep onset. Such periodicity and central apnea is shown in the right graph. (© Richard L. Horner, PhD, University of Toronto.)

other causes. Likewise, the equilibrium point for sleeping ventilation could shift to the right with drug-induced respiratory depression. In either case, it is the arousal from sleep per se that acts as the initial perturbation to elicit the unstable breathing and central apnea.

UPPER AIRWAY MOTOR TONE AND COMPENSATORY REFLEX RESPONSES ARE PARTICULARLY SENSITIVE TO DEPRESSION IN SLEEP

Principle

The key source of respiratory drive to the hypoglossal motor pool is *different* than for spinal respiratory neurons; being from the reticular formation for the former and from bulbo-spinal respiratory neurons for the latter (see Figs. 85-2 and 85-3). As a consequence of this and other organizational features, hypoglossal motoneurons are not inhibited in expiration unlike spinal inspiratory motoneurons (see Fig. 85-3). This point identifies that the activity of the genioglossus muscle in expiration is simply a manifestation of the

prevailing tonic inputs. The key physiologic and clinical implications of this organizational principle are explained in the following subsection: “Application”. For now, however, it is important to reiterate that the reticular formation contains cell groups with sleep state-dependent activity (see “Wakefulness and Sleep” and Figs. 85-1 and 85-2). This organizational feature imparts a significant modulation of excitability of the hypoglossal motor pool across natural sleep-wake states, as well as a particular susceptibility to the suppressant effects of neurodepressive drugs (see Fig. 85-1).

Although the reticular formation exerts major effects on the excitability of the upper airway motor pools, it influences the spinal motor pools via the reticulospinal tract (see Fig. 85-3). Notably, this reticular influence on the phrenic motor pool is significantly reduced compared to the upper airway motor pools, because of the reduced density/impact of those reticulospinal connections. The key physiologic and clinical implications of this organizational feature are that the upper airway muscles are more susceptible to changes in activity across the sleep-wake state and with neurodepressive drugs than is the diaphragm. This notion

explains the principle that activity of the diaphragm is relatively preserved across sleep-wake states compared to other respiratory muscles, especially those that serve dual respiratory and nonrespiratory or postural functions such as the muscles of the tongue and chest wall.

Application

There are several implications arising from the differential effects of sleep on the respiratory and tonic components of respiratory muscle activity, particularly for the upper airway muscles (see Fig. 85-3). For example, the tonic activity of the tongue and palatal musculature contributes to both baseline airway size and stiffness, and the decreased activity in sleep is linked to airway narrowing and the pathogenesis of obstructive sleep apnea. Suppression of chest wall muscle activity in sleep is thought to increase the compliance of the chest wall and contribute to a decreased functional residual capacity; these effects can contribute to hypoventilation especially in infants because of the already highly compliant chest wall.

OVERARCHING PRINCIPLE: VARIOUS TRAJECTORIES CAN LEAD TO A SLEEP-DISORDERED PHENOTYPE

As outlined in the previous sections, different individuals can “find their way” to respiratory dysfunction in sleep for varying reasons; that is, different combinations of factors contribute to both pathogenesis and severity in varying degrees. Given that the involvement of these factors in the pathogenesis of respiratory dysfunction in sleep can also vary within and between subjects—including across the night, between sleep states, and at different ages and body weights, and with prescription and nonprescription drugs—there is not one critical mechanism for pathogenesis and not one critical target for therapy for all types of sleep-disordered breathing. The clinical challenge is to devise simple and effective ways to identify the physiologic phenotype of each patient and target the relevant mechanisms operating in each individual. In short, various trajectories can lead to a sleep-disordered phenotype and the specific mechanisms mediating the trajectories need to be identified for each patient to individualize therapy.

CLINICALLY RELEVANT CONCEPTS IN RESPIRATORY CONTROL IDENTIFIED AS “PERTURBATIONS”

OBSESITY

The high and increasing prevalence of obesity has led to an increasing appreciation of its important effects on respiratory function. Whereas the obesity-related syndromes of obstructive sleep apnea and obesity hypoventilation are fairly well defined, obesity also impacts other conditions such as asthma and chronic obstructive pulmonary disease.

Principle

The respiratory effects of obesity can be broadly classified into mechanical influences on the upper airway and chest

wall, neurohumoral effects of various adipocytokines, and the possible effects on central respiratory drive as described by the arterial PCO_2 set point. By its mechanical effects, obesity has an impact on the upper airway via fat accumulation around the air space that increases the propensity for airway collapse.¹⁶ The transmural pressure across the pharyngeal airway is an important variable determining its patency; fat deposition leads to a more negative (less positive) transmural pressure, favoring its collapse. Abdominal fat deposition can further worsen pharyngeal patency by causing small end-expiratory lung volumes that reduce upper airway dimensions by decreasing traction forces. Lowered lung volumes also increase the plant gain and thereby increase the tendency toward unstable breathing in response to a given perturbation (see “[Loop Gain and Its Importance](#)”). By its generation of proinflammatory cytokines, obesity has also been implicated in airway inflammation, perhaps contributing to the development of asthma in obese people. Mouse models have suggested an important role for leptin in the control of breathing; ob/ob leptin-deficient mice hypoventilate and leptin repletion restores their ventilation. However, the impact of leptin on ventilation in humans with obesity is less clear.¹⁷ Finally, by altering arterial PCO_2 set points, obesity may affect central respiratory drive. Some morbidly obese individuals have elevated arterial PCO_2 set points, likely as a result of cumulative CO_2 retention, initially during sleep. It is thought that the elimination of CO_2 following arousal is insufficient to eliminate the CO_2 that has accumulated during antecedent sleep; the result is a gradual elevation of arterial PCO_2 during sleep that eventually persists into wakefulness. However, the underlying genetic and/or neurobiologic mechanisms of obesity hypoventilation syndrome remain to be established.

Application

Obesity is the major reversible risk factor for obstructive sleep apnea. Substantial data show the importance of weight loss in reducing apneas and the magnitude of associated arterial oxygen desaturations. However, several points about this relationship between obesity and obstructive sleep apnea deserve further emphasis. First, weight loss is difficult to achieve through diet and exercise, and thus bariatric surgery is being used increasingly in the management of obstructive sleep apnea. Second, even with substantial weight loss, the improvement in obstructive sleep apnea severity is often modest. For example, weight loss of 10.7 ± 0.7 kg led to a reduction in the apnea-hypopnea index of only 9.7 ± 2 events per hour of sleep.¹⁸ Thus, considerable weight loss may be required to resolve apnea for many patients. Third, several studies have shown that, following either medical or surgical weight loss, obstructive sleep apnea can redevelop over time even without regain of weight. Presumably redistribution of fat and aging both contribute to the recurrence of sleep apnea in these patients. Fourth, some data as well as clinical experience suggest that treatment of sleep apnea is often associated with weight gain.¹⁹ The mechanisms underlying this observation have been debated, but are likely related to the fact that treatment of obstructive sleep apnea reduces energy expenditure during sleep and restores social behaviors associated with calorie intake, such as going out for dinner. Regardless of

the underlying mechanism, diet and exercise instructions should be provided to the majority of obstructive sleep apnea patients regardless of the treatment approach.

HEART FAILURE

Accumulating literature has suggested a *bidirectional* relationship between sleep disturbance and heart disease.²⁰ Sleep deprivation and sleep apnea have both been associated with an increased incidence of cardiovascular disease. In addition, patients with cardiovascular disease have a very high prevalence of sleep-disordered breathing. For example, roughly two thirds of patients with impaired left ventricular systolic function have either central or obstructive sleep apnea. Obstructive and central apneas exist on a spectrum; they often manifest in the same patient and may have similar underlying mechanisms. While some physiologic literature exists regarding the mechanisms underlying unstable breathing in congestive heart failure, the underlying neurobiology is less well defined. However, definitive therapeutic data are lacking, making these associations intriguing but they currently fall short of improving patient care.

Principle

Multiple mechanisms underlie disordered breathing in patients with heart disease. First, chemoreceptor activity is high in patients with congestive heart failure and central sleep apnea (Cheyne Stokes breathing) compared to matched heart failure patients without central apnea.²¹ Thus, controller gain, a major component of overall loop gain (see “[Loop Gain and Its Importance](#)”), is likely high in congestive heart failure patients with central sleep apnea. In patients with pulmonary edema, hypoxemia is commonly present, which may further increase ventilatory drive. Second, because baseline arterial PCO₂ is often low in patients with congestive heart failure, these patients are closer to their apnea threshold than are patients with more stable breathing patterns (see “[Breathing Is Dependent on Feedback Regulation in Sleep](#)” and “[Arousal from Sleep: A Consequence and Cause of Respiratory Disturbance](#)”).²² Third, elevated left atrial pressure per se can increase ventilatory drive and the propensity for apnea by reducing the CO₂ reserve.²³ Fourth, accumulation of extravascular lung water lowers end-expiratory lung volume by increasing elastic lung recoil as well as stimulating juxtacapillary receptors to drive ventilation. Edema formation around the upper airway may also be important in the predisposition to upper airway closure seen in congestive heart failure.²⁴ Thus, both obstructive and central sleep apnea can develop in these patients due to unstable ventilatory control as well as impaired pharyngeal mechanics.

Application

The treatment of sleep-disordered breathing in congestive heart failure is focused on therapy for the underlying heart failure. Medications to promote diuresis and lower cardiac afterload can reduce the predisposition to unstable breathing. Diuretic therapy can reduce extravascular lung water, left atrial pressure, and upper airway edema. Angiotensin-converting enzyme inhibitors can improve cardiac function thus leading to lower cardiac filling pressures and improved

pulmonary edema via increased forward flow. Other therapies such as oxygen and acetazolamide can help to stabilize breathing,²⁵ particularly for patients with elevated loop gain. This effect can be mediated through a reduction in loop gain, itself probably due to a reduction in the sensitivity of the ventilatory control system (i.e., controller gain, see [Fig. 85-6](#)). Nasal continuous positive airway pressure therapy can benefit some patients, although disordered breathing frequently persists.²⁶ In theory, positive airway pressure should be beneficial for these patients because it can reduce cardiac preload as well as afterload. Multicenter trials assessing the impact of positive-pressure therapy on clinical outcome are ongoing. The data thus far are suggestive, but not definitive, that treatment of obstructive or central sleep apnea is beneficial for patients with congestive heart failure.

AGING

Aging is a major risk factor for both obstructive and central sleep apnea. Other than for children, who have risk of obstructive sleep apnea if they have adenotonsillar hypertrophy, obstructive sleep apnea increases in prevalence with increasing age. For women, menopause is a risk factor whereas, in men, obstructive sleep apnea becomes increasingly common with advanced age. Central sleep apnea is uncommon in children and also increases in prevalence with increasing age. However, the mechanisms underlying these observations are unclear.

Principle

Aging influences many of the physiologic traits underlying sleep apnea. Aging has been associated with impairment in many reflexes important to the upper airway patency; one such reflex is the *negative pressure reflex* that increases pharyngeal dilator muscle activity in response to subatmospheric airway-collapsing pressures.²⁷ Such reflex impairments plus loss of tensile tissue strength over time both likely contribute to the observed increase in collapsibility of the pharyngeal airway during sleep in older compared with younger individuals. Because fat also tends to deposit preferentially around the upper airway with aging, the parapharyngeal fat pads are increased in size in older versus younger individuals, independent of overall body weight. Aging is also known to reduce lung elastic recoil, although the impact of this finding on pharyngeal mechanics remains unclear. Regarding control of breathing, several studies have shown no major impact of aging on overall loop gain,²⁸ although ongoing research is further examining this issue.

Application

Given that the mechanisms underlying sleep apnea in older individuals may be different from those in younger individuals, there may be clinical implications to these findings. For example, an individualized approach to therapy may target an impaired negative pressure reflex in an older individual by pharmacologic manipulation of its sensory or central neural components, whereas other approaches may be more fruitful in younger obstructive sleep apnea patients. In addition, because the mechanisms underlying apnea may differ in older individuals, the adverse consequences

may well be different in older than in younger obstructive sleep apnea patients. For example, esophageal pressures become less negative in older obstructive sleep apnea patients compared to younger patients,²⁹ presumably due to aging-related differences in either the arousal threshold or the ventilatory drive. Because esophageal pressure is a surrogate for the pressure outside the heart, it would be predicted that transmural cardiac pressures (and hence cardiac wall stress/afterload) would be lower in older than in younger obstructive sleep apnea patients. Such pathophysiologic findings may help explain the apparent lack of consequences to obstructive sleep apnea in older compared to younger patients.³⁰ Indeed, sleep apnea in older adults may be a different condition than in younger individuals, with different underlying causes, consequences, and therapeutic approaches.

OTHER CLINICAL CONDITIONS

The majority of respiratory disorders show deterioration in gas exchange during sleep. The integrative physiologic principles and mechanisms underlying this worsening in sleep are explained in “[Integrative Physiologic Mechanisms Underpinning Respiratory Dysfunction and Instability in Sleep](#).” Although the neurobiologic basis underlying the observed abnormalities is less well understood, several principles can be discussed further regarding hypoventilation syndromes, neuromuscular disease, and parenchymal lung disease.

Principles

At least three factors are likely critical to the deterioration of gas exchange that is frequently observed during sleep in patients with respiratory disorders. First, the behavioral influences or the wakefulness stimulus to breathing introduced in “[Integrative Physiologic Mechanisms Underpinning Respiratory Dysfunction and Instability During Sleep](#)” and [Figure 85-5](#) are withdrawn upon transition from wakefulness to non-REM sleep. Accordingly, with the onset of sleep, the drive for ventilation is reduced almost immediately. As a result, arterial PCO_2 levels tend to rise in sleep, and hypoventilation tends to get worse in patients with respiratory acidosis. During REM sleep, however, the behavioral influences may be restored to some extent compared to non-REM sleep, leading to improvement in gas exchange in some patients (see “[Breathing Is Dependent on Feedback Regulation in Sleep](#)”). Second, as discussed earlier, the upper airway narrows during non-REM sleep so that controller gain as defined by chemoresponsiveness is reduced. This reduction of controller gain leads to lower minute ventilation for any given increase in arterial PCO_2 . Third, during REM sleep, there is atonia of the accessory muscles of respiration so that patients reliant on these muscles become more dependent on diaphragmatic activity to achieve ventilation. For some patients, REM sleep thus leads to marked hypercapnia and hypoxemia due to a concomitant decrease in chemosensitivity compared to non-REM sleep (see “[Chemoreceptors and Chemoreflexes](#)”). End-expiratory lung volume also decreases in various stages of sleep, likely as a function of decreased motor output to the muscles of the chest wall, leading to a reduced functional residual capacity and increased propensity for oxygen desaturation and

unstable breathing by alterations in plant gain (see “[Loop Gain and Its Importance](#)”).

Application

The aforementioned conditions lead to deterioration of gas exchange in patients with most respiratory conditions including those with hypoventilation, neuromuscular disease, and parenchymal lung disease.

Hypoventilation. Patients with baseline hypercapnia often experience worsening hypercapnia during non-REM sleep. The effect of REM sleep is quite variable, however, in that some patients such as those with central congenital hypoventilation syndrome actually see improvement in gas exchange during REM sleep. On the other hand, some hypoventilation patients such as those with obesity hypoventilation may experience further worsening of gas exchange during REM sleep than in non-REM sleep. In general, bilevel ventilation is effective at maintaining gas exchange during non-REM and REM sleep in hypoventilation patients. Various respiratory stimulants have also been considered but in general the results have been disappointing.

Neuromuscular Disease. Patients with neuromuscular disease also experience deterioration of gas exchange during non-REM sleep with further worsening during REM sleep. The loss of the wakefulness stimulus, the compromise of upper airway motor tone, the atonia of the accessory respiratory muscles during REM sleep, and the fall in functional residual capacity may all contribute to respiratory compromise in these patients. Treatment of these patients involves addressing the underlying cause (if possible) and using bilevel noninvasive ventilation as part of supportive care.

Parenchymal Lung Disease. In patients with parenchymal lung disease, such as emphysema or pulmonary fibrosis, similar mechanisms can underlie the worsening gas exchange experienced during non-REM and REM sleep. Treatment is again supportive; treatment should also address the underlying lung disease to the extent possible. A subset of patients also exists with the so-called overlap syndrome, which consists of the combination of chronic obstructive pulmonary disease with obstructive sleep apnea. These patients are known to have excess cardiovascular mortality although no clinical trials to date have addressed the optimal treatment of such overlap patients.

INDIVIDUALIZED THERAPY TARGETING UNDERLYING MECHANISMS

The current treatment of choice for obstructive sleep apnea is nasal continuous positive airway pressure. This treatment option has excellent efficacy, but is often poorly tolerated, leading to variable results in clinical practice. Alternative therapies exist but these also have limited effectiveness and can be both expensive and cumbersome for the patient. As a result, many investigators have advocated for further mechanistic-based research to define new therapeutic

approaches based on the individual predisposition to sleep-disordered breathing. The appreciation for the multifactorial nature of obstructive sleep apnea³¹ has opened the way to treatment for this disorder based on underlying mechanisms; for example, there may be anatomic abnormalities at the level of the soft palate (the velopharynx) or behind the tongue (the retroglossal air space). Clinical studies show that the upper airway almost always collapses at the level of the velopharynx in patients with obstructive sleep apnea, but in about half of these patients the obstruction also extends caudally to the retroglossal air space.³² In REM sleep, the lower level of the obstruction can extend to even more caudal levels compared with non-REM sleep, most likely due to the greater suppression of pharyngeal muscle activity in REM sleep. For those individuals with a primary problem of velopharyngeal compromise, palatal surgery such as uvulopalatopharyngoplasty would be predicted to have reasonable efficacy, but less so for individuals with retroglossal airway collapse.

For those individuals with obstructive sleep apnea driven primarily by elevated loop gain, interventions that effectively lower loop gain, such as inhaled oxygen or oral acetazolamide would be predicted to improve respiratory abnormalities. Some individuals may have a primary problem of upper airway muscle tone in sleep and/or reflex compensatory responses; such individuals may respond to pharmacological approaches to increase hypoglossal output³³ or potentially to hypoglossal nerve stimulation.³⁴ Individuals who have multiple predisposing factors contributing to obstructive sleep apnea may benefit from combinations of therapies to resolve the underlying abnormalities. The potential for an individualized approach to obstructive sleep apnea therapy based on underlying mechanisms has received attention using the concept of personalized medicine. This concept can be applied to the spectrum of respiratory abnormalities during sleep.

Key Points

- Obstructive sleep apnea is common, resulting in major neurocognitive and cardiovascular consequences. Combinations of upper airway anatomic abnormalities, instabilities in ventilatory control, and variations in upper airway dilator muscle control all contribute to the predisposition to upper airway obstruction within an individual.
- Non-REM sleep plus sedative- and anesthetic-induced neurodepressive brain states are associated with reduced hypoglossal motor output that can contribute to upper airway obstruction, particularly in individuals who are anatomically predisposed.
- REM sleep is associated with generalized skeletal muscle atonia that also affects the tone in the upper airway dilators such as the genioglossus. Mechanisms of genioglossus muscle atonia are thought to include withdrawal of excitatory inputs from wakefulness-

dependent cell groups and active inhibition mediated through a muscarinic receptor pathway coupled to G protein-coupled potassium channels.

- Opioid narcotics contribute to central apneas and respiratory depression by activating opioid receptors and thereby suppressing the output from the pre-Bötzinger complex. The pre-Bötzinger complex is a key source of respiratory rhythm generation that drives the expression of rhythmic activity in other components of the respiratory network.
- Opioid narcotics can also contribute to severe respiratory depression in sleep by blunting the tonic excitatory stimulation of wakefulness to the respiratory network, especially in those with sleep-disordered breathing who are dependent on such tonic behavioral inputs.
- Obesity contributes to obstructive sleep apnea primarily through anatomic effects on the upper airway and the chest wall, although influences of adipocytokines on ventilatory control may also be important.
- Loop gain is an engineering term used to describe the predisposition to instability in a feedback control system. Elevated loop gain defines a system that is prone to instability, that is, one that can develop periodic behavior with even minor perturbations. Congestive heart failure is associated with elevated loop gain. As a result, heart failure patients frequently experience sleep apnea.
- Aging is associated with impaired protective upper airway reflexes and anatomic changes that may make the pharyngeal airway vulnerable to collapse. Older obstructive sleep apnea patients may have altered consequences of this disorder since the underlying pathophysiology of their condition can be different from that in younger obstructive sleep apnea patients. For example, lesser swings in subatmospheric intrathoracic airway pressures in older versus younger patients may reduce cardiovascular risk through reduced cardiac wall stress.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION

Carbon dioxide (CO₂) is produced during aerobic cellular respiration and is a “waste product” produced by all aerobic life forms. Arterial CO₂ tension (arterial PCO₂) represents the balance between CO₂ produced, the CO₂ eliminated, and in some cases inspired (either rebreathed or directly added to the breathing circuit) CO₂. Inspired CO₂ (FICO₂) is usually negligible, while alterations in CO₂ production are an unusual—but possible—contributor to systemic CO₂ tension. As an example, CO₂ production increases in hypermetabolic states such as fever or thyrotoxicosis; however, these are generally offset by modest increases in alveolar ventilation, sufficient to normalize the arterial PCO₂. Therefore, for practical purposes, the most important determinant of arterial PCO₂ is its rate of elimination.

Hypocapnia remains a common—and generally underappreciated—component of many disease states, including early mild asthma, high-altitude pulmonary edema, and acute lung injury. In addition, deliberate induction of hypocapnia remains a common, if controversial, practice in both adults and children with acute brain injury, as a strategy to control raised intracranial pressure. In contrast, hypercapnia has historically been avoided by clinicians, with high tidal volumes and minute ventilation

employed to normalize arterial PCO₂, in an effort to keep it within a “normal physiologic” range.

Advances in current understanding of the biology of CO₂ have prompted the idea that hypocapnia or hypercapnia may play roles in the development of acute organ dysfunction or injury.¹ In preclinical models, deliberate hypercapnia may protect against lung and systemic organ injury, beyond effects of reduced tidal volume. In addition, hypocapnia may exert independent harmful effects. Limited clinical data suggest potential beneficial effects of hypercapnia in patients exposed to high lung stretch. This chapter reviews the current clinical status of hypocapnia and hypercapnia in health and disease, discusses the insights gained from basic studies of CO₂, identifies key unresolved concerns regarding hypocapnia and hypercapnia, and considers the potential clinical implications for the management of patients with lung disease.

REGULATION OF ARTERIAL CO₂ TENSION

In health, arterial PCO₂ is tightly regulated via a feedback loop between CO₂ tension and alveolar ventilation. CO₂

has a fundamental role in regulating and controlling breathing, and hypercapnic acidosis is a potent ventilatory stimulant. Type I glomus cells in the carotid body near the bifurcation of the carotid artery and chemosensitive neurons in numerous brain stem regions respond to changes in pH and arterial PCO₂. During normal tidal respiration, the carotid chemoreceptors are critical for maintaining stable arterial PCO₂ levels.^{1a} The response time of the peripheral chemoreceptors to transient changes in arterial PCO₂ is more rapid than that of the central neurons²; however, the central chemosensitive neurons exert a quantitatively larger contribution to stimulating ventilation in response to hypercapnia.³

The effect of alterations in arterial PCO₂ on ventilation is—at least in part—pH dependent, via the production of protons following its spontaneous and carbonic anhydrase-catalyzed combination with water to form carbonic acid, which in turn dissociates to form bicarbonate (HCO₃⁻) and H⁺ ions. Changes in CO₂ and CO₂/H⁺ levels are sensed in special chemosensitive neurons in the carotid body and in several regions of the hindbrain,^{4,5} although it is not certain whether these cells detect pH, CO₂, HCO₃⁻, or a pH gradient across the cell membrane. Nonetheless, the ventilatory response to hypercapnia is greater than that to metabolic acidosis,^{6,7} suggesting the existence of a CO₂ receptor. The peripheral chemoreceptors appear to respond primarily to alterations in arterial PO₂ and H⁺ concentrations, and their function is to maintain arterial PO₂ and H⁺ concentrations constant. The central chemoreceptors appear to respond primarily to alterations in CO₂/H⁺ levels and act to maintain the H⁺ concentration of the cerebrospinal fluid constant. Any acute change of H⁺ in these compartments is counteracted almost instantly by alterations in pulmonary ventilation and more slowly corrected by the kidney.⁸

CAUSES OF ALTERED ARTERIAL CO₂

Arterial PCO₂ is usually expressed in terms of a relationship among CO₂ production, CO₂ elimination, and rarely, a contribution from inspired CO₂ (FiCO₂ is usually close to zero).

$$PaCO_2 \propto \frac{CO_2 \text{ production}}{CO_2 \text{ elimination}} + \text{inspired } [CO_2]$$

ACCIDENTAL HYPERCAPNIA OR HYPOCAPNIA

Accidental hypercapnia is reported most commonly in the operating room or the intensive care unit, and is due to errors associated with mechanical ventilation. The key errors are those that result in hypoventilation, such as circuit disconnection or inadequate minute ventilation. Alternatively, expired gas (which contains approximately 5% CO₂) can be rebreathed as a result of circuit malconnection or depletion of CO₂ absorbers.⁹

Additional causes of acute hypercapnia include hypoventilation secondary to drug-induced respiratory depression,¹⁰ or severe airways obstruction such as status asthmaticus¹¹ or massive aspiration (e.g., grain inhalation).¹² Increased

dead space (e.g., pulmonary embolism) will result in decreased alveolar ventilation and hypercapnia if the minute ventilation is fixed (e.g., the patient is paralyzed on mechanical ventilation), although in most cases, the patient will increase minute ventilation to maintain CO₂ in the normal or slightly low range. Chronic hypercapnia may result from progressive restrictive or obstructive lung diseases such as pulmonary fibrosis or chronic obstructive airways disease or obstructive sleep apnea. Increases in CO₂ production can result from hypermetabolic states such as fever, sepsis, malignant hyperthermia, thyroid crisis, or sometimes overfeeding. In addition, use of bicarbonate buffers (NaHCO₃) results in generation of excess CO₂. Finally, significant increases in CO₂ production will directly increase arterial PCO₂ if the alveolar ventilation is not increased; however, even a slight increase in alveolar ventilation will easily compensate for this.

In the setting of mechanical ventilation, accidental hypocapnia might be more common than accidental hypercapnia, especially in the absence of end-tidal CO₂ monitoring, such as outside the operating room. In one study, severe hypocapnia (end expired CO₂ < 30 mm Hg) was found in 70% of patients transferred by helicopter to a U.S. trauma center.¹³ In children, accidental hypocapnia readily develops during high-frequency ventilation or during extracorporeal support (e.g., *extracorporeal membrane oxygenation* [ECMO], cardiopulmonary bypass).¹⁴⁻¹⁶

PERMISSIVE HYPERCAPNIA

Permissive hypercapnia refers to the elevated arterial PCO₂ that results from hypoventilation of mechanically ventilated patients that is aimed at reducing ventilator-associated lung injury (e.g., *acute respiratory distress syndrome* [ARDS], status asthmaticus).

Deliberate hypoventilation was initially described in 1984 by Darioli and Perret,¹⁷ wherein a series of 29 mechanically ventilated patients (34 episodes of ventilation) with status asthmaticus were managed with deliberate hypoventilation (resulting in severe hypercapnia) with the goal of reducing barotrauma. There were no fatalities in the series, which was very unusual at the time for intubated patients with status asthmaticus. The following year, Wung and colleagues¹⁸ described a series of 15 neonates with persistent pulmonary hypertension of the newborn. This case series was remarkable given that, up to then, vigorous hyperventilation (to achieve hypocapnia in an attempt to reduce the pulmonary vascular resistance) was considered a vital aspect of management; in such cases, death was common and chronic lung disease the rule. There were no deaths in the series of Wung and colleagues¹⁸ and only a single case of chronic lung disease.

Subsequently, the term “permissive hypercapnia” was coined by Hickling and associates¹⁹ in their seminal descriptions of improved survival in ARDS in which plateau pressures and tidal volumes were limited.^{19,20} In all these series, hypercapnia was tolerated (permissive); it was not specifically induced. Rather, the aim was to diminish barotrauma from excessive tidal volumes and airway pressure, and the hypercapnia was simply a result of this strategy. Nonetheless, because of these advances, clinicians became more accepting of hypercapnia in critically ill patients.

DELIBERATE HYPERCAPNIA OR HYPOCAPNIA

Historically the administration of inspired CO_2 was used to hasten emergence from anesthesia; the idea was that stimulation of spontaneous ventilation enhanced clearance of inhaled volatile anesthetic gases (of course increasing minute ventilation using the mechanical ventilator would equally clear the volatile gases, but would result in profound hypocapnia and therefore prolonged apnea). Such administration of inhaled CO_2 at the end of anesthesia was originally termed *de-etherization*,²¹ and the practice was discontinued in the 1980s, largely because of concerns with inadvertent hypercapnia.

More recent clinical studies confirm that therapeutic hypercapnia hastens emergence from anesthesia, even with the more insoluble modern anesthetic agents,²² and capnography—not available in the 1980s—can help avoid excess hypercapnia. Such hypercapnic hyperpnea in spontaneously breathing patients can reduce by half the required recovery time from anaesthesia²³ and could have benefits for postoperative cognitive function and operating room efficiency.

Therapeutic hypercapnia refers to the concept that elevated CO_2 may have specific benefits in critical illness, beyond benefits resulting from lessening barotrauma. If this concept proves to be clinically applicable, then “therapeutically” elevating arterial PCO_2 might be beneficial in ARDS, in addition to tidal volume reduction. Whereas there is some pre-clinical evidence to suggest benefit for hypercapnia in specific experimental models, this approach has not been directly tested in critically ill patients.

In contrast, *therapeutic hypocapnia* is often used in the management of acute brain injury in both adults and children.²⁴⁻²⁶ Hypocapnia is induced to lower *intracranial pressure* (ICP) by decreasing the cerebral blood volume through cerebral artery vasoconstriction. Because elevated ICP is generally adverse and hypocapnia has traditionally been thought to be benign, hyperventilation has been widely practiced in patients with acute brain injury, even in the absence of elevated ICP.²⁶ This reasoning led to the idea that more profound hyperventilation might be even better, and sometimes extremes of hypocapnia were advocated for acute brain injury,²⁷⁻³¹ although more recently this concept has been discredited.

TRANSPORT OF CO_2 IN THE BLOOD

The vast bulk of CO_2 is produced in the mitochondria, where cellular CO_2 concentrations are highest. The pathway for transportation, involving step-wise decreases in CO_2 partial pressure gradients, originates in the mitochondria and proceeds through the cytoplasm, cell membranes, capillaries, venules, larger veins, and ultimately into the mixed venous blood before elimination through the alveoli.

Transportation of CO_2 in the blood is accomplished via three different mechanisms with the exact proportions carried by each mechanism varying depending on whether it is arterial or venous blood.³² Dissolved CO_2 in plasma, reported as arterial PCO_2 (i.e., partial pressure) accounts for

only 5% to 10% of the total CO_2 transported in blood. Almost 90% of total CO_2 in the blood is converted to bicarbonate ions (HCO_3^-), almost all catalyzed by carbonic anhydrase within the red blood cells. The remainder (5% to 10%) is transported as carbamino-hemoglobin, in which CO_2 is bound to terminal amino groups in *hemoglobin* (Hb) molecules.³² The usual amount of CO_2 in the arterial blood is 21.5 mmol per liter of blood, with slightly more (23.3 mmol/L) in venous blood. Overall, more than 80% of the CO_2 is carried within the red blood cells.

OXYGEN-INDUCED HYPERCAPNIA

CO_2 transport in the blood is altered by oxygen, leading to an elevated PCO_2 ; this oxygen-induced hypercapnia is seen in patients with end-stage lung disease who inhale supplemental O_2 . The mechanism of oxygen-induced hypercapnia was formerly thought to be oxygen-induced inhibition of ventilatory drive in patients thought to be critically dependent on hypoxic ventilatory drive. In fact, minute ventilation is not diminished in such patients.^{33,34} The mechanism is now better understood as having three key components: the Haldane effect, impaired hypoxic pulmonary vasoconstriction, and inability to increase minute ventilation.³⁵

The *Haldane effect*³⁶ is the term given to the phenomenon whereby increasing arterial PO_2 reduces the ability of the blood to store CO_2 (as Hb-bound, carbamino Hb; or as HCO_3^-), thereby increasing the CO_2 partial pressure. There are two elements to the Haldane effect. First, increased arterial PO_2 decreases formation of carbamino compounds; this reduces the quantity of CO_2 bound to Hb, thereby elevating the dissolved CO_2 (PCO_2). Second, histidine is important for the buffering properties of Hb; it contains an imidazole group that, at physiologic pH, is an effective buffer of H^+ ions but is also an important molecular link between heme groups and the Hb chains. Elevated PO_2 results in greater quantities of O_2 bound to Hb, which causes allosteric modifications of the Hb conformation. These conformational changes impact the heme-linked histidine and reduce its ability to buffer H^+ ion; with less H^+ buffering by Hb, there is more H^+ binding to HCO_3^- and release of stored CO_2 .

In patients with end-stage lung disease, hypoxic pulmonary vasoconstriction is an important mechanism to divert pulmonary artery blood from poorly ventilated regions (see Chapters 4 and 6). Increasing arterial PO_2 inhibits hypoxic pulmonary vasoconstriction, thus pulmonary artery blood containing CO_2 is diverted to less well-ventilated regions, and the efficiency of CO_2 excretion is impaired. Finally, while most patients would easily compensate for the increased PCO_2 with minimal increases in minute ventilation, this is not possible in many patients with end-stage lung disease.

MOLECULAR EFFECTS OF CO_2

ACID BASE AND IONIC BALANCE

CO_2 plays a key role in acid-base regulation, because the bicarbonate- CO_2 buffer system is the predominant buffer in the bloodstream. During metabolic acidosis, excess H^+ ions in the blood combine with HCO_3^- to form the weak

(carbonic) acid H_2CO_3 . Hypercapnia generally results in acidosis, by combining with water to form carbonic acid, which in turn dissociates to form bicarbonate (HCO_3^-) and H^+ ions. The protons thus generated can react with titratable groups in certain amino acids, resulting in structural changes in many proteins and enzymes in cell membranes and cellular aqueous environments.³⁷ Because acidosis suppresses most cellular functions, the body uses a number of strategies to defend its intracellular and extracellular pH within remarkably narrow limits.³⁸ The intracellular acidosis produced by hypercapnia may be corrected within a few hours, as opposed to 1 to 2 days needed for renal compensation.³⁹ This buffering is accomplished via active cell membrane ion transporters that extrude protons and exchange them for extracellular sodium.

CO_2 has effects on intracellular and extracellular ion concentrations. Following the onset of hypocapnia, there is rapid efflux of hydrogen ions; this compensatory mechanism is exhausted easily and, if hypocapnia persists, systemic alkalosis develops. The kidney effects a more efficient compensatory mechanism, reducing its hydrogen ion excretion and increasing bicarbonate loss, as well as decreasing excretion of ammonium.⁴⁰ During (hypocapnic) alkalemia, movement of H^+ from intracellular to extracellular space is accompanied by an opposite movement of K^+ (and Na^+) into the cell, although the resulting hypokalemia is usually modest.⁴¹ In addition, phosphate moves into the cell because of increased cellular phosphorylation.⁴² During alkalemia, albumin releases bound H^+ , swapping it for Ca^{2+} , and lowering the ionized calcium fraction,⁴³ which may be severe.⁴⁴

PROTEIN FUNCTION AND METABOLIC EFFECTS

CO_2 molecules can bind directly with free amine groups in proteins to form carbamate residues.⁴⁵⁻⁴⁷ This binding of CO_2 also modifies protein structure and function and may account for some of the observed differences in the effects of acidosis caused by CO_2 compared to acidosis resulting from other causes. The Bohr effect, wherein increased arterial PCO_2 results in a rightward shift of the hemoglobin-oxygen dissociation curve, resulting in a lowered affinity of Hb for O_2 and facilitation of oxygen unloading at the tissues, is a good example of this phenomenon.

One consequence of intracellular alkalosis is activation of glycolysis due to inhibition of the rate-limiting enzyme phosphofructokinase.⁴⁸ A feedback system functions as a mechanism to generate H^+ ions to counter intracellular alkalosis, whereby lactic acid production is increased by alkalemia (and decreased by acidemia).⁴⁹

RESPIRATORY SYSTEM EFFECTS

PULMONARY VASCULATURE

The effects of CO_2 on the pulmonary vasculature contrast with those in the systemic circulation. Hypercapnia can increase pulmonary vascular pressure by increasing both cardiac output and pulmonary vascular resistance⁵⁰ (Table 86-1). While hypercapnia increases pulmonary arterial pressure and pulmonary vascular resistance, this effect might not be as significant in preexisting pulmonary hypertension.⁵¹ Hypercapnia is a less potent pulmonary vasocon-

strictor than hypoxia, and its more important effect may be in augmenting hypoxic vasoconstriction.³⁷ While relatively little is understood about the cellular mechanism of CO_2 -induced pulmonary vasoconstriction, much of this effect appears to be catecholamine-mediated.⁵²

Hypocapnic alkalosis produces pulmonary vasodilation,⁵³ which is commonly used to reduce elevated pulmonary artery pressure, particularly in the setting of congenital heart disease and persistent pulmonary hypertension of the newborn (Table 86-2).

AIRWAY RESISTANCE AND LUNG COMPLIANCE

CO_2 can impact airway tone, with hypocapnia producing bronchoconstriction and hypercapnia causing bronchodilation in isolated airway preparations.^{54,55} Hypercapnia has been variably reported to either increase⁵⁶ or decrease⁵⁷ airway resistance. This paradox may be explained by direct dilation of small airways and indirect—vaguely mediated—large airway constriction. Indeed, in spontaneously breathing unanesthetized subjects, the CO_2 -related changes of respiratory mechanics are entirely caused by upper airway resistance.⁵⁶ In mechanically ventilated subjects, hypercapnia may decrease airway resistance,⁵⁸ although opposing actions of CO_2 may result in little net change in airway resistance.⁵⁹

Parenchymal lung compliance increases in response to hypercapnic acidosis, arising from active relaxation in response to increased alveolar CO_2 ⁶⁰ or due to increased surfactant secretion or more effective surface tension-lowering properties under acidic conditions.⁶¹

GAS EXCHANGE

In the normal lung, CO_2 modifies pulmonary vascular and airway tone. Increasing alveolar PCO_2 causes bronchodilation, while increasing pulmonary arterial PCO_2 increases pulmonary vascular resistance. The physiologic role of these contrasting effects of CO_2 on bronchial versus pulmonary arterial smooth muscle tone is to facilitate matching of regional ventilation and perfusion. For example, pulmonary artery occlusion results in regional hypocapnia, which results in bronchoconstriction,^{62,63} thereby directing airflow away from these unperfused alveoli. By this same mechanism, CO_2 administration improves matching of ventilation and perfusion and increases arterial oxygenation in both normal⁶⁴⁻⁶⁶ and injured⁶⁷ lungs.

Alveolar CO_2 can alter distribution of ventilation among acini and larger lung units,⁶⁸ as well as augment global ventilation-perfusion matching,^{64,69} which leads to improved gas exchange.⁷⁰ A dose-response relationship exists between FICO_2 and arterial PO_2 .^{65,66} However, in ARDS, permissive hypercapnia (produced via lowering tidal volume) is associated with increased shunt, although this is likely due to atelectasis from low tidal volumes.⁷¹

Severe hypocapnia produces bronchoconstriction,⁵⁶ reduces collateral ventilation,^{72,73} and impairs parenchymal lung compliance.⁶⁰ Hypocapnia also attenuates hypoxic pulmonary vasoconstriction and increases intrapulmonary shunting.⁶⁴ The overall effect can be a net decrease in arterial PO_2 .

Hypocapnic alkalosis impairs pulmonary capillary permeability in the rodent isolated lung.⁷⁴ In contrast,

Table 86-1 Effects of Hypercapnia

Organ System	Physiologic Effects	Pathophysiologic Consequences
Cardiovascular	Cardiac output and myocardial perfusion Increased cardiac output Direct reduction in cardiac contractility ¹²⁸ Counterbalanced by indirect sympathoadrenal effects (increased preload, heart rate, myocardial contractility) and decreased afterload (reduced vascular tone) ¹²⁹ Coronary vasodilation, mainly mediated by nitric oxide ¹³⁰	Improved cardiac output and oxygen delivery to tissues ¹²⁹
	Systemic oxygen delivery Rightward shift of hemoglobin-oxygen dissociation curve (Bohr effect) ¹³⁴ May acutely increase hematocrit ¹³¹	Improved oxygen delivery and unloading in tissues ¹³³
	Oxygen demand HCA reduces cellular respiration and oxygen consumption ¹³²	Reduction in tissue O ₂ demand
Respiratory	Control of respiration Changes in CO ₂ /H ⁺ levels sensed in special chemosensitive neurons in the carotid body and in hindbrain ^{4,5}	Oxygen-induced hypercapnia (see text for mechanism)
	Pulmonary vascular resistance Increased cardiac output and pulmonary vascular resistance ⁵⁰ Augments hypoxic pulmonary vasoconstriction ³⁷	Acute hypercapnia can worsen pulmonary hypertension Enhances ventilation-perfusion matching
	Airway resistance Direct dilation of small airways ⁵⁷ Indirect—vagally mediated—large airway constriction ⁵⁶	Opposing actions of CO ₂ may result in little net change in airway resistance ⁵⁹ Contribution to ventilation-perfusion matching (e.g., during pulmonary embolism)
	Lung compliance Increased surfactant secretion ⁶¹ Increased parenchymal compliance ⁶⁰	Improved lung compliance
	Gas exchange CO ₂ modifies pulmonary vascular and airway tone to help match regional ventilation and perfusion	Improved matching of ventilation and perfusion Increased arterial oxygenation by this mechanism in both normal ⁶⁴⁻⁶⁶ and injured ⁶⁷ lungs
Neurologic	Intracranial pressure Increased cerebral blood flow and volume ⁹⁰	Increased intracranial pressure
	Cerebral oxygenation Increased cerebral blood flow ⁹⁰ Increased cerebral oxygenation ²⁶³	Increased cerebral oxygenation—potential benefit in ischemic states ²⁶²
	Cerebral oxygen demand Decreases central nervous system O ₂ demand ²⁶³	Improved cerebral oxygen supply-demand ratio ²⁶³
Inflammation and immunity	Neutrophil and macrophage function Inhibition of neutrophil and macrophage migration and adhesion ¹⁷¹ Decreased secretion of important proinflammatory cytokines (e.g., TNF- α , IL-8, IL-6) ¹⁵² Inhibits phagocytosis and intracellular killing of bacteria (by reduction of nicotinamide adenine dinucleotide phosphate-oxidase activity) ¹⁷⁷	Reduced host response to injury Reduced proinflammatory response Potential increased susceptibility to prolonged sepsis
	Free radicals Decreased xanthine oxide free radical generation ¹⁶² Decreased production of NO-derived radicals (NO ₂ , NO ₃) and may shift the balance from O ₂ -derived toward N ₂ -derived (i.e., nitration) reactions ¹⁶⁵	Reduced free radical mediated injury Reduced microbicidal efficacy
Metabolic	Intracellular metabolism Intracellular acidosis causes inhibition of glycolysis due to inhibition of the rate-limiting enzyme phosphofructokinase ⁴⁸ Feedback system whereby lactic acid production is decreased by acidemia ⁴⁹	Decreased metabolism—potentially beneficial in ischemic states Decreased metabolic demand

hypercapnia reduces alveolar fluid clearance in healthy isolated perfused lungs by endocytotic withdrawal of Na⁺/K⁺-ATPase from the basolateral membrane of alveolar epithelial cells.⁷⁵ Whether this is the case *in vivo* or in injured lungs remains to be determined.

DIAPHRAGMATIC FUNCTION

The effects of hypercapnia on the diaphragm are complex and incompletely understood. Hypercapnia has been demonstrated to impair diaphragmatic function in preclinical

studies in which alveolar ventilation was not controlled. Rats exposed to prolonged environmental hypercapnia (7.5% CO₂ for 6 weeks) demonstrate significantly depressed diaphragmatic muscle function, as well as altered diaphragmatic composition with increased slow-twitch and decreased fast-twitch fibers.⁷⁶ In fact, even 15 minutes of exposure to 7% inspired CO₂ may transiently⁷⁷ and reversibly⁷⁸ impair neuromuscular function. In contrast, in studies in which ventilation is controlled and CO₂ increases moderately, hypercapnia may protect the diaphragm from injury.⁷⁹ Thus it remains unclear whether any deleterious

Table 86-2 Effects of Hypocapnia

Organ System	Physiologic Effects	Pathophysiologic Consequences
Cardiovascular	Cardiac output and myocardial perfusion Reduced cardiac output Increased systemic vascular resistance ¹⁴⁰ Hyperventilation additionally impairs venous return ¹⁴² Decreased myocardial blood flow, independent of myocardial workload ¹³⁹ Increased myocardial oxygen extraction (as a result of hyperventilation) ¹⁴¹	Reduced cardiac output May worsen myocardial ischemic injury
	Systemic oxygen delivery Leftward shift of the hemoglobin-oxygen dissociation curve (increased affinity of hemoglobin for oxygen) ¹³⁴ Compensated to some extent by a rapid increase in lactate production ¹³⁷ and by an increase in the concentration of 2,3-diphosphoglycerate ¹³⁸ over a period of several hours Systemic arterial vasoconstriction decreases global and regional O ₂ supply ^{135,136}	Decreased oxygen delivery to tissues
	Oxygen demand Increased cellular excitation and oxygen demand ¹²⁰	Oxygen supply/demand imbalance
Respiratory	Control of respiration Changes in CO ₂ /H ⁺ levels sensed in special chemosensitive neurons in the carotid body and in hindbrain ^{4,5}	Cheyne-Stokes respiration and central sleep apnea are thought to be due to decreased cerebral chemosensitivity to CO ₂ and left ventricular systolic dysfunction ²⁹¹
	Pulmonary vascular resistance Hypocapnic alkalosis produces pulmonary vasodilation ⁵³	Acute hypocapnia is used to alleviate pulmonary hypertension especially in setting of congenital heart disease and persistent pulmonary hypertension of the newborn Worsens ventilation-perfusion matching
	Airway resistance Direct constriction of small airways ^{54,55}	Contribution to ventilation-perfusion matching, which could be beneficial (e.g., during localized perfusion deficits such as pulmonary embolism), or harmful (e.g., during asthma)
	Lung compliance Increased alveolar permeability, ⁷⁴ decreased compliance, ²³⁷ and reduced surfactant production ²³⁸ These effects can be ameliorated by normalizing alveolar CO ₂ , ^{66,238,239,241} and in some cases prevented by elevated inspired CO ₂ ^{66,163,165,213}	Reduced lung compliance and worsened lung injury
	Gas exchange Worsened bronchoconstriction ⁵⁶ Reduced collateral ventilation ^{72,73} and impaired parenchymal lung compliance ⁶⁰ Attenuated hypoxic pulmonary vasoconstriction and increased intrapulmonary shunting ⁶⁴	Worsens matching of ventilation and perfusion The overall effect can be a net decrease in arterial PO ₂ Attenuation of hypoxic pulmonary vasoconstriction; can worsen intrapulmonary shunt and systemic oxygenation ⁶⁴
Neurologic	Intracranial pressure (ICP) Reduced ICP via arteriolar vasoconstriction and decreased cerebral blood volume	Acute hypocapnia decreases ICP, which is potentially lifesaving where ICP is critically elevated
	Cerebral oxygenation Decreases cerebral blood flow ¹⁰⁸ Decreases systemic oxygenation	Decreases cerebral oxygenation—potentially harmful in ischemic states Cerebral vasoconstriction may reduce overall perfusion ¹¹³ ; in focal ischemia, blood flow to hypoxic regions is selectively lowered ²⁶³ and infarct size increased ^{263,268} Termination of sustained hypocapnia can precipitate cerebral hyperemia and raised intracranial pressure ¹¹⁶
	Cerebral oxygen demand Increased CNS O ₂ demand through increasing neuronal excitability, ²⁶⁹ through increased excitatory synaptic transmission, ²⁶⁹ and by direct effect on the neuronal membrane itself ¹²⁰	Worsens cerebral oxygen supply-demand ratio
Acid-Base	Initial rapid cellular efflux of hydrogen ions (which is exhausted easily) Followed by renal compensatory mechanism: reduced hydrogen ion excretion, increased bicarbonate loss, and decreased excretion of ammonium ⁴⁰	Movement of H ⁺ from intracellular to extracellular space is accompanied by (1) an opposite movement of K ⁺ (and Na ⁺) into the cell (the resulting hypokalemia is usually modest ⁴¹), (2) phosphate movement into the cell due to increased cellular phosphorylation, ⁴² and (3) albumin release of bound H ⁺ , swapping it for Ca ²⁺ and lowering the ionized calcium fraction, ⁴³ which may be severe ⁴⁴
Metabolic	Intracellular alkalosis causes activation of glycolysis due to inhibition of the rate-limiting enzyme phosphofructokinase ⁴⁸ Feedback system whereby lactic acid production is increased by alkalemia ⁴⁹	Increased tissue O ₂ demand

effects of hypercapnia on the diaphragm are due to direct effects of CO_2 or result from diaphragmatic fatigue from the induced increase in ventilation.

CENTRAL NERVOUS SYSTEM EFFECTS

CEREBRAL BLOOD FLOW

The change in *cerebral blood flow* (CBF) during variations of arterial PCO_2 depends on several factors, including baseline CBF, cerebral perfusion pressure, and the presence of anesthesia. Across a broad range of conditions, most studies report an increase in global CBF of 1 to 2 $\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ for each 1 mm Hg increase in arterial PCO_2 ⁸⁰⁻⁸²; reducing arterial PCO_2 to 20 to 25 mm Hg decreases the global CBF by 40% to 50%, with minimal effect from further arterial PCO_2 reduction. Increasing the arterial PCO_2 to 80 mm Hg produces a maximal increase in CBF of 100% to 200% in anesthetized animals,⁸³ but in the awake state, arterial PCO_2 of 80 mm Hg can increase CBF by up to sixfold; in such cases, one half of the increase in CBF results from release of endogenous catecholamines and activation of neuronal metabolism.⁸⁴ Thus, in awake subjects, severe hypercapnia may increase the flow by two mechanisms: a direct effect of CO_2 on cerebral blood vessels and an indirect effect increasing neuronal metabolic rate and catecholamine release.

However, these effects are not sustained: with hypocapnia for up to 4 hours, CBF recovers to within 10% of baseline⁸⁵ due to reduced cerebrospinal fluid and extracellular HCO_3^- and due to correction toward a normal extracellular pH.

The extent to which CO_2 modulates CBF varies depending on baseline CBF, which is not homogeneous across the brain. Areas of the brain that receive more blood flow have a steeper flow response to changes in arterial PCO_2 . In patients with traumatic brain injury, there is a 3% change in CBF per mm Hg change in arterial PCO_2 ,⁸⁶ but because the response depends on baseline flow, it is reduced in patients with lower CBF.⁸⁶ The regional differences are significant. In the cerebral cortex of the anesthetized cat, the baseline CBF is $86 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, and a 1 mm Hg change in arterial PCO_2 changed CBF by 1.7 mL .⁸¹ In contrast, the spinal cord has a blood flow of $46 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, and each 1 mm Hg change in arterial PCO_2 changed CBF by 0.9 mL .⁸¹ Similar findings have been reported in rabbits⁸² and humans.⁸⁷

HYPOCAPNIA AND CEREBRAL VASOCONSTRICTION

The mechanisms by which arterial CO_2 tension modulates cerebral vasoactivity depend on the size and type of blood vessel. The effects on cerebral vascular tone are mediated via changes in pH rather than CO_2 per se.⁸⁸ The diameter of cerebral arterioles responds only to changes in pH and not to buffered changes in CO_2 tension.⁸⁹ In addition, the effect of CO_2 on cerebrovascular tone is largely confined to the cerebral arterial vasculature, with little effect on associated veins or capillaries.⁹⁰

Hypercapnic acidosis induces precapillary dilation of cerebral arterioles,⁹¹ and whereas all cerebral arteries show some responsiveness to altered CO_2 tension, the larger arteries are less sensitive while the small pial arterioles are most responsive.⁹² Changes in these arterioles are not detected using noninvasive technologies, such as transcranial Doppler, which focuses on the larger vessels.⁹²

Whereas direct and indirect mechanisms mediate the effects of CO_2 on CBF, cerebral vascular tone is altered by CO_2 only via a direct effect on the arteriole wall^{88,93,94} and not by alterations in catecholamine release or sympathetic tone.^{83,95} The vascular endothelium and smooth muscle layer play a central role. Several lines of evidence suggest that endothelial release of *nitric oxide* (NO) in response to alterations in PCO_2 is a key mechanism. Administration of an exogenous NO donor reduces basal cerebrovascular resistance and blunts the cerebral vasoconstrictor effect of hypocapnia in humans.⁹⁶ Damage to cerebrovascular endothelium is associated with impaired CO_2 cerebrovascular reactivity, which parallels impaired release of NO from the endothelium.⁹⁷ Inhibition of NO synthase reduces hypercapnia induced cerebral vasodilation.^{98,99} Specific inhibition of the neuronal isoform of NO synthase reduces hypercapnia induced vasodilation in the parietal cortex¹⁰⁰ and retinal circulation.¹⁰¹

In contrast, in adult rodents, damage to the endothelium *in vivo* does not alter the response of the cerebral arteries to hypercapnia,¹⁰² suggesting alternative pathways. CO_2 ultimately regulates vascular tone by modulating intracellular calcium concentration and sensitivity.¹⁰³ Alkalosis induces increases in concentrations of intracellular calcium in the vascular smooth muscle, increasing the vascular tone.¹⁰⁴ In addition, NO activates guanylate cyclase in vascular smooth muscle, increasing the cyclic guanosine monophosphate concentration,¹⁰⁵ which in turn phosphorylates calcium channels.¹⁰⁶

Elevation of extracellular calcium prevents acidosis-induced dilation of cerebral arterioles, suggesting that reduced vascular smooth muscle calcium reentry may mediate in part the acidosis-reduced vascular tone.⁹³ In addition, opening of potassium channels during acidosis allows egress of potassium, hyperpolarizing the cell, closing voltage-gated calcium channels, and reducing vascular tone by reducing calcium entry.¹⁰⁷

CEREBRAL PERFUSION—FLOW VERSUS VOLUME

The primary aim of inducing hypocapnia in the setting of raised ICP is to reduce cerebral blood volume (Fig. 86-1). However, the effect of CO_2 on cerebrovascular tone is largely confined to the cerebral arteries⁹⁰; thus the effect of changing arterial PCO_2 on CBF is substantially larger than its effect on cerebral blood volume (Fig. 86-2). Fortune and colleagues¹⁰⁸ demonstrated that hypocapnia in volunteers decreased cerebral blood volume by 7% while reducing CBF by greater than 30%. Because low CBF is common in the first 24 hours after traumatic brain injury, there is particular concern for inducing ischemia by hyperventilation.¹⁰⁹ In summary, the cost of hypocapnia in terms of reduced cerebral perfusion may outweigh any benefit in terms of reducing intracranial volume. Even so, hypocapnia remains in

widespread use in the management of patients with acute brain injury²⁶ (Fig. 86-3).

CEREBRAL OXYGENATION

In humans, when arterial PCO_2 is reduced to 20 to 25 mm Hg, CBF is reduced to 20 to 25 mL/100 g \cdot min $^{-1}$,^{110,111} but does not reach lower levels even during extreme hypocapnia in anesthetized (arterial PCO_2 10 mm Hg)¹¹¹ or nonanesthetized humans (arterial PCO_2 16 mm Hg).⁸⁵ In nonanesthetized, normothermic humans and primates, the earliest signs and symptoms of cerebral ischemia, such as confusion, inability to follow commands, focal neurologic deficits, and slowing of the

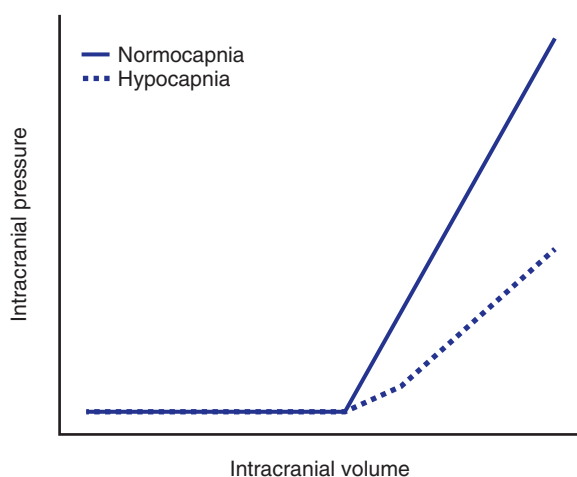


Figure 86-1 Rationale for the use of hypocapnia in patients with raised intracranial pressure. Because the cranial cavity represents a fixed volume, an increase in the volume of brain tissue due to edema, tumor or hematoma formation can initially be compensated by displacement of volume from another compartment. Acute hypocapnia can reduce cerebral blood volume, thereby temporarily attenuating the rise in intracranial pressure. (From Curley G, Kavanagh BP, Laffey JG: Hypocapnia and the injured brain: more harm than benefit. *Crit Care Med* 38:1348–1359, 2010.)

electric activity of the brain, measured by an electroencephalogram, are seen at global CBF levels of 20 to 30 mL/100 g \cdot min $^{-1}$; however, CBF must be reduced to less than 10 mL/100 g \cdot min $^{-1}$ to cause neuronal cell death.^{112,113}

Hyperventilation can reduce CBF to ischemic levels; in humans and animals, reducing the arterial PCO_2 to 20 to 25 mm Hg slows the electroencephalogram¹¹⁴ and impairs mental function,¹¹⁵ both of which suggest mild cerebral ischemia. Severe hypocapnia also increases *central nervous system* (CNS) lactate, consistent with impaired oxidative metabolism,^{116,117} and cortical PO_2 is reduced during hypocapnia. Indeed, severe hypocapnia (10 mm Hg arterial PCO_2) can reduce cortical PO_2 despite a plateau low level of CBF, indicating that further hypocapnia additionally increases local O_2 consumption or inhibits local delivery.^{118,119} Marked alkalosis also shifts the oxyhemoglobin dissociation curve to the left, which can enhance uptake in the lung, but limits oxygen delivery to systemic organs, including the brain.

Hypocapnia increases neuronal excitability^{120,121} via a direct effect on the neuronal membrane,¹²² which increases cerebral glucose utilization,^{123,124} leads to neuronal glucose depletion, and increases anaerobic metabolism.^{125,126} Also, alkalosis, especially respiratory alkalosis, inhibits the usual negative feedback by which low pH limits production of endogenous organic acids (e.g., lactate) during ischemia.¹²⁷ This may prevent cellular metabolic down-regulation in the setting of diminished nutrient supply, a potentially protective mechanism.

Overall, most studies indicate that, in the normal brain, hypocapnia can reduce CBF to the point of cerebral ischemia but not to levels of CBF that cause rapid neuronal death. If hypocapnia causes cerebral ischemia in the normal brain, it is likely mild and not associated with gross disturbances of brain oxidative metabolism. However, the long-term effect of hyperventilation on the normal brain is not known. Thus, in aggregate, hypocapnia may cause brain

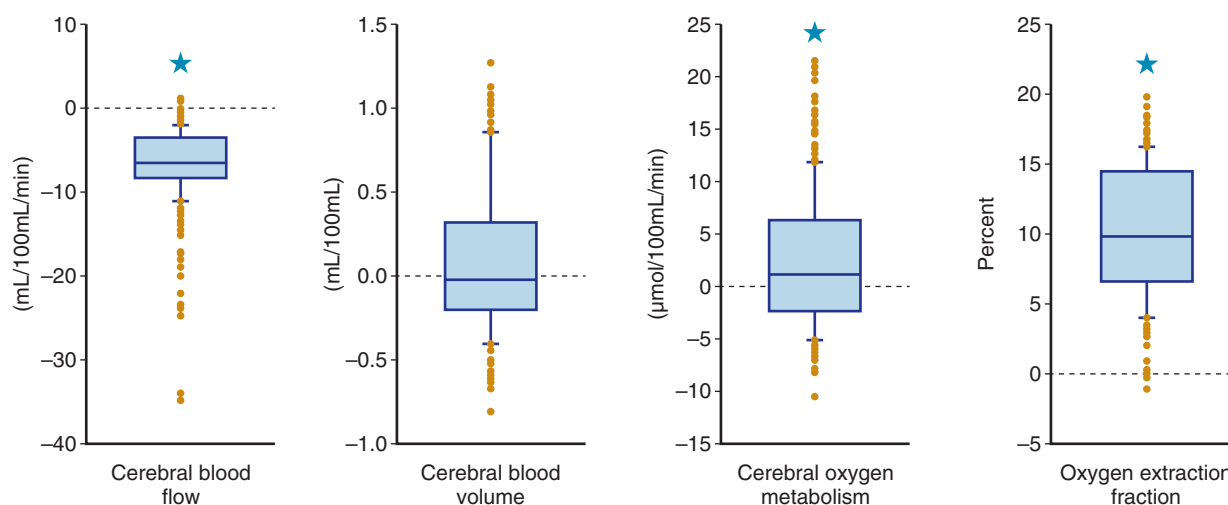


Figure 86-2 Hypocapnia decreases regional cerebral perfusion and increases oxygen extraction in patients following traumatic brain injury. Box and whisker plots of changes (Δ) in cerebral blood flow, cerebral blood volume, cerebral oxygen metabolism, and oxygen extraction fraction produced by hyperventilation, measured in 15 regions of interest in 18 subjects between 2 and 7 days after traumatic brain injury. The central lines in each box denote median values, the lower and upper boundaries the 25th and 75th centile, the error bars the 10th and 90th centile, and the closed circles outlying data points. $\star P < 0.001$, Wilcoxon's signed-rank test with Bonferroni correction, comparing normocapnic and hypercapnic values. (From Coles JP, Fryer TD, Coleman MR, et al: Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. *Crit Care Med* 35:568–578, 2007.)

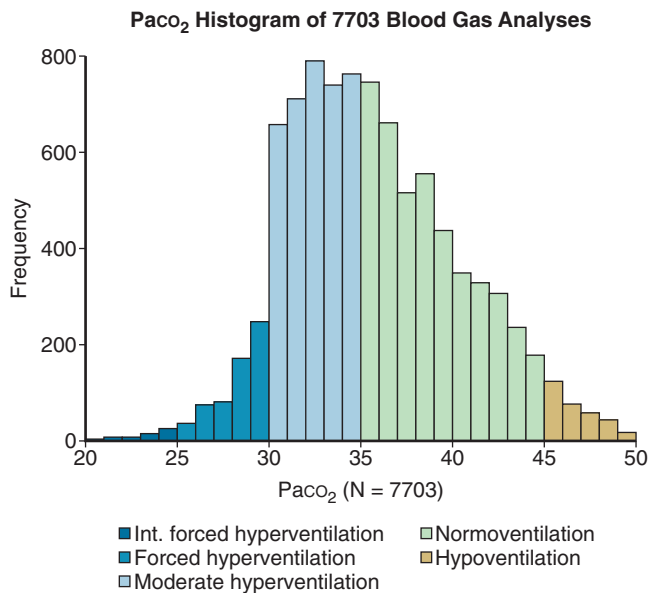


Figure 86-3 Frequency of hypocapnia in adults with traumatic brain injury. The distribution of arterial PCO₂ values in blood gas analyses is skewed toward hypocapnia, with most values in the range of 30 to 35 mm Hg, suggesting that hyperventilation therapy is still in widespread use. Int, intensified. (From Neumann JO, Chambers IR, Citerio G, et al: The use of hyperventilation therapy after traumatic brain injury in Europe: an analysis of the BrainIT database. *Intensive Care Med* 34:1676–1682, 2008.)

ischemia by increasing cerebral oxygen demand as well as decreasing cerebral oxygen supply. These concerns limit the utility of hypocapnia to the setting of life-threatening increases in ICP, where it can be lifesaving by allowing time for definitive intervention.

CARDIOVASCULAR SYSTEM EFFECTS

SYSTEMIC CIRCULATION

Hypercapnic acidosis directly reduces contractility of cardiac¹²⁸ and vascular smooth muscle. This is counterbalanced by the hypercapnia-mediated sympathoadrenal effects of increased preload and heart rate, increased myocardial contractility, and decreased afterload, leading to a net increase in cardiac output.¹²⁹ Hypercapnia results in a complex interaction of altered cardiac output, hypoxic pulmonary vasoconstriction, and intrapulmonary shunt to produce a net increase in arterial PO₂. Because hypercapnia generally elevates cardiac output, global O₂ delivery is increased. Hypercapnic acidosis causes coronary vasodilation, mainly mediated by NO.¹³⁰ Hypercapnia and acidosis shift the hemoglobin-oxygen dissociation curve rightward, reducing the oxygen affinity of Hb, and hypercapnic acidosis may acutely elevate hematocrit by a mechanism that may involve sympathetically mediated autotransfusion,¹³¹ further increasing tissue oxygen delivery. Acidosis may reduce cellular respiration and oxygen consumption,¹³² which may further benefit a supply and demand imbalance. In addition, hypercapnic acidosis increases O₂ tension in both subcutaneous tissues and the intestinal wall.¹³³

Hypocapnia and alkalosis, on the other hand, increase the affinity of Hb for oxygen (leftward displacement of the dissociation curve)¹³⁴ and reduce microcirculatory blood flow,^{135,136} further impairing local oxygen delivery. This is compensated to some extent by a rapid increase in lactate production¹³⁷ and by an increase in the concentration of 2,3-diphosphoglycerate,¹³⁸ which, over a period of several hours, may have an opposite effect on the dissociation curve.

Hypocapnia depresses myocardial blood flow, independent of myocardial workload.¹³⁹ In patients with coronary artery disease, mild hyperventilation slightly increases systemic vascular resistance and reduces cardiac index.¹⁴⁰ In addition, hyperventilation increases myocardial oxygen extraction.¹⁴¹ More pronounced levels of hypocapnia reduce cardiac output,¹⁴² and indirect effects of intrathoracic pressure associated with passive hyperventilation may additionally impair venous return and further depress cardiac output.¹⁴³

SPLANCHNIC EFFECTS OF ALTERED CO₂

Hypercapnia improves regional—including mesenteric—blood flow¹⁴⁴ and enhances peripheral microcirculatory flow,¹⁴⁵ thereby increasing organ oxygen delivery and splanchnic tissue oxygenation. Hypercapnia preserves tissue oxygenation of the gastrointestinal mucosa in uninjured animals,¹⁴⁶ and it reverses decrements in gastric mucosal oxygenation during hemorrhagic shock^{147,148} and following captopril administration.¹⁴⁶

The effects of CO₂ on the splanchnic organs are less well understood. CO₂ and acid-base status modulate splanchnic organ cellular function. Acidosis protects hepatocytes from anoxic¹⁴⁹ or chemical hypoxia-induced cell death,¹⁵⁰ while restoration of normal pH abolishes this protection. This effect may represent a protective adaptation against hypoxic and ischemic stress. In the kidney, acidosis protects isolated renal cortical tubules from anoxia-induced injury.¹⁴⁹ Hypercapnic acidosis, particularly in the setting of concomitant hypoxia, may produce marked sympathetic activation, which can lead to intense renal vasoconstriction and tubular sodium reabsorption, causing depressed glomerular filtration and increased fluid retention.¹⁵¹

INFLAMMATION AND REPAIR

MEDIATOR PRODUCTION

Hypercapnia and acidosis inhibit cytokine signaling in immune effector cells.¹⁵²⁻¹⁵⁵ Acidosis reduces secretion of important proinflammatory cytokines (e.g., TNF- α , IL-8, IL-6) from *polymorphonuclear leukocytes* (PMNs)¹⁵² and macrophages¹⁵⁴; especially important may be the production of IL-8 by PMNs, which is pivotal in mediating the acute inflammatory response to infection.¹⁵² However, the inhibition of PNM IL-8 secretion is blocked by pretreatment with acetazolamide, a drug that lessens the impact of PCO₂ on neutrophil intracellular pH.¹⁵²

CO₂-induced inhibition of cytokines can be sustained. Indeed, peritoneal macrophages had reduced TNF- α production up to 3 days after peritoneal insufflation of CO₂ (as

used during laparoscopic surgery),¹⁵⁶ a phenomenon that may result from inhibition of *nuclear factor-kappa B* (NF- κ B), a regulator of the transcription of mediators in inflammation, injury, and repair.¹⁵⁷

COMPLEMENT ACTIVATION

Innate immunity requires the complement system in order to target pathogens for phagocytosis or lysis; complement is activated by acidosis. Acid activation of C5 combines with C6, forming a lytic complex, C5b6a¹⁵⁸ via the classic activation pathway. The alternative complement pathway is also activated by acidosis with increased activity of C3 convertase, in turn increasing complement binding to—and lysis of—erythrocytes.¹⁵⁹ C3 (and C5) is activated with H⁺ from hypercapnic or lactic acidosis, as well as with hydrochloric acid,¹⁶⁰ and is due to the acidosis per se.¹⁶⁰

FREE RADICAL GENERATION

Hypercapnic acidosis reduces free radical tissue damage in brain¹⁶¹ and lung,¹⁶² as well as following lung ischemia-reperfusion.¹⁶³ It lessens production of NO-derived radicals (NO₂, NO₃) following ventilator¹⁶⁴ and endotoxin-induced¹⁶⁵ injury, and may shift the balance from O₂-derived toward N₂-derived (i.e., nitration) reactions.^{166,167} This effect may be beneficial where greater injury is associated with oxidative versus nitration reactions.¹⁶⁸ However, it is not clear whether hypercapnic acidosis reduces in vivo tissue oxidative damage beyond its impact on neutrophils.

INNATE IMMUNE RESPONSE

Neutrophils, macrophages, and circulating monocytes are major elements in the innate immune response, and are especially important in responses to bacterial infection.¹⁶⁹ They are directly activated by bacteria, bacterial products, or inflammatory molecules such as complement. Neutrophils rapidly localize to areas of infection or inflammation, migrating from the bloodstream, and rapidly phagocytosing bacteria on contact. Phagocytosis is rapidly followed by bacterial lysis and destruction because the phagosomes fuse with toxic granules containing powerful enzymes such as elastases, proteases, nicotinamide adenine dinucleotide phosphate-oxidase (generates superoxide and hydrogen peroxide) and myeloperoxidase (generates hypochlorous acid).¹⁷⁰ Migration of PMNs is key and impairment of migration to infection sites worsens outcome in sepsis.¹⁶⁹ Circulating monocytes (and their macrophage counterparts in tissues) coordinate lymphocyte activation in sepsis by presenting bacterial antigen and secreting chemokines, and macrophages are activated by bacteria or by molecules such as endotoxin or complement components. Finally, monocytes and macrophages phagocytose and kill pathogens by similar mechanisms as—but at a slower rate than—neutrophils.

Hypercapnic acidosis inhibits neutrophil and macrophage function, and this inhibition can be sustained. For example, ex vivo inhibition of peritoneal macrophages lasts up to 3 days.^{153,156} The mechanisms are unclear but hypercapnic inhibition of macrophage TNF- α production requires

more than transient (~30 min) exposure, happens despite normal TNF- α mRNA levels, and persists long after ambient CO₂ has normalized.¹⁵⁴ Hypercapnia or acidosis may impact these processes in other ways, including alteration of intracellular pH, reduction of neutrophil recruitment or migration, inhibition of phagocyte oxidizing function, impairment of cytokine signaling among effector cells, or potentiating neutrophil death.

Phagocyte Migration, Chemotaxis, and Adhesion

Neutrophil migration is key to immune defense, and depends on processes such as cytoskeleton remodeling, membrane recycling (endocytosis, exocytosis), integrin-mediated focal adhesion attachment and reattachment, and regulation of cell volume. Many of these processes are pH dependent, and hypercapnic acidosis may therefore reduce neutrophil and macrophage recruitment to a septic focus. Acidosis impairs neutrophil chemotaxis and migration,^{171,172} and hypercapnic acidosis reduces neutrophil expression of chemokines, selectins, and intercellular adhesion molecules,^{152,157,173,174} which mediate the neutrophil-endothelial interactions required for migration out of blood vessels. Finally, hypercapnic acidosis reduces lung neutrophil migration following in vivo endotoxin.¹⁶⁵

Phagocyte Microbial Killing

Pathogens are internalized by neutrophils and macrophages within phagosomes, which merge with endosomes and lysosomes, and are lysed by powerful enzymes. This process requires bacterial phagocytosis and an intact “respiratory burst,” which produces the reactive oxygen species (O₂⁻, H₂O₂, HClO) within the endosomes and lysosomes needed for bacterial killing. Acidosis—both hypercapnic and metabolic—impairs neutrophil and macrophage phagocytosis; specifically, failure to recover intracellular pH (pHi) after acidification impedes ROS production and killing of phagocytosed bacteria in macrophages,¹⁷⁵ and metabolic¹⁷⁶ or hypercapnic¹⁷⁷ acidosis inhibits neutrophil phagocytosis. In contrast, moderate alterations of ambient pH have little effect on neutrophil phagocytosis, but markedly reduce subsequent bacterial lysis.¹⁷⁸ Finally, incubation in organic acid inhibits macrophage phagocytosis.¹⁷²

One of the enzymes largely responsible for the production of these oxygen-derived radicals, nicotinamide adenine dinucleotide phosphate-oxidase, is markedly pH sensitive.¹⁷⁹ For example, macrophage O₂⁻ production decreases linearly with reduction in pHi (below 6.8),¹⁸⁰ and hypercapnic^{152,181} and metabolic^{176,182-184} acidosis inhibits oxidant production in neutrophils that are nonstimulated^{152,181} or stimulated with a variety of chemical and microbial stimuli.^{152,184} Although marked reduction of extracellular pH to 6.5 may activate neutrophils (i.e., increasing H₂O₂ and integrin CD18) this may reflect experimental use of strong HCl.¹⁷⁴

Mechanism of Phagocyte Inhibition

Regulation of pHi is key to cell function; in general, acidosis reduces enzyme activity and protein function, particularly when pHi is less than 6.8. Because CO₂ is diffusible, hypercapnia can rapidly lower pHi and thereby inhibit neutrophil¹⁵² and macrophage¹⁸⁵ function. Two key systems regulate pHi in immune cells: the Na/H exchanger (NHE) and

the plasmalemmal V-type H ATPase.¹⁸⁶ These enzymes maintain pHi in the physiologic range (6.8 to 7.3), necessary for immune responses, as well as for other key functions including proliferation, differentiation, apoptosis, migration, cytoskeletal organization, and maintenance of cell volume.

Neutrophil pHi decreases following stimulation and activation^{152,187} and then reverts toward normal if extracellular pH is physiologic. This is important because PMNs that are unable to regulate cytosolic pH demonstrate impaired migration^{188,189} and apoptosis.^{152,190} However, extracellular hypercapnic acidosis rapidly lowers neutrophil pHi,^{152,174,188} and activated neutrophils from foci of inflammation are unable to maintain pHi following an acid challenge.¹⁹¹ Therefore persistent “acid loading,” as with ongoing permissive (or other) hypercapnia, could overwhelm the capacity of PMNs to maintain pHi and normal cell homeostasis and function. This may be especially so with PMNs that have already been activated.¹⁹¹

Neutrophil Death

Neutrophils have a short life span (<48 hours after release into the circulation) that is terminated by apoptosis, a physiologic fate following phagocyte activity. In contrast, necrosis of neutrophils after phagocytosis is a maladaptive response because microbe killing and digestion may be incomplete, and in contrast to apoptosis, enzyme release causes tissue destruction.¹⁹² Lower extracellular pH—as with hypercapnic acidosis—may delay neutrophil apoptosis and extend PMN life span.¹⁷⁴ However, hypercapnic acidosis also lowers pHi,¹⁵² which may increase neutrophil propensity to undergo necrosis rather than apoptosis.¹⁹⁰ Thus the net effect of hypercapnic acidosis on neutrophil fate—whether beneficial or deleterious—remains unclear.

ADAPTIVE IMMUNE RESPONSE

Adaptive immunity is especially important in many cancers, which characteristically involve poor vascularization, tissue hypoxia, and acidosis,¹⁹³ a setting wherein acidosis may impair host responses to tumor cells, resulting in tumor growth and metastases. However, the impact of acidosis is complex. For example, acidosis inhibits cytotoxicity of activated killer lymphocytes¹⁹⁴ and natural killer cells,¹⁹⁵ reduces lysis of tumor cells by cytotoxic T lymphocytes,¹⁹⁶ and inhibits IL-2 stimulated lymphocyte proliferation.¹⁹⁷ In contrast, IL-2 stimulated lymphocyte motility is enhanced by acidosis,^{198,199} as is the antigen presenting capacity of dendritic cells.²⁰⁰ The net effect of these contrasting actions of acidosis is unclear. However, hypercapnic acidosis does enhance murine tumor spread,²⁰¹ raising concerns about hypercapnia-induced suppression of cell-mediated immunity.¹⁵³

BACTERIAL PROLIFERATION

Hypercapnia and acidosis exert distinct effects on bacterial proliferation. For example, optimal anaerobic growth of *Escherichia coli* is seen at a PCO₂ of approximately 0.05 atmospheres (similar to the usual gut *E. coli* environment); it is not inhibited at a PCO₂ of approximately 0.2 atmo-

spheres but is inhibited at greater than 0.6 atmospheres.²⁰² Indeed, *E. coli* colony counts were halved at a CO₂ of approximately 350 atmospheres, a massive dose.²⁰³ Although the mechanisms are unclear, such inhibition is mediated directly by CO₂,²⁰⁴ and the effects are broadly similar among microbes, with yeasts being more resistant and gram-negative organisms being more susceptible.²⁰⁵

Although important, the levels of CO₂ in these studies are far higher than encountered in humans. In fact, clinically relevant levels of metabolic acidosis can enhance bacterial proliferation, as has been observed when mechanically stretched lung epithelial cells can develop lactic acidosis that augmented *E. coli* growth.²⁰⁶ Such acidosis-induced *E. coli* proliferation has been demonstrated due to H⁺-ions (not CO₂) and is abolished by local buffering.²⁰⁶

While many bacteria (*E. coli*, *Proteus mirabilis*, *Serratia rubidaea*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*) isolated from patients with ventilator-associated pneumonia grew better in acidified media,²⁰⁶ at least one important pathogen (i.e., methicillin-resistant *Staphylococcus aureus*) grew optimally at alkaline pH.²⁰⁶ In summary, while bacterial growth can be inhibited by extremely high levels of CO₂, it can be enhanced by clinically relevant levels of acidosis; thus the net impact of hypercapnic acidosis on bacterial growth is a concern.

EFFECTS OF CO₂ ON REPAIR AND RESOLUTION

RESTORATION OF EPITHELIAL INTEGRITY

Elevated CO₂ directly inhibits alveolar epithelial plasma membrane resealing,²⁰⁷ and decreases repair of alveolar epithelial wounds,²⁰⁸ both important mechanisms contributing to repair following injury to the lung. Hypercapnic acidosis exerts a direct pH-dependent inhibition of lung epithelial cell membrane healing following ventilation-induced injury,²⁰⁹ a repair mechanism that depends on translocating lipids to the injured membrane.²¹⁰ In contrast, the effect of elevated CO₂ on pulmonary epithelial wound repair appears dependent on the hypercapnia rather than the acidosis per se, and appears to be mediated via effects on cell migration.²¹¹ CO₂ (pH-independent) induction of microRNA-183 (miR-183), albeit with high PCO₂ levels (120 mm Hg), may lead to mitochondrial dysfunction, which in turn impairs cell proliferation and survival.²¹²

LUNG PERMEABILITY AND FLUID CLEARANCE

Lung water accumulation and clearance are important contributors to injury and repair, respectively. Hypercapnic acidosis directly reduces,²¹³ while hypocapnic alkalosis worsens,⁷⁴ ischemia-reperfusion-induced pulmonary capillary permeability. In contrast, hypercapnia reduces alveolar fluid clearance in healthy isolated perfused lungs.⁷⁵ Hypercapnia appears to activate extracellular signal-regulated kinase,²¹⁴ which in turn activates adenosine monophosphate-activated protein kinase, leading to endocytotic withdrawal of Na⁺/K⁺-ATPase from the basolateral membrane of alveolar epithelial cells.⁷⁵

CELLULAR SENSING AND GENE ACTIVATION

MECHANISMS OF CELLULAR SENSING

As discussed in the section on regulation of arterial CO_2 , cellular sensing of CO_2 is best characterized in central and peripheral nerve cells in relation to control of breathing. However, it remains unclear whether these chemosensitive neurons detect alterations in CO_2 directly or via changes in H^+ concentrations. In addition, HCO_3^- (but not CO_2 or H^+) directly activates adenylate cyclase,²¹⁵ increasing cyclic adenosine monophosphate²¹⁶ and activating protein kinase A; this in turn results in opening of L-type Ca^{2+} channels, permitting Ca^{2+} influx.⁵ Such changes may mediate responses of putative (but as yet unidentified) CO_2 receptors. In addition, increased CO_2 (independent of pH) activates L-type calcium channels in the glomus cells of the carotid nucleus, also resulting in calcium influx.^{217,218}

GENE ACTIVATION

An important downstream consequence of cell sensing is gene activation. Key insights into CO_2 -induced gene activation have been gained by gene array studies in murine lung tissue,^{219,220} nematode (*Caenorhabditis elegans*),²²¹ and the fruit fly (*Drosophila melanogaster*)²²² following exposure to high concentrations of CO_2 .

Neonatal mice exposed to atmospheric hypercapnia demonstrated increased expression of lung genes involved in regulating cell adhesion, growth and signal transduction, and suppression of genes involved in innate immunity.²¹⁹ Hypercapnia also suppressed lipopolysaccharide-induced cytokine production (and phagocytosis) by murine macrophages, possibly explained by concomitant suppression of NF- κB ²²⁰ and consistent with impaired NF- κB signaling induced by hypercapnia in mouse embryonic fibroblasts and other mammalian cell types.²²³

CO_2 exposure also caused altered gene expression in model organisms *C. elegans*²²¹ and *D. melanogaster*,²²² where such transcription regulation has been largely attributed to inhibition of the NF- κB family of transcription factors. For example, hypercapnia-impaired innate immune responses in *D. melanogaster* increased susceptibility to bacterial infection and were associated with suppression of Relish (an NF- κB homolog) and its associated genes.²²¹

Thus CO_2 causes common gene expression patterns that are conserved across diverse species. Key features include suppression of genes associated with innate immunity and inhibition of NF- κB signaling²²⁴ (Fig. 86-4). NF- κB is sequestered in the cytosol by inhibitory molecules (I κB s), and inflammatory stimuli activate upstream signaling cascades, causing phosphorylation and degradation of I κB ; this liberates NF- κB , permitting its translocation to the nucleus where it activates expression of genes involved in innate immunity and inflammation.²²⁵ CO_2 directly inhibits the NF- κB pathway, likely through CO_2 -induced nuclear

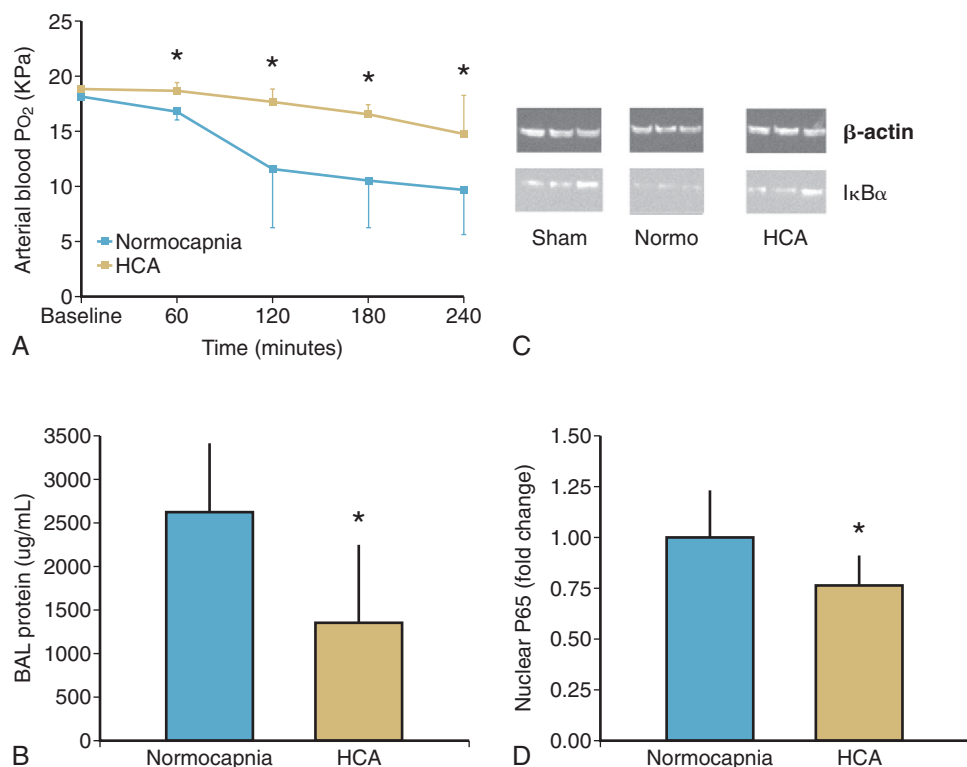


Figure 86-4 Hypercapnic acidosis (HCA) reduced high stretch ventilation-induced lung injury and indices of activation of the NF- κB pathway in the rodent. HCA reduced the decrement in arterial oxygen pressures (A) and reduced bronchoalveolar lavage (BAL) protein concentrations (B) compared to normocapnia. HCA inhibited the activation of the NF- κB pathway by excessive mechanical stretch. Specifically, HCA abolished the decrease in cytoplasmic concentrations of the NF- κB inhibitor, I $\kappa\text{B}\alpha$ concentrations (C). This results in a decreased nuclear concentration of the active P65 subunit of NF- κB , with HCA compared to normocapnia (D). *Significantly different from normocapnia ($P < 0.05$, ANOVA). (From Contreras M, Ansari B, Curley G, et al: Hypercapnic acidosis attenuates ventilation-induced lung injury by a nuclear factor-kappaB-dependent mechanism. *Crit Care Med* 40(9):2622–2630, 2012.)

localization of the IKK α subunit, thereby preventing degradation of I κ B.²²³ The protective effects of hypercapnia in mechanical stretch-induced injury in vitro and in ventilation-induced lung injury in vivo appeared to be mediated via inhibition of the NF- κ B pathway.²²⁶

PULMONARY PATHOPHYSIOLOGY

PRECLINICAL MODELS

Hypercapnic acidosis is protective in several in vivo and ex vivo lung injury models, including lung injury caused by endotoxin,¹⁶⁵ pulmonary,^{162,163} and mesenteric⁶⁶ ischemia-reperfusion, in addition to ventilator-induced lung injury^{66,164,227,224} (see Fig. 86-4). In *E. coli* pneumonia, hypercapnia attenuates histologic injury²²⁸ by a neutrophil-independent mechanism,²²⁹ and it attenuates lung injury caused by short-term and more prolonged systemic polymicrobial sepsis.²⁰⁸ In contrast to acute pulmonary hypertension, chronic exposure to hypercapnia causes reversal of hypoxia-induced pulmonary hypertension in adult²³⁰ and neonatal²³¹ rats, and protects against parenchymal and vascular injury in neonatal lungs.²³²

In contrast to protective effects, hypercapnia has several adverse effects on immunity and repair. While protective in acute²²⁹ and more established²²⁸ lung sepsis, hypercapnia over a longer period (48 hours) is associated with increased bacterial proliferation and more marked lung injury.¹⁷⁷ Furthermore, hypercapnia induced by lowered respiratory rate and tidal volume exacerbated endotoxin-induced lung injury²³³ and increased neutrophil adhesion and adhesion molecule expression.²³⁴ Finally, as discussed earlier, important aspects of injury resolution may also be impaired by hypercapnia, such as epithelial wound repair^{207,211}—likely via inhibition of NF- κ B²¹¹—and clearance of alveolar edema.⁷⁵

Hypocapnia has long been recognized as associated with adverse lung effects and was thought to be pathogenic in ARDS.²³⁵ Hypocapnia may contribute to lung injury in two ways. First, high tidal volume that induces hypocapnia can separately cause ventilator-induced lung injury.²³⁶ Second, hypocapnia may directly injure the lung in the absence of ventilator-induced injury and can increase permeability,⁷⁴ decrease compliance,²³⁷ inhibit surfactant,²³⁸ and potentiate inflammation.^{66,239,240} These effects can be ameliorated by normalizing alveolar CO₂,^{66,238,239,241} and in some cases the effects can be prevented by elevated inspired CO₂.^{66,163,165,213} Finally, alveolar hypocapnia attenuates hypoxic pulmonary vasoconstriction, worsening intrapulmonary shunt, and systemic oxygenation.⁶⁴

ACUTE RESPIRATORY DISTRESS SYNDROME

Trials of low tidal volume ventilation provide little direct insight into any independent role of CO₂ because patients have not been randomized to hypercapnia per se; in fact, in the large ARDS Network trial comparing target tidal volumes of 6 versus 12 mL/kg, there was only a mean 5 mm Hg greater arterial PCO₂ in the lower tidal volume arm.²³⁶ Nonetheless, using the database from this large trial, multivariable analysis suggested that moderate levels

of hypercapnic acidosis (pH 7.15 to 7.35; arterial PCO₂ 45 to 65 mm Hg) significantly lowered the odds ratio for death in the 12 mL/kg (but not in the 6 mL/kg) group,²⁴² suggesting that permissive hypercapnia may limit ventilator-induced lung injury. In addition, a smaller study by Amato and colleagues²⁴³ reported reduction in mortality from a combination of lower tidal volume and higher positive end-expiratory pressure (resulting in substantially greater arterial PCO₂) on survival in ARDS. This study²⁴³ and the retrospective studies on permissive hypercapnia^{19,20} demonstrate a link, but not a cause-and-effect relationship, between higher arterial PCO₂ and improved outcome.

ASTHMA

Among common causes of respiratory failure, status asthmaticus is associated with the highest levels of hypercapnia (arterial PCO₂ often greater than 100 mm Hg, pH often approaching 7)^{244,245}; this is usually transient and well tolerated, and survival is the rule. In the first substantial series of patients with severe acute asthma requiring mechanical ventilation, institution of controlled hypoventilation (i.e., permissive hypercapnia),¹⁷ complications, and mortality were considerably lower than previously reported. Although such findings have been confirmed repeatedly,²⁴⁶⁻²⁵² it is not possible to determine whether hypercapnia provided any benefit beyond minimization of barotrauma due to the lower tidal volumes.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Hypercapnia in chronic obstructive pulmonary disease is associated with poor prognosis,²⁵³⁻²⁵⁶ although any prognostic impact of hypercapnia is confounded by the influence of other underlying factors, including alveolar loss, hypoxemia, and airway obstruction.²⁵⁷ However, in patients receiving long-term domiciliary O₂, higher arterial PCO₂ may be associated with lower mortality²⁵⁸; this would suggest a distinction between progressive hypercapnia due to terminal respiratory failure versus adaptive hypercapnia due to respiratory center recalibration and tolerance of higher arterial PCO₂, thereby lowering respiratory drive and lessening respiratory work.^{259,260} Such an “adaptive” mechanism would cause a progressive decline in arterial PO₂ due to progressively decreasing minute ventilation, but this could be addressed by supplemental oxygen therapy.

NEONATAL AND PEDIATRIC RESPIRATORY FAILURE

Hypercapnia appears to be safe and is associated with some benefits in the setting of neonatal and pediatric respiratory failure. Neonatal respiratory distress syndrome is a disorder of surfactant production in the preterm newborn and results in parenchymal stiffness and alveolar collapse. In this setting, ventilation strategies involving permissive hypercapnia (45 to 55 mm Hg) was demonstrated in a randomized clinical trial to facilitate weaning from mechanical ventilation, although there was no clear effect on chronic lung disease or survival in this small study²⁶¹ (Fig. 86-5). Data also exist supporting the use of permissive hypercapnia in other pediatric respiratory pathologies, such as

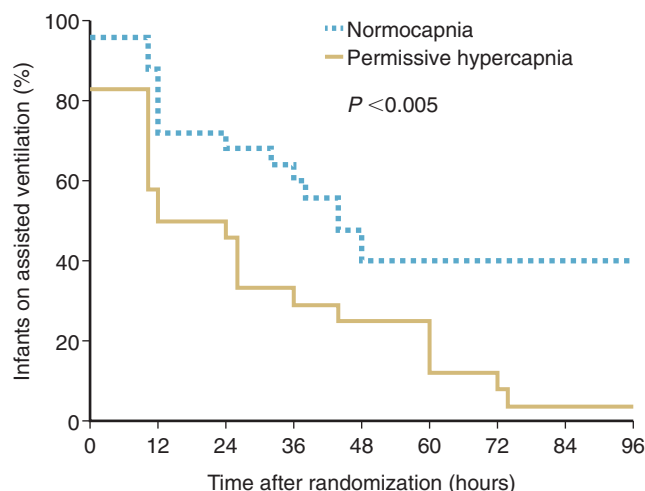


Figure 86-5 A ventilation strategy incorporating permissive hypercapnia reduced the duration of mechanical ventilation in neonates with respiratory failure compared to conventional therapy. (From Mariani G, Cifuentes J, Carlo WA: Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics* 104(5 Pt 1):1082–1088, 1999.)

congenital diaphragmatic hernia, pulmonary hypertension of the newborn, and congenital heart disease.

CENTRAL NERVOUS SYSTEM PATHOPHYSIOLOGY

Hypocapnia is widely used in the management of acute brain injury, and may be lifesaving when ICP is critically elevated, but the use of hypocapnia outside this specific setting can produce neuronal ischemia and injury, resulting in harm. Hypercapnia is usually avoided in the setting of acute brain injury because it increases CBF and volume, which may cause or exacerbate intracranial hypertension. Even so, hypercapnia may have protective effects in the brain in specific circumstances.

PRECLINICAL MODELS

Hypocapnia has been demonstrated to exert potentially harmful effects in acute brain injury. Hypocapnia worsens ischemic brain injury,²⁶² diminishes neuronal energy status (i.e., glucose utilization, phosphate reserves),²⁶³ and worsens CNS functional and histologic outcomes following experimental cardiac arrest in dogs.²⁶⁴ Severe hypocapnia increases *N*-methyl-D-aspartate receptor-mediated neurotoxicity in the newborn^{265,266} and may impair neuronal membrane function through increased incorporation of choline into membrane phospholipids.²⁶⁷

Through increasing O_2 demand and decreasing supply, hypocapnia can adversely shift the global CNS O_2 supply-demand balance. Cerebral vasoconstriction may reduce overall perfusion,¹¹³ and in focal ischemia, blood flow to the hypoxic regions is selectively lowered²⁶³ and infarct size increased.^{263,268} Hypocapnia also increases CNS O_2 demand by increasing neuronal excitability,²⁶⁹ increasing excitatory synaptic transmission,²⁶⁹ and affecting the neuronal membrane itself.¹²⁰

Termination of sustained hypocapnia can precipitate cerebral hyperemia and raised ICP. During sustained hypocapnia, brain extracellular fluid becomes depleted of HCO_3^- , thereby reducing buffering capacity; thus any subsequent increase in arterial PCO_2 —because it is less buffered—will result in an exaggerated increase in CBF. This has been experimentally verified in rabbits²⁷⁰ and goats.¹¹⁶

In contrast, hypercapnia may exert direct protective effects in the injured brain. Hypercapnic acidosis decreases disruption of the blood-brain barrier in hypertensive crisis²⁷¹ and attenuates hypoxic-ischemic^{262,263} and hypoxia/reoxygenation¹⁶¹ brain injury. Hypercapnic acidosis is more effective than comparable degrees of metabolic acidosis in prevention of lipid peroxidation in cortical homogenates.²⁷²

TRAUMATIC BRAIN INJURY

Hypocapnia is commonly used in the management of patients with traumatic brain injury despite there being no evidence to show that it improves outcome. On the contrary, a randomized controlled trial of prolonged hyperventilation in traumatic brain injury demonstrated that it worsened outcome.²⁷³ Patients with severe traumatic brain injury were randomized to normal (arterial PCO_2 35 mm Hg) versus prophylactic hyperventilation (arterial PCO_2 25 mm Hg) targets; among the less severely injured patients (Glasgow Coma Scale motor score 4–5), fewer in the hyperventilation group had a favorable outcome at 3, 6, and 12 months than did those managed with normocapnia.²⁷³ Important insights were gained from this study: there was greater ICP variability and higher mean ICP levels after 60 hours of hyperventilation. Thus hyperventilation was at best ineffective in terms of its primary rationale (i.e., reduction of ICP); in fact, it worsened ICP.²⁷³ Finally, the adverse effects of hypocapnia seemed less serious in a third study group who received hyperventilation plus buffering (with tromethamine); however, these patients may have been less severely injured.

NEONATAL BRAIN INJURY

Hypocapnia (either deliberate or accidental) is common in neonatal practice. Unfortunately it appears to be particularly injurious to the premature human brain, especially in neonatal white matter injury.^{274–279} Hypocapnia is a key risk factor for several specific lesions, including periventricular leukomalacia, causing significant neonatal mortality and long-term neurodevelopmental deficits²⁸⁰; pontosubicular necrosis, a pattern of acute brain injury seen in premature infants²⁷⁷; and the pathogenesis of cerebral palsy.²⁸¹

The mechanisms predisposing premature neonates to injury from hypocapnia include vulnerable regions due to poorly developed vasculature²⁸²; reduced defenses because of antioxidant depletion by excitatory amino acids²⁸³; lipopolysaccharide²⁸⁴ and inflammatory mediators²⁸⁵ potentiating white matter destruction.

Preterm infants exposed to severe (arterial PCO_2 < 15 mm Hg) hypocapnia, even if only for a brief period, may develop considerable long-term neurologic abnormalities compared with matched, nonexposed controls.²⁸⁶ Risk factors for hypocapnia in small infants include

hyperventilation,²⁸⁶ high-frequency ventilation,¹⁶ or ECMO.¹⁴ Indeed, hypocapnia in infants prior to the initiation of ECMO is associated with an increased incidence of sensorineural hearing loss by school age.¹⁴ Finally, abrupt termination of hyperventilation results in reactive hyperemia, which may cause intracranial hemorrhage, particularly in premature infants.²⁸⁷

ACUTE STROKE

Hyperventilation has traditionally been used as a therapy in patients with acute stroke for two reasons. First, hypocapnia was thought to shunt blood preferentially to ischemic areas by selective vasoconstriction in normal autoregulated brain regions; this was called the *inverse steal* phenomenon. Second, hypocapnia was considered to correct regional acidosis adjacent to the ischemic zone, in order to minimize the extension of the infarct.²⁸⁸ However, the inverse steal phenomenon is no longer accepted²⁶⁸; in fact, hypocapnic alkalosis has been associated with poor prognosis in patients with acute cerebrovascular accidents.^{289,290} Cheyne-Stokes respiration and central sleep apnea, which can be observed after stroke, are thought to be due to decreased cerebral chemosensitivity to CO₂ in the setting of significant cerebral infarction and left ventricular systolic dysfunction.²⁹¹

NEUROPSYCHOLOGICAL IMPACT

Marked intraoperative hypocapnia—even briefly—can cause detectable neuropsychological impairment for up to 48 hours after general anesthesia²⁹²; older patients are more susceptible with greater impairment after exposure to low CO₂ levels. The impairment includes slowed reaction times,¹²⁶ as well as higher functions including attention, learning, and personality changes.^{293,294} More severe hypocapnia (arterial PCO₂ of approximately 15 mm Hg) lowers psychomotor performance in healthy volunteers²⁹⁵; in contrast, elevated arterial PCO₂ during anesthesia is associated with improved neuropsychological performance.^{292,296} Hypocapnia is also associated with adverse neurologic outcome following cardiopulmonary bypass,²⁹⁷ although in this setting there are multiple additional contributors.

Whereas adverse neuropsychological effects of transient hypocapnia appear to be reversible,^{111,292} this is not the case following prolonged exposure. Impairment following exposure at extremes of altitude can be long-standing; the deficits are better correlated with the levels of hypocapnia versus the degree of hypoxemia,²⁹⁸ consistent with the idea that individuals who can develop the lowest arterial PCO₂ levels—required to maximize alveolar O₂ content and minimize hypoxemia—are most at risk. Thus a paradox exists: climbers with greater levels of physical fitness, that is, who can develop the greatest minute ventilation, may be the most vulnerable to CNS sequelae. It is likely that profound CNS alkalosis is the basis for the deficit: intense cerebral vasoconstriction and left-shift of the hemoglobin-oxygen dissociation curve markedly diminish O₂ delivery, negating any advantage of increased oxygen loading in the lung, while alkalosis concomitantly increases neuronal cell excitability and local O₂ consumption. Such alkalosis is ameliorated by acetazolamide pretreatment.²⁹⁹ Finally, it is likely

that induced hypocapnia (e.g., with mechanical ventilation) may result in more severe CNS compromise in those with preexisting neurologic deficit.

In contrast, as discussed earlier, hypercapnia appears to speed restoration of consciousness and neurocognitive function following anesthesia.^{22,23} The deleterious effects of hypocapnia on neurocognitive function may therefore be reversed by CO₂ administration.

CEREBRAL ISCHEMIA

The impact of hypocapnia on cerebral ischemia is most apparent in neuropsychological studies^{111,292-296,298} and in studies of cerebral perfusion or oxygenation in traumatic brain injury,^{125,300,301} cardiac arrest and resuscitation,^{302,303} and neonatal brain injury^{14,274,286,304} and stroke.^{289,290}

An initial response in traumatic brain injury is reduced cerebral perfusion,³⁰⁵ which is worsened by hypocapnia,¹²⁵ and even moderate levels (<34 mm Hg) can reduce overall CBF and increase the proportion of injured brain that is inadequately perfused.³⁰⁶ This is of particular concern because regional flow deficits can be critical in common conditions including brain contusions, underlying hematomas, and diffuse injury.^{307,308} The responsiveness of the cerebral vasculature to CO₂ is increased following brain trauma,³⁰⁰ increasing the likelihood of ischemia and consistent with the worsening of outcome that is associated with prophylactic hyperventilation in such patients.²⁷³ Hypocapnia has also been shown to induce critical cerebral ischemia in pediatric traumatic brain injury.³⁰¹

Neurologic deficit is perhaps the most important complication of cardiac arrest. Following reestablishment of spontaneous circulation, the cerebral O₂ supply and demand balance is altered, with CBF at approximately 50% of normal but with cerebral O₂ consumption increased above prearrest levels.³⁰² In this setting, hypocapnia causes cerebral ischemia³⁰³ and may therefore contribute to adverse outcome.

Premature infants are especially susceptible to a variety of brain injury syndromes, and hypocapnia contributes to several of these, including periventricular leukomalacia.^{274,304} In terms of outcome, prior exposure of premature infants to hypocapnia increases the risk of neurologic deficits,²⁸⁶ including sensorineural hearing loss.¹⁴

Finally, outcome following acute stroke appears to be worsened by hypocapnia,^{289,290} which is consistent with experimental data demonstrating that hypocapnia increases the extent of ischemic injury.²⁶³

CARDIOVASCULAR PATHOPHYSIOLOGY

MYOCARDIAL ISCHEMIA

The principal cardiac impact of major alterations in arterial PCO₂ is on myocardial oxygenation. Myocardial function following recovery from ex vivo³⁰⁹ or in vivo³¹⁰ ischemia is improved in the setting of hypercapnic acidosis, with reduction in infarct size. Accordingly, endothelial function is better preserved in aortic rings that are subjected to ischemia in the setting of acidosis.³¹¹

In contrast, hypocapnia adversely alters myocardial O₂ supply and demand balance,^{312,313} increasing cardiac contractility^{314,315} and heart rate,³¹⁶ and by increasing systemic vascular resistance, increases left ventricular work.³¹⁷ Because these parameters are key determinants of myocardial O₂ consumption, O₂ demand is precipitously increased.^{140,312,315,318,319} Compounding this, hypocapnia restricts myocardial O₂ supply. Because heart rate is increased and diastolic duration is lessened, perfusion is reduced.^{141,312,313,320-323} In addition, the hemoglobin-oxygen dissociation curve is shifted leftward, increasing the avidity of Hb for O₂. Oxygen delivery is further compromised because alkalosis results in greater capillary permeability,³²² increasing the propensity to local edema. These features explain the observation that experimental hypocapnia is associated with increased coronary arteriovenous oxygen difference and decreased coronary flow.¹⁴¹

Hypocapnia may precipitate coronary artery spasm, resulting in variant angina that may be seen in the context of hyperventilation.³¹³ Finally, hypocapnia may augment propensity to thrombosis because it can increase platelet levels and aggregation.³²⁴

CARDIAC RHYTHM DISORDERS

Both hypocapnia and hypercapnia may cause cardiac rhythm disorders. Hypocapnia is associated with dysrhythmias in the acutely ill³²⁵; it can cause paroxysmal atrial arrhythmia³²⁶ and, rarely, ventricular tachycardia³²⁷ or fibrillation.³²⁸ Such effects may be mediated by development of myocardial ischemia, especially in variant angina.³²⁷ Conversely, alkalosis may suppress arrhythmias caused by local anesthetic³²⁹ or tricyclic antidepressant³³⁰ toxicity. Hypercapnia may also cause tachyarrhythmias via activation of the sympathetic nervous system.³³¹ Restoration of normocapnia following hypercapnia has been demonstrated to increase the risk for atrial fibrillation in preclinical models.³³²

SYSTEMIC OXYGENATION

In experimental sepsis, hypercapnic acidosis improved tissue oxygenation analogous to dobutamine administration.³³³ In addition, hypercapnia may increase peripheral tissue oxygenation in healthy surgical patients independently of its effects on cardiac output.^{334,335} It appears that augmentation of tissue perfusion and oxygenation may be maximal at arterial PCO₂ levels of 150 mm Hg.¹⁴⁵

CLINICAL EVIDENCE

Arterial blood gas management during cardiopulmonary bypass can be managed using so-called pH-stat (more CO₂ is added to maintain arterial PCO₂ during temperature correction) or α -stat (no additional CO₂ added). In a randomized controlled trial involving children undergoing cardiopulmonary bypass for repair of congenital heart lesions, the pH-stat strategy was associated with better postoperative cardiac and neurologic function,³³⁶ suggesting a net benefit associated with additional perioperative CO₂ exposure.

INFECTION AND SEPSIS

EXPERIMENTAL PNEUMONIA

Adding CO₂ to the inspired gas (vs. normocapnia) resulted in less severe lung injury in an experimental model of early *E. coli* instillation²²⁹ in the rat; protective effects were observed in severe²²⁹—and not in mild³³—disease. In addition, protection was not mediated by altered neutrophil function,²²⁹ and in vivo bacterial proliferation was unchanged.^{229,337} These effects were confirmed in more established *E. coli* pneumonia (about 6 hours), in the presence or absence of appropriate antibiotics, although protection was enhanced with antibiotic therapy.²²⁸

In contrast to short-term lung infection, hypercapnia (raising atmospheric CO₂ levels) worsened lung injury during longer term established *E. coli* pneumonia in the rat.¹⁷⁷ In this setting, hypercapnia (vs. no added CO₂) was associated with lower compliance, increased PMN infiltration, and increased bacterial load. The likely mechanism for increased bacterial numbers was inhibition of neutrophil function, because PNMs obtained from the hypercapnic animals demonstrated impaired phagocytosis.¹⁷⁷ These findings have subsequently been confirmed in a murine model of established *Pseudomonas* pneumonia,³³⁸ wherein survival was also worsened. Importantly, appropriate antibiotic therapy negated the harmful effects of hypercapnia (i.e., lung injury, bacterial proliferation) in prolonged *E. coli* pneumonia.¹⁷⁷

EXPERIMENTAL SEPSIS

In a rodent model of early systemic sepsis induced by fecal peritonitis (i.e., cecal ligation and puncture), hypercapnic acidosis reduced the severity of shock as well as the extent of lung injury.²⁰⁸ The mechanisms of protection are unclear and it is unknown whether the effects on systemic hemodynamics (preservation of mixed venous SO₂, systemic perfusion pressure, serum lactate level) were independent of the pulmonary impact (i.e., better oxygenation, less edema, reduced bronchoalveolar lavage mediator levels and neutrophil count), because peritoneal and bloodstream bacterial loads were similar with and without hypercapnia exposure.²⁰⁸ In addition, survival was unaltered.

Similar effects were reported in a sheep model of established fecal peritonitis³³³ (Fig. 86-6). In this study, animals were randomized to hypercapnic acidosis, dobutamine infusion, or control conditions after development of peritonitis. Key hemodynamic parameters (i.e., heart rate, cardiac index, and oxygen delivery) were similar after randomization to hypercapnia versus dobutamine (both greater than controls), and lactate levels were lower than in normocapnic controls. However, hypercapnia—but not dobutamine—reduced indices of lung injury (e.g., lung water accumulation, shunt fraction, and oxygenation).³³³ There was no impact of hypercapnia on survival.

Intraperitoneal CO₂ is extensively used during laparoscopic surgery and results in very high levels of CO₂ in the peritoneal cavity and in the plasma. CO₂ pneumoperitoneum (vs. helium insufflation) improved survival when administered before³³⁹ or during³⁴⁰ experimental endotoxin sepsis; these findings were replicated in experimental

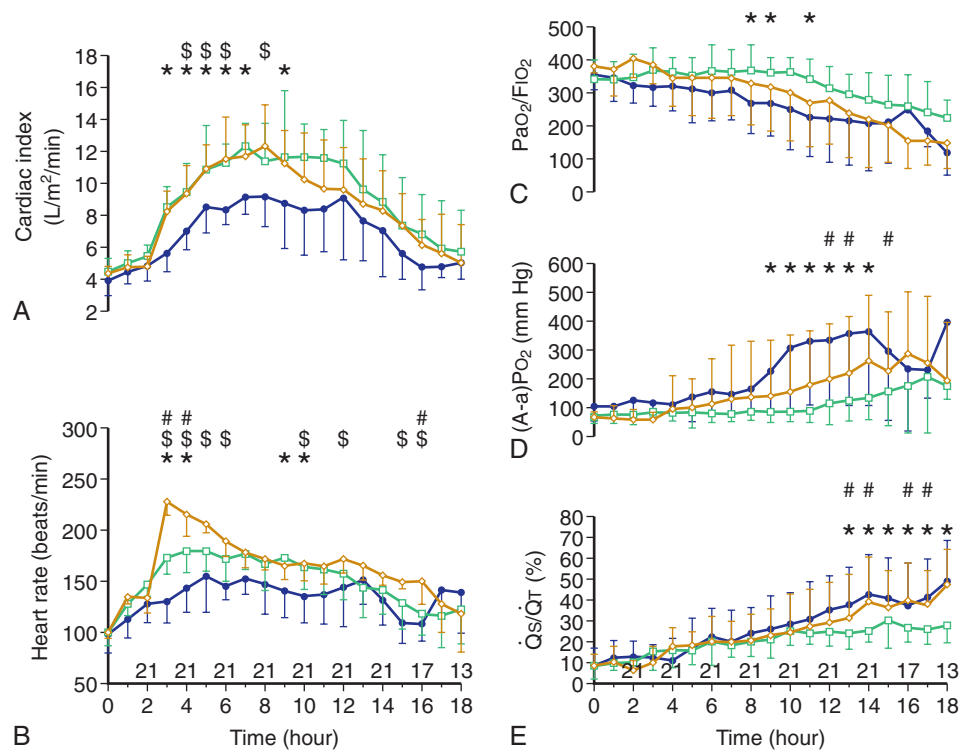


Figure 86-6 Hypercapnic acidosis improves hemodynamic function and decreases lung injury following systemic sepsis in an ovine model. Hypercapnia (green line) increased cardiac index (A) and heart rate (B) over time compared to the normocapnic animals (blue line), to an extent comparable to normocapnic animals treated with dobutamine (brown line). Hypercapnic acidosis (green line) increased the arterial PO₂/FiO₂ ratio (C), decreased the alveolar-to-arterial oxygen tension difference ((A-a)PO₂) (D), and decreased the shunt fraction (Q_s/Q_T) (E) over time compared to normocapnia (blue line) and to animals treated with dobutamine (brown line). *, *P* < 0.05 hypercapnia versus control; #, *P* < 0.05 hypercapnia versus dobutamine; \$, *P* < 0.05 dobutamine versus control. The numbers above the abscissa indicate the numbers of surviving animals at the corresponding time point. (Modified from Wang Z, Su F, Bruhn A, et al: Acute hypercapnia improves indices of tissue oxygenation more than dobutamine in septic shock. *Am J Respir Crit Care Med* 177:178–183, 2008. Figs 2 and 3.)

polymicrobial peritonitis in mouse³⁴¹ and rabbit³⁴² models (Fig. 86-7). Such protection seems to be due to immunomodulatory effects of hypercapnia³⁴³ (e.g., IL-10 mediated down-regulation of TNF- α) in conjunction with localized peritoneal acidosis—and not via a systemic effect.^{344,345}

APPROACHES TO MINIMIZE HYPERCAPNIA

Hypercapnia remains a cardinal sign of ventilatory failure and, as such, has traditionally been avoided. Advances in current understanding of the deleterious effects of excessive mechanical lung stretch in the setting of severe respiratory failure have prompted clinicians to be more tolerant of hypercapnia. Indeed, a body of literature exists that demonstrates full recovery following exposure to extreme levels of hypercapnia—termed *supercarbia*—in both adults and children. Full recovery without sequelae has been reported in several children exposed to extremes of arterial PCO₂ (155 to 269 mm Hg)³⁴⁶ and there are reports of arterial PCO₂ tensions up to 375 mm Hg (pH 6.6) in adults^{347,348} who survived without demonstrable deficits. Nevertheless, severe hypercapnia may be problematic, depressing cardiac function and potentially worsening pulmonary hypertension, particularly if rapidly accumulated.³⁴⁹ Clinicians must be mindful of the tradeoff between the beneficial and

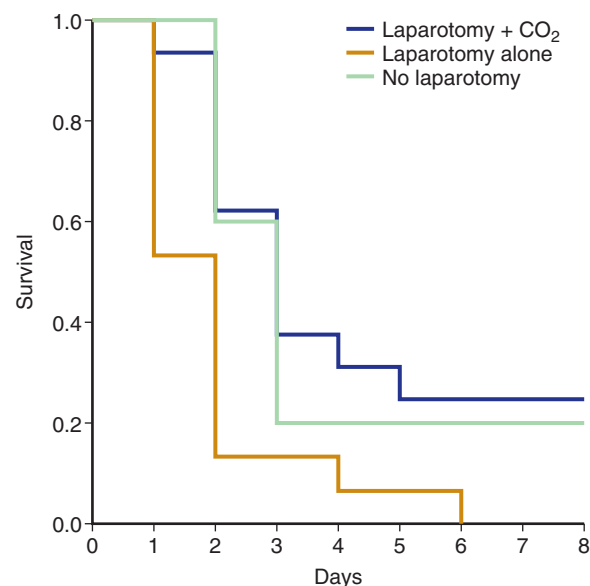


Figure 86-7 Insufflation of CO₂ into the peritoneal cavity improves survival following cecal ligation and puncture-induced systemic sepsis. Animals were first subjected to cecal ligation and puncture. Four hours later, animals underwent a laparotomy and induction of a CO₂ pneumoperitoneum (laparotomy + CO₂), laparotomy alone or no laparotomy, and survival was determined over the following 8 days. (Modified from Metzelder M, Kuebler JF, Shimotakahara A, et al: CO₂ pneumoperitoneum increases survival in mice with polymicrobial peritonitis. *Eur J Pediatr Surg* 18:171–175, 2008. Fig 3b.)

deleterious effects of hypercapnia, and tailor treatment in each individual case. For example, in the case of combined lung and head injury, regional monitors of cerebral oxygenation and ICP may be used to guide therapy.

STRATEGIES TO REDUCE DEAD SPACE

These approaches aim to minimize any contribution of circuit and anatomic dead space to hypercapnia. At the end of expiration, the ventilator circuit distal to the Y-piece and the anatomic dead space both contain CO₂-rich alveolar gas, which is then delivered back to the distal lung with the next inspiration. The significance of this *rebreathing* is enhanced with low tidal volume ventilation strategies, because the anatomic dead space is relatively fixed. Techniques that aim to replace dead space gas with fresh gas have therefore been advocated as an adjunct to protective ventilator strategies. These techniques can increase effective alveolar ventilation, which could facilitate further reductions in tidal volume and enhance any protective effect.

Tracheal gas insufflation (TGI) delivers fresh gas into the central airways either continuously or in a phasic fashion during expiration. Preclinical studies in ARDS models demonstrate promise,³⁵⁰ with evidence to suggest that TGI may attenuate the development of ventilation-induced lung injury in surfactant-depleted lungs.³⁵¹ TGI has been demonstrated to augment CO₂ clearance when combined with high-frequency oscillation.³⁵² However, some concerns persist with regard to the safety and monitoring of TGI that continue to impede its introduction into clinical practice.³⁵³ Aspiration of dead space gas during expiration and controlled replacement with fresh gas is a related technique. A feasibility study of eight patients with chronic obstructive pulmonary disease who were managed with permissive hypercapnia demonstrated that aspiration of dead space gas resulted in a similar decrease in arterial PCO₂ but with less intrinsic positive end-expiratory pressure compared with TGI.³⁵⁴ Lastly, coaxial double-lumen endotracheal tubes, which eliminate the contribution to dead space from the ventilator circuit distal to the Y-piece, may improve the efficiency of ventilation.³⁵⁵

HIGH-FREQUENCY OSCILLATORY VENTILATION

High-frequency oscillatory ventilation (HFOV) is a nonconventional mode of ventilation in which breathing frequencies from 60 to 2400 breaths per minute (conventionally measured in hertz, with 1 hertz = 60 breaths per minute) with tidal volumes that are lower than the dead space volume (i.e., 35 to 150 mL) are used. The lung is exposed to a continuous positive pressure, and an “oscillatory” tidal volume is superimposed. Since the tidal volume is usually less than the anatomic dead space, gas exchange cannot be explained in terms of simple convective bulk transport to the alveoli. Whereas HFOV is generally used for patients with severe hypoxemia, it can be used to manage hypercarbia, especially in neonates and children.³⁵⁶ HFOV has been successfully applied to neonates since 1981,³⁵⁷ and more recently to adolescents and adults.³⁵⁸ HFOV results in better pulmonary outcomes than conventional mechanical ventilation for very-low-birth-weight infants suffering with respiratory

distress syndrome.³⁵⁹ In adults suffering from ARDS, while an earlier multicenter trial by Derdak and colleagues³⁶⁰ demonstrated promise, more recent large-scale multicenter trials have cast significant doubt on the role of HFOV in the management of ARDS.^{361,362}

EXTRACORPOREAL TECHNOLOGIES

Extracorporeal CO₂ removal (ECCO₂R) refers to the process by which an extracorporeal circuit is used for the primary purpose of removing CO₂ from the body, thereby providing partial respiratory support (see Chapter 103). ECCO₂R systems can be *arteriovenous* (AV) or *venovenous* (VV). AV-ECCO₂R systems involve the insertion of a gas exchange membrane across an AV shunt, usually created between the femoral artery and the contralateral femoral vein using percutaneously inserted cannulas. The gas exchange membrane is connected to oxygen, which acts as a “sweep gas” to remove CO₂ that has diffused out of the patient’s blood.

Theoretically, an ultra-efficient ECCO₂R system could eliminate all the CO₂ that the body produces with flow rates of just 0.5 L/min, because a liter of blood with an arterial PCO₂ of 35 mm Hg contains around 500 mL of CO₂ and the body produces approximately 250 mL/min. The potential for ECCO₂R systems to oxygenate blood is much more limited because there is effectively a limit to the amount of oxygen a given volume of blood can carry, and the extracorporeal flow rate would have to be much higher to meet the demand for O₂. By removing CO₂, ECCO₂R allows ventilation strategies that are focused on oxygenation rather than CO₂ elimination.

Until recently, the primary use of ECCO₂R has been in cases of severe hypercapnic acidosis that are refractory to mechanical ventilation. In the vast majority of cases, this has been in the context of ARDS.^{363,364} There are a number of reports of its use in other clinical scenarios, namely, as a bridge to transplant,^{365,366} in combined head and chest injury,^{367,368} in near fatal asthma,^{369,370} as an aid to weaning from mechanical ventilation,³⁷¹ to facilitate thoracic surgery,^{372,373} and to facilitate transfer.^{374,375} None of these case reports or very small case series provide any definitive evidence of benefit.

The focus of ECCO₂R is now to allow protective ventilation in patients with ARDS in whom hypercapnic acidosis has not yet become refractory; this is likely to be where its role lies in the future. Sometimes the severity of lung injury makes it impossible to stay within the low tidal volume limits of the ARDSNet ventilation strategy and ECCO₂R may have a role in facilitating protective ventilation in these situations. Furthermore, ECCO₂R could be used to reduce the tidal volume to less than 6 mL/kg when the plateau pressure is already less than 30 cm H₂O (“ultra-protective” ventilation).^{375a} Whether or not there is any benefit to ultra-protective ventilation is debatable. Indeed, the initial clinical trial of low-frequency positive pressure ventilation ECCO₂R showed promise,³⁷⁶ but a subsequent randomized controlled trial failed to demonstrate a survival benefit.³⁷⁷

Terragni and colleagues³⁷⁸ used VV-ECCO₂R to facilitate ultra-protective ventilation. They recruited 32 patients with early (<72 hr) ARDS and ventilated them according to the ARDSNet protocol for 72 hours, at which point the tidal volume was reduced from 6 to 4 mL/kg in all patients

($n = 10$) who had a plateau pressure of between 28 and 30 cm H₂O and VV-ECCO₂R commenced. This technique successfully treated the hypercapnic acidosis in all cases and allowed the protective ventilation strategy (4 mL/kg tidal volumes and higher levels of positive end-expiratory pressure) to continue. The study also demonstrated a reduction in bronchoalveolar inflammatory cytokines after 72 hours of ventilation with 4 mL/kg but not 6 mL/kg. More recently, Bein and colleagues³⁷⁹ demonstrated similar outcomes in a larger study of patients with established ARDS randomized to either the ARDSNet ventilation approach or to lower tidal and minute ventilation combined with ECCO₂R. Taken together, these studies, while relatively small, suggest that there may be benefit to an ultra-protective ventilation strategy facilitated by VV-ECCO₂R in patients with ARDS.

Overall, there is good evidence that ECCO₂R can effectively reduce arterial PCO₂ and make a small contribution to oxygenation in patients with ARDS. Perhaps more importantly, studies^{363,371,372,379} have demonstrated that ECCO₂R facilitates a lung-protective ventilation strategy by allowing a reduction in tidal volumes and inspiratory airway pressures. However, it is not possible at this stage to draw any valid conclusions about the effect of ECCO₂R on survival in patients with ARDS. Furthermore, the threshold at which a hypercapnic acidosis requires treatment is unclear and may vary depending on the clinical situation

BUFFERING A HYPERCAPNIC ACIDOSIS

One approach to the management of hypercapnia is to buffer the resultant acidosis. This remains a common—if controversial—practice in the management of patients with severe respiratory failure with protective ventilation strategies. However, there is no evidence to support buffering, and indeed, there are a number of specific concerns regarding this practice. In particular, concerns exist regarding sodium bicarbonate, the buffer used most frequently in the clinical setting. The effectiveness of bicarbonate infusion as a buffer is dependent on the ability to excrete CO₂, rendering it less effective in buffering hypercapnic acidosis. In fact, bicarbonate may further raise arterial PCO₂ where alveolar ventilation is limited, such as in ARDS. While bicarbonate may correct arterial pH, it may worsen an intracellular acidosis because the CO₂ produced when bicarbonate reacts with metabolic acids diffuses readily across cell membranes, whereas bicarbonate cannot. However, where buffering is considered in the setting of hypercapnia, there may be a role for the amino alcohol tromethamine (*tris-hydroxymethyl aminomethane*, THAM). THAM penetrates cells easily and can buffer pH changes and simultaneously reduce arterial PCO₂.³⁸⁰ Unlike bicarbonate, which requires an open system for CO₂ elimination in order to exert its buffering effect, THAM is effective in a closed or semiclosed system. THAM rapidly restores pH and acid-base regulation in acidemia caused by CO₂ retention.³⁸⁰ In ARDS patients, THAM has been demonstrated to attenuate the hemodynamic consequences of a rapidly induced hypercapnic acidosis.³⁴⁹ Therefore, if a clinician elects to buffer a hypercapnic acidosis, the rationale for this practice should be clear (e.g., to ameliorate potentially deleterious hemodynamic consequences of acidosis), and THAM should be considered rather than bicarbonate.

Key Points

- Advances in current understanding of the deleterious effects of excessive mechanical lung stretch have prompted clinicians to use ventilation strategies that result in hypercapnia. Consequently, hypercapnia has become increasingly prevalent in the critically ill.
- Both hypercapnia and hypocapnia exert potent physiologic effects: hypercapnia enhances hypoxic pulmonary vasoconstriction, ventilation/perfusion matching, cardiac output, and systemic and tissue oxygenation, and increases cerebral blood flow and volume, while hypocapnia generally has opposite effects.
- Hypocapnia remains a common—and generally underappreciated—component of many disease states, including early asthma, high altitude pulmonary edema, and acute lung injury. Induction of hypocapnia remains a common, if controversial, practice in both adults and children with acute brain injury.
- Both hypocapnia and hypercapnia can be harnessed to produce benefit, or can result in harm.
- The timing and duration of application of alterations in CO₂ tension are critically important. Based on current evidence, hypocapnia should be avoided in the setting of acute brain injury except where *intracranial pressure* (ICP) is critically elevated and, when induced, should be for a short period, while definitive measures are undertaken.
- Initial benefits of short-term application of hypocapnia or hypercapnia may be offset when the altered CO₂ state is allowed to persist, such as in hypocapnia for raised ICP, where the ICP lowering effects are gradually lost with cerebrospinal fluid buffering over several hours, and the ICP may rebound upon restoration of normocapnia.
- The effect of altered CO₂ tension depends on the specific mechanism of injury, for example, in preclinical studies, hypercapnic acidosis is beneficial in early sepsis, via inhibitory effects on the host immune response. However, hypercapnia worsens prolonged untreated pneumonia because an intact host immune response is central to effective bacterial clearance.

Complete reference list available at [ExpertConsult](#).

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CONSEQUENCES OF SLEEP DISRUPTION

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INTRODUCTION

Disturbed sleep is increasingly being recognized as a major contributor to various deleterious health outcomes. Sleep deprivation is well known to impair cognition, mood, and memory, but more recent evidence indicates that sleep deprivation also has a major impact on cardiometabolic function. *Obstructive sleep apnea* (OSA), a common condition with well-established neurocognitive and cardiovascular sequelae, is covered elsewhere in this book (Chapter 88). Other causes of sleep fragmentation such as central sleep apnea (Chapter 89), periodic limb movements, and hypoventilation syndromes (Chapter 85) are also being studied. The term *sleep disruption* is often used in a general sense to refer to conditions of sleep fragmentation (such as OSA) and sleep deprivation (in which total sleep time is reduced).

SHORT-TERM CONSEQUENCES WITH POTENTIAL LONG-TERM SEQUELAE

NEUROCOGNITIVE CHANGES

Sleep disruption is associated with major neurocognitive changes that can affect performance in the short term and may impact long-term cognitive function. The cognitive dysfunction associated with sleep restriction for 28 hours has been shown to be roughly equivalent to that associated with consuming alcohol up to a blood alcohol level of 0.10%, which is above the legal driving limit in most states.¹ Studies of partial and total sleep deprivation indicate a decline in many separate measures of broad cognitive performance, including slowed response time, decrease in short-term and working memory, reduced learning of cognitive tasks, and decreased situational awareness.² Sleep deprivation decreases related executive function (via the pre-frontal cortex), which is responsible for working memory.³ For the individual who has been sleep deprived, this influence may result in decreased insight into the scope of a problem, decreased flexibility in thinking, a propensity for perseveration, and difficulty assimilating and integrating new information, as well as understanding the temporal order of information.^{3,4} Similarly, studies of cognitive function in patients with *sleep disordered breathing* (SDB) indicate that, compared with the general population, sleep apnea

patients exhibit moderate to severe defects in sustained attention tasks (such as the psychomotor vigilance task), driving simulation, and working memory tasks requiring flexibility and insight in thought.⁵ SDB patients also demonstrate moderate deficits in verbal fluency, short attention tasks, decreased vigilance, and decreased intellectual function.⁶

More recently, functional magnetic resonance imaging and positron emission tomography studies have been employed to evaluate the cognitive effects of sleep deprivation and fragmentation by evaluating metabolic fluctuations in glucose uptake in specific brain regions. Some data indicate that sleep deprivation results first in global decreases in cortical and subcortical structures.⁷ As people become cognitively impaired, metabolism decreases more specifically in the prefrontal cortex, thalamus, and posterior association cortices, which are believed to be responsible for supporting attention.⁷ At 24 hours of sleep deprivation, the thalamus is activated when given an attention-demanding task, which has been characterized as the need for increased “mental energy” to maintain attention during sleep deprivation.⁸ When given a verbal working memory task after 35 hours of sleep deprivation, increased parietal lobe activity is noted, which may be a compensatory mechanism to help improve overall declining working memory.⁹ Further studies are necessary to elucidate better the mechanisms of cognitive dysfunction associated with sleep deprivation.

SLEEP AND IMMUNE FUNCTION

Disrupted and restricted sleep has also been implicated in proper functioning of the immune system. A prospective study by Patel and colleagues¹⁰ assessing nearly 57,000 female nurses (ages 37 to 57 years) found that both short and long sleep duration predicted increased risk of community-acquired pneumonia. Compared with those who slept for 8 hours, women who slept less than 5 hours had a relative risk of 1.4 (CI 1.1 to 1.8) of developing pneumonia. Women who slept more than 9 hours had a similar increased risk for developing pneumonia. A correlation was also found between perceived sleep quality and increased pneumonia risk.¹⁰ Another study evaluated 153 healthy volunteers (both men and women) and found that those who reported sleep of less than 7 hours were 2.9 times (95% CI 1.2 to 7.3) more likely to develop symptoms of a common cold following study-administered intranasal

exposure to rhinovirus.¹¹ Studies to elucidate the mechanism of impaired immunity have found that sleep-deprived humans have lower *natural killer* (NK) cell activity and IL-2 production, along with increased production of inflammatory biomarkers.¹² In animals, chronic sleep deprivation has been found to reduce monocyte numbers, complement C3 levels, and spleen weight. Furthermore, studies of sleep-deprived animals have shown increased rates of bacteremia.¹³

Along these lines, studies in healthy mice have shown that sleep deprivation ablates the response to influenza vaccination to such an extent that the sleep-deprived mice appeared to have no development of immunity after receiving the vaccine.¹⁴ A study of hepatitis B vaccination titers in humans showed that short sleep duration (as evaluated by actigraphy, i.e., activity monitors, and sleep journals) was associated with a lower secondary antibody response to the vaccine.¹⁵ Similarly, another study showed that one period of 24-hour sleep deprivation significantly reduced H1N1 antibody titers at 5 days postimmunization in healthy volunteers.¹⁶ This effect, however, was not prolonged because total antibody titers were not significantly different at 10, 17, and 52 days postimmunization. This study had a small sample size ($n = 24$) and larger studies are necessary. The impact of sleep deprivation on immunity and vaccine titers is particularly relevant in critically ill patients in which iatrogenic infections may have devastating consequences. Further studies will need to quantify and mitigate the risk associated with sleep deprivation and infections in *intensive care unit* (ICU) patients.

SLEEP AND THE INTENSIVE CARE UNIT

Besides effects on immunity, sleep deprivation has other important implications for ICU patients.²⁴ The ICU setting leads to sleep disruption due to excessive environmental stimuli such as alarms, noise from health care providers and other patients, as well as routine interruptions for patient care. Sleep disruption has been hypothesized to contribute to delirium, impaired immune function, and prolongation of mechanical ventilation in critically ill patients. Delirium has been associated with prolonged ICU stays, as well as increased ICU mortality.

The relationship between disrupted sleep and delirium is controversial in part due to the difficulty in distinguishing cause and effect. Key features of delirium are also seen in sleep-disrupted patients, including inattention, fluctuating mental status, and cognitive dysfunction. A study by Trompeo and colleagues¹⁷ of mechanically ventilated patients examined the relationship of ICU delirium with sleep patterns. The authors prospectively followed intubated patients until their sedation had been discontinued for more than 24 hours and the patients were alert, cooperative, and ready to wean from the ventilator. At this point, they measured nocturnal *polysomnograms* (PSGs) on each patient for one night. Among patients with severe *rapid eye movement* (REM) sleep reduction ($<6\%$ REM), 73% had delirium.¹⁷ Among the patients with more than 6% REM sleep, only 9% had delirium. Although interesting, this study does not address whether the primary event was sleep deprivation or delirium. Further studies will be necessary to determine the mechanisms by which sleep disruption

impacts delirium, as well as the potential impact of various interventions on clinical outcomes.

A study by Rompaey and colleagues¹⁸ randomized adult ICU patients to earplugs at bedtime (during the night shift) versus no earplugs and assessed self-reported sleep perception and delirium on the basis of the NEECHAM scale (a standardized test for confusion based on neurocognitive processing, behavior, and physiologic control). They found that the patients using earplugs had better perceived sleep, a lower incidence of confusion, and delayed onset of confusion.¹⁸ No difference was noted in the rate of delirium, a finding that is not surprising because it is unlikely that one intervention would eliminate delirium given the multifactorial nature of this syndrome. This study was encouraging in that it showed that a simple, inexpensive intervention may be beneficial as an adjunct to caring for the critically ill.

Ventilator dyssynchrony is also a likely culprit causing sleep disruption in the ICU. In one study in critically ill mechanically ventilated patients, better synchrony with the use of proportional assist ventilation versus standard pressure support ventilation improved sleep quality.¹⁹ Another study demonstrated that air leak during noninvasive ventilation was associated with disrupted sleep. This finding may be related to a disruption in respiratory pattern versus orofacial mechanoreceptors.²⁰

Currently, it is unclear what the implications of sleep loss are on pulmonary mechanics and ventilator weaning in ICU patients. A study in healthy men who were sleep deprived for 30 hours revealed a decrease in inspiratory muscle endurance and maximum voluntary ventilation.²¹ Sleep deprivation was initially thought to reduce chemoreceptor-mediated hypercapnic ventilator drive, but a more recent study by Spengler and colleagues²² showed that 24 hours of sleep deprivation did not affect the sensitivity of central chemoreceptors during resting ventilation. In critically ill tracheostomized patients undergoing a prolonged weaning from ventilation, sleep quality was similar whether on a ventilator or not overnight, but sleep quantity was greater on the ventilator; the authors recommended that patients in prolonged weaning will have greater sleep efficiency if ventilated at night.²³ Further research is necessary to understand the implications of sleep deprivation on weaning from mechanical ventilation.

Poor sleep has been reported in up to 61% of critical care survivors. The impact of this finding is unclear, but poor sleep may contribute to depression, post-traumatic stress disorder, and possibly impaired exercise tolerance among ICU survivors.^{25,26}

EFFECT ON CHRONIC DISEASE STATES

METABOLIC

Basic science, translational, and epidemiologic studies indicate that diminished and disrupted sleep predisposes an individual to both obesity and diabetes via altered glucose metabolism, insulin resistance, and dysregulation of appetite control via the neuroendocrine system. Many studies

have found a higher prevalence of diabetes within the OSA population with odds ratios from 1.4 to 2.2.²⁷⁻²⁹ Furthermore, restricted and disrupted sleep has been shown to predict glucose control in type 2 diabetes. A study by Aronsohn and colleagues³⁰ performed an in-laboratory PSG and measured HbA1c in 60 diabetic patients. They found that compared with patients without OSA, the adjusted mean HbA1c was increased by 1.5% in patients with mild OSA, 1.9% in patients with moderate OSA, and 3.7% in patients with severe OSA.³⁰

An initial sleep debt study looked at healthy male volunteers and subjected them to 4 hours of sleep nightly for 6 days followed by 7 nights of 12 hours in bed. The subjects underwent IV glucose tolerance tests on days 5 and 6 and after 7 nights of rest. They found that the acute response to insulin was diminished by 30% in the sleep-restricted compared with the well-rested state. Furthermore, their disposition index (a product of the acute response to insulin and insulin sensitivity) was 40% lower during sleep restriction.³¹ A low disposition index indicates a higher risk of type II diabetes, and these patients in fact had disposition indices in the range similar to those reported in epidemiologic studies of patients at higher risk for type II diabetes (i.e., Hispanic women with prior gestational diabetes). A proposed mechanism for this finding may be via sympathoexcitation and release of counter-regulatory hormones associated with sleep disruption.³²

CARDIOVASCULAR DISEASE

Multiple studies have documented a relationship between clinical cardiovascular disease and sleep disruption. A large, prospective 10-year cohort study followed more than 70,000 U.S. female health care workers with no known heart disease at baseline to evaluate the incidence of coronary heart disease and its relationship to self-reported daily sleep duration. Fascinatingly, this study showed that short sleep and long sleep were independently associated with a modest increase in incidence of coronary heart disease. This finding mimics the bimodal distribution seen in studies of sleep deprivation and immune dysfunction. The age-adjusted relative risks for individuals reporting fewer than 5 hours per night, 6 hours per night, 7 hours per night, and 9 hours per night were 1.8 (1.3 to 2.4), 1.3 (1.1 to 1.6), 1.1 (0.9 to 1.3), and 1.6 (1.2 to 2.1), respectively.³³

A similar study of more than 98,000 Japanese men (42%) and women (58%) aged 40 to 79 years investigated cardiovascular mortality in relation to self-reported sleep duration. The study group had a median follow-up of 14.3 years from 1988 to 1990 through 2003. Compared with a sleep duration of 7 hours, a sleep duration of 4 hours was associated with increased mortality from cardiovascular disease in women (hazard ratio of 2.3), as well as an increase in mortality from all causes among both men and women (hazard ratios of 1.3 for men and 1.3 for women).³⁴ Interestingly, an association was not seen for reduced sleep and cardiovascular mortality in men. Another study examined the relationship between short sleep duration and incident coronary calcification in healthy middle-aged adults. Computed tomography performed in 2000-2001 and 2005-2006 in the cohort revealed that longer sleep duration was associated with a reduced incidence of coronary artery

calcification with an adjusted odds ratio of 0.7 per extra hour of sleep.³⁵ This conclusion was made after accounting for potential confounders (age, sex, race, education, apnea risk, smoking status) and mediators (lipids, blood pressure, body mass index, diabetes, inflammatory markers, alcohol consumption, depression, hostility, self-reported medical conditions). Thus considerable epidemiologic data support a strong association between reduced sleep duration and coronary disease.

Disrupted sleep has a role in the pathogenesis of hypertension, perhaps secondary to disrupted balance of sympathovagal tone. Prospective studies have demonstrated that nocturnal blood pressure is a better predictor of cardiac risk than daytime blood pressure.^{36,37} One prospective study evaluated cardiovascular outcomes for more than 5000 patients with hypertension over a median period of 8.4 years and found that nocturnal blood pressure was the strongest predictor of cardiovascular mortality and that an increase of 10 mm Hg in mean nocturnal blood pressure corresponded with a 21% increase in cardiovascular mortality.³⁶ Another prospective study evaluated the effect of 24 hours' sleep deprivation on systolic and diastolic blood pressure in 8 healthy normotensive young adults (mean age 24) versus 8 healthy normotensive older adults (mean age 64) and found a significant increase in both diastolic and systolic blood pressure in the elderly group.³⁸ OSA has a significant correlation with both systemic and pulmonary arterial hypertension. There is strong evidence from animal studies that OSA contributes to systemic hypertension through mechanisms of intermittent hypoxia, sympathetic activation, and alterations in the renin-angiotensin system.

Disrupted sleep has also been shown to predict arrhythmias. OSA has been documented to have an association with atrial fibrillation, nonsustained ventricular tachycardia, and complex ventricular ectopy.³⁹ Even in healthy young adults without OSA, a single night of sleep deprivation has been associated with increased atrial electromechanical delay, a marker of risk for various arrhythmias such as atrial fibrillation.⁴⁰

MECHANISMS

The pathophysiologic consequences of sleep disruption are related to multiple alterations that take place following attenuated or disrupted sleep, including low-grade systemic inflammation, increased oxidative stress, dysautonomia, and endothelial dysfunction (Fig. 87-1).

Systemic Inflammation

Both total sleep loss and even modest sleep reduction (to 6 hours/night) are known to be associated with an increase in secretion of the proinflammatory cytokines IL-6 and *tumor necrosis factor* (TNF)- α .⁴¹ Though the biologic consequences of these increases have been relatively underexplored, elevations of IL-6 and TNF- α have been noted in disease states associated with systemic inflammation including insulin resistance and cardiovascular disease.⁴² Development and rupture of the vascular atherosclerotic plaque is a complex inflammatory-modulated cascade of events⁴³ involving cytokine-mediated recruitment and adhesion of T cells and monocytes to the vascular wall. Both IL-6 and TNF- α are synthesized and secreted by white

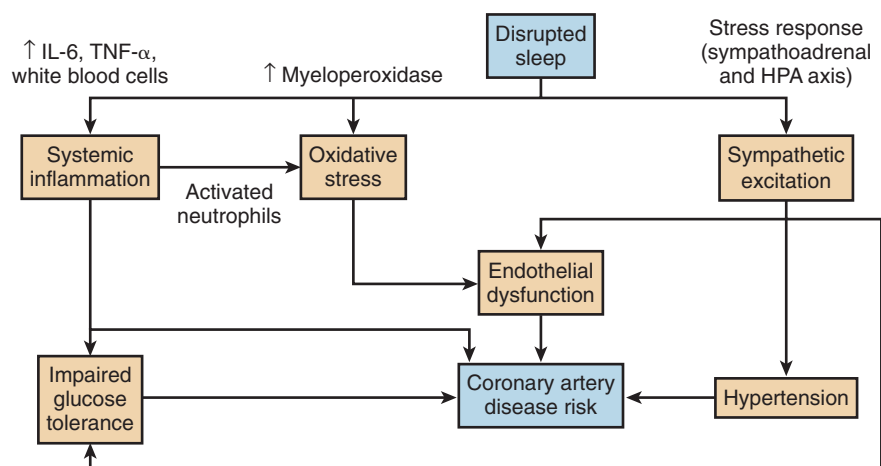


Figure 87-1 Proposed mechanisms by which sleep disruption increases the risk for coronary artery disease. Disrupted sleep may act by several mechanisms to increase coronary artery disease, mainly by effects on systemic inflammation, oxidative stress, and sympathetic excitation. The challenge in studying the role of sleep is in isolating particular mechanisms when they are closely inter-related. HPA, hypothalamic-pituitary-adrenal.

blood cells, endothelial cells, and adipocytes.⁴⁴ C-reactive protein, an acute-phase reactant and a well-established clinical indicator of systemic inflammation, is synthesized in the liver predominantly by IL-6 activation.^{45,45a} Multiple experimental studies (both animal and human) have shown elevations of IL-6, TNF- α , white blood cell count, and C-reactive protein in both acute and long-term partial and total sleep deprivation. Furthermore, patients reporting chronically shortened or disrupted sleep have been shown to have elevated levels of C-reactive protein and IL-6.⁴⁶ Disrupted or diminished sleep may thus induce chronic systemic inflammation, which itself may contribute to cardiovascular disease and diabetes.

Oxidative Stress

Sleep deprivation is associated with increased total leukocyte counts⁴⁶ and increased neutrophil counts.^{47,48} Activated neutrophils are known to release potent oxidative enzymes from their azurophilic granules including *myeloperoxidase* (MPO), and epidemiologic studies have shown that increased leukocyte counts are associated with increased cardiovascular disease risk.^{49,50} MPO is an enzyme in the blood that catalyzes oxidation via the release of reactive halogenating and nitrating species. MPO is a marker of oxidative stress that has potent atherogenic properties via MPO-modified LDL, an oxidative species associated with increased cardiovascular risk.⁵¹ Thus it is interesting that both MPO and MPO-modified LDL levels are elevated in healthy young adults after a period of chronic sleep restriction and recovery. For example, after a period of five sleep-deprived nights in healthy young adults, MPO levels were elevated and MPO levels peaked on the first day of sleep recovery.⁵² These data suggest the notion that periods of chronic sleep deprivation and recovery may lead to cardiovascular disease via leukocyte-mediated elevations of pro-atherogenic oxidative biomarkers.

Dysautonomia

Disrupted sleep results in activation of the neuroendocrine stress response and an overall increase in sympathetic tone.⁵³ The two primary systems involved with the neuroendocrine stress response in humans and other organisms are the sympathoadrenal system and the hypothalamic-

pituitary-adrenal axis. Onset of sleep has been associated with a rapid decrease in plasma levels of epinephrine and norepinephrine as a result of decreased sympathetic output in humans and rodents.^{54,55} Both norepinephrine and epinephrine plasma levels have also been shown to be higher during wakefulness, considered a state of higher vigilance. Sleep disruption itself may be associated with the stress response, and additionally chronic sleep deprivation disrupts the circadian balance of autonomic tone via the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis.^{56,57} Studies of heart rate variability, a useful tool for estimating autonomic tone, indicate a shift to a dominant state of parasympathetic tone compared with sympathetic tone in the heart during normal circadian sleep.⁵⁸ This notion is further supported by the observation that, during normal sleep compared with wakefulness, there is a decrease in systemic blood pressure. This phenomenon of “nocturnal dipping” is at least in part related to decreased sympathetic output during sleep.⁵⁹

During normal human sleep, glucocorticoid release follows a circadian pattern as directed by the suprachiasmatic nucleus of the hypothalamus. More particularly, glucocorticoid levels decrease after the onset of sleep and peak just before the end of sleep, helping to mobilize energy substrates. Disrupted sleep leads to altered glucocorticoid release secondary to stress activation of the hypothalamic-pituitary-adrenal axis. Studies have shown an overall modest increase in endogenous glucocorticoids in association with disrupted and restricted sleep in healthy volunteers.^{31,60} However, some studies have shown no association between the two and others have even shown a slight decrease in endogenous glucocorticoid release in relation to disrupted sleep.^{61,62} This paradoxical finding may be explained by overall global suppression of sympathetic activity in relation to fatigue and daytime sleepiness. The bulk of the literature indicates that disrupted or restricted sleep leads to dysautonomia with an overall shift to greater sympathetic tone.

Endothelial Dysfunction

Perhaps related to the oxidative stress and dysautonomia, sleep disturbance has been associated with endothelial dysfunction. The increase in reactive oxygen species leads

to increased expression of adhesion molecules that activate leukocytes. Studies in a rat model suggest that sleep deprivation can alter endothelial function and vasodilation via disruption in the pathways for nitric oxide synthase and cyclooxygenase.⁶³ Studies of sleep apnea patients have demonstrated a relationship with markers of endothelial dysfunction including circulating levels of the adhesion molecules intercellular adhesion molecule-1 and L-selectin.⁶⁴ There is also an association with increased vascular endothelial growth factor. These changes lead to abnormal vasodilatory responses, which can predispose to hypertension and cardiovascular disease.⁶⁵ In a recent systematic review, OSA was found to be an independent predictor of subclinical cardiovascular disease, as assessed by measures such as coronary artery calcification and brachial artery flow-mediated dilation.⁶⁶ The impact of sleep disturbance on endothelial dysfunction and cardiac events is undergoing investigation.

Key Points

- Sleep disruption is increasingly emerging as a major predictor of chronic disease and poor health.
- Poor sleep has been associated with short-term and long-term cognitive impairment.
- Poor sleep has been associated with immune dysfunction.

- Poor sleep has been associated with cardiometabolic implications such as increased risk for diabetes, hypertension, and coronary artery disease.
- Both inadequate sleep duration and excessive sleep duration have been associated with adverse health consequences.
- Sleep quality is poor in critically ill patients, and efforts to optimize ventilator synchrony and to decrease noise, disruptions, and air leaks may improve sleep and perhaps reduce delirium and improve immune function.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION AND DEFINITIONS**PATHOGENESIS OF OSA**

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Upper Airway Collapsibility
Neuromuscular Factors
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Fluid Shift

CLINICAL FACTORS PREDISPOSING TO OSA

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Cognitive Impairment
Depression
Other Complications

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Arrhythmias
Myocardial Infarction
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Congestive Heart Failure
Pulmonary Hypertension
Insulin Resistance
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Oral Appliances
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PERIOPERATIVE CONSIDERATIONS IN OSA**DISEASE MANAGEMENT STRATEGIES FOR OSA****INTRODUCTION AND DEFINITIONS**

Sleep-disordered breathing is a very common clinical problem. Pathologic changes in breathing during sleep may take the form of discrete episodes of absent (apnea) or reduced (hypopnea) breathing or of more sustained reductions in breathing during sleep compared with wakefulness (hypoventilation). The most common form of sleep-disordered breathing results from closure of the upper airway during sleep and is called *obstructive sleep apnea* (OSA). Apneas may also be due to transient loss of respiratory drive output from the central respiratory controller (central apnea). “Mixed apneas” are individual events that begin as central apneas but become obstructive. Mixed apnea should not be confused with the combination of pure obstructive and pure central events in the same patient during sleep. The latter situation is referred to as “complex sleep apnea.” Complex sleep apnea is used specifically when there is either a combination of obstructive and central events on the diagnostic sleep study or when central events emerge during titration of *continuous positive airway pressure* (CPAP) for obstructive sleep apnea. Sleep-associated hypoventilation is defined as a sustained reduction in breathing associated with an increase in PCO_2 or sustained decrease in arterial *oxygen saturation* (SO_2) of less than 90% during sleep without discrete apneas or hypopneas.

Fundamental to identifying sleep-disordered breathing is a description of breathing events that happen during sleep^{1,2} (Fig. 88-1). In adults an apnea is defined as a cessation of breathing that lasts longer than 10 seconds. *Apneas* are identified as being obstructive if there are sustained respiratory efforts during the event, usually identified by use of thoracic and abdominal respiratory inductance plethysmography bands, which demonstrate paradoxical thoracoabdominal motion. In contrast, during central apneas there is absence of respiratory effort during the event. *Hypopneas* are events associated with a reduction rather than complete cessation of airflow. These discrete reductions in ventilation may be associated with a fall in oxygen saturation or may terminate in association with a brief arousal from sleep (*microarousal*). Although the definition of apneas is well standardized, several different criteria have been used to identify hypopneas, based on the extent of flow reduction, degree of oxygen desaturation, and the presence of microarousal.¹⁻³ For example, the *American Academy of Sleep Medicine* (AASM) currently recognizes two alternate definitions of hypopnea² (Table 88-1). Another type of event is termed a *respiratory effort-related arousal* (RERA). These are episodes characterized by mild upper airway narrowing during sleep, with increased respiratory effort required to maintain a slightly reduced level of airflow not large enough to be scored as hypopnea.⁴ When the increased inspiratory effort required to maintain ventilation is associated with a microarousal, a RERA is scored (Fig. 88-2).

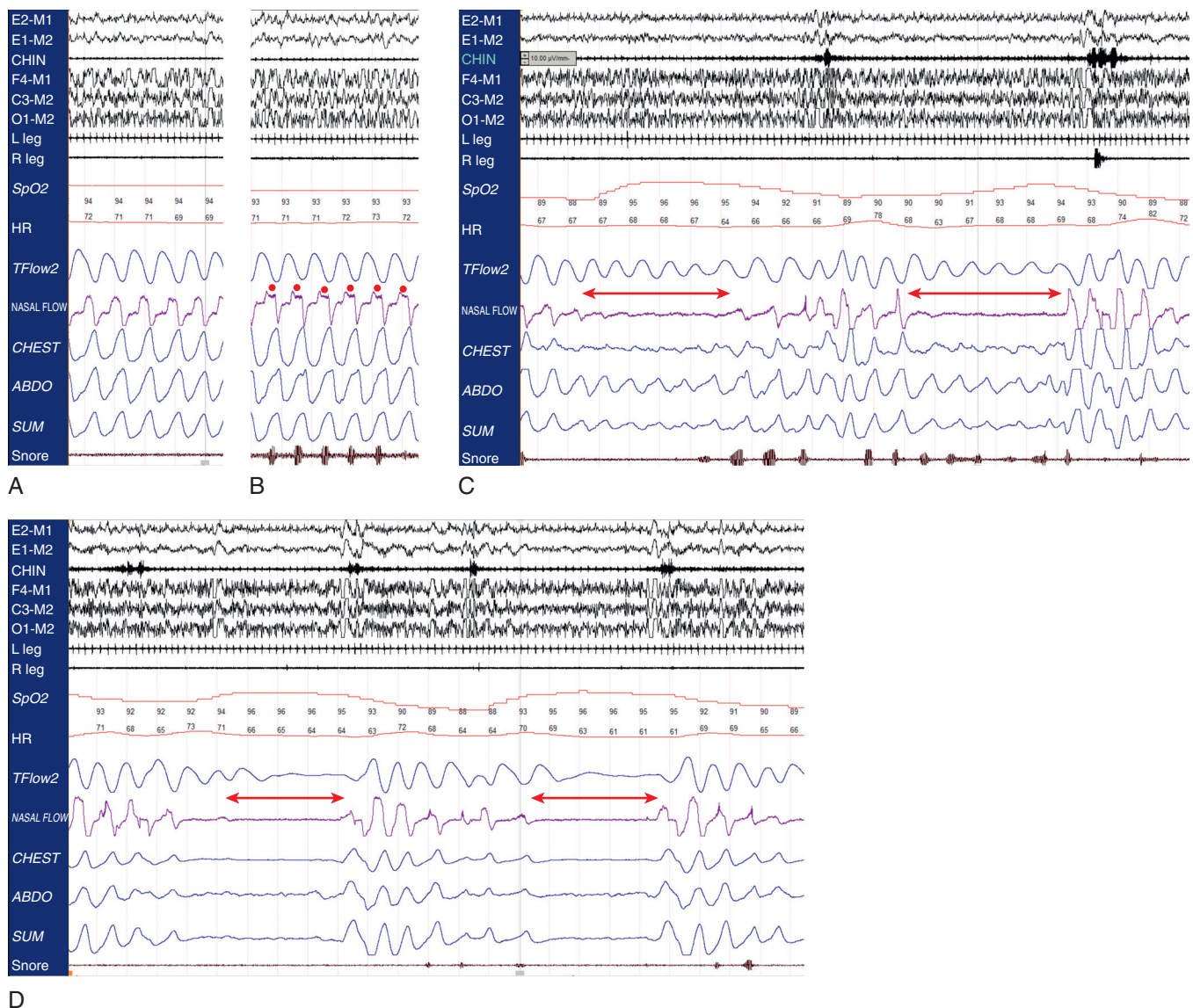


Figure 88-1 Polysomnographic tracings illustrating stable breathing (A), simple snoring (B), obstructive hypopneas (red arrows, C), and central apneas (red arrows, D). Note in **B** that the snores are shown as a microphone signal (Snore) along with an inspiratory flattening on the nasal pressure flow signal (red dots). Note in **C** that there is evidence of persistent airflow during events on the thermistor (TFlow2) signal while the nasal pressure signal shows no flow. The event is therefore scored as a hypopnea because flow must be absent on both signals to score an apnea (as in **D**). The events in **C** are considered obstructive because there is persistent effort during the event with paradoxical inward motion of the ribcage on the thoracic effort channel (CHEST). The events in **D** are considered central because the absence of airflow is accompanied by an absence of effort (CHEST, ABDO).

Traditionally detection of RERAs has required use of an esophageal pressure catheter to measure respiratory effort.⁵ However, with the advent of nasal pressure cannula for measurement of airflow, subtle reductions in flow, accompanied by airflow limitation identified as flattening of the inspiratory airflow signal, can now be used to score RERAs.² Changes in pulse transit time (the time from the onset of the electrocardiographic QRS complex to the pulse wave in the finger) also accurately reflect increasing effort and arousal.⁶ The scoring criteria for respiratory events recommended by the AASM are shown in Table 88-1.

The standard metric for assessment of OSA severity is the *apnea-hypopnea index* (AHI), which is calculated as the number of apneas and hypopneas during sleep divided by total sleep time. OSA severity is graded as follows: normal (no OSA; AHI < 5 episodes/hr), mild sleep apnea (AHI ≥ 5

and < 15 episodes per hour), moderate sleep apnea (AHI ≥ 15 and < 30 episodes per hour), and severe sleep apnea (AHI ≥ 30 episodes per hour). Current AASM criteria for *polysomnographic* (PSG) analysis also define the respiratory disturbance index as the number of apneas, hypopneas, and RERAs per hour of sleep.²

Several factors can influence the AHI value derived from PSG recordings.^{1,7-9} For example, the technology used to assess airflow has evolved from reliance on oronasal thermistor technology to addition of the nasal pressure signal, which is more sensitive for detection of mild reductions in airflow.⁷ The current prevalence estimates for OSA are derived from studies that used thermistor technology only.^{10,11} Addition of nasal pressure analysis would likely increase detection of respiratory events and thus OSA prevalence. Differences in hypopnea definitions can also lead to

Table 88-1 Definitions of Respiratory Events for Diagnostic Polysomnography

Apnea: An event lasting ≥ 10 sec characterized by $\geq 90\%$ reduction from pre-event baseline in oronasal thermistor airflow. An apnea is scored as:

- Obstructive, if there is continued or increasing respiratory effort throughout the event
- Central, if effort is absent throughout the entire event
- Mixed, if effort is initially absent, then resumes in the latter part of the event

There is no minimum desaturation or microarousal requirement for scoring of an apnea.

Hypopnea: An event lasting ≥ 10 sec characterized by a $\geq 30\%$ reduction from pre-event baseline in peak nasal pressure inspiratory airflow that is associated with:

- Definition 1A: Either a $\geq 3\%$ reduction in arterial oxygen saturation (SO_2) pre-event baseline or a microarousal
- Definition 1B: A $\geq 4\%$ reduction in arterial SO_2 from pre-event baseline value

The hypopnea is scored as *obstructive* if during the event there is any snoring, inspiratory airflow limitation, or paradoxical thoracoabdominal motion that was not present during pre-event breathing.

The hypopnea is scored as *central* if none of the events described above is present.

Respiratory effort-related arousal (RERA): A sequence of breaths lasting ≥ 10 sec that does not meet criteria for apnea or hypopnea, which is characterized by increasing respiratory effort or inspiratory flattening of the nasal pressure flow signal leading to arousal.

Hypoventilation: An increase in PCO_2 to > 55 mm Hg for ≥ 10 min or PCO_2 increase ≥ 10 mm Hg above awake supine values to > 50 mm Hg for ≥ 10 min.

Adapted from Berry RB, Brooks R, Garmaldo CE, et al: *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2.0*, Darien, IL, 2013, American Academy of Sleep Medicine.

Table 88-2 Epworth Sleepiness Scale

Situation	Chance of Dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (such as a theater or meeting)	
Riding as a passenger in a car for an hour without a break	
Lying down in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
Score = total (normal < 11)	

Instructions to patient:
“What is the chance that you would doze off or fall asleep (not just “feel tired”) in each of the following situations? Rate the chance for each situation. If you are never or rarely in the situation, please give your best guess for that situation.”
Chance of dozing: 0, never; 1, slight chance; 2, moderate chance; 3, high chance.

sizeable differences in measurement of OSA severity.^{8,9} In one analysis performed by the Sleep Heart Health Study investigators, varying the hypopnea scoring criteria (from no requirement for associated desaturation or arousal to a severe desaturation requirement) led to as much as a 10-fold difference in mean AHI value.⁸ This may therefore affect both the severity estimate and the presence versus absence of OSA based on AHI cutoff criteria. Thus it is essential in interpreting clinical reports of PSG studies or published research data that the criteria for respiratory event scoring be stated clearly and taken into account in interpreting the findings.

Not all patients with OSA will have symptoms related to the respiratory disturbance. The term *sleep apnea syndrome* is used to refer to the concurrence of OSA with symptoms referable to the respiratory disturbance, such as *excessive daytime sleepiness* (EDS).¹² The latter can be identified by subjective questionnaires. A commonly used questionnaire is the Epworth Sleepiness Scale,¹³ in which the respondent indicates the likelihood of dozing (scale from 0 to 3) in eight common circumstances associated with sleepiness (Table 88-2). A score of 11 or higher (out of 24) is commonly accepted as indicating excessive sleepiness.¹³ The *International Classification of Sleep Disorders*, third edition (ICSD-3) identifies a diagnosis of OSA in adults based on a AHI of 5 or higher with symptoms, or AHI of 15 or higher regardless of symptoms¹² (Table 88-3).

Another term used in the spectrum of obstructive sleep-disordered breathing is the *upper airway resistance syndrome*. Whereas this entity is now subsumed under “Obstructive Sleep Apnea” in ICSD-3, the term was originally used by Guilleminault and colleagues⁴ to describe patients with increased upper airway resistance during sleep, recurrent arousals, and daytime symptoms, but in whom conventional criteria for thermistor-based identification of hypopneas were not met (eFig. 88-1). The definition and identification of this syndrome has evolved in the ensuing years, and it is now commonly characterized as a

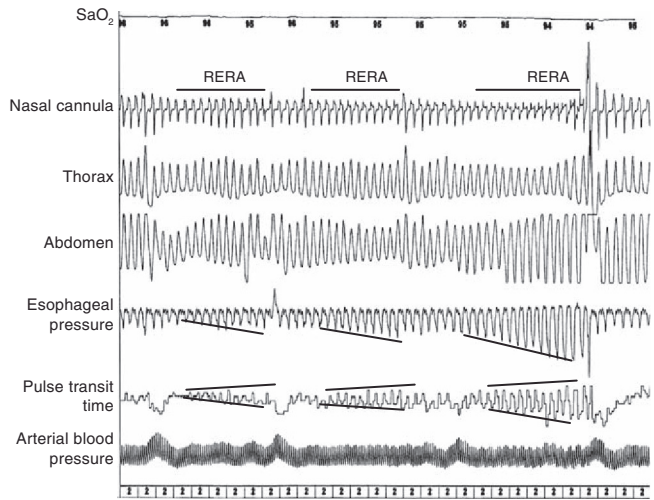


Figure 88-2 Sleep tracing illustrating respiratory effort-related arousals (RERAs). Note the flattening (flow limitation) on the nasal cannula pressure signal, with increasing inspiratory efforts reflected on the esophageal (pleural) pressure tracing. Electroencephalogram is not shown on this tracing but would demonstrate microarousal at the termination of the RERA events. Autonomic activation at the end of the events is evident from the pulse transit time and arterial blood pressure signals. (From Pepin JL, Guillot M, Tamisier R, Levy P. The upper airway resistance syndrome. *Respiration* 83[6]:559–566, 2012.)

Table 88-3 Definition of Adult Obstructive Sleep Apnea (OSA)

OSA is present when either A and B, or C are present:

A. At least one applies:

- The patient complains of daytime sleepiness, unrefreshing sleep, fatigue, or insomnia
- The patient awakens with breath-holding, gasping, or choking
- The bed partner reports loud snoring, breathing interruptions, or both during the patient's sleep
- The patient has been diagnosed with hypertension, mood disorder, cognitive dysfunction, coronary artery disease, congestive heart failure, stroke, atrial fibrillation or type 2 diabetes

AND**B. Sleep recording* shows the following:**

- Five or more predominantly obstructive respiratory events (obstructive or mixed apneas, hypopneas, or RERAs) per hour

OR**C. Sleep recording* shows the following:**

- Fifteen or more predominantly obstructive respiratory events (obstructive or mixed apneas, hypopneas, or RERAs) per hour

RERA, respiratory effort–related arousal.

*Sleep recording may be either laboratory polysomnography (PSG) or out of laboratory portable testing which usually does record signals to allow sleep staging. Respiratory event numbers are expressed per hour of sleep for PSG and per hour of recording for portable monitors. Portable monitors tend to underestimate event indices as compared with PSG as patients usually are not asleep for an entire recording period. Hypopneas associated with arousals and RERAs cannot be scored from portable monitors without sleep staging capability as arousals cannot be identified.

Adapted from *International classification of sleep disorders*, ed 3, Westchester, IL, 2014, American Academy of Sleep Medicine.

sleep-disordered breathing syndrome in which PSG shows more than 50% of events are RERAs. A recent review of the upper airway resistance syndrome is available.¹⁴

PATHOGENESIS OF OSA

The pathogenesis of OSA involves a complex interaction of factors, including altered upper airway anatomy tissue characteristics and neuromuscular function, sleep-related decrements in upper airway dilator muscle activity, attenuated protective dilator reflexes, and altered ventilatory and arousal responses to chemical and other respiratory stimuli (Fig. 88-3). Different factors may predominate in different individuals, yielding different OSA phenotypes. The upper airway in OSA closes only during sleep, indicating that sleep-dependent changes in output to the dilator muscles of the upper airway are clearly a fundamental mechanism. Airway collapse ensues when dilator muscle activity and compensatory reflexes are no longer sufficient to maintain patency of the compromised airway. The key elements of sleep-related influences on respiratory motor output are discussed in Chapter 85 and will not be covered here. Rather this section will focus on structural and functional changes in the upper airway that predispose to airway closure. Several comprehensive reviews of OSA pathogenesis are available.^{15,16}

UPPER AIRWAY SIZE

A variety of imaging methods have shown that upper airway dimensions are reduced in OSA.¹⁷ The reduction in airway caliber is predominantly in the lateral rather than anteroposterior dimension. Airway size may be compromised by alterations in bony structures such as a small

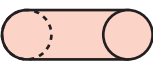
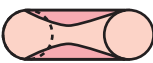
Factors affecting upper airway patency	Patency	Collapse
Anatomic configuration (bony structure, soft tissue, fat)	 Normal	 Reduced dimensions
Lung volume	Traction on upper airway	Lower lung volume; less traction
Lining fluid surface tension	Normal	Increased
Intraluminal pressure	Less negative	More negative
Extraluminal tissue pressure	Less positive	More positive
Airway collapsibility (P_{crit})	Lower	Higher
Sleep-related decrements in muscle activity	Normal, mild compared with wakefulness	Marked compared with heightened compensatory levels during wakefulness
Chemosensitivity	Normal	Blunted or heightened
Negative pressure reflexes	Mild sleep-related decrement	Blunted (latency, amplitude)
Dilator muscle activation	Adaptation	Injury, dysfunction
Denervation (sensory, motor)	Absent	Neural, muscular dysfunction
Edema: inflammation; nocturnal fluid shift	Absent	Altered airway caliber, tissue characteristics

Figure 88-3 Schema illustrating factors that favor upper airway collapse during sleep in obstructive sleep apnea (OSA). For explanation, see text and also Chapter 85. P_{crit} , critical closing pressure. (Adapted from Kimoff R: The upper airway. In Hamid Q, Shannon J, Martin JG, editors: *The physiologic basis of respiratory disease*, Hamilton, Canada, 2005, BC Dekker.)

retrognathic mandible¹⁸ or by increased volume of soft tissues (tongue, lateral walls).¹⁹ Although cross-sectional dimensions are reduced, airway length may be increased in OSA patients, with increased length predisposing to collapse.^{20,21} Upper airway caliber is also influenced by lung volume due to tracheal traction, so that in obese subjects, marked reductions in lung volume during recumbency can lead to reduced upper airway patency.^{22,23}

UPPER AIRWAY COLLAPSIBILITY

Due to a lack of rigid supporting structures, much of the human upper airway is a collapsible tube. Pressure-flow relationships in the airway have been modeled using the Starling resistor model, in which collapsibility is expressed as the *critical closing pressure* (P_{crit}). P_{crit} is measured during sleep by changing intraluminal pressure (e.g., lowering CPAP level in an OSA patient or applying negative pressure in a normal subject) and assessing flow reductions. A more negative P_{crit} denotes a less collapsible airway. Studies have shown a continuum of upper airway collapsibility in subjects with normal breathing ($P_{crit} < -10$ cm H₂O), nonapneic snoring (P_{crit} range, -10 to -5 cm H₂O), obstructive hypopnea (P_{crit} range, -5 to 0 cm H₂O), and obstructive apnea ($P_{crit} > 0$ cm H₂O).²⁴⁻²⁶ These values are for “passive” P_{crit} , which reflects the passive mechanical properties of the airway. Techniques are also available to measure “active” P_{crit} , which reflects active neuromuscular compensation for reduced intraluminal pressure. Active P_{crit} measurements demonstrate a significant impairment in neuromuscular compensation in OSA patients.^{26,27}

NEUROMUSCULAR FACTORS

Several factors may contribute to impaired neuromuscular upper airway function in OSA in addition to the attenuation of protective reflexes during sleep discussed in Chapter 85. Upper airway muscle function may be impaired in OSA, although this remains controversial.^{28,29} In response to the loading of the upper airway dilators, the muscles appear to adapt, and whereas contractility appears preserved in most patients, the muscles are more fatigable.³⁰ In some patients with severe OSA, muscles may be injured, leading to reduced contractility, as in the English bulldog model of OSA.³¹ There is also evidence for upper airway neuropathy in OSA, with evidence for sensory/afferent impairment^{32,33} and efferent neuropathy in the form of muscle denervation,^{34,35} both of which could impair neuromuscular compensatory responses.¹⁵

UPPER AIRWAY INFLAMMATION

There is increased inflammation in upper airway tissues in OSA, which may contribute to OSA pathogenesis.^{36,37} Tissue trauma from snoring, oxidative stress, acid-pepsin reflux, smoking, and alcohol could all lead to inflammation. Increased inflammation in turn may produce edema and airway narrowing, lead to changes in soft tissue composition (e.g., increased collagen deposition) and mechanics, adversely affect muscle contractility, and contribute to upper airway afferent and efferent neuropathy.^{15,37} Few studies to date have assessed the effects of anti-

inflammatory therapy on OSA, though inhaled nasal steroids have been shown to improve mild OSA.³⁸

FLUID SHIFT

Studies by Bradley and colleagues have provided evidence that spontaneous shifts in fluid volume from the legs to the neck during recumbency or sleep may play a role in the pathophysiology of OSA.³⁹ Cephalad displacement of fluid from the legs in normal subjects using shock pants increases neck circumference and pharyngeal resistance,⁴⁰ as well as upper airway collapsibility.⁴¹ The extent of spontaneous overnight fluid shift correlates with AHI in nonobese OSA subjects.⁴² In OSA patients with venous insufficiency, the use of compression stockings to prevent daytime fluid accumulation in the legs was associated with a significant reduction in nocturnal fluid shift and in AHI.⁴³ Consideration should therefore be given to this approach in managing OSA among older sedentary patients with venous insufficiency.

CLINICAL FACTORS PREDISPOSING TO OSA

OBESITY

There are strong links between obesity and OSA.^{44,45} Approximately 58% of patients with moderate to severe OSA are obese.⁴ Obesity may reduce upper airway caliber because of adipose tissue deposition as well as through a lung volume-dependent effect.²³ Obesity and OSA are both associated with oxidative stress and systemic inflammation, and the two conditions may interact to potentiate each other.⁴⁶ Weight change is associated with a change in AHI. In the Wisconsin cohort over 8 years' follow-up, a 10% increase in body weight was associated with a 32% increase in AHI and a sixfold increase in risk for developing an AHI of 15 or higher. A 10% weight loss was associated with a 26% reduction in AHI.⁴⁷ Weight-related changes in AHI are more marked in men than women.^{44,45} Despite the strong links between OSA and obesity, many obese individuals do not have OSA, and up to one third of OSA patients are not obese.

UPPER AIRWAY ANATOMIC ABNORMALITIES

Abnormalities that may predispose to OSA include marked craniofacial disproportion as is seen in Pierre Robin syndrome,⁴⁸ benign tonsillar hypertrophy, oropharyngeal malignancies,⁴⁹ macroglossia, and acromegaly.⁵⁰ Nasal obstruction may contribute to OSA⁵¹ by increasing negative inspiratory driving pressure to maintain airflow, which may contribute to dynamic oropharyngeal collapse. However, surgical correction of mechanical nasal obstruction alone typically has minimal effects on OSA severity.^{52,53}

GRAVITY/BODY POSITION

The frequency of OSA events may increase in the supine position compared with the lateral decubitus position because of the effects of gravity on upper airway size and shape. Positional OSA is commonly defined as a supine AHI

at least double that in the lateral position.⁵⁴ The duration of obstructive events and extent of associated oxygen desaturation may also worsen in the supine position.⁵⁵ Although prevalence estimates vary,⁵⁴ positional OSA has been identified in 49.5% of mild (AHI 5 to 15), 19.4% of moderate (AHI 15 to 30), and 6.5% of severe (AHI \geq 30) OSA patients.⁵⁶

GENETIC FACTORS

Studies in diverse populations have demonstrated familial propensity for OSA. The relative risk for OSA in a first-degree relative of an affected patient is approximately 2.0.⁵⁷⁻⁵⁹ Pedigree and twin studies indicate that the heritability of the AHI is approximately 35% to 40%.⁶⁰ Thus inquiring about a family history of snoring and other symptoms should be part of the routine evaluation of patients for OSA. Obesity, which is a major OSA risk factor, also has a genetic basis, and it is estimated that approximately 40% of the genetic variance in AHI is shared with pathways that mediate obesity.^{60,61} The remainder of heritability likely resides in genes controlling craniofacial structure, ventilatory control, sleep-wake patterns, and inflammation.^{58,59,62} Various techniques have been used to identify specific genetic pathways that mediate OSA and its complications. Although progress has been made, there are few findings with direct clinical impact. Several reviews of genetic studies in OSA are available.⁵⁷⁻⁵⁹

ENDOCRINE DISTURBANCES

OSA has been reported to be present in 25% to 35% of patients with untreated hypothyroidism.^{63,64} Predisposition to OSA may be due to increased mucopolysaccharide and protein deposition in upper airway tissues. Altered central respiratory control or neuropathic changes in upper airway muscles may also play a role. Thyroid replacement therapy improves OSA in many patients, though there may be residual sleep-disordered breathing that requires continued standard treatment.^{63,64} Although a clinical history suggesting hypothyroidism should be sought during evaluation of OSA patients, routine biochemical screening of all potential OSA patients is not warranted.⁶⁵

Sleep-disordered breathing is found in approximately 70% of patients with acromegaly.⁶⁶ Although OSA predominates, central sleep apnea may also be observed. Upper airway dimensions are reduced due to both soft tissue (glycosaminoglycan and collagen deposition, edema) and bony changes.⁵⁰ Upper airway myopathy may also play a role. Correction of the endocrine disturbances in acromegaly results in variable improvements in OSA; continued treatment with CPAP is often required.⁶⁴

OSA is found in up to 70% of women with polycystic ovary syndrome.⁶⁷ Potential mechanisms include hormonal changes (relative androgen excess) and increased central adiposity. Polycystic ovary syndrome is associated with a high rate of metabolic dysfunction. OSA may worsen metabolic function, and OSA treatment may improve metabolic parameters in these patients.⁶⁸ Clinicians managing patients with these endocrine disturbances should have a low threshold for requesting sleep studies if symptoms suggestive of OSA are present.

SMOKING

Cigarette smoking has been linked to snoring and OSA in cross-sectional epidemiologic studies.^{69,70} Although the Sleep Heart Health Study investigators found that smoking was less prevalent in OSA than non-OSA patients,⁷¹ analysis of a subset of the Wisconsin cohort study found a significant positive dose-response relationship between cigarette smoking and OSA severity.⁷² Possible mechanisms include worsening of upper airway inflammation and sleep-disruptive effects of nicotine producing respiratory instability.

ALCOHOL, DRUGS

Alcohol is known to worsen snoring and OSA. This may be due to direct effects on upper airway motor activity or to a deepening of sleep and impairment of arousal responses.⁷³ Other drugs with similar effects include muscle relaxants, sedative-hypnotics, and opioids, although the latter may also produce central and/or complex sleep apnea. Pharmacologic effects on upper airway motor control have been reviewed.⁷⁴

EPIDEMIOLOGY OF OSA

PREVALENCE

The first major community-based assessment of OSA prevalence was the Wisconsin Sleep Cohort Study, which reported the prevalence of OSA syndrome (AHI \geq 5 events per hour with daytime sleepiness) as 4% in men and 2% in women.⁷⁵ The prevalence of AHI of 15 or higher regardless of symptoms was 9% in men and 4% in women. Although other prevalence estimates have varied somewhat based on ethnicity, recruitment methods, technology used to record airflow, and definitions of hypopnea, other studies performed in the United States, Australia, Asia, and Spain have yielded similar values. However, it is important to note that, since the original estimates published in the early to mid-1990s, obesity has increased markedly in the United States and other Western countries.⁷⁶ Given the links between OSA and obesity, the earlier figures likely now underestimate the true prevalence. The Wisconsin Cohort investigators published updated estimates of OSA prevalence⁷⁷ with OSA syndrome (AHI \geq 5 events per hour with Epworth sleepiness score \geq 11) estimated at 14% in men and 5% in women 30 to 70 years of age. OSA is therefore highly prevalent in the general population.

GENDER DIFFERENCES

Epidemiologic studies have consistently demonstrated that OSA is two to three times more prevalent among men than women. Several factors may account for this male predominance, including differences in body fat distribution, upper airway anatomy (length, cross-sectional area) and collapsibility, and a protective effect of female sex hormones. The latter is supported by the observation that OSA is approximately three times more prevalent among postmenopausal than premenopausal women.^{78,79} However, the

mechanisms by which sex hormones affect OSA remain unclear. Epidemiologic studies suggest that hormone replacement therapy may have a protective effect,^{78,80} but hormone replacement appears to have little impact on OSA once present.⁸¹

ETHNICITY

Most of the data on OSA prevalence are derived from predominantly white populations, though several studies have addressed OSA prevalence in African American, Hispanic, and Asian populations. In African Americans, overall OSA prevalence is similar to that in whites,⁸² although prevalence is comparatively higher among African Americans younger than 25⁸³ or older than 65 years of age.⁸⁴ Initial reports suggested that symptoms of OSA were more prevalent among Hispanics than whites,^{85,86} but a more recent study found similar rates of OSA.⁸⁷ Several studies^{88,89} have shown that OSA prevalence in Asians is comparable to whites, despite a lower prevalence of obesity among Asians. Although obesity remains an important risk factor for OSA among Asians, craniofacial structure may play a more prominent role in OSA pathogenesis.^{88,89} Studies on ethnicity and OSA may be confounded by socioeconomic and residential factors. Poor socioeconomic status has been linked to OSA risk among children.^{90,91} Living in poor neighborhoods is associated with shorter sleep time and increased sleep disruption; air quality may also be worse, which could contribute to worsening of OSA through increased airway inflammation.⁹² CPAP compliance appears to be lower in African American patients, which may be related to socioeconomic status⁹³ and shorter sleep duration.⁹⁴

AGING

The prevalence of OSA increases with age through midlife. In the update from the Wisconsin Sleep Cohort, the estimated prevalence of OSA (AHI ≥ 5 with Epworth sleepiness score ≥ 11) among men was 12% for age 30 to 49 and 18% for age 50 to 70 and among women 3% for age 30 to 49 and 8% for age 50 to 70.⁷⁷ Studies evaluating OSA prevalence in individuals older than 65 years have reported a high incidence of OSA ($>50\%$). In one sample of community-dwelling men and women 65 years or older, 81% had an AHI of 5 or higher, and 62% had an AHI of 10 or higher.⁹⁵ In another study the *odds ratio* (OR) for having an AHI of 10 or higher was 6.6 (95% *confidence interval* [CI], 2.6 to 16.7) for men 65 to 100 years, compared with 20 to 44 years.⁹⁶ The comparable OR for women for an AHI of 15 or higher was 6.8 (95% CI, 0.8 to 25.9). Although it is clear that elderly patients with symptomatic OSA benefit from treatment, controversy exists with respect to the adverse health consequences of OSA in older adults.^{97,98} Randomized controlled trials evaluating effects of OSA treatment in older adults are required to advance knowledge in this area.

PREGNANCY

A growing body of data indicates that OSA may develop or worsen over the course of pregnancy.⁹⁹ Although there are no large-scale prospective epidemiologic PSG studies in pregnant women, based on symptoms of OSA (e.g., snoring)

and witnessed apneas, together with limited PSG studies, OSA may be present in up to 20% of pregnant women by the third trimester.⁹⁹ This is clinically relevant in that maternal OSA appears to contribute to gestational hypertension and preeclampsia, gestational diabetes, and possibly low infant birth weight.¹⁰⁰

DIAGNOSIS OF OSA

QUESTIONNAIRES/PREDICTION EQUATIONS

Several questionnaires such as the Berlin¹⁰¹ and Stop-BANG¹⁰² questionnaires have been developed to grade OSA risk. Clinical prediction models that incorporate symptoms and anthropometric measurements (e.g., body mass index, neck circumference) have been developed.¹⁰³⁻¹⁰⁷ These models tend to be relatively sensitive (76% to 96%) but not very specific (13% to 54%) when compared with PSG.¹⁰⁸ Thus, although questionnaires or prediction models are useful for screening or estimating pretest probability, objective sleep recording is required to establish a diagnosis of OSA (Fig. 88-4A).

LABORATORY POLYSOMNOGRAPHY

The gold standard test for OSA has long been considered to be in-laboratory, technologist-attended complete overnight PSG, referred to as “type 1 sleep testing.” Standards for the performance and analysis of full PSG have been established by the AASM.² Type 1 recordings include monitoring of electroencephalography, electro-oculography, chin electromyography, electrocardiography, oronasal airflow and snoring, pulse oximetry, thoracic and abdominal movement, body position, and tibialis anterior electromyography for scoring periodic leg movements (see Fig. 88-1). Infrared video monitoring is also used to record complex behaviors and movements to diagnose parasomnias. Sleep-wake state is scored using electroencephalography, electrooculography, and electromyography signals. Respiratory events are scored based on airflow, thoracoabdominal motion, and oximetry signals using the criteria described in Table 88-1. PSG records should be scored manually by trained technologists according to standard criteria² and summary data on sleep, respiratory, and other associated events generated in tabular and graphic summary format.

UNATTENDED SLEEP STUDIES

Although complete in-laboratory PSG is the gold standard for OSA diagnosis, there is limited access to this resource in many locations.¹⁰⁹ There are now “out-of-center” or portable sleep testing options available that are adequate for diagnosis of OSA in many instances. In addition to type 1 sleep testing (in-laboratory PSG) there are three other types of sleep testing defined by the AASM based on number of channels recorded. Type 2 PSG testing, which involves complete PSG performed in an unattended, nonlaboratory setting, has been used in population-based studies¹¹ and has clinical utility when complete PSG recording is desirable but the patient cannot come to the sleep laboratory (e.g., intensive care unit or disabled patients). Type 3 monitors acquire

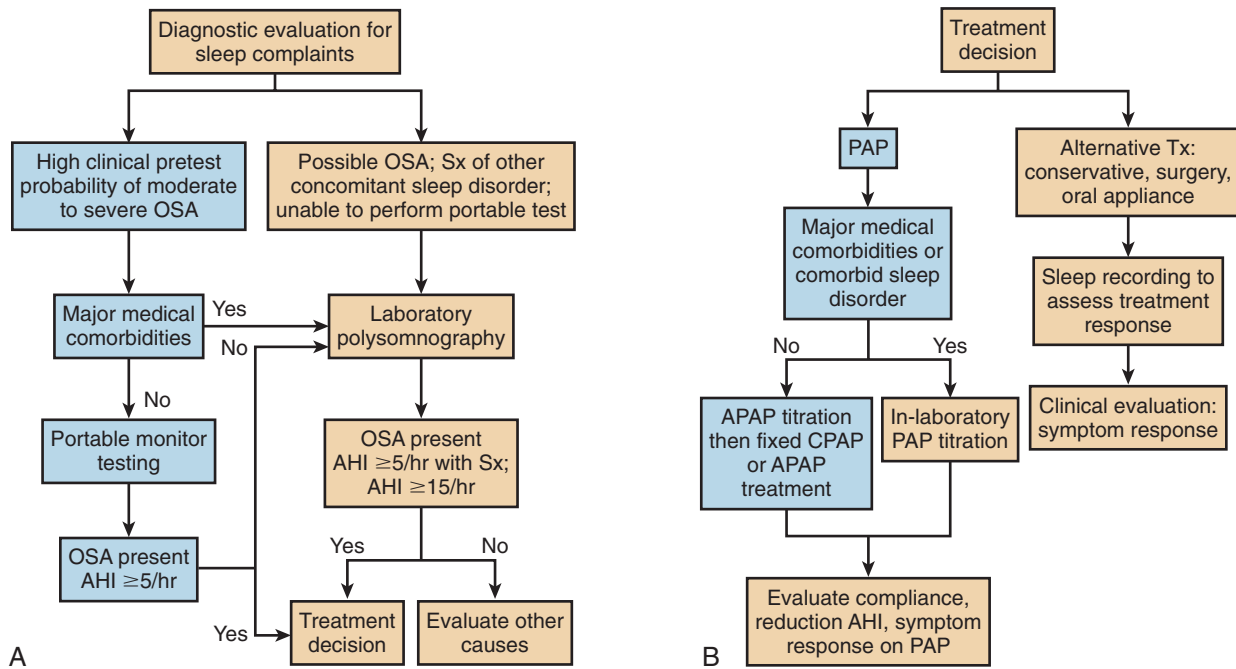


Figure 88-4 Schema illustrating an approach to diagnosis (A) and treatment (B) of OSA. An ambulatory pathway for patients with symptomatic moderate to severe OSA without other major comorbidities is shown in blue. AHI, apnea-hypopnea index; APAP, auto-PAP; CPAP, continuous positive airway pressure; PAP, positive airway pressure; Sx, symptoms; Tx, treatment.

respiratory airflow (nasal pressure and/or oronasal thermistor), respiratory effort, oximetry, and often snoring and body position (eFig. 88-2). Type 4 monitors record oximetry and sometimes one other signal such as airflow, thus yielding less information than type 3 monitors. Type 3 devices in particular are being increasingly used for the diagnosis and management of OSA. Recent guidelines recommend use of portable monitoring for evaluation of moderate- to high-pretest probability patients.¹¹⁰ Positive test results in such patients will rule in a diagnosis of OSA, whereas negative test results do not exclude more subtle forms of disease, and complete PSG should then be performed. Current guidelines do not recommend the use of portable monitoring for OSA diagnosis in the presence of major medical comorbidities or for diagnosis of sleep hypoventilation or central sleep apnea. However, for patients with moderate to severe OSA, data show that the use of portable monitors in ambulatory-based clinical management algorithms results in treatment adherence and clinical outcomes similar to conventional type 1-based approaches¹¹¹ (see “Disease Management Strategies for OSA” section later).

CLINICAL PRESENTATION OF OSA

SYMPTOMS, SIGNS

The classic clinical presentation of OSA is a history of heavy habitual snoring and EDS. However, OSA is a heterogeneous condition and may present with a variety of manifestations, and some patients with even moderate to severe OSA have few if any symptoms. OSA symptoms typically develop over many years in association with aging, weight gain, or onset of menopause and may be underappreciated by the patient.

Table 88-4 Symptoms of Obstructive Sleep Apnea

NOCTURNAL

Heavy, habitual snoring
Apneas witnessed by bed partner
Nocturnal choking
Nocturia
Restless sleep
Sweating
Erectile dysfunction
Gastroesophageal reflux
Unrefreshing sleep
Headache upon awakening

DAYTIME

Excessive daytime sleepiness
Difficulty concentrating
Memory loss
Irritability, personality change
Depressive symptoms
Fatigue

A comprehensive sleep history should be obtained in evaluating patients to assess not only features of OSA but the impact of sleep habits and other potential sleep disorders on clinical symptoms.

Patients with OSA should be questioned about having symptoms at night or during the day (Table 88-4). When possible, the spouse or partner should be questioned as well. During sleep most OSA patients manifest loud, disruptive snoring, which may lead the spouse to sleep in a separate room. Snoring is not a specific symptom for OSA and has a high prevalence in the general population. An important finding is a report by the bed partner of witnessed apneas. Although the frequency or duration of events reported may

not be accurate, a description of episodes during which breathing stops, followed by loud gasping or snoring is highly suggestive of OSA. Patients themselves are often unaware of apneic episodes, and it is surprisingly uncommon for patients to report nocturnal choking or shortness of breath upon awakening. The differential diagnosis for nocturnal choking includes paroxysmal nocturnal dyspnea related to heart failure and Cheyne-Stokes respiration, nocturnal asthma, laryngospasm (idiopathic or due to acid-pepsin reflux), orthopnea due to diaphragm dysfunction, or insular cortical seizures.¹¹² Most patients with OSA do not complain of insomnia, which when present often appears to be a separate process because OSA treatment does not generally reduce complaints of insomnia. However, OSA may rarely present with prominent insomnia symptoms that respond to OSA treatment. Other nocturnal symptoms of OSA include restless sleep, nocturia, enuresis (in severe cases), diaphoresis, and reduced libido and impotence. These symptoms also respond to OSA treatment, suggesting a causal link. Patients may complain of dry mouth upon awakening and a feeling of awakening unrefreshed. Morning headache may be present, which may be associated with nocturnal hypercapnia due to concomitant obesity hypoventilation.

The cardinal daytime symptom of OSA is EDS,¹¹³ defined as a propensity to fall asleep in unwanted situations during normal waking hours. EDS may develop insidiously and be underrecognized by the patient, with many patients describing symptoms of fatigue or lack of energy rather than sleepiness per se.¹¹⁴ Patients undergoing evaluation for OSA should be asked whether they have experienced drowsiness while driving or have fallen asleep at the wheel, because OSA increases the risk for crashes or near misses.^{115,116} Other symptoms of OSA include cognitive impairment such as difficulty with concentration or memory loss, mood disturbances such as irritability or depression, and impaired quality of life (discussed in “[Neurocognitive Complications of OSA](#)” section later).

MEASUREMENT OF SLEEPINESS

Questionnaires

The most commonly used questionnaire to quantify daytime sleepiness is the Epworth sleep questionnaire described earlier (see [Table 88-2](#)).¹³ Values of 11 or higher indicate excessive sleepiness. The Stanford Sleepiness Scale¹¹⁷ asks subjects to rate their degree of sleepiness at a single moment in time, such as just prior to a multiple sleep latency test. Choices range from “feeling active and vital, alert wide awake” to “almost in reverie, sleep onset soon.” This scale has been used more commonly in research, and normative clinical values have not been established, limiting its applicability.

Objective Sleepiness Measurements

Objective measurements can be made in the sleep laboratory during a series of scheduled daytime nap sessions to measure either physiologic sleepiness (multiple sleep latency test) or the ability to remain awake (maintenance of wakefulness test).^{118,119} A more accessible behavioral test that does not require PSG recording (Osler Test) has been found

Table 88-5 Differential Diagnosis of Excessive Daytime Sleepiness

Insufficient sleep (behaviorally induced)
Hypersomnia of central origin
Narcolepsy
Idiopathic hypersomnia
Periodic hypersomnia (e.g., Klein-Levin syndrome)
Sleep-related movement disorders
Restless legs syndrome
Periodic limb movement disorder
Circadian rhythm disorders
Delayed sleep phase syndrome
Advanced sleep phase syndrome
Shift work disorder
Parasomnias
REM sleep behavior disorder
Sleepwalking
Confusional arousals
Sleepiness due to medical disorders, medication, and other conditions

REM, rapid eye movement.

to approximate findings on the maintenance of wakefulness test.^{120,121}

DIFFERENTIAL DIAGNOSIS OF EXCESSIVE SLEEPINESS

Although EDS is a common symptom of OSA, it is important to consider other potential causes of sleepiness ([Table 88-5](#)). The commonest cause of EDS is insufficient sleep duration. This may be due to poor sleep or social habits, the demands of work and family life, unfavorable sleeping environment, or other factors. It is therefore essential to obtain details of usual bedtime, time to fall asleep, number and duration of nocturnal awakenings, usual waking time, and whether wakening is spontaneous or requires one or more alarms. The regularity and timing of work and sleep schedules should also be ascertained. Short sleep duration during the week, with recovery sleep time on weekends is often a sign of insufficient sleep. When habitually present for 3 months or longer, this is termed “insufficient sleep syndrome.”¹² Management involves altering the sleep schedule on a consistent basis to provide adequate nocturnal sleep.

Central Disorders of Hypersomnolence

Other medical sleep disorders may also produce EDS.¹² These include *central disorders of hypersomnolence*, the most common of which is narcolepsy. Narcolepsy typically presents in the second or third decade of life and is characterized by a tetrad of symptoms, including daytime sleepiness, cataplexy, hypnagogic or hypnopompic hallucinations (hallucinations that take place in the transition between wakefulness and sleep), and sleep paralysis.^{122,123} Narcolepsy is a disorder of *rapid eye movement* (REM or stage R) with an “unpackaging” of REM phenomena so that aspects of REM sleep become apparent during wakefulness. Cataplexy is the sudden loss of muscle tone, as takes place in REM sleep, which is precipitated by emotion (laughter, anger, surprise) during wakefulness. Cataplexy is highly specific to narcolepsy and is a virtually pathognomonic symptom, although narcolepsy can be seen without

cataplexy. The atonia of cataplexy can be intense, leading to collapse, and can mimic syncope, though there is no true loss of consciousness. Cataplexy is associated with objective transient areflexia. Hypnagogic or hypnopompic hallucinations are vivid dreams typically with a strong visual component that are experienced either at sleep onset or when awakening from sleep. Individuals with sleep paralysis wake up from sleep unable to move, because they are emerging from REM sleep and the REM-associated atonia has not been switched off.^{122,123} Although particularly common in narcolepsy, sleep paralysis may also be experienced by otherwise healthy individuals.

Excessive sleepiness in narcolepsy is commonly treated with stimulant medication.^{124,125} Modafinil (Provigil) is the drug of choice. When ineffective, alternate stimulants are methylphenidate (Ritalin) or amphetamine preparations.¹²⁴ Improvements in EDS can be associated with improvement in other symptoms such as cataplexy and sleep paralysis, though specific medication may be required. Cataplexy is treated with antidepressants (tricyclic, selective serotonin-noradrenalin reuptake and monoamine oxidase inhibitor classes).^{124,125} Sodium oxybate (Xyrem) is approved for treatment of cataplexy and may also improve nocturnal sleep quality and EDS, although its use is limited by cost and potential side effects.¹²⁶

Periodic Hypersomnia

Klein-Levin syndrome is a rare cause of EDS that usually presents in adolescence and is characterized by intermittent episodes of intense hypersomnia with normal intervening sleep and alertness.^{12,125} The episodes may last for days, and patients may sleep for up to 20 hr/day. Episodes are associated with behavioral abnormalities, including binge eating and hypersexuality. Treatment is usually supportive during the episodes, with a limited role for stimulants; lithium may be effective in some cases.¹²⁵

Idiopathic Hypersomnia

This disorder is a diagnosis of exclusion and is characterized by persistent marked excessive sleepiness despite documented adequate sleep duration and hygiene, frequent daytime napping, subjectively uninterrupted nocturnal sleep, and normal nocturnal PSG recording, without symptoms of another sleep disorder or medical cause for hypersomnolence.¹² Although most patients have prolonged nocturnal sleep, some may not. The ICSD-3 does not distinguish between these two variants.¹² Management is with stimulant medication similar to narcolepsy, although symptoms may be more difficult to control.^{124,125}

Sleep-Related Movement Disorders

Movement disorders during sleep may cause sleep disruption and EDS. The most common is the *restless legs syndrome* (RLS), which is characterized by an urge to move the legs usually accompanied by uncomfortable or unpleasant sensations in the legs that (1) gets worse with periods of physical inactivity or rest, (2) is partially or totally relieved by movement such as walking or stretching, and (3) is worse or is felt only in the evening or night. The timing of symptom onset is such that the patient has difficulty falling asleep until the uncomfortable sensations and urge to move subside, which may be only after 2 to 3 hours after bedtime.

There are several factors that can precipitate or exacerbate RLS, the most common of which is iron deficiency. Serum iron and ferritin levels should be checked in all RLS patients. Caffeine, stimulants, and other medications may exacerbate RLS. RLS is common in renal dialysis and congestive heart failure patients and in patients with neuropathic disorders and may emerge or worsen during pregnancy.¹²⁷ Familial RLS has been described. Genetic studies have identified several loci linked to RLS, though to date these have not led to major insights into etiology, prevention, or treatment.¹²⁸

Treatment of RLS^{129,130} first involves correction of potential precipitating factors, in particular iron replacement if stores are low. A variety of medications may be used to treat RLS, including dopamine agonists such as pramipexole (Mirapex) and ropinirole (Requip),¹³¹ as well as anticonvulsants such as gabapentin and pregabalin.¹³⁰⁻¹³²

Circadian Rhythm Sleep-Wake Disorders

This set of clinical disorders is characterized by disturbances of the internal “biologic clock”¹³³ so that sleep is usually normal, but takes place at abnormal times.¹³⁴ The most common disturbance is delayed sleep-wake phase disorder.^{12,134} Affected individuals are unable to fall asleep until the early morning hours (e.g., 3 AM or later), sleep normally once asleep, and awaken late in the morning (e.g., 11 AM). If able to follow their “natural” sleep schedule, there are few daytime symptoms. However, when work or school imposes a different schedule, sleep time is restricted and daytime sleepiness ensues. Management of delayed sleep-wake phase disorder includes interventions to shift the biologic clock, such as administration of melatonin in the evening and exposure to bright light in the morning.^{134,135} Although changes in sleep schedule can be achieved, the effects may not be dramatic, and patients tend to revert easily to a delayed schedule if circadian measures are not rigorously maintained. Some patients choose occupations or work schedules that are compatible with their delayed phase.

Other circadian disorders include advanced sleep-wake phase disorder, in which sleep begins in the early evening, with early morning awakening. Treatment includes sleep schedule modifications and bright light exposure in the evening.¹³⁵ Jet lag disorder results from circadian misalignment because of travel across time zones with subsequent sleep disruption and daytime symptoms.¹³⁶ Management includes sleep scheduling, appropriately timed light therapy, and possible use of melatonin.^{134,135} Shift work disorder is characterized by more than 1 month of excessive sleepiness during scheduled work time, and insomnia during scheduled sleep times in the context of nonconventional and/or rotating work schedules.¹² Management includes optimizing the sleep environment and sleep schedule, preshift napping, bright light exposure during night shifts, and avoidance of bright light during the return trip home in the morning. Evidence supports the use of melatonin and judicious use of hypnotics to promote sleep, and modafinil and caffeine to promote wakefulness during work.¹³⁵

Other Conditions and Medications

Many medical conditions may be associated with sleep disruption and/or result in excessive sleepiness. These include

nocturnal respiratory disease with nocturnal cough or dyspnea, gastroesophageal reflux, nocturnal urinary frequency, chronic renal failure, various infectious diseases, and chronic pain syndromes.¹³⁷ Psychiatric disorders such as depression may present with excessive sleepiness. Numerous medications can affect nocturnal sleep quality and/or contribute to excessive sleepiness. Thus medication history and potential side effects should be carefully assessed.

NEUROCOGNITIVE COMPLICATIONS OF OSA

PATHOPHYSIOLOGY

A majority of apnea and hypopnea events terminate in association with arousal (see Fig. 88-1). Thus recurrent respiratory events over the course of the night lead to marked disruption of sleep continuity or sleep fragmentation. OSA is also typically associated with a reduction in the duration of deeper, more “restorative” sleep, including stage N3 (slow-wave) and stage R (rapid eye movement) sleep. These characteristic changes in sleep architecture are one factor leading to EDS and other neurocognitive sequelae of OSA. Application of nasal CPAP to treat OSA restores sleep continuity and may be associated acutely with a rebound increase in N3 and stage R sleep, which patients perceive as improved sleep quality.¹³⁸

Although respiratory-related sleep fragmentation alone (i.e., obstructive events without associated oxygen desaturation) can produce EDS, in studies of moderate to severe OSA, sleepiness and other neurocognitive sequelae correlate more closely with OSA-associated hypoxemia than with measures of sleep disruption.^{16,113,139} Studies in mice of cycling intermittent hypoxia mimicking OSA showed that severe hypoxia can produce excessive sleepiness, which persists up to 6 months following return to normoxia.¹⁴⁰ Veasey and colleagues identified neuronal injury in specific wake-promoting areas (monoaminergic neurons in locus coeruleus, periaqueductal gray) in these mice and have shown that injury is mediated by *nicotinamide adenine dinucleotide phosphate*, reduced form (NADPH) oxidase-dependent oxidative injury.^{140,141} Nair and colleagues¹⁴² demonstrated that intermittent hypoxia in mice also induces deficits in learning and memory, with the hippocampus being a particular site of neuronal injury. Neuroimaging studies in OSA patients have demonstrated changes in the hippocampal region and in other areas that subserve cognitive functions known to be impaired in OSA.^{143,144} It is therefore likely the hypoxia-reoxygenation associated with human OSA may produce sleepiness and other neurocognitive changes through similar pathways to those identified in experimental animals. However, debate continues concerning the relative roles of sleep fragmentation and hypoxic-mediated injury in producing OSA-related neurocognitive deficits.^{145,146}

Excessive sleepiness in OSA patients may also be influenced by factors other than those directly related to OSA itself. In addition, several studies have demonstrated that sleep schedule, obesity per se, and depression may all contribute to symptoms of sleepiness in OSA patients.^{147,148}

EXCESSIVE SLEEPINESS, REDUCED PERFORMANCE, AND TRAFFIC /WORKPLACE COMPLICATIONS

EDS is the most common symptom of OSA and can have profound adverse effects on quality of life, social relationships, and professional safety and performance. Patients with untreated OSA and daytime sleepiness are at significantly increased risk for motor vehicle crashes. Two meta-analyses^{115,149} have identified a twofold to threefold increase in risk for vehicular crashes among patients with untreated OSA (e.g., OR, 2.4; 95% CI, 1.2 to 4.9¹¹⁵). A recent meta-analysis found that treatment with positive airway pressure for severe OSA decreased the risk ratio for motor vehicle crashes to 0.28 (95% CI, 0.22 to 0.35),¹⁵⁰ translating into a reduction of between 65% and 78% in crash rate with OSA treatment.

There are important public safety and medicolegal implications of OSA for the practicing physician. The American Thoracic Society has recently published an updated practice guideline on OSA, sleepiness, and crash risk.¹¹⁶ Although the prediction of crash risk in individual OSA patients is imprecise, it is important to identify high-risk patients with symptoms of excessive sleepiness and a previous crash or near miss due to sleepiness. Such individuals should be warned of the dangers of driving before treatment, undergo diagnostic sleep testing within 1 month, and start CPAP treatment following a positive diagnostic test.¹¹⁶ Clinicians should also familiarize themselves thoroughly with legal requirements in their jurisdiction for reporting of OSA and driving restrictions.

One area of particular concern is the increased rate of motor vehicle crashes among commercial drivers.^{151,152} Several studies have shown a high prevalence of OSA among commercial drivers.¹⁵³⁻¹⁵⁵ Although no study to date has demonstrated that OSA leads to increased accident rates specifically among commercial drivers, extension from the general OSA driving literature, combined with the long distances driven commercially raises substantial concern. Screening for OSA is recommended as part of the general medical evaluation for commercial drivers.¹⁵¹ However, such screening relies heavily on self-reporting of sleepiness and OSA symptoms by drivers, who are known to under-report due to concerns about work restrictions.¹⁵⁵ One study suggests that drivers may be more likely to report symptoms if they can do so anonymously online.¹⁵⁶ A multisociety statement includes recommendations concerning OSA screening of commercial drivers and assessment of fitness for duty and return to work following OSA treatment.¹⁵¹

COGNITIVE IMPAIRMENT

OSA is associated with cognitive impairment.¹⁴⁴ OSA produces impairments in attention and vigilance, visuospatial construction abilities, verbal episodic and visuospatial memory, and subdomains of executive function.¹⁵⁷⁻¹⁵⁹ Treatment of OSA can improve global cognitive function, attention/vigilance, verbal and visual memory, and executive function.^{157,159} Most studies have evaluated treatment effects after only a few months, however, so that long-term effects are unknown. The *Apnea Positive Pressure Long-term*

Efficacy Study (APPLES) assessed domains of cognitive function in OSA at 2 and 6 months of effective versus sham CPAP treatment.¹⁶⁰ Improvement was observed in a measure of executive and frontal lobe function at 2 months but was not sustained at 6 months. However, baseline function was high in study participants; further studies on long-term treatment in OSA patients with more marked baseline cognitive impairment are required.

DEPRESSION

Depressive symptoms are common in OSA patients and are more prevalent in women.¹⁶¹ Although epidemiologic studies indicate that the presence of untreated OSA is a risk factor for developing depression,¹⁶² the interaction between depression and OSA remains poorly understood.^{161,163} Depression may worsen symptoms of sleepiness and fatigue in OSA.¹⁴⁸ Although responses are not uniform, some studies report improvement in depression scores with OSA treatment.¹⁶³ The prevalence of OSA among patients with clinical depression is not known,¹⁶¹ but symptoms of OSA should be sought in patients with depression, given the potential beneficial effects of OSA treatment.

OTHER COMPLICATIONS

OSA can lead to erectile dysfunction,^{164,165} which has been linked to nitric oxide and NADPH-related pathways in animal models.^{166,167} Treatment of OSA may improve erectile function.¹⁶⁸

The effects of OSA can have a substantial negative impact on patients' overall quality of life. Disease-specific indices have been developed to assess the impact of OSA on quality of life, including the Functional Outcomes of Sleep Questionnaire,¹⁶⁹ Calgary Sleep Apnea Quality of Life Index,¹⁷⁰ and the Quebec Sleep Questionnaire.¹⁷¹ Studies using these measures indicate that OSA-related impairment can be substantial, and that OSA treatment can significantly improve quality of life.^{172,173}

CARDIOMETABOLIC COMPLICATIONS OF OSA

PATHOPHYSIOLOGY

Obstructive apneas and hypopneas trigger a cascade of acute hemodynamic, autonomic, biochemical, inflammatory, and metabolic effects that can produce both acute and long-term changes in cardiovascular function^{174,175} (Fig. 88-5). Autonomic tone is altered during apneas, with acute sympathetic-mediated increases in blood pressure and heart rate observed at airway reopening¹⁷⁶ (Fig. 88-6). Blood vessel shear stress is also increased due to hypertension and hemodynamic surges. The negative intrathoracic pressures generated during obstructed inspiratory efforts increase left ventricular transmural pressure and therefore afterload, a stimulus for ventricular hypertrophy and an excessive load for a compromised ventricle.¹⁷⁵ The increased sympathetic neural activity during apneas may persist into

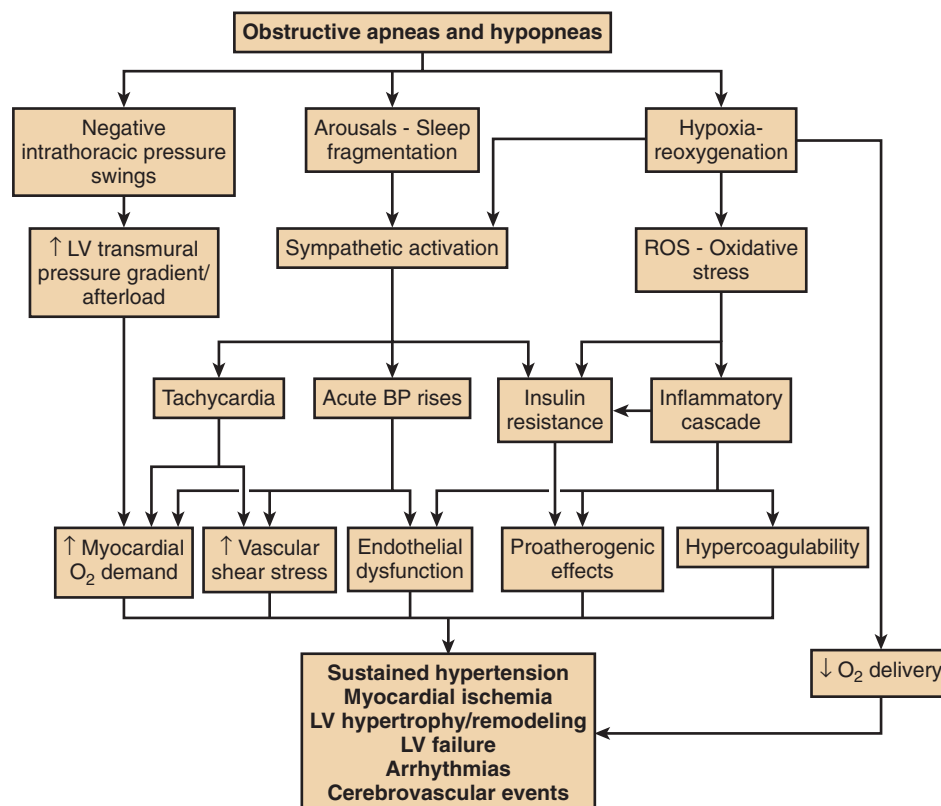


Figure 88-5 Schema indicating mechanisms of cardiometabolic complications of OSA. BP, blood pressure; LV, left ventricular; ROS, reactive oxygen species.

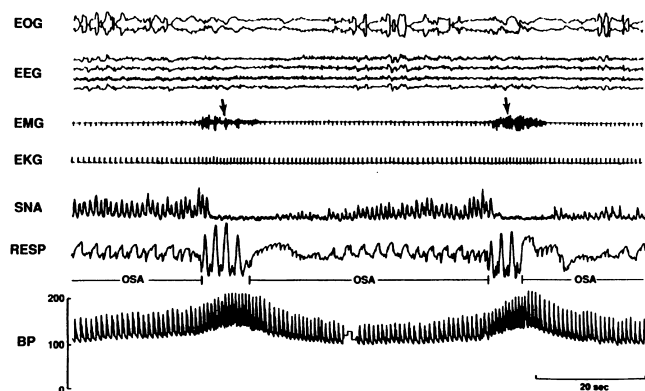


Figure 88-6 Sympathetic nerve activity during obstructive apneas. Tracing demonstrating increased sympathetic nerve activity (SNA) during obstructive apneas together with associated changes in blood pressure (BP) and heart rate. Increase in muscle tone (EMG) and cessation of rapid eye movements (EOG) toward the end of the apneic period indicates arousal from REM sleep (arrows). (Somers VK, Dyken ME, Clary MP, Abboud FM: Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 96:1897–1904, 1995.)

wakefulness, contributing to sustained hypertension. OSA-associated hypoxia-reoxygenation has analogous biologic effects to ischemia-reperfusion, leading to generation of reactive oxygen species.¹⁷⁷ This oxidative stress activates nuclear transcription factors, including hypoxia inducible factor-1 α and nuclear factor- κ B, which activate a diversity of proinflammatory pathways.^{177,178} Inflammatory mediators in turn may adversely affect endothelial cell function¹⁷⁹ and promote atherogenesis,¹⁸⁰ have antifibrinolytic/prothrombotic effects that could contribute to acute vascular events, and, in concert with increased sympathetic activity, may increase insulin resistance, further contributing to cardiovascular risk.^{181,182} Animal studies indicate that intermittent hypoxia can also adversely affect lipid metabolism, further contributing to the proatherogenic effects of OSA.¹⁸⁰ There is growing evidence that, on the basis of these pathophysiologic mechanisms, OSA has important clinical effects on cardiovascular morbidity and mortality.

HYPERTENSION

The evidence linking OSA to cardiovascular complications is strongest for hypertension. Experimental studies have shown that repeated airway obstruction during sleep in dogs induces hypertension during wakefulness¹⁸³ and that intermittent hypoxia produces hypertension in rodents.¹⁸⁴ Cross-sectional studies demonstrate an independent association of OSA with hypertension after controlling for obesity,^{185,186} although findings regarding the development of hypertension in longitudinal cohort studies have been discrepant.^{187–189} Recent observational¹⁹⁰ and interventional¹⁹¹ studies reported reductions in hypertension with OSA treatment. The weight of evidence from randomized controlled studies is that *positive airway pressure* (PAP) treatment improves hypertension. Several meta-analyses have been published.^{192–194} In the most recent,¹⁹⁴ PAP was associated with improvements of -2.6 mm Hg (95% CI, -3.6 to -1.6) in systolic and -2.0 mm Hg (95% CI, -2.8 to -1.2) in diurnal blood pressure compared to control, while noctur-

nal values improved by -4.1 mm Hg (95% CI, -6.2 to -1.9) for systolic and -1.90 mm Hg (95% CI, -3.5 to -0.2) diastolic blood pressure. Although these changes appear small, at the population level they could have significant implications for primary cardiovascular prevention.¹⁹⁵ PAP could have additional vascular protective benefits by alleviating the marked surges in blood pressure that accompany OSA.¹⁹⁴ Several studies have reported a high prevalence of OSA (50% to 60%) in patients with refractory hypertension, with OSA representing the most common cause of secondary hypertension in these patients.¹⁹⁶ Two randomized controlled trials have demonstrated significant improvement in blood pressure with PAP treatment in refractory hypertensive patients with OSA.^{197,198}

ARRHYTHMIAS

OSA is associated with cardiac arrhythmias.^{199,200} Bradyarrhythmias, including sinus pauses and atrioventricular block, are more common in severe OSA than in the general population. Although some data suggest that CPAP may improve bradyarrhythmias, there are no randomized trials demonstrating this.¹⁹⁹ Studies linking OSA to ventricular arrhythmias have produced conflicting results.¹⁹⁹ However, there is growing evidence linking OSA to atrial fibrillation.^{199–201} Atrial fibrillation is more common in individuals with severe OSA than in those without OSA.^{199,202} Untreated OSA is associated with a higher rate of recurrent atrial fibrillation after either cardioversion^{203–205} or catheter ablation.^{205,206} Although randomized controlled trials need to be done to confirm an effect of OSA treatment on control of atrial fibrillation, evaluation for OSA and, if present, institution of treatment should be considered in patients with atrial fibrillation.

MYOCARDIAL INFARCTION

OSA has been associated with ischemic heart disease in epidemiologic studies. In the Sleep Heart Health Study there was a modest association of OSA with coronary heart disease (adjusted OR, 1.3 [95% CI, 1.0 to 1.6]).²⁰⁷ In a meta-analysis of four cohort studies, OSA was associated with a risk for coronary disease of 1.9 (95% CI, 1.1 to 3.5) in men,²⁰⁸ although no significant association was observed in the one study of women.²⁰⁹ However, OSA is reported to be prevalent among patients who have suffered acute myocardial infarction²¹⁰ and, if present, OSA is associated with worse cardiovascular outcomes.^{211–213} In observational studies, coronary patients who accepted OSA treatment suffered fewer subsequent cardiovascular events^{214,215} than those who declined.

Similarly, in unselected OSA patients, compliance with OSA treatment has been associated with reduced cardiovascular morbidity and mortality compared to refusal of treatment.²¹⁶ However, refusal of CPAP may be a marker of poor health behavior that could also adversely affect outcomes. Thus, randomized controlled trials are needed. There are currently at least three large clinical trials being conducted to assess the effects of OSA treatment on incident cardiovascular events (*Sleep Apnea Cardiovascular Endpoints* [SAVE],²¹⁷ *Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea* [RICCDSA],²¹⁸ and CPAP

in Patients With Acute Coronary Syndrome and Obstructive Sleep Apnea²¹⁹). The recently published *Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular (MOSAIC)* trial evaluated the effects of CPAP compared to control on reduction of a surrogate cardiovascular risk score and found that calculated risk was not significantly reduced.²²⁰ However, CPAP was associated with a significant improvement in endothelial function in a subgroup of MOSAIC subjects.²²¹ Follow-up of MOSAIC subjects for long-term “hard” cardiovascular outcomes may yield additional findings. A recent randomized trial by the Spanish collaborative group showed no significant difference over 7 years in the incidence of cardiovascular events and hypertension in CPAP-treated compared to control groups.¹⁹¹ However, there was a significant reduction in events for patients compliant with CPAP for 4 or more hours per night (incidence density ratio, 0.7 [95% CI, 0.5 to 0.9]) compared with control group).

CEREBROVASCULAR EVENTS

Cross-sectional and longitudinal epidemiologic studies show that OSA is associated with stroke.²²²⁻²²⁴ A recent meta-analysis of five studies showed a significant association of OSA with incident stroke (OR, 2.2; 95% CI, 1.6 to 3.2).²⁰⁸ Thus OSA predisposes to stroke, though stroke may also in turn produce or worsen sleep-disordered breathing. However, studies suggest that in many cases OSA preceded the stroke.^{225,226} Overall, OSA is highly prevalent among those with stroke and transient ischemic attacks, with a recent meta-analysis reporting a prevalence of 63% (95% CI, 58% to 68%) for AHI greater than 10 episodes per hour (data from 24 studies).²²⁶ The presence of OSA after stroke appears to confer a worse prognosis for recurrent stroke and poststroke mortality.²²⁷ Treatment of OSA with CPAP in stroke patients may be challenging and, although several studies have suggested that OSA treatment may improve poststroke outcomes, these have methodologic limitations and are not conclusive.²²⁷

CONGESTIVE HEART FAILURE

OSA was found to be associated with congestive heart failure in the Sleep Heart Health Study (OR of 2.4 for the highest category of OSA severity) in the initial cross-sectional analysis²⁰⁷ and with development of new heart failure in longitudinal follow-up.²⁰⁹ OSA has been identified in 11% to 53% of patients with stable chronic congestive heart failure (with central sleep apnea–Cheyne-Stokes respiration also being present in 11% to 35%, yielding an overall apnea prevalence of approximately 50% in congestive heart failure patients).^{175,228} OSA may worsen left ventricular function. Experimentally induced severe OSA in a dog model produced changes in left ventricular dimensions and reduced systolic function after 8 weeks.²²⁹ A recent meta-analysis of six studies evaluating the effects of OSA treatment on left ventricular function showed a significant mean improvement in left ventricular ejection fraction of 5.2% (95% CI, 3.3% to 7.1%).²³⁰ However, randomized controlled trials are required to demonstrate long-term improvement in cardiac function and prognosis with OSA treatment in patients with congestive heart failure.

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) may develop in OSA either secondary to left ventricular hypertrophy and diastolic dysfunction (e.g., in systemic hypertension [postcapillary PH]) or through pulmonary vascular changes related to acute apnea-related hemodynamic changes and hypoxic vasoconstriction^{231,232} (precapillary PH). The prevalence of PH in OSA remains somewhat uncertain. Pooled data from one larger²³³ and several smaller studies totaling 519 OSA subjects yielded a 10% PH prevalence (defined as *mean pulmonary artery pressure* [Ppa] > 25 mm Hg at cardiac catheterization).²²⁸ However, many patients had comorbidities, and the main predictors of PH were daytime PO₂, PCO₂, and reduced lung function.^{233,234} The weight of evidence indicates that the majority of OSA patients without comorbidities have normal Ppa, and PH, when present, is mild.²²⁸ PH can be more severe, but this is almost invariably associated with both underlying lung function abnormalities (*chronic obstructive pulmonary disease* [COPD], obesity restriction, neuromuscular disease) and daytime hypoxemia and hypercapnia.^{228,233-235} Early studies in severe OSA patients showed that Ppa can improve substantially following tracheostomy but may not normalize.^{232,236} There have been few controlled trials assessing the effect of CPAP treatment on PH, though one recent sham-CPAP controlled study showed reductions in echocardiographically determined Ppa systolic pressure from 28.9 ± 8.6 to 24.0 ± 5.8 mm Hg ($P < 0.001$), with the greatest reductions seen in patients with initially elevated Ppa.²³⁷

INSULIN RESISTANCE

There is growing evidence that independent of obesity, OSA is a risk factor for insulin resistance, hyperglycemia, and type 2 diabetes.^{181,182} When one looks at patients with OSA, there appears to be a significantly increased prevalence of insulin resistance and/or hyperglycemia, with prevalence estimates varying from 20% to 67%.^{182,238} In addition, the prevalence of type 2 diabetes in OSA patients is increased compared to those without OSA, with an estimated prevalence of 15% to 30%.¹⁸² When one looks instead at patients with type 2 diabetes, OSA has been found to be highly prevalent, ranging from 58%²³⁹ to 88%.²⁴⁰

A key issue is whether treatment of OSA improves insulin sensitivity and glycemic control. A variety of uncontrolled trials and seven randomized controlled trials involving relatively small sample sizes (reviewed by Pamidi and Tasali¹⁸²) have shown either improvement or no change, so this issue remains unresolved. However, there should be a high level of clinical suspicion for OSA among patients with type 2 diabetes, and treatment of OSA in such patients may have a host of beneficial effects beyond improvement in glucose control.

MORTALITY

In keeping with the links between OSA and cardiometabolic dysfunction, OSA is associated with increased mortality. Most of the increased mortality is cardiovascular and is seen largely in individuals with severe OSA.²⁴¹⁻²⁴⁴ Of note, survival for patients with severe OSA was identical whether

or not patients complained of sleepiness.²⁴¹ This supports the notion that treatment should be offered to nonsleepy patients with OSA.¹⁹¹ Data from two groups suggest that some of the excess mortality in OSA may be related to cancer.^{245,246} Animal studies have shown that intermittent hypoxia and sleep fragmentation may promote tumor growth through vasogenic or other mechanisms.²⁴⁷ However, further research is required to confirm a link between OSA and cancer mortality.

TREATMENT OF OSA

Although there are a growing number of therapeutic options for OSA, the mainstay of treatment for moderate to severe OSA is PAP therapy. However, conservative measures may produce meaningful improvements in some patients with milder OSA, and there is a role for oral appliance therapy and for upper airway surgery in some patients (see Fig. 88-4B).

WEIGHT LOSS AND OTHER CONSERVATIVE TREATMENT

Reductions in weight are associated with an improvement in AHI.^{44,45} Although achieving meaningful sustained weight loss in clinical practice remains challenging, there are three randomized, controlled trials that demonstrate improvements in OSA severity with dietary and/or lifestyle modifications.²⁴⁸⁻²⁵⁰ In one study in patients with type 2 diabetes, diet and lifestyle modification led to a mean reduction of 10.7 kg and 5.5 kg body weight in the intervention group, with a reduction in AHI that was on average 9.7 and 7.7 events per hour greater than control group at 1 and 4 years, respectively.²⁵⁰ At 4 years, OSA had resolved in 21% of the intervention group compared with 3% of the control group. Thus OSA treatment strategies should include a major emphasis on lifestyle modification and weight reduction for obese patients.

There are very few studies addressing the effects of pharmacologic weight-reducing agents on OSA. The addition of sibutramine to diet and lifestyle modification improved OSA,^{251,252} although there are concerns about cardiovascular side effects of this medication. A study in patients with moderate to severe OSA showed that a combination of phentermine and sustained-release topiramate led to significantly greater weight reduction and improvement in AHI (fall of 31.5 versus 16.6 events per hour in controls) at 28 weeks, with few side effects.²⁵³

Bariatric surgery in the morbidly obese can produce dramatic reductions in weight and substantial improvements in OSA.²⁵⁴ A meta-analysis of 12 studies²⁵⁵ found a reduction in mean body mass index from 55.3 to 37.7 kg/m² following bariatric surgery, with a significant fall in mean AHI from 54.7 to 15.8. Of note, however, residual disease requiring treatment (i.e., AHI > 15 events per hour) was still present in 62% of subjects. Thus OSA may be cured following bariatric surgery, but this is not common.

Other conservative measures for management of OSA include avoidance of alcohol or sedatives/muscle relaxants. Up to 50% of OSA patients have a significant positional

component with supine worsening.⁵⁶ For such patients, positioning treatment (tennis balls sewn into a pajama top, dedicated positioning belt, etc.) may be effective. However, this may be poorly tolerated or ineffective in maintaining the supine position, and long-term compliance may be poor.²⁵⁶

ORAL APPLIANCES

The best-studied and most effective intraoral appliances are *mandibular advancement devices* (MADs). These should be custom-made by a dental health professional with specific expertise. Prefabricated (“boil and bite”) MADs are less expensive but less effective. Tongue-retaining devices are also available but less effective.²⁵⁶ MADs compared with placebo improve AHI and daytime sleepiness but are less efficacious in reducing AHI and improving nocturnal arterial SO₂ than PAP.²⁵⁷ Thus MADs are recommended for patients with mild to moderate OSA or for those unable or unwilling to use PAP.²⁵⁸ Patients with severe OSA and/or severe symptoms should have a trial of PAP.^{256,258} A randomized trial of MAD versus CPAP in moderate to severe OSA showed that the MAD was less effective in lowering AHI after 1 month of treatment, but compliance with the MAD was better. The two treatments produced comparable improvements in sleepiness and quality of life.²⁵⁹ Once MADs have been fitted and advanced optimally based on comfort, snoring, and OSA symptoms, a follow-up sleep study should be performed to document effective OSA control.^{256,258}

POSITIVE AIRWAY PRESSURE

PAP therapy in OSA delivers positive pressure to the upper airway via a sealed mask serving as a “pneumatic splint” that distends the airway and prevents collapse during sleep. PAP is highly efficacious and successfully alleviates OSA in a large majority of patients. The standard form of PAP is fixed CPAP, in which a continuous pressure is delivered throughout inspiration and expiration. The conventional, gold-standard approach for determining the effective CPAP level is manual titration during attended PSG (see Fig. 88-6). The effective pressure may vary with body position (higher pressure is usually required in the supine position) and with sleep stage because of greater upper airway muscle atonia during REM. The final pressure prescribed is the lowest level that alleviates respiratory events in all body positions and sleep stages.²⁶⁰

Randomized controlled trials have demonstrated that PAP improves daytime sleepiness and quality of life,^{173,261,262} with the greatest improvements in subjective sleepiness being observed in severe OSA.²⁶¹ However, the *CPAP Apnea Trial North American Program* (CATNAP trial) demonstrated significant improvements in OSA-specific quality of life, sleepiness, and mood with CPAP in patients with mild to moderate OSA.²⁶³ PAP treatment of OSA is associated with a reduced rate of motor vehicle crashes.¹⁵⁰

Improvement in clinical outcomes correlates positively with PAP compliance.²⁶² However, compliance with PAP is challenging for some patients, with long-term estimates varying from 30% to 85%.²⁶⁴ Diverse practical and psychosocial issues need to be considered in optimizing PAP

compliance. Different interfaces are available, including nasal or nasal-oral (full face) masks and intranasal interfaces. Patients may need to try several different masks to optimize seal and comfort. The routine use of in-line heated humidification is recommended to reduce nasal symptoms and improve compliance.²⁶⁵ Educational interventions at CPAP initiation and supportive or cognitive behavioral interventions help improve PAP compliance.²⁶⁴

Compliance can be documented objectively via microprocessors integrated within PAP units. Data on the hours of use, the degree of residual sleep-disordered breathing, and mask leak are available and are generally reliable.²⁶⁶ Objective usage data are more reliable than patients' self-reported compliance. Microprocessor data provide the opportunity to improve compliance through feedback and counseling and to optimize therapy based on objective data (correction of mask leak, pressure adjustment to reduce residual AHI). Adherence early in PAP use is important in predicting long-term use.²⁶⁷ Compliance monitoring and close follow-up after initiation of PAP should be key components of treatment programs.²⁶⁵

Modifications of conventional fixed CPAP pressure profiles have also been developed to improve patient comfort and compliance. *Bilevel PAP* (BPAP) delivers a higher pressure during inspiration and a lower pressure during expiration. This may improve tolerance, particularly in patients with high CPAP requirements.²⁶⁸ For OSA patients who require ventilatory support because of concomitant nocturnal hypoventilation (e.g., due to obesity, COPD, or neuromuscular disease), BPAP both maintains airway patency and provides an increase in inspiratory pressure to augment ventilation.²⁶⁵ Several manufacturers have developed an expiratory pressure reduction option that can be engaged on standard PAP units. Although patient comfort may be improved by pressure profile modification, this does not translate into overall improved compliance.²⁶⁹ Some patients with demonstrated poor compliance may show improved compliance with pressure profile modification.²⁷⁰

PAP devices are now available that continuously self-adjust the pressure to treat OSA based on analysis by an internal microprocessor of flow amplitude reductions, inspiratory flow limitation, and/or snoring.²⁷¹ These are referred to as *auto-PAP* (APAP) or *auto-BPAP*. Although the application of auto-BPAP has been somewhat limited, APAP has assumed a prominent role in the management of OSA. A major advantage of APAP is that OSA patients without major comorbidities can start effective PAP treatment without the requirement for in-laboratory manual titration. In such patients, APAP can be used either to determine a pressure for fixed CPAP after several nights of autotitration, or APAP treatment can be continued long term.²⁷¹ A meta-analysis²⁷² found that CPAP and APAP were equally effective in reducing AHI, although CPAP was slightly superior in improving minimum arterial SO_2 by 1.3% (95% CI, 0.4% to 2.2%) more than APAP. Two meta-analyses^{269,272} found that objective compliance and reduction in Epworth sleepiness score were similar for APAP and CPAP, with a minor, likely clinically insignificant, advantage to APAP. Few studies to date have addressed potential differences in cardiovascular outcomes between CPAP and APAP.

SURGICAL TREATMENT

Surgical procedures that aim to relieve sites of upper airway narrowing have been developed. Overall, the success of surgical treatments for OSA in adults is limited, difficult to predict, and considerably less than with PAP therapy.^{131,256,273} The most commonly applied techniques are aimed at palatal reduction either using conventional surgical methods (uvulopalatopharyngoplasty) or laser-assisted uvulopalatoplasty and radiofrequency-based procedures. Surgeries for nasal and palatal reduction, as well as tongue reduction or tongue advancement surgeries, are referred to as phase 1 surgeries and may be performed in combination ("multilevel surgery") or separately from phase 2 surgeries such as maxillomandibular advancement.

Tracheostomy is an effective treatment for OSA but is recommended only when all other options have been exhausted due to complications and poor patient tolerance.¹³¹ Based on recent reviews,^{256,273} current recommendations are that uvulopalatopharyngoplasty does not reliably normalize AHI in moderate to severe OSA, so that severe OSA patients should be offered PAP and moderate OSA patients should be offered PAP or MAD.¹³¹ Laser-assisted uvulopalatoplasty is not recommended for OSA of any severity, whereas radiofrequency ablation can be considered for mild to moderate OSA patients who are unwilling or unable to tolerate PAP or MAD.¹³¹ The quality of evidence supporting more invasive surgical procedures such as maxillomandibular advancement or multilevel surgery is low, and these procedures are recommended only when alternative treatment approaches have failed.^{131,256} All patients who undergo surgical intervention for OSA should have repeat objective sleep testing after appropriate healing to document OSA resolution.

OTHER TREATMENT APPROACHES

There is currently no definitive pharmacotherapy for OSA.^{274,275} There is limited, short-term evidence that upper airway exercises may be beneficial in mild to moderate OSA, although exercise has to be continued to maintain beneficial effects.²⁵⁶ Expiratory nasal pressure valves (Provent) applied to the nostrils may be effective in mild to moderate²⁷⁶ but not severe OSA.²⁷⁷ Hypoglossal nerve stimulation devices are currently being evaluated for effectiveness in OSA.²⁷⁸⁻²⁸⁰ Although preliminary results are promising, application will likely be limited due to the high cost of neurostimulators. The use of therapies selected on the basis of OSA phenotyping (e.g., oxygen for high loop gain, sedatives to diminish arousal response) is discussed in Chapter 85. To date, however, these approaches have limited practical applicability for moderate to severe OSA.

PERIOPERATIVE CONSIDERATIONS IN OSA

Untreated OSA is associated with an increased risk for perioperative complications.^{281,282} This is related to perioperative administration of sedatives, anesthetics, and opioids,

which increase pharyngeal collapsibility, decrease ventilatory responses to respiratory stimuli, and impair arousal responsiveness.²⁸² In a meta-analysis,²⁸¹ OSA was associated with a significantly increased risk for postoperative cardiac events (OR, 2.1; 95% CI, 1.2 to 3.5), acute respiratory failure (OR, 2.4; 95% CI, 1.3 to 4.4), postoperative desaturation (OR, 2.3; 95% CI, 1.2 to 4.3), intensive care unit transfer (OR, 2.8; 95% CI, 1.5 to 5.4), and a tendency to increased reintubation (OR, 2.1; 95% CI, 0.9 to 4.4). Several societies have made recommendations for evaluation and management of OSA patients in the preoperative, intraoperative, and postoperative periods.²⁸³⁻²⁸⁵ Attention should be paid to preoperative identification of known or high-probability OSA patients. For elective surgery, patients with suspected OSA should undergo diagnostic testing and be established on effective PAP treatment before admission for surgery, with continuation of PAP throughout the hospitalization. Suspected or known OSA patients should be managed perioperatively as “difficult airway” patients, with minimization of opioid use, use of short-acting sedatives/anesthetics, and regional anesthesia when possible. Postoperative monitoring should be performed and PAP applied postoperatively when possible.

DISEASE MANAGEMENT STRATEGIES FOR OSA

Given the high prevalence of OSA and the high costs and limited access in many countries to laboratory PSG,¹⁰⁹ alternate strategies to conventional PSG-based diagnosis and titration in highly specialized centers are needed for management of OSA.^{286,287} Mulgrew and colleagues²⁸⁸ demonstrated that ambulatory-based diagnosis of severe OSA followed by titration using APAP and then treatment with fixed CPAP yielded equivalent clinical outcomes at 3 months compared with a conventional in-laboratory diagnostic and manual titration approach. A series of subsequent publications have supported these findings, with some of the later studies also including more moderate OSA.²⁸⁹⁻²⁹³ All of these studies, however, were conducted in specialty sleep centers and involved traditional interactions between patients and specialized sleep physicians.

Recently Australian investigators evaluated the ability of specialist sleep center nurses to direct algorithm-based ambulatory management of moderate to severe OSA and compared outcomes with traditional PSG and specialist physician-based management. Improvements in Epworth sleepiness scores were noninferior for the nurse-led strategy, and CPAP compliance and other clinical outcomes were also similar.²⁹⁴ This group performed a subsequent study in which the experimental arm was management of OSA by family physicians and community clinic nurse practitioners who had received training from a specialist sleep center.²⁹⁵ The primary care management arm was found to yield noninferior improvement in Epworth scores; CPAP compliance and other clinical outcomes were also similar. Thus ambulatory-based programs for management of moderate to severe OSA in patients without major medical comorbidities are feasible, but need to be conducted within or in close

relationship with specialist sleep centers. A very helpful clinical guideline for OSA diagnosis and management has been published.²⁹⁶

Key Points

- Obstructive sleep apnea (OSA) is a frequent health problem in the general population, estimated to affect approximately 14% of men and 5% of women, with the risk increasing further in women after menopause.
- Pathogenic factors contributing to OSA may differ between individuals and include reduced airway dimensions, sleep-associated decrements in upper airway muscle activity and protective reflexes, changes in upper airway tissue characteristics and neuromuscular function, nocturnal fluid shift, and altered chemosensitivity and arousal responsiveness.
- OSA is associated with daytime sleepiness and increased motor vehicle accidents and may adversely affect cognitive function, mood, and quality of life.
- There is evidence linking OSA to hypertension, arrhythmias, vascular ischemic events, congestive heart failure, pulmonary hypertension, and increased mortality.
- Diagnosis of OSA syndrome rests on both clinical history and a diagnostic sleep recording documenting the presence of obstructive events during sleep.
- The standard of care for moderate to severe OSA is treatment with *positive airway pressure* (PAP). Mandibular advancement devices or surgical intervention may be useful in selected patients.
- OSA is associated with an increased risk for perioperative complications. OSA treatment should be started before elective surgery when possible; patients with known or suspected untreated OSA undergoing emergency surgery should be monitored closely in the postoperative period.
- Technologic advances in diagnostic recording and self-adjusting (auto-PAP) machines have made ambulatory management feasible for OSA patients without major comorbidities.

Complete reference list available at *ExpertConsult*.

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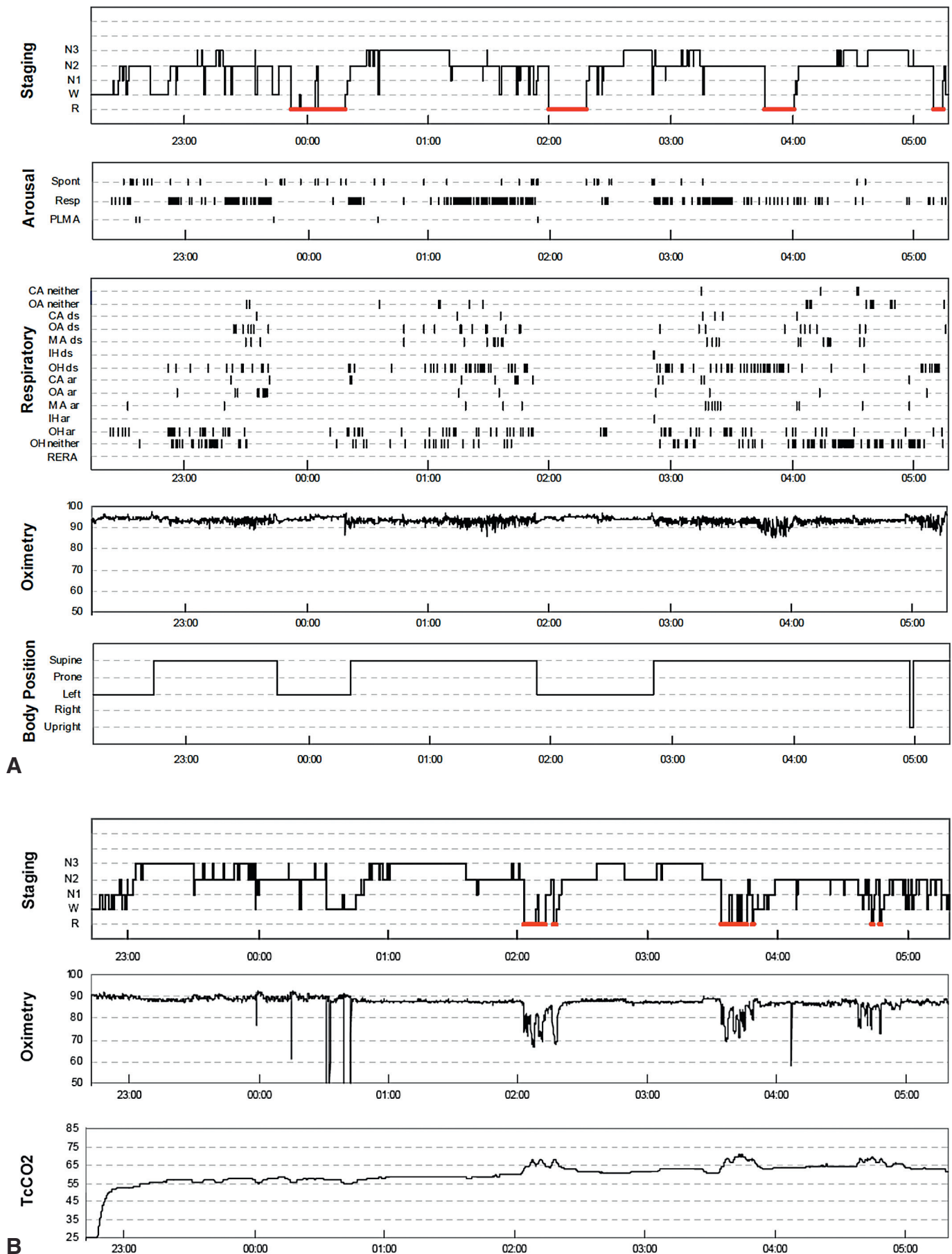


Figure 88-1 Composite hypnograms generated by sleep analysis software after manual scoring by a technologist of sleep-wake stages and respiratory events. A, Typical report from a patient with OSA. In this patient, apneas and hypopneas happen predominantly when the patient is sleeping supine; oxygen desaturation is more marked for events in supine stage R (REM sleep) (red bar) than in stages N (non-REM), which is often the case. **B,** Sleep-associated hypoventilation, with a progressive rise in transcutaneous carbon dioxide (TcCO₂) over the night from an initial value of 54 mm Hg to a peak of 72 mm Hg, with an absence of apneas or hypopneas. There is worsening of hypoventilation during periods of stage R (REM sleep) (red bar), when arterial SO₂ falls and carbon dioxide rises markedly.

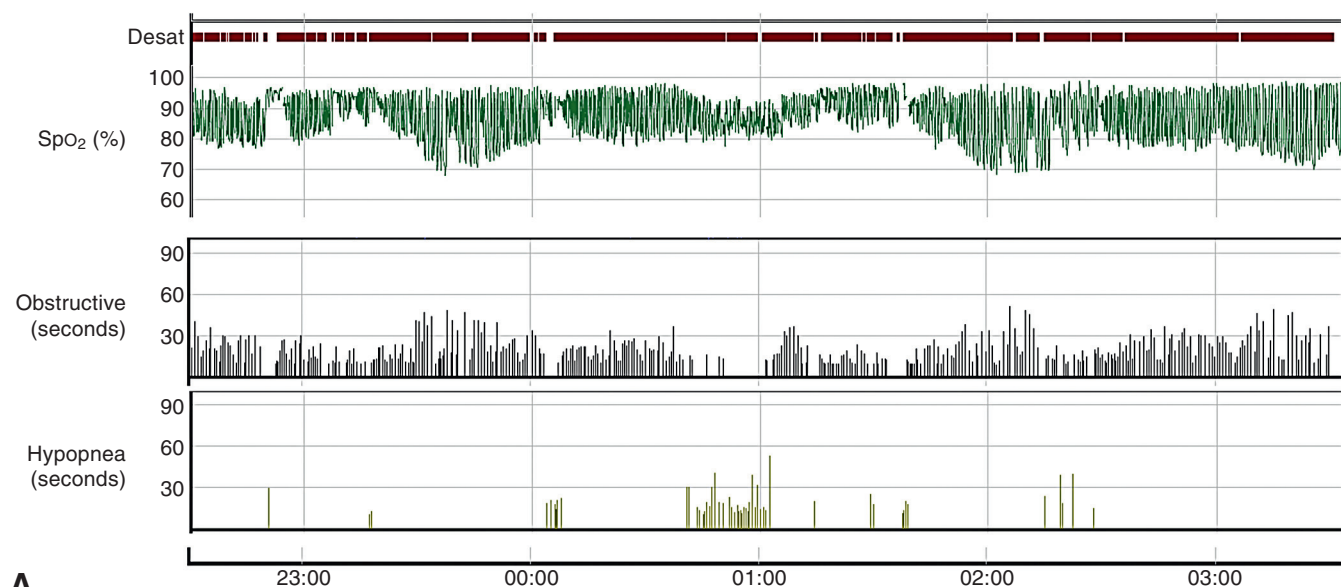
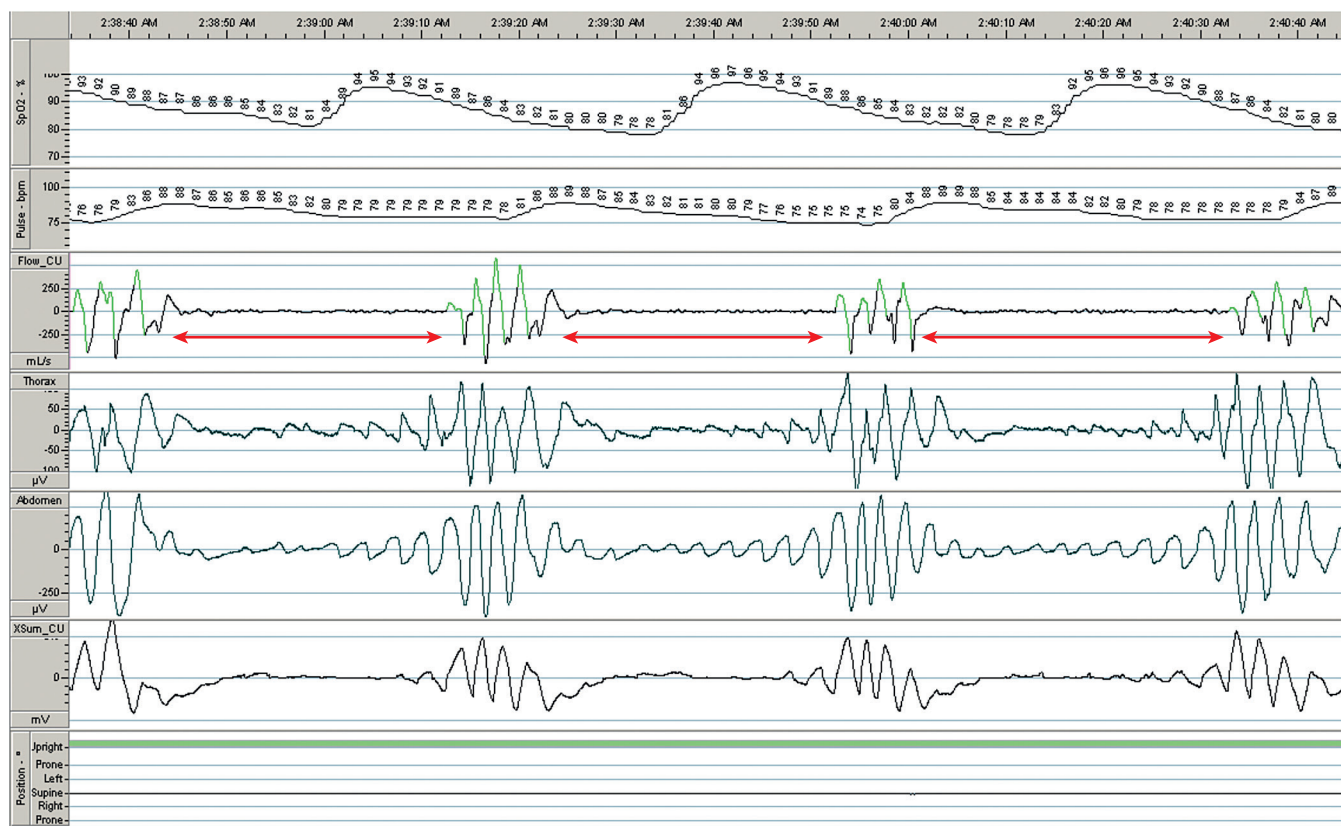
**A****B**

Figure 88-2 Summary data (A) and data tracings (B, apneas shown with red arrows) from a portable type 3 sleep recording performed in a patient's home, demonstrating severe OSA.

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INTRODUCTION DIAGNOSIS OF CENTRAL SLEEP APNEA

CLASSIFICATION OF CENTRAL SLEEP APNEA Hypercapnic Central Sleep Apnea

Nonhypercapnic Central Sleep Apnea

INTRODUCTION

A *central sleep apnea* (CSA) results from a transient abolition of central respiratory drive to the respiratory muscles leading to cessation of airflow; this is most often due to a fall in arterial PCO_2 below the threshold required to stimulate breathing. By convention, in adults, apnea is defined as an absence or reduction of airflow to less than 90% of the baseline level for at least 10 seconds. During a central apnea, there is no respiratory effort and therefore no movement of the chest wall; this is in contrast to obstructive apneas, during which central drive and respiratory efforts continue. Hypopneas can also be part of a CSA disorder. In this case, airflow and tidal volume decrease by 50% to 90% compared with normal breathing for at least 10 seconds usually in association with oxygen desaturation or an arousal from sleep, but without evidence of airflow limitation due to upper airway obstruction. Distinguishing central from obstructive hypopneas can be difficult depending on the type of instrumentation used to detect them (see later for more details).

A CSA disorder is defined as recurrent central apneas and hypopneas during sleep. However, a clear threshold above which a CSA disorder can be said to exist has not been well defined owing to its relative rarity and its heterogeneous pathophysiology, clinical symptoms, and complications. Nevertheless, the following criteria—albeit rather arbitrary—have been proposed to define a CSA disorder: an *apnea-hypopnea index* (AHI) of 5 to 15 (mild), 15 to 30 (moderate), or greater than 30 (severe), of which the majority of events are central. Similarly, criteria for a CSA syndrome have not been clearly defined but include the presence of a CSA disorder accompanied by symptoms, which could include habitual snoring, restless sleep, nocturnal awakenings, morning headaches, insomnia, or excessive daytime sleepiness (Table 89-1).^{1,2}

DIAGNOSIS OF CENTRAL SLEEP APNEA

Full overnight polysomnography with instrumentation capable of detecting respiratory effort and airflow limitation is required to diagnose CSA.^{3,4} Respiratory effort is best determined noninvasively by respiratory inductance plethysmography.⁵⁻⁸ Techniques such as piezo-electric crystal bands, oronasal thermistors, and measurement of nasal pressure are not reliable in ruling out respiratory

efforts and therefore of distinguishing central from obstructive events.⁹⁻¹¹ Most laboratories do not differentiate hypopneas as being central or obstructive, which is a problem because in patients with OSA or CSA, most respiratory events are hypopneas. Thus, in many cases, the classification of the type of sleep apnea disorder is made on the basis of apneas, which constitute a minority of respiratory events. Central hypopneas are characterized by attenuated in-phase thoraco-abdominal motion due to reduced respiratory drive and in the absence of airflow limitation due to upper airway obstruction.³ In some cases, more sensitive techniques may be required to detect the presence of respiratory effort or airflow limitation, such as measurement of esophageal pressure or diaphragm electromyographic activity.^{8,12} The use of oxygen desaturation criteria for hypopneas is controversial because central events in patients with heart failure are accompanied by less oxygen desaturation than obstructive events of similar duration,¹³ and it is unclear to what extent oxygen desaturation contributes to morbidity or mortality.¹⁴

CLASSIFICATION OF CENTRAL SLEEP APNEA

CSA is not a single disease entity but rather includes several heterogeneous disorders as outlined in Table 89-2. Nevertheless, common to all forms of CSA is that arterial PCO_2 comes to lie below the level required to stimulate breathing during sleep (i.e., the apnea threshold). The PCO_2 can be lower than the apnea threshold because of either a decrease in PCO_2 or an increase in the apnea threshold. A CSA caused by an increase in the apnea threshold with onset of sleep is illustrated in Figure 89-1. On the basis of theoretical, experimental, and clinical considerations, two distinct underlying mechanisms can account for cessation of central respiratory output during sleep.

First, outright defects in the respiratory control system or in the respiratory neuromuscular apparatus can lead to central apneas. Such defects generally result in suppressed respiratory drive, manifested by some degree of daytime hypercapnia. However, the full impact of such defects becomes most apparent during sleep, when nonchemical waking neural drive to breathing is abolished, and the stimulatory influence of behavioral, cortical, and reticular inputs to the brain stem respiratory neurons are reduced. In this situation, breathing becomes critically dependent on the defective metabolic respiratory control system, resulting

Table 89-1 Clinical Characteristics of Patients with Central Sleep Apnea

Characteristic	Hypercapnic	Nonhypercapnic
Sex distribution	Equal	Predominantly male
History of respiratory failure	Frequent	Not reported
Peripheral edema and cor pulmonale	Frequent	Not reported
Polycythemia	Frequent	Not reported
Muscle weakness	Frequent	Not reported
Morning headaches	Common	Uncommon
Snoring	Common	Frequent
Nasal obstruction	Uncommon	Common
Hypertension	Uncommon	Common
Nocturnal choking	Uncommon	Common
Nocturnal awakenings and insomnia	Uncommon	Common
Daytime sleepiness	Frequent	Frequent
Restless sleep	Common	Common

From Bradley TD, Phillipson EA: Central sleep apnea. *Clin Chest Med* 13:493–505, 1992.

Table 89-2 Classification of Central Sleep Apnea

Hypercapnic ($\text{PCO}_2 > 45$) (Decreased respiratory drive)	Central alveolar hypoventilation Secondary Brain stem tumors, infarcts Bulbar polio Encephalitis Primary Respiratory neuromyopathy Neuromyopathies Myotonic dystrophy Muscular dystrophy Myasthenia gravis Amyotrophic lateral sclerosis Postpolio syndrome Diaphragm paralysis
Nonhypercapnic ($\text{PCO}_2 \leq 45$) (Normal or increased respiratory drive)	Secondary Congestive heart failure (Cheyne-Stokes respiration) Brain lesions Renal failure Acromegaly Cerebrovascular disease Atrial fibrillation High-altitude periodic breathing Opioid related Complex sleep apnea Primary Idiopathic central sleep apnea

in more pronounced hypercapnia during sleep than during wakefulness.^{15,16} In this case, central apnea is triggered by a fall in PCO_2 below the apnea threshold but in conjunction with a markedly elevated PCO_2 apneic threshold. **Figure 89-2** illustrates a typical central apnea in a patient with hypercapnic CSA: As respiratory drive diminishes during sleep, there is a gradual reduction in tidal volume until breathing stops.

Second, transient fluctuations or instabilities in an otherwise intact respiratory control system can lead to central apneas. These instabilities typically arise during drowsiness and during light, *non-rapid eye movement* (non-REM) sleep

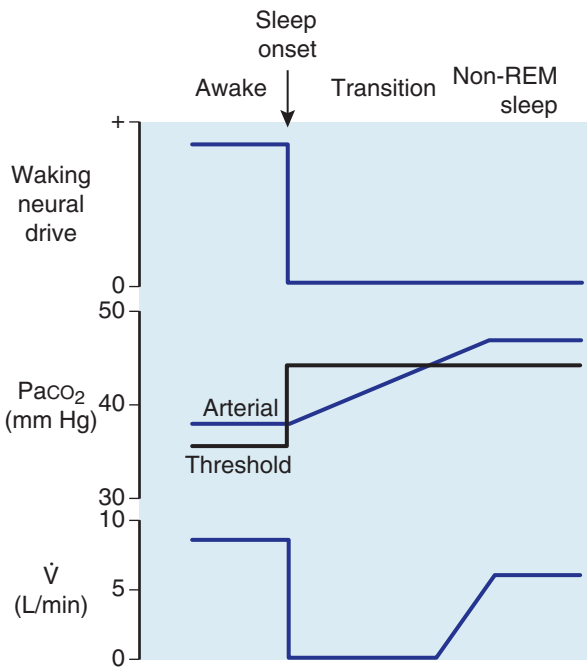


Figure 89-1 Schematic diagram showing a proposed mechanism underlying central sleep apnea at sleep onset. With the loss of the waking neural drive to breathing at sleep onset, there is an increase in the apnea threshold (black line labeled Threshold), the arterial PCO_2 (PaCO_2) required to maintain respiratory rhythm. As a result, the arterial PCO_2 (blue line labeled Arterial) that was present during wakefulness may now be below the threshold arterial PCO_2 for rhythm generation in sleep. Hence, ventilation (\dot{V}) falls to zero and apnea ensues until arterial PCO_2 rises above the threshold level for rhythm generation in sleep, whereupon rhythmic breathing resumes. non-REM, non-rapid eye movement. (From Bradley TD, Phillipson EA: Central sleep apnea. *Clin Chest Med* 13:493–505, 1992.)

and, because there is no suppression of respiratory drive, arterial PCO_2 levels during wakefulness or sleep are normal or low. This type of CSA is typically triggered by a sudden increase in ventilation that causes PCO_2 to fall below the apnea threshold, often due to an arousal from sleep as illustrated in the upper panel of **Figure 89-3**. This type of CSA is characteristically associated with periodic breathing, during which there are regularly recurring alterations in tidal volume between central apneas/hypopneas and hyperpneas. Several theoretical and experimental models have been developed to account for such transient fluctuations in central respiratory drive. Common to all these models is a PCO_2 level during sleep that falls transiently close to (hypopnea) or below (apnea) the critical threshold value required for maintenance of regular respiratory rhythm.

Such transient discrepancies in PCO_2 levels arise in a number of conditions, the most common of which is the transition from wakefulness to sleep. Because of the waking neural drive to breathe, ventilation is higher and PCO_2 levels are lower during wakefulness than during sleep.¹⁶ Withdrawal of this drive at the transition from wakefulness to sleep results in a PCO_2 level that, although appropriate for wakefulness, is below the value appropriate for sleep (see **Fig. 89-1**). If this PCO_2 level of wakefulness is below the threshold value for rhythm generation during sleep, apnea will ensue at sleep onset until PCO_2 rises to the critical threshold value when ventilation will resume. If sleep becomes firmly established at this point, regular breathing

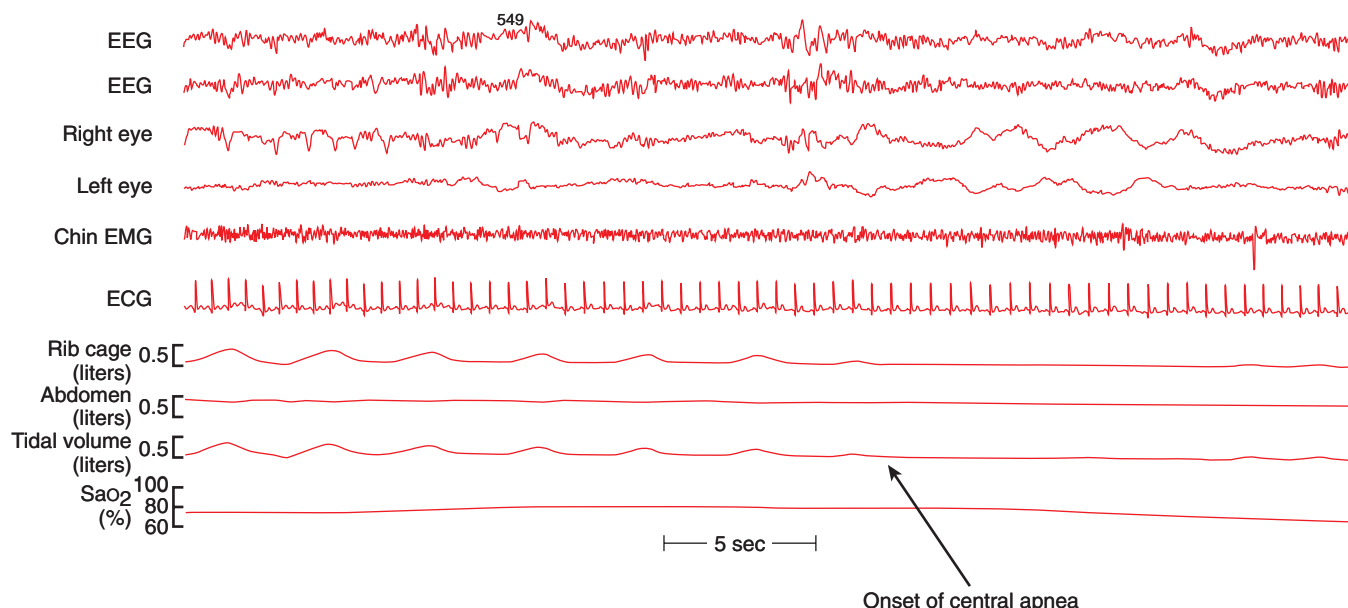


Figure 89-2 Hypercapnic central sleep apnea. Polysomnographic recording of central apnea obtained from a patient with hypercapnic central sleep apnea due to primary central alveolar hypoventilation syndrome. Note the typical gradual reduction in tidal volume just before the onset of the central apnea (arrow) and severe degree of hypoxemia with arterial oxygen saturation (SaO₂) below 80% throughout the recording. ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram.

resumes without further apneas or hypopneas. However, in some individuals prone to periodic breathing, the transition from wakefulness to sleep is characterized by repeated fluctuations in central nervous system state between “awake” and “asleep.” With each momentary arousal from sleep toward wakefulness, the PCO₂ levels that were present during sleep represent a hypercapnic stimulus during wakefulness, and ventilation therefore increases in accordance with the awake response to carbon dioxide, resulting in a hyperpneic phase during which there is ventilatory overshoot causing PCO₂ to fall below the apnea threshold on the transition to sleep. In this scheme, the magnitude of fluctuation in ventilation with changes in central nervous system state depends on the difference between the awake and sleeping values of PCO₂ and the steepness of the ventilatory response to carbon dioxide during wakefulness.¹⁷ Any factor that magnifies these variables enhances the tendency to periodic breathing and CSA.

HYPERCAPNIC CENTRAL SLEEP APNEA

The automatic process of breathing originates from the central respiratory rhythm generator located in the pons and medulla. This central generator provides most of the input to spinal motoneurons responsible for activation of respiratory muscles. Hypercapnic CSA results from processes that damage the cerebral cortex, brain stem, spinal cord, muscles, or motor nerves. CSA with hypercapnia almost always presents as chronic respiratory failure with hypercapnia both during wakefulness and sleep due mainly to a reduction in central respiratory drive. At the transition from wakefulness to sleep, the already reduced central drive is further reduced, causing a gradual reduction in ventilation until there is complete cessation of respiratory drive that leads to transient central apneas (see Fig. 89-2). Coincident with this reduction in ventilation, PCO₂ rises and

arterial SO₂ falls. In contrast to nonhypercapnic CSA, apneas and hypopneas are more frequent during REM sleep than non-REM sleep owing to a further reduction in ventilator drive and partial paralysis of the respiratory muscles in REM sleep.¹⁸

Secondary Forms of Hypercapnic Central Sleep Apnea

Developmental and Degenerative Diseases. The brain stem includes the medulla, midbrain, and pons. Although the central respiratory controller is located predominantly in the medulla, it has projections to other areas of the brain stem. Diseases affecting the brain stem, such as tumors, stroke, Chiari malformations, and neurodegenerative diseases, may induce hypoventilation and CSA via a number of mechanisms such as (1) physical compression of the brain stem resulting in damage to the respiratory center and reticular activating system, (2) stretching of the lower cranial nerves and damage to the peripheral chemoreceptors that carry inputs from the carotid bodies to the medulla, (3) depletion of medullary chemosensitive respiratory neurons,¹⁹ or (4) degeneration of the central pattern generator located in the dorsolateral pons.

Chiari malformations are congenital abnormalities of the craniocervical junction with downward displacement of the cerebellar structures often in association with syringomyelia, myelomeningocele, hydrocephalus, and aqueductal stenosis. Chiari malformations are classified into three types. Chiari malformation type I is characterized by abnormally shaped cerebellar tonsils with herniation below the foramen magnum that is associated with the Klippel-Feil anomaly and spinal cavitations. Type II is characterized by the downward displacement of the cerebellar vermis and tonsils below the foramen magnum with associated obstruction of cerebrospinal fluid flow and hydrocephalus, in addition to a myelomeningocele. Type III is downward

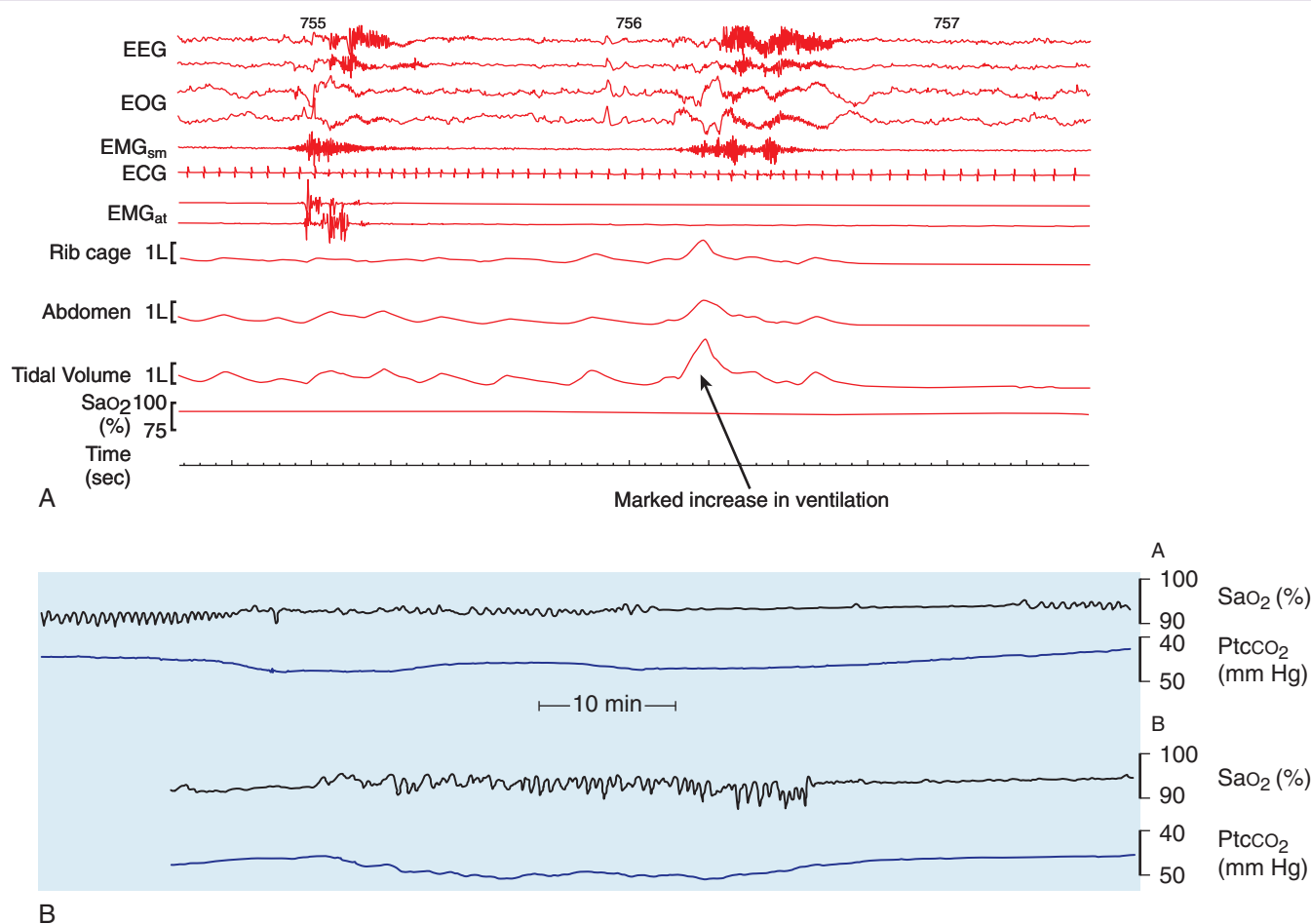


Figure 89-3 Nonhypercapnic central apnea. Upper panel: Polysomnographic recording obtained from a patient with nonhypercapnic central sleep apnea due to idiopathic central sleep apnea (ICSA). Note that in contrast to the central apnea shown in Figure 89-2, central apnea in this case follows an abrupt increase in ventilation (arrow) triggered by an arousal, after which there is an abrupt decrease in ventilation to zero. In addition, note that in contrast to the recording shown in Figure 89-2, arterial oxygen saturation (SaO₂) is within normal limits. **Lower panel:** Compressed records of nocturnal arterial SO₂ and transcutaneous PCO₂ (PtCCO₂) in a patient with ICSA (A) and in a patient with obstructive sleep apnea (B). Record reads from right to left. Note that in patient A, the segments containing recurrent apneas (indicated by oscillations in SaO₂) are preceded by a small decrease in PtCCO₂. In contrast, in patient B the segment containing recurrent apneas is accompanied by a small increase in PtCCO₂. Note also that in the PtCCO₂ scales, an upward deflection of the signal indicates a fall in PtCCO₂ and vice versa. ECG, electrocardiogram; EEG, electroencephalogram; EMG_{at}, anterior tibialis electromyogram; EMG_{sm}, submental electromyogram; EOG, electrooculogram. (Upper panel from Xie A, Wong B, Phillipson EA, et al: Interaction of hyperventilation and arousal in the pathogenesis of idiopathic central sleep apnea. *Am J Respir Crit Care Med* 150:489–495, 1994; Lower panel, Bradley TD, Phillipson EA: Central sleep apnea. *Clin Chest Med* 13:493–505, 1992.)

displacement of the medulla with an occipital or cervical encephalocele. These anatomic abnormalities can lead to degeneration of brain stem respiratory neurons with resulting hypoventilation and, in some cases, CSA.

In those with type I Chiari malformation, a prospective study in children showed a prevalence of CSA of 9%, with an increased risk of CSA in those with hydrocephalus.²⁰ In adults with Chiari malformations (types I and II), CSA prevalence was reported to be 15%.²¹ In a small cross-sectional study of patients with Chiari malformation type II and associated myelomeningocele, the prevalence of CSA was much higher: 63%.²²

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disease with an incidence of approximately 1 in 200,000 live births, caused by a mutation of the *PHOX2B* gene.^{23–25} The majority of cases present in the neonatal period or in early childhood with acute or chronic respiratory failure as a result of a loss of respiratory drive. However, it may present de novo in adults following a severe

respiratory infection with combined central and obstructive sleep apnea (OSA).^{26,27} A diagnosis is considered only in those in whom metabolic, neurologic, pulmonary, and medication-induced disorders have been excluded. When CCHS is suspected, the *PHOX2B* screening test is recommended for purposes of genetic counseling.^{28,29}

Neurodegenerative diseases of the brain stem including multiple system atrophy, Leigh syndrome, and Parkinson disease can be accompanied by CSA.^{30–32} Prevalence rates vary depending on the severity of the disease. In one study, 80% of subjects had sleep apnea, of whom 20% had CSA.³³ In patients with multiple sclerosis, a demyelinating disease that can affect both the brain stem and spinal cord, CSA may develop in those with medullary lesions affecting the respiratory neurons.³⁴ The prevalence of CSA in such patients is, however, unknown.

Tumors. There have been fewer than a dozen documented cases of CSA associated with brain stem tumors, suggesting

that tumors are a rare cause of hypoventilation with CSA.³⁵⁻⁴¹ Tumors such as gliomas, meningiomas, astrocytomas, or neurofibromas have been implicated. The tumor type is probably less important than its location, which usually involves the medulla or pons. In a retrospective 8-year series of children with brain stem tumors referred for assessment to a sleep clinic, CSA was found in 14% (2 out of 14).³⁷

Cerebrovascular Disease. CSA can also result from stroke. The stroke location associated with hypercapnic CSA is usually the nucleus tractus solitarius region of the medulla responsible for neural output to the diaphragm.⁴²⁻⁴⁵ Prevalence is probably low because there are only a small number of cases reported in the literature. Interestingly, in Fabry disease, an X-linked recessive multisystem disease characterized by vasculopathic changes and ischemia, CSA was reported in 22% of those with white matter lesions in the brain stem.⁴⁶

Neuromuscular Diseases. Muscular dystrophies, myotonic dystrophy, and other types of inherited and acquired myopathies may result in hypoventilation and hypercapnic CSA. These diseases impair inspiratory muscle function including the diaphragm, leading to alveolar hypoventilation. At the transition from wakefulness to sleep, the associated reduction in ventilatory response to carbon dioxide and hypoxia, combined with the loss of respiratory muscle tone can lead to apneas without respiratory effort (i.e., CSA).^{18,47} Although some central output to the respiratory muscles may be present, and therefore, strictly speaking, events may not be central in origin, the muscles are unable to respond, so there is either markedly reduced or no muscle force generation. The resulting hypopneas and apneas have the appearance of central events. From the clinical viewpoint, it is reasonable to classify these as hypercapnic CSA because their treatment is similar to that for CSA arising from an absence of central drive.

Many of these disorders present in childhood. Although phenotypically variable, most individuals develop progressive muscular weakness and hypoventilation over time. In addition to the high prevalence of hypoventilation, between 20% and 60% of both adults and children develop CSA.⁴⁸⁻⁵⁰ When there is associated cardiomyopathy and heart failure, nonhypercapnic *Cheyne-Stokes respiration* (CSR)—CSA may also be seen in myotonic dystrophy or Duchenne muscular dystrophy.^{51,52}

Diseases of the motor neurons include amyotrophic lateral sclerosis, spinal muscular atrophy, and postpolio syndrome. With degeneration of the respiratory motor neurons, there can be hypoventilation and CSA. The prevalence of CSA is reported to be approximately 18% in amyotrophic lateral sclerosis⁵³ and approximately 5% in postpolio syndrome.⁵⁴

Myasthenia gravis is a disease of the postsynaptic neuromuscular junction. The reported prevalence of CSA in myasthenia gravis is highly variable (0% to 35%) and is probably dependent on disease severity.^{49,55,56}

Primary Hypercapnic Central Sleep Apnea

Primary Central Alveolar Hypoventilation Syndrome. This rare syndrome presents as chronic hypercapnic respiratory failure with normal respiratory mechanics, chest

wall configuration, and muscle strength in the absence of any of the previously mentioned secondary causes. The primary abnormality giving rise to hypoventilation is reduced sensitivity of the central and peripheral chemoreceptors.⁵⁷ In some cases, this may be due to CCHS.⁵⁸ There have only been a few cases of CSA described in association with primary central alveolar hypoventilation syndrome.^{18,59} This diagnosis is made only following the exclusion of other causes of CSA and hypoventilation syndromes, including CCHS.

Clinical Features

As indicated in Table 89-1, patients with hypercapnic CSA characteristically present with a clinical picture dominated by symptoms and sequelae of chronic respiratory failure with hypercapnia and hypoxemia that can include cyanosis, polycythemia, peripheral edema, and cor pulmonale.² Patients may present at variable time points following the onset of the underlying disease. Symptoms suggestive of CSA may include snoring, restless sleep, morning headaches, excessive daytime sleepiness, and fatigue. However, some patients with hypercapnic CSA may not have symptoms suggestive of a sleep apnea syndrome.²

Treatment

The initial approach to treatment of hypercapnic CSA is to determine the underlying cause. In some cases, treatment and/or correction of the underlying etiology will alleviate the CSA. For example, in those with tumors compressing the pons or medulla, resection may abolish CSA.⁶⁰ Surgical treatment of Chiari II malformations is dependent on the severity of the malformation, and despite posterior fossa decompression for the Chiari II malformation, CSA will often persist.²² In acute stroke patients, no specific intervention is usually required for CSA because recovery may accompany improvement from the stroke. However, if respiratory failure and CSA persist, specific therapy for these conditions may be indicated as described later. For those with neuromuscular disease, pharmacologic therapies available for some inherited myopathies or myasthenia gravis may also alleviate CSA by improving muscle strength.⁶¹

In most patients the management of CSA is the same as for chronic alveolar hypoventilation syndromes. However, few studies have specifically addressed the treatment of hypercapnic CSA. The main aim of treatment is to augment ventilation and thereby improve gas exchange and abolish CSA.

It is important that patients be cautioned against the use of sedative medications that can induce acute respiratory failure and aggravate CSA. In patients with CSA in association with central alveolar hypoventilation, a trial of the respiratory stimulant, medroxyprogesterone, can be tried but is usually successful in only a minority of patients.⁶² Supplemental nocturnal oxygen may alleviate hypoxia and CSA and may even lower PCO₂ if hypoxia is a cause of central nervous system depression.^{57,59} However, supplemental oxygen can also abolish hypoxic respiratory drive and worsen CSA. Therefore, a trial of supplemental oxygen should be accompanied by careful monitoring of PCO₂ and either Po₂ or arterial SO₂.

Where pharmacologic therapies are unavailable or ineffective, noninvasive ventilation is often indicated, either via

bilevel positive airway pressure support ventilation (BiPAP) or volume-cycled ventilators.⁶³ The aim of noninvasive ventilation is to reduce PCO_2 below 45 mm Hg while awake and below 50 mm Hg while asleep while maintaining arterial SO_2 greater than or equal to 90%. This is best achieved by performing polysomnography during a trial of noninvasive ventilation in which transcutaneous PCO_2 or fraction of end-tidal CO_2 and arterial SO_2 are monitored. It is sometimes possible to maintain normal gas exchange during both sleep and wakefulness through noninvasive ventilation only during sleep. If the underlying disease progresses despite the previously mentioned measures, tracheotomy and invasive mechanical ventilation may be required. Unfortunately, there are no randomized trials or long-term observational studies that have determined the effects of noninvasive and invasive mechanical ventilation on morbidity, mortality, and quality of life in patients with hypercapnic CSA.

NONHYPERCAPNIC CENTRAL SLEEP APNEA

The clinical picture of nonhypercapnic CSA differs in many ways from that of hypercapnic CSA (see Table 89-1). This table is based mainly on symptoms related to idiopathic CSA. Nevertheless, symptoms related to the many secondary forms of nonhypercapnic CSA are, in general, similar.

Secondary Forms of Nonhypercapnic Central Sleep Apnea



Central Sleep Apnea in Association with Heart Failure—Cheyne-Stokes Respiration. An expanded discussion of the pathophysiology of respiratory dysfunction in CSR-CSA is available online at ExpertConsult.

CSA in heart failure is manifest by a Cheyne-Stokes respiratory pattern that can exist during both sleep and wakefulness. Because this chapter focuses on central apnea during sleep, we discuss Cheyne-Stokes respiration with central apneas during sleep and refer to it as CSR-CSA (see also Chapter 85). CSR-CSA is distinguished from other forms of CSA and periodic breathing by its characteristic crescendo-decrescendo pattern of tidal volume in which hyperpneas are markedly prolonged compared with those without heart failure owing to reduced cardiac output and prolonged lung to chemoreceptor circulation time (upper panel of Fig. 89-4). Therefore, a finding of CSR-CSA on a polysomnogram is highly suggestive of low cardiac output and the presence of cardiac dysfunction.

Mechanisms that mediate CSR-CSA remain incompletely understood. However, as in all other forms of nonhypercapnic CSA, central to the process is respiratory control instability resulting from the dependence of the sleep state on metabolic control of ventilation, especially PCO_2 .² A proposed pathophysiologic scheme for CSR-CSA is illustrated in Figure 89-5.

In heart failure, a key factor destabilizing the respiratory control system and predisposing to CSR-CSA is the presence of chronic hyperventilation that lowers arterial PCO_2 both during wakefulness and sleep and maintains it close to the apnea threshold. Because arterial PCO_2 is closer to the apnea threshold than normal, small perturbations, such as arousals from sleep that augment ventilation, may be sufficient to drive arterial PCO_2 below the apnea threshold and trigger

central apneas. The main factor contributing to this instability and hyperventilation is increased loop gain. *Loop gain* is an engineering term first used in the context of sleep-disordered breathing in a mathematical model developed to explain factors involved in the instability within the respiratory control system in patients with CSR-CSA.⁶⁴ Simply put, it is the ratio of ventilatory output to a given stimulus. Ventilation becomes unstable when loop gain is elevated so that the ventilatory output for a given stimulus is higher than normal. So, for example, if central sensitivity to carbon dioxide is augmented, any given increase in PCO_2 will cause a greater than normal increase in ventilation that can then drive PCO_2 close to, or below, the apnea threshold.

It appears that low cardiac output and prolonged circulation time are not crucial to the pathogenesis of the central apneas because there is evidence that cardiac output in heart failure patients with CSR-CSA does not differ significantly from that in heart failure patients without CSR-CSA.⁷⁴ Moreover, in dogs, prolongation of lung-to-carotid body circulation time only precipitated period breathing in a minority of experiments and then only when circulation times approached 1 minute or longer, a time far exceeding that observed in human heart failure.⁷⁵ However, these factors play a role in sculpting the crescendo-decrescendo pattern of hyperpnea because the rate of rise of tidal volume and the duration of the hyperpnea are directly proportional to lung to chemoreceptor circulation time and indirectly proportional to cardiac output.⁷⁶ As a consequence, in patients with heart failure, cardiac output is lower and lung-to-chemoreceptor circulation time, hyperpnea, and periodic breathing cycle duration of CSR-CSA are longer than they are in CSA in patients without heart failure (see Fig. 89-4).⁷⁶

Heart failure is a prevalent condition affecting approximately 1.5% of the general population.⁷⁷ Among patients with symptomatic heart failure, earlier studies involving only men reported a prevalence of CSR-CSA of approximately 40%.⁷⁸ However, more recent epidemiologic studies involving both men and women with heart failure have shown a substantially lower prevalence of CSR-CSA of 15% to 26%,⁷⁹⁻⁸² probably because CSR-CSA is uncommon in women. CSR-CSA also appears to be common in patients with asymptomatic left ventricular systolic dysfunction.⁸³ Risk factors for CSR-CSA include older age (>60), male sex, atrial fibrillation, awake hypoxemia ($PCO_2 \leq 38$ mm Hg), diuretic use, more severe heart failure defined by lower left ventricular ejection fraction, higher New York Heart Association class, higher brain natriuretic peptide level, higher pulmonary capillary wedge pressure,⁶⁶ and higher left ventricular end-diastolic volume.^{78-80,82,84}

OSA and CSA can coexist in patients with heart failure. In a significant minority of patients, there may be a shift between the two types of apnea overnight or over longer periods.^{74,85-87} The shift from predominantly obstructive to central events is associated with reductions in the PCO_2 and prolongation of circulation time and the hyperpnea phase.^{86,87} This suggests a deterioration in cardiac output and elevation in left ventricular filling pressure as a result of the adverse hemodynamic effects of OSA.⁸⁸ Conversely, the shift from central to OSA is associated with improvements in left ventricular ejection fraction and shortening of circulation time.⁸⁵ These observations suggest

Although a detailed discussion of loop gain is beyond the scope of this chapter, several factors interact to increase the tendency to respiratory instability and hyperventilation: (1) increased peripheral and central chemoresponsiveness⁶⁵; (2) elevated pulmonary capillary wedge pressure that causes pulmonary congestion and activation of the pulmonary juxta-capillary irritant receptors that augment central drive and ventilation⁶⁶; (3) impaired cerebral vascular reactivity and blood flow responses to changes in the arterial PCO_2 , leading to instability of breathing.⁶⁷⁻⁶⁹ Whereas this has been proposed as a mechanism for ventilatory instability, it requires a differential effect of PCO_2 on the cerebral arterial and venous vessels that has not been fully demonstrated or explained. Consequently, this potential mechanism remains controversial and not fully established; (4) sleep state instability in which arousals from sleep during the hyperpneic phase of CSR-CSA cause a transient awakening with an associated engagement of the wakefulness drive to breathe, increased chemosensitivity, and a lower arterial PCO_2 apnea threshold.^{70,71} Unlike in OSA, in which arousals happen at apnea termination and contribute to airway opening and resumption of airflow, arousals following central apnea generally develop several seconds after resumption of airflow but before the peak of hyperventilation.⁷² Thus they appear not to have the same protective role as they do in OSA. Indeed, recurrent arousals during the ventilatory phase have been shown to trigger and propagate CSR-CSA.^{70,73}

CSR-CSA is typically seen during non-REM sleep and resolves or becomes less prominent in REM sleep^{2,70} because of several reasons. First, breathing is predominantly under metabolic control during non-REM sleep and is therefore highly dependent on arterial PCO_2 . Thus, reductions in arterial PCO_2 below the apnea threshold will invariably give rise to central apneas. However, breathing is largely independent of metabolic control during REM sleep, so it is not nearly as dependent on arterial PCO_2 as in non-REM sleep. Second, ventilatory responses to carbon dioxide and hypoxia are brisker in non-REM than in REM sleep, so the potential to hyperventilate is greater in the former than in the latter state. Third, arousal thresholds for arterial PCO_2 and arterial PO_2 are significantly lower in non-REM than in REM sleep. Thus, people are more arousable and therefore more prone to respiratory control system instability in non-REM than in REM sleep. Fourth, the respiratory muscles, save for the diaphragm, are essentially paralyzed in REM but not non-REM sleep. Thus, for any given chemical (e.g., arterial PCO_2) or nonchemical (e.g., arousal) stimulus, the augmentation in ventilation will be greater in non-REM than in REM sleep, making hyperventilation more likely in the former state.

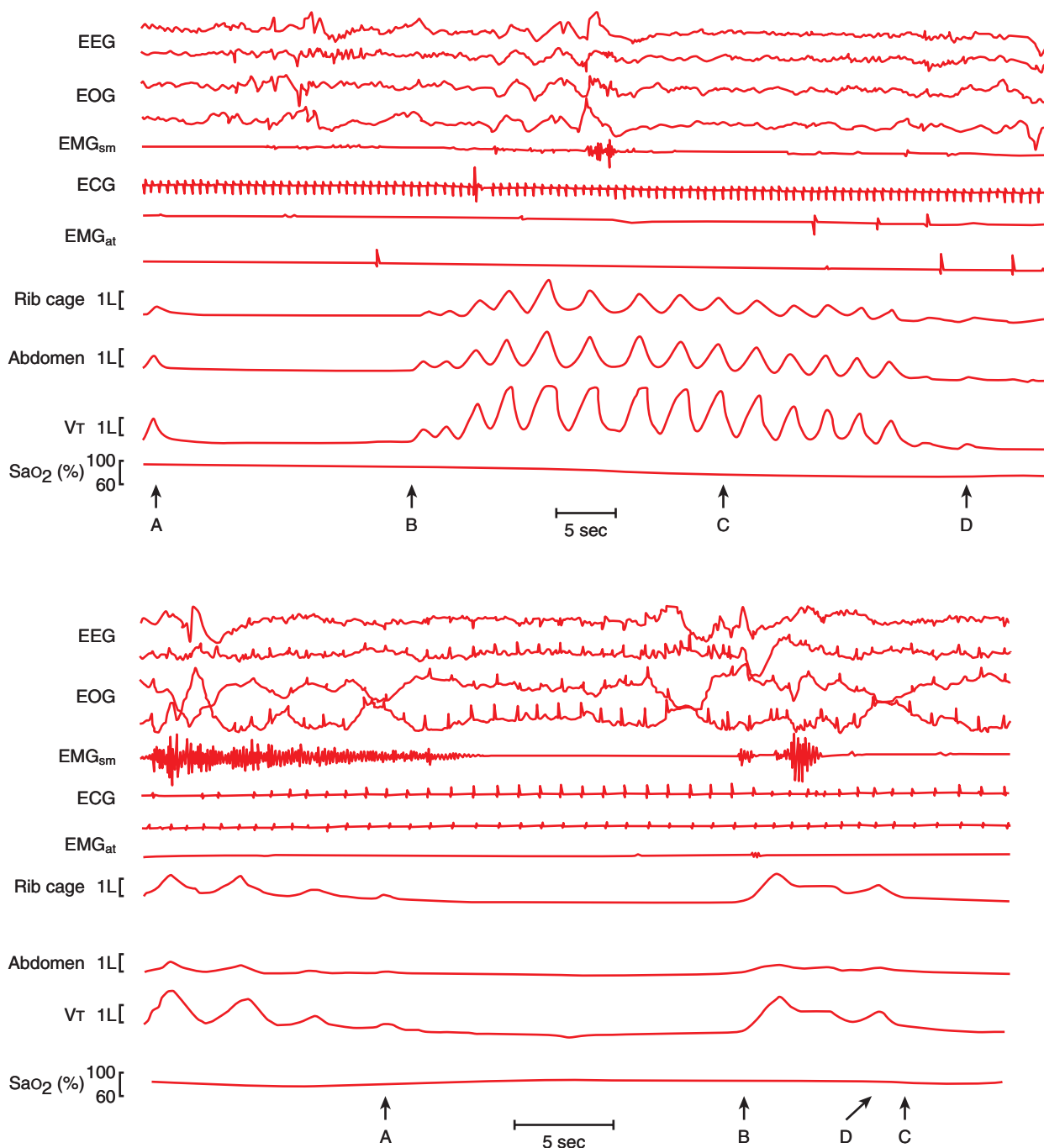


Figure 89-4 Nonhypercapnic central apneas: Cheyne-Stokes and idiopathic CSA. **Upper panel:** Polysomnographic recording of Cheyne-Stokes respiration with a central sleep apnea (CSR-CSA) in a patient with heart failure. Note the absence of rib cage and abdominal motion when there is no tidal volume (VT) excursion, indicating an absence of central respiratory drive. Following apnea, there is a crescendo-decrescendo pattern of VT typical of CSR-CSA in association with a prolonged periodic cycle duration. A and B are the beginning and end of the apnea, respectively. C is the lowest arterial oxygen saturation (SaO₂), so B to C represents the time taken for the lowest arterial SO₂ in the lung at end apnea to be detected by an oximeter placed on the ear (i.e., lung-to-ear circulation time). D is the end of the hyperpnea. Compared with the subject with idiopathic CSA (ICSA) shown in the lower panel, apnea duration in the patient with CSR-CSA (A to B) is similar (21 seconds), but lung-to-ear circulation time (B to C = 26 seconds), total cycle duration (A to D = 65 seconds), and hyperpnea duration (B to D = 46 seconds) are much longer. This is due to lower cardiac output in this patient because total cycle and hyperpnea durations, as well as lung-to-ear circulation time, are inversely proportional to cardiac output. **Lower panel:** Polysomnographic recording of a central apnea in a patient with ICSA. Note that compared with the patient with CSR-CSA in the upper panel, apnea length is similar (A to B = 18 seconds), but lung-to-ear circulation time (B to C = 8 seconds), total cycle duration (A to D = 25 seconds) and hyperpnea duration (B to D = 7 seconds) are much shorter. ECG, electrocardiogram; EEG, electroencephalogram; EMG_{at}, anterior tibialis electromyogram; EMG_{sm}, submental electromyogram; EOG, electrooculogram. (From Hall MJ, Xie A, Rutherford R, et al: Cycle length of periodic breathing in patients with and without heart failure. *Am J Respir Crit Care Med* 154(2 Pt 1):376–381, 1996.)

One factor that might contribute to poor prognosis in CSR-CSA is elevated sympathetic nervous system activity that is known to have a deleterious effect on the prognosis of patients with heart failure.¹⁰² There is evidence that CSR-CSA increases sympathetic nervous activity both during sleep and during wakefulness,¹⁰³ probably via intermittent apnea-related hypoxia and arousals from sleep.¹⁰⁴⁻¹⁰⁶ High sympathetic nervous activity induces activation of the aldosterone-renin pathway and reduces myocardial contractility over time due to abnormalities in calcium handling with precipitation of cardiac arrhythmias.⁸³ It is this combination of autonomic dysfunction and propensity to arrhythmias and sudden death that are the presumed mechanisms by which CSA contributes to increased mortality in heart failure.^{79,107}

On the other hand, there is some evidence that CSR-CSA does not cause adverse hemodynamic effects in patients with heart failure. A recent study demonstrated that in contrast to obstructive apneas, during which stroke volume and cardiac output decrease, during central apneas, stroke volume and cardiac output actually increase slightly.⁸⁸ The cause of this effect was not identified, but this observation raises the possibility that under certain circumstances, CSR-CSA may provide some compensatory effect for low cardiac output and may not be entirely detrimental to cardiovascular function.

Treatment

Because few symptoms have been attributed to CSR-CSA, symptomatic targets for therapy are difficult to identify. However, because CSR-CSA is associated with increased risk of morbidity and mortality, a logical aim in treating CSR-CSA would be to reduce morbidity or mortality. Nevertheless, no treatments have been shown to affect these outcomes in randomized trials. Thus, because there are no clear-cut indications for treating CSR-CSA, a decision to treat CSR-CSA rests on clinical judgment and the following possibilities can be considered with the proviso that therapies that reduce the severity of CSR-CSA may not lead to improvements in patient symptoms, quality of life, or long-term outcomes. All interventions in current use for CSR-CSA require further study to assess their long-term effectiveness and safety.

Treatment of Heart Failure

Because CSR-CSA arises as a consequence of heart failure, it is reasonable to optimize pharmacologic and device treatments for the underlying heart failure. A few nonrandomized observational studies suggest that angiotensin-converting enzyme inhibitors,¹⁰⁸ β -blockers,¹⁰⁹ and cardiac resynchronization therapy¹¹⁰ may reduce the severity of CSR-CSA in CHF. However, these findings have not been confirmed in randomized trials, and one large epidemiologic study showed no reduction in frequency or severity of CSR-CSA with institution of β -blockers.⁷⁹ In one study, atrial overdrive pacing led to a reduction in the AHI in patients with bradyarrhythmias and CSA, but without heart failure.¹¹¹ However, these findings have not been reproduced. In another small study, it was reported that cardiac transplantation for end-stage heart failure reduced severity of CSR-CSA.⁷³ Although consideration can be given to the implementation of one or more of the previ-

ously mentioned approaches, none of them is specifically indicated for therapy of CSR-CSA, and their use should be reserved to treat the underlying heart failure as required.

Positive Airway Pressure

Continuous Positive Airway Pressure. *Continuous positive airway pressure* (CPAP) has been studied extensively in patients with heart failure and CSR-CSA. Its acute application in patients with heart failure increases intrathoracic pressure, thereby reducing right and left ventricular volumes (i.e., preload), left ventricular transmural pressure (i.e., afterload), and the work of breathing by unloading the inspiratory muscles.^{103,112} It also augments stroke volume and cardiac output in those with elevated left ventricular filling pressures but has the opposite effect in those with normal or reduced left ventricular filling pressures.¹¹³

Several small randomized trials in heart failure patients with CSR-CSA lasting 1 to 3 months have demonstrated that CPAP reduces the AHI by 50% to 60%.^{103,114} The means by which it reduces the AHI are not well understood but may include raising lung volume, thereby increasing the lung O₂ reservoir and thus dampening fluctuations in PaO₂, reducing lung water and thus pulmonary irritant receptor stimulation, and reducing ventilation and allowing arterial PCO₂ to rise above the apnea threshold.¹⁰³ Other small randomized trials in heart failure patients with CSR-CSA also demonstrated that CPAP increases left ventricular ejection fraction, reduces mitral regurgitation, and decreases sympathetic nervous system activity.^{103,115}

The largest randomized trial involving CPAP was the *Canadian Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure* (CANPAP), which involved 258 patients over a mean and maximum follow-up of 24 and 64 months.¹¹⁶ CPAP reduced the AHI by approximately 55%, improved left ventricular ejection fraction and 6-minute walking distance, and reduced sympathetic nervous system activity. However, it had no effect on the primary outcome, which was heart-transplant free survival. Therefore, it cannot be recommended for routine use as therapy for CSR-CSA. However, in a post hoc analysis of the trial, patients in whom CPAP reduced the AHI to less than 15 had significantly higher heart-transplant free survival than the control group and the CPAP subgroup in whom the AHI remained above 15.¹¹⁷ These results suggest that a trial of CPAP may be given to heart failure patients with CSR-CSA and, if their AHI is reduced to below 15, then CPAP can be continued because of its potential to reduce morbidity and mortality. However, if the AHI remains above 15, CPAP should be stopped because of the potential for harm.¹¹⁷

Adaptive Servoventilation. *Adaptive servoventilation* (ASV) is a form of positive airway pressure specifically designed to alleviate CSR-CSA. For CSR-CSA, ASV is analogous to a cardiac pacemaker: When it detects a central apnea, it provides intermittent pressure support ventilation, but when it detects that the patient is breathing spontaneously, inspiratory assist is turned off. In heart failure patients with CSR-CSA, it causes a greater fall in the AHI than CPAP, bilevel positive airway pressure, and supplemental O₂.¹¹⁸⁻¹²⁰ However, the clinical effects of ASV in heart failure patients with CSR-CSA are inconsistent. In one randomized trial involving 72 patients over 3 months, ASV did not cause any

significant changes in left ventricular ejection fraction, NT-proBNP level, or quality of life compared with control.¹²¹ In another randomized trial involving 26 patients over 4 weeks, ASV improved an objective measure of alertness and reduced BNP levels but had no effect on LVEF, subjective daytime sleepiness, simulated driving performance, or quality of life.⁹³ There have been no long-term randomized trials of ASV that have assessed effects on morbidity or mortality. Accordingly, there are insufficient clinical outcomes data from randomized trials to support the use of ASV to treat CSR-CSA in patients with heart failure. Further evidence from large-scale randomized trials is required.

Supplemental Oxygen. Supplemental oxygen reduces central apnea-related dips in arterial PO_2 , thereby reducing peripheral chemoreceptor stimulation; this reduces loop gain and lessens the chance of ventilatory overshoot and dips in arterial PCO_2 below the apnea threshold.¹²² Where PCO_2 has been measured during supplemental oxygen administration, it was reported to increase when the AHI was markedly reduced,¹²³ but remain the same when the AHI only decreased marginally,¹²⁴ suggesting that one of the mechanisms by which oxygen attenuates CSR-CSA is via dampening of ventilation and raising PCO_2 above the apnea threshold.

Small randomized trials, from one night to 1 month duration, have demonstrated that nocturnal oxygen reduces AHI by approximately 50% in heart failure patients with CSR-CSA.^{123,125-127} However, the effects of oxygen on physiologic and clinical outcomes have been inconsistent. Staniforth and colleagues¹²⁶ found that supplemental oxygen for 1 month reduced overnight urinary norepinephrine excretion but had no effect on daytime plasma norepinephrine, brain natriuretic peptide, neurocognitive function, sleepiness, or quality of life. In another randomized trial, Andreas and colleagues¹²⁵ reported that administration of nocturnal oxygen for 7 days to 22 patients with heart failure improved peak oxygen consumption and ventilatory efficiency but had no effect on quality of life. Arzt and colleagues¹²⁸ allocated 10 consecutive patients to nocturnal oxygen and the next 16 consecutive patients to CPAP at 8 to 10 cm H_2O for 3 months. Both CPAP and oxygen reduced the AHI by 67%, but only CPAP improved ventilatory efficiency and LVEF. Neither intervention had any effect on peak exercise oxygen consumption. The *Home Oxygen Trial* (HOT)¹²⁹ randomized 51 patients to receive or not receive supplemental oxygen over 1 year. Those who received oxygen had a significant reduction in severity of CSR-CSA and a significant improvement in quality of life as measured by the Specific Activity Scale compared with the control group. However, there was no difference in cardiac event rates among the groups.

Although oxygen attenuates CSR-CSA in patients with heart failure and can reduce nocturnal sympathetic activity, there is no consistent evidence that it improves cardiovascular function or clinical outcomes in such patients. Moreover, administration of supplemental oxygen to patients with heart failure could cause hyperoxia, and by doing so, induce oxidative stress that can exert adverse hemodynamic effects, such as raising vascular resistance, blood pressure, and left ventricular filling pressure, and lowering cardiac output.¹³⁰⁻¹³² Therefore, there is currently

insufficient evidence to support the use of oxygen to treat CSR-CSA in patients with heart failure.

Respiratory Stimulants. Acetazolamide is a carbonic anhydrase inhibitor that causes a metabolic acidosis that increases the stimulus to breathe while lowering the arterial PCO_2 apneic threshold.¹³³ One small 6-day randomized trial demonstrated a modest (38%) reduction in the AHI in heart failure patients with CSR-CSA in association with reductions in daytime sleepiness and fatigue.¹³⁴ Theophylline is an adenosine antagonist that stimulates central respiratory drive and augments cardiac contractility. In a 5-day randomized trial involving 15 patients with heart failure and CSR-CSA, theophylline reduced the AHI but did not improve left ventricular ejection fraction.¹³⁵⁻¹³⁷ However, although once used widely for therapy of acute heart failure, theophylline is no longer used for this purpose because it increases the risk of cardiac arrhythmias and sudden death.^{138,139} Consequently, neither of these agents can be recommended for therapy of CSR-CSA.

Carbon Dioxide. Raising arterial PCO_2 above the apnea threshold either by inhalation of carbon dioxide or the addition of dead space abolishes CSR-CSA instantaneously in patients with heart failure (Fig. 89-6).^{66,140} However, there is no evidence that raising PCO_2 through these means provides any clinical benefits. Moreover, because carbon dioxide increases sympathetic nervous activity and disrupts sleep¹⁴¹ and because no long-term studies have demonstrated its safety or clinical efficacy, it cannot be recommended for therapy of CSR-CSA.

Transvenous Phrenic Nerve Pacing. Modulation of respiration by unilateral transvenous phrenic nerve stimulation via the superior vena cava is under investigation as a treatment for CSR-CSA. A small, open-label study over one night, during which intermittent phrenic nerve stimulation was delivered for several minutes, was associated with a reduction in the AHI. However, the study design and pattern of intermittent phrenic stimulation were not well defined, making it difficult to evaluate the results.¹⁴² Further studies are awaited to determine whether such an intervention is feasible for chronic use and whether it improves clinical outcomes.

Central Sleep Apnea Associated with Cerebrovascular Disease. Nonhypercapnic CSA has been observed in 10% to 15% of patients with cerebrovascular accidents.^{143,144,144a} Its pathogenesis and clinical features have not been well described. However, several studies have found no relationship between the presence of CSA and the location, size, or type of stroke.^{143,144} In some patients, CSA appears in a CSR-CSA pattern. In such cases, CSR-CSA was invariably associated with asymptomatic left ventricular systolic dysfunction.¹⁴⁵ This observation strongly suggests that CSR-CSA in patients with stroke is related to underlying occult cardiac dysfunction and therefore probably shares the same pathogenesis as CSR-CSA in patients with heart failure. However, neither the clinical significance of this finding in patients with stroke nor the therapeutic approach have been studied in any depth. Nevertheless, the implications of finding CSR-CSA in patients following stroke

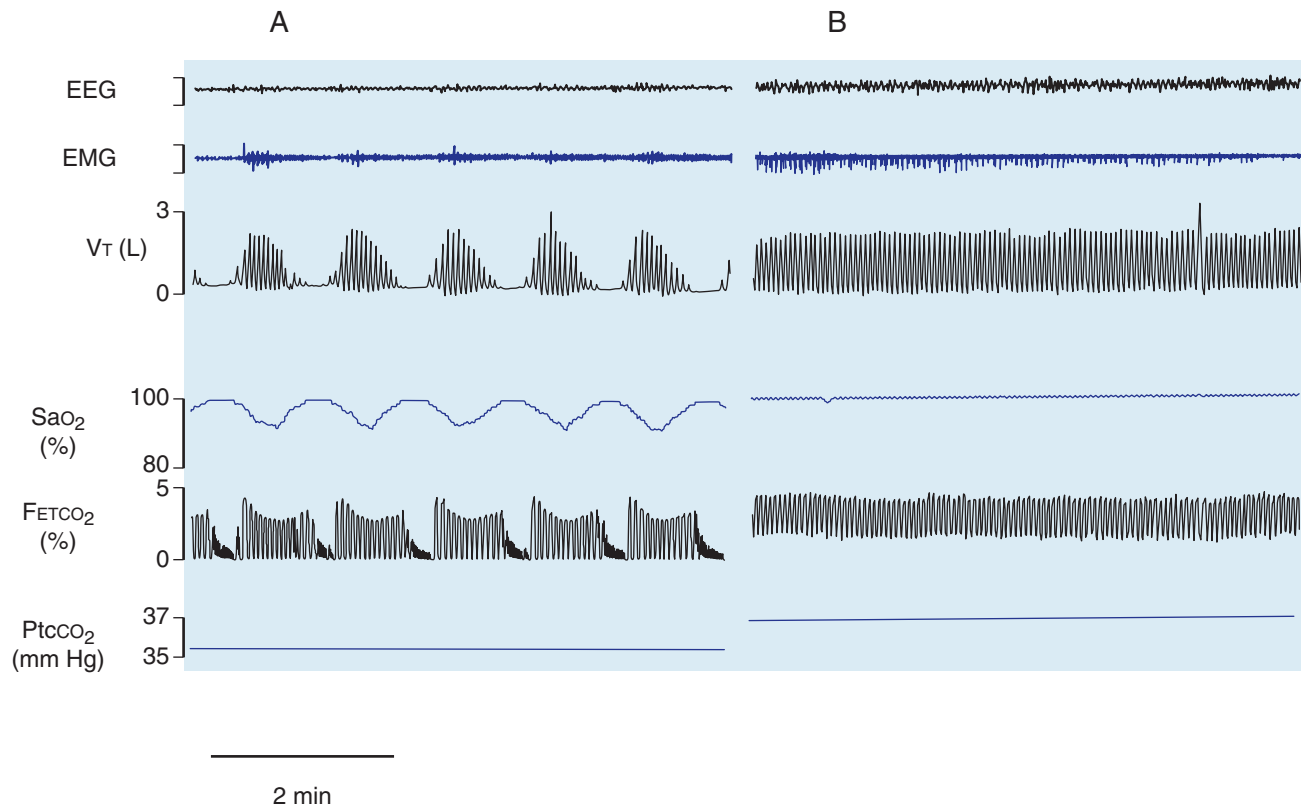


Figure 89-6 Inhaled carbon dioxide abolishes Cheyne-Stokes respiration. Polysomnographic recordings are shown from a patient with recurrent central apneas associated with Cheyne-Stokes respiration during stage 2 sleep while breathing air (**A**) and 1% carbon dioxide in air (**B**). Note abolition of both central apneas on the tidal volume (VT) trace and of recurrent decreases in arterial oxygen saturation (SaO_2) during carbon dioxide inhalation, in association with an increase in transcutaneous PCO_2 (PtCO_2) of 1.6 mm Hg. EEG, electroencephalogram; EMG, submental electromyogram; FETCO_2 , end-tidal carbon dioxide concentration. EEG, electroencephalogram; EMG, electromyogram. (From Lorenzi-Filho G, Rankin F, Bies I, et al: Effects of inhaled carbon dioxide and oxygen on Cheyne-Stokes respiration in patients with heart failure. *Am J Respir Crit Care Med* 159:1490–1498, 1999.)

is that one should investigate for evidence of left ventricular systolic dysfunction.

Central Sleep Apnea Associated with Atrial Fibrillation. Among patients with heart failure, atrial fibrillation is associated with increased odds of having CSR-CSA.⁷⁹ In patients with CSA, but without heart failure or cerebrovascular or renal disease, atrial fibrillation was observed in 27% versus only 1.7% of patients with OSA and 3.3% of those without sleep apnea.¹⁴⁶ The reason for the strong association between CSA and atrial fibrillation was not identified. However, the most likely possibility is that atrial fibrillation predisposes to CSA by mechanisms similar to those of heart failure, by lowering cardiac output and raising pulmonary venous pressure and thereby triggering hyperventilation and hypocapnia through stimulation of pulmonary vagal irritant receptors.

Central Sleep Apnea Associated with Renal Failure. CSA has also been described in patients with end-stage renal disease.^{147,148} Prevalence rates are difficult to estimate because many of the studies are small. In earlier studies the prevalence of CSA was reported to be 9% to 75%.¹⁴⁸⁻¹⁵⁰ In a more recent study of 89 patients with stage 4 or 5 chronic kidney disease and 75 patients with end-stage renal disease on hemodialysis, CSA was uncommon and the median central apnea index was 0 to 0.7.¹⁵¹ However, the combination of obstructive, central, and mixed events is frequently

reported in hemodialyzed patients with end-stage renal disease.^{149,150,152} Predictors for CSA include atrial fibrillation, an increased cardiothoracic ratio on a chest radiograph, and low PCO_2 , all of which suggest mechanisms for CSA in renal disease similar to those in heart failure and atrial fibrillation, including fluid volume overload.¹⁴⁸ Non-randomized studies showed that one night of CPAP alleviated CSA in six patients with end-stage renal disease¹⁵⁰ and that conversion from conventional thrice-weekly hemodialysis to more intense nocturnal hemodialysis in 14 subjects with a mixture of OSA and CSA reduced all types of events in association with an increase in PCO_2 .¹⁴⁹ Nocturnal fluid removal may have contributed to alleviation of CSA and other types of respiratory events, probably through reductions in overnight fluid shifts into the neck, in the case of OSA, and into the lungs, in the case of CSA.^{89,153}

Central Sleep Apnea Associated with Acromegaly. Acromegaly is associated with high prevalences of both OSA and CSA. In one study, 20% of 54 patients with acromegaly had CSA.¹⁵⁴ Slopes of the hypercapnic ventilator responses were related to GH and IGF-1 levels, suggesting that these substances have effects on breathing control. Moreover, the severity of CSA was directly related to carbon dioxide responsiveness and the level of IGF-1.

Clinical features of CSA in acromegaly have not been well characterized but appear to be similar to that of OSA, including loud snoring and excessive daytime sleepiness.¹⁵⁴

In one nonrandomized study involving 19 patients with acromegaly and sleep apnea, treatment of acromegaly by the somatostatin analogue, octreotide, was associated with a 50% decrease in the AHI that involved both central and obstructive events.¹⁵⁵ Similarly, in another nonrandomized study involving 6 patients with acromegaly and a mixture of OSA and CSA, treatment of acromegaly by transsphenoidal adenomectomy alleviated both CSA and OSA, but effects on symptoms of sleep apnea were not assessed.¹⁵⁶

High-Altitude Central Sleep Apnea (see Chapter 77). At high altitude, hypobaric hypoxia provokes hyperventilation, which causes arterial PCO_2 to fall recurrently below the apnea threshold during sleep.¹⁵⁷ At high altitude, natives of both high and low altitudes can exhibit CSA, but not everyone is susceptible.¹⁵⁸ For unknown reasons, men are more likely to develop CSA at high altitude than women, just as they are more prone to other forms of nonhypercapnic CSA.¹⁵⁹

In lowlanders, there is a progressive increase in the frequency of central events and a reduction in the periodic breathing cycle length with increasing altitude from 2400 m to 7546 m.¹⁶⁰⁻¹⁶² The progressive reduction in cycle length is probably due to increasing cardiac output and therefore reduced lung-to-chemoreceptor circulation time. Over time, as individuals acclimatize to high altitude, CSA attenuates.^{163,164} This is due mainly to metabolic compensation for respiratory alkalosis that happens over 2 to 3 days. As a consequence, the difference between arterial PCO_2 and the apnea threshold increases, causing periodic breathing to dampen over time.¹³³ Complaints related to CSA at high altitude include poor-quality sleep, nocturnal dyspnea, morning headaches, and impaired cognition.¹⁶⁵⁻¹⁶⁸

Return to low altitude quickly reverses high-altitude CSA. Specific therapies for CSA while at altitude include supplemental oxygen that causes arterial PCO_2 to rise above the apnea threshold with immediate reversal of CSA and subjective improvement in sleep quality.¹⁶⁷ Respiratory stimulants can alleviate high-altitude CSA. For example, in a randomized trial involving 30 subjects with high-altitude CSA, acetazolamide or theophylline virtually eliminated CSA. However, 60% of subjects on acetazolamide reported paresthesias and altered taste and 70% of subjects receiving theophylline complained of palpitations.¹⁶⁹

In a randomized trial involving 33 subjects at high altitude, the sedative medication temazepam caused a modest reduction in severity of CSA.¹⁷⁰ The proposed mechanism of action of this sedative is that by reducing the frequency of arousals from sleep it prevents abrupt hyperventilation and consequent fall in PCO_2 below the apnea threshold. At present, although firm recommendations cannot be given regarding the pharmacologic treatment of high-altitude CSA, it seems most logical to use supplemental oxygen and/or acetazolamide because they are routinely used at high altitude in any case to correct hypoxemia and to prevent acute mountain sickness and high-altitude pulmonary edema, respectively.

Opioid-Induced Central Sleep Apnea. Both OSA and CSA have been described in patients using opioids.¹⁷¹⁻¹⁷³

There are at least two physiologic effects of opioids that could predispose to CSA. First, opioids activate endogenous opioid receptors in areas of the brain that inhibit inspiratory drive and cause respiratory depression, particularly in the pre-Botzinger complex of the medulla.¹⁷⁴ Exaggeration of such inspiratory depression at the onset of sleep could therefore cause central apneas and hypopneas. If so, then one would expect it to happen in the presence of hypercapnia. However, when arterial blood gas analyses have been performed in wake subjects with methadone-related CSA, PCO_2 has generally been within normal limits and has borne no relationship to the presence or severity of CSA.^{172,175-177} Consequently, opiate-induced CSA appears not to be associated with hypercapnia and respiratory depression per se but rather to fall into the nonhypercapnic category.

Second, opioids also cause arterial and venous dilation in both the pulmonary and systemic circulation via stimulation of histamine receptors.^{178,179} This venous dilating effect causes peripheral venous pooling and, in patients with acute cardiogenic pulmonary edema, this reduces left ventricular filling pressure and pulmonary congestion.¹⁸⁰ It is therefore possible that chronic opioid use could cause chronic venous pooling in the capacitance vessels of the splanchnic circulation and legs. If so, there may be substantial rostral fluid shift on lying down at night that could accumulate in the lungs and stimulate vagal irritant receptors that would provoke hyperventilation and a fall in PCO_2 toward the apnea threshold similar to that described in patients with heart failure and CSA.^{89,181} However, such a mechanism remains speculative.

The severity of CSA in those on narcotics may vary from night to night depending on the dosage: the higher the dose, the higher the AHI.^{172,182,183} In retrospective studies of opioid users referred to sleep clinics, the prevalence of isolated CSA ranged between 14% and 30%.^{172,182,184,185}

Central nervous system symptoms of opioids include dizziness, nausea, neurocognitive impairment, and hypersomnolence.¹⁸⁶ The extent to which these symptoms are due to opioid use per se or CSA is difficult to determine. Chronic opioid use can increase the risk of sudden death, possibly due to cardiac arrhythmias, but there is no evidence to date that this is related to CSA or other sleep-related breathing disorders.¹⁸⁷

In patients with opioid-induced CSA, opioid withdrawal resolves or reduces the severity of CSA and daytime hypersomnolence.^{188,189} However, opioid withdrawal is often not feasible because of addiction or chronic pain. CPAP, BiPAP, and ASV have been tested for therapy of opioid-induced CSA in small, retrospective, nonrandomized trials. Conflicting results have been reported for CPAP from two small retrospective studies: in one, CPAP was ineffective and, in the other, it reduced the AHI to less than or equal to 5 in 54% of individuals.¹⁹⁰ In this latter study, the addition of supplemental oxygen to CPAP abolished CSA in 81%.¹⁹⁰ BiPAP with supplemental oxygen abolished CSA in a further 10% of subjects. ASV has been evaluated in only a few small studies with conflicting results.^{189,191,192,192a}

Complex Sleep Apnea. Complex sleep apnea was originally described as the emergence of CSA in patients with

OSA during or following initiation of CPAP therapy, called *CPAP-emergent CSA*. Subsequently, the emergence of CSA in patients with OSA has also been described following maxilomandibular advancement surgery,^{193,194} application of mandibular advancement devices,¹⁹⁵ tracheostomy,¹⁹⁶ and nasal surgery¹⁹⁷ and is called *treatment-emergent CSA*. There is, however, controversy as to the definition of complex sleep apnea and whether or not it is a distinct entity. The term *complex sleep apnea* has also been used to describe persistence of only the central events following treatment of a combination of central, mixed, and obstructive sleep apnea, called *CPAP-persistent CSA*. Therefore, a clear definition of complex sleep apnea has yet to emerge.^{198,199} For the purposes of this chapter we use the term *complex sleep apnea* to include both *treatment-emergent CSA* and *treatment-persistent CSA*.

The main postulated mechanism of CSA emergence on initiation of CPAP and the other therapies mentioned earlier in patients with OSA is that relief of upper airway obstruction in someone with a high central respiratory drive facilitates augmented ventilation that reduces PCO_2 below the apneic threshold.^{198,200}

During CPAP titration in patients with OSA with and without heart failure, the prevalence of treatment-emergent CSA ranges from 5% to 20%.²⁰⁰⁻²⁰⁵ After 2 to 3 months' acclimatization to CPAP, treatment-emergent CSA dissipates in greater than 50% of subjects without heart failure.^{201,203} Treatment-emergent CSA has also decreased over a period of 6 months after tracheostomy.²⁰⁶

In unselected sleep cohorts, risk factors identified for the development of treatment-emergent CSA were poorer sleep efficiency, hypertension, coronary artery disease, heart failure, opioid use, and more severe OSA.^{201,203,207} In the heart failure population, predictors for development of CPAP-emergent CSA included older age, lower arterial PCO_2 , poorer New York Heart Association class, less diuretic therapy, and increased ventilatory responsiveness to CO_2 .²⁰⁵ However, up to one third of those with CPAP-emergent CSA do not have any of these risk factors.²⁰⁸

In most patients no specific treatment is necessary for treatment-emergent CSA because, over 2 to 3 months, these events dissipate in the majority of subjects. Furthermore, even in those with persistent treatment-emergent CSA, daytime sleepiness is usually alleviated.²⁰¹ For those in whom complex CSA persists despite CPAP or other therapies, there is no available information on long-term consequences.

Treatments for persistent treatment-emergent CSA include BiPAP, ASV, oxygen, and addition of dead space. In most studies, decisions to treat complex CSA were not based on patient symptoms. Studies with BiPAP are conflicting, with one study demonstrating an improvement²⁰⁹ and two studies showing no improvement in CSA.^{210,211} A retrospective study evaluating the addition of 50 to 200 mL of dead space via a nonvented mask to a standard CPAP unit reported abolition of CSA.²¹² In retrospective studies ASV was reported to abolish CPAP-emergent CSA in 79% to 100% of patients on titration studies.²¹³⁻²¹⁵ In small prospective randomized trials, treatment of CPAP-emergent CSA was abolished by ASV in 97% to 100% of patients after between 6 and 12 weeks.^{205,207,216}

Primary Nonhypercapnic Central Sleep Apnea

Idiopathic Central Sleep Apnea. *Idiopathic CSA* (ICSA) is a form of CSA in which there are central apneas and hypopneas without evidence of cardiovascular diseases or other lesions that might explain their presence. Two large epidemiologic studies reported a prevalence of CSA of 0.4% in men²¹⁷ but essentially 0% in women.²¹⁸ Because these populations were considered healthy, one can assume that most cases of CSA they identified were ICSA. Accordingly, ICSA appears to be rare.

Similar to CSR-CSA, patients with ICSA hyperventilate with low arterial PCO_2 during both wakefulness and sleep. The tendency to hyperventilate is related to increased responsiveness of the peripheral and central chemoreceptors that increase loop gain and lead to respiratory instability.^{71,219,220} Episodes of central apneas and hypopneas during sleep are typically precipitated by an abrupt increase in ventilation usually triggered by an arousal following which arterial PCO_2 drops below the apnea threshold. Their dependence on hypocapnia is illustrated by the observation that raising arterial PCO_2 either by inhalation of a small concentration of carbon dioxide or addition of deadspace immediately abolishes this breathing disorder.²²¹ As in CSR-CSA, central events are seen predominantly during non-REM sleep with a reduction in frequency or complete cessation of events during REM sleep for similar reasons. Compared with heart failure patients with CSR-CSA, the durations of the hyperpnea and periodic breathing cycle are much shorter due to shorter lung-to-chemoreceptor circulation time and higher stroke volume and cardiac output (see Fig. 89-4).⁷⁶

In some respects, the clinical presentation of ICSA resembles that of OSA. Patients are usually middle-aged or older men who are overweight, complain of snoring, have restless sleep, and may also complain of excessive daytime sleepiness, but they more often complain of insomnia. There are no studies on the natural history of this disorder, so its overall clinical significance is difficult to assess. Treatments assessed include the respiratory stimulant acetazolamide,^{169,222} which provides a constant stimulus to breathe and therefore reduces fluctuations in ventilation. Studies evaluating acetazolamide have been nonrandomized and produced inconsistent results without careful evaluation of clinical outcomes. Therefore acetazolamide cannot be recommended as chronic treatment for this disorder at this time.

Because increased arousals and sleep instability can precipitate CSA, sedative medications have been tested in order to reduce arousability and thereby alleviate ICSA. In a non-randomized, open-label, 9-week trial of the nonbenzodiazepine GABA receptor agonist, zolpidem,²²³ the AHI fell by 55% in association with a reduction in arousal frequency and subjective daytime sleepiness. In a one-night randomized trial, the benzodiazepine hypnotic, triazolam,²²⁴ was also reported to reduce the AHI modestly in association with a reduction in arousal frequency. Because both of these studies included only small numbers of subjects, much larger randomized studies will be required before more evidence-based treatment recommendations can be made. There are no published studies evaluating the effects of positive airway pressure devices in ICSA.

Key Points

- Central sleep apnea (CSA) is a rare but heterogeneous disorder in which the arterial PCO_2 comes to lie below the apnea threshold during sleep, either because the PCO_2 falls or the apnea threshold rises.
- In CSA, there are recurrent reductions (hypopnea) or cessations (apnea) of airflow due to a reduction in central respiratory drive in the absence of airflow limitation from upper airway obstruction.
- Classification of CSA is based on the presence or absence of hypercapnia. There are two major types:
 - CSA associated with hypercapnia arises from impaired central respiratory drive or neuromuscular weakness affecting the respiratory muscles that is exacerbated during the transition from wakefulness to sleep by the withdrawal of the waking drive to breathe and is most prominent in *rapid eye movement* (REM) sleep.
 - CSA associated with normocapnia or hypocapnia (i.e., nonhypercapnic) is often associated with augmented central respiratory drive that predisposes to alternating periods of hyperventilation that drive PCO_2 recurrently below the apnea threshold. It is most prominent in non-REM sleep.
- Cheyne-Stokes respiration with CSA, a form of nonhypercapnic CSA usually associated with heart failure, is characterized by a waxing and waning pattern of respiration typically seen during non-REM sleep and is associated with increased mortality risk.
- Complex sleep apnea is a form of CSA that arises following treatment of obstructive sleep apnea by continuous positive airway pressure or other interventions (i.e., treatment-emergent CSA) or persists following treatment of a combination of central, mixed, and obstructive sleep apnea (i.e., treatment-persistent CSA).

Complete reference list available at **ExpertConsult**.

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RESPIRATORY MANIFESTATIONS OF EXTRAPULMONARY DISORDERS

90

PULMONARY COMPLICATIONS OF HIV INFECTION

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INTRODUCTION

Since the recognition of the first cases of *acquired immunodeficiency syndrome* (AIDS) in 1981, our understanding of *human immunodeficiency virus* (HIV) and its myriad infectious and noninfectious complications has markedly increased. The prognosis for persons infected with HIV has undergone dramatic change for those with access to effective combination *antiretroviral therapy* (ART) to suppress HIV replication and medications for treatment and prevention of HIV-associated complications. ART in this chapter refers to the use of *combination ART*, often taken in a fixed-dose combination, that suppresses viral replication and prevents selection of drug-resistant HIV. These therapeutic advances have resulted in a dramatic decline in the incidence of new AIDS cases and in the number of AIDS-associated deaths in countries where this care is widely and consistently available.¹ Unfortunately, access to ART and other medications is not universal, and an HIV vaccine remains elusive. Therefore, efforts to prevent the spread of new HIV infection, to identify and treat those persons who are already HIV infected, and to slow the progression from HIV to AIDS continue to be worldwide priorities.

The lungs are one of the chief target organs of HIV and, accordingly, a major source of morbidity and mortality. The spectrum of pulmonary manifestations is broad and includes many infectious and noninfectious complications ([Table 90-1](#)).² These complications include diseases that are AIDS-defining (e.g., *Pneumocystis pneumonia*) or HIV-associated (e.g., bacterial pneumonia), disorders that are not classified as HIV-associated but appear to be more common in those with HIV infection (e.g., lung cancer, *pulmonary arterial hypertension* [PAH], and *chronic obstructive pulmonary disease* [COPD]), and conditions whose association with HIV is inconclusive or purely coincidental (e.g., sarcoidosis). HIV-infected patients may also frequently experience critical illness either as a result of pulmonary complications or other diseases and, although uncommon, lung transplantation in HIV-infected patients has been performed.^{3,3a} This chapter provides a brief review of the epidemiology of HIV infection and its immunologic abnormalities, followed by an approach to the evaluation of pulmonary disease in an HIV-infected patient. Then, the major HIV-associated pulmonary diseases are discussed, with an emphasis on clinical features, diagnosis, treatment, and prevention.

Table 90-1 Spectrum of Pulmonary Complications**INFECTIONS****Bacteria***

Streptococcus pneumoniae
Haemophilus species
Staphylococcus aureus
Pseudomonas aeruginosa
 Other bacteria

Mycobacteria

Mycobacterium tuberculosis[†]
Mycobacterium avium complex[†]
Mycobacterium kansasii[†]
 Other mycobacteria[‡]

Fungi

Pneumocystis jirovecii (formerly *P. carinii*)[§]
Cryptococcus neoformans[‡]
Histoplasma capsulatum[‡]
Coccidioides immitis[‡]
Aspergillus species (most often *A. fumigatus*)
Blastomyces dermatitidis
Penicillium marneffei
 Other fungi

Viruses

Cytomegalovirus[§]
 Other viruses

Parasites

Toxoplasma gondii^{||}
 Other parasites

MALIGNANCIES

Kaposi sarcoma[§]
 Non-Hodgkin lymphoma[§]
 Bronchogenic carcinoma

INTERSTITIAL PNEUMONITIDES

Lymphocytic interstitial pneumonitis[§]
 Nonspecific interstitial pneumonitis

OTHER

Chronic obstructive pulmonary disease
 Asthma
 Pulmonary arterial hypertension
 Sarcoidosis
 Immune reconstitution inflammatory syndrome

*Acquired immunodeficiency syndrome (AIDS)—defining diagnosis in adults and adolescents (>13 years) if recurrent (≥2 episodes in 12 months). Not applicable as AIDS-defining diagnosis in children.

†AIDS-defining diagnosis in adults and adolescents. AIDS-defining diagnosis in children if extrapulmonary or disseminated.

‡AIDS-defining diagnosis if extrapulmonary or disseminated.

§AIDS-defining diagnosis.

||AIDS-defining diagnosis if central nervous system is involved.

¶AIDS-defining diagnosis in children. Not applicable as AIDS-defining diagnosis in adults or adolescents.

Modified from Murray JF, Mills J: Pulmonary infectious complications of human immunodeficiency virus infection. *Am Rev Respir Dis* 141:1356–1372, 1582–1598, 1990.

EPIDEMIOLOGY

The AIDS epidemic has had a major impact throughout the world. A disproportionate number of all of the HIV-infected people in the world live in low- and middle-income countries, especially in sub-Saharan Africa, which has the world's highest prevalence of HIV infection. Global estimates indicate that 35.3 million people were living with

HIV in 2012.⁴ Overall, approximately 0.8% of adults aged 18 to 49 years are infected with HIV worldwide. In sub-Saharan Africa, 4.9% of adults are living with HIV. Following sub-Saharan Africa, the regions with the highest burden of HIV infection are the Caribbean, Eastern Europe, and Central Asia. The *Centers for Disease Control and Prevention* (CDC) estimates that 1.1 million people were living with HIV in the United States as of 2012.⁵

Encouragingly, new HIV infections have declined over the past decade. Although 2.3 million people worldwide were newly infected with HIV in 2011, this number represents a 20% drop from the number in 2001.⁴ AIDS-related mortality has also declined: in 2012, 1.6 million people died of AIDS-related causes compared with 2.3 million in 2005.⁴ Because survival has improved for HIV-infected patients since the introduction of ART, more people are living with HIV in the United States than ever before.⁶ Furthermore, HIV-infected adults in clinical care in the United States are more likely in the recent era to be prescribed ART, to have a suppressed HIV viral load, and to have a higher median CD4⁺ T cell-count.⁷

The gender and racial/ethnic demographics of HIV-infected populations vary worldwide. In sub-Saharan Africa, women account for approximately 58% of people estimated to be living with HIV.⁴ In the United States, women comprise approximately 21% of adult AIDS cases.⁸ Although early in the epidemic HIV was predominantly seen among non-Hispanic white men who have sex with other men (MSM), HIV is increasingly affecting minorities, with new infections disproportionately represented in minorities, especially blacks and Hispanic/Latin Americans.^{9,10}

IMMUNOLOGIC ABNORMALITIES

After infection with HIV and without ART, HIV-infected persons experience a gradual but inexorable loss of host immunity that has been characterized as a syndrome of immune dysregulation, dysfunction, and deficiency, involving many components of the immune system. HIV is tropic for CD4⁺ lymphocytes and monocytes.¹¹ After initial infection, HIV leads to massive depletion of CD4⁺ lymphocytes of the effector-memory type from mucosal associated lymphoid tissue.¹² During the chronic phase of untreated HIV infection, there is a generalized immune activation and ultimately a progressive decline in the naive and memory T-cell pool that results in systemic CD4⁺ lymphocyte depletion.^{12,13} As well as being decreased in number, T cells are also dysfunctional and mount abnormal host responses to T-cell-dependent antigens. HIV infection is also associated with B-cell dysfunction. Abnormal polyclonal activation, hypergammaglobulinemia, and lack of specific antibody responses ensue. This combination of immune dysfunction, dysregulation, and depletion of CD4⁺ lymphocytes results in a substantially increased risk for infections and other complications. Effective ART substantially decreases opportunistic infections and mortality in HIV-infected patients.¹ The chronic immune activation that takes place in the second phase of HIV infection can be decreased by ART.¹² Nonetheless, immune activation and chronic inflammation can persist, particularly in those who initiated ART at lower CD4⁺ cell counts or who have treatment interrupted.^{14,15}

Premature mortality and comorbidities such as cardiovascular, renal, and liver disease have been associated with residual inflammation and immunodeficiency despite treatment with ART.^{16,17}

HIV infection also causes alteration in several lines of host defense in the lung and respiratory tract that contribute to an increased risk for pulmonary infections.¹⁸ These include abnormalities in both mucociliary function and soluble defense molecules within respiratory secretions. Within the lung parenchyma, innate and adaptive immune responses to pathogens may be impaired. For example, alveolar macrophages from HIV-infected individuals have been shown to have deficiencies in pathogen recognition, including abnormalities in Toll-like receptor 4 signaling.^{19,20} Bronchoalveolar CD4⁺ T cells from HIV-infected individuals display impaired responses to important respiratory pathogens, including influenza and *Mycobacterium tuberculosis*.²¹ Evidence also suggests that HIV results in chronic stimulation and activation of inflammatory cells within the alveolar space.²² Furthermore, animal models suggest that HIV-related proteins may disrupt the barrier function of the alveolar epithelium.²³

The consequences of persistently increased inflammation and immune activation related to HIV on the pathogenesis of chronic lung complications are less clear. Within the alveolar space, HIV infection is associated with changes in the cellular profile¹⁸; however, the mucosal depletion of CD4⁺ T cells that takes place in the gastrointestinal tract does not appear to happen within the lung. Instead, *bronchoalveolar lavage* (BAL) fluid from HIV-infected individuals has more CD4⁺ T cells than does the terminal ileum.²⁴ Lung cells that can be infected with HIV include alveolar macrophages, T cells, and fibroblasts.¹⁸ While alveolar macrophages have been viewed as a potential reservoir of HIV-infected cells within the lung, recent evidence suggests that T cells instead may be a long-lived reservoir of infection within the lung.²⁵ The clinical significance of the lung as a protected compartment for HIV-infected cells is incompletely understood.²⁶

DIAGNOSTIC APPROACH

The evaluation of an HIV-infected patient with pulmonary disease is aimed at making a specific diagnosis. Definitive diagnosis is preferred over empirical therapy for a number of reasons. Although each of the HIV-associated pulmonary diseases has characteristic clinical and radiographic features, these features overlap. Occasionally, the presenting features are atypical or more than one pulmonary disease is present. Without appropriate therapy, HIV-infected patients with pneumonia can progress rapidly to respiratory failure and death. The therapies used to treat HIV-associated pulmonary diseases have substantial toxicities and interactions with other medications.

The evaluation should begin with the history and physical examination.²⁷ Laboratory testing should be performed and a chest radiograph obtained in patients with suspected pulmonary disease. Frequently, the results of this evaluation suggest a specific differential diagnosis and management plan. Occasionally, additional studies such as pulmonary function testing, chest *computed tomography*

(CT), or high-resolution CT are needed to narrow the differential diagnosis and to refine the management plan.

Owing to their particular importance in the diagnostic evaluation of many patients with known or suspected HIV-related pulmonary disease, the value of CD4⁺ lymphocyte counts and fiberoptic bronchoscopy is briefly reviewed here. The utility of other diagnostic tests is considered in the discussions of the specific complications and disorders that follow this section. Additional information on specific diagnostic tests is also available in Chapter 17.

CD4⁺ LYMPHOCYTE COUNT

The CD4⁺ lymphocyte count is an indicator of an HIV-infected patient's risk for development of a specific opportunistic infection or HIV-associated neoplasm. Many HIV-associated pulmonary diseases present at or below a characteristic CD4⁺ lymphocyte count and are seldom seen at higher counts.²⁸ Exceptions are diseases that can present in persons without HIV infection, such as bacterial pneumonia, tuberculosis, and *non-Hodgkin lymphoma* (NHL). In HIV-infected persons, these diseases can present at any CD4⁺ lymphocyte count, although their incidence increases and their characteristic presentation changes as the CD4⁺ lymphocyte count declines (see later disease discussion).

At CD4⁺ lymphocyte counts less than 200 cells/ μ L, bacterial pneumonia is often accompanied by bacteremia, and *M. tuberculosis* disease is often extrapulmonary or disseminated. Moreover, below this CD4⁺ lymphocyte count, *Pneumocystis* and *Cryptococcus* pneumonia become important considerations, whereas neither typically presents in a patient with a count significantly higher than 200 cells/ μ L. At CD4⁺ lymphocyte counts less than 50 to 100 cells/ μ L, endemic fungi, certain viruses (*cytomegalovirus* [CMV]), protozoa (*Toxoplasma gondii*), nontuberculous mycobacteria (*Mycobacterium avium complex* [MAC]), and *Kaposi sarcoma* (KS) become important considerations. Many of these diseases present with extrapulmonary or disseminated manifestations that may dominate the clinical presentation.

The risk of opportunistic infections is best reflected by the current CD4⁺ lymphocyte count.²⁹ Primary and secondary *Pneumocystis* prophylaxis can be safely discontinued in patients whose CD4⁺ lymphocyte counts increase above 200 cells/ μ L for at least 3 months in response to ART; similar evidence has emerged indicating that it is safe to discontinue prophylaxis against MAC, *Cryptococcus*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Toxoplasma* when CD4⁺ lymphocyte counts have been restored to greater than certain CD4⁺ thresholds.²⁹

FIBEROPTIC BRONCHOSCOPY

In general, bronchoscopy should be considered for any HIV-infected patient with pulmonary disease whose severity warrants a prompt and accurate diagnosis, for patients with suspected pulmonary KS, for patients with suspected NHL (if other diagnostic procedures are thought to be more hazardous or less likely to provide the diagnosis), for patients whose diagnosis remains unknown despite less invasive diagnostic studies (e.g., induced sputum), and for patients whose empirical therapy is failing. Conventional

contraindications pertain to HIV-infected patients; HIV infection should not be considered a contraindication to bronchoscopy.

The decision to perform BAL with or without *transbronchial biopsy* (TBB) depends on the suspected diagnosis and on the sensitivities of these procedures for that diagnosis. At the beginning of the AIDS epidemic, both BAL and TBB were usually performed during the initial bronchoscopy. Studies demonstrated that the yield from these two procedures was complementary in identifying pathogens: the sensitivity of BAL was 86% and that of TBB 87%; when the two procedures were combined, the sensitivity was 98% for all pathogens and 100% for *Pneumocystis*.³⁰ Currently, BAL alone is generally performed when *Pneumocystis pneumonia* (PCP) is the suspected pathogen.³¹ The sensitivity of BAL fluid examination for *Pneumocystis* is 97% or higher; therefore, a negative BAL fluid examination for *Pneumocystis* rules out the diagnosis of PCP in all but the rarest cases.³¹

In contrast, TBB improves the sensitivity of bronchoscopy for diagnosing a number of other important pathogens, including tuberculosis and endemic fungal pneumonias. Furthermore, tissue confirmation from TBB or another biopsy specimen is required for a definitive diagnosis of invasive aspergillosis, CMV pneumonia, and NHL. Therefore, when the clinical and radiographic features suggest one of these diseases, both BAL and TBB are warranted during the initial bronchoscopy.

INFECTIOUS COMPLICATIONS

In this section, the major pulmonary infectious complications of HIV disease are reviewed according to category of infectious microorganism (see [Table 90-1](#)).

BACTERIA

Early in the AIDS epidemic, bacterial pneumonia accounted for only a small proportion of reported pulmonary diseases. Subsequently, bacterial pneumonia became recognized as a frequent complication of HIV infection and one that often preceded other opportunistic infections. As a result, recurrent bacterial pneumonia (defined as two or more episodes within 12 months) was included as an AIDS-defining illness in the 1993 CDC Expanded Surveillance Case Definition for AIDS.³²

Prior to the ART era, Hirschtick and coworkers³³ in the *Pulmonary Complications of HIV Infection Study* (PCHIS) confirmed the increased incidence of community-acquired bacterial pneumonia in HIV-infected persons. In this study, there were 5.5 episodes of bacterial pneumonia per 100 person-years in the HIV-infected cohort compared with 0.9 episodes per 100 person-years in the HIV-seronegative control cohort ($P < 0.001$). Bacterial pneumonia was more common in HIV-infected patients than in the HIV-seronegative controls, even in the subset of HIV-infected patients with CD4⁺ lymphocyte counts greater than 500 cells/ μ L ($P < 0.004$). Furthermore, the rate of bacterial pneumonia in the HIV-infected cohort increased as the CD4⁺ lymphocyte count declined. The rate of bacterial pneumonia was 2.3 episodes per 100 person-years in subjects with a CD4⁺ lymphocyte count greater than 500

cells/ μ L compared with 10.8 episodes per 100 person-years in persons with a CD4⁺ lymphocyte count less than 200 cells/ μ L. The incidence of bacterial pneumonia was significantly greater in intravenous drug users than in either MSM or female partners of HIV-infected men. Cigarette smoking was also associated with an increased incidence of bacterial pneumonia, especially in HIV-infected individuals with a CD4⁺ lymphocyte count less than 200 cells/ μ L.

During the ART era (1996 to present), the incidence of community-acquired bacterial pneumonia among HIV-infected persons has declined, although not to the same extent as opportunistic pneumonias such as PCP.³⁴ In the CDC-sponsored Adult/Adolescent Spectrum of HIV Disease project, a prospective medical record review of HIV-infected persons aged 13 years and older in 11 U.S. cities, the incidence of recurrent pneumonia declined from 22 per 1000 person-years in 1992 to 10.7 per 1000 person-years in 1997.³⁵ Other studies have reported similar decreases from the use of ART in both community-acquired pneumonia³⁶ and hospital-acquired pneumonia.³⁷ Thus, ART is clearly associated with a decreased risk for bacterial pneumonia. Another reason credited for decreased bacterial pneumonia among HIV-infected patients is the use of *trimethoprim-sulfamethoxazole* (TMP-SMX) as prophylaxis for PCP.³⁸

Yet despite the significant decrease in incidence, bacterial pneumonia remains more frequent in HIV-infected individuals than in noninfected individuals.^{39,40} Furthermore, bacterial pneumonia is a common cause of morbidity and is associated with increased short- and long-term mortality in HIV-infected patients in the ART era.^{38,41} One reason for the persistence of bacterial pneumonia despite effective ART is the high prevalence of cigarette smoking in HIV-infected populations.⁴² Cigarette smoking is associated with substantially increased rates of pneumonia in multiple studies of HIV-infected patients, at all CD4⁺ lymphocyte cell counts,^{33,38,43,44} whereas smoking cessation decreases the risk for pneumonia.⁴⁵ Intravenous drug use remains a significant risk factor for bacterial pneumonia in the ART era. Additionally, neutrophil number and function can be impaired in HIV infection, which may be exacerbated by concomitant cigarette smoking and contribute to increased risk for bacterial pneumonia.

Several bacterial species can cause pneumonia in HIV-infected patients. Similar to community-acquired bacterial pneumonia in non-HIV-infected populations, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified pathogens in people with HIV infection. In several studies, the two organisms have accounted for approximately 50% to 60% of cases combined,^{33,46} and they remain the most commonly isolated bacterial organisms in the ART era.^{47,47a} *Staphylococcus aureus* can be isolated as a cause of community-acquired pneumonia in patients both with and without a history of intravenous drug use.⁴⁷⁻⁴⁹ In addition to being a cause of nosocomial disease, *Pseudomonas aeruginosa* is well recognized as a cause of community-acquired bacterial pneumonia in HIV-infected persons, especially those with advanced AIDS. *S. pneumoniae* and *P. aeruginosa* ([eFig. 90-1](#)) were the two most common bacteria seen in a series of 111 cases.⁴⁸ Although this series included community-acquired as well as hospital-acquired pneumonias, most cases of pneumococcal pneumonia (91%) as well as pseudomonal pneumonia (63%) were community acquired. Other bacteria that are occasionally identified as

causes of community-acquired bacterial pneumonia in HIV-infected persons include atypical organisms such as *Legionella* species, *Rhodococcus equi*, and *Nocardia* species; these are discussed in more detail later.

Of hospital-acquired pneumonias, the two most common bacterial causes in HIV-infected persons are *S. aureus* and *P. aeruginosa*. Both of these organisms are more likely to be isolated in patients with lower CD4⁺ lymphocyte counts.^{37,46} Staphylococcal pneumonia is frequently complicated by bacteremia, methicillin resistance, and high mortality.³⁷ *S. pneumoniae* and *Klebsiella pneumoniae* are also relatively frequent causes of pneumonia in HIV-infected hospitalized patients.³⁷

Clinical Features. In HIV-infected persons, the clinical and radiographic features of bacterial pneumonia are similar to those in immunocompetent persons, with a few important exceptions.⁵⁰ Of note, HIV-infected individuals have a substantially increased risk for bacteremia and invasive disease due to *S. pneumoniae*. The rate of pneumococcal bacteremia in HIV-infected patients has been estimated to be almost 100 times greater than that in age-matched non-HIV-infected persons.⁵¹ Findings that confer greater risk for bacteremic pneumococcal pneumonia include alcohol abuse, cigarette smoking, recent hospitalization, and presence of comorbid illnesses.⁵² The risk of invasive pneumococcal disease is decreased in those on ART and in those who have received pneumococcal vaccine.⁵³ However, while the incidence of invasive pneumococcal disease has decreased in the current era, the clinical presentation can be severe and may be complicated by respiratory failure.⁵⁴ Providers should consider HIV testing for individuals with unknown serostatus presenting with such disease without other obvious risk factors for invasive pneumococcal disease.⁵³

CD4⁺ Lymphocyte Count. Bacterial pneumonia can develop throughout the course of HIV infection and at any CD4⁺ lymphocyte count. As the CD4⁺ lymphocyte count declines, both the incidence of bacterial pneumonia and the frequency of bacteremia increase. Most cases of *P. aeruginosa* pneumonia are seen in HIV-infected patients with a CD4⁺ lymphocyte count less than 100 cells/ μ L, and usually less than 50 cells/ μ L.^{55,56}

Imaging. As illustrated in Figure 90-1, the majority of bacterial pneumonias due to *S. pneumoniae* in HIV-infected patients present with segmental, lobar, or multilobar consolidation on chest radiograph.⁵⁷ Radiographic findings of pneumococcal pneumonia do not appear to be different among patients on ART than in those not on ART.⁵⁸ Although less common, focal or diffuse alveolar patterns as well as interstitial opacities in association with *S. pneumoniae* or *Haemophilus influenzae* are also seen.^{59,60} Pneumonia due to *P. aeruginosa* may present with focal consolidation, similar to pneumococcal or *Haemophilus* pneumonias, although a significant proportion of radiographs demonstrate cavitary opacities.^{55,61}

Diagnosis. The diagnostic approach to bacterial pneumonia is the same for HIV-infected as for non-HIV-infected persons.^{29,62} HIV-infected patients continue to be at increased risk for invasive pneumococcal disease in the

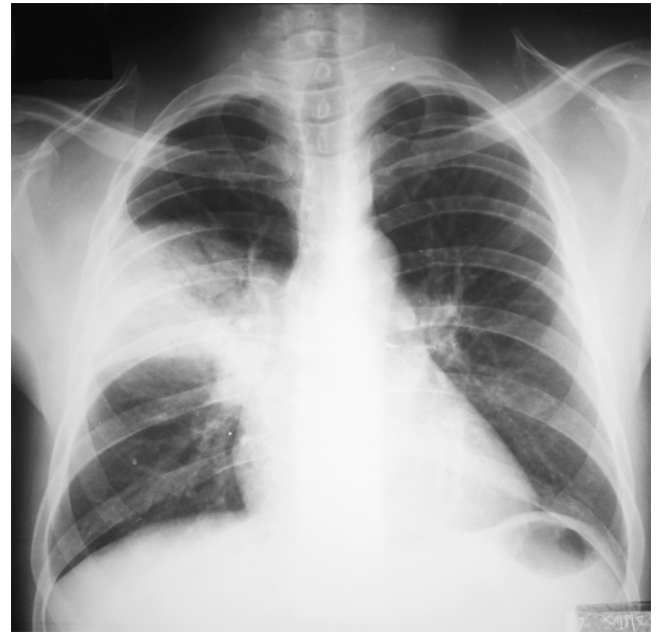


Figure 90-1 Pneumococcal pneumonia. Frontal chest radiograph in a 50-year-old HIV-infected man with positive urinary pneumococcal antigen shows homogeneous opacity with air bronchograms, extending to the pleural surface, representing a “lobar pneumonia” pattern, typical of pneumococcal pneumonia. (Courtesy Stephen Aston, MBChB; Malawi-Liverpool-Wellcome Trust Clinical Research Programme.)

ART era.⁶³ Blood cultures should be obtained, particularly in those with low CD4⁺ cell counts, given the increased risk for bacteremia in this group. Thoracentesis should be considered for patients with pleural effusion, especially if the effusion is large or if there is concern about a possible empyema. Efforts to culture the causative bacteria to enable drug susceptibility testing are especially important in communities where drug-resistant bacteria are prevalent.

Pneumococcal urinary antigen testing offers the potential for early, specific diagnosis. In a study of 70 adults with pneumococcal pneumonia, 47 of whom were HIV-infected, pneumococcal urinary antigen testing had a sensitivity of 81%, specificity of 98%, positive predictive value of 98%, and negative predictive value of 82%.⁶⁴ The test appeared to perform equally well in HIV-infected and non-HIV-infected persons.

Serum procalcitonin and C-reactive protein levels may assist in the early differentiation of bacterial community-acquired pneumonia and pulmonary tuberculosis in HIV-infected patients; procalcitonin and C-reactive protein levels were higher in patients with bacterial pneumonia than in patients with pulmonary tuberculosis, although overlap exists between these causes of pneumonia, particularly in regions endemic for tuberculosis.^{65,65a} Because procalcitonin increases in response to bacterial infections and decreases in the presence of viral infections, levels are sometimes used as a biologic marker of community-acquired bacterial pneumonia.⁶⁶ Elevated procalcitonin levels can predict increased mortality in HIV-infected patients with lower respiratory tract infections, due either to tuberculosis or to bacterial causes.^{66a} However, further studies of these biomarkers in larger cohorts of HIV-infected individuals with pneumonia are needed.

Treatment. The treatment of patients with community-acquired pneumonia is similar for HIV-infected and non-HIV-infected persons (Chapter 33).^{29,62} The choice of antimicrobial agent should be based on a number of factors, such as the results of a sputum Gram stain, the presence of comorbid conditions (e.g., COPD, congestive heart failure, alcohol use), the clinical and radiographic presentation, and the severity of the pneumonia. As in non-HIV-infected persons, treatment should be initiated promptly. Initial empirical therapy should include coverage against frequently identified organisms (e.g., *S. pneumoniae* and *Haemophilus* species). Local prevailing drug resistance patterns must be considered when the antibiotic is selected. Empirical monotherapy with a macrolide is not advised in HIV-infected patients, particularly when they are already on macrolide prophylaxis for MAC, because of increasing pneumococcal resistance to macrolides.²⁹ Patients on TMP-SMX prophylaxis may be more likely to have penicillin- and TMP-SMX-resistant *S. pneumoniae*.⁶⁷ For patients with CD4⁺ lymphocyte counts less than 100 cells/ μ L, especially if associated with recent hospitalization, neutropenia, or broad-spectrum antimicrobial use, consideration should be given to including coverage against *P. aeruginosa*.

Prevention. Pneumococcal vaccine should be given to HIV-infected patients. For adult (age 19 and older) immunocompromised patients including those with HIV who have not been previously immunized, current recommendations from the Advisory Committee on Immunization Practices to the CDC are for the 13-valent pneumococcal conjugate vaccine to be given first followed by 23-valent pneumococcal polysaccharide vaccine at least 8 weeks or more later.⁶⁸ For those who have already received the 23-valent pneumococcal polysaccharide vaccine, the 13-valent pneumococcal conjugate vaccine should be given at least 1 year later. A repeat dose of 23-valent pneumococcal polysaccharide vaccine should be given 5 years after the first, with another dose given after age 65 years. These recommendations may be revised based on ongoing clinical trials; refer to the Advisory Committee on Immunization Practices and CDC, *National Institutes of Health* (NIH), and the *HIV Medicine Association of the Infectious Diseases Society of America* (HIVMA/IDSA) guidelines for additional details.^{29,68} Because influenza is a major risk factor for bacterial pneumonia, prevention also includes yearly administration of inactivated influenza vaccine in all HIV-infected individuals.

Other Bacteria

Legionella pneumonia is an infrequent cause of bacterial pneumonia in HIV-infected patients and can be community acquired or nosocomial.⁶⁹ Cases have been reported in persons with severe immunosuppression and in individuals with well-controlled HIV on ART.⁷⁰ The chest radiograph typically reveals alveolar opacities; bilateral involvement is common. Extrapulmonary manifestations can also be seen, especially of the gastrointestinal tract and central nervous system. In one series, respiratory failure developed in 12 of 15 hospitalized, HIV-infected subjects (80%) with confirmed *Legionella* pneumonia and 3 died.⁷⁰ Although *Legionella pneumophila* is the most common species identified, other *Legionella* species have been reported. Rapid diagnosis

of *Legionella* pneumonia can be obtained with urinary antigen testing. However, cultures and/or serology should still be considered as part of the diagnostic evaluation, in that the urinary antigen primarily detects *L. pneumophila* serogroup 1 and can have a lower sensitivity in cases of mild disease.⁷¹ Its performance has not been prospectively evaluated in HIV-infected patients.

R. equi pulmonary disease has been reported in HIV-infected persons. A review of more than 100 reported cases of *R. equi* infection found that approximately two thirds were in HIV-infected persons, with pulmonary disease present in the majority.⁷² HIV-infected persons were more likely to have *R. equi* bacteremia or extrapulmonary manifestations, or both, than persons without HIV infection. Most cases present when the CD4⁺ lymphocyte count is less than 200 cells/ μ L and usually less than 100 cells/ μ L.⁷² In one multicenter series of 67 HIV-infected patients with *R. equi* infection, the mean CD4⁺ lymphocyte count was 35 cells/ μ L (range, 1 to 183 cells/ μ L).⁷³ The chest radiograph often reveals cavitory lesions that may mimic tuberculosis or nocardiosis, or focal consolidation that may mimic bacterial pneumonia.⁷⁴ Sputum, blood, bronchoscopy, and pleural fluid specimens can establish the diagnosis of *R. equi* pneumonia.⁷³ The optimum treatment regimen and duration are not well defined.⁷² Combination antimicrobial therapy is generally recommended, and treatment for a minimum of 2 months (and frequently 6 months) is often required. Because relapses are common, chronic suppressive therapy is probably indicated.

Nocardia asteroides is the most common species identified in several reports of *Nocardia* infection in HIV-infected patients, and the lung is the most commonly affected site. Most cases present when the CD4⁺ lymphocyte count is less than 200 cells/ μ L. In one series of 30 HIV-infected patients with nocardiosis, the mean CD4⁺ lymphocyte count was 109 cells/ μ L (median 92 cells/ μ L; range, 12 to 266 cells/ μ L).⁷⁵ The presenting symptoms often mimicked tuberculosis. Imaging (eFig. 90-2) usually reveals cavitory lesions or lobar or multilobar opacities, especially in the upper lung zones, although reticulonodular opacities, solitary masses, and pleural effusions are seen also.⁷⁶ Sputum or bronchoscopy can establish the diagnosis of pulmonary nocardiosis. A modified *acid-fast bacilli* (AFB) stain may provide an early presumptive diagnosis in the proper clinical setting. Long-term TMP-SMX is the treatment of choice.

MYCOBACTERIA

Early in the AIDS epidemic, mycobacteria were recognized as major sources of HIV-associated morbidity and mortality. Initially, disseminated MAC was noted to develop in HIV-infected patients. Subsequently, the strong association between HIV and *M. tuberculosis* and nontuberculous mycobacteria, such as *Mycobacterium kansasii*, became clearer. Other nontuberculous mycobacteria are also occasionally identified as causes of pneumonia in HIV-infected persons.

Mycobacterium tuberculosis

Tuberculosis is the most prevalent opportunistic infection complicating the HIV epidemic worldwide. Although other pathogens may predominate in individual areas, no other pathogen poses as great a global threat to persons

immunocompromised by HIV infection as *M. tuberculosis*. Moreover, unlike most HIV-associated infections, *M. tuberculosis* is transmissible from person to person, including to those without HIV infection. In fact, clusters of transmission of tuberculosis that include at least one HIV-infected person are larger, last longer, and have a shorter time period between successive cases than clusters of solely HIV-negative persons.⁷⁷

The AIDS epidemic contributed to a veritable explosion of tuberculosis throughout the world, especially in low-income countries, where it is often the first manifestation of HIV and a leading cause of mortality. The World Health Organization estimated that there were 1.1 million cases of tuberculosis in persons with HIV in 2011.⁷⁸ Almost 80% of these cases were in residents of sub-Saharan Africa.⁷⁸ There are also approximately 11 million HIV-infected individuals with latent tuberculosis.⁷⁸ More than 400,000 HIV-infected persons died of tuberculosis in 2011, making it the leading cause of death in HIV-infected populations worldwide.⁷⁸

The AIDS epidemic has also affected tuberculosis in the United States. Before 1985, the incidence of tuberculosis in the United States regularly declined by 5% to 6% per year. From 1985 through 1992, tuberculosis cases increased by 20%, which resulted in 51,700 additional cases of tuberculosis being reported in excess of that predicted by the annual decline previously noted.⁷⁹ Since 1992, tuberculosis cases have decreased again. Indeed, in 2012, fewer than 10,000 cases were reported, the lowest number since tuberculosis reporting began in 1953.⁸⁰ The proportion of tuberculosis cases with known HIV infection has also decreased from 15% in 2003 to 7.7% in 2012.⁸⁰

It remains unclear whether HIV-infected persons are more likely to acquire tuberculous infection after exposure to *M. tuberculosis* than non-HIV-infected persons. Once an individual becomes infected, however, there is no doubt that HIV infection increases the risk for development of primary tuberculosis as well as progressing from *latent tuberculosis infection* (LTBI) to active tuberculous disease. Instead of a 5% lifetime risk of disease, the risk for tuberculosis among HIV-infected persons with LTBI in the pre-combination ART era has been estimated to be as high as 10% per year.

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampin (also known as rifampicin in many countries), poses a particularly grim prospect for the HIV-infected person. The risk of drug-resistant tuberculosis has been reported to be greater among HIV-infected patients than among others, and drug-resistant tuberculosis appears to be associated with decreased survival, particularly in those with lower CD4⁺ cell counts or in individuals not receiving ART.⁸¹⁻⁸³ In a multivariate analysis, HIV infection was found to be an independent risk factor for isoniazid resistance, for both isoniazid and rifampin resistance, and especially for rifampin monoresistance.⁸⁴ A meta-analysis of risk factors for MDR-TB in Europe found that HIV was an independent risk factor (odds ratio, 3.52).⁸⁵ In addition, HIV-infected patients treated with intermittent rifabutin-based therapy have been found to have a high risk for acquired rifamycin resistance, including monoresistance, particularly if their CD4⁺ lymphocyte counts are less than 100 cells/ μ L.⁸⁶ Factors that lead to acquired drug resistance include an inadequate

initial treatment regimen, patient nonadherence with the prescribed regimen, and the addition of a single drug to a failing regimen. Studies using restriction fragment length polymorphism analysis have shown that MDR-TB can also develop as a result of exogenous reinfection from a multidrug-resistant source.⁸⁷

Extensively drug-resistant tuberculosis (XDR-TB), defined as resistance to at least isoniazid and rifampin (i.e., MDR-TB), plus resistance to any fluoroquinolone and at least one second-line injectable drug, was first reported in 2006.⁸⁸ It has been documented in all regions of the world and in HIV-infected persons.⁸⁹⁻⁹¹ The true extent of XDR-TB is unknown because many laboratories worldwide are unable to perform susceptibility tests, particularly to second-line drugs, and rely only on smear results for diagnosing tuberculosis. A case series of 53 persons with XDR-TB in South Africa found that, of the 44 patients who underwent HIV testing, all were HIV infected; 52 of the 53 patients died, and the median survival was only 16 days.⁹² Epidemiologic evidence strongly suggested that the outbreak of XDR-TB was a result of person-to-person transmission, especially in a nosocomial setting.

Clinical Features. Worldwide, tuberculosis is the most common initial manifestation of underlying HIV infection.⁹³ The clinical and radiographic features of tuberculosis in both HIV-infected and non-HIV-infected persons vary and are fully discussed in Chapter 35. HIV infection is independently associated with an increased risk for extrapulmonary tuberculosis.⁹⁴ HIV infection is also associated with a lower frequency of cavitary tuberculosis, especially in patients with fewer than 200 CD4⁺ T lymphocytes/ μ L at the time of tuberculosis diagnosis.⁹⁵

CD4⁺ Lymphocyte Count. Tuberculosis may develop throughout the course of HIV infection, regardless of the CD4⁺ lymphocyte count, but the incidence of tuberculosis increases as the count decreases. Tuberculosis is much less common in patients receiving ART, but can still happen. The clinical expression of tuberculosis in HIV-infected persons is largely dependent on the degree of host immunosuppression, as indicated by the CD4⁺ lymphocyte count (Table 90-2). HIV-infected persons with early HIV disease typically present with a picture suggestive of reactivation tuberculosis, with disease usually limited to the lungs. In contrast, persons with more advanced HIV disease typically

Table 90-2 Manifestations of HIV-Related Tuberculosis in “Early” and “Late” HIV Infection

Feature	Early HIV	Late HIV
Extrapulmonary	10-15%	>50%
Radiographic distribution	Upper zones	Lower and middle zones
Radiographic findings		
Cavitation	Common	Uncommon
Adenopathy	Uncommon	Common
Miliary	Uncommon	Common
Pleural effusion	Uncommon	Rare

Adapted from Murray JF: Cursed duet: HIV infection and tuberculosis. *Respiration* 57:210-220, 1990.

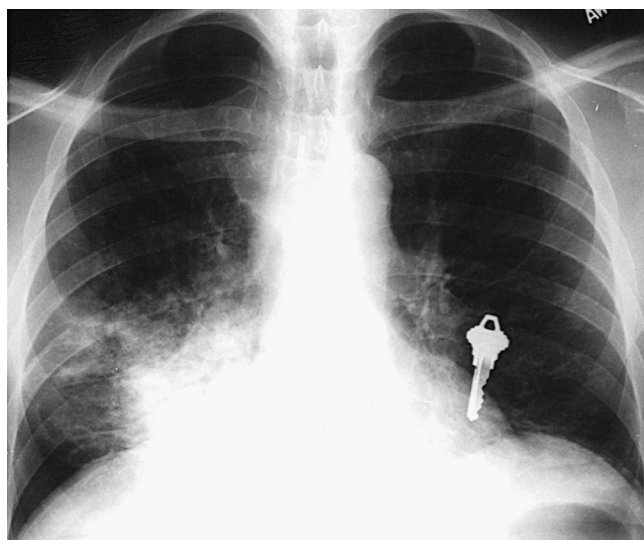


Figure 90-2 Tuberculosis. Frontal chest radiograph of an HIV-infected patient showing focal right lung consolidation with air bronchograms. Culture of sputum revealed *Mycobacterium tuberculosis* that was monorifampin resistant. Knowledge of the patient's CD4⁺ lymphocyte count (<50 cells/μL) and understanding that tuberculosis can present with middle to lower lung zone consolidation during "late" HIV infection were instrumental in making the diagnosis of tuberculosis. The key was in the patient's pocket. (Courtesy L. Huang.)

present with a picture reminiscent of primary pulmonary tuberculosis, often with disseminated or extrapulmonary tuberculosis. In a series of 97 HIV-infected patients with tuberculosis, Jones and colleagues⁹⁶ reported that extrapulmonary tuberculosis was seen in 30 of 43 patients (70%) with a CD4⁺ lymphocyte count of 100 cells/μL or fewer, in 10 of 20 patients (50%) with a count between 101 and 200 cells/μL, in 7 of 16 patients (44%) with a count between 201 and 300 cells/μL, and in only 5 of 18 patients (28%) with a count greater than 300 cells/μL. Virtually any extrapulmonary site may be involved; common sites include lymph nodes (usually cervical, supraclavicular, and axillary), bone marrow, genitourinary tract, central nervous system, and liver.⁹⁷

Imaging. The prevalence of specific chest radiograph features of tuberculosis also depends on the degree of host immunosuppression. Early in the course of HIV infection, tuberculosis mirrors that encountered in immunocompetent persons: upper lung zone opacities, often with cavitation, on chest radiograph. However, later in the course of HIV infection, tuberculosis often presents with middle and lower lung zone opacities (Fig. 90-2, eFig. 90-3); with diffuse opacities, including a miliary pattern (eFig. 90-4); or with a normal chest radiograph. As the CD4⁺ lymphocyte count declines, cavitation becomes less common⁹⁵ and intrathoracic adenopathy (Fig. 90-3, eFig. 90-5) becomes more common. Jones and colleagues⁹⁶ reported that adenopathy was seen on the radiographs of 20 of 58 HIV-infected patients (34%) with a CD4⁺ lymphocyte count of 200 cells/μL or fewer compared with 4 of 29 patients (14%) with a CD4⁺ lymphocyte count greater than 200 cells/μL ($P = 0.04$). ART also affects the chest radiographic appearance in HIV-infected patients with tuberculosis; in one study of 209 patients, 82% of patients receiving ART presented with

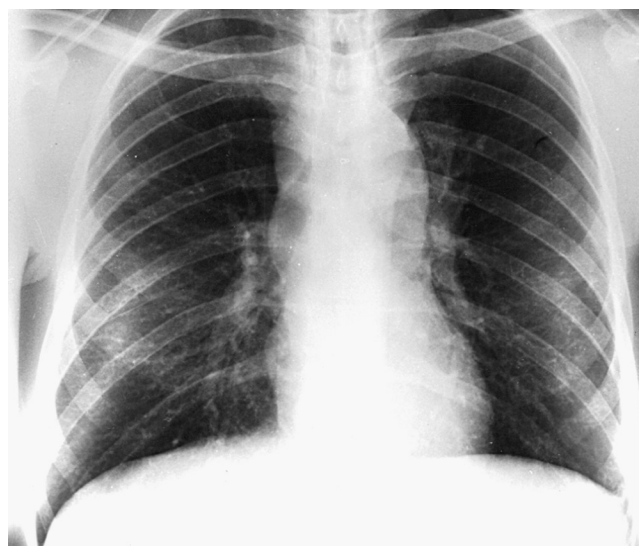


Figure 90-3 Tuberculosis. Frontal chest radiograph of an HIV-infected patient showing mediastinal adenopathy. Culture of biopsy material revealed *Mycobacterium tuberculosis*. Among HIV-infected persons, the proportion of cases that present with intrathoracic adenopathy on chest radiograph increases as the CD4⁺ lymphocyte count decreases. (From Murray JF, Mills J: Pulmonary complications of HIV infection. *Am Rev Respir Dis* 141:1356–1372, 1582–1598, 1990.)

a radiographic pattern of tuberculosis resembling that in immunocompetent persons, compared with 44% of patients not receiving ART ($P < 0.001$).⁹⁸

Diagnosis. The diagnostic approach to tuberculosis is the same for HIV-infected as for non-HIV-infected persons, with the "gold standard" diagnostic test being isolation and identification of *M. tuberculosis* by culture or by nucleic acid amplification (Chapter 35). Three sputum specimens should be examined for AFB and cultured for mycobacteria.²⁹ Current recommendations support the use of nucleic acid amplification testing of at least one sputum specimen because these tests can confirm the presence of tuberculosis or another mycobacteria in smear-positive patients and because nucleic acid amplification testing is more sensitive than AFB smear, allowing more rapid identification of smear-negative, culture-positive samples.^{29,99-101} In patients with a nonproductive cough or scant secretions, sputum induction should be performed. Virtually any specimen can be studied for mycobacteria, including sputum, pleural fluid, urine, cerebrospinal fluid, and BAL fluid; Wang needle, fine-needle, and bone marrow aspirates; and all biopsy and tissue specimens. The sensitivity of mycobacterial culture of induced sputum for HIV-infected patients with pleural effusions due to tuberculosis has been reported to be as high as 77%, and cultures of samples from extrapulmonary sites have a higher sensitivity in those with advanced immunodeficiency.¹⁰² Blood cultures are specific and should be obtained, especially from those persons with a CD4⁺ lymphocyte count less than 200 cells/μL.

All cultures positive for *M. tuberculosis* should be submitted for susceptibility testing, because the results are essential in identifying cases of drug resistance and in tailoring definitive treatment. More rapid identification of drug-resistance may be possible with genotypic testing to identify

drug-resistance mutations in places where these tests are available.^{29,99,100,103}

Treatment. The treatment of patients with tuberculosis is similar for HIV-infected and non-HIV-infected persons (Chapter 35).²⁹ Because tuberculosis is transmissible, persons with suspected tuberculosis should be started promptly on empirical antituberculosis treatment to reduce the risk of transmission. The detection of AFB on smear or in culture, regardless of the source, is an indication for empirical antituberculosis treatment until final identification is obtained. HIV-infected persons with suspected tuberculosis should be started on four antituberculous drugs: isoniazid, rifampin, pyrazinamide, and ethambutol along with pyridoxine.^{29,104} Directly observed therapy is recommended.²⁹ If resistance to rifampin is suspected or confirmed, moxifloxacin or levofloxacin and an aminoglycoside or capreomycin should be included in the initial regimen and a tuberculosis expert consulted.²⁹ When results of species identification and susceptibility testing become available, treatment can be tailored as needed. In the United States, the response to tuberculosis therapy and the time to convert sputum cultures from positive to negative appear to be similar in HIV-infected and non-HIV-infected patients.¹⁰⁴ In sub-Saharan Africa, however, the likelihood of death, especially during the first 2 months of therapy, and of relapse following apparently successful treatment is considerably higher in HIV-infected than in non-HIV-infected patients.¹⁰⁵

HIV-infected patients with tuberculosis are more likely to experience toxicity from antituberculous drugs than are non-HIV-infected persons. One series found that 40% of HIV-infected persons suffered serious adverse events from antituberculous drugs compared with 26% of non-HIV-infected persons ($P = 0.008$).¹⁰⁶ HIV-infected patients are frequently receiving a number of additional medications, and it is often difficult to distinguish an adverse drug effect to antituberculous drugs from adverse effects to these other medications. As a result, the first-line antituberculous drugs (especially isoniazid and rifampin) should only be discontinued permanently if there is strong evidence that these medications were the cause.¹⁰⁴

Despite challenges in ART use during TB therapy, as described later, ART given concurrently with tuberculosis treatment rather than sequentially has been associated with decreased mortality, greater AIDS-free survival, and more rapid conversion of sputum smears and culture in randomized studies.^{29,107-111} Thus, all HIV-infected individuals with TB should receive ART.²⁹ If the patient is naive to ART, it is recommended that ART be initiated within 2 weeks of tuberculosis treatment initiation in individuals with CD4⁺ cell counts less than 50 cells/ μ L and within 8 to 12 weeks in all others.²⁹ Individuals receiving ART should continue its use during TB therapy.

Clinicians need to be aware of several challenges of ART use during TB treatment. HIV-infected patients with tuberculosis who begin therapy for both *M. tuberculosis* and HIV infection may develop *immune reconstitution inflammatory syndrome* (IRIS), a paradoxical reaction presenting as a temporary exacerbation of clinical and radiographic features, which is more common with ART started early during antituberculosis therapy and among those with disseminated

tuberculosis.¹⁰⁸⁻¹¹² Furthermore, simultaneous treatment of HIV and *M. tuberculosis* poses additional challenges in terms of drug interactions. Both HIV *protease inhibitors* (PIs) and *non-nucleoside reverse transcriptase inhibitors* (NNRTIs) have significant interactions with the rifamycins, principally related to the induction or inhibition (or both) of the hepatic *cytochrome P-450* (CYP) enzyme system.¹⁰⁴ Decreased drug levels are associated with development of drug resistance by both HIV and *M. tuberculosis*, whereas increased drug levels are correlated with toxicity. In persons receiving PIs, rifabutin is preferred over rifampin because it is a less potent CYP 3A4 inducer. Information on the interactions between specific antiretroviral drugs and different rifamycins is regularly updated and can be found on such websites as the CDC website <http://www.cdc.gov/tb>. Clinicians caring for HIV-infected patients with tuberculosis should consult experts for aid in management prior to initiating tuberculosis or HIV therapy.

Prevention of Exposure. In hospitals and health care facilities, all persons with HIV infection and signs or symptoms compatible with tuberculosis should be placed in respiratory isolation until three sputum smears are negative. Prevention of transmission of drug-resistant tuberculosis is particularly important, for those with and without HIV infection. In a modeling study, measures such as improved ventilation, rapid drug sensitivity testing, HIV treatment, and tuberculosis isolation facilities were found to be effective preventive measures, but involuntary detention for XDR-TB treatment was thought to lead to an increase in transmission. This study also estimated that mask use and a shift to outpatient therapy could prevent about one third of XDR-TB cases in a highly prevalent area.¹¹³ A subsequent randomized study of patient mask use demonstrated a 56% decrease in TB transmission.^{29,114}

Prevention of Disease. HIV-infected persons are at a high risk for progressing from LTBI to active tuberculosis. Therefore, HIV-infected persons should be tested for LTBI by either a tuberculin skin test or *interferon- γ* (IFN- γ) release assay when HIV infection is first identified.^{29,115} HIV-infected persons who are at risk for exposure to *M. tuberculosis* (either ongoing or repeated) should be tested for LTBI annually.²⁹ In addition, persons who initially had a negative test, but subsequently experienced an increase in their CD4⁺ lymphocyte count to ≥ 200 cells/ μ L due to ART should be retested for LTBI.²⁹ Any individual with a positive test for LTBI should be screened for symptoms and chest radiographic findings suggestive of active TB.²⁹

Several studies document that the risk of LTBI reactivation is virtually eliminated if an HIV-infected person who has been infected with a drug-susceptible organism takes adequate prophylaxis.^{29,115-117} HIV-infected persons with a positive tuberculin skin reaction (defined as 5-mm induration or greater), a positive IFN- γ release assay, or with a history of either of these and who have not received prior treatment for either LTBI or active tuberculosis should receive prophylaxis. HIV-infected individuals who are close contacts of anyone with active TB should also receive prophylactic therapy.²⁹ The standard prophylaxis treatment is isoniazid (300 mg daily or 900 mg twice weekly) plus pyridoxine for 9 months.²⁹ An alternative treatment for LTBI is

rifampin daily for 4 months. The two-drug regimen of rifampin plus pyrazinamide for 2 months is no longer recommended due to an increased incidence of severe hepatotoxicity and death. Although a 12-week regimen of high-dose isoniazid and rifapentine by weekly directly observed therapy is another alternative,¹¹⁸ this regimen is not recommended for HIV-infected patients who are on ART due to drug interactions between certain antiretrovirals and rifapentine. Expert consultation should be sought for patients receiving ART or for individuals exposed to drug-resistant tuberculosis. Routine use of preventive therapy in anergic or purified protein derivative–negative HIV-infected persons is not generally recommended.^{29,115}

Mycobacterium avium Complex

As discussed in Chapter 36, MAC consists of several related *Mycobacterium* species, including *M. avium* and *M. intracellulare*. Until 1980, only 24 cases of disseminated MAC had been reported.¹¹⁹ Coincident with the onset of the AIDS epidemic, the number of cases rose dramatically. With the use of ART, however, the incidence of disseminated MAC has declined since 1996.¹

The pathogenesis of disseminated MAC is incompletely understood, but it is believed to result from primary acquisition of the microorganism, which is ubiquitous in the environment, rather than reactivation of latent infection.¹²⁰ These mycobacteria probably enter the body chiefly through the gastrointestinal tract and occasionally through the lungs.¹²¹ Person-to-person transmission is believed to be uncommon. Nearly all cases of disseminated MAC are caused by *M. avium* serotypes, which suggests that there are important differences in exposure to or virulence of these particular strains.

Clinical Features. Although the lungs are an important potential portal of entry for MAC into the bloodstream, isolated MAC pulmonary disease is rare in the context of AIDS.¹²² The most common clinical presentation of disseminated MAC disease is a febrile wasting syndrome consisting of fever, night sweats, fatigue, anorexia, and weight loss; other manifestations include abdominal pain and chronic diarrhea, hepatosplenomegaly, lymphadenopathy, progressive anemia, and, rarely, extrabiliary obstructive jaundice.¹²³ Laboratory abnormalities include anemia, which is often severe, and an elevated alkaline phosphatase level.

CD4⁺ Lymphocyte Count. More than 95% of cases of disseminated MAC are seen in HIV-infected patients whose CD4⁺ lymphocyte count is 50 cells/ μ L or less.¹²³ Other risk factors for disseminated MAC include a plasma HIV viral level greater than 100,000 copies/mL, history of previous opportunistic infection, and previous MAC colonization of the respiratory or gastrointestinal tract.²⁹

Imaging. The chest radiograph is typically normal, even when the organism is cultured from respiratory tract secretions.¹²¹ Focal pneumonia has been reported (eFig. 90-6) but is extremely rare,¹²² as is presentation as a solitary pulmonary nodule (eFig. 90-7). More frequently seen—but still uncommon—are endobronchial lesions without pneumonia.¹²⁴ These endobronchial lesions appear to be

submucosal “pearls” (eFig. 90-8) that are teeming with AFB on biopsy. Lymphadenopathy—with or without necrosis—is one of the more common imaging manifestations of thoracic MAC infection in HIV-infected patients (eFig. 90-9). Many of the cases of isolated pulmonary MAC were reported in patients who received ART, thus raising the possibility that this particular manifestation is an example of immune reconstitution. Clinicians should be aware of this possibility when starting patients on ART because IRIS may be seen either in patients with diagnosed disease or in those with subclinical infection.

Diagnosis. In HIV-infected patients with MAC, the organism can be cultured from numerous sites, but the most productive sources are blood, bone marrow, liver, or lymph nodes.¹²³ The sensitivity of blood cultures for disseminated MAC has ranged from 86% to 98% of cases in which disseminated disease was confirmed by autopsy. The diagnosis of disseminated MAC can also be established by cultures from any normally sterile body site. Often, MAC is cultured from respiratory specimens such as sputum or BAL fluid but, depending on the clinical situation, this finding may not indicate either pulmonary or disseminated disease.^{121,125} If patients have abnormal chest radiographs with positive sputum cultures, the diagnostic criteria for nonimmunosuppressed hosts recommended by the *American Thoracic Society and the Infectious Disease Society of America* (ATS/IDSA), listed in Table 36-3, should be applied.¹²⁵ The pathologic findings of MAC infection are characteristic, but not definitive; AFBs are remarkably abundant and are often packed within foamy macrophages or histiocytes; granulomas are usually absent or poorly formed.

Treatment. As emphasized in Chapter 36, the key to any regimen is the use of at least two drugs including a macrolide: clarithromycin (500 mg twice daily) is preferred, but azithromycin (500 to 600 mg daily) can be substituted if needed.²⁹ One of these should be combined with ethambutol (15 mg/kg/day). Use of a third or fourth agent such as rifabutin (300 mg daily), an aminoglycoside (i.e., amikacin 10 to 15 mg/kg intravenously daily), or a fluoroquinolone (i.e., levofloxacin 500 mg daily) can be considered in patients with advanced immunosuppression, high mycobacterial burden, or the inability to take ART.²⁹ As with tuberculosis, the use of rifabutin must be carefully scrutinized with concurrent administration of an NNRTI or a PI.

Prevention of Exposure. Although MAC can be found in environmental sources such as food and water, there are no specific recommendations regarding exposure avoidance as a prevention strategy.²⁹ Similarly, although the presence of MAC in a stool or respiratory specimen is predictive of disseminated disease, routine screening of either is not recommended.

Prevention of Disease. The CDC, NIH, and HIVMA/IDSA guidelines recommend that MAC prophylaxis be administered to HIV-infected patients with a CD4⁺ lymphocyte count less than 50 cells/ μ L and no clinical evidence of disseminated MAC.²⁹ Preferred MAC prophylaxis regimens include azithromycin (1200 mg weekly or 600 mg twice weekly) or clarithromycin (500 mg twice daily). Rifabutin

(300 mg daily) is an alternative regimen if patients are intolerant of azithromycin or clarithromycin.²⁹ If rifabutin is to be used, tuberculosis must first be ruled out, because its use for MAC has been associated with rifampin monoresistance in *M. tuberculosis*. Primary MAC prophylaxis should be discontinued in persons who have experienced a significant response to ART with an increase in their CD4⁺ lymphocyte count to greater than 100 cells/ μ L for at least 3 months.²⁹ Individuals with a history of disseminated MAC should receive secondary prophylaxis/chronic maintenance therapy with a MAC treatment regimen cited earlier. In the setting of ART with increases in the CD4⁺ lymphocyte count to more than 100 cells/ μ L for at least 6 months—and after a minimum of 12 months of a macrolide-based MAC treatment regimen—most patients can discontinue therapy without relapse.²⁹

Mycobacterium kansasii

As described in Chapter 36, *M. kansasii* has a particular geographic distribution, predominantly in the southern and central United States.¹²⁵ Clusters of disease have also been reported in Europe, Asia, and Africa. Before the AIDS epidemic, infection and disease due to *M. kansasii* were uncommon; thereafter, a dramatic increase in the incidence associated with HIV infection was observed, even in areas where *M. kansasii* was not thought to be endemic. Bloch and associates¹²⁶ found a cumulative incidence of *M. kansasii* infection of 2.4 cases per 100,000 HIV-infected adults in three counties in northern California, a rate that is almost five times higher than the national rate. Although *M. kansasii* pulmonary disease can be clinically indistinguishable from tuberculosis,¹²⁷ person-to-person transmission has not been documented, and infection is thought to arise from environmental sources.

CD4⁺ Lymphocyte Count. Similar to tuberculosis in HIV-infected persons, *M. kansasii* pneumonia can develop at any CD4⁺ lymphocyte count. Most HIV-infected patients with *M. kansasii*, however, have evidence of severe immunosuppression with CD4⁺ lymphocyte counts typically less than 100 cells/ μ L.¹²⁶⁻¹²⁸ In a study from the ART era, Canueto-Quintero and colleagues¹²⁷ reported a mean CD4⁺ lymphocyte count of 20 cells/ μ L among 25 HIV-infected patients with *M. kansasii*. Witzig and coworkers¹²⁸ found that 32 of 49 HIV-infected patients (65%) with *M. kansasii* had isolated pulmonary disease (mean CD4⁺ lymphocyte count, 75 cells/ μ L), whereas the remainder had disseminated disease (mean CD4⁺ lymphocyte count, 28 cells/ μ L).

Imaging. The chest radiographic findings of *M. kansasii* are varied. The most common radiographic findings resemble tuberculosis and include alveolar opacities, diffuse opacities, and cavities (see Fig. 36-5; eFig. 90-10); masses, intrathoracic adenopathy, and pleural effusions have also been reported. In a series of 83 HIV-infected patients with *M. kansasii*, the most frequent findings were consolidation (66%) and nodules (42%); abnormalities were most often located in the mid-lung and lower lung zones (89%), and in 10%, radiographs were normal.¹²⁹

Diagnosis. The diagnosis of *M. kansasii* rests on its isolation and subsequent identification by culture. Pulmonary

disease can be diagnosed by all of the techniques used for the diagnosis of tuberculosis. Unlike tuberculosis, however, in which identification of *M. tuberculosis* is diagnostic of disease, the identification of *M. kansasii* can occasionally represent colonization rather than disease.¹³⁰ As previously mentioned, the ATS/IDSA guidelines have defined criteria for diagnosis of nontuberculous mycobacterial pulmonary disease that includes *M. kansasii* (see Table 36-3).¹²⁵ In addition, the use of subtyping defined by PCR-restriction enzyme analysis of the *hsp65* gene may help distinguish pathogenic from nonpathogenic isolates.¹³¹

Treatment. The recommended regimen for treatment of *M. kansasii* pulmonary disease consists of isoniazid (300 mg daily), rifampin (600 mg daily), and ethambutol (15 mg/kg daily).¹²⁵ Patients should also receive pyridoxine (50 mg daily) during treatment. Patients who take PI or NNRTI therapy for HIV infection should receive rifabutin or clarithromycin in place of rifampin. Pyrazinamide is unacceptable as an alternative drug because all *M. kansasii* isolates are resistant. Patients should receive treatment for a minimum of 12 months after their cultures become negative.

Prevention. There are no recommended prevention strategies for *M. kansasii*.

Other Mycobacteria

MAC and *M. kansasii* account for the great majority of nontuberculous mycobacterial infections complicating HIV disease. Other mycobacteria, however, have occasionally been identified.^{123,132} Increased frequency of exposure or specific defects in host defenses might account for the predominance of MAC and *M. kansasii* over other nontuberculous mycobacteria in AIDS patients; differences in the virulence of the various mycobacterial species are also likely to play an important role.

FUNGI

Early in the AIDS epidemic, fungi were recognized as major sources of morbidity and mortality. Despite the overall decline in HIV-associated opportunistic infections in the United States, fungi remain important causes of disease. Several fungi can cause pulmonary disease in HIV-infected persons.¹³³ *Pneumocystis jirovecii*, formerly *Pneumocystis carinii*, previously classified as a protozoan but currently considered a fungus, remains the most common AIDS-defining opportunistic infection in the United States and Western Europe and is a common cause of HIV-associated pneumonia. *Cryptococcus neoformans*, the most common cause of meningitis in HIV-infected persons, often presents with an associated pneumonia. The endemic fungi *H. capsulatum*, *C. immitis*, *Penicillium marneffei*, and, to a lesser extent, *Blastomyces dermatitidis* are among the chief causes of HIV-associated disease seen in their particular geographic regions, and all have important pulmonary presentations. Finally, invasive aspergillosis is often a devastating pulmonary disease seen in HIV-infected persons with severe immunodeficiency. Further information about fungal pulmonary diseases is provided in Chapters 37 and 38.

Pneumocystis jirovecii

PCP (shorthand for *Pneumocystis pneumonia*) remains the most common AIDS-defining opportunistic infection in the United States, even though its overall incidence has declined substantially.¹ Early in the AIDS epidemic, PCP accounted for nearly two thirds of AIDS-defining diagnoses, and PCP developed in an additional 15% to 20% of patients at some time during their HIV disease. Two factors—the use of ART and *Pneumocystis* prophylaxis—have dramatically reduced the overall number of cases. Nevertheless, PCP remains a risk, chiefly among persons who are unaware of their HIV infection, those who fail to seek medical care, and those who fail to adhere to or respond to ART or *Pneumocystis* prophylaxis.¹³⁴⁻¹³⁶ Recent reports of increased PCP cases in immunosuppressed non-HIV populations have unclear implications for HIV-infected populations.^{137,138}

History and Epidemiology. First identified early in the 20th century by Chagas, *Pneumocystis* was initially recognized as a human pathogen in the 1940s and 1950s. Despite more than a century of experience, several gaps in our understanding of this omnipresent organism remain.¹³⁹⁻¹⁴² One major obstacle that has impeded further advances has been the inability to culture *Pneumocystis* in vitro. Although mammals are the only known hosts of *Pneumocystis* and a number of mammals are susceptible to infection, *Pneumocystis* has been demonstrated to be species-specific.¹⁴³ Although *Pneumocystis* can be easily transmitted between mammals of the same species, animal studies that have attempted to transmit *Pneumocystis* from one species to another have been unsuccessful.¹⁴³ In recognition of the host-species specificity of *Pneumocystis*, the *Pneumocystis* that causes *Pneumocystis pneumonia* in humans is now referred to as *P. jirovecii*, in honor of Otto Jirovec, the parasitologist who is credited with first identifying *Pneumocystis* as the cause of pulmonary disease in humans.^{144,145}

The precise ecologic niche for *P. jirovecii* and its mode of transmission is unknown.^{141,146} The inability to maintain human *Pneumocystis* in culture suggests that *P. jirovecii* may be unable to grow outside of its human host. Given its species specificity, it is doubtful that other mammals are the reservoir for *P. jirovecii*. This host-species specificity also implies coevolution of humans and *P. jirovecii* that, in turn, implies long-term carriage of *P. jirovecii* in its human host. Infection with *P. jirovecii* is almost ubiquitous. Up to 85% to 100% of the U.S. population have specific antibodies directed against *P. jirovecii* by the age of 3 years.^{147,148} Clearly, PCP never develops in most of these individuals. In the setting of severe immunosuppression, however, PCP can affect significant proportions of people. These studies and others suggest that reactivation of latent infection is a cause of *P. jirovecii* disease among immunocompromised hosts. Outbreaks of newly acquired infection after de novo exposure to persons with PCP have also been documented among immunocompromised patients in pediatric wards, cancer clinics or wards, transplantation units, and other confined spaces, which suggests person-to-person transmission of *P. jirovecii* and the rapid development of disease. Results of studies that have used molecular tools to detect *Pneumocystis* are consistent with transmission of *P. jirovecii* from patients with PCP to their household and hospital con-

tacts,^{149,150} probably via inhalation of a *Pneumocystis*-containing aerosol.^{151,152}

Risk Factors. Traditional risk factors for the development of PCP among HIV-infected adults include a CD4⁺ lymphocyte count less than 200 cells/μL, a history of PCP, and oropharyngeal candidiasis.^{153,154} In the current ART era, HIV-infected persons with a CD4⁺ lymphocyte count between 101 and 200 cells/μL, but a suppressed HIV RNA level on ART appear to be at low risk for primary PCP.^{155,156}

CD4⁺ Lymphocyte Count. Approximately 95% of adolescent and adult cases of PCP are seen in HIV-infected patients whose CD4⁺ lymphocyte count is less than 200 cells/μL.¹⁵⁴ The Multicenter AIDS Cohort Study found a markedly increased risk for PCP among HIV-infected subjects with a CD4⁺ lymphocyte count of 200 cells/μL or fewer at study entry.¹⁵³ These subjects had a nearly fivefold greater risk of developing PCP than did subjects who had a CD4⁺ lymphocyte count higher than 200 cells/μL at study entry. This study also demonstrated that the presence of fever for 2 weeks or more and the development of thrush were independent predictors for PCP. Stansell and colleagues¹⁵⁴ found that the incidence of PCP increased as the CD4⁺ lymphocyte count declined. Subjects with a CD4⁺ lymphocyte count between 101 and 200 cells/μL had an incidence of 5.95 cases of PCP per 100 person-years, whereas those with a CD4⁺ lymphocyte count of 100 cells/μL or fewer had 11.13 cases per 100 person-years. In persons on ART, the most recent CD4⁺ lymphocyte count is generally a better indicator of an HIV-infected person's risk for PCP than their nadir CD4⁺ lymphocyte count.

Clinical Features. HIV-infected adults, unlike other immunocompromised persons, usually have a prolonged prodromal illness associated with PCP. Kovacs and coworkers¹⁵⁷ found the median duration of symptoms in 40 HIV-infected patients was 28 days, which was significantly longer than the median duration of 5 days seen in 37 patients with other underlying conditions ($P < 0.0002$). Kales and colleagues¹⁵⁸ reported a median duration of symptoms of 3 weeks in 145 HIV-infected patients with PCP and found that 72 patients (50%) had a duration of symptoms of 2 weeks or longer. This duration of symptoms can often be used to distinguish PCP from pyogenic pneumonia, which typically presents with 3 to 5 days of symptoms.

Classically, PCP presents with fever, a nonproductive cough, and dyspnea on exertion. Fever was noted in 86%, cough in 91%, and dyspnea in 95% in one series of 145 HIV-infected patients with PCP.¹⁵⁸ High temperature, rigors, purulent sputum, and pleuritic chest pain are uncommon and can be used to distinguish PCP from pyogenic pneumonia. In a multivariable analysis, Selwyn and associates¹⁵⁹ found that the presence of purulent sputum was an independent predictor of bacterial pneumonia, rather than of PCP or tuberculosis.

Physical examination of the chest may be normal. In the series reported by Kales and colleagues,¹⁵⁸ 78 patients (54%) with PCP had a normal lung examination. When abnormal, the most frequent findings on lung auscultation are inspiratory crackles, which have been reported to be

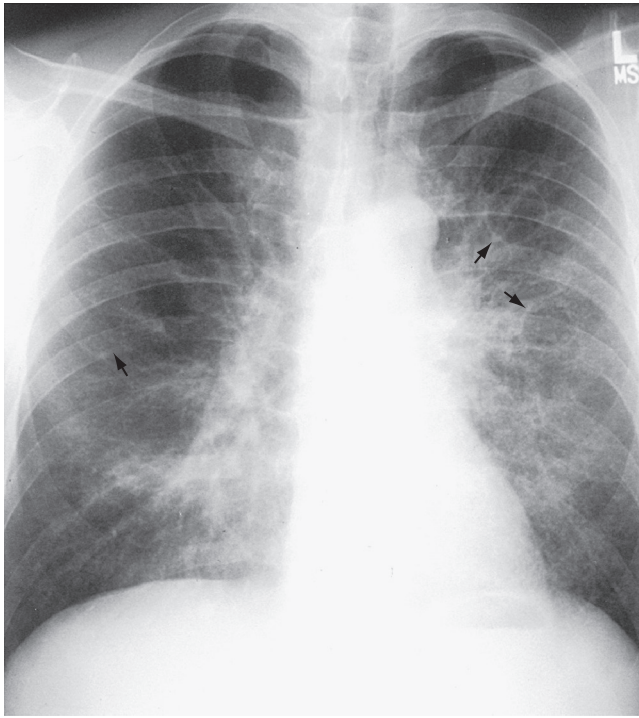


Figure 90-4 *Pneumocystis pneumonia*. Frontal chest radiograph of an HIV-infected patient with *Pneumocystis pneumonia* showing bilateral, predominantly perihilar, granular opacities and three pneumatoceles (arrows). Pneumatoceles may be single or multiple in number, and small or large in size, and may predispose patients to pneumothorax. (Courtesy L. Huang.)

associated with a greater disease severity and an increased mortality.¹⁵⁸ Oxygen desaturation with exertion is a sensitive but nonspecific indicator of PCP.

Numerous studies have shown that the serum *lactate dehydrogenase* (LDH) level is increased in patients with PCP; however, an elevated serum LDH level does not establish the diagnosis of PCP, nor does a normal serum LDH value rule out the diagnosis. Serum *S*-adenosylmethionine concentration¹⁶⁰ and β -D-glucan,^{161,162} have also been reported to be potential diagnostic tools for PCP.

Imaging. Classically, PCP presents with bilateral, symmetrical reticular opacities, often manifesting as peribronchovascular indistinctness (eFig. 90-11), or as granular or a ground-glass appearance (eFig. 90-12A);¹⁶³ these opacities typically begin in the perihilar region and extend outward as the disease severity increases. The ground-glass opacity appearance is particularly associated with the chest CT manifestations of this disorder (see eFig. 90-12B). Occasionally, the opacities are unilateral or asymmetrical (eFig. 90-13); a lobar or focal radiographic pattern is uncommon. Thin-walled cysts, or pneumatoceles, are seen in 10% to 20% of cases (Fig. 90-4).¹⁶⁴ Pneumatoceles may be present at the time of diagnosis or may develop during PCP therapy. Pneumatoceles may be single (eFig. 90-14A) or multiple (eFig. 90-14B-D), and small or large, and predispose patients to pneumothorax (eFig. 90-15), which is another radiographic presentation of PCP. Usually pneumatoceles resolve (see eFig. 90-14B-D), but occasionally they persist despite successful therapy.

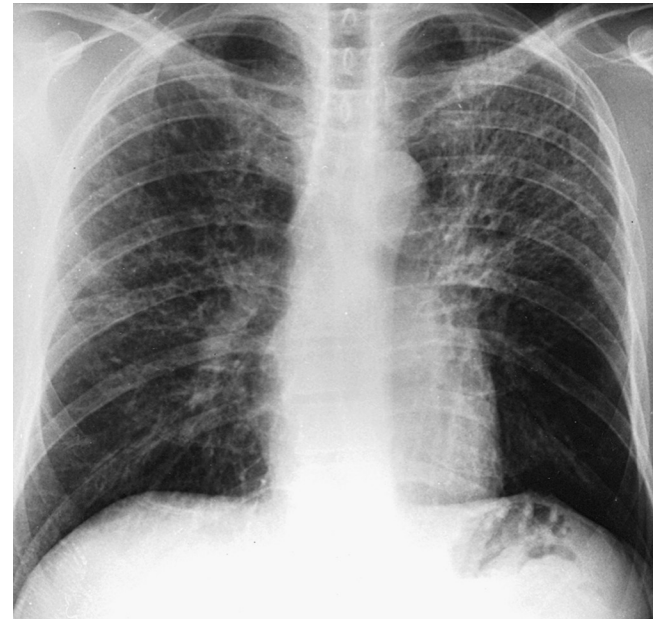


Figure 90-5 *Pneumocystis pneumonia*. Frontal chest radiograph of an HIV-infected patient who had been receiving aerosolized pentamidine showing reticular infiltration, predominantly of the upper lung zones, secondary to relapsed *Pneumocystis pneumonia* (PCP). This radiographic presentation, however, may also be seen in patients on no PCP prophylaxis. (From Murray JF, Mills J: Pulmonary complications of HIV infection. *Am Rev Respir Dis* 141:1356–1372, 1582–1598, 1990.)

Virtually every possible radiographic finding, including focal, lobar, or segmental consolidation (eFigs. 90-16 through 90-18), nodules (eFig. 90-19) with or without cavitation, and a miliary pattern, can be seen occasionally.¹⁶⁴ Apical or upper lung zone disease that mimics tuberculosis (Fig. 90-5, eFig. 90-20) is typically associated with aerosolized pentamidine prophylaxis, although this presentation can be seen as well in patients taking oral prophylaxis or no preventive therapy. Intrathoracic adenopathy and pleural effusions are rarely due to PCP. These radiographic findings should prompt a search for an alternate or at least a coexisting process such as bacterial pneumonia, tuberculosis, fungal pneumonia, or pulmonary KS. PCP may also present with a normal chest radiograph. Published studies report the incidence of a normal radiograph to range from 0% to 39%.¹⁶³⁻¹⁶⁵ In persons with a high clinical suspicion for PCP but a normal chest radiograph, chest high resolution CT can be useful.¹⁶⁶

Diagnosis. The diagnosis of PCP rests on the microscopic visualization of the characteristic *P. jirovecii* cysts or trophic forms (or both) on stained respiratory specimens. The standard methods for detection of *P. jirovecii* have been with cyst wall stains such as methenamine silver and toluidine blue-O or with Giemsa and Diff-Quik, which stain both the cysts and trophic forms; monoclonal antibodies to *P. jirovecii* are also used.¹⁶⁷ PCR-based techniques have also been employed and have been reported to be more sensitive but also less specific than these other methods.^{167,168}

Pneumocystis jirovecii can be detected in expectorated (infrequently) or induced sputum; in pulmonary secretions obtained by endotracheal suction, BAL, or percutaneous

aspiration of lung parenchyma; and in pulmonary tissue obtained by transbronchial, thorascopic, or open-lung biopsy. Of these, sputum induction and BAL are the most widely used. Sputum induction is an appropriate initial diagnostic procedure for PCP, but the sensitivity of induced sputum is less than 100% and thus a negative result should be followed by a more definitive procedure, namely bronchoscopy with BAL.³¹ BAL is performed in the most affected lobe visualized on chest radiograph. For patients with diffuse radiographic disease, BAL in the right middle lobe is usually performed. For patients with an upper lung zone predominance on radiograph, lavage in both an upper lobe and the right middle lobe should be considered. Despite the widespread use of TMP-SMX and dapsone for PCP prophylaxis, no studies have evaluated whether the yield of diagnostic studies is changed in persons receiving one of these medications. Clinical experience suggests that, although the severity of chest radiograph abnormalities may be milder in patients receiving prophylaxis than in those receiving no prophylaxis, the diagnostic yields from both sputum induction and BAL remain the same.

Treatment. The treatment of choice for patients with mild, moderate, and severe PCP remains TMP-SMX administered for 21 days.²⁹ TMP-SMX possesses many benefits, including availability in both an intravenous and an oral form, excellent oral bioavailability, and activity against many community-acquired bacteria that may cause concomitant pyogenic infection. The usual dose of TMP is 15 mg/kg/day (range, 15 to 20 mg/kg/day) and that of SMX is 75 mg/kg/day (range, 75 to 100 mg/kg/day), divided into three or four daily doses (Table 90-3). Dosing may be intravenous (recommended for patients with moderate or severe PCP) or oral. Unfortunately, adverse effects from TMP-SMX are frequent in HIV-infected patients and include rash, fever, gastrointestinal complaints (nausea, vomiting), elevated transaminases, hyperkalemia, and bone marrow suppression, especially anemia and neutropenia.

These effects often develop during the second week of therapy. In a significant proportion of HIV-infected patients, the side effects of TMP-SMX are ultimately treatment-limiting. Rare adverse reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, and a clinical syndrome resembling septic shock with hypotension, fever, pulmonary opacities, and renal and hepatic dysfunction. Studies are conflicting regarding the presence of potential TMP-SMX drug resistance in *Pneumocystis*.^{169,170}

For patients with an allergy to or intolerance of TMP-SMX, alternative treatment regimens (see Table 90-3) include intravenous pentamidine, clindamycin plus primaquine, trimethoprim plus dapsone, and atovaquone.²⁹ Aerosolized pentamidine should not be used for PCP treatment.²⁹ Small reports describe successful PCP treatment with echinocandins.^{171,172} Similar to tuberculosis, HIV-infected patients with PCP who begin therapy for *Pneumocystis* and initiate ART may develop paradoxical reactions, usually a temporary exacerbation of clinical and radiographic features but occasionally respiratory failure, due to immune reconstitution.^{173,174} The diagnosis of IRIS is one of exclusion. Patients with paradoxical reactions only rarely require discontinuation of antiretroviral therapies, and symptomatic therapy is recommended.

Corticosteroid Therapy. In 1990, the NIH-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for *Pneumocystis* Pneumonia¹⁷⁵ concluded that adjunctive corticosteroid therapy “can clearly reduce the likelihood of death, respiratory failure, or deterioration of oxygenation in patients with moderate-to-severe *Pneumocystis* pneumonia.” The panel recommended that corticosteroids be given to adults or adolescents with documented or suspected PCP if they have an arterial PO₂ level less than 70 mm Hg or an alveolar-arterial PO₂ difference greater than 35 mm Hg. Adjunctive corticosteroids, either oral prednisone or intravenous methylprednisolone, should be started at the same time as specific anti-*Pneumocystis*

Table 90-3 Treatment Regimens for *Pneumocystis* Pneumonia*

Treatment Regimen	Dose(s), Frequency	Toxicities
MILD PCP[†] (PaO₂ >70 mm Hg AND ALVEOLAR-ARTERIAL O₂ DIFFERENCE <35 mm Hg)		
Trimethoprim-sulfamethoxazole (TMP-SMX)	15-20 mg/kg (TMP component) daily (q 6-8 hours)	Fever, dermatologic, gastrointestinal, hematologic
Trimethoprim plus Dapsone	15-20 mg/kg daily (q 6-8 hours) 100 mg once daily	Dermatologic, gastrointestinal, hematologic
Clindamycin plus Primaquine	1800 mg daily (q 6-8 hours) 30 mg (base) once daily	Dermatologic, gastrointestinal, hematologic
Atovaquone	750 mg thrice daily	Dermatologic, gastrointestinal
MODERATE-SEVERE PCP[‡] (PaO₂ ≤70 mm Hg OR ALVEOLAR-ARTERIAL O₂ DIFFERENCE ≥35 mm Hg)		
Trimethoprim-sulfamethoxazole (TMP-SMX)	15-20 mg/kg (TMP component) daily (q 6-8 hours)	Fever, dermatologic, gastrointestinal, hematologic
Pentamidine	3-4 mg/kg IV once daily	Renal, pancreatic
Clindamycin plus Primaquine	1800-2400 mg (q 6-8 hours) 30 mg (base) once daily	Dermatologic, gastrointestinal, hematologic

*Recommended duration of therapy = 21 days.

[†]Oral route is preferred for patients with mild *Pneumocystis* pneumonia (PCP) who are treated as outpatients.

[‡]Intravenous (IV) route is preferred (at least until clinical improvement) for patients with moderate-severe PCP. Adjunctive corticosteroids (prednisone 40 mg, PO, twice daily for 5 days, then 40 mg, PO, once daily for 5 days, then 20 mg, PO, once daily for 11 days or potency-equivalent Solu-Medrol IV) should also be administered.

treatment is begun regardless of whether the diagnosis has been confirmed.

Early in the AIDS epidemic, it was realized that acute respiratory failure secondary to PCP, if severe enough to warrant mechanical ventilation, had a mortality rate of 86% or greater.¹⁷⁵ Subsequent reports from individual hospitals confirmed this gloomy prognosis; 39 of 45 patients who were intubated and ventilated for PCP at San Francisco General Hospital from 1981 to 1985 died, a mortality rate of 87%.⁷⁷ Although the mortality associated with acute respiratory failure secondary to PCP remains significant (approximately 30% to 50%), encouraging progress has been made.^{176,177} HIV-infected patients with PCP and respiratory failure requiring mechanical ventilation should be managed with lung-protective strategies as for patients with acute respiratory distress syndrome.¹⁷⁸ At least one retrospective study by Morris and colleagues¹⁷⁶ suggests that ART may be beneficial in these cases, although prospective randomized clinical trials in the intensive care unit involving mechanically ventilated patients are lacking.^{179,180}

Prevention of Exposure. The natural reservoir for human *Pneumocystis* remains unknown.¹⁸¹ Both an environmental and a human reservoir have been suggested.^{146,182} Whether PCP results from reactivation of latent infection or also from a recent infection is debated; reports of cluster outbreaks of PCP among different immunocompromised populations support the theory that PCP can result from a recent exposure and person-to-person transmission. Accordingly, some authorities have argued that HIV-infected and other immunocompromised persons who are at risk for PCP should avoid close contact with any individuals who have PCP. However, the current CDC, NIH, and HIVMA/IDSA guidelines state “data are insufficient to support isolation as standard practice.”²⁹

Prevention of Disease. HIV-infected adults or adolescents (including those on ART) who have a CD4⁺ lymphocyte count less than 200 cells/ μ L or a history of oropharyngeal candidiasis should receive primary *Pneumocystis* prophylaxis, and persons with prior PCP should receive secondary prophylaxis (Table 90-4).²⁹ Once started, HIV-infected adults and adolescents should remain on PCP prophylaxis, unless their CD4⁺ lymphocyte counts increase from less than 200 cells/ μ L to greater than 200 cells/ μ L for at least 3 months as a result of ART; several studies have demonstrated that primary and secondary PCP prophylaxis

can be safely discontinued in the vast majority of these persons.²⁹ In rare cases, however, PCP has recurred after the discontinuation of secondary PCP prophylaxis, despite an apparent ART-associated immune reconstitution.¹⁸³

TMP-SMX, dapsone, atovaquone suspension, and aerosolized pentamidine are the standard options for PCP prophylaxis.²⁹ TMP-SMX is the first-line choice for primary and secondary prophylaxis against *Pneumocystis*. For those patients intolerant of TMP-SMX, dapsone and atovaquone are both oral drugs that can be used. Many authorities would add pyrimethamine to these drugs for patients with a history of PCP, a CD4⁺ lymphocyte count less than 100 cells/ μ L, or both. For patients who are *T. gondii* immunoglobulin G antibody positive, pyrimethamine should be added. Aerosolized pentamidine remains an effective and well-tolerated prophylaxis option; however, caution must be exercised when using this drug for secondary prophylaxis or in patients with a CD4⁺ lymphocyte count less than 100 cells/ μ L because prophylaxis break-through may be more frequent in this population.

Cryptococcus Species

Cryptococcosis is a disease caused by *C. neoformans* or *C. gattii*. Cryptococcus is the only encapsulated fungus that infects humans, either healthy or immunocompromised, and India ink or mucicarmine staining can identify its polysaccharide capsule.¹⁸⁴ *C. neoformans* and *C. gattii* can be subclassified into four serotypes, based upon capsular agglutination reactions, and two species with two varieties. *Cryptococcus* infection is transmitted after inhalation of a yeast-containing aerosol. *C. neoformans* is global in distribution, and is most commonly isolated from bird excrement, decaying fruit, and soil. Most cryptococcal disease in HIV-infected persons is due to *C. neoformans*. *Cryptococcus gattii* has been isolated from trees in Australia, as well as the Pacific Northwest of the United States and Southwestern Canada, where outbreaks of disease have been reported. *C. gattii* is more likely to infect immunocompetent hosts, although it also causes disease in HIV-infected individuals.

The incidence of cryptococcosis in HIV-infected persons has dramatically declined since the introduction of ART. In one population-based surveillance study, the annual incidence of cryptococcosis decreased from 66 per 1000 persons with AIDS in 1992 to 7 per 1000 persons in 2000 in the Atlanta area, and from 24 per 1000 persons with AIDS in 1993 to 2 per 1000 persons in 2000 in the Houston area.¹⁸⁵ Using national surveillance data, a study from

Table 90-4 Prevention of *Pneumocystis* Pneumonia

Prevention Regimens	Alternative Dosing	Comments
Trimethoprim-sulfamethoxazole 1 double-strength (DS) tablet daily Dapsone 100 mg daily	1 single-strength tablet daily or 1 DS tablet thrice weekly	Also effective prophylaxis against <i>Toxoplasma gondii</i> and many bacterial pathogens Combine with pyrimethamine and leucovorin in persons who are <i>T. gondii</i> immunoglobulin G antibody positive. Consider combining with pyrimethamine and leucovorin when used for secondary prophylaxis
Atovaquone suspension 1500 mg daily, or 750 mg twice daily		Improved bioavailability compared to tablets
Aerosolized pentamidine 300 mg monthly via RespirGard II nebulizer		May be associated with increased risk of extrapulmonary disease

France found a 46% decrease in the incidence of cryptococcosis in HIV-infected patients from the pre-combination ART period (1985-1996) to the early combination ART period (1997-2001).¹⁸⁶

Despite a declining incidence, exposure to *Cryptococcus* and cryptococcal disease is increasingly recognized in Africa and Southeast Asia. In a study from Uganda, *Cryptococcus* was isolated from 11% of BAL specimens in patients who presented with cough of greater than 2 weeks duration.¹⁸⁷ Although cryptococcal pneumonia can be a rare cause of mortality in this population,¹⁸⁸ not all cases in which *cryptococcus* was isolated were treated with antifungal therapy, raising the possibility of colonization or isolated infection.¹⁸⁷ *Cryptococcal antigen* (CRAG) testing suggests that cryptococcal infection may be more widespread than previously appreciated. In a study from Thailand of patients hospitalized with acute respiratory symptoms, 13% of HIV-infected patients compared to none of the HIV-uninfected patients had a positive CRAG test.¹⁸⁹ The proportion of HIV-infected patients with a positive CRAG in other similar studies ranged from 5% to 11%; the likelihood of a positive test increases among patients with CD4⁺ cell counts less than 100 cells/ μ L.¹⁹⁰⁻¹⁹²

Clinical Features. Although the portal of entry is the lung, cryptococcal pulmonary infection is often asymptomatic or minimally symptomatic, and the most commonly encountered manifestation of cryptococcal disease is meningitis.^{186,193,194} In a large series of 106 HIV-infected patients with cryptococcal disease, 89 patients (84%) had meningitis, and only 4 patients (4%) had isolated pneumonia.¹⁹³ In a population-based surveillance study that included 1322 HIV-infected patients with cryptococcal disease, only 45 patients (3%) had pulmonary disease in the absence of both fungemia and meningitis.¹⁸⁵ Autopsy studies suggest that pulmonary disease is underdiagnosed, particularly in settings where diagnostic facilities are limited.¹⁹⁵

When present, the most frequent respiratory complaints are cough and dyspnea.^{193,196} Pleuritic chest pain and productive cough have also been reported,¹⁹⁷ perhaps distinguishing pulmonary cryptococcosis from PCP. Although more rare, cases of acute respiratory failure have been reported.¹⁹⁵

CD4⁺ Lymphocyte Count. In most cases, cryptococcosis infects patients with a CD4⁺ lymphocyte count less than 200 cells/ μ L, and usually less than 100 cells/ μ L. A study of 1644 patients reported a median CD4⁺ count of 24 cells/ μ L with a range of 0 to 480 cells/ μ L.¹⁸⁶ A study from Uganda from the current ART era reported a median CD4⁺ count of 23 cells/ μ L.¹⁹⁸

Imaging. Cryptococcal pneumonia most commonly presents with diffuse bilateral interstitial opacities.^{197,199} In one study, Meyohas and associates²⁰⁰ reported interstitial opacities in 60 of 92 radiographs (65%) (eFig. 90-21); in addition, focal consolidation (13%) (eFig. 90-22), nodular opacities (11%) (eFig. 90-23), cavitation (11%) (Fig. 90-6), pleural effusion (14%), and hilar adenopathy (27%) (eFig. 90-24) were noted. More rarely, radiographic findings include a miliary pattern (eFig. 90-25),²⁰¹ solitary pulmonary nodules,²⁰² pulmonary masses,²⁰³ isolated pleural

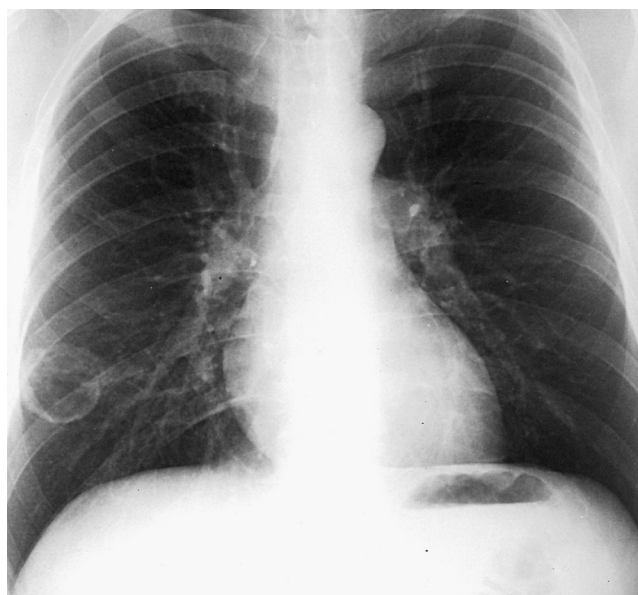


Figure 90-6 Cryptococcal infection. Frontal chest radiograph of an HIV-infected patient showing a solitary cavitary lesion in the right lower lung field. Culture of bronchoalveolar lavage fluid revealed *Cryptococcus neoformans*. In HIV-infected patients, cryptococcal disease can present with a wide range of chest radiographic findings, including a normal chest radiograph. (From Stansell JD: Fungal disease in HIV-infected persons: cryptococcosis, histoplasmosis, and coccidioidomycosis. *J Thorac Imaging* 6:28-35, 1991.)

effusion,²⁰⁴ and pneumothorax.²⁰⁵ Finally, cryptococcal pneumonia may also present with a normal chest radiograph; in the review by Meyohas and associates,²⁰⁰ for example, radiograph results were normal in 11% of the 92 cases.

Diagnosis. The diagnosis of cryptococcal infection begins with the CRAG test. The test can be performed on serum, cerebrospinal fluid, urine, BAL fluid,²⁰⁶ or pleural fluid. The serum CRAG test is sensitive and specific for cryptococemia. A negative serum CRAG test virtually rules out the diagnosis of cryptococcal meningitis, but can be seen in some cases of isolated pulmonary cryptococcosis. A positive serum CRAG test should prompt an evaluation for disseminated disease, especially meningitis, but false-positive results can be seen in the presence of rheumatoid factor or infection with the fungus *Trichosporon asahii* (formerly *T. beigeli*), or with bacteria from the *Stomatococcus* or *Capnocytophaga* genera. As noted, a positive CRAG can sometimes be found in individuals without clinical evidence of disease. Blood fungal cultures are specific and should be obtained as part of the diagnostic evaluation. New cutaneous lesions may be signs of dissemination, and their sudden appearance should prompt consideration for biopsy.

The diagnosis of pulmonary cryptococcosis is usually established by culture of sputum or BAL fluid and occasionally of pleural fluid. Specimens from TBB and pleural biopsy can also be diagnostic. Batungwanayo and coworkers¹⁹⁷ found that BAL diagnosed 27 of 33 cases (sensitivity 82%) of cryptococcal pneumonia compared with TBB, which diagnosed 10 of 21 cases (sensitivity 48%). In some cases, cultures are negative, but a BAL or pleural fluid CRAG test

can establish the diagnosis.²⁰⁰ Alternatively, because the treatment is identical, the diagnosis of pneumonia may be inferred in the presence of disseminated cryptococcal disease (e.g., meningitis) and a compatible radiographic presentation. However, caution must be exercised with this approach, because other opportunistic infections such as PCP may be present concurrently and can demonstrate identical radiographic findings.

Treatment. In contrast to cryptococcal meningitis, there are no randomized controlled trials for HIV-infected patients presenting with isolated cryptococcal pneumonia or with concurrent cryptococcal pneumonia and meningitis.²⁰⁷ Some authorities would treat isolated cryptococcal pneumonia that is mild in severity with fluconazole alone (400 mg daily for 12 months) in combination with effective ART²⁰⁸; however, patients with clinically significant cryptococcal pneumonia should be considered at high risk for early deterioration and treated similarly to those with disseminated disease using the lipid formulation of amphotericin B (3 to 4 mg/kg/day) in combination with flucytosine for at least 2 weeks.²⁰⁸ Treatment should be continued until the patient is clinically improved, at which point the patient can be switched to fluconazole (400 mg daily) to complete at least an 8-week course. The patient should then be maintained on fluconazole (200 mg daily) to complete at least 12 months of azole therapy. As in patients with tuberculosis or PCP, IRIS may develop in HIV-infected patients with cryptococcosis who begin dual therapy for *C. neoformans* and HIV infection.²⁰⁹ Patients who had cryptococcal meningitis may present with aseptic meningitis and have elevated intracranial pressure. In addition, patients with cryptococcal pneumonia and nodules on chest radiograph may develop cavitation of their nodules or new intrathoracic adenopathy.²⁰⁹

Prevention. There are no specific recommendations regarding exposure avoidance or chemoprophylaxis for *C. neoformans* (e.g., fluconazole).²⁰⁸ In addition, routine screening of asymptomatic persons with serum CRAG testing is not recommended.

Histoplasma capsulatum

Histoplasmosis is a disease caused by the dimorphic, soil-dwelling fungus *H. capsulatum*. The fungus is found on all continents except Antarctica, but it is most endemic to North America and the Caribbean basin.^{184,210} The heaviest concentration is found in the Mississippi, Ohio, and St. Lawrence River valleys. In these areas, the fungus exists in microenvironments related to the enrichment of the soil with bird or bat excrement, which helps promote sporulation. In the soil, the fungus exists in a mycelial form producing asexual spores, the characteristic tuberculate macroconidia and microconidia. Microconidia are easily aerosolized when disturbed and inhalation leads to primary pulmonary infection that is usually clinically silent.

Once deposited in the alveoli, *H. capsulatum* transforms into its yeast (or parasitic) form, and an area of pneumonitis develops. During this period before cell-mediated immunity develops, the organism spreads to regional lymph nodes and to reticuloendothelial organs. Two to 3 weeks after exposure, a flulike syndrome with fever, chills, myalgias, a

nonproductive cough, and chest pain develops in about 40% of immunocompetent individuals. As emphasized in Chapter 37, 99% of these cases spontaneously resolve with the development of specific cell-mediated immunity. In contrast, progressive disseminated histoplasmosis develops in HIV-infected and other persons lacking cell-mediated immunity. Although most cases of HIV-associated histoplasmosis appear to result from de novo exposure, the disease can reactivate. These cases account for the histoplasmosis seen in nonendemic areas such as San Francisco or New York.²¹¹

Clinical Features. Although the portal of entry is the lung, in HIV-infected persons, histoplasmosis most often presents as a febrile wasting illness with disseminated infection. In a large series of 72 HIV-infected patients with disseminated histoplasmosis, 69 patients (96%) presented with fever and weight loss; in approximately 10% of cases, the presentation was dramatic with a sepsis-like syndrome associated with hypotension, respiratory failure, liver and renal failure, and coagulopathy.²¹² Prognosis in these patients is poor. Respiratory complaints at presentation, chiefly cough and dyspnea, are found in patients who are likely to have abnormal chest radiographs.^{212,213}

CD4⁺ Lymphocyte Count. Most cases of disseminated histoplasmosis are seen in patients with a CD4⁺ lymphocyte count less than 100 cells/ μ L and often less than 50 cells/ μ L. Isolated respiratory disease is more likely in patients with CD4⁺ cell counts greater than 300 cells/ μ L.²⁹ Frequent laboratory findings include anemia, leukopenia, thrombocytopenia, and liver function test elevations. Serum LDH and serum ferritin elevations, often pronounced, have also been reported.^{29,210}

Imaging. Disseminated histoplasmosis presents with a normal chest radiograph in 35% to 55% of cases.^{199,212,214} In patients with abnormal findings, the most frequent are diffuse, coarse reticular or reticulonodular opacities as shown in Figure 90-7. Occasionally, alveolar opacities are present¹⁹⁹; focal opacities are less common and seen in 7% to 11% of cases.²¹³ Hilar and mediastinal adenopathy and calcified granulomata are each found in less than 5% of patients, attesting to the low incidence of reactivation disease.²¹²

Diagnosis. The workup of histoplasmosis begins with the histoplasma antigen test, which is a sensitive method for rapid diagnosis of disease.²⁹ The antigen test can be performed on urine, serum, cerebrospinal fluid, or BAL fluid. The performance of the newer quantitative histoplasma antigen test is excellent; in AIDS patients with disseminated histoplasmosis, the antigen was detected in the urine of 100% and in the serum of 92% of patients.²¹⁵ In isolated, chronic pulmonary disease, serum or urine antigen testing is less sensitive.²⁹ In patients with pulmonary involvement, antigen testing of BAL fluid combined with cytopathology evaluation can complement serum or urine testing and increase the sensitivity for diagnosis of disease.^{29,216} With successful therapy, antigen values fall and, during relapses, antigen values rise; thus changes in antigen values can be useful for assessing response to therapy and for evaluating



Figure 90-7 Disseminated fungal infection. Frontal chest radiographic close-up of the left mid-lung of an HIV-infected patient showing a medium to coarse reticulonodular pattern characteristic of disseminated fungal disease. (From Stansell JD: Fungal disease in HIV-infected persons: cryptococcosis, histoplasmosis, and coccidioidomycosis. *J Thorac Imaging* 6:28–35, 1991.)

possible relapse.²¹⁷ A persistently positive histoplasma antigen test indicates continued disease and warrants continued therapy. False-positive histoplasma antigen test results have been seen in patients with other disseminated fungal diseases (blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and penicilliosis, and rarely with aspergillosis), but such results have not been described in patients with cryptococcosis or candidiasis. Histoplasma can also be cultured from involved sites, although results may not be available for several weeks. Blood fungal cultures are specific and should be obtained as part of the diagnostic evaluation. Wheat and colleagues²¹² reported that fungal blood cultures were positive in 65 of their 72 cases (90%). Occasionally, the peripheral blood smear reveals intracellular yeast. Other potential diagnostic sources include bone marrow, lymph node, and skin. Serologic tests are generally less helpful in those with disseminated disease, but may be useful in patients who are less severely immunocompromised with isolated pulmonary disease.²⁹

Treatment. A lipid formulation of amphotericin B is the treatment of choice for HIV-infected patients with moderate to severe disseminated histoplasmosis, whereas itraconazole is an alternative for patients with mild disease.²⁹ Treatment with amphotericin B should be continued for at

least 2 weeks or until the patient is clinically improved, at which point the patient can be switched to itraconazole to complete at least a 12-month course. Patients with isolated pulmonary disease and CD4⁺ cell counts greater than 300 cells/ μ L should be treated similarly as for non-HIV-infected patients (Chapter 37).

Prevention of Exposure. In areas endemic for *H. capsulatum*, HIV-infected patients, especially those with CD4⁺ lymphocyte counts less than 150 cells/ μ L, should avoid activities that would potentially increase their exposure, including cleaning chicken coops, disturbing native soil beneath bird-roosting sites, cleaning, remodeling, or demolishing old buildings, and exploring caves.²⁹

Prevention of Disease. Routine serologic testing, even in histoplasmosis-endemic areas, is not recommended. Itraconazole for primary *H. capsulatum* prophylaxis can be considered in those who have a CD4⁺ lymphocyte count less than 150 cells/ μ L and who are at high-risk due to occupation or who live in hyperendemic regions.²⁹

Coccidioides immitis

Coccidioidomycosis is caused by the dimorphic, soil-dwelling fungi *C. immitis* and *Coccidioides posadasii*. As described in Chapter 37, the chief manifestation of coccidioidomycosis is as a mild flulike, often undiagnosed illness, from which most previously healthy people spontaneously recover. Chronic pulmonary disease manifests in roughly 5% of infected persons and disseminated disease in even fewer. Manifestations of coccidioidomycosis in HIV-infected persons include focal or diffuse pneumonia, cutaneous disease, meningitis, liver or lymph node involvement, or disseminated disease that can be fatal. The fungus is endemic to the semiarid regions of North America, notably the southwestern United States (central California, southern Arizona, southern New Mexico, and west Texas) and also northern Mexico.^{184,218} California's southern San Joaquin Valley and southern Arizona are hyperendemic areas.²¹⁸ *Coccidioides* is also found in South America, especially central Argentina. In soil, the fungus exists in a mycelial form with characteristic arthrospores. When the soil is disrupted, the few micrometer-diameter arthrospores, which are just the right size for deposition in the distal airways and alveoli after inhalation, become airborne. After deposition in the lungs, the arthrospores transform into spherules that may develop several hundred endospores. Rupture of the spherules allows widespread dissemination of the endospores, which then form additional spherules, replicating the cycle. Although most cases of HIV-associated coccidioidomycosis appear to result from de novo inhalation, disease may also reactivate.

Clinical Features. The clinical presentation is often nonspecific; fever and chills (68%), night sweats (36%), and weight loss (50%) are all common.²¹⁹ Although the portal of entry is the lung, coccidioidomycosis can present with disseminated disease and meningitis. Other frequently involved sites include the skin, lymph nodes, liver, and skeletal system. In one study, 42% of HIV-infected patients with coccidioidomycosis presented with disseminated disease; overall, 25% of the patients in this series died.²²⁰ Focal

pneumonia can present similarly to bacterial pneumonia, and diffuse pulmonary involvement can be difficult to distinguish from PCP.

CD4⁺ Lymphocyte Count. Most cases of disseminated coccidioidomycosis are seen in patients with a CD4⁺ lymphocyte count less than 100 cells/ μ L and often fewer than 50 cells/ μ L.^{219,220} Focal pneumonia is more common when the CD4⁺ cell count is greater than 250 cells/ μ L.²⁹ Cerebrospinal fluid examination is warranted in all patients with suspected disseminated coccidioidomycosis.

Imaging. In a series of 91 HIV-infected patients with coccidioidomycosis, diffuse reticulonodular opacities (see Fig. 37-5) were seen in 65%; focal opacities were less common, in 14% of cases, and consisted of focal opacities, single or multiple nodules, and cavities.²¹⁹ A miliary pattern may be seen (eFig. 90-26). Pleural effusion and hilar adenopathy as well as normal chest radiographs have all been reported.

Diagnosis. Serologic tests are useful in the evaluation of suspected coccidioidomycosis. Several studies have found an 80% to 90% sensitivity of complement fixation and tube precipitin tests.²²¹ Sensitivity of enzyme-linked immunoassays may be higher, but may be less specific. False-negative titers usually arise in the most severely immunocompromised patients with diffuse pulmonary disease; in those with positive tests, the titer appeared to reflect the disease activity and proved useful for monitoring response to therapy.²²² A urinary and serum antigen test specific to coccidioides has been developed and is useful for diagnosis of severe cases of coccidioidomycosis; however, other endemic fungi, including *Histoplasma* or *Blastomyces*, can cross-react.^{223,224}

A definitive diagnosis can be established by isolation and identification of the fungus by culture or identification of pathognomonic giant spherules in cytologic or histologic preparations. In cases of suspected coccidioidomycosis, it is critical to alert the microbiology laboratory so that proper precautions can be implemented to prevent laboratory transmission. Direct examination and culture of sputum, BAL fluid, or TBB can establish the diagnosis of pulmonary coccidioidomycosis in HIV-infected patients. Singh and associates²¹⁹ found that sputum culture in 13 of 19 cases (68%) and cytology in 8 of 11 cases (73%) had a high yield. BAL fluid culture diagnosed 29 of 42 cases (69%), and BAL fluid cytology diagnosed 32 of 48 cases (67%); in addition, TBB culture diagnosed 8 of 10 cases (80%), and biopsy histology diagnosed all 14 cases (100%).

Treatment. Either amphotericin B or a lipid formulation of amphotericin B is the treatment of choice for HIV-infected patients with severe (i.e., diffuse) pulmonary or disseminated coccidioidomycosis.²⁹ Treatment with amphotericin B should be continued until the patient is clinically improved, at which point the patient can be switched to fluconazole or itraconazole. Monitoring complement-fixing antibody titers every 12 weeks can be useful to assess response to therapy.²⁹ In patients with clinically mild infection, such as focal pneumonia, fluconazole or itraconazole may be used throughout.²⁹ Although clinical experience is limited,

voriconazole or posaconazole may be considered in refractory coccidioidomycosis.²²⁵ In patients with severe, diffuse disease, lifelong suppressive therapy with fluconazole or itraconazole should be continued after initial treatment is complete, particularly in those with meningeal involvement because the risk of relapse is high.²⁹ In patients who have had focal coccidioid pneumonia, and who have had a sustained response to ART with CD4⁺ lymphocyte counts greater than 250 cells/ μ L, therapy may be discontinued after 12 months, but periodic surveillance with chest radiograph and coccidioides serology is recommended.²⁹

Prevention of Exposure. In areas endemic for *C. immitis*, HIV-infected persons should avoid activities that will potentially increase their exposure, such as visits to construction or other sites where soil is being disturbed.

Prevention of Disease. Routine serologic testing is reasonable only in endemic areas. Pre-emptive treatment for persons living in or who have traveled to an endemic area is recommended only if the serology test result is newly positive and CD4⁺ lymphocyte count is less than 250 cells/ μ L.²⁹

Aspergillus Species

Species of *Aspergillus* are found worldwide, and exposure is universal. Nevertheless, disease is infrequent unless phagocyte number or function is reduced.²²⁶ Presently, greater than 180 species within the *Aspergillus* genus have been identified. *Aspergillus fumigatus*, however, is the most common disease-causing species, and it accounts for approximately 90% of cases of invasive aspergillosis. Although invasive aspergillosis is a well-documented complication of various immunosuppressive disorders, particularly in patients with hematologic malignancy or organ transplantation, it is an uncommon problem in patients with HIV disease. Risk factors for the development of aspergillosis other than HIV-induced immunosuppression included use of corticosteroids, neutropenia, marijuana use, and broad-spectrum antimicrobial drugs.²²⁷ In the ART era, the incidence of invasive aspergillosis has further declined. Holding and coworkers²²⁸ reported an aspergillosis incidence of 3.5 cases per 1000 person-years among HIV-infected individuals enrolled in the CDC-led Adult and Adolescent Spectrum of HIV Disease study.

Clinical Features. The entire spectrum of *Aspergillus*-related lung disease (Chapter 38) has been observed in HIV-infected persons, from colonization of the respiratory tract or a preexisting cavity, to tracheobronchitis or obstructing bronchial aspergillosis, to invasive aspergillosis, by far the most severe manifestation.^{227,229-231} Although most patients with invasive aspergillosis have a CD4⁺ lymphocyte count lower than 100 cells/ μ L, the classic risk factors for the disease relate more to phagocyte number and function (as determined by neutropenia and/or monocytopenia and use of corticosteroids or broad-spectrum antibiotics) than to absolute CD4⁺ lymphocyte counts. Patients with aspergillosis typically present with fever, cough, dyspnea, and occasionally pleuritic chest pain. Hemoptysis is another presenting feature. The imaging findings are variable and include unilateral or bilateral opacities, cavitary lesions

(eFigs. 90-27 and 90-28), nodular (see eFig. 90-28) and pleural-based opacities, and pleural effusions.²³²

Diagnosis. The definitive diagnosis of aspergillosis requires both demonstration of tissue invasion and isolation of the organism by culture. Neither sputum nor BAL is sufficient. Microscopy alone cannot distinguish *Aspergillus* species from *Fusarium* or *Pseudallescheria* species. The results of TBB are usually negative, but specimens from sputum, BAL fluid, or percutaneous aspirates are often positive on culture. The absence of histologic proof of tissue invasion is always somewhat disquieting, especially in attempting to distinguish invasive disease from possible colonization of damaged airways. Repeated isolation of the fungus in large numbers with a compatible clinical setting makes the diagnosis more tenable.

Galactomannan antigen testing on serum or BAL specimens is useful in the diagnosis of invasive pulmonary aspergillosis in other immunocompromised patients (see also Chapters 17 and 38),²³³ although its performance has not been prospectively evaluated in HIV-infected patients with suspected aspergillosis. Several other fungi, including *Histoplasma* and *Blastomyces*, can cross-react.²³⁴

Treatment. Compared with the fungi previously discussed, there is relatively little experience treating aspergillosis in HIV-infected patients.²²⁶ Voriconazole is the first-line recommended therapy.²⁹ Alternative agents include amphotericin, caspofungin, and posaconazole. Interactions with ART drugs must be considered because the antifungal azoles inhibit the cytochrome P450 system. Even with the prompt institution of therapy, the prognosis is poor, largely because aspergillosis is nearly always a late complication of advanced HIV disease.

Prevention of Exposure. Given the ubiquitous nature of *Aspergillus* species, it is impossible to prevent exposure to the organism. However, patients with advanced HIV disease should avoid activities that will potentially increase their exposure, including being near decaying vegetation (e.g., compost) and soil.

Prevention of Disease. There are no specific recommendations regarding chemoprophylaxis for *Aspergillus* species.²⁹

Blastomyces dermatitidis

Blastomycosis is a disease caused by the endemic, dimorphic fungus *Blastomyces dermatitidis*. Blastomycosis is co-endemic with histoplasmosis throughout much of the central United States (Chapter 37), but it is less common than histoplasmosis, and reports of HIV-associated blastomycosis are infrequent.^{235,236}

Clinical Features. The largest case series reported 15 cases of HIV-associated blastomycosis; all but one patient had a CD4⁺ lymphocyte count less than 200 cells/ μ L.²³⁵ The authors noted two distinct patterns of disease: one group of patients had disease that was clinically limited to the respiratory system, whereas the other group had disseminated blastomycosis, commonly involving multiple organ systems, including the lungs. Eleven of 15 patients (73%) had abnormal chest radiographs, with diffuse interstitial or miliary

disease (55%) as the most common radiographic finding. Definitive diagnosis requires the growth of *B. dermatitidis*, although visualization of the characteristic budding yeast form is strongly suggestive and therefore warrants antifungal therapy while awaiting the results of culture.

Treatment. Intravenous amphotericin B is the treatment of choice for HIV-infected patients with severe disease.^{235,236} Treatment with amphotericin B should be continued until there is clinical improvement; patients can then be switched to oral itraconazole maintenance therapy for at least 12 months, with itraconazole continued indefinitely for AIDS patients without immune reconstitution.²³⁷ With prompt institution of therapy, most patients with disease limited to the lungs respond well; in contrast, patients with disseminated disease do poorly (40% mortality in 30 days).²³⁵

Penicillium marneffei

Penicilliosis is a disease caused by *P. marneffei*, a dimorphic, soil-dwelling fungus. *P. marneffei* is endemic in southeastern Asian countries, and, in northern Thailand, it is the third most common opportunistic infection (after tuberculosis and cryptococcosis) in HIV-infected patients with AIDS, accounting for 15% to 20% of all AIDS-related illnesses.^{238,239} Disease is related to soil exposure, especially during the rainy season (May to October), and infection is probably acquired via inhalation.

Clinical Features. Most cases of penicilliosis are seen in patients with a CD4⁺ lymphocyte count less than 100 cells/ μ L. The clinical presentation is often mistaken for tuberculosis, cryptococcosis, or histoplasmosis. The most common symptoms include fever, weight loss, cough, and generalized papular skin lesions, usually with central umbilication.²⁴⁰ Symptoms are often present for weeks. In addition to the cutaneous findings, physical examination often reveals peripheral lymphadenopathy and hepatomegaly. Anemia is a prominent laboratory finding.

Diagnosis. *P. marneffei* is most commonly a disseminated disease in HIV-infected patients, and the diagnosis is usually made by fungal blood cultures. Other involved sites include the skin, lymph nodes, bone marrow, and lungs. In contrast to other *Penicillium* species that cause disease in humans, *P. marneffei* converts to a yeast form in its host, and yeast-laden macrophages can often be seen in peripheral blood, bone marrow aspirates, and touch preparations from tissue biopsies.

Treatment. Amphotericin B, followed by itraconazole, is the standard treatment for *P. marneffei*.²⁹ Mild forms of disease can be treated initially with itraconazole. The duration of amphotericin B treatment is 2 weeks, followed by an additional 10 weeks of itraconazole. This regimen is reported to have a greater than 97% response rate for disseminated *P. marneffei* infection.²⁴¹ Voriconazole is an alternative drug for primary treatment.²⁹ Without secondary prophylaxis, most patients will suffer a relapse within 6 to 12 months. Secondary prophylaxis can be discontinued in patients who are started on ART and have a sustained CD4⁺ lymphocyte count more than 100 cells/ μ L for more than 6 months.²⁹

Prevention of Exposure. Given the strong association with soil exposure, especially during the rainy season, HIV-infected patients living in endemic areas should avoid activities that will potentially increase their exposure. Current CDC, NIH, and HIVMA/IDSA guidelines suggest that HIV-infected patients avoid visiting endemic areas if possible.²⁹

Prevention of Disease. Itraconazole is recommended as primary prophylaxis against *P. marneffei* for subjects in endemic areas who have CD4⁺ cell counts less than 100 cells/ μ L.^{29,242} Fluconazole is a second-line alternative.

Candida Species

Despite the high frequency of mucocutaneous candidiasis in HIV-infected patients, pulmonary candidiasis is distinctly uncommon and is rarely diagnosed during life.²⁴³ Because of the small number of documented cases of pulmonary candidiasis, neither the clinical features nor the treatment is well established. Tissue invasion must be demonstrated by biopsy for a convincing diagnosis; the mere identification of the fungus in respiratory secretions by culture alone is insufficient.

VIRUSES

Many viruses are known to cause pulmonary disease in immunosuppressed persons; however, only CMV is regarded as a potentially important agent of pulmonary disease in HIV-infected persons.

Cytomegalovirus

CMV, a double-stranded DNA virus in the Herpesvirus family, is described in Chapter 32. The risk of exposure to CMV increases with age, and evidence of CMV infection is extremely common in healthy persons. In HIV-infected patients, CMV disease is believed to result chiefly from reactivation of latent infection; however, disease has been documented from de novo infection in recipients of solid organs, bone marrow, and blood, which raises the possibility that new infection or superinfection from exogenous sources may also arise in HIV-infected persons. Although clearly the source of significant pathologic conditions in the retina, gastrointestinal tract, and nervous system, the role of CMV in producing pulmonary disease in HIV-infected persons is open to question. Many consider this ubiquitous virus a “passenger” rather than a pathogen in most instances. However, there are also clear instances in which documented pulmonary disease results from CMV.

Clinical Features. Retinitis and gastrointestinal disease are the two most common forms of HIV-associated CMV disease. CMV is a frequent isolate from the BAL fluid of patients with advanced immunosuppression who undergo evaluation for opportunistic infections, notably *Pneumocystis*. Because CMV is shed in respiratory secretions, its mere presence in BAL fluid cannot be construed as diagnostic of CMV pulmonary disease. When dual pulmonary infection is discovered, treatment directed against the coexisting disease and not against CMV usually results in clinical resolution²⁴⁴; however, sometimes CMV causes pulmonary disease, and the challenge for clinicians is to recognize these instances.^{245,246}

The most common symptoms of CMV pneumonia are cough, dyspnea, and fever. In a study by Salomon and associates,²⁴⁶ these symptoms were seen in 94%, 94%, and 89%, respectively, of the 18 patients reported. Respiratory symptoms were present for up to 2 weeks in 50% and between 2 and 4 weeks in an additional 44%.

CD4⁺ Lymphocyte Count. Most cases of CMV disease are seen in patients with a CD4⁺ lymphocyte count less than 50 cells/ μ L. In one study of 18 patients with biopsy-proven CMV pneumonia, the median CD4⁺ lymphocyte count was 4 cells/ μ L.²⁴⁶ The serum LDH has been reported to be elevated in CMV pneumonia.²⁴⁶

Imaging. The imaging findings of CMV pneumonia vary and include reticular or ground-glass, alveolar, and nodular opacities (eFig. 90-29).²⁴⁶ Pleural effusions may be seen as well.

Diagnosis. When CMV pulmonary disease is suspected in conjunction with other end-organ disease (e.g., retinitis), CMV therapy must be initiated immediately. CMV is usually a disseminated disease and commonly involves multiple organ systems simultaneously. Treatment of CMV disease in one end-organ treats all affected organs, although the length of therapy can differ by organ system. The therapeutic dilemma is much greater when only the lungs appear to be afflicted. The only precise criterion for diagnosis of CMV pulmonary disease is the demonstration of widespread specific cytopathic changes in the lungs. Neither culture of BAL fluid²⁴⁷ nor cytopathic inclusions on TBB specimens are sufficient to make the diagnosis of CMV pneumonitis. Patients suspected of having CMV pneumonitis should undergo a careful dilated retinal examination performed by an experienced ophthalmologist, even if there are no ocular complaints.

Treatment. Data for treatment of CMV pneumonia in HIV-infected patients are limited. Intravenous ganciclovir or foscarnet is recommended for severe pneumonitis.²⁹ Although oral valganciclovir has been suggested for less severe pneumonitis, there are no data regarding its use in this setting.²⁹ With these drugs, an initial course of induction therapy should be continued until there is clinical improvement; the length of induction therapy for CMV pneumonia, however, is undetermined. A 21-day course for isolated CMV pneumonitis has been recommended. The usefulness of maintenance therapy in preventing a relapse of CMV pneumonitis is unclear.

Prevention of Exposure. HIV-infected patients who are CMV immunoglobulin G negative should be given CMV-negative blood in the event that a transfusion is necessary.

Prevention of Disease. CMV disease is best prevented by maintaining CD4⁺ lymphocyte counts greater than 100 cells/ μ L with ART.²⁹

Other Viruses

Symptomatic pulmonary viral infection other than CMV is uncommon. Herpes simplex virus, while frequently cultured from BAL fluid, is usually a contaminant from upper

airway carriage. Lower respiratory tract involvement is rare in HIV-infected persons (0.2% to 4% of autopsy cases) and appears to be more frequent in other immunosuppressed hosts. Herpes simplex virus pulmonary disease causes a focal pneumonia or a diffuse interstitial pneumonitis.²⁴⁸ The focal pneumonias appear to result from contiguous spread of herpes simplex virus to the lung parenchyma and are often associated with necrotizing tracheobronchitis, whereas the diffuse interstitial pneumonias appear to be a manifestation of hematogenous herpes simplex virus dissemination. Varicella-zoster virus is a rare cause of pneumonia in HIV-infected adult patients.²⁴⁹ Epstein-Barr virus DNA has been identified in lung biopsy specimens of infants and children with lymphocytic interstitial pneumonitis, but the precise role of the virus in this disease is uncertain.²⁵⁰

Influenza-related mortality is increased in adults with AIDS compared to the general population in studies using data from the United States as well as from sub-Saharan Africa.^{251,252} Influenza-related mortality is decreased in the ART era, but remains greater in those with AIDS compared to the general U.S. population. Influenza generally presents similarly and has a comparable clinical course in HIV-infected as in non-HIV-infected adults. Studies focused on H1N1 influenza generally confirmed these findings, although HIV-infected patients with more advanced HIV disease had a poorer prognosis than those with well-controlled HIV.²⁵³⁻²⁵⁸ Prompt initiation of antiviral therapy directed against influenza in HIV-infected patients with suspected or confirmed disease is recommended. All HIV-infected persons should receive the inactivated influenza vaccine annually.²⁹

PARASITES

Of the classic unicellular and multicellular parasites that afflict otherwise healthy humans (Chapter 39), several also cause pulmonary disease in HIV-infected hosts. Of these, *T. gondii* is the most frequent.

Toxoplasma gondii

Toxoplasmosis is a zoonosis caused by the intracellular protozoan *T. gondii*, with domestic cats as its definitive host, but with an infectious reservoir that encompasses all animals. Infection is transmitted to humans when raw or undercooked meat containing *T. gondii* is eaten. Domestic cat feces in litter boxes are an additional source of potential *T. gondii* infection. Infection can be transmitted vertically from mother to fetus. In HIV-infected patients, the majority of cases of toxoplasmosis result from reactivation of chronic, latent infection. Thus, the keys to preventing toxoplasmosis are prevention of exposure for those not yet infected and prophylaxis for those already seropositive. The seroprevalence of *Toxoplasma* antibodies varies. In the United States, the seroprevalence is 10% to 50%, whereas in Western Europe, the seroprevalence may be as high as 90%.

Clinical Features. Central nervous system complications of *T. gondii* are well recognized in HIV disease and include encephalitis as well as focal brain abscess. Pulmonary involvement is uncommon, but is seen in patients with central nervous system or disseminated disease, can present

as isolated pneumonia, and can rarely be associated with acute respiratory distress syndrome.²⁵⁹⁻²⁶¹

CD4⁺ Lymphocyte Count. Toxoplasmosis presents at the lower range of CD4⁺ lymphocyte counts. In a large study of 64 patients with pulmonary toxoplasmosis conducted in France, the mean (\pm standard deviation [SD]) CD4⁺ lymphocyte count was 40 (\pm 75) cells/ μ L.²⁶⁰

Imaging. The chest radiograph usually reveals bilateral opacities, either in a fine reticulonodular pattern indistinguishable from PCP or in a coarse nodular pattern similar to that seen with tuberculosis or fungal pneumonias.²⁶² Pleural effusions can be seen, and a variety of other radiographic findings have also been described.²⁶³

Diagnosis. The diagnosis of pulmonary toxoplasmosis is usually established by bronchoscopy and study of BAL fluid. In one review, BAL fluid examination was diagnostic in 16 of 17 immunocompromised patients with pulmonary disease.²⁶³

Treatment. The treatment for pulmonary toxoplasmosis is identical to that for central nervous system toxoplasmosis. First-line treatment is sulfadiazine plus pyrimethamine with leucovorin to decrease the likelihood of hematologic toxicities associated with pyrimethamine.²⁹ The preferred alternative regimen is clindamycin plus pyrimethamine with leucovorin.²⁹

Prevention of Exposure. Persons who are *Toxoplasma* antibody negative should be instructed to avoid potential sources of infection.

Prevention of Disease. HIV-infected persons should be tested for *T. gondii* antibodies; antibody seronegative patients should be re-tested if their CD4⁺ lymphocyte count falls below 100 cells/ μ L. Toxoplasma seropositive patients receive primary prophylaxis once their CD4⁺ lymphocyte count falls below 100 cells/ μ L.²⁹ As a practical matter, this is often accomplished when the CD4⁺ lymphocyte count reaches 200 cells/ μ L or fewer because the prophylaxis of choice (TMP-SMX) is also the prophylaxis of choice for *Pneumocystis*. For patients who are intolerant of TMP-SMX, dapsone plus pyrimethamine/leucovorin or atovaquone with or without pyrimethamine/leucovorin can also be used.²⁹ Primary and secondary *T. gondii* prophylaxis can be discontinued in HIV-infected persons on ART who have experienced an increase in their CD4⁺ lymphocyte count to greater than 200 cells/ μ L for at least 3 to 6 months.²⁹

Other Parasites

In general, pulmonary helminth infections are uncommon in HIV-infected persons.^{264,265} Both pulmonary cryptosporidiosis and pulmonary microsporidiosis in HIV-infected patients with concurrent intestinal disease have been reported.²⁶⁶ In these cases, aspiration from the gastrointestinal tract appears to be the most probable route of pulmonary infection. Occasionally, patients have presented with disseminated disease, raising the likely possibility of hematogenous spread. The most common respiratory symptoms are cough, dyspnea, and pleuritic chest pain. One review

found that these symptoms were present in 77%, 58%, and 33%, respectively, of patients with cryptosporidial pulmonary disease.²⁶⁶ The diagnosis of *Strongyloides stercoralis* pulmonary disease (eFig. 90-30) can be made by either sputum study or bronchoscopy.^{267,268} *Strongyloides* hyperinfection syndrome has also been reported in HIV-infected patients,²⁶⁹ but does not appear to be an important HIV-associated complication, even in countries where the parasite is endemic.²⁷⁰

NONINFECTIOUS DISORDERS

The evaluation of respiratory complications usually focuses on the diagnosis of HIV-associated opportunistic infections because of their frequency, the need for prompt therapy, and, in the case of tuberculosis, the concern for transmission to other persons, both HIV-infected and non-HIV infected. As more people are living with HIV/AIDS and are living longer on effective ART, noninfectious complications and comorbid illnesses among these HIV-positive patients have increased in frequency.²⁷¹ In addition to an increased risk for infectious diseases, HIV-infected patients appear to have an increased risk for a number of noninfectious pulmonary diseases, including COPD, lung cancer, and PAH.²⁷² Increasing age and a high prevalence of cigarette smoking combined with an independent risk from HIV infection itself may all contribute, particularly to the increases in COPD and lung cancer.^{273,274} Noninfectious pulmonary diseases that may be encountered in HIV are reviewed here.

MALIGNANCIES

Two different HIV-associated malignancies, KS and NHL, may involve the thorax, including the lung parenchyma, airways, pleura, or hilar or mediastinal lymph nodes. Intrathoracic disease from either neoplasm is usually a manifestation of disease already recognized elsewhere, but occasionally both KS and NHL may present with isolated pulmonary disease.²⁷⁵

Kaposi Sarcoma

The most common HIV-associated malignancy is KS, although its incidence has decreased dramatically with ART.²⁷⁶⁻²⁷⁸ KS is an angioproliferative tumor that is associated with *human herpesvirus 8* (HHV8; also termed the KS-associated herpesvirus).²⁷⁹⁻²⁸¹ KS most commonly presents with mucocutaneous involvement. The lymph nodes, gastrointestinal tract, and lungs can also be involved. Approximately 90% to 95% of cases of KS are seen in MSM.²⁸²

Clinical Features. Pulmonary KS is detected clinically in approximately one third of patients with known KS, with the proportion detected at autopsy approaching 50% to 75%. Most but not all patients with pulmonary KS have concomitant mucocutaneous disease. Huang and coworkers²⁸³ found that 85% of 168 consecutive patients diagnosed with pulmonary KS by bronchoscopy had evidence of mucocutaneous involvement at the time of bronchoscopy. The 15% without mucocutaneous involvement had pulmonary disease that ranged from isolated tracheal

lesions to diffuse endobronchial involvement that was ultimately fatal. A significant proportion of patients with pulmonary KS also have a concurrent opportunistic infection. For example, in the study by Huang and coworkers,²⁸³ 45 of the 168 patients (27%) with pulmonary KS had accompanying opportunistic infection, most frequently PCP. These observations underscore the need to evaluate each patient with KS who presents with respiratory symptoms not only for pulmonary KS, but also for opportunistic infection. Patients with pulmonary KS who develop opportunistic infection may also experience a rapid progression of their KS that mimics an infectious process.

CD4⁺ Lymphocyte Count. Pulmonary KS presents at the lower range of CD4⁺ lymphocyte counts. In one study of 168 patients with pulmonary involvement from KS, the median CD4⁺ lymphocyte count was 19 cells/ μ L; 68% had a CD4⁺ lymphocyte count less than 50 cells/ μ L, and only 4% had a CD4⁺ lymphocyte count greater than 200 cells/ μ L.²⁸³ Patients with KS pulmonary involvement appear to have lower CD4⁺ lymphocyte counts than those without pulmonary involvement.

Imaging. Pulmonary KS characteristically presents with bilateral opacities in a central or perihilar distribution, as shown in Figure 90-8 and eFig. 90-31A. Typical findings include linear opacities, nodules or nodular opacities of varying size, pleural effusions, and intrathoracic adenopathy. Gruden and associates²⁸⁴ reviewed the chest radiographic presentation of 76 consecutive patients with pulmonary KS diagnosed by bronchoscopy whose BAL was negative for infectious organisms. In this study, 95% of the radiographs had peribronchial cuffing and “tram track” opacities, with or without more extensive perihilar coalescent opacities (see eFig. 90-31A). Small nodules or nodular opacities were seen in 78%, Kerley B lines in 71%, and pleural effusions in 53% of the radiographs. Although these

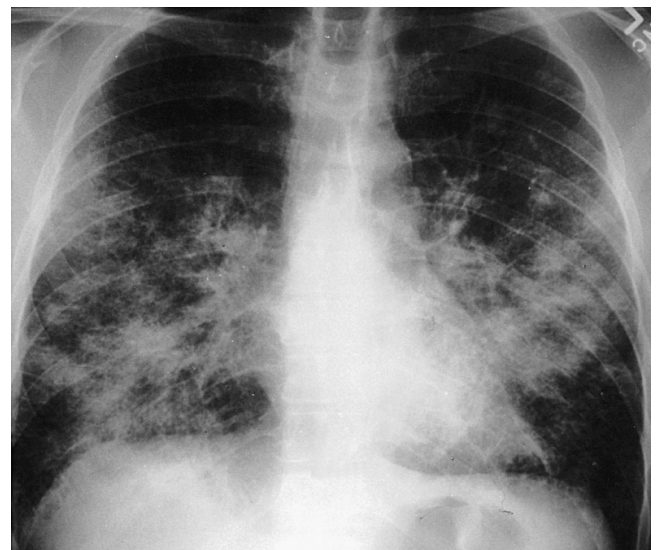


Figure 90-8 Kaposi sarcoma. Frontal chest radiograph of an HIV-infected patient with pulmonary Kaposi sarcoma diagnosed by bronchoscopy showing the characteristic bilateral, perihilar distribution of abnormalities consisting of nodules and nodular opacities. (Courtesy L. Huang.)

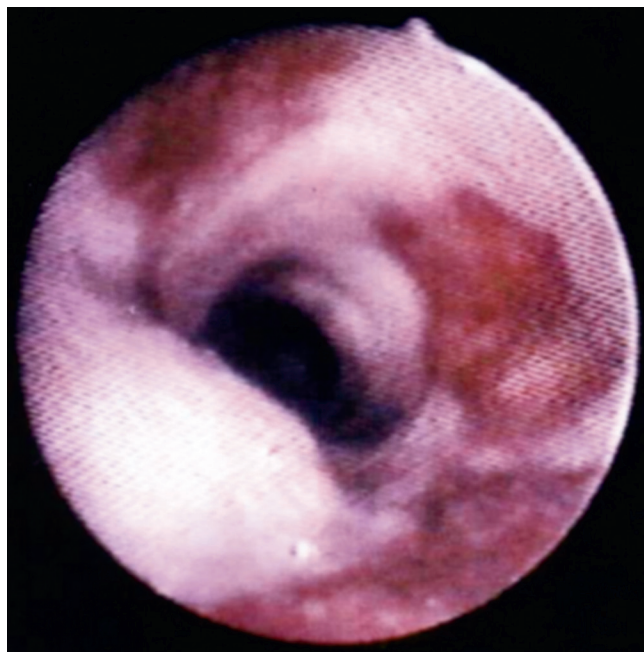


Figure 90-9 Kaposi sarcoma. Characteristic Kaposi sarcoma lesions in the trachea of an HIV-seropositive patient seen via bronchoscopy. (Courtesy L. Huang.)

radiographic findings strongly suggest the diagnosis of pulmonary KS in HIV-infected MSM, no radiograph is diagnostic for KS. Therefore, patients with suspected pulmonary KS should have their diagnosis confirmed. Chest CT findings in patients with pulmonary KS (see eFig. 90-31B-D) include “flame-shaped” areas of peribronchovascular ground-glass opacity and nodularity, often with interlobular septal thickening and pleural effusion, and, less commonly, lymphadenopathy. Atypical imaging manifestations of KS are occasionally encountered (eFig. 90-32).

Diagnosis. The diagnosis of pulmonary KS is usually established by bronchoscopy. The observation of characteristic endobronchial, red or violaceous, flat or slightly raised lesions is sufficient to diagnose pulmonary involvement (Fig. 90-9). The presence of these mucosal lesions does not preclude a concurrent infection, nor does their absence in the observable airway preclude more distal disease or parenchymal, pleural, or nodal involvement. Although endobronchial or transbronchial biopsy of the airway or parenchymal abnormalities, respectively, is usually unnecessary, we have occasionally established the diagnosis by TBB in patients in whom there was a strong clinical and radiographic suspicion for pulmonary KS, but who had no visible endobronchial lesions. HHV8 may be detected in BAL. Patients with cutaneous KS who develop new respiratory complaints should undergo a thorough evaluation to rule out an opportunistic infection or other process; however, patients in whom there is a strong clinical suspicion for pulmonary KS should undergo bronchoscopy as the initial procedure. Cytologic evaluation of pleural fluid and thoracoscopic biopsy of the pleura in patients with KS are not typically useful for diagnosis.²⁸⁵

KS is negative on gallium scans. In contrast, opportunistic infections and NHL are gallium avid. Among HIV-

associated pulmonary diseases, this unique feature of KS has created a clinical niche for the use of gallium scans. In the absence of either a bronchoscopic or tissue diagnosis of pulmonary KS, its presence may be inferred by the finding of significant chest radiographic abnormalities and a negative gallium scan.

Treatment. Tumors can regress in size and number in response to ART, and therefore all patients with KS should receive ART if no contraindications exist.²⁸⁶ Treatment of more advanced systemic disease also includes chemotherapy, with doxorubicin or daunorubicin generally recommended as first-line agents. Mortality in patients with KS may be related to an increased rate of other malignancies, particularly lymphomas.²⁸⁷ Survival in patients with pulmonary KS appears substantially worse when compared with that in patients without pulmonary involvement: 5-year overall survival was reported to be 49% in patients with pulmonary KS compared with 82% in patients without pulmonary involvement ($P < 0.0001$).²⁸⁸ Of malignancies, KS is the most likely to be associated with IRIS in patients who initiate ART. KS-associated IRIS may manifest with worsening of underlying pulmonary lesions,²⁸⁹ and can result in death, particularly in patients with visceral KS.²⁹⁰

Non-Hodgkin Lymphoma

Almost all HIV-associated NHLs are of B-cell origin. Most are classified as small, noncleaved Burkitt, diffuse large cell with centroblastic features, or diffuse large cell with immunoblastic features.²⁹¹ The majority are associated with Epstein-Barr virus infection. Many HIV-infected patients have an advanced stage of disease at the time of presentation. As with KS, the incidence of NHL has declined dramatically in the era of ART.²⁷⁸

Clinical Features. Most HIV-infected patients with NHL present with disseminated disease and extranodal involvement.²⁹² Frequent extranodal sites include the liver, spleen, bone marrow, meninges, gastrointestinal tract, and pericardium. Intrathoracic involvement is seen in a smaller proportion. The reported incidence of intrathoracic disease ranges up to 31% of patients at the time of clinical diagnosis and is usually higher at the time of autopsy. Occasionally, the lung is the only site involved.

CD4⁺ Lymphocyte Count. NHL can present at a wide range of CD4⁺ lymphocyte counts, although typically patients are more severely immunocompromised. The median CD4⁺ T-lymphocyte count is approximately 100 cells/ μ L, and 75% of patients have a CD4⁺ lymphocyte count greater than 50 cells/ μ L. In one study of 38 patients with NHL, the mean (\pm SD) CD4⁺ lymphocyte count was 67 (\pm 65) cells/ μ L.²⁹³

Imaging. The most common chest radiograph parenchymal findings include single (Fig. 90-10; eFig. 90-33) or multiple nodules (eFig. 90-34), nodular opacities or masses (eFig. 90-35), lobar opacities, and diffuse interstitial opacities (eFig. 90-36).²⁹³ More rarely, cases of endobronchial lesions have been reported.²⁹⁴ Pleural effusions are the most common radiographic abnormality, seen in 40% to 70% of cases, and are often bilateral.²⁹³ Bilateral hilar and

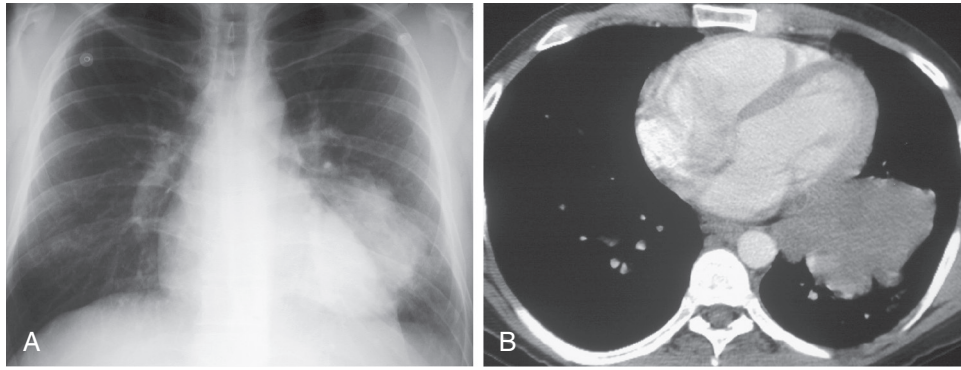


Figure 90-10 Non-Hodgkin lymphoma. **A**, Frontal chest radiograph from an AIDS patient with non-Hodgkin lymphoma showing a large left lower lobe mass. **B**, Axial CT shows a mass in the left lower lobe without an air bronchogram, suggestive of a neoplasm. (Courtesy Michael B. Gotway, MD.)

mediastinal adenopathy can be found in up to 60% of patients. Isolated intrathoracic adenopathy without identifiable extrathoracic nodal involvement is a rare presentation for HIV-associated NHL.

Diagnosis. The diagnosis of NHL requires demonstration of malignant lymphocytes on cytology or biopsy specimens. Most often the diagnosis is made by needle aspiration or biopsy of an extrathoracic site. Persons who present with isolated intrathoracic involvement should undergo bronchoscopy with TBB and needle biopsy, if abnormal nodes are within reach through the bronchoscope.²⁹³ For lesions outside the sampling distance of the bronchoscope, fluoroscopic or CT-guided fine-needle aspiration should be considered. Other options include mediastinoscopy and open-lung biopsy. For patients with pleural effusions, pleural fluid cytology, biopsy, or both are often diagnostic.²⁹³ Pleural fluid is exudative, lymphocytic predominant, and often has very high levels of LDH.²⁹³ The yield of pleural cytology is significantly higher in HIV-associated pulmonary lymphoma than in non-HIV-infected cases.²⁹⁵

Treatment. Pulmonary involvement in NHL is treated as part of systemic disease. Median survival from AIDS-related NHL has greatly improved as a result of combining ART with chemotherapy.²⁹⁶ Chemotherapy is frequently complicated by the development of opportunistic infections, particularly PCP, and by the presence of decreased bone marrow reserve. Therefore, *Pneumocystis* prophylaxis should be considered in all cases, regardless of CD4⁺ lymphocyte count.

Primary Effusion Lymphoma

Classic primary effusion lymphoma is a distinct subtype of NHL that presents with isolated effusions in body cavities, including the pleura (eFig. 90-37), pericardium, and peritoneum.²⁹⁷ Primary effusion lymphoma typically presents with lymphomatous effusions in the absence of a discrete nodal or extranodal mass. A rare disease, these tumors are found nearly exclusively in HIV-infected MSM. HIV infection is usually advanced; in one study peripheral CD4⁺ lymphocyte counts averaged 200 cells/ μ L.²⁹⁷ HIV-infected patients with primary pleural effusion lymphoma typically present with symptoms related to the space-occupying nature of the effusion (i.e., dyspnea). Diagnosis is estab-

lished by pleural fluid histology and identification of HHV8, which can be found in all cases.²⁹⁸ Primary effusion lymphomas are of a null phenotype, lacking classic B-cell and T-cell markers.²⁸⁶ Prognosis is poor, with median survival of approximately 6 months. Treatment options include ART and systemic chemotherapy. Chemotherapy agents known to have activity against intermediate- and high-grade NHL may be used. Prolonged survival has been reported in patients treated with cidofovir or ganciclovir as adjunctive antiviral therapy.²⁸⁶

Multicentric Castleman Disease

Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder of the plasma cell type.²⁹⁹ It is characterized histologically as angiofollicular lymph node hyperplasia.²⁸⁵ MCD may be associated with KS in HIV-infected as well as in non-HIV-infected patients. Most HIV-infected patients with MCD are also infected with HHV8. MCD can be seen in patients with controlled or uncontrolled HIV. Common presenting symptoms and signs of systemic MCD can mimic lymphoma and include fever, weakness, generalized lymphadenopathy (eFig. 90-38), anemia, and hypergammaglobulinemia as well as hemophagocytic syndrome in life-threatening forms of MCD.²⁸⁵ MCD can present with nonspecific respiratory symptoms such as cough and dyspnea in 33% to 75% of cases.²⁸⁵ Bilateral crackles may be present on physical examination. Chest radiographic findings include reticular and/or nodular interstitial patterns, with mediastinal lymphadenopathy and less commonly, bilateral pleural effusions.^{285,300} In another study, bronchovascular nodularity, consolidation, and mediastinal lymphadenopathy were described on chest CT.³⁰¹ PCR-assessed HHV8 viral load is usually increased; if a BAL is obtained, HHV8 may be detected, although bronchoscopy is not usually necessary for diagnosis of MCD.²⁸⁵ Instead, the diagnosis is typically based on pathologic evaluation of an involved lymph node or extranodal mass to confirm MCD, and to rule out other diseases such as tuberculosis or lymphoma. Involved cells are B cells with plasma-cell differentiation. HHV8-infected cells can be detected by immunohistochemistry. Prognosis is generally poor, and disease can recur. Treatment options are based on expert opinion and include initiation of ART, if the patient is not already on it, and anti-HHV8 therapy such as with ganciclovir.²⁸⁵ Systemic chemotherapy as well as monoclonal antibodies

against CD20 (rituximab) and interleukin-6 receptor (atlizumab) may be considered; reports of sustained remission have been associated with rituximab therapy.²⁸⁶ Cases of IRIS, some of them fatal, have been reported in patients with MCD initiated on ART.

Non–Small Cell Lung Cancer

The incidence of non–small cell lung cancer, but not small cell lung cancer, is greater among HIV-infected persons than among non–HIV-infected persons (see also Chapter 52).²⁷⁵ Whether this increased incidence is due to HIV infection or to other potential confounders such as increased smoking among HIV-infected populations has been controversial. Studies that account for potential confounding factors include work by Kirk and colleagues,³⁰² who analyzed lung cancer deaths in the ART era and found that HIV infection was an independent risk factor for lung cancer, after controlling for smoking status as well as age and sex (hazard ratio of 3.6; 95% confidence interval [CI], 1.6 to 7.9). In a study by Engels and colleagues,³⁰³ HIV infection was also associated with lung cancer, after adjusting for estimates of smoking prevalence (standardized incidence ratio of 2.5; 95% CI, 1.6 to 3.5). In the largest study to date with 457 cases of lung cancer in HIV-infected and 614 in non–HIV-infected patients, Sigel and colleagues³⁰⁴ also found an independently increased risk for lung cancer associated with HIV infection after controlling for smoking status and other risk factors (incidence rate ratio of 1.7; 95% CI, 1.5 to 1.9). Whereas AIDS-defining cancers such as KS and NHL have decreased, non–AIDS-defining cancers in HIV-infected patients have increased, primarily among HIV-infected persons aged 50 years and older.^{278,305} In HIV-infected persons, lung cancer is now the most common infection-unrelated, non–AIDS-defining cancer and is a leading cause of mortality.^{278,305-310}

Clinical Features. HIV-infected patients develop lung cancer at slightly younger ages than do non–HIV-infected patients after controlling for demographic differences (50 vs. 54 years in one study).³¹¹ A number of reports have suggested that lung cancer has a more aggressive course in HIV-infected patients, although this remains unclear. Most HIV-infected patients in whom lung cancer develops are cigarette smokers. Although all pathologic types are seen, adenocarcinoma has been the most frequent pathologic type reported, similar to that seen in non–HIV-infected patients; squamous cell carcinoma is the second most frequently observed pathologic type.^{303,304} It has been suggested that HIV-infected patients may be more likely to have advanced-stage disease at presentation, but whether this is due to detection bias is uncertain, and age-matched data do not support this finding.³¹² Furthermore, the study by Sigel and colleagues did not find a difference in stage of presentation by HIV status where nearly 70% of all patients were diagnosed at stage III/IV.³⁰⁴ Although lung cancer can develop at any CD4⁺ lymphocyte count, immunodeficiency is postulated as a mechanism for the enhanced risk for lung cancer associated with HIV.^{307,313,314} Prior lung disease and infections, particularly bacterial pneumonia and tuberculosis, are also purported risk factors and may partially explain the risk for lung cancer.³¹⁵ There is no apparent relationship between HIV viral load and use of ART with

lung cancer risk.³⁰² The characteristic presentation and radiographic finding of bronchogenic carcinoma, as described in Chapter 53, are similar in HIV-infected and non–HIV-infected patients (eFig. 90-39).

Diagnosis and Treatment. Diagnosis and treatment of lung cancer in an HIV-infected patient is similar to that in a non–HIV-infected individual. HIV infection should be considered an important concurrent underlying medical problem, much the same as one would consider underlying cardiopulmonary disease. Overall, mortality in HIV-infected patients with lung cancer appears to be independent of HIV, and median survival in HIV-infected patients with lung cancer is similar to age-matched non–HIV-infected lung cancer patients.³¹² Whether lung cancer screening with annual low-dose CT will have a beneficial effect on mortality in HIV-infected smokers as it has in older, non–HIV-infected heavy smokers in the national Lung Cancer Screening Trial³¹⁶ is unclear.^{316a,b}

PULMONARY ARTERIAL HYPERTENSION

Studies have reported an increased frequency of PAH in the HIV-infected population, with a prevalence of approximately 0.5%.³¹⁷ There is some debate about whether this diagnosis has decreased in the era of ART, but it still seems to be overrepresented in HIV-infected individuals.³¹⁸ PAH may be underdiagnosed in this population because screening echocardiograms detect increased pulmonary artery pressures in as many as 35% to more than 50% of HIV-infected cohorts.³¹⁹⁻³²¹ Echocardiography may not accurately reflect right heart pressures obtained on catheterization.³²² HIV-infected individuals with elevated echocardiographic pulmonary artery pressures have more respiratory complaints and lower diffusing capacity for carbon monoxide.³²⁰ Possible causes of PAH in HIV include the direct effects of HIV proteins, opiate use, and inflammation.³²³⁻³²⁵

Clinical Features

HIV-infected patients are significantly younger, and the proportion with New York Heart Association functional class III or IV is significantly lower (50% vs. 75%, $P = 0.01$), than in non–HIV-infected individuals with idiopathic PAH, and 1-year survival is approximately 51% to 88% depending on the cohort.^{326,327} Intravenous drug use is commonly reported in HIV-infected patients with PAH, and patients may be more likely to have more advanced HIV disease.^{320,327,328} In a review of 131 cases of PAH in HIV-infected patients,³²⁹ presenting symptoms and radiographic, pulmonary function, electrocardiographic, echocardiographic, and pathologic findings were similar to those in non–HIV-related idiopathic PAH (Chapter 58).

Treatment

The optimal treatment of HIV-associated PAH is unclear.³³⁰ Small studies have reported improved functional and hemodynamic parameters in patients with HIV and PAH during treatment with epoprostenol and bosentan.³³¹ Other treatments such as sildenafil and iloprost may also be useful.^{332,333} Epoprostenol may be associated with intravascular infections in the HIV-infected population, and high levels of

sildenafil can be seen when used in combination with anti-retrovirals, particularly ritonavir. Although still controversial, some studies have found a benefit in treating patients with ART or the combination of ART and bosentan.^{317,334}

OBSTRUCTIVE LUNG DISEASE

Frequently, obstructive lung disease develops in HIV-infected individuals, and a variety of pulmonary function test abnormalities are seen.³³⁵ Prior to ART, the PCHIS researchers performed serial pulmonary function tests in more than 1100 HIV-infected individuals and demonstrated that advanced HIV infection, characterized by a CD4⁺ lymphocyte count less than 200 cells/ μ L or HIV-associated symptoms, as well as race, cigarette smoking, and intravenous drug use, were associated with reductions in *diffusing capacity for carbon monoxide* (DL_{CO}).³³⁶ A PCHIS multivariable analysis found that both PCP and bacterial pneumonia were independently associated with an accelerated decline in the *forced vital capacity* (FVC), *forced expiratory volume in 1 second* (FEV₁), FEV₁/FVC, and DL_{CO}.³³⁷ Several studies have found that significant proportions of HIV-infected individuals report respiratory symptoms and have abnormal pulmonary function testing including decreases in forced expiratory flow rates, significant response to bronchodilators, and impairment of DL_{CO}.^{146,338-343} Impairment in FEV₁ in HIV-infected individuals is associated with decreased health status.^{343a,b} Impairments in DL_{CO} have been reported in HIV-infected individuals without a history of smoking,³⁴⁴ and data from multicenter studies of HIV-infected individuals and non-HIV-infected controls found that HIV was an independent risk factor for decreased DL_{CO}.^{345,346}

HIV-infected individuals may have asthma that precedes their HIV infection or that develops after the onset of HIV. HIV-infected patients are more likely than non-HIV-infected patients to have bronchial hyperresponsiveness to methacholine.³⁴² In one clinic-based study, a history of asthma was reported in 21% and current asthma in 17% of 136 patients attending a primary care clinic for HIV infection.³⁴⁷ Another study found that physician-diagnosed asthma was present in 21% of participants and bronchodilator responsiveness was present in 9%.³⁴⁸ CD4⁺ lymphocyte counts greater than 200 cells/ μ L are associated with current asthma in those with HIV infection,³⁴⁷ and one report has linked use of asthma medication to ART use in HIV-infected children, suggesting that immune responses are important, but this association has not been replicated in all cohorts.^{348,349} Other factors such as female sex and obesity have also been found to be associated with asthma in HIV-infected individuals.³⁴⁸

Obstructive airway disease, chronic bronchitis, and bronchiectasis are well-recognized sequelae of opportunistic infection,^{350,351} although evidence also suggests that HIV infection is associated with an increase in emphysema/COPD apart from the effects of opportunistic infections.³⁵² Data from a large cohort of HIV-infected and non-HIV-infected military veterans have demonstrated that HIV infection is an independent risk factor for COPD prevalence and incidence by self-report and *International Classification of Diseases*, Ninth revision diagnosis.^{272,353} The role of ART in COPD is unclear and may depend on the population studied. Two studies have found increased airway obstruction

in HIV-infected individuals receiving ART,^{344,354} but other groups have found that a high HIV RNA level is associated with a more rapid decline in FEV₁ and a greater prevalence of obstructive lung disease.³³⁸⁻³⁴⁰

Treatment

In general, treatment of asthma and COPD should be similar to that for the non-HIV-infected population (Chapters 42 and 44). PIs, particularly ritonavir, have been reported to increase systemic levels of inhaled or intranasal fluticasone, leading to Cushing syndrome or adrenal suppression when corticosteroids are tapered.³⁵⁵ Use of high-dose inhaled steroids for COPD in individuals with HIV also requires careful monitoring for oral candidiasis and bacterial pneumonia.³⁵⁶

INTERSTITIAL PNEUMONITIDES

Although opportunistic infection and neoplasia dominate the clinical spectrum of HIV-associated pulmonary diseases, a small number of patients present with signs and symptoms that are attributable to one of the interstitial pneumonitides, *lymphocytic interstitial pneumonitis* (LIP) or *nonspecific interstitial pneumonitis* (NSIP).³⁵⁷

Lymphocytic Interstitial Pneumonitis

Described by Carrington and Liebow more than 30 years ago, it remains speculative whether LIP is a pathogenically distinct entity or a disorder of multiple causes that produce a similar pathologic reaction (Chapter 63).

Clinical Features. The most striking feature of HIV-associated LIP is the effect of age on its incidence. Early in the AIDS epidemic, one third to one half of AIDS-defining diagnoses in HIV-infected children in high-income, industrialized countries were due to LIP. In contrast, LIP is rare in adults.³⁵⁸

The chest radiograph presentation of LIP is nonspecific (Fig. 90-11) and is characterized by bilateral reticulonodular interstitial opacities with a middle to lower lung zone predominance.³⁵⁹ Areas of alveolar opacity that are thought to result from bronchial compression caused by more severe lymphocytic infiltration are rare. Hilar or mediastinal adenopathy is occasionally seen. Chest CT scans may reveal small (2- to 4-mm) nodules, often in a peribronchovascular distribution (eFig. 90-40), or diffuse areas of ground-glass opacity.³⁶⁰

Diagnosis and Treatment. The definitive diagnosis of LIP requires histologic confirmation by biopsy. There are so few studies of LIP among HIV-infected adults that neither definitive therapy nor benefit of therapy has been determined. Cases of LIP that responded to ART alone have been reported.^{358,361}

Nonspecific Interstitial Pneumonitis

NSIP is a pulmonary disorder characterized histologically by infiltration of mononuclear cells, predominantly lymphocytes and plasma cells, into the peribronchiolar and perivascular interstitium (Chapter 63). NSIP has been reported with various frequencies in HIV-infected patients. Because it is a histologic diagnosis, its incidence depends on

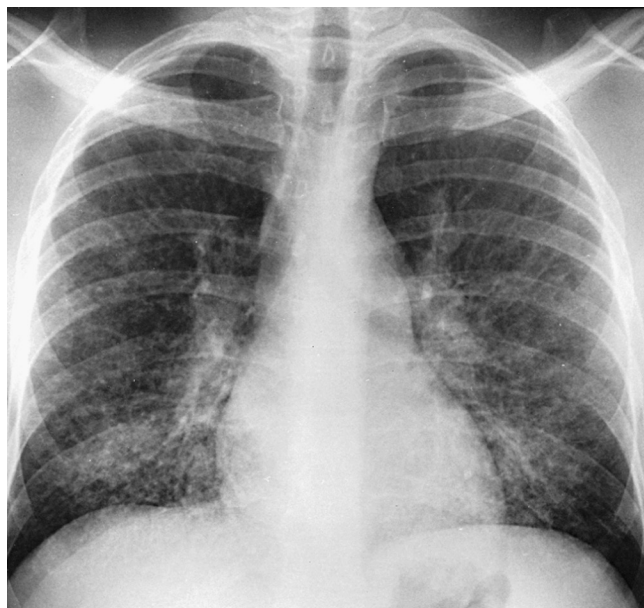


Figure 90-11 Lymphocytic interstitial pneumonitis. Frontal chest radiograph of an HIV-infected patient showing diffuse reticulonodular infiltration. Biopsy specimen revealed lymphocytic interstitial pneumonitis.

the frequency with which biopsy is performed during the diagnostic evaluation.

Clinical Features. The clinical features of NSIP are indistinguishable from those of PCP; however, NSIP may present at CD4⁺ lymphocyte counts greater than 200 cells/ μ L, whereas PCP rarely ($\leq 5\%$) does. For example, in a series of 67 HIV-infected patients with NSIP, the mean CD4⁺ lymphocyte count in the patients with NSIP was 492 cells/ μ L compared with 57 cells/ μ L for the matched control subjects with PCP.³⁶² The chest radiographic presentation of NSIP is usually a nonspecific diffuse interstitial pattern, which is also indistinguishable from that of PCP; however, one study reported that 16 of 36 (44%) patients with HIV-related NSIP had normal radiographs.³⁶³

Diagnosis and Treatment. The diagnosis of NSIP requires both histologic confirmation and the exclusion of other etiologies. The natural history of HIV-associated NSIP is poorly understood, but it usually resolves or stabilizes without therapy.³⁶² Observation is all that is required, but if the patient becomes severely ill, repeat bronchoscopy and biopsy are indicated to look for a different, usually infectious, disorder.

SARCOIDOSIS

Although sarcoidosis would seem an unlikely disorder among patients with HIV, a number of cases of sarcoidosis or sarcoid-like disease have been reported in this population. Many of these case reports have correlated the use of ART with the development of sarcoidosis.^{364,365} Whether sarcoidosis in HIV represents a manifestation of IRIS is debated. Approximately 75% of HIV-infected patients with sarcoidosis have CD4⁺ lymphocyte counts above 200 cells/ μ L.³⁶⁴

Both the clinical and imaging findings (eFig. 90-41) of sarcoidosis in HIV-infected patients mirror findings of sarcoidosis in non-HIV-infected patients.^{364,365} As described in Chapter 66, granulomatous inflammation of the lungs and other involved organs is characteristic. Stains and cultures of tissue should be obtained and, to diagnose sarcoid, must be negative for microorganisms (e.g., mycobacteria, fungi). Lymphocytic alveolitis with a high percentage of CD4⁺ lymphocytes may be encountered.³⁶⁶ Because no studies have evaluated treatment of sarcoidosis specifically in HIV-infected persons, until further data are available, management should follow guidelines as outlined for non-HIV-infected persons with sarcoidosis.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

IRIS describes a paradoxical worsening of clinical status related to recovery of the immune system following a period of immunosuppression. The syndrome typically develops after the initiation of ART in HIV-infected patients. IRIS is thought to result from the reconstitution of the immune system leading to host inflammatory responses to previously recognized or subclinical infections. Immune reconstitution may also result from an inflammatory or immune response to cancer or self antigens, because cases of IRIS have been reported to present with worsening tumor or autoimmune disease.³⁶⁷

Numerous disease processes have been associated with IRIS. These include many infections, sarcoidosis, autoimmune conditions, and tumors.^{368,369} Among infectious triggers, mycobacterial infections—particularly *M. tuberculosis* (eFig. 90-42) and MAC—are most frequently encountered. Fungal infections, including PCP and *Cryptococcus*, as well as viral infections, such as CMV, can also be exacerbated by IRIS. The majority of cases of IRIS are seen within the first 1 to 3 months following the initiation of ART, although cases may present several months after the initiation of ART.³⁶⁹ In most studies, IRIS is significantly associated with starting ART in close proximity to treatment for an acute opportunistic infection.^{370,371} Nonetheless, recent studies support starting ART concurrently or very soon after starting treatment of opportunistic infection, because this strategy results in improved survival.^{109-111,372} Recommendations regarding the exact timing of ART initiation depends on the patient's CD4⁺ cell count, type of infection or complication, and organ system involved.

In general, ART should be continued in patients who have IRIS, although careful review on a case-by-case basis is required and expert consultation is recommended.²⁹ Nonsteroidal anti-inflammatory agents can be used to decrease inflammation. Less commonly, steroids may be indicated if the excessive inflammatory response can be particularly harmful, for example in tuberculosis meningitis, or with other lesions that are life threatening, such as those involving the central nervous system or those causing airway compromise. Optimal dosage and duration have not been studied, but prednisone or methylprednisolone at approximately 1.5 mg/kg of body weight per day for 2 weeks followed by 0.75 mg/kg/day for an additional 2 weeks while monitoring clinical response may be used.²⁹

Key Points

- HIV infection results in immune dysregulation, dysfunction, and deficiency, with a progressive decline in the circulating CD4⁺ lymphocyte count, particularly in patients that are not receiving effective combination antiretroviral therapy (ART). HIV infection also causes alteration in several lines of host defense in the lungs and respiratory tract.
- The peripheral CD4⁺ lymphocyte count influences the risk for pulmonary complications in HIV-infected persons; as the CD4⁺ count decreases, the risk of opportunistic infections and HIV-associated malignancies increases progressively.
- Worldwide, tuberculosis is the most common infectious lung complication and a major cause of HIV-associated morbidity and mortality. Drug-resistant tuberculosis is increasing in incidence and seems to have a predilection for persons infected with HIV.
- Bacterial pneumonia and *Pneumocystis pneumonia* (PCP) are also common infectious lung complications associated with HIV; noninfectious conditions that may be encountered with increased frequency in patients with HIV include lung cancer, idiopathic pulmonary arterial hypertension, and chronic obstructive pulmonary diseases.
- The differential diagnosis for pulmonary diseases in HIV-infected patients is broad, and the clinical features and radiographic findings of many diseases may overlap significantly. Definitive diagnosis is highly recommended in patients with HIV. When feasible, early bronchoscopy with bronchoalveolar lavage should be performed in patients with pneumonia who do not have an established microbiologic diagnosis.
- In HIV-infected patients recently started on ART, immune reconstitution inflammatory syndrome may develop, presenting with paradoxical worsening of conditions that include infections (e.g., tuberculosis, *Mycobacterium avium* complex, and PCP), malignancies (e.g., Kaposi sarcoma), and inflammatory diseases (e.g., sarcoidosis).

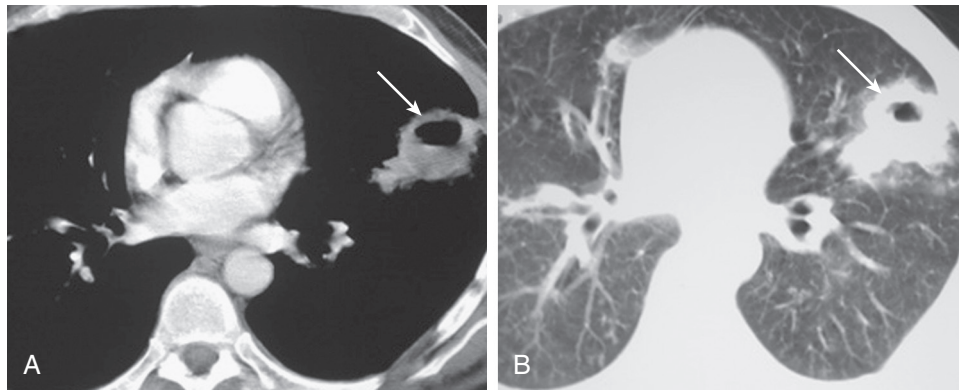
Complete reference list available at *ExpertConsult*.

Key Readings

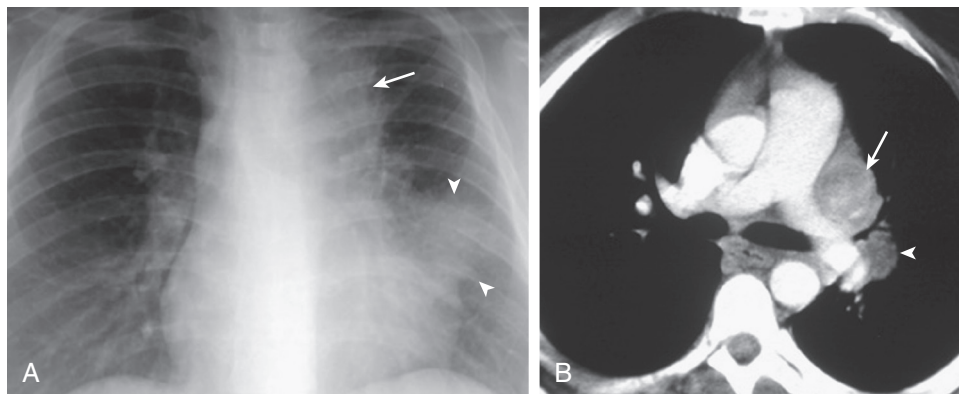
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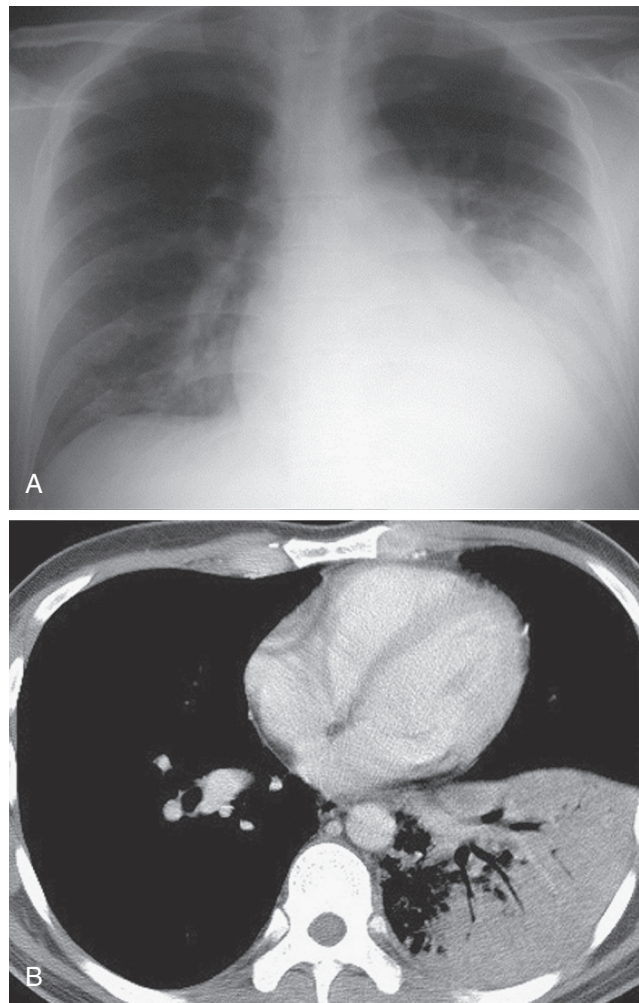
eFIGURE IMAGE GALLERY



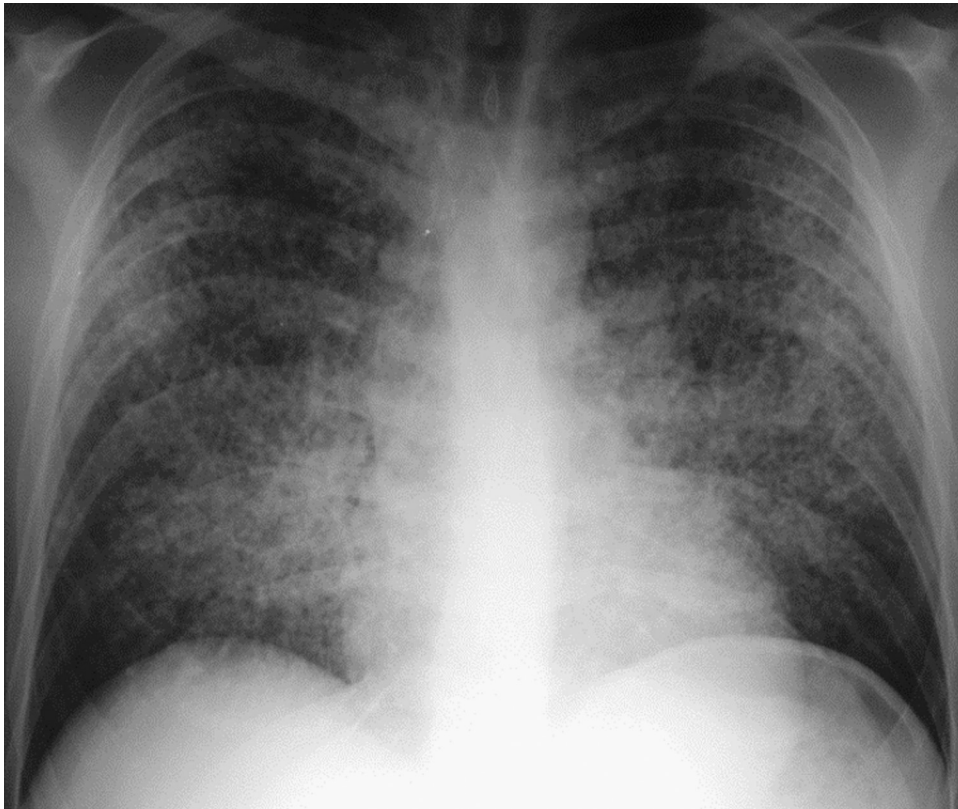
eFigure 90-1 *Pseudomonas aeruginosa* pulmonary abscess. Axial chest CT scans in soft tissue (**A**) and lung windows (**B**) show a thick-walled lingular cavity (arrows) with surrounding consolidation. *Pseudomonas aeruginosa* was recovered from blood and sputum. The imaging appearance is nonspecific and could be seen with other causes of pulmonary abscess as well as malignancy (note similarity with primary lung malignancy shown in eFig. 90-39). (Courtesy Michael Gotway, MD.)



eFigure 90-2 *Nocardia asteroides* thoracic infection. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows left superior mediastinal widening (arrow) consistent with mediastinal lymphadenopathy. A lingular masslike opacity (arrowheads) is present. **B**, Axial chest CT displayed in soft tissue windows shows subaortic (arrow) and left peribronchial (arrowhead) lymphadenopathy. (Courtesy Michael Gotway, MD.)



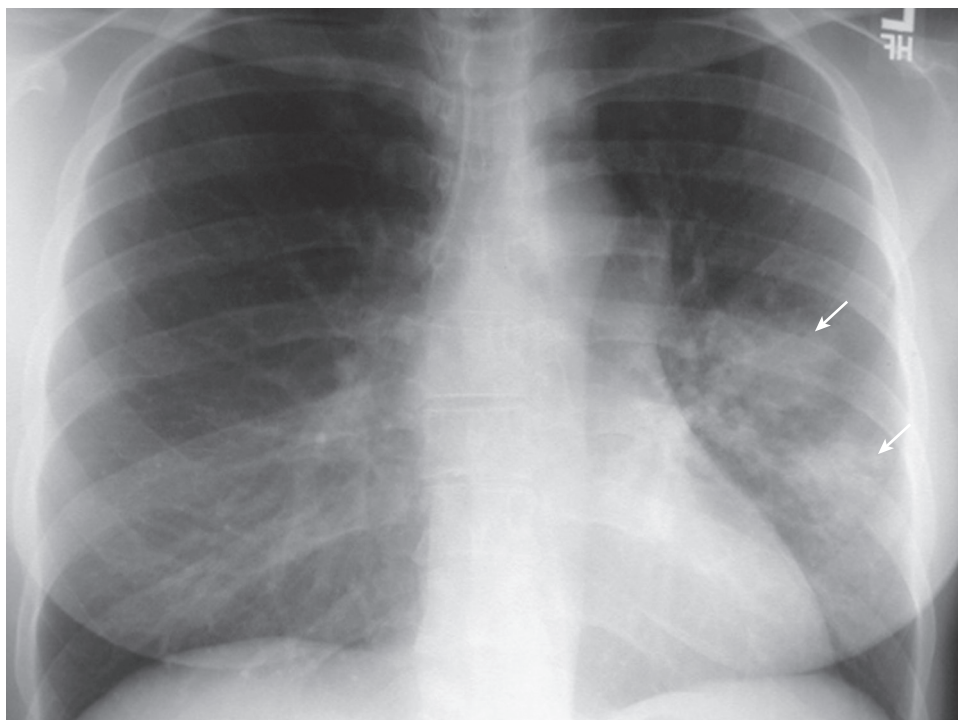
eFigure 90-3 Primary *Mycobacterium tuberculosis* infection in an HIV-infected patient. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows dense opacification of the left lower lobe. **B**, Axial chest CT displayed in soft tissue windows shows left lower lobe consolidation. The imaging appearance is entirely consistent with a lobar pneumonia pattern, often seen with pneumococcal or *Klebsiella* pneumonias. Sputum grew *Mycobacterium tuberculosis* and the patient responded to antituberculous therapy. (Courtesy Michael Gotway, MD.)



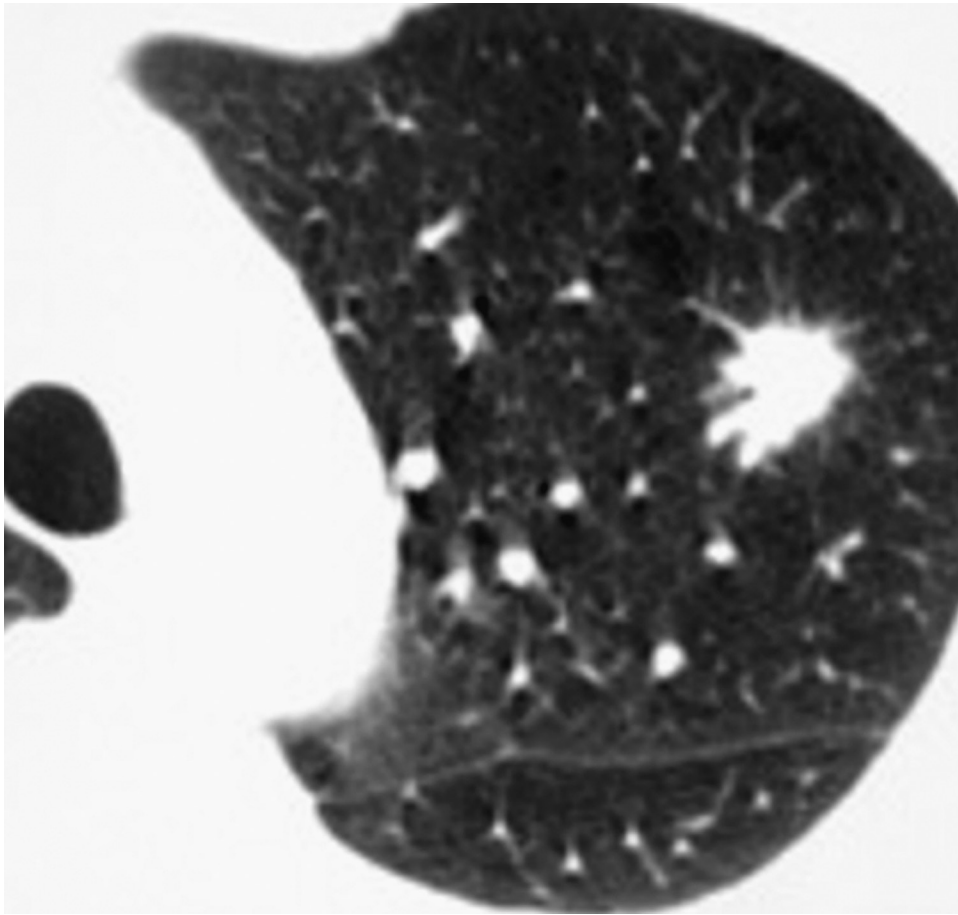
eFigure 90-4 *Mycobacterium tuberculosis* miliary pulmonary infection. Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows numerous, bilateral, randomly disseminated, small pulmonary nodules. (Courtesy Michael Gotway, MD.)



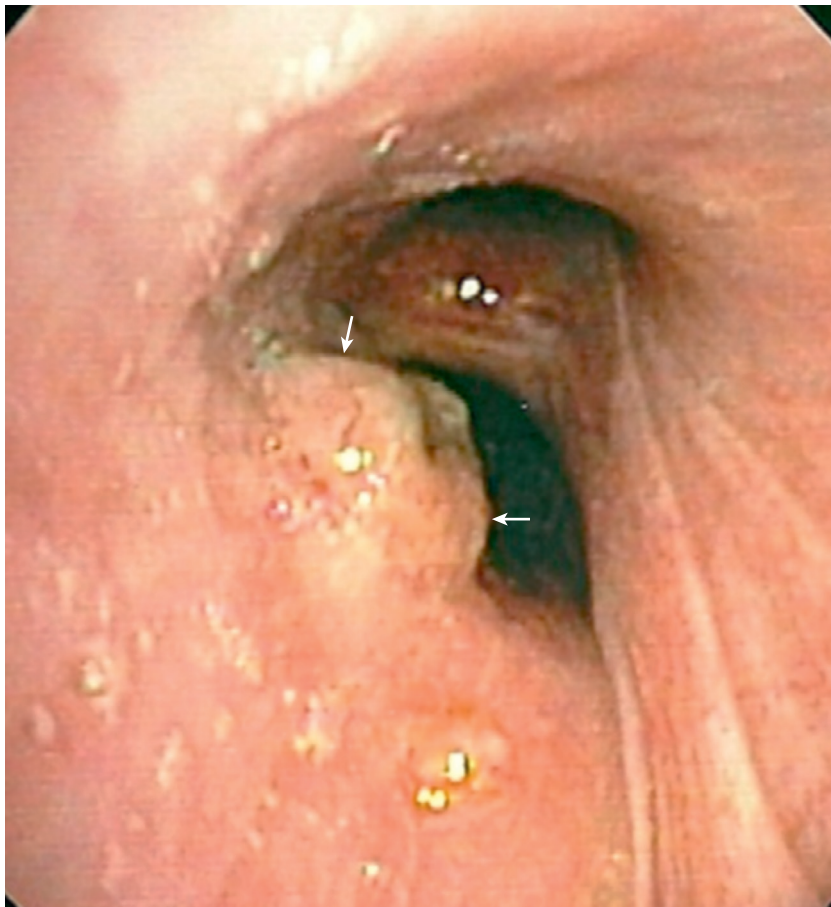
eFigure 90-5 *Mycobacterium tuberculosis* lymphadenitis. Frontal chest radiograph shows right hilar (arrow) and right paratracheal (arrowheads) lymphadenopathy in an HIV-infected patient with a low CD4⁺ count. (Courtesy Michael Gotway, MD.)



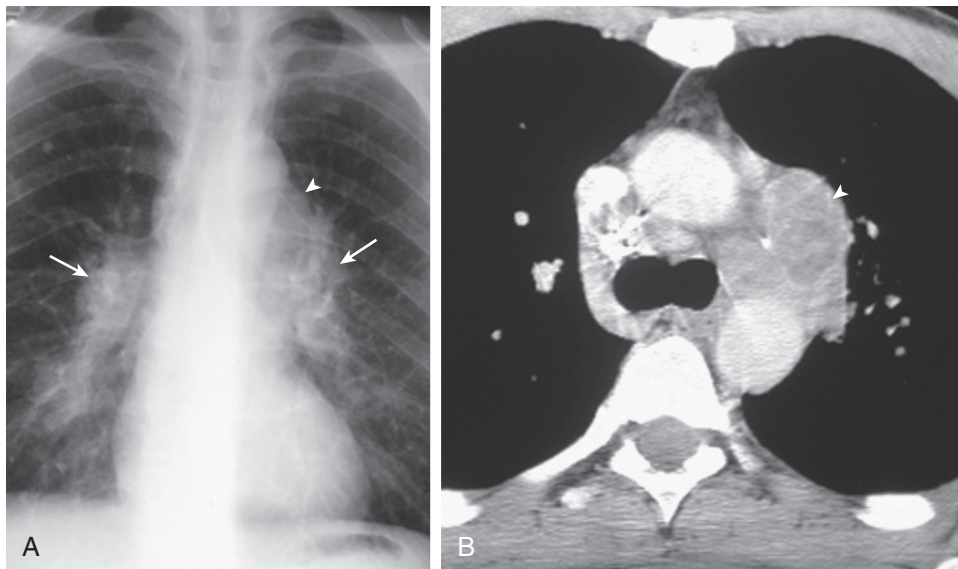
eFigure 90-6 *Mycobacterium avium* complex focal pulmonary infection. Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 50 cells/ μ L shows focal nodular left perihilar opacities (arrows) representing MAC infection. (Courtesy Michael Gotway, MD.)



eFigure 90-7 *Mycobacterium avium* complex presenting as a pulmonary nodule. Chest CT displayed in lung windows performed in an HIV-infected patient with a CD4⁺ count less than 50 cells/ μ L shows a spiculated left upper lobe nodule suspicious for primary pulmonary malignancy. Transthoracic percutaneous needle biopsy proved MAC infection. (Courtesy Michael Gotway, MD.)



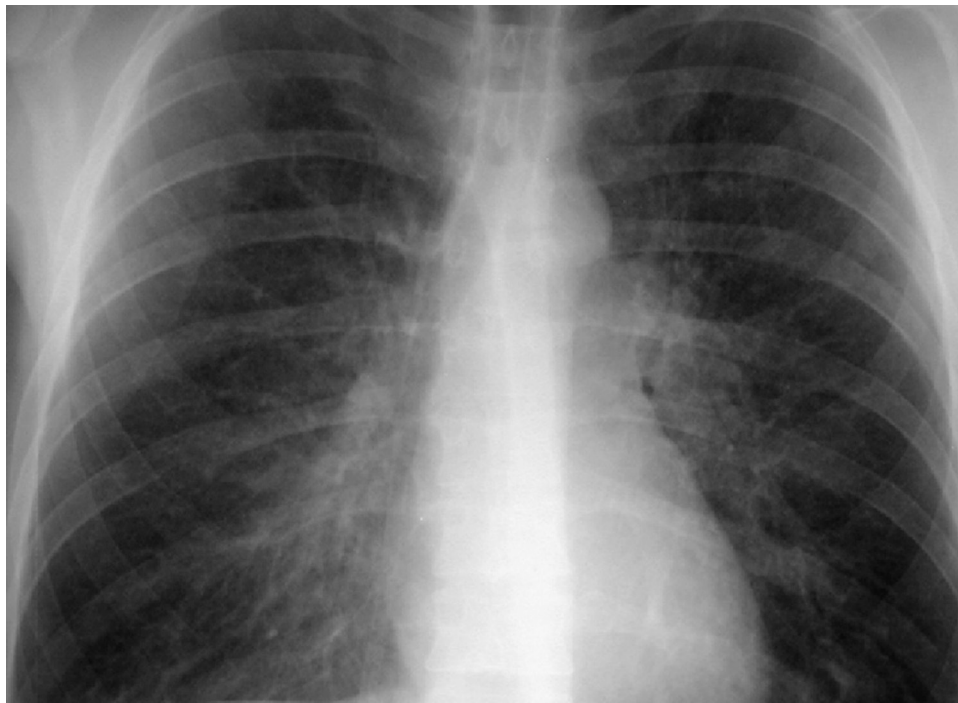
eFigure 90-8 *Mycobacterium avium* complex endo-bronchial infection in an HIV-infected patient with a low CD4⁺ count. Bronchoscopic image shows small white nodular areas (*arrows*). Biopsy recovered *Mycobacterium avium* complex organisms. (Courtesy Michael Gotway, MD; case by Syed A.J. Zaidi, MBBS, FCCP, Pulmonary-Critical Care section, Maricopa Medical Center, Phoenix, AZ.)



eFigure 90-9 *Mycobacterium avium* complex lymphadenitis. **A**, Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 50 cells/ μ L shows bilateral hilar (*arrows*) and left mediastinal (*arrowhead*) lymphadenopathy. **B**, Axial enhanced chest CT confirms presence of enlarged aortopulmonary lymph nodes (*arrowhead*) as well as left tracheobronchial lymphadenopathy. Note the presence of low attenuation areas, consistent with necrosis. (Courtesy Michael Gotway, MD.)



eFigure 90-10 *Mycobacterium kansasii* pulmonary infection. Frontal chest radiograph performed in an HIV-infected patient with a CD4⁺ count less than 50 cells/ μ L shows linear bronchovascular thickening in the left upper lobe associated with left apical thin-walled cavities (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 90-11 Typical imaging appearance of *Pneumocystis jirovecii* pneumonia. Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows bilateral, symmetric perihilar indistinctness. Sputum induction recovered *Pneumocystis jirovecii*. (Courtesy Michael Gotway, MD.)

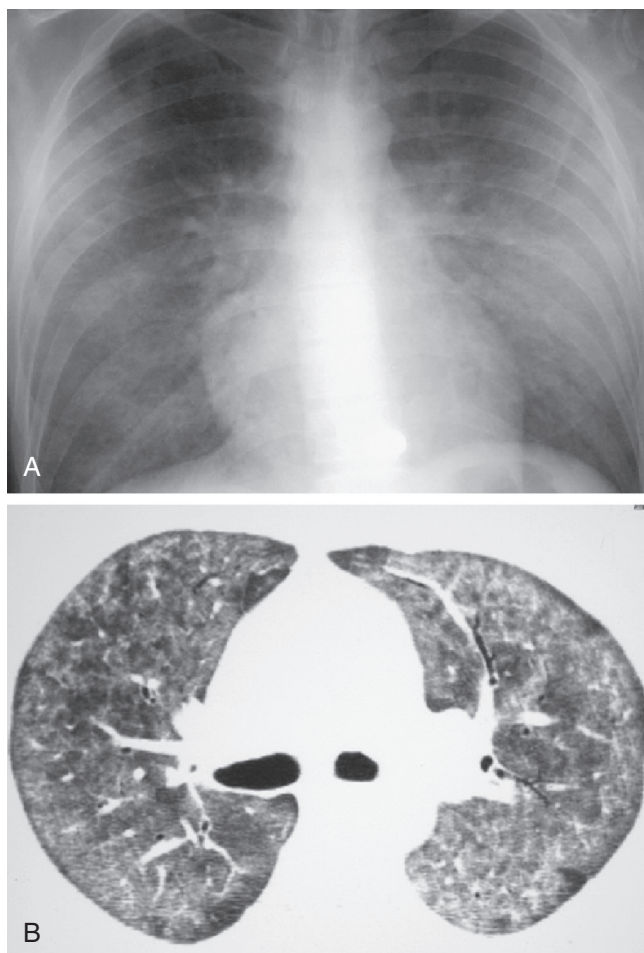
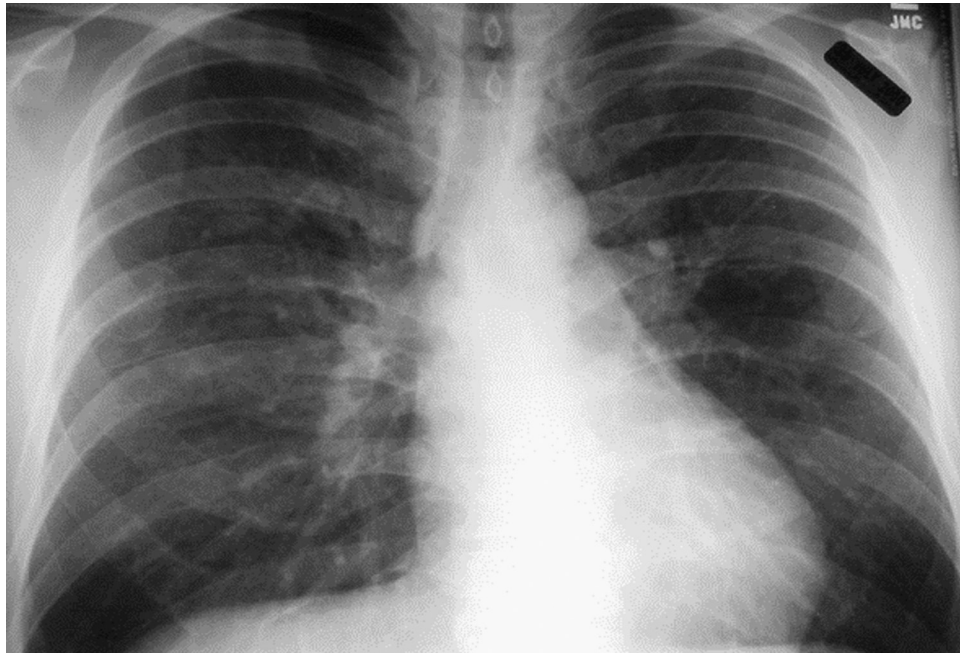
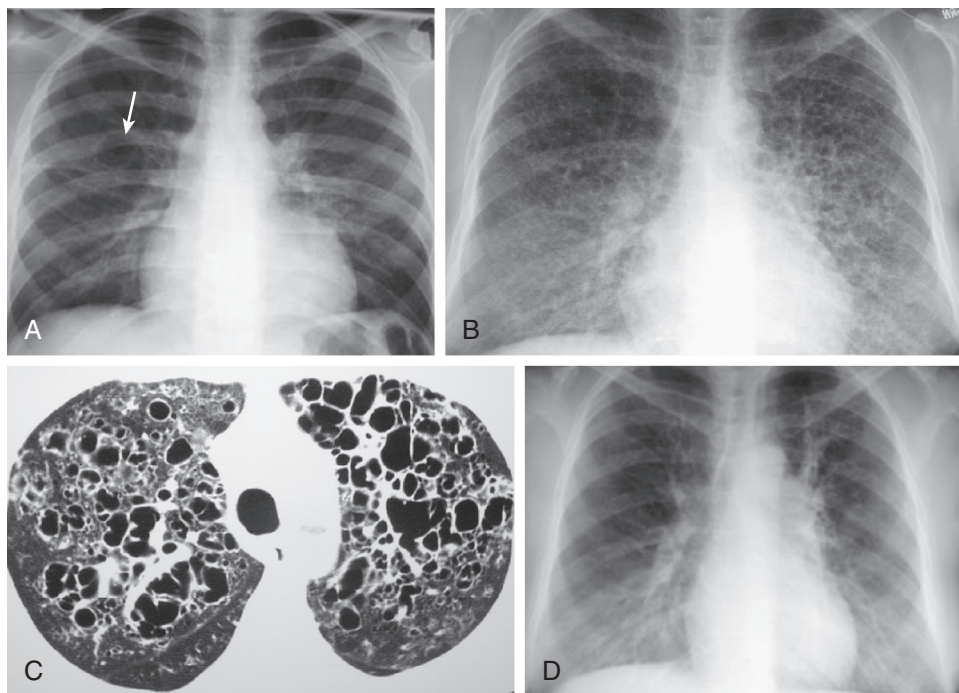


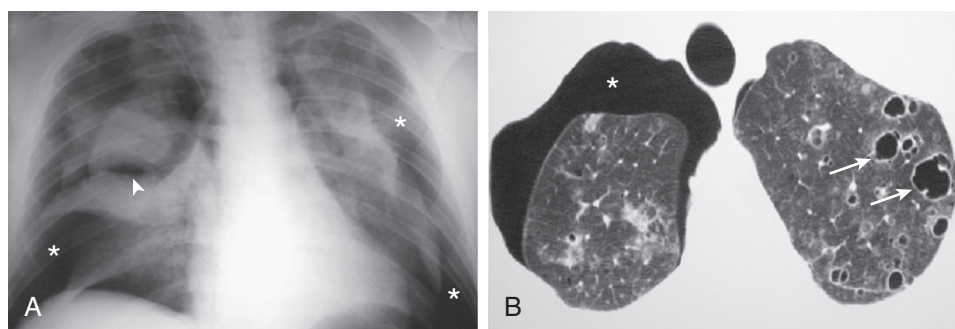
Figure 90-12 Typical imaging appearance of *Pneumocystis jirovecii* pneumonia. **A**, Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows bilateral, interstitial thickening with increased attenuation consistent with a ground-glass appearance (increased pulmonary attenuation without obscuration of the underlying vascular and bronchial margins). Sputum induction recovered *Pneumocystis jirovecii*. **B**, Axial chest CT displayed in lung windows shows the typical appearance of multifocal, bilateral ground-glass opacity in HIV-infected patients with *Pneumocystis jirovecii* pneumonia. (Courtesy Michael Gotway, MD.)



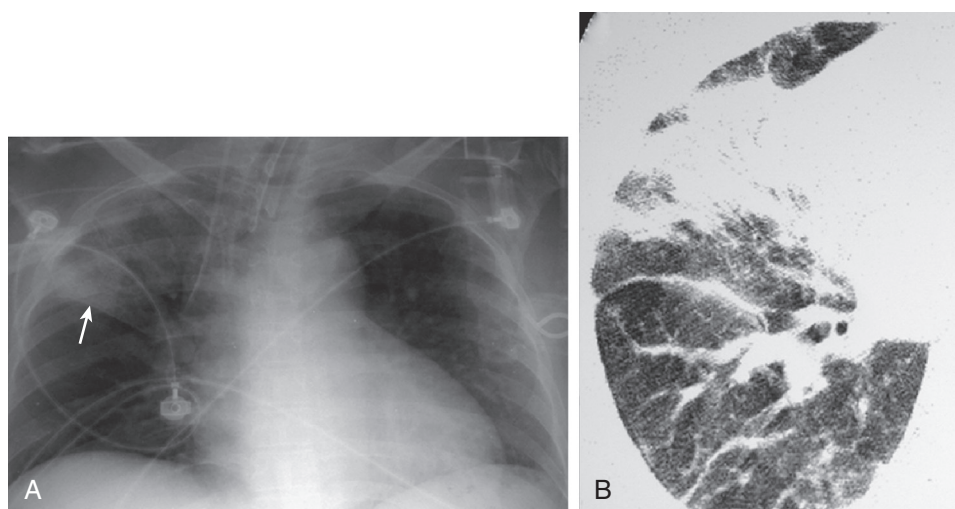
eFigure 90-13 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia. Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows faint predominantly right perihilar bronchovascular indistinctness; minimal left perihilar indistinctness is present. Asymmetry or frankly unilateral pulmonary findings are an atypical imaging manifestation of *Pneumocystis jirovecii* pneumonia. Nevertheless, in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L such an imaging appearance is suspicious for *Pneumocystis jirovecii* pneumonia. (Courtesy Michael Gotway, MD.)



eFigure 90-14 Imaging appearance of *Pneumocystis jirovecii* pneumonia: pneumatocele formation. **A,** Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows bilateral mild bronchovascular thickening and indistinctness, consistent with *Pneumocystis jirovecii* pneumonia. A thin-walled right perihilar cyst (arrow) is present, consistent with a pneumatocele. **B,** Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows innumerable bilateral linear, reticular, and cystic foci. **C,** Axial chest CT displayed in lung windows shows numerous, bilateral thin-walled cysts with a few areas of ground-glass opacity also visible. The appearance is somewhat reminiscent of Langerhans cell histiocytosis. **D,** Follow-up chest radiograph obtained several months after (A) shows resolution of the cysts. (Courtesy Michael Gotway, MD.)



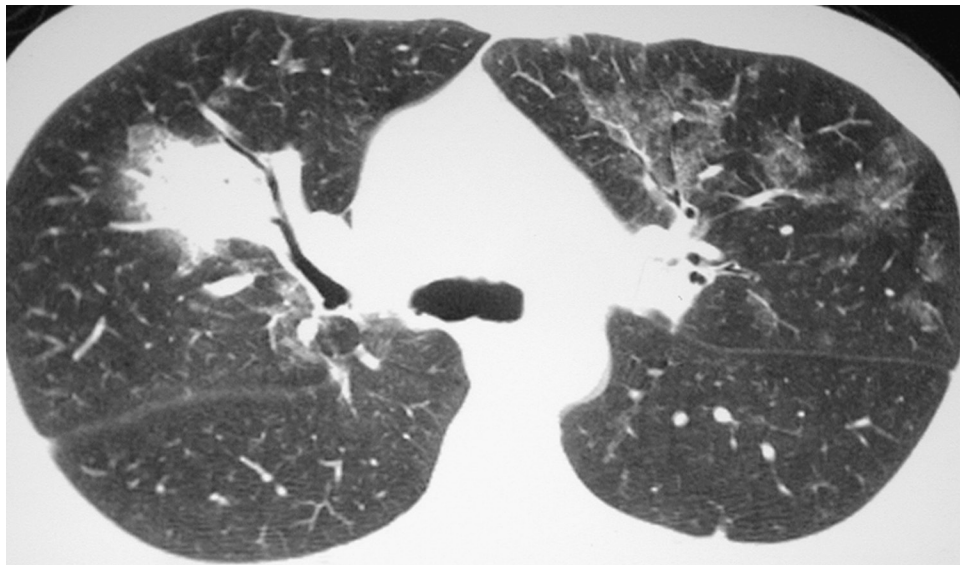
eFigure 90-15 Imaging appearance of *Pneumocystis jirovecii* pneumonia: pneumothorax due to pneumatocele formation. **A**, Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows bilateral pneumothoraces (*), on the right side tracking into the fissural surfaces (arrowhead). **B**, Axial chest CT displayed in lung windows in a different patient shows patchy bilateral ground-glass opacity, consistent with *Pneumocystis jirovecii* pneumonia, complicated by thin-walled cysts (arrows), representing pneumatoceles. A right-sided pneumothorax (*) is present. (Courtesy Michael Gotway, MD.)



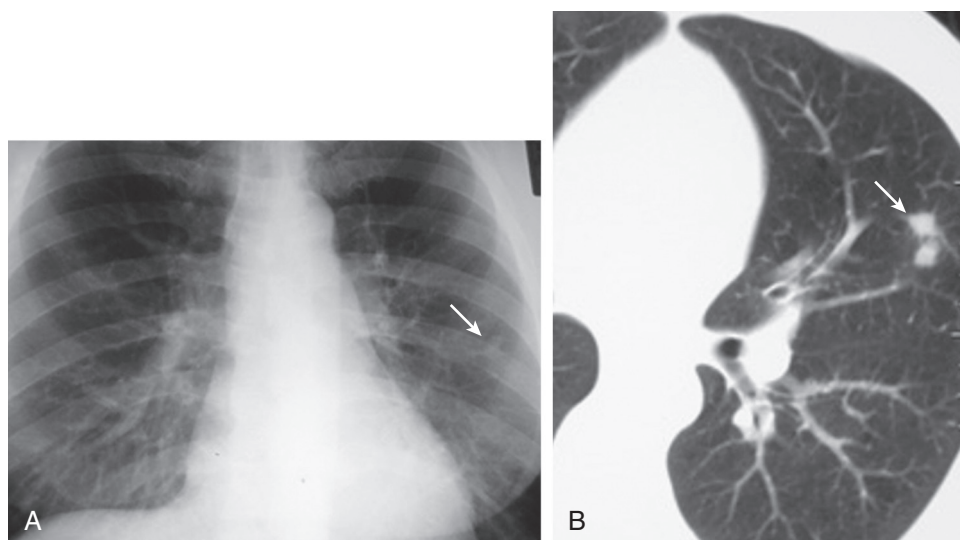
eFigure 90-16 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia: focal consolidation. **A**, Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows focal right upper lobe opacity (arrow), demarcated by the right horizontal fissure. **B**, Focused axial chest CT displayed in lung windows in a separate patient shows air space consolidation in the right middle lobe. Sputum induction recovered *Pneumocystis jirovecii* in both patients. (Courtesy Michael Gotway, MD.)



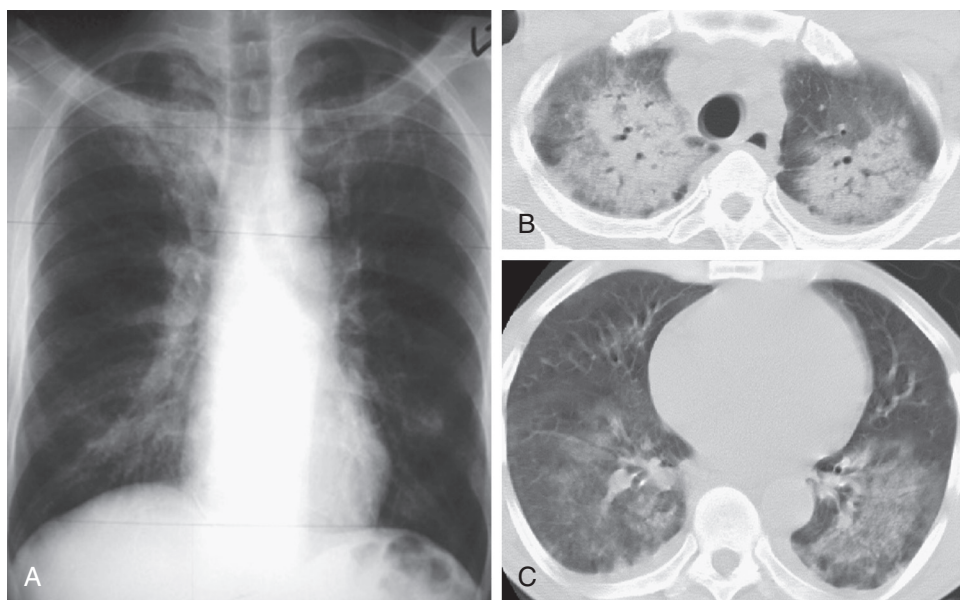
eFigure 90-17 Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows patchy bilateral opacities consistent with *Pneumocystis jirovecii* pneumonia. The more focal left mid-lung opacity (arrow) raises the possibility of a second, superimposed process, but no other organisms could be recovered and the pulmonary abnormalities resolved with treatment of *Pneumocystis jirovecii*. (Courtesy Michael Gotway, MD.)



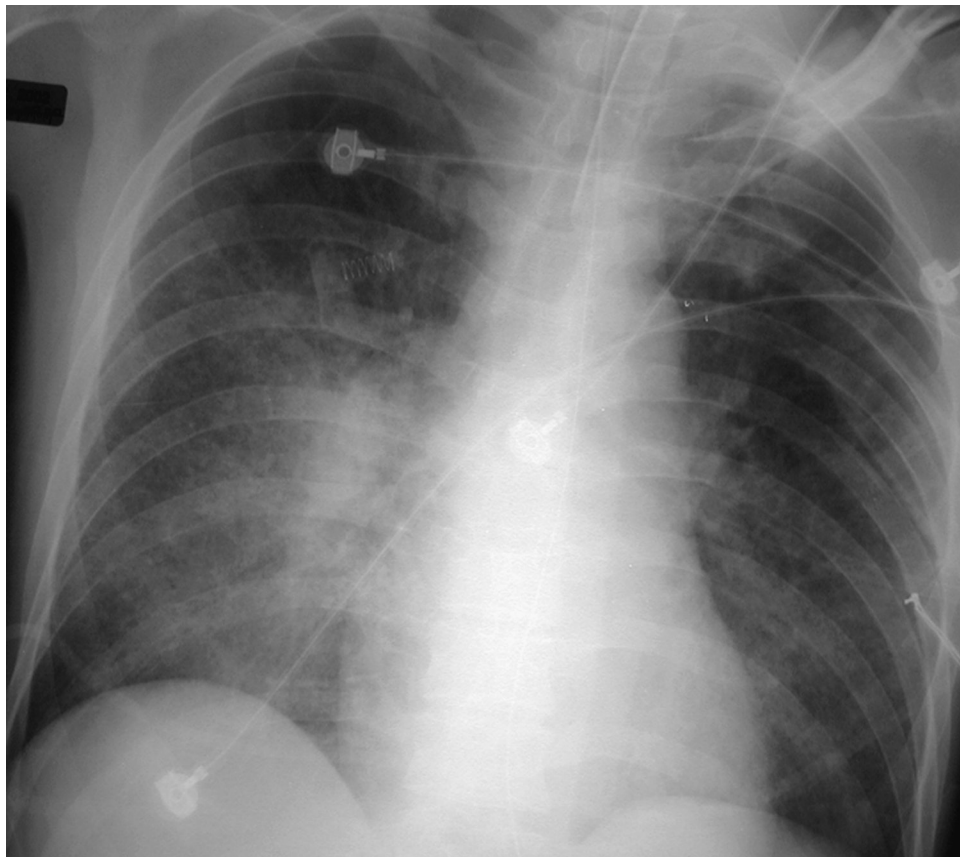
eFigure 90-18 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia: focal lung opacity. Axial chest CT displayed in lung windows performed in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows air-space consolidation in the right upper lobe. Patchy left upper lobe ground-glass opacity is also present, consistent with *Pneumocystis jirovecii* pneumonia. The patient underwent transthoracic percutaneous lung biopsy of the focal opacity to exclude the possibility of a second process superimposed on *Pneumocystis jirovecii* pneumonia; this biopsy showed only *Pneumocystis jirovecii* organisms. (Courtesy Michael Gotway, MD.)



eFigure 90-19 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia: focal nodules. **A**, Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows faint left mid-lung nodular opacity (arrows). **B**, Axial chest CT displayed in lung windows shows two focal lingular nodules. Transthoracic percutaneous lung biopsy showed only *Pneumocystis jirovecii* organisms. (Courtesy Michael Gotway, MD.)



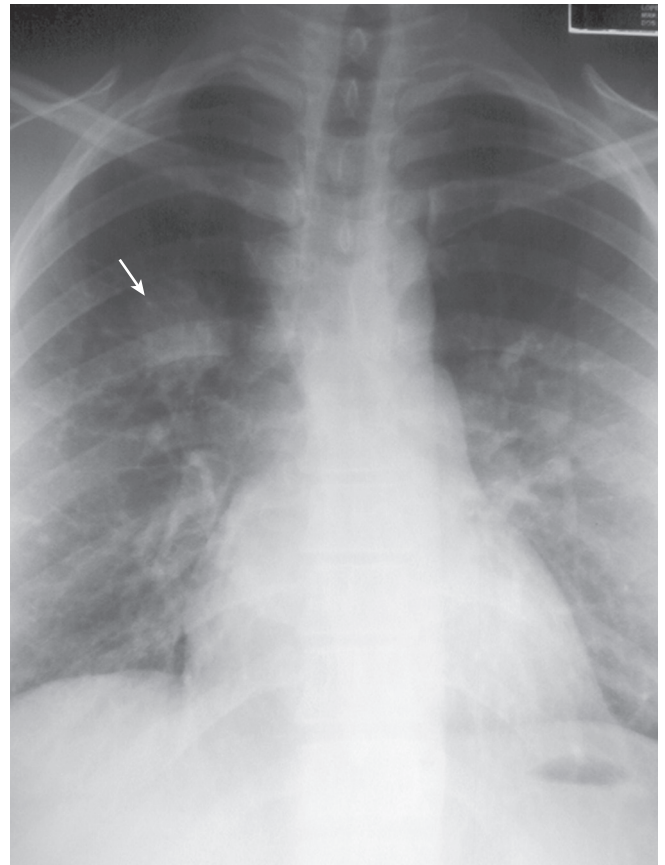
eFigure 90-20 Atypical imaging appearance of *Pneumocystis jirovecii* pneumonia: upper lobe predominant pulmonary opacity. **A**, Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count less than 200 cells/ μ L shows bilateral, right-greater-than-left, upper lobe opacities. **B** and **C**, Given the atypical chest radiographic findings, the patient underwent axial chest CT, displayed in lung windows, due to continued suspicion for *Pneumocystis jirovecii* pneumonia, which shows bilateral upper lobe consolidation and less pronounced bibasal ground-glass opacity. Bronchoscopy recovered *Pneumocystis jirovecii*. (Courtesy Michael Gotway, MD.)



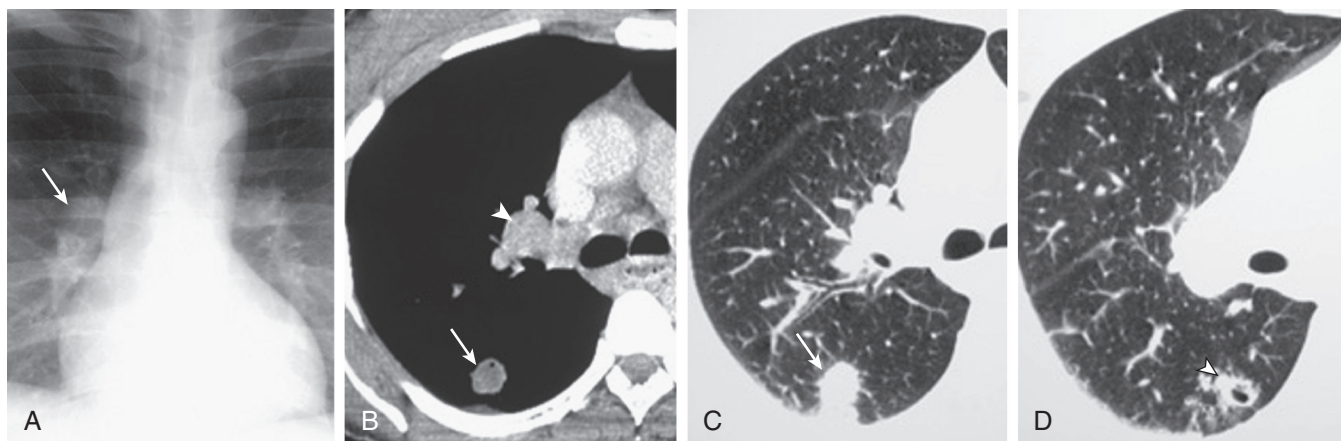
eFigure 90-21 Cryptococcal pulmonary infection: interstitial appearance. Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows bilateral, right-greater-than-left, perihilar ground-glass attenuation and linear, interstitial thickening, suspicious for *Pneumocystis jirovecii* pneumonia; however, the opacities were proven to be the result of cryptococcal pulmonary infection. (Courtesy Michael Gotway, MD.)



eFigure 90-22 Cryptococcal pulmonary infection: focal pulmonary opacity. Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows focal right lower lobe consolidation superimposed on more diffuse interstitial thickening throughout the right lung. (Courtesy Michael Gotway, MD.)



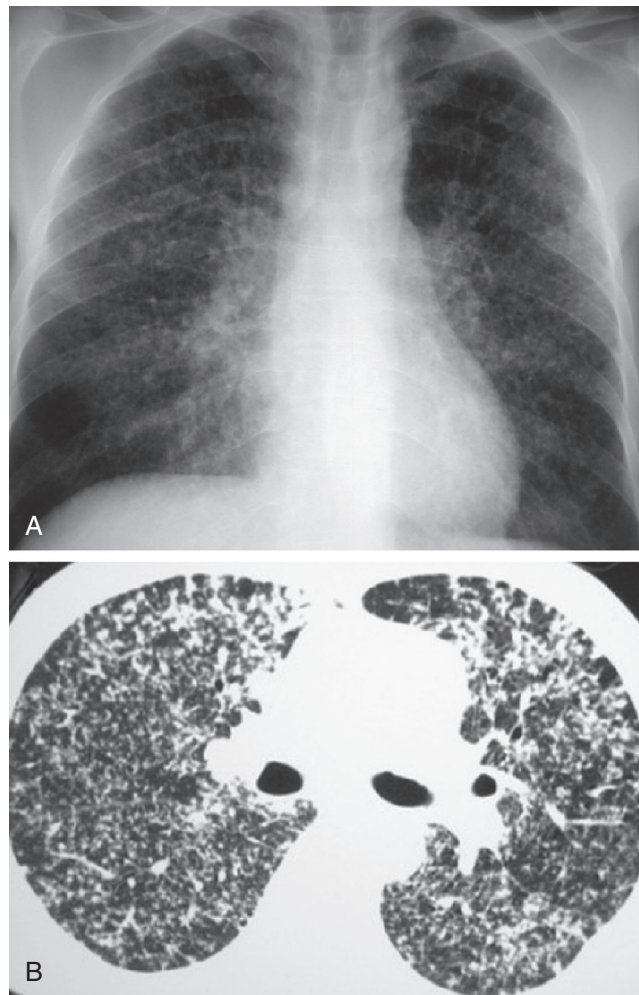
eFigure 90-23 Cryptococcal pulmonary infection: pulmonary nodule. Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows a right suprahilar pulmonary nodule (arrow). Transthoracic percutaneous lung biopsy demonstrated cryptococcal infection. (Courtesy Michael Gotway, MD.)



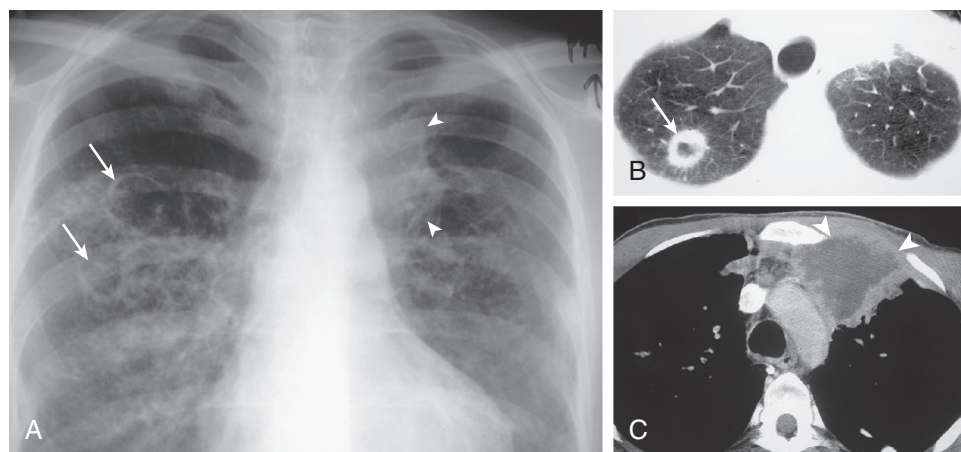
eFigure 90-24 Cryptococcal pulmonary infection: thoracic lymphadenopathy and nodules. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows right hilar lymph node enlargement (*arrow*). **B–D**, Axial chest CT displaced in soft tissue (**B**) and lung (**C** and **D**) windows confirms right peribronchial lymph node enlargement (*arrowhead*, **B**) and shows a nodule in the right lower lobe (*arrows*, **B** and **C**); note the tiny focus of cavitation evident within the nodular anteriorly in (**B**). A separate cavitary nodule (*arrowhead*, **D**), with surrounding satellite opacities, is seen slightly more inferiorly in the superior segment of the right lower lobe. (Courtesy Michael Gotway, MD.)



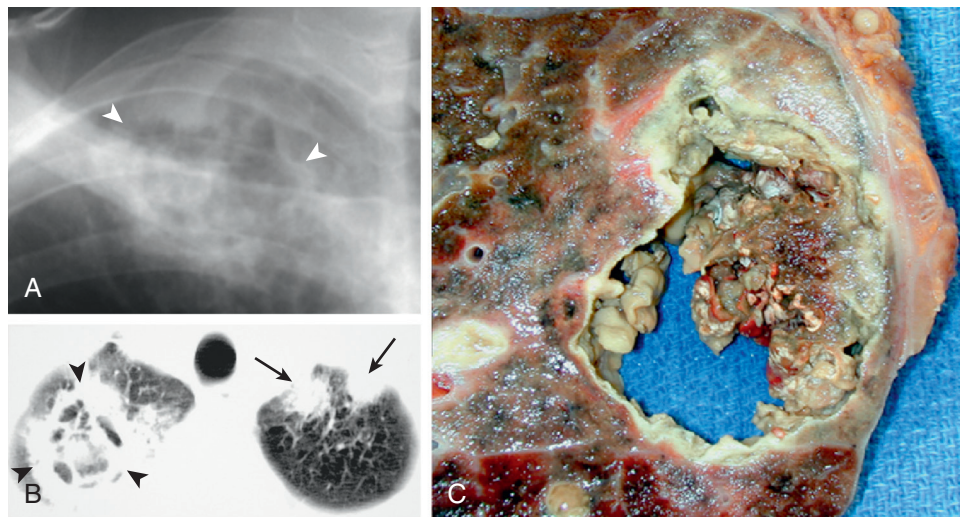
eFigure 90-25 Cryptococcal pulmonary infection: miliary infection. Frontal chest radiograph performed in an HIV-infected patient with a low CD4⁺ count shows numerous symmetrical bilateral small pulmonary nodules. (Courtesy Michael Gotway, MD.)



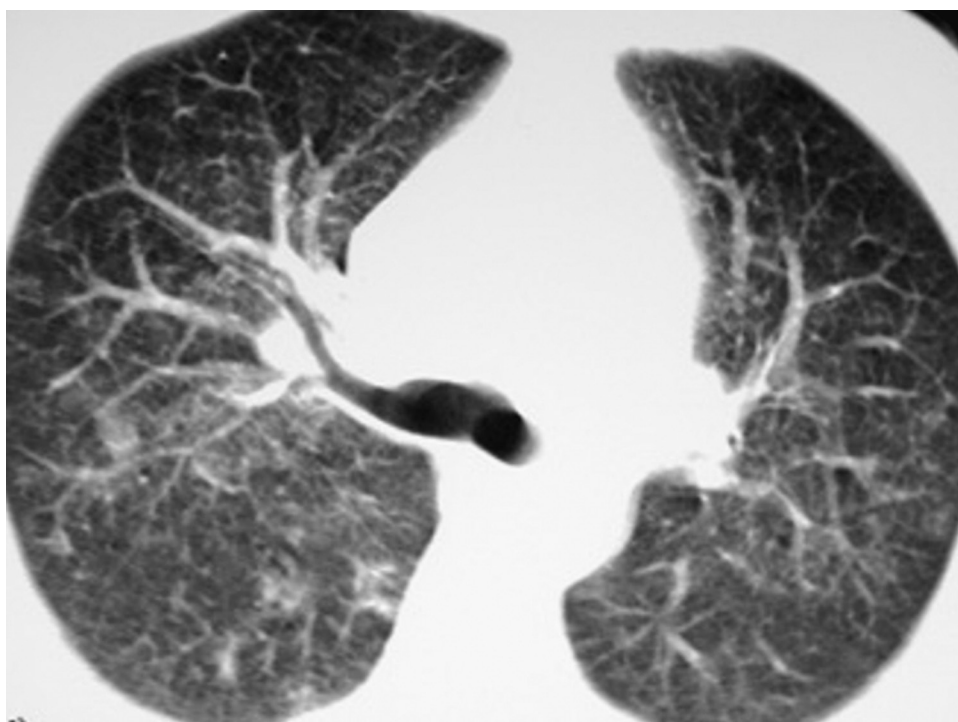
eFigure 90-26 *Coccidioides immitis* pulmonary infection: miliary infection. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows numerous symmetrical bilateral small pulmonary nodules. **B**, Axial chest CT shows numerous bilateral pulmonary nodules, consistent with a random small nodular, or miliary, pattern. Bronchoscopy with transbronchial biopsy proved *Coccidioides immitis* infection. (Courtesy Michael Gotway, MD.)



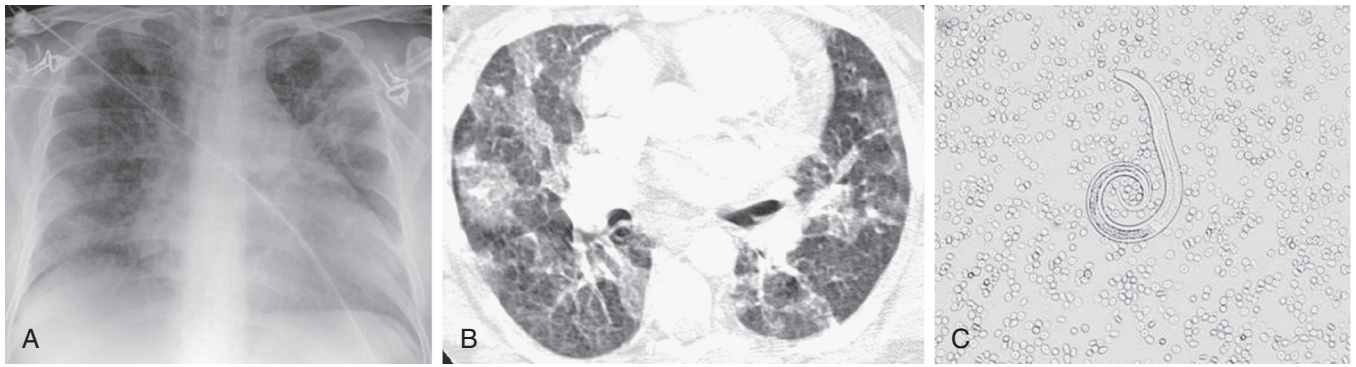
eFigure 90-27 *Aspergillus* pulmonary infection. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows right upper lobe cystic lesions (arrows) with surrounding small nodules and left superior mediastinal soft tissue (arrowheads). Axial chest CT displayed in lung (**B**) and soft tissue (**C**) windows shows a right apical cavity (arrow, **B**) and a necrotic mass in the left superior mediastinum (arrowheads, **C**) invading the chest wall anteriorly. Transthoracic percutaneous lung biopsy of the left-sided mass recovered *Aspergillus fumigatus*. (Courtesy Michael Gotway, MD.)



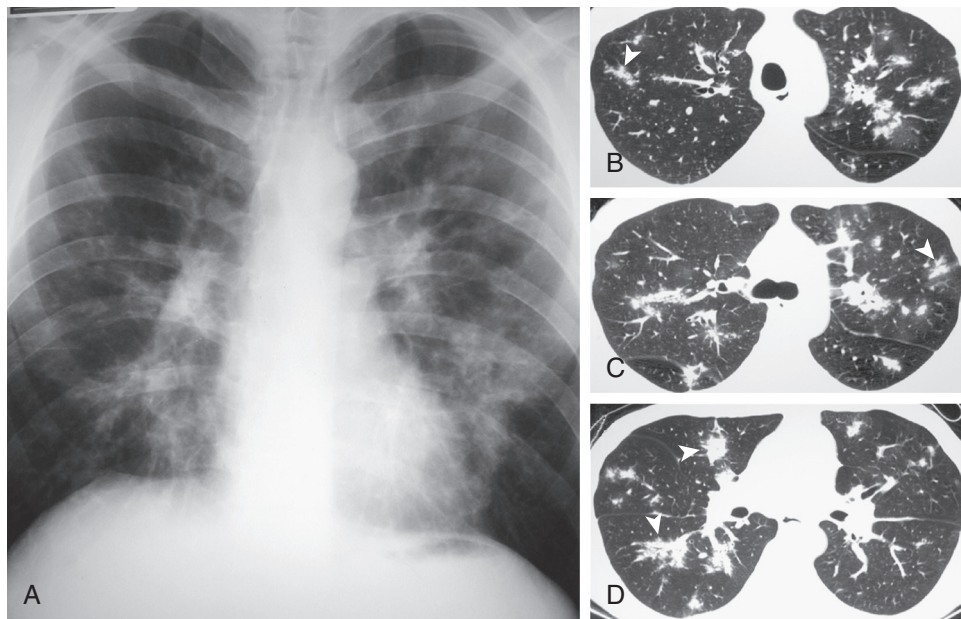
eFigure 90-28 *Aspergillus* pulmonary infection. **A**, Focused frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows an irregular cavity (arrowheads) in the right apex. **B**, Axial chest CT displayed in lung windows shows a complex cavity with internal opacity (arrowheads) as well as right apical lung nodules (arrows). **C**, Postmortem right lung specimen shows a necrotic right apical cavity with complex internal material, correlating with the CT findings. Numerous areas of arterial and venous invasion with thrombosis and infarction were identified, and *Aspergillus fumigatus* was recovered from the material within the cavity. (Modified from Gotway MB, Dawn SK, Caoili EM, et al: The radiologic spectrum of pulmonary *Aspergillus* infections. *J Comput Assist Tomogr* 26:159–173, 2002.)



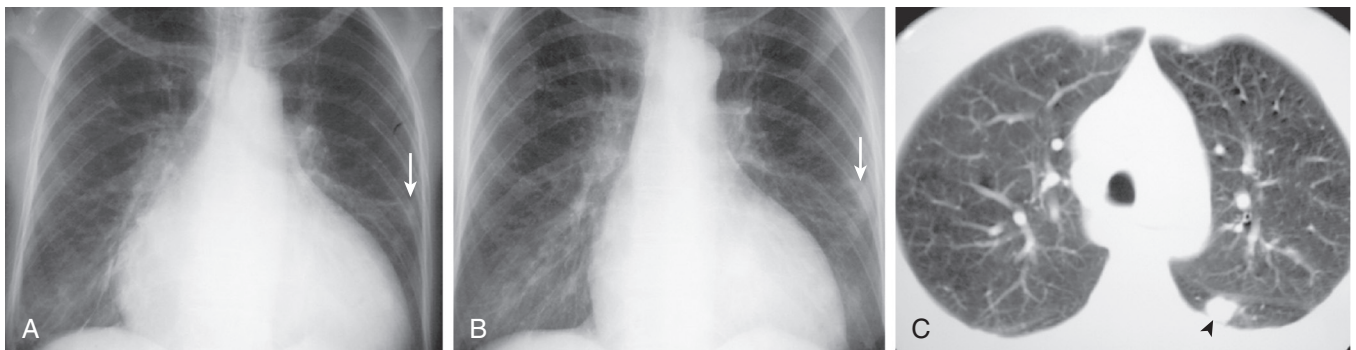
eFigure 90-29 Cytomegalovirus infection. Axial chest CT in an HIV-infected patient with a low CD4⁺ count shows patchy, variably-sized pulmonary nodular opacities. The imaging features are very nonspecific. (Courtesy Michael Gotway, MD.)



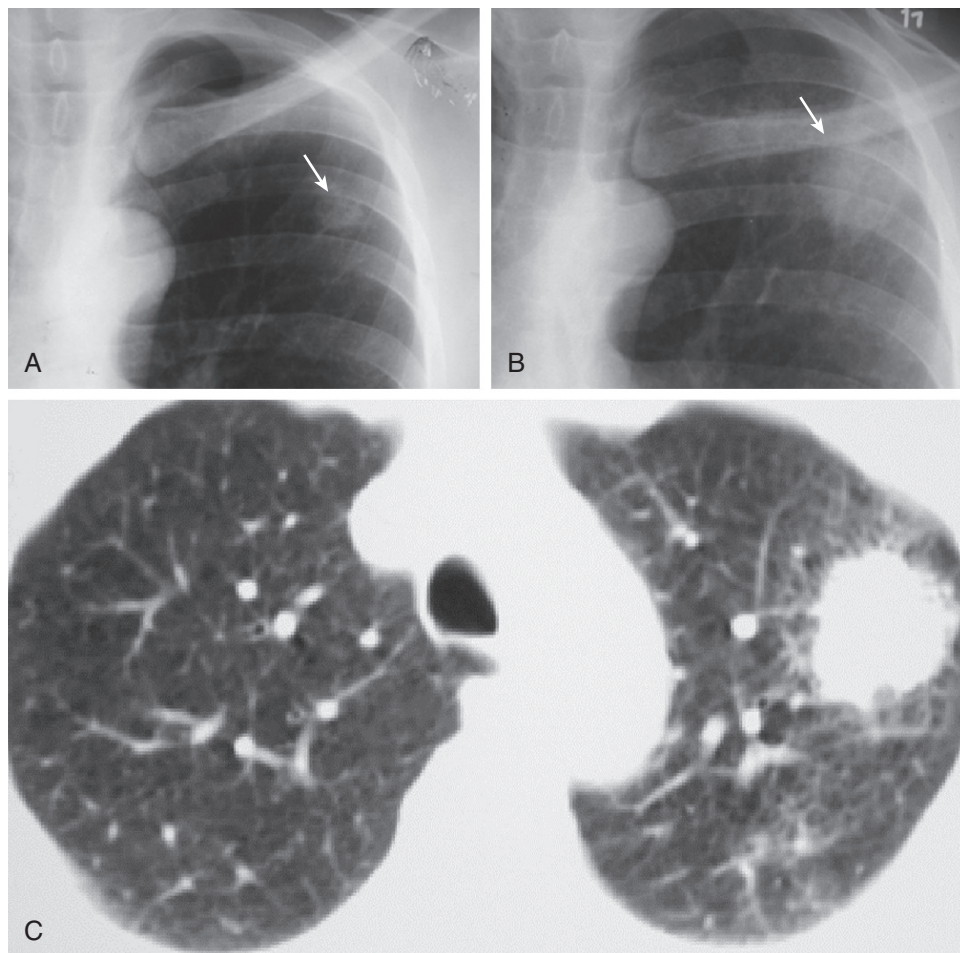
eFigure 90-30 *Strongyloides stercoralis* pulmonary infection. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows nonspecific bilateral areas of linear opacity and interstitial thickening, predominating in the perihilar regions. **B**, Axial chest CT displayed in lung windows shows patchy, multifocal, bilateral areas of ground-glass opacity associated with mild linear and reticular opacities. **C**, Surgical lung biopsy recovered *Strongyloides stercoralis* organisms. (**A** and **B**, Courtesy Michael Gotway, MD.)



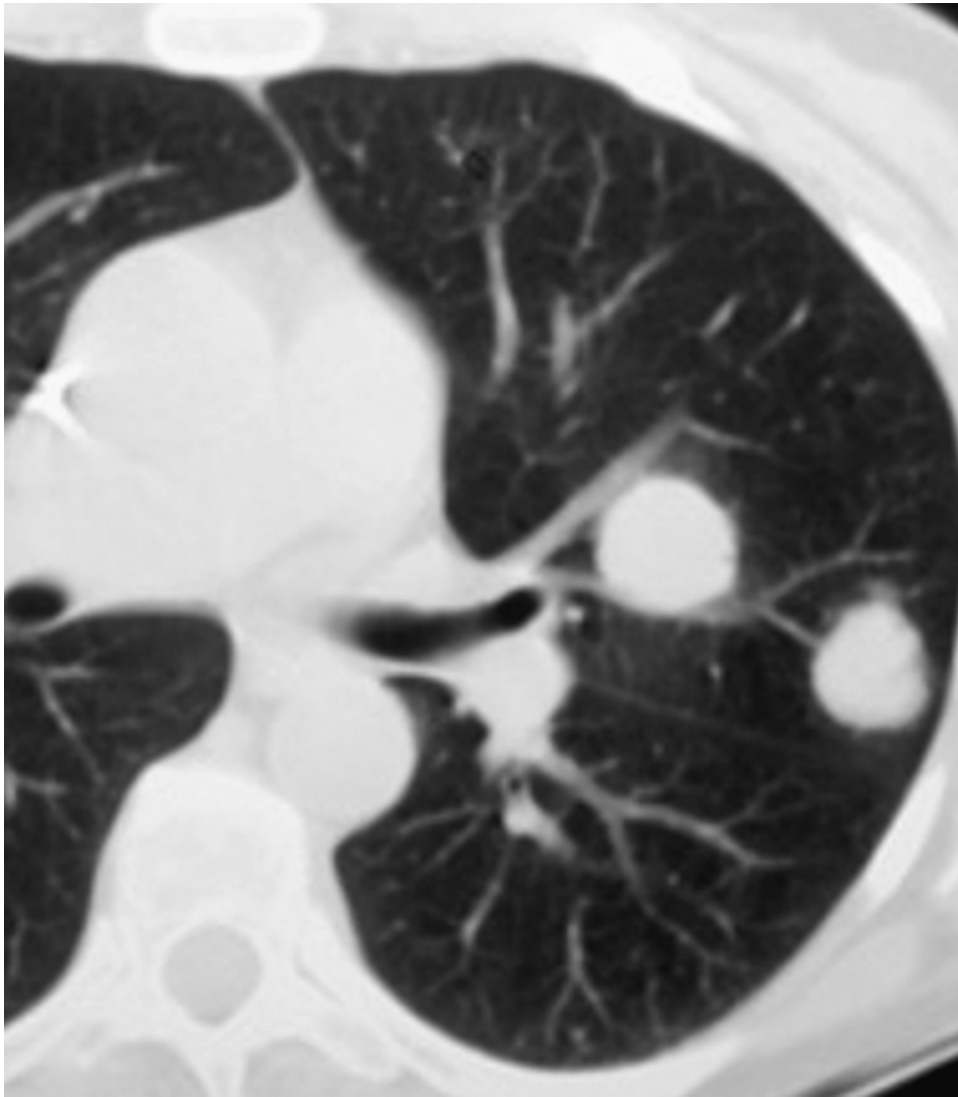
eFigure 90-31 Pulmonary Kaposi sarcoma: typical imaging appearance. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows multifocal, bilateral, perihilar bronchovascular thickening and nodularity. **B–D**, Axial chest CT displayed in lung windows shows patchy multifocal peribronchovascular nodular thickening (arrowheads). Note the presence of some patchy peribronchovascular ground-glass opacity (left upper lobe in **A** and **B**). (Courtesy Michael Gotway, MD.)



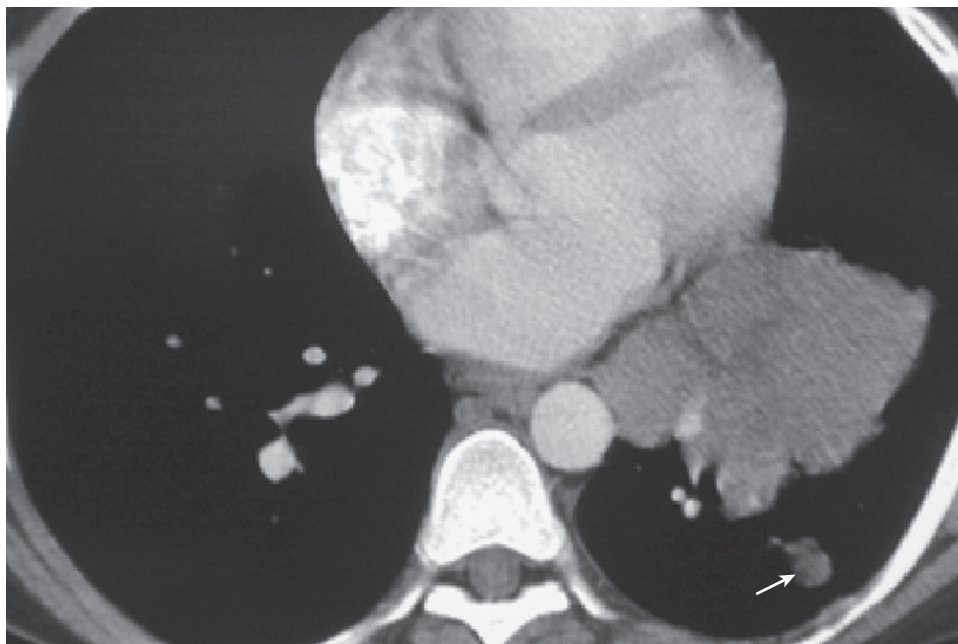
eFigure 90-32 Pulmonary Kaposi sarcoma: atypical imaging appearance. **A**, Frontal chest radiograph in an HIV-infected woman with cardiomyopathy and a low CD4⁺ count shows cardiomegaly and a faint peripheral left lung nodular opacity (arrow). **B**, Frontal chest radiograph 8 months after (**A**) shows growth in the peripheral left lung opacity (arrow). **C**, Axial chest CT displayed in lung windows performed at the time of (**B**) shows a subpleural, superior segment left lower lobe nonspecific nodule (arrowhead); this nodule was not calcified. Percutaneous transthoracic fine needle aspiration and core lung biopsy was performed, but was nondiagnostic. Surgical lung biopsy subsequently proved Kaposi sarcoma. (Courtesy Michael Gotway, MD.)



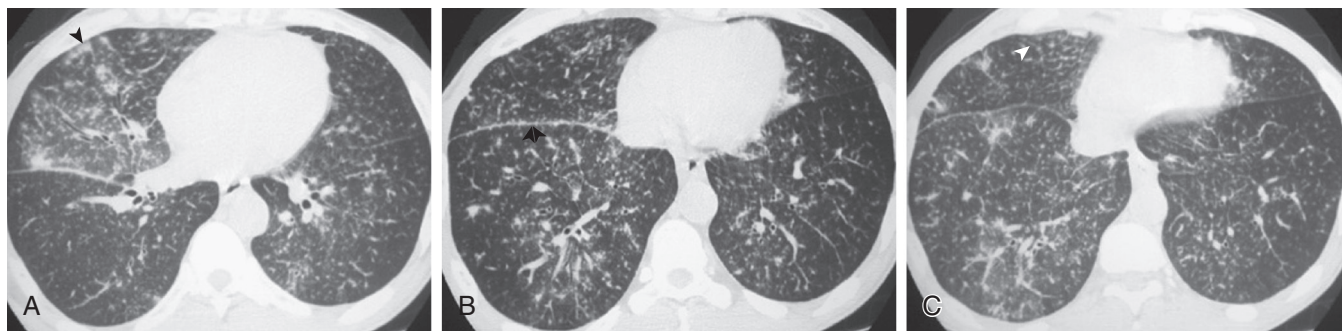
eFigure 90-33 Non-Hodgkin lymphoma in HIV infection: solitary nodule/mass. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows an ill-defined left upper lobe nodule (*arrow*). **B**, Frontal chest radiograph obtained three months following (**A**) after presumptive anti-microbial therapy shows that the left upper lobe lesion (*arrow*) has grown into a mass. **C**, Axial chest CT displayed in lung windows shows a poorly defined peripheral left upper lobe mass. Percutaneous transthoracic fine-needle aspiration and core lung biopsy showed non-Hodgkin lymphoma. (Courtesy Michael Gotway, MD.)



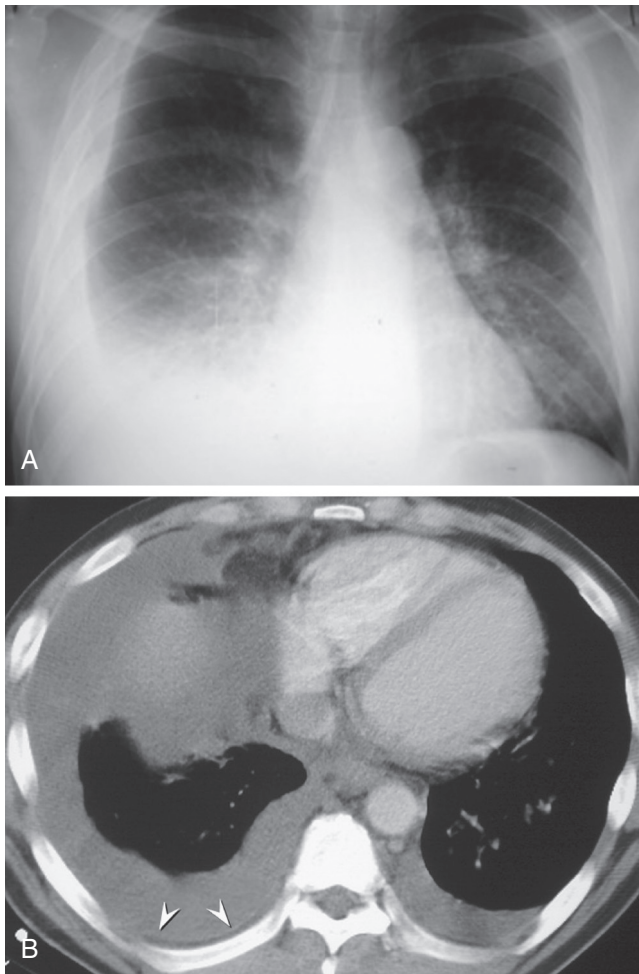
eFigure 90-34 Non-Hodgkin lymphoma in HIV infection: multiple nodules. Axial chest CT performed in an HIV-infected patient with a low CD4⁺ count displayed in lung windows shows two circumscribed, minimally lobulated left upper lobe nodules proven by percutaneous transthoracic fine-needle aspiration and core lung biopsy to be due to non-Hodgkin lymphoma. (Courtesy Michael Gotway, MD.)



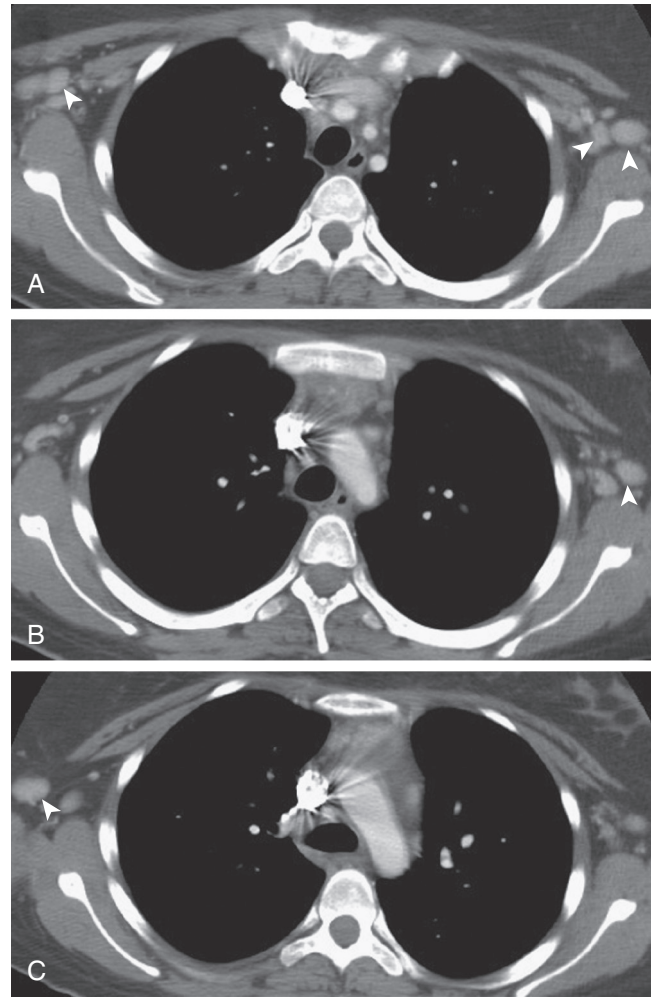
eFigure 90-35 Non-Hodgkin lymphoma in HIV infection: pulmonary mass. Axial chest CT performed in an HIV-infected patient with a low CD4⁺ count displayed in soft tissue windows shows a left lower lobe soft tissue mass proven by percutaneous transthoracic fine-needle aspiration and core lung biopsy to be due to non-Hodgkin lymphoma. An additional tumor nodule (*arrow*) is also present. (Courtesy Michael Gotway, MD.)



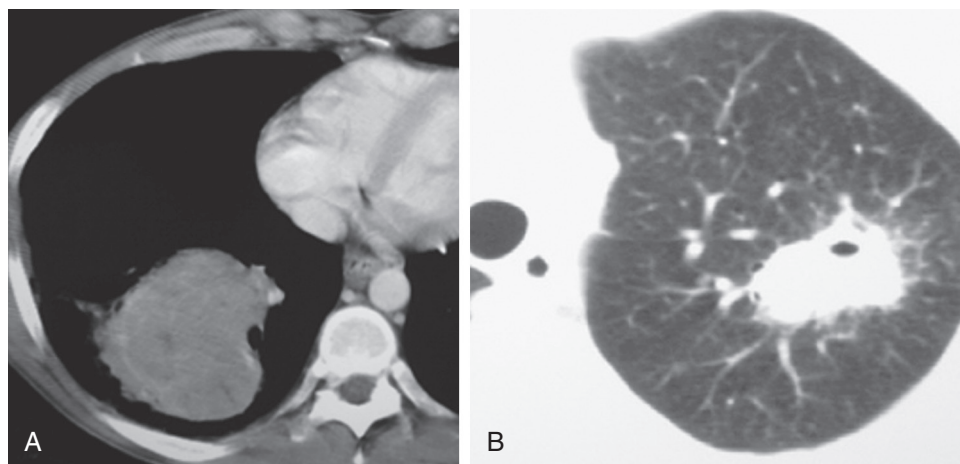
eFigure 90-36 Non-Hodgkin lymphoma in HIV infection: small nodules in a perilymphatic distribution. A–C, Axial chest CT performed in an HIV-infected patient with a low CD4⁺ count displayed in lung windows shows innumerable small, well-defined nodules distributed along the fissures (*double arrowheads, B*), in the centrilobular region (*black arrowhead, A*), and along mildly thickened interlobular septae (*white arrowhead, C*). These nodules are located in the regions of pulmonary lymphatics; this small nodular pattern is referred to as a perilymphatic nodule distribution at high-resolution CT. Bronchoscopy with transbronchial biopsy showed that these nodules were due to non-Hodgkin lymphoma. (Courtesy Michael Gotway, MD.)



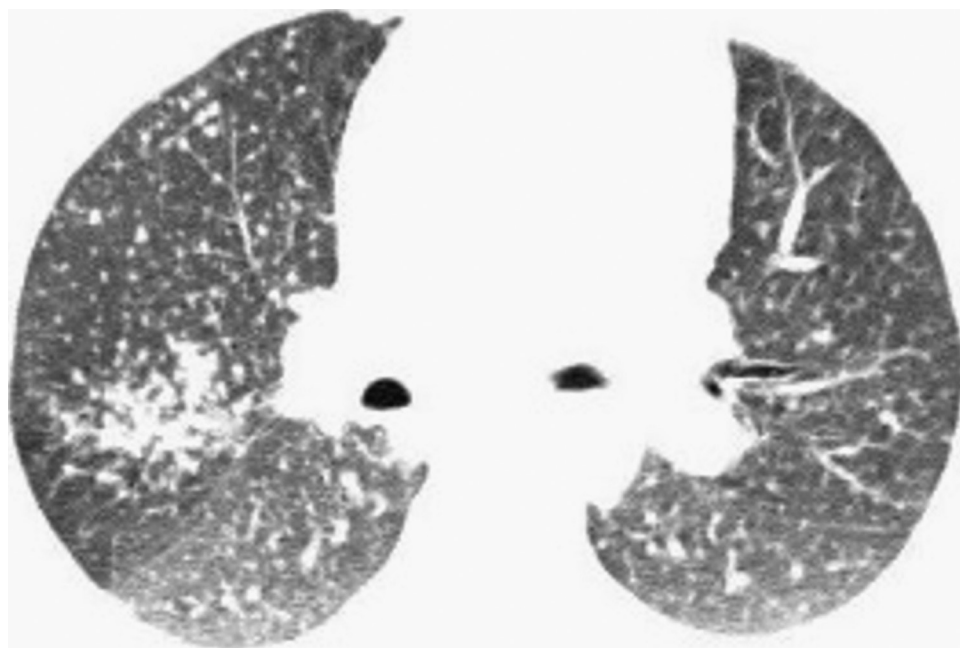
eFigure 90-37 Primary effusion lymphoma in HIV infection. **A**, Frontal chest radiograph in an HIV-infected patient with a low CD4⁺ count shows a right pleural effusion and moderate, right-greater-than-left linear interstitial thickening. **B**, Axial enhanced chest CT displayed in soft tissue windows shows bilateral pleural effusions; trace pleural thickening (*arrowheads*) may be present on the right. Thoracentesis showed the presence of lymphoma. (Courtesy Michael Gotway, MD.)



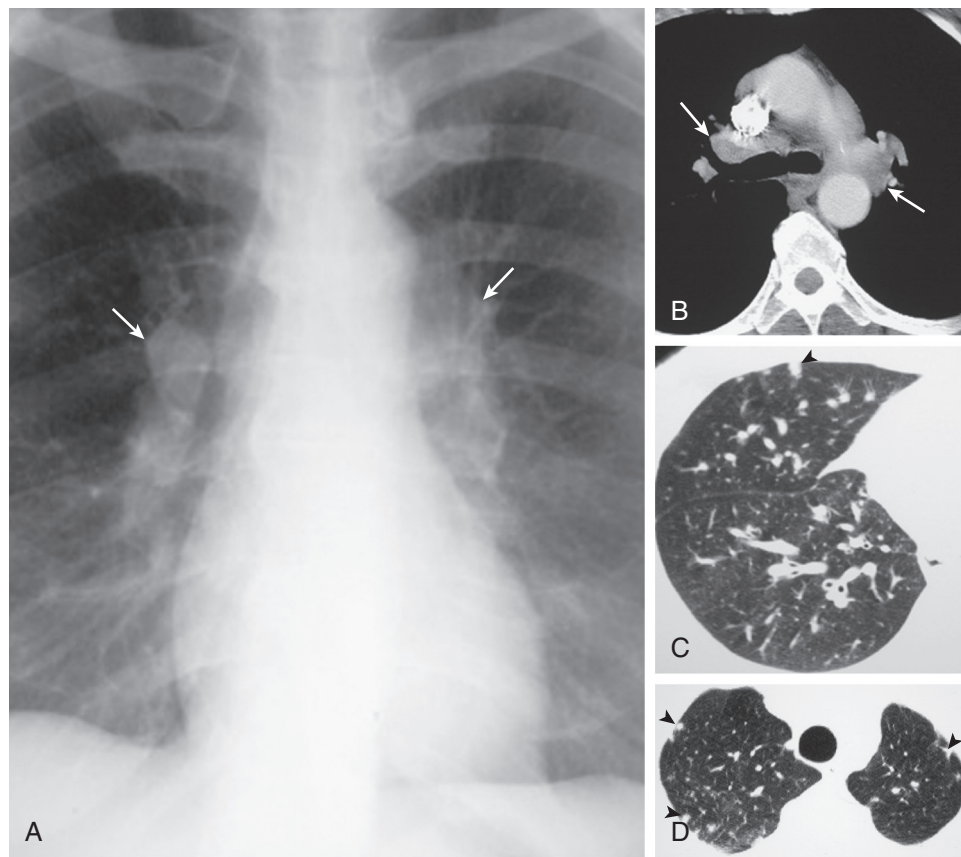
eFigure 90-38 Multicentric Castleman disease in HIV infection. **A–C**, Axial enhanced chest CT displayed in soft tissue windows performed in an HIV-infected patient with a low CD4⁺ count shows bilateral, mildly enhancing axillary lymphadenopathy (*arrowheads*), proven to reflect Castleman disease on excision. (Courtesy Michael Gotway, MD.)



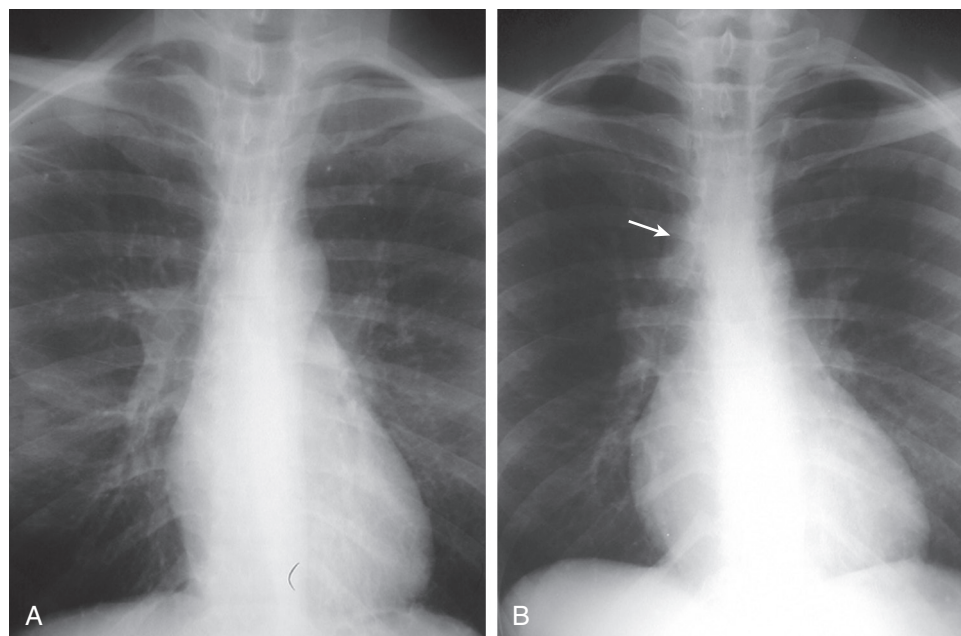
eFigure 90-39 Bronchogenic carcinoma in HIV infection. **A**, Axial enhanced chest CT shown in soft tissue and **B**, lung windows shows two bronchogenic carcinomas in patients with HIV infection. The right lower lobe mass (**A**) represented large cell malignancy; the cavitary left upper lobe lesion (**B**) represented squamous cell carcinoma. (Courtesy Michael Gotway, MD.)



eFigure 90-40 Lymphocytic interstitial pneumonia in HIV infection. Axial chest CT displayed in lung windows in a child with HIV infection shows multiple circumscribed small nodules proven on transbronchial biopsy to represent lymphocytic interstitial pneumonia. (Courtesy Michael Gotway, MD.)



eFigure 90-41 Sarcoidosis in HIV infection. **A**, Frontal chest radiograph in an HIV-infected patient with a CD4⁺ count greater than 200 cells/ μ L shows bilateral symmetrical hilar lymphadenopathy (arrows). **B**, Axial enhanced chest CT displayed in soft tissue windows shows bilateral lymph node enlargement (arrows). **C** and **D**, Chest CT displayed in lung windows shows the upper lobe predominant perilymphatic nodules (arrowheads) typical of sarcoidosis. (Courtesy Michael Gotway, MD.)



eFigure 90-42 Immune reconstitution inflammatory syndrome. **A**, Frontal chest radiograph appears normal in an HIV-infected patient with a low CD4⁺ count, in whom *Mycobacterium tuberculosis* was recently diagnosed. **B**, Frontal chest radiograph performed 2 months following institution of combination antiretroviral therapy shows development of right paratracheal lymphadenopathy (arrow). (Courtesy Michael Gotway, MD.)

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PULMONARY COMPLICATIONS OF STEM CELL AND SOLID ORGAN TRANSPLANTATION

DAVID K. MADTES, MD

INTRODUCTION
INFECTIOUS COMPLICATIONS
Bacterial

Viral
Fungal

NONINFECTIOUS COMPLICATIONS
Early Complications
Late Complications

INTRODUCTION

Stem cell transplantation (SCT) is the only known curative treatment for many patients with life-threatening hematologic and solid tumor malignancies. Likewise, *solid organ transplantation* (SOT) provides life-saving treatment for many patients with end-stage organ disease. Approximately 20,000 SCT and 28,000 SOT procedures are performed each year in the United States.^{1,2} These patients are at constant risk for opportunistic infections, drug-related pulmonary toxicities, and malignancies due to their chronic state of immune suppression.³⁻⁶ The aim of this chapter is to review the infectious and noninfectious pulmonary complications of stem cell and solid organ transplantation with a focus on the diagnostic and therapeutic challenges presented by these patients.

INFECTIOUS COMPLICATIONS

Despite effective prophylaxis strategies, infections in the lower respiratory tract remain a common life-threatening complication. The risk of infection is primarily determined by epidemiologic exposures of the donor and recipient and “the net state of immune suppression.”⁷ The spectrum of microorganisms responsible for posttransplantation infections is similar among SCT and SOT recipients, and the infections follow a fairly characteristic pattern. [Figures 91-1](#) and [91-2](#) show timelines for the pulmonary complications, both infectious and noninfectious, following SCT and SOT, respectively.

The *first phase* of infection risk is considered the first month after transplant. For SCT recipients, infectious risks in the first month are due to neutropenia and immune suppression related to the development of acute *graft-versus-host disease* (GVHD) and its treatment. Conventional nosocomial infections with gram-positive and gram-negative bacteria, as well *herpes simplex virus* (HSV) and *Candida* species, predominate. For SOT recipients, during the first month posttransplantation, infectious risks are predominantly related to surgery and intensive care, along with the initiation of immunosuppressive therapy.

The *second phase* of infection risk extends from 1 to 6 months during the period of maximum immunosuppression prescribed to treat GVHD in SCT patients or to avoid

acute allograft rejection in SOT recipients. This interval is characterized by the emergence of opportunistic pathogens. The *third phase* of infection risk is after 6 months when immunosuppressive therapy can be decreased in the majority of patients. Infections during this phase are predominantly due to community-acquired organisms and, to a lesser extent, opportunistic pathogens.

Previously common pathogens such as *Pneumocystis jirovecii* (PCP) and *cytomegalovirus* (CMV) are now less common due to routine use of antimicrobial prophylaxis. However, prophylactic antimicrobials and nosocomial exposures have contributed to the emergence of antimicrobial-resistant pathogens such as *Stenotrophomonas* species, mucormycosis, and ganciclovir-resistant CMV.⁸ In addition, improved microbiologic diagnostic techniques have allowed the recognition of previously undiagnosed infections.⁸

The lung is the leading site of infection in lung and heart transplant recipients⁹⁻¹³ and is the second most common site in liver transplant recipients.¹⁴ In a retrospective, multicenter study of 236 lung transplant recipients, pneumonia was reported in 25.8% of recipients. The microbiologic etiology was established in 57 (67%) of the cases. Of the microbiologically proven cases, 82.7% were bacterial, 14% were fungal, and 10.3% were due to viruses.¹³

Given the broad spectrum of pathogens that cause pneumonia in transplant recipients and the potential for complications from empiric antibiotics, it is important to identify the causative organisms whenever possible. Bronchoscopy is the procedure of choice in most transplant recipients. The diagnostic yield of bronchoscopy in SCT recipients is reported to range from 42% to 65%¹⁵⁻²¹ and is highest when performed before the initiation of antimicrobials¹⁵ and within 24 hours of presentation.¹⁶ Likewise, in SOT recipients, the diagnostic yield of bronchoscopy ranges from 30% to 72% and is highest when performed for pulmonary opacities within the first 6 months of transplantation.^{20,22-28} The recommended laboratory evaluation of bronchoscopic specimens for specific pathogens in the lower respiratory tract of transplant recipients is listed in [eTable 91-1](#).

BACTERIAL

Bacterial pneumonia after transplantation can be either nosocomial or community acquired with each mode having a characteristic time of onset, causative organisms, and

e-Table 91-1 Routine Laboratory Evaluation of Bronchoalveolar Lavage Specimens for Specific Infectious Pulmonary Complications after Transplantation (see also Chapter 17)

PATHOLOGY

- Stains
 - Wright-Giemsa stain
 - Papanicolaou stain
 - Silver stain
 - Modified Jimenez stain (or other stain suitable for *Legionella* species)
 - Direct fluorescent antibody stain for *Pneumocystis*

MICROBIOLOGY

- Stains
 - Gram stain
 - Wet mount potassium hydroxide or calcofluor white stain
 - Acid-fast
 - Modified acid-fast stain
 - Fluorescent antibody stain for *Legionella* species
- Culture
 - Bacterial (aerobic), semiquantitative culture method
 - Fungal
 - *Legionella* species (chocolate yeast extract)
 - Acid-fast
 - Nocardia
 - Actinomyces
- Immunoassay
 - Galactomannan ELISA assay for *Aspergillus*
 - Urinary *Legionella* antigen (depends on renal function; only detects antigen of *Legionella pneumophila* serogroup 1)
- Molecular diagnostics
 - PCR assay for *Aspergillus*, *Chlamydia*, *Mycoplasma*

VIROLOGY

- Direct fluorescence staining with antibodies against CMV, RSV, HSV, VZV, influenza, parainfluenza, adenovirus
- Molecular diagnostics
- PCR or reverse transcription-PCR for RSV, influenza A & B, parainfluenza, human metapneumovirus, rhinovirus, bocavirus, adenovirus, rhinovirus, coronavirus
- Culture
 - Rapid centrifugation (shell vial) culture for CMV, RSV
 - Routine viral culture

CMV, cytomegalovirus; ELISA, enzyme-linked immunosorbent assay; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

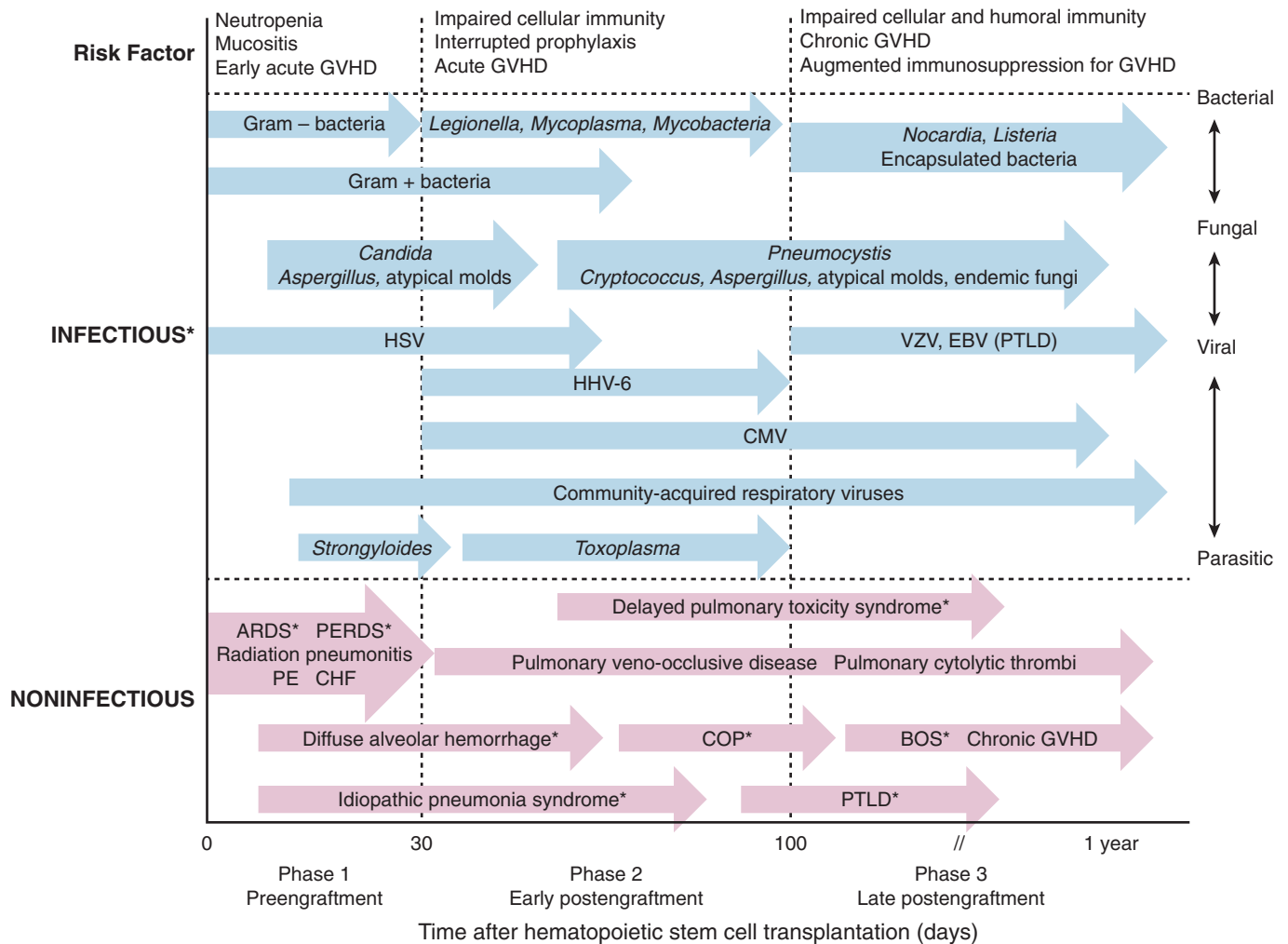


Figure 91-1 Timeline of infectious and noninfectious pulmonary complications following stem cell transplantation. ARDS, acute respiratory distress syndrome; COP, bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia; BOS, bronchiolitis obliterans syndrome; CHF, congestive heart failure; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; HHV-6, human herpes virus-6; PE, pulmonary embolism; PERDS, peri-engraftment respiratory distress syndrome; PTLD, posttransplant lymphoproliferative disorder; VZV, varicella-zoster virus. *Consider diagnostic bronchoscopy to (1) establish or rule out an infectious etiology and/or to (2) diagnose a noninfectious process. (Adapted from Soubani AO: Respiratory infections following hematopoietic stem cell transplantation. In Agusti C, Torres A, editors: Pulmonary infection in the immunocompromised patient: strategies for management. West Sussex, UK, 2009, Wiley-Blackwell, pp 213–256 and from Afessa B, Peters SG: Chronic non-infectious pulmonary complications in hematopoietic stem cell transplantation. In Agusti C, Torres A, editors: Pulmonary infection in the immunocompromised patient: strategies for management. West Sussex, UK, 2009, Wiley-Blackwell, pp 257–284 and from Harris B, Lowy FD, Stover DE, Arcasoy SM: Diagnostic bronchoscopy in solid-organ and hematopoietic stem cell transplantation. *Ann Am Thorac Soc* 10(1):39–49, 2013.)

outcome. Bacterial pneumonia develops in 21% to 38% of lung transplant,^{11–13} 5% to 34% of liver transplant,^{29,30} 11% to 19% of heart transplant,^{10,22,31} and 4% to 7% of renal transplant recipients.^{25,28,32,33} The most frequently documented bacterial pathogens in lower respiratory tract infections (LRTI) after SOT are gram-negative organisms, including *Pseudomonas* (eFig. 91-1), *Klebsiella*, *Escherichia*, *Legionella*, *Acinetobacter*, and *Stenotrophomonas*, as well as gram-positive bacteria such as *Staphylococcus*, *Corynebacterium*, and *Enterococcus*. Anaerobic infections are rare.^{12,13,29,34,35}

Although the precise incidence of bacterial pneumonia after SCT is difficult to ascertain due to the frequent use of empiric broad-spectrum antibiotics in the early posttransplant period, bacterial pneumonia has been reported in 7% to 11% of allogeneic and 5% to 15% of autologous SCT recipients.^{36–38} The most common bacterial pathogens

include *Escherichia*, *Pseudomonas*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.^{38,39} Late-onset bacterial pneumonia, defined as beyond day 100 posttransplant, is frequently due to *K. pneumoniae*, *Pseudomonas*, *S. pneumoniae*, and *Staphylococcus* species.⁴⁰

The prevalence of active tuberculosis following SCT has been estimated to be 0.23% to 0.79%,^{41,42} whereas the prevalence ranges 0.5% to 15% for SOT recipients depending on the prevalence of tuberculosis in the general population.⁴³ The median time to tuberculosis onset is 9 months (range, 0.5 to 13 months), although the disease can arise as late as 2 years after transplantation.^{44,45} First-line antituberculosis therapy in transplant recipients generally includes isoniazid, pyrazinamide, and ethambutol.⁴³ Rifampin is generally avoided due to its ability to induce cytochrome P450 isoenzymes resulting in decreased serum concentrations of several immunosuppressants, including cyclosporine,^{45,46}

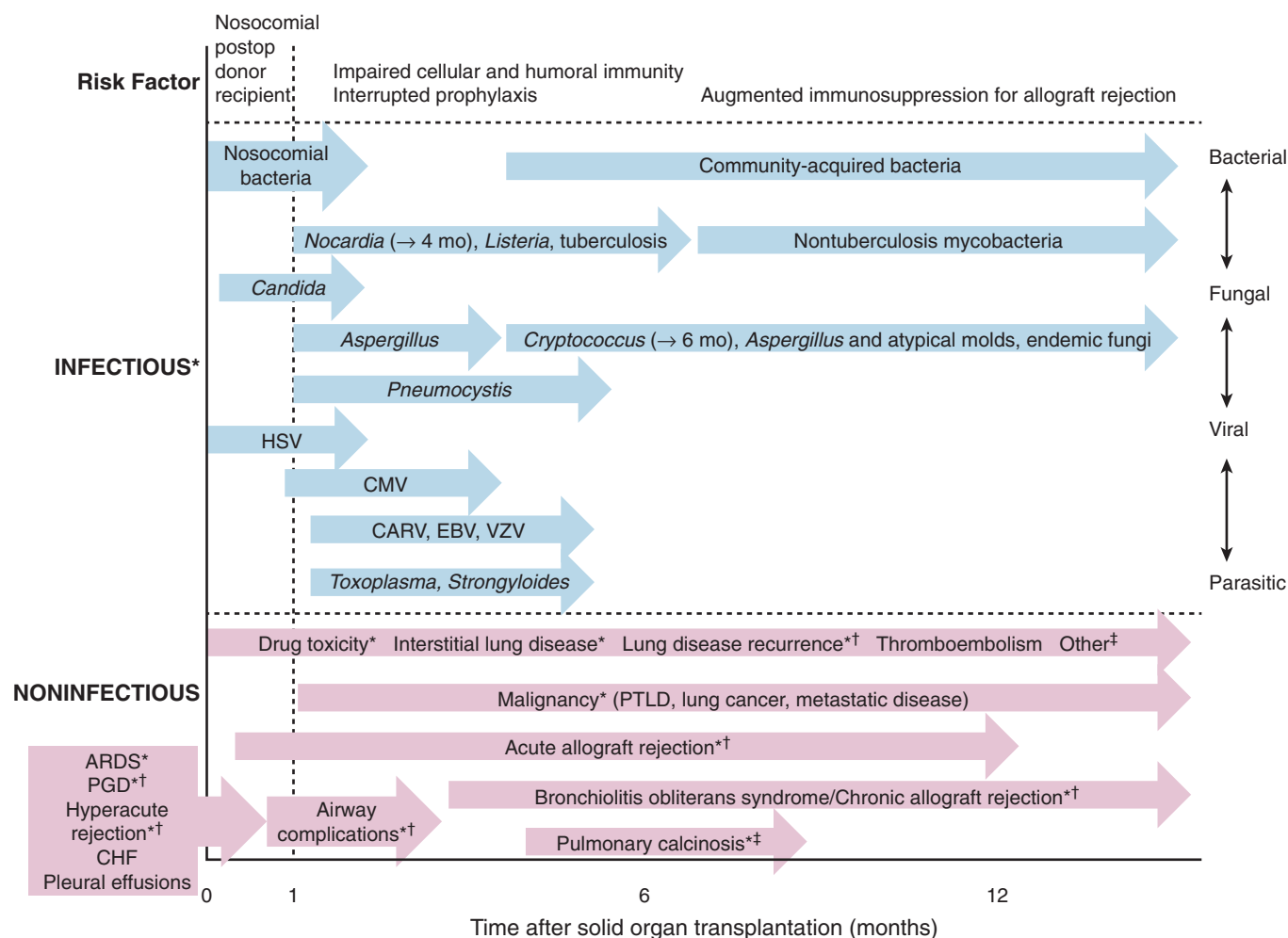


Figure 91-2 Timeline of infectious and noninfectious pulmonary complications following solid organ transplantation. ARDS, acute respiratory distress syndrome; CARV, community-acquired respiratory viruses; CHF, congestive heart failure; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; PGD, primary graft dysfunction; PTLD, posttransplant lymphoproliferative disorder; VZV, varicella-zoster virus. *Consider diagnostic bronchoscopy to (1) establish or rule out an infectious etiology; (2) diagnose a noninfectious etiology, such as acute allograft rejection, malignancy, or interstitial lung disease; or (3) inspect bronchial anastomoses and other airway abnormalities. †Lung transplant recipients only. ‡Diagnostic bronchoscopy is warranted for pulmonary metastatic calcinosis for atypical presentations on imaging in renal transplant recipients. (Adapted from Harris B, Lowy FD, Stover DE, Arcasoy SM: Diagnostic bronchoscopy in solid-organ and hematopoietic stem cell transplantation. *Ann Am Thorac Soc* 10(1):39–49, 2013; based on data from Fishman JA: Infection in solid-organ transplant recipients. *N Engl J Med* 357:2601–2614, 2007)

tacrolimus,⁴⁷ sirolimus,^{48,49} everolimus,⁵⁰ and mycophenolate mofetil,^{51,52} which could result in allograft rejection. Interactions between common antimicrobial agents and immunosuppressants used in transplantation patients are listed in [eTable 91-2](#).

VIRAL

SCT and SOT recipients are vulnerable to two categories of viral infections: opportunistic viruses, especially herpesviruses, and community-acquired respiratory viruses. Opportunistic viruses responsible for pulmonary disease posttransplantation include CMV, HSV, *varicella zoster virus* (VZV), and *Epstein-Barr virus* (EBV). In the era of early detection and prophylactic or preemptive treatment, the incidence of CMV pneumonia is 4% to 32% for lung ([eFigs. 91-2](#) and [91-3](#)),⁵³⁻⁵⁸ 0% to 9.2% for liver,⁵⁹⁻⁶² 0.8% to 6.6% for heart,^{63,64} and less than 1% for kidney ([eFig. 91-4](#)) transplant recipients.⁶⁵ The incidence rate of CMV pneumonia

after SCT ([eFig. 91-5](#)) is 2% to 6%.^{40,66,67} CMV infection traditionally develops within the first 3 months after SCT and SOT; however, the use of antiviral prophylaxis has delayed its onset until after prophylaxis has been discontinued.

Current guidelines for diagnosis and management of CMV in SCT and SOT recipients support the use of either detection of pp65 antigen via immunoassay or quantitative *polymerase chain reaction* (PCR) for the recognition of CMV infection in serum or *bronchoalveolar lavage* (BAL).⁶⁸⁻⁷⁰ There are two accepted strategies for the prevention of CMV disease in transplant recipients: (1) universal prophylaxis in which antivirals are administered to all posttransplantation patients at risk and (2) preemptive therapy in which at-risk patients are monitored for viral replication and antivirals are initiated at a predetermined level of virus replication.^{68,69,71,72} Intravenous (IV) ganciclovir is recommended for the treatment of severe CMV disease, whereas oral valganciclovir is an alternative in less severe cases.^{68,69}

e-Table 91-2 Antimicrobial Agent Interactions with Immunosuppressants Used in Transplantation

Immunosuppressant	Antimicrobial Agent	Effect on Immunosuppressant	Reference
Cyclosporine	Chloramphenicol	↑ Concentrations	344
	Clarithromycin	↑ Concentrations	345
	Erythromycin	↑ Concentrations	344, 346
	Rifampin	↓ Concentrations	45, 46
	Trimethoprim	↓ Concentrations	151
	Ketoconazole	↑ Concentrations, 3×	125
	Fluconazole	↑ Concentrations	126
	Itraconazole	↑ Concentrations, 2×	127
	Voriconazole	↑ Concentrations, 1.7×	128
Tacrolimus	Posaconazole	↑ Concentrations, 2×	129, 130
	Chloramphenicol	↑ Concentrations	47, 344
	Erythromycin	↑ Concentrations	47
	Clarithromycin	↑ Concentrations	47
	Clotrimazole	↑ Concentrations	47
	Rifampin	↓ Concentrations	47
	Ketoconazole	↑ Concentrations	131, 132
	Fluconazole	↑ Concentrations	133
	Itraconazole	↑ Concentrations	134, 135
Sirolimus	Voriconazole	↑ Concentrations, 3×	125
	Posaconazole	↑ Concentrations, 4.5×	130
	Erythromycin	↑ Concentrations, 5×	48, 347
	Clarithromycin	↑ Concentrations	348
	Rifampin	↓ Concentrations	48
	Ketoconazole	↑ Concentrations	48, 136
	Fluconazole	↑ Concentrations	137, 138
Everolimus	Itraconazole	↑ Concentrations	139
	Voriconazole	↑ Concentrations, 11×	140, 141
	Erythromycin	↓ Clearance, ≈20%	142
	Rifampin	↓ Concentrations	50, 52
	Rifabutin	↓ Concentrations	50
	Ketoconazole	↑ Concentrations	142
	Fluconazole	↑ Concentrations	143
Mycophenolate mofetil	Voriconazole	↑ Concentrations, 7.5×	144
	Posaconazole	↑ Concentrations, 3.8×	144
	Amoxicillin-clavulanate	↓ Concentrations	349, 350
	Ciprofloxacin	↓ Concentrations	349
	Norfloxacin	↓ Concentrations	351
	Metronidazole	↓ Concentrations	351
	Rifampin	↓ Concentrations	51

HSV disease develops in 35% to 68% of transplant recipients not receiving prophylaxis.⁷³ HSV most commonly reactivates during the first month posttransplantation.⁷³ For this reason, it is recommended that all HSV-seropositive transplant recipients receive at least 4 weeks of antiviral prophylaxis after transplantation, usually with acyclovir.⁷⁴ The clinical picture of HSV pneumonitis in posttransplant patients ranges from dyspnea with normal radiographic findings to failure to wean and *acute respiratory distress syndrome* (ARDS). Direct fluorescent antibody testing or real time PCR assay of BAL or other samples provides a rapid diagnosis.⁷⁵ HSV pneumonia should be treated with IV acyclovir, 10 mg/kg every 8 hours, and, if the HSV disease is life-threatening, a reduction in immunosuppression should be considered.^{74,76,77} Foscarnet is recommended for the treatment of acyclovir-resistant HSV, although this is an infrequent problem in transplant patients.⁷⁸

VZV has been reported as a rare and usually late cause of pneumonia in transplant recipients typically presenting with a vesicular rash that precedes respiratory symptoms. IV acyclovir 10 mg/kg IV every 8 hours is the treatment of choice.

Community-acquired respiratory viruses (CARVs) are a common cause of infection after SCT and SOT. CARVs include *respiratory syncytial virus* (RSV), influenza, *metapneumovirus* (MPV) and parainfluenza serotypes 1 and 2, which have their peak primarily in the winter months, and parainfluenza serotype 3 and adenovirus, which are present year round. Risk factors for progression of upper respiratory tract CARV infection to pneumonia in SCT recipients include infection early after transplantation, allogeneic SCT, myeloablative conditioning, GVHD, and lymphopenia.⁷⁹⁻⁸⁴ Risk factors for progression to pneumonia in SOT recipients have not been as well defined; however, the most-immunosuppressed recipients appear to be at greatest risk of severe disease and poor outcome.⁸⁵ CARV infections in transplantation recipients are often characterized by prolonged viral shedding and can be complicated by coinfection with other viral, bacterial, or fungal pathogens.^{84,86-90} In addition to the direct effects, CARV infections can have indirect effects that include an increased risk of acute and chronic rejection such as bronchiolitis obliterans after lung transplantation^{91,92} and concurrent allograft rejection in non-lung SOT recipients.⁹³

Respiratory Syncytial Virus

The incidence of RSV infection after SCT is 1% to 12% with 17% to 70% of infections involving the lower respiratory tract. Mortality rates range from 7% to 33% in the setting of pneumonia.⁷⁹ The incidence of RSV in lung transplant recipients is 5% to 12% with a 10% to 15% mortality rate,^{94,95} while the incidence in liver transplant recipients is 4%.⁹⁶ RSV disease can range from a mild upper respiratory tract infection to life-threatening pneumonia. The most sensitive method for diagnosing RSV infection in symptomatic patients is by *reverse transcriptase* (RT)-PCR assay of nasal wash or BAL.⁹⁷ Ribavirin (orally or IV \pm inhaled ribavirin) is approved for treatment of RSV pneumonitis in SCT recipients^{98,99} and may be combined with IV immunoglobulin or IV palivizumab, a humanized monoclonal antibody against RSV used for prophylaxis. Although there is no controlled study of ribavirin therapy in SOT recipients, inhaled

ribavirin is commonly prescribed for RSV infection in heart and lung transplant recipients.¹⁰⁰⁻¹⁰²

Influenza

The incidence of influenza infection after SCT is 1% to 4%. Mortality rates are 15% to 28% in the setting of influenza pneumonia.⁷⁹ The incidence of influenza in lung transplant recipients is 3% to 14% with progression to lower tract infection in up to 5% of patients.^{94,95,103} Influenza infection is diagnosed in nasal wash, nasopharyngeal swabs, or BAL by rapid antigen detection or RT-PCR methods.¹⁰⁴ Susceptible influenza A strains are treated with the antiviral agents amantadine and rimantadine, and both influenza A and B strains can be treated with zanamivir and oseltamivir.^{93,105} Because oseltamivir-resistant strains of influenza A have been found in transplant patients who continue to shed virus during therapy, these infections may need to be treated with investigational drugs currently in development. Prolonged shedding of influenza virus during treatment of transplant patients also mandates close attention to infection control procedures to prevent spread to staff and other patients.

Parainfluenza and Metapneumovirus

Parainfluenza (PIV), usually serotype 3, is reported to infect 0.2% to 18% of SCT recipients, with lower respiratory tract involvement in 12% to 50% of cases.⁷⁹ The incidence of parainfluenza infection in lung transplant recipients is 2% to 17%.^{94,95} MPV is reported to infect 3% to 7% of SCT recipients (eFig. 91-6) with 27% to 41% of cases involving the lower respiratory tract and has an associated mortality of 33% to 40% for those with pneumonia.⁷⁹ The incidence of MPV infection in lung transplant recipients is 4% to 6%.^{79,94,95} Isolated cases of MPV have also been reported following liver and kidney transplantation.^{95,106,107} MPV infection appears to increase acute allograft rejection.^{95,108} Infection by PIV or MPV is diagnosed by RT-PCR of nasopharyngeal swab, nasal wash, or BAL. Treatment is supportive care; however, IV or inhaled ribavirin and/or IV immunoglobulin has been used to treat lower respiratory tract disease despite the absence of controlled trials.^{95,105,109}

FUNGAL

On the basis of the *Transplant-Associated Infection Surveillance Network* (TRANSNET), the 1-year incidence of *invasive fungal infections* (IFIs) in SOT recipients, in the order of decreasing frequency, is small bowel transplants (11.6%), lung (8.6%), liver (4.7%), heart (4.0%), pancreas (3.4%), and kidney (1.3%).¹¹⁰ The most common pathogens are invasive candidiasis (53%), *invasive aspergillosis* (IA) (19%) (eFigs. 91-7 and 91-8), *Cryptococcus* (8%), non-*Aspergillus* molds (8%) (eFig. 91-9), endemic fungi (5%), and *Zygomycetes* (2%).¹¹⁰ The mortality associated with candidal infections in SOT recipients ranges from 5% to 77% with the highest mortality seen in liver transplant recipients.^{111,112} The mortality rate for IA is related to the type of transplant and ranges from 20% for lung transplants to 66.7% for heart and kidney transplants.^{111,113} Risk factors for IFI in SOT recipients include environmental exposures, the use of high-dose steroids, antilymphocyte therapy, and viral infections, particularly CMV infection.^{114,115} Lung transplant

patients are at particular risk for fungal infections in the anastomotic site.

The incidence of IA infection after SCT (eFig. 91-10, also see Figs. 38-4 and 38-7) ranges from 0.08% to 23% depending on the stem cell source and conditioning regimen.^{113,116} Mortality at 3 months from the time of IA diagnosis ranges from 54% of autologous recipients to 85% for unrelated donor recipients and does not differ for those with early-versus late-onset infections.^{113,116}

Aspergillus infection can present in posttransplantation patients as airway colonization, tracheobronchitis, pulmonary aspergillosis, sinusitis, or disseminated disease.¹¹⁴ Symptoms of invasive pulmonary aspergillosis include dyspnea, fever, productive cough, chest pain, and hemoptysis; however, up to 41% of transplant recipients may have no respiratory symptoms.¹¹⁷ After recovery from neutropenia, 64% of allogeneic SCT recipients with invasive filamentous fungal infection presented with dyspnea, but only 32% were febrile.¹¹⁸

Diagnostic strategies vary. Culture remains the gold standard for the diagnosis of *Candida* infections.¹¹⁹ Similarly, the gold standard for the diagnosis of IA is biopsy with culture in the setting of compatible clinical and radiographic features, although alternative approaches include serologic and molecular testing. For SCT recipients, the serum galactomannan assay has a sensitivity and specificity of 82% and 86%, respectively, for the diagnosis of IA¹²⁰; in contrast, for SOT recipients, the serum galactomannan assay is of uncertain utility, with a sensitivity and specificity of 22% and 84%, respectively.^{120,121} Compared with serum, BAL appears to have higher specificity; galactomannan testing of BAL has a sensitivity of 60% to 82% and a specificity of 95%.¹²²⁻¹²⁴ PCR-based methods for the detection of *Aspergillus* are not yet standardized for clinical use, although published studies indicate that BAL analysis using quantitative RT-PCR has a sensitivity of 67% to 77% and specificity of 90% to 100%.¹²⁴

Treatment of IFI in transplant recipients should be based on the isolated pathogen, hospital-specific susceptibility patterns, and the patient's clinical condition. Gabardi and colleagues¹¹¹ have reviewed potential pathogen-specific treatment options. In general, a two-pronged approach is advised: (1) reduction of the level of immunosuppression to the extent possible and (2) use of an appropriate antifungal agent. It is important to recognize that all clinically relevant azole antimicrobials inhibit cytochrome P450 isoenzyme activity to varying degrees, resulting in increased serum concentrations of cyclosporine,¹²⁵⁻¹³⁰ tacrolimus,^{125,130-135} sirolimus,^{48,136-141} and everolimus¹⁴²⁻¹⁴⁴ that could lead to neurotoxicity and/or nephrotoxicity (see eTable 91-2). Voriconazole is the agent of choice for the treatment of IA based on its superior efficacy and survival benefit in comparison with amphotericin.¹⁴⁵ However, voriconazole is contraindicated in patients receiving sirolimus.¹¹⁴ Liposomal amphotericin B is an alternative in patients who are azole intolerant. Echinocandins (caspofungin, micafungin, anidulafungin) are also an option for the treatment of AI and have low potential for drug interactions, although they may lower tacrolimus levels.¹¹⁴ Surgical resection for invasive pulmonary aspergillosis is a reasonable option in neutropenic patients.¹⁴⁶ Inhaled liposomal amphotericin B can be used for the treatment of *Aspergillus* tracheobronchitis.

Current data support the use of antifungal prophylaxis with either azole antifungal agents or liposomal amphotericin B for SOT recipients.¹⁴⁷ This topic is discussed further in Chapter 38.

Mucormycosis has emerged as an important IFI and accounts for 8% and 2% of IFIs in SCT (see eFigs. 38-8 through 38-12) and SOT (see eFig. 91-9) recipients, respectively, most often as a late complication (>3 months after transplantation) with pulmonary involvement in more than half of cases. The overall mortality rates among SOT recipients are 38% to 48%, while in SCT recipients mortality is at least 75%.¹⁴⁸ First-line therapy is liposomal amphotericin B for at least 6 to 8 weeks and extensive early surgical debridement. A combination of liposomal amphotericin and an echinocandin may be considered in cases that are refractory to first-line therapy.

Pneumocystis jirovecii (previously *Pneumocystis carinii*) remains a potentially life-threatening infection after SCT and SOT, developing in 5% to 15% of recipients in the absence of prophylaxis and having an attributable mortality of 18%.^{39,149} The risk of infection is greatest during the first 6 months after transplantation and decreases significantly after 1 year in all patients except lung transplant recipients.¹⁴⁹ The clinical presentation can include progressive dyspnea, cough, fever, and hypoxemia. Chest radiographs typically show bilateral abnormalities that can include perihilar, interstitial or alveolar opacities, nodules, cystic lesions, or pneumothorax. The diagnosis of PCP is confirmed by the morphologic identification of the *Pneumocystis* organisms in induced sputum, BAL fluid, or tissue.^{149,150} First-line therapy for PCP is high-dose trimethoprim-sulfamethoxazole combined with corticosteroids. Trimethoprim induces cytochrome P450 activity and can lead to decreased serum concentrations of cyclosporine.¹⁵¹ Most transplantation centers use low-dose TMP/SMX for PCP prophylaxis, which is discontinued at 1 year for all groups except lung transplant recipients for whom it is continued indefinitely.¹⁵²

Endemic fungal infections (EFIs) such as blastomycosis (see eFig. 37-15) or histoplasmosis develop in less than 1% of SCT and SOT recipients. The median time from transplant to onset of EFI is 10.5 months (range 2 to 192 months), although 20% of cases are diagnosed 5 or more years after transplantation.^{110,153} The lungs are the most common site of infection, reported in up to 83% of EFI cases; however, the disease can disseminate in more than half of SOT recipients.¹⁵³ In posttransplant patients, disease with blastomycosis or histoplasmosis has an attributable mortality of 25% to 36% and 0% to 11%, respectively.¹⁵³ The incidence of posttransplant coccidioidomycosis in the era of targeted prophylaxis is less than 3%; however, the rates of dissemination and mortality are high at 30% and 29%, respectively.¹⁵⁴⁻¹⁵⁶ *Coccidioides* serology is of uncertain utility in posttransplant recipients due to its low sensitivity.¹⁵⁷

NONINFECTIOUS COMPLICATIONS

Although transplantation recipients are clearly at increased risk for infection, these patients can also

experience noninfectious pulmonary complications. These noninfectious complications can be attributed to pulmonary toxicities of chemoradiation therapy used in preparative regimens or associated with immunosuppressive medications, postoperative surgical complications, allograft rejection or GVHD or as a result of malignancies impacting the lung (see Figs. 91-1 and 91-2). eTable 91-3 describes the most common complications in the immediate postoperative period.

Individual components of some chemotherapy regimens used in SCT are associated with pulmonary toxicity. Carmustine (or *bischloroethylnitrosourea*, BCNU), used as a single agent or in combination before autologous SCT for solid tumor and hematologic malignancies, is associated with acute-onset pneumonitis with an incidence of 4% to 59%.¹⁵⁸⁻¹⁶³ Prior mediastinal radiation therapy, BCNU dose greater than 1000 mg, and age younger than 54 were independent risk factors for developing pneumonitis after autologous SCT for lymphoma.¹⁵⁸ The mechanism of BCNU-associated pulmonary toxicity has not been entirely elucidated but is thought to include oxidative stress, glutathione dysfunction, and immune-mediated lung injury.^{164,165}

Cyclophosphamide is another agent used in combination with total body radiation or other chemotherapy agents in preparative regimens for autologous and allogeneic SCT, which is associated with pulmonary toxicity thought to be related to increased reactive oxygen species generation and depletion of glutathione stores.¹⁶⁶⁻¹⁷⁰ Pulmonary toxicity associated with other chemotherapeutic agents and radiation are discussed elsewhere in this text.

EARLY COMPLICATIONS

Respiratory Failure

Postoperative respiratory failure has been well described in the transplantation literature as an early cause of mortality. After liver transplantation, the incidence of postoperative respiratory failure is reported to be 4% to 42%.^{34,171-174} In a single-center, retrospective study of 212 liver transplant recipients, the causes of postoperative respiratory failure were pneumonia (56%), pulmonary edema (17%), *acute lung injury* (ALI)/ARDS (17%), and neurologic dysfunction (8%).³⁰ In the immediate posttransplantation period, the most common risk factors for noncardiogenic pulmonary edema include reperfusion syndrome, *transfusion-related acute lung injury* (TRALI), sepsis, pneumonia, gastric aspiration, and acute allograft rejection.^{175,176} After kidney and cardiac transplantation, perioperative respiratory failure is less common. In a single-center retrospective study, perioperative respiratory failure was identified in 4% of 178 kidney transplant recipients.¹⁷⁷ Similarly, heart transplantation has a low risk of respiratory failure. In a retrospective single-center study by Lenner and associates,²² 4% of 157 cardiac transplant recipients developed respiratory failure posttransplantation with 71% of episodes in the first 6 months.

After lung transplantation, respiratory failure in the early postoperative period is most commonly the result of infections or *primary graft dysfunction* (PGD). PGD, a form of acute lung injury arising within 72 hours of lung transplantation, is a severe form of ischemia/reperfusion injury

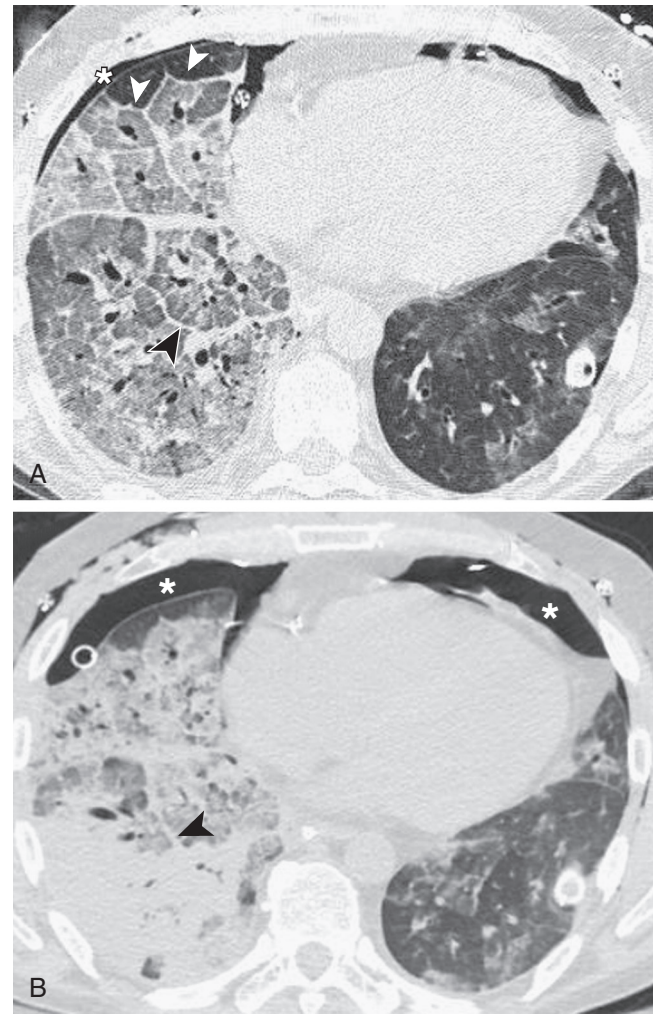


Figure 91-3 Primary graft dysfunction in a lung transplant recipient. A and B, Axial chest CT images (A and B) in a recent lung transplant recipient show extensive right-greater-than-left lower-lobe ground-glass opacity associated with interlobular septal thickening (arrowheads) and dense consolidation. These imaging findings are not specific but are consistent with acute lung injury. Small bilateral pneumothoraces (*) are consistent with the recent bilateral lung transplantation. (Courtesy Michael Gotway, MD.)

(Fig. 91-3). The incidence is 10% to 30% of all lung transplant recipients.¹⁷⁸⁻¹⁸² Treatment is primarily supportive care including low-stretch ventilation strategies and avoidance of excessive fluid administration.¹⁸³ (A more detailed discussion of PGD is presented in Chapter 106).

For SCT patients, a spectrum of noninfectious pulmonary complications can develop in the early posttransplantation period that falls under the category of the *idiopathic pneumonia syndrome* (IPS). IPS is broadly defined as widespread alveolar injury seen after SCT in the absence of active lower respiratory tract infection, cardiac dysfunction, acute renal failure, or iatrogenic fluid overload (eFig. 91-11).^{184,185} IPS encompasses a spectrum of clinical presentations thought to result from a variety of lung insults including toxic effects of the SCT conditioning regimen, immunologic cell-mediated injury, inflammatory cytokines, and occult pulmonary infections.^{184,186-193}

The cumulative incidence of IPS after *allogeneic* SCT ranges from 2.2% following nonmyeloablative conditioning

e-Table 91-3 Most Common Noninfectious Complications in the Immediate Postoperative Period for Solid Organ Transplant Recipients

Transplantation	Noninfectious Postoperative Complications
Liver	Pulmonary edema/Acute respiratory distress syndrome Diaphragmatic dysfunction Pleural effusions
Lung/Heart-lung	Reperfusion pulmonary edema Primary graft dysfunction Bronchial anastomosis dehiscence Acute hyperinflation of native lung Diaphragmatic dysfunction
Heart	Diaphragmatic dysfunction Mediastinitis Pulmonary edema Pleural effusions
Kidney	Pulmonary edema Venous thromboembolic disease

to 8.4% following conventional, full-intensity radiation containing preparative regimens.¹⁹⁴ The median time of onset after allogeneic SCT is 19 days (range, 4 to 106 days) with mortality rates ranging from 60% to 80% overall to greater than 95% for patients requiring mechanical ventilation.^{184,185,194-196} Although IPS also develops after *autologous* SCT, the incidence is lower, the median time to onset is generally later (63 days; range 7 to 336 days), the response to corticosteroids is usually prompt and the prognosis is favorable compared with IPS in allogeneic SCT recipients.^{40,197-202} Risk factors for IPS after allogeneic SCT include full-intensity conditioning with total body irradiation, acute GVHD, older recipient age, and an underlying diagnosis of acute leukemia or myelodysplastic syndrome.^{185,194,197,197a} Risk factors for IPS following autologous SCT include older patient age, severe oral mucositis, conditioning regimens using total body irradiation or BCNU, chest irradiation within 2 weeks before transplant, female gender, and an underlying diagnosis of solid tumor.¹⁹⁸⁻²⁰¹

Current standard treatment strategies of IPS include broad-spectrum antibiotics and IV corticosteroids and supportive care with lung protective mechanical ventilation and venovenous ultrafiltration for those with respiratory failure. Response to corticosteroids (≤ 2 mg/kg/day) has shown mixed efficacy in allogeneic SCT recipients, which likely reflects the diversity of underlying causes responsible for the lung insult. Compared with lower doses, higher doses of corticosteroid therapy (>2 mg/kg/day) have not been shown to improve outcome but are associated with increased complications including fungal infection.^{194,203} Prophylaxis against filamentous fungal infection with voriconazole or micafungin is recommended during treatment with corticosteroids (≥ 0.5 mg/kg/day) because fungal pneumonia was identified in 16% (4/25) of IPS patients at the time of autopsy in a single-center study.²⁰⁴

Preclinical and clinical studies suggest that neutralization of *tumor necrosis factor* (TNF)- α may be a useful thera-

peutic strategy for IPS. In a single-center study, etanercept (0.4 mg/kg administered subcutaneously twice weekly for 4 weeks) in conjunction with systemic corticosteroids and empiric antibiotics was associated with significant clinical improvement in 66% (10/15) of IPS patients.²⁰⁵ In a multicenter, Phase II single-arm, open-label study by Yanik and colleagues²⁰⁶ in pediatric SCT recipients, treatment with etanercept (0.4 mg/kg/dose twice weekly for 8 doses) plus corticosteroids (2 mg/kg/day) resulted in a complete response in 71% (20 of 28) of patients and was associated with a high overall survival compared with historical controls.¹⁸⁵

As a clinical spectrum, IPS encompasses several descriptive forms of lung dysfunction.^{184,185} One such subset is termed *diffuse alveolar hemorrhage* (DAH), also called *acute pulmonary hemorrhage* (Fig. 91-4 and Video 91-1) or *hemorrhagic alveolitis*. DAH generally develops in the immediate posttransplant period and is characterized by progressive dyspnea, cough, and hypoxemia with or without fever. The cumulative incidence of DAH is 5% to 12% of SCT patients with a median time of onset of 19 days (range, 5 to 34 days) in allogeneic recipients and 12 days (range, 0 to 40 days) in autologous patients.^{198,207-211} The diagnosis of DAH is based on progressively bloodier return of BAL fluid (see Fig. 67-3).¹⁹⁸ Treatment of DAH consists of aggressive platelet support to maintain a platelet count greater than or equal to 100,000 and high-dose systemic corticosteroids (2 mg/kg/day to 1 g/m²/day).²¹² The addition of aminocaproic acid or recombinant factor VII may further improve outcomes.^{209,213-215} Despite these interventions, the mortality from DAH ranges from 60% to 100% with death usually due to multiorgan failure within 3 weeks of diagnosis.^{208,209,216}

Peri-engraftment respiratory distress syndrome (PERDS) is another clinical subset of IPS. PERDS by definition develops within 5 days of engraftment and accounts for 33% of IPS cases after allogeneic SCT (eFig. 91-12 and Video 91-2).²¹⁷

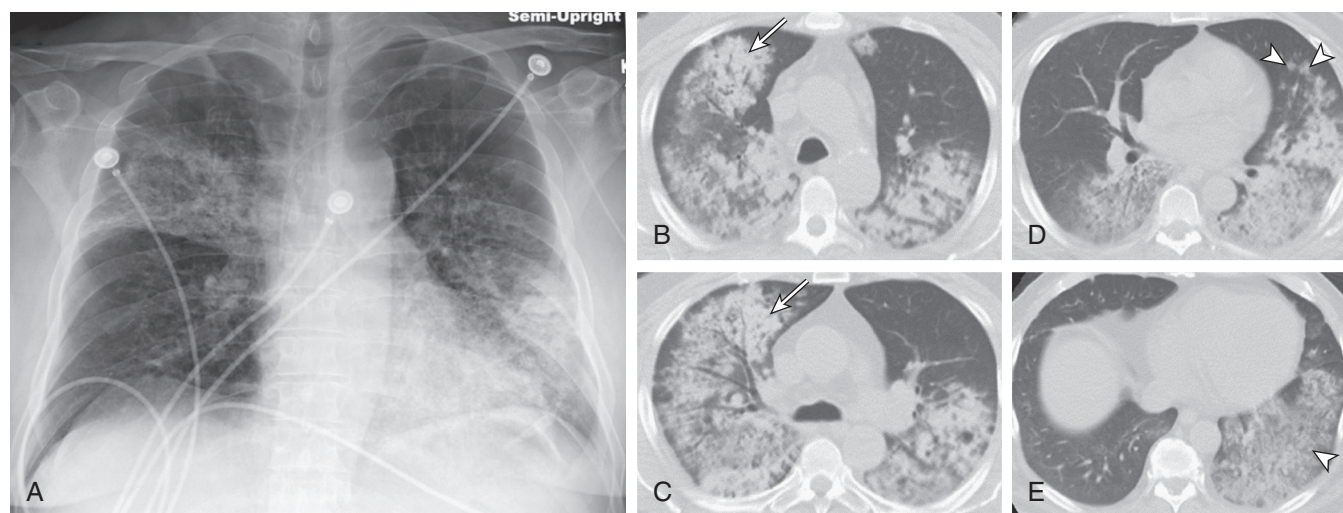


Figure 91-4 Diffuse alveolar hemorrhage following stem cell transplantation. A, Frontal chest radiograph performed in a patient 17 days following stem cell transplant shows multifocal bronchovascular thickening and consolidation. B–E, Axial chest CT at the level of the aortic arch (B), carina (C), right middle lobe bronchus (D), and lung bases (E) displayed in lung windows shows multifocal ground-glass opacity with areas of consolidation (arrows, B and C) shown to represent diffuse alveolar hemorrhage. Numerous centrilobular nodules (arrowheads, D and E), commonly seen in patients with pulmonary hemorrhage, are present. (See Video 91-1 for the CT scan.) (Courtesy Michael Gotway, MD.)

Although the clinical presentation of PERDS after SCT is similar to other subsets of IPS, lung dysfunction is more responsive to corticosteroids and the prognosis is better.²¹⁸⁻²²⁰

Delayed pulmonary toxicity syndrome (DPTS) also falls within the spectrum of IPS.²²¹ The incidence of DPTS is 29% to 64% in autologous SCT recipients (eFig. 91-13) receiving chemotherapy with regimens containing BCNU, cyclophosphamide, and cisplatin. The median time of onset is 45 days (range, 21 to 149 days), and treatment with corticosteroids (1 mg/kg/day) results in resolution in up to 92% of cases.²²¹⁻²²³

Venous Thromboembolic Disease

Venous thromboembolism (VTE) is an under-recognized complication of SOT, especially in lung transplant recipients. In an autopsy series, pulmonary embolism was diagnosed in 34 (27%) of 126 lung and heart-lung transplant recipients.²²⁴ By comparison, pulmonary embolism is diagnosed in 5% to 7% of lung transplant recipients antemortem, suggesting underdiagnosis of this complication.²²⁵ In renal transplant patients, the incidence of VTE ranges from 0.6% to 25%²²⁶⁻²²⁸ and is associated with advanced renal insufficiency, acute CMV infection, and cyclosporine use,²²⁹⁻²³¹ whereas in liver transplant patients, the incidence of pulmonary embolism was 1% overall.^{232,233} In a cohort of 159 heart recipients from a single center, only 2 patients developed VTE.²²

SCT patients are at increased risk of developing VTE. In a retrospective study of 1514 SCT recipients, the incidence of symptomatic VTE within the first 180 days post-transplantation was 4.6% including a 0.7% incidence of non-catheter-associated lower extremity DVT and 0.6% incidence of pulmonary embolism.²³⁴ This result is comparable with a smaller, retrospective study of 589 SCT patients.²³⁵ The median time after SCT admission to the development of non-catheter-associated lower extremity DVT was 63 days and for pulmonary embolism, 66 days.²³⁴ Independent risk factors for the development of VTE were prior VTE and GVHD.^{234,236} Importantly, thrombocytopenia was only partially protective against the development of VTE.²³⁴ The safety and efficacy of thromboprophylaxis in SCT patients remains uncertain, and anticoagulant therapy for documented VTE should be accompanied by platelet transfusions to maintain a platelet count of $50 \times 10^9/L$ or greater to reduce the risk of bleeding complications.

Diaphragmatic Dysfunction

Diaphragmatic dysfunction can develop due to injury to the phrenic nerve, perhaps from hypothermia or mechanical damage during surgery. The incidence of diaphragmatic dysfunction after heart or heart-lung transplantation has been reported from 12% to 43% and after lung transplantation from 7% to 30%.²³⁷⁻²³⁹ The reported incidence of diaphragmatic paralysis among liver transplant recipients ranges from 38% to 44% and is attributed to right phrenic nerve crush injury at the time of suprahepatic vena cava clamping.^{240,241} Diaphragmatic dysfunction has been associated with a significantly increased number of ventilator days and ICU length of stay for liver, heart-lung, and lung-only transplant recipients compared with recipients without phrenic nerve damage.^{239,240,242}

LATE COMPLICATIONS

Drug-Induced Pulmonary Toxicity

A spectrum of drug-induced lung diseases has been reported after transplantation in association with immunosuppressive therapies. Implicated immunosuppressive agents and their patterns of pulmonary toxicity are listed in eTable 91-4.

Monoclonal antibodies used as induction immunosuppressive therapy after SOT are infrequently associated with pulmonary toxicity. Infusion of muromonab-CD3 (OKT3) can produce a cytokine release syndrome thought to be from a transient activation of T cells before they undergo cell lysis.²⁴³ The clinical manifestations of this syndrome are fever, chills, headache, dyspnea, myalgia, and hypotension and can result in pulmonary edema and intra-allograft thrombosis.^{244,245} Basiliximab is linked to severe noncardiogenic pulmonary edema within 48 hours of infusion.^{246,247} Alemtuzumab is associated with DAH.²⁴⁸ The off-label use of rituximab, as part of the induction immunosuppressive regimen for renal transplantation, has also been reported to result in a cytokine release syndrome, with ARDS and DAH developing within hours of administration.^{244,249} Additional patterns of rituximab-induced lung injury include interstitial pneumonitis and cryptogenic organizing pneumonia, which can develop within weeks of administration and in most cases completely resolve after discontinuation of therapy with or without corticosteroids.²⁵⁰⁻²⁵⁴

IV and oral cyclosporine given after liver, kidney, and bone marrow transplantation has been reported to cause a noncardiogenic pulmonary edema and ARDS that resolves when the medication is discontinued. The reaction is postulated to be idiosyncratic.²⁵⁵⁻²⁵⁹

The *mammalian target of rapamycin* (mTOR) inhibitors, sirolimus and everolimus, bind to rapamycin-FK-binding protein-12 to inhibit T and B lymphocyte proliferation for induction and long-term maintenance of immunosuppression. Pulmonary toxicity has been reported in up to 11% of SOT recipients receiving sirolimus.^{260,261} Pulmonary toxicity developed within 6 months of the initiation of sirolimus therapy in 47% of cases and within 12 months in 65% of recipients.²⁶² The clinical presentation includes cough (96%), fatigue (83%), fever (67%), dyspnea (33%), and hemoptysis (8%). Physical examination is notable for hypoxemia (50%) and inspiratory crackles (50%).²⁶⁰ Radiographic findings on CT scan include patchy bilateral asymmetrical peripheral consolidations (organizing pneumonia-like pattern) (79%), reticular and ground-glass opacities (17%), and lobar consolidation (4%).²⁶⁰ BAL is reported to show lymphocytic or eosinophilic alveolitis in up to 92% of cases.^{260,263,264} The predominant histologic patterns are organizing pneumonia, pulmonary hemorrhage, diffuse alveolar damage, and, in a minority of cases, pulmonary alveolar proteinosis.^{265,266} Drug discontinuation with or without corticosteroids (1 mg/kg/day) is the mainstay of treatment, with complete resolution of symptoms within 2 to 4 months.^{260,261,263,265} Less severe cases can be managed by a reduction in the sirolimus dose with close monitoring of serum levels; however, relapses have been reported with this approach.²⁶¹ Sirolimus is also thought to be a potent antifibroproliferative agent and has been associated with severe wound healing complications leading to a

e-Table 91-4 Pulmonary Toxicity of Immunosuppressant Agents

Immunosuppressant	Pulmonary Toxicity
MONOCLONAL ANTIBODIES	
Muromonab-CD3 (OKT3)	Capillary leak (noncardiogenic pulmonary edema), ARDS
Basiliximab-CD25 (anti-IL-2 receptor) antibody	Capillary leak (noncardiogenic pulmonary edema)
Alemtuzumab anti-CD52 antibody	Diffuse alveolar hemorrhage
Rituximab anti-CD20 antibody	ARDS, diffuse alveolar hemorrhage, interstitial pneumonitis, cryptogenic organizing pneumonia, pulmonary fibrosis, hypersensitivity pneumonitis
CALCINEURIN INHIBITORS	
Cyclosporine	Capillary leak (noncardiogenic pulmonary edema), ARDS
Tacrolimus	Cryptogenic organizing pneumonia
mTOR INHIBITORS	
Sirolimus	Organizing pneumonia, diffuse alveolar hemorrhage, ARDS, pulmonary alveolar proteinosis
Everolimus	Interstitial pneumonitis, diffuse alveolar hemorrhage, ARDS
Mycophenolate mofetil	Pulmonary edema, ARDS, pulmonary fibrosis, bronchiectasis
Azathioprine	Cryptogenic organizing pneumonia, diffuse alveolar hemorrhage, interstitial pneumonitis, laryngeal edema, vasculitis

ARDS, acute respiratory distress syndrome.

high rate of bronchial anastomosis dehiscence after lung transplantation.^{267,268} As a consequence, sirolimus administration is not started until 3 months after transplantation or after bronchial wound healing is complete.^{268,269}

Everolimus, a derivative of sirolimus, is associated with pulmonary toxicity in 3.3% of heart transplant recipients with clinical, radiographic, and histologic features similar to those reported with sirolimus.²⁷⁰⁻²⁷³

Obliterative Bronchiolitis and Cryptogenic Organizing Pneumonia

In allogeneic SCT recipients, late-onset noninfectious pulmonary complications have been reported in 13% to 26%.^{274,275} Obliterative bronchiolitis, also called *bronchiolitis obliterans syndrome* (BOS), and *cryptogenic organizing pneumonia* (COP), formerly called *bronchiolitis obliterans organizing pneumonia* (BOOP), are two late-onset noninfectious pulmonary complications of allogeneic SCT strongly associated with GVHD.²⁷⁶⁻²⁸⁰ The clinical hallmark of BOS is the development of new-onset, fixed airflow obstruction that is pathologically characterized by progressive circumferential fibrosis of the terminal bronchioles.²⁸¹

Historically, the incidence of BOS after SCT has ranged from 2% to 26%, depending on the definition of airflow obstruction used in the study.^{277,282} In an attempt to standardize the definition of BOS after SCT for clinical and research purposes, the National Institutes of Health Chronic GVHD consensus project published in 2005 diagnostic criteria, which define BOS by five characteristics: (1) *forced expiratory volume in 1 second* (FEV₁) less than 75% predicted; (2) FEV₁/forced vital capacity (FVC) ratio less than 0.7; (3) evidence of air trapping, small airway thickening, or bronchiectasis on high-resolution computed tomography (eFig. 91-14) or *residual volume* (RV) greater than 120% predicted or pathologic confirmation of constrictive bronchiolitis; (4) absence of respiratory tract infection; and (5) clinical manifestation of chronic GVHD in at least one other organ.²⁸³ Using the consensus diagnostic criteria in a single-center, retrospective study of 1145 allogeneic SCT recipients, Au and colleagues²⁸¹ reported the overall prevalence of BOS to be 5.5% among all transplanted patients and 14% among patients with chronic GVHD. In this study, the median time from transplant to diagnosis of BOS was 439 days (range, 274 to 1690 days). BOS conferred a 1.6-fold increased risk for death after diagnosis.²⁸¹ Multivariate analysis of this same cohort of SCT recipients identified chronic GVHD and lower IgG levels (<350 ng/dL) as independent risk factors for the development of BOS.²⁸¹

The onset of BOS is usually insidious, with nonproductive cough (60% to 100%), dyspnea (50% to 70%), and wheezing (40%).²⁸⁴ Although histologic evaluation of lung tissue is considered the gold standard for the diagnosis of bronchiolitis obliterans, the utility of transbronchial biopsies is limited by low sensitivity (≈20% to 50%) attributed to the heterogeneity of the lesions and small biopsy size.²⁸⁵⁻²⁸⁷ In general, more invasive procedures such as open-lung biopsy or *video-assisted thorascopic* (VATS) procedures are reserved for unusual presentations. In most instances, the diagnosis of BOS is based on the presence of persistent expiratory airflow obstruction on spirometry in the absence of other causes such as asthma, tobacco-related emphysema, or lower respiratory tract infection.²⁸⁴

Although the etiology of BOS remains uncertain, the suspected cause is immune-mediated injury of lung epithelium due to allorecognition of lung antigens.^{277,288}

There are no prospective studies of the treatment of airflow obstruction after SCT. Given the presumed alloimmune pathogenesis of BOS, immunosuppressive therapy remains the foundation of treatment. The historic clinical approach to BOS treatment has been with high-dose systemic corticosteroids for extended periods of time such as 12 to 24 months. However, given the limited response to treatment and substantial morbidities associated with high-dose systemic corticosteroid therapy, adjunctive approaches have been tried, including the use of inhaled corticosteroids,^{288,289} azithromycin,²⁹⁰ and montelukast, a leukotriene inhibitor,^{291,292} which have shown some efficacy in small clinical trials of BOS after SCT. Other emerging therapies for BOS include extracorporeal photophoresis,²⁹³⁻²⁹⁶ TNF- α blockade with infliximab,²⁹⁷ imatinib,²⁹⁸ and statins.²⁹⁹ Despite aggressive treatment, BOS after SCT has a poor prognosis with an overall survival rate of 44% at 2 years and 13% at 5 years.^{278,300-303,303a}

After lung transplantation, the BOS that develops has similar clinical manifestations and histologic characteristics as the BOS of allogeneic SCT recipients. However, BOS is much more common after lung transplantation, developing in 50% of lung transplant recipients at 5.6 years post-transplantation (see Fig. 106-5).²⁸⁵ A detailed discussion on obliterative bronchiolitis syndrome after lung transplantation is available in Chapter 106.

After SCT, COP is an infrequent, late-onset noninfectious complication. In a single-center, retrospective case-control study, Freudenberger and colleagues³⁰⁴ identified 49 cases (0.9%) of biopsy-proven COP among 5340 allogeneic patients. In a smaller, retrospective study COP was diagnosed in 12 (2%) of 603 allogeneic SCT recipients.³⁰⁵ The median time to diagnosis following SCT is reported to be 108 days (range 5 to 2819 days).³⁰⁴ Patients commonly present with fever (61%), dyspnea (45%), and nonproductive cough (43%) with a median symptom duration of 13 days (range 3 to 65 days). Pipavath and associates³⁰⁶ reported the imaging features of biopsy-proven COP in a cohort of 16 allogeneic SCT recipients. The CT findings included ground-glass opacities (94%), consolidation (50%) (Fig. 91-5), and linear opacities (50%) with an upper lobe predominance (63%). The pulmonary physiologic changes associated with a diagnosis of COP were predominantly new restrictive (43%) and diffusing capacity abnormalities (64%) and, to a lesser extent, a new obstructive pattern (11%).^{304,305}

Bronchoscopy and BAL are recommended to rule out lower respiratory tract infection and to establish the diagnosis of COP. BAL is characterized by lymphocytosis (>20% lymphocytes) with a decreased CD4/CD8 ratio.³⁰⁵ Unlike bronchiolitis obliterans, COP can usually be diagnosed by bronchoscopic biopsy, although VATS may be required in cases presenting with atypical features.^{305,307,308} The histologic characteristics included (1) patchy filling of respiratory bronchioles, alveolar ducts, and peribronchiolar sacs with polypoid masses of granulation tissue; (2) widening of alveolar septa and infiltration by mononuclear cells; and (3) accumulation of foamy macrophages within alveoli (see Figs. 63-34 and 63-35).³⁰⁴ There is an association between

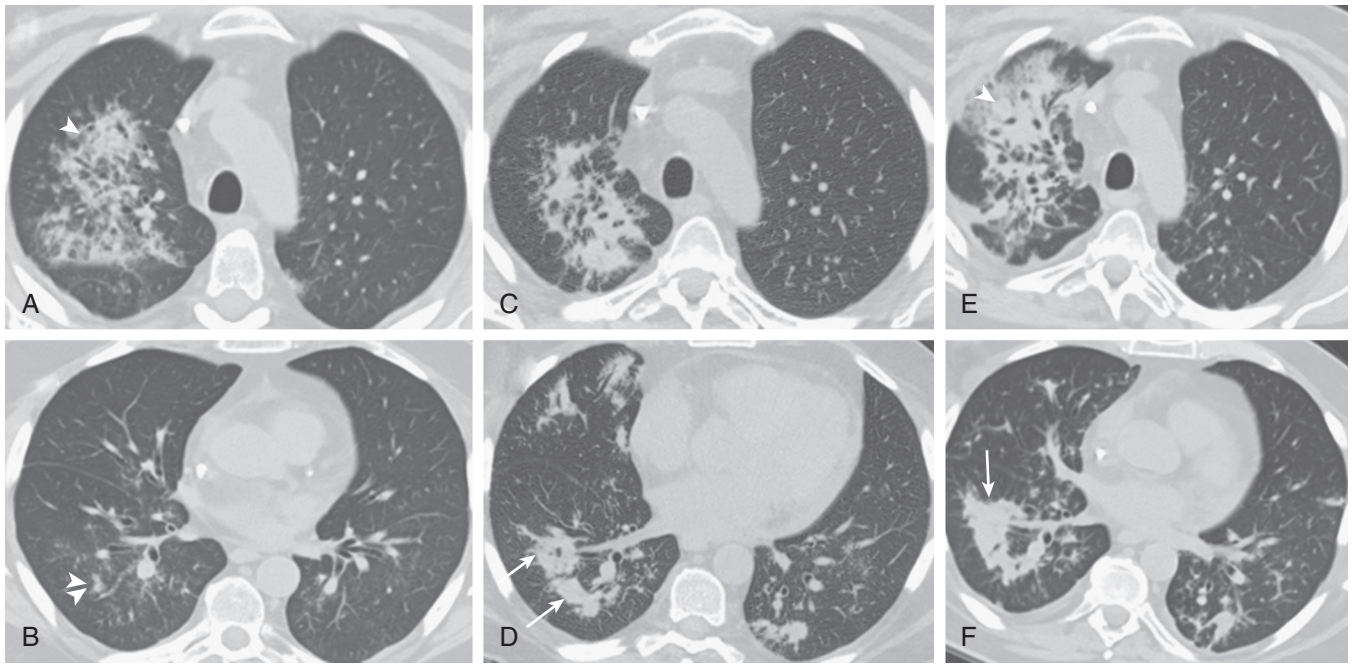


Figure 91-5 Graft-versus-host disease in an allogeneic stem cell transplant recipient presenting as organizing pneumonia. **A** and **B**, Axial chest CT shows patchy upper lobe consolidation (arrowhead, **A**) and right lower lobe nodules (double arrowheads, **B**). **C** and **D**, Several weeks following **A**, repeat chest CT shows progression of the abnormalities seen previously. The peripheral, peribronchial nature of the consolidation is particularly evident in the right lower lobe (arrows, **D**). **E** and **F**, Follow-up chest CT 1 month following **B** shows continued progression in upper (arrowhead) and lower (arrow) consolidation. Biopsy subsequently showed organizing pneumonia. (Courtesy Michael Gotway, MD.)

acute and chronic GVHD and subsequent development of COP.³⁰⁴ Patients with COP were more likely to have acute GVHD involving the skin and chronic GVHD involving the gut and oral cavity, suggesting that the pathogenesis is, at least in part, related to alloreactive lung injury.

Corticosteroid therapy is the standard treatment for COP after SCT, although doses and duration have been empirically derived. Historically, prednisone doses of 0.75 to 1.5 mg/kg/day were prescribed with a progressive decrease for a total duration of 24 weeks.^{309,310} However, in order to limit the risk of iatrogenic complications, current recommendations are to start with prednisone at 0.75 mg/kg/day for 4 weeks and taper over a total of 12 weeks, possibly in conjunction with use of a macrolide.³¹¹⁻³¹³ The prognosis of COP in SCT recipients is generally favorable with resolution in 57%, stable disease in 21%, and progressive COP in 22% despite corticosteroids with 16% of patients dying from respiratory failure.³⁰⁴ Up to 75% of patients relapse during the corticosteroid taper or after stopping treatment and typically respond to reinitiation or increased dosing of corticosteroid therapy.^{305,311}

Pulmonary veno-occlusive disease (PVOD) is a rare, late-onset complication after SCT that presents with the insidious onset of fatigue and exertional dyspnea within 3 to 4 months after transplant.³¹⁴⁻³¹⁹ The physical examination typically shows hypoxemia and resting tachycardia consistent with pulmonary hypertension. Right heart catheterization demonstrates elevated pulmonary artery pressures with normal pulmonary capillary wedge pressure, and angiography is used to exclude pulmonary emboli as the etiology for the pulmonary hypertension. The diagnosis of PVOD is strongly supported by the triad of pulmonary artery hypertension, radiographic evidence of pulmonary

edema, and normal pulmonary artery occlusion pressures; however, lung biopsy confirms the diagnosis by the presence of extensive and diffuse intimal proliferation and fibrosis of pulmonary venules.³²⁰ Treatment consists of high-dose corticosteroids (methylprednisolone 2 mg/kg/day) with anecdotal success, but the overall prognosis of PVOD after SCT remains poor.³¹⁶

Pulmonary cytolytic thrombus (PCT) is another noninfectious pulmonary complication that involves the pulmonary vasculature, seen exclusively in allogeneic SCT recipients and almost always in children. The incidence of PCT has been reported to range from 1.2% to 4%^{321,322} with a median onset at 3 months (range 1.3 to 11.3 months) after transplant.³²² The clinical manifestations include fever, cough, and respiratory distress, and CT findings range from small, peripheral nodules to diffuse opacities.^{321,323-325} Diagnosis requires lung biopsy that is characterized by vascular occlusions in distal pulmonary vessels, entrapment of leukocytes, endothelial disruption, and infarction of adjacent tissue.³²¹ In a single-center, retrospective study, grades II to IV acute and chronic GVHD were independent risk factors for developing PCT.³²² Treatment for PCT consists of systemic corticosteroids (prednisone 1 to 2 mg/kg/day) until pulmonary symptoms resolve (typically within 2 weeks) followed by a steroid taper over 2 to 4 weeks.³²² The strong association with acute and chronic GVHD, as well as the response to corticosteroid therapy, suggest that PCT is an alloreactive lung injury. The prognosis with PCT is favorable, and there have been no reported deaths attributable to this entity.^{322,326}

Pulmonary Metastatic Calcifications

Pulmonary metastatic calcification is a well-known complication of chronic renal failure and a rare complication in

renal transplant recipients.^{327,328} The lesions are typically nodular opacities of 2 to 12 mm in diameter that may be unilateral or diffuse with a predilection for the upper lobes (eFig. 91-15).³²⁸ Patients can be asymptomatic, although progression of the lesions may lead to dyspnea along with a restrictive pattern and diffusing capacity abnormality on pulmonary function testing.³²⁸ The clinical significance of pulmonary metastatic calcification is distinguishing this entity from pulmonary infections or malignancy in the transplant recipient.

Malignancy

Organ transplantation is associated with an increased risk of developing malignancies. Risk factors for malignancy include prolonged use of immunosuppressive therapy, infection with oncogenic viruses, progressive aging of transplant recipients, longer survival after transplantation and, less commonly, malignant cells transmitted in the donor tissue.³²⁹⁻³³¹ Transplant-related malignancies affecting the lung include non-Hodgkin lymphoma, bronchogenic carcinoma, posttransplantation lymphoproliferative disorder, and *Kaposi sarcoma* (KS). In a large, population-based, registry linkage study of 175,732 SOT recipients, the incidence of non-Hodgkin lymphoma was 7.54-fold higher in transplant recipients compared with the general population.³³⁰ Likewise, the incidence of lung cancer was increased 6.13-fold in lung, 2.67-fold in heart, 1.95-fold in liver, and 1.46-fold in kidney transplant recipients compared with the general population.³³⁰ For further discussion of lung cancer in lung transplant recipients, see Chapter 106.

Posttransplantation lymphoproliferative disorder (PTLD) is an infrequent but serious complication composed of a heterogeneous group of altered B-cell monoclonal and polyclonal proliferation disorders that can develop in association with immunosuppressive therapy. After SOT, the incidence of PTLD in adults varies among studies but is generally higher in lung (4.2% to 10.0%), heart-lung (2.2% to 5.8%) and heart (1% to 6.3%) compared with liver (1% to 2.8%) and kidney (1% to 2.3%) (eFig. 91-16) recipients.^{332,333-335} The incidence appears to have a bimodal distribution after lung transplantation with 25% to 47% of cases developing within the first 12 months of transplantation.^{333,335} Risk factors for the development of PTLD after SOT include age at the time of transplantation, degree of immunosuppression, use of OKT3 or antilymphocyte globulin, number of episodes of acute rejection, seronegativity to EBV before transplantation (especially with an EBV-seropositive donor) and CMV or hepatitis C infection.^{336,337}

After allogeneic SCT, PTLD is a rare but serious complication as well (eFig. 91-17). In a multicenter study of 18,014 allogeneic SCT recipients, the overall incidence of PTLD was 1% with 82% of cases diagnosed within the first year posttransplantation.³³⁸ For early-onset PTLD after SCT, risk factors included unrelated or HLA mismatched related donor stem cell source, T-cell depletion of the donor marrow, and use of antithymocyte globulin or anti-CD3 monoclonal antibody for prophylaxis or treatment of acute GVHD. For late-onset PTLD, the only risk factor identified was chronic extensive GVHD. The incidence of PTLD increased to 8% for patients with two risk factors and to 22% for those with three or more risk factors. Pulmonary involvement with

PTLD after allogeneic SCT has been reported in 18% of cases.³³⁹ Overall long-term survival was lower for SCT recipients (35%) compared with SOT recipients (55%) and was the worst for patients transplanted for hematologic malignancies.³³⁹ Additional information on PTLD is presented in Chapter 106.

KS is a soft tissue malignancy associated with immunosuppression in SOT recipients. In a large population-based study, among 234,127 recipients, the incidence of KS was 8.8 per 100,000 person-years with the median time from transplantation to KS of 1.5 years.³⁴⁰ Risk factors for the development of KS posttransplantation in the United States included male gender, older recipient age, Hispanic ethnicity, non-U.S. citizenship, and number of mismatches at the HLA-B locus.³⁴⁰ KS develops primarily in transplant recipients with preexisting human herpesvirus-8 infection.³⁴¹⁻³⁴³ Twenty percent of KS cases after organ transplantation have visceral involvement including the lungs.³⁴⁰

Key Points

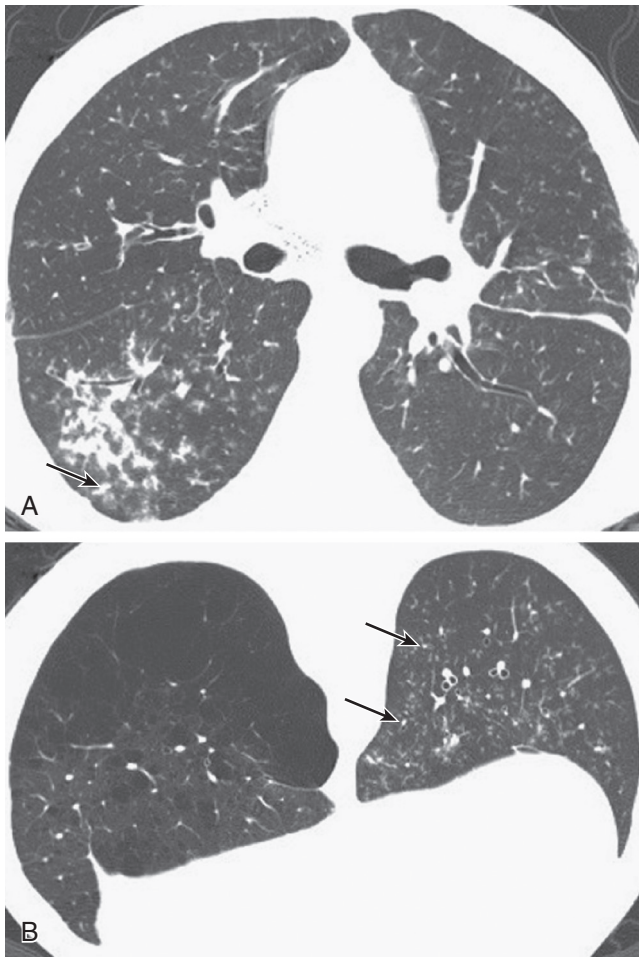
- Pulmonary complications are common following stem cell and solid organ transplantation, and their incidence follows a characteristic pattern.
- Risk factors for the development of pulmonary complications are varied and include the type of organ or tissue transplanted, degree and duration of immunosuppression, preexisting lung disease, concomitant medication administration, perioperative insults, and environmental exposures.
- Infectious etiologies must be aggressively assessed, often requiring invasive lung sampling for accurate diagnosis, and then promptly treated.
- The use of antimicrobial prophylaxis for commonly encountered pathogens has reduced the incidence of certain pulmonary infections in transplant recipients. However, antimicrobial prophylaxis has also led to the emergence of resistant pathogens.
- Noninfectious complications after transplant can be seen early, including acute respiratory distress syndrome, idiopathic pneumonia syndrome, venous thromboembolic disease, and diaphragmatic dysfunction, or late, including drug-induced toxicity, bronchiolitis obliterans syndrome, and posttransplantation lymphoproliferative disorder.

Complete reference list available at [ExpertConsult](#).

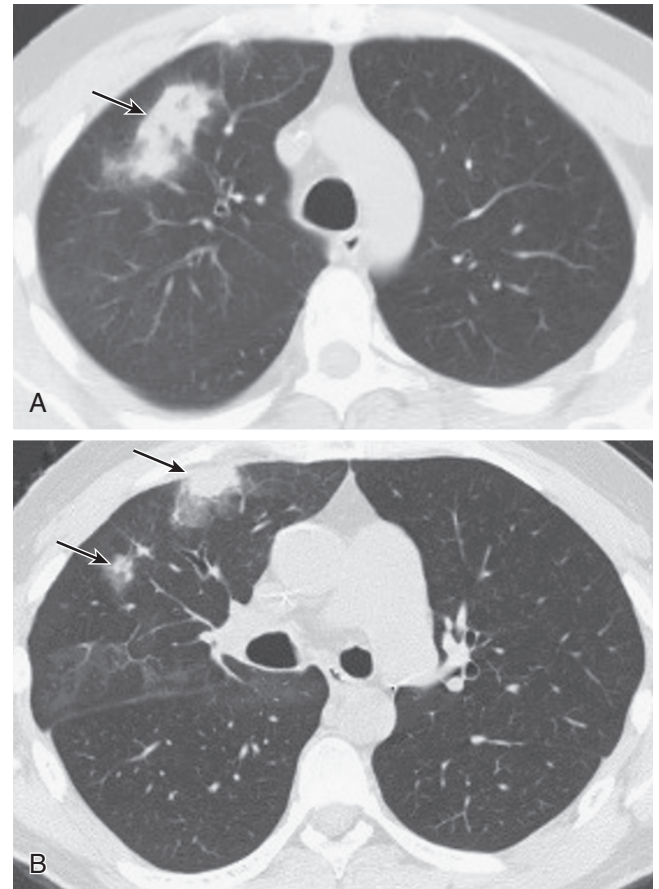
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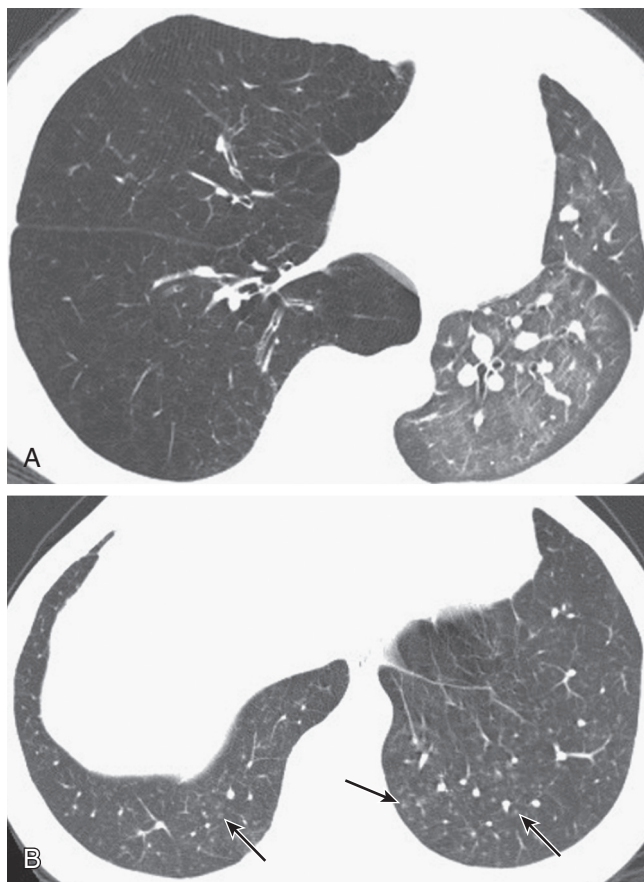
eFIGURE IMAGE GALLERY



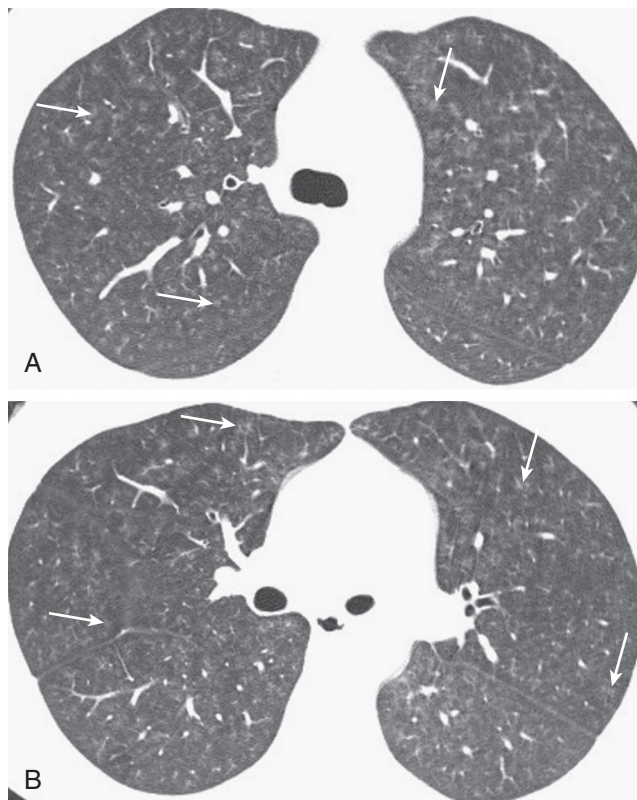
eFigure 91-1 *Pseudomonas* bacterial pneumonia in lung transplant recipients. A and B, Axial (A) and prone (B) chest CT through the lower lungs in two lung transplant recipients shows consolidation and small nodules (arrows), the latter consistent with infectious bronchiolitis. (Courtesy Michael Gotway, MD.)



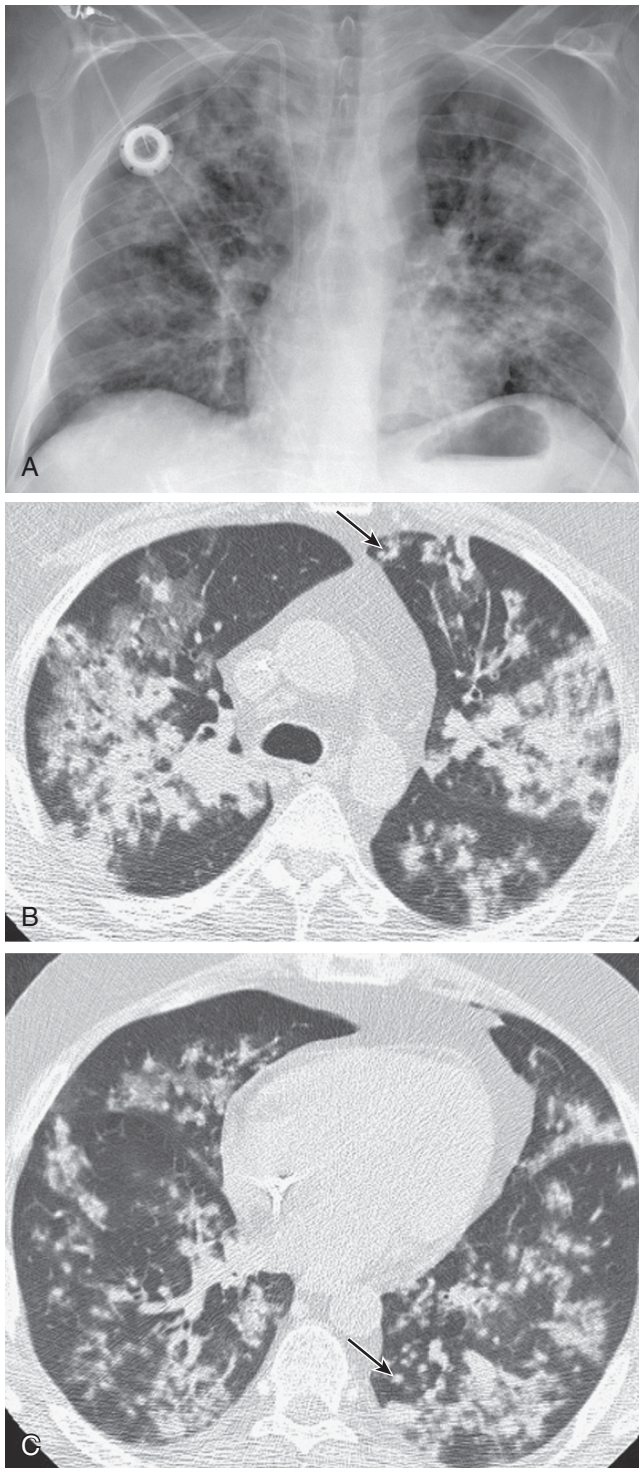
eFigure 91-2 Cytomegalovirus infection in a lung transplant recipient. A and B, Axial chest CT through the upper (A) and mid (B) lungs shows nodular opacities (arrows) with peripheral ground-glass opacity halos, suggesting the possibility of invasive fungal infection. Tissue sampling, however, established the presence of cytomegalovirus infection. (Courtesy Michael Gotway, MD.)



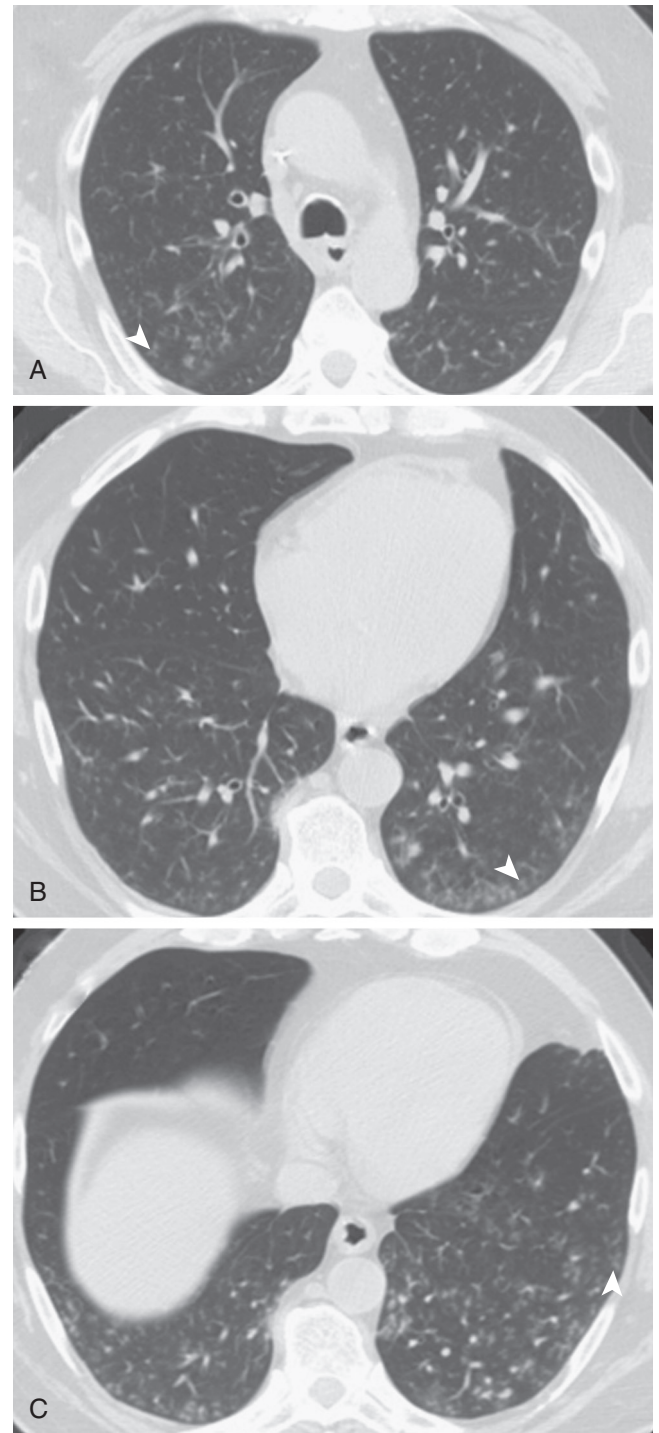
eFigure 91-3 Cytomegalovirus infection in a lung transplant recipient: variable chest CT appearances. **A** and **B**, Axial chest CT through the lower lungs in two lung transplant recipients shows patchy left lower lobe ground-glass opacity in one patient with proven cytomegalovirus infection (**A**) and small nodules (**B**), also proven to represent cytomegalovirus infection, in a different patient (**B**). (Courtesy Michael Gotway, MD.)



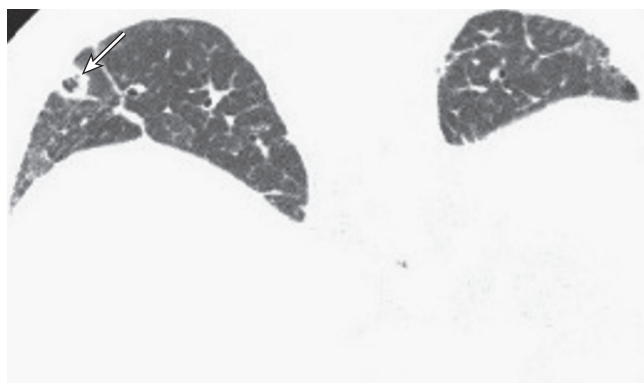
eFigure 91-4 Cytomegalovirus infection in a renal transplant recipient. Axial chest CT through the upper (**A**) and mid (**B**) lungs shows diffuse, bilateral, poorly defined centrilobular nodules (*arrows*) shown to represent cytomegalovirus infection. The appearance resembles hypersensitivity pneumonitis. (Courtesy Michael Gotway, MD.)



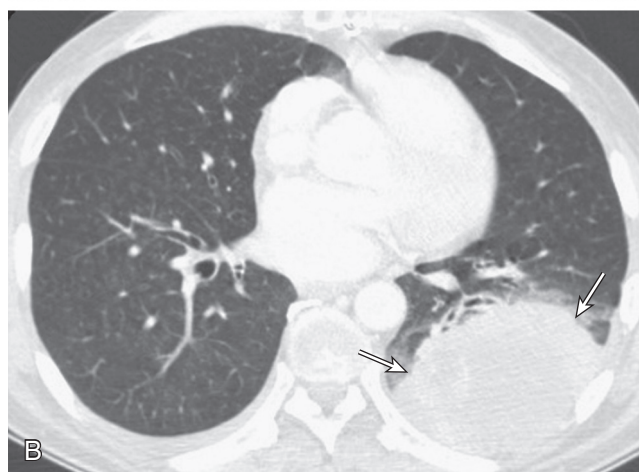
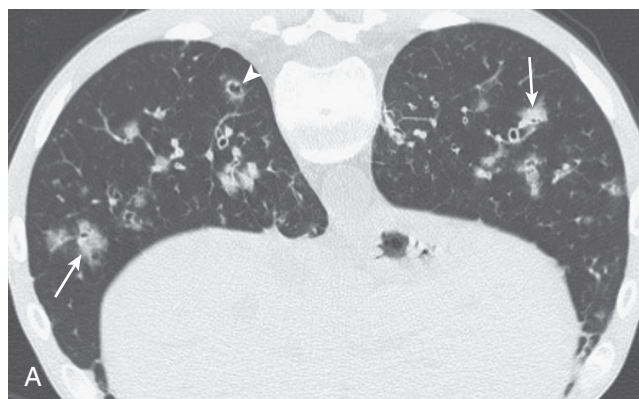
eFigure 91-5 Cytomegalovirus infection in a stem cell transplant recipient. Frontal chest radiograph (A) shows extensive, bilateral poorly defined nodular consolidation without pleural effusion. Axial chest CT through the mid (B) and lower (C) lungs shows extensive ground-glass opacity and consolidation with small, solid, centrilobular nodules (arrows). (Courtesy Michael Gotway, MD.)



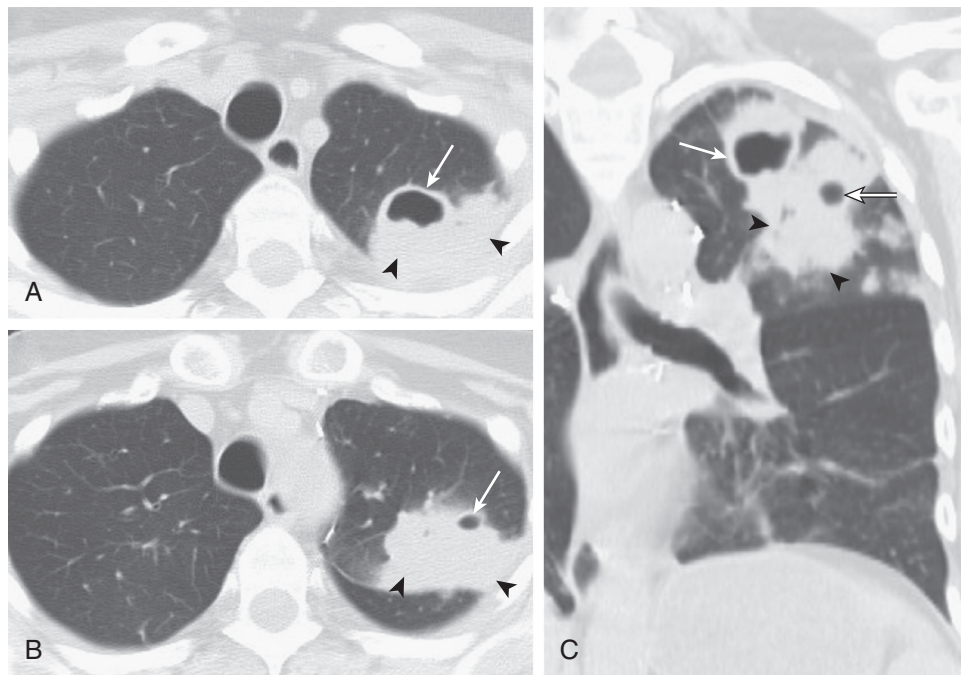
eFigure 91-6 Metapneumovirus infection in a stem cell transplant recipient. Axial chest CT through the upper (A) and lower (B and C) lungs shows small nodules with branching configurations (arrowheads), consistent with tree-in-bud opacities and infectious bronchiolitis. (Courtesy Michael Gotway, MD.)



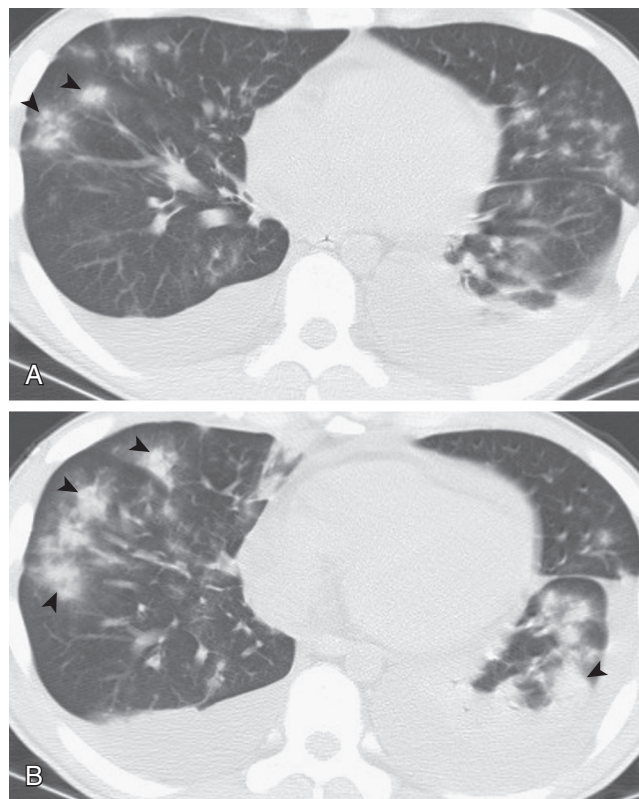
eFigure 91-7 *Aspergillus fumigatus* infection in a lung transplant recipient. Prone chest CT shows a subpleural right lower lobe cavitory nodule (arrow) proven to represent *Aspergillus* infection. (Courtesy Michael Gotway, MD.)



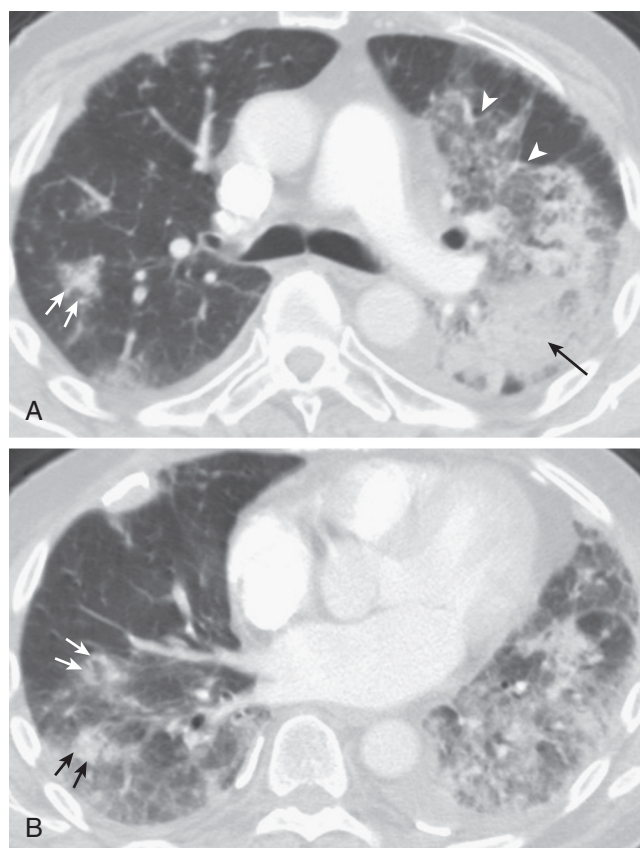
eFigure 91-8 *Aspergillus fumigatus* infection in a lung transplant recipient: variable chest CT appearances. Prone (A) and axial (B) chest CT in two separate lung transplant recipients shows extensive peribronchial ground-glass opacity and consolidation (arrows, A) and a small cavitory nodule (arrowhead, A) in one patient and a large mass (arrows, B) in another patient, both shown to represent *Aspergillus* infection. (Courtesy Michael Gotway, MD.)



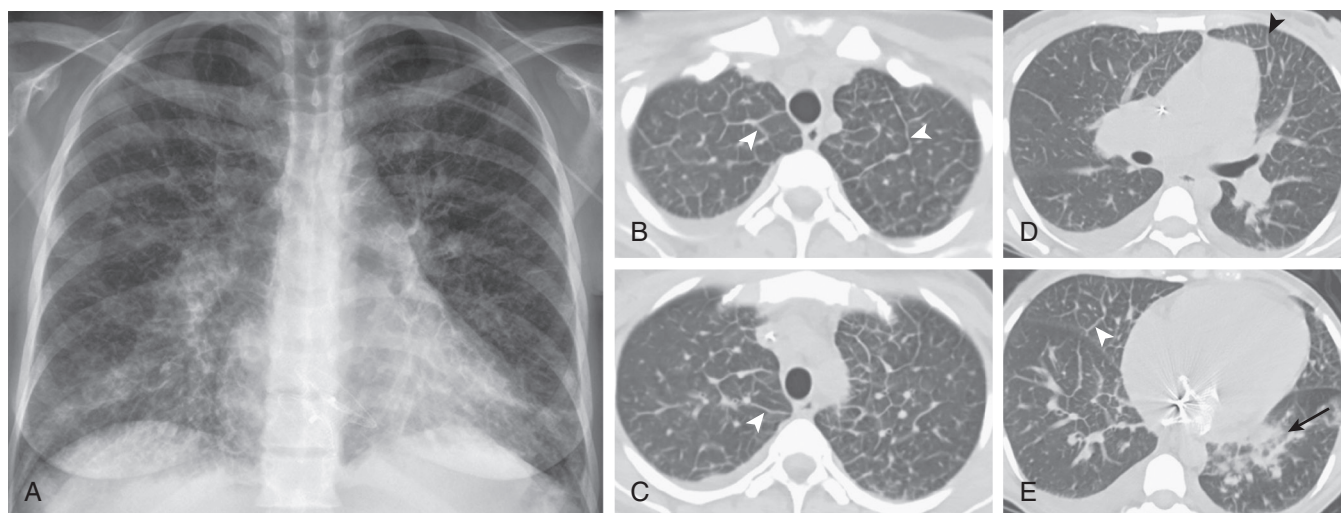
eFigure 91-9 Non-*Aspergillus* mold infection in a lung transplant recipient: mucormycosis. Axial (A and B) and C, coronal chest CT shows a left upper lobe subpleural mass (arrowheads) with areas of cavitation (arrows), consistent with invasive fungal infection, proven to represent mucormycosis. (Courtesy Michael Gotway, MD.)



eFigure 91-10 Invasive *Aspergillus fumigatus* infection in a stem cell transplant recipient. A and B, Axial chest CT through the lower lungs shows basal consolidation and pleural effusions with poorly defined nodules with surrounding ground-glass opacity halos (arrowheads); the latter finding is consistent with the “ground-glass halo” sign, typical of angioinvasive aspergillosis when encountered in severely immunocompromised patients. (Courtesy Michael Gotway, MD.)



eFigure 91-11 Idiopathic pneumonia syndrome following stem cell transplantation. **A** and **B**, Axial chest CT in a patient who underwent allogeneic stem cell transplant 40 days earlier and then developed a cough shows extensive multifocal consolidation (arrow, **A**), nodular on the right side (double arrows), as well as patchy ground-glass opacity associated with reticular abnormalities (arrowheads, **A**). Imaging findings are nonspecific and could reflect infection or hemorrhage, among other noninfectious pulmonary complications following stem cell transplant. Evaluation excluded diffuse alveolar hemorrhage and infection as causes of the opacities. (Courtesy Michael Gotway, MD.)



eFigure 91-12 Peri-engraftment syndrome following stem cell transplantation. **A**, Frontal chest radiograph in a patient who recently underwent stem cell transplantation shows extensive multifocal, bilateral linear opacities representing interstitial thickening and interlobular septal thickening. **B–E**, Axial chest CT performed through the upper (**B** and **C**), mid (**D**), and lower (**E**) lungs, shown in lung windows, shows extensive, smooth, multifocal interlobular septal thickening (arrowheads) and patchy ground-glass opacity and consolidation (arrow, **E**) consistent with engraftment syndrome (see [Video 91-2](#) for the CT scan). (Courtesy Michael Gotway, MD.)

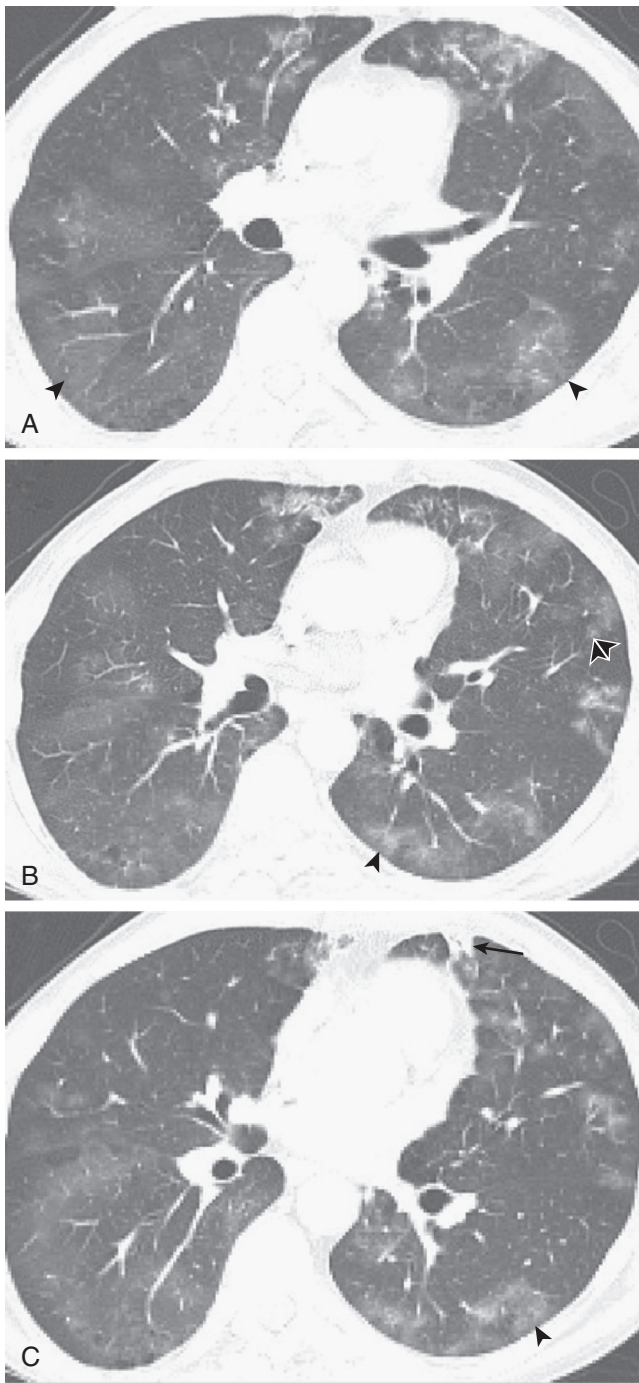
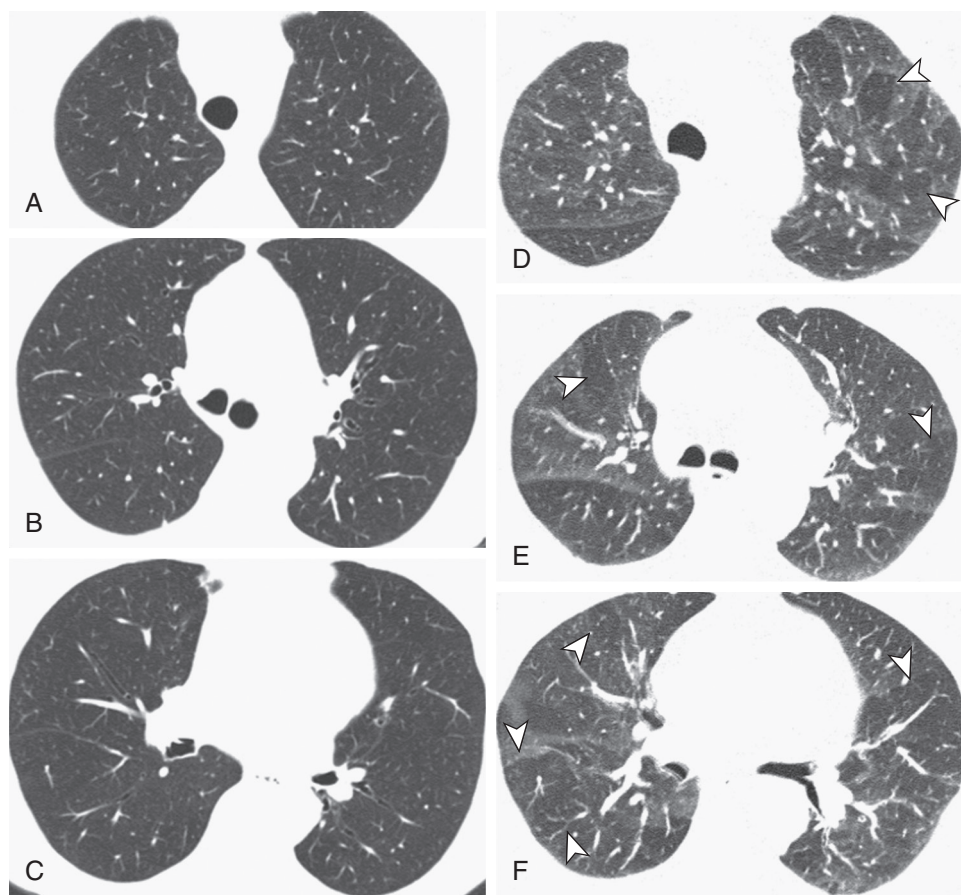
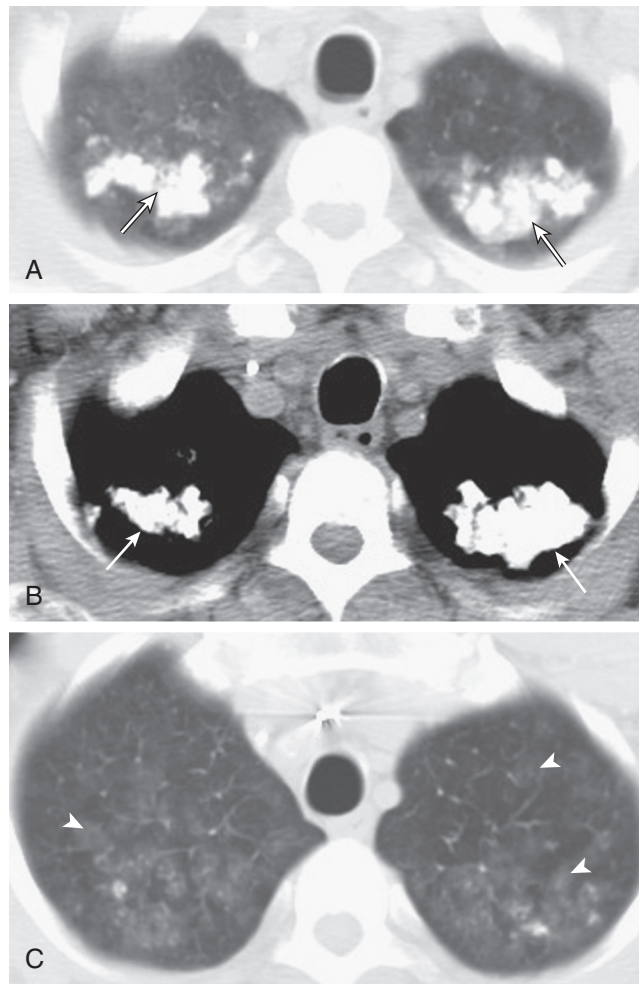


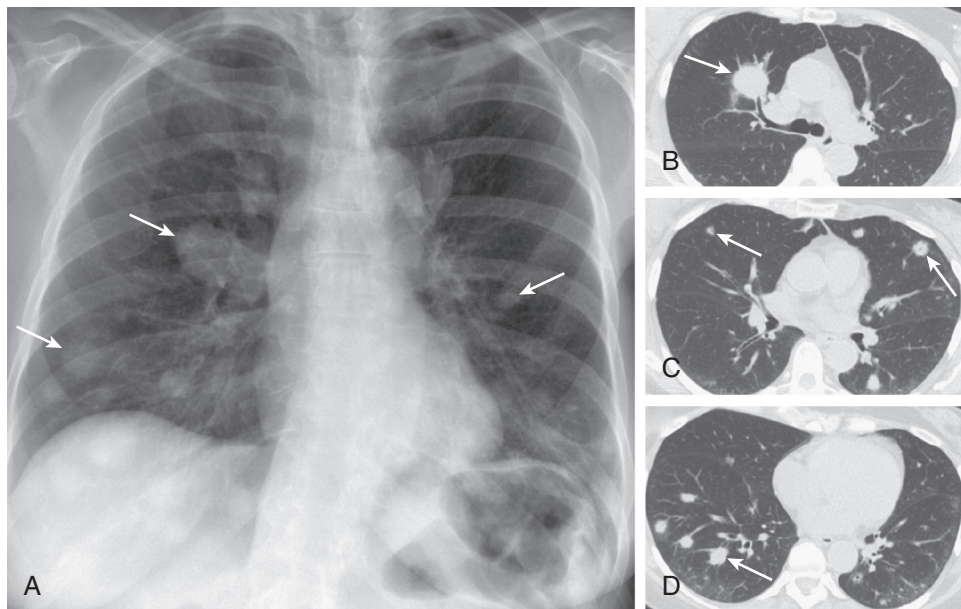
Figure 91-13 Delayed pulmonary toxicity syndrome following stem cell transplantation. A–C, Axial chest CT through the mid and lower lungs in a patient treated with bischloroethylnitrosourea who underwent stem cell transplant 70 days earlier and then developed nonproductive cough and shortness of breath shows multifocal ground-glass opacity (*arrowheads*), small nodular opacities (*double arrowheads*, B), and areas of consolidation (*arrow*, C). Imaging findings are nonspecific and could reflect infection or hemorrhage, among other noninfectious pulmonary complications following stem cell transplant. Evaluation excluded diffuse alveolar hemorrhage and infection causes of the opacities. (Courtesy Michael Gotway, MD.)



eFigure 91-14 Bronchiolitis obliterans in an allogeneic stem cell transplant recipient with graft-versus-host disease. A–C, Axial chest CT at inspiration through the upper (A), mid (B), and lower (C) lungs shows no significant abnormalities. D–F, Postexpiratory axial chest CT shows development of inhomogeneous lung opacity, with areas of decreased attenuation (*arrowheads*) representing multifocal air trapping, typical of bronchiolitis obliterans. (Courtesy Michael Gotway, MD.)



eFigure 91-15 Metastatic calcification in a renal transplant patient. A–C, Axial chest CT in lung (A) and soft tissue (B) windows shows nodular, calcified opacities (arrows) in the apices bilaterally. Axial chest CT performed through the upper lobes (C), slightly inferior to A and B, shows ground-glass centri-lobular nodules (arrowheads), typical of pulmonary metastatic calcinosis. (Courtesy Michael Gotway, MD.)



eFigure 91-16 Posttransplant lymphoproliferative disease in a renal transplant recipient. A, Frontal chest radiograph shows multiple, bilateral pulmonary nodules (arrows). B–D, Axial chest CT performed through the upper (B), mid (C), and lower (D) lungs, displayed in lung windows, shows multiple nodules (arrows), many associated with bronchi. Tissue sampling established the diagnosis of posttransplant lymphoproliferative disorder. (Courtesy Michael Gotway, MD.)

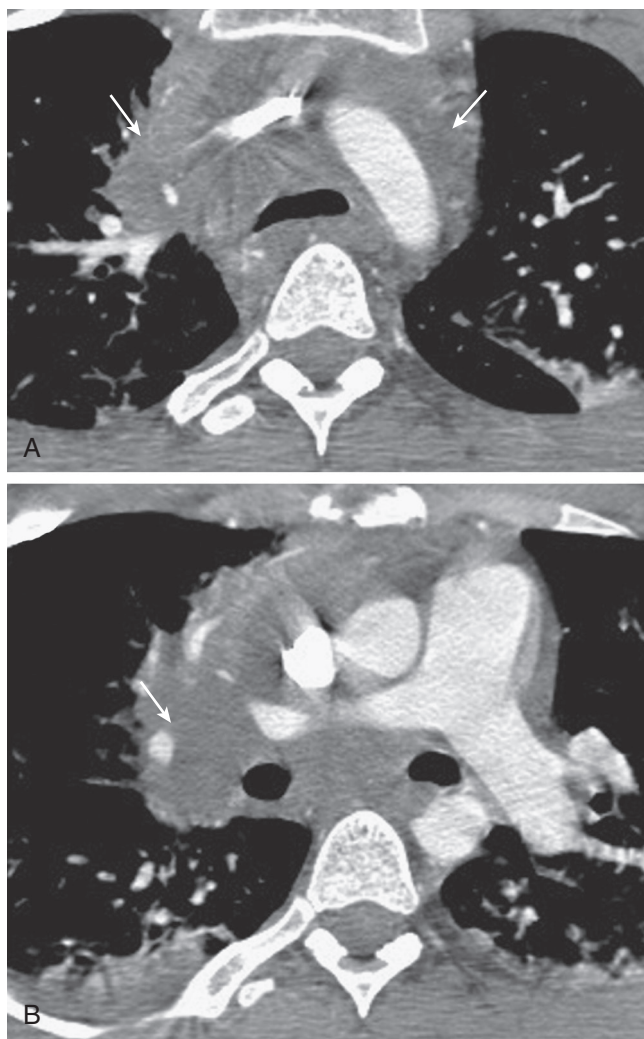


Figure 91-17 Posttransplant lymphoproliferative disease in an allogeneic stem cell recipient. A and B, Axial enhanced chest CT through the upper (A) and mid (B) lungs shows extensive mediastinal and hilar lymphadenopathy (arrows), proved to represent posttransplant lymphoproliferative disorder. (Courtesy Michael Gotway, MD.)

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PULMONARY COMPLICATIONS OF PRIMARY IMMUNODEFICIENCIES

JOHN M. ROUTES, MD

INTRODUCTION

DIAGNOSTIC WORKUP

Antibody Deficiencies
Cellular Immunodeficiency
Complement Deficiencies
Phagocyte Deficiencies

DEFICIENCY IN BOTH CELLULAR IMMUNITY AND ANTIBODY PRODUCTION

Severe Combined Immunodeficiency

ANTIBODY DEFICIENCIES

Immunoglobulin A Deficiency
X-Linked Agammaglobulinemia

Common Variable Immunodeficiency

Specific Antibody Deficiency

Immunoglobulin G Subclass Deficiency

X-Linked Lymphoproliferative Syndrome

Hyper-Immunoglobulin M Syndrome

X-Linked Hyper-IGM Syndrome

COMBINED IMMUNODEFICIENCIES OR SYNDROMIC IMMUNODEFICIENCIES

GATA-2 Deficiency

DiGeorge Syndrome

Wiskott-Aldrich Syndrome

Ataxia-Telangiectasia

Hyper-Immunoglobulin E Syndrome

PHAGOCYTIC CELL DISORDERS

Phagocytic Defects: Increased Apoptosis of Neutrophils

Decreased Adherence/Chemotaxis

Disorders of Leukocyte Signaling

DISORDERS IN INNATE IMMUNITY

MyD88 and IRAK-4 DEFICIENCIES

Complement Deficiencies

INTRODUCTION

Primary immune deficiency disorders (PIDDs) are disorders of the immune system that predispose individuals to infection and frequently malignancy and autoimmunity as well.¹ Most PIDDs are inherited disorders. However, in some PIDDs, such as *common variable immunodeficiency* (CVID), a family history is often lacking and a genetic cause has yet to be found. Furthermore, in some diseases, somatic mutations, not germline mutations, cause the particular disorders.² Thus, we should not limit the diagnosis of PIDD to disorders that are inherited.

Many incorrectly believe that PIDDs are rare and are diagnosed almost exclusively in children. The frequency of clinically important PIDDs is approximately 1 in 2000 individuals.³ The majority of people affected with PIDD are now adults, not children.⁴ Among the patients in the United States receiving *intravenous immune globulin* (IVIG), 23% are ages 30 to 44 years and 34% are in the 45- to 65-year age group. The increasing age of patients with PIDD is due in part to improvements in recognition, diagnosis, and treatment with a concomitant increase in survival rates.

A diagnostic evaluation for PIDD is a fundamental but often-overlooked issue in the evaluation of patients with pulmonary infections. Numerous studies indicate the importance of the early diagnosis of PIDD in reducing the morbidity and mortality associated with recurrent infections. For example, early *hematopoietic stem cell transplantation* (HSCT) (<3.5 months of age) results in dramatically improved outcome in infants with *severe combined immunodeficiency* (SCID).² Treatment with high-dose IVIG can prevent many of the infectious sequelae in patients with primary antibody deficiency states.⁵ Many routine childhood vaccines use attenuated, live organisms. Because the use of such vaccines may lead to disseminated infections in patients with antibody or cellular immunodeficiencies, these vaccines are contraindicated. Thus, the early diagno-

sis of PIDD can prevent these life-threatening infections, further supporting the contention that early detection leads to improved outcomes.

The decision to evaluate patients with pulmonary infection for primary immunodeficiencies cannot be made in the context of the pulmonary infection alone; several additional factors need to be considered (Table 92-1). In general, an evaluation of the immune system is warranted in patients with two or more radiographically documented pneumonias. However, a single infection of the lung with an opportunistic pathogen warrants an evaluation to exclude both primary and secondary immunodeficiencies. A patient with first pneumonia, but with a history of intractable sinus disease or recurrent gastrointestinal infection or with other disorders found more frequently in patients with PIDD (e.g., autoimmunity, intractable eczema, unusual facies), should also be evaluated for a PIDD. Approximately 20% of patients with CVID are diagnosed at 50 years of age or later. Therefore, older age should not be used to exclude the diagnosis of a PIDD.

Several clues in the history and clinical presentation of patients with primary immunodeficiencies suggest the type of immunologic defect present (Table 92-2). The onset of diseases associated with cellular immunodeficiencies usually begins in early infancy. Infections may be seen with opportunistic or unusual pathogens or mycobacteria; there may be disseminated viral infections or severe oral candidiasis. Diarrhea and malabsorption are common, and growth is delayed. In contrast, the onset of infections in patients with antibody deficiencies, such as *X-linked agammaglobulinemia* (XLA), is usually delayed until after 6 months, when maternal antibodies are no longer present. Recurrent and severe upper and lower respiratory tract infections are the usual mode of presentation. Complement deficiencies may present in a manner similar to antibody deficiencies or with recurrent *Neisseria* spp. infections. In contrast to patients with cellular immunodeficiencies,

growth is usually not delayed in patients with complement or antibody deficiencies.

One common misconception is that opportunistic pathogens are overwhelmingly the cause of most infections in patients with primary immunodeficiencies. In fact, many infections in immunodeficient patients are with pathogens that are common in the community; however, in patients with PID, these infections may be of unusual severity and respond poorly to therapy. For example, recurrent infections with *Streptococcus pneumoniae* are frequent in patients with several types of PID, such as antibody deficiencies; com-

plement deficiencies; Toll-like receptor signaling deficiencies (MyD88, IRAK-4); and mutations in nuclear factor- κ B essential modulator.⁶ Finally, although this section deals exclusively with PIDs, it is essential to exclude secondary immunodeficiencies or other medical conditions (e.g., lymphoproliferative disorders and malignancy, malnutrition, immunosuppressive drugs, protein-losing states, kidney failure, liver failure, heart failure, sickle cell anemia) that predispose patients to recurrent infection.

DIAGNOSTIC WORKUP

A number of readily available and inexpensive screening tests should be used in the evaluation of a patient with a possible immunodeficiency (Table 92-3).⁷ In an adult, CVID would be the most likely diagnosis, and phagocytic defects and combined immunodeficiencies only rarely present; thus, for adult patients, the following algorithm can be used for screening (Fig. 92-1). Abnormalities found in these screening tests indicate the need for additional sophisticated studies in collaboration with a clinical immunologist. The goal in the evaluation of immunodeficient patients should be to define the specific genetic abnormality whenever possible.

Table 92-1 General Criteria that May Warrant an Immunologic Evaluation

Chronic infections
Recurrent infections
Opportunistic or unusual pathogens
Unusual sites of infections
Incomplete clearing of infection
Poor response to antimicrobial therapy
Associated conditions (unusual facies, tetany, failure to thrive, intractable diarrhea, thrush, intractable eczema, autoimmunity)

Table 92-2 Examples of Primary Immunodeficiencies

Type of Immunodeficiency	Example	Mode of Presentation
Antibody	XLA, CVID	Upper and lower respiratory tract infections (encapsulated and atypical bacteria), giardiasis
T cell	DiGeorge syndrome	Abnormal facies, lymphopenia, thrush, recurrent sinopulmonary infections
Combined B cell and T cell	SCID (multiple causes)	Opportunistic infections, thrush, intractable diarrhea, failure to thrive
Cellular/complex	IFN- γ /IL-12/IL-23 axis	Atypical mycobacteria, <i>Salmonella</i> , and <i>Pseudomonas</i> infections
Phagocyte	CGD	Recurrent abscesses (<i>Staphylococcus aureus</i> , <i>Burkholderia cepacia</i> , <i>Aspergillus</i> spp.)
Complement	C5-C9	Recurrent <i>Neisseria meningitidis</i> infections

CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IFN, interferon; IL, interleukin; SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia.

Table 92-3 Screening Tests for Immune Function

Immune Function	Quantitative Assays	Functional Assays
Cellular immunity	<u>CBC with differential*</u> Flow cytometry CD3 ⁺ CD4 ⁺ CD3 ⁺ CD8 ⁺ CD16 ⁺ CD56 ⁺ FISH for 22q11 and 10p11 deletion	Cutaneous delayed hypersensitivity Enzyme assays (ADA, PNP) NK cell cytotoxicity assay
B cells	Flow cytometry CD19 ⁺ or CD20 ⁺	<u>IgG, IgA, IgM levels</u> Specific antibody response to immunization
PMN	<u>CBC with differential</u> Flow cytometry LFA-1 (CD18/CD11a) CD15	Oxidase function (NBT, DHR, chemiluminescence) Enzyme assays (MPO, G6PD) Phagocyte function Chemotaxis
Complement	C3, C4 Specific complement components Complement split products	<u>AH₅₀</u> (alternative pathway) <u>CH₅₀</u> (classical pathway)

*Preferred initial screening tests are underlined.

ADA, adenosine deaminase; CBC, complete blood count; DHR, dihydrorhodamine; FISH, fluorescence in situ hybridization; G6PD, glucose 6-phosphate dehydrogenase; Ig, immunoglobulin; LFA-1, lymphocyte function-associated antigen 1; MPO, myeloperoxidase; NBT, nitroblue tetrazolium; NK, natural killer; PMN, polymorphonuclear leukocytes; PNP, purine nucleoside phosphorylase, a key T-cell enzyme.

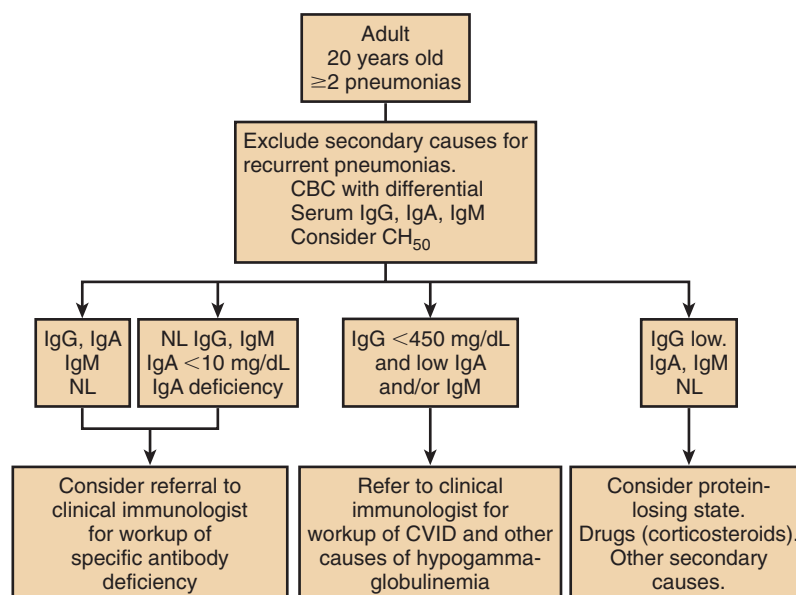


Figure 92-1 A diagnostic algorithm for an adult with possible primary immunodeficiency. In an adult, with CVID as the most common diagnosis, a screening approach is shown. It would be unusual for an adult to present with a phagocytic defect or combined immunodeficiency; thus, antibody levels, complete blood count, and complement are appropriate for initial screening. If CH_{50} is ordered, an absent CH_{50} is consistent with complement deficiency and should result in referral to the clinical immunologist, whereas a low CH_{50} is consistent with complement consumption. CVID, common variable immunodeficiency; NL, normal; R/O, rule out.

ANTIBODY DEFICIENCIES

The quantitative measurement of *immunoglobulin G* (IgG), *immunoglobulin A* (IgA), and *immunoglobulin M* (IgM) is the single best test to screen for primary antibody deficiencies.⁸ An abnormality in the level of one or more of these classes of immunoglobulins is present in the majority of patients with primary antibody deficiencies. The pattern of the levels of IgG, IgA, and IgM gives important insight into the likely etiology of the antibody deficiency. For example, clinical immunologists are frequently consulted about whether a patient on corticosteroids has a primary antibody deficiency. In steroid-induced hypogammaglobulinemia, IgG levels are usually only moderately depressed (usually > 400 mg/dL) and the magnitude of reduction reflects the dosage and duration of corticosteroid usage.⁹ IgA and IgM levels tend to be preserved. In CVID, IgG levels are usually more profoundly depressed (<400 mg/dL), IgA levels are reduced (<10 mg/dL) in 70% of patients, and IgM levels are reduced (<25 mg/dL) in more than 80% of patients.⁸ Finally, in comparison with patients with steroid-induced hypogammaglobulinemia, patients with CVID have a more profound defect in their ability to make antigen-specific antibodies following immunization.¹⁰

The enumeration of B cells, typically measured by flow cytometry using monoclonal antibodies directed against the CD19 or CD20 surface antigens, may also provide clues to the type of B-cell immunodeficiency present. In XLA and *autosomal recessive* (AR) forms of agammaglobulinemia, the numbers of B cells are usually severely reduced. In contrast, the number of B cells in CVID is frequently, but not always, normal. It is important to obtain a careful medication history because novel agents such as rituximab, a chimeric monoclonal antibody directed against CD20, can lead to profound decreases in B-cell numbers for months after treatment.

In assessing response to immunization, it is important to immunize with both a protein and *polysaccharide* (PS) antigen and to assess the response 4 to 6 weeks post immunization. The immunologic requirements to make antibodies (e.g., T-cell help, cytokine requirements) in response to immunization with a protein or PS antigen differ. Some patients with normal quantitative immunoglobulins or selective IgA deficiency exhibit a selective inability to make antibody to PS, but not to protein antigens. This immunologic defect (specific antibody deficiency) results in recurrent sinopulmonary infections and, in selected instances, may require replacement immunoglobulin therapy.

Protein antigens commonly used to assess specific antibody responses include tetanus and diphtheria toxoids. The *Haemophilus influenzae type B* (Hib) vaccine in present use conjugates the capsular *polyribose phosphate* to a protein carrier. Therefore, quantitation of antibodies to *H. influenzae* following immunization with the Hib vaccine measures competence of the immune system to make specific antibodies to a protein, not to PS antigens. Many adults have not been immunized to Hib, making the Hib vaccine particularly useful in the evaluation of this group of patients.

PS antigens used to test antibody responses are available in two unconjugated vaccines: the pneumococcal PS and *Neisseria meningitidis* vaccines. (Some pneumococcal vaccines are conjugated to a protein carrier and do not measure a response to the PS antigen [e.g., Prevnar]). When using the pneumococcal vaccine, the measurement of antibody responses to several (12 or more) capsular antigens is indicated. There is considerable controversy about what constitutes a normal response to the pneumococcal vaccine, and a clinical immunologist should make the interpretation of specific antibody responses.^{11,12} Finally, children younger than 2 years of age frequently do not make antibody responses to PS antigens. Thus, the use of PS vaccines to

diagnose antibody-deficient states in this age group is not indicated.

CELLULAR IMMUNODEFICIENCY

Many patients with impaired cellular immunity will have either reduced T-cell numbers, abnormal T-cell function, or both (see Table 92-3). T-cell numbers are easily screened by flow cytometry. The CD3 antigen measures the total number of T cells, whereas CD4 and CD8 antigens are present on the T-helper and T-cytotoxic subsets, respectively. T-cell function is easily assessed by testing cutaneous *delayed-type hypersensitivity* (DTH). In the DTH test, a small amount of an antigen is injected into the dermis and a positive reaction is indicated by induration (>2 mm) 48 to 72 hours later at the site of the injection. Antigens such as tetanus toxoid, *Candida*, and *Trichophyton* are frequently used because most individuals will have had a prior immune response to these antigens. However, DTH responses are frequently absent in normal infants, and in vitro assays of T-cell function are indicated in this group of patients.¹³ The measurement of *natural killer* (NK) cell numbers (CD16⁺/CD56⁺) and function is indicated in the evaluation of infants for possible SCID or of patients with recurrent, severe herpesvirus infection. The pattern of abnormalities in the numbers of specific lymphocyte subpopulations (T cells, NK cells, B cells) is helpful in identifying the molecular abnormality in infants with SCID (Table 92-4).

COMPLEMENT DEFICIENCIES

The screening tests for complement deficiency states associated with increased infections are the CH₅₀ and AH₅₀, which measure the integrity of the classical and alternative pathways of complement activation, respectively¹⁴ (see Table 92-3). The CH₅₀ measures the volume (or dilution) of serum required to lyse 50% of the sample erythrocytes; AH₅₀ is a similar measure testing the alternative pathway. Abnormalities in CH₅₀ or AH₅₀ could be due to inappropriate activation and consumption of complement or to deficiencies in individual components of complement. Many times these possibilities can be distinguished by the measurement of two or more individual components of the classical or alternative complement pathway and the measurement of complement split products. Complement *consumption* is indicated by low levels of more than one component of complement,

which may vary over time, and by the elevation of complement split products. In contrast, complement *deficiency* states show fixed, depressed levels of individual members of the complement pathway with normal levels of complement split products.

PHAGOCYTE DEFICIENCIES

The initial screening test for phagocytic defects includes a complete blood count, with quantitation of leukocyte number and morphology (see Table 92-3). The *dihydrorhodamine* (DHR) test has replaced the *nitroblue tetrazolium* (NBT) test in most centers to diagnose defects in the generation of superoxide, such as is seen in *chronic granulomatous disease* (CGD).¹⁵ Advantages to the DHR test include its ease, rapidity, and reproducibility, along with the capacity to detect CGD carrier states. Both the NBT and DHR tests measure the ability of phagocytes to generate superoxide free radicals. In the DHR test, phagocytes are loaded with a fluorescent dye (DHR) and activated with phorbol myristate acetate. Activated phagocytes then produce superoxide free radicals that reduce DHR, leading to a change in fluorescence that is quantitated by flow cytometry. Other functional assays for phagocytes include enzyme assays for myeloperoxidase and glucose 6-phosphate dehydrogenase, chemotaxis assays, phagocytic tests, and bactericidal assays. Abnormalities in the adhesion molecules CD18 and CD15 that result in leukocyte adhesion deficiency 1 and leukocyte adhesion deficiency 2, respectively, are detected by flow cytometry.

DEFICIENCY IN BOTH CELLULAR IMMUNITY AND ANTIBODY PRODUCTION

SEVERE COMBINED IMMUNODEFICIENCY

SCID is a syndrome that encompasses a variety of molecular defects that result in absent or severely impaired T-cell and B-cell number and function.^{16,17} One commonly used method to classify SCID is based on whether the molecular defects decrease the numbers of T, B, and/or NK cells (see Table 92-4).

The molecular defects that lead to SCID include mutations that lead to abnormalities in cytokine signaling (e.g., the common γ chain [γ c] of the *interleukin* [IL]-2 receptor; *Janus activating kinase 3* [JAK3], or IL-7 receptor) and T-cell receptor signaling (e.g., CD45, ZAP-70, CD3y, CD3e, CD3C); defective T-cell and B-cell receptor gene recombination (e.g., *RAG1*, *RAG2*); defective nucleotide salvage pathway (*adenosine deaminase* [ADA] deficiency); and defects in the expression of major histocompatibility complex class I or class II molecules. X-linked SCID caused by the mutation in the common γ c of the IL-2 receptor is the most common form of SCID, accounting for approximately 50% of all cases. The γ c of the IL-2 receptor is utilized by several other cytokine receptors, including the receptors for IL-4, IL-7, IL-11, IL-15, and IL-21. Consequently, the immunodeficiency due to mutation of the γ c is due to the combined effects of loss of function in all of these cytokine receptors.

Table 92-4 Common Etiologies of Severe Combined Immunodeficiencies

Form of SCID	Prevalence	Absent Cell Type	Inheritance
Common γ chain IL-2 receptor deficiency	45%–50%	T/NK	X-linked
IL-7 receptor	10%	T	AR
ADA deficiency	15%	T/B/NK	AR
RAG1/RAG2	5%–8%*	T/B	AR
JAK3	5%–10%	T/NK	AR

*Total prevalence of patients with mutations in either *RAG1* or *RAG2* gene. ADA, adenosine deaminase; AR, autosomal recessive; JAK, Janus activating kinase; SCID, severe combined immunodeficiencies.

Atypical forms of SCID may also result from mutations of genes associated with classical SCID that are *hypomorphic*, meaning that the mutation leads to a protein with reduced function. One such example is the Omenn syndrome, whose clinical manifestations include severe skin disease (erythroderma, granuloma, and desquamation), hepatosplenomegaly, lymphadenopathy, and high IgE levels. Additionally, there are other single gene defects that can lead to combined immunodeficiencies such as Wiskott-Aldrich syndrome, DiGeorge syndrome, Ataxia-telangiectasia, X-linked lymphoproliferative disorder, and some forms of hyper-IgM syndrome. For purposes of this chapter, these latter diseases are discussed separately from SCID.

The clinical presentation of SCID is characterized by severe infections, most commonly of the respiratory and gastrointestinal tract in early infancy. Infections are caused by common and opportunistic pathogens, and disseminated infections are frequent. Other common manifestations of the syndrome include oral thrush, persistent diarrhea, interstitial pneumonitis, impaired growth, and the absence of lymph nodes. Engraftment of maternal T cells in an infant with SCID can lead to graft-versus-host disease. The prompt treatment of infection, administration of IVIG, and prophylaxis against *Pneumocystis jirovecii* are indicated until HSCT can take place. In the event blood transfusions are necessary, only irradiated, *cytomegalovirus* (CMV)-negative blood should be used. No live virus vaccinations should be given to infants with known or suspected SCID.

Early diagnosis and treatment by HSCT (<3.5 months of age) of SCID leads to a markedly improved prognosis.² Therefore, it is incumbent on the physician to make a prompt diagnosis of SCID. Several U.S. states, starting with Wisconsin in 2008, now screen all newborns for SCID.^{17a,17b} The disease has been added to the Uniform Panel of newborn screening tests recommended by the U.S. government.^{18,19} In the absence of newborn screening, the lack of a thymic shadow on chest radiograph and severe lymphopenia (<2500/ μ m) in an infant with recurrent infections should prompt further studies to exclude the diagnosis of SCID. The diagnosis of SCID is confirmed by enumerating lymphocytes and subsets of naïve T cells, B cells, and NK cells by flow cytometry and detecting a deficiency in the capacity of T cells to proliferate to mitogens.

HSCT is the preferred treatment for SCID, except for SCID due to ADA deficiency.^{19a} For SCID due to ADA deficiency, the administration of polyethylene glycol-ADA is an alternative treatment. In addition, for X-linked SCID and SCID due to ADA deficiency, gene therapy has been successfully used.^{20,21} However, the retroviral vectors used in these earlier studies led to insertional mutagenesis with activation of the proto-oncogene LMO-2 leading to $\gamma\delta$ T-cell leukemia in some patients.^{22,23} Trials of gene therapy for SCID using lentiviral vectors, which are safer in preclinical studies, are ongoing.^{24,25,25a}

ANTIBODY DEFICIENCIES

IMMUNOGLOBULIN A DEFICIENCY

The prevalence of IgA deficiency varies among different ethnic groups, but the overall prevalence is approximately

1 in 400 live births.^{26,27} The etiology of IgA deficiency remains obscure. Rarely, IgA deficiency may evolve into CVID, and families may develop both IgA deficiency and CVID, suggesting a common genetic basis.²⁸ Medications, in particular anticonvulsants, infrequently cause IgA deficiency or panhypogammaglobulinemia, and immunoglobulins may normalize with discontinuation of the drug.

There is considerable controversy as to whether IgA deficiency alone predisposes people to infection.^{26,29} Most patients with IgA deficiency do not have increased frequency of infections and are often discovered during an evaluation for problems unrelated to infection. However, some patients with IgA deficiency have recurrent infections, predominantly respiratory tract infections.³⁰ Whether IgG subclass deficiency and/or deficiencies in mannose-binding lectin identify a subgroup of patients with IgA deficiency who are more prone to infection is not clear.³¹ Unlike patients with more severe forms of antibody deficiency such as CVID or X-linked agammaglobulinemia, replacement therapy with IVIG is not warranted with isolated IgA deficiency. In patients with IgA deficiency and concomitant IgG subclass deficiency who have recurrent and persistent respiratory tract infections, determination of the antibody response following vaccination should be used to ascertain if IVIG therapy is warranted.³²

Clinical manifestations of IgA deficiency are highly variable. Infectious complications of IgA deficiency include recurrent upper (otitis media, sinusitis) and lower respiratory tract infections.³⁰ Gastrointestinal tract infections, in particular recurrent giardiasis, may be present. The prevalence of atopic diseases (asthma, allergic rhinitis, eczema) and autoimmune diseases (systemic lupus erythematosus, celiac disease, rheumatoid arthritis) is increased in patients with IgA deficiency.

Serologic studies in IgA deficiency may be subject to false-positive and false-negative results due to the presence of heterophile antibodies.³³ Heterophile antibodies react to the immunoglobulins of other species and may be increased in IgA-deficient patients due to increased exposure of antigens at the gut mucosa to the systemic circulation. The diagnosis of celiac disease in patients with IgA deficiency is problematic because the most specific serologic assay for celiac disease, IgA anti-tissue transglutaminase, is absent in IgA-deficient patients. Therefore, other assays should be performed in the laboratory assessment of celiac disease in IgA-deficient patients.

X-LINKED AGAMMAGLOBULINEMIA

XLA (Bruton agammaglobulinemia) is a primary antibody deficiency with an estimated prevalence of 1 in 190,000 male live births.³⁴ Mutations in the gene for *Bruton tyrosine kinase* (Btk) are responsible for this immunodeficiency.³⁵ Btk is required for B-cell receptor signaling, playing a key role in the phosphorylation of phospholipase $C\gamma 2$. Btk function is essential for the survival and differentiation of immature B cells. Consequently, nearly all patients with XLA have a marked deficiency in B cells (<2% of lymphocytes) and profound panhypogammaglobulinemia. XLA accounts for approximately 85% of inherited forms of agammaglobulinemia due to defects in early B-cell development, with AR forms of antibody deficiency accounting for the

remainder.³⁵ The clinical manifestations of the AR forms of agammaglobulinemia are similar to XLA.

In addition to B cells, Btk is expressed on myeloid cells and platelets but not on NK cells or T cells. Consequently, T-cell function is normal in XLA, which contrasts with some other antibody deficiency disorders such as CVID or some forms of the hyper-IgM syndrome in which abnormalities in cellular immunity are frequently present. Up to 25% of patients with XLA present with neutropenia, which may contribute to the severity of infection.³⁶

Small or absent tonsils and lymph nodes are the only characteristic physical findings in XLA. The vast majority of patients with XLA have recurrent upper (otitis media; sinusitis) and lower respiratory tract infections, with more than 50% of patients having recurrent infections by 1 year of age and nearly all patients symptomatic by age 5. The most common pathogens causing pneumonia are encapsulated bacteria (*S. pneumoniae* and *H. influenzae*).³⁴ Respiratory tract infections due to atypical bacteria such as *Mycoplasma pneumoniae* or *Ureaplasma urealyticum* are also frequently encountered. Gastrointestinal tract infections develop in nearly one quarter of patients and are most commonly due to *Giardia lamblia*, although bacteria (*Salmonella* spp., *Shigella* spp., *Campylobacter fetus*, *Helicobacter pylori*) and viruses (*Rotavirus*, enteroviruses) are also frequently isolated. Disseminated infections that include encephalitis due to infection with enteroviruses, in particular echovirus, were a major cause of mortality in patients with XLA. However, these infections appear to be declining with use of high-dose immunoglobulin replacement therapy.³⁴

The pulmonary complications of XLA continue to be a major cause of morbidity and mortality and include bronchiectasis and cor pulmonale.³⁴ Complete pulmonary function tests (if possible) and a *high-resolution computed tomography* (HRCT) scan of the chest are indicated in the initial evaluation of these patients. High-dose IVIG has been shown to decrease pulmonary infections in these patients but may not prevent the progression of bronchiectasis. Bronchiectasis, if detected, should be treated with daily pulmonary hygiene (e.g., inhaled β -agonists, hypertonic saline, chest physiotherapy) and aggressive antimicrobial therapy for intercurrent pulmonary infections. The efficacy of rotating antibiotics or chronic antimicrobial therapy in patients with bronchiectasis and immunodeficiency is unknown.

IVIG and *subcutaneous infusion of gamma globulin* (SCIG) are the most commonly used forms of antibody replacement for the treatment of profound antibody deficiencies such as XLA and CVID. Compared with IVIG, SCIG has far fewer infusion-related adverse reactions.³⁷ High doses of gammaglobulin (400 to 600 mg/kg/month) are superior in preventing infections compared with “conventional” doses of IVIG (100 to 150 mg/kg), and the optimal dose should be based on prevention of infection rather than level of IgG.^{38,39} Intercurrent sinopulmonary infections should be aggressively treated with appropriate antimicrobial therapy to include coverage of common encapsulated bacteria, as well as coverage of atypical bacterial pathogens (*Mycoplasma* spp., *Ureaplasma*).⁴⁰

A common mistake in managing patients with profound antibody deficiencies (e.g., XLA, CVID) is the inappropriate use of serologic assays in the diagnosis of infectious disorders.

With the exception of IgA and IgG subclass deficiency, patients with antibody deficiency do not make specific antibodies in response to exogenous antigens. Therefore, the use of diagnostic studies to detect specific antibodies against pathogens is unreliable and, if positive, usually reflects antibodies present in the IVIG used to treat such patients. Diagnostic studies that detect microbial antigens or nucleic acids (polymerase chain reaction assays) from the pathogen must be used in place of serologic assays.

COMMON VARIABLE IMMUNODEFICIENCY

CVID, also known as acquired hypogammaglobulinemia, is a primary immunodeficiency affecting approximately 1:20,000 to 1:50,000 live births.⁴¹ CVID is a clinical syndrome representing a family of disorders that exhibit a common phenotype. Although highly variable, the mean onset of symptoms in patients with CVID is in the third decade of life. There remains a considerable delay, up to 10 years, between the onset of symptoms and the diagnosis of CVID.^{8,42,43} Unlike in XLA, T-cell abnormalities are common in patients with CVID and contribute to the more protean clinical manifestations of this disease.⁸ The diagnosis of CVID should be considered in any person older than age 4 with recurrent respiratory tract infections (i.e., two or more confirmed pneumonias).

The etiology in the vast majority of cases of CVID is unknown. Heterozygous mutations in the gene encoding TACI (a *tumor necrosis factor* [TNF] receptor family member involved in isotype switching in B cells) are found in approximately 5% to 10% of patients and markedly increase the risk of developing CVID while biallelic mutations always lead to the development of CVID.⁴⁴⁻⁴⁷ Mutations in *inducible T-cell co-stimulator* (ICOS), *CD19*, *CD20*, *CD21*, *CD81*, and *BAFFR* are other monogenic causes of CVID in a small percentage of patients.⁴⁸⁻⁵² Collectively, mutations or polymorphisms of these genes account for less than 10% to 15% of all cases of CVID.

The laboratory evaluation of patients with CVID demonstrates the complex nature of the disease.⁸ The definitive diagnosis of CVID requires the demonstration of a low serum level of IgG (usually < 450 mg/dL), low serum level of IgA and/or IgM, impaired capacity to make specific antibodies in response to immunization or infection, and the exclusion of other primary or secondary antibody deficiencies. B-cell numbers are variable in CVID and, if reduced, may indicate a poor prognosis.⁸ B-cell subset analysis by flow cytometry is valuable in predicting risk to develop certain complications of CVID. Low numbers of switched memory B cells (CD27⁺, IgM⁻, IgD⁻) in the peripheral blood are frequently found in patients with splenomegaly and systemic granulomatous disease involving the lungs.⁵³⁻⁵⁶ T-cell abnormalities are found in approximately 40% of patients and include anergy, T-cell lymphopenia, and poor in vitro proliferative responses to mitogens and antigens.

Nearly all patients present with recurrent upper or lower respiratory tract infections, including bronchitis, sinusitis, otitis media, and pneumonia. Common pathogens include encapsulated (*H. influenzae*, *S. pneumoniae*) or atypical (*Mycoplasma* spp.) bacteria.^{8,40,57} Pulmonary infections can also be caused by gram-negative rods, in particular in patients with long-standing CVID or impaired cellular

immunity. Opportunistic infections develop in less than 10% of patients.³⁹ Because patients with CVID appear to be particularly susceptible to infections with atypical bacteria such as *Mycoplasma* spp. and *Ureaplasma* spp., antimicrobial therapy of respiratory tract infections that is effective against these organisms should be used.⁴⁰ Apart from respiratory tract infections, joint and bone infections due to these organisms have also been reported. Gastrointestinal tract infections with pathogens similar to those found in XLA (*Campylobacter jejuni*, *Salmonella* spp., *G. lamblia*) are also common.⁸ The prevalence of hepatitis is increased in CVID (in $\approx 12\%$ of patients). The prognosis from hepatitis C is poor and may be rapidly progressive in patients with CVID.

The mortality of CVID due to common infectious pathogens has declined with the increased use of high-dose immunoglobulin replacement.⁵ Complications such as chronic lung disease, malignancy, liver, and gastrointestinal tract disease are now the most common risk factors for early mortality.⁵⁶ Although patients with CVID are unable to make antibodies to foreign antigens, they exhibit an increased propensity to make autoantibodies. Consequently, the prevalence of autoimmune disorders, in particular *idiopathic thrombocytopenic purpura* (ITP) and *autoimmune hemolytic anemia* (AHA) is increased.^{8,58} Oral corticosteroids, the use of immunomodulatory dosages of IVIG (2 g/kg per month), and rituximab have been used to treat ITP and AHA in patients with CVID.⁵⁹

Patients with CVID are at high risk for developing malignancy. In particular, the prevalence of non-Hodgkin lymphomas and gastric carcinoma are increased in CVID and are a major cause of morbidity and mortality in this disorder.⁶⁰ Careful periodic examination of the lymph nodes and spleen is important because patients with CVID also frequently have adenopathy and splenomegaly that are nonmalignant in nature. The use of periodic abdominal *computed tomography* (CT) scans to assess spleen size and/or the presence of intra-abdominal and retroperitoneal adenopathy, along with upper and lower endoscopic evaluation for gastrointestinal symptoms, may also be useful.

The pulmonary disorders associated with CVID are complex and a major cause of mortality.⁶¹⁻⁶⁵ Bronchiectasis is the most common pulmonary disorder, seen in more than 20% of patients. It is not clear whether high-dose gamma globulin replacement therapy can prevent the development of bronchiectasis in patients with CVID.⁴³ On the basis of studies of patients with bronchiectasis without immunodeficiency, bronchiectasis in patients with CVID is managed with standard approaches including mobilization of pulmonary secretions through the use of medications such as hypertonic saline or β_2 -agonists combined with chest physiotherapy and the chronic administration of macrolides.⁶⁶⁻⁶⁸ Bronchiolitis obliterans organizing pneumonia (now termed *cryptogenic organizing pneumonia*) has also been described and appears to respond to corticosteroid therapy.^{69,70}

Diffuse interstitial lung disease, including granulomatous lung disease, *lymphocytic interstitial pneumonia* (LIP), follicular bronchiolitis, and cryptogenic organizing pneumonia (bronchiolitis obliterans with organizing pneumonia), develops in approximately 10% to 25% of patients with CVID; these diffuse interstitial lung diseases are refractory to IVIG therapy.^{61,62-65,71} The presence of granuloma-

tous lung disease led some to believe that this represents a form of sarcoidosis.⁷² Common features shared with sarcoidosis include the systemic nature of the disease, frequent presence of mediastinal and hilar adenopathy, and noncaseating granulomas in the lungs and other organs. However, it now appears likely that this lung disorder represents a distinct disease entity.^{61,65} Unlike in sarcoidosis, both granulomatous and lymphoproliferative histopathologic patterns (LIP, follicular bronchiolitis, and lymphoid hyperplasia) often appear together. Thus, the term *granulomatous-lymphocytic interstitial lung disease* (GLILD) has now been used to characterize the pulmonary disorder in CVID.⁵¹ In comparison with sarcoidosis, GLILD exhibits a lack of spontaneous remission of lung disease; a poor response to corticosteroid therapy; panhypogammaglobulinemia with low numbers of switched memory B cells; a high prevalence of autoimmune disease, in particular ITP; a history of recurrent infections; and large areas of organizing pneumonia on biopsy.^{72a} Patients with GLILD and CVID more frequently have hepatosplenomegaly, typically have diffuse adenopathy, and are at increased risk for developing non-Hodgkin lymphoma.^{61,65} HRCT of the chest is indicated in the evaluation of patients with GLILD and demonstrates numerous abnormalities, including mediastinal adenopathy; diffuse ground-glass, nodular opacities; and areas of consolidation. The parenchymal abnormalities in GLILD are typically in the lower lung zones, which also contrasts with sarcoidosis.⁷³

The etiology of GLILD is unknown. The overproduction of TNF- α may contribute to the granulomatous disease in these patients.⁷⁴ Case reports have demonstrated that the use of TNF- α antagonists may lead to regression of granulomatous disease in patients with CVID, lending further support to this hypothesis.⁷⁵ Limited anecdotal experience suggests that the GLILD may also respond to low-dose cyclosporine therapy.⁷⁶ In a retrospective study of seven patients, the use of rituximab and azathioprine improved the radiographic abnormalities and pulmonary function of patients with CVID and GLILD without an increased incidence of infection.⁷⁷ This approach, although promising, needs to be validated in a properly controlled prospective study.

The combination of CVID in conjunction with a thymoma is known as Good syndrome.^{78,79} Whether this disorder is distinct from CVID or represents another manifestation of the disease is unclear. The thymoma is often not apparent on routine chest radiograph. Immune evaluation frequently demonstrates low numbers of CD4 T cells and B cells. Autoimmune disorders and opportunistic infections appear to be more common in this group of patients, and diffuse pan-bronchiolitis has also been described.⁸⁰ Resection of the thymoma is recommended, although this will not resolve the immunodeficiency or autoimmunity.⁷⁸

Due to the complexity of the pulmonary disease, patients with CVID should undergo periodic chest radiographs, full pulmonary function tests, and HRCT scans of the chest. In the diagnostic evaluation of patients with GLILD or other forms of interstitial lung disease, it is essential to obtain sufficient tissue to exclude the diagnosis of lymphoma or cryptogenic organizing pneumonia. Therefore, we perform video-assisted thoracoscopic lung biopsies in the evaluation of patients with diffuse interstitial lung disease and CVID.⁷⁷

SPECIFIC ANTIBODY DEFICIENCY

Specific antibody deficiency (SAD) is a primary antibody deficiency disorder that is characterized by normal levels of IgG, IgA, and IgM but an inability to make specific antibodies, most commonly in response to PS antigens such as Pneumovax.^{81,82} Patients with specific antibody deficiency present with recurrent sinopulmonary infections, similar to other forms of hypogammaglobulinemia. The diagnosis of SAD is made by measuring an absence of specific antibody responses following immunization with PS vaccines, most commonly the unconjugated pneumococcal vaccine. Cellular immunity is normal in this disorder. The initial treatment of SAD is similar to IgA deficiency; however, IVIG may be indicated in patients with SAD who have recalcitrant sinopulmonary infections and fail more conservative treatment.

IMMUNOGLOBULIN G SUBCLASS DEFICIENCY

IgG subclass deficiency is defined by normal total serum IgG levels with a low level of one or more IgG subclasses. There are four isotypes of IgG in humans: IgG1, IgG2, IgG3, and IgG4. The predominant subclass is IgG1, accounting for more than 60% of the total IgG. In some patients evaluated for recurrent sinopulmonary infections, low levels of one of the IgG subclasses are found. However, the significance of IgG subclass abnormality is unclear.^{83,84} Some believe that isolated IgG subclass deficiencies predispose patients to recurrent sinopulmonary infections. In contrast, IgG subclass deficiencies, including genetic deletions of IgG subclass loci, are well documented in healthy individuals.⁸⁵ Because the clinical significance of isolated IgG subclass deficiencies is unclear, the measurement of IgG subclasses is not warranted in the initial evaluation of patients with recurrent sinopulmonary infections. In patients with an isolated IgG subclass deficiency and recurrent infections, the decision to use IVIG should be based on antibody responses following vaccination.

X-LINKED LYMPHOPROLIFERATIVE SYNDROME

X-linked lymphoproliferative syndrome (XLP), or Duncan disease, is a rare primary immunodeficiency characterized by an extreme sensitivity to infection with *Epstein-Barr virus* (EBV). Approximately 80% of XLP (XLP-1) is caused by mutations in the adaptor protein gene *SH2D1A* (also known as *SAP*; the gene for *slam-associated protein*).^{86,87} The *SH2D1A* adaptor protein affects multiple intracellular signaling pathways in several different lymphocyte subpopulations, including T cells, B cells, and NK cells, a property that leads to the complex immunologic abnormalities seen in these patients. Mutations in the *X-linked inhibitor of apoptosis* gene (*XIAP*) account for the remainder of patients with XLP (XLP-2), which results in premature apoptosis of lymphocytes in response to a variety of stimuli.⁸⁷ Patients with XLP have a unique predisposition to infection with EBV, an infection that triggers the immunodeficiency in the vast majority of cases. Approximately 60% of patients with XLP present with overwhelming EBV infection leading to hemophagocytic lymphohistiocytosis. Therefore, the diagnosis of XLP should be considered in males with fulminant EBV

infections. The clinical phenotypes of XLP-1 and XLP-2 overlap with the exception that lymphoma is seen only in XLP-1 and splenomegaly is frequently the first clinical manifestation in XLP-2.^{88,89} Lymphomas or hypogammaglobulinemia develops following EBV infection in approximately 30% of patients with XLP-1. The only definitive therapy for XLP is HSCT,^{90,91} although IVIG is commonly used in an effort to prevent infections.

HYPER-IMMUNOGLOBULIN M SYNDROME

Hyper-IgM syndrome (HIGM) is a descriptive term that reflects a common laboratory abnormality (high serum IgM level with low serum IgA and IgG levels) found in several otherwise dissimilar types of immunodeficiencies (Table 92-5). Despite the name, high levels of IgM are inconsistently found in all forms of hyper-IgM syndrome.^{92,93} Furthermore, many believe that grouping these distinct immunodeficiencies together, some of which are intrinsic B-cell abnormalities, whereas others are complex combined cellular and humoral immunodeficiencies, leads to diagnostic confusion and is fundamentally flawed. Nevertheless, the classification remains widely used despite the obvious drawbacks. Although we group HIGM under “predominantly antibody deficiencies,” only mutations in *activation-induced cytidine deaminase* (*AICDA*)⁹⁴ or *uracil nucleotide glycosylase* (*UNG*)⁹⁵ result in primary immunodeficiencies that are largely due to antibody deficiency. The other forms of HIGM are complex cellular and humoral immunodeficiencies.

X-LINKED HYPER-IGM SYNDROME

The classic, *X-linked form of HIGM* (XHIGM), which accounts for approximately two thirds of cases, is due to a mutation in the *CD40 ligand* (*CD40LG*) gene.^{92,96} *CD40L* is inducibly expressed on activated CD4 T cells and interacts with *CD40*,

Table 92-5 Etiologies of Hyper-IgM Syndrome

Mutation	Inheritance	Clinical Phenotype
<i>CD40LG</i>	X-linked	Abnormal cellular immunity, neutropenia in 50%, early onset, recurrent sinopulmonary infections, <i>Pneumocystis jirovecii</i> pneumonia, chronic diarrhea due to <i>Cryptosporidium</i> infection, diarrhea, inflammatory bowel disease, autoimmunity
<i>CD40</i>	Autosomal recessive	Similar to <i>CD40LG</i> mutation
<i>NEMO</i> (<i>IKK-γ</i>)	X-linked	Impaired cellular immunity, variable serum levels of IgM or IgA, ectodermal dysplasia (most), recurrent pyogenic infections, viral infections, mycobacterial infections
<i>AICDA</i> or <i>UNG</i>	Autosomal recessive	Impaired humoral immunity, normal cellular immunity, later age of onset than other types of hyper-IgM syndrome, increased autoimmunity and lymphadenopathy
Unknown	Variable	Similar to <i>AICDA/UNG</i> mutations

AICDA, activation-induced cytidine deaminase; *AR*, autosomal recessive; *Ig*, immunoglobulin; *UNG*, uracil nucleotide glycosylase; see text for other abbreviations.

which is expressed on the surface of B cells. The interaction of CD40 on B cells with CD40L on activated T cells in conjunction with specific cytokines (IL-4) is required for immunoglobulin class switching. Consequently, mutations in *CD40LG* (or *CD40*) result in a failure to class switch, leading to defective production of the later immunoglobulin isotypes (IgG, IgA, immunoglobulin E [IgE]) and to persistence of IgM. CD40 is also expressed on monocytes and dendritic cells. The lack of CD40L T-cell interaction with CD40 on monocytes and dendritic cells also contributes to defective cellular immunity.⁹⁷ Mutations within the *CD40* gene are a rare cause of HIGM with a clinical phenotype similar to that of XHIGM. Serum levels of IgG are consistently low, and serum levels of IgA are reduced in the majority of patients. However, serum levels of IgM are inconsistently high in approximately 50% of patients.⁹² Antibody responses to immunization show a weak IgM response, without development of IgG- or IgA-specific responses and the absence of immunologic memory. The numbers of switched memory B cells (CD27⁺, IgD⁻, IgM⁻) are extremely low. Neutropenia is found in approximately 50% of patients and may respond to treatment with *granulocyte colony-stimulating factor* (G-CSF).

Patients with XHIGM have recurrent infections beginning early in life. More than half of patients with XHIGM are diagnosed by age 1 and nearly all by age 4. Pneumonia, frequently caused by infection with *P. jirovecii*, is common, seen in up to 80% of patients. Sinusitis, otitis media, and other respiratory tract infections are frequent. Intractable diarrhea, sometimes due to infection with *Cryptosporidium* or more frequently idiopathic, develops in nearly one third of patients. *Cryptosporidium* infection is also a major cause of sclerosing cholangitis in these patients. Infection of the central nervous system (encephalitis, meningitis), frequently due to infection with echovirus, is a major cause of morbidity and mortality. Treatment of XHIGM includes IVIG, prophylaxis against *P. jirovecii*, G-CSF for neutropenia, and consideration for HSCT.⁹⁸

Mutations of NF- κ B Essential Modifier

Hypomorphic mutations within the *NF- κ B essential modifier* (*NEMO*) gene, an X-linked gene, cause an immunodeficiency characterized by recurrent pyogenic infections, increased susceptibility to mycobacterial infections, and variable B-cell and T-cell abnormalities.^{99,100} *NEMO*, also known as IKK- γ , is part of the *I κ B kinase* (IKK) complex. IKK is responsible for phosphorylating the inhibitor of NF- κ B (I κ B), thereby releasing NF- κ B and allowing for its nuclear translocation. The protean immunologic and clinical manifestations due to mutations in *NEMO* reflect the importance of NF- κ B in multiple biologic processes. Approximately 80% of patients with mutations in *NEMO* have ectodermal dysplasia (abnormal teeth, decreased numbers of sweat glands, fine hair, frontal bossing). The ectodermal dysplasia in these patients is due to the inability of the ectodysplasin A receptor to induce the activation of NF- κ B. The susceptibility to mycobacterial infection is likely due to an inability of CD40 ligation to activate the NF- κ B pathway, leading to deficient IL-12 production by monocytes and dendritic cells and deficient *interferon* (IFN)- γ production by T cells and NK cells.¹⁰¹

Common immunologic screening tests of immune function may be normal in patients with *NEMO* deficiency. For

example, hypogammaglobulinemia or decreased specific responses to vaccination are found in approximately 60% of patients and high serum level of IgM in only 15% of patients. NK cell function has been reported to be abnormal in all patients with mutations in *NEMO* and may be a reasonable adjunctive screening test for this disorder.^{100,102}

Patients with *NEMO* mutations have severe infections usually beginning early in life. Common sites of infection include the lung, sinuses, middle ear, skin, and deep tissues (abscesses), blood (septicemia), gastrointestinal tract, and central nervous system. Pyogenic infections, frequently due to *Staphylococcus aureus*, *S. pneumoniae*, and *H. influenzae*, are seen in nearly 90% of patients. Mycobacterial infections (pneumonia, cellulitis, lymphadenitis, osteomyelitis) are seen in over 40% of patients and are usually caused by *Mycobacterium avium-intracellulare*. Severe viral infections (encephalitis, gastroenteritis, viremia) develop in approximately 20% of patients. Herpesviruses (herpes simplex virus, CMV) and adenoviruses are the most frequent viral pathogens. Opportunistic infections due to *P. jirovecii* or fungi develop in 10% of patients. Autoimmune disease—in particular, inflammatory colitis—afflicts approximately 20% of patients and can lead to intractable diarrhea. Treatment of patients with *NEMO* mutation frequently includes replacement gamma globulin and antimicrobial prophylaxis (*Pneumocystis*, mycobacteria). HSCT has had variable success in treating this disorder.¹⁰³

Mutations in *AICDA* or *UNG*

Mutations in *AICDA*⁹⁴ or *UNG*⁹⁵ are causes of AR forms of hyper-IgM. *AICDA* and *UNG* are essential for class switch recombination.¹⁰⁴ Hence, mutations in *AICDA* or *UNG* result in high serum levels of IgM, with low serum levels of IgG and IgA. Patients with mutations in either *AICDA* or *UNG* have a similar clinical phenotype with impaired humoral immunity and intact cellular immunity,¹⁰⁵ resulting in recurrent upper and lower respiratory tract infections and gastrointestinal tract infections. Lymphadenopathy is frequent, and autoimmunity (AHA and ITP) develops in approximately 20% of patients.

COMBINED IMMUNODEFICIENCIES OR SYNDROMIC IMMUNODEFICIENCIES

GATA-2 DEFICIENCY

An autosomal dominant inherited deficiency in *GATA2* underlies a unique combined immunodeficiency.^{106-112,112a} This rare disorder is also known as “dendritic cell, monocyte, B and NK cell deficiency,” familial myelodysplasia/leukemia with lymphedema, or MonoMac (monocytopenia with *M. avium* complex).

As the many names illustrate, the clinical manifestations, which usually present in adolescence or adulthood, are diverse. The immunologic features include a loss of dendritic cells, monocytes, NK cells, and B cells. Patients may develop pulmonary alveolar proteinosis not associated with anti-*granulocyte-macrophage* (GM)-CSF antibodies. Opportunistic

infections with *nontuberculous mycobacteria* (NTM), usually *M. avium* complex, are common. Infection with human papillomaviruses leads to warts and increased carcinomas in situ and cervical carcinoma. The bone marrow typically shows cytogenetic abnormalities, fibrosis, megakaryocyte dysplasia, and cytopenias; leukemia may develop. The monocytopenia may precede the clinical manifestations for years. HSCT is the only known cure for the disorder.¹¹³

DIGEORGE SYNDROME

DiGeorge syndrome (DGS), also known as 22q11.2 deletion syndrome or velocardiofacial syndrome, is one of the most common primary immunodeficiencies, found in approximately 1 in 3000 live births. The vast majority of patients with DGS have hemizygous deletion of varying degrees in chromosome 22q11.2, with rare cases due to deletion of 10p13. The molecular basis for many of the clinical manifestations of DGS appears to be deletions or mutations in *TBX1*, a T-box transcription factor important in embryonic development.¹¹⁴ Background genes are also thought to contribute to the phenotype in DGS because patients with identical deletions of 22q11.2 may have markedly different clinical phenotypes. Patients with DGS exhibit a characteristic facies that includes hypertelorism (wide spacing of the eyes), saddle nose, shortened philtrum, and low-set ears.¹¹⁵ Other common features of DGS include hypoplasia of the thymus and parathyroid glands, immunodeficiency, autoimmunity, cardiac abnormalities, velopharyngeal insufficiency, speech delay, developmental delay, and behavioral and psychiatric problems. Nearly 90% of infants diagnosed with DGS have cardiac abnormalities, and screening for DGS should be considered in an infant with any form of congenital heart disease, especially for those forms associated with DGS such as interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, and anomalous aortic arch, with or without a ventral septal defect.^{41,115}

The immunodeficiency associated with DGS is highly variable and correlates with the degree of thymic hypoplasia.¹¹⁵⁻¹¹⁷ Patients with *complete* DGS, comprising less than 0.5% of the overall numbers of DGS patients, have a profound deficiency of T cells and T-cell function that requires thymic transplantation.¹¹⁸ In contrast, the majority of patients with DGS are referred to as *partial* DGS. Patients with partial DGS generally have a variable, usually non-life-threatening immunodeficiency. Patients with partial DGS may have moderately diminished numbers of T cells, and T-cell defects in these patients are usually mild with relatively normal in vitro and in vivo (i.e., delayed-type hypersensitivity skin tests) assessment of T-cell function. Intact thymic function is essential for deletion of autoreactive T cells. Consequently, patients with DGS have an increased prevalence of autoimmune disorders. Approximately 10% of patients with DGS have autoimmune disease. Juvenile arthritis, autoimmune hemolytic anemia, and immune thrombocytopenia are the most common autoimmune diseases in DGS. Studies of humoral function have yielded conflicting results. Abnormalities in humoral immunity requiring immunoglobulin replacement therapy are low in patients with DGS.¹¹⁹

Most patients with DGS tolerate live virus vaccines without complications, but an assessment of humoral and

cellular immune function should be performed before their administration. Infectious complications of partial DGS usually include recurrent sinopulmonary infections and otitis media. Structural abnormalities of the palate may contribute to recurrent sinus disease in these patients. Opportunistic infections are infrequent in partial DGS, although oral and esophageal thrush is seen. Patients with complete DGS are highly susceptible to infection with opportunistic pathogens, reflecting the much more severe cellular immunodeficiency. In these patients, attenuated live virus vaccines should be avoided and irradiated blood and blood products used to avoid graft-versus-host disease.

WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome (WAS) is an X-linked disorder characterized by recurrent infections, eczematous skin disease, and thrombocytopenia due to a mutation in the gene for *WAS protein* (WASp).¹²⁰ The function of WASp is complex but, through its interaction with a variety of adaptor molecules and kinases, WASp is involved in the integration of cytoplasmic signaling with the reorganization of the actin cytoskeleton. Consequently, WASp function is critical in the formation of the immunologic synapse (i.e., the molecular interface between lymphocytes and target cells or antigen-presenting cells), cellular motility, cellular trafficking, and protection against autoimmunity.¹²¹ Mutations in the gene for WASp cause four distinct diseases: (1) classic WAS; (2) X-linked thrombocytopenia; (3) intermittent thrombocytopenia; and (4) congenital X-linked neutropenia without other features of WAS.¹²² We limit this section to classic WAS.

The laboratory evaluation of patients with WAS usually demonstrates increased levels of serum IgE and IgA with a low level of IgM and normal level of IgG. Despite normal serum IgG levels, antibody responses following immunization to PS antigens are consistently impaired.¹²³ T-cell and NK-cell function is frequently abnormal, resulting in a partial combined immunodeficiency.¹²⁴ Decreased platelet counts, platelet function, and platelet size are hallmarks of the disorder and lead to the marked bleeding diathesis.

The clinical expression of WAS includes prolonged bleeding episodes beginning in infancy, recurrent pyogenic infections, autoimmunity, eczematous dermatitis, and an increased prevalence of EBV-related lymphomas. Upper and lower respiratory infections due to encapsulated organisms (*S. pneumoniae* and *H. influenzae*) are common and reflect the inability of patients with WAS to make specific antibody to PS antigens.¹²³ Pulmonary infections with opportunistic pathogens (*P. jirovecii*, herpesviruses) are also common. Infection and hemorrhage are common causes of death. The treatment of WAS includes aggressive treatment of intercurrent infections and administration of IVIG.¹²³ The thrombocytopenia usually responds to splenectomy. HSCT is the treatment of choice for WAS, with long-term survival rates over 70%.¹²¹ Recently, gene therapy using a lentiviral vector successfully treated three patients with WAS.²⁵

ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia (AT) is an AR disorder due to a mutation in the *ATM* gene, which is involved in the repair of DNA

breaks.^{125,126} The clinical manifestations of AT include neurologic dysfunction (cerebellar ataxia, oculomotor apraxia, delayed motor development), telangiectasias, and immunodeficiency. Elevated levels of carcinoembryonic antigen and alpha-fetoprotein are present in nearly all patients with AT. The mutation in the *ATM* gene with an attendant increased radiosensitivity leads to the increased prevalence of malignancies such as lymphomas and epithelial tumors.^{125,126} Serum immunoglobulins are usually normal in AT, but selective IgA deficiency with impaired responses to polysaccharide antigens is common. Patients with AT develop recurrent sinopulmonary infections either due to the immunodeficiency or to a swallowing dysfunction, usually in infancy or early childhood. *Interstitial lung disease* (ILD) develops in approximately 20% of patients with AT. The optimal treatment of the ILD is not known, although corticosteroids have been used with some success.¹²⁷ There is no definitive treatment of AT. Antibody replacement has been used in patients to prevent the infectious complications of AT.

HYPER-IMMUNOGLOBULIN E SYNDROME

Hyper-IgE syndrome (HIES), also known as Job syndrome, is a syndrome characterized by recurrent skin and lung infections, severe eczema, and elevated levels of serum IgE. There are two forms of HIES. The more common *autosomal dominant* (AD) form of HIES (HIES type 1) is caused by mutations in the gene coding for the transcription factor *signal transducer and activator of transcription-3* (*STAT-3*) and has extra-immunologic features (connective tissue disorders, skeletal abnormalities) not present in the AR form (HIES type 2).¹²⁸ In addition, the AR form is complicated by a much higher incidence of cutaneous viral infections (HPV, *Molluscum contagiosum*) and neurologic complications and lacks the characteristic facies present in the AD form of HIES.^{128,129} Most of the AR forms of HIES have been found to be due to mutations and large deletions in the gene coding for the *dedicator of cytokinesis 8* (*DOCK8*), a protein involved in intracellular signaling.^{130,131} The remainder of this discussion focuses on the AD form of HIES.

The clinical features of HIES include the onset of moderate to severe eczema and eosinophilic pustular folliculitis in early infancy, skin infections (abscesses), mucocutaneous candidiasis, and recurrent pneumonias with pneumatoceles. Pneumatoceles are thought to develop as a consequence of disordered healing following primary infection of the lung. Common primary pathogens in HIES syndrome include *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *Candida albicans*.

Secondary infection of the pneumatoceles with *Aspergillus* spp. or *Pseudomonas aeruginosa* often results in invasion of the pulmonary vasculature leading to pulmonary hemorrhage or central nervous system infection, which are major causes of death.¹³² The signs and symptoms of serious infection are frequently absent in patients with HIES. Abscesses may develop without signs of external inflammation (cold abscess) or pneumonia may be present with limited clinical symptoms. Bronchopulmonary fistulas leading to empyema frequently form following pulmonary surgery performed to manage the complications of HIES.¹³³

Several nonimmunologic features of HIES aid in the early diagnosis of this disease. Patients with HIES have a characteristic facies (coarse facial features with a protuberant mandible and forehead, hypertelorism, and a broad, fleshy nasal tip); retained primary teeth; severe osteopenia with fractures following minimal trauma; scoliosis; and hyperextensible joints.¹³⁴ More recently, it has been discovered that patients with HIES have the proclivity to develop aneurysms, in particular aneurysms of the coronary arteries.¹³⁵ The clinical significance of the aneurysms and proper management are unknown at this time.

The diagnosis of HIES cannot be made by routine assays of immunologic function. Typical abnormalities in the laboratory evaluation of patients with HIES include an elevated IgE (>2000 IU/mL) and eosinophilia. These laboratory abnormalities are not pathognomic of HIES and may be present in patients with severe atopic dermatitis. Elevated levels of serum IgE may wane with age, and a normal IgE level does not exclude the diagnosis of HIES.

An understanding of the molecular pathogenesis of HIES was significantly advanced with the discovery that mutations in the *STAT3* gene are the cause of this disorder. The *STAT3* gene codes for a transcription factor that is essential for the biologic activities of numerous cytokines, including IL-6 and IL-10.¹³⁶ The absence of the anti-inflammatory effects of IL-10 likely contributes to the dysregulated inflammatory response seen in HIES patients.¹³⁷ IL-6 is required for the genesis of CD4⁺ Th17 cells in humans and, therefore, there is a deficiency of Th17 cells in HIES.¹³⁸ Th17 cells are important in the defense against extracellular bacteria and fungi.¹³⁹

The treatment of HIES focuses on the prevention and prompt treatment of infection. Antimicrobial prophylaxis is often given to prevent infection with *S. aureus*. The role of antifungal prophylaxis is unknown. Optimal skin care, including the use of bleach baths, topical corticosteroids, and hydrating measures for eczema, is essential. IVIG or IFN- γ may benefit some patients.¹⁴⁰ In contrast to AD-HIES, HSCT has been used successfully to treat AR-HIES due to *DOCK8* deficiency.^{141,142}

PHAGOCYTIC CELL DISORDERS

Phagocytic defects can initially be categorized by whether the abnormalities are intrinsic or extrinsic to the phagocyte. *Intrinsic* phagocyte defects include defects in adhesion, chemotaxis, signaling, or killing. *Extrinsic* defects exist when phagocytic cell function is normal but auxiliary components necessary for optimal phagocytic function are absent such as immunoglobulins or complement.

There are several clinical indications for evaluation for phagocytic abnormalities, including neutropenia or the lack of neutrophilia with significant infection, infections with unusual or opportunistic pathogens (e.g., fungi such as *Aspergillus* or *Nocardia*; bacteria such as *Serratia marcescens* or *Burkholderia cepacia*); unusual sites of infection (e.g., recurrent osteomyelitis, abscesses in the brain, lung, or liver); systemic bacterial infections; recurrent skin or upper or lower respiratory tract infections; and cold abscesses. Apart from infection, patients with phagocytic defects may have ongoing chronic inflammatory responses

in the skin (e.g., eczematoid dermatitis) or mucous membranes (e.g., periodontitis, aphthous stomatitis) and disordered inflammatory responses leading to delayed or abnormal wound healing.

PHAGOCYTIC DEFECTS: INCREASED APOPTOSIS OF NEUTROPHILS

Cyclic Neutropenia and Congenital Agranulocytosis (Kostmann Syndrome)

Cyclic neutropenia is an autosomal dominant disorder due to a mutation in the gene for neutrophil *elastase-2* (ELA2). It is thought that mutations of *ELA2* induce premature apoptosis of neutrophil precursors by the induction of the unfolded protein response.¹⁴³ In cyclic neutropenia there is a regular, 21-day fluctuation of neutrophils and other blood components (platelets, monocytes, reticulocytes).^{143,144} During the periods of neutropenia, patients are predisposed to bacterial infection with pyogenic bacteria and opportunistic pathogens. The diagnosis of cyclic neutropenia should be suspected when a cyclic hematopoiesis and neutropenia coincides with recurrent infections. To document concurrent infection with neutropenia, serial complete blood counts (two to three times/week) for at least 6 weeks should be performed. Most cases of autosomal recessive congenital agranulocytosis (Kostmann syndrome) are due to mutations in the gene for HAX1, a mitochondrial protein thought to protect myeloid cells against apoptosis.¹⁴⁵ Other causes of congenital neutropenia include mutations in *WASP*, *GFI*, and *G6PC3*.¹⁴⁶

The clinical manifestations of congenital agranulocytosis typically begin in early infancy with life-threatening infections such as cellulitis, meningitis, perirectal abscesses, or sepsis.¹⁴⁷ Patients with congenital agranulocytosis have severe neutropenia with an absolute neutrophil count of fewer than 200 cells/mm³. The clinical manifestations of congenital agranulocytosis are more severe than those of cyclic neutropenia. The use of G-CSF is indicated in cyclic neutropenia and congenital agranulocytosis; it will increase neutrophil counts and reduce infection in the vast majority of patients with these disorders.¹⁴⁷ In patients with severe neutropenia unresponsive to G-CSF, HSCT should be performed.¹⁴⁸

DECREASED ADHERENCE/CHEMOTAXIS

Leukocyte Adhesion Deficiency Types I-III

The influx of leukocytes in general and neutrophils in particular to sites of infection is a complex process involving the production and release of neutrophils from the bone marrow, the activation of neutrophils by chemotactic factors with subsequent adhesion of neutrophils to the endothelium, and finally the transmigration of neutrophils through the endothelium of postcapillary venules. The first step in the egress of neutrophils from the circulation to sites of infection is mediated by the rolling (loose) adhesion of neutrophils to endothelium, mediated predominantly by CD15s (sialyl Lewis_x) on the neutrophil and its counterligands (E-selectin, P-selectin) on the endothelium. The following step in adhesion, which is of higher affinity, is

mediated predominantly by the interaction of the integrin *leukocyte function-associated antigen* (LEA-1; CD11a/CD18) on the leukocyte with its counter-ligand intracellular adhesion molecule-1 on the endothelium. Integrins are composed of two subunits (α , β), which are noncovalently associated. The common β chain of CD18 associates with CD11a (LEA-1), CD11b (Mac-1 or CR3), CD11c (gp150/95), and CD11d, which are expressed on a variety of leukocytes. Therefore, mutations in *CD18* reduce the expression of CD11a/CD18, CD11b/CD18, and CD11c/CD18, resulting in defects in the endothelial adhesion of all leukocytes. Defective expression of CD18 and CD15s lead to the primary immunodeficiencies *leukocyte adhesion deficiency type I* (LAD-I) and *LAD type II* (LAD-II), respectively.^{149,150} LAD type III, which is inherited in an autosomal recessive manner, is caused by a mutation in the gene encoding kindlin-3, a member of a protein family that may regulate integrin function.¹⁵¹⁻¹⁵³

LAD-I is divided into two broad categories on the basis of whether the deficiency of LEA-1 is severe (<0.5% of normal levels) or moderate (5% to 10% of normal levels).¹⁵⁴ Patients with a complete deficiency in LEA-1 expression often present in the neonatal period with delayed separation of the umbilical cord, infection of the umbilical cord (omphalitis), and severe infections of the skin, gingiva, and gastrointestinal and upper and lower respiratory tracts. Moderate deficiencies of LEA-1 result in a milder phenotype that may contribute to a delay in the diagnosis. Patients with LAD-I exhibit neutrophilia, even in the absence of systemic infection, due to the inability of leukocytes to adhere to the endothelium. The definitive diagnosis of LAD-I deficiency is made by the demonstration of extremely low levels of LEA-1 on neutrophils by flow cytometry. The treatment of LAD-I includes the aggressive use of antimicrobials in the treatment of infection. HSCT is the only definitive treatment for patients with severe deficiencies of LEA-1.^{149,155} Moderate deficiencies of LEA-1 may improve with recombinant IFN- γ therapy and chronic antimicrobial prophylaxis.

LAD-II is an extremely rare disorder characterized by developmental delay, mental retardation, and recurrent infection similar to LAD-I. A mutation in the GDP-fucosyl transporter leads to the absence of CD15s on leukocytes and expression of the Bombay blood phenotype (hh).¹⁵⁶ Oral fucose administration can induce the expression of CD15s, leading to improvement of the central nervous system abnormalities and decreased infection.¹⁵⁷ LAD III is characterized by a profound bleeding tendency, recurrent bacterial and fungal infections, and failure to form pus despite a marked leukocytosis.¹⁵¹⁻¹⁵³

Chronic Granulomatous Disease

CGD is a rare (1 in 1 million live births) immunodeficiency due to mutation in one of the four subunits of the *phagocyte NADPH oxidase* (PHOX) system. The function of NADPH oxidase is to transfer an electron to molecular oxygen, leading to the formation of superoxide.¹⁵⁸⁻¹⁶⁰ Approximately two thirds of cases of CGD are X-linked due to a mutation in the g91phox subunit of NADPH oxidase. Mutations of the other subunits of NADPH oxidase (p22, p47, p67) are inherited in an autosomal recessive pattern and account for the remainder of cases.

The clinical manifestations of CGD usually begin early in life (mean age of onset, 4.4 years) but may not manifest until adulthood. CGD is characterized by recurrent infections with catalase-positive organisms (*Aspergillus* spp., *S. aureus*, *B. cepacia*, and others). Residual NADPH oxidase function, which is more common in autosomal recessive forms of CGD, leads to a milder phenotype, improved survival, and delayed onset of disease.^{161,162} Pneumonias and skin infections are the most common infections, but osteomyelitis, liver abscesses, lymphadenitis, and anorectal infections are frequent as well.¹⁶³ Aerosolized exposure to organic dust can lead to fulminant fungal pneumonia termed “mulch pneumonitis” and may be the presenting manifestation of CGD, in particular the autosomal recessive forms of CGD.^{164,165} Prolonged antimicrobial or antifungal therapy, often in conjunction with systemic corticosteroids, is necessary to treat many of the infectious complications of CGD.¹⁶⁶⁻¹⁶⁸ The most common chest CT abnormalities include areas of consolidation and nodular opacities, both associated with either infection or granulomatous inflammation.¹⁶⁹ Invasive aspergillosis is the most common primary cause of death. Autoimmune diseases appear to be increased in CGD, and carriers of X-linked CGD are at increased risk for discoid lupus and photosensitivity.¹⁷⁰ As previously discussed, the diagnosis of CGD is readily made by the use of either the NBT or DHR test for phagocytic function.

Apart from infectious complications, disordered inflammation and wound healing are hallmark manifestations of the disease.¹⁶⁶ Inflammatory granuloma formation may lead to urinary or gastrointestinal tract obstruction, which are treated by systemic corticosteroids. Exuberant granulation tissue leads to disordered wound healing, including wound dehiscence following surgical procedures. The molecular basis for the disordered inflammatory response that is characteristic of CGD is complex. Comparison of global gene expression of normal and X-linked CGD neutrophils indicate that CGD neutrophils constitutively overproduce proinflammatory mediators and exhibit defective neutrophil apoptosis due to the overproduction of the anti-apoptotic protein Bcl-xl.¹⁷¹ Additionally, on apoptosis, CGD neutrophils do not properly externalize phosphatidylserine, the ligand that enables macrophages to recognize and clear apoptotic cells.¹⁷² Consequently, there is a delay in the removal of apoptotic CGD neutrophils by macrophages.¹⁷³ The deficiency in uptake of apoptotic cells may also lead to decreased production of anti-inflammatory mediators such as transforming growth factor- β , thereby contributing to the overproduction of inflammatory cytokines.¹⁶⁶ Thus, the increased production of proinflammatory mediators, reduced apoptosis, and delayed clearance of apoptotic neutrophils all likely lead to the disordered inflammatory response in CGD.

The therapy of CGD includes aggressive treatment of infection, including early surgical incision and drainage when indicated.¹⁷⁴ The prophylactic administration of trimethoprim-sulfamethoxazole markedly reduces infection, in particular infections caused by *S. aureus*.¹⁷⁵ Prophylactic itraconazole reduces serious fungal infections.¹⁷⁶ IFN- γ reduces infections and decreases mortality in both X-linked and autosomal recessive CGD, although the benefits of interferon therapy have been challenged.^{163,177} HSCT

is an increasingly preferred option for the definitive treatment of CGD.^{178,178a} Gene therapy has also been successfully performed in a small number of patients.¹⁷⁹

DISORDERS OF LEUKOCYTE SIGNALING

Defects in the IFN- γ /IL-12/IL-23 Axis

Th1-type T cells are defined by their capacity to produce high levels of cytokines (IL-2, IFN- γ , TNF- α) that are essential in the generation of a robust cellular immune response. IFN- γ , which is also produced by NK cells, interacts with a heterodimeric receptor, *IFN- γ receptor 1* (IFN- γ R1), the ligand binding receptor, and *IFN- γ receptor 2* (IFN- γ R2), which is required for downstream signaling. On ligand binding by IFN- γ R1/R2, the JAK1 and JAK2 are activated, which subsequently phosphorylate the STAT-1 protein in the cytoplasm, leading to homodimerization of STAT-1, translocation to the nucleus, and transcriptional activation of STAT-1-dependent genes. One important biologic function of IFN- γ is to induce the production of IL-12 p70 by dendritic cells and macrophages, which then feeds back in a positive loop to induce more production of IFN- γ by NK cells and T cells. IL-12 p70 is composed of two disulfide-linked subunits, p35 and p40, the latter of which also associates with the p19 subunit to form IL-23. The *IL-12 receptor* (IL-12R) is composed of two subunits, IL-12R β 1 and IL-12R β 2. IL-12R β 1 also serves as part of the heterodimeric IL-23 receptor (IL-12R β 1 and IL-23R). Thus, the IFN- γ /IL-12/IL-23 axis is intrinsically linked due to the biologic functions of IFN- γ and IL-12, the shared cytokine subunit of IL-12 and IL-23 (p40), and the common cytokine receptor subunit of IL-12R and IL-23R (IL-12R β 1).

Mutations of the genes for IFN- γ R1 or IFN- γ R2, STAT-1, IL-12 p40, IL-12R β 1, IRF-8, ISG15, and NEMO (see earlier discussion) define a group of primary immunodeficiencies known as *mendelian susceptibility to mycobacterial disease* (MSMD) (Table 92-6).¹⁸⁰⁻¹⁸⁴ Due to the marked heterogeneity in inheritance, the functional consequences of mutations in these six genes (complete or partial) leads to 13

Table 92-6 Etiologies of Mendelian Susceptibility to Mycobacterial Disease *

Gene	Inheritance	Defect	Patients with MSMD	Treatment
<i>IFNγR1</i>	AR/AD	C/P	39%	AR-C: HSCT AD-P: IFN- γ
<i>IFNγR2</i>	AR	C/P	4%	AR-C: HSCT AR-P: IFN- γ
<i>STAT1</i>	AD	P	5%	Varies depending on location of mutation
<i>IL12B</i>	AR	C	9%	IFN- γ
<i>IL12Rβ1</i>	AR	C	40%	IFN- γ
<i>NEMO (IKK-γ)</i>	X-linked	P	3%	HSCT

*Rare cases of MSMD have been found due to mutations in *ISG15* (AR) or *IRF8* (AD/AR).

AD, autosomal dominant; AR, autosomal recessive; C, complete deficiency; HSCT, hematopoietic stem cell transplantation; IFN, interferon; MSMD, Mendelian Susceptibility to Mycobacterial Disease; P, partial deficiency.

distinct genetic disorders associated with MSMD. Patients with mutations in one of these six genes are susceptible to infection with *Mycobacteria* and/or *Salmonella* but are usually resistant to infections with most other pathogens.^{180,181} This narrow susceptibility to infection in humans is somewhat surprising on the basis of the importance of Th1 responses in combating infection with a wide variety of pathogens in studies using mice.

AR complete IFN- γ R1 deficiency is characterized by the onset of infection with environmental mycobacteria, frequently rapid growers such as *Mycobacterium fortuitum* and *Salmonella*, at an early age (<3 years). Without treatment with HSCT, the disorder is fatal. However, HSCT is frequently not successful in patients with IFN- γ R1 deficiency due to preexisting high IFN- γ levels that prevent engraftment. AD partial IFN- γ R1 deficiency has a much less severe phenotype, with a mean age of onset at 13 years of age. These patients are susceptible to infection with environmental mycobacteria and may develop disseminated disease following vaccination with bacille Calmette-Guérin. Additionally, patients with partial IFN- γ R1 deficiency are uniquely predisposed to mycobacterial osteomyelitis, a complication that should trigger an evaluation for this disorder. AR complete IFN- γ R2 deficiency and AR partial IFN- γ R2 deficiency are rare, and the described phenotype to date is similar to AR complete IFN- γ R1 deficiency and AD partial IFN- γ R1 deficiency, respectively. The phenotype of patients with a *STAT1* mutation varies depending on the site of the mutation. As previously discussed, *STAT-1* homodimers mediate the transcriptional effects of IFN- γ . *STAT-1* also forms a heterodimer with *STAT-2*, which is the transcription factor formed following binding of IFN- α/β with its receptor. Consequently, some patients with mutations in *STAT2* are susceptible to viral infections and mycobacterial disease. AR complete mutations of *IL12B*, which is the only described immunodeficiency of a cytokine gene to date, result in a markedly increased susceptibility to infection with *Salmonella* in addition to mycobacterial disease. Similarly, AR complete *IL-12R β 1* deficiency, which is the most common cause of MSMD, also results in an increased susceptibility to infection with mycobacteria and *Salmonella*. Patients with deficiency in *IL-12B* and *IL-12R β 1* are also susceptible to mucocutaneous candidiasis.^{184,185} The clinical phenotype of AR complete *IL-12R β 1* deficiency is milder than complete defects in IFN- γ R1 or IFN- γ R2, and only a few patients succumb to disease. IFN- γ is useful in the treatment of patients with either *IL-12B* or *IL-12R β 1* deficiency.

DISORDERS IN INNATE IMMUNITY

MYD88 AND IRAK-4 DEFICIENCIES

Toll-like receptors (TLRs) are a family of pattern recognition receptors that are activated following microbial infection, resulting in the activation of innate immune responses. TLRs recognize conserved motifs derived from a variety of pathogenic microorganisms, including bacteria, fungi, and viruses. On ligand binding, all members of the TLR family, with the exception of TLR3, use MyD88 as a key adaptor molecule to recruit *IL-1 receptor-associated kinases* (IRAKs) leading to downstream signaling events, resulting in the

activation of the transcription factors NF- κ B and AP-1. Mutations in the genes for either MyD88 or IRAK-4 result in phenotypically similar primary immunodeficiencies. The primary immunodeficiencies caused by mutations in either *MYD88* or *IRAK4* are characterized by noninvasive and invasive infections (meningitis, septicemia, liver abscess) predominantly with *S. pneumoniae* (40% of patients) or *S. aureus* (26% of patients) and *P. aeruginosa* (18% of patients).¹⁸⁶⁻¹⁸⁸ No severe infections with viruses, fungi, or parasites have been observed, which is surprising based on the broad immunodeficiency found in mice with targeted deletion of the murine gene, *Myd88*. The onset of invasive infection is early in life, with the vast majority before age 2; the condition improves with age. All deaths in patients with IRAK-4 deficiency take place by age 8. Patients with MyD88 or IRAK-4 deficiency are frequently unable to generate a normal inflammatory response (e.g., fever, increased CRP and WBC), which contributes to the severity of the invasive infections. Standard screening tests of immune function are often normal. Peripheral blood mononuclear cells exhibit decreased inflammatory cytokine production in response to IL-1 and to all TLR agonists except agonists of TLR3. The proper management of patients with *MYD88* or *IRAK4* mutations remains to be determined, but prophylactic antibiotics and IVIG may be useful.

COMPLEMENT DEFICIENCIES

Complement has many important functions that include the modulation of inflammatory responses (e.g., vasodilation, leukocytosis, chemotaxis); clearance of immune complexes; modulation of the immune response (e.g., enhanced production of antibodies); and microbial elimination (e.g., opsonization, neutralization, microbicidal activity). Complement may also be important in the efficient removal of apoptotic cells, resulting in the presentation of self-antigens and the induction of autoimmunity. Deficiencies in components of the complement system are usually manifest by an increased propensity to infection or autoimmunity.^{1,189} There are several indications for the evaluation of the complement system, such as a strong family history of autoimmune diseases; recurrent infections caused by encapsulated bacteria; a family history of meningococcal disease; infection caused by unusual types of meningococcus (Y, W-135); age older than 9 at the time of meningococcal disease; and recurrent angioedema.

Defects in the early components of complement (C1q, C1s, C2, C4), which are inherited in an autosomal codominant manner, typically lead to an increased prevalence of autoimmune disease (primarily systemic lupus erythematosus). Redundancies in the complement pathway, including the alternative and mannose-binding lectin pathways, may explain why only a minority of patients with early complement deficiencies develops serious bacterial infections. Encapsulated bacteria (*S. pneumoniae*, *H. influenzae*) are the most common pathogens in people with recurrent infection due to deficiency in early complement components.¹⁴ C2 deficiency is the most common early component deficiency, seen in 1:10,000 to 1:28,000 live births.

The classical, alternative, and mannose-binding lectin pathways all converge at C3. For this reason, deficiencies in C3 result in more severe infections than deficiencies in other

components of complement. Patients with C3 deficiency have an increased prevalence of autoimmune disease and present in a manner similar to those with antibody deficiency.

Deficiencies in the late components of the complement pathway (C5 to C9) are also inherited in an autosomal codominant manner. Patients with late-component deficiencies are highly predisposed to infection with *N. meningitidis* and *Neisseria gonorrhoeae*. For reasons that are not clear, meningococcus serogroups W-135 and Y account for the vast majority of meningococcal meningitis infections in these patients. The prevalence of autoimmune disease is also increased, but to a much lesser extent than with deficiencies in the early components of the complement cascade. Patients with late-component deficiencies usually have the onset of infection at an older age, and many are asymptomatic well into adolescence.¹⁴

Deficiencies in components of the alternative pathway (factor D, properdin) are extremely rare and present with recurrent bacterial infections, including infections with *Neisseria* spp. Properdin deficiency is an X-linked inherited disorder in contrast to the other complement deficiencies (with the exception of hereditary angioneurotic edema), which are inherited in an autosomal codominant manner.

Therapy for complement deficiencies is primarily supportive. Individuals should be vaccinated against common bacterial pathogens associated with complement deficiency (e.g., *S. pneumoniae*, *H. influenzae*, *N. meningitidis*). Prophylactic antibiotics may be used in selected situations.

Key Points

- Patients with recurrent upper airway infections, intractable sinusitis, or more than one radiographically documented pneumonia should be evaluated for primary immune deficiency disorders (PIDDs). Abnormal screening tests for PIDDs should lead to referral to a clinical immunologist for a specific diagnosis.
- Although infection with opportunistic pathogens should always prompt a search for primary or secondary immune deficiencies, infections in patients with PIDDs are often caused by common pathogens.
- PIDDs frequently are not diagnosed in a timely manner, leading to increased morbidity and mortality. Treatment can include intravenous immune globulin or hematopoietic stem cell transplantation.
- PIDDs can be due to deficiencies in antibody production, cellular immunity, complement, or phagocytic

function. In an adult, common variable immunodeficiency is the most common diagnosis and phagocytic defects and combined immunodeficiencies are rare.

- Although immunodeficiency in adults is more commonly secondary than primary, PIDDs are seen in adults. In fact, there are more adults with PIDDs than children.
- Diffuse lung disease develops in 10% to 25% of patients with common variable immunodeficiency and has been termed granulomatous-lymphocytic interstitial lung disease.
- In patients with profound antibody deficiencies, diagnosis of microbial infection cannot rely on serologic (antibody) responses but must instead use culture or detection of microbial antigens or nucleic acids.

Complete reference list available at ExpertConsult.

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PULMONARY COMPLICATIONS OF ABDOMINAL DISEASES

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INTRODUCTION

GASTROESOPHAGEAL AND GASTROINTESTINAL DISORDERS

Gastroesophageal Reflux
Inflammatory Bowel Disease

HEPATIC DISEASES

Pleural Effusion
Pulmonary Function Disturbances
Hepatopulmonary Syndrome

Portopulmonary Hypertension

Primary Biliary Cirrhosis
Chronic Active Hepatitis
Sclerosing Cholangitis
Alpha₁-Antitrypsin Deficiency

PANCREATITIS

Respiratory Failure
Pleural Effusion
Other Manifestations

KIDNEY DISEASES

Pulmonary Edema
Pleural Disease
Pulmonary Calcification
Sleep Apnea
Hemodialysis-Induced Hypoxemia

INTRODUCTION

This chapter is devoted to the pulmonary complications of abdominal disease and begins with a discussion of the most relevant esophageal and bowel diseases, followed by the specific liver disorders associated with particular pulmonary complications. Finally, the respiratory consequences of diseases of the pancreas and kidney are described. The objective in each section is the same: to update the most relevant clinical, pathophysiologic, pathogenetic, and therapeutic aspects of the principal abdominal disease states and thereby assist the clinician in diagnosing and managing their sometimes complex and challenging pulmonary complications.

GASTROESOPHAGEAL AND GASTROINTESTINAL DISORDERS

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux disease (GERD) is “a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications,” which are subclassified as esophageal and extraesophageal.¹ Among the esophageal symptoms are episodes of chest pain, which may vary from recurrent mild retrosternal “heartburn” to acute crushing substernal distress indistinguishable from the pain of angina or even acute myocardial infarction (see also Chapter 31). Among the extraesophageal symptoms, chronic cough, chronic laryngitis, and refractory asthma have attracted the most attention, but other respiratory disorders include *chronic obstructive pulmonary disease* (COPD), chronic bronchitis, pulmonary aspiration complications (aspiration pneumonia, lung abscess, bronchiectasis), and pulmonary fibrosis.

Prevalence

GERD is a common condition with a prevalence that varies from 10% to 20% in North America and Western Europe, but is lower in Asia.^{1,2} GERD is associated with cough in 10% to 40% of patients with chronic cough and with

asthma in 30% to 80% of asthmatics, depending on the patient population, diagnostic test, and number of ascertained etiologies.³ A link between GERD and chronic cough has been reported in patients of all age groups, and coexisting GERD-related chronic cough seems especially prevalent in patients with asthma, laryngitis, and bronchitis.⁴ Ambulatory monitoring studies—pH or impedance-pH—provide strong evidence linking reflux and cough.⁵ By measuring the electrical impedance of liquid boluses between pairs of electrodes along the probe, impedance-pH monitoring can detect the presence and direction of movement of boluses and correlate that with changes in pH and with symptoms. Thus, with impedance-pH monitoring, the sensitivity for the diagnosis of reflux, whether of acid or nonacid material, is increased. In the past, when the diagnosis of GERD was made by history, endoscopy, or barium esophagogram, reflux was found in approximately 10% of patients with chronic cough⁶; in contrast, when the diagnosis is made by ambulatory impedance-pH monitoring, GERD has been found in up to 40% of patients with chronic cough.⁷ The exact contribution of reflux to the patient's symptoms is often difficult to evaluate; for example, Irwin and associates⁸ reported that GERD was clinically silent in 24% of patients with difficult-to-control asthma.

The spectrum of GERD-induced respiratory disorders comprises a wide variety of complications. These disorders include chronic bronchitis, pneumonia,⁹ bronchiectasis,¹⁰ idiopathic pulmonary fibrosis,^{11,12} stable COPD and COPD exacerbations,¹³⁻¹⁶ bronchiolitis obliterans syndrome after lung transplantation,¹⁷⁻¹⁹ and nontuberculous mycobacterial lung disease, which may arise as a complication of presumed bronchiectasis and/or treatment by antacids.²⁰

Pathogenesis

Three basic GERD-associated mechanisms lead to respiratory disorders. First, gross aspiration-linked pulmonary syndromes are usually the result of free esophageal reflux with large-volume retrograde flow. Frequently, there is reduced basal lower esophageal tone and both impaired esophageal motility and clearance.²¹ Affected patients may have recurrent aspiration pneumonia, bronchiectasis, or pulmonary opacities. Endoscopic examination usually

reveals severe anatomic changes, such as visible breaks or Barrett epithelialization of the distal esophagus.

The second pathogenic mechanism is related to the microaspiration of gastric contents from the proximal (upper) esophagus. Small-volume aspirates produce an exudative mucosal reaction in the larynx and in the tracheobronchial tree. Respiratory symptoms are less obvious and range from hoarseness or chronic cough to difficult-to-control asthma. Jack and coworkers,²² using simultaneous tracheal and esophageal pH measurements in asthmatics with GERD, showed episodes of reflux that were followed by a fall in intratracheal pH; episodes with a fall in intratracheal pH resulted in a marked fall in peak expiratory flow rate that was several times greater than that observed when reflux was not followed by a change in intratracheal pH (Fig. 93-1). Accordingly, microaspiration into the bronchial tree not only takes place but also may induce an important increase in airway resistance.

Lastly, the third pathogenic mechanism linked to GERD is gastroesophageal reflux activation of a vagal reflex acting between the distal (lower) esophagus and the tracheobron-

chial tree; this reflex mechanism can be reproduced by the infusion of hydrochloric acid into the esophagus of some,²³ but not all,²⁴ patients with asthma.

The relationship between GERD and respiratory disorders is further complicated by the fact that physiologic alterations associated with asthma or cough, or with bronchodilator therapy, may themselves promote gastroesophageal reflux. Episodes of bronchospasm and cough are accompanied by an increase in the negative pressure within the thorax, and hence in the esophagus, which favors reflux; obstructive sleep apnea syndrome may act by the same mechanism to increase nocturnal reflux.²⁵ In addition, hyperinflation and "gas trapping" may flatten the diaphragm, allowing the lower esophageal sphincter to be drawn up into the thorax and impairing the antireflux barrier. Bronchodilator therapy may also promote gastroesophageal reflux. Theophylline increases gastric acid secretion and decreases lower esophageal sphincter tone. Indeed, asthmatics with gastroesophageal reflux who receive theophylline show an increase in esophageal acid exposure and reflux symptoms.²⁶ Specific β -adrenergic

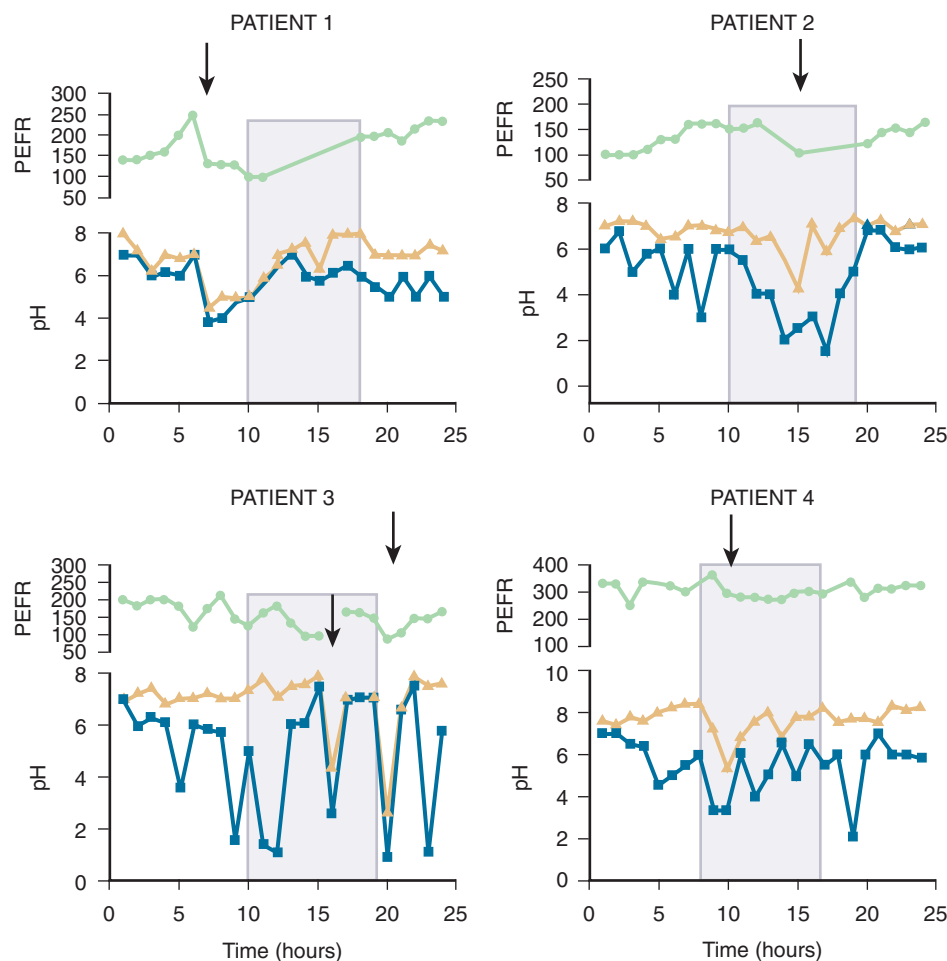


Figure 93-1 Graphs showing simultaneous esophageal (solid blue squares) and tracheal (solid beige triangles) pH measurements in four patients with both gastroesophageal reflux and asthma, along with recordings of peak expiratory flow rate (PEFR, solid pale-green circles), over a 24-hour period. In the study, there were 37 significant falls in esophageal pH suggestive of gastroesophageal reflux. Five of these episodes were followed by a fall in tracheal pH (from a mean of 7.1 to 4.1) and were associated with a significant decrease in PEFR (mean change -84 ± 16 L/min), whereas during the remaining 32 episodes of gastroesophageal reflux without tracheal aspiration, the mean change in PEFR was minimal (-8 ± 4 L/min). Gray areas show when the patient is supine. Arrows show episodes of falls in esophageal pH, tracheal pH, and PEFR. (From Jack CI, Calverley PMA, Donnelly RJ, et al: Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. *Thorax* 50:201–204, 1995.)

agents relax smooth muscle tone throughout the body thereby promoting gastroesophageal reflux. A decrease in lower esophageal sphincter pressure has been shown with β -adrenergic drugs administered orally or intravenously,²⁷ but not when these agents were given by inhalation.²⁸

Diagnosis

Guidelines provide recommendations for the diagnosis and management of GERD.^{29,30} The possibility of associated gastroesophageal reflux should be suspected in patients with refractory chronic cough or difficult-to-treat asthma. Patients should be questioned about symptoms of gastroesophageal reflux, which include heartburn, regurgitation, or dysphagia. Patients may complain of atypical symptoms, however, including substernal chest pain, hoarseness, sore throat, otalgia, hiccups, or even tooth erosion. It is important to note whether asthma or cough worsens with recumbency, after meals, or while drinking alcohol. If the clinical history is typical of gastroesophageal reflux and a trial of *proton pump inhibitor* (PPI) therapy is successful, no further diagnostic workup may be necessary.

Vocal cord dysfunction is another respiratory disorder found in patients with GERD. Vocal cord dysfunction is an intermittent paradoxical adduction of the vocal cords, mainly arising during inspiration, leading to airflow obstruction and dyspnea; patients with vocal cord dysfunction may have repetitive emergency department visits due to acute dyspnea, often mimicking exacerbations of asthma.³¹

GERD may be clinically silent in numerous patients and tests to support its diagnosis should be considered. Ambulatory reflux monitoring (pH or impedance-pH) is the test of choice to determine the presence of abnormal esophageal acid exposure, reflux frequency, and symptoms associated with reflux episodes. As mentioned, use of a multichannel intraluminal impedance-pH catheter adds impedance measurements to those of pH and provides additional data about the role of nonacid or weakly acid reflux as a cause of atypical symptoms; in addition, the catheter helps evaluate ongoing reflux in patients receiving acid-suppression therapy. Useless investigations in diagnosing GERD include barium swallows, which are restricted to evaluating putative complications; upper gastrointestinal endoscopy and esophageal biopsy, which are limited to investigating alarming symptoms and/or to excluding non-GERD causes; and esophageal manometry, which is used chiefly for preoperative evaluation.

Treatment

Treatment recommendations^{29,30} for patients with GERD include weight loss in the case of overweight/obesity, elevation of the head of the bed, and avoidance of eating within 2 to 3 hours before bedtime. PPI is the therapy of choice for symptom relief and healing of erosive esophagitis. PPIs should be initiated once a day, 30 to 60 minutes before the first meal of the day. For patients with partial responses to once-daily PPI therapy, tailored administration with adjustment of dose, its timing, and/or twice daily dosing should be considered. Treatment with PPIs must be given in sufficient doses for at least 3 months to reliably determine effectiveness. Nonresponders to PPIs should be referred for further evaluation. Maintenance PPI therapy should be administered in the lowest effective dose—including on

demand or intermittent therapy—in GERD patients who have recurrent symptoms after stopping PPIs and/or in patients with complications, such as erosive esophagitis or Barrett esophagus. When PPI treatment fails to control reflux, other treatment strategies to consider include prokinetic agents and surgical interventions. Prokinetic agents improve esophageal contractility and increase both lower esophageal sphincter pressure and gastric emptying. Surgery, such as the Nissen fundoplication, is an alternative therapy to consider when all other therapeutic approaches have failed.

Whatever the therapy, remission of GERD-induced lung symptoms is unusual, which supports the hypothesis that GERD is an aggravating rather than causative factor in most patients with extraesophageal symptoms. Indeed, there are insufficient data to provide definitive conclusions one way or the other about the role of GERD in lung symptoms. According to a Cochrane analysis,³² PPIs are not efficacious for GERD-induced cough in very young children; in adults, data are insufficient to conclude that treating GERD with PPIs is universally beneficial for GERD-induced cough. Clinicians should be aware of the possibility of spontaneous resolution of cough over time and of the placebo effect of assuming that “apparently effective” medications are beneficial. Despite a high prevalence of asymptomatic GERD among patients with poorly controlled asthma, treatment with PPIs has not been shown to improve asthma control.³³ Moreover, although many uncontrolled studies suggest that surgical procedures may improve asthmatic symptoms, conclusive studies are lacking. In patients with COPD, antireflux therapy does not have a protective effect against exacerbations.¹⁴ In idiopathic pulmonary fibrosis, no published studies demonstrate that antireflux therapy benefits the natural history of idiopathic pulmonary fibrosis. Considering that GERD is more likely only an aggravating factor for GERD-associated lung diseases, PPI can be tested in these diseases and carried on if efficacious.

INFLAMMATORY BOWEL DISEASE

Extraintestinal complications of *inflammatory bowel disease* (IBD) have been described in virtually all organ systems; but, surprisingly, disease in the lungs appears “much less frequently” than manifestations in other organs.³⁴ We say “surprisingly” because the gut and lungs share a common embryologic origin, and thus might possess similar vulnerability to immunologically mediated comorbidities. Pulmonary complications arise more commonly with ulcerative colitis than with Crohn disease; respiratory involvement may develop at any age, and some conditions (e.g., airway disease) appear more often in women than in men.³⁴ In most cases, respiratory symptoms develop after the diagnosis of IBD has been made, frequently several years afterward. Nonetheless, respiratory symptoms can antedate or be concomitant with those of the bowel disease.³⁵ Even in patients without symptoms, there may be impaired pulmonary function, such as a decrease in *diffusing capacity for carbon monoxide* (DL_{CO}) and forced expiratory volume in 1 second, and an increase in residual volume and bronchial hyperresponsiveness. Reviews³⁴⁻³⁶ of published cases have confirmed and extended earlier observations about the

Table 93-1 Noniatrogenic Respiratory Involvement in Inflammatory Bowel Disease**AIRWAY DISEASE**

Epiglottic-subglottic stenosis
 Tracheobronchitis
 Chronic bronchitis
 Chronic bronchial suppuration
 Bronchiectasis
 Bronchiolitis
 Bronchiolitis obliterans
 Diffuse panbronchiolitis

PARENCHYMAL LUNG DISEASE

Cryptogenic organizing pneumonia
 Sarcoidosis
 Eosinophilic pneumonia
 Interstitial lung disease
 Pulmonary fibrosis
 Nodules
 Chronic pneumonia (esophagobronchial or colobronchial fistula)

SEROSITIS

Pleural effusion
 Pleuropericarditis

PULMONARY VASCULAR DISEASES

Pulmonary vasculitis
 Pulmonary embolism
 Chronic thromboembolic pulmonary hypertension

noniatrogenic pulmonary complications of IBD, which can be classified as shown in Table 93-1.

Most intrinsic (non-drug-related) pulmonary complications involve the airways—anywhere from the larynx to the bronchioles—and may take the form of epiglottitis, tracheal stenosis, bronchiectasis, chronic bronchitis, or bronchiolitis. Endoscopic examination shows marked erythema, swelling of the mucosa, and deformation of the airway lumen. Biopsy specimens have revealed mucosal ulceration, thickening of the basement membrane, and marked infiltration by neutrophils and plasma cells.^{34,35} In some cases, the inflammatory process in the subglottic area can take the form of pseudotumoral lesions, with the potential of producing life-threatening acute upper airway obstruction requiring aggressive airway management.^{35,37} This panoply of discrete airway pathology has been enriched by the addition of asthma, which proved to be the most common pulmonary comorbidity of both ulcerative colitis and Crohn disease identified in a large cohort. The association between IBD and asthma supports the belief that patients suffering from one autoimmune condition are more likely than the general population to have a second immune-mediated disorder, which may result from shared susceptibility genes.³⁸

Another major category of pulmonary complications of IBD is the group of parenchymal disorders, including interstitial lung diseases, such as cryptogenic organizing pneumonia, sarcoidosis, interstitial fibrosis, and pulmonary infiltration with eosinophilia. Pulmonary function test results in patients with IBD, even when asymptomatic and with normal chest radiographs, may reveal a variety of abnormalities. Probably the most common is an obstructive ventilatory defect, as described earlier, but pulmonary restriction is also well described. A reduction in DL_{CO} during the active phases of IBD has been reported,³⁹ which also

suggests that subclinical pulmonary parenchymal involvement may be more prevalent than previously suspected. Furthermore, bronchoalveolar lavage examination in patients with Crohn disease—who did not have clinical evidence of pulmonary involvement—has revealed the presence of a lymphocytic alveolitis, chiefly owing to an increase of CD4-positive T lymphocytes.³⁸

Other pulmonary lesions include necrobiotic nodules, corresponding histologically to aggregates of neutrophils with areas of necrosis, which have been reported in a few patients.³⁵ Serositis affecting the pleura or the pericardium, or both, has been reported in a small number of cases, especially during periods of increased disease activity. Finally, colobronchial fistulas have been reported in some cases of Crohn disease, the majority of them presenting with left lower lobe pneumonia.³⁴ Involvement of the esophagus is rare in Crohn disease, but a few cases of bronchoesophageal fistula associated with esophageal Crohn disease have been reported.³⁴ Although conservative management has been tried, most patients with fistulas require surgical treatment.

Pulmonary thromboembolic events and chronic thromboembolic pulmonary hypertension are more frequent in patients with IBD, even in those who are asymptomatic, than in control subjects.^{36,40-42} The study by Grainge and colleagues indicates that patients with stable IBD have a higher risk of venous thromboembolism than controls, (*hazard ratio* [HR], 3.4); in addition, those patients with an IBD flare have an even higher incidence of thromboembolism (HR, 8.4).⁴³ Because deep vein thrombosis and pulmonary embolism may be clinically silent, an early diagnosis of thromboembolism can be challenging, and the duration of systemic anticoagulation must take into account the individual risk of intestinal bleeding.⁴⁴

In addition, drugs are a frequent cause of pulmonary manifestations in patients with IBD.³⁴ Antiinflammatory drugs, often the first step in the treatment of IBD, consist of aminosalicylates (sulfasalazine, mesalamine) and glucocorticosteroids. Immune system suppressors (azathioprine, methotrexate) and *tumor necrosis factor-α* (anti-TNF-α) inhibitors serve to maintain remission. Because most of these medications induce respiratory side effects, consequences of therapy must be considered in the differential diagnosis of new-onset lung disease; offending medications must be recognized and discontinued to prevent a potentially fatal outcome. The spectrum of medication-induced respiratory manifestations includes eosinophilic and granulomatous pneumonitis, interstitial lung disease, pulmonary fibrosis, and a heightened susceptibility to infections.^{45,46} Azathioprine increases the risk of both infection and disease by viruses, glucocorticosteroids by fungi, and TNF-α inhibitors by intracellular microorganisms (mycobacteria, fungi).

The majority of patients with pulmonary disorders associated with IBD are treated with glucocorticosteroids, either by inhalation or by mouth, which usually results in rapid control of symptoms,^{35,47} especially in those patients who do not have severe structural impairment (e.g., bronchiectasis). Lung transplantation has been performed in some patients with severe respiratory compromise associated with IBD.³⁵

HEPATIC DISEASES

PLEURAL EFFUSION

Pleural effusion develops in 5% to 10% of patients with cirrhosis of the liver and is traditionally referred to as *hepatic hydrothorax* in the absence of coexisting cardiopulmonary disease (see Chapter 79). Unless the pleural fluid is complicated by infection, hepatic hydrothoraces are transudates and are most commonly located in the right hemithorax. Effusions may also be left-sided or bilateral, and may or may not be associated with concurrent ascites. The effusion is usually mild to moderate in size and asymptomatic, but in some cases it can be massive and provoke shortness of breath. The mechanism is related to the presence of anatomic communications—usually small diaphragmatic defects—and to the prevailing pressure gradient between the abdominal and pleural cavities that facilitates movement of ascitic fluid into the chest. The presence of pleural fluid disturbs lung mechanics, resulting in decreased lung volumes and pulmonary compliance, and pulmonary gas-exchange abnormalities.⁴⁸

The clinical management of pleural effusion associated with liver disease is often difficult. Repeated thoracenteses have only transitory effects, and thoracostomy tube drainage may result in substantial protein loss. Transjugular intrahepatic portosystemic shunting decreases portal hypertension and, in turn, reduces the size of both the ascites and hydrothorax; transjugular intrahepatic portosystemic shunting is often beneficial, at least in the short term, but long-term outcome depends on the severity of the underlying liver dysfunction.⁴⁹ If the patient is not a candidate for transjugular intrahepatic portosystemic shunting, other approaches, including video-assisted thoracoscopic surgery to repair diaphragmatic defects and/or induce a pleurodesis, should also be considered.⁵⁰

PULMONARY FUNCTION DISTURBANCES

The most common lung function abnormality in patients with end-stage hepatic disease is a decreased DL_{CO} ; likewise, both obstructive and restrictive ventilatory defects have been observed.⁵¹ The coexistence of massive ascites can decrease lung compliance, increase pleural pressure, and reduce diaphragmatic motility. Together, these pathophysiologic alterations restrict ventilatory capacity and reduce the efficiency of gas exchange, causing increased alveolar-arterial PO_2 difference values with or without clinically evident hypoxemia.⁵²

HEPATOPULMONARY SYNDROME

Severe hypoxemia (arterial $PO_2 < 60$ mm Hg) is uncommon in patients with uncomplicated chronic hepatic disease and, when present in patients without coexisting cardiopulmonary disease, should strongly suggest *hepatopulmonary syndrome* (HPS). Because patients with advanced liver disorders characteristically hyperventilate and are hypocapnic, measurement of the alveolar-arterial PO_2 difference becomes more sensitive than arterial PO_2 alone to detect gas-exchange disturbances in HPS.⁵³

Table 93-2 Grading of Severity of Hepatopulmonary Syndrome*

Stage	Alveolar-Arterial Oxygen Difference	Arterial Partial Pressure of Oxygen
Mild	≥ 15 mm Hg	≥ 80 mm Hg
Moderate	≥ 15 mm Hg	< 80 to ≥ 60 mm Hg
Severe	≥ 15 mm Hg	< 60 to ≥ 50 mm Hg
Very severe	≥ 15 mm Hg	< 50 (< 300 mm Hg [40 kPa] on 100% oxygen breathing)

*All with positive contrast-enhanced echocardiography, breathing room air at rest and at sea level.

HPS is rigorously defined as a syndrome characterized by a clinical triad: (1) advanced chronic liver disease; (2) arterial oxygenation defect, which ultimately leads to severe arterial hypoxemia; and (3) widespread pulmonary vascular dilations.^{54,55} The pulmonary gas-exchange disturbance is characterized by arterial oxygen desaturation that may be mild, moderate, severe, or extremely severe (Table 93-2). There is an increased alveolar-arterial PO_2 difference, commonly associated with hypocapnia and respiratory alkalosis. At sea level, while breathing ambient air, resting alveolar-arterial PO_2 difference values at or above 15 mm Hg can be considered abnormal for most adults; for those older than 64 years, an alveolar-arterial PO_2 difference equal to or above 20 mm Hg can be considered abnormal. Although HPS is prevalent in most kinds of common chronic liver diseases, it may also be seen in other unusual liver disorders such as Budd-Chiari syndrome.^{56,57}

The most conspicuous pathologic finding is pronounced vascular dilation of all peripheral branches of the pulmonary vasculature, at both the precapillary and capillary levels of the lung (15 to 150 μ m in diameter), near the gas-exchange area in an otherwise intact pulmonary parenchyma.

Pathogenesis

The precise mechanism underlying HPS remains uncertain despite numerous investigations. Whether the mechanism of hemodynamic disturbances is related to a failure of metabolism, to insufficient production of one or more circulating vasoactive substances by the injured liver, or to altered clearance of putative vasodilator molecules produced by endothelial cells⁵⁸ remains unknown.

Nitric oxide (NO), a ubiquitous biologic agent considered to be a “fine-tuner” of vascular tone, has been presumed to be a pivotal signaling molecule of importance in the pathobiology of HPS.^{54,59} Persistent induction of *NO synthase* (NOS) could account for the hyperkinetic circulatory hallmarks of HPS.⁵⁹ Both a constitutive isoform of NOS, expressed in endothelial cells (eNOS, or type III NOS),⁶⁰ and the inducible NOS (iNOS, or type II NOS), expressed in target tissues such as human bronchial epithelial cells after exposure to proinflammatory cytokines,⁶¹ have been implicated in experimental models of HPS. In keeping with this contention, increased levels of exhaled NO have been observed in patients with advanced hepatic cirrhosis and in those with HPS.⁶² However, after interventions designed to improve

HPS, changes in measurements of exhaled NO have been discrepant.⁶³⁻⁶⁵

In patients with liver cirrhosis, the close correlations between exhaled NO concentration and the Child-Pugh score and levels of alkaline phosphatase, bilirubin, aspartate and alanine aminotransferases, and albumin suggest that NO formation in the lung may be triggered by stimulating factors normally inactivated by the liver.⁶³ More recent work suggests that endothelin-1 and TNF- α can both interact in the development of experimental HPS.^{54,66,67} Carboxyhemoglobin, a known vasodilator and breakdown product of hemoglobin, has also been associated with abnormal gas parameters in HPS, suggesting a possible contributory role.⁶⁸

Clinically, most patients with HPS are cyanotic, show conspicuous finger clubbing, may complain of shortness of breath and platypnea (increased dyspnea after assuming the upright position and relieved by recumbency), and have a hyperkinetic circulation. The majority of patients exhibit the typical clinical and functional stigmata of advanced liver failure, such as portal hypertension; in a few cases, severe pulmonary abnormalities may antedate those of hepatic dysfunction. The presence of abundant cutaneous spider angiomas has been postulated as a clinical marker of the severity of the systemic and pulmonary circulatory and gas-exchange abnormalities observed in HPS.⁶⁹ The severity of HPS generally correlates with the severity of hepatic failure, as shown by higher Child-Pugh scores and hepatic venous pressure gradients,⁷⁰ as well as scores from the Model for End-Stage Liver Disease.⁷¹ In approximately one third of patients with HPS, the syndrome can coexist with other chronic respiratory comorbidities such as COPD or pulmonary fibrosis. Nevertheless, the prevailing clinical and functional pulmonary features in patients with such comorbidities are generally those of HPS.⁷²

Diagnosis

Systemic hypotension, a normal or low *pulmonary artery pressure* (PPA), an inordinately high cardiac output, and a reduced pulmonary vascular resistance are the hemodynamic hallmarks of HPS. When the constellation of hypoxemia, normal or low PPA, spider nevi, and finger clubbing is observed in a patient with advanced liver disease, the diagnosis of HPS is likely.

The diagnostic criteria for HPS are as follows⁵⁴: presence of liver disease; gas-exchange abnormalities, more specifically an increased alveolar-arterial PO_2 difference (>15 mm Hg), with or without concomitant arterial hypoxemia (arterial $PO_2 < 80$ mm Hg); and a positive contrast-enhanced echocardiogram or an abnormal intravenous radiolabeled perfusion lung scan, or both. Additional features that can be useful for further establishing the diagnosis of HPS include a decreased DL_{CO} , dyspnea with or without platypnea and orthodeoxia (i.e., arterial hypoxemia that worsens by at least 5% or 4 mm Hg when the patient is upright vs. recumbent), and a hyperkinetic circulatory state with normal or low PPA. Although thoracic computed tomography scanning appears to be nonspecific, it may be used to exclude coexistent respiratory comorbidities.⁵⁴

Two-dimensional contrast-enhanced echocardiography appears to be the most sensitive and accurate noninvasive diagnostic procedure to identify right-to-left shunts by finding microbubbles of air in the left heart cavities within 3 to 6 beats of their visualization in the right-sided chambers⁵⁴ (Fig. 93-2) (see Video 61-1). Normally, echogenicity in the left chambers is not detected because the intravenously injected microbubbles (60 to 90 μ m in diameter) are trapped in the pulmonary capillaries (8 to 15 μ m in diameter). Contrast-enhanced echocardiography cannot distinguish among the different forms of pulmonary vascular deformities (i.e., precapillary, capillary, and pleural

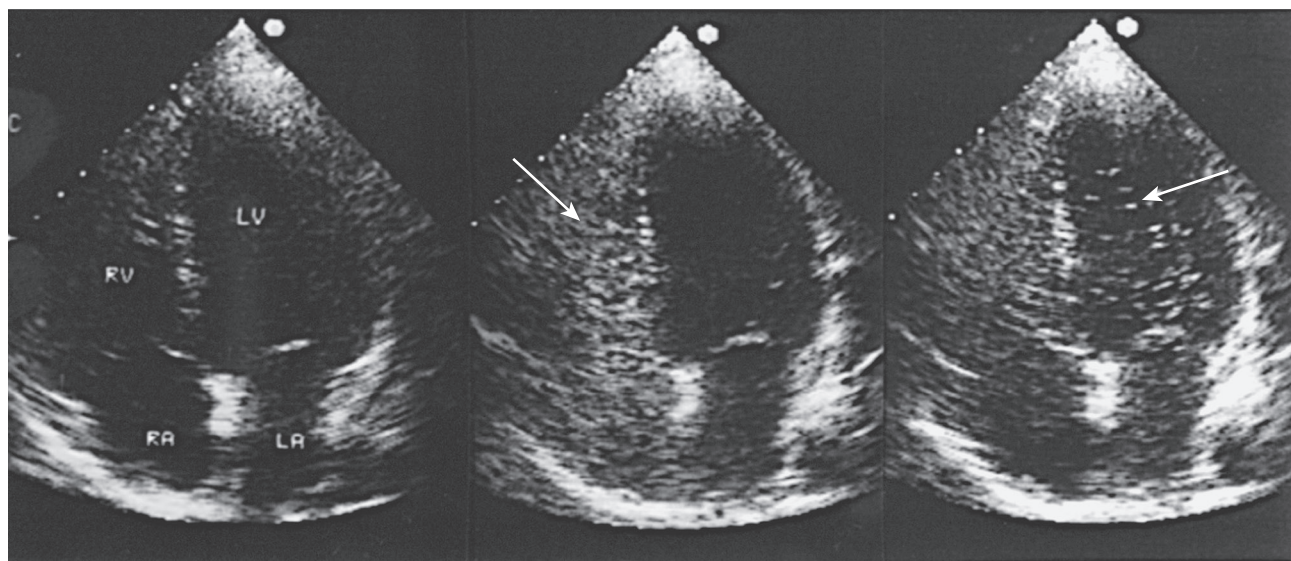


Figure 93-2 Contrast-enhanced echocardiograms in a patient with hepatopulmonary syndrome. Left, Normal four-chamber view (LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle). Center, Injected microbubbles appear in the RV (arrow). Right, Within five beats, microbubbles appear in the LV (arrow). The demonstration of microbubbles in the left cardiac chambers is highly suggestive of the presence of intrapulmonary vascular dilations, or, alternatively, of anatomic arteriovenous malformations. (See also Video 61-1.) (Courtesy Dr. C. Paré, Hospital Clínic, Universitat de Barcelona, Barcelona.)

dilations vs. direct arteriovenous communications), but it can clearly differentiate them from intracardiac malformations, such as a patent foramen ovale, in which the microbubbles appear in the left heart almost simultaneously with their appearance in the right. Alternatively, the demonstration of technetium-99m-macroaggregated albumin activity over extrapulmonary organs (e.g., liver, spleen, kidneys, and brain) strongly suggests the presence of right-to-left shunting, because under normal conditions the albumin macroaggregates (20 to 60 μm in diameter) are completely trapped in the pulmonary capillary bed.⁵⁴ This test does not distinguish between intrapulmonary and intracardiac shunting but can serve to estimate the severity of the shunt.

The prevalence of HPS ranges between 5% and 32%.⁵⁴ Using contrast-enhanced echocardiography—the “gold standard” for identifying intrapulmonary vascular dilations—the prevalence of a positive echocardiography test in patients with chronic liver disease is approximately 20%.^{57,73} However, patients with a positive contrast-enhanced echocardiogram without coexisting gas-exchange disturbances, are considered to have a *forme fruste* of HPS whose natural history is not yet known.^{73,74}

Although data describing the natural history of HPS are scant, it appears that patients with HPS not undergoing liver transplantation worsen progressively and have an adverse outcome, with median survival of 41 months following the diagnosis of HPS.⁵⁴ In a prospective study, HPS was an independent risk factor for poor prognosis in patients with cirrhosis; those with HPS had a significantly shorter median survival (approximately 11 months) than those without HPS (41 months), even after adjusting for differences in liver disease.⁷⁵

Gas-Exchange Abnormalities

When HPS is mild to moderate, the predominant mechanism of hypoxemia is ventilation-perfusion inequality, essentially due to the presence of areas in which ventilation is preserved but perfusion is profoundly increased. In contrast, when HPS is severe, increased intrapulmonary shunt develops and worsens along with coexisting ventilation-perfusion imbalance, and constitutes the primary abnormality. Collectively, with increasing severity of the liver dysfunction, there is greater systemic and pulmonary dilation, a lower hypoxic pulmonary vascular response, and a greater degree of ventilation-perfusion inequality, including increased intrapulmonary shunt.^{54,76} A “diffusion-perfusion defect” has also been postulated to explain an increased diffusion gradient for oxygen in dilated pulmonary capillaries (Fig. 93-3). The contention is that pulmonary vascular dilation causes inadequate diffusion of oxygen to the center of the enlarged capillary. Moreover, the coexistence of a hyperkinetic state and the resulting shorter transit time of red blood cells would exaggerate this diffusion-induced gas-exchange disturbance.⁷⁷

Treatment

Many therapeutic agents have been tried in HPS, including bismesylate almitrine, long-term oxygen therapy, methylene blue, and propranolol, with disappointing results.⁷⁷ The only successful treatment thus far is liver transplantation. In theory, replacement of the damaged organ should prevent all HPS-induced abnormalities, except for persistent

low DL_{CO} , whose mechanism remains unclear.⁵⁴ As might be expected, the worse the hypoxemia before transplantation, the longer it takes to resolve after surgery.⁷⁸ In the largest reported single-institution study thus far, 5-year survival after liver transplantation for HPS was 76% and did not differ from the survival rate after transplantation in patients without HPS.⁷⁹

Youth, a good arterial PO_2 response to 100% oxygen breathing, and less presurgical hypoxemia are all factors that seem to predict a favorable response to liver transplantation.⁸⁰ Collectively, these elements may indicate a more reactive pulmonary vasculature and less profound intrapulmonary shunt. However, a more recent study of patients with HPS undergoing liver transplantation indicated that survival was not correlated with arterial PO_2 at the time of diagnosing HPS.⁸¹

PORTOPULMONARY HYPERTENSION

Pulmonary arterial hypertension (PAH) associated with portal hypertension—also known as *portopulmonary hypertension* (POPH)—is another mysterious pulmonary vascular disorder that appears to be associated with chronic hepatic disease.^{55,80,82} Because both the diagnosis and the outcome of POPH, particularly in relation to the therapeutic benefits of liver transplantation, appear to be substantially different from those of HPS, it is important to highlight the distinctions between the two disorders. POPH is defined by the following triad of hemodynamic abnormalities in a patient with portal hypertension: (1) mean PPA exceeding 25 mm Hg at rest; (2) mean pulmonary artery wedge pressure less than 15 mm Hg; (3) pulmonary vascular resistance greater than $240 \text{ dynes} \cdot \text{sec}^{-1} \cdot \text{cm}^{-5}$ (normal, less than $130 \text{ dynes} \cdot \text{sec}^{-1} \cdot \text{cm}^{-5}$).⁸²

Various studies have estimated the prevalence of portopulmonary hypertension in those evaluated for liver transplantation as between 5% and 6%.⁸³ Furthermore, findings from a large cooperative trial of 536 patients with portal hypertension established that female gender and associated autoimmune hepatitis conferred increased risk for development of POPH, whereas hepatitis C was associated with decreased risk.⁸³

In classic retrospective postmortem studies, the prevalence of histopathologic evidence of PAH in patients with liver cirrhosis or POPH (or both) ranged between 0.25% and 0.73%.⁸⁴ In a case-control study conducted by the International Primary Hypertension Study Group, the incidence of primary (or idiopathic) PAH was found in 7.3% of patients with cirrhosis, 3.1% of those with human immunodeficiency virus infection, and none of the controls.⁸⁵ According to these and subsequent observations, POPH has been classified as a category of PAH with hemodynamic criteria consistent with the standard classification and definition of PAH, as discussed in Chapter 58 (see Table 58-1).^{55,86,87}

From a histopathologic viewpoint, the vascular lesions in POPH are indistinguishable from those identified in idiopathic (primary) PAH (see Chapter 58), namely intimal thickening, smooth muscle proliferation, plexogenic pulmonary arteriopathy, and in situ thrombosis,⁸⁸ all of which—plus vasoconstriction—contribute to the greatly increased pulmonary vascular resistance.⁸⁹ Chemla and colleagues⁹⁰ postulated that the portosystemic shunting of vasoactive

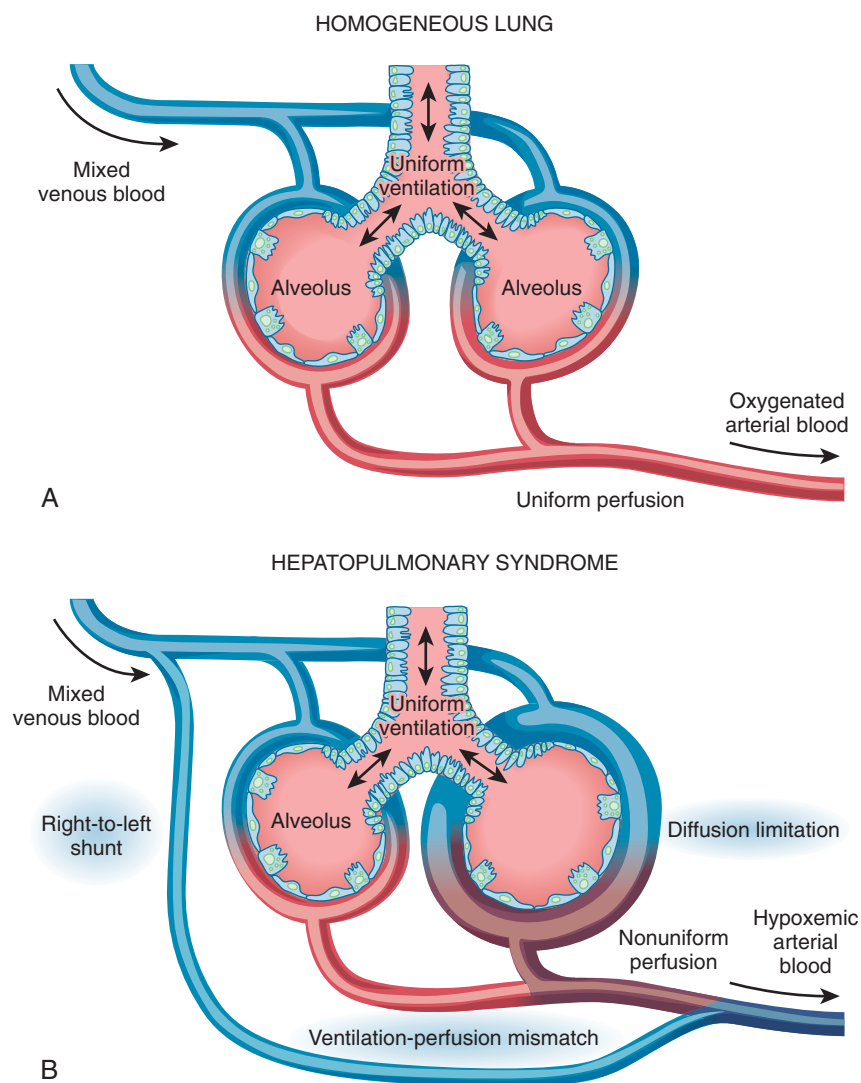


Figure 93-3 Mechanisms of arterial hypoxemia in hepatopulmonary syndrome in a two-compartment gas exchange model. **A**, In the homogeneous lung of a healthy individual, with uniform alveolar ventilation and pulmonary blood flow, the capillary ranges between 8 and 15 μm in diameter and oxygen diffuses properly into the capillary while ventilation-perfusion is well balanced. **B**, In hepatopulmonary syndrome, where many capillaries are dilated and blood flow is nonuniform, alveolar ventilation-to-pulmonary perfusion mismatch emerges as the predominant mechanism at any clinical stage, either with or without the presence of intrapulmonary shunt and coexistent with oxygen diffusion limitation into the center of the dilated capillaries in the most advanced stages. (From Rodriguez-Roisin R, Krowka MJ: Hepatopulmonary syndrome—a liver-induced lung vascular disorder. *N Engl J Med* 358:2378–2387, 2008.)

agents such as thromboxanes, serotonin, bradykinin, and neuropeptide Y, which are normally metabolized by the healthy liver, may result in pulmonary arterial vasoconstriction; an attractive alternative hypothesis is that pulmonary endothelial dysfunction leads to a decreased production of the endogenous vasodilator NO.

The most common symptom of POPH is shortness of breath on exertion; patients may also experience chest pain, syncope, and hemoptysis.⁹¹ Radiographically, both an enlarged cardiac silhouette and a pulmonary artery prominence are noted in approximately one half to two thirds of patients with POPH.^{83,91} Overall, maximal airflow rates and lung volumes are normal or nearly normal, whereas DL_{CO} , arterial PO_2 , and alveolar-arterial PO_2 difference may be reduced, although less so than in HPS.⁸³ Compared with patients with idiopathic PAH, patients with POPH have a lower mean PPA and a higher cardiac index and mixed venous oxygen saturation.⁸⁹

Transthoracic echocardiography is now done routinely in patients being considered for liver transplantation because the presence of POPH affects the outcome of surgery. Characteristic echocardiographic findings of idiopathic PAH in the setting of portal hypertension suggest,

but do not prove, POPH. Right heart catheterization is needed to confirm the diagnosis. Until recently, it was believed that median survival in POPH was extremely poor; new information, however, indicates overall survival rates at 1 and 3 years of 88% and 75%, similar to that in patients with idiopathic PAH.^{86,88}

Treatment for POPH, however, remains challenging because there are no randomized controlled studies for guidance: available agents include epoprostenol, iloprost, sildenafil, and bosentan.⁹² In a retrospective study, the safety and efficacy of inhaled iloprost and bosentan were assessed in 31 patients with POPH for up to 3 years; although both agents were safe with regard to liver function, bosentan proved to be better than iloprost in improving exercise capacity, hemodynamics, and—of note—survival rates.⁹³ Prospective trials are clearly needed to provide further guidance.

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis, an autoimmune disease, is characterized by a chronic, cholestatic, granulomatous, and destructive process that involves the intrahepatic bile

ducts.⁹⁴ When severe, these processes result in cholestasis, cirrhosis, and liver failure. The autoimmune basis is reflected in the presence of several immunologic alterations, such as depressed T-suppressor cell function, hypergammaglobulinemia, and the presence of antimitochondrial antibodies. Connective tissue diseases such as the sicca complex, Sjögren syndrome, and scleroderma are frequently associated with primary biliary cirrhosis,^{95,96} which also has an association with POPH.⁸³ Several respiratory abnormalities have been associated with primary biliary cirrhosis: interstitial lung disorders, such as lymphocytic interstitial pneumonitis and fibrosing alveolitis; subclinical intrapulmonary granulomas that mimic sarcoidosis⁹⁷; increased numbers of CD4⁺ lymphocytes in the bronchoalveolar lavage fluid; and obstructive airway disease, such as bronchiectasis.⁹⁸ Occasionally, the pulmonary manifestations precede the liver involvement.⁹⁹ In addition, thoracic wall deformities secondary to osteopenic vertebral complications induced by abnormal vitamin D metabolism related to poor absorption of fat-soluble vitamins can be also observed.⁹⁸ A reduced DL_{CO}, with or without ventilatory defects, is one of the functional hallmarks of the disease, particularly when a connective tissue disorder coexists.⁹⁹⁻¹⁰¹

CHRONIC ACTIVE HEPATITIS

Chronic active hepatitis, an increasingly frequent liver disease that is characterized by diffuse parenchymal inflammation and hepatic cell necrosis, may be caused by viral hepatitis (most commonly hepatitis C virus), autoimmune disorders, and drug-related liver injury. Pulmonary fibrosis and lymphoid interstitial pneumonitis have been reported but are rare.^{100,102} After years of smoldering inflammation, which is often asymptomatic, chronic active hepatitis can lead to cirrhosis and liver failure, which has been associated with HPS.⁹⁸ Patients with chronic hepatitis C virus infection and coexistent COPD may demonstrate an accelerated annual decline in forced expiratory volume in 1 second.¹⁰³

SCLEROSING CHOLANGITIS

Sclerosing cholangitis is an unusual disease that results from chronic inflammation affecting both intrahepatic and extrahepatic bile ducts. It has been linked with inflammatory obstructive airway diseases such as bronchiectasis; however, the relationship remains unproven because ulcerative colitis, a frequent clinical accompaniment, has also been associated with the same respiratory complications.¹⁰⁴

ALPHA₁-ANTITRYPSIN DEFICIENCY

The discovery that certain patients with COPD had low levels of circulating alpha₁-antitrypsin led to the current protease-antiprotease theory of the pathogenesis of pulmonary emphysema (see Chapter 43 for complete discussion). This hereditary disorder is nearly always associated with the homozygous PiZZ phenotype. Genetically predisposed infants often present with hepatomegaly or hepatosplenomegaly and evidence of cholestasis. Most children with alpha₁-antitrypsin-induced liver disease recover, but cirrho-

sis develops in about 15%, presumably from toxic effects of the mutant antitrypsin protein retained in the endoplasmic reticulum of hepatocytes¹⁰⁵; HPS has been reported as a complication of this form of cirrhosis.¹⁰⁶ COPD is the most common pulmonary complication. COPD is unrelated to the presence of liver disease, develops in adults, and is characterized by panacinar emphysema, especially in the lower lung zones, and bronchial abnormalities, including bronchiectasis.⁹⁸

PANCREATITIS

Pancreatitis may be acute or chronic and has two main origins: gallstone migration and chronic alcoholism. But more and more causes of pancreatitis have been identified and a classification of etiologies has been proposed according to the following acronym TIGAR-O: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, and obstructive.¹⁰⁷ Most episodes of acute pancreatitis are mild, but can be severe in about 20% of patients, of whom 15% to 25% die.¹⁰⁸ Pulmonary complications are frequent and account for significant mortality; intrathoracic complications contribute to death in 22% to 29% of patients who succumb from fatal pancreatitis, and arterial hypoxemia (PO₂ < 60 mm Hg) is a major factor affecting survival.¹⁰⁹ Besides hypoxemia, pleural effusion and *acute respiratory distress syndrome* (ARDS) influence the outcome of respiratory failure in acute pancreatitis.^{110,111}

RESPIRATORY FAILURE

Gas exchange disturbances, ranging from mild hypoxemia to ARDS may arise during episodes of acute pancreatitis. Arterial hypoxemia and normal results on chest radiograph is a frequent finding of acute pancreatitis in its early stages.¹¹² Initially, arterial hypoxemia may be asymptomatic and mild, but patients who present with hypoxemia during an episode of acute pancreatitis should be closely monitored for worsening respiratory failure; for example, Ranson and associates¹¹³ reported that, of 67% of patients who had an initial arterial PO₂ less than 66 mm Hg in whom clinical respiratory symptoms developed afterward, 39% died.¹¹³

The mechanisms of arterial hypoxemia in the setting of a normal chest radiograph finding during acute pancreatitis remain poorly understood. Murphy and associates¹¹⁴ showed that hypoxemia in these patients was caused by an increase in the right-to-left shunt fraction, which usually improved after recovery. No changes were seen in expiratory flow rates, lung volumes, or closing capacity, compared with measurements performed after recovery. These authors suggested that hypoxemia in the absence of radiologic abnormalities may be related to changes in pulmonary vascular permeability, similar but milder than that described in ARDS.¹¹⁴ De Troyer and associates¹¹⁵ measured a transient reduction of DL_{CO}, and suggested that increased capillary permeability and impaired DL_{CO} result from factors released by the injured pancreas. In addition, Greenberg and coworkers¹¹⁶ demonstrated a reduction in the oxygen affinity of hemoglobin related to the increase in circulating fatty acids.

ARDS developed in about 15% to 20% of patients with severe acute pancreatitis, with a reported mortality rate of 56%.¹¹⁷ The incidence of ARDS is higher in patients with hemorrhagic than with nonhemorrhagic pancreatitis.^{118,119} Respiratory symptoms typically appear 2 to 7 days after the onset of the acute episode, when the chest radiograph usually shows signs of pulmonary vascular congestion that progresses to bilateral diffuse opacities. Severe hypoxemia is usually associated with marked hypocapnia. Pathologic findings reveal evidence of acute lung injury indistinguishable from that observed in ARDS attributable to other causes.¹¹⁸

Lung injury associated with acute pancreatitis may result from a direct toxic effect of pancreatic products, from secondary release of inflammatory mediators, or from both. Several pancreatic products have the potential to induce lung injury. Phospholipase A₂ binds to pulmonary capillaries and has the ability to induce the enzymatic degradation of the phospholipid components of surfactant, thereby promoting alveolar collapse and increased vascular permeability.^{108,110} Free fatty acids from triglyceride degradation by circulating lipase may induce alveolar edema and hemorrhage.¹¹⁰ Pancreatic enzymes can induce lung injury and increase vascular permeability.¹²⁰ In addition to the direct effect of pancreatic products, sequestration of neutrophilic leukocytes within the alveolar and interstitial spaces is believed to play an important role in inducing lung injury and increasing pulmonary vascular permeability¹⁰⁸; moreover, mediators released during pancreatic injury, such as reactive oxygen species,¹²¹ adhesion molecules, platelet-activating factor,^{110,122} and many cytokines, may contribute to associated pulmonary vascular permeability.¹¹⁰

Because initially chest radiographs often appear normal, arterial hypoxemia may be clinically unsuspected and undetected but profound; therefore a high index of suspicion should be present for respiratory impairment in patients with acute pancreatitis, and arterial blood gases should be measured periodically during the initial 48 to 72 hours following hospitalization.¹²³ When hypoxemia develops, patients should receive supplemental oxygen to raise the arterial Po₂ above 70 mm Hg. Treatment of pancreatitis-associated lung injury is essentially supportive and does not differ from that for other forms of lung injury (see Chapter 43). Key measures include cardiovascular support and lung-protective ventilation.¹⁰⁸

Additional treatment includes suppression of the secretory function of the pancreas by elimination of oral intake, use of nasogastric suction, and inhibition of gastric acid secretion with histamine₂ blockers. Studies suggest that octreotide, a potent inhibitor of exocrine pancreatic secretion, may decrease both mortality rates and the incidence of ARDS among patients with severe acute pancreatitis.^{124,125} Nevertheless, controlled randomized trials of the effectiveness of octreotide in the prevention and treatment of pancreatitis-associated ARDS are needed.¹²⁵

PLEURAL EFFUSION

Pleural effusions may be associated with both acute and chronic pancreatitis (see Chapter 79). In acute pancreatitis, pleural effusion is a relatively frequent finding, being present

in about 20%¹²⁶ to 50% of patients.¹¹¹ In most cases these effusions are of small size; the majority (68%) are left sided, 22% are bilateral, and only 10% are right sided.¹¹⁰

Various pathogenic mechanisms have been proposed to explain the development of pleural effusions associated with acute pancreatitis¹²⁶: (1) increased fluid leak caused by pancreatic enzymes that may diffuse from the peritoneal side to the thoracic side of the diaphragm, (2) impaired lymphatic drainage of pleural exudate caused by obstruction of lymphatic vessels by the high enzymatic content of the pleural fluid, and (3) increased permeability of diaphragmatic capillaries caused by the inflammatory process in the adjacent pancreas.

In patients with pleural effusion associated with acute pancreatitis, symptoms are primarily abdominal (pain, nausea, and vomiting); occasionally, respiratory symptoms (pleuritic pain and dyspnea) may be present. The diagnosis is established by demonstrating an elevated amylase concentration in pleural fluid, a concentration that may be up to 30 times higher than that in plasma.¹⁰⁸ The pleural fluid usually is an exudate, which is sometimes bloody, and has a high concentration of both protein and lactic acid dehydrogenase; the differential white blood cell count reveals a predominance of polymorphonuclear cells.

Pleural effusions associated with acute pancreatitis usually are self-limited and resolve when the pancreatic inflammation subsides without requiring therapeutic drainage. Therefore, if the pleural effusion does not resolve within 2 weeks after treatment for the pancreatic disease, the possibility of a pancreatic abscess or a pseudocyst should be considered.

Chronic pleural effusions are usually associated with chronic relapsing pancreatitis and pancreatic pseudocyst. In most cases, a history of alcohol abuse is present.¹²⁷ Chronic effusions are large, may occupy the entire hemithorax, and reaccumulate rapidly after thoracentesis.

The typical mechanism of a chronic effusion is a pancreaticopleural fistula, a direct communication between the pancreas and the pleural space. In chronic pancreatitis, the pancreatic duct may rupture because of high internal pressure. Once the duct is disrupted, pancreatic secretions can flow into the retroperitoneum, then into the mediastinum through the esophageal or aortic hiatuses, and then into the pleural space (Fig. 93-4, see also Fig. 79-9). Occasionally, a direct communication may develop between a pancreatic pseudocyst and the pleural cavity through the left hemidiaphragmatic dome.¹²⁷

Patients with chronic pancreatic effusions usually complain of respiratory symptoms such as chest pain and shortness of breath. Surprisingly, abdominal symptoms may be absent, probably because the pancreaticopleural communication decompresses the pseudocyst.¹²⁶ Therefore the diagnosis of a chronic pancreatic pleural effusion should be suspected in any patient with a large pleural effusion who appears to be chronically ill or has a history of pancreatic disease or alcohol abuse.¹²⁸ The diagnosis is established by the demonstration of a high concentration of amylase in the pleural fluid; in the setting of a pancreaticopleural fistula, amylase concentrations can be exceedingly high, often greater than 10,000 U/L. Ultrasonography and computed tomographic scanning of the chest and abdomen

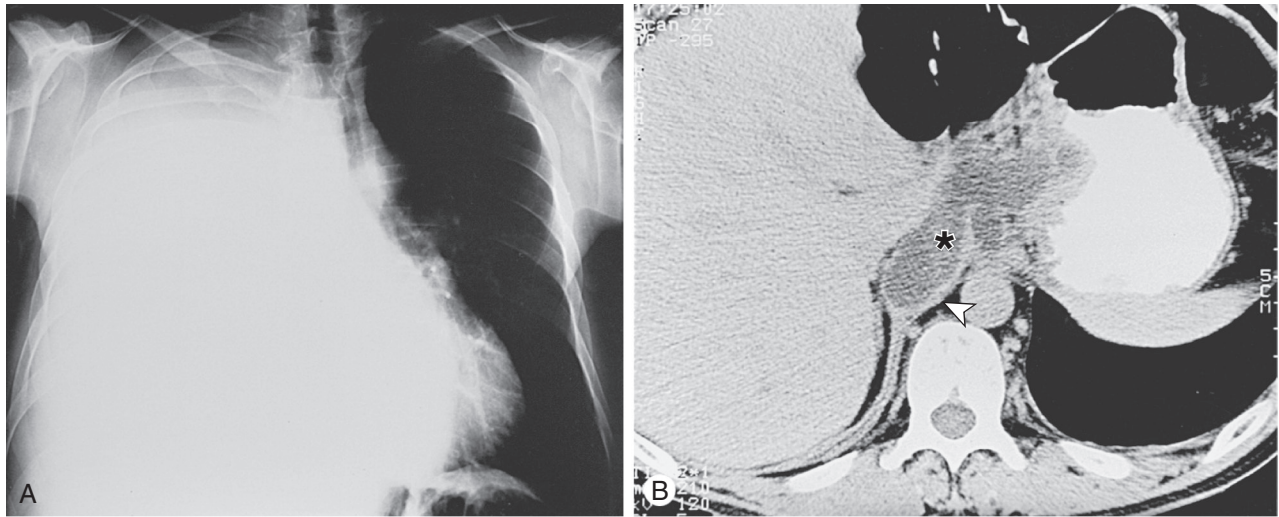


Figure 93-4 A massive pleural effusion associated with a pancreatic pseudocyst. **A**, Chest radiograph demonstrates a massive pleural effusion in the right hemithorax. **B**, CT scan of the upper abdomen performed after pleural drainage shows the cephalad extension of the pseudocyst (*asterisk*) through the right crural insertion (*arrowhead*) and the esophageal hiatus. (Courtesy Dr. S. Navarro, Hospital Clinic, Universitat de Barcelona, Barcelona.)

usually reveal the presence of a pseudocyst and occasionally may even show the pancreaticopleural fistula¹²⁸ (see Fig. 93-4). Endoscopic retrograde cholangiopancreatography provides additional information on ductal structures and may demonstrate passage of contrast material from the pancreatic duct or a pseudocyst into the peritoneal cavity, although visualization of the fistula may be difficult.^{127,129} Endoscopic retrograde cholangiopancreatography and computed tomographic scanning together provide complementary information, which is especially useful if the patient has to undergo surgical intervention.

Patients with chronic pancreatic disease–related pleural effusions should be treated initially with nasogastric tube suction, no oral intake, parenteral nutrition, and therapeutic thoracenteses as needed to improve symptoms. Inhibition of pancreatic secretion with octreotide has been shown to be useful in promoting the closure of pancreaticopleural fistulas in some cases.¹³⁰ Nonetheless, if after 2 to 3 weeks of medical therapy the pleural fluid continues to accumulate and the patient remains symptomatic, surgery to close the fistula should be considered.

OTHER MANIFESTATIONS

A condition called *autoimmune* or *sclerosing pancreatitis* has been linked to the presence of elevated serum IgG₄ concentrations.¹³¹ IgG₄-related disease is a fibroinflammatory condition characterized by a dense lymphoplasmacytic infiltrate rich in IgG₄-positive plasma cells, a swirling appearance of fibroblasts called a “storiform” fibrosis, and, sometimes, elevated serum IgG₄ concentrations.¹³² Furthermore, IgG₄-related disease has been recognized as a systemic condition involving virtually every organ, including the lung; all components of the respiratory system may be implicated, such as parenchymal inflammatory pseudotumor, interstitial pneumonia, central airway stenosis, and mediastinal fibrosis; lung involvement usually improves along with improvement of pancreatitis when treated with glucocorticosteroids.¹³³⁻¹³⁵

KIDNEY DISEASES

Acute and chronic renal diseases are associated with a variety of respiratory manifestations. Pulmonary edema can develop with either acute or chronic renal disease, and pleural disease, pulmonary calcification, and sleep apnea syndrome are fairly common with chronic renal disease. Historically, treatment with hemodialysis caused transient changes in pulmonary gas exchange. These disorders are discussed in this section. Systemic necrotizing vasculitis and diseases associated with autoantibodies, which usually affect both the lung and the kidney, are considered in Chapters 60 and 67.

PULMONARY EDEMA

Pulmonary edema is common in patients with acute or chronic renal functional impairment. A variety of conditions may favor edema formation: fluid overload, left ventricular failure, hypoalbuminemia, and increased pulmonary microvascular permeability. The relative importance of increased microvascular permeability on the one hand versus left ventricular failure on the other has caused controversy for decades. Autopsy findings showing the presence of protein-rich edema fluid, hyaline membranes, and alveolar hemorrhage^{136,137} all pointed to increased pulmonary vascular permeability as the likely mechanism of pulmonary edema formation, as discussed in Chapter 62. The demonstration of an increased protein content in edema fluid sampled directly by endotracheal aspiration reinforced this hypothesis.¹³⁸ Furthermore, pulmonary edema has been reported in the absence of volume overload and in the presence of normal intracardiac and pulmonary wedge pressures.

In contrast, studies using a double-isotope technique have failed to show a significant accumulation of radiolabeled transferrin in patients with renal injury and pulmonary edema.¹³⁹ The rate of protein accumulation in patients with impaired renal function was similar to that in

patients with cardiogenic pulmonary edema and in normal volunteers, and was significantly lower than in patients with ARDS; these observations suggest that pulmonary edema in some if not most patients with renal disease is probably not related to increased pulmonary vascular permeability.¹³⁹

Heart failure is believed to play an important role in the development of pulmonary edema associated with chronic renal disease. Cardiac disorders are common in end-stage renal dysfunction, and a variety of factors, including hypertension, diabetes mellitus, anemia, surgical arteriovenous fistulas, and ischemic heart disease, may adversely affect cardiac function.^{140,141} Left ventricular dysfunction may be reversible after dialysis or renal transplantation, which suggests that patients with chronic renal impairment may have a specific “uremic cardiomyopathy.”^{140,142,143}

Subclinical lung congestion in patients with chronic renal insufficiency may reduce lung volumes and maximal expiratory flow rates, which usually reverse after hemodialysis.¹⁴⁴⁻¹⁴⁶ In contrast to the findings in patients with left ventricular dysfunction,¹⁴⁷ subclinical pulmonary edema in renal injury is not associated with bronchial hyperresponsiveness, either before or after hemodialysis.¹⁴⁸

From a clinical standpoint, most instances of pulmonary edema associated with renal impairment, both acute and chronic, involve increased intravascular volume from abnormal left ventricular function and fluid overload. Accordingly, its treatment should essentially consist of removal of excess body fluid with dialysis.

PLEURAL DISEASE

Approximately 20% to 40% of patients who die of chronic renal insufficiency have fibrinous pleuritis detected at autopsy.^{136,149} This fibrinous pleuritis can be manifested as pleuritic chest pain with pleural friction rubs,¹⁵⁰ pleural effusion,¹⁵¹ or fibrothorax.^{152,153}

Pleural effusions were detected in 20% of 257 hospitalized patients receiving long-term hemodialysis; the most common symptom was dyspnea.¹⁵⁴ Other patients may be asymptomatic or they may present with fever, chest pain, or cough. The effusions usually are unilateral and, in some cases may be large, occupying more than 50% of the hemithorax. In one study, the pleural fluid was transudative in about two thirds of the patients and exudative in the remainder.¹⁵⁴ In patients with exudates, the leukocyte count revealed a predominance of lymphocytes, and the biopsy specimens usually demonstrated chronic fibrinous pleuritis.¹⁵⁵ The pathogenesis of “chronic uremic pleuritis” associated with renal dysfunction is not known, but it is probably related to the effect of retained metabolic toxins.

The effusion usually disappears gradually after several weeks of dialysis but, in about 25% of patients, it may persist, progress, or recur. If fibrothorax develops and produces a symptomatic restrictive ventilatory impairment, surgical decortication should be considered.^{152,153}

PULMONARY CALCIFICATION

Metastatic calcification is a common complication of chronic renal disease that may affect many visceral organs and is found in 60% to 80% of dialysis patients at autopsy

or by bone scintigraphy.¹⁵⁶ Similar diffuse calcifications may be found in other systemic or pulmonary conditions.¹⁵⁷ Pulmonary involvement is common, but it is generally undetectable by ordinary chest films and most patients are asymptomatic.¹⁵⁸ At times, the chest radiograph or computed tomogram may show nodular opacities less than 2 mm in diameter that can be diffuse or localized (see Fig. 95-2). The opacities are relatively stable, in contrast to what would be seen with infectious processes. Pulmonary function tests may reveal a restrictive ventilatory defect and/or a reduction in DL_{CO} .

The pathogenesis of pulmonary calcification in patients with chronic renal insufficiency is complex; several factors—in concert—may play a role: (1) the effect of chronic acidosis, which leaches calcium from bones; (2) the effect of intermittent alkalosis, which favors the deposition of calcium salts; (3) the effect of hyperparathyroidism, which causes bone reabsorption and intracellular hypercalcemia; and (4) the effect of low glomerular filtration rate, which causes hyperphosphatemia and a greatly elevated calcium-phosphorus product.¹⁵⁶

The diagnosis of pulmonary calcification can be confirmed by pulmonary uptake during technetium-99m-diphosphonate scanning (see Fig. 95-3).¹⁵⁹ Treatment is generally unsatisfactory and consists of maintaining adequate dialysis, lowering the calcium-phosphorus product, and treating hyperparathyroidism, when present; renal transplantation may sometimes improve or actually worsen the condition.¹⁵⁶

SLEEP APNEA

Disturbed sleep, including sleep apnea, has long been recognized in patients with end-stage renal disease. (Other causes of sleep apnea, as well as its pathophysiology and treatment, are described in Chapter 88.) The mounting evidence in favor of a high prevalence of sleep apnea in dialysis patients—greater than 50%¹⁶⁰—has been reinforced by the results of comparisons between patients on standard thrice-weekly hemodialysis and closely matched control subjects from the community-based Sleep Heart Health Study: dialysis patients had a fourfold increase in sleep apnea and episodes of severe nocturnal hypoxemia, after adjusting for comorbid conditions that might have affected outcome.¹⁶¹

Various mechanisms have been proposed to explain the high prevalence of sleep apnea in patients with end-stage renal disease undergoing hemodialysis. Perhaps the most persuasive of the pathogenetic speculations involves the importance of fluid overload and the shift of fluid to the upper body during sleep, thereby facilitating airway obstruction.¹⁶² Support for this postulate comes from the increased pharyngeal resistance that accompanies shifts of fluid produced by applying high pressure to the lower body in healthy subjects.¹⁶³ Follow-up studies using the same methodology documented an increase in upper airway collapsibility.¹⁶⁴ Such studies support the hypothesis that fluid displacement during recumbency predisposes to obstructive sleep apnea.

Accumulation of uremic toxins might also play a role, independently or in conjunction with fluid overload, in the pathogenesis of sleep disorders. Increasing the frequency and length of nocturnal hemodialysis, which does

not distinguish between the presence of toxins and fluid overload as possible mechanisms, caused a significant decrease in the severity of sleep apnea in all 14 patients in whom it was tried,¹⁶⁵ thus offering a potential, but logistically complicated, solution to an otherwise difficult-to-treat and serious clinical problem.

Standard treatment of obstructive sleep apnea might be beneficial, but experience in patients with end-stage kidney disease is limited.¹⁶⁶ There are anecdotal reports of improvement after renal transplantation,¹⁶⁷ but according to one report, only 3 of 18 patients had significant improvement after the procedure.¹⁶⁸

HEMODIALYSIS-INDUCED HYPOXEMIA

Another clinical problem that was associated with end-stage renal disease and hemodialysis—now largely of historic interest only—was the prompt reduction in arterial PO_2 of 10 to 15 mm Hg after initiation of dialysis, which reached a nadir after 30 to 60 minutes and persisted for the duration of the procedure.¹⁶⁹⁻¹⁷¹ The severity of hypoxemia varied according to the type of dialysis membrane and the chemical nature of the dialysate buffer.^{172,173} Once popular explanations for the phenomenon, pulmonary vascular leukostasis and activation of complement, have since been excluded. Exposure of blood to certain dialysis membranes activates the alternative complement pathway and, within minutes, C3a and C5a are generated, which may induce intrapulmonary sequestration of leukocytes and a fall in circulating leukocytes. Based on the temporal association between the onset of hypoxemia and the transient leukopenia, it was postulated that the decrease in arterial PO_2 resulted from ventilation-perfusion mismatching due to leukostasis in small pulmonary vessels.¹⁷⁴ However, studies using the multiple inert gas elimination technique ruled out ventilation-perfusion mismatching as the principal mechanism of hypoxemia,¹⁷⁵⁻¹⁷⁷ even though Romaldini and colleagues¹⁷⁶ showed a tendency for ventilation-perfusion matching to improve during the dialysis procedure, which was most likely explained by a dialysis-induced decrease in extravascular lung water. Furthermore, hypoxemia was observed during dialysis with membranes that do not cause leukopenia.¹⁷⁸

Currently, the most accepted explanation for the decrease in arterial PO_2 during hemodialysis is the onset of hypoventilation associated with the removal of carbon dioxide by the dialysate, which is substantial with acetate buffer but minimal with bicarbonate buffer¹⁷⁹; in addition, acetate buffer may further reduce respiratory carbon dioxide elimination due to carbon dioxide consumption during acetate metabolism.¹⁸⁰ In one study of patients undergoing hemodialysis with acetate buffer, minute ventilation dropped from an average of 7.2 L/min to 5.7 L/min within 15 minutes of the start of hemodialysis.¹⁸¹ The alveolar-arterial PO_2 difference value during hemodialysis remains stable despite a significant fall in arterial PO_2 .^{171,176} An additional consequence of the nonrespiratory carbon dioxide “unloading” was to destabilize resting ventilation, which was manifested by an irregular breathing pattern, with the development of periodicity and sometimes apneas.^{181,182}

Today, the former complications of leukopenia and hypoxemia during hemodialysis have been largely elimi-

nated by the use of synthetic (inert) membranes, which do not activate complement and thus avoid leukopenia, and dialysates such as bicarbonate, which do not remove carbon dioxide. Supplemental oxygen should still be given during the procedure to patients with coexisting cardiopulmonary diseases.

Key Points

- Gastroesophageal reflux, a common disorder, may cause recurrent chest pain, varying from heartburn to myocardial ischemia-like distress, may provoke or exacerbate chronic cough, and may trigger asthma attacks or worsen other underlying respiratory conditions.
- Inflammatory bowel diseases, ulcerative colitis more so than Crohn disease, have been associated with a variety of chronic pulmonary diseases, particularly of the airways; these include asthma, chronic bronchitis, and bronchiectasis, and, less commonly, disorders of the lung parenchyma, such as interstitial fibrosis and cryptogenic organizing pneumonia.
- Patients with end-stage liver disease can have characteristic pulmonary complications: hepatic hydrothorax develops in 5% to 10%; hepatopulmonary syndrome, characterized by hypoxemia from marked dilation of pulmonary capillaries, develops in as many as 20%; portopulmonary hypertension (mean PPA > 25 mm Hg) develops in another 6% of patients.
- Episodes of severe acute pancreatitis are associated with a high frequency of pulmonary complications, especially hypoxemia, pleural effusions, and acute respiratory distress syndrome, which are major causes of excess morbidity and mortality.
- Diseases of the kidney are important causes of pulmonary edema, pleural disease, pulmonary calcifications, and sleep apnea, some of which may be alleviated by dialysis and/or renal transplantation.

Complete reference list available at *ExpertConsult*.

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PULMONARY COMPLICATIONS OF HEMATOLOGIC DISEASES

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INTRODUCTION

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INTRODUCTION

Hematologic diseases and their specific therapies can adversely affect several aspects of cardiopulmonary function, by reducing the oxygen-carrying capacity of the blood, by impairing pulmonary vascular function and pulmonary immune defenses, and by direct pulmonary parenchymal damage. This chapter reviews the clinical manifestations, epidemiology, pathophysiology, and treatment of pulmonary complications of disorders of the hematologic system.

RED BLOOD CELL DISORDERS

ANEMIA

Anemia is defined as a reduction in the number of circulating red blood cells. By decreasing oxygen-carrying capacity of the blood, anemia can impair cardiopulmonary function. However, because multiple compensatory mechanisms exist to adjust to a reduced oxygen-carrying capacity of blood, the signs and symptoms induced by anemia depend on the degree of anemia, the rate at which it evolves, the oxygen demands of the patient, and the presence of chronic cardiopulmonary disease. For instance, in resting adults subjected to acute isovolemic anemia, oxygen delivery can be maintained at hemoglobin concentrations as low as 5 g/dL,¹ a finding also seen in individuals with chronic severe anemia.² As such, anemia, even when severe, rarely causes heart failure or pulmonary edema and, when it does, it is likely that heart failure from chronically high cardiac output is superimposed on some other coexisting cardiac abnormality. From the hemodynamic standpoint, as the hemoglobin level decreases (particularly with hemoglobin values < 7 g/dL), cardiac output increases, filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease. Further, these changes are readily reversible after red blood cell transfusions.^{2,3} Finally, when anemia is severe, in the absence of coexisting cardiopulmonary disease, gas exchange is usually well maintained.

Pulmonary hypertension (PH) is an increasingly recognized complication of chronic hereditary and acquired hemolytic anemias. Remarkably, virtually every cause of hemolytic anemia has been associated with PH (Table

94-1). The PH associated with hemolytic disorders is now considered in the Group 5 classification of pulmonary hypertension, characterized by unclear/multifactorial mechanisms (see Chapter 58).^{3a} In contrast, there have been no reports of PH associated with nonhemolytic anemias such as the anemia of chronic disease or iron deficiency anemia. This suggests that the hemolytic component of anemia is necessary for the development of PH, which is discussed in detail in the section on [hemoglobinopathies](#).

POLYCYTHEMIA

Polycythemia is characterized by an abnormally high hematocrit (>48% and >52% in women and men, respectively), hemoglobin concentration (>16.5 or >18.5 g/dL in women and men, respectively), or red blood cell count. These measurements are dependent on the plasma volume as well as the red blood cell mass; thus, before classifying a patient as having true polycythemia, one must exclude a decrease in plasma volume as the etiology for these abnormalities. A state of chronically reduced plasma volume with elevated hemoglobin or hematocrit has been called Gaisböck disease,⁴ spurious polycythemia, stress erythrocytosis, apparent polycythemia, and pseudopolycythemia and has been associated with use of diuretics, alcohol, obesity, hypertension, and renal disease. On the other hand, patients with true elevations in red blood cell mass have absolute polycythemia and are categorized in primary and secondary forms. Primary polycythemia is caused by an acquired or inherited mutation such as in the *JAK2* gene,⁵ leading to an abnormality within red blood cell progenitor cells; it includes polycythemia vera and rare familial variants (e.g., activating mutations of the erythropoietin receptor or Chuvash polycythemia). Secondary polycythemia is caused by a circulating factor stimulating erythropoiesis, usually related to the production of erythropoietin as a physiologic response to chronic hypoxia (e.g., chronic hypoxic lung disorders and disorders affecting hemoglobin oxygen affinity), but can also result from erythropoietin-secreting tumors.

Most of the symptoms of polycythemia are related to an increase in blood viscosity, which leads to impairment in systemic and pulmonary blood flow. Thromboembolic events have been described in approximately 30% of patients with polycythemia vera and account for 31% of their

Table 94-1 Hemolytic Disorders Associated with Pulmonary Hypertension

Hemoglobinopathies
Sickle cell disease
Thalassemia intermedia and major
Hb Mainz unstable hemoglobin hemolytic anemia
Red cell membranopathies
Hereditary spherocytosis
Hereditary stomatocytosis
Paroxysmal nocturnal hemoglobinuria
Alloimmune hemolytic anemia
Red cell enzymopathies
Pyruvate kinase deficiency
Glucose-6-phosphate dehydrogenase deficiency
Microangiopathic hemolytic anemia
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Hemolysis from mechanical heart valves
Left ventricular assist devices and cardiopulmonary bypass procedures
Malaria

deaths.⁶ Pulmonary nodular lesions secondary to thrombosis, stasis, or infarction have been described in these patients.⁷ Late-stage polycythemia vera, which is characterized by myelofibrosis, may cause pulmonary and pleural masses that are related to extramedullary hematopoiesis.⁸

PH has been reported in patients with polycythemia and other myeloproliferative disorders (recently reviewed by Machado and Farber).^{7,9-11,11a} In a retrospective review, 26 patients—12 with myeloid metaplasia, 5 with essential thrombocythemia, 6 with polycythemia vera, 2 with myelodysplastic syndrome, and 1 with chronic myeloid leukemia—had echocardiographic or hemodynamic evidence of PH. Interestingly, the median survival after the diagnosis of PH was 18 months and the majority of deaths were related to cardiopulmonary causes, suggesting that the presence of PH was a direct cause of death.⁹ In a subsequent retrospective study of 10 patients with PH and myeloproliferative disorders (8 with polycythemia vera and 2 with essential thrombocytosis), 6 patients had chronic, thromboembolic PH and 4 had unexplained PH; these findings were most likely associated with the myeloproliferative disorder because other risk factors for PH could not be identified.¹² In a cohort of 14 patients with Chuvash polycythemia, the prevalence of PH (defined as an estimated pulmonary artery systolic pressure ≥ 35 mm Hg) was 36%.¹¹ The pathogenesis of PH in these disorders is not well established but can involve chronic thromboembolic disease or hypercoagulability and hyperviscosity leading to in situ thrombosis, as well as hemoglobin-dependent scavenging of endothelium-derived *nitric oxide* (NO)¹³⁻¹⁷ and up-regulation of HIF-1 α -mediated pathways, such as endothelin-1.¹¹

In patients with polycythemia vera, the mainstay of therapy is phlebotomy and myelosuppression with hydroxyurea, to keep the hematocrit below 42% in women and 45% in men, and antithrombotic therapy with aspirin or anagrelide.^{18,19} In case series, treatment of the myeloproliferative disorder has been shown to improve PH.⁹ In patients with chronic hypoxic disorders such as *chronic obstructive pulmonary disease* (COPD) and interstitial lung disease, long-term oxygen therapy should reduce the number of patients

who become severely polycythemic. In patients with COPD and severe polycythemia, phlebotomy—to achieve a hematocrit of about 50%—is associated with both a decrease in mean pulmonary artery pressure and in pulmonary vascular resistance, as well as an improvement in exercise performance.²⁰ However, the use of phlebotomy should be reserved as adjunctive therapy in the management of markedly polycythemic and symptomatic patients who remain significantly polycythemic despite appropriate long-term oxygen therapy.

HEMOGLOBINOPATHIES

SICKLE CELL DISEASE

Sickle cell anemia, the most common and most severe form of sickle cell disease, is seen in individuals who are homozygous for a single nucleotide substitution in the β globin gene. This results in the synthesis of *hemoglobin S* (Hb S), a structural variant that, when deoxygenated, is much less soluble than normal hemoglobin (Hb A).^{21,22} Deoxygenated Hb S polymerizes and aggregates inside sickled erythrocytes as they traverse the microcirculation. Rigid, dense, and sickled cells can become entrapped in the microcirculation, a process that is enhanced by their increased propensity to adhere to endothelium. Mechanistic studies in transgenic mice expressing exclusively human Hb S suggest that microvascular occlusion results in ischemia and reperfusion injury, which promotes inflammatory, thrombotic, and oxidant stress.²³⁻²⁶ In patients with sickle cell disease, vaso-occlusion leads to the frequent episodes of bone pain and acute chest syndrome that complicate sickle cell disease. Furthermore, the membrane of erythrocytes containing intracellular Hb S polymer is constantly exposed to mechanical and oxidant injury as the erythrocytes traverse the microcirculation. Ultimately, cumulative membrane damage shortens red cell life span so that sickle cell disease is characterized by a chronic hemolytic anemia. Intravascular hemolysis releases cell-free hemoglobin into the plasma, which scavenges NO and releases red blood cell arginase into the plasma, which catabolizes arginine, the substrate for NO synthesis.^{14,27,28} Intravascular hemolysis thus produces a state of endothelial dysfunction, vascular proliferation, and pro-oxidant and proinflammatory stress.²⁹⁻³⁵

It is estimated that around 250,000 children worldwide are born with homozygous sickle cell anemia every year.³⁶ Approximately 0.15% of African-Americans are homozygous for sickle cell disease, and 8% have the sickle cell trait. Despite significant improvements in the life expectancy of patients with sickle cell disease, estimates of the median age at death range from 48 to 58.5 years for women and 42 to 53 years for men.^{37,38}

Acute and chronic pulmonary complications of sickle cell disease are common but often underappreciated by health care providers. Acute complications include asthma and the *acute chest syndrome* (ACS), while chronic complications include pulmonary fibrosis, PH, and cor pulmonale. Pulmonary complications account for a large proportion of deaths among adults with sickle cell disease.^{37,39,40} According to the *Cooperative Study of Sickle Cell Disease* (CSSCD), a prospective multicenter study of 3764 patients, more

than 20% of adults presumably had fatal pulmonary complications of sickle cell disease.³⁷ Among the 299 patients enrolled in the long-term follow-up study of patients who participated in the *Multicenter Study of Hydroxyurea in Sickle Cell Anemia* (MSH), pulmonary disease was the most common cause of mortality, accounting for 28% of all deaths.⁴¹

Acute Chest Syndrome

ACS represents a lung injury syndrome in patients with sickle cell disease that is related to the increased membrane permeability that characterizes the *acute respiratory distress syndrome* (ARDS). In a patient with sickle cell disease, ACS is clinically defined by the development of a new pulmonary opacity involving at least one complete lung segment, consistent with alveolar consolidation, not atelectasis, and accompanied by chest pain, fever, tachypnea, wheezing, or cough.⁴²

Epidemiology. ACS is the second most common cause of hospitalization in patients with sickle cell disease and the leading cause of both admission to an intensive care unit and premature death.^{37,40} More recently, however, increased awareness, the chronic use of hydroxyurea, and the early and aggressive use of transfusion therapy appear to have decreased ACS-related morbidity and mortality, as evidenced by a lower rate of ACS in a recently completed multicenter trial of inhaled NO for vaso-occlusive crises.⁴³

ACS can develop in any of the sickle hemoglobinopathies but is more common in individuals with homozygous sickle cell disease (Hb SS). In the CSSCD, there was a 29% incidence of the ACS in 3751 subjects over a 2-year period, representing an attack rate of 12.8 episodes per 100 patient-years for Hb SS disease.³⁷ The incidence was higher in children than in adults (24.5 events vs. 8.8 events per 100 patient-years). Up to half of ACS episodes develop in association with vaso-occlusive pain crisis, and a sizable proportion of patients will have a painful event within 2 weeks of the diagnosis.^{44,45} Because up to 20% of patients admitted with acute vaso-occlusive pain crisis will develop ACS in the first 3 days of hospitalization, physicians must be vigilant for this common and potentially lethal complication.

Steady-state laboratory parameters associated with an increased risk for the development of ACS include an elevated white blood cell count, a higher steady-state hemoglobin level, and a lower steady-state fetal hemoglobin level.^{44,45} In children, a number of studies now suggest that asthma is a risk factor for the development of ACS.⁴⁶⁻⁴⁸ Other clinical events that appear to increase the risk of (or are associated with) the development of ACS include major surgical procedures, acute rib infarcts, avascular necrosis of the hips, pregnancy, use of narcotics, acute anemic events, and previous pulmonary events.^{44,45}

During acute hospitalization for vaso-occlusive crisis, the development of ACS is often preceded by an abrupt drop in hemoglobin levels (mean decrease of 0.78 g/dL from steady-state values) and increases in markers of hemolysis, such as *lactate dehydrogenase* (LDH). ACS may also be preceded by a drop in the platelet count, and levels less than 200,000 per μ L constitute an independent risk factor for ACS severity, associated with increased risk of neurologic complica-

tions and mechanical ventilation. In our units, we monitor trends in hemoglobin and platelet counts and pay careful attention to patients with drops in steady-state values.

Pathophysiology. Three major mechanisms appear to be involved in the pathogenesis of ACS: infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction (Table 94-2, Fig. 94-1).

The most common etiology of ACS in both children and adults is infection by a community-acquired pathogen (eFig. 94-1), followed by an excessive inflammatory lung injury response. More than 80% of adults with sickle cell disease report a history of having been admitted to the hospital for "pneumonia."²⁹ The National Acute Chest Syndrome Study Group analyzed 670 episodes of ACS in 538 patients with sickle cell disease to determine the cause, outcome, and response to therapy, and respiratory samples obtained from sputum and bronchoalveolar lavage were analyzed for viral and bacterial infections.⁴² Among the infectious agents identified most frequently were atypical bacteria and viruses, including *Chlamydia pneumoniae*

Table 94-2 Causes of 670 Episodes of Acute Chest Syndrome*

Cause	Episodes (n) and (%) of total	NO. OF EPISODES OF ACUTE CHEST SYNDROME IN EACH AGE GROUP		
		0-9 yr (n = 329)	10-19 yr (n = 188)	≥20 yr (n = 153)
Fat embolism, with or without infection [†]	59 (8.8)	24	16	19
<i>Chlamydia</i> [‡]	48 (7.2)	19	15	14
<i>Mycoplasma</i> [§]	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	15	12
Mixed infections	25 (3.7)	16	6	3
<i>Legionella</i>	4 (0.6)	3	0	1
Miscellaneous infections	3 (0.4)	0	3	0
Infarction [¶]	108 (16.1)	50	43	15
Unknown [#]	306 (45.7)	139	88	79

*Data on one episode were excluded because the patient's birth date was not known.

[†]Nineteen of the episodes of pulmonary fat embolism were associated with infectious pathogens.

[‡]This category included episodes in which *Chlamydia* alone was identified but not episodes involving mixed infections or pulmonary fat embolism.

[§]This category included only episodes in which *Mycoplasma pneumoniae* or *Mycoplasma hominis* was identified, but not episodes involving mixed infections, *Mycobacterium tuberculosis*, or pulmonary fat embolism.

^{||}This category included two cases of tuberculosis and one case of *Mycobacterium avium* complex infection.

[¶]A pulmonary infarction was presumed when the results of the analysis for pulmonary fat embolism, bacterial studies, viral isolation studies, and serologic tests were complete and were all negative.

[#]The cause of episodes for which some or all of the diagnostic data were incomplete and no etiologic agent was identified was considered to be unknown.

Reproduced with permission from Vichinsky EP, Neumayr LD, Earles AN, et al: Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 342:1855-1865, 2000, Table 4.

VICIOUS CYCLE OF VASO-OCCLUSIVE CRISIS AND ACUTE CHEST SYNDROME

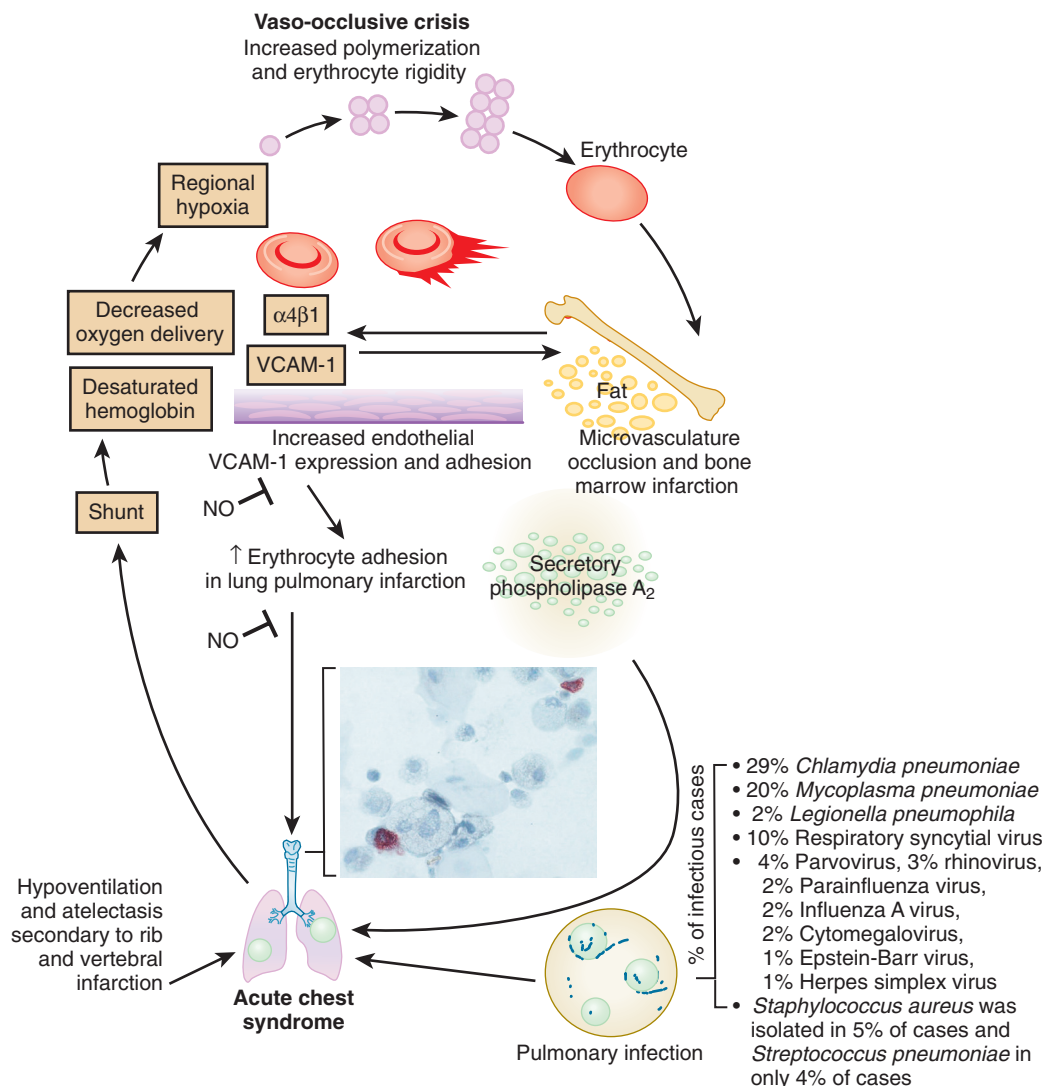


Figure 94-1 Pathogenesis of the acute chest syndrome. Three major triggers are associated with the development of acute chest syndrome (ACS): infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction. Lung injury results in ventilation-perfusion mismatch/shunt and hypoxemia, which leads to increased hemoglobin S polymerization, and erythrocyte vaso-occlusion. This worsens bone marrow infarction and pulmonary vaso-occlusion to promote a vicious cycle. Fat embolization can be diagnosed by Oil Red O staining of pulmonary alveolar macrophages, revealing the characteristic red lipid inclusions, as shown in the panel. Common infectious organisms and other causes of ACS are listed in Table 94-2. NO, nitric oxide.

(29%), *Mycoplasma pneumoniae* (20%), *Legionella pneumophila* (2%), respiratory syncytial virus (10%), parvovirus (4%), rhinovirus (3%), parainfluenza virus (2%), influenza A virus (2%), cytomegalovirus (2%), Epstein-Barr virus (1%), and herpes simplex virus (1%). Community-acquired encapsulated bacteria were rarely isolated, despite the fact that patients with Hb SS disease rarely have normal splenic function. *Staphylococcus aureus* was isolated in 5% of cases and *Streptococcus pneumoniae* in only 4% of cases. Cases of severe ACS related to outbreaks of seasonal influenza have also been described.^{49,50}

Fat embolization syndrome is the second most common cause of the ACS. It arises as a complication of vaso-occlusive pain crisis involving multiple bones, which results in bone marrow edema, infarction, and necrosis. As a consequence, bone marrow contents are released into the systemic circulation and trapped in the pulmonary circulation,

producing acute PH, severe lung inflammation, and hypoxemia (Fig. 94-2) (eFig. 94-2).⁵¹ Bone marrow fat released into the bloodstream is also converted by secretory phospholipase A₂ to free fatty acids, which can produce direct inflammatory lung injury.⁵²

Finally, in approximately 20% of patients, direct lung infarction or vaso-occlusion is associated with the development of ACS, with a small percentage of patients actually developing triangular-shaped pulmonary infarction (eFig. 94-3), sometimes followed by central cavitation.⁵³ Direct pulmonary arterial in situ thrombosis is also seen in patients with ACS. A French study evaluated the presence of pulmonary artery thrombosis by computed tomography (CT)–pulmonary angiography in 125 consecutive patients with 144 episodes of ACS and noted a 17% prevalence of subsegmental thromboembolism without evidence of peripheral venous thrombosis in any of their cases.⁵⁴

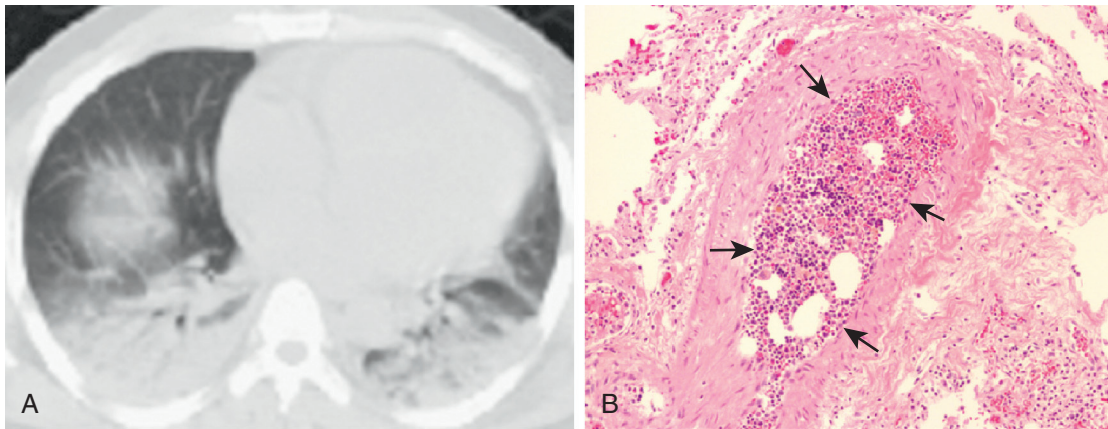


Figure 94-2 Fat embolization in acute chest syndrome. **A**, Chest CT scan of a patient with acute chest syndrome and fat embolization syndrome. **B**, Postmortem examination specimen of a patient who died suddenly during an episode of vaso-occlusive crisis and acute chest syndrome demonstrating bone marrow elements (arrows) lodged in the small pulmonary artery.

A potential role for hemolysis-derived plasma-free hemoglobin and free heme as novel mechanisms in ACS is emerging. Ghosh and colleagues⁵⁵ administered lysed red blood cells into the circulation of sickle cell mice, which resulted in increased pulmonary vascular permeability without affecting permeability in other organs; moreover, preliminary studies from the same group have demonstrated that intravenous administration of heme to sickle cell mice induces severe and lethal acute lung injury. These data suggest that plasma-free hemoglobin and/or heme specifically may contribute directly to lung injury. The relationship between increased intravascular hemolysis and thrombocytopenia indicates that a possible *thrombotic thrombocytopenic purpura* (TTP)-like mechanism may exist in a subset of patients with ACS as suggested by studies demonstrating that free hemoglobin may inhibit activity of ADAMTS13, a protease whose deficiency underlies most cases of TTP.⁵⁶⁻⁵⁸

Clinical Features and Evaluation. The clinical features at presentation are age dependent, which likely reflects the different etiologies of ACS in different age groups, with children having a higher proportion of infectious etiologies in comparison with adults, who tend to have fat embolization as a major etiology. Overall, 80% of patients present with fever, 62% with cough, and approximately 40% have chest pain, tachypnea, dyspnea, and abdominal, arm, leg, rib, or sternal pain.⁴² Most adult patients present with severe extremity or chest pain and 24 to 72 hours later develop ACS. Reactive airway disease is observed in 13% of cases of ACS and is much more common in children.

ACS is associated with signs of systemic inflammation, with mean peak temperatures of 38.9° C and mean white blood cell counts of 23,000 cells/ μ L.⁴² As mentioned earlier, although a high steady-state hemoglobin level is a major risk factor for developing ACS, the acute presentation is often associated with a drop in hemoglobin levels (mean decrease of 0.78 g/dL from steady-state levels) and increases in markers of hemolysis. A platelet count less than 200,000 per μ L appears to be a marker of ACS severity, associated with increased risk of neurologic complications and mechanical ventilation.⁴³ Secretory phospholipase A₂ levels are elevated early in the course of ACS, even before the

development of radiographic changes, and have been used to predict the onset of the syndrome.⁵⁹

Because the clinical manifestations can be indistinguishable from the other causes of ACS, the diagnosis of pulmonary fat embolization syndrome relies on the identification of Oil Red O-positive lipid accumulations within alveolar macrophages (see Fig. 94-1). In a 30-center clinical trial, the National Acute Chest Syndrome Study Group identified fat embolization syndrome in 16% of ACS cases in adults and children on the basis of positive lipid accumulations in alveolar macrophages.⁴² Traditionally bronchoscopy has been used as the diagnostic modality of choice for the diagnosis of pulmonary fat embolization syndrome. However, induced sputum may be a noninvasive alternative; in one study, induced sputum sampling of alveolar macrophages was found to have a similar yield as samples obtained from bronchoalveolar lavage, with a modest but significant correlation between the two measurements ($r = 0.65$).⁶⁰

Some patients with ACS manifest evidence of *systemic fat embolization*, also called the *acute multiorgan failure syndrome*. This syndrome should be suspected in patients presenting with acute multiorgan failure characterized by the development of acute hypoxic respiratory failure, right heart failure, renal and hepatic dysfunction, alterations in mental status, seizures, thrombocytopenia, and coagulopathy.^{61,62} In patients with ACS, those with lipid-laden macrophages in induced sputum have significantly more extrathoracic pain, evidence of fat emboli, more neurologic symptoms, a lower platelet count, and higher transaminase levels than do those without lipid-laden macrophages.⁶⁰ This suggests that the fat embolization syndrome is both a major cause of ACS and has a more severe course with systemic complications.

The mean length of hospitalization for ACS is 10.5 days, compared with 3 to 4 days for uncomplicated vaso-occlusive pain crisis. Thirteen percent of all patients with ACS require mechanical ventilation, and the overall mortality is 3% for all patients and 9% for adults. Risk factors for mechanical ventilation and poor outcome include a platelet count less than 200,000 per μ L (likely indicative of the fat embolization syndrome), a larger number of lobes involved on chest radiograph, and a self-reported or medical record history of cardiac disease. The latter complication is now

thought to represent occult PH and cor pulmonale. In fact, in a study of 84 consecutive hospitalized patients with ACS, 13% of patients manifested right heart failure, a subgroup that had the highest risk for mechanical ventilation and death.⁶³ Thus, PH and right heart dysfunction likely represent a major comorbidity during ACS, and right heart failure should be considered in patients presenting with shock or severe hypoxemia. Interestingly, despite these issues, the outcome of patients with severe ACS on mechanical ventilation is better than that of patients with ARDS, with a mortality rate of 19% in contrast to the approximate 30% mortality rate reported in current ARDS studies.⁴²

Treatment. In the outpatient setting, patients with a history of ACS should be treated with hydroxyurea because hydroxyurea has been shown to reduce the risk of developing ACS by approximately 50%.^{64,65} A chronic transfusion regimen is also effective in reducing the incidence of ACS.⁶⁶ Because the triggers and risk factors for ACS are well known, clinical surveillance plus aggressive and early therapy of this patient population are likely to improve prognosis. This could be accomplished by close monitoring of patients during a vaso-occlusive crisis, during a febrile illness, and in the postoperative state.

If ACS develops, a range of treatment strategies is recommended, as outlined in Table 94-3. Oxygen therapy should be given routinely to maintain oxygen saturation above 92%. Aggressive pain management and incentive spirometry can minimize chest wall splinting, with consequent relief of atelectasis and alveolar hypoxia. In fact, the use of incentive spirometry has been shown to decrease the incidence of new pulmonary opacities in patients admitted with vaso-occlusive pain affecting the chest wall.⁵³

Given the high prevalence of infectious etiologies for ACS, we recommend the use of empirical antimicrobial therapy in all patients. Considering the high prevalence of

atypical bacteria and encapsulated organisms, empirical coverage should include agents, such as the macrolides or fluoroquinolones, effective against these organisms. It is also important to consider alternative organisms such as methicillin-resistant *S. aureus* or influenza viruses, especially in patients not responding to therapy or during the annual influenza season.

Blood transfusion remains the mainstay of ACS therapy, although its value has not yet been demonstrated in randomized trials. Acute red cell transfusion increases arterial PO_2 and hemoglobin oxygen saturation and may rapidly resolve the pulmonary event.^{42,67} Transfusion can also increase blood viscosity and the consequent risk of vaso-occlusion, so it is recommended that the hemoglobin level not rise above 11 g/dL. The National Acute Chest Syndrome Study Group found no significant differences in outcomes between patients treated with simple transfusion or with erythrocytapheresis, a red cell exchange, suggesting that simple transfusion is preferred as initial therapy.⁴² For patients with high initial hemoglobin concentrations (>9 g/dL) or with more severe disease, however, erythrocytapheresis is recommended. However, because most patients have a significant decrease in hemoglobin at presentation, the transfusion of 2 to 4 units of packed red cells over 24 to 48 hours can usually be performed without complication. In order to decrease the risk of delayed hemolytic transfusion reactions related to alloimmunization against minor red blood cell antigens, all transfused blood should be matched to Rh, C, E, and Kell antigens.

Some potentially promising treatments have not proven to have a role in ACS. Although treatment with corticosteroids has been shown to reduce the severity of pain and length of hospitalization, this therapy is complicated by a high rate of rebound pain and hospitalization.^{68,69} A study evaluating a slow tapering protocol to maintain the beneficial effects of corticosteroids while limiting rebound pain and re-admission was terminated early because of slow accrual.⁷⁰ The placebo-controlled study by Gladwin and coworkers⁴³ evaluated the role of inhaled NO therapy for patients presenting in vaso-occlusive crisis and did not demonstrate an effect of inhaled NO compared with placebo on the duration of pain crisis, narcotic use, pain scores, or the development of ACS. In a prospective, randomized, open, single-center study of 67 adult patients with ACS, *noninvasive mechanical ventilation* (NIV) use improved respiratory rate and gas exchange but did not reduce the number of patients remaining hypoxemic at day 3 and was associated with greater patient discomfort. Additionally, NIV did not change transfusion rates, pain scores, narcotic dose, or hospital length of stay but instead prolonged length of stay in the step-down unit.⁷¹

Pulmonary Hypertension

PH has emerged as a major threat to the well-being and longevity of patients with sickle cell disease. PH is defined hemodynamically by a *mean pulmonary artery pressure* (PAP) greater than or equal to 25 mm Hg. Sickle cell disease could represent one of the most common causes of PH. Because there are 30 million individuals worldwide with sickle cell disease,⁷⁴ of whom 10% to 30% may have PH, there may be as many as 3 to 9 million patients with the complication.

Table 94-3 Treatment of the Acute Chest Syndrome (ACS)

Oxygen therapy to maintain arterial hemoglobin oxygen saturation above 92%
Pain control and incentive spirometry to reduce chest wall splinting and pulmonary atelectasis
Close clinical observation Monitor PO_2/FIO_2 ratio: Particular attention to diagnosis of worsening respiratory function
Asthma therapy if indicated
Empirical antibiotics Cover typical and atypical respiratory pathogens. Consider the regional and seasonal risk of methicillin-resistant <i>Staphylococcus aureus</i> . Anticipate influenza A or B infections and treat/prevent accordingly.
Transfusion therapy Main indication for transfusion therapy in ACS is worsening respiratory function. Simple transfusion is as effective as erythrocytapheresis in the usual patient. Patients with high initial hemoglobin concentrations (≥ 9 g/dL) or patients with more severe disease should receive erythrocytapheresis. Transfused blood should be matched to Rh, C, E, and Kell antigens, and transfusion records documenting history of prior alloantibodies should be obtained.

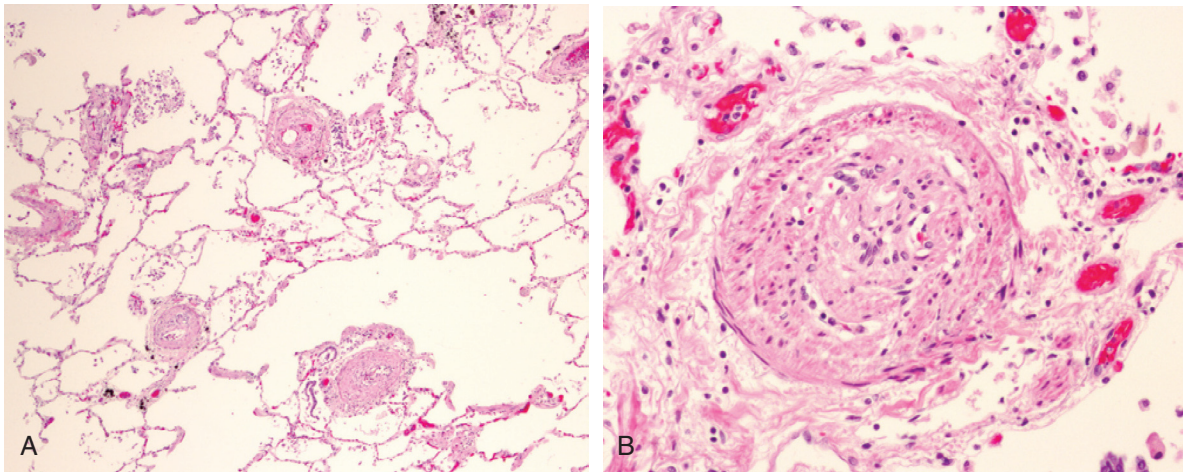


Figure 94-3 Pulmonary arteriopathy in sickle cell-related pulmonary hypertension. **A**, Low-power photomicrograph demonstrating pulmonary arterial smooth muscle hypertrophy (hematoxylin and eosin stain). **B**, Higher-power photomicrograph of one of the arteries showing a plexogenic lesion, with medial thickening, laminar intimal hyperplasia, recanalization, and fibrosis (hematoxylin and eosin stain).

Epidemiology. A variety of studies, both retrospective and prospective, have identified a high prevalence of PH in patients with sickle cell disease. Retrospective studies have reported that 20% to 30% of patients with sickle cell disease have an elevated pulmonary artery systolic pressure estimated noninvasively by Doppler echocardiography by a *tricuspid regurgitant jet velocity* (TRV) that is 2 standard deviations above the normal mean value (≥ 2.5 m/sec).^{62,75} Autopsy studies suggest that up to 75% of sickle cell patients have histologic evidence of PH at the time of death (Fig. 94-3).⁷⁷

These data are now corroborated by three prospective studies.^{29,78,79} In the *National Institutes of Health* (NIH) PH echocardiographic screening study, 23% of patients with sickle cell disease had borderline to mild elevations in pulmonary artery systolic pressures (defined by a TRV of > 2.5 to 2.9 m/sec, which corresponds to a pulmonary artery systolic pressure of 30 to 39 mm Hg) and 9% had moderately to severely elevated pressures (defined by a TRV > 3.0 m/sec, which corresponds to a pulmonary artery systolic pressure of approximately 40 to 45 mm Hg).²⁹ Similar rates were found in echocardiographic screening studies performed at two other centers.^{78,79}

Measurement of *N-terminal pro-brain natriuretic peptide* (NT-proBNP), a prohormone released by the right and left ventricular myocardium under pressure stress, in stored plasma samples has shown a high prevalence of abnormal values that may correlate with PH. Of those enrolled in the MSH in 1996, 30% of individuals had elevated levels suggesting the possible presence of PH.⁸⁰ Similarly, among patients enrolled in the CSSCD from 1978 to 1988, 27.6% of adults had elevated levels of NT-proBNP.⁸¹ In both studies, elevated NT-proBNP was independently associated with a higher risk of death.

PH has been shown to increase over time and with increasing age. Two centers independently reported the follow-up of adult sickle patients who on initial echocardiographic screening had normal TRVs. After 2 to 3 years of follow-up, 13% to 15% of these patients developed high TRVs, suggesting an increasing incidence of PH of about 4% to 7% per year.^{72,82} Increasing age is associated with an increased risk of elevated TRV. For example, in the NIH PH

echocardiographic screening study, patients with an elevated TRV were significantly older than patients without (38 ± 19 years for patients with TRV > 3.0 m/sec and 39 ± 12 years for patients with TRV 2.5 to 2.9 m/sec, compared with 34 ± 10 years for patients with TRV < 2.5 m/sec; $P = 0.02$).²⁹ An increasing number of studies suggests that PH is developing in children with sickle cell disease; however, few children have TRV values greater than 3.0 m/sec, and the implications in terms of functional capacity and associated mortality have not been determined.⁸³⁻⁸⁵

Epidemiologic risk factors associated with PH include a history of renal or cardiovascular complications, increased systemic systolic blood pressure, elevations in the marker of hemolysis (LDH), elevated alkaline phosphatase, and low transferrin levels.^{29,80,87} In men, a history of priapism was also an independent factor associated with PH.²⁹ These risk factors have also been observed in recently published studies using right heart catheterization to define PH.⁸⁸⁻⁹⁰ Interestingly, the development of PH was not associated with the number of vaso-occlusive episodes, markers of inflammation, fetal hemoglobin levels, or platelet counts.^{29,80,88-90} Although a high pulmonary artery pressure could also result from the high cardiac output state associated with chronic anemia, this hyperdynamic state does not seem to be a major contributor to significant elevations in pulmonary artery pressures because there has been no report of PH associated with nonhemolytic anemia. In sum, PH represents a component of the systemic vasculopathy of sickle cell disease (characterized by systemic hypertension, renal failure, and priapism).

Finally, three studies have provided new insights into the prevalence of PH in sickle cell disease using the gold standard diagnostic test for the disease, right heart catheterization. In the NIH screening study (2001–2010, median follow-up of 4.4 years),⁹⁰ 86 of the 533 subjects underwent right heart catheterization and, of these, 56 (10.5%) were diagnosed with PH. Similarly, in a screening study of 80 patients from Brazil, 32 (40%) had an elevated TRV and, of those who underwent right heart catheterization, 8 (10% of the total population) had PH.⁸⁸ In a third large screening study of 398 patients with sickle cell disease in France using right heart catheterization,⁹¹ 6% were shown to have

PH. Of note, the French study excluded approximately 10% of patients, those with “severe” renal, liver, or lung disease, with severity defined as a creatinine clearance of less than 30 mL/min, an abnormal prothrombin time (international normalized ratio > 1.7), and chronic restrictive lung disease defined by a TLC of less than 70% predicted. It is not clear why these patients would be excluded from a prevalence study of sickle cell disease–related PH, especially considering the fact that all of these complications develop as a direct consequence of sickle cell disease and all three represent significant published risk factors for developing PH in sickle cell disease.

Mortality. An elevated pulmonary artery pressure increases the risk of death for patients with sickle cell disease. In the NIH study, compared with patients with TRV less than 2.5 m/sec, the rate ratios for death for TRVs of 2.5 to 2.9 m/sec and greater than 3.0 m/sec were 4.4 and 10.6, respectively.²⁹ In support of these findings, De Castro and colleagues⁷⁹ found that 6 of 42 patients (14%) with PH and only 2 of 83 patients (2%) without this finding died during a 2-year follow-up period. Similarly, in the study by Ataga and colleagues,⁷⁸ 9 of 36 patients with PH and only 1 of 57 patients without PH died during the 2.5-year follow-up period (relative risk, 9.3). Consistent with these data, in a cohort of 632 patients with SCD from the United States and England, 11.2% had TRV \geq 3.0 m/sec and 24.1% had NT-proBNP level \geq 160 pg/mL. Of 22 deaths during follow-up, 50% had a TRV \geq 3.0 m/sec. At 24 months, the cumulative survival was 83% with TRV \geq 3.0 m/sec and 98% with TRV < 3.0 m/sec. The hrs for death were 11.1 (95% CI 4.1–30.1; $p < 0.0001$) for TRV \geq 3.0 m/sec, 4.6 (1.8–11.3; $p = 0.001$) for NT-proBNP \geq 160 pg/mL, and 14.9 (5.5–39.9; $p < 0.0001$) for both TRV \geq 3.0 m/sec and NT-proBNP \geq 160 pg/mL.^{91a}

When documented by right heart catheterization, the presence of PH is a major risk factor for death in patients with sickle cell disease. Castro and colleagues⁹² reported a 50% two-year mortality rate in patients with PH; with each increase of 10 mm Hg in PAP, there was a 1.7-fold increase in the rate of death. In the NIH study, the mortality rate was significantly higher in the PH group (20 deaths, 36%) than in either the group without PH by right heart catheterization (3 deaths, 10%), or the general sickle cell group with normal Doppler echocardiographic estimates of pulmonary artery systolic pressure (50 deaths, 13%).⁹⁰ Similarly, in both the Brazilian⁸⁸ and French⁹¹ cohorts, the mortality rate was significantly higher in the PH group (38% and 23%, respectively) than in the other patients. In the NIH study, specific hemodynamic variables were independently and significantly related to mortality, including PAP, diastolic PAP, systolic PAP–pulmonary capillary wedge pressure, transpulmonary gradient, and pulmonary vascular resistance.⁸⁹ These data suggest that mortality in adults with sickle cell disease and PH is proportional to the physiologic severity of pulmonary vascular disease.

Pathogenesis. Epidemiologic studies suggest that the central risk factor for the development of PH in patients with sickle cell disease is the severity of hemolytic anemia (Fig. 94-4).^{29,78,79,93} The association between the development of PH and the intensity of hemolytic anemia has been

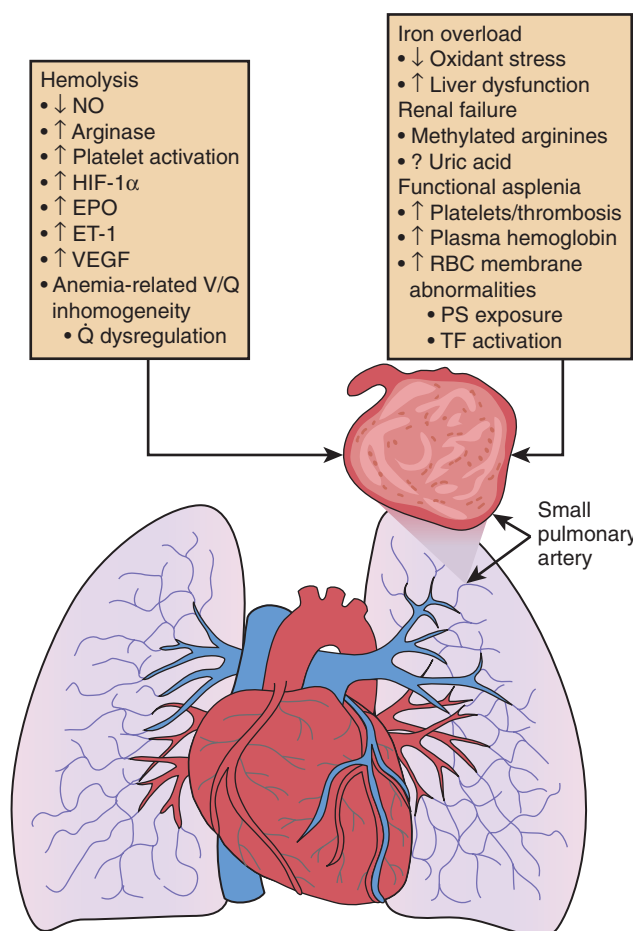


Figure 94-4 Multifactorial pathogenesis of pulmonary hypertension in sickle cell disease, focusing on changes at a small pulmonary artery. PH is thought to arise from multifactorial effects of hemolysis, as well as from the anemia leading to increased cardiac output and multiorgan damage from iron overload, renal failure, and asplenia. EPO, erythropoietin; ET-1, endothelin-1; HIF, hypoxia inducible factor; NO, nitric oxide; PS, phosphatidylserine; Q, cardiac output; TF, tissue factor; VEGF, vascular endothelial growth factor.

observed in three prospective screening studies of adult patients with sickle cell disease.^{29,78,79} in an expanding number of pediatric studies,^{83–85,94,95} and in studies using right heart catheterization to define PH.^{88–90} This suggests that hemolysis is related mechanistically to PH. That relationship is plausible and biologically significant because free hemoglobin inactivates the intrinsic vasodilator NO.^{14,28} Hemolysis also releases arginase, which depletes L-arginine, the substrate for NO synthesis.²⁷ These combined mechanisms result in a state of decreased NO bioavailability and “resistance” to NO-dependent vasodilation.¹⁴

Hemolysis and decreased NO bioavailability also induce platelet activation,⁹⁶ thrombin generation, and tissue factor activation.⁹⁷ There is also a correlation between the rate of hemolysis and the levels of procoagulant factors in blood in patients with sickle cell disease.^{98–100} Hemolysis is also associated with the formation of red blood cell microvesicles expressing phosphatidylserine, which activates tissue factor.^{100,101} These factors all contribute to an increased risk of thrombosis. In addition, sickle cell patients with functional asplenia and thalassemia patients with surgical

splenectomy have increased levels of cell-free hemoglobin and red cell microvesicles, providing a potential mechanism for the hypercoagulability associated with both diseases, with possible exacerbation by asplenia.¹⁰⁰ Finally, the accumulation of redox-active heme and iron from lysed red blood cells further contributes to the generation of reactive oxygen species that can exacerbate ischemia-reperfusion injury, thrombosis, and vascular proliferative responses.¹⁰² Another downstream effect of hemolytic anemia includes increased endothelin-1-mediated vasoconstrictive and proliferative responses. In patients with sickle cell disease, both at steady state and during vaso-occlusive pain crises, plasma endothelin-1 levels are increased.¹⁰³ In vitro, sickled erythrocytes increase endothelin-1 production by cultured human endothelial cells. All told, hemolysis acts via multiple mechanisms to block NO-induced vasodilation, activate procoagulant activity, injure endothelial cells, and exacerbate vasoconstriction and proliferation.

Functional or surgical asplenia could also contribute to the development of PH in patients with sickle cell disease. Splenectomy has been reported to be a risk factor for the development of PH,¹⁰⁴ particularly in patients with hemolytic disorders.¹⁰⁵⁻¹⁰⁷ Loss of splenic function may trigger platelet activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.¹⁰⁸ The spleen also plays a critical function in the removal of senescent and damaged erythrocytes.^{109,110} Following splenectomy, moreover, the rate of intravascular hemolysis increases.¹⁰⁰

Historically, PH in patients with sickle cell disease was thought to derive from the repetitive episodes of pulmonary vaso-occlusive crisis and ACS leading to pulmonary fibrosis, vascular obstruction, and chronic hypoxemia. However, this association has not been supported by epidemiologic studies in which the number of episodes of vaso-occlusive crisis and ACS have not been shown to be associated with PH.^{29,80}

Clinical Features and Evaluation. The diagnostic evaluation of patients with sickle cell disease suspected of having PH should follow the same guidelines established for other causes of PH.^{111,112} Given the high prevalence of PH in this population and the associated high mortality, we recommend that all adults with sickle cell disease undergo universal noninvasive screening with Doppler echocardiography or with assessment of steady-state plasma NT-proBNP levels.^{112a} In patients with sickle cell disease, as described earlier, the echocardiographic estimation of pulmonary artery systolic pressures (where pulmonary artery systolic pressure = $4 \times \text{TRV}^2$ + estimate of the right atrial pressure) correlates reasonably well with measured pulmonary systolic pressures by right heart catheterization.^{29,113}

Although no prospective data on prevalence and risk of PH are available for children, we currently recommend that children with hypoxemia, high hemolytic rates (hemoglobin values < 7 g/dL with high LDH values), and/or recurrent ACS be screened. It is important that such screening be performed in the steady state because pulmonary pressures rise during vaso-occlusive painful crisis.¹¹⁴

The diagnosis of PH in patients with sickle cell disease can be challenging (Fig. 94-5; Videos 94-1 and 94-2). Exertional dyspnea, the most typical presentation of PH, is also a cardinal symptom of chronic anemia, and therefore a

high index of suspicion for PH is necessary. Other conditions that commonly present in patients with sickle cell disease, such as left ventricular dysfunction, pulmonary fibrosis, and liver cirrhosis, could also present in a similar fashion and result in PH. Patients with PH tend to be older and have higher systolic arterial blood pressure, lower hemoglobin levels, higher indices of hemolysis (such as high bilirubin or LDH values), lower hemoglobin oxygen saturation, greater degree of renal and liver dysfunction, and a higher number of lifetime red blood cell transfusions.²⁹ As such, the diagnostic evaluation of these patients should include an aggressive search for other conditions that might contribute to PH, such as iron overload, chronic liver disease, *human immunodeficiency virus* (HIV), nocturnal hypoxemia, and thromboembolism.

A diagnostic right heart catheterization is essential to confirm the diagnosis and exclude diastolic dysfunction (see later).⁹⁸ The 6-minute walk test is a useful surrogate for functional capacity in this patient population even considering the high prevalence of confounding factors such as the presence of avascular necrosis of the hip. Specifically, the 6-minute walk test inversely correlates with the severity of PH,¹⁰² and PH-specific therapy improves walk distance.¹⁰³

The Doppler echocardiogram is an important tool for population screening and estimation of pulmonary artery pressure, but it cannot be used to diagnose or define PH in an individual patient. For a given patient, a diagnosis of PH is based on the measurement of the mean pulmonary artery pressure via a right heart catheterization. In a single individual, the use of a TRV ≥ 2.5 m/sec has low specificity for a diagnosis of PH,⁹¹ with only 25% of patients with a TRV ≥ 2.5 m/sec having the diagnosis of PH. A TRV ≥ 2.9 m/sec has a higher positive predictive value of 64%, but high false-negative rate of 42%. Combining a TRV ≥ 2.5 m/sec, a high NT-proBNP level (>164.5 pg/mL), and a low 6-minute walk distance of less than 333 m, the positive predictive value for PH is 62%, with a false-negative rate of 7%.

Abnormal pulmonary function can be found in most patients with sickle cell disease. The pulmonary function abnormalities are characterized by mild restrictive lung disease (mean total lung capacity values of about 79% of predicted), abnormal diffusing capacity, and radiographic signs of mild pulmonary fibrosis,^{40,117-121} and the severity of these defects seems to be slightly greater in those patients with PH.¹¹⁵ However, in these patients the degree of pulmonary function abnormalities is rarely severe enough to be a major contributor to the etiology of PH.

A ventilation-perfusion scan is an indispensable component of the evaluation because chronic thromboembolic PH, if amenable to pulmonary endarterectomy, is a potential curable cause of PH reported in patients with chronic hemolytic disorders. In the majority of cases, scintigraphic evidence of thromboembolic disease is uncommon and the most commonly seen abnormality is of patchy areas of abnormal perfusion, similar to findings described in other forms of PH.^{115,122} Chronic thromboembolic PH is present in approximately 5% of sickle cell patients with severe PH,¹¹⁵ and the disease has been successfully treated surgically in two patients with sickle cell disease (Fig. 94-6).¹²³ As such, patients should undergo imaging studies and, if

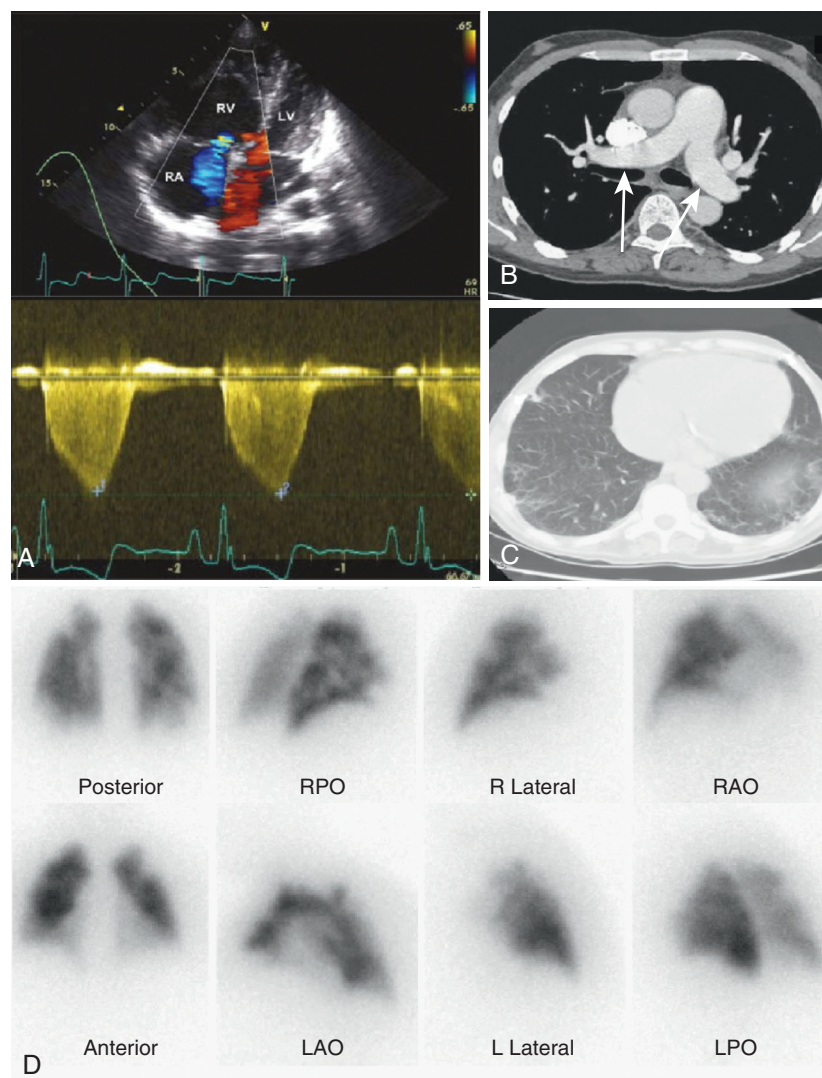


Figure 94-5 Imaging features of sickle cell disease and pulmonary hypertension. **A**, Echocardiographic four-chamber view of the heart, illustrating severe right ventricular (RV) and right atrial (RA) dilation and moderate tricuspid regurgitation (blue color Doppler). Below, Doppler tracing from a patient with severe pulmonary hypertension reveals a jet velocity of more than 4 m/sec. **B**, Axial chest CT scan showing enlargement of pulmonary arteries (*arrows*) in severe pulmonary hypertension. **C**, Chest CT showing mild pulmonary fibrosis typical of patients with sickle cell disease and pulmonary hypertension. **D**, Perfusion scan demonstrating patchy areas of abnormal perfusion. Ventilation scans were normal (not shown).

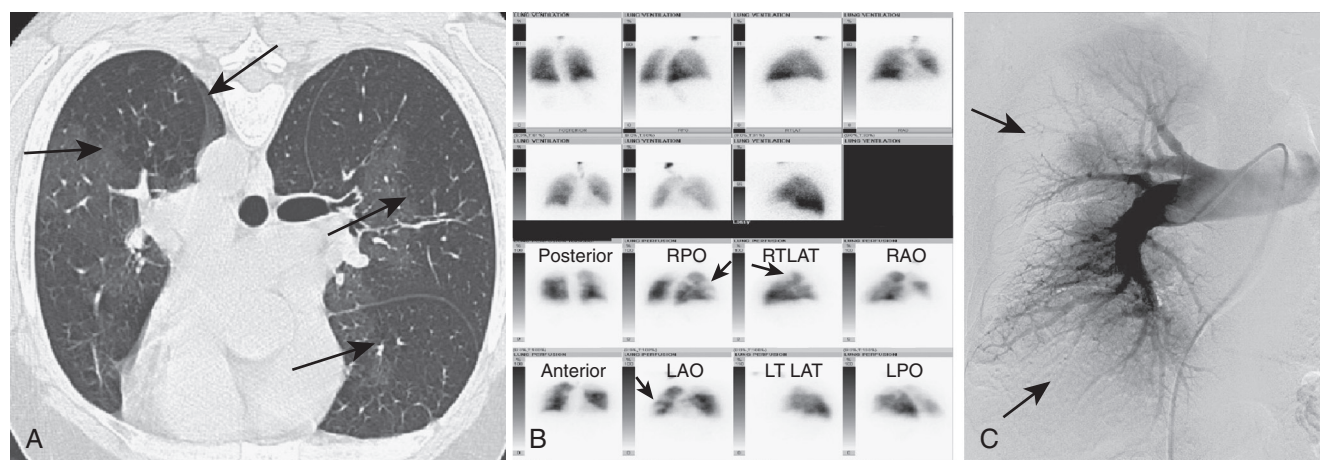


Figure 94-6 Chronic thromboembolic pulmonary hypertension in a patient with sickle cell disease. **A**, High-resolution CT scan demonstrating mosaic pattern of attenuation. Multiple hyperlucent regions represent areas with decreased perfusion (*arrows*). **B**, Ventilation-perfusion scan demonstrating multiple unmatched perfusion defects (*arrows*). Ventilation scans, top 7 images; perfusion scans, bottom 8 images. **C**, Digital subtraction pulmonary angiogram that shows diffuse peripheral areas of hypoperfusion, which represent multiple peripheral small filling defects (*arrows*).

suggestive of chronic thromboembolic PH, should undergo more invasive studies (i.e., angiography) to exclude this potentially surgically treatable condition.

Measurement of NT-proBNP levels can be used as a PH biomarker for diagnosis and risk stratification in patients with sickle cell disease.⁸⁰ In a contemporaneous cohort, NT-proBNP levels were higher in patients with sickle cell disease–associated PH and correlated directly with the severity of PH and the degree of functional impairment. An NT-proBNP level of 160 pg/mL or greater had a 78% positive predictive value for finding an elevated TRV and was an independent predictor of mortality. In a subset of individuals participating in the MSH follow-up study in 1996, 30% of patients had an NT-proBNP level of 160 pg/mL or greater. An NT-proBNP level of 160 pg/mL or greater in the MSH cohort was independently associated with mortality. Similarly, in patients enrolled in the CSSCD from 1978 and 1988, elevated levels of NT-proBNP were independently associated with a higher risk of death.⁸¹

In contrast to patients with traditional forms of PH (e.g., idiopathic pulmonary arterial hypertension, scleroderma associated PAH) (see Chapters 58 and 59), who are symptomatic with P_{AP}s in the range of 50 to 60 mm Hg, in patients with sickle cell disease the degree of elevation in P_{AP} is mild to moderate, in the range of 30 to 40 mm Hg, with mild elevations in pulmonary vascular resistance. These patients also have coexistent mild elevation in pulmonary capillary wedge pressure, suggesting left heart failure (Table 94-4). Right heart catheterization data from these multiple studies^{18,20-23} show that the hemodynamic etiology of the PH in patients with sickle cell disease is multifactorial: precapillary PH (defined by an P_{AP} ≥ 25 mm Hg and a wedge pressure ≤ 15 mm Hg) is present in 50% of catheterized patients, whereas pulmonary venous hypertension secondary to left ventricular diastolic dysfunction disease (defined by an P_{AP} ≥ 25 mm Hg and a wedge pressure > 15 mm Hg) is present in 50%.

Further, using echocardiography in a cohort of 141 patients with sickle cell disease, Sachdev and associates¹²⁴ found that 47% of patients had PH, diastolic dysfunction, or both (29% had PH alone, 11% had diastolic dysfunction and PH, and 7% had diastolic dysfunction alone). PH and diastolic dysfunction were associated with a relative risk of death of 5.1 and 4.8, respectively, while the relative risk of death when both were present was 12.0.¹²⁴ These data suggest that both PH and diastolic dysfunction indepen-

dently carry mortality risk. In addition, in a series of 483 patients with homozygous sickle cell disease, markers of diastolic dysfunction were independently associated with a low 6-minute walk distance.

Regardless of the hemodynamic etiology, sickle cell disease patients with chronic anemia, who maintain a high compensatory resting cardiac output in order to ensure adequate oxygen delivery, normally have a reduced pulmonary vascular resistance and appear to be poorly tolerant of even small increases in pulmonary vascular resistance. When compared with age-, gender-, and hemoglobin-matched patients with sickle cell disease without PH, individuals with PH exhibited a lower 6-minute walk distance (435 ± 31 vs. 320 ± 20 meters; *P* = 0.002), lower peak oxygen consumption on cardiopulmonary exercise testing (50 ± 3% vs. 41 ± 2% of predicted; *P* = 0.02), and higher ventilatory equivalent for CO₂ at anaerobic threshold (31.6 ± 1.5% versus 39.2 ± 1.6; *P* = 0.035) on cardiopulmonary exercise testing.¹⁰² Patients with sickle cell disease and PH appear to have worse function than is reported for patients with PH from other etiologies.¹²⁵ In addition, in patients with sickle cell disease, pulmonary artery vascular resistance sharply rises with exercise, suggesting that pulmonary vascular disease contributes to functional limitation in these patients.¹¹⁴ Taken together, these data suggest that, in sickle cell disease patients with chronic anemia, mild to moderate PH has a severe adverse impact on functional and aerobic exercise capacity.

Treatment. Data on the specific management of patients with sickle cell disease and PH are limited. Most of the recommendations are based on expert opinion or extrapolated from data derived from other forms of PH.^{125a} The general approach should include maximization of sickle cell disease–specific therapy (i.e., treatment of primary hemoglobinopathy), treatment of hypoxia with chronic oxygen therapy, treatment of associated conditions (such as iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, and thromboembolic disorders). For patients with sickle cell disease with PH (P_{AP} ≥ 25 mm Hg and wedge pressures < 15 mm Hg with a relatively high pulmonary vascular resistance, > 160 dyn•sec⁻¹•cm⁻⁵), targeted therapy with pulmonary vasodilator/antiremodeling agents can be considered (Fig. 94-7).

Because chronic intravascular hemolysis is a central mechanism in the development of PH, it is likely that optimizing sickle cell disease therapy would be beneficial through amelioration of the principal mechanism involved in the pathogenesis of PH. Hydroxyurea has been shown to decrease the incidence of pain episodes and ACS, reduce the need for transfusions, and lower overall mortality.^{41,64} It is possible that some of the decreases in pulmonary and cardiovascular deaths seen in hydroxyurea-treated patients could be related to an improvement in PH. For patients with creatinine levels less than 1 mg/dL, hydroxyurea is started at a dose of 15 mg/kg/day and titrated up to a maximum of 35 mg/kg/day. Detailed treatment guidelines have been published.^{65,126} Patients with renal dysfunction tend not to tolerate the myelosuppressant effects of hydroxyurea and, in those cases, we recommend adding erythropoietin to the regimen. Long-term transfusion therapy lowers the risk of most complications of the disease, including the risks of

Table 94-4 Hemodynamic Profiles in Patients with Sickle Cell Disease

	Without PH	With PH
P _{AP} (mm Hg)	19 ± 0.7	36 ± 1
PRA (mm Hg)	6 ± 0.4	10 ± 1
PPW (mm Hg)	11 ± 0.5	17 ± 1
CO (L/min)	10 ± 0.5	9 ± 0.3
PVR (dyn•sec ⁻¹ •cm ⁻⁵)	59 ± 6	197 ± 14

CO, cardiac output; P_{AP}, mean pulmonary artery pressure; PPW, pulmonary wedge pressure; PRA, right atrial pressure; PVR, pulmonary vascular resistance.

Data from references 76, 115, 220 except PVR, which comes from 115, 220.

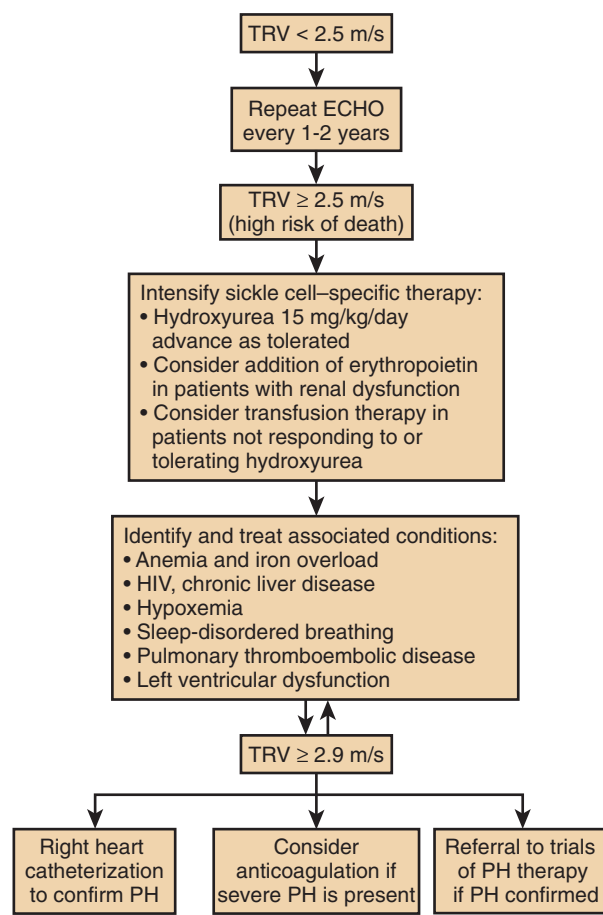


Figure 94-7 Treatment algorithm in patients with sickle cell disease and pulmonary hypertension. Depending on the echocardiographic determination of PAP by assessment of TRV, treatment is accelerated. TRV, tricuspid regurgitation velocity.

pulmonary events and central nervous system vasculopathy,¹²⁷⁻¹²⁹ and might improve cardiopulmonary function and prevent the progression of PH.

The potential benefits of warfarin therapy observed in patients with idiopathic pulmonary arterial hypertension (Group 1, see Chapter 58) have to be weighed against the risk of hemorrhagic stroke in adults with sickle cell disease or hemorrhage in chronically anemic individuals. We believe that the relatively low risk of hemorrhagic stroke (0.21 events per 100 patient-years¹³¹) compared with the high risk of death in patients with severe PH supports anticoagulation in patients without a specific contraindication who have hemodynamic evidence of PH or chronic thromboembolic PH.

There are no long-term data on the specific treatment of PH in sickle cell disease, and the choice of agents is largely empirical and based on the safety profile of the drugs and physician preference. However, there are specific treatment concerns regarding the use of these drugs in patients with hemolytic diseases. The use of prostanoids can produce systemic vasodilation and increases in cardiac output, raising the concern for the potential development of high-output heart failure in anemic patients. In addition, the risk of chronic intravenous-line-related complications such as thrombosis and sepsis is likely higher in patients with sickle

cell disease. The main toxicity of endothelin-1 receptor antagonists is hepatocellular injury, which could limit their applicability in patients with sickle cell disease at risk for liver dysfunction (e.g., iron overload, hepatitis C). Another class effect of these agents is a dose-related decrease in hemoglobin levels, usually by approximately 1 g/dL.¹²⁵ The main concern related to the use of sildenafil is the potential for the development of priapism in men with sickle cell disease.

Sildenafil functions by inhibiting the metabolism of cyclic guanosine monophosphate, the second messenger that mediates the effects of NO. In a series of seven patients with either thalassemia or sickle-thalassemia and severe PH, treatment with sildenafil from 4 weeks to 48 months resulted in an improvement in TRV, New York Heart Association functional class, and 6-minute walk distance.¹³² In another case series of 12 patients with sickle cell disease treated with sildenafil for a mean of 6 months, mean pulmonary artery systolic pressure decreased by 9 mm Hg, 6-minute walk distance improved by 78 m, and mean NT-proBNP decreased by 448 pg/mL.¹¹⁶

The published experience with endothelin antagonists in the treatment of PH is also limited. Minniti and colleagues¹³³ reported on the use of bosentan and ambrisentan in a cohort of 14 patients with sickle cell disease and PH documented by right heart catheterization. Endothelin antagonist therapy either as monotherapy or in combination with sildenafil was well tolerated and resulted in a modest improvement in 6-minute walk distance (baseline 357 ± 22 vs. 398 ± 18 m 6 months post therapy). There are no published case series of prostanoid therapy in this population.

Randomized multicenter placebo-controlled studies evaluating the role of PH therapy in patients with sickle cell disease have not yet provided clear guidance. In the ASSET-1 and ASSET-2 studies of bosentan versus placebo, insufficient recruitment led to early termination of the studies. In the limited sample of patients, bosentan was well tolerated with no significant differences in serious adverse events or abnormal laboratory tests, but efficacy end points could not be formally analyzed.¹³⁴ The Walk-PHaSST (Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy) evaluated the safety and efficacy of oral sildenafil for the treatment of Doppler-defined PH (tricuspid regurgitant jet velocity ≥ 2.7 m/sec) in adults and children (older than 12) with sickle cell disease.¹³⁵ After 74 (out of a planned 132) subjects were enrolled, the study was discontinued due to a significant increase in hospitalizations caused by vaso-occlusive pain crises in the sildenafil arm (45% sildenafil, 22% placebo). Subject hospitalization for pain was the predominant cause for this difference. Although underpowered at the time the study was stopped, there was no evidence of a treatment effect on 6-minute walk distance or NT-proBNP. In that study, patients were not required to be on hydroxyurea and/or chronic transfusion therapy for sickle cell disease. Thus, it is uncertain whether these adverse effects could be mitigated by intensification of sickle cell disease-specific therapy before the initiation of sildenafil treatment. A case of severe pulmonary arterial hypertension related to pulmonary veno-occlusive disease has been reported in a patient with SCD. This patient failed medical therapy and underwent a successful bilateral lung transplantation.^{135a}

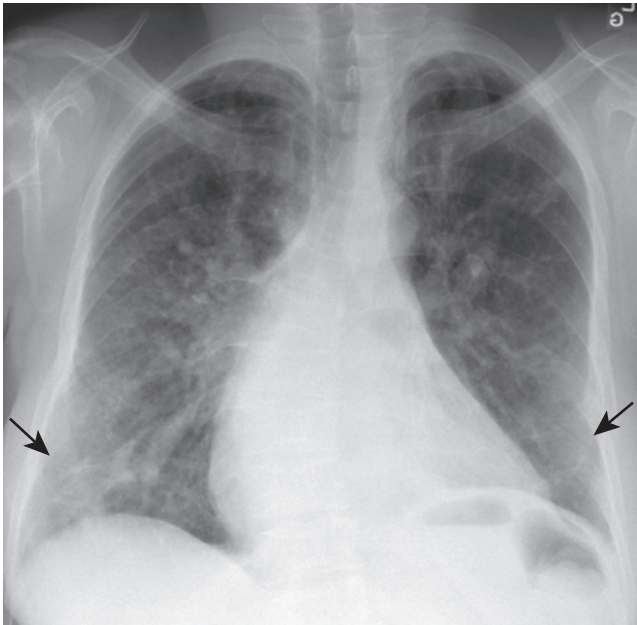


Figure 94-8 Pulmonary fibrosis complicating multiple episodes of acute chest syndrome. Bibasilar (right greater than left) reticular opacities (arrows) are seen in the chest radiograph.

Chronic Lung Disease

Sickle cell chronic lung disease has been used as a wastebasket term to encompass pulmonary fibrosis resulting from recurrent ACS and PH.⁴⁰ Our current understanding of sickle cell chronic lung disease suggests that pulmonary fibrosis is quite mild, and that PH is a more important cause of chronic pulmonary disease. For this reason, we feel that this older terminology should be replaced with a more specific diagnostic classification.

In patients with sickle cell disease, repetitive episodes of *acute lung injury* (ALI) related to ACS can result in parenchymal damage and typically mild restrictive lung disease (Fig. 94-8). In a study of 310 patients with homozygous sickle cell disease, pulmonary function was abnormal in 90% of adult patients; the most common abnormalities included mild restrictive physiology and decreased diffusing capacity.¹³⁶ These abnormalities worsen with age and are associated with increases in pulmonary artery pressures.^{115,136} In contrast, airway hyperactivity is much more common in children.¹³⁷ Data are conflicting on whether children with sickle cell disease have a much higher prevalence of asthma and airway hyperactivity, when compared with ethnically and aged-matched controls.^{47,138} It is increasingly apparent that children with asthma appear to have a higher incidence of ACS, cerebral vascular accidents, and need for blood transfusions, arguing for aggressive diagnosis and treatment of asthma in this population.^{47,48,139}

Sleep-disordered breathing has been reported in both children and adults with sickle cell disease. In children, sleep-related upper airway obstruction and hypoxemia are the most common disturbances. In an uncontrolled study, adenotonsillectomy led to symptomatic improvement and amelioration of oxygen desaturation.^{140,141} Several lines of evidence suggest that nocturnal hypoxemia contributes to the development of neurologic events and

vaso-occlusive crisis via mechanisms that could involve up-regulation of several inflammatory endothelial cell adhesion molecules.¹⁴²⁻¹⁴⁴

THALASSEMIA

Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one or more α or β globin chains. β -Thalassemia results from impaired production of β globin chains, which leads to a relative excess of α globin chains.¹⁴⁵ These excess α globin chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within the cell, leading to ineffective erythropoiesis and hemolytic anemia.¹⁴⁵ Thalassemia major, or homozygous β -thalassemia, is a severe disorder due to the inheritance of two β -thalassemia alleles. Starting during the first year of life, patients develop severe and lifelong transfusion-dependent anemia, hepatosplenomegaly, and skeletal deformities due to bone marrow expansion; they are prone to infection and skeletal fractures.

β -Thalassemia minor, also called β -thalassemia trait, arises in heterozygotes who have inherited a single gene leading to reduced β globin chain production. Such patients are asymptomatic, may be only mildly anemic, and are usually discovered when a blood count has been obtained for other reasons. β -Thalassemia intermedia is seen in patients with disease of intermediate severity, such as those who are compound heterozygotes of two thalassemic variants. Such patients may have the skeletal abnormalities and hepatosplenomegaly seen in thalassemia major. However, their hemoglobin concentrations usually range from 5 to 10 g/dL and they usually require transfusions only when they have an intercurrent event, such as an infection, that impairs erythropoiesis. Their clinical symptoms may not be apparent until well after the first year of life. Hemoglobin E, which has a point mutation in the β globin gene, is the most common hemoglobin variant in the world. In the heterozygous or homozygous states, it is mostly asymptomatic or associated with a mild microcytic anemia. When hemoglobin E is present along with β -thalassemia, the condition is called hemoglobin E-thalassemia; about half of these patients are phenotypically similar to patients with thalassemia major and require regular transfusion therapy, with the other half having courses similar to patients with thalassemia intermedia.

Several cardiopulmonary abnormalities arise in patients with β -thalassemia, including restrictive and obstructive defects, hyperinflation, abnormal diffusing capacity, and decreases in aerobic exercise capacity.¹⁴⁶⁻¹⁴⁸ However, in the majority of cases, these pulmonary function abnormalities are not associated with clinical symptoms. Several of the clinical complications related to thalassemia are related to complications of therapy such as transfusion-related iron overload, infection, thrombosis, possibly acute deterioration in pulmonary function associated with the use of the iron chelator deferoxamine, and PH related to splenectomy. In patients who are poorly transfused, extramedullary erythropoiesis can rarely cause pulmonary parenchymal masses, mediastinal masses (see eFigs. 83-44 and 83-45, and pleural effusions.

Similar to sickle cell disease, PH is a common complication of thalassemia. Approximately 40% to 50% of patients

with thalassemia intermedia¹⁴⁹ and 10% to 75% of patients with thalassemia major have echocardiographic evidence of PH.¹⁵⁰⁻¹⁵² In a multicenter cross-sectional study of 1309 Italian β -thalassemia patients, patients with a tricuspid-valve regurgitant jet velocity ≥ 3.2 m/s (3.6% of the population) on transthoracic echocardiography underwent right heart catheterization to confirm the diagnosis of PH (defined as mean pulmonary arterial pressure ≥ 25 mm Hg and pulmonary capillary wedge pressure ≤ 15 mm Hg). The prevalence of PH on right heart catheterization was 2.1% (4.8% in patients with thalassemia intermedia and 1.1% in patients with thalassemia major).^{152a} In spite of its potential complications, chronic transfusion therapy in severe thalassemia has changed the clinical course of the disease and is likely to have a favorable impact in individuals with PH. This idea is supported by a report that, in well-transfused, iron-chelated patients with thalassemia major, PH was completely prevented.¹⁵³ A favorable response to sildenafil has been reported in patients with thalassemia major and intermedia.^{132,154} In a recent open-label study of 10 patients with β -thalassemia and a TRV > 2.5 m/sec on Doppler echocardiography (none of the patients underwent confirmatory right heart catheterization), treatment with sildenafil resulted in a significant decrease in TRV and improved left ventricular end-systolic/diastolic volume but did not improve 6-minute walk distance.¹⁵⁵ There are also case reports of favorable response to bosentan¹⁵⁶ and epoprostenol¹⁵⁷ in patients with right heart catheterization-confirmed precapillary PH. To date, however, there are no studies evaluating either the specific hemodynamic derangements associated with PH or the impact of PH on survival in this patient population.

OTHER HEMOGLOBIN DISORDERS

Hemoglobin gene mutations can result in functional abnormalities in the globin chains that alter gas ligand affinity and alter oxygen uptake and delivery. Remarkably, there are more than 120 human hemoglobin gene mutations that have been associated with abnormal hemoglobin oxygen affinity.¹⁵⁸ Patients with moderately high-affinity hemoglobins usually present with erythrocytosis and are typically asymptomatic, but patients with variants associated with high oxygen affinity can present with cyanosis or symptoms related to increased red blood cell mass (polycythemia). In addition, whereas patients with low oxygen affinity hemoglobin variants are usually asymptomatic, some can present with cyanosis. The initial step in the workup of patients suspected of having a hemoglobinopathy affecting oxygen affinity is to evaluate the red cell oxygen equilibrium curve, whereby both the oxygen saturation of hemoglobin and partial pressure of oxygen are directly measured to obtain a p50, the partial pressure of oxygen at which hemoglobin is 50% saturated. This approach should obviate the need for unnecessary and potentially invasive diagnostic procedures.

Methemoglobin is a nonfunctional state of hemoglobin in which the irons of heme are oxidized to the ferric (Fe^{3+}) state and are unable to bind oxygen. In addition, the oxygen affinity of any accompanying ferrous hemes in the hemoglobin tetramer is increased so that the oxygen dissociation curve is “left shifted” and oxygen delivery to the tissues is

impaired.¹⁵⁹ Three mechanisms are associated with the development of methemoglobinemia: a genetic mutation resulting in abnormal hemoglobin (hemoglobin M), a congenital deficiency of methemoglobin reductase enzyme (cytochrome b_5 or cytochrome- b_5 reductase deficiency), and a drug/toxin-induced oxidation of hemoglobin. Most individuals with congenital methemoglobinemia are asymptomatic, and their primary complaint is “cyanosis” presenting as a slate-blue color of the skin and mucous membranes.

Cyanosis is clinically apparent when the absolute concentration of methemoglobin exceeds 1.5 g/dL, equivalent to approximately 10% methemoglobin.¹⁶⁰ In cases associated with drugs and toxins, the severity of the methemoglobinemia depends on the dose of the agent and the individual's susceptibility. At methemoglobin levels greater than 35%, patients can complain of headaches, weakness, and dyspnea; levels greater than 80% are typically incompatible with life.¹⁵⁸ Symptomatic patients should be treated with methylene blue given intravenously at a dose of 1 to 2 mg/kg, which acts as a cofactor for the enzyme NADPH methemoglobin reductase. Electrons are transferred from NADPH to methylene blue, which leads to a reduction of the heme iron, in the form of deoxyhemoglobin.¹⁶¹ Methylene blue should not be administered to individuals with glucose-6-phosphate dehydrogenase deficiency because it may precipitate hemolysis.¹⁶²

Carbon monoxide (CO) binds to hemoglobin to form *carboxyhemoglobin* (COHb). CO has a much greater affinity than oxygen for hemoglobin. The binding of CO to heme creates an allosteric change that diminishes the ability of hemoglobin to release oxygen to peripheral tissues, resulting in impaired oxygen transport and utilization. As such, CO poisoning is a major cause of morbidity and mortality. The clinical effects of CO poisoning are nonspecific and easily confused with other illnesses, such as viral illness, benign headache, and various cardiovascular and neurologic syndromes.¹⁶³ As the severity of exposure increases, patients develop more pronounced symptoms, with oxygen-dependent organs (the brain and the heart) showing the earliest signs of injury. Oxygen therapy improves tissue hypoxia and accelerates elimination of CO. Hyperbaric oxygen therapy should be considered in patients with severe CO poisoning (e.g., COHb $> 25\%$, evidence of tissue ischemia and loss of consciousness) and may reduce the incidence of the late neurocognitive deficits associated with severe CO intoxication.^{164,165}

Cyanide binds the ferric ion (Fe^{3+}) of cytochrome oxidase a3, inhibiting this final enzyme in the mitochondrial cytochrome complex and thereby preventing oxygen utilization by tissues. A small amount of cyanide can also bind to the ferrous (Fe^{2+}) iron of hemoglobin to form cyanhemoglobin, which is unable to transport oxygen and thus further exacerbates tissue hypoxia.¹⁶⁶

WHITE BLOOD CELL DISORDERS

LEUKEMIAS

Although the majority of clinical pulmonary manifestations in patients with leukemia are not related to the disease

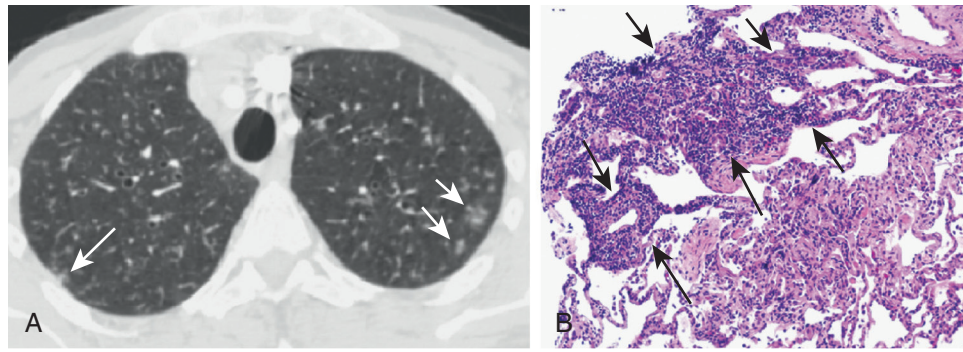


Figure 94-9 Leukemic infiltrates in a patient with chronic lymphocytic leukemia. **A**, Diffuse nodular opacities (arrows). **B**, Transbronchial biopsy specimen demonstrating diffuse infiltration of lung interstitium by leukemic cells (especially between arrows). (H&E stain).

itself, autopsy studies show that thoracic involvement is common in all leukemia types. Overall, the most common finding is mediastinal and lymph node involvement, but pleural and pulmonary infiltration is found in 20% to 65% of autopsy series.¹⁶⁷⁻¹⁶⁹

The mediastinum is the most commonly affected intrathoracic site. This is often manifest as a focal mass (eFig. 94-4) or as generalized mediastinal involvement. Hilar adenopathy is seen in 15% to 25% of patients.^{170,171} Pleural effusion, usually unilateral, can present in up to 25% of cases and is seen more frequently in myeloid leukemias.¹⁷² In the majority of cases, the effusion is related to lymphatic obstruction, congestive heart failure, or infections, with only approximately 5% of cases caused by leukemic infiltration.¹⁷²

Leukemic pulmonary infiltrates are clinically significant in approximately 10% of patients (Fig. 94-9).¹⁶⁷ The usual radiographic pattern of involvement is a bilateral reticular pattern with septal lines resembling interstitial edema or lymphangitic carcinomatosis (eFig. 94-5). Interlobular smooth or nodular septal thickening is the most common high-resolution CT finding, followed by thickening of bronchovascular bundles. Other manifestations include peribronchovascular or random nodules, which can coalesce into masslike consolidation, focal areas of air space disease, and ground-glass opacities.¹⁷²⁻¹⁷⁵ The diagnosis of leukemic infiltrates is one of exclusion because most of the pulmonary parenchymal abnormalities in these patients are associated with processes other than the hematologic disease, such as infections, hemorrhage, or pulmonary edema.

Pulmonary leukostasis or hyperleukocytosis is characterized by the distention of small pulmonary vessels by leukemic blast cells. It is most commonly seen in patients with acute leukemias and white blood cell counts greater than 100,000 cells/ μ L with a predominance of blast cells.¹⁷⁶ Clinical and radiographic findings include dyspnea and hypoxemia associated with a bilateral reticular pattern with septal lines or air space consolidation.^{176,177} Symptomatic leukostasis is a medical emergency, and efforts should be made to lower the white blood cell count rapidly. In most patients, rapid cytoreduction can be achieved by chemotherapy, but leukapheresis should be considered in severe cases or in patients who cannot receive chemotherapy immediately. Finally, patients can present with acute spurious hypoxemia caused by an ex vivo decrease in arterial PO_2 mediated by the enhanced metabolism of the malignant cells; this process has been referred to as “leukocyte larceny.”

Pulse oximetry provides an accurate assessment of arterial oxygen saturation in such circumstances.

Leukemic cell lysis pneumopathy arises in patients with high leukocyte counts undergoing chemotherapy and is part of the spectrum of tumor lysis syndrome. Severe hypoxia and diffuse bilateral opacities develop within 48 hours after the initiation of chemotherapy, resembling the clinical and pathologic presentation of ARDS.¹⁷⁸ In patients at intermediate or high risk for the development of tumor lysis syndrome, preventive measures are recommended such as aggressive intravenous hydration, urine alkalinization in selected patients, and the use of agents to decrease uric acid levels such as allopurinol and rasburicase.¹⁷⁹ These therapeutic strategies also apply to patients with established tumor lysis syndrome.

PLASMA CELL DISORDERS

Thoracic involvement in multiple myeloma is common, seen in 46% of patients, with the majority of cases related to neoplastic infiltration of the skeleton.¹⁸⁰ Pleural effusion caused by malignant infiltration has been reported, and for unclear reasons the effusion appears to involve the left lung more frequently.¹⁸¹ Pulmonary parenchymal or airway involvement is also rare, taking the form of single or multiple masses, diffuse parenchymal opacities, or endobronchial lesions.¹⁸⁰ Pulmonary amyloidosis can also result from systemic amyloid deposition (eFig. 94-6).¹⁸²

Plasmacytoma is a circumscribed proliferation of plasma cells not associated with a plasma cell disorder. The vast majority of plasmacytomas involving the respiratory tract arise in the pharynx, followed by the trachea and, much less commonly, the lower airways and the pulmonary parenchyma.^{183,184} Pulmonary parenchymal plasmacytomas present as a nodule or mass that is indistinguishable from bronchogenic carcinoma and may rarely present as a chest wall (eFigs. 94-7 and 94-8) or mediastinal (eFig. 94-9) mass.

THROMBOSIS AND DISORDERS OF COAGULATION

INHERITED THROMBOPHILIA

Inherited thrombophilia encompasses the various mutations associated with venous thromboembolism. The most

Table 94-5 Inherited Thrombophilic Disorders

Disorder	Prevalence in Healthy Individuals (%)	Frequency in Patients with VTE (%)	Relative Risk of First Episode of DVT	Relative Risk of Recurrence
Factor V Leiden (heterozygous)	0.05–4.8	18.8	7	1.4
Factor V Leiden (homozygous)	0.02	1.5	80	n/a
Prothrombin G20210A allele	0.06–2.7	7.1	2.8	1.7
Protein C deficiency	0.2–0.4	3.7	6.5	1.8
Protein S deficiency	0.16–0.21	2.3	5.0	1.0
Antithrombin III deficiency	0.02	1.9	20	2.6
Hyperhomocysteinemia	5–7	10	3.0	0.9

DVT, deep venous thrombosis; VTE, venous thromboembolism.

Adapted from Whitlatch NL, Ortel TL: Thrombophilias: when should we test and how does it help? *Semin Respir Crit Care Med* 29:25–39, 2008; and Dalen JE: Should patients with venous thromboembolism be screened for thrombophilia? *Am J Med* 121:458–463, 2008.

frequent causes of an inherited thrombophilia are the factor V Leiden mutation and a prothrombin gene (*G20210A*) mutation, which together account for 50% to 60% of cases. Mutations in the genes coding for protein S, protein C, and antithrombin account for most of the remaining cases, while dysfibrinogenemias are rare causes of hypercoagulability (Table 94-5).^{185,186} Patients with these disorders usually present with recurrent thromboembolism at a young age, typically younger than 50 (see also Chapter 57).

Several of these disorders are associated with an increased risk of initial and recurrent thromboembolism (see Table 94-5). There is, however, controversy about whether screening of individuals with venous thromboembolism for the presence of these inherited defects is warranted. Expert opinion suggests that evaluation for inherited thrombophilic disorders should be pursued in individuals presenting with idiopathic thrombosis who are younger than 50, with a history of recurrent thrombosis, or with thrombosis in an unusual site; in those with a first-degree relative with thrombosis at a young age; or in women with thrombotic events during pregnancy or while taking oral contraceptives.¹⁸⁷⁻¹⁸⁸ These recommendations must be contrasted with the results of epidemiologic studies suggesting that a thrombophilic workup after a first thrombotic event is unlikely to confer clinical benefit.¹⁹⁰⁻¹⁹² The presence of a thrombophilic disorder does not impact the acute management of a thromboembolic event but could have an impact on the duration of chronic anticoagulant therapy.¹⁹³ Patients with antithrombin, protein C, or protein S deficiency should be considered for lifelong anticoagulation. Patients with heterozygous factor V Leiden or prothrombin gene mutations generally do not need lifelong anticoagulation but will likely benefit from extended anticoagulant therapy to reduce the risk of recurrence, as shown in other patients with idiopathic thromboembolism.^{194,195} Patients with more than one allelic abnormality should also be considered for lifelong anticoagulation.

COAGULOPATHIES AND PLATELET DISORDERS

Spontaneous pulmonary hemorrhage does not appear to be a common complication of disorders of coagulation such as the hemophilias, von Willebrand disease, or thrombocytopenia. The risk of bleeding appears to increase in individuals with preexisting pulmonary lesions or after physical or procedural trauma to the respiratory system.

However, episodes of pulmonary hemorrhage, hemomediastinum, and tracheal and pleural hematomas have been described in patients with hemophilias.¹⁹⁶ Radiographic abnormalities such as scarring, fibrosis, pleural thickening, abnormalities in pulmonary vessels, and hyperinflation and cases of PH have also been described in patients with hemophilia.¹⁵⁸

COMPLICATIONS OF TRANSFUSION

TRANSFUSION-ASSOCIATED ACUTE LUNG INJURY

Transfusion-related acute lung injury (TRALI) is an acute lung injury syndrome resulting from the transfusion of blood products containing plasma, most commonly whole blood, fresh frozen plasma, platelets, and packed red blood cells. TRALI is currently the leading cause of transfusion-related morbidity and mortality.¹⁹⁷ TRALI is defined as the acute onset of hypoxemia ($PO_2/FiO_2 < 300$ mm Hg) and the appearance of new chest radiographic opacities, without evidence of elevated left atrial pressure, within 6 hours of infusion of a blood product.¹⁹⁸

Epidemiology

The incidence of TRALI is not well established but appears to be one episode for every 5000 blood component transfusions.¹⁹⁹ This likely underestimates the true incidence of the disease. Studies using systematic methods to identify TRALI cases suggest that the incidence can be 5 to 50 times higher than previously thought.²⁰⁰⁻²⁰³ A 2012 TRALI study group determined the incidence of TRALI by prospective, active surveillance in a case-control design in two academic medical centers.²⁰⁴ The annual TRALI incidence decreased from 2.6 per 10,000 units transfused in 2006 to 0.8 per 10,000 units transfused in 2009, most likely related to TRALI mitigation strategies implemented in these centers.

TRALI has been reported in all age groups and with equal incidence in men and women. A single-center study suggested that patients with hematologic malignancies or cardiovascular disease requiring cardiopulmonary bypass operations are at a higher risk of developing this complication.²⁰⁰ Administration of fresh frozen plasma, prolonged storage of blood products, and acute underlying conditions

such as recent surgery, massive transfusion, cytokine therapy, sepsis, and thrombocytopenia have also been implicated as risk factors for TRALI.^{200,202,205-209} Multiparous women are the donors most commonly associated with cases of TRALI, which probably reflects the role of the antibodies formed due to exposure to paternal leukocyte antigens during pregnancy (see next section on pathogenesis).^{199,210,211}

In the recent TRALI study group report, risk factors for transfusion recipients identified by multivariate analysis included higher IL-8 levels, liver surgery, chronic alcohol abuse, shock, higher peak airway pressure on mechanical ventilation, current smoking, and positive fluid balance. Transfusion risk factors were receipt of plasma or whole blood from female donors, volume of HLA class II antibody with normalized background ratio more than 27.5, and volume of anti-human neutrophil antigen positive by granulocyte immunofluorescence test. Little or no risk was associated with older red blood cell units, noncognate or weak cognate class II antibody, or class I antibody.²⁰⁴

Pathogenesis

Two leading hypotheses have been put forth to explain the mechanisms underlying the pathogenesis of TRALI. One theory proposes that transfused leukocyte antigens interact with antibodies to cause granulocyte activation and lung injury. An alternative “two-hit” hypothesis proposes that active substances accumulate as the blood product is stored and are transferred to a susceptible host, priming granulocytes that then secondarily produce lung injury in the setting of systemic inflammation from another insult such as sepsis.

The antileukocyte antibody hypothesis has support from several lines of evidence. Antileukocyte antibodies are found in donors or recipients after clinical episodes of TRALI, and infusion of antileukocyte antibodies in animals causes a similar form of lung injury.^{212,213} In three case reports, TRALI was produced in healthy volunteers by infusions of plasma containing strong leukocyte antibodies.²¹⁴ Antibodies against HLA class I and II antigens and HNA-3a antigens are also found in patients with TRALI.²¹⁵

The other “two-hit” hypothesis is also supported by several studies. The age of transfused blood has been reported as a risk factor for multiorgan failure in trauma patients.²¹⁶ The presence of bioactive lipids implicated in the pathogenesis of lung injury, such as lysophosphatidyl choline, is higher in blood products given to patients who develop TRALI.^{202,208} CD40 ligand, which induces injury to activated microvascular endothelial cells, accumulates in stored blood products, and significantly higher levels have been found in blood products given to patients who develop TRALI.²¹⁷

Clinical Features and Evaluation

Patients typically present with the sudden onset of respiratory distress 1 to 2 hours after the transfusion of blood products. Clinical signs include fever, tachypnea, tachycardia, and occasionally hypotension.²⁰⁶ The patients may cough pink frothy secretions with a high albumin content indicative of increased permeability (noncardiogenic) pulmonary edema. Chest radiography (see eFigs. 71-25, 71-26A) classically reveals bilateral alveolar opacities with a

normal cardiac silhouette and without pleural effusion. The finding of granulocyte, leukoagglutinating, or lymphotoxic antibodies in the serum from either the donor or recipient supports the diagnosis of TRALI, but these abnormalities are not found in all patients. The main differential diagnosis in these patients is transfusion-associated circulatory overload, and the differentiation of these two conditions can be difficult. The measurement of brain natriuretic peptide levels has been described as a helpful tool to differentiate these two entities.²¹⁸

Approximately 70% of patients require mechanical ventilation at the time of presentation.²¹⁵ The illness tends to resolve rapidly, within the first 48 hours, and with few exceptions, chest radiographs typically return to normal in 4 days. The estimated mortality associated with TRALI is 5%.²¹⁵

Treatment

Because patients usually improve spontaneously, the management of TRALI is supportive. In patients requiring mechanical ventilation, the approach should be the same as recommended for patients with ARDS. There is no convincing evidence to support the use of corticosteroids in patients with TRALI. Individuals developing TRALI should not receive further blood products from the implicated donor but do not appear to be at increased risk for recurrent episodes with products from other donors.²¹⁹ Finally, in the TRALI study group case-control study, the incidence of TRALI decreased after the reduction of transfusion of plasma from female donors.²⁰⁴

Key Points

- Primary polycythemia is caused by either an acquired or inherited genetic abnormality; secondary polycythemia is mainly related to excess erythropoietin production from chronic hypoxia.
- The acute chest syndrome and pulmonary hypertension are leading causes of recurrent disability and premature death in sickle cell disease. Acute chest syndrome is thought to result from infection, bone marrow fat embolization, and/or direct red cell intravascular sequestration causing lung injury and infarction. Pulmonary hypertension is now thought to result from hemolysis that alters nitric oxide activity and endothelial function.
- Thalassemia major is a severe heritable lifelong, multisystem disease owing to the presence of two β -thalassemia alleles; by contrast, thalassemia minor patients inherit just a single gene and may be asymptomatic with only mild anemia.
- Leukemias and plasma cell disorders involve the pulmonary parenchyma uncommonly, although mediastinal involvement, lymphadenopathy, and pleural infiltration are common at autopsy.
- There is controversy about whether screening of individuals with venous thromboembolism for the presence of inherited thrombophilic defects is warranted; criteria for diagnosis have been suggested, but epidemiologic studies show little clinical benefit. Optimal chronic management of patients with inherited thrombophilia is not well established.

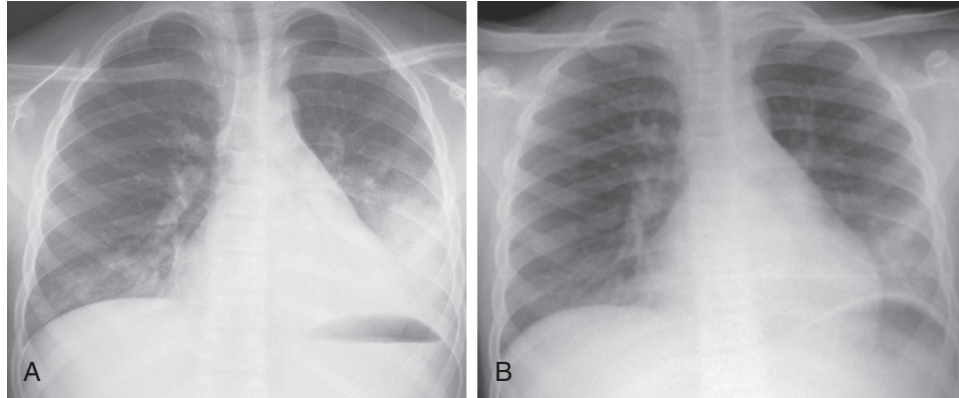
- Transfusion-related acute lung injury is the leading cause of transfusion-related morbidity and mortality. Several risk factors have been identified and multiple causes may play a role. The overall incidence appears to be diminishing and clinical management remains supportive.

Complete reference list available at *ExpertConsult*.

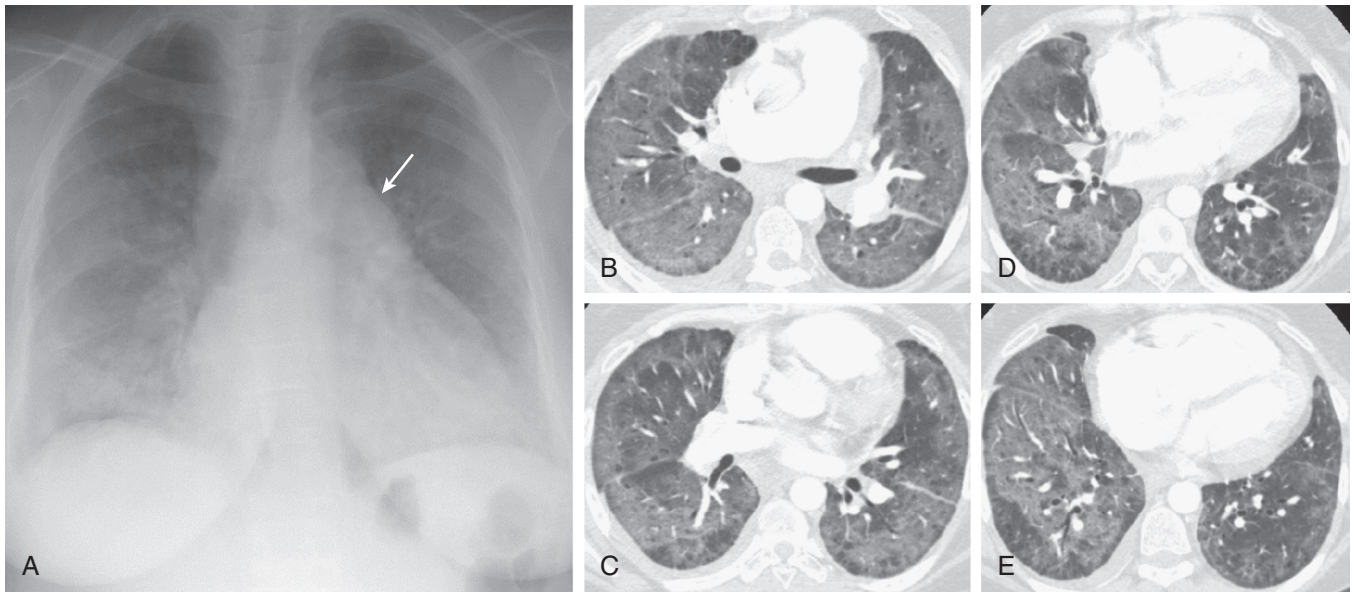
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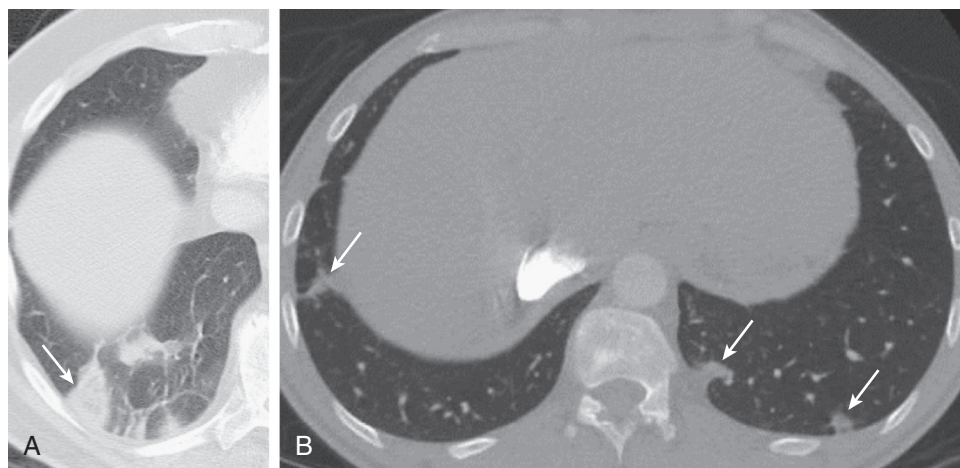
eFIGURE IMAGE GALLERY



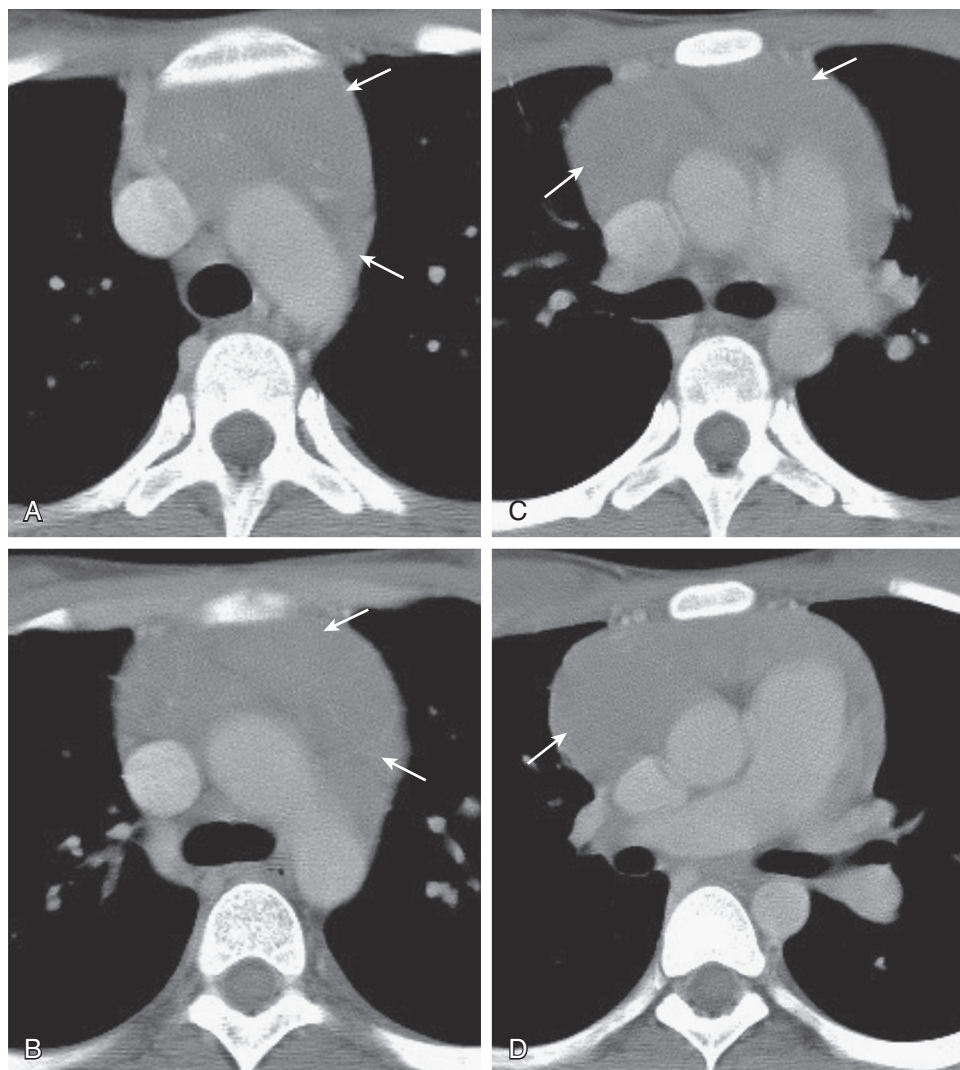
eFigure 94-1 Acute chest syndrome in sickle cell disease: pneumonia. **A**, Frontal chest radiograph shows left-greater-than-right lower lobe consolidation, consistent with pneumonia. **B**, Frontal chest radiograph 5 days later following antibiotic therapy shows improvement in the lower lobe opacities. (Courtesy Michael Gotway, MD.)



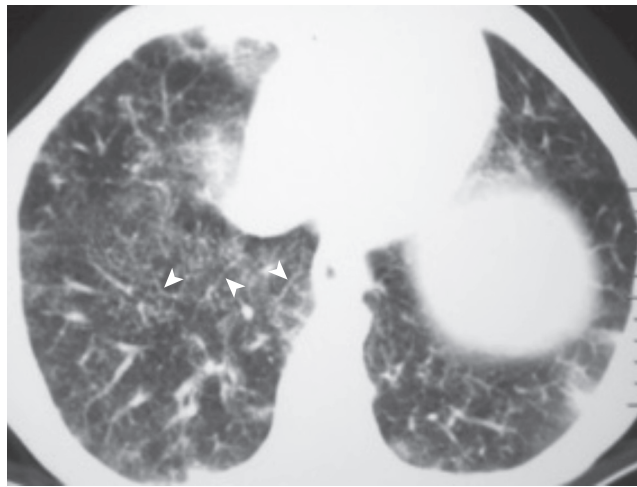
eFigure 94-2 Acute chest syndrome in sickle cell disease: fat embolization. **A**, Frontal chest radiograph in a patient with acute chest pain accompanied by hypoxemia and thrombocytopenia shows bilateral right-greater-than-left increased opacity associated with cardiomegaly and pulmonary arterial enlargement (*arrow*). **B–E**, Axial chest CT displayed in lung windows shows bilateral, essentially diffuse ground-glass opacity associated with mild reticular elements. Bronchoscopy revealed intra-alveolar macrophages containing fat. (Courtesy Michael Gotway, MD.)



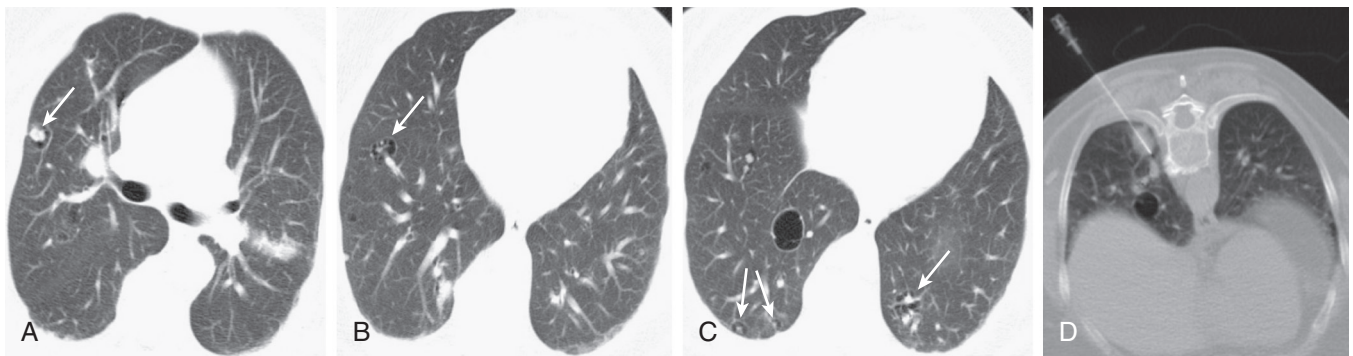
eFigure 94-3 Acute chest syndrome in sickle cell disease: pulmonary infarction. **A**, Axial chest CT through the lower lobes shows triangular-shaped, subpleural opacity (*arrow*) with the apex of the triangle facing toward the pulmonary hilum. The internal opacity is ground-glass attenuation, surrounded by consolidation. The appearance is typical of acute pulmonary infarction. **B**, Axial chest CT through the lower lobes shows irregular, somewhat nodular subpleural opacities (*arrows*) bilaterally, consistent with pulmonary infarction from previous thromboembolic episodes. (Courtesy Michael Gotway, MD.)



eFigure 94-4 Thoracic leukemia: mediastinal mass. **A–D**, Axial enhanced chest CT shows a soft tissue mass (*arrows*) in the anterior mediastinum proven to represent leukemic infiltration. (Courtesy Michael Gotway, MD.)



eFigure 94-5 Thoracic leukemia: pulmonary parenchymal infiltration. Axial chest CT shows small nodules in the lung bases bilaterally associated with interlobular septal thickening (*arrowheads*); biopsy revealed pulmonary leukemic infiltration. (Courtesy Michael Gotway, MD.)



eFigure 94-6 Amyloidosis. **A–C,** Axial chest CT shows multiple pulmonary nodules associated with cystic change (*arrows*), proven on biopsy (**D**) to represent pulmonary amyloidosis. (Courtesy Michael Gotway, MD.)

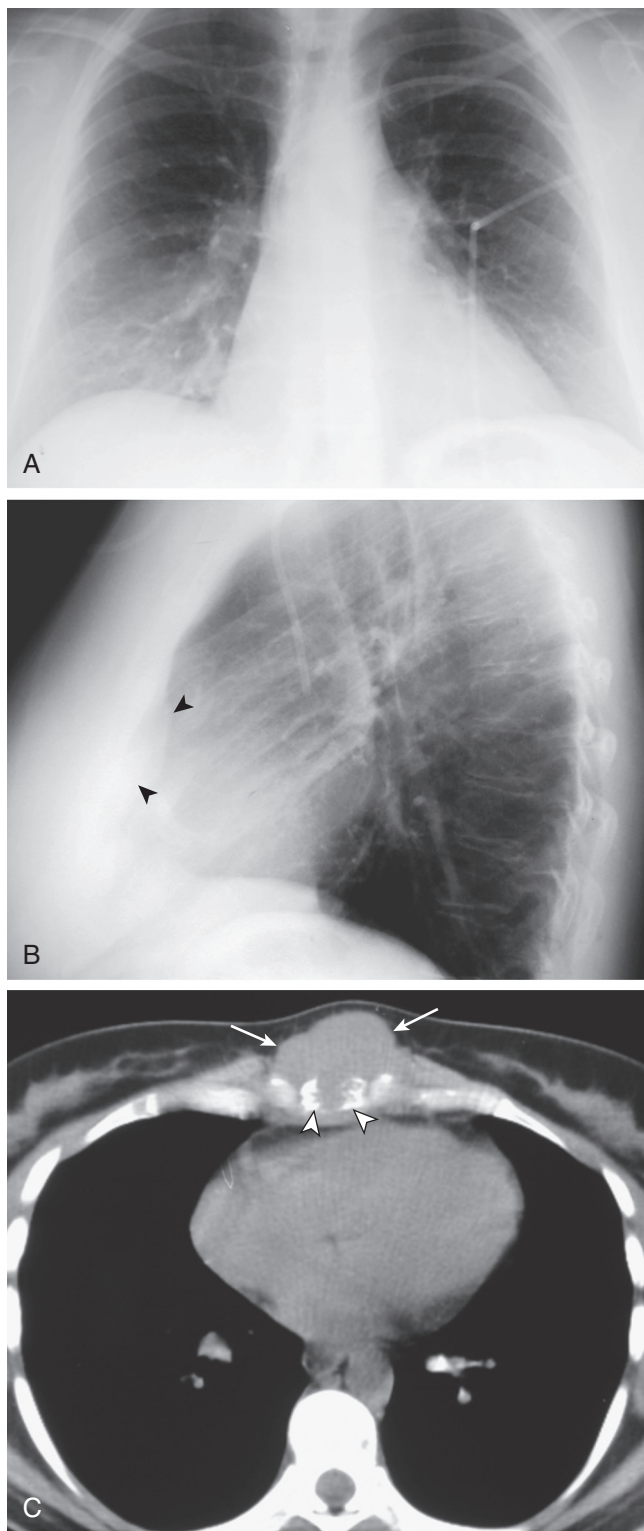
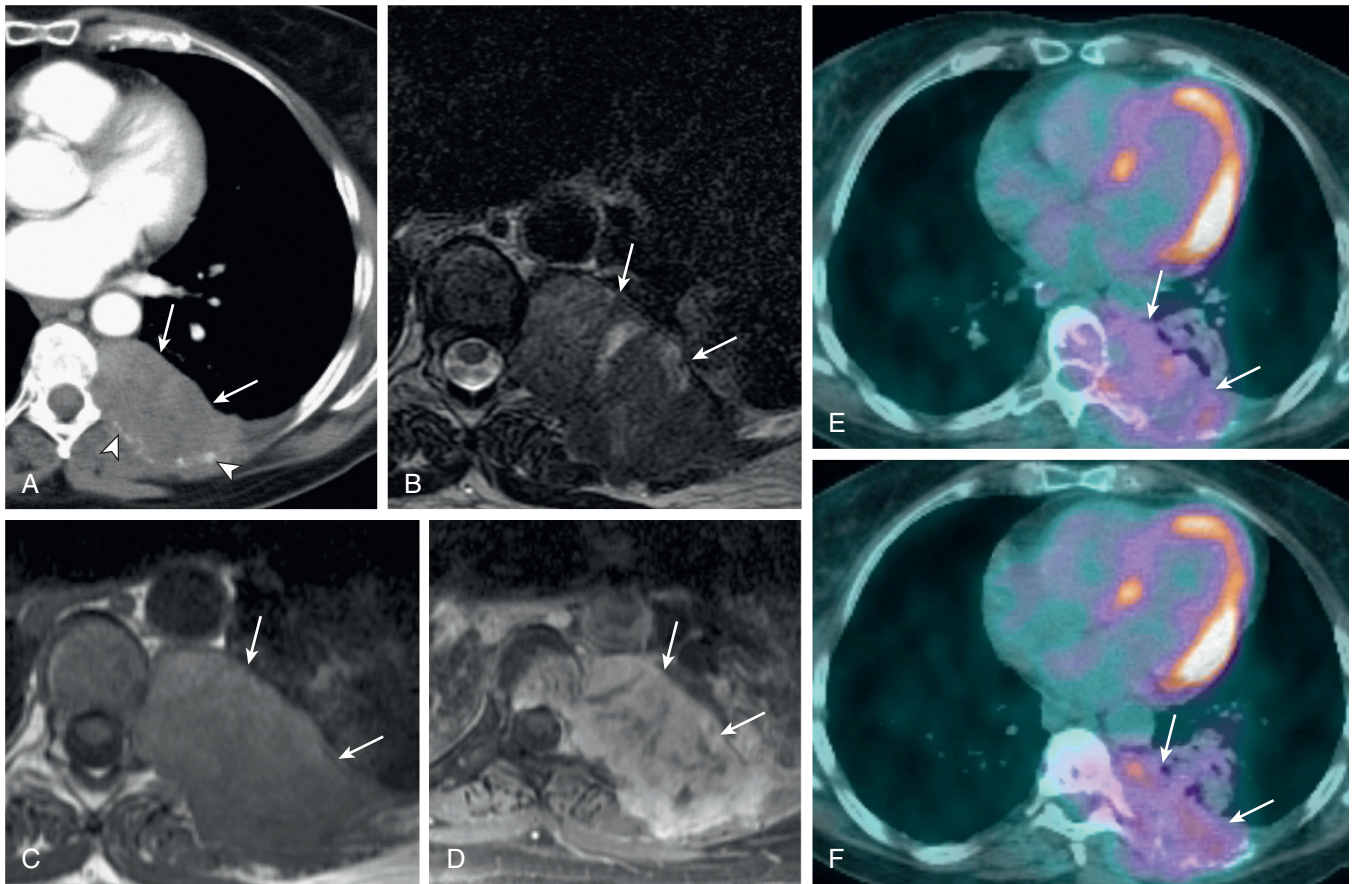
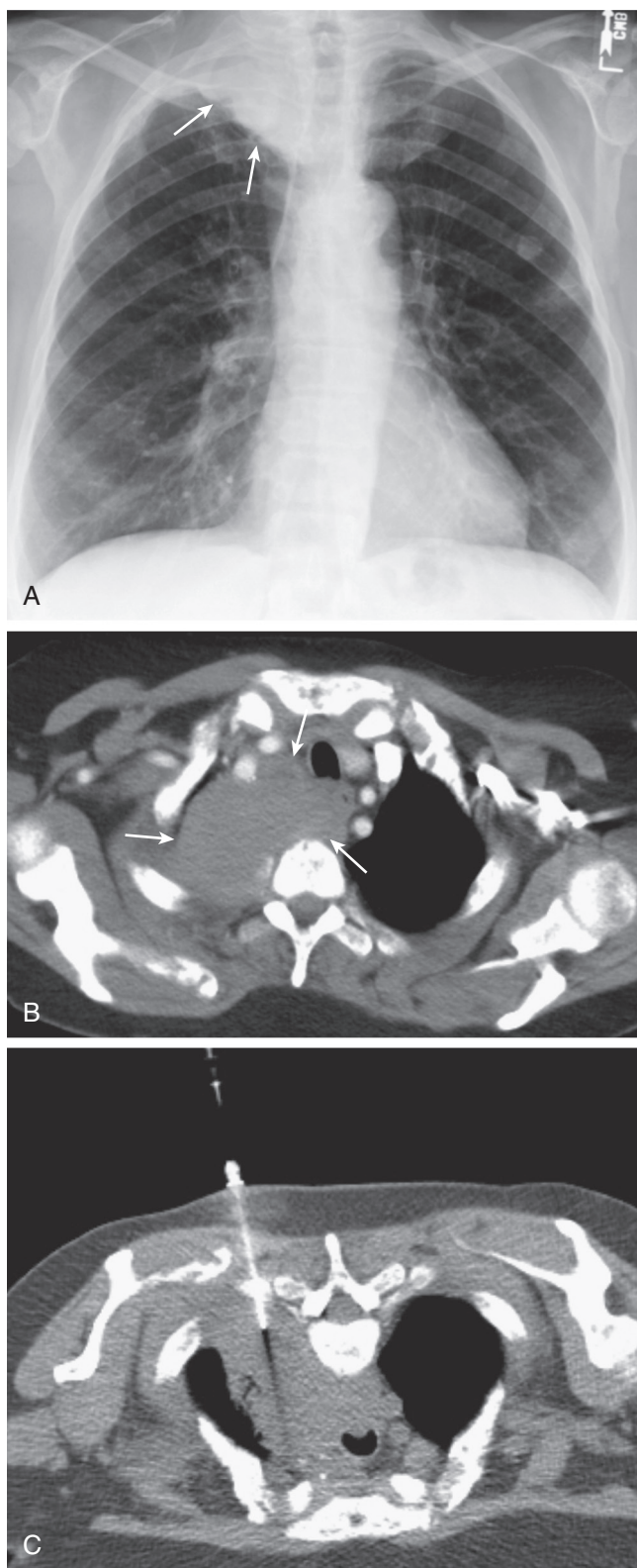


Figure 94-7 Thoracic plasmacytoma: chest wall origin. **A**, Frontal and **B**, lateral chest radiographs show a substernal contour deformity (*arrowheads*). **C**, Axial unenhanced chest CT shows sternal destruction (*arrowheads*) associated with a soft tissue mass (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 94-8 Thoracic plasmacytoma: chest wall origin. **A**, Enhanced chest CT. **B**, T2-weighted, **C**, unenhanced, and **D**, enhanced fat saturation T1-weighted MRI shows a mass (*arrows*) arising from the posterior medial chest wall, proven to represent plasmacytoma. Note the extensive rib destruction seen on the CT (*arrowheads*, **A**) and profound enhancement best seen at enhanced MR (**D**). **E** and **F**, FDG-PET shows intense metabolic activity within the lesion (*arrows*). (Courtesy Michael Gotway, MD.)



eFigure 94-9 Thoracic plasmacytoma: mediastinal origin. **A,** Frontal chest radiograph shows a superior thoracic mass (*arrows*). **B,** Axial chest CT shows the mass (*arrows*). The extensive contact with mediastinal structures (posterior wall of the trachea, esophagus, and great vessels) indicates a mediastinal origin for the lesion. **C,** Percutaneous transthoracic biopsy proved plasmacytoma. (Courtesy Michael Gotway, MD.)

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PULMONARY COMPLICATIONS OF ENDOCRINE DISEASES

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INTRODUCTION

Common endocrine disorders may affect the respiratory system in a variety of ways, from an increased risk of specific infections in patients with diabetes to upper airway compression in patients with goiter. There have been many studies of pulmonary physiology in patients with endocrine disorders, some of which have revealed clinically significant functional abnormalities. In other studies, however, physiologic abnormalities have not translated into clinical dysfunction, but they have helped add to our understanding of lung parenchymal growth and development, response to extrathoracic influences, and perhaps even aging. This chapter reviews the effects of various endocrine abnormalities on the pulmonary system.

DIABETES MELLITUS

The prevalence of diabetes is continuing to soar; in 2012, 29.8 million Americans, or 9.3% of the population, were diabetic.¹ The obesity epidemic appears to have largely driven the substantial increase in the prevalence of type 2 diabetes (the most common subset of diabetes mellitus) in recent decades. In addition to genetic predisposition, obesity, and other factors such as diet and inflammatory mediators, active cigarette smoking is associated with the development of insulin resistance and type 2 diabetes.²⁻⁴ The reason for this association has yet to be elucidated, although nicotinic acetylcholine receptors are expressed on pancreatic islet cells⁵ and nicotine exposure has been associated with beta cell dysfunction and increased beta cell apoptosis.⁶ Although less dramatic, there has also been an increase in the incidence of type 1 diabetes mellitus in the United States and worldwide.^{7,8} Type 1 diabetes results from autoimmune destruction of pancreatic beta cells in genetically susceptible patients, most likely triggered by environmental agents. The genetic basis of autoimmune type 1 diabetes has now been largely determined, and there are some shared genetic associations with known atopy-related traits.⁹

The relationship between asthma and diabetes is less clear. Asthma, diabetes, and obesity are common, complex disorders for which the prevalence among youth has increased since the 1990s. In a large observational trial,¹⁰ the prevalence of asthma was 10% among persons younger than 20 years old with type 1 diabetes and 16.1% among youth with type 2 diabetes, and differed according to race/ethnicity. Young persons with asthma were more likely to

have poorer glycemic control and higher *body mass index* (BMI) values, particularly in the group with type 1 diabetes. In the group with type 2 diabetes, more than 90% were overweight or obese, which may account for why BMI did not correlate with asthma in this group.

In terms of *chronic obstructive pulmonary disease* (COPD), the Offspring Cohort of the Framingham Heart Study¹¹ did not show an association between the diagnosis of diabetes and COPD, nor did diabetes seem to accelerate COPD in smokers. However, in patients hospitalized with COPD exacerbations, there is a high prevalence of comorbid diseases, including diabetes mellitus; of the patients hospitalized with COPD in a large multicenter study, 35.8% had diabetes.¹² In a large population-based cohort study¹³ of more than 350,000 patients with COPD or asthma, the use of inhaled corticosteroids was associated with an increased risk of requiring initial drug therapy for diabetes and an increased risk of requiring insulin in patients previously treated with oral antidiabetics over the 5-year observation period, with the caveat that diabetes mellitus prevalence increases with age. While a mainstay of treatment of asthma, inhaled corticosteroids are recommended in COPD patients for those who have more severe disease or who have frequent exacerbations¹⁴ and should not be prescribed unless warranted.

As for pulmonary function findings, a meta-analysis¹⁵ collectively representing the data from more than 3000 subjects with no prior pulmonary disease found that the presence of diabetes was associated with a mild to modest impairment in pulmonary function (Table 95-1). The pattern was restrictive with a mild decrease in diffusing capacity for carbon monoxide and was irrespective of BMI, smoking, diabetes duration, and HbA1c levels. In subanalyses, the association seemed to be more pronounced in type 2 diabetes than in type 1 diabetes. These mild functional abnormalities—generally well within 80% of the reference value¹⁶—have been ascribed to premature aging of the lungs in a fashion similar to nonenzymatic protein glycosylation and microangiopathic changes that develop in many affected organs in patients with diabetes.¹⁷ In summary, diabetes mellitus (in the absence of cystic fibrosis) may cause a mild decline in pulmonary function measurements, but does not appear to cause clinically significant pulmonary impairment, and routine pulmonary function testing in patients with diabetes is not warranted.

Compared with patients with cystic fibrosis alone, patients with cystic fibrosis-related diabetes had a higher rate of pulmonary infection with multiple antibiotic-resistant

Table 95-1 Pulmonary Complications of Diabetes Mellitus

Restrictive pattern on pulmonary function tests (mild)
Left ventricular dysfunction
Pleural effusions
Obstructive sleep apnea
Infections
Poor outcome from community-acquired pneumonia
Infections
<i>Legionella</i> pneumonia
Increased risk of aspiration pneumonia
Zygomycetes (mucormycosis)
Tuberculosis

*Pseudomonas aeruginosa*¹⁸ and a higher rate of treatment failure.¹⁹ Whether cystic fibrosis–related diabetes is associated with a higher rate of decline in pulmonary function compared with cystic fibrosis subjects without diabetes is unclear, because study outcomes have been mixed.^{20,21}

Cardiovascular and end-organ dysfunction develop in many patients with diabetes because of its chronic metabolic derangements. Cardiovascular factors appear to contribute more than pulmonary factors to impaired physical performance in patients with diabetes. In addition to the increased risk for cardiovascular events in patients with diabetes, there is an increased frequency of heart failure not explained by hypertension or coronary artery disease.²² Left ventricular systolic and diastolic dysfunction with exercise appears to be more common in patients with insulin-dependent diabetes than in those without diabetes.²³ In addition, when compared with patients with similar degrees of left ventricular dysfunction, exercise limitation and pleural effusions are more common in patients with diabetes.²⁴

Active cigarette smoking is a risk factor for the development of type 2 diabetes.²⁵ Smoking cessation has important health benefits in terms of risk reduction for a wide variety of complications, including cardiovascular events. However, weight gain is common with smoking cessation, typically 4 to 5 kg in the first year after cessation.^{26,27} In a large prospective multisite cohort study²⁸ of subjects who did not have diabetes at baseline, subjects who newly quit smoking had more significant increases in weight, waist circumference, and fasting glucose levels and a higher risk for development of type 2 diabetes than did persons who never smoked. These metabolic changes were more common in older men with heavy smoking habits before quitting; the increased risk for diabetes peaked within 3 years after quitting. Despite weight gain with smoking cessation, overall cardiovascular events decreased in patients who quit smoking.²⁹ In summary, both active smoking and the post-cessation period are associated with an increased risk for type 2 diabetes. Targeting the immediate post-quit period with more aggressive weight management and lifestyle changes in higher risk patients may be warranted.

Acute respiratory distress syndrome (ARDS) has been reported as a complication of diabetic ketoacidosis.³⁰ But diabetes mellitus—excluding diabetic ketoacidosis—is not associated with increased risk for development of ARDS compared to patients without diabetes, and it may even be

protective.^{31,32} Diabetes has been associated with a higher risk for development of idiopathic pulmonary fibrosis.^{33,34}

Newborn babies of diabetic mothers are at increased risk for macrosomia and preterm delivery^{35,36}; infants born to mothers with poor self-care are at greatest risk.³⁶ However, with good maternal metabolic control and accurate estimations of gestational age, most pregnant women with diabetes can deliver at or near term without associated respiratory distress syndrome.^{37,38}

Obesity is a risk factor for both type 2 diabetes mellitus and for obstructive sleep apnea. (See Chapter 88 for a full discussion of obstructive sleep apnea.) The prevalence of obstructive sleep apnea in patients with type 2 diabetes has been reported as 23% to 36%, and in patients with BMI greater than 35 kg/m², prevalence has been reported to be as high as 70%.^{39,40} Higher apnea-hypopnea indexes in diabetic patients with obstructive sleep apnea are associated with poorer glucose control.⁴¹ In addition, obstructive sleep apnea may impose a stress that increases sympathetic neural output during sleep, which in turn contributes to insulin resistance⁴²; moreover, oxygen desaturation is specifically associated with insulin resistance in severely obese patients.⁴³ In patients with diabetes, obstructive sleep apnea may increase the risk for diabetic peripheral neuropathy, perhaps due to increased oxidative stress and impaired microvascular regulation.⁴⁴ Continuous positive airway pressure therapy in diabetic patients with obstructive sleep apnea may not improve metabolic control unless there is also weight loss, at least in short-term follow-up.⁴⁵

Patients with diabetes are at increased risk for upper and lower airway infections, and are particularly predisposed to infection with Zygomycetes (mucormycosis), a group of infections caused by fungi in the *Mucor*, *Rhizopus*, and *Cunninghamella* genera. Angioinvasion is a hallmark of infections with mucormycosis. These ubiquitous saprophytic fungi are found in soil and decaying vegetation; infection is caused by inhalation of spores, hence the predilection for paranasal sinus and lung disease. Infection typically develops during or after an episode of diabetic ketoacidosis, perhaps because the fungi have an enzyme, ketone reductase, which favors growth in an acidic, hyperglycemic environment. Most patients have some underlying predisposition, of which diabetes mellitus is the most significant.⁴⁶ Five infectious manifestations have been described: rhinocerebral, pulmonary, disseminated, cutaneous, and gastrointestinal. Rhinocerebral infection is the most common form, especially in patients with diabetes. Presentation includes sudden periorbital or paranasal swelling and pain, bloody nasal discharge, and black necrotic nasal mucosa. Computed tomography (CT) findings are mostly nonspecific, but can include an air crescent sign (rim of air between necrotic lung and surrounding parenchyma) as well as the halo sign (rim of surrounding ground-glass opacities around dense consolidation).⁴⁷ Treatment requires control of the diabetes, antifungal therapy, and often aggressive surgical debridement. Mortality remains high, especially in patients with intracranial involvement.⁴⁸

Pulmonary mucormycosis mimics invasive aspergillosis and is found mostly in patients with diabetes, hematologic malignancy, or organ transplantation or in patients on glucocorticoid or deferoxamine therapy. Inhaled mold spores

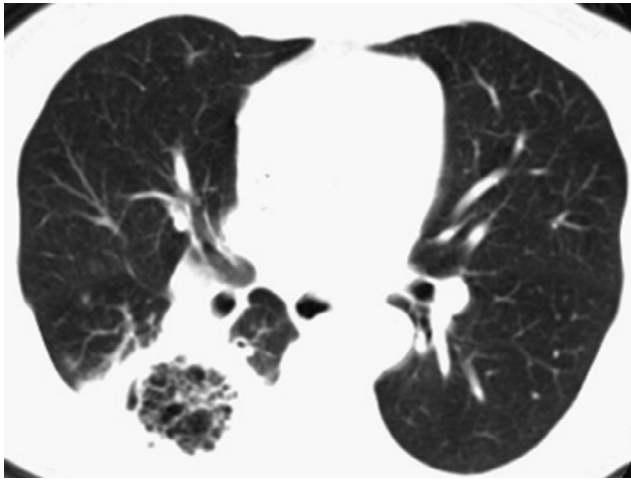


Figure 95-1 Mucormycosis. Radiograph showing pulmonary infarction of the right lower lobe in a diabetic patient with pulmonary mucormycosis.

penetrate bronchiole walls, invade arterioles, and cause thrombosis and ischemia (Fig. 95-1). Nonspecific cough, fever, and pleuritic chest pain develop. Hemoptysis may develop in one fourth of cases and can be massive.⁴⁹ The most common chest radiographic pattern is consolidation; cavitation is seen in about one third of patients,⁵⁰ and adenopathy and pleural effusions may also be present but are less common. Patients with diabetes appear to have a predilection for endobronchial disease; however, sputum culture appears to have a very low yield for diagnosis. For specimens obtained at bronchoscopy, histopathologic examination appears to be more sensitive than fungal cultures. Treatment requires antifungal therapy (see Chapter 38) and, if localized, surgical resection. Bronchial stenosis is a potential sequela.

Diabetes mellitus is an independent risk factor for drug-sensitive⁵¹⁻⁵⁵ and multidrug-resistant tuberculosis.³⁸ A review of 13 observational studies revealed that diabetes mellitus was associated with an increased risk for tuberculosis (relative risk, 3.11; 95% CI 2.27-4.26),⁵³ an association that is supported by studies of diabetic children in South Africa and adults in Brazil.⁵⁵ Patients with tuberculosis and diabetes tended to be older, were more likely to yield positive smears for acid-fast bacilli, and had a higher mortality than patients with tuberculosis without diabetes.⁵⁵ The radiographic location of tuberculosis in diabetes (i.e., upper or lower lobe predilection) depends on the case series; patients with diabetes and tuberculosis appear to have a higher rate of cavitation.^{52,56} Treatment of latent tuberculosis in patients with diabetes with either a positive purified protein derivative skin test of greater than 10 mm of induration⁵⁷ or a positive interferon-gamma release assay is currently recommended.

Bacterial pneumonia may or may not be more frequent in patients with diabetes. In a study of more than 4000 elderly inhabitants in one township, diabetes mellitus was not an independent risk factor for community-acquired pneumonia.⁵⁸ Study findings are mixed as to whether diabetes portends a poorer outcome in persons in whom pneumonia develops.⁵⁹⁻⁶¹ Diabetes does not appear to be an independent risk factor for either health care-associated

pneumonia or ventilator-associated pneumonia.⁶² Given the demonstrated efficacy of pneumococcal vaccine and the increasing prevalence of penicillin resistance in pneumococcal strains, pneumococcal vaccination is recommended for virtually all people with diabetes. Diabetes appears to be a risk factor for *Legionella* pneumonia⁶³ and is associated with high mortality in infected persons.⁶⁴ Pharyngeal dysfunction and diabetic gastroparesis in persons with diabetes may predispose them to aspiration pneumonia.⁶⁵ Diabetes is a risk factor for chronic oral infections of caries and periodontitis, which also may contribute to the increased risk for aspiration pneumonia.⁶⁶ There is an increased incidence of bacterial pneumonia and associated mortality in patients with diabetes during seasonal influenza outbreaks.⁶⁷ Consistent with the recommendations of the Advisory Committee on Immunization Practices, influenza vaccination is recommended for patients with diabetes who are older than 6 months of age.⁶⁸ Regarding preventive practices in patients with known diabetes, approximately 60% have obtained annual influenza vaccines, whereas just 49% have met goals of pneumococcal vaccination.⁶⁹ As for other pathogens, preexisting diabetes has been associated with a higher mortality in patients with severe acute respiratory syndrome.⁷⁰

THYROID DISORDERS

The incidence of multinodular goiter is declining in the United States due to the routine use of iodized salt; nevertheless, neglected goiters are still detected. Because of the thyroid's ability to expand easily in the anterior space, bound only by skin, thin muscle, and connective tissue, even large goiters may not cause tracheal impingement. However, some goiters can cause dyspnea, stridor, wheezing, hoarseness, and cough via tracheal deviation—typically if there is unilateral or unequal lobe enlargement—and airway compression.⁷¹⁻⁷³ (Video 95-1). Compression or concentric narrowing of the trachea is more common if the goiter extends posteriorly to the trachea (Fig. 95-2). Although goiters typically grow slowly, occasionally patients present with acute respiratory distress requiring urgent intubation or semiurgent surgery.

Some goiters are substernal and/or intrathoracic. There is variability of the definition of “intrathoracic goiter”; most experts concur that some portion of the goiter is permanently retrosternal (below the sternal notch), even when the neck is retroflexed.⁷⁴ Bulky and/or substernal goiters may cause orthopnea because of airflow limitation in the supine position. In these patients, flow-volume loops in the recumbent position may demonstrate upper airway obstruction not apparent in upright testing.⁷³ CT scanning and magnetic resonance imaging generally are the most useful diagnostic imaging studies and can estimate the degree of tracheal compression.⁷⁵

Of particular note, CT scanning with iodinated contrast media should generally be avoided because it precludes thyroid nuclear imaging for several weeks and can trigger hyperthyroidism. Surgical resection of substernal goiters is recommended and usually relieves compressive symptoms.^{71,76} Postoperative tracheomalacia appears to be rare.⁷¹

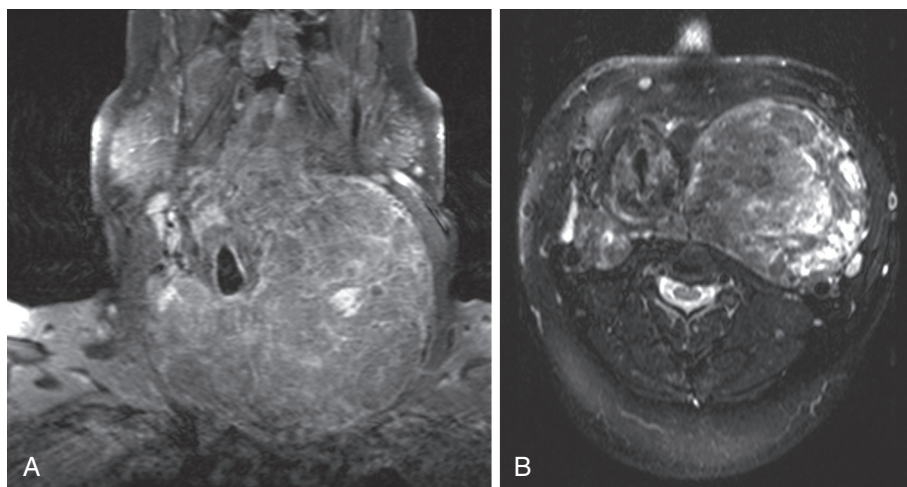


Figure 95-2 Thyroid goiter. Magnetic resonance images show a massive goiter in a 55-year-old man who presented with a change in his voice and increased shortness of breath. Endotracheal intubation required flexible bronchoscopy, followed by uneventful resection of a 900-g multinodular goiter. Coronal (A) and axial (B) gadolinium-enhanced images of the neck reveal tracheal deviation and compression.

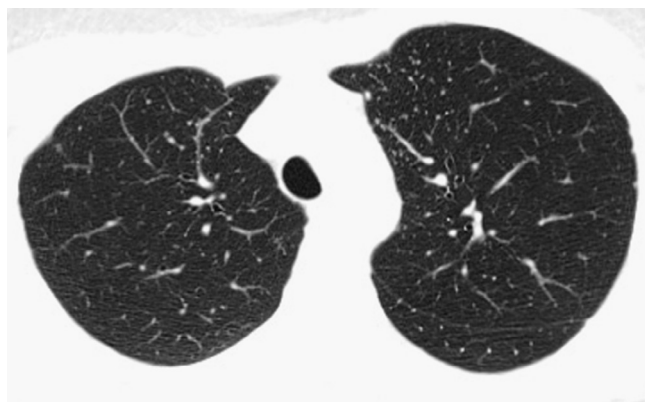


Figure 95-3 Metastatic thyroid cancer. Computed tomography scan of a patient showing metastatic thyroid cancer with micrometastases. (Courtesy Michael B. Gotway, MD.)

Iodine-131 is an alternative therapy for some patients with large goiters including those with intrathoracic extension who are not surgical candidates because of comorbid illnesses.^{77,78} For patients with baseline tracheal compression, there is often some temporary goiter enlargement from edema and additional airway compromise in the week following ¹³¹I treatment. Even so, with glucocorticoid prophylaxis, most patients do well and have subsequent goiter shrinkage.⁷⁹ Alternatively, bronchoscopic insertion of tracheal stents can relieve large airway obstruction from compressive benign or malignant nonoperable thyroid disease.⁸⁰ Large, multinodular goiters with retrolaryngopharyngeal extension can also cause obstructive sleep apnea, which can resolve after total thyroidectomy.^{81,82}

Thyroid carcinoma accounts for 1% of all new malignancies; the most common is papillary thyroid carcinoma. Of these, 10% to 15% will develop metastases, the vast majority of which are within the thoracic cavity. A miliary pattern of metastases can be seen, as well as larger nodules, and even localized pulmonary opacities⁸³ (Fig. 95-3 and Video 95-2). Depending on the lung burden of cancer, dyspnea may be present. Thyroid cancer can also directly invade the

trachea. In patients who are otherwise good surgical candidates, resection with tracheal reconstruction has been successful.⁸⁴

Smoking is a risk factor for hyperthyroidism, including Graves disease, toxic nodular goiter, and autoimmune hypothyroidism (Hashimoto thyroiditis), especially in women.⁸⁵⁻⁸⁷ Smoking increases the risk of Graves ophthalmopathy beyond the risk associated with hyperthyroidism alone.

HYPERTHYROIDISM

Many patients with hyperthyroidism complain of both resting and exertional dyspnea. Congestive heart failure likely explains some of these complaints⁸⁸ and is the presenting feature in 6% of patients with newly diagnosed hyperthyroidism.⁸⁹ Some hyperthyroid patients have decreased vital capacity,⁹⁰ decreased respiratory muscle strength,⁸⁹⁻⁹³ and elevated resting minute ventilation (perhaps due to increased central ventilatory drive) that becomes excessive with exercise.⁹² With treatment, vital capacity and respiratory muscle strength improve,⁹⁰ although some patients have persistent dyspnea.⁹¹

Patients with coincident asthma and thyrotoxicosis may have worsening asthma control if β -blocker agents are used to control manifestations of hyperthyroidism. There may be an association between atopic disease, asthma, and Graves disease.⁹⁴ Approximately 30% of patients with hyperthyroid Graves disease have an elevation in serum *immunoglobulin E* (IgE) levels, and those with elevated serum IgE are more likely to have a personal or family history of atopy.⁹⁵

Several reports have suggested a link between hyperthyroidism, especially Graves disease, and pulmonary hypertension in which the pulmonary artery pressures can improve and even normalize with treatment of the hyperthyroidism.⁹⁶⁻⁹⁸ The explanation for this association is not clear, but may be due to a generalized autoimmune state, a direct influence of thyroid hormone on pulmonary vasculature, changes in metabolism of pulmonary vasculature vasodilators/vasoconstrictors, decreased surfactant production and function, or excess cardiovascular

stimulation by the sympathoadrenal system. Treatment of the hyperthyroidism is important to relieve the additional burden of cardiovascular stress on the pulmonary vascular system.⁹⁷ Rarely, mothers with hyperthyroidism from Graves disease deliver infants with hyperthyroidism via placental passage of maternal thyrotropin receptor-stimulating antibodies. In addition to a variety of infant metabolic and developmental problems, neonatal Graves disease has been associated with persistent pulmonary hypertension in newborns.⁹⁹ Interestingly, there may also be an increased prevalence of hypothyroidism in patients with primary pulmonary hypertension.¹⁰⁰

Furthermore, several reports of an increased presence of antinuclear cytoplasmic antibodies and even granulomatosis with polyangiitis (Wegener granulomatosis) have been documented in patients with Graves disease treated with propylthiouracil.¹⁰¹ Propylthiouracil-induced nonspecific interstitial pneumonia¹⁰² and alveolar hemorrhage¹⁰³ have also been reported.

HYPOTHYROIDISM

Hypothyroidism has been associated with dyspnea on exertion, alveolar hypoventilation, respiratory failure, obstructive and central sleep apnea, and pleural effusions. Lung volumes are generally normal or mildly decreased in mixed populations of obese and nonobese hypothyroid patients.^{104,105} Lung volumes typically, although not uniformly, improve with thyroid replacement and/or weight loss. A reduced diffusing capacity for carbon monoxide can be seen in some hypothyroid, nonobese patients with normal lung volumes and arterial blood gases that improve to near-normal after replacement therapy.¹⁰⁵ Hypothyroidism is associated with overall respiratory muscle weakness as measured by maximal inspiratory and expiratory pressures, and the degree of impairment is linearly related to the degree of pretreatment hypothyroidism.¹⁰⁶ Diaphragmatic muscle weakness in both obese and nonobese hypothyroid patients may range from mild impairment, which limits exercise tolerance, to severe dysfunction, with marked resting dyspnea and chronic hypercarbia.¹⁰⁴ Thyroid replacement therapy can improve respiratory muscle strength. Some nonobese and obese hypothyroid patients have a markedly blunted ventilatory response to hypoxia and hypercapnia,^{105,107} which improves often within weeks of initiation of thyroid hormone replacement. This improvement is not associated with changes in spirometric function or maximal voluntary ventilation, thus suggesting a central cause for the abnormal ventilatory response. Hypothyroidism can cause respiratory failure that may require prolonged mechanical ventilation.¹⁰⁷

Although up to 25% of patients with hypothyroidism have radiographic evidence of a pleural effusion, most patients also have underlying congestive heart failure (Table 95-2).¹⁰⁸ A small percentage of hypothyroid patients do not have another disease process that would explain the effusion. In these patients, the hypothyroid-related effusions tend to be small, less than one third of the pleural space; unilateral or bilateral; serous or serosanguineous; and transudates or exudates, although generally noninflammatory.¹⁰⁸ Hypothyroid-related effusions typically resolve with treatment of the hypothyroidism.¹⁰⁸

Table 95-2 Etiologies of Pleural Effusions in Hypothyroid Patients (n = 28)

Etiology	No.
Nonhypothyroid-associated pleural effusions	22
Pneumonia	7
Congestive heart failure	7
Malignancy	4
Atelectasis	2
Pancreatitis	1
Cirrhosis with ascites	1
Hypothyroid pleural effusion	5
Hypothyroid-associated effusion due to pericardial involvement	1

Modified from Gottehrer A, Roa J, Stanford GG, et al: Hypothyroidism and pleural effusions. *Chest* 98:1130–1132, 1990.

Hypothyroidism can predispose patients to sleep apnea,^{109,110} possibly from narrowing of the upper airway from mucopolysaccharide and protein deposition in the tongue and oropharynx,¹¹¹ from abnormalities in ventilatory control, and/or from weight gain. Hypothyroidism can contribute to the neurocognitive impairment found in patients with sleep apnea.¹¹² In one case series, only 3.1% of patients with obstructive sleep apnea were found to have hypothyroidism¹¹⁰; in contrast, 25% of newly diagnosed hypothyroid patients were found to have obstructive sleep apnea. Age and body weight were the best predictors of associated obstructive sleep apnea.¹¹⁰ Hypothyroid patients with obstructive sleep apnea have blunted ventilatory responses to both hypoxia and hypercapnia. Some studies have shown improvement in sleep respiratory disturbance index and awake ventilatory response to hypoxia and hypercapnia with thyroid replacement^{110,113}; in other studies, however, investigators found less than full improvement or no improvement in sleep apnea with thyroid replacement.^{114,115} Central sleep apnea can also be detected in hypothyroid patients, and the blunted ventilatory response to hypoxia may improve with thyroid replacement.¹¹⁴

Thyroid hormones play an important role in the growth and development of the lung and in the maturation of the lung's surfactant system.^{116,117} Transient hypothyroxinemia is common in premature infants, as is respiratory distress syndrome. However, the administration of maternal antenatal thyrotropin-releasing hormone, which increases fetal thyroid hormone levels, did not decrease the frequency or severity of respiratory distress syndrome in premature babies in a large multicenter trial.¹¹⁸ Treatment of premature infants with thyroxine also did not decrease the incidence of respiratory distress syndrome, the use of surfactant therapy, or the overall developmental outcome at 24 months.¹¹⁹

The “brain-thyroid-lung syndrome”^{120–122} is a rare form of neonatal progressive respiratory failure characterized by chorea or cerebral dysgenesis, congenital hypothyroidism, and respiratory disease. It is related to defects of the *NKX2-1* gene encoding thyroid transcription factor-1, which appears to be critical for central nervous system, thyroid, and lung development and function. In the lung, thyroid transcription factor-1 deficiency syndrome leads to a disturbance of surfactant protein-A production, resulting in

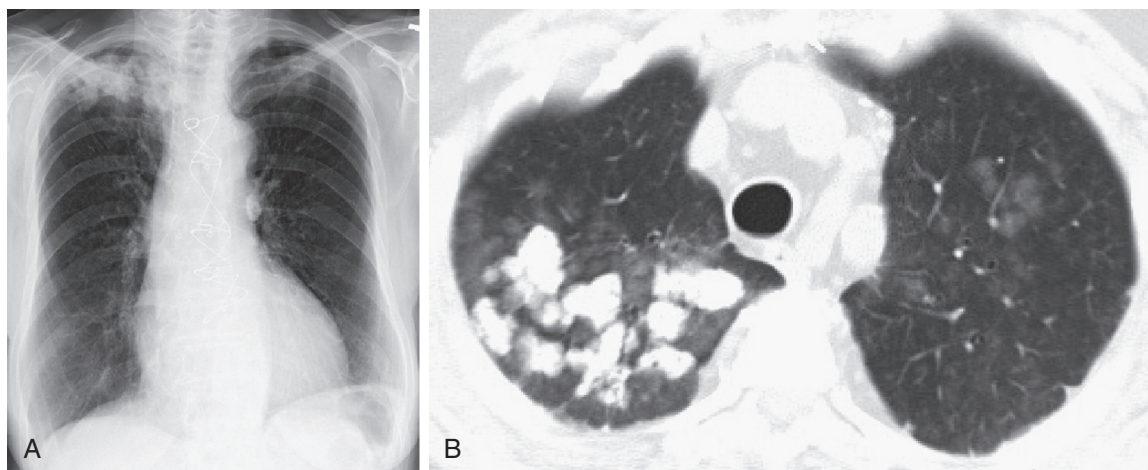


Figure 95-4 Metastatic calcification. Frontal chest radiograph (A) and corresponding axial chest CT scan (B) show the apical predilection of metastatic pulmonary calcification that can be seen in hyperparathyroidism.

spectrum of disease from mild to progressive and fatal respiratory failure.

PARATHYROID DISEASES

Hyperparathyroidism, typically secondary hyperparathyroidism in patients with end-stage renal disease, can cause diffuse metastatic calcification in the lungs. Metastatic calcification is the deposition of calcium salts in previously normal tissue; in contrast, dystrophic calcification is the calcification of diseased or abnormal tissue, as in granulomatous processes. Despite dietary phosphate restriction, administration of phosphate binders, and hemodialysis, patients with renal failure are at risk for metastatic calcification, especially when the calcium-phosphorus concentration product increases above $70 \text{ mg}^2/\text{dL}^2$. Calcium salts tend to precipitate in alkaline conditions. Indeed, metastatic calcification has a predilection for the apical portions of the lungs (Fig. 95-4), the stomach, and the kidneys—all tissues with relative alkalinity, because of either carbon dioxide removal or hydrogen ion excretion. Due to the higher ventilation-perfusion ratio and lower carbon dioxide concentration at the lung apex, it is estimated that the pH at the apex is 7.5 compared to a pH of 7.3 at the base.^{123,124} Other common sites of deposition include soft tissues and the skin. Pulmonary metastatic calcific nodules may deposit predominantly in the alveolar septa and are associated with varying degrees of fibrosis and septal thickening. This phenomenon appears to be common; from 60% to 80% of dialysis patients on long-term therapy have autopsy or scintigraphic evidence of pulmonary metastatic calcification.¹²⁵

Most patients with end-stage renal disease and metastatic pulmonary calcification are asymptomatic and have normal chest radiographs and pulmonary function. However, patients with heavy deposition of calcific nodules may complain of dyspnea and nonproductive cough, and can rarely progress to respiratory failure.¹²⁶ Radiographically, patients with more extensive calcification typically have numerous nodules about 3 to 10 mm in size that are better visualized on CT scans than on plain chest radiographs (Fig. 95-5).¹²⁷



Figure 95-5 Metastatic calcification in the lungs secondary to chronic renal failure. A 59-year-old man with end-stage renal disease for 5 years complained of chronic progressive shortness of breath. The serum calcium level was 9.9 mg/dL (normal range, 8.5 to 10.5 mg/dL) and the parathyroid hormone level was 271 pg/mL (normal for the laboratory, 11 to 54 pg/mL). High-resolution computed tomography revealed numerous nodular ground-glass densities in a peribronchial pattern, most prominently in the upper lobes. (Courtesy Marcia McCowin, MD.)

In addition to the nodular densities, patchy consolidation and ground-glass attenuation may be seen. The calcific nature of the nodules may not be apparent on plain radiographic or even CT images, perhaps due to the small size of the calcium deposits. However, radionuclide bone scans usually reveal intense uptake in the lungs and other affected organs (Fig. 95-6).¹²⁵ Pulmonary function tests in patients with extensive metastatic calcification may show ventilatory restriction with hypoxemia and low diffusing capacity for carbon monoxide.¹²³ Parathyroidectomy or treatment with vitamin D analogues can decrease the calcium-phosphorus double product, reverse bone scan abnormalities and organ deposition, and presumably improve pulmonary function.

Hyperparathyroidism is also associated with calcification in pulmonary arterial and bronchial walls. Of note, about one third of patients with end-stage renal disease on long-term hemodialysis via arteriovenous access have pulmonary hypertension,^{128,129} but pulmonary hypertension does not seem to correlate with the presence or severity of pulmonary artery calcification or parathyroid hormone levels.^{128,130}



Figure 95-6 Metastatic calcification in the lungs caused by chronic renal failure. This is the same patient as in Figure 95-5. Whole-body bone imaging with technetium-99m-diphosphonate revealed diffuse soft tissue avidity in both lungs.

Rarely, enlarged mediastinal parathyroid cysts can cause tracheal compression with stridor or vocal cord impingement and hoarseness, or both. Surgical excision is the treatment of choice.¹³¹

Hyperparathyroidism is frequently associated with muscle weakness and fatigue. Respiratory muscle function can be affected as well, and post-parathyroidectomy improvement in forced vital capacity and forced expiratory volume in 1 second values correlates with preoperative serum calcium and preoperative parathyroid hormone values.¹³²

Vitamin D deficiency and metabolic bone disease from a variety of causes can affect skeletal muscle strength and bone integrity and, in turn, may impair pulmonary function. Unrelated to skeletal effects, vitamin D deficiency has been associated with increased severity of asthma¹³³ and increased risk for asthma exacerbations in children.^{134,135} Vitamin D deficiency has been associated with impaired pulmonary function in adults^{136,137} and a more rapid decline in pulmonary function in smokers.¹³⁸ Vitamin D deficiency has not been associated with COPD exacerbations,¹³⁹ and supplementation with high-dose vitamin D does not reduce future COPD exacerbations.¹⁴⁰ Hypophosphatasia from mutations in the gene for the tissue-nonspecific isozyme of alkaline phosphatase can lead to rickets or osteomalacia. Fatal respiratory insufficiency due to progressive chest deformity can develop in severely affected babies. Enzyme replacement therapy is associated with improved findings

on skeletal radiographs and improved pulmonary and physical function in affected children.¹⁴¹

ADRENAL DISEASES

Endogenous Cushing syndrome (i.e., not from glucocorticoid administration) may be caused by pituitary Cushing disease, adrenal neoplasia, or ectopic adrenocorticotrophic hormone production from small-cell lung cancer or from carcinoids arising from a variety of organs, especially the lung, including the variation of pulmonary carcinoid tumorlets.¹⁴²⁻¹⁴⁴ Cortisol levels tend to be much higher with ectopic adrenocorticotrophic hormone production and adrenal neoplasia than with pituitary Cushing disease and pose a greater risk for infection. Hypercortisolism particularly predisposes patients to mucocutaneous fungal infections and opportunistic pulmonary infections. The most common pulmonary infections are caused by *Cryptococcus*, *Aspergillus*, *Nocardia*, *Pneumocystis*, and *Mycobacterium tuberculosis*.¹⁴⁵⁻¹⁴⁸ *Pneumocystis jirovecii* pneumonia tends to develop in patients with especially high morning cortisol levels.¹⁰³ Correction of hypercortisolism is an important adjunct to antimicrobial therapy. Cushing syndrome is also associated with a hypercoagulable state and an increase in clinically significant thromboembolic events.^{149,150} Even in patients without baseline hypercortisolism, cortisol levels increase in stress and extremely elevated cortisol levels at presentation appear to be independent predictors of worse outcomes in community-acquired pneumonia.^{151,152}

Adrenal insufficiency may be due to either primary adrenal failure (Addison disease) or secondary adrenal insufficiency. Secondary adrenal insufficiency is most commonly iatrogenic as a result of the withdrawal of exogenous glucocorticoid therapy, or results directly from disease of the hypothalamic-pituitary axis. In industrialized countries, 70% to 80% of cases of Addison disease are autoimmune in origin; in contrast, in resource-poor countries, tuberculosis remains the most common cause.^{153,154} CT scanning is sometimes helpful in determining the cause of Addison disease, because tuberculosis and histoplasmosis may cause adrenal calcification.¹⁵⁵ Adrenal insufficiency via hypothalamic-pituitary axis dysfunction may be seen in stressed, very-low-birth-weight infants and may render them more susceptible to bronchopulmonary dysplasia.¹⁵⁶

ACROMEGALY

Acromegaly is a disorder of excess growth hormone secretion in adults, most commonly from a benign pituitary adenoma. Rarely, bronchial carcinoid or small-cell lung cancer can produce excess growth hormone-releasing factor, which stimulates excess growth hormone secretion. Clinically, acromegaly is characterized by excessive bone growth, soft tissue hypertrophy, and coarsening of facial features. These changes appear to be due to high levels of growth hormone and *insulin-like growth factor I* (IGF-I), which is secreted in response to growth hormone; the net effect is an increase in somatic growth and metabolic disturbances. Mortality in acromegaly is increased primarily

from cardiovascular disease,¹⁵⁷ although control of acromegaly can lead to a significant decrease in coronary heart disease risk factors, especially in patients whose IGF-I levels are normalized.¹⁵⁸

Patients with acromegaly can develop macroglossia, nasal polyps, oropharyngeal airway narrowing, and vocal cord restriction and edema. In addition, coincidental goiter is not uncommon and can contribute to upper airway narrowing.^{157,159} Respiratory manifestations of acromegaly include sleep apnea, extrathoracic airway obstruction, vocal cord dysfunction, and difficult intubation.^{157,159} The prevalence of sleep apnea has been reported as between 20% and 60%.¹⁶⁰⁻¹⁶² Increased rates of obstructive sleep apnea may be due to a narrowed upper airway from osseous enlargement, hypertrophy of tissues in the oropharynx, inspiratory collapse of the hypopharynx, and macroglossia. The circumference of the neck and fingers, but not BMI, are predictive of the development of sleep apnea in acromegaly.¹⁶² Obstructive sleep apnea may improve with treatment of acromegaly with pituitary ablation¹⁶³ or somatostatin analogues, but is highly variable.^{160,161,164,165} Persistence of obstructive sleep apnea after treatment may be due to irreversible upper airway remodeling. Central sleep apnea is also common. Patients with central sleep apnea and acromegaly have higher growth hormone and IGF-I levels and higher ventilatory responses to carbon dioxide than acromegalic patients with obstructive sleep apnea.¹⁶⁶ Central sleep apnea in these patients may therefore be due to altered ventilatory control.

Total lung capacity and vital capacity are typically increased in patients with acromegaly compared with controls,¹⁶⁷⁻¹⁷² and appear to correlate with both the duration of acromegaly and in level of IGF-I.^{169,173} Possible causes for the increased lung volumes in these patients include hypertrophy or enlargement of individual alveoli, or an increase in the number of alveoli.^{167,170,171} Diffusing capacity for carbon monoxide may be within normal limits^{167,170} or elevated.¹⁶⁸ Changes in vertebrae and rib morphology contribute to the barrel chest of patients with acromegaly. In addition, with acromegaly, there is a decrease in respiratory muscle force that may contribute to increased dyspnea and fatigue with exercise.¹⁷²

Evidence of a variable extrathoracic airway obstruction on flow-volume loops is seen in 30% to 50% of patients with acromegaly.¹⁶⁹ As noted, intubation may be more difficult in patients with acromegaly because of vocal cord fixation, vocal cord edema, prolapse of an enlarged tongue, and soft tissue thickening of the oropharynx.¹⁷⁴ Preoperative treatment of patients with somatostatin analogues may decrease soft tissue swelling and enable easier intubation.¹⁶⁵

Key Points

- Diabetes mellitus, by far the most common endocrine disorder, is associated with sleep apnea and predisposes to certain bacterial, fungal, and mycobacterial respiratory infections. Cigarette smoking is a risk factor for type 2 diabetes. Patients with diabetes should receive pneumococcal and influenza vaccinations and, because of an increased risk for progression to active tuberculosis, should receive treatment for latent tuberculosis infection if they have a tuberculin skin test greater than 10 mm or a positive interferon-gamma release assay.
- Thyroid enlargement may cause upper airway compression. Patients with hyperthyroidism may have dyspnea worsened by decreases in vital capacity and respiratory muscle strength. More commonly, patients with hypothyroidism suffer from dyspnea, alveolar hypoventilation, pleural effusion, and, sometimes, respiratory failure.
- Secondary hyperparathyroidism from end-stage renal disease often causes diffuse metastatic pulmonary calcification, which frequently is asymptomatic.
- Endogenous Cushing syndrome predisposes to a variety of opportunistic infections, whereas acromegaly from excess growth hormone is associated with a high prevalence of sleep apnea, and may lead to upper airway structural disorders.

Complete reference list available at [ExpertConsult](#).

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THE LUNGS IN OBSTETRIC AND GYNECOLOGIC DISEASES

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INTRODUCTION

Both respiratory physiology and the respiratory tract's susceptibility to disease are uniquely altered in gynecologic and obstetric conditions, including normal pregnancy. This chapter summarizes normal physiologic alterations during pregnancy and considers pathologic diseases and disorders that arise during pregnancy. Airway disorders, infectious diseases, pulmonary vascular and embolic disorders, and acute lung injury are discussed. Finally, pleural and parenchymal diseases that arise as a consequence of gynecologic conditions are addressed.

PHYSIOLOGIC ALTERATIONS DURING NORMAL PREGNANCY

Profound alterations of respiratory function and cardiovascular physiology accompany normal pregnancy in healthy women; these conditions contribute to many of the disorders of the lungs during pregnancy. The adaptive changes during the gravid period are designed to support maternal and fetal well-being during the special stresses of fetal growth and parturition, but they may exacerbate some underlying disorders and confuse interpretation of laboratory and imaging studies used to assess many other common conditions.

ALTERATIONS IN RESPIRATORY PHYSIOLOGY

Upper airway, particularly nasal, mucosal edema is common in normal pregnancy. About 20% of gravid women complain of rhinitis symptoms, now attributed at least partially to placental growth hormone's effects on mucosal congestion.¹ The symptoms begin in the first trimester and persist throughout gestation. Many patients thought to have rhinitis of pregnancy may actually have other or coincident causes of rhinitis.² An important implication of nasal mucosal edema in pregnancy is that it predisposes to nosebleeds, including from nasal intubations, so an oral approach is favored if intubation is required at the time of delivery.

Chest wall configuration is also altered, partially due to a 50% increase in the average costal angle³ and partially due to an increase in the circumference of the lower chest wall. Diaphragmatic position is elevated 4 to 5 cm, but excursion does not diminish.³ Muscle strength, as measured by maximum transdiaphragmatic pressure, does not appear to be diminished from its usual mean value of about 95 cm H₂O,⁴ allowing reserve for both the augmented minute ventilation of normal pregnancy and the stresses of delivery.

Important changes take place in lung function and lung volumes. The loss of lung volume resulting from elevation of the diaphragm is only partially offset by the increase in chest wall diameter, and therefore *functional residual capacity* (FRC) is diminished by about 18%, or 300 to 500 mL.⁵ This reduction in FRC comprises an equal reduction in both the expiratory reserve volume and the residual volume.^{3,5} The loss of FRC at term is made worse by recumbency, when diaphragm elevation is greatest because of the higher intra-abdominal pressure. Increased pulmonary blood volume in pregnancy may also serve to lower the FRC.⁶ This reduction in FRC is associated clinically with increased uptake and elimination of inhalational anesthetics and with rapid desaturation during hypopnea, as a result of the loss of the oxygen reservoir function of end-expiratory lung volume.⁷ Endotracheal intubation at term is thus substantially more hazardous than in nonpregnant patients.

Airway function is largely unchanged during pregnancy.³ Airway resistance may actually decrease slightly. Routine measurements of air flow, such as the FEV₁ and flow rates at midexpiratory lung volume (forced expiratory flow between 25% and 75% of FVC, or FEF_{25%-75%}) are thus valuable in assessing dyspnea during pregnancy.

The most striking changes are in respiratory drive and minute ventilation. Central drive, as assessed by the inspiratory pressure measured 100 msec after airway occlusion at the onset of inspiration (P_{0.1}), is increased by 13 weeks and continues to increase to week 37 of gestation, returning to normal by 24 weeks after delivery.⁴ These serial changes in respiratory drive appear to correlate with changes in serum progesterone levels.^{4,8} Carbon dioxide production itself increases one third to one half by the last trimester, but this is more than made up for by the greatly augmented ventilation, so primary respiratory alkalosis with renal

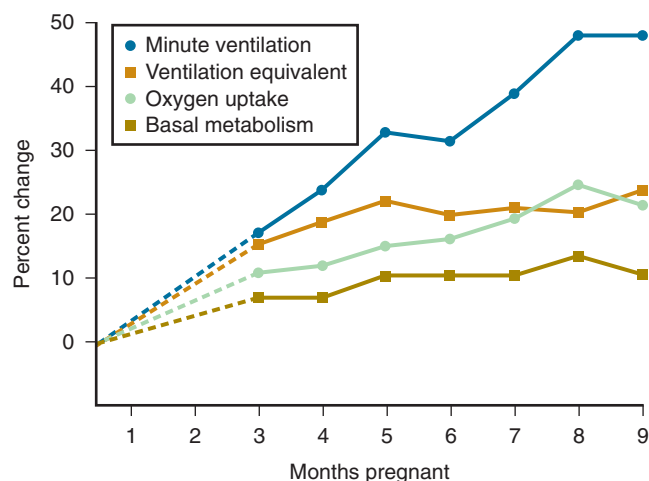


Figure 96-1 The physiology of pregnancy. The expected values for minute ventilation, the ventilatory equivalent for oxygen, oxygen uptake, and basal metabolism are shown at monthly intervals throughout pregnancy. (From Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. *Anesthesiology* 26:381, 1965.)

bicarbonate wasting as compensation is a normal finding.⁹ Arterial blood gas measurements typically show the pH ranging from 7.40 to 7.47, with PCO_2 reaching as low as 28 to 32 mm Hg. PO_2 rises slightly as a result of the increase in alveolar ventilation.

Most of the increase in minute ventilation is due to a 30% to 35% increase in tidal volume. Respiratory rate is unchanged early and rises only about 10% later in pregnancy. Oxygen consumption increases 20% to 33% in pregnancy, owing to both maternal and fetal metabolic demands. Changes in some of these parameters are shown in Figure 96-1.

ALTERATIONS IN CARDIOVASCULAR PHYSIOLOGY

Adaptive cardiovascular changes are designed to support both maternal and fetal circulations but contribute to the risk for hydrostatic pulmonary edema; accordingly, cardiac disorders during pregnancy often present as respiratory failure. During normal pregnancy, maternal blood volume increases by about 2 L, or 40%.^{10,11} Red blood cell mass increases as well, but only by 20% to 30%, accounting for the normal 10% to 12% decrease in hematocrit.^{11,12} Plasma oncotic pressure also drops as intravascular volume expands, increasing the risk for pulmonary edema at lower intravascular hydrostatic pressures. During the 24 hours after parturition, oncotic pressure falls further because of blood loss and mobilization of extravascular fluid.

The enlarged intravascular volume of pregnancy is accommodated chiefly by venous capacitance vessels. Central venous pressure and pulmonary capillary occlusion (“wedge”) pressure are unchanged, reflecting an increase in left ventricular compliance, as evidenced by the enlarged cardiac silhouette seen on chest radiograph. The increased left ventricular end-diastolic volume results in an augmented stroke volume (ejection fraction is little changed), but *systemic vascular resistance* (SVR) diminishes.^{12,13} These changes account for the 30% to 45% increase in cardiac

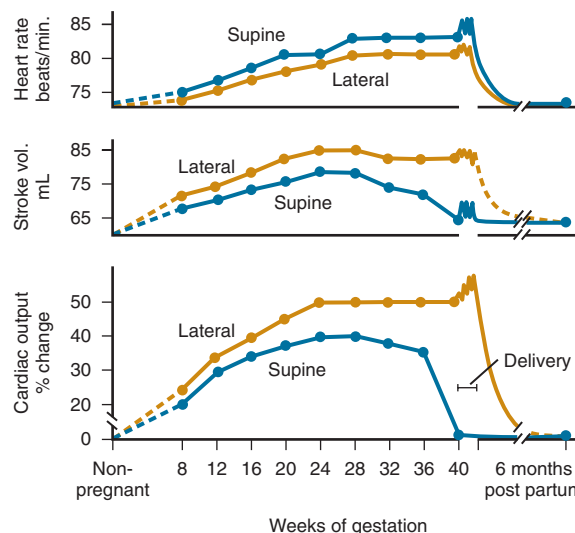


Figure 96-2 Changes in physiology in the supine position. Because the gravid uterus compromises venous return, there are characteristic changes in maternal heart rate, stroke volume, and cardiac output during pregnancy with the pregnant subject in the supine compared to the lateral position. (From Yanagihara N, von Leden H, Werner-Kukuk E: The physical parameters of cough: the larynx in a normal single cough. *Acta Otolaryngologica* (Stockholm) 61:495–510, 1966.)

output reached by 25 to 32 weeks of gestation. After 5 weeks, heart rate increases as well,¹⁴ but less so than stroke volume. Some of these changes, as well as the effects of supine versus lateral positioning, are depicted in Figure 96-2.

OBSTETRIC DISORDERS AND THE LUNGS

Gravid and newly postpartum patients may develop pregnancy-specific disorders but also continue to experience common disorders that arise outside of pregnancy; the natural history or frequency of coexisting disorders is sometimes altered by the gravid state. Even for diseases not altered by pregnancy, management requires special knowledge of the safety of therapies. Specific diseases are considered here with these principles in mind.

OBSTRUCTIVE AIRWAY DISEASE

Asthma

Asthma affects 4% to 8% of the general population and is the most common pulmonary disorder in pregnancy. The *Working Group on Asthma and Pregnancy of the National Asthma Education and Prevention Program* (NAEPP) estimated that 3.7% to 8.4% of pregnancies are complicated by asthma.¹⁵ Maternal asthma increases the risk of preeclampsia, preterm birth, infants with low birth weight, intrauterine growth restriction or congenital malformations, and perinatal death.¹⁶

Studies examining the hormonal milieu have suggested that progesterone might diminish smooth muscle contractility in the lung, as it does in the uterus and gut. Juniper

and colleagues¹⁷ performed serial measurements of bronchial reactivity to methacholine challenge in 16 women before and during pregnancy and found a decrease in airway hyperresponsiveness. Clinical and epidemiologic studies, however, have failed to provide convincing evidence of any consistent change in the natural history of asthma during pregnancy. Turner and coworkers,¹⁸ for example, compiled the results of nine studies of asthma symptoms reported by pregnant women. Among them, 22% reported worsening, 29% reported improvement, and 49% reported no change. Other studies have reported similar figures, with about 23% to 42% worsening, 18% to 36% improving, and 40% exhibiting no change.^{19,20} The differences reported in the natural history probably reflect differences in study populations, smoking history, ethnicity, or other variables.²¹

Fetal and maternal outcome for asthma and pregnancy have also been examined in a variety of studies since 1980. Adverse outcomes, including an increased incidence of preterm labor, low neonatal birth weight, increased perinatal mortality, preeclampsia, vaginal hemorrhage, chronic hypertension, and complicated labor, have been reported.^{15,21} A large epidemiologic study from Sweden did confirm an association of asthma with perinatal mortality and low birth weight.²² Nonetheless, adequate therapy tailored to disease severity is associated with good outcomes.²³ Therapy of asthma in pregnancy should be individualized according to severity of disease and frequency of symptoms, as outlined by the NAEPP.¹⁵ Objective measurement of lung volumes and flow should be part of the regimen. Initial office spirometry is recommended, and home peak flow monitoring should be considered. For women who have asthma attacks during labor, fetal monitoring is considered essential by the NAEPP.

Therapy should be based on a step approach.¹⁵ Mild intermittent asthma is best managed with inhaled short-acting β_2 -agonists, for symptomatic relief. Asthma that causes more than occasional symptoms should be treated daily with anti-inflammatory therapy, with the preferred choice being inhaled corticosteroids. Budesonide is the best studied and hence preferred, although substantive safety data exist for beclomethasone as well. Alternative therapies include cromolyn, sustained-release theophylline, or a leukotriene antagonist.¹⁵ Frequent need for short-acting β_2 -agonists should prompt institution of, or an increase in, the use of anti-inflammatory agents to treat, rather than to mask, a deteriorating clinical course. Long-acting β -agonists should only be used concurrently with long-acting inhaled corticosteroids.²¹ Finally, the addition of rapidly tapered courses of oral corticosteroids should be considered for those with acute severe asthma or patients with active symptoms who are already using inhaled steroids and β -agonists. Daily or alternate-day oral steroid administration (e.g., prednisone 40 mg/day) is sometimes required.¹⁵ Extensive practice algorithms have been made available by the NAEPP Working Group on Asthma and Pregnancy.¹⁵

A large body of literature has examined the topic of possible teratogenicity of agents used in the pharmacotherapy of asthma in pregnancy. In general, the risks of poorly controlled asthma far outweigh the possible hazards of drug therapy. Both animal and human studies of β_2 -agonists, administered either by inhalation or systemically, have

indicated an acceptable safety profile for the fetus. They are also safe for use during lactation. Nonselective β -agonists, such as epinephrine, carry a risk of uterine vasoconstriction in animal models²⁵ and are probably best avoided. Acceptable β_2 -agonists in pregnancy include metaproterenol, albuterol, pirbuterol, bitolterol, and terbutaline. Because the toxicology and pharmacology of the long-acting β -agonists salmeterol and formoterol are expected to be similar to shorter-acting β_2 -agonists, these drugs have been recommended in patients with poor control on a combination of inhaled long-acting corticosteroids and short-acting β -agonists.^{23,24} Limited data suggest that these drugs are safe in pregnancy.²⁶

Theophylline also has a long history of use during pregnancy and is considered safe, but the therapeutic range in plasma should be lowered to 5 to 12 $\mu\text{g/mL}$ because of diminished protein binding during pregnancy. Theophylline passes freely to the fetus, and newborns occasionally show signs of theophylline toxicity, particularly when maternal blood levels are high. Theophylline is also transmitted to breast milk, with a milk-to-serum ratio of about 0.70; but, in general, less than 1% of the maternal dose is transferred to the infant. Animal studies suggest that the leukotriene inhibitors montelukast and zafirlukast are safe in pregnancy, and they can be continued in patients who have previously responded.^{25,27,28} Zileuton should be avoided because animal studies have raised questions about its safety in pregnancy.

Animal studies have shown an increased incidence of cleft palate with use of corticosteroids, and limited human data support this association, with an estimated excess risk of 0.2% to 0.3% when used in the first trimester.¹⁵ Systemic corticosteroids have also been reported to cause intrauterine growth restriction, but of a relatively modest degree. Halogenated corticosteroids do not cross the placenta easily, and so fetal and neonatal adrenal suppression is not a major concern with these compounds.¹⁵ Overall, risk-benefit considerations nonetheless favor their use in persistent severe asthma with exacerbations unresponsive to other measures. One study suggests that higher doses of inhaled corticosteroids (i.e., beclomethasone > 1000 mcg/day) may be associated with a small increased risk of congenital abnormalities, although the confounding effect of increased asthma severity cannot be excluded.²⁹ There are limited data to confirm the safety of newer inhaled corticosteroids.²⁶ Table 96-1 summarizes the U.S. Food and Drug Administration (FDA) safety classification for agents useful for the treatment of asthma in pregnancy.

Labor and delivery can be especially hazardous for asthmatic patients, partly because of the drugs commonly administered. Narcotics other than fentanyl release histamine, which may worsen bronchospasm. Lumbar epidural analgesia is generally preferred, but if general anesthesia is to be used, pretreatment with atropine or glycopyrrolate assists bronchodilation. Ketamine is the preferred anesthetic, although halogenated anesthetics at low concentrations may provide bronchodilation as well.¹⁵ Preterm labor may be safely treated with nifedipine or magnesium sulfate. Oxytocin is the optimal labor induction agent and is useful for postpartum hemorrhage, but 15-methyl prostaglandin F_{2a} , methylergonovine, and ergonovine may cause bronchospasm and should be avoided if possible.

Table 96-1 Potential Fetal Risk of Drug Therapy in Pregnancy According to the FDA Classification for Safety in Pregnancy*

Drug	FDA Classification [†]
ASTHMA THERAPY	
Inhaled Bronchodilators	
Albuterol (salbutamol)	C
Terbutaline	C
Ipratropium	B
Salmeterol	C
Formoterol	C
Inhaled Corticosteroids	
Beclomethasone	C
Budesonide	B
Fluticasone	C
Leukotriene Antagonists	
Zafirlukast	B
Montelukast	B
Zileuton	C
Other Agents for Asthma	
Theophylline	C
Cromolyn	B
Systemic corticosteroids	B
ANTICOAGULANTS	
Heparin	C
Low-molecular-weight heparin	B
Warfarin	X
ANTIBIOTICS	
Penicillins	B
Cephalosporins	B
Macrolides	B/C
Quinolones	C
Clindamycin	B
Tetracyclines	D

*Although the U.S. Food and Drug Administration (FDA) classification provides an overview of fetal risk, it is being replaced by a narrative description of known drug effects. Detailed information should therefore be consulted for individual drugs. Classification of individual drugs may change as the literature evolves.

[†]Class B: Animal studies do not indicate a risk to the fetus, and there are no controlled human studies; or animal studies do show an adverse effect on the fetus, but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Class C: Studies in animals have shown the drug to have teratogenic or embryocidal effects, but there are no controlled studies in women; or no studies are available in either animals or women. Class D: Positive evidence of human fetal risk exists, but benefits in certain situations (e.g., life-threatening situations or diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks. Class X: Studies in animals or humans have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, and the risk of the drug clearly outweighs any possible benefit. These drugs are contraindicated in pregnancy.

Cystic Fibrosis

Cystic fibrosis (CF), present in about 1 in 1500 whites and 1 in 17,000 blacks, is a common genetic disease. With improved therapy, median survival has now increased to 37 years.³⁰ Up to 4% of female CF patients between the ages of 17 and 37 may be pregnant at any time,³¹ despite the frequent infertility of women due to delayed sexual development. Pregnancy in CF patients, as might be anticipated, has been associated with adverse fetal and maternal outcomes.^{32,33} Several recent small case series have demon-

strated good maternal and neonatal outcome in women with CF.³⁴⁻³⁶ Premature delivery was more common in women with worse baseline FEV₁, and gestational diabetes was common. In a large U.S. review of 680 gravid women with CF enrolled in the U.S. Cystic Fibrosis Foundation National Patient Registry, from 1985 to 1997, survival was actually better in the gravid group than in the matched 3327 control patients with CF.³⁷ Women with CF who became pregnant had higher predicted percentages of FEV₁ and higher weights. Pregnancy was not clearly harmful in any subgroup, after severity adjustment for age, *Pseudomonas aeruginosa* colonization, pancreatic function, and FEV₁. In another case-control study, pregnancy had little effect on patients with stable CF, although poor outcomes were seen in those with severe disease.³⁸ As might be anticipated, most studies suggest that risk stratifies according to severity of illness.^{33,38} Declines in pulmonary function tend to mirror severity-adjusted control subjects, and clearly CF patients require substantially more care and have more visits to physicians when pregnant than when not.³⁹ Prepregnancy counseling, particularly for women with more severe disease, is essential in limiting excessive maternal and fetal risk.

INFECTIOUS DISEASES

Bacterial Pneumonia

Pneumonia is a leading cause of maternal and fetal morbidity and mortality.⁴⁰⁻⁴² Maternal mortality from pneumonia in nonimmunocompromised hosts ranged from 0% to 4% in series published since 1980.⁴⁰⁻⁴² The reported incidence varies widely, from 0.4 to 2.7 per 1000 deliveries,⁴³ but may not be higher than that in the general population. One report, however, indicated that pneumonia may be increasing in incidence, with *human immunodeficiency virus* (HIV) infection and chronic disease the major risk factors.⁴⁰ Postpartum pneumonia may develop in the first 6 weeks after delivery and is more common after Cesarean section.⁴⁴

Pregnancy increases the risk for major complications of pneumonia. In the series by Madinger and colleagues,⁴² of 25 patients culled from 25,000 deliveries, 40% suffered major complications, including five intubations, two empyemas, one pneumothorax, and one pericardial tamponade. Similarly, in the series by Briggs and associates,⁴⁵ 7 of 34 patients required mechanical ventilation, and 2 died. The *Pneumonia Severity Index* (PSI)⁴⁶ used to identify severity of pneumonia for hospital admission does not appear to perform well in the obstetric population, underestimating the need for hospital admission.⁴⁷ Pneumonia increases the risk of preterm labor from 4% to 44%.⁴⁰⁻⁴² The small-for-gestational-age rate is as high as 12%,⁴⁰ and intrauterine and neonatal death rates have ranged from 1.9% to 12.0%.^{41,42} In all series, underlying chronic illness in the mother has been a powerful predictor of adverse outcome in both fetus and mother.

Pneumonia in pregnancy is most commonly bacterial in origin; the microbiologic spectrum mirrors community-acquired pneumonia, with *Streptococcus pneumoniae* and *Haemophilus influenzae* the most common organisms.⁴⁰⁻⁴² Other common organisms include *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. As in other community-acquired

pneumonias, the causative agent is identified in only about half of the cases. Unfortunately, the diagnosis of pneumonia is frequently delayed because of reluctance to obtain a chest radiograph; a posteroanterior radiograph performed with a grid and a peak voltage of 90 to 120 kV exposes the mother to 5 to 30 mrad but the fetus to 100 times less, or about 300 μ rad.⁴⁸ A lateral chest radiograph produces greater maternal exposure (150 to 250 mrad) but is usually not required.⁴⁸ The hazard to both fetus and mother of delaying the diagnosis greatly exceeds the risk of this small radiation dose. Antibacterial therapy is similar to treatment in the nonpregnant patient, although tetracyclines, quinolones, and metronidazole should be avoided if possible.⁴⁸ Erythromycin, azithromycin, and β -lactam antibiotics are preferred because of their favorable safety profile (see Table 96-1).

Viral Pneumonia

Viral pneumonia remains a serious concern in pregnancy. In the influenza pandemic of 1918, the maternal rate of mortality from pneumonia was as high as 50%. In the epidemic of 1957, pregnant women accounted for 10% of fatalities, and about half of the women of childbearing age who died were pregnant.⁴⁹ Since then, the maternal mortality rate from influenza A and B pneumonia has been relatively low but still much higher than that in the general population. Because of this, the *Centers for Disease Control and Prevention* (CDC) recommends inactivated influenza vaccine in otherwise healthy women during the second and third trimesters of pregnancy.⁵⁰ Although influenza virus does cross the placenta, current opinion holds that it is not likely to be teratogenic to the fetus, despite isolated reports that link influenza with neural tube and other malformations. Amantadine has been used in pregnancy successfully, both as treatment and as prophylaxis, although there have been case reports of cardiovascular defects noted after first-trimester use; and there is considerable influenza viral resistance to the drug.

In the spring of 2009, a previously unrecognized strain of influenza A (H1N1) virus emerged and quickly spread around the world. Reports of clinical experiences with large numbers of hospitalized patients with H1N1 influenza in Australia-New Zealand and throughout the United States confirm that pregnancy confers a high risk of serious disease and appreciable mortality.^{51,52} Early treatment of pregnant women and women up to 2 weeks postpartum with oseltamivir or zanamivir appears to be beneficial.⁵³ Pregnant women are also strongly urged to be vaccinated with the monovalent inactivated injectable H1N1 vaccine—not with the live attenuated vaccine.⁵⁴

Varicella pneumonia, caused by a virus of the DNA herpesvirus group, has also been linked to particularly adverse outcomes during pregnancy. Haake and coworkers⁵⁵ report an increased incidence of pneumonitis in pregnant women with primary varicella infection and a 35% mortality rate in this group (over a time period dating back to 1964), compared with 10% in other adults. Data are conflicting, and not all prospective studies have confirmed an increased incidence or mortality in pregnancy.⁴⁸ Treatment with acyclovir does appear to reduce mortality in gravid patients and should be used as therapy for active disease.⁵⁶ Use of *varicella-zoster immune globulin* (VariZIG) should be consid-

ered within 96 hours for susceptible pregnant women who have been exposed to varicella. Administration of VariZIG reduces but does not abolish risk for fetal infection or congenital varicella syndrome, and it is effective in preventing complications of varicella in the mother. Patients should be evaluated similarly to other adults, and a decision made to administer the immune globulin on the basis of immune status, type of exposure, and health status. The currently licensed attenuated live vaccine against varicella is contraindicated in pregnancy.

Severe acute respiratory syndrome (SARS), due to a novel coronavirus (HuCoV-SARS), causes pneumonia and *acute respiratory distress syndrome* (ARDS), with respiratory failure in 15% of patients and a mortality rate of 8% to 30%.^{57,58} Although data are limited, pregnant women appear to do worse than nonpregnant patients, with four of seven patients requiring ventilatory support in one series.⁵⁹ SARS infection adversely affects pregnancy, with miscarriage, fetal distress, and intrauterine death reported, presumably related to hypoxemia.

Fungal Pneumonias

Fungal pneumonias are uncommon in pregnancy. Although there is no evidence that blastomycosis and histoplasmosis are more severe during pregnancy, it does appear that coccidioidomycosis is more likely to disseminate in pregnancy.⁶⁰ In the southwestern United States, about 1 in 5000 pregnancies is complicated by *Coccidioides immitis* (see eFig. 37-7).⁶¹ Dissemination is highly probable during the third trimester and has been related to both subtle impairment of cell-mediated immunity and a stimulatory effect of progesterone and 17- β -estradiols on fungal proliferation.⁶² Amphotericin is the accepted therapy for disseminated coccidioidomycosis; azoles administered in the first trimester have been associated with branchial cleft abnormalities and should be used only after delivery.

Tuberculosis

Tuberculosis does not appear to be more common or severe in pregnancy. However, presentation may be atypical and disease is often extrapulmonary.⁶³ Diagnosis may be delayed by a reluctance to perform appropriate imaging studies. Pregnancy does not alter reactivity to tuberculin skin testing, and hence the test should be performed in the recommended groups during pregnancy. Interferon- γ -release assays are also an acceptable means of testing for tuberculous infection (see Chapter 35). Asymptomatic patients with positive skin tests should have their chest radiograph deferred until after 16 weeks of gestation. Symptomatic patients with positive skin tests merit chest radiographs regardless of gestational stage. Isoniazid, rifampin, and ethambutol have acceptable safety profiles in pregnancy and are part of the standard treatment regimens advised by the CDC and American Thoracic Society for pregnant women.⁶⁴ There is less collective experience with pyrazinamide, but this drug is recommended for use in pregnancy by the World Health Organization.⁶⁴ Worldwide data are accumulating, and pyrazinamide appears to be emerging as a drug that can be considered for treating multidrug-resistant tuberculosis and for HIV-infected women. Streptomycin, by contrast, is clearly associated with congenital deafness and is contraindicated during pregnancy.

PULMONARY EDEMA AND PULMONARY VASCULAR DISEASE

Gravid women are at special risk for pulmonary edema for a variety of reasons, including the hypervolemia and high cardiac output of pregnancy, the occasional need for tocolytic drugs that affect the vascular bed, and the unique vascular and endothelial disorders of pregnancy.

Among these effects, it is noteworthy that colloid osmotic pressure diminishes during pregnancy, although the effect on transcapillary pressure gradients is partially offset by a decrease in interstitial fluid colloid osmotic pressure (as explained in Chapter 6).⁶⁵ Etiologically, underlying cardiac disease, use of tocolytic drugs, fluid overload, and preeclampsia are the most common causes for acute pulmonary edema in pregnancy.⁶⁵

Increased Pressure (Cardiogenic) Pulmonary Edema

The cardiovascular adaptations to pregnancy have already been summarized. Their effects on underlying cardiac disorders are predictable. Stenotic valvular lesions are particularly poorly tolerated.⁶⁶ Of these, mitral stenosis is the most common symptomatic valvular disease in pregnancy and frequently presents with pulmonary edema, not only during gestation but also immediately postpartum, because of the large shifts in intravascular volume associated with delivery. The gradient across a stenotic mitral valve is augmented by the increases in blood volume, cardiac output, and heart rate that take place during gestation and the puerperium. In aortic stenosis, the increase in cardiac output required for pregnancy worsens the gradient across the valve. As a compensatory mechanism, the left ventricular end-diastolic volume increases, but the low SVR impairs coronary artery filling during diastole and can precipitate ischemic syndromes. The reduction in SVR of pregnancy mitigates the consequences of mitral and aortic regurgitation and of the left-to-right intracardiac shunts of endocardial cushion defects but worsens the consequences of Eisenmenger syndrome and uncorrected tetralogy of Fallot. Depending on the cardiac disorder, perturbations induced by pregnancy can alter fractional shunts, induce hypoxemia, or precipitate pulmonary edema.

A special problem of pregnancy is peripartum cardiomyopathy, a disorder that develops in 1 of 1300 to 15,000 deliveries, may present with congestive heart failure, and is associated with a special propensity for both pulmonary and systemic embolization during the last month of pregnancy and for up to 5 months thereafter.⁶⁷ Standard therapy for heart failure, including β -blockers, diuretics, angiotensin-converting enzyme inhibitors and blockers, are usually effective, but sometimes implantable defibrillators and even left ventricular assist devices and heart transplantation are required.^{67,68}

Tocolysis-Associated Pulmonary Edema

The use of drugs such as β_2 -sympathomimetic agents to retard premature labor is uncommon in current obstetric practice but, in the past, was associated with a 0% to 4% incidence of pulmonary edema.⁶⁹ The etiology of this disorder is controversial and likely multifactorial in nature,

related to myocardial effects, vascular permeability impairment, and fluid retention. It usually presents after at least 24 hours of β -adrenergic therapy, with relatively acute onset of dyspnea and pulmonary edema seen on chest radiographs. Simple discontinuation of β -adrenergic therapy often results in rapid improvement; whether diuretics need to be given is unresolved, but furosemide is usually administered. Pulmonary edema has also complicated tocolysis performed with calcium channel blockers.⁷⁰

Pulmonary Edema Associated with Preeclampsia

About 2.9% of patients with preeclampsia or eclampsia develop pulmonary edema.⁷¹ The spectrum of hemodynamic findings associated with pregnancy-induced hypertension and preeclampsia is wide but, in general, left ventricular preload is normal or low, afterload is high, and cardiac output is normal or low (Fig. 96-3). Systolic and diastolic function may also be impaired.⁷² The pulmonary edema commonly first presents in the postpartum period,^{71,72} reflecting fluid administration at delivery. Low colloid oncotic pressure and abnormal vascular permeability likely contribute as well. Hemodynamic monitoring of these patients is probably warranted if oliguria complicates the picture.

Pulmonary Embolism

Pulmonary embolism is a leading cause of maternal mortality,⁷³ accounting for 9% of 95 pregnancy-related deaths in a large health care delivery system in the United States between 2000 and 2006.⁷³ Even though the risk for venous thromboembolism in pregnant women is about five times as great as in age-matched and sex-matched nongravid controls, it is still relatively infrequent. A Danish population-based study of 63,000 deliveries found a cumulative incidence of 0.85 in 1000 deliveries from 1984 to 1994.⁷⁴ In this study, the incidence of detected venous thromboembolism increased to 1.23 in 1000 deliveries after the introduction of ultrasonography, demonstrating that its reported incidence may depend on the adequacy of diagnostic procedures employed. Other studies have reported rates of 0.6 to 2 per 1000 pregnancies.⁷⁵ The risk for thrombosis is increased in pregnancy, partly because of the increase in coagulation factors, particularly V, VIII, X, and von Willebrand factor antigen, and partly because of a marked fall in protein S.⁷⁶ Venous stasis, an important contributor to thrombosis, is caused by uterine compression of the inferior vena cava and the left iliac vein. Local trauma to pelvic veins at the time of delivery probably accounts for the peak incidence of thromboembolism in the postpartum period, especially after cesarean section. Specific risk factors for thromboembolism include previous thromboembolism during pregnancy or while taking oral contraceptives, prolonged bed rest, a complicated or cesarean delivery, age, thrombophilia, obesity, and smoking. The inherited defects include deficiencies of antithrombin, protein S, protein C, factor V Leiden, and prothrombin G20210A.⁷⁶ Antiphospholipid syndrome is an acquired thrombophilia. Previous thromboembolism or antithrombin deficiency warrant prophylactic heparin administration throughout pregnancy, now commonly accomplished with *low-molecular-weight heparins* (LMWHs) due to their safety and decreased risk of heparin-induced osteopenia and thrombocytopenia.

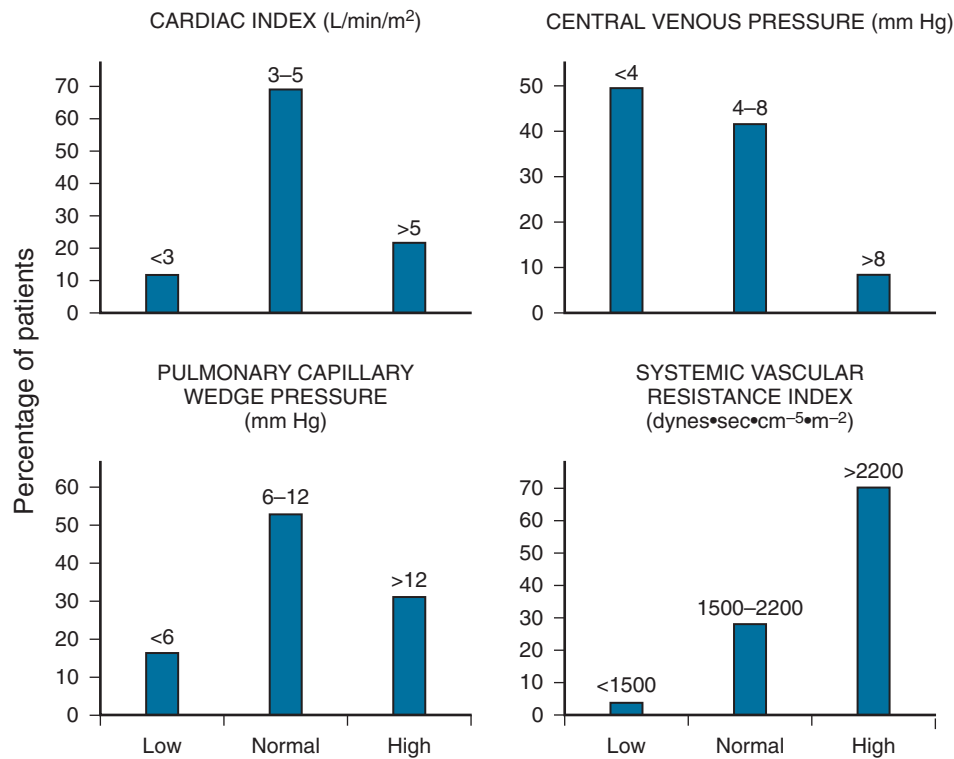


Figure 96-3 Pregnancy-induced hypertension. The spectrum of hemodynamic profiles is shown for 45 women with severe pregnancy-induced hypertension, one of the disorders sometimes complicated by pulmonary edema. Pulmonary edema in pregnancy-induced hypertension usually does not reflect simple volume overload. (From Cotton DB, Lee W, Huhta JC, et al: Hemodynamic profile of severe pregnancy-induced hypertension. *Am J Obstet Gynecol* 158:523–529, 1988.)

Clinical diagnosis of deep venous thrombosis during pregnancy and the puerperium is even more difficult than in the nonpregnant patient because of the peripheral edema associated with pregnancy and the asymmetrical compression of the left-sided common iliac vein by the gravid uterus. The initial diagnostic test should be duplex ultrasonography (combined real-time B-mode compression ultrasonography plus Doppler venous ultrasonography). In the patient with high clinical suspicion but a negative test, a repeat examination at 5 to 7 days may be valuable. When venous thrombosis of the lower extremity is documented, it is usually left sided, as it was in 84 of 96 (88%) cases reported by Chan and colleagues.⁷⁷

The diagnosis of pulmonary embolism in pregnant women is relatively straightforward. Both ventilation-perfusion scanning and *computed tomography* (CT) pulmonary angiography can be performed during pregnancy in a modified fashion. Estimated fetal radiation exposure for a perfusion scan is about 0.011 to 0.022 cGy (11 to 22 mrad), and simply halving the perfusion dose is standard practice in pregnancy, without greatly impairing resolution.⁷⁸ There is no need for the ventilation portion of the study if perfusion is normal. CT pulmonary angiography is an acceptable imaging modality and is associated with similarly low radiation doses to the fetus (Fig. 96-4).^{78,79} However, a risk to consider is the potential carcinogenic effect of radiation exposure to the mother's breasts,^{78,80} although shielding can reduce exposure (see Fig. 96-4B). Pulmonary angiography, when performed by the brachial route, exposes the fetus to only about 0.050 cGy

(50 mrad),⁸¹ but this procedure has a limited role in pregnancy. Such levels of exposure are not believed to cause teratogenicity, which is associated with exposure of greater than 5 to 10 cGy (5 to 10 rad). However, an increased incidence of childhood leukemia has been documented with lower fetal radiation exposure, in the range of 1 to 5 cGy (1 to 5 rad). A comparison of lung scintigraphy and pulmonary CT angiography concluded that the former method was more accurate than the latter for diagnosing pulmonary embolism during pregnancy.⁸² Ventilation-perfusion scanning in pregnancy, due to the patient's younger age and lack of comorbidity, is associated with a lower incidence of intermediate scans and higher rate of normal scans.⁸³ CT angiography may more often be technically suboptimal, due to the increased cardiac output in pregnancy.⁸⁴ *Magnetic resonance imaging* (MRI) with gadolinium contrast also has promise because it can image pelvic and lower extremity veins, as well as the pulmonary arteries, and it has little contrast-associated toxicity. Its widespread use will require increased availability of ultrafast scanners and more evaluation of its accuracy.

Venous thromboembolism in pregnancy is treated with heparin because warfarin crosses the placenta and causes nasal, ophthalmologic, and central nervous system abnormalities in the fetus. LMWH appears to be safe in pregnancy and, compared with unfractionated heparin, is associated with fewer adverse effects.^{85,86} LMWH is preferred over unfractionated heparin in pregnancy, using a weight-adjusted dosing regimen.⁸⁷ Weight gain in pregnancy makes formulaic dosing less reliable, and some authors also

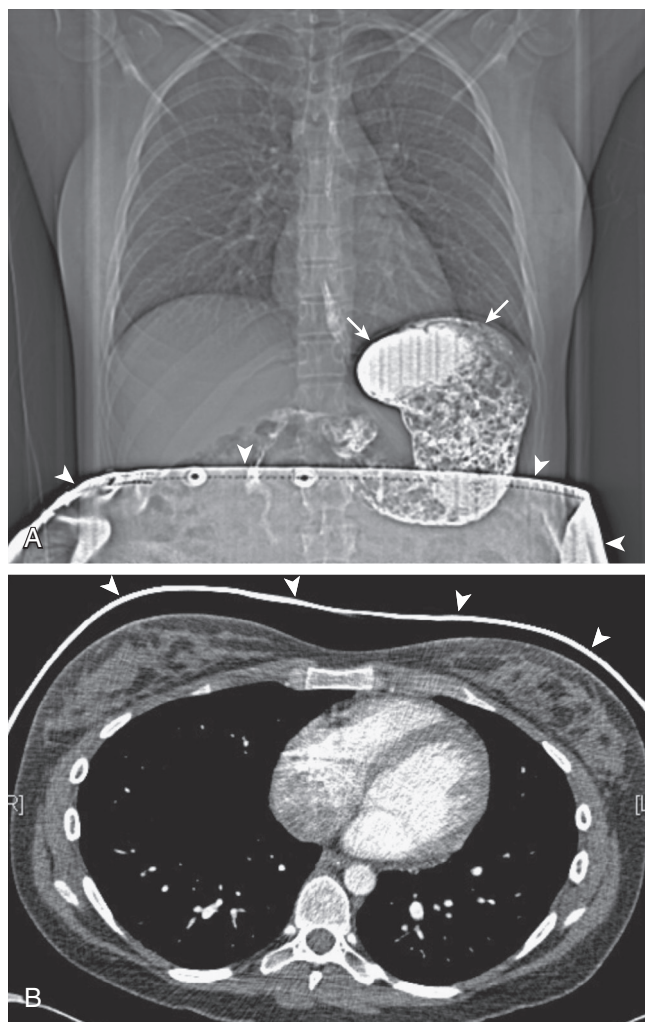


Figure 96-4 Dose-reduction methods for chest CT in the pregnant patient. **A**, Scout view before the CT acquisition shows an “internal barium shield” (arrows) created by having the patient swallow a dilute mixture of barium and water several minutes before CT scanning. The barium distributes within the stomach and proximal small bowel and attenuates internal maternal radiation that may otherwise expose the fetus. A lead apron (arrowheads) also reduces fetal radiation exposure. **B**, Axial chest CT pulmonary angiogram obtained with manual reduction of both the tube current and tube voltage shows excellent vascular opacification, providing high-quality assessment for pulmonary embolism and other thoracic disorders. A maternal breast shield (arrowheads) has also been placed; these shields selectively filter low-energy x-ray photons that would otherwise deposit preferentially in maternal breast tissue, significantly contributing to maternal breast radiation exposure. (Courtesy Michael Gotway, MD.)

advocate titrating the dose to achieve anti-factor X levels of 0.5 to 1.24 units/mL 4 hours after injection.^{85,86} However, the lack of good data and lack of correlation of levels with efficacy or complications makes routine monitoring difficult to justify.⁸⁷ LMWH treatment is usually given for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months). LMWH should be held 24 hours before induction, cesarean section, or neuraxial anesthesia (for twice-daily dosing) or after a 50% dose the morning before delivery for daily dosing regimens.⁸⁷ Postpartum, warfarin can be given safely during lactation.

Thrombolytic therapy has been used successfully in life-threatening thromboembolism during pregnancy, with a complication rate similar to that in nonpregnant women.⁸⁸

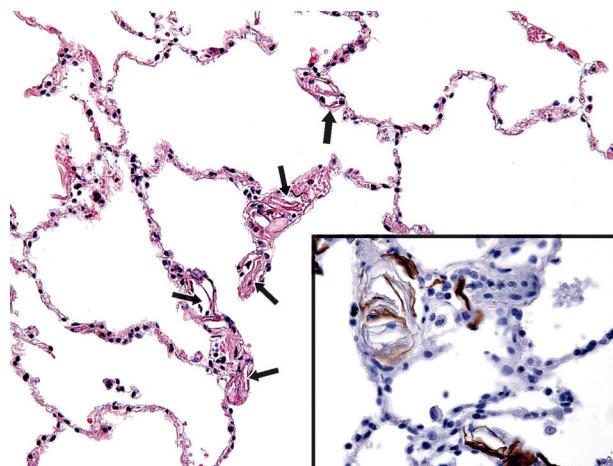


Figure 96-5 Amniotic fluid embolism. Interstitial pulmonary capillaries filled and expanded by eosinophilic fetal squamous cells (arrows) from a case of amniotic fluid embolism in a 39-year-old woman who succumbed within 4 hours of delivery. (H&E stain; original magnification $\times 200$). *Insert:* High-molecular-weight keratin stain, CK5/6 staining the intravascular fetal squamous cells (shown by brown color)(original magnification $\times 400$). (Courtesy Dr. Gerald Berry, Stanford University.)

Amniotic Fluid Embolism

Small amounts of amniotic fluid may enter the circulation during uncomplicated pregnancy but rarely cause the catastrophic syndrome of amniotic fluid embolism.⁸⁹ The reported incidence varies from 2 to 6 per 100,000 pregnancies, the variation being largely dependent on the method of case identification.⁹⁰ The onset is usually during labor and delivery or immediately after uterine manipulation, with development of severe dyspnea, hypoxemia, and then seizures and cardiovascular collapse or arrest. If the patient survives the initial insult, disseminated intravascular coagulation and ARDS usually supervene.⁹¹ Risk factors include older maternal age, induction of labor, high parity, cesarean section, low uterine segment laceration, and meconium staining of amniotic fluid.⁸⁹⁻⁹¹ Abruptio placentae is present in 50% of cases, and fetal demise in 40%.⁹¹ The maternal mortality rate has been as high as 86%,⁹² but a more recent report suggests a mortality of 11% to 43%.⁹⁰ Overall, amniotic fluid embolism may account for 14% of all maternal deaths.⁷³

In a U.S. registry of cases, 78% of the patients with amniotic fluid embolism had ruptured membranes, and several had just undergone intrauterine procedures,⁹³ clearly implicating traumatic opening of uterine vessels in the pathogenesis. The exact quantity or constituents of amniotic fluid required to initiate the syndrome is unknown. Pathologically, fetal squamous cells are found in the maternal pulmonary circulation at autopsy (Fig. 96-5) but, even in symptom-free patients, fetal cells may be aspirated from pulmonary artery catheters placed for other reasons.⁹⁴ Hemodynamically, the process is often biphasic, with pulmonary hypertension initially, followed by left ventricular failure.^{95,96} These changes may be caused by leukotrienes and arachidonic acid metabolites, particularly prostaglandin F_{2a} , which appear in amniotic fluid during labor. An immunologic basis for some of the changes seems likely because women with male fetuses are more likely to acquire the disorder.⁹⁰ Clark and associates⁹³ seized on the similarities to anaphylaxis and suggested that the disorder be renamed

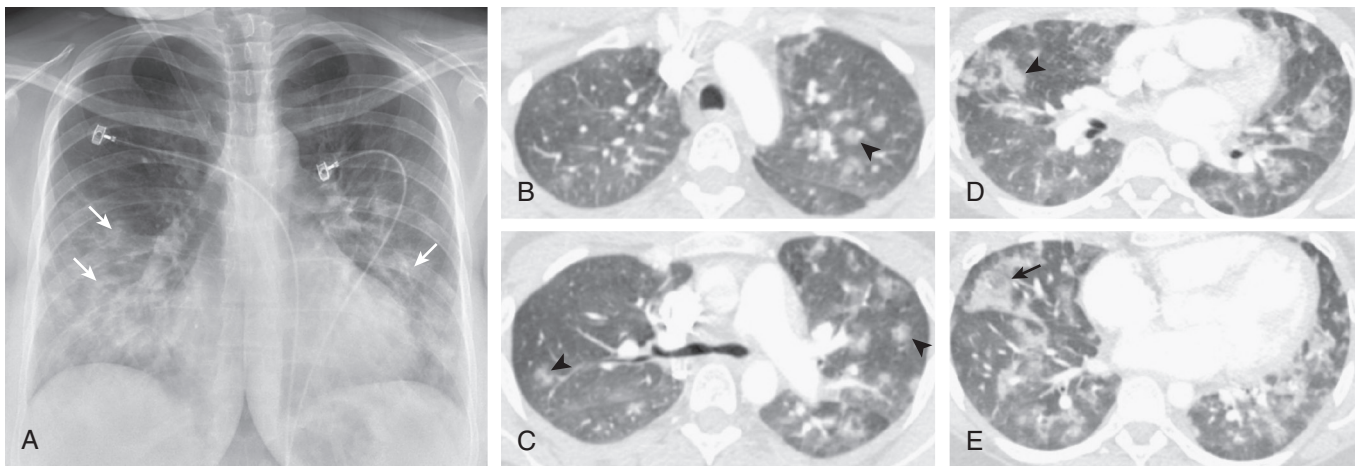


Figure 96-6 Amniotic fluid embolism. **A**, Frontal chest radiograph in a patient who developed shortness of breath and cardiovascular instability during delivery shows multifocal, poorly defined opacities (arrows) along the bronchovascular bundles, distributed in the mid and lower lungs bilaterally. **B–E**, Axial chest CT pulmonary angiogram obtained for pulmonary embolism evaluation, displayed in lung windows, shows multifocal nodular appearing ground-glass opacities (arrowheads), somewhat more confluent in the right middle lobe (arrow). No features to suggest increased pressure edema, such as pleural effusion or interlobular septal thickening, are present, and no pulmonary embolism was detected. The CT features are consistent with an acute lung injury pattern. (Courtesy Michael Gotway, MD.)

anaphylactoid syndrome of pregnancy. A small study did not demonstrate evidence of mast cell degranulation but suggested a role for complement activation.⁹⁷

On imaging studies, affected patients usually develop bilateral parenchymal opacities consistent with pulmonary edema associated with increased permeability lung injury (Fig. 96-6). Treatment consists of supportive care for the associated disseminated intravascular coagulation and left ventricular and respiratory failure. The fetus should be promptly delivered. In cases of maternal demise, emergency postmortem or periresuscitative cesarean section is warranted, as it is in other instances of cardiopulmonary resuscitation in pregnancy.⁹⁸

Arteriovenous Malformations

Pulmonary arteriovenous malformations may expand during pregnancy because of hormonal changes, the increase in blood volume, and venous distensibility.⁹⁹ This increases the likelihood of bleeding, with life-threatening complications in about 1% of pregnant women with hereditary hemorrhagic telangiectasia.^{100,100a} Embolization and surgical management have been utilized successfully during pregnancy.

Air Embolism

Occasionally, venous air embolism can happen during pregnancy, presumably through the subplacental venous sinuses.¹⁰¹ This disorder has been clearly documented during labor and delivery, during cesarean sections and abortions, in patients with placenta previa, and in those engaging in orogenital sex during pregnancy or the early puerperium.

ACUTE LUNG INJURY IN PREGNANCY

Aspiration Pneumonitis

Since Mendelson's¹⁰² original report of 66 cases of gastric aspiration in 44,016 deliveries between 1932 and 1945 (an incidence of 0.15%), aspiration has continued to be

a major cause of maternal morbidity and mortality. Increased intra-abdominal pressure due to the gravid uterus, the inhibitory effect of progesterone on the tone of the esophageal sphincter, and the assumption of the supine position for delivery all contribute. Eating during or just before labor increases the volume of emesis.¹⁰³ Aspiration of gastric contents with pH 2.5 or lower is known to cause chemical pneumonitis and increased permeability edema. Both in Mendelson's original report and today, about two thirds of cases of aspiration take place in the delivery suite. Emergency endotracheal intubation of patients with obstetric crises is particularly difficult,¹⁰⁴ and intubation in the delivery suite fails at a rate eight times that in the general surgical population.¹⁰⁵ To minimize the chance of acid aspiration at intubation, oral administration of histamine-2 blockers with antacids before intubation,¹⁰⁶ in conjunction with a formal airway assessment, is desirable. Identified risk factors in intubation include a high Mallampati class indicating poor visibility of the posterior pharynx, a short neck, protruding maxillary incisors, and a receding mandible.¹⁰⁷

Acute Respiratory Distress Syndrome

ARDS is more common in pregnancy than in the general population, with an incidence of 1/6000 deliveries.¹⁰⁸ In one obstetric intensive care unit, ARDS was the leading cause of maternal death during a 6-year period.¹⁰⁹ The three most common nonobstetric causes are pneumonia, sepsis, and aspiration. The 2009 influenza A (H1N1) epidemic resulted in a significant increase in the incidence of ARDS in pregnancy, generating numerous publications on the epidemiologic and management issues. Australian investigators described a series of pregnant women treated with extracorporeal membrane oxygenation with reasonable outcome.¹¹⁰ Common obstetric causes of ARDS include chorioamnionitis, amniotic fluid embolism (see Fig. 96-6), and trophoblastic embolism.¹¹¹ Ventilator management is unaltered in pregnancy and, although pregnancy was an exclusion criterion in the ARDS Network studies, the clear benefit in nonpregnant patients supports the use of

low-volume ventilatory strategies in pregnant patients, with tidal volume (6 mL/kg) based on the patient's ideal weight.^{111,112} The prognosis also appears to be similar to the nonpregnant patient,¹¹³ although ARDS outcome is dependent on the underlying etiology.

OTHER RESPIRATORY DISEASES IN PREGNANCY

Obstructive Sleep Apnea

Pregnancy may be complicated by *obstructive sleep apnea* (OSA), potentially adversely affecting both mother and fetus.¹¹⁴ Although upper airway edema may potentiate obstructive events, apnea and hypopnea are uncommon in pregnancy because of the respiratory stimulatory effect of progesterone.¹¹⁵ OSA usually develops in obese patients, precipitated by the airway mucosal edema and vascular congestion that accompany pregnancy. OSA is associated with preeclampsia and gestational diabetes.^{115,116} Nocturnal hypoxemia may produce poor fetal growth, although snoring alone is not associated with fetal risk.¹¹⁷ Pregnant women with documented obstructive sleep apnea are at increased risk of developing preeclampsia and preterm birth.¹¹⁸ Treatment with nasal continuous positive airway pressure is safe and effective for women with documented significant OSA.¹¹⁵

Interstitial Lung Disease

Interstitial lung disease is usually seen in patients older than those in their childbearing years.¹¹⁹ When interstitial disease exists in pregnant women, the reduced diffusing capacity may cause difficulty in meeting the increased oxygen consumption requirements of pregnancy. Associated pulmonary hypertension, regardless of its causes, carries significant risks because cardiac output increases during pregnancy. Few data exist on the management and outcome in these patients, but restrictive lung disease appears reasonably well tolerated in pregnancy.^{120,120a} Lymphangioleiomyomatosis and systemic lupus erythematosus may worsen as a result of pregnancy.¹¹⁹ Some drug therapy used for interstitial lung disease may be acceptable during pregnancy (e.g., prednisone, azathioprine), but other therapy (e.g., cyclophosphamide, rituximab, mycophenolate mofetil) is usually avoided.¹¹⁹

Pleural Disease

Pleural effusions may accompany obstetric complications such as preeclampsia and choriocarcinoma, but many women with normal pregnancies develop small, asymptomatic pleural effusions in the postpartum period.¹²¹ They develop as a result of the increased blood volume and reduced colloid osmotic pressure in pregnancy, as well as from impaired lymphatic drainage due to repeated Valsalva maneuvers during labor. Moderate-size effusions or the presence of symptoms should prompt a full clinical evaluation. The Valsalva maneuvers of labor may also produce spontaneous pneumothorax and pneumomediastinum, particularly in patients with predisposing conditions such as asthma. This diagnosis should be considered in women who develop chest discomfort and dyspnea during, or immediately following, delivery.

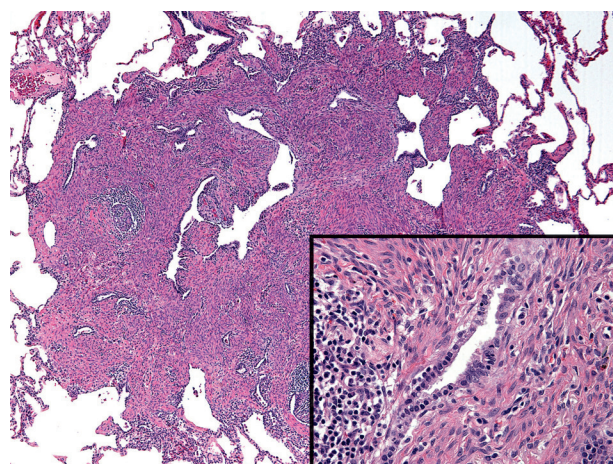


Figure 96-7 Pulmonary endometriosis. Wedge resection of right upper lobe subpleural nonencapsulated lesion in a 43-year-old woman with a history of pelvic endometriosis and recurrent pneumothoraces with menstrual cycles. (H&E stain; original magnification $\times 40$). *Insert:* The discrete nodule is composed of endometrial stromal cells admixed with endometrial glands. (H&E; original magnification $\times 200$.) (Courtesy Dr. Gerald Berry, Stanford University.)

GYNECOLOGIC DISORDERS AND THE LUNGS

CATAMENIAL PNEUMOTHORAX

Lillington and colleagues¹²² introduced in 1972 the term *catamenial pneumothorax* to describe the already reported phenomenon of spontaneous pneumothorax within 24 to 72 hours after onset of menses. It appears to account for about 2.8% to 5.6% of spontaneous pneumothoraces in women,^{123,124} most often affecting women in the third or fourth decade of life. About 30% to 60% of cases are attributable to thoracic endometriosis, as judged by inspection at thoracotomy (Fig. 96-7)¹²⁵; other cases have a more obscure etiology, however, so a number of theories have been advanced. The first theory is that, during menstruation, the absence of the normal cervical mucus plug permits an open connection between ambient air and the abdominal cavity through the uterus and fallopian tubes.¹²⁴ Air can move transdiaphragmatically through right-sided diaphragmatic fenestrations into the pleural space, as it sometimes does during abdominal laparoscopy,¹²⁶ accounting for the condition's right-sided predominance.¹²⁴ A second theory is that high levels of prostaglandin F_{2a} during menstruation cause bronchospasm with attendant air trapping and pneumothorax, but wheezing is not a common symptom of this disorder. A third theory is that pleural blebs or bullae are more susceptible to rupture during menstruation because of hormonal changes,^{124,125} but visceral pleural leaks are rarely found at surgery (see also Chapter 81 for a full discussion).

For cases of endometriosis-associated pneumothorax, a trial of gonadotropin-releasing hormones is warranted if the phenomenon is repetitive but not life-threatening. Oral contraceptives, other progestational agents, and tubal

ligation have also been used with some success. For cases not clearly associated with systemic endometriosis, thoracoscopy during menstruation serves to define the etiology and can be used to achieve pleurodesis.¹²⁶

ENDOMETRIOSIS

Endometriosis probably affects about 10% of women, shows no clear ethnic differences in prevalence, and is most commonly diagnosed at 30 to 34 years of age.¹²⁷ Although pelvic pain, dysmenorrhea, and infertility are its predominant manifestations, atypical locations, including diaphragmatic, pleural, and endobronchial sites, have been documented. As described previously, endometriosis can result in recurrent catamenial pneumothorax, which is its most common thoracic presentation (see Fig. 96-7). In one review of 110 cases with thoracic endometriosis, catamenial pneumothorax was the presenting symptom in 73% of cases, followed by hemothorax in 14% and hemoptysis in 7%.¹²⁷ It also has been associated with right-sided pleural pain, pleuritic effusions, and hemothorax. Inspection at thoracotomy or thoracoscopy typically reveals blue-brown nodules on the pleural surface, sometimes in a “gunshot” distribution.¹²⁸ The absence of known pelvic endometriosis does not exclude the diagnosis because only 20% to 70% of patients have associated pelvic disease. The diagnosis is suspected on clinical grounds because neither CT nor endoscopy is specific.¹²⁹ Rarely, the endometriosis deposits are found in lung parenchyma, accounting for the catamenial hemoptysis. Most pleural and diaphragmatic disease is thought to arise from transdiaphragmatic spread from retrograde menses, even when abdominal disease is not evident. Massive ascites is sometimes related, although only 27 cases have been reported.¹³⁰ Pneumothoraces may be attributed to cyclical sloughing of tissue on key surfaces, such as the visceral pleura,¹³¹ or to air trapping from airway involvement or compression.¹²² Pulmonary parenchymal disease may be embolic in origin, as is presumed to be in the case of central nervous system endometriosis. The diagnosis can be established only by biopsy showing the characteristic ectopic endometrial glands in involved sites. Medical therapy consists of progestational agents or gonadotropin-releasing hormones; surgical approaches include excision, local laser ablation, or pleurodesis.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis (LAM) is a rare disorder that afflicts predominantly premenopausal women.^{132,133} The most common presenting event is a pneumothorax, reported in 86.5% of patients in the National Heart, Lung, and Blood Institute registry.¹³² It is fundamentally a disorder of smooth muscle proliferation that results in functional obstruction of vessels, lymphatics, and airways. (See Chapter 69 for a complete discussion of LAM.) Involvement of pulmonary vascular structures is responsible for the hemoptysis, whereas lymphatic obstruction accounts for the chylous effusions. Mediastinal and retroperitoneal lymphatic proliferation may be a feature of the disease as well. LAM is also associated with renal angiomyolipomas, another hamartomatous disorder, and with tuberous scler-

osis. Conventional therapy has included oophorectomy or progestational agents, mainly medroxyprogesterone acetate. Lung transplantation has been performed in more than 60 patients with this disorder, but it has clearly recurred in some of them. Sirolimus, in a trial in patients with angiomyolipomas and tuberous sclerosis complex or LAM, showed ameliorative effects on lung function and volume of angiomyolipomas, presumably by suppressing signaling pathways involved in products of the defective genes.¹³⁴ LAM is now included in the group of perivascular epithelioid cell tumors, whose molecular pathology is being elucidated, opening the possibility of targeted therapy.¹³⁵

TROPHOBLASTIC EMBOLIZATION

Trophoblastic embolism is a rare complication of hydatidiform mole, an abnormal type of pregnancy in which nonviable fertilized tissue grows in the uterus. In one series, only 2.6% of 189 patients with hydatidiform mole had an embolic event, so most episodes of respiratory distress in such patients are not caused by embolic events but, rather, pulmonary edema, anemia, or another complicating event.¹³⁶ Embolization, when it happens, is most common at the time of evacuation of the mole. Chorionic neoplasms that arise during gestation are suggested by a large discrepancy between gestational date and uterine size and should be evaluated by transvaginal ultrasonography.¹³⁷

OVARIAN HYPERSTIMULATION SYNDROME

The use of exogenous gonadotrophins to stimulate ovulation for in vitro fertilization has been associated with pulmonary complications.¹³⁸ This ovarian hyperstimulation syndrome usually manifests with ovarian cysts, bilateral pleural effusions, ascites, and intravascular volume depletion. Hypovolemic shock, renal failure, and ARDS may result. Pulmonary embolism and upper limb or superior venal caval thrombosis may result from the hypercoagulable state induced by estrogens and intravascular volume depletion. The mechanism of the effusions is unclear but is likely related to increased permeability due to release of vasoactive mediators, of which vascular endothelial growth factor appears to be the most important.¹³⁹ Evidence points to mutations in the follicle-stimulating hormone receptor as etiologic in at least some cases.¹⁴⁰ Treatment is supportive and involves maintaining intravascular volume, thoracentesis when required for respiratory compromise from abundant pleural effusion(s), and thromboprophylaxis.

Key Points

- Normal pregnancy is associated with profound alterations in respiratory and cardiovascular physiology, which—although designed for maternal and fetal well-being—may exacerbate underlying cardiopulmonary conditions or cause new ones.
- Major physiologic perturbations found in normal pregnancies include (1) an increase in central drive to breathe, with resulting changes in P_{CO_2} (28 to 32 mm Hg) and pH (7.40 to 7.47); and (2) an increase in both

maternal blood volume, of about 2 L (40%), and cardiac output, after 25 to 32 weeks of gestation, of 30% to 45%.

- The most common pulmonary disorder of pregnancy is asthma, but the effects of pregnancy on asthma are variable: it worsens, improves, or remains unchanged in roughly one third of afflicted women.
- The risks of poorly controlled asthma for both mother and fetus during pregnancy far outweigh the risks of drug therapy. Some standard drugs are safer than others (see [Table 96-1](#)) and should be selected whenever possible.
- Cystic fibrosis and infectious pneumonias have all been linked with adverse fetal and maternal outcomes, the risk of which depends largely on the severity of the complicating disorder. Prepregnancy counseling and avoidance of certain antimicrobial drugs (as noted in [Table 96-1](#)) are strongly recommended.
- Pulmonary edema may develop during pregnancy in women with underlying heart disease, especially valvular stenosis, cardiomyopathy, and preeclampsia. Because the causative mechanisms differ, so does specific therapy.
- Pulmonary embolism is a leading cause of maternal mortality. When indicated during pregnancy, low-molecular-weight heparins are safe for both treatment and prevention; warfarin is contraindicated. Ventilation-perfusion imaging, CT pulmonary angiography, and magnetic resonance imaging can be used as needed.

Complete reference list available at *ExpertConsult*.

Key Readings

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THE RESPIRATORY SYSTEM AND NEUROMUSCULAR DISEASES

JOSHUA O. BENDITT, MD • F. DENNIS MCCOOL, MD

INTRODUCTION

FUNCTIONAL ANATOMY OF THE RESPIRATORY SYSTEM

Central Nervous System
Peripheral Nervous System
Controller Feedback

DISEASES AFFECTING THE RESPIRATORY SYSTEM

Central Nervous System Diseases
Peripheral Nervous System Diseases

SPECIAL TOPICS

Neuromuscular Disease Related to Critical Illness
Diseases Affecting Diaphragm Function

APPROACH TO RESPIRATORY EVALUATION AND MANAGEMENT OF THE INDIVIDUAL WITH NEUROMUSCULAR DISEASE

Ventilatory Support
Data Supporting Noninvasive Positive-Pressure Ventilation in Neuromuscular Disease
Cough Support

INTRODUCTION

Gas exchange between the atmosphere and the human body depends not only on the lungs but also in large part on the function of the “ventilatory pump,” which consists of the respiratory control centers located in the brain, the bony rib cage, diaphragm, and intercostal, accessory, and abdominal muscles. A wide variety of neuromuscular disorders can result in dysfunction of the ventilatory pump that in turn can lead to respiratory failure, pneumonia, and even death. Breathing disorders are recognized as the leading cause of mortality in neuromuscular disease,^{1,2} and appropriate interventions can prevent complications and prolong life in individuals with neuromuscular disease affecting the respiratory system.³ Diseases of the chest wall are discussed in Chapter 98.

FUNCTIONAL ANATOMY OF THE RESPIRATORY SYSTEM

The ventilatory pump is designed to bring oxygen into the body to fuel energy generation and remove carbon dioxide as a waste product of cellular metabolism. The system is made up of the cortex of the brain that controls voluntary breathing; the brain stem, which is involved with automatic breathing; the spinal cord and motor neurons that transmit nerve impulses; the respiratory muscles that are the effectors of the system; and a complex system of feedback receptors and nerves that regulate ventilation (Fig. 97-1). The system is remarkably flexible and can precisely maintain carbon dioxide and acid-base balance despite encountering large variations in metabolic demands that result from the activities of daily living. The following is a discussion of each of the components of this complex network.

CENTRAL NERVOUS SYSTEM

Voluntary Breathing Controllers

Voluntary breathing is controlled by signals from the cerebral cortex. Centers located within the parietal cortex send

volitional signals that initiate inspiration and expiration.⁴ These cortical areas project to the motor neurons in the spinal cord via the corticospinal tracts. These corticospinal tracts are separate pathways from the reticulospinal pathways that connect the central automatic breathing centers to the motor neurons.

Automatic Breathing Controllers

Automatic breathing is controlled by a complex system that includes respiratory centers in the pons and medulla, nerve tracts in the lower brain stem, the reticulospinal pathways in the spinal cord, and the feedback mechanisms that are both chemical and mechanical in nature. There are thought to be three centers that generate the rhythm and drive to breathe, one located in the pons and two in the medulla. More detailed reviews of this topic are available.^{5,6}

Spinal Cord

The spinal cord and motor nerves conduct nerve impulses from the cortex and brain stem to the anterior horn cells of the motor neurons supplying the respiratory muscles. As noted previously, the nerve fiber tracts in the spinal cord responsible for voluntary (corticospinal tract) and automatic (reticulospinal tract) breathing are separate within the spinal cord.⁷ The fibers in both of these tracts travel through the spinal cord to synapse with the lower motor neurons.

PERIPHERAL NERVOUS SYSTEM

Lower Motor Neurons

The lower motor neuron has its cell body in the spinal cord (anterior horn cell) but exits the spinal cord to become the spinal nerve roots and the nerves that supply the respiratory muscles. When the nerves arrive at the muscle, they divide into branches known as *twigs* that, upon reaching the muscle fiber, further divide into bulbous projections called *boutons* that apply themselves to the muscle membrane at a specialized anatomic junction called the *motor end plate*. These boutons contain acetylcholine, which is the chemical transmitter that serves to excite the muscle to contract. With nerve firing, there is release of acetylcholine at

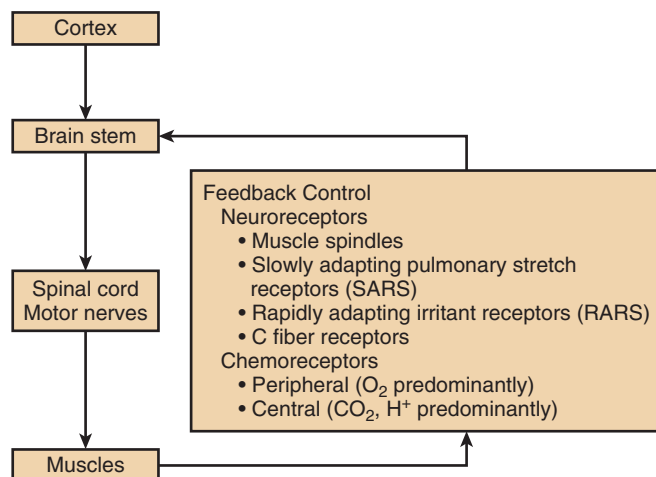


Figure 97-1 Respiratory system feedback control. Neuromechanical respiratory system shows the neuromuscular pathways and feedback control.

the motor end plate into the cleft between the nerve and the muscle. The acetylcholine binds to receptors on the muscle side of the motor end plate, which results in a *suprathreshold excitatory end plate potential* and depolarization of the muscle membrane.⁸ A muscle action potential then results in contraction of the muscle fiber.

Total Lung Capacity

Respiratory Muscles. The respiratory muscles are the mechanical effectors of the breathing system. They are often divided into three major groups: (1) the inspiratory muscles, (2) the expiratory muscles, and (3) the accessory muscles of respiration. The muscles that maintain patency of the upper airway during the respiratory cycle are sometimes also considered muscles of respiration because of their close interaction with the other respiratory muscles.

The diaphragm is the major muscle of inspiration and accounts for approximately 70% of the inhaled tidal volume in the normal individual⁹ (Fig. 97-2). Contraction of the diaphragm results in a downward piston motion of the muscle as well as outward and upward movement of the ribs through the *zone of apposition*. The innervation of the diaphragm is via the phrenic nerve that originates from cervical nerve roots 3 through 5.

The intercostal muscles are thin sheets of muscular fibers that run between the ribs in the costal spaces.¹⁰ There are two sheets of muscle fibers, the external and internal intercostals. The external intercostals function to expand the rib cage during inspiration. The internal intercostals are deeper and function to decrease rib cage size during expiration. The mechanism of action of the intercostal muscles on the ribs is shown in Figure 97-3. The orientation of the muscle fibers with respect to the ribs results in the increase or decrease in the size of the rib cage; as the muscles contract, the greater torque is applied to the point more distal from the spine. In the case of the external (inspiratory) intercostal muscles, the distal attachment is at the lower rib, so contraction tends to pull the lower rib upward, thereby expanding the chest; for the internal (expiratory) intercostal muscles, the distal attachment is at the upper rib and thus contraction of the muscle tends to pull the upper rib

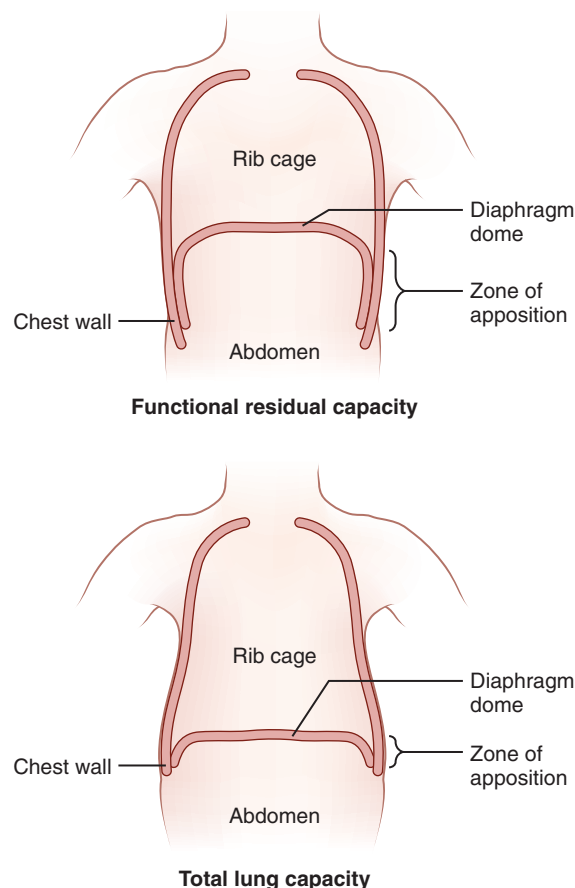


Figure 97-2 Diaphragmatic positions at rest (top) and at full contraction (bottom). At functional residual capacity (top), the diaphragm lies within the chest with a zone of apposition along the chest wall. At total lung capacity (bottom), the contracted diaphragm has displaced abdominal contents and, via the increase in abdominal pressure, has expanded the chest wall outward.

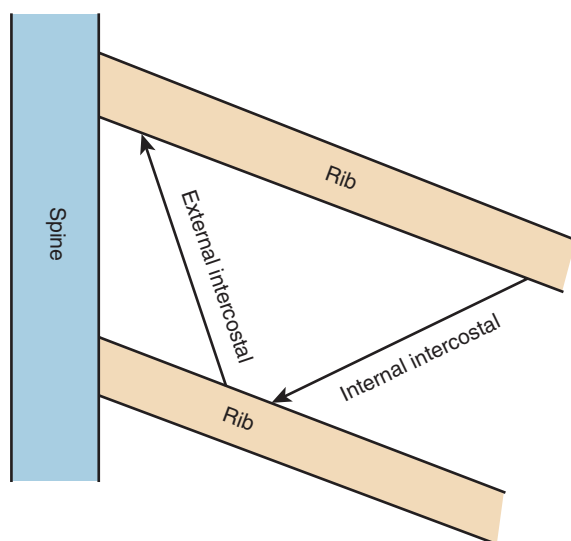


Figure 97-3 Actions of the intercostal muscles on the ribs. Contraction of the external intercostals results in an upward and outward movement of the ribs during inhalation. Contraction of the internal intercostals results in a downward and inward movement of the ribs during exhalation.

down, thereby decreasing the chest. Innervation of the intercostals is via the intercostal nerves originating from the thoracic spinal nerve roots.

The abdominal muscles (rectus abdominis, internal oblique, external oblique, and transversus abdominis) serve a number of functions in respiration that mainly assist expiration but can also function in inspiration. The internal and external obliques and the transversus abdominis result in an inward movement of the abdominal wall that displaces the diaphragm upward into the thoracic cavity and assists exhalation. The rectus abdominis as well as the internal and external obliques pull the lower rib cage caudally and thereby increase pleural pressure and exhalation. The abdominal muscles also may play a minor role in inspiration¹¹; if their contraction reduces lung volume below *function residual capacity* (FRC), abdominal muscles can store elastic recoil energy in the chest wall that then assists expansion of the chest wall during the next inspiration. This “inspiratory assist” may be seen during exercise where expiration becomes active.

The accessory muscles of respiration (sternocleidomastoid, scalenes, trapezii, latissimus dorsi, platysma, and pectoralis major and minor muscles) can expand the rib cage and assist inspiration during situations of increased ventilatory demand such as during exercise or when other inspiratory muscles are impaired as in tetraplegia or chronic obstructive pulmonary disease. It is now clear that some of them function during minimal exertion and even during quiet tidal breathing.¹²

The muscles of the upper airway are also considered to be muscles of respiration because they maintain patency of the upper airway and allow air to flow into and out of the lungs without interruption.¹³ Some of these also participate in protection of the lower airway during swallowing, a key function in the defense of the respiratory system. The upper airway muscles include the abductors of the vocal cords, the palatal elevators, retractors of the tongue, and dilators of the nares. These muscles are innervated by cranial nerves V, VII, and IX–XII. The central control centers for these muscles are the same as those described previously for the more commonly considered ventilatory muscles.

CONTROLLER FEEDBACK

The respiratory control mechanisms depend on both neural and chemical receptors found in peripheral and central sites. An excellent discussion of this topic is available.¹⁴ The automatic respiratory centers in the brain stem respond to feedback from these receptors and adjust neural output to the ventilatory and upper airway muscles that expand the chest wall and maintain upper airway patency (see Fig. 97-1).

Neural receptors are present in the upper airway, respiratory muscles, lungs, and pulmonary vessels.¹⁴ Once stimulated, these receptors project signals to the central respiratory controller via the vagus nerve. The respiratory centers then adjust their output to the respiratory muscles to alter ventilation and modulate reflexes such as cough and sneeze. There are several different types of neural receptors. *Muscle spindles* and *slowly adapting pulmonary stretch receptors* predominantly respond to changes in tho-

racic cage and lung volume, respectively. As the chest wall and lung inflate, these receptors are stretched and dampen the output from the inspiratory centers in the medulla. These receptors are involved in the “Hering-Breuer” reflex in which inspiration is halted as lung volume increases.¹⁵ These are critical for initiating cough. *Rapidly adapting irritant receptors* respond to changes in lung volume, to chemical stimuli such as histamines and prostaglandins, and to noxious stimuli. *C fibers* in the airways and lung are stimulated by chemical stimuli in the local environment. The C fibers likely mediate the hyperventilation that is seen in normoxic circumstances in a number of pulmonary disorders such as asthma, pulmonary embolism, pneumonia, and pulmonary edema.

Chemical receptors or *chemoreceptors* are located both peripherally as well as in the central nervous system.¹⁴ The *peripheral chemoreceptors*, which include the carotid and aortic bodies, are the primary site for sensing low levels of *arterial oxygen pressure* (arterial PO_2) but also respond to a lesser extent to changes in *arterial carbon dioxide pressure* (arterial PCO_2) and pH. They are stimulated when the arterial PO_2 falls below 75 mm Hg as well as when the arterial PCO_2 increases and pH decreases. Whereas both receptors stimulate ventilation in hypoxia, the aortic chemoreceptors are more important in infants and the carotid receptors are more important in adults.¹⁶ Once stimulated, the carotid bodies send impulses via cranial nerve IX to the nucleus tractus solitarius where neurotransmitters are released that increase ventilation.¹⁷ Although the control of ventilation during exercise is not completely understood, the predominant stimulus for increased ventilation is thought to arise from the peripheral receptors. It is postulated that additional peripheral receptors exist that are yet to be identified because the hyperventilatory response of exercise cannot be fully accounted for by the carotid bodies.¹⁸ The *central chemoreceptors* are crucial in the adjustments of ventilation to acid-base disturbances and arterial PCO_2 . There are four groups of chemosensitive neurons in the brain stem: the locus ceruleus, the nucleus tractus solitarius, the midline raphe, and the ventrolateral quadrant of the medulla. The central chemoreceptors are responsible for most of the response to carbon dioxide. They respond to increases in arterial PCO_2 by their detection of the fall in pH of the cerebrospinal fluid associated with an increase in cerebrospinal fluid arterial PCO_2 ,³ which closely follows an increase in serum arterial PCO_2 . Of note, it appears that the parasympathetic nervous system is important in the response to cerebrospinal fluid pH changes because inhibition of acetylcholine transmission can abolish the central pH response in animals.¹⁷

DISEASES AFFECTING THE RESPIRATORY SYSTEM

The diseases of the neurorespiratory system can be organized most logically in the framework of functional anatomy. Diseases of the central nervous system known to affect the respiratory system are listed in Table 97-1 and those affecting the peripheral nervous system are listed in Table 97-2.

Table 97-1 Diseases of the Central Nervous System Associated with Respiratory Dysfunction

Cerebral Cortex	Brain Stem/Basal Ganglia	Spinal Cord
Stroke	Stroke	Trauma
Neoplasm	Neoplasm	Infarction or hemorrhage
Cerebral degeneration	Poliomyelitis	Demyelinating disease
Seizures	Central alveolar hypoventilation	Disc compression
	Progressive bulbar palsy	Syringomyelia
	Multiple system atrophy	Tumor
	Anoxic encephalopathy	Epidural abscess
	Encephalitis	
	Multiple sclerosis	
	Parkinson disease	
	Chorea	
	Dyskinesias	

Table 97-2 Diseases of the Peripheral Nervous System Associated with Respiratory Dysfunction

Motor Nerves/ Anterior Horn Cell	Neuromuscular Junction	Myopathies
Acute idiopathic demyelinating polyneuropathy (Guillain-Barré syndrome)	Myasthenia gravis	Muscular dystrophies
Motor neuron disease	Lambert-Eaton myasthenic syndrome	Myotonic dystrophy
Amyotrophic lateral sclerosis	Toxins	Poly- and dermatomyositis
Spinal muscular atrophy	Botulism	Glycogen storage diseases
Primary lateral sclerosis	Snake venoms	Pompe disease
Critical illness neuropathy	Scorpion bites	Forbes-Cori disease
Vasculitides	Shellfish	Thick filament myopathy
Toxins (e.g., lithium, arsenic, gold)	Crab poisoning	Mitochondrial myopathy
Metabolic	Drugs	Nemaline body myopathy
Diabetes	Antibiotics	Severe hypokalemia
Porphyria	Neuromuscular junction blockers	Hypophosphatemia
Uremia	Anticholinesterase inhibitors	
Diphtheria	Corticosteroids	
	Lidocaine	
	Quinidine	
	Lithium	
	Antirheumatics	

CENTRAL NERVOUS SYSTEM DISEASES

Cortical and Brain Stem Disorders

Diseases of Voluntary Breathing. The pathways that connect the voluntary respiratory centers of the cortex with spinal motor neurons (corticospinal tracts) can be affected in a number of disorders. Midpontine strokes can damage the corticospinal tracts and cause what is known as the “locked-in syndrome,”¹⁹ a syndrome with total paralysis with the exception of eye movement. Because injury to the reticulospinal tracts causes loss of volitional but not automatic breathing, the response to automatic breathing is preserved.²⁰ This syndrome is most commonly due to ischemic stroke but can be due to pontine tumor, central pontine myelinolysis, high cervical demyelination, syphilitic arteritis, and head injury. Extrapontine disorders such as parkinsonism can also affect voluntary breathing.²¹ In these disorders, patients have less ability to alter their

breathing pattern voluntarily. They also may demonstrate periodic breathing or a Cheyne-Stokes respiratory pattern.

Diseases of Automatic Breathing. Automatic breathing but not voluntary breathing is classically disrupted in central alveolar hypoventilation, otherwise known as “Ondine’s curse,”²² caused by injury to the automatic respiratory centers in the brain stem. Because automatic triggering controls breathing during sleep, individuals with central hypoventilation develop central sleep apnea. Congenital central alveolar hypoventilation is a rare genetic disorder affecting infants and children, although it has now been described in adults as well.²³ Acquired central alveolar hypoventilation can result from unilateral or bilateral medullary infarction, bulbar poliomyelitis, or bilateral cervical tractotomy performed to control chronic pain. Although disorders of the neurorespiratory system generally lead to hypoventilation and the need for ventilatory support, diseases of the automatic respiratory centers in the brain stem can also lead to hyperventilation. This may be caused by diseases such as central nervous system infection or tumor²⁴ or by stimulation of an otherwise normal autonomic respiratory center by fever, sepsis, pain, pregnancy, medications such as progesterone or salicylates, or high altitude. A variety of irregular breathing patterns have also been associated with central nervous system disease including Cheyne-Stokes respiration and ataxic breathing.²⁵

Diseases of the Spinal Cord

Spinal Cord Injury. *Spinal cord injury* (SCI) is most commonly due to traumatic injury caused by motor vehicle accidents, falls, sports accidents, and gunshot wounds. In the United States, an estimated 250,000 individuals have suffered significant SCI; the incidence is approximately 12,000 incident cases per year with 78% of the injuries seen in males (National Spinal Cord Injury Statistical Center <http://www.spinalcord.uab.edu>). Respiratory complications including atelectasis, pneumonia, and respiratory failure are the leading cause of morbidity and mortality for individuals with SCI.^{26,27} Immediately following acute SCI, a number of physiologic changes can affect the respiratory system and predispose to respiratory complications. These aberrations include (1) cough inefficiency due to expiratory muscle weakness, (2) ciliary dysfunction, (3) mucous hypersecretion possibly due to impairment of the peripheral autonomic nervous system, (4) glottic dysfunction or gastric hypomotility increasing the risk of aspiration, (5) bronchial hyperreactivity due to sympathectomy, and (6) loss of consciousness at the time of the injury, increasing the risk of aspiration.^{28,29}

Acute respiratory failure immediately after the injury may be due to direct disruption of respiratory muscle innervation (cervical cord injury), aspiration at the scene due to loss of consciousness, pulmonary edema, or other traumatic injuries to the chest or head. Many individuals with SCI are intubated at the scene of the accident or shortly thereafter. Prevention of further respiratory complications is important. Preventive measures include encouragement of deep breathing and cough, frequent changes of position, postural drainage, assisted cough (manual or mechanical), and bronchoscopy when other measures fail. Patients with SCI are at high risk for venous thromboembolism with the

Table 97-3 Respiratory Muscles and Their Innervation

Muscle Group	Spinal Cord Level	Nerve
INSPIRATORY MUSCLES		
Diaphragm	C3-5	Phrenic
Parasternal intercostals	T1-7	Intercostal
Lateral external intercostals	T1-12	Intercostal
Scalenes	C4-8	Cervical (deep branches)
Sternocleidomastoids	Above spinal cord	Spinal accessory
EXPIRATORY MUSCLES		
Lateral internal intercostals	T1-12	Intercostal
Rectus abdominis	T7-L1	Lumbar
External and internal obliques	T7-L1	Lumbar
Transversus abdominis	T7-L1	Lumbar
UPPER AIRWAY MUSCLES		
Muscles of mastication	–	CN V, VII
Laryngeal and pharyngeal		
Abductors	–	CN IX-XII
Adductors	–	CN IX-XII

CN, cranial nerve.

greatest risk 3 days to 2 weeks after injury. Prophylaxis for deep venous thrombosis is highly recommended during the initial hospitalization.

The extent of respiratory muscle impairment following SCI mainly depends on the level and severity of the spinal injury because the function of respiratory muscles innervated below the level of the cord injury is lost. The innervation of the respiratory muscles is shown in Table 97-3. The overall pattern of pulmonary function abnormality is one of restriction.³⁰ In the first few months to a year following the initial SCI, there is a significant improvement in lung volumes and maximal inspiratory and expiratory pressures,^{31,32} possibly due to resolution of spinal cord edema and/or strengthening of the diaphragm and accessory muscles of inspiration.

In general, the higher the SCI, the more likely that ventilatory assistance will be needed.³² Treatment of ventilatory failure following SCI can be accomplished by invasive (tracheostomy) or noninvasive (mask or mouthpiece) methods.³³ Many individuals are ventilated through a tracheostomy tube for some time after their injury; however, transfer to noninvasive means can often be achieved even for those requiring full-time ventilatory support. The choice of invasive versus noninvasive ventilation is determined by the degree of local expertise with these forms of ventilation as well as by patient preference. For those with high cervical SCI (C1-2) and intact phrenic nerve function, diaphragm pacing either via a laparoscopic approach or thoracic approach is also a possibility. It should be noted that those with diaphragm pacemakers implanted still need a tracheostomy in place to avoid airway obstruction during sleep owing to the absence of the normal neurologic coordination of diaphragm contraction and upper airway dilation during inspiration. Although traumatic SCI is the major cause of spinal cord pathology, other causes include vascular accidents, demyelinating diseases (multiple sclerosis, transverse myelitis), syringomyelia, tumors, and epidural abscess (see Table 97-1).

Ventilator dependence in patients with SCI is more common with high (cervical) SCI. Because the diaphragm is the major muscle of inspiration (C3-5 spinal nerve roots), those with lesions at C3 and above invariably require ventilatory support and are at the highest risk of respiratory complications.^{27,34} Those with injuries between C3 and C5 vary in their requirements for ventilatory support. Even if they require ventilation initially, these individuals may become independent of ventilatory support eventually.^{32,35} The risk for ventilator dependence in this group of patients is greatest for those with injury close to C3 or age older than 50 years.³² Individuals with lesions below C5 almost always become independent of continuous ventilator support. In contrast to inspiratory muscle function, expiratory muscle function is impaired after all levels of cervical cord injury resulting in expiratory muscle weakness and ineffective cough. Because an effective cough depends in large part on abdominal and intercostal muscle function (spinal nerve roots T1-L1), cervical, thoracic, and even some high lumbar SCIs can impair the ability to cough and clear secretions. Therefore, measurement of cough function in these patients is very important.

Other Respiratory Effects of Spinal Cord Injury. For unknown reasons, the frequency of sleep apnea appears to be increased by as much as fourfold in patients with SCI compared to a normal population of similar age.^{36,37} A sleep study should be considered when symptoms of nocturnal hypoventilation such as morning headache, daytime hypersomnolence, or unexplained nocturnal awakenings are present or when daytime hypercarbia (arterial PCO₂ > 45 mm Hg), unexplained cor pulmonale, or *forced vital capacity* (FVC) less than 50% predicted are present.³⁸ Bronchial hyperreactivity and bronchial hypersecretion are also present in some individuals following SCI likely due to interference with normal autonomic control of the airways after injury.³⁹

PERIPHERAL NERVOUS SYSTEM DISEASES

Diseases of Motor Nerves or Anterior Horn Cells and Diseases of the Neuromuscular Junction

Disorders of the motor nerves and the *neuromuscular junction* (NMJ) can arise acutely as in acute inflammatory polyneuropathy (Guillain-Barré syndrome) or botulinum toxicity or can arise more chronically as in motor neuron disease (e.g., *amyotrophic lateral sclerosis* [ALS]) or myasthenia gravis (see Table 97-2). The level of motor nerve root involvement dictates the effects of the disorder on the respiratory system.

Acute Diseases Affecting Motor Nerves

Acute Immune-Mediated Polyneuropathy. Acute immune-mediated polyneuropathy, also referred to as Guillain-Barré syndrome, is a heterogeneous group of diseases that are now thought to be caused by antiglycolipid antibodies.⁴⁰ Acute idiopathic demyelinating polyneuropathy is the most common form, making up about 85% to 90% of cases. It is an acute progressive process characterized by symmetrical, ascending muscle weakness progressing over a 2-week period and associated with loss of deep tendon

reflexes. It is thought that an antecedent viral infection induces an immune response to viral epitopes that then cross-react with lipid components of the peripheral nerve.⁴¹ The process usually starts in the lower extremities but may start in the arms or the face, head, and neck primarily (Miller-Fisher variant).⁴²

Acute idiopathic demyelinating polyneuropathy affects the respiratory system by causing (1) weakness of the upper airway muscles, (2) weakness of the inspiratory and expiratory muscles, and (3) secondary complications such as pneumonia or pulmonary embolism.⁴³ Approximately 25% to 50% of patients develop respiratory insufficiency severe enough to necessitate intubation and mechanical ventilation.^{44,45} A number of variables used to predict impending respiratory failure and the need for mechanical ventilatory support have been used including FVC, *maximal inspiratory pressure* (MIP), maximal expiratory pressure, and nocturnal desaturation. Generally accepted guidelines for intubation and mechanical ventilation include an FVC less than 15 mL/kg, an FVC less than 1 L, a decline in FVC to 50% or less of the normal predicted value for that individual or an MIP of 30 cm H₂O or less.⁴³ FVC and MIP should be monitored frequently (multiple times per day depending on rapidity of progression). With rapidly progressive disease, the *intensive care unit* (ICU) is considered the best location for monitoring. Absolute indications for intubation include impaired consciousness, respiratory or cardiac arrest, shock, arrhythmias, blood-gas alterations, or bulbar dysfunction with confirmed aspiration.⁴³ Noninvasive ventilation is generally not an option for these individuals because they are at a high risk for aspiration because of bulbar muscle involvement. Successful extubation may be achieved once treatment such as steroids, immune globulin, and plasmapheresis is begun and respiratory muscle strength returns.⁴⁶ Until respiratory muscle strength returns, scrupulous supportive ICU care including tracheostomy for prolonged mechanical ventilation is required to prevent complications such as ventilator-associated pneumonia and sepsis.

Poliomyelitis. Poliomyelitis is a viral disease affecting the anterior horn cell and therefore motor nerve caused by a human enterovirus that caused significant epidemics with frequent respiratory complications in the United States and Western Europe during the 20th century. Owing to improved sanitation and vaccine development, polio is no longer a major public health issue in the developed world. However, in the developing world, acute infections still happen.⁴⁷

In the developed world, the major health issue arising from polio currently is the postpolio syndrome, in which new weakness develops in survivors of the polio epidemics of the mid-20th century.^{48,49} The cause of progressive neurologic deterioration in postpolio syndrome is unknown. Theories of pathogenesis suggested include (1) progressive degeneration of reinnervated motor units, (2) persistence of poliovirus in neural tissue, or (3) induction of autoimmunity with subsequent destruction of neural structures.^{50,51} The average time to onset from the time of the initial infection is 35 years but ranges from 8 to 71 years. A high percentage of polio survivors, between 20% and 60% of individuals, complain of new muscle weakness.⁵¹ Although the exact incidence of respiratory system involvement in postpolio syndrome is not known, sleep-disordered

breathing is common and noninvasive nocturnal ventilation can be highly effective.⁵² Fortunately, it appears that frank hypoventilation associated with the postpolio syndrome is unusual.⁵³

Chronic Diseases Affecting Motor Nerves

Amyotrophic Lateral Sclerosis. *Amyotrophic lateral sclerosis* (ALS) is a progressive neurodegenerative disease with no known cure. The usual clinical presentation is that of an individual with gradually progressive asymmetrical weakness associated with hyperreflexia due to upper motor nerve involvement and muscle fasciculations due to lower motor nerve involvement. Like most neurologic diseases, ALS has no direct effect on the lung; however, it significantly affects the upper airway, chest wall, and diaphragm, thereby impairing respiratory muscle function. Indeed, ALS affects all of the major muscle groups of the respiratory system including (1) upper airway muscles leading to abnormal swallowing and inadequate cough, (2) expiratory muscles leading to inadequate cough, and (3) inspiratory muscles leading to inadequate ventilation. Therefore, all patients with ALS are at significant risk for respiratory complications. Respiratory failure, the leading cause of death in this population, has been reported as the initial clinical presentation of ALS.⁵⁴ Patients may complain of dyspnea, difficulty managing secretions, or inability to cough effectively. Monitoring pulmonary function in the outpatient setting is crucial. The FVC is the most commonly used measurement and has prognostic significance.^{55,56} Attention must be given to glottic and cough function as well because aspiration and pneumonia are significant contributors to morbidity and mortality.⁵⁷ Sleep-disordered breathing is very common in ALS and *noninvasive positive-pressure ventilation* (NPPV) has been used both at night and, as the disease progresses, during the day to improve quality and duration of life.⁵⁸⁻⁶⁰ Patients often have difficulty managing secretions owing to swallowing dysfunction. Secretions can be reduced by using anticholinergic agents,⁶¹ by low-dose irradiation of salivary glands,⁶² or by injecting the glands with botulinum toxin.^{61,63} As ALS progresses, NPPV ceases to be effective and a decision needs to be made concerning the appropriateness of tracheostomy and long-term invasive ventilation. Although tracheostomy can prolong survival substantially,⁶⁴ it does not alter the progression of the disease and patients ultimately become completely paretic. Due to different cultural approaches, rates of invasive ventilation vary substantially among countries.⁶⁵

Neuromuscular Junction Diseases

Myasthenia Gravis. Myasthenia gravis is the most common disease affecting neuromuscular transmission. It is an autoimmune disease characterized by an antibody-mediated immune attack directed at acetylcholine receptors and/or receptor-associated proteins in the postsynaptic membrane of the NMJ. It causes weakness of several muscle groups including the respiratory muscles. The respiratory muscles are particularly susceptible to fatigue during the severe, potentially life-threatening, exacerbations known as *myasthenic crises*.⁶⁶ The clinical considerations during myasthenic crisis are very similar to those for acute idiopathic demyelinating polyneuropathy noted earlier and the indications for intubation are the same.⁴³ Acute treatment

of myasthenic crisis focuses on rapid therapies including intravenous immunoglobulin as well as plasmapheresis and corticosteroid therapy.^{67,68} Assiduous attention to respiratory care provides support of the patient, allowing time for therapy of the underlying myasthenia to be effective.

Myasthenia gravis can also arise as a paraneoplastic syndrome in association with thymoma. It has been estimated that approximately 15% of all patients with thymoma will exhibit myasthenia gravis. Removal of the thymoma may result in amelioration of the myasthenia symptoms. Predictors of improvement after thymectomy have been reported to be age younger than 35 years, less than 24 months from the onset of symptoms, and absence of perioperative steroid use.⁶⁹

The *Lambert-Eaton myasthenic syndrome* (LEMS) is a myasthenic syndrome associated with small cell lung cancer that can affect the respiratory muscles in a fashion similar to that of myasthenia gravis. In patients with small cell lung cancer, LEMS may be present in approximately 3% of cases.⁷⁰ However, in patients with LEMS, as many as 50% to 60% will have a tumor, almost always a small cell lung cancer. The small cell lung cancer may be occult and should be sought for up to 5 years after the diagnosis of LEMS. LEMS is thought to be due to autoantibodies directed against presynaptic voltage-gated calcium channels,⁷¹ thereby interfering with synaptic function. These voltage-gated calcium channels may be shared by the neuroendocrine cells of the small cell lung cancer, thus explaining the association of the two conditions. Although respiratory involvement is often a late finding, frank respiratory failure can be a manifestation of LEMS,⁷² and this disorder should be considered in individuals with unexplained neuromuscular weakness. Although LEMS shares a similar pathophysiologic mechanism with myasthenia gravis, the clinical presentation is different; LEMS is characterized by (1) an increase in the compound muscle action potential with repetitive nerve stimulation, a feature not seen in myasthenia, (2) more frequent presence of proximal leg weakness, which is worse in the morning, (3) greater autonomic dysfunction, and (4) frequent association with malignancy.⁷³

Botulism. Botulism is a neuroparalytic syndrome caused by a toxin produced by the gram-positive bacterium *Clostridium botulinum* that acts at the NMJ. It can be acquired by humans in one of five ways: (1) food-borne botulism, in which there is ingestion of food contaminated with preformed toxin, (2) wound botulism, in which the bacteria growing in the wound produce toxin in vivo, (3) infant botulism, in which there is ingestion of clostridial spores allowing colonization of the host's gastrointestinal tract by the bacteria and production of the toxin in vivo, (4) adult enteric infectious botulism, which is similar to infant botulism, and (5) inhalational botulism, which follows inhalation of aerosolized toxin released in an act of bioterrorism⁷⁴ (see Chapter 40).

C. botulinum produces a number of toxins that can produce paralysis by binding to synaptotagmin I and II receptors that mediate toxin entry into the nerve cell cytoplasm.⁷⁵ Once intracellular, the toxin produces irreversible disruption in stimulation-induced acetylcholine release. The botulinum toxin is one of the most potent toxins known. Recovery from the injury requires regrowth of

new synapses, a process that can take 6 months. The clinical syndrome is one of progressive paralysis with early cranial nerve involvement causing blurred vision, dysphagia, dysarthria, and facial weakness. Descending muscle weakness is the usual course and involvement of the upper airway, diaphragm, and intercostal muscles often leads to the requirement for intubation and mechanical ventilation.⁷⁶ All patients should be monitored in the ICU and intubation should be undertaken for those who cannot protect their airway or who have a vital capacity of less than 30% predicted. Botulism antitoxin (intravenous botulinum immune globulin) is available for use in the United States and is given to infants younger than 1 year of age.⁷⁷ For adults in the United States, an investigational equine serum heptavalent botulism antitoxin is available through the Centers for Disease Control and Prevention.⁷⁸ For all patients, supportive care is the mainstay of therapy, and when necessary, intubation and mechanical ventilation are critical to improved survival. Prolonged hospitalization is common.

OTHER NEUROMUSCULAR JUNCTION TOXINS. A number of other toxins can affect the NMJ. The insecticides organophosphates and carbamates are potent inhibitors of acetylcholinesterase, leading to high levels of acetylcholine in the NMJ and resulting in parasympathetic and sympathetic overstimulation, skeletal muscle paralysis, and sometimes respiratory failure.⁷⁹ Several species of tick produce toxins that can inhibit NMJ neurotransmission (tick paralysis) by inhibiting influx of sodium ions and preventing presynaptic terminal axon depolarization and the release of acetylcholine at the nerve terminal.⁸⁰ Snake venom from a number of families of snakes produces neurotoxins that can cause paralysis, respiratory failure, and death owing to inhibition of neurotransmission.⁸¹ Finally, a wide range of medications can cause NMJ blockade including D-penicillamine, aminoglycoside antibiotics, fluoroquinolone antibiotics, phenytoin and other anticonvulsants, lithium, β -blockers, glucocorticoids, and magnesium sulfate.⁸²

Diseases of the Respiratory Muscles

A large number of disorders, both acute and chronic, can directly affect the respiratory muscles (see Table 97-2). Many causes of chronic muscle disease result in respiratory muscle dysfunction including genetic muscular dystrophies, myopathies, and myotonias as well as inflammatory myopathies and those associated with systemic diseases.

Duchenne and Becker Muscular Dystrophies. Duchenne and Becker muscular dystrophies are both progressive myopathic disorders caused by mutations of the dystrophin gene on chromosome Xp21.⁸³ Dystrophins are glycoproteins that coat sarcolemmal, sarcomeric, and cytosolic muscle proteins. In Duchenne muscular dystrophy, dystrophin is absent, whereas in Becker dystrophy, a milder variant, dystrophin is reduced in quantity or quality. Both disorders are inherited as X-linked recessive traits and are characterized by progressive muscle wasting and weakness.⁸⁴ Typically, weakness of limb muscles is more severe in Duchenne muscular dystrophy. Both diseases can involve the respiratory muscles, leading to substantial morbidity and mortality. The diaphragm, however, may be less susceptible than limb muscle because of different gene

transcription patterns.⁸⁵ Duchenne dystrophy can also involve cardiac muscle.

In Duchenne muscular dystrophy, weakness of proximal muscle groups usually manifests by age 2 to 3 years, while weakness of the respiratory muscles becomes evident later in childhood.⁸⁶ In Becker muscular dystrophy, weakness manifests later in childhood and individuals can remain ambulatory often into adult life. Because limb muscles are more affected than the respiratory muscles, exercise is initially limited by limb muscle weakness rather than dyspnea due to respiratory muscle weakness. However, with time, the respiratory muscles progressively weaken and dyspnea may appear with minimal exertion or at rest. Inspiratory muscle weakness can be assessed by measuring MIP. In children unable to perform this maneuver, maximal sniff pressures may provide a useful surrogate.⁸⁷ With severe inspiratory muscle weakness (MIP < 50% predicted), lung volumes are reduced and vital capacity may decline at a rate of 6% to 11% per year. This restrictive process can be worsened by concurrent scoliosis, kyphosis, or muscle contractures. Glucocorticoids and idebenone, a quinone-like drug that may enhance energy production at the mitochondria and has antioxidant properties, have been used to slow the rate of decline of lung function.⁸⁸⁻⁹³ Therapies based on genetic manipulation such as gene transfer or exon skipping to restore the proper reading frame show promise but need further evaluation.⁹⁴⁻⁹⁶

The diagnosis is often suspected by noting an elevated serum creatine kinase. However, this finding is not specific for these disorders. Often, a muscle biopsy is obtained to distinguish muscular dystrophies from inflammatory skeletal muscle disorders and other forms of dystrophy. With muscular dystrophy, there is degeneration and regeneration of muscle fibers as well as replacement of muscle by fat and connective tissue. Immunoblots for dystrophin can aid in distinguishing Duchenne from Becker muscular dystrophy. Analysis for deletions in the dystrophin gene may be useful, but detection of point mutations of this gene may be difficult.⁹⁷ Female siblings of individuals with Duchenne or Becker muscular dystrophy should be tested to determine whether they are carriers of the disease. Carriers often have elevated creatine kinase levels.⁹⁸ It is important to identify carriers not only for genetic counseling but also because they may be at higher than average risk for development of cardiomyopathy.

The combination of a restrictive pulmonary deficit and expiratory muscle weakness impairs cough and therefore predisposes these individuals to development of respiratory complications such as atelectasis and pneumonia. Methods for preventing atelectasis and infection are discussed later in this chapter.

As the inspiratory muscles further weaken, the restrictive lung dysfunction becomes severe, with total lung capacity and vital capacity dropping to less than 60% predicted. Individuals with a vital capacity less than 30% predicted are at high risk for nocturnal hypoventilation. These individuals often experience symptoms related to nocturnal hypoventilation such as non-refreshing sleep and fatigue. Nocturnal ventilation is usually initiated if symptoms are related to nocturnal hypoventilation, right heart failure, or elevated arterial PCO₂ (>45 mm Hg) either at night or during the day. In general, daytime measures of respiratory

muscle strength or lung volumes are poor predictors of nocturnal hypoventilation and overnight oximetry or a sleep study should be considered in high-risk individuals. Noninvasive ventilation is a therapeutic intervention that typically can be delivered with a positive-pressure device using an interface such as a nasal mask, nasal-oral mask, or mouthpiece (discussed later). Although there are no randomized controlled trials in patients with muscular dystrophy, noninvasive ventilation is likely to improve quality of life, physical activity, and hemodynamics and to normalize arterial blood gases.^{99,100} Extension of noninvasive ventilation into waking hours may provide relief of dyspnea in more severely affected patients. Endurance and strength training targeting the inspiratory muscles may slow the progression of the disease in individuals with mild to moderate weakness.¹⁰¹ Individuals with Duchenne or Becker muscular dystrophy who require surgery may be at higher risk for respiratory complications.¹⁰² A consensus statement has been published addressing the respiratory and other risks of anesthesia and suggesting methods for avoiding excessive morbidity and mortality.¹⁰³

Other muscular dystrophies such as limb girdle muscular dystrophy, fascioscapulohumeral dystrophy, and myotonic dystrophy can affect the respiratory muscles but do not generally cause respiratory impairment until later in the course of the disease.

Chronic Inflammatory Myopathies. *Dermatomyositis* (DM), *polymyositis* (PM), and *inclusion body myositis* (IBM) are systemic inflammatory diseases of unknown etiology that cause profound skeletal muscle weakness.¹⁰⁴ PM and DM, with a prevalence of roughly 1 : 100,000, affect females more than males.¹⁰⁵ Both DM and PM are characterized by muscle fiber inflammation and necrosis. With DM, the inflammatory process may be due to complement-mediated microangiopathy or related to type 1 interferons. The locus of inflammation in DM is the perifascicular fibers and blood vessels. With PM, the inflammatory response is cell-mediated and involves the muscle fascicles themselves. IBM is characterized by perivascular inflammation, inflammation of the perimysium, the sheath of connective tissue surrounding groups of skeletal muscle fibers, and the presence of characteristic vacuoles. Tau protein and beta-amyloid precursor protein may contribute to muscle injury.^{106,107}

DM and PM involve proximal muscle groups, whereas IBM may involve both proximal and distal muscle groups. DM can be seen in children and adults, whereas PM and IBM are generally seen only in adults with IBM involving those older than age 50 years with a male predominance. DM may be associated with a rash or underlying carcinoma.

Inflammatory myopathies generally cause symmetrical proximal muscle weakness with insidious onset of symptoms due to slowly progressive muscle weakness. Inflammatory myopathies can also involve the diaphragm, intercostal muscles, and accessory muscles but other peripheral muscle groups are usually more severely affected than the respiratory muscles.¹⁰⁸ IBM is similar to PM except onset of symptoms is usually after age 50 years; it is more commonly seen in men than in women. Symptoms related to respiratory muscle weakness usually are not the presenting complaints. However, respiratory muscle weakness can develop in 5%

to 10% of the patients with DM and PM¹⁰⁸ and may be found in as many as 75% of individuals when respiratory muscle function is carefully evaluated.¹⁰⁹

Interstitial lung disease may develop in up to 70% of patients with DM or PM.¹¹⁰ Interstitial lung disease may be especially aggressive with the presence of antisynthetase antibodies.¹¹¹ Individuals with DM or PM should be evaluated for the presence of restrictive pulmonary disease, which may be due to respiratory muscle weakness as well as underlying interstitial lung disease. If respiratory muscle weakness is pronounced (MIP < 30% of predicted), ventilatory failure may ensue.¹⁰⁸ Respiratory muscle weakness can also impair cough, which, in concert with esophageal dysfunction and lymphopenia, can predispose these patients to pneumonia.

Diagnostic workup includes measuring muscle enzymes and autoantibodies, magnetic resonance imaging, and muscle biopsy. Muscle enzymes (creatine kinase, aldolase, and lactate dehydrogenase) can be elevated in all inflammatory myopathies but more so in DM and PM than in IBM. Serologic markers that are specific for DM and PM include autoantibodies such as anti-Jo-1; antibodies to signal recognition particle (anti-SRP antibodies); and antibodies to Mi-2, a nuclear helicase.^{112,113} Type 1 interferon-inducible transcripts can be detected in blood in DM and PM and may play a pathogenic role.¹¹⁴ Magnetic resonance imaging provides a broad sampling of muscle and is helpful in distinguishing between PM and IBM. With IBM, abnormal changes can be seen throughout the muscle; whereas changes are only noted along fascial planes in PM.¹¹⁵ The presence of typical inclusion bodies on muscle biopsy is diagnostic of IBM.

Metabolic Myopathies

Glycogen Storage Disease. A number of enzyme deficiencies can lead to disordered glycogen metabolism, resulting in accumulation of glycogen in tissue including skeletal and cardiac muscle. The glycogen storage diseases that are most likely to affect the respiratory system are acid maltase deficiency (type II—Pompe disease) and debranching enzyme deficiency (type III—Forbes-Cori disease). These disorders usually present in childhood, but some, such as Pompe disease, have separate adult-onset forms. McArdle disease (type V) results from myophosphorylase deficiency and can lead to exercise intolerance.¹¹⁶ In general, glycogen storage disorders are inherited as autosomal recessive conditions.

Acid Maltase Deficiency. Acid maltase deficiency, also known as glycogen storage disease type II or Pompe disease, is due to the deficiency of acid α -glucosidase, an enzyme responsible for the degradation of glycogen polymers to glucose. Deficiency of this enzyme allows accumulation of glycogen within cardiac and skeletal muscle lysosomes, resulting in myopathy. Although typically involving infants, this disease can manifest in adulthood.¹¹⁷ Complete enzyme deficiency results in cardiorespiratory failure and death, usually in the first year of life.¹¹⁸ When the onset of weakness begins after age 1 year, the disease is less severe and does not involve the heart. Initially, subjects develop symptoms related to muscle weakness. Those with a later onset of symptoms have a better prognosis. With diaphragm

involvement, there may be restrictive ventilatory limitation, intolerance of the supine position, and in most severe cases, respiratory failure.¹¹⁹ Results from trials of enzyme replacement therapy with recombinant acid α -glucosidase are promising, showing stabilization of pulmonary function^{120,121} and increased survival.¹²²

Other Metabolic Myopathies. Myopathies can be caused by defects of lipid metabolism (carnitine palmitoyl transferase deficiency) or disorders involving the mitochondria directly. Disorders of lipid metabolism may be caused by an abnormal carnitine transporter protein (“primary” carnitine deficiency) or a deficiency of carnitine secondary to other metabolic diseases.¹²³ These disorders usually do not cause respiratory disability but involve other skeletal muscle groups (arms and legs) and may involve cardiac muscle.

Mitochondrial disorders include those due to deficiencies of enzymes in the mitochondrial respiratory chain complexes and to defects of phosphorylation-respiration coupling. Disorders of mitochondrial metabolism involving complexes I, II, III, IV, and V cause multiple respiratory chain defects¹²⁴ and alter the kinetics of oxygen metabolism during exercise.¹²⁵ The main consequences of mitochondrial myopathy are muscle weakness, muscle wasting, and exercise intolerance. Dyspnea that accompanies exercise may be due to an exaggerated ventilatory response to metabolic demands.¹²⁵ Individuals may exhibit external ophthalmoplegia, ptosis, and hypertrophic or dilated cardiomyopathy. Occasionally, mitochondrial myopathies cause significant respiratory muscle weakness resulting in nocturnal hypoventilation and the need for assisted ventilation. Treatments that focus on bypassing the defective mitochondria include dietary supplements based on dietary substances involved in adenosine triphosphate production such as creatine.¹²⁶

SPECIAL TOPICS

NEUROMUSCULAR DISEASE RELATED TO CRITICAL ILLNESS

Neuromuscular weakness is a very common finding in patients who are in the ICU. Neuromuscular weakness develops in more than 25% of patients who are ventilated in the ICU for more than 7 days.¹²⁷ Potential causes of weakness in this context include Guillain-Barré syndrome, rhabdomyolysis, cachectic myopathy, ventilator-induced diaphragm dysfunction, and critical illness neuropathy and myopathy.

The combination of critical illness neuropathy and myopathy is now often referred to as “ICU-related weakness” or critical illness polyneuromyopathy. The incidence of critical illness polyneuromyopathy is high, with prospective studies estimating risk of 33% to 82%.¹²⁸⁻¹³⁰ Patients with sepsis, multiorgan failure, systemic inflammatory response syndrome,¹³¹ and hyperglycemia¹²⁹ are at a higher risk for this complication.¹³² Other factors that are thought to contribute to this disorder include treatment with steroids¹²⁷ or neuromuscular blocking agents,¹³³ total parenteral nutrition, aminoglycoside use, catecholamines, hyperosmolality,

female gender, longer duration of multiorgan failure, greater illness severity, and renal failure.¹³⁴

The pathophysiologic mechanisms leading to critical illness polyneuromyopathy are not well understood. However, the pathology of the myopathy has been well described and includes two major patterns of disease: (1) myocyte atrophy with thick filament (myosin) destruction¹³⁵ and (2) widespread myocyte necrosis with intracellular vacuolization and phagocytosis of muscle fibers.¹³⁶ The neuropathic changes described by electrophysiologic testing with nerve conduction studies reveal reduced motor and often sensory nerve action potentials and muscle fibrillation suggestive of denervation.¹³⁷

Critical illness polyneuromyopathy should be distinguished from other neuromuscular diseases. Compared with demyelinating diseases such as Guillain-Barré syndrome, critical illness polyneuromyopathy has normal nerve conduction velocity; compared with rhabdomyolysis, critical illness polyneuromyopathy will have a normal creatine phosphokinase, lack of muscle tenderness, and minimal electromyographic changes; and compared with cachectic myopathy, critical illness polyneuromyopathy is not usually associated with severe malnutrition.¹³⁸

The only intervention thus far shown to reduce the incidence of ICU-acquired neuromuscular disorders is intensive insulin therapy. In one randomized, controlled study, the use of insulin to maintain serum glucose at 80 to 110 mg/dL, compared with a conventional range of 180 to 200 mg/dL, reduced critical illness polyneuromyopathy in patients in the ICU for at least 1 week by 44%.¹³⁹

Ventilator-induced diaphragm dysfunction is another important cause of respiratory muscle weakness in the ICU and is associated with atrophy of both fast and slow myofibers.^{140,141} It can begin after only 24 to 36 hours of mechanical ventilation. Diaphragm ultrasound may provide a noninvasive means of assessing the function of the diaphragm in ventilated patients.¹⁴²

DISEASES AFFECTING DIAPHRAGM FUNCTION

The diaphragm, the major muscle of inspiration, is a dome-shaped structure that separates the thorax from the abdomen and is composed of two muscular leaflets attached to a central tendon (see Fig. 97-2). The diaphragm inserts into the bony rib cage along the inner surface of the lower six ribs and costal cartilages anterolaterally and the upper three lumbar vertebral bodies posteriorly. It separates the thorax from the abdomen and, when it contracts, increases the volume of the thorax and inflates the lung by decreasing intrapleural pressure. The diaphragm increases thoracic size in two main ways: by the descent of the diaphragm in a piston-like fashion and by the expansion of the rib cage via an increase in abdominal pressure. It is innervated by the phrenic nerve which arises from the C3 to C5. Diaphragm weakness or paralysis can involve either one of the diaphragm leaflets (unilateral) or both (bilateral).

Unilateral Diaphragm Paralysis

Unilateral diaphragm paralysis is more common than bilateral diaphragm paralysis. The list of potential causes is similar (Table 97-4). The most frequent causes of unilateral paralysis include phrenic nerve injury related to cardiac or

Table 97.4 Causes of Diaphragm Weakness and Paralysis

Neuropathic Causes	Myopathic Causes
Trauma Cardiac surgery with cold cardioplegia Blunt trauma Spinal cord injury Radiation injury Cervical manipulation Scalene and brachial nerve block	Muscular Dystrophies Limb-Girdle Duchenne and Becker
Tumor Compression Lung cancer Metastatic mediastinal tumor	Metabolic Myopathies Hyper or hypothyroidism Acid maltase deficiency
Metabolic Diabetes Vitamin deficiency (B6, B12, folate) Hypothyroidism	Rheumatologic Systemic lupus erythematosus Dermatomyositis Mixed connective disease
Inflammatory Neuritis Idiopathic (neuralgic amyotrophy, Parsonage-Turner) Mononeuritis multiplex Vasculitis Paraneoplastic	Miscellaneous Amyloidosis Malnutrition Idiopathic
Miscellaneous Cervical spondylosis Poliomyelitis Amyotrophic lateral sclerosis	

thoracic surgery, herpes zoster, cervical spinal disease, or invasive or compressive tumors.¹⁴³ With unilateral diaphragm paralysis, patients may be asymptomatic at rest but have dyspnea with exertion.¹⁴⁴ Orthopnea may be present but is not as common or severe as in bilateral paralysis. When dyspnea is present in patients with unilateral paralysis, co-morbid conditions such as obesity and underlying heart or lung disease may be present and other disorders that cause muscle weakness should also be evaluated.

The diagnosis is often suggested by an elevated hemidiaphragm on chest radiograph and confirmed with a fluoroscopic sniff test or by diaphragm ultrasonography.¹⁴⁵ In this test, an upward or “paradoxical” movement of the paralyzed hemidiaphragm is seen during a vigorous sniff maneuver and can be visualized by fluoroscopy or ultrasound imaging of the diaphragm dome (see Video 18-1). The paradoxical motion is due to the passive movement of a paralyzed hemidiaphragm in response to the increase in abdominal pressure (and decrease in pleural pressure) created by the contraction of the normal hemidiaphragm. Thus, the unilateral hemidiaphragmatic paralysis can be recognized readily by the different function of the two hemidiaphragms. Ultrasonographic imaging of the diaphragm in the zone of apposition provides an alternate means of diagnosing chronic unilateral diaphragm paralysis by showing a thin diaphragm that fails to thicken with inspiration (Video 97-1).¹⁴⁶ There is no specific treatment for this disorder, but recovery following the initial injury is occasionally seen. When disabling symptoms are present and there is significant elevation of the hemidiaphragm on chest radiography, surgical plication of the paralyzed hemidiaphragm to minimize its paradoxical motion has had some success in improving vital capacity and forced expiratory volume in 1 second, especially in the supine position, and in reducing dyspnea.^{147,148}

Bilateral Diaphragm Paralysis

Bilateral diaphragm paralysis is most often seen in the setting of a disease producing severe generalized muscle weakness. The most common causes are diffuse muscle diseases or motor neuron disease such as ALS. However, bilateral paralysis may develop with a myriad of disorders that involve the cervical spinal cord, phrenic nerve, or NMJ. Examples include neuralgic amyotrophy (Parsonage-Turner Syndrome) or complications following cardiac, thoracic, or neck surgery.¹⁴⁹

Patients with bilateral paralysis primarily complain of dyspnea,¹⁵⁰ either at rest, with activity, or especially when supine. Orthopnea is very common and patients may need to use a recliner to sleep.¹⁵¹ In addition, they often complain of dyspnea during activities that require bending or lifting. Dyspnea on immersion in water also has been described.¹⁵² These symptoms are related to increases in abdominal pressure and cranial displacement of the diaphragm in either the supine position or when bending. Because sleep-disordered breathing with hypoventilation and hypoxemia is common,^{153,154} these individuals generally respond well to NPPV.¹⁵⁵

Bilateral diaphragmatic paralysis can be difficult to diagnose. It may be suspected by observing paradoxical rib cage and abdomen motion during inspiration, especially in the supine patient. Pulmonary function tests show moderate restriction with the vital capacity decreasing by more than 30% when supine. Since there is no normal hemidiaphragm to use for comparison with an abnormal one, chest radiography and sniff testing can yield false-negative and false-positive results. Two-dimensional echocardiography of the movement of the diaphragm dome shares the same limitations as fluoroscopy.¹⁵⁶ Phrenic nerve conduction studies can be useful in diagnosing a neuropathic cause of diaphragmatic paralysis but can have technical limitations.¹⁵⁷ Measures of maximal inspiratory and expiratory pressures will be reduced but these tests are not specific for diaphragm dysfunction. The “gold standard” diagnostic test is measuring transdiaphragmatic pressure using thin balloon-tipped polyethylene catheters placed in the esophagus and stomach (Fig. 97-4A) and showing a lack of ability to generate a transdiaphragmatic pressure¹⁵⁸ (see Fig. 97-4B). Ultrasound of the diaphragm muscle in the zone of apposition is less invasive than measures of transdiaphragmatic pressure and is diagnostic of bilateral diaphragm paralysis when no diaphragmatic thickening is seen on either side with inspiration.¹⁵⁹

Bilateral diaphragm paralysis is rarely reversible unless the underlying disease is treatable. Spontaneous recovery, however, has been noted in more than 50% of individuals with idiopathic unilateral diaphragmatic paralysis or paralysis due to neuralgic amyotrophy (brachial plexus neuritis) with the recovery taking an average of 15 months from the onset of symptoms.¹⁵⁷ Ultrasonography has been used to follow recovery from bilateral and unilateral paralysis.¹⁶⁰ Phrenic nerve pacing can be considered but requires intact phrenic nerves and normal diaphragmatic motor function and is thus not applicable in most cases of diaphragm paralysis. Phrenic nerve pacing has been used in patients with cervical cord injuries above C-3. Direct diaphragmatic pacing involves the implantation of electrodes in the

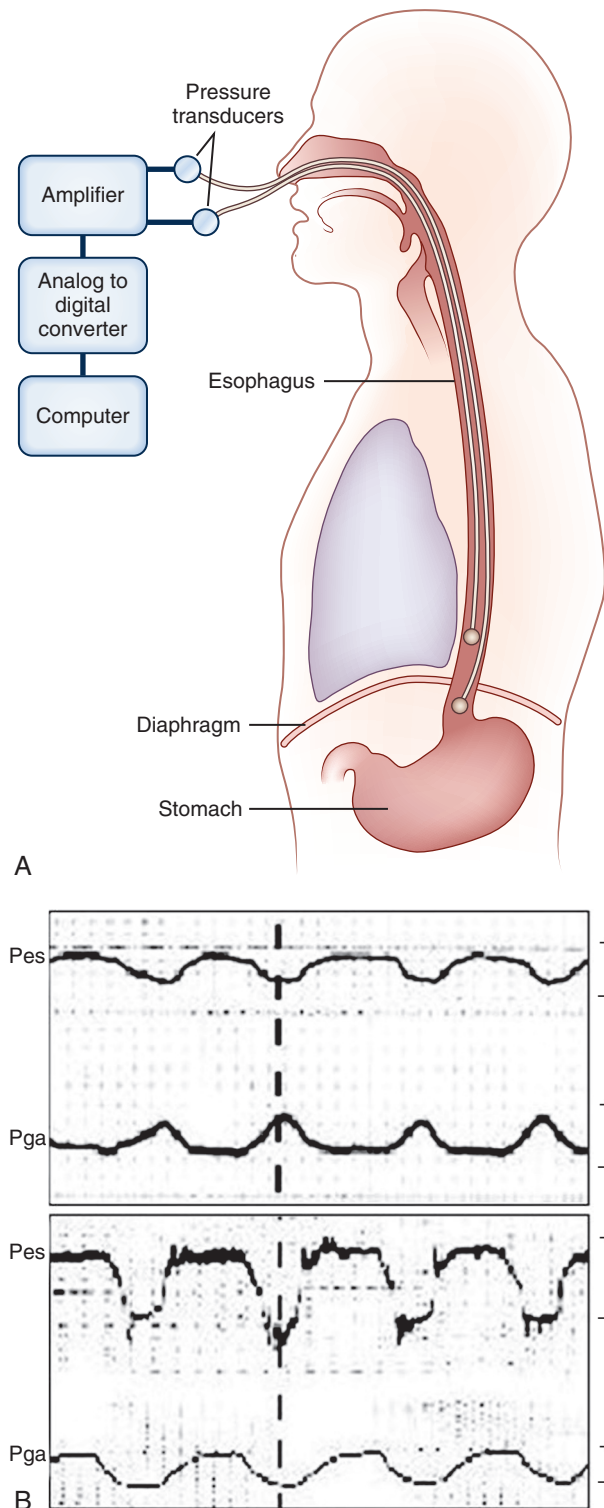


Figure 97-4 Transdiaphragmatic pressure testing for diaphragmatic function. **A**, Apparatus used to measure transdiaphragmatic pressure. Esophageal and gastric balloons placed through the nose into the esophagus and stomach, respectively, allow measurement of the pressures above and below the diaphragm simultaneously. **B**, *Top*, Normal esophageal (Pes) and gastric (Pga) pressure tracings. Note Pes becomes more negative and Pga more positive during normal inspiration owing to the action of the diaphragm. *Bottom*, Diaphragmatic paralysis where Pes and Pga deflect in the same direction showing no muscular activity of the diaphragm.

diaphragm. Identification of the entrance points of the phrenic nerve into the diaphragm is a prerequisite for direct pacing because uniform diaphragm activation requires placing the intramuscular electrodes in these locations. Direct pacing has been used in patients with high spinal cord injury and in patients with ALS with limited success in extending time free of ventilator support.¹⁶⁰ As mentioned previously, in unilateral diaphragm paralysis, hemidiaphragm plication has been used to shorten the paralyzed hemidiaphragm and allow the unaffected hemidiaphragm to contract more effectively. Plication is not indicated in patients with bilateral diaphragm paralysis because one of the compensatory mechanisms used by these individuals to breathe requires the transmission of low subdiaphragmatic pressure across a flaccid diaphragm to the pleural space.

APPROACH TO RESPIRATORY EVALUATION AND MANAGEMENT OF THE INDIVIDUAL WITH NEUROMUSCULAR DISEASE

Although each neuromuscular disease has a different etiology and natural history as well as potential treatment, the respiratory effects of neuromuscular diseases can be approached in a systematic way that can be applied to any neuromuscular diagnosis. This approach uses the fact that the three major muscle groups involved in maintaining ventilation and protecting the airway and lungs are (1) the inspiratory muscles responsible predominantly for ventilation, (2) the expiratory muscles responsible predominantly for cough, and (3) the upper airway muscles responsible for cough, swallowing, and airway protection (Fig. 97-5). For the patient with neuromuscular disease, cough function and airway protection from an intact swallowing mechanism are as important as maintenance of ventilation.^{161,162} For patients with Duchenne muscular dystrophy, a consensus committee of the American Thoracic Society¹⁶² has recommended that clinic visits should include evaluation of each of the three areas by eliciting appropriate history, physical examination, and laboratory testing.

Inspiratory function can be tested by measurement of FVC, MIP, and carbon dioxide levels. Carbon dioxide can be measured as arterial PCO₂, the traditional measure of adequate ventilation, or as exhaled or end-tidal carbon dioxide, transcutaneous carbon dioxide, or capillary PCO₂. Arterial blood gas sampling is the most accurate means of assessing alveolar ventilation but can be uncomfortable for the patient. End tidal carbon dioxide measurement in patients without intrinsic lung disease is an easy and accurate method of estimating arterial PCO₂.¹⁶³ Transcutaneous carbon dioxide has been successfully measured in children and improving technology may allow more widespread use.¹⁶⁴

Hypoventilation usually manifests itself with symptoms associated with sleep fragmentation. Symptoms consistent with sleep-disordered breathing include more frequent nocturnal awakenings, nocturia, vivid nightmares, night sweats, daytime hypersomnolence, morning headaches, nausea, depression, decreased concentration, and diminished daytime performance. Polysomnography can be used

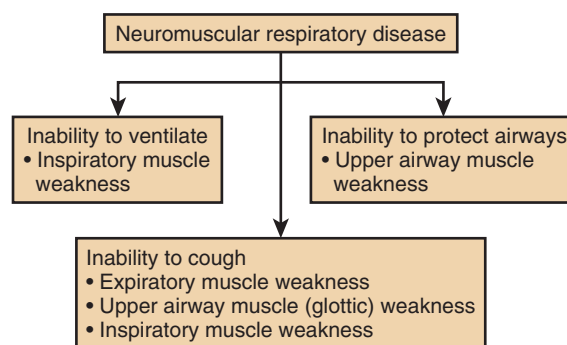


Figure 97-5 Clinical effects of weakness or dysfunction of inspiratory, expiratory, and upper airway muscles. Neuromuscular conditions lead to respiratory disease mainly via inability to ventilate, to cough, or to protect the upper airway from aspiration.

to evaluate sleep in patients with neuromuscular disease, but an overnight stay in a sleep laboratory may be especially difficult for such individuals if they require a personal care attendant, position changes, or help with toileting. Thus, ensuring a high pretest probability before ordering a sleep study is important. Baseline values of awake arterial PCO₂ of 45 or greater or base excess of 4 mEq or greater may correlate with sleep hypoventilation.¹⁶⁵ An unattended sleep study in the home¹⁶⁶ or overnight oximetry and end tidal carbon dioxide monitoring¹⁶² may substitute for a full laboratory polysomnogram; however, the sensitivity and specificity of these portable tests remains to be determined in this population.¹⁶⁶ These studies may serve to screen for those who will benefit from a full polysomnographic study in a sleep laboratory.

Cough insufficiency may be suspected if the patient describes an inability to bring secretions to the mouth for expectoration or if there is a history of frequent respiratory tract infections. Cough function is best assessed by measuring *peak cough flow* (PCF) rate. This can be easily measured with an asthma peak flowmeter connected to a face mask or mouthpiece (Fig. 97-6). Normal values range from 360 to 960 L/min¹⁶⁷; a value below 160 L/min may place individuals at high risk for cough insufficiency and ventilator dependence.¹⁶¹ During a respiratory tract infection, PCF may drop substantially and a PCF below 270 L/min during a healthy period can drop below 160 L/min during infection. Cough assistance is suggested for those with a PCF below 160 L/min.

Patients with neuromuscular diseases such as ALS frequently develop bulbar muscle dysfunction due to motor neuron involvement in the brain stem. Dysfunction of the lips, tongue, and pharyngeal and laryngeal muscles can result in an increased risk of aspiration as well as difficulty with generating adequate glottic closure for effective cough function. Swallowing may be impaired and ingesting adequate nutrition can be challenging for the patient. Choking is common and may even be triggered by aspiration of saliva. Malnutrition or rapid weight loss should signal the clinician to assess the swallowing mechanism.¹⁶⁸ Swallowing may be tested by barium swallow or direct visualization of swallowing endoscopically.¹⁶⁹⁻¹⁷¹ Referral to a speech and swallowing clinic can be very helpful in diagnosing swallowing and airway protection problems as well as instructing patients and their families in ways to reduce the risk of aspiration.

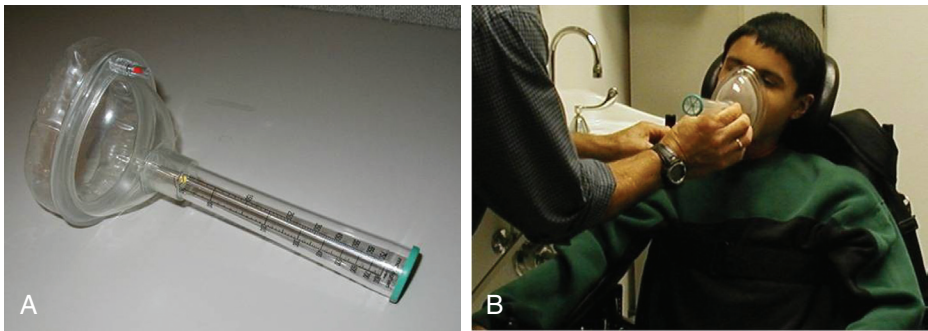


Figure 97-6 Testing of cough function. **A**, Device to measure peak cough flow consists of an asthma peak flowmeter connected to a face mask. **B**, Peak cough flow device being used for measurement in a patient with muscular dystrophy.

Table 97-5 Methods of Ventilation Used in Treatment of Neuromuscular Disease
NEGATIVE-PRESSURE VENTILATORS¹⁷²
Tank ventilator (iron lung)
Raincoat ventilator (poncho or pneumowrap)
Cuirass ventilator (chest shell)
Pneumosuit ventilator with leggings
POSITIVE-PRESSURE VENTILATORS
Invasive (tracheostomy)
Noninvasive
Via full face mask
Via nasal mask
Via mouthpiece
VENTILATORS RESULTING IN PASSIVE MOVEMENT OF THE DIAPHRAGM
Pneumbelt
Rocking bed
PHRENIC NERVE PACING
DIAPHRAGM PACING

VENTILATORY SUPPORT

Ventilatory support for patients with neuromuscular disease has been available for more than 60 years¹⁷² (Table 97-5). Some of the first ventilators were known as body ventilators and included devices such as the iron lung, rocking bed, and pneumobelt.¹⁷³ With the advent of positive pressure via either invasive (tracheostomy) or noninvasive (face mask) ventilation, these body ventilators are used only very rarely, generally for patients who have already been using them for years.

Invasive positive-pressure ventilation using an indwelling tracheostomy has been successfully employed in neuromuscular disease. Benefits of this type of ventilator support include complete control of machine-delivered tidal volume and ease of access to the central airways for suctioning of secretions. In addition, if there is an acute decline in respiratory function, the same method of ventilation can be used for ventilatory support. The development of convenient, portable, positive-pressure generators has made this form of ventilation practical even in the home environment.¹⁷⁴ Invasive positive pressure should be considered in those with (1) coexisting lung disease, (2) copious secretions, (3) poor oropharyngeal muscle strength associated with ineffective clearing of secretions, (4) uncontrolled seizure dis-

orders that can cause upper airway obstruction, (5) a preference for invasive rather than noninvasive methods, (6) orthopedic or other conditions that interfere with placement of noninvasive devices, and (7) limited access to individuals with expertise in noninvasive techniques.

Unfortunately, invasive long-term positive-pressure ventilation via a tracheostomy has been associated with several complications such as damage to the trachea from the indwelling tracheostomy tube leading to tracheal necrosis, stenosis, hemorrhage, or tracheoesophageal fistulas.¹⁷⁵ However, the development of low-pressure, high-volume cuffed plastic tracheostomy tubes has lowered the incidence of these complications. Tracheostomy tubes can interfere with the normal swallowing mechanism and predispose patients to swallowing problems and food aspiration; they can also increase the risk of airway colonization with bacteria and lower respiratory tract infection. The use of a tracheostomy tube requires supplemental humidification, an additional daily respiratory care task. Finally, social interactions and psychological well-being may be impaired by the inability to speak. However, a number of devices and techniques have been designed to allow speech and communication while a patient has a tracheostomy and is mechanically ventilated. These include one-way valves that allow gas to pass through the vocal cords during exhalation (Passy-Muir valve, Irvine, CA) or channels to direct compressed air through the vocal cords (“Trach Talk” tracheostomy tube). Unfortunately, not all individuals can use these devices.

NPPV is becoming the preferred method for treatment of patients with neuromuscular respiratory disease.¹⁷⁶ The noninvasive delivery of positive-pressure ventilation was first used during the polio epidemics of the 1950s to allow patients time outside the iron lung. Since the 1980s, there have been considerable refinements in the application of this technique. There are currently three ways in which NPPV may be delivered: (1) via full face mask, (2) via nasal mask, or (3) via mouthpiece with or without a lip seal (Fig. 97-7). Occasionally, more than one method may be used in the same patient, for instance, a mouthpiece may be used during the day and a nasal mask used at night.

The mouthpiece was the first interface to be used with a positive-pressure ventilator. Patients hold the mouthpiece devices between their teeth and often are able to use them while sleeping, especially when lip seal devices are added.¹⁷⁷ Since the late 1990s, nasal interfaces have been developed and used successfully. Initially, nasal masks were designed to deliver continuous positive airway pressure for the



Figure 97-7 Different means of delivering noninvasive positive-pressure ventilation. **A**, Full mask. **B**, Nasal mask. **C**, Mouthpiece.

treatment of patients with sleep apnea.¹⁷⁸ Currently, they are also used to deliver intermittent positive pressure to patients with neuromuscular disease. Tidal volume is most effectively delivered when there are no leaks around the nasal mask or through the mouth. Patients who experience air leaks may develop oxyhemoglobin desaturation, elevation of arterial PCO_2 , and associated symptoms. In this situation, the use of a full face mask interface may be more appropriate. Using custom-designed appliances also can eliminate leaks via the mouth and may be more comfortable for some patients. Pressure-cycled rather than volume-cycled devices are generally used for mask ventilation. With these machines, positive pressure can be delivered at two levels, a higher level during inspiration and a lower level during expiration (bilevel support, BiPAP). The positive-pressure gradient during inspiration results in delivery of a tidal volume to the patient. Exhalation is passive and is terminated when the airway pressure returns to the lower expiratory level. Maintenance of a positive expiratory pressure is important for two reasons. First, the gas flow needed to maintain end-expiratory positive airway pressure flushes the ventilator tubing of exhaled carbon dioxide and prevents rebreathing.¹⁷⁹ Second, because the expiratory pressure is positive and greater than atmospheric, the end-expiratory lung volume is increased, which may be associated with less atelectasis and fewer areas of low ventilation-perfusion or shunt than seen with low end-expiratory lung volumes.

DATA SUPPORTING NONINVASIVE POSITIVE-PRESSURE VENTILATION IN NEUROMUSCULAR DISEASE

Nocturnal Ventilatory Support

The use of nocturnal ventilation in patients with neuromuscular disease with sleep-disordered breathing has been shown to have a number of benefits, including (1) reduced arterial PCO_2 and increased arterial PO_2 on and off the ventilator, (2) decreased symptoms of sleep-disordered breathing such as morning headache, nocturnal awakenings,

vivid nightmares, and night sweats, (3) improved quality of life, and (4) reduced morbidity and most likely reduced mortality. Nocturnal ventilation has become widely accepted, providing ventilatory assistance for patients while sleeping and allowing them to breathe on their own during the day. In one early study of patients with late-stage Duchenne muscular dystrophy who had symptoms of ventilatory failure and arterial PCO_2 of 60 mm Hg or greater, nocturnal negative-pressure ventilation using cuirass or tank ventilators significantly improved daytime arterial PCO_2 values (60.8 mm Hg before treatment to 45.5 mm Hg after treatment) and arterial PO_2 values (59.3 mm Hg before treatment and 74.6 mm Hg after treatment).¹⁸⁰ Since that 1981 study, a number of studies have been published using nocturnal ventilation that have supported these findings and, 20 years after, an excellent review of these data is available.¹⁸¹

The mechanism by which nocturnal ventilation improves daytime symptoms and arterial blood gases in patients with neuromuscular disease is not entirely clear. A number of explanations have been suggested including (1) resting of chronically fatigued respiratory muscles, (2) reversal of mechanical problems associated with neuromuscular disease such as reduced chest wall and lung compliance, and (3) a resetting of the central respiratory control centers with an increase in chemosensitivity to arterial PCO_2 during the daytime, thus maintaining blood gas homeostasis.¹⁸²⁻¹⁸⁴ In addition to improvement in arterial blood gases, other measures of physiologic function have been shown to improve with intermittent ventilation; for example, nocturnal ventilation can increase vital capacity, improve right heart function, and reduce erythrocytosis.¹⁸⁵

For ethical reasons, the effects of mechanical ventilation on survival generally have not been studied in a randomized controlled fashion in patients with neuromuscular disease. In most progressive neuromuscular diseases, once an elevation in arterial PCO_2 and a decrease in arterial PO_2 are noted, cor pulmonale and death are inevitable within a short period of time. It is therefore generally accepted that mechanical ventilation in the home leads to improved survival in most patients.

Full-time Ventilatory Support

For those who require full-time ventilatory support, it is possible to provide NPPV for 24 hours per day.¹⁸⁶⁻¹⁸⁸ As with nocturnal NPPV for neuromuscular disease, there have been no randomized controlled trials of continuous ventilation. In one cohort study, 24 patients with Duchenne muscular dystrophy using NPPV were compared with 22 patients who received positive-pressure ventilation by tracheostomy.¹⁸⁹ The individuals who used NPPV had significantly fewer hospitalizations and hospital days per year. In another retrospective study by the same group, patients with Duchenne muscular dystrophy using a protocol consisting of mouthpiece positive-pressure ventilation and breath stacking plus mechanical insufflation-exsufflation to assist cough (see [Cough Support](#)) had significantly less mortality (3 of 34 patients) than a group that did not have access to the protocol and either received tracheostomy or used NPPV on a near-continuous basis (27 of 31 patients).¹⁹⁰ Further studies of continuous NPPV are needed to assess whether this treatment is truly better than tracheostomy ventilation in a community setting. A consensus statement of the American Thoracic Society on the respiratory care of patients with Duchenne muscular dystrophy has suggested that NPPV be considered when expertise is available for initiation of appropriate protocols.¹⁹¹

COUGH SUPPORT

Therapeutic interventions aimed at improving cough and airway clearance are equally if not more important than ventilatory support because pneumonia is one of the leading causes of morbidity and mortality in patients with neuromuscular respiratory disease.^{162,176} Normally, the cough reflex is initiated by stimulation of cough receptors in the airways that activate brain stem centers that initiate inhalation, glottic closure, and forceful contraction of expiratory muscles during which intrathoracic air is compressed

under high pressures.¹⁶⁷ The glottis then rapidly opens allowing an explosive release of air from the airways through the vocal cords. The high velocity air flow shears secretions away from the airway walls and propels them out of the lung. Adequate cough is essential for airway hygiene. Fortunately, there are a number of ways that an impaired cough can be augmented and pulmonary hygiene maintained without the use of a tracheostomy.

Manually assisted cough is a method of applying a rapid positive pressure to the abdomen. The increase in abdominal pressure is transmitted to the thorax and induces expiratory flow, leading to airway clearance and enhanced cough expiratory flow rates. A number of techniques are available for an attendant to apply rapid abdominal thrusts, resulting in effective clearance of secretions.¹⁹² Increasing the volume of air in the respiratory system prior to the assisted cough increases the volume available for exhalation, optimizes the length-tension relationship of the expiratory muscles to increase potential intrathoracic pressure generation, and increases the inward elastic recoil pressure of the respiratory system, which can further increase the expiratory pressures. This maximal achievable inspired volume has been labeled the maximal insufflation capacity.¹⁹³ Inspired lung volume can be increased by patients using breath stacking or glossopharyngeal (“frog breathing”) techniques¹⁹⁴ or by use of a resuscitator bag and mouthpiece ([Fig. 97-8A](#)). Breath stacking involves taking multiple breaths to increase lung volumes above the single breath volume, holding each successive breath in the lungs using the glottis. Glossopharyngeal breathing is a form of respiration that involves forcing air into the trachea using the tongue and pharyngeal muscles.¹⁹⁴

Increasing the lung volume to the greatest possible volume, known as lung volume recruitment, by using breath stacking or a mechanical device may help both with cough function as well as maintaining lung compliance and forced vital capacity in progressive neuromuscular disease.^{195,196} A very effective secretion management device,

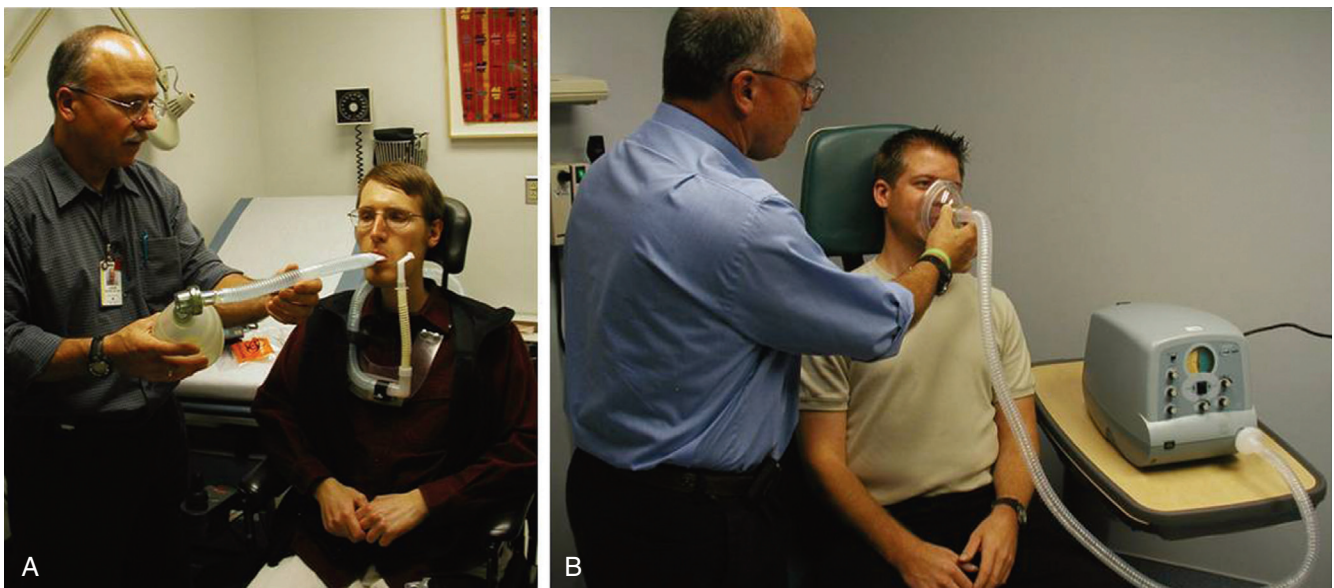


Figure 97-8 Methods to assist cough. **A**, Resuscitator bag used to “stack breaths” to increase lung volume and thereby increase cough flow. **B**, Mechanical insufflator-exsufflator being used to assist in secretion removal.

available for more than 50 years but only recently used to any great extent, is the mechanical insufflator-exsufflator or CoughAssist (In-exsufflator, JH Emerson Co.) (see Fig. 97-8B). This device consists of an electric motor that can generate positive and negative pressures of up to 50 cm H₂O to insufflate and then rapidly exsufflate the lung. The pressure is applied to the patient's airway via a face mask or mouthpiece; first, a positive pressure of 30 to 50 cm H₂O is applied over a 1- to 3-second period followed immediately by a negative pressure of between 30 and 50 cm H₂O for a short duration. By simulating a cough, this technique moves secretions out of the airway noninvasively without violating airway integrity (Video 97-2).¹⁹⁷ Other noninvasive mechanical aids include devices that oscillate the chest wall or airway directly.¹⁹⁸ These have not been well studied in neuromuscular disease patients without tracheostomy and their role in support of secretion management of these disorders is unclear.

The decision to initiate cough assistance is determined by measurement of PCF. Normal values for PCF range from 360 to 960 L/min. It is recommended that one or more of the previously discussed techniques should be made available to the patient when values of PCF fall below 270 L/min while the patient is well, because this correlates with a value of less than 160 L/min when the patient develops a respiratory tract infection.¹⁶¹ This drop in cough function with respiratory illness may be due to increased muscle weakness or to the effects of the secretions themselves in reducing expiratory flow.

Besides problems with cough, patients with neuromuscular disease often have problems with swallowing and airway protection. However, treatments for swallowing muscle dysfunction are limited. The risk of aspiration and development of pneumonia in patients with ALS is due primarily to problems with upper airway function and cough. Pharyngeal and laryngeal muscle dysfunction can lead directly to aspiration of oral contents into the lungs. Other than surgical diversion of the airway,¹⁹⁹ no treatment directly aimed at laryngeal and glottic function is available. When patients develop significant dysphagia and aspiration of solids or liquids, many experts recommend placement of a percutaneous endoscopic gastrostomy tube.^{200,201}

Key Points

- Respiratory failure is a leading cause of morbidity and mortality in individuals with neuromuscular disease.
- Spinal cord injury, a common traumatic injury worldwide, impairs respiratory function depending on the level of spinal injury.
- Acute immune-mediated polyneuropathy (acute idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome) is an ascending paralytic disease thought to be caused by antiglycolipid antibodies. Intubation can be life-saving and should be considered when the FVC is 15 mL/kg or less, the FVC is 1 L or less, or the MIP is 30 cm H₂O or less, or there is a lack of upper airway protection.
- Diaphragm paralysis can be unilateral or bilateral: unilateral disease is most commonly due to injury to the phrenic nerve whereas bilateral disease is most

commonly due to diffuse muscle or motor neuron disease.

- Respiratory assessment of the individual with neuromuscular respiratory impairment should include evaluation of muscle groups responsible for inspiration, expiration and cough, and airway protection.
- Either nocturnal or full-time noninvasive ventilation is now commonly used in chronic neuromuscular respiratory disease and likely prolongs survival.
- Neuromuscular weakness arises commonly in the ICU and results in increased mortality and hospital length of stay.
- Cough can be aided noninvasively by manual or motorized means; cough support should be considered when the peak cough flow rate is less than 270 L/min in a patient without respiratory tract infection and definitely when the peak cough flow rate is less than 160 L/min.

Complete reference list available at ExpertConsult.

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THE RESPIRATORY SYSTEM AND CHEST WALL DISEASES

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OBESITY

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INTRODUCTION

Disorders of the soft tissue and bony structures of the chest wall generally cause restrictive dysfunction by limiting motion or causing disordered movement of the chest wall. Kyphoscoliosis and ankylosing spondylitis are disorders that involve the spine and its articulations, pectus excavatum involves the sternum, flail chest affects the ribs, and obesity adds to the soft tissues of the rib cage and abdomen. Kyphoscoliosis has the most severe impact on respiratory function and pectus excavatum the least. Alterations in respiratory mechanics produced by these disorders are discussed in concert with the most recent developments in diagnosis and treatment. Neuromuscular diseases that affect the chest wall are reviewed in Chapter 97.

KYPHOSCOLIOSIS

DIAGNOSIS AND ETIOLOGY

The term *kyphoscoliosis* is derived from the Greek words *kuphos* and *scolios* (“humpback” and “crooked”) and refers to a group of disorders characterized by excessive spinal curvature in the lateral plane (scoliosis) and sagittal plane (kyphosis) as well as rotation of the spinal axis (Fig. 98-1). Scoliosis, which is defined as a lateral spinal curvature greater than 10 degrees, is generally associated with kyphosis and rotation of the spine around its long axis.¹ First described in detail by Hippocrates, kyphoscoliosis is one of the most common abnormalities of the spine, with an estimated prevalence for mild deformity of 1 in 1000 people and for severe deformity of 1 in 10,000 people in the United States.¹

Kyphoscoliosis is classified as idiopathic (no known cause), secondary or paralytic (associated with neuromuscular disease), and congenital (associated with vertebral malformation present at birth) (Table 98-1). Idiopathic kyphoscoliosis, the most common form, usually manifests in late childhood or early adolescence and involves females more often than males with a ratio of 4:1. Idiopathic kyphoscoliosis is often seen in multiple members of one

family. It is believed to be a multigene condition, with autosomal or sex-linked inheritance with variable phenotypic expression.¹ A defect in the chromatin-remodeling gene family, *CHD7*, and several other genetic loci have been associated with susceptibility to idiopathic kyphoscoliosis.^{2,3} The most important sequelae of progressive kyphoscoliosis are back pain, psychosocial problems, and development of respiratory failure.

The diagnosis of kyphoscoliosis is made by examining the chest wall. In severe cases, typical physical findings are the dorsal hump, which is due to angulated ribs and shoulder asymmetry, and the hip tilt, which is related to spinal rotation. In mild cases, the physical findings are more subtle. In children and adolescents, it is important to inspect the spine for asymmetry and to perform the Adam forward bend test. With this test, the examiner inspects the spine for thoracic or lumbar asymmetry while the patient bends forward at the waist until the spine becomes parallel to the floor. The Adam forward bend test can be used by community programs to screen for idiopathic kyphoscoliosis. When kyphoscoliosis is severe and complicated by right heart failure, clinical examination may reveal cyanosis, distended neck veins, peripheral edema, and hepatomegaly.

The diagnosis of kyphoscoliosis is confirmed by obtaining radiographs of the chest or spine. The severity of the spinal deformity can be assessed by measuring the Cobb angle of the vertebrae located within the spinal curvature.⁴ The Cobb angle is formed by the intersection of two lines, one parallel to the top and the other parallel to the bottom vertebrae of the scoliotic or kyphotic curves (Fig. 98-2). The greater the Cobb angle, the more severe the deformity. Angles greater than 100 degrees are usually associated with respiratory symptoms such as dyspnea on exertion, and angles greater than 120 degrees with respiratory failure.^{5,6}

PATHOPHYSIOLOGY

Pulmonary Function and Respiratory Mechanics

Kyphoscoliosis can produce the most severe restrictive impairment of all chest wall diseases (Table 98-2).⁷⁻¹⁰ A

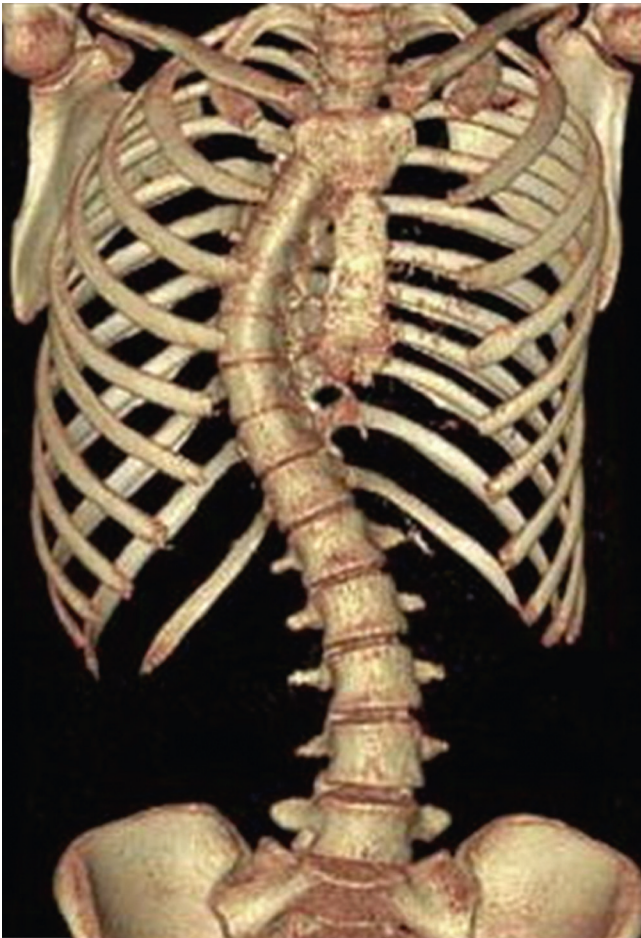


Figure 98-1 Kyphoscoliosis. Chest CT reconstruction showing the rotation of the spine and rib cage in kyphoscoliosis. (Adapted from Chun EM, Suh SW, Modi HN, et al. The change in ratio of convex and concave lung volume in adolescent idiopathic kyphoscoliosis. *Eur Spine J* 17:224–229, 2008).

number of factors contribute to the severity of the restrictive impairment. With idiopathic kyphoscoliosis, restrictive lung physiology is invariably present when the Cobb angle is greater than 90 degrees.⁸ With such severe deformity, *total lung capacity* (TLC) and *vital capacity* (VC) may be reduced to as low as 30% of predicted values. In contrast, *residual volume* (RV) may be normal or slightly increased, resulting in an elevated RV/TLC ratio.^{8,11} In children with severe spinal deformity, hypoplastic lung may contribute to reduced lung volumes.^{12,13} Other factors contributing to the restrictive process include the number of vertebrae involved, thoracic location of the curve, patient age, presence of kyphosis, degree of spinal rotation, and presence of weak respiratory muscles.^{14,15}

The etiology of the kyphoscoliosis also influences the degree of respiratory impairment for any given Cobb angle. For example, in idiopathic kyphoscoliosis, those with Cobb angles less than 50 degrees usually have normal respiratory muscle strength whereas those with angles greater than 50

Table 98-1 Causes of Kyphoscoliosis

IDIOPATHIC

Multigene disorder, developing by childhood/adolescence

PARALYTIC OR SECONDARY

Neuromuscular (poliomyelitis, muscular dystrophy, cerebral palsy, Friedreich ataxia, Charcot-Marie-Tooth disease)

Disorders of connective tissue (Marfan syndrome, Ehler-Danlos syndrome, Morquio syndrome)

Vertebral disease (osteoporosis, osteomalacia, vitamin D-resistant rickets, tuberculous spondylitis, spina bifida)

Post-thoracoplasty

CONGENITAL

Due to spinal/vertebral malformations at birth

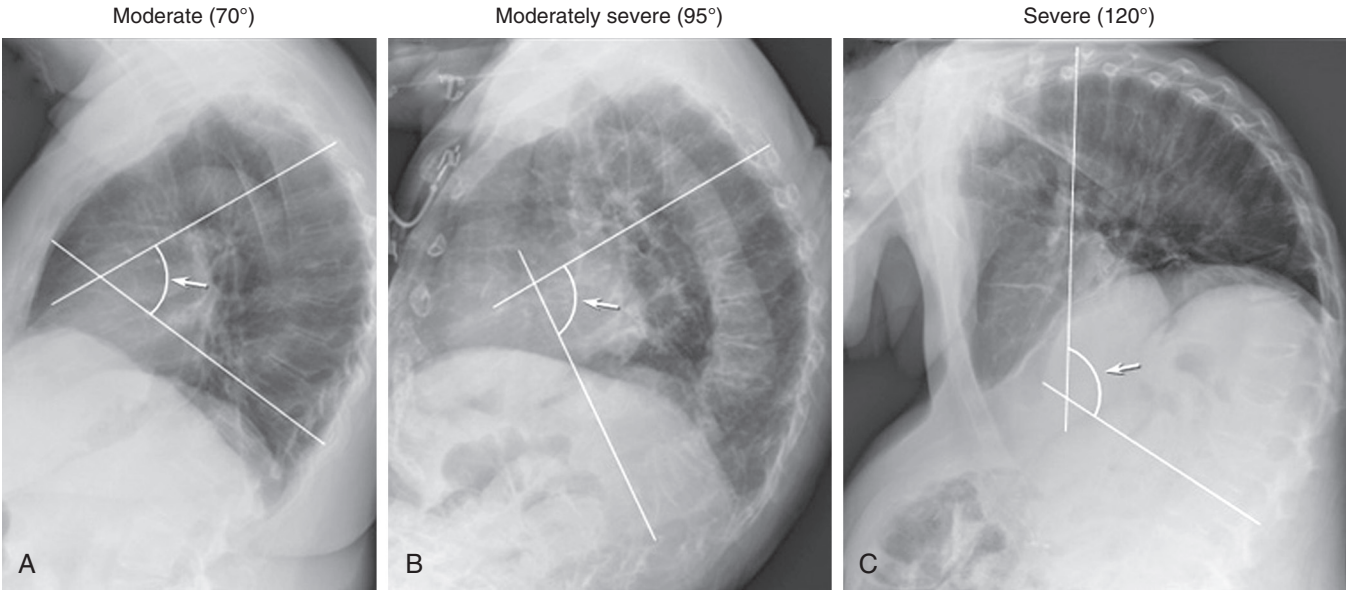


Figure 98-2 Different degrees of kyphoscoliosis showing the calculation of the Cobb angle on the lateral chest radiograph. Lines are drawn through the superior end plate of the vertebral body marking the cranial portion of the curve and the inferior end plate of the vertebral body marking the caudal portion of the curve. The angle of intersection between these two lines is the Cobb angle (arrow). Patients are shown with moderate (A), moderately severe (B) and severe (C) kyphoscoliosis along with their calculated Cobb angles. (Courtesy Michael Gotway, MD.)

degrees may show mild to moderate reductions in *maximal inspiratory pressure* (PI_{max}) and *maximal expiratory pressure* (PE_{max}) due to either respiratory muscle weakness or altered mechanical advantage of the muscles.^{14,16-18} In comparison, individuals with secondary (paralytic) kyphoscoliosis also have primary respiratory muscle weakness and therefore may have a profound degree of pulmonary restriction, even when the Cobb angle is less than 50 degrees.¹⁹ In general, perhaps because of this primary involvement of the respiratory muscles, individuals with paralytic kyphoscoliosis have a greater restrictive defect for a given degree of spinal deformity than those with idiopathic kyphoscoliosis.²⁰ Likewise, compared to those with idiopathic kyphoscoliosis, individuals with congenital kyphoscoliosis tend to have a greater restrictive impairment for a comparable degree of spinal deformity.²⁰ In general, in congenital kyphoscoliosis, the loss in VC is 15% greater than in patients with idiopathic kyphoscoliosis and a similar Cobb angle, most likely due to associated rib deformities and underlying lung abnormalities.²⁰

Table 98-2 Representative Values for Pulmonary Function and Respiratory Mechanics in Chest Wall Diseases

Parameter	KS	Post-Thor	PE	AS
TLC (% pred)	45	65	90	85
VC (% pred)	30	50	90	80
RV (% pred)	95	90	100	100
FEV ₁ (% pred)	40	40	95	80
FEV ₁ /FVC	80	60	80	75
CRS (% pred)	50	50	—	70
CCW (% pred)	30	40	—	60
CL (% pred)	60	50	80	80
PI_{max} cm H ₂ O	40	50	90	80
MVV L/min	37	37	107	80

AS, ankylosing spondylitis; CCW, compliance of chest wall; CL, compliance of lungs; CRS, compliance of respiratory system; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; KS, kyphoscoliosis; MVV, maximum voluntary ventilation; PE, pectus excavatum; PI_{max} , maximum inspiratory pressure; Post-Thor, post-thoracoplasty; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

Representative values are from Bergofsky EH: Thoracic deformities. In Roussos C, editor: *The thorax*. New York, 1995, Dekker, pp 1915–1949.

Respiratory system compliance is reduced in kyphoscoliosis of any etiology, primarily due to the reduction in chest wall compliance and, to a lesser degree, a reduction in lung compliance due to microatelectasis.^{1,9,21,22} Cobb angles up to 50 degrees have minimal impact on respiratory compliance, whereas angles greater than 100 degrees may reduce compliance to levels seen in the adult respiratory distress syndrome.^{9,21,22} The stiff chest wall reduces the *functional residual capacity* (FRC). These factors combine to move the tidal breathing to a flatter, stiffer portion of the respiratory volume-pressure curve. This requires greater inspiratory effort for relatively small tidal breaths, which increases the work and oxygen cost of breathing (Fig. 98-3). The increase in the oxygen cost of breathing may reach values three to five times those measured in healthy individuals and thus place patients at risk for respiratory muscle fatigue.²³

Exercise Capacity

Those with mild idiopathic kyphoscoliosis usually have normal exercise capacity.^{14,24} If exercise is limited, it is typically due to deconditioning rather than diminished ventilatory reserve.^{17,24,25} In contrast, individuals with *moderate* idiopathic kyphoscoliosis (Cobb angles 25 to 70 degrees), *moderately severe* kyphoscoliosis (Cobb angles 70 to 100 degrees), or *severe* kyphoscoliosis (Cobb angles greater than 100 degrees) may have exercise limitation due to ventilatory constraints.^{17,25,26} With severe deformities (Cobb angles greater than 100 degrees), cardiovascular factors may further contribute to exercise limitation.^{25,27} Supplemental O₂ may improve oxygenation during exercise but usually does not affect walk distance.

Control of Breathing and Sleep-Disordered Breathing

The disordered chest wall geometry in patients with kyphoscoliosis constitutes an elastic load placed on the inspiratory muscles. To compensate for this increased load, these individuals adopt a rapid shallow breathing pattern consisting of low *tidal volumes* (V_T) and shortened *inspiratory time* (T_i).^{8,28} This breathing pattern reduces the *pressure needed to inhale* (P_{breath}) and minimizes the work per breath, thereby lowering the risk for developing respiratory muscle fatigue. Both parameters of rapid shallow breathing, V_T and T_i , decrease as the Cobb angle increases.²⁸ However, rapid

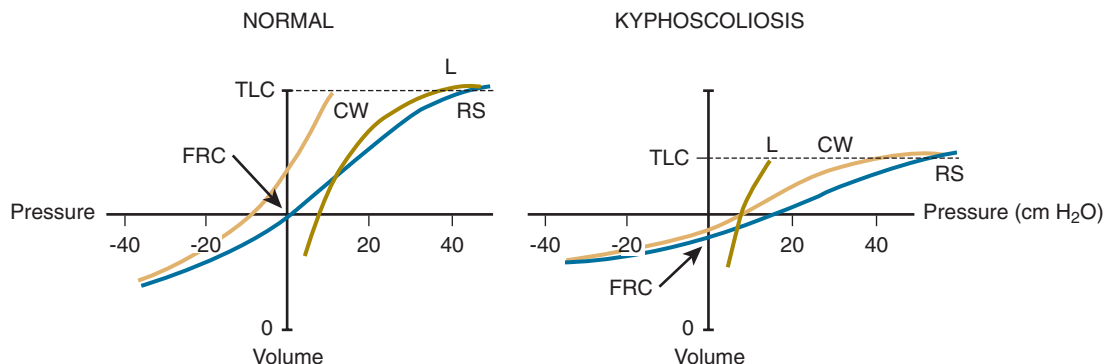


Figure 98-3 Schematic illustration of alterations in the volume-pressure relationship of the lung (L), chest wall (CW), and total respiratory system (RS) in kyphoscoliosis. In kyphoscoliosis, the chest wall is less compliant, leading to a reduction in functional residual capacity (FRC), and tidal breathing takes place on a flatter portion of the respiratory system volume-pressure curve. TLC, total lung capacity.

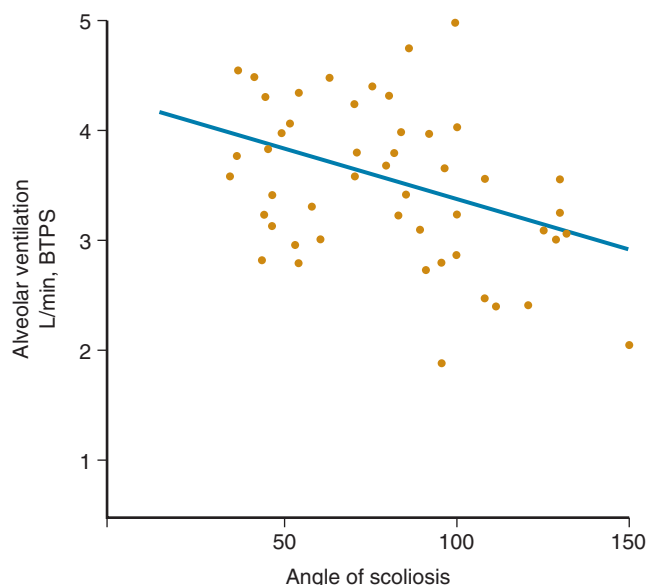


Figure 98-4 Idiopathic kyphoscoliosis. The relationship between alveolar ventilation and angle of scoliosis in patients with idiopathic kyphoscoliosis. (Adapted from Kafer ER: Idiopathic scoliosis. Gas exchange and the age dependence of arterial blood gases. *J Clin Invest* 58:825–833, 1976.)

shallow breathing has the negative consequence of increasing dead space ventilation and promoting microatelectasis. As an additional compensatory mechanism, patients with increased elastic load also increase neural drive to the respiratory muscles. Indirect evidence for this compensatory strategy is the elevated mouth occlusion pressure at 100 ms ($P_{0.1}$) seen during quiet breathing, exercise, or breathing stimulated by hypercapnia.^{28,29} As the degree of kyphoscoliosis increases, the neural output to the respiratory muscles increases. That is, $P_{0.1}$ correlates positively with the Cobb angle in these patients.²⁸ The increase in neural drive does not necessarily translate into increased minute ventilation because of the mechanical constraints imposed by the stiffened chest wall.

Hypoventilation is the most common sleep-related breathing disorder affecting individuals with kyphoscoliosis (Fig. 98-4). Hypoventilation results in hypercapnia and hypoxemia and is most severe during REM sleep when there is a reduction in neural drive to the respiratory muscles.^{30,31} Nocturnal hypoxemia typically predates the onset of respiratory failure in these patients and significantly impacts the clinical course and quality of life of patients with kyphoscoliosis.^{5,31} Adverse sequelae of nocturnal hypoxemia and hypercapnia include respiratory muscle dysfunction, persistent hypercapnia and hypoxemia, pulmonary vascular remodeling, pulmonary hypertension, and ultimately cardiorespiratory failure and death.³¹ Of note, the Cobb angle does not correlate with the magnitude of nocturnal oxyhemoglobin desaturation. Accordingly, it is important to screen for nocturnal hypoventilation with overnight oximetry even in patients with only moderate spinal deformity.³² Obstructive sleep apnea may be seen with a frequency similar to that in the general population and, if present, can further aggravate nocturnal hypoventilation.³³ Because sleep-related abnormalities and their effects on cardiorespiratory function are potentially treatable, they should always be evaluated in patients with kyphoscoliosis well in

advance of development of daytime hypercapnia so that noninvasive ventilation can be instituted early.^{31,33}

CLINICAL COURSE

The etiology of kyphoscoliosis is a major determinant of the clinical course.^{6,34} Idiopathic kyphoscoliosis has the most benign clinical course. Secondary kyphoscoliosis may progress rapidly, largely dependent on the underlying cause of neuromuscular weakness and age of onset of the spinal deformity. An early age of onset with rapid curve progression during growth and progression after skeletal maturity increase one's risk for serious respiratory complications.^{34,35} Congenital kyphoscoliosis may also progress rapidly.

In mild idiopathic kyphoscoliosis, the probability of developing respiratory failure with aging is similar to that in a healthy population. However, the risk is higher for patients with moderate or severe deformities. Large spinal curves at presentation, skeletal immaturity, and a thoracic, as opposed to a thoracolumbar or lumbar, location of the curve apex are generally considered risk factors for curve progression.⁶ The presence of respiratory muscle weakness enhances the likelihood of developing respiratory failure.⁸ In general, the spinal deformity worsens at a rate of about 1 degree per year in individuals with thoracic deformities greater than 50 degrees at skeletal maturity.³⁶

Individuals with severe idiopathic kyphoscoliosis and Cobb angles around 100 degrees should be monitored closely for respiratory complications, especially if they are middle-aged or older. Initially, individuals may experience dyspnea only with exertion but, as they age and the spinal deformity progresses, they may develop dyspnea even at rest. Cardiopulmonary problems and psychosocial concerns develop at a variable rate.⁶ When cor pulmonale develops, the prognosis is poor and, without therapy, death may supervene within one year. In addition to the degree of chest wall deformity, other factors that contribute to ventilatory failure in patients with idiopathic kyphoscoliosis are inspiratory muscle weakness, sleep-disordered breathing, and airway compression due to distortion of the lung parenchyma and twisting of airways. When respiratory failure develops in a patient with kyphoscoliosis and a Cobb angle less than 100 degrees, other causes for respiratory failure should be sought, particularly treatable causes such as sleep disordered breathing.

TREATMENT

Medical Treatment

General supportive measures include immunizations against influenza and pneumococci, smoking cessation, maintenance of a normal body weight, supplemental oxygen, and prompt treatment of respiratory infections. Physical activity should be encouraged to minimize deconditioning. Orthopedic braces have been used in skeletally immature patients with idiopathic kyphoscoliosis in an effort to prevent or correct the spinal deformity. A brace is generally recommended for growing children with angles between 25 and 40 degrees.^{37,37a}

Noninvasive nocturnal ventilation constitutes a major advance in the treatment of individuals with severe

kyphoscoliosis. Indications for instituting noninvasive nocturnal ventilation include symptoms suggestive of nocturnal hypoventilation or signs of cor pulmonale with either an elevated daytime arterial PCO_2 or nocturnal oxygen saturation less than 88% for 5 consecutive minutes (Table 98-3).³⁸ Either pressure or volume preset ventilators are effective in providing noninvasive ventilation.³⁹ Supplemental oxygen is indicated if hypoxemia persists despite correction of hypoventilation. For chronic respiratory failure, chest physiotherapy, bronchodilators, and diuretics may be needed in addition to noninvasive positive pressure ventilation. In those intolerant of noninvasive ventilation or unable to manage excessive bronchial secretions, tracheostomy constitutes another option.³⁹

The benefits of noninvasive ventilation are well established and include improvements in gas exchange, hemodynamic parameters, sleep architecture, quality of life, and perhaps survival (Table 98-4).^{39,40} Long-term noninvasive ventilation has been shown to reduce the number and duration of hospitalizations⁵ and possibly increase survival, although this evidence is not yet supported by randomized controlled studies.^{42,43} Interestingly, noninvasive ventilation does not appear to improve respiratory muscle strength or endurance; instead, noninvasive ventilation may improve respiratory failure by enhancing central chemosensitivity to carbon dioxide.⁴¹

Table 98-3 Indications for Instituting Long-Term Noninvasive Ventilation for Kyphoscoliosis (and other Chest Wall Diseases)

Symptoms (e.g., fatigue, morning headaches, dyspnea) or signs of cor pulmonale and one of the following:
 Daytime arterial $\text{PCO}_2 \geq 45$ mm Hg
 Nocturnal oxygen saturation $< 88\%$ for > 5 consecutive minutes
 Progressive neuromuscular disease with $\text{P}_{\text{Imax}} < 60$ cm H_2O or $\text{FVC} < 50\%$ of predicted

FVC, forced vital capacity; P_{Imax} , maximal static inspiratory pressure.
 Adapted from Consensus Conference: Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. *Chest* 116:521–534, 1999.

Table 98-4 Benefits of Noninvasive Nocturnal Ventilation in Chest Wall Diseases

GAS EXCHANGE

Increased arterial PO_2
 Decreased arterial PCO_2

HEMODYNAMICS

Decreased pulmonary arterial pressure
 Improved right ventricular function

MECHANICS

Reduced work of breathing
 Increased maximal inspiratory pressure (P_{Imax})

SLEEP HYGIENE

Normalized sleep patterns
 Fewer apneic episodes

OUTCOME

Fewer hospitalizations
 Improved quality of life
 Relief of dyspnea
 Possible increased survival

Surgical Treatment

In general, surgery involves fusion of the affected vertebral bodies via the posterior approach and the use of devices such as rods, wires, hooks, and pedicle screws to support the spine. This approach, which has seen significant advances since the initial introduction of implantable Harrington rods in the 1960s, allows for multiplanar correction, stable fixation with less spinal fusion, and early postoperative mobilization without a cast or brace.⁶ Newer nonfusion techniques use growth-friendly rods such as expandable spinal rods, titanium rib implants, or remotely operated magnetic growth rods.^{44,45} Surgery is currently recommended in individuals with skeletal immaturity and a Cobb angle greater than 45 degrees.³⁷

The benefits of spinal surgery on pulmonary function remain unclear.^{46,47} Immediately following surgery, pulmonary function may be impaired due to rib cage trauma and changes in the chest wall caliber.²¹ In the long-term, pulmonary function is more likely to improve in young children and adolescents than in adults. In the absence of randomized controlled studies assessing the efficacy of surgery, the overall role of surgical management in restoring function and minimizing the possibility of respiratory failure is not clear.^{6,48,49}

THORACOPLASTY

Before the advent of effective antituberculosis chemotherapy, thoracoplasty was commonly employed to reduce lung volume as a way to control pulmonary tuberculosis. Thoracoplasty reduced lung volume using a variety of means: removing or fracturing ribs (Fig. 98-5), resecting the phrenic nerve, or filling the pleural space with foreign material (i.e., Lucite spheres [Fig 98-6], oil [Fig. 98-7], and ping



Figure 98-5 Thoracoplasty. Frontal chest radiograph in a patient with history of prior *Mycobacterium tuberculosis* infection shows extensive deformity of the left hemithorax consistent with prior thoracoplasty. Scoliosis of the thoracic spine is probably secondary to the chest wall deformity.

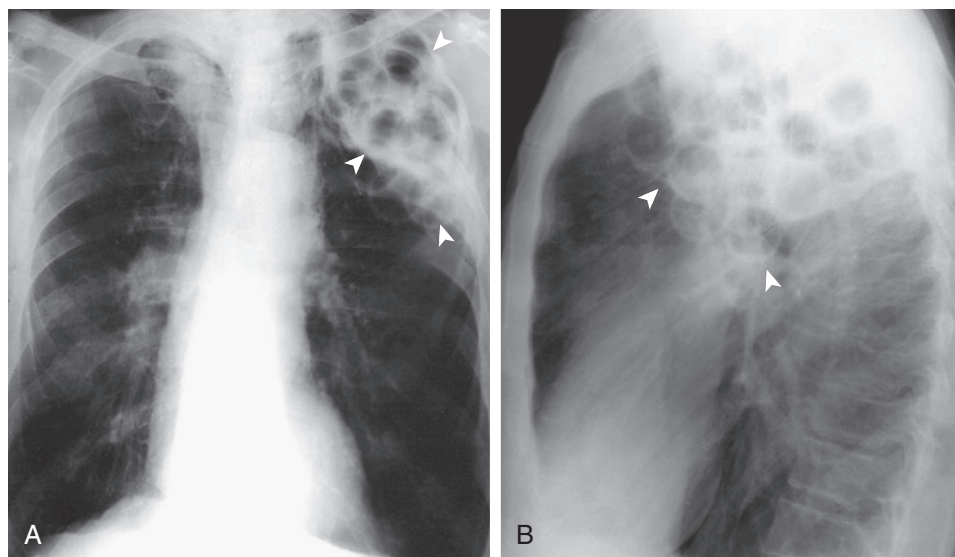


Figure 98-6 Lucite sphere plombage. Frontal (A) and lateral (B) chest radiographs show regular lucencies (arrowheads) representing Lucite sphere plombage in a patient with prior left upper lobe *Mycobacterium tuberculosis* infection. (Courtesy Michael Gotway, MD.)

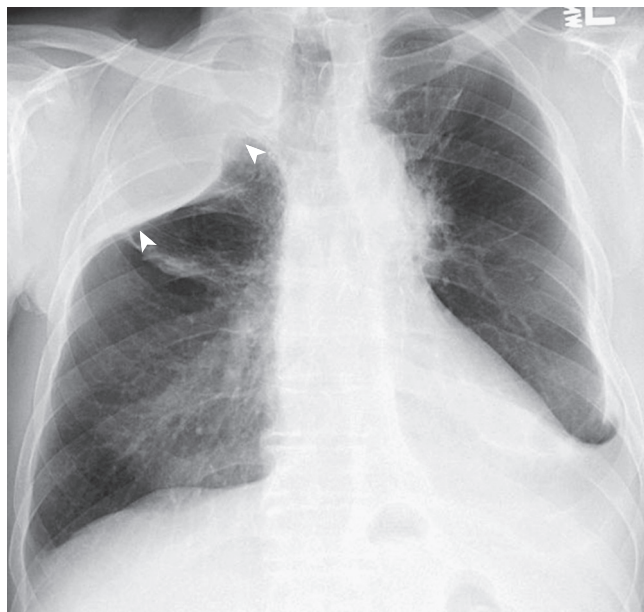


Figure 98-7 Oleothorax. Frontal chest radiograph shows a homogeneous right upper thoracic opacity (arrowheads) representing extraparenchymal oil injection as a form of pulmonary collapse therapy in a patient with *Mycobacterium tuberculosis* infection. (Courtesy Michael Gotway, MD.)

pong balls). Severe restrictive impairment may manifest itself decades after the procedure; after several years without symptoms, individuals may become dyspneic, initially with exertion and then at rest, and may eventually develop chronic respiratory failure. Factors such as slowly progressive kyphoscoliosis, in part, account for the delay in the onset of symptoms. The severity of the restrictive defect, which can be similar to that seen in kyphoscoliosis (see Table 98-2), may be due to a reduction in respiratory system compliance, fibrothorax, lung resection, phrenic nerve damage, scoliosis, and lung fibrosis related to prior underlying granulomatous disease.^{50,51}

Since this procedure was abandoned for tuberculosis therapy after the 1950s, very few post-thoracoplasty

patients are alive today.^{50,51} However, knowledge of the sequelae of thoracoplasty is of more than historical interest. Thoracoplasty is occasionally still performed to treat bronchopleural fistulas that have failed to close following decortication or persistent empyema in which decortication is not feasible or has failed to eradicate the infection.⁵² Surgery similar to thoracoplasty includes aggressive surgery on the rib cage, as may be performed to resect tumors.⁵³ Such surgeries may stiffen the chest wall and lead to an increase in the work of breathing, impaired gas exchange, and ultimately cor pulmonale. As with severe kyphoscoliosis, the treatment consists of oxygen, antibiotics when appropriate, and noninvasive nocturnal mechanical ventilation. Patients undergoing extensive chest wall surgery of any type should have their pulmonary function monitored periodically.

PECTUS EXCAVATUM

DIAGNOSIS AND ETIOLOGY

Pectus excavatum is a common congenital chest wall deformity characterized by excessive depression of the sternum and its adjacent costal cartilages (Fig. 98-8).⁵⁴ It is the most common chest wall deformity, seen in approximately 0.5% to 2% of the population, more frequently in males than in females (ratio 4:1).^{54,55} Diagnosed by inspecting the rib cage, pectus may be apparent in infancy but, in most cases, becomes noticeable at puberty.

Pectus excavatum may result from abnormal cartilage growth displacing the sternum inward.⁵⁵ A genetic predisposition is supported by a large study in which 43% of patients with this deformity gave a family history of pectus excavatum.⁵⁶ Approximately 6% of patients have a connective tissue disorder such as Marfan or Ehlers-Danlos syndromes, and 40% to 60% have scoliosis.⁵⁷ Congenital heart disease may coexist in roughly 2% of cases.^{54,55}

The magnitude of sternal deformity is best assessed by computed tomography (CT) of the chest. The transverse (Tr)

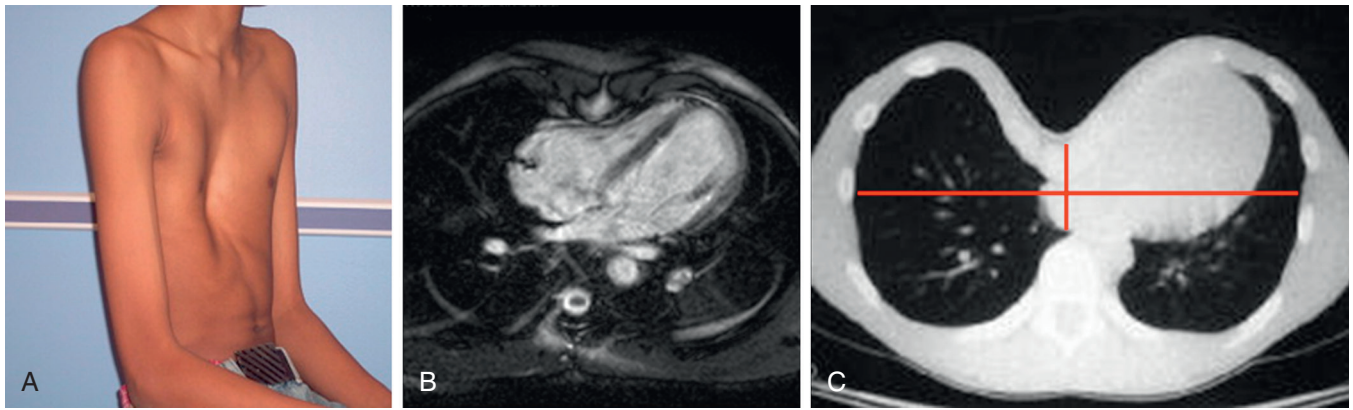


Figure 98-8 Pectus excavatum. **A**, Individual with severe pectus excavatum deformity. **B**, MR imaging of the same individual showing compression of the right ventricle by the deformity. **C**, The Haller index is calculated on chest CT images by the ratio of the transverse diameter and the anteroposterior diameter of the rib cage at the level of the deepest sternal depression. In this patient, the Haller index is 4.8.

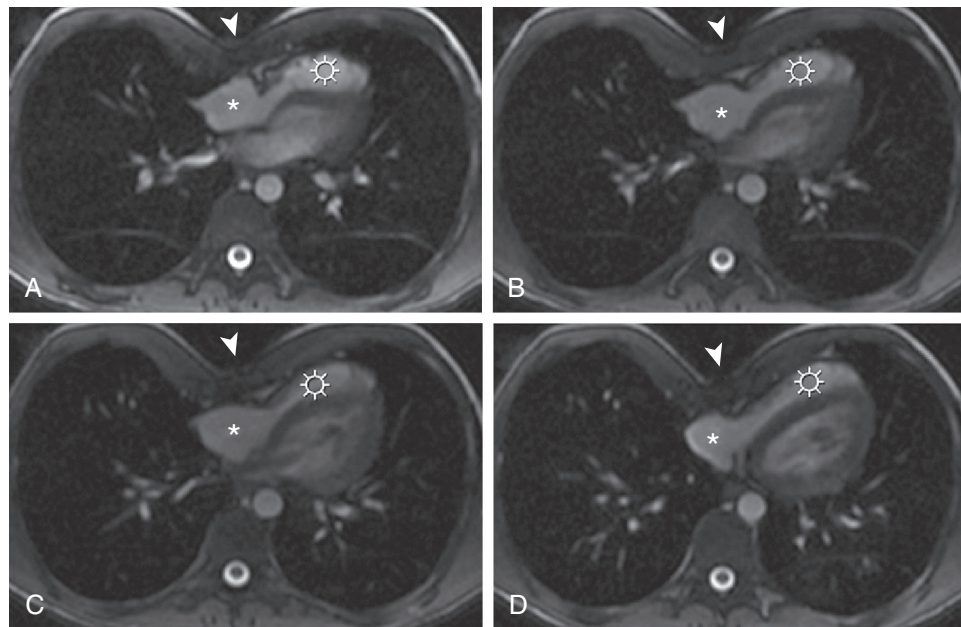


Figure 98-9 Pectus excavatum with right ventricular compression. Sequential steady-state free-precession axial MR images show right ventricular compression by the sternum (arrowheads) induced by the pectus deformity (* = right atrium, ⊙ = right ventricle). Images **A** through **D** were taken at different times in the cardiac cycle. (Courtesy Michael Gotway, MD.)

and anteroposterior (AP) diameters of the rib cage are measured at the level of the deepest sternal depression. The normal Tr/AP ratio, also known as the Haller index, is 2.5 or less (see Fig. 98-8). A Haller index of greater than 3.25 indicates a significant pectus deformity that may need surgical correction.⁵⁸ Individuals with a significant deformity commonly have cosmetic complaints and, in addition, 30% to 70% of individuals may complain of exercise limitation or dyspnea with exertion, often out of proportion to recognized abnormalities in cardiopulmonary function.

PATHOPHYSIOLOGY

Respiratory Mechanics and Exercise Capacity

Most patients with pectus excavatum have normal pulmonary function with a normal mobility of the rib cage.^{59,60}

Occasionally, patients will have a mild restrictive deficit,^{55,57} often when there is concomitant scoliosis.⁶¹ Cardiopulmonary exercise testing is usually normal, although those with the most severe deformities may exhibit a mild reduction in maximal work rate and oxygen consumption.^{62,63} Although the concept is not widely accepted, right ventricular compression by the depressed sternum (Fig. 98-9 and Video 98-1) may be a mechanism contributing to exercise limitation in some individuals.⁶⁴

TREATMENT

Surgical correction of pectus excavatum is usually considered for patients with a Haller index greater than 3.5 in conjunction with symptoms or evidence of cardiac or pulmonary impairment.^{55,65,65a} The modified Ravitch procedure consists of resection of costal cartilage and a sternal

osteotomy, with or without fixation of the sternum by external or internal supports.⁵⁸ The less invasive Nuss procedure entails placing a curved metal rod under the sternum through small incisions on each side of the rib cage. The rod is rotated under the sternum forcing and holding it outward; the rod is removed after 2 to 4 years once the sternum is stabilized in its proper position.⁶⁶ The rate of complications does not differ significantly between these surgical approaches.⁶⁷ Another minimally invasive procedure under investigation uses magnets to pull out the sternum and correct the deformity gradually, in a fashion analogous to that of braces, which gradually correct the position of teeth.⁶⁸ Complications of procedures that involve cartilage resection include sternal necrosis, infection, or recurrence of the deformity. With corrective procedures, improvement of symptoms and function is difficult to predict. To date, there is no convincing evidence that correction of the deformity improves either cardiopulmonary function or exercise capacity.⁶⁹⁻⁷¹

FLAIL CHEST

DIAGNOSIS AND ETIOLOGY

Flail chest arises when a segment of the rib cage moves inward rather than outward during inspiration⁷² (Video 98-2). Production of a flail segment of chest wall requires multiple rib fractures, specifically double fractures of three or more contiguous ribs or combined sternal and rib fractures, to uncouple the segment from the surrounding chest wall. An unstable segment of the chest wall can also result from multiple single rib fractures along a straight line that partially uncouples the segment from the surrounding chest wall. This condition is referred to as “nonintegrated chest wall” rather than “flail chest.”⁷³

The most common cause of flail chest is blunt chest trauma.⁷² Flail chest is most commonly seen after automobile accidents and falls, although it may also develop after aggressive cardiopulmonary resuscitation or in patients with pathologic rib fractures.^{74,75} In children, flail chest is infrequent because the chest wall is more compliant; thus, when a child does have a flail chest, it signifies a much greater degree of trauma.⁷⁶ Rarely, flail chest may complicate corrective rib resection or appear in neonatal life due to congenital rib abnormalities.^{77,78}

The diagnosis of flail chest is made by examining the rib cage and noting the characteristic paradoxical movement of a chest wall segment inward rather than outward during inspiration (and outward rather than inward during expiration) with spontaneous breathing (Fig. 98-10 and see Video 98-2). In subtle cases, the paradoxical motion of the flail chest can be appreciated by palpation of the chest wall. Chest radiographs may confirm the presence of multiple rib fractures; however a three-dimensional reconstruction of a chest CT is a more sensitive technique for identifying rib fractures and the other pulmonary injuries, such as pulmonary contusion or hemothorax related to chest wall trauma.⁷⁹ In the mechanically ventilated trauma patient, the diagnosis of flail chest may be delayed for days or even weeks and become apparent only after withdrawal of sedation and resumption of spontaneous breathing.⁸⁰

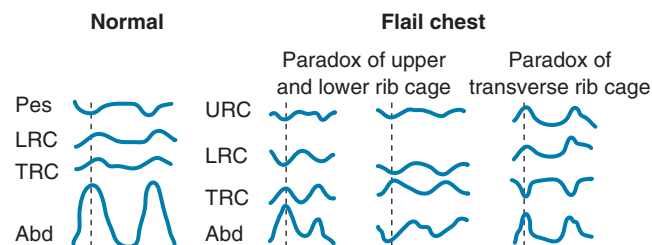


Figure 98-10 Flail chest. Tracings derived from magnetometers depict normal and different patterns of chest wall motion seen in two patients with flail chest. In each patient, at the point of maximal inspiration (dotted line), a portion of the rib cage moves paradoxically. In the patient with a paradox of the upper rib cage (URC) and lower rib cage (LRC), the URC and LRC segments move inward (downward tracing) with outward movement of the abdomen and transverse rib cage (TRC). In the patient with a paradox of the transverse rib cage, the TRC is the only segment moving inward with inspiration. (Modified from Tzelepis GE, McCool FD, Hoppin FG Jr: Chest wall distortion in patients with flail chest. *Am Rev Respir Dis* 140:31–37, 1989.)

TRAUMA AND FLAIL CHEST

The presence of flail chest following trauma signifies severe thoracic injury and is an independent risk factor for respiratory complications, respiratory failure, and death.^{76,81,82,82a} Patients with flail chest may have pulmonary complications such as lung contusion, pneumothorax, or hemothorax.^{76,81,82} Flail chest and its associated pain promote atelectasis, impair cough, and may lead to respiratory failure. Patients with flail chest are twice as likely to develop respiratory failure and require mechanical ventilation as patients with isolated lung contusion.^{76,82}

The presence of flail chest is thus associated with a poor prognosis and should alert the clinician that there may be traumatic injury to other organs. The presence of flail chest is a marker of increased mortality both in patients with isolated chest wall trauma and in patients with multiple sites of trauma. Without flail chest, mortality from chest wall trauma ranges from 7% to 14%; with concomitant flail chest, mortality increases further.^{76,82} Similarly, in patients with multiple sites of trauma, mortality is roughly 30%; in those with concomitant flail chest, mortality may be as high as 68%.^{76,82} The high mortality associated with flail chest is in part due to coexistence of other injuries such as fractures of long bones or vertebrae, head trauma, rupture of major vascular structures, or laceration of abdominal organs. Concomitant head injury and age older than 65 years are particularly poor prognostic factors in patients with traumatic flail chest.^{81,83} In patients who survive the acute injury, chronic disability related to flail chest may develop, with chest tightness, chest pain, or dyspnea on exertion. However, with operative fixation of the flail segment even years after the injury, these symptoms can improve dramatically.^{80,84}

PATHOPHYSIOLOGY

Respiratory Mechanics

Flail chest disrupts the anatomic and functional integrity of the chest wall and can seriously alter its function. With flail chest, a segment of the chest wall is uncoupled from the forces that expand the rib cage. Consequently, this

uncoupled segment moves passively with the variations of pleural pressure. With inspiration and the decrease in pleural pressure, the flail segment moves inward and, during expiration with less negative pleural pressure, it moves outward. If the normal swings in pleural pressure are amplified by a decrease in lung compliance due to concomitant pulmonary contusion and/or atelectasis, the paradoxical motion of the flail segment can increase.

The location of the flail segment is dependent on the site of rib fractures. The most common location is the lateral rib cage. However, for any flail segment, one may see different patterns of movement. For example, motion may be paradoxical within the rib cage itself or between the rib cage and the abdomen (see Fig. 98-10).⁸⁵ The degree of paradoxical motion may also differ at different locations. Posterior rib fractures exhibit less paradoxical motion due to splinting provided by the paraspinal muscles. Normal recruitment patterns of the intercostal muscles may be altered because of severe chest wall pain and may increase or decrease the degree of rib cage paradox.^{86,87} Different pain-induced respiratory muscle recruitment patterns may explain why some cases of flail chest remain unstable following prolonged mechanical ventilation^{88,89} and why lateral flail segments have a higher propensity for dislocation following surgical fixation.^{88,89}

Respiratory Failure

The pathogenesis of respiratory failure in flail chest is multifactorial; hypoventilation due to pain, flail-induced impairment in respiratory muscle function, and concomitant lung injury all play a role. The simplistic theory that respiratory failure resulted from the movement of air back and forth from the injured to uninjured side (*pendelluft*) has been abandoned. A flail segment has important physiologic consequences, even in the absence of contusion. First, pain impairs cough and promotes shallow tidal breathing, both of which may lead to atelectasis. Second, the flail segment impairs respiratory muscle performance.⁸⁵⁻⁸⁷ The paradoxical motion of the chest wall increases the degree of muscle shortening for a given tidal volume and, because the muscles are shortening further, the work they perform is increased per breath.⁸⁵ Increased work of breathing, together with an inefficient use of respiratory muscles increase the oxygen cost of breathing. When these factors are compounded by increases in elastic loads related to lung contusion and/or atelectasis along with hypoxemia, the respiratory muscles are predisposed to fatigue and respiratory failure or weaning difficulties (Fig. 98-11).^{23,85}

Pulmonary Function Tests

Forced vital capacity (FVC) and **FRC** are reduced immediately following trauma sufficient to cause flail chest. VC may be reduced to 50% of predicted. These reductions are related to pain, disordered chest wall motion, and underlying lung contusion. In patients with flail chest without lung contusion treated conservatively, FVC and FRC generally return to baseline values within 6 months of the acute injury. In contrast, in patients with flail chest complicated by lung contusion treated conservatively, pulmonary function may be reduced up to 4 years after injury, most likely due to fibrosis of the contused area. Compared with conservative management, operative fixation of flail chest may be a

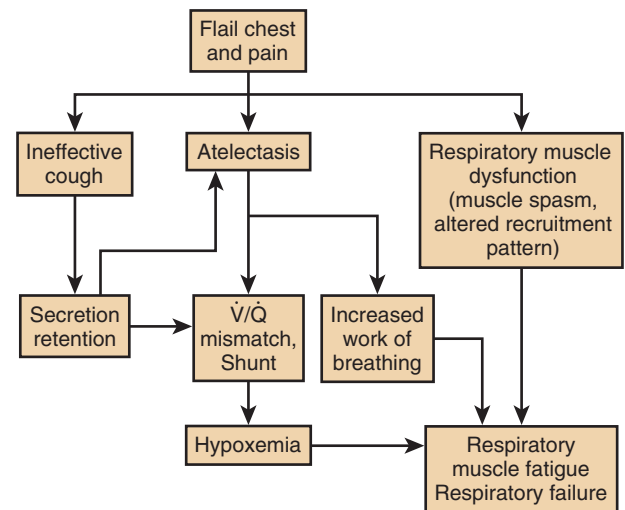


Figure 98-11 Factors involved in the pathophysiology of respiratory failure in flail chest.

better option to preserve pulmonary function, as indicated from both controlled⁹⁰ and uncontrolled studies.⁸⁹

TREATMENT

General Aspects

The restoration of anatomic and functional integrity of the chest wall is a key for avoiding complications related to flail chest. Surgical and nonsurgical approaches can be used to stabilize the flail segment (Fig. 98-12). Nonsurgical management is based on administration of adequate analgesia, clearing of bronchial secretions, and mechanical ventilatory assistance if needed.⁹¹ Control of pain is crucial in averting atelectasis and achieving an effective cough. Adequate pain relief can be accomplished by oral medications, patient-controlled analgesia pumps, intercostal nerve blocks, or epidural anesthesia.⁹¹ Adequate analgesia in combination with supplemental oxygen, effective tracheo-bronchial toilet, and cautious fluid replacement, often results in successful treatment of flail chest and avoidance of respiratory failure. If needed, mechanical ventilation can act as a pneumatic splint to stabilize the flail segment by keeping pleural pressure positive. However, mechanical ventilation delivered via a tracheostomy or endotracheal tube solely for the purpose of providing stability to the chest wall is not recommended due to the increased morbidity and mortality associated with mechanical ventilation. In contrast, positive pressure ventilation delivered noninvasively via a nasal or face mask to patients who are spontaneously breathing and able to protect their upper airway provides an alternate means of stabilizing the flail segment.⁹¹ Noninvasive ventilation, in conjunction with patient-controlled analgesia, improves gas exchange, allows for early patient mobilization and access for physiotherapy, and significantly reduces morbidity and mortality when compared with mechanical ventilation.^{92,93} If intubation and mechanical ventilation is needed, a low impedance ventilator mode that minimizes the likelihood of generating subatmospheric pleural pressure are optimal choices for stabilizing the flail segment and for weaning.⁸⁵

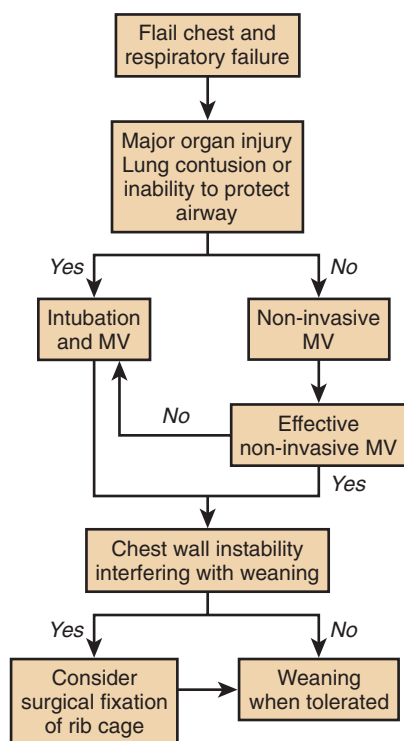


Figure 98-12 Algorithm for the management of acute respiratory failure due to flail chest. MV, mechanical ventilation.

Surgical procedures that are used to stabilize a flail segment include mobilization of large chest wall flaps, or inserting devices such as medullary wires or nails, Judet struts, or titanium plates to stabilize the rib cage.^{72,94} The few controlled studies that are available suggest that surgical fixation may be superior to conservative management by reducing the need for ventilatory support, lowering the infection rate, and minimizing the duration of intensive care unit stay.⁹⁵⁻⁹⁸ The indications for operative fixation of flail chest are not fully defined; candidates may be those with flail chest who are unable to be weaned from mechanical ventilation due to chest wall instability, those undergoing thoracotomy for concurrent injuries, those with persistent pain or severe chest wall instability, or those with a progressive decline in pulmonary function.^{72,90,91,97,98} The indications for surgical stabilization need to be clarified by randomized well-controlled studies.^{97,98a}

ANKYLOSING SPONDYLITIS

DIAGNOSIS AND ETIOLOGY

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease involving primarily the ligamentous structures of the spine, the sacroiliac joint, and large peripheral joints.⁹⁹ It usually affects men, with the most common age of onset between 15 and 25 years. The annual incidence is 6.6 per 100,000 white Americans and three to four times less in African Americans. There is a genetic predisposition for the disease, with nearly 95% of white patients positive for the HLA-B27 antigen.⁹⁹ Chronic inflammation eventually leads to fibrosis and ossification of the spine and

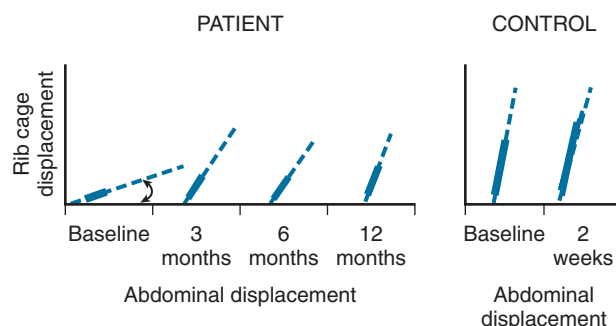


Figure 98-13 Representative plots of the rib cage and abdominal displacements during quiet breathing in a seated patient with ankylosing spondylitis, before and at various time points during therapy with anti-tumor necrosis factor α . Note the diminished contribution of the rib cage to tidal volume at baseline and the progressive increase in the rib cage contribution to breathing with treatment, becoming closer to the normal patterns obtained about 2 weeks apart in a healthy individual (control). B, baseline; M, months. (Adapted from Tzelepis GE, Kalliakosta G, Tzioufas AG, et al: Thoracoabdominal motion in ankylosing spondylitis: association with standardized clinical measures and response to therapy. *Ann Rheum Dis* 68:966-971, 2009.)

adjacent structures as well as of the costovertebral and sternoclavicular joints.

PATHOPHYSIOLOGY

Respiratory Mechanics

AS impairs chest wall function by limiting rib cage motion (Fig. 98-13).¹⁰⁰ This limited motion is due to stiffening and fusion of the costovertebral and sternoclavicular articulations (Fig. 98-14), to rigidity of the spine (Fig. 98-15), and possibly to intercostal muscle atrophy with advanced disease.¹⁰¹ Despite a pronounced reduction in rib cage mobility, lung compliance remains normal except in cases with fibrobullous (Fig. 98-16) or interstitial lung disease.^{101,102} Because the abdomen is compliant while the rib cage is stiff, the lung expands preferentially by caudal descent of the diaphragm and abdominal displacement than by expansion of the rib cage (i.e., the lung expands along the “path of least resistance”).^{103,104} This strategy likely minimizes the work and energy needed to inflate the lung.¹⁰⁴ Thus, during quiet breathing, exercise, or speech, the lung volume changes mostly by caudal displacement of the diaphragm and expansion of the abdominal wall.^{101,103,104} It has been found that transdiaphragmatic pressure increases by 2.4-fold in patients with AS at levels of ventilation at which healthy individuals increase transdiaphragmatic pressure by 1.4-fold.¹⁰¹

Pulmonary and Respiratory Muscle Function

Restrictive lung disease may be seen in patients with AS. Mild reductions in TLC and VC may be related to disease activity and duration, to spinal and rib cage immobility, or to concomitant kyphosis.^{100,105} Kyphosis may develop in up to 50% of patients with long-standing AS due to either advanced disease or osteoporosis.¹⁰⁶ Kyphosis may be worsened and respiratory function further impaired by fractures involving the rigid spine (Fig. 98-17).¹⁰⁷ Patients with AS are also at risk for respiratory failure if cervical spine fractures (typically C6 or C7) cause tetraplegia.



Figure 98-14 Ankylosing spondylitis. Bone scan in a patient with ankylosing spondylitis shows increased uptake (arrows) in the sternoclavicular and manubriosternal joints. (Adapted from Ramonda R, Lorenzin M, Lo Nigro A, et al: Anterior chest wall involvement in early stages of spondyloarthritis: advanced diagnostic tools. *J Rheumatol* 39:1844–1849, 2012.)

Respiratory muscle strength and endurance may be reduced in AS. PI_{max} and PE_{max} may be mildly reduced and respiratory muscle endurance may be impaired even in individuals with normal respiratory muscle strength.^{100,108,109} Mild reductions in strength and endurance may be related to intercostal muscle atrophy secondary to decreased rib cage mobility¹⁰¹ or to poor coordination of the respiratory muscles.¹¹⁰

Gas Exchange and Exercise Capacity

Regional ventilation is usually normal despite the limited expansion of the rib cage.¹¹² However, a mild impairment in gas exchange may be seen along with a reduction in DL_{CO} likely related to a mild reduction in lung volumes.¹⁰⁰ However, when fibrobullous disease (see Fig. 98-16) is present, gas exchange may be severely compromised and arterial PO_2 reduced.¹¹¹

Exercise capacity may be reduced in patients with AS.¹⁰⁸ The reduction in exercise capacity may be related more to deconditioning than to a limitation of ventilation because maximal oxygen consumption does not correlate with the degree of rib cage expansion.¹⁰⁸

Interstitial Lung Disease

Fibrobullous upper lobe disease is present in 1% to 4% of patients with AS (see Fig. 98-16).¹¹¹ The cause of apical fibrobullous disease is unknown. Possible causes include diminished upper lobe ventilation and apical mechanical stress due to thoracic rigidity, as well as recurrent pulmonary infections due to impaired cough. Fibrobullous disease may be unilateral or bilateral and affects males more than females. The spectrum of disease ranges from minimal upper lobe interstitial opacities to marked fibrosis, honeycombing, and cavitory lesions that may be mistaken for tuberculosis.¹¹¹ In a limited number of cases, histologic examination has revealed prominent interstitial fibrosis with hyaline and elastic degeneration of collagen, and

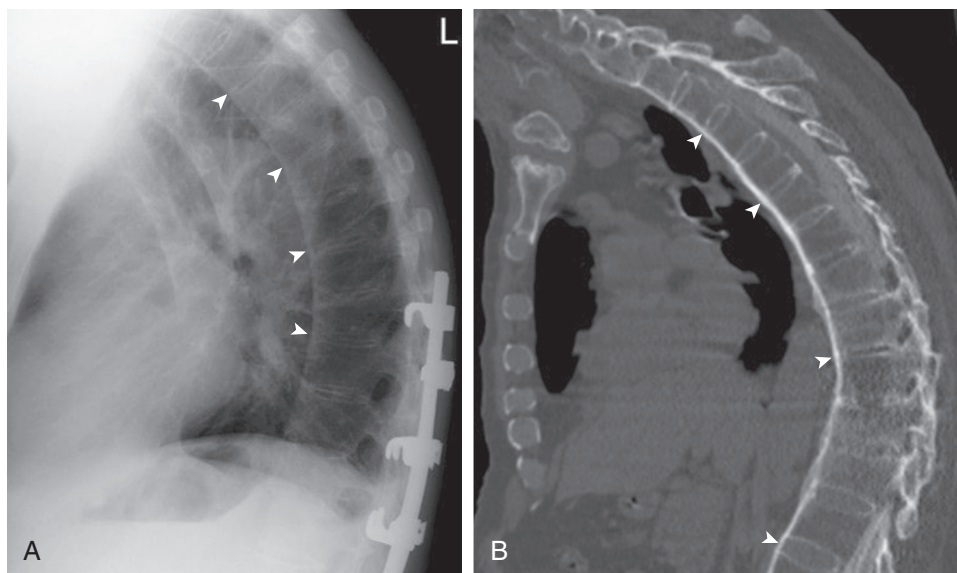


Figure 98-15 Ankylosing spondylitis: fused thoracic spine. Lateral chest radiograph (A) and sagittal reformatted chest CT myelogram image from a different patient (B) show flowing syndesmophytes (arrowheads) representing ossification of the outer fibers of the annulus fibrosis, bridging one vertebral body corner to another. When accompanied by longitudinal ligament ossification, fusion and kyphosis of the spine result. (Courtesy Michael Gotway, MD.)

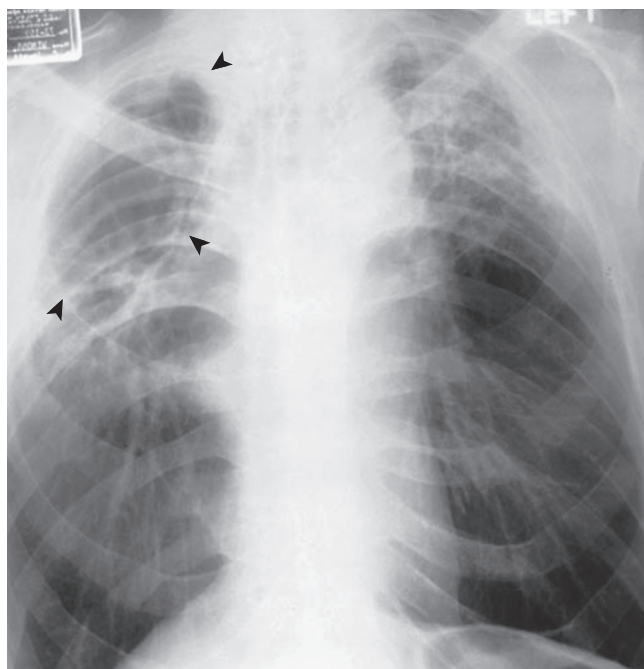


Figure 98-16 Ankylosing spondylitis: upper lobe fibrobullous disease. Frontal chest radiograph shows a thin-walled cystic structure in the right upper lobe (*arrowheads*) associated with upper lobe fibrosis bilaterally, evidenced by bilateral hilar retraction and architectural distortion. (Courtesy Michael Gotway, MD.)

absence of granulomas.¹¹¹ Patients are usually asymptomatic but, with severe disease, they may develop dyspnea and be at risk for spontaneous pneumothorax, aspergillosis (Fig. 98-18) or mycobacterial infection. Corticosteroids do not prevent progression of the disease. Because lung resection can be complicated by bronchopleural fistula in 50% to 60% of patients,¹¹¹ it is only recommended for treatment of major hemoptysis.¹¹¹ Another 10% to 20% of patients with AS develop nonapical interstitial lung disease, which can be detected by high-resolution CT scans of the chest.¹¹³

TREATMENT

The use of biological agents has constituted a significant advance in the treatment of AS.^{114,115} The TNF- α antagonists (infliximab, etanercept, adalimumab, and golimumab) provide symptom relief, reduce spinal inflammation, and improve the quality of life in these patients.¹¹⁴⁻¹¹⁶ Anti-TNF- α therapy can be shown to improve rib cage mobility resulting in greater ribcage and less abdominal displacement during tidal breathing (see Fig. 98-13).¹⁰⁴ In addition, exercise and physical therapy are key components of standard care.¹¹⁷ Cardiorespiratory fitness and spinal mobility may be enhanced by exercise and physiotherapy programs.^{99,118,118a} Tobacco use should be avoided. Patients should be monitored with baseline chest radiography and spirometry and receive repeat studies should respiratory symptoms develop. For patients treated with anti-TNF- α agents, a high index of suspicion for possible reactivation of latent tuberculosis is required.¹¹⁹ If intubation is planned, it should be performed with caution because these patients are at increased risk for spinal cord injury because

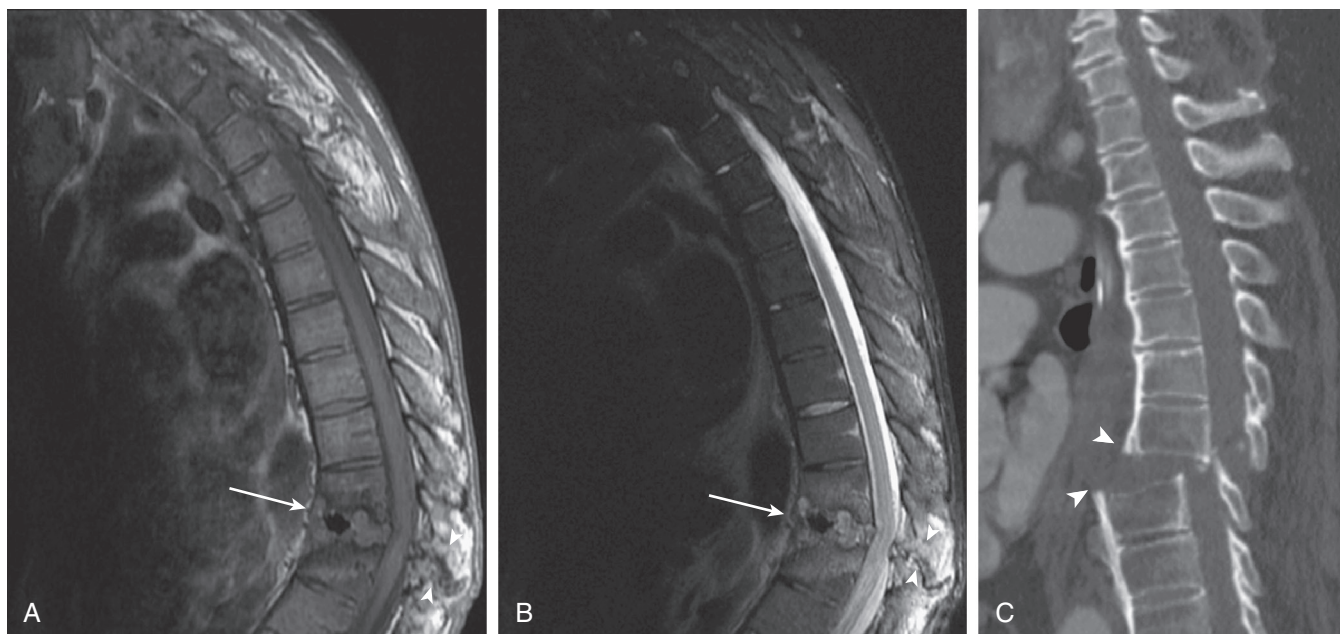


Figure 98-17 Ankylosing spondylitis: fused thoracic spine complicated by fracture. Sagittal T1-weighted (**A**) and T2-weighted (**B**) MRI shows irregular intermediate and centrally low signal (*arrow*) extending transversely through the intervertebral disc space, associated with kyphosis centered at this level. Note that the injury extends into the posterior elements (*arrowheads*); this pattern of spinal fracture is common in ankylosing spondylitis. The T2-weighted image (**B**) shows increased signal in the involved vertebral bodies consistent with bone marrow edema, and reveals spinal cord compression. Sagittal reformatted image from a chest CT in a different patient (**C**) shows a similar three-column fracture pattern, although more severe, complicated by distraction and displacement; note anterior widening of the intervertebral disc space (*arrowheads*). (Courtesy Michael Gotway, MD.)

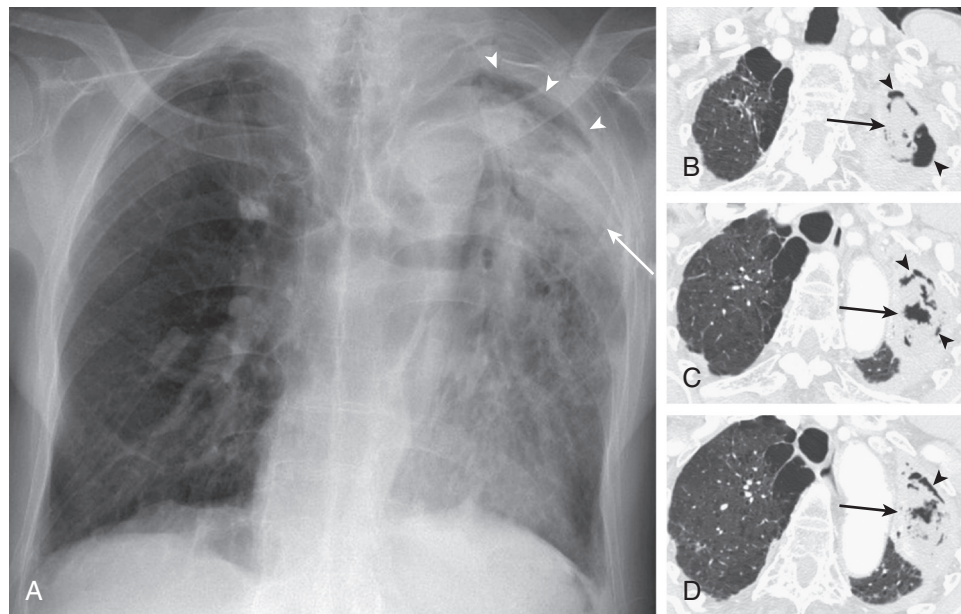


Figure 98-18 Ankylosing spondylitis: fibrobullous disease complicated by mycetoma. Frontal chest radiograph in a patient with ankylosing spondylitis and upper lobe fibrobullous disease (**A**) shows an irregular mass-like opacity at the left lung apex (arrow, **A**), with lucency (arrowheads, **A**) along the cranial margin of the opacity. Axial chest CT displayed in lung windows (**B–D**) confirms the presence of the opacity (arrows, **B–D**) within the cavity (arrowheads, **B–D**) in the left apex, consistent with mycetoma. (Courtesy Michael Gotway, MD.)

hyperextension of a rigid cervical spine may lead to fracture and, rarely, of upper airway compromise due to involvement with fixation of the cricoarytenoid joint.

OBESITY

DIAGNOSIS AND ETIOLOGY

Obesity is a major health problem throughout the world.¹²⁰ It is estimated that two thirds of the U.S. population are either overweight or obese.¹²¹ Approximately \$168 billion or 16.5% of the total health care budget is spent annually to treat obesity and obesity-related comorbidities.¹²² Body fat usually constitutes 15% to 20% of body mass in healthy men and 25% to 30% in healthy women. In obesity, the body fat content may increase by as much as 800% in men and 500% in women.¹²³ Fat-free mass also increases in obese individuals, accounting for 15% to 30% of the total weight gain.^{124,125} A number of parameters have been used to assess obesity, the most common being *body mass index* (BMI), which is calculated as the *body weight* (BW) in kilograms divided by the square of the *height* (Ht) in meters (BW/Ht^2). (The BMI can also be calculated as the body weight in pounds multiplied by 703 and divided by the square of the height in inches.) Individuals with a BMI between 18.5 and 24.9 kg/m^2 are normal, with a BMI between 25 and 29.9 kg/m^2 are overweight, and with a BMI greater than 30 kg/m^2 are obese. Obesity is severe (morbid) when the BMI is greater than 40 kg/m^2 .¹²⁰

Overweight and obese individuals are at greater risk for death than healthy individuals with a normal BMI.^{126,127} When compared with those with a normal BMI, the overweight have a 20% to 40% higher risk for death and the obese have a 300% to 400% higher risk for death.¹²⁶

Morbidity also increases as BMI increases¹²⁶ and is primarily due to cardiovascular and respiratory factors, with intra-abdominal fat constituting an independent risk for cardiovascular disease.^{128–130}

The most frequent respiratory complaints of obese individuals are dyspnea and exercise intolerance.¹³⁰ These complaints may be related to abnormal pulmonary function, disordered respiratory control, and elevated levels of mediators of inflammation, such as those linking obesity to airway hyperresponsiveness.^{130a} The severity of the respiratory impairment may not correlate with the degree of obesity.

PATHOPHYSIOLOGY

Obese individuals with the same BMI may exhibit different abnormalities in respiratory function. In particular, in some obese individuals, the arterial PCO_2 may be normal while, in others with the same BMI, the PCO_2 may be elevated. Indeed, the level of arterial PCO_2 is used to distinguish obese individuals who have *simple obesity* (SO; individuals who are eucapnic), from those who have *obesity hypoventilation syndrome* (OHS; individuals who retain CO_2). In addition, pulmonary function, respiratory mechanics, gas exchange, respiratory control, and exercise capacity may be significantly different in patients with SO and OHS.

Pulmonary Function

In obesity, the most common abnormalities of pulmonary function are reductions in *expiratory reserve volume* (ERV) and *FRC*¹³¹ (Fig. 98-19). For each unit increase in BMI from 20 to 30 kg/m^2 , FRC and ERV decrease by approximately 3% and 5%, respectively; thereafter, for each unit increase in BMI, both FRC and ERV decrease approximately 1%.¹³¹ Consequently, an individual with a BMI of 30 kg/m^2 can

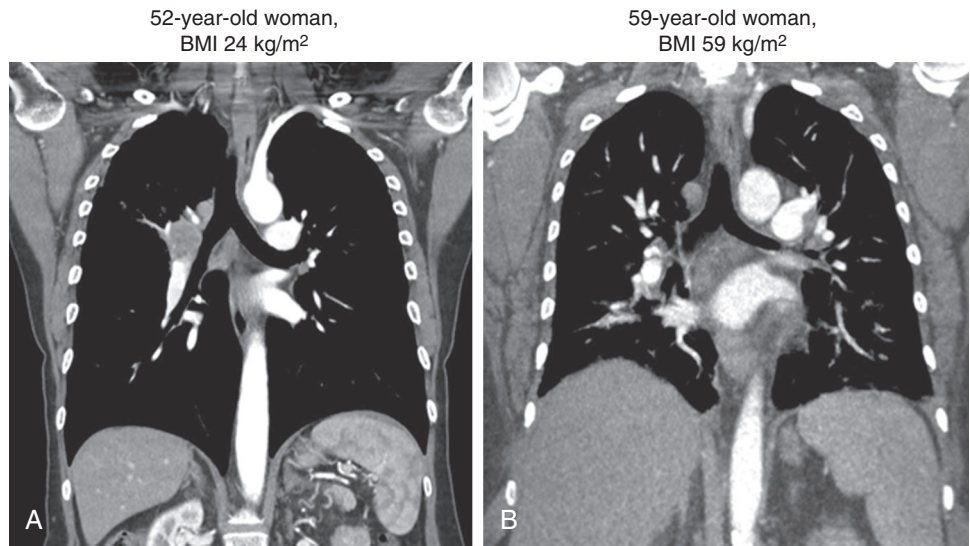


Figure 98-19 Coronal CT images of a non-obese (A) and an obese (B) individual of similar height, age, and predicted total lung capacity. The lung volume of the obese individual (B) is noticeably less than that of the non-obese individual (A). This may be due to the added load of excess fatty tissue on the respiratory system, which is most pronounced in the supine position. Typically, functional residual capacity and expiratory reserve volume are most affected with obesity.

Table 98-5 Representative Values of Respiratory Pathophysiology of Simple Obesity and Obesity Hypoventilation Syndrome			
Parameter	Normal	Simple Obesity	Obesity Hypoventilation
BW (% ideal)	100	200	200
BMI (kg/m ²)	24	45	45
TLC (% pred)	100	95	80
CRS (L/cm H ₂ O)	0.10	0.05	0.06
Rrs (cm H ₂ O•L ⁻¹ •s ⁻¹)	1.2	4.0	7.8
Work of ventilation (J/L)	0.43	0.74	1.64
MVV (L/min)	160	130	90
PI _{max} (cm H ₂ O)	100	95	60

BMI, body mass index; BW, body weight; CRS, compliance of the respiratory system; J, joule; MVV, maximum ventilatory volume; PI_{max}, maximal static inspiratory pressure; Rrs, respiratory system resistance; TLC, total lung capacity.
Adapted from Rochester DF: Obesity and abdominal distention. In Roussos C, editor: *The thorax*. New York, 1995, Dekker, pp 1950–1973.

be expected to have an FRC of approximately 75% of predicted and an ERV of only 47% of predicted.¹³¹ The FRC is reduced by adipose tissue compressing the rib cage and abdomen thereby reducing the outward elastic recoil of the chest wall and shifting the balance of recoil between the lung and chest wall to lower lung volumes. Because RV is affected to a lesser extent than FRC, ERV is preferentially reduced.¹³²⁻¹³⁴ In patients with OHS, FRC and ERV may be reduced even further.^{135,136}

While TLC, VC, and RV may be normal or only minimally reduced in individuals with SO, they may be significantly reduced (TLC and VC < 80% of predicted) in those with OHS or morbid obesity (Table 98-5).^{135,136} Because pulmonary function is more severely affected in OHS than in SO, factors other than the BMI must be involved. The more substantial

reductions in TLC and VC in those with OHS may be due to weakness of the respiratory muscles.¹³⁷ In addition, the distribution of fat may contribute to differences in lung volumes. For example, the distribution of body fat to the upper body (central fat distribution) impairs pulmonary function more than a distribution to the lower body (below the hips).¹³⁸⁻¹⁴⁰ Upper body fat distribution is indicated by a waist circumference of 35 inches (89 cm) or more for women and 40 inches (102 cm) or more for men.¹³⁸⁻¹⁴⁰ The correlation of respiratory impairment with upper body fat appears to be more apparent in men than in women.¹³⁸ The single-breath diffusion capacity is usually normal or increased in simple obesity and slightly reduced in OHS.¹⁴¹ Other tests of pulmonary function such as the FEV₁/FVC ratio, MVV, peak inspiratory flow rate, and the ratio of dead space to tidal volume (V_D/V_T) are usually normal.^{135,136}

Respiratory Mechanics

Obesity reduces *respiratory system compliance* (CRS), primarily by lowering lung compliance.^{133,142-145} In SO, values for CRS are approximately 80% to 90% of normal and are further reduced as BMI increases or when changing from the upright to supine position.^{133,142-145} In OHS, CRS is generally less than 45% of normal.¹⁴⁶ The reduced compliance is thought to be due to the weight of adipose tissue forcing FRC and tidal breathing to low lung volumes, near RV, where the lung is stiff due to airway closure.^{133,142,143} In addition, the excess chest wall adipose tissue creates a threshold load by making pleural and alveolar pressure less subatmospheric or even positive at end-expiration (*intrinsic positive end-expiratory pressure*, PEEPi).¹⁴² The inspiratory muscles must lower pleural pressure sufficiently to overcome PEEPi before inspiratory flow ensues. The inspiratory threshold load is greater in the supine position and may account for much of the disordered chest wall mechanics in obesity.^{132,142,147}

Airway and total respiratory system resistance are increased in obesity, with values usually twice as much as

those in non-obese individuals.^{145,148} Total respiratory system resistance is elevated primarily due to an increase in airway resistance related to breathing at low lung volumes.^{145,148} However, since airway resistance remains elevated even after normalizing for lung volume (e.g., specific airway conductance is reduced to 50% to 70% of normal), other unknown factors, in addition to breathing at low lung volumes, may account for some of the increase in resistance.^{148-150,150a} The normal FEV₁/FVC ratio suggests that the greatest resistance to airflow may be at the level of the small airways rather than the large airways. The transition from the upright to supine position may further increase airway resistance.¹⁴⁵ The increase in the intra-abdominal pressure when supine may further reduce FRC resulting in expiratory flow limitation during tidal breathing and orthopnea in severe obesity.^{147,151,152} The negative impact of the supine position on respiratory mechanics must be considered when evaluating obese patients for risks following general anesthesia.¹⁵³

The work of breathing is increased in both simple obesity and OHS.^{146,154,155} Three factors that contribute to the increase in work include increased elastic loads (reductions in compliance), threshold loads (increases in the pressure needed to initiate inspiration), and resistive loads (increases in pressure imposed by the airways).¹⁴³ The work of breathing can be up to 60% greater in simple obesity and as much as 250% higher in OHS.^{146,154,155} The increased work together with a reduced efficiency of breathing increases the oxygen cost of breathing fivefold in simple obesity and tenfold in OHS.¹⁴¹ The increased oxygen cost of breathing may place obese patients at risk for respiratory failure during states of increased ventilatory demands such as during inter-current illness.¹⁵⁵ To minimize the elastic load during inspiration and optimize the oxygen cost of breathing, obese patients adopt a rapid, shallow breathing pattern. This strategy is more pronounced in OHS than in SO.¹⁵⁶⁻¹⁵⁸ In subjects with SO, the respiratory rate during quiet breathing is about 40% higher than in normal-weight subjects with most of the lung volume change during tidal breathing accomplished by rib cage rather than by abdominal displacement.¹⁵⁸ In OHS, however, breathing frequency is 25% higher and V_T 25% lower than in simple obesity.^{157,159} The adverse effect of adopting a rapid shallow breathing pattern is increased dead space ventilation which may contribute to carbon dioxide retention.^{155,159}

Gas Exchange

In patients with simple obesity, the arterial PO₂ is usually normal or slightly reduced.¹⁶⁰ However, in patients with OHS or morbid obesity, the hypoxemia is more pronounced.^{135,136,160} In addition to hypoventilation, ventilation-perfusion mismatch and shunt due to premature airway closure widen the alveolar-arterial oxygen tension gradient and contribute to hypoxemia.^{160,161} The hypoxemia is worse in the supine position and in males.^{145,161,162} During exercise, oxygenation may improve due to enhanced ventilation of the lung bases.^{162,163} Weight loss will improve oxygenation by shifting FRC towards normal; an increase in FRC lessens the degree of airway closure during tidal breathing and improves arterial PO₂ roughly by 1 mm Hg for every 5 kg reduction in weight.¹⁶⁰ A practical corollary of hypoxemia and the increased metabolic rate in obesity is that,

during apnea, the arterial oxygen saturation may fall three times faster in obese individuals than in normal-weight subjects.¹⁶⁴

Control and Pattern of Breathing

Differences in the control of breathing may also explain why hypercapnia is found in some but not all obese individuals of similar BMI. In eucapnic obese individuals, central respiratory drive is intact. Respiratory drive, as measured by the P_{0.1}, ventilatory, or electromyographic responses to hypoxia or hypercapnia, is normal or even increased because of the elastic and threshold loads placed on the inspiratory muscles.^{141,147,165} If the elastic and threshold loads are lessened by weight loss, the compensatory increase in ventilatory drive decreases.^{166,167} In patients with OHS, however, respiratory drive is blunted and the P_{0.1}, ventilatory, or electromyographic response to hypoxia or hypercapnia is reduced.^{165,168} The exact mechanism underlying the attenuated ventilatory drive in OHS is unknown. Mechanical disadvantage in OHS does not adequately explain the hypercapnia as most patients with OHS can normalize arterial PCO₂ through volitional hyperventilation.¹⁶⁹ A genetic predisposition is unlikely because ventilatory drive is intact in first-degree relatives of patients with OHS.¹⁷⁰ Instead, in those with OHS, the central chemoreceptors may be “reset” because of chronic hypoxemia or hypercapnia or because of reduced leptin or leptin resistance. Leptin is a protein produced by adipose tissue that acts in the hypothalamus to decrease appetite, increase metabolic rate, and stimulate breathing. The development of leptin resistance or a relative leptin deficiency may contribute to diminished ventilatory responsiveness and hypercapnia in OHS.^{135,171} Because serum leptin levels are generally increased in obesity, both in SO and even more so in OHS, a central resistance to leptin has been proposed.^{171,172}

The increased respiratory drive in simple obesity may contribute to the sensation of dyspnea.^{163,167,173} However, dyspnea is also a frequent and disabling symptom in OHS and may be related to airways disease, or disordered respiratory mechanics (decreased compliance, increased airway resistance, or expiratory flow limitation).^{154,163,173-176} Finally, dyspnea may be due to cardiac disease, a frequent comorbid condition.

Respiratory Muscle Function

In patients with simple obesity, respiratory muscle strength is usually normal; in fact, strength may be maintained by the chronic threshold and elastic loads imposed on the inspiratory muscles.^{145,147,176} In patients with OHS, respiratory muscle strength is usually decreased, perhaps because of deconditioning or other factors related to chronic disease.^{135,176} In severely obese subjects, especially those with dyspnea or OHS, diaphragm function may be impaired, especially in the supine position.^{176,177} This may be related to increased intra-abdominal pressure and cranial displacement of the diaphragm.¹⁷⁷

Exercise Capacity

In absolute terms, exercise capacity in those with simple obesity, as measured by symptom-limited maximal oxygen uptake, is similar to that of lean individuals. When normalized to fat-free mass, however, maximal oxygen uptake is

lower in obese than in non-obese individuals.^{163,178} For a given rate of work, obese individuals require a greater $\dot{V}O_2$ and minute ventilation. Likewise, dyspnea scores at any submaximal work rate are higher in obese individuals, reflecting the higher ventilation and metabolic costs of obesity.^{163,178} Obese individuals may increase end-expiratory volume during exercise to attenuate expiratory flow limitation due to breathing at low lung volumes.¹⁶³ This breathing strategy may assist them in accommodating their higher metabolic demands. In support of this notion, at any given $\dot{V}O_2$ or minute ventilation, dyspnea scores are similar to those of non-obese individuals, suggesting that respiratory mechanical factors do not contribute significantly to respiratory discomfort.^{163,174}

TREATMENT

Weight loss is the optimal therapy but is not always attainable, and long-term weight loss maintenance is even more difficult.¹⁷⁹ Generally, weight loss programs emphasize diet, enhanced physical activity, and behavioral therapy as initial treatments in all obese individuals regardless of the severity of obesity. Bariatric surgery can produce not only a substantial weight loss but also long-term maintenance of weight loss.¹⁸⁰ It is indicated in obese individuals with a BMI of at least 40 kg/m² and in those with a BMI of at least 35 kg/m² with serious comorbidities.^{179,181} Weight loss in obese individuals is associated with improved ERV and FRC¹⁸²; however, there is no correlation between the magnitude of weight loss and the degree of improvement of lung volumes. Weight loss also may improve respiratory muscle performance,¹³⁷ resting gas exchange,¹⁸³ diffusion capacity,¹⁶⁰ dyspnea scores,^{167,184} sleep apnea,¹⁸⁴ 6-minute walk test¹⁸⁵ airway responsiveness,¹⁸⁶ and respiratory drive.¹⁶⁷ Overall, weight reduction appears to be the most effective solution to OHS, with bariatric surgery providing the best option for the various comorbid conditions related to extreme obesity, such as hypertension, hyperlipidemia, cardiac dysfunction, and type 2 diabetes.^{187,188}

Key Points

- Diseases that affect the chest wall, including obesity, primarily affect the respiratory system by reducing chest wall compliance. The degree to which the chest wall stiffens varies with the disease process. Individuals with kyphoscoliosis may have the greatest degree of chest wall stiffness whereas individuals with pectus excavatum or ankylosing spondylitis may have normal chest wall compliance.
- The lung is usually an “innocent bystander” in the sense that it is usually not primarily affected by a pathologic process. When restrictive chest wall disorders limit full inflation of the lung, microatelectasis

ensues which can lead to a reduction in lung compliance and impaired gas exchange.

- Of the chest wall disorders, flail chest is most likely to precipitate acute respiratory failure whereas kyphoscoliosis and severe obesity are most likely to lead to chronic ventilatory failure, pulmonary hypertension, and cor pulmonale. Coincident inspiratory muscle weakness in any of these disorders will further worsen restrictive pathophysiology and predispose to respiratory failure.
- Acute respiratory failure may complicate flail chest and can be treated with positive-pressure ventilation. In some patients with flail chest, surgical fixation of the flail segment may reduce the duration of mechanical ventilation and improve long-term pulmonary function.
- Chronic respiratory failure, which can be seen in kyphoscoliosis or with severe obesity, can be successfully managed with noninvasive nocturnal positive-pressure ventilation. This latter intervention has markedly improved morbidity and mortality in this group of individuals.

Complete reference list available at *ExpertConsult*.

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MANAGEMENT OF RESPIRATORY FAILURE

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ACUTE VENTILATORY FAILURE

NICHOLAS S. HILL, MD

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ACUTE VENTILATORY FAILURE DUE TO VASCULAR IMPAIRMENT

INTRODUCTION

Respiratory failure exists when the respiratory system cannot maintain gas exchange, causing dysfunction in other organs or threatening life. Such impairment primarily affects oxygenation, manifested by hypoxemia, or affects ventilation, manifested by hypercapnia and respiratory acidosis. This chapter deals with this latter circumstance, commonly called ventilatory failure.

Carbon dioxide (CO_2) tension in the arterial blood (PaCO_2) is a function of *alveolar ventilation* (\dot{V}_A) and CO_2 production ($\dot{V}\text{CO}_2$), according to the following relationship.

$$\text{PaCO}_2 = (\dot{V}\text{CO}_2 \times k) / \dot{V}_A \quad (1)$$

Total minute ventilation is the sum of both \dot{V}_A and dead space ventilation. Either a decrease in total minute ventilation or an increase in dead-space ventilation can thus

decrease \dot{V}_A . Any decrease in \dot{V}_A or increase in $\dot{V}\text{CO}_2$ relative to \dot{V}_A results in an increase in arterial PCO_2 . Because bicarbonate retention by the kidney in response to hypercapnia is slow, a sudden increase in arterial PCO_2 will not be buffered quickly by bicarbonate and thus will abruptly lower arterial pH. Ventilatory failure exists whenever arterial PCO_2 is substantially elevated, and acute ventilatory failure is present when the change from the patient's baseline state develops rapidly enough to produce a clinically important drop in arterial pH. Because patients with severe *chronic obstructive pulmonary disease* (COPD), chronic neuromuscular disease, and other disorders may already have hypercapnia at baseline, the presence of a component of acute (acute-on-chronic) ventilatory failure is determined not so much by the arterial PCO_2 value as by the presence of acidemia, typically to an arterial pH of less than 7.35. The presence of acute ventilatory failure cannot be

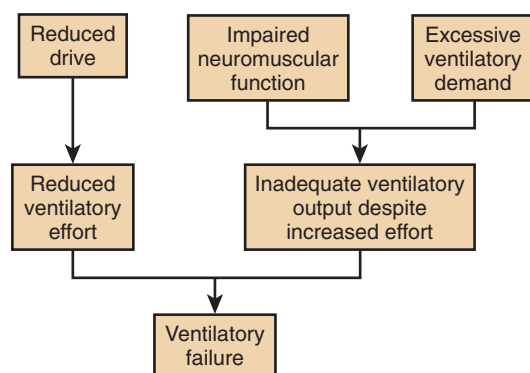


Figure 99-1 The physiologic mechanisms of acute ventilatory failure. The two major causes of acute ventilatory failure are either a reduced ventilatory effort or a reduced ventilatory output despite increased effort.

determined accurately by physical examination, pulse oximetry, exhaled CO_2 , or other noninvasive tests. Thus, making the diagnosis requires arterial blood gas analysis.¹

PATHOPHYSIOLOGY OF ACUTE VENTILATORY FAILURE

Alveolar ventilation becomes inadequate in relation to CO_2 production either because of a failure of the patient's ventilatory capability (pump failure) or ventilatory effort (drive failure)^{2,3} (Fig. 99-1). These two mechanisms are distinct in their clinical presentations. Patients with acute failure of the ventilatory pump are dyspneic and tachypneic with other signs of distress, whereas patients with failure of ventilatory drive are not short of breath and typically demonstrate bradypnea or apnea.

Although acute ventilatory failure is primarily a disorder of alveolar ventilation, hypoxemia is also usually present. Alveolar hypoventilation causes a proportional fall in *alveolar oxygen pressure* (PAO_2), according to the alveolar gas equation.

$$\text{PAO}_2 = \text{PIO}_2 - (\text{PaCO}_2 / R) \quad (2)$$

where arterial PCO_2 is assumed to be nearly the same as alveolar PCO_2 , PIO_2 is the inspired PO_2 (i.e., the inspired oxygen fraction multiplied by the difference of barometric pressure and 47 [water vapor pressure at body temperature]), and R is the respiratory exchange ratio. This relationship explains the fall in arterial PO_2 that accompanies alveolar hypoventilation, as shown in Figure 99-2.² Calculating alveolar PO_2 using Equation 2 permits determination of the *alveolar-arterial oxygen pressure difference* ($(A-a)\text{PO}_2$) (commonly but imprecisely called the “A-a gradient” and more precisely called the “A-a oxygen tension difference”). This calculation distinguishes between pure hypoventilation as an explanation for hypoxemia (in which case, $(A-a)\text{PO}_2$ is normal) and the presence of other mechanisms such as low *ventilation-perfusion* (\dot{V}/\dot{Q}) ratios and right-to-left shunt (in which case, $(A-a)\text{PO}_2$ is increased).

Finally, hypercapnia can be a feature of hypoxemic respiratory failure if the derangement in gas exchange is sufficiently severe. Both right-to-left shunt and low \dot{V}/\dot{Q} ratios are present in the *acute respiratory distress syndrome*

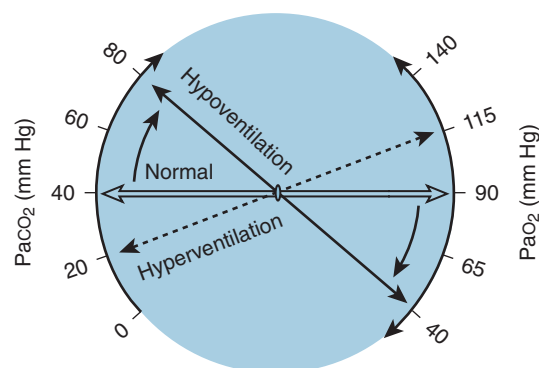


Figure 99-2 Relationship between arterial PO_2 and arterial PCO_2 . There is a reciprocal relationship between arterial oxygen pressure (PaO_2) and arterial carbon dioxide pressure (PaCO_2) as ventilation increases or decreases, assuming that the $(A-a)\text{PO}_2$ difference does not change and the respiratory exchange ratio is 0.8. (Redrawn from Pierson DJ, Kacmarek RM, editors: *Foundations of respiratory care*. New York, 1992, Churchill Livingstone, p 298.)

(ARDS) and can increase *dead space-to-tidal volume ratios* (V_D/V_T) as determined by the Bohr equation,⁴ thus impairing CO_2 elimination and contributing to hypercapnia.

Table 99-1 classifies the typical clinical presentations of acute ventilatory failure according to the site or type of defect and the physiologic mechanism or category of disorder responsible. Not every listed example is discussed in this chapter.

More than one mechanism may coexist in a given patient, producing a life-threatening condition even when the individual processes are only moderate in severity. For example, in decompensated obesity-hypoventilation syndrome, a patient whose underlying respiratory drive is reduced and whose obesity poses an increased elastic load on the ventilatory pump may develop acute-on-chronic ventilatory failure in the presence of a relatively modest increase in the work of breathing from an additional restrictive effect of cardiomegaly and pleural effusions.

ACUTE VENTILATORY FAILURE DUE TO INSUFFICIENT VENTILATORY DRIVE

CONGENITAL CAUSES

Congenital disorders that may be associated with diminished hypoxic or hypercapnic ventilatory drive include primary alveolar hypoventilation (or Ondine's Curse),⁵ Prader-Willi syndrome,^{6,7} hypogonadism treated with exogenous testosterone,⁸ and Arnold-Chiari malformation.⁹ These disorders contribute to the development of acute ventilatory failure through diminished ventilator drive, often in combination with other contributing mechanisms (such as acute infection), and are most often seen in pediatric settings.

ACQUIRED CAUSES

Decreased ventilatory drive is a frequent contributor to the development of chronic ventilatory insufficiency but is

Table 99-1 Clinical Classification of Ventilatory Failure by Site

Site of Defect	Mechanism or Type	Clinical Examples
Ventilatory drive	Congenital Acquired Combination	Primary alveolar ventilation (Ondine's Curse) Drug overdose (opioids, sedatives, alcohol); general anesthesia Cerebrovascular accident; neoplasm; carotid body resection Obesity-hypoventilation syndrome; myxedema
Neural transmission Spinal cord	Trauma Vascular Tumor Other Demyelinating	Cervical spinal cord injury Vascular accident Primary or metastatic Poliomyelitis; amyotrophic lateral sclerosis Acute idiopathic demyelinating polyneuropathy (Guillain-Barré syndrome)
Peripheral nerves Neuromuscular junction	Phrenic nerve lesion Pharmacologic Autoimmune Infectious/toxins	Trauma; cardiac surgery; neoplasm; idiopathic Neuromuscular blocking agents Myasthenia gravis Botulism, tetanus, tick paralysis
Ventilatory muscles	Congenital Autoimmune Acquired	Muscular dystrophy Polymyositis; dermatomyositis Hypophosphatemia; hypokalemia; hypomagnesemia; myxedema
Thoracic Vertebrae and rib cage Soft tissues	Decreased mobility Extrapulmonary restriction and decreased mobility	Kyphoscoliosis; tight casts or bandages; ankylosing spondylitis; flail chest Severe obesity
Pleura	Extrapulmonary restriction	Pneumothorax; pleural effusion; pleural thickening; malignancy
Airways Upper airways Lower airways	Obstruction Obstruction	Epiglottitis, foreign body, tumor, vocal cord paralysis, tracheomalacia COPD, acute severe asthma
Parenchyma	Increased dead space and very high \dot{V}/\dot{Q} Very low \dot{V}/\dot{Q} ; shunt	COPD Severe ARDS
Pulmonary circulation	General hypoperfusion Localized hypoperfusion	Hypovolemic or cardiogenic shock, CPR, pulmonary hyperinflation (intrinsic PEEP) Pulmonary thromboembolism; venous air embolism
Other	Increased CO ₂ production (inflammation; hypermetabolism; muscle activity) Exogenous CO ₂ inhalation	Fever; sepsis; burns; severe trauma; shivering; tetany; seizures; malignant hyperthermia Laboratory or industrial accident; therapeutic use; rebreathing

ARDS, acute respiratory distress syndrome; CO₂, carbon dioxide; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; PEEP, positive end-expiratory pressure; \dot{V}/\dot{Q} , ventilation-perfusion ratio.

typically not the sole mechanism for acute ventilatory failure, except for those patients presenting with drug-induced suppression.

PHARMACOLOGIC CAUSES

Depression of the drive to breathe by drugs is by far the most common circumstance of this form of acute ventilatory failure. The opioids are potent depressors of both hypoxic and hypercapnic ventilatory drive; however, any sedative, hypnotic, or anxiolytic agent causes respiratory depression if administered in sufficient quantity.¹⁰ Propofol, in particular, is a potent respiratory depressant used commonly for sedation during procedures or during mechanical ventilation and must be dosed with caution in patients breathing spontaneously.¹¹ Respiratory depression resolves as the drug is cleared from the body or is pharmacologically antagonized, as signaled by the return of spontaneous breathing efforts. Because the central nervous system effects of some agents may wax and wane due to the enterohepatic circulation, lipid storage, or other mechanisms, patients should be observed until it is clear that the ventilatory drive has been reestablished before they are weaned from ventilatory support. In the case of drug overdoses and other poisoning,

identifying the specific agent or agents involved and the use of any specific therapies available, such as antidotes or dialysis, is important to expedite the weaning process from ventilatory support.¹⁰ Patients who fail to wean from mechanical ventilation because of inadequate drive from depressant drugs breathe slowly or not at all when ventilatory support is briefly discontinued. The much more common reason for difficulty weaning after drug overdose is that other mechanisms (e.g., aspiration pneumonia or sepsis) intervene. In these circumstances, with a return of respiratory drive, patients become tachypneic and manifest signs of respiratory distress when ventilatory support is discontinued.¹²

OTHER ACQUIRED CAUSES

Myxedema^{13,14} may present with hypercapnia related to acquired depression of ventilatory drive, and hypothyroidism may be a cofactor when patients present with worsening hypercapnia. Thyroid function testing should be done routinely in patients with new or worsening hypercapnia, especially when a clear physiologic explanation is inapparent. Patients with underlying abnormalities of ventilatory drive who develop respiratory infections, congestive heart failure, or other acute illnesses are more likely to develop

acute ventilatory failure compared with individuals without such defects.

The obesity-hypoventilation syndrome, discussed in Chapter 89, is characterized by blunted responses to hypoxia and hypercapnia¹⁵ and is one disorder in which patients may first present in acute ventilatory failure. Typically, such patients have a history of recent weight gain and are found to be markedly fluid-overloaded, with features of cor pulmonale. The increased work of breathing from decreased chest wall compliance, cardiomegaly, and often large pleural effusions, as well as worsening hypoxemia, all contribute to respiratory muscle fatigue and the development of severe hypercapnia and respiratory acidosis. Hypoventilation and acute ventilatory failure related to obesity are more common among hospitalized patients with severe obesity than has previously been reported.^{16,17} As the prevalence of obesity increases, ventilatory failure from decompensation of the obesity-hypoventilation syndrome is likely to be encountered more frequently.

Acute stroke is another setting in which disordered ventilatory drive may contribute to acute ventilatory failure, even though other processes are usually present, especially the inability to protect the lower airway and to clear respiratory tract secretions.^{18,19} The prognosis of patients with ischemic and hemorrhagic strokes who require intubation and mechanical ventilation is poor both in the short and long term, with a survival rate of 50% at 30 days and 30% after 1 year.^{18,20,21} Prognosis is especially unfavorable after basilar artery occlusion due not only to depressed respiratory drive but also to the swallowing impairment and problems with secretion clearance seen with brain stem injury.²²

Although data are not encouraging and the mortality rate is still high, American Heart Association guidelines recommend mechanical ventilation for patients with acute stroke if needed (Level IC).²³ Of course, this necessitates an ethical discussion with the patient and/or family to determine the patient's wishes regarding aggressive support (see Chapter 104).

PRINCIPLES OF MANAGEMENT

Because the underlying physiologic defect is inadequate ventilatory drive despite a presumably normal ventilatory pump, management focuses on restoring normal alveolar ventilation. Although *noninvasive ventilation* (NIV) is being applied in an increasing number of clinical settings to augment alveolar ventilation, its utility lies mainly in maintaining respiration in patients with failure of the ventilatory pump, whereas endotracheal intubation is generally necessary following acute failure of respiratory drive. NIV can be quite effective in treating chronic congenital or acquired central hypoventilation in outpatients, but in the setting of acute loss of respiratory drive, invasive mechanical ventilation restores alveolar ventilation more rapidly and reliably and is more effective for airway protection and secretion clearance than is NIV.

Because of the patient's impaired ventilatory drive, a ventilator mode that provides full support, such as volume-targeted assist-control ventilation, should initially be chosen. In the absence of acute lung injury or severe airflow obstruction, ventilator settings should be chosen to aim for values of arterial pH and arterial PCO₂ in the normal

range, and supplemental oxygen should be supplied (with *positive end-expiratory pressure* [PEEP] if necessary) to maintain normal arterial PO₂. Unless there are serious coexisting pulmonary conditions, weaning should be carried out as soon as there is evidence that ventilatory drive is restored (see Chapter 101). Extubation is probably safe if the patient has a spontaneous cough, does not require frequent suctioning, and is judged to be able to protect the airway, even if alertness remains impaired.²⁴

ACUTE VENTILATORY FAILURE DUE TO NEURAL TRANSMISSION IMPAIRMENT (see Chapter 97)

CERVICAL SPINAL CORD INJURY

Injury to the upper cervical spinal cord may interrupt transmission of the stimulus to breathe from the respiratory centers in the brain stem to the diaphragm and other ventilatory muscles, depending on the injury level. Because the phrenic nerve roots that supply the diaphragm arise from spinal segments C3 to C5, patients with acute injury at this level or above usually require ventilatory assistance. Patients with C1–C2 spinal injury levels are permanently ventilator dependent, whereas those with C3–C4 injuries may eventually achieve at least partial ventilator independence. Lesions below C4 are usually compatible with unassisted ventilation unless there are complicating processes such as intrinsic lung disease or impaired mental status.

Adverse physiologic effects can happen within the first days or weeks after the injury, including loss of lung volumes and inability to take deep breaths (which predisposes to atelectasis), inability to cough normally (which predisposes to the development of pneumonia and complicates its management), and impaired hypoxic pulmonary vasoconstriction (which predisposes to severe and often refractory hypoxemia after atelectasis or pneumonia).²⁵ These physiologic effects depend on the level of injury, being more frequent with lesions above C4, and on the degree of injury, being more frequent with complete, than with incomplete, lesions.²⁶

The short-term prognosis of spinal cord lesions is generally related to the level of the injury,²⁵ even though some retrospective studies have shown that both mortality^{27,28} and *intensive care unit* (ICU) length of stay²⁵ are more strongly influenced by the development of pneumonia and other respiratory complications than by the specific cord injury level.

Although there are reports of initial management of patients with high cervical spinal cord injury (C3–4 or higher) with NIV,²⁹ great expertise is required to avoid aspiration and other complications. Decisions about NIV should be made on a case-by-case basis²⁶; in most centers, invasive ventilatory support is preferable, at least initially. Phrenic nerve^{30–32} or diaphragm pacing,³³ permitting extubation or removal of the tracheostomy tube (decannulation), has also been reported in the later period following injury. The eventual ability to wean from ventilatory support and to undergo decannulation from tracheostomy are major determinants not only of survival but also of quality of life for patients with cervical spinal cord injury.^{25,27}

MOTOR NEURON DISEASE

Amyotrophic lateral sclerosis (ALS) and other motor neuron diseases demonstrate a variable but progressive weakness of the bulbar and ventilatory muscles. This progression determines the course of ventilatory failure and pulmonary complications, which represent the most common cause of death in these patients.^{34,35} Typically, ventilatory muscle weakness develops gradually after the diagnosis is already well established; therefore repeated assessments during outpatient evaluation are useful to monitor the progression of ventilatory muscle impairment.³⁴⁻³⁸ This permits intervention with NIV or, less often, tracheostomy before the onset of acute ventilatory failure. However, some cases present with acute ventilatory failure as the initial manifestation of the disease.³⁹

Elective initiation of noninvasive ventilation is becoming a standard of care in motor neuron disease patients with progressive ventilatory impairment because it improves both quality of life and survival rate^{37,38,40} in patients without significant bulbar involvement. NIV has been successful not only in the chronic, slowly progressive setting, but also in acute ventilatory failure complicating ALS.⁴¹ However, bulbar weakness and a high risk of aspiration make invasive mechanical ventilation a preferred choice for ALS patients with acute ventilator failure, at least initially. With appropriate counseling about end-of-life planning, only a small proportion of patients with ALS receive invasive mechanical ventilation, and presentation to an emergency department with acute ventilatory failure should be unusual.⁴²

INJURY OR DISEASE AFFECTING THE PHRENIC NERVE

Loss of diaphragm function leading to ventilatory failure is often due to spinal cord injury, immunologic diseases (such as Guillain-Barré syndrome or multiple sclerosis), or neuropathy (ALS, Charcot Marie Tooth). Unilateral paralysis of the diaphragm leading to ventilatory failure may be a result of phrenic nerve injury or disease. Its presentation ranges from an incidentally discovered radiographic abnormality without clinical impact to acute ventilatory failure requiring long-term mechanical ventilation, although the latter is quite unusual and generally due to multiple factors.^{31,43} In the past, unilateral diaphragmatic palsy following phrenic nerve injury was most often caused by cold cardioplegia during open-heart surgery or direct injury during internal mammary artery harvesting.⁴⁴ Since routine use of insulation for the phrenic nerves during cardiac surgery, this complication is now rare, but unilateral or bilateral phrenic nerve palsies are still seen as a consequence of direct invasion by neoplasm, infectious diseases (such as herpes zoster and Lyme disease), metabolic peripheral neuropathy (diabetes or porphyria), and radiotherapy.⁴⁵ Although acute ventilatory failure as a consequence of bilateral diaphragmatic paralysis is unusual, these patients are much more symptomatic than those with unilateral paralysis and usually have severe orthopnea.

IMMUNOLOGIC NEUROPATHIES

Guillain-Barré syndrome, now known as *acute idiopathic demyelinating polyneuropathy* (AIDP), is an autoimmune

polyneuropathy that accounts, together with myasthenia gravis, for the majority of admissions for ventilatory failure due to neuromuscular impairment.⁴⁶⁻⁵¹ Therapy with plasma exchange and intravenous immunoglobulin improves outcomes in AIDP, although 2% to 10% still die, and up to 20% of individuals who survive remain seriously disabled.⁵² Theoretically, death should be preventable in the vast majority of patients with this disease because mortality is primarily from potentially avoidable respiratory complications (see the discussion in Chapter 97). It remains unclear whether the need for mechanical ventilation can be predicted before the onset of frank ventilatory failure in this condition.⁵³

NEUROMUSCULAR JUNCTION IMPAIRMENT

Immunologic Disease

Myasthenia gravis is less common than AIDP as a cause of acute ventilatory failure, although up to 15% to 20% of myasthenic patients experience a crisis during their lifetime. These events usually happen in patients with an established diagnosis of myasthenia gravis. With adequate therapy (plasmapheresis and intravenous immunoglobulin) and respiratory support through noninvasive or invasive mechanical ventilation, the mortality rate is 5% to 10%.^{54,55} Isolated ventilatory muscle weakness requiring mechanical ventilation has been reported as the initial manifestation of the disorder.⁴⁶

Infectious Disease

Botulism remains an infrequent but important cause of acute ventilatory failure worldwide. In western countries, the incidence of ventilator failure due to food-borne illness has been unusual but steady in recent decades, with about 23 cases/year in the United States. On the other hand, due to subcutaneous injection of black-tar heroin, the incidence of wound botulism has been rising since the 1990s among injectable drug users.⁵⁶⁻⁵⁸ The vast majority of patients with both forms of botulism manifest respiratory symptoms and up to 75% of individuals develop clinically significant respiratory failure due to progressive descending flaccid paralysis, requiring mechanical ventilation, which is usually more prolonged in wound botulism patients.^{59,60} Recovery may likewise be prolonged, with residual ventilatory muscle weakness detectable as long as 2 years after presentation.⁶¹

Myopathies

Primary myopathies due to muscular dystrophies or other congenital myopathies are an uncommon cause of acute respiratory failure in most acute care hospitals but are more common in the pediatric setting. These patients usually develop ventilatory failure gradually and are begun on NIV in an outpatient setting. When they present with acute ventilator failure, it is usually in the setting of a precipitating factor such as pneumonia or bronchitis that causes problems with secretion retention. In such an event, they should be placed in an intensive care unit and treated with an aggressive regimen to assist with secretion clearance.⁶² Endotracheal intubation may be necessary to control secretions with weaning to NIV once the acute crisis subsides. Dermatomyositis may also cause respiratory muscle

weakness severe enough to lead to acute ventilatory failure,^{63,64} although not as an initial manifestation in the absence of other typical symptoms and signs of this condition. In these reported cases, ventilatory function recovered as the disease was brought under control with immunosuppressive therapy.

Pharmacologic Causes

Neuromuscular blocking drugs are sometimes administered to ventilated patients, in conjunction with sedation, to facilitate mechanical ventilation, reduce oxygen consumption, or control intracranial pressure. The clinical kinetics of these agents have been determined mainly in the context of short-term general anesthesia, and their effects on ventilatory muscle function in critically ill patients are much more variable. For example, most neuromuscular blocking drugs are cleared more slowly in the presence of hepatic or renal insufficiency. This is particularly true for pancuronium and vecuronium; the effects of these drugs can last days or even weeks in the presence of renal failure.⁶⁵ In contrast, atracurium and cisatracurium are metabolized in plasma and do not depend on renal or hepatic function for clearance; thus, they are not associated with prolonged muscle weakness as a result of delayed clearance.⁶⁶

Train-of-four stimulation can be used to monitor the depth of neuromuscular blockade, avoiding excessive paralysis and reducing the quantity of drug used, as well as the recovery time of neuromuscular function in critically ill patients.⁶⁷ Although these benefits may not be seen when atracurium and cisatracurium are used,⁶⁸ train-of-four testing is sufficiently simple and inexpensive to perform that many experts believe it should be employed routinely.⁶⁹ Minimizing the use of neuromuscular blocking drugs in ventilator management and using train-of-four stimulation to monitor the degree of muscle relaxation, as well as employing daily interruptions of paralysis, may reduce the incidence of prolonged paralysis.⁷⁰

NEUROMUSCULAR WEAKNESS ASSOCIATED WITH CRITICAL ILLNESS

Neuromuscular dysfunction associated with critical illness commonly contributes to the subsequent inability to wean such patients from mechanical ventilation.⁶⁶ Several forms of critical illness-associated neuromuscular dysfunction are recognized.

Intensive Care Unit–Acquired Weakness

Unexpected acute weakness and prolonged ventilatory failure were first reported in patients with status asthmaticus treated with corticosteroids and neuromuscular blocking drugs.^{71,72} Subsequently, a similar syndrome was recognized in other groups of ICU patients, especially those with sepsis and systemic inflammation, even without corticosteroid administration or therapeutic paralysis.⁶⁶ Either muscle or nerve abnormalities can predominate, leading to a confusing array of diagnostic terms, such as “critical illness myopathy,” “critical illness polyneuropathy,” “post-paralytic myopathy,” “ICU-acquired paresis,” “acute quadriplegic myopathy,” and the preferred term, *ICU-acquired weakness*.

The pathophysiology of ICU-acquired weakness is poorly understood but may involve elements of disuse and active muscle catabolism sparked by systemic inflammation. Electromyography reveals reduced compound muscle action potentials on motor nerve stimulation (with normal conduction velocity); increased action potential duration; and spontaneous electrical activity on muscle needle recording (e.g., fibrillation potentials, positive sharp waves).⁷³ Biopsy findings may include primary axonal degeneration, type II muscle fiber atrophy, thick filament (myosin) loss, and (occasionally) necrotizing myopathy.

One quarter to one half of all patients who require more than 7 days of ICU care and the majority of patients who develop the systemic inflammatory response syndrome can be shown by neurophysiologic testing to have ICU-acquired weakness.⁶⁶ These neurophysiologic abnormalities arise early, accumulate during the course of illness, and usually affect both nerves and muscles.⁷⁴ Prospective studies have shown that about one third of critically ill patients exhibit weakness on clinical evaluation.^{66,75} The typical patient exhibits symmetrical extremity weakness in which proximal function is more impaired than distal function and the facial muscles are spared. Clinically, this disorder can produce severe neuromuscular weakness, often affects the respiratory muscles, and may prolong the need for ventilatory support.^{75,76} This syndrome should be suspected in patients who are weak (*Medical Research Council* score < 48⁷⁵) in the context of critical illness, have the typical clinical examination, and in whom no better alternative cause for weakness can be identified. Handgrip strength may serve as a simple test to identify ICU-acquired weakness.⁷⁷ Nerve conduction studies, electromyography, and muscle biopsy generally are not necessary, but their role in diagnosis remains an area of active investigation. The prognosis for recovery of strength is variable, with many patients improving rapidly over days to weeks while others remain weak for many months or longer. The incidence of ICU-acquired weakness may be reduced by intensive insulin therapy,^{76,78,79} avoiding neuromuscular blocking drugs and corticosteroids where possible, and possibly by early mobilization.^{80,80a} Because ICU-acquired weakness is so strongly associated with severity of illness, length of ICU stay, and the presence of multiple organ system dysfunction, prevention focuses on scrupulous attention to good general ICU care and avoidance of sepsis.⁶⁶

Ventilator-Induced Diaphragmatic Dysfunction

Many critically ill patients develop muscle weakness that impedes functional recovery and is associated with prolonged mechanical ventilation. Some component of this represents ICU-acquired weakness,⁸¹ but mechanical ventilation itself (without systemic inflammation) can induce respiratory muscle weakness.⁸²⁻⁸⁴ The lack of neural stimulation or associated contraction plays a role in the evolution of weakness because measures to keep muscles contracting can ameliorate weakness. The diaphragm, the muscle most responsible for sustaining the work of breathing, may be even more sensitive than other skeletal muscles to the effects of critical illness. In animal models, the diaphragm weakens during the first 1 to 3 days of mechanical ventilation. Using phrenic nerve stimulation, one study demonstrated weakness by measuring a reduction in maximal

transdiaphragmatic pressure in a group of continuously ventilated patients in comparison with findings in normal volunteers.⁸⁵ As in studies of peripheral skeletal muscle, stimulating the diaphragm attenuates the loss of strength.⁸⁶ This suggests that partial rather than full ventilatory support may serve to maintain diaphragmatic strength, potentially reducing time on the ventilator.⁸⁶

ASSESSMENT OF NEED FOR MECHANICAL VENTILATION IN NEUROMUSCULAR WEAKNESS

Respiratory muscle weakness can be suspected when there is obvious peripheral muscle weakness, but neuromuscular abnormalities may not always be evident. Respiratory muscle weakness should also be suspected when dyspnea is out of proportion to radiographic and respiratory mechanical abnormalities seen during mechanical ventilation. Orthopnea raises the possibility of diaphragmatic weakness or paralysis. Further, suspicion is raised when maximal inspiratory pressure is reduced or, in some instances, when ultrasound examination of the diaphragms is abnormal.

Early clinical indicators of the need for mechanical ventilation in patients with neuromuscular weakness remain controversial. In addition to subjective assessments of symptoms of dyspnea and respiratory distress, objective assessments of vital capacity and maximum inspiratory and expiratory pressures have been used to evaluate ventilatory muscle capability.

In AIDP, rapid disease progression, bulbar and bilateral facial weakness, and dysautonomia are highly correlated with the need for intubation and mechanical ventilation. Moreover, a reduced vital capacity (<20 mL/kg), maximum inspiratory pressure (less negative than -30 cm H₂O), and maximum expiratory pressure (<40 cm H₂O) are associated with the need for intubation.⁵⁰ However, no prospective randomized studies have assessed these variables, and predictors of the need for intubation may merely reflect the criteria in current use to determine when a patient should be intubated.

One study on AIDP reported an association between electrophysiologic evidence of demyelination and the need for intubation and mechanical ventilation.⁸⁷ Another study on 44 AIDP patients who required mechanical ventilation showed greater cranial nerve involvement and *immunoglobulin G* (IgG) anti-GQ1b antibody levels than 87 AIDP patients not requiring intubation.⁸⁸ These could also be markers of greater disease severity, thus explaining the higher intubation rates.

In *myasthenia gravis* (MG), the criteria to predict the need for intubation are not as reliable as for AIDP, mostly due to the fluctuating nature of MG.⁸⁹ Nonetheless, serial assessments of vital capacity and the use of the same predictors as for AIDP are still recommended in MG as long as the patient is monitored closely in an ICU and caregivers are prepared for emergent intubation if necessary.^{90,91}

In ALS, as previously noted, serial ventilatory muscle assessments during outpatient management are required for the timely initiation of NIV to avoid respiratory crises and the need for emergency intubation. Evaluation of clinical signs of respiratory muscle weakness (such as use of accessory muscles and paradoxical or diminished excursion of the abdomen) and symptoms of diaphragm weak-

ness (such as orthopnea) are important to assess. We recommend serial measurement of pulmonary function tests, nocturnal oximetry, and sniff inspiratory pressure as an index of diaphragm strength. Recommendations for starting NIV in ALS patients vary widely from FVC less than 80% predicted, with the idea that deterioration in respiratory muscle function can be slowed, to less than 50% predicted in the United States as per the threshold for Medicare reimbursement for NIV.⁹²⁻⁹⁴ The authors believe that data are insufficient to make firm recommendations on any specific FVC threshold for NIV initiation but that, in association with pulmonary dysfunction, NIV should be started when patients develop symptoms that are likely to respond to NIV. For example, dyspnea at rest or orthopnea can respond to NIV, as can symptoms attributable to poor sleep, such as daytime fatigue, hypersomnolence, or morning headaches.

Although the optimal means for monitoring respiratory muscle function remain uncertain, it is clear that initiation of NIV or, if that fails, intubation and mechanical ventilation (if patients desire it) should be undertaken before the development of severe respiratory acidosis or respiratory arrest. For this reason, patients with acute neuromuscular disease who show signs of pulmonary compromise should be monitored in an ICU. Although the rate of progression may fluctuate, serial measurements of vital capacity and maximal inspiratory pressure along with repeated physical examinations focusing on bulbar function and ability to cough are advisable to avoid emergent intubations (Fig. 99-3).⁹⁵

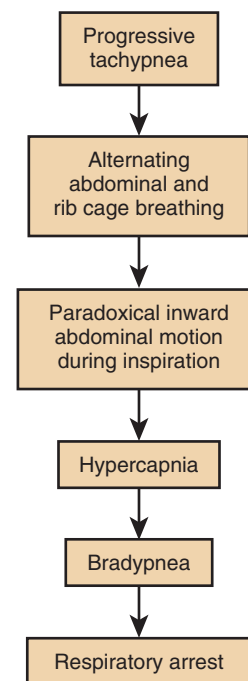


Figure 99-3 The sequence leading from ventilatory pump failure to respiratory arrest. Individual patients proceed through the steps shown at variable rates and may skip one or more stages. However, except for sudden events affecting the central nervous system or the administration of paralyzing drugs, respiratory arrest does not present abruptly without preceding physical manifestations. (Adapted in part from Cohen CA, Zagelbaum G, Gross D, et al: Clinical manifestations of inspiratory muscle fatigue. *Am J Med* 73:308–316, 1982.)

PRINCIPLES OF VENTILATOR MANAGEMENT

Patients with acute ventilatory failure due to neuromuscular disease usually have normal underlying lung parenchyma. Although NIV is often used successfully in these patients, significant bulbar involvement is associated with a high likelihood of NIV failure and patients with these deficits should be intubated if the goal is prolongation of life. Intubated patients are usually supported with volume-targeted ventilators using tidal volumes of 6 to 8 mL/kg, rates slightly below spontaneous, and 5 to 10 cm H₂O PEEP to prevent atelectasis. These targets can also be achieved using portable pressure-limited ventilators with the pressure difference between inspiratory and expiratory pressure adjusted to achieve similar tidal volumes (pressure difference usually at least 8 to 10 cm H₂O) while avoiding respiratory alkalosis. In patients requiring continuous ventilatory assistance, settings should aim not only to maintain gas exchange but also comfort, considering that there is no convincing evidence that “exercising” respiratory muscles in neuromuscular disease speeds recovery. Some advocate a new protocol using prophylactic NIV and mechanical cough assistance to facilitate extubation and avert the need for reintubation in patients with neuromuscular disease who are weaning from invasive mechanical ventilation.^{62,96}

ACUTE VENTILATORY FAILURE DUE TO CHEST WALL DEFECTS

(see Chapter 98)

Many restrictive diseases of the lungs or chest wall progress insidiously over months or years. Critical illness may represent the natural history of the underlying condition but may also signal an acutely superimposed, potentially reversible crisis such as infection, pneumothorax, or thromboembolism.

CHEST WALL SKELETAL ABNORMALITIES

Thoracic restriction and ventilatory muscle dysfunction due to severe kyphoscoliosis typically lead to gradually progressive ventilatory insufficiency. Such patients can present with acute or acute-on-chronic ventilatory failure and require intensive care. Physiologic studies have shown that both lung and chest wall mechanics are impaired during acute respiratory failure in patients with kyphoscoliosis.⁹⁷ Chest trauma, especially when leading to flail chest due to rib fractures, may also cause the development of acute hypercapnic respiratory failure. In either case, the ventilator pump fails because of inability to sustain ventilatory work due to abnormalities that compromise ventilatory function, such as increased chest wall stiffness in kyphoscoliosis and decreased ventilator efficiency due to paradoxical chest wall motion and pain in flail chest.

PLEURAL DISEASE

Primary disease of the pleura, such as asbestos-related diffuse pleural thickening or postinflammatory fibrothorax,

could potentially present in a similar way as skeletal deformities, but dyspnea and hyperventilation are more common with these chronic pleural diseases. Respiratory acidosis develops late in the course of the disorder unless ventilatory drive is depressed or there is concomitant lung involvement. Pleural effusion or pneumothorax can likewise precipitate acute ventilatory failure, usually in the presence of underlying obstructive or restrictive pulmonary parenchymal disease.

PRINCIPLES OF MANAGEMENT

Long-term NIV appears to be beneficial in selected patients with kyphoscoliosis and other chest wall diseases⁹⁸ and has been reported to be successful in acute-on-chronic ventilatory failure.⁹⁹⁻¹⁰² Some recent studies report that NIV reduces the need for intubation and leads to a shortened hospital stay in patients with chest trauma.^{103,104}

Parenchymal Lung Disease

Idiopathic pulmonary fibrosis and other pulmonary parenchymal restrictive diseases are usually associated with hyperventilation rather than hypoventilation. However, acute ventilatory failure can arise in the late stages of these conditions, either as a manifestation of the primary disease process^{105,106} or, more often, in conjunction with pneumonia, surgery, or other intercurrent illness.¹⁰⁷⁻¹⁰⁹ Physiologic assessment has demonstrated marked increases in lung stiffness and airway resistance in patients with end-stage idiopathic pulmonary fibrosis requiring mechanical ventilation,¹⁰⁹ explaining the development of hypercapnia and acute ventilatory failure.

Several case series have documented the poor prognosis of patients who present with acute respiratory failure in the setting of advanced interstitial fibrosis.^{106,108,109} In one retrospective report, all 14 consecutive patients with acute respiratory failure and idiopathic pulmonary fibrosis admitted to the ICU died despite aggressive ventilatory support.¹⁰⁷ In another report of 23 similar patients, 22 patients died; the single survivor received a lung transplant shortly after admission.¹⁰⁸ In a third series of 19 patients with idiopathic pulmonary fibrosis and AREF, 13 died.¹⁰⁹ Outcomes appear equally poor regardless of whether ventilation is invasive or noninvasive.¹¹⁰

Principles of Ventilator Management

Due to increased lung stiffness, NIV for restrictive disease usually requires higher airway pressures than are used for COPD. Thus, avoiding gastric insufflation and air leaks around the mask is more challenging. Furthermore, considering that a superimposed condition such as a respiratory infection often precipitates the acute bout of respiratory failure, accompanied by increased work of breathing and secretion retention, invasive ventilatory support is often warranted. The best way to ventilate patients with acute respiratory failure in the setting of underlying restrictive thoracic or lung disease has not been determined by clinical trials. The potential for hemodynamic compromise, barotrauma, and ventilator-induced lung injury with the use of high pressures and the physiologic similarity to ARDS in patients with deteriorating pulmonary fibrosis make it reasonable to apply similar lung-protective ventilator strategies

and management targets (see Chapter 101). Low tidal volumes (e.g., 6 mL/kg predicted body weight) should be applied, attempting to keep the end-inspiratory plateau pressure below 30 cm H₂O if possible. Patients with restrictive lung disease typically breathe rapidly and shallowly, so tachypnea may not be avoidable during the weaning process and should not be used as the sole reason for delaying extubation if gas exchange and other assessments are acceptable.

ACUTE VENTILATORY FAILURE DUE TO AIRWAY OBSTRUCTION

UPPER AIRWAY OBSTRUCTION

Upper airway obstruction is an occasional cause of acute ventilatory failure. The onset can be precipitous, as with occlusion of the glottis by an aspirated foreign body (i.e., “café coronary”) or a swollen and edematous epiglottis due to acute epiglottitis.¹¹¹ The onset can also be insidious, progressing over months, as with a tracheal tumor. The severity and length of narrowing and air flow determine the airway resistance and thus the additional work of breathing imposed by the obstruction. Gradually progressive upper airway narrowing may be well tolerated, at least while breathing at rest, until a critical limit is reached, often when the airway diameter drops to the range of 5 to 6 mm.

The location and variability of the narrowing are also important in determining the clinical manifestations. Extrathoracic variable upper airway narrowing affects mainly inspiratory flow because the negative intraluminal pressure exacerbates the narrowing during inspiration. During expiration, the positive intraluminal pressure widens extrathoracic airways. Vocal cord paralysis is an excellent example of a variable extrathoracic upper airway obstruction, producing stridor and severe airway obstruction during inspiration but no significant obstruction during expiration. The opposite pertains to variable intrathoracic obstructions, with narrowing becoming less severe during inspiration because pressure gradients favor airway widening. During expiration, the airways narrow and the severity of the obstruction worsens. Tracheomalacia can cause variable intrathoracic airway obstruction. Fixed obstructions affect both inspiration and expiration regardless of their location.

Upper airway obstruction causes ventilatory failure by increasing airway resistance to the point where respiratory muscles can no longer sustain minute volume at a level adequate to maintain CO₂ homeostasis. Negative-pressure pulmonary edema can also contribute to the gas-exchange impairment.¹¹² Ideally, the therapeutic aim is to relieve the obstruction. This may be achieved by removal of a foreign body, laser therapy of an endotracheal tumor, placement of a stent in an area of tracheomalacia or stenosis, or tracheostomy to bypass an area of obstruction. Inhalation of heliox (to reduce airway resistance), *continuous positive airway pressure* (CPAP), or noninvasive ventilation using pressure support and PEEP can help to reduce the work of breathing and avoid intubation in patients who have reversible causes of their upper airway obstruction, such as

postextubation stridor, or who are awaiting tracheostomy or surgical repair of an obstruction. However, these temporizing measures require close monitoring with the recognition that the patient can deteriorate abruptly.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is the third leading cause of death among adults aged 65 to 84 in the United States, being the primary contributor to mortality caused by lower respiratory disease, and poses enormous costs to the U.S. health care system, mostly due to hospitalization.¹¹³ The vast majority of hospitalizations are due to acute exacerbations of COPD, but other causes such as acute pneumonia, congestive heart failure, pulmonary embolism, and pneumothorax may contribute to the deterioration.

PATHOPHYSIOLOGY

Hyperinflation associated with severe COPD places the respiratory muscles at a mechanical disadvantage (Fig. 99-4). The loss of elastic structures is responsible for an increase in lung compliance leading to hyperinflation (with an increase in total lung capacity and functional residual capacity) and the collapse of small airways during expiration that contributes to an increase of residual volume, often referred to as “air trapping.” The flattening of the diaphragm increases the radius of curvature, which, according to the Law of Laplace, also increases muscle tension and impedance to blood flow. In addition, ventilatory efficiency is reduced because the shortened diaphragm operates at a disadvantageous position on its length-tension curve and the horizontal orientation of the flattened diaphragm causes the lower rib cage to move paradoxically during inhalation, inward rather than outward (“Hoover sign”).

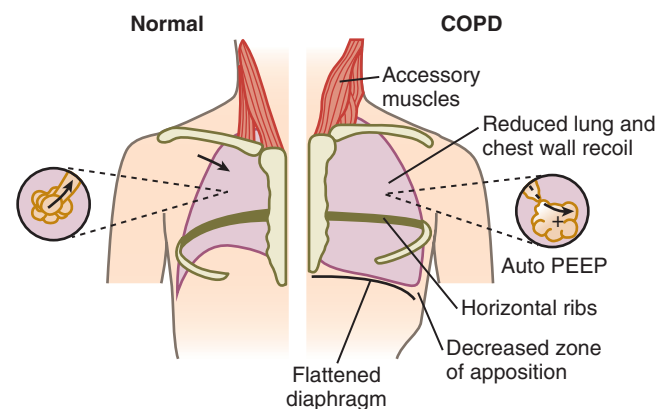


Figure 99-4 Schema depicting the chest wall configuration at functional residual capacity of a normal individual (left) and a patient with severe COPD (right). The COPD patient has a flattened diaphragm, which increases its radius of curvature and increases the tension for a given pressure. The COPD patient's ribs are horizontal, and the zone of apposition between the diaphragm and chest wall is reduced, greatly reducing the diaphragm's efficiency in expanding the chest wall. Also, intrinsic positive end-expiratory pressure (auto PEEP) poses an inspiratory load, adding further to the inspiratory work. Exhalation is slowed by airway collapse and the loss of elastic recoil. (Redrawn from Hill NS: Current concepts in mechanical ventilation for chronic obstructive pulmonary disease. *Semin Respir Crit Care Med* 20:375–395, 1999.)

The hyperinflation and impairment in diaphragm function necessitate the recruitment of accessory muscles to maintain ventilation at higher lung volumes, contributing to the already increased oxygen cost of breathing. Finally, the collapse of small airways predisposes to incomplete emptying and positive intrathoracic pressure at end-expiration (intrinsic or auto-PEEP). Auto-PEEP poses an inspiratory threshold load requiring that inspiratory muscles lower the elevated alveolar pressure to subatmospheric in order to initiate airflow for the next breath.^{114,115}

During an exacerbation of COPD, the combination of airway swelling, secretions, and bronchospasm caused by acute inflammation increases airway resistance, further worsening the expiratory flow-limitation and increasing end-expiratory lung volume. As depicted in Figure 99-5, COPD patients adapt by attempting to maintain airflow by breathing at even higher lung volumes. In addition, they adopt a rapid, shallow breathing pattern that further limits the time available for expiration, aggravating intrinsic PEEP and adding further to the work of breathing. The diaphragm flattens more and develops increased tension, further impeding diaphragmatic blood flow. The resulting limitation in substrate delivery to muscle is aggravated by progressive hypoxemia, caused by worsening hypoventilation and \dot{V}/\dot{Q} imbalance related to secretion retention. Thus, as the demand for breathing increases, the capacity to supply breathing work diminishes. As respiratory drive increases in a futile attempt to reverse the worsening alveolar

hypoventilation, muscular performance deteriorates and the diaphragm fatigues.¹¹⁶ A vicious cycle ensues, leading inexorably to worsening respiratory muscle fatigue, ventilatory failure, and death unless therapeutic interventions interrupt the cycle.

Clinical Assessment

Patients with exacerbations of COPD must be carefully evaluated to identify those at risk of developing respiratory failure and to exclude other causes of respiratory failure. History and physical examination are useful. Although the Borg or visual analogue scales help gauge the level of dyspnea in clinical studies, a subjective assessment that dyspnea is worse than at baseline and of at least moderate severity suffices to identify patients who may be at risk for respiratory failure. Physical findings seen with severe exacerbations include tachypnea; accessory muscle use; abdominal paradox; Hoover sign (inspiratory inward motion of the lower, lateral rib cage); cyanosis; and mental status alterations.

In addition to a sputum examination for purulence, a white blood cell count, electrocardiogram, chest radiograph, and arterial blood gas should be obtained to assess the severity of an exacerbation. The widespread use of continuous pulse oximetry and of venous blood gases has decreased, but not eliminated, the need for arterial blood gases. Whereas venous pH values generally agree with arterial values, venous PCO_2 poorly reflects arterial PCO_2 ; nonetheless, a normal venous PCO_2 may be useful in excluding hypercapnia.¹¹⁷ Arterial blood gases provide a rapid assessment of arterial PCO_2 and pH, information that is critical when deciding to place patients in critical care units or to initiate mechanical ventilation and to assess response to therapy. During severe exacerbations, patients with chronic CO_2 retention develop acute-on-chronic hypercapnia, manifested by a drop in pH indicative of retained CO_2 uncompensated by bicarbonate, an important indicator of ventilatory failure that can be detected only by measurement of arterial blood gases.

Medical Therapy

Medical therapy, consisting of bronchodilators, corticosteroids, and antibiotics, should be promptly started in patients with severe exacerbations. Additional therapies, including diuretics, nitrates, or anticoagulation, should be started whenever comorbidities such as congestive heart failure or pulmonary embolism are suspected.

Oxygen should be supplemented routinely to improve hypoxemia, but it should be carefully titrated in patients with CO_2 retention to maintain a target SpO_2 of 88% to 92%. Overzealous oxygen supplementation in such patients has long been known to aggravate CO_2 retention, by either blunting the hypoxic ventilatory drive, increasing physiologic dead space (perhaps due to oxygen-induced bronchodilation in poorly perfused lung regions), or both. Because hypoxemia in COPD patients is usually due mainly to hypoventilation and is easily reversed, initial supplementation with nasal oxygen at 2 L/min is often adequate.¹¹⁸ In patients with severe exacerbations, arterial blood gases should be repeated periodically to assess the effect of oxygen supplementation on arterial PCO_2 .

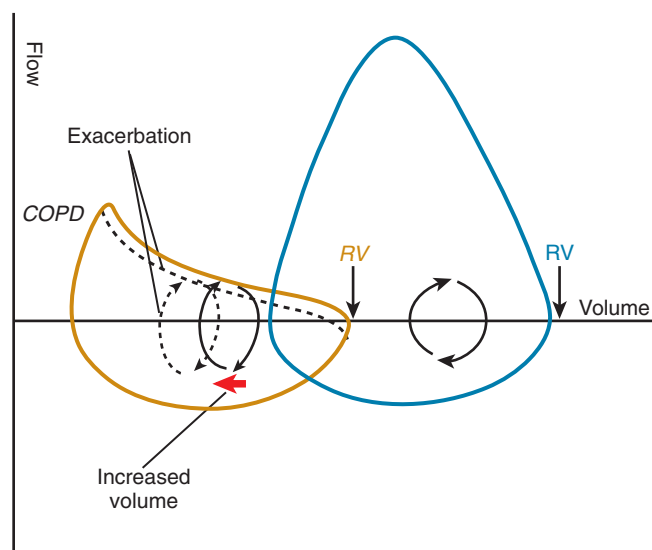


Figure 99-5 Flow-volume loops for a patient with a normal lung (blue line on right) and one with COPD (brown line on left) along with their respective tidal volume loops (inner black loops with arrows). Note that the expiratory flow during tidal breathing in the COPD patient reaches maximal expiratory flow. During an exacerbation (dashed lines), expiratory flow drops; because the flow during tidal breathing is already maximal, the only mechanism available for maintaining flow is to increase lung volume during tidal breathing (leftward shift of tidal breathing loop, shown by red arrow). Although this strategy maintains expiratory flow, it increases the work of breathing and oxygen consumption, predisposing to inspiratory muscle fatigue and eventual respiratory failure. RV, residual volume. (Redrawn from Hill NS: Current concepts in mechanical ventilation for chronic obstructive pulmonary disease. *Semin Respir Crit Care Med* 20:375–393, 1999.)

Noninvasive Ventilation

Although medical therapy alone is usually effective in mild COPD exacerbation, it is often not sufficient in severe exacerbations. In severe exacerbations, tachypnea, dyspnea, and CO₂ retention may persist or worsen despite initial medical therapy. Before 10 years ago, patients in such a predicament would usually be intubated and mechanically ventilated. If they declined intubation, they were kept comfortable while medical therapy was continued, but they often died. Invasive mechanical ventilation was successful in the majority of cases, but hospital mortality rates were substantial, averaging 30% in several studies.¹¹⁹ Complications of invasive mechanical ventilation were common, including upper airway trauma, pneumothorax, and nosocomial infection, all contributing to patient mortality.¹²⁰

In 1990 Brochard and coworkers¹²¹ demonstrated that the noninvasive delivery of pressurized air into the lungs via a face mask was effective in providing partial ventilatory assistance during COPD exacerbations. These workers used a device designed to provide pressure support that reduced diaphragmatic work of breathing by increasing airway pressure with each inhalation. Later, Appendini and colleagues¹²² demonstrated that combining extrinsic PEEP (to counterbalance the effects of intrinsic PEEP) with pressure support even more effectively reduced the work of breathing in COPD patients than either CPAP or pressure support alone. By reducing the work of breathing, NIV restores the balance between supply and demand for the work of breathing, thereby serving as a “crutch” during COPD exacerbations and halting the progression of respiratory muscle fatigue while medical therapies are given time to work.

Since Brochard’s groundbreaking study, multiple randomized controlled studies and meta-analyses have demonstrated the efficacy of NIV to treat exacerbations of COPD.¹²⁰ When compared with conventional therapy alone, NIV for severe exacerbations of COPD more rapidly improves dyspnea, respiratory and heart rates, arterial PCO₂, and encephalopathy scores.¹²³⁻¹²⁵ In addition, intubation and mortality rates drop precipitously (from roughly 75% and 30% in controls to 25% and 10%, respectively, in NIV-treated patients).^{123,124,126} NIV also lowers complication rates and hospital lengths of stay compared with controls.¹²³⁻¹²⁵ One study has reported that NIV failed to lower intubation or mortality rates or hospital lengths of stay in patients with COPD exacerbations, but it is notable that blood gases were only mildly deranged and there were no intubations or mortality in the control group. This result suggests that patients with relatively mild COPD exacerbations are unlikely to derive benefit from NIV, and the modality should usually be reserved for those with mild to severe symptoms.^{127,128}

Several meta-analyses^{129,130} have concluded that NIV is effective in avoiding intubation (relative risk 0.42 and absolute risk reduction 28%, respectively), reducing mortality (relative risk 0.41 and absolute risk reduction 10%, respectively), and shortening hospital length of stay (by ≈4 days). A recent study on a large cohort of patients (25,628) with COPD exacerbations requiring mechanical ventilation showed reduced mortality, length of stay, and cost with NIV compared to invasive ventilation.^{130a} On the basis of this

evidence, the authors of these meta-analyses, reviews, and guidelines¹²⁹⁻¹³⁵ have advised that NIV should be the ventilatory modality of first choice and should be started early in the course of moderate to severe COPD exacerbations.

Heliox Combined with Noninvasive Ventilation. By virtue of its lower density than nitrogen, helium can be combined with oxygen to lower the airway resistance attributable to turbulent flow. The oxygen concentration can be increased to about 40% in the helium-oxygen mixture but not higher without losing the density advantage of the added helium. Heliox has been combined with NIV to treat patients with COPD exacerbations, with beneficial physiologic responses including reduced airway resistance and more rapid improvements in gas exchange.¹³⁶ However, subsequent randomized, prospective trials on patients with COPD in respiratory failure found that the addition of heliox to NIV offered no significant advantages over NIV alone in terms of intubation or mortality rates or hospital lengths of stay.^{137,138}

COPD Complicated by Pneumonia

COPD patients may develop acute or acute-on-chronic respiratory failure due to an exacerbation complicated by pneumonia. When evaluating a COPD patient with worsening of baseline symptoms, concomitant pneumonia should be considered as a contributing factor. By virtue of impairment in cellular and molecular defense mechanisms and the common use of inhaled corticosteroids, which have been associated with increased pneumonia rates, COPD patients are at risk for pneumonia.¹³⁹ In addition, pneumonia is related to a more severe presentation of community-acquired pneumonia in hospitalized patients, without being a risk factor for mortality.¹⁴⁰

Pneumonia has been associated with a poor outcome in patients treated with NIV.¹⁴¹ However, in one trial on severe community-acquired pneumonia, NIV reduced intubation (21% vs. 50%, $P = 0.03$) and mortality rates, and shortened ICU length of stay (1.8 vs. 6.0 days, $P = 0.04$) compared with standard oxygen therapy. Benefit, however, was confined to the subgroup of patients with underlying COPD.¹⁴² Thus, although the presence of pneumonia is a risk factor for poorer outcome with NIV, COPD patients with pneumonia can still benefit.

Postoperative Patients

Postoperative pulmonary complications are defined as pulmonary abnormalities (such as atelectasis, pulmonary embolism, ALI/ARDS) that arise frequently in the postoperative period, particularly in COPD patients. These complications, due to general anesthesia, postoperative immobility, or to the surgery itself, increase morbidity, mortality, and length of stay.

NIV has been reported to be effective in reducing the need for intubation, ICU length of stay, and mortality rate in post-lung resection patients with acute respiratory insufficiency.^{143,144} Although only a portion of these patients had COPD, accumulating evidence now supports the use of NIV in selected postoperative (including COPD) patients to maintain improved gas exchange and avoid reintubation and its attendant complications. NIV techniques are also

being used prophylactically to reduce secretion problems, atelectasis, and hypoxemia after thoraco-abdominal and major abdominal surgery.¹⁴⁵⁻¹⁴⁷

Postextubation in COPD

Between 10% and 15% of patients develop respiratory failure after a standard extubation, increasing the length of stay on mechanical ventilation and in the ICU and therefore the risk of related complications including mortality.¹⁴⁸⁻¹⁵⁰ In this context, NIV can be used in several ways: (1) to permit earlier removal of the endotracheal tube by assisting ventilation postextubation, (2) to prevent the onset of respiratory failure and need for reintubation in patients at risk for respiratory failure postextubation, and (3) to avoid the need for reintubation in patients who develop frank respiratory failure postextubation.¹⁵¹

Using NIV to allow earlier removal of the endotracheal tube is supported by randomized controlled trials. One trial demonstrated that extubation to NIV after 48 hours of intubation increased overall weaning rate after 60 days (88% vs. 68%), shortened the duration of mechanical ventilation (10.2 vs. 16.6 days), shortened the stay in the ICU (15 vs. 24 days), and improved 60-day survival (92% vs. 72%) (all $P < 0.05$) compared with patients left intubated.¹⁵² A second randomized, controlled trial in patients with “persistent weaning failure” (failure of spontaneous weaning trials on 3 consecutive days) showed that early extubation to NIV significantly reduced ICU and hospital length of stay, incidence of nosocomial pneumonia (from 59% to 24%, $P < 0.05$), complication rate, and hospital and 90-day mortality (odds ratio 3.5).¹⁵³

These randomized studies support use of NIV to facilitate early extubation of invasively ventilated COPD patients. However, if early extubation is contemplated, it should be reserved for carefully selected patients.¹⁵¹ Patients should be recovering from COPD exacerbations, be on 15 cm H₂O or less of pressure support, be able to sustain 5 to 10 minutes of unassisted breathing, have an adequate cough without excessive secretions, be easy to intubate, and have few if any comorbidities.

Using NIV in patients who develop respiratory failure postextubation to avoid reintubation has less support in the literature. Two randomized trials of patients at high risk for extubation failure used NIV prophylactically to prevent reintubation but failed to show the anticipated benefit. In one,¹⁵⁴ NIV provided no reduction in the need for intubation, duration of mechanical ventilation, length of hospital stay, or mortality. In the other, NIV failed to show benefit in these variables and was associated with increased ICU mortality.¹⁵⁵ In the latter study, the increased mortality was thought to be related to a 10-hour longer delay before proceeding with reintubation compared with controls. Furthermore, only 10% of patients in both of these studies had COPD, leading to the speculation that results might have been favorable if more patients with COPD had been enrolled.

This speculation has been borne out by two subsequent randomized, controlled trials, one showing dramatic reductions in respiratory failure, need for reintubation, and mortality in a subgroup of hypercapnic patients,¹⁵⁶ and the other demonstrating that patients with hypercapnia postextubation have a significant reduction in acute ventilatory

failure if treated prophylactically with NIV compared with standard oxygen supplementation.¹⁵⁷ Thus, the best current recommendation is to use NIV selectively in patients with extubation failure, mainly for COPD or other hypercapnic patients, and to avoid delays in intubation should NIV fail.

Do-Not-Intubate Patients

The use of NIV to treat respiratory failure in patients who have declined intubation accounted for 10% of acute applications in one survey.¹⁵⁸ This application has been controversial, with some arguing that there is little to lose because it may reverse the acute deterioration or, at least, provide relief of dyspnea and a few extra hours to finalize affairs.¹⁵⁹ Others have argued that this merely prolongs the dying process, consumes resources inappropriately, and may add to discomfort or counter patients' wishes about avoiding life-prolonging measures.¹⁶⁰ In prospective observational studies of 113¹⁵⁸ and 131¹⁶¹ *do-not-intubate* (DNI) patients treated with NIV, survival to hospital discharge was greater than 50% for COPD and congestive heart failure patients, whereas it was lower (14% to 25%) for those with a diagnosis of hypoxemic respiratory failure (pneumonia) or advanced cancer. Thus, NIV can be used to treat respiratory failure for DNI patients with acutely reversible processes such as COPD exacerbations. Alternatively, it can be used to palliate DNI patients, by alleviating dyspnea or providing temporary support. The patient or family should be informed that NIV is being used as a form of life support that may be uncomfortable and can be removed at any time.

Practical Application of Noninvasive Ventilation

A thorough discussion of the application of NIV is beyond the scope of this chapter, and the reader is referred to Chapter 102 and elsewhere for more complete descriptions.^{132,162} The following sections focus on aspects relevant to applications in COPD patients with acute respiratory failure.

Patient Selection. Selection of appropriate patients is key to the successful application of NIV. The selection process should take into account the patient's clinical characteristics and risk of failure on NIV (Table 99-2). Predictors of success of NIV have been identified^{139,163} (Table 99-3) and include a good neurologic status (and hence more cooperativeness), ability to protect the airway, and only mild-moderate acid-base or gas-exchange derangement. Several studies have also found that improvements in pH, arterial PCO₂, and level of consciousness within the first hour or two of NIV initiation are strong predictors of success.^{139,163} These studies indicate that there is a “window of opportunity” when initiating NIV that opens when patients need ventilatory assistance but closes if they progress too far and become severely acidemic. Ultimately, it becomes a clinical judgment that takes into account the patient's diagnosis that led to the respiratory failure, the need for ventilator assistance, and the absence of contraindications (see Table 99-2).¹⁶⁴

Mask Selection. Tolerance of the mask is key to the success of NIV. Thus, the mask must be a good fit and strapped on sufficiently to control air leaks while avoiding excessive strap tension. For acute applications, the standard

Table 99-2 Selection Criteria for Noninvasive Positive-Pressure Ventilation in Acute Exacerbations of Chronic Obstructive Pulmonary Disease**ESTABLISH NEED FOR VENTILATORY ASSISTANCE**

Moderate to severe respiratory distress
 Tachypnea (RR > 24 breaths/min)
 Accessory muscle use or abdominal paradox
 pH < 7.35, arterial PCO₂ > 45 mm Hg or
 Arterial PO₂/FIO₂ < 200

EXCLUDE PATIENTS WITH CONTRAINDICATIONS TO NONINVASIVE VENTILATION

Respiratory arrest
 Medically unstable (septic or cardiogenic shock, uncontrolled upper gastrointestinal bleeding, acute myocardial infarction with planned intervention, uncontrolled arrhythmias)
 Unable to protect airway
 Excessive secretions
 Uncooperative or agitated
 Unable to fit mask
 Recent upper airway or upper gastrointestinal surgery

FIO₂, fractional concentration of oxygen in inspired gas; NIV, noninvasive ventilation; PCO₂, partial pressure of carbon dioxide; PO₂, partial pressure of oxygen; RR, respiratory rate.

Adapted from Liesching T, Kwok H, Hill NS: Acute applications of noninvasive positive pressure ventilation. *Chest* 124:699–713, 2003.

Table 99-3 Predictors of Success for Noninvasive Positive-Pressure Ventilation in the Acute Setting**EFFECTIVE SYNCHRONY OF PATIENT WITH VENTILATOR**

Able to cooperate
 Good neurologic status
 Younger age
 Minimal air leaks
 Dentate
 Compliance*

ABLE TO PROTECT AIRWAY

Low volume of secretions
 Low aspiration risk

NOT TOO ACUTELY ILL

No pneumonia
 Lower APACHE II score (<34)
 Initial arterial PCO₂ < 92 mm Hg
 Initial pH > 7.10

GOOD INITIAL RESPONSE (WITHIN FIRST HOUR OR TWO)

Improvement in pH
 Reduction in respiratory rate
 Reduction in arterial PCO₂
 Improved level of consciousness

*"Compliance" refers to the clinician's assessment of the patient's acceptance of the technique.

APACHE, Acute Physiology, Age, and Chronic Health Evaluation; NIV, noninvasive ventilation; PCO₂, partial pressure of carbon dioxide.

Adapted from Ambrosino N, Foglio K, Rubini F, et al: Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. *Thorax* 50:755–757, 1995; and SooHoo GW, Santiago S, Williams AJ: Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. *Crit Care Med* 22:1253–1261, 1994.

full-face (oronasal) mask is usually preferred because it is better tolerated and avoids the leaking of air through the mouth that can limit the efficacy of nasal masks.¹⁶⁵ Nasal masks, however, may be more comfortable for long-term applications,^{166,167} so transitioning from a full face mask to a nasal mask should be contemplated after the first few days if NIV is to be continued. The helmet, consisting of a plastic cylinder that seals over the neck and shoulders, offers an alternative interface. It is effective for delivery of CPAP in particular. Although difficulty achieving patient-ventilator synchrony has been reported when it is used to deliver pressure support ventilation, increasing the PEEP level to render the mask less compliant seems to help.¹⁶⁶ Within each mask category, many types of masks are available. Practitioners should have a current knowledge of available masks and their proper application in order to maximize the likelihood of NIV success.

Ventilator Selection. In the acute setting, both "critical care" and "bilevel" ventilators (portable pressure-limited devices designed especially for the administration of noninvasive positive pressure ventilation) have been used with similar success rates. A bilevel device designed for use in the acute care setting that includes an oxygen blender and displays waveforms has gained popularity. In addition, many ventilators designed primarily for invasive mechanical ventilation now offer noninvasive modes that are programmed to improve leak compensation, silence "nuisance" alarms that are triggered by air leaks, and permit limitation of inspiratory time to enhance patient-ventilator synchrony.¹⁶⁸ The capabilities of these modes differ considerably, however, and may require additional adjustment if there are mask leaks.¹⁶⁹

NIV Initiation. At the start of NIV, the properly sized mask is placed on the patient's face and attached to the ventilator. Patients often feel more comfortable if they can hold the mask themselves. Pressure-limited modes may be better tolerated than volume-limited modes.¹⁷⁰ Initial ventilator pressures are usually low, to enhance patient comfort and acceptance, but adjusted upward as tolerated to provide adequate ventilatory assistance. Typical initial settings on pressure-limited ventilators are 8 to 12 cm H₂O for inspiratory pressures and 4 to 5 cm H₂O for expiratory pressures (e.g., PEEP), with subsequent adjustments as needed to alleviate respiratory distress or counterbalance intrinsic PEEP or treat hypoxemia. The difference between inspiratory and expiratory pressure is the level of pressure support and should be adequate to alleviate inspiratory effort while avoiding excessive discomfort.

Some ventilators permit adjustments in airflow to enhance synchrony, such as the "rise time," which determines the time to reach the target inspiratory pressure and the adjustable inspiratory time. These may be helpful in optimizing comfort in COPD patients who tend to prefer relatively high inspiratory flows¹⁷¹ (and hence short rise times, often 0.1 sec) and short inspiratory times (usually < 1 sec) to avoid prolongation of delivered inspiratory pressures during expiration.

Oxygenation and Humidification. Most patients with COPD exacerbations do not have severe oxygenation defects

and can be managed successfully with pressure-limited bilevel ventilators. With these ventilators, oxygen is administered at rates up to 15 L/min into ports in the mask or via a T-connector at the proximal end of the ventilator tubing, adjusted to maintain the desired level of oxygenation (usually to an *arterial oxygen saturation* [SaO_2] > 90% to 92%). Because FiO_2 using this arrangement cannot be generated at more than 45% to 50%, ventilators with oxygen blenders are necessary when a higher FiO_2 is needed, such as for patients with COPD complicated by pneumonia. Humidification should be used routinely because it may reduce the work of breathing and enhance comfort and tolerance during NIV.^{166,172,173}

Adaptation and Monitoring. Coaching and encouragement, especially during the first few hours, are critical in achieving adaptation. Judicious administration of low doses of sedatives may enhance patient acceptance. Close bedside monitoring is essential until the patient's respiratory status stabilizes. Although NIV can easily be administered on general medical wards, the acuteness of the patient's illness and need for close monitoring should dictate the site of administration. Acutely ill patients should be treated in an ICU or step-down unit until their condition stabilizes.^{125,174} As shown in Table 99-4, patient comfort and tolerance are key initial goals, together with a reduction in work of breathing and respiratory distress and optimization of patient-ventilator synchrony. Arterial SO_2 is monitored continuously, and blood gases are obtained as is clinically indicated, at baseline and at least once during the first hour or two.

Commonly Encountered Problems and Possible Remedies. Noninvasive ventilation is safe and well tolerated in most properly selected patients. The most commonly encountered problems in COPD patients are similar to those in other patients and are related to the mask, air pressure, or airflow (see Table 99-4). Minimizing air leaks is also an important aim.

Table 99-4 Monitoring Noninvasive Positive-Pressure Ventilation in Chronic Obstructive Pulmonary Disease

ACUTE SETTING

Patient comfort
Mask fit and leak
Patient-ventilator synchrony
Sternocleidomastoid muscle activity
Vital signs (heart and respiratory rate; systemic blood pressure)
Continuous oximetry (until stabilized)
Occasional blood gases (initial and after 30–120 minutes, then as clinically indicated)

CHRONIC SETTING

Patient comfort
Mask fit and leak
Hours of use
Problems with adaptation (e.g., nasal congestion, dryness, gastric insufflation, conjunctival irritation, inability to sleep)
Symptoms (e.g., dyspnea, fatigue, morning headache, hypersomnolence)
Gas exchange (daytime, nocturnal oximetry, blood gases periodically to assess arterial PCO_2)
Polysomnography (if symptoms of sleep disturbance persist or nocturnal desaturation persists without clear explanation)

PCO_2 , partial pressure of carbon dioxide.

Increasing Use of NIV for COPD

The use of NIV in a French ICU increased from 20% of initial ventilator starts to 80% during the 1980s. Concomitantly, the rate of ICU-acquired pneumonia dropped from approximately 20% in 1994 to 8% in 2001.¹⁷⁵ More recent studies using nationwide hospital databases have shown similar trends in the United States, with use of NIV increasing approximately 2.5- to 4.5-fold during the decade from 2000 to 2010, especially in patients older than 85 years,^{175a} accompanied by a drop in the use of invasive mechanical ventilation and a gradual decline in mortality. The mortality rate for patients failing NIV and having to transition to invasive ventilation has crept up over the same time period, raising the concern that NIV may be used occasionally in excessively ill patients who should have been intubated initially.¹⁷⁶

Invasive Mechanical Ventilation

Indications and Patient Selection. Although invasive mechanical ventilation is being used less often for acute exacerbations, it still has an important role in supporting patients who want aggressive support and those who are not eligible or who fail NIV. These and other indications for the use of invasive mechanical ventilation for COPD are listed in Table 99-5.

Invasive mechanical ventilation in COPD must be administered with care to minimize the risk of complications. Excessive tidal volumes and rates must be avoided, and the urge to normalize arterial PCO_2 must be repressed in an effort to minimize intrinsic PEEP and excessive hyperinflation. Excessive respiratory rates reduce the respiratory cycle, shorten expiratory time, and prevent complete exhalation. This problem is aggravated by large tidal volumes. The potential adverse consequence is air trapping and intrinsic PEEP. With intrinsic PEEP, increased intrathoracic pressure reduces venous return and lowers cardiac output. Patients with severe intrinsic PEEP may be hypotensive with

Table 99-5 Indications for Invasive Mechanical Ventilation in Chronic Obstructive Pulmonary Disease

Severe dyspnea with the use of accessory muscles and paradoxical abdominal motion
Respiratory frequency > 35 breaths/min
Life-threatening hypoxemia (arterial PO_2 < 40 mm Hg or arterial PO_2/FiO_2 < 200)
Severe acidosis (pH < 7.25) and hypercapnia (arterial PCO_2 > 60 mm Hg)
Respiratory arrest
Somnolence; impaired mental status
Cardiovascular complications (hypotension; shock; heart failure)
Other complications (metabolic abnormalities; sepsis; pneumonia; pulmonary embolism; barotrauma; massive pleural effusion)
Failure of noninvasive positive-pressure ventilation

FiO_2 , fractional concentration of oxygen in inspired gas; PCO_2 , partial pressure of carbon dioxide; PO_2 , partial pressure of oxygen.

From Pauwels RA, Buist AS, Calverley PM, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 163:1256–1276, 2001.

low cardiac output and elevated pulmonary artery wedge pressure due to transmission of the intrathoracic pressure. Their clinical presentation may therefore mimic that of cardiogenic shock. Temporary disconnection from the ventilator can differentiate hemodynamic compromise due to intrinsic PEEP from true cardiogenic shock because the release of intrathoracic pressure permits rapid resolution of the former but not the latter. Intrinsic PEEP may also cause patient-ventilator asynchrony if ventilator triggering is missed when patients cannot reach the triggering threshold due to the inspiratory threshold load.

Recommended Ventilator Settings. Volume-limited or pressure-limited modes can be used, but volume-limited assist-control is the most frequent choice initially and provides control over the tidal volume, which is important in avoiding dynamic hyperinflation. A small tidal volume (e.g., 5 to 7 mL/kg predicted body weight) should be used. Care should be taken to avoid overventilation and alkalemia. The backup respiratory rate for COPD patients receiving invasive mechanical ventilation should be set between 10 and 14/min. Given an inspiratory time of 1 second, if the respiratory rate is 20/min, the expiratory time is only 2 seconds; at a respiratory rate of 15/min, expiratory time increases to 3 seconds. Thus, relatively small changes in rate have large effects on expiratory time. Another way to increase expiratory time is to shorten the inspiratory time by increasing the inspiratory flow rate. However, this strategy is not as fruitful because substantial increases in flow rate result in only minor decreases in inspiratory time. For example, if the inspiratory time is 1 second and inspiratory flow is 60 L/min, an increase in the inspiratory flow rate to 100 L/min decreases the inspiratory time to 0.6 second (if tidal volume is held constant); thus, expiratory time increases only from 2.0 to 2.4 seconds. Furthermore, rapid flow rates may increase the spontaneous respiratory rate¹⁷⁷ and sensation of respiratory distress. COPD patients prefer flow rates in the 60 L/min range and tend to sense faster or slower rates as less comfortable.¹⁷¹

ASTHMA

Acute ventilatory failure due to acute asthma should be unusual if patients adhere to a medical regimen including inhaled corticosteroids, monitor their peak flows, and alter their medical regimen (with the addition of oral steroids) when peak flow declines. Unfortunately, some patients are not treated with optimal regimens: some do not adhere to the regimen, and others have severe exacerbations even with optimal regimens. Although less commonly encountered than in the past, acute ventilatory failure in asthmatics remains a problem. Studies on near-fatal asthma have identified several risk factors for exacerbation, including poor access to health care, substance abuse, nonadherence with therapy, underuse of corticosteroids, and underestimation of the severity of attacks.¹⁷⁸

Medical Management of Acute Asthma

Patients presenting with severe asthma should be promptly treated with systemic, as well as inhaled, corticosteroids and bronchodilators. Rapidly acting β_2 -agonists are administered by inhalation, although no optimal route of admin-

istration or dose has been established. Metered-dose inhalers with spacers or nebulizers may be used, usually every 20 minutes for the first hour. Some centers use continuous nebulization for severe acute asthma. Magnesium, either intravenous or inhaled, has been administered, with some evidence to suggest that it aids aggressive β_2 -agonist therapy, especially in the most severely ill asthmatics.¹⁷⁹

Heliox has been used since the 1930s to lower resistance to flow related to turbulence in the airways of asthma patients, just as in COPD patients. Several randomized, controlled trials of heliox have been performed with patients with acute asthma, but the results are inconclusive. Two demonstrated more rapid improvements in dyspnea and airflow with heliox than with oxygen alone,^{180,181} but another showed no improvement in airflow rates (although dyspnea was reduced more by heliox).¹⁸² The study showing little or no improvement with heliox enrolled less severely obstructed patients than the favorable studies, but a subgroup analysis of sicker patients in the negative study showed no benefit in that subgroup either. A Cochrane analysis concluded that there is no defined role for heliox in treating severe acute asthma.¹⁸³

Ventilatory Management

Assessment of Ventilatory Status. In patients with acute asthma exacerbations, frank ventilatory failure is unusual. Signs of severe respiratory distress, such as excessive use of accessory muscles, extreme tachypnea, or abdominal paradox, warrant the initiation of ventilatory assistance. Arterial blood gases showing normocapnia in a patient with severe respiratory distress should also cause alarm because patients reach a “crossover” point as they fail, when they can no longer sustain hyperventilation but have not become sufficiently fatigued to retain CO_2 . These patients should be monitored closely so that noninvasive ventilatory aids can be initiated promptly in order to avert the need for invasive ventilation with its attendant potential complications.

Continuous Positive Airway Pressure. CPAP alone or NIV may ameliorate respiratory distress in asthmatics by reducing the work of breathing via a direct bronchodilator effect of positive pressure,¹⁸⁴ enhancing the effect of inhaled albuterol and offsetting intrinsic PEEP. However, the unequal distribution of airway resistance in asthma, in contrast to the more simultaneous closure of airways in COPD, creates areas with different expiratory time constants. In this setting, CPAP can promote overdistention of some lung regions. Thus, caution should be exercised when applying CPAP to these patients, at least at levels exceeding 5 cm H_2O , and CPAP should be reduced to 5 cm H_2O if there is no further amelioration of respiratory distress at higher levels.

Noninvasive Ventilation. The role of NIV in the management of asthma exacerbations has not been clearly defined. An early cohort study observed substantial improvements in blood gases (arterial PCO_2 dropping from 65 to 52 mm Hg in the first 2 hours) in 17 patients treated with NIV, only 2 of whom required intubation.¹⁸⁵ More recent studies have shown more rapid improvement in airflow¹⁸⁶ or equivalent improvement with less β -agonist medication.¹⁸⁷ In a

study assessing the effects of bilevel ventilation on airflow in asthmatics, bronchodilators were withheld for the first hour of therapy and the higher bilevel setting was associated with greater improvement in FEV₁ than oxygen therapy alone.¹⁸⁸ These results suggest that positive airway pressure might exert a bronchodilator effect; however, in the absence of evidence of favorable effects on other outcomes like intubation, mortality rate, or ICU or hospital lengths of stay, the benefits of NIV have not been adequately established.

Nonetheless, considering that cohort studies suggest that some patients with severe asthma treated with NIV can avert intubation, a trial of NIV may be considered when patients fail to respond promptly to initial bronchodilator therapy, particularly if they manifest signs of respiratory muscle fatigue, including a respiratory rate of more than 30 breaths/min, accessory muscle use, abdominal paradox, normocapnia in patients with respiratory distress, hypercapnia or hypoxemia. Such patients should be monitored closely in an ICU and intubated if they fail to improve promptly.

Invasive Mechanical Ventilation. Invasive mechanical ventilation in patients with acute ventilatory failure due to asthma should be used as a last resort but is necessary when patients present with coma or delirium or with hemodynamic instability. Another clear indication is failure of medical therapy that may include NIV. Of patients admitted to the ICU with acute severe asthma, about one third have been reported to require invasive mechanical ventilation.^{178,189} Invasive mechanical ventilation is best avoided because of the frequency and severity of the potential complications but, if needed, it should be initiated before a respiratory arrest intervenes. Complications of mechanical ventilation in asthmatics include barotrauma such as pneumothorax and pneumomediastinum, reported in 6.5% of patients in one series,¹⁹⁰ and the need for sedation and paralysis, which should be avoided because of the risk of postparalysis myopathy, ventilator-associated pneumonia, and mortality rates in the 5% to 10% range.¹⁹¹

If invasive mechanical ventilation is necessary, great care must be exercised to minimize the risk of complications, using an approach similar to that used for COPD patients. Excessive respiratory rates and tidal volumes should be avoided, with the ultimate goal of keeping plateau pressures under 30 to 35 cm H₂O. "Permissive hypercapnia,"¹⁹² first described in invasively ventilated asthma patients,¹⁹³ remains a sensible approach in severely obstructed patients. With permissive hypercapnia, plateau pressures are maintained in a relatively safe range (<30 cm H₂O) as the first priority while allowing the CO₂ to rise, in some reports up to 70 to 100 mm Hg. Using this strategy, the major risks of positive-pressure ventilation can be minimized while providing time for the medical therapy to take effect. Bicarbonate or other buffers such as *tris-hydroxymethyl aminomethane* (THAM) can be administered if the pH drops too low, but this is probably not necessary and may not even be effective in raising the pH, a situation also described in patients with acute lung injury.¹⁹⁴ Because of the variability of resistance between airways, some of which may be entirely obstructed, measurement of intrinsic PEEP using the expiratory hold technique may underestimate the severity of regional hyperinflation.¹⁹⁵ When ventilation remains difficult, even

with use of lung-protective ventilation and permissive hypercapnia, the addition of heliox to the ventilator circuit may help (although heliox may alter ventilator performance and not all ventilators can accommodate heliox). As a last resort, extreme measures such as general anesthesia with bronchodilator anesthetics (e.g., halothane)¹⁹⁶ or induced hypothermia may be helpful.

ACUTE VENTILATORY FAILURE DUE TO VASCULAR IMPAIRMENT

An increase in physiologic dead space by disorders affecting the pulmonary vasculature reduces alveolar ventilation in relation to overall minute ventilation. Although hypercapnia might be expected in such a circumstance, it is typically prevented by a modest increase in overall ventilation. Thus, acute ventilatory failure is seldom seen in primary pulmonary vascular disease. In pulmonary thromboembolism, for example, hypercapnia is unusual. Hypercapnia following pulmonary embolism can be seen, however, in patients with a comorbid condition such as severe COPD or a depression of the ventilatory drive by drugs that impair the function of the ventilatory pump. Indeed, acute respiratory acidosis, with or without concomitant worsening in oxygenation, may be the initial manifestation of pulmonary thromboembolism in a patient on controlled mechanical ventilation or with a high cervical spinal cord injury or pharmacologic paralysis who cannot increase minute ventilation.

Another rare circumstance in which acute ventilatory failure may develop as a result of a disorder of the pulmonary circulation is venous air embolism, in which hypercapnia and a marked discrepancy between arterial and end-tidal exhaled CO₂ levels may be observed.¹⁹⁷ Hypercapnia may also complicate the acute chest syndrome in patients with sickle cell disease; one series documented respiratory acidosis in 42% of patients who developed this syndrome.¹⁹⁸

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Key Points

- Ventilatory failure is the consequence of inadequate alveolar ventilation, generally due to poor central drive, neuromuscular disease, profound mechanical derangement of lung parenchyma or chest wall, or some combination of these factors. Depression of central drive is infrequently a major contributor to the development of acute ventilatory failure, except for depression due to drugs.
- Respiratory muscle weakness, regardless of the origin of the impairment (e.g., immunologic, motor neuron disease, myopathic), may either precipitate ICU admission or be acquired in the ICU.
- Clinical assessment including physical examination, measurement of maximal inspiratory and expiratory

pressures, or bedside ultrasound to visualize the diaphragm can be helpful in identifying respiratory muscle weakness.

- COPD exacerbation is the most common cause of acute ventilatory failure seen in acute care hospitals. COPD patients may develop acute or acute-on-chronic ventilatory failure due not only to bronchitis but also to complicating pneumonia, congestive heart failure, pulmonary embolism, or pneumothorax.
- Noninvasive positive-pressure ventilation reduces work of breathing by applying extrinsic *positive end-expiratory pressure* (PEEP) to counterbalance intrinsic PEEP and pressure support to assist inspiration. It is especially useful in exacerbations of COPD but may also play a role in other forms of acute ventilatory failure due to COPD, such as in facilitating extubation of those who fail a trial of spontaneous breathing or in avoiding reintubation in those who fail extubation.
- Invasive mechanical ventilation can generally be accomplished using small tidal volumes of roughly 6 mL/kg, which limits intrinsic PEEP in COPD, reduces the risk of ventilator-induced lung injury in those with parenchymal lung disease, and minimizes the circulatory compromise that can complicate restrictive chest wall conditions.
- When initiating noninvasive ventilation, there is a “window of opportunity” that opens when patients need ventilatory assistance but closes if they progress too far and become severely acidemic. Improvements in pH, arterial PCO₂, and level of consciousness within the first hour or two of noninvasive ventilation are strong predictors of success.

- In patients with respiratory failure due to asthma or COPD, attempts to normalize arterial PCO₂ generally lead to dynamic hyperinflation, thereby risking hypotension and pneumothorax; instead, “permissive hypercapnia” is used to limit minute ventilation and maintain airway pressures in a safe range while allowing the arterial PCO₂ to rise.

Complete reference list available at *ExpertConsult*.

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ACUTE HYPOXEMIC RESPIRATORY FAILURE AND ARDS

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HYPOXEMIC RESPIRATORY FAILURE
CLASSIFICATION OF HYPOXEMIA
CLINICAL FEATURES AND
DIAGNOSTIC APPROACH
CAUSES OF ACUTE RESPIRATORY
FAILURE

ACUTE RESPIRATORY DISTRESS
SYNDROME
 Diagnosis and Epidemiology
 Etiology and Pathogenesis
 Mortality and Complications
 Therapy

MECHANICAL VENTILATION
 Pressure and Volume Limitation
LONG-TERM OUTCOMES

HYPOXEMIC RESPIRATORY FAILURE

Hypoxemic respiratory failure has classically been defined as an arterial PO_2 of less than 60 mm Hg. It is distinguished from hypercapnic respiratory failure ($PCO_2 > 45$ mm Hg), although the two conditions often coexist. There are a number of important qualifications to this definition that must be made. The threshold of 60 mm Hg is somewhat arbitrary and reflects the shape of the oxyhemoglobin dissociation curve, marking the arterial PO_2 below which the saturation of hemoglobin with oxygen falls precipitously in most people. An important caveat is that it is important whether hypoxemic respiratory failure is acute (over hours to days) or chronic (over weeks to months) as it has implications not just for diagnosis and treatment, but also for the physiologic adaptations to hypoxemia that develop over time. For example, an individual living at high altitude may have an arterial PO_2 less than 50 mm Hg because of a low inspired partial pressure of oxygen. Such an individual could well be asymptomatic because of acclimatization to that environment and would not be considered to have hypoxemic respiratory failure even if she had an arterial PO_2 of 45 mm Hg. It is also important to realize that this definition of hypoxemic respiratory failure (arterial $PO_2 < 60$ mm Hg) encompasses a broad spectrum of severity of illness. For example, both a patient on a general medical ward with community-acquired pneumonia and a mechanically ventilated patient on 100% oxygen in the critical care unit can fulfill the definition.

This definition of hypoxemic respiratory failure (based on the arterial PO_2) does not fully address the importance of oxygenation at the level of the tissues. Oxygen delivery to the tissues is the product of cardiac output and oxygen content. Oxygen content is critically dependent on the hemoglobin concentration and its saturation with oxygen; although the oxygen saturation depends on arterial PO_2 (as described by the oxyhemoglobin dissociation curve), the direct contribution of dissolved oxygen to blood oxygen content is very low under most conditions. In other words, in the anemic patient or in patients with very low cardiac output, tissue hypoxia may exist despite a seemingly adequate arterial PO_2 . Finally, as indicated earlier, both hypoxemic and hypercarbic respiratory failure may

coexist. A patient may initially present with isolated hypoxemia yet, upon tiring, may develop hypercarbia. Analogously, hypoventilation can cause both hypercarbia and hypoxemia.

This chapter focuses on acute hypoxemic respiratory failure. In particular, much of our discussion pertains to the etiology and management of hypoxemia at the “severe” end of the spectrum. This is not to say that mild hypoxemia is not important; certainly the condition of a patient on the medical ward with pneumonia and mild hypoxemia can deteriorate and the patient would require intubation and mechanical ventilation.

CLASSIFICATION OF HYPOXEMIA

The traditional approach to the causes of arterial hypoxemia classifies them into five pathophysiologic mechanisms: decreased inspired PO_2 , hypoventilation, impaired diffusion, *ventilation-perfusion* (\dot{V}/\dot{Q}) mismatch, and right-to-left shunt. Whereas hypoxemia from \dot{V}/\dot{Q} mismatch is responsive to supplemental oxygen, hypoxemia from a right-to-left shunt is not. This physiologic approach is probably most useful in understanding how a particular disease causes hypoxemia, but is not usually very illuminating when trying to make a specific diagnosis, other than in situations in which a patient is hypoxemic due to profound hypercapnia. In a hospital setting, a decreased inspired PO_2 can usually be excluded, because most patients will be placed on supplemental oxygen. Hypoventilation can rapidly be excluded if the patient is not hypercapnic. Impaired diffusion by itself is not an important cause of acute hypoxemia, in that oxygen transfer across the alveolar-capillary membrane to red blood cells is usually perfusion-limited, not diffusion-limited. What this means is that there is usually ample time for diffusion of oxygen, even in the presence of intrinsic lung disease. In sum, most patients in the intensive care unit with acute hypoxemic respiratory failure have some combination of \dot{V}/\dot{Q} mismatch and right-to-left shunt.

Another classification of acute hypoxemic respiratory failure is structural-anatomic (Fig. 100-1). Causes of acute arterial hypoxemia can be classified based on whether the primary pathology is located in the air spaces, interstitium, heart and pulmonary vasculature, airways, or pleural

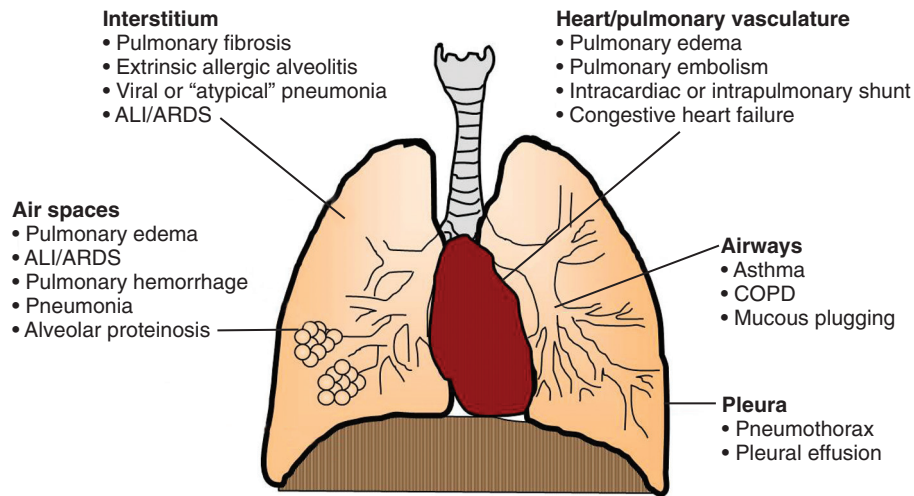


Figure 100-1 Schematic depicting a structural-anatomic approach to the diagnosis of acute hypoxemic respiratory failure.

space. Such an approach would quickly lead one to consider such causes as pulmonary edema or pneumonia, hypersensitivity pneumonitis, pulmonary embolism, bronchospasm, and pneumothorax. Although disorders involving other structures such as the central nervous system and respiratory muscles can lead to hypoxemia, these causes would be expected to have associated hypercarbia.

CLINICAL FEATURES AND DIAGNOSTIC APPROACH

The clinical features of acute hypoxemic respiratory failure vary based on the underlying cause. Assuming an intact drive to breathe and that the patient has not fatigued, the hypoxemic patient is usually tachypneic and tachycardic. Cyanosis of the lips or tongue (so-called central cyanosis) would indicate that the concentration of reduced (deoxygenated) hemoglobin is greater than 5 g/100 mL.

Given the extensive differential diagnosis of acute hypoxemic respiratory failure and the often urgent need for therapy, the clinician must be practical yet thoughtful. A basic history should be obtained to identify risk factors for cardiac dysfunction, pulmonary infection or aspiration, venous thromboembolism, or obstructive lung diseases. In the setting of trauma to the chest, pneumothorax, hemothorax, and pulmonary contusion must be considered. Further questions to identify less common causes of acute hypoxemic respiratory failure can be posed as appropriate. A focused physical examination of the cardiac and respiratory systems often can establish the presence or absence of congestive heart failure or a focal area of consolidation or effusion. Similarly, the diagnosis of a pneumothorax is more satisfying (and prompt) when made on physical examination rather than later, after chest imaging.

Implementation of therapy is simultaneous with the diagnostic workup. As always, this starts with the "ABCs" of airway, breathing, and circulation. Once the ABCs are assured, the patient should be given supplemental oxygen (if coexistent hypercapnia is present, care must be taken in

the dose of supplemental oxygen) and intravenous access should be obtained. Continuous cardiac monitoring and pulse oximetry should be available.

The initial investigations are dictated by the findings on history and physical examination. However, all patients should have a chest radiograph, an electrocardiogram, and routine blood work, including a complete blood count with differential and serum chemistry. An arterial blood gas should be obtained and the alveolar-arterial PO_2 gradient should be calculated; a normal alveolar-arterial PO_2 gradient in the setting of arterial hypoxemia suggests hypoventilation as the sole cause of the hypoxemia. The blood gas is also useful for diagnosing other acid-base disturbances and hemoglobinopathies such as carbon monoxide poisoning. The need for further investigations, including bronchoscopy, computed tomographic angiography of the chest, and echocardiography, depends on the results of the initial assessment. A completely normal chest radiograph in the setting of hypoxemic respiratory failure narrows the differential diagnosis substantially. In this uncommon circumstance, the clinician should consider pulmonary embolism and right-to-left shunts (i.e., intracardiac or pulmonary arteriovenous malformations) as possibilities. A more common scenario is that the chest radiograph of a patient with pneumonia can appear surprisingly normal (or may show only a "small" opacity) due to concomitant intravascular volume depletion. Once intravascular volume has been restored, the extent of the opacity can be appreciated.^{1,2}

CAUSES OF ACUTE RESPIRATORY FAILURE

In a large multicenter international prospective cohort study of patients requiring mechanical ventilation, the most common reported causes of acute respiratory failure were postoperative respiratory failure, pneumonia, congestive heart failure, sepsis, and trauma.³ In a small prospective cohort study that included 41 patients with hypoxemic

respiratory failure, chronic obstructive pulmonary disease and pneumonia were the most common causes.⁴ Other data from small randomized controlled trials of noninvasive ventilation identified congestive heart failure, pneumonia, trauma, acute respiratory distress syndrome, and mucous plugging as the most common causes of respiratory failure.^{5,6} However, in these studies, patients with certain diseases were excluded, including those with chronic obstructive pulmonary disease^{5,6} and asthma,⁶ limiting the ability to generalize from these findings. Indeed, in the one randomized study that specifically enrolled patients with acute hypoxemic respiratory failure, only patients with bilateral lung opacities on chest radiography were included.⁶

For a detailed discussion of many of the specific causes of acute hypoxemic respiratory failure (e.g., pneumonia), refer to the appropriate chapters in this book. The remainder of this chapter focuses on a particular subtype of acute hypoxemic respiratory failure, known as *acute respiratory distress syndrome* (ARDS).

ACUTE RESPIRATORY DISTRESS SYNDROME

DIAGNOSIS AND EPIDEMIOLOGY

Diagnosis

ARDS is characterized by noncardiogenic pulmonary edema, lung inflammation, hypoxemia, and decreased lung compliance. Unlike some disorders (e.g., coronary artery disease), ARDS, as its name suggests, is a syndrome, reflecting a constellation of clinical and physiologic observations thought to represent a common pathology. In coronary artery disease, narrowing of the coronary vasculature and disruption of an unstable atherosclerotic plaque are known to underpin the symptoms of angina and unstable angina, respectively. A diagnostic “gold standard,” namely coronary angiography, exists. In contrast, the pathogenesis of ARDS remains elusive and there is no gold standard diagnostic test. The heterogeneity of the clinical conditions associated with ARDS (discussed later) would be consistent with the possibility that ARDS is in fact a collection of different diseases that have not yet been separately identified. These problems necessarily permeate any discussion or research into ARDS, and this chapter is no exception.

The first description of ARDS appeared in a remarkable case series reported in 1967.⁷ Ashbaugh and colleagues described 12 patients ranging in age from 11 to 48 years who presented with respiratory distress, hypoxemic respiratory failure, and patchy bilateral opacities on chest radiographs (Fig. 100-2). Most of the cases were preceded by severe trauma or viral infection and the onset of symptoms was relatively rapid, with most patients developing respiratory distress within 48 to 72 hours of the beginning of their illness. Many patients required positive pressure ventilation and exhibited low respiratory system compliance, and some experienced improvement in oxygenation with the application of *positive end-expiratory pressure* (PEEP). This syndrome was initially termed the *adult* respiratory distress syndrome to distinguish it from the respiratory distress syndrome seen

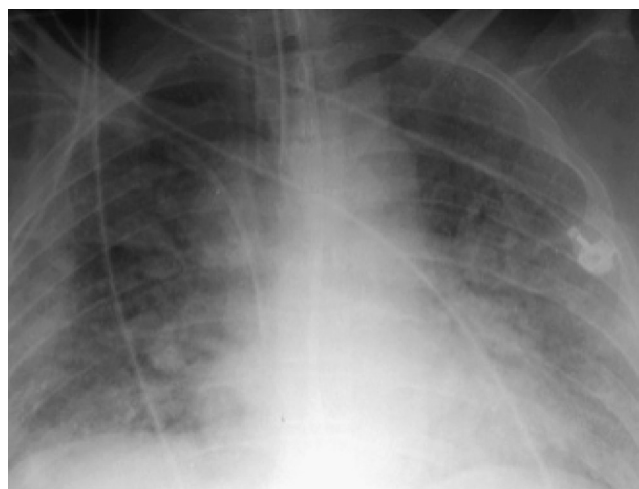


Figure 100-2 Acute Respiratory Distress Syndrome. Frontal chest radiograph in a patient with acute respiratory distress syndrome. Note the presence of bilateral opacities.

in infants. Subsequently, recognizing that the syndrome can also develop in children, it was renamed the *acute* respiratory distress syndrome.

The cases described by Ashbaugh and colleagues generated interest and research into ARDS. Unfortunately, the lack of specific diagnostic criteria and an understanding of the pathogenesis of the disorder made it difficult to undertake research and to compare studies. In 1988, a formalized and expanded definition of ARDS was proposed that consisted of three parts: (1) determining whether the illness was acute or chronic, (2) determining whether there were any associated risk factors or medical conditions (e.g., sepsis),⁸ and (3) assigning points based on the severity of pulmonary dysfunction (the Lung Injury Score), as measured by the degree of hypoxemia, the level of PEEP required, the respiratory system compliance, and the degree of radiographic abnormality. An average score was calculated and a final value greater than 2.5 was used to diagnose ARDS. One advantage of this system was its description of associated medical conditions, which might be pertinent to the etiology of ARDS. Because ARDS from different etiologies might reflect different pathogenesis and perhaps confer a different response to therapy, it was thought that knowing the cause of ARDS might be important in the conduct and comparison of studies. The definition, however, made no attempt to exclude cardiogenic pulmonary edema; it was assumed that clinicians would do so automatically.

In 1994, a consensus conference of American and European investigators published their definition of ARDS, which was widely adopted.⁹ Aiming for simplicity, ARDS was defined as a syndrome of acute onset, with bilateral opacities on chest radiography consistent with pulmonary edema, pulmonary artery occlusion pressure of 18 mm Hg or less (or absence of clinical evidence of left atrial hypertension), and hypoxemia as measured by the ratio of the *arterial partial pressure of oxygen* (arterial PO_2) to the *fraction of oxygen inspired* (FI_{O_2}). Recognizing that there was a spectrum of severity of the disease, the consensus panel recommended that arterial PO_2/FI_{O_2} ratio ≤ 300 would define

an entity termed *acute lung injury* (ALI). ARDS was the most severe form of ALI and was diagnosed when arterial $\text{PO}_2/\text{FIO}_2 \leq 200$. The simplicity of the definition led to its general acceptance by clinicians and its incorporation into clinical research. At the same time, such a straightforward definition could not take into account the heterogeneity of the disease or the ambiguity of clinical practice.

For example, the requirement for bilateral opacities on chest radiograph is open to interpretation. One study presented a random series of chest radiographs from intubated hypoxemic patients (arterial $\text{PO}_2/\text{FIO}_2 < 300$) to an international group of expert clinicians, the majority of whom conduct clinical research on ARDS. The clinicians were asked to examine each radiograph and to decide whether it fulfilled the *American-European Consensus Conference* (AECC) definition of ARDS (bilateral opacities consistent with pulmonary edema). This select group of physicians demonstrated only moderate agreement (kappa statistic 0.55) in their classification of the radiographs; when the percentage of radiographs deemed to be consistent with ARDS by each physician was examined, the percentages were evenly distributed from a low of 36% to a high of 71%.¹⁰ Another larger study on the issue also demonstrated only moderate agreement when two physicians were asked to rate radiographs on the presence or absence of diffuse bilateral opacities consistent with ARDS. However, with prior training and discussion, the agreement between an intensivist and a radiologist in the rating of the films was excellent.¹¹

The AECC definition has also been criticized for not taking the level of PEEP into consideration. Clinicians have long appreciated that applying PEEP can improve oxygenation, an observation that was noted in the first description of ARDS. This implies that the arterial PO_2/FIO_2 will change with changes in the level of PEEP; indeed, a patient who meets the AECC criteria for ARDS may no longer meet them once PEEP has been increased.¹² It has also been shown that patients meeting the AECC definition for ARDS can be stratified based on their response to standard ventilator settings 24 hours later; many of the patients at that point have a lesser degree of hypoxemia and a significantly lower mortality rate.¹³ Thus, the AECC definition, while simple to use, encompasses a heterogeneous group of patients.

In 2012, the so-called Berlin definition of ARDS was developed to address some of these limitations (Table 100-1).^{14,15} The degree of hypoxemia was stratified into mild, moderate, and severe based on the arterial PO_2/FIO_2 ratio and a requirement for a PEEP level of 5 cm H_2O or greater was included (whether applied by endotracheal tube or, in the setting of mild disease, by noninvasive ventilation). The term ALI was eliminated (but is used as needed in this chapter to help readers interpret older literature). Given that the use of pulmonary artery catheters has fallen off dramatically due to a demonstrated lack of benefit,^{16,17} the need for a pulmonary arterial wedge pressure measurement was eliminated and instead it was recommended that objective testing (e.g., echocardiography) be performed to exclude cardiogenic edema if no risk factor for ARDS could be identified. "Acute" was explicitly defined as ARDS developing within 1 week of a known risk factor. Although considerable effort went into its design, when compared with the AECC criteria, the Berlin definition is only slightly better at predicting mortality attributable to ARDS.¹⁴

Table 100-1 Berlin Definition of ARDS

Criterion	Definition
Timing	Within 1 week of a known precipitant, or new/worsening respiratory symptoms
Chest imaging (chest radiograph or CT scan)	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload If no risk factor for ARDS is present, need objective assessment (e.g., echocardiogram) to exclude hydrostatic edema
Oxygenation	
Mild	200 mm Hg < arterial $\text{PO}_2/\text{FIO}_2 \leq 300$ mm Hg with PEEP or CPAP ≥ 5 cm H_2O
Moderate	100 mm Hg < arterial $\text{PO}_2/\text{FIO}_2 \leq 200$ mm Hg with PEEP ≥ 5 cm H_2O
Severe	Arterial $\text{PO}_2/\text{FIO}_2 \leq 100$ mm Hg with PEEP ≥ 5 cm H_2O

CPAP, continuous positive airway pressure; FIO_2 , fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

Adapted from Ranieri VM, Rubenfeld GD, Thompson BT, et al: Acute respiratory distress syndrome: the Berlin Definition. *J Am Med Assoc* 307(23):2526–2533, 2012.

Two additional points should be made about the diagnosis of ARDS. First, while physicians properly think of ARDS as being distinct from cardiogenic pulmonary edema, it is important to acknowledge that many patients with ARDS will have left atrial hypertension during the course of their illness.¹⁸ Second, despite the increasing use of B-type natriuretic peptides as diagnostic tools for acute congestive heart failure, their ability to distinguish ARDS from cardiogenic pulmonary edema is unclear.^{19,20}

Incidence

Given the multitude of definitions and the difficulty in making a diagnosis of ARDS, it is not surprising that determining the incidence of the disease has been challenging. The reported incidence of ARDS has ranged from 75 per 100,000 population²¹ to as low as 1.5 per 100,000²² in Europe; the European numbers appear fairly constant over time.²³ Many older studies did not use the AECC definition and did not include ALI; the Berlin definition is too recent to have been widely studied. The incidence of ALI has been estimated to be 78.9 cases per 100,000 person-years.²⁴ One study calculated an incidence of ALI of 22 cases per 100,000 using data from a large prospective trial of ARDS and from the American Hospital Association.²⁵ One of the methodologic strengths of the study was its inclusion of cases of ALI over a 3-year period, thereby decreasing the impact of seasonal variability. The heterogeneity in the literature of the estimates of incidence may reflect differences in the methodology of the various studies, but may also reflect true variation. Regional differences in genetic or environmental factors and specific disease-associations such as cardiopulmonary bypass or lung transplant may account for some of the regional variability in the incidence of ALI.²⁶

Risk Factors

Sepsis, aspiration of gastric contents, and multiple transfusions (>15 units/24 hours in one study) are associated with the highest risk for development of ARDS.²⁷ In particular, ARDS develops in almost 40% of patients with sepsis. The presence of more than one presumed risk factor for ARDS may increase the incidence of ARDS, although the sample sizes of these subsets have been quite small.²⁷ ARDS has been seen to develop in more than one third of patients receiving massive blood transfusion and in one fourth of patients with multiple trauma (one or more pulmonary contusions, multiple fractures, multiple transfusions).²⁸

One of the predisposing factors for the development of ARDS is a history of chronic alcoholism (relative risk, 2.0; 95% confidence interval, 1.3–2.9).²⁹ This relationship has been shown to remain significant after adjustment for gender, at-risk diagnosis, and severity of illness. Among those in whom ARDS developed, patients with a history of alcoholism had a higher mortality rate than those without such history (odds ratio, 6.3; 95% confidence interval, 2.2–20.4).²⁹ The mechanisms of this association are unknown.

The same researchers examined whether patients with diabetes might be protected against development of ARDS, the rationale being that hyperglycemia is known to impair neutrophil function, and neutrophils are thought to be central to the pathogenesis of ARDS (see [Pathogenesis](#)). More than 100 patients admitted to the intensive care unit with septic shock were followed prospectively for the development of ARDS. Over a 2-year period, diabetes was associated with a significantly decreased risk of ARDS (relative risk, 0.53; 95% confidence interval, 0.28–0.98), which persisted after adjustment for the source of sepsis and other potential confounders. Interestingly, there was no difference in mortality between patients with ARDS who did and did not have diabetes.³⁰

A systematic overview of studies examining potential risk factors for ARDS concluded that the strongest evidence of a causal relationship was for sepsis, trauma, multiple transfusions, aspiration of gastric contents, pulmonary contusion, pneumonia, and smoke inhalation.³¹ More recently, active or passive exposure to cigarette smoke has been associated with the development of ARDS after trauma.³²

The heterogeneity of risk factors for ARDS is remarkable. At the AECC, investigators divided the known risk factors into those thought to cause *direct* lung injury (e.g., pneumonia) and those in which the mechanism of lung injury was thought to be *indirect* (e.g., pancreatitis) ([Table 100-2](#)). While conceptually attractive, this classification scheme may not reflect underlying differences in the mechanisms, severity, or outcome of lung injury.³³ This issue is discussed in more detail in the section on outcomes.

ETIOLOGY AND PATHOGENESIS

Overview of Pathophysiology

In the past, ARDS was also called noncardiogenic pulmonary edema, a descriptive term that nonetheless reflected

Table 100-2 Conditions Associated with ARDS, Categorized by Possible Mechanisms of Injury

Direct injury	Indirect injury
Pneumonia	Sepsis
Aspiration	Major trauma
Pulmonary contusion	Multiple blood transfusions
Toxic inhalation	Pancreatitis
Near-drowning	Cardiopulmonary bypass
Reperfusion injury (e.g., after lung transplantation)	Drug overdose
	Adverse effect of medication

what was known of the pathogenesis of the disorder. Unlike congestive heart failure, in which elevated left-sided cardiac pressures cause hydrostatic pulmonary edema, in ARDS, the edema fluid that fills the alveoli is exudative in origin. In other words, the alveolar-capillary barrier exhibits increased permeability, allowing for the leakage of protein-rich fluid into the air spaces. Alveolar filling leads to decreased respiratory system compliance as well as right-to-left shunting and profound hypoxemia. Although arterial PCO₂ is generally within the normal range, dead space ventilation is significantly increased, as demonstrated by elevated minute ventilation. Pulmonary hypertension is also commonly observed in ARDS, and a number of mechanisms have been proposed including hypoxic vasoconstriction, intravascular fibrin deposition in the pulmonary capillaries, and compression of blood vessels by the positive pressure ventilation used to treat the disorder. This section reviews the pathology of ARDS and discusses current theories regarding its pathogenesis. Much of the research into ARDS has focused on determining the basis for the increase in alveolar-capillary permeability.

Pathology

The pathologic features of ARDS have classically been described using three overlapping and sequential stages.³⁴ In the first or exudative phase of lung injury, the pathologic findings have been termed *diffuse alveolar damage*. There are hyaline membranes lining the alveolar walls and protein-rich edema fluid in the alveolar spaces, as well as epithelial disruption and infiltration of the interstitium and air spaces with neutrophils. Areas of hemorrhage and macrophages can also be found in the alveoli. This phase, which is thought to last for approximately 5 to 7 days, is followed in some patients by the so-called proliferative phase. At this point, hyaline membranes are reorganized and fibrosis begins to be observed. Obliteration of pulmonary capillaries and deposition of interstitial and alveolar collagen may be observed, along with a decrease in the number of neutrophils and the extent of pulmonary edema. This proliferative stage has traditionally been described as being followed by a fibrotic phase, essentially emphasizing the appearance of pulmonary fibrosis in a subset of patients with persistent (i.e., >2 weeks) ARDS. More recently, it has been realized that areas of fibrosis may actually develop sooner than usually appreciated: elevated levels of N-terminal procollagen peptide III, thought to represent collagen synthesis, can be detected in bronchoalveolar lavage fluid of patients with ARDS as early as 24 hours into the course of the illness. In addition, the bronchoalveolar lavage fluid from

these patients has been shown to stimulate cultured fibroblasts to proliferate.³⁵ These and other observations have led some investigators to hypothesize that fibroproliferation may be initiated simultaneously with (rather than after) inflammatory lung injury.³⁶

Alveolar-Capillary Membrane

If ARDS is a disorder of increased alveolar-capillary permeability, it stands to reason that the pulmonary microvascular endothelium or the alveolar epithelium (or both) must be involved in its pathophysiology. Damage to the alveolar epithelium is thought to be a key event.³⁷ Once ARDS has begun, the importance of the alveolar epithelium is also clear: Type II pneumocytes must differentiate into type I cells to help cover the denuded epithelial surface, while both type I and II cells express the Na^+, K^+ -ATPase, which is thought to be important in clearance of edema fluid (discussed later). Injury to type II pneumocytes impairs the production and metabolism of surfactant. In addition to damage to the alveolar epithelium, loss of lung endothelial barrier integrity is both necessary and sufficient for the development of ARDS.^{38,39} How the alveolar-capillary membrane is damaged is not known for certain, although mediators of epithelial and endothelial apoptosis⁴⁰ and neutrophils are suspected of playing a role (see later).

Surfactant. Surfactant is a complex mixture of phospholipids and surfactant proteins that reduces alveolar surface tension. Many researchers have described alterations to the surfactant obtained from patients with ARDS. There are decreased amounts of surfactant-related protein and decreased dipalmitoylphosphatidylcholine and phosphatidylglycerol in the surfactant of patients with ARDS. The proportion of large (active) to small (inactive) aggregates of surfactant is diminished, due to both decreased production of surfactant and increased conversion of the large to small forms. In addition, plasma proteins that have leaked through the alveolar-capillary barrier may interfere with surfactant function.⁴¹ For example, damage to surfactant protein A has been demonstrated in patients with ARDS.⁴² The impairment in surfactant function observed in ARDS would theoretically predispose alveolar units to collapse. In addition, surfactant proteins have been found to have antimicrobial properties,^{43,44} although whether the loss of these properties is relevant to the pathogenesis of ARDS is not known. Indeed, despite the litany of abnormalities in surfactant that have been described,⁴⁵ the extent to which these alterations contribute to the pathogenesis of ARDS remains controversial: unlike the *neonatal* respiratory distress syndrome, in which a deficiency of surfactant underlies the pathophysiology of the disease, it is possible that the abnormalities of surfactant in ARDS are the result rather than the cause of altered physiology. Indeed, four large randomized controlled trials of exogenous surfactant supplementation in ARDS failed to demonstrate any improvement in mortality or requirement for mechanical ventilation⁴¹ (see Treatment). Only one trial, using calfactant (a natural surfactant, distinct from the synthetic surfactants used in previous trials) in pediatric patients with ARDS, has shown any benefit⁴⁶; whether this is due to the unique surfactant used in this study or to differences

between the patients enrolled in this trial and the negative trials is unknown.

Neutrophils and Other Inflammatory Mediators

Histologically, one of the hallmarks of ARDS is the accumulation of neutrophils in the microvasculature of the lung.⁴⁷ As key players in innate immunity, neutrophils can generate an impressive array of cytotoxic compounds. These include reactive oxygen species, cationic peptides (e.g., defensins), eicosanoids, and proteolytic enzymes such as leukocyte elastase. In addition, once activated, neutrophils release growth factors and cytokines (e.g., *tumor necrosis factor* [TNF]- α and *interleukin* [IL]-1 β) that may enhance the inflammatory response. Given this destructive potential, it has long been theorized that neutrophils may be central to the pathogenesis of ARDS⁴⁸ (Fig. 100-3). There is an abundance of clinical and preclinical data to support this hypothesis. For example, in humans with ARDS following sepsis, bronchoalveolar lavage neutrophilia is associated with a poor prognosis.⁴⁹ Neutrophil-depleted mice exposed to hyperoxia develop less lung injury than normal mice.⁵⁰ Similarly, in a hamster model of ARDS induced by endotoxin inhalation, the administration of a specific inhibitor

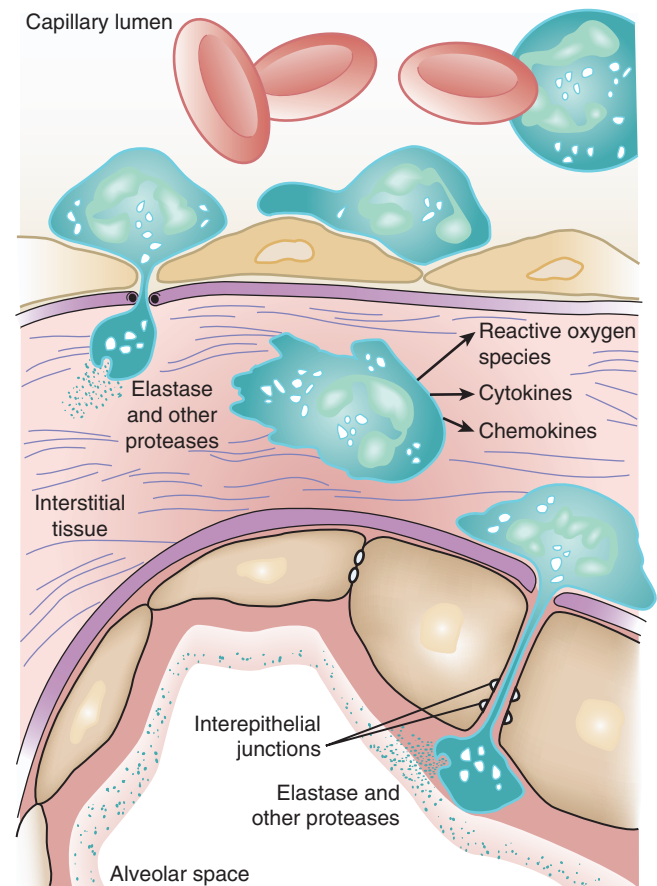


Figure 100-3 Role of neutrophils in the pathogenesis of acute lung injury. Activated neutrophils exit the bloodstream and transmigrate across the alveolar-capillary membrane, releasing cytokines, proteases, reactive oxygen species, and other compounds. Although crucial to host defense against pathogens, the compounds secreted or released by the neutrophil have the capacity to damage the tissue of the host. (Adapted from Lee WL, Downey GP: Leukocyte elastase: physiological functions and role in acute lung injury. A state of the art review. *Am J Respir Crit Care Med* 164:896–904, 2001.)

of neutrophil elastase (even hours after administration of endotoxin) prevented the development of lung injury.⁵¹

If neutrophils are involved in the pathogenesis of ARDS, some defect in their regulation must be invoked. For example, in an uncomplicated bacterial pneumonia, the pulmonary inflammatory response is limited by counter-regulatory processes that prevent tissue damage. Whether this regulation is ineffective or insufficient in ARDS is a fascinating and unanswered question.⁵²

One of the earliest manifestations of ARDS, even before hypoxemia, is a transient leukopenia due to sequestration of neutrophils in the lung microvasculature.⁵³ The average pulmonary capillary is smaller than the average neutrophil, and neutrophils therefore have to deform to pass through the microvasculature. Activated neutrophils “stiffen” and cannot negotiate narrow capillary segments.⁵⁴ Inhibitors of actin polymerization can abrogate this stiffening, implicating a change in the actin cytoskeleton in neutrophil sequestration in the lung.⁵⁵ Neutrophil sequestration also involves interactions between molecules on the surface of the neutrophil and the lung capillary endothelium. For example, in rabbits, blocking the adhesion molecule L-selectin on the surface of the neutrophil prevented neutrophil sequestration in alveolar capillaries induced by exposure to endotoxin.⁵⁶

After the initial sequestration, neutrophils must translocate (via diapedesis) across the alveolar-capillary barrier to the alveolar space. The determinants of this seemingly simple movement remain incompletely understood. Integrins on the surface of the neutrophil are thought to mediate emigration of neutrophils from the pulmonary circulation in response to some, but not all, inflammatory stimuli.⁵⁷ Proteases secreted by the alveolar epithelium, in concert with regional cytokine production and glycosaminoglycans on the epithelial surface, may act together to form a chemotactic gradient for neutrophils to follow.⁵⁸

Many studies are focusing on the mechanisms of neutrophil activation whereas others are focusing on the interaction between platelets and neutrophils and how mutual activation may contribute to ARDS or sepsis.⁵⁹⁻⁶² Other studies have looked at various components of intracellular signal transduction pathways, such as kinases (enzymes that phosphorylate substrates) and transcription factors. For example, one such kinase is the p38 mitogen-activated protein kinase, which is activated when cells are stimulated with *lipopolysaccharide* (LPS).⁶³ Activation of this kinase stimulates TNF- α production and macrophage inflammatory protein-2 release (a chemotactic factor for macrophages).⁶⁴ Interestingly, inhibition of p38 mitogen-activated protein kinase in mice, even hours after the mice are exposed to aerosolized LPS, attenuates neutrophil chemotaxis and migration from the lung microvasculature into alveoli.⁶⁵ Another kinase often discussed in the context of inflammation is phosphatidylinositol 3-kinase. This enzyme phosphorylates phosphatidylinositol, a lipid-derived second messenger whose phosphorylated forms have been implicated in a myriad of intracellular signaling events. Phosphatidylinositol 3-kinase γ is preferentially activated in neutrophils exposed to IL-8 or fMLP (a bacterial-derived peptide).⁶⁶ Despite exposure to intraperitoneal endotoxin, phosphatidylinositol 3-kinase γ knockout mice displayed decreased neutrophil accumulation, cytokine production,

and lung injury compared to control mice. The neutrophils in the lung of the knockout mice also demonstrated diminished activation of NF- κ B, an important transcription factor known to mediate the up-regulation of numerous cytokines and proinflammatory mediators.⁶⁷

There are many potential mechanisms by which activated neutrophils might mediate ALI. In addition to secreting cytokines and growth factors that might stimulate the local and systemic inflammatory response, neutrophils release defensins⁶⁸ and generate reactive oxygen species that can mediate tissue damage.⁶⁹ In animal studies, inhibition of the assembly of NADPH oxidase (the major source of reactive oxygen species) by apocynin has been shown to attenuate sepsis-induced lung injury.⁷⁰ The *nitric oxide synthase* (NOS) pathway has also been implicated in mediating lung injury; knockout mice lacking the gene for inducible NOS developed less severe lung injury than wild-type animals upon injection with LPS.⁷¹

In addition, neutrophils contain proteolytic enzymes that may be involved in the pathogenesis of ALI. In particular, both neutrophil elastase and metalloproteinases have been extensively studied.⁵² Because of its ability to degrade multiple substrates including growth factors and cytokines, neutrophil elastase may be involved in regulation of the inflammatory response. It has also been shown to degrade epithelial and endothelial cadherins, proteins that are major components of adherens junctions, which hold cells together. It is possible that elastase-mediated destruction of cadherin could predispose to alveolar flooding. Despite its potential to cause unwanted tissue damage, *neutrophil elastase* (NE) is likely crucial to host defense. In NE-deficient mice, the administration of intraperitoneal *Klebsiella pneumoniae* causes 100% mortality within 48 hours, whereas mortality in normal mice was only 50%.⁷² However, NE-deficient mice are paradoxically resistant to normally lethal doses of LPS. Furthermore, mice that lack both NE and another neutrophil protease (cathepsin G) are protected against alveolar damage induced by endotoxic shock.⁷³ These apparently contradictory results suggest that NE, while important in a regulated inflammatory response, may nonetheless participate in inflammatory injury under certain circumstances. In numerous studies of multiple different experimental models in multiple species of animals, NE has been shown to play an important role in the pathogenesis of ALI. Whether it is as important in the development of ARDS in *humans* remains unanswered. A clinical trial of a leukocyte elastase inhibitor in ARDS was halted because preliminary analysis suggested lack of efficacy.⁷⁴

Metalloproteinases may also be important mediators of leukocyte-mediated lung injury. Elevated concentrations of the matrix metalloproteinases gelatinase A and B have been found in the epithelial lining fluid of patients with ARDS.⁷⁵ Mice lacking the genes for gelatinase B or stromelysin 1 had less severe injury in an animal model of ALI.⁷⁶ As mentioned earlier, matrilysin (matrix metalloproteinase 7) has been shown to regulate the formation of a chemotactic gradient and the transmigration of neutrophils across the alveolar epithelium in a mouse model of ALI.⁵⁸ Finally, administration of an inhibitor of elastase and metalloproteinases (chemically modified tetracycline-3) attenuated ALI after cardiopulmonary bypass in pigs.⁷⁷

Despite the emphasis on neutrophils as potentially causative for lung injury, it is important to note that ARDS has certainly been described in patients with profound neutropenia.^{78,79} Indeed, it is possible that the neutrophil infiltration observed in some cases of ARDS is adaptive (i.e., a physiologic response to a primary injury) rather than destructive. At present, however, it is generally believed that neutrophils are a causative factor in the development of most cases of ARDS. Comparatively little is known about the mechanisms of neutrophil-independent ARDS and this must be a goal of future investigations.

Inflammation and Coagulation

Because one of the most common precipitants for ARDS is sepsis, it is hoped that therapies for sepsis may either prevent or improve the outcome of ARDS. Our current concept of sepsis is that there is an initial inflammatory state, with up-regulation of inflammatory cytokines such as TNF- α and IL1 β and recruitment and activation of inflammatory cells such as neutrophils. This early stage of inflammation is followed by a relatively depressed immunity, in which the patient is vulnerable to nosocomial infections.⁸⁰ The theory that dysregulation of the inflammatory response is responsible for sepsis has led to the search for agents that would selectively block components of the inflammatory pathway. It has also been appreciated that there are important connections between the molecular cascades that regulate both inflammation and coagulation; for example, TNF- α causes an increase in thrombin and fibrin formation, while fibrin fragments themselves are known to be chemotactic for neutrophils.⁸¹ TNF- α increases tissue factor expression on endothelium and inhibits fibrinolysis, both of which favor fibrin formation. *Activated protein C* (APC), an endogenous anticoagulant, has direct and indirect anti-inflammatory effects, which include reducing levels of IL-6 and attenuating neutrophil activation in sepsis.^{82,83} Because sepsis is the most common cause of ARDS and because abnormalities of coagulation are very common in sepsis, investigators have wondered whether altered coagulation is involved in the genesis of ARDS. How this might happen is largely speculative, but intraalveolar, interstitial, and intravascular fibrin deposition have all been observed in patients with ARDS. Indeed, fibrin is a major component of hyaline membranes. Intraalveolar fibrin has been postulated to serve as a nidus for fibroblast proliferation and potentially, as ALI resolves, as a stimulus for pulmonary fibrosis. Fibrin might contribute as well to ongoing lung injury through its chemotactic properties, and intravascular fibrin deposition, as in microthrombi, might contribute to the elevated pulmonary vascular pressures observed in ARDS.

Interest in the role of coagulation in the pathogenesis of ARDS was buttressed in part by observations in animal studies that anticoagulation can attenuate the severity of sepsis-induced lung injury,⁸⁴ although studies in humans have been disappointing. Indeed, a small randomized controlled trial of APC in patients with ALI was stopped prematurely due to lack of efficacy,⁸⁵ and APC was pulled from the market after a large multicenter trial showed it provided no mortality benefit in patients with septic shock.⁸⁶

Other molecular determinants of inflammation continue to be elucidated. Some data have implicated transforming growth factor- β in an animal model of ALI.⁸⁷ In one study,

transforming growth factor- β was postulated to cause increased alveolar epithelial cell permeability by depleting intracellular glutathione levels.⁸⁸ Other investigators have attempted to improve the endogenous counter-inflammatory response; in one study, the gene for heat shock protein 70 was ligated to an adenoviral promoter, and the resultant recombinant construct was administered into the lungs of rats in which ARDS had been induced by cecal ligation and perforation. Administration of the heat shock protein 70 construct increased heat shock protein 70 expression specifically in the lung; remarkably, this increased expression was associated with a significant reduction in pulmonary edema and inflammation and even mortality.⁸⁹ Indeed, mice deficient in heat shock protein 70 showed increased mortality and lung injury after cecal ligation and perforation.⁹⁰ The mechanisms underlying this effect are not clear, but may involve suppression of the proinflammatory transcription factor NF- κ B or decreased lung parenchymal apoptosis.⁹¹

Na⁺ and Water. Na⁺ channels at the apical surface of alveolar epithelial cells mediate intracellular Na⁺ uptake from the alveoli. This creates an osmotic gradient that causes alveolar fluid to follow, thereby allowing for the clearance of pulmonary edema. Na⁺,K⁺-ATPases in the basolateral membrane of the epithelial cell exchange intracellular Na⁺ for extracellular K⁺, maintaining the intracellular sodium concentration low enough for the apical Na⁺ resorption to continue. This process allows for the net removal of Na⁺ and fluid from the alveolar space, and can be accelerated (at least experimentally) by catecholamines.

Dysfunction of either the apical Na⁺ channels or the basolateral Na⁺,K⁺-ATPases (or both) have been postulated to be involved in the pathogenesis of ARDS. For example, it is known that hypoxia decreases epithelial Na⁺ reabsorption by impairing the expression of subunits of the epithelial Na⁺ channel.⁹² Hypoxia also decreases the activity of both the apical Na⁺ channel⁹³ and the Na⁺,K⁺-ATPase.⁹⁴ In an animal model of hemorrhagic shock-induced lung injury, the normal up-regulation of alveolar fluid reabsorption in response to catecholamines was absent. This defect was attributed to an increase in *nitric oxide* (NO) in the lung, possibly due to an effect on β -adrenergic receptor signaling.⁹⁵ In a study of patients with ARDS, alveolar fluid clearance was calculated from the change in alveolar fluid protein concentrations. When patients were stratified by their rate of fluid clearance, those with the highest rates had the shortest duration of mechanical ventilation and the lowest mortality.⁹⁶ In a model of *ventilator-induced lung injury* (VILI) in rats, overexpression of the Na⁺,K⁺-ATPase improved the clearance of lung liquid.⁹⁷ However, attempts to increase alveolar fluid clearance in a clinical setting (e.g., by β -adrenergic agonists) have so far been disappointing⁹⁸; further details are provided later under Novel Therapies (see also Chapter 9).

Angiopoietins. Angiopoietins are peptides involved in embryonic vascular development. Of the four angiopoietins that have been identified, *angiopoietin 1* and *angiopoietin 2* (ANGPT1 and ANGPT2, respectively) are the best described. ANGPT1 is expressed by numerous cell types while ANGPT2 is mostly limited to endothelial cells. Both act on the TIE2

receptor tyrosine kinase that is found predominantly on endothelial cells and hematopoietic stem cells.⁹⁹ A number of observations have generated interest in the potential role of these proteins in the pathophysiology of ARDS. First, elevated levels of ANGPT2 have been described in patients with sepsis and ARDS¹⁰⁰ and its administration to mice causes pulmonary vascular leak.^{101,102} The effect of ANGPT2 in disrupting endothelial cell integrity could be reversed in vitro by ANGPT1. Second, overexpression of ANGPT1 was protective against both endotoxin-induced septic shock and ALI in mice¹⁰³; a similar benefit was observed using a synthetic peptide agonist of the TIE2 receptor.³⁸ While the cellular mechanism of these effects remains uncertain and is the subject of intense investigation,^{104,105} the data to date emphasize the important role for endothelial cells in the development of and recovery from ARDS.

Ventilator-Induced Lung Injury

Although mechanical ventilation for ARDS may be lifesaving, there is abundant preclinical and clinical evidence that it can also be harmful.^{106,106a} While it was quickly recognized that excessive airway pressure could lead to *barotrauma* (Fig. 100-4), including pneumothorax, pneumomediastinum and subcutaneous emphysema, attention has since turned to subtler but more common manifestations of lung injury related to mechanical ventilation. Mechanical ventilation can induce pulmonary edema by causing increases in both epithelial and endothelial perme-



Figure 100-4 Barotrauma as a consequence of acute respiratory distress syndrome. Note the presence of a pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous air in this patient receiving positive-pressure ventilation. (Courtesy Thomas E. Stewart, MD, University of Toronto.)

ability.¹⁰⁶ Indeed 40 years ago Webb and Tierney demonstrated that ventilation of rats with high peak airway pressures could lead to severe pulmonary edema,¹⁰⁷ and more than 20 years ago, investigators noted that mechanical ventilation could produce a form of increased permeability pulmonary edema remarkably similar to ARDS.¹⁰⁸ Now, the accumulated evidence suggests that certain mechanical ventilation strategies may aggravate if not induce ARDS in some patients.¹⁰⁹

A major mechanism causing VILI is overdistention of lung units, rather than the absolute airway pressure per se. Normal rats ventilated with high airway pressure due to a high tidal volume developed increased permeability, whereas rats ventilated with smaller tidal volumes, but with the same end-inspiratory pressure (obtained by strapping the chest walls of the rats) did not develop increased permeability.¹⁰⁶ Rats were also ventilated with low airway pressure using negative inspiratory pressure (applied at the chest wall) and high tidal volumes. Their results demonstrated that the rats ventilated with high tidal volumes had significantly more edema than others. In particular, the negative (low) pressure and high tidal volume group had the worst edema. These important observations, confirmed in other species,¹¹⁰ led to the appreciation that large tidal volumes, rather than high airway pressures per se, are an important determinant of ventilator-induced pulmonary edema. The term *volutrauma* was created to recognize this fact.

The repetitive opening and closing of terminal lung units associated with mechanical ventilation is also considered to be detrimental. The mechanism of this injury, which has been termed *atelectrauma*,¹¹¹ is thought to be the high shear stresses generated at the interface of collapsed and aerated tissue when a collapsed airway is reopened.¹¹² Theoretically, PEEP should be helpful in minimizing this injury by keeping the lung recruited and promoting greater lung homogeneity; any such advantage of PEEP would have to be balanced against the potential harm caused by a potentially greater overdistention of lung units due to the higher PEEP levels (see Video 100-1).

It is important to point out that patients with ARDS may be especially vulnerable to VILI because of the heterogeneous nature of the pulmonary parenchymal injury. On computed tomography scans of the lungs, normal-appearing lung and densely consolidated injured lung are both seen; as a consequence, there are marked regional differences in lung compliance¹¹³ (Fig. 100-5). A tidal volume designed to inflate an entire lung would preferentially inflate the normal-appearing areas, potentially leading to overdistention and volutrauma. Patients with ARDS may similarly be more vulnerable to atelectrauma. Although some evidence suggests that normal lungs can tolerate at least short periods of cyclic opening and closing of airways from mechanical ventilation,¹¹⁴ injured lungs, such as in ARDS, would be exposed to much higher shear stresses and would not be expected to fare as well.¹¹⁵

Over the past 15 years, there has been a growing appreciation that VILI is not only a mechanical injury, but also reflects an underlying complex cellular and molecular response. The term *biotrauma* has been coined to emphasize this change in thinking.¹¹⁶ In our understanding of VILI, one of the most significant advances made is that mechanical ventilation per se can induce both a local and systemic



Figure 100-5 Axial chest CT in a patient with acute respiratory distress syndrome. Note the presence of dense consolidation with air bronchograms in the dependent dorsal lung with relative sparing of the ventral lung. (Courtesy Thomas E. Stewart, MD, University of Toronto.)

inflammatory response. In animal studies of ex vivo lungs, it has been shown that, compared to a control ventilation strategy with moderate tidal volumes and PEEP, ventilation either with high tidal volumes or with zero PEEP causes elevations in lung lavage levels of inflammatory cytokines. Lungs ventilated both with high tidal volumes and with zero PEEP had a synergistic elevation in cytokine levels.¹¹⁷ This inflammatory response to an injurious ventilation strategy has also been shown to extend beyond the lung. In an acid aspiration rat model of lung injury, a ventilatory strategy using high tidal volumes and zero PEEP was associated with an increase in blood levels of various cytokines; this was not observed in groups ventilated with a small tidal volume or in the group ventilated with the large tidal volume but higher PEEP levels.¹¹⁸

Most importantly, similar observations have been made in humans with ARDS. In one study, patients were randomized to “lung-protective” ventilation, in which the tidal volume was set to avoid overdistention and PEEP was set above the lower inflection point of the pressure volume curve.¹¹⁹ The control group received a strategy that would have been considered conventional ventilation at the time. While alveolar-lavage and plasma cytokine levels declined in the lung-protective group, they rose significantly in the control group. Post hoc analyses revealed a significantly higher number of ventilator-free days in the lung-protective group than in controls and significant correlations between the development of multisystem organ failure and plasma cytokines. The impact of ventilator strategy on the development of biotrauma can be remarkably quick. Within 1 hour after switching patients from a protective ventilatory strategy, Stuber and colleagues found an increase in a number of proinflammatory cytokines in the lungs and plasma of patients with ARDS.¹²⁰

Mortality and Complications

As discussed in the section on outcomes, patients with ARDS often die of the systemic inflammatory response syndrome and multiorgan dysfunction. Hence, the observation that mechanical ventilation can influence pulmonary and systemic cytokine levels is intriguing. Taken together, these findings suggest that mechanical ventilation has the poten-

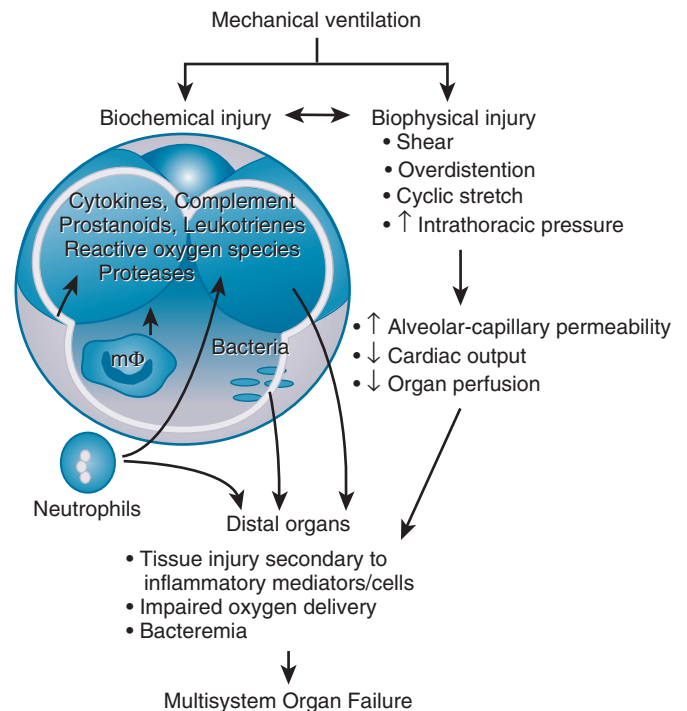


Figure 100-6 Potential mechanisms by which mechanical ventilation might cause or contribute to multisystem organ failure. Alveoli are represented showing the multiple mechanisms by which the mechanical ventilation may induce inflammatory damage and mechanical damage which can then “spill over” to affect distal organs. mφ, macrophage. (Redrawn from Slutsky AS, Tremblay LN: Multiple system organ failure: is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med* 157:1721–1725, 1998.)

tial not only to injure the lungs, but also to lead to a loss of compartmentalization of the pulmonary inflammatory response. Systemic dissemination of this response could be associated with the development of systemic inflammatory response syndrome and potentially with multisystem organ failure (Fig. 100-6).¹²¹ In one study, injurious mechanical ventilation in rats not only caused elevated plasma and lung cytokine levels, but also caused increased renal epithelial cell apoptosis and associated renal dysfunction.¹²² Furthermore, pretreatment with either IL-10 (an anti-inflammatory cytokine) or IL-22 (a member of the IL-10 family that has immunoregulatory and tissue protective properties) reduced lung injury and reduced mortality in animal models of VILI.¹²³

Finally, patients with ARDS often require very high inspired fractions of oxygen. The toxic effects of hyperoxia on the lung have been well described,¹²⁴ and the histologic appearance mirrors that of human ARDS. Oxygen toxicity is thought to be mediated by the formation of both reactive oxygen and nitrogen species, which can damage tissues by a multitude of mechanisms,⁶⁹ and hyperoxia appears to worsen VILI.¹²⁵ Antioxidants have been considered as a potential therapeutic strategy for preventing and treating ARDS, although clinical trials have so far been disappointing (see [Therapy](#)).

Genetic Determinants

To date, relatively little is known about which genes might affect the development or prognosis of ARDS. Genome-wide

association studies have suggested a number of candidate genes,¹²⁶⁻¹²⁹ including those coding for angiopoietin 2 and the angiotensin-converting enzyme,¹³⁰ that might affect the incidence and/or outcome of ARDS. Subsequent studies have reported conflicting results.^{131,132} The heterogeneity of patients with ARDS is likely to make it difficult to identify clinically important genetic associations except in clearly defined subsets of patients.

MORTALITY AND COMPLICATIONS

Mortality

The mortality rate for ARDS has decreased over the past 10 to 15 years, with a number of studies describing a decline in the rate from more than 60% to less than 40% since 1993.¹³³⁻¹³⁵ Mortality rates in adults and children with ARDS appear to be similar.¹³⁶ The reasons for the improvement in survival over time are not known, although some have attributed it to better supportive care in the intensive care unit and the use of lung-protective strategies.

Predictors of Poor Prognosis

Despite the prominence of hypoxemia among the clinical manifestations of ARDS, early trials did not find that the severity of hypoxemia early in the course of the illness was a good predictor of subsequent mortality.¹³⁷ Pulmonary injury scoring systems, such as the Lung Injury Score and the ARDS score, have been shown to predict a prolonged (>2 weeks) requirement for intubation and ventilation,¹³⁸ while scoring systems that measure the overall severity of illness, such as the Simplified Acute Physiology Score, correlate better with survival.¹³⁹ The classic teaching is that patients with ARDS do not usually die of refractory hypoxemia, which may seem paradoxical given that hypoxemia is frequently the focus of resuscitative efforts. In fact, most patients with fatal ARDS die of sepsis and multiorgan failure.^{140,141} The explanation for this apparent paradox is unknown, although it has been hypothesized that injurious mechanical ventilation during the course of ARDS may be involved.¹²¹ As discussed earlier, ventilation using excessive tidal volumes has been shown to cause elevations in pulmonary and systemic cytokine levels, and has been linked in an animal model to apoptosis of renal cells and renal dysfunction.¹²²

The mortality rate from ARDS varies depending on the precipitant. The highest risk of death has consistently been reported in sepsis, while ARDS in the setting of major trauma has a much better prognosis.¹⁴² In addition, it is known that chronic liver disease,¹³⁷ older age,¹⁴³ chronic alcoholism,²⁹ and nonpulmonary organ dysfunction¹³⁷ are associated with higher mortality from ARDS. Other predictors of death from ARDS have included a history of organ transplantation and infection with human immunodeficiency virus,¹⁴⁴ while one study described a higher mortality rate in men and also in African-Americans compared to non-African-Americans.¹⁴⁵

As mentioned earlier, risk factors for ARDS have been classified as being pulmonary or nonpulmonary in origin, thereby leading to an injury to the lung by *direct* or *indirect* means. It remains unclear whether this distinction has prognostic importance. In one prospective cohort study of

ARDS patients, investigators found a trend toward higher mortality in patients with a pulmonary precipitant, although the difference was not statistically significant.¹⁴⁶ In contrast, the ARDS Network investigators retrospectively analyzed the data from their large randomized study of low tidal volume ventilation versus traditional tidal volume ventilation. While confirming that the mortality rate for ARDS was highest in patients with sepsis and lowest in patients with trauma, there was no difference in mortality, days off the mechanical ventilator, or the development of organ failure between patients with pulmonary or nonpulmonary risk factors. In addition, there was no statistically significant evidence that the low tidal volume strategy was less efficacious in any subgroup.¹⁴² A meta-analysis came to a similar conclusion.³³ The consensus group that developed the Berlin definition of ARDS decided not to include pulmonary versus nonpulmonary ARDS as distinct categories.

Because hypoxemia is not a reliable predictor of mortality from ARDS, investigators have searched for other lung-specific markers of prognosis. In one prospective study of 179 patients with ARDS, a multiple logistic regression was performed to identify which clinical and physiologic variables predicted mortality.¹⁴⁷ The analysis found that the dead space fraction (as calculated by the Bohr equation) was elevated in ARDS and was an independent predictor of mortality. For every increase of 0.05 in the dead space fraction, the odds of death from ARDS increased by 45%. The mechanism of this association is not known: it is possible that the pulmonary vascular injury in ARDS that accounts for the increase in dead space may be important to overall outcome.

The development of pulmonary fibrosis is also thought to connote a worse prognosis. Elevated procollagen III levels, thought to be indicative of collagen synthesis, have been found in the pulmonary edema fluid of patients with ARDS and have been shown to correlate with increased mortality.^{148,149} In another study, 22 of 25 consecutive patients with ARDS underwent transbronchial biopsies of the most abnormally appearing areas on the chest radiographs. In those whose biopsies showed any fibrosis, the mortality rate was significantly higher than in patients whose biopsies showed no fibrosis.¹⁵⁰ Of note, there is evidence in animal models that the stress induced by mechanical ventilation may lead to lung fibrosis via epithelial-mesenchymal transition.¹⁵¹

Finally, there is extensive interest in the identification of biomarkers to predict outcome from ARDS. For instance, associations have been reported between elevated levels of cytokines such as IL-6 and IL-8¹⁵² and growth factors such as angiopoietin 2¹⁰⁰ and a poor prognosis from ARDS. However, even a combination of biomarkers when used together with clinical predictors is only slightly more predictive for mortality than the clinical predictors alone.¹⁵³

Complications

ARDS is complicated by ventilator-associated pneumonia in about 30% to 65% of cases (see also Chapter 34). In this setting, ventilator-associated pneumonia usually develops more than 5 to 7 days after the onset of mechanical ventilation and is often preceded by colonization of the lower respiratory tract by potential pathogens.¹⁵⁴ The likely organisms

include nonfermenting gram-negative rods, methicillin-resistant *Staphylococcus aureus*, and *Enterobacteriaceae*.¹⁵⁵ Although the development of VAP prolongs the duration of mechanical ventilation in ARDS, it does not appear to increase mortality.^{154,156,157} Making a definitive diagnosis of VAP in patients with ARDS can be challenging, because patients with ARDS already have radiographic abnormalities, and not uncommonly have leukocytosis and fever. If diagnostic techniques such as bronchoalveolar lavage or protected specimen brushes are used, the yield is higher when the lung is sampled bilaterally and when the patient is off antibiotics.^{157,158}

Another feared complication of ARDS is barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema, eFig. 100-1) due to the effect of positive pressure ventilation in heterogeneous lungs with diminished compliance. Because most patients with ARDS will be supine (rather than erect), diagnosing a pneumothorax requires vigilance; the radiographic appearance of a pneumothorax is different and can be subtler in the supine patient (e.g., air in the costophrenic angle, the “deep sulcus” sign). Data from a number of prospective studies suggest that the incidence of barotrauma in ARDS currently is about 10% or less.^{109,159,160}

THERAPY

Supportive Care

One of the first goals of therapy in ARDS is to treat the underlying cause. In particular, patients with sepsis may respond to aggressive source control, including antibiotics and, when appropriate, surgical débridement and drainage. In patients with ARDS and sepsis of unknown origin, both the lung and the abdomen should be considered and excluded as foci of infection.^{140,141} Additional goals are the prevention of complications and the provision of supportive care (e.g., nutrition, ventilation) to allow the body time to heal. Typically, such treatment should include prophylaxis against gastrointestinal stress ulceration and deep venous thrombosis.

Hemodynamic Management

The optimal approach to hemodynamic management in ARDS has become less controversial with the publication of studies comparing different strategies. Before these studies, it had been unclear whether clinicians should attempt to diurese to decrease pulmonary edema at the expense of potentially causing hypovolemia and shock or to liberalize fluids to maintain perfusion.

This issue was addressed by a large multicenter randomized controlled trial from the ARDS Network, made up of investigators at multiple American hospitals. The trial randomized 1000 patients with ARDS to one of two highly protocolized fluid strategies: through the administration of fluids, diuretics, or vasoactive agents, the two protocols targeted either a higher or lower intravascular pressure (as measured by a pulmonary artery or central venous catheter) for 7 days. Patients randomized to the conservative fluid strategy (targeting a lower intravascular pressure) had significant improvements in oxygenation and more ventilator-free and intensive care unit-free days than the patients in

the liberal strategy. Importantly, patients in the conservative arm did not have a higher incidence of dialysis or shock than those in the liberal arm; in addition, mortality rates in the two arms were similar. Thus, the results of this study suggest that conservative administration of fluids is safe and beneficial to patients with ARDS.

At first, this recommendation may seem at odds with the principle of early goal-directed therapy, whereby patients with sepsis are aggressively resuscitated with fluid in accordance with the randomized controlled trial reported by Rivers and coworkers.¹⁶¹ However, the apparently disparate results of these clinical trials are not difficult to reconcile. First, it is important to note that patients in the ARDSNet study were enrolled an average of 24 hours after meeting the criteria for ALI, much later than the 6-hour window in the study by Rivers. In addition, the study protocol of the ARDSNet trial was strictly designed to avoid aggravating or inciting shock or pulmonary edema.

One last caveat is that the ARDSNet study used a very complex algorithm for fluid administration that may not be widely adopted. A simplified protocol has since been proposed but has not been validated.¹⁶² In the meantime, we recommend that clinicians manage fluids conservatively in patients who are not in shock, nonetheless taking care to avoid overdiuresis and hypovolemia.

Clinicians had historically inserted a pulmonary artery catheter into patients with pulmonary edema to help establish the diagnosis and to guide therapy. The consensus from numerous clinical trials is that, for most patients, the information from a pulmonary artery catheter does not improve outcome.¹⁶ For this reason, we do not recommend the routine use of these catheters in patients with ARDS.

Which fluid to use in patients with ARDS remains an open question. The use of starch-based colloids has fallen out of favor in patients with severe sepsis, because of a randomized trial that found a higher incidence of renal failure in patients with severe sepsis receiving 10% pentastarch compared to patients receiving Ringer lactate.¹⁶³ Whether pentastarch has the same detrimental effect in patients with ARDS without severe sepsis is unknown. On a theoretical basis, the use of albumin is appealing, because it would increase intravascular oncotic pressure and predispose to less pulmonary edema. A small placebo-controlled study in ARDS demonstrated that a regimen of albumin and furosemide infusions over 5 days caused a substantial and statistically significant improvement in oxygenation accompanied by a decrease in heart rate. However, most of the patients had ARDS as a result of trauma, with less than 5% having sepsis. There were no differences in important clinical outcomes (e.g., mortality), although the study was not powered to address these issues.¹⁶⁴ A follow-up study established that the beneficial effect on oxygenation was due to the albumin, not the furosemide.¹⁶⁵ Although a large clinical trial of patients admitted to the intensive care unit has concluded that albumin was as safe as crystalloid,¹⁶⁶ the study did not specifically enroll patients with ARDS and only looked at short-term outcomes. It is also important to remember that as a blood product, the administration of albumin is associated with a very small but finite risk of transmissible diseases. Thus, pending further trials, the role of albumin in the management of patients with ARDS is unclear.

Nutrition

It has been hypothesized that manipulations in diet could enhance the immune system and improve the outcome of inflammatory diseases such as sepsis and ARDS. Such strategies have involved supplementing enteral feeds with one or more of arginine, glutamine, omega-3 fatty acids, and antioxidants.

One small randomized study examined the effect of a modified enteral feed containing eicosapentaenoic acid, gamma-linolenic acid, and various antioxidants compared to a control enteral feed in patients with ARDS.¹⁶⁷ The authors found that the modified feed improved oxygenation, reduced the number of neutrophils in alveolar lavage fluid, decreased length of stay, and decreased the requirement for mechanical ventilation. In a more recent study, modified enteral feeds (containing eicosapentaenoic acid, gamma-linolenic acid, and various antioxidants) also improved oxygenation, although clinically important outcomes were unchanged.¹⁶⁸ Many other studies of modified enteral feeds (often called immunonutrition) have been conducted in less well-defined populations of critically ill patients, with conflicting results. A meta-analysis on the topic highlighted the heterogeneity of the studies and suggested that the effect of immunonutrition varied depending on the group of patients being studied.¹⁶⁹ At this point, the role of immunonutrition in the management of ARDS remains unclear.

A related issue in this area has been how much enteral nutrition should be given. In a recent randomized controlled trial, the rate of enteral feeding (e.g., at a regular rate versus a low, so-called trophic rate that delivered one third as many calories) did not affect the outcome of ALI.¹⁷⁰

Pharmacotherapy

Attempts to develop pharmacologic therapies for ARDS have been frustrating and largely unsuccessful, with no pharmacotherapies that unequivocally reduce mortality from ARDS, despite a multitude of randomized controlled trials of dozens of potential agents.¹⁷¹ Despite the heterogeneity of the agents that have been evaluated, three generalizations can be made:

1. Despite showing effectiveness *in vitro* or in animal studies, most potential therapies have failed to reduce mortality or other important clinical outcomes in human clinical trials.
2. A number of agents improve oxygenation but do not affect mortality from ARDS.
3. Post hoc analyses of subsets of patients from a number of studies of various agents suggest benefit, but prospective data are lacking.

The following section reviews the biologic rationale for various potential therapies for ARDS, with an emphasis on evidence from clinical trials when available.

Corticosteroids. Because of the presumed inflammatory pathophysiology underlying ARDS, a number of trials of high-dose corticosteroids have been performed. In some, the goal was the prevention of ARDS in patients at risk (e.g., with septic shock), while in others, steroids were given in established ARDS. The usual regimen was methylprednisolone 30 mg/kg every 6 hours for 1 to 2 days. None of the trials using this treatment regimen showed any benefit from

the use of steroids,^{172,173} and one showed a higher incidence of infection in patients who received steroids.¹⁷⁴ More recently, the use of steroids has been contemplated later in the course of ARDS, during the fibroproliferative phase. Persistently elevated plasma cytokine levels have been shown to correlate with worsened survival from ARDS, prompting some to theorize that late ARDS (>7 days after onset) is characterized by persistent inflammation that might be responsive to treatment with steroids. A small study randomized 24 patients with late ARDS to 2 mg/kg of methylprednisolone (followed by a 32-day taper) or placebo. Patients in the steroid group had lower mortality, improved oxygenation, decreased organ dysfunction, and earlier extubation, but also had a higher (but not statistically significant) rate of infection.¹⁷⁵ However, these data are difficult to interpret because of the small sample size and the number of patients who crossed over to the alternate therapy.

A randomized placebo-controlled trial of 180 patients with ARDS of at least 7 days' duration was subsequently performed by the ARDS Network.¹⁷⁶ Patients were randomized to either placebo or a single dose of 2 mg/kg of methylprednisolone followed by 0.5 mg/kg every 6 hours for 14 days, then every 12 hours for 7 days, then tapering. Although the patients randomized to steroids showed improvements in the number of ventilator-free and shock-free days (during the first 28 days) as well as in oxygenation, there was no difference in 60-day mortality. A subgroup analysis revealed that patients who received steroids more than 14 days after the onset of ARDS had a significantly increased 60- and 180-day mortality rate. The issue of whether to use steroids in late ARDS remains controversial,¹⁷⁷ but it seems reasonable to consider steroids in patients who are not improving between about days 7 and 14 in that benefit has been suggested in subgroups and harm has not been proven.

Vasodilators. Prostaglandin E₁ is a vasodilator that has been studied as a potential therapy for ARDS, based largely on its putative anti-inflammatory properties. In vitro and preclinical studies in animals suggested that prostaglandin E₁ given parenterally, especially when administered in a liposome, had the potential to decrease neutrophil activation. Despite promising early data,¹⁷⁸ a large randomized double-blind multicenter trial of liposomal prostaglandin E₁ found no improvement in survival or in ventilator dependence even though the drug improved oxygenation.¹⁷⁹

Prostacyclin is another vasodilator which, when administered by nebulizer, acts selectively on the pulmonary vasculature. Because the aerosolized solution tends to go to the better ventilated areas of the lung, vasodilatation of the branches of the pulmonary artery that supply these areas lead to improved \dot{V}/\dot{Q} matching and improved oxygenation. Although prostacyclin has been used as rescue therapy for refractory hypoxemia and is well tolerated,¹⁸⁰ there are no large randomized studies and no placebo-controlled studies of its use in ARDS.^{181,182}

NO is a highly reactive gas formed endogenously by NOS from the amino acid arginine. It stimulates cellular guanylate cyclase, leading to increased cyclic guanosine monophosphate levels. It acts as a potent vasodilator, and when given by inhalation, NO causes vasodilatation of the pulmonary circulation. NO is rapidly inactivated in the

bloodstream by combining with hemoglobin to form methemoglobin, which is usually rapidly metabolized and does not accumulate to levels that are thought to be toxic (i.e., methemoglobin < 5%). Because of this rapid inactivation, NO is a selective vasodilator that does not affect the systemic circulation. Like aerosolized prostacyclin, NO causes the most vasodilatation in the areas of the lung that are best ventilated, thereby improving \dot{V}/\dot{Q} matching.¹⁸³ In addition, NO has both antiinflammatory and proinflammatory properties, although the contribution of these properties to its effects in a clinical setting is unclear.¹⁸⁴ NO can also react with oxygen and water to form toxic metabolites, such as NO₂ and nitrous and nitric acid, although at concentrations of NO of less than 40 ppm, this problem is not usually clinically significant. A soda lime absorber can be placed in the inspiratory limb of the NO circuit in order to remove any NO₂ before the inspired gas reaches the patient.

In the largest randomized, double-blind, placebo-controlled study of NO in ARDS to date, more than 170 patients were randomized to different doses of NO (from 1.25 to 80 ppm) or placebo. Although approximately 60% of patients had a significant improvement in oxygenation within 4 hours of NO administration, there was no difference in survival or in liberation from mechanical ventilation between patients receiving NO and those in the placebo group.¹⁸⁵ In addition, the initial improvement in oxygenation from NO was not sustained over the course of study. There were few adverse effects of NO, and for patients who were administered less than 40 ppm, methemoglobin and NO₂ levels were the same as in the placebo group. The results of this study confirmed the findings of other smaller unblinded trials of NO in ARDS^{186,187} and were repeated in a systematic review.¹⁸⁸ In another large randomized but unblinded study of NO in ARDS, a higher proportion of patients in the NO group required renal replacement therapy than in the control group.¹⁸⁹ A meta-analysis of trials using NO for ARDS concluded that, while NO caused initial improvement in oxygenation, it had no impact on survival and was associated with an increased risk of renal dysfunction.¹⁹⁰ We suggest that NO should not be used routinely in the treatment of patients with ARDS, other than perhaps as a "rescue" therapy for extreme life-threatening hypoxemia. In fact, in a recent individual patient meta-analysis, inhaled NO did not improve mortality in patients with ARDS regardless of severity as assessed by arterial PO₂/Fio₂ ratios as low as 70.¹⁹¹

Surfactant. As discussed in the section on pathogenesis, a number of abnormalities of surfactant have been described in ARDS. These include an increase in relatively inactive forms, inactivation of surfactant by proteins that have leaked into the alveolar space, damage to type II epithelial cells (which produce surfactant), and destruction of surfactant constituents by the inflammatory process.⁴⁵ These changes, along with the efficacy of surfactant supplementation in the neonatal respiratory distress syndrome, led to the hypothesis that surfactant supplementation might be beneficial in ARDS. Data from animal studies and small case series were promising.¹⁹² A small randomized controlled trial administered bovine surfactant through an endotracheal catheter in patients with ARDS and showed in one subgroup of patients an improvement in oxygenation and a trend to decreased mortality.¹⁹³

However, enthusiasm for surfactant was greatly dampened by the results of a large multicenter randomized, blinded, placebo-controlled trial. In this study, investigators administered an aerosolized synthetic (protein-free) surfactant or saline placebo continuously for up to 5 days to patients with new onset (<48 hours) of sepsis-induced ARDS. There was no physiologic or clinical benefit from the surfactant. Despite its methodologic rigor, the study has been criticized because less than 5% of the administered dose of surfactant was thought to have reached the distal lung. In addition, the lack of surfactant proteins in the synthetic surfactant may have diminished its ability to reduce surface tension.¹⁹⁴ Because of these issues, the role of surfactant supplementation continues to be studied.

In a phase I/II trial, 40 patients with new-onset ARDS were randomized to a surfactant protein C-based preparation (given up to four times over 24 hours) or to no drug. The surfactant was administered through a catheter placed in the endotracheal tube. The drug had no effect on oxygenation or on ventilator-free days, which were the primary outcomes of the study. The authors reported a significant decrease in IL-6 levels in bronchoalveolar lavage fluid from patients who received the surfactant preparation, although it is unclear whether this was a prespecified end point.¹⁹⁵

Finally, two phase III trials of the recombinant surfactant protein C-based preparation have been completed. The studies demonstrated that the surfactant improved oxygenation, but had no impact on mortality or ventilator-free days. Only one trial, using calfactant (a natural surfactant, distinct from previous trials) in pediatric patients with ARDS, has shown any mortality benefit⁴⁶; whether this is due to the unique surfactant used in this study or to differences between the patients enrolled in this trial and the negative trials (e.g., adult vs. pediatric) is unknown. Whether surfactant will prove to be useful in well-defined subgroups of patients with ARDS remains an open question.⁴¹

Antioxidants and Anti-inflammatory Agents (Other Than Steroids). Oxidative stress has long been postulated to be involved in the pathogenesis of ARDS.⁶⁹ In fact, lung injury due to hyperoxia is a commonly used model to study ARDS in animals. Reactive oxygen species form as a by-product of activation of neutrophils and macrophages; in addition, the requirement by many patients with ARDS for a high inspired fraction of oxygen may predispose to oxidative stress. Decreased levels of glutathione, a major endogenous scavenger of reactive oxygen species, have been observed in the alveolar fluid of patients with ARDS. Small clinical trials with N-acetylcysteine and procysteine were promising.¹⁹⁶ Unfortunately, despite this optimism, larger clinical trials of antioxidants in ARDS have been disappointing. A multi-center trial of the antioxidant procysteine in ARDS showed no beneficial effect of the drug.⁴⁷

Various agents with putative anti-inflammatory effects have been tested in ARDS. These include ketoconazole, liso-fylline, and (in patients with sepsis at risk for ARDS) the nonsteroidal anti-inflammatory drug ibuprofen. In separate well-conducted, randomized, blinded, controlled trials, none of these agents demonstrated benefit in ARDS.¹⁹⁷⁻¹⁹⁹ A prospective randomized controlled trial evaluated the effect of recombinant platelet activating factor acetylhydrolase at preventing ARDS in patients with severe sepsis. This trial of more than 100 patients showed no decrease in the

development of ARDS in patients who received the drug; however, the mortality rate was lower in patients receiving an intermediate dose of the study drug.²⁰⁰ Other trials of so-called anti-inflammatory therapies in sepsis have been disappointing.^{80,171}

Novel Therapies. As discussed earlier in the section on Pathogenesis, alveolar fluid clearance can be augmented by catecholamines. A small trial randomized 40 patients with ARDS to intravenous salbutamol or placebo for 7 days.²⁰¹ Patients receiving salbutamol had a decrease in extravascular lung water but a higher incidence of arrhythmias. A follow-up study was performed in almost 50 intensive care units in the United Kingdom and enrolled more than 300 patients with ARDS. However, the trial was halted earlier than planned because of an increase in mortality in the group receiving intravenous salbutamol.⁹⁸ A similar-sized trial of aerosolized albuterol (given every 4 hours for up to 10 days) for ARDS found no benefit.²⁰² Thus, routine use of β_2 -agonists cannot be recommended in ARDS.

Stem cell therapy for ARDS is being explored.²⁰³ Beneficial effects have been noted in animals with endotracheal and intravenous delivery of stem cells²⁰⁴ and may be augmented by using stem cells transfected with ANGPT1.²⁰⁵ A schematic of novel potential therapeutic approaches is shown in Figure 100-7.

Discrepancies Between Studies in Animals and Humans. As discussed earlier, virtually all large-scale clinical trials of pharmacotherapy for ARDS have been negative, despite promising and often exciting animal studies. There are a number of reasons why results from these animal studies have not been replicated in human clinical trials. First, in animal studies, the agent being investigated is often administered at the same time or shortly after the lung is injured (e.g., cecal ligation and perforation followed by administration of the drug within a few hours). In contrast, the onset of lung injury in humans is often much more difficult to define, and potential therapies are given many hours after the diagnosis is made. Thus, agents that might have been effective at preventing or attenuating ARDS may have been given too late. Second, “proof of principle” animal studies are of relatively short duration and do not mimic the complicated clinical course of human ARDS. Third, animals in most studies represent essentially a homogeneous group; in contrast, human patients have multiple comorbidities and have multiple cointerventions. Fourth, the underlying precipitant for ARDS, even in carefully selected subgroups of patients, differ in severity and duration, unlike in animals wherein a uniform injury is applied. This heterogeneity makes it challenging to identify agents that may be of only modest clinical benefit. Finally, as discussed, the current definition of ARDS is problematic, and studies may include many patients with markedly different pathophysiology/biology.

MECHANICAL VENTILATION

Mechanical ventilation is lifesaving and is the standard therapy for ARDS. Ventilatory management of ARDS has undergone dramatic changes over the last 20 years, in large

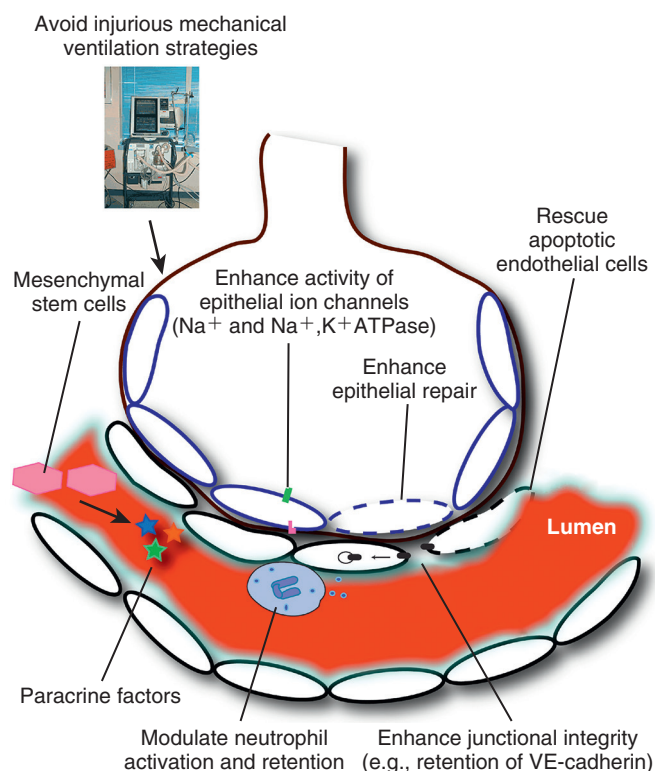


Figure 100-7 Schematic of an alveolus depicting potential novel therapeutic strategies for ARDS. Mesenchymal stem cells have been shown to alleviate lung injury in animal models, a benefit that has been attributed to their paracrine effects. Modulation of neutrophil recruitment, activation (e.g., degranulation), and apoptosis has long been investigated as a means of preventing or abrogating lung injury, which is often considered to be neutrophil-dependent. Epithelial repair or enhancement of alveolar fluid clearance is another strategy that is being pursued, such as by up-regulation of epithelial apical sodium channels. More recently, there has been interest in increasing the integrity of the lung endothelial barrier by preventing the internalization (and loss of function) of junctional proteins such as VE-cadherin and claudin-5 or by attenuating endothelial apoptosis. Lastly (top left), clinical trials have demonstrated that certain ventilator strategies are less injurious to the lungs than others.

part due to increased use of computed tomography to image the lungs and to advance understanding of VILI.

PRESSURE AND VOLUME LIMITATION

Mechanical ventilation of patients under anesthesia for surgery traditionally involves large tidal volumes of 10 to 15 mL/kg, with the dual goals of achieving normal arterial oxygenation and arterial pH. A similar approach to ventilating patients with ARDS was followed in the past. This emphasis on achieving normal physiologic parameters in patients with ARDS was understandable at the time: in addition to being characterized by profound hypoxemia and diminished pulmonary compliance, ARDS was thought to involve the lungs diffusely and homogeneously based on plain radiography.⁷ A large tidal volume therefore appeared to be the only way to both ventilate patients and maintain oxygenation. Subsequently, studies using computed tomography²⁰⁶ demonstrated that the lungs of many patients with ARDS are actually heterogeneous: instead of the diffuse involvement suggested by plain radiographs, computed

tomography scans often show patchy opacities interspersed with more normal-appearing areas of lung (see Fig. 100-5). The heterogeneous distribution of the injury in ARDS implies that the tidal volume administered to a patient will preferentially inflate the more compliant (or normal) areas of lung. These regions of the lung, exposed to tidal volumes meant for an entire lung, are therefore at risk for overdistention and ventilator-associated lung injury. As discussed earlier, mechanical ventilation with excessive tidal volumes can cause pulmonary edema due to increased alveolar-capillary permeability, with remarkably similar histology to ARDS.

Despite the clear physiologic rationale and abundant experimental data to support pressure and volume limitation when ventilating patients with ARDS, it was not until the late 1990s that data from randomized clinical trials in humans began to accrue. Between 1998 and 2000, five randomized controlled trials of ventilation strategies in ARDS were published.^{109,160,207-209} In all of the trials, patients were randomized either to a strategy involving some degree of tidal volume and pressure limitation, or to a “conventional” ventilation strategy with higher tidal volume and pressure limits.

Of the five studies, the largest was conducted by the ARDS Network, composed of investigators from multiple American hospitals and supported by the National Heart, Lung, and Blood Institute of the United States.¹⁰⁹ This study, which was more than seven times larger than any of the other four, randomized 861 patients to lower tidal volumes or traditional tidal volumes. In the traditional group, plateau pressure was also kept below 50 cm H₂O. In the small volume group, tidal volume was set at 6 mL/kg of predicted body weight and reduced if necessary to maintain plateau pressure between 25 and 30 cm H₂O. Respiratory acidosis was treated aggressively, with the ventilator rate being set at six to 35 breaths per minute to achieve a pH of 7.3 to 7.45. Bicarbonate infusions were allowed for acidosis that persisted despite a ventilator rate of 35 breaths per minute. Tidal volume was increased for refractory acidemia, if pH was less than 7.15. Only preset combinations of PEEP and FIO₂ were allowed in the two groups, for a target oxygen saturation of 88% to 95% (Table 100-3). Patient-

ventilator dyssynchrony was reduced by sedating the patient, when necessary.

The trial, which originally set out to accrue 1000 patients, was stopped early because an interim analysis showed benefit in the small tidal volume group. The mortality rate was 39.8% in the traditional group, compared with 31% in the small tidal volume group ($P=0.007$). Breathing without assistance at day 28 was also significantly more frequent in the small volume group, and the number of ventilator-free days was higher. The number of days without organ failure was also higher in the small volume arm.

A key factor in comparing trials is to appreciate that the ARDS Network study used predicted body weight, while other studies used ideal body weight or measured body weight to set the tidal volume. The rationale underlying the use of predicted body weight is that it correlates much better with lung size than measured body weight, and the goal in individualizing the tidal volume for any patient is to match the tidal volume to the size of the lung. The distinction is important, since data from the ARDS Network study demonstrate that measured body weight was approximately 20% higher than predicted body weight. In other words, the tidal volumes used in other studies may have been higher than appreciated. Predicted body weight in kilograms can be calculated for male patients as $50 + 0.91(\text{centimeters of height} - 152.4)$, and for female patients as $45.5 + 0.91(\text{centimeters of height} - 152.4)$.¹⁰⁹

The ARDS Network study adopted an aggressive approach to hypercarbia and acidemia, including use of higher respiratory rates, bicarbonate infusions, and loosening of ventilatory restrictions. As a result, hypercarbia and subsequent low pH in the treatment arm was less marked than in some other studies. This too may have contributed to the lower mortality in the lower tidal volume arm.

Some investigators have proposed that mechanical ventilation of a given patient be set based on the static inspiratory pressure-volume curve of the patient's respiratory system.²⁰⁹ In ARDS, such curves often have a sigmoidal shape, with a lower inflection point at low lung volumes, and an upper inflection point at high volumes. Initially, it was thought that the lower inflection point represented the pressure at which collapsed lung units reexpand, accounting for the abrupt change in compliance. The upper inflection point was thought to represent the pressure at which the alveoli become overdistended. On this basis, it was proposed that PEEP should be set higher than the pressure of the lower inflection point, while plateau pressure should be kept lower than the upper inflection point. Although conceptually appealing, this interpretation of the static inspiratory pressure-volume curve is likely erroneous. Recruitment of the lung is known to continue even above the lower inflection point.²¹⁰ Conversely, during tidal ventilation, alveoli may be continually recruited so that the ventilatory cycle takes place in a region closer to the deflation limb rather on the inflation limb of the pressure-volume curve.²¹¹ Thus, limiting tidal volume or plateau pressure based on the inspiratory pressure-volume curve is not used widely.²¹²

Neuromuscular Blockade

Mechanical ventilation of patients with ARDS is often complicated by patient-ventilator dyssynchrony, which can worsen oxygenation and ventilation. To overcome this,

Table 100-3 Ventilation Protocol Used in the ARDS Network Study¹⁰⁹

Parameter	Protocol
Mode of ventilation	Volume assist control
Tidal volume	≤6 mL/kg predicted body weight*
Plateau pressure	≤30 cm H ₂ O
Frequency	6–35 breaths/min, titrated for pH 7.3–7.45
I:E ratio	1:1 to 1:3
Oxygenation goal	Arterial PO ₂ 55–80 mm Hg, or SpO ₂ 88%–95%
FIO ₂ /PEEP (cm H ₂ O)	0.3/5, 0.4/5, 0.4/8, 0.5/8, 0.5/10, 0.6/10, 0.7/10, 0.7/12, 0.7/14, 0.8/14, 0.9/14, 0.9/16, 0.9/18, 1/18–24
Weaning	By pressure support, required when FIO ₂ /PEEP ≤ 0.4/8

*See text for formula to calculate predicted body weight. I:E ratio, ratio of inspired to expired gas; SpO₂, saturation by pulse oximetry.

clinicians have traditionally sedated patients and even paralyzed them using neuromuscular blocking agents. Many clinicians have since become reluctant to use neuromuscular blocking agents because of concerns of inducing myopathy and prolonging the duration of mechanical ventilation. However, a multicenter randomized controlled trial of more than 300 patients with early (<48 hours) and severe ARDS compared a 48-hour infusion of cisatracurium to placebo.²¹³ Both groups received lung-protective ventilation based on the ARDSNet trial, discussed earlier. The authors reported a significant reduction in 90-day mortality (the primary end point) as well as a number of secondary end points, including barotrauma and organ failure. There was no increase in intensive care unit-acquired weakness. The mechanism of benefit from neuromuscular blocking agents is unknown, but may involve decreased ventilator-induced lung injury.²¹⁴ These provocative data, while promising, await replication before being widely adopted.

The Role of PEEP and Recruitment Maneuvers

As mentioned earlier, the first description of ARDS commented on the apparent utility of PEEP in improving oxygenation. From a theoretical standpoint, PEEP may be beneficial in avoiding damage from cyclic opening and closing of terminal lung units (atelectrauma, see [Pathogenesis](#)), and in allowing for a reduction in tidal volume (and hence volutrauma). In addition, PEEP, by improving oxygenation, may allow for lowering of the FiO_2 , thereby decreasing the risk for oxygen toxicity. On the other hand, PEEP that is too high can itself cause excessive end-inspiratory lung volume and volutrauma. Many clinicians are also familiar with the potential effect of PEEP to depress cardiac output and blood pressure. The optimal level of PEEP to use in patients with ARDS has therefore been a source of controversy.²¹⁵⁻²¹⁷

Along the same lines, the low tidal volumes and pressures advocated for lung-protective ventilation can lead to progressive de-recruitment of the lung, which can worsen hypoxemia and potentially aggravate atelectrauma. To counteract de-recruitment, so-called recruitment maneuvers have been proposed. These maneuvers involve an increase in airway pressure for a certain duration, although the pressure to be applied and its duration have not been standardized. One example of a recruitment maneuver would be 40 cm H_2O of continuous positive airway pressure for 40 seconds. Similar to the problems with setting the level of PEEP, however, it is difficult to predict which patients might benefit from recruitment maneuvers and which might be harmed by overdistention. Overdistention of well-perfused lung units could result in diversion of blood to poorly perfused alveoli, with consequent worsening of right-to-left shunt and hypoxemia.²¹⁸

A number of randomized controlled trials have addressed the issue of PEEP and recruitment maneuvers in the management of ARDS.

The ARDS Network investigators randomized 549 patients with ARDS to lower or higher PEEP levels, according to preset combinations of PEEP and FiO_2 . The patients in the lower PEEP arm received the PEEP/ FiO_2 levels used in the original ARDSNet trial of lung-protective ventilation (see earlier). The precise level of PEEP used in the higher

arm varied with the FiO_2 , but was on average 5 cm H_2O higher than the control arm (mean of 13 to 15 cm H_2O over the first 7 days). Recruitment maneuvers were initially used in the higher PEEP group but were discontinued after the first 80 patients because they were not very effective.²¹⁹ The study was stopped early due to perceived futility and the mortality rate in both arms was about 25%, significantly lower than had been reported in other trials of ARDS.²²⁰

A second large trial randomized almost 1000 patients with ALI to what was described as an “open lung” strategy versus the ventilation protocol used in the original ARDSNet trial.²²¹ The “open lung” strategy consisted of pressure control ventilation with plateau pressure (P_{plat}) less than 40, recruitment maneuvers, and high PEEP, together with the low tidal volumes (6 mL/kg) used in the control group. On average, on day 1 of the study, PEEP in the open lung arm was 16 cm H_2O , compared with 10 cm H_2O in the control group. This trial also found no difference in the mortality rates between the two groups (about 40%), although the open lung group had improvements in secondary end points related to hypoxemia.

Finally, a large French trial randomized 767 patients with ALI to PEEP of 5 to 9 cm H_2O or PEEP maximized as long as P_{plat} was less than 28 to 30.²²² On day 1 of the study, the mean applied PEEP level in the control arm was about 7 cm H_2O , or marginally lower than that of patients in the original ARDSNet trial of lung-protective ventilation, while the higher PEEP arm had an average applied PEEP of 15 cm H_2O . The study demonstrated no difference in mortality, but the higher PEEP arm had improved compliance, oxygenation, and a decreased duration of mechanical ventilation and organ failure.²²²

Taken together, the data from these trials suggest that higher PEEP levels than used in the original ARDSNet trial are safe and may improve oxygenation, but there are insufficient data to argue that higher PEEP improves survival. Why these clinical studies are generally negative despite very strong animal data demonstrating the benefits of higher PEEP levels is somewhat of a puzzle. One possibility is the yin-yang of PEEP. To the extent that PEEP recruits lung units, it may be beneficial; to the extent that it leads to greater overdistention of lung units, it may be harmful. In all studies to date, PEEP has been applied to all patients whether or not their lungs are recruitable. As such, one reasonable approach to be tested in future studies of PEEP is to randomize only patients to a high/low PEEP strategy if they have lungs that are potentially recruitable.^{217,223} Indeed, a meta-analysis that included these trials found that while higher PEEP was associated with a lower mortality in patients with arterial $\text{PO}_2/\text{FiO}_2 < 200$ mm Hg (i.e., ARDS), there was less benefit and a trend to harm in patients with a higher arterial PO_2/FiO_2 and hence less severe lung injury.²²⁴

The data also suggest that the role of recruitment maneuvers in the management of ARDS is only supportive, and the data currently available do not demonstrate improvement in clinically important outcomes. The major putative benefit of recruitment maneuvers is to decrease ventilator-induced lung injury. Many studies report a variable and transient improvement in oxygenation after some form of recruitment,²¹⁹ which can be better maintained with a higher level of PEEP after recruitment. It is also possible that the same degree of recruitment could be achieved by

simply raising the level of PEEP.^{225,226} Although recruitment maneuvers are generally safe, the patient must be closely monitored for any adverse effects on hemodynamics or oxygenation.

Permissive Hypercapnia and Tracheal Gas Insufflation

The use of lower tidal volumes (to avoid VILI) often results in respiratory acidemia, an effect that has been termed *permissive hypercapnia*. The theoretical detrimental effects of hypercapnia include myocardial depression, increased pulmonary vascular resistance, and decreased renal blood flow. Hypercapnia may have an injurious effect on alveolar epithelial cells.²²⁷ Perhaps the most clinically important adverse effect of hypercapnia is elevated intracranial pressure from increased cerebral blood flow. However, data also suggest that hypercapnia has protective effects, including attenuation of free radical-mediated lung injury and pulmonary inflammation.^{228,229}

Given the uncertainty about permissive hypercapnia, it is worth remembering that the only large randomized controlled trial to show a reduction in mortality in ARDS treated respiratory acidosis fairly aggressively (discussed earlier).¹⁰⁹ In the absence of other data, following the protocol used in that study seems prudent.

One approach that has been used to decrease high levels of arterial PCO₂ is tracheal gas insufflation, a technique whereby a gas flow is introduced via a small catheter placed in the endotracheal tube, with its tip near the carina. Tracheal gas insufflation has been proposed as an adjunct to permissive hypercapnia, because the insufflated gas improves CO₂ clearance from the anatomic dead space and ventilator tubing. However, the gas flow has the potential to increase alveolar volume and pressure, and may increase PEEP.²³⁰ Although there are many case reports describing the use of tracheal gas insufflation,²³¹ there have been no randomized studies in ARDS. Because of technical and monitoring issues, we do not recommend its routine use of tracheal gas insufflation in ARDS.

Mechanical Ventilation of Patients in the Prone Position (Proning)

Placing patients with ARDS in the prone position (proning) was described almost 30 years ago as a means of improving oxygenation. The mechanisms by which the prone position improves oxygenation are multiple, but probably the most important factor is the effect that proning has on chest wall and lung compliance.²³² In the supine position, the most dorsal and caudal regions of lung (along the spine and diaphragm) are the worst affected in many patients with ARDS. Some of this is due to gravity, but the weight of the heart and of the abdominal organs on the lungs also contributes. When a patient is placed in the prone position, the anterior chest wall is fixed (by the bed) and becomes less compliant, thus increasing the proportion of ventilation directed to the dorsal lung. In addition, the volume of lung that is being compressed by the heart due to gravity is substantially decreased. The net result is more homogenous ventilation of the lung and presumably improved \dot{V}/\dot{Q} matching. Data from a study in dogs suggest that ventilation in the prone position can attenuate the severity of VILI.²³³

A number of multicenter randomized controlled trials have now examined the efficacy of proning in patients with ARDS. One study enrolled more than 300 patients with ALI and randomized them to conventional treatment (supine) or treatment in the prone position for 6 or more hours for 10 days. The study found that oxygenation improved in approximately 70% of proning procedures and that most of the improvement was evident within 1 hour of proning. However, although oxygenation improved significantly in prone patients, there was no difference in mortality between the groups. Retrospective analyses of the quartile of patients with the poorest oxygenation or the highest acuity of illness (or the highest tidal volume) showed a lower mortality rate at 10 days in the patients who were prone, but this difference did not persist beyond discharge from the intensive care unit.²³⁴ The study has been criticized for the relative short duration of the intervention, as well as the fact that most patients spent the majority of the day supine.²³⁵

A subsequent study randomized more than 700 patients with acute hypoxemic respiratory failure (which included but was not limited to patients with ARDS) to ventilation in the prone or supine position; patients were prone an average of 50 hours after intubation for a median of 8 hours per day, for a median of 4 days.²³⁶ Prone patients exhibited improved oxygenation but no improvement in mortality or duration of ventilation. These patients also suffered from a higher incidence of complications, including pressure sores, selective intubation, and endotracheal tube obstruction.

A pediatric study (median age 2 years) of proning in ARDS was similarly negative,²³⁷ and two Spanish trials of proning for adults with ARDS were inconclusive but suggestive of benefit.^{238,239}

In 2013, a multicenter randomized trial of prolonged (>16 hours) proning was reported in more than 400 patients with early (<36 hours) and severe ARDS.²⁴⁰ ARDS was defined according to the AECC criteria, with severe ARDS denoting arterial PO₂/FIO₂ < 150 mm Hg with FIO₂ ≥ 0.6, PEEP ≥ 5 cm H₂O and tidal volume of about 6 mL/kg predicted body weight. Patients were prone within the first hour after randomization and kept prone for at least 16 consecutive hours; proning was performed every day up to day 28. Remarkably, the 28-day survival rate was 16% in the prone group and 33% in the supine group.

These results are very impressive and are likely to increase the adoption of proning by intensivists. While proning in that trial was not associated with any complications, it is important to note that it was conducted in centers with significant expertise in prone-position ventilation, which requires some attention to detail, and that it did not involve use of a rotating bed. Lines and tubes are vulnerable to dislodgement during the process, and sufficient staff should be on hand to assist with the move. Personnel should be ready and capable of immediate reintubation in case the endotracheal tube is displaced. Prone patients are more susceptible to development of pressure sores, and exquisite care must be taken to ensure that no stray objects (e.g., syringes, electrocardiogram leads) are left under the patient, because these leave impressions and even scars on the body. An unstable spinal injury is an absolute contraindication to proning. In addition, if cardiopulmonary resuscitation is required, the patient must be returned to the supine

position emergently. Finally, in the most recent trial, there were a number of exclusion criteria, including elevated intracranial pressure, massive hemoptysis, recent tracheal or facial surgery, and low mean arterial pressure (<65 mm Hg).²⁴⁰

Volume-Control Versus Pressure-Control Ventilation

The volume and pressure-limited protocol used in the ARDS Network study employed volume-assist control as the mode of ventilation. The Lung Open Ventilation study (described earlier) demonstrated that pressure-control ventilation could be used with equivalent outcomes.²²¹ Other studies that have examined this issue have also found little difference in physiologic parameters or outcome between the two modes of ventilation.^{241,242}

High-Frequency Jet Ventilation and High-Frequency Oscillation

In high-frequency jet ventilation, a small gauge catheter is used to introduce gas under high pressure into the endotracheal tube. The high velocity of the gas entrains additional oxygen and humidified air from side ports in the system. This form of mechanical ventilation achieves a tidal volume of 2 to 5 mL/kg and involves frequencies of 100 to 200 breaths per minute.²⁴³ Exhalation is passive, requiring recoil of the lungs and chest wall. There is little evidence that high-frequency jet ventilation is superior to conventional mechanical ventilation for ARDS. An early randomized trial of over 300 oncology patients with ARDS compared conventional ventilation (using volume-cycled ventilation) with high-frequency jet ventilation. Because the end points of the study differed between the two groups of patients, it is difficult to interpret the data. Nonetheless, the authors found no significant difference in any clinically important outcome.²⁴⁴

In *high-frequency oscillatory ventilation* (HFO), lung recruitment is maintained using a constant mean airway pressure generated by an inspiratory bias flow and limitation of gas outflow from the circuit. Ventilation is achieved through rapid (e.g., 5 Hz) regular oscillations of a piston or diaphragm. The push and pull action of the piston causes oscillations in pressure in the endotracheal tube and proximal airways, creating peak and trough pressures around the set mean airway pressure. The tidal volumes achieved through HFO are small, on the order of 1 to 5 mL/kg. In theory, HFO seems ideally suited for avoiding VILI. Atelectrauma is minimized because of the relatively high mean airway pressure, which along with small tidal volumes limits derecruitment of the lung, and volutrauma is minimized because the small tidal volumes limit end-inspiratory stretch.²⁴⁵ With HFO, loss of pressure from the circuit can lead to de-recruitment, thus recruitment maneuvers (e.g., application of continuous positive airway pressure for approximately 30 to 40 seconds) should be applied after each patient disconnect from the ventilator (e.g., open suctioning).

In an early randomized trial of HFO in adults, 148 patients with ARDS were randomized to conventional ventilation using pressure-control mode or to HFO.²⁴⁶ The specific ventilatory parameters for both the conventional group and the HFO group were adjusted to achieve adequate

oxygenation at a minimum FiO_2 (i.e., 88% at $\text{FiO}_2 \leq 0.60$), as well as an arterial pH greater than 7.15. Because the study was begun before the publication of the ARDS Network trial on tidal volume limitation, the conventional ventilation arm of this study targeted tidal volumes of 6 to 10 mL/kg. The trial was not powered to detect a mortality difference, and there was no significant difference in 30- or 90-day mortality, or in any other outcome. The authors performed a retrospective analysis of predictors of mortality, and discovered that being on conventional ventilation for more than 5 days correlated with a poor outcome.

More recently, two large randomized trials of HFO were published and showed no benefit in terms of survival or the duration of mechanical ventilation^{247,248} compared with conventional lung-protective ventilation. Indeed, one of the studies suggested that HFO might be harmful due to the amount of sedation required or due to impairment of hemodynamics. Because of these findings, the routine use of HFO for ARDS cannot be recommended, although its role as “rescue” therapy is not clear.

Liquid Ventilation

Liquid ventilation relies on the oxygen and carbon dioxide carrying capacity of organic liquids such as perfluorocarbons. Perfluorocarbons are modified hydrocarbons in which hydrogen atoms are replaced with fluorine, generating inert liquids that are nontoxic and minimally absorbed through the respiratory epithelium. The most widely studied perfluorocarbon, perflubron (perfluorooctyl bromide, [eFig. 100-2](#)), can dissolve about 17 times more O_2 than saline solution and almost 4 times more CO_2 .²⁴⁹ Total liquid ventilation is a technique in which the lungs are completely filled with liquid and an extracorporeal exchanger is used to add O_2 and remove CO_2 from the liquid. Partial liquid ventilation, which is much easier to use clinically, involves partially filling the lung with liquid and then using a traditional ventilator to deliver gas tidal volumes.²⁵⁰

The theoretical benefits of liquid ventilation stem largely from improved lung recruitment, due to the lower surface tension of the perfluorocarbons and because the liquid tends to distribute to the dependent regions of the lung. Deposition of liquid with low surface tension in these areas may enhance alveolar recruitment; in addition, the weight of the liquid is thought to cause diversion of pulmonary blood flow to the nondependent (better ventilated) areas, improving \dot{V}/\dot{Q} matching. Clearance of secretions (due to their displacement by the liquid) is also improved. Anti-inflammatory effects of perflubron have been described, although the clinical relevance of these effects is not well understood. To date, two randomized controlled trials of partial liquid ventilation in adults with ARDS have been published.²⁵¹ The first enrolled 90 patients with ARDS to partial liquid ventilation with perflubron or to conventional mechanical ventilation. Other than very general guidelines (e.g., target arterial $\text{SO}_2 > 90\%$), neither of the two ventilation strategies was protocolized. In addition, the inclusion and exclusion criteria were modified slightly during the course of the study. There was no significant difference in the number of ventilator-free days (the primary outcome measure) or in any other predefined outcome. More patients in the liquid ventilation arm experienced hypoxia, bradycardia, and respiratory acidosis, although the increase in

the incidence of these adverse events was not statistically significant.

In 2006 a multicenter randomized trial of partial liquid ventilation with perfluorocarbon compared with conventional mechanical ventilation (VT 10 mL/kg) enrolled more than 300 patients with ARDS. The study found a trend toward higher mortality in the groups receiving perfluorocarbon in addition to a higher incidence of barotrauma, hypoxia, and hypotension.²⁵² Based on these data, partial liquid ventilation cannot be recommended for patients with ARDS.

Extracorporeal Membrane

Oxygenation (see Chapter 103)

Extracorporeal membrane oxygenation (ECMO), also referred to as extracorporeal life support or extracorporeal lung assist, refers to the process by which the patient's blood is circulated to an external machine that provides oxygenation and/or carbon dioxide removal.²⁵³ In theory, ECMO could be used to oxygenate patients with ARDS while minimizing VILI and oxygen toxicity and allowing the lungs time to heal. There are multiple case reports of ECMO being used in ARDS, and it is used routinely in neonates with severe respiratory failure. A randomized controlled trial of ECMO in ARDS was completed almost 30 years ago and did not show any benefit.²⁵⁴ It is worth pointing out that the mortality rate in that study was approximately 90% in both the ECMO and the control arm. Subsequently, a variant of ECMO dedicated to carbon dioxide removal (extracorporeal CO₂ removal, or ECCO₂R) was developed and showed promise in a case series when compared with a historical control group.²⁵⁵ This was followed by a randomized controlled trial using pressure-controlled *inverse-ratio ventilation* (IRV) and ECCO₂R in ARDS that failed to find any improvement in survival.²⁵⁶ This study illustrates the importance of using concurrent controls when assessing a novel therapy.

One of the complications of ECMO is bleeding; in an early randomized trial, patients randomized to the device were transfused an average of 1.7 L of blood *per day*. More recent data suggest that, because of many technological improvements, ECMO can be relatively safely performed by specialized centers. In 2009, a randomized controlled trial of conventional ventilation versus ECMO for acute respiratory failure was reported.²⁵⁷ The vast majority of patients in each arm had ARDS; referral to an ECMO center conferred a statistically significant survival benefit (relative risk of death at 6 months, 0.69; confidence interval, 0.05–0.97). However, patients in the conventional ventilation arm were cared for in multiple hospitals, did not have a standardized ventilation protocol, and experienced a mortality rate of 53%. In contrast, of the patients referred to the ECMO center, 75% actually received ECMO and a significantly higher percentage of patients in this group received lung-protective ventilation. Thus, it is unclear whether the improvement in survival was attributable to ECMO or to better care in a specialized hospital. A cohort study by the same authors examining ECMO for H1N1 influenza-induced ALI also suggested lower mortality from the treatment.²⁵⁸

There is also growing interest in using extracorporeal life support as an adjunctive therapy to maximize the benefit of lung-protective ventilation. Even at the recommended tidal

volume of 6 mg/kg, the lungs of patients with ARDS may be damaged by overdistention and VILI. Thus, the promise of ECMO is that tidal volumes of less than 6 mL/kg predicted body weight can be used and the resultant respiratory acidosis can be managed by extracorporeal removal of CO₂.²⁵⁹ Because of ongoing technological improvements that have reduced the requirement for anticoagulation and the invasiveness of the devices,^{260,261} this is likely to be a fertile area of research in coming years.

Summary

The modern approach to mechanical ventilation of patients with ARDS is based on two facts: first, that the diffuse lung injury of ARDS affects the lung heterogeneously; second, that mechanical ventilation itself can cause ALI. Thus, until new data emerge, the lung-protective ventilatory strategy adopted by the ARDS Network study¹⁰⁹ is the standard of care and is associated with both short-term and long-term improvement²⁶² in survival. Plateau pressure should be maintained at less than 30 cm H₂O, and tidal volume should be limited to 6 mL/kg predicted body weight as much as possible. The prone position should be seriously considered in patients with P/F less than approximately 150 mm Hg in centers with medical staff experienced in proning patients. Given the dangers inherent in this approach, proning must be performed with caution and following published protocols.

The optimal level of PEEP in ARDS remains unclear, although randomized trial data indicate that using higher PEEP levels than the original ARDS Network study is safe and may improve oxygenation. We favor high levels of PEEP in order to prevent atelectrauma, reduce FIO₂ and prevent hyperoxic lung injury in patients with greater hypoxemia (i.e., P/F < approximately 150 mm Hg), as long as the patient's hemodynamic status remains stable. We use the lowest possible FIO₂ that maintains oxygen saturation above 90%, and we empirically adopt a target FIO₂ of less than 0.6.

The use of neuromuscular blocking agents may also improve outcome by reducing ventilator-induced lung injury when used early in the clinical course of patients with relatively severe ARDS. Finally, despite the theoretical appeal of HFO ventilation, randomized controlled trials have shown that it does not improve survival over conventional lung-protective ventilation.

LONG-TERM OUTCOMES

Despite the profound derangement in oxygenation and respiratory system compliance that is characteristic of ARDS, it is remarkable that patients who survive often have near-normal pulmonary function tests 6 to 12 months later. Lung volumes and flows are generally slightly reduced or normal at 6 to 12 months, while the diffusion capacity may remain slightly reduced.^{263,264} Follow-up chest radiographs are usually normal, with a minority showing subtle abnormalities including pleural thickening or small cysts.²⁶⁴

Despite this impressive physiologic and radiologic recovery, patients who survive ARDS continue to have important functional limitations and a decreased health-related quality of life for at least 5 years after their illness.^{265,266} This reduction in quality of life seems attributable to ARDS or to

its management or complications because, in one parallel cohort study in which patients with ARDS were matched with patients with sepsis or trauma with an equivalent severity of illness, the ARDS survivors reported significant decrements in health-related quality of life, particularly as related to physical function and pulmonary symptoms.²⁶⁷ This reduced quality of life (in areas reflecting physical function) has been correlated with the presence of persistent abnormalities in pulmonary function tests.²⁶³ In other patients, functional capacity (as measured by a 6-minute walk test) was persistently reduced and was ascribed to persistent muscle weakness and wasting.²⁶⁴ In a multivariate analysis in that study, better functional capacity was associated with a lack of systemic corticosteroid administration, absence of illness acquired in the intensive care unit, and rapid resolution of lung injury and multiorgan dysfunction. Patients who ultimately survive an episode of ARDS do *not* appear, however, to have increased mortality compared with other, similarly ill intensive care unit survivors.²⁶⁸

Psychological problems, including depressive symptoms,²⁶⁹ have been described in survivors of ARDS. In a retrospective case-control study, survivors of ARDS were found to have significantly more signs and symptoms of posttraumatic stress disorder than patients who had undergone maxillofacial (and presumably elective) surgery; they also had more signs and symptoms of posttraumatic stress disorder than soldiers who had served for prolonged periods of time in Bosnia.²⁷⁰ Persistent cognitive impairment has also been observed in survivors of ARDS for as long as 1 year after hospital discharge.²⁷¹ Most patients in this study had impairments in at least one of memory, concentration, attention, or mental processing speed. Interestingly, these abnormalities were correlated to the degree and duration of hypoxemia of the patients.

ARDS is, by definition, a syndrome caused by a heterogeneous group of insults and is not a specific diagnosis. In particular, the clinician must search for an underlying cause to begin appropriate therapy. What has changed in the past 20 years, however, is our realization that in ARDS, regardless of the precipitant, inappropriate mechanical ventilation can do more harm than good. Amidst all the heterogeneity that is ARDS, it is perhaps ironic that this potential for iatrogenic injury may turn out to be one of the few common elements.

Key Points

- ARDS is a syndrome defined by acute hypoxemia, bilateral opacities on chest radiograph, and the absence of left atrial hypertension.
- The pathogenesis of ARDS is not clear, but increased permeability of the alveolar-capillary membrane due

to neutrophilic infiltration of the lungs is thought to be an important factor.

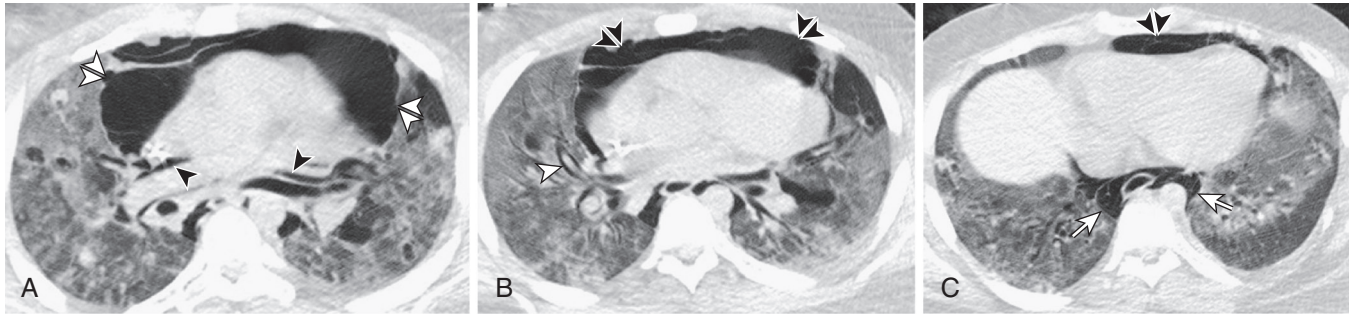
- ARDS is a syndrome, not a specific diagnosis; clinicians must, therefore, look for the cause in order to institute specific therapy.
- The mortality rate for ARDS has fallen since the 1980s and is now less than 40%.
- Mechanical ventilation is lifesaving but, when inappropriately applied, can induce or aggravate lung injury.
- Most deaths in patients with ARDS are from multiorgan failure rather than hypoxia per se.
- No pharmacologic therapies have been shown to improve survival in ARDS; thus, management consists of treating the underlying cause, lung-protective ventilation, conservative management of fluids, and excellent supportive care.
- Many survivors of ARDS suffer from a reduced quality of life and cognitive impairment.

Complete reference list available at ExpertConsult.

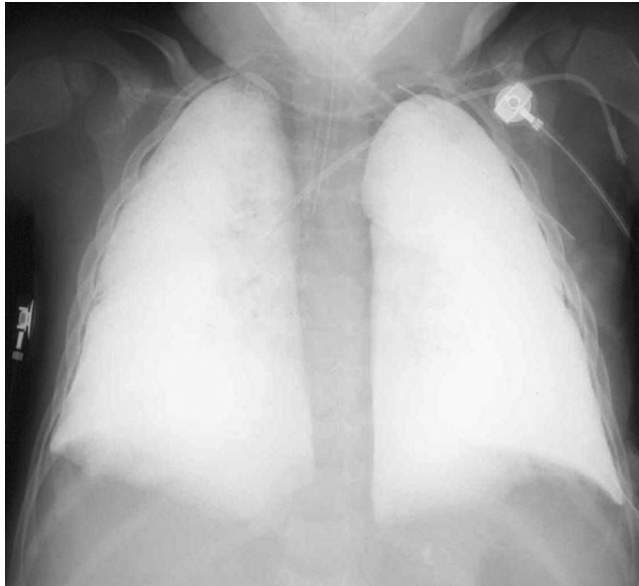
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eFIGURE IMAGE GALLERY



eFigure 100-1 Mechanical ventilation in hypoxemic respiratory failure, complicated by barotrauma. A–C, Axial chest CT scan in a patient with hypoxemic respiratory failure undergoing mechanical ventilation shows development of pneumomediastinum anteriorly (*double arrowheads*) and posteriorly (*arrows*, C) as well as interstitial emphysema (*single arrowheads*, A and B). (Courtesy Michael Gotway, MD.)



eFigure 100-2 Liquid ventilation: perflubron (perfluorooctyl bromide). Frontal chest radiograph in a patient with hypoxemic respiratory failure undergoing liquid ventilation shows diffuse, extremely highly attenuating material completely filling the lungs bilaterally. (Courtesy Michael Gotway, MD.)

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INTRODUCTION

Mechanical ventilation is the process of using a device (ventilator) to support, partially or totally the delivery of gas to the lungs. The desired effect of mechanical ventilation is to maintain adequate levels of PO_2 and PCO_2 in arterial blood while also unloading the inspiratory muscles. Although negative-pressure chambers or wraps might fulfill this definition, this discussion focuses on the use of devices that use positive airway pressures.

Positive-pressure mechanical ventilation is used widely. In the United States, about 1 to 3 million patients annually are estimated to receive mechanical ventilatory support outside the operating room.¹ Traditionally, this support has been provided in *intensive care unit* (ICU) settings, but there are clear trends toward expanding the venues to subacute facilities, long-term care facilities, and the home. As the number of elderly increases and as more aggressive surgical and immunosuppressive therapies are developed, the need for mechanical ventilation in all of these venues is likely to increase.¹ In addition, increasing concerns about widespread outbreaks of respiratory pandemics has led many government agencies to stockpile large numbers of mechanical ventilators.²

POSITIVE-PRESSURE MECHANICAL VENTILATOR DESIGN FEATURES**GAS DELIVERY SYSTEMS****Positive-Pressure Breath Controller**

Most modern ventilators utilize piston/bellows systems, turbines, or controllers of high-pressure sources to drive gas flow.^{3,4} Tidal breaths are generated by this gas flow and can either be controlled entirely by the ventilator or be interac-

tive with patient efforts. Pneumatic, electronic, or micro-processor systems provide for various breath types. In general, these can be classified by what initiates the breath (trigger variable), what regulates gas delivery during the breath (target or limit variable), and what terminates the breath (cycle variable).^{5,6}

Breath triggers are generated by either a change in pressure or flow initiated by patient effort (assisted/supported breath) or by a set time (controlled breath). During the breath, gas delivery is regulated to meet a target or limit variable, which is generally either a set flow or a set inspiratory pressure. The breath is then terminated by a cycle variable, which can either be a set volume, a set inspiratory time, or a set flow. A high-pressure cycle variable is usually also present to limit lung over distention. [Figure 101-1](#) uses this classification scheme to describe the five most common breath types available on the current generation of ventilators: *volume assist* (VA), *volume control* (VC), *pressure assist* (PA), *pressure control* (PC), and *pressure support* (PS).

Mode Controller/Feedback Systems

The availability and delivery logic of different breath types define the “mode” of mechanical ventilatory support.^{3,5,6} The mode controller is an electronic, pneumatic, or microprocessor-based system that is designed to provide the proper combination of breaths according to set algorithms and feedback data (conditional variables) ([Table 101-1](#)).

The simplest mode is *assist-control ventilation* (ACV), which can provide either flow-targeted volume-cycled breaths (*volume assist-control ventilation* [VACV]) or pressure-targeted time-cycled breaths (*pressure assist-control ventilation* [PACV]). A simple feedback system is employed with ACV that guarantees a set number of positive-pressure breaths. If the patient’s underlying respiratory rate exceeds this guarantee, all breaths are patient-triggered breaths (VA or PA breaths). If the patient’s respiratory rate is below this guarantee, the ventilator will “make up the difference” with mandatory (controlled) breaths (VC or PC breaths).

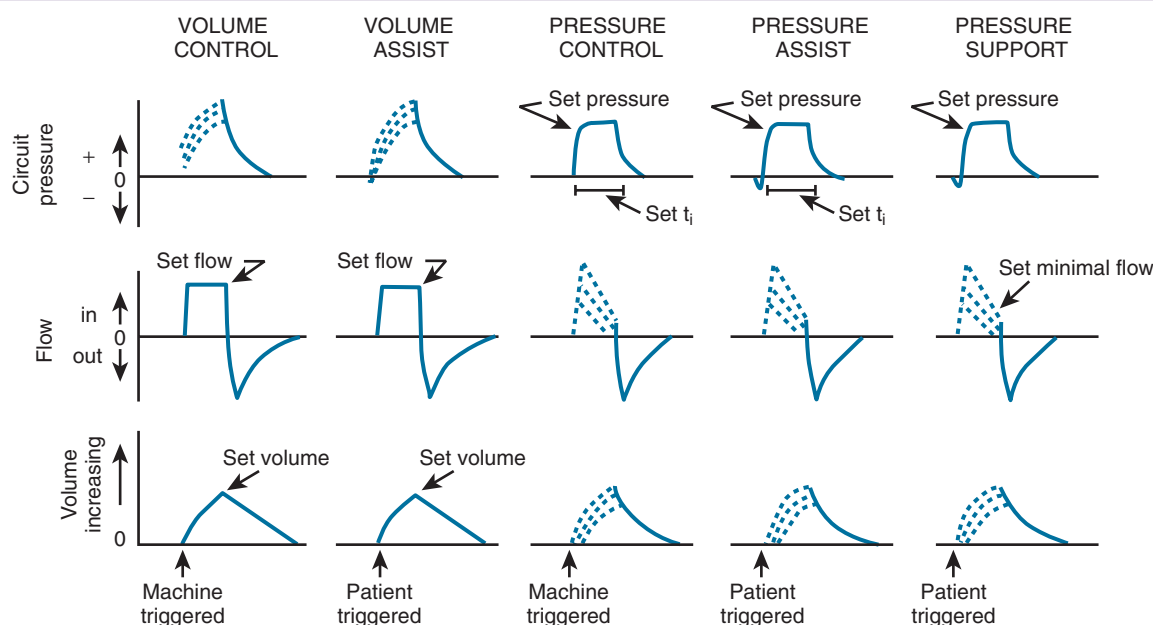


Figure 101-1 Circuit pressure, flow, and volume tracings over time depicting the five basic breaths available on most modern mechanical ventilators. Breaths are classified by the variables that determine the trigger (machine time or patient effort), target/limit (t_i , set flow or set pressure), and cycle (set volume, set time, or set flow). The solid lines represent set or independent responses, and the dashed lines represent dependent responses. In all of these breaths, pressure is usually a “backup” cycle variable designed to terminate gas delivery if circuit pressure rises above an alarm limit.

Table 101-1 Breath Types Available on Common Modes of Mechanical Ventilation*

Mode	BREATH TYPES AVAILABLE [†]					
	VC	VA	PC	PA	PS	Sp
Volume assist—control	X	X				
Pressure assist—control			X	X		
Volume SIMV	X	X			X	X
Pressure SIMV			X	X	X	X
Pressure support					X	

*In addition to the five “basic” breaths depicted in Figure 101-1, this table also includes spontaneous unassisted/unsupported breaths.

[†]VC, volume control; VA, volume assist; PC, pressure control; PA, pressure assist; PS, pressure support; Sp, spontaneous unassisted. SIMV, synchronized intermittent mandatory ventilation.

Another relatively simple mode is *synchronized intermittent mandatory ventilation* (SIMV), which can provide either flow-targeted volume-cycled breaths (volume SIMV) or pressure-targeted time-cycled breaths (pressure SIMV). Like ACV, SIMV guarantees a set minimal number of positive-pressure breaths. Unlike ACV, however, if the patient’s respiratory rate exceeds this guarantee, the ventilator will provide assisted breaths up to the set rate and then allow unassisted (simple SIMV mode) or flow-cycled pressure support breaths (SIMV + PS mode) thereafter. If the patient’s respiratory rate is below the set guarantee, the ventilator will again “make up the difference” with mandatory (controlled) breaths. Note that although PS breaths are often provided during SIMV, PS breaths can also be provided as a stand-alone mode without any guaranteed breaths (pressure support ventilation). Importantly, many modern systems also have algorithms to generate breaths when an

apnea is detected; this represents a safety feature for modes with either low or no set guaranteed rates in case patient respiratory efforts are suddenly reduced or absent.

In recent years, more sophisticated feedback systems have been developed for these basic modes and are now available on many modern devices. These include *pressure-regulated volume control* (PRVC), *volume support* (VS), and *adaptive support ventilation* (ASV).

PRVC (also known by proprietary names such as “VC+,” “Autoflow,” and others) is an assist-control PACV that uses tidal volume as a feedback control for continuously adjusting the pressure target.⁷ The clinician sets a tidal volume target, and the ventilator then automatically sets the inspiratory pressure within a clinician-set range to achieve this goal.

VS is also based on a feedback design using patient-triggered, pressure-targeted, flow-cycled PS breaths. If a patient’s respiratory drive exceeds the clinician-set guaranteed rate, some PRVC systems will provide additional patient-triggered, time-cycled PRVC breaths while others will provide patient-triggered flow-cycled VS breaths. It is important to note that, with both PRVC and VS breaths, an improvement in respiratory mechanics will result in a lower applied inspiratory pressure, whereas a worsening in respiratory mechanics will result in a higher applied inspiratory pressure. Similarly, increasing respiratory effort by the patient will result in a lower applied inspiratory pressure, whereas decreasing respiratory effort by the patient will result in a higher applied inspiratory pressure.

ASV is also an assist-control, pressure-targeted, time-cycled mode of ventilation PACV that utilizes respiratory system mechanics to set the tidal volume-frequency pattern.⁸ The clinician sets only a desired minute ventilation and patient weight (for estimating anatomic dead space). Using controlled breaths, ASV initially calculates

resistance and compliance, as well as the expiratory time constant (resistance \times compliance). The ASV algorithm then adjusts the frequency–tidal volume pattern to minimize ventilator work (integral of pressure over volume) and thus conceptually to minimize applied forces to the lungs. The breathing pattern is also modulated by incorporating the expiratory time constant to avoid air trapping. As respiratory mechanics change, the frequency–tidal volume pattern is automatically adjusted to maintain minimal ventilatory work. In contrast, if patient efforts are triggering breaths with ASV, it behaves much like VS.

SUBSYSTEMS OF MECHANICAL VENTILATORS

Effort (Demand) Sensors

Current ventilators have sensors that detect patient effort, thus allowing for a number of interactions between the patient and the ventilator.^{9–11} Examples include patient-triggered breaths in which the ventilator initiates flow in response to patient demand and pressure-targeted/limited breaths in which the ventilator adjusts flow in response to patient demand (see “[Patient-Ventilator Interactions](#)” later). These sensors are usually either pressure or flow transducers in the ventilatory circuitry and are characterized by their *sensitivity* (the circuit pressure or flow change needed to initiate a ventilator response) and their *responsiveness* (the time needed to provide this response).¹²

Gas Blenders

Blenders mix air and O₂ to produce a *fractional concentration of O₂ in inspired gas* (FiO₂) ranging from 0.21 to 1.0. On newer systems, blenders are also available for other gases such as heliox, *nitric oxide* (NO), and anesthetic agents.

Humidifiers

With the upper airway bypassed by tracheal intubation, sufficient heat and moisture must be added to the inspired gas mixtures to avoid mucosal desiccation. *Active* humidifiers utilize external water sources and electrical power to adjust blended gas mixtures to near body conditions (tracheal temperature of $> 35^\circ\text{C}$, water content of $> 40\text{ mg/L}$).¹³ Heated wire circuits help facilitate this by preventing condensation and “rainout” in the ventilator tubing. *Passive* humidifiers use simple heat/moisture exchange devices in the ventilator circuit that reutilize heat and moisture trapped from expired gas. These disposable units can usually supply adequate heat and moisture (i.e., $> 30^\circ$ to 33°C and > 28 to $32\text{ mg/L H}_2\text{O}$) for many patients, particularly those receiving mechanical ventilation for only short periods of time.¹³

Expiratory Pressure Generator

Positive end-expiratory pressure (PEEP), or positive airway pressure throughout expiration, can be generated to help maintain alveolar patency and improve *ventilation-perfusion* (\dot{V}/\dot{Q}) matching (see “[Physiologic Effects of Positive-Pressure Mechanical Ventilation](#)” later). PEEP is usually applied by regulating pressure in the expiratory valve of the ventilator system but can also be applied by providing a continuous flow of source gas during the expiratory phase. Some expiratory valves have measurable resistance even when fully

open; this may result in inadvertent PEEP.¹⁴ As discussed in more detail later, a positive alveolar pressure may be present at end expiration if the expiratory time is inadequate for the lung to return to its “resting volume” or if significant flow limitation exists. Such inadvertent PEEP is referred to as *intrinsic PEEP* (PEEP_i), or as “auto-PEEP,” “occult PEEP,” or “air trapping.”¹⁵

Gas Delivery Circuit

The circuit linking the ventilator to the patient usually consists of flexible tubing that often contains pressure or flow sensors, closed suctioning systems, and an exhalation valve. It is important to remember that, because this tubing has measurable compliance (2 to 4 mL/cm H₂O are representative values), high circuit pressures may induce significant amounts of delivered gas to distend the circuitry rather than to enter the patient’s lungs.

Patient–Ventilator Circuit Interface

Positive-pressure ventilation is usually delivered through a tube inserted into the patient’s airway (orotracheal or nasotracheal tube or tracheostomy). These tubes generally have air-filled balloons, which are inflated to provide a proper airway seal. An alternative to the tracheal tube is a mask system. Both full-face and nasal masks have been utilized with a variety of ventilatory support systems and modes.¹⁶ Leaks around masks, however, can be significant and thus ventilatory support modes using masks must be able to provide adequate volumes and proper inspiratory timing. To this end, special mask ventilators with pressure-targeted and either time-cycled or leak-compensated, flow-cycled capabilities have been developed.¹⁶

Aerosol Generators (see Chapter 11)

Therapeutic aerosols (e.g., bronchodilators, steroids, vasodilators, antibiotics) can be delivered through the ventilator circuitry¹⁷ either by in-line nebulizers or by special adapters designed for metered-dose inhalers. Lung deposition is generally less in an intubated than in a nonintubated patient because the endotracheal tube serves as a significant barrier to aerosol delivery. Higher dosing is thus advisable.

The location of the aerosol generator in the ventilator circuit can affect deposition. The optimal site appears to be in the inspiratory limb several centimeters proximal to the patient’s “wye” connector.¹⁷ This location allows either nebulized medications or a metered-dose actuation to “charge” the inspiratory limb of the circuit during exhalation. Aerosol particle velocity is also slowed and becomes the leading portion of the next inspiration, both of which facilitate delivery.

Monitors and Graphic Displays

Although electronic and microprocessor-based systems have considerable internal monitoring of electronic and pneumatic function, the three variables generally displayed for clinical use are circuit pressures, flows, and volumes.¹⁸ Pressure sensors in the esophagus to estimate pleural pressures are also available.¹⁹ Alarms can be utilized on all of these monitors.^{6,20} Importantly, trending capabilities for up to 72 hours or more are now available on many modern systems. Most modern positive-pressure ventilators also

have oxygen sensors in the circuitry to ensure that the desired FIO_2 is being delivered. In addition, some ventilators may also have analyzers for measuring exhaled carbon dioxide and inhaled therapeutic gases such as NO or heliox.

PHYSIOLOGIC EFFECTS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

VENTILATION AND RESPIRATORY SYSTEM MECHANICS (see Chapter 5)

Alveolar Ventilation and the Equation of Motion

Alveolar ventilation is the term for the delivery of fresh gas to the gas exchange regions of the lungs. Mathematically, this is expressed as:

$$\dot{V}_A = f \times (V_T - V_D)$$

where \dot{V}_A = alveolar ventilation, f = breathing frequency, V_T = tidal volume, and V_D = wasted ventilation or dead space. \dot{V}_A needs to be adequate to eliminate the carbon dioxide production (\dot{V}_{CO_2}) while maintaining a reasonable arterial PCO_2 (and pH) according to the following relationship:

$$\text{PaCO}_2 = (\dot{V}_{\text{CO}_2} / \dot{V}_A) \times 800$$

The lungs are inflated by mechanical ventilation when pressure and flow are applied at the airway opening. These applied forces overcome respiratory system compliance (both lung and chest wall components), airway resistance, and respiratory system inertance and lung tissue resistance to effect gas flow.^{21,22} For simplicity, because inertance and tissue resistance are relatively small, they can be ignored yielding the simplified equation of motion:

$$\text{Driving pressure} = (\text{flow} \times \text{resistance}) + (\text{volume} / \text{system compliance})$$

In the mechanically ventilated patient, this relationship is expressed as:

$$\Delta P_{\text{cir}} + \Delta P_{\text{mus}} = (\dot{V} \times R) + (V_T / \text{CRS})$$

where ΔP_{cir} is the change in ventilator circuit pressure above baseline (peak pressure minus set end-expiratory pressure: $P_{\text{peak}} - \text{PEEP}$); ΔP_{mus} is patient inspiratory muscle pressure generation (if present); \dot{V} is the flow into the patient's lungs; R is the resistance of the circuit, artificial airway, and natural airways combined; V_T is the tidal volume; and CRS is the respiratory system compliance. If there is PEEP_i , it must be overcome by muscle and circuit pressure before flow and volume can be delivered and thus PEEP_i will add to the driving pressure requirement.

During an inspiratory hold at end-inspiration in a patient who is not making respiratory efforts (i.e., no-flow condition: $\dot{V} = 0$, $P_{\text{mus}} = 0$), the ventilator circuit pressure “plateaus” at a pressure commonly referred to as the *plateau pressure* (P_{plat}). In this way, the components of P_{cir} can be determined. Specifically, the difference in P_{cir} during flow and during no-flow (the “peak to plateau difference”) allows for a calculation of total inspiratory resistance:

$$R = (P_{\text{peak}} - P_{\text{plat}}) / \dot{V}$$

Also, when $\dot{V} = 0$ at end-inspiration, $P_{\text{plat}} - \text{PEEP}$ allows calculation of the static respiratory system compliance:

$$\text{CRS} = V_T / (P_{\text{plat}} - \text{PEEP})$$

Separating chest wall and lung compliance (CCW and CL , respectively) requires measurement of *esophageal pressure* (P_{es}) to estimate pleural pressure.^{22a} With this measurement, the inspiratory change in P_{es} (ΔP_{es}) can be used in the following calculations:

$$\text{CCW} = V_T / \Delta P_{\text{es}}$$

$$\text{CL} = V_T / (P_{\text{plat}} - \text{PEEP} - \Delta P_{\text{es}})$$

In clinical practice, because CCW is usually quite high and ΔP_{es} is thus quite low, P_{plat} alone is often taken as an approximation of end inspiratory lung-distending pressure. However, there are many situations in which there is a stiff chest wall and this crude approximation is not valid (e.g., obesity, *acute respiratory distress syndrome* [ARDS], ascites, surgical dressings). Under these situations, the impact of a stiff chest wall must be considered when using these measurements to assess lung stretch.^{19,23,24}

Flow-Targeted Versus Pressure-Targeted Breaths

There are two basic approaches to delivering positive-pressure breaths: flow targeting and pressure targeting (see Fig. 101-1).^{3,5} With flow targeting (breaths 1 and 2 in Fig. 101-1), the clinician sets the inspiratory flow; circuit pressure is then the dependent variable. With pressure targeting (breaths 3 through 5 in Fig. 101-1), the clinician sets an inspiratory pressure target (with either time or flow as the cycling criterion); flow and volume are then the dependent variables (i.e., varying with the lung mechanics and patient effort). With a flow-targeted breath, changes in compliance, resistance, or patient effort will change P_{cir} (but not flow); in contrast, with a pressure-targeted breath, similar changes in compliance, resistance, or effort will cause a change of tidal volume (but not P_{cir}) (see dashed lines in Fig. 101-1).

Each strategy has advantages.²⁵ For flow-targeted breaths, a minimal tidal volume is guaranteed. For pressure-targeted breaths, the rapid initial flow and subsequent adjustable flow of pressure targeting may enhance gas mixing and patient synchrony (see discussions “[Distribution of Ventilation](#)” and “[Patient-Ventilator Interactions](#)” later).

Pressure-targeted breaths can also be modified with a volume feedback feature described earlier for PRVC and VS breaths to combine the enhanced gas mixing and patient-ventilator synchrony effects of a pressure-targeted breath with a certain volume guarantee. However, it is important to realize that providing a volume guarantee negates the pressure-limit feature set by the clinician because, with PRVC/VS, worsening respiratory system mechanics will drive applied pressures up. Another potential problem with PRVC/VS is that it may not adequately unload the patient if patient effort inappropriately increases due to pain or anxiety.²⁶

PEEP_i and the Ventilatory Pattern

PEEP_i is the positive alveolar end-expiratory pressure that arises because of inadequate expiration, caused by either inadequate expiratory time or airway collapse during expiration (or both). PEEP_i increases with increased minute

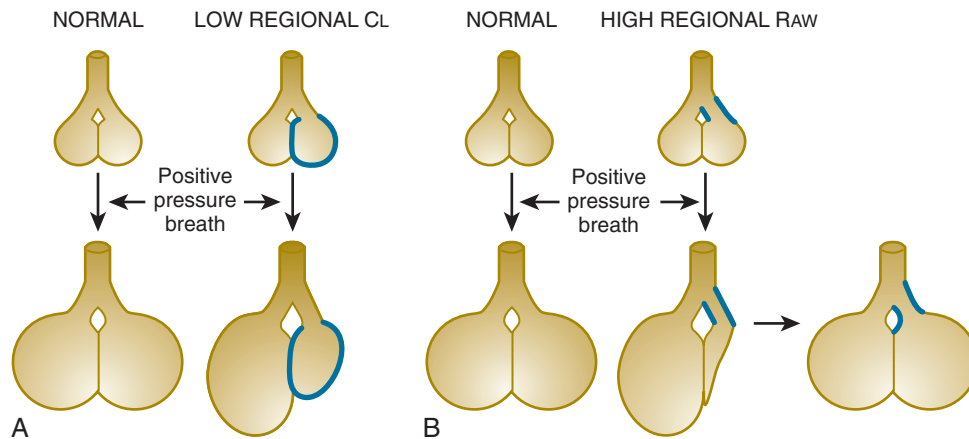


Figure 101-2 The distribution of ventilation in lung models with heterogeneous mechanical properties. Models of the lung are shown as two units with homogeneous mechanical properties (normal): (A) with abnormal compliance distribution (low regional lung compliance [CL]) and (B) abnormal resistance distribution (high regional airway resistance [RAW]). Note that in situations with heterogeneous lung mechanics, positive-pressure breaths are preferentially distributed to “healthier” regions of the lung and can produce regional overdistention—even when a normal-sized tidal volume is delivered. Note that in the obstructed example (high regional RAW), the overdistention may be transitory as gas moves from the low-resistance to the high-resistance unit over time (*pendelluft*). (Redrawn from MacIntyre NR: Mechanical ventilatory support. In Dantzker D, MacIntyre NR, Bakow E, editors: *Comprehensive respiratory care*. Philadelphia, 1995, WB Saunders, p 453.)

ventilation, decreased expiratory time fraction, and the increased respiratory system expiratory time constant (the product of resistance and compliance).²⁷

The development of PEEP_i will have different effects on flow-targeted compared with pressure-targeted ventilation. In flow-targeted ventilation, the constant delivered flow and volume (and thus ΔP_{cir}) in the setting of a rising PEEP_i will increase both the P_{peak} and the P_{plat} . In contrast, in pressure-targeted ventilation, the set P_{cir} limit coupled with a rising PEEP_i level will decrease ΔP_{cir} and thus the delivered tidal volume (and minute ventilation). Importantly, this may help limit the build-up of PEEP_i.

In the patient without respiratory effort, PEEP_i can be recognized in two ways. First, when PEEP_i is produced by an inadequate expiratory time, analysis of the flow graphic will show that expiratory flow has not returned to zero before the next breath is given. Second, PEEP_i in alveoli with patent airways can be quantified during an expiratory hold maneuver that permits equilibration of the PEEP_i with P_{cir} .²⁷

In the patient with active respiratory effort, PEEP_i can be assumed to be present if the expiratory flow has not reached zero before the next breath begins. However, the expiratory hold maneuver cannot be interpreted in an actively breathing patient. As noted in more detail later, in an actively breathing patient, PEEP_i can function as an inspiratory threshold load. This is best quantified by using P_{es} to estimate pleural pressures. With this technique, the change in P_{es} before a change in P_{cir} is a reflection of the threshold load imposed by PEEP_i (see “[Patient-Ventilator Interactions](#)” later).

Distribution of Ventilation

A positive-pressure tidal breath must be distributed among the millions of alveolar units in the lung.^{28,29} Factors affecting this distribution include patient-related factors: regional resistances, compliances, and functional residual capacities. Breaths will tend to distribute more to units with high

compliance and low resistance and away from obstructed or stiff units (Fig. 101-2A, Low Regional CL). This creates the potential for regional overdistention of healthier lung units, even in the face of “normal”-sized tidal volumes (see “[Ventilator-Induced Lung Injury](#)” later).

The flow pattern set on the ventilator may also affect ventilation distribution. For example, when there are marked inhomogeneities in airway resistance, slow and constant flows will tend to distribute gas more evenly (although consequent shorter expiratory times may worsen air trapping).²⁸ In addition, inspiratory pauses can also allow *pendelluft* action to fill slowly filling alveoli (Fig. 101-2B, High Regional RAW). In contrast, when there is parenchymal lung injury with minimal inhomogeneities in airway resistance, initially rapid flows with subsequent deceleration (typically seen in pressure-targeted breaths) may distribute gas more evenly and will pressurize lung units rapidly, producing a higher mean inspiratory alveolar pressure for a given breath volume.³⁰

It should be noted that more uniform ventilation distribution does not necessarily mean better \dot{V}/\dot{Q} matching (i.e., more homogeneous ventilation distribution may actually worsen \dot{V}/\dot{Q} matching in a lung with inhomogeneous perfusion). Because of all these considerations, predicting which flow pattern will optimize ventilation-perfusion matching is difficult and often requires trial and error.

ALVEOLAR RECRUITMENT AND GAS EXCHANGE

Because of alveolar flooding, inflammatory exudates, and collapse, parenchymal lung injury leads to \dot{V}/\dot{Q} mismatching and shunts.³¹ In many (but not all) of these disease processes, substantial numbers of collapsed alveoli can be recruited during a positive-pressure ventilatory cycle.³²⁻³⁵ Additional recruitment can sometimes be provided with the use of formal recruitment maneuvers or prolongation of inspiratory time.^{36,37} The application of PEEP is designed to prevent derecruitment during exhalation.

Recruitment Maneuvers

Recruitment maneuvers (RMs) can be performed using sustained inflations (e.g., 30 to 40 cm H₂O) for up to 30 to 120 seconds, by transient elevations of the PEEP-tidal volume settings, and by single or multiple “sighs” that take the lung briefly to near total lung capacity.³⁶ To avoid patient inspiratory or expiratory efforts, additional sedation or even neuromuscular blockade may be used. Importantly, RMs can have adverse hemodynamic consequences; close monitoring of the patient is mandatory during RMs. RMs provide initial alveolar recruitment only—maintenance of recruitment requires setting PEEP appropriately to prevent subsequent derecruitment.³⁶

Inspiratory Time Prolongations

A positive-pressure breath produces a flow magnitude and a flow profile that, as noted previously, can affect ventilation distribution (and thus \dot{V}/\dot{Q}). Prolonging inspiratory time, generally by adding a pause, often in conjunction with a rapid decelerating flow (i.e., pressure-targeted breath), has several physiologic effects. First, the longer inflation period may recruit more alveoli.^{38,39} Second, increased gas mixing time may improve \dot{V}/\dot{Q} matching in parenchymal lung injury (*pendelufft*).³⁸ Third, the development of PEEPi from consequently shorter expiratory times can have effects similar to those of applied PEEP (see earlier).³⁹ It should be noted, however, that the distribution of PEEPi, which is most pronounced in lung units with long expiratory time constants, may be different from that of applied PEEP and thus the effects on \dot{V}/\dot{Q} may also be different with intrinsic compared with applied PEEP. Fourth, because these long inspiratory times significantly increase total intrathoracic pressures, cardiac output may be reduced (see “[Positive-Pressure Ventilation and Cardiac Function](#)” later). And finally, inspiratory-to-expiratory ratios that exceed 1:1 (so-called inverse-ratio ventilation) are uncomfortable, and patient sedation/paralysis is often required unless a relief mechanism allows spontaneous breathing during the inflation period (see “[Airway Pressure Release Ventilation](#)” later).

Positive End-Expiratory Pressure

PEEP is defined as an elevated airway pressure at the end of expiration.³² As noted earlier, PEEP can be produced by either expiratory circuit valves (applied PEEP) or inadequate expiratory times in lung units with long expiratory time constants (PEEPi).^{21,22,38} Note that expiratory muscle contraction can also raise intrathoracic pressures at end-expiration, but this does not have the same effects on the lungs because transpulmonary pressure is not increased.

PEEP helps to recruit or maintain alveolar units open, providing several potential benefits. First, recruited alveoli improve \dot{V}/\dot{Q} matching and gas exchange throughout the ventilatory cycle.³² Second, as discussed in more detail later, patent alveoli throughout the ventilatory cycle are not exposed to the risk of injury from the shear stress of repeated opening and closing.^{40,41} Third, open alveoli with intact surfactant monolayers improve lung compliance.⁴² This is the rationale behind applying PEEP after an RM: recruited alveoli are on the deflation limb of the pressure-volume relationship and thus the pressure required to maintain

recruitment is lower than that required for initial recruitment.

PEEP, however, can also be detrimental. Because the tidal breath is delivered on top of the baseline PEEP, end-inspiratory pressures are usually raised by the application of PEEP (although this increase may be less than the actual added PEEP because of improved compliance). This increase must be considered if the lung is at risk for regional overdistention (see “[Ventilator-Induced Lung Injury](#)” later). Moreover, since parenchymal lung injury is often quite heterogeneous, appropriate PEEP in one region may be suboptimal in another and excessive in yet another.^{35,43,44} Optimizing PEEP is thus a balance between recruiting the recruitable alveoli in diseased regions without overdistending already recruited alveoli in healthier regions. Another potential detrimental effect of PEEP is that it raises mean intrathoracic pressure, thereby compromising cardiac filling in susceptible patients (see “[Positive-Pressure Ventilation and Cardiac Function](#)” section later).

MECHANICAL LOADS

Mechanical loads describe the physical requirements of ventilation with a single value, either the *pressure-time product* (PTP—the integral of pressure over time) or *work* (W—the integral of pressure over volume).^{21,22} Because mechanical loads correlate with inspiratory muscle oxygen demands,^{45-47a} the concept of load is useful in considering inspiratory muscle energy requirements during spontaneous or interactive ventilatory support. Moreover, as described in more detail later, load referenced to muscle strength and/or endurance properties (e.g., PTP or W divided by muscle pressure-generating capability) can be used to set levels of partial ventilatory support or predict spontaneous breathing capabilities.⁴⁷

Compliance, resistance, flow, and volume all contribute to the magnitude of the load per breath. During spontaneous breaths, P_{cir} is zero and integrating P_{es} over time or volume (referenced to the passive inflation pressure) describes the load borne by the inspiratory muscles to inflate the lungs. During a controlled breath, integrating P_{cir} over time or volume describes the load borne by the ventilator to inflate the entire respiratory system (lungs and chest wall) and integrating P_{es} over time or volume describes the loads imposed by the chest wall only. During interactive breaths the load is shared between patient and ventilator.⁴⁸

Under heavy loading conditions (e.g., the patient with abnormal respiratory system mechanics and thus high pressure requirements), the duration of pressure (i.e., the PTP) correlates better with muscle energetics and fatigue potential than does the volume moved with pressure (i.e., work).^{45,46} Indeed, during ventilation requiring high pressures, multiplying PTP by the inspiratory time fraction and referencing this to the maximal pressure that the inspiratory muscles can generate results in the *pressure-time index* (PTI). Muscle fatigue can be expected if the PTI value exceeds 0.15.^{48,49} The concern with high pressure loads in patients receiving partial ventilatory support is one of the rationales for providing ventilator pressure assistance with every spontaneous effort (i.e., pressure-assisted or supported breaths), as opposed to supporting only some breaths

as in intermittent mandatory ventilation without pressure support (see “[Patient-Ventilator Interactions](#)” later).⁵⁰

Inspiratory muscle overload is one of the major determinants of continuing ventilator dependency and can result either from excessive mechanical loads or from inspiratory muscle dysfunction. Excessive mechanical loads can result from disease or from inappropriate ventilatory assistance (see “[Patient-Ventilator Interactions](#)” later). Clinically, inspiratory muscle overload is manifested by rapid, shallow breathing patterns, paradoxical abdominal motion, and patient distress. Inspiratory muscle dysfunction can be a result of the systemic inflammatory response syndrome, metabolic disturbances, drugs (e.g., steroids, previous use of neuromuscular blockers), malnutrition, or malpositioning (i.e., diaphragm flattening from lung overinflation).⁵¹ Finally, insufficient loading may also affect inspiratory muscles. Specifically, controlled mechanical ventilation without any patient effort, perhaps for as little as 24 hours, may produce muscle changes similar to disuse atrophy—a condition described as *ventilator-induced diaphragmatic dysfunction* (VIDD).⁵²⁻⁵⁴

PATIENT-VENTILATOR INTERACTIONS

Mechanical ventilation modes that permit spontaneous ventilatory activity are termed “interactive” modes. These interactions can range from simple triggering of mechanical breaths to more complex processes affecting delivered flow patterns and breath timing. Interactive modes allow for muscle “exercise,” which, when performed at nonfatiguing or physiologic levels, may prevent VIDD and facilitate fatigue recovery.^{11,52-54} In addition, permitting spontaneous patient ventilatory activity with “comfortable” interactive modes may reduce the need for the sedation and/or neuromuscular blockers that may otherwise be used to prevent patients from “fighting the ventilator.”^{11,55} Interactions take place during all three phases of breath delivery: breath triggering, flow delivery, and breath cycling and are described in detail later in “Patient-Ventilator Dys-synchrony.”

POSITIVE-PRESSURE VENTILATION AND CARDIAC FUNCTION

In addition to affecting ventilation and ventilation distribution, positive-pressure ventilation can also affect cardiovascular function.⁵⁶⁻⁵⁸ In general, as mean intrathoracic pressure increases, right ventricular filling decreases and cardiac output/pulmonary perfusion consequently decreases. This is the rationale for using volume repletion to maintain cardiac output in the setting of high intrathoracic pressure. Of note, the effect of reduced cardiac filling on cardiac output may be partially counteracted by improvement in left ventricular function due to elevated intrathoracic pressure, which can reduce left ventricular afterload.⁵⁹ Importantly, in patients with left heart failure, the reduced cardiac filling and reduced left ventricular afterload effects of elevated intrathoracic pressure may improve cardiac function to the point that the removal of intrathoracic pressure may worsen cardiac function and thereby produce weaning failure.⁶⁰

Intrathoracic pressures can also influence distribution of perfusion. The relationship of alveolar pressures to perfu-

sion pressures in the three-zone West lung model helps explain this.⁶¹ Specifically, the dependent lung is generally in a zone 3 (capillary distention) state. As intra-alveolar pressures rise, however, zone 2 and zone 1 (capillary collapse/dead space) regions can appear, creating high \dot{V}/\dot{Q} units. Indeed, increases in dead space can be a consequence of ventilatory strategies employing high ventilatory pressures, as well as with those producing PEEPi.

Positive-pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate ventilatory support can lead to stress-related catecholamine release with subsequent increases in myocardial oxygen demands and risk of dysrhythmias.⁶⁰ In addition, coronary blood vessel oxygen delivery can be compromised by inadequate gas exchange from the lung injury coupled with low mixed venous PO_2 due to high oxygen consumption demands by the inspiratory muscles.

COMPLICATIONS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

VENTILATOR-INDUCED LUNG INJURY

The lung can be injured when it is stretched excessively. The most obvious injury is barotrauma: alveolar rupture presenting as extra-alveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleural space (pneumothorax), or vasculature (air emboli).⁶² The risk for extra-alveolar air increases as a function of the magnitude and duration of alveolar overdistention. Thus interactions of respiratory system mechanics and mechanical ventilation strategies (high regional VT and PEEP—both applied and intrinsic) that produce regions of excessive alveolar stretch create alveolar units at risk for rupture.

Even without producing extra-alveolar air and rupture, mechanical ventilation can induce *ventilator-induced lung injury* (VILI).^{62a,62b} In experimental animals, acute lung injury can be produced by mechanical ventilation strategies that stretch the lungs beyond the normal maximum volume (at transpulmonary distending pressures of 30 to 35 cm H₂O).⁶³⁻⁶⁵ In engineering parlance, this is termed mechanical “stress.”⁶⁶ A number of clinical trials clearly indicate that ventilator strategies exposing the injured human lung to transpulmonary pressures in excess of 30 to 35 cm H₂O are associated with lung injury.⁶⁷⁻⁷⁰ Importantly, VILI may be more than simply a consequence of excessive end-inspiratory stretch. Even in the setting of transpulmonary pressures less than 30 cm H₂O, excessive tidal stretch from repetitive cycling of the lung with tidal volumes in excess of 8 to 10 mL/kg *ideal body weight* (IBW) may contribute to VILI.^{67,68} Interestingly, this VILI risk may be better quantified by referencing the tidal volume to the resting lung volume and can be termed mechanical “strain.”⁶⁶ Other ventilatory pattern factors, such as the frequency of stretch⁷¹ or the acceleration/velocity of stretch,⁷² may also be involved in the development of VILI. VILI appears to be

potentiated by a shear stress phenomenon that takes place when injured alveoli repetitively open and collapse during the ventilatory cycle (i.e., cyclical atelectasis).^{40,73,74} Vascular pressure elevations may also contribute to VILI.⁷⁵

VILI likely develops regionally when low-resistance/high-compliance units receive a disproportionately high regional tidal volume in the setting of high alveolar distending pressures (see Fig. 101-2). This can be appreciated using computed tomography under circumstances when pressures required for recruitment of diseased atelectatic regions simultaneously produce overdistention in already open, less-diseased regions (Fig. 101-3).⁷⁶ Regional protection of these healthier lung units is the rationale for using “lung-protective” ventilator strategies that accept less than normal values for pH and arterial PCO_2 in exchange for lower (and safer) distending pressures (see “Applying Mechanical Ventilatory Support” later).⁷⁷ Interestingly, data suggest that a permissive respiratory acidosis might also have therapeutic effects on alveolar injury from VILI, although the clinical applicability of this observation is not clear.⁷⁸

VILI is manifest pathologically as diffuse alveolar damage.^{40,63,64,79} Moreover, VILI is associated with cytokine release^{79,80} and bacterial translocation,⁸¹ which are implicated in the systemic inflammatory response with multorgan dysfunction that results in VILI-associated mortality.

OXYGEN TOXICITY

Very high inspired oxygen concentrations can cause oxidant injury in airways and lung parenchyma.⁸² Much of the data supporting this concept, however, has come from animals that often have quite different tolerances to oxygen than humans. It is thus not clear what the “safe” oxygen concentration or duration of exposure is in sick humans. Most consensus groups have argued that FiO_2 values less than 0.4 are safe for prolonged periods of time and that FiO_2 values of greater than 0.70 should be avoided if possible. Interestingly, several observational trials suggest that even with a “safe” FiO_2 less than 0.4, maintaining an arterial PO_2 greater than 120 to 130 mm Hg may produce systemic oxygen toxicity over time.^{83,84}

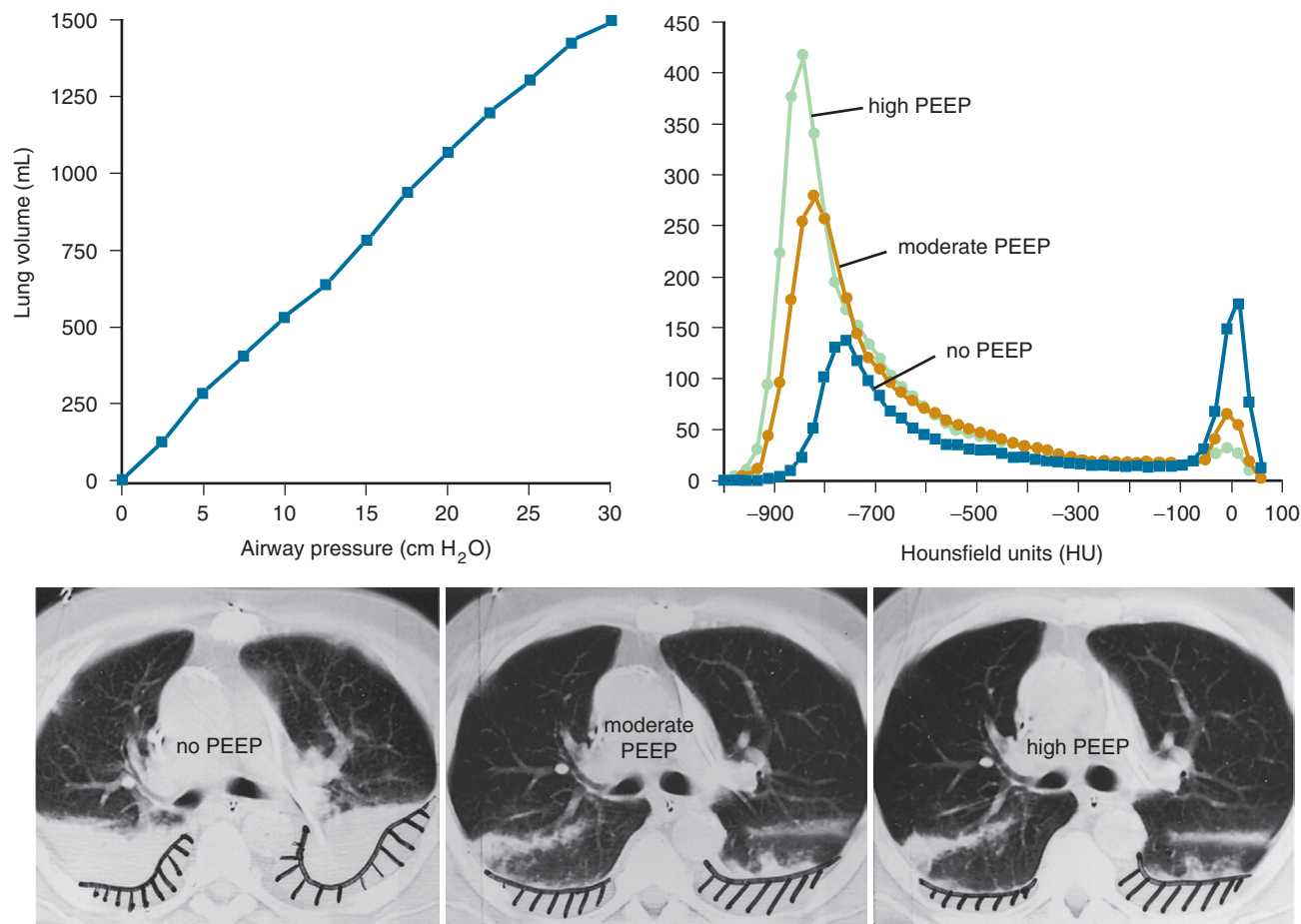


Figure 101-3 Effects of positive airway pressure in a lung with heterogeneous injury. The upper left panel shows the almost linear pressure-volume relationships as positive airway pressure is applied to the lungs. At the bottom are three representative CT lung slices at low, midrange, and maximal airway pressure. In the lung at low airway pressure (no PEEP, lower left), note the substantial atelectasis in the dependent lung regions, which is progressively reduced as airway pressure is increased (moderate PEEP and high PEEP, in the right two images). The upper right panel depicts the distribution of Hounsfield units (HUs) in each of these three CT slices, at low pressure (dark blue), at midrange airway pressure (brown), and at the highest airway pressure (light green). Note that, although increasing pressure progressively reduces the number of atelectatic units (those with CT numbers near zero), these same pressures simultaneously increase the number of overdistended lung units elsewhere in the lungs (those with CT numbers < -900 HU). (From Vieira SR, Puybasset L, Lu Q, et al: A scanographic assessment of pulmonary morphology in acute lung injury. *Am J Resp Crit Care Med* 159:1612–1623, 1999.)

PATIENT-VENTILATOR INTERFACE COMPLICATIONS

The patient must be connected to the ventilator via ventilator circuitry and an artificial airway. Problems with this interface can lead to complications. The most obvious issue is disconnection from the ventilator (including artificial airway dislodgment). Disconnections have been reported in up to 8% to 13% of ventilated patients⁸⁵ and, if left uncorrected, can be fatal. Because circuit pressure and flow can be maintained despite the disconnection of the ventilator from the patient (e.g., if the airway is in the esophagus or if the disconnected circuit remains partially occluded), it is critical that carefully set, redundant (i.e., pressure, flow, and even exhaled carbon dioxide) alarms are present.⁶ Other complications of the patient-ventilator interface include obstructions from secretions, circuit leaks, airway injury from inadequate heat/humidity, tracheal injury from the artificial airway, and loss of delivered tidal volume in a compliant circuit.

PATIENT-VENTILATOR DYS-SYNCHRONY

Patient-ventilator dys-synchrony describes the delivery of a breath from a mechanical ventilator that is not matched to patient effort. As noted earlier, this can take place during the triggering process, flow delivery, and breath cycling.

Ventilator Breath Triggering

Ventilators may sense a spontaneous effort by either an airway pressure drop or an airway flow change.^{9,10,86} Even with modern sensors, there is unavoidable dys-synchrony in the triggering process. First, a certain level of sensor insensitivity must be incorporated to avoid artifacts triggering the ventilator (i.e., “auto-triggering” due to cardiogenic oscillations). Second, even when the patient effort has been sensed, there is an inherent delay (up to 100 msec or more) in activating a valving system to open and achieve target airway flow (system responsiveness). Both of these factors can result in significant “isometric-like” pressure loads on the inspiratory muscles during the triggering process. In addition, in the setting of air trapping and PEEP_i, the elevated end-expiratory alveolar pressure acts as a triggering threshold load on the inspiratory muscles. Under these conditions, judicious use of applied PEEP can equilibrate expiratory pressure throughout the lungs and the ventilator circuit to reduce this triggering load.^{87,88}

Excessive triggering can also result from auto-triggering as noted earlier or from the triggering of a second breath when the mechanical breath cycles before the termination of patient effort (“breath stacking”). A recently described phenomenon, “entrainment,” can also result in a double breath.⁸⁹ Entrainment can be seen during a machine-triggered breath when the delivered gas flow elicits an effort. Sometimes this simply extends the breath, but if the effort persists beyond machine breath termination, a second breath can be triggered.

Ventilator-Delivered Flow Pattern

During an interactive breath, inspiratory muscles are contracting^{90,91} and the ventilator flow delivery should be adequate to provide proper muscle unloading. This does not

mean that muscle loads are eliminated. Instead, it means that a delivered flow pattern is associated with a muscle loading pattern that resembles normal, comfortable breathing¹¹ (“synchronous” flow delivery).

In general, flow synchrony is best assessed by clinical assessment and analyzing the graphic representation of circuit pressure over time.^{11,92} Flow synchrony is manifest clinically as a relaxed patient who does not appear dyspneic. In contrast, flow dys-synchrony is often manifest as tachypnea, air hunger (dyspnea), and the appearance of “flow starvation.”¹¹ With synchronous flow delivery, the circuit pressure graph should maintain either a steady baseline profile (a CPAP breath) or a convex upward shape (assisted/supported breath) indicating that flow is proportional to demand. Dys-synchrony (and imposed loading) is said to exist when the circuit pressure graph is literally “sucked downward” by effort in excess of flow delivery, often below the baseline^{11,93} (Fig. 101-4).

Breath Cycling

Cycling dys-synchrony can arise in one of two ways. First, if the mechanical breath lasts beyond the duration of patient effort, an inadequate expiratory time may develop (along with air trapping) and/or patient expiratory efforts may be required to terminate the breath.¹¹ This can be a particular concern when using PS breaths in obstructive airway disease—the relatively steady inspiratory flow with PS in these patients coupled with the PS flow-cycling algorithm may significantly delay breath termination.⁹⁴ Second, if the mechanical breath terminates before the patient effort is finished, the patient may be left demanding additional flow without any being delivered. Significant imposed

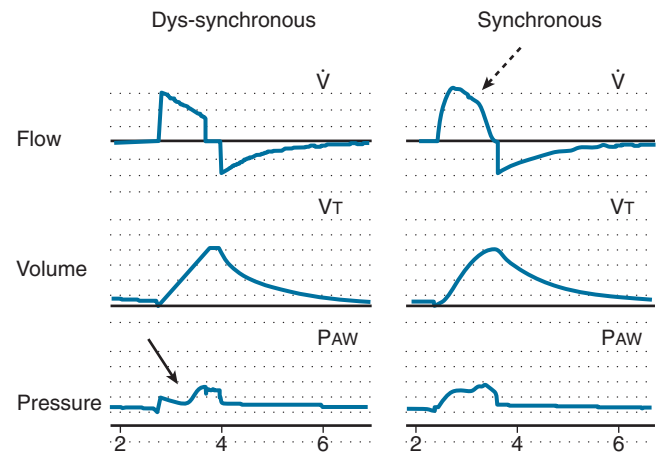


Figure 101-4 Flow and pressure pattern differences during dys-synchronous and synchronous breaths in a patient with a vigorous inspiratory effort. Depicted are flow (upper panel), volume (middle panel), and pressure (lower panel) for a dys-synchronous flow-targeted breath (left) and a more synchronous pressure-targeted breath (right) with matched mean flow, inspiratory time, and tidal volume. Note that, during the flow-targeted breaths (left), the fixed flow does not respond to the vigorous inspiratory effort, resulting in the circuit pressure being “sucked” downward (solid arrow). In contrast, with the pressure-targeted breath, flow adjusts and increases to meet the inspiratory effort better (dashed arrow). (Redrawn from Yang LY, Huang YC, MacIntyre NR: Patient-ventilator synchrony during pressure-targeted versus flow-targeted small tidal volume assisted ventilation. *J Crit Care* 22:252–257, 2007.)

loading and, as noted earlier, double breath triggering may result.¹¹

Clinical Implications

Determining the prevalence of patient-ventilatory dys-synchrony is difficult because studies examining this question have used heterogeneous patient populations and different definitions of dys-synchrony, methods of detection, duration and timing of observation, and ventilatory modes.^{11,95} Triggering dys-synchronies have been the most well studied. Depending on patient population, ventilator settings, and measurement techniques, triggering dys-synchronies have been reported in 26% to 82% of mechanically ventilated patients. Not surprisingly, trigger dys-synchronies were more common in patients with COPD and those at risk for intrinsic PEEP development.^{11,95} Double triggering is the other commonly reported triggering dys-synchrony but is generally described in less than 10% of patients in these various studies.^{11,95}

The incidence of other forms of dys-synchrony (flow dys-synchrony and cycle dys-synchrony) has not been as well characterized. However, a retrospective evaluation of the National Institutes of Health ARDS Network small tidal volume study reported cycling dys-synchronies associated with double triggering in 9.7% of all breaths analyzed.⁹⁶ Indeed, it is likely that patient-ventilatory dys-synchrony is ubiquitous if any patient is observed long enough during assisted/supported mechanical ventilation, especially if more sophisticated monitors (e.g., Pes or diaphragmatic electromyograms) are employed to detect patient effort.

Although there is no doubt that many dys-synchronies are subtle and of little clinical relevance, significant dys-synchronies may be missed, thus overloading respiratory muscles and producing patient discomfort, which is a frequently cited indication for the administration of sedatives.^{11,95} This may impact ventilator duration because high sedation usage is linked to longer ventilator use. Indeed, several observational studies have noted more days of mechanical ventilation and even trends toward higher mortality in patients with trigger dys-synchronies taking place more than 10% of the time.⁹⁵

Managing Dys-synchronies

Synchronous ventilator settings first require setting the trigger to as sensitive a setting as possible (without auto-triggering). If PEEP_i is creating a triggering load, attempts should be made to minimize PEEP_i and then judicious use of applied PEEP added to counterbalance the imposed triggering load as described later. If entrainment is present, reducing sedation and the need for a mandatory (controlled) breath rate should be re-assessed.

Flow synchrony is often easier to achieve with variable flow pressure-targeted breaths, as noted earlier. Pressure-targeted breaths can also allow for adjustments in the rate of pressure rise and can compensate for endotracheal tube resistance, as means of further enhancing synchrony (see “Recent Innovations in Mechanical Ventilatory Support” later). If flow-targeted breaths are desired, synchrony can be addressed with adjustments in flow magnitude and profile (sine wave, square wave, decelerating pattern). Importantly, because the patient’s respiratory drive is modulated by mechanical feedback from the lungs and thorax,

modes that avoid multiple different breath types (i.e., avoiding SIMV) tend to facilitate flow synchrony.¹¹ Finally, breath duration should be optimized for comfort and for elimination of double breaths by using adjustments in the cycle variable (volume, time, or flow).

Two new modes (*proportional assist ventilation* [PAV] and *neurally adjusted ventilatory assistance* [NAVA]) have been used over the past decade to enhance synchrony further. These are described in more detail later in “Recent Innovations in Mechanical Ventilatory Support.”

PULMONARY INFECTIOUS COMPLICATIONS

Mechanically ventilated patients are at risk for pulmonary infections for several reasons.⁹⁷ First, the natural glottic closure protective mechanism is compromised by an endotracheal tube. This permits continuous seepage of oropharyngeal material into the airways. Second, the endotracheal tube itself impairs the cough reflex and serves as an additional potential portal for pathogens to enter the lungs. This is particularly important if the circuit is contaminated. Third, airway and parenchymal injury both from the underlying disease and from management complications make the lung prone to infections. Fourth, the ICU environment itself, with its heavy antibiotic use and presence of sick patients in close proximity, increases risk for a variety of infections.

Preventing *ventilator-associated pneumonia* (VAP) is critically important because the development of VAP heavily influences both length of stay and mortality.⁹⁷⁻¹⁰⁰ Care “bundles” linked to better outcomes include handwashing, elevating the head of the bed, oral care with chlorhexidine, and carefully chosen antibiotic regimens for other infections. Management strategies that avoid breaking the integrity of the circuit (e.g., by changing the circuit only when visibly contaminated) also appear to be helpful.^{98,99} Continuous drainage of subglottic secretions may be another simple way of reducing lung contamination by oropharyngeal material.^{98,99} More controversial are devices to cleanse the endotracheal tube or make it resistant to biofilm buildup.¹⁰¹

Another concept explored in small trials is the use of aerosolized antibiotics in patients with purulent secretions to reduce progression of tracheobronchitis to ventilator-associated pneumonia.¹⁰² Finally, prompt discontinuation of ventilatory support when clinically appropriate will help minimize the time patients are exposed to infection risks.

APPLYING MECHANICAL VENTILATORY SUPPORT

MECHANICAL VENTILATORY SUPPORT INVOLVES TRADEOFFS

The goals of providing adequate support while minimizing the risk of VILI and other complications involves tradeoffs. Specifically, the need for potentially injurious pressures, volumes, and supplemental O₂ must be weighed against the benefits of supporting gas exchange. To this end, a “re-thinking” of gas exchange goals has taken place over

the past 2 decades so that now, pH levels as low as 7.15 to 7.20 and Po_2 values as low as 55 mm Hg are often considered acceptable in order to protect the lung.^{70,78,103} Ventilator settings are thus selected to provide at least this level of gas-exchange support while meeting three mechanical goals: (1) provision of enough PEEP to recruit the “recruitable” alveoli, (2) avoidance of a PEEP-tidal volume combination that unnecessarily overdistends lung regions at end-inspiration, and (3) limiting tidal volumes to the physiologic range. These goals embody the concept of a lung-protective mechanical ventilatory strategy. Currently, these principles guide recommendations for the specific management of various forms of respiratory failure.¹⁰⁴⁻¹⁰⁷

CONSIDERATIONS IN CHOOSING VENTILATOR SETTINGS FOR DIFFERENT FORMS OF RESPIRATORY FAILURE

Parenchymal Lung Injury

Parenchymal lung injury means injury that involves the air spaces and the interstitium of the lung.³¹⁻³⁵ In general, parenchymal injury stiffens lungs and decreases lung volumes. It is important to realize that there are often marked regional differences in the degree of mechanical abnormalities, which interact with the particular ventilatory strategy. This is because delivered gas will preferentially go to the more normal regions, those with higher compliance and lower resistance, rather than to abnormal regions (see Fig. 101-2). A “normal-sized” tidal volume may thus be distributed preferentially to the healthier regions, resulting in a regional overdistention injury. Parenchymal injury can also affect the airways, especially the bronchioles and alveolar ducts. These narrowed and collapsible small airways can also reduce regional ventilation to injured lung units, leading to regions of air trapping and possibly cyst formation during the healing phase.

Gas-exchange abnormalities in parenchymal lung injury are a consequence of alveolar consolidation, flooding, and/or collapse producing a maldistribution of ventilation and resulting in \dot{V}/\dot{Q} mismatching and shunts.³¹⁻³⁵ Because \dot{V}/\dot{Q} mismatching and shunt are more of an issue than dead space in parenchymal lung disease, hypoxemia tends to be more of a clinical problem than carbon dioxide elevation.

Frequency-tidal volume settings for patients with parenchymal lung injury must focus on limiting end-inspiratory stretch. The benefit of reducing stretch in improving outcome has been suggested by several clinical trials^{67-70,108} but has been most convincingly demonstrated by the National Institutes of Health (NIH)-sponsored ARDS Network Trial in which a ventilator strategy using a V_T of 6 mL/kg predicted body weight (PBW) as compared with 12 mL/kg PBW led to a 10% absolute reduction in mortality.⁷⁰ Thus initial V_T settings should start at 6 mL/kg PBW.^{68,109} Moreover, strong consideration should be given to reducing this setting further if end-inspiratory Pplat exceeds 30 cm H_2O .⁶⁷⁻⁷⁰ Increases in the V_T settings might be considered if there is marked patient discomfort or suboptimal gas exchange provided that the subsequent Pplat values do not exceed 30 cm H_2O .⁶⁷⁻⁷⁰ Respiratory rate settings are then adjusted to control pH. Unlike the case in obstructive

diseases, the potential for air trapping in parenchymal lung injury is low if the breathing frequency is less than 35 breaths/min; air trapping may not develop even at frequencies exceeding 50 breaths/min.

There is controversy as to whether *neuromuscular blockade* (NMB) and totally machine-controlled mechanical ventilation should be used in the initial 24 to 48 hours of parenchymal lung injury. NMB use producing flaccid ventilatory muscles reduces total body oxygen demands and eliminates potential dys-synchronous interactions. Indeed, one study in patients with severe hypoxemia (arterial Po_2/Fio_2 ratios < 120) showed improved mortality with NMB use for 48 hours.¹¹⁰ However, as noted earlier, ventilatory muscles inactive for as little as 24 hours are at risk for VIDD and long-term disability.⁵²⁻⁵⁴ Moreover, the use of NMB usually requires substantial sedative use. As a consequence, many authorities would argue that assisted/supported breaths are preferable early in the course of mechanical ventilatory support. The inspiratory time and the I:E ratio in parenchymal injury is set with consideration of several issues. The usual initial I:E ratio setting is 1:2 to 1:4, the normal and the most comfortable setting. The flow graphic should also be assessed to ensure that cycle synchrony is present and the expiratory time is adequate to avoid air trapping. An I:E ratio greater than 1:1 is referred to as *inverse-ratio ventilation* (IRV). In severe respiratory failure, IRV can be employed as an alternative to increasing PEEP to improve \dot{V}/\dot{Q} matching.^{38,39} The beneficial mechanisms involved include longer mixing times, recruitment of slowly filling alveoli, and development of PEEPi. A variation on IRV is *airway pressure release ventilation* (APRV).¹¹¹⁻¹¹⁵ APRV incorporates the ability to breathe spontaneously during the long inflation period of a pressure-controlled breath—a feature that may enhance recruitment and gas mixing. APRV is discussed in more detail in “Recent Innovations in Mechanical Ventilation” later.

The PEEP/ Fio_2 settings are optimized using both mechanical and gas-exchange considerations. Conceptually, in setting the PEEP level in parenchymal lung injury, the goal is to provide ventilator settings between the upper and lower inflection points on the deflation limb of the pressure-volume curve.¹¹⁶ The most direct mechanical approaches use the static pressure-volume plot to set the PEEP and V_T . This traditionally involves multiple $\text{V}_\text{T}/\text{Pplat}$ measurements and requires considerable clinician time along with patient sedation or even neuromuscular blockade and is not widely used. Another mechanical approach uses step changes in PEEP to determine the PEEP level that gives the best compliance.¹¹⁷ A simpler mechanical approach analyzes the $\text{P}_{\text{c}}\text{ir}$ profile during a constant-flow breath (stress index) to detect overdistention (late rising profile) or collapse/reopening injury (early rising profile).¹¹⁸ With all of these approaches, a recruitment maneuver can be used to recruit the maximal number of recruitable alveoli before setting the PEEP. Fio_2 adjustments are then set as low as clinically acceptable.

PEEP can also be guided by gas-exchange criteria, usually involving algorithms that adjust PEEP and Fio_2 according to certain targets. Note that constructing a PEEP/ Fio_2 algorithm is usually an empirical exercise in balancing distending pressure, arterial O_2 saturation, and Fio_2 and depends on the clinician’s perception of the relative “toxicities” of high thoracic pressures, high Fio_2 , and low arterial

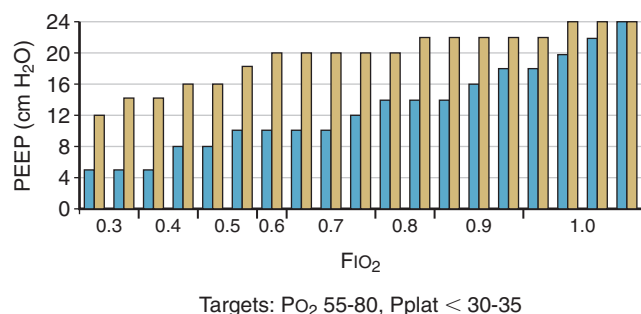


Figure 101-5 Two positive end-expiratory pressure (PEEP)/F_{IO}₂ algorithms that have been used in National Institutes of Health Acute Respiratory Distress Syndrome Network clinical trials. Plotted are F_{IO}₂ on the horizontal axis and PEEP on the vertical axis. With both approaches, the oxygenation target (PaO₂ 55 to 80 mm Hg, SPO₂ 88% to 95%) and the maximal allowable plateau pressure (35 cm H₂O) is the same. Patients are moved in steps up and down the algorithm according to these targets. The two algorithms depicted either focus on higher PEEP levels (“high PEEP”—brown bars) or lower PEEP levels (“low PEEP”—blue bars). (Courtesy Art Wheeler, MD, personal communication and Ref. 70.)

O₂ saturation. Although most of the reported PEEP/F_{IO}₂ algorithms generally target modest levels of oxygenation (e.g., arterial PO₂ 55 to 80 mm Hg or SO₂ 88% to 95%), they tend to segregate into approaches that focus either on higher PEEP levels (“high PEEP” algorithms) or lower PEEP levels (“low PEEP” algorithms) (Fig. 101-5). Several trials have compared high versus low PEEP algorithms in conjunction with low tidal volume/limited Pplat strategies in patients with ARDS.¹¹⁹⁻¹²¹ A meta-analysis of trials with mild ARDS (arterial PO₂/F_{IO}₂ > 200) compared with more severe ARDS (arterial PO₂/F_{IO}₂ < 200) demonstrated that higher PEEP strategies had a significant mortality benefit in more severe ARDS, whereas low PEEP strategies showed a trend toward a potential benefit in mild ARDS.¹²²

In patients with abnormal chest wall mechanics (i.e., stiff chest walls from obesity, anasarca, abdominal compartment syndrome, and even systemic inflammation), the reliance on circuit airway pressures to guide ventilator settings will ignore the effect of elevated pleural pressures on reducing transpulmonary pressure, the ultimate determinant of VILI and alveolar recruitment. Under these circumstances, clinicians should consider modest empirical increases in applied PEEP and allowances of an increased Pplat beyond the limits described earlier. Alternatively, an esophageal catheter to measure Pes could be inserted to assess transpulmonary pressure directly and adjust settings accordingly.^{19,123} Indeed, one clinical trial using Pes to guide PEEP settings suggested improved outcomes.¹²³

Obstructive Airway Disease

Increases in airway resistance lead to respiratory failure from airflow obstruction and create two important pathophysiologic changes. First, the increased pressures required for airflow may overload inspiratory muscles, producing a “ventilatory pump failure” in which spontaneous minute ventilation becomes inadequate for gas exchange. Second, the narrowed airways create regions of lung that cannot properly empty and return to their normal “resting volume,” thereby producing PEEPi.²⁷ These regions of overinflation create dead space and put inspiratory muscles at a substan-

tial mechanical disadvantage that further worsens muscle function. Overinflated regions may also compress more healthy regions of the lung, impairing \dot{V}/\dot{Q} matching. Regions of air trapping and PEEPi also function to increase the threshold load the patient must overcome to trigger mechanical breaths, as noted earlier.

The gas-exchange abnormalities in the setting of worsening airflow obstruction are several. First, although there may be a transient hyperventilation due to dyspnea in the asthmatic patient, the worsening respiratory failure in obstructive lung disease is generally characterized by a falling minute ventilation as inspiratory muscles fatigue in the face of airflow obstruction. The result is termed *hypercapnic respiratory failure*. Second, as noted earlier, regional lung compression and regional hypoventilation produce \dot{V}/\dot{Q} mismatch that results in progressive hypoxemia. Alveolar inflammation and flooding, however, are not characteristic features of respiratory failure due to pure airflow obstruction, and thus shunts are less of an issue than in parenchymal lung injury. Third, overdistended regions of the lung coupled with underlying emphysematous changes in some patients result in capillary loss and increasing dead space. This wasted ventilation further compromises the ability of the inspiratory muscles to supply an adequate ventilation for alveolar gas exchange. These emphysematous regions also have low recoil properties, which can worsen air trapping. Fourth, hypoxemic pulmonary vasoconstriction coupled with chronic pulmonary vascular changes in some airway diseases overload the right ventricle, further decreasing blood flow to the lung and increasing dead space further.

Frequency-tidal volume settings in obstructive diseases are chosen on the basis of many considerations similar to those in parenchymal lung injury. Specifically, tidal volumes should be in the 6 to 8 mL/kg (IBW) range with Pplat targets of less than 30 cm H₂O.⁶⁷⁻⁷⁰ In obstructive diseases, however, clinicians should also be aware that high *peak* airway pressures, even in the presence of acceptable values for Pplat, may transiently subject regions of the lung to periods of overdistention injury (see Fig. 101-2). Finally, setting the VT should also take into consideration the potential to develop PEEPi with its consequent impact on Pplat elevations and the risk of overdistention injury.

The ventilatory rate is used to control pH. Unlike the situation in parenchymal disease, however, the elevated airway resistance (and often the low recoil pressures of emphysema) greatly increase the potential for PEEPi and thus limit the range of breath rates available. Indeed, reductions in both VT and ventilatory rate to levels resulting in hypoventilation and “permissive (or even “therapeutic”⁷⁸) hypercapnia” may be an appropriate tradeoff to limit PEEPi development and overdistention.

The I:E ratio in obstructive lung disease is generally set as low as possible to minimize the development of air trapping. For the same reason, approaches using IRV strategies are almost always contraindicated.

The PEEP/F_{IO}₂ settings assume a different role in obstructive lung disease than in parenchymal lung disease. Because alveolar recruitment is less of an issue and overdistention is more of an issue in obstructive lung injury than in parenchymal lung injury, the strategy in using the PEEP/F_{IO}₂

steps in Figure 101-5 should probably be shifted more toward the use of FiO_2 for oxygenation support instead of PEEP. A specific role for PEEP in the obstructed patient arises when PEEPi serves as an added inspiratory threshold load on the patient attempting to trigger a breath, as described earlier. Under these conditions, judicious application of circuit PEEP (at levels up to 75% to 85% of PEEPi) can “counterbalance” PEEPi throughout the ventilator circuitry to reduce this triggering load and facilitate the triggering process.^{87,88}

In severe airflow obstruction, the use of the low-density gas helium can help facilitate ventilation. Helium mixtures are available as 80:20, 70:30, or 60:40 helium:oxygen breathing gas mixtures (heliox) and can both reduce patient inspiratory work and facilitate lung emptying (recall that driving pressure decreases and/or flow increases as gas density decreases).¹²⁴ However, to date there have been no studies demonstrating improved outcomes with the use of heliox. With a helium:oxygen gas mixture, it should be remembered that many flow sensors must be recalibrated to account for the change in gas density.

Finally, it is important to note that noninvasive ventilation has been demonstrated most convincingly to improve outcomes in patients with obstructive diseases.¹²⁵ In setting up noninvasive ventilation, the same principles described previously for invasive mechanical ventilation also apply (see Chapter 102).

Neuromuscular Respiratory Failure

The risk of VILI is generally less in a patient with neuromuscular failure (e.g., central nervous system injury, drug overdoses, anesthesia) because lung mechanics are often near normal and regional overdistention less likely. More “generous” VTs (e.g., up to 10 mL/kg PBW) have thus been proposed as being useful to improve comfort, maintain recruitment, prevent atelectasis, and avoid hypercarbia that may adversely affect central nervous system function. However, this notion has been challenged recently by clinical trials of patients with normal lungs in the perioperative period showing reduced postoperative complications when VTs are used in the 6 to 8 mL/kg (IBW) range. Regardless of VT settings, maximal distending pressures should be kept as low as possible while still being compatible with the other goals noted previously.⁶⁷⁻⁷⁰

Mode selection in neuromuscular disease patients is often determined by patient comfort and reliability of the respiratory drive. PEEP, even at low levels, is often beneficial at preventing derecruitment (atelectasis) in these patients, who are often supine and unable to clear secretions or sigh.

Recovering Respiratory Failure—“Weaning” and Discontinuation Process

As respiratory failure stabilizes and begins to reverse, clinical attention shifts to the process of ventilator withdrawal. Unfortunately, a number of large clinical trials have clearly demonstrated that current assessment/management strategies are not optimal, resulting in considerable delay in ventilator withdrawal.^{125,126} Such delay leads to increased length of ICU stay, increased costs, prolonged exposure to circuit pressure, and increased risk of infection. Attempts to speed withdrawal, however, must be balanced against the

risk of premature withdrawal with consequent loss of airway patency, aspiration, and inspiratory muscle fatigue. An evidence-based task force¹²⁵ has recommended a two-step process:

1. Consider a patient a candidate for withdrawal if (a) the lung injury is stable/resolving, (b) the gas exchange is adequate with low PEEP/ FiO_2 requirements, (c) the hemodynamics are stable without pressors, and (d) the patient has the capability to initiate spontaneous breaths.
2. In these patients, perform a spontaneous breathing trial (using T-piece, CPAP, or pressure support at 5 cm H_2O) for 30 to 120 minutes. Assessments should include the ventilatory pattern, gas exchange, hemodynamics, and comfort. Patients “passing” this trial should be considered for ventilator withdrawal.

In patients passing the *spontaneous breathing trial* (SBT), separate assessments are required to determine if the artificial airway can be removed. These involve cough strength, suctioning frequency, and, to a certain extent, the ability to follow commands.¹²⁵ Cuff leak, a bedside test that may demonstrate whether there is airway edema or compression around the endotracheal tube that could lead to postextubation airway obstruction, does not appear to be an important predictor of success, except perhaps in the setting of prior upper airway injury. Extubation failures can be expected in 10% to 20% of all extubations. Many of these involve airway protection issues and thus indicate the need for prompt reintubation. However, in some patients, especially those with chronic obstructive pulmonary disease, an extubation failure caused by increasing inspiratory muscle overload might be managed by noninvasive ventilation.^{127,128}

In patients failing the SBT, a stable and comfortable level of support should be provided until the next SBT.¹²⁵ Frequent (e.g., every 2 to 12 hours) support reductions are usually not necessary because they have not been shown to speed up the withdrawal process and only serve to consume resources and expose the patient to the risks of muscle overload. Repeat assessments for SBTs, however, should be done daily.^{125,126} Importantly, aggressive strategies to reduce sedation can accelerate this process.¹²⁹ Indeed, some have advocated “spontaneous awakening trials” coupled to SBTs, but it is not clear if this approach is superior to carefully targeted sedation protocols.¹³⁰

A common problem seen in patients recovering from respiratory failure but still deemed in need of an artificial airway is the presence of large VTs despite low levels of ventilatory support (e.g., inspiratory pressure levels of 5 cm H_2O). Under these circumstances, a search should be made for causes of an excessive respiratory drive such as pain, metabolic acidosis, or anxiety, and these issues should be addressed. Most would argue that, in the absence of reversible causes, sedation should not be used simply to lower the VT.

Regardless of the clinical scenario, whenever assisted-supported breaths are used, attention must be paid to assuring synchronous interactions. As noted earlier, this first means addressing the appropriateness of respiratory drive to ensure that reversible causes of excess drive (e.g., pain, anxiety, acidosis) are managed and then providing settings

that maximize trigger sensitivity. It also ensures proper flow and cycle synchrony.

RECENT INNOVATIONS IN MECHANICAL VENTILATORY SUPPORT

INNOVATIVE STRATEGIES FOR “LUNG PROTECTION”

Several innovations introduced recently may assist clinicians in reducing ventilator-induced lung injury. Among the more interesting are *airway pressure release ventilation* (APRV) and *high-frequency ventilation* (HFV). In addition, ventilating patients in the prone position, although not novel, can also be viewed as an interesting strategy to facilitate lung protective ventilation.

Airway Pressure Release Ventilation

APRV (also known as *biphasic ventilation*, *bilevel ventilation*, and *bilevel positive airway pressure*) is a time-cycled, pressure-targeted form of ventilatory support.¹¹¹⁻¹¹⁵ It is actually a modification of pressure-targeted SIMV that allows spontaneous breathing (with or without PS) during both the inflation and deflation phases.

The putative advantages of this approach are similar to others that utilize long inspiratory times. Specifically, the long inflation phase recruits more slowly filling alveoli and raises mean airway pressure without increasing applied PEEP (although PEEPi can develop with short deflation periods). Unlike older IRV strategies that required paralysis, however, the additional spontaneous efforts during inflation may enhance both recruitment and cardiac filling when compared with other controlled forms of support. Although IRV strategies are usually reserved for severe forms of respiratory failure in which airway pressures and FIO_2 levels are approaching potentially injurious levels, the comfort and recruitment potential associated with APRV may prompt consideration of its use even in less severe forms of lung injury.

Good gas exchange has been demonstrated with APRV in several small observational clinical trials, often with lower maximal airway pressures than used with control ventilation.¹¹¹ However, the end-inspiratory lung distention in APRV may not be less than that provided during other forms of support (and, indeed, it could be substantially higher) because spontaneous VTs can expand the lung beyond the volume at the APRV set pressure. In the few randomized studies that compare APRV to a true lung-protective strategy, no differences in important outcomes have been found.¹¹³⁻¹¹⁵

High-Frequency Ventilation

HFV uses high breathing frequencies (120 to 900 breaths/min in the adult) coupled with small VTs (usually < anatomic dead space and often < 1 mL/kg IBW at the alveolar level) to provide gas exchange in the lungs.¹³¹ Gas transport under these seemingly unphysiologic conditions may involve such mechanisms as Taylor dispersion, coaxial flows, and augmented diffusion.¹³²

HFV can be supplied by either jets or oscillators. Jets inject high-frequency pulses of gas into the airways. Oscillators literally vibrate a fresh bias flow of gas delivered at the tip of the endotracheal tube. Because of this, oscillatory HFV has sometimes been referred to as “CPAP with a wiggle.”

The putative advantages of HFV are twofold. First, the small alveolar tidal pressure swings minimize cyclical overdistention and derecruitment. Second, a high mean airway pressure can also prevent derecruitment. Interestingly, mean pressures used during HFV are often reported to exceed the 30 to 35 cm H_2O threshold employed during conventional ventilation. This tolerance of a higher mean pressure with HFV may be explained by a better maintained alveolar structure with a slowly applied (albeit vibrating) constant pressure as opposed to cyclical brief tidal pressures.¹³³

Clinical experience with HFV has been most extensive in the neonatal and pediatric age groups where a number of trials show improved long-term lung function when HFV is used in acute respiratory failure.^{134,135} Although adult experience with HFV is less, a meta-analysis of randomized trials using HFV in adult respiratory failure suggested an outcome benefit to HFV.¹³⁶ Two large subsequent trials, however, have called this conclusion into question. In one, mortality was identical in both the HFV and lung-protective conventional strategy¹³⁷; in the other, the trial was stopped early because of increased mortality in the HFV group.¹³⁸ Of concern in both of these trials was the use of many centers that had little or no previous experience with HFV. Nevertheless, both trials make it clear that HFV, if used, is best reserved for patients failing conventional lung protective strategies and should be employed by clinicians experienced in the use of HFV.

Positive-Pressure Ventilation in the Prone Position

Mechanical ventilation of patients in the prone position offers several physiologic advantages.¹³⁹ Chief among these are two mechanisms that can improve ventilation distribution. First, the heart no longer rests on the left lower lobe and this allows better ventilation distribution to that region. Second, the sternum is restricted in its ability to move outward. This functionally stiffens the chest wall and forces a more even distribution of positive pressure.

Prone positioning has its challenges, primarily from a nursing perspective. The act of proning requires careful teamwork (although automated proning beds exist). More importantly, management of vascular lines, feeding tubes, artificial airways, ostomies, and so on need careful attention because they can be easily dislodged. Avoiding facial pressure sores also requires careful nursing care.

There have been a number of randomized controlled trials of proning in patients with ARDS and, until recently, despite consistently better oxygenation, no consistent outcome benefit could be demonstrated.¹³⁹ However, the largest study to date focusing on ARDS patients with arterial PO_2/FIO_2 ratios less than 150 recently showed a significant mortality benefit to lung protective mechanical ventilation provided in the prone position for more than 16 hours/day.¹⁴⁰

AUTOMATED WEANING STRATEGIES

Over the years, a number of attempts have been made to “automate” the weaning process.⁷ An early example is minimum minute ventilation, which adjusted the intermittent mandatory breath rate according to the level of spontaneous ventilation. The concept behind automated weaning was that significant clinician time could be saved and ventilatory support could be automatically reduced in a timely fashion on the basis of simple ventilator measurements.

Volume support (VS, also known by trade names such as “Automatic Pressure Ventilation”) is a newer strategy with the potential for automatic support reduction.⁷ As described earlier, VS is a pressure support mode that uses tidal volume as a feedback control for continuously adjusting the pressure support level. Proponents claim that this approach could “automatically” wean a patient by reducing pressure support as patient effort increases and respiratory system mechanics improve. Conversely, pressure support would increase if patient effort diminished or respiratory system mechanics worsened. Similarly, it has also been suggested that VS may be a useful way to maintain a more constant level of partial support in patients with fluctuating levels of effort related to drugs or neurologic conditions. All of these effects have been demonstrated in small studies focused on patients with rapidly recovering respiratory failure.⁷

Unfortunately, the simplicity of VS may introduce problems.^{7,26} For instance, if the volume set by the clinician is excessive for patient demand, a recovering patient may not attempt to take over the work of breathing for that volume and thus weaning may not progress. In addition, if the pressure level increases in an attempt to maintain an inappropriately high-set V_T in the patient with airflow obstruction, PEEP_i may result. Conversely, if the volume set by the clinician is not adequate for patient demand, a patient may not receive adequate support. Under these conditions, a patient will perform excessive work to maintain a certain V_T even as the inspiratory pressure is being reduced. A transient increase in patient demand from pain or anxiety could also result in inappropriate support reduction with VS.²⁶

Adaptive support ventilation (ASV) has a sophisticated algorithm to adjust the ventilatory pattern during machine-triggered breaths as described earlier. However, ASV performs similarly to VS during patient-triggered breaths. Small clinical studies have demonstrated that ASV can automatically wean ventilatory support safely.¹⁴¹ However, large trials comparing ASV weaning to regular daily SBT strategies have not been done.

Another commercially available feedback system for weaning pressure-targeted breaths uses not only V_T but also respiratory rate and end-tidal carbon dioxide to adjust ventilator settings.¹⁴² Randomized trials with this system, however, have not shown faster ventilator withdrawal when compared with strategies using protocols for regular SBTs.¹⁴³

Inherent in all of these automated weaning systems is the notion that gradual support reductions (weaning) in between SBTs facilitates ventilator withdrawal—a notion that has little, if any, evidence supporting it in patients recovering from acute respiratory failure.¹⁴⁴ Two clinical

scenarios, however, may be amenable to these automated approaches: The first is the patient rapidly recovering from sedatives/anesthesia where these systems can alert clinicians to the return of adequate spontaneous efforts. The second is the patient requiring prolonged mechanical ventilation who has failed multiple SBTs. Under these circumstances, an automated support reduction system could serve as a diagnostic tool alerting the clinician to recovery of respiratory function and the possibility of reinstating SBTs.

OPTIMIZING SYNCHRONY DURING INTERACTIVE BREATHS

Interactive breaths are commonly used during mechanical ventilatory support to improve comfort (and reduce sedation), especially during the recovery phase of respiratory failure. As noted previously, interactive breaths need to be synchronous with patient efforts during all three phases of breath delivery: trigger, flow delivery, and cycle. A number of recent innovations have been introduced and are reviewed here.

Although all of these innovations have conceptual appeal and have been shown to perform as designed in both bench testing and small clinical observational trials, patient outcomes, including sedation needs, ventilator days, or patient comfort assessments, have generally not been studied. Nevertheless, their straightforward designs, ease of operation, and safety make these innovations appropriate to consider in patients receiving interactive breaths.

Endotracheal Tube Resistance Compensation

The endotracheal tube provides a significant resistance to flow during both inspiration and expiration. During the inspiratory phase, this means that pressure build-up in the airways “lags” behind the pressure build-up in the ventilator circuitry. Thus the “square” wave of pressure in the circuitry provided by a pressure-targeted breath is distorted in the airways to a slower rise of pressure. This may create significant initial flow dys-synchrony in patients with vigorous inspiratory efforts. During expiration, a similar gradient between airway pressures and set circuit PEEP can develop.

One way to address this is to target ventilator pressures to a measured tracheal pressure distal to the endotracheal tube. Unfortunately, readings from intra-airway pressure sensors over prolonged periods are not reliable. Another approach is to account for endotracheal tube resistance mathematically in the ventilator flow delivery pattern.^{145,146} Known by various trade names (e.g., “Automatic Airway Compensation,” “Automatic Tube Compensation”), this approach initially provides an inspiratory pressure higher than the set pressure target. As inspiration proceeds, this delivered pressure then tapers to the set inspiratory pressure target. This compensation mechanism can also operate in expiration with an initial expiratory airway pressure below the set PEEP that then rises to the set PEEP. A more square wave pattern of inspiratory and expiratory tracheal pressures is the result.^{145,146}

Applying endotracheal tube resistance compensation is relatively straightforward. Clinicians must input the characteristics of the endotracheal tube. Thereafter, the

ventilator provides the appropriate circuit pressure profile during both inspiration and expiration to create the desired square wave pattern in the trachea. Although outcome studies using this compensation approach have not been done, the conceptual appeal should make it a consideration in virtually all patients receiving assisted/supported pressure-targeted breaths—especially those with vigorous inspiratory efforts.

Pressure Rate of Rise (Slope) Adjusters

The original design for pressure-targeted breaths (pressure support and pressure assist-control) had a programmed flow delivery algorithm that attempted to reach the target inspiratory pressure quickly, without causing an uncomfortable overshoot. Newer ventilators, however, allow the clinicians to adjust the rate of rise of this pressure (slope adjusters), and clinical studies have suggested that slope adjustment could significantly enhance flow synchrony in many patients.¹⁴⁷ Specifically, these studies found that a rapid rate of rise was often desired in a patient with vigorous flow demands, whereas a much slower rate of rise was often preferable in patients with less vigorous demands.

There are several approaches to setting the slope adjuster. The most direct way is to use the circuit pressure graph and adjust the slope to create a “smooth square wave” appearance to the circuit pressure profile. Studies have also shown that an optimal slope setting correlates with the greatest VT for a given pressure setting.¹⁴⁷ Patient comfort should always be considered in determining optimal slope settings.

Pressure Support Cycle Adjusters

Pressure support breaths have a flow cycling mechanism to terminate the breath. On earlier machines, a set flow termination criterion was usually set by the manufacturer (e.g., 25% to 35% of peak flow). Although this set flow was often effective, it could sometimes terminate breaths too early in patients with long inspiratory demands and it could sometimes terminate too late, typically in patients with obstructive airway disease. In this latter situation, air trapping could also be made worse because of the resulting shorter expiratory time.

There are several approaches to improving cycle synchrony with pressure support. One is to switch from pressure support to a pressure-assist breath (patient-triggered, pressure-targeted, time-cycled breath as is usually available on most machines providing pressure ACV if the set rate is turned low or off). This breath provides direct clinician control of inspiratory time and thus of cycling. Another strategy is to adjust the pressure slope setting described previously on pressure support breaths. A rapid peak initial flow will have a correspondingly high flow cycle variable (and thus short inspiratory time); a very slow peak initial flow will have a correspondingly low flow cycle variable (and thus long inspiratory time).

A newer approach is to allow adjustments of the flow criteria of the pressure support cycle to assure appropriate synchrony of the cycle with the end of patient effort.¹⁴⁸ As with other adjustments of interactive breaths, airway pressure graphics and assessments of patient comfort should guide adjustments. Proper breath synchrony is character-

ized by a comfortable patient without evidence on the circuit pressure graph of continued inspiratory effort after cycling (premature cycling) or of expiratory efforts beginning during the inspiratory phase (delayed cycling). Although no outcome studies have been performed using these cycle adjusters, their physiologic appeal, ease of use, and apparent safety should make them a consideration in virtually every patient receiving pressure support.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is a novel approach to assisted ventilation in which the clinician sets the “gain” on patient-generated flow and volume.¹⁴⁹⁻¹⁵⁰ In PAV, there is thus no set pressure, flow, or volume. Instead, the sensed patient effort is boosted according to a proportion of the measured work of breathing set by the clinician.

PAV requires that “test breaths” (controlled breaths with fixed flow and volume) be given. This allows for the calculation of respiratory system mechanics, which can be coupled with the measured ventilation to calculate work of breathing (resistive and elastic ventilatory muscle loads). These load calculations are repeated at regular intervals in order to maintain reliable inputs for the PAV algorithm.

PAV breaths are patient-initiated breaths triggered in a conventional way using circuit pressure or flow sensors. Thereafter, the ventilator continues to monitor flow and volume demanded by the patient and puts a clinician-set “gain” on this demand to augment flow and pressure in proportion to the desired reduction in the patient’s work of breathing. The PAV breath cycles when sensed flow demand has ceased.

Like pressure-targeted breaths, PAV flow delivery varies with patient effort; unlike pressure-targeted breaths, pressure also varies with patient effort. The conceptual upside to PAV is that flow and cycle synchrony should be enhanced over conventional flow- or pressure-targeted breaths. Another conceptual upside is that patient-driven tidal volume variability with its theoretical lung protective benefits may be enhanced.¹⁵¹ The downside, however, is that, unlike conventional pressure-targeted breaths, there is no minimum pressure or flow provided. Thus PAV must be used with caution in patients with unreliable ventilatory drives from either disease or drugs. Indeed, with all patients on PAV, careful monitoring and backup support modes should be available.

Most clinical studies with PAV have shown enhanced synchrony compared with conventional modes.¹⁴⁹⁻¹⁵⁶ However, it is not clear what the ideal PAV gain(s) should be in various clinical settings. Moreover, to date, there have been no good randomized trials looking at important outcome benefits (e.g., ventilator duration, sedation needs, mortality) when PAV is compared with conventional assisted/supported ventilation.

Neurally Adjusted Ventilatory Assistance

Neurally adjusted ventilatory assistance (NAVA) utilizes the diaphragmatic *electromyographic* (EMG) signal to trigger, adjust flow, and cycle assisted breaths.^{153,157} NAVA requires placement of a unique esophageal catheter with an array of diaphragm EMG sensors. These sensors detect the onset, intensity, and termination of inspiratory efforts directly.

Like PAV, a clinician-set gain is then applied, which determines flow and pressure delivery in proportion to the EMG signal.

The conceptual benefit to NAVA is that synchrony with all three phases of breath delivery (trigger, gas delivery, and cycle) should be enhanced over conventional flow- or pressure-targeted breaths. Like PAV, another conceptual benefit is that patient-driven tidal volume variability with its theoretical lung protective benefits may be enhanced. Also like PAV, the downside is that there is no minimum pressure or flow provided. Thus, like PAV, NAVA must be used with caution in patients with unreliable ventilatory drives from either disease or drugs. Moreover, with NAVA, there is also concern about the stability of the EMG signal coming from a catheter that can move within the esophagus. Thus all patients on NAVA require careful monitoring and backup support modes.

Most clinical studies with NAVA have shown enhanced synchrony compared with conventional modes.¹⁵⁸⁻¹⁶¹ However, like PAV, it is unclear what the optimal EMG gain setting(s) should be in various clinical settings. To date there have been no good randomized trials looking at important outcome benefits (e.g., ventilator duration, sedation needs, mortality) when NAVA is compared with conventional assisted/supported ventilation.

Key Points

- Positive-pressure breaths are characterized by three variables: the breath trigger, the flow delivery target (pressure or flow), and the cycle criteria.
- The interactions of positive-pressure breaths and respiratory system mechanics are described by the equation of motion: $\text{Pressure} = (\text{flow} \times \text{resistance}) + (\text{volume}/\text{system compliance})$.
- In lungs with collapsed alveoli, alveolar recruitment is accomplished by transient increases in positive-pressure inflation and is maintained by positive end-expiratory pressure.
- Ventilator-induced lung injury can be caused by several mechanisms, including alveolar overdistention and repetitive alveolar collapse/reopening.
- Removing mechanical ventilatory support expeditiously requires regular sedation adjustments and assessments of spontaneous breathing capabilities.

Complete reference list available at ExpertConsult.

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INTRODUCTION

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Cardiogenic Pulmonary Edema

Hypoxemic Acute Respiratory Failure

Prevention of Postoperative
Complications

Do-Not-Intubate Patients

During the Weaning Process and
Post-extubation

Preventive Use During Procedures

Home Noninvasive Ventilation

EPIDEMIOLOGY OF NONINVASIVE VENTILATION IN ACUTE CARE

INTRODUCTION

Mechanical ventilation (MV) is a life-saving procedure with applications in acute and chronic respiratory failure. Since the late 1950s, mechanical ventilation has been preferentially delivered by direct access to the lower airways through an endotracheal tube, such as during general anesthesia and surgery, or via a tracheostomy cannula.

Since the late 1980s, home MV has been increasingly applied in patients with chronic restrictive or obstructive respiratory disorders via noninvasive techniques, with the main objective of improving patients' quality of life compared with home tracheostomy. Manufacturers have devoted considerable technologic effort to develop specific home ventilators for "leaky" ventilation and to provide comfortable and adaptable interfaces. The recognition that major sleep disturbances could be caused by abnormal respiration has also contributed to the widespread use of different kinds of home ventilatory support. *Noninvasive ventilation* (NIV) is therefore the standard of care for home mechanical ventilation.

In the early 1990s in parallel with the expansion of home NIV, clinicians started to demonstrate a major interest in this technique as a way of avoiding endotracheal intubation in the acute care setting.¹⁻³ The indications have progressively been extended from acute hypercapnic respiratory failure to a large variety of clinical situations with different degrees of respiratory failure significantly expanding the number of patients currently treated with NIV.^{3a} In the acute care field, technical improvements and specific equipment came late and benefited from improvements made for home ventilation. Currently, there are a number of specific indications for the use of NIV as the standard of care for acute respiratory failure. However, there are also many situations where there is uncertainty about the usefulness or the limits of this technique, explaining large variations in its use internationally (Table 102-1).

Soon after the introduction of invasive MV via a tube in the trachea, many complications of positive pressure ventilation were identified.⁴⁻⁵ These complications generated

concern about the invasiveness of MV. The endotracheal intubation procedure and the tube itself have been implicated in a large number of complications. Some are directly related to the intubation procedure, such as cardiac arrest following endotracheal intubation, and laryngeal or tracheal injury leading to long-term sequelae. Others are related to the fact that the endotracheal tube bypasses the barrier of the upper airway, setting the stage for ventilator-associated pneumonia that carries its own risk of morbidity and mortality. Mechanical ventilation often requires sedation, which itself is often a cause of prolonged weaning and prolonged mechanical ventilation. These major safety considerations prompted the development of noninvasive methods for delivering positive pressure ventilation. Thus, in patients with acute respiratory failure, the main goal of NIV has been—and still is—to provide ventilatory assistance while lowering the risk of adverse events by reducing the need for invasive MV. Convincing evidence that NIV diminishes the risk of infectious complications has been obtained from randomized controlled trials and meta-analyses, as well as from large cohort studies and case-control studies, which have demonstrated substantial decreases in all categories of nosocomial infection.⁶⁻⁸ The reason is that NIV is in general associated with a reduction in the overall invasiveness of patient management: Sedation is usually not required or, if necessary, it is administered at low doses, and the use of central venous lines, urinary catheters, and other invasive devices is reduced compared with patients receiving endotracheal MV⁹ (Fig. 102-1).

Another important factor favoring the use of NIV is the growing number of patients who are unwilling to accept *endotracheal intubation* (ETI) or are considered poor candidates for endotracheal MV because of a fragile underlying health status.¹⁰⁻¹¹ In these patients, NIV offers a chance of recovery with a low risk of complications and can be considered as a ceiling of therapy with acceptable risks. By postponing ETI, NIV may also provide a window of opportunity for the physician, family, and patient to make informed decisions about the goals of therapy in patients treated with palliative care.¹² Potential benefits and risks

Table 102-1 Recommendations for the Use of Noninvasive Ventilation During Acute Respiratory Failure According to Disease and Clinical Status

Recommended	DISEASE			CLINICAL STATUS	
	Intermediate Recommendation	Weak Recommendation	No, or Contraindication	Yes	No
Exacerbations of COPD	Asthma	Mild-moderate ARDS	Severe ARDS	Conscious and cooperative (except encephalopathy in COPD)	Hemodynamic instability
Acute cardiogenic pulmonary edema	Hypoxemic respiratory failure in nonimmunocompromised patients	Community-acquired pneumonia (non-COPD)	ARDS with multiple organ dysfunction	Hypercapnic failure	Loss of consciousness, drowsiness
Acute respiratory failure in immunocompromised patients	Preventive use during procedures (upper endoscopies, endotracheal intubation)	Trauma	End-stage interstitial pulmonary fibrosis	Hemodynamically stable	Abdominal distention, nausea or vomiting
Facilitation of weaning/extubation in patients with COPD	Community-acquired pneumonia in patients with COPD	Extubation failure (non-COPD)	Facial trauma	No multiple organ failures	Uncooperative patient
Postoperative hypoxemia after major abdominal or lung surgery	Extubation failure in patients with COPD	Postoperative preventive following esophageal or lung surgery (using low pressures)	Facilitation of weaning (non-COPD)	Improvement in gas exchange, respiratory, and heart rate within first 2 hr	Inexperienced staff
Acute respiratory failure in patients with obesity-hypoventilation	Postoperative preventive (cardiac, upper abdominal-bariatric surgery)		Undrained pneumothorax		Upper airway obstruction
Do-not-intubate patients	Neuromuscular disease		Upper gastrointestinal bleeding		

ARDS, Acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.



Figure 102-1 Noninvasive ventilation in the ICU. Photograph shows a patient treated in the intensive care unit (ICU) by noninvasive ventilation using a face mask covering the nose and the mouth. An ICU ventilator with a double circuit is used. (Written informed consent of the patient was obtained.)

Table 102-2 Potential Benefits and Risks of Noninvasive Ventilation for Acute Respiratory Failure

Benefits	Risks
Unload the respiratory muscles	Intolerance related to interface
Improve gas exchange	Abdominal distention and regurgitation
Decrease left ventricular afterload (in non-preload-dependent patients)	Skin lesions
Decrease right and left ventricular preload	Masking deterioration of underlying disease
Reduce the invasiveness of patient management	Frequent unrecognized patient-ventilator asynchrony
Decrease ICU and hospital stay	May promote large tidal volumes and high transpulmonary pressure swings (potential for VILI)
Diminish the risk of nosocomial infections	
Decrease complications	
Decrease mortality	

ICU, intensive care unit; VILI, ventilation-induced lung injury.

of the technique are discussed later and summarized in [Table 102-2](#).

PATHOPHYSIOLOGY, RATIONALE, AND EXPECTED BENEFITS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

Exacerbation of *chronic obstructive pulmonary disease* (COPD) is a common cause of admission to the hospital and *intensive care unit* (ICU). Worsening of dyspnea and symptoms of acute bronchitis are accompanied by rapid and shallow breathing leading to hypoxemia and hypercapnia. Right ventricular failure, encephalopathy, and cardiorespiratory arrest can ensue. The main pathophysiologic pathway

comes from an inability to maintain adequate alveolar ventilation in the presence of major abnormalities in respiratory mechanics. The transdiaphragmatic pressure generated by these patients can be considerably higher than normal and represents a high percentage of their maximal diaphragmatic force, a situation that carries a risk of respiratory muscle fatigue.¹ These changes are accompanied by a high respiratory drive, due to strong stimulation of the respiratory centers by acidosis and hypoxemia. This vicious circle can be modified by NIV, which allows the patient to take larger tidal volumes with less effort, thus reversing the clinical abnormalities resulting from hypoxemia, hypercapnia, and acidosis.^{1,13} The main role of NIV is to allow the patient to increase tidal volume at a lower level of energy expenditure. Ventilatory support working in synchrony with the patient's efforts allows larger breaths to be taken with less effort. As a result of increased alveolar ventilation, *arterial partial carbon dioxide pressure* (arterial PCO₂) and pH

values improve and this, in turn, reduces the patient's ventilatory drive, thereby lowering the respiratory rate and improving dyspnea.

CARDIOGENIC PULMONARY EDEMA

In *cardiogenic pulmonary edema* (CPE), breathing becomes difficult because pulmonary congestion reduces lung compliance, causes hypoxemia and increases the work of breathing. Most patients with CPE improve rapidly with medical therapy. A few, however, develop severe respiratory distress and/or refractory hypoxemia/hypercapnia and require ventilatory support until the medical treatment starts to work. This is particularly common in elderly patients, who may also have a mild degree of chronic bronchitis.¹⁴⁻¹⁵ Several NIV modalities have been used successfully, with the main goal of preventing the need for ETI and/or hastening the improvement provided by medical therapy. The negative swings in intrathoracic pressure increase venous return, while at the same time the negative intrathoracic pressure can impede left ventricular ejection. Respiratory distress and hypercapnia develops, especially if underlying pulmonary abnormalities are present. *Continuous positive airway pressure* (CPAP) and other types of NIV can elevate intrathoracic pressure and reduce the negative pleural swings, decrease shunt, and improve arterial oxygenation and dyspnea in patients with CPE. Interestingly, NIV can substantially lessen the work of breathing and, at the same time, improve cardiovascular function by decreasing left ventricular afterload in non–preload-dependent patients¹⁶ and reduce right and left ventricular preload.¹⁷ In one trial, high-dose nitrate bolus therapy was far more effective clinically than NIV with a low dose of nitrates.¹⁸ It is important to stress the vulnerability of patients with CPE, particularly those with coronary heart disease, and to emphasize that NIV cannot replace adequate medical therapy.¹⁹⁻²⁰

HYPOXEMIC ACUTE RESPIRATORY FAILURE

Unlike exacerbations of COPD or even CPE, hypoxemic *acute respiratory failure* (ARF) represents a heterogeneous group of diseases with different prognoses and treatments. The main common characteristic is hypoxemia, and it is frequently not associated with frank ventilatory failure, at least in the initial phase. Robust large randomized controlled trials are relatively scarce in this setting, and guidelines and recommendations are often not straightforward.²¹⁻²² The heterogeneity of these patients explains some of the contradictory results in the literature, suggesting that the outcome may vary with the study population. The various subgroups of hypoxemic ARF may thus need to be examined separately.

The hallmark of hypoxemic ARF is acute hypoxemia (arterial PO_2/FiO_2 ratio ≤ 300) that necessitates high levels of oxygen and is accompanied by clinical signs of respiratory distress reflecting a high respiratory drive often causing hyperventilation and hypocapnia. The development of hypercapnia is considered a serious late complication, generally indicating impending respiratory muscle fatigue. The rationale for using NIV in hypoxemic ARF is to alleviate the high load imposed on the respiratory muscles (prevention of latent pump failure) and to “treat” hypoxemia (lung

failure). Two specific issues regarding the use of NIV for this indication should therefore be mentioned: (1) NIV is not a cure for the disease and, when interrupted or poorly delivered, the patient immediately returns to the pre-NIV state. In fact, a beneficial effect of NIV on gas exchange and dyspnea may mask disease deterioration. This could lead to life-threatening respiratory failure in case NIV is subsequently interrupted. (2) During the initial phase, patients sometimes are able to cope with the workload imposed on the respiratory muscles with no apparent need for ventilatory support. However, by the time they become completely unable to meet the respiratory requirements, NIV use may be ineffective or even harmful. Therefore there is probably a time and/or a severity window for delivering NIV as a preventive support beyond which its use may become risky²³ (Fig. 102-2).

Moreover, many patients with *acute respiratory distress syndrome* (ARDS) may not be favorable candidates for NIV due to the need for delivering lung protective ventilation. During NIV, high transpulmonary pressure swings and large tidal volumes may be generated, which could lead to the development of *ventilator-induced lung injury* (VILI) and contribute to the poor outcome observed in intubated patients who fail NIV. Most patients with hypoxemic ARF have a high respiratory drive, and it has been shown experimentally that the increased drive caused by a severe metabolic acidosis may cause lung injury.²⁴

In clinical practice, the total pressure delivered during NIV is limited by the leaks that result from high pressures in the mask. To determine the effects of different combinations of pressure support and *positive end-expiratory pressure* (PEEP), the work of breathing and gas exchange was measured in patients with acute lung injury receiving NIV for ARF.²⁵ The highest level of PEEP studied (10 cm H_2O)

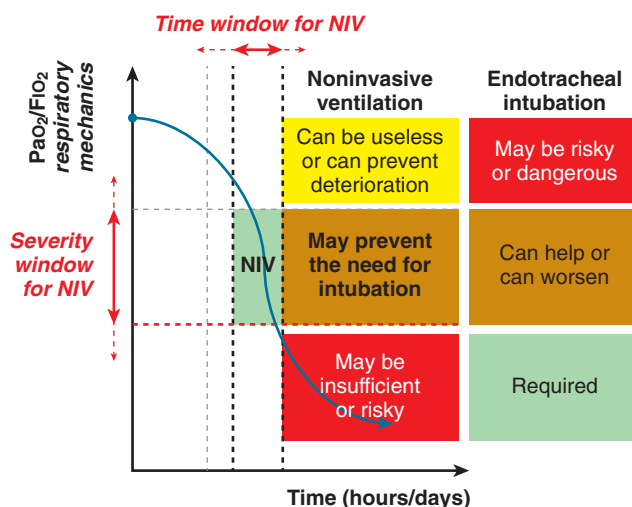


Figure 102-2 The decision windows for noninvasive ventilation (NIV) or endotracheal intubation (ETI). There is an optimal window of time and severity of injury to consider NIV. As a patient worsens over time (see curve of patient course), one must consider whether the severity is appropriate for NIV or ETI. For the right level of severity, NIV can be valuable in offering needed support and perhaps preventing the need for intubation. If the severity worsens further, NIV may be insufficient or risky and ETI is required. If the condition is mild, neither NIV nor ETI would be warranted. Unfortunately, there are no strictly objective criteria which delineate the windows of severity or of time for determining exactly when NIV should be used.

resulted in the greatest oxygenation improvement, but CPAP alone failed to unload the respiratory muscles. Decrease in the work of breathing and dyspnea necessitated the provision of pressure support. To handle the lung and pump failure with NIV, clinicians should provide a sufficient level of PEEP to improve oxygenation, while ensuring an optimal pressure support to unload the respiratory muscles. These two additive but sometimes conflicting pressures generate the peak airway pressure, one of the major determinants of leaks and asynchrony. Patients with poor respiratory mechanics requiring high airway pressures may thus prove difficult to manage with NIV.

PRACTICAL AND TECHNICAL ASPECTS

MODES OF VENTILATION AND SETTINGS

Continuous Positive Airway Pressure and Pressure-Support Ventilation

Continuous positive airway pressure (CPAP) represents the application of a constant level of positive pressure at the airway opening during spontaneous breathing and is widely used in the ICU, particularly in neonates and infants in whom it was first applied. Positive pressure applied at the mouth was shown as early as the 1930s to improve dyspnea in CPE.²⁶ CPAP is not always considered to be a true mode of ventilatory support, but it often provides ventilatory assistance in terms of a patient's work of breathing and oxygenation and achieves the usual goals of ventilatory support. Although there is some debate in the literature, in this chapter, CPAP is considered as a type of NIV. An advantage of CPAP over more complex modes of mechanical ventilatory assistance is that CPAP does not require patient-ventilator synchronization. CPAP results in a higher mean intrathoracic pressure than unassisted spontaneous breathing, with beneficial effects on atelectasis and improvement in oxygenation. Lung compliance can increase, reducing work of breathing, and the presence of *intrinsic PEEP* (PEEPi) can be counterbalanced with a partial reduction of inspiratory effort.

In patients without COPD, CPAP can increase functional residual capacity and may displace ventilation up from the lower flat portion of the respiratory system volume-pressure curve to a more linear portion. Through this mechanism, CPAP can improve oxygenation and respiratory mechanics and potentially reduce the work of breathing.²⁷ L'Her and colleagues²⁵ could not find any significant effect of CPAP on respiratory effort in patients with acute lung injury, in contrast with marked reduction under *pressure-support ventilation* (PSV). Delclaux and colleagues²⁸ evaluated whether CPAP, compared with conventional medical treatment and oxygen alone, reduced the need for ETI in normocapnic patients with acute lung injury. Despite a favorable early physiologic response to CPAP in terms of oxygenation, no outcome benefits were observed. This failure of noninvasive CPAP to provide clinical benefits may be due to the absence of any effect on respiratory effort.

This differs from the results of studies in CPE, in which PSV was comparable or only slightly superior to CPAP alone in terms of the decrease in respiratory effort. In patients

with CPE, CPAP raises intrathoracic pressure, improves oxygenation and dyspnea,²⁹ and lessens the work of breathing.¹⁶ In addition, an increase of intrathoracic pressure decreases transmural pressure of the left ventricle and of the thoracic aorta, reducing left ventricular afterload. Chadda and colleagues found that CPAP and PSV resulted in similar cardiac and hemodynamic effects, by producing similar reductions in right and left ventricular preload mediated by similar effects on intrathoracic pressure.¹⁷

One early clinical trial found more ischemic cardiac events using pressure support than using CPAP, but it was difficult in this small study to differentiate randomization imbalance from true physiologic effects.³⁰ Although these effects were not confirmed in later studies, it raised doubts on its use in patients with ischemic cardiac diseases.³¹

Pressure support is the most frequently used ventilatory mode during NIV.³² In patients with severe hypoxemia, ventilatory support should be able to relieve the dyspnea, improve oxygenation, and decrease the patient's effort to breathe. Combined PEEP and pressure support are needed to achieve these goals. As discussed earlier,²⁵ the compromise between setting PEEP and pressure support during NIV use may be challenging. The total pressure delivered by the ventilator is often reduced to avoid inducing excessive leakage that would complicate NIV administration and impair patient-ventilator synchrony; however, insufficient pressure may translate into unsatisfactory inspiratory muscle unloading.

Asynchronies During Noninvasive Pressure-Support Ventilation

Success of NIV is strongly associated with good clinical tolerance³²⁻³³. Problems of intolerance can be related to the patient, interface, ventilator, and/or ventilator settings. A specific problem during NIV is the presence of leaks around the mask, which may lead to discomfort and patient-ventilator asynchrony, thereby further worsening the clinical situation. Patient-ventilator asynchrony is defined as a mismatch between the patient's neural inspiratory time and the ventilator insufflation time.³⁴ Two types of asynchrony can be directly caused by leaks during NIV with pressure support: prolonged inspiration due to inspiratory leaks³⁵ and auto-triggering due to expiratory leaks. An optimal adjustment of ventilatory settings may improve patient-ventilator synchrony, work of breathing, comfort, and, potentially, the success of NIV.

An observational study used surface diaphragmatic electromyographic activity to evaluate the incidence of patient-ventilator asynchrony in 60 patients during 30-minute sessions of NIV.³⁶ Frequent asynchronies accounting for more than 10% of the respiratory efforts were present in 43% of the patients. Most of these patients were ventilated with an ICU ventilator with no specific "NIV function" activated, which probably contributed to this high incidence.³⁷ Prolonged insufflation due to delayed cycling was the most frequent asynchrony, seen in about 25% of the patients. When large leaks develop during inspiration, the ventilator continues to deliver pressure because the delivered flow remains above the cycling criterion (also referred to as *expiratory trigger value*), so the cycle does not turn off until a time limit is reached. In this situation, the patient attempts to exhale and can fight against the ventilator because the expiratory valve remains closed, generating ineffective

efforts during persistent insufflation. The magnitude of delayed cycling and the number of ineffective breaths are directly associated to the magnitude of leaks.³⁸ This problem is much more prevalent when using an ICU ventilator with no “NIV” mode but may arise also with NIV-dedicated ventilators. Limiting the total inspiratory pressure by reducing the pressure support and/or the PEEP level may be helpful. Persistent leaks indicate a need for limiting the ventilator insufflation time by increasing the expiratory trigger and/or reducing the maximal inspiratory time.^{35,39} Most of the new-generation intensive-care ventilators and many NIV-dedicated ventilators allow adjustment of the expiratory trigger or maximal inspiratory time.

Expiratory leaks can also generate a pressure drop below the external PEEP level or a drop in expired bias flow, simulating the patient’s effort and triggering a ventilator breath. Auto-triggering may promote a short cycle or a flow distortion because the patient does not generate any effort and “fights” the ventilator. NIV-dedicated ventilators have specially designed algorithms that markedly limit auto-triggering.⁴⁰

Other Modalities

Volume-Targeted Ventilation. Volume-targeted ventilation delivers set flow, inspiratory time, and tidal volume with each breath; inflation pressure varies with the intensity of the patient’s effort. Volume-targeted ventilation is rarely used in ARF because it may induce high peak mask pressures, causing discomfort and leaks, risk of gastric distension, pressure sores, and skin necrosis. Controlled modes may, however, be preferred in patients with apnea and hypopnea or unstable ventilatory drive (pressure- or volume-targeted modes), and volume-targeted modes will be preferred in case of unstable respiratory mechanics or failure of pressure-targeted modes to augment spontaneous breathing.

Negative pressure ventilation is available in a few centers in the world. In acute exacerbations of COPD, it seems to provide better outcomes than conventional invasive MV and may be similar to face mask NIV.⁴¹⁻⁴³ The use of a *helium-oxygen mixture* (heliox) for NIV has received much interest because its decreased density leads to decreased resistance in regions with turbulent flow. There were some early promising results in patients with COPD exacerbations.⁴⁴⁻⁴⁵ Unfortunately, large clinical trials were unable to demonstrate a significant clinical benefit when heliox was compared with a conventional gas mixture during NIV.⁴⁶⁻⁴⁷ One possible reason for these negative results is that the rate of NIV failure has progressively declined in the groups treated with standard air-oxygen mixtures, making it more difficult to demonstrate a difference in favor of heliox.

Proportional assist ventilation (PAV) is a physiologically sound mode designed to deliver ventilatory support in response to the patient’s needs.⁴⁸⁻⁵¹ Several studies have compared PAV to PSV during NIV, and the efficacy of the two techniques appears similar.⁴⁹ The largest prospective randomized trial, by Fernandez-Vivas and associates,⁴⁸ was performed in 117 patients with mixed causes of ARF and showed no difference in clinical outcomes between NIV delivered with PSV or proportional-assist ventilation. PAV was more comfortable, and intolerance was less common.

Noninvasive estimation of resistance and elastance are needed for PAV, and leaks make the settings of this mode particularly difficult during NIV.

Neurally adjusted ventilatory assist (NAVA) is based on the detection and quantification of the *electrical activity of the diaphragm* (EAdi) by means of an esophageal array of bipolar electrodes. NAVA uses the EAdi to control not only the timing but also the amount of pressure delivered. The ventilator is triggered, limited, and cycled-off directly by EAdi. Neural control of mechanical ventilation has the capability of enhancing the synchrony between mechanical ventilation and respiratory muscle activity, hence improving patient comfort. Another advantage is that NAVA should not be affected by leaks. Recently, Beck and colleagues showed, in rabbits, that NAVA can deliver assist that is in synchrony and proportional to EAdi even when a “leaky” noninvasive interface was used.⁵² It has also been tested with a helmet, which covers the entire head, in hypoxemic patients after extubation. In 10 hypoxemic patients after extubation, Cammarota and colleagues⁵³ found that NAVA delivered by helmet improved patient-ventilator interaction and synchrony compared with pressure support ventilation. More work needs to be done to determine whether NAVA can maintain adequate levels of ventilator assistance and ensure harmonious patient ventilator interaction in different kinds of respiratory failure.

VENTILATORS

CPAP Systems

Many systems can be used to deliver CPAP. One of the most frequently used consists of a high-flow generator producing an air/oxygen mixture based on the Venturi effect, with an additional source of oxygen and a mechanical expiratory valve. An inspiratory reservoir and a CPAP water valve or a standard mechanical ICU ventilator in CPAP mode can also be used. The Boussignac CPAP device is a small cylindrical plastic adaptor that fits onto a modified face mask. The system uses the incoming flow of oxygen to generate a turbulent virtual pressure valve in the open expiratory side of the mask. The gas is accelerated and circumferentially enters into the open-ended cylinder, generating air entrainment and positive pressure.⁵⁴⁻⁵⁵

ICU or Specific NIV Ventilators

Because ICU ventilators can become less efficient in the presence of leaks,^{57,62} most manufacturers have developed a specifically designed “NIV mode.” This mode detects leaks and automatically adjusts the inspiratory trigger to avoid auto-triggering and the expiratory cycling criterion to avoid prolonged inspiration.⁴⁰ These new NIV modes reduce several of the asynchronies observed during NIV.^{37,40} NIV can be delivered using ICU ventilators or ventilators specifically dedicated for NIV. In a survey from North America of NIV use,⁵⁶ these NIV-dedicated ventilators were the most frequently used ventilators, accounting for two thirds of cases, whereas CPAP generators represented around 30% and ICU ventilators less than 5%. By contrast, a survey in French ICUs found that an ICU ventilator was used in almost 80% of the cases and NIV and home ventilators represented less than 20% of the cases.³²

NIV ventilators perform well in the presence of leaks,⁵⁷ but important differences exist among NIV ventilators.⁵⁸⁻⁶¹ The advantages of ICU ventilators are better monitoring capabilities and the ability to continue invasive mechanical ventilation and full ventilatory support in the event of ETI. No outcome data, such as NIV success or failure, have been shown to be associated with specific asynchronies but, if an ICU ventilator is used, it seems reasonable to use the dedicated NIV algorithm. Adequate patient monitoring may be essential to assess patient-ventilator interaction, detect leaks, and fine-tune pressure levels. A randomized clinical study showed that careful observation of the airway pressure and flow-time curves on the ventilator screen can detect patient-ventilator asynchronies and accelerate arterial PCO₂ normalization and patient adaptation.⁶³ Whether this also ensures higher NIV success rates remains to be determined.

Airway gas conditioning (i.e., the warming and humidification of the inspired gas) constitutes a physiologic procedure performed by the human airway during normal breathing. When the upper airway is bypassed, as during invasive MV, it is necessary to heat and humidify the gas before delivery. During NIV, gas is transferred to the alveoli through the mouth and nose, but the normal airway gas conditioning mechanisms can be insufficient when there are high-flow, high-airway pressure settings and high inspired oxygen fractions. Artificial heating and humidification are usually necessary because inadequate humidification during NIV can cause damage to the nasal mucosa, induction of high nasal airway and possible difficulty with intubation in cases of NIV failure.⁶⁴⁻⁶⁵ ICU ventilators provide much lower levels of humidity compared with turbine or piston NIV ventilators due to the exclusive use of dry gases, and with ICU ventilators, gas humidification is mandatory. Two types of humidification systems can be used: heated humidifiers or heated and moisture exchanger filters. Firm recommendations cannot be made between the two systems—the humidification ability of moisture exchanger filters is reduced in the presence of leaks,⁶⁵ and their internal volume may impose an additional workload by generating carbon dioxide rebreathing. In patients with hypercapnic respiratory failure, this can diminish the ability of NIV to reduce blood carbon dioxide levels and correct respiratory acidosis.⁶⁶⁻⁶⁷ Leaks, however, may reduce the impact of this problem by removing carbon dioxide-rich gas from the mask. A randomized trial did not find any difference in the rate of NIV failure using a moisture exchanger filter or a heated humidifier on ICU ventilators.⁶⁸ A similar problem of carbon dioxide rebreathing may arise when ventilators (using ambient room air), equipped with a one-line circuit, are used with the minimal level of PEEP allowed on these ventilators.⁶⁹⁻⁷⁰

INTERFACES

The interface is an essential component that differentiates NIV from invasive MV. The interface used to connect the patient to the ventilator is usually a full face mask covering both the nose and the mouth. An important distinction concerns leaky masks for single-circuit ventilators versus masks without intentional leaks for double-circuit or for a single circuit equipped with an expiratory valve. New masks

are often made of two or more parts hooked or glued together: a frame made of stiff transparent material and a cushion of soft material to seal the frame against patient face.⁷¹⁻⁷² Improvements have been realized by using different cushions with new materials (such as hydrogel), by improving the fixation system with particular attention to skin and eye care, and by increasing the number of the attachment points permitting a more uniform distribution of pressure.

Masks can be used for the nose or the mouth. Nasal interfaces are available, but their use in ICU patients frequently results in major leakage through the mouth that diminishes the effectiveness of NIV and promotes asynchrony and discomfort.⁷³⁻⁷⁴ There are two existing types of nasal interfaces: nasal masks, designed to cover either the full nose or the nares only, and nasal “pillows” directly inserted into the nostril.⁷⁵ Like oral interfaces, the nasal interfaces are mostly used for chronic NIV.^{71,76} The use of a nasal mask in the ICU leads to mask failure in more than 70% of the patients.⁷⁷ Oral interfaces are associated with significantly more leaks and asynchrony and require better patient cooperation.⁷⁸

Full face masks could be either oronasal or total face; both appear to have similar efficacy and patient tolerance.⁷⁹ Large masks enclosing the entire face or head have been developed.⁸⁰⁻⁸¹ Interestingly, clinical physiologic studies comparing these large masks to standard full face masks have shown comparable efficacy in terms of respiratory muscle unloading, suggesting that the theoretical risk of rebreathing associated with the large internal volume may be small or nonexistent in clinical practice.^{78,82-91} Fraticelli and colleagues⁷⁸ studied the effect of four interfaces—a mouthpiece, a facial mask, and two oronasal interfaces (with small and large internal volume)—on minute ventilation, gas exchange, and work of breathing of patients with acute respiratory failure. Despite large variations in the internal volume of the devices, the authors found no difference in patients’ respiratory effort, arterial blood gases, and breathing pattern.

Helmets, which cover the entire head, have been tested. Use of a helmet was originally proposed for CPAP primarily for patients with acute hypoxemic respiratory failure⁸³⁻⁸⁴; a specifically designed helmet has also been used for NIV.⁸⁵ Helmets may induce more rebreathing than other masks and may be less suitable for patients with hypercapnic respiratory failure.⁸⁶ The helmet requires higher pressures than conventional masks to produce the same efficacy.⁸⁷ Rebreathing with the helmet, compared with other NIV interfaces (two oronasal masks, a total face mask) was studied by Fodil and coauthors⁸²; in this *in vitro* study, the authors showed a large difference between the internal volume of mask (which is about 10 L for the helmet) and the *dynamic effective dead space*, which can be much smaller due to the streaming effect of gases.

The oronasal mask appears to be the best first choice interface. The nasal mask may be comfortable, but because some patients breathe largely through their mouths, outcomes for patients with respiratory distress are usually less favorable. The total/full-face mask has not demonstrated a clear superiority to the oronasal mask in terms of clinical effectiveness and tolerability but is a possible alternative. The helmet can be used as a first-line interface in

experienced hands and for some indications such as pulmonary edema. There is no ideal NIV interface for all patients in all circumstances, and several interfaces should be available at the bedside. With few exceptions (such as the nasal mask and the mouthpiece), interfaces are largely interchangeable in the acute care setting.

INDICATIONS

EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

An international consensus conference published in 2001⁸⁸ recommended that NIV should be considered as the first-line treatment in patients with COPD exacerbations; more recently, different national guidelines advocated this practice.⁸⁹ A Cochrane database review demonstrated that, in these patients, NIV use was associated with decrease in mortality, reduced need for intubation, less treatment failure, faster clinical improvement, and a reduction in treatment complications and length of hospital stay.⁹⁰ The Global Initiative for Chronic Obstructive Lung Disease in 2013 reinforced the importance of NIV when treating COPD exacerbations based on the high success rate (80% to 85%).⁹¹

The first evidence that NIV markedly reduced the need for ETI came from a case-control series reported in 1990.¹ Subsequently, several prospective randomized trials confirmed that NIV reduced the need for ETI and the rate of complications, shortened the length of stay, and improved survival in patients with COPD.⁹²⁻⁹⁸ Studies conducted in the United Kingdom established that NIV was also effective in non-ICU settings.^{92,98} In the largest ICU study, Brochard and colleagues⁹⁹ randomized 85 patients with COPD to treatment with or without face mask PSV. The ETI rate was 74% in the group that received standard medical treatment and 26% in the NIV group. Benefits in the NIV group included a decreased rate of complications during the ICU stay, a shorter length of hospital stay, and, more importantly, a significant reduction in mortality (from 29% to 9%). The overall decrease in mortality was due to reductions in the need for ETI and in various ICU-related complications.

Plant and colleagues¹⁰⁰ conducted a prospective multicenter randomized trial comparing standard therapy alone (control group) to NIV in 236 COPD patients admitted to general respiratory wards for ARF. Treatment failure (defined as fulfillment of criteria for ARF) was more common in the control group (27%) than in the NIV group (15%), and NIV was associated with a lower in-hospital mortality rate. These studies made clear that early NIV should be an important component of first-line therapy of COPD exacerbations to prevent further deterioration.

A recent study used a large database¹⁰¹ and analyzed more than 7 million admissions for acute exacerbations of COPD in the United States from 1998 to 2008, of which 612,650 (8.1%) required respiratory support. The authors showed an increase in the use of NIV (from 1% to 4.5% of all admissions) and a 42% decline in invasive MV (from 6% to 3.5% of all admissions). Intubation and in-hospital mortality declined during this period. By 2008, NIV was used more frequently than invasive MV as the first-line therapy for acute exacerbations of COPD.

A learning curve exists for NIV. In a single-center study by Carlucci and colleagues,¹⁰² the NIV success rate remained stable over the study period but patients treated with NIV during the last few years of the study period had more severe disease, higher arterial PCO₂ levels, and lower pH values. This indirectly reflected that more severe exacerbations could be treated with NIV out of the ICU over the years. In an 8-year study performed in a French university referral hospital, NIV use increased gradually, in step with a decline in conventional treatment with ETI.⁶ In parallel, the nosocomial infection and mortality rates significantly diminished.

NIV for patients with COPD exacerbations can be administered by experienced staff outside the ICU, but it is recommended that the most severely affected patients, such as those with an arterial pH less than 7.30 on admission,¹⁰⁰ should be managed in the ICU. A low pH, marked mental status alterations at NIV initiation, presence of comorbidities, and a high severity score are associated with a higher rate of early NIV failure.³³ A few patients experience late or secondary failure after an initial improvement.¹⁰³ In a recent observational prospective study, the presence of pneumonia and the serum albumin as an indicator of patient's nutritional status were identified as the most important determinants of NIV outcome in COPD patients.^{103a} These patients with late NIV failure (need for intubation after 72 hours or persistent dependence on NIV) may have more severe disease and exhibit sleep deprivation.¹⁰³⁻¹⁰⁴ A longer time from onset of the COPD exacerbation to NIV initiation may also reduce the likelihood of success. Every effort should be made to deliver NIV early, and close monitoring is necessary when NIV is initiated at a late phase, a situation where its use is less effective.¹⁰⁵ Several observational studies and one small randomized trial showed positive clinical results in patients with hypercapnic encephalopathy due to COPD exacerbation and suggested that even at this stage it may be worth trying to "wake up" the patient with NIV.¹⁰⁶⁻¹⁰⁷

A few studies have suggested that NIV use may be associated with higher 1-year survival rates, as compared with standard ICU therapy or invasive MV.^{105,108-110} These studies have a number of methodologic flaws, but the consistency of the results suggests interesting long-term benefits of NIV. Some authors argue for continuing NIV at home after exacerbations. One of the benefits could be a reduction of the readmission rate, as suggested in one small randomized controlled trial.¹¹¹⁻¹¹²

In conclusion, NIV offers many advantages over standard medical therapy and invasive MV to treat exacerbations of COPD and there is strong evidence that NIV is cost effective, being both more efficient and cheaper compared with standard therapy alone.^{22,113}

ASTHMA

NIV can be used in asthmatic patients not responding well to medical treatment, and there is a growing interest in this technique and its combination with aerosol therapy.¹¹⁴ A recent report using a large U.S. database indicated that there has been a substantial increase in the use of mechanical ventilation for acute asthma over the past years, accompanied by a shift from invasive mechanical ventilation to NIV.¹¹⁵ Only a few small randomized trials have rigorously

evaluated the benefits. Two cohort studies found beneficial short-term effects of NIV in asthmatic patients whose condition was deteriorating despite medical therapy.¹¹⁶⁻¹¹⁷ In a randomized trial,¹¹⁸ all patients treated for acute asthma were randomized to either NIV with two different levels of pressure support and PEEP or to oxygen. A greater reduction in dyspnea was observed in the NIV groups compared with the control group. The NIV group with the higher pressure demonstrated a significant improvement in the forced expired volume in 1 second compared with the control group. Two other trials found faster improvement in lung function using NIV with a shorter length of stay or a reduced need for hospitalization.¹¹⁹⁻¹²⁰

EXACERBATION OF OTHER CHRONIC LUNG DISEASES

All forms of acute-on-chronic ventilatory failure share several common pathophysiologic pathways. NIV seems to be an interesting option in patients with restrictive lung disease, especially when respiratory system compliance is still preserved.¹²¹ A recent large cohort study compared the efficacy of NIV in patients with COPD ($n = 543$) and in patients with acute respiratory failure due to obesity hypoventilation syndrome ($n = 173$).¹²² Patients with obesity hypoventilation had fewer late NIV failures, but overall survival adjusted for confounders, length of stay, and hospital readmission were similar in both groups. In patients with COPD, obesity was associated with less late NIV failure and hospital readmission. These data strongly argue for the fact that patients with obesity hypoventilation syndrome can be treated with NIV during an episode of acute exacerbation with similar efficacy and better outcomes than patients with COPD.

CARDIOGENIC PULMONARY EDEMA

Clinical Results

The first evidence of therapeutic efficacy of positive pressure use during acute CPE was shown in 1985.¹²³ Rasanen and colleagues¹²³ randomized 40 patients with acute CPE and respiratory failure to conventional therapy or face mask CPAP of 10 cm H₂O. The interventional group demonstrated better improvement of gas exchange, a decrease of respiratory work, and a tendency to a lower intubation rate. Subsequently, other randomized trials conducted in the emergency department or in the ICU comparing CPAP with pressure support plus PEEP (PSV plus PEEP) with standard therapy found that the two techniques improved arterial blood gases and respiratory rate and significantly reduced the rate of ETI.^{19,124-126}

Recently published guidelines¹²⁷ recommend NIV use in patients with acute CPE, dyspnea, and respiratory rate greater than 20 breaths/min to improve clinical symptoms. Nevertheless, intubation is often the best option in patients with cardiogenic shock and low blood pressure (systolic blood pressure < 85 mm Hg) or altered level of consciousness. In more recent European guidelines, the level of evidence (level B-class IIa) for NIV use to treat acute CPE¹²⁷ was lower than that formerly recommended. This decrease in the level of recommendation was mainly due to the publication of the 3CPO trial,¹²⁸ the largest multicenter con-

trolled study to date. It was performed in the emergency department and evaluated the possible benefits of NIV in acute CPE. Patients admitted with a clinical and radiologic diagnosis of acute CPE, respiratory rate greater than 20 breaths/min and pH less than 7.35 were randomized to conventional pharmacologic therapy plus NIV (CPAP or PSV plus PEEP) or standard oxygen therapy. The study included 1069 patients and showed that NIV was associated with faster reduction in dyspnea, heart rate, and earlier resolution of metabolic abnormalities than standard oxygen therapy. Intubation rates were low and not different between groups (3%), and 7- and 30-day mortality rates (9.8% vs. 9.5% and 16.4% vs. 15.2%) were similar in the control and NIV groups, respectively. The control group was characterized by a high incidence of crossover (15%) to PSV plus PEEP or CPAP. Without this crossover, a much higher rate of intubation might have been observed in the oxygen group. Other study limitations were (1) severely ill patients, who required "lifesaving or emergency intervention," were excluded and might have benefited from NIV; (2) patients had mild hypoxemia; and (3) a low intubation rate was observed.

A more recent multicenter clinical trial of 207 patients with acute CPE¹²⁹ compared oxygen therapy at 15 L/min to 7.5 to 10 cm H₂O CPAP initiated outside the hospital and continued in-hospital in the ICU. The CPAP intervention group demonstrated a significantly greater and faster resolution of clinical symptoms, as well as a lower presence of intubation criteria and a tendency for a lower death rate at day 7, although this last parameter was not statistically different.

Most studies indicating benefits of CPAP or PSV plus PEEP included patients who, on average, had hypercapnia and acidosis indicating acute frank ventilatory failure.^{19-20,124,126} A relatively large multicenter study conducted by Nava and colleagues¹³⁰ in patients with CPE found major benefits of NIV only in the subgroup of hypercapnic patients, with no significant benefits in terms of ETI rate or outcome in the overall population that included both hypercapnic and normocapnic patients. Despite the long use of NIV in CPE and the publication of guidelines, there is considerable heterogeneity among hospitals regarding its clinical application. Notably, it seems that the higher the experience of the hospital in the use of NIV in CPE the greater the benefit in terms of avoiding patient intubation.^{130a}

Choice Between CPAP or Pressure Support Plus PEEP

In clinical practice, CPAP is often considered to be easier to apply compared with pressure support plus PEEP. In some small studies in patients with CPE, PSV plus PEEP was more effective than CPAP regarding improvement in physiologic parameters¹⁷ or rapidity of respiratory failure amelioration,¹³¹ but not different in mortality rate or tracheal intubation. In the 3CPO trial¹²⁸ both modes of NIV (CPAP or PSV plus PEEP) had similar clinical outcomes. Another clinical study comparing both modes of NIV demonstrated similar results.¹³²

In summary, NIV use during CPE seems to be an efficient approach that could reduce mortality, especially in the subgroup presenting with hypercapnia. Conventional medical therapy remains the cornerstone, and NIV, whether it is

performed with CPAP or PSV plus PEEP, should be combined with it as soon as possible. CPAP and PSV plus PEEP seem to have similar effects, both in physiologic end points and in clinical outcome, and CPAP can be recommended as a first-line treatment. PSV plus PEEP may be preferred to CPAP in patients with hypercapnia, often associated with comorbidities like COPD or obesity, who are at increased risk of intubation.

HYPOXEMIC ACUTE RESPIRATORY FAILURE

NIV to Prevent Intubation in de Novo Respiratory Failure

The use of NIV in patients with mixed causes of hypoxemic ARF remains debatable. Contrasting results exist between the benefits observed in short-term physiologic studies and in some randomized controlled trials, as well as the high rates of failure in observational studies and the risk of delaying intubation.¹³³ For instance, one trial in patients with severe pneumonia showed that NIV reduced intubation rate (21% vs. 50%) and ICU length of stay,⁹⁷ but this study is often quoted to stress that this benefit was entirely driven by the subgroup of hypercapnic COPD patients. Other RCTs, in nonhypercapnic patients, did not demonstrate any benefit for this indication.¹³⁴ By contrast, NIV has also clearly been shown to be beneficial in selected patients with a variety of patterns of hypoxemic respiratory failure,^{9,97,135-140} reducing the need for ETI and improving outcomes.^{139,141-143} In this setting, PSV plus PEEP seems much more efficient than CPAP.

In a large randomized controlled trial of patients with hypoxemic ARF, Delclaux and colleagues¹³⁴ showed that the use of CPAP resulted in a greater subjective response and improvement in oxygenation at 1 hour but CPAP did not reduce the need for ETI or improve any clinical outcome. In addition, a few patients suffered from specific complications only observed in the CPAP group, including cardiac arrest at the time of intubation or at the time of mask removal. Antonelli and coworkers¹⁴⁴ showed that NIV using PSV plus PEEP was highly beneficial and associated with fewer adverse effects compared with conventional mechanical ventilation in hypoxemic patients ($\text{PaO}_2/\text{FiO}_2 < 200$ mm Hg). These patients did not have COPD, hemodynamic instability, or neurologic impairment and were randomized when they reached predefined criteria for ETI. Improvements in oxygenation were similar with the two approaches. Despite a 30% failure rate, patients treated with NIV had overall shorter durations of ventilation and ICU stays and experienced fewer complications.

A study performed in three centers by Ferrer and colleagues¹⁴⁰ also included normocapnic patients with persistent hypoxemic ARF and used PSV plus PEEP compared with a standard medical treatment with high-concentration oxygen. Patient selection was rigorous, necessitating clinical cooperation of the patient, no alteration in the state of consciousness, and the absence of organ dysfunction, abundant secretions, cardiac arrhythmias, or ischemia. Patients could have pneumonia, CPE, or immunocompromise. NIV reduced the intubation rate by half and ICU mortality from 39% to 18%. These significant effects were found in the group of patients with pneumonia. Extrapolating

these results to individual patients requires the same careful selection process, with exclusion of patients with contraindications. The presence of shock, loss of consciousness, or major secretions should be considered to be contraindications.

However, observational studies describing the use of NIV in pneumonia have often shown high rates of failure.^{137,145-147} Selection of patients, skills, and experience in the application of NIV and in the decision for intubation may all have contributed to these differences. Great care is required when applying NIV to hypoxemic patients because of the possible disadvantages.^{134,148} In a large observational study on the use of NIV in France, Demoule and colleagues¹⁴⁸ compared the overall results of NIV in patients with acute exacerbation of chronic cardiac or respiratory failure with those with hypoxemic de novo respiratory failure. In the “acute-on-chronic” group, the use of NIV was significantly associated with a better outcome (adjusted OR 0.33). In the de novo group, the use of NIV was not significantly associated with a better or worse outcome. This suggests that NIV should not be used when the risk of failure is high and intubation should not be delayed when clinical signs and symptoms suggest impending NIV failure.¹⁴⁹

In sum, finding which subgroup of hypoxemic patients is highly likely to benefit from NIV with minimal risk is still a field for investigation. The following categories of patients have been more carefully studied.

NIV for ARDS

Observational studies and subgroup analysis of randomized controlled trials identified ARDS as a strong predictor of NIV failure.^{147,150-153} A multicenter survey¹⁵⁴ evaluated NIV as first-line therapy in early ARDS patients and found that a higher severity score and a ratio of arterial PO_2/FiO_2 less than or equal to 175 mm Hg 1 hour after initiation of NPPV were independently associated with NIV failure. This survey showed that, with NIV use, ETI was avoided in no more than 50% of patients, even in experienced centers. A recent small prospective, multicenter, randomized controlled trial¹⁵⁵ included 40 patients with mild ARDS. Fewer patients were intubated in the NIV group compared with the control group, and NIV use was associated with less organ failure. The recent Berlin definition of ARDS suggested that NIV may be indicated only in mild ARDS, and not in severe and moderate ARDS, but also emphasized that the role of NIV in ARDS has to be further evaluated.¹⁵⁶ NIV failure in ARDS patients is highly predictable in case of shock, metabolic acidosis, high severity scores of illness, and a greater degree of hypoxemia.¹⁵³

With the H1N1 pandemic, a large number of patients with severe respiratory failure were admitted into ICUs over the world. Many patients developed ARDS requiring intubation and mechanical ventilation and even extracorporeal membrane oxygenation,¹⁵⁷ but NIV was also used widely in these patients with relatively favorable results, albeit with a high rate of failure.¹⁵⁸⁻¹⁶¹ This aspect is interesting because after the SARS experience, a concern was raised about the risk of viral transmission during intubation or while using NIV ventilation.^{162,163} Viral transmission did not seem to be an issue in the setting of H1N1, but more data are necessary to completely address this issue.

NIV in Immunocompromised Patients

The prognosis of immunocompromised patients with ARF has clearly improved in the past 15 years. Invasive MV was repeatedly identified as an independent mortality predictor in this population, and the potential to reduce infectious complications was a strong rationale for NIV use in immunocompromised patients.^{9,139,141,143} NIV was shown to be beneficial in cancer patients with respiratory failure, and decreased mortality.¹⁴¹ The first randomized trial in hypoxemic ARF after solid organ transplantation assessed the role of NIV in 40 patients⁹: NIV reduced intubation rate from 70% to 20%, ICU length of stay in survivors, and ICU mortality (20% vs. 50%), with no difference in hospital mortality. Another trial confirmed the benefit of a sequential use of NIV at an early stage in 52 immunocompromised patients with respiratory failure and pulmonary opacities.¹³⁹ Intubation rates (46% vs. 77%) and ICU mortality (38% vs. 69%) were reduced in the NIV group. Similarly, early preventive use of CPAP for neutropenic patients with mild respiratory dysfunction prevented subsequent evolution to frank respiratory failure, ICU admission, and the need for intubation.¹⁶⁴

The generalizability of the results coming from expert centers and their applicability to real-life practice has often been discussed.²² In an observational study in Italy, NIV was used in 21% of patients with hematologic malignancies requiring ventilatory support.¹⁵⁰ Despite a high failure rate of 46%, NIV was associated with lower mortality than invasive mechanical ventilation after adjustment using a propensity score. Patients intubated from the beginning had a higher severity score but a lower mortality than patients who failed NIV (50% vs. 61%). A trial of NIV as a first-line intervention in selected immunocompromised patients with hypoxemic respiratory failure appears justified but, as stated in a recent editorial, the message is “don’t push too hard!”¹⁶⁵

In summary, the use of NIV in hypoxemic respiratory failure is supported by a strong rationale. The literature has yielded some conflicting results that probably reflect both the heterogeneity of the underlying diagnoses and some real difficulties in the use of the technique in these patients. Selecting the appropriate patients with pneumonia for a trial of NIV will therefore depend on the experience of the team, on the patients’ cooperation, and on excluding patients with hemodynamic instability, mental status alteration, or abundant secretions.

PREVENTION OF POSTOPERATIVE COMPLICATIONS

Respiratory complications constitute a major cause of morbidity after surgery, and mortality is often related to reintubation and complications of mechanical ventilation. NIV is becoming increasingly popular for the prevention or treatment of postoperative respiratory complications.¹⁶⁶⁻¹⁶⁹

Pathophysiology of Postoperative Respiratory Complications

After thoracic or upper abdominal surgery, the patient’s pulmonary condition can worsen due to residual anesthe-

sia or pain. This is associated with a large reduction in functional residual capacity and transient diaphragmatic dysfunction. Perioperative fluid overload, transfusion-related acute lung injury, inflammation, sepsis, and aspiration may coexist and further worsen respiratory function. Respiratory deficits are maximal in the first hours after surgery and generally recede after 1 or 2 weeks. Because it can restore lung volume, CPAP is frequently used in postoperative patients.¹⁶⁹ Some authors advocate the use of postoperative NIV (CPAP or PSV plus PEEP) for both prophylactic and treatment purposes.^{168,170}

Thoracic Surgery

In the postoperative period following lung resection, pulmonary complications are the leading cause of death. Postoperative MV increases the risk of bronchial stump disruption, bronchopleural fistula, persistent air leaks, and pulmonary infection. NIV was proposed to prevent reintubation, atelectasis, and infection postoperatively after chest surgery.¹⁷¹ Prophylactic use of NIV preoperatively and postoperatively was shown to improve spirometry and oxygenation in 32 patients at high risk of complications after lung resection surgery.¹⁷² Comparable results have been obtained with prophylactic use of NIV following cardiac surgery: The largest study randomized 500 patients scheduled for elective cardiac surgery to nasal CPAP for at least 6 hours or standard care.¹⁷³ The number of pulmonary complications was significantly reduced within the CPAP group, but the reintubation rate was low in both groups. Similar results have been obtained after thoraco-abdominal aortic aneurysm repair.¹⁷⁴

NIV has also been used for the treatment of respiratory failure after lung surgery. Auriant and colleagues¹⁴² performed a controlled trial in which 48 patients with ARF after lung resection were randomly assigned to NIV or standard treatment. NIV significantly decreased the ETI rate (50% vs. 21%) and hospital mortality (13% vs. 38%), mostly by preventing intubation-related complications. A recent multicenter trial, however, was unable to find any benefit of a systematic administration of NIV in obstructive patients submitted for lung resection.¹⁷⁵ Similarly, the beneficial effect of NIV (lower intubation rate) was suggested in patients with ARF after esophagectomy; in addition, there was no increase in anastomotic leakage.¹⁷⁶⁻¹⁷⁷ Because the risk of surgical complications induced by positive pressure ventilation is unclear, it is probably wise to keep airway pressures at the lowest effective level.¹⁷⁶

Abdominal Surgery

NIV can potentially counteract several of the anesthetic and surgical consequences that can explain the high incidence of postoperative hypoxemia after abdominal surgery. Restoring lung volume, preventing atelectasis, improving gas exchange, and decreasing the work of breathing may be achieved through different forms of NIV, including CPAP.¹⁶⁷⁻¹⁶⁹ Squadrone and colleagues¹⁷⁰ showed that early CPAP delivered by helmet in 209 patients with arterial PO_2/FiO_2 less than 300 at 1 hour after elective major abdominal surgery was able to reduce the intubation rate (1% vs. 10%, $P=0.005$), as well as the incidence of pneumonia and sepsis. The ICU and hospital length of stay did not significantly differ. NIV was used in this study with the intention

of preventing overt deterioration and more serious complications, suggesting that early use is ideal.

Jaber and colleagues¹⁶⁷ reported that ETI was avoided in 48/72 (67%) patients treated with NIV for acute respiratory failure after abdominal surgery. Arterial PO_2/FIO_2 ratio increased and respiratory rate decreased only in patients who were successfully treated with NIV and avoided ETI. A similar rate of NIV failure in postoperative patients has also been reported in other observational studies.¹⁷⁸

Trauma Patients

Trauma patients present a high risk of pulmonary dysfunction with subsequent hypoxemic respiratory failure. Compared with a high-flow oxygen mask, the use of NIV has been shown to reduce the intubation rate (12% vs. 40%) and hospital length of stay in a single-center randomized controlled trial of 50 patients with persistent hypoxemia within the first 48 hours after thoracic trauma.¹⁷⁹ NIV may constitute a useful adjunct to manage hypoxemic patients with chest trauma, but adequate analgesia remains of paramount importance in this situation. Larger trials are required to clarify the role of NIV for this indication.

DO-NOT-INTUBATE PATIENTS

NIV is now used frequently in patients in whom intubation is not desirable.¹⁸⁰⁻¹⁸⁶ Several reports have described the effects of NIV in patients with ARF who were poor candidates for ETI because of advanced age, debilitation, or a “do-not-resuscitate” order.^{10-11,180,185-186} This approach to NIV is feasible and well tolerated, with an overall survival rate of 50% to 70%, depending on the patient population.¹⁸⁰⁻¹⁸¹ An important distinction should be made between NIV administered as the upper limit of care versus NIV as part of palliative care to relieve dyspnea at the end of life.^{180,184} Regarding the first indication, NIV offers an interesting possibility to improve a substantial number of patients. Outcomes are better in patients with COPD or pulmonary edema than in purely hypoxemic patients.^{181,183,185} In a large observational multicenter trial, Azoulay and coworkers¹⁸¹ assessed patients’ mortality, health-related quality of life and for patients and relatives, signs of anxiety, depression, and posttraumatic stress at 90 days. They compared patients receiving NIV as a ceiling of therapy with patients with no treatment limitation. Hospital mortality in the do-not-intubate group was 46%, but there was no decline at 90 days in health-related quality of life and there were no differences between the two groups in terms of mental health, anxiety, depression, or posttraumatic stress disorder of patients and their relatives. For NIV used in purely palliative care, we have only limited information on its real benefit.^{182,184}

DURING THE WEANING PROCESS AND POST-EXTUBATION

Weaning

A number of patients with COPD require ETI because they fail NIV, have a contraindication to NIV (such as a need for surgery), or exhibit criteria for immediate ETI. When there

is a need for prolonged ventilatory assistance, these patients can be switched to NIV after a few days of ETI to reduce the time of intubation.^{187,188,188a} This approach was examined in several trials with contradictory results.¹⁸⁷⁻¹⁹⁰ Times to extubation were usually reduced, but this was not consistently translated into a reduction in hospital and ICU stay and mortality.¹⁹⁰⁻¹⁹¹ No difference between early NIV weaning and the standard weaning process was reported in several studies.^{188,192} Complications associated with mechanical ventilation, notably pneumonia and sepsis, were either reduced or remained unaffected by this strategy.¹⁹⁰⁻¹⁹² In the most recent multicenter trial, extubation followed by NIV or extubation followed by standard oxygen therapy were identical with respect to weaning success and reintubation.¹⁸⁹ On the basis of the current evidence, NIV cannot be recommended as an alternative to the standard weaning process.

Post-extubation

NIV has been proposed as a way to minimize reintubations in the approximately 10% to 20% of critically ill patients who fail extubation, even after fulfilling all weaning criteria and having successfully completed a weaning trial.¹⁹³⁻¹⁹⁴ The physiologic rationale for this approach in patients with COPD was well demonstrated by Vitacca and coworkers,¹⁹⁵ who showed equivalent values of the work of breathing under the same ventilatory support delivered before extubation or with NIV after extubation. Several studies addressed the role of NIV in preventing reintubation with unequivocal results.¹⁹⁶⁻¹⁹⁷ When post-extubation respiratory failure has developed, delivering NIV is often futile and, indeed, may delay reintubation and increase mortality, as suggested by a large multicenter trial of Esteban and associates.¹⁹⁷⁻¹⁹⁸ By contrast, early delivery of NIV after extubation to prevent subsequent respiratory failure in patients at risk seems to be useful.^{198a} In patients at high risk of extubation failure, NIV was demonstrated to prevent post-extubation respiratory failure and reintubation in several trials.

A survival benefit of preventive NIV was demonstrated in patients who were hypercapnic during the weaning test.¹⁹⁹⁻²⁰⁰ Intubation rates and mortality have been shown to be reduced in high-risk patients (i.e., older than age 65 with cardiac or respiratory comorbidities).^{196,201} These beneficial effects are not observed if NIV is applied routinely in all extubated patients as shown by Su and coworkers,²⁰² who randomized 406 unselected patients to either NIV or supplemental O_2 mask, early following their extubation. They did not observe any difference in terms of reintubation or mortality rates. In conclusion, in the post-extubation period, NIV can be useful provided the appropriate patient is selected: risk factors for reintubation include underlying cardiac and respiratory disease and/or hypercapnia during the weaning test. NIV should be applied immediately after extubation and before development of respiratory failure.

PREVENTIVE USE DURING PROCEDURES

Bronchoscopy

Flexible bronchoscopy is a relatively invasive procedure with an increased risk of complications in critically ill

patients.²⁰³ Bronchoscopy increases work of breathing in spontaneously breathing patients and leads to a decrease in arterial PO_2 by 10 to 20 mm Hg that can persist or even worsen for a few hours after the procedure. Saline instillation for bronchoalveolar lavage and repeated suctioning can lead to a reduction in end-expiratory lung volume. Several feasibility studies showed that NIV with different interfaces can be useful during bronchoscopy in at-risk patients.²⁰⁴⁻²⁰⁷ NIV can prevent alveolar derecruitment and compensate for the extra work of breathing imposed by the procedure. In a randomized trial of 30 hypoxemic patients, CPAP reduced desaturations and the incidence of respiratory failure necessitating ventilatory support (1 vs. 7 patients in the oxygen group).²⁰⁷ In another trial of 26 hypoxemic patients, during bronchoscopy, arterial PO_2/FiO_2 ratio increased by 82% in the NIV group and decreased by 10% in the standard oxygen group.²⁰⁵ NIV can help to maintain oxygenation in hypoxemic patients undergoing bronchoscopy. This may translate into a reduction of procedure-related intubations, although more studies are necessary to answer this question.

Endotracheal Intubation

Severe hypoxemia during intubation of hypoxemic patients is common, and the standard bag-mask preoxygenation procedure is often not effective. Baillard and colleagues²⁰⁸ evaluated 53 patients with significant hypoxemia (arterial $PO_2 < 100$ mm Hg while on a high FiO_2 mask) who required ETI in the ICU. The patients were allocated to 3 minutes of preoxygenation, before ETI, performed using a nonbreathing bag-valve mask (control group), or PSV plus PEEP (NIV group) used as a preoxygenation method. The NIV group had a statistically significant improvement in pulse oximetry and arterial PO_2 levels with a lower incidence of pulse oximetry saturation values below 80% during the ETI procedure. NIV intolerance requiring its interruption was not observed. A recent review²⁰⁹ proposed that NIV should be

used for preoxygenation and ventilation in patients who cannot reach oxygen saturation greater than 93% to 95% with high FiO_2 .

HOME NONINVASIVE VENTILATION

Epidemiology

Home NIV refers to the long-term (>3 months) daily application of MV in the home setting through a nasal, oral, or oronasal interface.²¹⁰ Prescriptions for home NIV have markedly increased over the past decades as a result of the increasing prevalence of COPD and *obesity-hypoventilation syndrome* (OHS), although home NIV in COPD patients remains a subject of debate (Table 102-3). Major technological improvements in ventilators and interfaces, with a progressive shift from volume-cycled to less expensive, lighter, and often more comfortable pressure-cycled ventilators, have also contributed to accelerating this approach.²¹⁰⁻²¹¹ The EuroVent Survey²¹⁰ studied patterns of home ventilator use in 16 European countries. The prevalence of patients receiving long-term ventilation varied widely among countries, ranging from 1 to 17/100,000 with an average of 6.6/100,000. Similarly, the relative proportion of patients with neuromuscular, thoracic cage, or lung/airway disorders also differed markedly. Neuromuscular and chest wall disorders were the main indications for NIV in northern Europe, whereas NIV for lung/airway disease was more frequent in southern Europe. Because the prevalence of these conditions presumably does not vary substantially, different patterns of home NIV use probably reflect national policies and differences in the allocation of available resources. Although a similar survey is not available for the U.S. population, extrapolation of the same prevalence suggests that more than 20,000 patients are currently using home NIV in the United States.²¹²

Table 102-3 Recommendations for the Use of Home Noninvasive Ventilation During Chronic Respiratory Failure According to the Type of Disease

Type of Disease	Examples	Benefits
RESTRICTIVE DISORDERS	Obesity hypoventilation syndrome Chest wall disorders Kyphoscoliosis Tuberculosis sequelae Neuromuscular Duchenne muscular dystrophy, poliomyelitis sequelae, ALS, cervical spinal cord injury, phrenic nerve paralysis. Rarely: myositis, acid maltase deficiency	Major impact on survival, health care utilization, respiratory and sleep symptoms, quality of life.
OBSTRUCTIVE DISORDERS	COPD Overlap syndrome Bronchiectasis and cystic fibrosis	Insufficient evidence to promote the systematic use of home NIV in stable hypercapnic COPD. One RCT with improved survival at the expense of reduced health-related quality of life. Good evidence to promote positive pressure treatment in overlap syndrome. A "bridge to transplantation" in cystic fibrosis.
OTHER CONDITIONS	Respiratory center depressant drugs, neurologic conditions (Arnold-Chiari, tumors, infection, stroke, or congenital central hypoventilation)	

ALS, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary disease; RCT, randomized clinical trial.

This section reviews the pathophysiology of respiratory failure in lung disease, the main indications for home NIV, and provides some details on three major indications (i.e., *neuromuscular diseases* [NMDs], OHS, and COPD). Monitoring of home NIV is also discussed.

Pathophysiology

Chronic hypoventilation develops when the respiratory system is unable to cope with the metabolic production of carbon dioxide as a result of pathologic changes in respiratory drive or respiratory pump failure (e.g., NMD, chest wall diseases), or both, as in patients with OHS. In chest wall and NMD, a typical vicious circle of decline begins with hypoventilation during rapid eye movement sleep, and HCO_3^- retention. As diaphragm dysfunction progresses, hypoventilation appears during non-rapid eye movement sleep and progresses to daytime hypercapnia.²¹³ The clinical course in COPD is more often punctuated with episodes of acute-on-chronic respiratory failure related to chest infections. Therefore aims and targets of home NIV may not be necessarily the same for all disease categories.

Indications for Home Noninvasive Ventilation

Subjects with a condition known to be associated with alveolar hypoventilation should undergo regular workups to determine whether they are eligible for home NIV. Patients should be questioned specifically to see if they have early symptoms suggestive of nocturnal hypoventilation,²¹⁴ such as excessive daytime sleepiness, fatigue, morning headaches, cognitive dysfunction, depression, and dyspnea.²¹⁵ In COPD, an indication for NIV takes into account not only the presence of symptoms of chronic hypercapnia but also the frequency and severity of exacerbations.²¹⁵ Patients should undergo a detailed physiologic assessment to detect nocturnal hypoventilation.

The *American Academy of Sleep Medicine* (AASM) recently²¹⁶ defined hypoventilation during sleep as (1) arterial carbon dioxide (or a surrogate such as transcutaneous or end-tidal PCO_2) > 55 mm Hg for ≥ 10 minutes or (2) an increase in $\text{PCO}_2 > 10$ mm Hg from awake supine value to a value exceeding 50 mm Hg for ≥ 10 minutes. Transcutaneous oximetry²¹⁷ has undergone recent improvements in ease of use and software. It is considered reliable for clinical use and allows for early detection and quantification of nocturnal hypoventilation without requiring arterial blood sampling. In addition to monitoring of early symptoms and detection of sleep hypoventilation, regular assessment of respiratory function and inspiratory muscle strength is essential for the decision to implement NIV electively for the prevention of ARF, especially in NMD. Measuring vital capacity is highly reproducible, and decreases in vital capacity below 50% predicted should lead to further investigations; the threshold may vary according to the underlying neuromuscular disorder. Measurement of supine vital capacity is a sensitive marker of diaphragmatic dysfunction,²¹⁸ and a fall greater than 15% when comparing values sitting versus supine correlates well with orthopnea²¹⁹; a decrease of greater than 20% is highly suggestive of diaphragmatic dysfunction. Inspiratory muscle strength (sniff nasal inspiratory pressure and maximal inspiratory mouth pressure) can be easily assessed with inexpensive portable devices. The former may be easier to perform in

NMD, but both measurements are complementary. A negative pressure lower than -70 cm H_2O for men and -60 cm H_2O for women reasonably excludes significant inspiratory muscle weakness.²²⁰

Special Features in Neuromuscular Disease

The clinical course of respiratory failure in NMD is dictated by the natural history of the underlying condition. Some patients remain stable for decades with reported survival rates greater than 90% at 5 years,²²¹⁻²²² whereas others are slowly progressive or rapidly fatal. Therefore the timing and frequency of clinical evaluation should take into account the underlying neurologic diagnosis. In NMD, an indication for home NIV is based on the reversal of early symptoms of hypoventilation and improvement of *quality of life* (QoL) in patients treated by NIV.²²³ Treating subjects with isolated nocturnal hypoventilation may be warranted. In a randomized controlled trial of NIV in NMD patients with nocturnal hypoventilation and daytime normocapnia,²²⁴ most patients in the control group required initiation of NIV within a few months after documentation of sleep hypoventilation. Those treated by NIV had improved health-related QoL, whereas the others were more likely to be admitted with acute-on-chronic ventilator failure (see also Chapter 97).

Amyotrophic lateral sclerosis (ALS) shares many similarities with other NMDs, but its rapid evolution requires a closer follow-up and more frequent respiratory assessment, usually every 3 months. In a randomized trial, Bourke and colleagues demonstrated that initiation of NIV resulted in a significant survival advantage of approximately 7 months in ALS patients with mild to moderate bulbar involvement with either daytime hypercapnia or orthopnea, but did not improve survival in those with severe bulbar involvement.²²⁵ However, even in the latter patients, some aspects of QoL and sleep-related symptoms were improved by NIV, and it may be considered to be an important component of palliative treatment for individuals with advanced disease.

Special Features of Obesity-Hypoventilation Syndrome

OHS refers to the appearance of awake hypercapnia (arterial $\text{PCO}_2 > 45$ mm Hg) in an obese patient (*body mass index* [BMI] > 30 kg/ m^2) after other causes for hypoventilation have been excluded.²²⁶ Prevalence of OHS is estimated to be between 10% and 20% in patients attending sleep clinics²²⁷ and reaches 50% in patients who are hospitalized and have a BMI greater than 50 kg/ m^2 .²²⁸ Sleep-disordered breathing is not part of the definition of OHS, but the prevalence of *obstructive sleep apnea* (OSA) syndrome may be as high as 90% in this patient group. Although global levels of obesity are rising, OHS frequently goes unrecognized until the onset of acute-on-chronic respiratory failure and admission to the ICU.¹²² Pathophysiologic mechanisms include impaired respiratory mechanics with increased work of breathing, upper airway obstruction responsible for sleep-disordered breathing, and decreased respiratory drive leading initially to sleep hypoventilation before overt daytime hypercapnia.²²⁶

The choice of CPAP or *bilevel ventilatory support* (BVS, i.e., CPAP plus intermittent positive pressure) for the initial management of OHS remains a complex issue, especially when patients present with a stable respiratory status,

despite hypercapnia, and a predominant OSA sleep pattern. Piper and colleagues compared CPAP versus BVS in OHS after exclusion of patients with profound nocturnal desaturations or a arterial PCO_2 increase of more than 10 mm Hg, despite optimal in-lab CPAP titration.²²⁹ Daytime blood gases were improved in both groups without differences after 3 months' treatment. Both groups experienced similar improvements in sleepiness, but BVS resulted in a better subjective sleep quality and psychomotor vigilance performance. In contrast, CPAP alone may not be able to resolve hypoventilation in patients with either a high BMI, severe hypoxemia at baseline, or severe restrictive impairment. For this reason, most experts recommend the use of BVS in the acute setting with consideration of a switch to CPAP after an initial period BVS and correction of hypoventilation. In this case, close monitoring of diurnal arterial PCO_2 is warranted.

During NIV, *expiratory positive airway pressure* (EPAP) and *inspiratory airway positive pressure* (IPAP) can be adjusted individually. EPAP is progressively increased to correct apnea and hypopnea and IPAP to correct hypoventilation. Use of a "spontaneous" versus a "spontaneous/timed" mode with a back-up rate is under debate. The 2012 AASM recommendations suggest that the default setting should be "spontaneous" unless central sleep apnea is documented. Recent clinical data have highlighted the importance of setting a back-up respiratory rate when using NIV in OHS with OSA even without previously documented central sleep apnea. Ventilation using the "spontaneous" mode with no back-up rate in OHS subjects on long-term NIV with a "spontaneous/timed" mode resulted in additional respiratory events, mainly central sleep apneic and mixed respiratory events.²³⁰ Data from a randomized crossover trial comparing standard NIV titration versus average volume-assured pressure support confirm that controlled ventilation, defined as less than 50% of patient-triggered cycles, is associated with improved diurnal arterial PCO_2 , better control of nocturnal hypoventilation, and improved health-related QoL at 3 months in a post hoc subgroup analysis.²³¹

OHS is also associated with increased cardiovascular morbidity related to the metabolic syndrome. Evidence concerning the impact of NIV on this aspect of OHS is controversial. In a highly selected group of OHS patients, home NIV was able to improve some aspects of the metabolic syndrome.²³² Conversely, in a randomized trial with unselected OHS patients, inflammatory markers, endothelial function, and arterial stiffness were not improved after 1 month of NIV, whereas blood gas measures and sleep quality did improve.²³³ Thus it appears that positive airway pressure therapy is only part of a multidisciplinary effort to reduce cardiovascular risk in OHS.²³⁴

Home Noninvasive Ventilation for Chronic Hypercapnic COPD

In contrast to home NIV treatment for patients with restrictive lung diseases associated with chest wall disorders or NMD, evidence for the use of NIV in stable hypercapnic COPD patients remains inconclusive. Two randomized controlled trials failed to demonstrate that home NIV had any impact on survival in COPD patients,²³⁵⁻²³⁶ although early hospital admissions (within 3 months) were reduced in one

trial.²³⁵ Another long-term randomized controlled trial suggested that survival may be improved with NIV combined with long-term oxygen therapy compared with long-term oxygen therapy alone, but at the expense of reduced health-related QoL.²³⁷ A recent meta-analysis concludes that NIV is effective in reducing hypercarbia and dyspnea and improving sleep quality, with no improvement in lung function and an unclear impact on survival.²³⁸ Higher positive pressures were associated with improved gas exchange, whereas lower inspiratory pressures were not. Several experts promote the use of high-intensity, noninvasive positive pressure ventilation (Hi-NPPV, with high inspiratory pressure close to 30 cm H_2O and a high back-up respiratory rate) aiming at a maximal reduction of arterial PCO_2 if improved survival is the target.²³⁹ Despite a high number of mask leaks, Hi-NPPV did not impair sleep quality in a randomized crossover trial.²⁴⁰ However, cautious administration of Hi-NPPV is still warranted in patients with pulmonary hypertension or underlying preexisting cardiac disease because deleterious hemodynamic consequences on cardiac output have been documented.²⁴¹ In summary, current evidence is insufficient to support the systematic use of NIV in stable hypercapnic COPD patients.

Despite the lack of clear evidence, COPD is one of the most rapidly increasing indications for home NIV.²¹⁰ Experts still recommend home NIV in stable COPD patients with either symptomatic hypercapnia (arterial $\text{PCO}_2 > 55$ mm Hg) or an arterial PCO_2 between 50 and 54 mm Hg and frequent episodes of ARF requiring hospital admission and ventilator support²¹⁵ in the hope that this may reduce health care costs.²⁴² Indeed, in a pilot randomized controlled trial with highly selected hypercapnic COPD patients surviving an episode of respiratory failure in the ICU, continuation of home NIV was associated with a lower risk of recurrent hypercapnic ARF.¹¹²

Recent guidelines have emphasized the importance of treating comorbidities that contribute to the overall burden of disease in COPD. OSA is now considered as one of these comorbidities in the latest version of The Global Initiative for Chronic Obstructive Lung Disease.⁹¹ Because COPD is projected to be the third leading cause of death worldwide by 2020²⁴³ and the prevalence of obesity—a major risk factor for OSA—is steadily increasing worldwide, it is not surprising that this overlap syndrome is also projected to increase and worsen COPD outcomes.²⁴⁴ In a large prospective cohort with a median follow-up of 9.4 years, Marin and colleagues demonstrated that the coexistence of COPD and OSA is associated with an increased risk of death from any cause and more hospitalizations for COPD exacerbations.²⁴⁵ Although there are no data from a randomized controlled study, most experts strongly encourage treatment of overlap syndrome with nocturnal NIV therapy. When OSA predominates, CPAP therapy is the most appropriate therapy. When nocturnal hypoventilation is the main pattern, nocturnal PSV plus PEEP should be the first choice.

Importance of Monitoring Home Noninvasive Ventilation

Several reports have shown that patients receiving home NIV may develop patient-ventilator asynchrony, unrewarded inspiratory efforts, unintentional leaks, and periodic breathing and respiratory events of obstructive,

central, and mixed origin.²⁴⁶ These complex events may have a detrimental effect on quality of sleep and control of nocturnal hypoventilation. It is therefore important to propose a stepwise strategy to detect respiratory events of clinical relevance in order to adapt ventilator settings and interface.

Medical history is important, although often nonspecific, and sometimes surprisingly unremarkable, despite significant nocturnal respiratory events. Disease-specific *health-related QoL* (HRQoL) questionnaires may be helpful to assess patient-centered end points as a complement to physiologic monitoring of NIV.²⁴⁷ The Severe Respiratory Insufficiency questionnaire was specifically developed for patients with chronic respiratory failure receiving home NIV and is now available in many languages.

Pulse oximetry remains an important and simple tool to ensure that adequate oxygenation is provided and to detect short recurrent or prolonged desaturations, although low specificity of pulse oximetry tracings during NIV remains a major drawback. In patients with NIV and long-term O₂ therapy, sensitivity of pulse oximetry is markedly decreased. Transcutaneous capnography discriminates between hypoxemia related to ventilation-perfusion mismatch or residual hypoventilation under NIV. Newer devices are reliable, provide a more realistic picture of the overnight transcutaneous PCO₂ trend, and can replace repeated arterial blood samples.²¹⁷ Built-in software of home ventilators provides data about compliance, pattern of NIV use, mask leaks, tidal volume, and rates of inspiratory or expiratory triggering by the patient. Multichannel ventilator modules combining oxygen saturation measurement with estimation of leaks and minute ventilation have been shown to be reliable.²⁴⁸ Unfortunately, the accuracy of estimated minute ventilation and leaks by the ventilator varies from one device to another²⁴⁹ and independent validation studies are still warranted for all commercially available ventilators. Therefore physicians should be aware of differences in the estimation of leaks and tidal volume between home NIV devices.

Finally, the use of noninvasive markers of sympathetic activation is becoming available for clinical use. For instance, pulse wave amplitude reduction is a sensitive marker with a high positive predictive value for the detection of micro-arousals associated with respiratory events during NIV, at least in OHS patients.²⁵⁰ If this technique is validated in other patient groups, it could be useful for assessment of sleep fragmentation and improve scoring of subtle respiratory events with simplified tools, such as home polygraphy (i.e., a home-based sleep study, without the need for a complete, in-lab, sleep study under NIV). Full-night polysomnography is time-consuming, costly, and not always available. However, until alternative monitoring options have been tested with evidence of proven efficacy, polysomnography during NIV remains the gold standard to monitor NIV in experienced centers.

EPIDEMIOLOGY OF NONINVASIVE VENTILATION IN ACUTE CARE

The use of NIV in the acute setting has increased markedly since the first small case-series were published in the

1990s.^{75,251} Three multicenter international observational studies on the use of MV applied in the ICU were performed in 1998, 2004, and 2010 by Esteban and colleagues²⁵²⁻²⁵⁴ in which up to 8000 consecutive patients receiving MV over a 1- or 2-month period were evaluated. The surveys showed that the use of NIV progressively increased from less than 5% to around 15% of all admitted ICU patients, with a consistent success rate and therefore a higher number of patients avoiding the need for intubation. A greater number of patients with COPD or heart failure were also successfully treated with NIV outside the ICU.

Similar observational studies performed in France in 1997, 2002, and 2011^{32-33,181} showed a major increase in NIV use as first-line ventilation support for all ICU patients requiring mechanical ventilatory support (16%, 24%, and 31%, $P < 0.0001$). Importantly, when comparing the three periods, a significant increase of NIV as first-line therapy (52% vs. 35%, $P < 0.0001$) was observed among those patients who were not intubated before or at ICU admission. The French survey published in 2006¹⁴⁸ indicated that pressure support was the most usual ventilatory mode (83%) during NIV (CPAP 8% and assist-control ventilation 7%). The last French observational¹⁸¹ study still showed a continuing increase in the overall use of NIV but, interestingly, with a slight but significant decrease in cases of hypoxemic respiratory failure.

The progressive interest in NIV use can be appreciated by examining the number of articles addressing NIV that have been published. Figure 102-3 illustrates the number of references concerning NIV for ARF or home NIV, review articles, and all types of articles published in the National Center for Biotechnology Information's PubMed from 1989-2013.

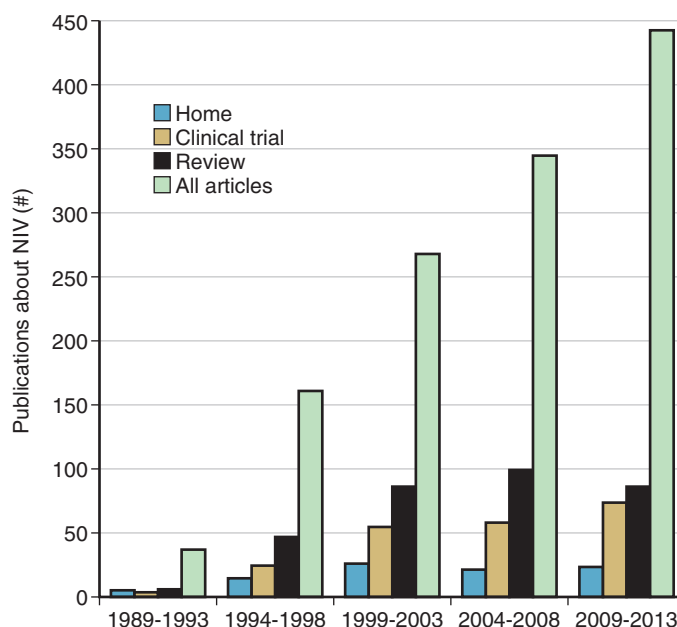


Figure 102-3 Published literature on NIV. Evolution of the number of published references in PubMed regarding NIV delivered for acute respiratory failure (clinical trial) and during home NIV (home) over a time period from 1989-2013. Review articles are also shown separately, as well as all articles about NIV.

Key Points

- The use of *noninvasive ventilation* (NIV) in the acute setting has increased markedly over the past decade. National and international multicenter studies have demonstrated that 15% of all admitted patients in intensive care units receive NIV, representing first-line ventilator strategy in 31% to 50% of those requiring mechanical ventilatory support.
- NIV can improve physiologic parameters, relieve dyspnea, reduce the invasiveness of patient management, and improve important clinical outcomes such as intensive care unit and hospital stay, complications, and mortality. There is convincing evidence that NIV diminishes the risk of nosocomial infections.
- The beneficial effects of NIV are best demonstrated in patients with acute exacerbation of COPD and obesity-hypoventilation syndrome. In these settings, NIV is recommended as first-line therapy to prevent further deterioration. Moreover, when combined with conventional medical therapy during acute cardiogenic pulmonary edema, NIV can reduce mortality, especially in the subgroup of patients with hypercapnia.
- Use of NIV in hypoxemic acute respiratory failure is controversial, and patients must be assessed carefully to ascertain which ones may benefit and which ones may be harmed by use of NIV because of a delay in intubation. Moreover, NIV may be useful during the post-extubation process as a preventive tool during the weaning process or during various procedures such as fiberoptic bronchoscopy.
- NIV success is strongly associated with good clinical tolerance. Problems with tolerance can be related to the patient, the interface, the ventilator, and/or the ventilator settings. Mask leaks lead to discomfort and patient-ventilator asynchrony, prolonged inspiration due to inspiratory leaks, and auto-triggering due to expiratory leaks. An optimal adjustment of ventilatory settings may improve patient-ventilator synchrony, work of breathing, comfort, and, potentially, the success of noninvasive ventilation.
- The interface is an essential component for NIV. Oral and nasal interfaces are mostly used for chronic NIV. In the acute care setting, the oronasal mask appears to be the best first choice. The total/full-face mask has not been demonstrated to be superior to the oronasal mask. The helmet can be used as a first-line interface in experienced hands and for pulmonary edema. There is no ideal interface for all patients, and several interfaces should be available at the bedside.
- NIV is the standard of care for home mechanical ventilation. Subjects with a condition known to cause alveolar hypoventilation should be evaluated regularly to determine whether they are eligible for home NIV.

Complete reference list available at *ExpertConsult*.

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EXTRACORPOREAL SUPPORT OF GAS EXCHANGE

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a technique of life support that consists of diverting a fraction of the patient's *blood flow* (BF) through an artificial lung for gas exchange (oxygenation and carbon dioxide [CO₂] removal) and then returning it to the patient. Thanks to improvement in technology and materials and to a deeper understanding of pathophysiology, the indications, timing, and management of ECMO have changed substantially over the years. This chapter introduces the concept of ECMO and discusses its use for respiratory support in patients with *acute respiratory failure* (ARF).

PRINCIPLES OF ECMO

ECMO is a generic term used to describe a number of different techniques used for prolonged artificial cardiac and/or respiratory support. Depending on the returning vessel (venous or arterial), ECMO can be used for cardiac (*veno-arterial bypass* [VA-ECMO]) or respiratory support. For respiratory support, blood can be drained either from a vein (*veno-venous ECMO* [VV-ECMO]) or from an artery (*arterio-venous ECMO* [AV-ECMO]). During VA- and VV-ECMO in which blood is drained from a vein, the blood is withdrawn with the action of a pump, whereas during AV-ECMO, the arterial pressure is the driving force. BF passes through the oxygenator (*membrane lung* [ML]), where oxygen is added and CO₂ removed. The efficiency in CO₂ removal is significantly higher than for oxygenation. Depending on the BF through the circuit, the technique may be used mainly for CO₂ removal (BF < 2 L/min) or for both CO₂ removal and oxygenation (BF up to 5 to 6 L/min). For an appreciation of the different techniques available for respiratory support, it is useful to provide a brief historical perspective.

ECMO INDICATIONS AND TECHNOLOGY: A HISTORICAL PERSPECTIVE

The birth of ECMO dates back to 1939 with the development of the first heart-lung machine by John Gibbon; this culminated in 1953 with the first open heart operation.¹ The first successful use of prolonged ECMO was reported by Hill and colleagues² in 1972 in a 22-year-old patient with *acute respiratory distress syndrome* (ARDS). In the following 2 years, other successful cases were reported. Due to the extremely high mortality rate of ARDS patients at the time, these first reports evoked great interest and were the impetus for the first multicenter randomized clinical trial of prolonged ECMO for adults with ARDS.³ The study, commissioned by the National Institutes of Health, failed to show any survival benefit from ECMO. The reasons for failure of this trial were not clear, but the negative results led to a virtual cessation of laboratory and clinical research on adult ECMO. Fortunately, a number of determined investigators continued studying and improving the technique. Currently, there is a resurgence of interest in ECMO and its clinical application.

Important factors contributing to the maintenance of the interest in ECMO were the encouraging results reported in neonatal respiratory failure. The first successful treatment in newborns was reported by Bartlett and colleagues⁴ in 1976, followed in the subsequent few years with several encouraging case series from different groups.⁵⁻⁷ Two prospective randomized controlled studies were then performed: the first by Bartlett's group in Michigan in 1985,⁸ the second by O'Rourke and coworkers in Boston in 1989.⁹ Both studies were positive and in a few years, ECMO became standard treatment for neonatal respiratory failure.

In adults, major advances came from the pioneering work of Kolobow and Gattinoni,¹⁰ who focused on why the NIH-ECMO trial had failed. At the time, the aim of ECMO was to provide reasonably normal blood gases, essentially buying time for the lungs to heal.¹¹ As such, high ECMO BF rates were necessary to improve oxygenation, and the veno-arterial configuration was the standard. In 1977, recognizing that oxygenation and carbon dioxide elimination were based on different physiologic mechanisms, Gattinoni and Kolobow¹² realized that by removing CO₂ through the membrane lung, ventilation of the *native lung* (NL) could be reduced virtually to zero. They showed that nearly all the metabolic CO₂ production could be removed through an artificial lung using much lower extracorporeal BFs than those required to oxygenate the blood.¹³ On the basis of these observations, in 1979, they developed the concept of *extracorporeal CO₂ removal* (ECCO₂R), proposing the use of a VV bypass configuration instead of the classical VA mode and the use of *low-frequency intermittent positive pressure ventilation* (LFPPV) to allow the lung to rest.¹³ In 1980 Gattinoni and colleagues¹⁴ reported the successful clinical application of this technique, and in 1986 they published the results of the first study on ECCO₂R-LFPPV in 43 patients with severe ARF.¹⁵ Unfortunately, these results were not confirmed by a subsequent single-center, randomized controlled trial conducted by Morris and colleagues¹⁶ in 40 ARDS patients. This second failure led to an almost complete stop of ECMO development in adults, confining its application to newborns. Nevertheless, a few centers around the world continued to apply ECMO in adult patients, with important technical improvements.^{17-21,21a}

At least five reasons have led to the recent resurgence of interest in ECMO:

1. Technical developments. There have been a number of technologic advances that have decreased the complications associated with the earlier application of ECMO. Oxygenators, propelling pumps, and cannulas have all undergone substantial improvements. The available equipment now allows easier, safer, and longer ECMO application. An important factor has been the miniaturization of the whole system, making it possible to use ECMO for interhospital transportation.
2. The *Extracorporeal Life Support Organization* (ELSO). Founded in 1989, ELSO includes most ECMO centers around the world. An important function of ELSO is to maintain a registry of ECMO cases and to provide annual reports provide, which information on ECMO usage, survival rates, and complication rates. ELSO has also developed guidelines that represent the most important reference for ECMO users worldwide.²²
3. The concept of *ventilator-induced lung injury* (VILI) and improvement in ARDS treatment.²³ Recognition that mechanical ventilation, though necessary to preserve life, can exacerbate lung damage eventually contributing to mortality, probably represents the most important advance in ARDS research. Ventilation with high *tidal volumes* (VT)²⁴⁻³⁰ and high distending pressures^{31,32} has been recognized as a major cause of VILI. In the seminal ARDS-Network randomized controlled trial, patients ventilated with a VT of 6 mL/kg of *predicted body weight* (PBW) had a significantly lower mortality than those ventilated with a VT of 12 mL/kg PBW.³⁰ These findings led to the concept of “protective ventilatory strategy,” largely consisting of low VT (6 to 8 mL/kg PBW) and limitation of plateau airway pressures (Pplat < 28 to 30 cm H₂O). It is important to understand that the concept of VILI was not recognized early in the history of ECMO; for this reason, in the two aforementioned ECMO randomized trials, no attention was paid to VT and airway pressures in either treatment group.
4. The *Conventional Ventilation or ECMO for Severe Adult Respiratory Failure* (CESAR) trial.³² The CESAR trial, conducted in the United Kingdom and published in 2009, was the first randomized clinical trial showing a survival advantage of ECMO in adults. Adult patients (18 to 65 years) with severe but potentially reversible ARF (defined as a Murray score ≥3 or uncompensated hypercapnia with a pH < 7.20) were enrolled. Patients randomized to receive ECMO were transferred to the Leicester ECMO center, while controls remained in designated treatment centers. Between 2001 and 2006, 180 patients were enrolled. Survival or absence of severe disability at 6 months was 63% in the ECMO group, comparing favorably with 47% in the control group; the authors concluded that referral of severely hypoxemic ARDS patients to a specialized center able to provide ECMO may increase survival. Two major limitations of the study have been identified. First, not all patients allocated to the ECMO group received ECMO because they died before or during transportation (5 patients) or they improved with conventional treatment after transportation to the ECMO center (17 patients). Second, there was no standardized protocol for mechanical ventilation in the control group, resulting in significantly fewer patients receiving a protective ventilatory strategy. As such, a criticism was that the patients randomized to ECMO were treated in a single specialized center, possibly receiving better care. However, despite these limitations, the results of the study have led to an increase in interest in ECMO worldwide.
5. The H1N1 influenza outbreak. During the 2009 Influenza A (H1N1) pandemic in Australia and New Zealand, 61 patients with H1N1-associated ARDS received ECMO for refractory hypoxemia: survival was 78%.³³ Following the Australian experience, several countries in the northern hemisphere prepared for the pandemic and case series were published reporting survival rates ranging from 68% to 83%.³³⁻³⁹ The British ECMO group recently published a cohort study in which patients with H1N1-associated ARDS referred for ECMO to one of the four adult ECMO centers in the United Kingdom were matched with similar non-ECMO treated patients using data from a concurrent, longitudinal cohort study. Hospital mortality rate of ECMO-referred patients was almost one half of that of non-ECMO-referred patients with all the three matching methods used.³⁶

INDICATIONS FOR VENO-VENOUS AND ARTERIO-VENOUS ECMO

The primary indication for VV-ECMO is hypoxemic respiratory failure in patients with a high risk of mortality.

According to ELSO guidelines, ECMO is indicated in patients with arterial PO_2 (PaO_2)/ FIO_2 less than 80 mm Hg with FIO_2 greater than 90% and a Murray score of 3 to 4.²² Although the evidence backing up this recommendation is weak, similar indications have been suggested by different groups as, for example, in relation to H1N1 patients.^{39a} An important finding, described by several investigators is the association between increased mortality and more days of mechanical ventilation before ECMO institution.^{39b} This observation brings to mind the concept of VILI and suggests the importance of starting ECMO before lung injury has become irreversible. In the past few years, several case reports have been published on the use of VV-ECMO for non-ARDS indications, such as ARF due to severe trauma,⁴⁰ pulmonary embolism,⁴¹ severe asthma,⁴² and as a bridge to lung transplant.⁴³

In comparison, the primary indication for AV-ECMO is hypercarbia in patients with respiratory failure and adequate cardiac function. Because the flow through the membrane lung is from the arterial blood, the ability to oxygenate the blood is less than if the inflow was venous blood; instead, the main value of AV-ECMO is the ability to remove CO_2 . AV-ECMO is discussed later in “Low-Flow CO_2 Removal: Indications and Technology,” under “Arterio-venous CO_2 removal.”

Contraindications to ECMO include advanced age, severe disability, and incurable malignancy. Uncontrolled coagulopathy, major bleeding, and prolonged mechanical ventilation are considered relative contraindications. The decision to start ECMO is made on a case-by-case basis.

MATERIALS NECESSARY TO IMPLEMENT VENO-VENOUS ECMO

Basic components necessary for VV-ECMO are the cannulas for vascular access, a pump to propel the blood, and a gas exchange unit (Fig. 103-1). Compared with the systems commonly used during cardiac surgery, ECMO systems are simpler. A schematic of the minimal requirements for a VV-ECMO circuit is shown in Figure 103-2.

OXYGENATORS

Hollow-fiber oxygenators with a polymethylpentene membrane have become the standard for long-term treatment.⁴⁴⁻⁴⁶ Compared with the original silicon membrane, hollow-fiber oxygenators have a smaller priming volume, higher gas transfer rates, and much lower resistance.⁴⁷ The use of polymethylpentene has also completely resolved the problem of plasma leakage that represented the main limitation to the use and diffusion of polypropylene hollow-fiber oxygenators.⁴⁸ The gas and blood compartments are channeled inside and outside the hollow fibers, respectively. A third compartment for heat exchange is commonly present. Each compartment has an input and an output port.

PUMPS

Similar to the diffusion of low-resistance, hollow-fiber oxygenators, centrifugal pumps have almost completely

replaced roller pumps for long-term applications. Modern centrifugal pumps have a hole in the center of the rotor (Mendler design)⁴⁹ and use a magnetically suspended and driven pump that eliminates stagnation, thrombosis, and heat production, which were common complications of earlier centrifugal pump models.

CANNULAS

Vascular cannulas for ECMO have a thin wall, commonly made of polyurethane, and are often reinforced with wire to prevent kinking or collapse. Venous cannulas have side holes close to the tip or along the last 15 to 20 cm (multi-stage cannulas) to facilitate drainage of blood from the venous system. Modern cannulas have heparin-coated surfaces to increase biocompatibility and reduce activation of the clotting cascade.⁵⁰ Recently, some double-lumen cannulas have become available. The most popular is the Avalon Elite designed by Wang and Zwischenberger.⁵¹ With this cannula, blood is drained from both the inferior and superior vena cava and returned directly into the right atrium. VV-ECMO with a single double-lumen cannula approach is gaining popularity over the traditional configuration with two cannulas.

TUBING

The tubing used for ECMO is made of polyvinylchloride, polyurethane, or silicon rubber. Appropriate connectors, with side ports for standard stopcocks, allow connection between different circuit components. All tubing and connectors surfaces can be coated with heparin and biocompatibility linings to reduce the risk and intensity of the thrombotic and inflammatory reactions triggered by the contact between blood and the artificial surfaces.

CANNULATION FOR VENO-VENOUS ECMO

The technique of choice for VV-ECMO cannulation is the percutaneous approach.^{52,53} This technique, introduced in the late 1980s, has essentially become the standard of care. The main advantages are reduced risk of bleeding, shorter operative time, and easier mobilization and nursing of the patient.

Choice of cannula size and positioning is crucial. As a general rule, the size of the cannula should not exceed two thirds of the vessel diameter. Drainage cannulas should be big enough to ensure adequate flow with relatively low suction pressure, and the holes and tip of the cannula should be positioned in a high-flow vessel. Common sizes for drainage cannulas in adults range from 21 to 28 French. Positioning is important to maximize flow and minimize recirculation. *Recirculation* is the shunting of the returned, oxygenated blood back into the intake for the ECMO. Recirculation will reduce the efficiency of ECMO and also increase the oxygenation of the intake blood so that it no longer reflects the true mixed venous oxygen saturation.

Veno-venous bypass may be accomplished using three different configurations: femoral-jugular, jugular-femoral,

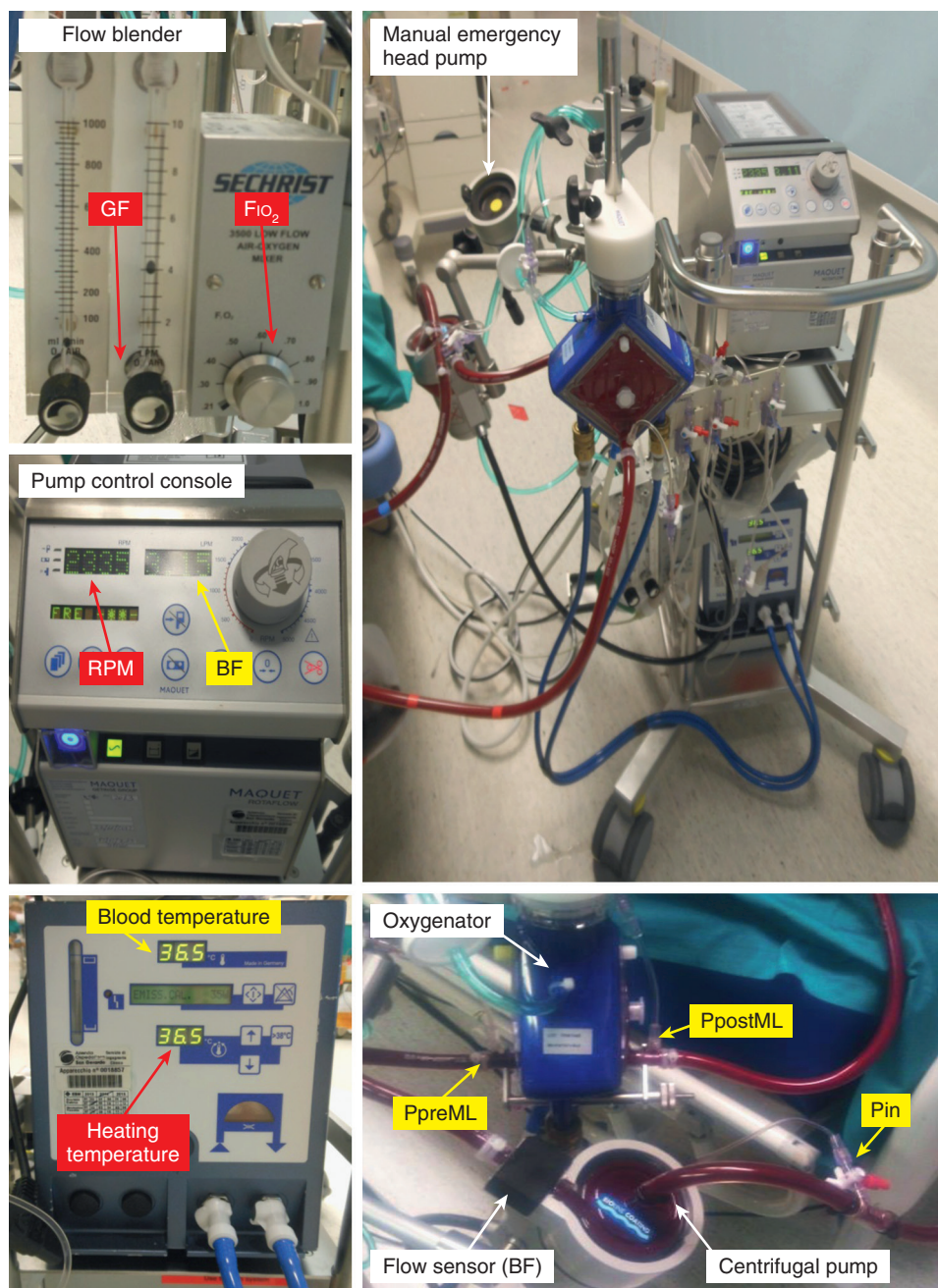


Figure 103-1 Pictures of the main hardware components of an extracorporeal membrane oxygenation (ECMO) unit. Yellow tags show main measured variables: blood flow (BF); temperature of blood drained from the patient (Blood temperature); drainage pressure (Pin); pressure before the oxygenator (PpreML); and pressure after the oxygenator (PpostML). Red tags show main ECMO setting parameters: speed of the centrifugal pump (RPM); sweep gas flow (GF); oxygen fraction of GF (FiO₂); heating temperature.

and femoral-femoral. Factors to consider when choosing the configuration are the drainage capability, recirculation risk, patient mobilization, and complications. The *femoral-jugular* access is the more frequently used; with a correctly positioned femoral cannula of 23 to 25 French, BF rates up to 6 to 7 L/min are easily obtained with minimal recirculation. The *jugular-femoral* approach, in which blood is drained directly from the right atrium, likely provides the best drainage but there is a high degree of recirculation, which can effectively nullify the drainage advantage. The *femoral-femoral* approach offers safer access with less possibility of accidental cannula dislocation; mobilization of the patient's

head is facilitated at the expense of lower limb mobilization. With this approach, however, minimization of recirculation requires careful positioning of the cannula tips, which is generally more difficult to obtain than with other approaches. The tip of the femoral drainage cannula should be positioned in the inferior vena cava superior to the renal veins, approximately at the level of L1-L2 lumbar vertebrae.

Double-lumen cannulas are commonly placed through the right internal jugular vein. To obtain blood flow rates comparable with those commonly achieved with the traditional two-cannula configurations, insertion of cannulas up to 31 to 35 French may be necessary.

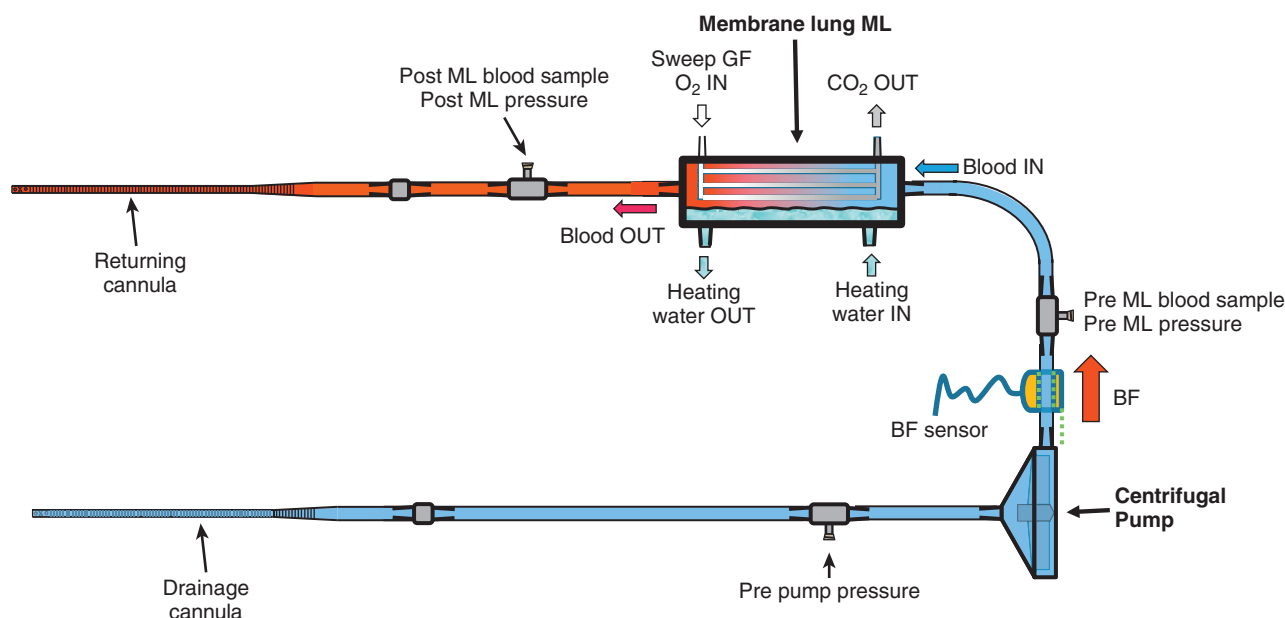


Figure 103-2 Schematic of a basic circuit for veno-venous ECMO (VV-ECMO). From the drainage to the returning cannula, a basic circuit for VV-ECMO includes a connector with stopcock for drainage pressure monitoring (pre pump pressure or P_{in}); the centrifugal pump; a flow sensor for monitoring blood flow (BF); a connector with stopcock for monitoring pressure and sampling for gas analysis of the input blood (pre membrane lung [ML] pressure); the membrane lung oxygenator (ML) (inlet and outlet port for blood, sweep gas, and heating water are represented); a connector with stopcock for monitoring pressure and obtaining samples for gas analysis of blood leaving the oxygenator (post membrane [ML] lung pressure).

Choice of the cannulas is also based on the clinical indication. For more severely hypoxemic patients, larger cannula sizes and configurations allowing higher blood flows should be selected from the beginning. Insertion of a second drainage cannula, an upgrade from a single- to a double-cannula configuration, or a switch from VV- to VA-ECMO is sometimes mandated by changes in the patient's needs.⁵⁴

PATIENT-MACHINE INTERACTION DURING VENO-VENOUS ECMO

The effect of VV-ECMO on arterial blood gas values is a function of the complex interplay among different factors. It is useful to discuss the effects on oxygenation and on CO_2 removal separately.

EFFECT OF VENO-VENOUS ECMO ON OXYGENATION

During VV-ECMO, the membrane lung and native lung are in series (Fig. 103-3). We can understand the physiology of VV-ECMO by following the changes in blood O_2 content from the vena cava ($CvCO_2$) to the arterial side (CaO_2). $CvCO_2$ is a function of CaO_2 , cardiac output (CO), and arterial-venous O_2 difference ($CaO_2 - CvCO_2$). A fraction of the venous return (BF/CO) is diverted through the membrane lung. The oxygen delivery of the membrane lung is given by $\dot{V}O_{2ML} = BF \times (CO_{2out} - CO_{2in})$, where CO_{2in} and CO_{2out} are the oxygen content of the blood, respectively, entering (input) and leaving (output) the membrane lung. The oxygen content of the blood returning to the lung (the mixed venous blood,

$\bar{C}\bar{V}O_2$) is the flow-weighted average of CO_{2out} and $CvCO_2$: $\bar{C}\bar{V}O_2 = (CO_{2out} \times BF + CvCO_2 \times [CO - BF]) / CO$. In practice, the resulting effect of the membrane lung is to increase the O_2 content of the blood returning to the lung from $CvCO_2$ to $\bar{C}\bar{V}O_2$. $\bar{C}\bar{V}O_2$ is then increased to CaO_2 by the residual oxygenating capacity of the patient's lung. The oxygen delivery of the native lung is $\dot{V}O_{2NL} = CO \times (CaO_2 - \bar{C}\bar{V}O_2)$, and the patient's total oxygen consumption is simply the sum of membrane lung and native lung oxygen delivery: $\dot{V}O_2 = \dot{V}O_{2ML} + \dot{V}O_{2NL}$.

Besides the oxygenation capability of both the membrane lung and patient's lung, the main determinants of blood O_2 content are hemoglobin saturation and hemoglobin concentration. Once the hemoglobin has been saturated, the only way to increase O_2 delivery and O_2 transport is by increasing the hemoglobin concentration (Fig. 103-4, left panel).^{54a}

Under VV-ECMO, arterial oxygenation will depend on the sum of the partial effects of $\dot{V}O_{2ML}$, mixed venous SO_2 , and $\dot{V}O_{2NL}$.

O_2 Delivery by the Membrane Lung ($\dot{V}O_{2ML}$)

The amount of oxygen delivered by the membrane lung depends on three main factors (see Fig. 103-4).

1. The intrinsic performance of the membrane lung. The oxygenator's oxygenation capability will depend on the membrane diffusion characteristics (thickness, material) and the membrane surface area (see Fig. 103-4, left panel).
2. The O_2 pressure gradient between the sweep gas flow and the blood. On the gas side, the O_2 partial pressure depends on the FIO_2 of the sweep gas. It is important to understand that, similarly to natural lung physiology,

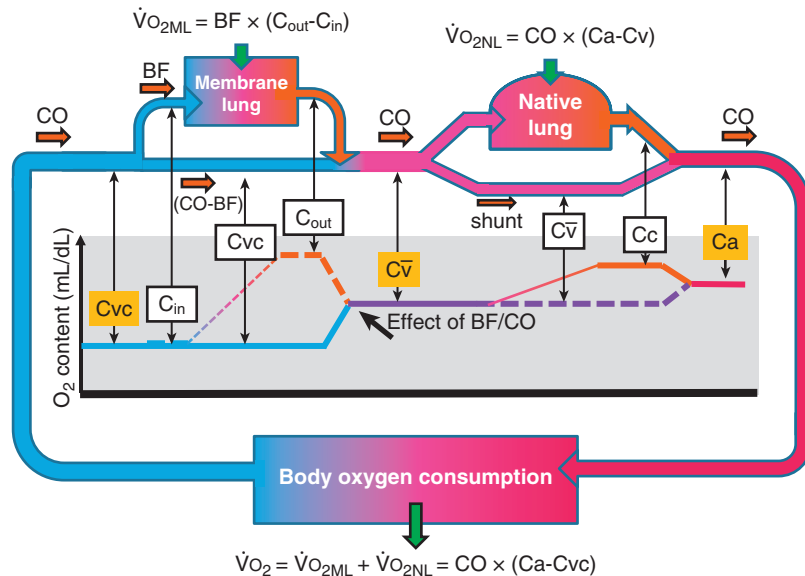


Figure 103-3 A schematic of a model of O_2 delivery and consumption during VV-ECMO. The main determinants of blood oxygen content (mL/dL) from venous return (content in vena cava [C_{vc}]) to arterial blood oxygen content (C_a) are represented. The oxygen content of the blood entering the native lung (mixed venous blood [C_v]) is determined by ECMO BF relative to the patient's cardiac output (CO). Oxygen content in arterial blood (C_a) is determined by the intrapulmonary shunt (shunt) relative to CO. Oxygen content of the blood entering the membrane lung (C_{in}), blood exiting the membrane lung (C_{out}), and blood exiting normally functioning regions of native lung (C_c) are also represented, as well as the oxygen delivery of the membrane lung (mL/min) ($\dot{V}O_{2ML}$), oxygen delivery of the native lung ($\dot{V}O_{2NL}$), and total patient's oxygen consumption ($\dot{V}O_2$). A more detailed description is provided in the text.

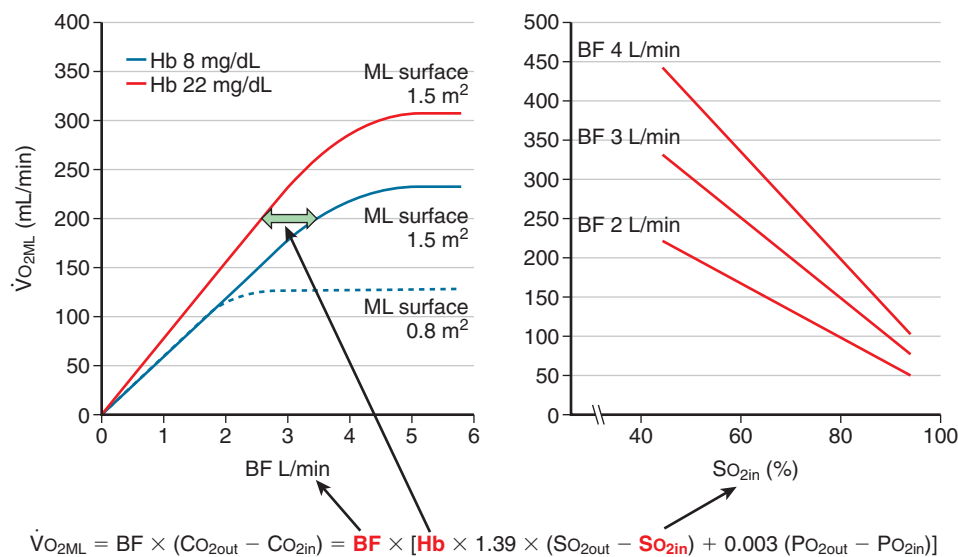


Figure 103-4 Oxygen delivery of the membrane lung ($\dot{V}O_{2ML}$, mL/min) as a function of ECMO (BF, L/min) (left panel) and oxygen saturation of the blood entering the membrane lung (SO_{2in} , %) (right panel). The effect of the hemoglobin (Hb) concentration and of the membrane lung surface area (m^2) is represented in the left panel. The formula for computation of $\dot{V}O_{2ML}$ is shown. CO_{2in} , SO_{2in} , and PO_{2in} are the oxygen content (mL/dL), saturation (%), and partial pressure (mm Hg) of the blood entering the membrane lung (ML); CO_{2out} , SO_{2out} , and PO_{2out} are the oxygen content, saturation, and partial pressure of the blood leaving the ML.

the transfer of O_2 through the membrane lung is governed by the ventilation/perfusion matching. However, once a high level of partial pressure has been reached in the outlet blood, further increase in gas flow will not lead to any major increase in O_2 delivery. On the blood side, the higher the oxygen saturation of incoming blood (SO_{2in}), the lower the quantity of O_2 that can be added to the blood (see Fig. 103-4, right panel). As described earlier, an important factor that may result in a high

SO_{2in} is recirculation (i.e., blood already oxygenated from the membrane lung sucked back into the ECMO circuit).

3. ECMO blood flow. Up to a determined blood flow, $\dot{V}O_{2ML}$ will increase directly with the increase in ECMO flow. However, depending on the membrane surface area and the membrane lung characteristics, there is a limit to the oxygenator flow ("rated flow") above which no more O_2 can be added to the blood (see Fig. 103-4, left panel).

Mixed Venous Blood Oxygenation ($\bar{S}vO_2$)

During VV-ECMO, the main determinants of *mixed venous oxygen saturation* ($\bar{S}vO_2$) are the oxygen saturation of the blood leaving the organs and the ratio between extracorporeal BF and CO (Fig. 103-5). At a given CO, the increased oxygenation contribution of the membrane lung resulting from an increase in BF will always lead to an increase in $\bar{S}vO_2$ and *arterial oxygenation saturation* (SaO_2). In contrast, when CO changes at constant BF, the effect on $\bar{S}vO_2$ and SaO_2 is primarily dependent on the level of BF, $CvcO_2$, and

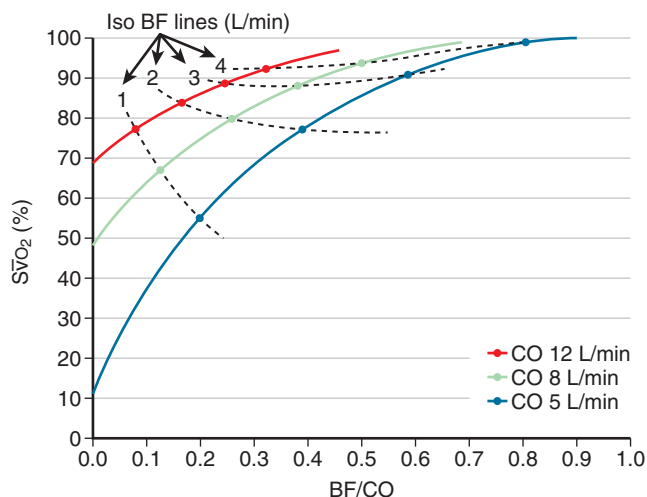


Figure 103-5 Oxygen saturation of blood entering the patient's lung ($\bar{S}vO_2$, continuous lines) as a function of the blood flow (BF)/cardiac output (CO) ratio, at different CO with constant oxygen consumption. At constant CO, increase of BF/CO through increase of BF results in increase of $\bar{S}vO_2$ by two mechanisms: first, because a higher fraction of venous return is oxygenated by passing through the membrane lung; second, because the resulting increase in arterial O_2 saturation will lead to an increase of oxygen saturation of the blood in the vena cava ($SvcO_2$) and therefore in the input (SO_{2in}). The effect of changing BF/CO by changing CO at constant BF (iso BF lines) is also represented. At a constant BF, an increase of CO can have contrasting effects on $\bar{S}vO_2$: An increase in CO increases $SvcO_2$ and SO_{2in} , but the increase in CO also decreases the fraction of venous return oxygenated through the membrane lung. The former effect prevails at lower BF (iso BF line 1 L/min) and the latter at higher BF (iso BF line 4 L/min). Note, at the higher BF (iso BF line 4 L/min), an increase in CO (from 5 to 12 L/min) results in a decrease in $\bar{S}vO_2$ (from 98% to 92%).

recirculation. A decrease in CO is associated with a parallel decrease in $CvcO_2$. Below a certain value of $CvcO_2$, the expected positive effect on oxygenation of the increase in the BF/CO ratio may be offset by the decrease in $CvcO_2$, resulting in a net decrease of $\bar{S}vO_2$ and SaO_2 . At BF commonly used in clinical practice (3 to 5 L/min), an increase in CO is commonly associated with a decrease in the oxygenation contribution of the membrane lung, resulting in a decrease in $\bar{S}vO_2$ (see the iso BF line with 4 L/min in Fig. 103-5) and ultimately a decrease in SaO_2 (Fig. 103-6C). Conversely, at lower BF (1 to 3 L/min), and at critically low arterial oxygenation, an increase in CO is associated with an increase in both $\bar{S}vO_2$ (see the iso BF line with 1 L/min in Fig. 103-5) and SaO_2 (see Fig. 103-6C). These relationships are the basis for the manipulation of BF and CO during VV-ECMO. However, there are limitations to how much the BF/CO ratio can be increased. First, in the presence of recirculation, either an increase in BF or a decrease in CO will increase the amount of recirculating blood, thereby blunting the expected positive effect on oxygenation. Second, an increase of BF is limited by the cannula size and blood volume status of the patient. Third, oxygen delivery to peripheral organs depends on both CaO_2 and CO; at low oxygenation levels, a higher CO is necessary to ensure sufficient organ oxygenation.

Oxygen Uptake from the Native Lung ($\dot{V}O_{2NL}$)

The native lung will contribute to arterial oxygenation by adding oxygen to the $C\dot{V}O_2$ according to its residual gas exchange capability, which depends on the severity of the lung disease (i.e., the intrapulmonary shunt fraction) (see Fig. 103-6A) and is heavily influenced by the ventilator management (see Fig. 103-6B) and cardiac output (see Fig. 103-6C). The main goal during VV-ECMO is to reduce and limit all the factors that may contribute to VILI, namely high ventilation volumes and pressures and high FiO_2 . However, a decrease of FiO_2 , *positive end-expiratory pressure* (PEEP), and/or minute ventilation may temporarily lead to worsening of gas exchange function of the native lung, increasing the reliance of patient oxygenation on ECMO effectiveness. Thus, the expected level of BF and indeed the choice of ECMO equipment and cannula sizes will be strongly influenced by the native lung management and,

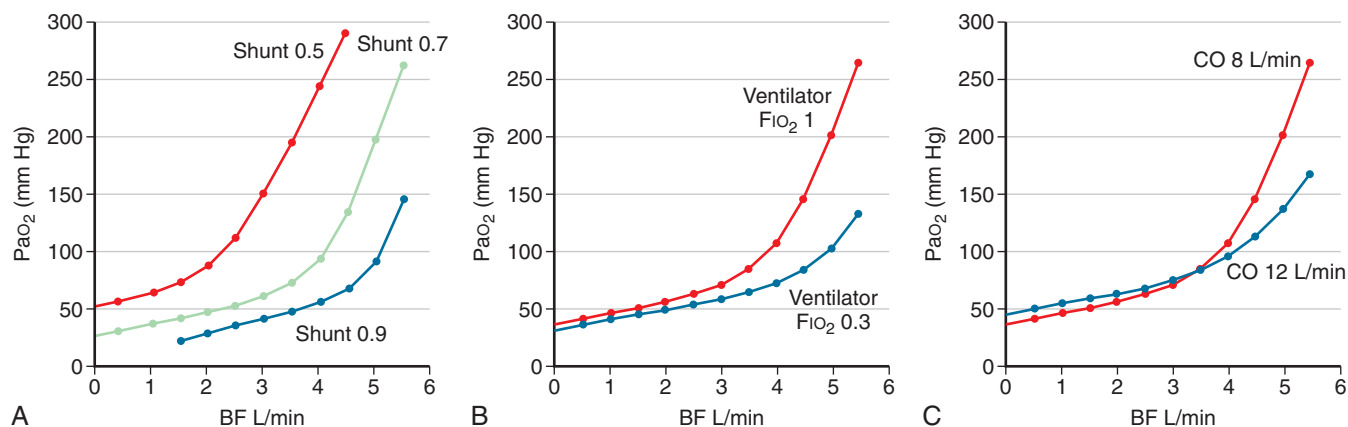


Figure 103-6 The effect of ECMO blood flow (BF) on the partial arterial pressure of oxygen (PaO_2). As BF increases, the PaO_2 rises; the degree of increase also depends on native lung function (intrapulmonary shunt, shunt) (A), the fraction of oxygen at the ventilator (B), and the cardiac output (C).

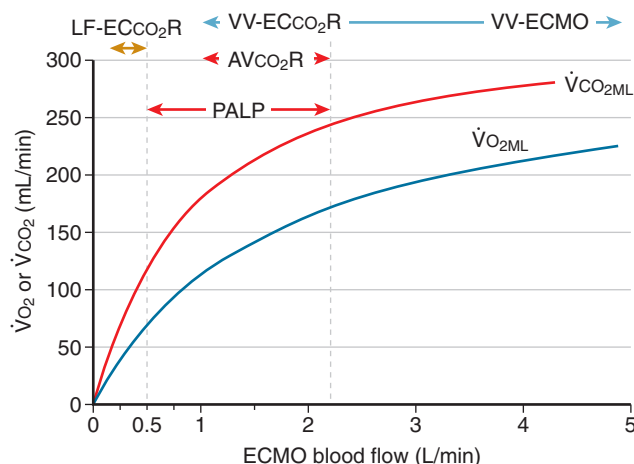


Figure 103-7 Oxygen delivery ($\dot{V}O_{2ML}$) and carbon dioxide removal ($\dot{V}CO_{2ML}$) as a function of ECMO blood flow (BF). Curves have been mathematically derived assuming a CO_2 removal efficiency of 40% with a P_{aCO_2} of the input blood of 60 mm Hg and complete equilibrium of partial pressure of oxygen between the blood and gas compartments. The operative range of BF of the major CO_2 removal techniques is represented. $AVCO_2R$, arteriovenous CO_2 removal; $LF-ECO_2R$, Low-flow CO_2 removal; PALP, pump assist lung protection; $VV-ECO_2R$, VV -classical VV -ECMO with different oxygenator sizes and operative BF.

most importantly, by the level of oxygenation that is considered clinically acceptable.

EFFECT OF VENO-VENOUS ECMO ON CO_2 REMOVAL

With any type of membrane lung, clearance of CO_2 is always more efficient than oxygenation (Fig. 103-7). Although the amount of O_2 delivery is limited to that which fully saturates arterialized blood, there is no specific limit to the amount of CO_2 that can be removed from venous blood. Most of the CO_2 is transported in blood in the form of bicarbonate ion. CO_2 transport in blood is defined by a high content at a relatively low partial pressure (40 to 50 mm Hg under normal conditions). Normal venous blood carries at least 50 mL of CO_2 / 100 mL. This means that half a liter of venous blood contains an amount of CO_2 equivalent to roughly the entire CO_2 production per minute of the body (≈ 250 mL/min for a 70-kg normothermic man). Thus, the entire patient CO_2 production can theoretically be removed with low BF provided that a high gas flow is used. At high sweep gas flow (8 to 15 L/min), the CO_2 concentration in the gas compartment remains close to 0 mm Hg and a high CO_2 pressure gradient is maintained. For example, at a normal bicarbonate ion concentration, a liter of blood can contain up to 500 mL of CO_2 . With the removal efficiency of current technology (about 20% to 40%), up to 200 mL of CO_2 per minute may be removed with an extracorporeal BF of 1 L/min. The strict relationship between $\dot{V}CO_{2ML}$ and gas flow is advantageous because it allows dissociation of CO_2 removal from oxygen delivery. In other words, we can use the gas flow to control CO_2 removal and can use extracorporeal BF to control oxygen delivery.

This removal of a large percentage of the CO_2 production allows the clinician the option of decreasing the minute

ventilation delivered by the ventilator. If 50% of $\dot{V}CO_2$ is removed by the membrane lung, minute ventilation of the native lung can roughly be halved. This is the physiologic basis for the use of ECMO to provide a more protective ventilation strategy, as discussed later.

MONITORING AND MANAGEMENT OF THE ARTIFICIAL LUNG

Management of ECMO is essentially based on setting three variables:

1. Device blood flow. As we have seen, extracorporeal BF is the main determinant of patient oxygenation and should be set to the lowest level that provides adequate oxygenation. The required flow will be a function of the target oxygenation level and the ventilator strategy applied to the native lung.
2. Gas flow. The main determinant of CO_2 removal by the ECMO device is the sweep gas flow; consequently, gas flow determines the minute ventilation needed from the ventilator.
3. FIO_2 of sweep gas. It is generally set to 1.0 and progressively decreased as soon as the patient's clinical condition improves.

The ECMO circuit should be monitored several times daily (at least once daily by a perfusionist). Careful monitoring of the ECMO system is aimed at answering the following questions:

1. Is the oxygenator performing well? If the FIO_2 of the sweep gas is 1, the expected PO_2 in the output blood (PO_{2out}) should be high (generally > 300 to 400 mm Hg). The PO_{2out} is usually higher than 500 mm Hg at lower blood flows and starts to decrease as flow increases to the rated flow for that type of oxygenator. Accounting for this effect, daily monitoring of the PO_{2out} allows detection of any decrease in oxygenator performance, which may prompt a circuit substitution. In addition, as the oxygenator performance worsens, increasing gas flow rates are necessary to maintain the same P_{aCO_2} .
2. Is drainage effective? Efficient blood drainage is crucial. Drainage effectiveness can be assessed by monitoring the pressure in the tubing proximal to the pump (suction pressure [P_{in}]) (see Figs. 103-1 and 103-2), and the BF/revolutions per minute (RPM) ratio: if drainage is insufficient, BF becomes unstable (sudden drops) and excessive suction pressure can cause "kicking" or "swinging" of drainage lines. P_{in} is an essential variable that should be monitored. Appropriate drainage cannula size and device blood flow should be selected to avoid excessively negative P_{in} . Values of P_{in} should be less negative (i.e., closer to zero) than -100 mm Hg. When drainage becomes less effective, P_{in} will become more negative, BF will decrease, and higher revolutions per minute of the pump must be set to maintain the same device BF. The commonest reason for a reduction of drainage effectiveness is a change in patient blood volume status and/or a decrease in venous BF proximal to the cannula tip. Volume expansion and temporary reduction of the extracorporeal BF are the easiest

solutions. It is always important to check for any change in cannula position, tube kinking, or obstruction.

- Is there thrombosis in the circuit? The oxygenator is the main site of activation of thrombosis. Clot formation in the oxygenator may be detected by daily inspection of oxygenator surfaces, by monitoring the transmembrane pressure (difference between post (PpostML) and pre (PpreML) oxygenator pressure), and by monitoring coagulation parameters (see later).

VENTILATORY MANAGEMENT OF THE NATIVE LUNG

The main objective during VV-ECMO is to ensure adequate gas exchange while minimizing VILI.²⁴ Optimal setting of the mechanical ventilator during ECMO is still a matter of debate, and strategies may vary from center to center.^{54b} An example of daily ventilatory management in an ARDS patient on VV-ECMO is presented in Figure 103-8. When ECMO is instituted, patients are generally sedated, paralyzed, and ventilated with relatively high ventilatory pressures, high respiratory rates, and an FiO_2 of 1. The first steps after initiating ECMO are to decrease the respiratory rate (e.g., to 8 to 15 bpm) and eventually lower V_T to 3 to 6 mL/kg PBW.^{32,37,39} This approach is made possible by the concomitant slow increase of gas flow. FiO_2 delivered by the ventilator is decreased to reduce oxygen toxicity and decrease the risk of resorption atelectasis.

All centers agree that plateau pressure should be kept below 25 to 30 cm H_2O ,²⁹⁻³² but there is less agreement

about how to set PEEP. Some centers suggest rapidly reducing PEEP to 10 to 15 cm H_2O ,³² whereas others suggest keeping PEEP unchanged or even increasing it.²² This is the dilemma: whether to let the lungs collapse or try to keep them open.⁵⁵⁻⁵⁹ Centers with greater expertise often apply different approaches in different patients or may even change the ventilatory approach in a given patient according to changes in clinical status. The ventilatory strategy has a big influence on the level of extracorporeal BF and gas flow necessary to maintain adequate oxygenation. In addition, if the residual gas exchange capability of the native lung is poor, a higher device BF and a larger cannula size will be necessary. As soon as the lung function and the patient's clinical condition improves, the patient may be switched from controlled to assisted mechanical ventilation. The current approach is to promote early mobilization. During this phase, oxygenation may not be a major problem anymore and it would now be possible to manipulate gas flow to modulate the patient's respiratory drive and effort.

Monitoring of native lung function may be difficult during VV-ECMO, and there is a paucity of data in the literature and guidelines on how to accomplish this. In many centers, a pulmonary arterial catheter is routinely used, allowing continuous measurement of SvO_2 that, as explained previously, provides an objective measure of the relative contribution of the membrane lung to systemic oxygenation. It also allows one to compute the intrapulmonary shunt fraction; during VV-ECMO, the intrapulmonary shunt fraction is probably the physiologic variable that best assesses native lung gas exchange capability while being least affected by the presence of ECMO. Finally, the

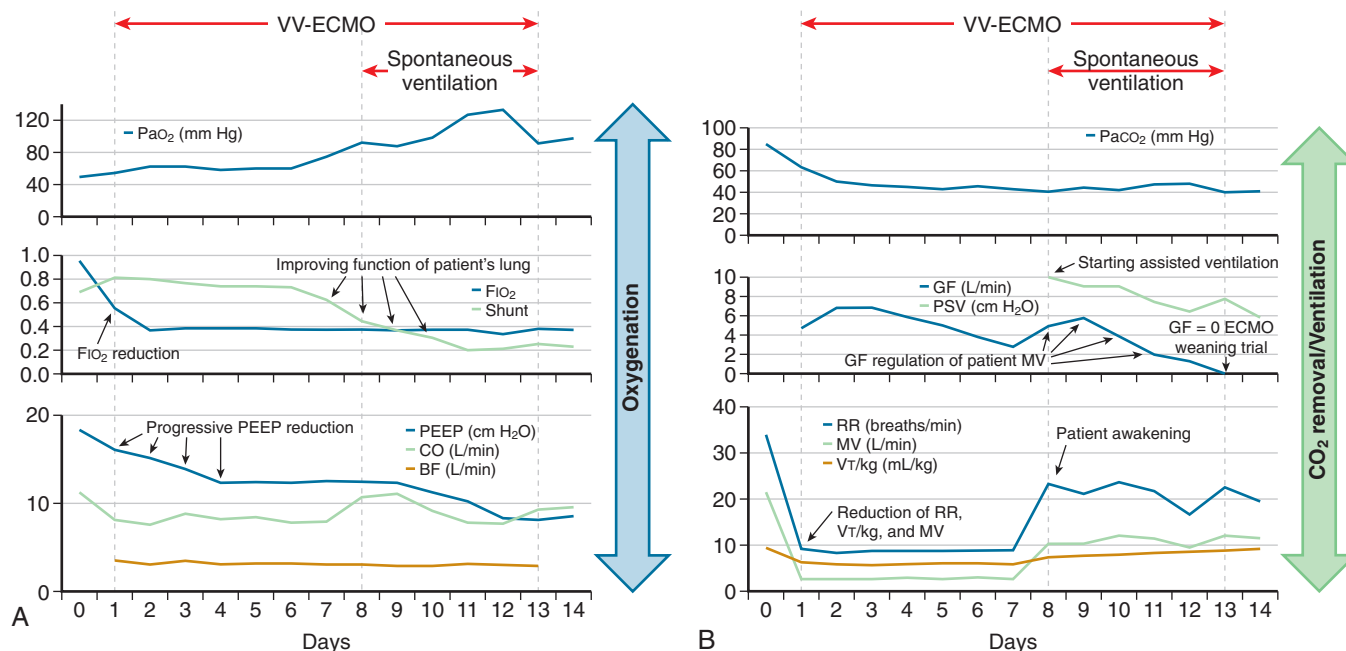


Figure 103-8 Example of ventilatory management in a patient with acute respiratory distress syndrome over 2 weeks. Oxygenation parameters (A) and ventilation parameters (B) are shown, including ventilator and ECMO settings, gas exchange, and hemodynamics day by day. As soon as ECMO starts, respiratory rate (RR), tidal volume ($\text{V}_\text{T}/\text{kg}$), and minute ventilation (MV) are reduced. Positive end-expiratory pressure and FiO_2 are reduced progressively. After the 6th day, intrapulmonary shunt (shunt) starts to decrease and PaO_2 improves. On the 8th day, the patient is awakened. RR, V_T , and mechanical ventilation (MV) are controlled by modulating ECMO sweep gas flow (GF) until the patient is ready to be weaned on the 13th day. Throughout the ECMO treatment, an ECMO blood flow (BF) of around 3 L/min is maintained while the cardiac output ranges between 7 and 10 L/min.

pulmonary artery catheter allows direct measurement of pulmonary arterial pressure, which is important because pulmonary hypertension is common in patients with ARDS treated with ECMO and has negative prognostic implications. A ventilator strategy directed at extreme lung rest is generally associated with worsening pulmonary hypertension, which may necessitate specific treatment (inhaled nitric oxide, sildenafil) to prevent right ventricular failure. It is not unusual that a patient has to be converted from VV-ECMO to VA-ECMO due to development of right ventricular failure.⁵⁴

ANTICOAGULATION AND HEMATOLOGIC MONITORING

Anticoagulation during VV-ECMO is commonly achieved by continuous intravenous heparin infusion, targeted to a *partial thromboplastin time* (aPTT) of 45 to 60 seconds and/or to an *activated clotting time* (ACT) of 1.5 to 2 times normal. The main advantage of ACT is its prompt availability at the bedside. Fibrinogen and antithrombin III should be maintained within the normal ranges.

After starting ECMO, the platelet count usually decreases. Platelet counts should be maintained above 50,000/ μ L in all patients, but a higher threshold of 100,000/ μ L is recommended in the presence of active bleeding.

Activation of the coagulation cascade with subsequent clot formation in the circuit is accompanied by a progressive decrease in platelet counts and fibrinogen levels, and consumption of coagulation factors that may lead to a syndrome similar to disseminated intravascular coagulation. D-dimer levels are a reliable indicator of circuit thrombosis.^{59a} Signs of activation of the coagulation cascade along with decreased performance of the oxygenator and/or increase of trans-membrane pressure should prompt replacement of ECMO circuit.

In the presence of heparin-induced thrombotic thrombocytopenia, the heparin infusion should be discontinued and an alternative anticoagulant such as argatroban should be used.⁶⁰⁻⁶¹

Red cell transfusion policy during ECMO is extremely variable because there is no consensus on the optimal hematocrit level. Available guidelines recommend maintenance of hematocrit within normal limits to minimize blood flow requirements and maximize oxygen delivery of both the membrane lung and native lung.

ECMO COMPLICATIONS

Bleeding complications remain the most frequent and serious complication in ECMO patients. The best sources of information on the incidence of complications are the ELSO registry reports.⁶² Localized bleeding, especially from cannula insertion sites or from surgical sites, are common, reported in approximately 17% and 16% of patients, respectively. Simple compression or packing maneuvers are often sufficient to treat these complications.

Intracranial bleeding is reported in 3.9% of patients and is associated with an overall survival rate of only

17%. Pulmonary and gastrointestinal hemorrhage have been observed in approximately 8% and 5% of patients, respectively.

In the presence of generalized and persistent bleeding, heparin should be reduced or discontinued, and transfusion of fresh frozen plasma and platelets should be considered. To prevent bleeding, it is worthwhile to minimize procedures such as intramuscular or subcutaneous injections, thoracentesis, chest tube insertion, and substitution of nasogastric or urinary catheters.

WEANING FROM VENO-VEIN ECMO

Weaning from ECMO is the progressive reduction of the ECMO contribution to oxygenation and CO₂ removal as the gas exchange capability of the native lung improves and the patient's clinical conditions stabilize (see Fig. 103-8). The decision to disconnect a patient from ECMO is based on the composite assessment of several aspects of the patient's respiratory function (gas exchange function, respiratory mechanics) and hemodynamics. According to the ELSO guidelines, ECMO discontinuation can be considered when 50% to 80% of total gas exchange is supported by the patient's lungs.^{20,22}

Patient readiness for weaning may easily be assessed during VV-ECMO by simply turning off the sweep gas flow. At zero flow, no oxygen is added and no CO₂ is removed from the blood flowing through the ECMO circuit; at this point, the only gas exchange system is the patient's lung. In patients still on controlled mechanical ventilation, during the trial off-ECMO respiratory rate, V_T and F_{IO₂} should be adjusted to values that are considered acceptable without ECMO. Most commonly, ECMO is discontinued when the patient is receiving assisted spontaneous ventilation. After the gas flow is stopped, the patient usually has to increase respiratory effort and minute ventilation, and ventilator support should be adjusted accordingly. When the patient is considered ready, the extracorporeal support can be definitively discontinued and cannulas removed. To remove cannulas placed percutaneously, a purse-string suture, inserted around the cannulation site, is tightened immediately after decannulation and localized pressure is applied for at least 30 minutes.

LOW-FLOW CO₂ REMOVAL: INDICATIONS AND TECHNOLOGY

Following the original concept developed by Kolobow and Gattinoni,^{12,13} several new devices and technical approaches have been recently implemented to perform extracorporeal CO₂ removal. The key is that because these approaches use a lower blood flow, smaller cannulas, and less anticoagulation, they have fewer side effects. The direct consequence of removing CO₂ through these devices is that it is possible to reduce the minute ventilation required through the native lung. Therefore, any clinical situation in which such a reduction may be beneficial represents a potential indication for extracorporeal CO₂ removal. These include clinical

situations in which the goal is to (1) decrease V_T and RR in ARDS patients for “ultraprotective ventilation,” (2) decrease dynamic hyperinflation and facilitate weaning in patients with exacerbations of *chronic obstructive pulmonary disease* (COPD) or severe asthma, or (3) avoid intubation or speed extubation of immunocompromised patients.

Depending on the range of operative blood flows and bypass configuration, the available techniques may be classified as follows:

1. *Low-flow $EC_{CO_2}R$ (LF- $EC_{CO_2}R$)*. Various devices are available that operate with low extracorporeal BF, ranging from 250 to 500 mL/min. Depending on the level of CO_2 content in the venous blood, these systems allow removal of up to about 80 to 100 mL of CO_2 /min (see Fig. 103-7). Most of these systems can be employed with small (14- to 17-French), double-lumen catheters similar to those used for continuous renal replacement techniques. Livigni and colleagues⁶³ were the first to describe one of these devices (Decap, Hemodec, Salerno, Italy) in 2006. A nonocclusive roller pump was used to drive the blood through an oxygenator at 300 mL/min; the device also included a hemofilter in series with the oxygenator to allow recirculation of plasma water in order to dilute the blood entering the oxygenator and prevent blood clotting. Since then, a number of similar devices have been described. The main limitation of these devices is the need for frequent circuit substitutions (every 24 to 48 hours). Recently, this problem has been partially solved by avoiding the use of the hemofilter and using polymethylpentene oxygenators instead of the less expensive polypropylene ones. A different device is the Hemolung (Hemolung, Alung Technologies), in which the membrane lung and the centrifugal pump are combined together, acting as one unit. The pump rotor (impeller) transmits a rotational motion to the blood increasing gas exchange efficiency.^{64,65} Compared with other low-flow systems, the Hemolung shows longer duration and slightly higher CO_2 removal performance.⁶⁶
2. *Arteriovenous CO_2 removal ($AV_{CO_2}R$)*. This AV-ECMO system uses a simplified, high-technology membrane lung (Novalung), characterized by an extremely low resistance to blood flow, high gas transfer efficiency, and absence of a heat exchanger. The Novalung device is applied to an arteriovenous shunt obtained by connecting the femoral artery to the femoral vein using two cannulas inserted percutaneously. According to the mean systemic arterial pressure and to the size of the arterial catheter (15- or 17-French), an extracorporeal BF up to 2.5 L/min can be achieved.⁶⁶ Main limitations of this system are the dependency on the patient's hemodynamic status and the risk of ischemia of the leg distal to the arterial cannulation site. Close monitoring of foot temperature and pulse oximetry is recommended; if signs of ischemia are noted, prompt action is required to prevent permanent damage to the lower limb.
3. *VV- $EC_{CO_2}R$* . Classical $EC_{CO_2}R$ techniques as proposed by Gattinoni and Kolobow use standard adult ECMO systems at a blood flow of 1.5 to 2.5 L/min. By mounting low-medium surface oxygenators such as pediatric or small adult oxygenators on small-size tubes and cannulas, different ranges of flow can be achieved (from

500 mL/min up to 2 to 2.5 L/min), allowing removal of up to 100% of the entire metabolic CO_2 production. For example, a standard pediatric ECMO system with small single- or double-lumen cannulas may be used in adult patients for most CO_2 removal indications. The latest device to enter the arena of CO_2 removal was the *Pump Assist Lung Protection* (PALP, Maquet, Germany). It consists of a small size centrifugal pump and a pediatric-size polymethylpentene oxygenator with no heat exchanger. According to the cannula size, the PALP allows BF from 500 mL/min up to 2.5 L/min and a wide range of CO_2 removal.

CO₂ REMOVAL FOR ULTRAPROTECTIVE VENTILATION IN ARDS

The idea of ultraprotective ventilation originates from the observation that, despite the use of a “protective” V_T , a substantial amount of lung³¹ can still be hyperinflated and hence a further reduction of V_T may be beneficial. Moreover, a direct consequence of the application of protective ventilatory settings is often the necessity of accepting not only lower levels of oxygenation but also a certain degree of respiratory acidosis (permissive hypercapnia). As such, extracorporeal CO_2 removal represents a powerful technique to ensure protective ventilation and prevent VILI, while maintaining adequate gas exchange in patients in whom oxygenation is not a major issue. In 2006, Bein and colleagues⁶⁷ published an important report about the clinical application of $AV_{CO_2}R$ in 90 ARDS patients with severe, unresponsive respiratory failure. With $AV_{CO_2}R$, they were able to reduce ventilation to less injurious settings while oxygenation, by whatever mechanism, was improved. In 22% of the cases, major complications were observed, the most common being ischemia of the leg distal to arterial cannulation. $AV_{CO_2}R$ has also been employed in patients with severe influenza A (H1N1). In these patients, the pumpless bypass allowed reduction of P_{aCO_2} levels, improvement in pH, and more protective mechanical ventilation.⁶⁸

In a recent application of $AV_{CO_2}R$, Bein and colleagues⁶⁸ investigated the effect of an ultraprotective ventilatory strategy on the number of ventilator-free days in ARDS patients. Seventy-nine patients randomly received ultraprotective ventilation with V_T of 3 mL/kg while on $AV_{CO_2}R$ or a conventional protective ventilatory strategy with V_T of 6 mL/kg. The study was underpowered and failed to show significant benefits in the 3 mL/kg group. However, a post hoc analysis showed a significant improvement in ventilator-free days at 60 days in the subgroup of patients who had more severe hypoxemia ($P_{aO_2}/F_{iO_2} < 150$) at baseline.⁶⁹

Terragni and colleagues⁷⁰ were the first to employ a LF- $EC_{CO_2}R$ device (the Decap device) in ARDS patients. They were able to decrease V_T from 6 to 4 mL/kg while keeping constant CO_2 and pH levels in a group of ARDS patients at risk of VILI (P_{plat} higher than 28 cm H_2O). They also showed a reduction of circulating inflammatory cytokines and a reduction of lung hyperinflation.

In summary, the available literature demonstrates that the use of very low V_T combined with some form of extracorporeal CO_2 removal is feasible without major side effects. However, future studies are required to demonstrate the potential survival benefits from the use of ultraprotective ventilatory strategies in ARDS patients.

CO₂ REMOVAL FOR COPD

COPD is the fourth leading cause of death in western countries and is a major cause of morbidity worldwide.⁷¹ COPD patients experience recurrent episodes of hypercapnic respiratory failure (acute exacerbation) that are associated with poor prognosis and increased mortality.⁷² Most patients are successfully managed with *noninvasive positive pressure ventilation* (NIPPV), which represents the standard first-line treatment in acute exacerbations of COPD.⁷³ However, intubation and invasive mechanical ventilation are still required in 26% to 54% of patients.^{74,75} In these patients, invasive mechanical ventilation is associated with a high rate of complications (ventilator-associated pneumonia, barotrauma, hemodynamic compromise and failure to wean), which ultimately increases morbidity and mortality.¹⁹ The main cause of NIPPV failure is the imbalance between the reduced capacity of the respiratory muscles to generate pressure and the respiratory load, which is increased as a result of the high ventilatory needs and expiratory flow limitation. The rationale for the use of CO_2 removal techniques is to decrease minute ventilation and consequently airflow limitation and respiratory effort while decreasing CaO_2 and increasing pH. ECCO_2R may play a role at different stages of COPD exacerbations: to avoid intubation during the NIPPV phase and to reduce the duration of invasive mechanically ventilation and facilitate weaning.

Surprisingly, the use of ECCO_2R in acute COPD patients has not been investigated until recently. Cardenas and colleagues⁷⁶ recently applied a low-flow extracorporeal system in a difficult-to-wean COPD patient; extracorporeal removal of CO_2 allowed a 30% decrease of minute ventilation with concomitant reduction in hyperinflation and improvement in gas exchange. Garcia and colleagues⁷⁷ applied VV- ECCO_2R in 10 COPD patients during weaning from mechanical ventilation or as a bridge to lung transplant. The range of blood flows was 1.6 to 4.9 L/min while the range of $\dot{V}\text{CO}_2$ of the membrane lung was 54 to 570 mL/min. Six patients were successful weaned or underwent transplantation.

The only available report on the use of LF- ECCO_2R techniques was published by Burki and colleagues,⁷⁷ who employed the Hemolung device in a mixed population of COPD patients: 7 patients undergoing NIPPV at high risk of intubation (group 1), 2 patients not weanable from invasive mechanical ventilation (group 2), and 11 patients on invasive mechanical ventilation who had already experienced unsuccessful weaning attempts (group 3). The average blood flow and $\dot{V}\text{CO}_2$ of the membrane lung were 430 ± 74 mL/min and 83 ± 16 mL/min, respectively. The average duration of LF- ECCO_2R treatment was 104 ± 59 hours. All patients in group 1 and 2 and three patients in group 3 were successfully treated.

CO₂ REMOVAL AS BRIDGE TO TRANSPLANT (see Chapter 106)

Several reports have described the use of ECMO as a bridge to lung transplant.⁷⁸⁻⁸⁰ Most commonly, standard ECMO or AVCO_2R has been employed. Fisher and colleagues⁷⁹ reported the use of AVCO_2R in 12 patients suffering from severe ventilation-refractory hypercapnia and respiratory acidosis, with high urgency for lung transplantation. The length of extracorporeal support was 15 ± 8 days; 10 patients were successfully bridged to lung transplant. The only report on the use of LF- ECCO_2R as a bridge to transplant is that of Ricci and colleagues,⁸¹ who applied AVCO_2R in 6 patients and LF- ECCO_2R in another 6 patients. Mean length of extracorporeal support was 13.5 ± 14.2 days, with no differences between the two devices. Finally, a novel and interesting application of ECMO as a bridge to lung transplantation is in patients who are awake and spontaneously breathing. Fuehner and colleagues⁸² reported the results of a retrospective analysis comparing 26 nonintubated patients receiving ECMO as a bridge to lung transplantation with a historical control group of patients treated with conventional mechanical ventilation. Duration of ECMO support or MV was comparable in both groups. Patients in the awake ECMO group were able to eat, drink, and talk. Nineteen of 26 patients in the awake ECMO group were managed without need for intubation.

The possibility of managing patients with acute respiratory failure using ECMO, while avoiding intubation, is exciting. A group of patients for whom awake ECMO may be promising are hematologic and immunocompromised patients.

Key Points

- *Extracorporeal membrane oxygenation* (ECMO) refers to a technique of life support that consists of diverting part of the patient's blood through an artificial lung for gas exchange (oxygenation and CO_2 removal) and then returning it to the patient.
- The primary indications for *veno-venous ECMO* (VV-ECMO) are hypoxemic respiratory failure in patients with a high risk of mortality (patients with $\text{PaO}_2/\text{FiO}_2 < 80$ mm Hg with $\text{FiO}_2 > 90\%$ and Murray score of 3 to 4), and reduction of tidal volume and plateau airway pressure in ARDS patients at high risk of ventilator-induced lung injury. Contraindications to ECMO include advanced age, severe disability, and incurable malignancy.
- Mortality during VV-ECMO correlates with a greater number of days of mechanical ventilation before ECMO institution. ECMO treatment should be established before lung injury has become irreversible.
- The efficiency in removing CO_2 is significantly higher than that of adding oxygen. Depending on the blood flow, the technique may be used mainly for CO_2 removal (ECMO blood flow < 2 L/min) or for both CO_2 removal and oxygenation (ECMO blood flow up to 5 to 6 L/min).

- With ECMO, blood flow is the main determinant of patient oxygenation. Blood flow should be set to the lowest level that provides adequate oxygenation. ECMO sweep gas flow is the main determinant of CO₂ removal and, consequently, determines the minute ventilation needed for the native lung.
- During VV-ECMO, the native lung is managed to prevent VILI. Respiratory rate, tidal volume, plateau airway pressure, and FiO₂ are generally decreased as much as possible while maintaining arterial oxygenation.
- Anticoagulation during VV-ECMO is commonly achieved by continuous intravenous heparin infusion, targeted to a partial thromboplastin time of 45 to 60 seconds and/or to an activated clotting time of 1.5 × normal values. Bleeding complications remain the most frequent complication in ECMO patients. Intracranial bleeding is reported in 3.9% of patients and is associated with an overall survival rate of only 17%.
- The main indications for CO₂ removal are to decrease the tidal volume and respiratory rate in ARDS patients for “ultraprotective ventilation,” decrease dynamic hyperinflation and facilitate weaning in patients with exacerbations of COPD or severe asthma, and avoid intubation or speed extubation of immunocompromised patients.

Complete reference list available at *ExpertConsult*.

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END-OF-LIFE CARE IN RESPIRATORY FAILURE

DOUGLAS B. WHITE, MD, MAS

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INTRODUCTION

Patients with acute, chronic, and acute-on-chronic respiratory failure often suffer from symptoms such as pain and dyspnea and have a high expected mortality rate. These patients may be aggressively treated when they, their families, and their physicians believe that doing so is reasonable and consistent with the patient's treatment preferences. Alternatively, therapies such as mechanical ventilation, which can often reverse respiratory failure in patients with acute decompensation, may be forgone for patients who refuse such treatments and for those whom a trial of intensive treatment fails to achieve the patient's medical goals. When clinically appropriate, the withholding and withdrawal of life-sustaining therapy is supported by ethical and legal principles. These principles, along with the process of medical decision making and the desirable components of end-of-life care, are discussed in detail in this chapter.

PREDICTING THE OUTCOME OF RESPIRATORY FAILURE

The prevalence of diseases that cause respiratory failure, coupled with the morbidity and mortality they cause, has prompted clinicians and investigators alike to seek prognostic information about patients with these disorders. Some of this prognostic information has been derived from single- or multi-institutional studies of specific conditions such as *chronic obstructive pulmonary disease* (COPD),¹ *Pneumocystis jirovecii* pneumonia in patients with the *acquired immunodeficiency syndrome* (AIDS),² and *acute respiratory distress syndrome* (ARDS).³ Other information has come from studies of

patients in certain age groups, such as the elderly,⁴ or from studies of interventions, such as mechanical ventilation.⁵ These studies in turn have been used to develop tools to predict not only patient outcome but also the need for admission to the *intensive care unit* (ICU) for diseases such as pneumonia.⁶

Additional information has been obtained from the use of prognostic scoring systems based largely on physiologic variables such as arterial PCO₂ and PO₂ recorded on hospital admission or at other times. Although many of these systems were developed specifically for patients in ICUs, where physiologic variables are routinely measured, they also have been applied to patients elsewhere. Perhaps the best known prognostic scoring system is the *Acute Physiology and Chronic Health Evaluation* (APACHE), which has gone through four iterations.⁷⁻¹⁰ Similar to APACHE, another prognostic system developed for the *Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatment* (SUPPORT) was based on patient diagnosis, age, number of days in the hospital before study entry, presence of cancer, neurologic function, and 11 physiologic variables recorded on day 3 of study entry.¹¹

Prognosis based on the experience of individual clinicians or institutions is necessarily limited; despite wide use, such prognostication has never been subjected to rigorous evaluation. Although prognostication based on broader investigations of specific diseases should be more accurate, the changing outcome from *P. jirovecii* pneumonia,¹² ARDS,¹³ and other conditions over time limits the use of these investigations in predicting outcome unless they are frequently updated. Furthermore, the tools based on these studies that may be used to determine the need for intensive care for pneumonia and other diseases have limited predictive value, presumably in part because the outcome from these conditions has changed over time.

Physiologically based prognostic scoring systems have been shown to be as accurate—or inaccurate—as clinical assessment by physicians and nurses.¹⁴ They have demonstrated good calibration in that the overall hospital mortality predicted by the systems is comparable with that actually observed in research studies. Nevertheless, the systems have not discriminated well between individual survivors and nonsurvivors. For example, recommended prediction criteria were not effective in identifying a SUPPORT population with a survival prognosis of 6 months or less, limiting their use in determining which patients might generally meet hospice eligibility requirements.¹⁵ Furthermore, the system is poor at predicting imminent death; when the SUPPORT prognostic system was used to derive the likelihood of survival for patients on the day before their actual death, the median predicted likelihood of survival for 2 months was 17% and, when derived 1 week before actual death, the predicted likelihood was 51%.¹⁶

Overall, prognostic scoring systems have contributed greatly to our understanding of the general outcomes of patients with respiratory failure and other conditions. Furthermore, the calibration and discriminatory power of the systems may improve as more studies of the systems are performed and more patients are entered into their databases. Yet, at present, the systems are imperfect in predicting outcome in an individual patient. For the foreseeable future, therefore, the use of prognostic scoring systems should continue to be adjunctive in that they provide information to help in medical decision making but cannot be used by themselves to decide who is destined to die despite intensive care.

TREATMENT GOALS AT THE END OF LIFE

The limitations of prognostication are unfortunate because patients' and their families' predictions of prognosis largely determine their treatment preferences, just as physicians often base their recommendations to patients and families on their own prognostic estimates. For example, many patients with acute respiratory failure due to potentially reversible causes, as well as their families, generally prefer goals focused on rescue and life prolongation until death appears highly likely.¹⁷ In contrast, patients with end-stage chronic lung diseases such as COPD and lung cancer often prefer care that is focused on maintaining comfort rather than on extending their lives.¹⁸ These preferences appear to be related to patients' perceptions of how far advanced their underlying conditions are. For example, hospitalized patients with lung cancer who thought they were going to live at least 6 months were more likely to favor life-sustaining treatment over comfort care than patients who thought they had at least a 10% chance of dying within the next 6 months.¹⁹ Of course, the treatment goals of life prolongation and maintenance of comfort need not be mutually exclusive. Life support and symptom relief are often sought simultaneously.

The term *end-of-life care* is meant to encompass two processes. One, the withholding and withdrawal of life support represents the tapering of life-sustaining interventions

such as pulmonary rehabilitation in the outpatient setting and mechanical ventilation in the ICU.²⁰⁻²³ The other, the administration of palliative treatment, applies, among other things, to improving patient comfort by giving sedatives and analgesics. Combining these two processes signifies that end-of-life care involves more than removing something—in this case, life-saving treatments—from patients. It also means giving something to them: proper medical decision making; thoughtful communication; an appreciation of their needs and those of their families, physicians, and other caregivers; the use of an appropriate setting for death; and the management of pain, dyspnea, and other symptoms. This comprehensive and compassionate approach is what is meant by the expression “intensive caring at the end of life.”²⁴

WHERE AND HOW PATIENTS DIE

In less developed countries, most patients with respiratory failure who die do so at home largely because they have limited access to hospitals and other institutional settings. In the United States and other developed nations, however, patients most often die outside the home. For example, of the large cohort of hospitalized patients in SUPPORT, 47% died within 6 months of study enrollment and 55% of these died during the enrollment hospitalization. Of the patients who survived the enrollment hospitalization, 46% died during hospitalization later that year and only a minority died in a nursing home or hospice, let alone at home.²⁵ Similarly, in one investigation of all the deaths recorded in six states during 1999, 38% of patients died in hospitals and 22% died following ICU admission.²⁶ Using these data to project national estimates, the investigators concluded that 540,000—fully one fifth—of all patients who die in the United States do so in ICUs each year.²⁷

Many factors account for the high prevalence of in-hospital and in-ICU deaths in the United States and, presumably, other developed countries. Among them are the availability of these facilities and of the physicians who admit patients to them and the fact that fewer elderly persons still reside with their families. In the United States, patients must be determined to have less than 6 months to live to qualify for hospice placement, but it is difficult to predict with accuracy which patients have such a limited life expectancy. Most patients want to live as long as possible unless life is a burden to them and their families, and many physicians will try to forestall death unless there is a high degree of certainty that patients will be left with unacceptably burdensome functional impairment.

When ICUs were first developed during the 1950s and 1960s in the United States and Europe, patients who died in them did so despite full support, including attempted *cardiopulmonary resuscitation* (CPR). The wishes of patients and their surrogates regarding such support rarely were solicited, and *do-not-attempt-resuscitation* (DNAR) orders were rarely written for the patients because most hospitals felt obligated to perform CPR on everyone. Indeed, a host of potentially restorative treatments were automatically provided with little concern about their effectiveness or desirability. This approach was based on the belief, held by both health professionals and the public, that technologies

should be used to preserve life whenever possible regardless of the human and economic costs.²⁸

In recent years, however, the “technologic imperative” has been challenged, just as the expenses of the ICU have been scrutinized.²⁹ CPR has been shown often to be ineffective in certain hospitalized patients.³⁰ Patients have been found not to prefer attempted restorative therapy in all instances, and courts in the United States have declared that these patients have a “right to die.”³¹ The ethical, legal, and economic consensus that has resulted from these developments has been reflected in a series of statements from professional societies^{32–37} on the appropriateness of forgoing life-sustaining therapies at the end of life. As a result, although hospitalized patients once died despite attempted restorative treatment, today they are more likely to die during the withholding and withdrawal of life support and the administration of palliative care, especially in the ICU.^{22,23}

ETHICAL AND LEGAL JUSTIFICATION FOR END-OF-LIFE CARE

JUSTIFICATION FOR WITHHOLDING AND WITHDRAWING LIFE-SUSTAINING THERAPY

The withholding and withdrawal of life support is justified by four ethical principles³⁸ (Table 104-1). The first principle is *beneficence*: the physicians’ obligation to do good for patients. Relieving pain and suffering, rather than sustaining life at all costs, may be beneficent in certain situations. The second principle is *nonmaleficence*: the physicians’ obligation to avoid harm. Life-sustaining interventions may be

painful and unlikely to sustain life in a way judged meaningful by the patient, and foregoing such interventions may reduce harm. The third principle is *autonomy*: respect for the patients’ right of self-determination. Patient autonomy is reinforced when patients are allowed to refuse unwanted life-sustaining therapies. The fourth principle is *justice*: the fair allocation of medical resources. Justice may be served if life support is withdrawn from one patient with a poor prognosis to help another patient with a better prognosis, such as during a mass casualty event or in an influenza pandemic.³⁹

In the United States, the withholding and withdrawal of life-sustaining therapies is justified legally by the principles of informed consent and refusal, which have strong roots in common law.⁴⁰ The right of adults who are capable of making medical decisions either to consent to or to refuse treatment was first established in *Schloendorff v. Society of New York Hospitals* in 1914.⁴¹ In this case, the New York Court of Appeals declared: “Every being of adult years and sound mind has the right to determine what should be done with his own body; and a surgeon who performs an operation without his patient’s consent commits an assault, for which he is liable in damages, except in cases of emergency when the patient is unconscious or when it is necessary to operate before consent can be obtained.”

The right of adults with decision-making capacity to refuse treatment was advanced in cases such as *Bartling v. Superior Court*⁴² and *Bouvia v. Superior Court*⁴³ in California. In the first of these cases, the Court of Appeals allowed a man with advanced COPD to have a mechanical ventilator removed against the wishes of his physicians and of the hospital. In the second, the appeals court ordered a hospital to stop force-feeding a quadriplegic woman against her will even though she might die in the process. Most states have dealt with similar cases, and the principle that adults with capacity can refuse unwanted therapies is now widely accepted.

The U.S. Congress supported the importance of respect for patient autonomy by passing the Patient Self-Determination Act. This statute mandates that patients admitted to medical facilities be asked whether they have advance directives and, if they do not already have them, that they be assisted in drawing up directives.⁴⁴ Advance directives are of two types: instructional directives that state what patients want done in a given situation (e.g., living wills) and proxy directives that appoint surrogates to make decisions for them in these situations (e.g., the durable power of attorney for health care). Although there are well-documented shortcomings,⁴⁵ advance directives have the potential for extending patient autonomy beyond the point of incapacity, even though this potential has not been fully realized.⁴⁶

Because of their illness and sedation, many critically ill patients cannot partake in the medical decision-making process. In this circumstance, family members and other surrogates, if available, may consent to or refuse treatment for them. Parents have a long-standing right, indeed an obligation, to speak for their dependent children. The legal right of surrogates to act for incapacitated adult patients was established in *In re Quinlan*⁴⁷ in which the Supreme Court of New Jersey allowed the parents of a vegetative patient to refuse mechanical ventilation for their daughter

Table 104-1 Ethical (Worldwide) and Legal (United States) Principles for Withholding and Withdrawing Life-Sustaining Therapy

ETHICAL PRINCIPLES

Beneficence
Nonmaleficence
Autonomy
Justice

LEGAL PRINCIPLES: RIGHT OF INFORMED CONSENT AND REFUSAL

Exercised by patients with decision-making capacity
Exercised by family members for incapacitated patients
 As authorized under proxy directives
 Using a substituted-judgment standard (facilitated by instructional directives)
 Using a best-interests standard
Exercised by a court-appointed conservator
 Using a substituted-judgment standard (facilitated by instructional directives)
 Using a best-interests standard
Exercised by physicians, often after ethics committee review
 Using a substituted-judgment standard (facilitated by instructional directives) (legal justification in a few states)
 Using a best-interests standard (no legal justification)

From Beauchamp TL, Childress JF, editors: Principles of biomedical ethics, ed 4. Oxford, 1994, Oxford University Press; and Luce JM, Alpers A: End-of-life care: what do the American courts say? *Crit Care Med* 29:N40–N45, 2001.

through the mechanism of surrogate decision making. Through this mechanism, family members also were allowed to make life-determining decisions for their adult relative in *Barber v. Superior Court*⁴⁸ in California. In this case, the court determined that not only mechanical ventilation but also nutrition and hydration—indeed, any therapy that was not clearly benefiting the patient—could be forgone.

The U.S. Supreme Court dealt with the issue of surrogate decision making in the case of *Cruzan v. Director, Missouri Department of Health*.⁴⁹ In this case, a family argued that it was unconstitutional for a chronic care facility in Missouri to deny their request to remove a feeding tube from their vegetative adult daughter. The facility argued that the daughter had not specified her wishes not to be fed artificially in advance of incapacity. In its *Cruzan* decision, the Supreme Court allowed Missouri and other states to require “clear and convincing evidence” of patients’ prior wishes before care was forgone for them. Nevertheless, it did not demand this requirement of other states, and it accepted the argument that the right of adult patients with decision-making capacity to refuse any and all therapies was protected under the Constitution.

Substituted judgment, through which surrogates make inferences about what treatment decisions patients *would* make if they were able to make decisions for themselves, is the highest standard under which surrogates may make medical decisions for incapacitated patients. Nevertheless, surrogates also may consider the patients’ best interests. One delineation of a best-interests standard is that of the New Jersey Supreme Court relative to *In re Conroy*.⁵⁰ In this case, a nephew asked that a feeding tube be withdrawn from his elderly aunt, who had not declared her wishes before becoming demented, on the grounds that forgoing nutrition and hydration was in her best interest. The court would allow the best-interests standard in this case only because the burdens of continuing the patient’s life outweighed the benefits and because the recurring, unavoidable pain of life with treatment was such that administering therapies such as nutrition and hydration was inhumane. These requirements were imposed because the court considered the best-interest standard less compelling than the substituted-judgment standard.

Another legal perspective on the standards of substituted judgment and best interests came in the case of *Wendland v. Wendland*.⁵¹ This case involved a middle-aged man who was conscious but hemiplegic, uncommunicative, and unable to feed himself after a motor vehicle accident. After his feeding tube repeatedly became dislodged, his wife, who was his conservator, refused to authorize its reinsertion. In support of her decision, she cited her husband’s statements before his accident that he would not want to live in a severely debilitated condition. At this point, his mother went to court to block the plan not to reinsert the feeding tube, and it was reinserted. Mr. Wendland subsequently died, but the California Supreme Court deliberated on the issue of whether a conservator could withhold or withdraw life support from a patient who was conscious but incapable of articulating his current wishes. The Court ultimately ruled that feedings could be discontinued only if there was clear and convincing evidence that “the patient wished to

refuse life-sustaining treatment or that to withhold such treatment would have been in his best interest,” which was not thought to be true of Mr. Wendland. The decision in this case suggests that the courts are unlikely to allow surrogates to limit treatment in patients who are neither terminally ill nor permanently unconscious unless the patients have specified what they would want done in such a situation.⁵²

Legal guidelines are less clear when incapacitated patients lack family members or other surrogates. Some states (e.g., Hawaii, Connecticut) allow physicians to make decisions for such patients on the basis of wishes expressed to the physicians when the patients had decision-making capacity. However, no state explicitly allows physicians to make decisions on the basis of a best-interests standard. Be that as it may, as shown in a study from seven U.S. medical centers, some physicians do make decisions to withhold or withdraw life-sustaining therapy from incapacitated patients on the basis of best interests, usually after consultation with their colleagues or with a hospital ethics committee.⁵³ Other physicians ask the probate court to appoint conservators or other advocates for the patients, presumably to ensure a fair, transparent, and deliberate process of decision making for these vulnerable patients.

Before leaving the subject of justification for withholding and withdrawing life support, it is important to mention that decisions regarding this process are different for brain-dead patients than they are in patients who have lesser degrees of neurologic impairment. In the United States, death is defined as the total and irreversible loss of either cardiopulmonary function or the function of the entire brain.⁵⁴ The determination of death by whole-brain criteria requires the demonstration of coma, indicating the loss of cerebral hemispheric function, and the documentation of absent corneal, oculovestibular, and ventilatory reflexes, indicating loss of function of the brain stem. Absence of ventilatory reflexes is demonstrated by an abnormal apnea test in which intubated, nonparalyzed patients removed from mechanical ventilation and given oxygen fail to initiate respiratory muscle efforts despite an increase of their arterial PCO₂ to at least 60 mm Hg.

Life-sustaining therapy usually can be forgone without a formal declaration of brain death. Conversely, some surrogates may insist that therapy be continued until patients die, in which case determining death by whole-brain criteria may be desirable. That said, the only patients in whom brain death must be determined are those who seem to be dead and whose organs will be transplanted after life support is withheld or withdrawn. Regarding the latter patients, one might argue that withdrawing life support from someone who is dead is an oxymoron. Because of this argument, and because brain-dead patients usually receive mechanical ventilation and other interventions only until their organs can be harvested, “life support” for them can be likened to “organ support.”

The ethical and legal justification for removing therapies from brain-dead patients is not just that the therapies generally are unwanted by patients and surrogates in this situation but also that the patients are dead and cannot benefit from them. Inasmuch as the patients are dead, physicians have no obligation to treat them, and they do not need to

obtain consent from surrogates before withholding or withdrawing treatment. Nevertheless, consent is required for organ retrieval and transplantation. Furthermore, the families of brain-dead patients frequently do not understand the concept of brain death and consider the patients to be alive because their chests rise and fall as the ventilator cycles and a tracing of their cardiac rhythms is displayed on the bedside monitor. Families also may reject the concept of brain death for religious reasons.

Motivated by consideration for such families and by a desire to gain their consent for organ donation, many physicians are appropriately nonconfrontational in addressing the issue of brain death. They take time to explain what death means in a biologic and legal sense, how brain death is determined, and how valuable transplantation can be for organ recipients, as well as for the families of patients who serve as organ donors and even for the patients themselves. This approach is generally helpful to families, regardless of whether they ultimately approve transplantation. It is also useful in maintaining emotional equilibrium during a difficult time for all parties in the ICU.⁵⁵

MEDICAL FUTILITY

Although the ethical principle of autonomy and the legal principles of informed consent and refusal are the most compelling justifications for withholding and withdrawing life support, the concept of futility has also been used as a justification. This concept is invoked on the relatively rare occasions when patients or their surrogates request interventions (particularly those that are costly, scarce, or both) that physicians object to because they believe the patients cannot benefit from them. Some treatments, such as brain transplantation for brain-dead patients, are physiologically futile in that they cannot be accomplished. Other treatments, such as the use of mechanical ventilation in a permanently comatose or brain-dead patient, can succeed physiologically, but some physicians may consider them inappropriate because they cannot result in an outcome that the clinician judges to be valuable.

One group of investigators⁵⁶ sought to define medical futility as an intervention that has been useless in the last 100 cases or that “merely preserves unconsciousness and cannot end dependence on intensive medical care.” In a similar vein, the American Thoracic Society³³ argued that “a life-sustaining intervention may be withheld or withdrawn from a patient without the consent of the patient or surrogate if the intervention is judged to be futile. A life-sustaining intervention is futile if reasoning and experience indicate that the intervention would be highly unlikely to result in a meaningful survival for that patient. Here, meaningful survival specifically refers to a quality or duration of survival that would have value to that patient as an individual. Survival in a state with permanent lack of consciousness (i.e., completely lacking cognitive and sentient capacity) may be generally regarded as having no value for such a patient.”

Despite what has been called the “futility movement,” a broad concept of futility has never achieved consensus within the medical community in the United States or elsewhere, and the American Thoracic Society position has not

gained broad support.⁵⁷ A contrary position has been advanced by the Society of Critical Care Medicine,⁵⁸ which holds that “treatments should be defined as futile only when they will not accomplish their intended goal. Treatments that are extremely unlikely to be beneficial, are extremely costly, or are of uncertain benefit may be considered inappropriate and hence inadvisable but should not be labeled futile. Futile treatments constitute a small fraction of medical care. Thus, employing the concept of futile care in medical decision making will not primarily contribute to a reduction in resource use.”

In some ways, the development of prognostic scoring systems can be seen as an attempt to predict which patients cannot benefit from therapies, especially those that are expensive, and thereby provide a rationale for denying such therapies to them.⁵⁹ Yet most patients and families are quite willing to forgo such therapies even when physicians are not, as indicated by SUPPORT.⁶⁰ Furthermore, a study of the theoretical implementation of a strict futility guideline for more than 4000 SUPPORT patients demonstrated that only minimal cost savings could be realized by not treating patients who were predicted to have a 1% or less 2-month survival.⁶¹ Nearly 75% of the savings in hospital days would have resulted from stopping treatment for 12 patients, one half of whom were younger than 51 years of age and 1 of whom lived 10 months when treatment was continued.

The emphasis on cost savings in the aforementioned study speaks to the fact that arguments about futility often have economic overtones. At one time, it appeared that American society could transition from a “rule of rescue,” in which large sums of money were spent on therapies providing only marginal benefit, to a “rule of reason,” in which this money could be used for primary and preventive care.⁶² Arguments based on futility seem to provide a rationale for forgoing treatment on the grounds that it is not worthwhile, apart from the matter of cost. Yet these arguments conceal value-laden assumptions, and they obscure the underlying issue of rationing.⁶³

Thus, the greatest problem with medical futility is not how it is defined but who defines it.⁶⁴ In this regard, the debate over futility pits physicians, who believe that their training and experience enable them to know what therapies are truly useful and cost-effective, against patients and families, who may feel entitled to such therapies regardless of whether they pay for them directly. Physicians certainly are able to identify physiologic futility, and they are not legally or ethically required to perform procedures they consider nonbeneficial and below professional standards. Benefit, however, seems often to be in the eyes of the beholder: although physicians may regard mere prolongation of life as undesirable in certain circumstances, patients and families may consider it valuable. When these persons want treatments that physicians consider futile in more than a physiologic sense, which party should decide?

The American Medical Association Council on Ethical and Judicial Affairs has stated that, “Since definitions of futile care are value laden, universal consensus on futile care is unlikely to be achieved.”⁶⁵ At the same time, the Council has recommended a process-based approach to futility determinations whereby patients or families who

insisted on therapies that physicians considered futile would be required to undergo a dispute resolution process. Central to this process would be mediation by a hospital ethics committee. If resolution was not reached through mediation, the patients would be transferred to another institution or care would be terminated if transfer were impossible. So-called futility policies based on this model have been developed in Houston, Texas, and other cities.⁶⁶

Based on the Houston experience, the State of Texas adopted a law providing an extrajudicial due process mechanism for resolving medical futility disputes. A survey⁶⁷ of Texas hospitals' experience with this law indicates that a minority of the hospitals had used the due process mechanism and that life-sustaining treatment was discontinued against patients' or surrogates' wishes in only a small number of cases. Furthermore, the constitutionality of the Texas statute has not been determined at the appellate or U.S. Supreme Court level. As a result, the implications of the Texas statute for that state and for the rest of the United States are unclear.

To date, legal cases such as *In re Helen Wanglie*⁶⁸ and *In the Matter of Baby K*⁶⁹ suggest that judges are unwilling to allow physicians to withhold or withdraw support from patients when the physicians ask to do so and the patients or families object. In the first of these cases, a court in Minneapolis refused to replace a husband who was seeking continued life support for his wife, life support which her physicians considered nonbeneficial, with another conservator who might allow support to be forgone. In the second, a Virginia court required that physicians repeatedly resuscitate an anencephalic infant at the request of its mother but against their own wishes, reasoning that to do otherwise would violate the Emergency Medical Treatment and Active Labor Act.

In contrast, the case of *Gilgunn v. Massachusetts General Hospital*⁷⁰ indicates that physicians are likely to obtain legal results more to their liking when they refuse to provide treatment they consider futile and defend their decisions in court as consistent with professional standards. In this case, a jury in Boston exonerated physicians at Massachusetts General Hospital for removing a patient from life support and writing a DNAR order for her over the objections of her daughter. The patient's husband and other children did not protest the physicians' actions, and the jury apparently believed that the physicians acted within the standard of care. This case does not set legal precedent because a written judgment was not rendered. Nevertheless, the jury decision in *Gilgunn* suggests some public support for the concept of futility.

How the debate over futility will be resolved is uncertain. Because patient autonomy is so widely accepted in the United States, because national health insurance does not exist there, and because patients and families are suspicious of managed care organizations, it seems unlikely that American physicians will soon be granted a mandate to restrict services on the basis of futility. This is not the case in other countries, however, where resources are limited, national health insurance exists, and physicians implicitly and explicitly are allowed to ration care.⁷¹ Whether physicians will continue to exercise this and other prerogatives if American-style patient autonomy becomes more prevalent in their countries remains to be seen.

JUSTIFICATION FOR ADMINISTERING PALLIATIVE CARE

The U.S. Supreme Court has provided ethical and legal justification for the administration of palliative care at the end of life, in the cases of *Washington v. Glucksberg*⁷² and *Vacco v. Quill*.⁷³ These cases dealt with the constitutionality of laws prohibiting physician-assisted suicide in the states of Washington and New York. In *Glucksberg*, the Court decided that terminally ill patients do not have a liberty interest in committing suicide or in receiving a physician's assistance in committing suicide because of the long tradition of prohibiting suicide in the United States and because of the states' legitimate interest in continuing to make suicide illegal. In *Vacco*, it distinguished between assisted suicide and withholding and withdrawal of life support. "Everyone, regardless of physical condition, is entitled, if competent, to refuse lifesaving medical treatment; no one is permitted to assist a suicide," the Court wrote. "When a patient refuses life-sustaining medical treatment, he dies from an underlying fatal disease or pathology; but if a patient ingests lethal medicine prescribed by a physician, he is killed by that medication."

In *Glucksberg* and *Vacco*, five justices reasoned that Washington and New York could prohibit assisted suicide because these states had no barriers that prevented patients from receiving medications to relieve pain and suffering. However, as Justice Breyer wrote, "Were state laws to prevent the provision of palliative care, including the administration of drugs as needed to avoid pain at the end of life, an action against such law might be called for by the Supreme Court." Through this and other statements, a majority of the justices suggested that being free of pain while dying was a liberty interest protected under the Constitution.⁷⁴

The Supreme Court distinguished assisted suicide from palliative care in *Glucksberg* and *Vacco* by accepting the ethical principle of double effect. Under this rule, acts such as giving sedatives and analgesics that lead to morally good effects, such as the relief of suffering, are permissible even if they produce morally bad effects, such as the hastening of death, provided that only the good effect is intended. The morally bad effect may be foreseen in that physicians are aware of its possibility and even its likelihood, but they may not wish it. The bad effect also may not be a means to the good effect, and the good effect must outweigh the bad one; that is, risking death is reasonable in palliating a terminally ill patient only if there are no less risky ways of relieving suffering.⁷⁵

The Supreme Court's approval of palliative care included sanctioning the practice of *terminal sedation*, in which patients are rendered unconscious while life-sustaining therapies, including nutrition and hydration, are withdrawn. Under *Vacco*, a state may allow terminal sedation if it is "based on informed consent and the double effect. Just as a state may prohibit assisted suicide while permitting patients to refuse unwanted lifesaving treatment, it may permit palliative care related to that refusal, which may have the foreseen but unintended 'double effect' of hastening the patient's death."

Some have argued that the rule of double effect has many shortcomings as an ethical guideline, in particular

because it overlooks the complexity of human intention.^{76,77} Such complexity was demonstrated in a study of the administration of sedatives and analgesics during the withholding and withdrawal of life support in two ICUs.⁷⁸ In this study, physicians indicated that they ordered these agents primarily to decrease pain, anxiety, and dyspnea—but also to hasten death—in 39% of critically ill patients. In another investigation, 16% of a sample of ICU nurses reported that they had engaged in assisted suicide or euthanasia while trying to relieve patient suffering, often without physicians' knowledge.⁷⁹

Just as some physicians and nurses have mixed motives in caring for dying patients, so do some family members want to ease suffering and hasten death simultaneously in their relatives. That such motivation is widespread presumably accounts for the fact that few physicians who are suspected of participating in assisted suicide or euthanasia have been punished through the criminal justice system in the United States.⁸⁰ In general, physicians and other caregivers are unlikely to be prosecuted or even criticized if they act compassionately in administering sedatives and analgesics to treat distressing symptoms in dying patients and do so with informed consent.

In *Glucksberg* and *Vacco*, the Supreme Court did not judge the laws prohibiting physician-assisted suicide in Washington and New York to be unconstitutional. Nevertheless, it also did not prevent other states from permitting physician-assisted suicide if they chose to do so. Physician-assisted suicide was legalized in Oregon in 1997 under that state's Death with Dignity Act. Experience over the subsequent 2 years indicated that few patients requested lethal medications, that physicians granted few requests, and that palliative interventions led some, but not all, patients to change their minds about assisted suicide.⁸¹ By and large, the decision to request and use a prescription for lethal medication stemmed from patients' concern about loss of autonomy or control of bodily functions, not from fear of intractable pain or financial loss.⁸²

Physician-assisted suicide (in which physicians prescribe potentially lethal medications that patients themselves can take) and euthanasia (in which physicians actually administer the medications) are practiced in several European countries.⁸³ Although none of these countries has legalized the practices, physicians in the Netherlands have not been punished for performing them since 1991, when a national study revealed that assisted suicide and euthanasia were being performed.⁸⁴ Instead, Dutch physicians are required to report all cases in which they administered or supplied drugs with the explicit intent of hastening death. Patient requests for assisted suicide or euthanasia rose from 8900 in 1990 to 9700 in 1995 and remained stable at 9700 in 2003 according to one Dutch study.⁸⁵ Assisted suicide was listed as the cause of death on only 0.2% of all death certificates in the Netherlands during the same years. In 1990, 64% of Dutch physicians thought that patients have a right to decide about their own life or death; the percentage of physicians was the same in 1995 but fell to 56% in 2001. These data suggest that, in the Netherlands as in Oregon, the demand for assisted suicide has not increased; in fact, over time, Dutch physicians appear to have grown more reluctant in their attitude toward this practice. How common assisted suicide will become in other European

countries and how their laws will deal with these practices are unclear.

MEDICAL DECISION MAKING AT THE END OF LIFE

TWO MODELS OF THE PHYSICIAN-PATIENT RELATIONSHIP

Medical decisions may be made by physicians, patients, their families, or other surrogates alone or in combination. How decisions are actually made depends in large part on the model of the physician-patient relationship that is used.

Perhaps the oldest model is *paternalistic*; this model has also been called parental or priestly. According to it, physicians act as guardians in defining what their patients' interests are and then serving these interests as they see fit, with little or no input from the patients themselves.⁸⁶ With pediatric patients, the families' input similarly might not be sought or might be disregarded. The paternalistic model overlooks the strong social norm of respect for patient autonomy and the reality that in pluralistic societies it is unlikely that physicians can reliably discern what treatments most advance the interests of their diverse patients. The paternalistic model once dominated medical decision making at the end of life in the United States. In fact, the early cases such as *Bartling*, *Bouvia*, and *Quinlan* were brought because physicians and hospitals were unwilling to let patients or surrogates refuse therapy. It is ironic—and perhaps a cautionary tale about the limits of medical paternalism—that some physicians today demand that patients and families forgo treatment that other physicians once insisted they accept.

In another model, the *deliberative* or shared model, physicians and patients/surrogates collaborate to help patients define their health-related values, discuss treatment options, and together decide which alternative is best. This process is more than the mere passing of information: It is a moral deliberation, based on a mutual understanding of the medical facts and the patient's values.⁸⁷ The shared model of medical decision making is best suited for situations in which physicians, patients, and families have adequate time to deliberate, when reasonable treatment options exist, and when the best course of action may vary according to patients' values and preferences. Evidence from audiorecording ICU family conferences suggests that the process of shared decision making about life support for incapacitated, critically ill patients is often suboptimal.⁸⁸ For example, clinicians frequently failed to explain principles of surrogate decision making, elicit patients' values and preferences, and discuss reasonable treatment options, including a purely palliative approach to care.⁸⁹⁻⁹²

Medical decision making and the attitudes that underlie it vary from country to country. For example, although the shared model is gaining popularity in France, the paternalistic model is still sometimes employed at the end of life in ICUs there. Physicians are granted legal decision-making prerogatives in these ICUs that are not permitted for their American counterparts. Furthermore, French families have had no legal right to make decisions for patients who cannot

make decisions for themselves.⁹³ Variations in attitudes also exist within a given country depending on its ethnic and cultural composition. For example, in one study in the United States, Korean Americans and Mexican Americans were significantly less likely than European Americans and African Americans to believe that a patient should be told the diagnosis of metastatic cancer or that the patient should make the decision about the use of life-sustaining therapy.⁹⁴ In another study, African Americans were more likely than European Americans to want to be kept alive on life support.⁹⁵ Interviews of these African Americans subjects documented a deep distrust of the health care system and a fear that access to health care was based on one's ability to pay.

IMPORTANCE OF PHYSICIAN, PATIENT, AND FAMILY COMMUNICATION

Of course, American families would not need to be so involved in medical decision making in the ICU setting if physicians facilitated such decision making when the patients' diseases were less advanced and they could speak for themselves.⁹⁶ Yet SUPPORT⁹⁷ and other studies have shown that physicians and patients rarely discuss end-of-life issues in advance of the patients' deterioration, even when patients reside in nursing homes. A study of patients with severe COPD enrolled in pulmonary rehabilitation revealed that almost all had health concerns, the most common of which was fear of increasing dyspnea.⁹⁸ Although many of the patients had concerns about being intubated, only a minority had completed an advance directive describing their choices. Furthermore, although the patients generally wanted discussions with their physicians, only 19% had such discussions, only 15% had discussed life support, and only 14% thought that their physicians understood their end-of-life wishes.

Why patients with chronic and terminal diseases do not discuss end-of-life care with their physicians has been the subject of several investigations. In the study of patients with COPD enrolled in pulmonary rehabilitation, those patients who had not had discussions gave the most important reasons as their own procrastination and the fact that their physicians had not brought up the topic.⁹⁸ When these patients participated in an end-of-life educational intervention as part of their rehabilitation, they were more likely to pursue such discussions with their physicians and to complete durable powers of attorney for health care.

In another study of patients with advanced AIDS, structured interviews of the patients and their physicians were used to identify barriers to communication.⁹⁹ Patients who had not had discussions with their physicians about end-of-life care most frequently agreed that, "I don't like talking about getting very sick" and "I would rather concentrate on staying alive than talking about death." Physicians who did not initiate discussions most often agreed that, "There is too little time during our appointments to discuss everything we should" and "I worry that discussing end-of-life with [patient name] will take away his or her hope." Many physicians in this study acknowledged that they felt uncomfortable discussing end-of-life issues, suggesting that their own discomfort was as important as the lack of time for discussions in inhibiting communication.

Limited communication between physicians and patients was also reported in SUPPORT.⁹⁷ Furthermore, SUPPORT revealed that communication was frequently inadequate between physicians and the families of critically ill patients. This finding was corroborated by a study from an ICU in France in which half the families of critically ill patients reported the same inadequacy.¹⁰⁰

A follow-up investigation from that and other ICUs in France indicated that family satisfaction with their relatives' care was due in part to their being of French descent and having a language and cultural values similar to those of the ICU caregivers.¹⁰¹ Family satisfaction also related to information provided by hospital physicians, a patient-to-nurse ratio of 3:1 or less, knowledge of the specific role of each caregiver, help from the family's own physician, sufficient time spent giving information, and an absence of perceived contradictions in information provided by caregivers.

In a study from one U.S. hospital, families were interviewed about their experiences in the ICU and the decision-making process for withholding or withdrawing life support.¹⁰² They reported a high incidence of conflicts, the vast majority of which were between themselves and physicians. The conflicts most often involved problems in communication or perceived unprofessional behavior, such as disregarding the primary caregiver in treatment decisions. These families identified pastoral care and prior discussion of treatment preferences as sources of psychological support. They appreciated lenient visiting hours and the availability of family conference rooms. Most of the families singled out attending physicians as the preferred source of information and reassurance.

IMPROVING COMMUNICATION AND THE QUALITY OF CARE AT THE END OF LIFE

Several strategies have been demonstrated to improve various aspects of decision making and surrogates' psychological outcomes in ICUs. Distribution of a family information leaflet in the ICUs improved family understanding of how the units functioned and increased their satisfaction with the care given therein.¹⁰³ Intensive communication achieved through proactive, frequent family meetings led by attending physicians increased family satisfaction and also decreased ICU length of stay among patients who died.¹⁰⁴ A brief communication intervention in French ICUs for families of patients judged to be certain to die resulted in improved bereavement outcomes.¹⁰⁵

Although the intervention decreased negative bereavement outcomes, it did not contain strategies to improve the quality of decision making. A large, randomized, controlled trial of ethics consultations¹⁰⁶ and two single-center, non-experimental studies of palliative care consultation^{107,108} addressed these issues; these interventions yielded shorter ICU length of stay among nonsurvivors, but there was no assessment of whether the intervention improved the patient-centeredness of end-of-life decisions or improved family outcomes.

UNDERSTANDING WHAT PHYSICIANS, PATIENTS, AND FAMILIES NEED AT THE END OF LIFE

End-of-life care could be optimized if the needs of the parties involved in the dying process were better understood. In this regard, a survey of seriously ill patients, recently bereaved families, physicians, and other caregivers revealed that decisions about treatment preferences, knowing what to expect about one's physical condition, and preparation for death were important to all four groups at the end of life.¹⁰⁹ Other important needs were sharing time with family and friends; being kept clean; being free of pain, anxiety, and dyspnea; and being treated as a "whole person." Patients also rated as important being mentally aware, coming to peace with God, not being a burden to their families, being able to help others, praying, having funeral arrangements planned, and gaining a sense of completion in life (Table 104-2).

The needs of families have also been assessed in several studies using a survey tool called the Critical Care Family Needs Inventory. In an overview of recommendations for end-of-life care in the ICU, the Ethics Committee of the Society of Critical Care Medicine¹¹⁰ combined these studies to determine what these needs are. Overall, family needs include being with the dying patient, being helpful to that patient, being informed of the dying patient's changing condition, understanding what is being done to the patient and why, being assured of the patient's comfort, being comforted, having an opportunity to express emotions, being assured that the family's decisions were right, finding meaning in the patient's death, and having personal needs attended to during the dying process.

Unfortunately, the needs of physicians and others who care for dying patients have not been well addressed.

Nevertheless, at a minimum, all caregivers probably need to feel comfortable during the dying process, to gain experience from it, to feel supported by their colleagues and by their institutions, and to have opportunities for bereavement themselves. Nurses, respiratory therapists, social workers, and clergy who work alongside physicians want to know that the physicians respect them, provide them with adequate information, take their opinions into account, and engage in proper decision-making practices at the end of life.¹¹¹

PROVIDING APPROPRIATE SETTINGS FOR DYING PATIENTS

Under the deliberative model of the physician-patient relationship, physicians are obligated to help patients understand their conditions, explore their therapeutic options, and decide what is best for them. Essential to this relationship is preparing patients for death when appropriate. Such preparation should include consideration of whether the patients' interests are best served by hospital and ICU admission when death is imminent, assuming that impending death can be identified. Many patients, especially those with COPD and other chronic diseases that allow time for advance planning as death approaches, decide to die in a hospice or at home if given the opportunity.

Terminal patients may choose a trial of attempted restorative treatment in the hospital or undergo it because their wishes are not known. If the trial fails, such patients should be allowed to die in an environment that is comfortable for them and their families. A private room with enough space to accommodate visitors might be such an environment. Visiting hours should be relaxed, if necessary, to allow families and friends to spend as much time as they wish with dying patients. Some hospitals have separate palliative care units for this purpose. Others offer palliative care teams or services that consult throughout the hospital.^{112,113}

Table 104-2 Factors Important to Patients and Family at End-of-Life

PHYSICAL NEEDS

Maintaining hygiene
Release from breathing difficulties
Remaining conscious and clearheaded to the end
Physical independence to the end

EMOTIONAL NEEDS

Regular update on medical condition
Opportunity to discuss fears and anxieties
Telling the absolute truth to patients
Involving patients in care policy and decisions

SPIRITUAL NEEDS

Being at one with God
Praying
Conversation with cleric about meaning of death

SOCIAL NEEDS

Capacity to help others

EMOTIONAL AND SPIRITUAL SUPPORT

Reviews of end-of-life care in and outside the ICU have emphasized the importance of providing emotional and spiritual support to dying patients and their families.¹¹⁴ Physicians contribute to this support, of course, and their regular communications and presence at the bedside are greatly appreciated. Nurses, social workers, clergy, and other members of the health care team deliver most of the support, however. Occasionally, patients or their families request that friends, caregivers, and religious persons from outside a particular institution provide consultations or participate in bedside rituals or observances. These should be allowed, if not encouraged, unless they interfere with patient care.

End-of-life care may extend after death in that physicians, nurses, and others who have helped the patients' families when the patients were alive have much to offer them thereafter. Advising on the disposition of bodies, reporting the

Adapted from Natan MB, Garfinkel D, Shachar I: End-of-life needs as perceived by terminally ill older adult patients, family and staff. *Eur J Oncol Nurs* 14:299–303, 2010.

results of autopsy studies, coordinating burials and funeral services, and attending funerals are among the professional responsibilities of caregivers that are greatly appreciated by families. These responsibilities can be assumed by independent bereavement follow-up services, which have been described at one hospital.¹¹⁵ Alternatively, caregivers who have established personal relationships with families in the ICU and other settings may maintain them after the patients' death.

Physicians, nurses, and other caregivers have their own emotional and spiritual needs, of course, and caring for dying patients and their families exacts an appreciable toll on them. Because of this, caregivers themselves should have opportunities to grieve. Conferences scheduled after patients die provide both an opportunity for bereavement and a mechanism for evaluating the processes of withholding and withdrawal of life support and of administering palliative care to them. Such evaluation may lead to improvements in these processes for future patients.

SYMPTOM MANAGEMENT

WHY SYMPTOMS MAY BE POORLY MANAGED

Management of pain and other symptoms is a traditional role and responsibility of the medical profession. Nevertheless, patients too frequently die with pain and other distressing symptoms. Nearly 50% of SUPPORT patients or their surrogates interviewed after study enrollment reported that the patients experienced pain during hospitalization.¹¹⁶ Nearly 15% reported extremely or moderately severe pain at least half the time, and many of those patients with pain were dissatisfied with its control. Uncontrolled pain was most common among patients with more dependence on others in activities of daily living and who had more comorbid conditions, more anxiety, more depression, and a poorer quality of life.¹¹⁶

The poor management of pain and other symptoms in some patients is probably due in large part to the strong emphasis placed on the diagnosis and treatment of diseases rather than on the relief of symptoms. Palliative care reverses this emphasis and, when properly applied, should help increase patient comfort at the end of life. Nevertheless, the transition from restorative to palliative care is far from seamless for many patients. In this regard, it is difficult for patients and their families to know when to stop requesting treatment, just as it is for physicians and other caregivers to stop recommending life-sustaining therapies.

Pain and other symptoms may also be poorly managed because they are subjective experiences that are not easily assessed by objective methods. Pain and sedation scales have been developed to quantify the levels of pain and anxiety among patients who can communicate. Nevertheless, some patients cannot adequately communicate these sensations, either because they cannot find the words or because they are intubated and sedated. To detect pain in these patients, physicians and other caregivers must attend to patient grimacing and other admittedly nonspecific manifestations of pain, including tachycardia and hypertension. Although bispectral analysis of the electroencephalogram has been used to assess the level of sedation in ICU patients,

the correlation of this technique with sedation scales and, most important, with the subjective experiences of patients is unclear.¹¹⁷

Another reason that symptoms are poorly managed at the end of life is that patients differ in their desire for symptom relief. Some patients value symptom relief highly and would prefer to be rendered unconscious rather than to experience pain, anxiety, or dyspnea, especially at the end of life. Others, however, would be willing to tolerate these symptoms or have them mitigated only slightly in order to stay awake. Dying patients may find it difficult to titrate sedatives and analgesics to their desired level of consciousness, although they should be encouraged to do so. Physicians and caregivers may find it even more difficult to achieve the ideal level of sedation and analgesia for patients who cannot communicate or administer drugs to themselves.

Finally, symptoms may be inadequately managed because physicians and other caregivers feel uncomfortable about giving high doses of sedatives, analgesics, and other mood-altering agents. In some instances, this discomfort stems from a reluctance to cause drug addiction in dying patients, a concern irrelevant to the patients' condition. Other discomfort results from awareness that the agents may hasten death by depressing not only consciousness but also respiratory and cardiovascular function. That the U.S. Supreme Court has justified the administration of sedatives and analgesics under the principle of the double effect should help put caregivers at ease. Although one third of physicians in one study who ordered these agents to dying adult patients did so in part to hasten death,⁷⁸ virtually all the physicians in a comparable study¹¹⁸ conducted in a pediatric ICU viewed hastening death only as an "acceptable, unintended side effect."

MANAGEMENT OF PAIN

Indirect approaches to pain control include nonpharmacologic means. For example, placing patients in a quiet environment where friends and family can visit may diminish the sense of pain, as may the proper treatment of anxiety and depression. Although respiratory depression due to drugs or underlying disease is usually undesirable in patients with COPD, the encephalopathy that results from the hypercapnia and hypoxia may be tolerated, if not favored, in terminal patients because it attenuates pain. Similarly, patients who forgo nutrition and hydration at the end of life may develop a euphoria that has been attributed to the release of endogenous opioids or the analgesic effects of ketosis.

Direct approaches to pain control generally center on the use of opioids, most commonly morphine. In addition to causing analgesia, morphine induces some degree of sedation, respiratory depression, constipation, urinary retention, nausea, and euphoria. It also produces vasodilation, which may cause hypotension, in part through the release of histamine. Fentanyl, a synthetic opioid that is approximately 100 times more potent than morphine, does not release histamine and, therefore, causes less hypotension. Hydromorphone, a semisynthetic morphine derivative, is more sedating than morphine and produces little euphoria.¹¹⁹

Morphine, fentanyl, and hydromorphone can be administered orally, subcutaneously, rectally, or intravenously. Opioids are usually given by the intravenous route to ICU patients, including those who are dying. These agents may be administered to inpatients and outpatients alike through the technique of patient-controlled analgesia. Long-acting oral preparations of morphine and hydromorphone are available for outpatients. Fentanyl can be administered orally in the form of a lollipop. It can also be given by the transcutaneous route, which makes this agent particularly suitable for patients who have difficulty with oral medications.

Opioids ideally should be administered in anticipation of pain and not afterwards. The optimal doses of these drugs given for pain relief are unknown and certainly vary among patients. Nevertheless, opioids generally should be started in relatively low doses if respiratory depression and other side effects are to be avoided and titrated upward until their analgesic effect is realized. In reports of critically ill patients undergoing the withholding and withdrawal of life support in both adult and pediatric ICUs, opioids were used in doses sufficient to achieve pain relief that caregivers considered adequate.⁷⁸ In dying patients, the use of opioids should not be limited by some arbitrary amount but by the balance between analgesia and any undesirable side effects.

MANAGEMENT OF ANXIETY

As in the case of pain, anxiety and its physical manifestation agitation can be managed nonpharmacologically. If drugs are required, benzodiazepines and propofol are preferred. Benzodiazepines cause anterograde amnesia in addition to anxiolysis, and they exert a synergistic sedating effect with opioids. Benzodiazepines also cause hypotension and cardiac depression, especially when administered quickly and in high doses. Lorazepam, an intermediate-acting agent, can be given by the oral, intramuscular, or intravenous route; when given intravenously, it can be done so by bolus or by constant infusion. Midazolam, which is short-acting, is usually administered intravenously by constant infusion, although boluses may be required when therapy is initiated.¹²⁰

Propofol is an intravenous general anesthetic agent with sedating, amnestic, and anxiolytic properties when administered in subanesthetic doses. In such doses, propofol is similar to midazolam in that it is usually given by constant infusion after bolus injection. The drugs are also comparable in the sedation they produce, although propofol has a greater propensity to cause hypotension.¹²⁰ Neither propofol nor midazolam is appropriate for the management of anxiety in outpatients and, in hospitals, their continuous use may be restricted to the ICU.

MANAGEMENT OF DELIRIUM

Delirium may be confused with anxiety because it can also cause agitation. The confusion is clinically important both because the conditions are treated pharmacologically with different drugs and because the drugs used to treat anxiety can exacerbate delirium.¹¹³ Delirious patients should be helped to obtain regular sleep, should be oriented regularly

to their environment, and should avoid benzodiazepines, which cloud consciousness. Haloperidol, a butyrophenone neuroleptic agent, is widely used to treat delirium in critically ill patients. It may be given orally, rectally, intramuscularly, or intravenously. Haloperidol may cause QT prolongation on the electrocardiogram and should be used cautiously with other agents that have a similar effect. Haloperidol can also cause rigidity, restlessness, and other dyskinesias.

MANAGEMENT OF DYSPNEA

Especially in the early stages of disease, dyspnea should be understood and managed according to its underlying pathophysiology^{121,122} (see Chapter 29). For example, patients with moderate to severe COPD may benefit from oral bronchodilators that decrease airflow resistance, inhaled corticosteroids that decrease airway inflammation, and lung volume reduction surgery that decreases hyperinflation. These patients may also become less dyspneic through exercise training and the emotional support available through pulmonary rehabilitation programs.¹²³ At the same time, patients with lung cancer may feel less breathless after drainage of malignant pleural effusions or placement of stents to overcome airway obstruction.

In patients with far advanced lung disease, attention to pathophysiologic mechanisms is less important, and treatment is more palliative than restorative. Bronchodilators may not reduce breathlessness in such patients, corticosteroids may cause more unwanted side effects than symptom relief, and lung reduction surgery may prove fatal. Patients with COPD who are dying, at home or in hospice, do not benefit from exercise training and may be too breathless to attend pulmonary rehabilitation programs; these patients should be encouraged to use wheelchairs and to rest. In most terminal cancer patients, malignant effusions and airway obstruction should not be diagnosed or treated.¹²¹

Patients with chronic respiratory failure of whatever cause should receive supplemental oxygen, which has been shown both to increase survival and to decrease breathlessness.¹²⁴ In the United States, Medicare reimbursement for long-term oxygen therapy is based on physiologic criteria (e.g., arterial $PO_2 < 55$ mm Hg while breathing room air), not symptomatology. Despite this fact, many patients use oxygen primarily to relieve dyspnea, and hospice patients do not have to meet physiologic criteria to receive reimbursement. Supplemental oxygen is usually started in low doses (e.g., 1 to 3 L/min) and titrated to effect. The results of titration are difficult to predict inasmuch as neither the flow rate nor the route of administration of oxygen determines its impact on breathlessness.¹²⁰ Furthermore, air may relieve dyspnea as well as oxygen does in patients with advanced malignancy.¹²⁵ In addition, breathless patients are frequently relieved by exposure to fresh air in the outdoors or during automobile rides with the windows down. Those who are bedridden may benefit from using fans to blow air over their faces.¹²¹

Opioids such as oral morphine have been demonstrated to increase exercise tolerance acutely and to alleviate dyspnea in occasional patients with COPD.¹²⁶ Nevertheless, the long-term administration of sustained-release

morphine has not been shown to be superior to placebo in reducing breathlessness in such patients, most of whom reported nausea, constipation, and other adverse effects.¹²⁷ Although many patients become tolerant to these adverse effects over time, opioids probably should be used only on a trial or as-needed basis for patients with recalcitrant dyspnea who do not respond to oxygen or air. However, because their analgesic properties are undisputed, these agents may be particularly useful in patients who have pain in addition to breathlessness, such as those with lung cancer.¹²¹ Although the use of morphine and other opioids to relieve dyspnea in patients with ARDS and other causes of acute respiratory failure is widespread and seems reasonable, this practice is not supported by research studies.

Benzodiazepines such as alprazolam have been shown to reduce dyspnea in some patients with COPD.¹²⁸ Yet these agents may also cause drowsiness, uncoordination, and dysphoria, and they should probably be used only in outpatients whose dyspnea is not relieved by oxygen and opioids.¹²¹ As is true of opioids, benzodiazepines and propofol are commonly used to reduce dyspnea, in addition to anxiety, among patients with acute respiratory failure, particularly those receiving mechanical ventilation. Again, this practice appears reasonable, especially if the patients are not experiencing unwanted side effects. Nevertheless, the benefits of treating dyspnea with sedatives in ICU patients have not been demonstrated scientifically.

MANAGEMENT OF NAUSEA AND VOMITING

Nausea and vomiting may result from systemic illnesses such as diabetes, renal failure, hypercalcemia, adrenal insufficiency, and viral infections. These symptoms may also be caused by central nervous system disorders, including cerebral metastases and other conditions that increase intracranial pressure; primary gastrointestinal diseases such as gastric outlet obstruction; and a variety of drugs, including theophylline, phenytoin, opioids, antibiotics, and chemotherapeutic agents. Nausea and vomiting may remit with treatment of the disorder or with discontinuation of the drugs that cause them. Because eating can increase nausea, patients may benefit by being placed on a nothing-by-mouth status or undergoing gastric decompression. Clear liquid diets may be administered to patients as tolerated. Supplemental oxygen has been shown to reduce the incidence of postoperative nausea and vomiting.¹²⁹

Patients with nausea and vomiting who do not respond to more conservative measures may be candidates for prophylactic or therapeutic antiemetic therapy, which can be given orally, intramuscularly, intravenously, or in suppository form. Among the older antiemetics are dexamethasone and other corticosteroids; butyrophenones such as haloperidol and droperidol; chlorpromazine, promethazine, prochlorperazine, and other phenothiazines; and muscarinic receptor antagonists such as scopolamine, which is particularly helpful in patients with vestibular symptoms. Of these agents, dexamethasone, droperidol, and promethazine are the most widely used.

Newer antiemetics include the serotonin receptor antagonists ondansetron, dolastron, granisetron, and tropisetron. These drugs have been tested primarily in the postoperative period and among patients who have received

chemotherapy or radiation therapy. Because of their expense, they probably should be used only after other agents are found to be unsuccessful in preventing or relieving symptoms.¹³⁰ Cannabinoids, administered either orally or through smoking the *Cannabis sativa* (marijuana) plant, are as effective as older antiemetic agents such as chlorpromazine, prochlorperazine, and metoclopramide in reducing nausea and vomiting caused by chemotherapy. Nevertheless, although some patients welcome the sedation and euphoria they experience with cannabinoids, others complain of dizziness and dysphoria.¹³¹

MANAGEMENT OF HUNGER AND THIRST

People eat food and drink fluids to relieve hunger and thirst and to sustain metabolic processes. Food and fluids are administered to hospitalized patients under the assumption that they are staples of life and components of routine medical and nursing care. Under this assumption, some have argued that a patient's refusal of nutrition and hydration is tantamount to suicide and that food and fluids should be administered to all patients other than those who reject them because of intolerable pain and suffering in the last moments of life.¹³² Others have noted that voluntary forgoing of nutrition and hydration by terminal patients represents only a refusal of unwanted treatment that is ethically and legally justified.¹³³ Still others have argued that force-feeding violates patient autonomy and that voluntary "terminal dehydration" on the part of patients offers substantial advantages over physician-assisted suicide with respect to self-determination, access, and professional integrity.¹³⁴

Of course, patients may desire food and fluids until they die; alternatively, they may choose not to eat or drink. In fact, one study has documented that, in Oregon, where physician-assisted suicide is allowed, many hospice patients forgo eating and drinking, perhaps as an alternative to assisted suicide.¹³⁵ As was the case in this study, another investigation conducted in a comfort care unit demonstrated that most cancer patients either never experienced hunger and thirst or did so only initially during their terminal illnesses.¹³⁶ In the few patients who were symptomatic, hunger, thirst, and dry mouth usually could be alleviated with small amounts of food and fluids or by the application of ice chips or lubrication to the lips. Similar measures can be used in other settings, including the ICU.

WITHHOLDING AND WITHDRAWAL OF LIFE-SUSTAINING THERAPY

WHAT THERAPIES ARE WITHHELD AND WITHDRAWN

Life-sustaining therapies are withheld and withdrawn in many settings. Nevertheless, most of the studies of this process have been conducted in ICUs. These studies, from pediatric and adult ICUs around the world, reveal that, although any and all interventions may be withheld or withdrawn, variation exists in the type, number, and

sequence of interventions forgone.^{21,22,137} In one investigation in an adult ICU in the United States, an average of five separate interventions were forgone per patient.¹³⁸ CPR, intubation and mechanical ventilation, and dialysis generally were the first interventions withheld; thereafter, vasopressors, transfusions, intravenous fluids, parenteral nutrition, antibiotics, and tube feedings were either withheld or withdrawn. Decisions regarding withholding therapy were reached sooner than decisions about withdrawing therapy. Whereas a decision not to intubate a patient was made early for patients not already on ventilators, once patients were on ventilators, decisions to withdraw ventilatory support were generally made late, after several other interventions were first forgone.

Another study in which physicians were surveyed about the withdrawal process indicated distinct preferences about the form of support withdrawn.¹³⁹ From most likely to least likely, the order was blood products, dialysis, vasopressors, parenteral nutrition, antibiotics, mechanical ventilation, tube feedings, and intravenous fluids. Four biases in decision making were also identified. Physicians preferred to withdraw (1) therapies supporting organs that failed for natural, rather than iatrogenic, reasons; (2) therapies that were instituted only recently; (3) therapies resulting in an immediate, rather than a delayed, death; and (4) therapies resulting in a delayed death only when faced with diagnostic uncertainty.

WITHHOLDING AND WITHDRAWAL OF INTUBATION AND MECHANICAL VENTILATION

Intubation and mechanical ventilation are often used in patients with acute, chronic, or acute-on-chronic respiratory failure and are among the therapies most commonly withheld or withdrawn. As noted earlier, some patients with advanced COPD and other causes of chronic respiratory failure have concerns about intubation and mechanical ventilation and decide against these therapies in advance of decompensation. Nevertheless, other patients with chronic respiratory failure request intubation and mechanical ventilation or are intubated and ventilated—either in the field, in the emergency department, or in the ICU—without having decided on their wishes or having communicated them. Similarly, patients with acute respiratory failure often end up on ventilators because their conditions are assumed to be reversible. When they and their counterparts with chronic respiratory failure do not improve, intubation and mechanical ventilation may be withdrawn. One study revealed that the strongest determinants of withdrawal of mechanical ventilation in critically ill patients were the physicians' perception that the patients preferred not to use life support, the physicians' prediction of a low likelihood of survival in the ICU and a high likelihood of poor cognitive function, and the use of inotropes or vasopressors.¹⁴⁰

How intubation and mechanical ventilation are withdrawn varies among institutions. One approach is rapid extubation: the patient is given analgesics and sedatives, and both the endotracheal (or tracheotomy) tube and the ventilator are removed. Patients are then given either supplemental oxygen or, more commonly, room air to breathe. Rapid extubation is direct and, in the pediatric setting, it

offers the potential advantage of allowing parents to hold their infants without being encumbered by the ventilator or its tubing. A potential disadvantage is that patients may appear distressed due to upper airway obstruction after the tube is removed.

A second process, called *terminal weaning*, involves decreasing the inspired oxygen fraction, the ventilator rate, the level of positive end-expiratory pressure, or some combination of these variables before the ventilator is removed. Patients are given drugs during this process, and they most often die before extubation. First described in 1983, this technique was developed in order to avoid abruptly discontinuing treatment in such a way that "might be interpreted with intent to kill" and might make patients and their families uncomfortable.¹⁴¹ The first part of this rationale is not relevant today because the differences between terminal weaning and euthanasia have been delineated by the U.S. Supreme Court. Nevertheless, terminal weaning still may cause less discomfort than rapid extubation by avoiding upper airway obstruction.

The relative advantages and disadvantages of rapid extubation and terminal weaning have been debated. They have not been compared scientifically, although one study of what was called "rapid terminal weaning" demonstrated that patients could be kept comfortable during the procedure with relatively low doses of opioids and benzodiazepines.¹⁴² A survey of critical care physicians indicated that 15% of respondents almost never withdrew intubation and mechanical ventilation from dying patients.¹⁴³ Of physicians who did, 13% preferred rapid extubation, 33% preferred terminal weaning, and the remainder used both methods. Reasons for preferring rapid extubation included the directness of the action, family perceptions, and patient comfort. Reasons for preferring terminal weaning included patient comfort, family perceptions, and the belief that terminal weaning was less abrupt.

When intubation and mechanical ventilation are withdrawn, most patients with respiratory failure die of their underlying diseases. Nevertheless, some survive, and their survival should not be prevented by drugs that hasten death. At the same time, even patients who are too sick to survive should not receive drugs that interfere with observing tachypnea and other signs that may signal the need for symptom relief. For these reasons, although sedatives and analgesics may be given to relieve suffering, neuromuscular blocking agents should not be introduced to patients while intubation and mechanical ventilation are withdrawn. Furthermore, if the patients are already receiving them, a common situation with infants, these agents should be continued only if two requirements are met. First, death is expected to be both rapid and certain after removal of the endotracheal tube, the ventilator, or both. Second, the burdens to patients and families of waiting for neuromuscular blockade to diminish to a reversible level exceed the benefits of allowing better assessment of the patients' comfort and possible interaction with their families.

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Key Points

- End-of-life care is a combination of palliative treatment and withholding and withdrawal of life-sustaining therapy provided to patients who are terminally ill, including those with acute, chronic, and acute-on-chronic respiratory failure.
- End-of-life care is justified by the ethical principles of beneficence, nonmaleficence, autonomy, and justice and by the legal right of informed patients to consent to or refuse any or all therapy, including that which sustains life.
- The legal right of consent or refusal may be exercised by patients themselves or by their family members and legally appointed surrogates through substituted-judgment and best-interests standards.
- End-of-life care is enhanced by a shared model of medical decision making and by intensive communication among patients, family members, and caregivers. Such care should attend to the needs of patients, families, and caregivers alike.
- When patients or their surrogates request treatments that clinicians believe are potentially inappropriate or futile, clinicians should generally pursue a stepwise approach to dispute resolution rather than unilateral action, including intensive communication with the patient/surrogate, involvement of expert consultants (e.g., ethics consultants), review by a hospital committee, and offering the opportunity to seek transfer to another facility.
- The components of end-of-life care include providing appropriate settings for dying patients; supplying emotional and spiritual support; managing such symptoms as pain, anxiety, delirium, dyspnea, nausea and vomiting, and hunger and thirst; and removing unwanted therapies.

Complete reference list available at *ExpertConsult*.

Key Readings

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INTRODUCTION**DEFINITION AND GOALS****HISTORY****RATIONALE****INDICATIONS****SMOKING CESSATION****COMPONENTS OF A COMPREHENSIVE
PULMONARY REHABILITATION
PROGRAM**

Exercise Training

Education

Psychosocial Training and Support

Nutritional Support

Breathing Training, Inspiratory Muscle
Training, and Chest Physical Therapy

Vaccination

Oxygen Assessment and Therapy

Long-term Adherence

Pulmonary Rehabilitation and the
Integrated Care of the Respiratory
PatientPromoting Physical Activity in the Patient
with Chronic Respiratory Disease**PROGRAM ORGANIZATION****OUTCOME ASSESSMENT****RECENT ADJUNCTS**

Advance Care Planning

INTRODUCTION

Patients with advanced chronic respiratory disease frequently have distressing symptoms, limitations in exercise ability, and reductions in health and functional status that persist despite optimal pharmacologic management. Pulmonary rehabilitation complements standard medical therapy and can lead to improved exercise and functional capacity, decreased dyspnea, improved health status, and (perhaps) reduced risk of premature morbidity and mortality. Pulmonary rehabilitation is now accepted as the standard of care for patients with *chronic obstructive pulmonary disease* (COPD), and it has been incorporated into international guidelines for this disease.^{1,2} Although pulmonary rehabilitation was designed and is applied primarily to symptomatic patients who are limited due to the burden of COPD, the same fundamental principles appear applicable to other chronic respiratory disease states.

DEFINITION AND GOALS

The American Thoracic Society and European Respiratory Society define pulmonary rehabilitation as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.”³ As this definition indicates, there is now a strong evidence base demonstrating the effectiveness of pulmonary rehabilitation, and it should be considered in the general care of patients with chronic respiratory disease.

Pulmonary rehabilitation and exercise training have been erroneously considered to be equivalent. Although exercise training is a necessary component of pulmonary rehabilitation, other interventions are integral to a rehabilitation program. These include patient assessment, education (especially involving collaborative self-management

strategies), nutritional intervention, psychosocial support, and a discussion of advance directives. Promotion of activity in the home and community settings is becoming recognized as an essential component in pulmonary rehabilitation. Smoking cessation, breathing retraining, chest physical therapy, oxygen therapy, and adjunctive therapies are also provided for selected individuals.

It may appear paradoxical that pulmonary rehabilitation does not have a significant, direct effect on pulmonary function, yet it provides the greatest improvements in dyspnea, exercise tolerance, and health status of any therapy for COPD. Emerging data suggest that it may also be beneficial for other chronic respiratory diseases. This apparent paradox is explained by the fact that COPD can be considered to be a systemic disease,^{4,5} and comorbidity (such as decreased oxidative capacity of the muscles of ambulation, physical deconditioning, fear of dyspnea-producing activities, improper pacing) contributes to patients' symptoms and disability. The 6-minute walk distance, which reflects the systemic nature of the disease, is therefore a stronger predictor of survival in COPD patients than measurements of airflow limitation such as the *forced expiratory volume in 1 second* (FEV₁).^{6,7} Similarly, the mid thigh cross-sectional⁸ and mid arm cross-sectional areas,⁹ measures of muscle mass, are better predictors of survival than lung function.

Pulmonary rehabilitation is effective in reducing the negative impact of comorbidities. For example, exercise tolerance in COPD is limited by multiple factors, including increased resistive work of breathing (due to breathing through narrowed airways), increased elastic work of breathing (due to static and dynamic hyperinflation), and abnormalities in the muscles of ambulation (leading to lactate production and fatigue at low exercise intensities). Exercise training leads to a decreased ventilatory requirement at a given level of exercise due in part to physiologic changes in the leg muscles. This decrease in ventilatory requirement allows the patient to breathe at a lower respiratory rate during exercise, thereby reducing the effects of dynamic hyperinflation. Thus, pulmonary rehabilitation exercise training leads to increased exercise capacity by its

direct effects on the leg muscles that reduce the ventilatory requirement and its direct effects on dynamic hyperinflation¹⁰ and cardiac output¹¹—despite the fact there is no measurable change in FEV₁.

Comprehensive pulmonary rehabilitation requires contributions from different health care professionals. Physicians, nurses, nurse practitioners, physical therapists, respiratory therapists, nutritionists, and occupational therapists may be involved in a particular program, depending on availability and resources. A physician medical director and a professional pulmonary rehabilitation coordinator are necessary for program certification in the United States. The goals of pulmonary rehabilitation are to reduce symptoms, improve functional status, and reduce health care costs.¹

HISTORY

Pulmonary rehabilitation and its components have been recognized by clinicians as an effective intervention since at least the middle of the 20th century.^{12,13} Since the mid-1990s, it has risen to prominence as a state-of-the-art, scientifically proven intervention for individuals with chronic lung disease. Its current importance as a therapeutic option is underscored by four events:

- Its incorporation as the “best therapy” to which lung volume reduction surgery was compared in the *National Emphysema Treatment Trial* (NETT).¹⁴
- A Cochrane report demonstrating the effectiveness of pulmonary rehabilitation in meta-analyses.¹⁵
- Its endorsement by the *Global Initiative for Obstructive Lung Disease* (GOLD) and its prominent position in the current treatment algorithm for COPD.¹⁶
- Its acceptance as an approved medical benefit in the United States under the *Centers for Medicare and Medicaid Services* (CMS) beginning in January 2010.¹⁷

Over time, what was considered a form of therapy reserved only for patients with the most severe impairment is now recommended for all patients with symptoms that limit their performance and a moderate severity of disease. Before 1991, much of the literature supporting pulmonary rehabilitation consisted of descriptions of comprehensive pulmonary rehabilitation and presentations of uncontrolled, pre-intervention/post-intervention studies showing its effectiveness primarily in reducing hospital utilization.^{18,19} However, in 1991 Casaburi and colleagues²⁰ reported on a study of 19 COPD patients who were randomized to either higher or lower levels of exercise training on a cycle ergometer. Training was 5 days per week for a total of 8 weeks. The patients who trained at lower levels exercised longer, so the total amount of work was roughly equivalent in the two groups. Both levels of training led to significant physiologic benefits manifested by reduced lactic acidosis and ventilatory requirement at the same work rate. However, those who trained at higher intensity had more physiologic benefit than those who trained at lower intensity. Before this study, many believed that patients with advanced COPD, often being ventilatory limited during exercise, could not derive true physiologic benefit from this type of intervention. This was the first randomized, con-

trolled trial to demonstrate that a training effect could result from exercise training, the cornerstone of pulmonary rehabilitation.

In 1994, Goldstein and associates²¹ reported a prospective, randomized, controlled trial of pulmonary rehabilitation. Eighty-nine patients with COPD were randomized to either pulmonary rehabilitation, initially given in an inpatient setting, or conventional medical care. The group that participated in pulmonary rehabilitation had significantly greater increases in the 6-minute walk distance, submaximal cycle endurance time, and health status compared with the group given standard medical care. This was the first of several randomized, controlled trials of pulmonary rehabilitation that established the effectiveness of pulmonary rehabilitation as a treatment option for chronic lung disease.

That same year, Reardon and coworkers²² reported on 20 COPD patients who were randomized either to comprehensive outpatient pulmonary rehabilitation or to a waiting period during which they were given conventional medical care. Rehabilitation led to significant improvements in exertional dyspnea, measured by incremental treadmill exercise testing and by questionnaire-rated dyspnea with daily activities. Exertional dyspnea was reduced at levels of exercise common to activities of daily living, underscoring its clinical meaningfulness. This was the first study to demonstrate the effectiveness of pulmonary rehabilitation on dyspnea, the most important symptom in advanced lung disease. Subsequent studies by O'Donnell and colleagues^{23,24} showed that the reduction in postexercise training dyspnea was associated with decreased ventilatory demand, probably due to physiologic changes in the leg muscles.

In 1995, Ries and associates²⁵ reported on 119 patients with COPD who were randomized either to comprehensive outpatient pulmonary rehabilitation with exercise training or to education alone. Compared with education alone, rehabilitation led to significant relief of dyspnea, maximal exercise capacity, exercise endurance, and self-efficacy for walking. “Self-efficacy” refers to the patient's confidence in successfully managing respiratory symptoms associated with an activity. Positive results declined over time, approaching those of the control group by 18 to 24 months. This was the first large randomized, controlled study showing the effectiveness of outpatient pulmonary rehabilitation on multiple outcomes. The decline in gains made over time underscored the importance of strategies to improve long-term adherence with rehabilitation.

In 1996, Maltais and coworkers²⁶ reported on 11 patients with COPD who were evaluated before and after 36 sessions of high-intensity endurance training. In addition to the expected physiologic training effect including reduced exercise-induced lactic acidosis, exercise training led to increased levels of oxidative enzymes in muscle biopsy specimens. Of additional importance, the improvement in biochemical markers correlated with reduced lactic acid production during exercise. Along with other work, this study showed that exercise training improves skeletal muscle oxidative capacity in COPD patients and that this improvement has clinical value.

In 2000, Griffiths and colleagues²⁷ presented data on 200 patients with chronic lung disease who were randomized to either 6 weeks of multidisciplinary pulmonary rehabilitation

or standard medical management. In addition to showing substantial improvements in exercise performance and health-related quality of life, the pulmonary rehabilitation intervention led to fewer days in the hospital and fewer primary care home visits in the 1-year follow-up period. Thus, this large randomized trial demonstrated that pulmonary rehabilitation led to a substantial reduction in health care utilization, confirming conclusions from earlier uncontrolled studies. A subsequent study from this group²⁸ provided evidence supporting the cost-effectiveness of pulmonary rehabilitation.

A study by Bourbeau and associates²⁹ suggested that a self-management program in the home led to fewer hospital admissions and other health utilization variables and improvement in health status. Subsequent trials have been less consistent, but a recent meta-analysis of 17 studies supports benefits in quality of life, fewer hospital admissions, but no differences in visits to the emergency department or survival.³⁰

In 2005, Casaburi and coworkers³¹ showed that increasing bronchodilation in patients with COPD led to enhanced outcomes from pulmonary rehabilitation. Patients with optimized lung function could exercise at higher intensities and achieve greater increases in exercise capacity. Thus, not only does pulmonary rehabilitation add to the positive outcomes from pharmacologic therapy, pharmacologic therapy also adds to the benefits from pulmonary rehabilitation.

In 2007, joint guidelines from the *American College of Chest Physicians (ACCP)* and the *American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR)*³² summarized the evidence base underlying pulmonary rehabilitation. The document cited strong evidence supporting the effectiveness of pulmonary rehabilitation on improvements in dyspnea and quality of life. There was also substantial evidence supporting its effectiveness in reducing health care utilization and improving psychological outcomes.

Pulmonary rehabilitation is the most effective therapy available for increasing the exercise capacity of patients with chronic respiratory disease. However, its effectiveness in promoting increased activity in the home and community setting was not proved until fairly recently. Increased physical activity is an important outcome because patients with COPD are often sedentary,³³ and lower levels of physical activity are associated with poorer long-term outcomes.³⁴ In 2008, Walker and colleagues³⁵ demonstrated that directly measured activity (from activity monitors) was increased following 8 weeks of pulmonary rehabilitation. This study corroborated results from two other studies that also demonstrated similar positive effects.^{36,37} These studies, therefore, provide strong support for the idea that the increased exercise capacity attained in the pulmonary rehabilitation center translates into increased activity in other settings.

RATIONALE

Pulmonary rehabilitation has a minimal, if any, effect on the abnormal lung function or respiratory physiology of individuals with chronic lung disease. The apparent paradox

is explained by the fact that a considerable portion of the dyspnea and the health status limitations from chronic lung disease results from extrapulmonary effects of the disease, which can respond to treatment. Some of the associated systemic manifestations of chronic lung disease include nutritional depletion,^{38,39} a decrease in lower extremity muscle mass and peripheral muscle weakness and fatigability,^{40,41} alterations in peripheral muscle fiber type,⁴² and a reduction in peripheral muscle oxidative enzymes.⁴³ In addition, poor pacing techniques, maladaptive coping skills, and fear of dyspnea-producing activities result in a vicious circle of further deconditioning and debilitation. Pulmonary rehabilitation is effective in interrupting this cycle, usually resulting in clinically meaningful improvement in multiple areas of importance to the patient, including a reduction in exertional dyspnea and the dyspnea associated with daily activities, improvement in exercise performance and in health status, and reduction in health care utilization.

INDICATIONS

Pulmonary rehabilitation is indicated for individuals with chronic respiratory disease who have persistent symptoms or disability despite standard medical therapy. [Figure 105-1](#) represents the course of patients with lung function limitation over time and the role of pulmonary rehabilitation. Patients are usually referred for one or more of the following symptoms or conditions⁴⁴:

1. Severe dyspnea and/or fatigue
2. Decreased exercise ability
3. Interference with performing activities of daily living
4. Impaired health status
5. Decreased occupational performance
6. Nutritional depletion
7. Increased medical resource utilization

It should be noted that persistent symptoms and/or limitation in these clinical areas—not just the specific physiologic impairment of the lungs (such as a low

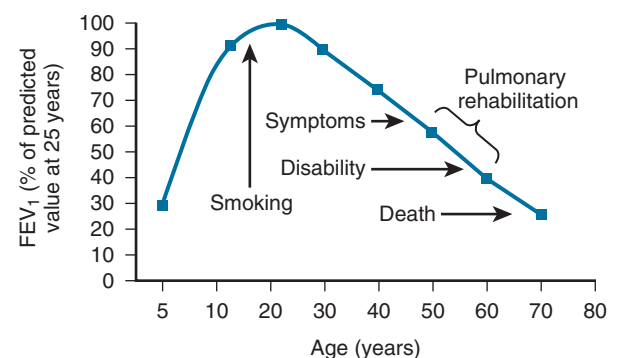


Figure 105-1 Change in forced expiratory volume in 1 second (FEV₁) over time in persons susceptible to the effect of cigarette smoking and who develop COPD. The progressive decline results in functional limitation, poor health status, and eventual death. Pulmonary rehabilitation has a role once persistent symptoms or disabilities develop and for as long as patients benefit.

FEV₁ or hypoxemia)—dictate the need for intervention. Furthermore, symptoms, exercise performance, functional status, and health status correlate relatively poorly with pulmonary function abnormalities. Because of this, there are no specific threshold pulmonary function inclusion criteria for pulmonary rehabilitation.

Often the referral to pulmonary rehabilitation has been reserved for advanced lung disease. Although patients in this category can still benefit from the intervention,⁴⁵ referral at an earlier stage would allow more emphasis on preventive strategies such as smoking cessation and would permit exercise training at higher levels of intensity.

Traditionally, pulmonary rehabilitation has dealt primarily with COPD, whereas its effectiveness for other pulmonary conditions has received less attention.⁴⁶ Nonetheless, patients with chronic asthma and airways remodeling, bronchiectasis, cystic fibrosis, chest wall disease, or interstitial lung disease may be appropriate candidates.⁴⁷ Pulmonary rehabilitation is the standard of care before and after lung transplantation and lung volume reduction surgery. On the basis of these accepted indications, pulmonary rehabilitation should also be useful to recondition patients for other major surgical procedures.

There are two primary exclusion criteria for pulmonary rehabilitation:

1. An associated condition that might interfere with the rehabilitative process. Examples include disabling arthritis and severe neurologic, cognitive, or psychiatric disease.
2. A comorbid condition that might place the patient at undue risk during exercise training. Examples include severe pulmonary hypertension or unstable cardiovascular disease.

It should be noted that many patients with pulmonary hypertension have safely (and successfully) participated in pulmonary rehabilitation programs, often while awaiting lung transplantation. The exercise training component has to be modified in this situation and patients require close monitoring. In addition, poor motivation is a relative contraindication to pulmonary rehabilitation. However, the level of motivation might change during therapy, especially if patients perceive demonstrable benefit from the sessions.

SMOKING CESSATION

Cigarette smoking is the cause of COPD in more than 90% of affected patients. Furthermore, there is no doubt that smoking cessation is the single most important therapy that can retard the progression of airflow limitation and positively influence survival. The various pharmacologic and behavior modification techniques that are available to assist persons to stop smoking are reviewed in Chapter 46. Although controversy still exists, active cigarette smokers are reasonable candidates for pulmonary rehabilitation provided smoking cessation interventions become an important component of the process. Indeed, frequent contact and reinforcement during the rehabilitation program can influence a patient to adopt a proactive role in cessation.

COMPONENTS OF A COMPREHENSIVE PULMONARY REHABILITATION PROGRAM

EXERCISE TRAINING

Exercise training, including upper and lower extremity endurance training and strength training, is an essential component of comprehensive pulmonary rehabilitation. This follows the current knowledge that the peripheral muscles in patients with chronic lung disease are not only wasted but also appear to have alterations in fiber type distribution and decreased metabolic capacity.^{47a} Exercise training improves endurance, increases the level of functioning, aids in performance of activities of daily living, helps reduce systemic blood pressure, improves lipid profiles, tends to counteract depression, reduces anxiety associated with dyspnea-producing activities, and facilitates sleep.

Exercise training for individuals with chronic lung disease, similar to that in healthy individuals, is based on general principles of intensity (higher levels of training produce more results), specificity (only those muscles trained show an effect), and reversibility (cessation of regular exercise training leads to loss of training effect).⁴⁸

Ventilatory or gas-exchange limitations are common in advanced chronic lung disease and limit the intensity of exercise training. However, exercise capacity in many patients is also limited by peripheral muscle and cardiovascular deconditioning, with an early onset of anaerobic metabolism and the production of lactic acidosis during exercise. Peripheral muscle dysfunction is responsive to the exercise training intervention. Many respiratory patients are capable of exercising for prolonged periods of time at levels close to capacity,⁴⁹ and the higher level of exercise training results in greater improvement in exercise performance.³⁸ The demonstrated reduction in ventilation and lactate levels at identical submaximal work rates²¹ following high-intensity exercise training strongly suggests that a training effect is attainable in many patients with advanced lung disease. A dose-related increase in oxidative enzymes in the peripheral muscles accompanies these physiologic adaptations to training.⁴³ A reduction in lactic acid production has been demonstrated to be associated with improvement in oxidative capacity of the peripheral muscles.⁵⁰

Most pulmonary rehabilitation programs emphasize endurance training of the lower extremities, often advocating sustained exercise for about 20 to 30 minutes two to five times a week. This may include exercise on a stationary cycle ergometer or motorized treadmill, climbing stairs, or walking on a flat surface such as a corridor or auditorium. Training is usually performed at levels at or greater than 50% or 60% of the maximal work rate. For those unable to maintain this intensity for the recommended duration, interval training, consisting of 2 to 3 minutes of high-intensity training (60% to 80% maximal exercise capacity), alternating with equal periods of rest, has similar results with less dyspnea.^{51,52} Optimization of bronchodilator therapy is desirable because it will allow patients to exercise at higher intensities. Similarly, supplemental oxygen therapy for hypoxemic patients, in addition to increasing safety, will allow patients to train at higher work rates.

Oxygen supplementation may even promote exercise training at higher intensities in nonhypoxemic COPD patients,⁵³ but further studies will be necessary to confirm that this approach is effective. If patients cannot achieve high work rates during exercise training, lower work rates have also been demonstrated to produce positive outcomes.⁵⁴

Although the strength of the upper extremity muscles is relatively preserved compared with that of the lower extremities in COPD,⁵⁵ the former are important to many activities of daily living. The use of upper extremity muscles is often associated with considerable dyspnea, probably because the arm muscles are also accessory muscles of respiration. Endurance training of the upper extremities is thus an important component of pulmonary rehabilitation. Its effectiveness has recently been demonstrated in a randomized clinical trial.⁵⁶ Training can be accomplished using supported arm exercises, such as with arm ergometry, or unsupported arm exercises, such as by lifting free weights or dowels or by stretching elastic bands.⁵⁷

Because peripheral muscle weakness and/or atrophy contributes to exercise limitation in patients with lung disease,⁵⁸ strength training is a rational component of exercise training during pulmonary rehabilitation.⁵⁹ Training in weight-lifting exercises alone, involving the upper and lower extremities, increases muscle strength and endurance performance on a cycle ergometer.⁶⁰ In the current practice of pulmonary rehabilitation, strength training is usually added to standard aerobic training. This combination increases muscle strength and mass, but its additive effect on health status has not been proved.⁶¹

The total duration of exercise training in pulmonary rehabilitation should reflect the patient's underlying respiratory disease, his or her level of physical and cardiovascular conditioning, and the progress made during the exercise training sessions. The GOLD guidelines¹⁶ report that the optimum length of exercise training has not been determined in randomized, controlled trials but suggests there is evidence that programs of longer duration provide greater benefit. Ideally, the optimal length of an exercise training program should depend on whether the patient continues to progress toward goals. However, in reality, the program length is generally set by resources, reimbursement, and continued patient motivation. Longer programs may provide more sustained benefits in outcomes.⁶²

Exercise training is typically given in the pulmonary rehabilitation facility under supervision. Generally, this is supplemented with patient-specific instructions for additional exercise training at home or in the community. Early incorporation of home exercise into the routine of daily life may promote long-term adherence with the exercise prescription. Carrying this concept one step further, a randomized trial demonstrated that, after 4 weeks of standardized education, 8 weeks of exercise training *in the home* was as effective in its primary outcome as 8 weeks of supervised training in the pulmonary rehabilitation center.⁶³ The primary outcome in this study was questionnaire-rated dyspnea at 1 year following rehabilitation. Similar improvements were noted in exercise capacity, although the mean changes in the 6-minute walk distance were well below the established minimum clinically important difference of 54 m. Of importance, there were no significant differences in adverse events in the two groups, and the treating physi-

cians and the study steering committee did not identify any serious adverse events attributable to the exercise training. It remains to be determined whether this home exercise approach to pulmonary rehabilitation will become a practical alternative to the traditional approach.

EDUCATION

Education is an important component of pulmonary rehabilitation programs, and its incorporation alongside exercise training provides a good setting to promote the health behavior change necessary to optimize disease control. Educational needs are determined as part of the initial patient assessment and then are reassessed over the course of the program. Education provides important information to the patient and family about the disease process, its comorbidity, and its treatment. This information encourages active participation in health care, thereby promoting adherence to therapy and important self-management skills.^{64,65} Education also helps the patient and family find ways to cope with chronic illness and its comorbidities.⁶⁶ Some standard educational topics are listed in [Table 105-1](#). In pulmonary rehabilitation, education is usually provided both in small-group settings and in a one-to-one format.

The educational process includes the promotion of a healthy lifestyle, the incorporation of adaptive techniques (such as self-pacing) into the home setting, and the promotion of long-term adherence with the postrehabilitative instructions. Education about self-management is an essential component of pulmonary rehabilitation. It emphasizes "learning through doing," enhances patient self-confidence, and encourages a "take-charge" attitude (in collaboration with the health care providers) toward managing the disease.¹⁷ Some strategies in collaborative self-management include interventions for smoking cessation, encouragement of regular exercise at home, incorporation of increased levels of physical activity into the home setting, and early recognition and treatment of respiratory exacerbations. The development of a patient-specific, collaborative self-management plan for COPD exacerbations is an important goal of pulmonary rehabilitation; this includes education about the symptoms and signs associated with

Table 105-1 Educational Elements of a Comprehensive Pulmonary Rehabilitation Program

Normal pulmonary anatomy and physiology
Pathophysiology of lung disease
Description and interpretation of medical tests
Collaborative self-management strategies
Breathing retraining
Bronchial hygiene
Medication use
Exercise principles
Activities of daily living and energy conservation
Respiratory modalities
Self-assessment and symptom management
Nutrition
Psychosocial issues
Ethical issues
Advance directives

Adapted from Casaburi R, ZuWallack R: Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. *N Engl J Med* 360:1329–1335, 2009.

exacerbations to foster early recognition followed by the implementation of an action plan, which often includes using filled prescriptions for a short course of systemic steroids and an antibiotic. Ongoing collaboration among the patient and the medical team members is the key to effective self-management. Advance directive discussions are also an important component of pulmonary rehabilitation (see later).⁶⁷⁻⁶⁹

Because education is a component of virtually all pulmonary rehabilitation programs, there are few studies evaluating its individual contribution to the overall effectiveness of the comprehensive program. However, self-management strategies applied to the home setting have been shown to be effective in improving health status and reducing utilization of medical resources.²⁹

PSYCHOSOCIAL TRAINING AND SUPPORT

Psychosocial problems, such as anxiety, depression, problems coping, and decreased self-efficacy, contribute to the burden of advanced respiratory disease.⁷⁰ Psychosocial and behavioral interventions vary widely among comprehensive pulmonary rehabilitation programs but often involve educational sessions or support groups, focusing on areas such as coping strategies or stress management techniques. Techniques of progressive muscle relaxation, stress reduction, and panic control may reduce not only anxiety but dyspnea as well.⁷¹ Educational efforts may also improve coping skills. Participation by family members or friends in pulmonary rehabilitation support groups is encouraged. Informal discussions of the common symptoms and concerns of patients with chronic lung disease may provide emotional support to patients and their families. Because of these interventions, it should come as no surprise that a randomized clinical trial has demonstrated that comprehensive pulmonary rehabilitation can decrease psychosocial morbidity in patients with severe COPD even when no specific psychological intervention is provided.⁷² Individuals with substantial psychiatric disease should, of course, be referred for appropriate professional care.

NUTRITIONAL SUPPORT

Nutritional depletion, including abnormalities in body composition such as decreased lean body mass, is present in 20% to 35% of patients with stable COPD.^{73,74} Depletions in lean body mass undoubtedly contribute to the morbidity of patients with chronic respiratory disease by leading to decreased respiratory muscle strength,⁷⁵ handgrip strength,⁷⁶ exercise tolerance,^{77,78} and health status.⁷⁹ Nutritional depletion and alteration in body composition are also significant predictors of the mortality of COPD, independent of FEV₁.^{8,9,80} Because of this, nutritional intervention is a recommended component of comprehensive pulmonary rehabilitation.

However, the benefit from simple nutritional supplementation to underweight patients with chronic lung disease has not been substantial, with one meta-analysis of nutritional intervention for COPD reporting only a 1.65-kg increase in weight following intervention.⁸¹ In view of these disappointing results with calorie supplementation alone,

consideration is being given to hormonal supplementation with anabolic steroids.⁸² This has led to increases in weight, lean body mass, respiratory muscle strength, and arm and thigh muscle circumference.⁸³ In addition, one study has demonstrated that the combination of testosterone and weight training in men with COPD and low testosterone levels leads to greater increases in muscle mass and strength than either alone.⁸⁴ Whether these preliminary findings in this select group can be applied with safety and efficacy to a more generalized population remains unknown. The Joint ACCP/AACVPR Guidelines on Pulmonary Rehabilitation² do not recommend routine use of anabolic steroids for COPD patients.

BREATHING TRAINING, INSPIRATORY MUSCLE TRAINING, AND CHEST PHYSICAL THERAPY

These modalities have been part of pulmonary rehabilitation over the years, but conclusive evidence supporting their effectiveness in pulmonary rehabilitation is for the most part lacking. Breathing training is aimed at controlling the respiratory rate and breathing pattern, with a goal of decreasing air trapping. *Pursed-lip breathing* takes place when the patient inhales through the nose and exhales over 4 and 6 seconds through lips pursed in a whistling/kissing position. This technique facilitates the recruitment of abdominal muscles during exhalation and has a favorable effect on the breathing pattern, thereby increasing tidal volume and reducing end-expiratory lung volumes. The result is less hypoxemia and decreased dyspnea. In selected patients, pursed-lip breathing has also been shown to reduce the oxygen cost of breathing.⁸⁵ Patients with COPD can usually be readily trained in pursed-lip breathing; in fact, they often spontaneously adopt this breathing pattern when dyspneic. *Breathing while bending forward* has been shown to decrease dyspnea in some patients with severe COPD, both at rest and during exercise. Similar improvements can be achieved by breathing in the supine and Trendelenburg positions. The best explanation for the reduction in dyspnea is that the increased abdominal pressure caused by bending over stretches the diaphragm, moving it into a better contracting position and leading to improved diaphragmatic function. *Diaphragmatic breathing* has not been shown to be beneficial; in fact, this technique may actually decrease breathing efficiency.⁸⁵

The rationale behind inspiratory muscle training is that COPD patients have weak inspiratory muscles and that training them may improve outcomes. The Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines reviewed the relatively numerous studies on inspiratory muscle training and concluded that this treatment increases inspiratory muscle strength, increases exercise performance, and decreases dyspnea. Their recommendation is to consider inspiratory muscle training in selected COPD patients with decreased inspiratory muscle strength and breathlessness despite optimal medical therapy.²

Chest physical therapy is used in an attempt to remove airway secretions. The techniques include postural drainage, chest percussion and vibration, and directed cough. Postural drainage uses gravity to help drain the individual lung segments. Chest percussion should be performed with

care in patients with osteoporosis or bone problems. Cough would be an effective technique for removing excess mucus from the larger airways; unfortunately, patients with COPD have impaired cough mechanisms (maximum expiratory flow is reduced, ciliary beat is impaired), and the mucus itself has altered viscoelastic properties. Because spasms of coughing may lead to dyspnea, fatigue, and worsened obstruction, directed cough might be helpful by enhancing the beneficial effect and preventing the untoward ones. With directed coughs, patients are instructed to inhale deeply, hold their breath for a few seconds, and then cough two or three times with the mouth open. They are also instructed to compress the upper abdomen to assist in the cough. These techniques are probably useful in selected patients with difficulty mobilizing secretions.

VACCINATION

The causes of exacerbations of COPD are poorly understood and probably multifactorial. Both influenza virus and *Streptococcus pneumoniae* may play a role, and there is no doubt that, with either of these infections, patients with chronic lung disease are at increased risk for serious complications, including death.⁸⁶ One of the national health objectives in the United States has been to increase influenza and pneumococcal vaccination levels to higher than 60% in persons at high risk for complications and for everyone 65 years of age or older.⁸⁷ As stated, this includes all patients with COPD and other forms of chronic lung disease, regardless of age. Because the influenza vaccine is type specific and serotypes are constantly changing, vaccination must be repeated every year, preferably at the beginning of the season in the fall. In contrast, the pneumococcal vaccine is polyvalent and its benefits should last a lifetime.⁸⁸ One of the responsibilities of a rehabilitation program is to educate enrollees about the importance of vaccination against influenza and pneumococcal infections and to ensure that it is carried out and (for influenza) repeated annually.

OXYGEN ASSESSMENT AND THERAPY

Background

Although not in itself a unique component of pulmonary rehabilitation, testing for oxygen needs and/or adjusting the oxygen to achieve its full benefits is part of all rehabilitation programs. Two landmark studies clearly showed improved survival in patients with COPD and hypoxemia (arterial oxygen pressure $PO_2 < 55$ mm Hg) who breathed supplementary oxygen at night compared with those who received no supplemental oxygen; there was even better survival in those who breathed oxygen for longer periods through the aid of an ambulatory delivery system.^{89,90} Contemporary guidelines for prescribing home oxygen for patients with COPD, based in part on these trials, are shown in Table 105-2. The chief criterion is significant hypoxemia, defined as an arterial PO_2 of 55 mm Hg or less for 3 weeks or more when the patient is in a clinically stable state (i.e., has been free from exacerbation of bronchitis, heart failure, or other intercurrent complications). Additional criteria were also used in the North American multicenter trial to

Table 105-2 Guidelines for Prescribing Home Oxygen for Advanced Chronic Obstructive Pulmonary Disease

PATIENT SELECTION CRITERIA

Accepted Indications

Patients with resting PaO_2 consistently 55 mm Hg or less
 Patients with resting PaO_2 consistently 55–59 mm Hg *plus* cor pulmonale clinically diagnosed and/or hematocrit >55% and stable course of disease on optimal therapy
 Patients with nocturnal hypoxemia (i.e., $PaO_2 < 55$ mm Hg on multiple occasions or hematocrit >55% or clinical evidence of pulmonary hypertension)

Possible Indications

Normoxic patients in whom oxygen has been shown to reduce dyspnea and substantially increase exercise capability
 For supplementation during exercise training

OXYGEN DOSE

Continuous flow by double or single nasal cannulas (see text) or by demand system with demonstration of adequate oxygen saturation
 Lowest flow to increase PaO_2 to 60–65 mm Hg or oxygen saturation to 90–94%
 Increase baseline flow by 1 L/min during exercise and sleep. Consider higher flows if patient traveling by air

PaO_2 , arterial oxygen pressure.

Adapted from Celli BR, MacNee W, ATS/ERS Task Force, et al: Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 23:932–946, 2004.

enroll stable patients with COPD whose arterial PO_2 values were between 55 and 59 mm Hg.⁸⁹ They included evidence of pulmonary hypertension as judged by radiographic abnormalities (an enlarged pulmonary outflow tract); electrocardiographic findings of elevated right-sided intracardiac pressures (P waves in standard leads II, III, and aVF > 2-mm amplitude); clinical evidence of cor pulmonale with heart failure; or secondary polycythemia from chronic hypoxemia. Patients with COPD who have echocardiographic evidence of right ventricular hypertrophy and/or pulmonary hypertension also qualify.

Dosage

The therapeutic goal of administering supplementary oxygen is to raise arterial PO_2 to 60 to 65 mm Hg or, alternatively, to reach an oxygen saturation of 90% to 94%. The results of the *Nocturnal Oxygen Therapy Trial* (NOTT)⁸⁹ established that the great majority of patients with advanced COPD and hypoxemia achieve this goal with oxygen delivered by nasal cannula at 1 to 2 L/min. Less than 10% of the patients require 3 L/min or more while at rest. Additional results obtained during the conduct of the trial indicate that additional oxygen of 1 L/min was required during the stress of exercise and while sleeping; those extra needs are undoubtedly caused by the increased metabolic demands of exercise and the modest degree of hypoventilation and/or worsening of gas exchange seen during sleep.

Thus, if the baseline flow of oxygen is 2 L/min with patients at rest, the flow rate should be turned up to 3 L/min when they are exercising or sleeping. Periodic monitoring of oxygenation is essential to determine who should receive supplementary oxygen in the first place; moreover, in those who are being treated, monitoring is used to evaluate

whether therapeutic goals are being met or exceeded. Two techniques are available: arterial puncture to measure PaO₂ and pulse oximetry to measure oxygen saturation. The latter is being increasingly used given the convenience and improved accuracy of the newer oximeters.

Delivery Systems

The oxygen delivery systems available for home use are as follows: compressed gas in high-pressure cylinders; liquid gas in lightweight canisters; and stationary oxygen concentrators. Large compressed gas cylinders are fixed in place, but patients can move short distances while using long (50-ft) tubing; smaller cylinders can be attached to wheelchairs or installed in automobiles to allow journeys out of the home. Ambulatory patients are best served with a small portable, liquid system, which is the only practicable way to deliver oxygen to someone who is working or active. Liquid gas-containing canisters and portable oxygen concentrators are constantly being improved to reduce weight and to increase duration of use. Because the goal of pulmonary rehabilitation is to restore the patients' functional capacity to its optimal level and exercise is a fundamental part of pulmonary rehabilitation, every effort must be made to provide hypoxemic patients with portable devices that help achieve these goals.

Oxygen as an Adjunct to Pulmonary Rehabilitation Exercise Training

In addition to life-prolonging effects, supplemental oxygen therapy increases exercise capacity in hypoxemic⁹¹ and even nonhypoxemic⁹² COPD patients. Part of this beneficial effect is probably mediated through a reduction in carotid body respiratory drive, resulting in a lower respiratory rate and, consequently, less dynamic hyperinflation. Because supplemental oxygen increases exercise capacity in COPD patients, it may enhance outcomes in pulmonary rehabilitation by allowing patients to exercise and train at higher intensities. Oxygen therapy for individuals with exercise-induced hypoxemia is a standard of care in the United States, but the role of oxygen therapy for nonhypoxemic patients as a potential exercise-enhancer is not well established. To date, a few clinical trials have demonstrated that supplemental oxygen (or oxygen plus helium) during pulmonary rehabilitation exercise training in nonhypoxemic patients with COPD may allow for exercise training at higher intensities and greater short-term improvement from the intervention.^{93,94} Further research is necessary in this area.

LONG-TERM ADHERENCE

Although the short-term effects of pulmonary rehabilitation in multiple outcome areas are firmly established, the long-term effectiveness of this therapy is often disappointing. In controlled trials of pulmonary rehabilitation, gains in exercise performance and health status obtained after 6 to 8 weeks of therapy essentially disappear by 18 to 24 months.²⁵ However, it seems illogical to expect that a therapy that is only applied for 6 to 8 weeks could substantially modify the natural course of the disease. In all likelihood, two factors are mainly responsible for this drop-off in effectiveness: (1) exacerbations of underlying lung disease,

leading to prolonged symptoms and resuming a more sedentary lifestyle and (2) a gradual decline in adherence with the postrehabilitation exercise prescription. With these factors in mind, the pulmonary rehabilitation program must include strategies to promote long-term adherence. One approach is to incorporate the principles of pulmonary rehabilitation, including exercise training, more actively into the home setting. This is supported by studies of home-based programs, which suggest that gains made in this setting may be longer lasting⁹⁵ than those of hospital-based programs. Promoting regular walking seems to help prolong effectiveness in some outcome areas.⁹⁶ Although regularly scheduled repeated pulmonary rehabilitation sessions do not give additional prolonged benefit,⁹⁷ giving a "booster shot" of pulmonary rehabilitation following an exacerbation, by emphasizing short periods of supervised exercise training to return the patient to baseline performance, appears to be a reasonable intervention in selected cases. Longer-duration pulmonary rehabilitation seems to confer longer-lasting effectiveness.⁶²

PULMONARY REHABILITATION AND THE INTEGRATED CARE OF THE RESPIRATORY PATIENT

The *American Thoracic Society/European Respiratory Society* (ATS/ERS) guidelines define pulmonary rehabilitation as "a spectrum of intervention strategies integrated into the life-long management of patients with chronic respiratory disease and involves a dynamic, active collaboration among the patient, family and healthcare providers."¹ Depending on the specific needs of the individual patient, this care might include smoking-cessation counseling and therapy, activity promotion, education about a healthy lifestyle, vaccinations, the incorporation of regular exercise training into the individual's lifestyle, optimization of pharmacology, an exacerbation prevention strategy, a collaborative management plan for the early recognition and treatment of exacerbations, and discussion of advance directives. These interventions can be conveniently bundled into a comprehensive outpatient or inpatient pulmonary rehabilitation program administered by a multidisciplinary staff. However, if pulmonary rehabilitation is not available or feasible for a particular patient, the onus of this patient-centered comprehensive management rests on the health care provider. Unfortunately, our current acute care health model is poorly suited for this type of management. Another approach—which has not yet been implemented to any significant degree—is the concept of *integrated care*.¹⁷ Integrated care, as it applies to individuals with respiratory disease, has been described as "a system-wide, multidisciplinary, collaborative approach that is individualized to the specific needs of the patient. This approach stresses comprehensive assessment, self-management education, agreement on an individually tailored care plan, and communication among health care professionals, patients, and families/caregivers."^{17,98} An integrated care approach would be particularly useful during COPD exacerbations, when there is an abrupt deterioration in the patient's condition and a far greater likelihood of increased health care utilization. Some data suggest that an integrated care approach in this setting reduces health care costs.⁹⁹

PROMOTING PHYSICAL ACTIVITY IN THE PATIENT WITH CHRONIC RESPIRATORY DISEASE

Daily activity energy expenditure is an important predictor of mortality in healthy community-dwelling older adults,¹⁰⁰ and patients with COPD are more sedentary than age-matched healthy individuals.¹⁰¹ Hypoxemic COPD patients are generally very sedentary and, disappointingly, supplemental oxygen is not particularly effective in reversing this maladaptive behavior.¹⁰² Because decreased physical activity in COPD patients appears to be related to increased health care utilization and mortality,^{103,104} an important goal of pulmonary rehabilitation is to promote increased physical activity in the home and community settings. Although pulmonary rehabilitation unequivocally increases exercise capacity, it is less clear whether the increase in exercise capacity is translated into increased physical activity outside the pulmonary rehabilitation environment. Clinical trials incorporating direct measurements of physical activity using motion detectors (accelerometers worn at the waist or on the leg) have demonstrated that pulmonary rehabilitation does indeed increase physical activity.³⁵⁻³⁷

PROGRAM ORGANIZATION

The pulmonary rehabilitation program needs a coordinator to organize the various components into a functioning unit. The coordinator develops the integrated program and monitors its progress and function. The program should have resources available to teach and supervise respiratory therapy (oxygen, use of inhalers, nebulizers); physical therapy (breathing techniques, chest physical therapy, postural drainage); exercise conditioning (upper and lower extremities); and activities of daily living (work simplification, energy conservation). Also desirable are services to evaluate and advise on nutritional, psychological, and vocational needs.

Whether to have an inpatient or an outpatient program depends on the methods of reimbursement, patient population, available personnel, and institutional policy. The ideal system is one that provides an in-hospital component for patients who may benefit from the program while recovering from acute exacerbations and an outpatient component (including home therapy) that could complete the program started in the hospital. This program ensures good continuity of care.

OUTCOME ASSESSMENT

Outcome assessment can be defined as the assessment of the “consequences” of an intervention. As stated earlier, pulmonary rehabilitation does not improve physiologic pulmonary function. However, exercise training in rehabilitation increases the content of oxidative enzymes in the trained muscles, accompanied by a beneficial delay in the generation of lactate (a marker of muscle performance). This results in improved exercise performance and reduced dyspnea and it may be responsible, at least in part, for improved functional capacity. Therefore, even though pul-

Table 105-3 Examples of Outcome Assessment for Pulmonary Rehabilitation

Measurement	Scales/Tests
Exertional dyspnea	Borg scale or visual analogue scale during exercise testing
Dyspnea with daily activities	Modified Medical Research Council (MRC) questionnaire, Baseline and Transitional Dyspnea Indexes (BDI/TDI), San Diego Shortness of Breath Questionnaire (SOBQ)
Functional exercise capacity	Six-minute walk test Incremental and endurance shuttle walk tests
Laboratory measures of exercise performance	Incremental cardiopulmonary exercise testing Endurance testing at constant work rate
Health status	Chronic Respiratory Disease Questionnaire (CRQ), St. George's Respiratory Questionnaire (SGRQ), Medical Outcomes Study Short Form-36 (SF-36)
Functional performance	Pulmonary Functional Status Scale (PFSS) Pulmonary Function Status and Dyspnea Questionnaire (PFSDQ)
Nutritional status/body composition	Body mass index (BMI) Body composition using bioelectrical impedance or dual-energy x-ray absorption (DEXA)
Psychological variables	Measurement of anxiety and depression using the Hospital Anxiety and Depression (HAD) questionnaire

monary rehabilitation does not improve lung function, it reduces the disability and handicap of the patient.

Outcome assessment for pulmonary rehabilitation encompasses three areas: (1) a general audit of the effectiveness of the global pulmonary rehabilitation program and its components; (2) evaluation of individual patient response to the intervention; and (3) assessment of the effect of pulmonary rehabilitation on society, especially with respect to its effect on health care utilization and its cost-effectiveness. Some commonly used outcome measures are listed in [Table 105-3](#).

Evaluating the effectiveness of the pulmonary rehabilitation program for its patient population as a whole is important in continuous quality assessment. Evaluation can be made of several of its components, especially in the measurements of dyspnea, exercise performance, and health status. Dyspnea evaluation falls into two categories: measurement of exertional dyspnea during standardized exercise testing and measurement of breathlessness by questionnaire. Exertional dyspnea is usually rated using a Borg scale¹⁰⁵ or a visual analogue scale. Measurement of dyspnea by questionnaire usually assesses the dyspnea associated with daily activities or the way in which exertional dyspnea limits activities.¹⁰⁶ Exercise performance can be measured in the laboratory using protocols involving incremental treadmill or stationary bicycle exercise. However, field tests of exercise performance, such as the 6-minute walk test or the shuttle walk test, are more commonly performed. The 6-minute test is easy to perform, relates well to functional status, and is responsive to the pulmonary rehabilitation intervention. As stated earlier, the 6-minute walk

test is a better predictor of mortality in patients with COPD than is lung function. For the shuttle walk test,¹⁰⁷ the patient is instructed to walk around a 10-meter course at gradually increasing speeds. Speed is determined by an auditory beeping signal that sets the pace. The test is terminated when the patient cannot complete the course in time, usually because of breathlessness. Total distance traveled is the variable assessed. Health status is often assessed using respiratory-specific questionnaires, such as the *Chronic Respiratory Disease Questionnaire* (CRQ)¹⁰⁸ or the *St. George's Respiratory Questionnaire* (SGRQ).¹⁰⁹ Some pulmonary rehabilitation programs may also use a generic instrument, such as the *Medical Outcomes Study Short Form-36* (SF-36),¹¹⁰ to complement information from the respiratory-specific questionnaires. Assessment in the areas of nutrition/body composition, educational goal achievement, and psychosocial variables (e.g., anxiety, depression, coping skills) is also possible. In sum, a pulmonary rehabilitation program can be judged on its ability to improve patient function by these component measures.

In the evaluation of the response to therapy of an *individual* patient, exercise tests such as the timed walk, a questionnaire assessment of dyspnea, or measurements of functional status or health status may provide some useful information. However, to date, these outcome measures, which have become routine for program assessment, have not been extensively validated for individual patient assessment. Traditional one-on-one clinical assessment remains necessary for the individual patient.

Finally, the pulmonary rehabilitation can be evaluated for its effect on society, especially with respect to its effect on health care utilization and its cost-effectiveness. Outcome assessment in health care utilization or cost-effectiveness generally requires participation of several centers in a multicenter study to accrue the necessary number of subjects for this type of analysis.

RECENT ADJUNCTS

Several adjuncts may prove to be beneficial in patients with severe disability from chronic respiratory disease. *Noninvasive positive-pressure ventilation* (NPPV; see Chapter 102), through its effect in helping unload the respiratory muscles, improves breathlessness and exercise endurance in COPD.¹¹¹⁻¹¹³ When NPPV is added to pulmonary rehabilitation in patients with hypercapnic COPD and used at home, there is an improvement in dyspnea, health status score, exercise endurance, arterial blood gases, and lung function compared with rehabilitation alone. However, it has failed to demonstrate a decrease in exacerbations and mortality.¹¹⁴ The use of proportional assist ventilation in pulmonary rehabilitation in patients without hypercapnia had no appreciable added benefits in mild COPD.¹¹⁵ However, in patients with more severe lung disease, this form of therapy allowed the patient to exercise at a higher intensity, resulting in the achievement of a greater maximum exercise capacity.¹¹⁶ The Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines stated that NPPV does confer a postrehabilitation benefit in patients with severe airflow limitation.² Similarly, the application of electrical stimulation combined with active limb mobilization in COPD

patients on mechanical ventilation or with other patients with severe disability improves muscle strength and provides other patient-centered outcomes.¹¹⁷⁻¹²⁰ Finally, the inhalation of less-dense, oxygen-enhanced gas mixtures, such as 72% helium/28% oxygen, can improve exercise performance in patients with severe COPD.¹²¹ These techniques remain fruitful topics for research.¹²²

The potential benefits of palliative care at home, at least in patients with COPD, are beginning to be studied, but initial results in a small randomized trial¹²³ indicate that a significant number of barriers exist before recommending this intervention widely for patients with severe, debilitating COPD. Research in this area is of utmost importance as the aging population and the impact of noninfectious, noncommunicable diseases become the most frequent cause of morbidity and death in the world.¹²⁴

ADVANCE CARE PLANNING

Participation in a pulmonary rehabilitation program provides an excellent environment to address discussions of advance care planning.⁶⁸ As part of the educational component of pulmonary rehabilitation, information can be provided about designating a health care proxy (also known as durable power of attorney for health care). Pulmonary rehabilitation provides a unique opportunity to provide family members with a clear sense of the individual patient's goals for treatment and preferences regarding the use of life-sustaining treatments, such as mechanical ventilation, cardiopulmonary resuscitation, feeding tubes, and dialysis. Advance care planning education in the context of a pulmonary rehabilitation program is generally well accepted.⁶⁹

Key Points

- Pulmonary rehabilitation is a multidisciplinary, patient-centered approach to the treatment of patients with chronic respiratory disease.
- Although pulmonary rehabilitation has no direct effect on lung function, it nonetheless produces substantial improvements in dyspnea, exercise performance, and quality of life and reduces health care utilization.
- Whereas most patients referred for pulmonary rehabilitation have COPD, this therapy can help patients with other respiratory diseases.
- Important components of pulmonary rehabilitation include education, exercise training, nutritional therapy, psychosocial support, and advance care planning.
- Exercise training is the cornerstone of pulmonary rehabilitation; high-intensity, low-intensity, and strength training of upper and lower extremities are all utilized.
- Promotion of physical activity in the home and community setting is an important goal of pulmonary rehabilitation.
- Optimization of pharmacologic therapy and supplemental oxygen (when indicated) may allow the patient to exercise at higher intensity and thereby achieve greater increases in exercise performance.

Complete reference list available at *ExpertConsult*.

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INTRODUCTION**INDICATIONS AND CANDIDATE SELECTION****TIMING OF REFERRAL AND LISTING ALLOCATION SYSTEM****BRIDGING TO TRANSPLANTATION: ARTIFICIAL LUNG TECHNOLOGIES****DONOR SELECTION AND MANAGEMENT****LUNG PRESERVATION****AVAILABLE SURGICAL TECHNIQUES**

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RETRANSPLANTATION**FUTURE DIRECTIONS****INTRODUCTION**

Human lung transplantation was first attempted in 1963, but it was not until nearly 2 decades later that extended survival was achieved. Further refinements in patient selection, surgical technique, immunosuppression, and postoperative care have since facilitated the successful application of lung transplantation to a wide variety of advanced disorders of the airways, lung parenchyma, and pulmonary vasculature. The field has realized dramatic growth, with more than 47,000 procedures performed worldwide to date with approximately 3700 now performed annually.¹ Nonetheless, serious problems persist that limit the utility of this procedure. The donor pool remains insufficient to meet the demands of the many desperately ill patients awaiting transplantation. Immunosuppressive therapy is associated with a number of troubling side effects, most notably a significant risk of infection and malignancy. Despite the use of immunosuppressive agents, rejection develops frequently and continually threatens organ function. Though lung transplantation offers the prospect of improved functional status and quality of life, long-term survival remains an elusive goal, with only half of recipients living beyond 5 years. In order to optimize outcomes in the face of these shortcomings, judicious selection of candidates is essential and care of recipients must be rendered in a meticulous and vigilant fashion by clinicians familiar with the hazards of posttransplant life.

INDICATIONS AND CANDIDATE SELECTION

Lung transplantation is a therapeutic option for a broad spectrum of chronic debilitating pulmonary disorders of the airways, parenchyma, and vasculature. Leading indications include *chronic obstructive pulmonary disease* (COPD;

28% of cases), *idiopathic pulmonary fibrosis* (IPF; 29% of cases), and *cystic fibrosis* (CF; 15% of cases).¹ Other less common indications include emphysema due to α_1 -antitrypsin deficiency, sarcoidosis, non-CF bronchiectasis, and lymphangioleiomyomatosis. Once a common indication for transplantation, idiopathic pulmonary arterial hypertension now accounts for less than 3% of procedures, reflecting major advances in the medical management of these patients. Transplantation of patients with lung involvement due to collagen vascular disease remains controversial due to concerns that extrapulmonary manifestations of the systemic disease could compromise the posttransplant course. In particular, the esophageal dysmotility and reflux that frequently characterize scleroderma could increase the risk of aspiration and accelerated graft loss. The demonstration that posttransplantation survival of scleroderma patients is comparable with other patient populations provides some reassurance that carefully selected patients can benefit from this procedure.^{2,3} Use of lung transplantation for locally advanced bronchioloalveolar carcinoma (now referred to as *adenocarcinoma in situ*) has largely been abandoned due to an unacceptably high rate of cancer recurrence.⁴

Many transplant centers define an age cutoff for transplant eligibility, typically 65–70 years. In support of this policy, advanced recipient age has been consistently identified as a risk factor for increased posttransplant mortality.¹ Nonetheless, there has been a growing trend to expand the age range on the basis of the argument that “functional” rather than chronologic age should be considered. This trend has been most pronounced in the United States, where patients 65 years and older accounted for 27% of transplant recipients in 2011 compared with 3% in 2001.⁵ Two recent single-center case series involving 50 and 78 patients, respectively, who were 65 years or older found no difference in 1-year and 3-year posttransplant survival rates compared with younger cohorts.^{6,7} However, the *United Network for Organ Sharing* (UNOS) database of U.S.

transplants documents a 10-year survival rate among recipients 65 and older of only 13% compared with 23% for those 50 to 64 years and 38% for those younger than 50 years.⁸

There are surprisingly few remaining absolute contraindications to lung transplantation. There is general consensus that the following contraindicate transplantation: (1) recent malignancy (other than nonmelanoma skin cancer); (2) active infection with hepatitis B or C virus associated with histologic evidence of significant liver damage; (3) active or recent cigarette smoking, drug abuse, or alcohol abuse; (4) severe psychiatric illness; (5) repeated noncompliance with medical care; and (6) absence of a consistent and reliable social support network.⁹ Infection with *human immunodeficiency virus* (HIV) is still viewed by most centers as an absolute contraindication, but promising results with liver, kidney, and heart transplantation in HIV-positive recipients, as well as a recent case report of successful lung transplantation, may soon remove this barrier.¹⁰

The presence of significant extrapulmonary vital organ dysfunction precludes isolated lung transplantation, but multiorgan procedures such as heart-lung or lung-liver can be considered in highly selected patients. Both obesity and underweight nutritional status increase the risk of posttransplant mortality, but cutoffs for exclusion of candidates vary among centers.¹¹ The risk posed by other chronic medical conditions such as diabetes mellitus, osteoporosis, gastroesophageal reflux, and coronary artery disease must be assessed individually on the basis of severity of disease, presence of end-organ damage, and ease of control with standard therapies.

Prior pleurodesis is associated with an increased risk of intraoperative bleeding, particularly when cardiopulmonary bypass is used, but is not a contraindication to transplantation in experienced surgical hands. Pleural thickening associated with aspergillomas similarly complicates anatomic dissection and explantation of the native lung and carries the additional risk of soiling the pleural space with fungal organisms.

Among candidates with CF, colonization with certain species comprising the *Burkholderia cepacia* complex, in particular *Burkholderia cenocepacia* (previously known as genomovar III), is considered a strong contraindication by the majority of centers, owing to the demonstrated propensity of this organism to cause lethal posttransplant infections.^{12,13} In contrast, the presence of pan-resistant *Pseudomonas aeruginosa* in this patient population is associated with acceptable outcomes and should not be viewed as a contraindication.¹⁴

Transplantation of patients on mechanical ventilation is associated with increased short-term posttransplant mortality though it does not appear to affect outcomes beyond the first year.¹ Although transplantation of these patients was previously discouraged, the new lung allocation system in the United States has prompted reconsideration of this perspective by assigning high allocation scores to ventilator-dependent patients. Many programs are now willing to maintain some ventilator-dependent patients on their active waiting list, anticipating that the high allocation score will expedite transplantation, but reserving the option of de-listing patients who develop intercurrent complications or progressive debility. An analysis of 586 ventilator-

dependent patients in the UNOS database documents inferior but not necessarily prohibitively poor short-term outcomes; 1-year and 2-year survival rates were 62% and 57%, respectively, compared with 79% and 70% for non-ventilated patients.¹⁵ Even more controversial is transplantation of patients on *extracorporeal membrane oxygenation* (ECMO) support, for whom 1-year and 2-year posttransplant survival rates were only 50% and 45%, respectively, in the UNOS database. More recent single-center reports document more promising outcomes,^{16,17} and increasing availability of ambulatory ECMO techniques may improve outcomes in the future.

TIMING OF REFERRAL AND LISTING

Listing for transplantation is considered at a time when the lung disease limits basic activities of daily living and is deemed to pose a high risk of death in the short term. Disease-specific guidelines for timely referral and listing of patients, based on available predictive indices, have been published (Table 106-1).⁹ The imprecise nature of these predictive indices can make decisions about transplant listing problematic for all but the most severely ill patients. The patient's perception of an unacceptably poor quality of life is an important additional factor to consider but should not serve as the sole justification for listing of a patient whose disease is not deemed to be at an advanced and potentially life-threatening stage.

ALLOCATION SYSTEM

Rules governing allocation of organs vary among countries but typically employ a time-based or need-based ranking of candidates on the waiting list, or some combination of the two systems. Examination of the systems that have been operative in the United States permits an appreciation of the advantages and limitations of both approaches. From 1990 to 2005, lung allocation in the United States prioritized candidates on the basis of the amount of time they had accrued on the waiting list, without regard to severity of illness. Based on a simple and objective parameter, this system was easily understood but was ultimately called into question because it failed to accommodate those patients with a more rapidly progressive course who often could not survive the prolonged waiting times.¹⁸ In response to the perceived inequities of the time-based system, and under mandate of the federal government, a new system was implemented in 2005. It allocates lungs on the basis of both medical urgency (risk of death without a transplant) and "net transplant benefit" (the extent to which transplantation will extend survival). It uses predictive models, incorporating more than a dozen variables, to generate predictions for a given patient of 1-year survival with and without transplantation.¹⁹ A raw *lung allocation score* (LAS) is then calculated on the basis of these survival predictions and normalized to a scale of 0 to 100 for ease of use. Because 1-year survival without transplantation is factored into net transplant benefit and medical urgency measures, it affects

Table 106-1 Disease-Specific Guidelines for Listing for Lung Transplantation**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

- BODE index of 7–10 **or** at least one of the following:
 - History of hospitalization for exacerbation associated with acute hypercapnia ($PCO_2 > 50$ mm Hg)
 - Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy
 - $FEV_1 < 20\%$ and either $DL_{CO} < 20\%$ or homogeneous distribution of emphysema

IDIOPATHIC PULMONARY FIBROSIS

- Histologic or radiographic evidence of UIP **and** any of the following:
 - $DL_{CO} < 39\%$ predicted
 - $\geq 10\%$ decrement in FVC during 6 months of follow-up
 - Decrease in pulse oximetry to $< 88\%$ during a 6MWT
 - Honeycombing on HRCT (fibrosis score > 2)

CYSTIC FIBROSIS

- $FEV_1 < 30\%$ of predicted or rapidly declining lung function if $FEV_1 > 30\%$ (females and patients < 18 yr have a poorer prognosis; consider earlier listing) **and/or** any of the following:
 - Increasing oxygen requirements
 - Hypercapnia
 - Pulmonary hypertension

IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

- Persistent NYHA class III or IV on maximal medical therapy
- Low (350 m) or declining 6MWT
- Failing therapy with intravenous epoprostenol or equivalent
- Cardiac index < 2 L/min/m²
- Right atrial pressure > 15 mm Hg

SARCOIDOSIS

- NYHA functional class III or IV **and** any of the following:
 - Hypoxemia at rest
 - Pulmonary hypertension
 - Elevated right atrial pressure > 15 mm Hg

BODE, [b]ody mass index, airflow [o]bstruction, [d]yspnea, [e]xercise capacity; DL_{CO} , diffusing capacity for carbon dioxide; FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; 6MWT, 6-minute walk test; NYHA, New York Heart Association; PCO_2 , pressure of carbon dioxide; UIP, usual interstitial pneumonia.

Modified from Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update. *J Heart Lung Transplant* 25:745–755, 2006.

the LAS more than posttransplantation survival, which is used only in the net transplant benefit calculation. As designed, the system preferentially allocates lungs to sicker patients while attempting to avoid situations in which outcomes are so poor that there would be no meaningful survival benefit.

Since its implementation, the LAS system has had a profound and favorable effect on the dynamics of lung transplantation in the United States.²⁰ Because there is no longer an incentive to place patients on the active waiting list simply to accrue time (many of whom were ultimately deactivated rather than transplanted), the number of actively listed patients has fallen to approximately one half of the previous level. Median waiting time, which had ranged from 2 to 3 years under the time-based allocation system, has decreased to less than 6 months, and one quarter of patients are waiting less than 35 days. Importantly, there has been a significant reduction in the annual death rate

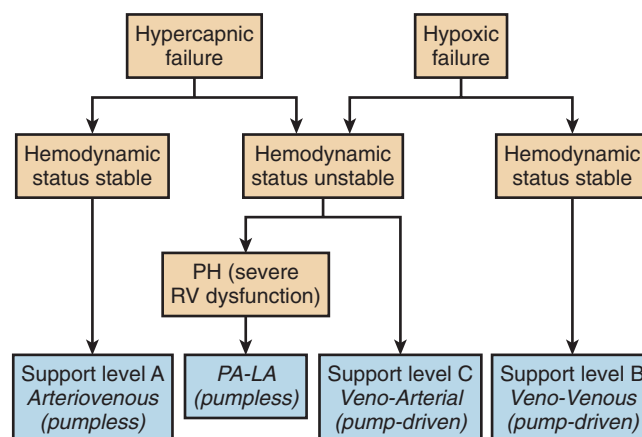


Figure 106-1 Selection of extracorporeal lung support device and configuration. The choice of support device is largely dependent on the type of respiratory failure (hypercarbic or hypoxic) and the hemodynamic status (stable or unstable). LA, left atrium; PA, pulmonary artery; PH, pulmonary hypertension; RV, right ventricle. (From Cypel M, Keshavjee S: Extracorporeal life support pre and post lung transplantation. ECMO Extracorporeal Cardiopulmonary Support in Critical Care (ELSO Red Book), ed 4. Ann Arbor, MI, 2011, Extracorporeal Life Support Organization.)

of patients on the waiting list, one of the stated objectives of the new system. Notably, preferential transplantation of sicker patients has not resulted in an increase in early mortality following transplantation. Further experience will be required to determine the impact of the new system on long-term outcomes following transplantation.

BRIDGING TO TRANSPLANTATION: ARTIFICIAL LUNG TECHNOLOGIES

As mentioned earlier, ECMO has been used to bridge critically ill patients to lung transplantation, though, historically, outcomes following transplantation have been suboptimal. Advances in artificial lung technology, including improved membranes, improved pumps, and even ambulatory support systems, make it increasingly possible to support selected patients successfully, permitting them to survive the wait for a suitable donor lung, and, importantly, to achieve a successful posttransplant outcome.²¹⁻²⁴

Patients with isolated hypercapnic failure can be bridged with pumpless devices such as the *interventional lung assist* (iLA) from Novalung, a low-resistance device with a meshwork of hollow fibers maximizing blood/gas diffusion; with this device, blood is propelled by arterial pressure. Patients requiring oxygenation support can be supported with veno-venous configured pump devices. Patients requiring circulatory support, as well as gas exchange support, can be managed with a conventional veno-arterial configuration. It is important to understand the underlying physiology of the patient and to select the device configuration that provides the necessary support (Fig. 106-1). An application unique to patients with pulmonary arterial hypertension is the application of the pumpless iLA device from pulmonary artery to left atrium

Table 106-2 Standard Lung Donor Criteria

- Age < 55 yr
- Clear chest radiograph
- PaO₂ > 300 mm Hg on FIO₂ 1.0, PEEP 5 cm H₂O
- Cigarette smoking history < 20 pack-years
- Absence of significant chest trauma
- No evidence of aspiration or sepsis
- No prior thoracic surgery on side of harvest
- Absence of organisms on sputum Gram stain
- Absence of purulent secretions and gastric contents at bronchoscopy
- Negative for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody
- No active or recent history of malignancy (excluding localized squamous or basal cell skin cancer, localized cervical cancer, and primary brain tumors with low metastatic potential and in the absence of invasive procedures to the brain and skull)
- No history of significant chronic lung disease

FIO₂, fractional concentration of oxygen in inspired gas; HIV, human immunodeficiency virus; PaO₂, arterial oxygen pressure; PEEP, positive end-expiratory pressure.

to offload the right ventricle and provide an “oxygenating septostomy” physiology. This strategy has effectively abolished wait list mortality in the group of patients that traditionally has the highest mortality on the wait list.^{22,25}

DONOR SELECTION AND MANAGEMENT

In addition to meeting strict criteria for declaration of brain death, cadaveric lung donors are selected on the basis of established guidelines (Table 106-2).²⁶ Lungs are a particularly fragile organ in the brain-dead patient and are frequently compromised by volume overload, contusion, aspiration of gastric contents, or pneumonia, as well as by extensive prior smoking. As a result, the vast majority of donors fail to meet standard criteria for lung donation, leading to a historical recovery rate of only 15% from cadaveric organ donors deemed able to donate other organs. Although it is reasonable to be conservative with patient safety in mind, there is mounting evidence that these standard criteria may in fact be too stringent, leading to unnecessary wastage of suitable lungs. In one study, 29 pairs of lungs that had been rejected for transplantation were assessed for the magnitude of extravascular water content, intactness of alveolar fluid clearance capacity, and presence of pneumonia or emphysema.²⁷ Twelve pairs (41%) were found to have minimal or no abnormalities and thus to be “potentially suitable” for transplantation. Additional evidence comes from published reports documenting that outcomes with use of “extended criteria” donors are similar to those achieved with use of donors meeting standard criteria.²⁸⁻³² Use of modified donor management protocols to optimize lung function through judicious fluid management, therapeutic bronchoscopy, and lung recruitment maneuvers has also been shown to enhance lung retrieval rates.^{33,34} Additionally, a recent multicenter, randomized trial demonstrated that use of a low tidal volume, lung-protective ventilatory protocol (6 to 8 mL/kg; PEEP 8 to

10 cm H₂O) in brain-dead potential organ donors resulted in a doubling of lung harvest rates (54% vs. 27%) compared with a conventional ventilatory protocol (10 to 12 mL/kg; PEEP 3 to 5 cm H₂O).³⁵

Despite increases in the number of organs successfully retrieved, the demand for organs continues to outstrip supply, prompting a search for alternatives to the brain-dead donor pool. One emerging source is the non-heart-beating or *donation after cardiac death* (DCD) donor who has experienced either an out-of-hospital (i.e., uncontrolled) arrest or a planned withdrawal of life support in the operating room. Currently only 1% of lung transplants performed in the United States utilize DCD donors⁵; in contrast, DCD donors account for 12% of lung transplants in Australia.³⁶ Data suggest that short- and medium-term outcomes are as good as or better than those associated with use of traditional brain-dead donors.^{36,37}

Once a donor has been identified, matching with potential recipients is based on size and ABO blood group compatibility. Prospective *human leukocyte antigen* (HLA) matching is not performed. However, potential candidates identified through standard pretransplant screening as having preformed circulating antibodies to foreign HLA antigens require either prospective donor-recipient lymphocytotoxic cross-matching or avoidance of donors with specific incompatible antigens.³⁸

LUNG PRESERVATION

The standard of lung preservation is hypothermic flush preservation. The most commonly used solution is Perfadex (Vitrolife, Sweden). Cold flush preservation at 4° C decreases the metabolic rate to 5% of normal and hence slows down the dying process of the lung. Although this approach has been useful for clinical lung transplantation, cold static preservation has significant limitations: (1) a decision regarding utilization must be made quickly with limited information in the donor hospital; (2) once the organ is flushed, there is no second chance to reevaluate the organ before removal of the cross clamp at reperfusion; and (3) the focus is on slowing down the dying process and it does not address or take advantage of opportunities to diagnose, treat, repair, or regenerate the donor lung.

Ex vivo lung perfusion has been developed to address these limitations. It is now possible to perfuse lungs ex vivo at normothermia for extended periods, thus creating a platform for more detailed assessment of lung function, more accurate diagnosis, and targeted treatment of donor lung injuries to improve the function of the lung after transplantation.³⁹⁻⁴¹ This creates the opportunity to engineer donor organs with gene therapy, cell therapy, and other advanced treatments to create “super-organs” that hopefully will one day afford the recipient long-term allograft function.^{42,43}

Ex vivo lung perfusion has been shown to increase donor lung utilization of lungs that previously could not be used.^{40,44} Short-term outcomes using lungs conditioned in this fashion have been highly favorable.^{40,41} Ex vivo lung perfusion is now standard practice in the Toronto Lung Transplant Program⁴¹ and is being increasingly applied worldwide.⁴⁵ The U.S. Food and Drug Administration

recently approved the XVIVO Perfusion System for use in the United States.

AVAILABLE SURGICAL TECHNIQUES

Four surgical techniques have been developed: *heart-lung transplantation* (HLT), *single-lung transplantation* (SLT), *bilateral-lung transplantation* (BLT), and living donor bilobar transplantation. The choice of procedure is dictated by such factors as the underlying disease, age of the patient, survival and functional advantages, donor organ availability, and center-specific preferences. Currently, SLT and BLT account for more than 97% of all procedures performed.¹

HEART-LUNG TRANSPLANTATION

HLT was the first procedure to be performed successfully, but it has largely been supplanted by techniques to replace the lungs alone. Currently, fewer than 100 procedures are performed worldwide annually.¹ Indications are largely restricted to Eisenmenger syndrome with surgically uncorrectable cardiac lesions and to advanced lung disease with concurrent severe left ventricular dysfunction or extensive coronary artery disease. In the past, the presence of profound right ventricular dysfunction in the setting of severe pulmonary hypertension was deemed to be an indication for heart-lung transplantation. However, subsequent experience with isolated lung transplantation has demonstrated the remarkable ability of the right ventricle to recover once pulmonary artery pressures have normalized.

SINGLE-LUNG TRANSPLANTATION

SLT was, until recently, the most commonly performed procedure. Traditionally, a standard posterolateral thoracotomy was utilized, but some surgeons now employ a less invasive anterior axillary muscle-sparing approach in selected cases. Three anastomoses are executed—mainstem bronchus, pulmonary artery, and left atrium (incorporating the two pulmonary veins). Compared with BLT, SLT permits more efficient use of the limited donor supply and is better tolerated by less robust patients, but it provides less functional reserve in the setting of allograft dysfunction. It is an acceptable option for patients with pulmonary fibrosis and COPD. SLT has also been performed successfully in carefully selected patients with severe pulmonary hypertension. In this setting, however, there is an increased risk of perioperative allograft edema because the freshly transplanted lung must bear the burden of nearly the entire cardiac output. This concern has prompted the vast majority of centers to abandon this approach in favor of the bilateral procedure. Because of infectious concerns, SLT is contraindicated in patients with suppurative lung disorders such as CF.

BILATERAL-LUNG TRANSPLANTATION

BLT involves the performance of two single-lung transplant procedures in succession during a single operative session.

Surgical approaches include transverse thoracosternotomy (“clamshell”) incision, bilateral anterolateral thoracotomies (sparing the sternum), and median sternotomy. In the absence of severe pulmonary hypertension, cardiopulmonary bypass can often be avoided by sustaining the patient on the contralateral lung during implantation of each allograft. The principal indications for this procedure are CF, other forms of bronchiectasis, and severe primary and secondary forms of pulmonary hypertension. In addition, many programs now advocate its use for patients with COPD, arguing that it offers functional and survival advantages over SLT.⁴⁶⁻⁴⁹ Although it is also being employed with increasing frequency in treatment of fibrotic lung disorders, the justification for this is less clear.^{50,51} As a result of these trends, BLT now accounts for three quarters of all procedures performed worldwide.¹

LIVING DONOR BILOBAR TRANSPLANTATION

Living donor bilateral-lobar transplantation was developed chiefly to serve the needs of candidates with far-advanced or deteriorating status that would not allow them to tolerate a protracted wait for a cadaveric donor. The procedure involves transplantation of lower lobes from each of two living, blood group-compatible donors. In order to ensure that the lobes will adequately fill the hemithoraces, it is preferable to employ donors who are taller than the recipient. Patients with CF are particularly well suited as a target population because, even as adults, they tend to be of small stature. Intermediate-term functional outcomes and survival among recipients are similar to those achieved with cadaveric transplantation.^{52,53} Concerns about excessive risk to the donor have thus far proved to be unfounded. In the two largest series published to date involving a combined total of 315 donors, there were no deaths or episodes of postoperative respiratory failure, and only 9 donors (2.9%) experienced complications of sufficient magnitude to warrant surgical reexploration.^{54,55} Donation of a lobe results in an average decrement in vital capacity of 17%, a degree of loss that should be of little functional significance in an otherwise normal individual.⁵⁶ Despite the apparent low risk posed to the donor, living donor transplantation has not gained widespread acceptance. Its use has been further undermined by the LAS allocation system, which expedites transplantation of more severely ill candidates; only nine living-donor transplantation procedures have been performed in the United States since implementation of the LAS system.⁵

ROUTINE POSTTRANSPLANTATION MANAGEMENT AND OUTCOMES

Care of the lung transplant recipient requires close surveillance to ensure that the allograft is functioning properly, that immunosuppressive medications are properly administered and tolerated, and that complications are detected early and treated expeditiously. Most centers require patients to return frequently for office visits, blood tests, and chest

radiographs during the initial 2 to 3 months following transplantation and to participate in an intensive pulmonary rehabilitation program during this time. Analogous to home glucose monitoring of the diabetic patient, lung transplant recipients chart their pulmonary function on a daily basis with a handheld microspirometer and are instructed to contact the transplant center if a sustained fall of greater than 10% in the *forced expiratory volume in 1 second* (FEV₁) or forced vital capacity is documented.

Many transplant programs employ frequent surveillance bronchoscopies and transbronchial lung biopsies within the first posttransplant year as a means of monitoring the allograft. Such an approach has been demonstrated to detect low-grade rejection and subclinical *cytomegalovirus* (CMV) pneumonitis in up to 30% of asymptomatic, clinically stable patients.⁵⁷ However, it has yet to be determined whether treatment of clinically silent disease has a beneficial impact on long-term graft function.

Immunosuppressive therapy is initiated immediately at the time of transplantation and is maintained lifelong. No consensus currently exists on the role of induction therapy with lymphocyte/thymocyte-depleting globulin preparations or *interleukin-2* (IL-2) receptor antagonists (basiliximab and daclizumab), and only half of all centers currently employ this strategy.¹ The lack of consensus reflects insufficient and conflicting data on the ability of these agents to reduce the incidence of acute rejection and *bronchiolitis obliterans syndrome* (BOS) in the lung transplant population. Maintenance therapy consists of a calcineurin inhibitor (cyclosporine or tacrolimus), purine synthesis inhibitor (azathioprine or mycophenolate), and prednisone. Sirolimus (also known as *rapamycin*), an inhibitor of IL-2-stimulated T-cell proliferation, is the newest immunosuppressive agent to be introduced into clinical practice. Use of this agent in place of a purine synthesis inhibitor does not reduce the incidence of acute rejection or BOS and is associated with a number of bothersome side effects that commonly lead to discontinuation of the drug.⁵⁸ Lacking inherent nephrotoxicity, sirolimus has been successfully substituted for calcineurin inhibitors in patients with renal insufficiency, leading to recovery of renal function without undue risk of rejection.^{59,60} Sirolimus impairs wound healing and has been associated with life-threatening bronchial anastomotic dehiscence when used immediately following transplantation.⁶¹ As a result, the drug should never be initiated until complete healing of the bronchial anastomosis has been documented.

Individuals providing care to transplant recipients must be familiar with the administration, side effects, and drug interactions of these immunosuppressive agents (Table 106-3). Although serving as the cornerstone of therapy, the use of calcineurin inhibitors is particularly challenging. When administered orally, the bioavailability of these agents is poor and unpredictable, necessitating frequent monitoring of blood levels to ensure appropriate dosing. These drugs are metabolized via the hepatic cytochrome P-450 system, and blood levels are influenced by the concurrent administration of other drugs that affect this enzymatic pathway. Adverse effects of these agents, as well as of the other drugs commonly utilized, are legion and contribute significantly to the morbidity associated with transplantation.

Management of medical comorbidities is an essential component of the care of the lung transplant recipient. Common medical issues that emerge in this population include osteoporosis, hypertension, renal insufficiency, coronary artery disease, diabetes mellitus, and hyperlipidemia.⁶² Treatment of these conditions is similar to that of the general population.

SURVIVAL

Current 1-, 5-, and 10-year survival rates following lung transplantation are 82%, 55%, and 33%, respectively. Survival rates have steadily improved over time, as indicated by an increase in median survival from 3.9 years in 1990–1997 to 6.1 years in 2005–2012.¹ Disease-specific differences in survival are apparent but may be confounded by differences in severity of illness, comorbidities, and average age among these populations. In descending order, median survival is 8.3 years for CF, 6.4 years for α_1 -antitrypsin deficiency, 5.7 years for sarcoidosis, 5.5 years for COPD and IPA, and 4.7 years for IPE.¹

Mortality is highest during the first year, with primary graft dysfunction and infection representing the most common causes of death. Factors portending an increased risk of early death include ventilator dependence of the recipient before transplantation, a pretransplant diagnosis of pulmonary arterial hypertension, elevated bilirubin, and advanced recipient age.¹ Beyond the first year, attrition slows to an annual rate of approximately 5% to 8%. Most late deaths are attributable to the development of BOS, the lethal effects of which are due to both progressive respiratory failure and an increased susceptibility to infection.

Whether lung transplantation truly extends survival compared with the natural history of the underlying disease remains a matter of some debate. In the absence of randomized trials, this question has been approached by comparing observed posttransplant survival to survival of wait-list patients or by simulating survival with and without transplantation by statistical modeling; both of these approaches suffer from significant methodologic shortcomings. In the case of IPE, a disease with an extremely poor short-term prognosis, studies have suggested that lung transplantation does confer a survival advantage.^{18,63} This has been more difficult to demonstrate for COPD, which typically follows a protracted course even in the advanced stages, and available studies comparing wait list and posttransplant survival have yielded conflicting results.^{18,64,65} A more complex analysis of this issue, employing prognostic models of survival with and without transplantation, found that approximately 45% of COPD patients would gain a survival benefit of at least 1 year by undergoing BLT; only 22% would derive such a benefit if SLT were employed.⁴⁹ Survival benefit was heavily influenced by pretransplant FEV₁, as well as a number of other functional and physiologic parameters. As an example, nearly 80% of patients with an FEV₁ less than 16% but only 11% of those with an FEV₁ greater than 25% were predicted to gain at least a year of life with BLT. Adults with CF also appear to derive a survival advantage from lung transplantation, though one study found that this was limited to those patients with a predicted 5-year survival without transplantation of less than 50% and without

Table 106-3 Commonly Used Immunosuppressive Medications

Medication (Class)	Dosing*	Adverse Effects	Drug Interactions
Cyclosporine and tacrolimus (calcineurin inhibitors)	Cyclosporine: dosed to achieve a whole blood trough level of 250–350 ng/mL (first year), then 200–300 ng/mL [†] Tacrolimus: dosed to achieve a whole blood trough level of 10–12 ng/mL (first year), then 6–8 ng/mL	Nephrotoxicity Hypertension Neurotoxicity (tremor, seizures, white matter disease, headache) Hyperkalemia Hypomagnesemia Hyperuricemia/gout Hemolytic-uremic syndrome Gastroparesis Hyperglycemia Hirsutism (cyclosporine) Gingival hyperplasia (cyclosporine)	INCREASED BLOOD LEVELS Macrolide antibiotics (except azithromycin) Azole antifungals Diltiazem, verapamil Grapefruit juice DECREASED BLOOD LEVELS Phenobarbital Phenytoin Rifampin
Sirolimus (mTOR inhibitor)	Dosed to achieve a whole blood trough level of 6–12 ng/mL	Thrombocytopenia Anemia Hyperlipidemia Peripheral edema Rash Impaired wound healing Interstitial pneumonitis	Same as calcineurin inhibitors
Azathioprine (purine synthesis inhibitor)	2 mg/kg/day	Leukopenia Macrocytic anemia Thrombocytopenia Hepatotoxicity Pancreatitis Hypersensitivity reaction (fever, hypotension, rash)	Synergistic bone marrow suppression when administered with allopurinol
Mycophenolate mofetil (purine synthesis inhibitor)	1000–1500 mg bid	Diarrhea Leukopenia Anemia	Concurrent use of cyclosporine may decrease serum concentrations of mycophenolate by limiting biliary secretion/enterohepatic recycling
Prednisone (corticosteroid)	0.5 mg/kg/day for 6–12 wk, then tapered to 0.15 mg/kg/day	Hyperglycemia Hypertension Hyperlipidemia Weight gain Osteoporosis Avascular necrosis Myopathy Mood changes Insomnia Cataracts	No significant interactions
Polyclonal antilymphocyte or antithymocyte globulin	Dose depends on specific preparation used	Leukopenia Thrombocytopenia Anaphylaxis Serum sickness “Cytokine release syndrome”—fever, hypotension	No significant interactions
Basiliximab (monoclonal IL-2 receptor antagonist)	20 mg IV on days 1 and 4	Hypersensitivity reactions (rare)	No significant interactions

*Dosing is based on the protocol used at the Hospital of the University of Pennsylvania; dosing may vary among transplant centers.

[†]Measured by high-performance liquid chromatography assay.

IL-2, interleukin-2.

B. cepacia and CF-arthritis.^{66,67} In contrast, modeling studies have suggested that CF patients younger than 18 years old rarely achieve a survival benefit.^{66,68} This contention has been challenged by several authors, who point out potential methodologic shortcomings of these studies.^{69,70}

PULMONARY FUNCTION

The peak effect of lung transplantation on pulmonary function parameters is usually not realized until 3 to 6 months following the procedure, at which time the adverse impact of such factors as postoperative pain, weakness, altered

chest wall mechanics, and ischemia-reperfusion lung injury has dissipated. Complete normalization of pulmonary function is the anticipated result of BLT. Following SLT for COPD, the FEV₁ increases several fold to a level of approximately 50% to 60% of the predicted normal value (Video 106-1). Similarly, SLT for pulmonary fibrosis results in marked but incomplete improvement in lung volumes, with persistence of a restrictive pattern.

Transplantation also leads to correction of gas exchange abnormalities. Oxygenation improves rapidly, permitting the majority of patients to be weaned off of supplemental oxygen within the first week. Hypercapnia may take longer

to resolve, due to lingering abnormalities in the ventilatory response to carbon dioxide.⁷¹

EXERCISE CAPACITY

Exercise tolerance improves sufficiently to permit the majority of transplant recipients to achieve functional independence and resume an active lifestyle. Although free of limitations with usual activity, transplant recipients with normal allograft function demonstrate a characteristic reduction in peak exercise performance as assessed by cardiopulmonary exercise testing. Specifically, patients typically achieve a maximum oxygen consumption at peak exercise of only 40% to 60% of predicted.⁷² Suboptimal exercise performance persists in subjects tested as late as 1 to 2 years following transplantation. Despite the greater magnitude of improvement in pulmonary function experienced by bilateral transplant recipients, there is no significant difference in peak exercise performance between this group and those who receive only one lung.⁷³

Characteristically, breathing reserve, oxygen saturation, and heart rate reserve remain normal during exercise while anaerobic threshold is reduced, a pattern most consistent with skeletal muscle dysfunction. Factors possibly contributing to this include chronic deconditioning, steroid myopathy, and calcineurin inhibitor-induced impairment in muscle mitochondrial respiration.^{72,74}

HEMODYNAMICS

When performed in patients with pulmonary hypertension, both SLT and BLT lead to immediate and sustained normalization of pulmonary arterial pressure and enhanced cardiac output.⁷⁵ In response to a decrease in afterload, right ventricular geometry and performance gradually normalize in the majority of patients.^{76,77} A threshold of right ventricular dysfunction below which recovery will not happen has yet to be defined.

QUALITY OF LIFE

After successful lung transplantation, quality of life measures improve markedly across most domains, achieving levels approximating that of the general population.⁷⁸⁻⁸² Nonetheless, several important limitations have been observed. Although improved from pretransplant status, impairments in psychological functioning—including increased levels of depression and anxiety, and poor perception of body image—persist.^{78,79} In addition, troubling side effects from immunosuppressive medications adversely affect quality of life.^{79,82} Finally, the development of BOS is associated with a significant deterioration in quality of life measures.⁸¹

Despite improvements in performance status and quality of life, fewer than half of lung transplant recipients return to the workforce.^{83,84} Factors cited by recipients as barriers to employment include employer bias against hiring an individual with a chronic medical condition, the potential loss of disability income or medical benefits, side effects of medications, concerns about risk of infection in the workplace, and prioritization of recreational activities over work as a posttransplantation goal.

COMPLICATIONS

PRIMARY GRAFT DYSFUNCTION

Primary graft dysfunction (PGD) is a term applied to the development within 72 hours of transplantation of radiographic opacities in the allograft(s) associated with impaired oxygenation, in the absence of identifiable insults such as volume overload, pneumonia, rejection, atelectasis, or pulmonary venous outflow obstruction.⁸⁵ PGD is presumed to be a consequence of ischemia-reperfusion injury, but inflammatory events associated with donor brain death, surgical trauma, and lymphatic disruption may be contributing factors. Supporting the concept of PGD as a form of acute, nonimmunologic lung injury, histologic examination of lung tissue from affected patients reveals a prevailing pattern of diffuse alveolar damage.⁸⁵ A widely used grading system classifies the severity of PGD based on the arterial oxygen pressure-to-fractional concentration of oxygen in inspired gas (arterial PO_2/FiO_2) ratio (Table 106-4).⁸⁶ In most cases, the process is mild and transient, but in approximately 10% to 20% of cases, injury is sufficiently severe to cause life-threatening hypoxemia (PGD grade 3) and a clinical course analogous to the acute respiratory distress syndrome.

A recent prospective, multicenter cohort study identified a number of risk factors for development of severe PGD.⁸⁷ Many of these were procedure-related factors: use of an elevated FiO_2 during reperfusion, use of cardiopulmonary bypass, SLT, and administration of large volume blood product transfusions. Recipient risk factors were a diagnosis of sarcoidosis, presence of pulmonary hypertension, and overweight or obese body habitus. The only donor-related risk factor identified was a history of smoking. Notably, graft ischemic time was not identified as a risk factor in this study. In another study, an elevated level of IL-8 in bronchoalveolar lavage (BAL) fluid recovered from the donor was associated with the development of severe PGD, supporting the notion that inflammatory events preceding organ harvest may play a role.⁸⁸

Treatment of severe PGD is supportive, relying on conventional mechanical ventilation utilizing low tidal volume strategies, as well as on such adjunct measures as independent lung ventilation and extracorporeal life support for selected patients who otherwise cannot be stabilized.^{89,90}

Table 106-4 Grading System for Primary Graft Dysfunction

Grade	PaO_2/FiO_2	Radiographic Evidence of Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

PaO_2/FiO_2 , ratio of arterial oxygen pressure to fractional concentration of oxygen in inspired gas.

From Christie JD, Carby M, Bag R, et al: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part II: Definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 24:1454–1459, 2005.

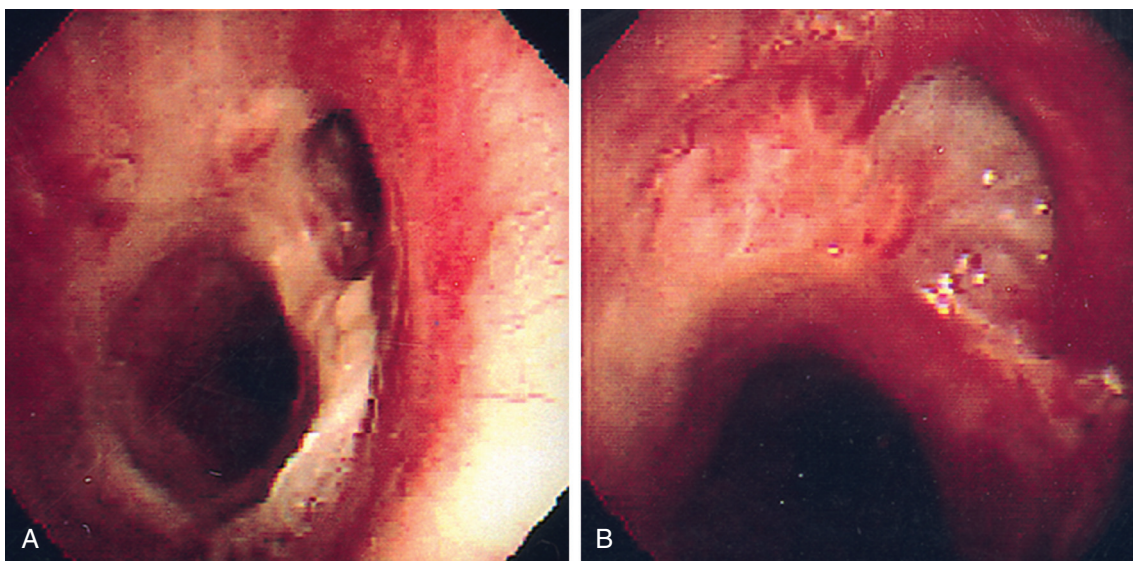


Figure 106-2 Bronchial anastomotic dehiscence. **A**, Bronchoscopic view immediately distal to the main carina demonstrates partial dehiscence of the right bronchial anastomosis at the 1 o'clock position. **B**, After several weeks of expectant management, a repeat bronchoscopy demonstrates near-complete healing of the dehiscence.

The use of nitric oxide in patients with established graft injury has been associated with sustained reduction in pulmonary artery pressures and improvement in oxygenation.⁹¹ However, the prophylactic administration of nitric oxide to all recipients at the time of reperfusion does not reduce the incidence of severe PGD.⁹² Results of emergency retransplantation in this setting have been poor.^{93,94}

With an associated perioperative mortality rate of 20% to 40%, severe PGD is a leading cause of early deaths among transplant recipients.^{87,95,96} The risk of death remains excessive even beyond the first year, suggesting that PGD has lingering adverse consequences well after resolution of the acute event. Recovery among survivors is often protracted and incomplete, though attainment of normal lung function and exercise tolerance is possible.⁹⁷ There appears to be an increased risk of BOS following development of PGD, but data are conflicting on whether the increased risk spans all grades of PGD or is seen exclusively following the most severe grade.^{98,99}

AIRWAY COMPLICATIONS

During implantation of the allograft, no attempt is routinely made to reestablish the bronchial arterial circulation. As a consequence, the donor bronchus is precariously dependent on retrograde blood flow through low-pressure pulmonary venous to bronchial vascular collaterals, placing the airway at risk for ischemic injury. Rarely, this may result in bronchial anastomotic dehiscence, which, when extensive, can lead to mediastinitis, pneumothorax, hemorrhage, and death. Treatment of this life-threatening complication previously required risky and often unsuccessful surgical intervention to buttress the anastomosis. More recently, success has been reported with temporary placement of a bare metal airway stent across the dehiscence in order to provide a scaffolding on which granulation tissue can form.¹⁰⁰ For lesser degrees of dehiscence, conservative management with reduction in corticosteroid dosing and chest

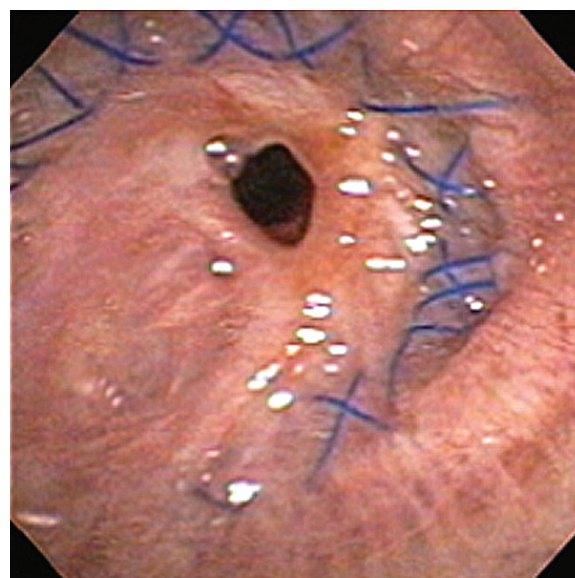


Figure 106-3 Bronchial anastomotic stricture. Bronchoscopic view of a left main-stem bronchial anastomosis demonstrates marked narrowing of the lumen due to formation of a fibrous web. The true outer margin of the bronchus is outlined by the suture material.

tube evacuation of associated pneumothorax will often lead to successful healing (Fig. 106-2).

Ischemic injury to the airway more commonly manifests as necrosis of the anastomotic cartilage and as patchy areas of bronchial mucosal ulceration and pseudomembranes. These devitalized areas in turn place the patient at increased risk for fungal superinfection of the airway (see later).

The most common airway complication currently encountered is bronchial anastomotic stenosis, with a reported frequency of 10% to 15% in contemporary series.^{101,102} Narrowing can be due to excessive granulation tissue, fibrotic stricture (Fig. 106-3), or bronchomalacia

(the latter two mechanisms likely a sequela of prior ischemic injury). Occasionally, fibrotic strictures can extend beyond the anastomosis, leading to narrowing of the bronchus intermedius (eFig. 106-1) or lobar bronchi. Anastomotic narrowing typically develops within several weeks to months following transplantation. Clues to its presence include focal wheezing on the involved side, recurrent bouts of pneumonia or purulent bronchitis, and suboptimal pulmonary function studies demonstrating airflow obstruction and truncation of the flow-volume loop. Bronchoscopy both confirms the diagnosis and permits therapeutic interventions including balloon dilation, laser debridement, endobronchial brachytherapy, and stent placement.¹⁰³ Although these measures are often successful in the short term, recurrent stenosis is common, necessitating repeated interventions and leading to compromised functional outcomes and excess mortality.¹⁰⁴

PHRENIC NERVE INJURY

Phrenic nerve injury following lung transplantation can result from intraoperative traction, use of an iced slurry to cool the allograft in the chest cavity before reperfusion, or transection of the nerve in the setting of extensive fibrous adhesions and difficult hilar dissection. Depending in part on whether screening is restricted to clinically suspected cases or more broadly to all recipients, the reported incidence of phrenic nerve injury ranges from 3% to 30%.¹⁰⁵⁻¹⁰⁸ Important albeit nonspecific clues to the presence of phrenic nerve injury include difficulty in weaning from mechanical ventilation, persistent hypercapnia, orthopnea, and radiographic evidence of persistent elevation of the diaphragm and associated basilar atelectasis. Phrenic nerve injury has been associated with increases in ventilator days, tracheostomy rates, and intensive care unit length of stay.¹⁰⁶ Achievement of a normal functional outcome is ultimately possible for those with reversible injury, but recovery in some cases may be protracted or incomplete. For severely impaired patients, nocturnal noninvasive ventilatory support and diaphragmatic plication have been successfully employed.^{109,110}

NATIVE LUNG HYPERINFLATION

Acute hyperinflation of the native lung leading to respiratory and hemodynamic compromise in the immediate postoperative period has been reported in 15% to 30% of emphysema patients undergoing SLT.^{111,112} Although risk factors remain poorly defined, the combination of positive-pressure ventilation and significant allograft edema serves to magnify the compliance differential between the two lungs and may predispose to this complication. Acute hyperinflation can be rapidly addressed by initiation of independent lung ventilation, ventilating the native lung with a low respiratory rate and a long expiratory time to facilitate complete emptying. Beyond the perioperative period, some SLT recipients with underlying emphysema demonstrate exaggerated or progressive native lung hyperinflation that more insidiously compromises the function of the allograft. In this setting, surgical volume reduction of the native lung can result in significant functional improvement.¹¹³

INFECTION

Infection rates among lung transplant recipients are several fold higher than among recipients of other solid organs. The greater risk is likely related to the unique exposure of the lung allograft to microorganisms via inhalation and aspiration and to the higher level of immunosuppression maintained in these patients. A comprehensive discussion of infectious complications is beyond the scope of this chapter; only the most common pathogens are discussed.

Bacteria

Bacterial infections of the lower respiratory tract account for the majority of infectious complications and have a bimodal temporal distribution.^{114,115} Bacterial pneumonia is most frequently encountered within the first month post-transplantation. In addition to the immunosuppressed status of the recipient, factors that predispose to early bacterial pneumonia include the need for prolonged mechanical ventilatory support, blunted cough due to postoperative pain and weakness, disruption of lymphatics, and ischemic injury to the bronchial mucosa with resultant impairment in mucociliary clearance. Although passive transfer of occult infection with the transplanted organ is an additional concern, the presence of organisms on Gram stain of donor bronchial washings is not predictive of subsequent pneumonia in the recipient.¹¹⁶ Bacterial infections, in the form of purulent bronchitis, bronchiectasis, and pneumonia, reemerge as a late complication among patients who develop BOS. Gram-negative pathogens, in particular *P. aeruginosa* (see eFig. 91-1), are most frequently isolated in association with both early and late infectious events.^{114,115}

Cytomegalovirus

CMV is the most common viral pathogen encountered following lung transplantation, though in the era of effective prophylaxis, its incidence and impact have diminished considerably.¹¹⁵ Infection can develop by transfer of virus with the allograft or transfused blood products or by reactivation of latent virus remotely acquired by the recipient. Seronegative recipients who acquire organs from seropositive donors are at greatest risk for developing infection, and these primary infections tend to be the most severe. Although donor-positive/recipient-negative mismatching has been identified as a risk factor for increased mortality in the International Society for Heart and Lung Transplantation Registry,¹ this may no longer be the case with the current widespread use of effective prophylactic regimens.¹¹⁷

In the absence of prophylaxis, CMV infection typically emerges 1 to 3 months following transplantation; antiviral prophylaxis shifts the onset to later in the course, often in the initial months after the antiviral agent is discontinued. Infection is often subclinical, evidenced only by silent viremia or shedding of virus in the respiratory tract. Clinical disease may present as a mononucleosis-like syndrome of fever, malaise, and leukopenia ("CMV syndrome") or as organ-specific invasion of the lung, gastrointestinal tract, central nervous system, or retina. Detection of virus in peripheral blood by either the pp65 antigenemia assay or *polymerase chain reaction* (PCR) techniques establishes a diagnosis of CMV infection but does not necessarily reflect

events at the tissue level. A diagnosis of CMV pneumonia, the most common manifestation of invasive disease in the lung transplant recipient (see eFigs. 91-2 and 91-3), is unequivocally established only by demonstration of characteristic viral cytopathic changes on lung biopsy or on cytologic specimens obtained by BAL, but the sensitivity of these findings is relatively low. Caution must be exercised in interpretation of a positive viral culture or PCR of BAL specimens because virus can be shed into the respiratory tract in the absence of tissue invasion.

Standard treatment of CMV syndrome and tissue-invasive disease consists of a 2- to 3-week course of intravenous ganciclovir at a dose of 5 mg/kg twice daily, adjusted for renal insufficiency. Monitoring of peripheral blood viral load should be performed weekly to confirm response to therapy. Treatment should be continued until at least 1 week after an undetectable viral load is documented.¹¹⁸ Some experts advocate the addition of CMV hyperimmune globulin in treatment of severe disease, but evidence supporting this practice is scant. Although treatment is effective, relapse rates of up to 60% in primary infection and 20% in seropositive recipients have been reported.¹¹⁹ Initiation of oral valganciclovir as secondary prophylaxis after completion of definitive treatment is a common practice, but its impact on relapse rates is uncertain.

In an attempt to minimize the adverse impact of CMV infection on the posttransplantation course, emphasis has shifted to preventive strategies. Numerous prospective, randomized trials have documented the efficacy of antiviral prophylaxis in delaying the onset and reducing the incidence and severity of CMV infection.¹²⁰ Oral valganciclovir has largely replaced intravenous ganciclovir as the prophylactic agent of choice, due to its excellent bioavailability, ease of administration, and demonstrated efficacy.¹²¹ Universal prophylaxis of all donor-seropositive/recipient-seronegative patients is recommended because the risk of CMV disease is high.¹¹⁸ Because the risk of disease is significantly lower in seropositive recipients (independent of donor status), it has been argued that universal prophylaxis of this group leads to overtreatment, increasing costs and unduly exposing patients to the risk of drug toxicity. In this population, preemptive strategies targeting antiviral therapy exclusively to patients demonstrating a rising viral load in peripheral blood have been advocated, but many programs still adhere to a universal prophylaxis strategy.¹²² Consensus guidelines recommend a minimum of 6 months of prophylaxis for donor-positive/recipient-negative patients and 3 to 6 months for recipient-positive patients.¹²³ However, a recent randomized, controlled trial of at-risk lung transplant recipients (either donor or recipient seropositive) demonstrated a marked reduction in the incidence of CMV disease with use of a 12-month course of valganciclovir prophylaxis compared with a 3-month course (4% vs. 32%).¹²⁴ Additional studies are required to determine whether 12 months is necessary or excessive and whether all at-risk subgroups require the same regimen.

Emergence of ganciclovir-resistant strains of CMV has been reported in 5% to 15% of lung transplant recipients with CMV infection.^{125,126} Risk factors that have been identified include donor-positive/recipient-negative CMV status, use of potent immunosuppressive agents such as antilymphocyte antibodies and daclizumab, increased number of

CMV episodes, and prolonged exposure to ganciclovir.^{127,128} Foscarnet, administered alone or in combination with ganciclovir, is the agent of choice for treatment of ganciclovir-resistant disease.¹²⁶ The drug is potentially nephrotoxic, and careful monitoring of renal function is essential. Although treatment is often successful, the presence of ganciclovir-resistant disease is associated with decreased survival in lung transplant recipients.^{128,129}

Aspergillus

Aspergillus species are the most frequently encountered fungal pathogens among lung transplant recipients. As a ubiquitous organism acquired by inhalation, *Aspergillus* colonizes the airways of approximately one quarter of transplant recipients.¹³⁰ Airway colonization itself does not appear to pose a major risk of subsequent progression to invasive disease.¹³⁰ Whether this is due to the inherently benign nature of colonization or to the common practice of initiating fungal prophylaxis when colonization is detected is unclear.

Aspergillus infects the bronchial tree in approximately 5% of lung transplant recipients.¹³⁰ In most cases, infection is localized to the bronchial anastomosis, where devitalized cartilage and foreign suture material create a nurturing environment. Less commonly, infection may present as a more diffuse ulcerative bronchitis with formation of pseudomembranes, typically following in the wake of a severe ischemic injury to the bronchial mucosa. Clustered within the first 6 months posttransplantation, these airway infections are usually asymptomatic and detected only by surveillance bronchoscopy. Although usually responsive to oral azoles or to inhaled or intravenous amphotericin, airway infections have rarely progressed to invasive pneumonia or have resulted in fatal erosion into the adjacent pulmonary artery.^{130,131} An increased risk of subsequent bronchial stenosis or bronchomalacia has also been reported, but it is unclear whether this is a consequence of the infection or of an underlying ischemic injury to the bronchus that predisposed to infection.^{132,133}

Invasive aspergillosis, a far more serious form of infection, develops in 5% of lung transplant recipients, most commonly within the first year.¹³⁰ It nearly always involves the lung but may disseminate to distant sites, particularly the brain, in a minority of patients. Symptoms are nonspecific and include fever, cough, pleuritic chest pain, and hemoptysis. Radiographically, pulmonary aspergillosis may appear as single (see eFigs. 91-7 and 91-8B) or multiple nodular (see eFig. 91-8A) or cavitary opacities or as alveolar consolidation (Fig. 106-4). The "halo sign"—a rim of ground-glass attenuation surrounding a central nodular opacity—is a suggestive but uncommon finding on chest computed tomography (CT) scans.

Diagnosing invasive pulmonary aspergillosis can be challenging. As discussed previously, many lung transplant recipients are colonized with *Aspergillus*, making it difficult to interpret the significance of positive fungal stains and cultures derived from BAL specimens. Conversely, the sensitivity of bronchoscopic studies has been reported in the range of only 45% to 62% in solid organ transplant recipients with invasive disease.¹³⁴ Measurement of galactomannan levels in serum or BAL fluid has been touted as a useful test for establishing a diagnosis of invasive disease in certain

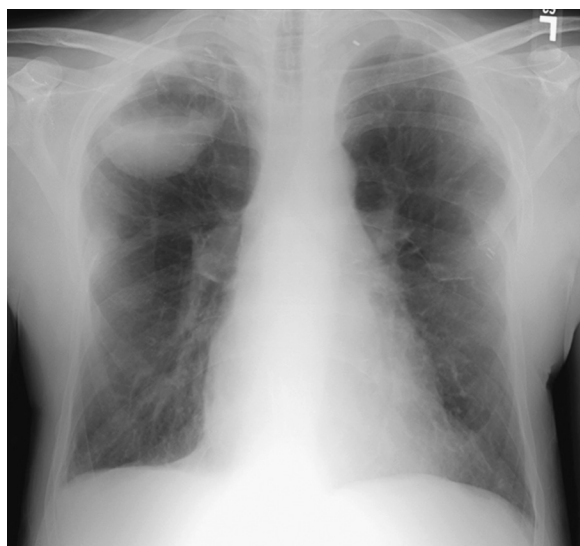


Figure 106-4 Invasive aspergillosis. Bilateral lung transplant recipient with a large right upper lobe cavity containing an air-fluid level. Transthoracic needle biopsy demonstrated fungal elements morphologically consistent with *Aspergillus* species. The patient failed to respond to antifungal therapy and required surgical resection for definitive cure.

patient populations; preliminary experience in lung transplant recipients suggests an unacceptably low sensitivity for both serum and BAL, though specificity appears to be high.^{135,136} In the context of compatible clinical and radiographic features and/or demonstration of *Aspergillus* in respiratory secretions by culture or cytology, the clinician must exercise judgment in deciding whether to initiate an empirical trial of antifungal therapy or pursue more definitive proof by means of transthoracic needle biopsy or surgical lung biopsy.

Amphotericin B was traditionally the mainstay of therapy for invasive aspergillosis. More recently, however, the triazole voriconazole has been shown to have superior efficacy and less toxicity than amphotericin B and has emerged as the treatment of choice.¹³⁷ Voriconazole is a potent inhibitor of the cytochrome P-450 hepatic enzyme system and can lead to dangerously high blood levels of concurrently administered calcineurin inhibitors and sirolimus if appropriate adjustments in the dosing of these agents are not made. The echinocandins (e.g., caspofungin) represent a third class of agents that have been successfully employed in the treatment of invasive aspergillosis.¹³⁸ Despite the availability of antifungal therapy, mortality rates in the range of 60% to 80% have been reported.^{130,139} The therapeutic role of surgical resection remains uncertain, but surgery has been advocated in cases of localized infection refractory to medical therapy.^{140,141}

REJECTION AND CHRONIC ALLOGRAFT DYSFUNCTION

Despite the use of potent immunosuppressive agents, allograft rejection and chronic allograft dysfunction remain pervasive problems that constrain long-term graft and patient survival. Humoral and cellular alloimmune mechanisms have been defined to varying degrees for the more acute insults, and thus the term “rejection” is an appropri-

ate descriptor (i.e., hyperacute rejection, acute cellular rejection, antibody-mediated rejection). However, the pathogenetic mechanisms underlying chronic forms of allograft dysfunction are less clear and both immunologic and nonimmunologic insults have been implicated. Although still part of the transplant lexicon, the term “chronic rejection” is misleading because it oversimplifies both the mechanism and the spectrum of phenotypes that characterize long-term allograft impairment. The term *chronic lung allograft dysfunction* (CLAD) is emerging as a preferred descriptor, comprising the most commonly encountered form, BOS, as well as newly recognized variants such as *restrictive allograft syndrome*. The various forms of rejection and CLAD are described in detail in the following sections. Features of the two most commonly encountered entities—acute cellular rejection and BOS—are summarized in Table 106-5.

Hyperacute Rejection

Hyperacute rejection is a rare but highly lethal complication mediated by preformed antibodies of recipient origin directed against HLA antigens contained in donor tissue. The pulmonary microvascular endothelium is the principal target, leading to complement- and neutrophil-mediated damage and widespread deposition of platelet/fibrin thrombi.¹⁴² Hyperacute rejection becomes clinically manifest within minutes to hours of establishing perfusion to the freshly implanted lung. The allograft appears dusky, mottled, and grossly edematous on direct inspection and densely opacified on chest radiograph. Reflecting the severity of pulmonary edema, copious amounts of pink, frothy edema fluid often are produced by the allograft and must be frequently suctioned from the endotracheal tube. Profound graft dysfunction and hemodynamic instability ensue. Four of the five cases reported in the literature resulted in death.¹⁴³ The one surviving patient was successfully managed with a combination of plasmapheresis, antithymocyte globulin, and cyclophosphamide.¹⁴⁴ Routine screening of all lung transplant candidates for preformed anti-HLA antibodies and either avoidance of donors with the targeted antigens or prospective cross-matching before transplantation have proved to be highly effective in minimizing the risk of hyperacute rejection.

Acute Cellular Rejection

Frequent surveillance of the allograft by transbronchial biopsy has demonstrated that most transplant recipients experience at least one episode of acute cellular rejection in the first year.⁵⁷ Beyond this initial period, the incidence of acute cellular rejection declines considerably. Risk factors for development of acute rejection remain poorly defined. Data are conflicting on whether the degree of HLA discordance between donor and recipient represents a risk factor.^{57,145,146} Polymorphisms in Toll-like receptor 4 that down-regulate recipient innate immune responsiveness are associated with a lower incidence of acute cellular rejection.¹⁴⁵

Episodes of acute cellular rejection may be clinically silent in up to 40% of cases.⁵⁷ When present, clinical manifestations are nonspecific and include malaise, low-grade fever, dyspnea, cough, and leukocytosis. Radiographic opacities (eFig. 106-2), a decline in arterial oxygenation at

Table 106-5 Features of Acute Cellular Rejection and Bronchiolitis Obliterans Syndrome (BOS)

Feature	Acute Cellular Rejection	BOS
Onset after transplant	Days to months; less common beyond the first year	Beyond first year
Risk factors	Uncertain	Acute rejection, lymphocytic bronchiolitis, community respiratory viruses, primary graft dysfunction, silent aspiration, CMV pneumonitis, airways colonization with <i>Aspergillus</i> or <i>Pseudomonas</i> species
Histology	Perivascular lymphocytic infiltrates	Bronchiolar submucosal inflammation and fibrosis; luminal obliteration
Signs and symptoms	Low-grade fever, dyspnea, cough, impaired oxygenation, leukocytosis	Dyspnea, chronic cough, recurrent bouts of purulent bronchitis
Chest radiograph	Alveolar or interstitial opacities, pleural effusions	Clear lung fields (may show hyperinflation)
High-resolution CT	Ground-glass or alveolar opacities, interlobular septal thickening	Tree-in-bud opacities, bronchiectasis, air trapping
Pulmonary function testing	Proportional decline in FEV ₁ and FVC	Disproportionate decline in FEV ₁ with worsening obstructive pattern
Yield of transbronchial biopsy	High	Low
Treatment	High-dose corticosteroids	Uncertain: azithromycin is a popular but unproven option
Outcome	Favorable response to treatment	Poor response to treatment; progressive allograft dysfunction in many cases

rest or with exercise, and an abrupt fall of greater than 10% in spirometric values are important clues to the possible presence of rejection, but similar findings accompany bouts of infection.

Reliance on clinical and radiographic criteria alone runs the risk of misdiagnosis and needless augmentation of immunosuppression. Transbronchial lung biopsy represents the “gold standard” for diagnosis of acute cellular rejection. The procedure is safe, can be performed in serial fashion over time, and has a high sensitivity and specificity. The histologic hallmark is the presence of perivascular lymphocytic infiltrates that, in more severe cases, spill over into the adjacent interstitium and alveolar air spaces. Lymphocytic bronchiolitis may accompany the parenchymal involvement or may be an independent feature. A histologic classification system has been universally adopted to grade the severity of acute cellular rejection (Table 106-6).¹⁴⁷

Conventional treatment consists of a 3-day pulse of intravenous Solu-Medrol at a daily dose of 15 mg/kg. In most cases, this results in rapid improvement in symptoms, pulmonary function, and radiographic abnormalities, but follow-up biopsies show histologic evidence of persistent rejection in 30% of patients with prior mild (A2) acute rejection and 44% of patients with prior moderate (A3) acute rejection.¹⁴⁸ Asymptomatic and functionally stable patients with minimal (A1) rejection have typically been observed without treatment, but data demonstrating progression to a higher grade of acute rejection in one quarter of cases and an increased risk of developing BOS have challenged this approach.¹⁴⁹ A variety of modalities have been employed for refractory or recurrent acute rejection including antilymphocyte antibody preparations and *photopheresis*, an immunomodulatory treatment using leukapheresis to collect *white blood cells* (WBCs), which are then treated with an ultraviolet light sensitizer, exposed to ultraviolet light, and returned to the body where they suppress T-cell function.

Table 106-6 Histologic Grading System for Acute Cellular Rejection

Grade	Description
0 (none)	Normal pulmonary parenchyma
1 (minimal)	Scattered, infrequent perivascular mononuclear infiltrates
2 (mild)	Frequent perivascular mononuclear infiltrates surrounding venules and arterioles; readily recognizable at low magnification
3 (moderate)	Easily recognizable cuffing of venules and arterioles by dense perivascular mononuclear cell infiltrates, with extension of the inflammatory cell infiltrate into perivascular and peribronchiolar alveolar septa and air spaces
4 (severe)	Diffuse perivascular, interstitial, and air space infiltrates of mononuclear cells with prominent alveolar pneumocyte damage and endothelialitis

From Stewart S, Fishbein MC, Snell GI, et al: Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant* 26:1229–1242, 2007.

Acute Antibody-Mediated Rejection

There is emerging evidence in support of a second form of acute rejection, mediated by donor-specific anti-HLA allo-antibodies that develop *de novo* following transplantation.^{150,151} The clinical presentation can be indistinguishable from acute cellular rejection, with dyspnea, hypoxemia, and diffuse radiographic opacities. Hemoptysis should raise suspicion of this entity, but it is present in only 25% of cases.¹⁵⁰ The suggested diagnostic criteria for acute antibody-mediated rejection are (1) presence of circulating donor-specific anti-HLA antibodies; (2) histopathologic evidence of capillaritis; and (3) detection of endothelial cell C4d deposition. Less than half of patients in the largest case series responded to corticosteroids alone; the addition of

plasmapheresis was beneficial in the majority of steroid-refractory cases.¹⁵⁰ Intravenous immunoglobulin and anti-CD20 monoclonal antibodies have also been used as adjunctive therapy.¹⁵¹

Bronchiolitis Obliterans Syndrome

Bronchiolitis obliterans, presumed to represent the consequences of “chronic rejection,” stands as the major impediment to long-term graft and patient survival. Bronchiolitis obliterans is a fibroproliferative process characterized by submucosal inflammation and fibrosis of the bronchiolar walls, ultimately leading to complete obliteration of the airway lumen. The functional consequence of this process is progressive and largely irreversible airflow obstruction. Because the characteristic histology is difficult to demonstrate by transbronchial lung biopsy, the FEV₁ has been adopted as an easily obtained diagnostic surrogate for histology, and the term *bronchiolitis obliterans syndrome* (BOS) has been applied to this functionally defined disorder (Table 106-7).¹⁵² Approximately 50% of transplant recipients develop BOS by 5 years and 75% by 10 years.¹ As originally conceived, BOS was defined as an otherwise unexplained and sustained fall in FEV₁ by at least 20% from posttransplant baseline. Concern that this definition might delay diagnosis beyond a stage amenable to treatment prompted

the more recent introduction of a BOS *O-potential* (BOS O-p) stage, defined as a decline in FEV₁ by 10% to 19% or in mean forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25%-75%}) by at least 25%. The FEV₁ criterion for BOS O-p has proved to be a reasonable predictor of patients at risk for progression to more advanced BOS, with a positive predictive value of 60% for progression within 1 year and 80% for progression within 4 years.^{153,154} The positive predictive value of the FEV₁ criterion is lower in SLT recipients with native lung emphysema, likely because of the confounding impact of native lung hyperinflation on lung function.¹⁵⁴ Notably, the FEF_{25%-75%} criterion suffers from a low positive predictive value in all recipient populations and is of questionable clinical utility.^{153,154}

Acute cellular rejection and lymphocytic bronchiolitis have been consistently identified as major risk factors for development of BOS, supporting the view that BOS is a consequence of alloimmune injury.^{155,156} Whereas the risk of BOS appears to correlate with the severity and frequency of these immunologic insults, even minimal (A1) acute rejection is associated with an increased risk.^{149,157} Other possible immune-mediated risk factors include the presence of anti-HLA antibodies (particularly donor specific) and the development of anti-type V collagen antibodies.^{158,159} Non-immune factors may also be important in initiating or perpetuating injury, suggesting that BOS may represent the end result of a wide array of insults to the airway epithelium. These factors include CMV pneumonitis, community respiratory viral infections, airway colonization with *Aspergillus* or *Pseudomonas*, primary graft dysfunction, and gastroesophageal reflux with occult aspiration.^{98,156,160-164}

Although often viewed as a late complication, BOS presents within the first 2 years after transplant in one third to one half of cases (“early-onset BOS”).^{165,166} The decline in FEV₁ that heralds the onset of BOS may be either insidious or abrupt. Dyspnea, weight loss, cough, and recurrent bouts of purulent tracheobronchitis, with recovery of *P. aeruginosa* from sputum cultures, are characteristic clinical features. Although chest radiographs are usually unremarkable, high-resolution CT commonly reveals air trapping (eFig. 106-3 and Videos 106-2 and 106-3), tree-in-bud opacities, and/or bronchiectasis (Fig. 106-5). The natural history of BOS is highly variable; those with early or abrupt

Table 106-7 Grading System for Bronchiolitis Obliterans Syndrome

Stage	Spirometric Criteria
0	FEV ₁ >90% of baseline and FEF _{25%-75%} >75% of baseline
0-potential	FEV ₁ 81%–90% of baseline and/or FEF _{25%-75%} ≤75% of baseline
1	FEV ₁ 66%–80% of baseline
2	FEV ₁ 51%–65% of baseline
3	FEV ₁ ≤50% of baseline

FEF_{25%-75%}, mean forced expiratory flow between 25% and 75% of forced vital capacity; FEV₁, forced expiratory volume in 1 second.

From Estenne M, Maurer JR, Boehler A, et al: Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 21:297–310, 2002.

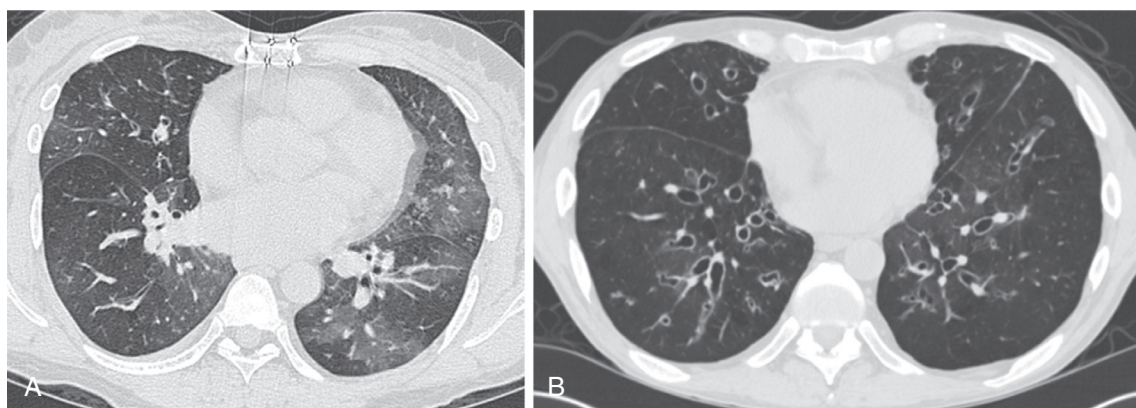


Figure 106-5 Radiographic features of bronchiolitis obliterans syndrome. **A**, High-resolution CT image obtained during expiration demonstrates a mosaic attenuation pattern consistent with air trapping. **B**, Image obtained from another patient with bronchiolitis obliterans syndrome demonstrates extensive bronchiectasis.

onset generally experience more rapid decline in lung function and higher mortality.^{165,166} Median survival from diagnosis is 1.5 years and 2.5 years for those with early- and late-onset BOS, respectively.¹⁶⁵

A myriad of immunosuppressive strategies have been employed in the treatment of BOS, including use of conventional agents (e.g., pulse corticosteroids), inhaled cyclosporine, antilymphocyte antibodies, photopheresis, and total lymphoid irradiation, but consensus is lacking on the optimal approach.^{167,168} At best, immunosuppressive measures appear to slow the rate of decline rather than to arrest or reverse the process. More recently, azithromycin has emerged as a popular alternative, based on retrospective studies documenting short-term improvement in the FEV₁ in approximately 30% to 40% of patients with BOS treated with this agent.¹⁶⁹⁻¹⁷² In contrast to nonresponders, responders demonstrate higher pretreatment levels of BAL neutrophilia and a marked reduction in neutrophilia following initiation of therapy. This lends credence to the notion that the beneficial effects of macrolides relate in large part to their ability to suppress airway IL-8 production and neutrophil recruitment.^{170,171} Although still controversial, performance of surgical fundoplication to control gastroesophageal reflux has been associated with improvement in lung function in some patients with BOS.¹⁷³ Adjuvant measures to mobilize respiratory secretions and control bacterial infection of the airways—including chest percussion, flutter or acapella valve, and inhaled and systemic antibiotics—may be of benefit in patients with accompanying bronchiectasis. At this time, the only definitive treatment for advanced BOS is retransplantation.

The development of strategies to prevent BOS is an area of intense interest but, to date, little substantive progress. In recognition of the established link between acute rejection and BOS, most transplant centers routinely perform surveillance lung biopsies to detect and treat clinically silent acute rejection, but the impact of this strategy on risk of BOS remains uncertain.¹⁷⁴ Early identification of recipients with gastroesophageal reflux and aggressive correction with fundoplication may delay or prevent onset of BOS, but this remains a controversial strategy.¹⁷⁵ In a small randomized trial, the addition of inhaled cyclosporine to a conventional immunosuppressive regimen was associated with a dramatic reduction in the incidence of BOS, but a subsequent multicenter trial failed to demonstrate benefit.^{176,177} A small, single-center, randomized, placebo-controlled trial demonstrated that the prophylactic administration of azithromycin after transplantation improved BOS-free survival, but larger, multicenter studies will be required to corroborate these findings.¹⁷⁸ Finally, some centers have employed a strategy to screen for donor-specific antibodies and, if detected, treat with intravenous immunoglobulin and rituximab in the hope of reducing the subsequent risk of developing BOS.¹⁷⁹ Again, however, additional studies are required to assess the efficacy of this approach.

Other Forms of Chronic Lung Allograft Dysfunction

Several other overlapping forms of CLAD that are distinct from BOS have recently been described. Various terms “restrictive allograft syndrome,”^{180,181} “restrictive-CLAD,”¹⁸² and “acute fibrinoid organizing pneumonia,”¹⁸³ these enti-

ties share in common a restrictive physiology and the presence of interstitial, alveolar, or ground-glass opacities on chest CT scans. The histologic findings vary among the published reports and include diffuse alveolar damage, interstitial fibrosis, and acute fibrinoid organizing pneumonia. There is remarkable agreement among the various reports on one point—survival of these patients is considerably worse than that of recipients with the more commonly encountered BOS.

POSTTRANSPLANTATION LYMPHOPROLIFERATIVE DISORDER

Posttransplant lymphoproliferative disorder (PTLD) describes a spectrum of abnormal proliferative responses involving B cells in the majority of cases and ranging from benign polyclonal hyperplasia to malignant lymphomas. In approximately 90% of cases, *Epstein-Barr virus* (EBV) is the stimulus for B-cell proliferation, which proceeds in an unchecked fashion due to the muted cytotoxic T-cell response in the immunosuppressed host. EBV-naïve recipients who acquire primary infection at the time of organ transplantation are at greatest risk of developing PTLD.¹⁸⁴ A higher intensity of immunosuppression and, in particular, the use of antilymphocyte antibody preparations have also been implicated as risk factors.

Among the myriad neoplasms that arise following lung transplantation, PTLD is second in frequency only to non-melanoma skin cancers, with an incidence of approximately 5%.¹⁸⁵ The risk of developing PTLD is greatest within the first posttransplantation year, though up to half of all cases are seen beyond this point. The majority of early-onset cases involve the allograft, typically presenting as one or more pulmonary nodules that may be accompanied by mediastinal adenopathy (Fig. 106-6). In contrast, beyond the first year, intra-abdominal and disseminated forms of disease predominate.¹⁸⁵

The diagnosis of PTLD is most firmly established by tissue biopsy, though fine-needle aspiration may occasionally



Figure 106-6 Posttransplantation lymphoproliferative disorder. CT scan demonstrates multiple nodules and masses, proven on biopsy to represent a high-grade B-cell lymphoma. In situ hybridization studies revealed the presence of Epstein-Barr virus RNA.

yield sufficient material to make a cytologic diagnosis. Care must be exercised in interpreting transbronchial lung biopsies because the aggregates of lymphocytes associated with acute cellular rejection can appear similar to foci of PTLD on these small tissue specimens. Demonstration of the presence of EBV-infected cells by in situ hybridization or immunohistochemical staining can help to confirm a diagnosis in difficult cases. Determination of EBV viral load in the peripheral blood using DNA amplification techniques has been touted as an ancillary diagnostic tool. Preliminary studies involving adult lung transplant recipients suggest that an elevated viral load correlates with the presence of PTLD with a high degree of specificity (i.e., low false-positive rate), but the sensitivity is as low as 39%.^{186,187} Additional studies employing uniform assay techniques and threshold values for positive results are required before conclusions can be drawn about the clinical utility of this test.

Initial treatment of PTLD involves reduction in the magnitude of immunosuppression to permit partial restoration of host cellular immunity against EBV. Regression of tumor is seen in up to two thirds of cases, but there is an attendant risk of precipitating acute or chronic rejection and patients must be monitored closely.¹⁸⁸ For patients who fail to achieve a complete remission, cannot tolerate reduced immunosuppression, or have rapidly progressive disease, immunotherapy with anti-CD20 monoclonal antibodies (rituximab) has emerged as the preferred option. Use of this agent in the solid organ transplant population is generally well tolerated and associated with a complete response rate of 60%.¹⁸⁹ In contrast, experience with standard chemotherapy has been poor, with up to one quarter of patients succumbing to treatment-related complications.¹⁸⁹ There is no proven role for antiviral therapy in the setting of established PTLD, though there is suggestive evidence that the prophylactic use of antiviral agents may reduce the subsequent risk of developing PTLD.¹⁹⁰

LUNG CANCER

The development of lung cancer following lung transplantation has been reported almost exclusively in patients with underlying COPD or pulmonary fibrosis, the majority of whom have had significant prior smoking histories. The reported incidence of lung cancer following transplantation is 2% to 6% in patients with COPD and 3% to 4% in patients with pulmonary fibrosis.¹⁹¹⁻¹⁹⁴ Data are conflicting on whether transplantation confers an increased likelihood of developing this form of cancer or whether the incidence is comparable with that of the general population with similar risk factors. Lung cancer most commonly arises in the native lung of SLT recipients. Less commonly, a previously unsuspected cancer may be incidentally detected in the explanted lung removed at the time of transplantation and may then recur in the allograft or in distant sites. A high rate of recurrence has also been documented in instances when lung transplantation has been performed as definitive treatment for underlying bronchioalveolar carcinoma.⁴ Finally, there are rare reports of lung cancer of donor origin transmitted to the recipient.¹⁹⁵

Lung cancer in the transplant recipient often progresses at a rapid pace, potentially leading to initial confusion with an infectious process (Fig. 106-7).¹⁹¹ This aggressive behavior may reflect loss of antitumor immune surveillance in the immunosuppressed host or may be due to a more specific effect of cyclosporine in promoting tumor growth.¹⁹⁶ Overall prognosis is poor but should not preclude attempts at curative resection in the rare instances in which early-stage disease is encountered.

RECURRENCE OF PRIMARY DISEASE

A number of primary disorders have been documented to recur in the allograft following transplantation.¹⁹⁷ Although

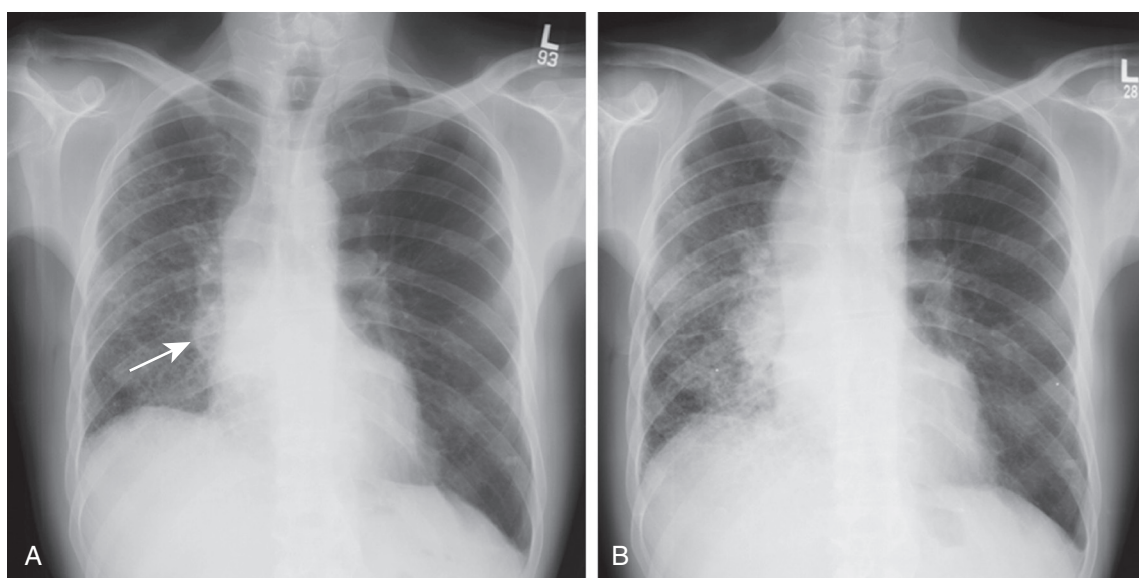


Figure 106-7 Bronchogenic carcinoma arising in the native lung. The patient had undergone a left single-lung transplant for idiopathic pulmonary fibrosis (IPF). **A**, Chest radiograph demonstrates slight fullness in the infrahilar region of the native right lung (arrow). **B**, Repeat chest radiograph only 2 months later demonstrates marked enlargement of the right infrahilar mass, as well as an increase in adjacent interstitial opacities. This proved to be a right lower lobe squamous cell lung cancer with associated lymphangitic spread.

accurate figures are not available, sarcoidosis appears to have the greatest propensity to do so. Recurrence of sarcoidosis is typically asymptomatic and marked by incidental recovery of noncaseating granulomas on bronchoscopy and occasionally by the presence of micronodular opacities in the upper lobes on CT scan. Cases of recurrent lymphangioleiomyomatosis have also been reported. The abnormal smooth muscle cells found in the allograft are of recipient origin, suggesting that the mechanism of recurrence involves migration or metastasis from an extrapulmonary site.¹⁹⁸ Other diseases for which recurrence has been reported include Langerhans cell histiocytosis, desquamate interstitial pneumonia, and diffuse panbronchiolitis.

Recurrence of emphysema in the allograft was documented in a recipient 11 years after transplantation for α_1 -antitrypsin deficiency.¹⁹⁹ The patient had resumed smoking and this was presumed to play a central role in accelerating the recurrence of disease. BAL fluid obtained after disease recurrence demonstrated free elastase activity, suggesting that the endogenous antiprotease defenses had been overwhelmed. These observations highlight the need for α_1 -antitrypsin-deficient transplant recipients to abstain from smoking but do not provide justification for the routine use of enzyme replacement therapy following transplantation.

As previously mentioned, attempts to utilize lung transplantation as a definitive treatment for bronchioalveolar carcinoma resulted in recurrence rates of approximately 50%, leading the vast majority of centers to abandon this approach.⁴

RETRANSPLANTATION

Retransplantation has been utilized as a salvage technique for refractory graft failure. Outcomes following early, emergent retransplantation for primary graft dysfunction are poor, and consequently, use of this intervention in this setting is discouraged.^{94,200} In contrast, retransplantation of carefully selected patients with chronic graft failure due to BOS results in survival rates that approach that of initial transplantation. The new allocation system introduced in the United States assigns a high priority to candidates with BOS, on par with that afforded to patients with IPF. This has led to shortened waiting times and to a doubling in number of retransplant procedures performed annually.⁹⁴ Although the feasibility and reasonable success of retransplantation for BOS have been established, the issue of its appropriateness in the setting of severe organ shortages remains a vexing ethical dilemma.

FUTURE DIRECTIONS

Since its introduction in 1963, lung transplantation has evolved from a heroic surgical therapy to a standard option for select patients with advanced lung disease. Nonetheless, major hurdles must yet be overcome in order to facilitate wider applicability of lung transplantation and more enduring results. The donor organ supply must be expanded to meet demand. More effective and less toxic immunosuppressive strategies must be developed to prevent graft loss

from chronic immunologic injury. An improved understanding of BOS and other forms of chronic allograft dysfunction is required in order to develop strategies to treat injuries of the transplanted lung in a targeted fashion.

Increased utilization of ex vivo lung perfusion for assessment and treatment may offer a partial solution to enhancing the number, quality, and durability of lung allografts. The ultimate solution to many of the current impediments will likely come with advances in gene therapy, stem cell therapy, and tissue engineering. Advances in immunologic manipulation of the recipient and immunologic modulation of the organs to look more like “self” will ultimately one day bring us closer to a state of immune tolerance (i.e., permanent graft acceptance in the absence of chronically administered immunosuppressive agents). It is only through these basic research initiatives that lung transplantation will truly fulfill its potential as a safe, effective, and durable treatment option.

Key Points

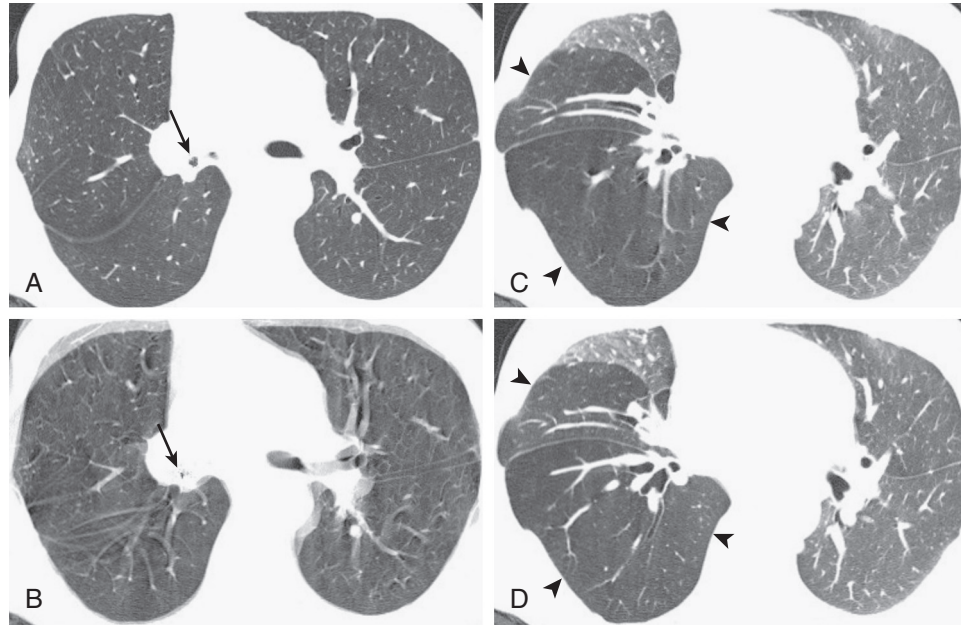
- Lung transplantation is a therapeutic option for a broad spectrum of advanced nonmalignant disorders of the airways, lung parenchyma, and pulmonary vasculature. The most common indications are COPD, idiopathic pulmonary fibrosis, and cystic fibrosis.
- Single-lung and bilateral-lung transplants account for 97% of all procedures; heart-lung transplantation and living donor bilobar transplantation account for the rest.
- The lung allocation system now utilized in the United States grants priority to patients with the greatest predicted “net transplant benefit”—the difference between predicted 1-year survival with versus without transplantation.
- One-, 5-, and 10-year survival rates following transplantation are 82%, 55%, and 33%, respectively.
- Common early complications include primary graft dysfunction due to ischemia-reperfusion injury, bronchial anastomotic stenosis, and bacterial pneumonias.
- Infection rates among lung transplant recipients are several fold higher than among recipients of other solid organs, presumably due to exposure of the allograft to microorganisms via inhalation and aspiration and the higher level of immunosuppression in the lung transplant patients.
- Acute cellular rejection, characterized by perivascular lymphocytic infiltration, is commonly encountered in the first year. It usually responds to high-dose corticosteroid therapy but is a major risk factor for subsequent development of bronchiolitis obliterans syndrome.
- The major limitation to long-term allograft function and patient survival is bronchiolitis obliterans, characterized histologically by fibroproliferative obliteration of the small airways and physiologically by progressive airflow obstruction.
- Newer approaches include ex vivo lung perfusion to assess lung function and perhaps to recondition lungs before transplantation and bridging recipients using extracorporeal artificial lungs, either with pumps or without, until transplantation.

Complete reference list available at *ExpertConsult*.

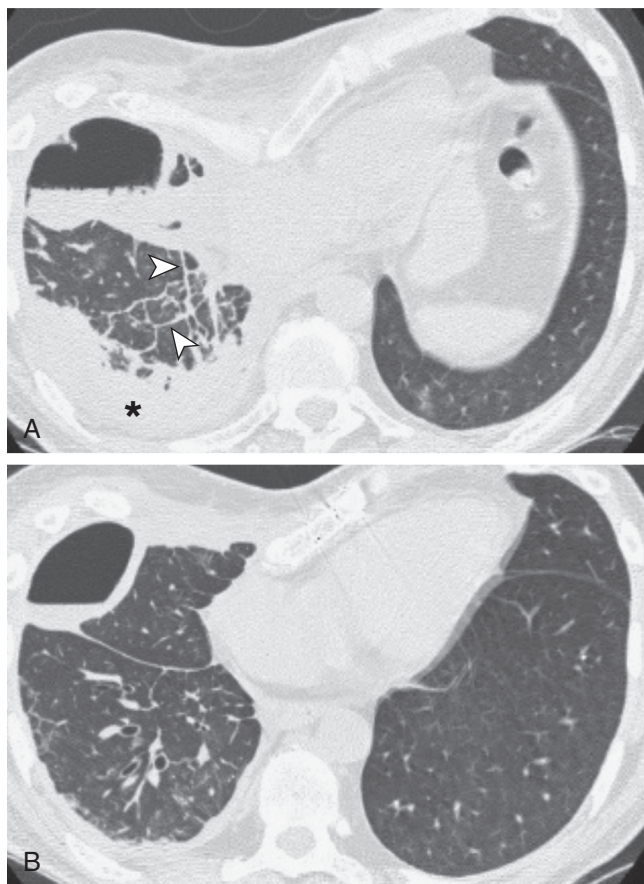
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eFIGURE IMAGE GALLERY



eFigure 106-1 Posttransplant ischemic anastomotic bronchostenosis. A–D, Axial chest dynamic expiratory CT (performed during a forced vital capacity maneuver) displayed in lung windows in a bilateral lung transplant recipient shows narrowing of the bronchus intermedius (*arrow*) associated with extensive hyperlucency and increased volume throughout the right lower lobe (*arrowheads*), reflecting air trapping in the lung subtended by the stenotic airway. (Courtesy Michael Gotway, MD.)



eFigure 106-2 Acute cellular rejection in a lung transplant recipient: high-resolution chest CT findings. **A** and **B**, Axial high-resolution CT displayed in lung windows shows smooth interlobular septal thickening (*arrowheads*) in the transplanted right lung and right pleural effusion (*) detected at the time of diagnosis of biopsy-proven acute cellular rejection; these findings are markedly reduced following augmentation of immunosuppression (**B**). The findings of interlobular septal thickening, volume loss, and pleural effusion are not specific for acute cellular rejection, although that diagnosis is uncommon when these high-resolution CT findings are absent. (Courtesy Michael Gotway, MD.)

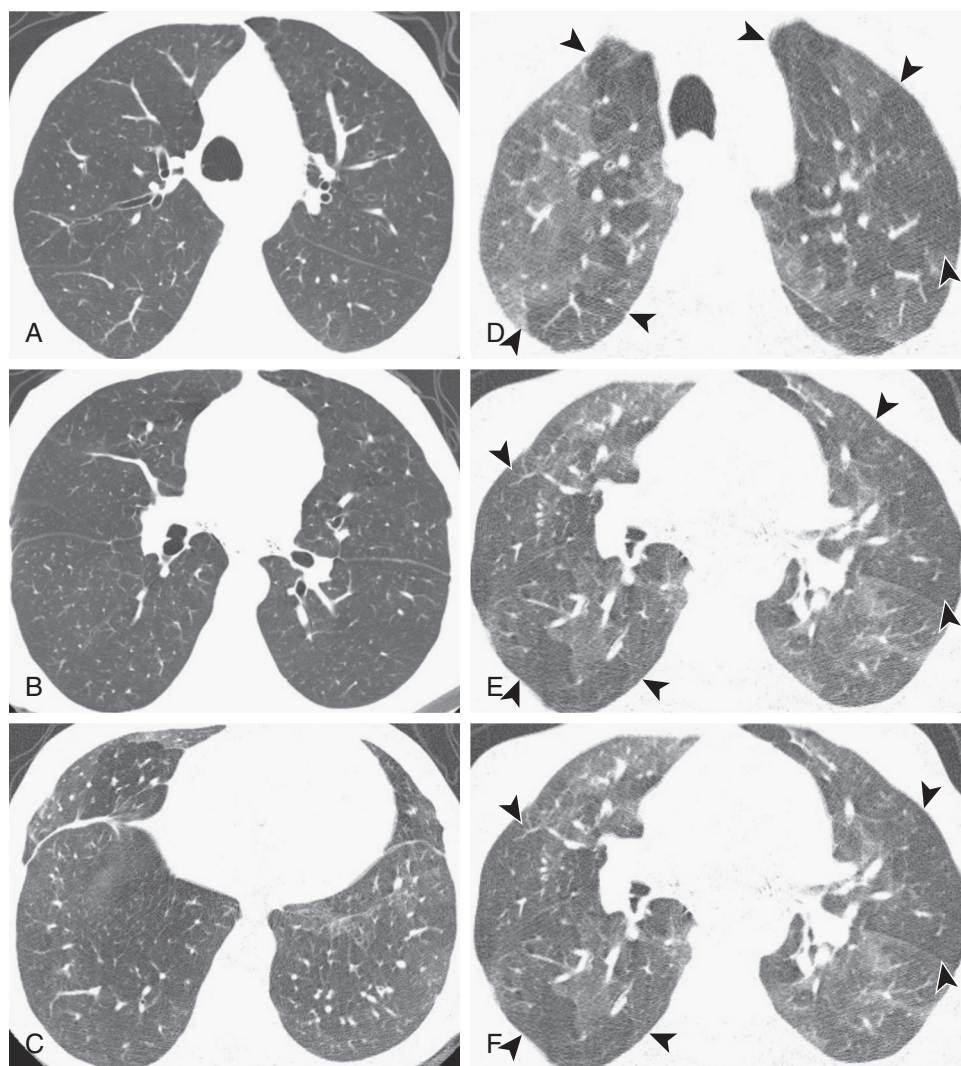


Figure 106-3 Bronchiolitis obliterans syndrome: high-resolution CT findings in a bilateral lung transplant recipient. A–C and [Video 106-2](#), Axial inspiratory high-resolution CT shows minimal findings, with only slightly inhomogeneous lung opacity best seen in the bases (C). D–F and [Video 106-3](#), Axial dynamic expiratory high-resolution CT (performed during a forced vital capacity maneuver) shows interval development of extensive, bilateral inhomogeneous lung opacity—the lighter regions reflect normal, collapsing lung at expiratory imaging, whereas the darker areas (arrowheads) represent air trapping due to small airway obstruction, reflecting bronchiolitis obliterans. (Courtesy Michael Gotway, MD.)

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GLOSSARY OF TERMS AND STANDARD SYMBOLS

I. PRIMARY AND QUALIFYING SYMBOLS

GENERAL

P	Pressure (Includes also <i>partial</i> pressure of a gas in a mixture of gases or in blood.)
L	Lung
W	Chest wall
RS	Respiratory system
Pl	Pleura

VENTILATION

V	Volume of gas
\dot{V}	Flow of gas
I	Inspired
E	Expired
A	Alveolar
T	Tidal
ET	End-tidal
D	Dead space
STPD	<i>Standard Conditions:</i> standard temperature (0°C), barometric pressure (760 mm Hg), and dry.
BTPS	<i>Body Conditions:</i> body temperature and ambient pressure, saturated with water vapor at these conditions.
ATPS	<i>Ambient Conditions:</i> ambient temperature and pressure, saturated with water vapor at these conditions.

GAS EXCHANGE–BLOOD FLOW

Q	Volume of blood
Q	Flow of blood
F	Fractional concentration of gas
C	Concentration in blood
S	Saturation in blood
b	Blood, in general
a	Arterial blood
v	Venous blood
\bar{v}	Mixed venous blood
c	Capillary blood
c'	Pulmonary end-capillary blood

II. VENTILATION AND LUNG MECHANICS

STATIC LUNG VOLUMES

VC	<i>Vital Capacity:</i> The maximum volume of gas that can be exhaled after fully inflating the lungs.
FRC	<i>Functional Residual Capacity:</i> The volume of gas remaining in the lungs at the end of quiet expiration.
TLC	<i>Total Lung Capacity:</i> The volume of gas in the lungs after a maximum inspiration.
RV	<i>Residual Volume:</i> The volume of gas remaining in the lungs after a maximum exhalation.
IC	<i>Inspiratory Capacity:</i> The volume of gas that can be inhaled from resting end-expiration (FRC) to full inflation (TLC).
ERV	<i>Expiratory Reserve Volume:</i> The volume of gas that can be exhaled from resting end-expiration (FRC) to full exhalation (RV).
IRV	<i>Inspiratory Reserve Volume:</i> The volume of gas that can be inhaled from resting end-inspiration to full inflation (TLC).

DESCRIPTORS OF FORCED BREATHING MANEUVERS

FVC	<i>Forced Vital Capacity:</i> The volume of gas that can be forcibly exhaled after fully inflating the lungs.
FEV _t	<i>Timed Forced Expiratory Volume:</i> The volume of gas exhaled at a specified time after beginning the forced vital capacity maneuver. For example, FEV ₁ = forced expiratory volume in 1 second.
FEV _t /FVC	<i>Ratio of Timed Expiratory Volume to Forced Vital Capacity:</i> For example, FEV ₁ /FVC, usually expressed as a percentage.

FEF _x	<i>Specified Forced Expiratory Flow:</i> The forced expiratory flow rate during a specified portion of the forced vital capacity. For example, FEF _{200–1200 mL} = forced expiratory flow rate between 200 and 1200 mL of the forced vital capacity; FEF _{25%–75%} = forced expiratory flow rate between 25% and 75% of the forced vital capacity.
$\dot{V}_{\max_x\%}$	<i>Specified Maximum Expiratory Flow:</i> The instantaneous expiratory flow rate when <i>x</i> percent of the forced vital capacity has been exhaled. For example, $\dot{V}_{\max_{50\%}}$ = maximum expiratory flow rate at 50% of the forced vital capacity.
MVV	<i>Maximum Voluntary Ventilation:</i> Volume of gas exhaled while making maximum breathing efforts during a certain time interval (often 12 seconds).
VR	<i>Ventilatory Reserve:</i> The difference between ventilatory capacity during maximum exercise (estimated as MVV or calculated from FEV ₁) and minute ventilation at peak exercise; VR, which is also known as <i>breathing reserve</i> , represents the potential for further increase in ventilation during maximum (or peak) exercise.
Pr _{max}	<i>Maximum Inspiratory Pressure:</i> The maximum pressure generated by the respiratory muscles during an attempted inspiration.
PE _{max}	<i>Maximum Expiratory Pressure:</i> The maximum pressure generated by the respiratory muscles during an attempted exhalation.

DESCRIPTORS OF VENTILATION

f	<i>Respiratory Frequency:</i> The number of breaths during 1 minute.
V _T	<i>Tidal Volume:</i> The volume of gas inspired or expired during each breath.
\dot{V}_E	<i>Expired Ventilation:</i> The volume of gas (BTPS), usually measured at the mouth, exhaled during 1 minute.
\dot{V}_I	<i>Inspired Ventilation:</i> The volume of gas (BTPS), measured or calculated, inhaled during 1 minute.
\dot{V}_A	<i>Alveolar Ventilation:</i> The volume of gas (BTPS), exhaled from the lungs during 1 minute, that contributed to gas exchange; calculated as expired ventilation minus dead space ventilation.

\dot{V}_D	<i>Dead Space Ventilation:</i> The volume of gas (BTPS), exhaled from the lungs during 1 minute, that did not contribute to gas exchange; also known as <i>wasted ventilation</i> . Calculated from the equation $\dot{V}_D = \dot{V}_E \frac{P_{aCO_2} - P_{ECO_2}}{P_{aCO_2} - P_{iCO_2}}$ where P _{aCO₂} , P _{ECO₂} , and P _{iCO₂} are the partial pressures of CO ₂ in arterial blood, mixed expired gas, and inspired gas, respectively.
V _D	<i>Dead Space Volume:</i> The volume of the physiologic dead space; calculated as \dot{V}_D/f .
V _D /V _T	<i>Ratio of Dead Space to Tidal Volume:</i> The proportion, usually expressed as a percentage, of each breath that does not contribute to CO ₂ removal (i.e., the proportion of each breath that is wasted).
VE	<i>Ventilatory Equivalent:</i> The minute ventilation required for each liter of gas exchanged, either O ₂ or CO ₂ ; used as a measure of the efficiency of the lungs as a gas exchanger. For O ₂ : $VE_{O_2} = \frac{\dot{V}_E \text{ (BTPS)}}{\dot{V}_{O_2} \text{ (STPD)}}$

VOLUME-PRESSURE RELATIONSHIPS

C	<i>Compliance:</i> General symbol for compliance, or the ratio of volume change of the structure per unit change in applied pressure across the structure.
CL	<i>Lung Compliance:</i> The volume change of the lung divided by the difference between alveolar pressure (Palv) and pleural pressure (Ppl), which is also known as the transpulmonary pressure (PL).
CW	<i>Chest Wall Compliance:</i> The volume change of the chest wall divided by the difference between pleural pressure (Ppl) and body surface pressure (Pbs), which is also known as the transthoracic pressure (PW).
Crs	<i>Respiratory System Compliance:</i> The volume change of the lung and chest wall divided by the difference between alveolar pressure (Palv) and body surface pressure (Pbs), or transpulmonary pressure (PL) plus transthoracic pressure (PW).
Cdyn	<i>Dynamic Compliance:</i> Value for compliance based on measurements made during uninterrupted breathing.

Cst	<i>Static Compliance:</i> Value for compliance based on measurements made during periods of no airflow.	RQ	<i>Respiratory Quotient:</i> The ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ during steady-state metabolic activity.
C/VL	<i>Specific Compliance:</i> Value for compliance divided by the lung volume at which it was measured, usually functional residual capacity.	RER	<i>Respiratory Exchange Ratio:</i> The ratio of $\dot{V}CO_2$ to $\dot{V}O_2$, as in RQ, but also including the influence of transient changes in body stores of respiratory gases.

FLOW-PRESSURE RELATIONSHIPS

R	<i>Resistance:</i> General symbol for frictional resistance, or the pressure difference divided by flow.
RAW	<i>Airway Resistance:</i> Resistance calculated from pressure difference between airway opening (Pao) and alveoli (Palv) divided by the airflow.
RL	<i>Total Pulmonary Resistance:</i> Resistance calculated by dividing flow-dependent transpulmonary pressure by airflow at the mouth.
GAW	<i>Airway Conductance:</i> The reciprocal of RAW.
GAW/VL	<i>Specific Conductance:</i> Value for airway conductance divided by the lung volume at which it was measured.

III. GAS EXCHANGE

BLOOD

Examples shown are for O₂; other gases (e.g., CO₂, N₂, CO) or other sites (e.g., \bar{v} , c') can be substituted when appropriate.

PO ₂	<i>Partial Pressure of O₂:</i> General designation (expressed in mm Hg); source usually specified (e.g., arterial PO ₂ or PaO ₂).	DL
SO ₂	<i>Blood Saturation:</i> General designation (expressed as a percentage); source usually specified (e.g., arterial SO ₂ or SaO ₂).	DM
CO ₂	<i>Oxygen Content:</i> General designation (expressed in mL/dL); source usually specified (e.g., arterial CO ₂).	1/DL
$\dot{V}O_2$	<i>Oxygen Consumption:</i> The volume of O ₂ (STPD) utilized by the body during 1 minute; usually calculated as the amount of O ₂ extracted from inspired gas.	
$\dot{V}O_{2max}$	<i>Maximum Oxygen Consumption:</i> The maximal volume of O ₂ (STPD) that can be utilized by the body during 1 minute of maximally attainable exercise.	
$\dot{V}CO_2$	<i>Carbon Dioxide Output:</i> The volume of CO ₂ (STPD) produced by the body during 1 minute; usually calculated as the amount of CO ₂ added to exhaled gas.	DL/VA

GAS TO BLOOD

(A-a)PO ₂	<i>Alveolar-Arterial PO₂ Difference:</i> The difference in PO ₂ between mean alveolar gas and arterial blood (expressed in mm Hg).
	<i>Alveolar Gas Equation:</i> Often used to calculate mean alveolar PO ₂ (PAO ₂):

$$PAO_2 = PIO_2 - \frac{PACO_2}{R}$$

where PIO₂ is the PO₂ of inspired gas; PACO₂ is the alveolar PCO₂ (usually assumed to equal arterial PCO₂); and R is the respiratory exchange ratio. Because of some assumptions, this equation is an approximation. For calculating the exact PAO₂, an additional term is needed, where FIO₂ is the fractional concentration of O₂ in inspired gas.

$$PAO_2 = PIO_2 - \frac{PACO_2}{R} + \left[PACO_2 \times FIO_2 \times \frac{(1-R)}{R} \right]$$

Diffusing Capacity of the Lung: Expressed as the volume of gas transferred per minute per unit of alveolar-capillary pressure difference for the gas used, which is usually specified (e.g., DL_{CO} or DL_{O₂}).

Diffusing Capacity of the Alveolocapillary Membrane.

Total Resistance to Diffusion: The sum of the resistance to diffusion of the test gas across the alveolocapillary membrane (1/DM) and the resistance to diffusion within the red blood cells attributable to the chemical reaction between the test gas and hemoglobin (1/θVC). These relationships are expressed by the Roughton-Forster equation:

$$\frac{1}{DL} = \frac{1}{DM} + \frac{1}{\theta VC}$$

Diffusion per Unit of Alveolar Volume: The value of DL (STPD) divided by VA (BTPS), both measured in the same breathing maneuver.

IV. HEMODYNAMIC DESCRIPTORS

\dot{Q}_T	<i>Cardiac Output:</i> The total output of the left ventricle during one minute.
\dot{Q}_S	<i>Pulmonary Shunt Flow:</i> The total amount of blood per minute perfusing completely nonventilated gas-exchange units; hence, blood that does not come in contact with inspired gas and does not contribute to oxygen uptake. Often called the <i>right-to-left shunt</i> , but this term also includes intracardiac shunts.
\dot{Q}_S/\dot{Q}_T	<p><i>Pulmonary Shunt Fraction:</i> The total pulmonary shunt (\dot{Q}_S), or venous admixture, expressed as a percentage of total cardiac output (\dot{Q}_T) according to the equation:</p> $\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - C\bar{V}O_2} \times 100$ <p>where $Cc'O_2$ is the O_2 content of end-capillary blood; CaO_2 is the O_2 content of arterial blood; and $C\bar{V}O_2$ is the O_2 content of mixed venous blood. While breathing 100% O_2 (and sampling systemic arterial blood, not end-capillary blood), \dot{Q}_S/\dot{Q}_T is a measure of right-to-left shunting of blood.</p>
PPA	<i>Pulmonary Artery Pressure:</i> The pressure—systolic, diastolic, or mean—measured in the pulmonary artery.
PLA	<i>Left Atrial Pressure:</i> The pressure, usually mean, measured in the left atrium.
Pcap	<p><i>Pulmonary Capillary Pressure:</i> The mean pressure in the pulmonary capillaries, sometimes abbreviated P_c, which cannot be measured directly in humans but is frequently estimated by the equation:</p> $P_{cap} = PLA + 0.4 (PPA - PLA)$
PPW	<i>Pulmonary Wedge Pressure:</i> The mean pressure measured by the pulmonary artery occlusion technique, which provides an estimate of the postcapillary, or pulmonary venous, pressure.
PVR	<p><i>Pulmonary Vascular Resistance:</i> The resistance to blood flow through the lungs; a calculated value from the equation:</p> $PVR = \frac{PPA - PLA}{\dot{Q}_T}$ <p>in which PPW is often used to approximate PLA.</p>

V. OTHER USEFUL TERMS AND EQUATIONS

PEEP	<i>Positive End-Expiratory Pressure:</i> The condition in which the pressure in the lungs at the end of expiration is positive (i.e., higher than atmospheric). Usually applied externally by ventilator adjustments; when PEEP results from failure to exhale fully at the end of expiration, it is called <i>intrinsic</i> (PEEPi).
$P_{0.1}$	<i>Mouth Occlusion Pressure:</i> The pressure measured in the mouth during the first 0.1 second of attempted inspiration after the airway is temporarily occluded while the subject is breathing. An estimate of the central drive to breathe.
T_i/T_T	<p><i>Duty Cycle:</i> The ratio of the duration of inspiration (T_i) to the duration of inspiration and expiration (T_T), a reflection of respiratory timing.</p> <p><i>Henderson-Hasselbalch Equation:</i> Useful for calculating any one of three variables, pH, HCO_3^-, or H_2CO_3, when two of them are known:</p> $pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]}$ <p>where pK, the dissociation constant, is 6.10 for plasma at 37°C; $[HCO_3^-]$ is the concentration of bicarbonate in plasma; and $[H_2CO_3]$ is the concentration of carbonic acid in plasma (both in mol/L). The equation can be rearranged by using PCO_2 (in mm Hg) and its solubility in plasma so that</p> $pH = pK + \log \frac{[HCO_3^-]}{[PCO_2 \times 0.0301]}$ <p><i>Starling Equation:</i> Net fluid exchange (J_v) across the microvascular barrier in the lungs:</p> $J_v = L_p S [(P_c - P_i) - \sigma d (\pi_c - \pi_i)]$ <p>where L_p is the hydraulic conductivity (“permeability”); S is the surface area; P_c is the microvascular hydrostatic pressure; P_i is the perimicrovascular hydrostatic pressure; σd is the osmotic reflection coefficient; π_c is the microvascular colloid osmotic pressure; and π_i is the perimicrovascular colloid osmotic pressure.</p>

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